

## Direct Catalytic Cross-Coupling of Organolithium Compounds

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Feringa, B. L. *et al.*  
*Nature Chem.* **2013**, 5, 667.



# Organolithium compounds

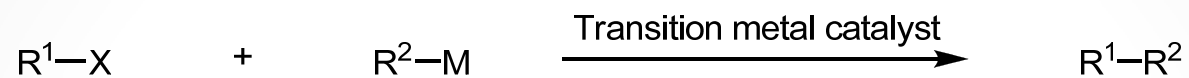
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## Uses and properties

- **Highly reactive nucleophiles and react with almost all types of electrophiles**
- **Deprotonate almost all hydrogen-containing compounds except alkanes**
- **Preparation of other organometallic compounds**  
Organocopper; Organozinc; Grignard reagents; Organotin; Organosilicon; Organoboron;  
Organophosphorus; Organosulfur
- **Aryllithium derivatives are intermediates in directed ortho metalation**  
 $\text{Me}_2\text{NCH}_2\text{C}_6\text{H}_4\text{-2-Li}$  was obtained from dimethylbenzylamine and butyllithium

# Catalytic cross-coupling reactions

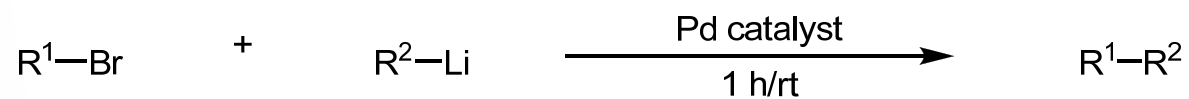
## Well established methods



X = halide or sulfonate

Stille (M = Sn); Negishi (M = Zn); Suzuki-Miyaura (M = B); Hiyama-Denmark (M = Si); Kumada (M = Mg)

## This work: M = Li



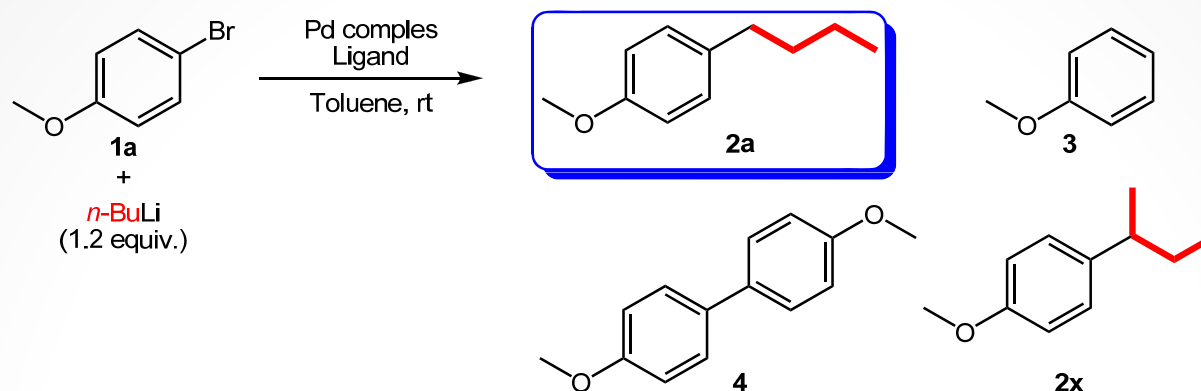
R<sup>1</sup> = alkenyl, aryl, heteroaryl

R<sup>2</sup> = alkyl, aryl, heteroaryl

Selectivity > 95%  
High yield

Feringa, B. L. *et al. Nature Chem.* **2013**, 5, ASAP.

