Aromatics in Synthesis

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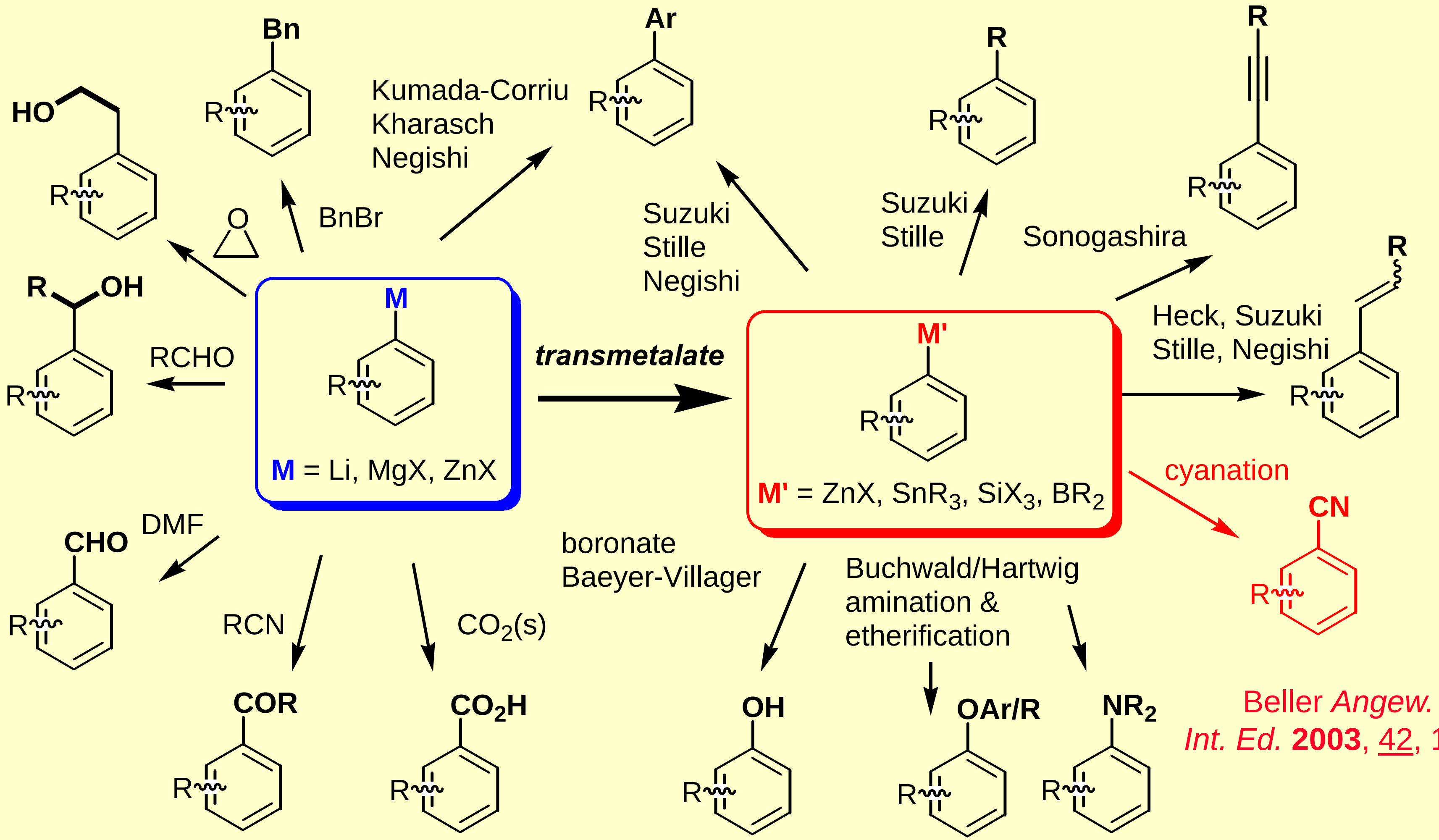
Format and scope of presentation

- ***Formation of metal aryls:***
  - Reductive metalation (Barbier conditions)
  - Halogen-metal exchange (halogen-lithium and Grignard metathesis)
  - Deprotonation [directed *ortho*-lithiation (DoM)]
- ***Transmetalation & cross-coupling reactions:***
  - Transmetalation to Cu, Zn, Sn, B, Ge, & Ce
  - Kumada-Corriu, Negishi, Stille, Suzuki, Hiyama/Denmark, Heck, Sonogashira & sp^3
- ***Buchwald/Hartwig amination & etherification:***
  - Amination of aryl chlorides
  - Biaryl ether formation
- ***Birch reduction:***
  - Reduction/alkylation
- ***'De novo' aryl synthesis reactions:***
  - Fischer carbene chemistry (Dötz reaction)
  - Cobalt mediated [2+2+2] reactions (Volhardt reaction)
  - Ring Closing Metathesis (RCM)

Utility of aryl metals - overview



Kumada-Corriu
Kharasch
Negishi

BnBr

RCHO

DMF

RCN

CO_2(s)

M = Li, MgX, ZnX

transmetalate

Suzuki
Stille
Negishi

Suzuki
Stille

Sonogashira

Heck, Suzuki
Stille, Negishi

cyanation

M' = ZnX, SnR_3, SiX_3, BR_2

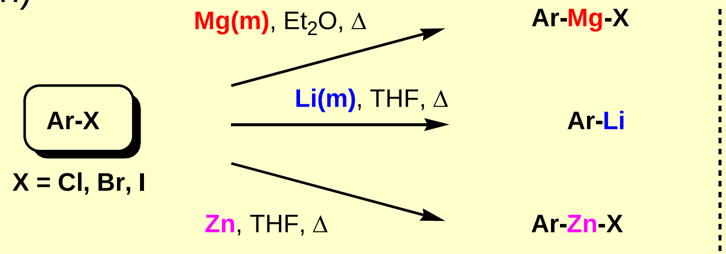
boronate
Baeyer-Villager

Buchwald/Hartwig
amination &
etherification

Beller *Angew. Chem*
Int. Ed. **2003**, 42, 1661 (**DOI**)

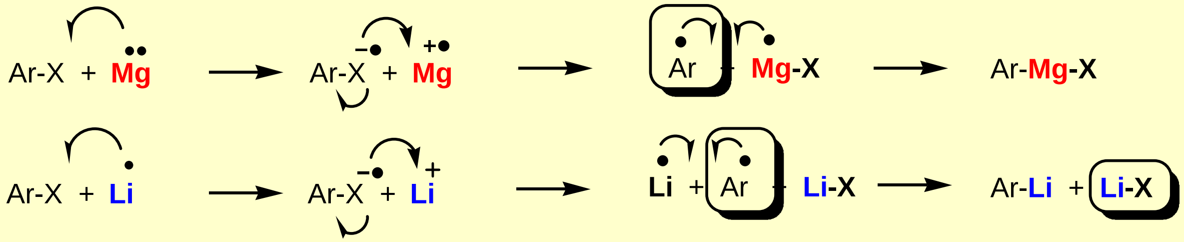
Reductive metalation

- By using an aryl halide and an activated ***free metal (Mg, Li, Zn)***
  - ***Review:*** Yus *Tetrahedron* **2003**, 59, 9255(**DOI**); Clayden 'Organolithiums: Selectivity for Synthesis' **2002** (Pergamon)

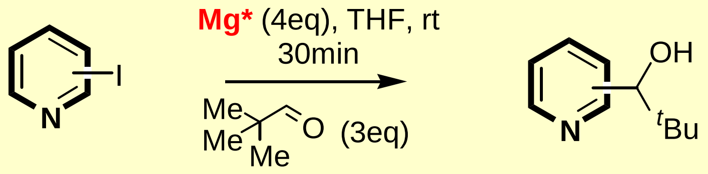


NB. alloys with 1-2% sodium often employed and/or metals with high surface area e.g. 'Reike metals'

  - ***Mechanism:*** ***S***ingle ***E***lectron ***T***ransfer (SET): Andrieux *J. Am. Chem. Soc.* **1986**, 108, 638 (**DOI**)



  - ***Features:***
    - Wurtz coupling a side reaction particularly for iodides and bromides
    - Requires elevated temperatures (*i.e.* >25 °C)
  - ***e.g. for pyridines*** (using ***Barbier in situ*** electrophile quenching)
    - Sugimoto *Tet. Lett.* **2002**, 43, 3355 (**DOI**) & *J. Org. Chem*. **2003**, 68, 2054 (**DOI**)

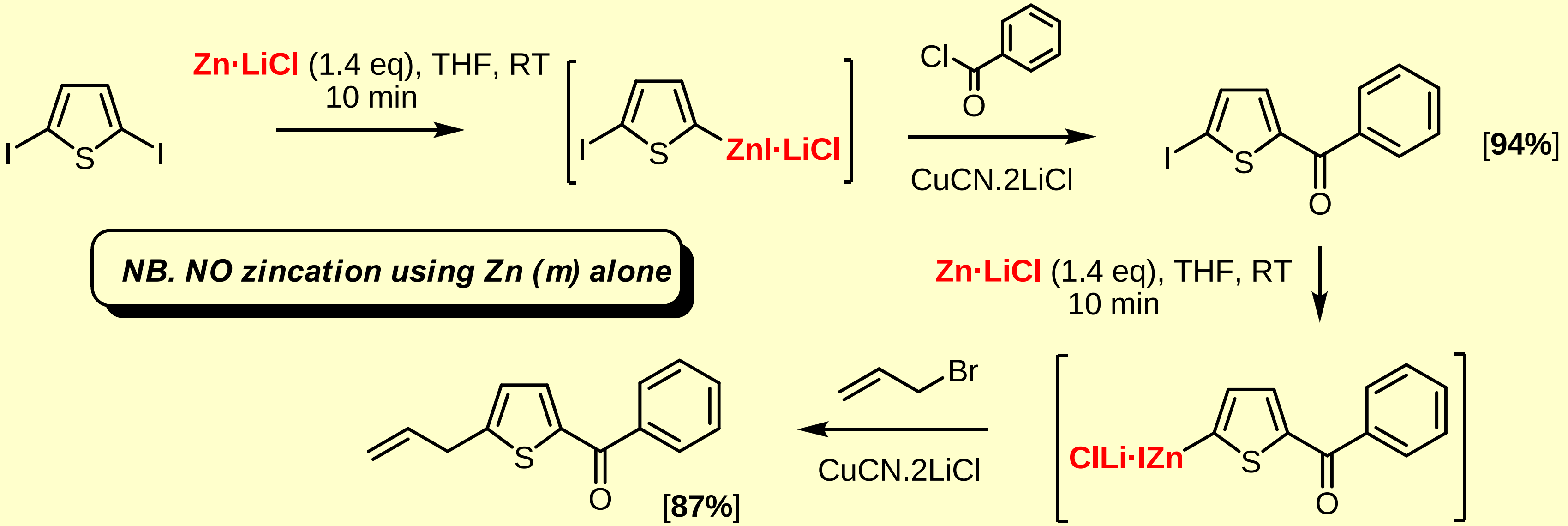


2-I [**67%**]
3-I [**73%**]
4-I [**64%**]

Mg* = activated Mg by reduction of $MgCl_2$ by Li and naphthalene in THF

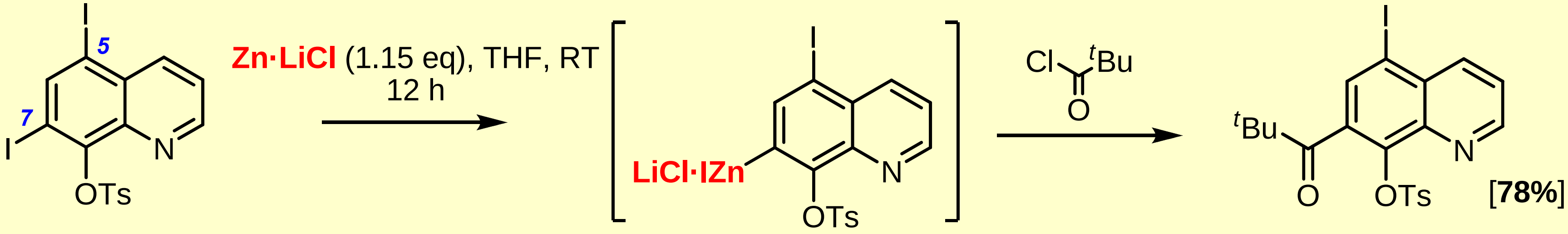
Reductive metalation – *zincation promoted by LiCl*

- ***reductive zincation promoted by LiCl:***
  - Knochel *Angew. Chem. Int. Ed.* **2006**, 45, 6040 (**DOI**)



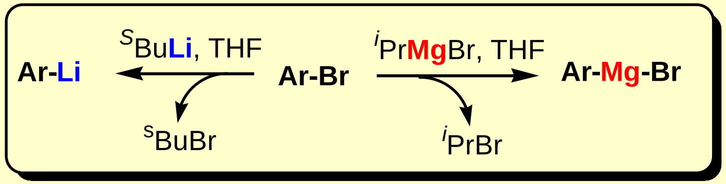
NB. NO zincation using Zn (m) alone

- ***ortho-directing affect of FGs –*** esters, ketones, aryl sulfonates, acetates, carbamates, triazenes:
  - Knochel *J. Am. Chem. Soc.* **2007**, 129, 12358 (**DOI**)



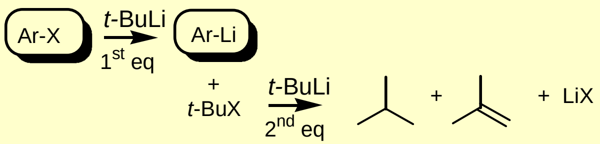
Halogen-metal exchange - *overview*

- By exchange of an aryl halide with an ***alkyl metal*** (discovered by Gilman & Wittig)
  - ***reviews:*** Schlosser *Synlett* **2007**, 3096 (**DOI**) – Hal-M exchange *and* deprotonation of heterocycles; Knochel *Chem. Comm.* **2006**, 583 (**DOI**); Schlosser *Angew. Chem. Int. Ed.* **2005**, 44, 376 (**DOI**); Yus *Tetrahedron* **2003**, 59, 9255(**DOI**); Clayden 'Organolithiums: Selectivity for Synthesis' **2002** (Pergamon); Knochel *Chem. Eur. J.* **2000**, 6, 767 (**DOI**)

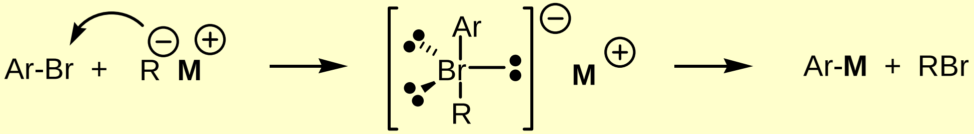


NB. use of ***2 equiv of t-BuLi*** common.

Irreversibility ensured by 2nd equiv. eliminating X^- from t-BuX:



  - ***Mechanism:*** depends on structure, for aryls halophilic displacement likely:
    - Driven by *thermodynamics*: sp^3 to sp^2 anion



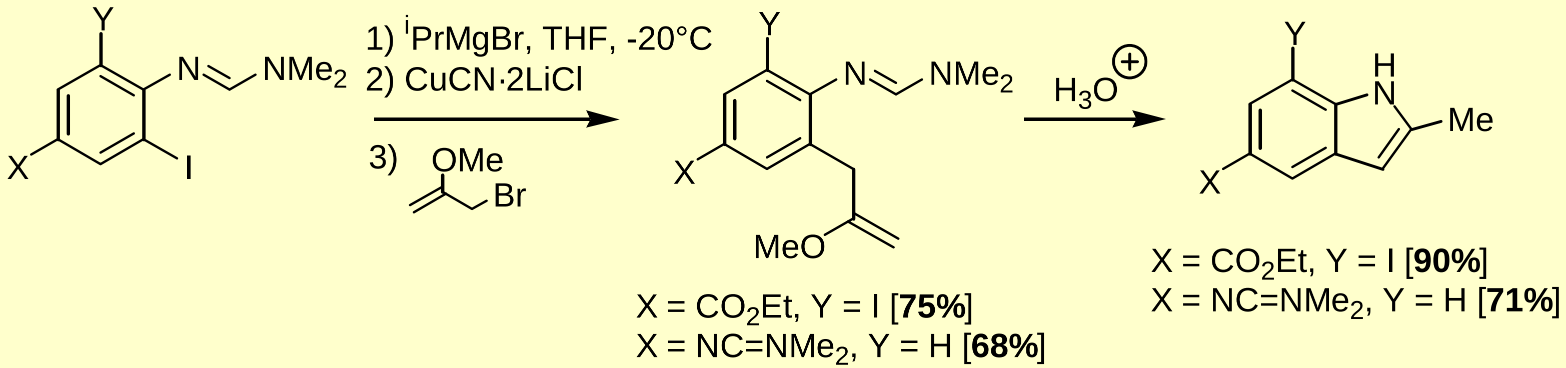
possible intermediate ate complex

    - Initial complexation of the alkyl metal to the halide supresses competitive addition
  - ***Features:***
    - Proceeds at low temperature (*e.g.* -100 °C); ***supresses addition to C=N groups & deprotonation***
    - ***Rate of exchange:*** Ar-I > Ar-Br > Ar-Cl >> Ar-F
    - ***Solvent dependent selectivity*** due to ***aggregation*** & Schlenck equilibrium (Grignard reagents):

$$2\ \mathrm{Ar\text{-}Mg\text{-}X} \rightleftharpoons \mathrm{Ar\text{-}Mg\text{-}Ar} + \mathrm{X\text{-}Mg\text{-}X}$$

Halogen-Mg exchange

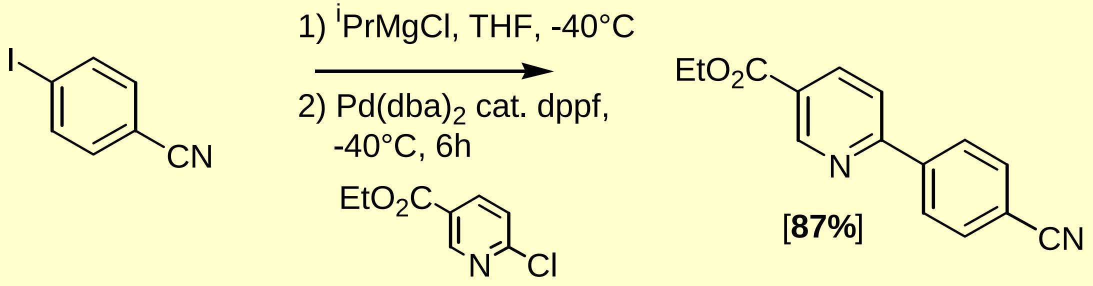
- ***^{i}PrMgBr at -40°C:***
  - ***indole synthesis:*** Knochel *Org. Lett.* **2002**, 4, 1819 (**DOI**)



X = CO_2Et, Y = I [**75%**]
X = NC=NMe_2, Y = H [**68%**]

X = CO_2Et, Y = I [**90%**]
X = NC=NMe_2, Y = H [**71%**]

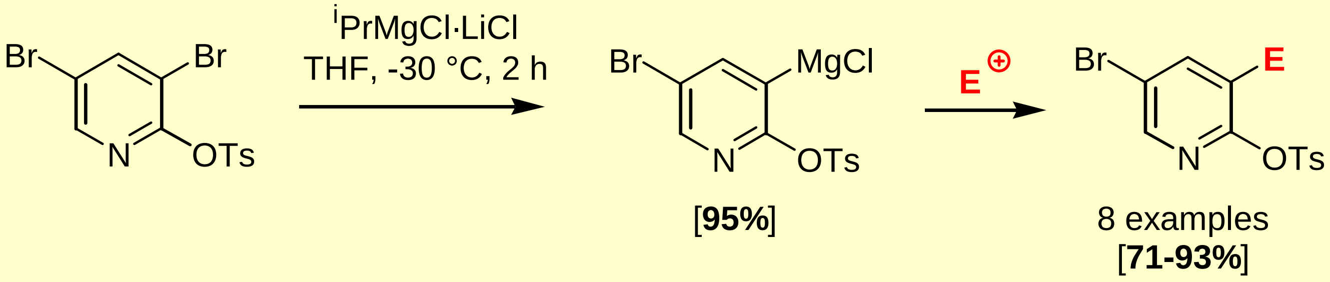
  - ***one-pot Mg-halogen exchange / Kharasch cross-coupling:***
  - Quéguiner *Tetrahedron* **2002**, 58, 4429 (**DOI**); Knochel *Synlett* **2002**, 1008 (**DOI**)



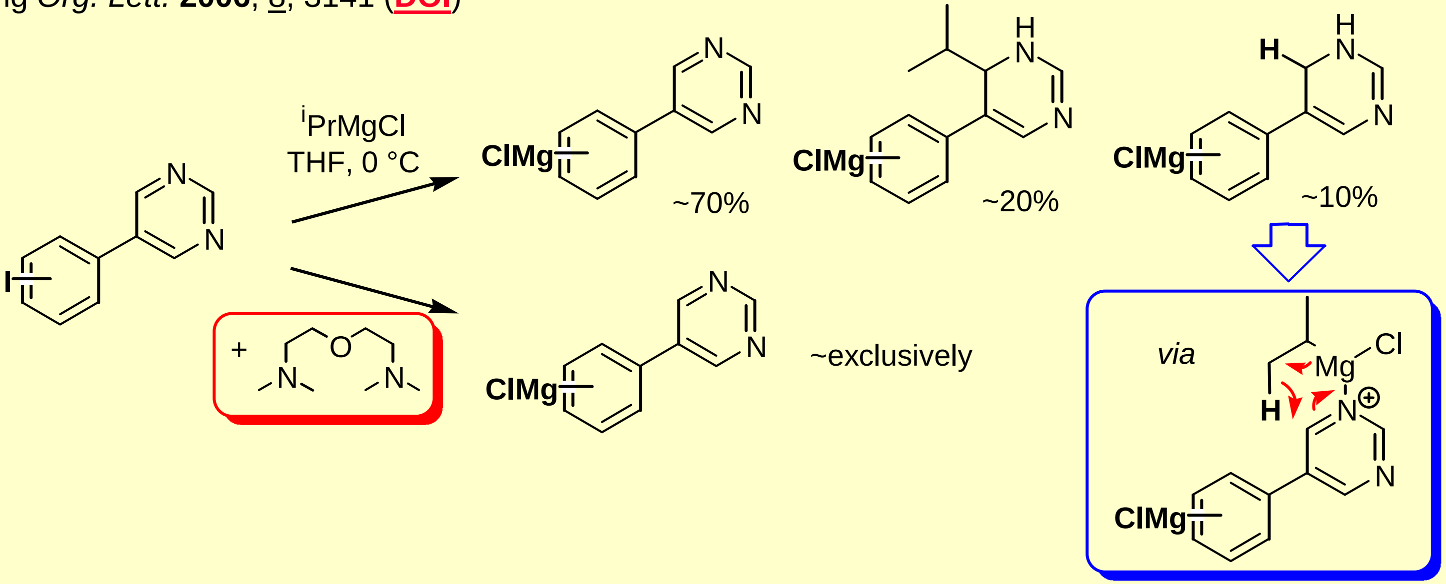
[**87%**]

Halogen-Mg exchange – *advances*

- ***LiCl acceleration:*** *^{i}PrMgCl·LiCl participates in* ***Br-Mg exchange*** *faster than ^{i}PrMgCl itself:*
    - Knochel *Angew. Chem. Int. Ed.* **2004**, 43, 3333 (**DOI**) & *Org. Lett.* **2004**, 6, 4215 (**DOI**) & *Chem. Commun.* **2005**, 543 (**DOI**); & *Synlett* **2007**, 980 (**DOI**) & *Chem. Commun.* **2007**, 2075 (with free carboxylic acids) (**DOI**)
    - *e.g.* Knochel *Chem. Commun.* **2006**, 726 (>998:1 regioselectivity) (**DOI**)

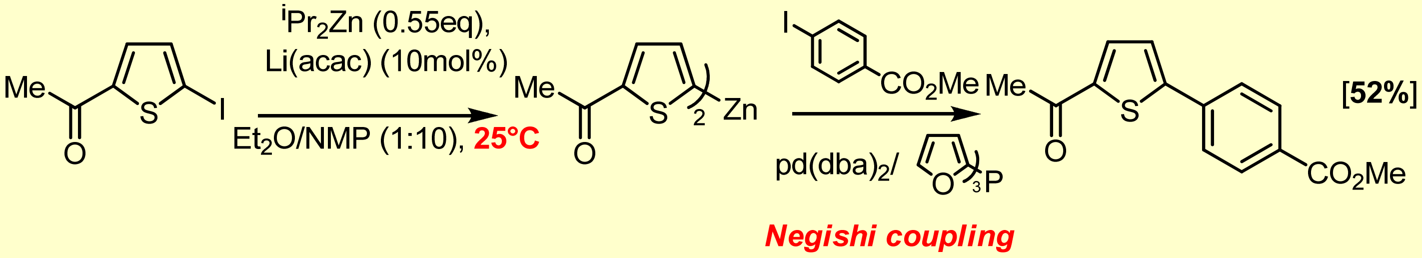


- ***chelating diamine supresses addition reactions – pyrimidine I-Mg exchange:***
    - Wang *Org. Lett.* **2006**, 8, 3141 (**DOI**)

