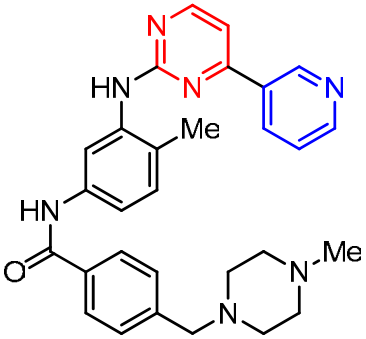
Palladium-catalysed heterocycle synthesis

Michael Greaney

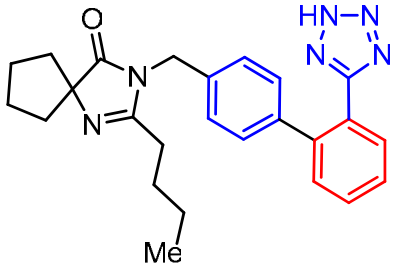
EaStCHEM
The Edinburgh and St Andrews Research School of Chemistry

SCI Nov 10

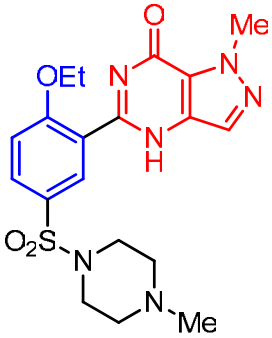
Bi(hetero)aryl drugs



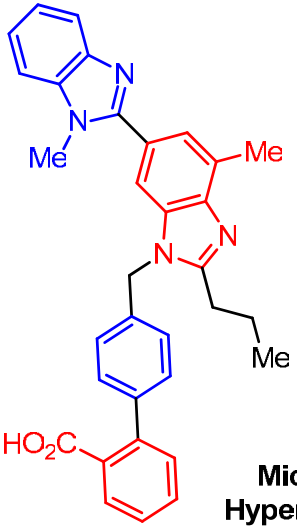
Gleevec
Leukemia



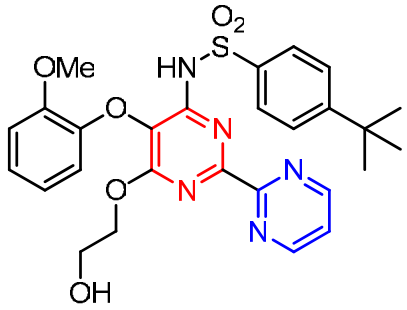
Irbesartan
Hypertension



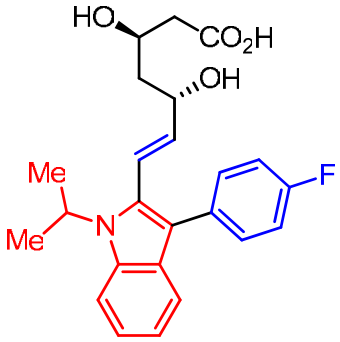
Viagra
Erectile dysfunction



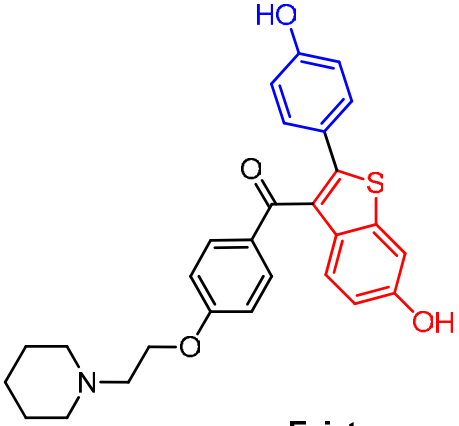
Micardis
Hypertension



Tracleer
Hypertension

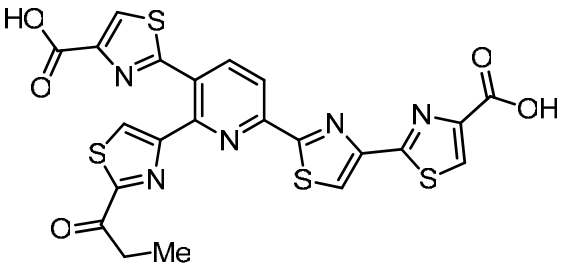


Lescol
Cholesterol lowering

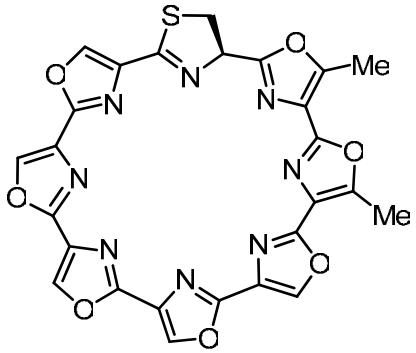


Evista
Osteoperosis

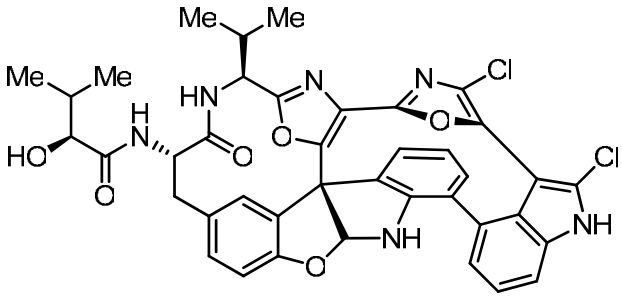
Heteroaryl Natural Products



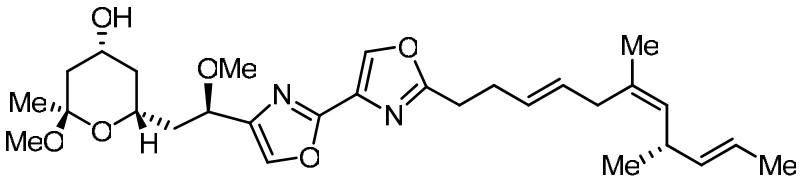
Micrococcinic acid



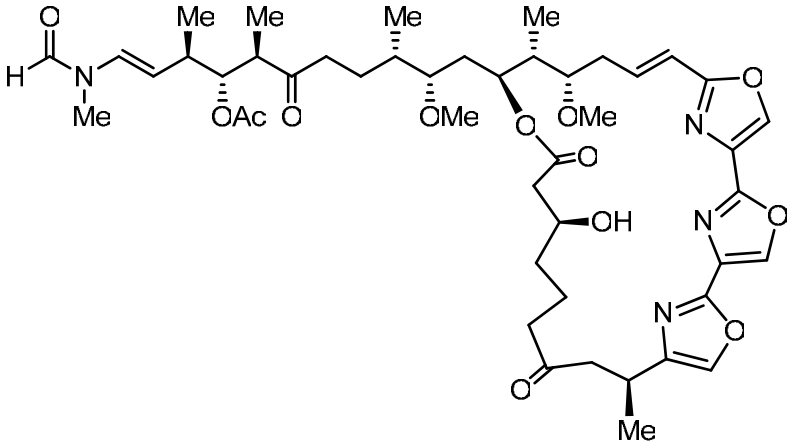
Telomestatin



Diazonamide A

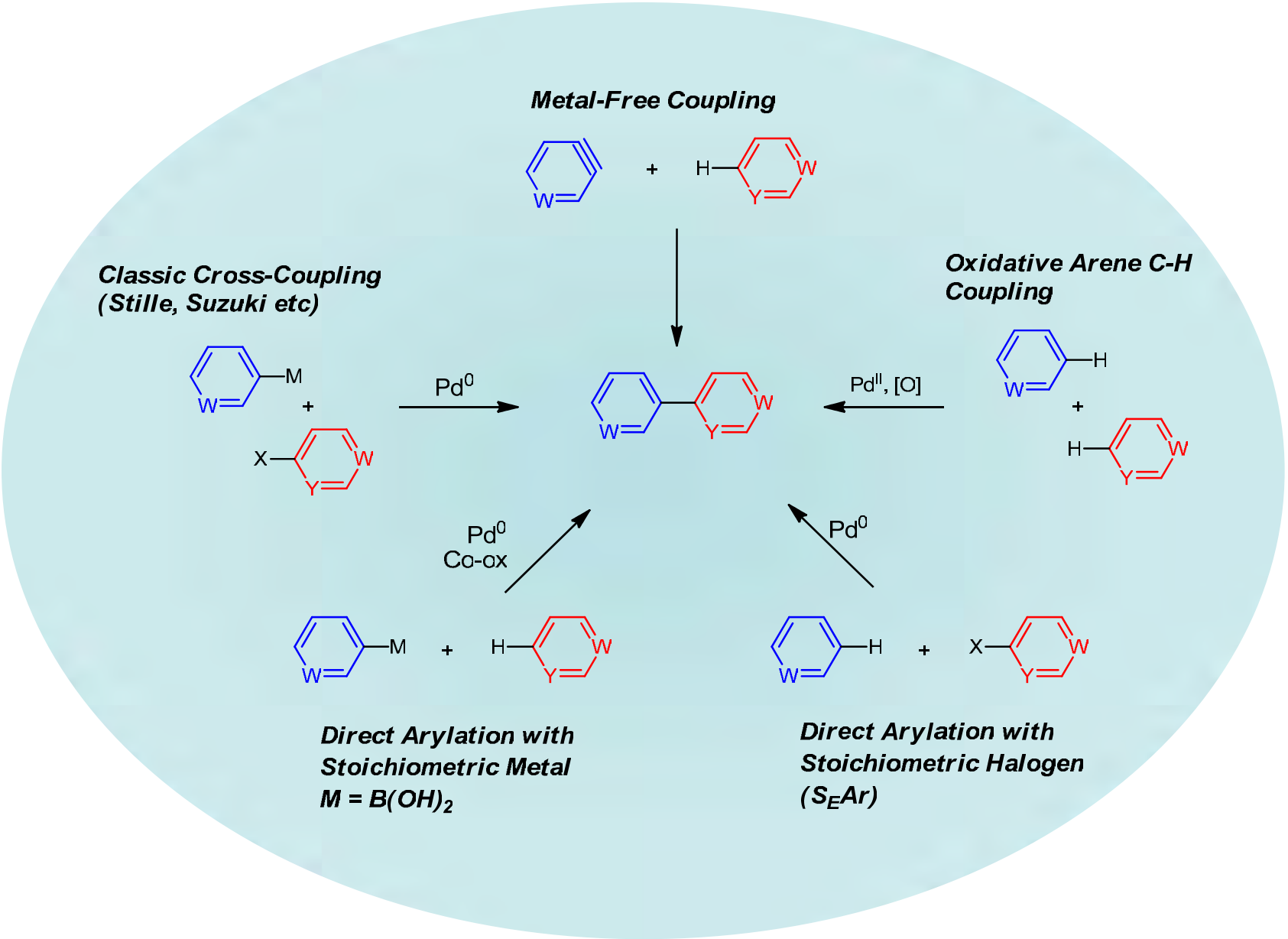


Hennoxazole A

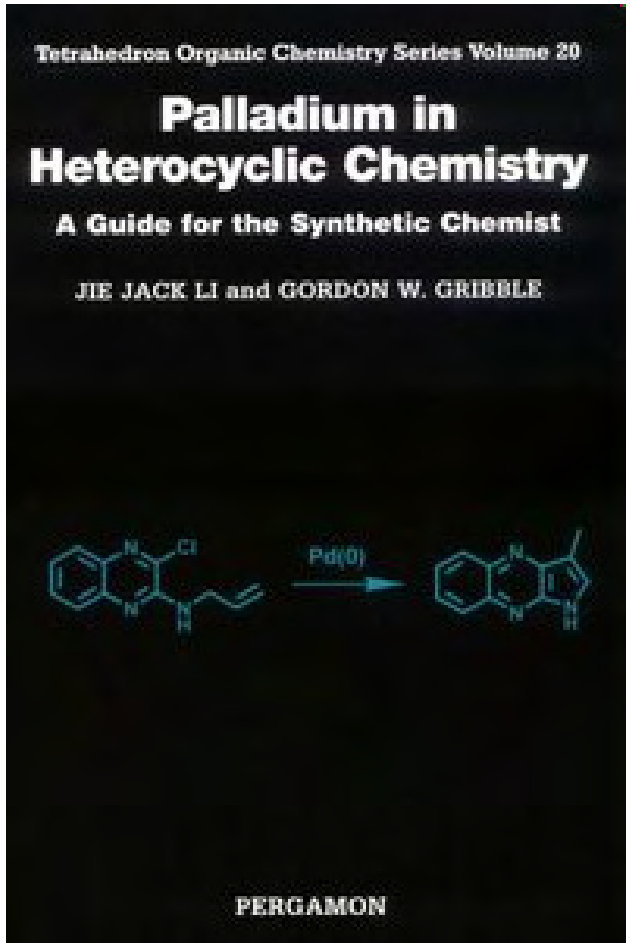


Ulapualide A

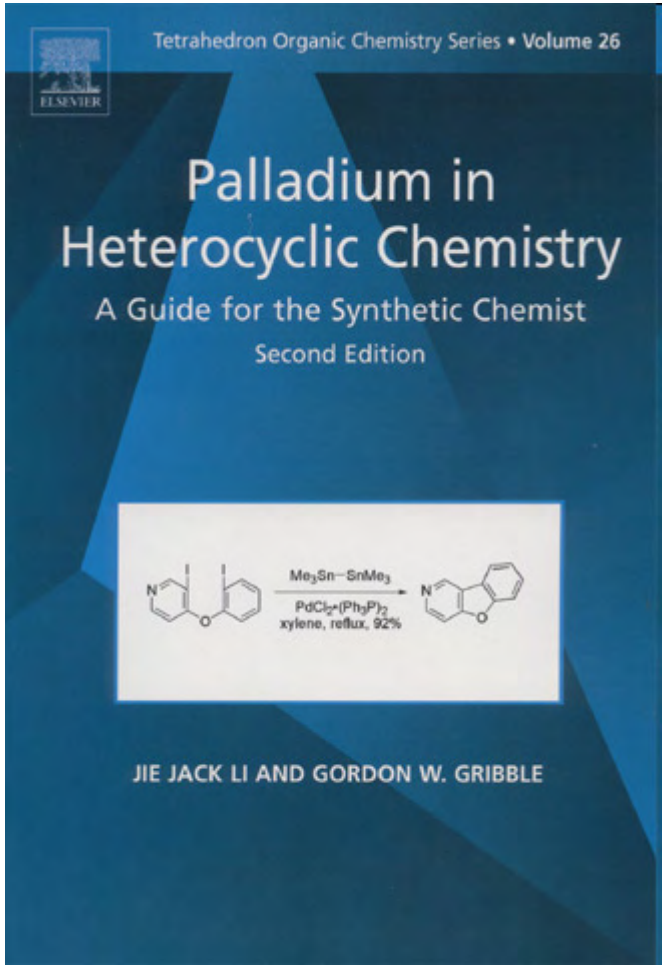
$sp^2 – sp^2$ Coupling



Texts

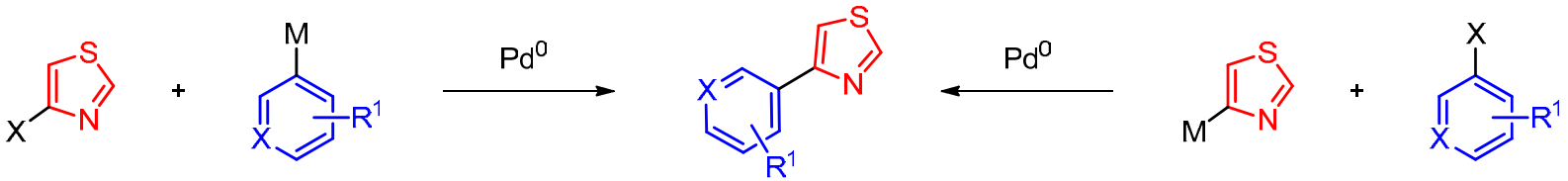


First Ed. 2000



Second Ed. 2007

Heteroaryl Cross Couplings: Challenges

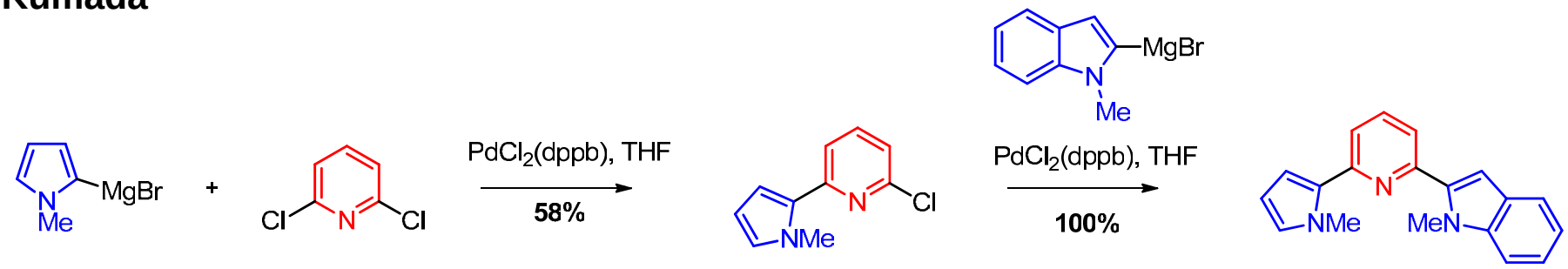


X = Cl, Br, I, OTf, $OP(OR)_2$
M = $B(OH)_2$, SnR_3, ZnCl *etc*

- Few heteroaryl halides commercially available, regioselective synthesis can be difficult
- Few metallated coupling partners commercially available, synthesis can be difficult (stability problems)
- Difficulties exacerbated for Het-Het coupling
- Fundamental difficulties associated with transition metal catalysed coupling of multi-heteroatom containing substrates

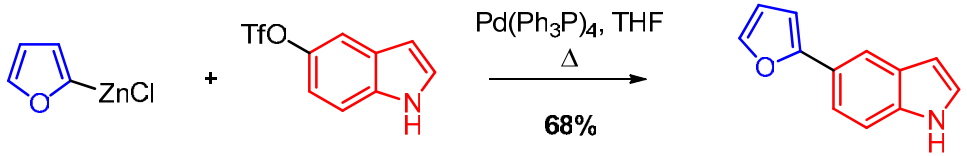
Heteroaryl Cross Couplings

Kumada



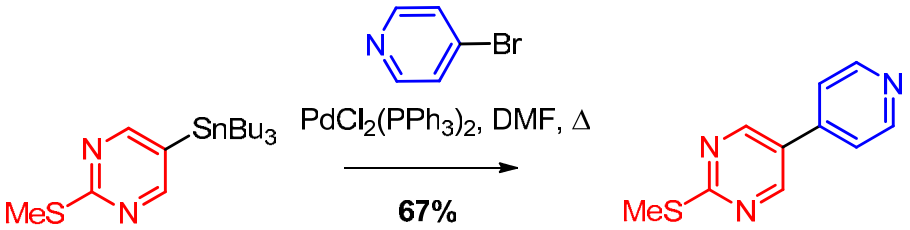
Minato, A.; Suzuki, K.; Tamao, K.; Kumada, M. *Chem. Commun.* **1984**, 511.