# Conditions screening

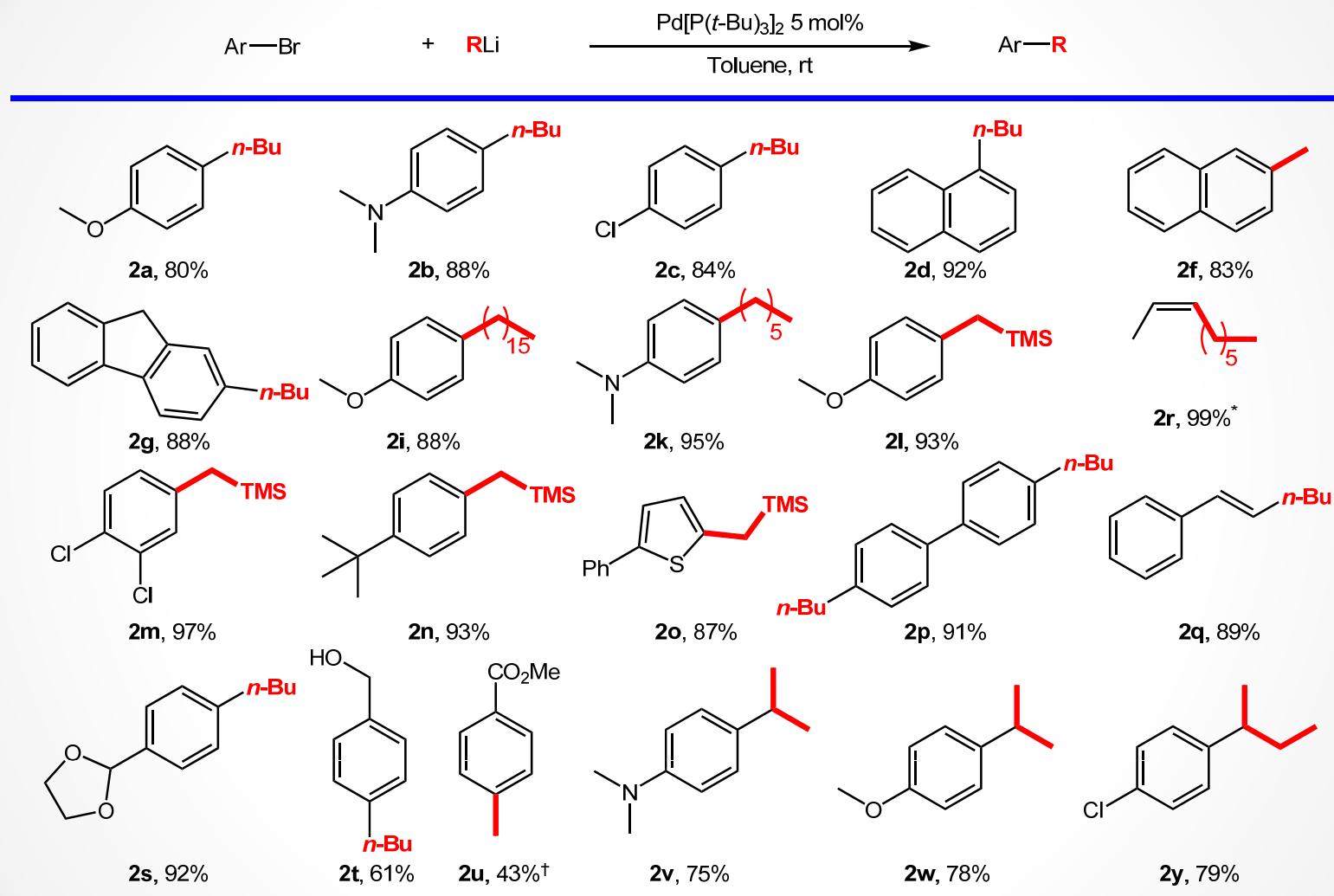


Entry	Pd complex	Ligand	Time (h)	Conv. (%)	<b>2a:3:4:2x*</b>
1	Pd <sub>2</sub> (dba) <sub>3</sub> , 2.5 mol%	XPhos, 10 mol%	3	Full	80:5:10:5
2	-	-	3	25	-:>95:-:-
3	Pd <sub>2</sub> (dba) <sub>3</sub> , 2.5 mol%	-	3	22	23:48:29:-
4	Pd <sub>2</sub> (dba) <sub>3</sub> , 2.5 mol%	SPhos, 10 mol%	1	Full	89:5:6:-
5	Pd <sub>2</sub> (dba) <sub>3</sub> , 2.5 mol%	P( <i>t</i> -Bu) <sub>3</sub> , 6 mol%	1	Full	90:6:4:-
6	Pd[P( <i>t</i> -Bu) <sub>3</sub> ] <sub>2</sub> , 5 mol%	-	1	Full	96:4:-:-
7	Pd[P( <i>t</i> -Bu) <sub>3</sub> ] <sub>2</sub> , 1 mol%	-	1	Full	95:4:1:-

\*Ratio of products determined by gas chromatography analysis.

Conditions: 1.2 equiv. *n*-BuLi (1.6 M solution in hexane diluted with toluene to a final concentration of 0.36 M) was added to a solution of 4-methoxy-bromobenzene (3 mmol) in toluene (2 ml).

