中国科学技术大学
University of Science and Technology of China

Transition-Metal-Catalyzed Coupling Reactions:

Old History, New Reactions & Novel Applications

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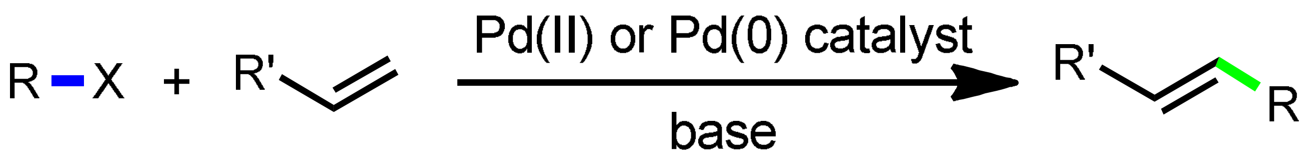
Heck (Mizoroki-Heck) Reaction

The Heck reaction is a cross-coupling reaction of an organohalide with an alkene to make a substituted alkene using palladium as a catalyst and a base.

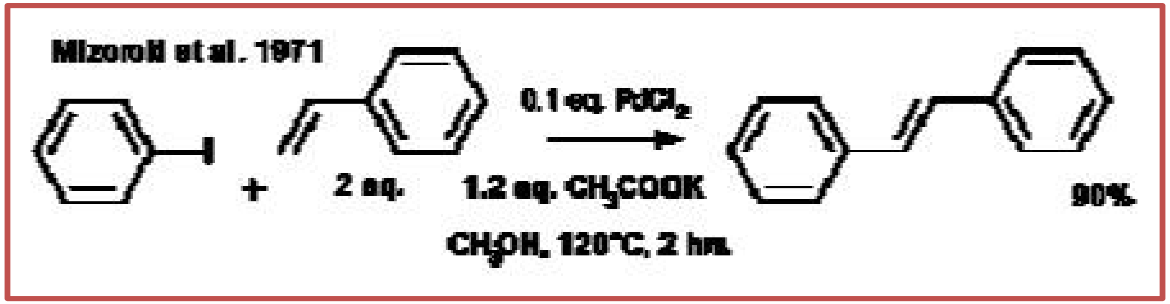
First carbon-carbon bond-forming reaction that followed a Pd(0)/Pd(II) catalytic cycle

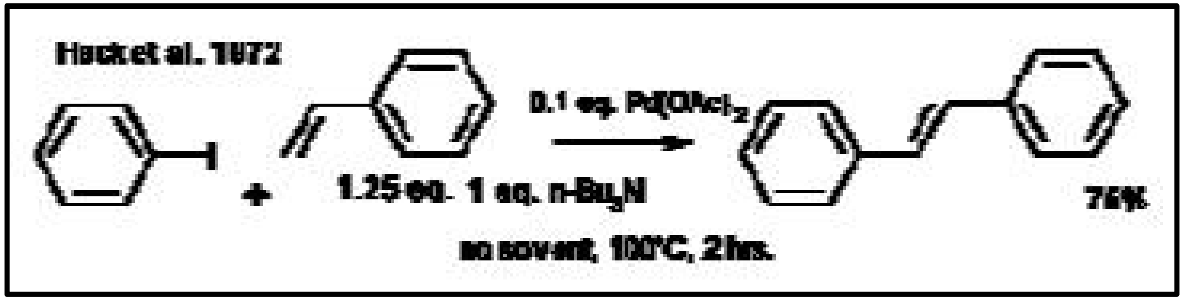


R = alkenyl, aryl, allyl, alkynyl, benzyl
X = halide, triflate
R' = alkyl, alkenyl, aryl, CO_2R, OR, SiR_3

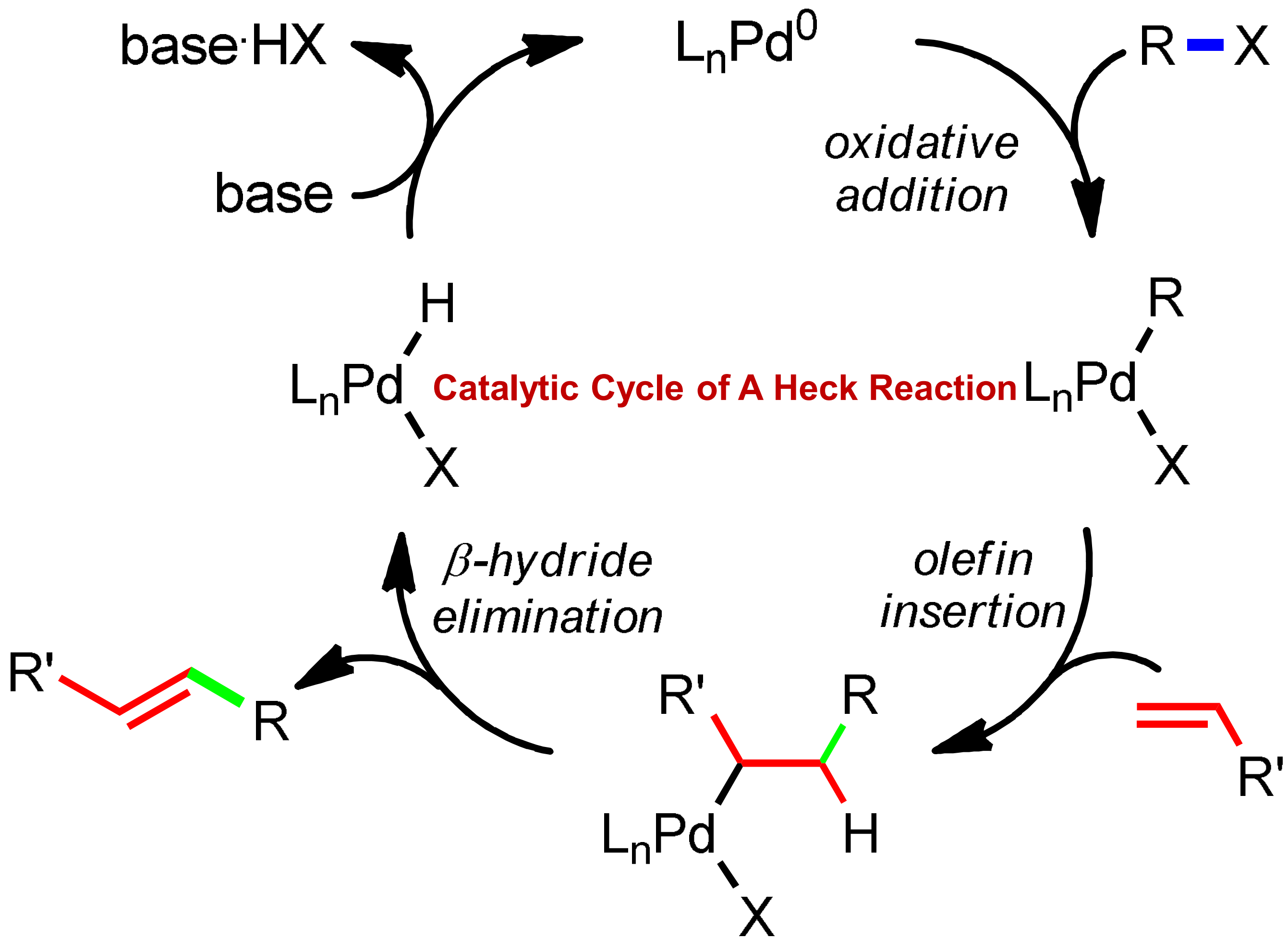
2010 Nobel Prize in Chemistry

Heck (Mizoroki-Heck) Reaction



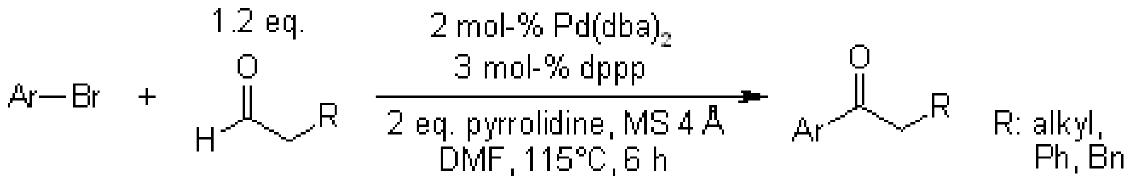


Heck (Mizoroki-Heck) Reaction

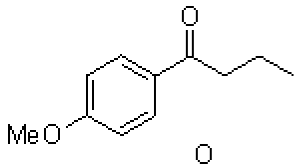
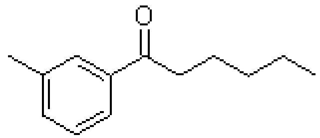
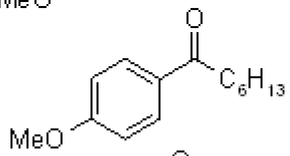
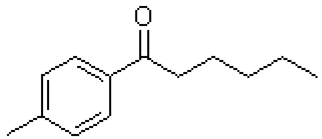
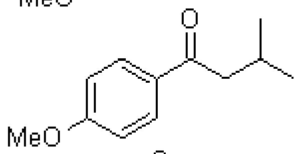
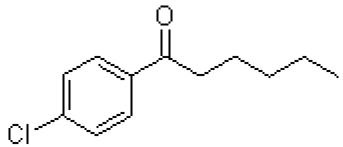
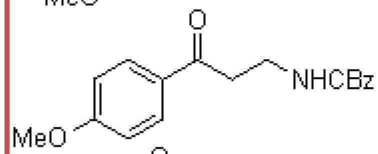
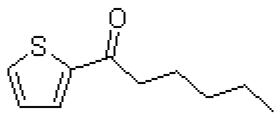
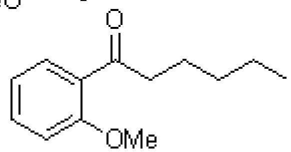
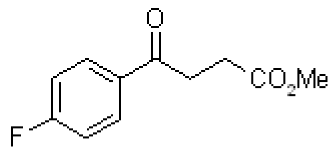


Heck (Mizoroki-Heck) Reaction

Direct Acylation of Aryl Bromides with Aldehydes by Palladium Catalysis

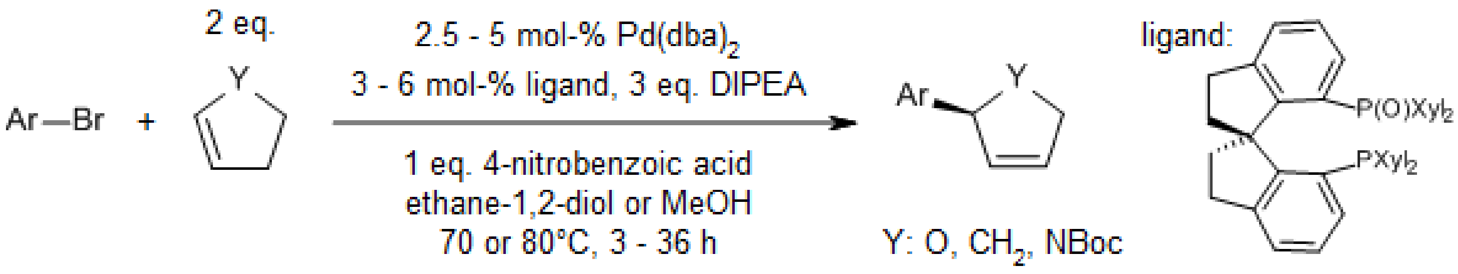


J. Am. Chem. Soc., **2008**, *130*, 10510

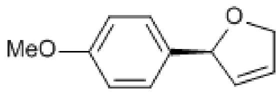
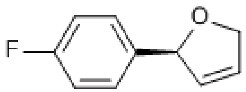
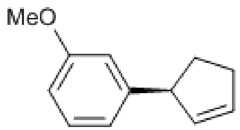
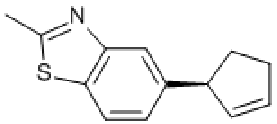
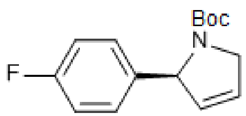
product	yield (%, isol.)	product	yield (%, isol.)
	81		72
	88		90
	75		81
	78		58
	60		78

Heck (Mizoroki-Heck) Reaction

Asymmetric Intermolecular Heck Reaction of Aryl Halides

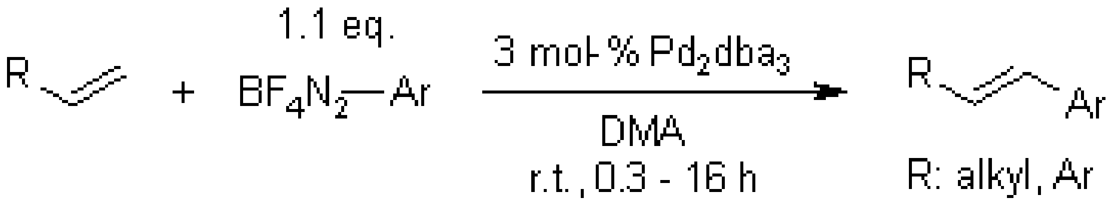


J. Am. Chem. Soc., **2014**, *136*, 650

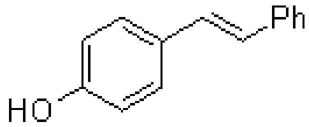
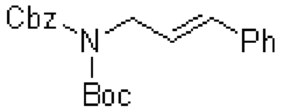
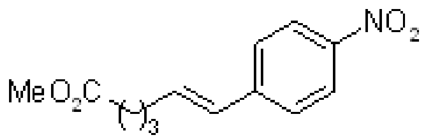
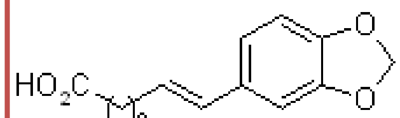
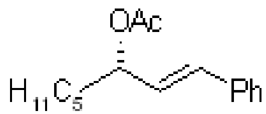
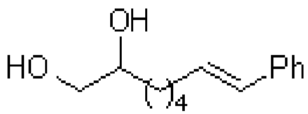
product	solvent	T (°C)	yield (%, isol.)	ee (%)
	ethanediol	80	93	98
	ethanediol	70	82	98
	ethanediol	40	70	88
	MeOH	80	92	87
	MeOH	80	80	88
	ethanediol	70	70	93

Heck (Mizoroki-Heck) Reaction

Operationally Simple and Highly (*E*)-Styrenyl-Selective Heck Reactions of Electronically Nonbiased Olefins

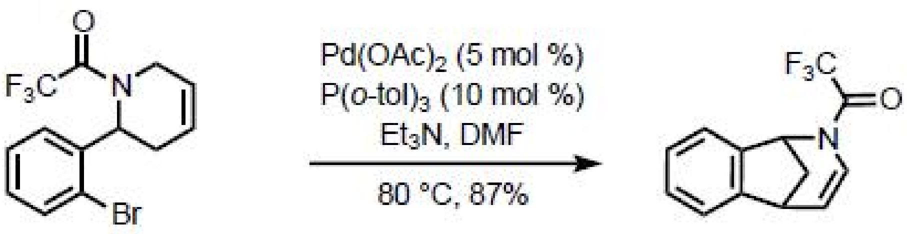


J. Am. Chem. Soc., **2011**, *133*, 9692

product	t (h)	yield (%, isol.)	product	t (h)	yield (%, isol.)
	0.33	89	 (BF_4N_2-Ph as substrate)	1.5	98
	16	96		0.33	97
 *E*:*Z* = 10:1	2	69	 (ee: 98%, no racemization)	16	91
	2	83			

Heck (Mizoroki-Heck) Reaction

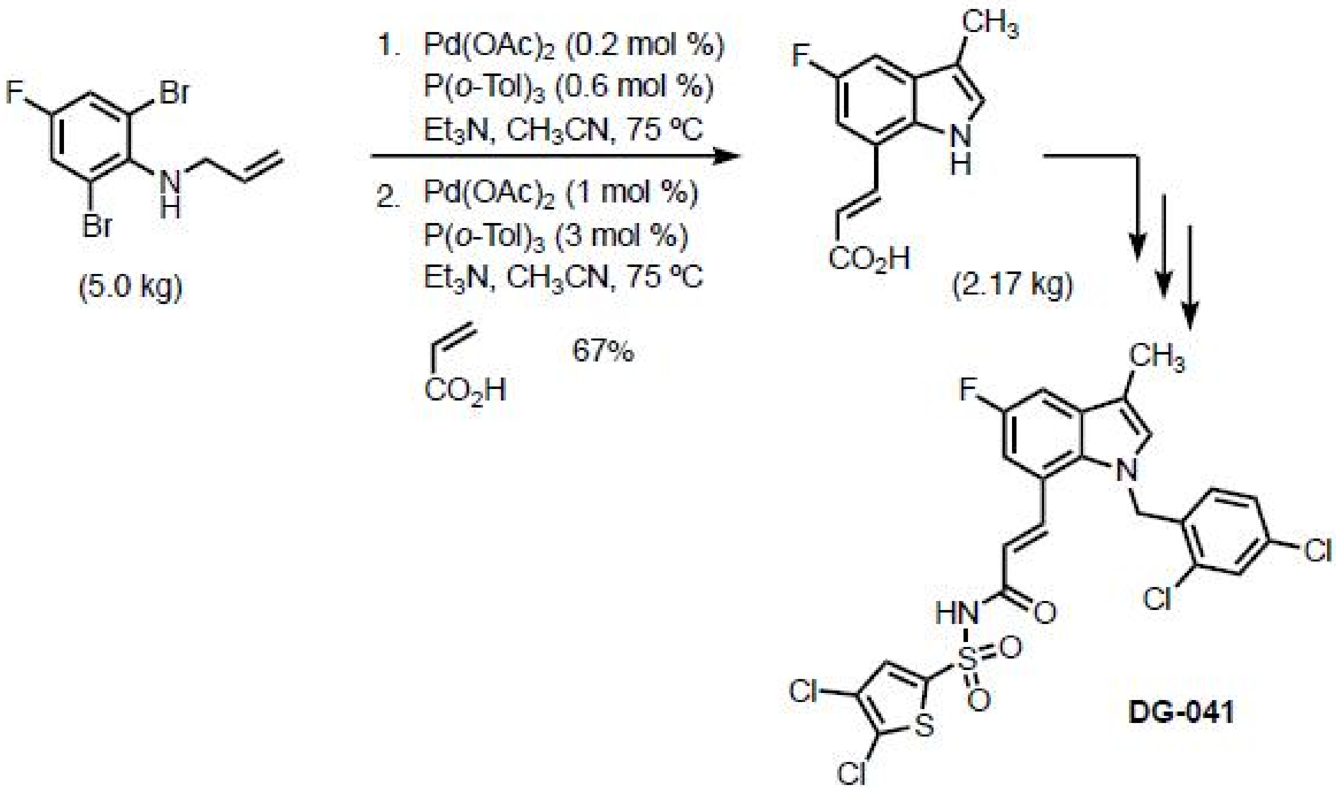
- Application to the synthesis of the anti-smoking drug, Chantix®:



Coe, J. W.; Brooks, P. R.; Vetelino, M. G.; Bashore, C. G.; Bianco, K.; Flick, A. C. *Tetrahedron Lett.* **2011**, *52*, 953–954.

Heck (Mizoroki-Heck) Reaction

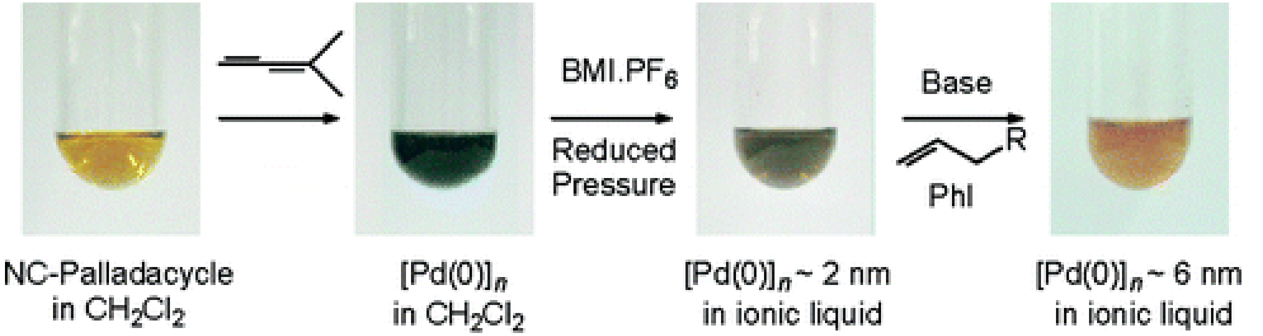
- Synthesis of an EP3 receptor antagonist via a double Heck cyclization reaction:



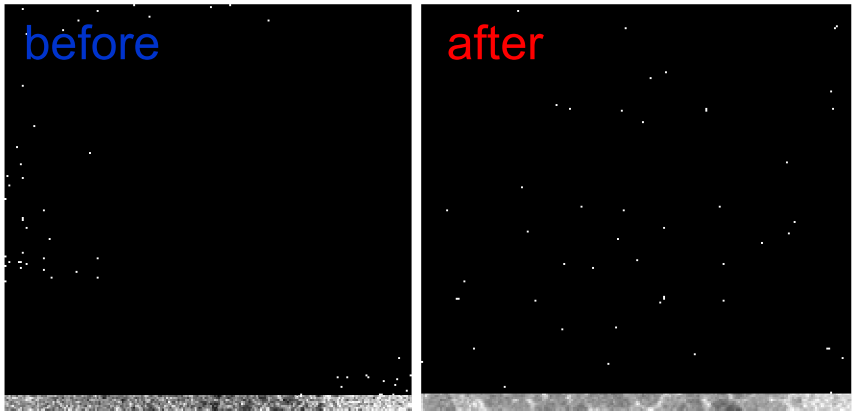
Zegar, S.; Tokar, C.; Enache, L. A.; Rajagopol, V.; Zeller, W.; O'Connell, M.; Singh, J.; Muellner, F. W.; Zembower, D. E. *Org. Proc. Res. Dev.* **2007**, *11*, 747–753.

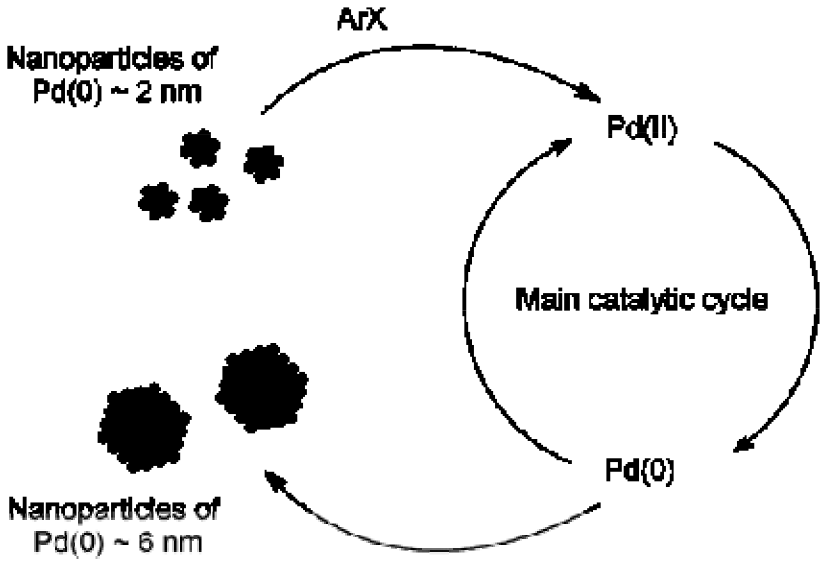
Heck (Mizoroki-Heck) Reaction

The Role of Pd Nanoparticles in Ionic Liquid in the Heck Reaction



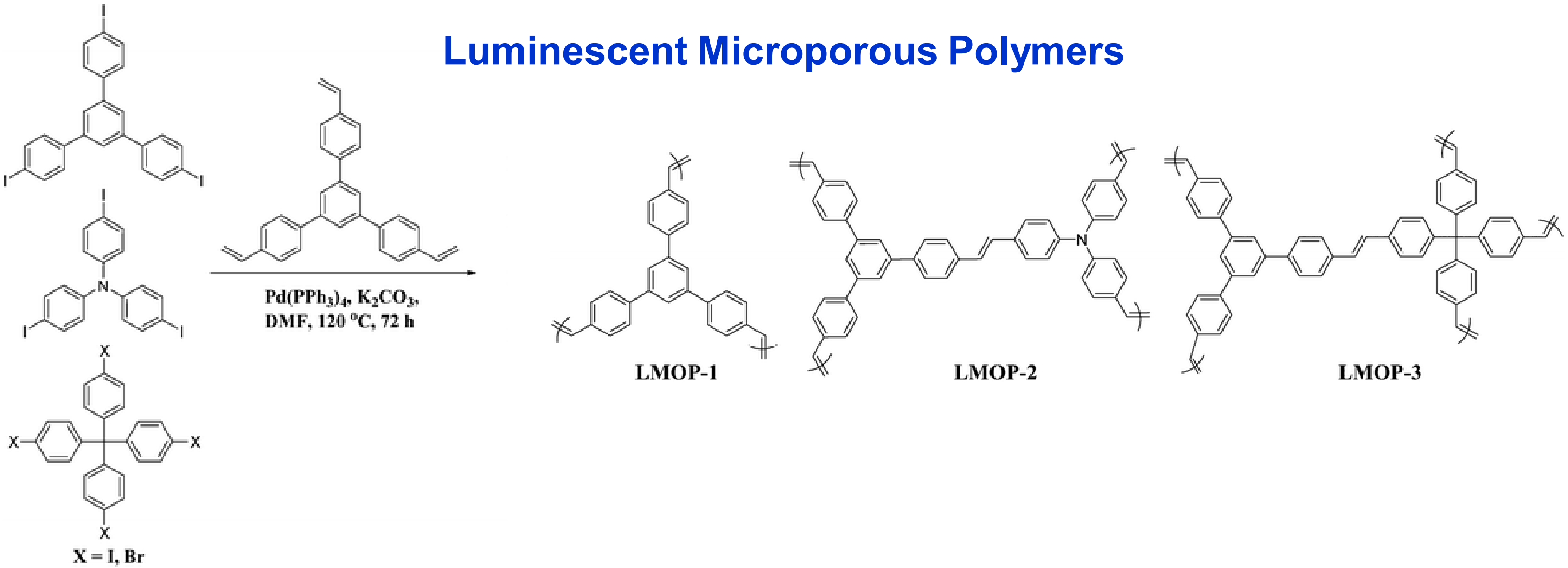
J. Am. Chem. Soc., **2005**, *127*, 3298.

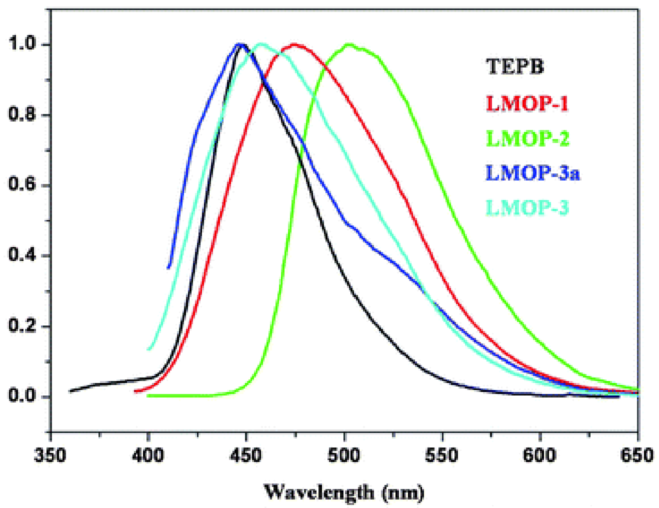


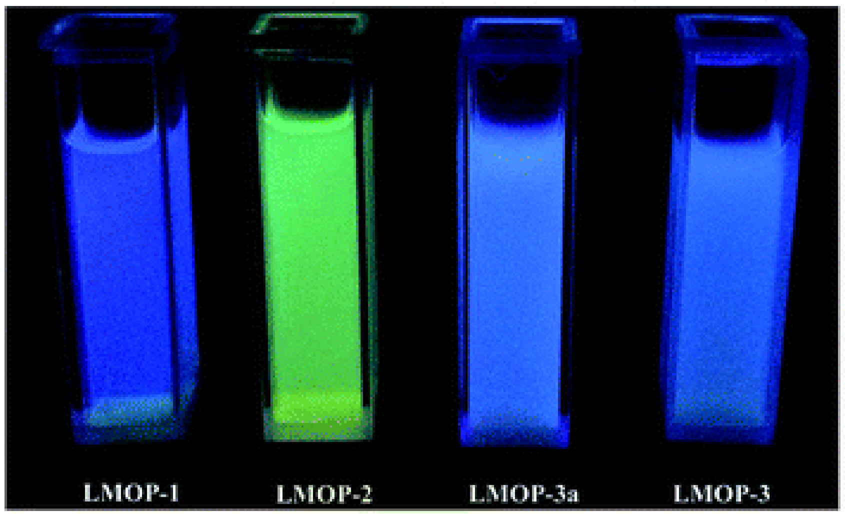


Heck (Mizoroki-Heck) Reaction

Luminescent Microporous Polymers

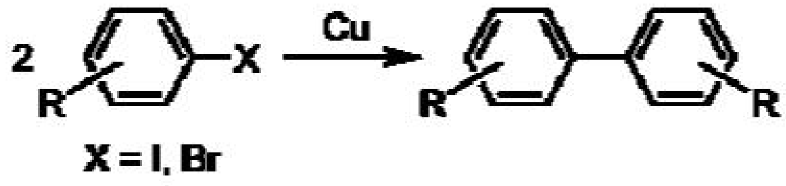






Ullmann Reaction

The Ullmann reaction is an organic reaction used to couple two molecules of aryl halide to form a biaryl using copper metal and thermal conditions. Discovered by Fritz Ullman.

