

Metal Catalysis – Michael Willis and Stephen Fletcher

CDT module 3rd/4th November 2016

Thursday

9.00-9.30 Introduction to different metals of the periodic table– MW + SF (introduce group exercise)

9.30-10.15 Pd catalysed C-C and C-X bond forming reactions – MW

10.15-10.45 Coffee break

10.45-11.45 Asymmetric conjugate addition chemistry – SF

11.45-12.15 Metathesis – MW

12.15-1.30 Lunch

1.30-5.00 Group work

Friday

9.30-10.30 Asymmetric allylic substitution chemistry – SF

10.30-11.00 Coffee

11.00-11.30 Non-linear effects/autocatalysis – SF

11.30-12.00 Desymmetrisation – MW

12.00-1.15 Lunch

1.15-1.45 C-H functionalization chemistry – MW

1.45-2.15 Group presentations

hydrogen 1 H 1.0079																	helium 2 He 4.0026			
lithium 3 Li 6.941	beryllium 4 Be 9.0122											boron 5 B 10.811	carbon 6 C 12.011	nitrogen 7 N 14.007	oxygen 8 O 15.999	fluorine 9 F 18.998	neon 10 Ne 20.180			
sodium 11 Na 22.990	magnesium 12 Mg 24.305											aluminum 13 Al 26.982	silicon 14 Si 28.086	phosphorus 15 P 30.974	sulfur 16 S 32.065	chlorine 17 Cl 35.453	argon 18 Ar 39.948			
potassium 19 K 39.098	calcium 20 Ca 40.078	scandium 21 Sc 44.956	titanium 22 Ti 47.867	vanadium 23 V 50.942	chromium 24 Cr 51.996	manganese 25 Mn 54.938	iron 26 Fe 55.845	cobalt 27 Co 58.933	nickel 28 Ni 58.693	copper 29 Cu 63.546	zinc 30 Zn 65.39	gallium 31 Ga 69.723	germanium 32 Ge 72.61	arsenic 33 As 74.922	seleเนียม 34 Se 78.96	bromine 35 Br 79.904	krypton 36 Kr 83.80			
rubidium 37 Rb 85.468	strontium 38 Sr 87.62	yttrium 39 Y 88.906	zirconium 40 Zr 91.224	niobium 41 Nb 92.906	molybdenum 42 Mo 95.94	technetium 43 Tc [98]	ruthenium 44 Ru 101.07	rhodium 45 Rh 102.91	palladium 46 Pd 106.42	silver 47 Ag 107.87	cadmium 48 Cd 112.41	indium 49 In 114.82	tin 50 Sn 118.71	antimony 51 Sb 121.76	tellurium 52 Te 127.60	iodine 53 I 126.90	xenon 54 Xe 131.29			
caesium 55 Cs 132.91	barium 56 Ba 137.33	57-70 * Lu 174.97	hafnium 72 Hf 178.49	tantalum 73 Ta 180.95	tungsten 74 W 183.84	rhenium 75 Re 186.21	osmium 76 Os 190.23	iridium 77 Ir 192.22	platinum 78 Pt 195.08	gold 79 Au 196.97	mercury 80 Hg 200.59	thallium 81 Tl 204.38	lead 82 Pb 207.2	bismuth 83 Bi 208.98	polonium 84 Po [209]	astatine 85 At [210]	radon 86 Rn [222]			
francium 87 Fr [223]	radium 88 Ra [226]	89-102 * * La [227]	actinium 89 Ac [227]	thorium 90 Th 232.04	protactinium 91 Pa 231.04	uranium 92 U 238.03	neptunium 93 Np [237]	plutonium 94 Pu [244]	americium 95 Am [243]	curium 96 Cm [247]	berkelium 97 Bk [247]	californium 98 Cf [251]	einsteinium 99 Es [252]	fermium 100 Fm [257]	mendelevium 101 Md [258]	nobelium 102 No [259]	unnilium 110 Uun [271]	ununium 111 Uuu [272]	unbinium 112 Uub [277]	ununquadium 114 Uuq [285]

* Lanthanide series

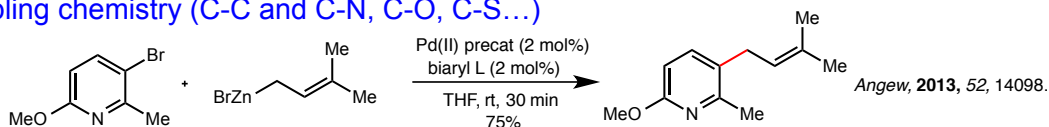
** Actinide series

lanthanum 57 La 138.91	cerium 58 Ce 140.12	praseodymium 59 Pr 140.91	neodymium 60 Nd 144.24	promethium 61 Pm [145]	samarium 62 Sm 150.36	europium 63 Eu 151.96	gadolinium 64 Gd 157.25	terbium 65 Tb 158.93	dysprosium 66 Dy 162.50	holmium 67 Ho 164.93	erbium 68 Er 167.26	thulium 69 Tm 168.93	ytterbium 70 Yb 173.04
actinium 89 Ac [227]	thorium 90 Th 232.04	protactinium 91 Pa 231.04	uranium 92 U 238.03	neptunium 93 Np [237]	plutonium 94 Pu [244]	americium 95 Am [243]	curium 96 Cm [247]	berkelium 97 Bk [247]	californium 98 Cf [251]	einsteinium 99 Es [252]	fermium 100 Fm [257]	mendelevium 101 Md [258]	nobelium 102 No [259]

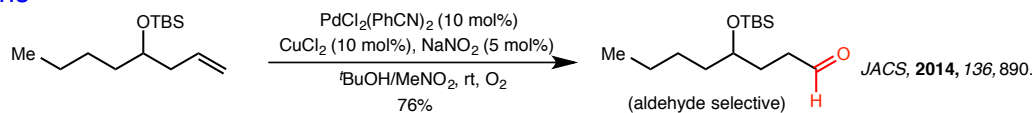
46
Pd
106

- the most employed TM catalysts?
- PdOAc₂, Pd₂(dba)₃, PdCl₂ (and others) – all commonly available
- most simple complexes relatively stable

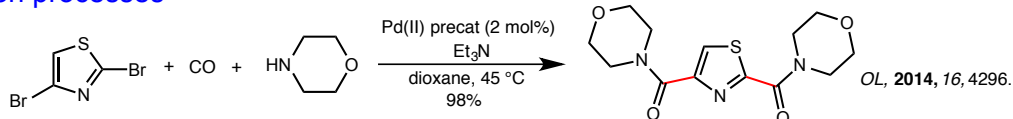
Cross-coupling chemistry (C-C and C-N, C-O, C-S...)



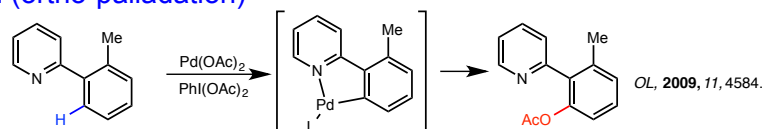
Wacker reactions



Carbonylation processes



C-H functionalisation (ortho-palladation)



Pd(II) Lewis acids – rearrangements

Allylic alkylation

Alkene insertion (Heck)

Tsuji "Palladium reagents and catalysts: New perspectives for the 21st century", Wiley, 2004
Bates "Organic synthesis using transition metals", Wiley, 2nd Ed., 2012.

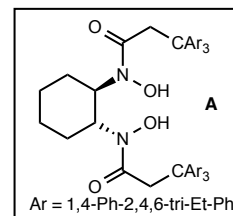
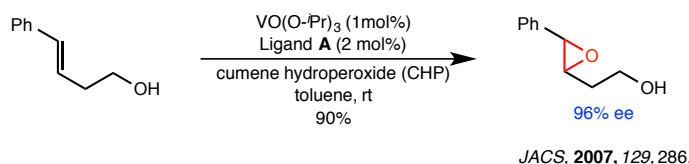
23
V
50.9

- Redox chemistry dominates, with the epoxidation of *homoallylic* alcohols being the most important reaction
- V(O)(acac)₂ most used cat, and commercially available

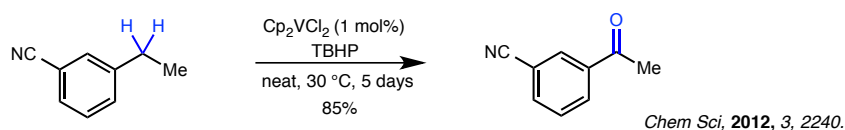
Epoxidation



Enantioselective variant



"C-H activation"

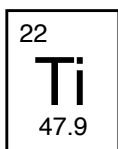


Lewis acid catalysis - epox. opening

nitrile reduction

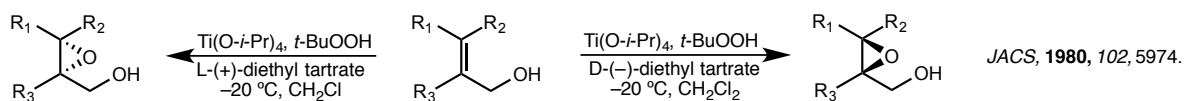
undirected epoxidations

Tsuji "The future of vanadium", Dalton Trans. 2013, 42, 11749.
Hirao "Vanadium in Modern Organic Synthesis", Chem. Rev. 1997, 97, 2707.

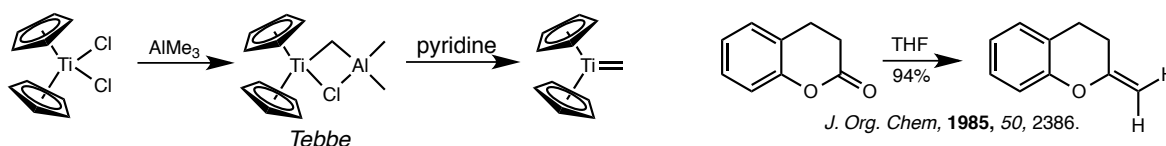


- Highly oxophilic. Ti^{IV} dominates, +3 also common.
- TiO₂ used extensively as pigment, metal alloy, medical devices, sunscreen
- Important as polymerization catalysts and Lewis acids
- Useful carbonyl (CO) and cyclopentadienyl (Cp) complexes

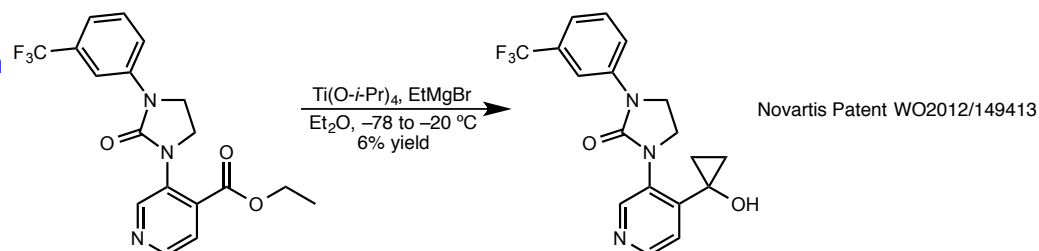
Katsuki-Sharpless epoxidation



Olefination of ketones and esters

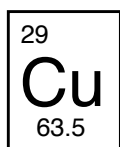


Cyclopropanation



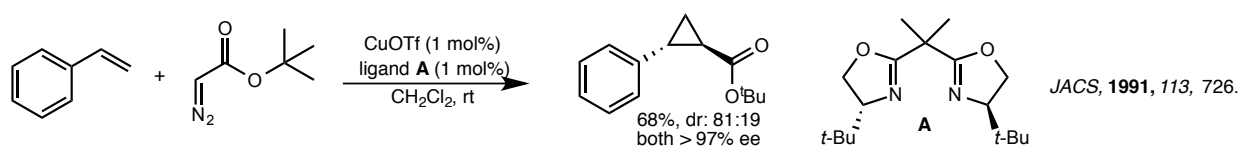
Lewis acids McMurry coupling Metathesis "Cp₂Ti" (+2) in cycloaddition / olefin activations

Marek (Ed) *Titanium and Zirconium in Organic Synthesis*, Wiley-VCH, 2002
Johnson and Sharpless, in *Catalytic Asymmetric Synthesis*. I. Ojima (Ed.) VCH, 1993, 103-158

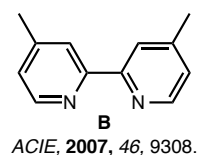
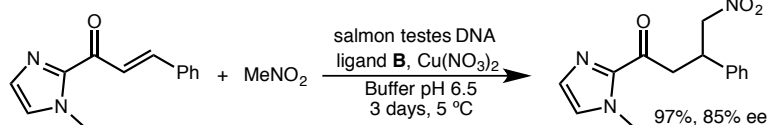
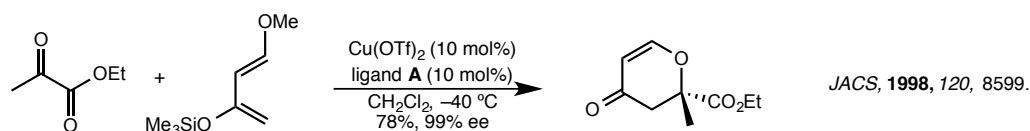


- One of the first metals to be extensively used in synthesis.
- Cu^I and Cu^{II} most important in catalysis, Cu⁰ in 'metals', Cu^{III} intermediates
- Many complexes commercially available. Many are air and/or moisture stable

Cyclopropanation (and aziridination)



Chiral Lewis Acids



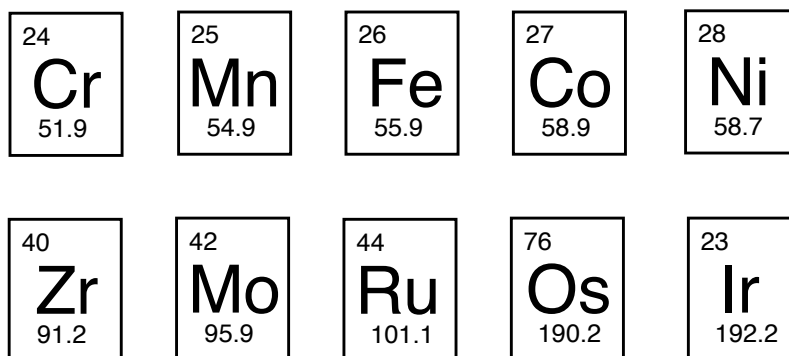
Asymmetric addition Carbo-metallation Allylic oxidation Redox (ox or co-oxidant)

Unit Assessment

Working in pairs, provide a one-page summary of an TM element's use in synthesis

Provide most important reaction(s), and up-to-date examples

The elements to choose from:



Include your names...

Pd (and some Cu) Catalysed C-C and C-X Bond Forming Processes

Michael Willis

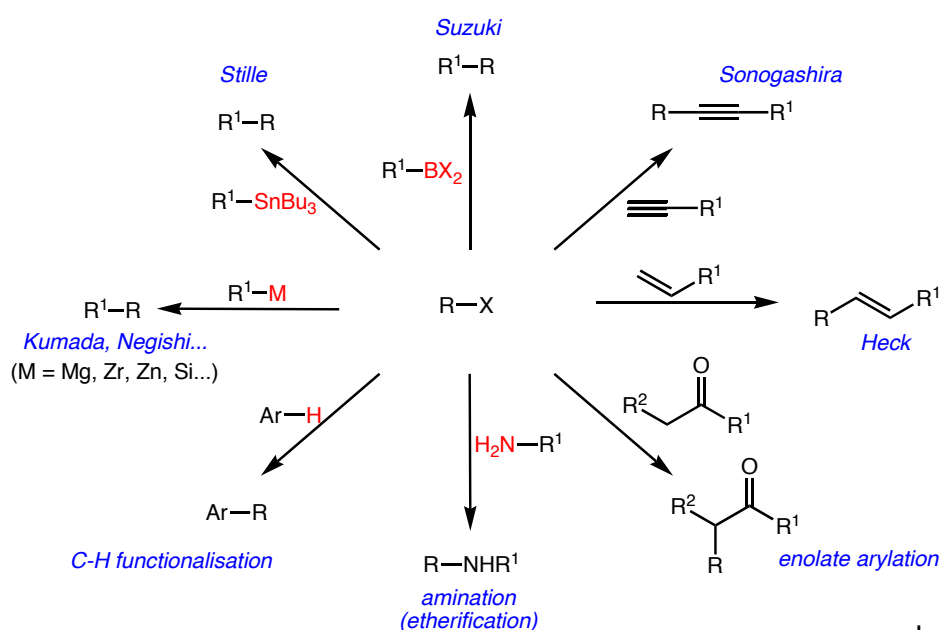
CDT - Metal Catalysis

3rd/4th November 2016

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Pd-Catalysed cross-coupling reactions

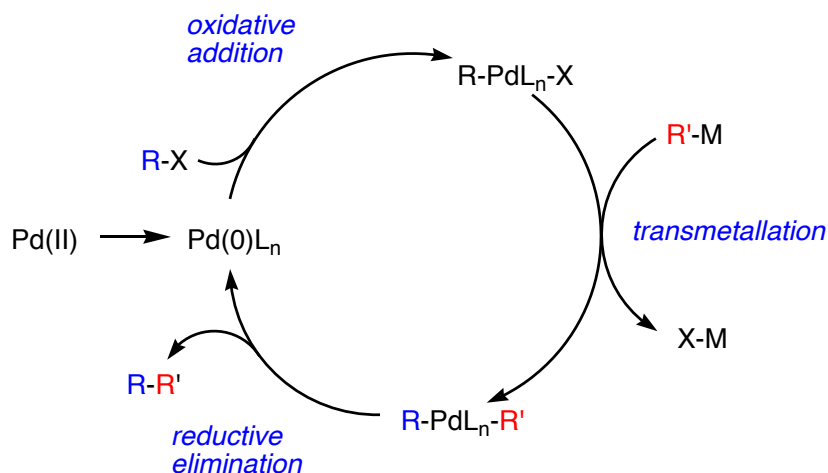
- Pd couplings are arguably the most widely used TM catalysed processes
- Generally good stability to O₂ and H₂O and have good functional group tolerance
- Large variety of coupling partners available



... and many more

Key mechanistic steps in coupling rxn's

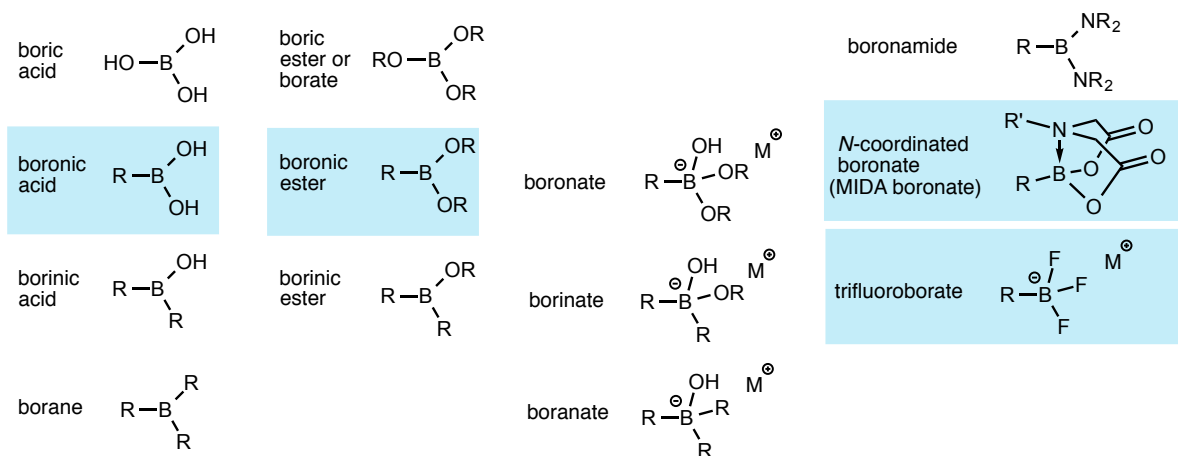
- Pd(II) salts are often used as precursors, Pd(OAc)₂ in particular
- Transmetalation is generally rate-limiting



General Pd reviews: *Metal-Catalysed Cross-Coupling Reactions*; Ed. Diederich and Stang, Wiley-VCH, 1998.
Handbook of Organopalladium Chemistry for Organic Synthesis; Ed. Negishi, Wiley, 2002.
Palladium Reagents and Catalysts: New Perspectives for the 21st Century; Tsuji, Wiley, 2004.

Suzuki couplings – Boron reagents

- Popular due to low toxicity and stability of boronic acids/esters - v widely available
- Aryl, alkenyl and alkylboranes have all been used
- Many catalysts available, and many boron reagents...



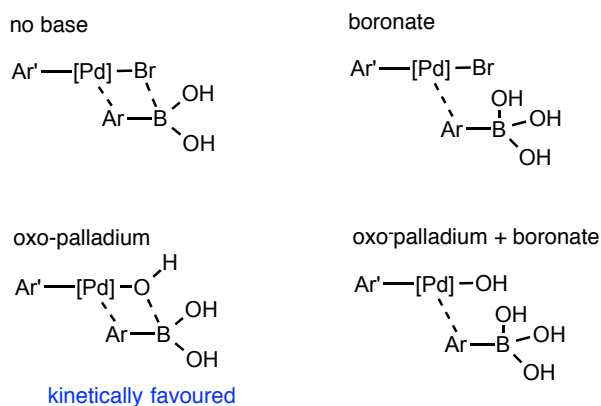
- Pd(PPh₃)₄ is traditional catalyst, but suffers from poor stability and activity

Suzuki, *Tet. Lett.* **1979**, 20, 3437.

Reviews: Suzuki, *Chem. Rev.* **1995**, 95, 2457; Miyaura, *Topics in Current Chem.* **2002**, 219, 11.

Suzuki couplings – the transmetalation step

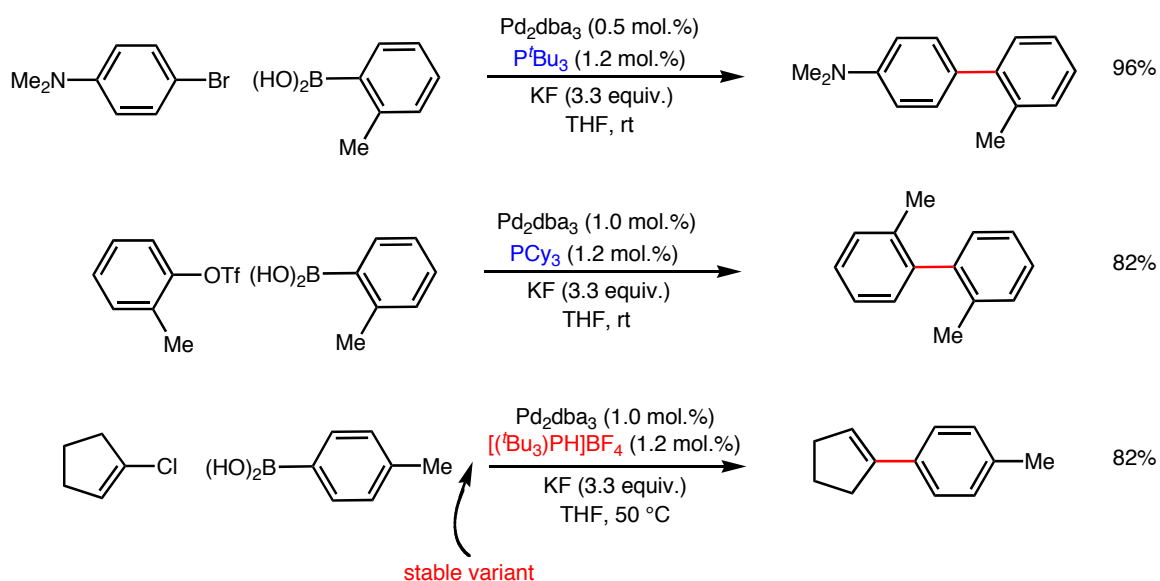
- Two main possibilities – boronate and oxo-palladium pathways
- Recent data suggests oxo-palladium for biphasic reactions (the majority)



Amatore and Jutand, *CEJ* **2011**, 17, 2492; Hartwig, *JACS* **2011**, 133, 2116; Lloyd-Jones, *JACS* **2012**, 137, 7431.

