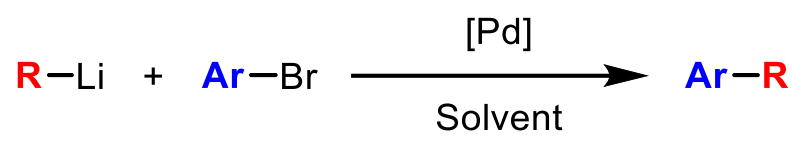
Taming Polar Organometallic Reagents:

Resurgence of the Murahashi Coupling and Organometallic Reactions “On” Protic Solvents

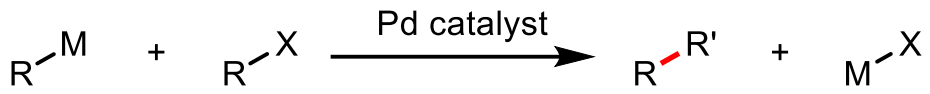


Nick Wade

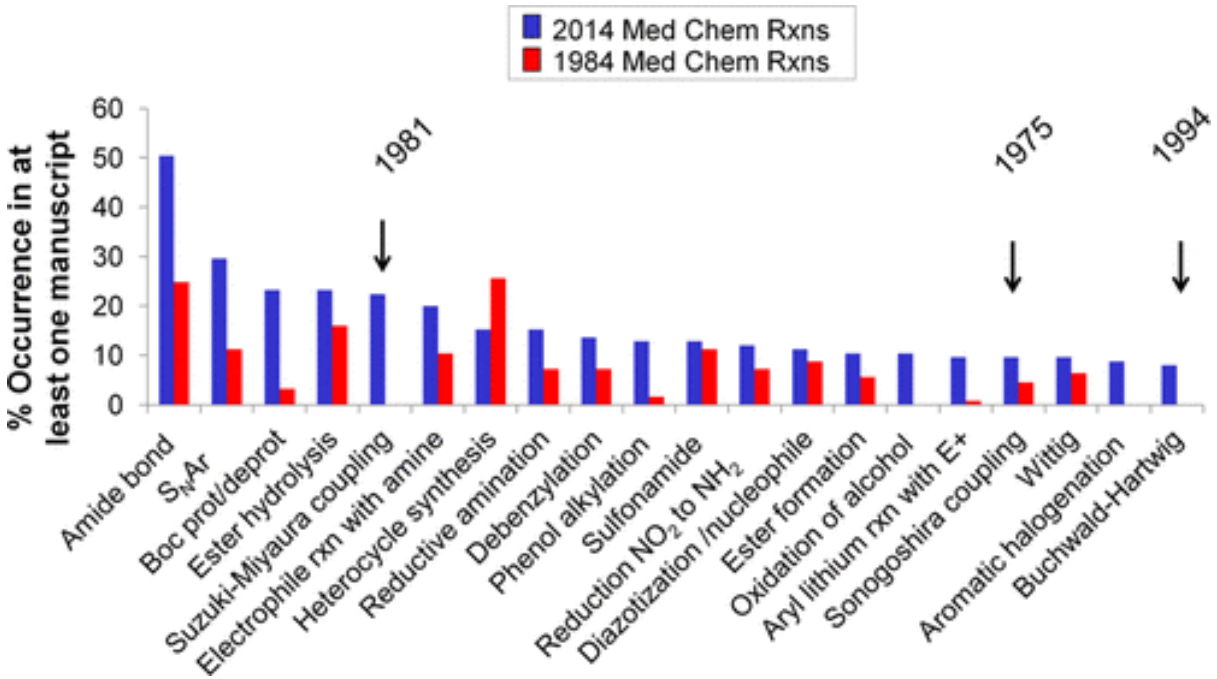
Denmark Group Meeting

February 20th, 2024

Cross-Coupling Synthetic Utility



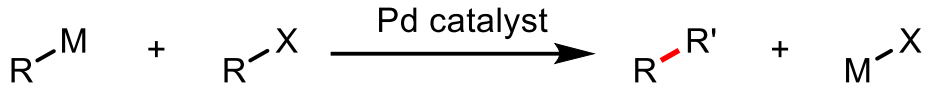
M=metal, metalloid
X=halide, pseudohalide



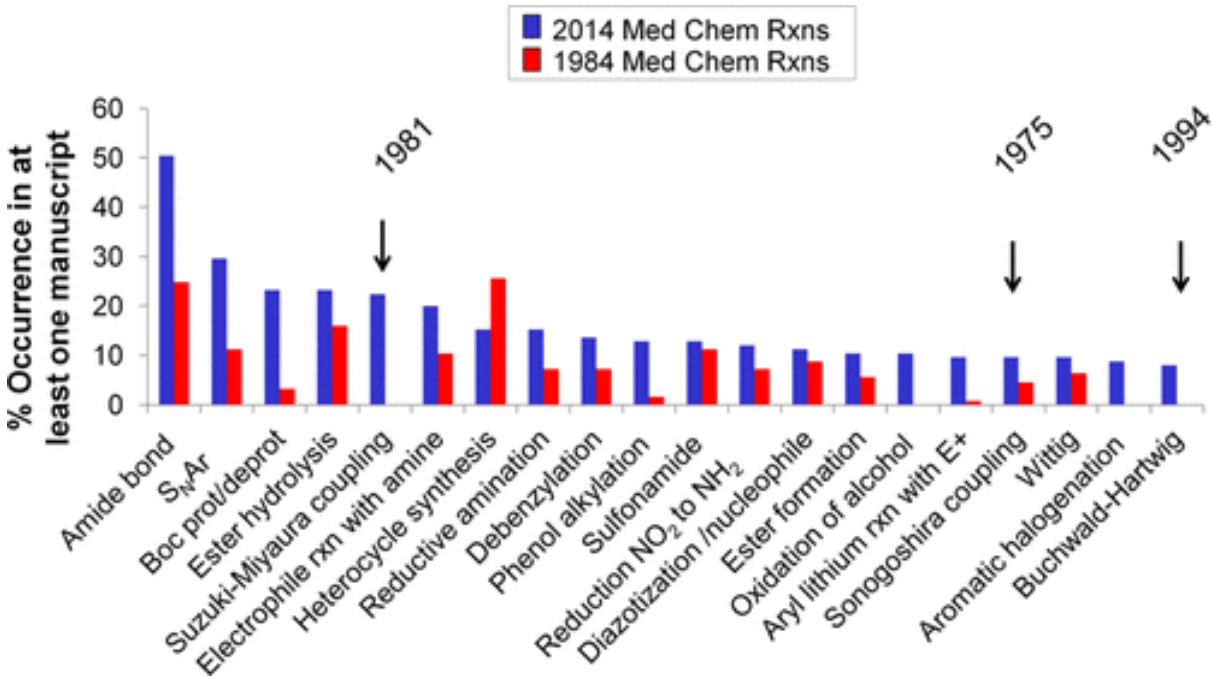
Richard Heck, Ei-Ichi Negishi and Akira Suzuki share the 2010 Nobel Prize in chemistry "for palladium-catalyzed cross couplings in organic synthesis"

D. G. Brown and J. Boström, *J. Med. Chem.* **2016**, 59, 10, 4443-4458., www.nobelprize.org/prizes/chemistry/2010/summary/

Cross-Coupling Synthetic Utility



M=metal, metalloid
X=halide, pseudohalide



Global Crop Protection:
$78 billion industry as of 2022
(S&P Global Commodity Insights)

BASF

DUPONT™

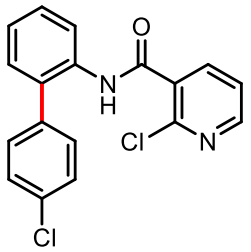
MONSANTO

syngenta

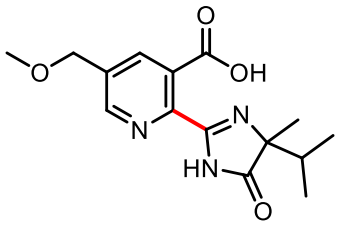
D. G. Brown and J. Boström, *J. Med. Chem.* **2016**, 59, 10, 4443-4458., www.spglobal.com/commodityinsights/en/ci/industry/agribusiness, "The Agrochemical Industry" *Handbook of Industrial Chemistry and Biotechnology*, **2017**.

