(Hetero)aromatic Functionalisation 2 – *Stoichiometric Metallation Reactions*

Alan Spivey

a.c.spivey@imperial.ac.uk

http://www.ch.ic.ac.uk/spivey/

Imperial College London

Villars Summer School
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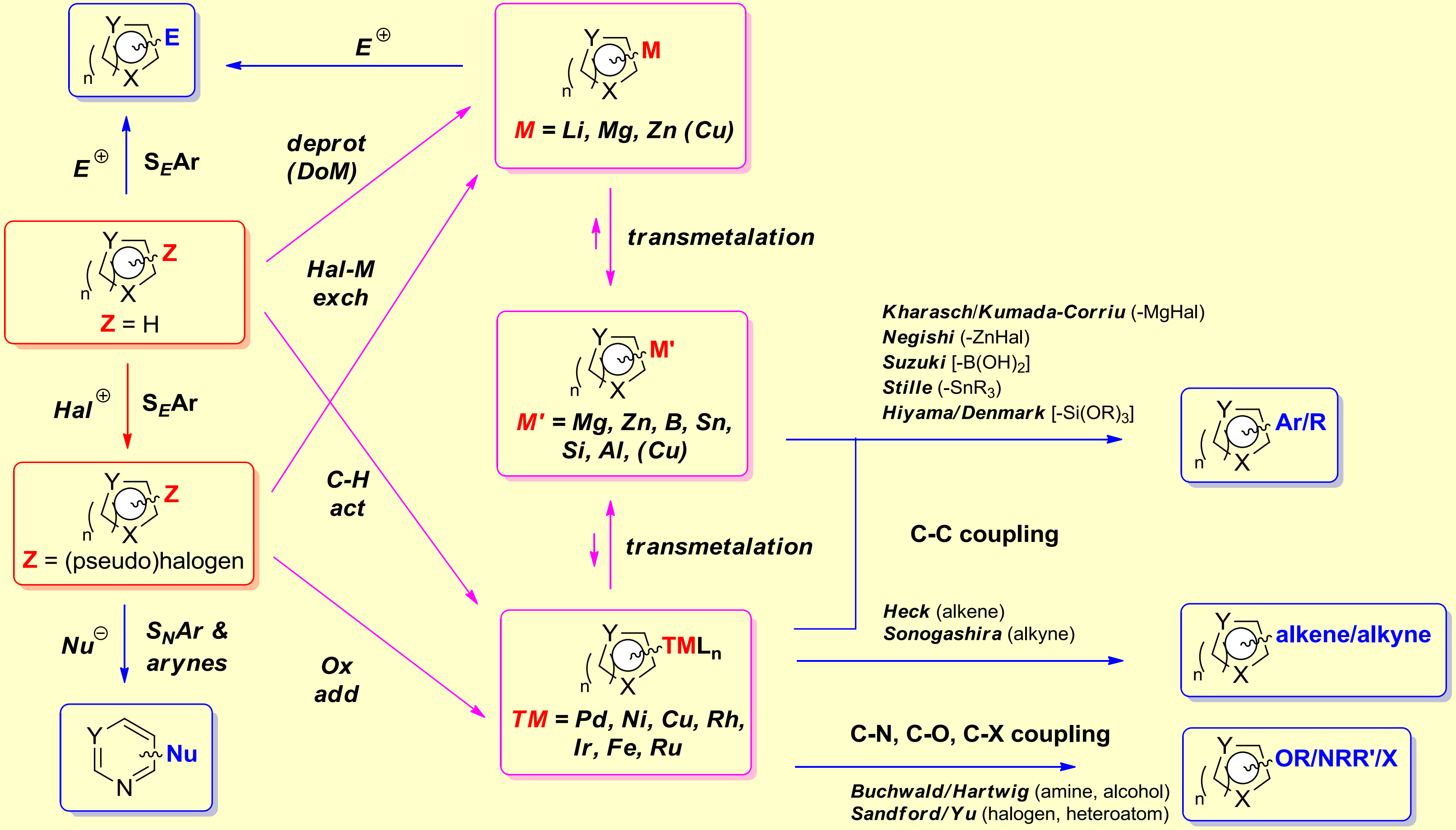
Format and scope of lecture

- ***Stoichiometric aromatic metalation reactions:***
  - halogen-metal exchange
  - metalation *ortho*- to ring heteroatoms
  - directed metalations (DoM & DreM)
  - ‘halogen dance’ rearrangements
  - Deprotonation *vs*. halogen metal exchange - *selectivity*

(Hetero)aromatic functionalisation strategies



E

$E^{\oplus}$

deprot (DoM)

M

***M* = Li, Mg, Zn (Cu)**

$E^{\oplus}$ S$_E$Ar

Z

Z = H

Hal-M exch

transmetalation

M'

***M'* = Mg, Zn, B, Sn, Si, Al, (Cu)**

$Hal^{\oplus}$ S$_E$Ar

Z

Z = (pseudo)halogen

C-H act

transmetalation

Kharasch/Kumada-Corriu (-MgHal)
Negishi (-ZnHal)
Suzuki [-B(OH)$_2$]
Stille (-SnR$_3$)
Hiyama/Denmark [-Si(OR)$_3$]

Ar/R

C-C coupling

$Nu^{\ominus}$ *S$_N$Ar & arynes*

Ox add

TML$_n$

***TM* = Pd, Ni, Cu, Rh, Ir, Fe, Ru**

Heck (alkene)
Sonogashira (alkyne)

alkene/alkyne

Nu

C-N, C-O, C-X coupling

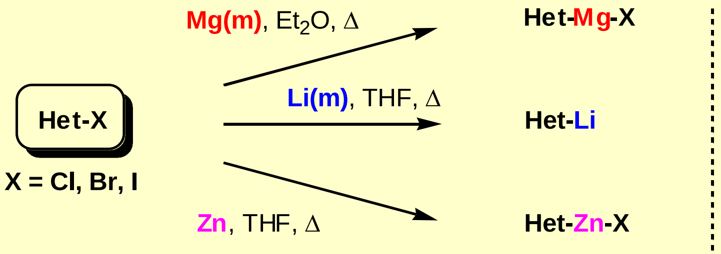
Buchwald/Hartwig (amine, alcohol)
Sandford/Yu (halogen, heteroatom)

OR/NRR'/X

Halogen-metal exchange

Reductive metalation – *overview*

- ***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)



$$\text{Het-X} \xrightarrow{\text{Mg(m), Et}_2\text{O, }\Delta} \text{Het-Mg-X}$$

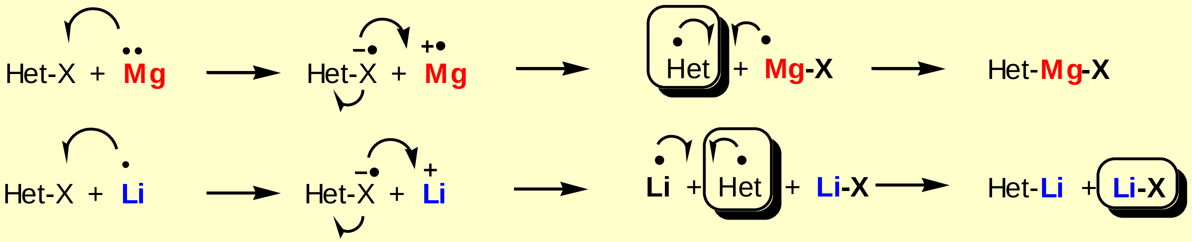
$$\text{Het-X} \xrightarrow{\text{Li(m), THF, }\Delta} \text{Het-Li}$$

$$\text{Het-X} \xrightarrow{\text{Zn, THF, }\Delta} \text{Het-Zn-X}$$

X = Cl, Br, I

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

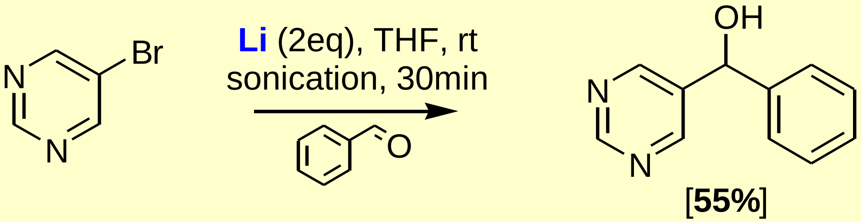
  - ***mechanism: S***ingle ***E***lectron ***T***ransfer (SET): Andrieux *J. Am. Chem. Soc.* **1986**, *108*, 638 (**DOI**)



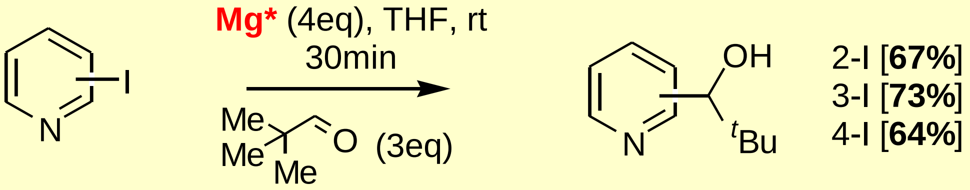
  - ***features:***
    - Wurtz coupling a side reaction particularly for iodides and bromides
    - requires elevated temperatures (i.e. >25°C)
    - ***solvent dependent selectivity*** due to varying solubility of Li-X, aggregation of aryl metals, and Schlenck equilibria (see later)

Reductive metalation - *Barbier conditions*

- ***Barbier-type reductive lithiation:***
  - ***acceleration by sonication***:
  - Queguiner *Tetrahedron* **2000**, *56*, 3709 (**DOI**)

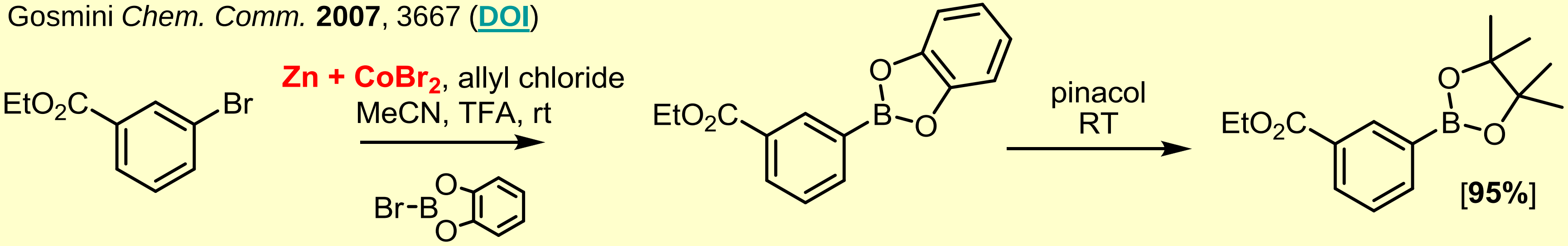


- ***Barbier-type reductive magnesiation:***
  - Sugimoto *Tet. Lett.* **2002**, *43*, 3355 (**DOI**) & *J. Org. Chem*. **2003**, *68*, 2054 (**DOI**)
  - See also acceleration of insertion of Mg into benzylic chlorides by LiCl and $ZnCl_2$: Knochel *Chem. Commun*. **2008**, 5824 (**DOI**)



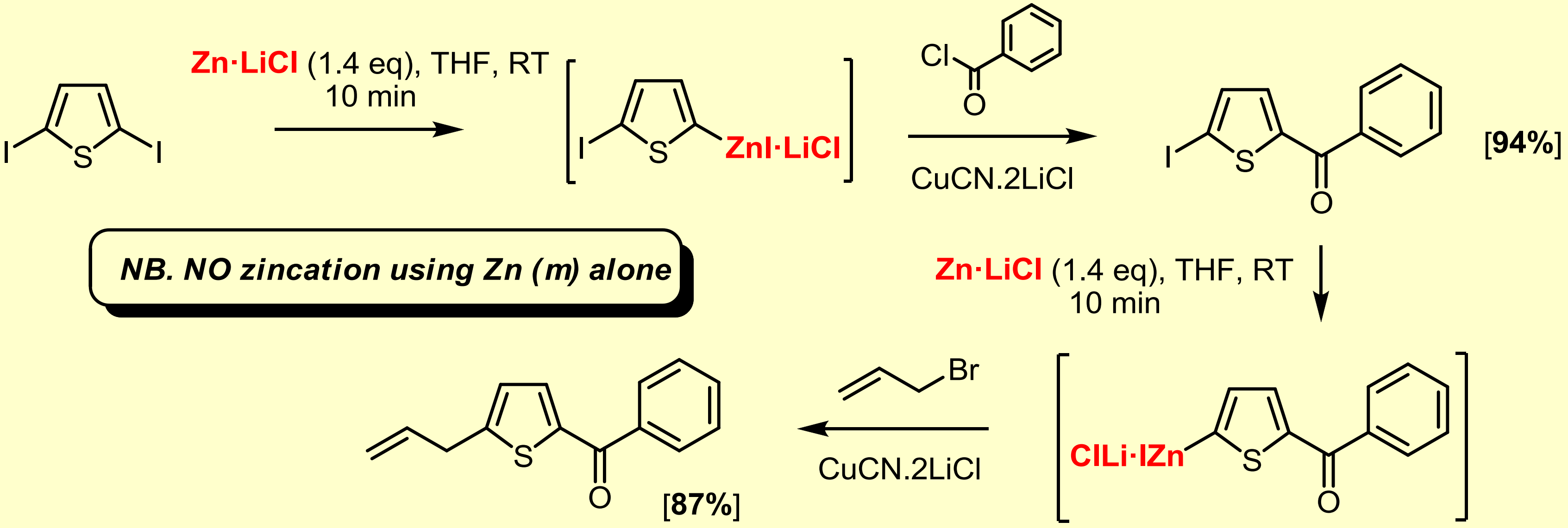
Mg* = activated Mg by reduction of $MgCl_2$ by Li and naphthalene in THF

- ***Barbier-type reductive zincation:***
  - Gosmini *Chem. Comm.* **2007**, 3667 (**DOI**)



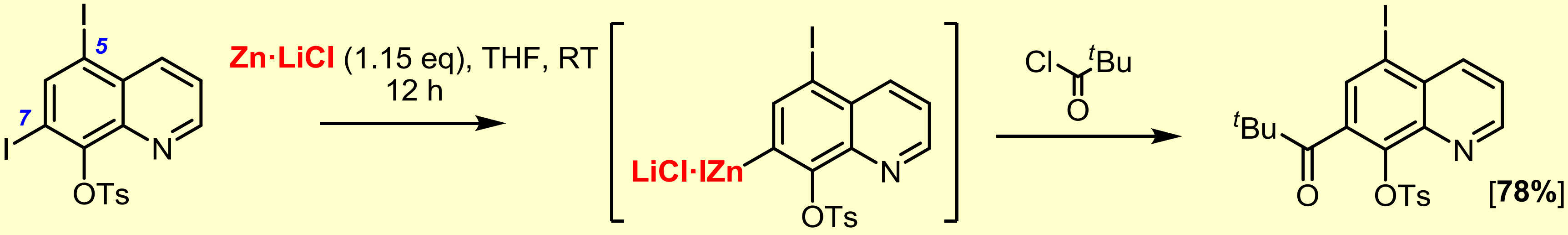
Reductive metalation – *zincation promoted by LiCl*

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



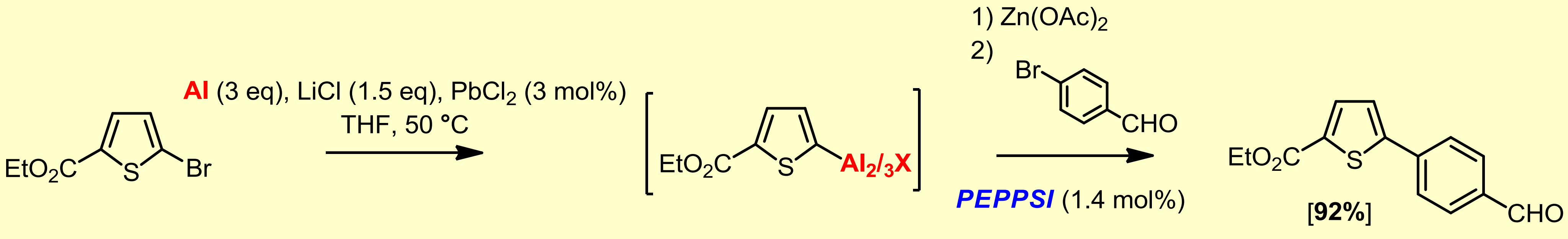
NB. NO zincation using Zn (m) alone

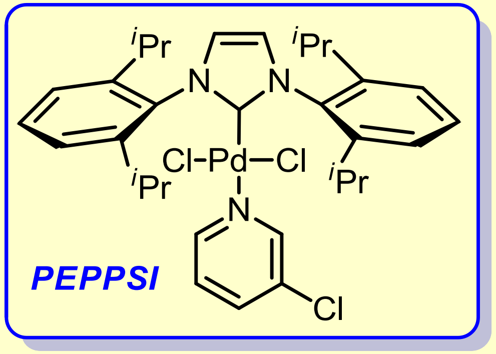
- ***ortho-directing affect of FGs –*** esters, ketones, aryl sulfonates, acetates, carbamates, triazenes:
  - Knochel *J. Am. Chem. Soc.* **2007**, *129*, 12358 (DOI)