Suzuki couplings: Effective ligands (1)

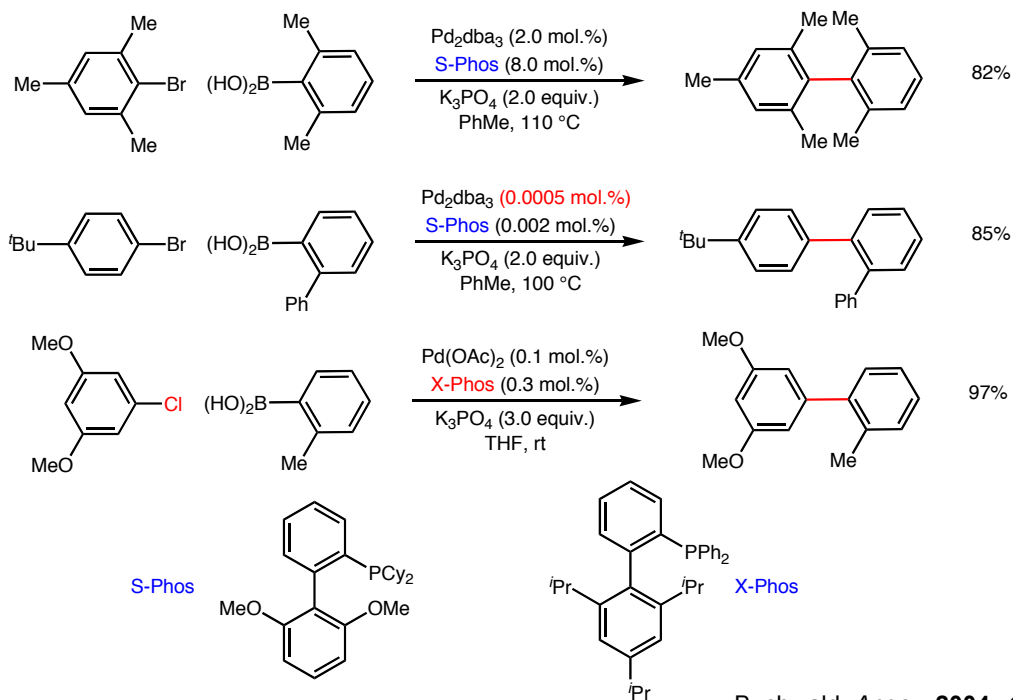
- Bulky electron-rich phosphines are most active
- P^tBu_3 or PCy_3 effective for many substrates - Cl, Br, I, OTf



Fu, *JACS* **2000**, 122, 4020.
Fu, *Org. Lett.* **2001**, 3, 4295.

Suzuki couplings: Effective ligands (2)

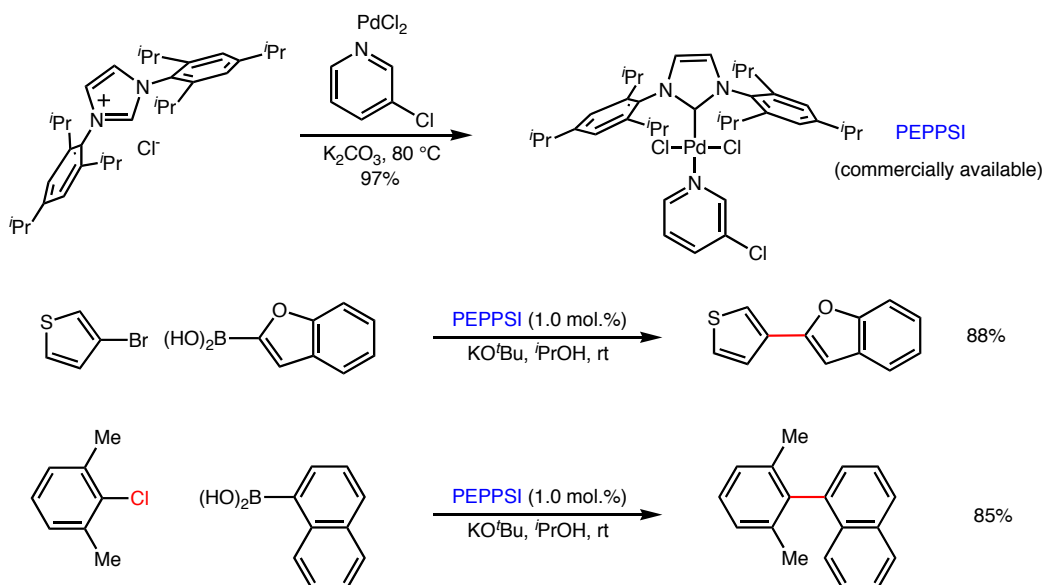
- Large variety of biphenyl-phosphines commercially available
- “S-Phos” and “X-Phos” particularly effective



Buchwald, *Angew* **2004**, 43, 1871.
 Buchwald, *JACS* **2005**, 127, 4685.

Suzuki couplings: N-Heterocyclic carbene ligands

- NHC ligands can rival performance of traditional P-ligands
- Sensitivity to O_2 and H_2O has been a problem
- An air stable multi-purpose catalyst?

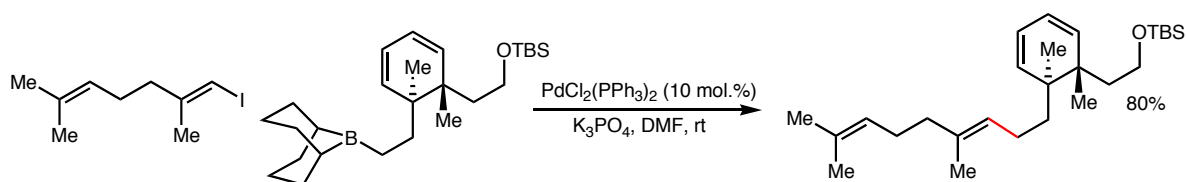


See also; Nolan, *JACS* **2006**, 128, 4101; *JOC* **2006**, 71, 3816;
 Beller, *Angew* **2002**, 41, 986; Caddick, *JACS* **2003**, 125, 10066.

Organ, *CEJ* **2006**, 12, 4743.

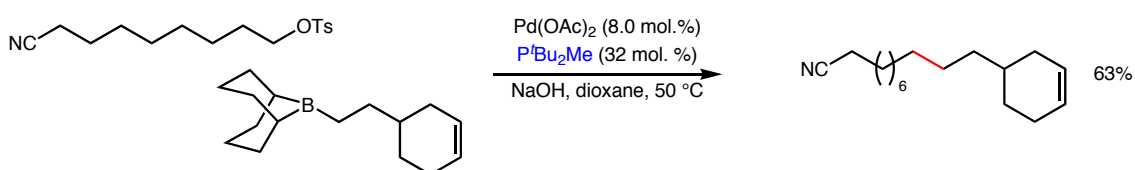
Suzuki couplings: Alkyl couplings

- β -Elimination is major problem
- Majority of examples employ 9-BBN derivatives as *B*-component



De Clercq, *Org. Lett.* **2006**, *8*, 4815.

- Alkyl halides and tosylates can also be used

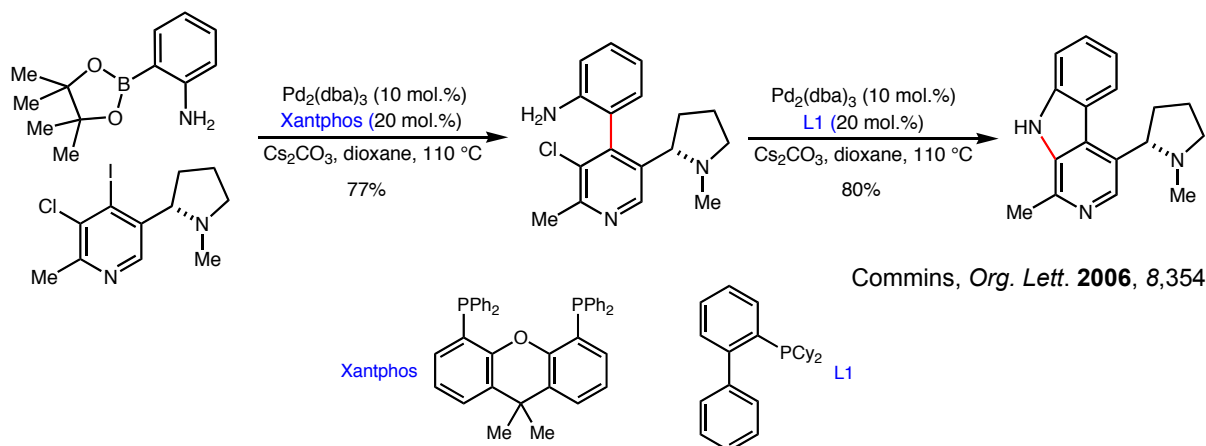


Reviews; Beller, *Angew*, **2005**, *44*, 674;
Fu, *ASC* **2004**, *346*, 1525; Danishefsky, *Angew* **2001**, *40*, 4544.

Fu, *Angew* **2002**, *41*, 3910.

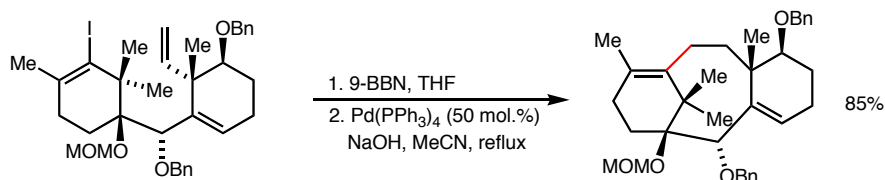
Suzuki couplings: Application to target synthesis

- Many total synthesis applications



Commins, *Org. Lett.* **2006**, *8*, 3549.

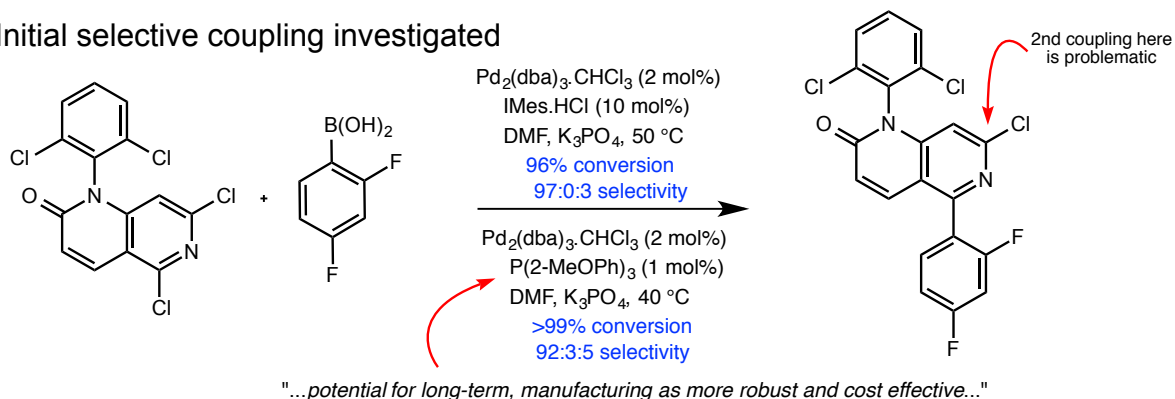
- Alkyl coupling towards Taxol



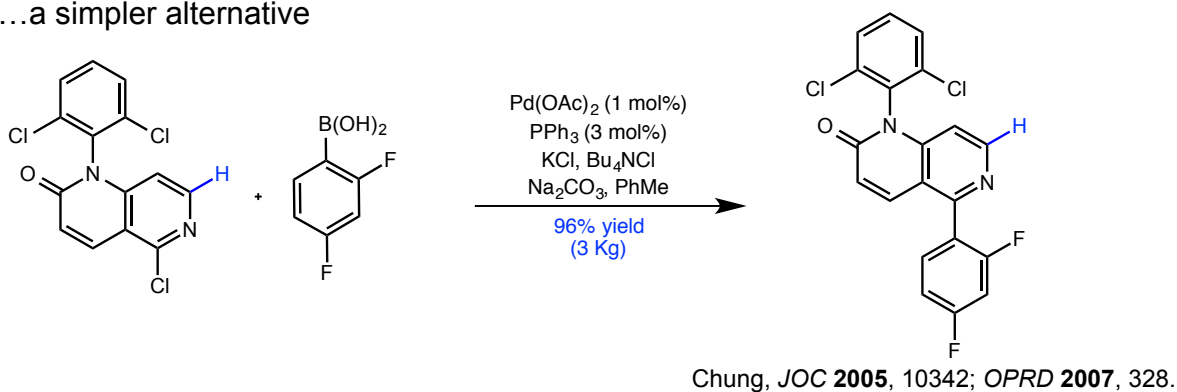
Nakada, *Org. Lett.* **2004**, *6*, 4491.

Suzuki couplings: Application in process chemistry

- Merck MAP kinase inhibitor
- Initial selective coupling investigated

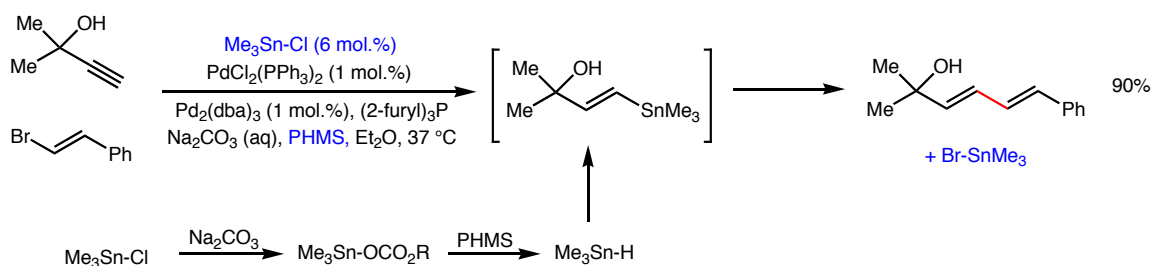


- ...a simpler alternative



Stille Couplings

- Widely used academically, but organotin waste is a concern
- reactions catalytic in tin



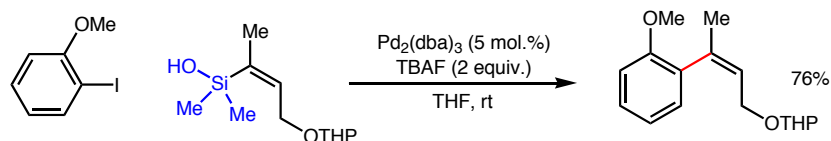
Maleczka, *JACS* **2001**, 123, 3194.

- Using mono-stannane reagents - Ni catalysis

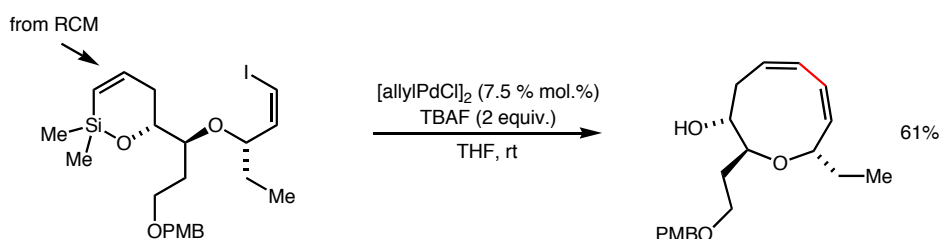


Silane couplings (Hiyama reaction)

- Attractive due to non-toxic silicon waste
- Silanes need activation



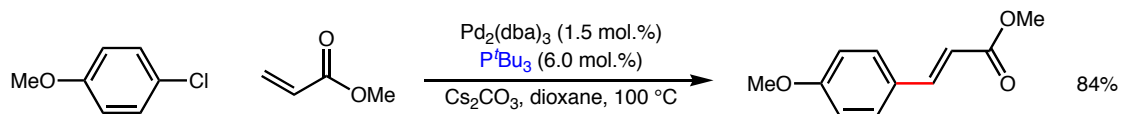
- Application to the synthesis of brasilenyne – also, see Ed Anderson...



Denmark, *ACR* **2002**, 35, 835.
Denmark, *JACS* **2004**, 126, 12432.

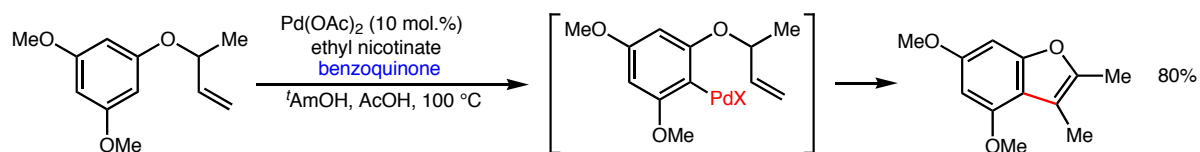
Heck reactions

- Significantly more complex than ‘simple’ coupling reactions
- Attractive because of no organometallic coupling partner
- Use of Ar-Cl substrates



Fu, *JOC* **1999**, 64, 10.

- “Oxidative” Hecks - generate Ar-Pd *in-situ*



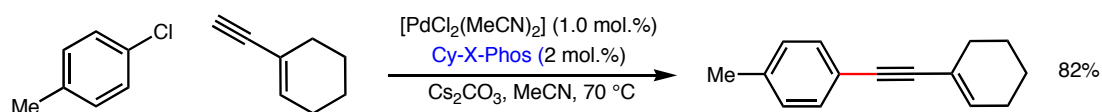
Review; Belatskaya, *Chem. Rev.* **2000**, 100, 3009.

Stoltz, *Angew* **2004**, 43, 6144.

For a regioselective intermolecular oxidative Heck on indoles, see; Gaunt, *Angew* **2005**, 44, 3125.

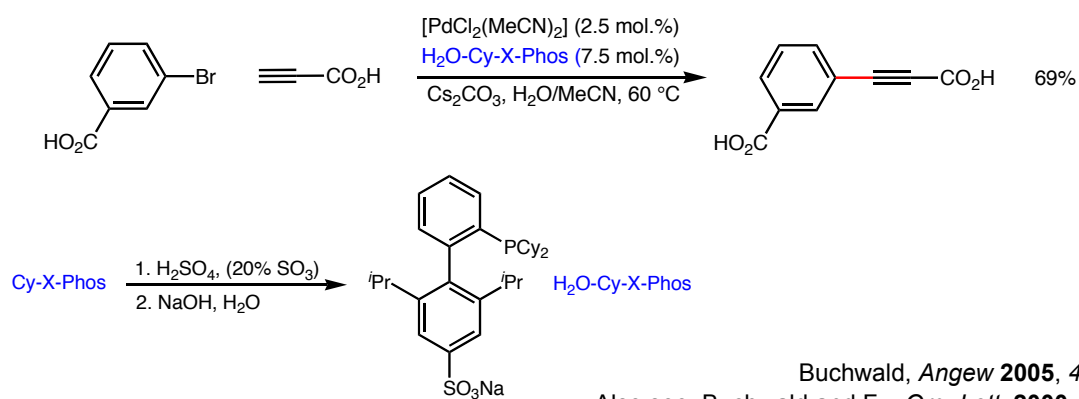
Sonogashira reactions

- No organometallic coupling partner
- Cu free reactions of Ar-Cl's



- Reactions in water - water soluble X-Phos (also for Suzuki's)

Buchwald, *Angew* **2003**, 42, 5993.

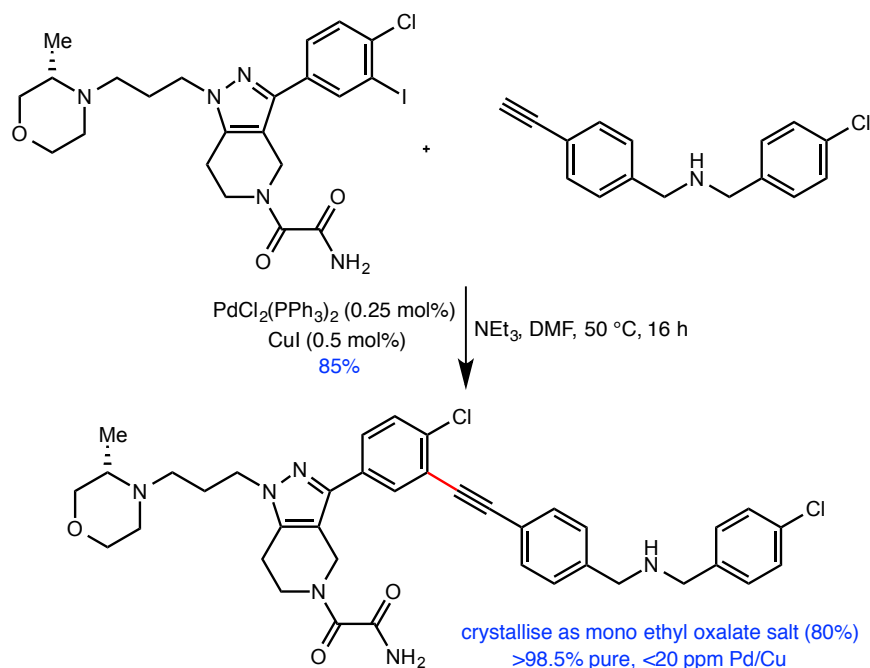


Buchwald, *Angew* **2005**, 44, 6173.

Also see; Buchwald and Fu, *Org. Lett.* **2000**, 2, 1729.

Sonogashira reactions – process example

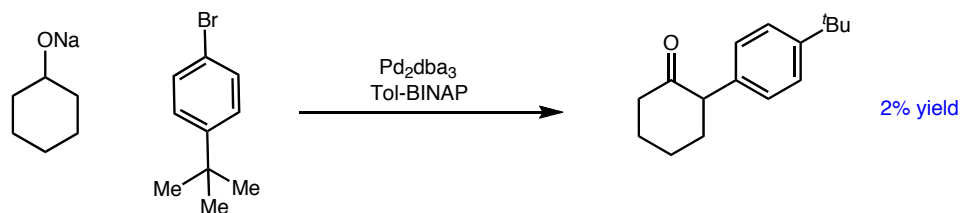
- Johnson & Johnson cathepsin S inhibitor – immunological disorders
- Final step of synthesis, therefore metal contamination a real issue



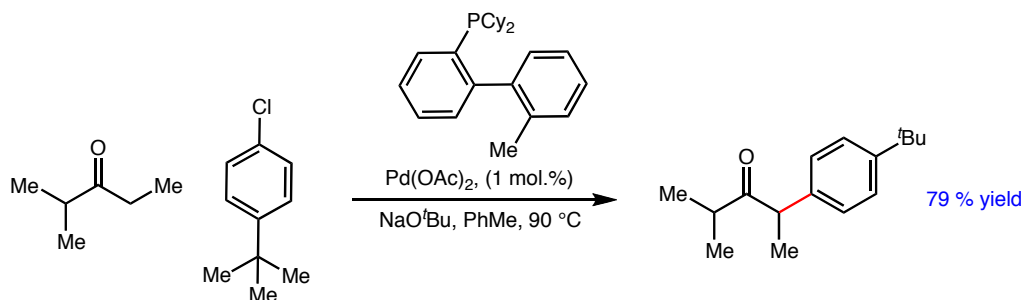
JOC **2007**, 72, 8243.

Discovery of a Pd-catalysed enolate arylation

- Attempted etherification using cyclohexanol delivered arylated ketone product



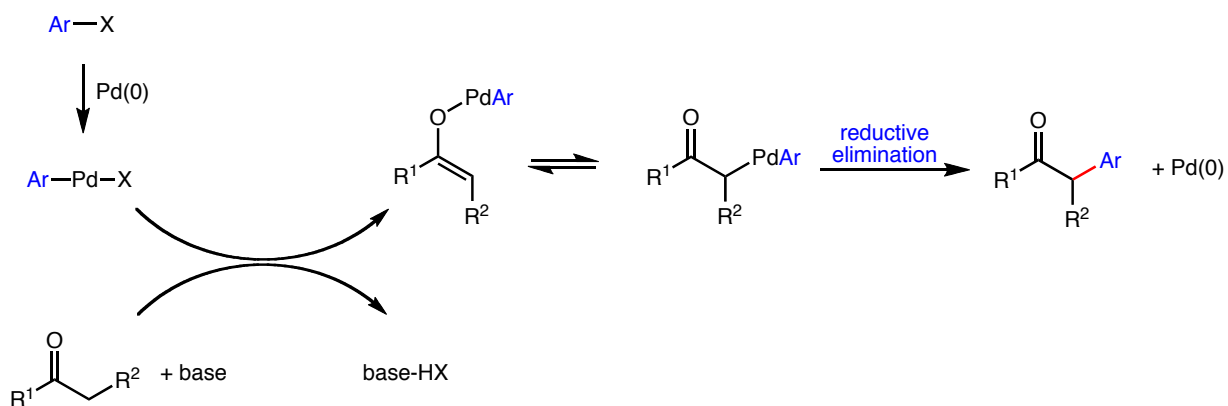
- Optimisation delivered a robust reaction



Buchwald, *J. Am. Chem. Soc.* **2000**, 122, 1360.