Synthetic Utility: Mass Production of Agrochemicals

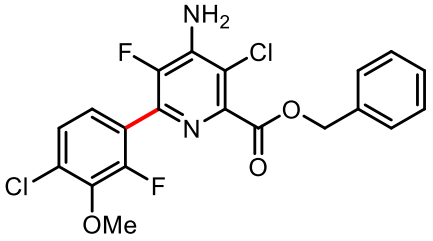
Common agrochemicals produced with at least cross coupling reaction:



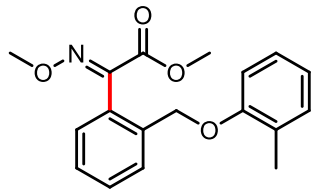
Boscalid



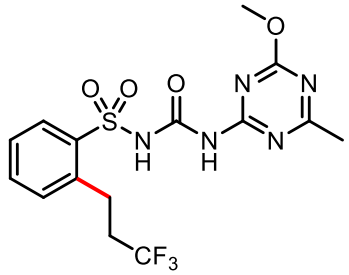
Imazamox



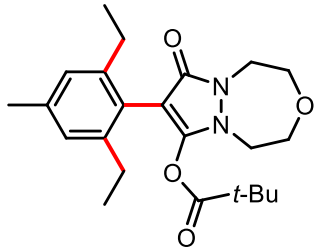
Florpyrauxifen-Benzyl Ester



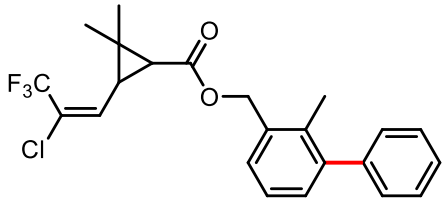
Bixafen



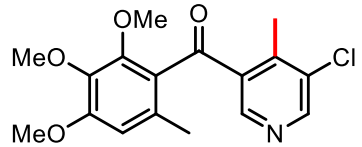
Prosulfuron



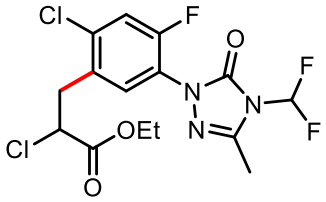
Pinoxaden



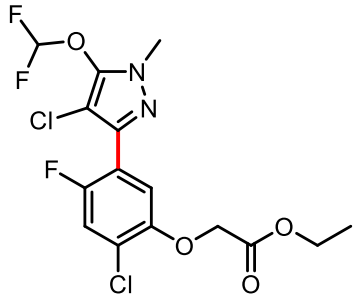
Bifenthrin



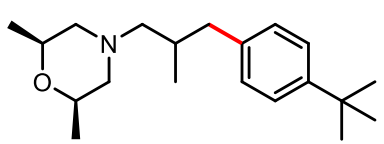
Pyrifenone



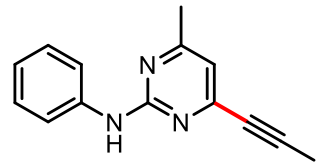
Carfenstrazone-Ethyl Ester



Pyraflufen-Ethyl Ester



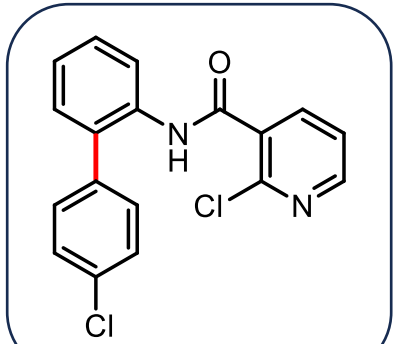
Fenpropimporh



Mepanipyrim

Tang et. al., *Advanced Agrochem*, **2022**, 125–138. “The Agrochemical Industry” *Handbook of Industrial Chemistry and Biotechnology*, **2017**.

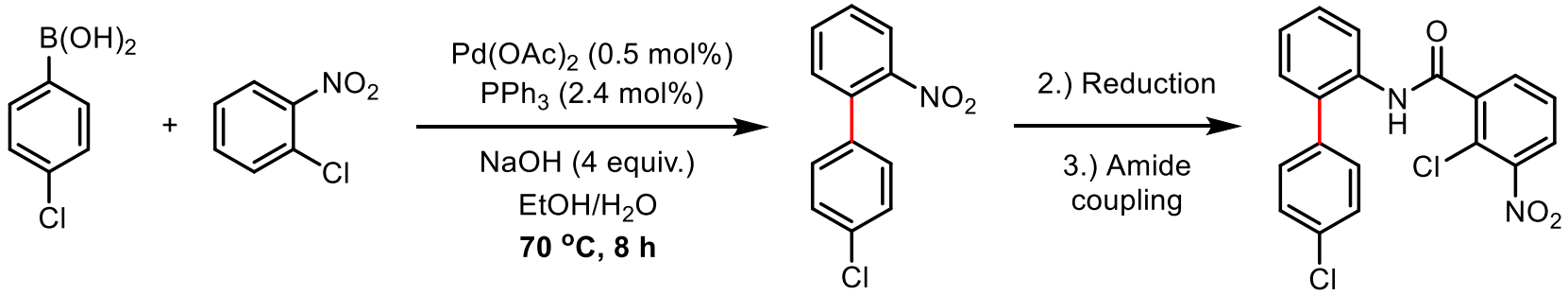
Motivation for Rapid, Efficient Cross-Couplings



Boscalid

- Boscalid – A wide range fungicidal reagent used widely on fruits and vegetables
- Production was first optimized on industrial scale by BASF in 2003.
- >1,000 tons/year still produced as of 2021.

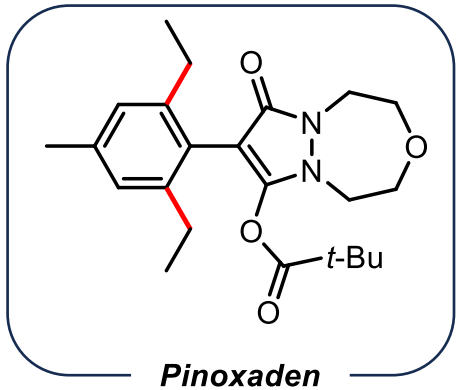
Suzuki-Miyaura Cross Coupling:



Optimization of the cross-coupling step from BASF resulted in a 98% yield and a >95% purity metric on large scale

Witschel et. al., *Modern Crop Protection Compounds,* **2011**, 11, 470-481., Tang et. al., *Advanced Agrochem*, **2022**, 125–138.

Motivation for Rapid, Efficient Cross-Couplings

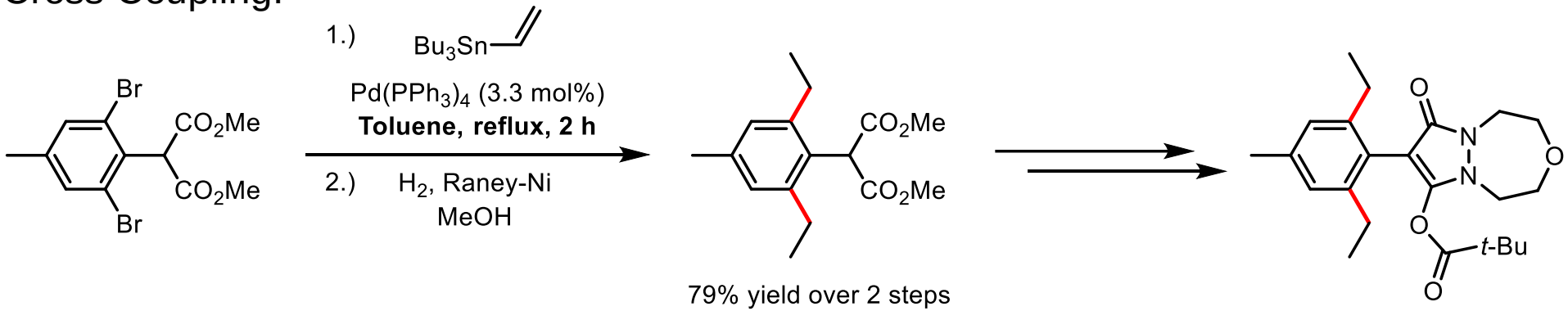


Pinoxaden

Pinoxaden – Used to stop undesired growth of wild grasses and weeds

- Production was first optimized on industrial scale by Syngenta in 2005.