Negishi



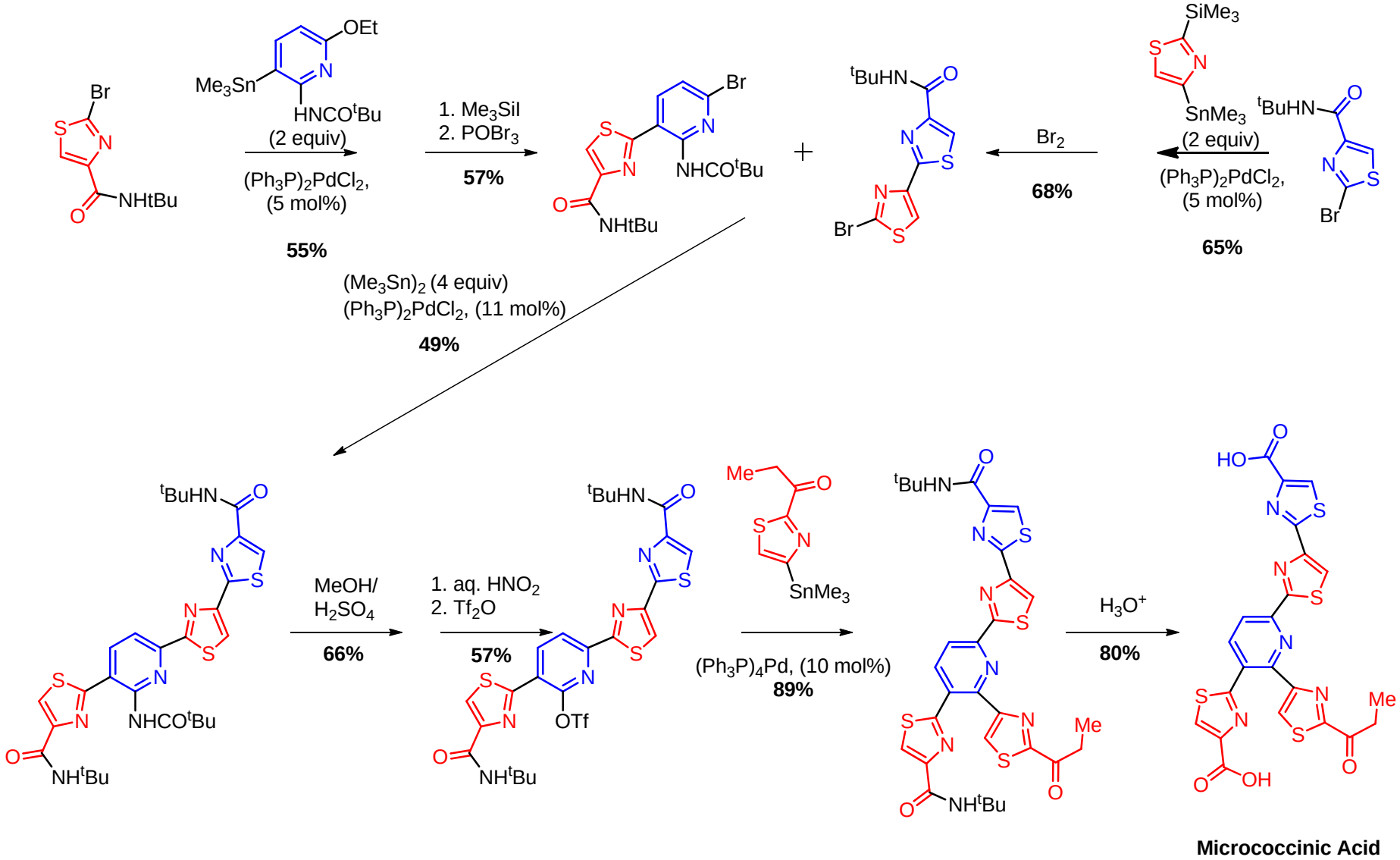
Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. *Synlett,* **1990**, 47.

Stille



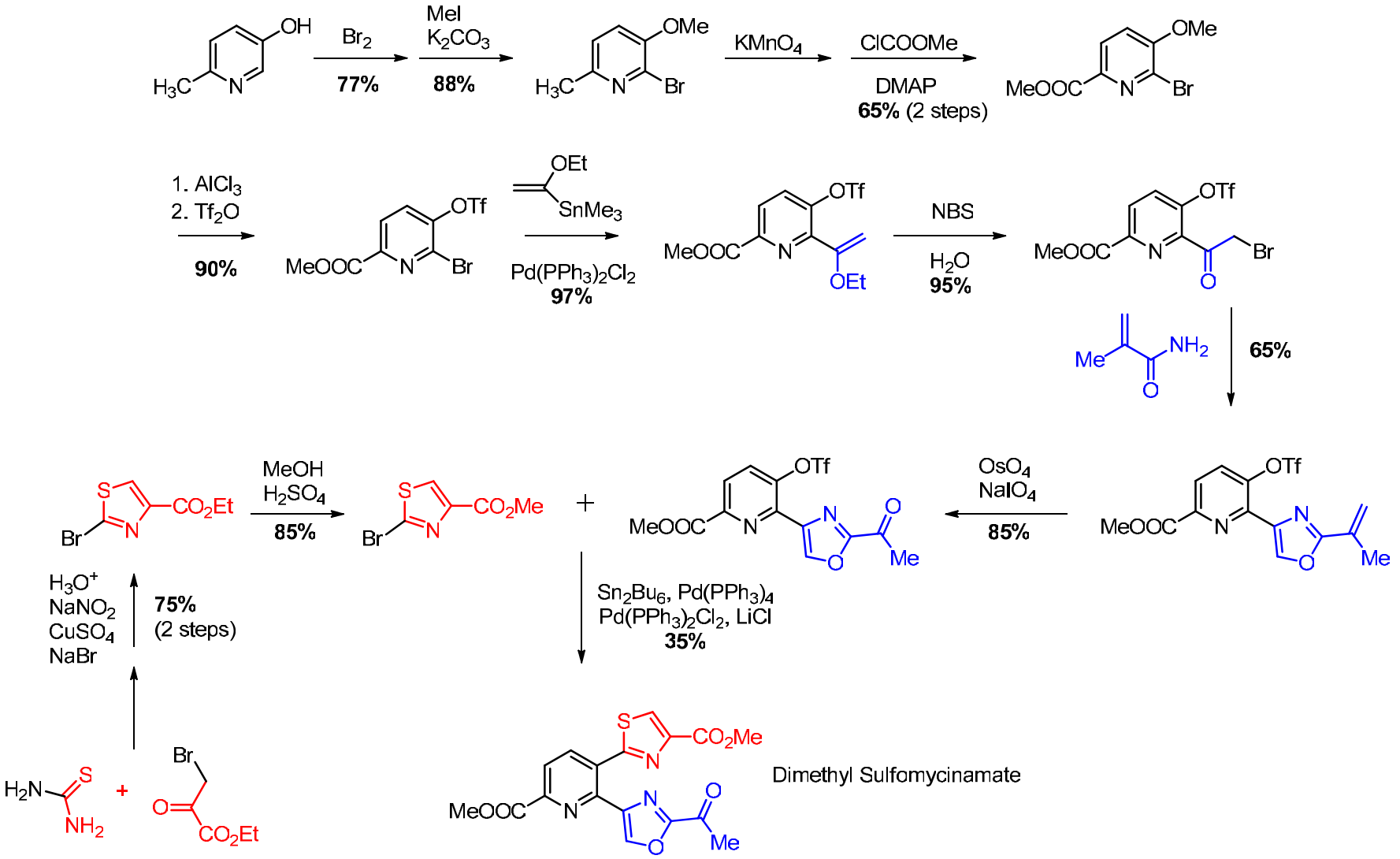
Sandosham, J.; Undhelm, K. *Acta Chem. Scand.* **1989**, *43*, 684.

Kelly's Synthesis of Micrococcinic Acid



Kelly, T. R.; Jagoe, C. T.; Gu, Z. *Tetrahedron Letters,* **1991**, *32,* 4263-4266

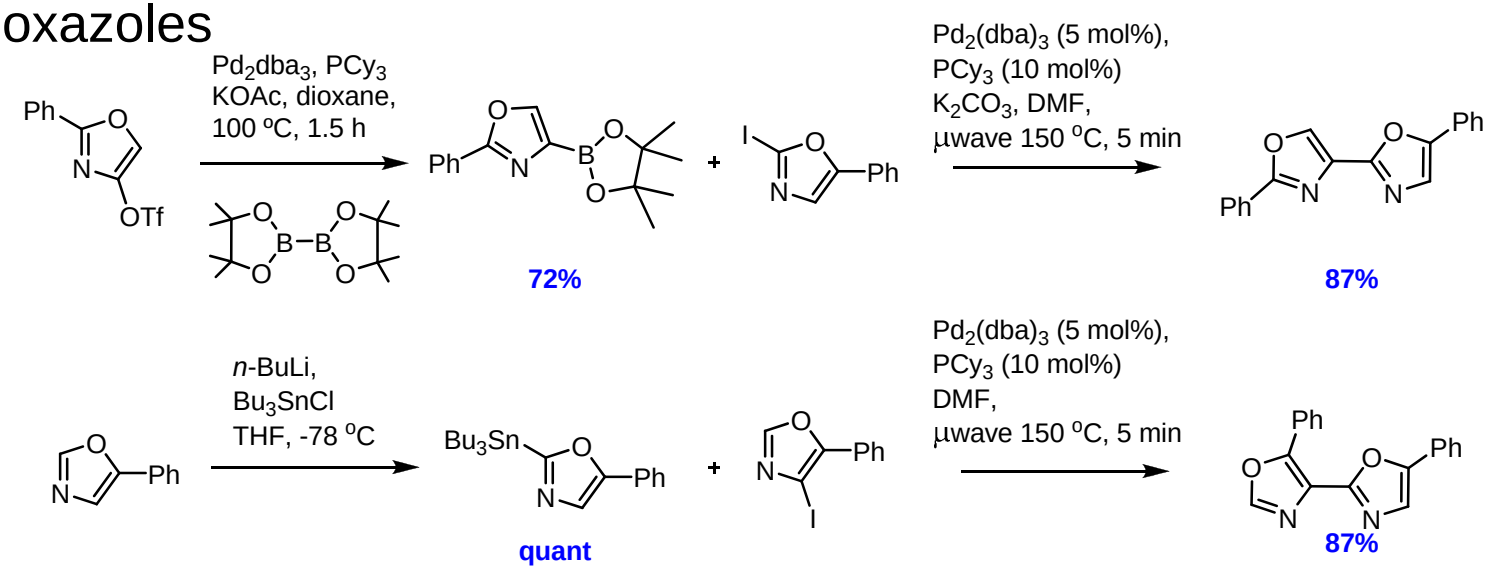
Kelly's Synthesis of Dimethyl Sulfomycinamate



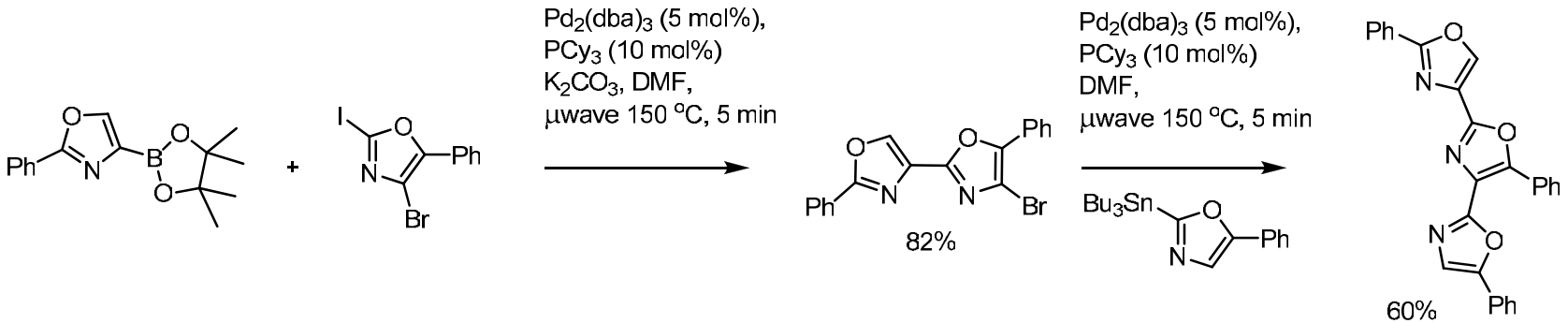
Kelly, T. R.; Lang. F. *J. Org. Chem.*,**1996**, *61*,4623-4633

Heteroaryl Suzuki Cross Couplings

2-4-Dioxazoles



Tris-oxazoles

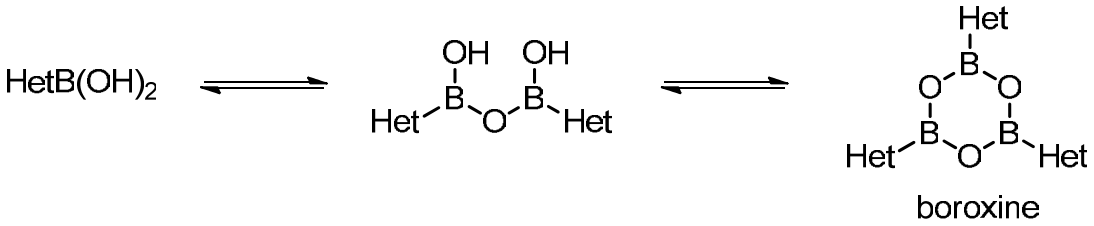


Ferrer Flegeau, E.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2006**, *8*, 2495 – 2498

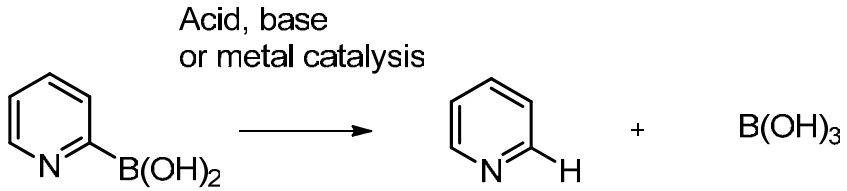
Ferrer Flegeau, E.; Popkin, M. E.; Greaney, M. F. *J. Org. Chem.* **2008**, *73,* 3303-3306.

Heteroarylboronic acids

• Boronic acids exist as equilibrium mixtures of monomers, dimers and trimers. Can be waxy solids that are difficult to purify.

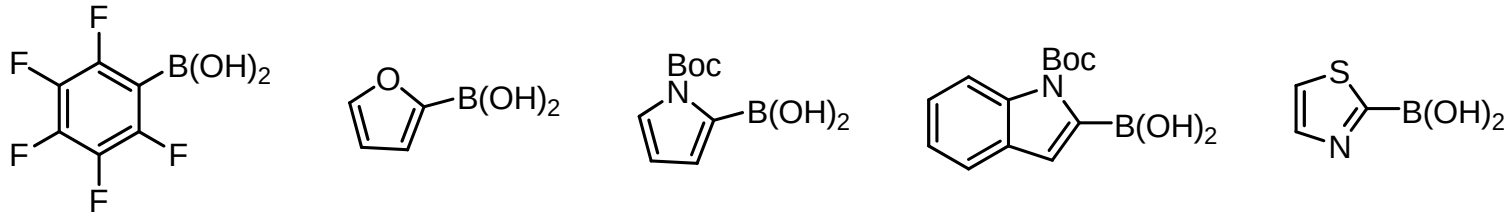


• Protodeboronation is a significant problem for electron deficient boronic acids. Occurs both in storage and in Suzuki coupling reactions (protic solvents).



• *Virtually every study focusing on heteroarylboronic acid coupling employs excess organoboron reagent (as high as 250%) to achieve satisfactory yields.*

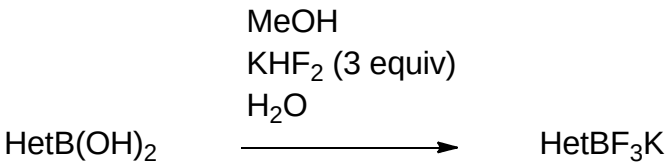
Classic protodeboronation substrates



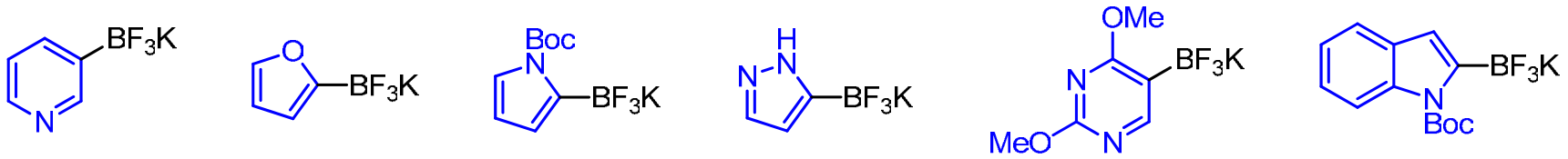
Protodeboronation mechanism: Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666.