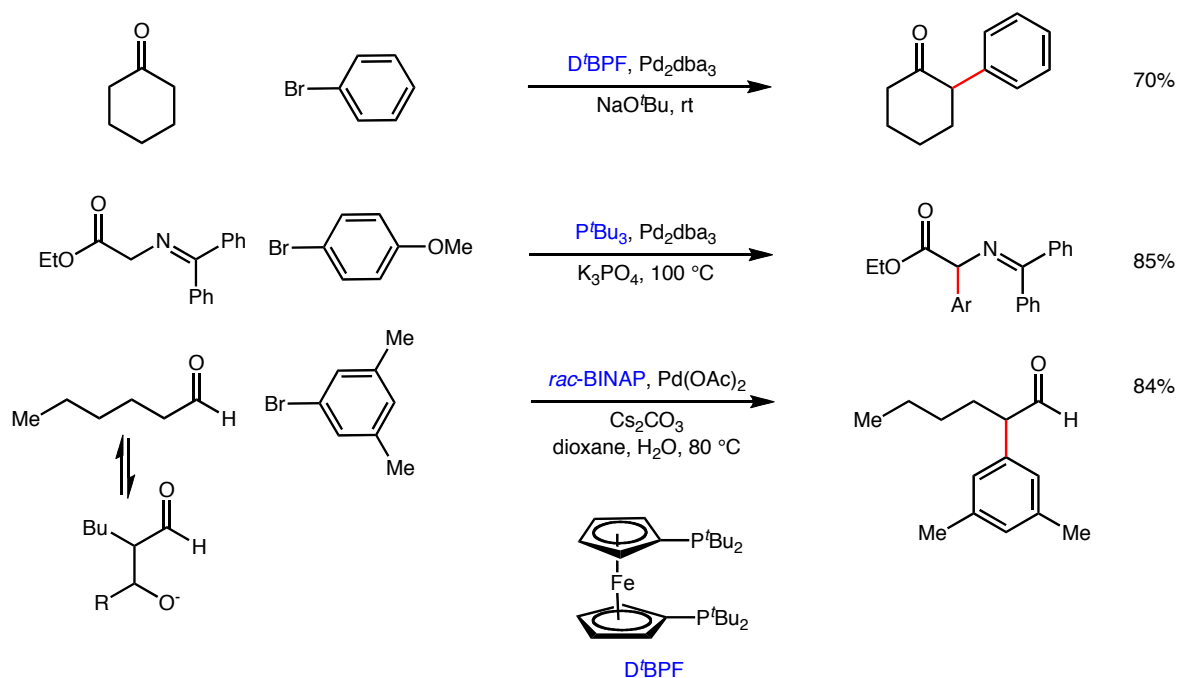
Enolate arylations

- Developed over last 15 years
- Range of carbonyl compounds, nitriles and enol silanes can all be employed
- Reactions proceeds *via* OA to Ar-X then formation of Pd-enolate



Enolate arylations

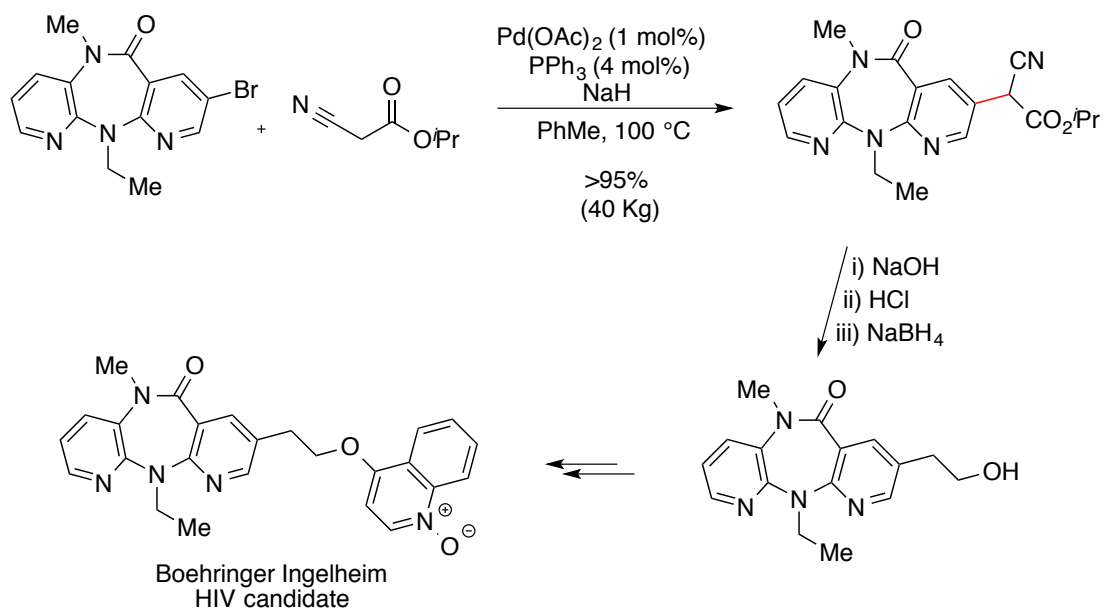
- Suzuki and amination ligands are effective



Buchwald, *JACS* 2000, 122, 1360.
Buchwald, *Angew* 2007, 46, 7236.
Hartwig, *Acc. Chem. Res* 2003, 36, 234.

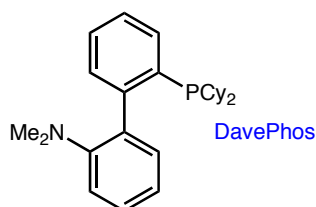
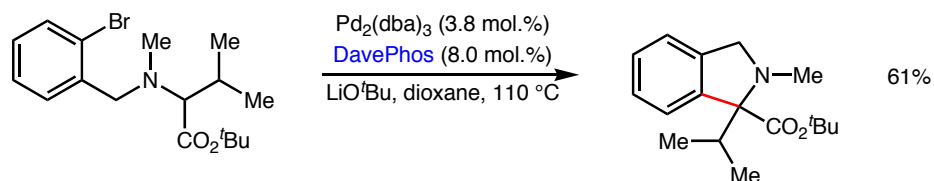
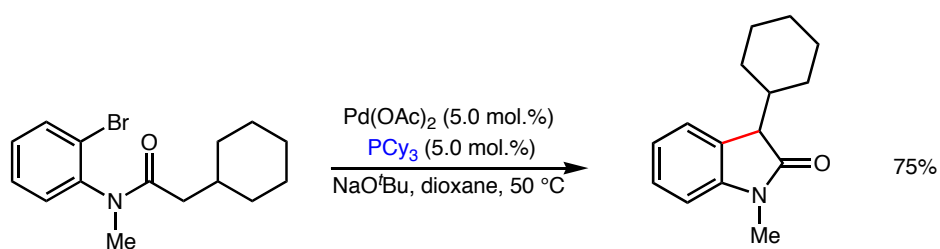
Enolate arylation - Application

- Arylation of a malonate equivalent



Enolate arylations: Intramolecular reactions

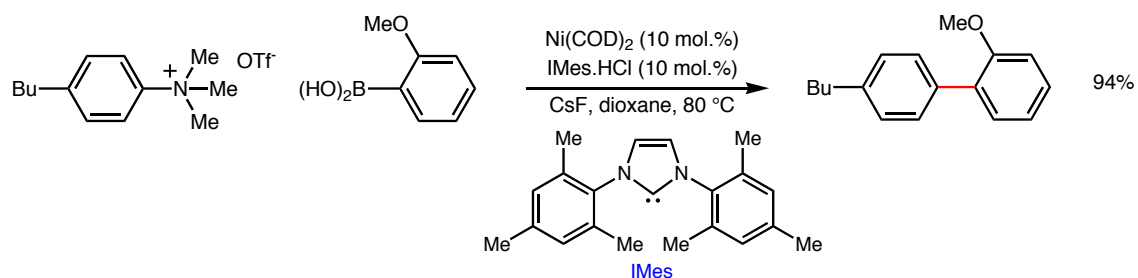
- Intramolecular substrates are readily prepared



Buchwald, *JOC* 2002, 67, 465.
Hartwig, *JOC* 2001, 66, 3402.

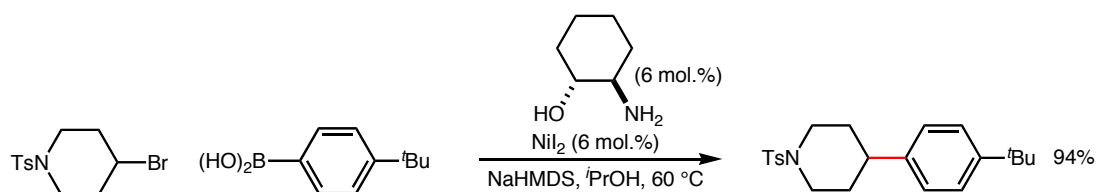
Ni Coupling reactions

- Much less developed than Pd, but recent revival
- Oxidative addition into ammonium salts



MacMillan, *JACS* 2003, 125, 6046.

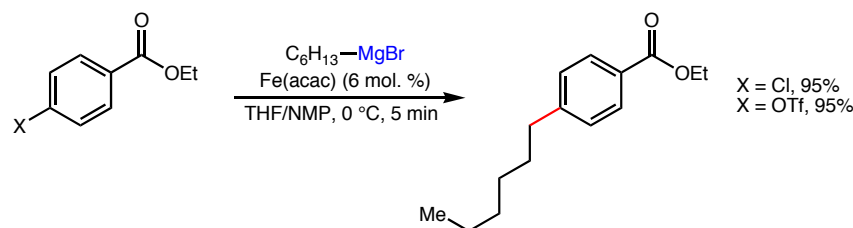
- Ability to use amino alcohols as ligands



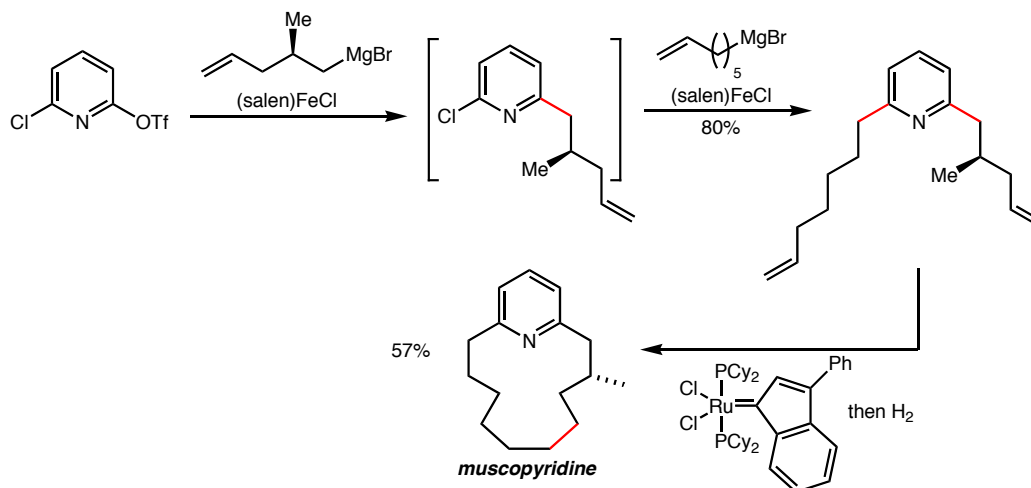
Fu, *JACS* 2006, 128, 5360.

Fe catalysed coupling

- Rapid reactions, high chemoselectivity



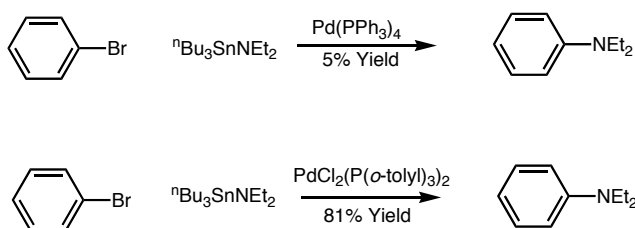
- Many applications in synthesis



Furstner, *Chem. Lett.* **2005**, 34, 624; *Angew.* **2004**, 43, 3955; *Angew.* **2003**, 42, 308.

Pd-Catalysed C-N bond formation

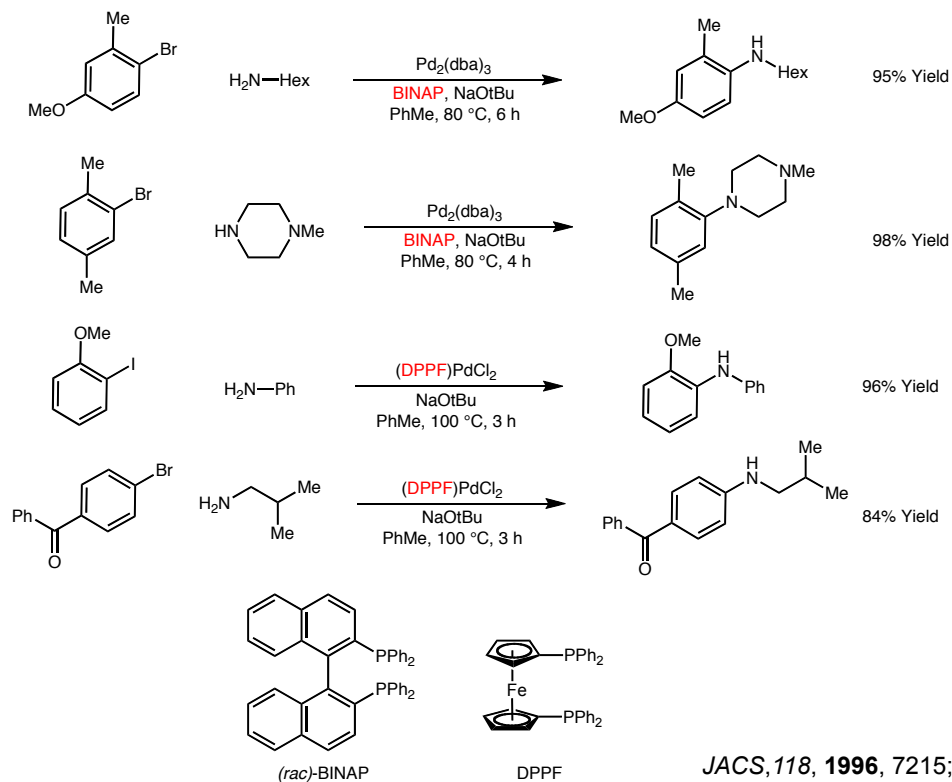
- THE coupling development of the last 15 years?
- Coupling of tin amides and aryl halides originally reported by Migita in 1983



- The use of tin reagents not attractive. System reinvestigated independently by both *Buchwald* (MIT) and *Hartwig* (Yale) in 1994...initially with tin systems; tin free systems soon followed

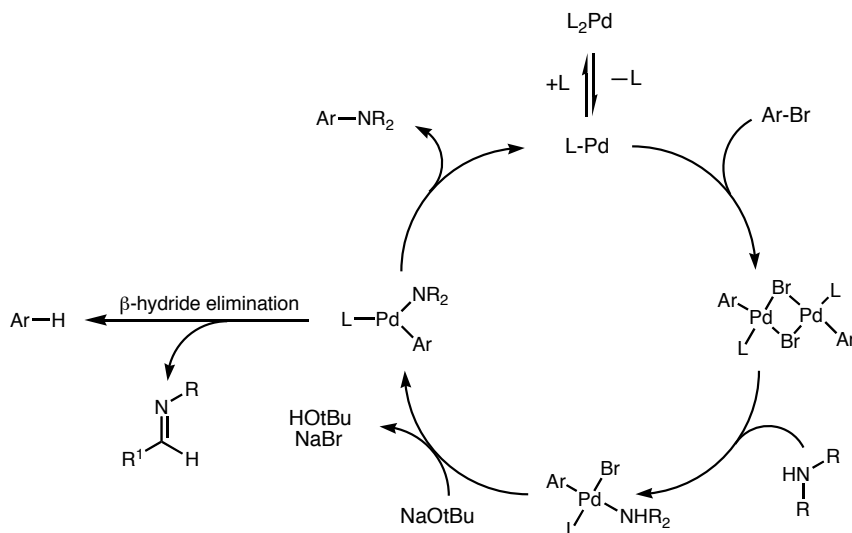
Tin free catalysis

- Back-to-back reports by Buchwald and Hartwig describe efficient tin-free systems that employ bidentate ligands

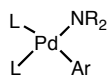


Mechanism

- Original mechanism proposed for monodentate ligands

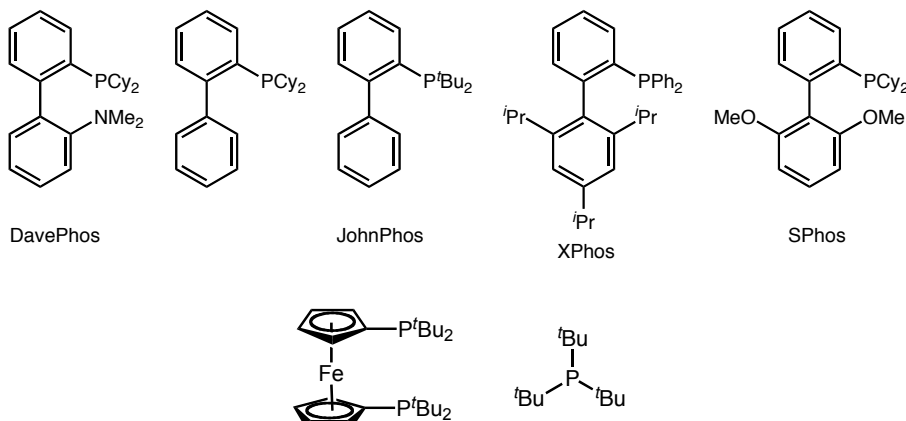


- Bidentate ligands enforce *cis*-orientation and reductive elimination becomes faster compared to β -elimination



Development of new ligands

- Aryl chlorides unreactive with BINAP, DPPF
- Bulky electron-rich ligands found to be ideal - bidentate systems not needed



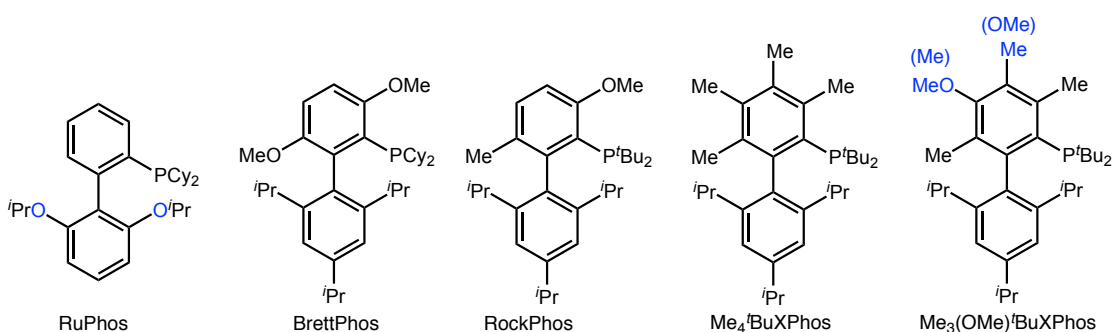
- Biphenyl ligands developed by Buchwald are the most general so far developed
- Modular, tunable ligands - probably hemi-labile in nature
- Resistant to oxidation
- Alternative ligands appear weekly...

Ligand synthesis: *Adv. Synth. Catal.* **2001**, 343, 789.

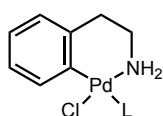
Review of ligand development: Buchwald, *Adv. Synth. Catal.* **2006**, 348, 23. Applications: *Angew*, **2008**, 47, 6338.

Latest generation of Buchwald ligands

- Even bulkier, more specific ligands



- Pre-catalyst system introduced – rapid access to mono-ligated Pd(0)



L = ligand
(not possible for all ligands)

XPhos, SPhos, RuPhos, BrettPhos and ^tBuBrettPhos pre-catalysts are commercially available

Buchwald, *JOC*, 2012, 77, 2543; *Chem. Sci.* 2011, 2, 57; *Angew*, 2012, 51, 4710.

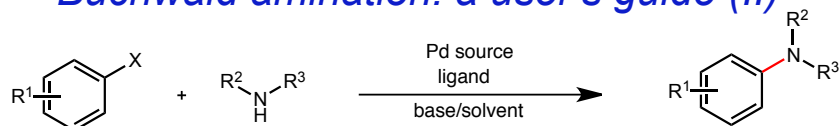
Pre-catalyst; Buchwald, *Chem. Sci.*, 2011, 2, 2321; *Chem. Sci.* 2013, 4, 916; *Org. Lett.* 2013, 15, 2876.

Buchwald amination: a user's guide (I)

- Pd source: pre-catalyst if available (no additives)
 - $\text{Pd}_2(\text{dba})_3$ – also no additives, but dba can retard reaction
 - $\text{Pd}(\text{OAc})_2$ – cheap, but needs reduction for anilines and amides
- Ligands: BrettPhos or RuPhos good first choices
 - BrettPhos: primary alkyl amines and primary anilines
 - RuPhos: secondary alkyl amines and secondary anilines
- Base: vary substrate dependent, NaO^tBu – very good, but very basic
 - LHMDS – good for protic substrates, strong base so compatibility issues
 - Cs_2CO_3 – weak base, expensive, stirring an issue on scale
 - K_3PO_4 – weak base, but high cat loadings and long reactions
- Solvent: Toluene most general, ROH can be good as can THF

Buchwald, *Chem. Sci.*, 2011, 2, 27.

Buchwald amination: a user's guide (II)

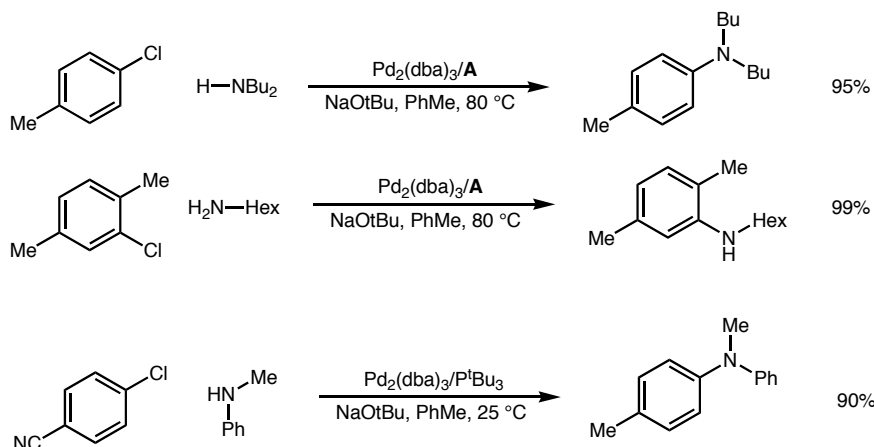


Problem	Possible Cause	Solution
low conversion	inefficient formation of catalyst slow reaction	use pre-catalyst increase cat loading use higher temperature
poor mass balance	incompatibility of base with functional groups	use weaker base (Cs_2CO_3 , K_3PO_4)
formation of	catalyst decomposition inefficient reductive elimination	use lower temperature use ligand faster for RE
formation of	presence of water in reaction	dry reagents use molecular sieves
formation of	presence of water in reaction	dry reagents use molecular sieves
formation of	inefficient transmetalation unsuitable solvent	use less hindered ligand, or more electron-deficient at P try <i>t</i> BuOH or ethereal solvent

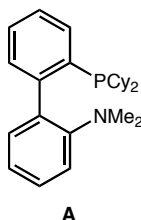
Buchwald, *Chem. Sci.*, 2011, 2, 27.