Stille Cross Coupling:



79% yield over 2 steps

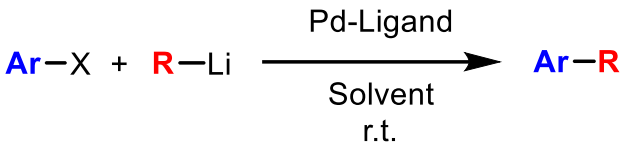
Common Issues:

Elevated reaction temperatures, poor atom economy, toxic byproducts, solvent quantities of organic waste to recycle, etc…

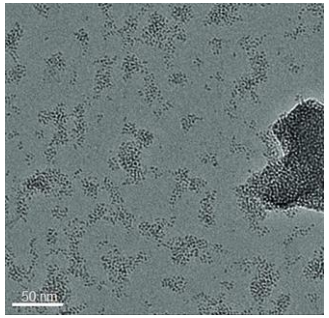
Witschel et. al., *Modern Crop Protection Compounds,* **2011**, 11, 470-481., Blaser et. al., *Synlett.*, **2006**, 3167–3169.

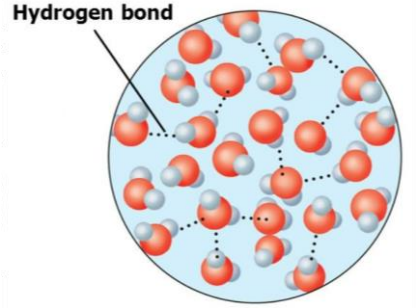
Presentation Overview

Initial Reports and Modern Revitalization

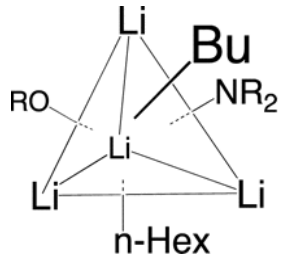


Mitigating Undesired Pathways: Two Strategies

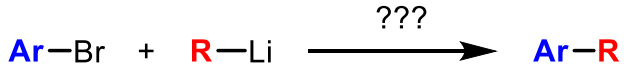




Conclusion and Outlook

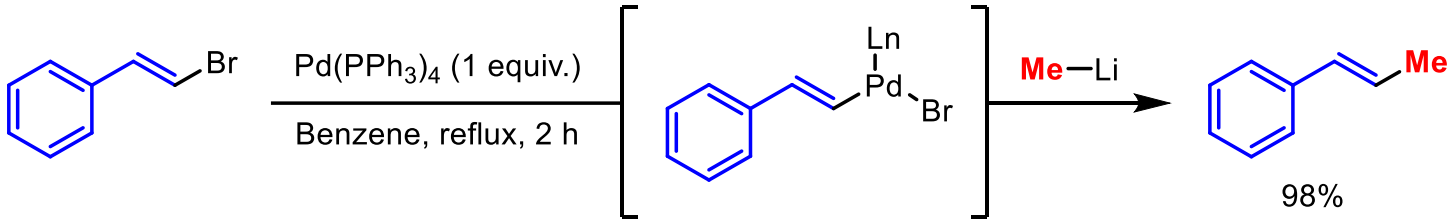


Pyrophoric?
Stable?
Soluble?

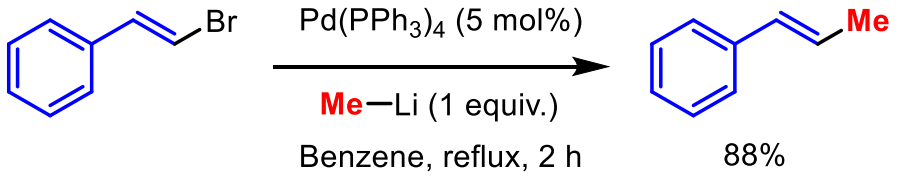


Initial Organolithium Cross-Coupling Reports

Stoichiometric in palladium:
(Murahashi, 1975)



First report catalytic in palladium:
(Murahashi, 1979)



>20 examples,
23-92% yield

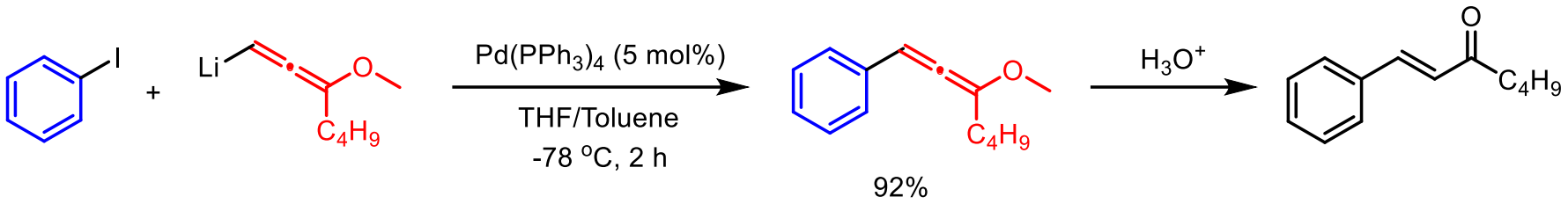
Notably, no desired product formed in the absence of palladium catalyst

Shun-Ichi Murahashi,
1972, at the Royal Society of Chemistry, London

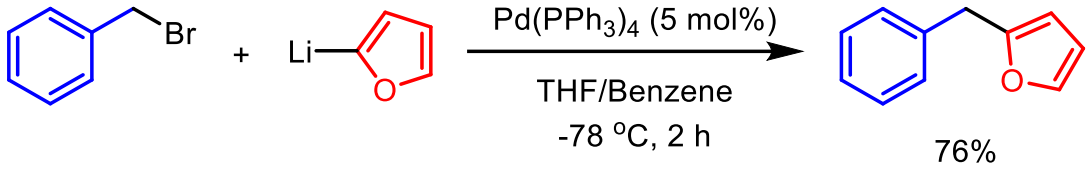
Murahashi, *J. Organomet. Chem.* **1975**, 2, 91., Murahashi, *J. Org. Chem.*, **1979**, 14, 44., Colacot et. al., *ACS Catal.* **2021**, 11, 21, 13188–13202.

Low Temperatures and Fast Coupling Reactions

Rapid coupling at -78 °C:
(Linstrumelle, 1982)

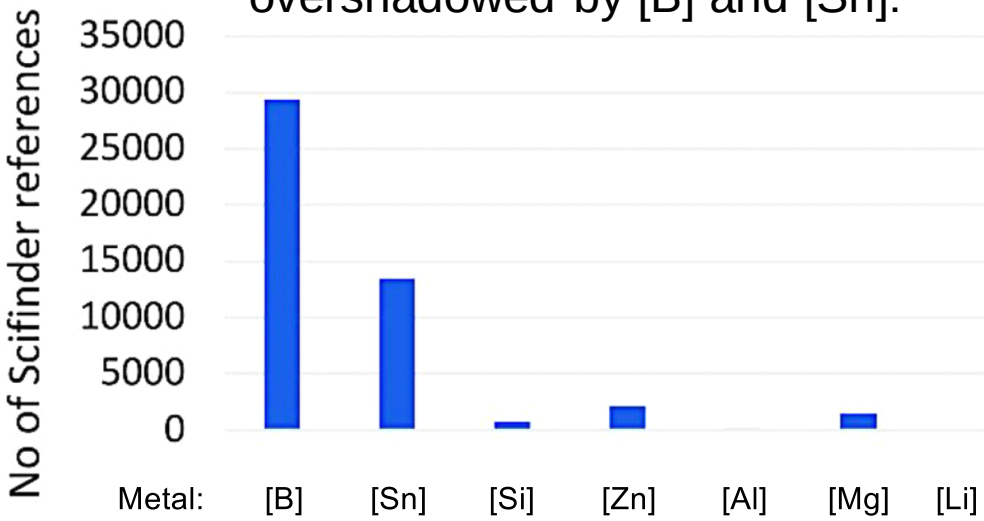


Heterocyclic coupling at -78 °C:
(Pelter, 1987)



