(Hetero)aromatic Functionalisation 3 – *Catalytic C-H Activation Reactions*

Alan Spivey
a.c.spivey@imperial.ac.uk
http://www.ch.ic.ac.uk/spivey/

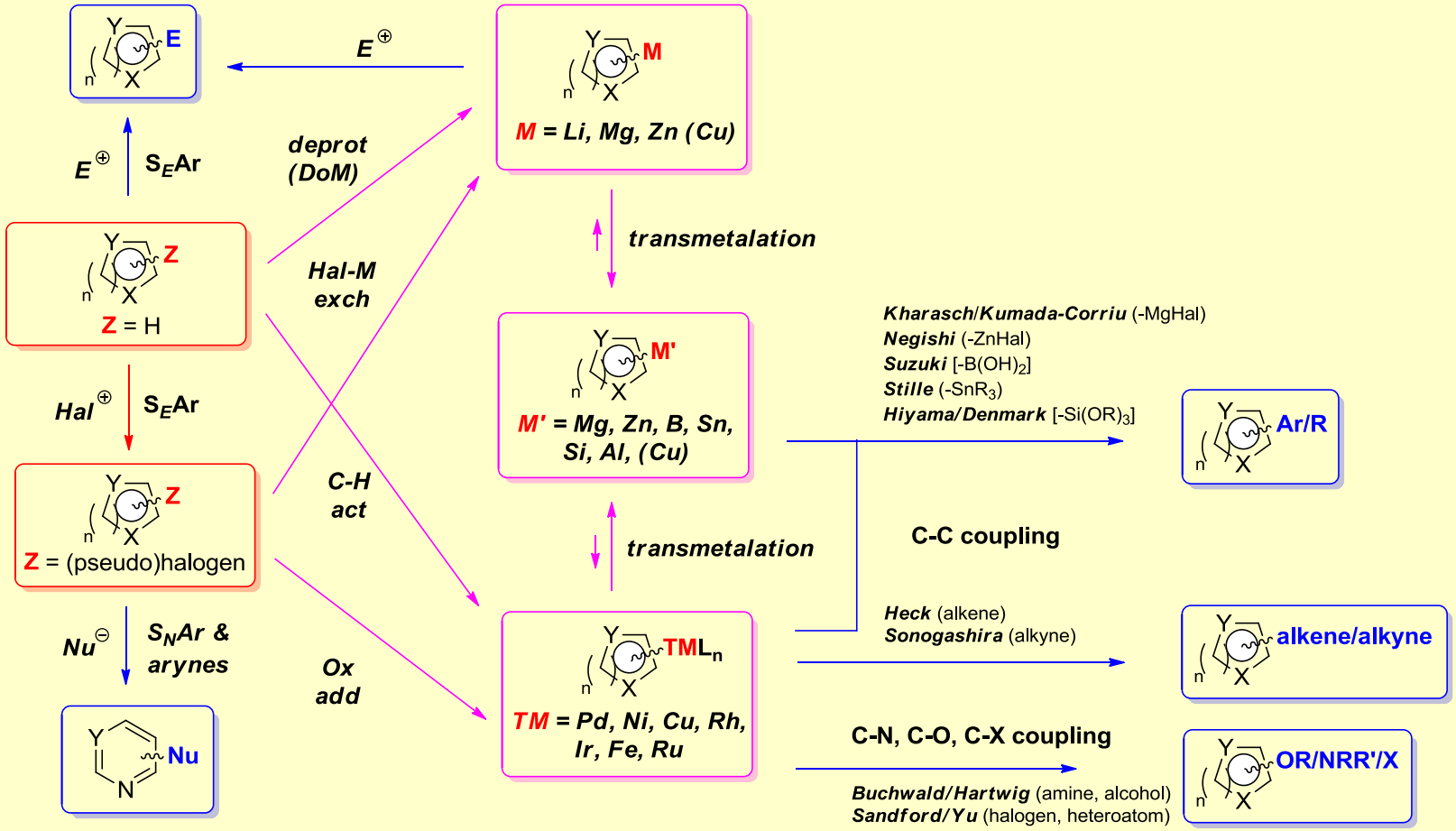
Imperial College London

Villars Summer School
29th Aug – 2nd Sept 2010

Format and scope of lecture

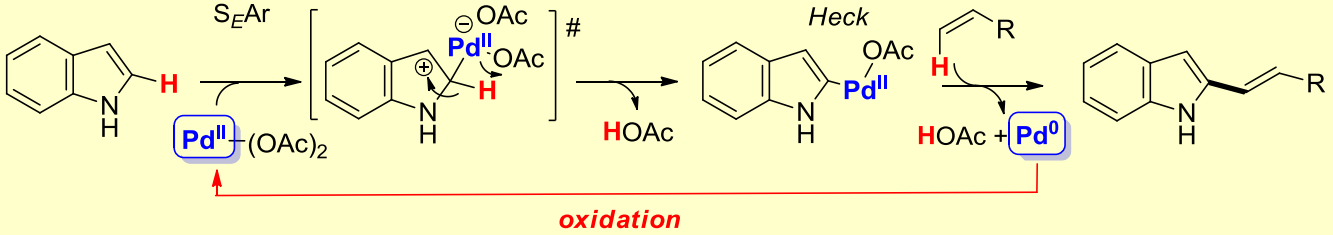
- ***Catalytic C-H activation reactions:***
  - Mechanistic considerations – classification as *direct* & *directed*
  - direct metalation (*e.g. ortho* to ring heteroatoms)
  - directing group assisted metalation (*e.g. ortho* to 2-pyridyl substituent)
  - applications in synthesis

(Hetero)aromatic functionalisation strategies



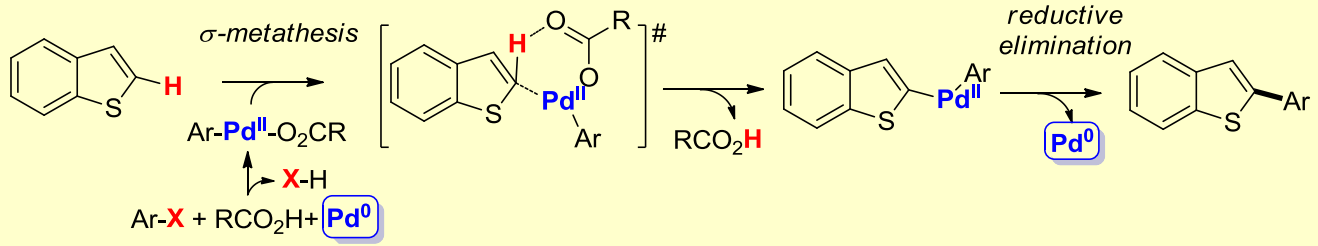
C-H activation – *overview*

- ***reviews:*** Ackermann *Angew. Chem. Int. Ed.* **2009**, *48,* 9792 (direct arylation) (DOI); Shi *Synlett* **2008**, 949 (direct Pd-catalysed arylation); Lautens *Chem. Rev*. **2007**, *107*, 174 (direct arylation) (DOI); Fagnou *Aldrichimica Acta* **2007**, *40(2*), 35 (direct arylation) (DOI); Yu *Org. Biomol. Chem.* **2006**, 4041 (directing group assisted) (DOI); Sanford *Tetrahedron* **2006**, *62*, 2439 (C-H activation/oxidation) (DOI)
- ***direct* CH activation :**
  - *e.g.* indoles with alkenes (CH/CH) *via* ***electrophilic metalation*** (S_EAr) of the indole:



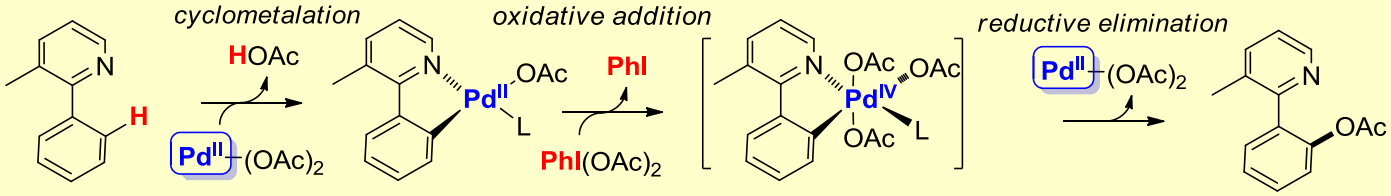
Key Factor
π-donor strength

  - *e.g.* benzothiophenes with aryl halides (CH/CX) *via* ***σ-metathesis metalation*** of benzothiophene:



Key Factor
σ-C-H polarity/acidity

- ***directing group assisted* CH activation:**
  - *e.g. o*-pyridylaryls with iodonium salts (CH/XY) *via* ***cyclometalation*** of *o*-pyridylaryl:

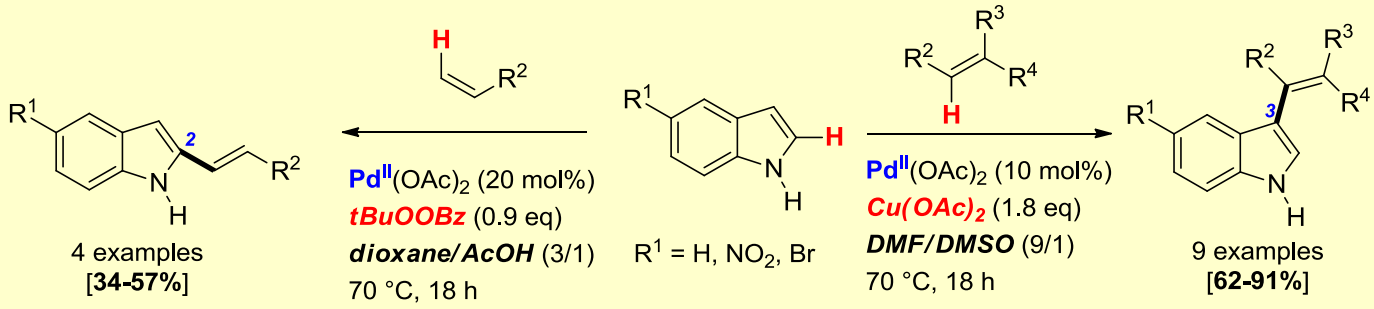


Key Factor
proximity of C-H to Lewis basic donor atom

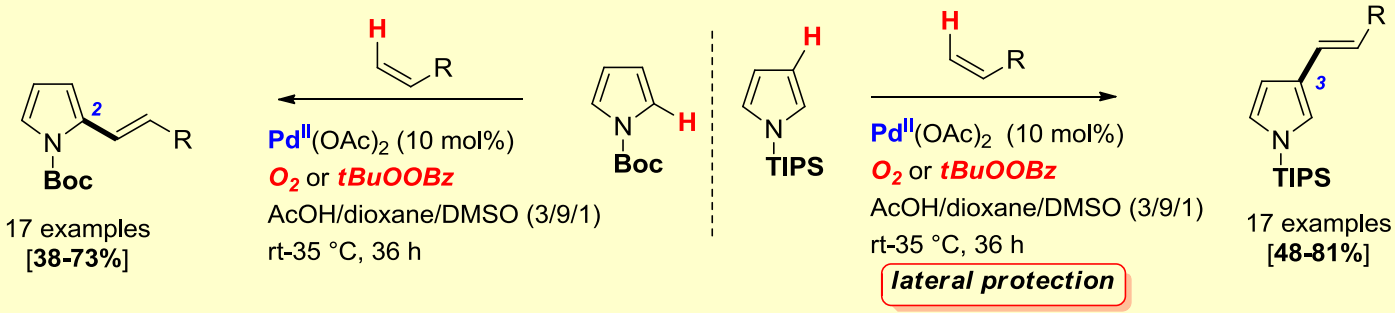
Direct C-H activation reactions

Direct CH/CH alkenylation – *indoles & pyrroles at C2 & C3*

- ***N-H indoles ↔ alkenes (CH/CH, Pd + Ox)***
  - Gaunt *Angew. Chem. Int. Ed.* **2005**, *44*, 3125 (DOI)
  - ***solvent controls regioselectivity:*** *dioxane/AcOH (3/1)* → ***C2*** product *cf.* DMF/DMSO (9/1) → ***C3*** product

