

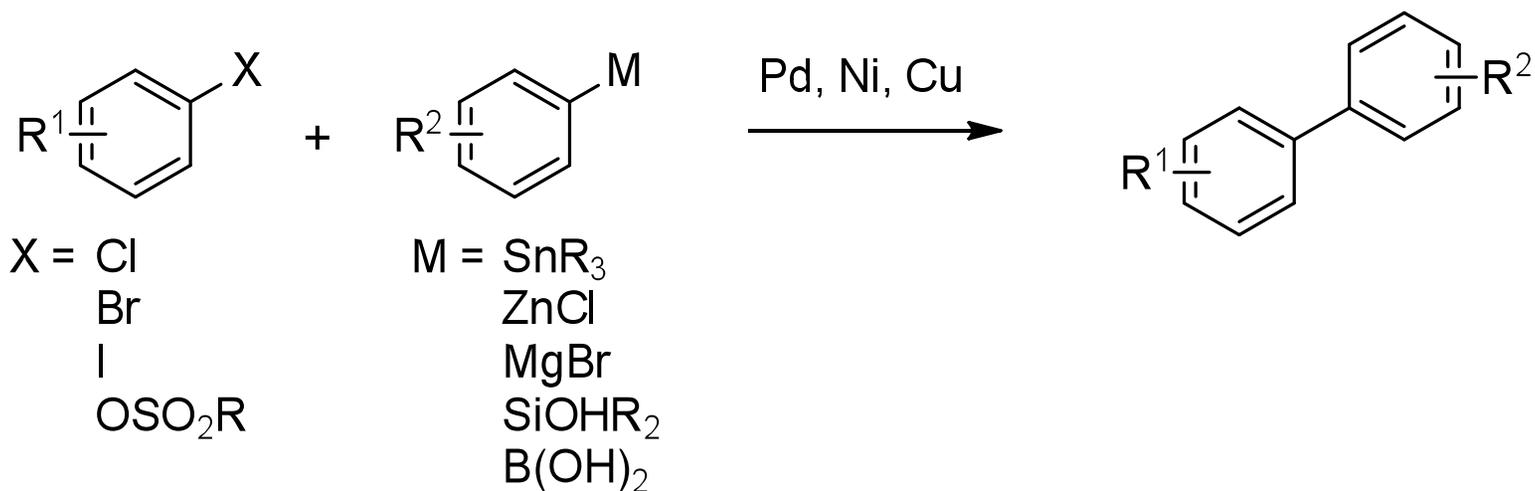
Organocatalytic C-H Activation or Homolytic Aromatic Substitution: a Cautionary Tale

William Kuester

Denmark Group Meeting Presentation

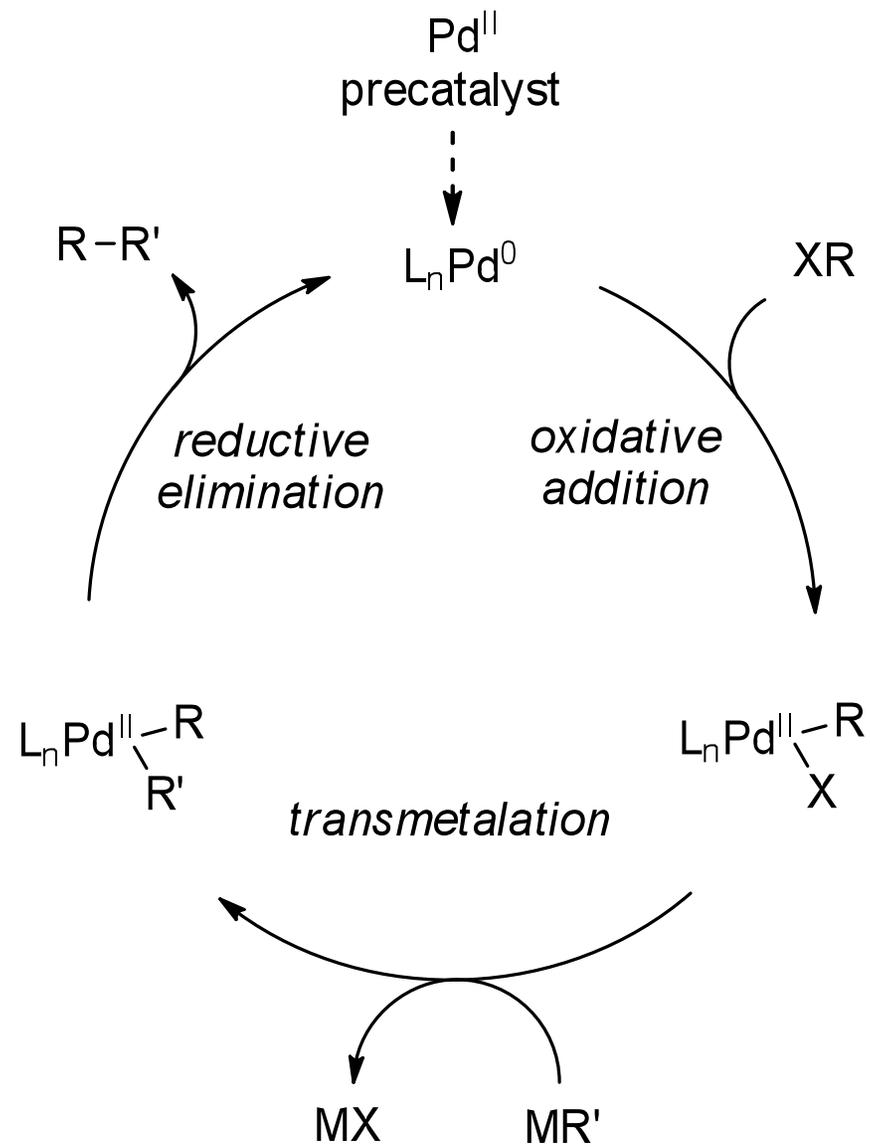
Tuesday May 29, 2012

Transition Metal Catalyzed Cross Coupling



- Versatile transformation
 - Pre-formed donor/acceptor substrates allows for complete regiochemical control
 - Expanded application to vinyl-aryl coupling, α -arylation of carbonyls, and more recently to sp^3 - sp^2 and sp^3 - sp^3 coupling.
- Sigma Catalog: 709 aryl boronic acids, 376 aryl boronic esters, 92 MIDA boronates, 481 aryl halides

Catalytic Cycle



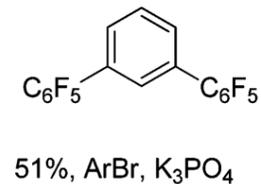
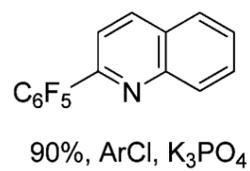
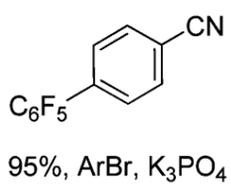
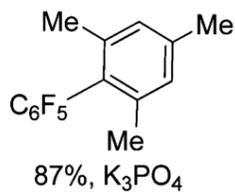
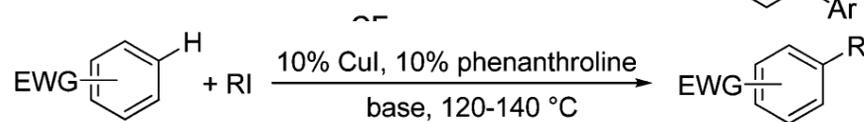
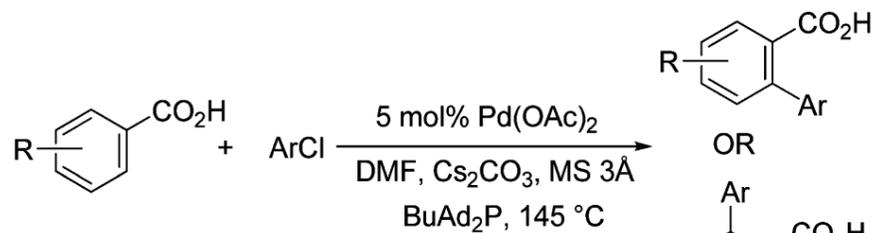
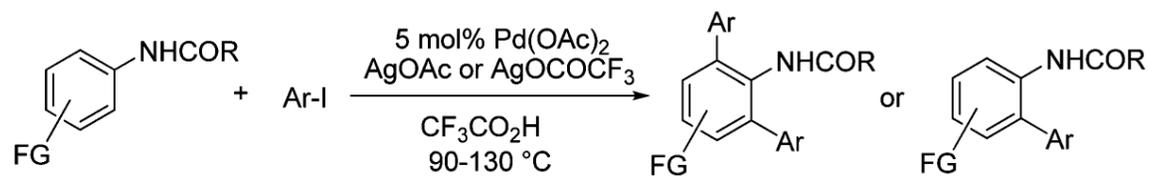
Limitations of Cross-Coupling