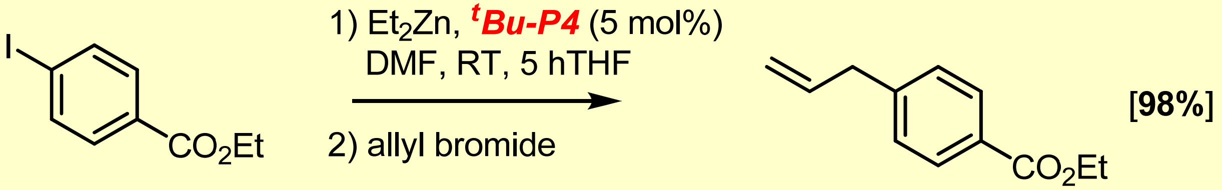


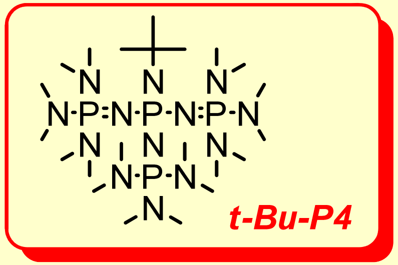
Halogen-Zn exchange

- ***using ^{i}Pr$_2$Zn & Li(acac) (presumed to form 'ate' complex):***
  - also tolerates ***ketones*** and ***aldehydes***
  - Knochel *Angew. Chem. Int. Ed.* **2004**, 43, 1017 (**DOI**)



- ***using Et$_2$Zn & a phosphazine base (tBu-P4) as catalyst:***
  - tolerates ***esters***
  - Kondo *Chem. Commun.* **2006**, 3549 (**DOI**)

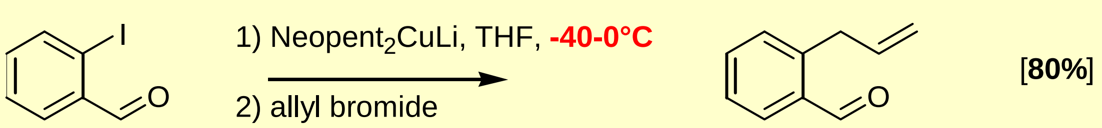


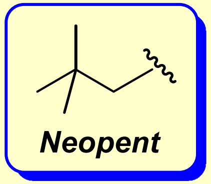


t-Bu-P4

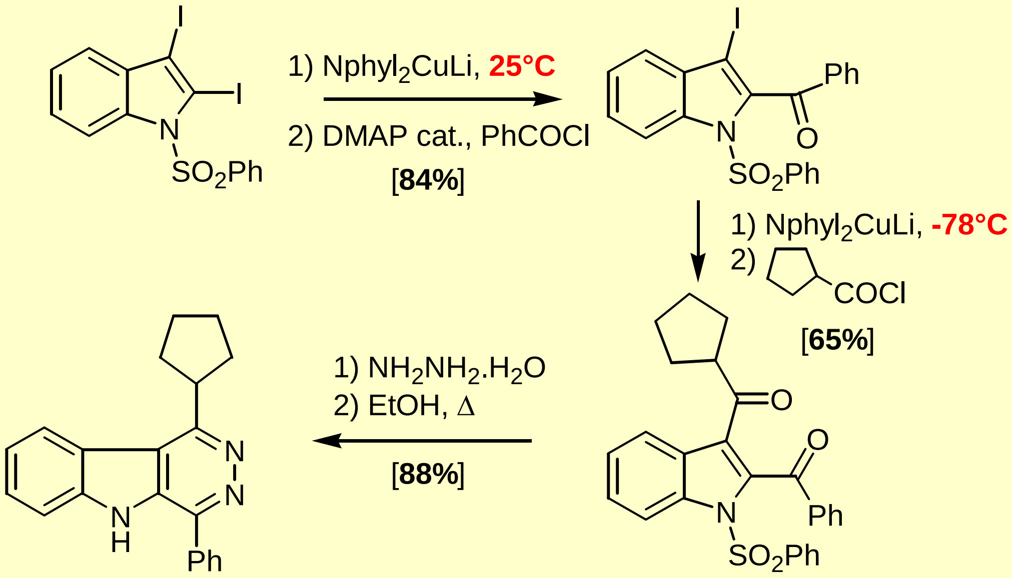
Halogen-Cu exchange

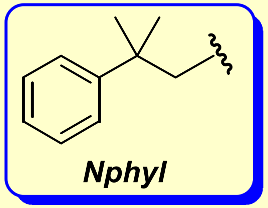
- ***even wider functional group tolerance:***
  - using ***lithium di(neopentyl)cuprates*** - tolerates ***ketones*** and ***aldehydes***
    - Knochel *Angew. Chem. Int. Ed.* **2002**, 41, 3263 (DOI)





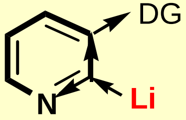
  - using ***lithium di(neophyl)cuprates*** – tolerates ***highly functionalised indoles***
    - Knochel *Org. Lett.* **2004**, 6, 1665 (DOI) & *Chem. Commun*. **2006**, 2486 (DOI)





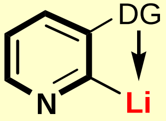
Deprotonation – *overview*

- ***Reviews:*** Schlosser *Synlett* **2007**, 3096 (**DOI**) – Hal-M exchange and deprotonation of heterocycles; Schlosser *Angew. Chem. Int. Ed.* **2005**, 44, 376 (**DOI**); Clayden '*Organolithiums: Selectivity for Synthesis*' **2002** (Pergamon).
- *Deprotonation of **benzene derivatives:***
  - ***thermodynamically possible*** for ***alkyl metals*** (pK_a BuH ~45, pK_a ArH ~38), but ***kinetically slow***
  - no regiocontrol (without directing groups)
- *Deprotonation of **aromatic heterocycles*** (ortho- *to ring heteroatoms):*
  - ***Thermodynamically more favourable*** (pK_a $Ar_{C=N}H$ ~35) and ***kinetically faster*** than for ***benzene*** particularly:
    - *ortho* to ring N
    - *ortho* to directing substituents (DoM – see later)

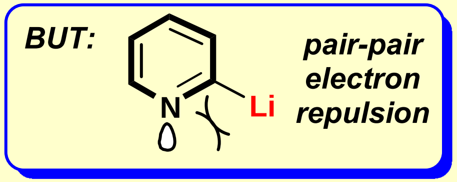


inductive stabilisation

and



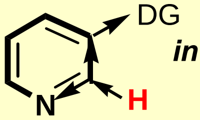
chelative stabilisation



BUT:

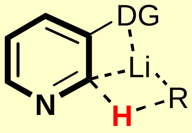
pair-pair electron repulsion

  - ***Kinetics:*** due to:



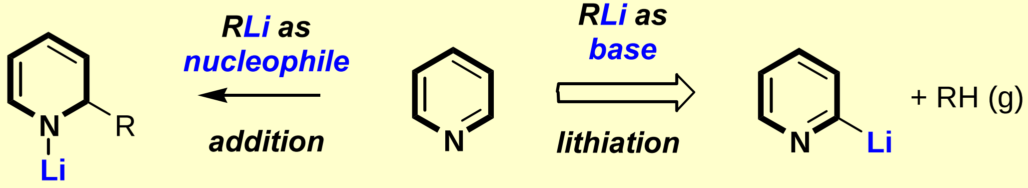
inductive acidification of ortho-protons

and



Complex Induced Proximity Effects stabilising $TS^{\#}$

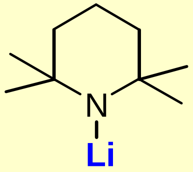
  - ***Low temperatures*** & ***bulky bases*** required to supress ***addition reactions*** to ***C=N function:***
    - Quéguiner *Tetrahedron* **2001**, 57, 4059 (**DOI**)



Thermodynamic *vs* kinetic deprotonation (Li)

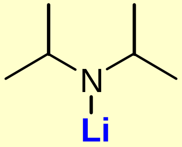
- ***thermodynamic deprotonation using hindered lithium/magnesium amide bases:***
  - amine anions are poorly nucleophilic and undergo slow competitive addition reactions
  - ***reversible equilibration***, success depends on the pK_a of the *ortho*-proton being lower than that of the amine:

$$\boxed{ArH + R_2NLi \underset{\textit{reversible}}{\rightleftharpoons} ArLi + R_2NH}$$



LiTMP
pK_a 37.3

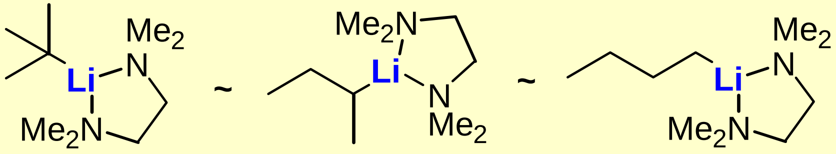
>



LDA
pK_a 35.7

- ***kinetic deprotonation using alkyl lithium bases (RLi):***
  - branched alkyl lithiums undergo slow competitive nucleophilic addition
  - ***irreversible loss of RH***, maximum basicity of alkyl lithiums in non-co-ordinating solvents *e.g.* hexane with TMEDA co-solvent
  - ***review*** (structures of lithium complexes): van Koten *Angew. Chem. int. Ed.* **2005**, 44, 1448 (**DOI**)

$$\boxed{ArH + RLi \xrightarrow[\textit{irreversible}]{} ArLi + RH\ (g)}$$

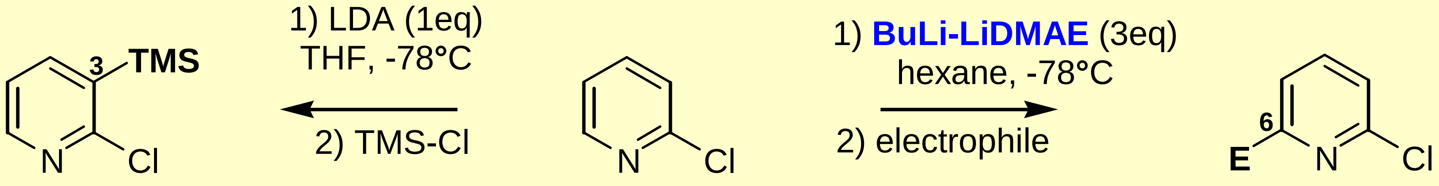


pK_a ~45

- ***mechanisms - disputed:***
  - acidity due to two factors: i) ***inductive activation***, and ii) ***Complex Induced Proximity Effects*** (CIPE)
  - ***review:*** Snieckus & Beak *Angew. Chem. Int. Ed.* **2004**, 43, 2206 (**DOI**); see also Collum *J. Am. Chem. Soc.* **2000**, 122, 8640 (**DOI**) & *J. Am. Chem. Soc*. **2007**, 129, 2259 (**DOI**); Mortier *Org. Lett.* **2005**, 7, 2445 (excellent discussion of specific case of DoM of *m*-anisic acid) (**DOI**)

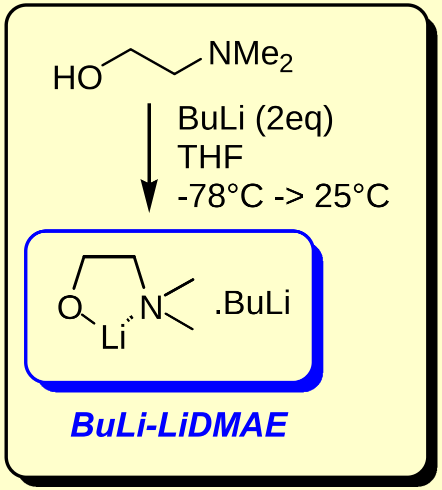
Thermodynamic *vs* kinetic deprotonation (Li)

- regioselectivity: ***kinetically and thermodynamically most acidic protons may differ:***
  - Fort *J. Org. Chem.* **2003**, 68, 2243 (**DOI**); *J. Org. Chem.* **2002**, 67, 234 (**DOI**); *Org. Lett.* **2000**, 2, 803 (**DOI**)



thermodynamic deprotonation

kinetic deprotonation

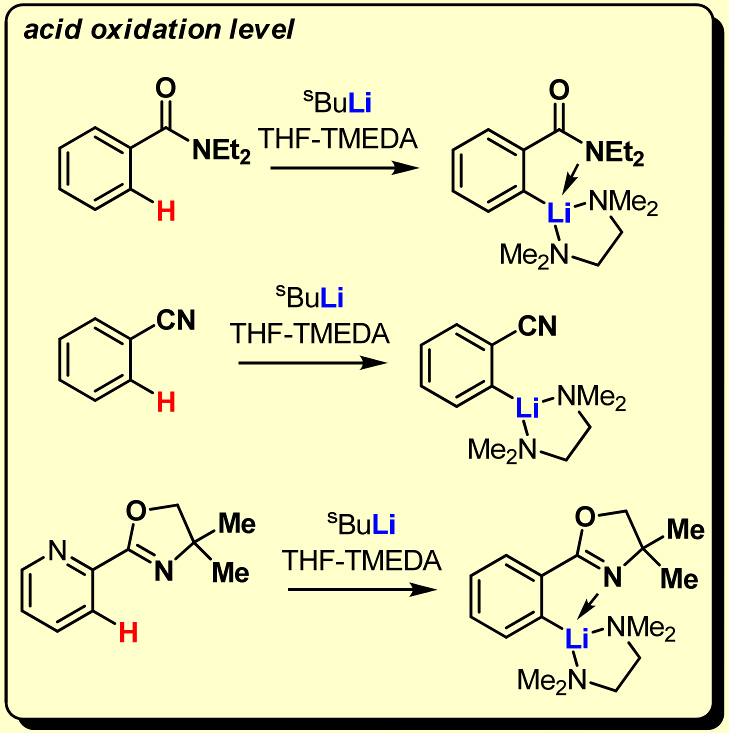


BuLi-LiDMAE

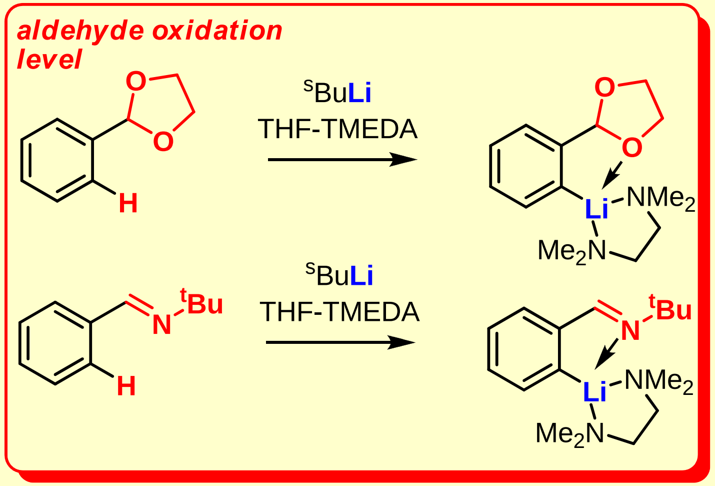
Electrophile	E	yield
MeI	MeI	70
I_2	I	80
t-BuCHO	CH(OH)*t*-Bu	90
MeCOEt	MeC(OH)Et	60
DMF	CHO	15
MeSSMe	SMe	92
$ClBu_3Sn$	$SnBu_3$	84

Directed *ortho*-metalation (DoM, Li)

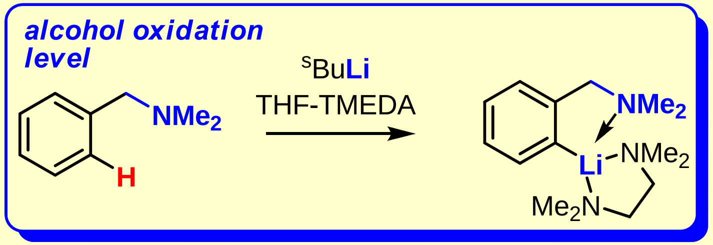
- directed metalation groups ***(DMGs) attached*** via ***carbon can assist*** ortho-***metalation***
  - ***Reviews:*** Snieckus & Beak *Angew. Chem. Int. Ed.* **2004**, 43, 2206 (**DOI**); Sniekus *J. Organomet. Chem.* **2002**, 653, 150 (**DOI**); Quéguiner *J. Het. Chem.* **2000**, 37, 615; Sniekus *J. Heterocyclic Chem.* **1999**, 36, 1453; Sniekus *Chem. Rev.* **1990**, 90, 879 (**DOI**)
  - ***benzylic carbon-based DMGs:***



acid oxidation level

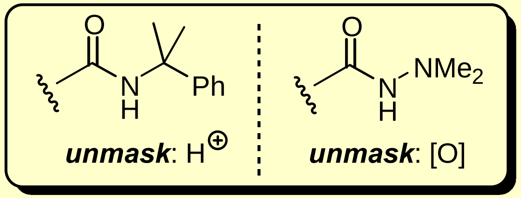


aldehyde oxidation level



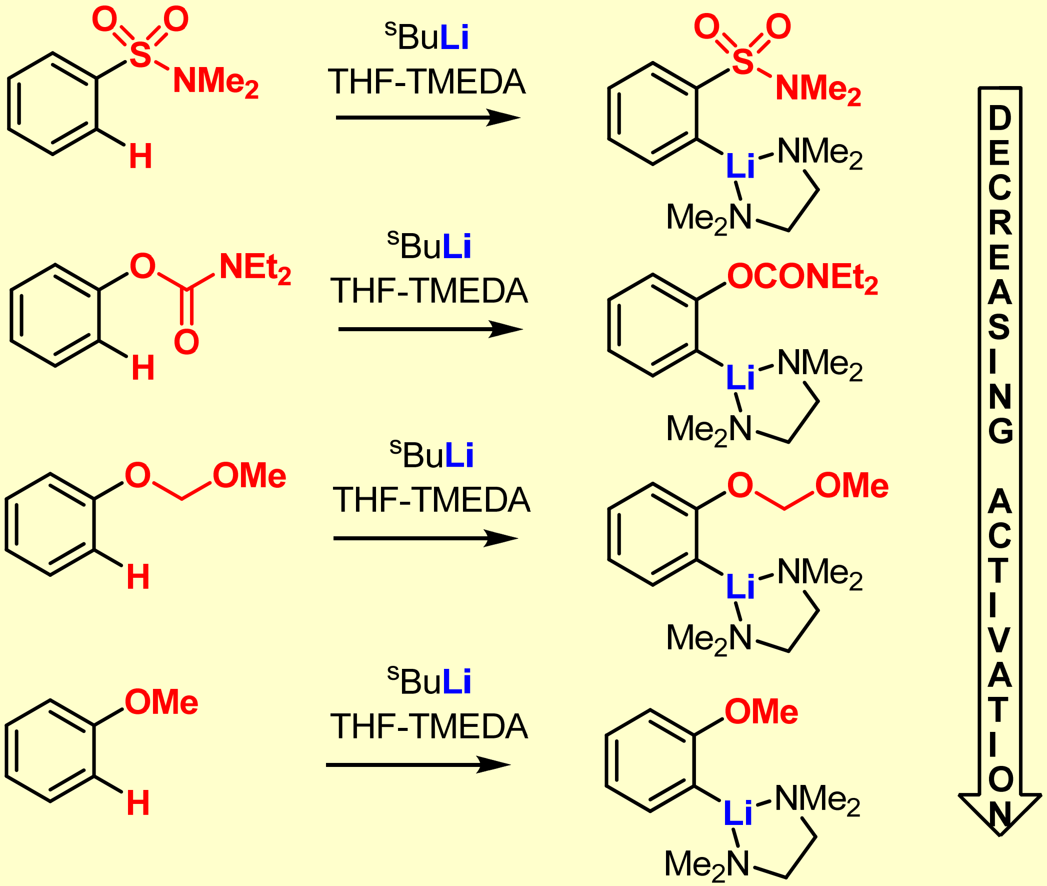
alcohol oxidation level

  - ***for DMGs readily 'unmasked' to give CO_2H see***:
    - Wutz *Tet. Lett.* **2000**, 41, 3559 (**DOI**); Sniekus *Org. Lett.* **1999**, 1, 1183 (**DOI**)



Directed *ortho*-metalation (DoM, Li)

- ***non carbon-based DMGs:***
  - Snieckus *Org. Lett.* **1999**, 1, 1183 (DOI)
  - Familoni *Synlett* **2002**, 1181 (sulfonamides, ***review***) (DOI)



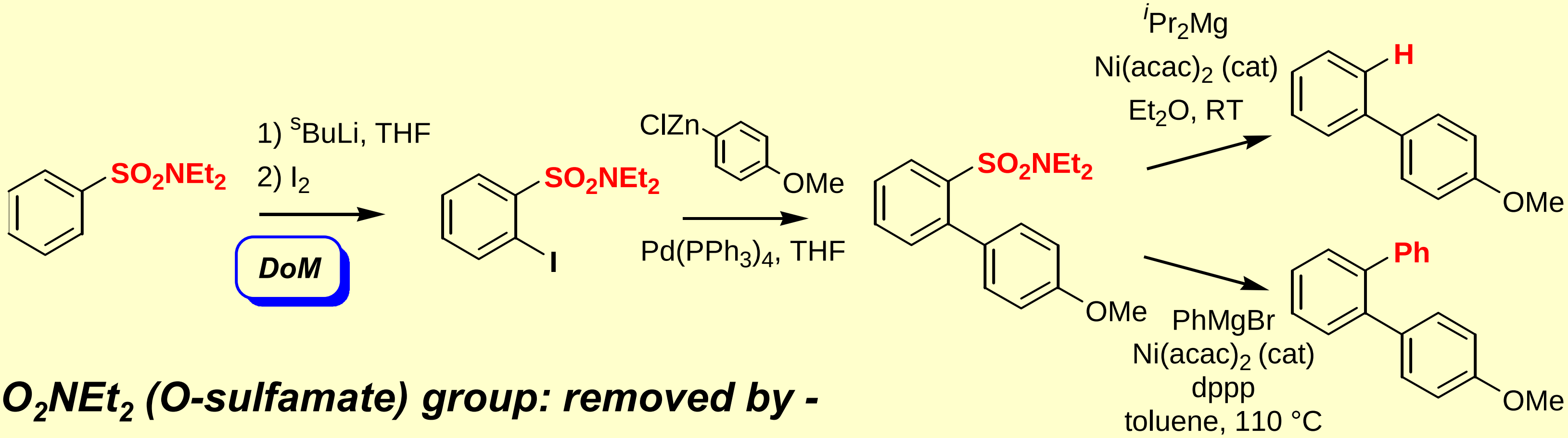
Other weak DMGs include:
F, **Cl**, **Br**, **CF_3**, **SR**, **NR_2**, **I**

halogen directing groups (review):
Schlosser *Eur. J. Org. Chem.* **2001**, 3975 (DOI)

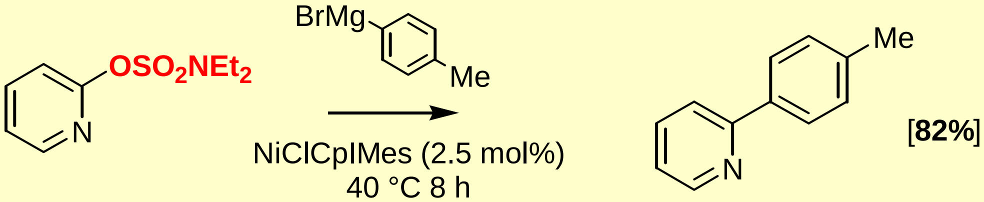
e.g. iodine as directing group:
Mattson *J. Org. Chem*. **1999**, 64, 8004 (DOI)

‘Temporary’ DoM groups

- ***the SO_2NEt_2 (sulfonamide) group: removed by -***
  - ***1) hydrogenolysis*** using $^{i}Pr_2Mg$/cat. $Ni(acac)_2$
  - ***2) Ni(0) catalysed Kharasch-type cross-coupling***
  - Snieckus *Angew. Chem. Int. Ed.* **2004**, 43, 888 (**DOI**) & 892 (**DOI**)