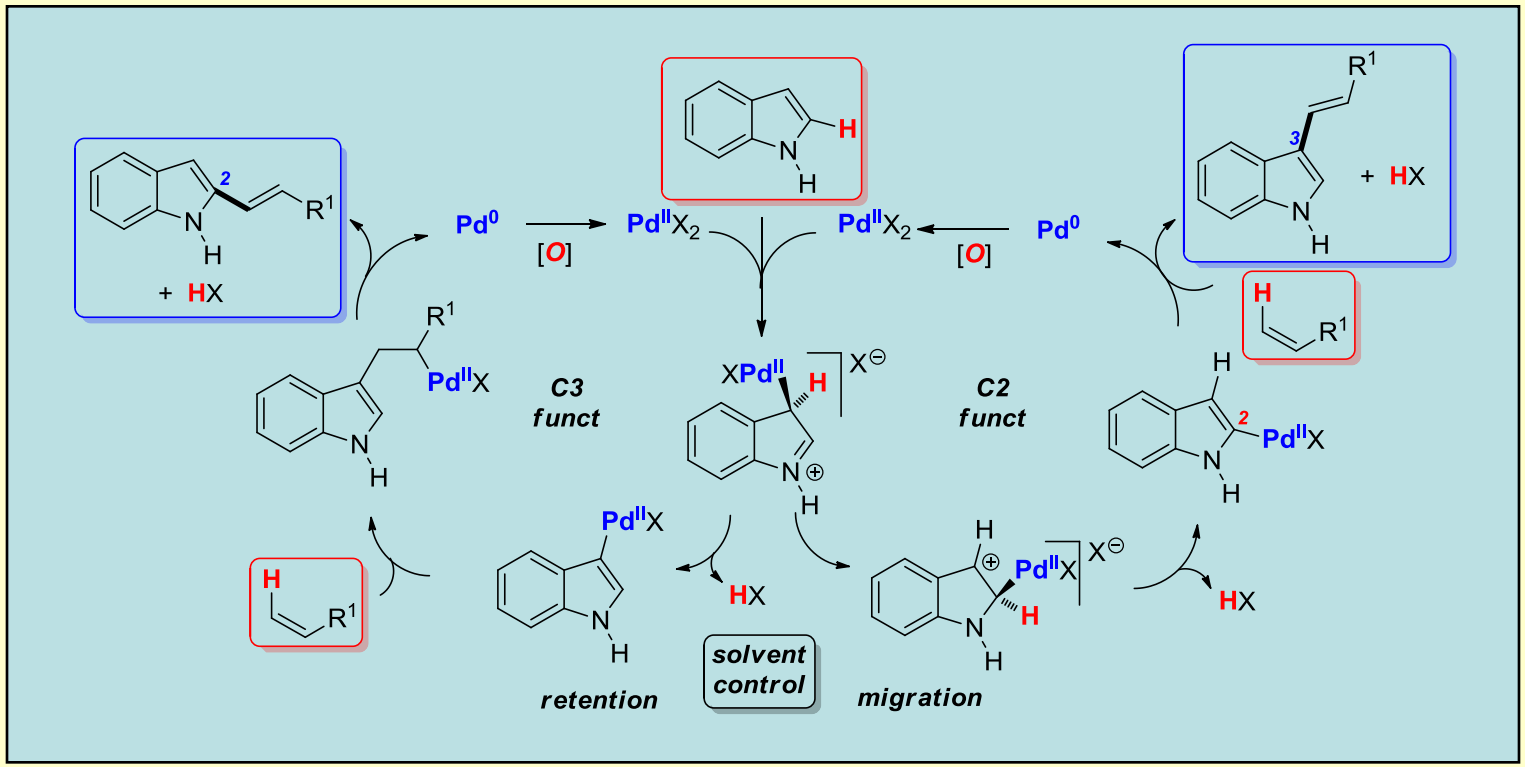


- ***N-Boc/N-TIPS pyrroles ↔ alkenes (CH/CH, Pd + Ox)***
  - Gaunt *J. Am. Chem. Soc.* **2006**, *128*, 2528 (DOI)
  - ***Protecting group controls regioselectivity:*** ***N*-Boc** → ***C2*** product *cf.* ***N*-TIPS** → ***C3*** product



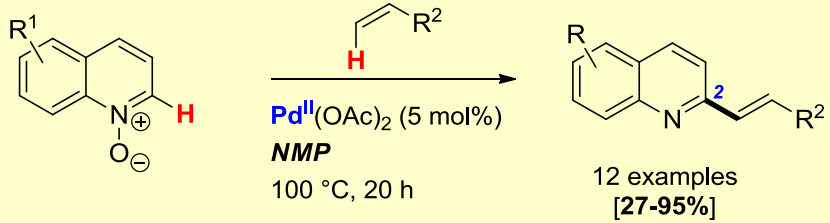
Mechanism – S_EAr by PdX_2 → Heck

- ***CH activation:*** electrophilic palladation by $Pd^{II}X_2$
  - Gaunt *Angew. Chem. Int. Ed.* **2005**, *44*, 3125 (DOI)
  - O_2 or **BzOOBz** as stoichiometric oxidant ($Pd^0 \rightarrow Pd^{II}$)

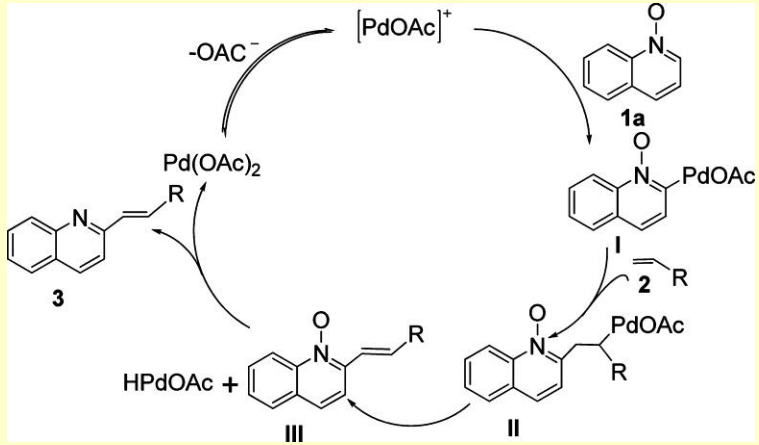


Direct CH/CH alkenylation/alkylation – *quinoline(-N-oxide)s at C2*

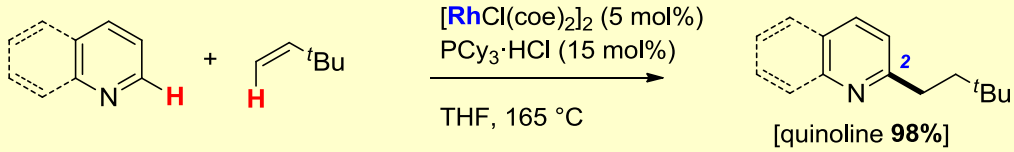
- ***quinolne-N-oxides ↔ alkenes (CH/CH, Pd + internal ox)***
  - Wu *J. Am. Chem. Soc.* **2009**, *131*, 13888 (DOI)
  - ***CH activation:*** σ-metathesis palladation
  - *N*-oxide acts as internal' oxidant ($Pd^0 \rightarrow Pd^{II}$) – no external oxidant required:



MECHANISM



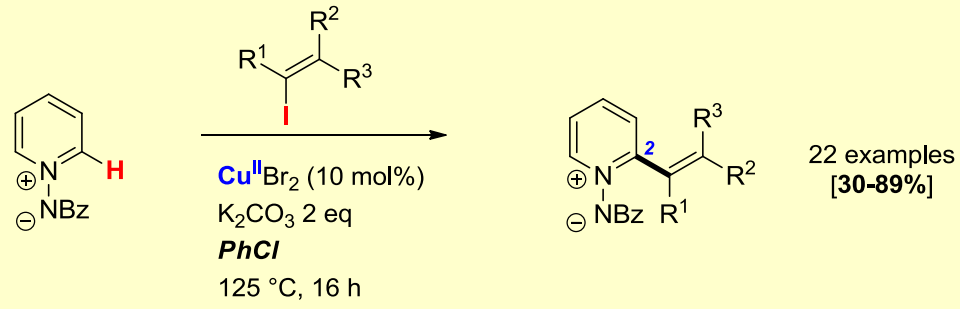
- ***Quinolines & pyridines ↔ alkenes (CH/CH, Rh + internal ox):***
  - Ellman *J. Am. Chem. Soc.* **2009**, *130*, 14926 (DOI) & *J. Am. Chem. Soc.* **2007**, *129*, 5332 (DOI)
  - Ellman *Org. Lett.* **2010**, *12*, 2978 (intramolecular) (DOI)
  - Product is alkylated – hydrogen consumed by hydrogenation of alkene – no external oxidant required



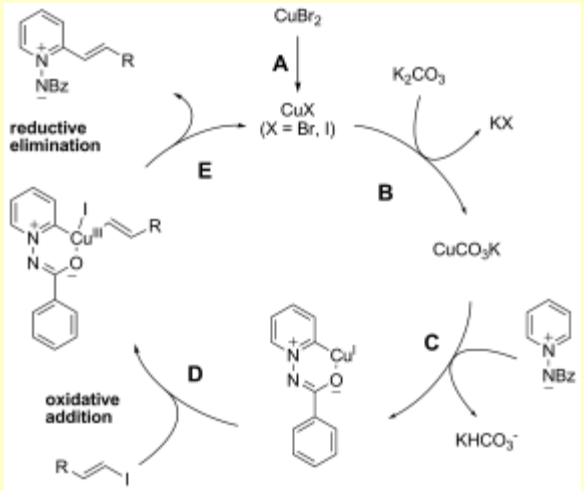
CH activation: NHC rhodation at C of the C=N function:
Ellman *J. Am. Chem. Soc.* **2006**, *128*, 2452 (DOI)
see later

Direct CH/CX alkenylation – *N-iminopyridinium ylides at C2*

- ***N-iminopyridinium ylides ↔ alkenyl halides (CH/CX, Cu)***
  - Charette *Angew. Chem. Int. Ed.* **2010**, *49*, 1115 (DOI)
  - ***CH activation***: σ-metathesis cupration/cyclocupration
  - no external oxidant required