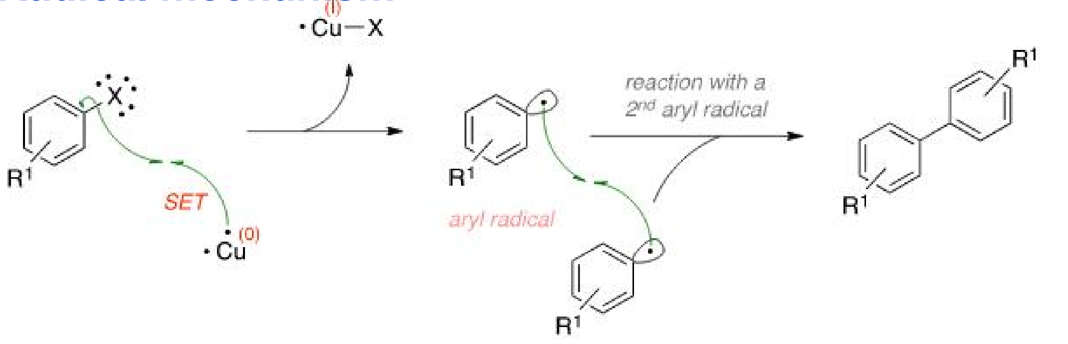


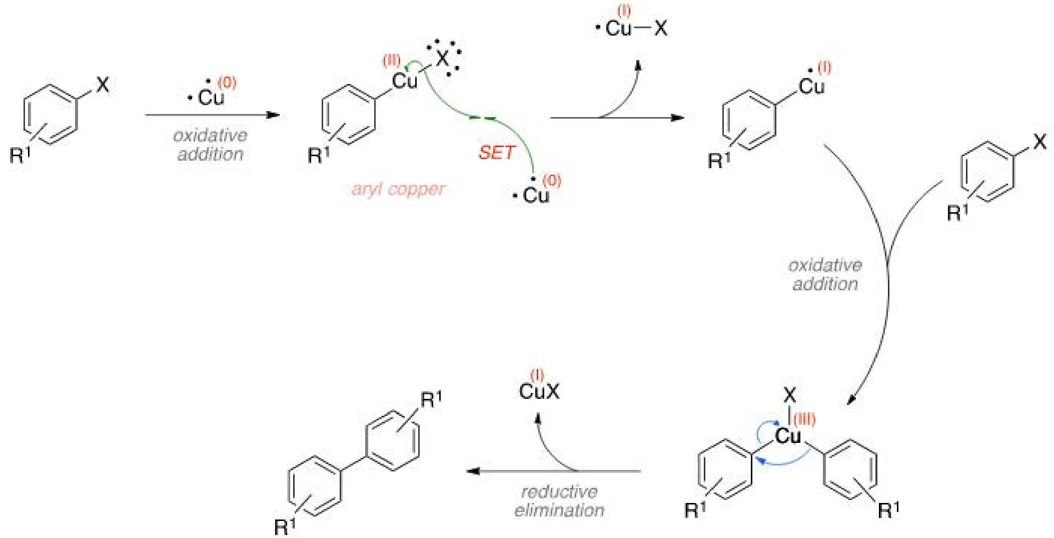
- Limited to electron deficient aryl halides and requires harsh reaction conditions

- Modern Ullman reaction employs palladium and nickel have widened the substrate scope of the reaction and rendered reaction conditions more mild

Ullmann Reaction

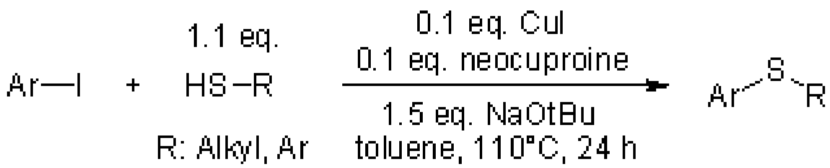
Radical mechanism



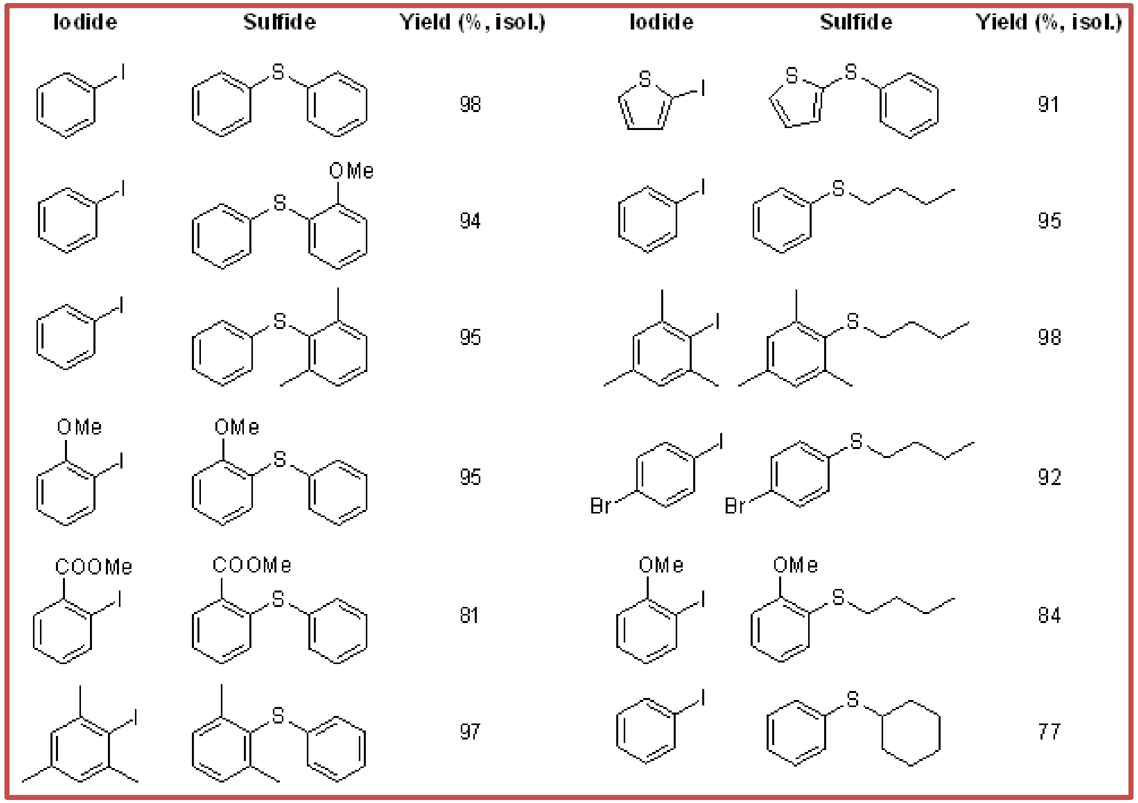


Mechanism involving aryl copper intermediate

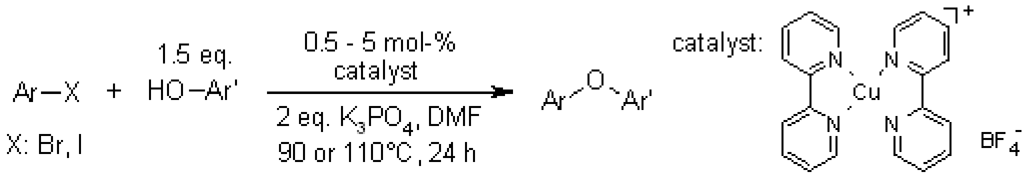
Ullmann Reaction



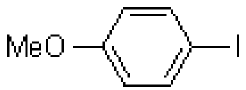
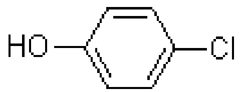
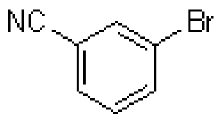
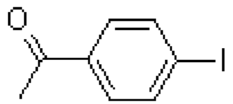
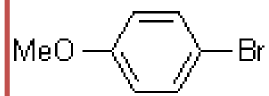
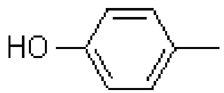
Org. Lett., **2002**, *4*, 2803



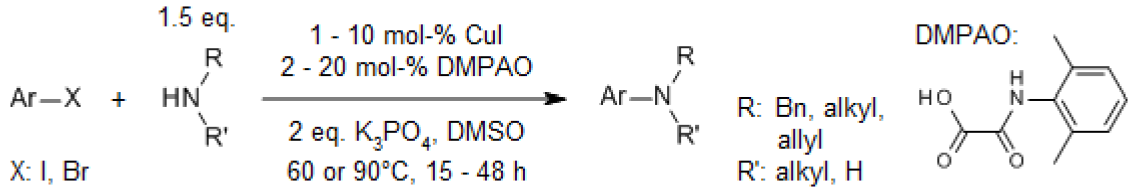
Ullmann Reaction



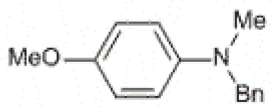
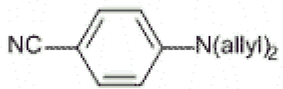
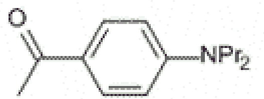
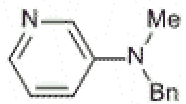
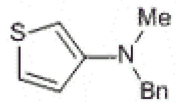
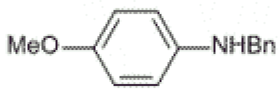
J. Org. Chem., **2008**, *73*, 7814

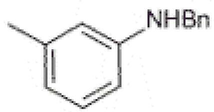
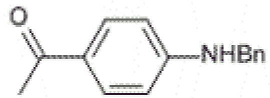
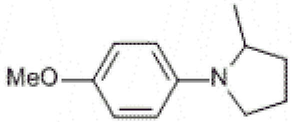
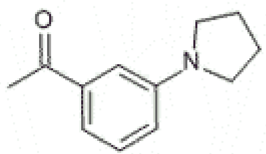
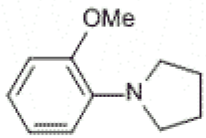
ArX	phenol	catalyst (mol-%)	T (°C)	yield (%, isol.)
		5	110 (48 h)	81
	HO–Ph	0.5	90	80
	HO–Ph	0.5	90	80
		3	110	70

Ullmann Reaction

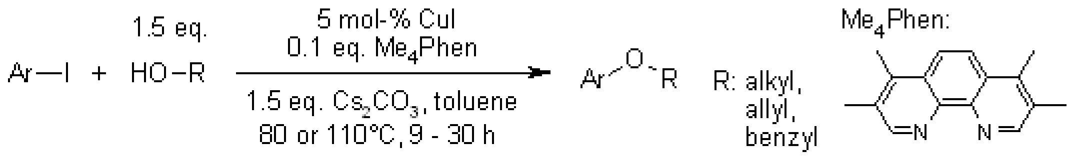


Org. Lett., **2012**, *14*, 3056

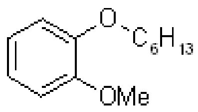
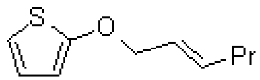
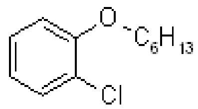
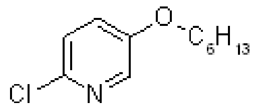
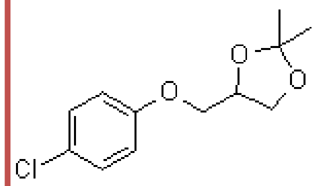
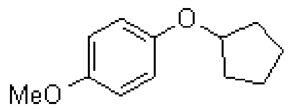
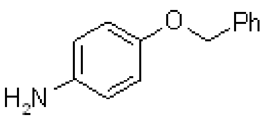
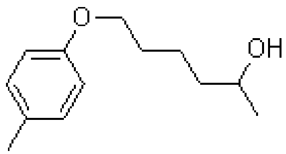
product	X	CuI (mol-%)	T (°C)	t (h)	yield (%, isol.)
	Br	10	110	48	62
	Br	10	90	24	70
	I	10	60	40	91
	Br	10	75	48	83
	Br	10	90	20	85
	Br	10	90	20	90
	Br	1	90	24	95

product	X	CuI (mol-%)	T (°C)	t (h)	yield (%, isol.)
	Br	1	90	24	87
	Br	1	90	48	99
	Br	1	90	24	100
	Br	1	90	24	90
	Br	1	90	24	95

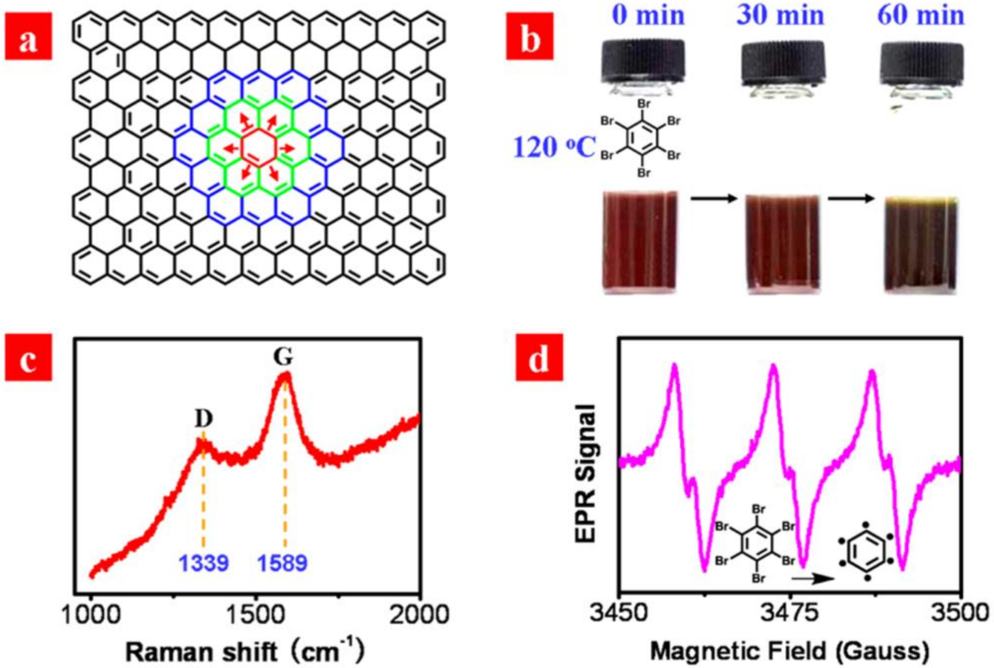
Ullmann Reaction

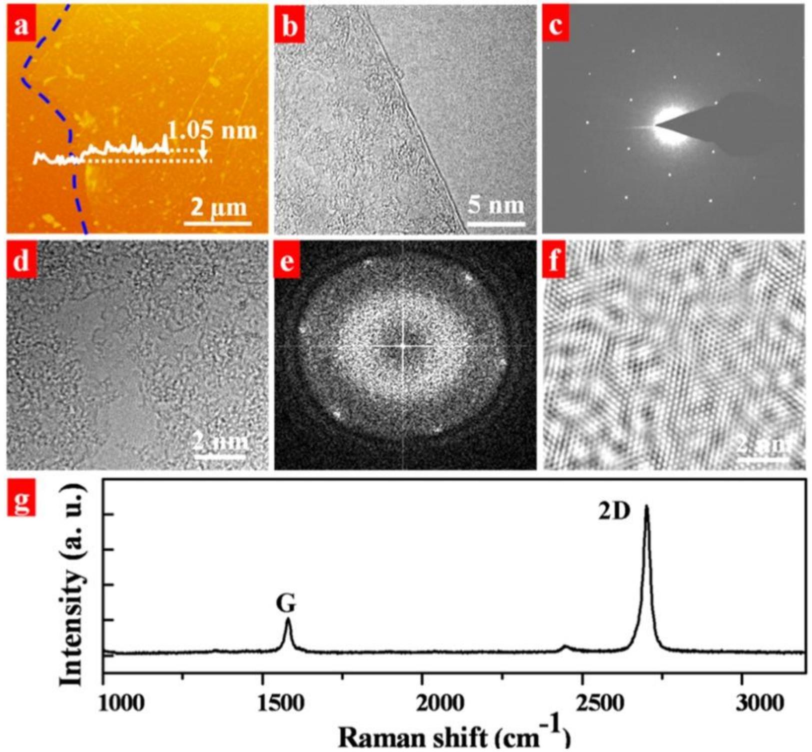


J. Org. Chem., **2008**, *73*, 284

product	T (°C)	t (h)	yield (%, isol.)	product	T (°C)	t (h)	yield (%, isol.)
	110	30	94		80	16	59
	110	24	80		80	16	86
	80	16	75		110	24	88
	80	16	81		80	24	73

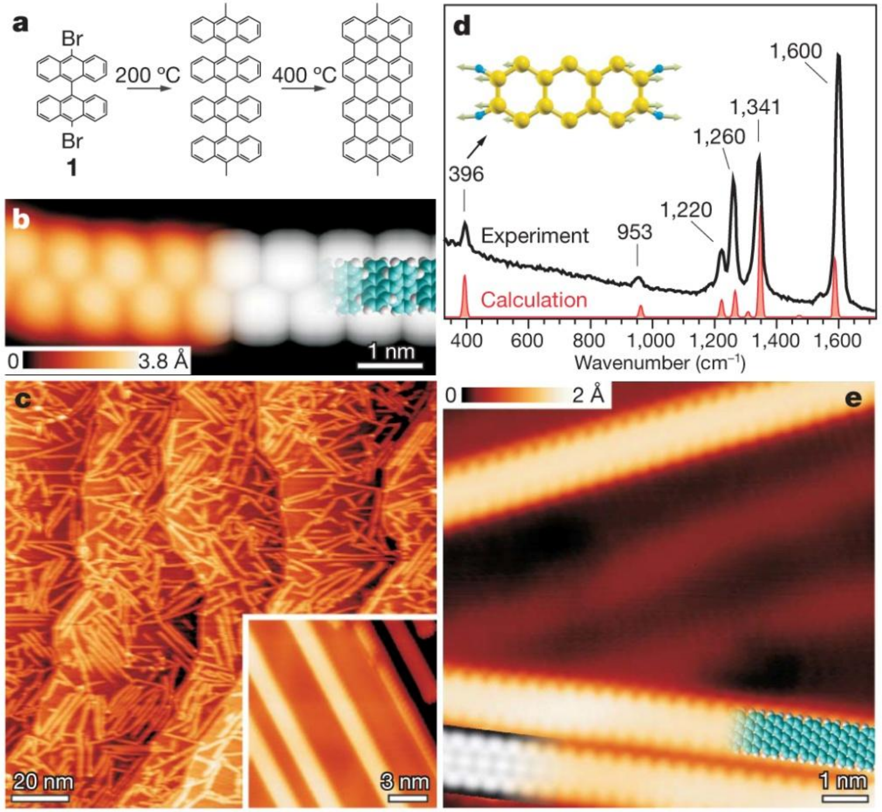
Ullmann Reaction

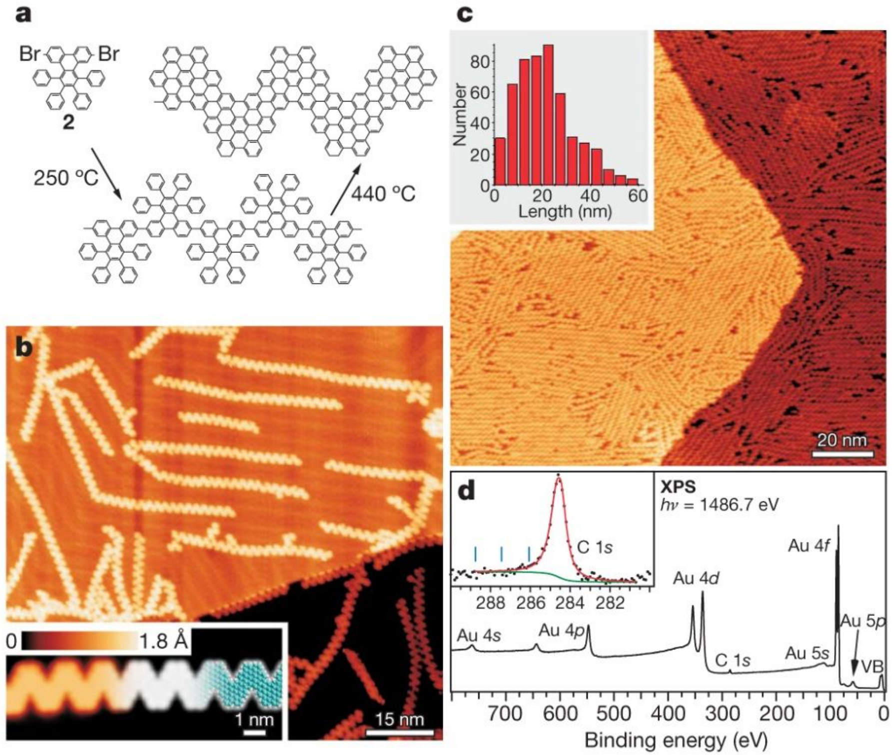




J. Am. Chem. Soc., **2013**, *135*, 9050

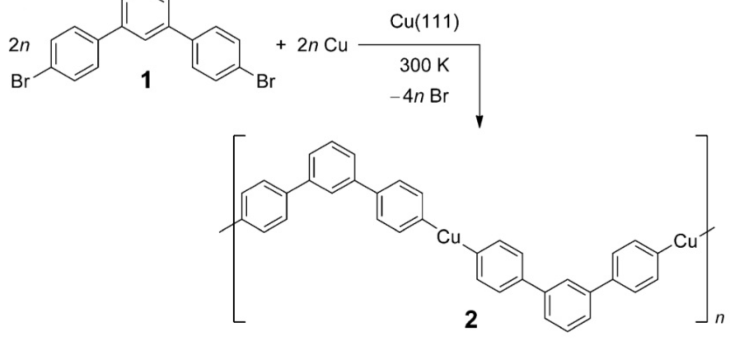
Ullmann Reaction

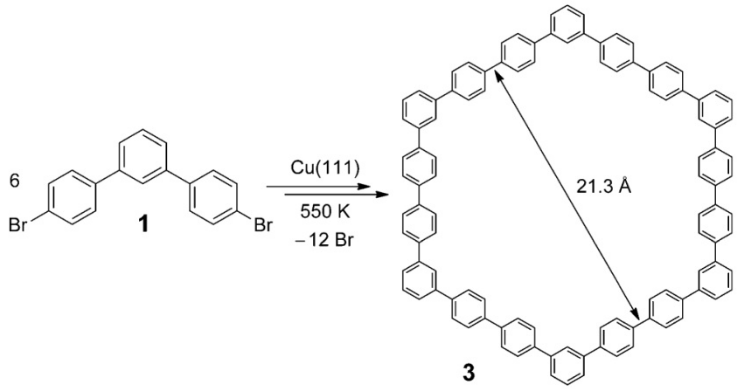


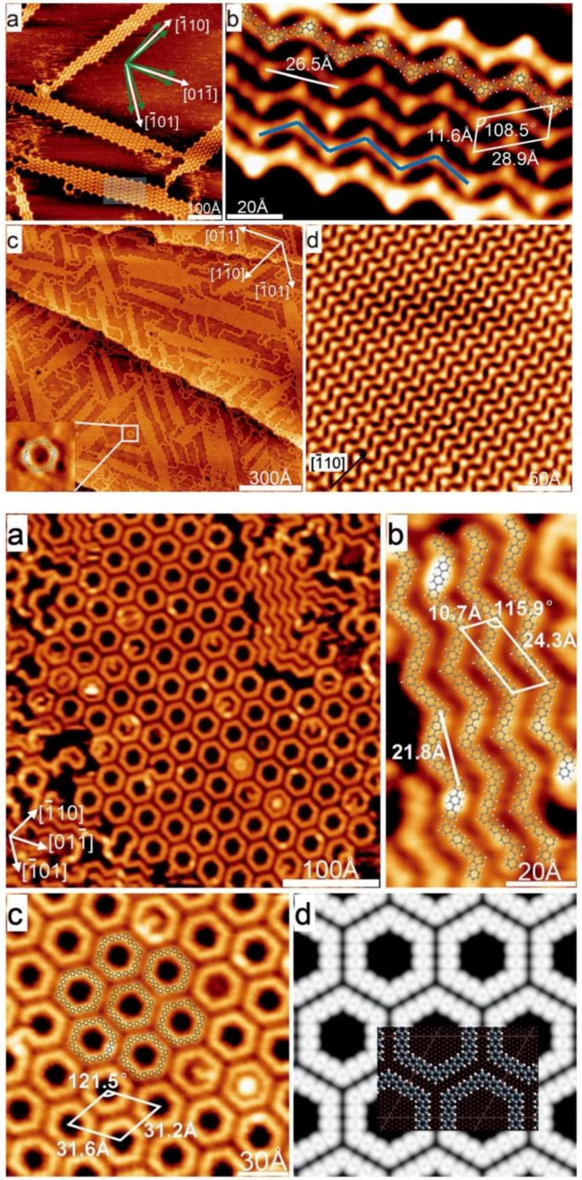


Nature, **2010**, *466*, 470

Ullmann Reaction

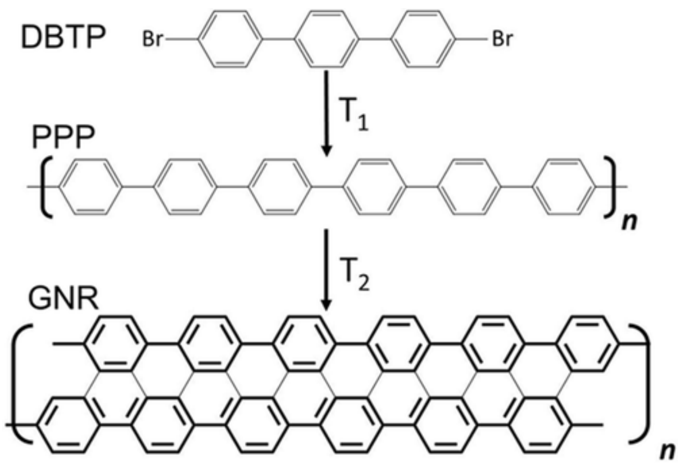


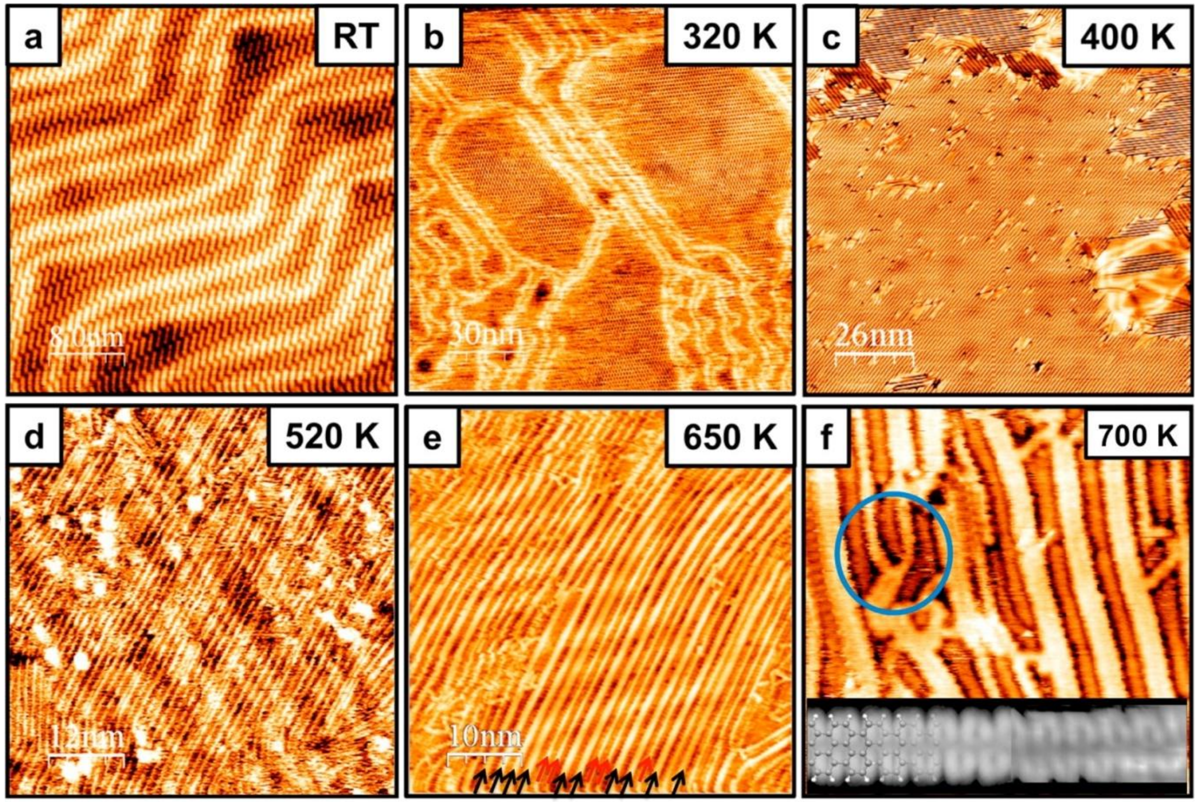




Angew. Chem. Int. Ed, **2013**, *52*, 4668

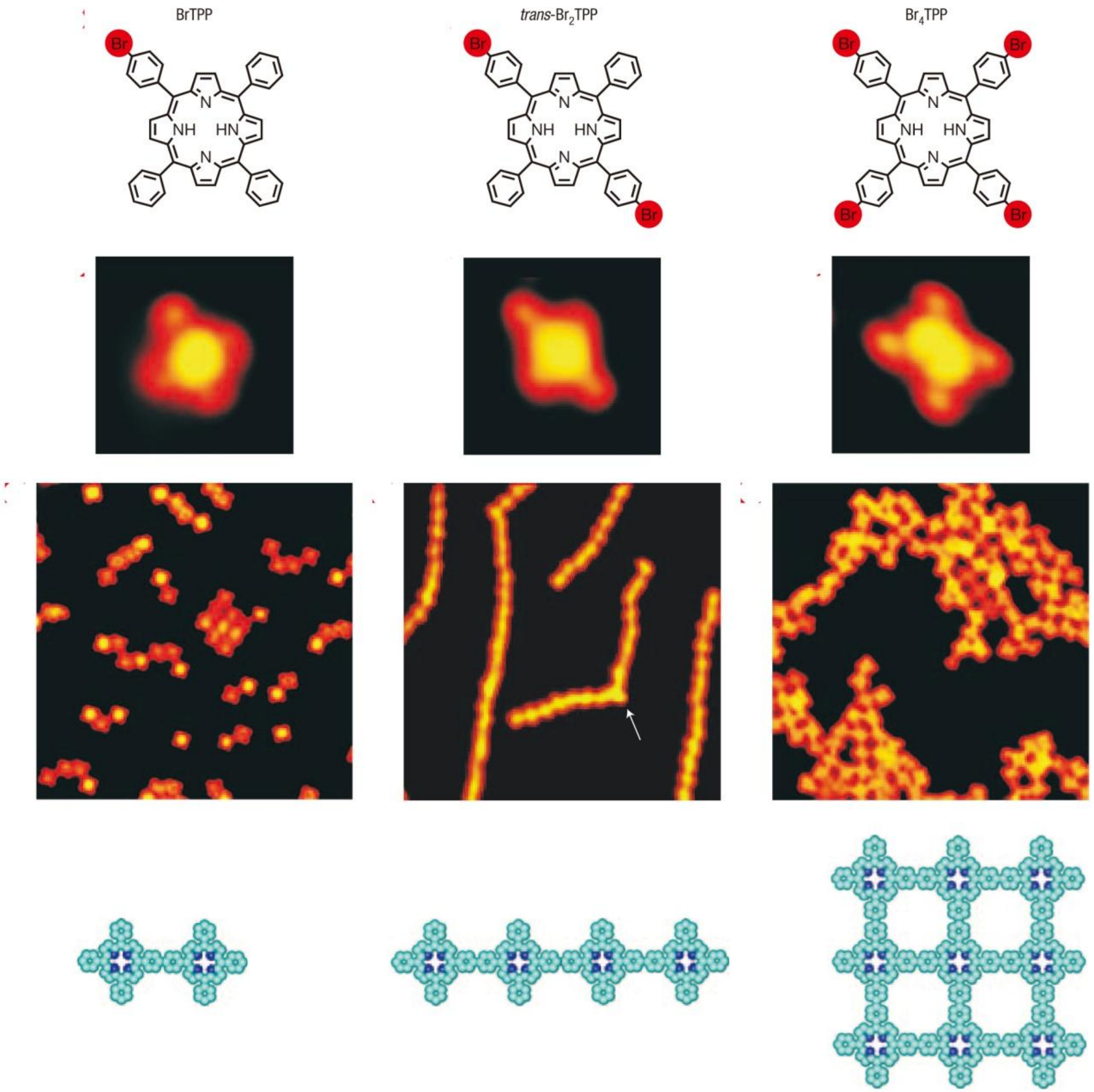
Ullmann Reaction





J. Am. Chem. Soc., **2015**, *137*, 1802

Ullmann Reaction



Nature Nanotech, **2007**, *2*, 687

Suzuki Cross-Coupling

The Suzuki cross-coupling reaction is the organic reaction of an organohalide with an organoborane to give the coupled product using a palladium catalyst and base.