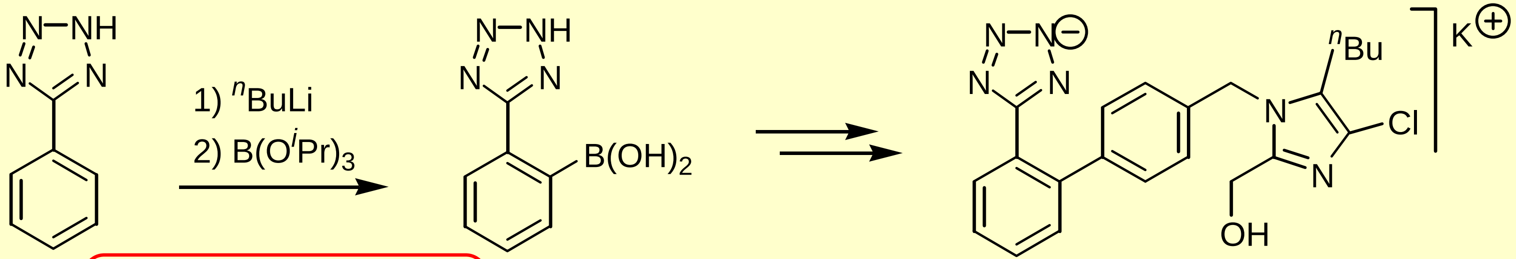
- ***the OSO_2NEt_2 (O-sulfamate) group: removed by -***
  - ***Ni(0) catalysed Kharasch-type cross-coupling***
  - Snieckus *Org. Lett.* **2005**, 7, 2519 (**DOI**)



- ***the SO_2NCMe_2Ph (N-cumyl sulfonamide) group: deprotected to SO_2NH_2 by -***
  - ***TFA → saccharin syntheses***
  - Snieckus *J. Org. Chem.* **2007**, 72, 3199 (**DOI**)

Pharmaceutical preparation by DoM

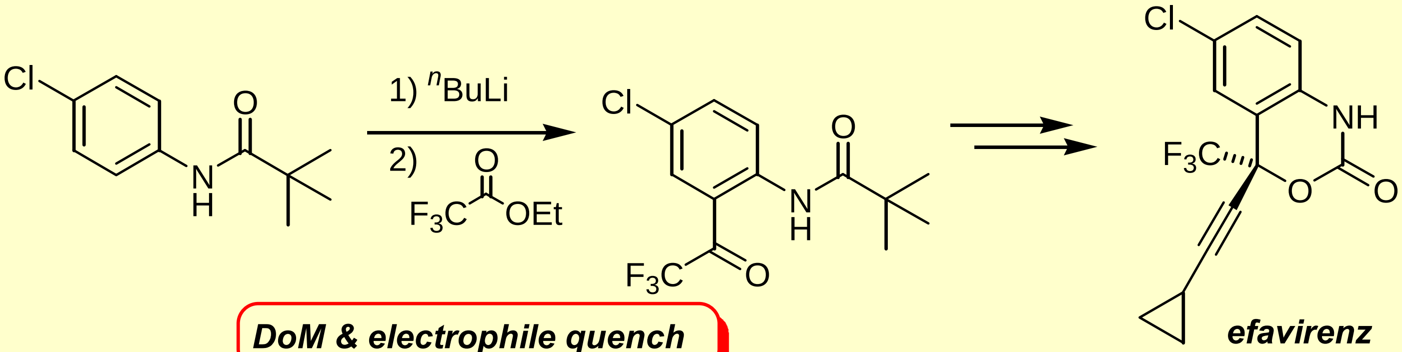
- ***losartan potassium: antihypertensive***
  - Process route for Merck (Rouhi *Chem. Eng. News* **2002**, *July 22*, 46) (DOI)



DoM & transmetalation

losartan potassium
angiotensin II receptor (type AT 1) antagonist

- ***efavirenz: anti-viral, anti-AIDS***
  - Process route for Bristol-Myers Squibb (Rouhi *Chem. Eng. News* **2002**, *July 22*, 46) (DOI)

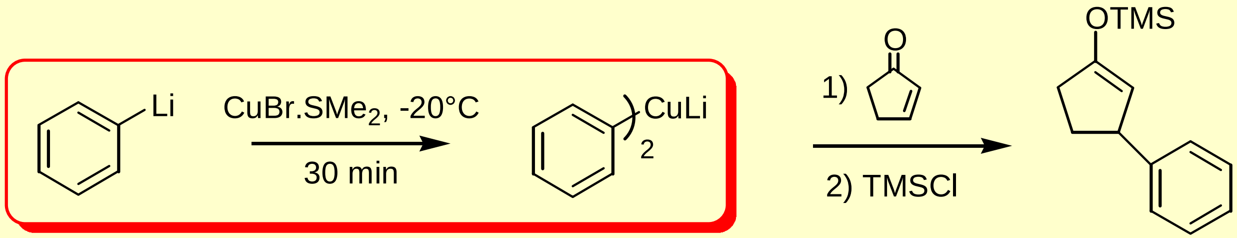


DoM & electrophile quench

efavirenz
non-nucleoside reverse transcriptase inhibitor

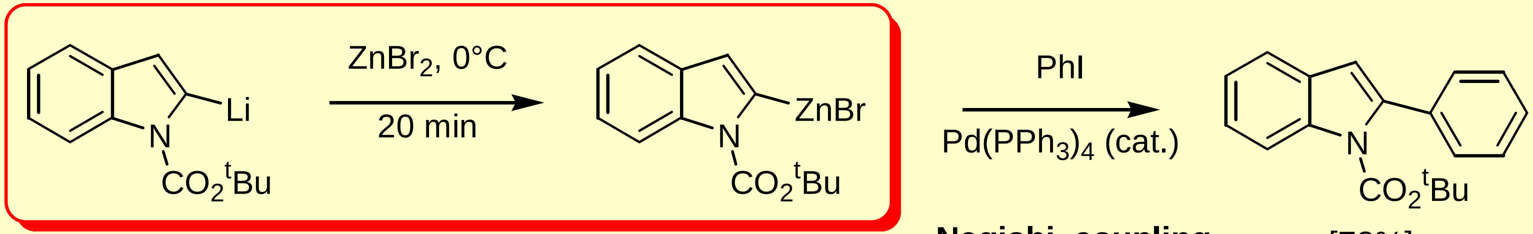
Transmetalation

- ***Aryl cuprate formation (ArLi → Ar_2CuLi):***
  - Aryl cuprates are ***less basic*** and ***more nucleophilic*** than aryl lithiums.
  - *e.g.* ‘Organocopper reagents’ **1994**, (Oxford), R.J.K. Taylor:



conjugate addition [93%]

- ***Aryl zincate formation (ArLi → ArZnX):***
  - Aryl zincates are ***less basic*** and ***more oxophilic*** than aryl lithiums & useful for Negishi coupling.
  - *e.g.* Sakamoto *Heterocycles* **1993**, *36*, 941 (**DOI**)

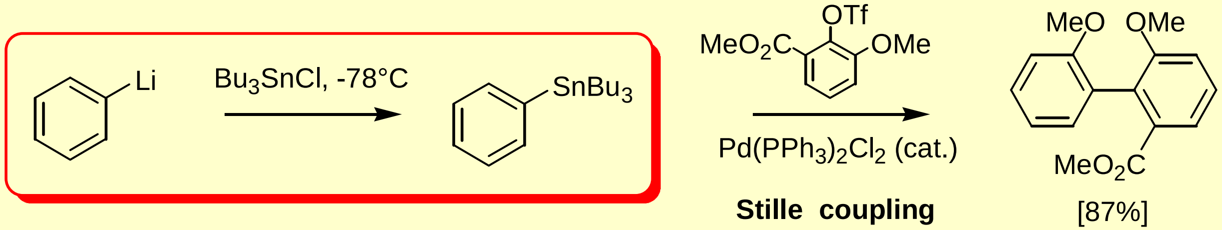


Negishi coupling [78%]

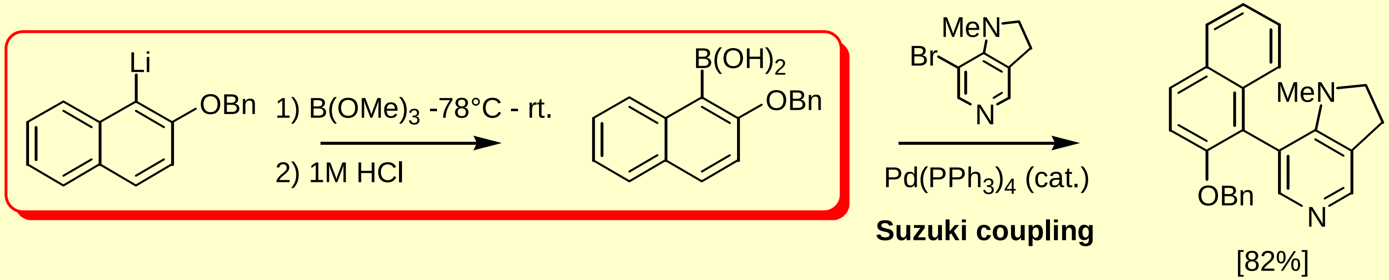
- *NB.* arylzincs can also be prepared by
  - *reductive metalation* of ArI with Zn (see previous slide)
  - DoM using $(tmp)_2Zn\cdot 2MgCl_2\cdot 2LiCl$. See: Knochel *Angew. Chem. Int. Ed.* **2007**, 46, 7685 (**DOI**)

Transmetalation

- ***Aryl stannane formation (ArLi → ArSnR$_3$):***
  - Aryl stannanes are useful for electrophilic *ipso*-substitution & Stille coupling.
  - *e.g.* Saá *J. Org. Chem.* **1992**, 57, 678 (**DOI**)



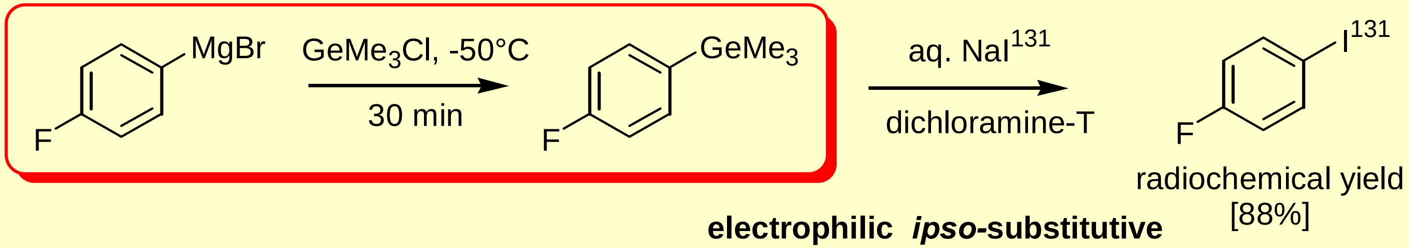
  - *NB.* arylstannanes can also be made by Pd(0) cat. stannylation of ArBr/I (see later).
- ***Aryl boronate formation [ArLi → ArB(OR)$_2$]:***
  - Aryl boronic acids and esters are useful for Suzuki coupling.
  - *e.g.* Spivey *Tet. Lett.* **1998**, 39, 8919 (**DOI**)



  - *NB. (1): in situ* quenching of ArLi with B(OR)$_3$ often superior: Vazquez *J. Org. Chem.* **2002**, 67, 7551 (**DOI**)
  - *NB. (2):* arylboronates can also be formed by Pd(0) cat. borylation of ArBr/I (see later).
  - *NB.* (3): arylboronates are excellent precursors to ***phenols*** by Baeyer-Villager-type process:
  - *e.g.* Hawthorne *J. Org. Chem*. **1957**, 22, 1001 (**DOI**)

Transmetalation

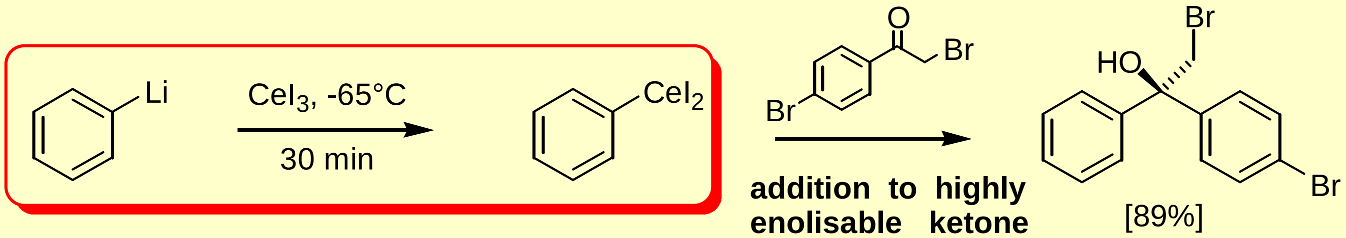
- ***Aryl germane/silane formation (ArLi → ArSiR$_3$/ArGeR$_3$):***
  - Aryl germanes/silanes are useful for electrophilic *ipso*-substitution reactions.
  - Moerlein *J. Chem. Soc., Perkin Trans. I* **1985**, 1941 (**DOI**)



radiochemical yield [88%]

electrophilic *ipso*-substitutive radio-iodination

- ***Aryl cerium formation (ArLi → ArCeX$_2$):***
  - Aryl ceriums are ***less basic*** and ***more oxophilic*** than aryl lithiums.
  - *e.g.* Imamoto *J. Org. Chem.* **1984**, 49, 3904 (**DOI**); H.-J. Liu *Tetrahedron* **1999**, 55, 3803 (**DOI**)

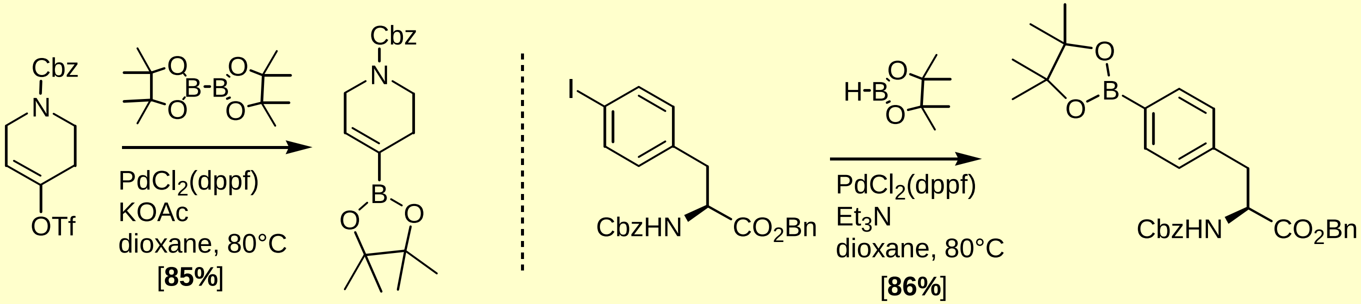


addition to highly enolisable ketone

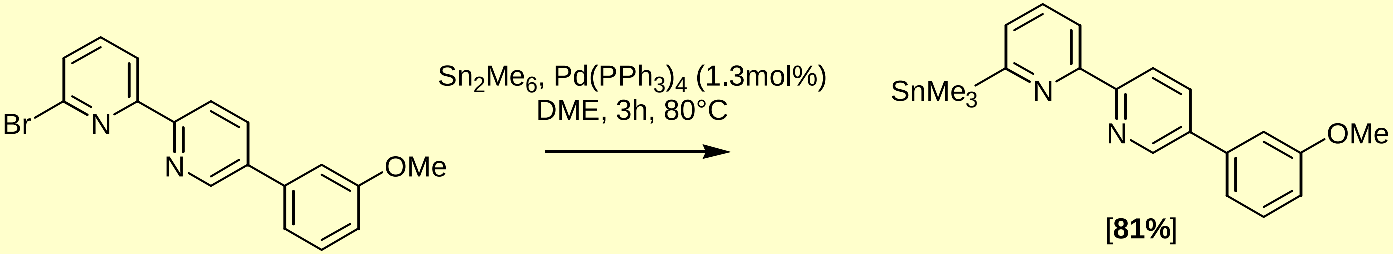
[89%]

Pd(0) Catalysed 'metalation' of aryl (pseudo)halides

- ***Aryl pinnacolatoboranes from pinnacolatoborane or bis(pinnacolato)diboron***
  - Developed originally by Miyaura: *J. Org. Chem.* **1995**, 60, 7508 (**DOI**)
  - ***Bis(pinnacolato)diboron:*** *e.g.* Eastwood *Tet. Lett.* **2000**, 41, 3705 (**DOI**)
  - ***Pinnacolatoborane:*** *e.g.* Yamamoto *Bull. Chem. Soc. Jpn.* **2000**, 73, 231 (**DOI**)

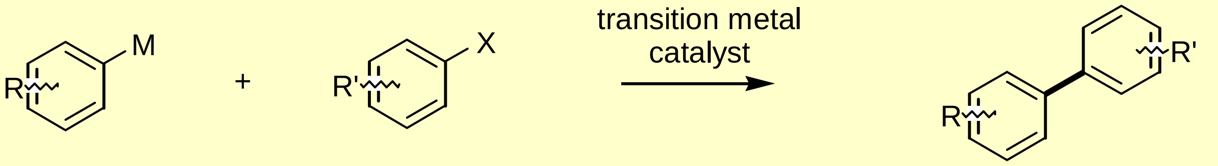


- ***Aryl silanes/stannanes from disilanes/distannanes:***
  - ***Hexamethyldisilane***: *e.g.* Goossen *Synlett* **2000**, 1801 (**DOI**)
  - ***Hexamethylditin:*** *e.g.* Siegel *Tet. Lett.* **1997**, 38, 4737 (**DOI**)



Catalytic biaryl cross-coupling

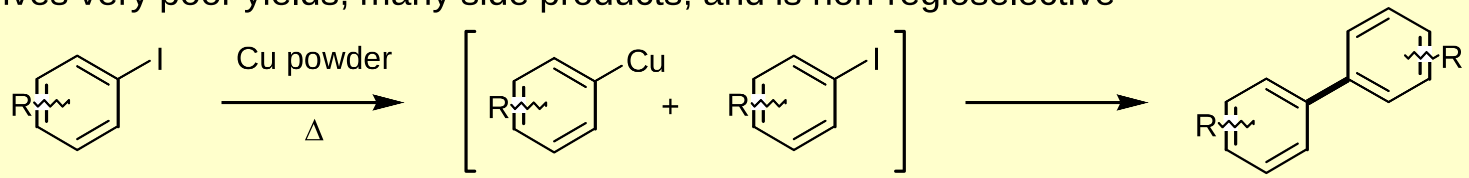
- ***General process is sometimes known as KUMADA-NEGISHI cross-coupling***
  - ***review:*** Hassan *Chem. Rev*. **2002**, 102, 1359 (**DOI**); Stanforth *Tetrahedron*, **1998**, 54, 263 (**DOI**); 'Metal-catalyzed Cross-coupling Reactions' **2004**, (Wiley-VCH), Armin de Meijere & François Diederich (Eds.) [**ISBN 3-527-30518-1**]



M = Li, **Mg**, Cu, **Zn**, Hg, Ti, Al, Zr, Tl, **Sn**, **B**
X = Cl, Br, I, OTf, OMs, OTs, ONf, N_2^+
cat. = Pd(0), Ni(0)

hetero- or homo- biaryl product

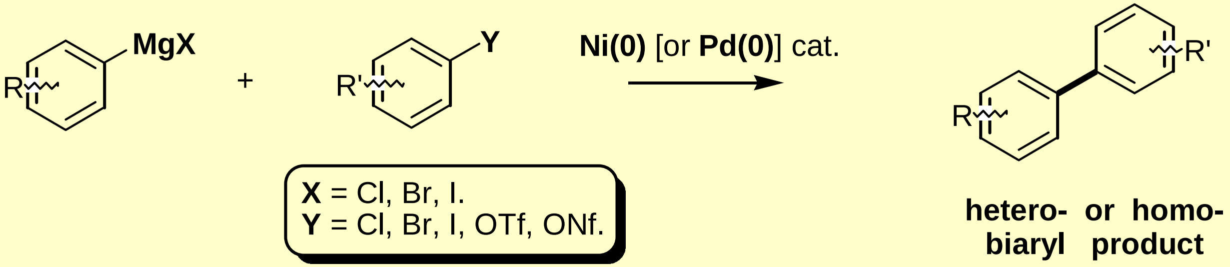
- ***The classical procedure is known as Ullmann biaryl coupling***
  - Not to be confused with Ullmann biaryl ether condensation.
  - gives very poor yields, many side products, and is non-regioselective



homo-biaryl product

Kumada-Corriu cross-coupling (MgX)

- ***Overall scheme:***
  - ***highlight:*** Negishi *J. Organometal. Chem.* **2002**, 653, 34 (DOI);

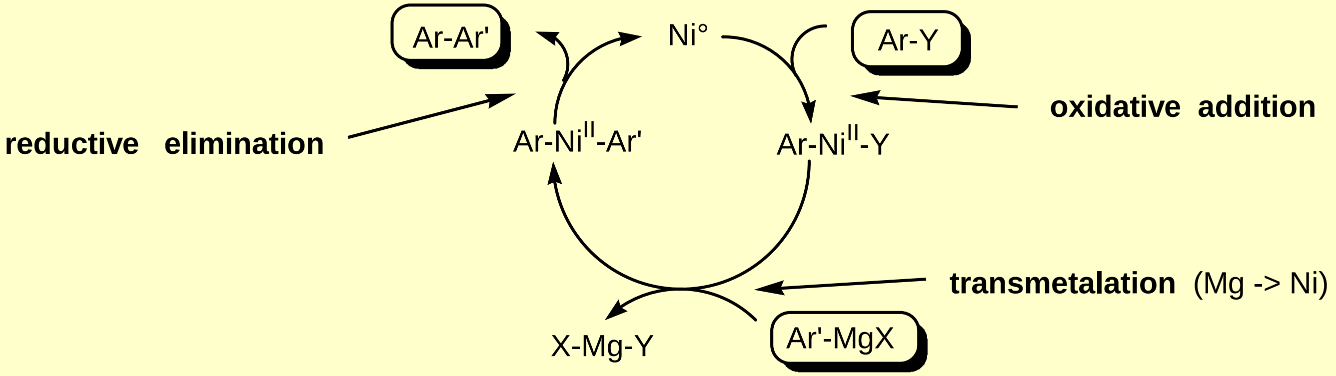


Ni(0) [or **Pd(0)**] cat.

