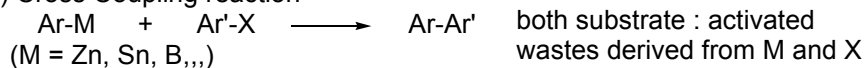
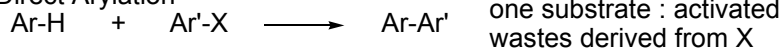


# Transition Metal Catalyzed Intermolecular Formations of Ar-Ar Bond : post-Cross Coupling

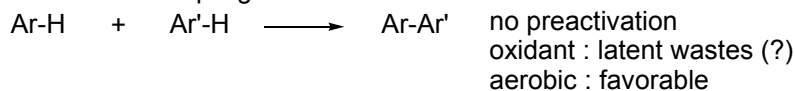
i) Cross Coupling reaction



ii) Direct Arylation



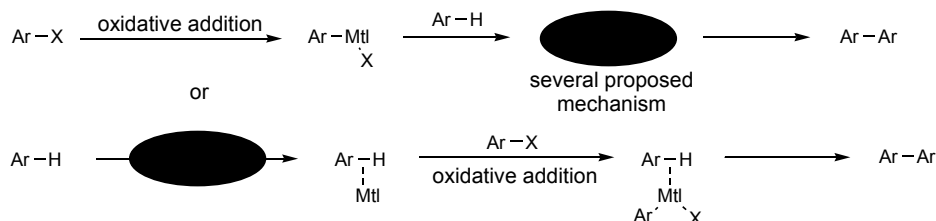
iii) Oxidative Ar coupling



Today's Topics

1. Direct Arylation via C-H activation -overview-
2. Heteroarene Direct Arylation
3. Arene Direct Arylation
4. Other Approaches
5. Catalytic Oxidative Coupling of Ar-H

## 1. Direct Arylation via C-H Activation -overview-



General Conditions

# Metal : second-row transition metals in low oxidation states(Rh, Ru, Pd,,)

# Ligand : depend on Ar-X and system

for Ar-I,Br :  $\text{PhP}_3$  etc

for Ar-Br,Cl : electron rich and bulky trialkylphosphine, Buchwald's ligand, NHC etc  
ligand-free conditions is also reported

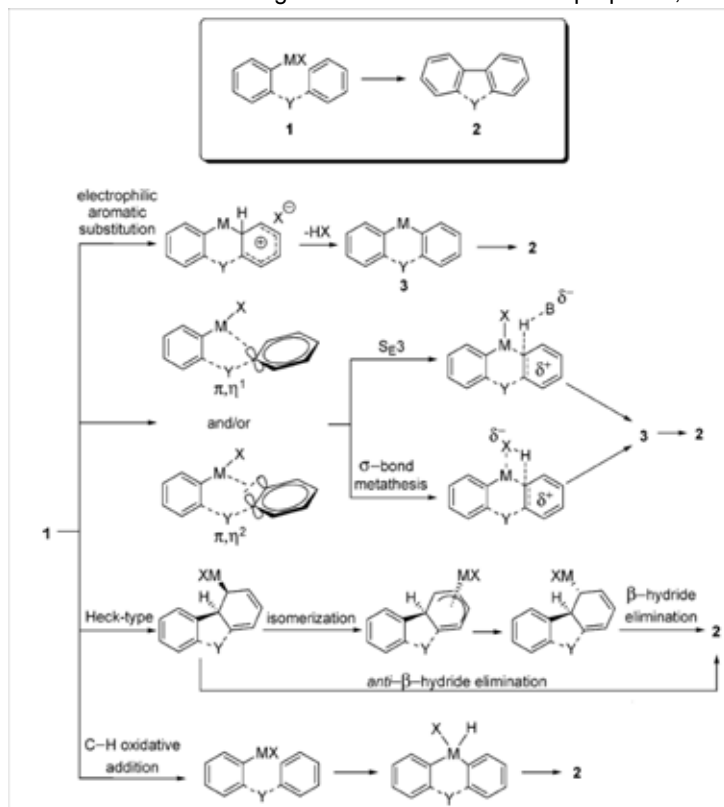
# Base : most cases inorganic bases such as  $\text{K}_2\text{CO}_3$ ,  $\text{Cs}_2\text{CO}_3$ , KOAc, tBuOK, CsOPiv,,,

# Solvent : polar, aprotic solvents such as DMF, DMA,  $\text{CH}_3\text{CN}$ , NMP, DMSO,,,

# temp. : > 100 C

# mechanism

Although several mechanisms are proposed, exact ones depend on substrate, cat. system and so on.

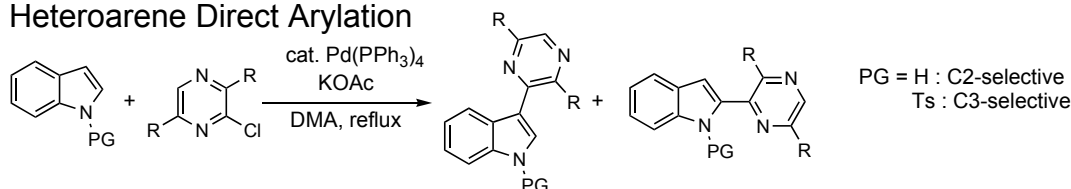


most supported

few support

limited case

## 2. Heteroarene Direct Arylation



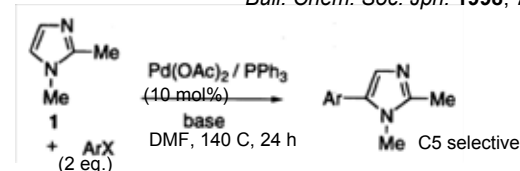
Ohta, A. et al. *Heterocycles* **1985**, *23*, 2327.  
*Chem. Pharm. Bull.* **1989**, *37*, 1477.

### Palladium-Catalyzed Arylation of Azole Compounds with Aryl Halides in the Presence of Alkali Metal Carbonates and the Use of Copper Iodide in the Reaction

Sommai Pivsa-Art, Tetsuya Satoh, Yoshiaki Kawamura, Masahiro Miura,\* and Masakatsu Nomura

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565

*Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.



Entry	Halide	Base	Yield of 3a <sup>b</sup> /%
1	2a	Na <sub>2</sub> CO <sub>3</sub>	23
2	2a	K <sub>2</sub> CO <sub>3</sub>	59
3	2a	Cs <sub>2</sub> CO <sub>3</sub>	83
4	2a	N(n-Bu) <sub>3</sub>	0
5 <sup>c</sup>	2a	Cs <sub>2</sub> CO <sub>3</sub>	72
6	2a'	Na <sub>2</sub> CO <sub>3</sub>	41
7	2a'	K <sub>2</sub> CO <sub>3</sub>	90
8	2a'	Cs <sub>2</sub> CO <sub>3</sub>	83
9 <sup>d</sup>	2a'	K <sub>2</sub> CO <sub>3</sub>	84
10 <sup>d</sup>	2a	Cs <sub>2</sub> CO <sub>3</sub>	67
11 <sup>d</sup>	2a	Cs <sub>2</sub> CO <sub>3</sub>	73
12 <sup>d</sup>	2a'	K <sub>2</sub> CO <sub>3</sub>	8