Aryl chloride couplings

- Buchwald's electron-rich biphenyl systems and P^tBu_3 are optimal



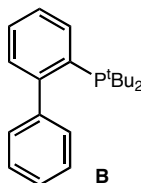
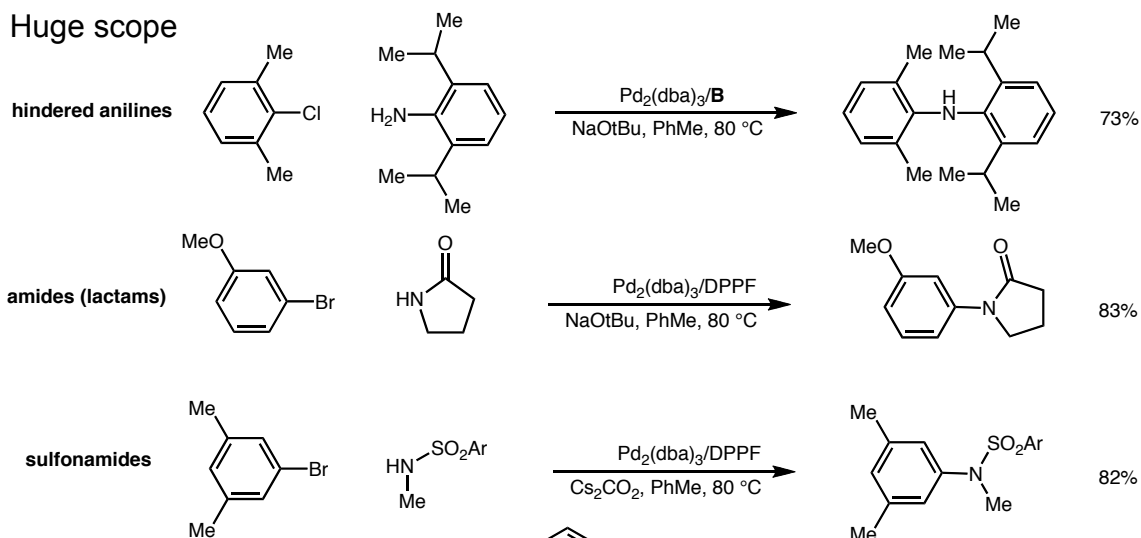
- P^tBu_3 can be difficult to handle
- Use of $P^tBu_3 \cdot HBF_4$; Fu, *OL*, 2001, 3, 4295.



Hartwig, *Angew*, **2005**, 44, 1371; Buchwald, *JACS*, **2007**, 129, 13001.

Scope of N-coupling partner

- Hindered and electron-poor nucleophiles perform well
- Weaker bases can be used with electron-poor N-units
- Huge scope

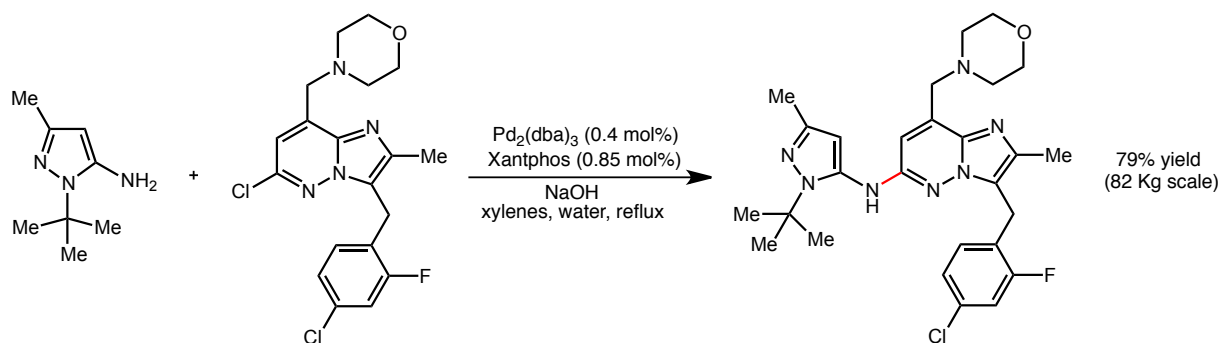


General review on Pd cat. C-N; Buchwald, In *Metal-Catalysed Cross-Coupling Reactions*, 2nd Ed., de Meijere, Ed., 2004; Hartwig, In *Modern Arene Chemistry*, Astruc, Ed., 2002.

For a detailed procedure for the Buchwald monoposphines, see; Buchwald, *Nature Protocols*, **2007**, 2, 2881.

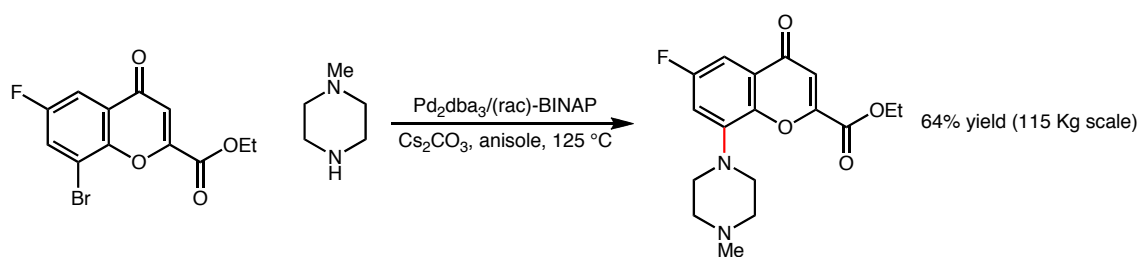
Applications: Medicinal chemistry

- Synthesis of JAK2 inhibitor – LY2784544 (Lilly)



Lilly group, *Org. Proc. Res. Dev.* **2012**, 16, 70.

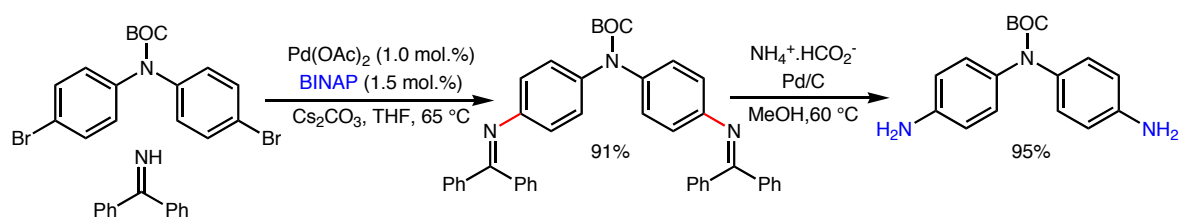
- Large scale preparation of a 5-HT receptor antagonist (AZ)



AZ group, *Org. Proc. Res. Dev.* **2004**, 8, 925.

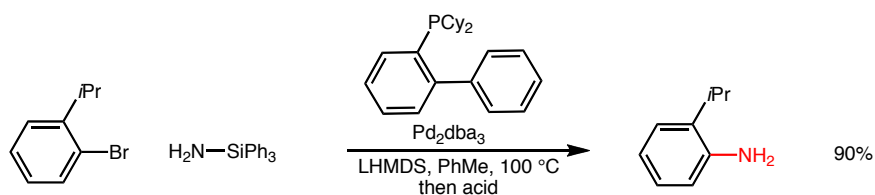
Ammonia equivalents

- Imines commonly used



Buchwald, *TL* **1997**, 38, 6367.

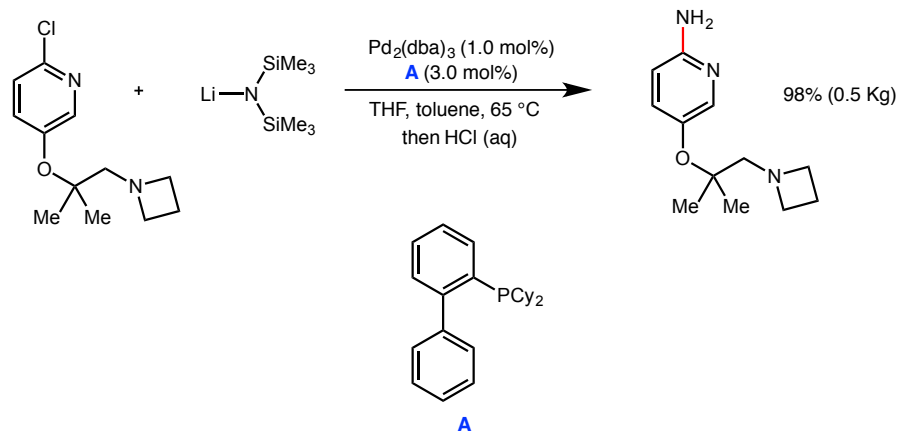
- Silylamines



Buchwald, *Org. Lett.* **2001**, 3, 3417. Hartwig, *Org. Lett.* **2001**, 3, 2729; **2005**, 7, 1169.

Ammonia equivalents: Application

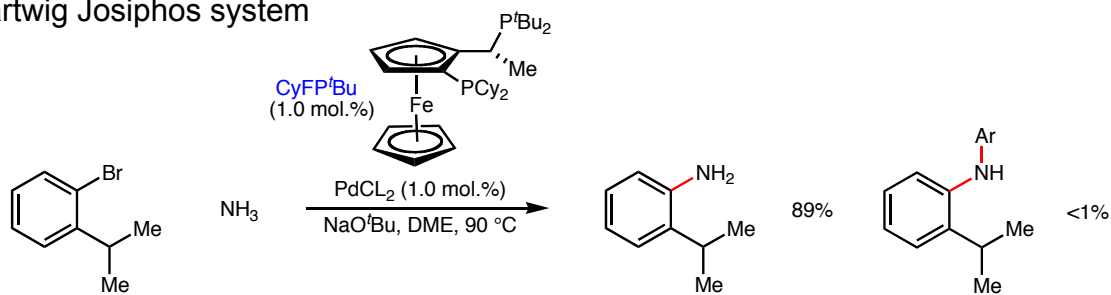
- Merck process group, towards an intermediate for a BTK inhibitor



Org. Proc. Res. Dev. **2013**, 17, 876.

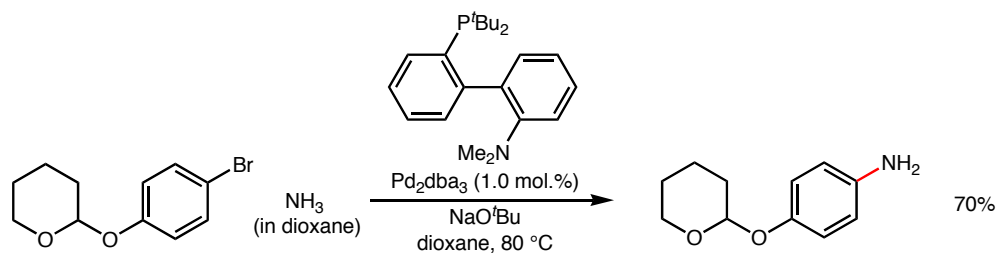
Ammonia itself

- Hartwig Josiphos system



Hartwig, *JACS* **2006**, 128, 10028.

- Buchwald biphenyl ligands

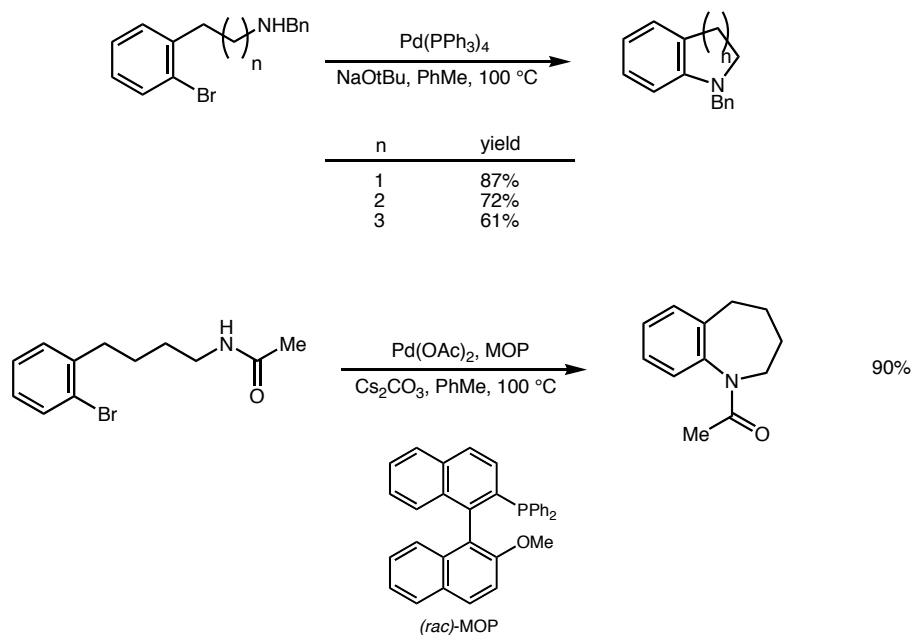


Buchwald, *JACS* **2007**, 129, 10354.

See also, Stradiotto, *Angew.* **2010**, 49, 4071.

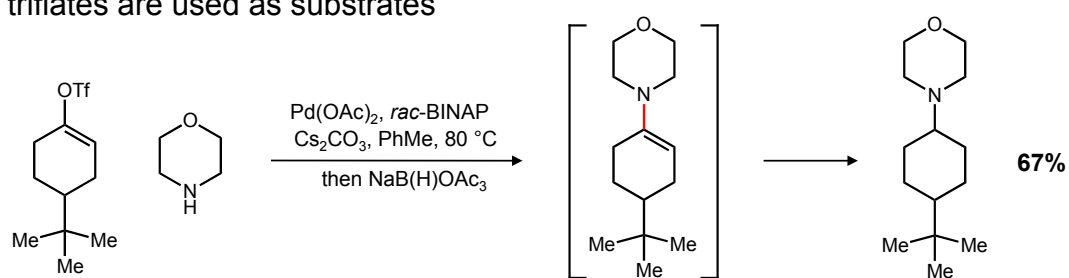
Intramolecular reactions

- Amines and amides (and others) can be used
- 4, 5, 6, 7-membered rings have all been prepared

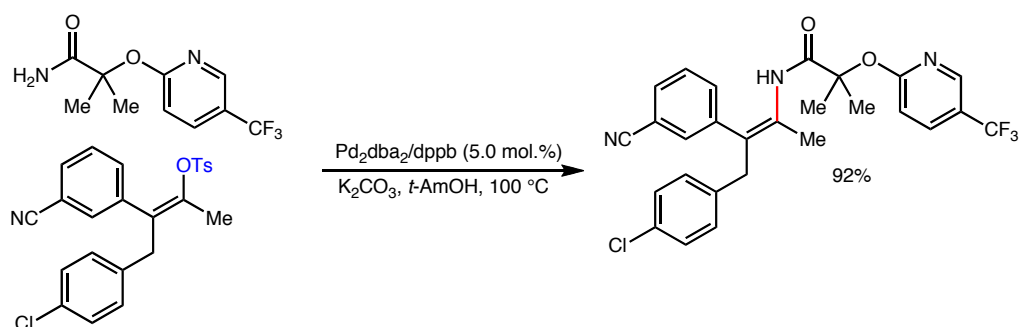


Extension to alkenyl systems

- Can be used for the synthesis of enamines and imines if alkenyl halides and triflates are used as substrates



Willis, *Tet. Lett.*, **2002**, 43, 9085; *Syn*, **2005**, 3229.
Barluenga, *Chem. Eur. J.* **2004**, 10, 494.

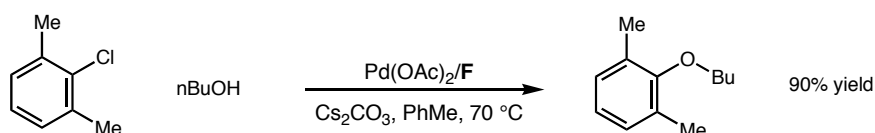
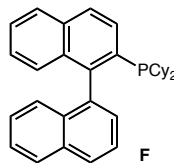


Wallace (Merck), *Org. Proc. Res. Dev.* **2009**, 13, 84.

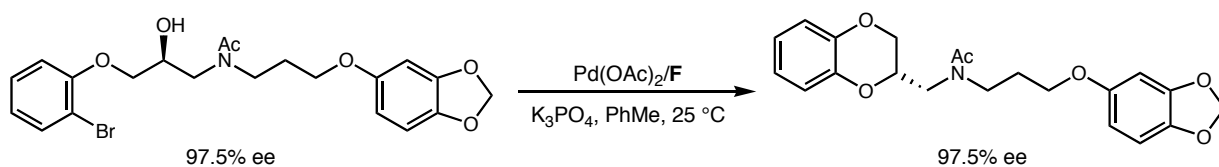
Etherification reactions

- Developed along similar lines to *N*-chemistry, however substrate scope was initially far more limited due to slow reductive elimination and hence faster β -elimination

- Ligand developed to overcome limitations



- Synthesis of MKC-242



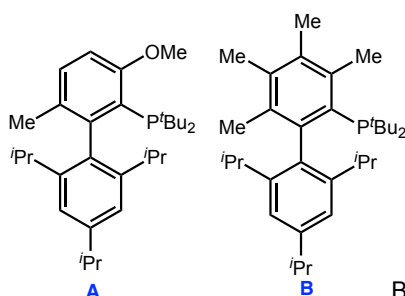
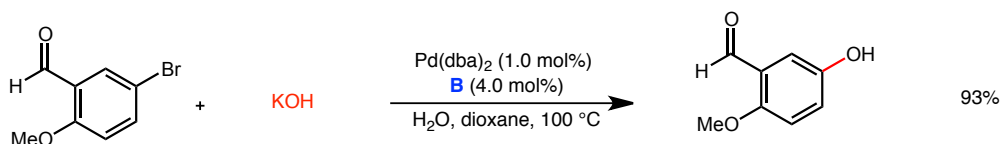
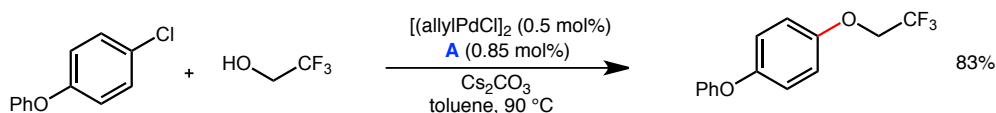
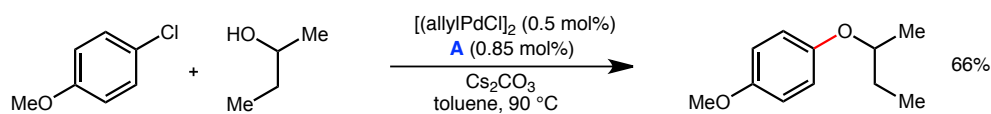
Buchwald, *J. Am. Chem. Soc.* **2001**, 123, 12202.

Review: Enthaler and Company, *Chem. Soc. Rev.* **2011**, 40, 4912.

Buchwald, *Org. Lett.* **2012**, 14, 170.

Pd catalysed C-O

- As with C-N, shows good functional group tolerance
- RockPhos effective for primary and secondary alcohols

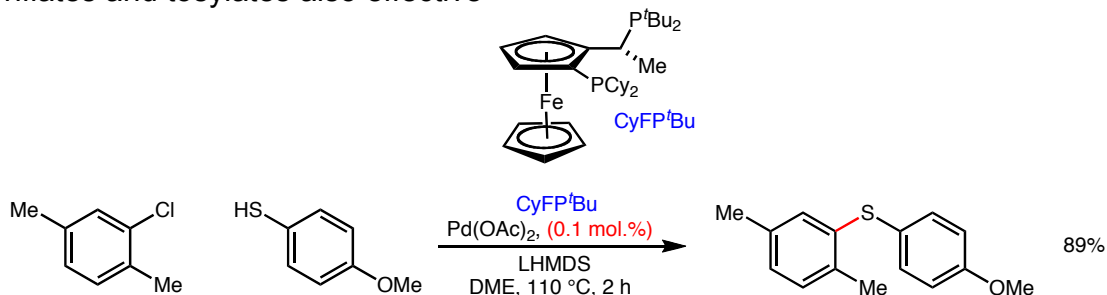


Buchwald, *Angew* 2011, 50, 9943.

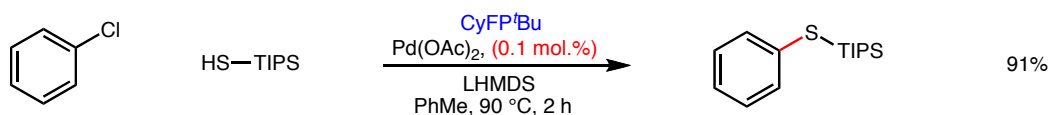
Buchwald, *JACS* 2006, 128, 10694.

Pd catalysed C-S bond formation

- S-Coupling generally efficient but catalyst poisoning and hence low TON
- Hartwig's bulky bidentate ligands work well
- Triflates and tosylates also effective



- A H_2S equivalent

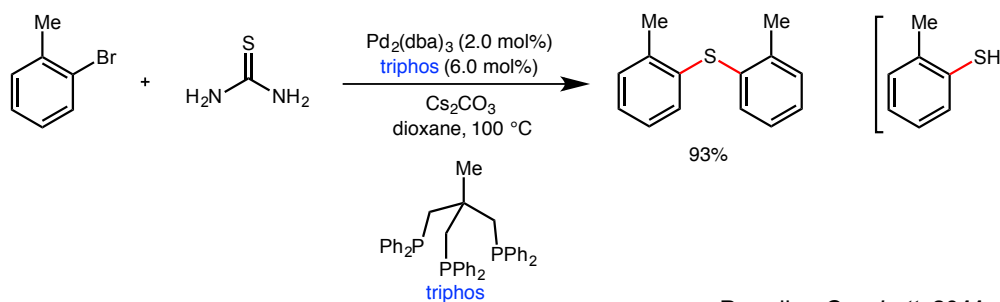


Hartwig, *JACS* **2006**, 128, 2180.

For aryl-*B* formation, see; Buchwald, *Angew* **2007**, 46, 5339; Molander *Org. Lett.* **2012**, 14, 4814.

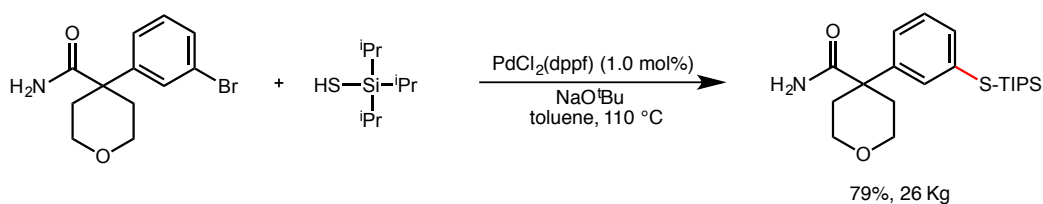
Pd catalysed C-S bond formation

- Thiourea as a H_2S equivalent.



Paradies *Org. Lett.* **2011**, 13, 4100.

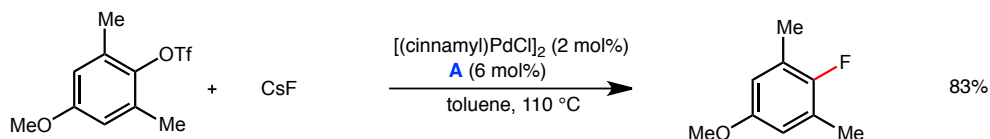
- Application from Pfizer (5-lipoxygenase inhibitor)



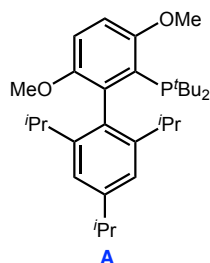
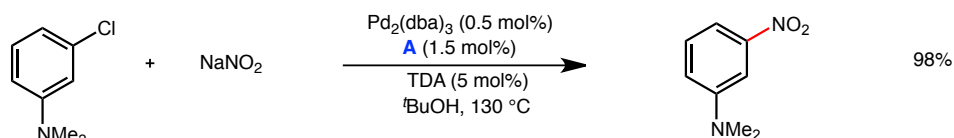
OPRD **2011**, 15, 1046.