- Coupling Partners
 - Coupling partners must be prepared if not commercially available
 - Grignards have low FG tolerance
 - Stille coupling is most mild but Sn is highly toxic
- Transition Metal Catalyst
 - Pd is expensive
 - Pd and Ni are toxic

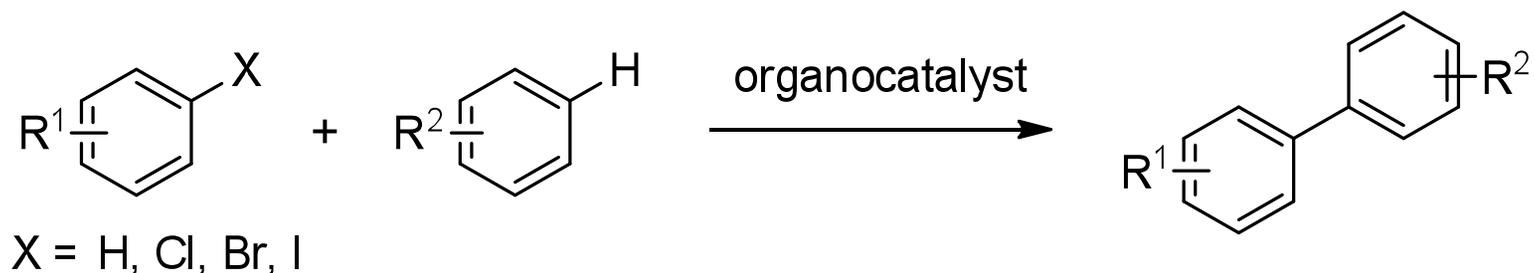
Research Pursuits

- C-H activation
 - C-H metallation/coupling
 - Single C-H activation
 - (C-H/C-X coupling)
 - Double C-H activation
 - (C-H/C-H coupling)
- Develop ligands and precatalysts that improve catalyst life. ↑ TON, ↓ loading.
- Use of less expensive and less toxic metals e.g. Cu, Fe
- Organocatalysis “Metal-Free”

C-H Activation

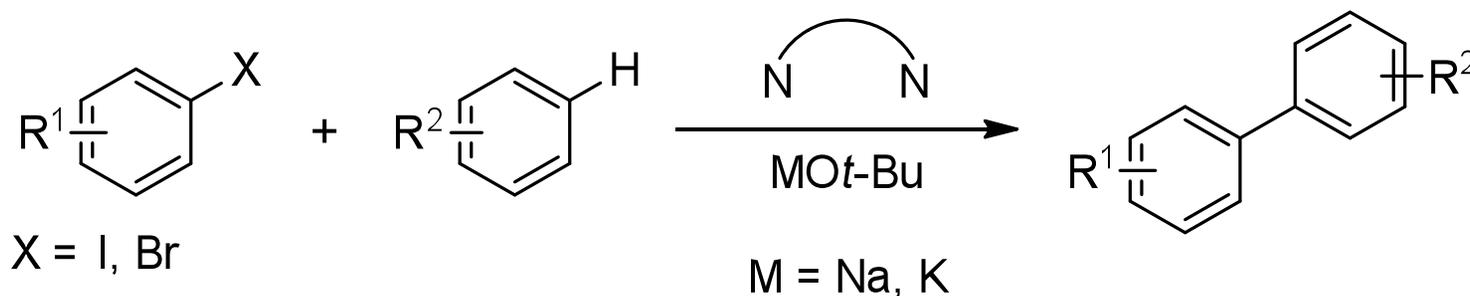


Criteria for an “Organocatalytic C-H Activation”



- C-H activation
 - Must exhibit high regioselectivity
 - Must be comparably efficient to traditional cross-coupling methods
- Organocatalysis
 - Must be rigorously free of any trace contaminants of transition metals
 - Must be comparably efficient to T.M. catalyzed methods.

Three Reports of “Organocatalytic C-H Activation”

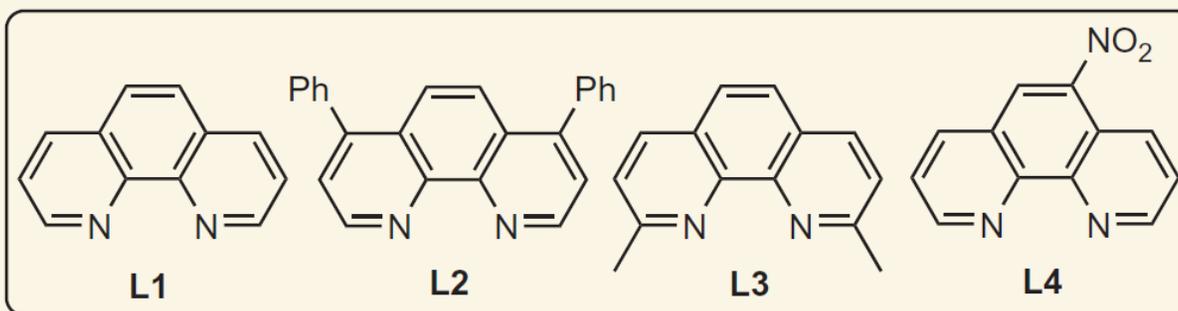
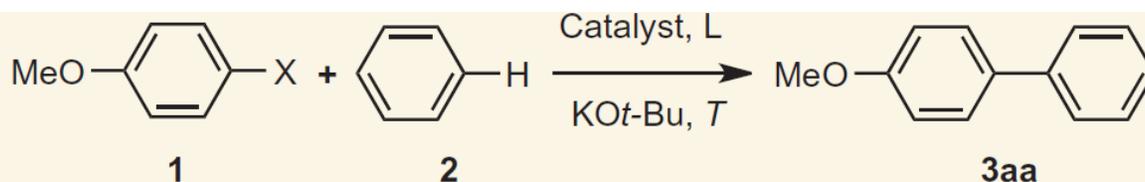


- Kwong, F. Y.; Lei, A. et al. **Organocatalysis** in Cross-Coupling: DMEDA-Catalyzed **Direct C-H Arylation** of Unactivated Benzene. *J. Am. Chem. Soc.* **2010**, *132*, 16737-16740.
- Shi, Z. J. et al. An Efficient **Organocatalytic** Method for Constructing Biaryls Through Aromatic **C-H Activation**. *Nat. Chem.* **2010**, *2*, 1044-1049.
- Shirakawa, E.; Hayashi, T. et al. tert-Butoxide-Mediated Arylation of Benzene with Aryl Halides in the Presence of a Catalytic 1,10-Phenanthroline Derivative. *J. Am. Chem. Soc.* **2010**, *132*, 15537-15539.

Language Used to Emphasize Novelty

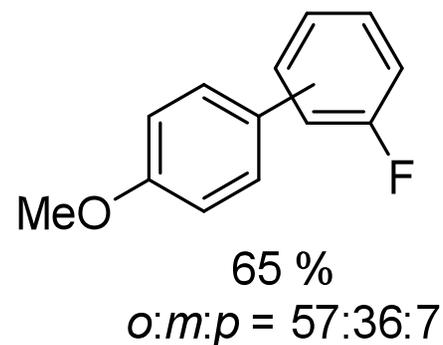
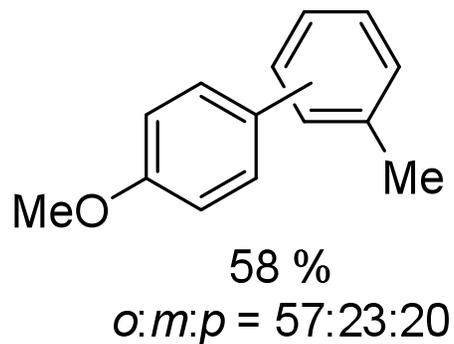
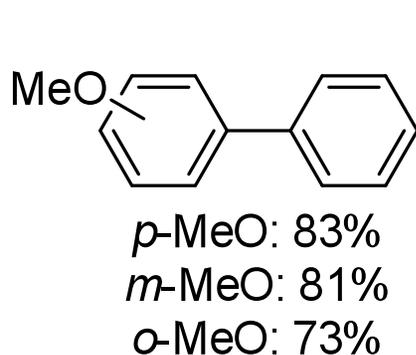
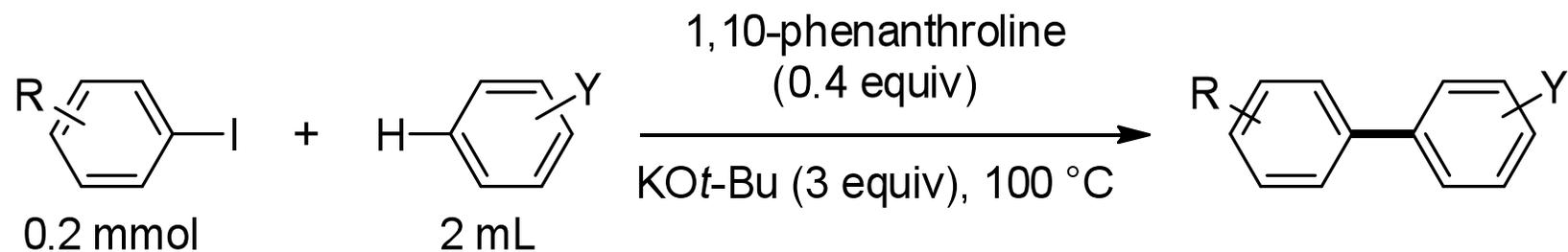
- Shi (3 instances)
 - “new methodology”
 - “novel cross-coupling in the absence of any added transition-metal catalyst”
 - “conceptual breakthrough”
- Lei/Kwong (8 instances)
 - “conceptually different”
 - “a new horizon for direct C-H/cross-coupling reactions”
- Shirakawa/Hayashi (0 instances)
 - ...