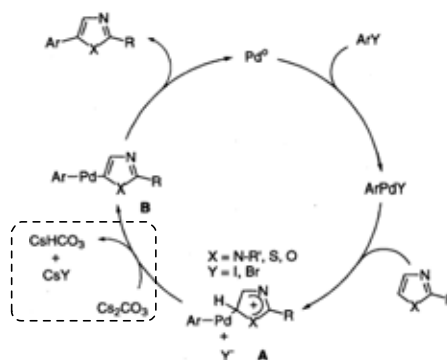
2a = Ph-I  
2a' = Ph-Br

role of base  
solubility of base : Cs<sub>2</sub>CO<sub>3</sub> > K<sub>2</sub>CO<sub>3</sub> > Na<sub>2</sub>CO<sub>3</sub>  
solubility of salt : KI(1.55), KBr(0.065)  
CsBr(0.024), CsI(0.23)

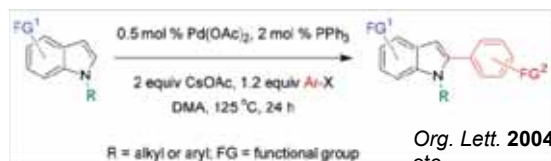
Reactivity order in S<sub>E</sub>Ar is known to C5 > C4 > C2,  
but generally relatively less reactive toward electrophiles.

↓  
activated electrophile is needed

catalytic reaction involves an electrophilic  
attack of the arylhalopalladium(II) species.



Indole produces C2-arylated product, which is "nonelectrophilic" regioselectivity.



*Org. Lett.* **2004**, *6*, 2897.  
etc...

### Direct Palladium-Catalyzed C-2 and C-3 Arylation of Indoles: A Mechanistic Rationale for Regioselectivity

Benjamin S. Lane, Meghann A. Brown, and Dalibor Sames\*

Contribution from the Department of Chemistry, Columbia University, 3000 Broadway, New York, New York 10027

*J. Am. Chem. Soc.* **2005**, *127*, 8050.

# support for S<sub>E</sub>Ar mechanism

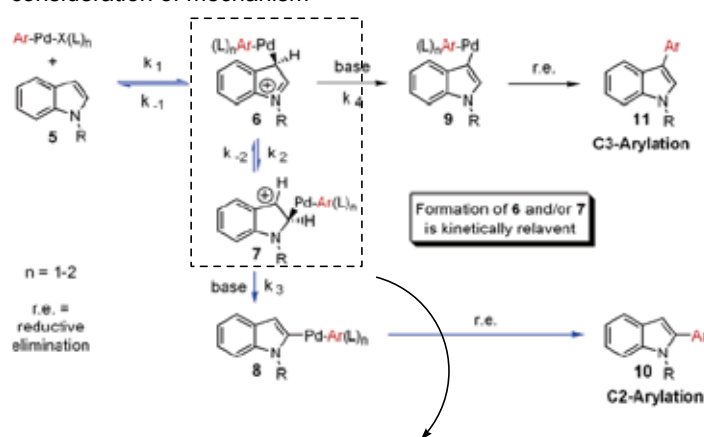
Table 1. C-2 Arylation of (NR)-Indoles (Substitution on Nitrogen)

entry	R	yield % <sup>a</sup>	entry	R	yield % <sup>a</sup>
1	CH <sub>3</sub>	88 (54) <sup>b</sup>	4	Ph	68
2	Bn	81	5	p-(CN)-C <sub>6</sub> H <sub>4</sub>	55
3	Pr	92	6	SO <sub>2</sub> Ph, SO <sub>2</sub> CH <sub>3</sub> , COCH <sub>3</sub>	0

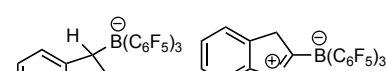
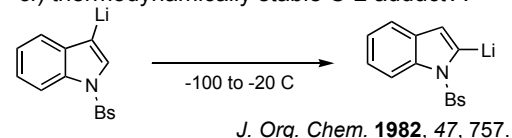
EWG = NR

<sup>a</sup> All values based on isolated yields. <sup>b</sup> Chlorobenzene used as donor and dicyclohexylphenylphosphine as a ligand at 150 °C.

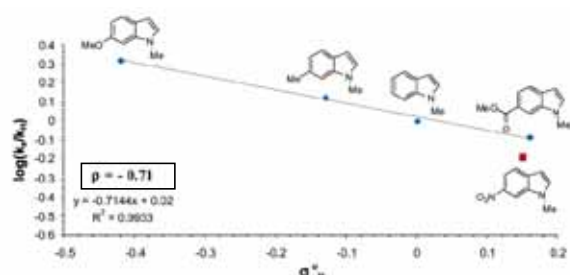
# consideration of mechanism



cf) thermodynamically stable C-2 adduct??

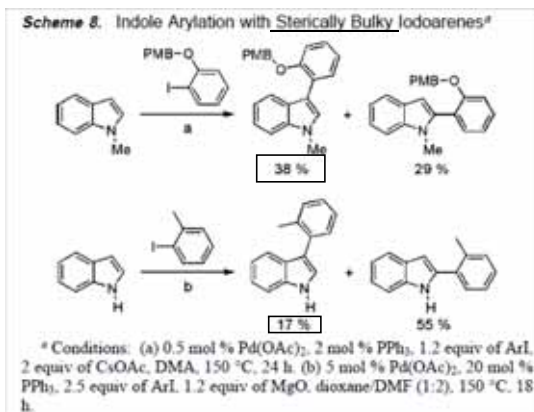


8.4 kcal/mol stable (DFT)  
*Organometallics* **2004**, *23*, 5135.

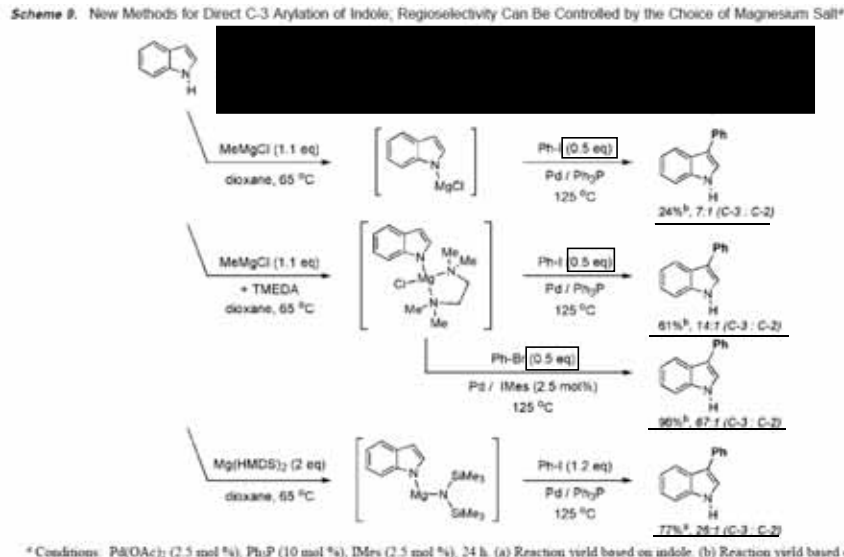
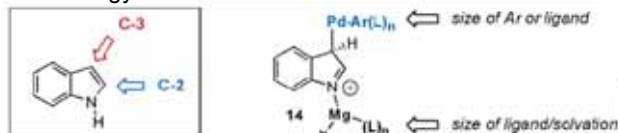


## # chance to C-3 selective reaction (?)

## # realization



## # strategy



## cf) other examples about regiocontrol

**Palladium-Catalyzed Intermolecular Alkenylation of Indoles by Solvent-Controlled Regioselective C–H Functionalization<sup>90</sup>**

Neil P. Grimster, Carolyn Gauntlett, Christopher R. A. Godfrey, and Matthew J. Gaunt<sup>\*</sup>

*Angew. Chem. Int. Ed.* **2005**, *44*, 3125.