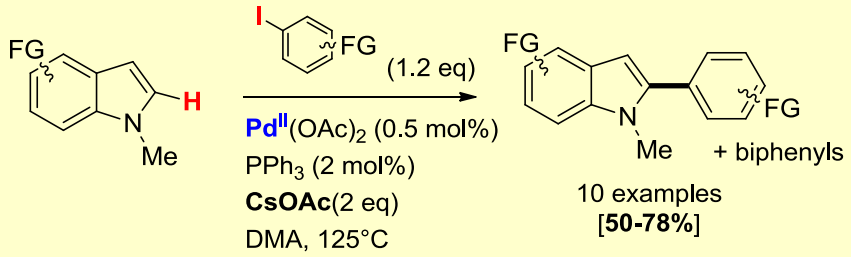


- ***MECHANISM:***

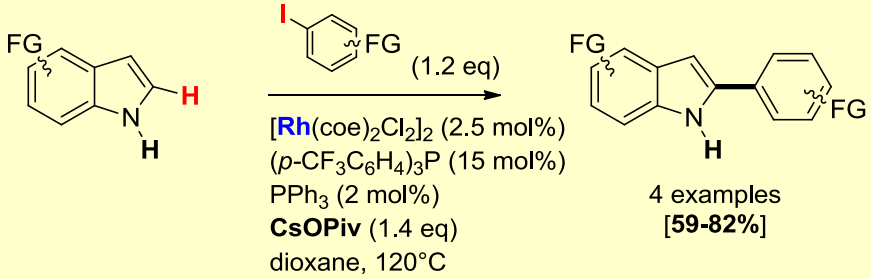


Direct CH/CX arylation – *indoles & azoles at C2*

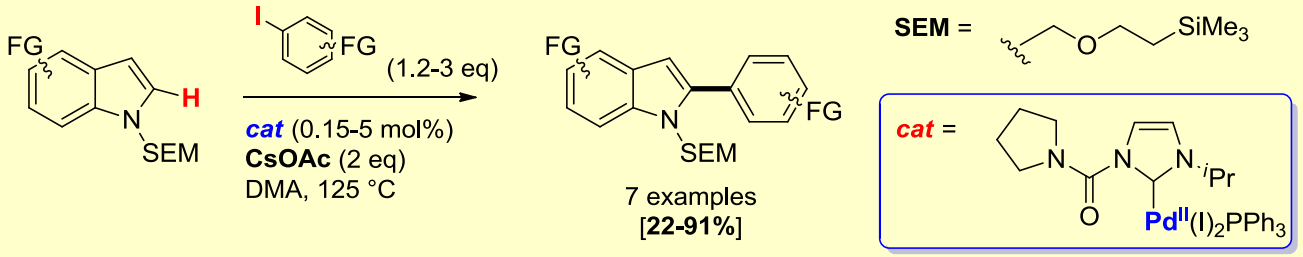
- ***N-Me indoles & azoles ↔ ArI (CH/CX, Pd & Rh):***
  - Sames *Org. Lett.* **2004**, *6*, 2897 (**Pd**) (DOI):
  - Itami *J. Am. Chem. Soc.* **2006**, *128*, 11748 (**Rh**) (DOI)
  - Larossa *J. Am. Chem. Soc.* **2008**, *130*, 2926 (**Pd**) (DOI)
  - Greaney *Angew. Chem. Int. Ed*. **2007**, *46*, 7996 (**Pd**) (DOI)
  - Greaney *Chem. Comm.* **2008**, 1241 (**Pd**) (DOI)
  - Daugulis *J. Am. Chem. Soc*. **2007**, *129*, 12404 (**Cu**) (DOI)



- ***N-H indoles ↔ ArI (CH/CX, Ru & Pd):***
  - Sames *J. Am. Chem. Soc.* **2005**, *127*, 4996 (**Ru**) (DOI):
  - Sames *J. Org. Chem.* **2007**, *72*, 1476 (**Pd**) (DOI)

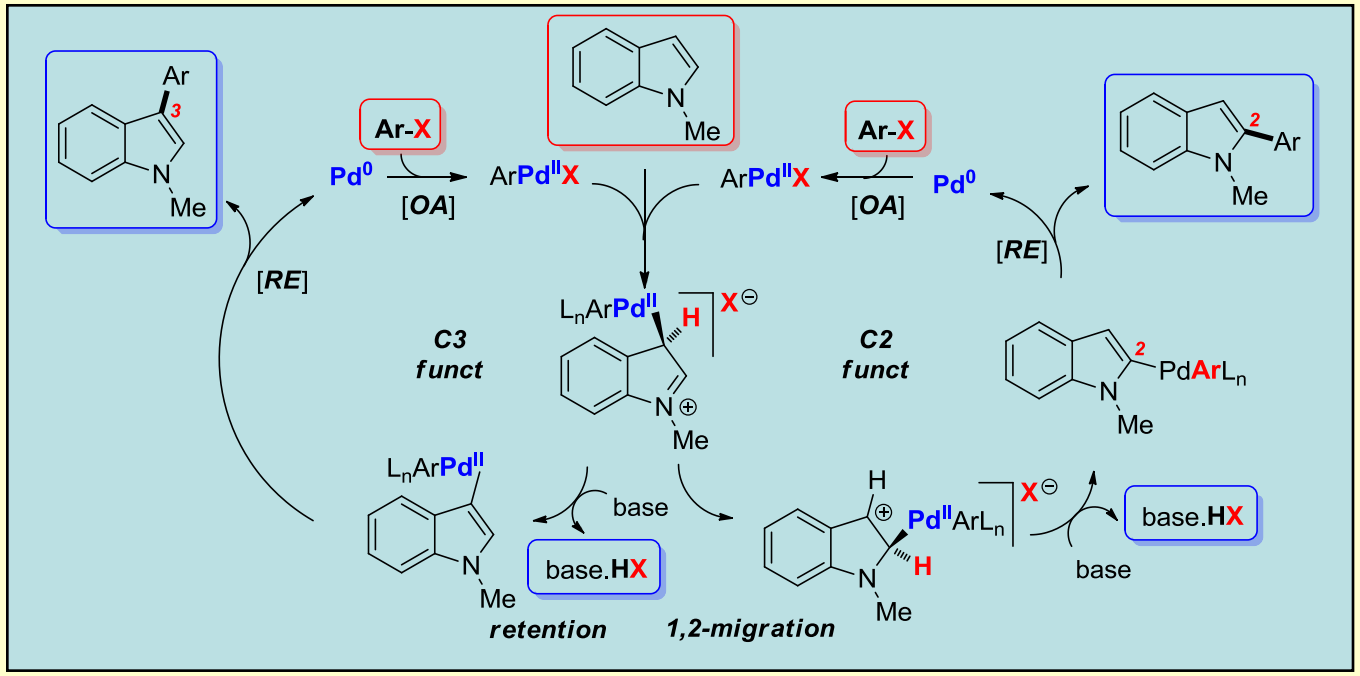


- ***N-SEM indoles & pyrazoles ↔ ArI (CH/CX, Pd):***
  - Sames *J. Am. Chem. Soc.* **2009**, *131*, 3024 (DOI)
  - Sames *Org. Lett.* **2006**, *8*, 1979 (DOI):



Mechanism – *S_EAr by X-Pd-Ar → reductive elimination*

- ***CH activation:*** electrophilic palladation by **Ar-Pd^{II}-X (**from OA of **Pd^0** to **Ar-X**)
  - Sames *J. Am. Chem. Soc.* **2005**, *127*, 8050 (DOI)
  - ***choice of base:*** MgO → ***C2*** product *cf.* $Mg(HMDS)_2$ → ***C3*** product



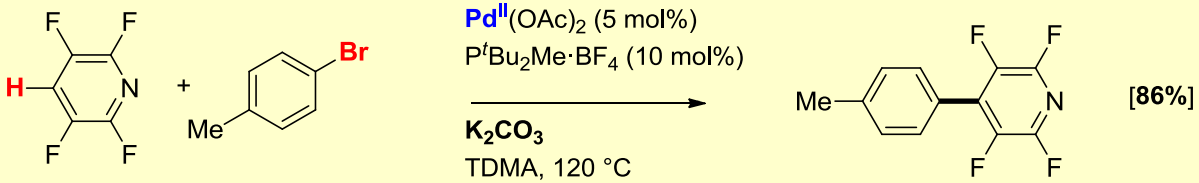
NB. 7 × related papers by Dalibor Sames have been retracted as 'irreproducible..'

- Sames *J. Am. Chem. Soc.* **2002**, *124*, 13372 (DOI); Sames *Org. Lett.* **2003**, *5*, 3607 (DOI); Sames *J. Am. Chem. Soc.* **2003**, *125*, 5274 (DOI); Sames *J. Am. Chem. Soc.* **2003**, *125*, 10580 (DOI); Sames *J. Am. Chem. Soc.* **2004**, *126*, 13244 (DOI); Sames *J. Am. Chem. Soc.* **2005**, *127*, 3648 (DOI); Sames *J. Am. Chem. Soc.* **2005**, *127*, 5284 (DOI)

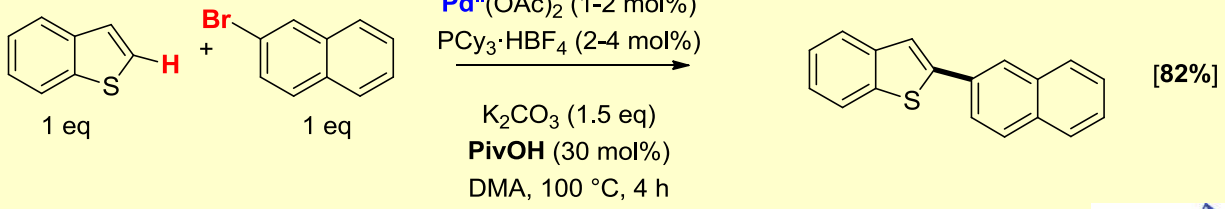
- ***CH activation by σ-metathesis metalation more likely for other heterocycles (e.g. azoles at C2)***

Direct CH/CX arylation – *other heterocycles*

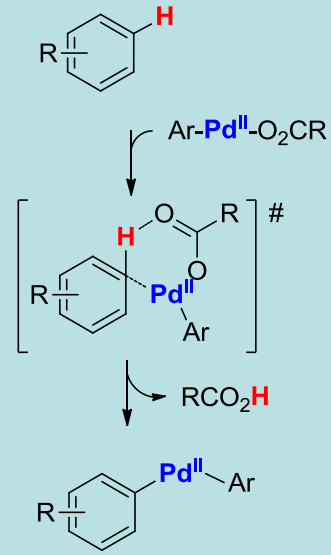
- ***(perfluoro)benzenes ↔ ArBr (CH/CX, Pd):***
  - Fagnou *J. Am. Chem. Soc.* **2006**, *128*, 8754 (DOI):



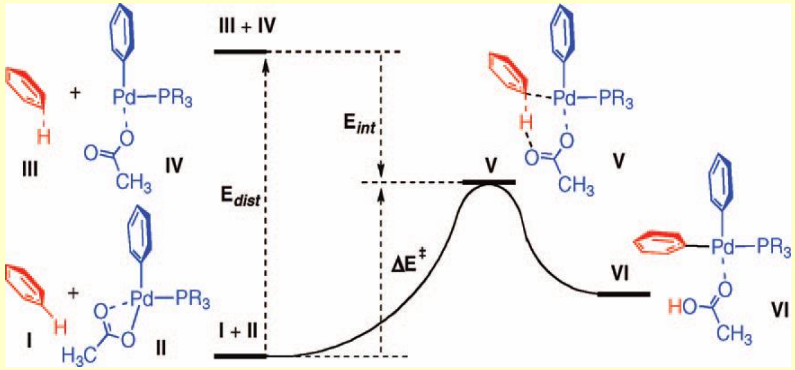
- ***thiophenes, benzothiophenes, furans, pyrroles, imidazoles, thiazoles, indolizines ↔ ArBr (CH/CX, Pd):***
  - Fagnou *J. Am. Chem. Soc.* **2008**, *130*, 10848 (DOI) & *J. Org. Chem.* **2009**, *74*, 1826 (DOI):



