Organolithium reagents as cross-coupling reaction partners

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Literature presentation

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Cross-coupling reactions

- Formation of new C-C bonds by combining two molecular fragments (electrophile-nucleophile)

$$\text{RML} + \text{R'-X} \xrightarrow{\text{cat.}} \text{R-R'} + \text{MLX}$$

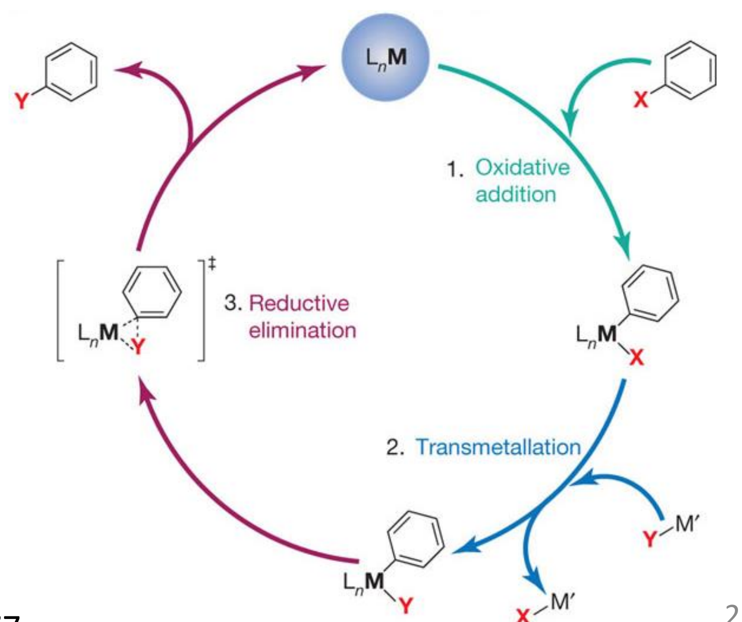
R= alkyl, aryl, vinyl
R'=alkyl, aryl, vinyl
M=B, Al, Zn, Sn, Si, Mg, Li
cat.=Pd, Ni, Cu, Fe
X=halide, triflate, tosylate, phosphonate, sulfonate
L=halide, oxygen, organic ligand

- Often catalysed by transition metals (Pd, Ni, Cu, Fe…), Pd most common:

    - Can promote reaction of less reactive partners (Ar-Cl)
    - Provides high turnover numbers (TONs) – suitable for large scale
    - Allows low T reactions

- Reaction optimisation:

    - Expand substrate scope
    - Lower catalyst loading
    - Functional group tolerance
    - Organocatalysis -(easier purification)
    - Green solvents



Magano, J.; Dunetz, J. R. *Chem. Rev.,* **2011**, *111*,2177-2250
Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature*, **2011**, *473*, 470-477

Cross-coupling reactions

- C-C bond formation key in the synthesis of natural products, pharmaceuticals, agrochemicals…
- Development of organic synthesis over the last three decades allowing access to complex structures
- Wide range of organic halides and organometallic reagents used but…
- … organolithium reagents not used directly in cross-coupling due to:
    - High reactivity
    - Poor selectivity

Giannerini, M.; Fañanás-Mastral, M.; Feringa, B.L. *Nature*, **2013**, *5*, 667-672

Nicolaou, K.C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.,* **2005**, *44*, 4442-4489

Organometallic reagents

- B, Sn, Zn, Si, Mg…

- Organoboron and organotin compounds usually made from organolithium…

  …Organolithium could be directly used instead!