Why we should always run controls without metals

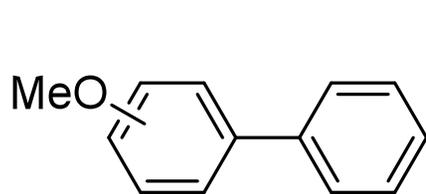
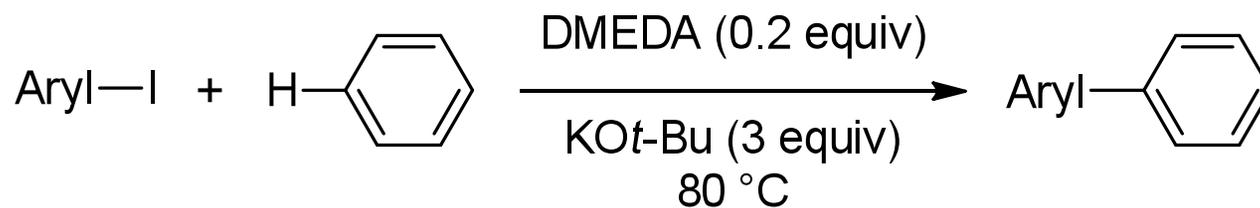


Entry	X	Co (10 mol%)	L (mol%)	T (°C)	Yield (%)
1	I	Co(acac) ₃	DMEDA (40)	80	69
2	I	Co(acac) ₃	L1 (40)	80	71
3	Br	Co(acac) ₃	L1 (40)	80	70
4	I	-	L1 (40)	80	62
5	Br	-	L1 (40)	80	5
6	I	-	L1 (20)	100	83
7	Br	-	L1 (20)	100	48
8	Br	-	L1 (40)	100	87

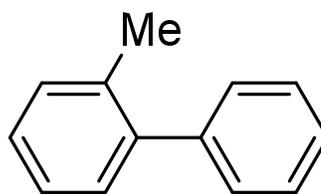
Scope of Phenanthroline Catalyzed Reaction



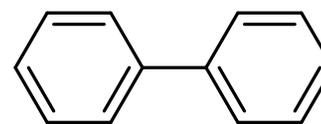
A Similar Reaction with DMEDA



p-MeO: 84%
m-MeO: 80%
o-MeO: 60%



38%

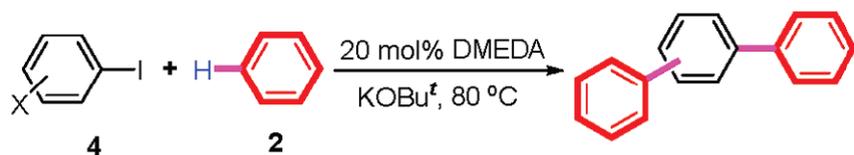


81%

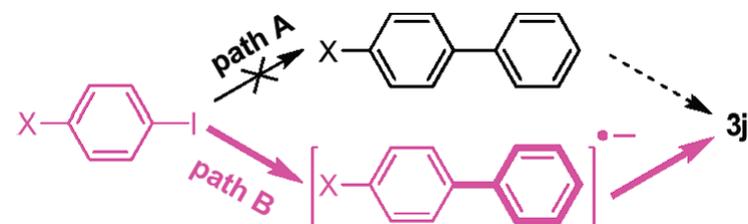
Trace Metal Contaminants

- Lei
 - Repurified KO t Bu with no change in results.
- Shi
 - Addition of various T.M. did not improve the rate of reaction.
 - KO t Bu from Sigma-Aldrich was sublimed.
 - Other sources of KO t Bu and 1,10-phenanthroline used.
 - New glassware used.
 - Another lab was asked to independently repeat the experiment

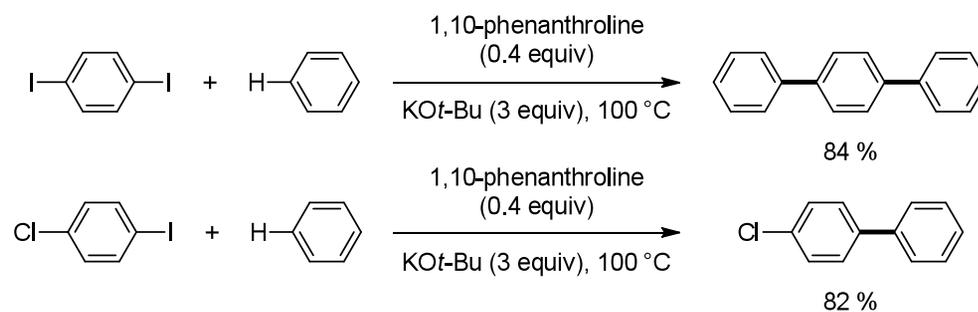
The Double Activation of Dihaloarenes



entry	4	product	yield(%)
1		3j	74
2		3j	68
3		3j	71
<hr/>			
4		5	79
5		5	60
6		5	32 ^b
<hr/>			
7		6	21 ^c
8		6	30 ^d
9		6	29 ^e



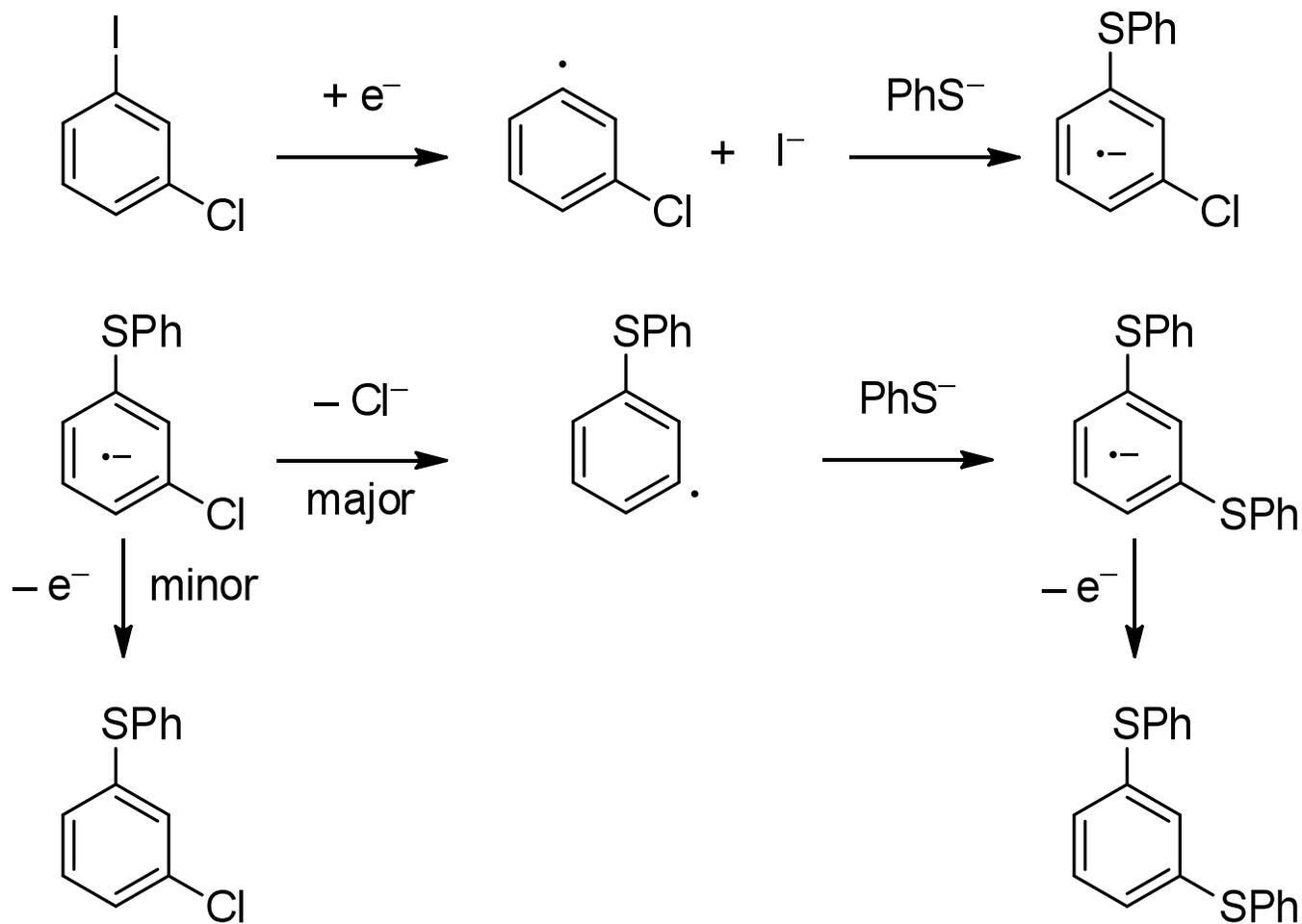
- Lei proposes the intermediacy of a radical anion