$$R_1\text{-}BY \quad + \quad R_2\text{-}X \xrightarrow[\text{base}]{\text{Pd catalyst}} R_1\text{-}R_2$$

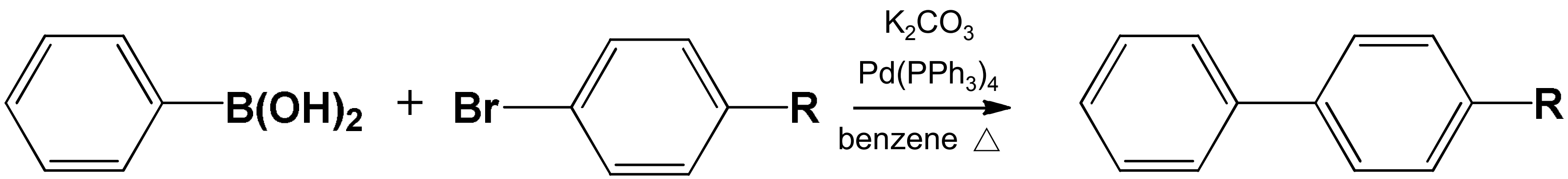
R1=aryl, alkenyl, alkyl

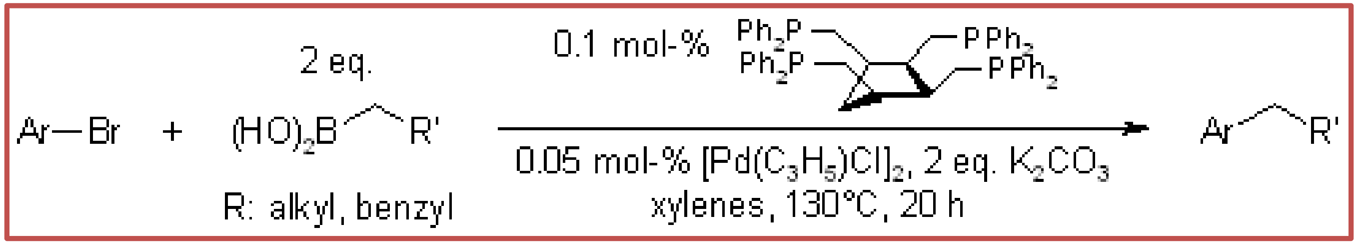
R2=aryl, alkenyl, alkyl, allyl

X=Cl, Br, I, OTf

2010 Nobel Prize in Chemistry

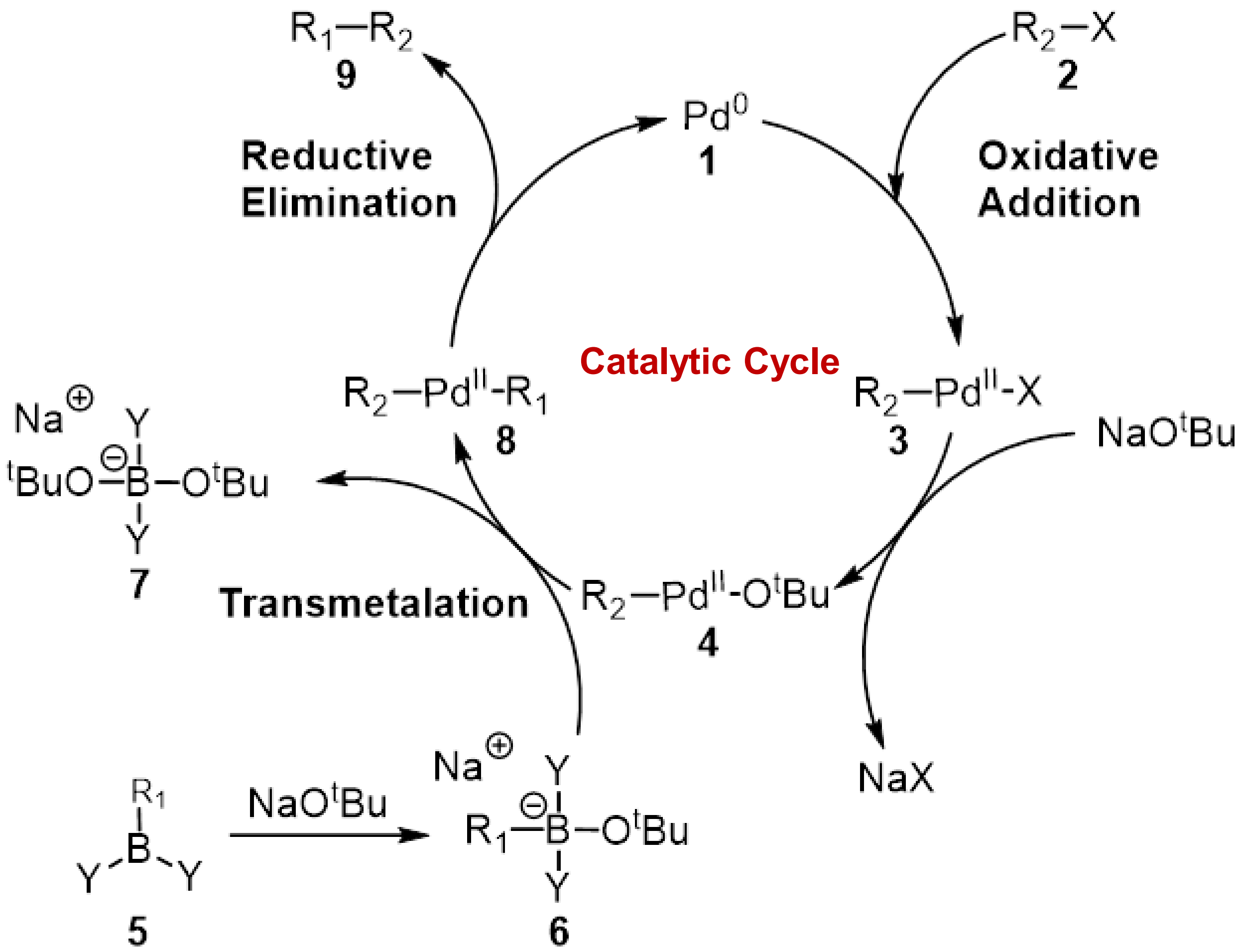
Suzuki Coupling





Tetrahedron, **2004**, *60*, 3813

Suzuki Coupling



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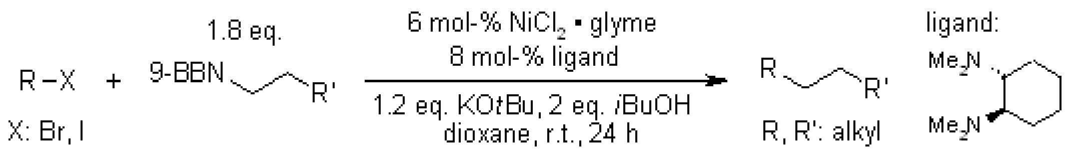
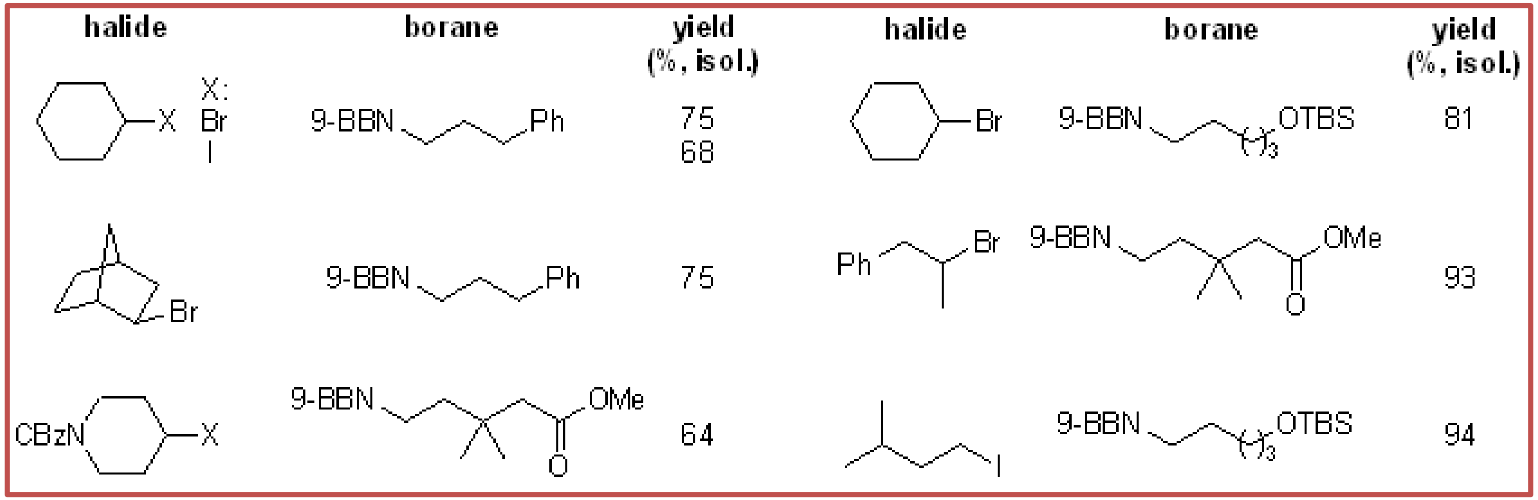
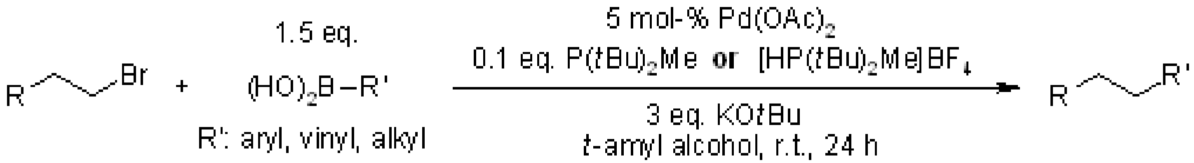


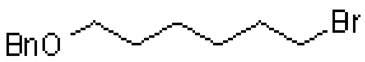
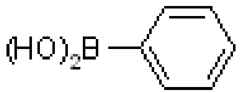
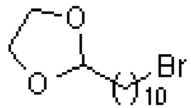
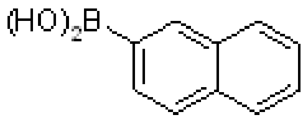
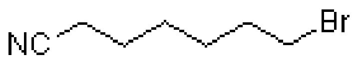
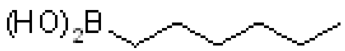
J. Am. Chem. Soc., **2007**, *129*, 9602



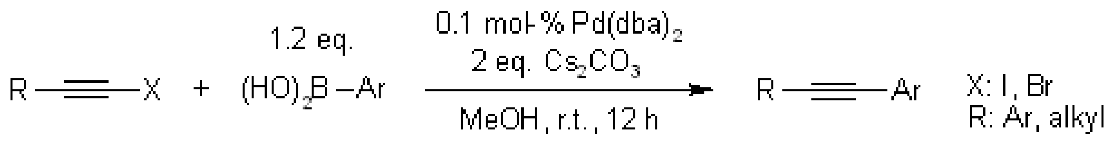
Suzuki Coupling



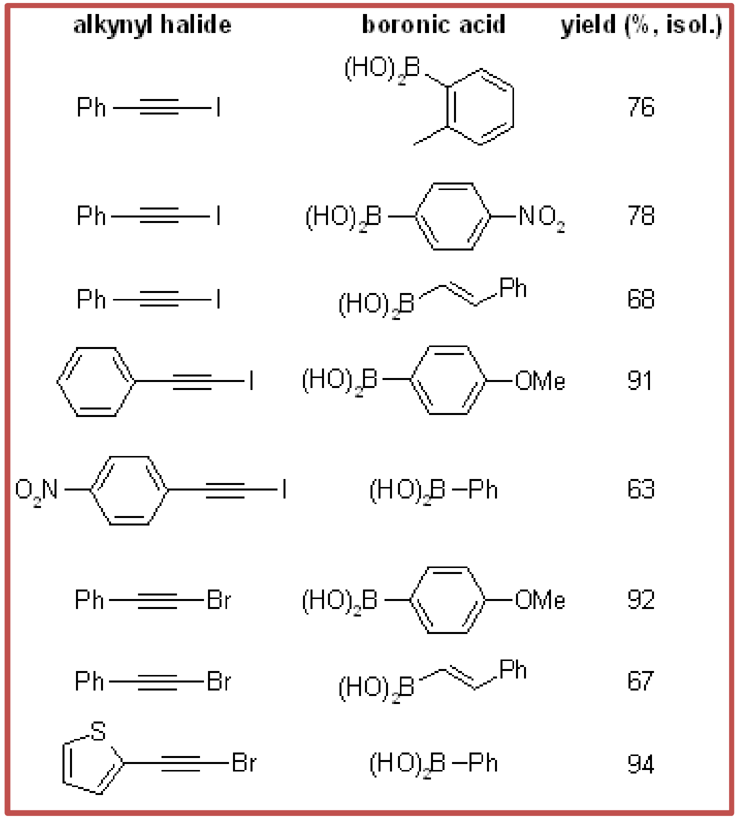
J. Am. Chem. Soc., **2002**, *124*, 13662

alkyl bromid	boronic acid	yield (%, isol.) $P(tBu)_2Me$	$[HP(tBu)_2Me]BF_4$
		85	94
		97	93
		85	87
$H_{25}C_{12}$—Br		66	62

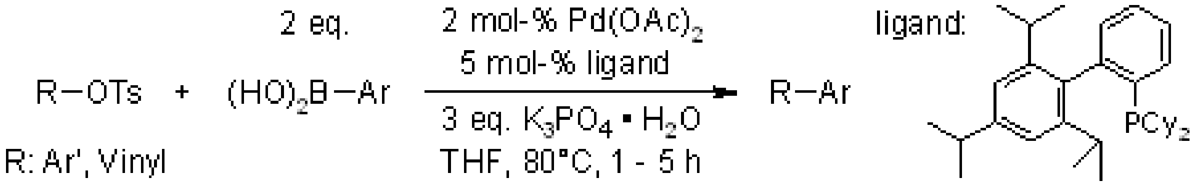
Suzuki Coupling



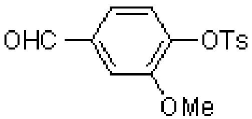
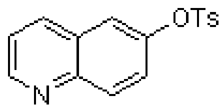
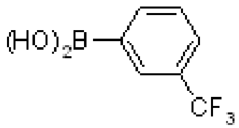
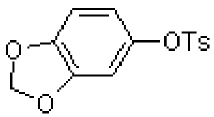
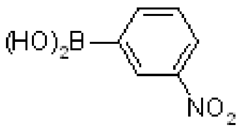
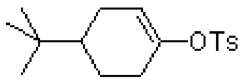
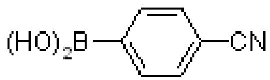
Synthesis, **2012**, *44*, 541



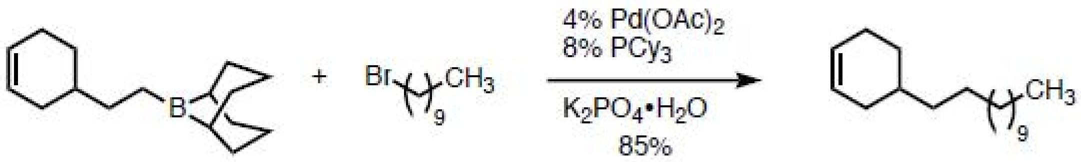
Suzuki Coupling



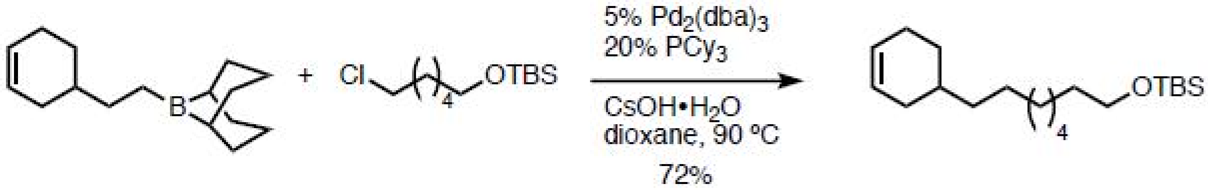
J. Am. Chem. Soc., **2003**, *125*, 11818

Tosylate	Boronic Acid	t (h)	Yield (%, isol.)	Tosylate	Boronic Acid	t (h)	Yield (%, isol.)
	(HO)$_2$B−Ph	3	91			3	90
		5	94			1	92

Suzuki Coupling



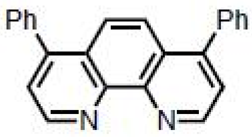
Netherton, M. R.; Dai, C.; Klaus, N.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100.



Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1945–1947.

Suzuki Coupling

- Fu and coworkers have developed a Ni^0-catalyzed Suzuki coupling of unactivated secondary alkyl bromides and iodides:



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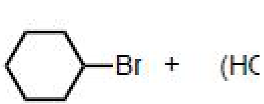
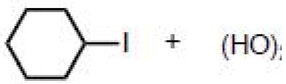
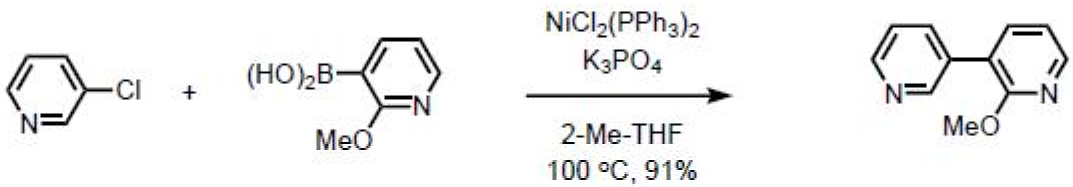


Nickel Catalyzed Suzuki Couplings



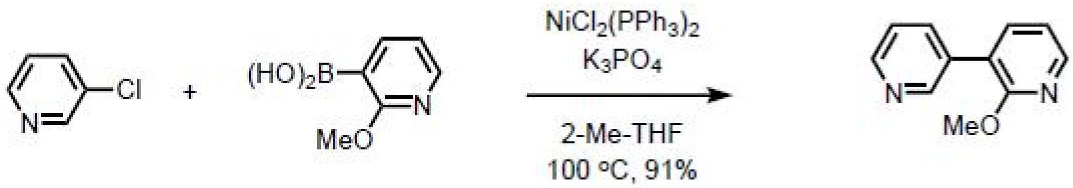


Zhou, J.; Fu, G. C. *J. Am.*

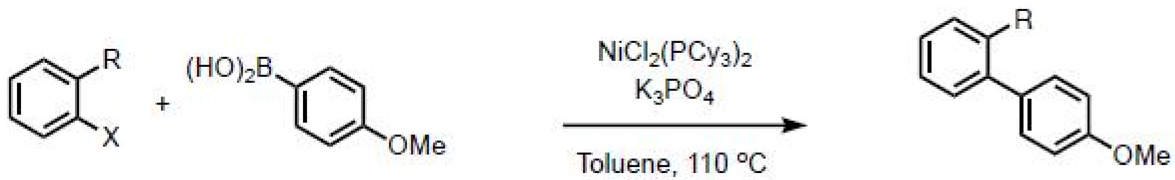
Ramgren, S.D.; Hien, L.; Ye, Y.; Garg, N. K. *Org. Lett.* **2013**, *15*, 3950–3953

Suzuki Coupling

Nickel Catalyzed Suzuki Couplings

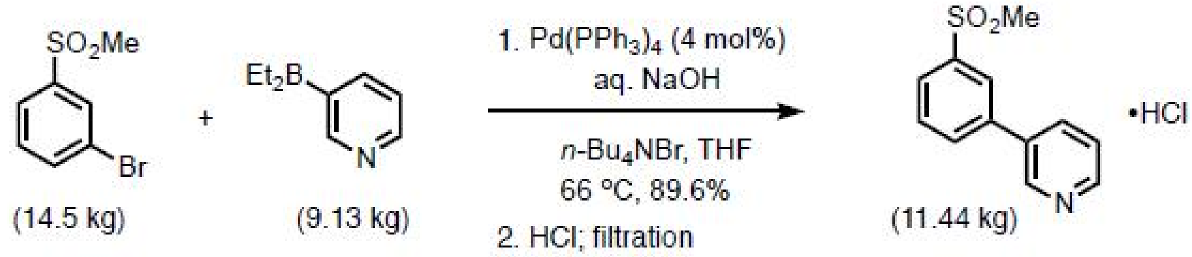


Ramgren, S.D.; Hien, L.; Ye, Y.; Garg, N. K. *Org. Lett.* **2013**, *15*, 3950–3953



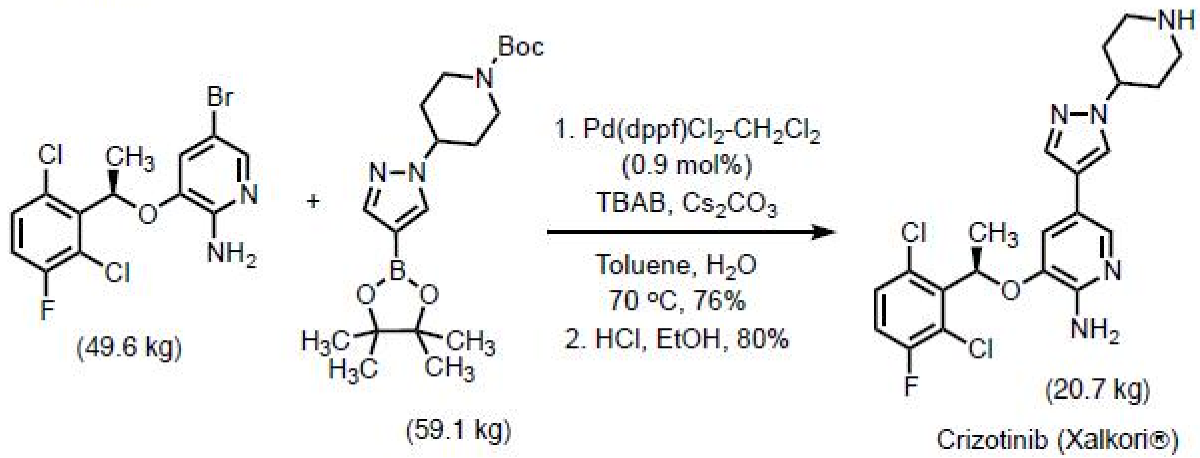
X = OC(O)NEt_2	R = H	52%
X = OSO_2NMe_2	R = H	83%
X = OPiv	R = Me	79%

Suzuki Coupling



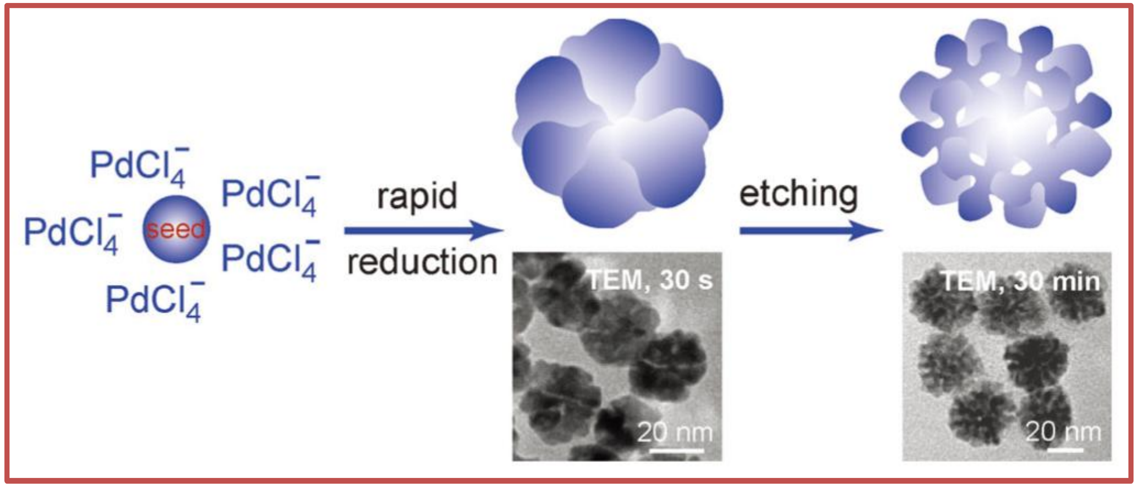
Lipton, M. F.; Mauragis, M. A.; Maloney, M. T.; Veley, M. F.; VanderBor, D. W.; Newby, J. J.; Appell, R. B.; Daugs, E. D. *Org. Proc. Res. Dev.* **2003**, *7*, 385–392.

