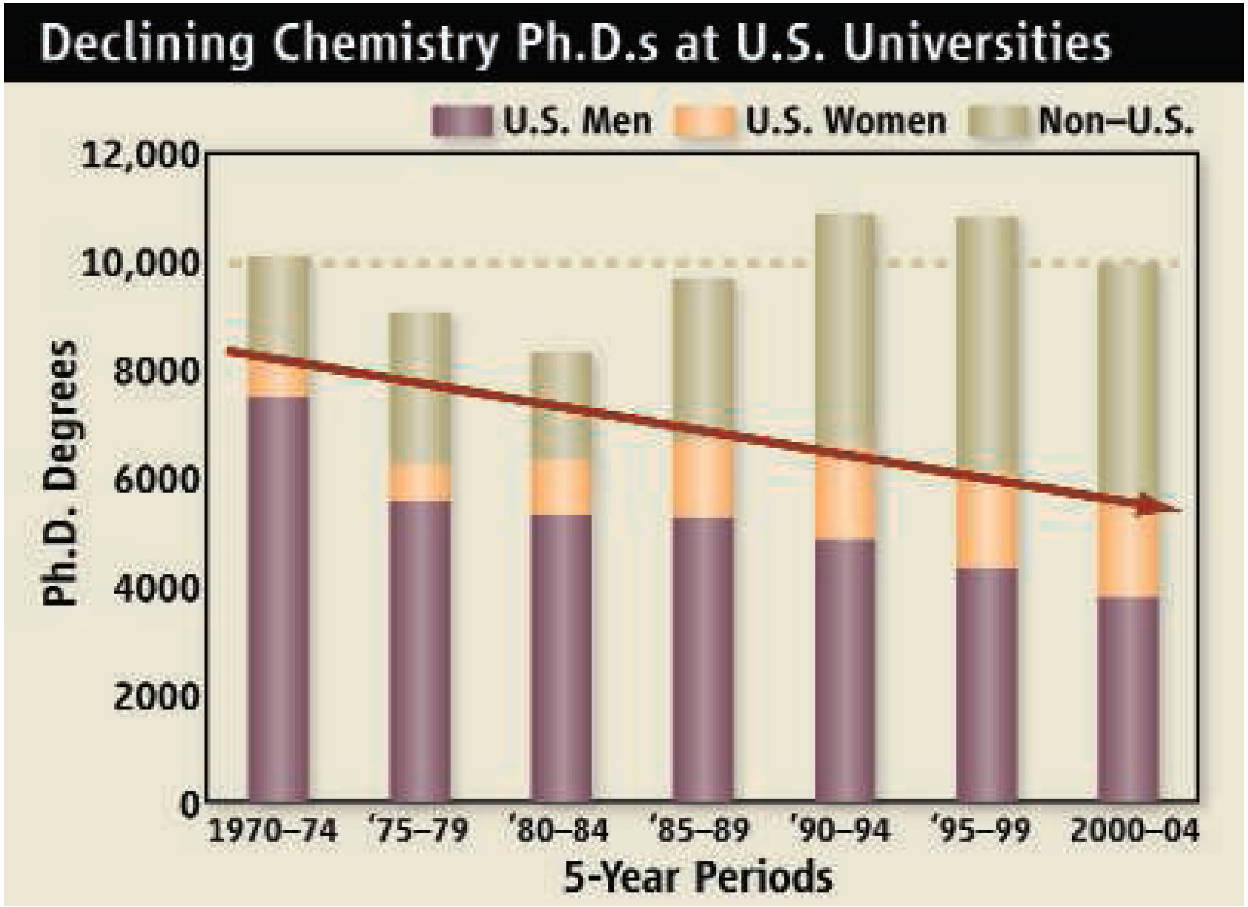


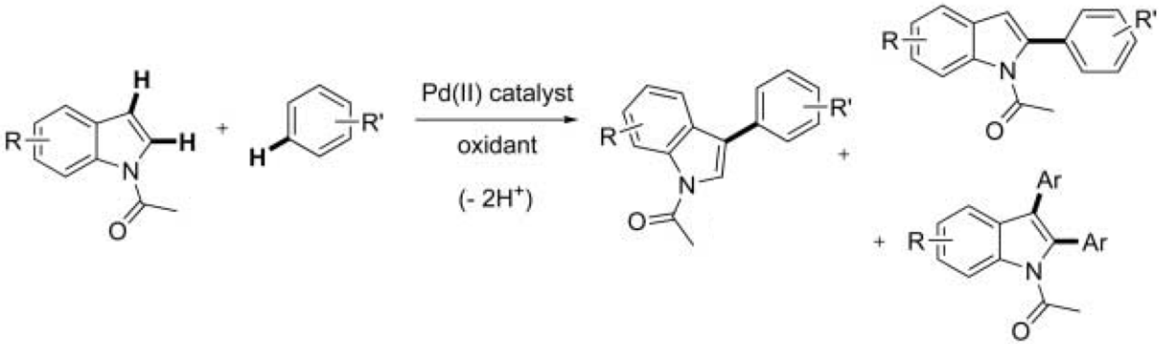
The upshot: “The U.S. will remain a leader in chemistry for the next 5 years,” Ceyer says. “But the U.S. lead will continue to shrink as the chemistry world becomes flatter and more competitive.”