Reductive metalation – *recent advances*

- ***reductive alumination of Ar-I with Al promoted by LiCl:***
  - Knochel *Nature Chem.* **2010**, *2*, 313 (**DOI**)
  - Aluminium powder + either $TiCl_4$, $BiCl_3$, $InCl_3$ or $PbCl_2$

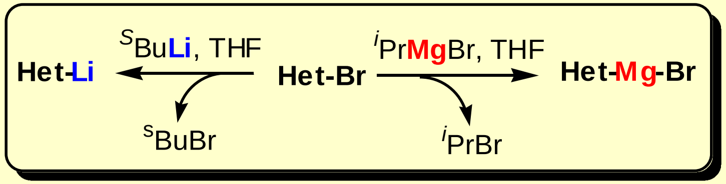




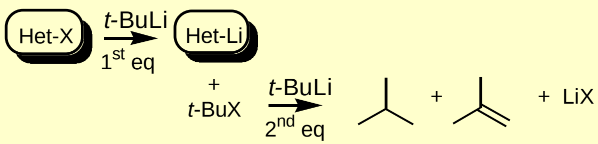
PEPPSI™(Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation)
see: http://www.sigmaaldrich.com/chemistry/chemical-synthesis/technology-spotlights/peppsi.html

Halogen-metal exchange – *overview*

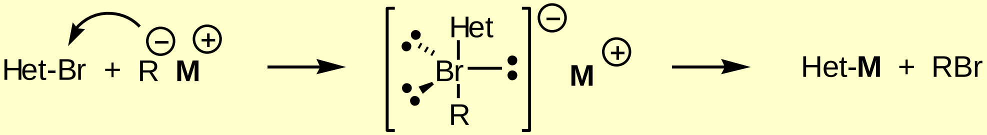
- ***by exchange of an aryl halide with an*** alkyl metal ***(discovered by Gilman & Wittig)***
  - ***reviews:*** Schlosser *Synlett* **2007**, 3096 (DOI) – Hal-M exchange *and* deprotonation of heterocycles; Knochel *Chem. Comm.* **2006**, 583 (DOI); Schlosser *Angew. Chem. Int. Ed.* **2005**, *44*, 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



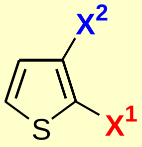
possible intermediate ate complex

    - 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):

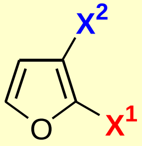
$$2\ \text{Het-}\mathbf{Mg}\text{-X} \rightleftharpoons \text{Het-}\mathbf{Mg}\text{-Het} + \text{X-}\mathbf{Mg}\text{-X}$$

Halogen-Li exchange - *polyhalogenated heterocycles*

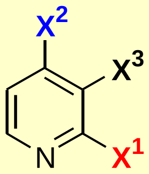
- ***exchange to give the most stabilised organolithium is fastest:***
  - *i.e.* α to a heteroatom (or more than one), S more stabilising than N
  - exchange α to pyrrole-like N faster than α to pyridine-like N (due to lone-pair repulsion in latter)
  - The ^{1}H NMR shifts of the corresponding protons in the non-halogenated heterocycles can also be used as an indicator – largest δ preferred see: Fairlam *Chem. Soc. Rev*. **2007**, *36*, 1036 (**DOI**)



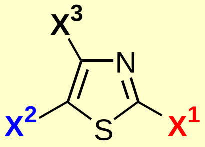
thiophenes



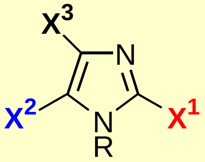
furans



pyridines

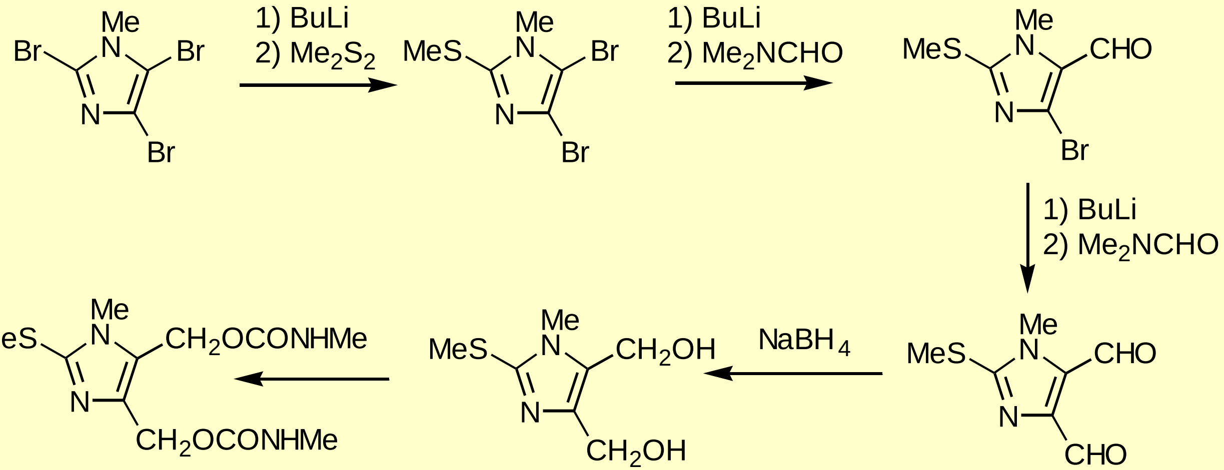


thiazoles



imidazoles

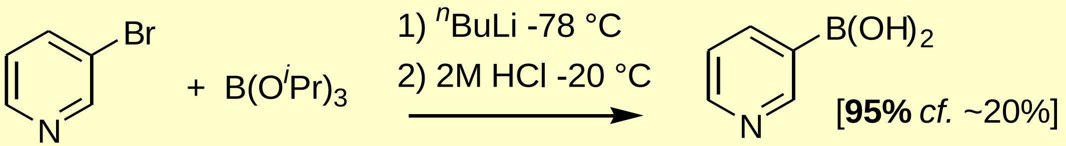
- ***useful levels of regioselectivity can therefore be achieved:***
  - *e.g.* Lipschutz *Tet. Lett.* **1992**, *33*, 5865 (**DOI**)



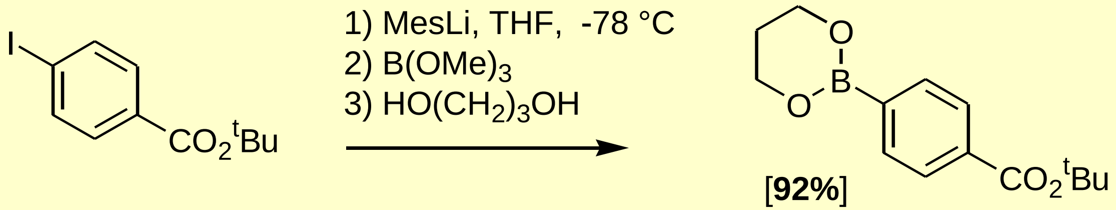
carmethizole
anti-tumour agent

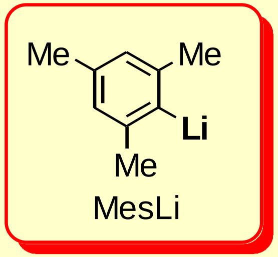
Halogen-Li exchange

- **in situ *electrophile quench useful for unstable anions:***
  - Li *J. Org. Chem*. **2002**, *67*, 5394 (**DOI**) & Cai *Tet. Lett*. **2002**, *43*, 4285 (**DOI**)



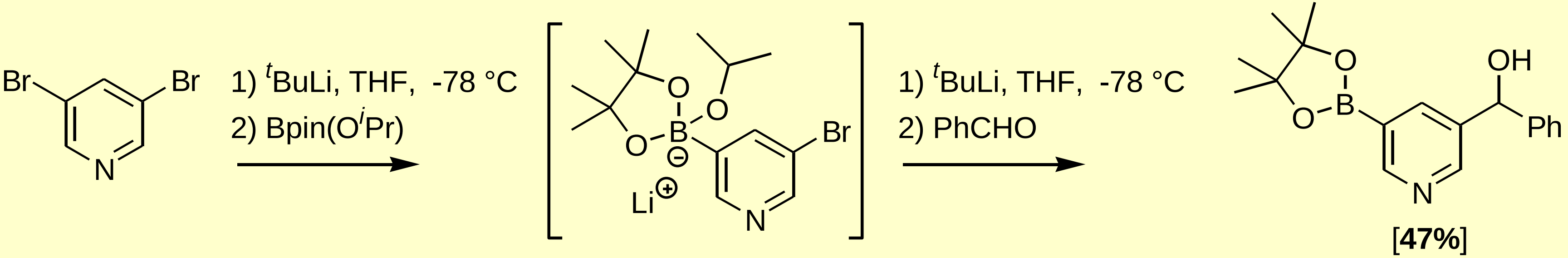
- ***mesityllithium - compatible with hindered esters, amides, nitriles* etc.*:***
  - Kondo *Org. Lett.* **2001**, *3*, 13 (**DOI**)





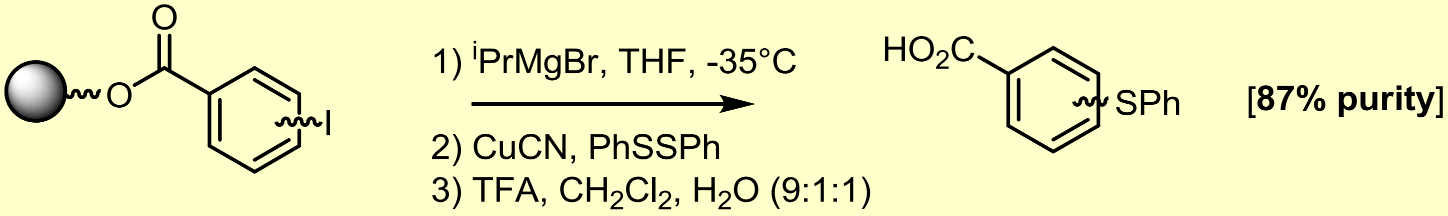
MesLi

- **in situ *protection of boronate esters by isopropoxide during Br-Li exchange:***
  - Zhichkin *J. Org. Lett.* **2007**, *72*, 6618 (**DOI**) [*cf.* Knochel *Angew. Chem. Int. Ed.* **2005**, *44*, 3133 (**DOI**) & Molander *J. Org. Chem*. **2006**, *71*, 7491 (**DOI**)]

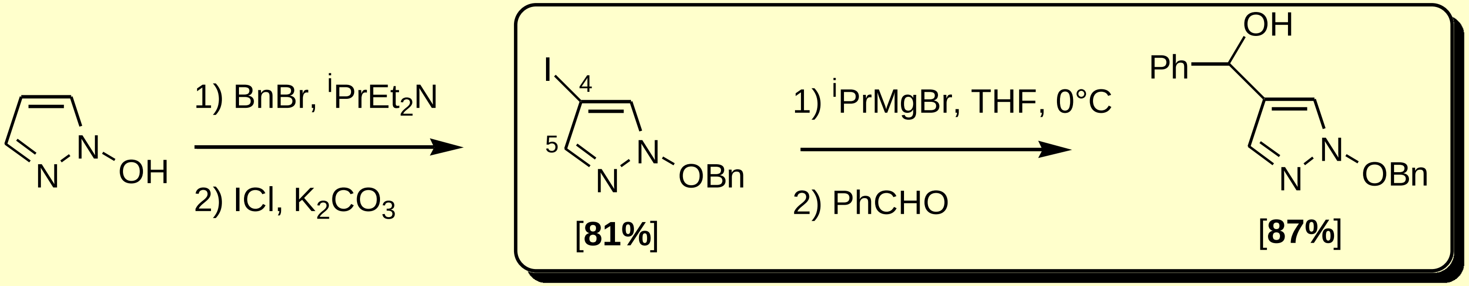


Halogen-Mg exchange

- ***^{i}PrMgBr at -40°C:***
  - ***wide functional group tolerance***: *e.g.* esters, amides, nitriles:
  - Knochel *Angew. Chem. Int. Ed.* **1998**, *37*, 1701 (**DOI**); Knochel *Chem. Eur. J.* **2000**, *6*, 767 (**DOI**); Knochel *Chem. Comm.* **2006**, 583 (***review***) (**DOI**)

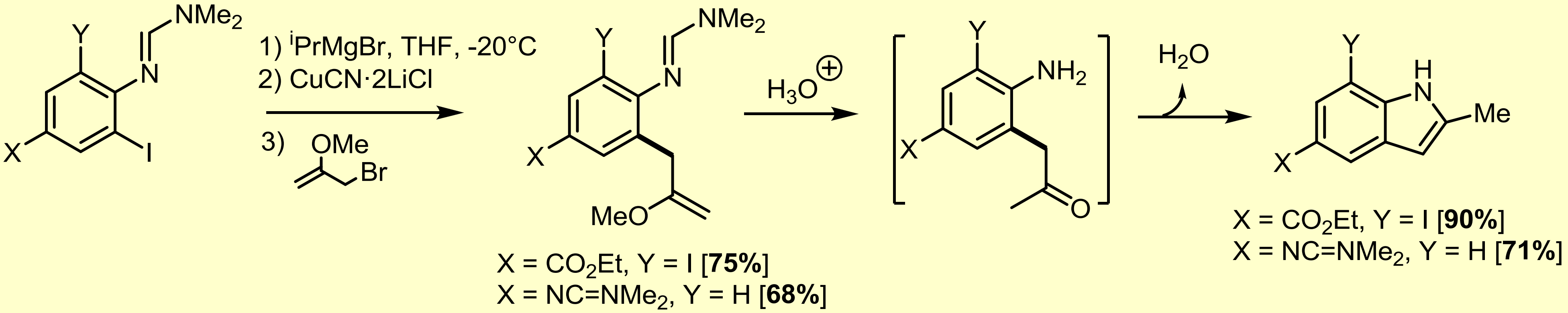


  - ***stability to isomerisation:*** *e.g.* pyrazole lithiation results in C-4 to C-5 isomerisation
  - Vedsø *J. Org. Chem.* **1999**, *64*, 4196 (**DOI**)



Halogen-Mg exchange

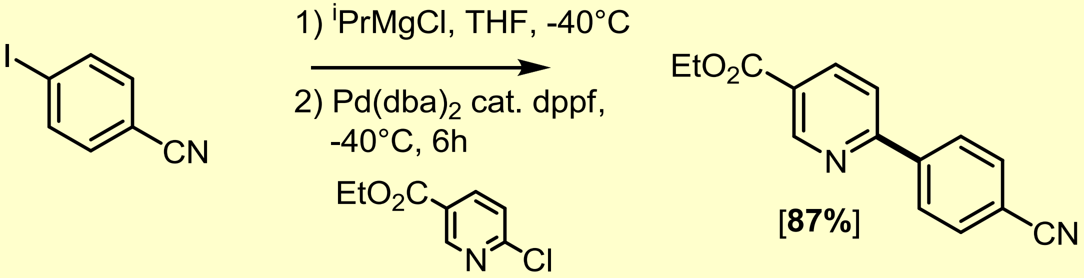
- ***^{i}PrMgBr at -40°C:***
  - ***indole synthesis:*** Knochel *Org. Lett.* **2002**, *4*, 1819 (**DOI**)



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%**]