- RLi:

pros	cons
- Cheap - Easy to access (commercially or *via* X-Li exchange)	- Highly reactive - Homocoupled byproducts (X-Li exchange >> Pd-cat C-C formation)

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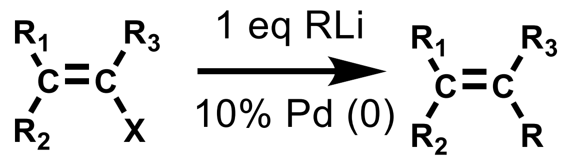
Selective cross-coupling with organolithium reagents

- Precedents
  - Murahashi and coworkers – high T, reflux



  - Yoshida and coworkers – flow microreactor

- **2013** - First efficient catalytic cross-coupling of RLi reported by Feringa *et al.*

Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.,* **1979**, *44 (14)*, 2408-2417

Nagaki, A.; Kenmoku, A.; Moriwaki, Y.; Hayashi, A.; Yoshida, J. *Angew. Chem. Int. Ed.,* **2010,** *49*, 7543-7547

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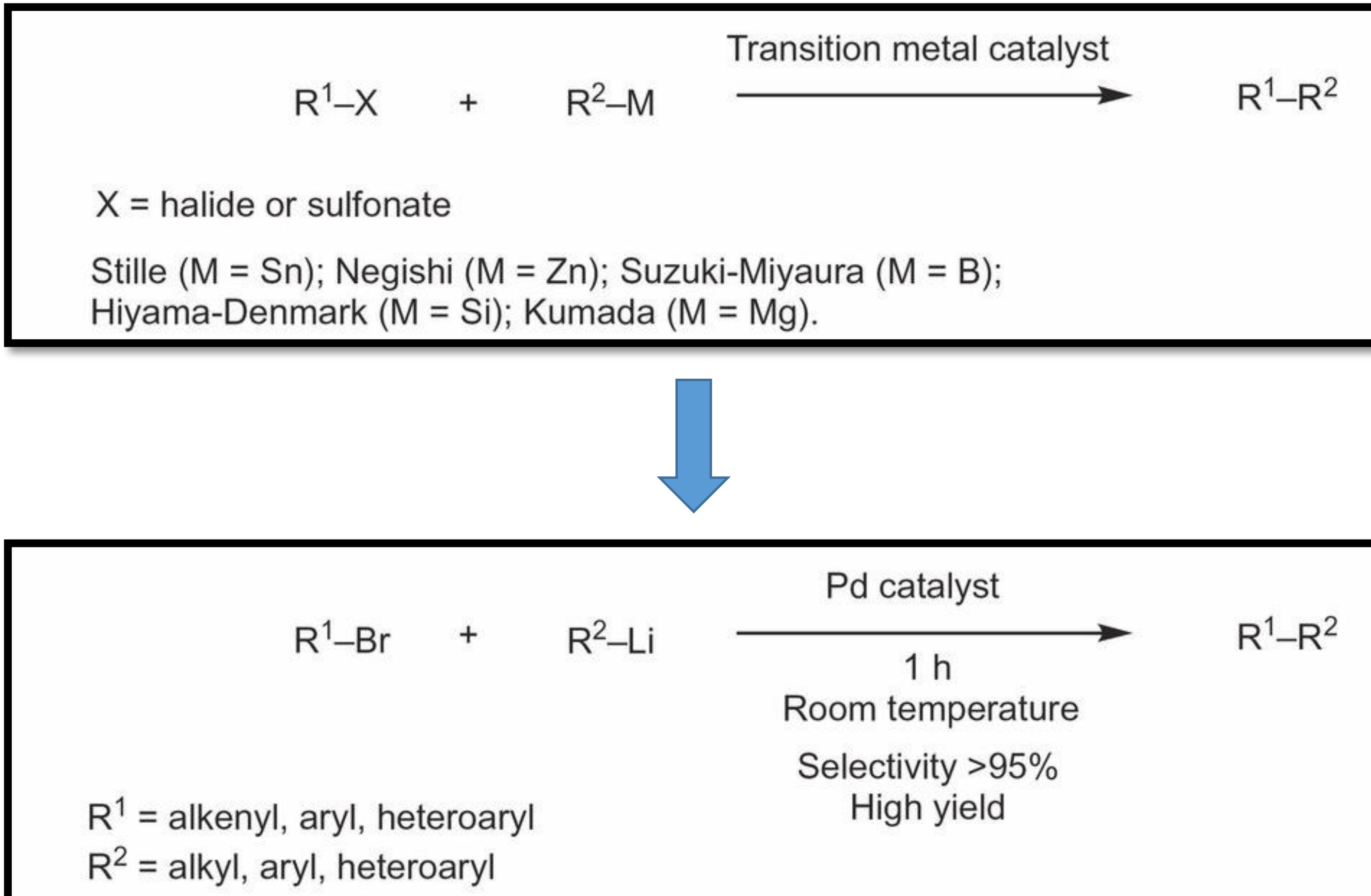
Selective cross-coupling with organolithium reagents