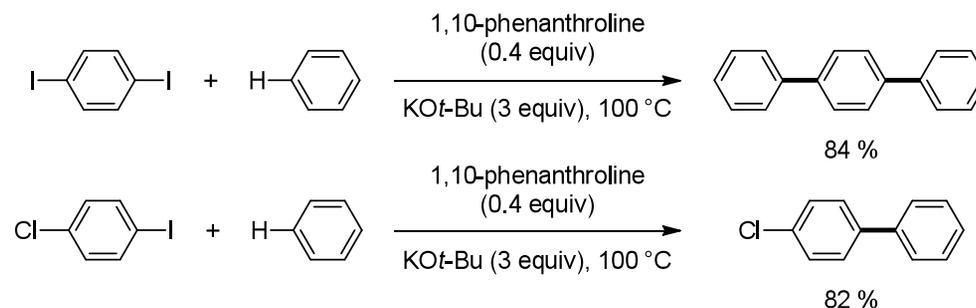
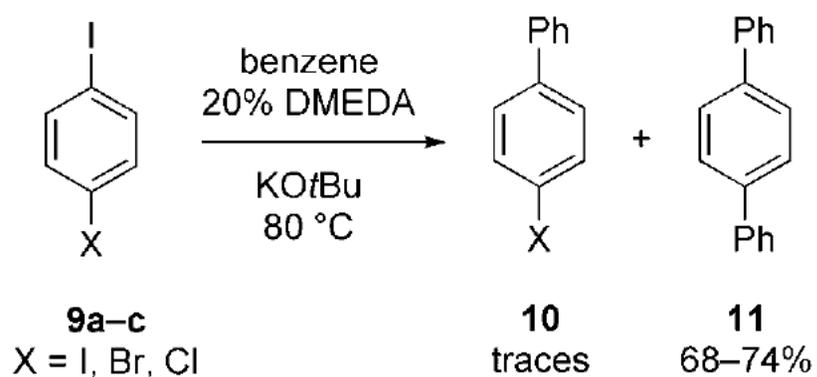


Shi, Z. *J. Nat. Chem.* **2010**, *2*, 1044-1049.

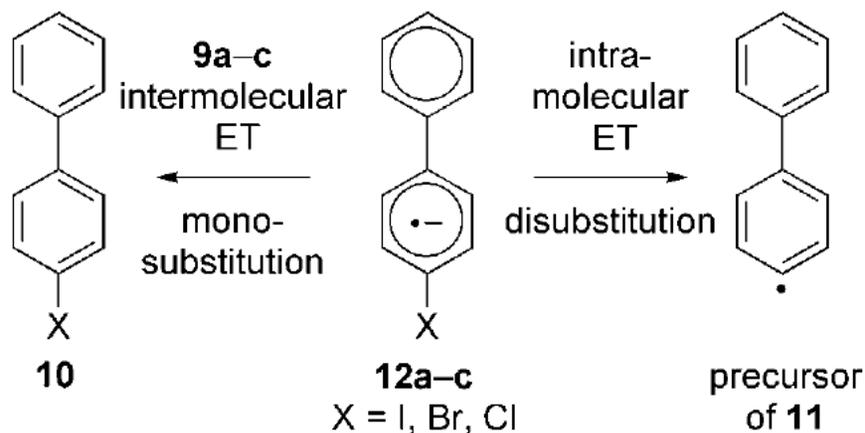
Kwong, F. Y.; Lei, A. et al. *J. Am. Chem. Soc.* **2010**, *132*, 16737-16740.

Precedence for Dihaloarene Substitution



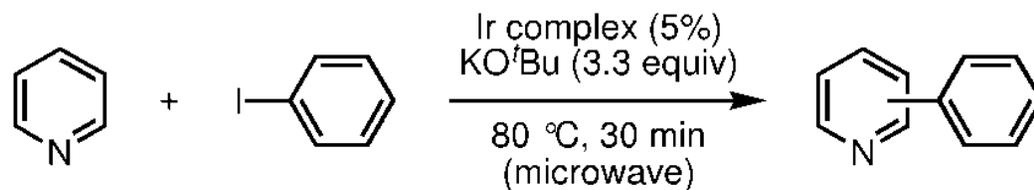


Competing ET reactions for the radical anions



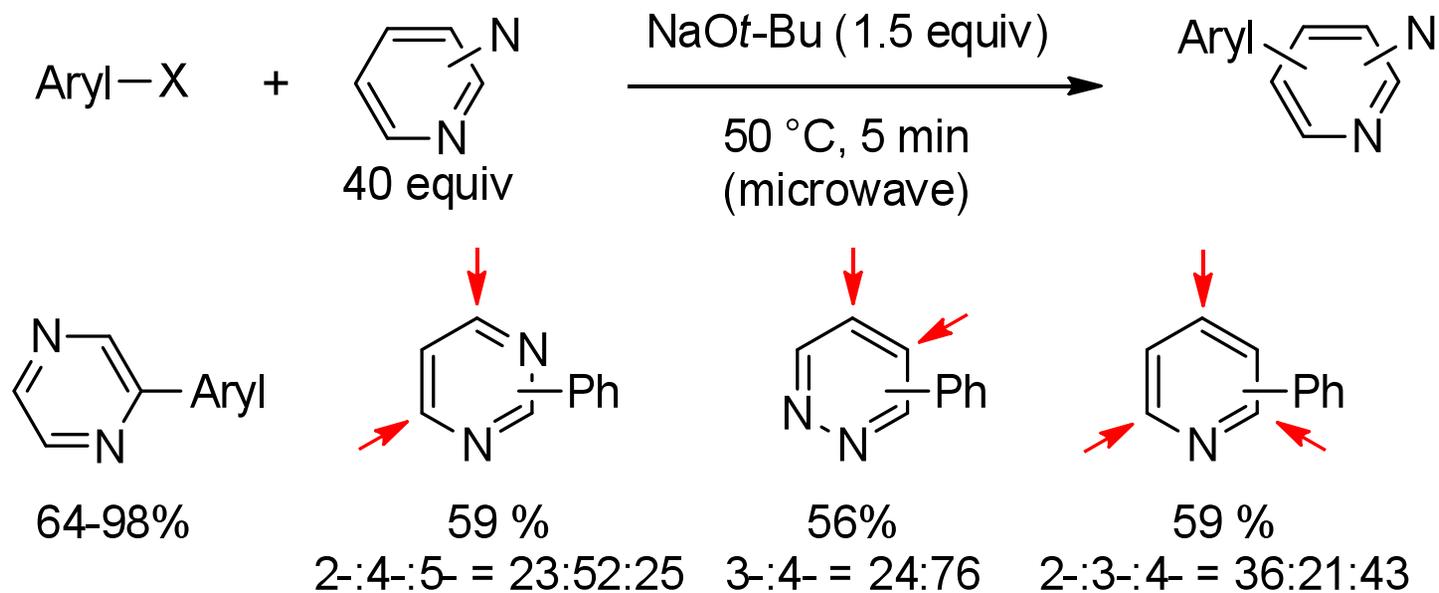
- Limited disubstitution of dihalides with phenanthroline may reflect a higher rate of intermolecular ET over intramolecular ET or that a radical anion is not intermediate.