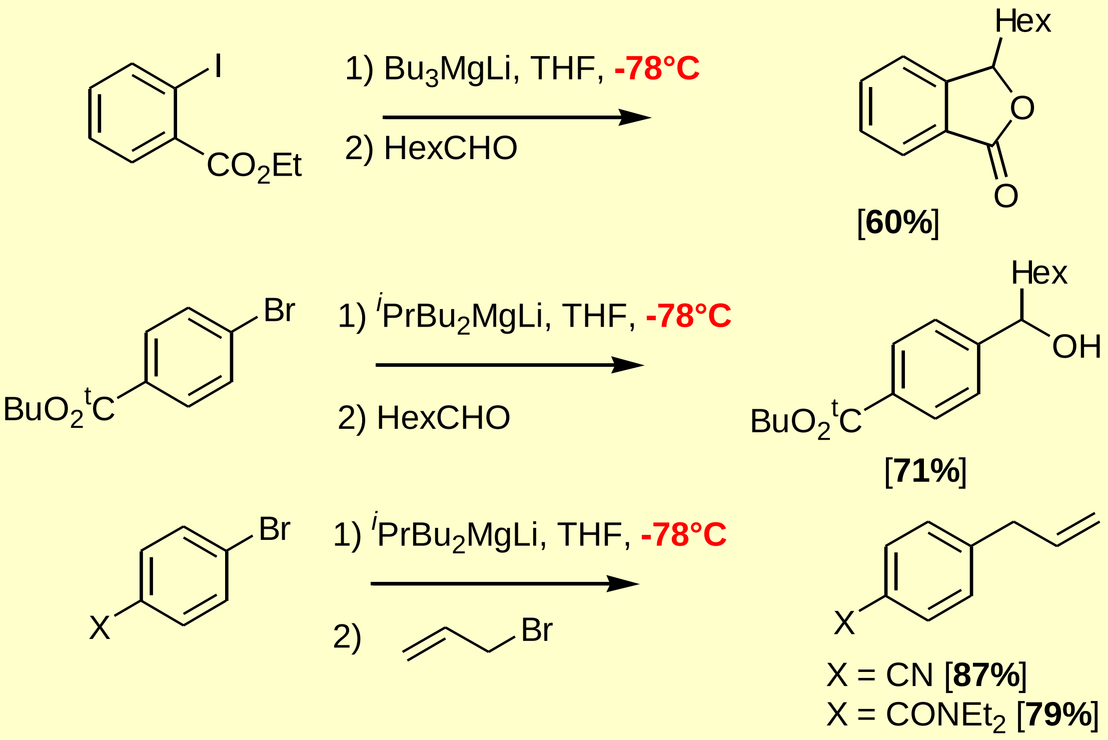
  - ***one-pot Mg-halogen exchange / Kharasch (Kumada-Corriu) cross-coupling:***
  - Quéguiner *Tetrahedron* **2002**, *58*, 4429 (**DOI**); Knochel *Synlett* **2002**, 1008 (**DOI**)



[**87%**]

Halogen-Mg exchange - trialkylmagnesiates

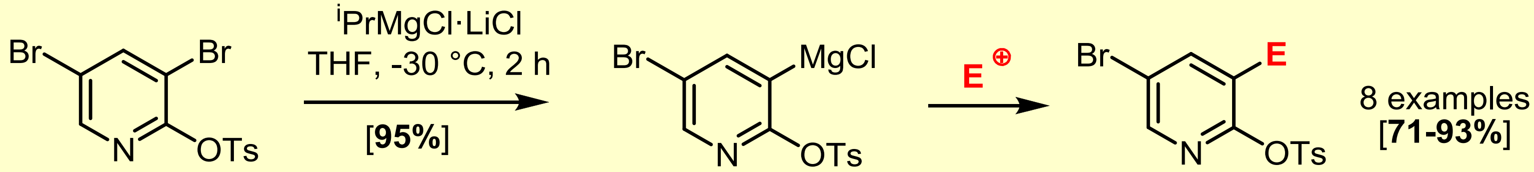
- ***trialkylmagnesates at -78°C:***
  - wide functional group tolerance:
    - Oshima *Angew. Chem. Int. Ed.* **2000**, *39*, 2481 (DOI)



- also effective for vinyl halides
- ate complex formation: RMgX + 2R'Li -> RR'$_2$MgLi + LiX
- the mixed magneseate (R = ^{i}Pr, R' = Bu) is more active and essential for Br-Mg exchange

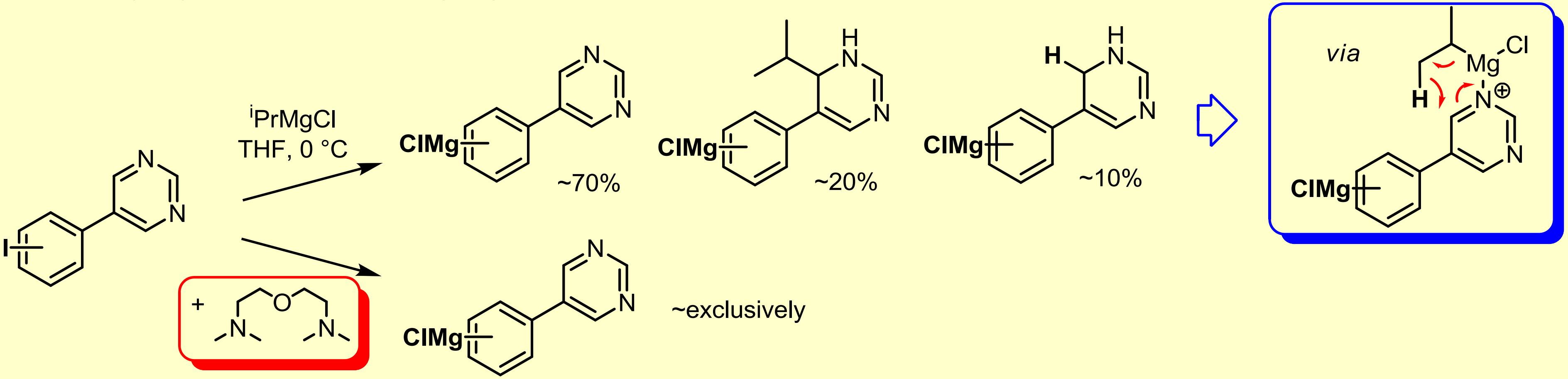
Halogen-Mg exchange – *advances*

- ***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**)



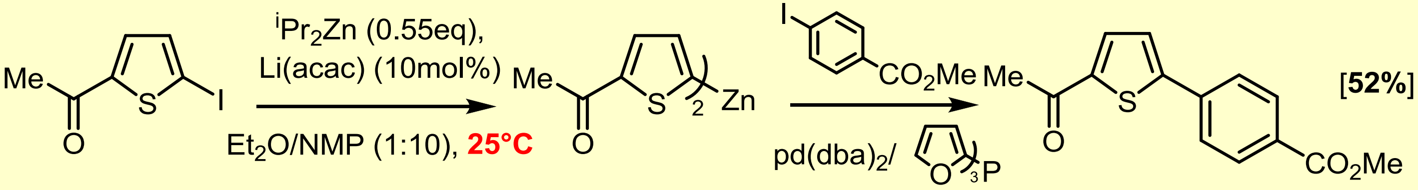
  - Kinetics of exchange for heteroaryl bromides: Knochel & Mayr *Org. Lett*. **2009**, *11*, 3502 (**DOI**)
  - Kinetics of exchange for *o-/m-/p*-substituted arylbromides: Knochel & Mayr *J. Org. Chem*. **2009**, *74*, 2760 (**DOI**)

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



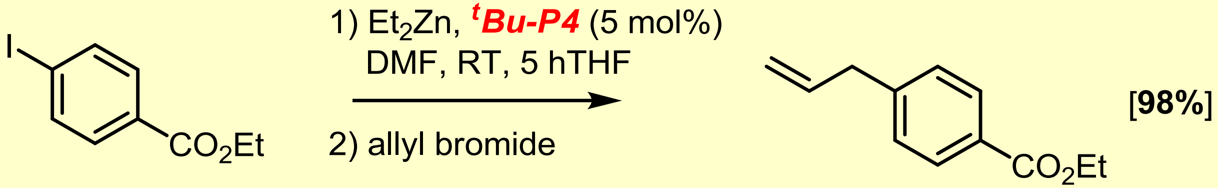
Halogen-Zn exchange

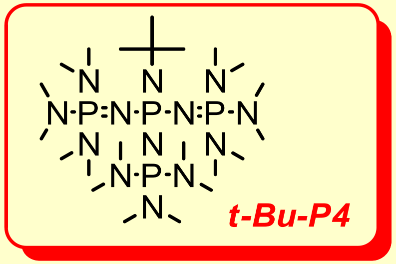
- ***using $^{i}Pr_2Zn$ & Li(acac) (presumed to form 'ate' complex):***
  - also tolerates ***ketones*** and ***aldehydes***
  - Knochel *Angew. Chem. Int. Ed.* **2004**, *43*, 1017 (**DOI**)



Negishi coupling

- ***using Et_2Zn & a phosphazine base (tBu-P4) as catalyst:***
  - tolerates ***esters***
  - Kondo *Chem. Commun.* **2006**, 3549 (**DOI**)

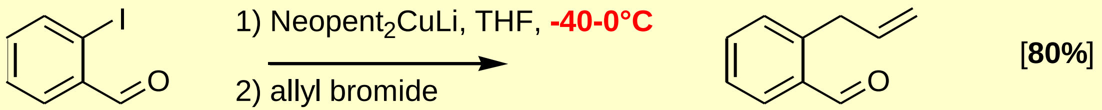


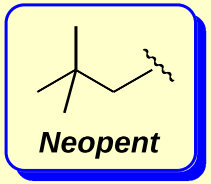


t-Bu-P4

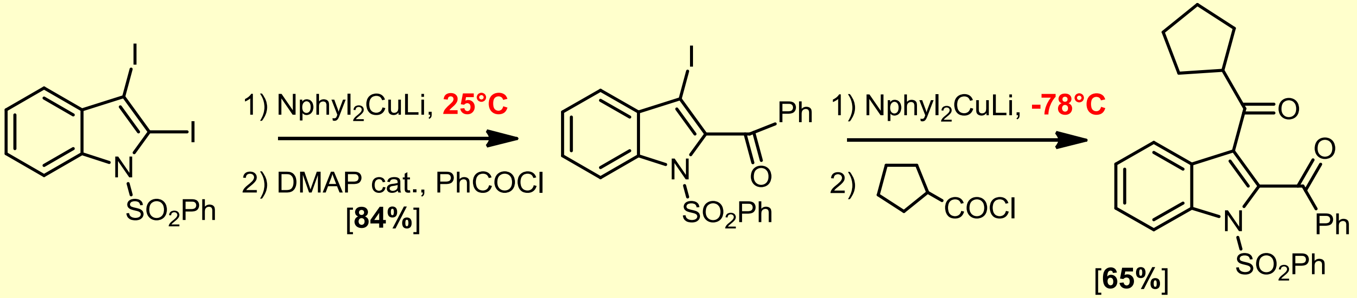
Halogen-Cu exchange

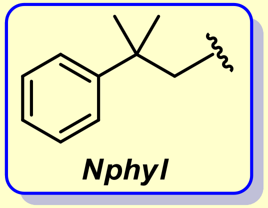
- ***even wider functional group tolerance:***
  - using ***lithium di(neopentyl)cuprates*** - tolerates ***ketones*** and ***aldehydes***
    - Knochel *Angew. Chem. Int. Ed.* **2002**, *41*, 3263 (**DOI**)



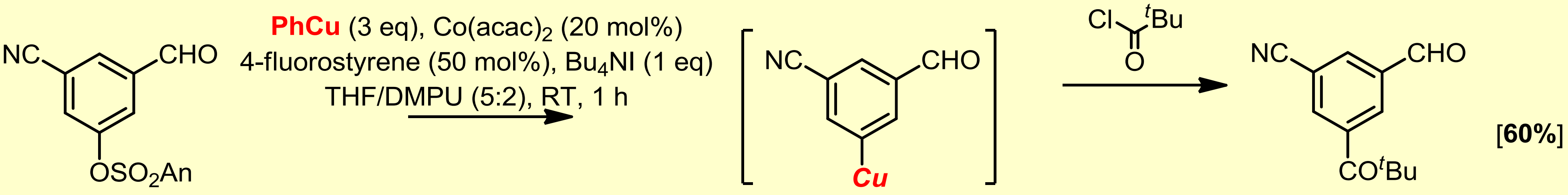

Neopent

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




Nphyl

  - Using phenyl copper reductive cupration of Ar-SO_2R (pseudohalides) catalysed by Co:
    - Knochel *Angew. Chem. Int. Ed.* **2010**, *49*, 1874 (**DOI**)

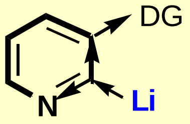


An = anisyl = $-C_6H_4OMe$

Deprotonation including Directed *ortho*-Metallation (DoM)

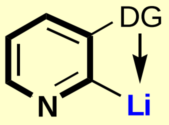
Deprotonation – *overview*

- ***Reviews:*** Schlosser *Synthesis* **2010**, 2111 (DOI); 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); Quéguiner *Tetrahedron* **2001**, *57*, 4059 (***pyridines***) (DOI); Quéguiner *J. Het. Chem.* **2000**, *37*, 615; Rewcastle *Adv. Het. Chem.* **1993**, *56*, 155
- Deprotonation of ***pyridines, quinolines & isoquinolines***
  - ***Thermodynamically more favourable*** and ***kinetically faster*** than for ***benzene*** particularly for protons:
    - *ortho* to ring N
    - *ortho* to directing substituents (DoM – see later)
  - ***Thermodynamics:*** (pK_a $Ar_{C=N}H$ ~35 *cf.* benzene ~40) due to:



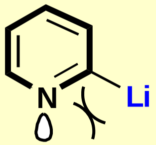
inductive stabilisation

and



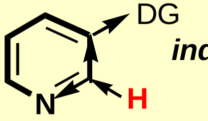
chelative stabilisation

BUT:



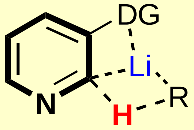
pair-pair electron repulsion

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



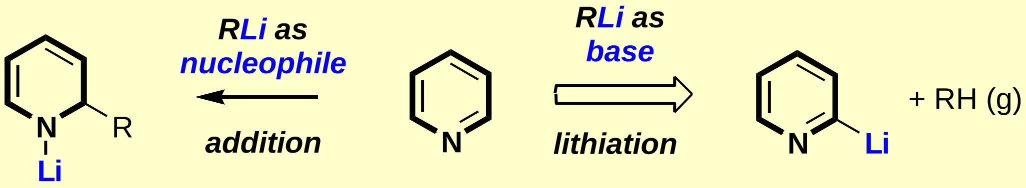
inductive acidification of ortho-protons

and



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

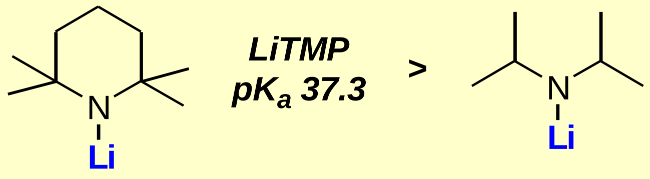
  - ***Low temperatures*** & ***bulky bases*** required to supress ***addition reactions*** to ***C=N function:***
    - Quéguiner *Tetrahedron* **2001**, *57*, 4059 (DOI)



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:

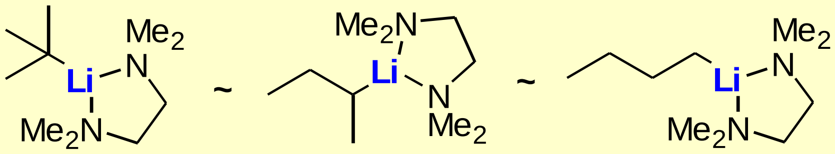
$$\mathrm{ArH} + \mathrm{R_2NLi} \xrightleftharpoons[\textit{reversible}]{} \mathrm{ArLi} + \mathrm{R_2NH}$$



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)