Pd catalysed C-NO₂ and C-F bond formation

- C-F reductive elimination very challenging
- CsF and triflate substrates optimal



- A basic alternative to traditional electrophilic nitration processes
- Chloride, triflate and nonaflates all used



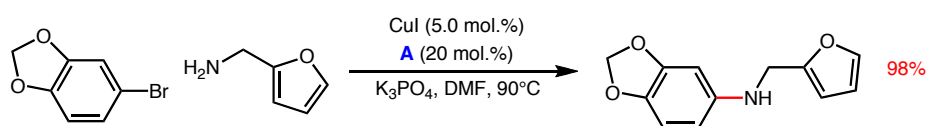
TDA = tris(3,6-dioxaheptyl)amine
(phase transfer catalyst)

Buchwald, *Science* **2009**, 325, 1661.

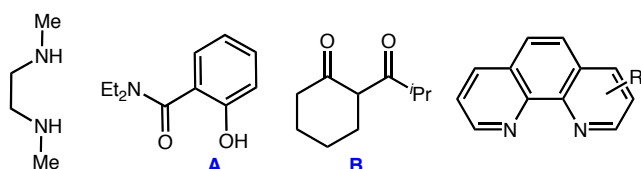
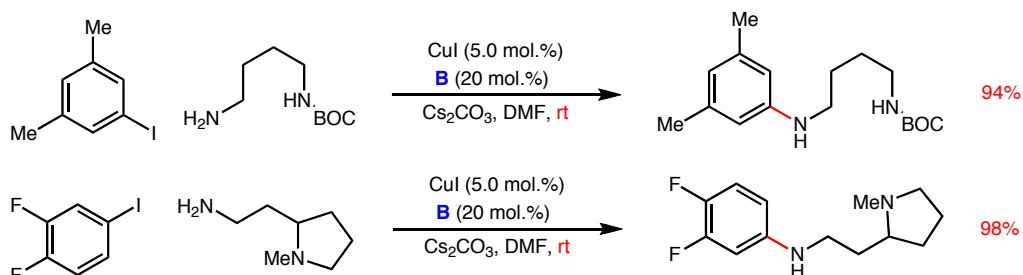
Buchwald, *JACS* **2009**, 131, 12898.

Modern Cu catalysed C-N from aryl halides

- Less developed than Pd
- Different types of ligands - reactions less general than Pd



- Newest ligands allow lower temperatures



Buchwald, *JACS* **2002**, 124, 7421.

Buchwald, *JACS* **2006**, **128**, 8742.

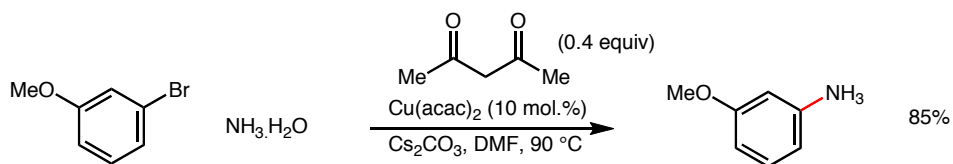
For a detailed procedure, see; Buchwald, *Nature Protocols*, **2007**, 2, 2474.

For a review, see; Buchwald, *Chem. Sci.* **2010**, 1, 13.

Mechanism, see; Buchwald, *JACS* **2009**, 131, 78.

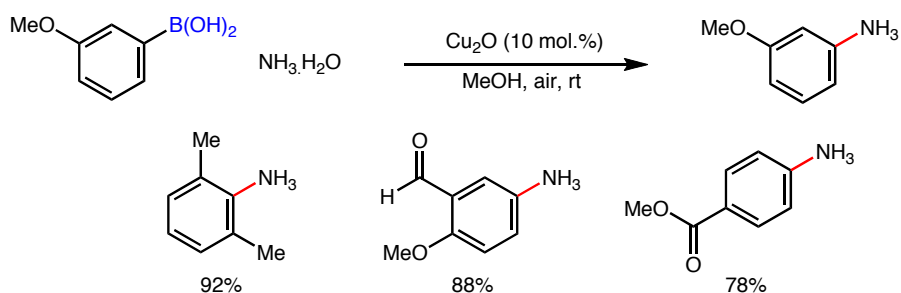
Cu catalysed coupling with ammonia

- Aqueous ammonia with aryl bromides and iodides



Taillefer, *Angew* **2009**, *48*, 337.

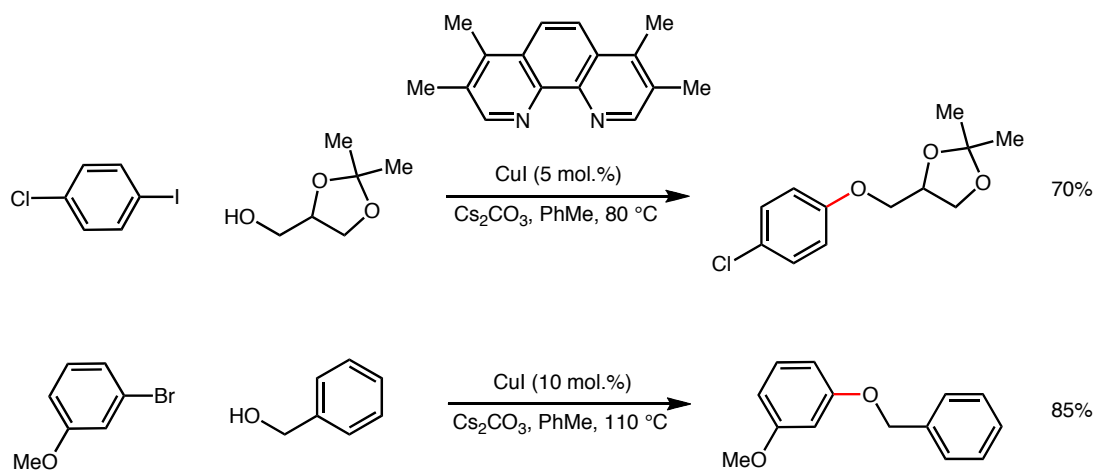
- Boronic acid substrates - extremely mild conditions



H. Fu, *Angew* **2009**, *48*, 1114.

Copper catalysed C-O from aryl halides

- Very good with aryl iodides, not as efficient with bromides

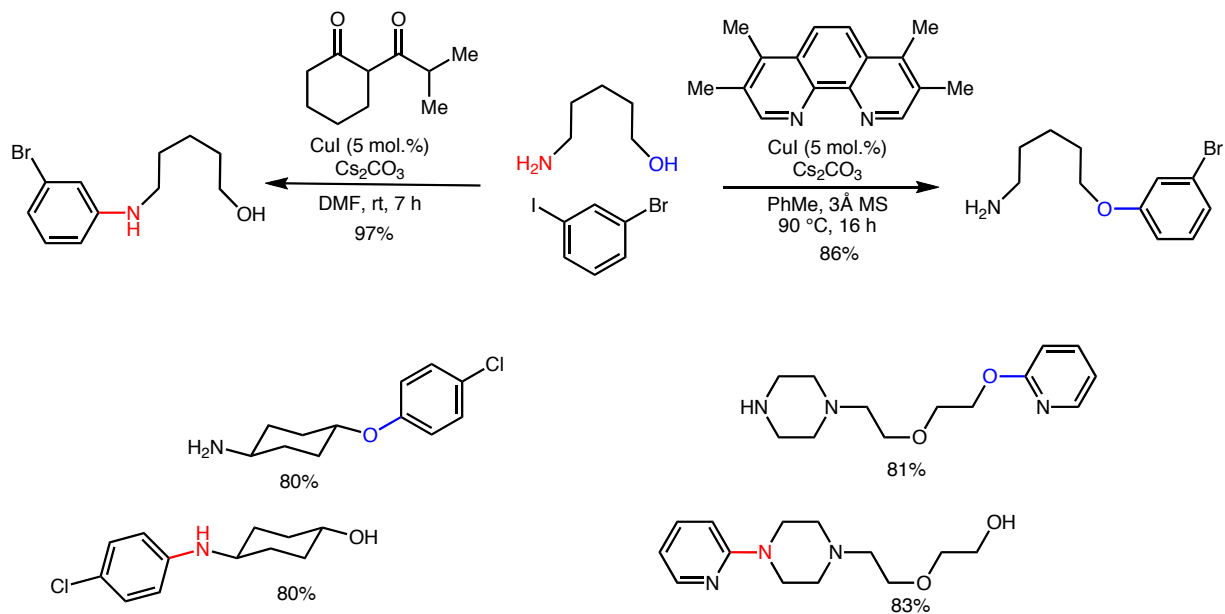


Buchwald, *JOC* **2008**, *73*, 284.

For Cu cat. C-P formation, see; Buchwald, *OL* **2003**, *5*, 2315.

Cu catalysed *N*- versus *O*-arylation

- Ligand dependent selectivity possible
- Requires at least three methylene spacers between *N* and *O*



Buchwald, *JACS* **2007**, *129*, 3490.

Enantioselective Desymmetrisation

Michael Willis

CDT - Metal Catalysis

3rd/4th November 2016

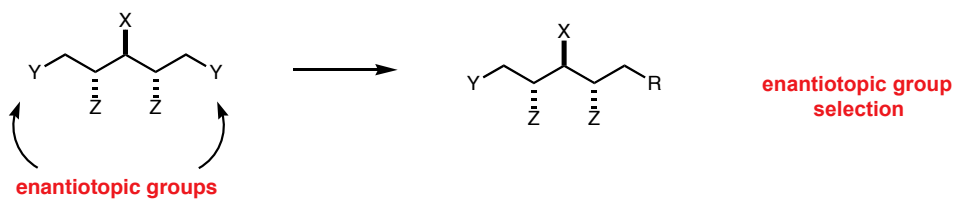
@RhPdCu

Review: M. C. Willis, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765

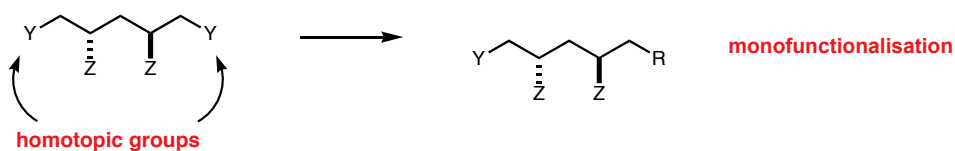
michael.willis@chem.ox.ac.uk

Desymmetrisation

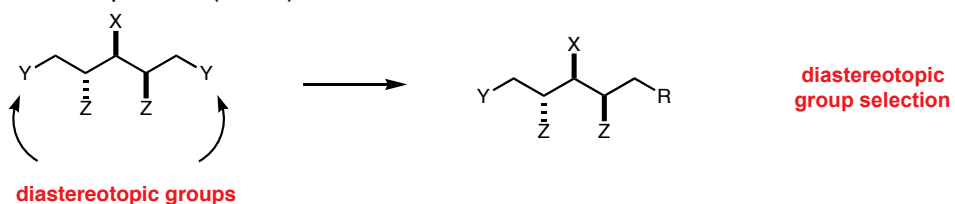
- Achiral and *meso* compounds



- C_2 -symmetric compounds (chiral)

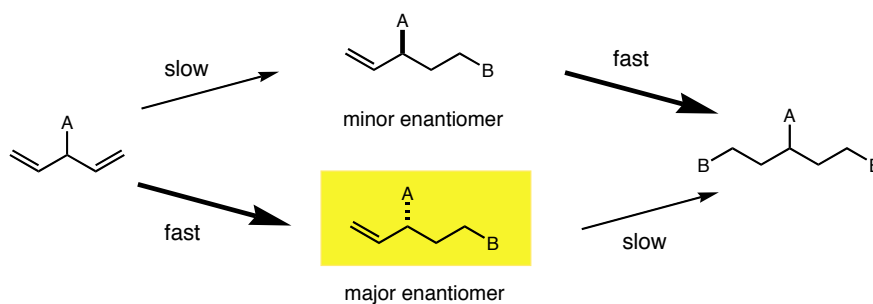


- Pseudo C_2 -symmetric compounds (chiral)



Desymmetrisation of *meso*- and achiral chains

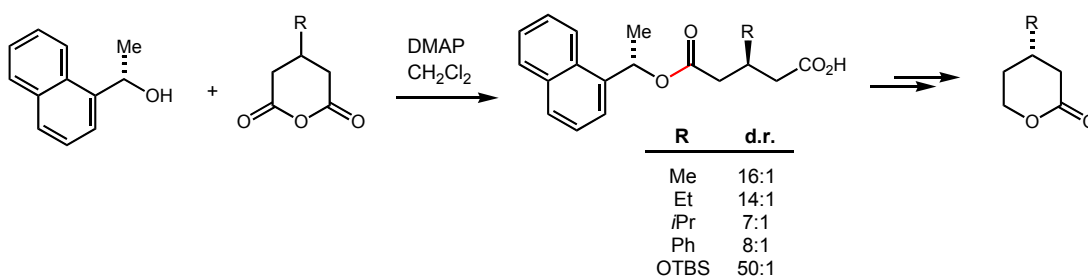
- Requires differentiation of enantiotopic groups
- Desirable features:
 - Readily available substrates (stereoselectively)
 - Deliver "useful" products
 - Catalytic process
 - Practical
- Potential to combine enantioselective selection with a kinetic resolution
- Possible to obtain extremely high enantioselectivity



For reviews, see; Willis, *Perkin1*, 1999, 1765; Ward, *Chem. Soc. Rev.*, 1990, **19**, 1.

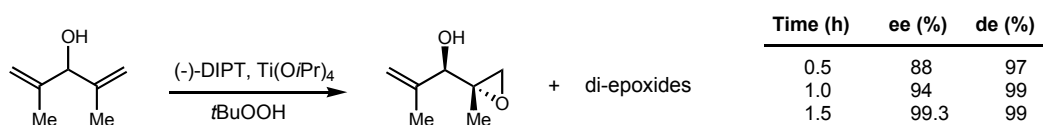
Anhydrides: chiral alcohol addition

- Early examples from Heathcock (stoichiometric)



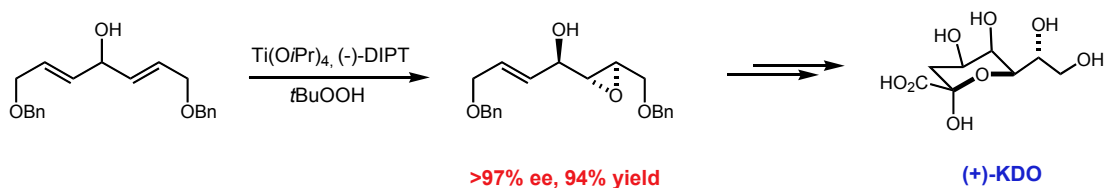
Alkenes: Sharpless epoxidation

- Enantioselection + kinetic resolution



Schreiber and Schreiber, *J. Am. Chem. Soc.*, 1987, **109**, 2487.

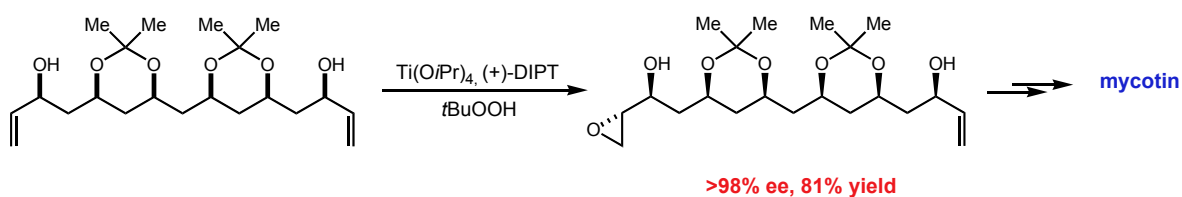
- Application to synthesis of KDO



Schreiber, *Tetrahedron*, 1990, **46**, 4793.

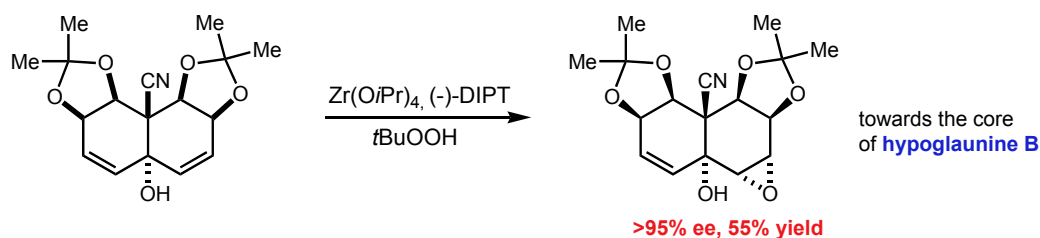
Alkenes: Sharpless epoxidation

- Multiple stereocentres in a single step



Schreiber, *J. Am. Chem. Soc.*, 1987, **105**, 4718.

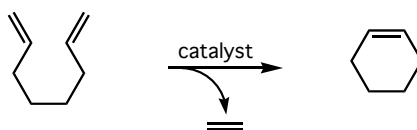
- Modified conditions
- 8 Contiguous centres in a single step



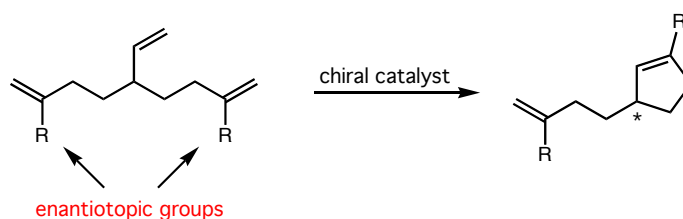
Spivey, *Angew.*, 2001, **40**, 769.

Alkenes: enantioselective metathesis

- Desymmetrisation allows the development of *new* enantioselective reactions
- Ring closing metathesis (RCM)

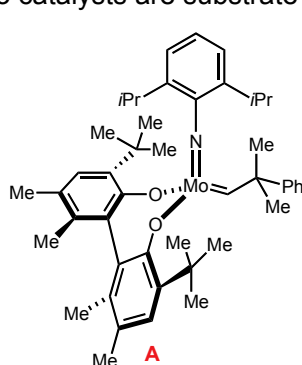


- Desymmetrising metathesis

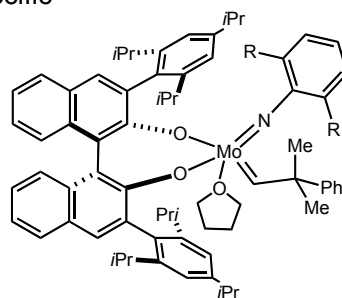


Alkenes: enantioselective metathesis

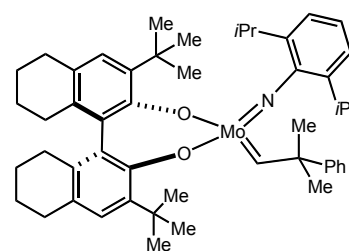
- Several Mo catalysts
- Mo catalysts are substrate specific



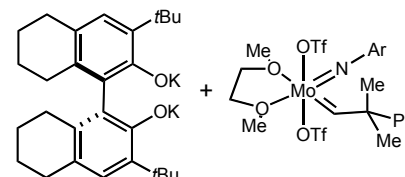
commercially available



B, R = Me
C, R = *i*Pr
D, R = Cl



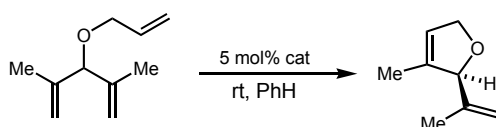
E $\xrightarrow[\text{THF, 1h}]{\text{"in situ"}}$



2 steps from BINOL

commercial

- Catalysts **E** is a good compromise of reactivity and selectivity



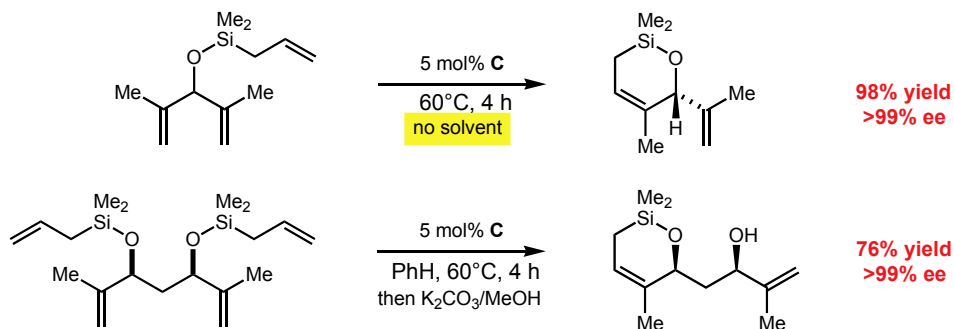
catalyst	time	yield	ee
A	6 h	86%	93%
C	1 h	72%	90%
E	1 h	81%	92%

Hoveyda and Schrock, *Angew*, 2001, **40**, 1452.

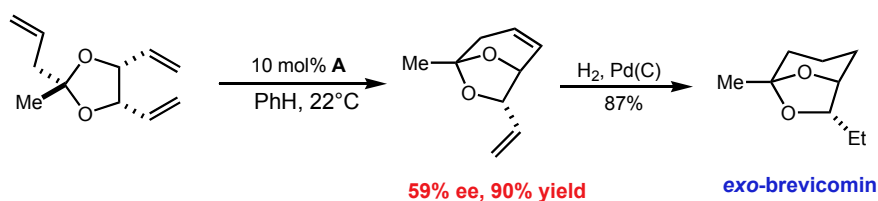
For a brief review of enantioselective RCM, see; Hoveyda and Schrock, *Chem. Eur. J.*, 2001, **7**, 945.

Alkenes: enantioselective metathesis

- Asymmetric ring-closing metathesis (ARCM)
- Solvent free conditions possible



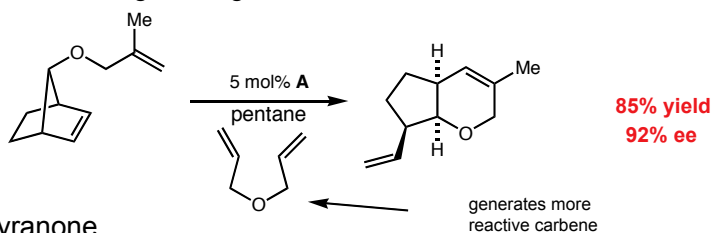
- Synthesis of *exo*-brevicommin



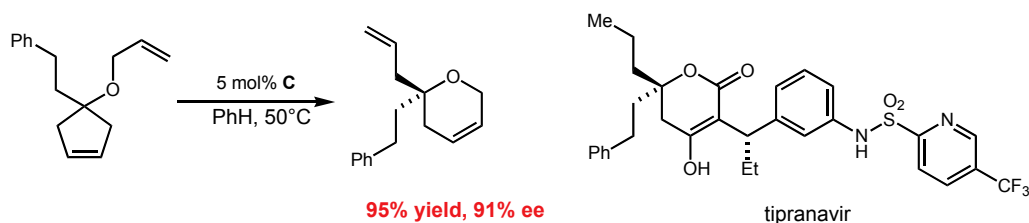
Burke, *Org. Lett.*, 1999, **1**, 1827.