X = Cl, Br, I.
Y = Cl, Br, I, OTf, ONf.

hetero- or homo-biaryl product

- ***Mechanism:***


Ni°

Ar-Y

oxidative addition

Ar-Ni^{II}-Y

transmetalation (Mg -> Ni)

Ar'-MgX

X-Mg-Y

Ar-Ni^{II}-Ar'

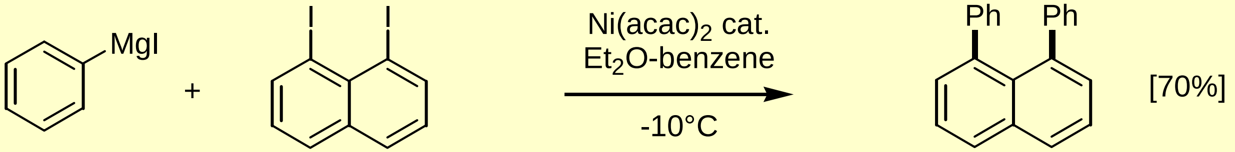
reductive elimination

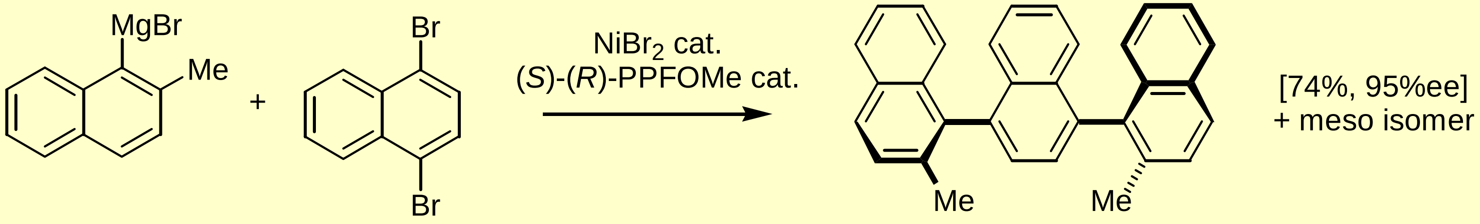
Ar-Ar'

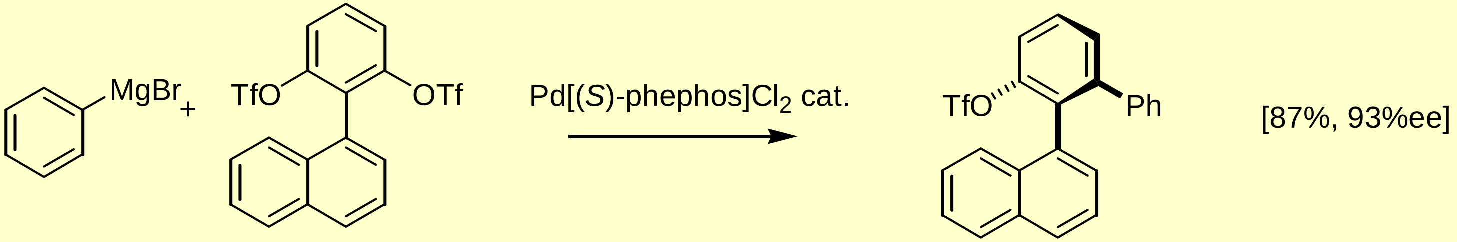
Kumada-Corriu cross-coupling (MgX)

- ***Features:***
  - Polar nature of aryl Grignard precludes use of several functional groups including: aldehydes, ketones, esters, & nitro groups.
  - Requires rigorous exclusion of oxygen which oxidises active Ni(0) catalyst.
  - Can provide very hindered biaryls (*cf.* Suzuki & Stille) and has asymmetric variants.
  - Often proceed efficently at low temperatures

- ***Examples:***

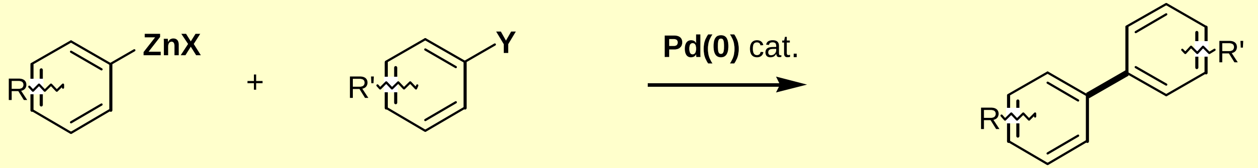






Negishi cross-coupling (ZnX)

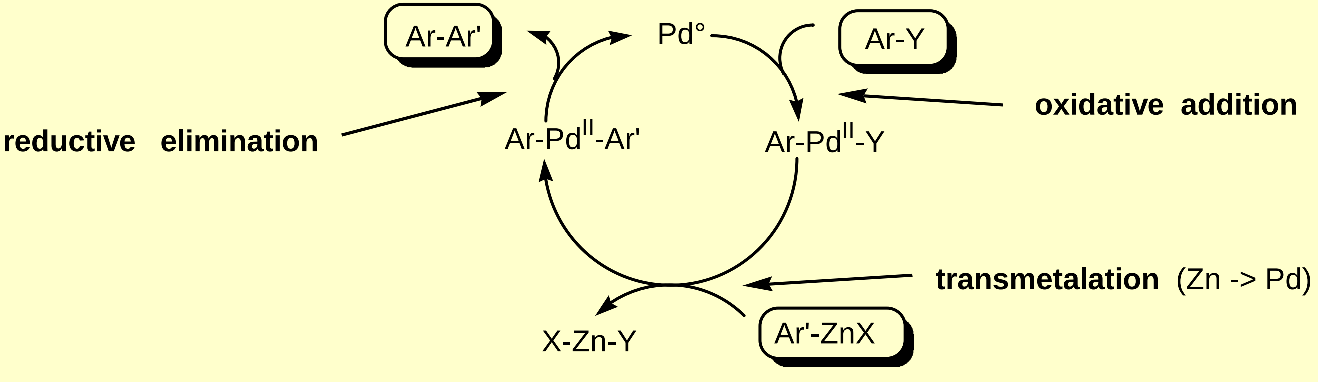
- ***Overall scheme:***
    - ***review:*** Negishi in 'Metal catalysed cross coupling reactions' Eds Diederich & Stang, Wiley-VCH **1998**, pp1-42



X = Cl, Br, I.
Y = Cl, Br, I, OTf, ONf.

hetero- or homo-
biaryl product

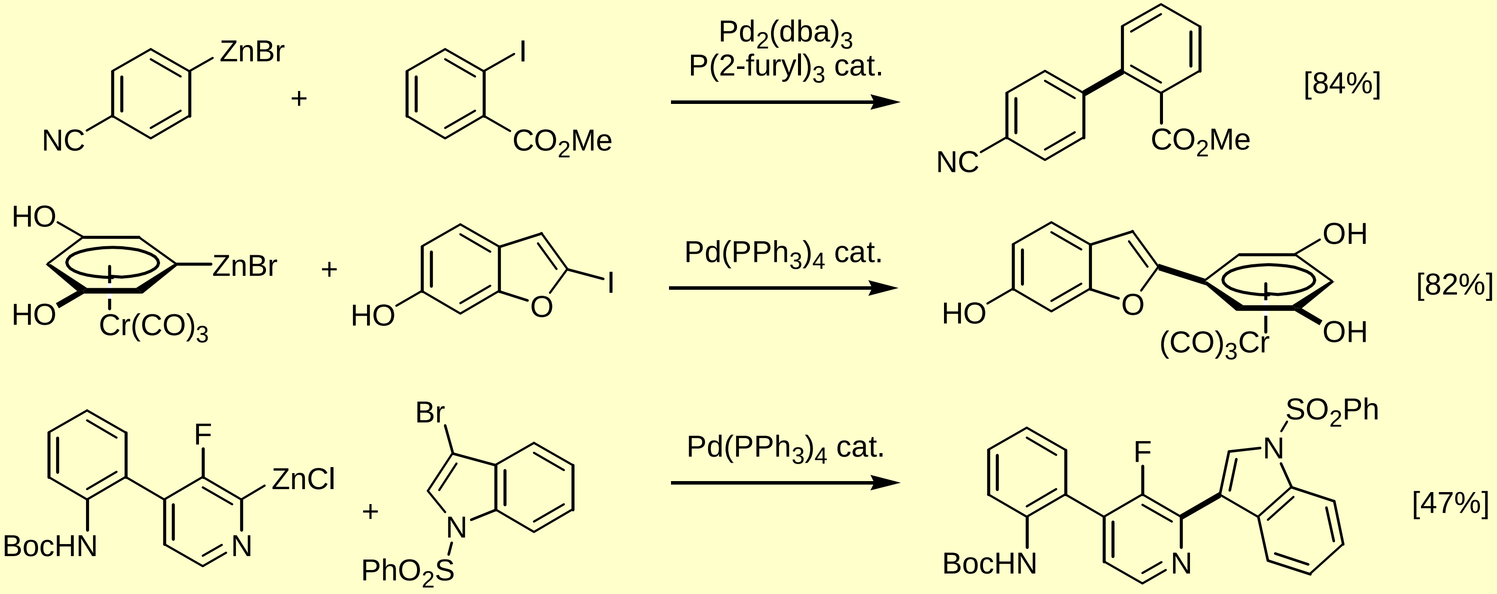
- ***Mechanism:***



Negishi cross-coupling (ZnX)

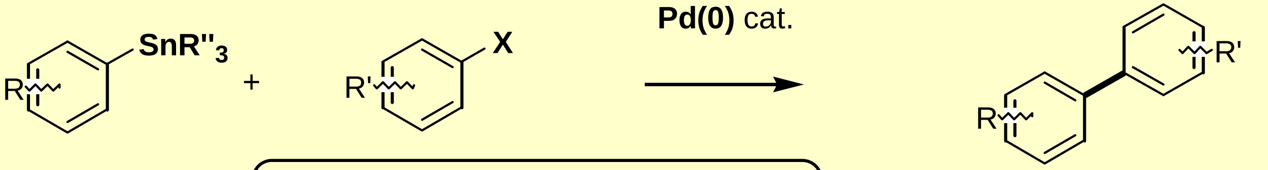
- ***Features:***
  - Tolerates aldehydes, ketones, esters, amines, nitrile, nitro groups etc.
  - Nickel aryls are less basic than arly Grignards and can be prepared under milder conditions.
  - Popular for heteroaryl cross-coupling.
  - Can provide relatively hindered biaryls

- ***Examples:***



Stille cross-coupling (SnR_3)

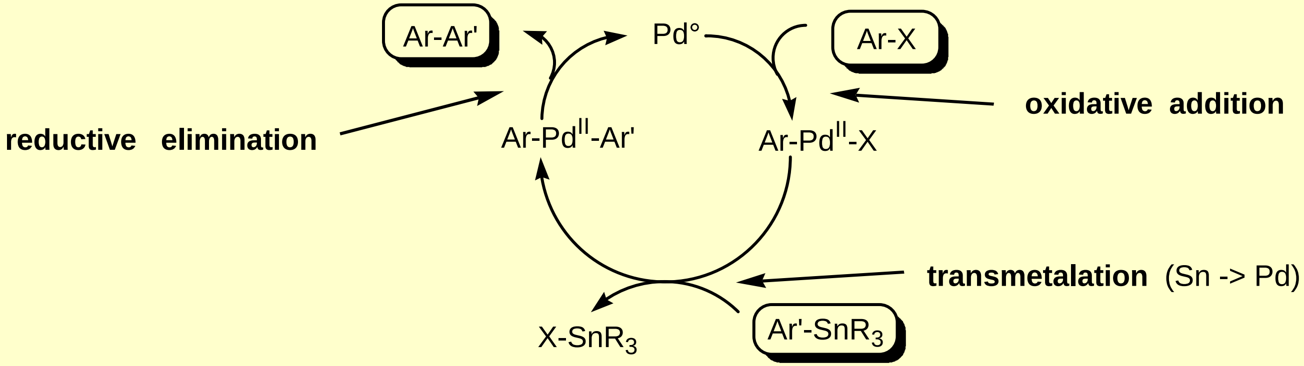
- ***Overall scheme:***
  - ***review:*** Mitchell in 'Metal catalysed cross coupling reactions' Eds Diederich & Stang, Wiley-VCH **1998**, pp167-197.



X = Cl, Br, I, OTf, OMs, OTs, ONf, N_2^+
R'' = Me, Bu

hetero- or homo-
biaryl product

- ***Mechanism:***



Pd°

Ar-X

oxidative addition

Ar-Pd^{II}-X

transmetalation (Sn -> Pd)

Ar'-SnR$_3$

X-SnR$_3$

Ar-Pd^{II}-Ar'

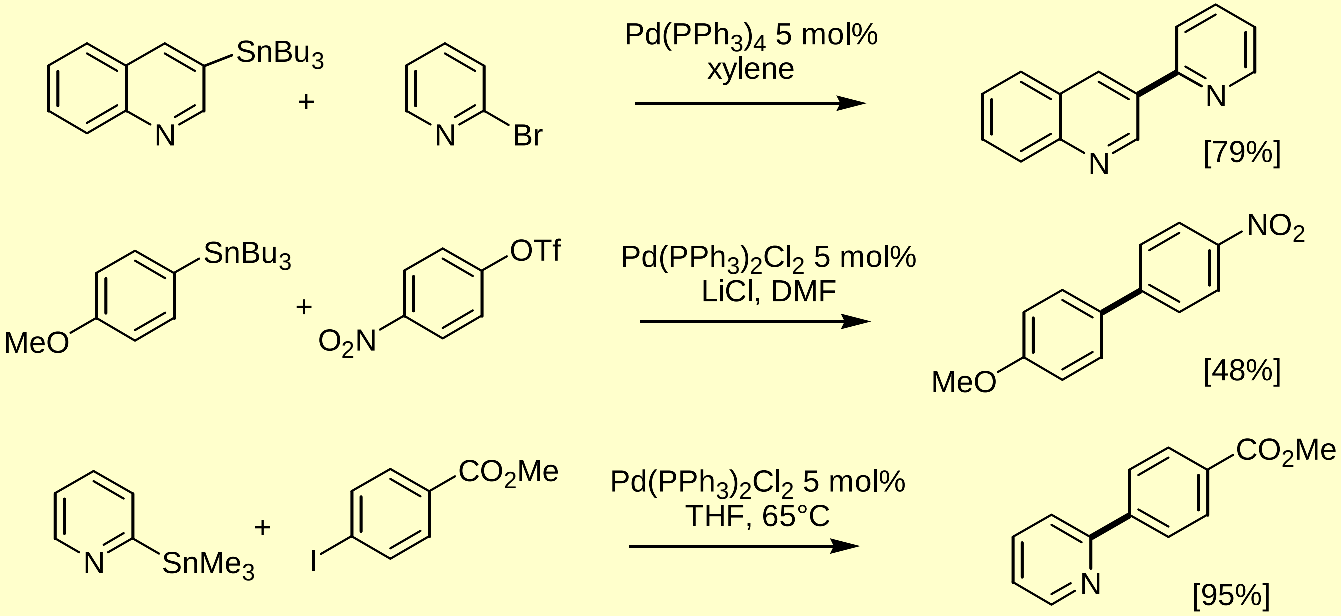
reductive elimination

Ar-Ar'

Stille cross-coupling (SnR_3)

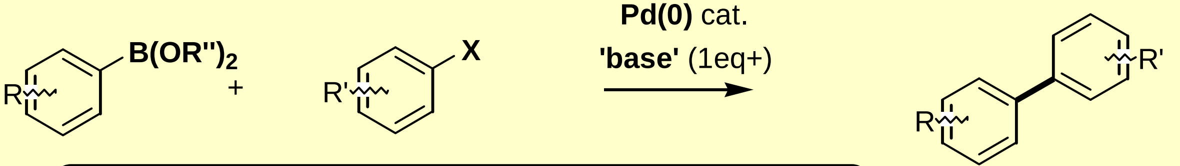
- ***Features:***
  - Reaction proceeds under very mild conditions & has wide functional group tolerance.
  - Expensive Pd catalyst, recyclable and only used in < 5 mol% quantities.
  - Also applicable to heteroaromatic systems.
  - Lithium chloride or bromide is an essential additive when using triflates.
  - Aryl stannanes and the halostannane by-products are ***very toxic!***

- ***Examples:***



Suzuki cross-coupling [B(OR$_2$)]

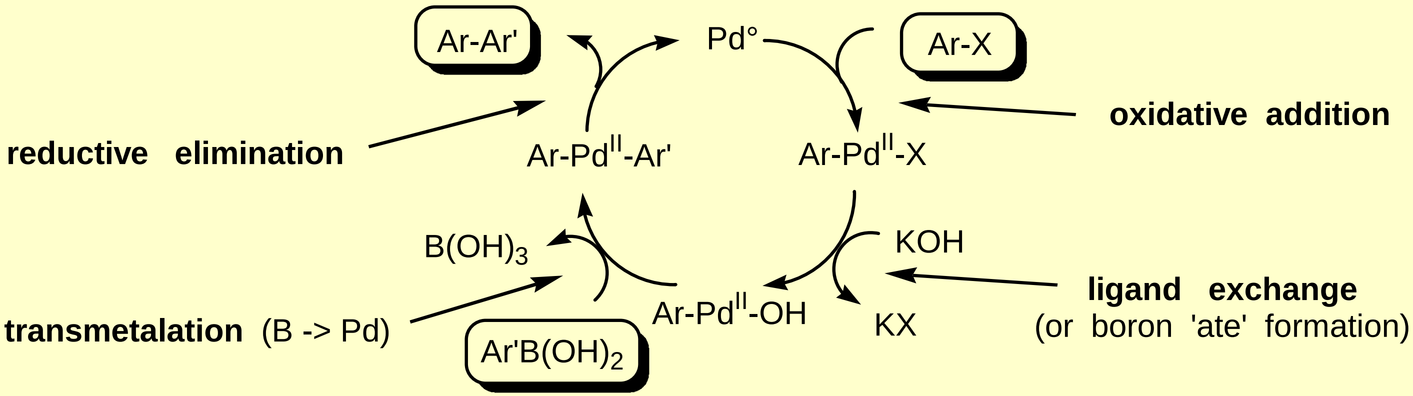
- ***Overall scheme:***
  - ***review:*** Kotha *Tetrahedron*, **2002**, 58, 9633 (**DOI**)



X = Cl, Br, I, OTf, OMs, OTs, ONf, N_2^+
R'' = H, Me, Bu, -CH_2CH_2-
base = KOH, K_3PO_4, Na_2CO_3, Cs_2CO_3, Tl_2CO_3,TlOH, Et_3N.

hetero- or homo-
biaryl product

- ***Mechanism:***



Ar-Ar'

Pd°

Ar-X

oxidative addition

reductive elimination

Ar-Pd^{II}-Ar'

Ar-Pd^{II}-X

B(OH)$_3$

KOH

ligand exchange
(or boron 'ate' formation)

transmetalation (B -> Pd)

Ar-Pd^{II}-OH

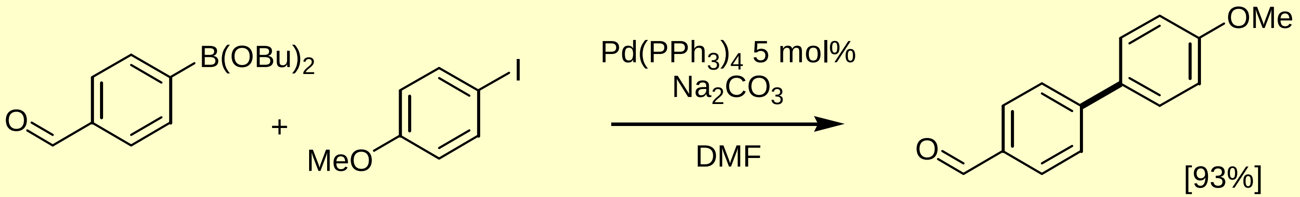
KX

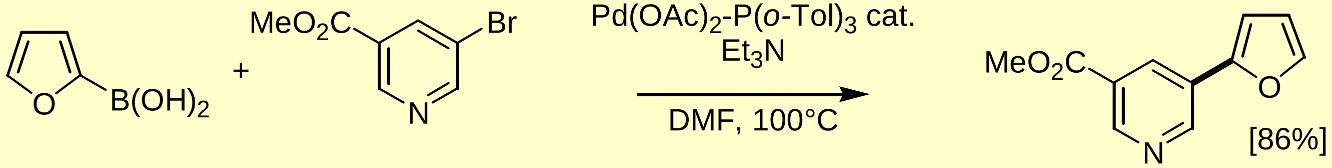
Ar'B(OH)$_2$

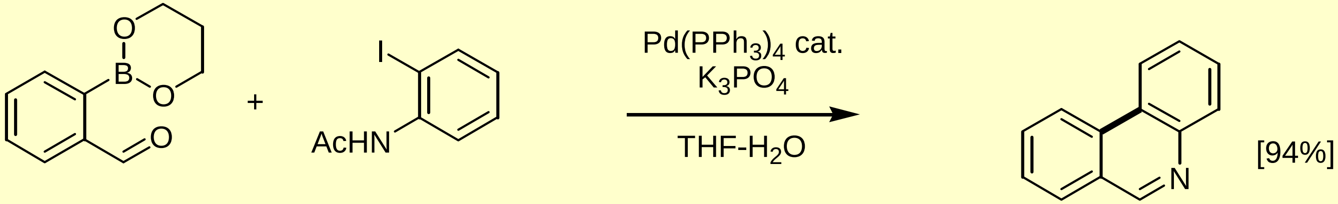
Suzuki cross-coupling [B(OR$_2$)]

- ***Features:***
  - Reaction also proceeds under very mild aqueous or non-aqueous conditions.
  - Nature of 'base' used can dramatically influence success of coupling, Cs_2CO_3 or TlOH in DME preferred for hindered coupling.
  - Wide functional group tolerance & applicable to most heteroaromatic systems.
  - Aryl boronic acids and esters are essentially non-toxic (*cf.* stannanes).

- ***Examples:***

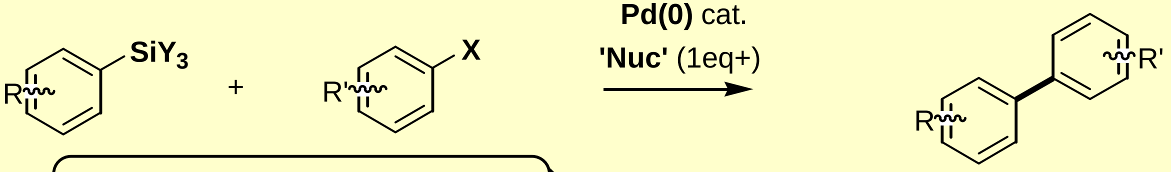






Hiyama/Denmark cross-coupling (SiX_3)

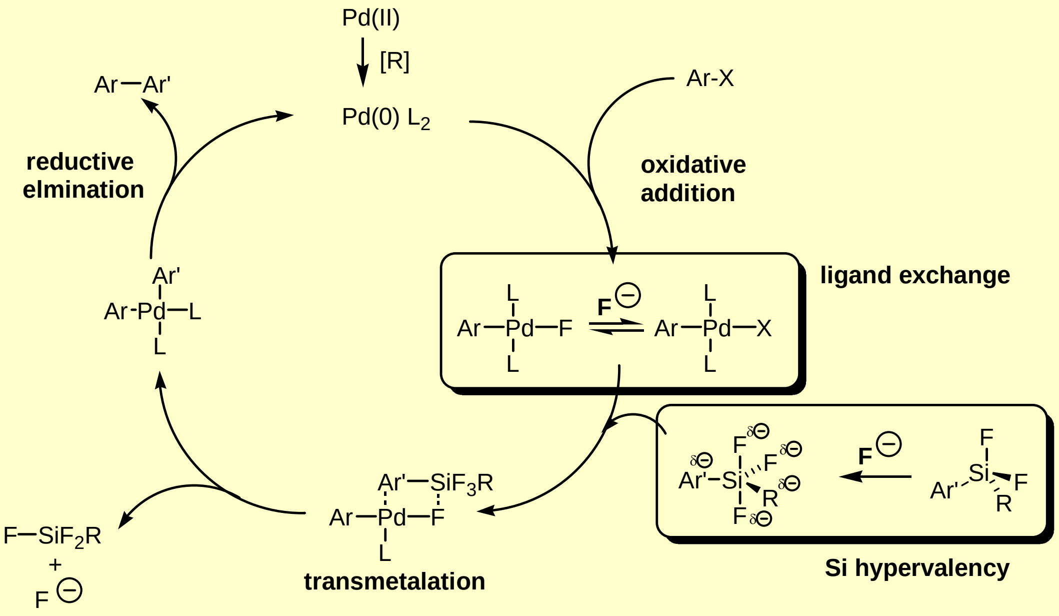
- ***Overall scheme:***
  - ***Review:*** Spivey *Curr. Org. Synth.* **2004**, 1, 211; DeShong *Tetrahedron* **2005**, 61, 12201 (DOI)



X = Cl, Br, I, OTf
Y = F, Cl, OH, OR
Nuc = F$^-$ (e.g. KF , CF, TBAF), OH$^-$

hetero- or homo- biaryl product

- ***Mechanism:***



reductive elmination

oxidative addition

ligand exchange

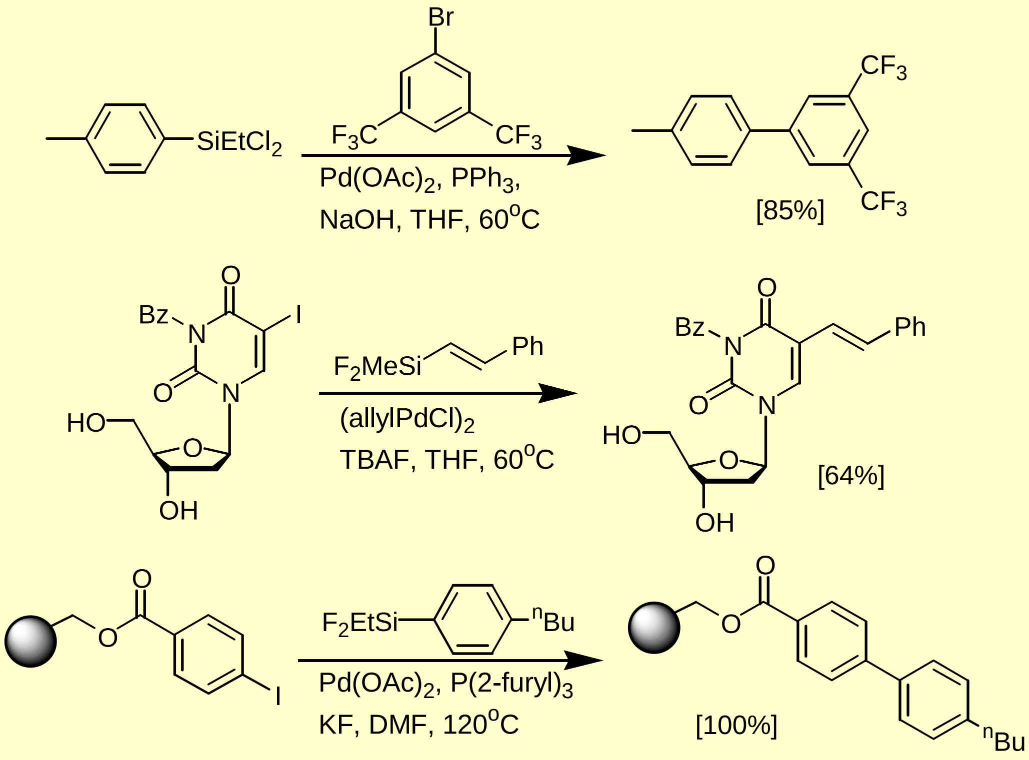
Si hypervalency

transmetalation

Hiyama/Denmark cross-coupling (SiX_3)