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Selective cross-coupling with organolithium reagents

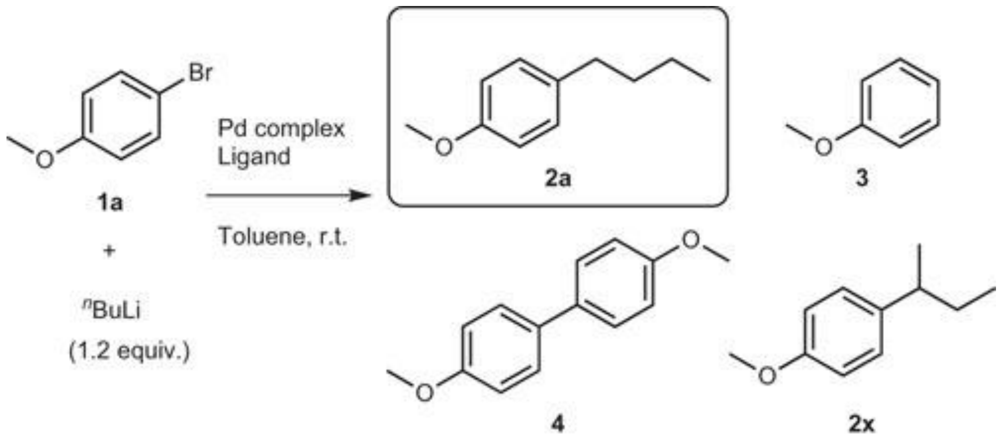
- Key: overcome fast Br-Li exchange

  - Pd catalyst design: promote OA, transmetallation and RE

  - Control reactivity of RLi: solvent choice

Selective cross-coupling with alkyllithium reagents

- Conditions



Entry	Pd complex	Ligand	Reaction time (h)	Conversion (%)	2a:3:4:2x
1	$Pd_2(dba)_3$, 2.5 mol%	XPhos, 10 mol %	3	Full	80:5:10:5
2	-	-	3	25	-:>95:-:-
3	$Pd_2(dba)_3$, 2.5 mol%	-	3	22	23:48:29:-
4	$Pd_2(dba)_3$, 2.5 mol%	SPhos, 10 mol %	1	Full	89:5:6:-
5	$Pd_2(dba)_3$, 2.5 mol%	PdP(^{t}-Bu)$_3$, 6 mol %	1	Full	90:6:4:-
6	Pd[P(*t*-Bu)$_3$]$_2$, 5 mol%	-	1	Full	96:4:-:-
7	Pd[P(*t*-Bu)$_3$]$_2$, 1 mol%	-	1	Full	95:4:1:-

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).