Sensitivity of polar organometallic reagents to water and oxygen led to other coupling methods seeing wider use

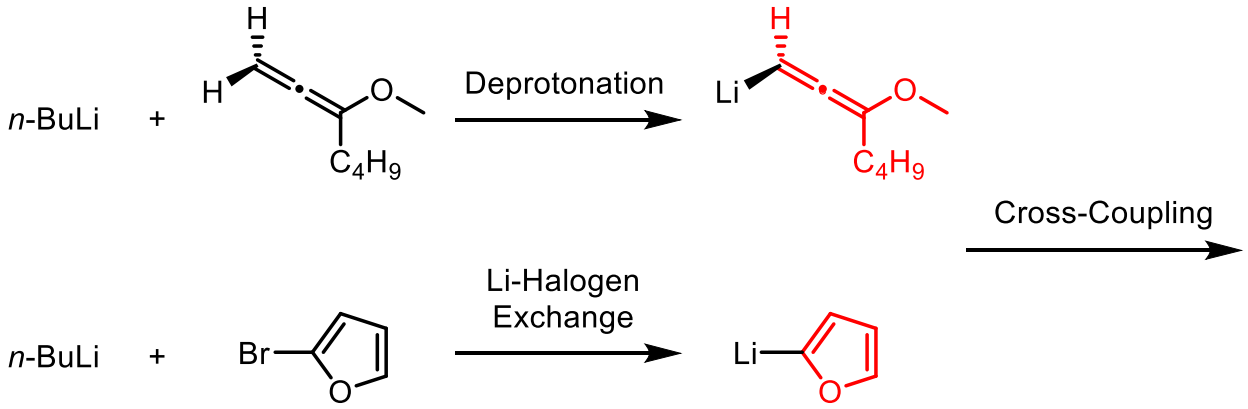
Murahashi Couplings are overshadowed by [B] and [Sn]:



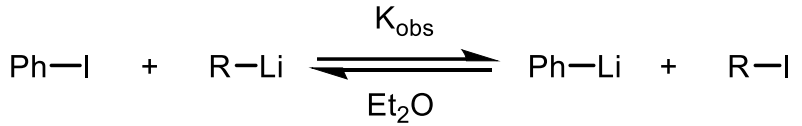
Linstrumelle et. al., *Synthesis*, **1982**, 738-740., Pelter, *Synthesis*, **1987**, 51-53., Colacot et. al., *ACS Catal.* **2021**, 11, 21, 13188–13202.

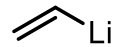
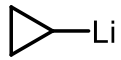
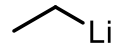
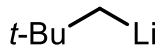
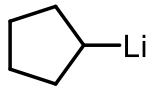
In-Situ Formation of Nucleophile

In-Situ metalation or Li-Halogen Exchange:



Equilibrium Position of Li-Halogen Exchange, correlated to pKa at -70 ºC:
(O'Brien and Applequist, 1963)



R=	pKa	K_{obs}
	36.5	0.004
	39	9.5
	42	7600
	42	30,000
	44	8,000,000

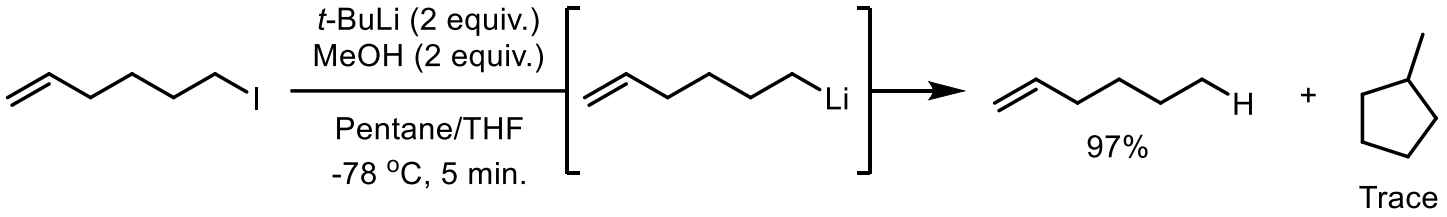
Cost ($) per mmol:
(Sigma-Aldrich, 2021)

n-BuLi	0.082	*n*-$BuSnBu_3$	0.22
n-BuMgCl	0.18	*n*-$BuB(OH)_2$	0.74

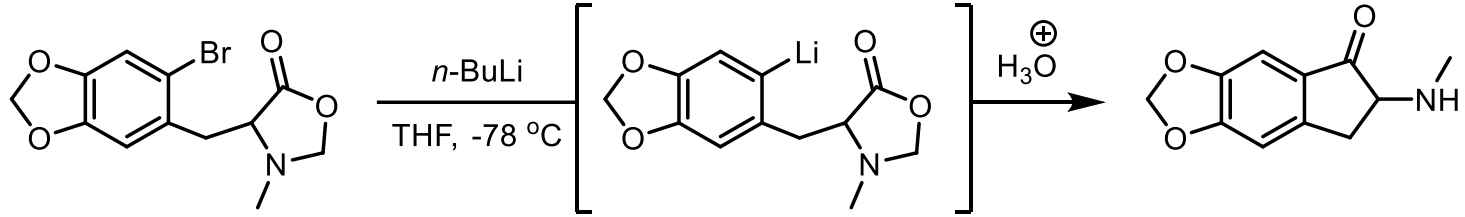
In-Situ preparation of coupling partner can improve atom economy and reduce synthetic overhead

O'Brien, *J. Am. Chem. Soc.*, **1963**, 85, 743-748., Linstrumelle et. al., *Synthesis*, **1982**, 738-740., Pelter, *Synthesis*, **1987**, 51-53., Colacot et. al., *ACS Catal.* **2021**, 11, 21, 13188–13202.