Is this really that novel?



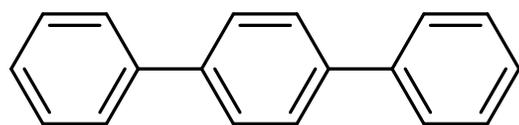
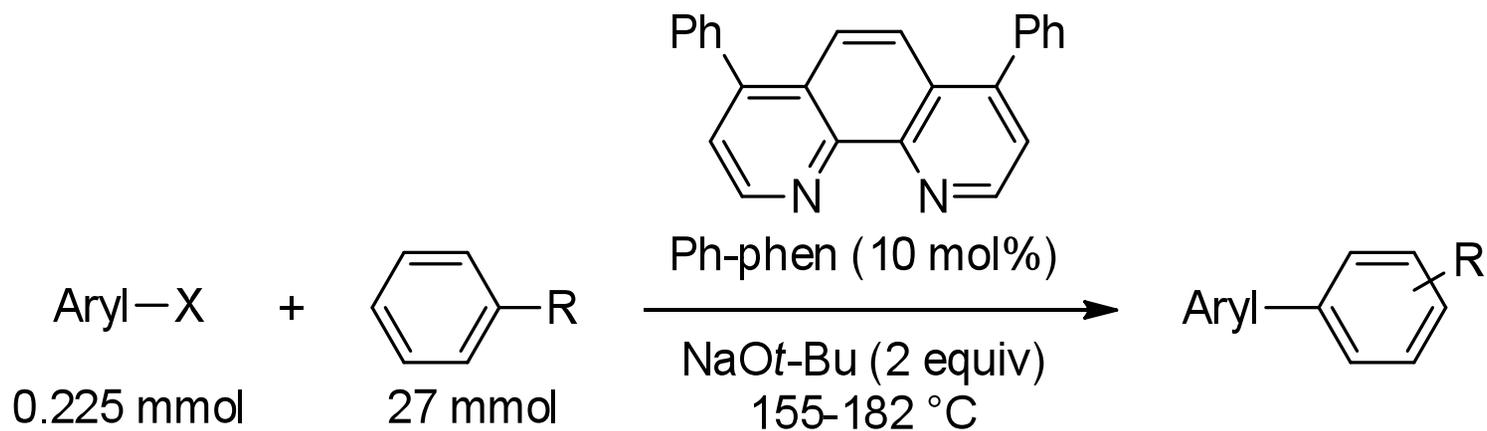
entry	Ir complex	yield (%) ^b
1	[Cp*IrHCl] ₂	30
2	[Cp*IrCl ₂] ₂	32
3	[IrCl(cod)] ₂	17
4	Ir(acac)(cod)	18
5	IrH(CO)(PPh ₃) ₃	29
6	IrCl(CO)(PPh ₃) ₂	41
7	(NH ₄) ₃ IrCl ₆	26
8	none	39

Heteroarylation of Aryliodides

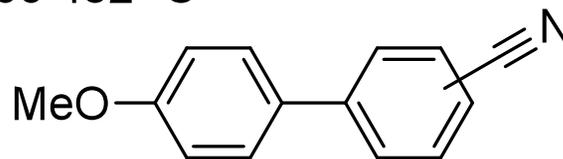


- Metal studies: glassware cleaned, T.M. were below detection limit by ICP-AES (Pd <0.06 ppm, Rh <0.2, Ru <0.3)
- TEMPO (2,2,6,6-tetramethyl pyridine 1-oxyl) inhibits the reaction.
- Propose homolytic aromatic substitution or $S_{RN}1$ as possible mechanisms.

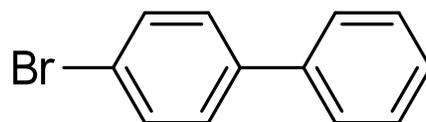
Phenanthroline Derivative Promoted Arylation



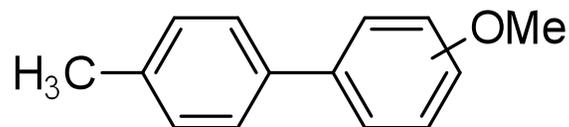
73%
from 1,4-I₂C₆H₄



68%
o:m:p = 56:16:28



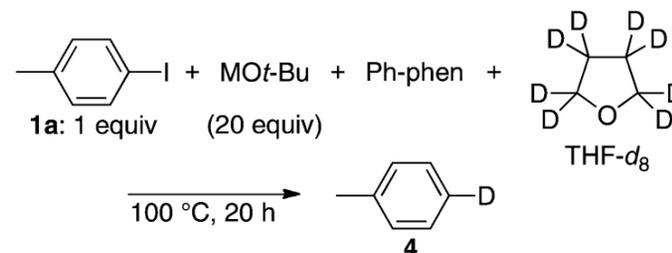
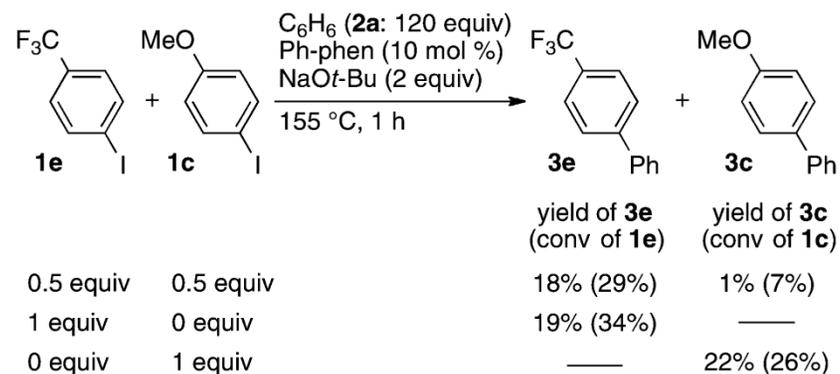
73%
terphenyl: 2%



51%
o:m:p = 59:26:15

Further Evidence for a Radical Chain Reaction

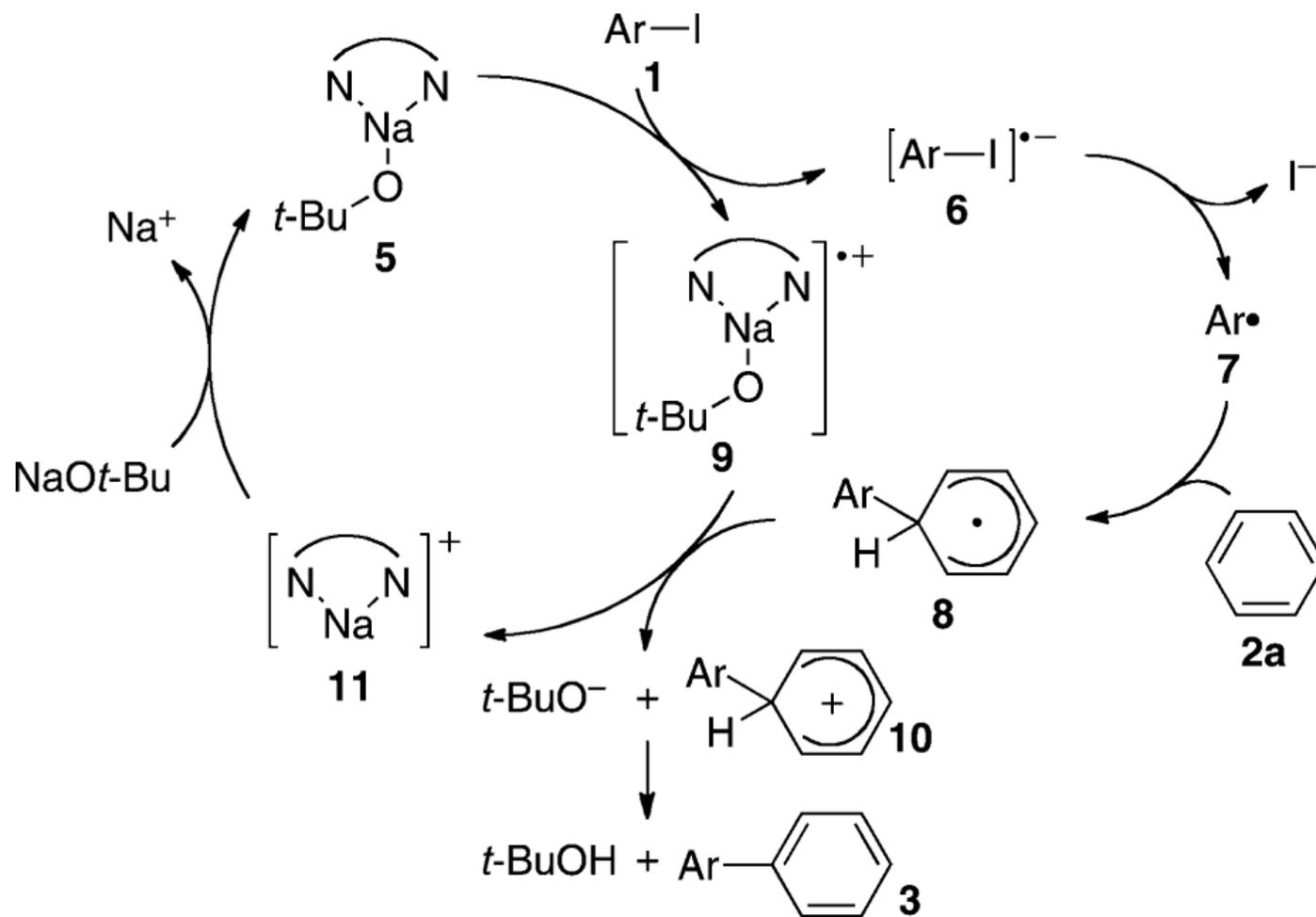
- Large excess of acceptor needed
- $k_H/k_D = \sim 1$
- TEMPO and other radical inhibitors block reactivity (Shi, Lei/Kwong)
- High *ortho* selectivities are consistent with addition of aryl radicals to substituted benzenes