Potassium trifluoroborates

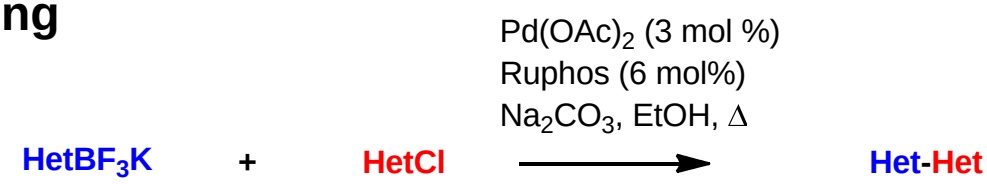
Synthesis

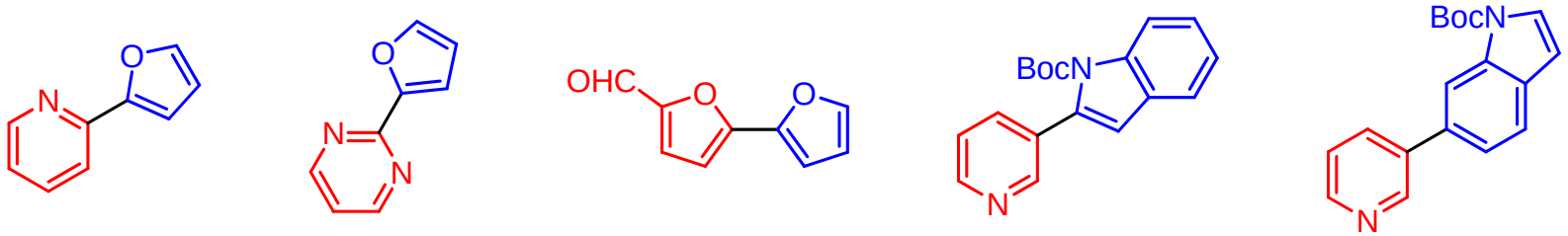


- Usually crystalline, air and moisture stable.
- Relatively resistant to protodeboronation



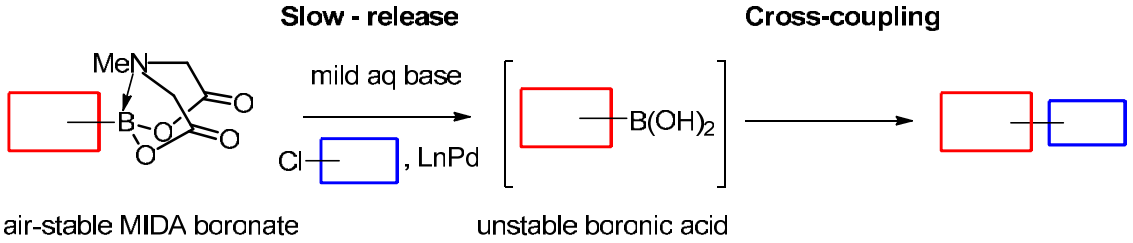
Suzuki Coupling

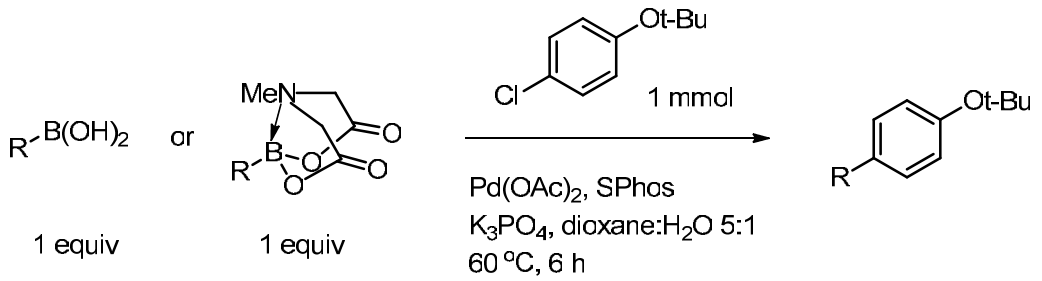


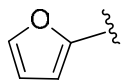
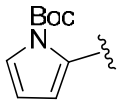
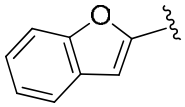
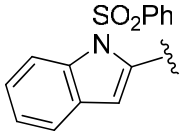
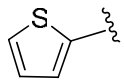
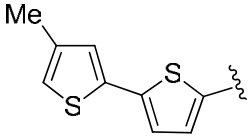
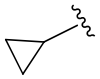


Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973–980

Slow-release cross coupling using air-stable MIDA boronates

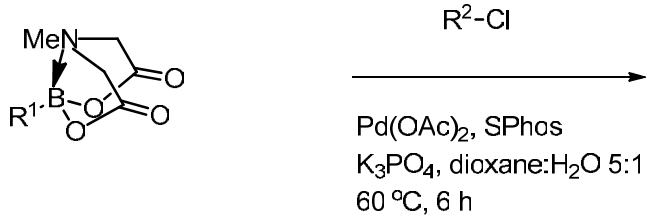


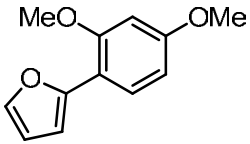


	% remaining under air after 15 days ($RB(OH)_2$) (60 days (MIDA))	cross-coupling yield (MIDA in brackets)		% remaining under air after 15 days ($RB(OH)_2$) (60 days (MIDA))	cross-coupling yield (MIDA in brackets)
	7 (>95)	68 (94)		<5 (>95)	61 (90)
	88 (>95)	50 (92)		<5 (>95)	14 (93)
	80 (>95)	37 (94)		5 (>95)	79 (98)
	80 (>95)	45 (96)		31 (>95)	95 (96)

Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961-6963.

Cross coupling using air-stable MIDA boronates





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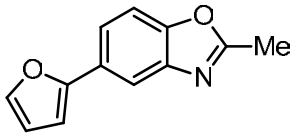

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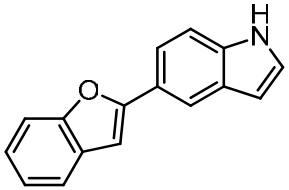

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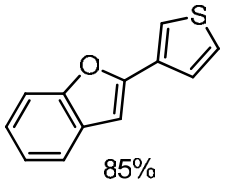

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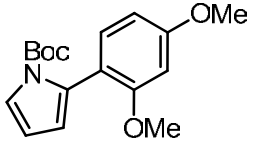

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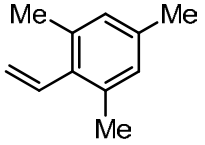

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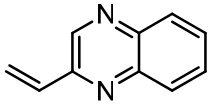

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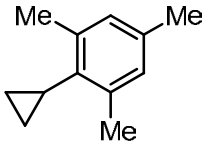

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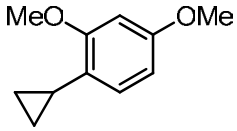

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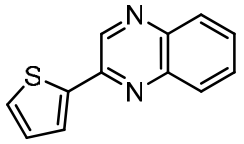

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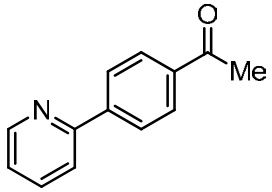

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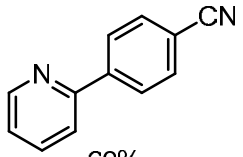

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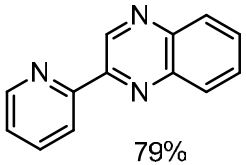

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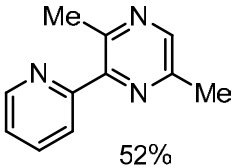
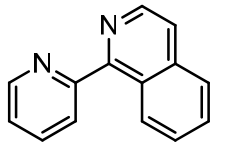


52%

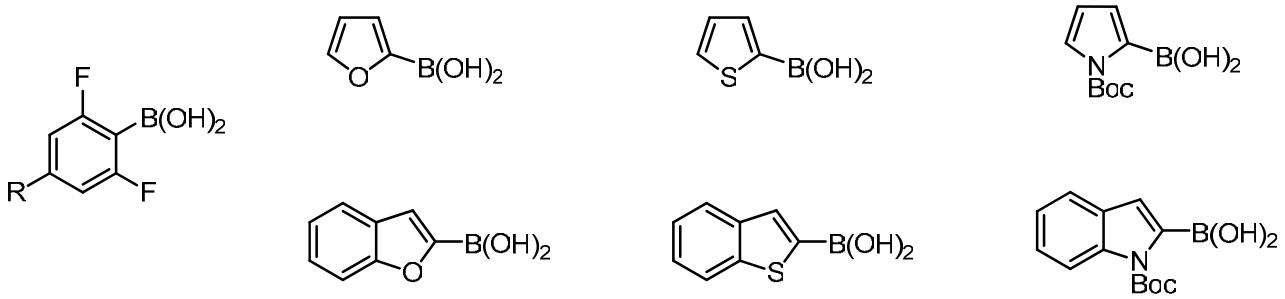


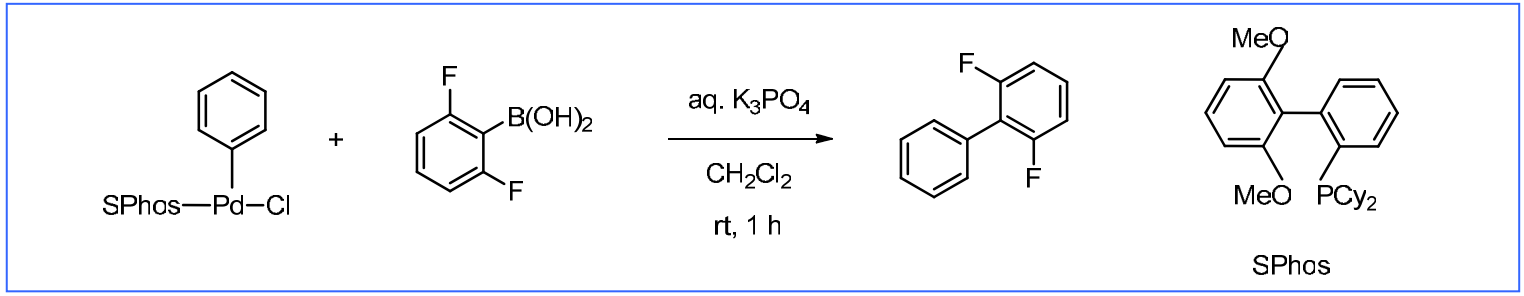
74%

Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961-6963.

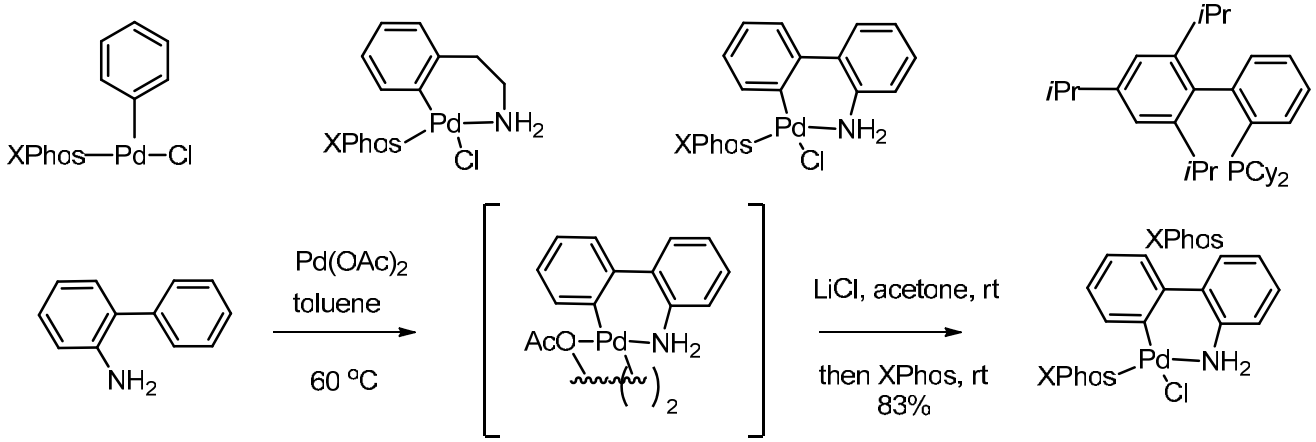
Pd precatalysts for Suzuki coupling of unstable boronic acids

Unstable boronic acids



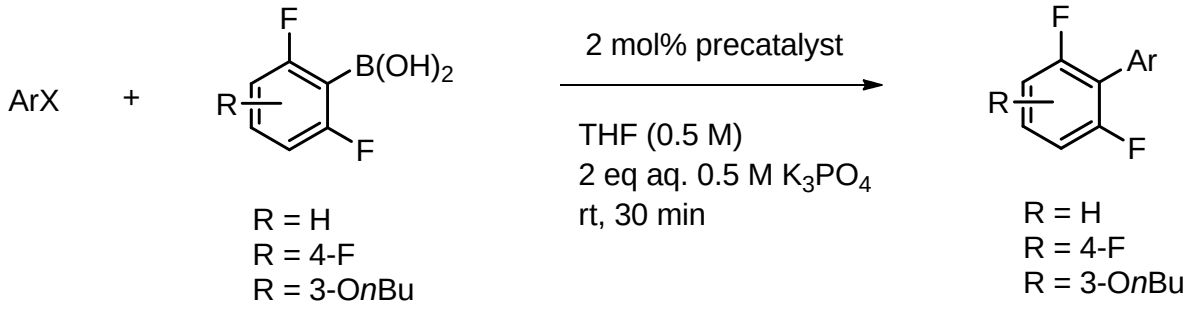


XPhos containing precatalysts



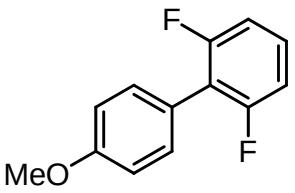
Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010,** *132*, 14073-14075.

Coupling of polyfluoroboronic acids to ArCl, ArBr and ArOTf

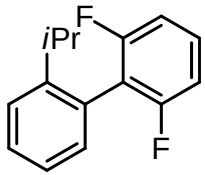


R = H
R = 4-F
R = 3-O*n*Bu

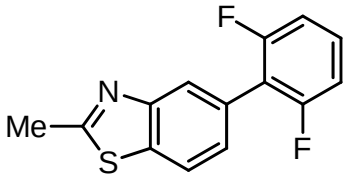
R = H
R = 4-F
R = 3-O*n*Bu



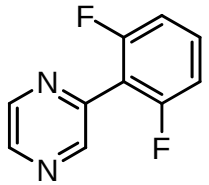
X = Cl: **95%**
X = Br **92%**
X = OTf: **95%**



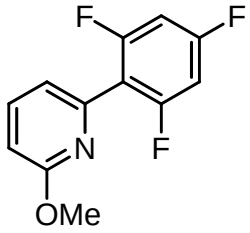
X = OTf: **89%**



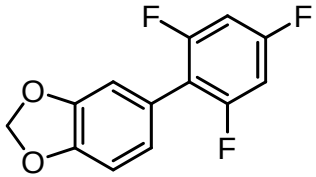
X = Cl: **99%**



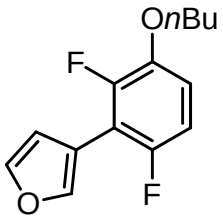
X = Cl: **77%**



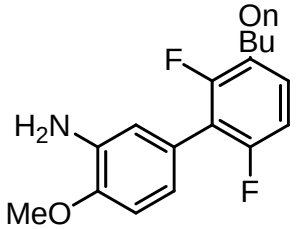
X = Cl: **95%**



X = Cl: **96%**



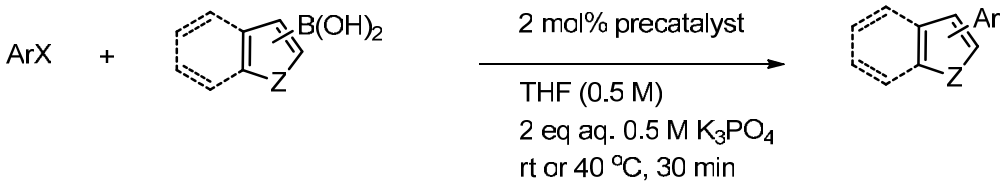
X = Br: **45%**

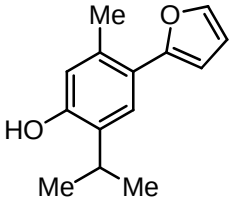


X = Cl: **97%**

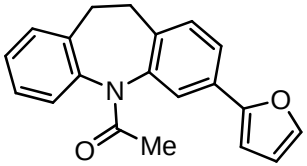
Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010,** *132*, 14073-14075.

Coupling of heterocyclic boronic acids to ArX and BzX

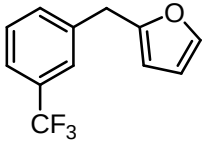




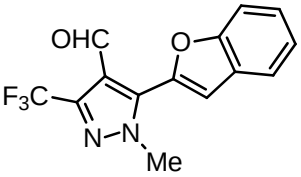
X = Cl, 40 °C
82%



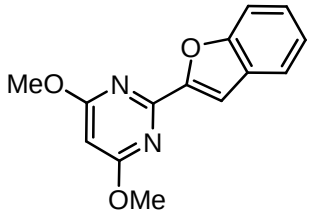
X = Cl, 40 °C
99%



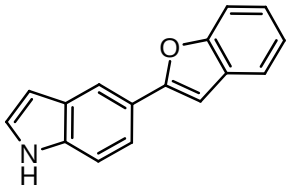
X = Cl, 40 °C
86%



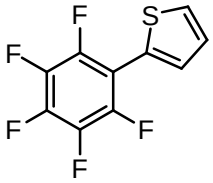
X = Cl, 40 °C 2 h
99%



X = Cl, 40 °C
97%

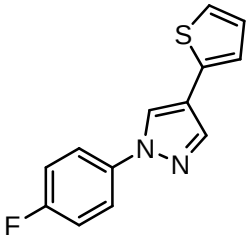


X = Cl, 40 °C
98%

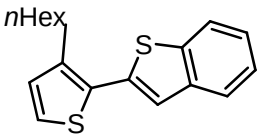


X = Cl, rt
86%

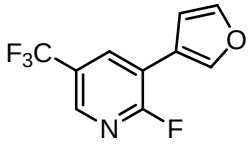
X = Cl, 40 °C 2 h
93%



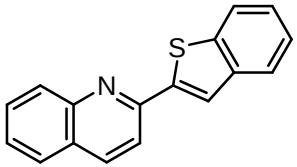
X = Br, 40 °C 2 h
89%



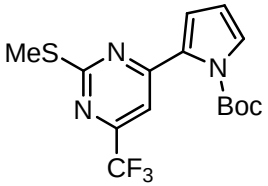
X = Br, 40 °C
89%



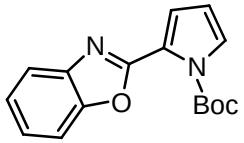
X = Cl, 40 °C
80%



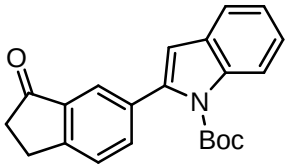
X = Cl, 40 °C
91%



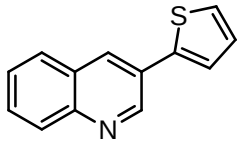
X = Cl, rt
99%



X = Cl, 40 °C 2 h
91%



X = Cl, rt
88%

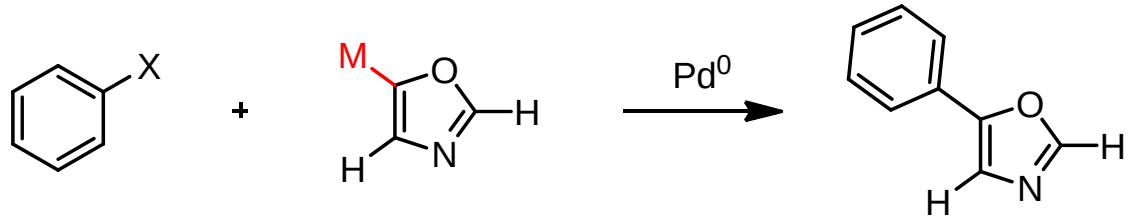


X = Br, 40 °C
96%

Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010,** *132*, 14073-14075.