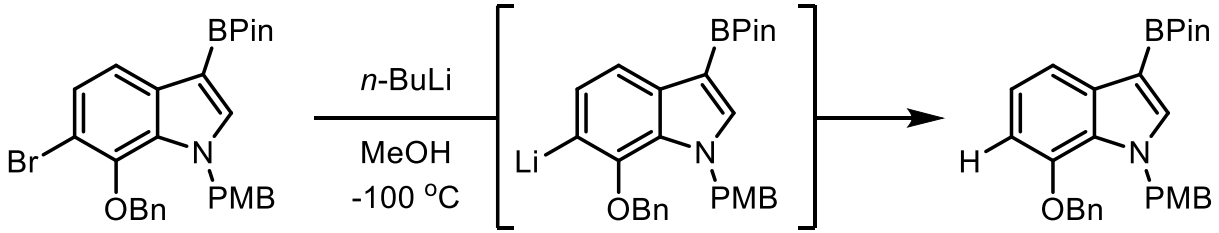
Li-Halogen Exchange Rate Comparison



Outcompeting protonation with 2 equiv. of MeOH



Outcompeting 1,2-addition into lactone

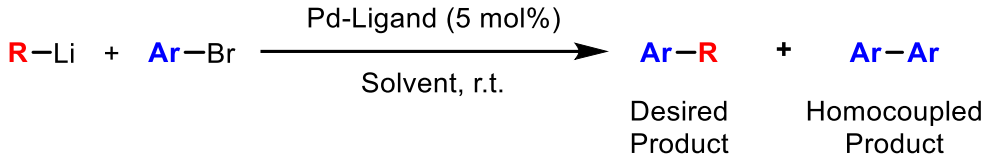


Outcompeting protonation with solvent quantities of MeOH

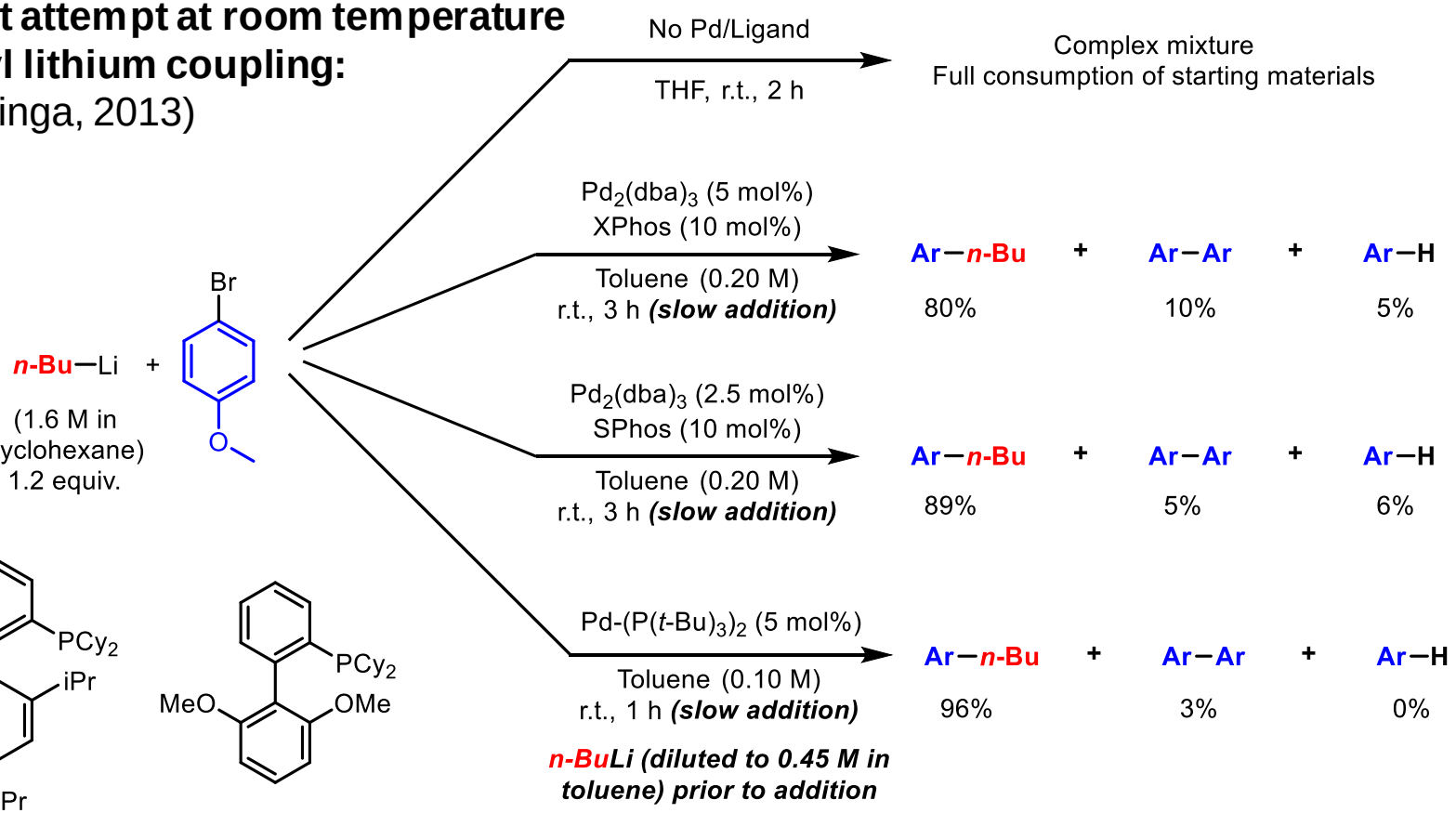
Dominguez, D. et. al., *J. Org. Chem.*, **1993**, 109, 27-33. Ahuja, et. al., *Tet. Lett.*, **1992**, 33, 3595-3598. Wang, W. et. al, *Tet. Lett.*, **1996**, 27, 1861-1865.

Revitalization by Ben Feringa and coworkers

Goal: Achieve rapid cross couplings at room temperature with polar organometallic reagents



First attempt at room temperature alkyl lithium coupling:
(Feringa, 2013)



XPhos

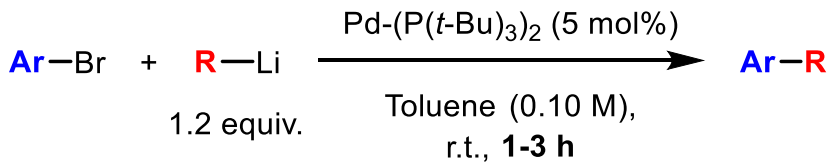
SPhos

Prof. Ben Feringa, **2021**
University of Groningen
(The Netherlands)

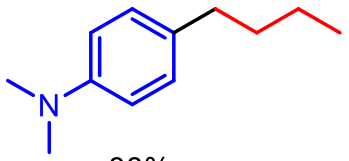
Highly engineered reaction conditions were required to avoid undesired side reactions

Feringa et. al., *Nat. Chem.*, **2013**, 5, 667–672.

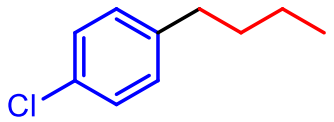
Abridged Substrate Scope



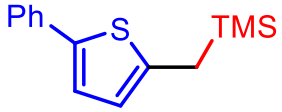
1° $C(sp^3)$-$C(sp^2)$ coupling:



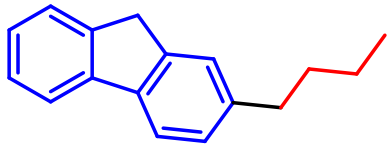
88%



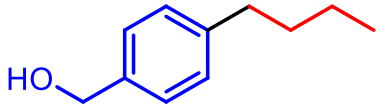
84%



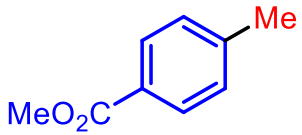
87%



88%

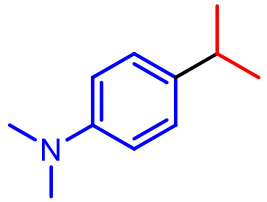


61%

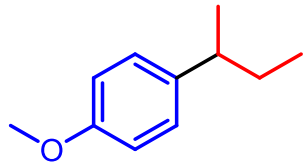


43%

2° $C(sp^3)$-$C(sp^2)$ coupling:

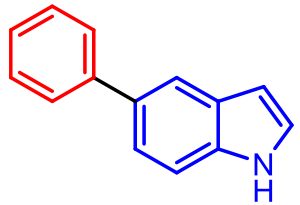


75%

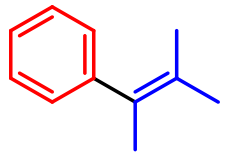


89%

$C(sp^2)$-$C(sp^2)$ coupling:



89%

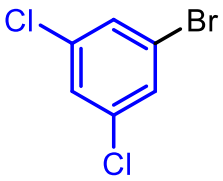


81%

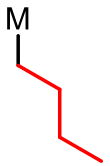
Rapid coupling and low concentration of alkyl-lithium in the pot at any point in time leads to compatibility with acidic and electrophilic functional groups

Feringa et. al., *Nat. Chem.*, **2013**, 5, 667–672.