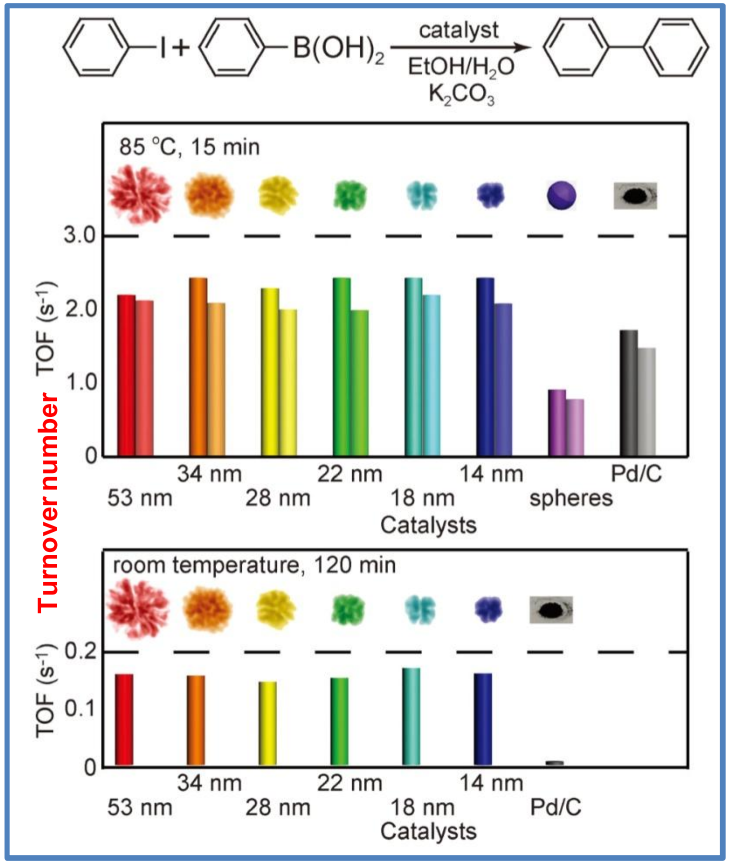
- Application to the synthesis of Xalkori®, an anti-cancer drug for treatment of non-small cell lung carcinoma:



de Koning, P. D. *et. al. Org. Proc. Res. Dev.* **2011**, *15*, 1018–1026.

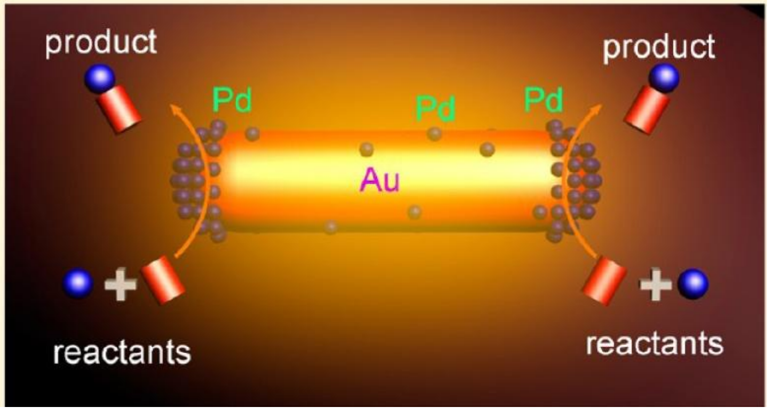
Suzuki Coupling

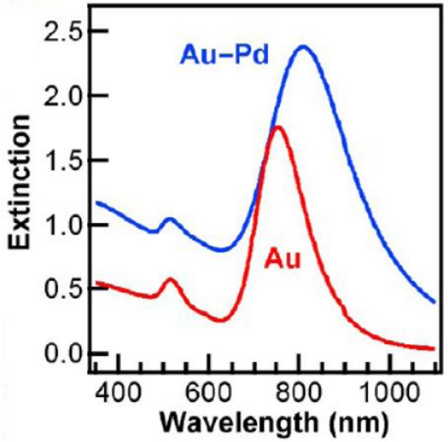


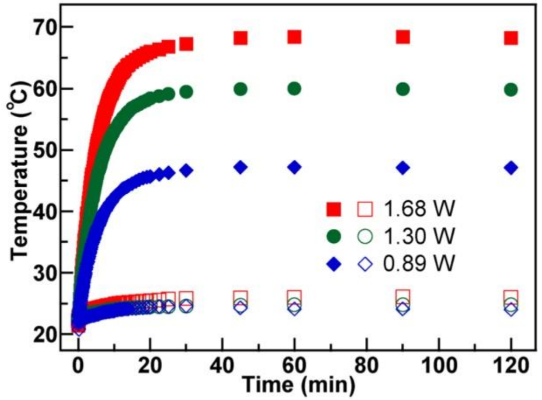


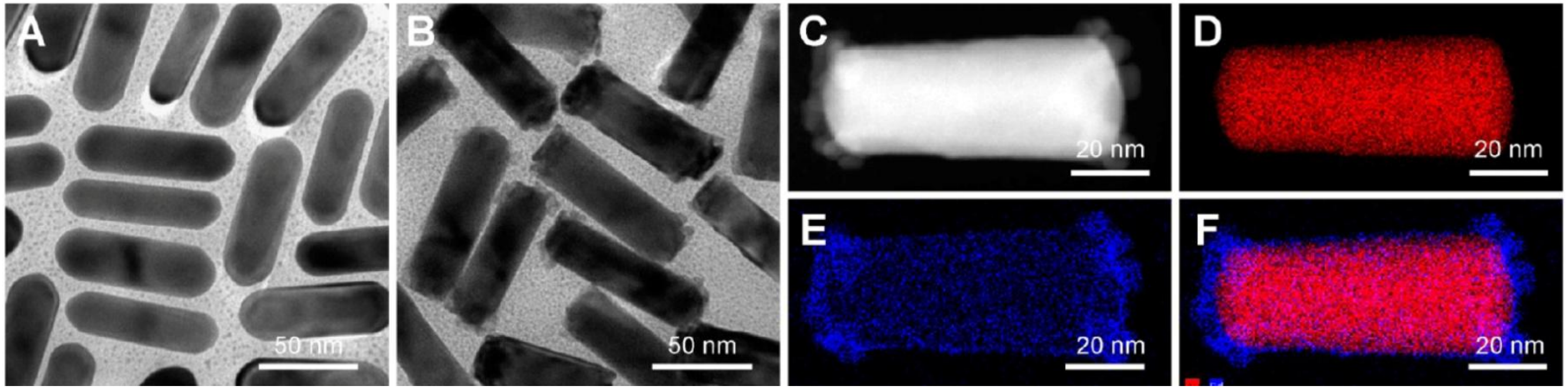
Angew. Chem. Int. Ed., **2012**, *51*, 4872

Suzuki Coupling

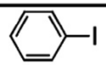
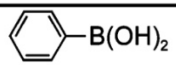
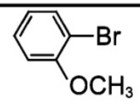
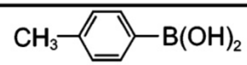
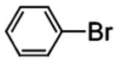
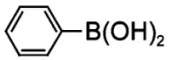
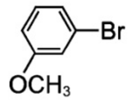
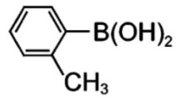
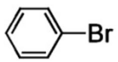
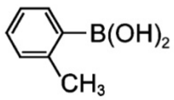
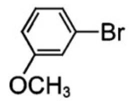
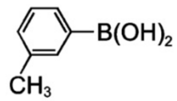
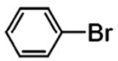
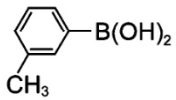
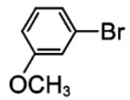
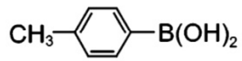
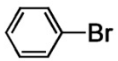
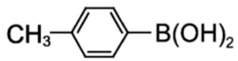
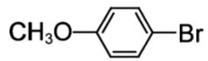
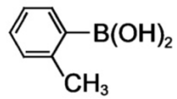
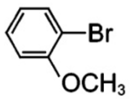
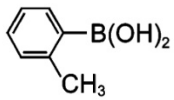
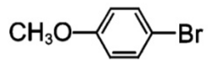
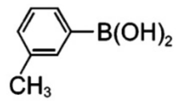
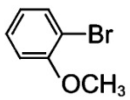
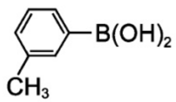
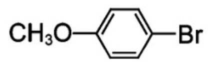
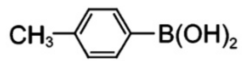




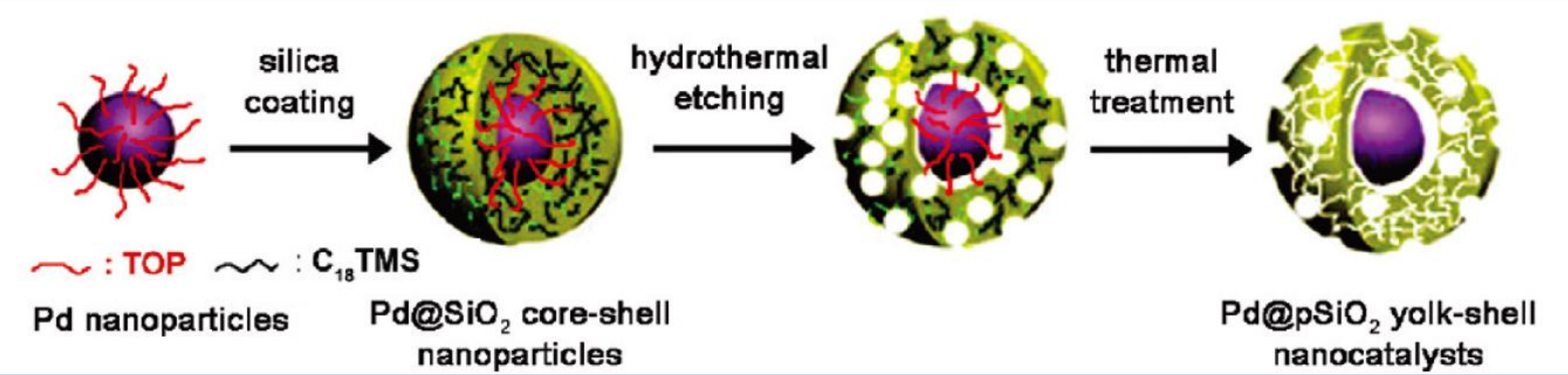


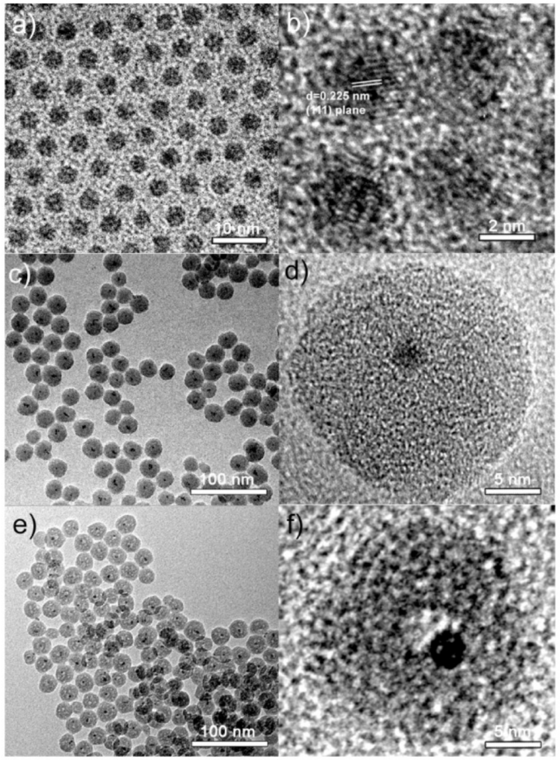


Suzuki Coupling

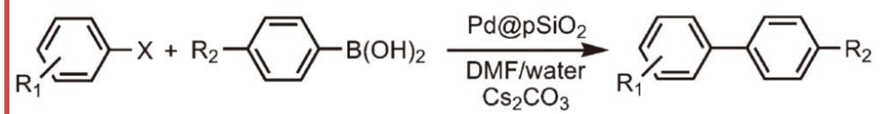
entry	halide	boronic acid	yield [%]	entry	halide	boronic acid	yield [%]
1			99	8			94
2			99	9			43
3			99	10			99
4			99	11			99
5			94	12			59
6			71	13			95
7			80	14			99

Suzuki Coupling



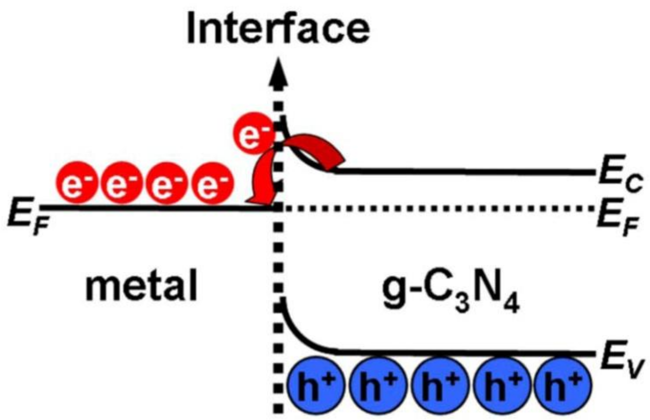


J. Phys. Chem. C., **2011**, *115*, 15772

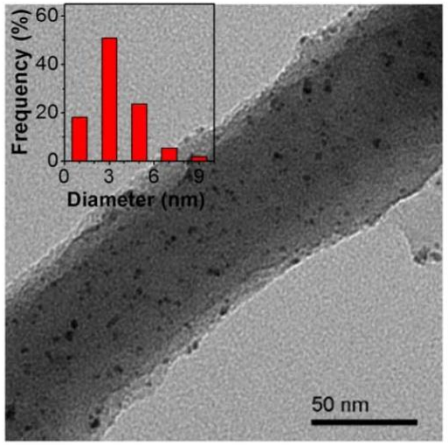


entry	R_1	R_2	X	*t* (h)	yield (%)[b]
1	H	H	Cl	3	100
2	4-OCH_3	H	Br	3	64
3	4-CHO	H	Br	3	64
4	2-CHO	H	Br	3	100
5	4-CF_3	H	Br	3	61
6	4-CHO	H	Cl	3	68
7	2-CHO	H	Cl	3	100
8	H	OMe	Br	3	100
9	H	Me	Br	3	87

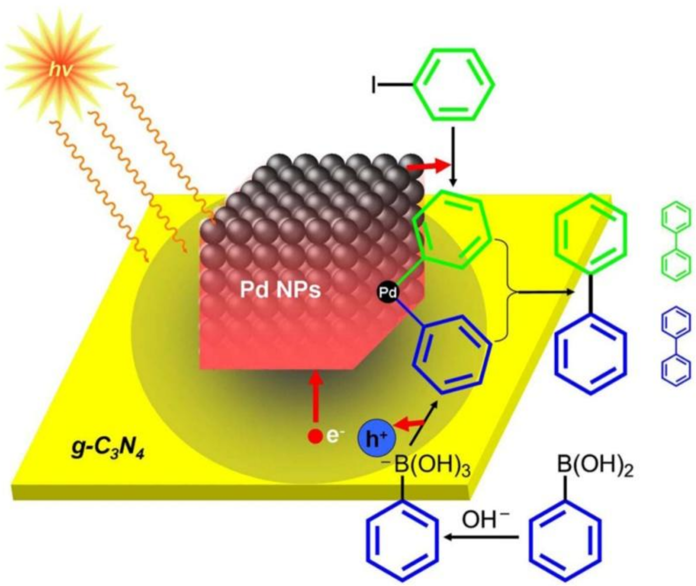
Suzuki Coupling



Mott-Schottky Heterojuction



Sci. Reports, **2013**, *3*, 1743



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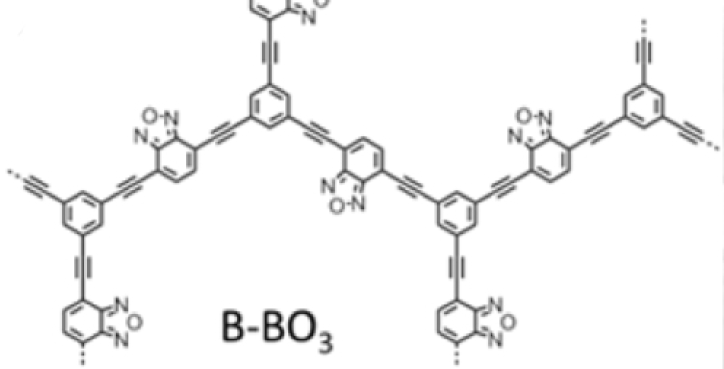
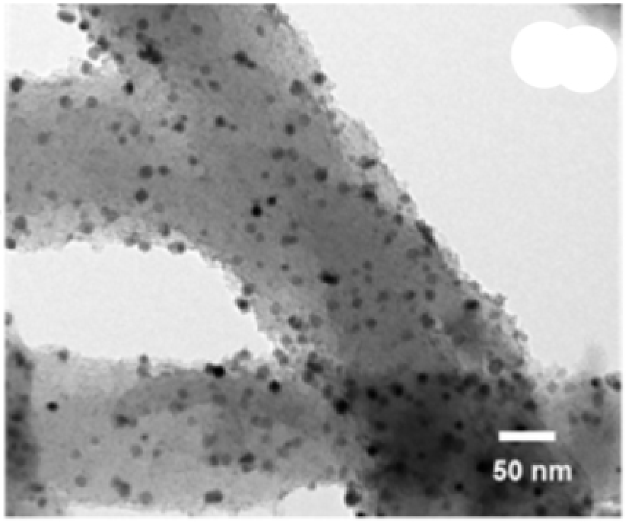
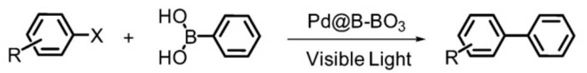
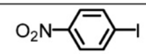
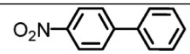
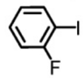
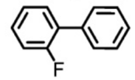
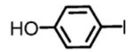
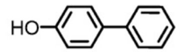
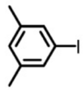
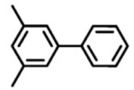
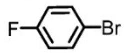
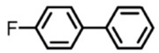
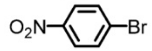
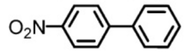
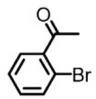
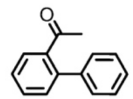
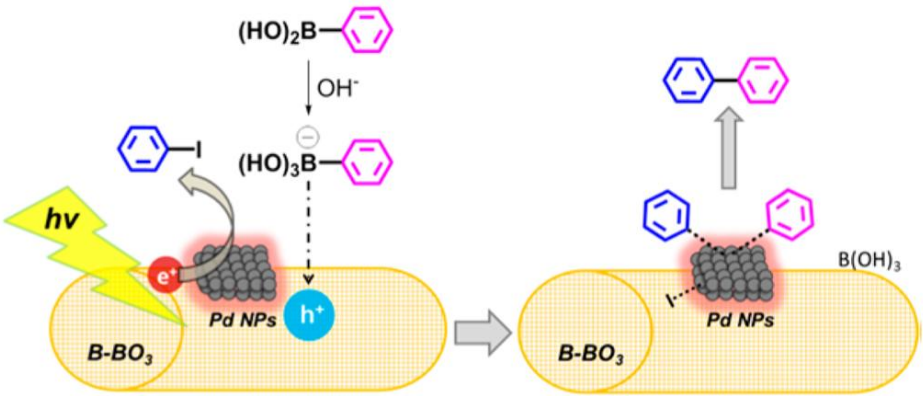




Chem. Mater. **2015**, *27*, 1921

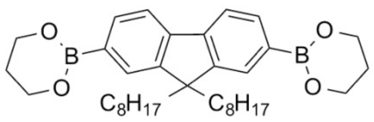


Entry	Aryl halide	Product	Time (h)	Yield[b] (%)
10			2	98
11			6	84
12			6	75
13			6	90
14			4	96
15			4	95
16			16	76



Suzuki Coupling

monomers



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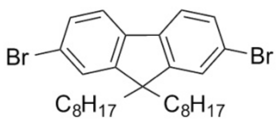

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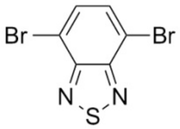

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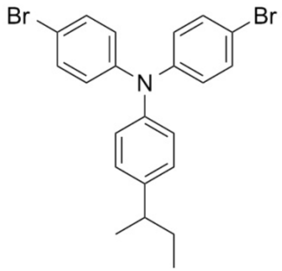

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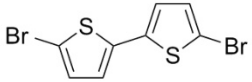

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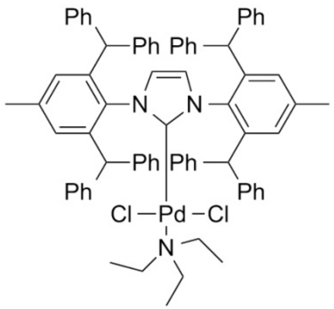

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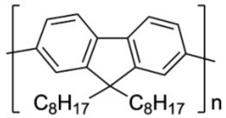
polymers



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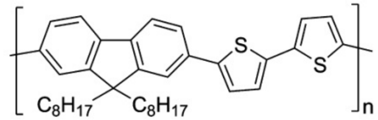

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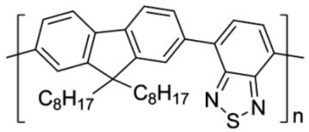

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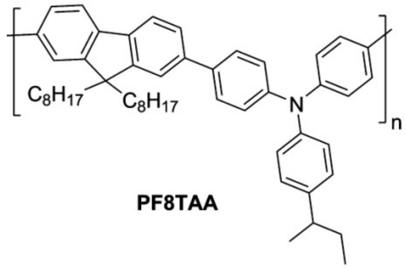

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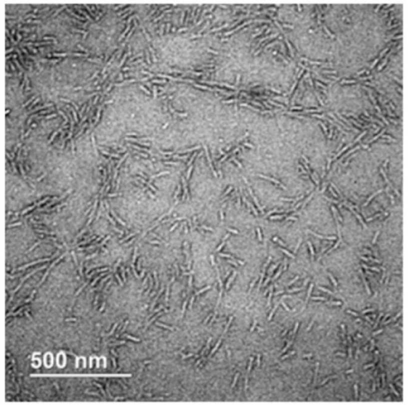

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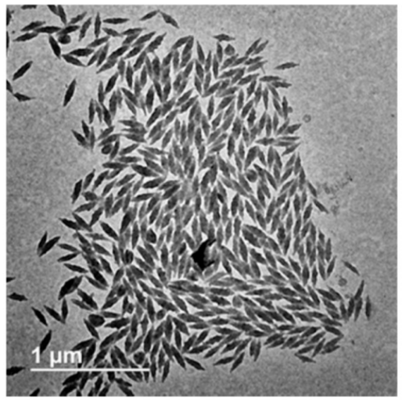
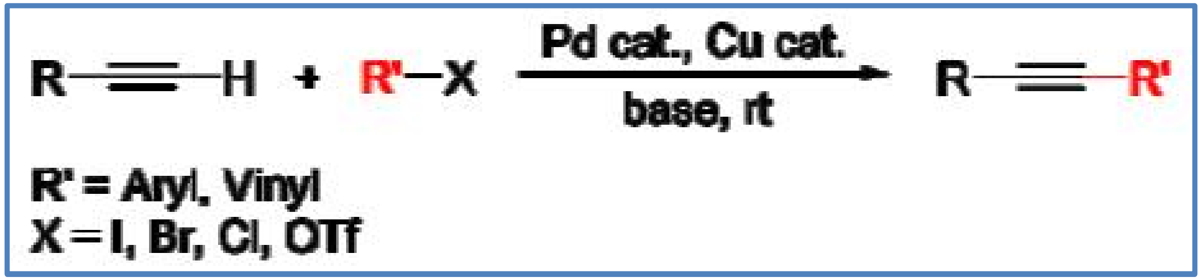


PF8T2

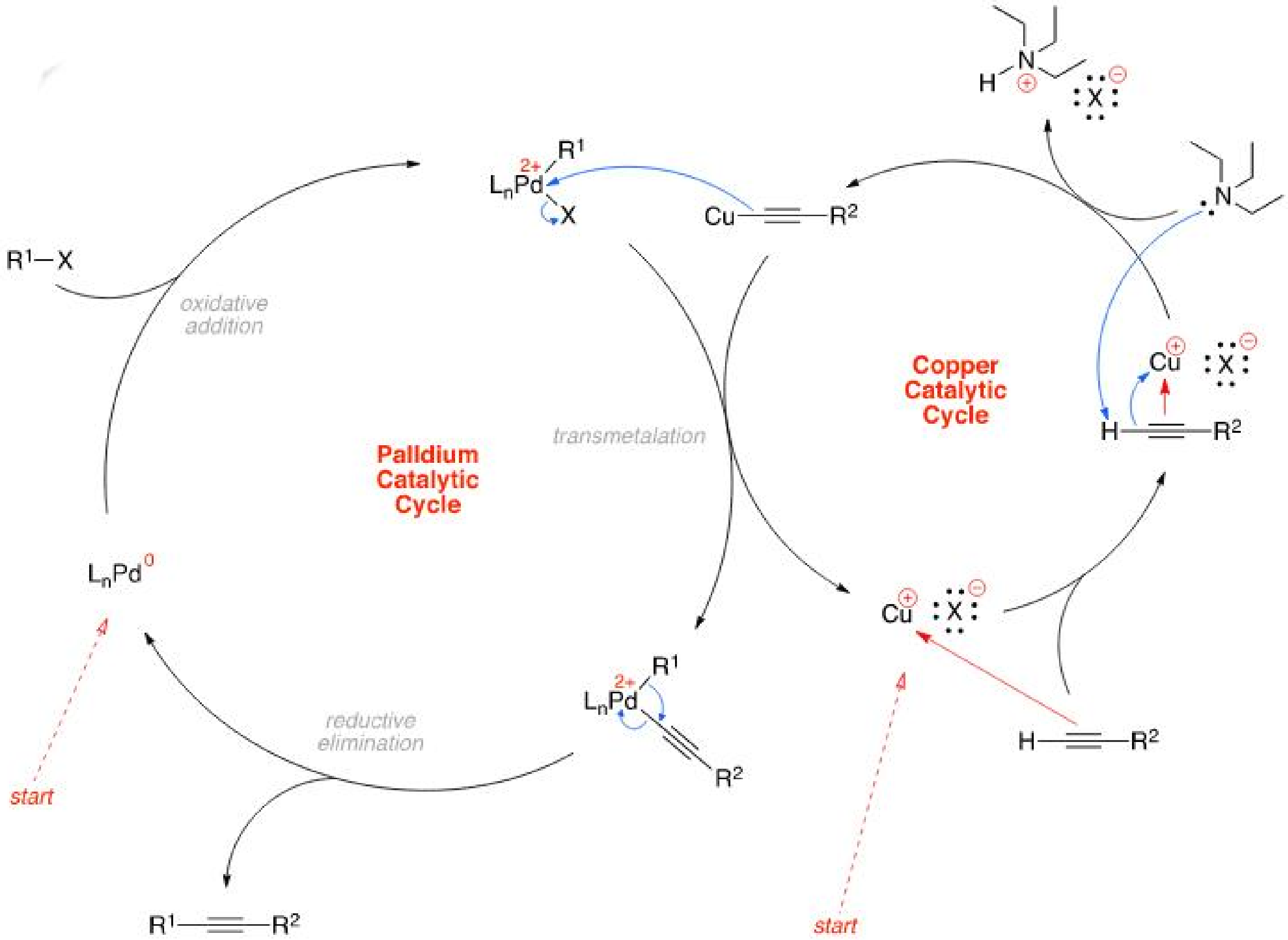
Sonogashira Coupling

The Sonogashira cross-coupling reaction is the organic reaction of an organohalide with a terminal alkyne to give the coupled product using a palladium catalyst, a copper catalyst, and base.

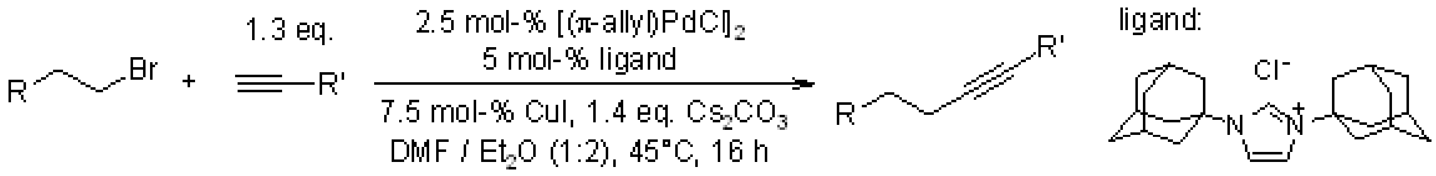


Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

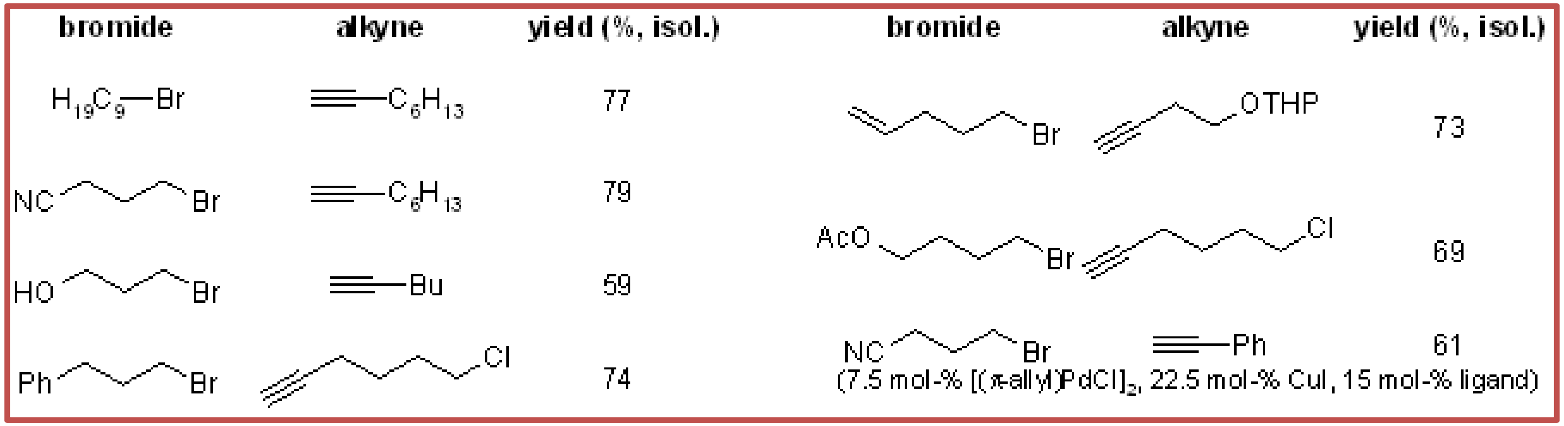
Sonogashira Coupling



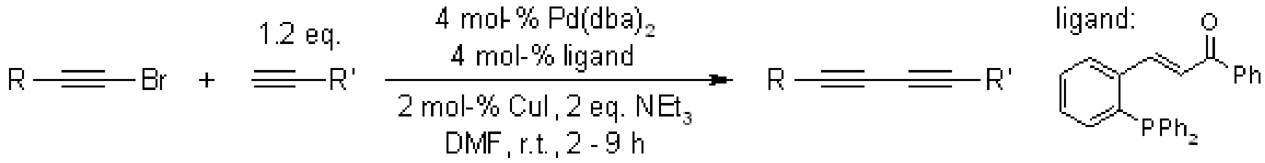
Sonogashira Coupling



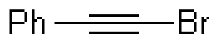
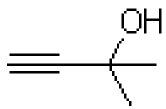
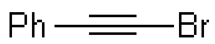
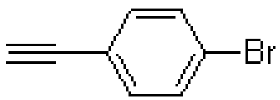
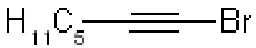
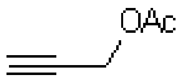
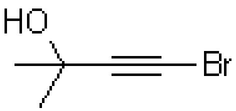
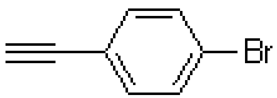
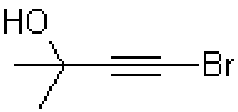
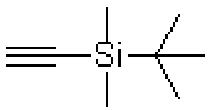
J. Am. Chem. Soc., **2003**, *125*, 13642.