Table 1: Optimization studies for indole functionalization.<sup>94</sup>

Entry	Catalyst loading [%]	Oxidant (equiv)	Solvent (v/v)	Yield of 2+3 [%] <sup>[a]</sup>	3a/2a
1	10	Cu(OAc) <sub>2</sub> (1.8)	DMF	54	>95:5
2	10	Cu(OAc) <sub>2</sub> (1.8)	DMSO	66	>95:5
3	10	Cu(OAc) <sub>2</sub> (1.8)	1,4-dioxane	n.r.	–
4	10	tBuOOBz (0.9)	1,4-dioxane	48	1:2
5	10	Cu(OAc) <sub>2</sub> (1.8)	DMF/AcOH (3:1)	54	1:1
6	20	tBuOOBz (0.9)	1,4-dioxane/AcOH (3:1)	58	1:7
7	10	Cu(OAc) <sub>2</sub> (1.8)	DMF/DMSO (10:1)	79	>95:5
8	10	tBuOOBz (0.9)	MeCN/AcOH (1:1)	65	>95:5
9	10	tBuOOBz (0.9)	1,4-dioxane/AcOH/DMSO (3:1:0.4)	66	>95:5

[a] For all reactions the mixture (0.4 M) was stirred for 18 h. [b] Yields after isolation and purification by flash silica-gel chromatography. n.r. = no reaction. Bz = benzoyl, DMF = *N,N*-dimethylformamide, DMSO = dimethyl sulfoxide.

**Mild Aerobic Oxidative Palladium (II) Catalyzed C–H Bond Functionalization: Regioselective and Switchable C–H Alkenylation and Annulation of Pyrroles**

Elizabeth M. Beck, Neil P. Grimster, Richard Hatley,<sup>†</sup> and Matthew J. Gaunt<sup>\*</sup>

*Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom*

*J. Am. Chem. Soc.* **2006**, *128*, 2528.

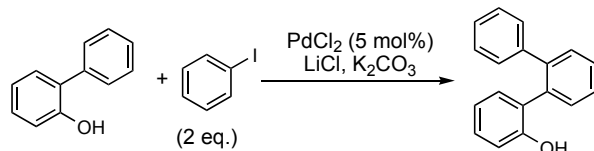
Table 1. Effect of *N*-Protecting Group on Pyrrole C–H Alkenylation

entry	catalyst loading (%)	R	yield of C2	yield of C3	ratio 2:3
1	10	Bn	48	23	2.1:1
2	10	SEM	48	21	2.3:1
3	10	Ac	65	–	>95:5
4	10	Bloc	73	–	>95:5
5	10	Ts	70	–	>95:5
6	10	TIPS	–	78	<5:95

## 3. Arene Direct Arylation

arene : lower electron density than heteroarene (lower reactivity as to S<sub>E</sub>Ar)

In order to overcome this problem, use of directing group is major strategy. (many reports)



Miura, M. et al. *Chem. Lett.* **1996**, 823.

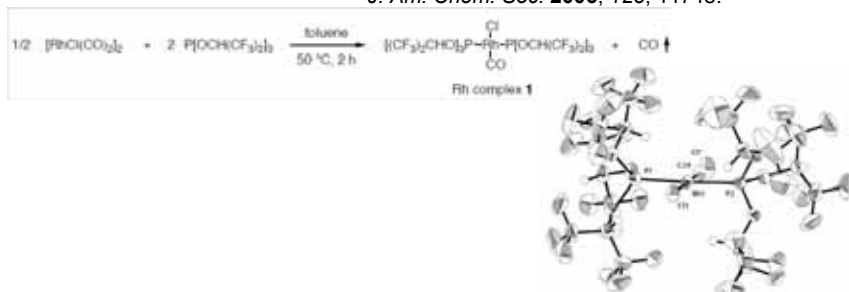
other directing groups are amide, ketone, imine, pyridine, quinoline,...

**Direct C–H Arylation of (Hetero)arenes with Aryl Iodides via Rhodium Catalysis**

Shuichi Yanagisawa,<sup>†</sup> Tomoko Sudo,<sup>†</sup> Ryoji Noyori,<sup>†</sup> and Kenichiro Itami<sup>1,2</sup>

*Department of Chemistry and Research Center for Materials Science, Nagoya University, Nagoya 464-8602, Japan, and PRESTO, Japan Science and Technology Agency (JST), Japan*

*J. Am. Chem. Soc.* **2006**, *128*, 11748.



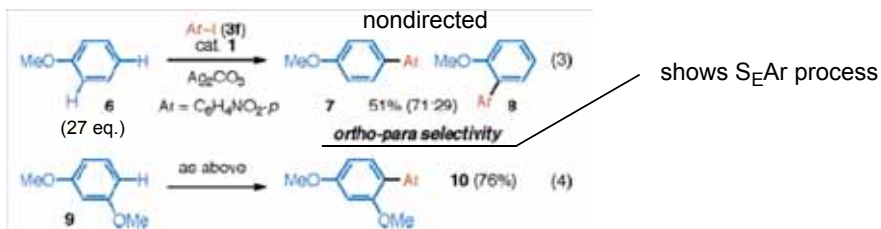
## # ligand screening

Table 2. Effect of Ligand in Rh-Catalyzed C–H Arylation

ligand (L)	yield of 4ab (%)	$\nu_{\text{Rh-CO}}$ RhCl(CO) <sub>2</sub> (cm <sup>-1</sup> )
P[OCH(CF <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	94	2070
P(C <sub>6</sub> H <sub>5</sub> )[OCH(CF <sub>3</sub> ) <sub>2</sub> ] <sub>2</sub>	31	2038
P(OC <sub>2</sub> H <sub>5</sub> ) <sub>3</sub>	6	2018
P[OCH(CH <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	9	2002
P(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub>	0	1983

bulky and strongly pi-accepting ligand is effective

## # nondirected direct arylation of simple arene



new mechanistic insights are appered from intramolecular rxn

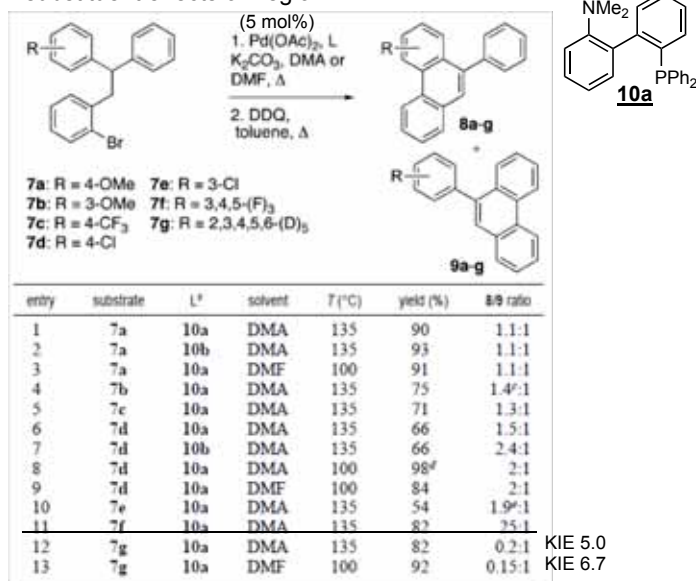
## Proton Abstraction Mechanism for the Palladium-Catalyzed Intramolecular Arylation