CH activation
carbonate or carboxylate ligand acts a 'proton shuttle':

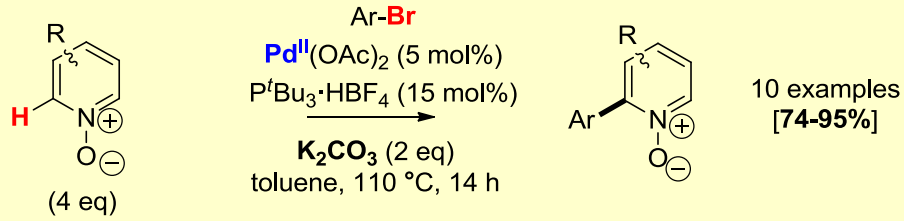


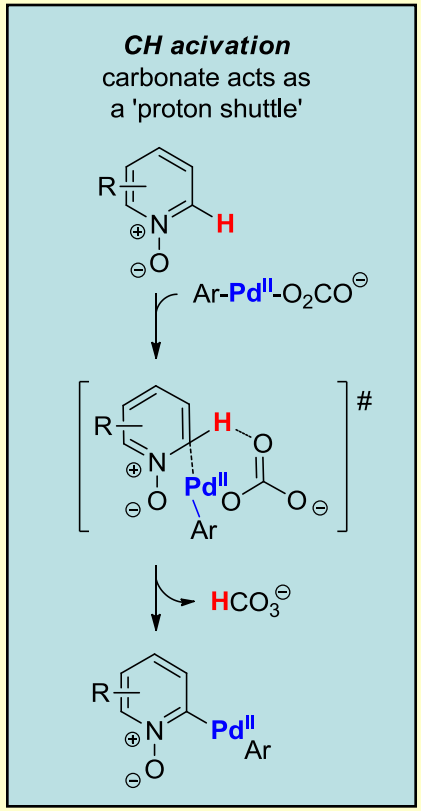
- ***CH activation:*** σ-metathesis palladation by **Ar-Pd^{II}-OCOR**
  - pivalic acid (PivOH) as proton shuttle – lowers TS #energy:
  - Fagnou *J. Am. Chem. Soc.* **2006**, *128*, 16496 (DOI)
  - Fagnou *J. Am. Chem. Soc.* **2008**, *130*, 10848 (calculations) (DOI):
  - Fagnou *J. Org. Chem*. **2010**, *75*, 1047 (Cl as directing/blocking group) (DOI)



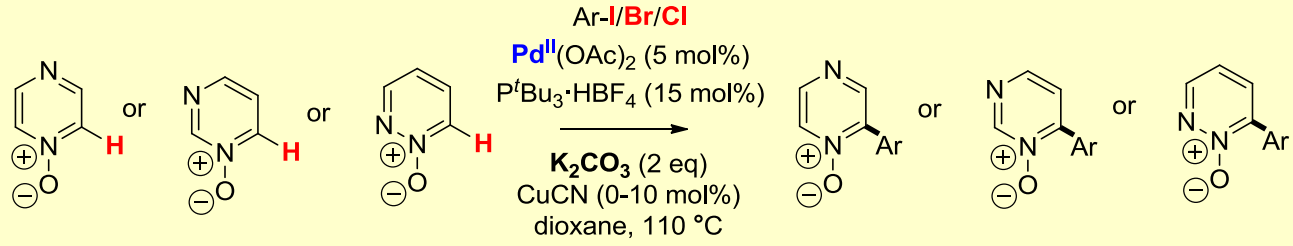
Direct CH/CX arylation – *azine-N-oxides at C2*

- ***pyridine-N-oxides ↔ ArBr (CH/CX, Pd):***
  - Fagnou *J. Am. Chem. Soc.* **2009**, *131*, 3291 (DOI) & *Org. Lett.* **2009**, *11*, 1357 (DOI) & *Tetrahedron* **2009**, *65*, 3155 (DOI) & *J. Am. Chem. Soc.* **2005**, *127*, 18020 (DOI); @ benzylic positions: Fagnou *J. Am. Chem. Soc.* **2008**, *130*, 3266 (DOI); *cf.* alkenylation: Chang *J. Am. Chem. Soc.* **2008**, *130*, 9254 (DOI) .
  - ***CH activation:*** σ-metathesis palladation





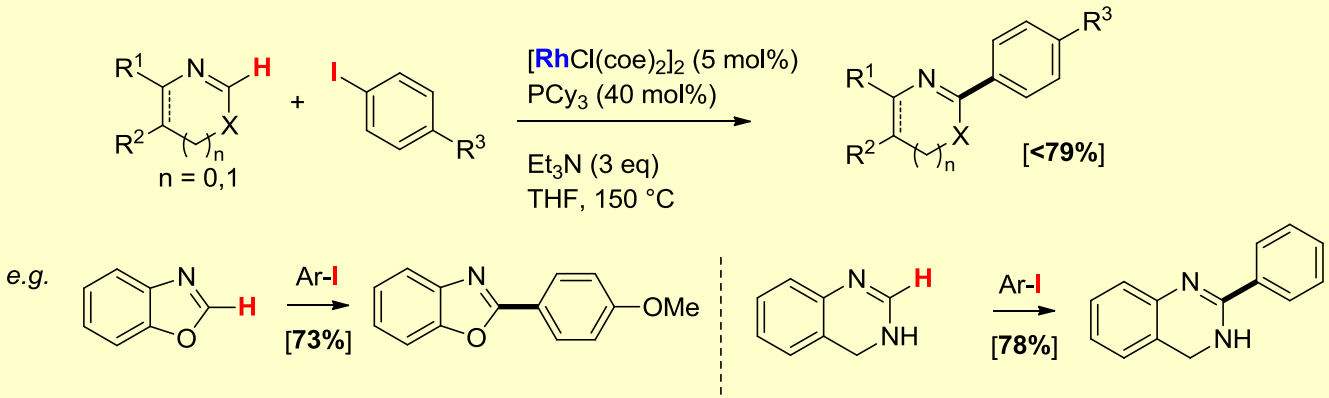
- ***diazine-N-oxides ↔ ArX (CH/CX, Pd):***
  - Fagnou *Angew. Chem. Int. Ed.* **2006**, *45*, 7781 (DOI)



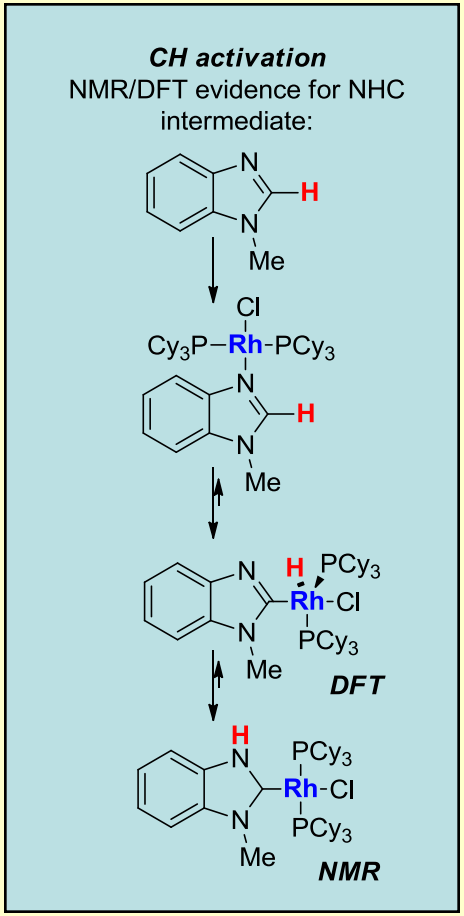
- ***CH activation:*** σ-metathesis palladation by **Ar-Pd^{II}-OCO$_2^-$**
  - Fagnou *Aldrichimica Acta* **2007**, *40(2)*, 35 (DOI)

Direct CH/CX arylation - *1,3-diazines at C2*

- ***1,3-heterocycles (azines & azoles) ↔ ArI (CH/CX, Rh):***
  - Ellman *Org. Lett.* **2004**, *6*, 35 (DOI), Ellman *J. Am. Chem. Soc.* **2008**, *130*, 2493 (DOI)

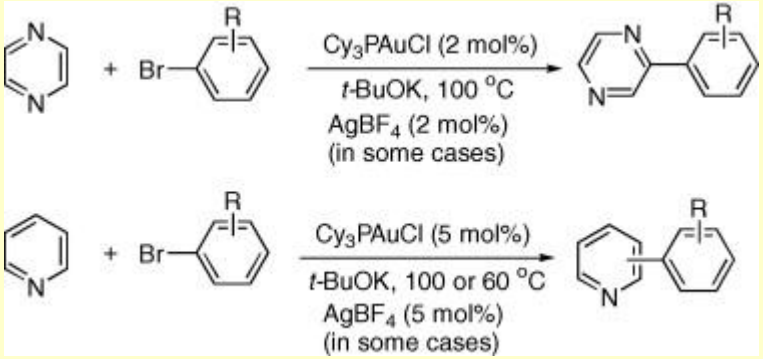


- ***CH activation:*** NHC rhodation at C of the C=N function:
  - see: Ellman *J. Am. Chem. Soc.* **2006**, *128*, 2452 (DOI)
  - Mechanism appears to operate with both electron rich (azole) and defficient (azine) systems
  - FG compatibility probably less wide than Cu and Pd based catalysis.