# Scope of Pd-catalysed cross-coupling of alkyl lithium reagents

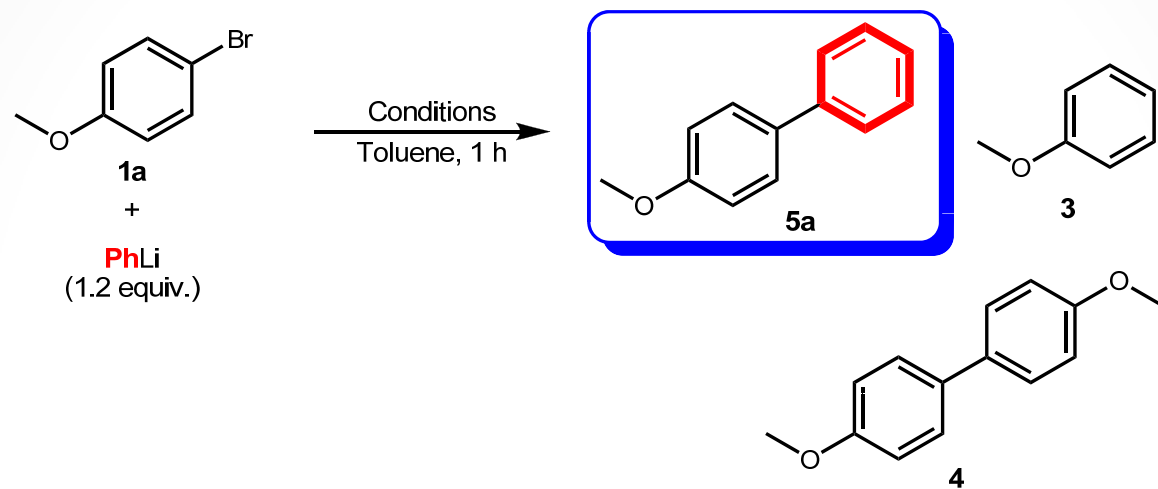


Conditions: aryl bromide (0.3 mmol), RLi (0.36 mmol, diluted with toluene to reach 0.36 M concentration and added over 1 h), Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub> 5 mol%, toluene (2 ml) at room temperature. Selectivity >95% in all cases, unless otherwise noted. Yield values refer to isolated yields after purification.

\*GC yield: product was not isolated due to volatility issues.

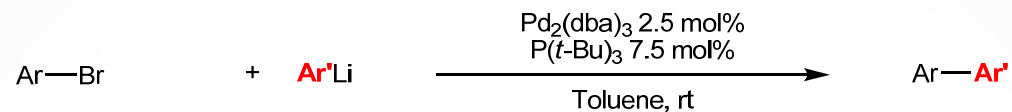
†Reaction carried out with the corresponding aryl iodide, 7.5 mol% Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub> at -10 °C.

# Cross-coupling of phenyllithium and 4-methoxy-bromobenzene



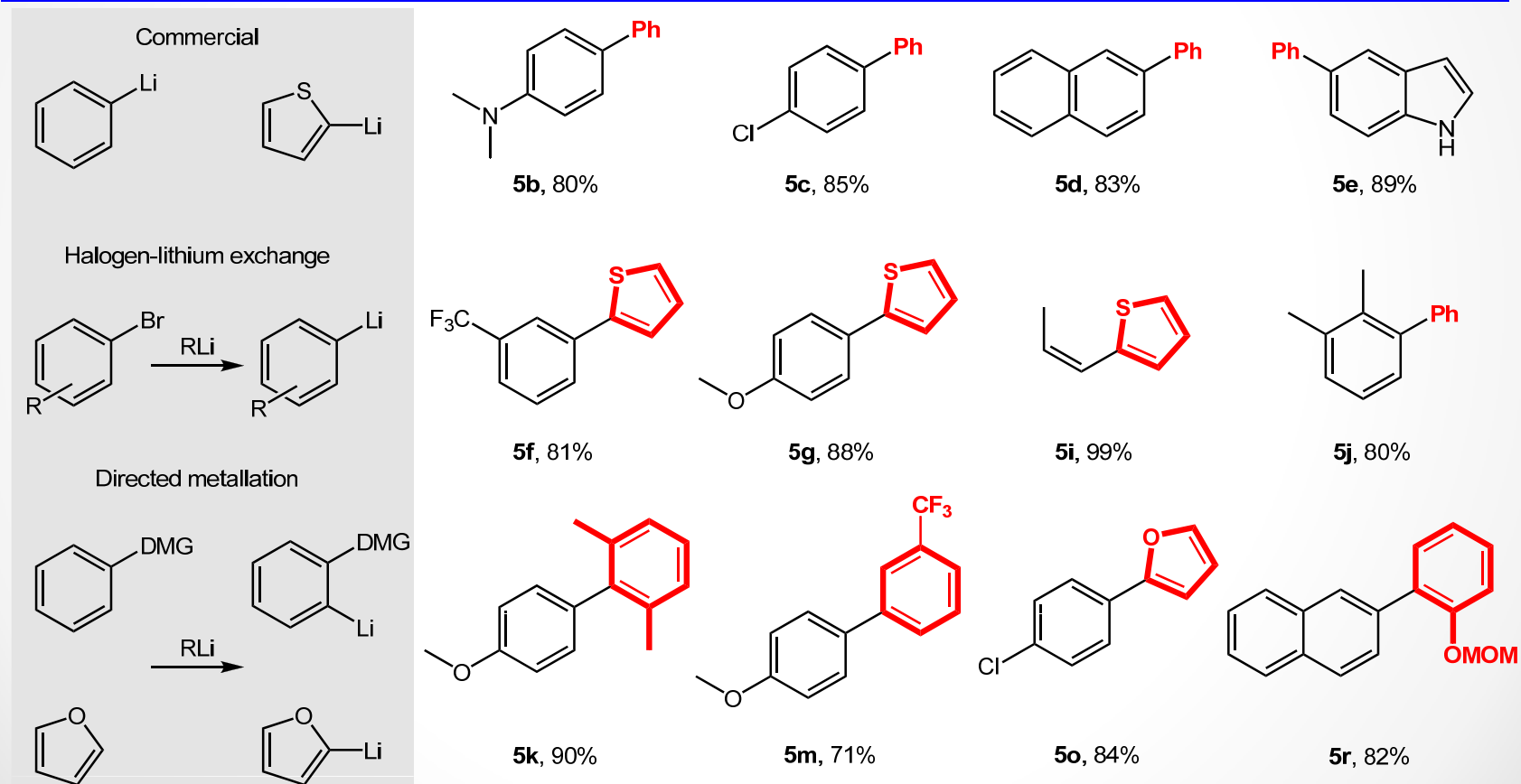
Conditions:	Conversion	<b>5a:3:4</b>
Pd[P( <i>t</i> -Bu) <sub>3</sub> ] <sub>2</sub> 5 mol%	70%	90:-:10
Pd <sub>2</sub> (dba) <sub>3</sub> 2.5 mol%, P( <i>t</i> -Bu) <sub>3</sub> 7.5 mol%	Full	98:-:2