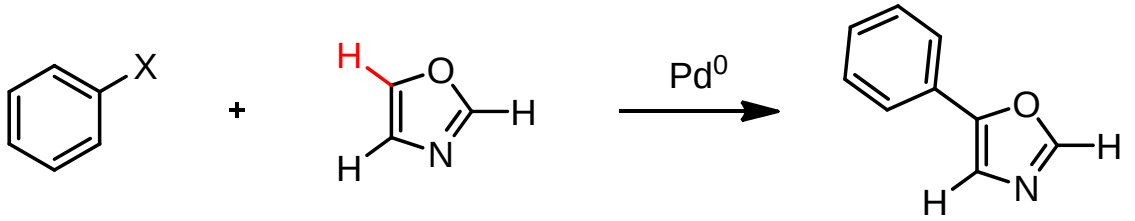
Direct Arylation

Classic cross-coupling



M = $B(OH)_2$, ZnCl, SnR_3 *etc*

Direct Arylation



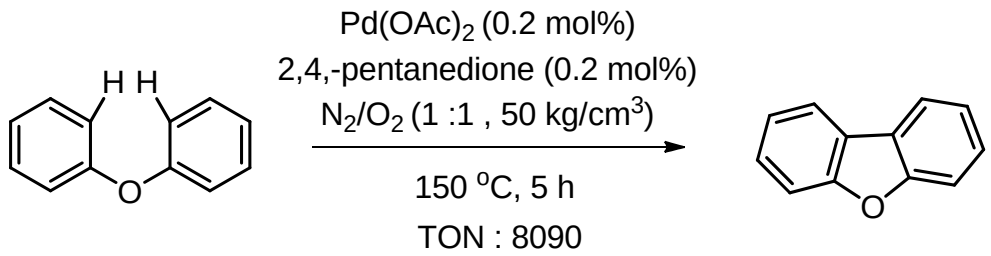
X = Cl, Br, I, OTf *etc*

- Completely removes requirement for stoichiometric metallation
- Improved atom economy, cost, environmental benefits (waste, toxicity), streamlined synthesis
- C-H bond viewed as a functional group - Regioselectvity

D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174.
L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.

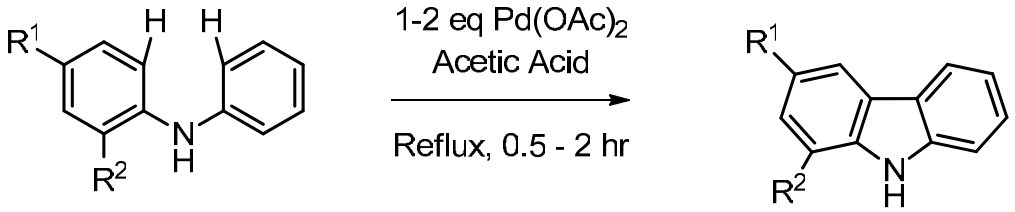
Classic Heteroaryl C-H Activation

Oxidative coupling (intramolecular)



Specific conditions developed to favour intramolecular ring closure.

Shiotani, A.; Itatani, H. *Angew. Chem. Int. Ed. Eng.* **1974**, *13*, 471-472.



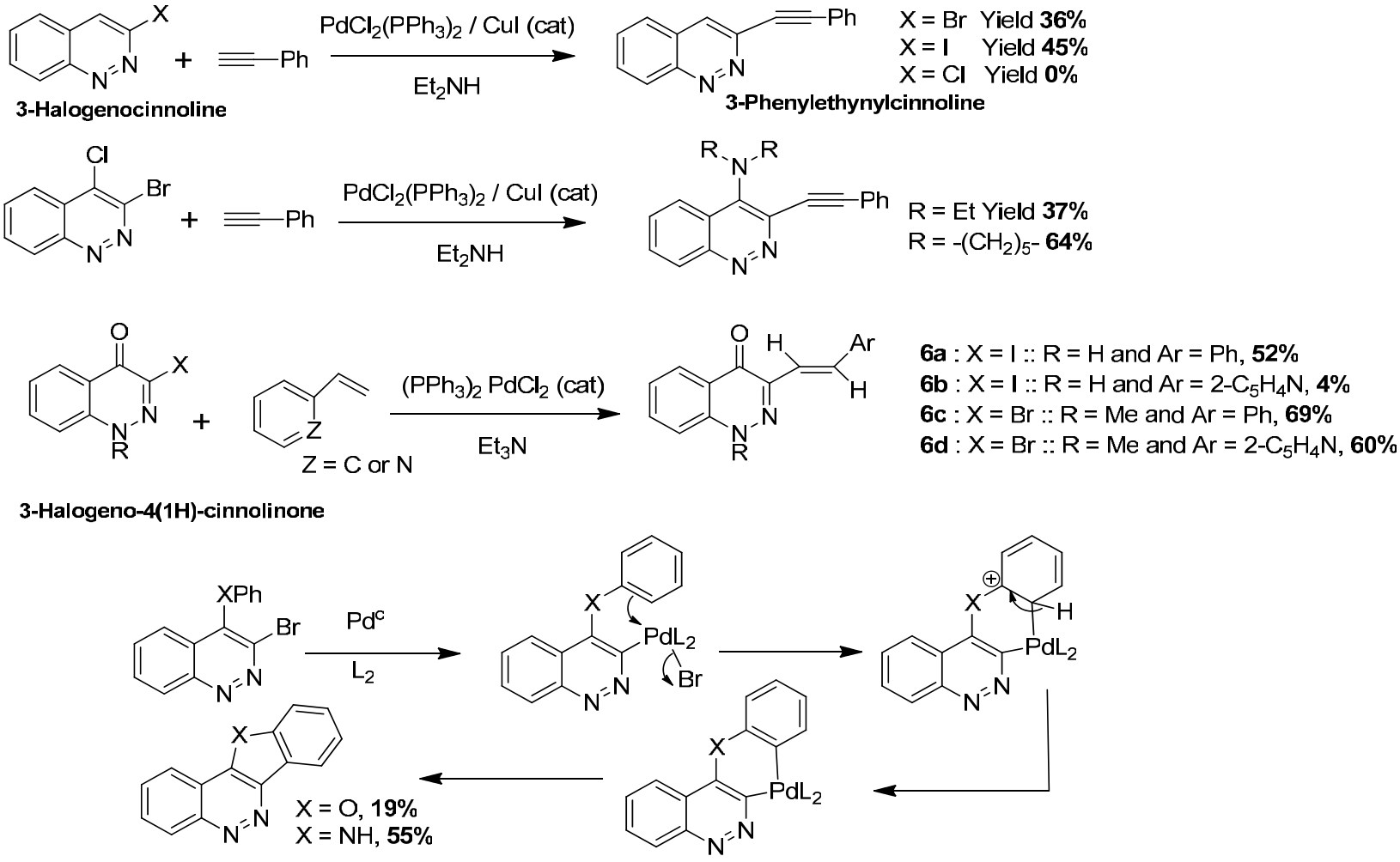
R^1 = H, Me, OMe, Br, NO_2, CO_2H
R^2 = H, Cl (with R^1 as H).

70 - 80 % yields

Akermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. *J. Org. Chem*. **1975**, *40*, 1365 – 1367.

Classic Heteroaryl C-H Activation

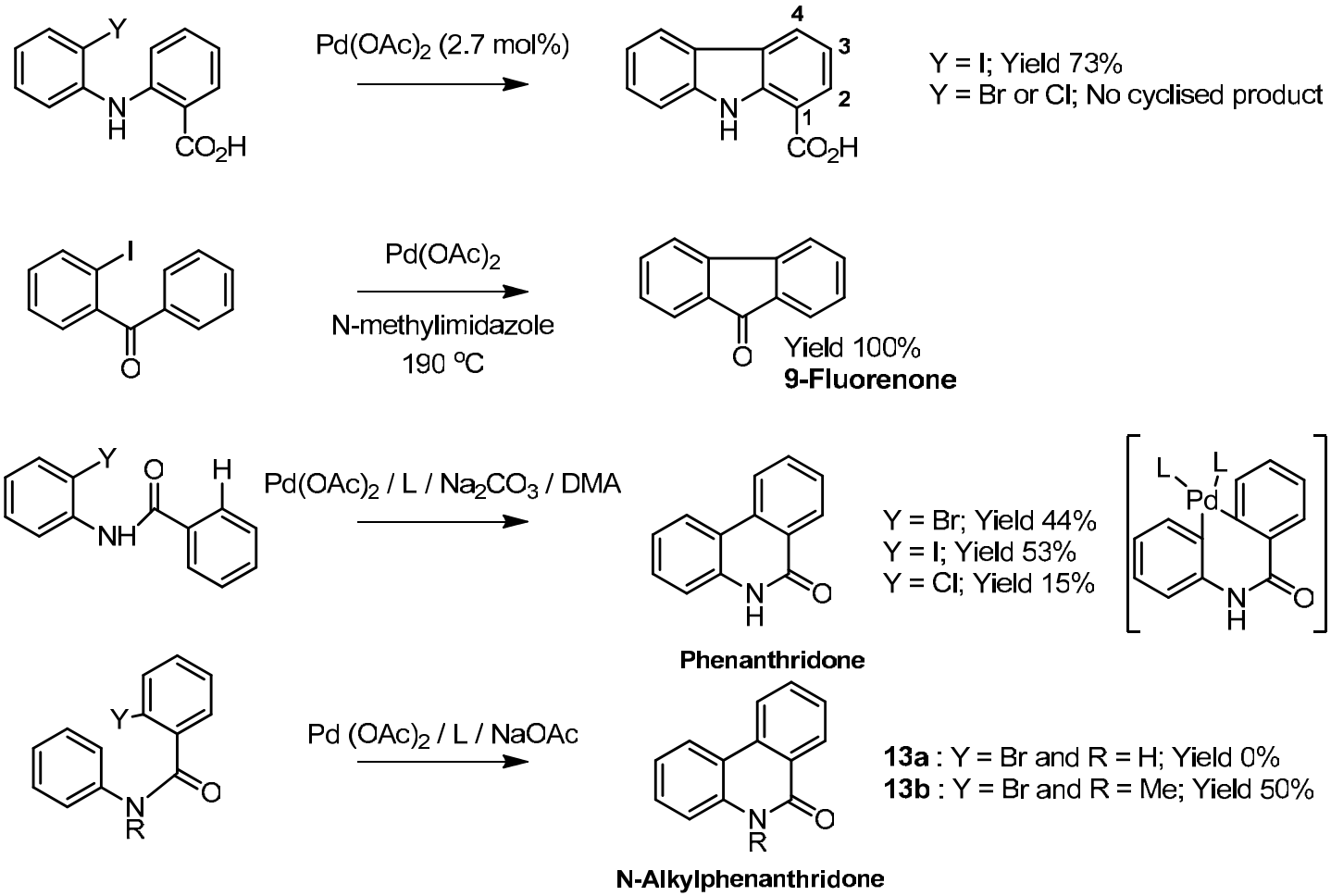
Reactions of 3-Halogenocinnolines Catalysed by Palladium Compounds



D. E. Ames and D. Bull, *Tetrahedron*, **1982**, *38*, 383.

Classic Heteroaryl C-H Activation

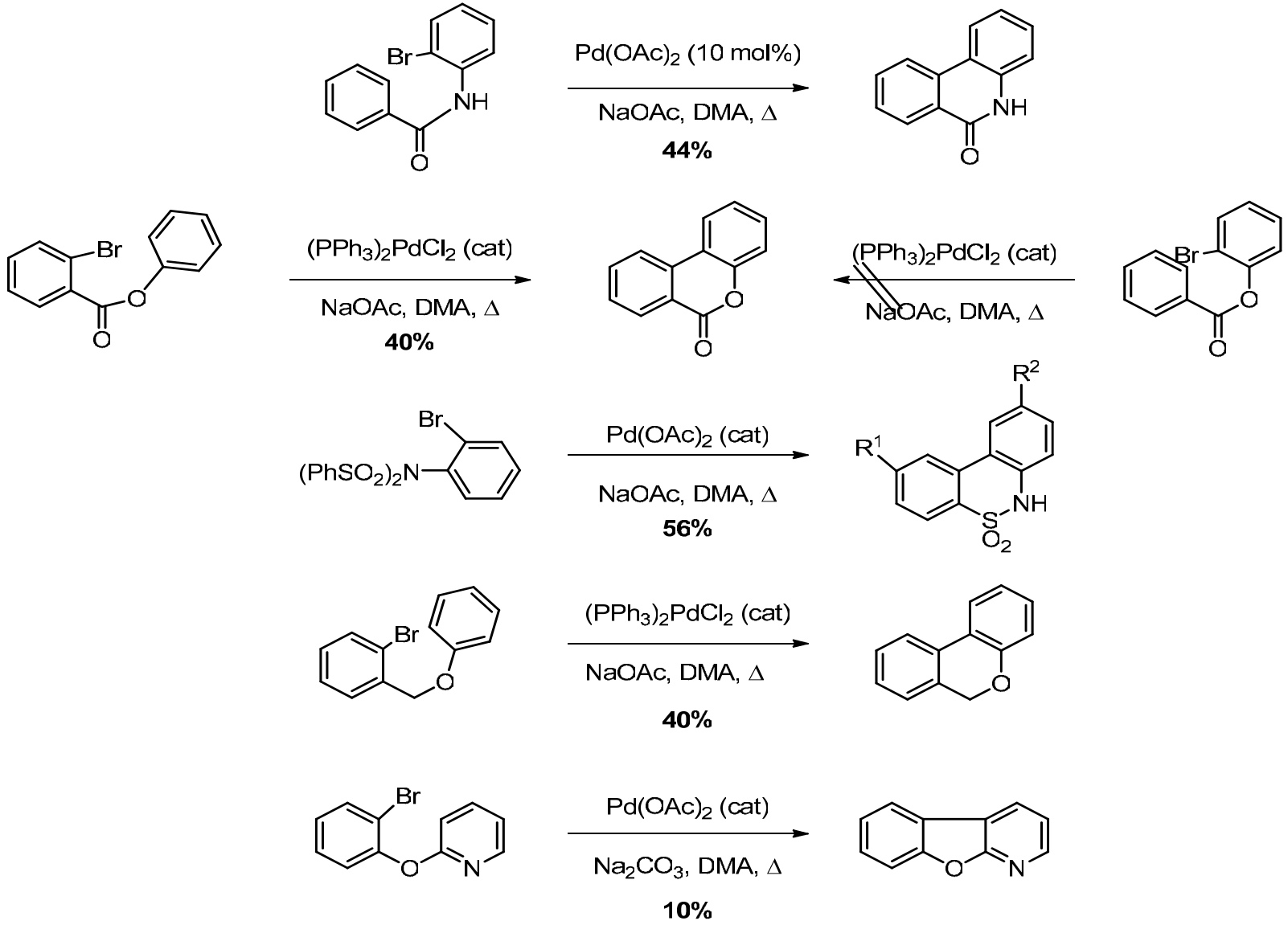
Pd-Catalysed Cyclisation of Halogenoarenes by Dehydrohalogenation



Ames, D. E.; Bull, D. *Tetrahedron*, **1984**, *40*, 1919.

Classic Heteroaryl C-H Activation

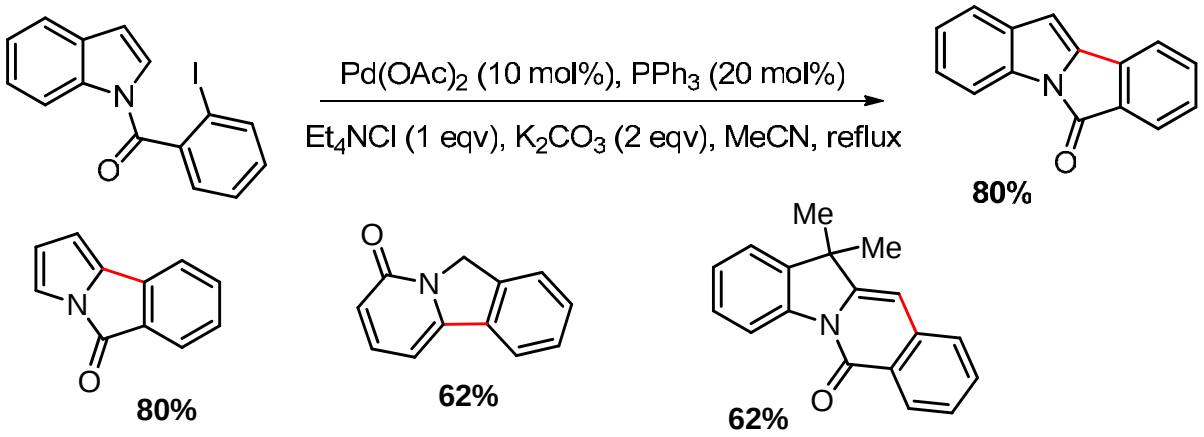
Pd-Catalysed Cyclisation of Halogenoarenes by Dehydrohalogenation



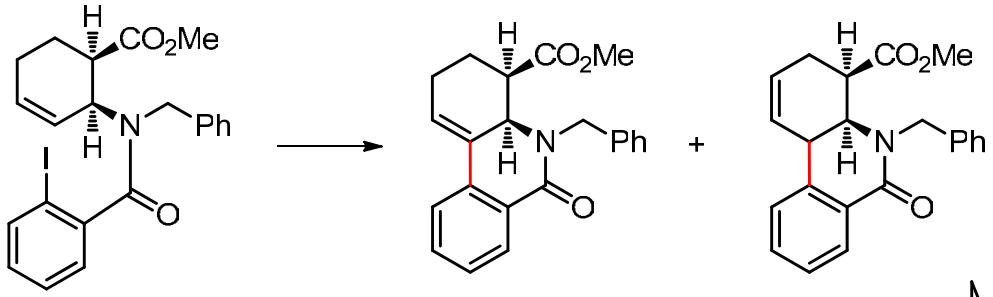
Ames, D. E.; Bull, D. *Tetrahedron*, **1984**, *40*, 1919.

Classic Heteroaryl C-H Activation

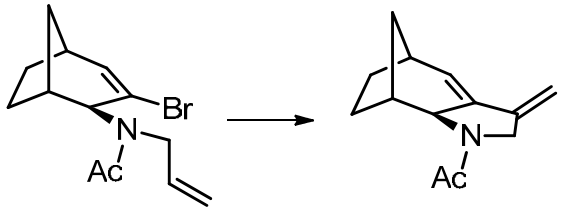
- **'Heck-type' reaction at sp^2 centres:**



- **Double bond regioisomers can be formed**



- **Conditions applicable to a range of substrates:**

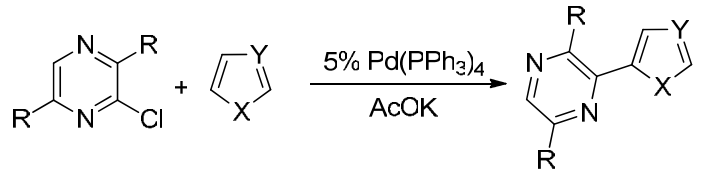


Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingama, S.; Worakumb, T. *Tetrahedron*, **1990,** *46* (11), 4003.