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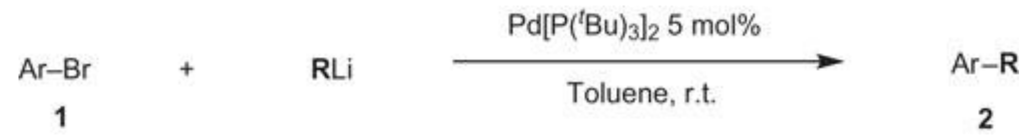
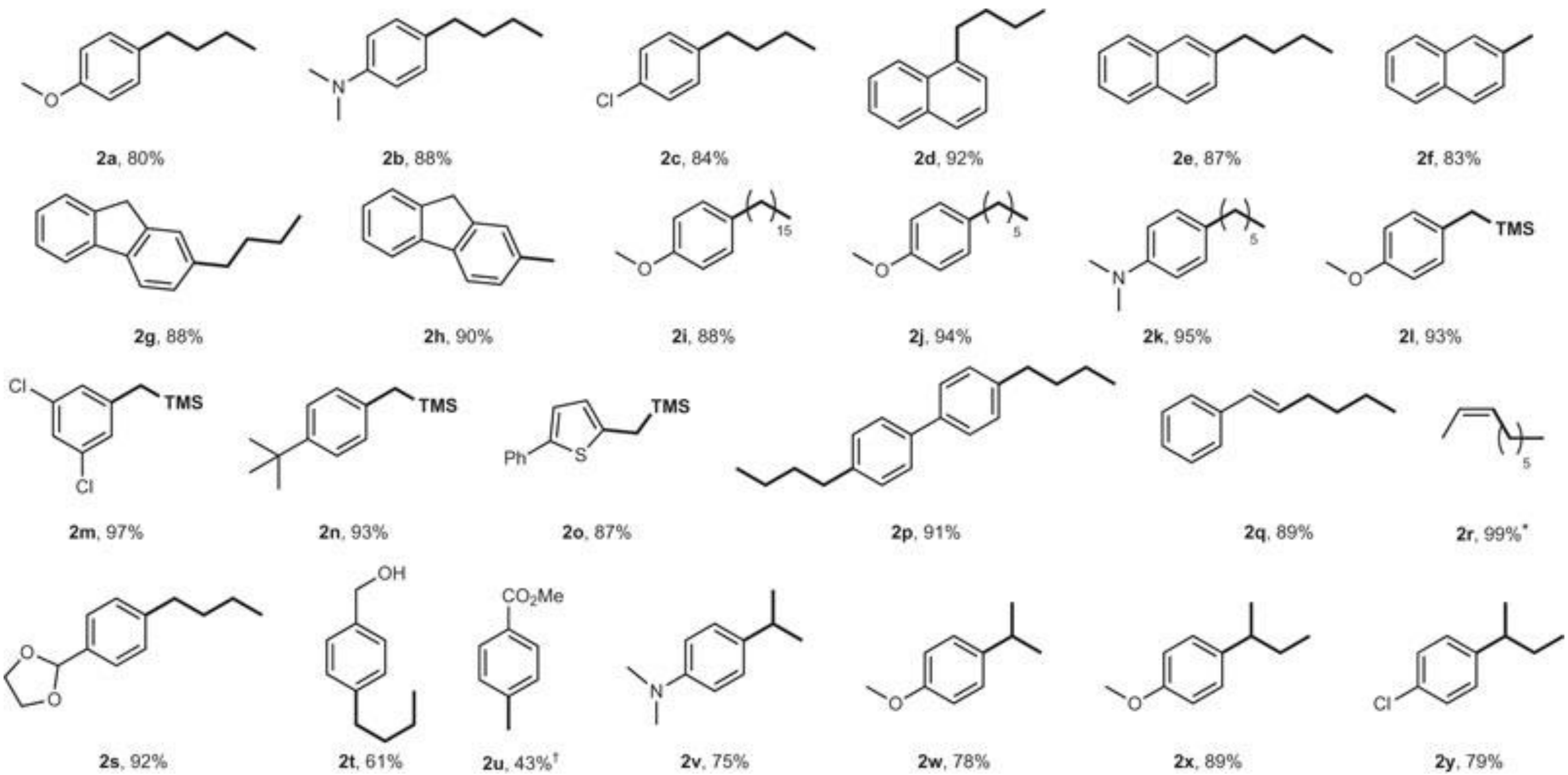
Selective cross-coupling with alkyllithium reagents