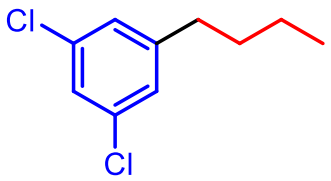
Comparison to Literature Conditions

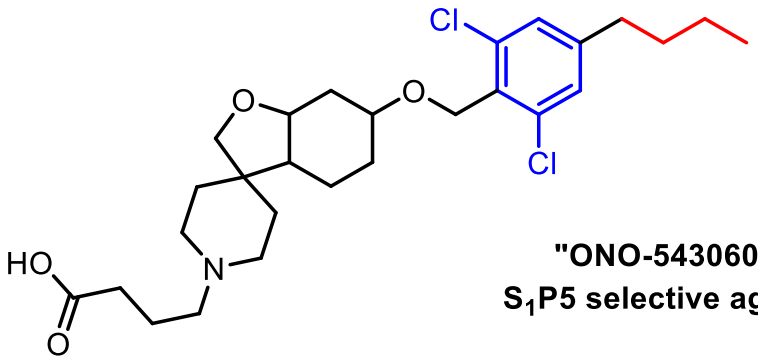


+



Cross Coupling





"ONO-5430608"
S_1P5 selective agonist

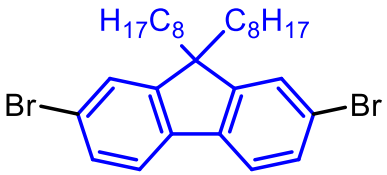
Demonstrates nueroprotective effects for patients with Alzheimer's and Huntington's disease

M = BF_3K

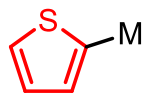
$Pd(dppf)Cl_2$ (5 mol%)
Cs_2CO_3, Toluene/H_2O, **90 °C, 48 h**
85% yield

M = Li

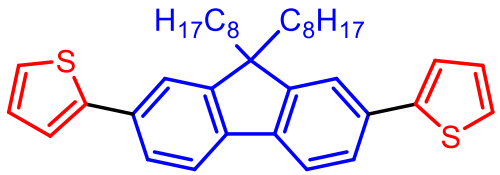
$Pd((Pt\text{-}Bu)_3)_2$ (5 mol%)
Toluene, **r.t., 1 h**
86% yield



+



Cross Coupling



M = $SnBu_3$

$Pd(PPh_3)_4$ (5 mol%),
DMF, 90 °C, **24 h**
73% yield

M = Li

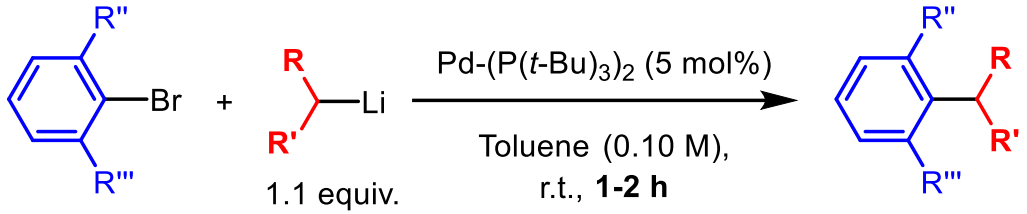
$Pd((Pt\text{-}Bu)_3)_2$ (5 mol%)
TMEDA (1.2 equiv.), Toluene, 40 °C, **1 h**
85% yield

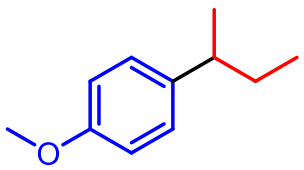
Modification of the ligand system and nucleophile allowed for rapid aryl-aryl or aryl-alkyl cross coupling at r.t. or 40 °C

Feringa et. al., *Nat. Chem.*, **2013**, 5, 667–672. Gusach, A. et. al., *Nat Commun*, **2022**, 13, 4736. Van Dongen, M. & Leflemme, N. J. PCT patent application WO 2012004378 (2012). Liu, et. al., *Adv. Funct. Mater.*, ***2008.***, 18, 2824–2833.

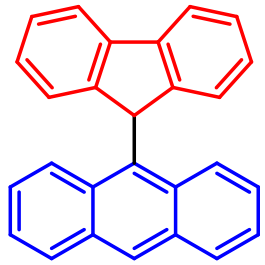
Comparison to Wenjun Tang and co-workers

Feringa, 2014:

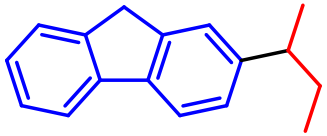




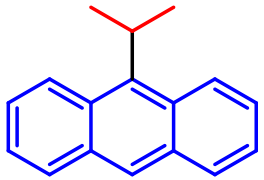
73%



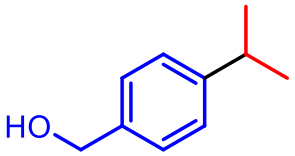
57%



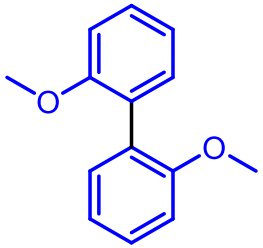
95%



97%
b/l = ~9:1

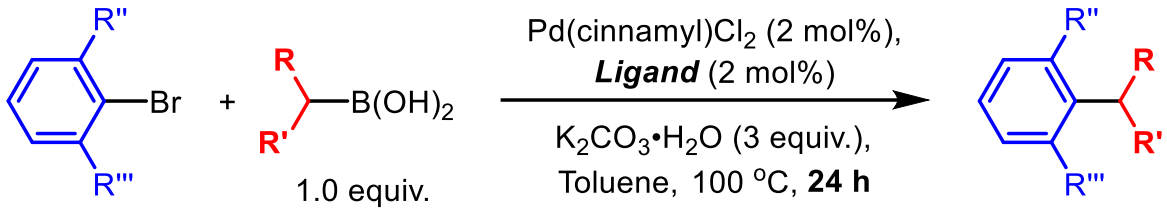


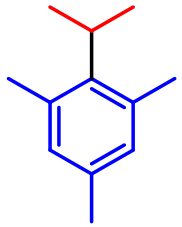
61%



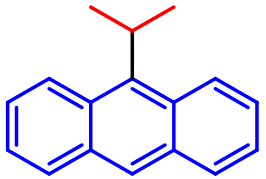
Undesired product exclusively observed

Tang, 2015:

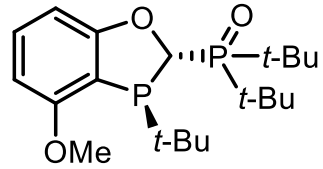




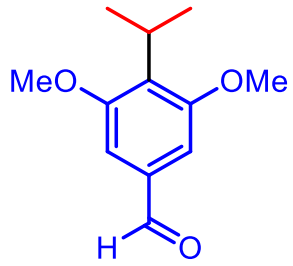
92%



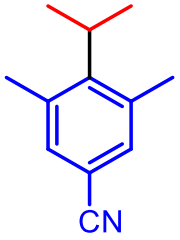
96%



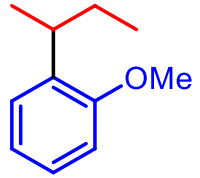
Ligand



99%



96%



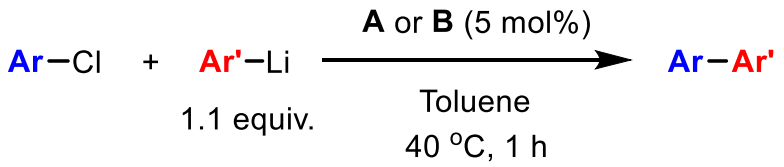
88%
No homocoupling observed

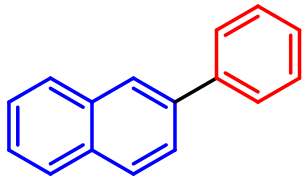
*All b/l ratios from Feringa and Tang are >20:1 unless otherwise specified

Feringa et. al., *Chem. Sci.*, **2014**, 5, 1361-1369., Tang et. al., *Angew. Chem. Int. Ed.*, **2015**, 54, 3792 –3796.