SCIENCE VOL 316 6 APRIL 2007

The Catalytic Cross-Coupling of Unactivated Arenes

-David R. Stuart and Keith Fagnou

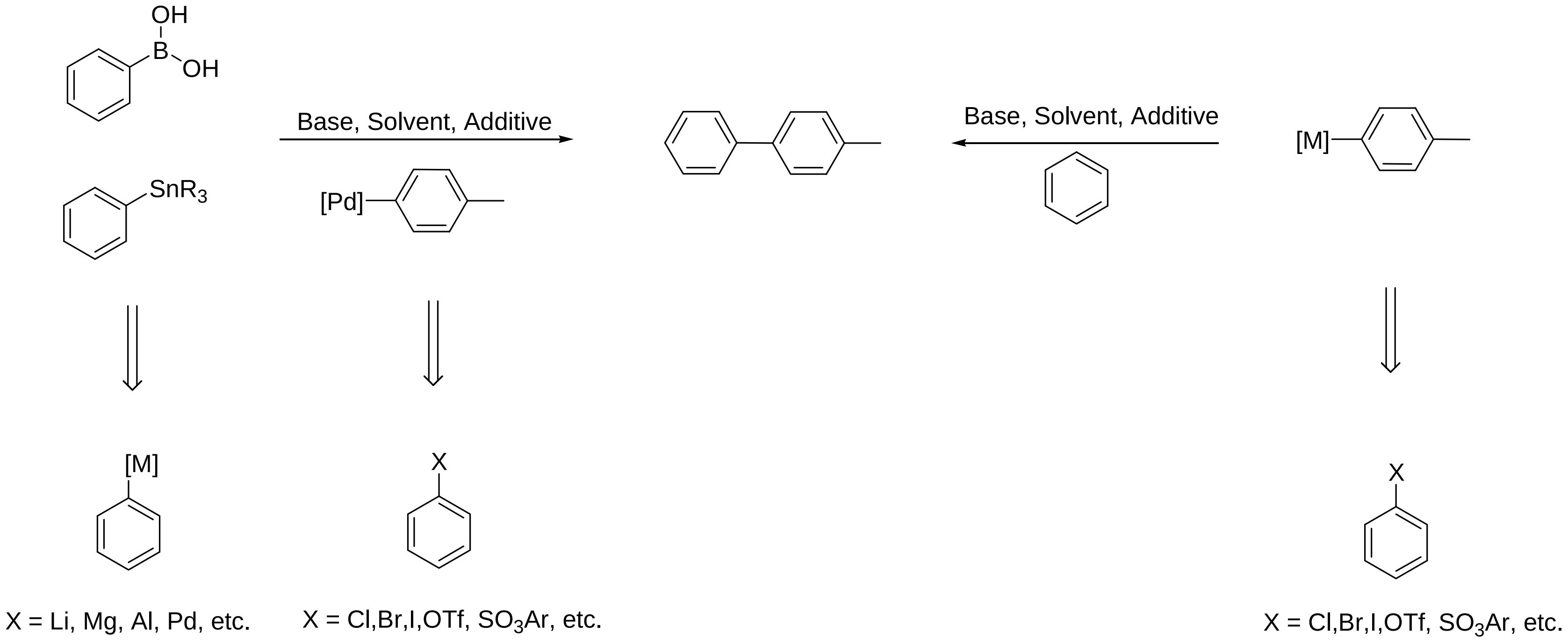
Center for Catalysis and Innovation, University of Ottawa, Canada