M	Ph-phen	conv of 1a	yield of 4
Na	1 equiv	>99%	79% (>95%-d)
Na	0 equiv	2%	2% (>95%-d)
K	1 equiv	>99%	72% (>95%-d)
Li	1 equiv	20%	<1%

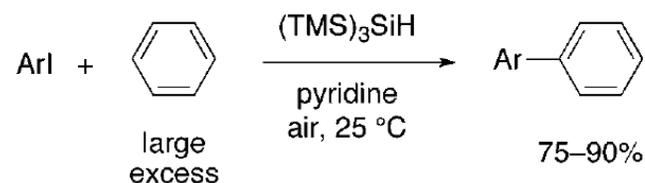
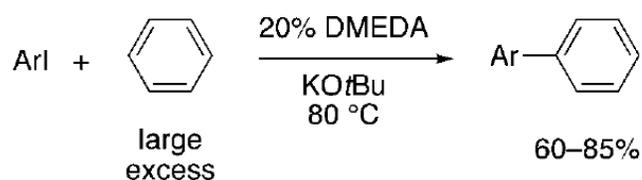
Shirakawa, E.; T.; Hayashi, et. al. *T. J. Am. Chem. Soc.* **2010**, *132*, 15537-15539.
 Studer, A.; Curran, D. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 5018-5022.

Hayashi's Proposed Mechanism

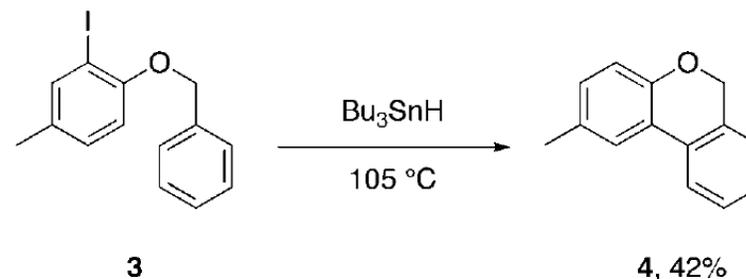
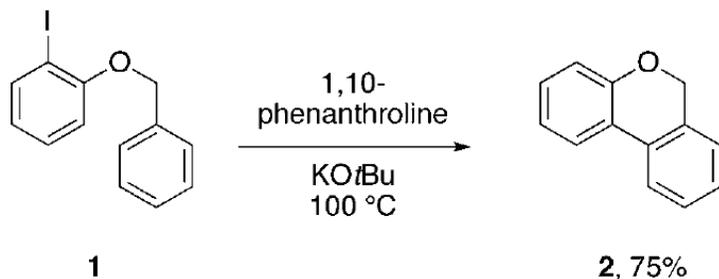


“C-H Activation” v. HAS

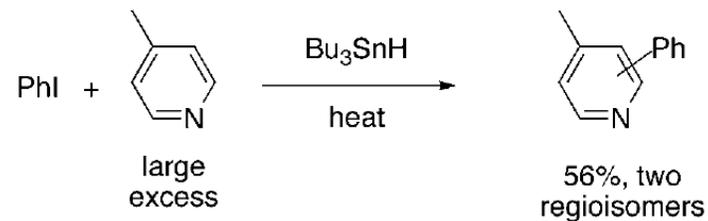
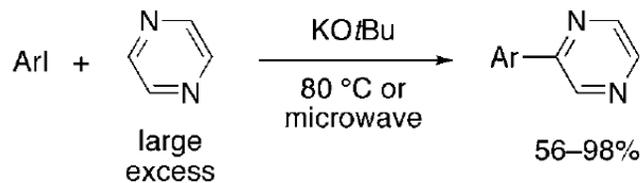
Kwong, Lei and co-workers, 2010