# Scope of Pd-catalysed cross-coupling of aryllithium reagents



## Organolithium source

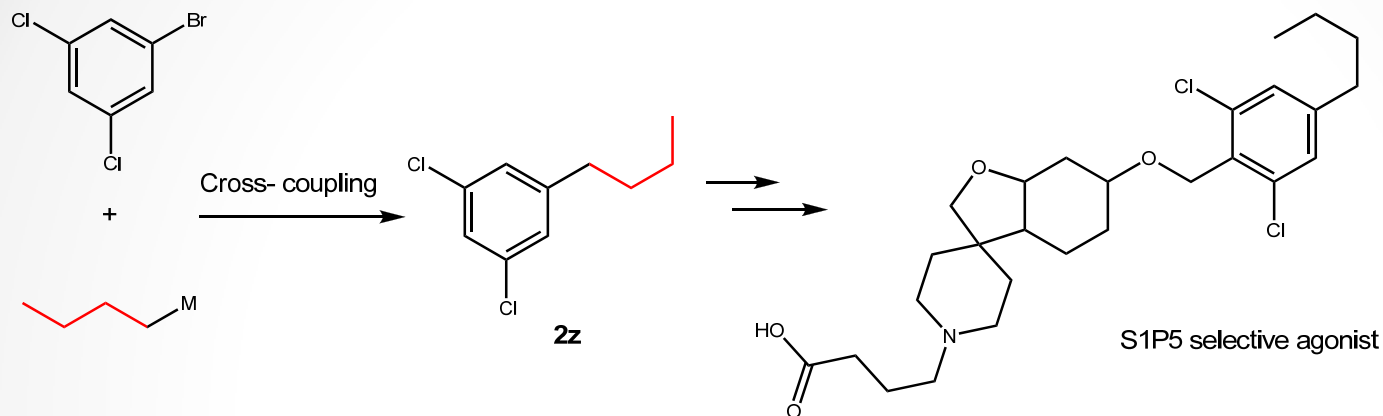
## Products



Conditions: bromide (0.3 mmol), ArLi (0.45 mmol, diluted with THF to reach 0.60 M concentration and added over 1 h), Pd<sub>2</sub>(dba)<sub>3</sub> 2.5 mol%, P(*t*-Bu)<sub>3</sub> 7.5 mol%, toluene (2 ml) at room temperature. Selectivity >95% in all cases.