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

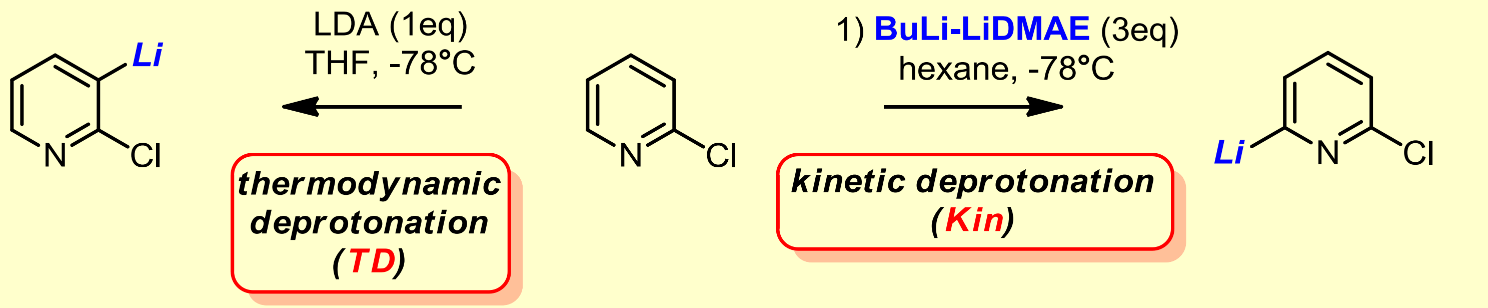


pK_a ~45

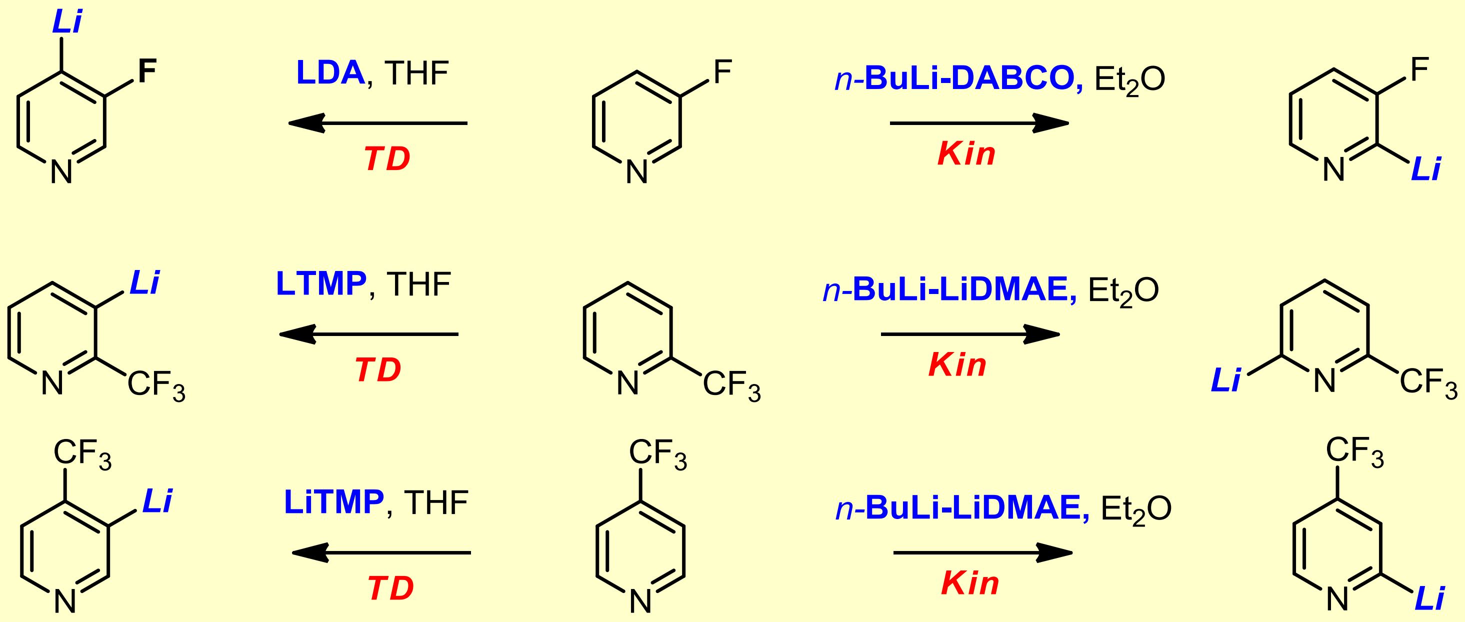
- ***mechanisms - disputed:***
  - acidity due to two factors: i) ***inductive activation***, and ii) ***Complex Induced Proximity Effects*** (CIPE)
  - ***review:*** Snieckus & Beak *Angew. Chem. Int. Ed.* **2004**, *43*, 2206 (DOI); see also Collum *J. Am. Chem. Soc.* **2000**, *122*, 8640 (DOI) & *J. Am. Chem. Soc*. **2007**, *129*, 2259 (DOI) & *J. Am. Chem. Soc*. **2008**, *130*, 18008 (complexities of LDA-THF deprotonations) (DOI) ; Mortier *Org. Lett.* **2005**, *7*, 2445 (excellent discussion of specific case of DoM of *m*-anisic acid) (DOI)

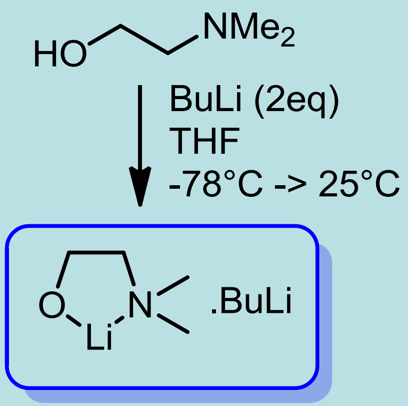
Thermodynamic *vs* kinetic deprotonation (Li)

- 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**)



  - Schlosser *Synthesis* **2010**, 2111 (**DOI**);



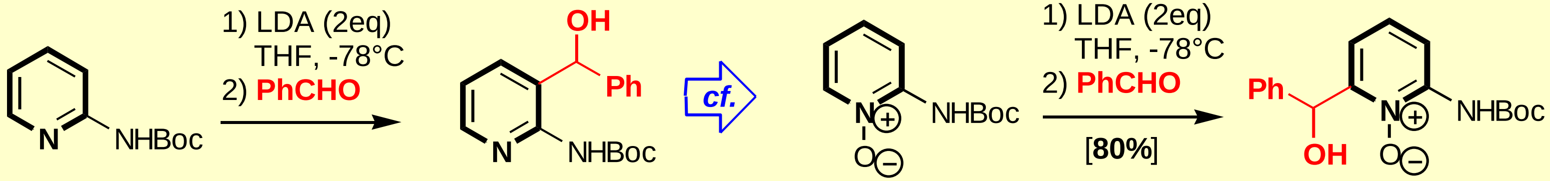


BuLi-LiDMAE

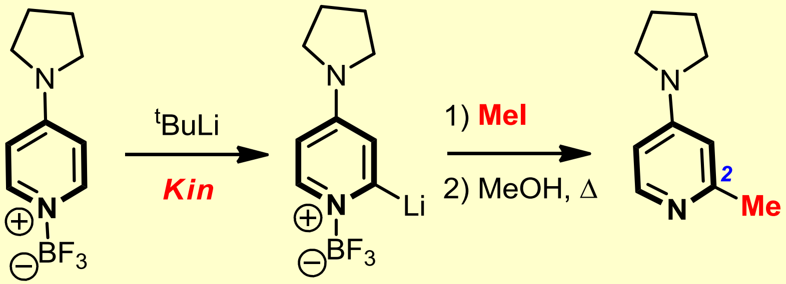
For a theoretical study of the origin of the selectivity of the ***BuLi-LiDMAE*** reagent see:
J. Am. Chem. Soc. **2010**, *132*, 2410 (**DOI**)

Deprotonation of dipolar adducts - *pyridines*

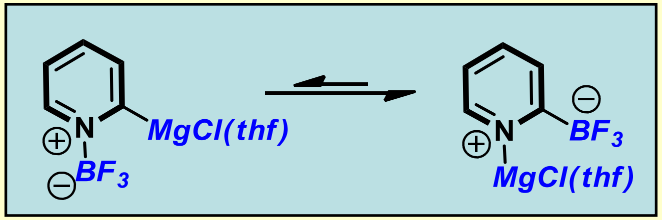
- ***Dipolar adducts increase both the thermodynamic and kinetic acidity of ortho-protons:***
  - ***N-oxides:*** decrease pair-pair electron repulsions and increase chelation
  - *e.g.* Mongin *J. Chem. Soc., Perkin Trans. 1* **1995**, 2503 (DOI)
  - See also: Almqvist *Tet. Lett*. **2008**, *49*, 6901 (using *i*-PrMgCl) (DOI)



  - ***BF$_3$-adducts:***
    - ***Reviews:*** Carboni *Tetrahedron* **1999**, *55*, 1197 (DOI); Kessar *Chem. Rev.* **1997**, *97*, 721 (DOI)
    - *e.g*. Gros *Chem. Commun*. **2006**, 2673 (***4-DMAP***) (DOI); Sammakia *J. Org. Chem.* **1999**, *64*, 4652 (***4-PPY***) (DOI)

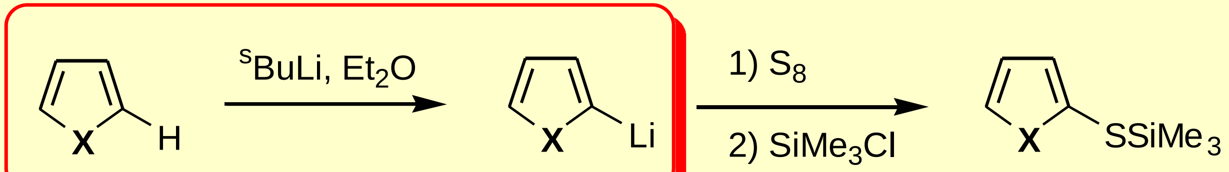


- See also *via* '***frustrated Lewis pairs***' using ***tmpMgCl·BF$_3$·LiCl***:
- Knochel *Angew. Chem. Int. Ed.* **2010**, *49*, 5451 (DOI)



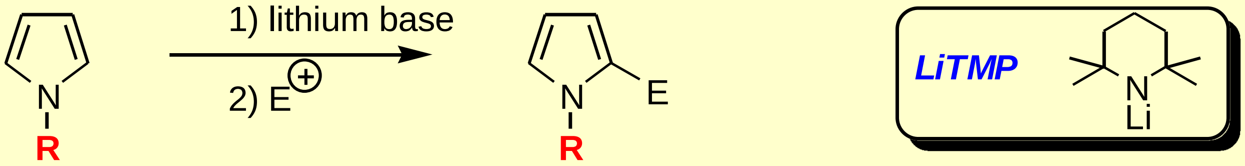
Deprotonation of 5-ring heteroarenes (Li)

- ***furans and thiophenes: facile kinetic metalation:***



X = O, S [**>80%**]

- ***pyrroles: N-protection is required***
  - electron withdrawing protecting groups enhance *kinetic* and *thermodynamic* acidity of *ortho*-protons
  - Katritsky *Prog. Het. Chem.* **1989**, 1, 1 (***review***)

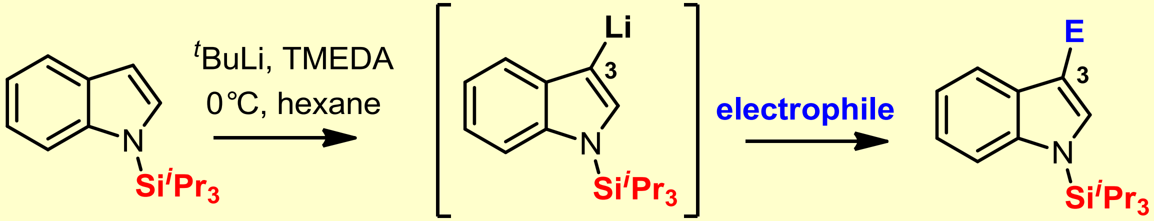


- ***R = SO_2Ph***, ***LiTMP*** or ^{t}BuLi, THF, -78 °C [**76-80%**] Hasan *J. Org. Chem*. **1981**, *46*, 157 (**DOI**)
- ***R = Boc***, ***LiTMP***, THF, -78 °C [**35-92%**] Hasan *J. Org. Chem*. **1981**, *46*, 157 (**DOI**)
- ***R = NMe_2***, BuLi, THF [**70-80%**] Martinez *J. Org. Chem*. **1981**, *46*, 3760 (**DOI**)
- ***R = SEM***, BuLi, DME, -10 °C, [**40-64%**] Edwards *Tetrahedron* **1986**, *42*, 3723 (**DOI**)
- ***R = CONH^{t}Bu***, 2 ^{t}BuLi, THF, -78 °C [**45-78%**] Gharpure *Synthesis* **1991**, 1079 (**DOI**)

- ***Dynamic equilibrium between C2 and C5 lithiated N-benzene sulfonyl-3-bromopyrrole:***
  - Using LDA: reactive electrophiles (*e.g*. TMSCl) → ***C2***; less reactive electrophiles (*e.g*. TIPSCl) → ***C5***
  - Iwao *Org. Letts.* **2010**, *12*, 2734 (**DOI**)

Lateral protection and PG tuning for deprotonation (Li)

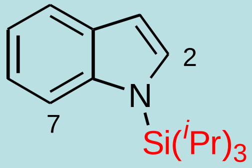
- ***lateral protection:***
  - Iwao *Tet. Lett.* **2001**, *42*, 7621 (DOI):



E = Me, TMS, Br, CHO, CO_2H, CO_2Et, $CONEt_2$
[**69-92%**]

Lateral protection:

protection of N- & neibouring 2 & 5 positions
also for indoles (protection of 2 & 7 positions):

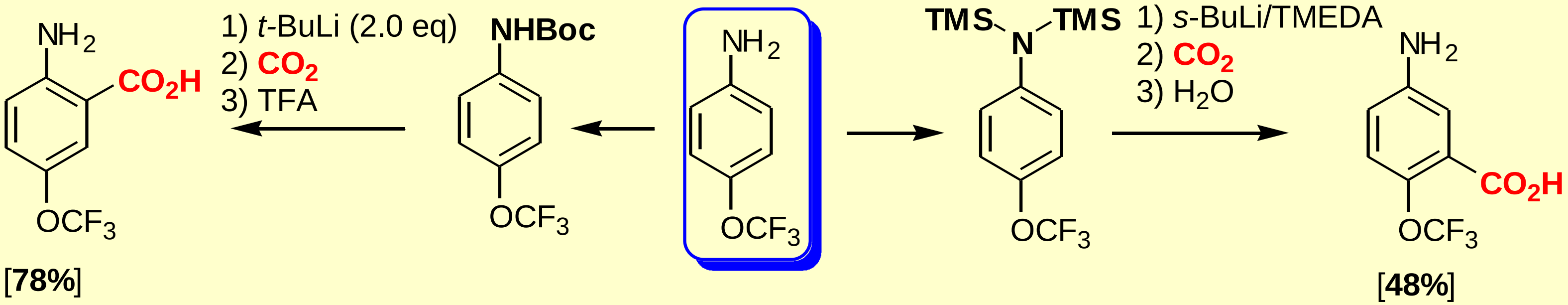


also effective for directed C-H activation

Review: Rucker *Chem. Rev.* **1995**, *95*, 1009 (DOI)

for *in situ* lateral protection of anilines by $SnBu_3$ to give selective *p*-bromination see:
Smith *Org. Lett.* **2002**, *4*, 2321 (DOI)

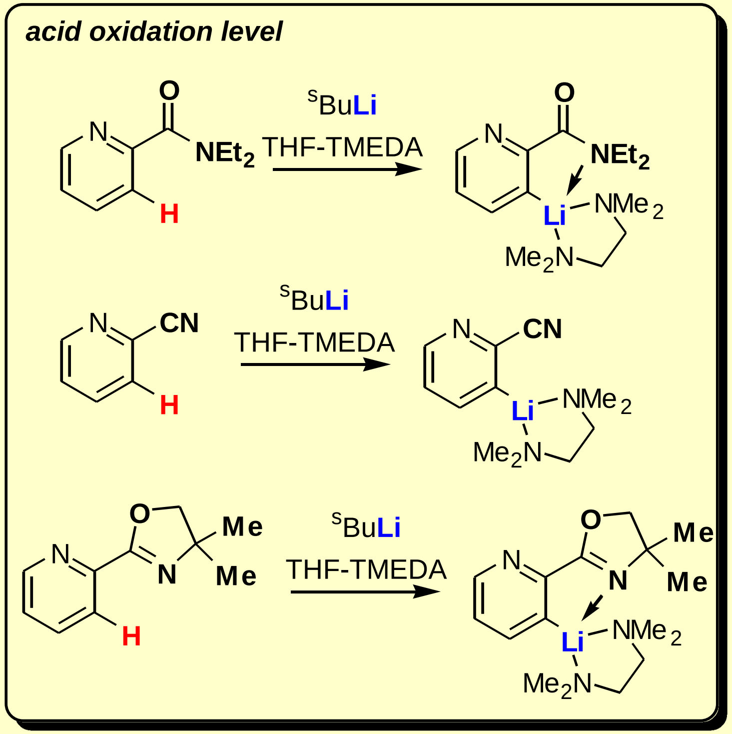
- ***tuning N-protecting groups to achieve regioselectivity:***
  - *e.g.* Schlosser *J. Org. Chem.* **2003**, *68*, 4693 (DOI)