Conventional Approaches to the Biaryl Cross-coupling

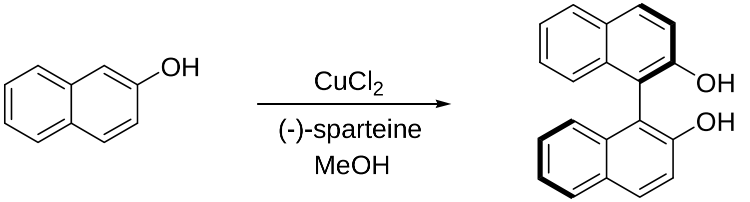
-Suzuki, Stille, and Heck type disconnections are standard, but require strategic installation of functionality.

-"Direct Arylation" reduces, but does not eliminate, the need for prefunctionalization.

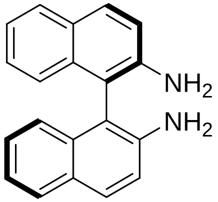


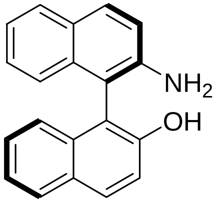
-A desirable modification of this manifold would remove all pre-functionalization.

Some Examples of Cross-couplings Across C-H Bonds



14 - 94%, 0 - 100% *ee*





-Stoichiometric oxidant present

-Low yields

25-100 eq.

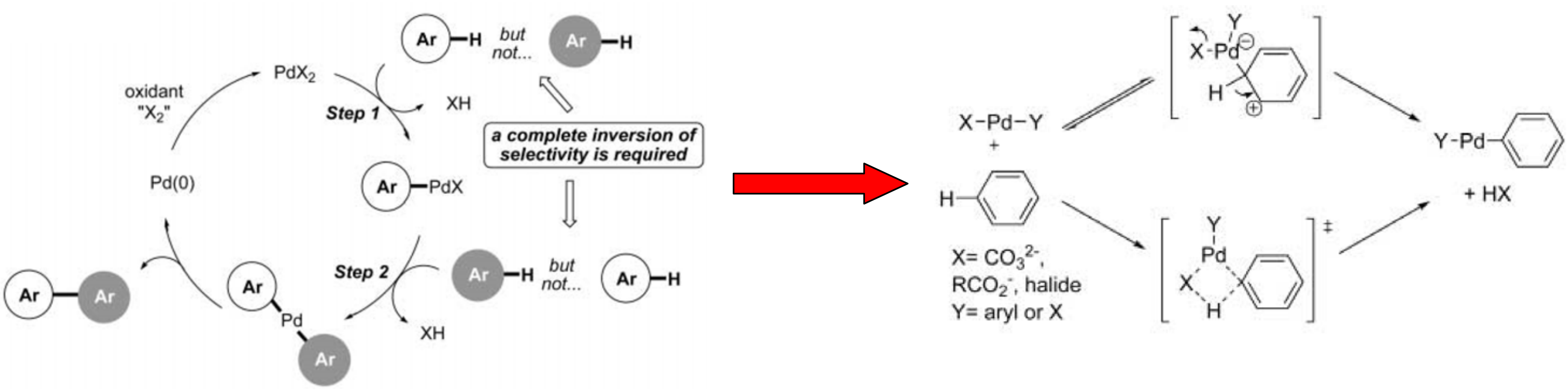
15 - 32 %

-Low yields and TONs

J. Org. Chem. **1992**, *57*, 1917
Organometallics, **2006**, *25*, 5973

-There is clearly room for improvement.