# The advantages of cross-coupling of organolithium compounds

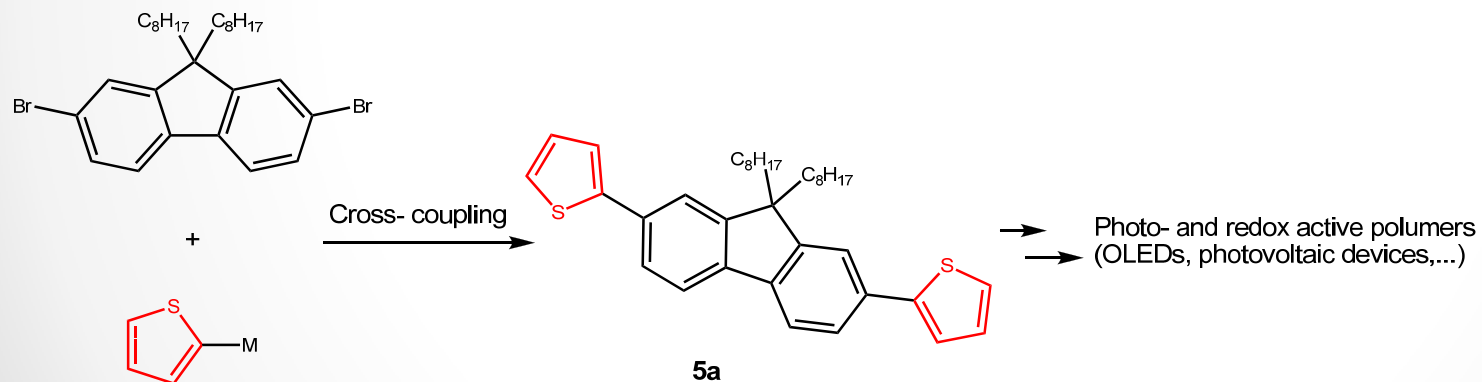


## Reported method

M:  $\text{BF}_3\text{K}$  ( $M_w$ : 106.96)  
 $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ , 5 mol%  
 $\text{Cs}_2\text{CO}_3$  (3 equiv.), toluene,  
 $90^\circ\text{C}$ , 48 h.  
85% yield

## This work

M; Li ( $A_w$ : 6.94)  
 $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$ , 5 mol%,  
toluene, rt, 1 h.  
86% yield



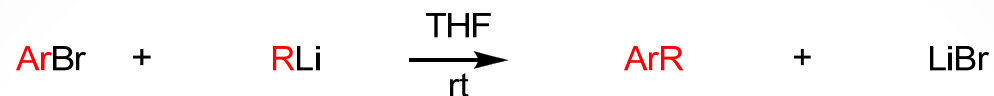
## Reported method

M:  $\text{SnBu}_3$  ( $M_w$ : 209.06)  
 $\text{Pd}(\text{PPh}_3)_4$ , 3 mol%  
DMF,  $90^\circ\text{C}$ , 24 h.  
73% yield

## This work

M; Li ( $A_w$ : 6.94)  
 $\text{Pd}_2(\text{dba})_3$ , 2.5 mol%,  
 $\text{P}(t\text{-Bu})_3$  7.5 mol%,  
TMEDA (1.2 equiv.),  
toluene,  $40^\circ\text{C}$ , 1 h.  
85% yield

## Tetrahydrofuran-promoted aryl-alkyl coupling

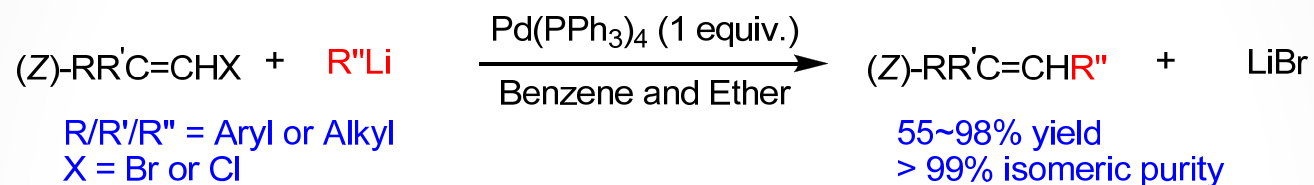


Entry	Ar	R	yield
1	<i>o</i> -Tolyl	<i>n</i> -Butyl	65
2	<i>p</i> -Tolyl	<i>n</i> -Butyl	69
3	1-Naphthyl	<i>n</i> -Butyl	66
4	1-Naphthyl	<i>sec</i> -Butyl	<1
5	1-Naphthyl	<i>t</i> -Butyl	<1
6	2-methyl-1-naphthyl	Ethyl	66

The reaction of aryl halides with organolithium compounds in diethyl ether or other less polar solvents is dominated by the halogen-metal interconversion.

Negishi, E. *et al. J. Org. Chem.* **1974**, 39, 3452.

## Stoichiometric cross-coupling with organolithium compounds

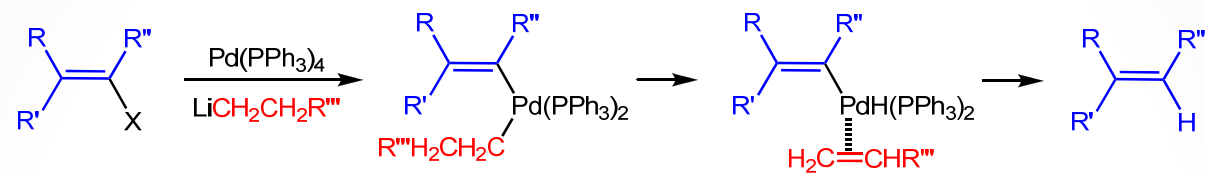


Recycling of the palladium catalyst is slower than metallation of vinyl halide by the alkyllithium, resulting in formation of an acetylenic compound