Pd-Catalysed Cross-Coupling of Chloropyrazines

Reactions with 5-membered ring heterocycles

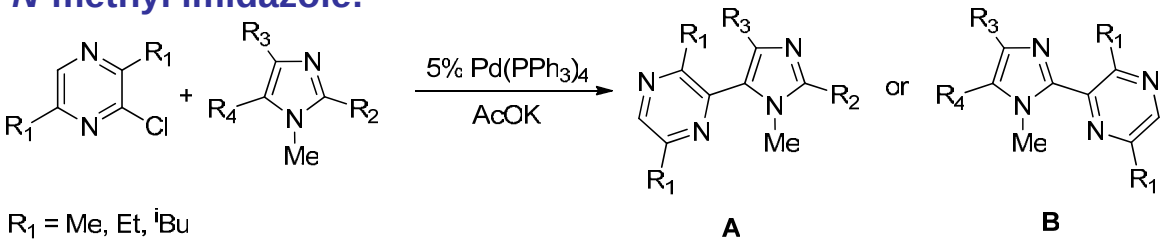
- Single heteroatom systems and azoles:



Entry	Y	X	Product (Yield %)
1	C	O	55-75
2	C	S	70-82
3	C	NH	25-29
4	C	NMe	25-28
5	N	O	68-80
6	N	S	61-73

- Direct arylation via C-H bond cleavage at the 2- or 5-positions
- Di-substitution possible for the rings with a single heteroatom
- Electron-rich 5-position predominantly activated for unsubstituted azoles

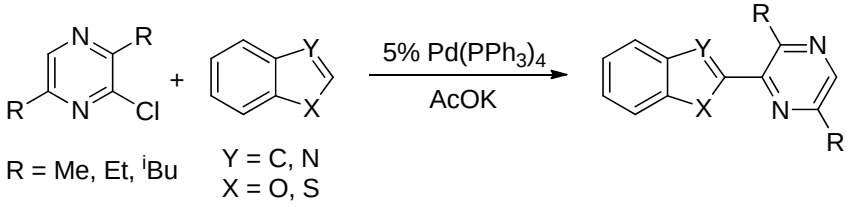
- *N*-methyl imidazole:



Entry	R_2	R_3	R_4	Product (Yield %)
1	H	H	H	**A** (40-44)
2	Me	H	H	**A** (62-83)
3	H	Me	H	**B** (32-43)
4	H	H	Me	**B** (23-44)

- Substituent at either 4- or 5- position leads to arylation at the 2-position

Reactions with Benzo-fused heterocycles

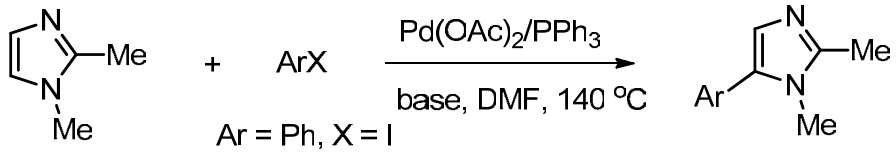


Entry	Y	X	Product (Yield %)
1	C	O	45-68
2	C	S	71-81
3	N	O	52-63
4	N	S	43-68

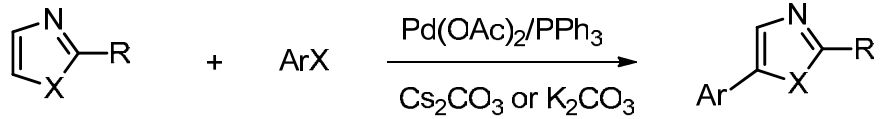
- Exclusive activation at the 2-position

Ohta, A. *et al Heterocycles*, **1992**, 33, 257-272

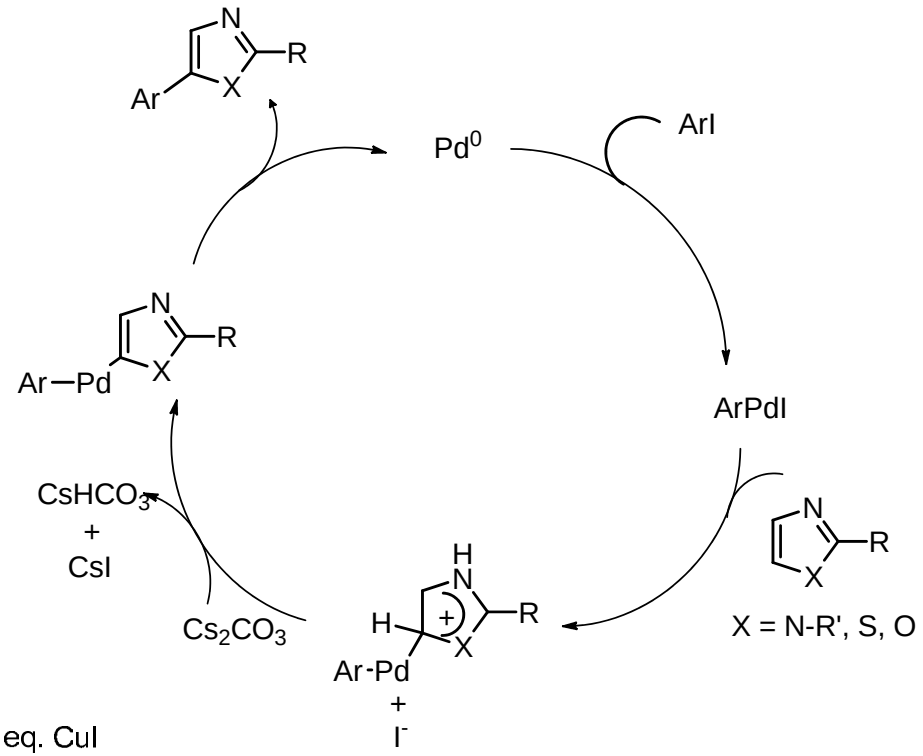
Palladium-Catalyzed Arylation of Azole Compounds



base	yield
$N(n\text{-}Bu)_3$	0%
Na_2CO_3	23%
K_2CO_3	59%
Cs_2CO_3	83%



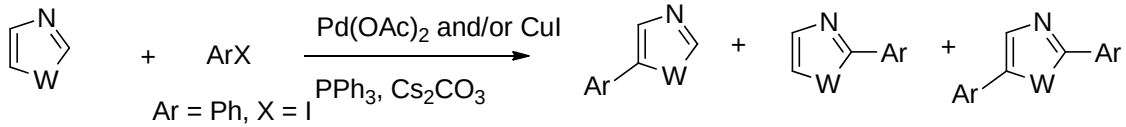
	base	yield
X = NCH_2Ph, R = Me	Cs_2CO_3	66%
	K_2CO_3	45%
X = O, R = Ph	Cs_2CO_3	88%
	K_2CO_3	66%
X = S, R = Me	Cs_2CO_3	43%
	Cs_2CO_3	68% with 2 eq. CuI



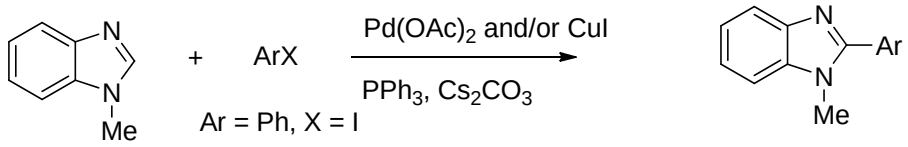
Effect of carbonate bases: $Cs_2CO_3 > K_2CO_3 > Na_2CO_3$ suggests that more soluble carbonate base in DMF may more effectively enhance the deprotonation step.

Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467-473

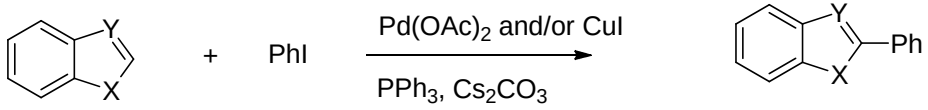
Palladium-Catalyzed Arylation of Azole Compounds



W = NCH_3,	without CuI	yield = 54%	0%	24%
	without $Pd(OAc)_2$		37%	
	$Pd(OAc)_2$ and CuI		37%	40%
W = S	without CuI	yield = 17%	0%	35%
	without $Pd(OAc)_2$		15%	
	$Pd(OAc)_2$ and CuI			66%

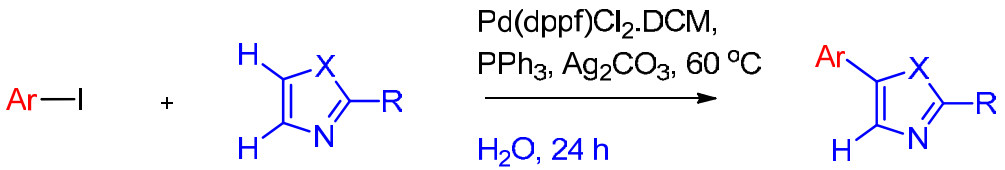


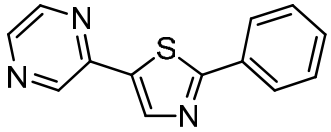
without CuI	yield = 2%
without $Pd(OAc)_2$	89%
$Pd(OAc)_2$ and CuI	91%



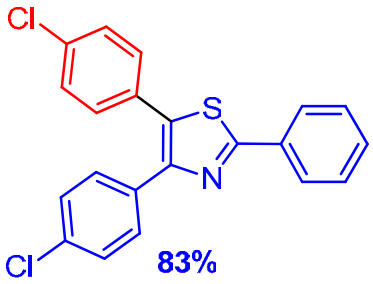
X = O, Y = N	without CuI	yield = 95%
	without $Pd(OAc)_2$	15%
X = S, Y = N	without CuI	yield = 40%
	without $Pd(OAc)_2$	15%
	$Pd(OAc)_2$ and CuI	82%
X = S, Y = CH	without CuI	yield = 16%
	without $Pd(OAc)_2$	23%
	$Pd(OAc)_2$ and CuI	41%

Direct Arylations On Water

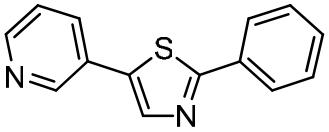




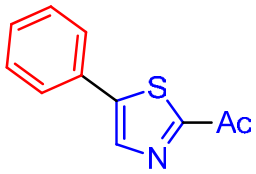
0%
99%



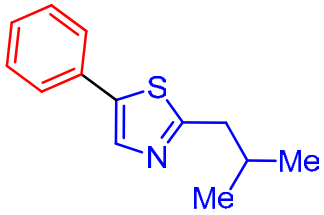
83%



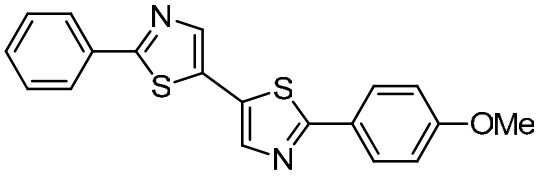
36%
99%



70%



99%



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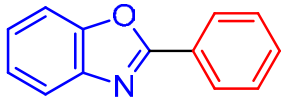
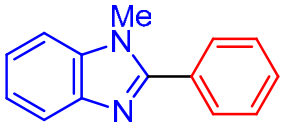
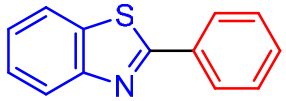
99%



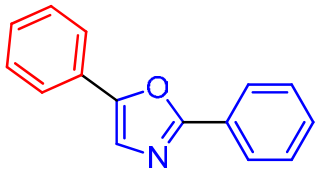
79%



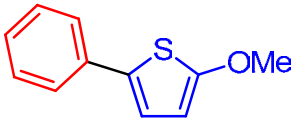
99%



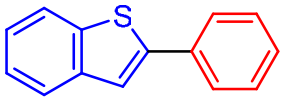
99%



92%

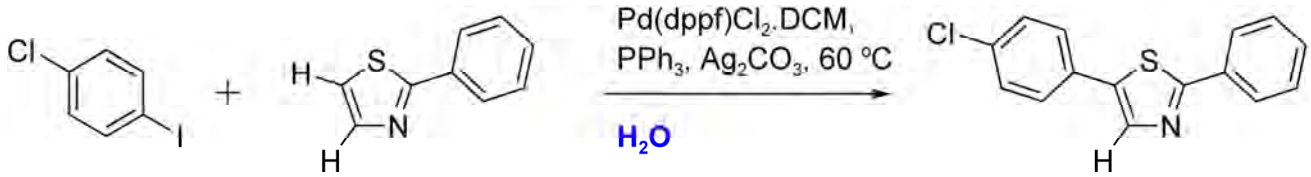


82%

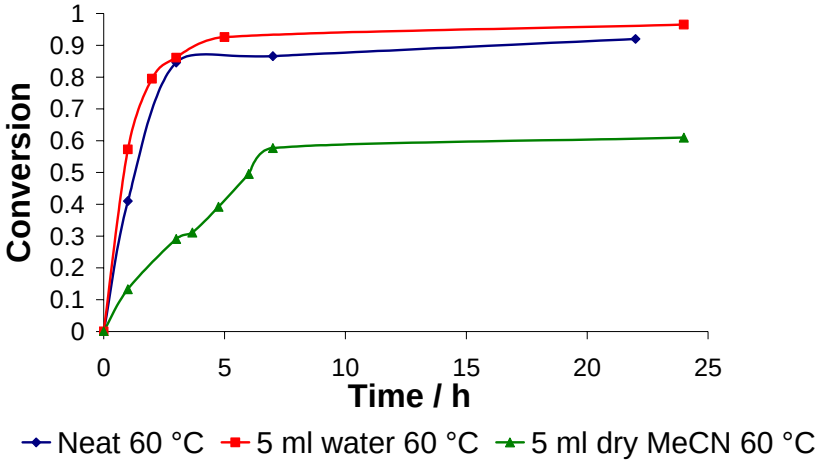


50%

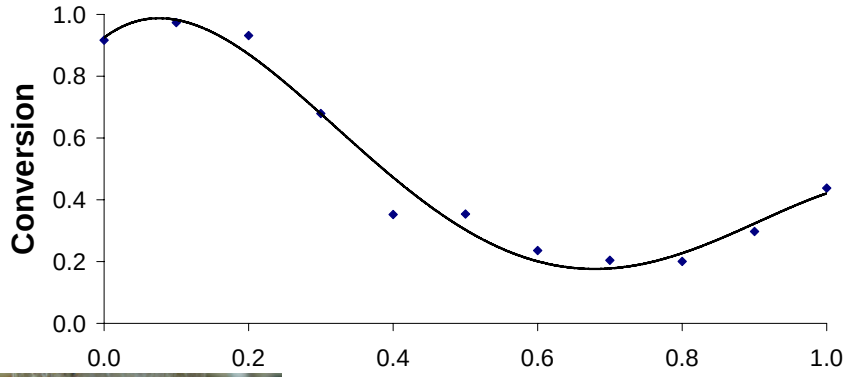
Direct Arylations On Water



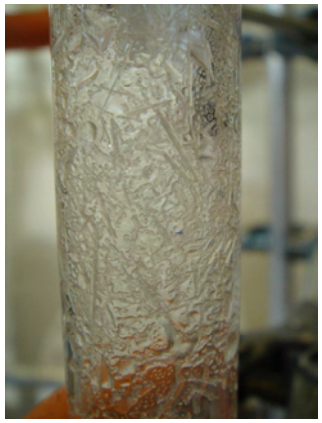
Graph A: Conversion at 60 °C

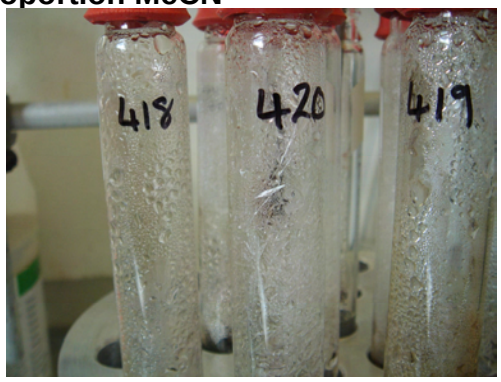


Graph B: MeCN/H_2O mix



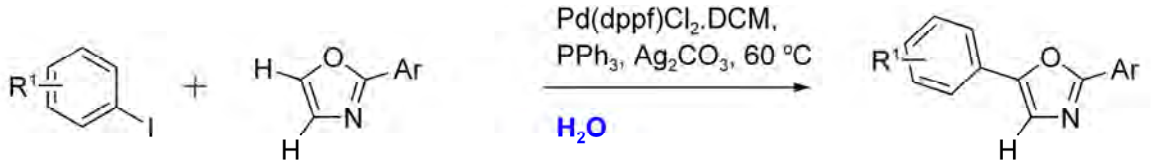
- Optimised conditions
  - $Pd(dppf)Cl_2.DCM$ (0.5 mol%)
  - Ag_2CO_3 (50 mol%)
  - 6 h, 60 ºC
  - on water



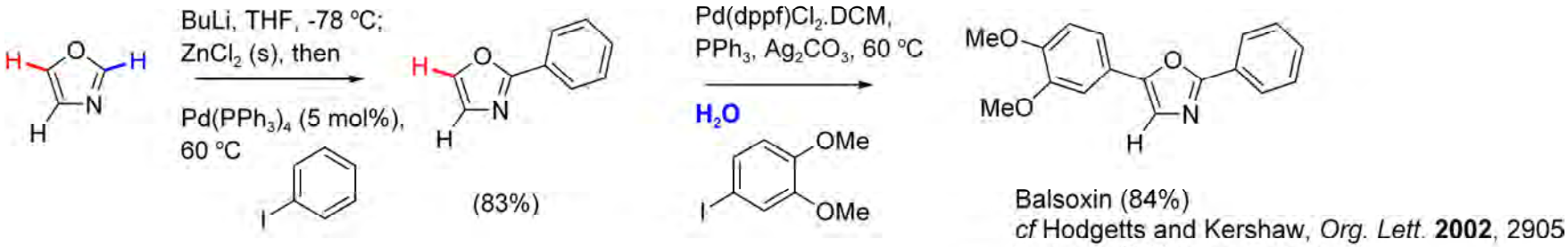


Turner, G. L.; Morris, J. A.; Greaney, M. F., *Angew. Chem., Int. Ed.* **2007**, *46*, 7996.