- Scope





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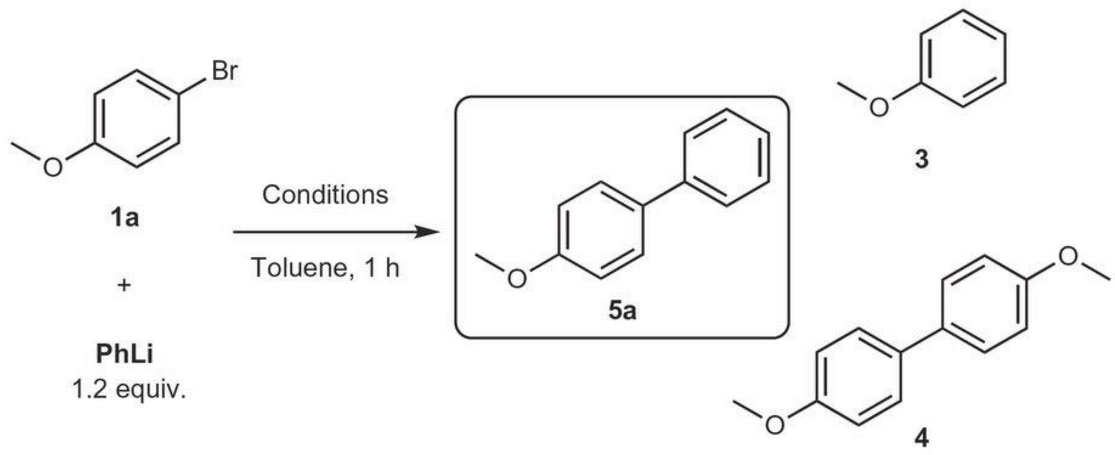
Selective cross-coupling with aryllithium reagents

- Conditions



		Conversion	5a:3:4
Conditions:	$Pd[P(^tBu)_3]_2$ 5 mol%	70%	90:–:10
	$Pd_2(dba)_3$ 2.5 mol%, $P(^tBu)_3$ 7.5 mol%	**Full**	**98:–:2**

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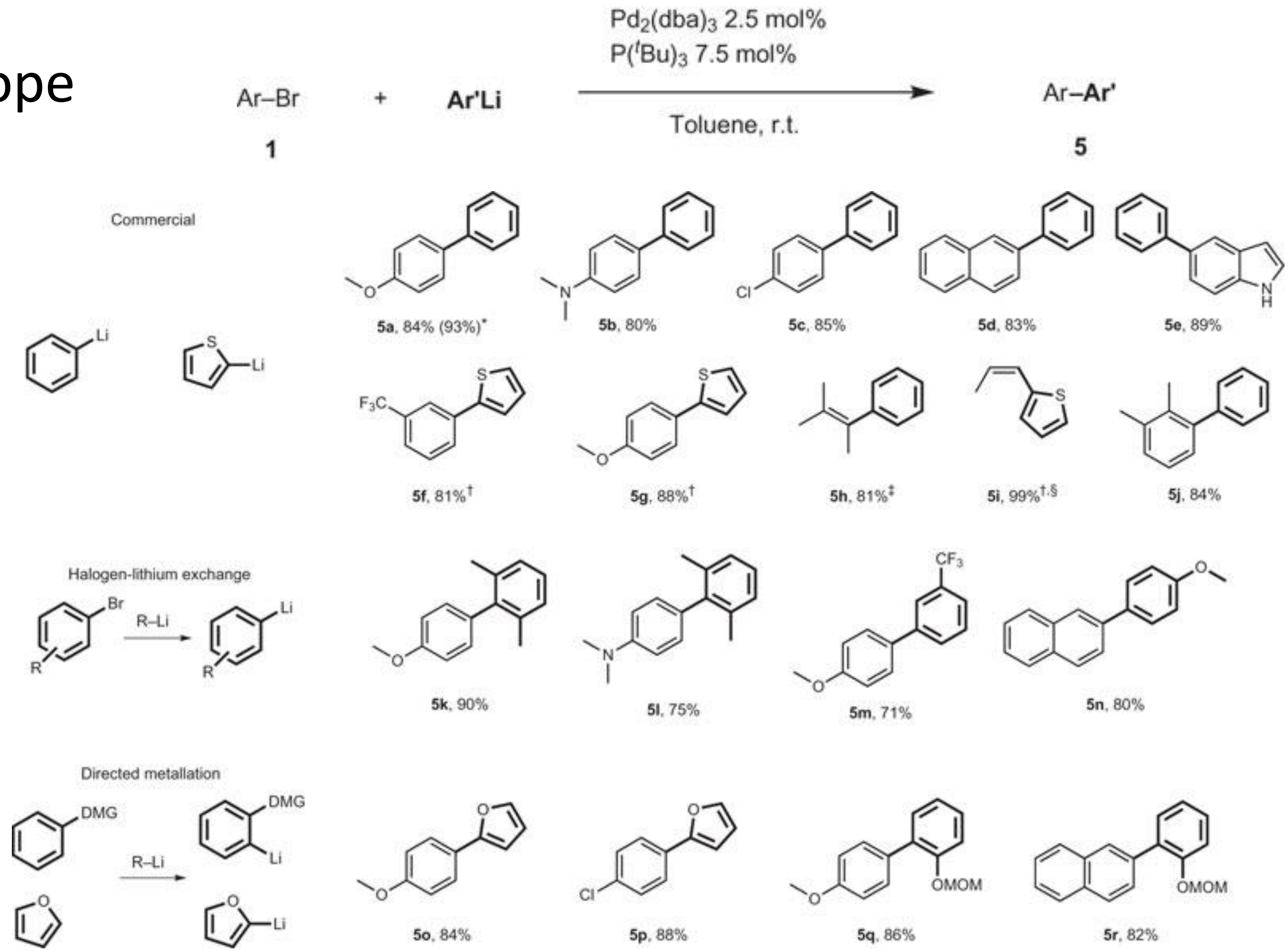
Selective cross-coupling with aryllithium reagents