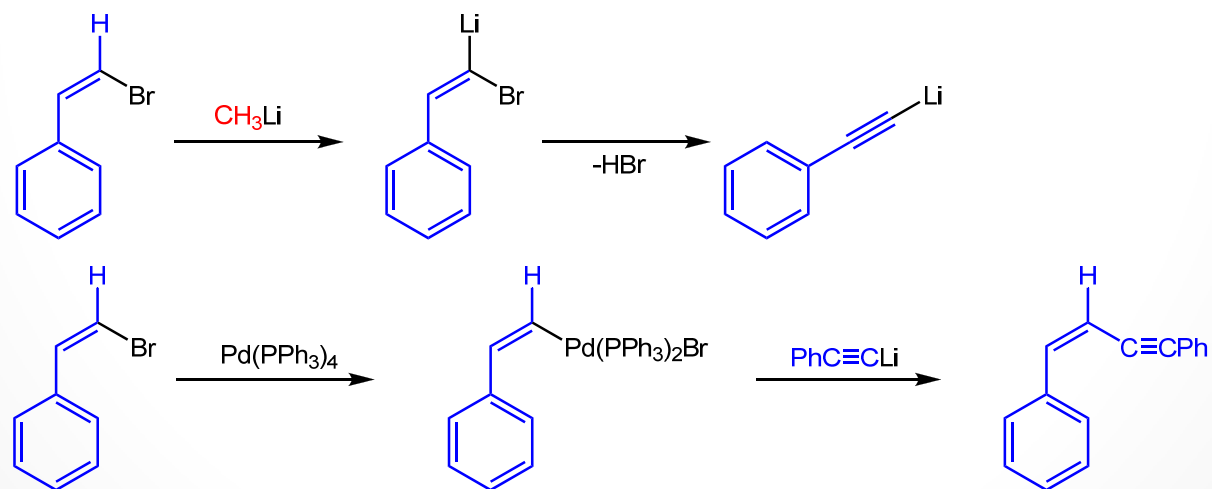
Murahashi, S.-I. *et al. J. Organom. Chem.* **1975**, 91, C39.

## Major side reactions

### $\beta$ -H elimination



### Butlenberg–Wiechell type rearrangement



Murahashi, S.-I. *et al.* *J. Org. Chem.* **1979**, *44*, 2408.

# Catalytic cross-coupling with organolithium compounds

## Control of the rate of addition of organolithium to keep going the catalytic cycle



Condition A: 1.0 mmol of alkenyl halides and 0.029 mmol of Pd(PPh<sub>3</sub>)<sub>4</sub>, Benzene, rt

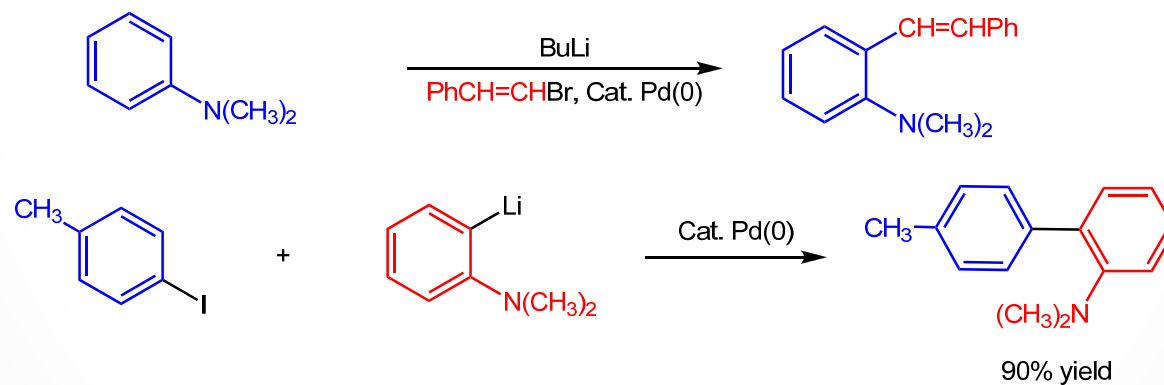
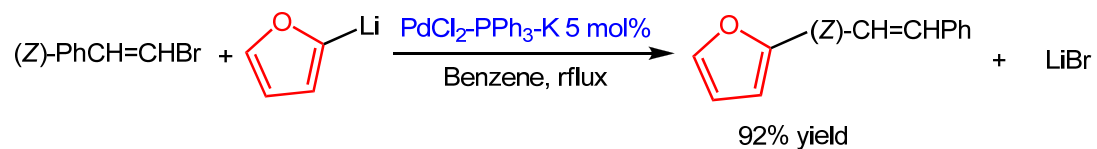
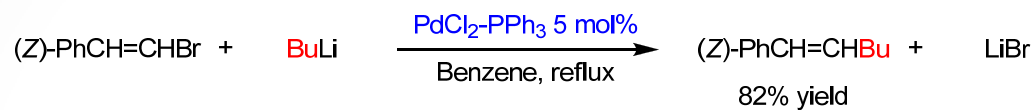
Condition B: 2.0 mmol of alkenyl halides and 0.10 mmol of Pd(PPh<sub>3</sub>)<sub>4</sub>, Benzene, reflux