Alkenes: enantioselective metathesis

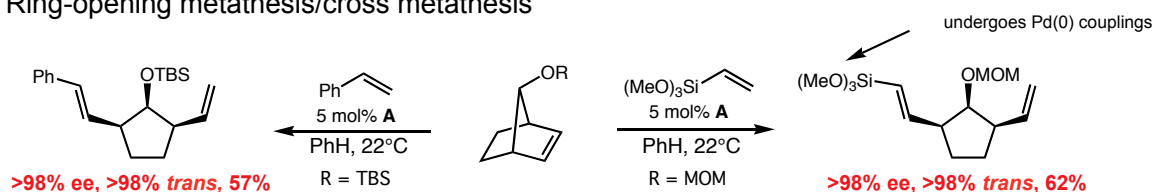
- Tandem ring-opening metathesis/ring-closing metathesis



- Synthesis of tipranavir pyranone



- Ring-opening metathesis/cross metathesis

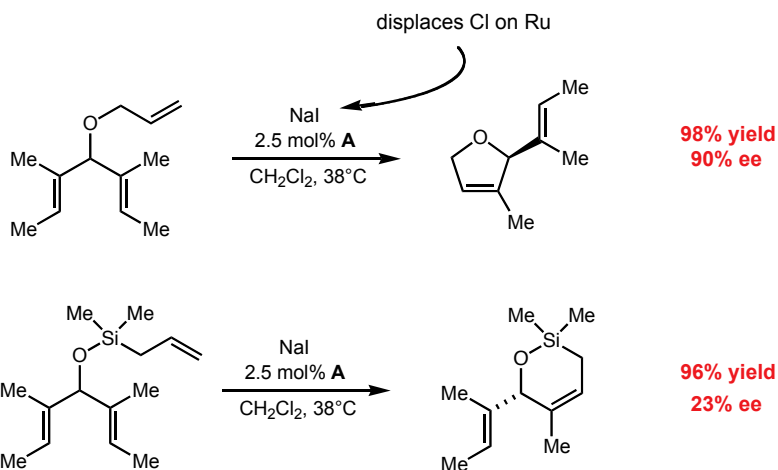
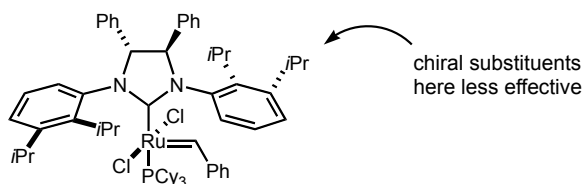


Hoveyda and Schrock, *J. Am. Chem. Soc.*, **2001**, *123*, 7767.

For an overview of his work see; Hoveyda, *JOC.*, **2014**, *79*, 4763.

Alkenes: enantioselective metathesis

- Ru catalysts
- *N*-heterocyclic carbene ligands
- Substrate specific



Grubbs, *JACS*, **2006**, 128, 1840.

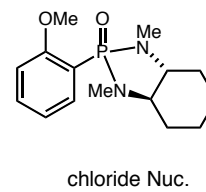
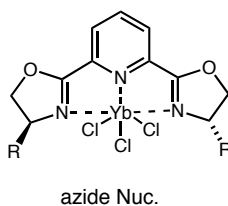
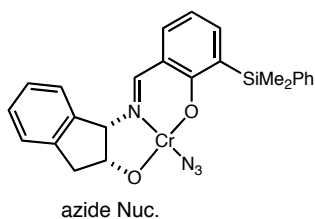
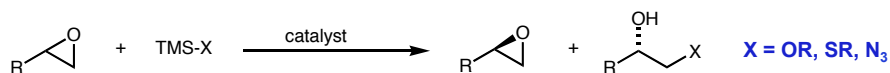
For an updated catalyst, see: Grubbs, *JACS*, **2014**, 136, 13029.

Nucleophilic opening of epoxides

- Readily available substrates (stereoselectively)
- Two types of enantioselective process
 - Desymmetrisation of *meso*-epoxides



- Kinetic resolution of unsymmetrical epoxides



Jacobsen, *Org. Lett.*, 1999, **1**, 1611.

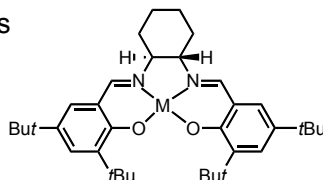
Jacobsen, *Org. Lett.*, 2000, **2**, 1001.

Buono, *Angew*, 2000, **39**, 2554.

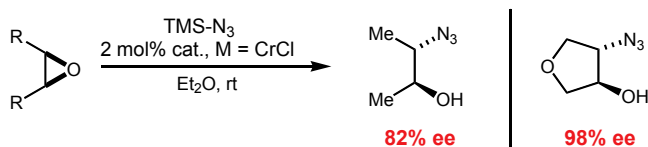
For a review of epoxide desymmetrisation, see; Hodgson, *Tetrahedron*, 1996, **34**, 798.

Desymmetrisation of epoxides: salen derived catalysts

- Different Nuc's need different metals

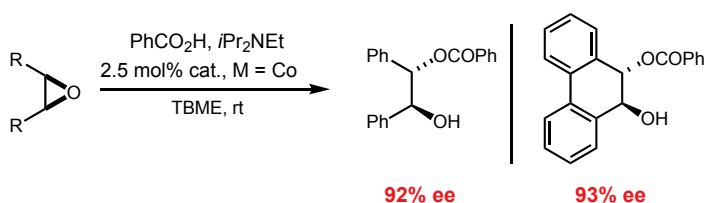


- Azide nucleophiles, Cr(III)
- Can use solvent free conditions



- Carboxylic acid nucleophiles, Co(III)

Jacobsen, *J. Am. Chem. Soc.*, 1995, **117**, 5897.



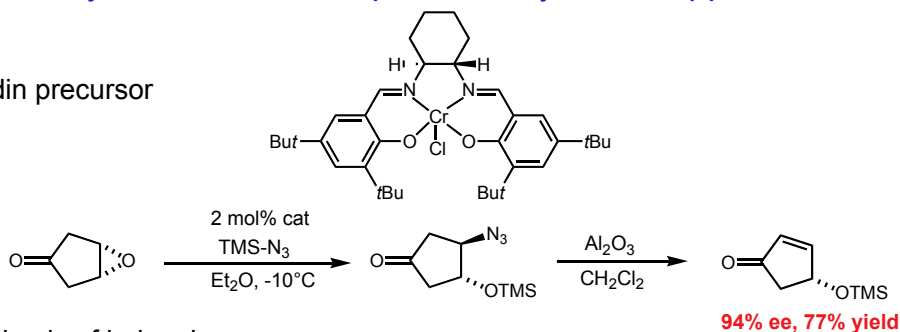
Jacobsen, *Tetrahedron Lett.*, 1997, **38**, 773.

- Mechanism involves activation of both epoxide (L.A.) and nucleophile

Review; Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421; Mechanism; *J. Am. Chem. Soc.*, 1996, **118**, 10924; *ibid*, 1998, **120**, 10780.

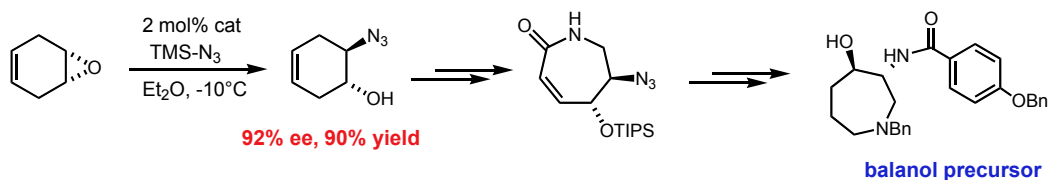
Desymmetrisation of epoxides: synthetic applications

- Prostaglandin precursor



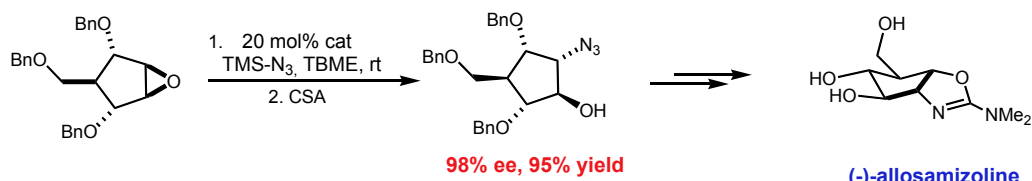
- Formal synthesis of balanol

Jacobsen, *J. Org. Chem.*, 1996, **61**, 389.



- Synthesis of allosamizoline

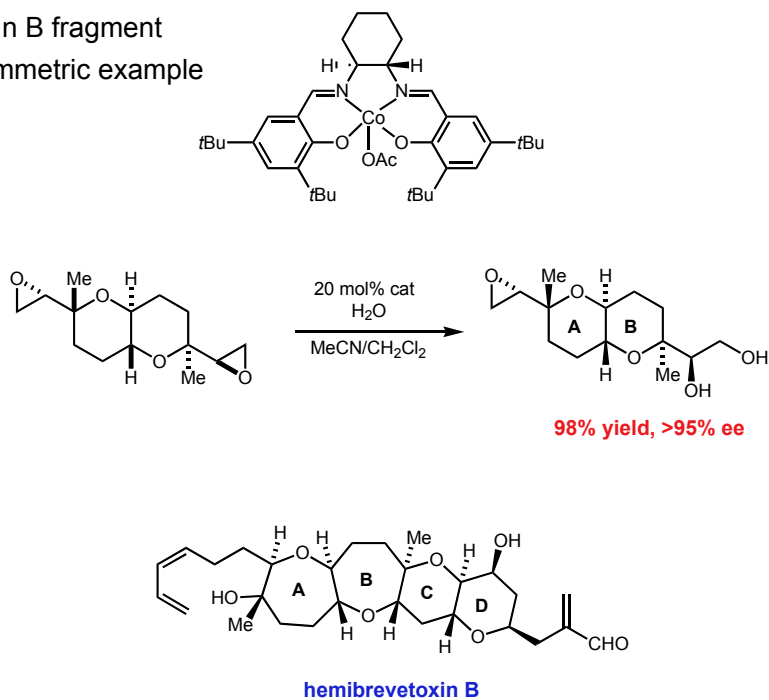
Jacobsen, *Tetrahedron Lett.*, 1997, **38**, 1693.



Ganem, *J. Org. Chem.*, 1999, **64**, 1782.

Desymmetrisation of epoxides: synthetic applications

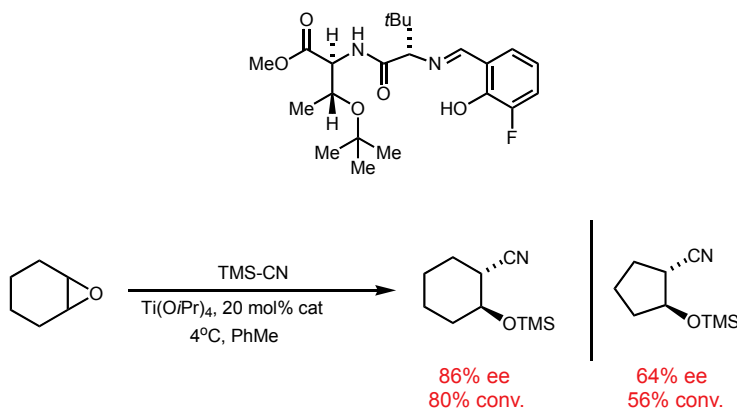
- Hemibrevetoxin B fragment
- First centrosymmetric example



Nelson, *Angew.*, 2001, **40**, 4082.

Desymmetrisation of epoxides: C-C bond formation

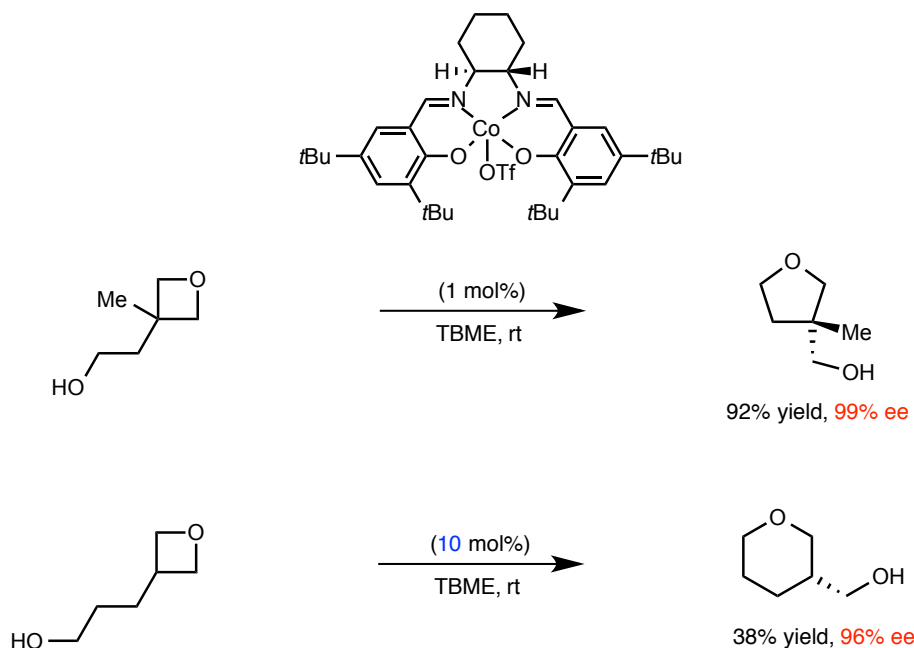
- Addition of TMS-CN
- Catalyst identified using "positional screening" methods - peptide like catalyst
- Catalysts are substrate specific



Hoveyda and Snapper, *Angew.*, 1996, **35**, 1668; *ibid.*, 1997, **36**, 1704.

Desymmetrisation of oxetanes

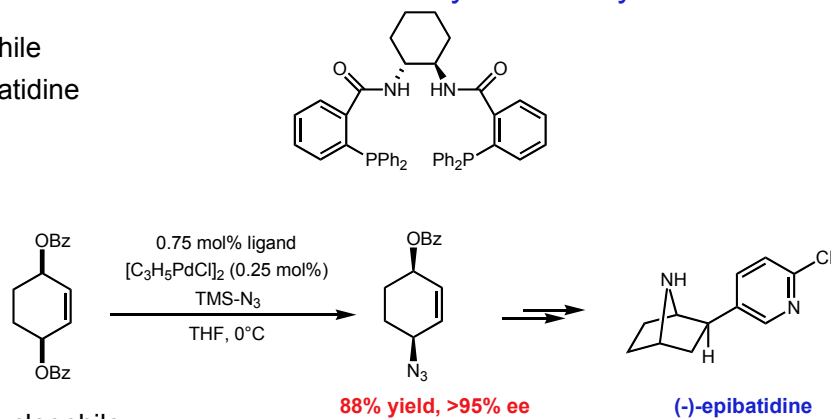
- Decreased ring-strain, increased Lewis basicity, relative to epoxides



Jacobsen, *JACS* **2009**, *131*, 2786.

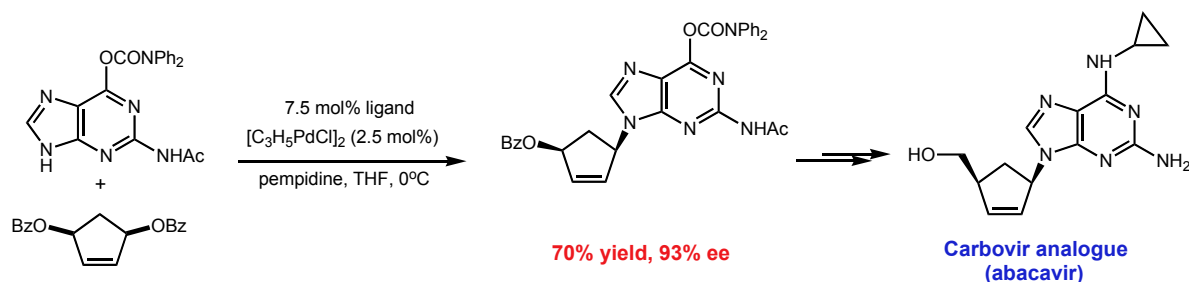
Palladium π -allyl chemistry

- Azide as nucleophile
- Synthesis of epibatidine



Trost, *Tet. Lett.*, 1996, **37**, 7485.

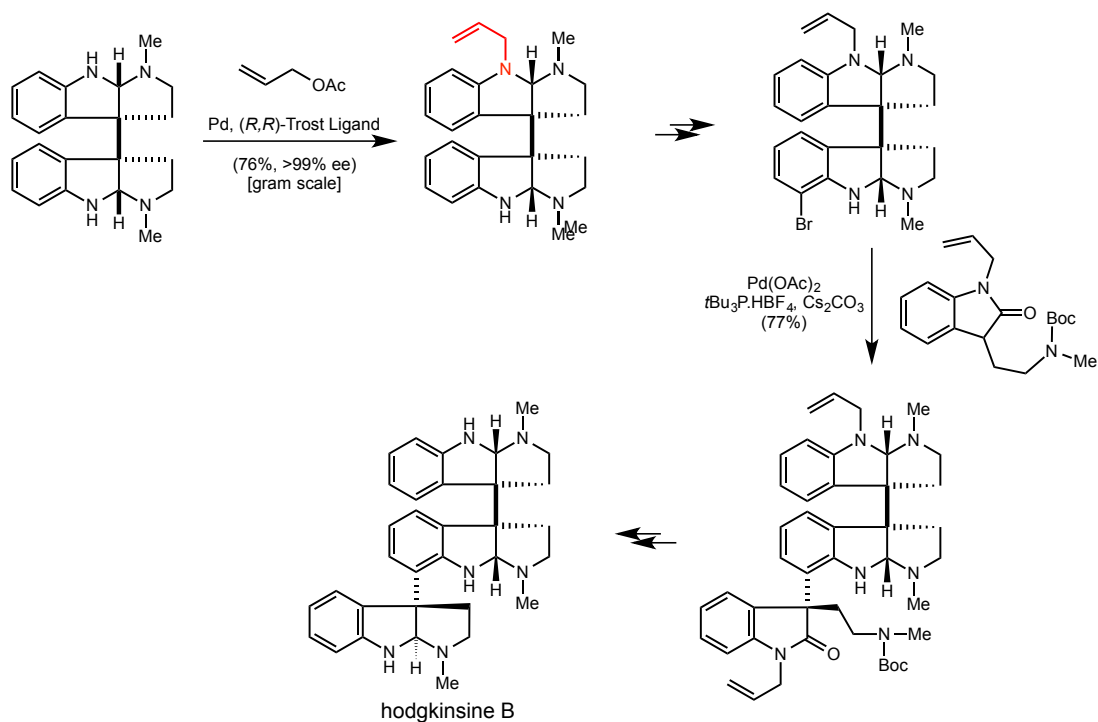
- Purine base as nucleophile
- Synthesis of a carbovir analogue



Trost, *J. Am. Chem. Soc.*, 2000, **122**, 5947; *Tet. Lett.*, 1997, **38**, 1707.

Palladium π -allyl chemistry – application in synthesis

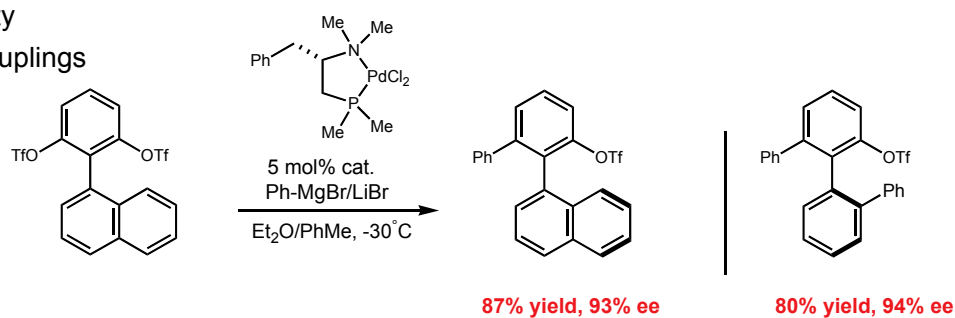
- Meso diamine nucleophile



Willis, *Angew.*, 2011, 50, 9116.

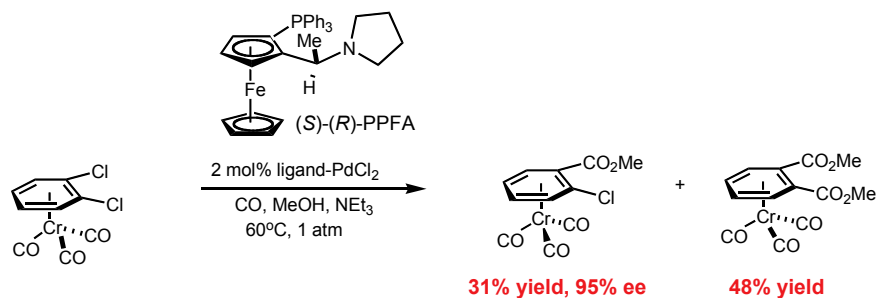
Palladium catalysed cross-coupling reactions

- Axial chirality
- Grignard couplings



Hayashi, *J. Am. Chem. Soc.*, 1995, 117, 9101; *Tet. Lett.*, 1996, 37, 3161.

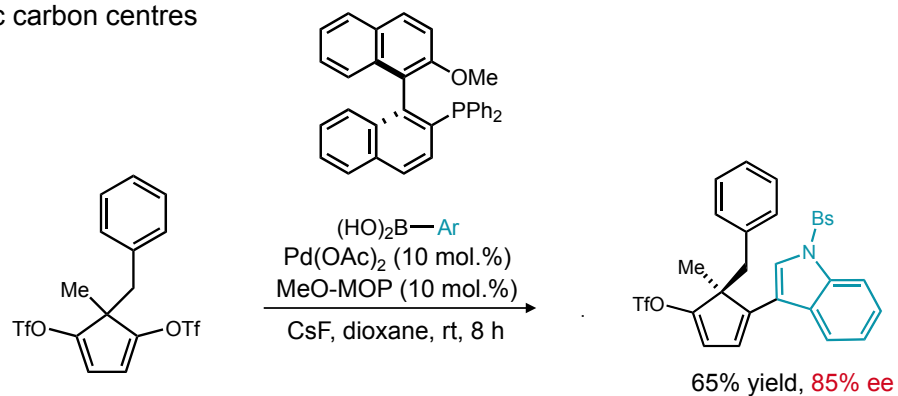
- Planar chirality
- Carbonylation



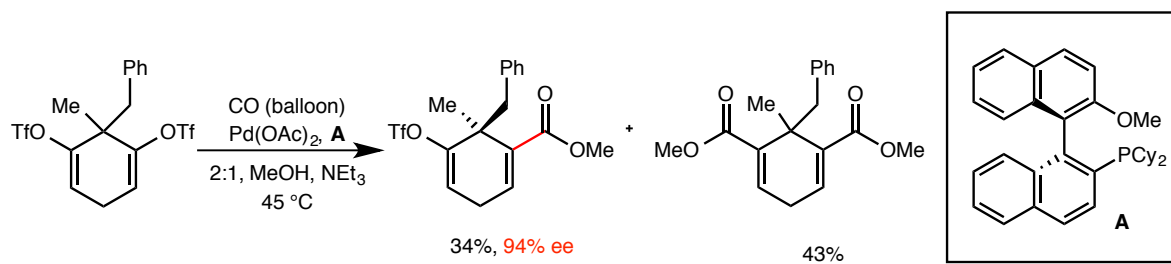
Schmalz, *Org. Lett.*, 2001, 3, 1753.

Palladium catalysed cross-coupling reactions

- Stereogenic carbon centres



Willis, Powell, Watson and Claverie, *Angew.*, 2004, **43**, 1249.



Willis and Bryne, *OBC.*, 2010, **8**, 758.