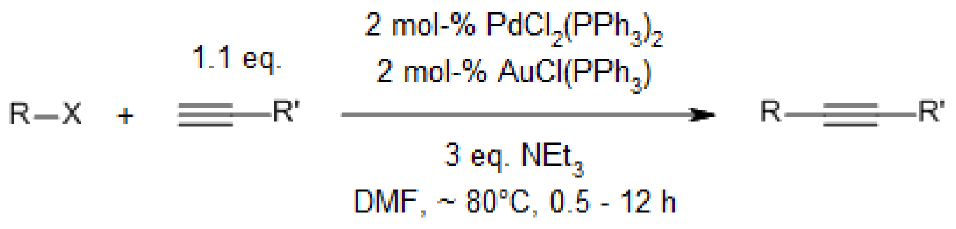
Sonogashira Coupling



J. Am. Chem. Soc., **2008**, *130*, 14713

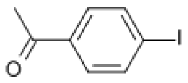
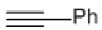
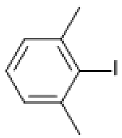
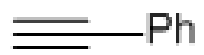
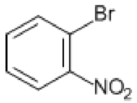
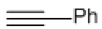
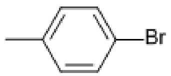
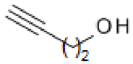
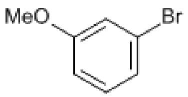
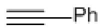
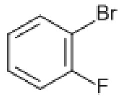
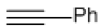
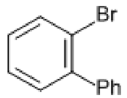
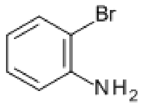
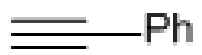
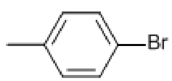
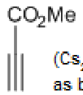
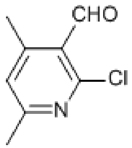
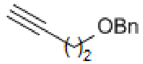
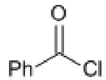
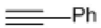
bromoalkyne	**terminal alkyne**	**yield (%, isol.)**
		82
		96
		87
		94
		91

Sonogashira Coupling



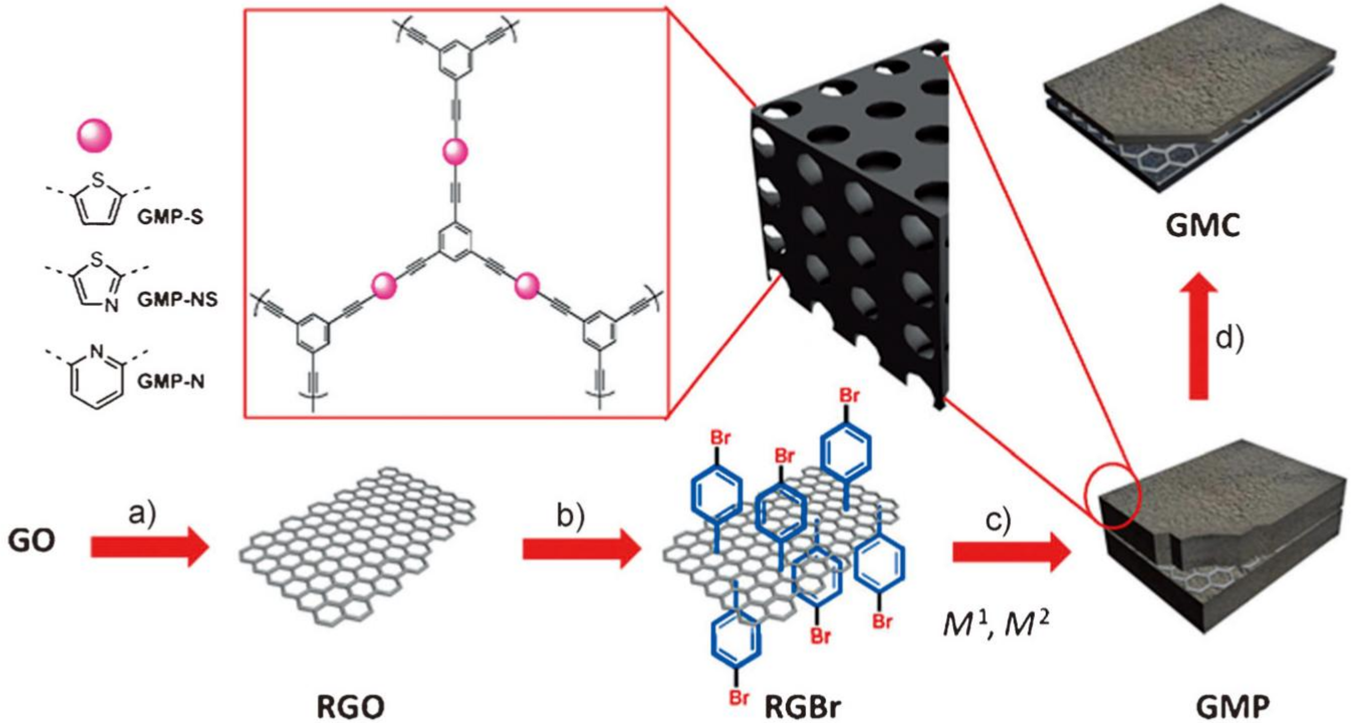
RX: ArI, ArBr, ArCl
vinyl-Br, PhCOCl
R': Ar, alkyl, CO_2Me

Synthesis, **2013**, *45*, 817

halide	alkyne	T (°C)	t (h)	yield (%, isol.)
		60	0.75	93
		80	1	98
		70	1	93
		80	3	91
		80	7	93
		80	3	92
		80	4	89
		80	4	62 (0)*
	 (Cs_2CO_3 as base)	80	5	70 (0)*
		80	3	90
Ph—Cl		100	12	62
		80	3	76

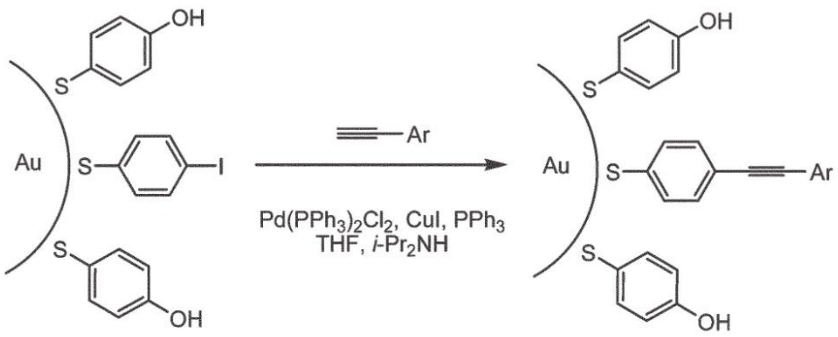
*using CuI in place of $AuCl(PPh_3)$

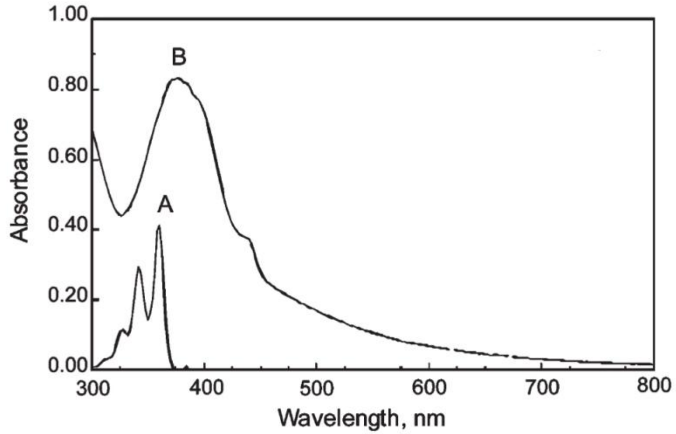
Sonogashira Coupling

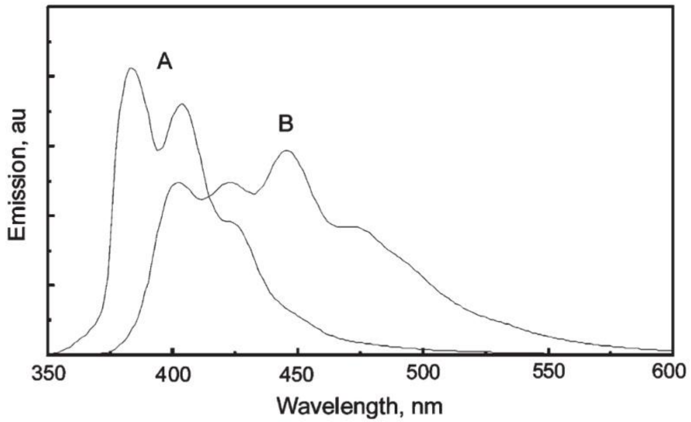


Angew. Chem. Int. Ed., **2013**, *52*, 9668.

Sonogashira Coupling

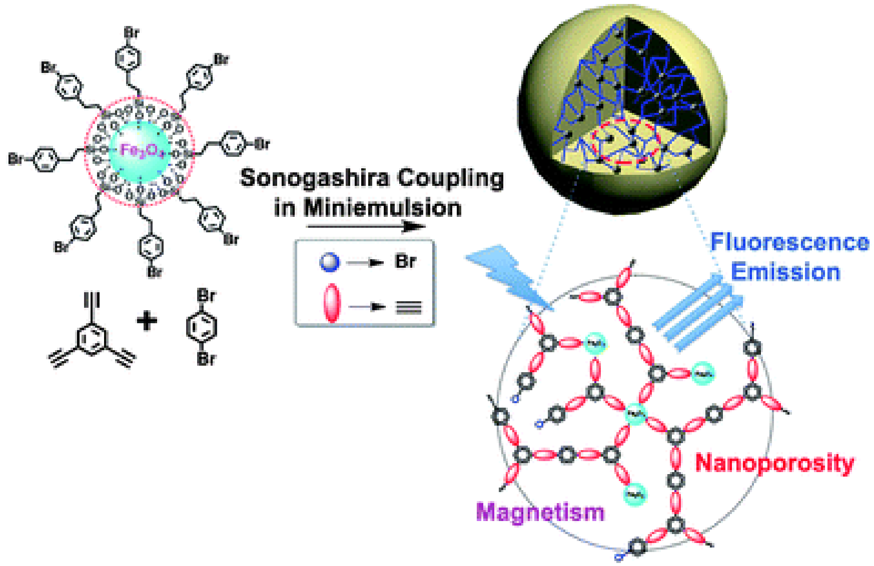


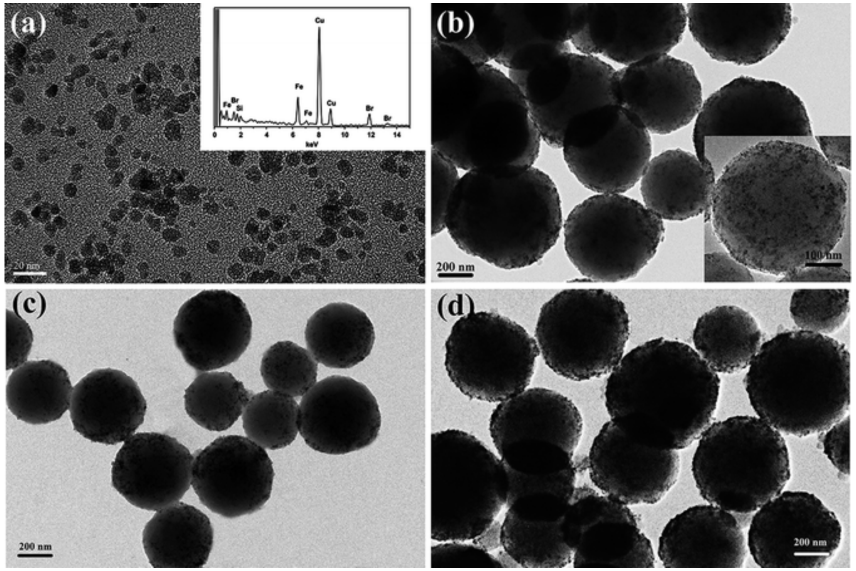


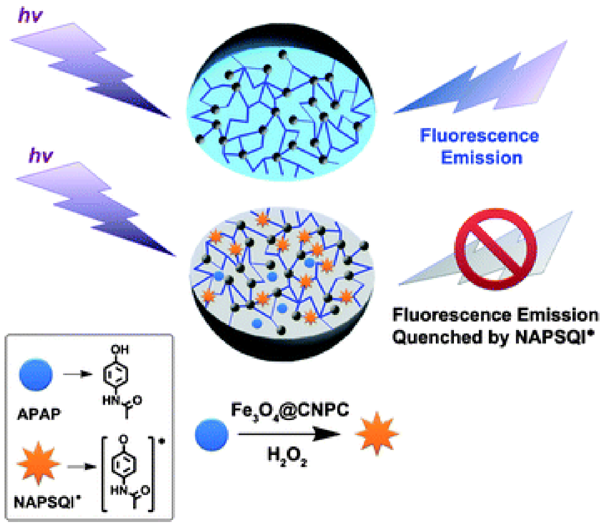


Chem. Commun., **2005**, 1055.

Sonogashira Coupling

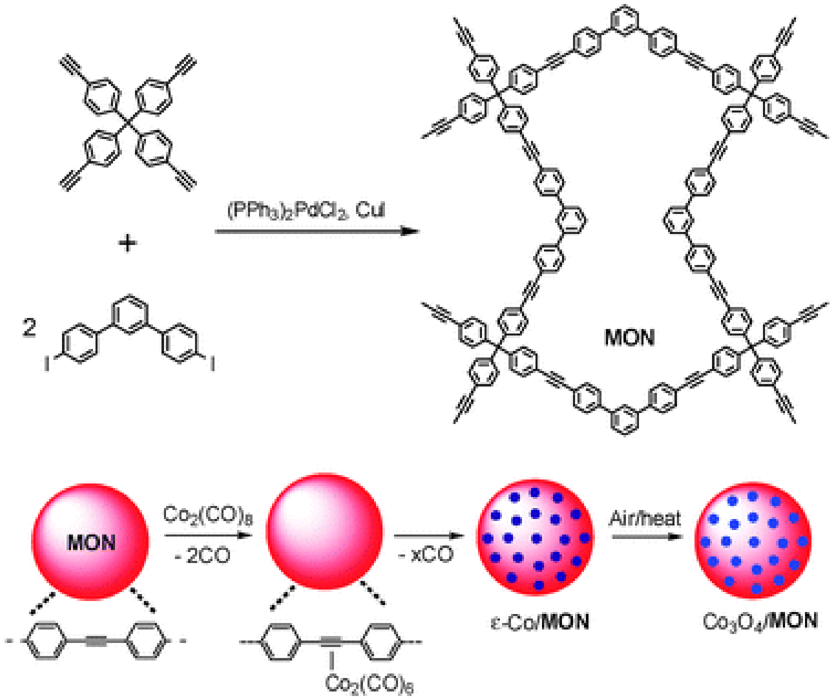


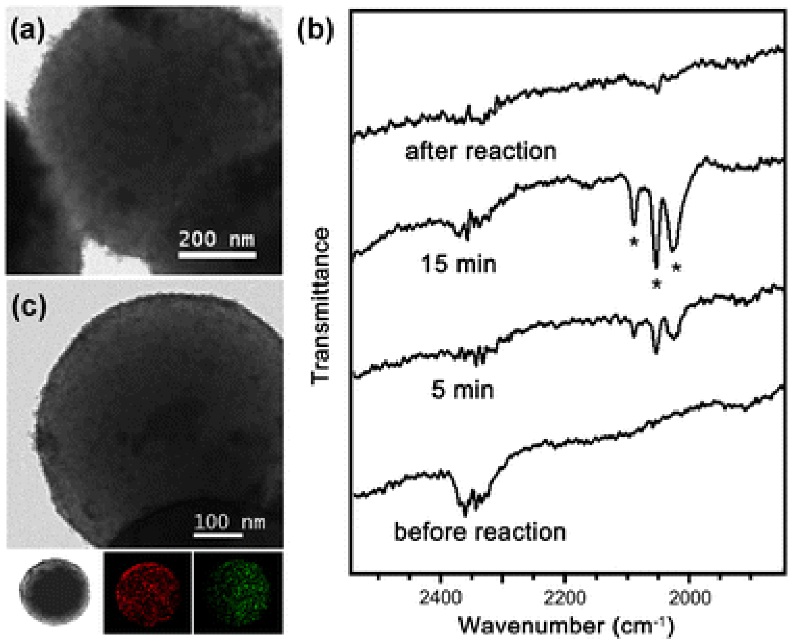




J. Mater. Chem., 2012, **22**, 21426

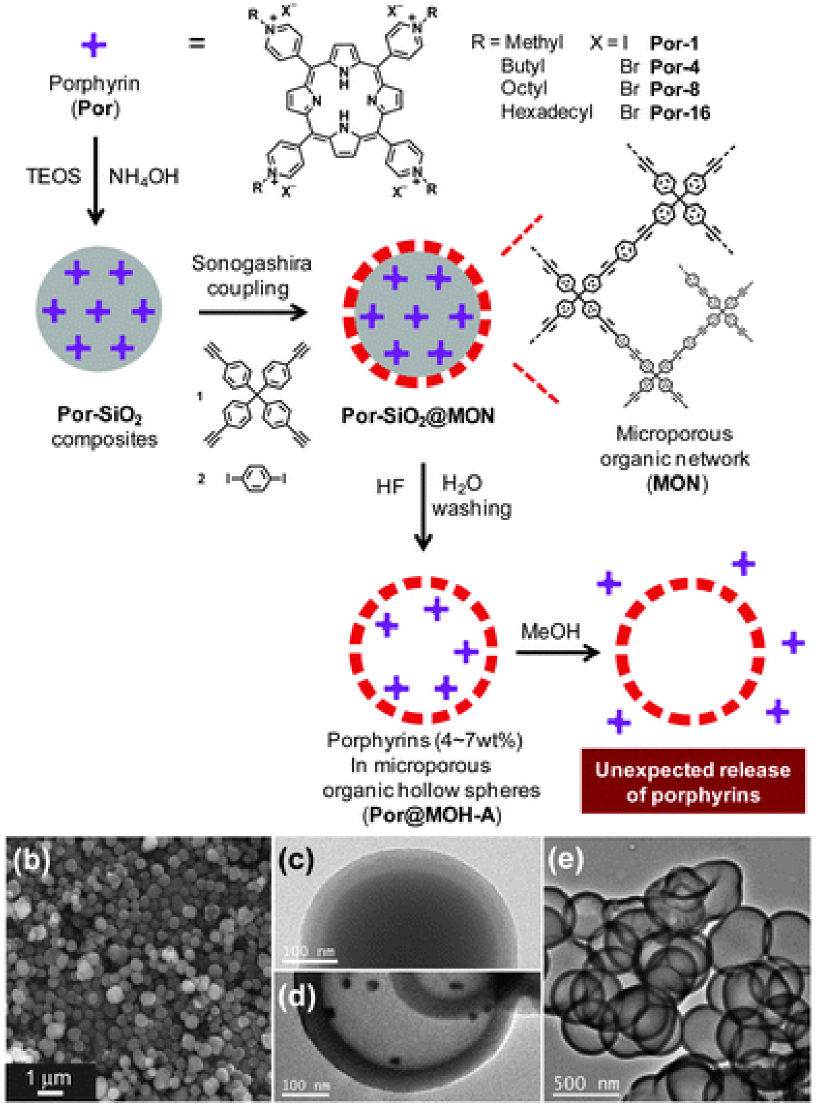
Sonogashira Coupling

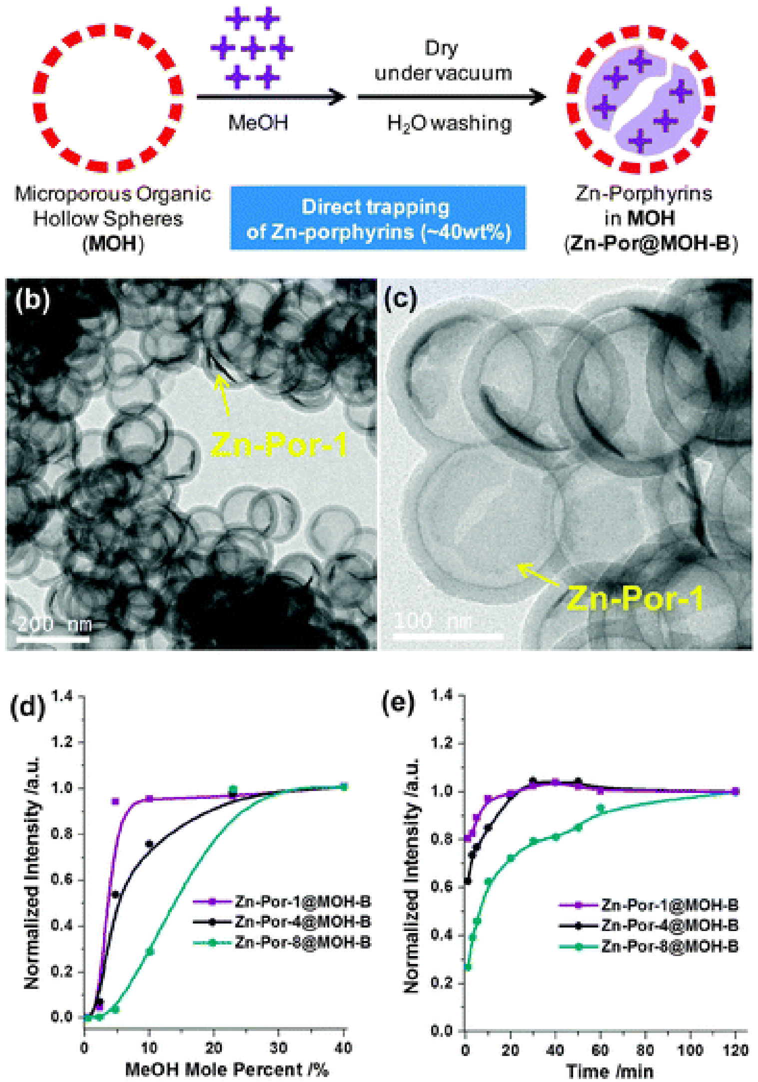




Chem. Commun., **2012**, *48*, 94

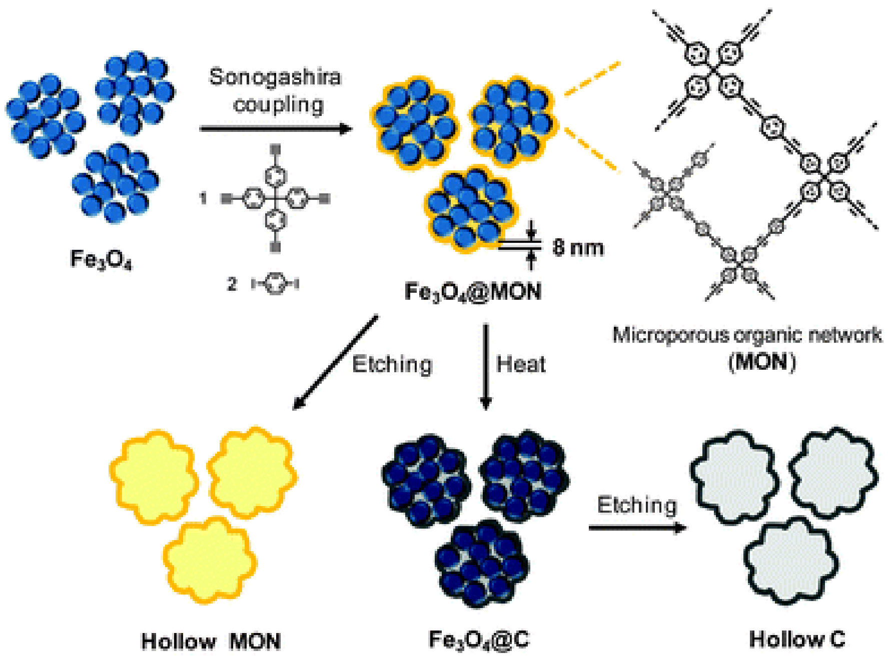
Sonogashira Coupling

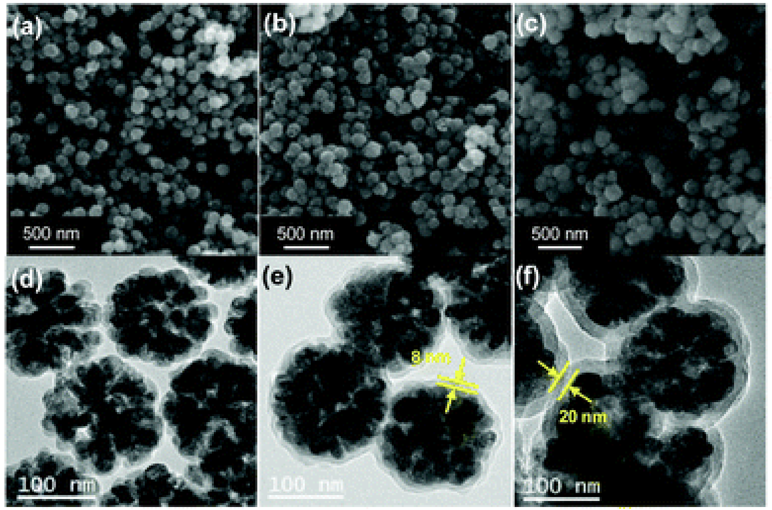


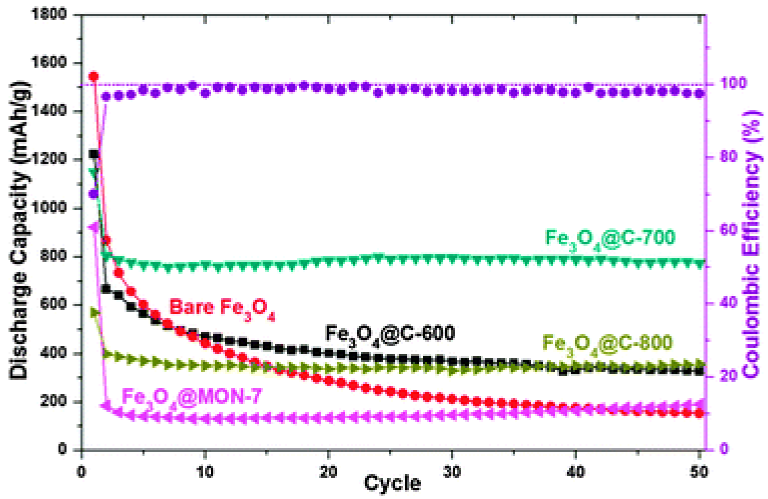


Chem. Commun., **2014**, *50*, 14885.