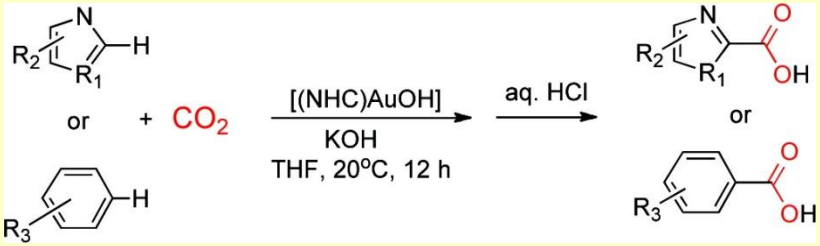


Direct CH/CX arylation – *pyridines & pyrazines at C2*

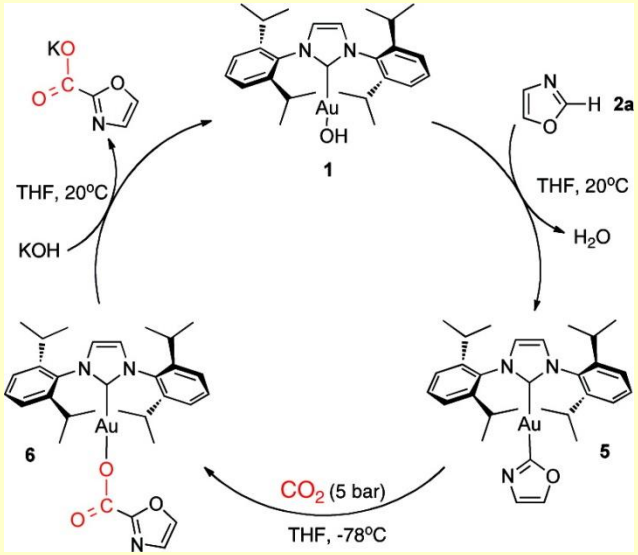
- ***pyridines & pyrazines ↔ ArI (CH/CX, Au):***
  - see: Hua *Tet. Lett.* **2009**, *50*, 1478 (DOI)
  - Electron deficient Ar-Br require Ag^{I} additive
  - yields often moderate; mixtures of *ortho, meta* and *para* in case of pyridine



- ***Au^{I} also catalyses the carboxylation of azoles:***
  - see: Nolan *J. Am. Chem. Soc.* **2010**, *132*, 8858 (DOI)

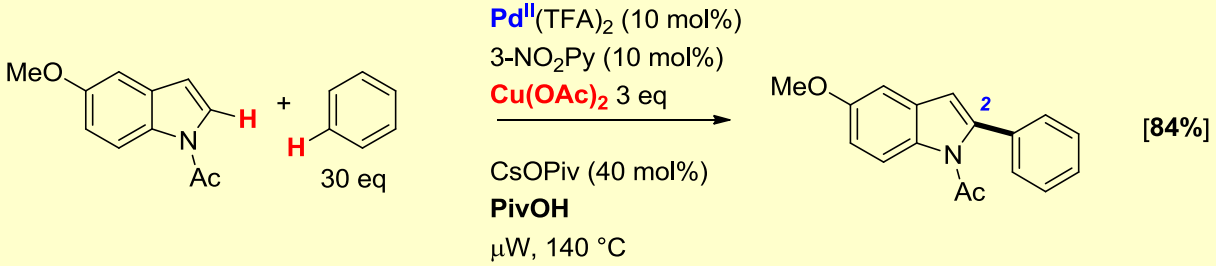


MECHANISM

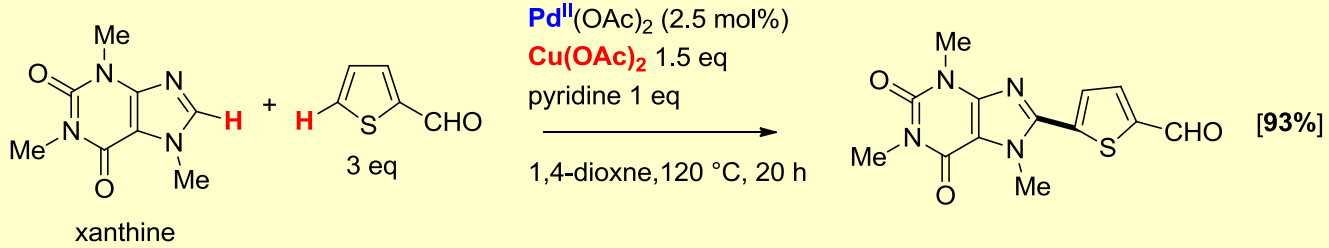


Direct CH/CH arylation – *Ar-H ↔ Ar'-H coupling*

- ***N-Ac-indoles ↔ benzene (CH/CH, Pd + Ox):***
  - *1st example* - orthogonal electrophilic palladation of indole & σ-metathesis palladation of benzene
  - Fagnou *Science* **2007**, *316*, 1172 (DOI) & *J. Am. Chem. Soc.* **2007**, *129*, 12072 (DOI) :



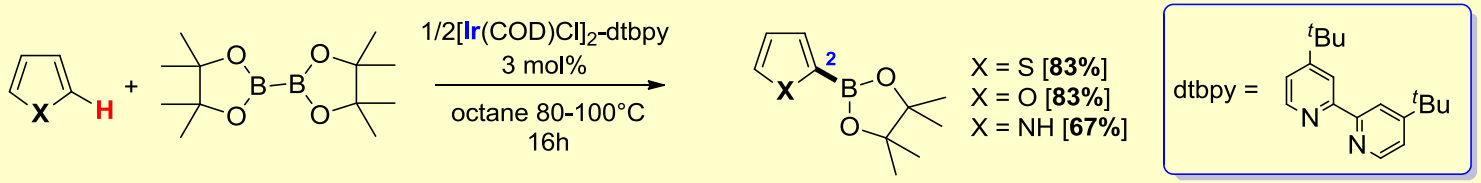
  - *Subsequently*, several others: Sanford *J. Am. Chem. Soc.* **2009**, *131*, 9651 (benzoquinone as oxidant - mechanisic insight) (DOI) & Fagnou *J. Org. Chem.* **2008**, *73*, 5022 (DOI); DeBoef *Tet. Lett*. **2008**, *49*, 4050 (DOI); Fagnou *Organometallics* **2008**, *27*, 4841 (DOI); Buchwald *Org. Lett.* **2008**, *25*, 5973 (DOI); Sanford *J. Am. Chem. Soc.* **2007**, *129*, 11904 (DOI); DeBoef *Org. Lett*. **2007**, *9*, 3137 (DOI); You *Organometallics* **2007**, *26*, 4869 (DOI); Shi *J. Am. Chem. Soc.* **2007**, *129*, 7666 (DOI)
  - *e.g.* You *J. Am. Chem. Soc*. **2010**, *132*, 1822 (DOI).



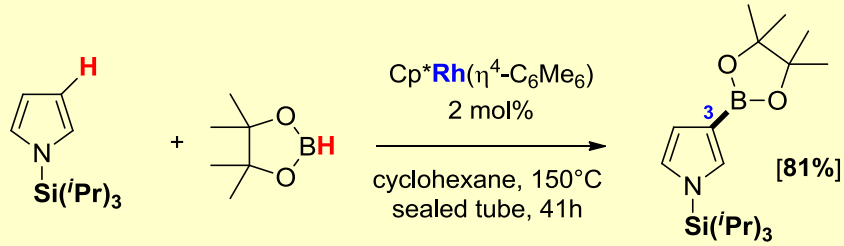
- ***However, there still remain serious deficiencies vis-à-vis substrate scope, low turnover numbers and inability to rationally tune selectivity…***

Direct CH/BX borylation – *pyrroles at C2 & C3*

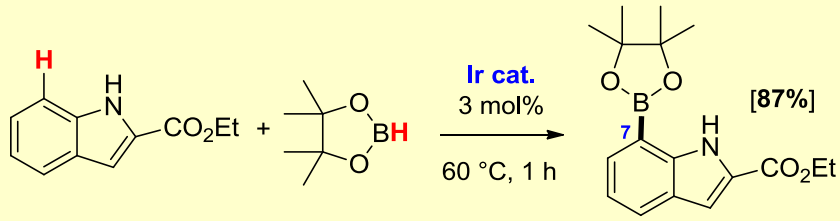
- ***NH-pyrroles, thiophenes & furans ↔ diborons/boranes (CH/BX, Ir):***
  - Hartwig *Tet. Lett.* **2002**, *43*, 5649 (DOI)
  - directed to *C3* by *C2* ester by silica supported Ir cat Sawamura *J. Org. Chem.* **2010**, *75*, 3855 (DOI)



- ***N-TIPS-pyrroles at C3 ↔ boranes (CH/BH, Rh):***
  - steric control of regioselectivity - lateral protection
  - Smith *Org. Lett.* **2001**, *3*, 2831 (DOI)



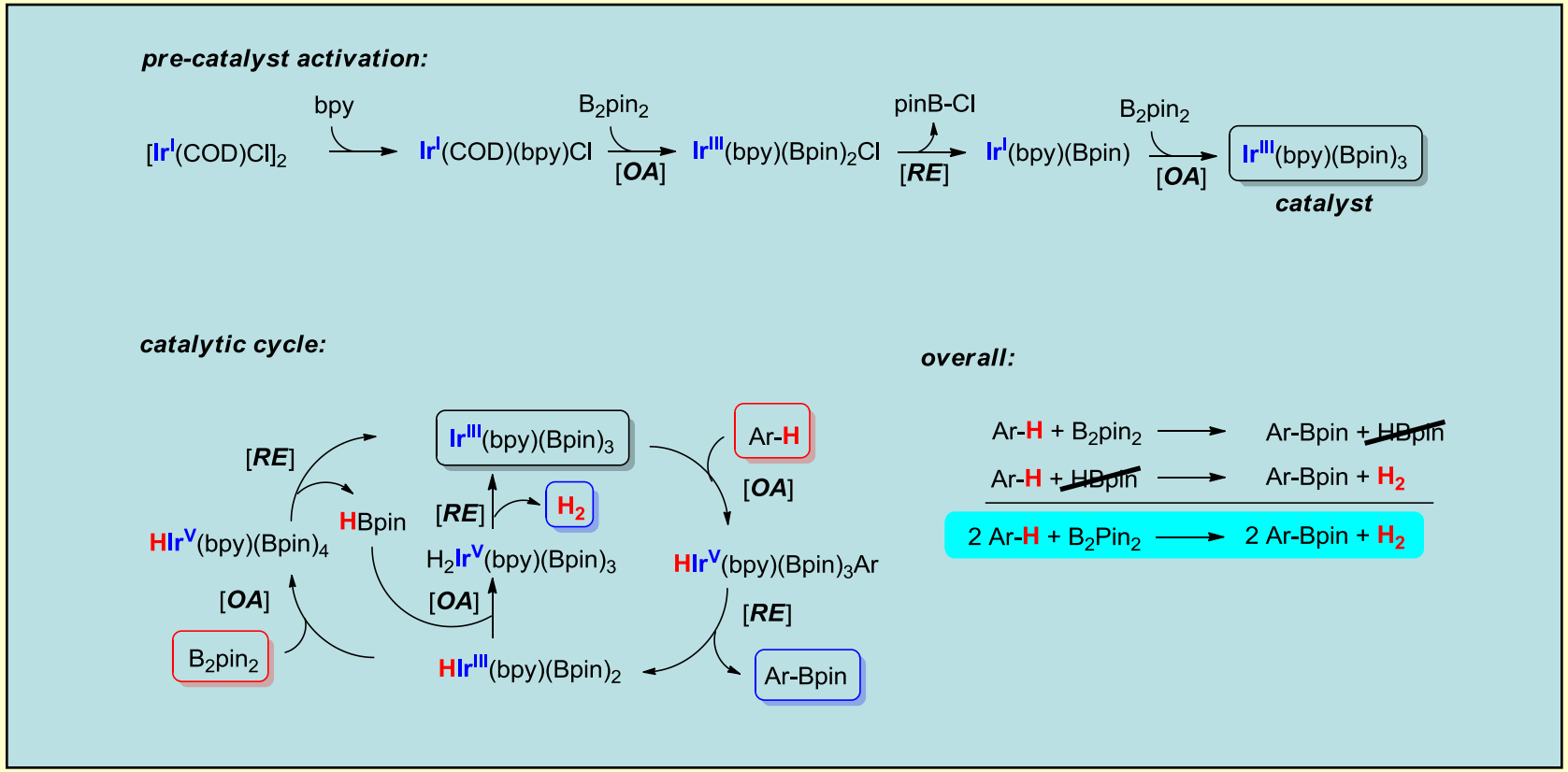
- ***2-substituted N-H-indoles at C7 ↔ boranes (CH/BH, Ir):***
  - control of regioselectivity by N-Ir coordination?
  - Smith *J. Am. Chem. Soc.* **2006**, *128*, 15552 (DOI)