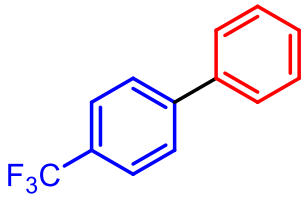
C(sp^2)-C(sp^2) Couplings with Aryl Chlorides

Electron neutral and electron poor electrophiles:

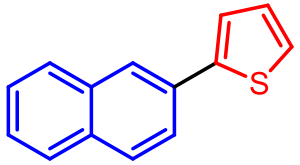




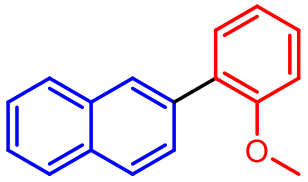
93% **B**



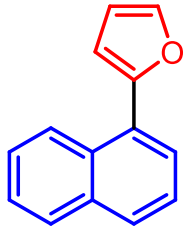
95% **B**



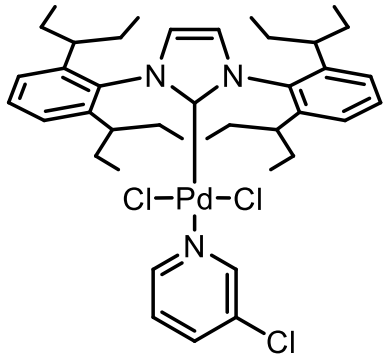
82% **A**



84% **A**



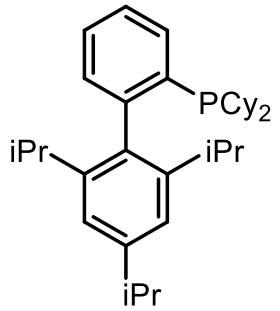
96% **A**



Pd-PEPPSI-IPent

Catalyst A

$Pd_2(dba)_3$
+



XPhos

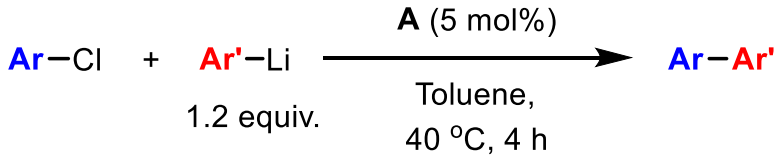
Catalyst B

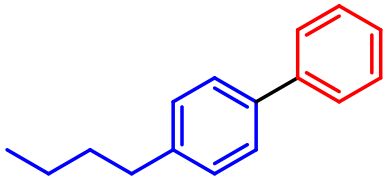
Oxidative addition with aryl chlorides is slower compared to aryl bromides. Heat is required to avoid homocoupling.

Feringa et. al., *Org. Lett.*, **2013**, 15, 19, 5114.

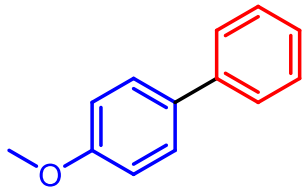
C(sp^2)-C(sp^2) Couplings with Aryl Chlorides

Electron rich electrophiles:

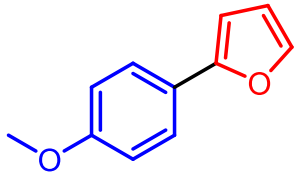




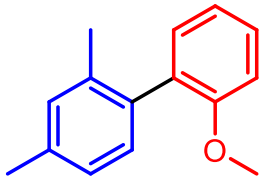
86%



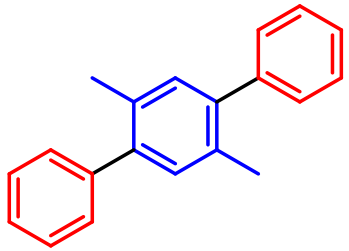
94%



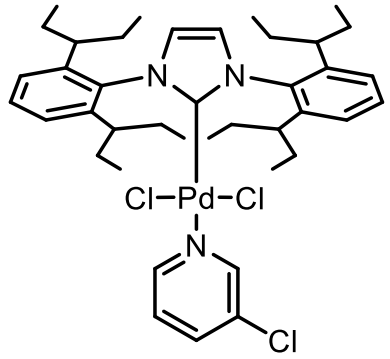
80%



86%

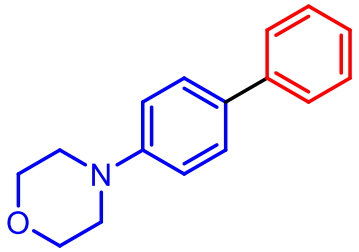


80%

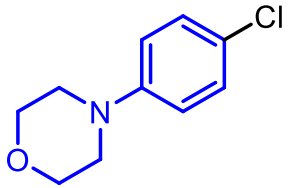


Catalyst A

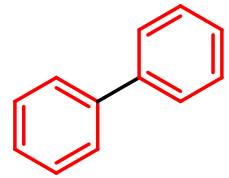
Pd-PEPPSI-IPent



Trace product

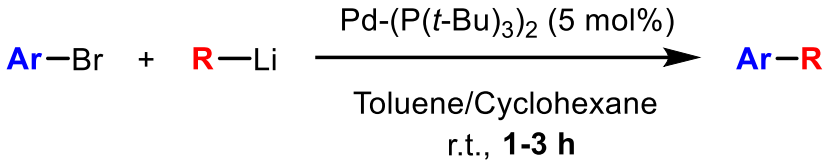


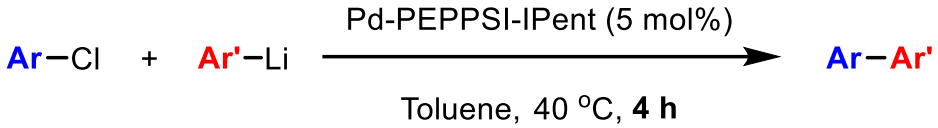
~60% recovered starting material

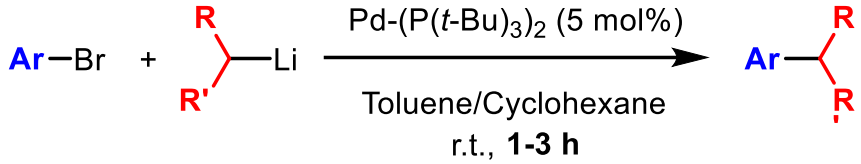


~15% homocoupling

Summary of Traditional Murahashi Couplings







1 mmol scale reaction:
Organolithium: diluted in toluene to 0.36 M then added via syringe pump at ***0.2 mL/hour !!!***

Pros:

Cross-couplings at room temperature (or 40 °C) in 1-4 hours

Functional group tolerance with some acidic and electrophilic groups

Cons:

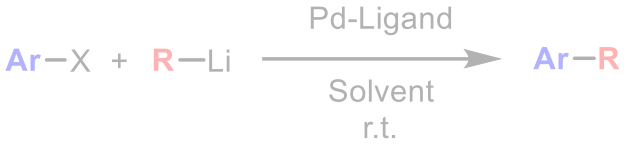
Homocoupling occurs with electron-rich aryl chlorides

All reactions are highly air and moisture sensitive

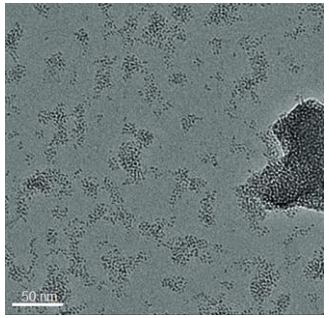
Engineered reaction conditions leads to issues with scalability and reproducibility