- Scope



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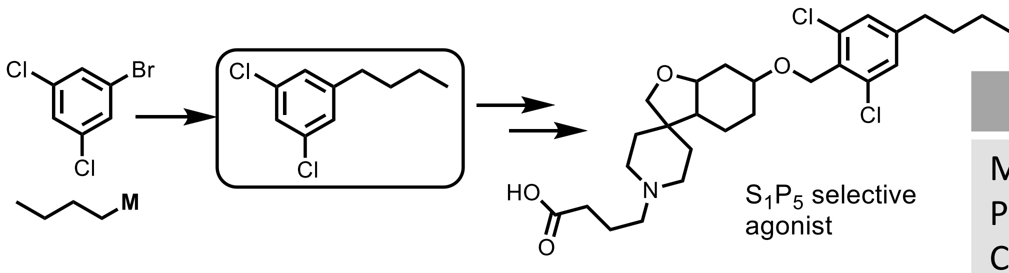
Application of selective cross-coupling with organolithium reagents

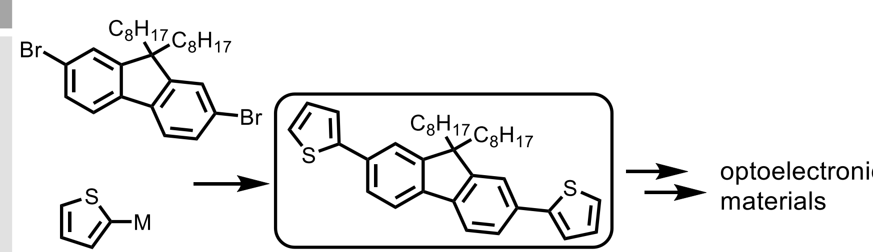
- **Aryl-alkyl coupling**



Reported method	**Feringa *et al.***
M: BF_3K $Pd(dppf)Cl_2.CH_2Cl_2$, 5 mol%, Cs_2CO_3 (3 eq.), toluene, 90°C, 48h 85% yield	M: Li $Pd[P(^tBu)_3]_2$, 5 mol%, toluene, r.t., 1h 86% yield

- **Aryl-aryl coupling**

Reported method	**Feringa *et al.***
M: $SnBu_3$ $Pd(PPh_3)_4$, 3 mol%, DMF, 90°C, 24h 73% yield	M: Li $Pd_2(dba)_3$, 2.5 mol%, $P(^tBu)_3$, 7.5 mol% TMEDA (1.2 eq.), toluene, 40°C, 1h 85% yield