- ***benzene derivatives at least hindered positions ↔ boranes (CH/BH, Ir & Fe):***
  - *e.g.* one-pot *meta* borylation/oxidation → ***phenols***: Smith *J. Am. Chem. Soc.* **2003**, *125*, 7792 (DOI); Hartwig *J. Am. Chem. Soc.* **2007**, *129*, 15434 (DOI); directing effect of silyl groups: Hartwig *J. Am. Chem. Soc.* **2008**, *130*, 7534 (DOI); Fe_2O_3 catalysed borylation of benzene derivatives Wang *Chem. Commun.* **2010**, *46*, 3170 (DOI)

Mechanism – *oxidative addition of C-H bond: $Ir^{III} \rightarrow Ir^{V}$*

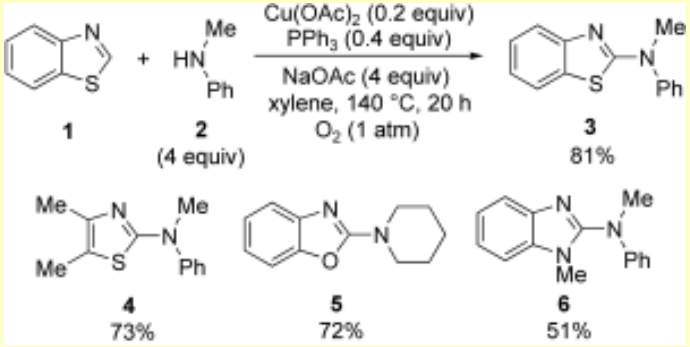
- ***CH activation:*** oxidative addition of **Ir^{III}** to C-H bond **($Ir^{III} \rightarrow Ir^{V}$)**
  - Smith *Science* **2002**, *295*, 305 (DOI); Tamura *J. Am. Chem. Soc.* **2003**, *125*, 16114 (DOI)
  - Iridium(IV) intermediate able to reductively eliminate molecular hydrogen (H_2) directly, obviating the need for a stoichiometric oxidant

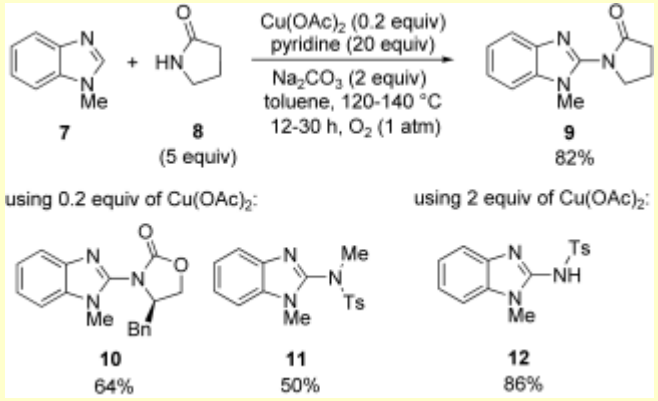


Direct CH/NH amination – *1,3-azoles at C2*

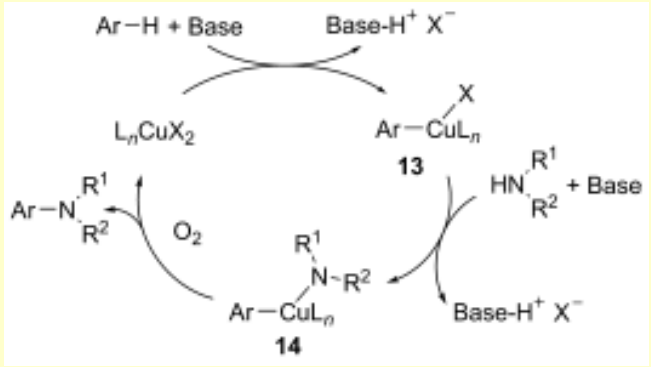
- ***Highlight:*** Armstrong *Angew. Chem. Int. Ed.* **2010**, *49*, 2282 (DOI)

- ***(benz)imidazoles, (benz)thiazoles, (benz)oxazoles ↔ amines, amides (CH/NH, Cu + Ox):***
  - Mori *Org. Lett.* **2009**, *11*, 1607 (DOI) Schreiber *Org. Lett.* **2009**, *11*, 5178 (DOI)
  - molecular oxygen (O_2) as the stoichiometric oxidant





- ***MECHANISM:***

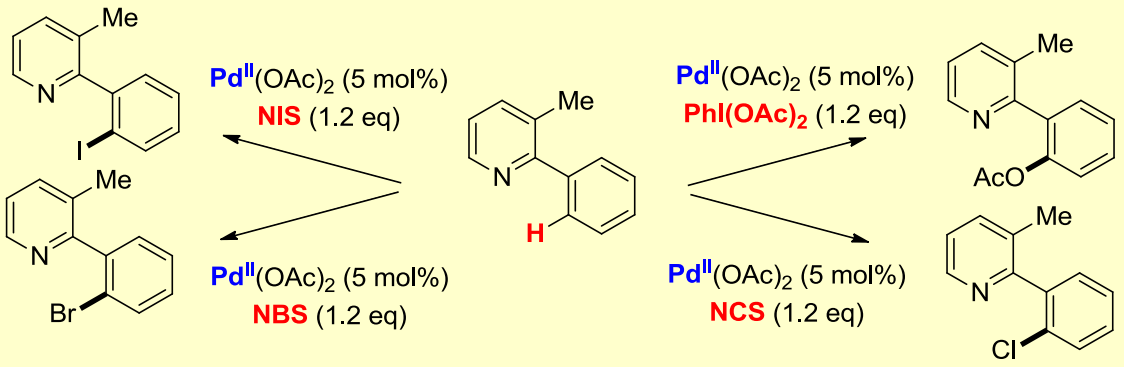


Directing group assisted C-H activation reactions

Directing group assisted CH activation – *2-pyridyl*

- ***Review of 'directing group strength':*** Sanford *J. Am. Chem. Soc.* **2008**, *130*, 13285 (DOI)

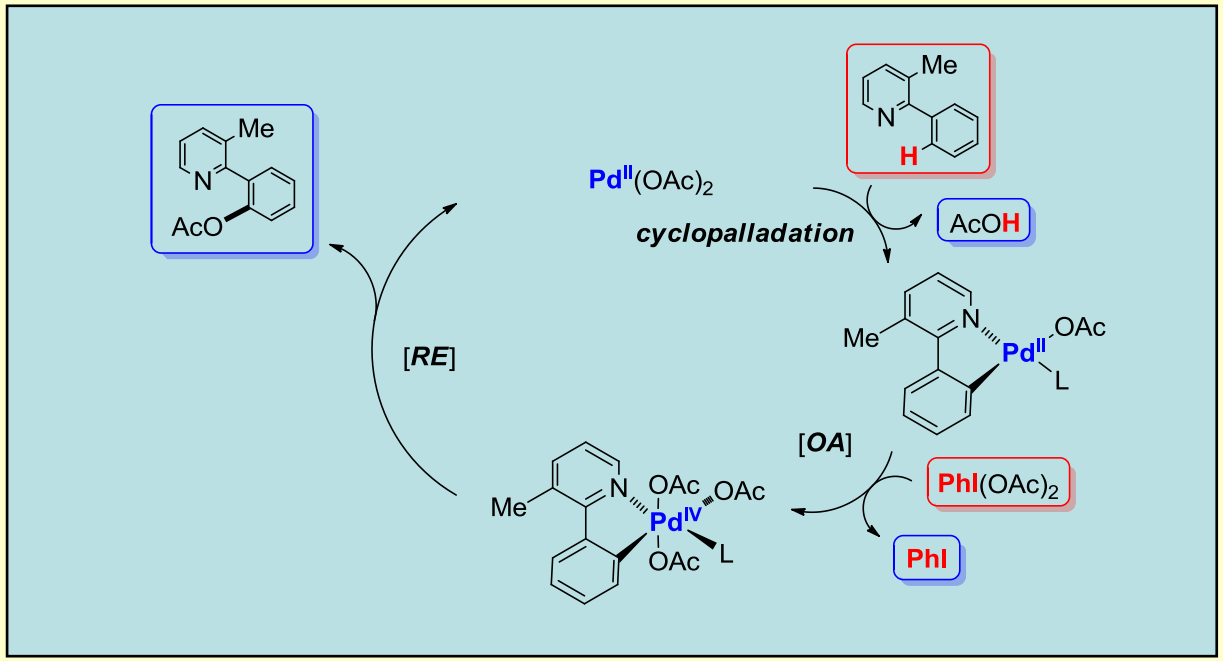
- ***2-pyridyl group as DG:*** directs *ortho*-functionalisation
  - ***acetoxylation & halogenation*** with halosuccinimides and iodonium salts ***(CH/XY, Pd):***
    - Sanford *Org. Lett.* **2005**, *7*, 4149 (***ox***) (DOI)
    - *Sandford J. Am. Chem. Soc.* **2005**, *127*, 12790 (***ox***) (DOI)
    - *Sandford Org. Lett.* **2006**, *8*, 2523 (***Hal***) (DOI)
    - ***CH activation:*** cyclopalladation directed by coordination to pyridyl N lone paiir



Mechanism – *cyclopalladation (Pd^{II}) → oxidative addition (Pd^{IV})*

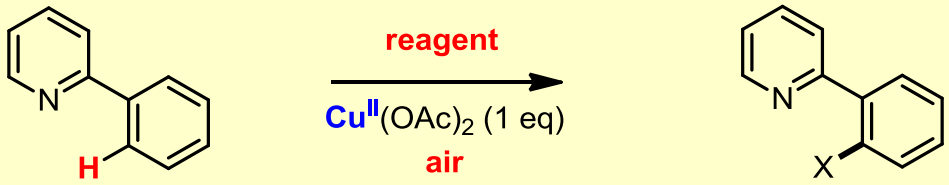
- ***CH activation:*** cyclopalladation by **$Pd^{II}(OAc)_2$**
  - Sanford *J. Am. Chem. Soc.* **2005**, *127*, 7330 (DOI) & *Organometallics* **2005**, *24*, 482 (DOI) & *J. Am. Chem. Soc.* **2005**, *127*, 12790 (DOI) & *Tetrahedron* **2006**, *62*, 2439 ***(review)*** (DOI)
  - The **Ar-Pd^{II}-OAc** intermediate undergoes oxidative addition by functionalising reagents
  - a **Pd^{II}** ↔ **Pd^{IV}** catalytic cycle:

- ***e.g. acetoxylation:***



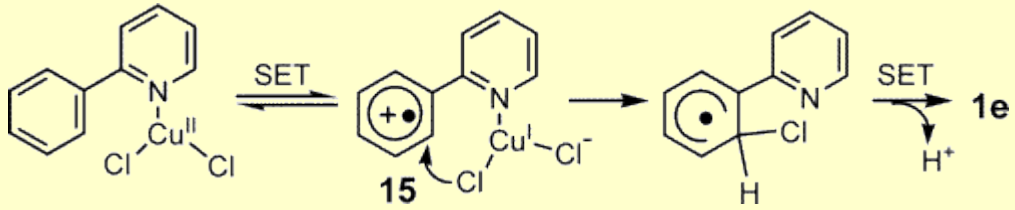
Directing group assisted CH activation – *2-pyridyl*