Domingo Garcia-Cuadrado, Ataulpa A. C. Braga, Felix Maseras,<sup>\*,†</sup> and Antonio M. Echavarren<sup>\*,†</sup>  
 Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain

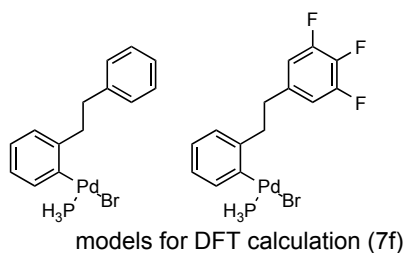
*J. Am. Chem. Soc.* **2006**, *128*, 1066.

*J. Am. Chem. Soc.* **2007**, *129*, 6880.(full)

## # substituent effects on regio

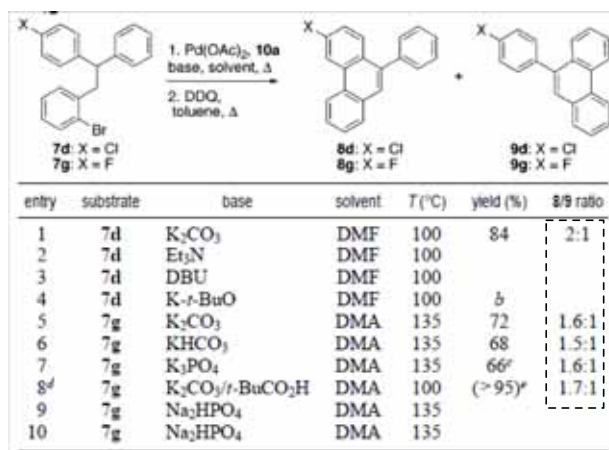


reaction proceeds at electron deficient ring.

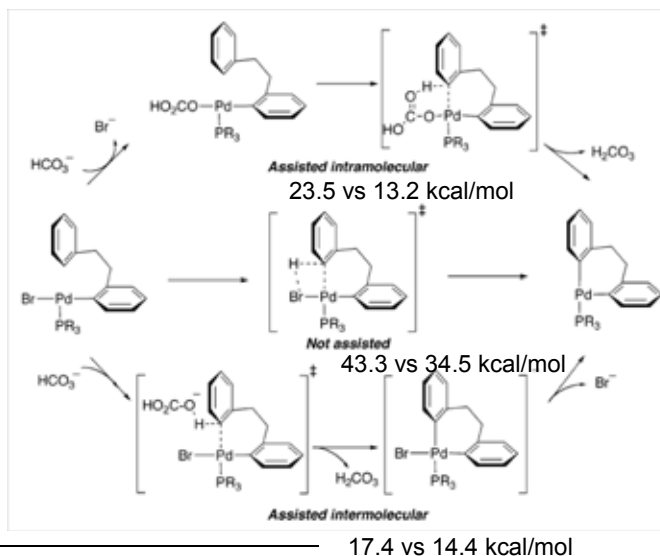


Authors insisted "Assisted intermolecular pass" is suited.  
 3.0 kcal/mol = 40:1 at 135 C (25:1, experimental)

## # base effect



base has little role on selectivity.

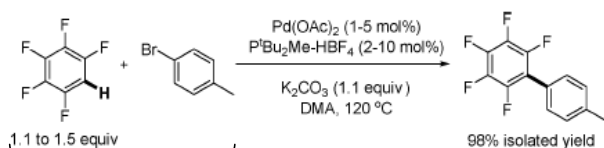


## Catalytic Intermolecular Direct Arylation of Perfluorobenzenes

Marc Lafrance, Christopher N. Rowley, Tom K. Woo, and Keith Fagnou<sup>\*</sup>

Center for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

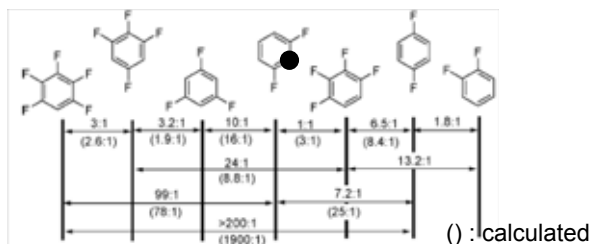
*J. Am. Chem. Soc.* **2006**, *128*, 8754.



broad substrate scope

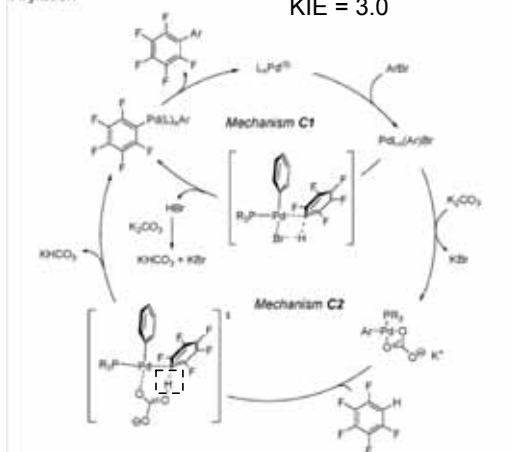
Even gives product in 8%.

chance to cat. modification!?



Reactivity parallels relative acidities.  
 more electron deficient, higher reactivity

Scheme 1. Proposed Catalytic Cycle of Perfluorobenzene Direct Arylation<sup>a</sup>



<sup>a</sup> For the C-H bond cleavage step, two possible mechanisms (C1, C2) are depicted involving concerted metalation of the fluoroarene and H-transfer to either a carbonate ligand or Br ligand on the catalyst.

DFT cal. showed C2 is the lowest reaction barrier.

There is no indication of catalyst-fluorine interactions. : nondirected

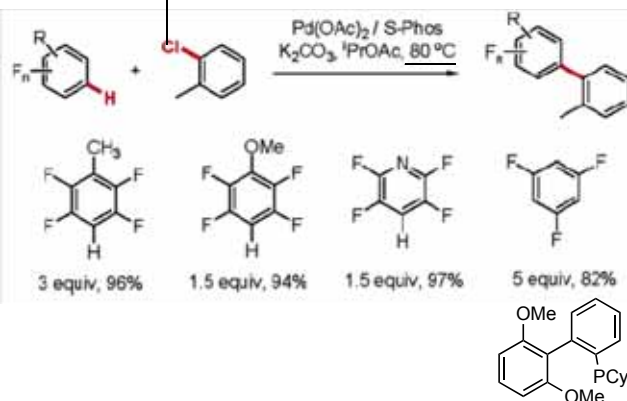
catalyst modification for neutral arenes

## Mild and General Conditions for the Cross-Coupling of Aryl Halides with Pentafluorobenzene and Other Perfluoroaromatics

Marc Lafrance, Daniel Shore, and Keith Fagnou<sup>a</sup>

<sup>a</sup> Center for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Canada K1N 6N5

*Org. Lett.* **2006**, *8*, 5097.