Sonogashira Coupling

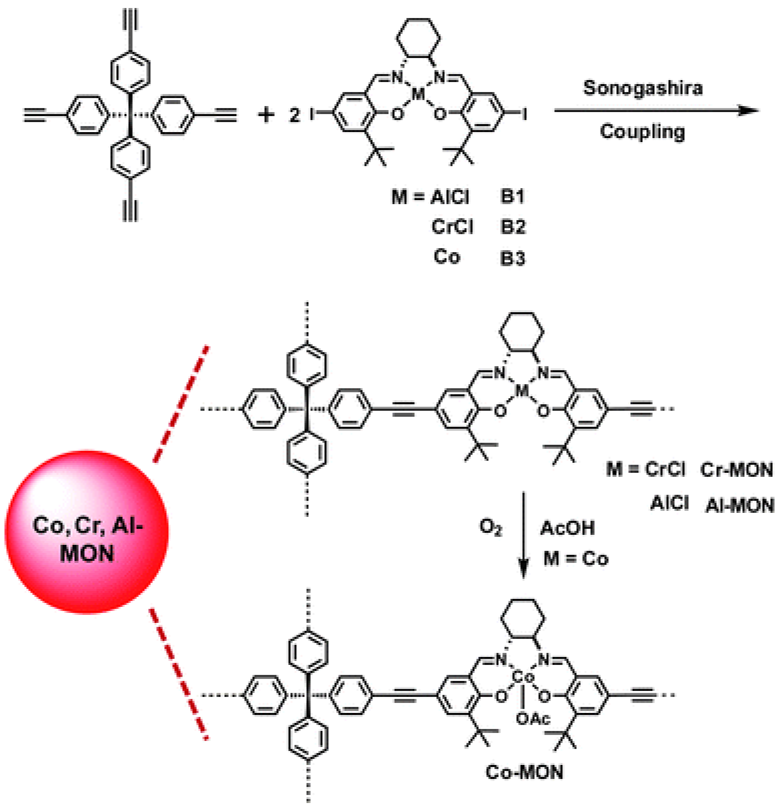


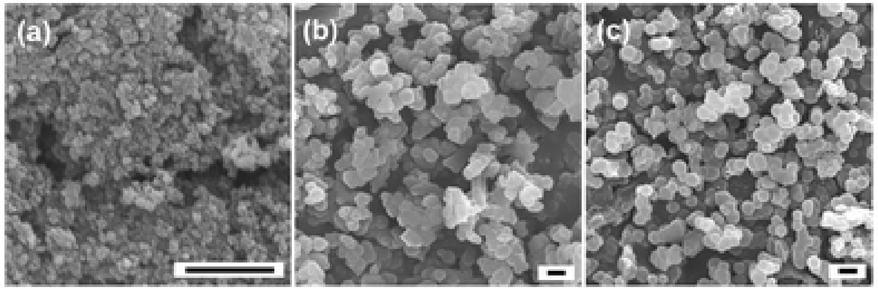


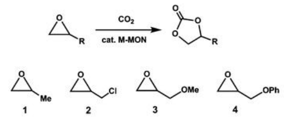


Chem. Commun., **2014**, *50*, 7723.

Sonogashira Coupling





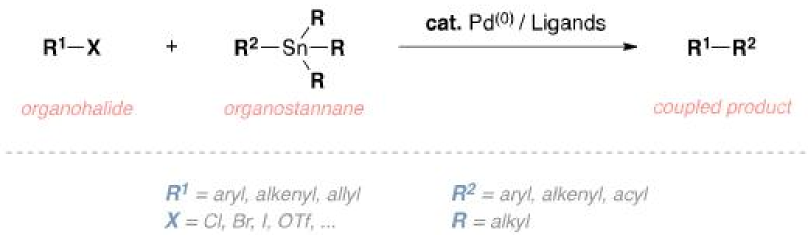


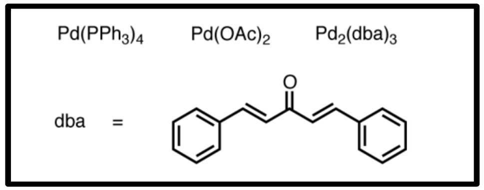
Cat./mol%[b]	P_{CO_2} (MPa)	Yield[c] (%)	TON	TOF (h^{-1})
Al-MON/0.05	1	51	1020	85
Al-MON/0.1	1	71	710	59
Cr-MON/0.05	1	66	1320	110
Co-MON/0.05	1	75	1500	125
Co-MON/0.05	1	71	1479	123
Co-MON/0.05	0.5	70	1400	117
Co-MON/0.05	3	76	1520	127
Co-salen /0.05	1	94	1880	157
Co-MON/0.05	1	93	1860	155
Co-MON/0.05	1	71	1420	118
Co-MON/0.05	1	24	480	40

J. Mater. Chem. A, **2013**, *1*, 5517

Stille Coupling

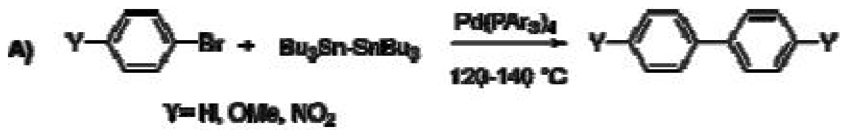
The Stille cross-coupling reaction is the organic reaction of an organohalide with an organostannane com-pound to give the coupled product using a palladium catalyst.

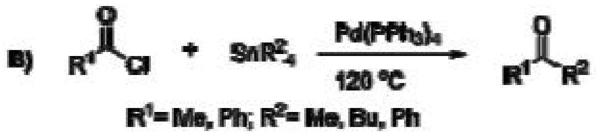




Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.

Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998.

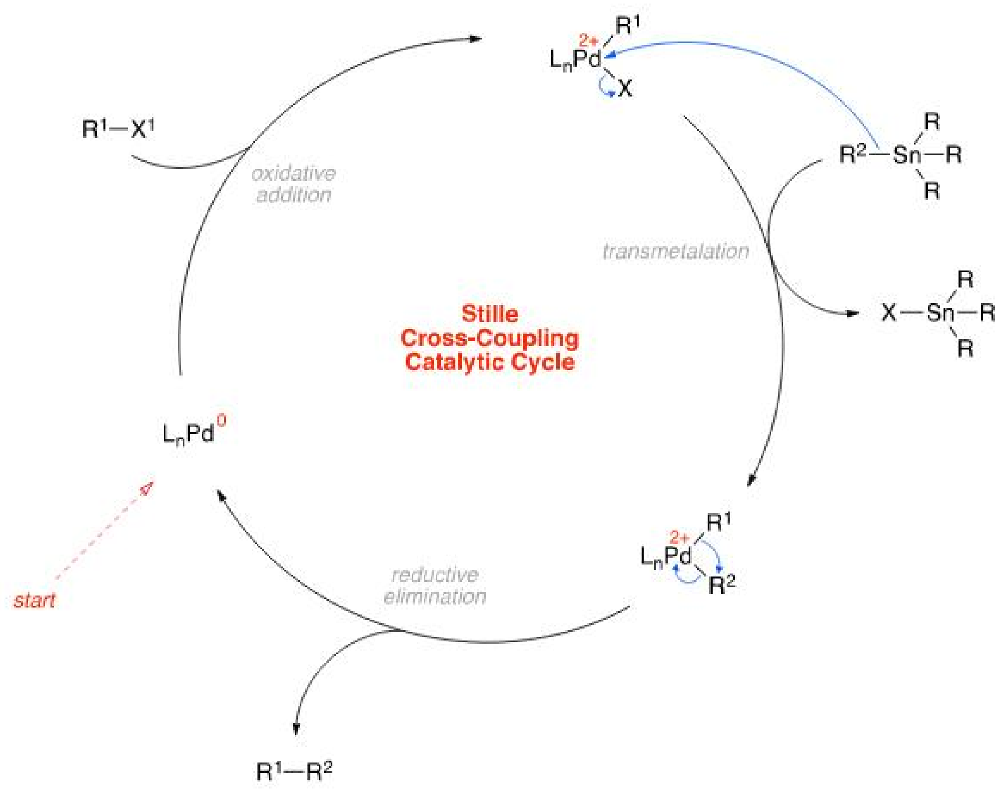




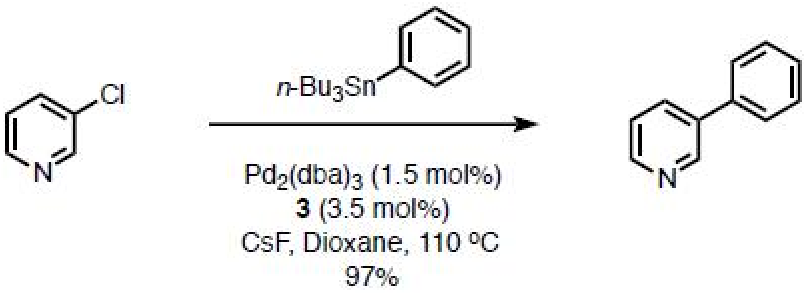
J. Organomet. Chem., **1976**, *117*, C55

Chem. Lett., **1977**, *6*, 1423

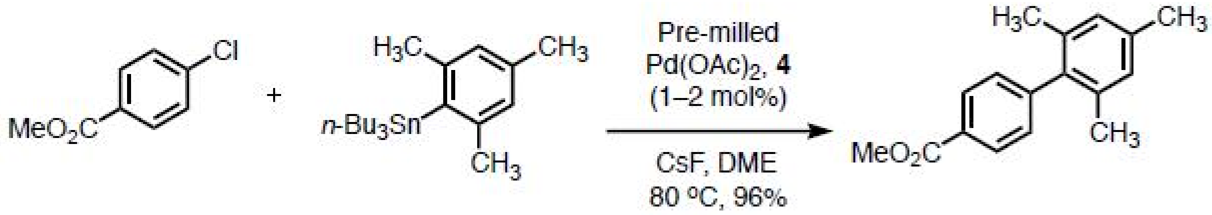
Stille Coupling



Stille Coupling



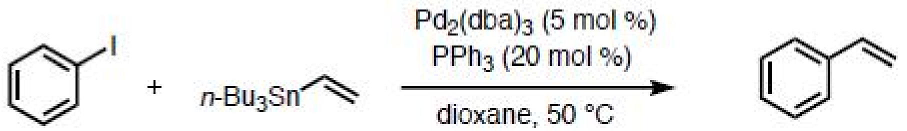
Verkade, J.G.; Su, W.; Urgaonkar, S.; McLaughlin, P.A. *J. Am. Chem. Soc.* **2004**, *126*, 16433-16439



Buchwald, S.L.; Naber, J.R. *Adv. Synth. Catal.* **2008**, *350*, 957-961

Stille Coupling

- **Additives**: CuI can increase the reaction rate by >10^2:

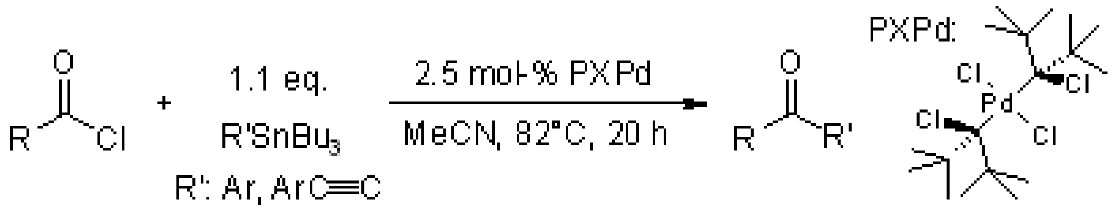


mol % CuI	relative rate
0	1
10	114

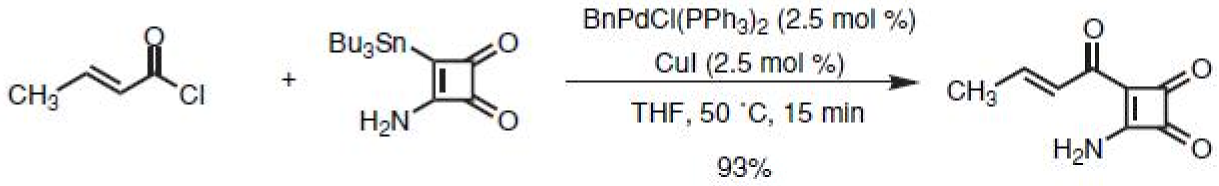
- The rate increase is attributed to the ability of CuI to scavenge free ligands; strong ligands in solution are known to inhibit the rate-limiting transmetalation step.

Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. J. Org. Chem. 1994, 59, 5905–5911.

Stille Coupling



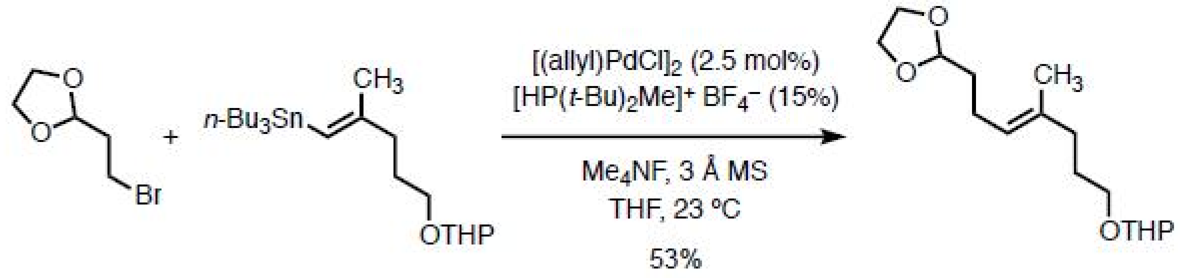
J. Org. Chem., **2005**, *70*, 8601



Liebeskind, L. S.; Yu, M. S.; Fengl, R. W. *J. Org. Chem.* **1993**, *58*, 3543–3549.

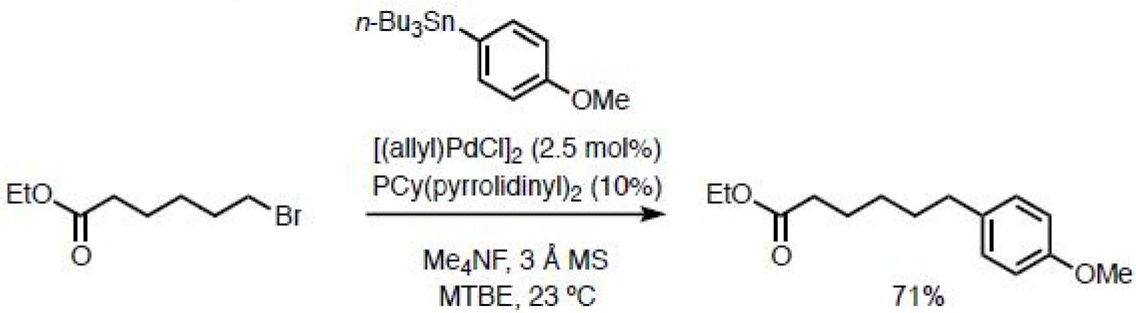
Stille Coupling

• **sp²-sp³ coupling:** alkyl-Br + vinyl-SnR_3



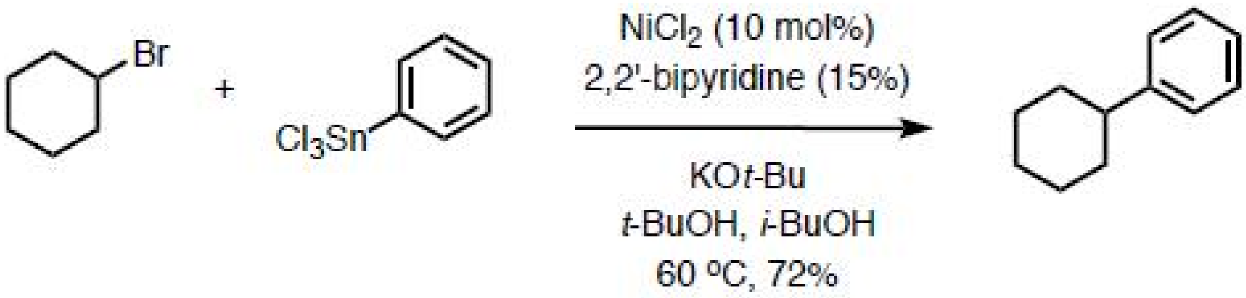
Fu, G.C.; Menzel, K. *J. Amer. Chem. Soc.* **2003**, *125*, 3718.

• using the electron-rich PCy(pyrrolidinyl)$_2$ ligand allows couplings of both vinyl and aryl stannanes with higher alkyl bromides:



Fu, G.C.; Menzel, K.; Tang, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 5079.

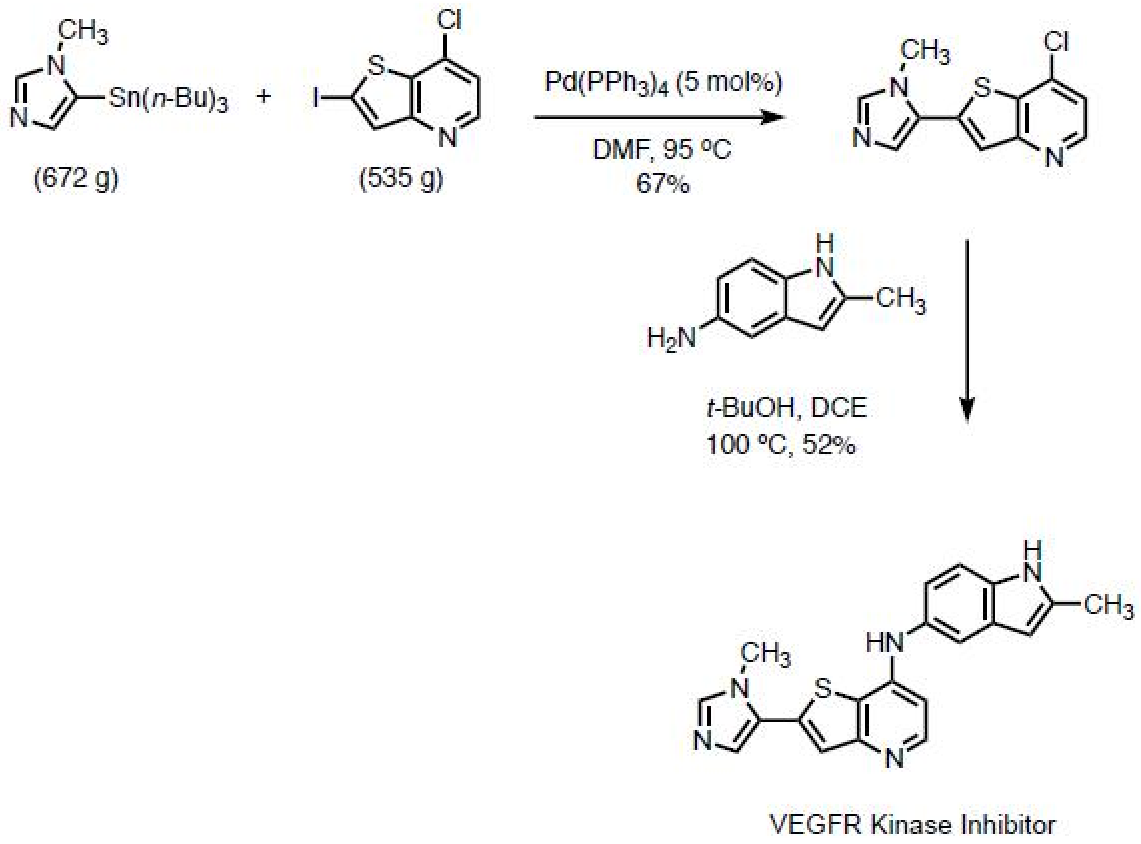
Stille Coupling



The use of $PhSnCl_3$ facilitated the removal of toxic by-products during reaction work-up.

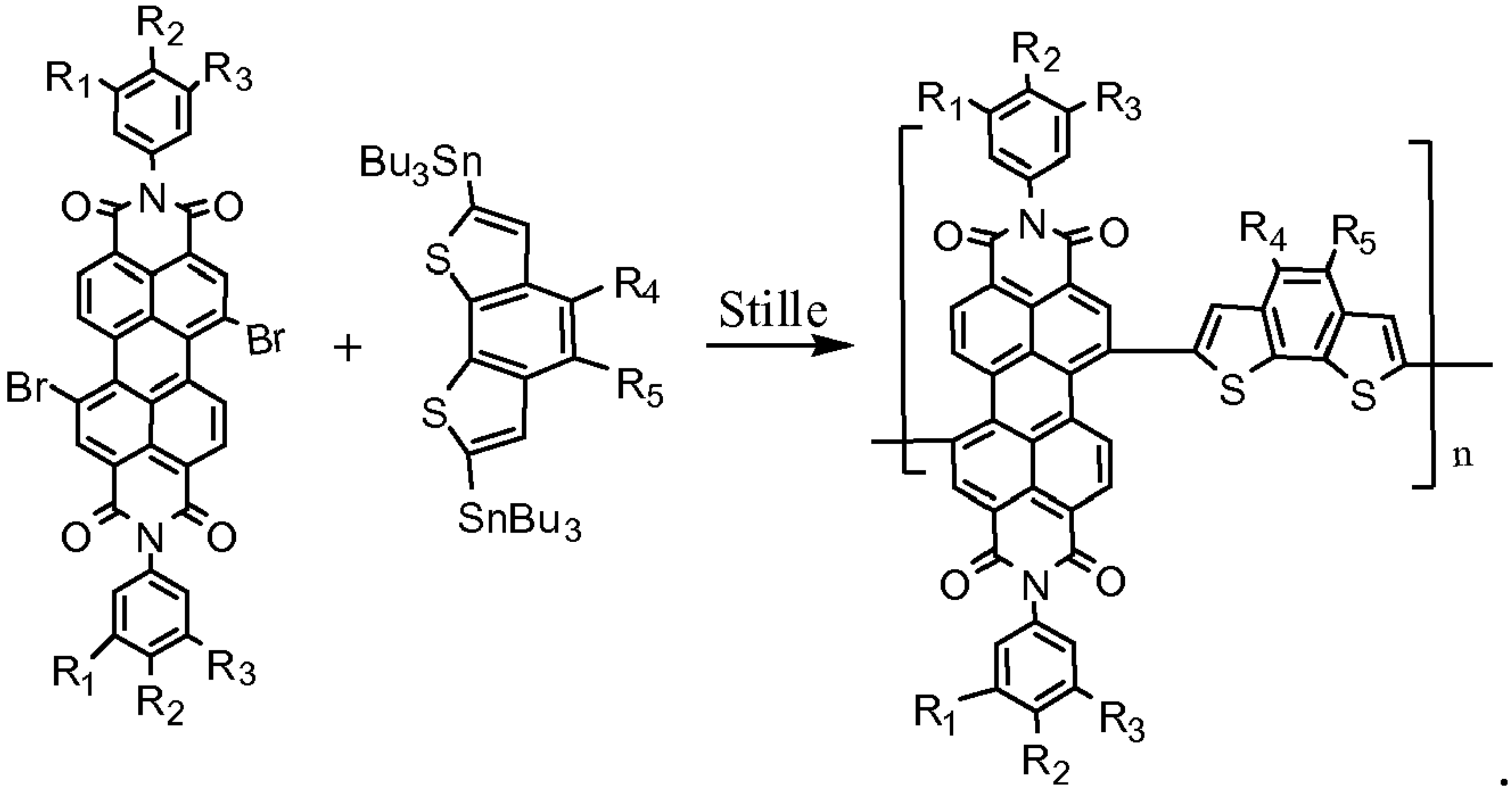
Fu, G.C.; Maki, T.; Powell, D.A. *J. Amer. Chem. Soc.* **2005**, *127*, 510

Stille Coupling

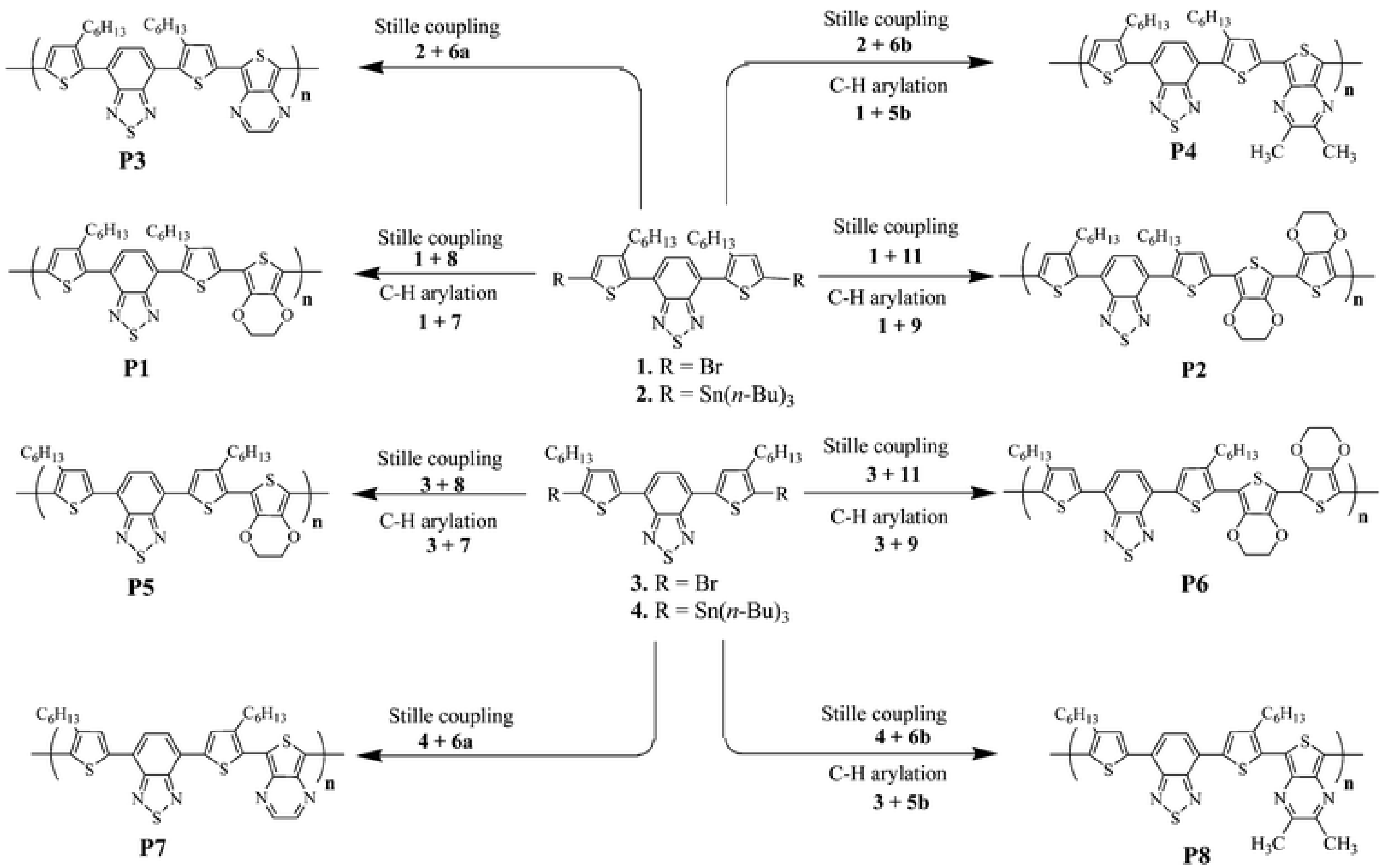


Stille reaction is the only reliable coupling method for > 50g scale synthesis.

Stille Coupling



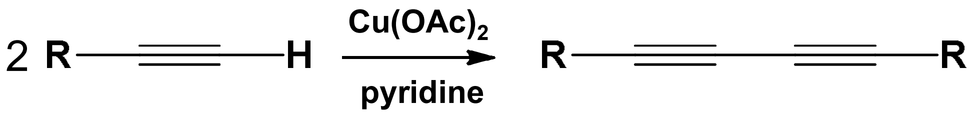
Stille Coupling



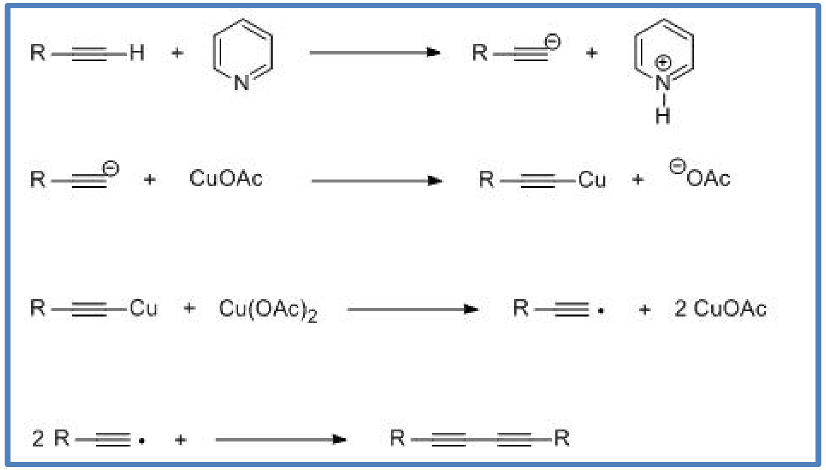
J. Mater. Chem. A, **2013**, *1*, 10306

Eglinton Reaction

The Eglinton Reaction is an oxidative coupling of terminal alkynes, and allows the synthesis of symmetric or cyclic bisacetylenes via reaction of the terminal alkyne with a stoichiometric amount of a copper(II) salt in pyridine.



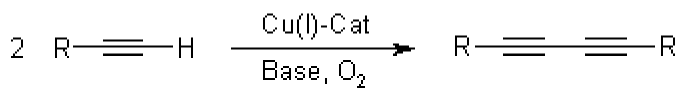
mechanism



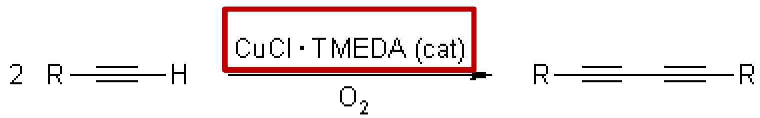
Glaser Coupling, Hay Coupling

Glaser/Hay Coupling is a synthesis of symmetric or cyclic bisacetylenes via a coupling reaction of terminal alkynes using catalytic copper (I).