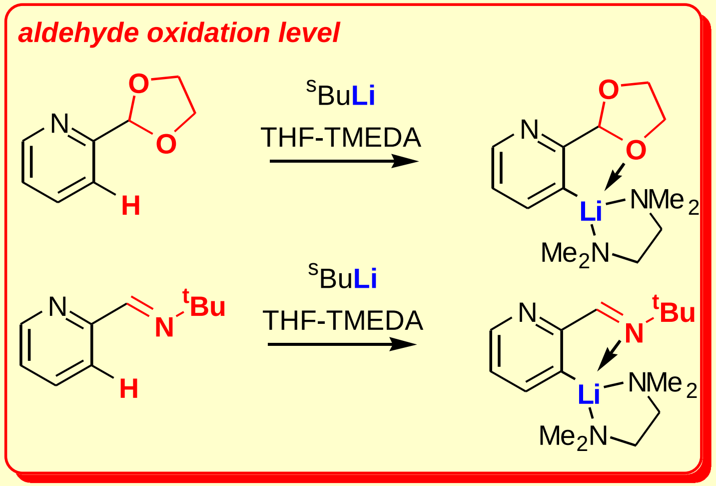


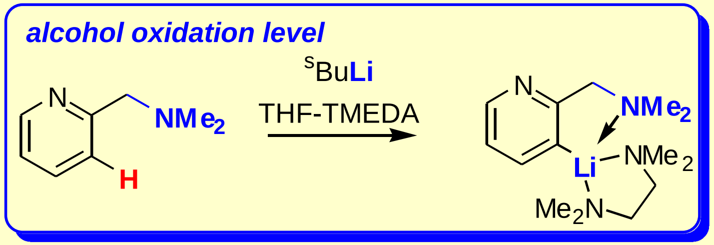
- → ***directed ortho-metalation (DoM)…***

Directed *ortho*-metalation (DoM, Li)

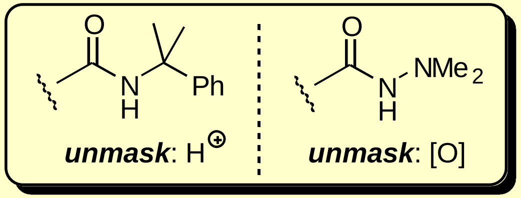
- directed metalation groups ***(DMGs) attached*** **via** ***carbon can assist*** **ortho-*metalation***
  - ***Reviews:*** Snieckus & Beak *Angew. Chem. Int. Ed.* **2004**, *43*, 2206 (**DOI**); Sniekus *J. Organomet. Chem.* **2002**, *653*, 150 (**DOI**); Quéguiner *J. Het. Chem.* **2000**, *37*,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





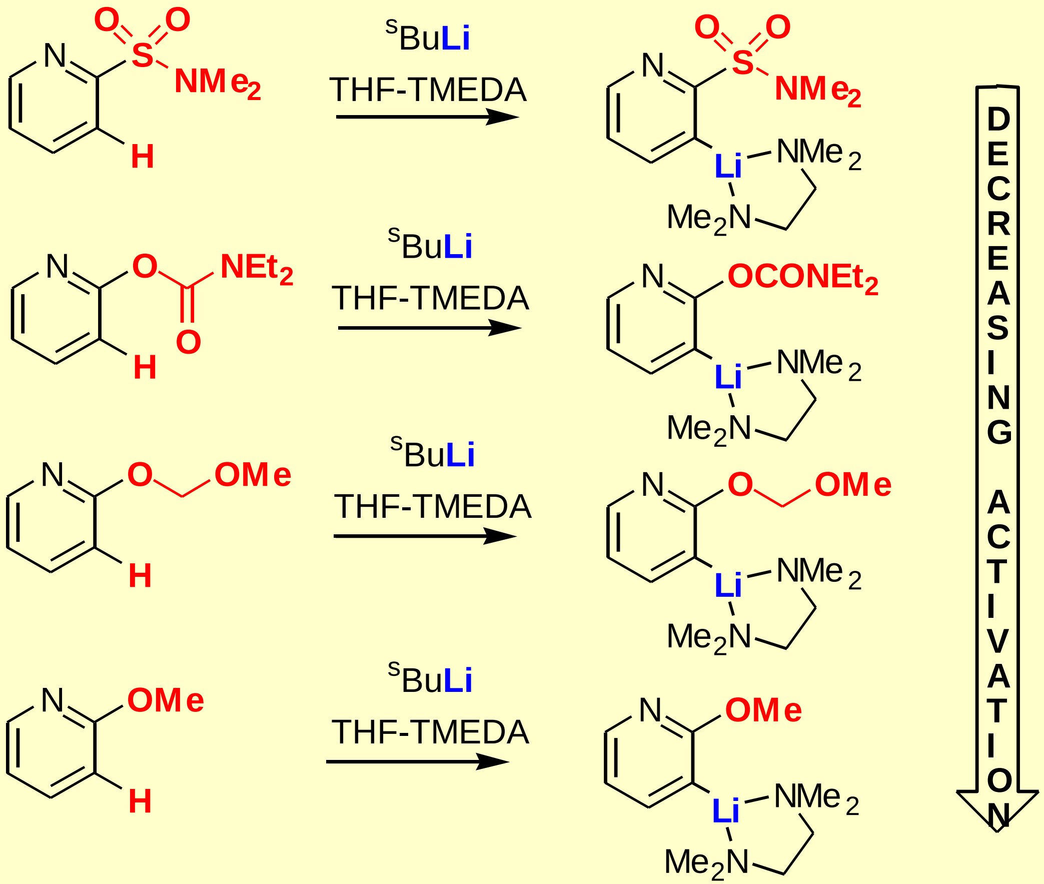


  - ***for DMGs readily 'unmasked' to give CO$_2$H see***:
    - Wutz *Tet. Lett.* **2000**, *41*, 3559 (**DOI**); Sniekus *Org. Lett.* **1999**, *1*, 1183 (**DOI**)



Directed *ortho*-metalation (DoM, Li)

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

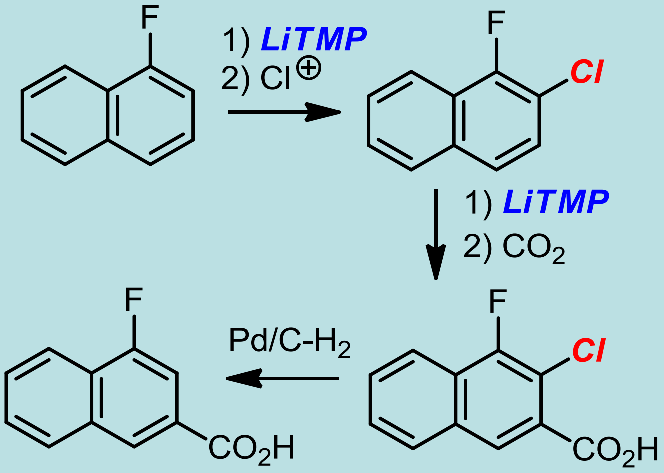


Other weak DMGs include:
F, Cl, Br, CF_3, SR, NR_2, I

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

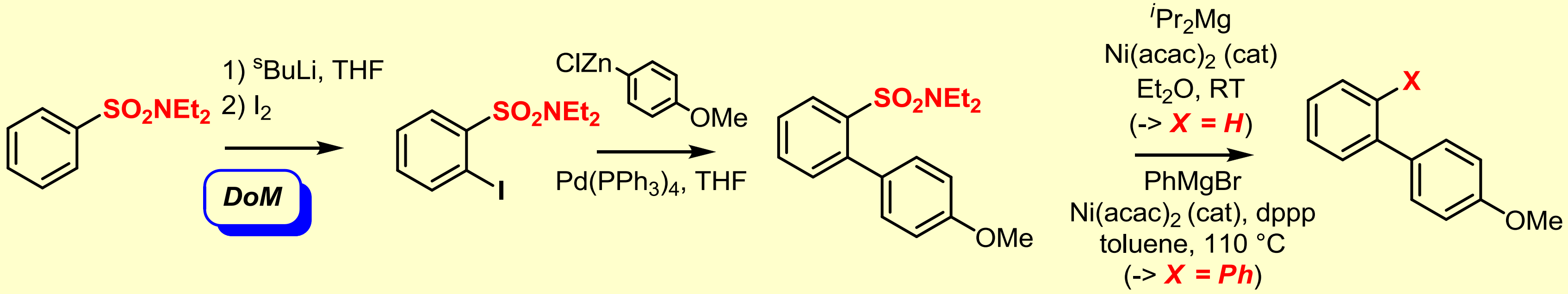
e.g. iodine as directing group:
Mattson *J. Org. Chem.* **1999**, *64*, 8004 (DOI)

NB. Chlorides can be regarded as temporary DMGs when removed subsequently by hydrogenolysis:
Schlosser *Synthesis* **2010**, 2111 (DOI)

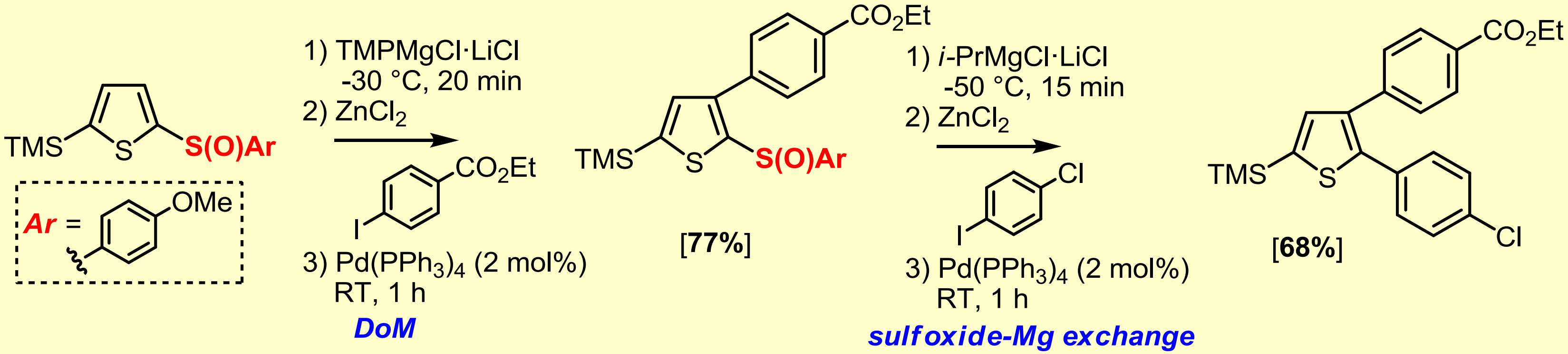


'Temporary' DoM groups

- ***the SO_2NEt_2 (sulfonamide), OSO_2NEt_2 (O-sulfamate) & $OCONEt_2$ (O-carbamate) groups:***
  - ***removed by: hydrogenolysis*** using $^iPr_2Mg$/cat. $Ni(acac)_2$ or ***Ni(0) catalysed Kharasch-type cross-coupling***
  - Snieckus *Angew. Chem. Int. Ed.* **2004**, *43*, 888 (**DOI**) & 892 (**DOI**) & *Org. Lett.* **2005**, *7*, 2519 [***OSO_2NEt_2*** (*O*-sulfamate) group] (**DOI**) & *J. Am. Chem. Soc* **2009**, *131*, 17750 [***$OCONEt_2$*** (*O*-carbamate) group] (**DOI**).

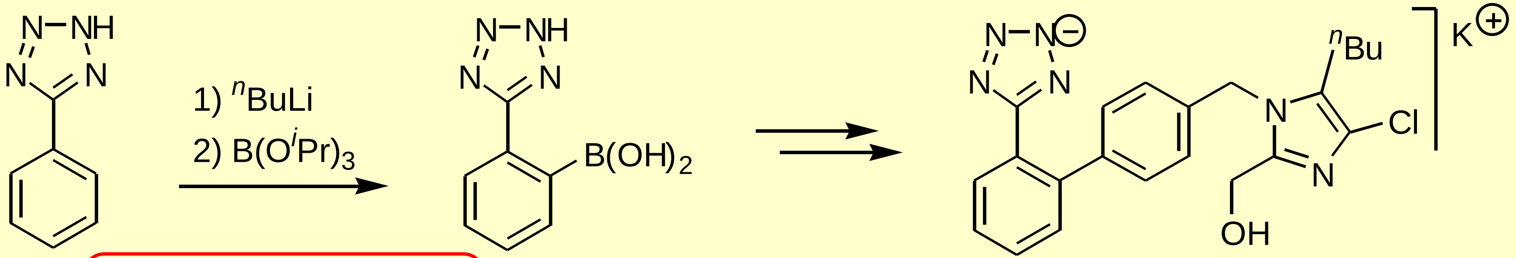


- ***the SO_2NCMe_2Ph (N-cumyl sulfonamide) group:***
  - ***deprotected to SO_2NH_2 by TFA → saccharin syntheses***. Snieckus *J. Org. Chem.* **2007**, *72*, 3199 (**DOI**)
- ***the S(O)p-$MeOC_6H_4$ (arylsulfoxide) group:***
  - ***'removed' by sulfoxide-Mg exchange:*** Snieckus *Chem. Commun.* **2009**, 3536 (**DOI**).