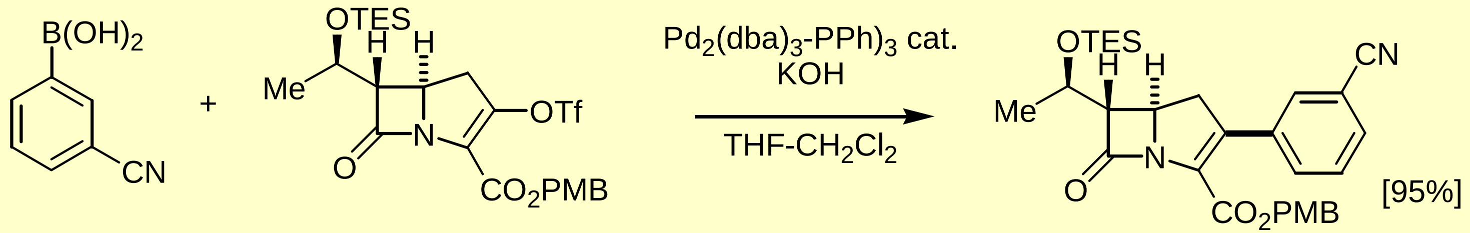
- ***Features:***
  - Uses ***non-toxic*** silanes as coupling partners (*cf.* stannanes for Stille).
  - Tri*alkyl*slianes do not couple; require heteroatom-substituted silanes.
  - Addition of ***nucleophile is essential*** to render silane pentavalent
  - Addition of fluoride makes most couplings incompatible with silyl ether protecting groups

- ***Examples:***

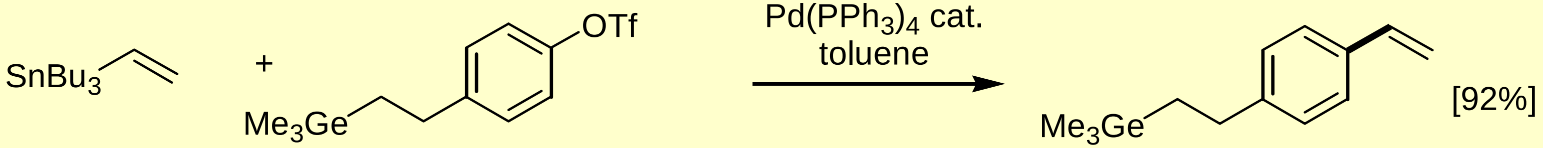


Ar-C(S*p*^{2}) alkene coupling

- ***Kumada-Negishi type cross-coupling can also be used to couple aromatics to alkenes***
- ***This type of coupling performed in two ways:***
  - using an **aryl metal** and **alkenyl halide/triflate**. *e.g.*:



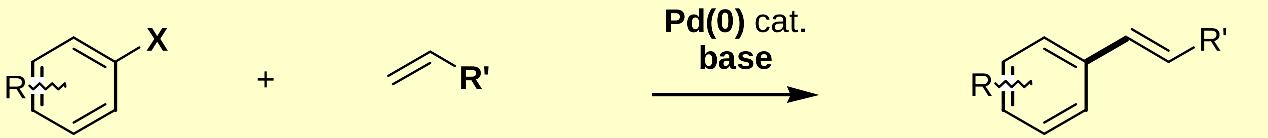
  - or an **aryl halide/triflate** and an **alkenyl metal**. *e.g.:*



- ***Alkenyl halides are often prepared by Wittig type processes or from alkynes***
- ***Alkenyl triflates are often prepared by O-triflation of enolates***
- ***Alkenyl metals are often prepared by halide-metal exchange, or by carbo- or hydro-metalation of alkynes (e.g. hydroboration of alkynes)***

The Heck reaction

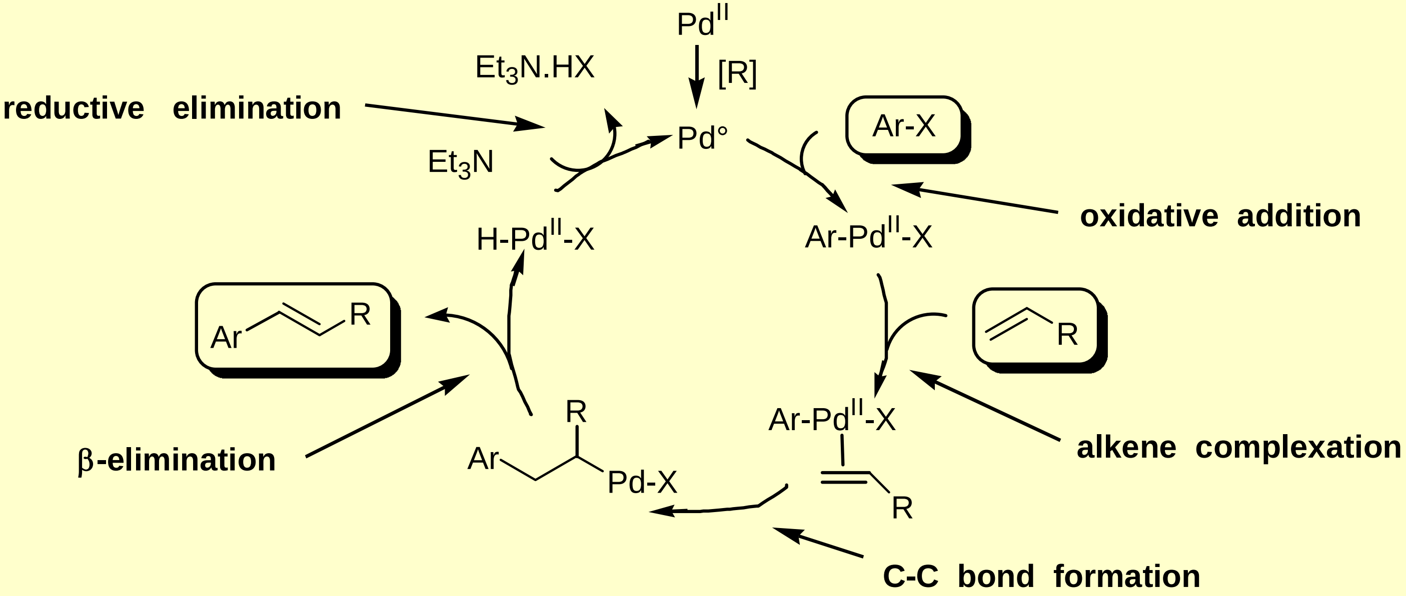
- ***Overall scheme:***
  - ***review:*** Overman in 'Metal catalysed cross coupling reactions' Eds Diederich & Stang, Wiley-VCH **1998**, pp231-266



X = Br, I, OTf
R' = almost anything
base = typically Et_3N

conjugated aromatic product

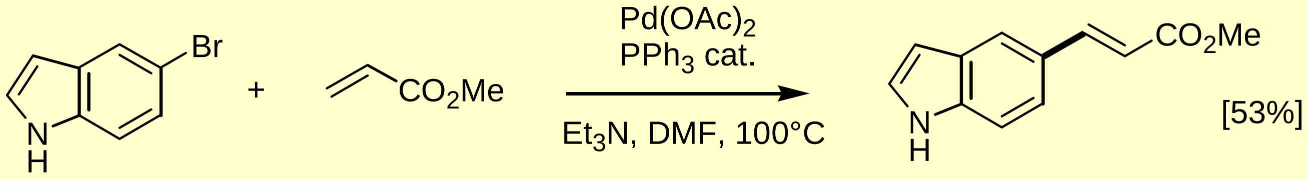
- ***Mechanism:***

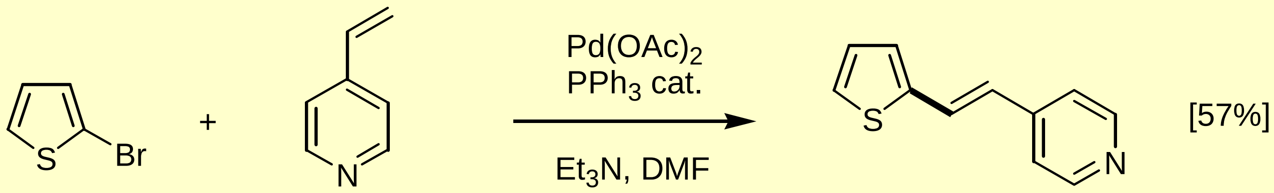


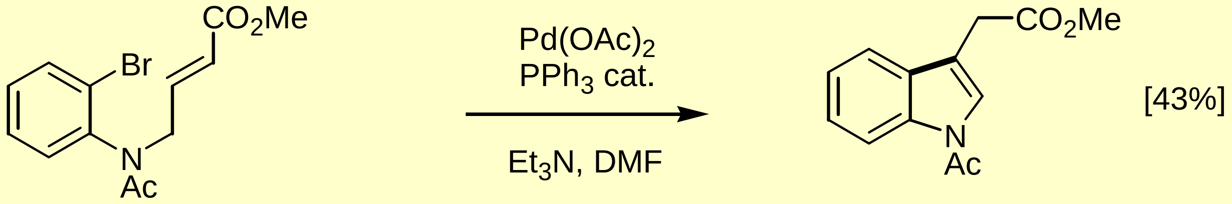
The Heck reaction

- ***Features:***
  - The palladium catalyst is generally added as a Pd(II) salt (these are generally more stable) which is reduced *in situ* either by the phosphine ligand or the Et_3N
  - The reaction works well for both electron withdrawing and electron donating substituents on the alkene
  - Stereochemistry of β–hydride elimination is always *syn* to the palladium

- ***Examples:***

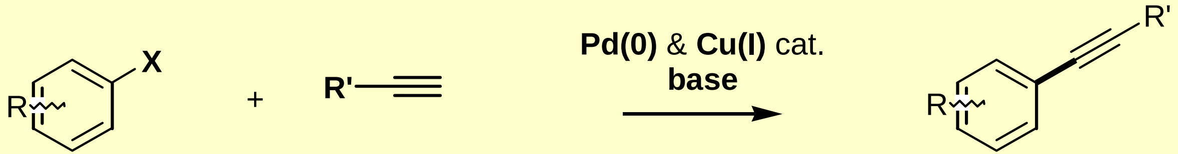






Ar-C(S*p*) Alkyne coupling: the Sonogashira reaction

- ***Overall scheme:***
  - ***review:*** Sonogashira in 'Metal catalysed cross coupling reactions' Eds Diederich & Stang, Wiley-VCH **1998**, pp203-227

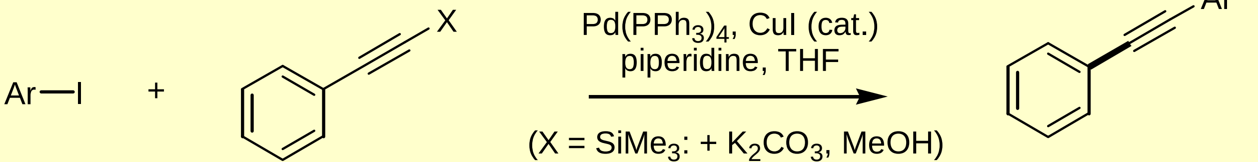


Pd(0) & **Cu(I)** cat.
base

X = Br, I, OTf
R' = usually alkyl or aryl
base = typically Et_2NH or $^iPrEt_2N$

tolan product

- ***Essentially a Heck reaction with an alkyne.***
  - Role of copper not well understood…in fact copper not necessary for some couplings.
  - Copper thought to form transient copper acetylide (*cf.* Stephens-Castro reaction).
- ***Useful variant involves use of trimethylsilyl alkynes which are 'deprotected'* in situ*:***
  - Nishihara *Chem. Lett.* **1997**, 1233; Schultz *J. Org. Chem.* **1998**, 63, 4034 (**DOI**)



$Pd(PPh_3)_4$, CuI (cat.)
piperidine, THF

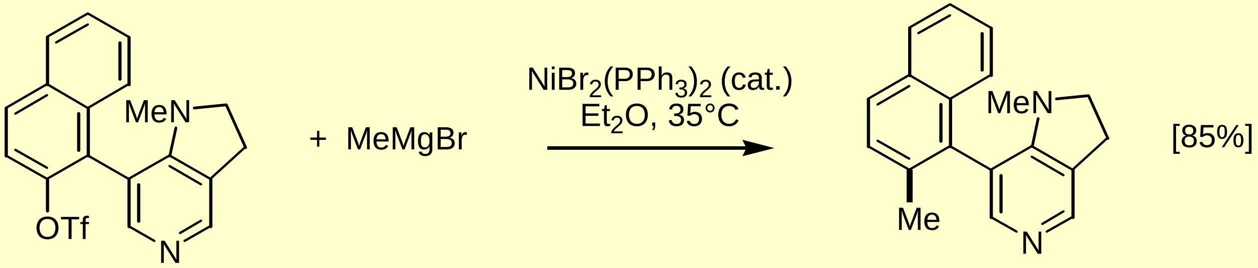
(X = $SiMe_3$: + K_2CO_3, MeOH)

Ar = porphyrin derivative
X = H or $SiMe_3$

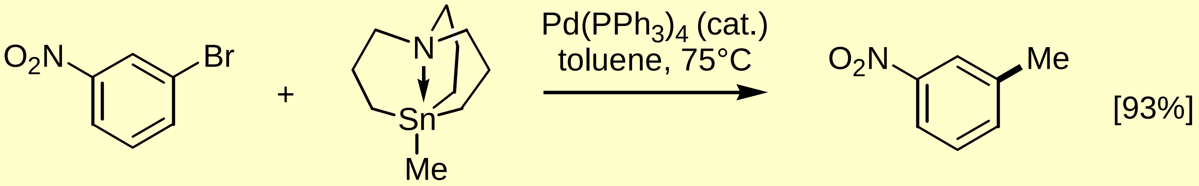
[X = H, 18%]
[X = $SiMe_3$, 79%]

Ar-C(S*p*^{3}) alkyl coupling

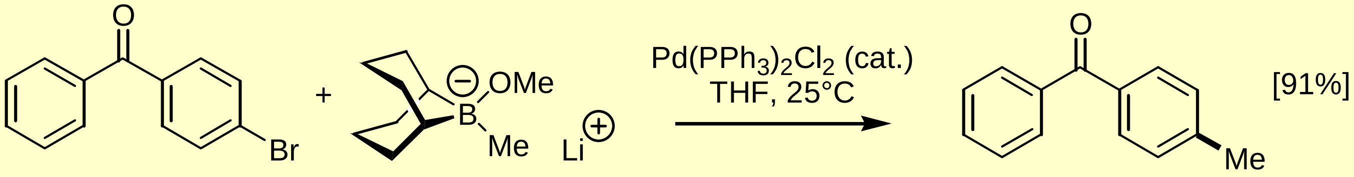
- ***Kumada-Corriu type couplings:***
  - *e.g.* Spivey *Tet. Lett.* **1998**, 39, 8919 (**DOI**)



- ***Stille type couplings:***
  - *e.g.* Vedejs *J. Am. Chem. Soc.* **1992**, 114, 6556 (**DOI**)

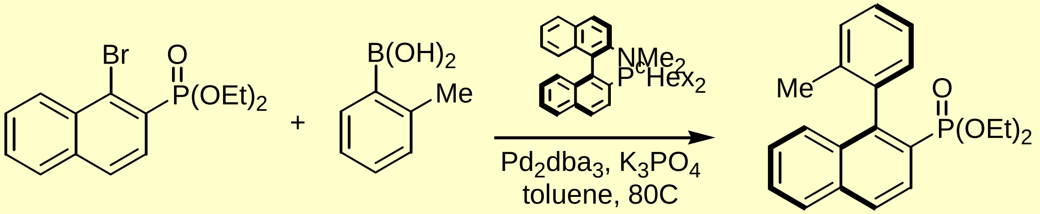


- ***Boronate couplings:***
  - *e.g.* Fürstner *Tetrahedron* **1995**, 51, 11165 (**DOI**)
  - see also potassium alkyltrifluoroborates: Molander *Org. Lett.* **2001**, *3*, 393 (**DOI**)



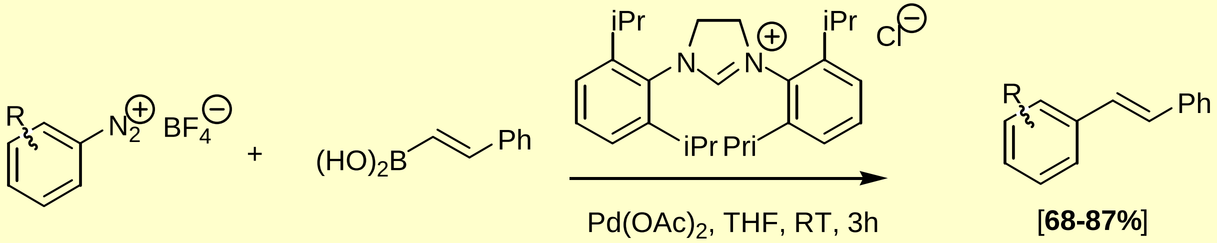
Advances/frontiers in cross-coupling technology

- ***Use of aryl chlorides as substrates (i.e. difficult oxidative addition):***
  - ***review:*** Fu *Angew. Chem. Int. Ed.* **2002**, 41, 4176 (**DOI**)
  - *e.g.* bulky alkyl phosphine ligands (bi-PhP^{t}Bu$_2$): Buchwald *J. Am. Chem. Soc.* **1999**, 121, 9550 (**DOI**) & Stable *N*-heterocyclic carbene ligands (IMes): Nolan *J. Organometal. Chem.* **2002**, 653, 69 (**DOI**)
- ***Atropisomer-selective asymmetric cross-coupling to form highly hindered biaryls:***
  - *e.g.* Suzuki with chiral binaphthyl ligand: Buchwald *J. Am. Chem. Soc.* **2000**, 122, 12051 (**DOI**)



[**97%**, 87%ee]

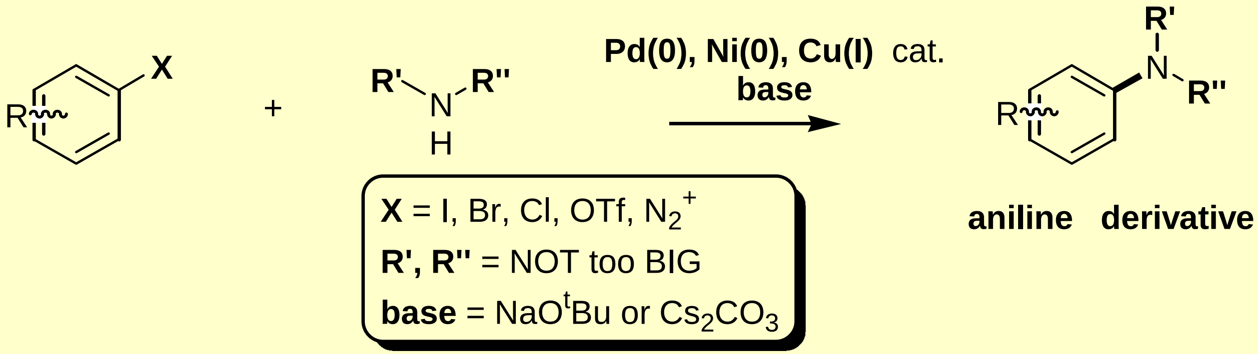
- ***ALKYL – ALKYL coupling:***
  - ligands that supress β-hydride eliminarion: *e.g.* Fu *J. Am. Chem. Soc.* **2007**, 129, 9602 (**DOI**)
- ***Room temperature coupling reactions:***
  - *e.g.* Heck reactions: Fu *J. Am. Chem. Soc.* **2001**, 123, 6989 (**DOI**)
- ***One-pot aryl metal formation/cross-coupling:***
  - Hydrostannylation/Stille coupling: *e.g.* Maleczka *J. Am. Chem. Soc.* **2001**, 123, 3194 (**DOI**)
- ***Diazonium salts as cross-coupling partners:***
  - Andrus *Org. Lett.* **2001**, 3, 3761 (**DOI**)



[**68-87%**]

C-N bond ‘cross-coupling’ – *nucleophilic amination*

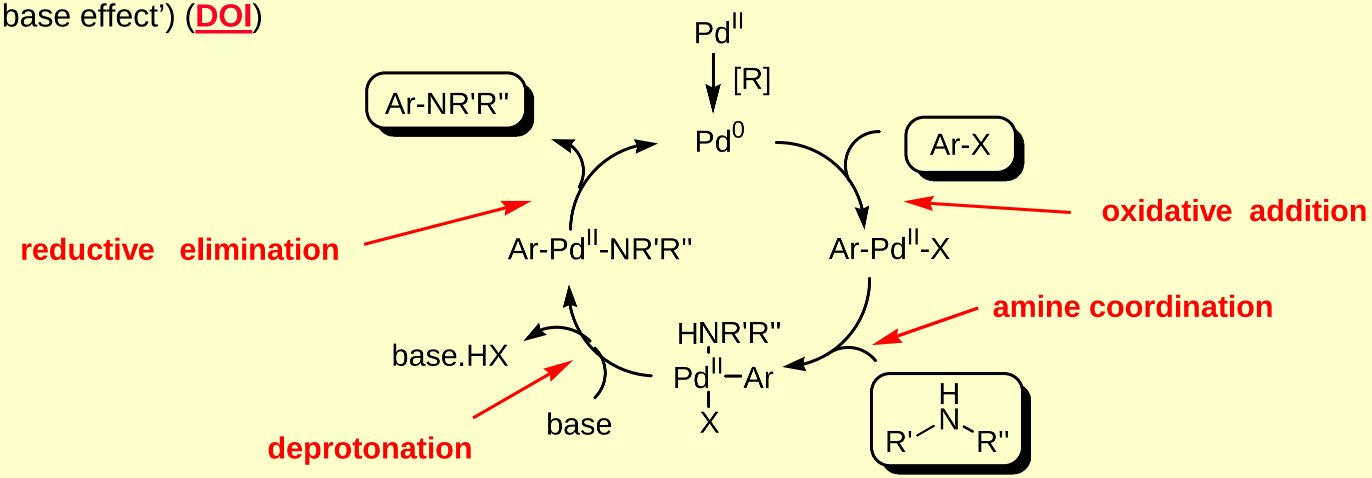
- ***prior art:*** *S_EAr nitration, then reduction, then alkylation or reductive amination; Goldberg reaction.*
- ***reviews:*** Mauger *Aldrichimica Acta* **2006**, 39, 17 (**DOI**); Kunz *Synlett* **2003**, 2428 (Cu) (**DOI**); Prim *Tetrahedron* **2002**, 58, 2041 (Pd) (**DOI**); Hartwig *Angew. Chem., Int. Ed.* **1998**, 37, 2046; Frost, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615 (**DOI**); Hartwig *Synlett* **1997**, 329 (**DOI**)
- ***overall scheme:***



X = I, Br, Cl, OTf, N_2^+
R', R'' = NOT too BIG
base = NaO^{t}Bu or Cs_2CO_3

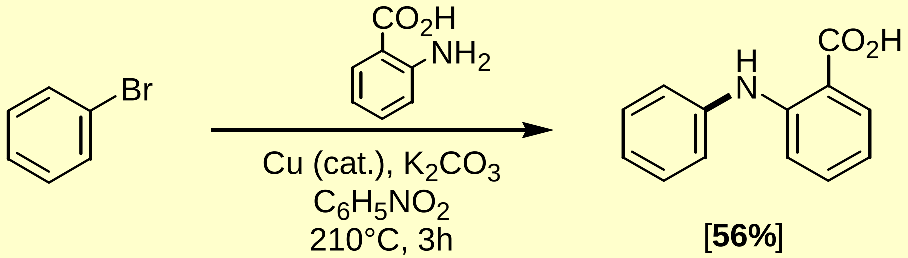
aniline derivative

- ***mechanism (Pd):***
  - Buchwald, Hartwig & Blackmond *J. Am. Chem. Soc.* **2006**, 128, 3584 (**DOI**)
  - Maes *J. Org. Chem.* **2004**, 69, 6010 (‘base effect’) (**DOI**)