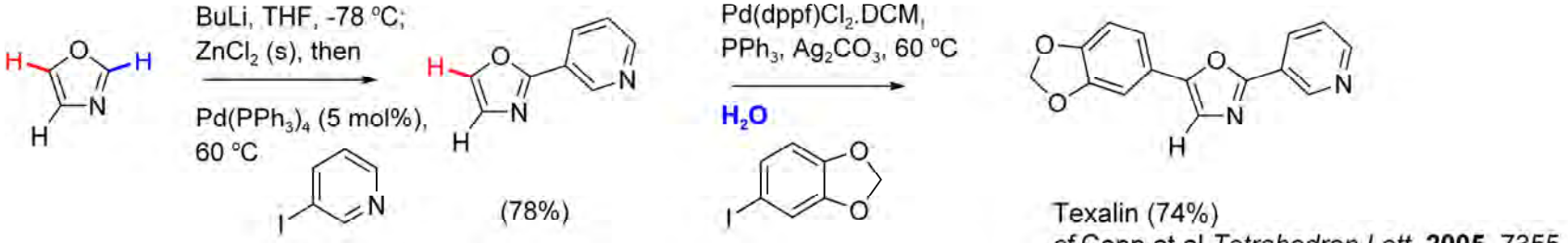
Oxazole Arylations On Water



30 examples,
76-92% yield
Average yield 84%



Balsoxin (84%)
cf Hodgetts and Kershaw, *Org. Lett.* **2002**, 2905
7 steps, 40% overall yield

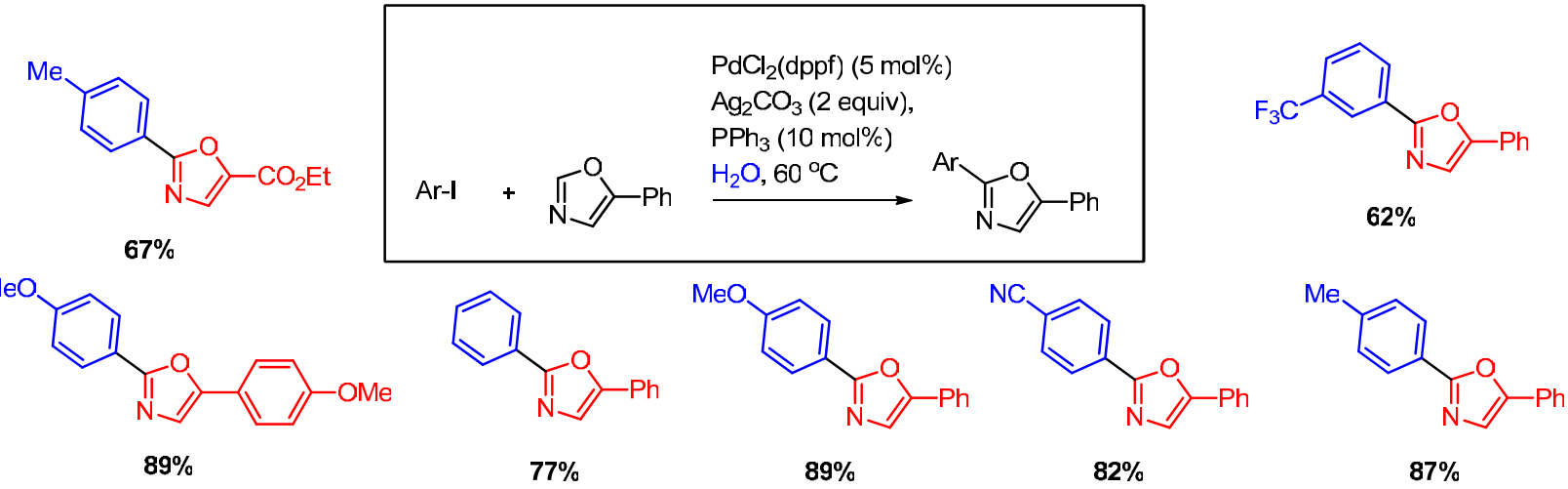


Texalin (74%)
cf Copp et al *Tetrahedron Lett.* **2005**, 7355
6 steps, 4% overall yield

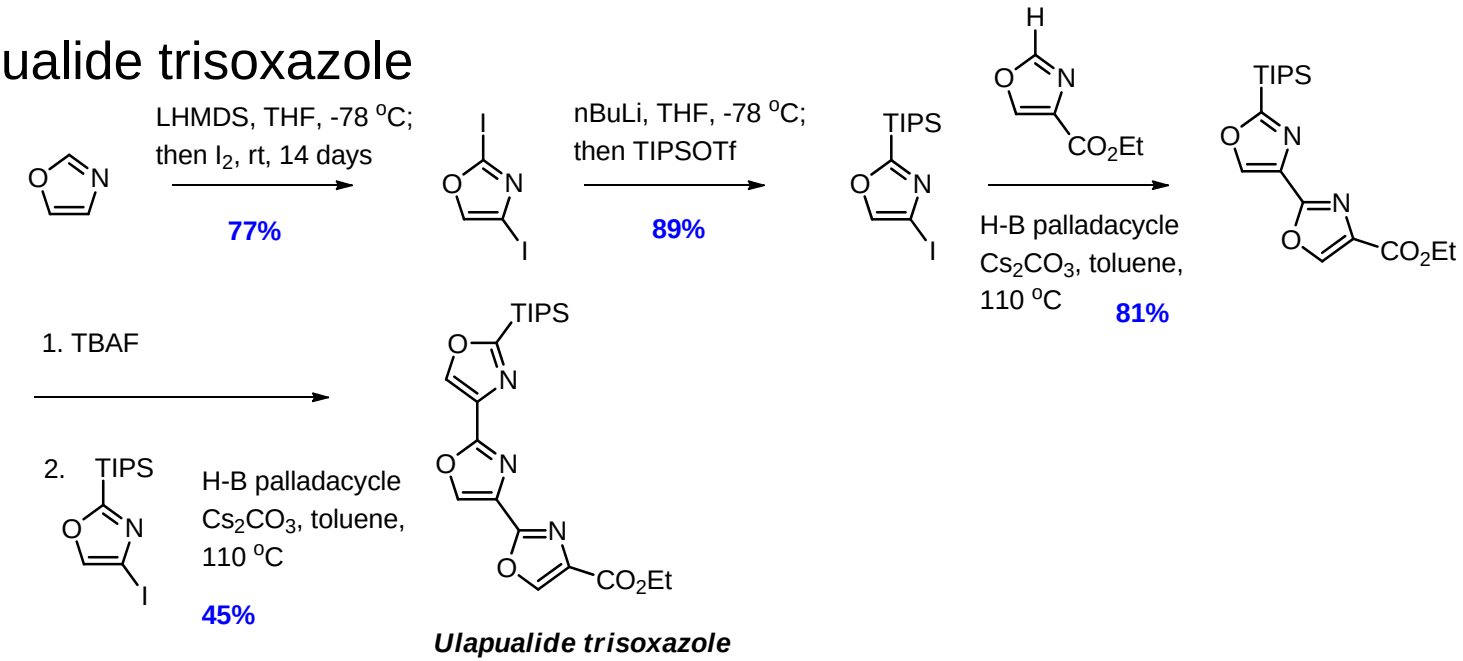
Ohnmacht, S. O.; Mamone, P.; Culshaw, A. J.; Greaney, M. F. *Chem. Commun.* **2008**, 1241-1242.

Other arylation approaches to Balsoxin: Hoarau, Piguel

Polyoxazoles: 2-Arylation

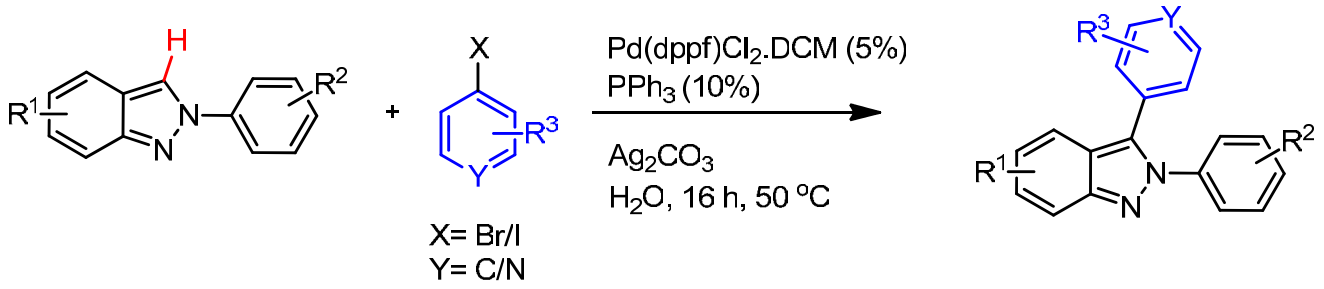


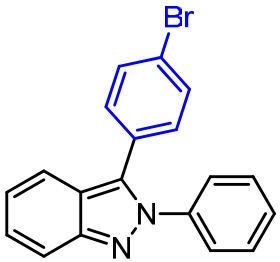
Ulapualide trisoxazole



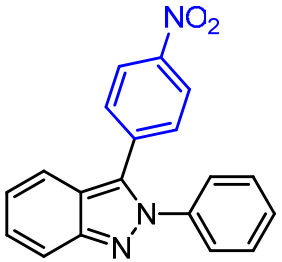
Ferrer Flageau, E.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717–2720.

2*H*-Indazoles

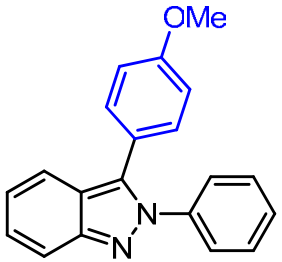




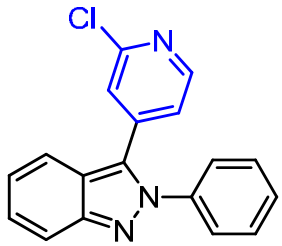
80%



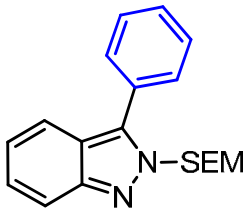
86%



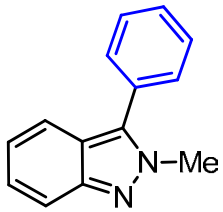
87%



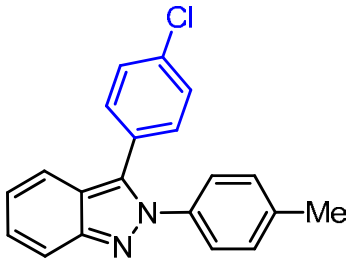
95%



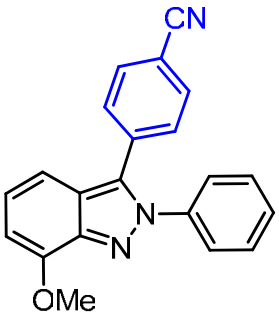
82%



77%



97%

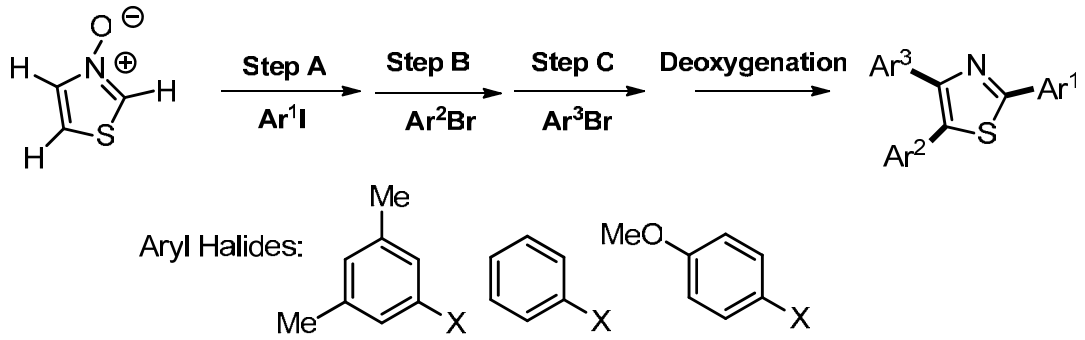


83%
Liver X receptor agonist

Ohnmacht, S. O.; Culshaw, A. J.; Greaney, M. F. *Org. Lett.,* **2010**, *12*, 224-226.

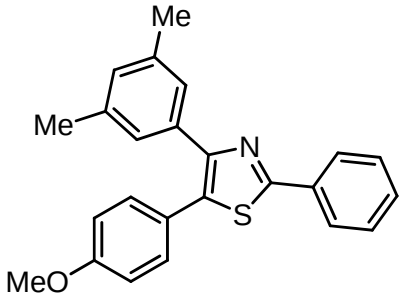
Thiazole N-oxide Arylation

C2, C5 and C4 Azole *N*-Oxide Direct Arylation Reactions.

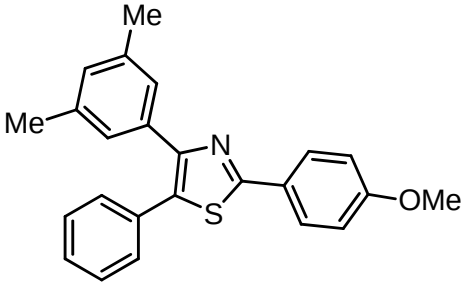


- N-oxides increases the reactivity in all positions for direct arylation.

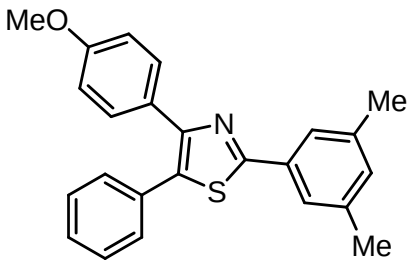
- They also change the weak bias for C5>C2 arylation to C2>C5>C4.



Step A: 84%
Step B: 86%
Step C: 59%
Deoxygenation: 72 %



Step A: 69%
Step B: 80%
Step C: 64%
Deoxygenation: 66%

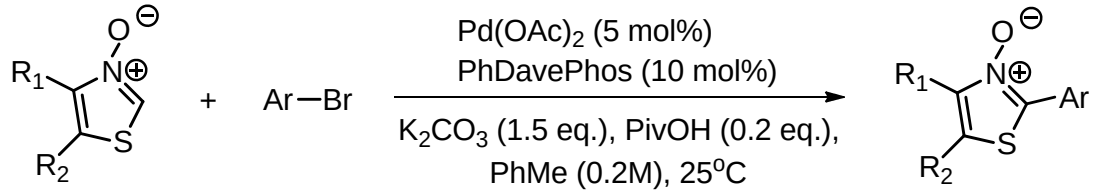


Step A: 75%
Step B: 85%
Step C: 84%
Deoxygenation: 64%

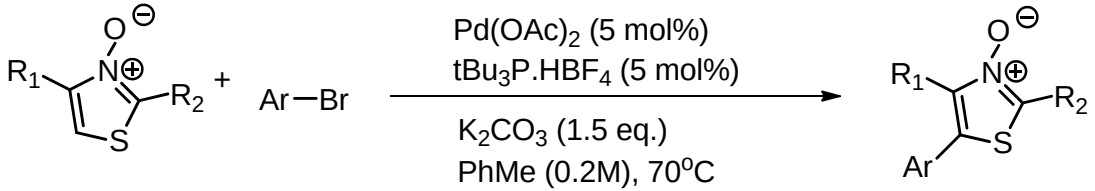
Fagnou, K. *et al, J. Am. Chem Soc,* **2008,** *130,* 3276-3277.

Thiazole N-oxide Arylation

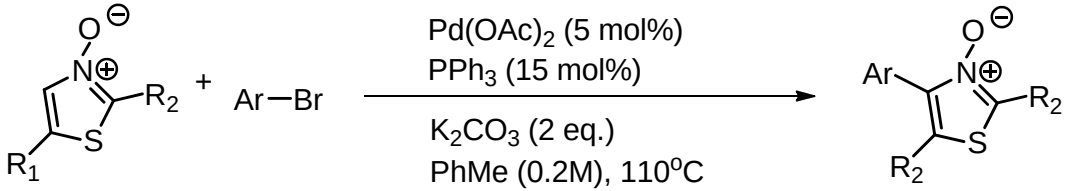
- Reactions proceed in 64-88% yields and tolerates e-withdrawing Ar, thiophene and pyridyl systems
- examples successful with R1 = R2 = H. Requires generally mild conditions



- C5 arylation is highly selective when C2 is blocked.
- Addition of pivalic acid reduces C5:C4 selectivity.