- ***2-pyridyl group as DG:*** directs *ortho*-functionalisation
  - ***acetoxylation, halogenation & other oxidative functionalisations*** with various oxidants ***(CH/XY, Cu):***
    - Yu *J. Am. Chem. Soc.* **2006**, *128*, 6790 (DOI)



reagent	X	yield
$Br_2CHCHBr_2$	Br	65%
I_1	I	61%
TMSCN	CN	67%
$TsNH_2$	TsNH	74%
PhSH	PhS	40%
MeSSMe	MeS	51%
H_2O	OH	22%

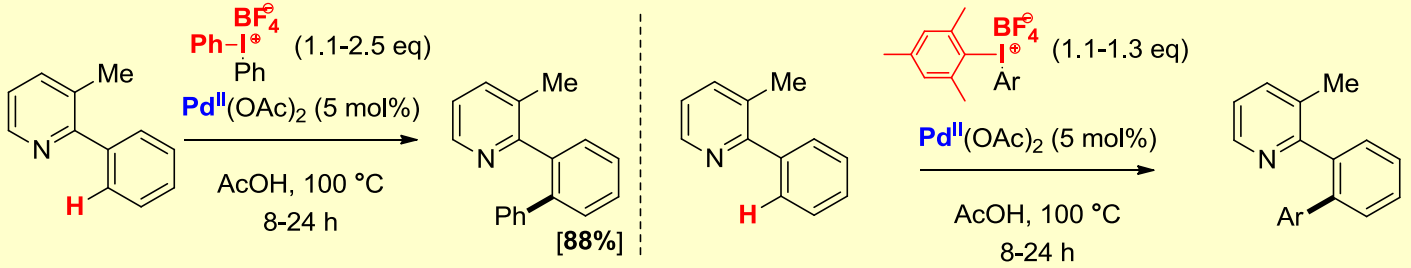
    - ***CH activation :*** 'single electron transfer (SET) from the aryl ring to the coordinated Cu^{II} leading to the cation−radical intermediate **15** is the rate-limiting step. The observed *ortho*-selectivity is explained by an intramolecular anion transfer from a nitrogen-bound Cu^{I} "ate" complex **15.'**



  - ***sulfonylation*** with arylsulfonyl chlorides ***(CH/SX, Pd):***
    - Dong *J. Am. Chem. Soc.* **2009**, *131*, 3466 (DOI)
    - C-S bond formation

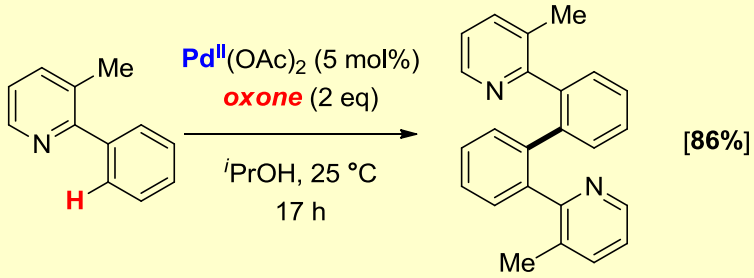
Directing group assisted CH activation – *2-pyridyl*

- ***2-pyridyl group as DG:*** directs *ortho*-functionalisation
  - ***arylation*** with aryl iodonium salts ***(CH/CX, Pd):***
    - Sanford *J. Am. Chem. Soc.* **2005**, *127*, 7330 (DOI) & *Organometallics* **2005**, *24*, 482 (DOI); *benzoquinone* as oxidant: Sanford *J. Am. Chem. Soc.* **2007**, *129*, 11904 (DOI); *cf.* Fe-catalysed: Nakamura *J. Am. Chem. Soc.* **2008**, *130*, 5858 (DOI); *cf.* aniline as director: Buchwald *Org. Lett.* **2008**, *10*, 2207 (DOI).
    - ***CH activation:*** cyclopalladation



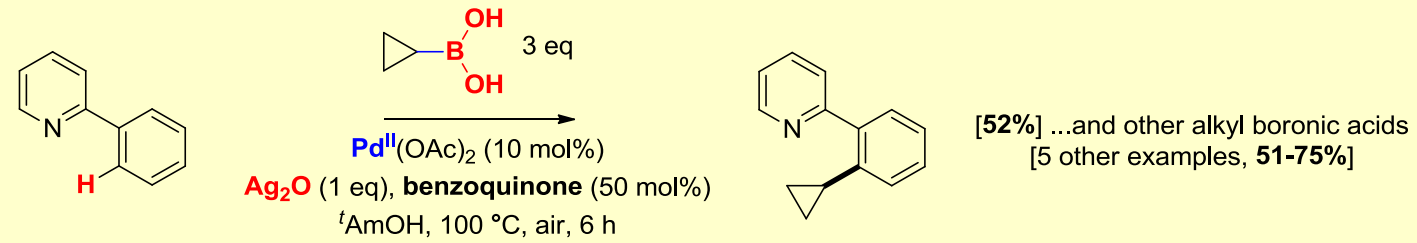
Ar = Ph [**85%**], *p*-$CF_3C_6H_4$ [**87%**], *p*-$MeOC_6H_4$ [**81%**], *o*-Tol [**72%**]

  - ***oxidative dimerisation (CH/CH, Pd + Ox):***
    - Sanford *J. Am. Chem. Soc.* **2006**, *128*, 14047 (DOI)
    - ***CH activation:*** cyclopalladation

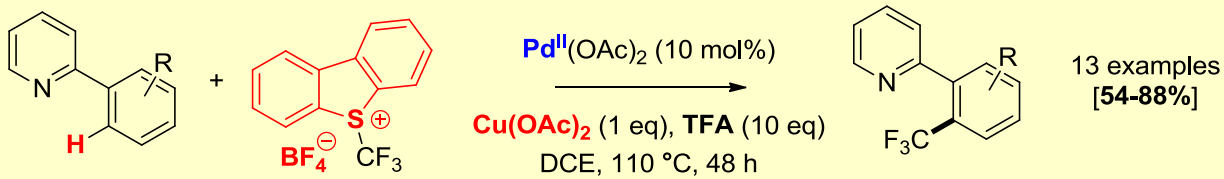


Directing group assisted CH activation – *2-pyridyl*

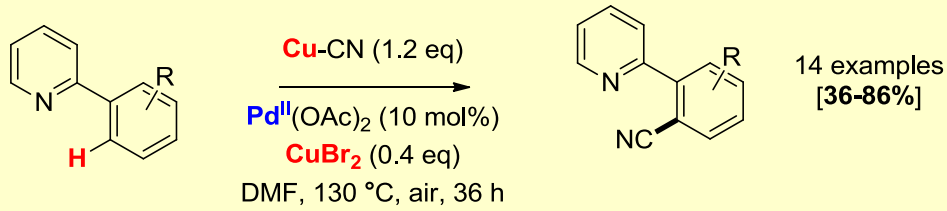
- ***2-pyridyl group as DG:*** directs *ortho*-functionalisation
  - ***alkylation*** with boronic acids ***(CH/CM, Pd + Ox):***
    - Yu *J. Am. Chem. Soc.* **2006**, *128*, 12634 (DOI); Yu *Org. Biomol. Chem.* **2006**, 4041 (review) (DOI)
    - also using **R_4Sn** as nucleophile: Yu *J. Am. Chem. Soc.* **2006**, *128*, 78 (DOI)



  - ***Trifluoromethylation*** with trifluorosulfonium salts ***(CH/CX, Pd + Ox):***
    - Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3648 (DOI); see also: Sandford , *J. Am. Chem. Soc.* **2010**, *132*, 2878 (mech) (DOI).



  - ***cyanation*** with copper(I) cyanide ***(CH/CM, Pd + Ox):***
    - Cheng *Org. Lett.* **2009**, *11*, 4716 (DOI)

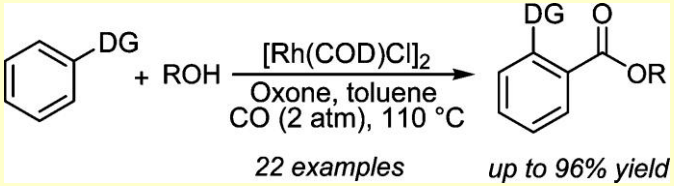


Directing group assisted CH activation – *2-pyridyl*

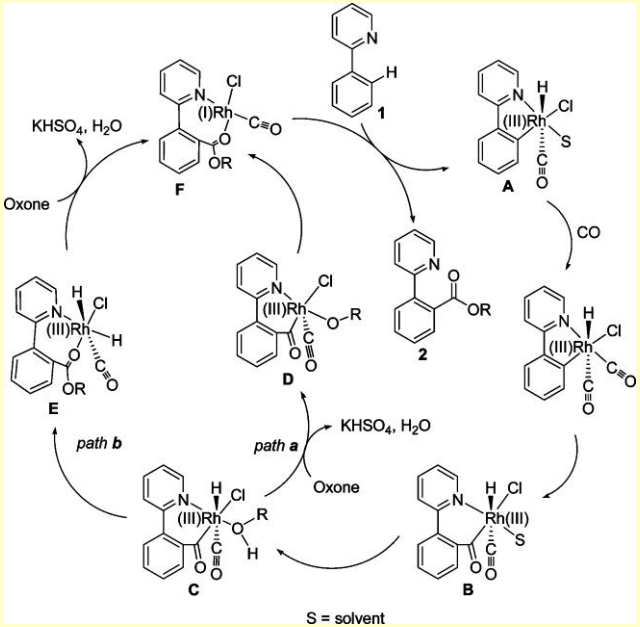
- ***2-pyridyl group as DG:*** directs *ortho*-functionalisation
  - ***alkenylation*** with alkenyl acetates ***(CH/CX, Ru):***
    - Kakiuchi *J. Am. Chem. Soc.* **2007**, *129*, 9858 (DOI)

  - ***ethoxycarbonylation*** with diethylazodicarboxylate ***(CH/CX, Pd + Ox):***
    - Yu *J. Am. Chem. Soc.* **2008**, *130*, 3304 (DOI)
    - **oxone** as stoichiometric oxidant

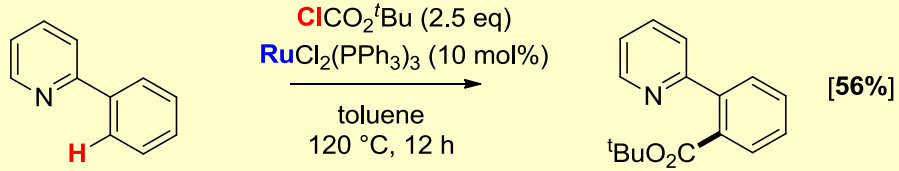
  - ***alkoxycarbonylation*** with CO & alcohols ***(CH/CX, Rh+ Ox):***
    - Zhang *J. Am. Chem. Soc.* **2009**, *131*, 729 (DOI)
    - **oxone** as stoichiometric oxidant
    - also directed by 2-pyrimidines, pyrazoles & *N*-acyl groups



MECHANISM

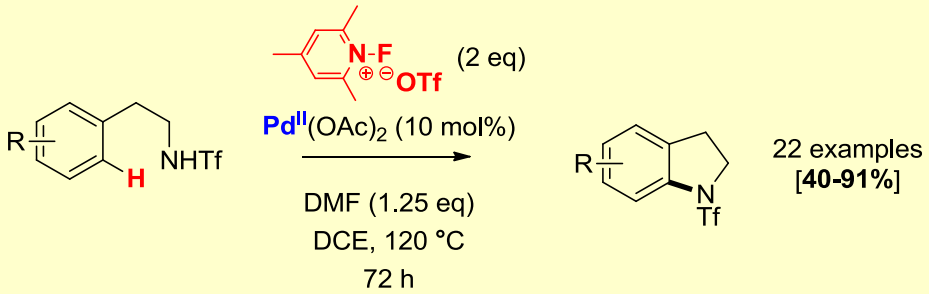


  - ***alkoxy- & aminocarbonylation*** with chloroformates & carbamoyl chlorides ***(CH/CX, Ru):***
    - Kakiuchi *J. Am. Chem. Soc.* **2009**, *131*, 2792 (DOI)