Halide	R''Li	Condition	Yield (%)
(Z)-PhCH=CHBr	MeLi	B	90
(Z)-PhCH=CHBr	<i>n</i> -BuLi	B	62
(Z)-PhCH=CHBr	2-furyllithium	B	85
(Z)-PhCH=CHBr	2-thienyllithium	A	94
(Z)-PhCH=CHBr	2-( <i>N,N</i> -dimethylamino)phenyllithium	B	87
(Z)-BuCH=CHBr	<i>n</i> -BuLi	B	40
(Z)-BuCH=CHBr	2-furyllithium	B	34

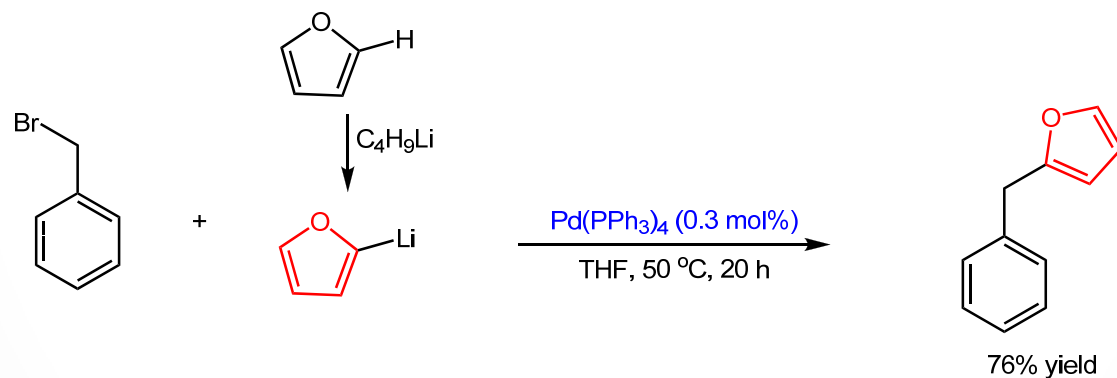
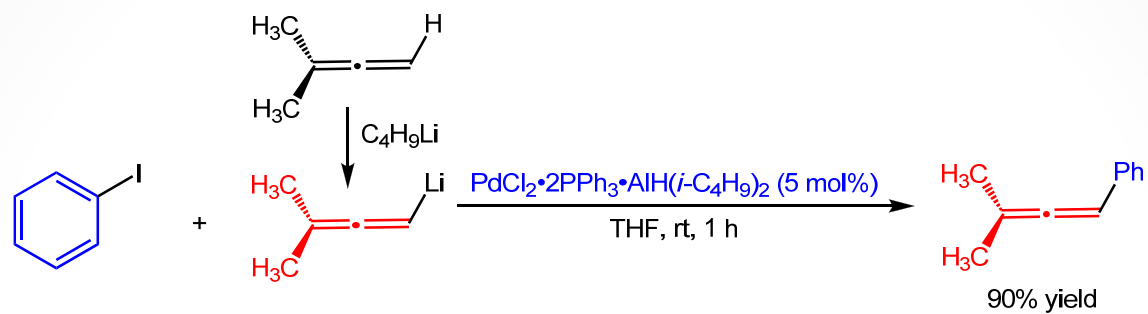
Murahashi, S.-I. *et al.* *J. Org. Chem.* **1979**, *44*, 2408.