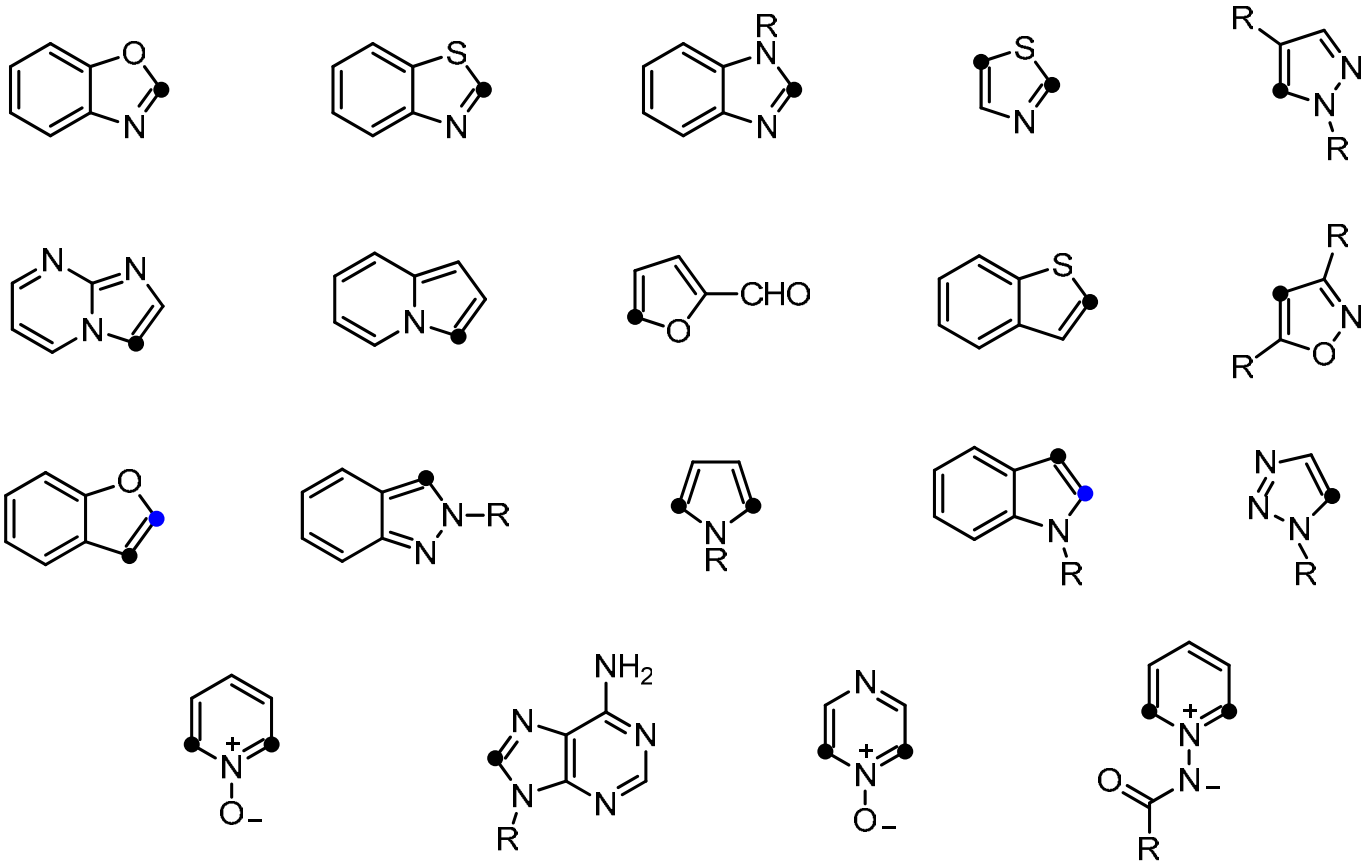


- N-Oxide moiety enables C4 arylation

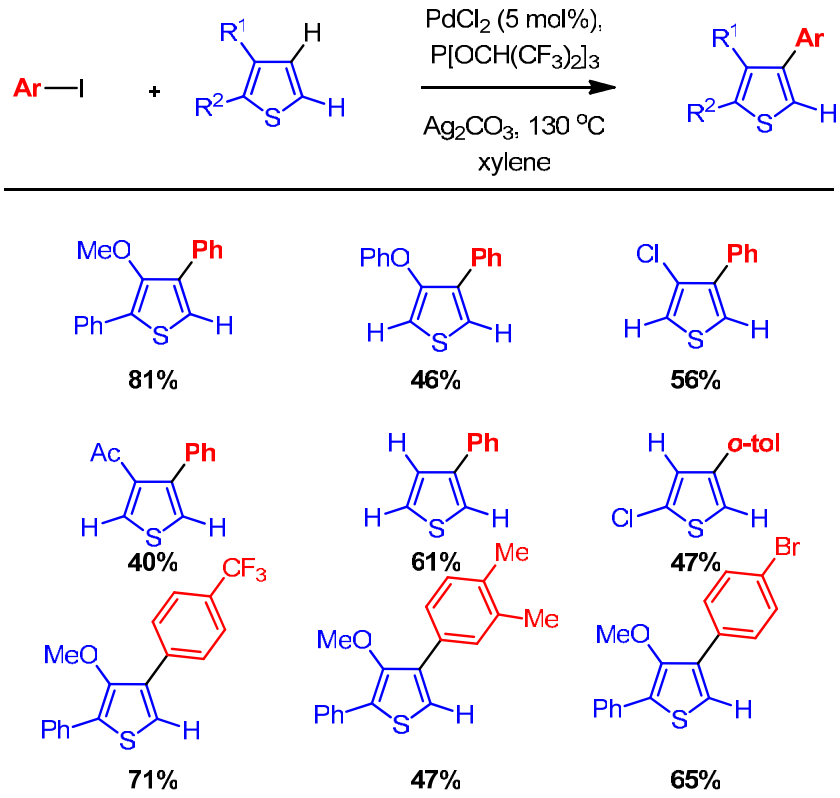


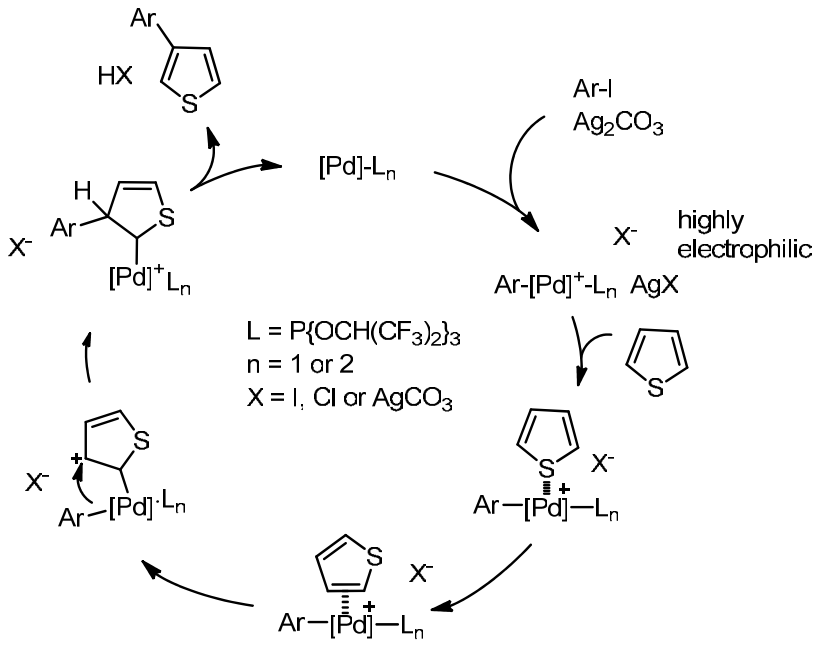
Fagnou, K. *et al, J. Am. Chem Soc,* **2008,** *130,* 3276-3277.

Regiocontrol in Arylation



C3 Arylation of Thiophene

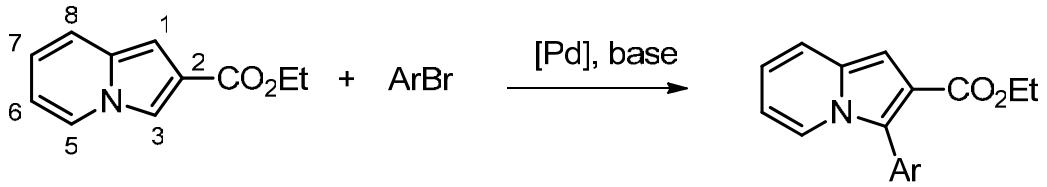




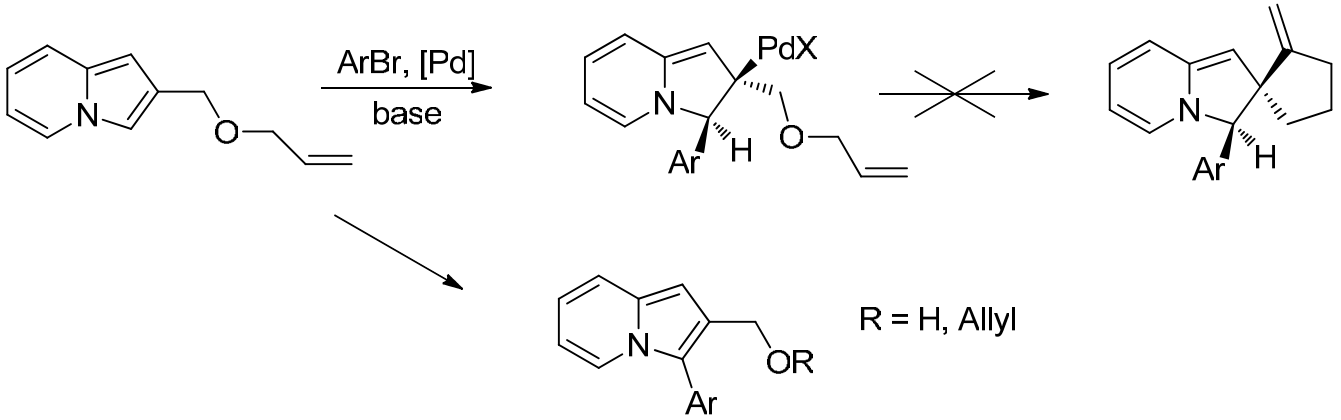
Itami, K. *et al, Angew. Chem. Int. Ed.* Early view, DOI=10.1002/anie201005082

Mechanistic Investigation for π-Excessive Heteroarenes

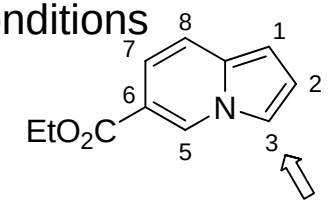
Indolizines (Gevorgyan)



- Heck-type mechanism proposed for analogous furan reaction*
  - Requires trans elimination or isomerisation
  - Could not be trapped in cascade Heck reaction



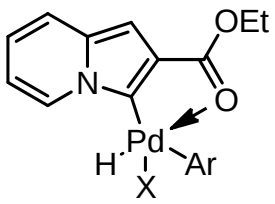
  - Could not detect expected product under reductive Heck conditions
  - 6-carboethoxy isomer gave selective arylation at C-3



Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. Org. *Lett.*, **2004,** *6*, 1159 –1162.
*Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. *Org. Lett.,* **2003,** *5*, 301– 304.

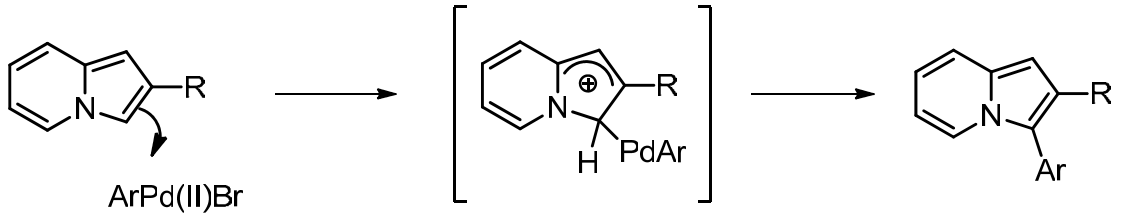
Mechanistic Investigation for π-Excessive Heteroarenes

• $k_{H/D}$=1 at C-3 disfavours direct coordination assisted C-H activation mechanism



• Cross-coupling type mechanism at acidic C-H sites favoured by Cu salts, CuI impeded reaction

• S_EAr mechanism consistent:

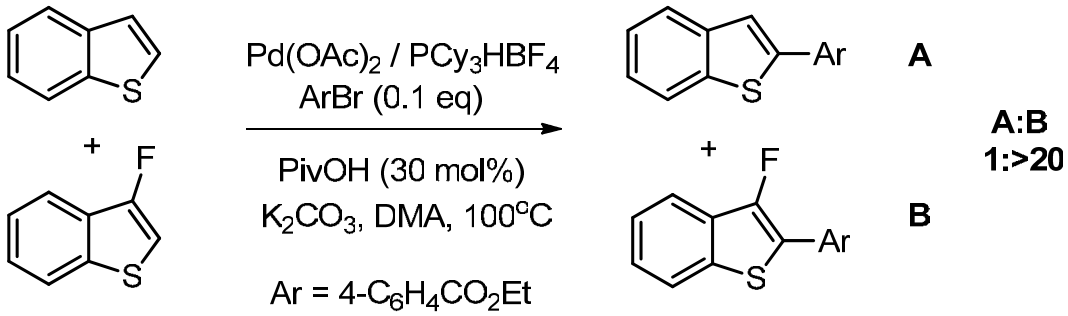


• DFT calculations indicate extended HOMO (even with EWG at C-6)

• Competition experiments, with R = H or EDG give same order as $AlCl_3$ catalysed F/C acylation

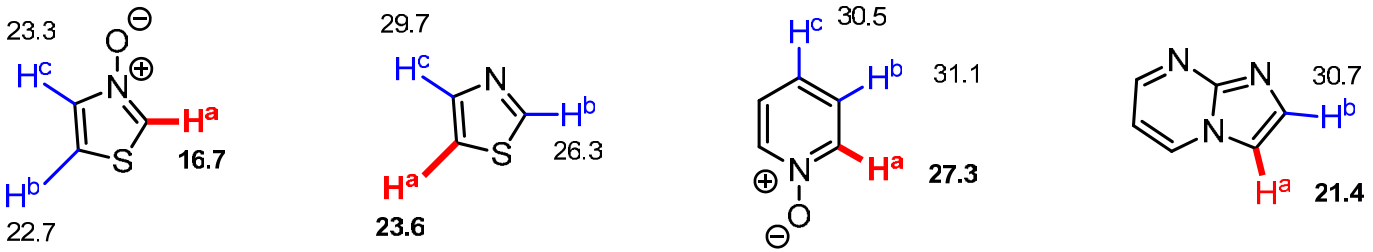
Mechanistic Investigation for π-Excessive Heteroarenes

Concerted Metalation-Deprotonation Mechanism (Fagnou).



- Experimentally, 3-fluorobenzothiophene reacts preferentially over benzothiophene.

- This is predicted in DFT calculations using a concerted metalation-deprotonation (CMD) mechanism



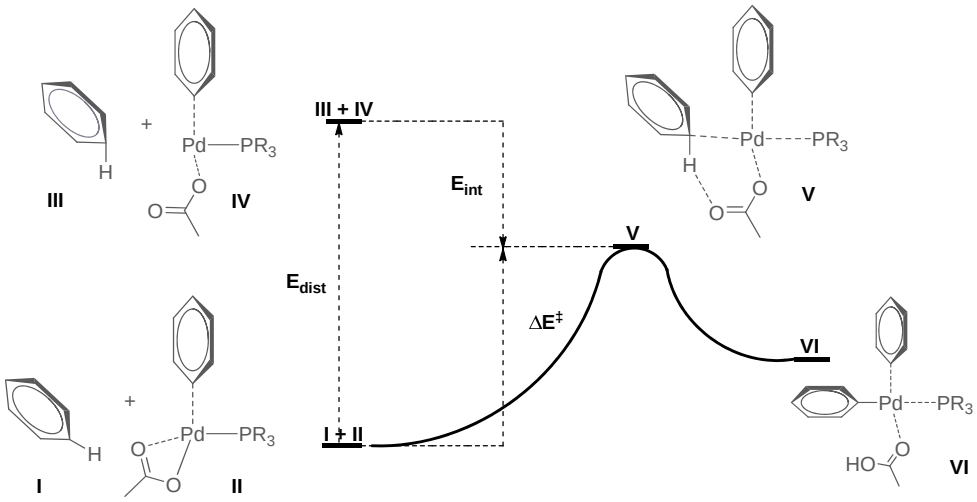
- Values indicate the free energy of activation for direct arylation via the CMD pathway involving an acetate ligand.

- Red bonds indicate the experimentally observed site of arylation.

Gorelsky, S. I.; Lapointe, D.; Fagnou, K.; *J. Am. Chem. Soc,* **2008,** *130*, 10848-10849.

Mechanistic Investigation for π-Excessive Heteroarenes

Analysis of the Concerted Metalation-Deprotonation Mechanism.



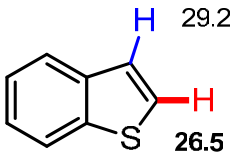
Activation - Strain analysis for the CMD mechanism.

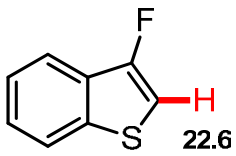
- **Edist** : the energetic cost associated with the distortion of the catalyst and arene.

- **Eint** : reflects the strength of the carboxylate-HAr and Pd-CAr interactions.

- p- e-rich arenes benefit from large negative Eint values but have large Edist penalties.

- e-deficient arenes have insignificant Eint however have more favourable Edist values.





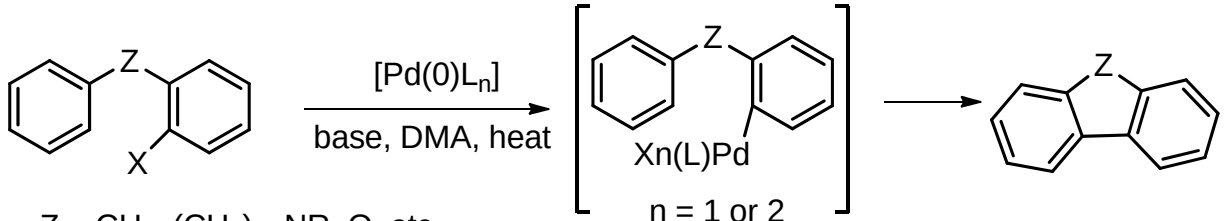
- The presence of fluorine in 3-fluorobenzothiophene has little impact on Eint

- It results in a large decrease in Edist allowing a more facile arene palladation.

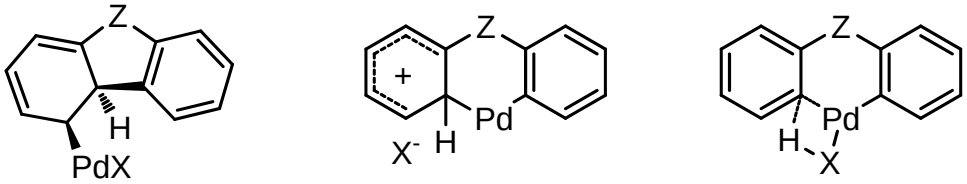
Gorelsky, S. I.; Lapointe, D.; Fagnou, K.; *J. Am. Chem. Soc,* **2008,** *130*, 10848-10849.

Mechanistic Investigation for π-Excessive Heteroarenes

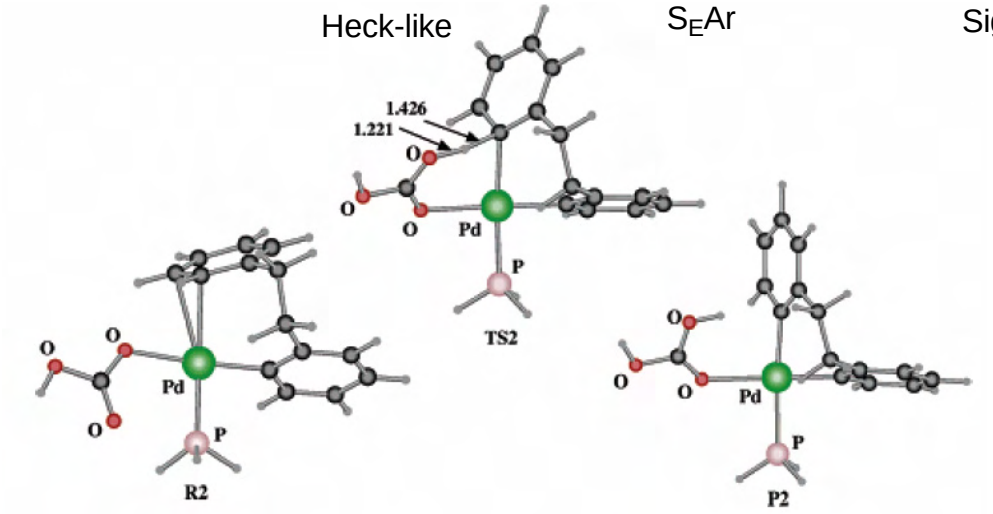
Proton Abstraction Mechanism (Eschevarren)



Z = CH_2, $(CH_2)_2$, NR, O, etc
X = Cl, Br, I, OTf



Heck-like S_EAr Sigma-bond metathesis

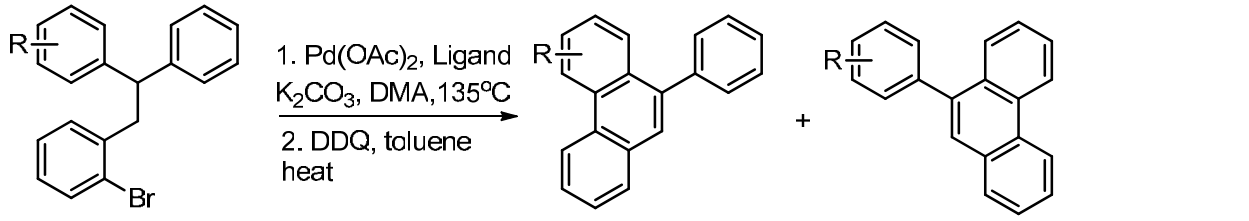


With excess of carbonate the basic anions HCO_3^- will replace Br^- the energy barrier is decreased from 43.3 to 23.5 Kcal/mol
K_H/K_D = 4.3 at 100 °C, 3.7 at 135 °C

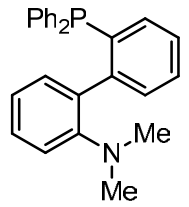
Computational DFT study: B3LYP optimized structures of species **R2**, **TS2**, and **P2**.