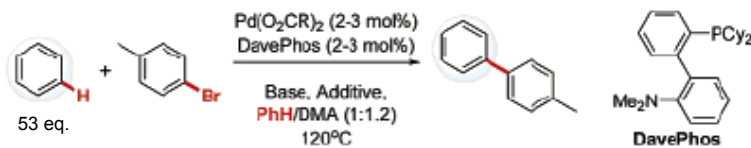


## Palladium-Catalyzed Benzene Arylation: Incorporation of Catalytic Pivalic Acid as a Proton Shuttle and a Key Element in Catalyst Design

Marc Lafrance and Keith Fagnou<sup>a</sup>

<sup>a</sup> Center for Catalysis Research and Innovation, University of Ottawa, Department of Chemistry, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

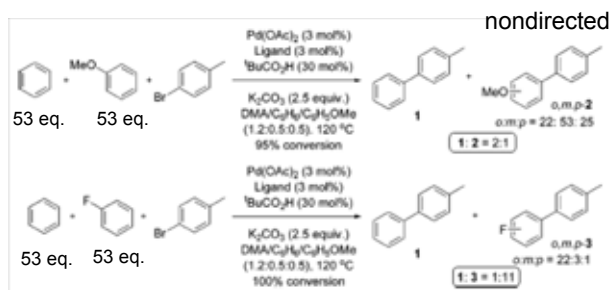
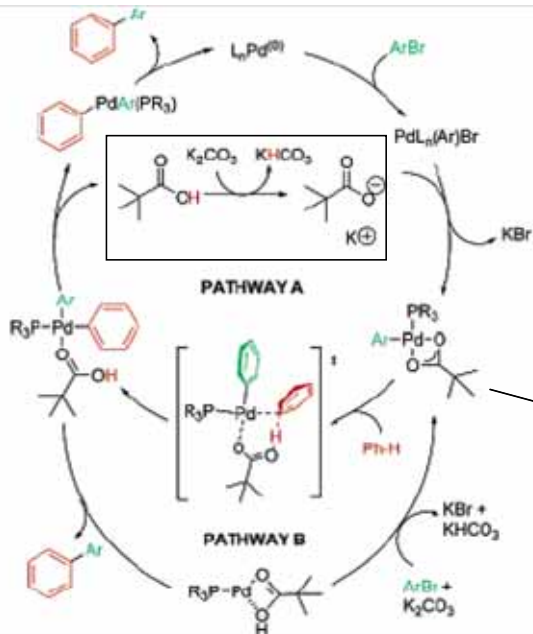
*J. Am. Chem. Soc.* **2006**, *128*, 16496.



Entry	Pd Source	Base	Additive	Conversion <sup>b</sup>	Yield <sup>b</sup>
1	Pd(OAc) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	none	<5	0
2	Pd(OPiv) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	none	13	10
3	Pd(OAc) <sub>2</sub>	AcOK	none	21	8
4	Pd(OAc) <sub>2</sub>	PivOK	none	65	41
5	Pd(OAc) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	AcOH (30 mol%)	20	11
6	Pd(OAc) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	EtCO <sub>2</sub> H (30 mol%)	14	6
7	Pd(OAc) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	<sup>t</sup> PrCO <sub>2</sub> H (30 mol%)	32	13
8	Pd(OAc) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	<sup>t</sup> BuCO <sub>2</sub> H (30 mol%)	100	82
9	Pd(OAc) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	1-AdCO <sub>2</sub> H (30 mol%)	60	36

with hydrodebromination and homocoupling

too bulky



reactivity compatible to proton-abstraction pathway

A pivalate anion results in a decrease in transition state energy of 1.3 kcal/mol compared to a bicarbonate anion. (DFT)

## 4. Other Approaches

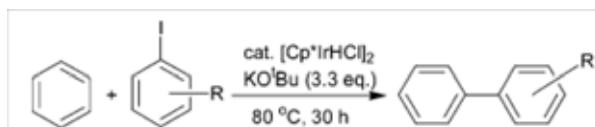
### Direct arylation of aromatic C–H bonds catalyzed by Cp\*Ir complexes†

Ken-ichi Fujita,<sup>a,b</sup> Mitsuru Nonogawa<sup>a</sup> and Ryohel Yamaguchi<sup>a\*</sup>

<sup>a</sup> Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan.  
E-mail: fujitaki@kugaku.mbox.media.kyoto-u.ac.jp; Fax: +81-75-753-6634; Tel: +81-75-753-6527

<sup>b</sup> Graduate School of Global Environmental Studies, Kyoto University, Kyoto 606-8501, Japan

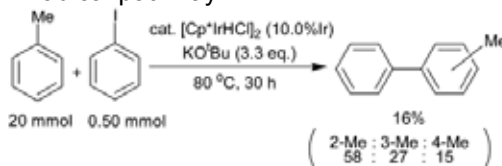
Chem. Commun. 2004, 1926.



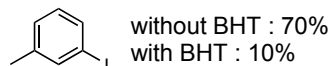
\* The reaction was carried out with aryl iodides (0.50 mmol), [Cp\*IrHCl]<sub>2</sub> (5.0 or 10% Ir), and KO<sup>t</sup>Bu (1.65 mmol) in benzene (20 mmol) at 80 °C for 30 h. <sup>b</sup> Determined by GC. The values in parentheses are isolated yields.

R = 4-NH<sub>2</sub>, 4-NO<sub>2</sub>, 4-CF<sub>3</sub> : noTM  
R = Me, OMe, 1-Napht  
yield : 20-70%

# radical pathway ?



reported ratio involved in Ph radical : 54/26/20

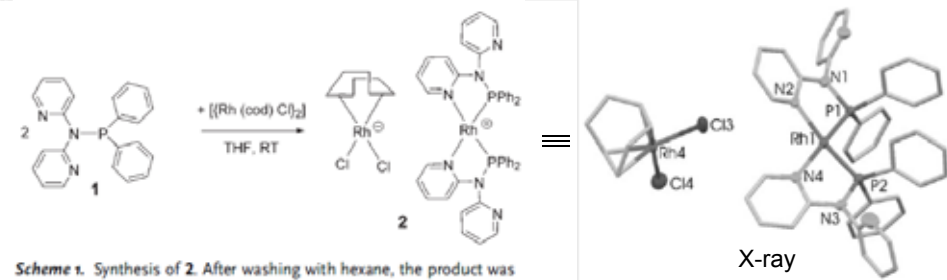


CP\*Ir(III) → CP\*Ir(II) → aryl iodide radical → aryl radical

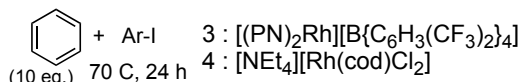
### An Efficient Bimetallic Rhodium Catalyst for the Direct Arylation of Unactivated Arenes<sup>†\*</sup>

Sebastian Proch and Rheit Kempe<sup>a\*</sup>

Angew. Chem. Int. Ed. 2007, 46, 3135.



Scheme 1. Synthesis of 2. After washing with hexane, the product was isolated in 98% yield.