Conceptual Development of Reaction



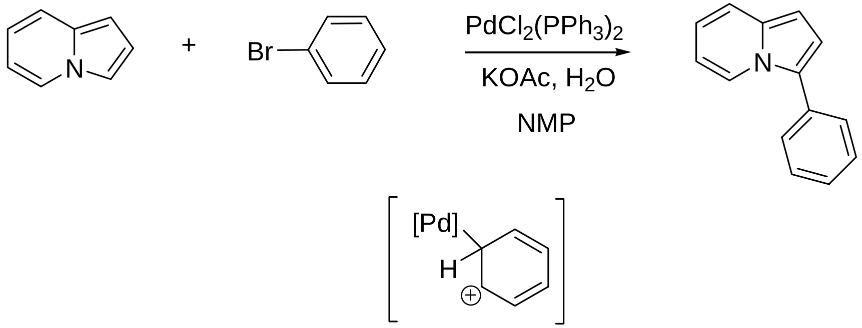
“…To meet this demand, the catalyst must be able to react with one arene in the first step of the catalytic cycle and then invert its selectivity in the second step to react exclusively with the other arene. Achieving such an inversion in reactivity and selectivity is simultaneously the most daunting challenge and the most crucial prerequisite.”

-Complimentary reactivity can be achieved by merging the known S_EAR for Pd with the “proton transer-palladation” mechanism, which shows acidity correlation.

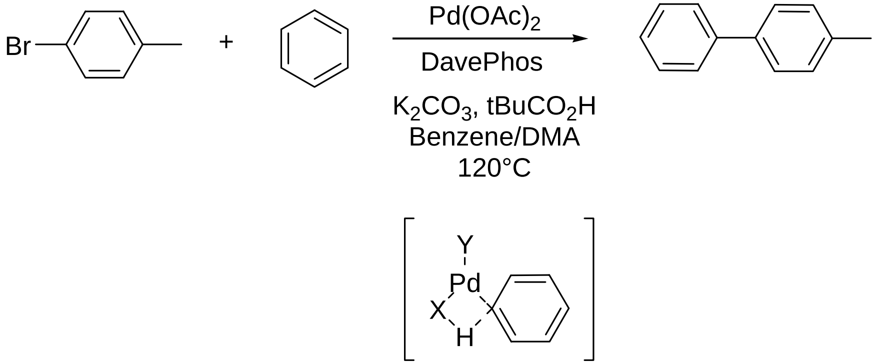
Org. Lett. **2004**, *6*, 1159
J. Am. Chem. Soc. **2006**, *128*, 16496

Individual Examples of Complimentary Reaction Manifolds

S_EAr type coupling:



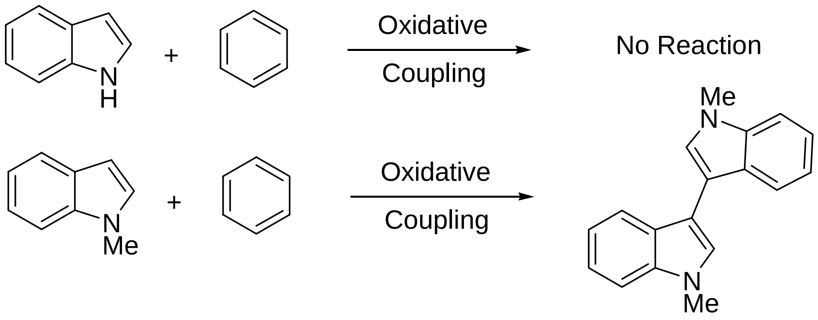
-C-H activation type coupling:

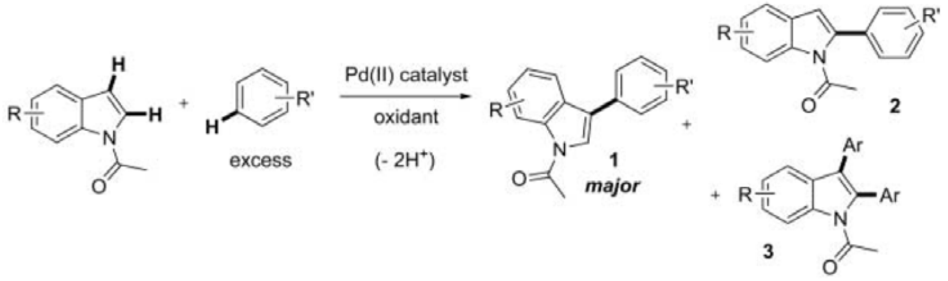


Org. Lett. **2004**, *6*, 1159
J. Am. Chem. Soc. **2006**, *128*, 16496

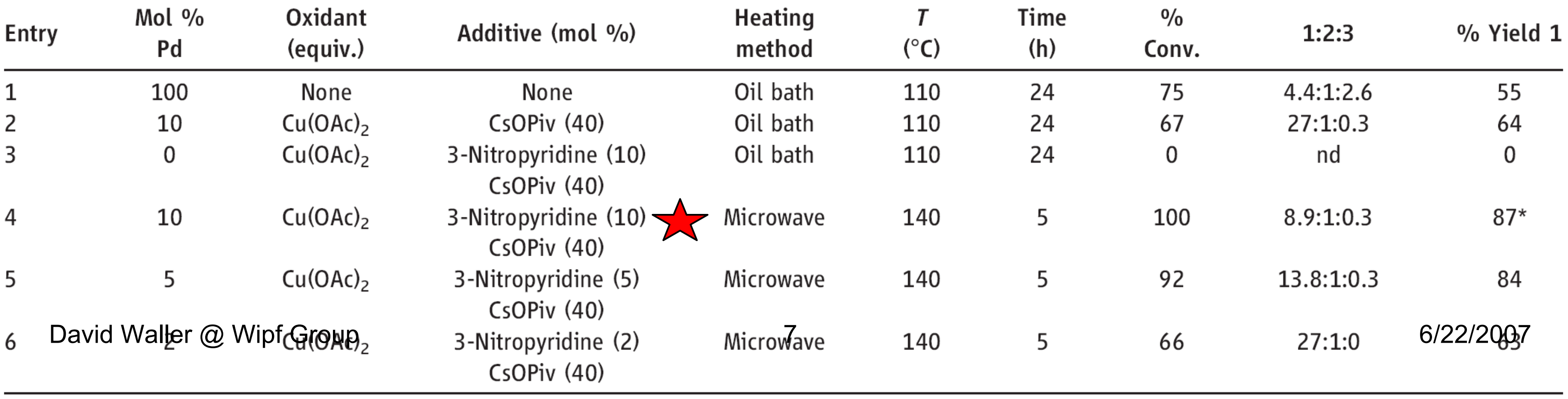
Reaction Optimization

- ***Free indole gave no reaction***
- ***N-methyl indole gave dimerization***
- ***N-acetyl indole provided optimum reactivity***
- ***Pd(TFA)$_2$ is optimum catalyst***
- ***3 eq. co-oxidant optimal***
- ***Solvent: Pivalic acid***



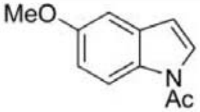
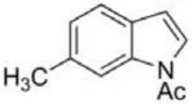
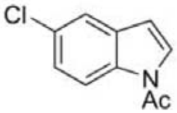
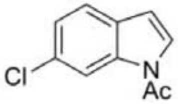
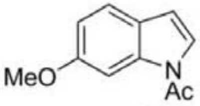
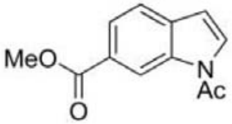
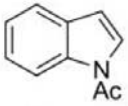
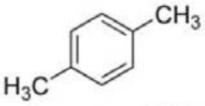
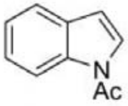
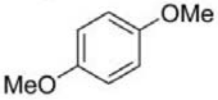
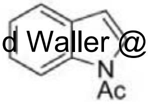


-Pyridine additive believed to stabilize Pd(0) complex.



Entry	Mol % Pd	Oxidant (equiv.)	Additive (mol %)	Heating method	*T* (°C)	Time (h)	% Conv.	1:2:3	% Yield 1
1	100	None	None	Oil bath	110	24	75	4.4:1:2.6	55
2	10	Cu(OAc)$_2$	CsOPiv (40)	Oil bath	110	24	67	27:1:0.3	64
3	0	Cu(OAc)$_2$	3-Nitropyridine (10) CsOPiv (40)	Oil bath	110	24	0	nd	0
4	10	Cu(OAc)$_2$	3-Nitropyridine (10) CsOPiv (40) ★	Microwave	140	5	100	8.9:1:0.3	87*
5	5	Cu(OAc)$_2$	3-Nitropyridine (5) CsOPiv (40)	Microwave	140	5	92	13.8:1:0.3	84
6	2	Cu(OAc)$_2$	3-Nitropyridine (2) CsOPiv (40)	Microwave	140	5	66	27:1:0	63