Glaser coupling

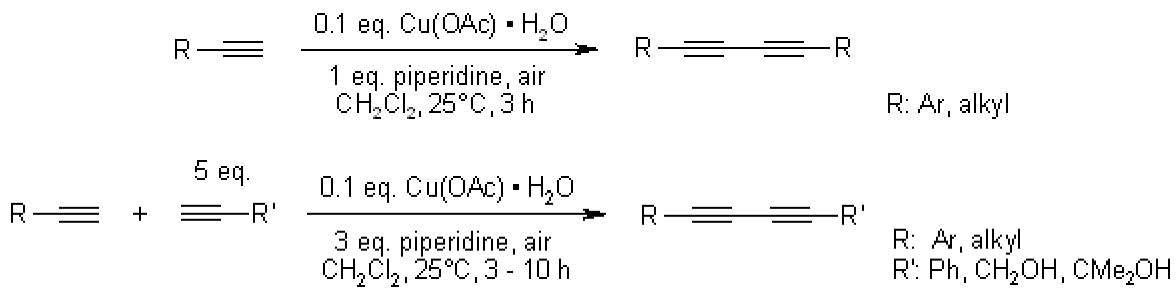


Hay coupling

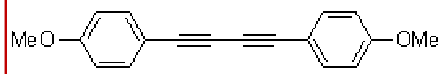
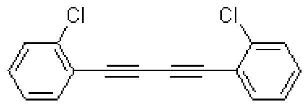
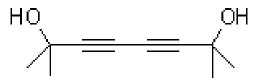
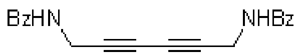
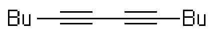
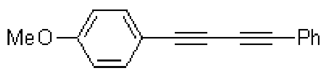
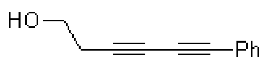
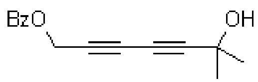


The related Hay Coupling has several advantages as compared with the Glaser Coupling. The copper-TMEDA complex used is soluble in a wider range of solvents, so that the reaction is more versatile.

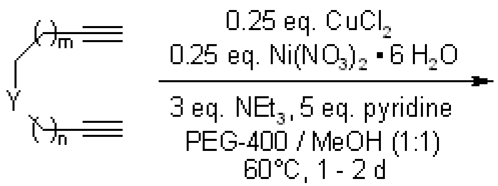
Glaser Coupling, Hay Coupling



Synthesis, **2010**, 3461

product	t (h)	yield (%, isol.)
	3	88
	3	94
	3	88
	3	77
	3	75
	8	79
	8	96
	3	90

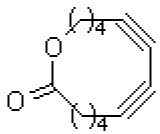
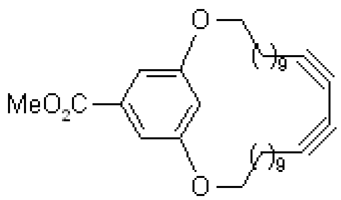
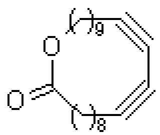
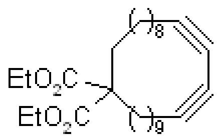
Glaser Coupling, Hay Coupling



m + n > 6

Y: CO_2, $C(CO_2Et)$, ...

J. Am. Chem. Soc., **2011**, *133*, 19976

product	yield (%, isol.)	product	yield (%, isol.)
	62		70
	78		63

Neghishi Coupling

Negishi cross-coupling reaction is the organic reaction of an organohalide with an organozinc compound to give the coupled product using a palladium or nickel catalyst.

$$R^1{-}X^1 \quad + \quad R^2{-}Zn{-}X^2 \xrightarrow[]{\textbf{cat. } Pd^{(0)} \text{ / Ligands or } \textbf{cat. } Ni \text{ / Ligands}} R^1{-}R^2$$

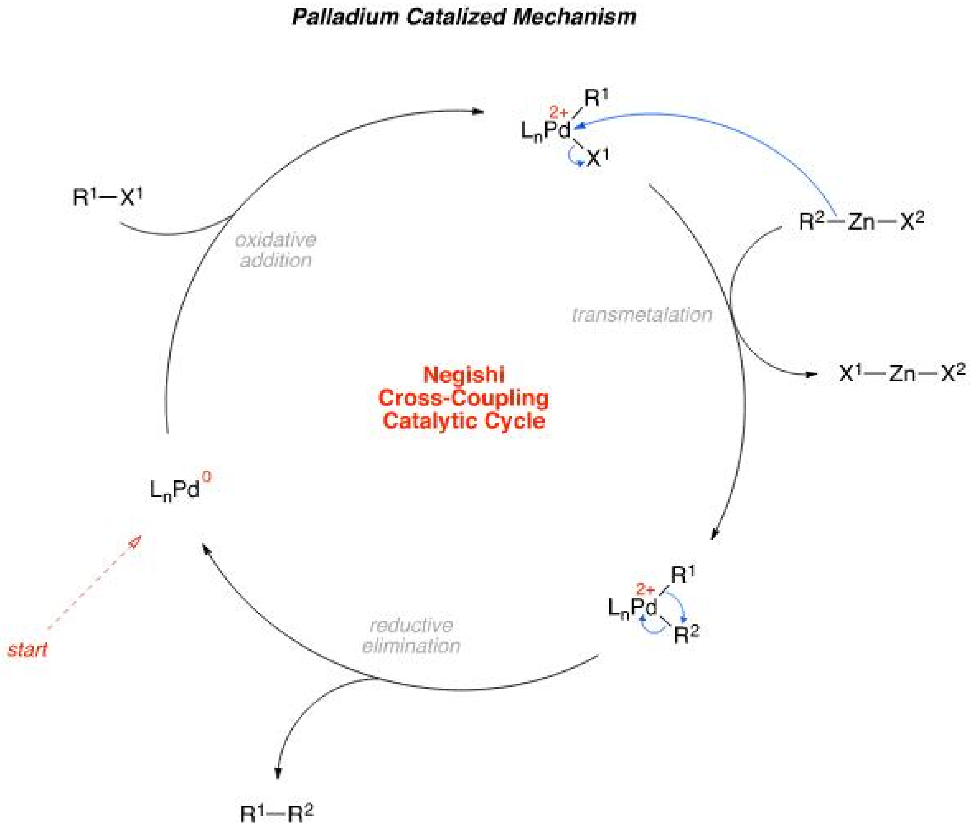
organohalide — *organozinc* — *coupled product*

R^1 = aryl, alkenyl, alkynyl, acyl, ...
X^1 = Cl, Br, I, OTf, OAc

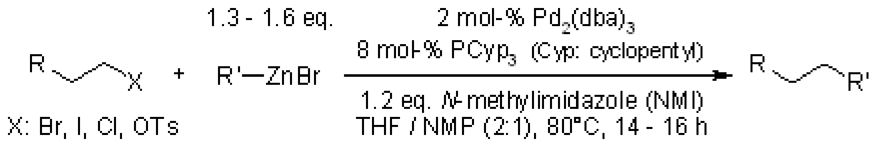
R^2 = aryl, alkenyl, allyl, benzyl, ...
X^2 = Cl, Br, I

Chem. Commun. **1977** 683–684.

Neghishi Coupling

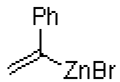
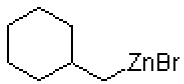
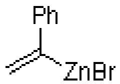
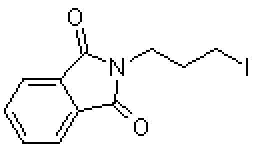
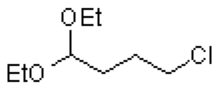
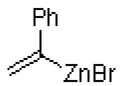


Neghishi Coupling

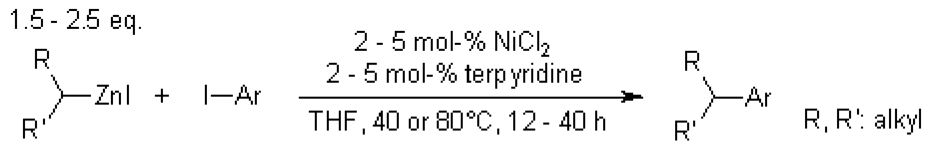


R'	R'ZnBr	t
Alkyl	1.3 eq.	14 h
Vinyl, Ar	1.6 eq.	16 h

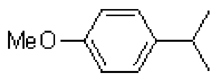
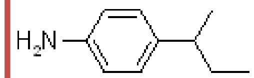
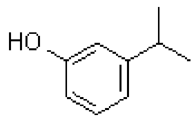
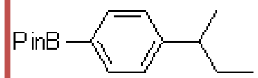
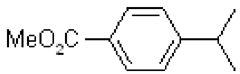
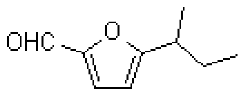
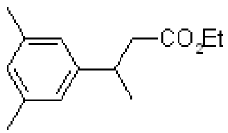
J. Am. Chem. Soc., **2003**, *125*, 12527

Halide	R'ZnBr	yield (%, isol.)	Halide	R'ZnBr	yield (%, isol.)
$H_{21}C_{10}$—Br	Bu—ZnBr	90	$H_{21}C_{10}$—Br		93
		83			
		67	$H_{21}C_{10}$—I		93
	Bu—ZnBr	48			73
$H_{21}C_{10}$—Cl	Bu—ZnBr	97	$H_{21}C_{10}$—I	Ph—ZnBr	65

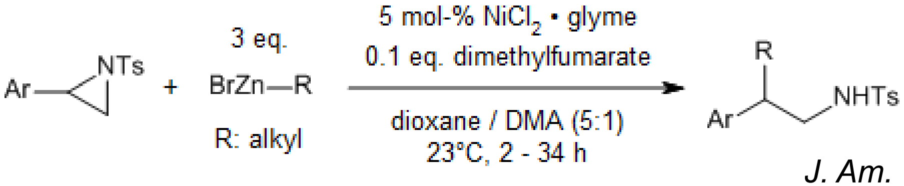
Neghishi Coupling



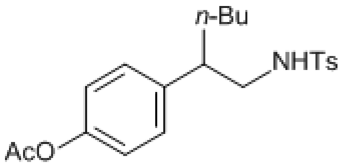
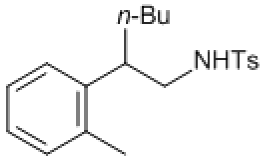
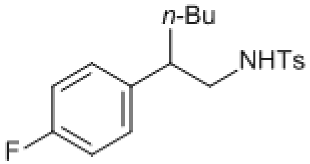
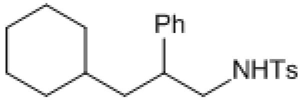
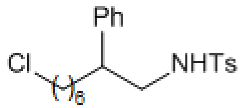
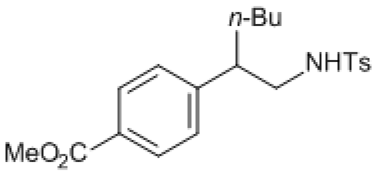
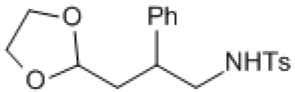
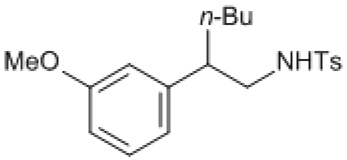
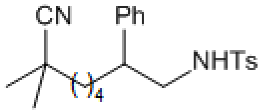
Org. Lett., **2011**, *13*, 1218

product	alkyl-ZnI (eq.)	$NiCl_2$ (mol-%)	T (°C)	t (h)	yield (%, isol.)
	1.5	2	40	17	91
	2.5	5	80	15	68
	2.5	5	80	17	82
	1.5	2	40	30	87
 (1 eq. $LiBF_4$ as additive)	1.5	5	40	40	91
	1.5	5	40	12	75
	1.5	5	80	15	80

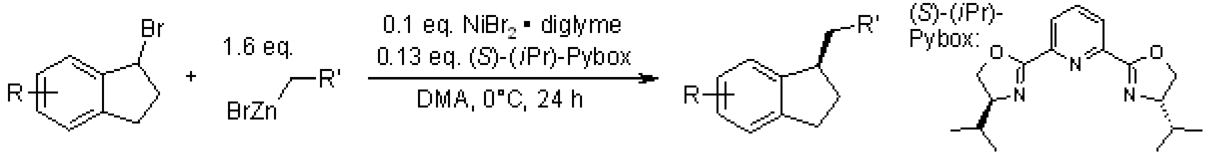
Neghishi Coupling



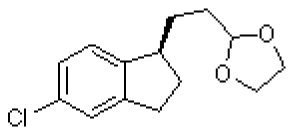
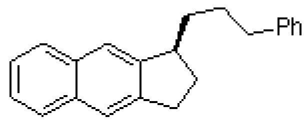
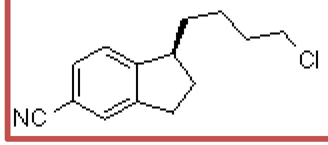
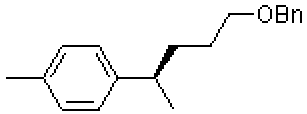
J. Am. Chem. Soc., **2012**, *134*, 9541

product	yield (%, isol.)	product	yield (%, isol.)
	79		58
	84		85
			70
	81		82
	76		90

Neghishi Coupling

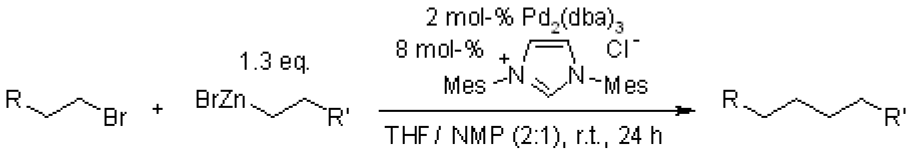


J. Am. Chem. Soc., **2005**, *127*, 10482

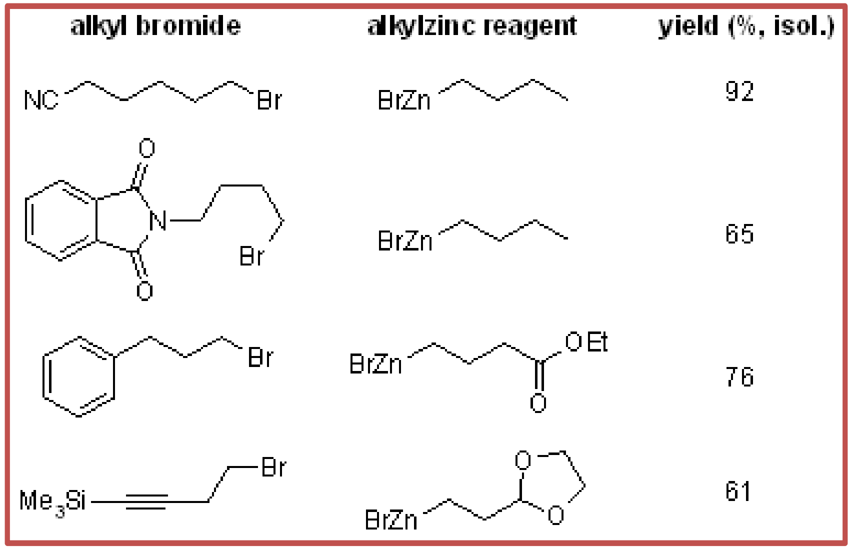
product	yield (%, isol.)	ee (%)	product	yield (%, isol.)	ee (%)
	82	91		76	98
	47	91		63	75

Neghishi Coupling

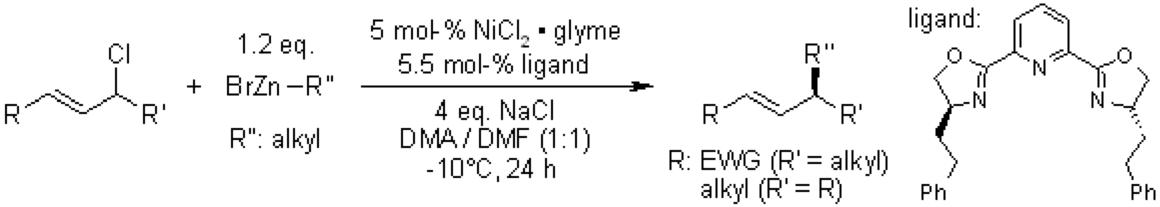
The First Negishi Cross-Coupling Reaction of Two Alkyl Centers Utilizing a Pd-N-Heterocyclic Carbene (NHC) Catalyst



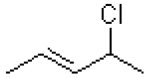
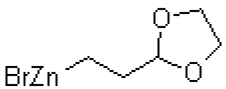
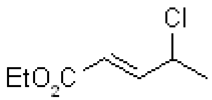
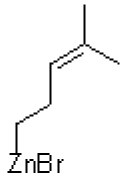
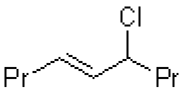
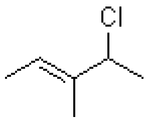
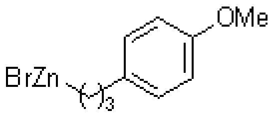
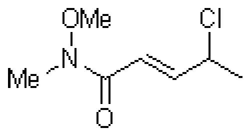
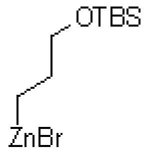
Org. Lett., **2005**, *7*, 3805



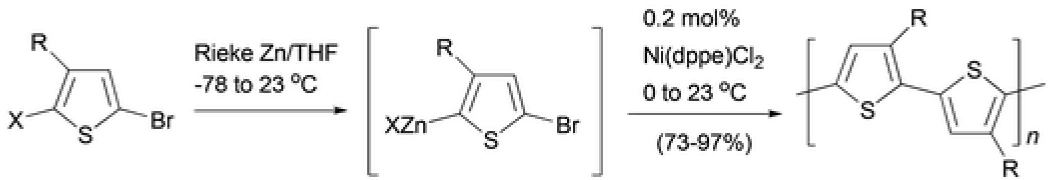
Neghishi Coupling



J. Am. Chem. Soc., **2008**, *130*, 2756

allylic chloride	R"ZnBr	ee (%)	yield (%, isol.)	allylic chloride	R"ZnBr	ee (%)	yield (%, isol.)
		90	93			96	86
		79	81				
		98	54			93	91

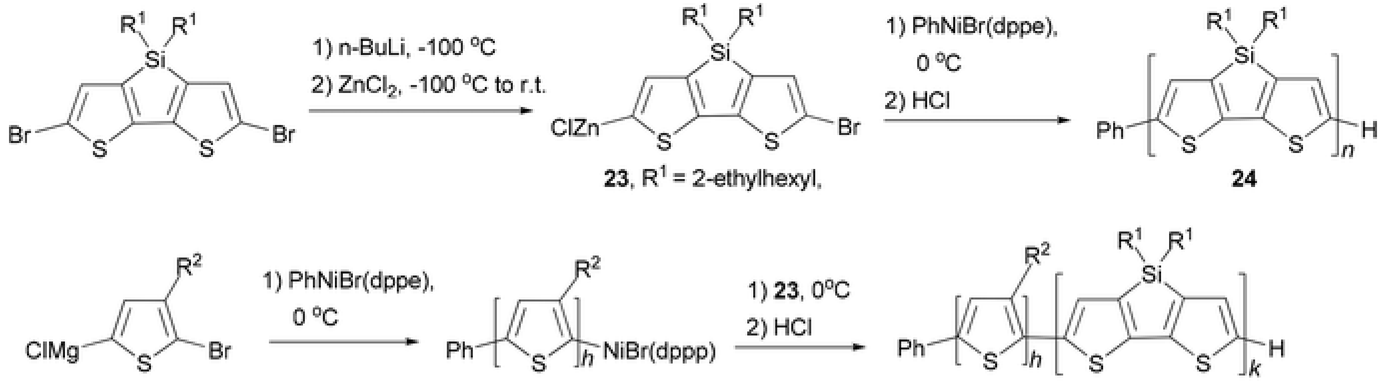
Neghishi Coupling



X = Br (**1**), I (**2**)

3, P3AT (>97% HT)

		Regioselectivity
R = butyl	(**3a**, P3BT),	97%
hexyl	(**3b**, P3HT),	>98.5%
octyl	(**3c**, P3OT),	>98.5%
decyl	(**3d**, P3DT),	>98.5%
dodecyl	(**3e**, P3DDT),	>98.5%



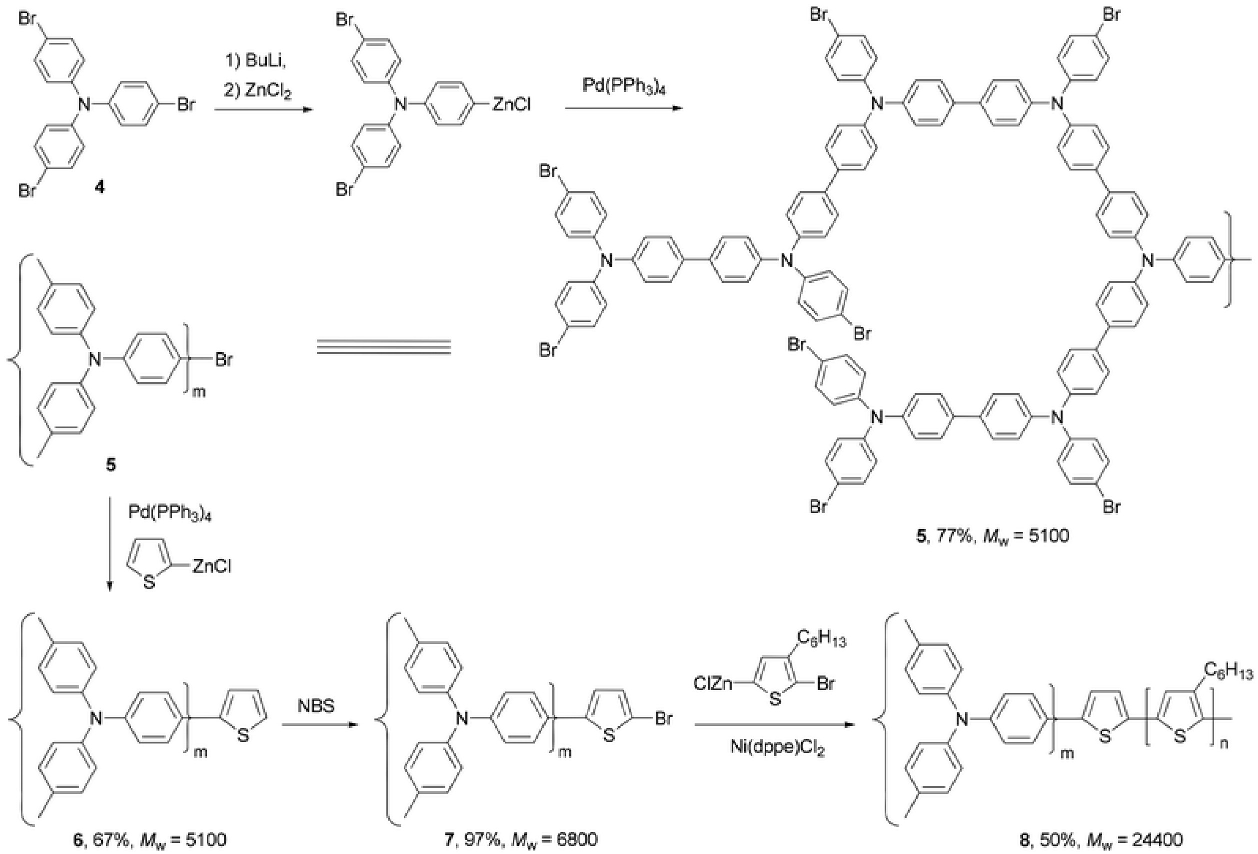
23, R^1 = 2-ethylhexyl,

24

25, R^2 = hexyl

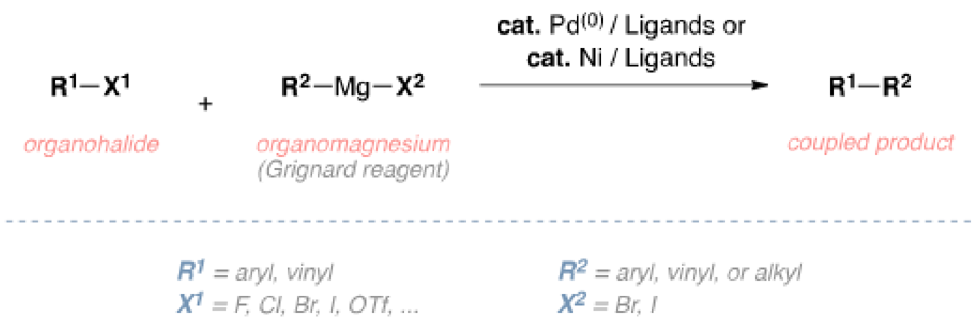
26

Neghishi Coupling

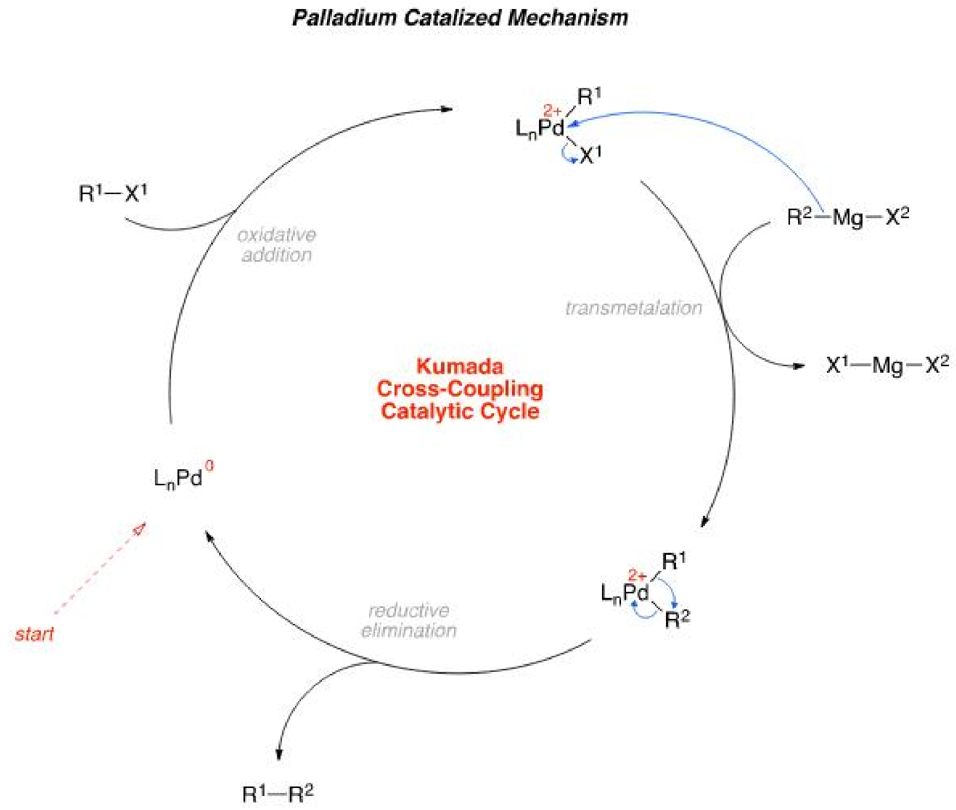


Kumada Coupling

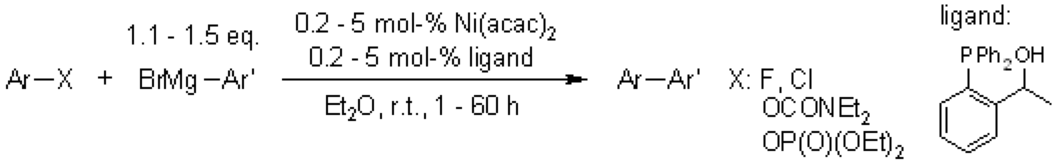
Kumada cross-coupling reaction is the organic reaction of an organohalide with an organomagnesium compound, also known as a Grignard reagent, to give the coupled product using a palladium or nickel catalyst.



Kumada Coupling

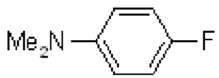
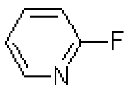
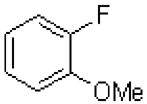
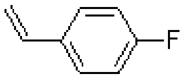
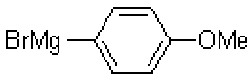
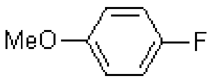
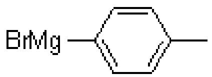
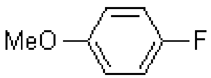
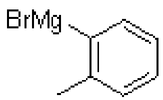


Kumada Coupling

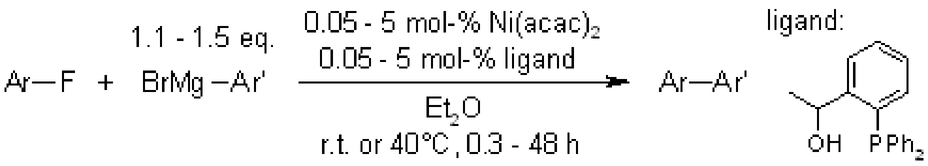


J. Am. Chem. Soc., **2009**, *131*, 9590

Hydroxyphosphine ligands (PO ligands) significantly accelerate nickel-catalyzed cross-coupling reactions of Grignard reagents with unreactive aryl electrophiles such as fluorides, chlorides, carbamates and phosphates.