Pharmaceutical preparation by DoM

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

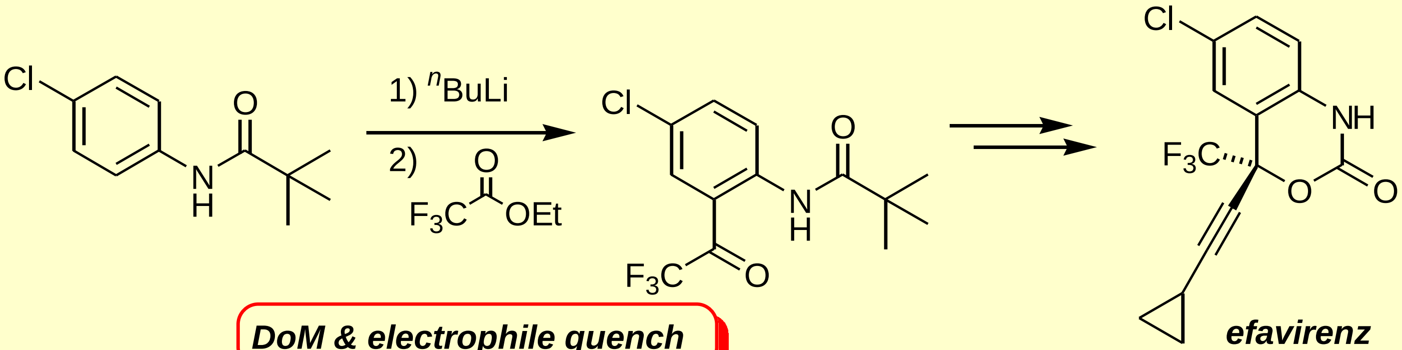


DoM & transmetalation

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**)



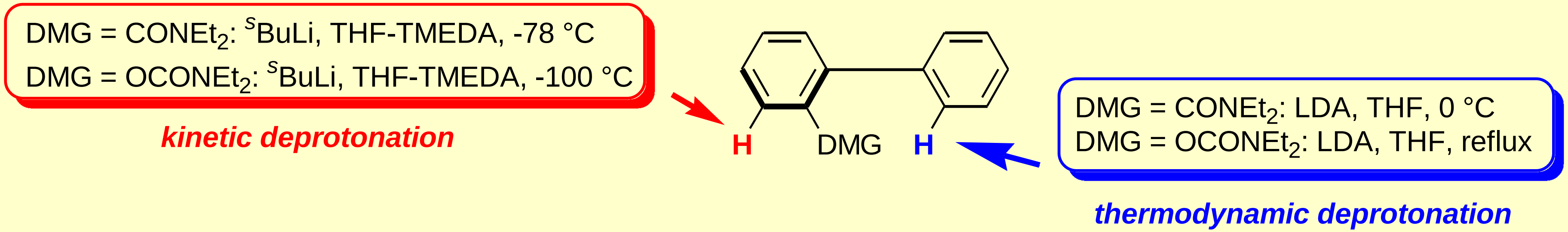
DoM & electrophile quench

efavirenz

non-nucleoside reverse transcriptase inhibitor

Metalation of biaryls – DoM *vs* DreM

- ***metalation of biaryls containing a DMG* ortho *to the biaryl axis show interesting thermodynamic* vs *kinetic selectivity:***
  - kinetic conditions give DoM at the *meta* position
  - thermodynamic conditions give ***Directed remote Metalation*** (DreM) on the other ring:
  - Snieckus *Angew. Chem. Int. Ed.* **2004**, *43,* 2206 (***review***) (DOI); Mongin *Tetrahedron* **2004**, *60*, 2181 (DOI); Snieckus *Org. Lett.* **2008**, *10*, 2617 (***2-aryl indoles***) (DOI) & *J. Org. Chem*. **2008**, *73*, 9710 (DOI) & *J. Org. Chem*. **2009**, *74*, 4080 (DOI)



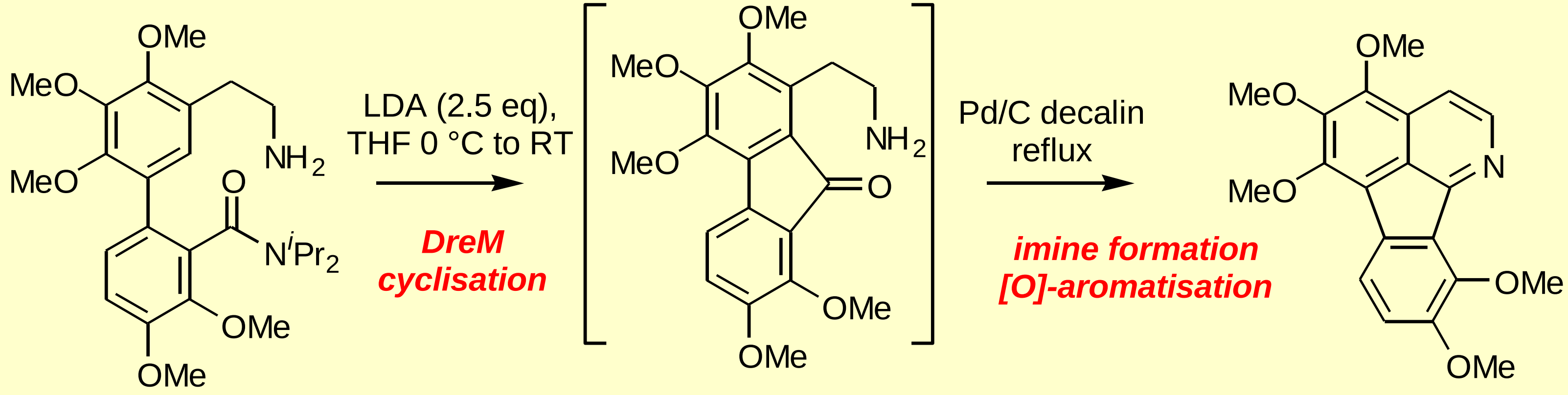
DMG = $CONEt_2$: ^{s}BuLi, THF-TMEDA, -78 °C
DMG = $OCONEt_2$: ^{s}BuLi, THF-TMEDA, -100 °C

kinetic deprotonation

DMG = $CONEt_2$: LDA, THF, 0 °C
DMG = $OCONEt_2$: LDA, THF, reflux

thermodynamic deprotonation

e.g. Synthesis of imelutein:



LDA (2.5 eq),
THF 0 °C to RT

DreM cyclisation

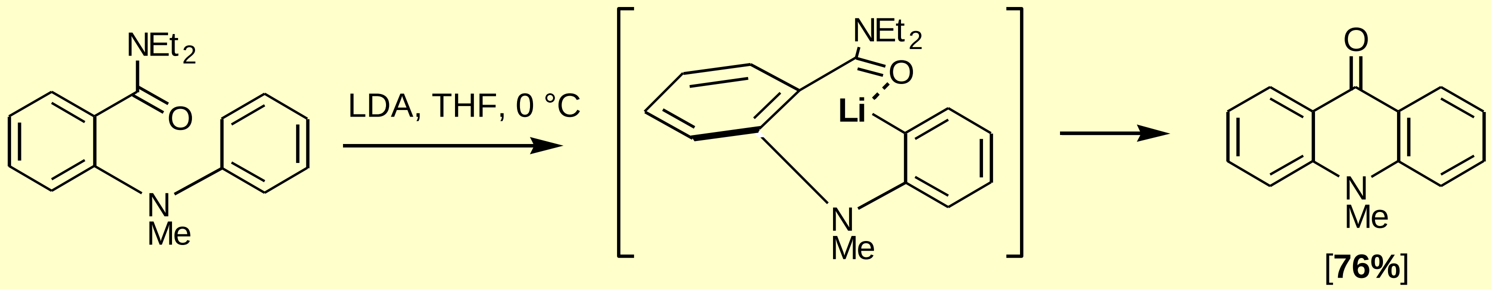
Pd/C decalin
reflux

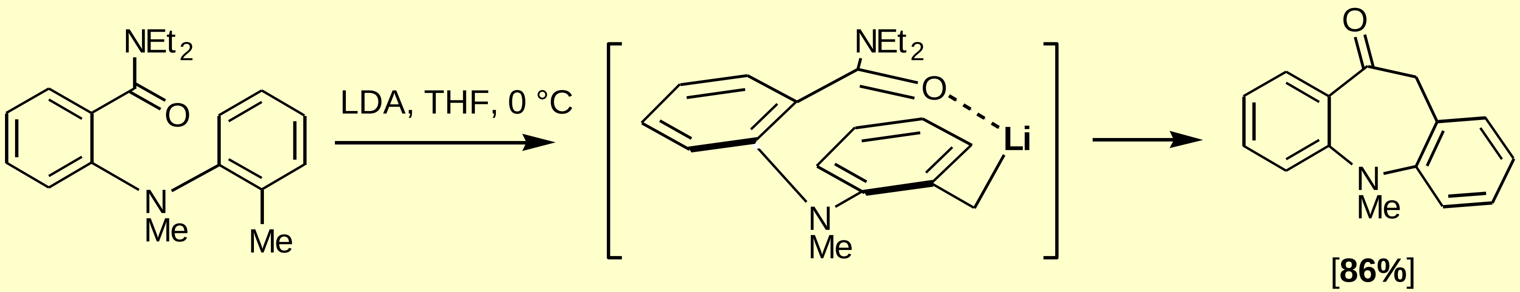
imine formation
[O]-aromatisation

imelutine
5 steps, 13%

Remote directed metalation (Drem)

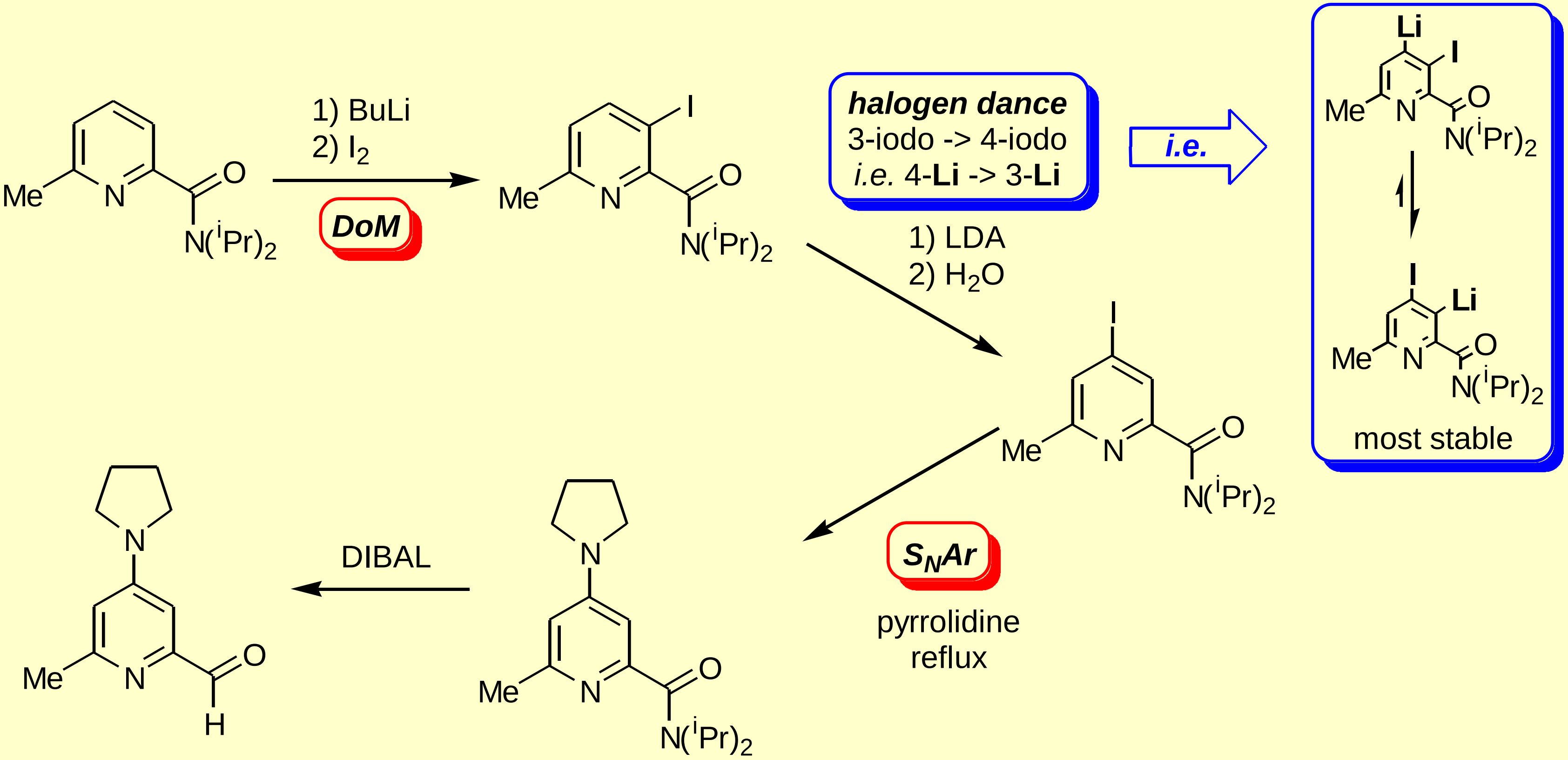
- ***Snieckus' approach to acridones & azepinones:***
  - Sniekus *Synlett* **1998**, 419 (**DOI**)





‘Halogen dance’ rearrangements

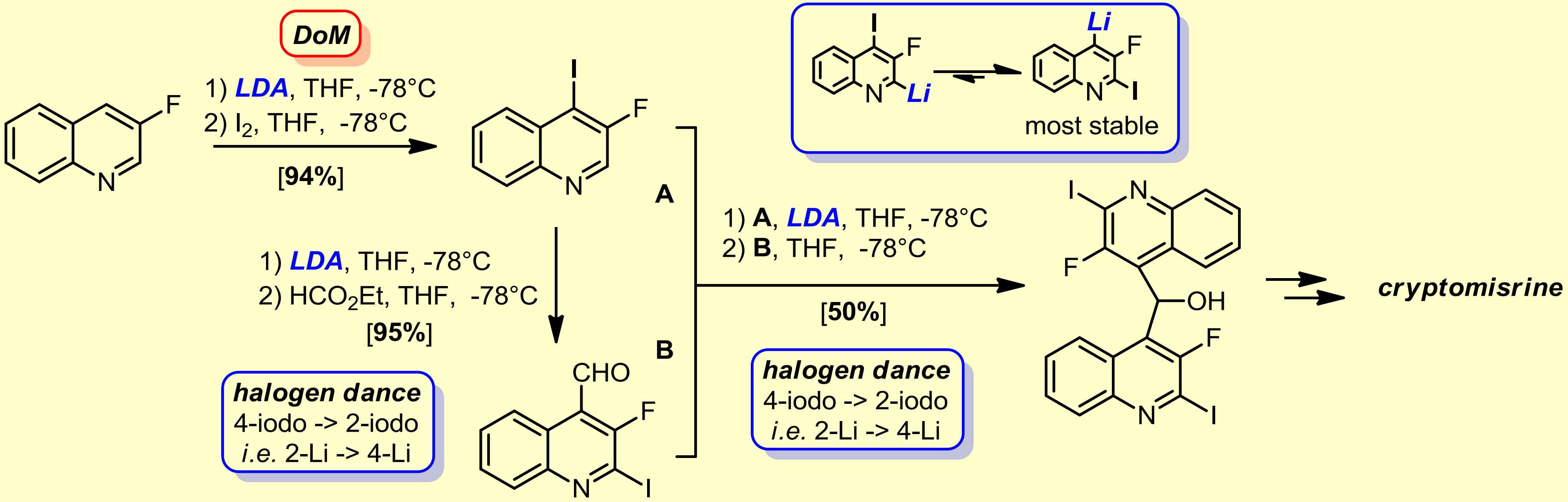
- ***Halogens can migrate under* thermodynamic *metalation conditions:***
  - driven by stability of anion
  - allows access to halogenated heterocycles not accessible easily by other means
  - Quéguiner *Adv. Het. Chem.* **1991**, *52*, 187 (***review***)
  - *e.g*. Sammakia *J. Org. Chem.* **1999**, *64*, 4652 (**DOI**)



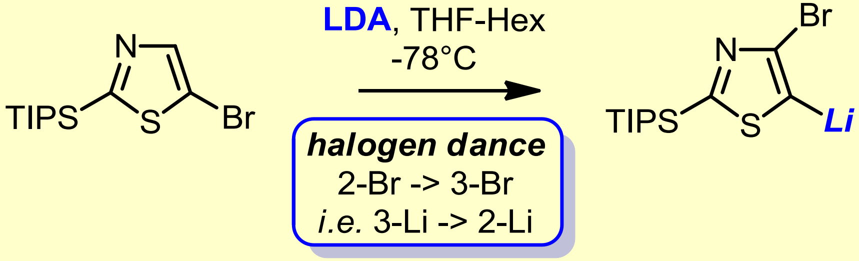
- ***mechanism:*** ~unknown

DoM & halogen dance in synthesis

- ***Quéguiner's total synthesis of cryptomisrine:*** ***antimuscarinic & antiviral alkaloid***
  - Quéguiner *Tetrahedron* **1999**, *55*, 12149 (DOI)



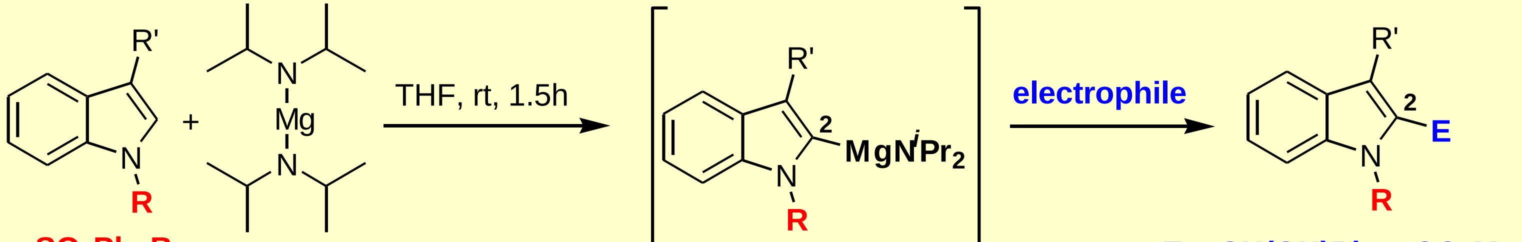
- ***Also in 5-memb heterocycles: e.g.***
  - MarderOrg. Letts. **2010**, *12*, 2136 (DOI)