Table of Results for Cross-coupling

Entry	Indole	Arene	*T* (°C)	Mol % Pd	% Conv.	1:2:3	% Yield 1
1			140	10	100	11.2: 1: 0.4	84
2			140	10	100	10: 1: 0.6	81
3			110*	10	83	6.5: 1: 0	63
4			110*	10	81	5.7: 1: 0	61
5			140	10	100	10.5: 1: 0.3	74
6			140	20	80	2.8: 1: 0	54
7			140	20	nd	10.4: 1: 0.4	45
8			140	20	72	6.7: 1: 0	52
9			140	20	nd	9.9: 1: 0	42

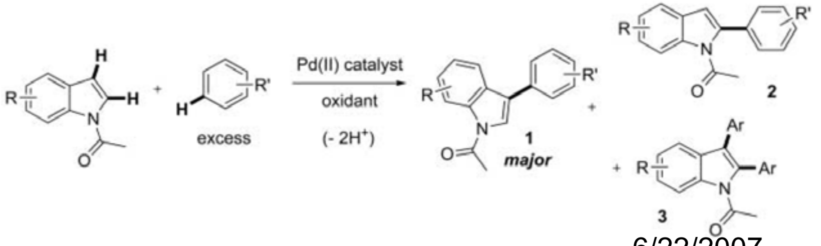
-Reaction completely selective for cross-coupling.

-Indoles with donating groups couple in superior fashion.

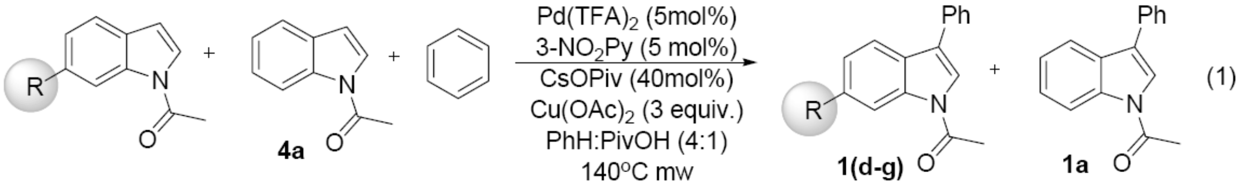
-No clear trend for benzene component.

-TON is ~ 33.

-Too little data for mechanistic proposal, according to authors.

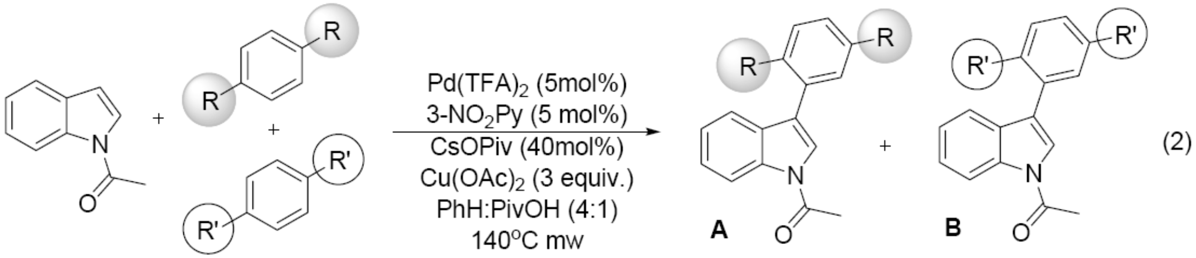


Competition Experiments



Entry	R-Group	1(d-g):1a (GCMS)
1	Me	1.6:1
2	OMe	1.8:1
3	Cl	1:1.4
4	CO_2Me	1:>99

-Note trend for indole substitution.



Entry	R-Group	R'-Group	A:B (GCMS)	Conversion /%
1	Me	OMe	1:2.2	54
2	Me	F	1:1.3	59
3	OMe	F	1.3:1	48
4	H	Me	2.9:1	78
5	H	F	2.2:1	57
6	H	OMe	2.6:1	60

-Note lack of trend for benzene substitution.

The Bottom Line

-A catalytic cross-coupling of two different unactivated arenes has been achieved.

-Complete selectivity for cross-coupling was observed.

-Continued development can improve rate and stoichiometry of reaction.