Shi and co-workers, 2010

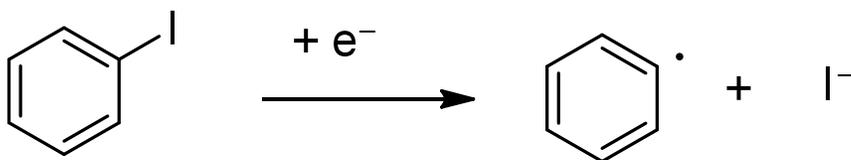


Itami and co-workers, 2008

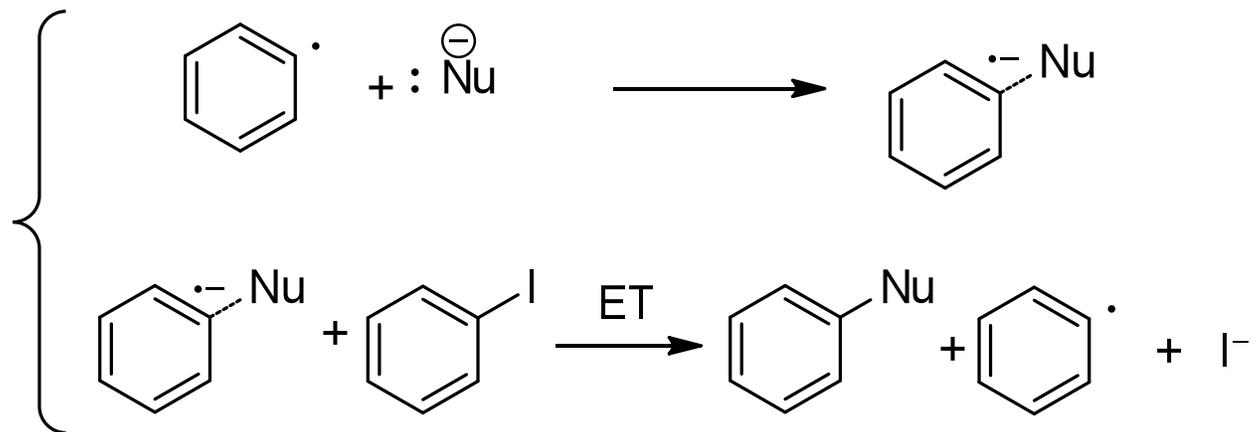


S_{RN}1

- Initiation

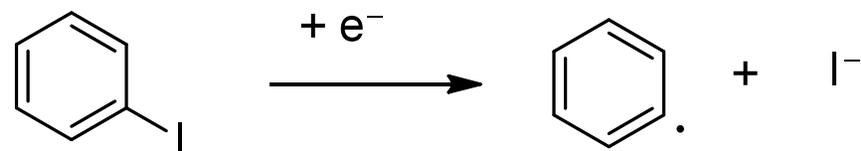


- Propagation

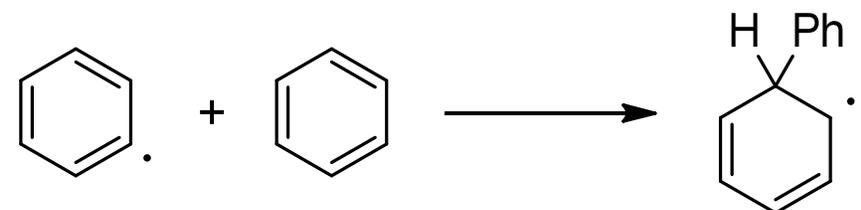


Homolytic Aromatic Substitutions

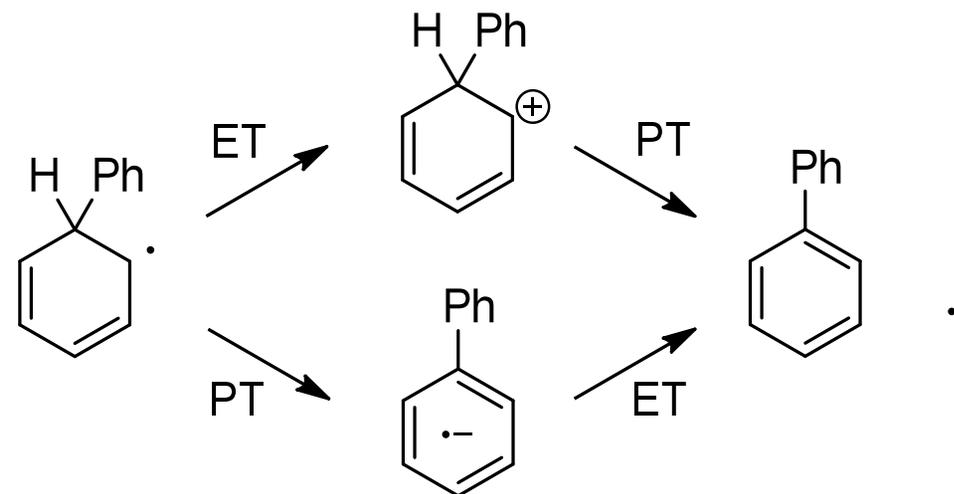
- Initiation



- Addition of aryl radical to arene

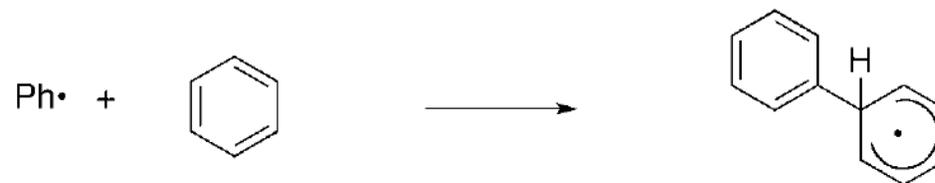


- Rearomatization
- ET to PhI (Not Shown)

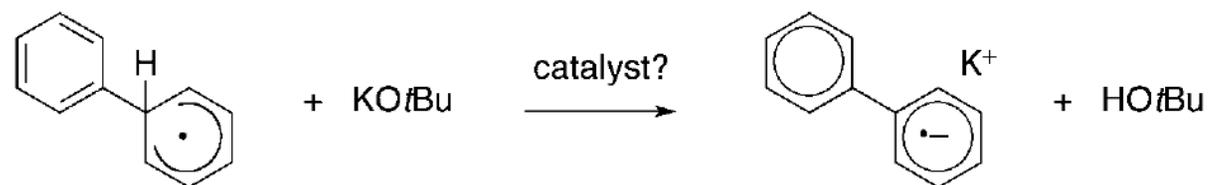


Alternate Mechanism

1) radical addition

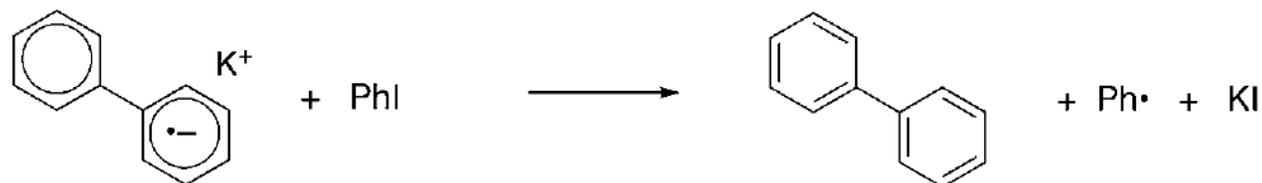


2) deprotonation

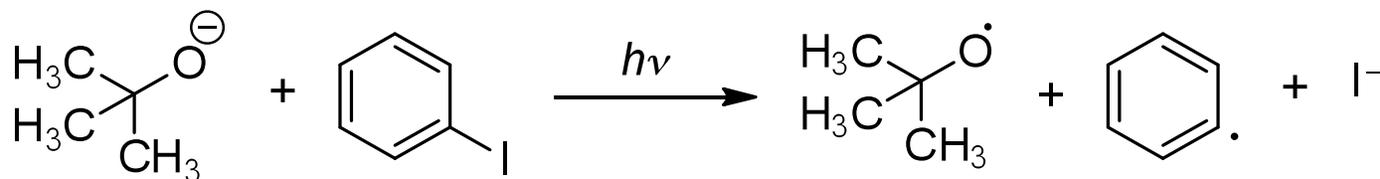


biphenyl radical anion

3) dissociative electron transfer



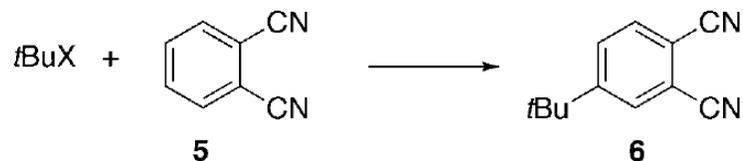
Initiation



- Initiation by *t*-BuO⁻ with photolysis is known as entrainment
- Common with other nucleophiles as well

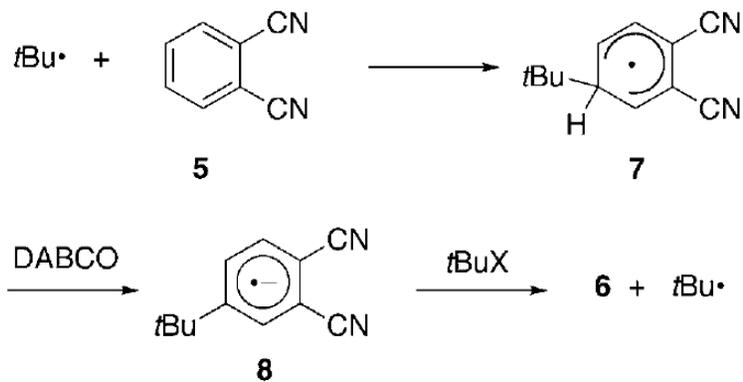
Precedence for Propagation Steps

Reaction



X = HgBr, DABCO, DMSO, 60 °C, $h\nu$
x = Br, (Bu₃Sn)₂, DABCO, C₆H₆, 60 °C

Proposed mechanism



X = HgBr, more efficient (chain length >20)
X = Br, less efficient (chain length \approx 3)

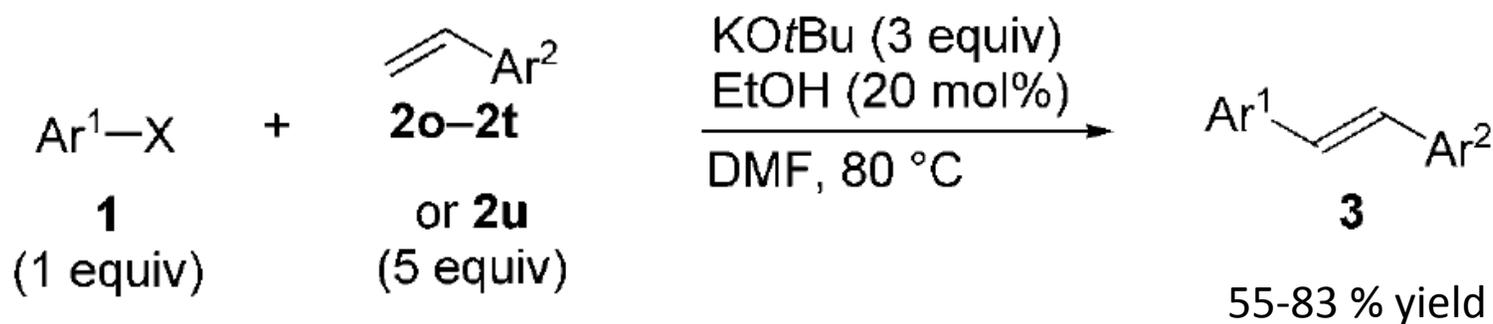
Studer, A.; Curran, D. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 5018-5022.