  - Not easily predictable…so always verify regiochemistry of products following thermodynamic metalation reactions when halogens are present in the substrate

Magnesiation & metal-free deprotonation

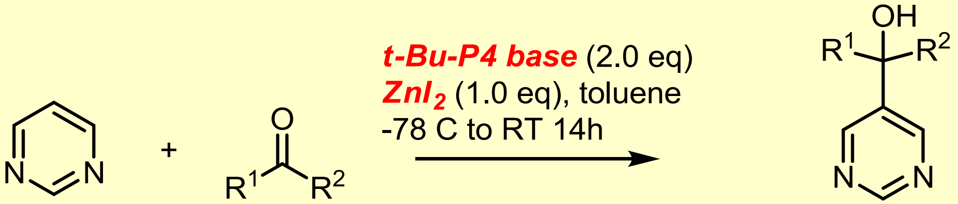
- ***deprotonation using magnesium bis(isopropyl)amides:***
  - similar regioselectivity to LDA but wider ***functional group tolerance***:
  - Eaton *Angew. Chem. Int. Ed.* **2002**, *41*, 2169 (DOI); Kondo *J. Chem. Soc., Perkin Trans 1* **1996**, 2331 (DOI); Kerr, *Chem. Eur. J.* **2001**, *7*, 3430 (***review***) (DOI)



R = SO_2Ph, Boc
R' = H, Me, CO_2Me, CN

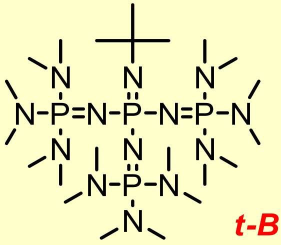
E = CH(OH)Ph, I, CO_2Me
[**44-93%**]

- ***deprotonation using t-Bu-P4 base:***
  - ***unique regioselectivity***: dominated by avoidance of pair-pair electron repulsion
  - Kondo *J. Am. Chem. Soc.* **2003**, *125*, 8082 (DOI)



t-Bu-P4 base (2.0 eq)
ZnI_2 (1.0 eq), toluene
-78 C to RT 14h

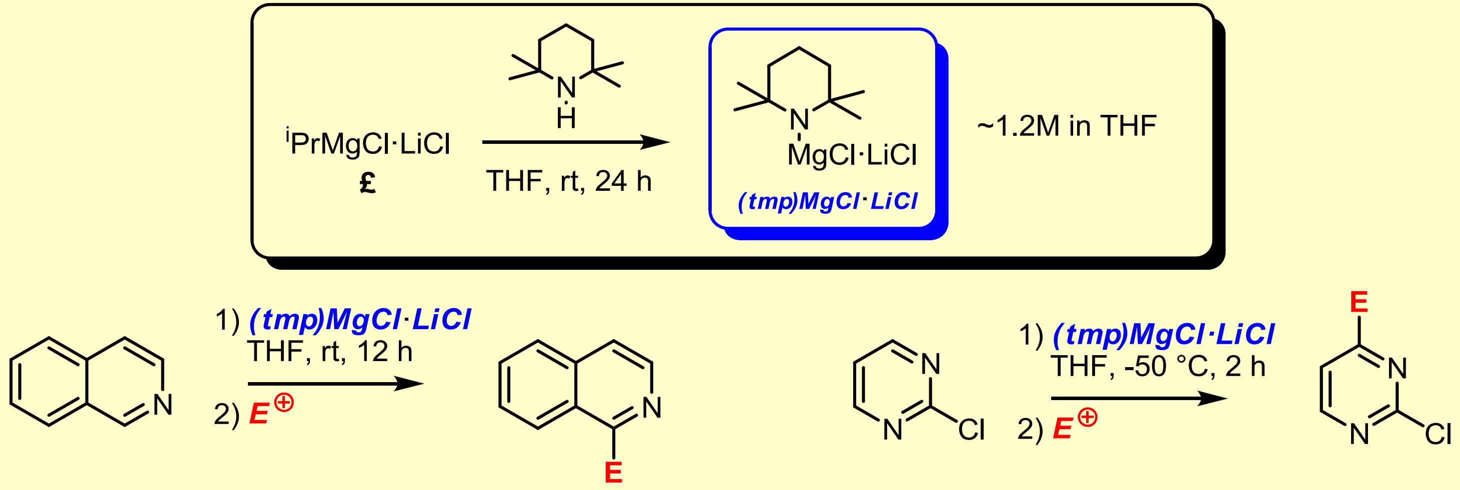
R^1 = Ph, R^2 = Ph [**48%**]
R^1 = Ph, R^2 = H [**80%**]
R^1 = *t*-Bu, R^2 = H [**65%**]



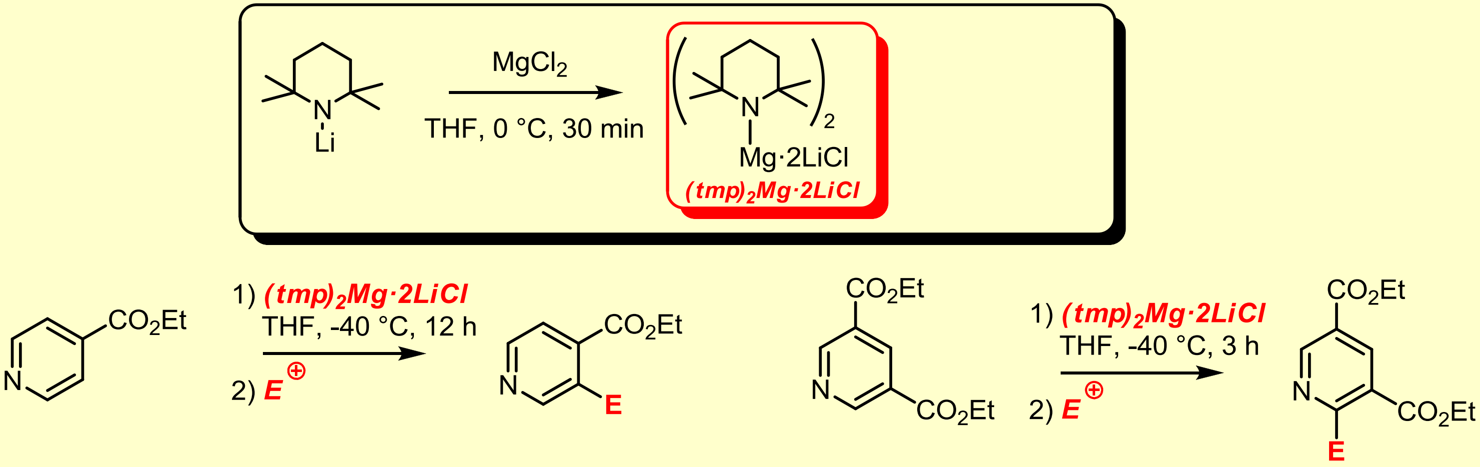
t-Bu-P4

Mixed Mg/Li amides

- ***(tmp)Mg·LiCl & $(tmp)_2Mg·2LiCl$ for direct magnesiation of polyfunctional heteroarenes:***
  - ***(tmp)Mg·LiCl* - stable for >6 months at RT in THF solution:** Knochel *Angew. Chem. Int. Ed.* **2006**, *45*, 2958 (DOI)

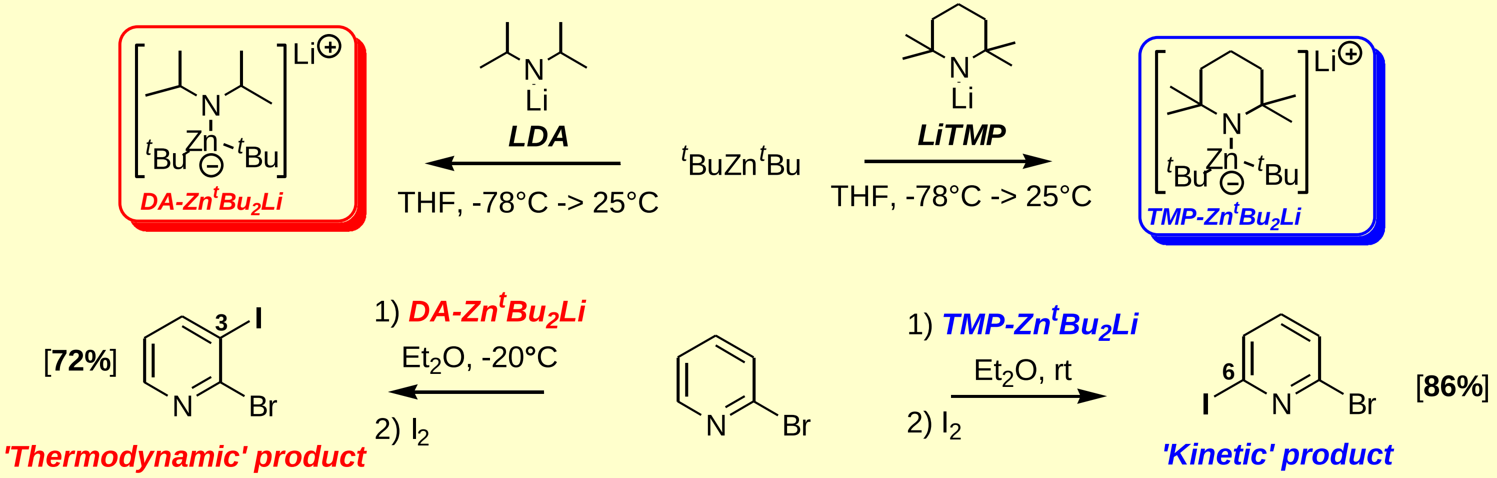


  - ***$(tmp)_2Mg·2LiCl$* – more reactive but tolerates esters:** Knochel *Angew. Chem. Int. Ed.* **2007**, *46*, 7681 (DOI); Knochel *Angew. Chem. Int. Ed.* **2009**, *48*, 7256 (DOI) & corrigendum.

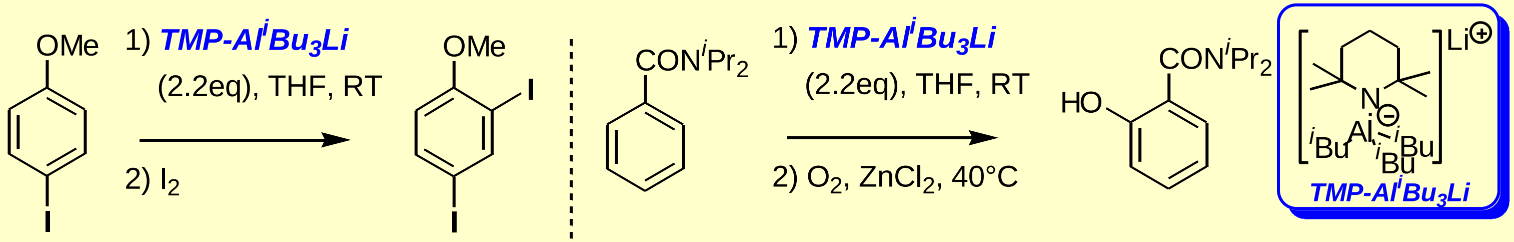


Zincation and alumination

- ***zincation shows wide*** functional group tolerance ***and allows access to ‘kinetic’ and ‘thermodynamic’ products by reagent control:***
  - Kondo *J. Am. Chem. Soc.* **2002**, *124*, 8514 (**DOI**); Kondo *Chem. Commun.* **2001**, 2450 (**DOI**); Kondo *J. Am. Chem. Soc.* **1999**, *121*, 3539 (**DOI**)

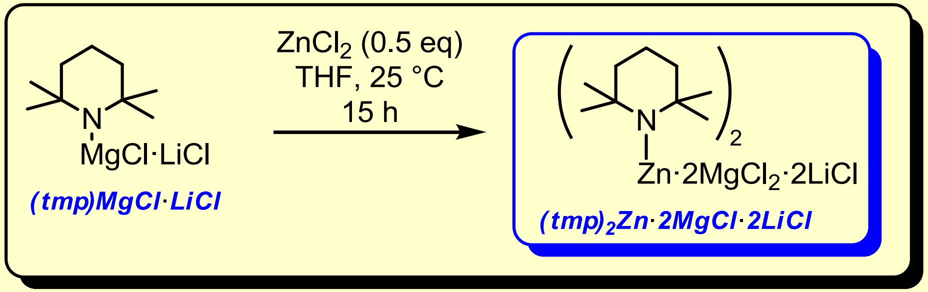


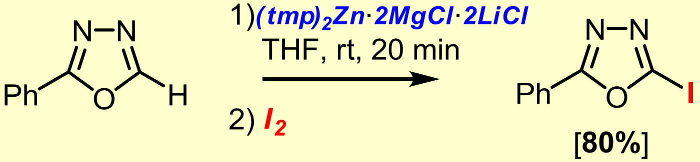
- ***alumination*** shows wide ***functional group tolerance*** and allows ***phenol formation:***
  - Uchiyama *J. Am. Chem. Soc.* **2004** *126,* 10526 (**DOI**)
  - ***review of phenol formation***: Slocum *Synthesis* **2005**, 3477 (**DOI**)

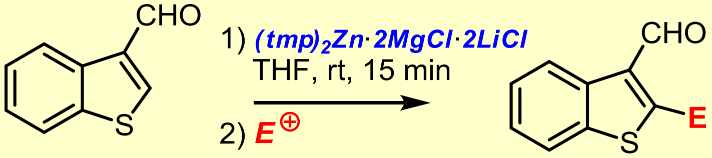


Directed *ortho* zincation, cupration & alumination

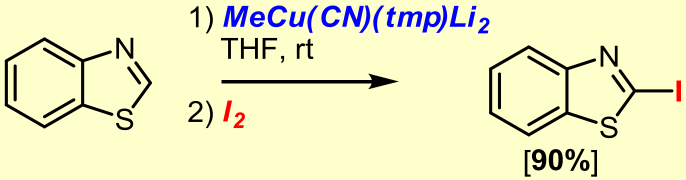
- ***(tmp)$_2$Zn·2MgCl$_2$·2LiCl for directed zincation of sensitive heteroarenes:***
  - Knochel *Angew. Chem. Int. Ed.* **2007**, *46*, 7685 (DOI) & *Chem. Commun*. **2008**, 6387 (DOI) & *Org. Lett*. **2009**, *11*, 1837 (use of ***(tmp)ZnCl·LiCl*** itself) (DOI) & *J. Org. Chem.* **2010**, *75*, 4686 (heteroaromatics) (DOI)

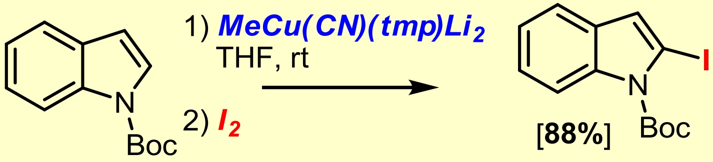






- ***MeCu(CN)(tmp)Li$_2$ for directed cupration of aryls:***
  - Uchiyama & Wheatley *J. Am. Chem. Soc.* **2007**, *129*, 15102 (DOI)