Product	TONs (yield)	3 <sup>[a]</sup>	4 <sup>[b]</sup>
	780 (78)	0	0
	45 (45)	0	0
	30 (31)	0	0
	40 (40)	0	0
	32 (32)	0	0
	13 (13)	0	0

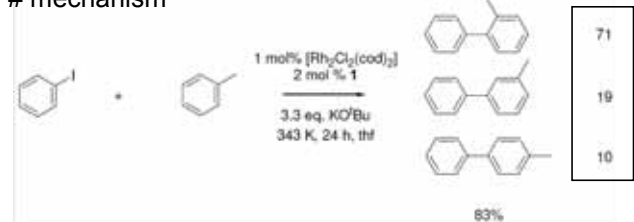
bimetallic Rh : essential

Table 2: Nondirected direct arylation of benzene by aryl bromides and chlorides.<sup>[a]</sup>

Aryl halide	Product	Yield [%]	
		X = Br <sup>[a]</sup>	X = Cl <sup>[a]</sup>
		65	46
		96	73
		87	61
		83	70
		83	59

[a] 70 °C, 24 h. Compound 2 was generated in situ from [Rh(cod)Cl]<sub>2</sub> and 1.<sup>[b]</sup> [b] 5 mol% 2. [c] 10 mol% 2.

# mechanism

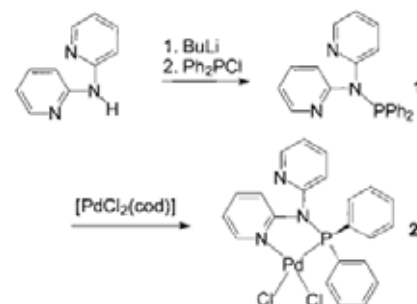


matched??

reported ratio involved in Ph radical : 54/26/20

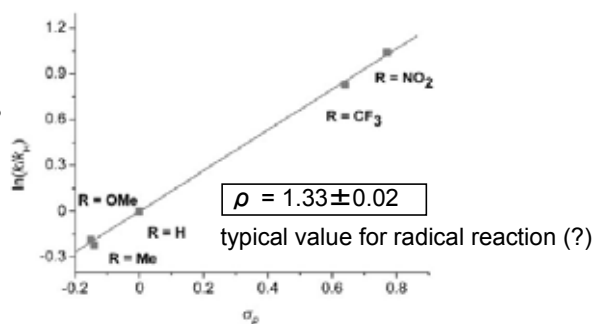
Authors insisted reaction proceeded via radical intermediates.

cf) effective catalyst for Suzuki-coupling of Ar-Cl



Scheme 1. Synthesis of 1 and 2.

Angew. Chem. Int. Ed. 2002, 41, 1521.

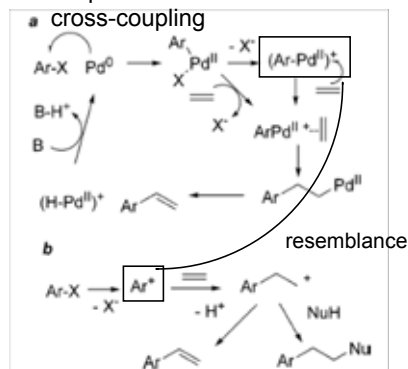


## Metal-Free Synthesis of Sterically Crowded Biphenyls by Direct Ar-H Substitution in Alkyl Benzenes<sup>\*,†</sup>

Valentina Dichiarante, Maurizio Fagnoni,<sup>\*</sup> and Angelo Albini

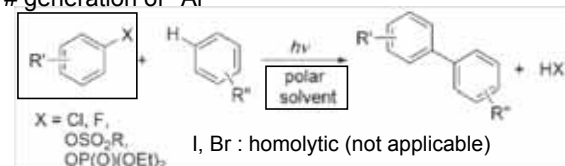
Angew. Chem. Int. Ed. 2007, 46, 6495.

# concept

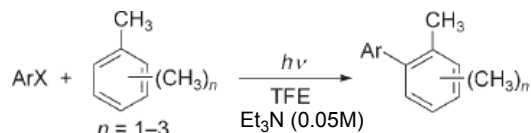


if Ar<sup>+</sup> is obtained directly from ArX,...

# generation of <sup>3</sup>Ar<sup>+</sup>



Ar-X with EDG in polar solvent gives triplet Ar cation under *hν*.  
polar solvent : stabilize ionic components



Entry	Alkyl benzene [1 M]	Aryl halide or ester (0.05 M)	<i>t<sub>r</sub></i> [h]	Product	Yield [%]
1	20 eq.	1a	7	12	76
2		1b	7	13	52
3		2	7	14	56
4 <sup>†</sup>		3a	7	15	77

5	4	8	15	70
6 <sup>†</sup>	5	7	16	71
7 <sup>†</sup>	3b	7	17	77 <sup>†</sup>
8	6	5	18	62
9 <sup>†</sup>	7	7	19	84
10 <sup>†</sup>	8	1.5	20	77

Et<sub>3</sub>N : 2eq.  
to prevent de-Si

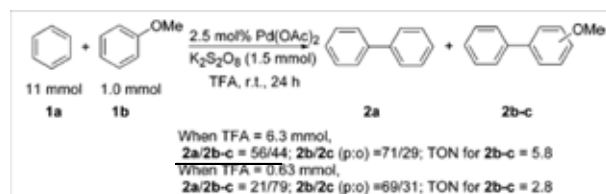
## 5. Catalytic Oxidative Coupling of Ar-H

### Intermolecular Cross-Coupling of Simple Arenes via C-H Activation by Tuning Concentrations of Arenes and TFA

Ruoshi Li, Li Jiang, and Wenjun Lu<sup>\*</sup>

Department of Chemistry, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, People's Republic of China

Organometallics 2006, 25, 5973.



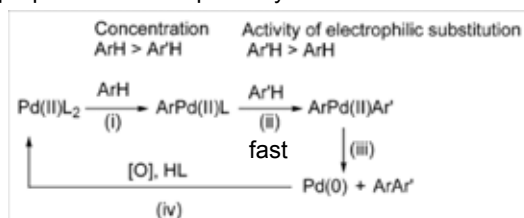
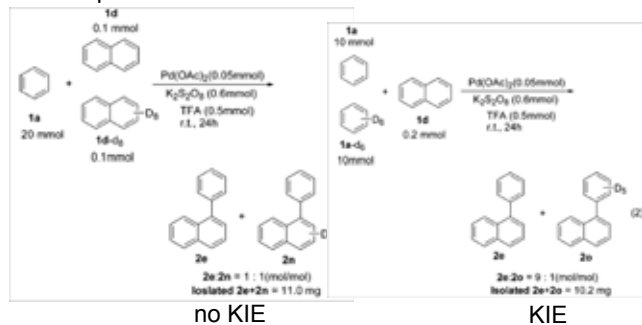
conc. of TFA is important for selectivity

entry	ArH	ArH/1d (mol/mol)	TFA (mmol)	product	yield <sup>b</sup> (%)	selectivity <sup>d</sup> (mol%)	TON
1	1a	25	0.5	2e	15	93 <sup>d</sup>	3.1 <sup>e</sup>
2 <sup>†</sup>	1a	100	1.3	2e	32	>99	3.2
3 <sup>†</sup>	1a	50	2.6	2e	11	55	22.0
4	1e	25	1.0	2f	16	>99	3.3
5	1e	25	2.6	2f	50	77	10.0
6	1c	15	0.5	2g	25	>99	5.0
7 <sup>†</sup>	1c	15	1.0	2g	21	>99	21.0
8	1b	5	0.1	2h-l	15	71 <sup>d</sup>	3.0 <sup>d</sup>
9 <sup>†</sup>	1f	50	1.0	2j-l	16	62 <sup>d</sup>	3.3 <sup>d</sup>

choice of Naphthalene : more electron rich than benzene

S<sub>E</sub>Ar is occurred to alpha-position (??)