C-H “Activation” in Synthesis

Michael Willis

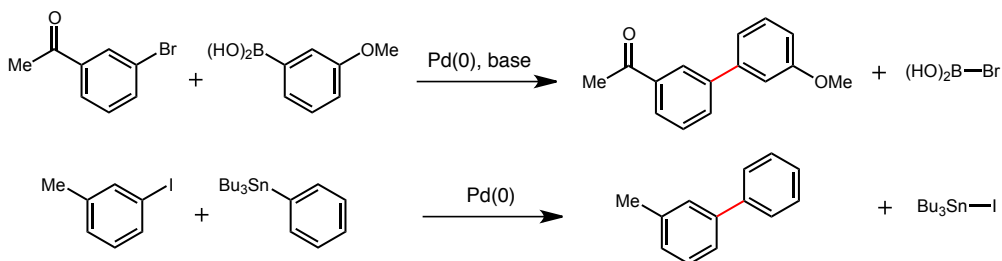
CDT - Metal Catalysis

3rd/4th November 2016

@PdRhCu
michael.willis@chem.ox.ac.uk

C-H Functionalisation, C-H activation, direct arylation

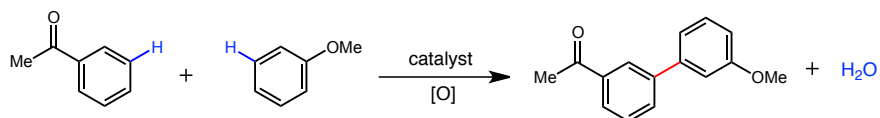
- Palladium (and other metal) catalysed cross-coupling reactions offer powerful methods for C-C bond formation (Suzuki, Stille etc...)
- There are limitations: waste generation and the synthesis of the substrates



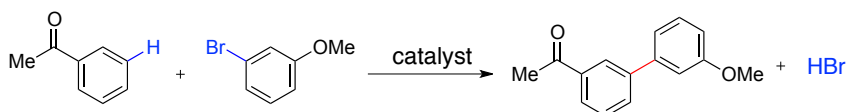
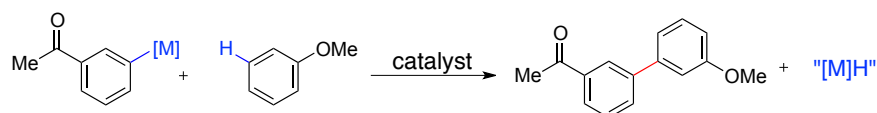
- A direct coupling from unfunctionalised compounds would be ideal...

C-H Functionalisation...

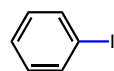
- Removing both functional groups would be ideal, but one at a time also useful



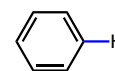
- Would allow removal or organometallic or electrophile (or both)



- Readily available substrates
- Less waste
- But there are significant reactivity and selectivity issues
 - (C-H bonds are strong, there are lots of them)



65 kcal/mol

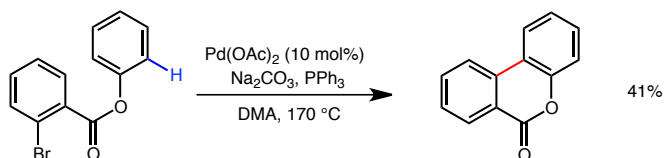
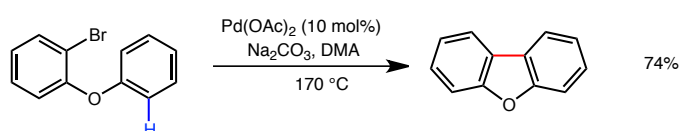


110 kcal/mol

For a recent review, see; Gevorgyan, *CSR* **2007**, 36, 1173.
For an overview, see; "Handbook of C-H Transformations", Dyker, Ed., Wiley, 2005.

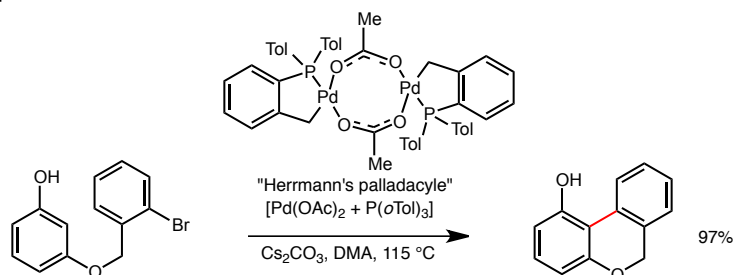
Early Intramolecular Reactions

- Performing intramolecular reactions helps with both reactivity and regioselectivity
- Pioneering studies from Ames; 5- and 6-membered rings



Ames, *Synthesis* **1983**, 2324.

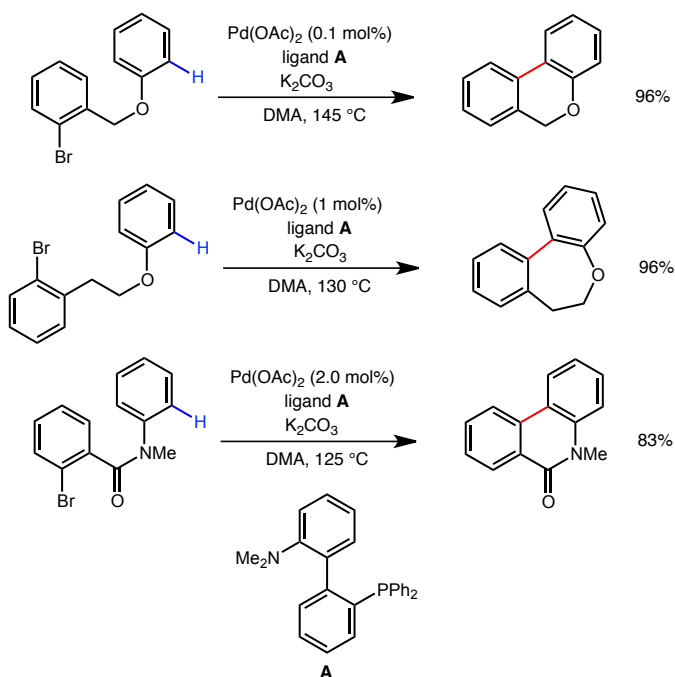
- Electron-rich phenols allow efficient reactions



Rawal, *J. Org. Chem.* **1997**, 2.

Intramolecular Reactions – New Catalysts

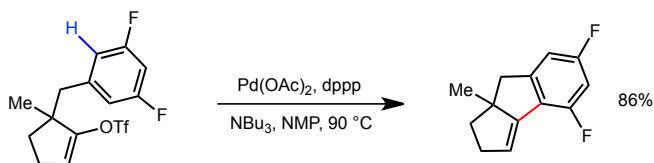
- Buchwald bulky e-rich ligands allow improved reactions: 5-, 6- and 7-rings



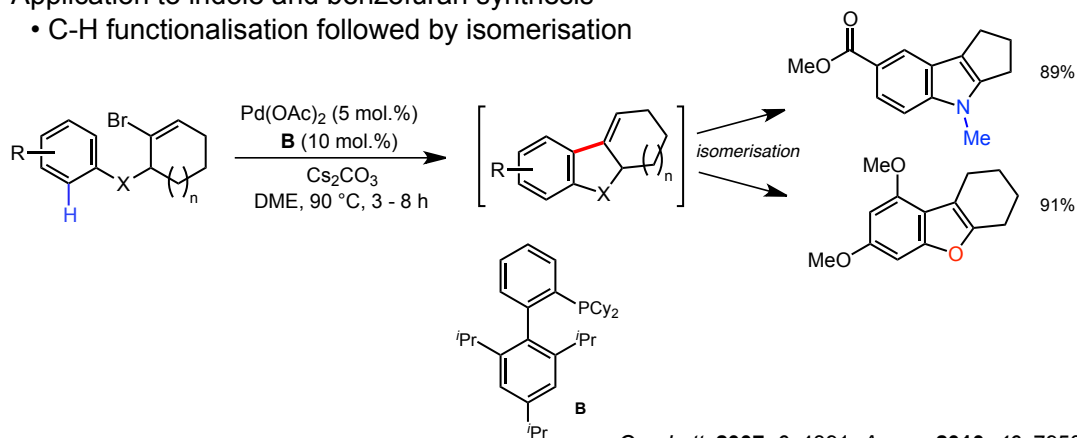
Fagnou, *JACS* **2004**, 126, 9186.

Intramolecular Reactions – Alkenyl halides

- Alkenyl halides and triflates can also be employed



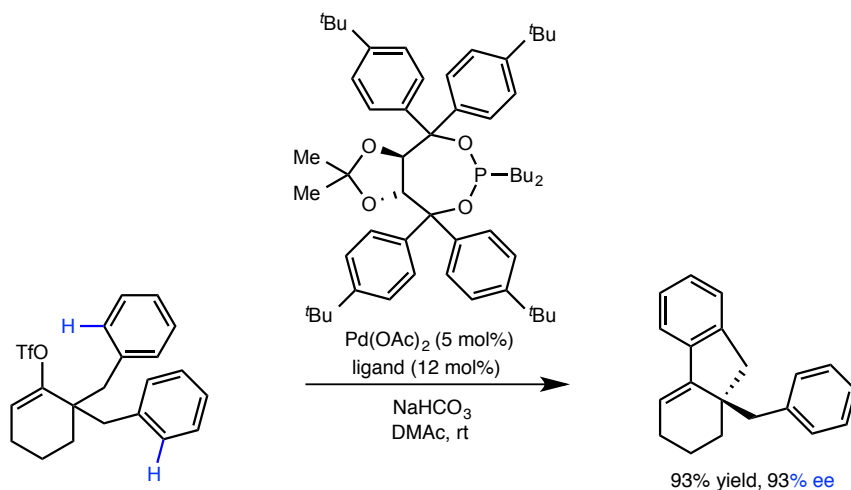
- Application to indole and benzofuran synthesis
 - C-H functionalisation followed by isomerisation



Org. Lett. **2007**, 9, 4391; *Angew* **2010**, 49, 7958.

Alkenyl halides – Enantioselective reaction

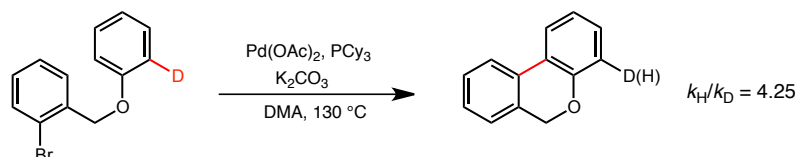
- Substrates with enantiotopic C-Hs



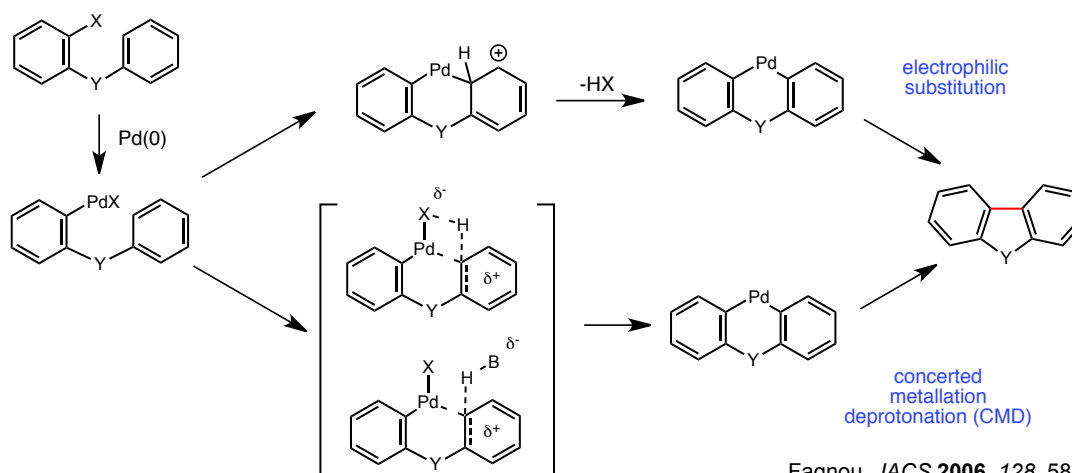
Cramer *Angew* **2009**, *48*, 9139.

Intramolecular Reactions – Mechanism

- Significant kinetic isotope effect observed



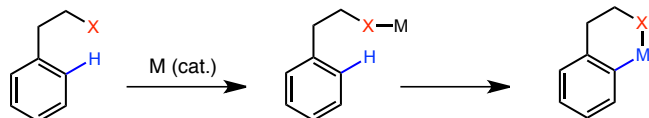
- Two (main) proposed mechanisms; the observed KIE favours CMD



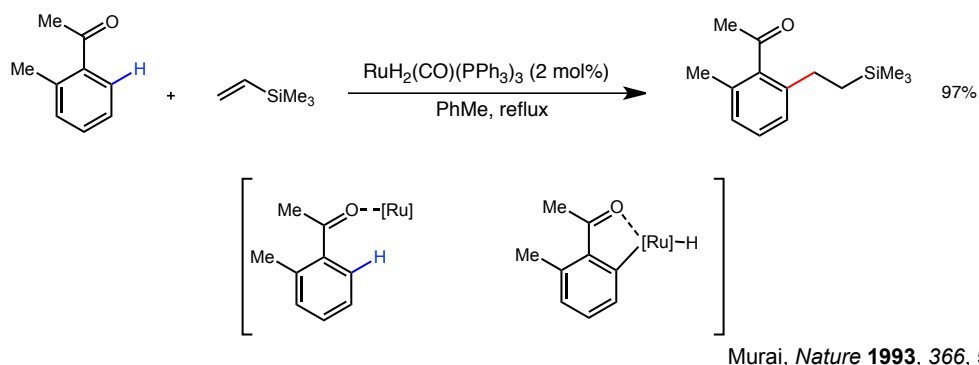
Fagnou, *JACS* **2006**, *128*, 581.

Intermolecular Reactions

- Cyclometallation – chelation control
 - A coordinating groups directs catalyst to C-H bond

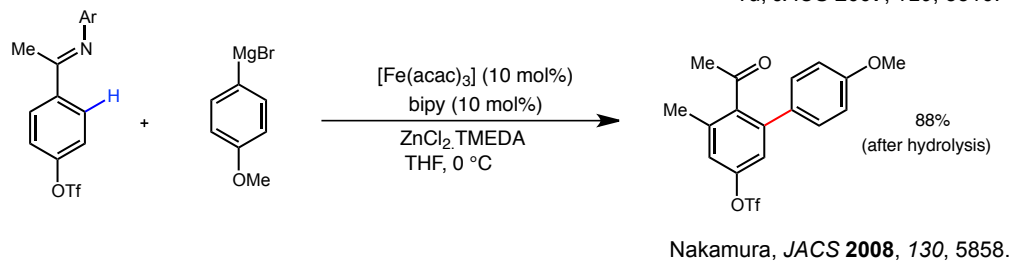
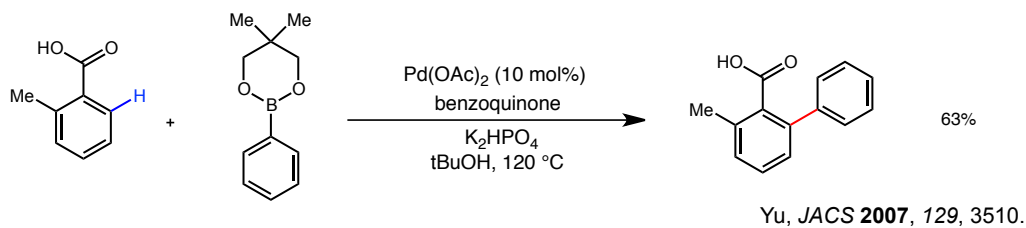
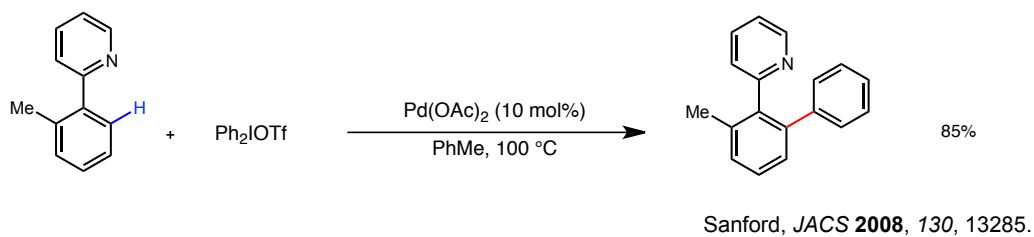


- Very successful strategy, but the need for a chelating group is a limitation
- Seminal paper from Murai... more later



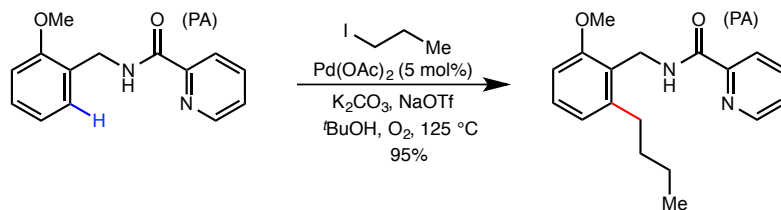
Chelation control – different groups/metals

- Applicable to a variety of directing groups, coupling partners and metals



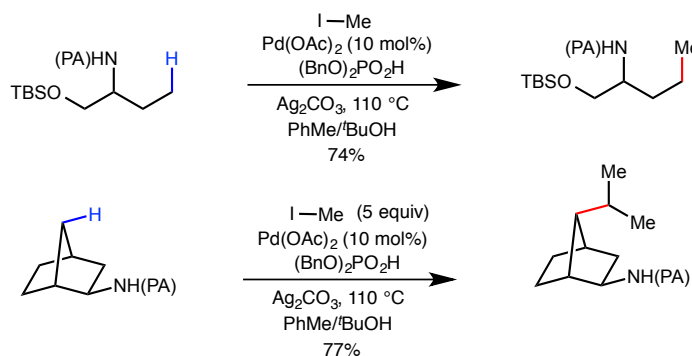
Chelation control – alkylation

- Picolinamide directing group very effective – allows alkylation



- Can be extended to C(sp³)-H activation

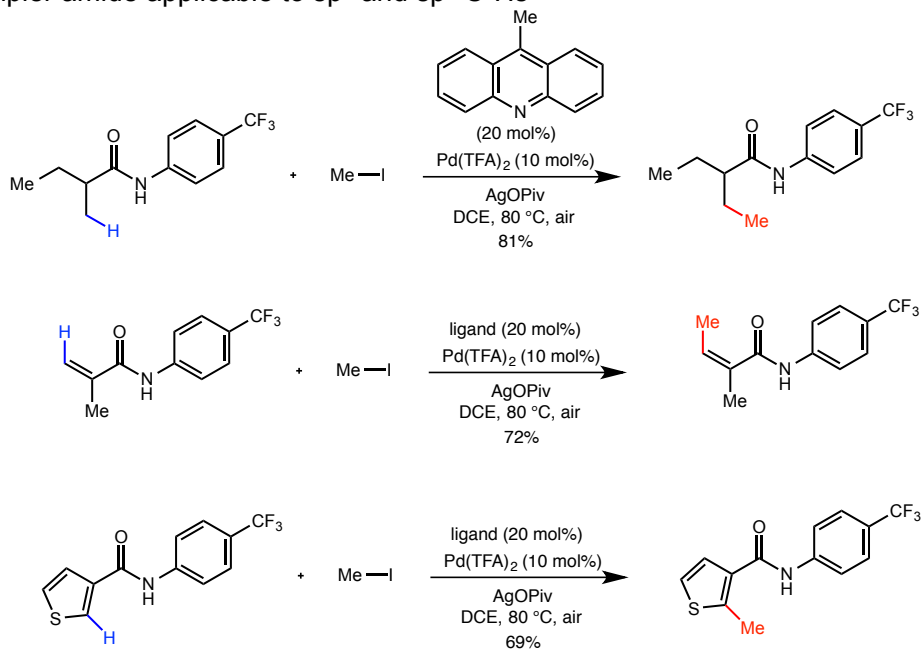
Chen, *OL*, 2011, 13, 4850.



Chen, *JACS* 2013, 135, 2124.

Chelation control – alkylation

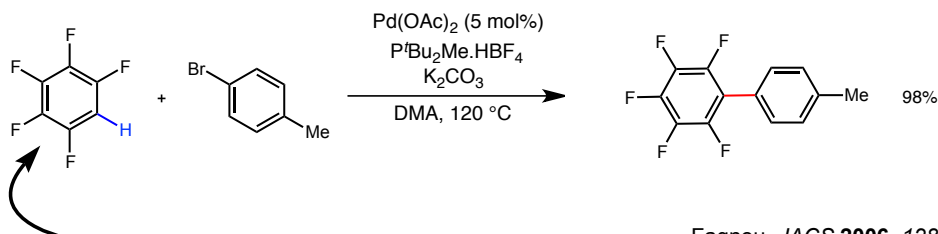
- Simpler amide applicable to sp³ and sp² C-Hs



Yu, *JACS* 2014, 136, 13194.

Intermolecular Reactions

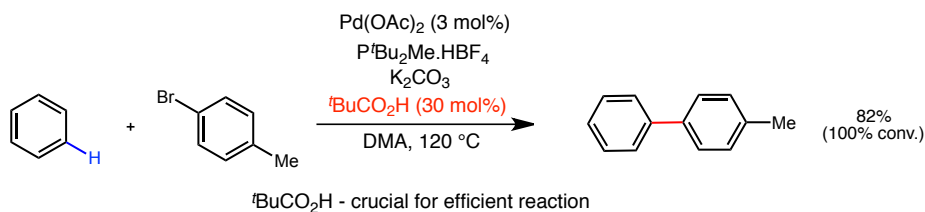
- Non-chelating systems
- Recognition of CMD mechanism for *intra* systems, led to *inter* reactivity...



inert to electrophilic substitution

Fagnou, *JACS* **2006**, *128*, 8754.

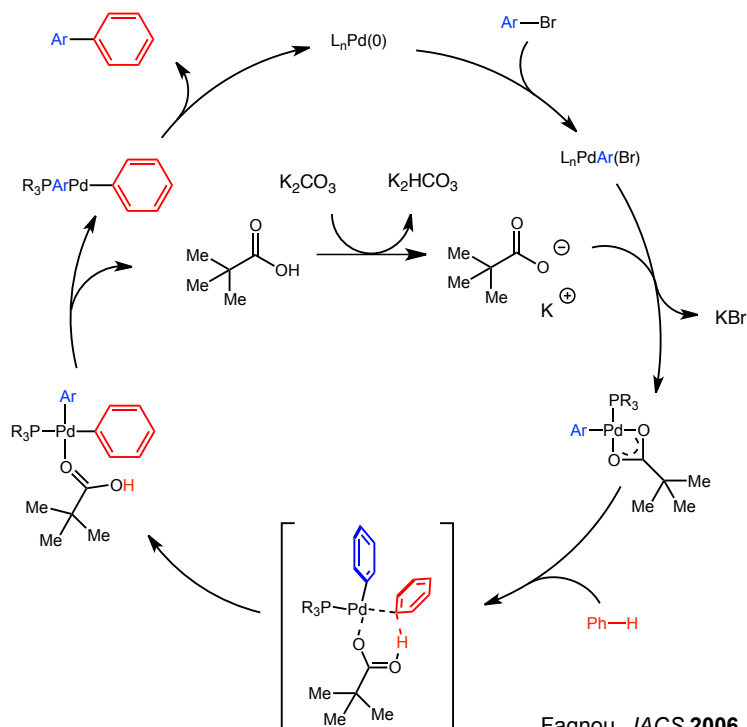
- ...even benzene as a coupling partner



Fagnou, *JACS* **2006**, *128*, 16496.