Historical development

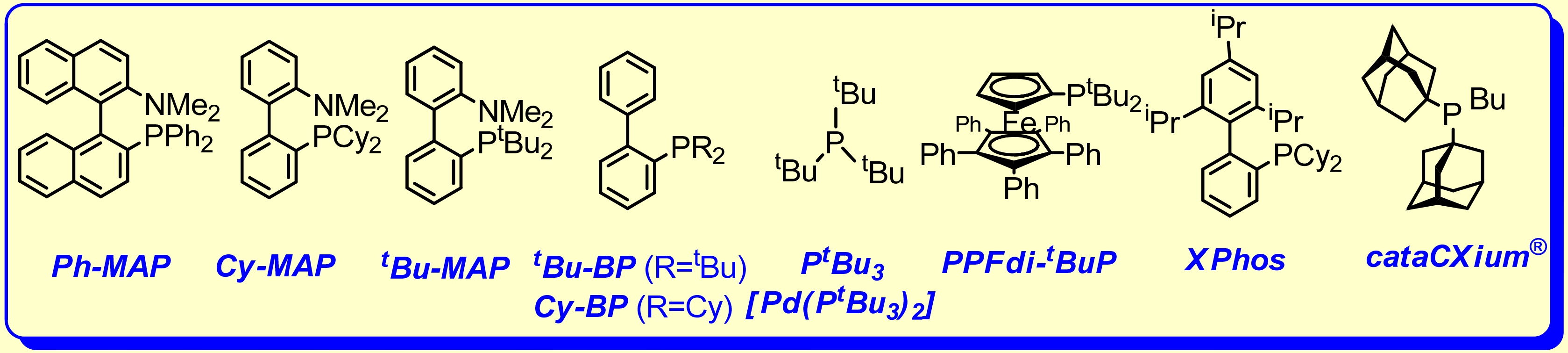
- ***1906: Goldberg reaction (Cu)***
    - Goldberg *Chem. Ber.* **1906**, *39*, 1691



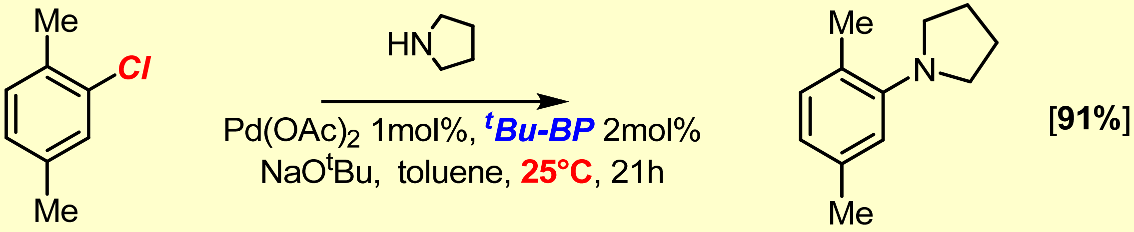
- ***1995-2000: Buchwald-Hartwig amination [Pd (& Ni)]***
    - ***FIRST GENERATION (G1):***
        - ***ligand:*** P(*o*-Tol)$_3$
        - ***aryl halide substrate:*** X = Br or I; Ar = non-hindered, electron poor or neutral
        - ***amine nucleophile:*** cyclic secondary
        - ***typical conditions:*** Pd(0), P(*o*-Tol)$_3$, NaO^{t}Bu or LiHMDS, toluene, 80-100 °C
    - ***SECOND GENERATION (G2):***
        - ***ligand:*** chelating diphosphines
        - ***aryl halide substrate:*** X = Br, I or OTf; Ar = electron rich, poor or neutral, heteroaromatic
        - ***amine nucleophile:*** cyclic secondary, primary and anilines
        - ***typical conditions:*** Pd(0),DPPF or BINAP, Cs_2CO_3 or K_3PO_4, toluene, 80-100 °C
    - ***THIRD GENERATION (G3):***
        - ***ligand:*** electron rich monodentate phosphines OR *N*-heterocyclic stable carbenes (NHCs)
        - ***aryl halide substrate:*** X = Cl, Br, I, OTf or OTs; Ar = electron rich, poor or neutral, heteroaromatic
        - ***amine nucleophile:*** secondary (cyclic & acyclic), primary and anilines
        - ***typical conditions:*** Pd(0),electron rich monophosphine/carbene, NaO^{t}Bu, Cs_2CO_3 or K_3PO_4, toluene, rt-100 °C
- ***2000-: Renaissance of Goldberg-type amination (Cu):***
        - chelating ***diamine*** and ***diol*** ligands

*Inter*molecular coupling of 2° amines (Pd)

- ***Ar-Br & Ar-Cl ↔ 2° amines (Pd):***
  - ***G3 phosphine ligand systems***. ***Highlight:*** Stürmer *Angew. Chem. Int. Ed.* **1999**, 38, 3307 (**DOI**)
  - ***Ph-MAP:*** Kocovsky *Tet. Lett*. **1998**, 39, 9289 (**DOI**)
  - ***Cy-MAP:*** Buchwald *J. Am. Chem. Soc.* **1998**, 120, 9722 (**DOI**)
  - ***^{t}Bu-MAP***, ***Cy-BP***, ***^{t}Bu-BP:*** Buchwald *Angew. Chem., Int. Ed.* **1999**, 38, 2413 (**DOI**) & *J. Org. Chem.* **2000**, 65, 1158 (**DOI**) & **2001**, 66, 3820 (solid-supported) (**DOI**) & *Org. Lett.* **2002**, 4, 2885 (**DOI**)
  - ***$P(tBu)_3$:*** Nishiyama *Tet. Lett.* **1998**, 39, 617 (**DOI**), & Hartwig *J. Org. Chem.* **1999**, 64, 5575 (**DOI**) & **2002**, 67, 6479 (**DOI**)
  - ***PPFditBuP:*** Hartwig *J. Org. Chem.* **2002**, 67, 5553 (**DOI**)
  - ***azaphosphatranes:*** Verkade *Org. Lett.* **2003**, 5, 815 (**DOI**) & *Org. Lett.* **2005**, 7, 4427 (vinyl halides) (**DOI**)
  - ***XPhos:*** Buchwald *J. Am. Chem. Soc.* **2003**, 125, 6653 (**DOI**) & *Org. Lett.* **2005**, 7, 3965 (heteroaryl halides) (**DOI**)
  - ***cataCXium®:*** Beller *Tetrahedron* **2005**, 61, 9705 (**DOI**)

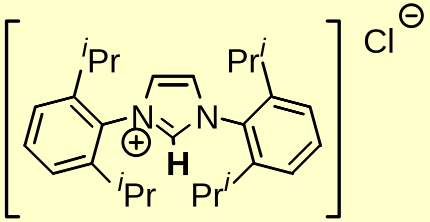


e.g.

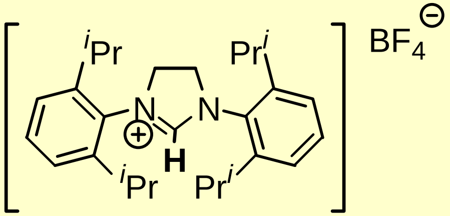


*Inter*molecular coupling of 2° amines (Pd) cont.

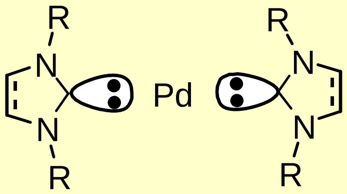
- ***Ar-Cl ↔ 2° amines (Pd):***
  - ***G3 N-heterocyclic carbene (NHC) ligand systems:***
  - ***in situ generation:*** Nolan *Org. Lett.* **1999**, 1, 1307 (**DOI**); Nolan *J. Org. Chem.* **2001**, 66, 7729 (**DOI**); Nolan *Org. Lett.* **2002**, 4, 2229 (**DOI**); Hartwig *Org. Lett.* **2000**, 2, 1423 (**DOI**)
  - ***pre-formed*:** Caddick *Chem. Commun.* **2001**, 1388 (**DOI**) & *Tetrahedron* **2005**, 61, 9710 (**DOI**)
  - ***no catalyst!:*** using $CsOH \cdot H_2O$ in DMSO *via* arynes? Adapa *Synlett* **2004** 1747 (**DOI**)



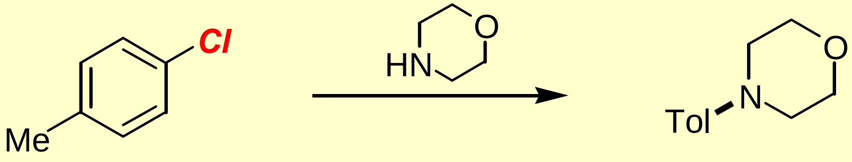
imidazolium salt ***NHC1***
(Nolan)



dihydroimidazolium salt ***NHC2***
(Hartwig)



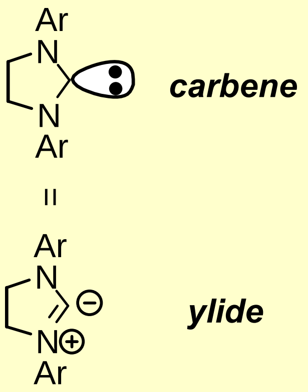
R = 2,6-di(^{i}Pr)C_6H_3 ***NHC3*** & R = *t*-Bu ***NHC4***
Pd(0) complexes (Caddick & Cloke)



$Pd_2(DBA)_3$, ***NHC1*** 1mol%, KO^{t}Bu, 1,4-dioxane, **100°C**: [**100%**]

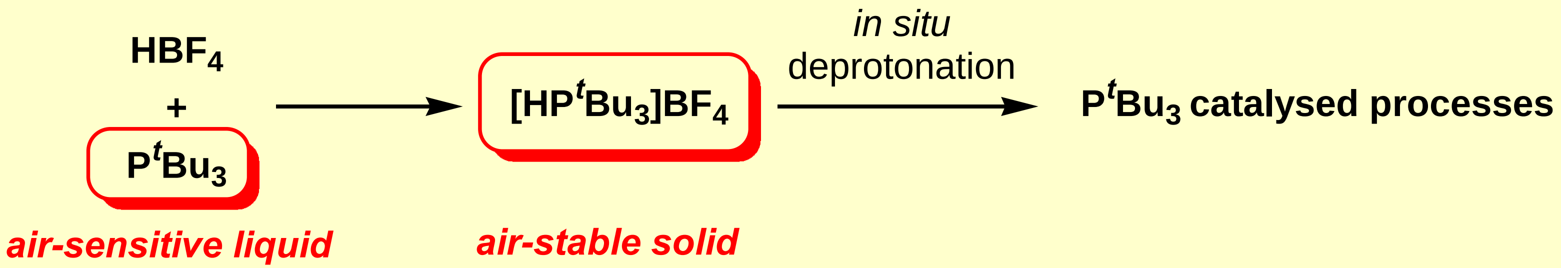
$Pd(DBA)_2$ 1mol%, ***NHC2*** 1mol%, NaO^{t}Bu, DME, **25°C**: [**82%**]

NHC3 1mol%, KO^{t}Bu, 1,4-dioxane, **100°C**: [**99%**]

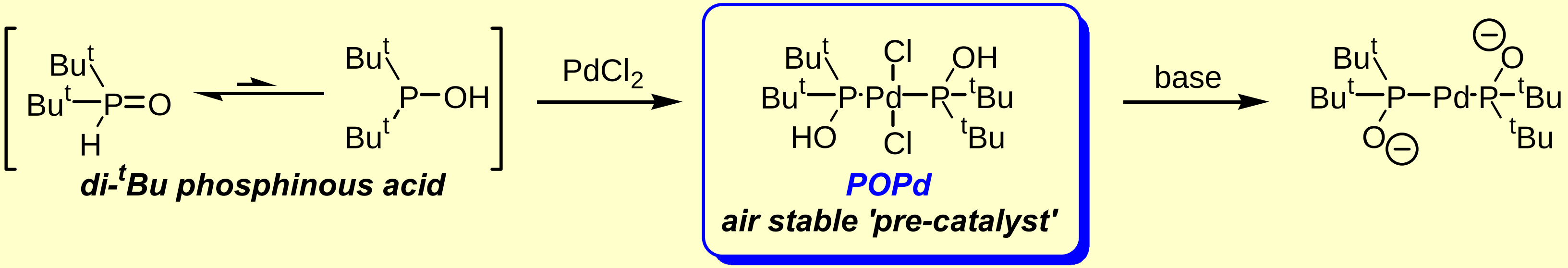


Air-stable trialkylphosphonium salts & pre-catalysts

- ***phosphonium salts as practical replacements for air-sensitive alkyl phosphines:***
  - Fu *Org. Lett.* **2001**, 3, 4295 (**DOI**)



- ***air stable Pd(II)-phosphinous acid complexes:***
  - Li *Angew. Chem. Int. Ed.* **2001**, 40, 1513 (**DOI**); Li *J. Org. Chem.* **2001**, 66, 8677 (**DOI**)

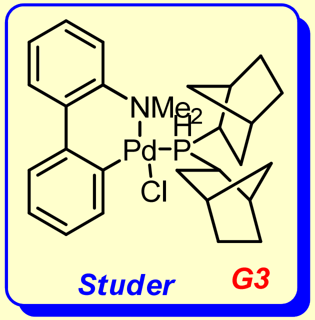


di-^{t}Bu phosphinous acid

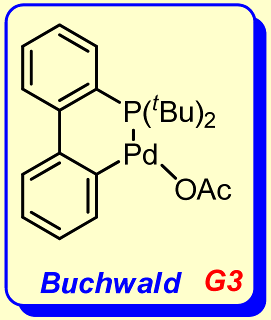
POPd

air stable 'pre-catalyst'

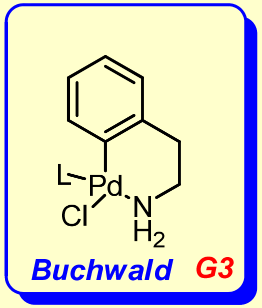
- ***air stable palladacycles:***
  - Studer *Angew. Chem. Int. Ed.* **2002**, 41, 3668 (**DOI**)
  - Buchwald *Org. Lett.* **2003**, *5*, 2413 (**DOI**)
  - Buchwald *J. Am. Chem. Soc.* **2008**, 130, 6686 (**DOI**)



Studer ***G3***



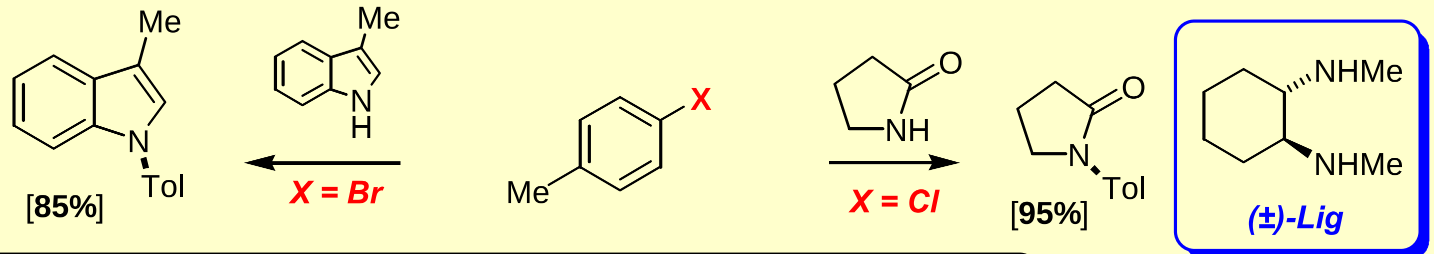
Buchwald ***G3***



Buchwald ***G3***

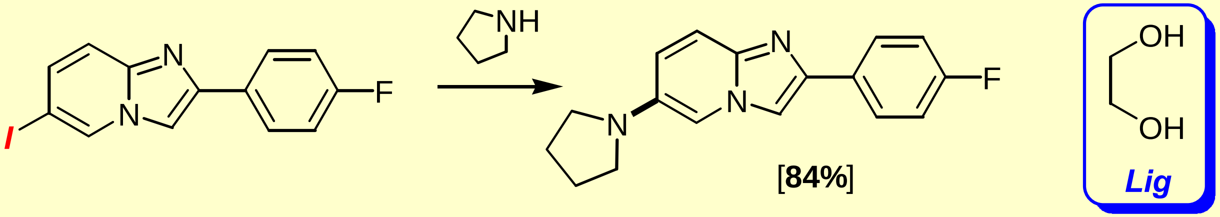
Cu catalysis

- ***Ar-Cl ↔ 2° amines, anilines, amides & azoles (Cu):***
  - ***catalytic Goldberg coupling - review:*** Kunz *Synlett* **2003**, 2428 (**DOI**); ***mechanism:*** Buchwald *J. Am. Chem. Soc.* **2005**, 127, 4120 (**DOI**); ***comparison of ligands:*** Wiederman *Tet. Lett*. **2006**, 47, 6011 (**DOI**)
  - ***diamine ligands:*** Buchwald *J. Am. Chem. Soc.* **2001**, 123, 7727 (**DOI**), Buchwald *J. Am. Chem. Soc.* **2002**, 124, 7421 (**DOI**); Buchwald *J. Am. Chem. Soc.* **2002**, 124, 11684 (**DOI**), Kang *Synlett* **2002**, 427 (**DOI**), Buchwald *J. Org. Chem*. **2004**, 69, 5578 (**DOI**), You *J. Org. Chem.* **2007**, 72, 2737 (**DOI**), Mino *Synlett* **2008**, 614 (**DOI**)



conditions: ***CuI 1 mol%***, **Lig** 10 mol%, K_3PO_4 2eq, 1,4-dioxane, **110 °C**

  - ***diol & triol ligands:*** Buchwald *Org. Lett.* **2002**, 4, 581 (**DOI**), Buchwald *J. Org. Chem.* **2003**, 68, 4367 (**DOI**), Chen *Org. Lett*. **2007**, 8, 5609 (**DOI**); ***MW acceleration*** see: Lange *Tet. Lett.* **2002**, 43, 1101 (**DOI**); ***solvent free*** see: Li *J. Org. Chem*. **2006**, 71, 8324 (**DOI**)

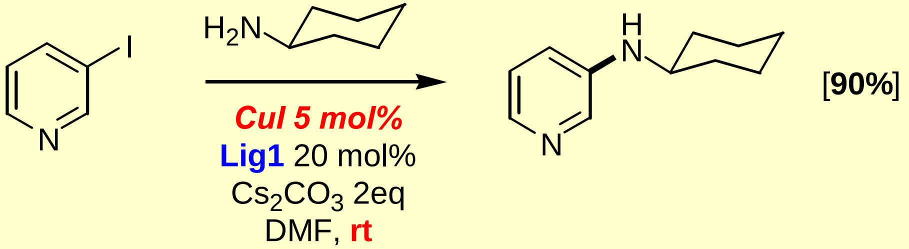


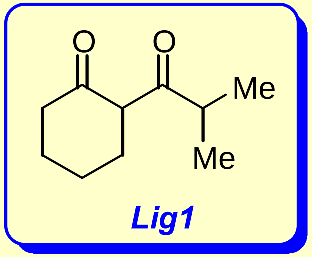
conditions: ***CuI 10 mol%***, **Lig** 200 mol%, K_3PO_4 2eq, IPA, **110 °C**

  - ***benzotriazole ligand:*** Verma *Tet. Lett*. **2007**, 48, 4207 (**DOI**); ***amino acid ligands:*** Ma *J. Org. Chem.* **2005**, 70, 5164 (**DOI**); ***diazaphospholane ligand:*** Liu *J. Org. Chem.* **2007**, 72, 8969 (**DOI**); ***N-hydroxyimide ligand:*** Jiang *J. Org. Chem.* **2007**, 72, 8943 (**DOI**); ***pyrrole-2-carboxylic acid ligand:*** Buchwald *J. Org. Chem.* **2008**, 73, 5167 (**DOI**); ***ligand free:*** with MW acceleration: Wu *Tet. Lett.* **2003**, 44, 3385 (***sulfonamides***) (**DOI**)

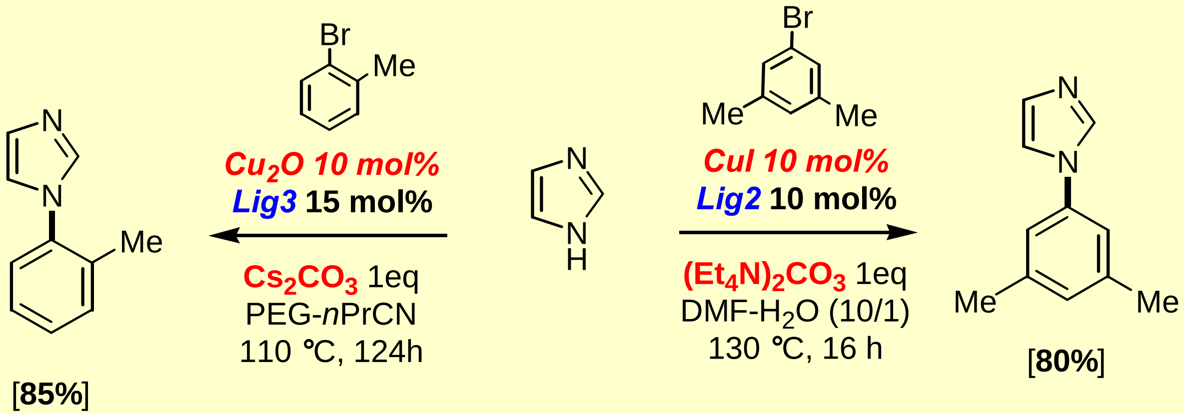
Cu catalysis *state-of-the-art*

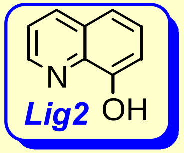
- ***Ar-I ↔ 1°/2° amines, anilines at RT (Cu):***
  - Buchwald *J. Am. Chem. Soc.* **2006**, 128, 8742 (DOI)

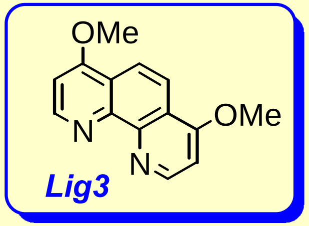




- ***Ar-Br/Ar-I ↔ imidazoles (Cu):***
  - Buchwald *Org. Lett.* **2006**, 8, 2779 (***Lig2***) (DOI), Liu *J. Org. Chem.* **2005**, 70, 10135 (***Lig3***) (DOI), Buchwald *J. Org. Chem.* **2007**, 72, 6190(DOI)



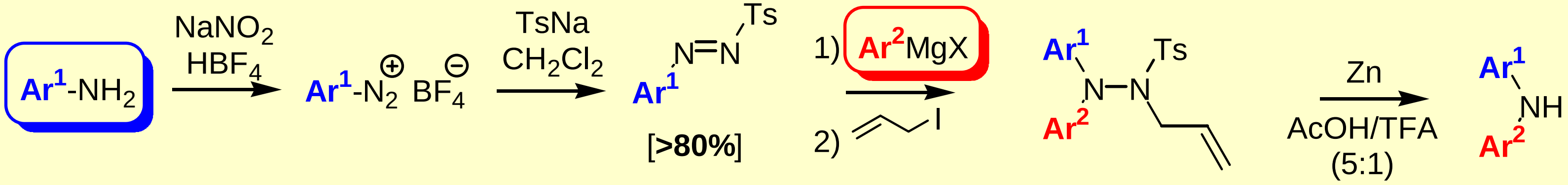




- ***Ar-Br/Ar-I ↔ R-NH$_2$ in water (Cu):*** Wan *Synthesis* **2006**, 3955 (DOI)
- ***Ar-Br/Cl ↔ imidazoles no ligand (Cu):*** You *J. Org. Chem.* **2007**, 72, 8535 (DOI)

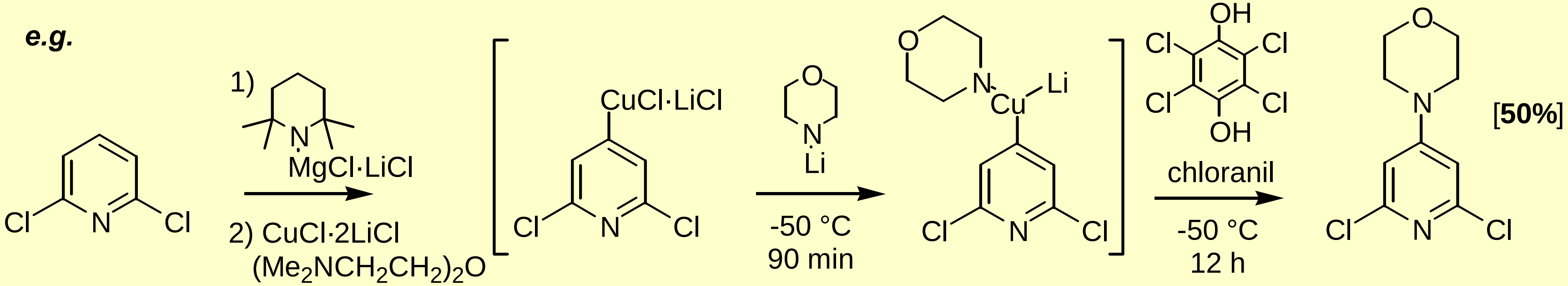
C-N bond formation – *electrophilic amination*

- ***aryl Grignard reagents + nitroarenes:***
  - Knochel *J. Am. Chem. Soc.* **2002**, 124, 9390 (**DOI**) (*NB.* requires 2 eq of Grignard reagent)
- ***aryl & alkyl Grignard reagents + arylazo tosylates:***
  - Knochel *Angew. Chem. Int. Ed.* **2004**, 43, 897 (**DOI**)



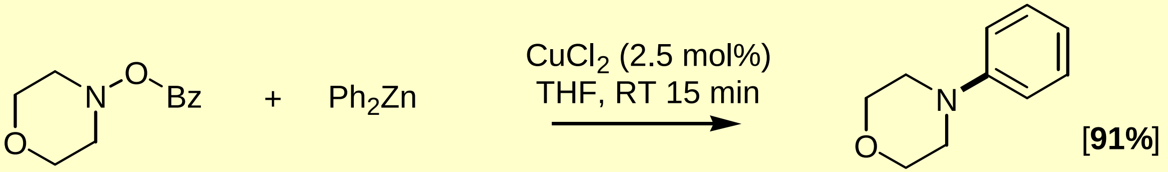
- ***oxidative coupling of aryl Cuprate reagents lithium amides:***
  - Knochel *Angew. Chem. Int. Ed.* **2006**, 45, 7838 (**DOI**) & Knochel *Synthesis* **2007**, 1272 (**DOI**)

e.g.