to prevent homocoupling : ratio higher about EWG-aromatic (entry9)  
lower about EDG-aromatic (entry8)



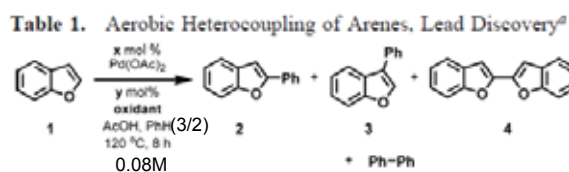
choice of TFA : Pd(OAc)<sub>2</sub> to more reactive Pd(TFA)<sub>2</sub> (??)  
why conc. of TFA is critical??

### C–C Bond Formation via Double C–H Functionalization: Aerobic Oxidative Coupling as a Method for Synthesizing Heterocoupled Biaryls

Timothy A. Dwight, Nicholas R. Rue, Dagmara Charyk, Ryan Josselyn, and Brenton DeBoer\*

Department of Chemistry, University of Rhode Island, Kingston, Rhode Island 02881  
bdeboer@chem.uri.edu

Org. Lett. 2007, 9, 3137.



entry	Pd(OAc) <sub>2</sub> (mol %)	oxidant	yield (%) <sup>b</sup>			
			2	3	4	Ph-Ph
1	100	none	73	trace	0	trace
2	25	Cu(OAc) <sub>2</sub> (4 equiv)	44	trace	0	0
3	25	AgOAc (4 equiv)	44	40	0	trace
4	25	PhI(OAc) <sub>2</sub> (2 equiv)	42	trace	0	trace
5	25	benzoquinone (2 equiv)	2	0	0	0
6	25	Cu(OAc) <sub>2</sub> (1 equiv) + O <sub>2</sub> <sup>c</sup> (1 atm)	55	20	0	10
7	25	AgOAc (1 equiv) + O <sub>2</sub> <sup>c</sup> (1 atm)	16	23	0	0
8	10	HPMV (10 mol %) + O <sub>2</sub> <sup>d</sup> (3 atm)	98	0	0	trace

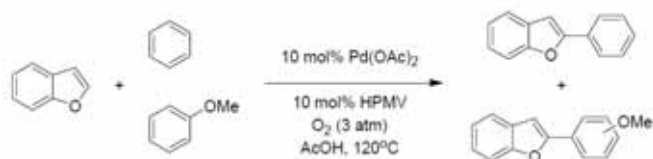
HPMV = H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub>

**Table 2. Examples of Intermolecular Oxidative Coupling**

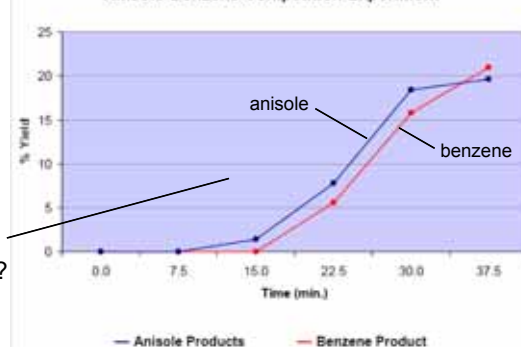
entry	substrates	method <sup>a</sup>	time	yield <sup>b</sup>	product
1		A	1.5	84%	
7		A	2	49%	
8		A	24 min	56%	

EDG seems to promote rxn rapidly (entry8), but things are not so simple...

#### Competition Experiment



**Anisole-Benzene Competition Experiment**

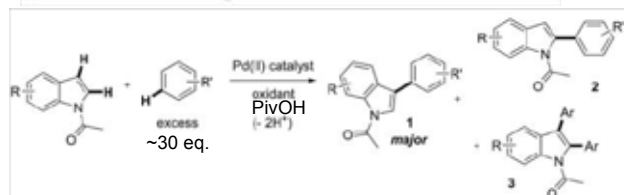


anisole itself involves in catalyst ??

### The Catalytic Cross-Coupling of Unactivated Arenes

David R. Stuart and Keith Fagnou\*

Science. 2007, 316, 1172.



N-H indole : NR  
N-Me indole : dimerization

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) <sub>2</sub>	CsOPiv (40)	Oil bath	110	24	67	27:1:0.3	64
3	0	Cu(OAc) <sub>2</sub>	3-Nitropyridine (10) CsOPiv (40)	Oil bath	110	24	0	nd	0
4	10	Cu(OAc) <sub>2</sub>	3-Nitropyridine (10) CsOPiv (40)	Microwave	140	5	100	8.9:1:0.3	87*
5	5	Cu(OAc) <sub>2</sub>	3-Nitropyridine (5) CsOPiv (40)	Microwave	140	5	92	<u>13.8:1:0.3</u>	84
6	2	Cu(OAc) <sub>2</sub>	3-Nitropyridine (2) CsOPiv (40)	Microwave	140	5	66	<u>27:1:0</u>	63

3-nitropyridien : stabilize Pd(0)  
CsOPiv : not clear



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

generally EDG promote and EWG retard, but entry 2 vs 5 doesn't follow this rule

### Elements of Regiocontrol in Palladium-Catalyzed Oxidative Arene Cross-Coupling

David R. Stuart, Elisia Villemure, and Keith Fagnou\*

Center for Catalysis Research and Innovation, University of Ottawa, Department of Chemistry, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N3

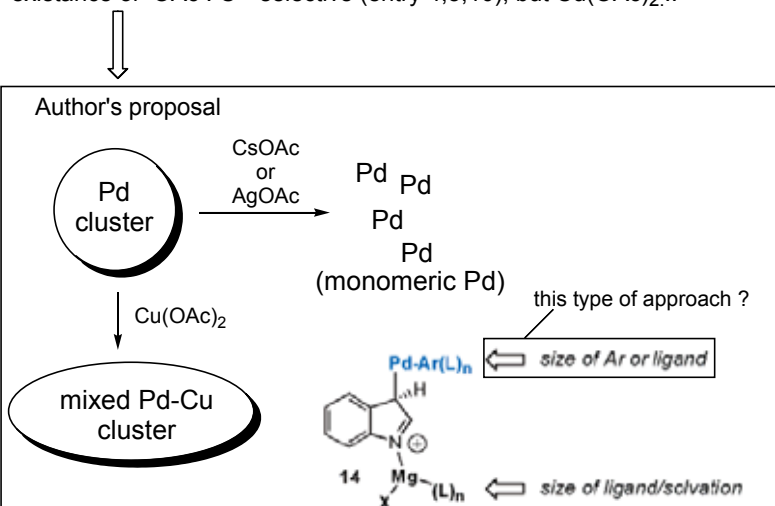
J. Am. Chem. Soc. 2007, 129, 12072.