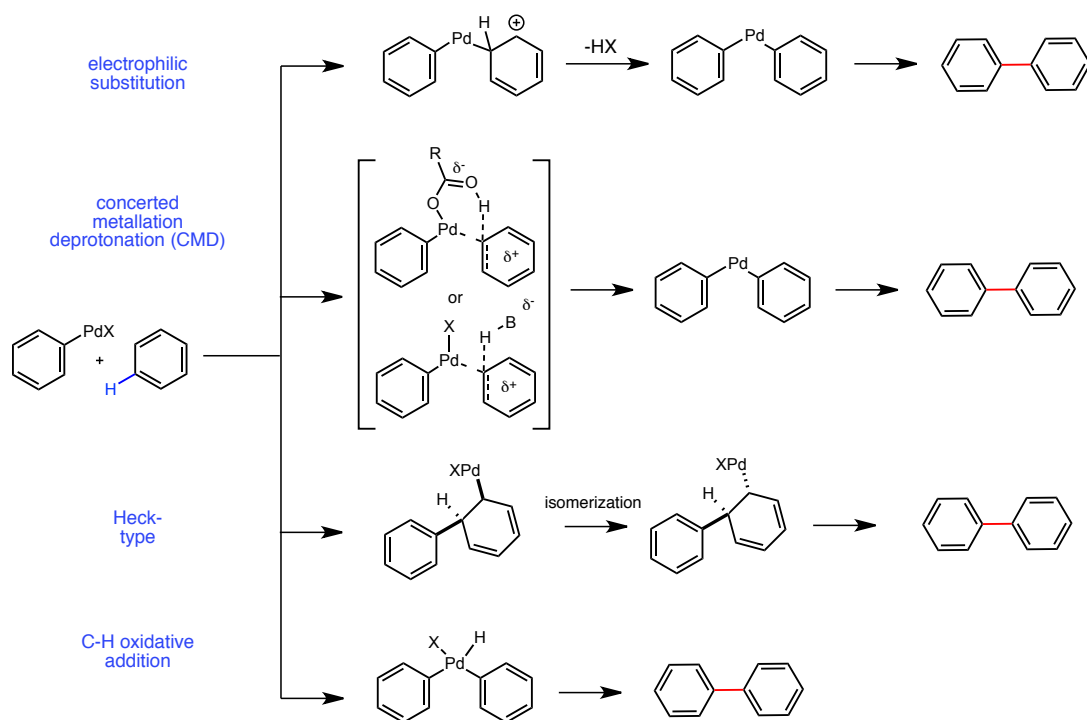
Intermolecular Reactions - Mechanism

- Role of pivalate in catalytic cycle



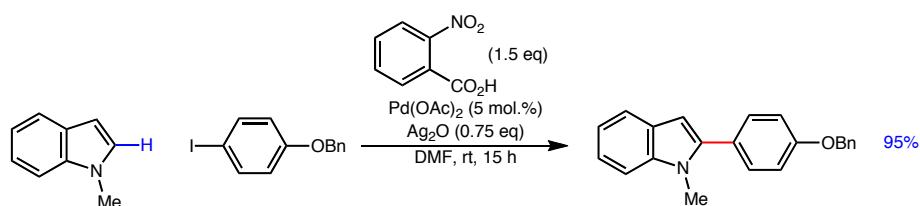
Fagnou, *JACS* **2006**, *128*, 16496.

Intermolecular Reactions – Mechanistic Possibilities



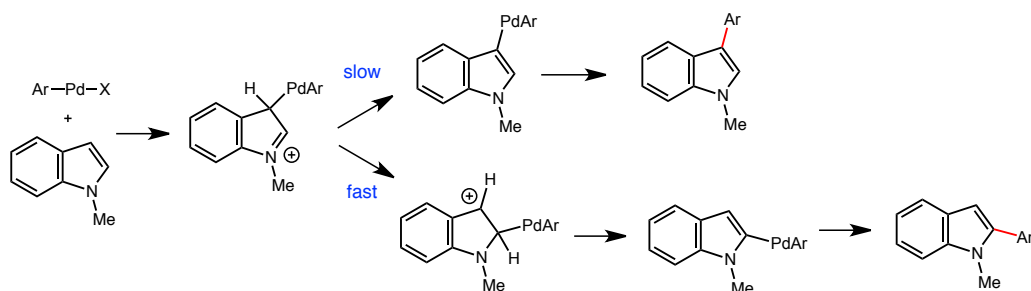
Heterocycle functionalisation

- Pd-catalysed reactions of electron-rich heterocycles dominate
- Electrophilic substitution mechanisms



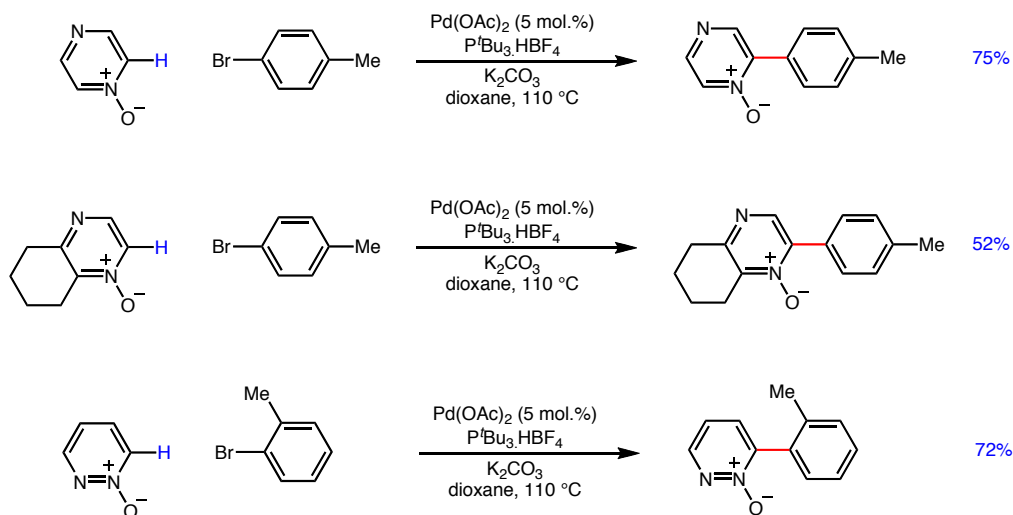
Larrosa, *JACS* **2008**, *130*, 2926.

- Reaction proceeds *via* initial C-3 Pd-intermediate



C-H functionalisation of diazine-N-oxides

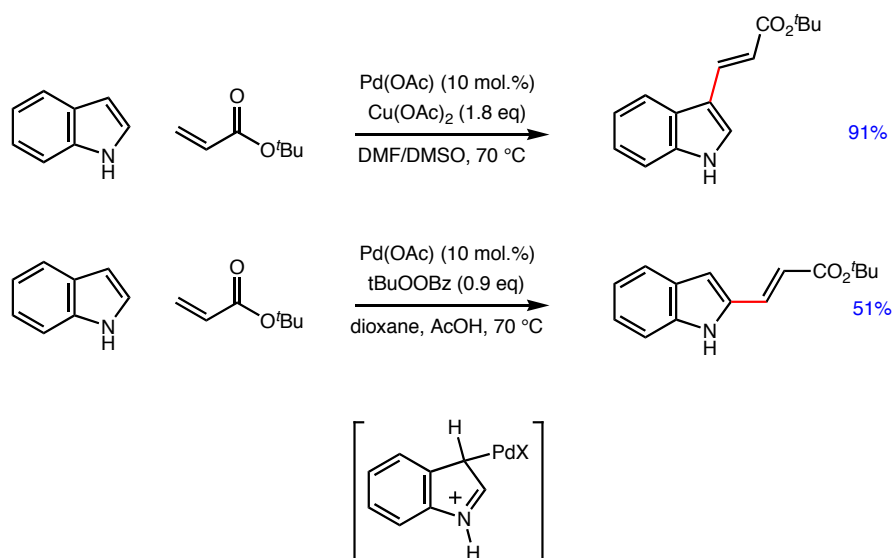
- Use of N-oxides allows electron-poor heterocycles to be employed



Fagnou, *Angew* **2006**, 45, 7781; *JACS*, **2008**, 130, 3276.

Regioselectivity in indole functionalisation

- Fujiwara-Moritani oxidative Heck
- Solvent and oxidant selective functionalisation
- Oxidant regenerates Pd(II)

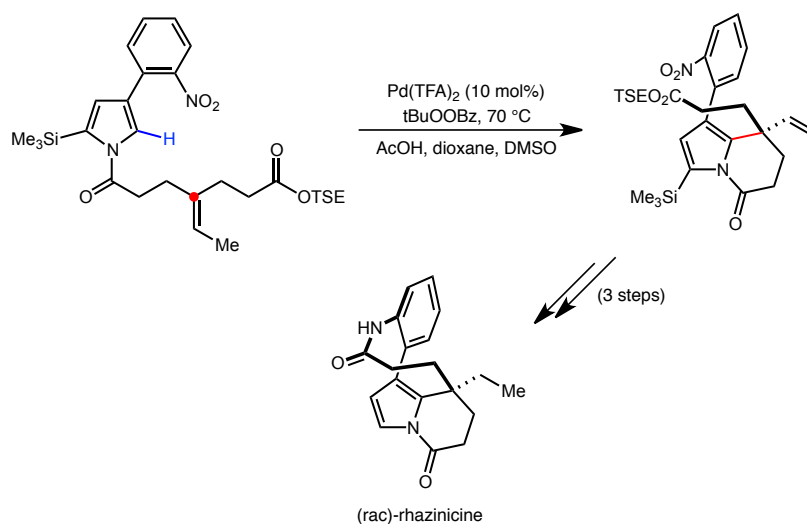


Gaunt, *Angew*, **2005**, 44, 3125.

For a similar approach to pyrroles, see; Gaunt, *JACS*, **2006**, 128, 2528.

C-H functionalisation in natural product synthesis

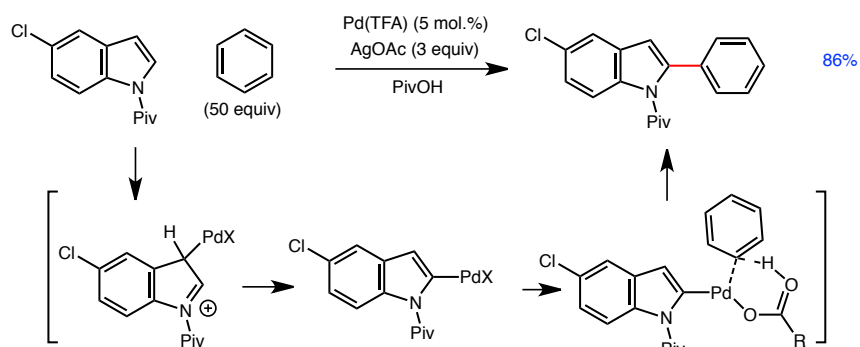
- C-H functionalisation/oxidative Heck applied to rhazinicine



Gaunt, *Angew* **2008**, 47, 3004.

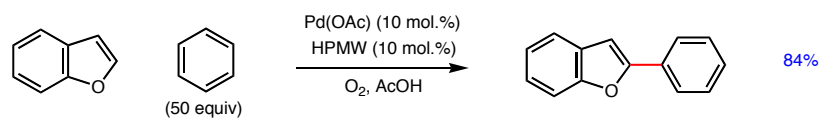
Direct cross-coupling

- Coupling with no activating groups
- Direct oxidative functionalisation on indole



Fagnou, *JACS*, **2007** 129, 12072; *Science*, **2007**, 317, 1172.

- Also Benzofurans

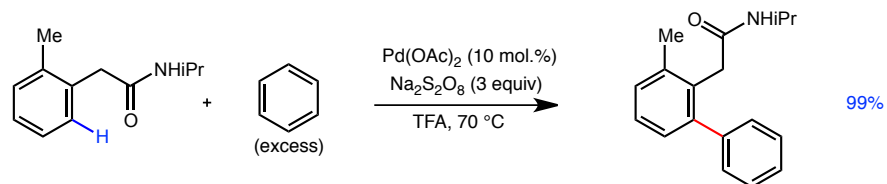


HPMW = heteropolymolybdovanadic acid $\text{H}_4\text{PMo}_{11}\text{VO}_{40}$

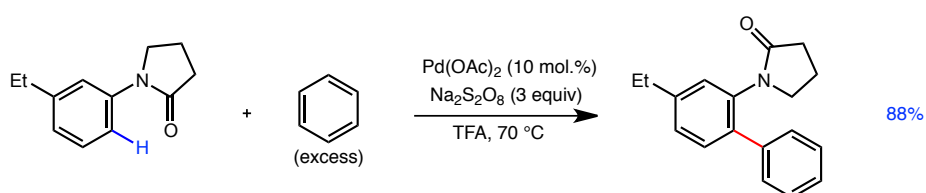
DeBoef, *OL*, **2007**, 9, 3137.

Direct cross-coupling – chelation controlled

- Amide directing groups
- Sodium persulfate as oxidant



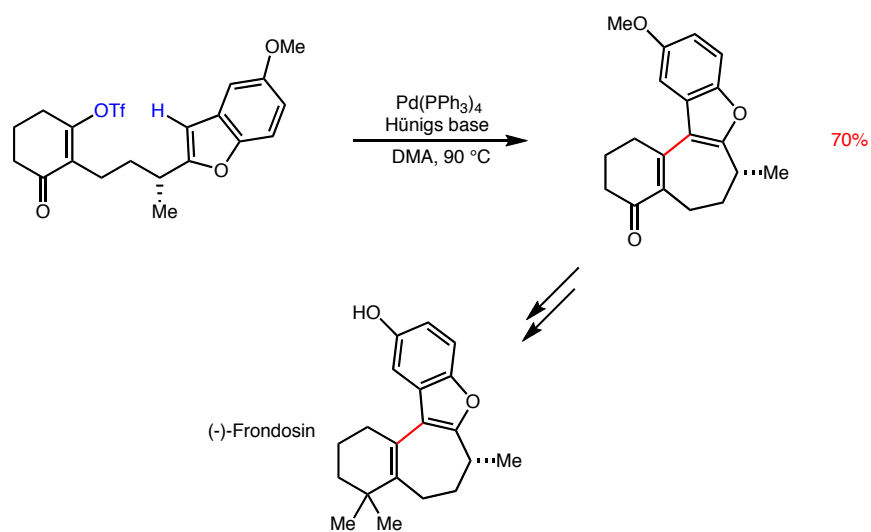
- Alternative amide arrangement



Dong, *Chem Sci*, **2010** 1, 331.

C-H functionalisation in natural product synthesis

- Intramolecular benzofuran C-H functionalisation
- Key step in the synthesis of Frondosin B

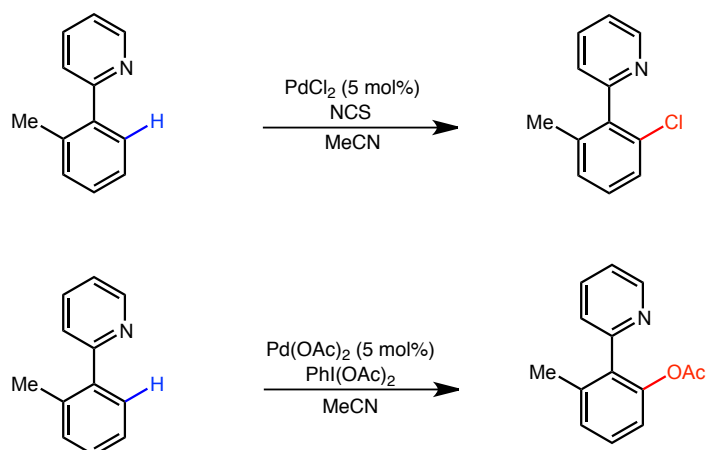


(-)-Frondosin

Trauner, *Angew* **2002**, 41, 1569.

C-X Bond formation

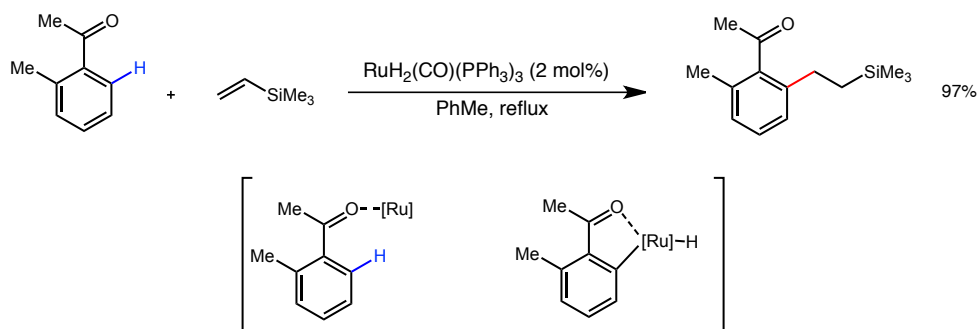
- A wide range of C-X bonds can also be formed by C-H functionalisation



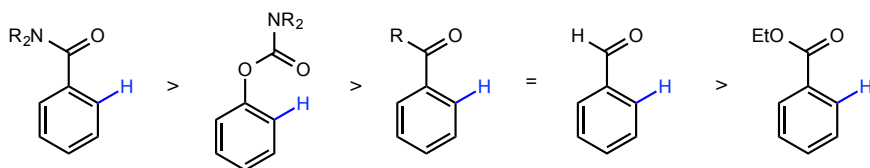
Sanford, *OL* **2009**, 11, 4584.

C-H functionalisation: Ruthenium

- Generally require a directing group, but it can be 'weakly' coordinating
- Early Murai work employed ketones as directing groups

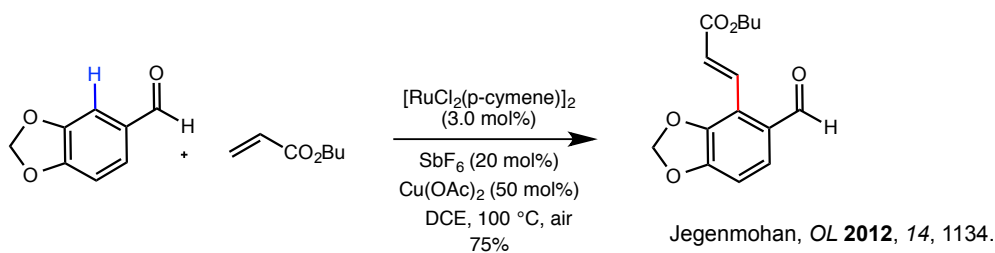
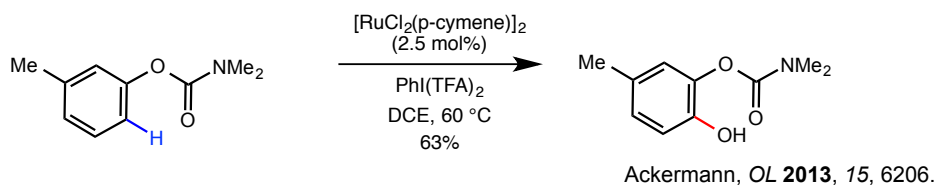
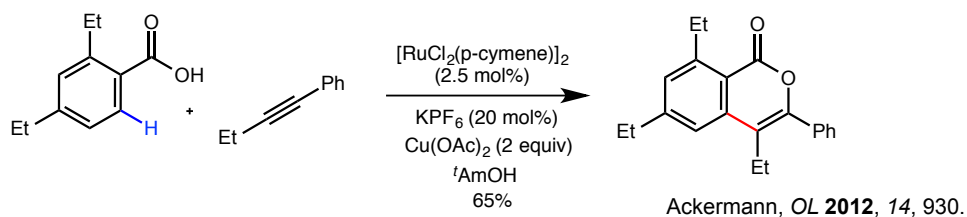


- Has recently been extended to many other 'weak' coordinating groups



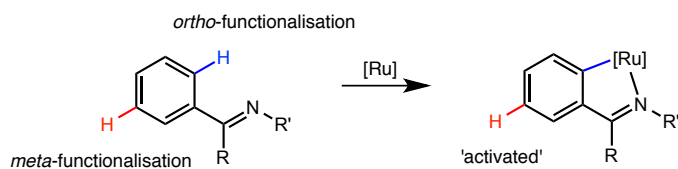
Ackermann, *ASC* **2014**, 356, 1461.

C-H functionalisation: Ruthenium

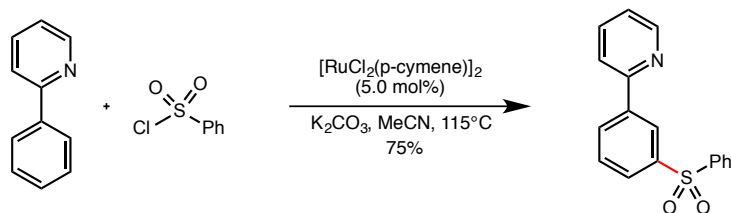


C-H functionalisation: Beyond ortho-selectivity

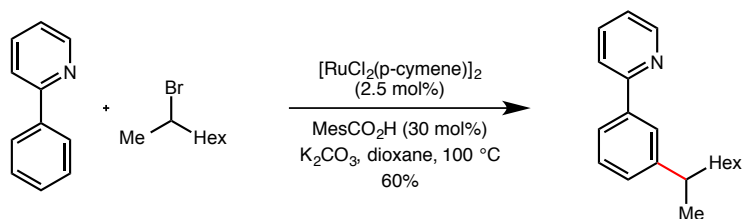
- Initial *ortho*-activation used to direct *meta*



- Sulfonylation



- Alkylation

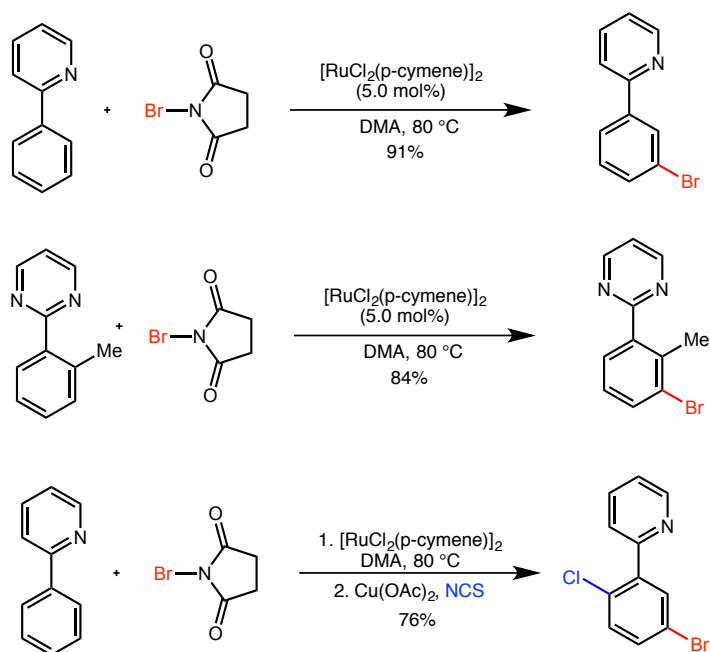


Frost, *JACS*, **2011**, 133, 19298.

Ackermann, *JACS*, **2013**, 135, 5877.

C-H functionalisation: Beyond ortho-selectivity

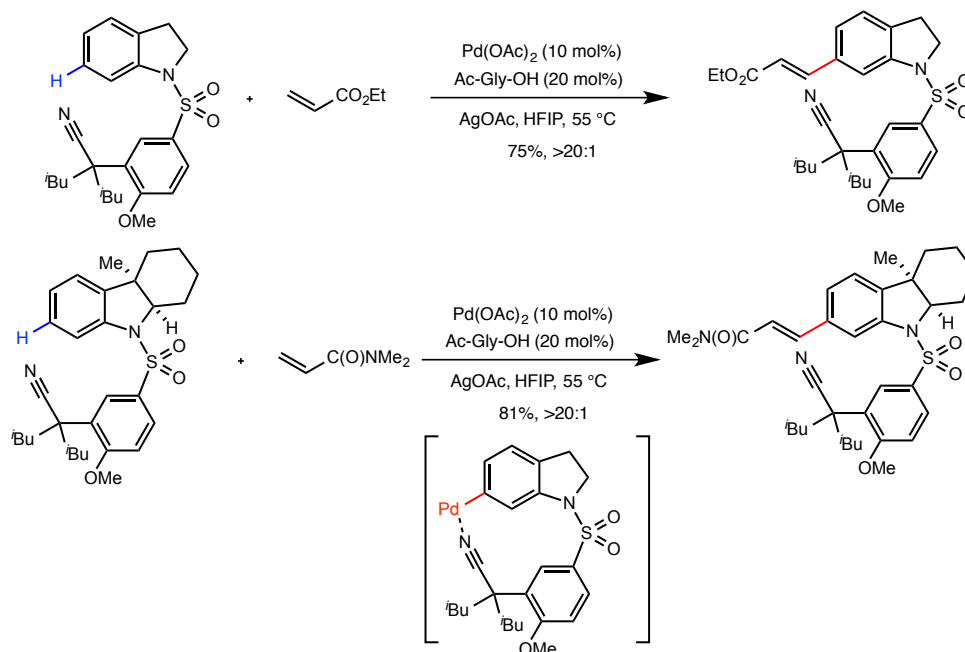
- extension to bromination



Greaney, *Angew* **2015**, *54*, 11677.

Meta-selectivity using Pd

- Corresponding Pd-catalysed process requires a “U-shaped template”



Yu, *JACS*, **2014**, *136*, 10807.