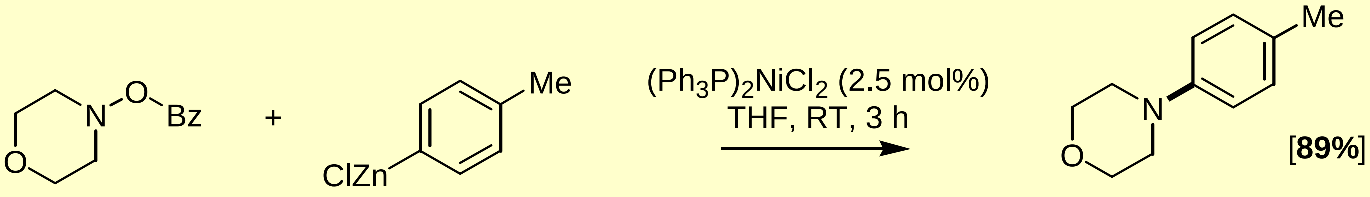


C-N bond formation – *electrophilic amination*

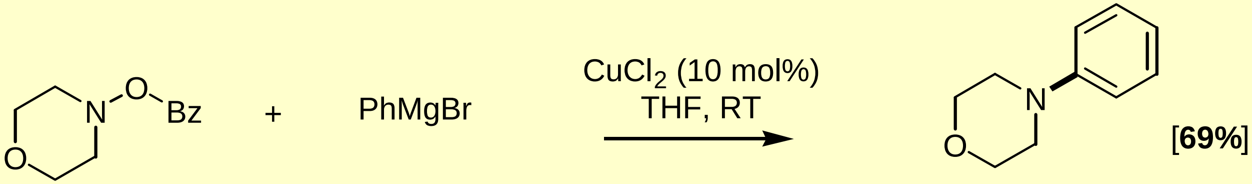
- ***R_2Zn* + *O-benzoylhydroxylamines with $CuCl_2$ (cat.):***
  - Johnson *J. Am. Chem. Soc.* **2004**, 126, 5680 (**DOI**) & *J. Org. Chem.* **2005**, 70, 364 (**DOI**) & *J. Org. Chem.* **2006**, 71, 219 (**DOI**)



- ***RZnX* + *O-benzoylhydroxylamines with $Ni(PPh_3)_2Cl_2$ (cat.):***
  - Johnson *Synlett* **2005**, 1799 (**DOI**)



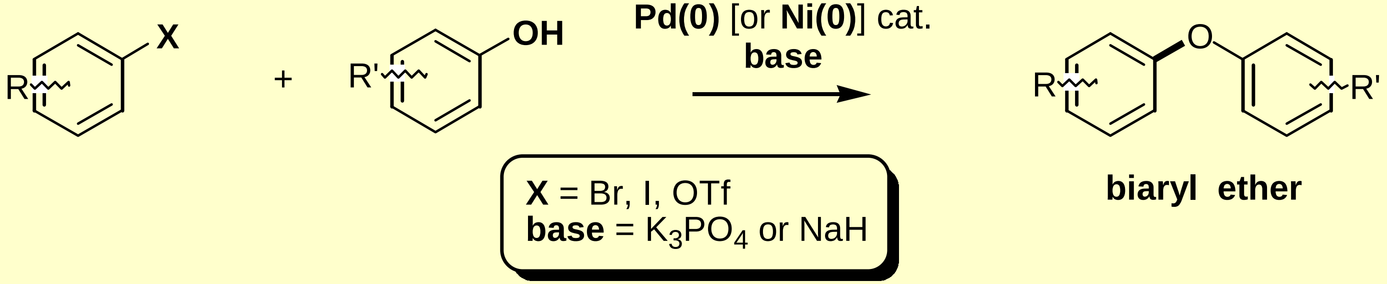
- ***RMgX* + *O-benzoylhydroxylamines with $CuCl_2$ (cat.):***
  - Johnson *Org. Lett.* **2007**, 9, 1521 (also mechanistic studies confirm S_N2) (**DOI**)



C-O bond cross-coupling - overview

- ***prior art:*** *the copper mediated Ullmann biaryl ether synthesis*
- ***reviews:*** Theil *Angew. Chem. Int. Ed.* **1999**, 38, 2345 (**DOI**); Hartwig *Angew. Chem. Int. Ed.* **1998**, 37, 2046 (**DOI**); Frost *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615 (**DOI**); Hartwig *Synlett* **1997**, 329 (**DOI**)

- ***overall scheme:***

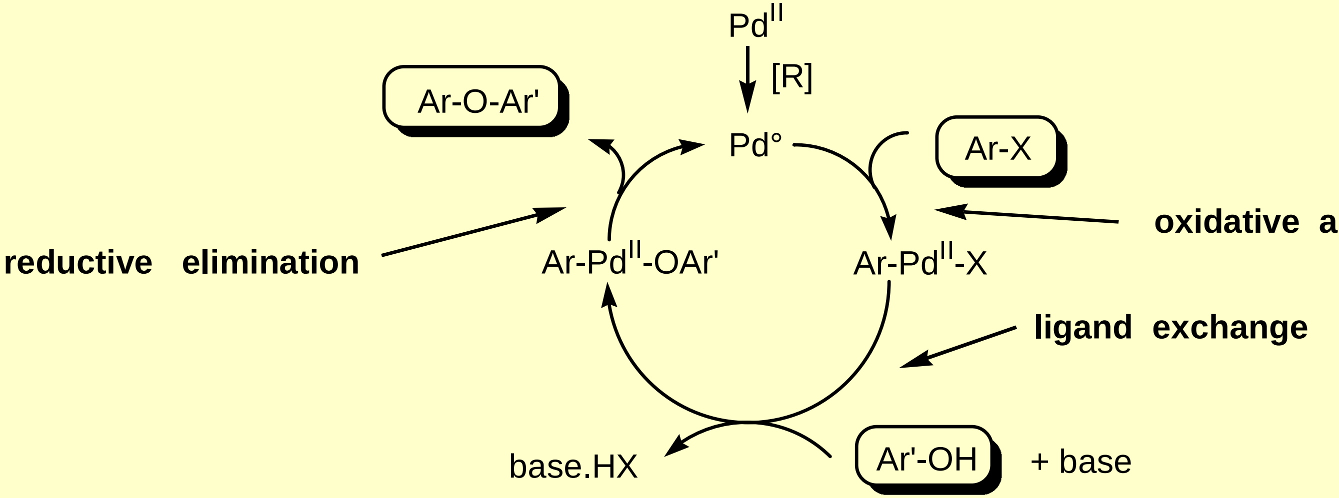


Pd(0) [or **Ni(0)**] cat.
base

X = Br, I, OTf
base = K_3PO_4 or NaH

biaryl ether

- ***mechanism:***



Pd^{II}

[R]

Pd°

Ar-X

oxidative addition

$Ar\text{-}Pd^{II}\text{-}X$

ligand exchange

Ar'-OH + base

base.HX

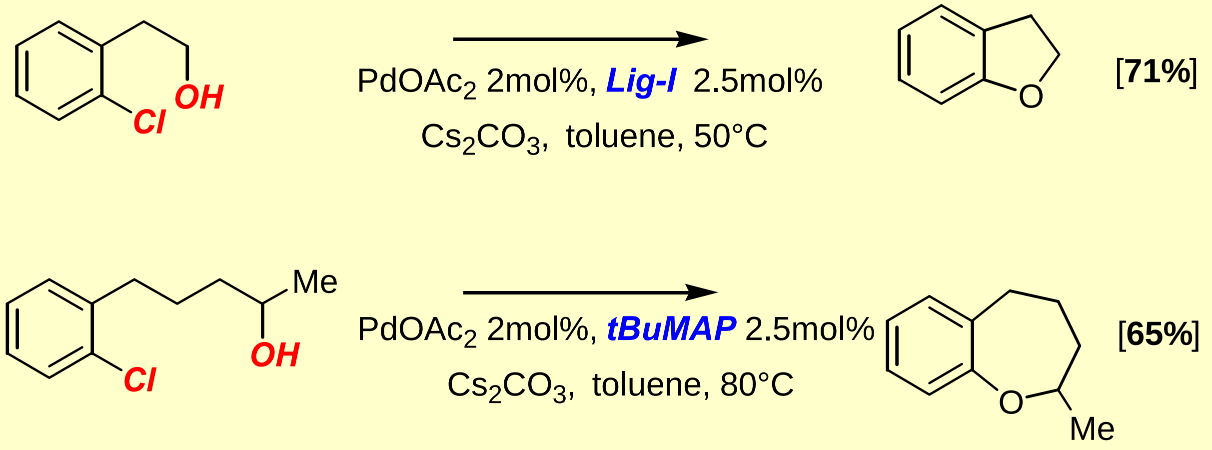
$Ar\text{-}Pd^{II}\text{-}OAr'$

reductive elimination

Ar-O-Ar'

Intramolecular etherification of arylchlorides (1°/2° OH)

- ***Pd(0) cat. intramolecular etherification of Ar-Cl with 1° and 2° alcohols:***
  - formation of 5-, 6-, and 7-membered rings
  - Buchwald *J. Am. Chem. Soc.* **2000**, 122, 12907 (DOI); Buchwald *J. Am. Chem. Soc.* **2001**, 123, 12202 (DOI)



$PdOAc_2$ 2mol%, ***Lig-I*** 2.5mol%

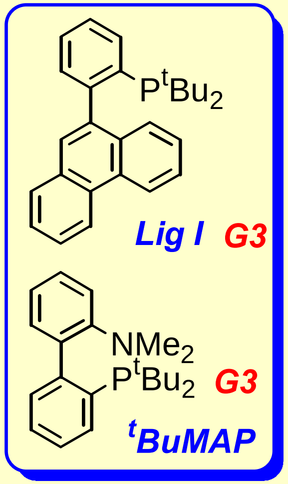
Cs_2CO_3, toluene, 50°C

[**71%**]

$PdOAc_2$ 2mol%, ***tBuMAP*** 2.5mol%

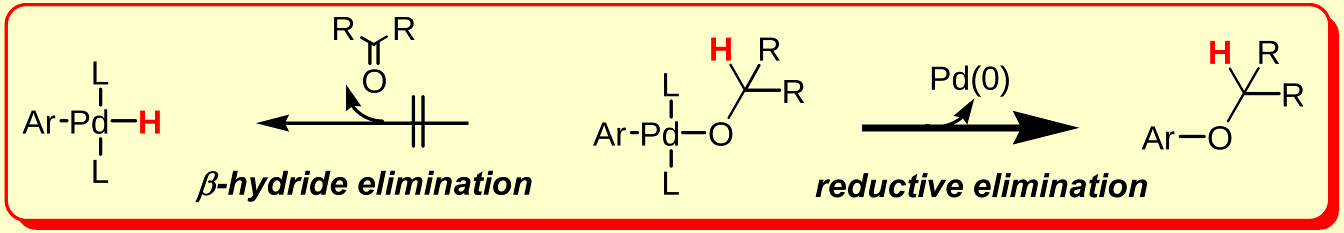
Cs_2CO_3, toluene, 80°C

[**65%**]



Lig I ***G3***

G3 ***^{t}BuMAP***



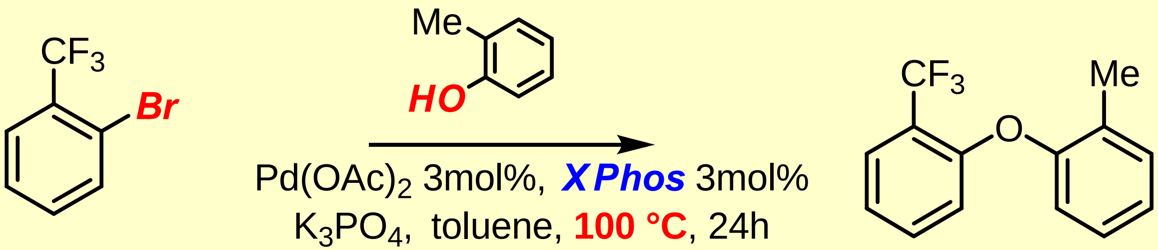
β-hydride elimination

reductive elimination

Pd(0) catalysed biaryl ether formation – *state-of-the-art*

- ***Pd(0) cat. etherification of Ar-Hal with phenols:***
  - Buchwald *Angew. Chem. Int. Ed.* **2006**, 45, 4321 (**DOI**)

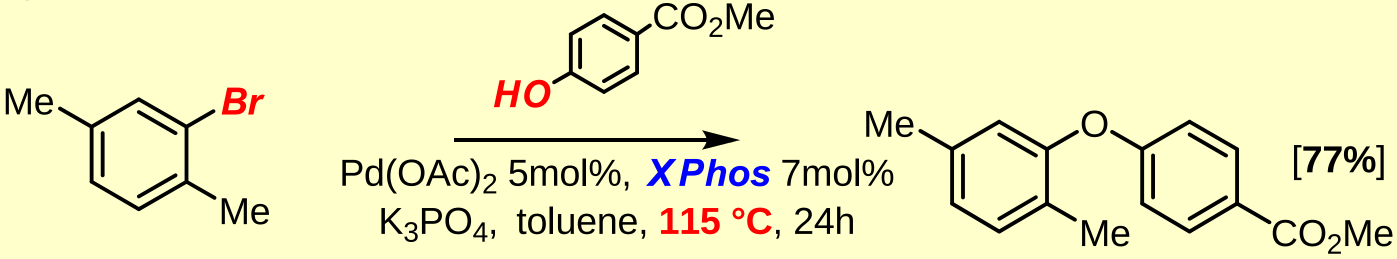
aryl halides with EWG at ortho position:



$Pd(OAc)_2$ 3mol%, ***XPhos*** 3mol%
K_3PO_4, toluene, **100 °C**, 24h

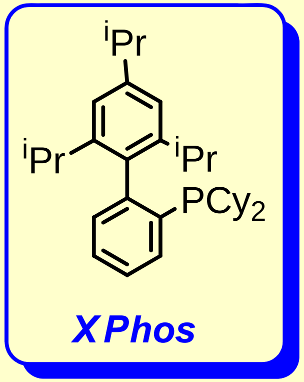
[85%]

phenols with EWGs:



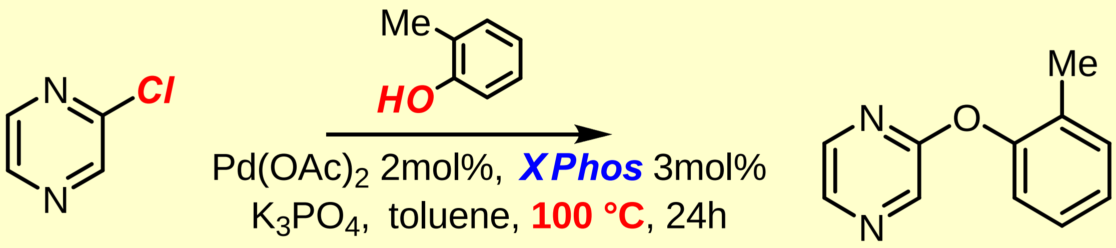
$Pd(OAc)_2$ 5mol%, ***XPhos*** 7mol%
K_3PO_4, toluene, **115 °C**, 24h

[77%]



XPhos

heteroaryl halides:

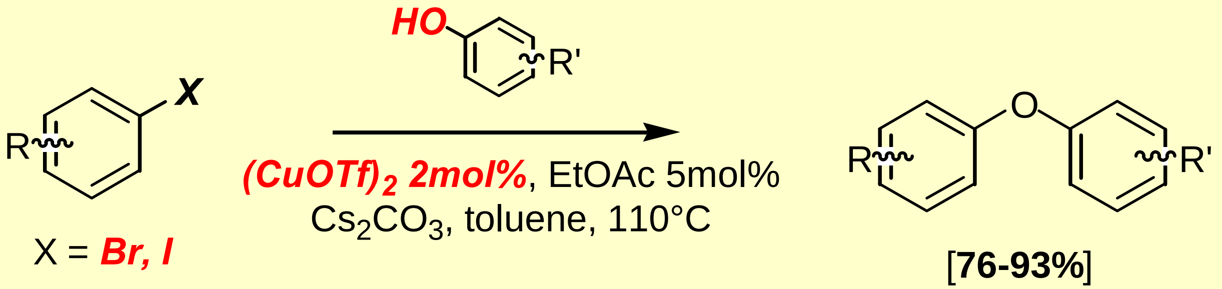


$Pd(OAc)_2$ 2mol%, ***XPhos*** 3mol%
K_3PO_4, toluene, **100 °C**, 24h

[87%]

Cu(I) catalysed biaryl ether formation

- ***Cu(I) cat. etherification of Ar-Br with phenols:***
  - ***catalytic Ullmann coupling:*** electron rich and deficient partners react; di-*ortho*-substituted phenols give low yields (20-30%)
  - Buchwald *J. Am. Chem. Soc*. **1997**, 119, 10539 (**DOI**)

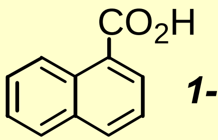


X = ***Br, I***

(CuOTf)$_2$ 2mol%, EtOAc 5mol%
Cs_2CO_3, toluene, 110°C

[76-93%]

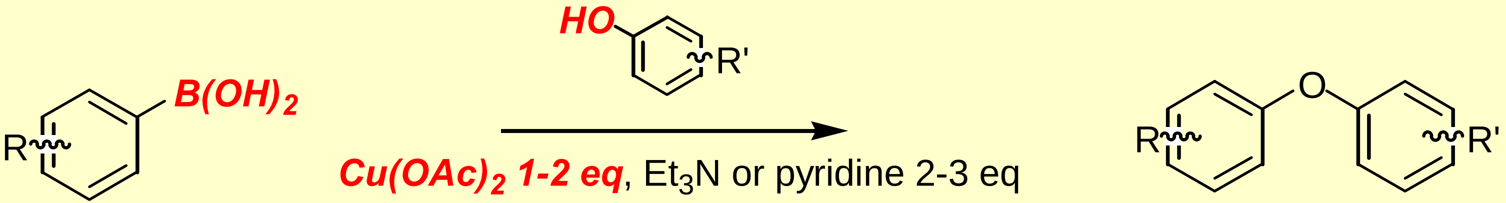
NB. 1 eq *1-NA* sometimes added to aid solubility of phenoxide



1-NA

  - See also Zhang *Chem.Commun.* **2007**, 3186 (**DOI**) – CuI (20 mol%), Cs_2CO_3, 145 °C, $Si(OEt)_4$ as solvent

- ***Cu(I) cat. etherification of Ar-B(OH)$_2$ with phenols:***
  - Chan *Tet. Lett*. **1998**, 39, 2933 (**DOI**); Evans *Tet. Lett*. **1998**, 39, 2937 (**DOI**)

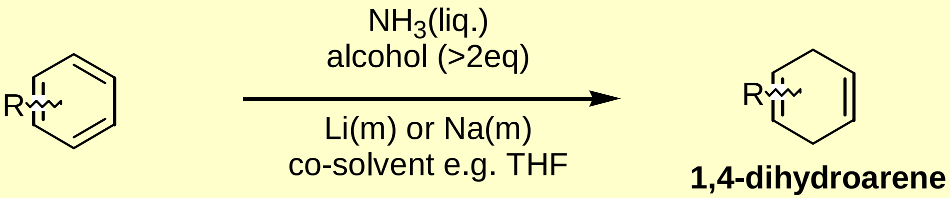


Cu(OAc)$_2$ 1-2 eq, Et_3N or pyridine 2-3 eq
CH_2Cl_2, 25°C

[excellent yields]

Birch Reduction

- ***Overall Scheme***
  - ***reviews:*** Mander *Comp. Org. Synth.* **1995**, 8, 489 & Donohoe *Tet. Asymm.* **1996**, 7, 317 (**DOI**)

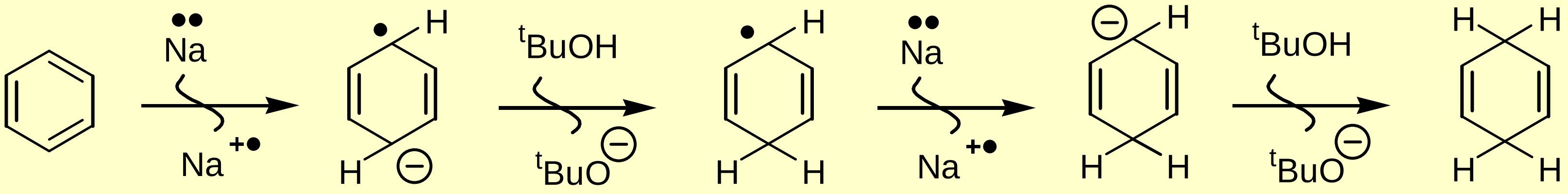


NH_3(liq.)
alcohol (>2eq)

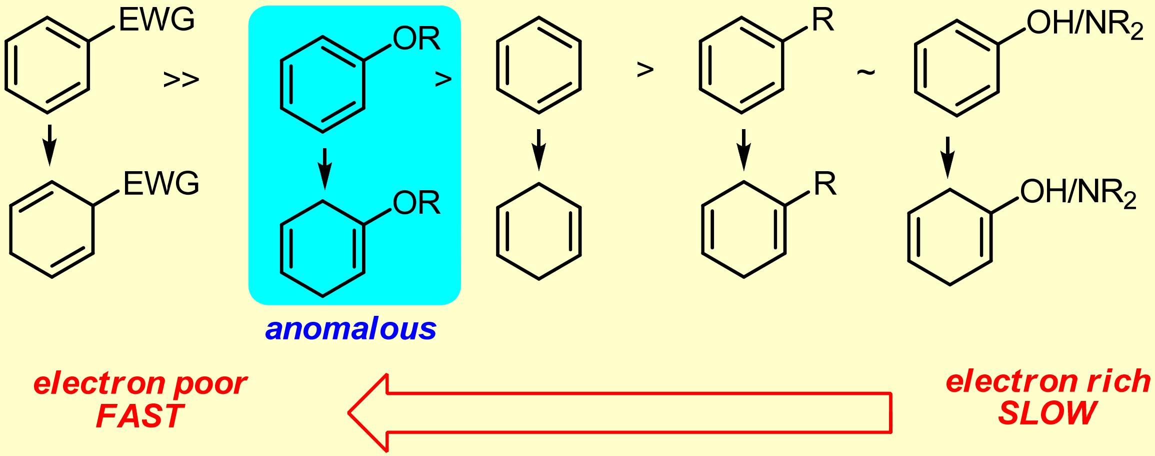
Li(m) or Na(m)
co-solvent e.g. THF

1,4-dihydroarene

- ***Mechanism:***



- ***Rates and Regioselectivity:***



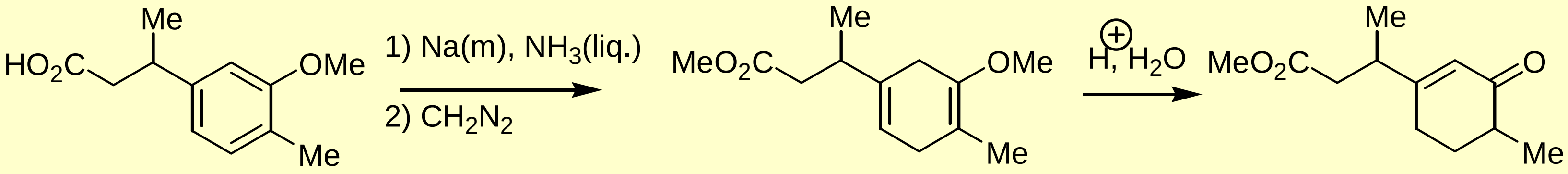
anomalous

electron poor
FAST

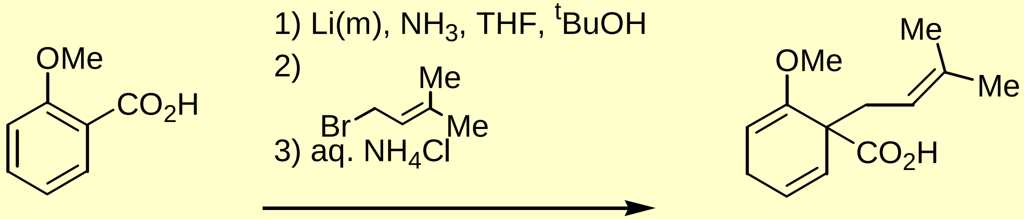
electron rich
SLOW

Birch reduction & alkylation

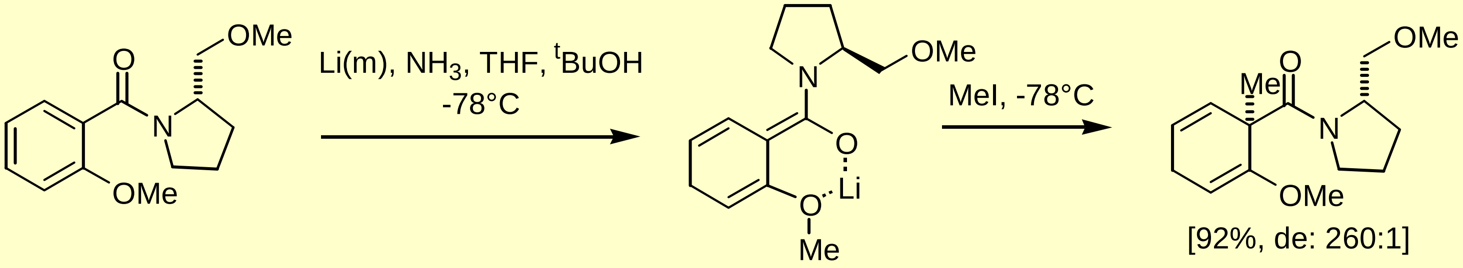
- Pinder *J. Org. Chem.* **1972**, 37, 2202 (**DOI**)