Russel, G. A.; et al. *J. Am. Chem. Soc.* **1997**, *7863*, 8795-8801.

Wang, C.; Russell, G. A.; Trahanovsky, W. S. *J. Org. Chem.* **1998**, *63*, 9956-9959.

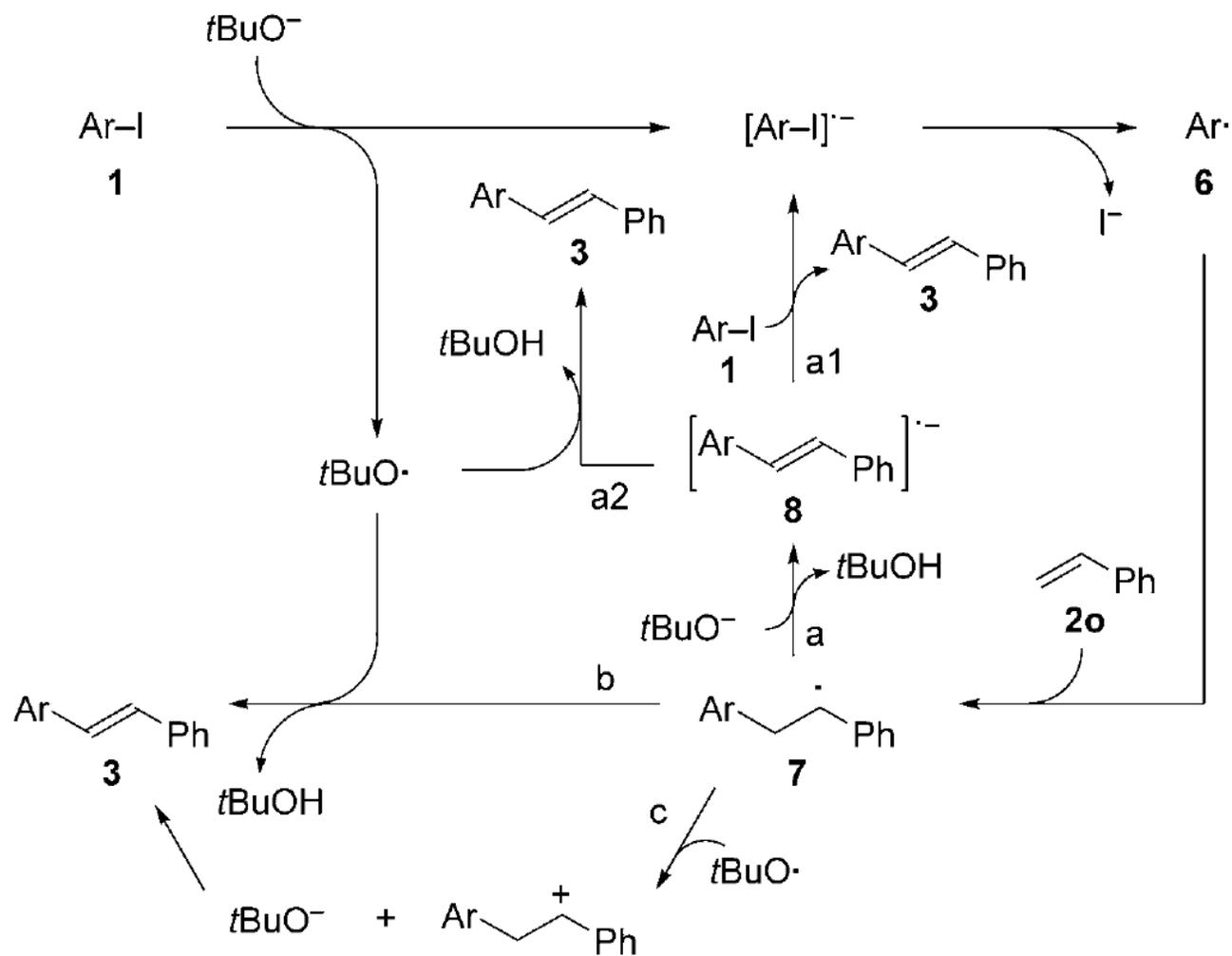
Kim, B. H.; et al. *J. Chem. Soc. Perkin Trans. 1* **2001**, 2035-2039.

Recent advances



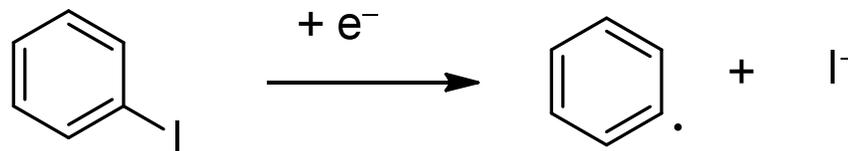
- Very low yield when 4-CH₃C₆H₄X (X = Br, Cl), or 4-CF₃C₆H₄I is employed
- Styrenes are better acceptors so stoichiometry is reduced.

The Proposed Mechanism

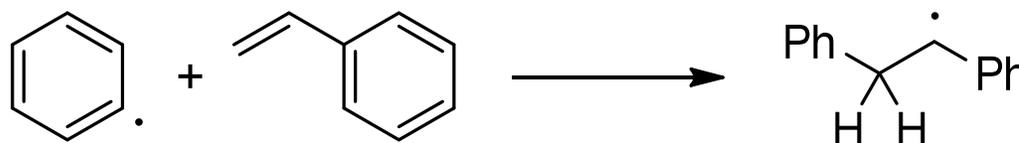


A More Likely Mechanism

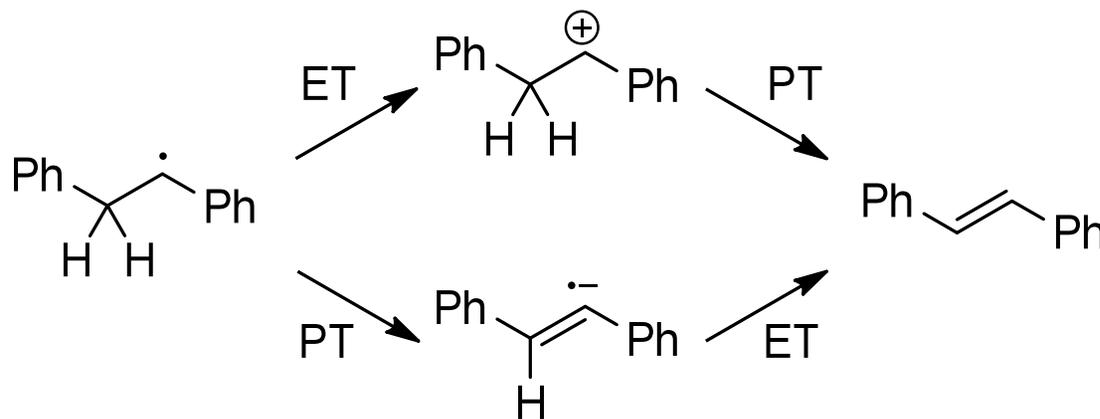
- Initiation



- Addition



- Reformation of conjugation



Validating the Claims

- Is this C-H activation?
 - This depends on whichever definition of C-H activation one is using at the time.
 - The ‘addition-deprotonation’ nature of HAS resembles Friedel-Crafts and other S_EAr transformations.
 - S_EAr is not typically viewed as C-H activation.
- Is this cross-coupling?
 - Like C-H activation, this may depend on the definition used.
 - Radical additions not typically thought of as “cross-coupling”
- Is this organocatalysis?
 - Possibly.
 - It is unclear what role DMEDA or 1,10-phenanthroline play
 - Organocatalysis is common in radical mechanisms.

Is this a “Conceptual Breakthrough?”

- Not really, but it might still be a breakthrough
 - Tertbutoxide promoted HAS is a novel methodology.
 - Base-promoted HAS with tertbutoxide may prove to have a greater scope than current methods.
 - If organocatalyzed HAS is possible, metal-catalyzed variants may be possible.

Of What are Lei/Kwong and Shi “Guilty?”

- Tunnel vision
- Allowing the excitement for an unexpected result get the better of their judgment
- Playing to fads
- Not following up on mechanistic leads that might have resulted in a different conclusion.
 - Itami, who both groups cited, suggested HAS as a possible mechanism.
 - Shi performed a control with Bu_3SnH instead of $\text{KO}t\text{-Bu}$ and phenanthroline.

Lessons to be Learned

- Be critical of your own hypotheses
- Be critical of the literature

The Hayashi Mechanism Simplified