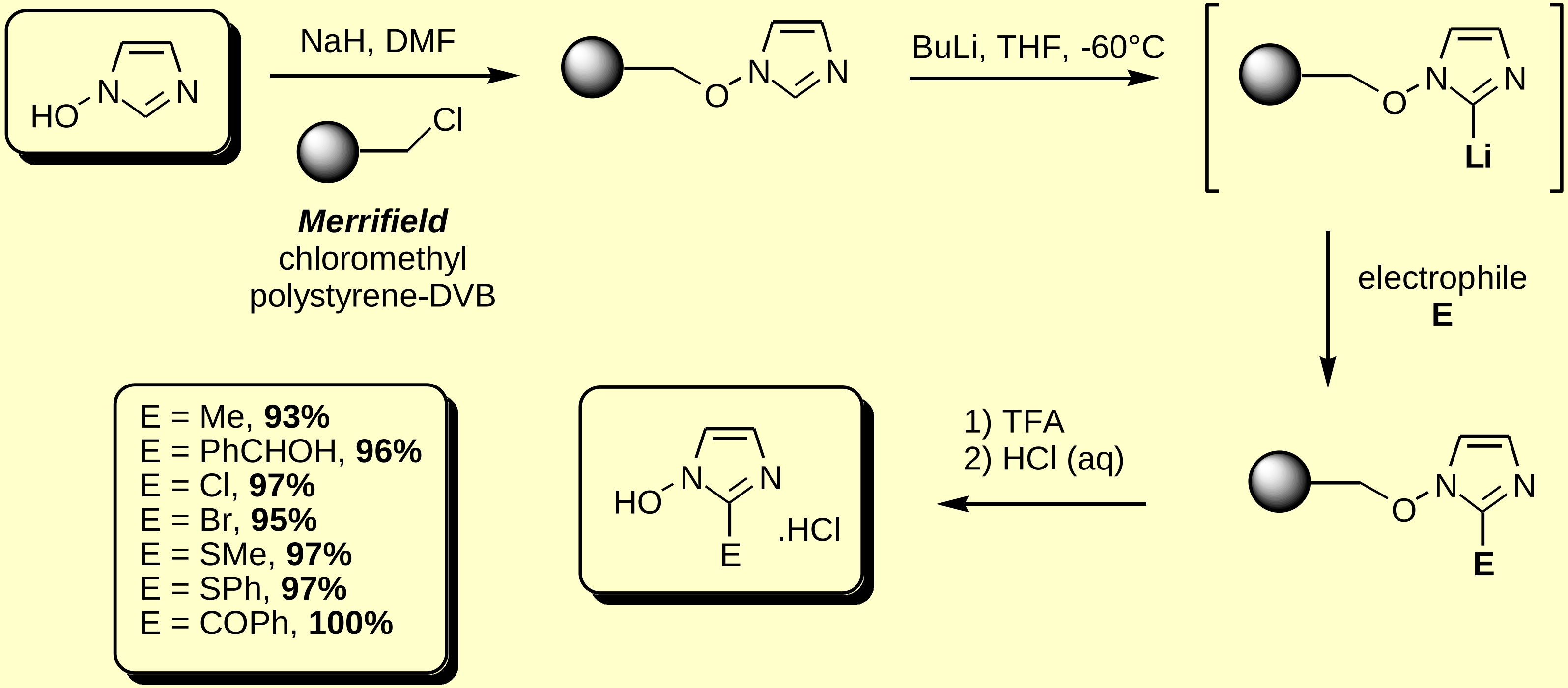




- ***Al(tmp)$_3$·3LiCl for directed alumination of aryls:***
  - Knochel *Angew. Chem. int. Ed.* **2009**, *48*, 1501 (DOI)
  - '…*particularly good regioselectivity for oxygen-containing directing groups*…'

Metalation on solid supports

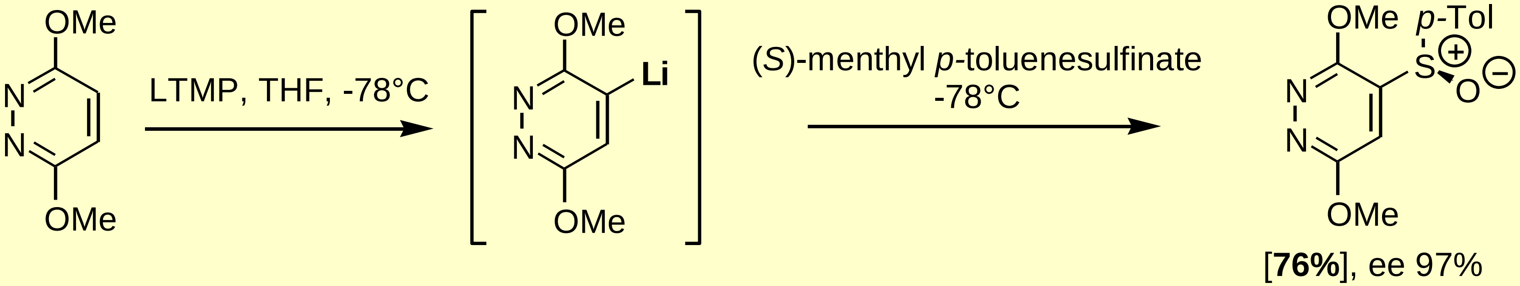
- ***solid phase metalation:***
  - PS-PEG graft resins (*e.g.* tentagel) can cause problems
    - Kondo *J. Comb. Chem.* **1999**, *1*, 123 (***review***) (DOI)
    - *e.g.* Havez *J. Org. Chem.* **1998**, *63*, 7418 (DOI)

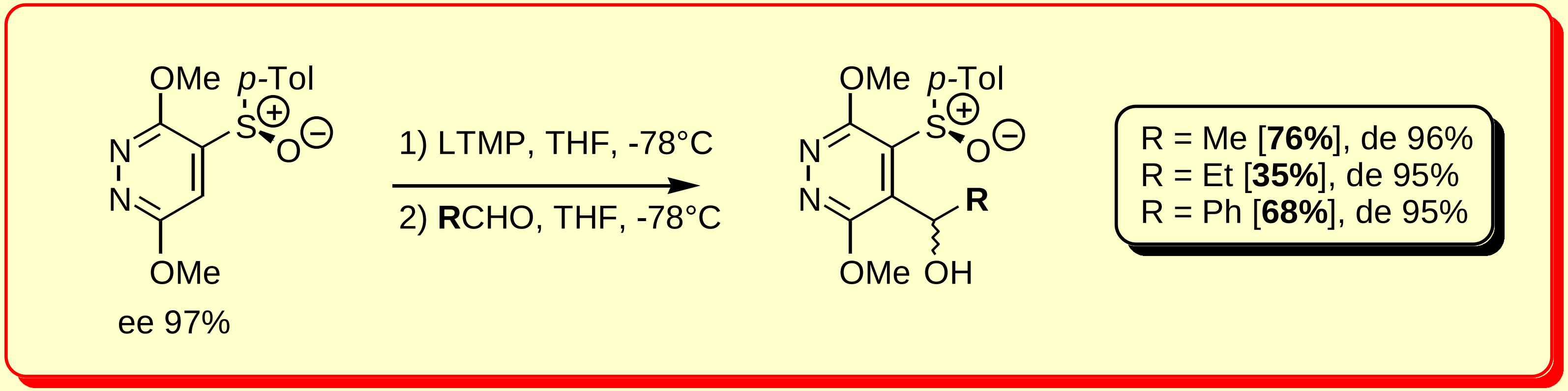


E = Me, **93%**
E = PhCHOH, **96%**
E = Cl, **97%**
E = Br, **95%**
E = SMe, **97%**
E = SPh, **97%**
E = COPh, **100%**

Asymmetric DoM

- ***Reaction of* ortho*-lithiated chiral sulfoxides with prochiral electrophiles:***
  - Pollet *J. Org. Chem.* **1999**, *64*, 4512 (**DOI**)

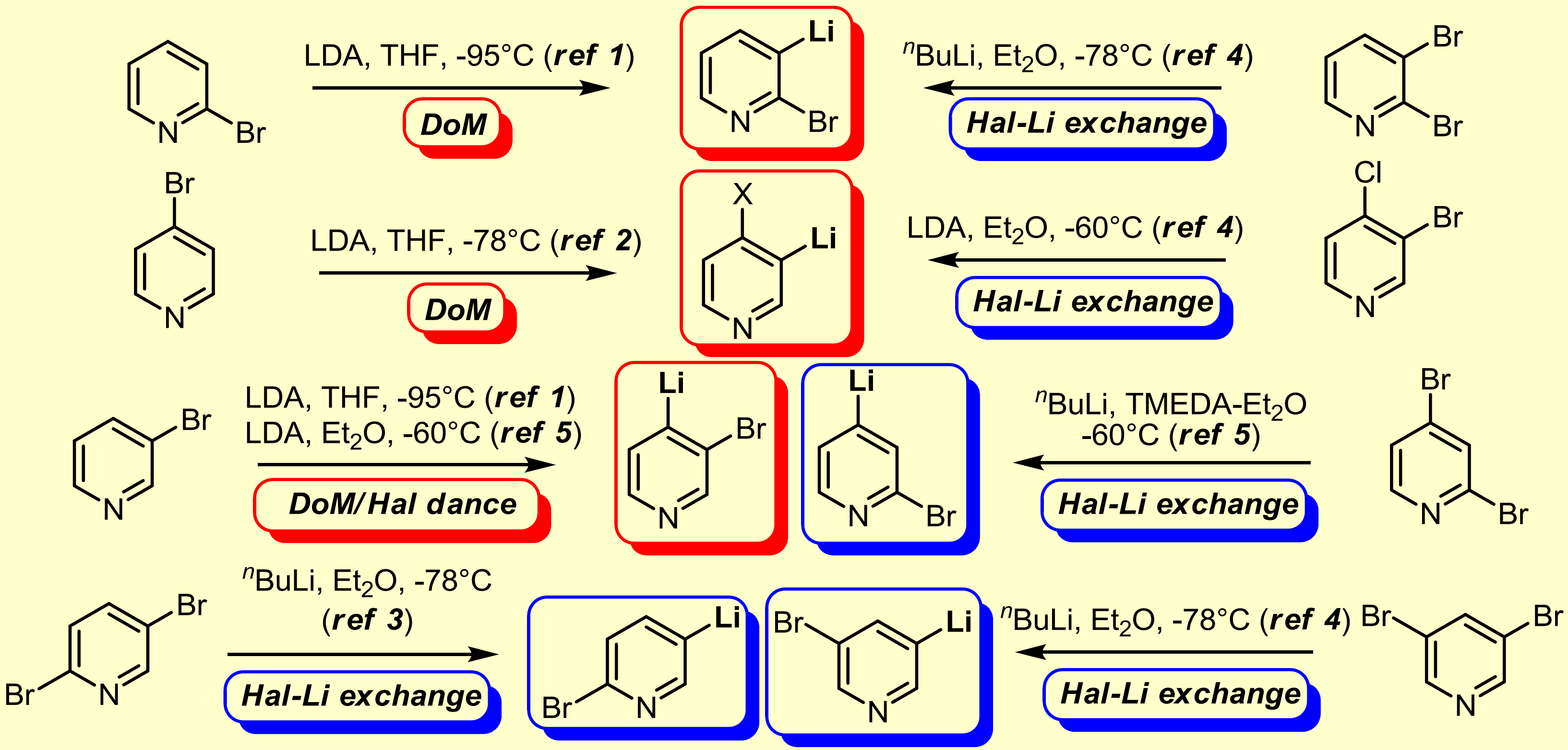




R = Me [**76%**], de 96%
R = Et [**35%**], de 95%
R = Ph [**68%**], de 95%

Deprotonation *vs* halogen-metal exchange

- ***Often difficult to predict:***
  - e.g. for metalated bromopyridines which are useful building blocks in synthesis



LDA, THF, -95°C (***ref 1***)

DoM

^{n}BuLi, Et_2O, -78°C (***ref 4***)

Hal-Li exchange

LDA, THF, -78°C (***ref 2***)

DoM

LDA, Et_2O, -60°C (***ref 4***)

Hal-Li exchange

LDA, THF, -95°C (***ref 1***)
LDA, Et_2O, -60°C (***ref 5***)

DoM/Hal dance

^{n}BuLi, TMEDA-Et_2O
-60°C (***ref 5***)

Hal-Li exchange

^{n}BuLi, Et_2O, -78°C
(***ref 3***)

Hal-Li exchange

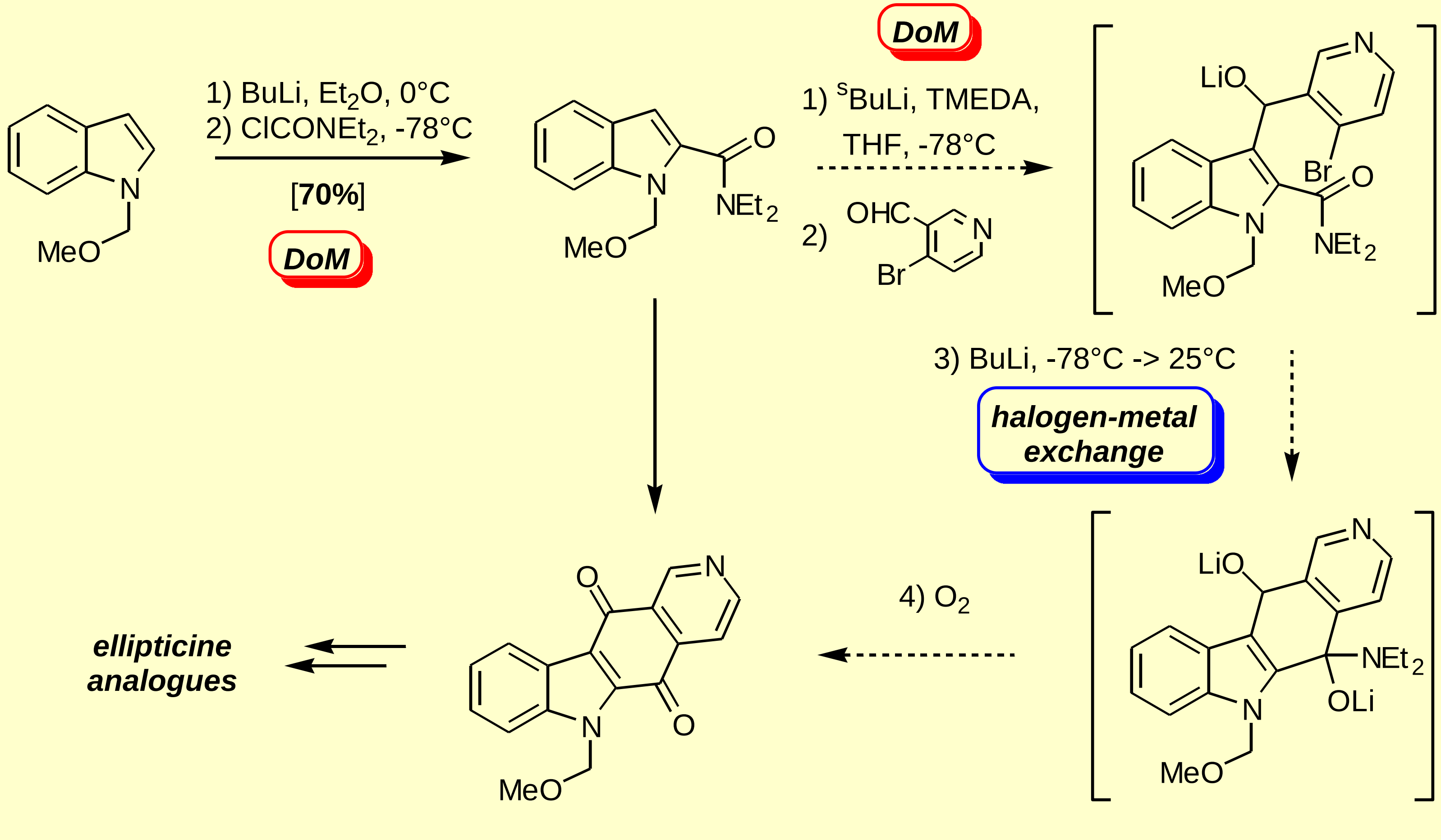
^{n}BuLi, Et_2O, -78°C (***ref 4***)

Hal-Li exchange

- ***ref 1***: Gallagher *Org. Lett.* **2001**, *3*, 835 (DOI); ***ref 2***: Gallagher *Synlett* **2002**, 808 (DOI); ***ref 3***: Rault *Tetrahedron* **2002**, *58*, 2885 (DOI); ***ref 4***: Rault *Tetrahedron* **2002**, *58*, 3323 (DOI); ***ref 5***: Rault *Tetrahedron* **2002**, *58*, 4369 (DOI)

Tandem DoM/halogen-metal exchange

- ***Snieckus' approach to antitumour ellipticine-type alkaloids:***
  - Sniekus *Pure & Appl. Chem.* **1990**, *62*, 2047



1) BuLi, Et_2O, 0°C
2) $ClCONEt_2$, -78°C
[70%]
DoM

DoM
1) ${}^{s}BuLi$, TMEDA, THF, -78°C
2)

3) BuLi, -78°C -> 25°C
halogen-metal exchange

4) O_2

ellipticine analogues

Summary

- ***Stoichiometric aromatic metalation reactions:***
  - halogen-metal exchange
  - metalation *ortho*- to ring heteroatoms
  - directed metalations (DoM & DreM)
  - ‘halogen dance’ rearrangements
  - Deprotonation *vs*. halogen metal exchange - *selectivity*