**Table 1.** Regioselectivity in Oxidative Arene Cross-Coupling<sup>a</sup>

entry	mol % Pd <sup>b</sup>	oxidant (equiv) <sup>c</sup>	additive (mol %) <sup>d</sup>	indole	time (h)	% conv. <sup>e</sup>	2:3:4 <sup>f</sup>
1 <sup>d</sup>	10	Cu(OAc) <sub>2</sub> (3)	3-nitropyridine (10) CsOPiv (40)	1a	5	100	8.9:1:0.26
2	10	AgOAc (2.2)	3-nitropyridine (10) CsOPiv (40)	1a	24	32	1:4:0
3	10	AgOAc (2.2)	3-nitropyridine (10) CsOPiv (40)	1b	24	78	1:8:7:0.3
4	5	AgOAc (3)	none	1b	3	99	1:25:0.7
5	2	AgOAc (3)	none	1b	15	87	1:14:0.4
6	20	none	none	1b	3	18	1:1:1:0
7	50	none	none	1b	3	45	1:3:1:0
8	100	none	none	1b	3	61	3:7:1:0
9	300	none	none	1b	3	100	99:1:0
10	20	none	CsOAc (200)	1b	3	15	1:99:0

<sup>a</sup> Conditions: Pd(TFA)<sub>2</sub> (5 mol %), oxidant, 3-nitropyridine, cesium pivalate, PivOH (6 equiv), and 1a/b were added to a screw-capped vial followed by the addition of benzene (30–60 equiv; see SI) and heating to 110 °C. <sup>b</sup> Relative to 1. <sup>c</sup> Determined by GC/MS. <sup>d</sup> Microwave heating.

in situ metalation of indole to Cu(II) or Ag : denied  
conc. of Pd : high to C-3 selective (entry 6–9)  
existence of OAc : C<sup>2</sup> selective (entry 4, 5, 10), but Cu(OAc)<sub>2</sub>...



**Table 2.** Scope of the Pd-Catalyzed Indole/Benzene Cross-Coupling<sup>a</sup>

Entry	Indole	Arene	Product	Selectivity <sup>b</sup>	Yield (%) <sup>c</sup>	Entry	Indole	Arene	Product	Selectivity <sup>b</sup>	Yield (%) <sup>c</sup>
1				25: 1: 0.7 <sup>d</sup>	84	6				31: 1: trace <sup>d</sup>	86
2				46: 1: 1 <sup>d</sup>	90	7 <sup>e</sup>				31: 1: trace <sup>d</sup>	58
3				31: 1: trace <sup>d</sup>	88	8 <sup>e</sup>				17: 2: 1 <sup>d</sup>	55
4				26: 1: trace <sup>d</sup>	76	9 <sup>e</sup>				30: 1: trace <sup>d</sup>	75
5				31: 1: 1 <sup>d</sup>	88	10 <sup>d</sup>				19: 2: 1 <sup>d</sup>	61

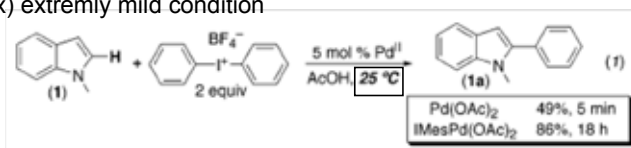
<sup>a</sup> Conditions: Pd(TFA)<sub>2</sub> (5 mol %), AgOAc (3 equiv), PivOH (6 equiv), and the *N*-pivalylindole were added to a screw-capped vial followed by benzene (approximately 60 equiv) and heating to 110 °C. <sup>b</sup> Determined by GC/MS. <sup>c</sup> Isolated yield. <sup>d</sup> Represents the ratio of C2/C3/double arylation. <sup>e</sup> Represents the ratio of the major (isolated) isomer to other minor isomers detected by GC/MS. <sup>f</sup> 10 mol % Pd used. <sup>g</sup> Cu(OAc)<sub>2</sub> used as the oxidant. See SI.

EWG on indole : not big effect on yield (entry 3,6) ⇒ encountering cat. with arene-H is rds ?? (like organometallics 2006)  
Substituent on benzene : significant effect

## 6. Trends and Perspectives

### # Heteroarene of Direct Arylation

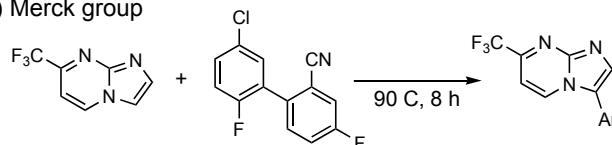
- rxn of many types of heteroaromatic ring almost used up??
  - rxn under milder conditions
- ex) extremely mild condition



M. S. Sanford et al. *J. Am. Chem. Soc.* **2006**, *128*, 4972.

- realization of real alternative synthetic strategy to cross-coupling

ex) Merck group

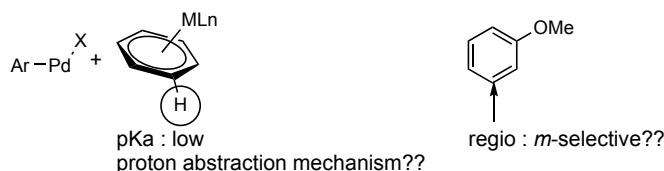


*Org. Proc. Res. Dev.* **2006**, *10*, 398.

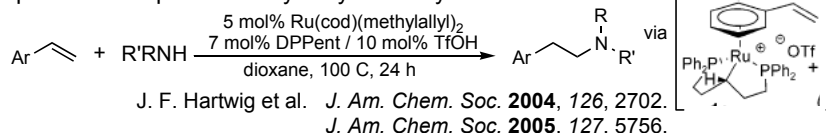
### # Arene of Direct Arylation

- regioselectivity, reactivity problem for nondirected system

妄想: use of pi-arene complex for arenen activation

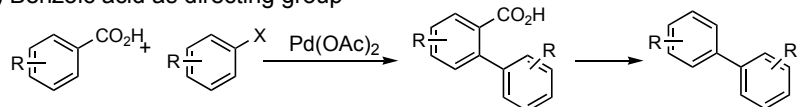


cf) Ru-pi-arene complex in catalytic cycle for hydroamination



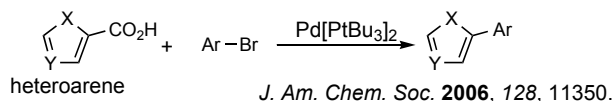
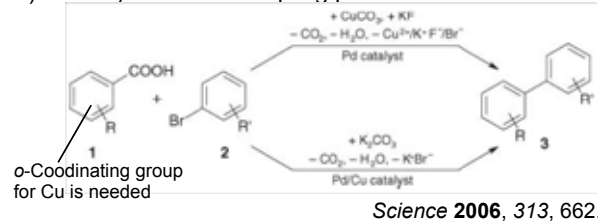
- removable directing group (but need environmentally benign)

ex) Benzoic acid as directing group



*J. Am. Chem. Soc.* **2007**, *129*, 9879.

cf) carboxylic acid as coupling partner



### # Other Approaches

- regioselectivity problem, but maybe difficult to overcome in radicalic or cationic pathway
- reactivity problem

### # Oxidative Coupling

- obtain some information and understand mechanism
- etc...



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