Mechanistic Investigation for π-Excessive Heteroarenes

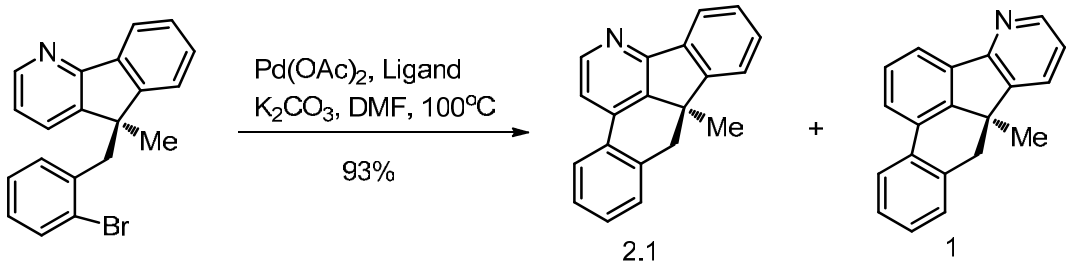
Effect of Substituents on Pd-catalyzed Arylation



R = 4-OMe	yield = 90%	1.1	:	1
R = 3-OMe	75%	1.4	:	1
R = 4-CF_3	71%	1.3	:	1
R = 4-Cl	66%	1.5	:	1
R = 3-Cl	54%	1.9	:	1
R = 3,4,5-$(F)_3$	82%	25	:	1
R = 2,3,4,5,6-$(D)_5$	82%	0.2	:	1



Ligand



2.1 1

The reaction of trifluorophenyl substrate gives almost exclusively at the trifluorophenyl ring, which is incompatible with the S_EAr mechanism.
These results would fit better in a mechanism where the hydrogen from the phenyl is transferred as a proton in the step deciding the selectivity.

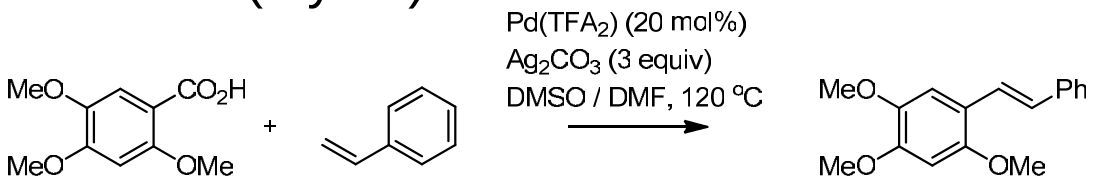
García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066-1067

Decarboxylative cross-coupling

Carboxylic acids: Cheap, readily available (both in scale and structural variation), easy to handle and store.

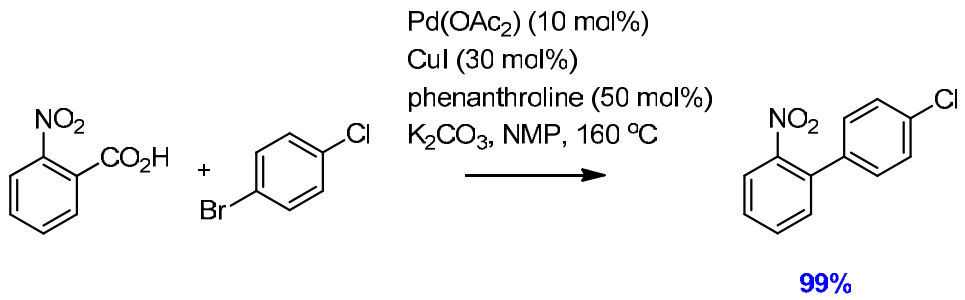
Two key reactions discovered that use carboxylic acids as functional handles for Pd-catalysed C-C bond formation:

Decarboxylative Heck (Myers)



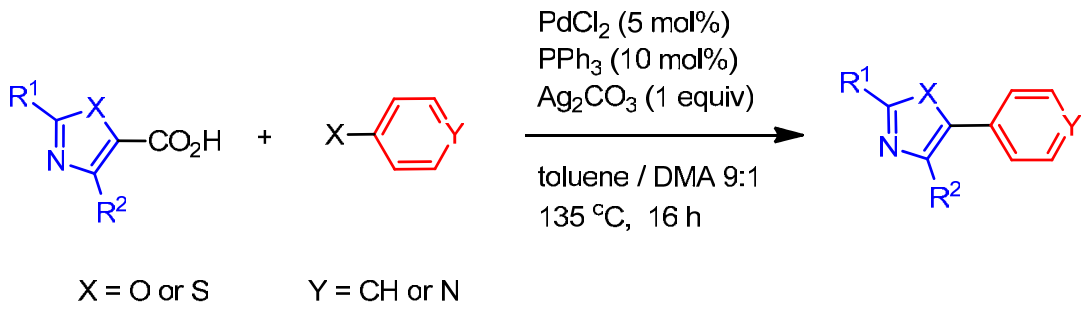
A. G. Myers, D. Tanaka, M. R. Mannion, *J. Am. Chem. Soc.* **2002**, *124*, 11250 – 11251.

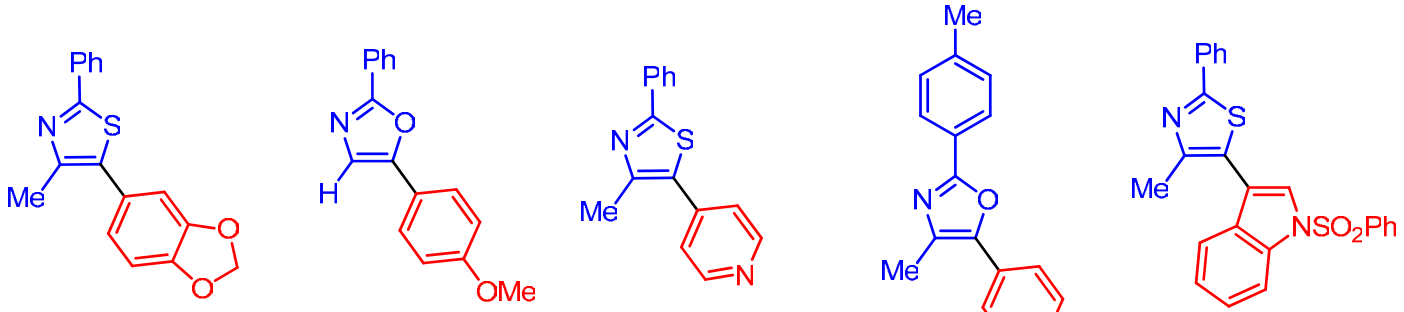
Decarboxylative cross coupling with aryl halides (Goossen)

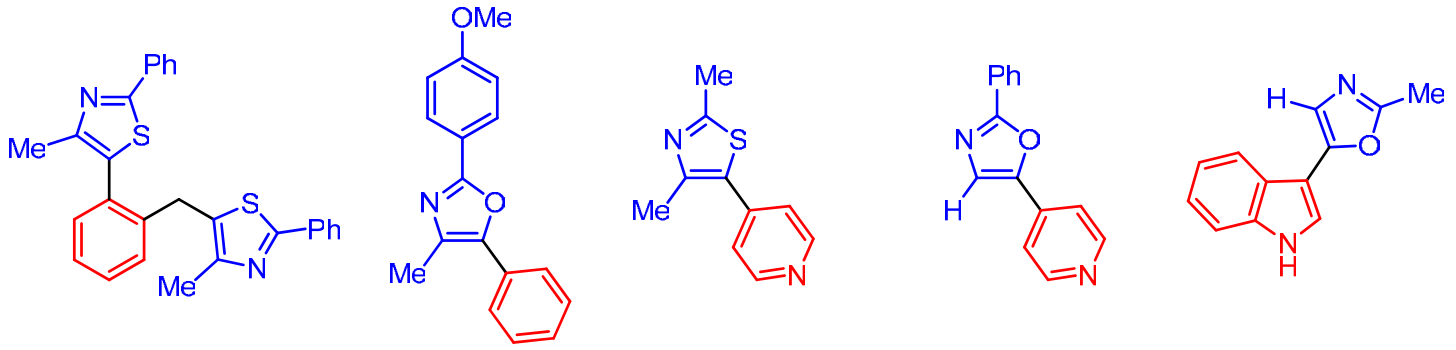


L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662 – 664.

Decarboxylative cross-coupling



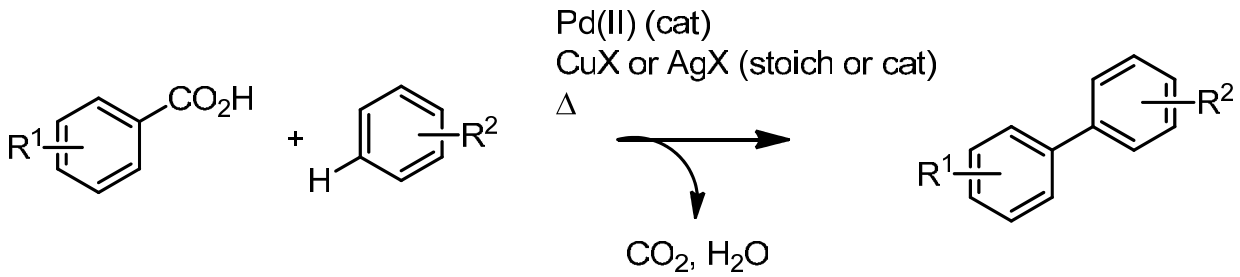




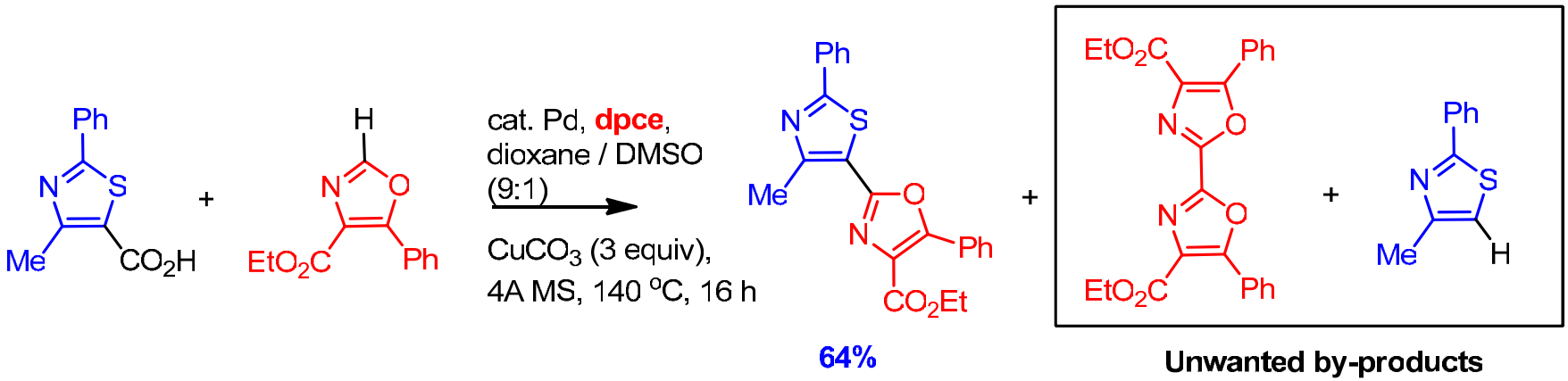
Zhang, F.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 4745.

Decarboxylative C-H cross-coupling

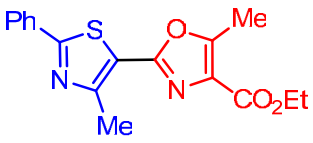
Can we harness decarboxylation for C-H activation?



Reaction development: Proto-decarboxylation and oxidative dimerisation pathways must be suppressed.



Decarboxylative C-H cross-coupling



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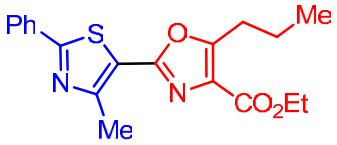

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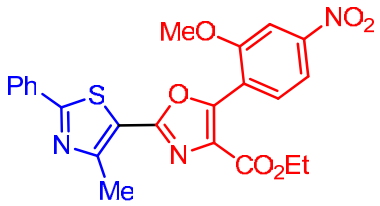

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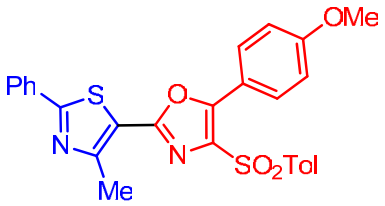

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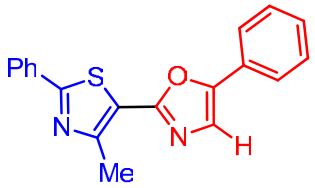

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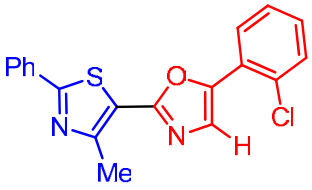

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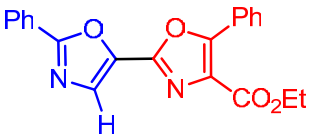

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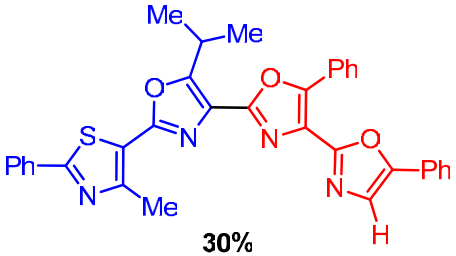

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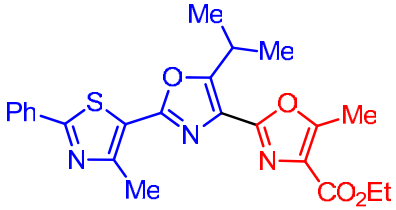

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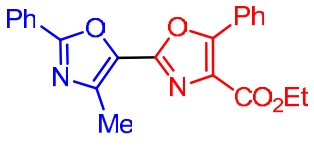

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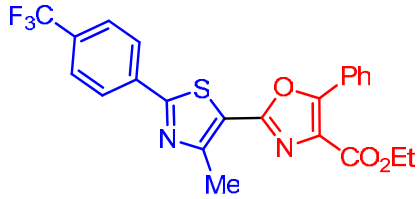

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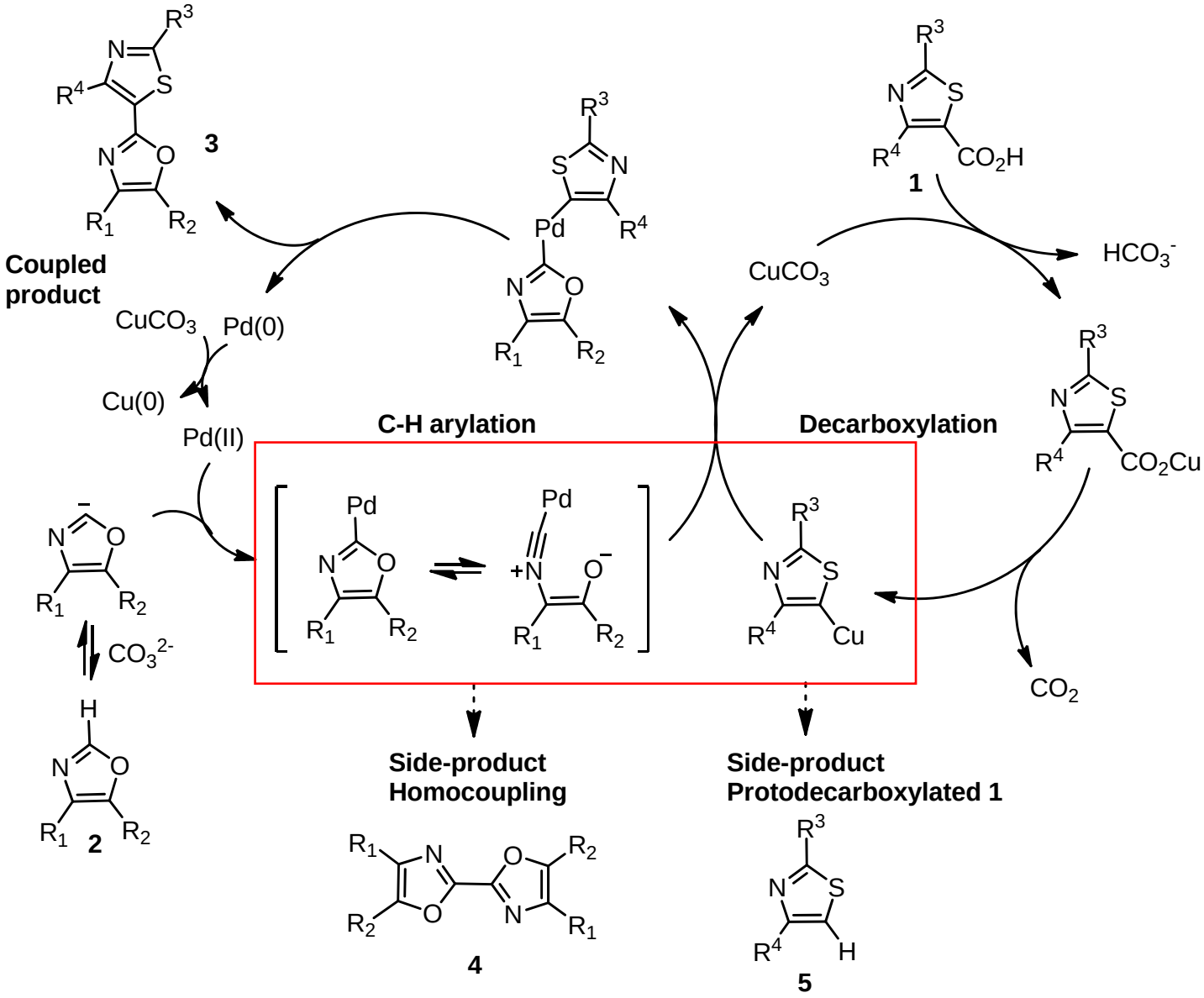
Zhang, F.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2768-2771.
See also reaction systems from Larrosa, Glorius, Ge, Guo

Mechanistic Scheme



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Fengzhi Zhang
Didier Pintori

MARIE CURIE ACTIONS

THE UNIVERSITY OF EDINBURGH

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