Shorter reaction times and milder conditions
No need to generate B, Sn reagents

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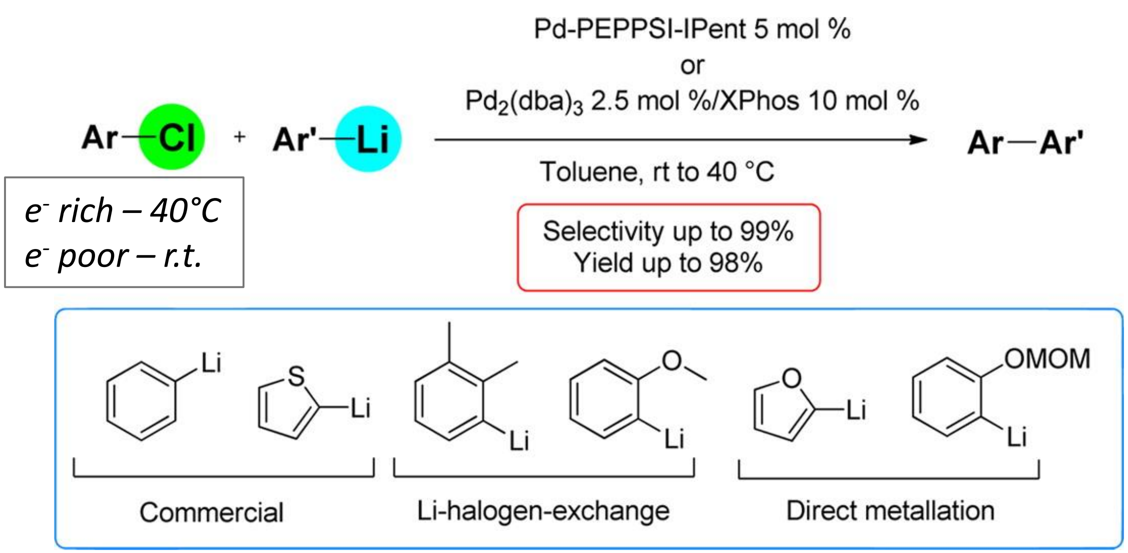
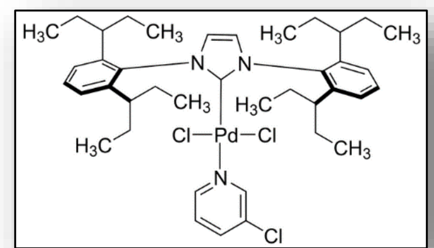
Catalytic cross-coupling between organolithium reagents and aryl chlorides

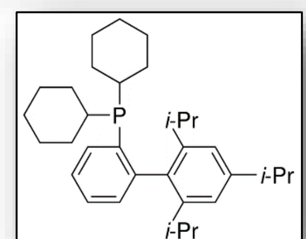
- RLi and Ar-Cl coupling is challenging. Ar-Cl cheap, commercially available but have low reactivity
- Sterically hindered phosphines and NHCs most commonly used ligands for cross-coupling of Ar-Cl
- Feringa *et al:* new cross-coupling between Ar-Li and Ar-Cl reagents (RT: 40min-4h).



Pd-PEPPSI-IPent



XPhos



Hornillos, V.; Giannerini, M.; Vila, C.; Fañanás-Mastral, M.; Feringa, B. L. *Org. Lett.*, **2013**, 15 (19), 5114-5117

Summary

- Until now organolithium reagents have been unexplored as cross coupling partners due to their high reactivity and poor selectivity, with common side products (homocoupling, dehalogenation…)
- First fast, selective method for catalytic cross-coupling of alkyl, aryl and heteroaryl-lithium reagents with aryl bromides has been reported
- Direct cross-coupling between aryl chlorides and aryl, heteroaryl-lithium reagents has also been reported
- Wide functional group tolerance (RBr-RLi coupling: not nitriles and ketones but esters)
- Great applicability for C-C bond formation in medicinal chemistry and organic materials