- Chandrasekaran *Tet. Lett.* **1982**, 23, 3799 (**DOI**)



- Schultz *Chem. Commun.* **1999**, 1263 (**DOI**)

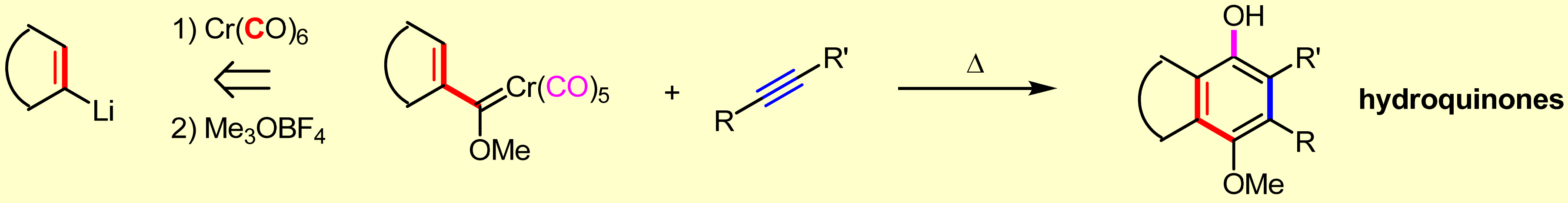


[92%, de: 260:1]

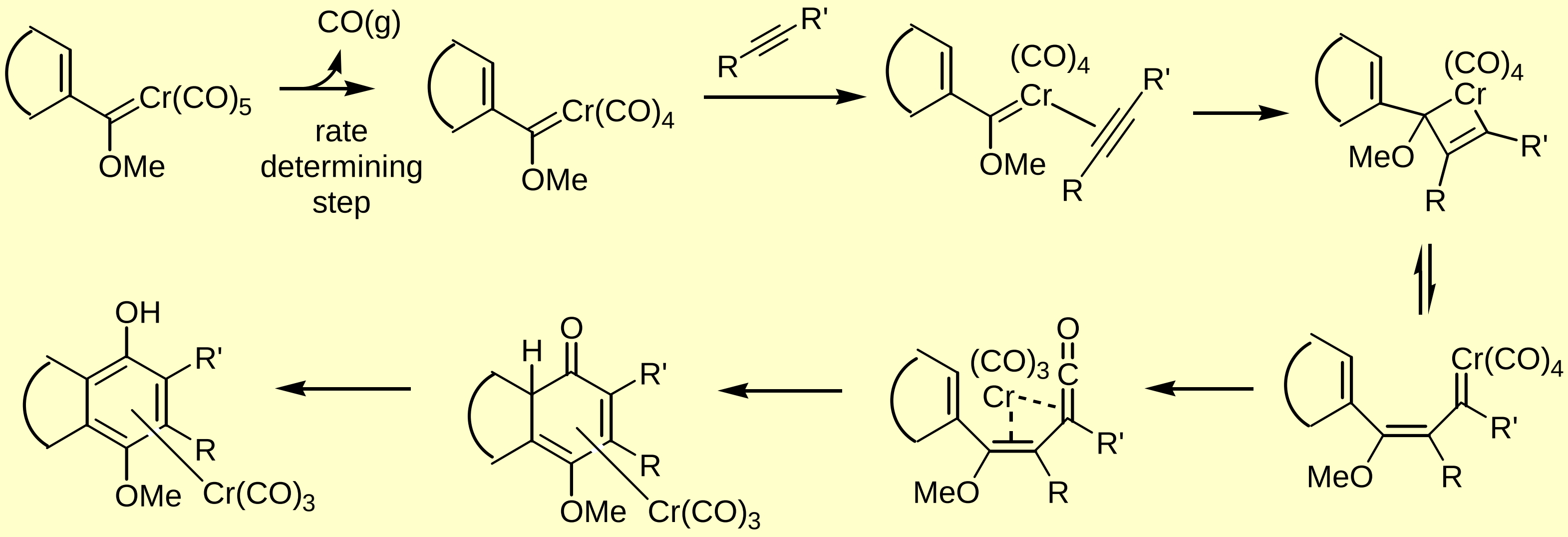
Dötz Benzannulation [3+2+1]

- ***Review:***
  - Shore *Chem. Rev.* **1988**, 88, 108 (**DOI**)

- ***Overall scheme:***

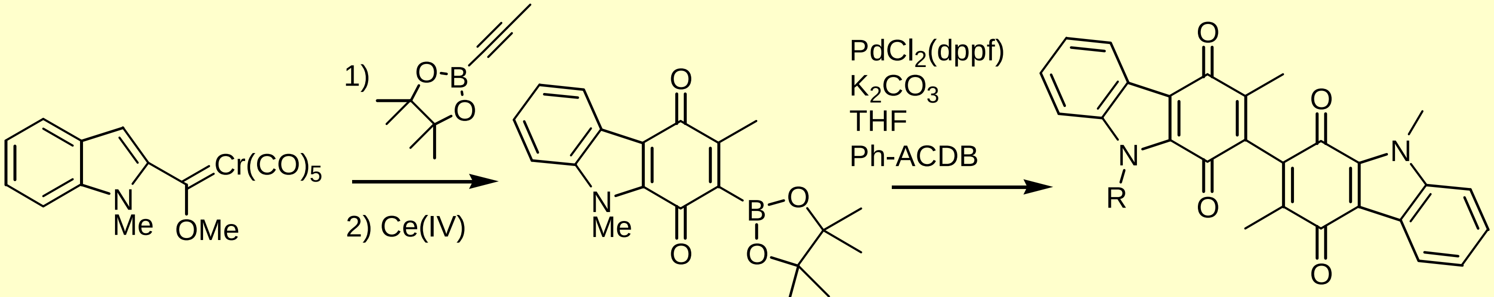


- ***Mechanism:***



Dötz Benzannulation

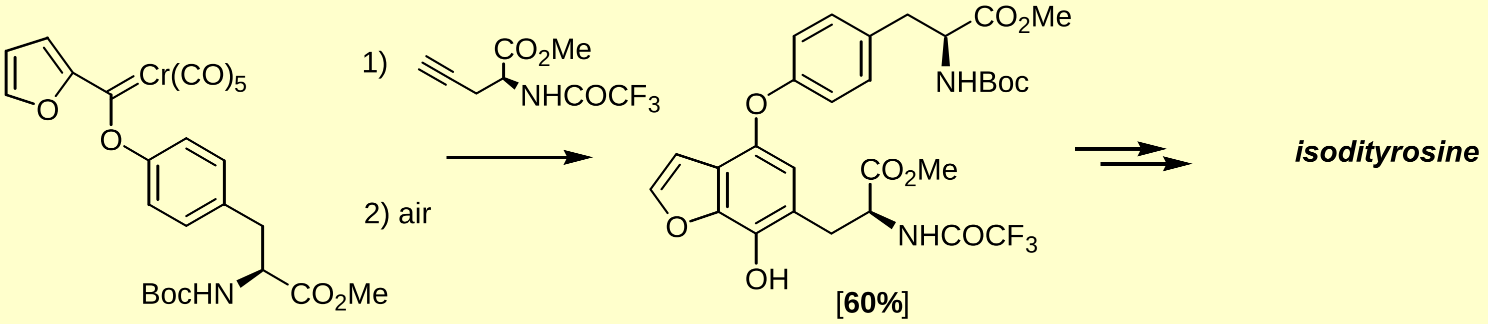
- ***Features:***
  - First reported by Dötz in 1975.
  - Only moderate regioselectivity if R and R’ are of similar size.
  - Can tolerate a wide range of functionality.
- ***Examples:***
  - Harrity *J. Org. Chem.* **2001**, 66, 3525 (**DOI**)



[**64%**]

R = Me [**42%**]
R = H, bismurrayaquinone A

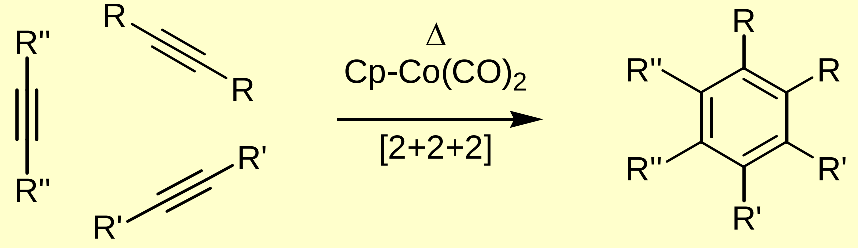
  - Pulley *J. Org. Chem.* **2005**, 70, 7422 (**DOI**)



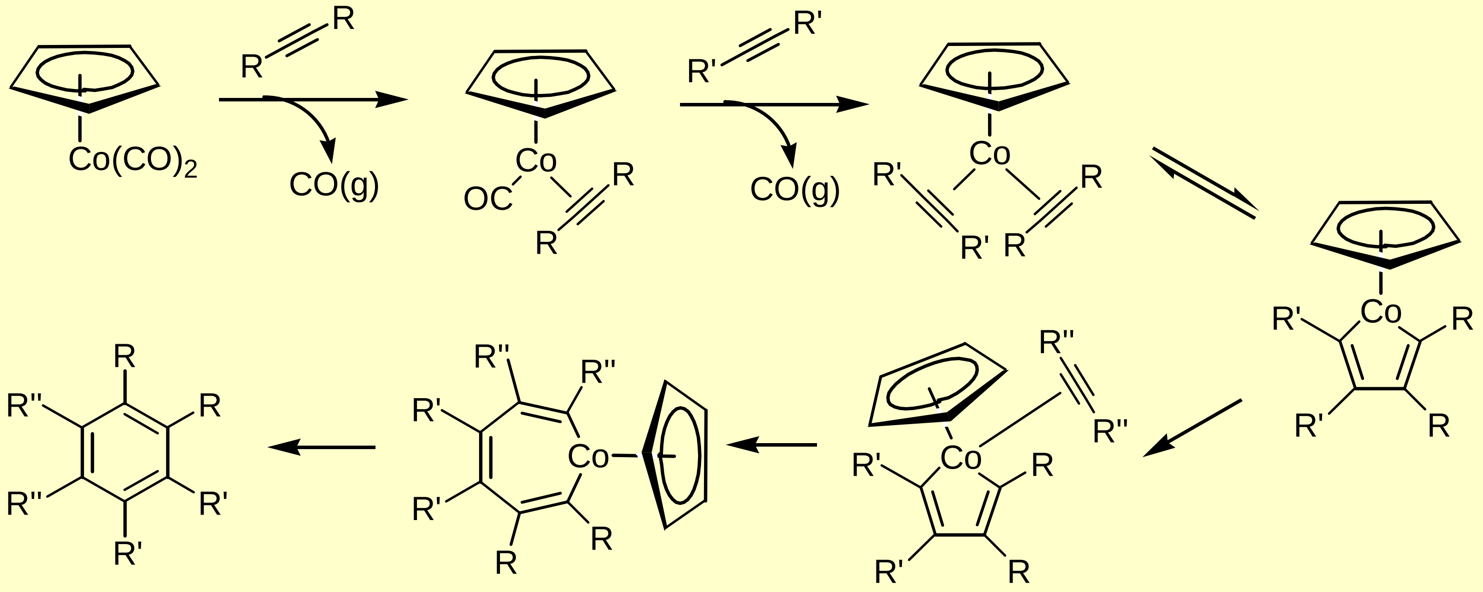
[**60%**]

Vollhardt [2+2+2] cycloaddition

- ***Review:***
  - Vollhardt *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 539 (**DOI**)
- ***Overall scheme:***



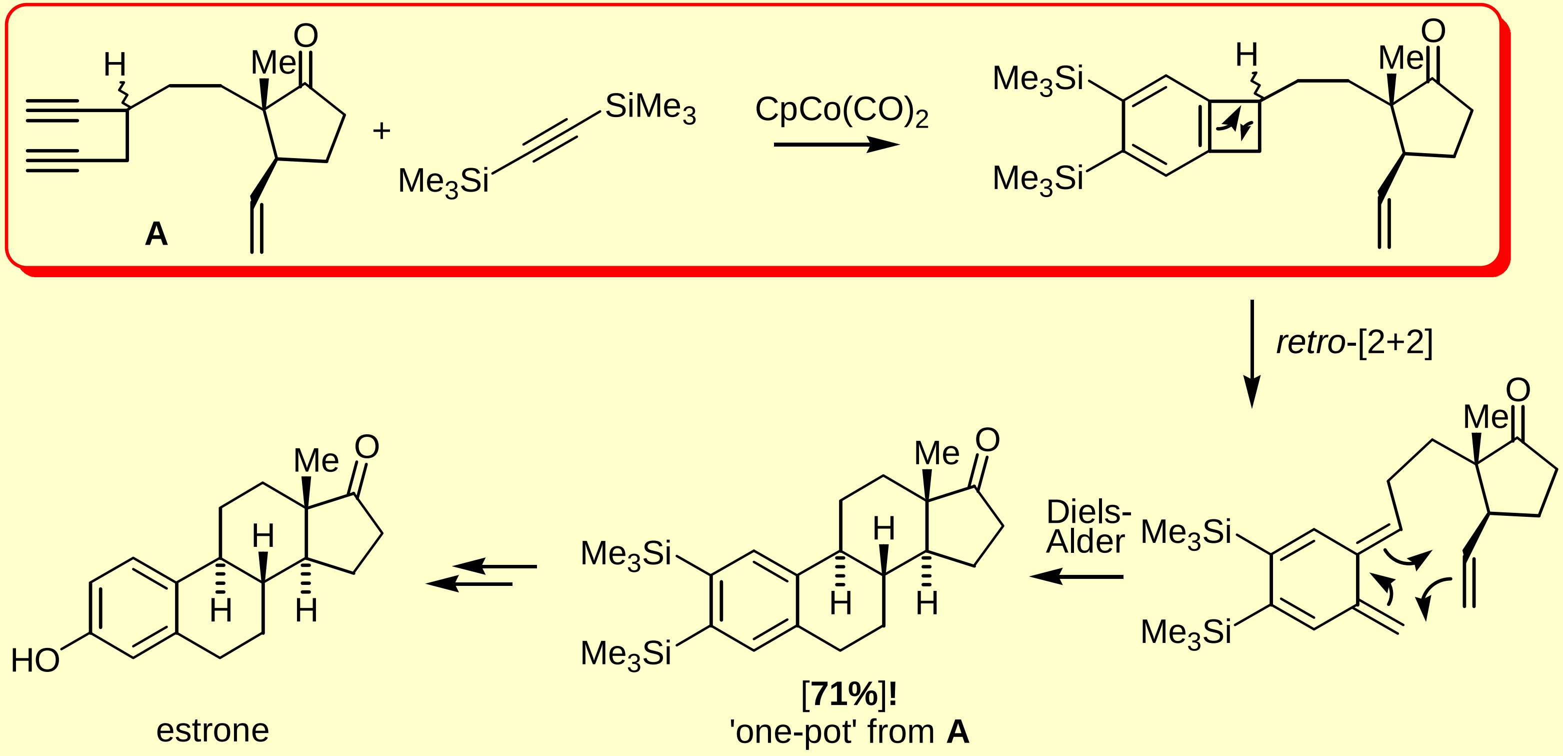
- ***Mechanism:***



Vollhardt [2+2+2] cycloaddition

- ***Features:***
  - Can also perform with 2 x alkynes and a nitrile to give pyridines

- ***Example***
  - Vollhardt *J. Am. Chem. Soc.* **1977**, 99, 5483 (**DOI**)



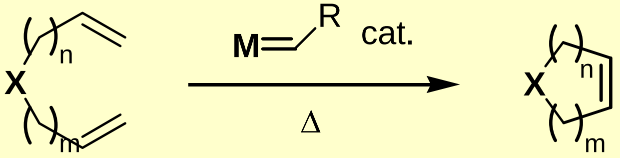
A

[71%]!
'one-pot' from **A**

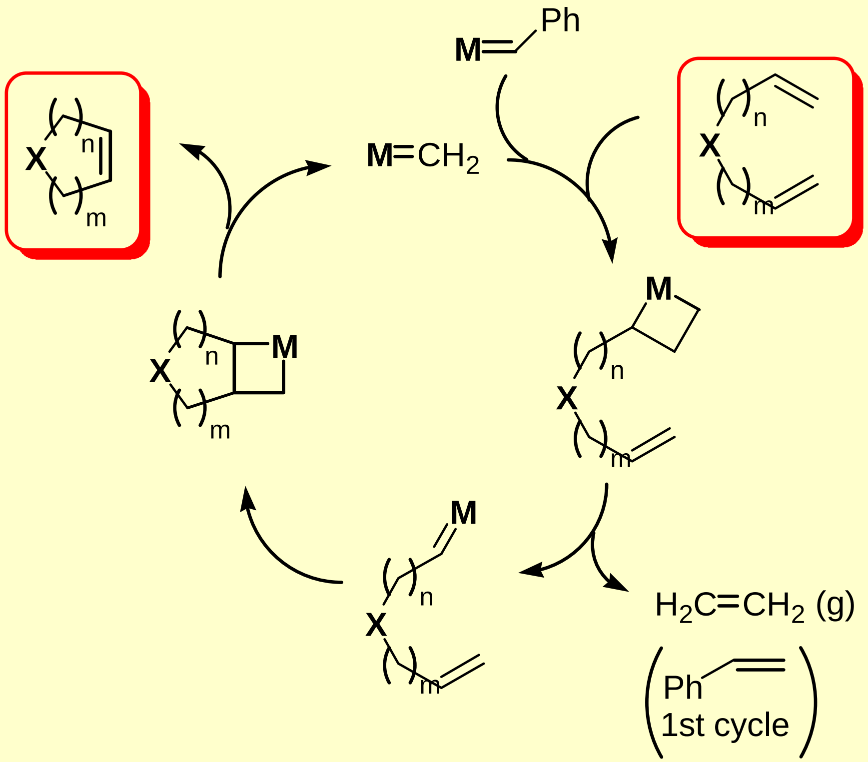
estrone

Ring Closing Metathesis (RCM)

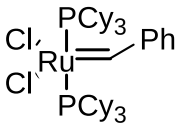
- ***Reviews:***
  - Furstner *Angew. Chem. Int. Ed.* **2000**, 39, 3012 (*general*) (**DOI**); Donohoe *Angew. Chem. Int. Ed.* **2006**, 45, 2664 (*aromatic ring synthesis*) (**DOI**)
- ***Overall scheme:***



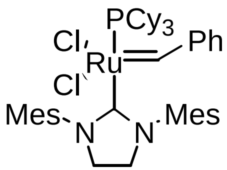
- ***Mechanism:***



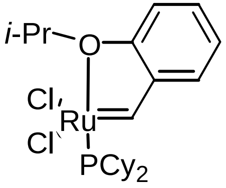
- Driving force is loss of ethylene
- 5-7 Membered rings generally easy to close
- High dilution sometimes required to avoid polymerisation (ADMET) with large ring sizes
- Grubbs & Grubbs-Hoveyda pre-catalysts are all commercially available:



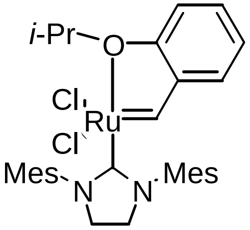
Grubbs I



Grubbs II



Grubbs-Hoveyda II

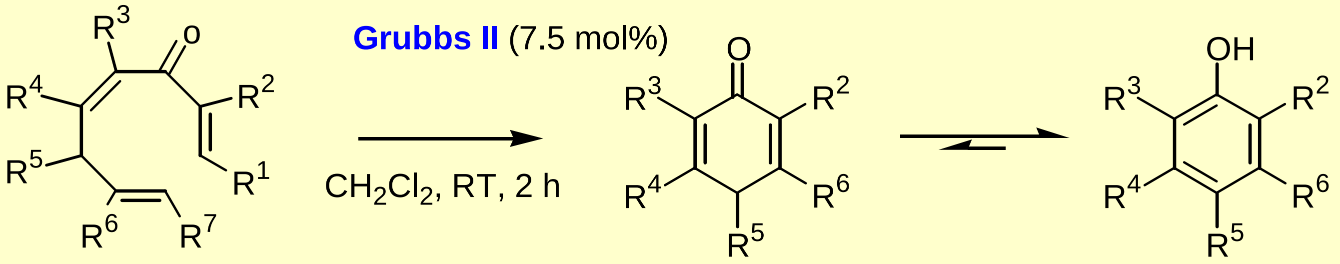


Grubbs-Hoveyda II

Ring Closing Metathesis (RCM)

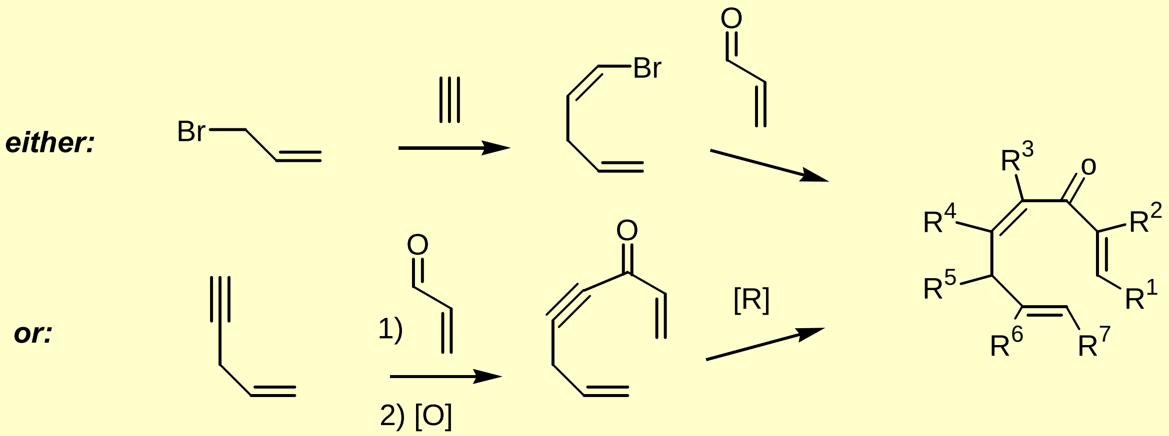
- ***Features:***
  - high functional group tolerance and mild thermal conditions

- ***Example***
  - Imamoto *J. Am. Chem. Soc.* **2005**, 127, 10470 (**DOI**)



R = H, Me, Et, C_2H_4OH, C_2H_4OAc, *n*-Pr, Ph

  - ***synthesis of substrates:***



Summary

- ***Formation of metal aryls:***
  - Reductive metalation (Barbier conditions)
  - Halogen-metal exchange (halogen-lithium and Grignard metathesis)
  - Deprotonation [directed *ortho*-lithiation (DoM)]
- ***Transmetalation & cross-coupling reactions:***
  - Transmetalation to Cu, Zn, Sn, B, Ge, & Ce
  - Kumada-Corriu, Negishi, Stille, Suzuki, Hiyama/Denmark, Heck, Sonogashira & sp^3
- ***Buchwald/Hartwig amination & etherification:***
  - Amination of aryl chlorides
  - Biaryl ether formation
- ***Birch reduction:***
  - Reduction/alkylation
- ***'De novo' aryl synthesis reactions:***
  - Fischer carbene chemistry (Dötz reaction)
  - Cobalt mediated [2+2+2] reactions (Volhardt reaction)
  - Ring Closing Metathesis (RCM)