Directing group assisted CH activation – *other C-based FGs*

- ***carboxylic acid group as DG:*** directs *ortho*-functionalisation
  - ***carboxylation*** of benzoic acids with CO / NaOAc ***(CH/CX, Pd + Ox):***
    - Yu *J. Am. Chem. Soc.* **2008**, *130*, 14082 (DOI)
    - **Ag_2CO_3** as stoichiometric oxidant
  - ***alkyltion*** of benzoic acids with dibromomethane & 1,2-dichloroethane ***(CH/CX, Pd):***
    - Yu *Angew. Chem. Int. Ed.* **2009**, *48,* 6097 (DOI)
  - ***iodination*** of phenylacetic acids with IOAc ***(CH/CX, Pd):***
    - Yu *Org. Lett.* **2010**, *12,* 3140 (DOI)
- ***aminoethyl group as DG:*** directs *ortho*-functionalisation
  - ***intramolecular amination*** of *N*-acyl arylethylamines ***(CH/NH, Pd + Ox):***
    - Yu *J. Am. Chem. Soc.* **2009**, *131*, 10806 (DOI)



- ***imine group as DG:*** directs *ortho*-functionalisation
  - ***arylation*** of acetophenone imines with diarylzincs ***(CH/CM, Fe + Ox):***
    - Nakamura *Angew. Chem. Int. Ed.* **2009**, *48*, 2925 (DOI)
    - **1,2-dichloroisobutane** (**DCIB**) as stoichiometric oxidant

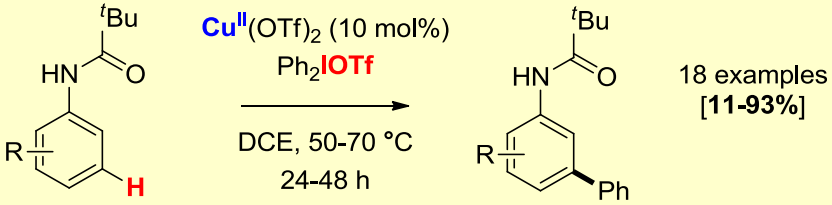
Directing group assisted CH activation – *N-based FGs*

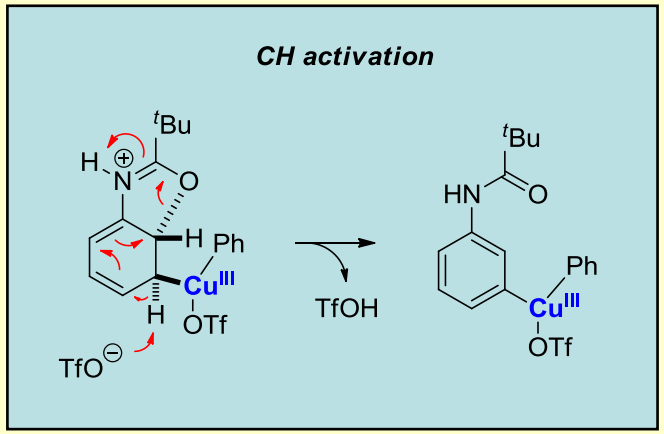
- ***urea group as DG:*** directs *ortho*-functionalisation
  - ***carboxylation*** of aniline derivatives with CO / MeOH ***(CH/CX, Pd):***
    - Booker-Milburn *Angew. Chem. Int. Ed.* **2009**, *48*, 1830 (DOI)

- ***N-acyl group as DG:*** directs *ortho*-functionalisation
  - ***arylation*** of aniline derivatives with aryliodonium salts ***(CH/CX, Pd):***
  - ***chlorination*** of aniline derivatives with NCS ***(CH/CX, Pd):***
    - Bedford *Chem. Commun.* **2010**, 3095 (solvent free) (DOI)

  - ***alkenylation*** of aniline derivatives with alkenes ***(CH/CH, Rh + Ox):***
    - Glorius *J. Am. Chem. Soc.* **2010**, *132*, 9982 (DOI)
    - **$Cu^{II}(OAc)_2$** & **air** as oxidant, **$AgSbF_6$** as co-catalyst

- ***N-acyl group as DG:*** directs ***meta*-functionalisation**: Liu *Angew. Chem. Int. Ed*. **2009**, *48*, 7126 (Highlight) (DOI)
  - ***arylation*** of aniline derivatives with ***(CH/CX, Cu):***
    - Gaunt *Science* **2009**, *323*, 1593 (DOI)
    - Bedford *Chem. Commun.* **2010**, 3095 (solvent free) (DOI)

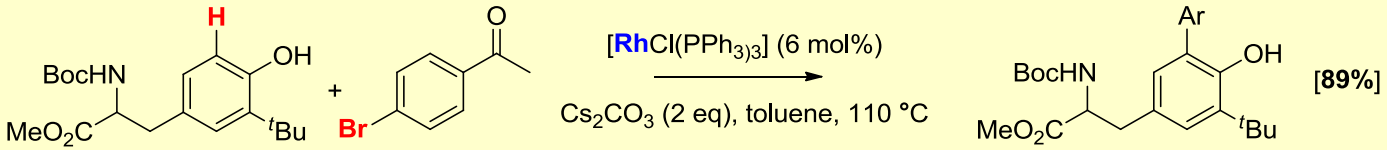




  - ***CH activation:*** possibly *via* dearomatising oxy-cupration:

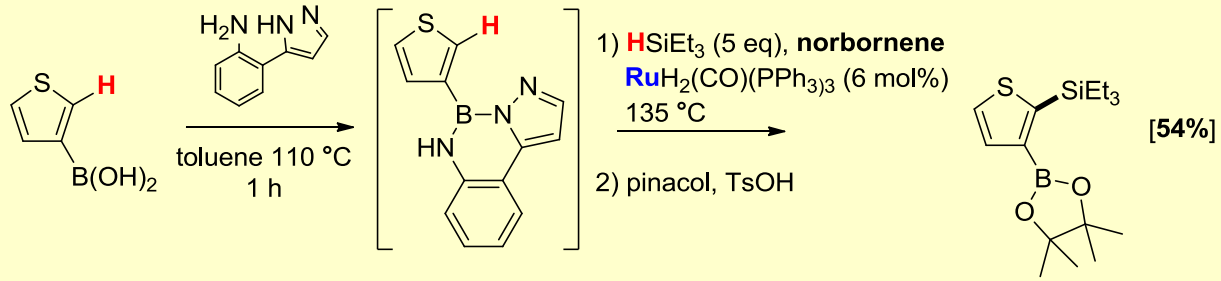
Directing group assisted CH activation – *O-based & other FGs*

- ***hydroxyl group as DG:*** directs *ortho*-functionalisation
  - ***arylation*** of phenols with aryl bromides ***(CH/CX, Rh):***
    - Bedford *Org. Biomol. Chem.* **2009**, *7*, 3119 (DOI)
    - tryosine arylation – accompanied by racemisation



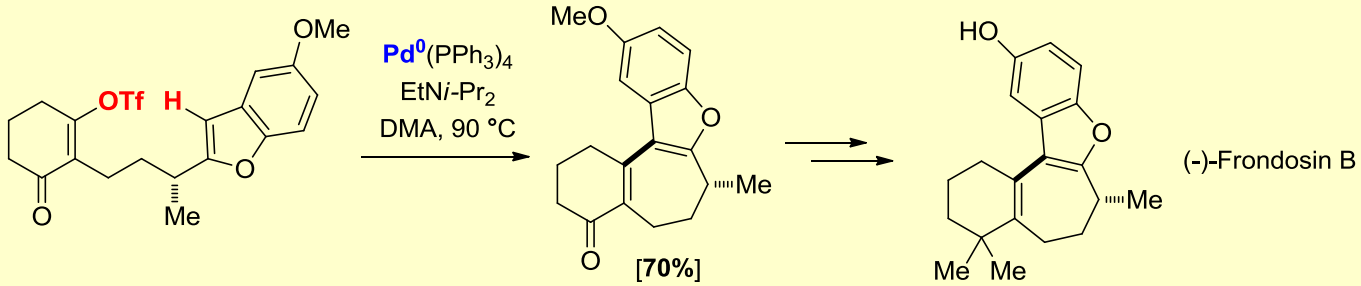
- ***O-carbamate group as DG:*** directs *ortho*-functionalisation
  - ***arylation*** of phenol derivatives with aryl iodonium salts ***(CH/CX, Pd)***
  - ***chlorination*** of phenol derivatives with NCS ***(CH/XY, Pd)***
    - Bedford *Chem. Commun.* **2010**, 3095 (DOI)

- ***functionalised boronic acid as DG:*** directs *ortho*-functionalisation
  - ***silylation*** of aryl boronic acid derivatives with silanes ***(CH/SiH, Ru):***
    - Suginome *J. Am. Chem. Soc.* **2009**, *131*, 7502 (DOI)

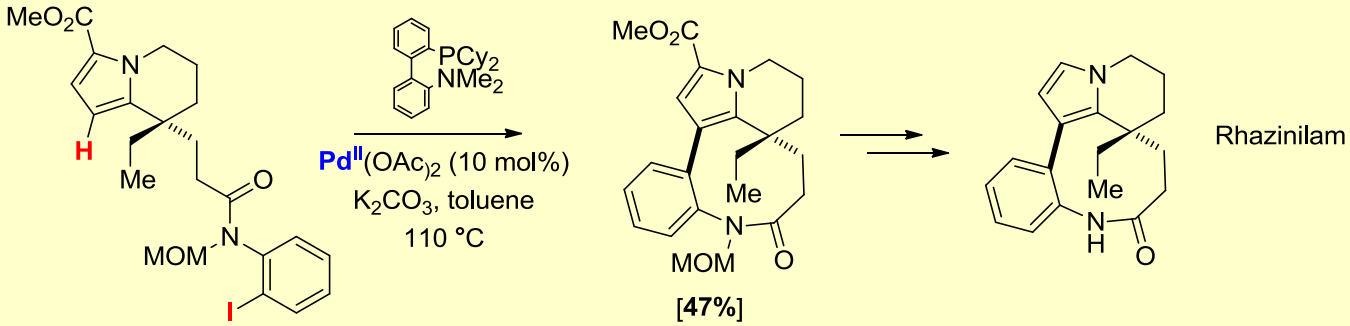


CH Activation in total synthesis

- ***Frondosin B***
  - Trauner *Angew. Chem. Int. Ed*. **2002**, *41*, 1569 (DOI)



- ***Rhazinilam***
  - Trauner *Org. Lett*. **2005**, *7*, 5207 (DOI)



Summary

- ***Catalytic C-H activation reactions:***
  - Mechanistic considerations – classification as *direct* & *directed*
  - direct metalation (*e.g. ortho* to ring heteroatoms)
  - directing group assisted metalation (*e.g. ortho* to 2-pyridyl substituent)
  - applications in synthesis