# Catalytic cross-coupling with organolithium compounds

## Use of highly active clean palladium(0) catalysts

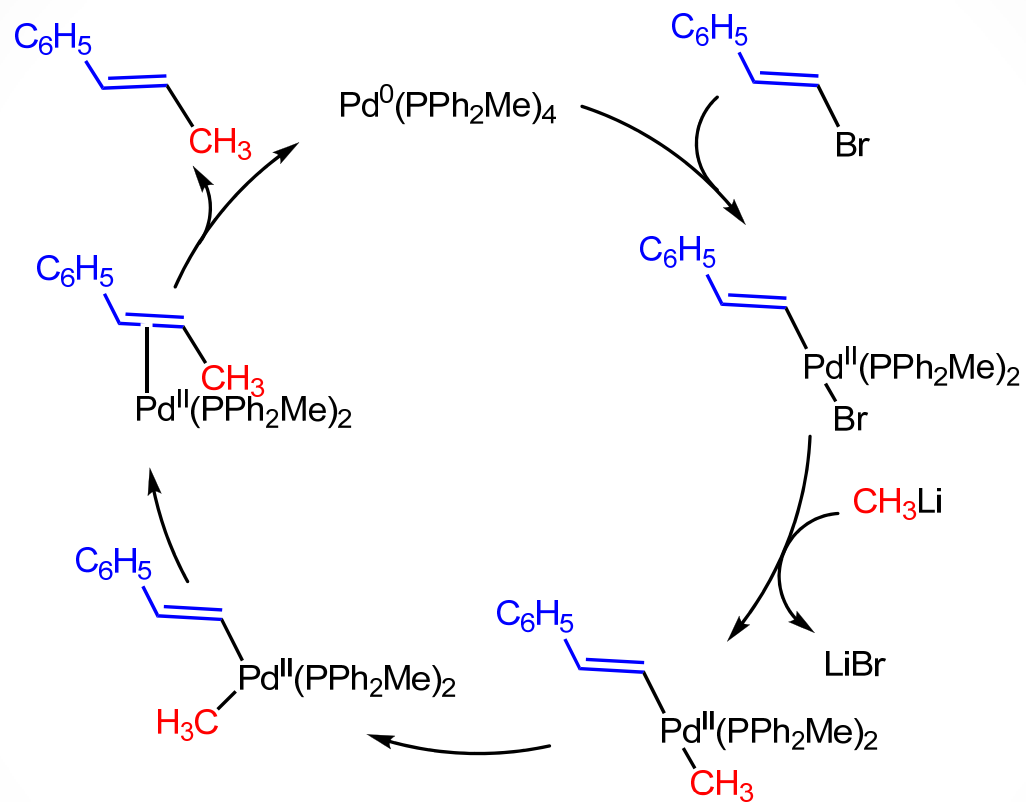


# Catalytic cross-coupling with organolithium compounds



Linstrumelle, G. *et al. Synthesis* **1982**, 738.  
Clements, G. *et al. Synthesis* **1987**, 51.  
Rowlands, M. *et al. Tetrahedron Lett.* **1987**, 28, 1203.

# Catalytic cross-coupling with organolithium compounds



Murahashi, S.-I. *et al. J. Organom. Chem.* **2002**, 653, 27.



## Catalytic cross-coupling with organolithium compounds

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The palladium-catalyzed cross-coupling reaction with the Grignard reagents and organolithium compounds will occur without any problem, when one keeps in mind the following points:

- careful treatment with exactly necessary amount of reagents, such as organolithium compounds
- use of highly active clean palladium(0) catalysts
- control of the rate of addition of a reagent to keep going the catalytic cycle

Murahashi, S.-I. *et al. J. Organom. Chem.* **2002**, 653, 27.

Transition metal-catalysed cross-coupling reactions for the selective formation of C–C bonds enable the facile preparation of myriad structurally diverse and complex molecules essential for the development of modern drugs and organic materials. Typically, Pd or Ni catalysis is used with an organic halide, and an organometallic or main-group reagent as nucleophilic coupling partner, although (directing-group based) coupling via C–H activation has recently emerged as a possible alternative. Although Stille (with organotin as the nucleophile), Suzuki–Miyaura (organoboron), Negishi (organozinc), Hiyama–Denmark (organosilicon) and Kumada (organomagnesium) couplings are well established, the direct application of organolithium reagents (among the most reactive and commonly used reagents in chemical synthesis) in cross-coupling reactions remains a formidable challenge. Some of the coupling partners are directly accessible; for instance, organoboron compounds can be prepared by hydroboration of unsaturated substrates (that is, alkyl and vinyl boranes) or by borylation of C–H bonds (alkyl and aryl boranes).



However, as aryl organoboron and organotin compounds, in particular, are frequently prepared from the corresponding lithium reagents, a concise method, taking advantage of the direct use of organolithium compounds in C–C bond formation, would eliminate the need for such additional transformations. Organolithium reagents are cheap and either commercially available or readily accessible through halogen–metal exchange or direct metallation. Early studies by Murahashi and co-workers on the use of organolithium reagents for cross-coupling reactions revealed the limitations of this transformation due to the very high reactivity of these organometallic compounds and also the high temperatures required. One major problem that has precluded the application of organolithium reagents is the competing formation of homocoupled products as a result of fast lithium–halogen exchange preceding Pd-catalysed C–C bond formation. Recently, a Murahashi-type biaryl coupling was performed using a flow-microreactor, while in an alternative approach, a stoichiometric silicon-based transfer agent was used. However, the development of an efficient catalytic protocol for cross-coupling of highly reactive organolithium species that does not suffer from lithium–halogen exchange and homocoupling has proven elusive until now.



In summary, we have developed a fast and highly selective method for the direct catalytic cross-coupling of alkyl- and (hetero)aryllithium reagents. The reaction takes place under mild conditions with a broad scope of alkenyl and (hetero)aryl bromides. Several functional groups, including halides, acetals, ethers, amines and alcohols, as well as acidic protons, are tolerated. Although this protocol is not compatible with ketones or nitriles, we have shown in a preliminary study that ester moieties can be used with good selectivity. The results from the present study have demonstrated that Pd-catalysed cross-coupling of cheap and readily available alkyl and aryllithium reagents represents a valuable alternative for the mild, selective and atom-economic formation of C–C bonds for the construction of building blocks for biologically active compounds and organic materials.