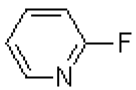
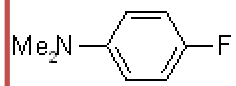
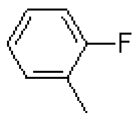
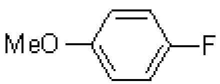
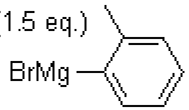
ArX	Ar'MgBr	Ar'MgBr (eq.)	catalyst (mol-%)	t (h)	yield (%, isol.)
	BrMg—Ph	1.1	1	5	87
	BrMg—Ph	1.1	0.2	2	96
	BrMg—Ph	1.1	1	9	93
		1.5	5	48	61
		1.1	1	12	97
		1.5	5	48 (reflux)	27

Kumada Coupling

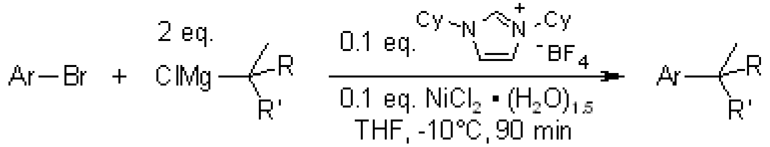


J. Am. Chem. Soc., **2005**, *127*, 17978

Nickel-catalyzed cross-coupling of Grignard reagents with aryl fluorides or chlorides can be achieved efficiently in the presence of a new triarylphosphine ligand.

aryl fluoride	RMgBr (eq.)	catalyst (mol-%)	T (°C)	t (h)	Yield (%, isol.)
	PhMgBr (1.1 eq.)	0.2	r.t	2	96
	PhMgBr (1.1 eq.)	1	r.t	5	87
	PhMgBr (1.1 eq.)	1	r.t.	5	94
	(1.5 eq.) 	5	40	48	27

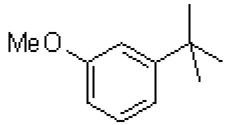
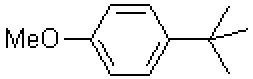
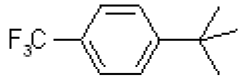
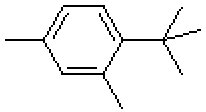
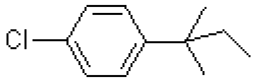
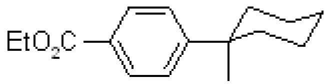
Kumada Coupling



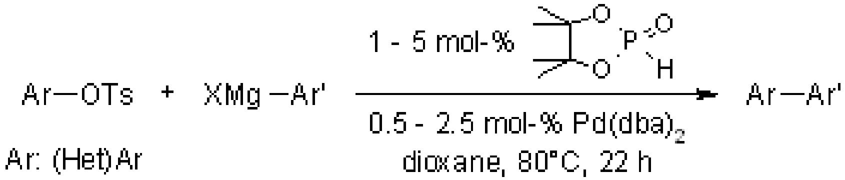
R, R': alkyl

J. Am. Chem. Soc., **2011**, *133*, 8478

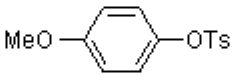
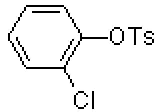
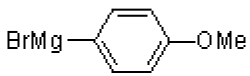
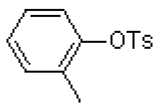
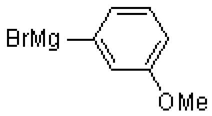
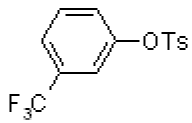
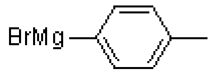
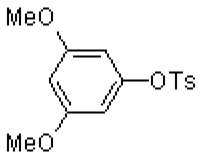
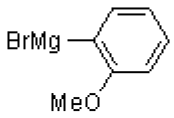
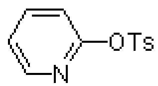
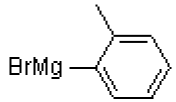
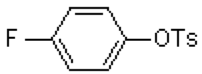
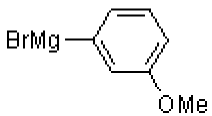
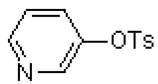
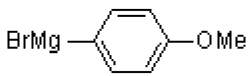
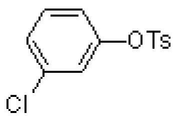
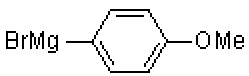
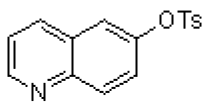
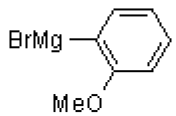
A Ni-catalyzed process for the cross-coupling of tertiary alkyl nucleophiles and aryl bromides is extremely general .

product	retent.:isomeriz.	yield (%, isol.)
	45:1	84
	34:1	75
	50:1	81
	10:1	55
	50:1	73
	12:1	76

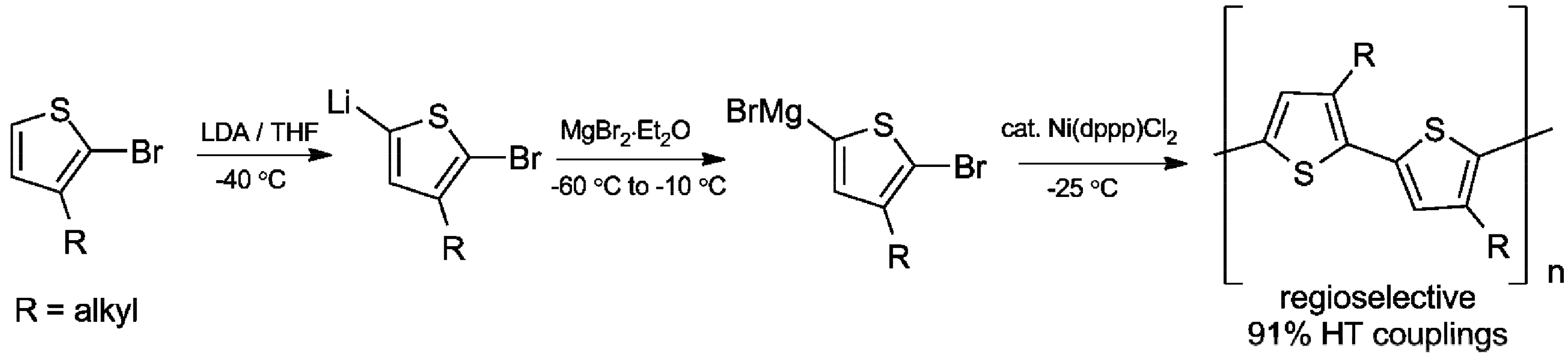
Kumada Coupling



Org. Lett., **2006**, *8*, 3457

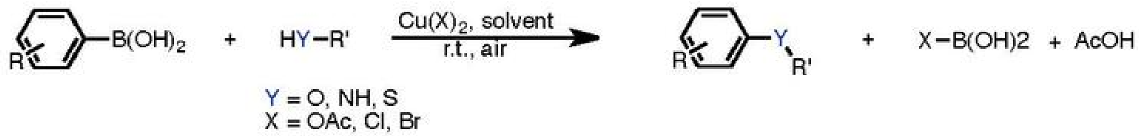
ArOTs	Ar'MgX	Pd(dba)$_2$ mol-%	Yield (%, isol.)	ArOTs	Ar'MgX	Pd(dba)$_2$ mol-%	Yield (%, isol.)
	ClMg —Ph	2.5	93			2.5	89
		2.5	86			0.5	87
		2.5	93			2.5	92
		2.5	78			2.5	98
		2.5	87			2.5	98

Kumada Coupling

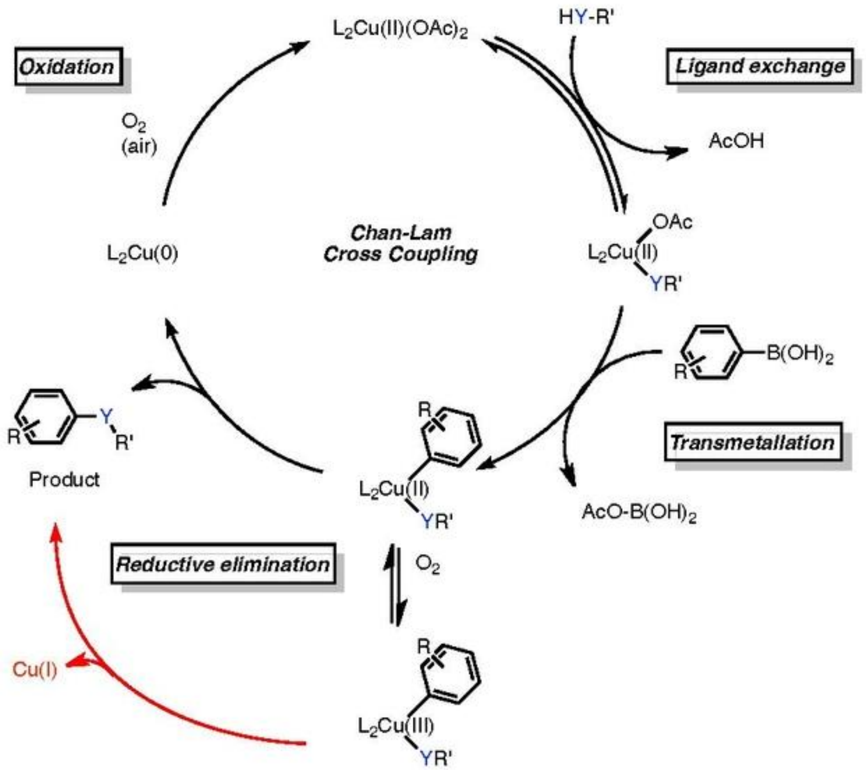


Chan-Lam Coupling

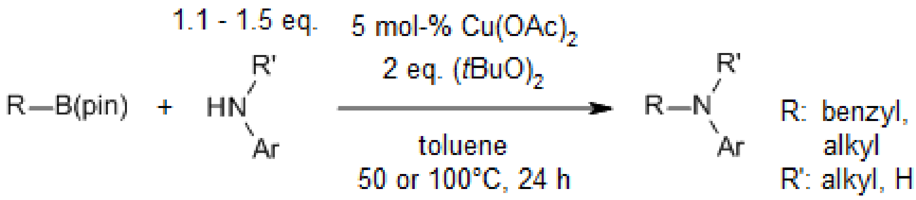
Chan-Lam coupling is a cross-coupling reaction between an aryl boronic acid and an alcoholor an amine to form the corresponding secondary aryl amines or aryl ethers, respectively. The process is catalyzed by copper salts and can performed under air.



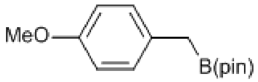
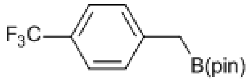
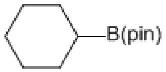
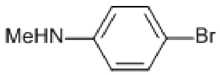
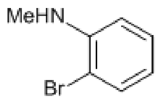
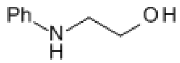
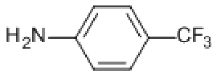
Chan-Lam Coupling



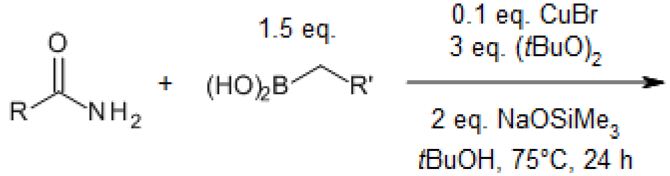
Chan-Lam Coupling



Org. Lett., **2013**, *15*, 1544

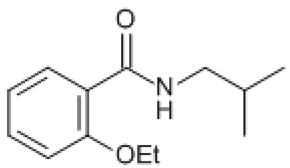
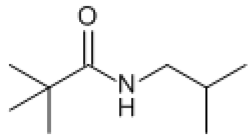
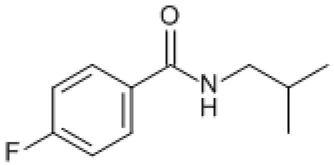
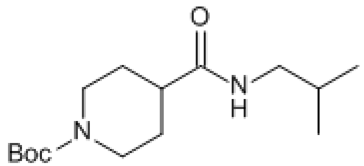
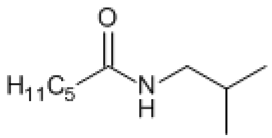
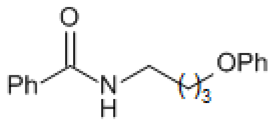
boronate	aniline	aniline (eq.)	T (°C)	yield (%, isol.)
	MeHN—Ph	1.1	100	57
	MeHN—Ph	1.5	100	48
	MeHN—Ph	1.5	80	51
	MeHN—Ph	1.5	100	51
		1.1	50	99
		1.1	100	78
		1.1	100	82
		1.1	50	78
		1.1	100	97

Chan-Lam Coupling

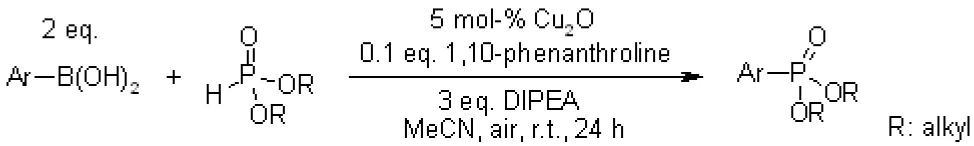


R: alkyl, Ar
R': alkyl

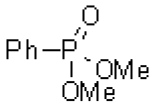
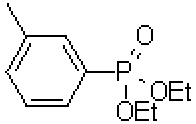
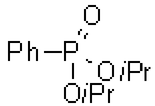
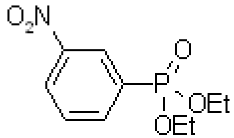
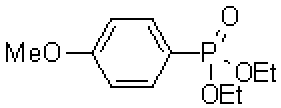
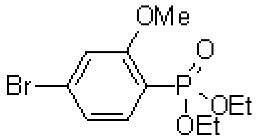
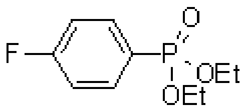
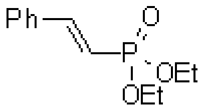
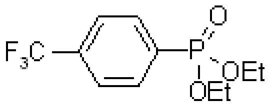
Org. Lett., **2013**, *15*, 2314

product	yield (%, isol.)	product	yield (%, isol.)
	85		79
	81		73
	70		69

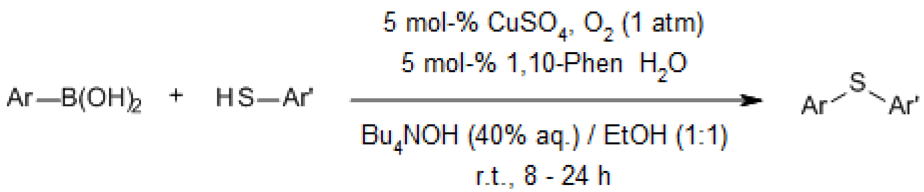
Chan-Lam Coupling



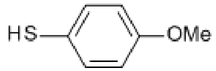
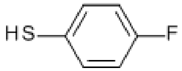
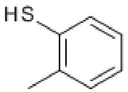
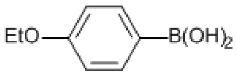
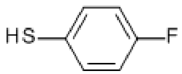
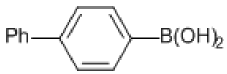
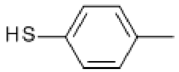
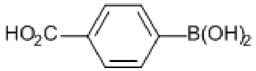
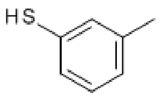
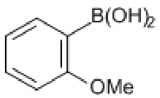
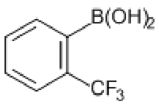
Org. Lett., **2011**, *13*, 2110

product	yield (%, isol.)	product	yield (%, isol.)
	72		86
	95		78
	83		71
	79		78
	71		

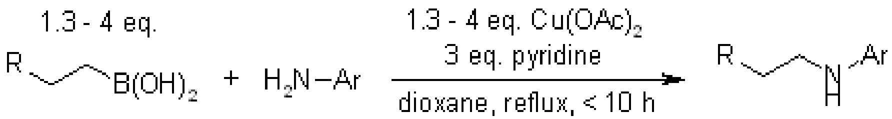
Chan-Lam Coupling



J. Org. Chem., **2012**, *77*, 2649

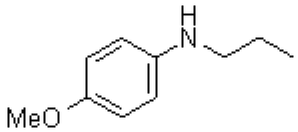
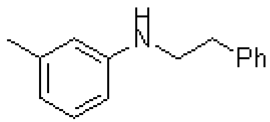
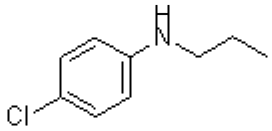
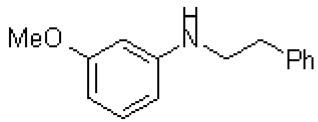
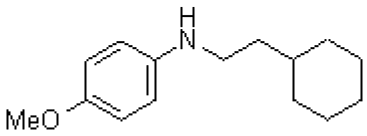
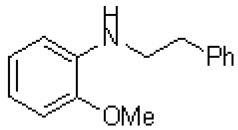
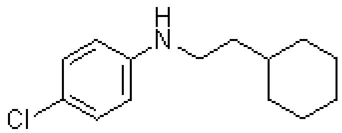
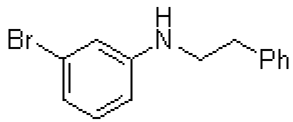
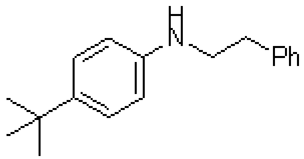
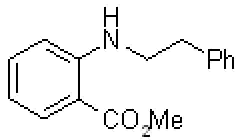
boronic acid	thiol	t (h)	yield (%, isol.)
Ph—B(OH)$_2$		8	82
Ph—B(OH)$_2$		8	80
Ph—B(OH)$_2$		8	82
		8	75
		24	68
		24	67
	HS—Ph	8	71
	HS—Ph	8	65

Chan-Lam Coupling

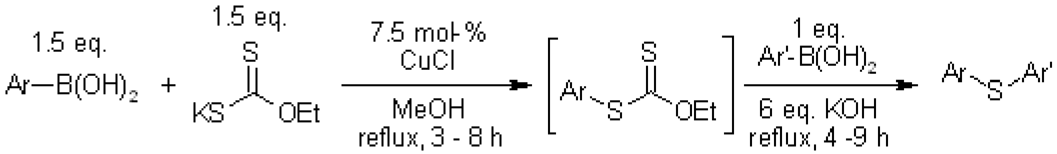


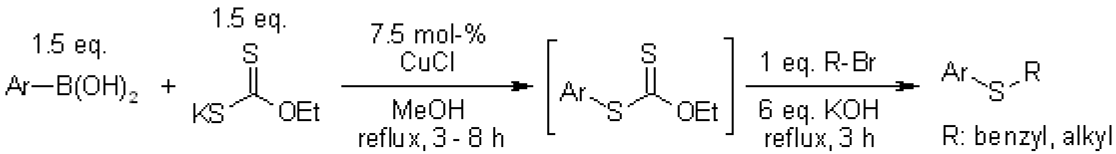
R: alkyl, Ph

Synlett, **2010**, 2101

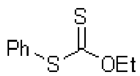
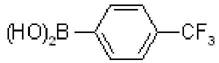
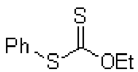
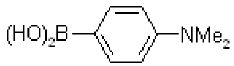
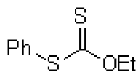
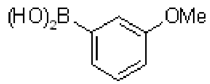
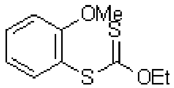
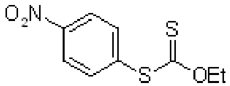
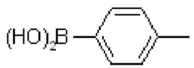
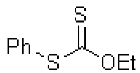
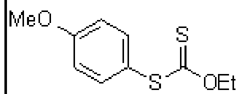
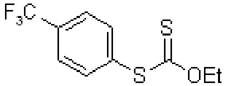
product	**boronic acid (eq.)**	**yield (%, isol.)**	**product**	**boronic acid (eq.)**	**yield (%, isol.)**
	4	95		1.3	65
	4	42		1.3	83
	4	69		1.3	69
	4	68		2	68
	1.5	83		2.5	64

Chan-Lam Coupling



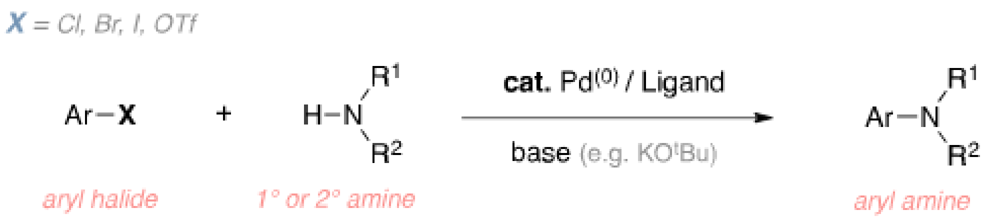


Synlett, **2011**, 3041

aryl xanthate intermediate	t_1 (h)	bromide or 2nd boronic acid	t_2 (h)	yield (%, isol.)
	3		9	89
	3		7	86
	3		5	93
	7	$(HO)_2B{-}Ph$	5	90
	8		4	67
	3		3	93
	3		3	98
	8		3	89

Buchwald-Hartwig Amination

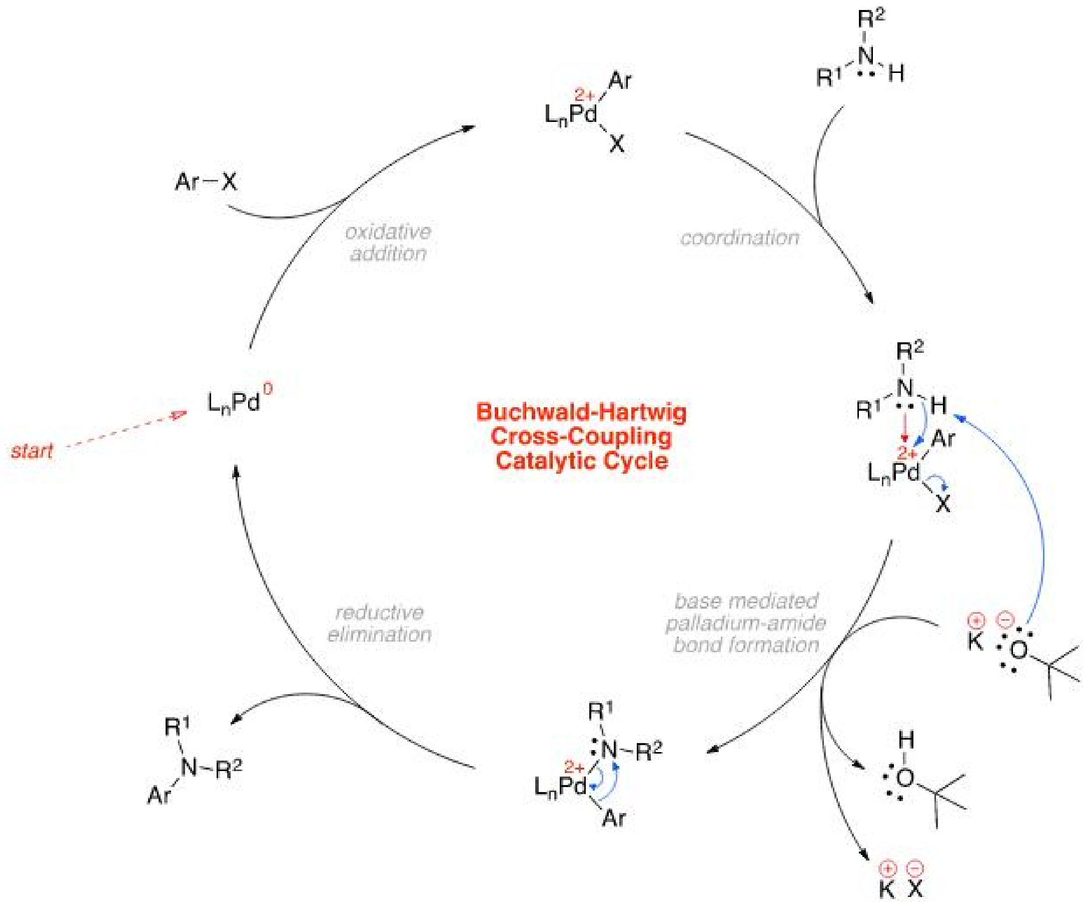
Buchwald-Hartwig amination is an organic reaction used to make carbon-nitrogen bonds. This is essentially a cross-coupling reaction of an aryl halide with an amine using palladium as a catalyst and a strong base.



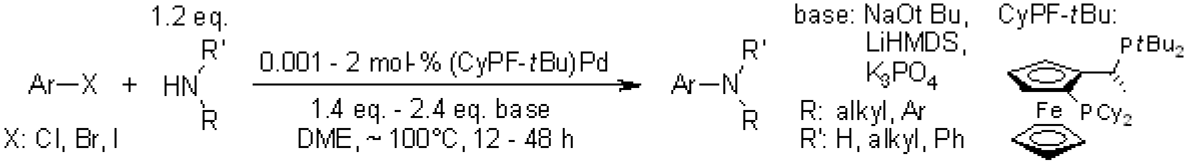
J. Am. Chem. Soc. **1994**, *116*, 5969–5970.

J. Am. Chem. Soc. **1994**, *116*, 7901–7902.

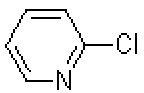
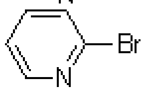
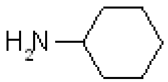
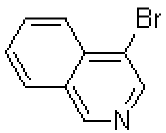
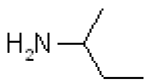
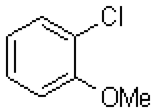
Buchwald-Hartwig Amination



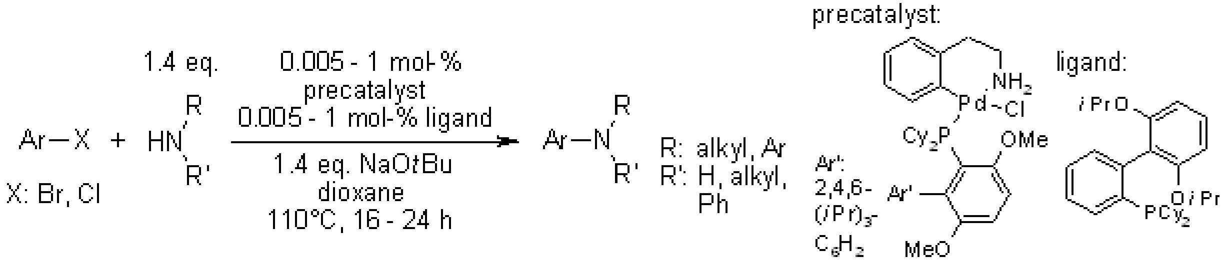
Buchwald-Hartwig Amination



air- and moisture-stable palladium catalyst, [(CyPF-*t*Bu)PdCl$_2$], for coupling of heteroaryl chlorides, bromides, and iodides with a variety of primary amines

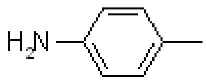
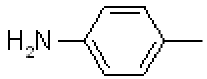
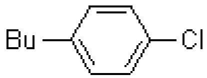
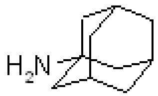
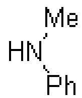
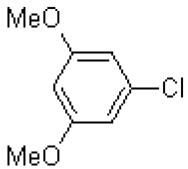
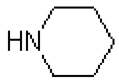
halide	amine	base	catalyst (mol-%)	T (°C)	t (h)	yield (%, isol.)
	$H_2N-C_8H_{17}$	1.4 eq. NaO*t*Bu	0.001	110	24	92
		1.4 eq. NaO*t*Bu	0.005	80	36	86
		1.4 eq. NaO*t*Bu	0.05	100	24	96
		1.4 eq. NaO*t*Bu	0.05	110	24	98

Buchwald-Hartwig Amination

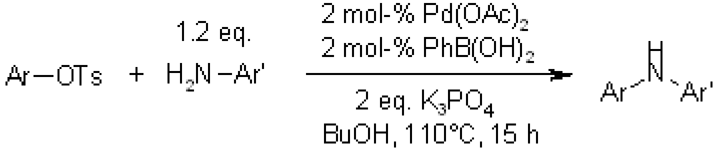


J. Am. Chem. Soc., **2010**, *132*, 15914

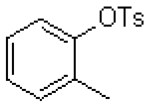
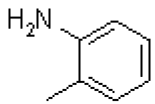
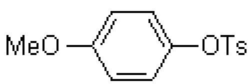
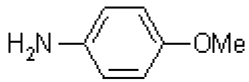
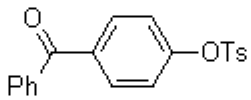
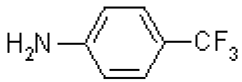
displays the highest reactivity and substrate scope of any system that has been reported to date for these reactions

aryl halide	amine	precatalyst (mol-%)	yield (%, isol.)
Ph–Cl		0.01	99
Ph–Br		0.005	99
		1	81
Ph–Cl		0.01	98
		0.05	80

Buchwald-Hartwig Amination



Synlett, **2011**, 955-958

aryl tosylate	amine	yield (%, isol.)	aryl tosylate	amine	yield (%, isol.)
	H_2N–Ph	93	Ph–OTs		88
	H_2N–Ph	96	Ph–OTs		95
	H_2N–Ph	95	Ph–OTs		59