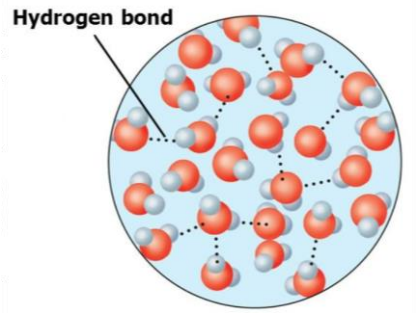
Presentation Overview

Initial Reports and Modern Revitalization

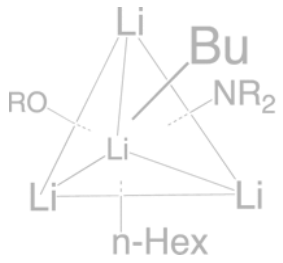


Mitigating Undesired Pathways: Two Strategies





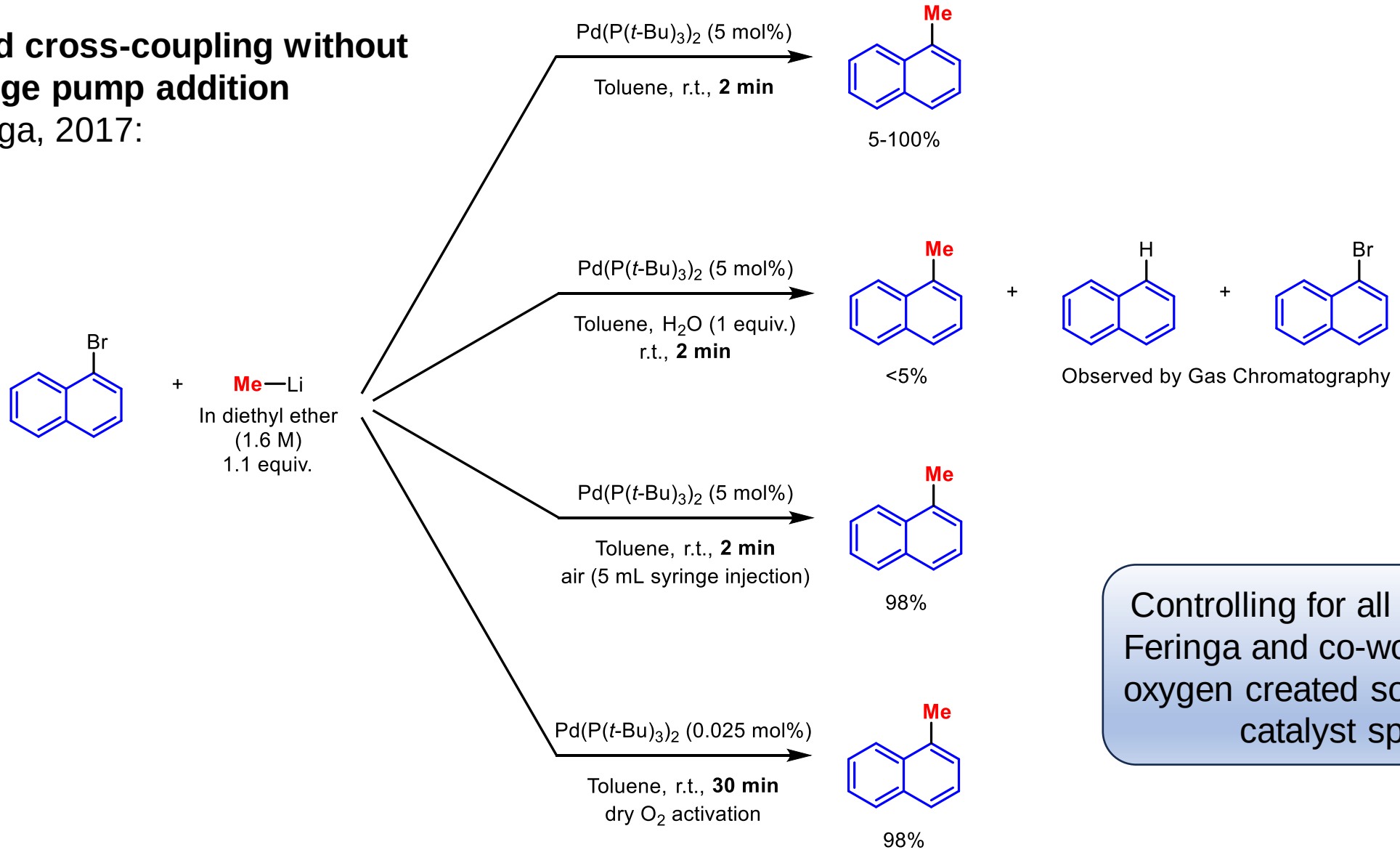
Conclusion and Outlook



Pyrophoric?
Stable?
Soluble?

Strategy: Rapid Coupling via a Highly Active Pd Catalyst

Rapid cross-coupling without syringe pump addition
Feringa, 2017:

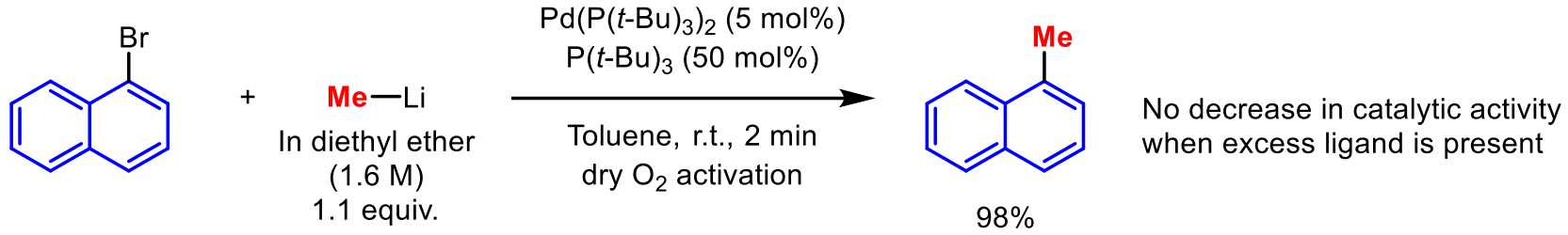


Controlling for all other factors, Feringa and co-workers noticed oxygen created some active Pd catalyst species.

Feringa et. al., *Angew. Chem. Int. Ed.,* **2017**, 56, 3354-3359.

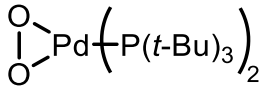
Active Catalyst Species?

Hypothesis:
Monoligated Pd-[P] species is the active catalyst.

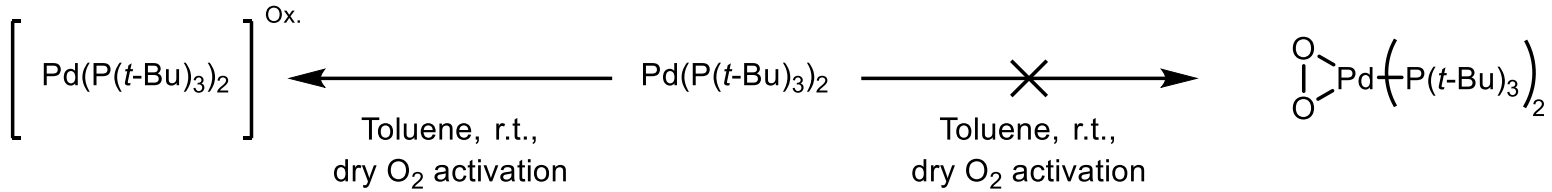


No decrease in catalytic activity when excess ligand is present

Hypothesis:

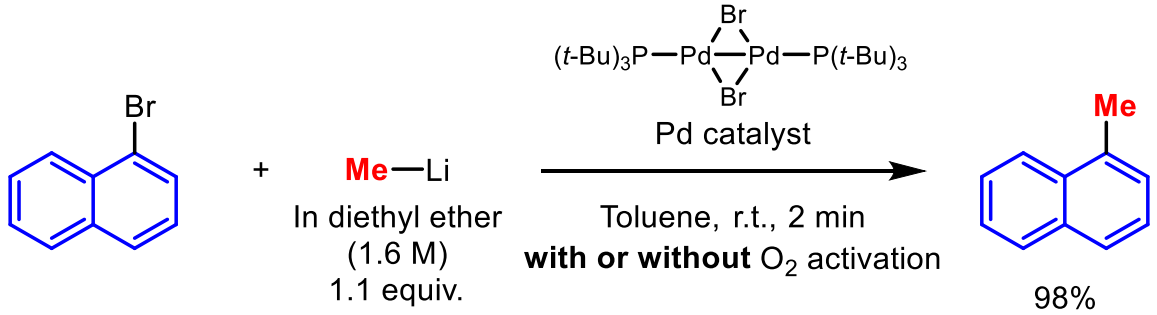


Forms in the presence of O_2, then is reduced to some active catalyst species



No characteristic spectroscopic evidence of a η^2-Oxo species by IR (800-915 cm^{-1})

Hypothesis:
Pd(I)-dimer is implicated in the catalytic cycle

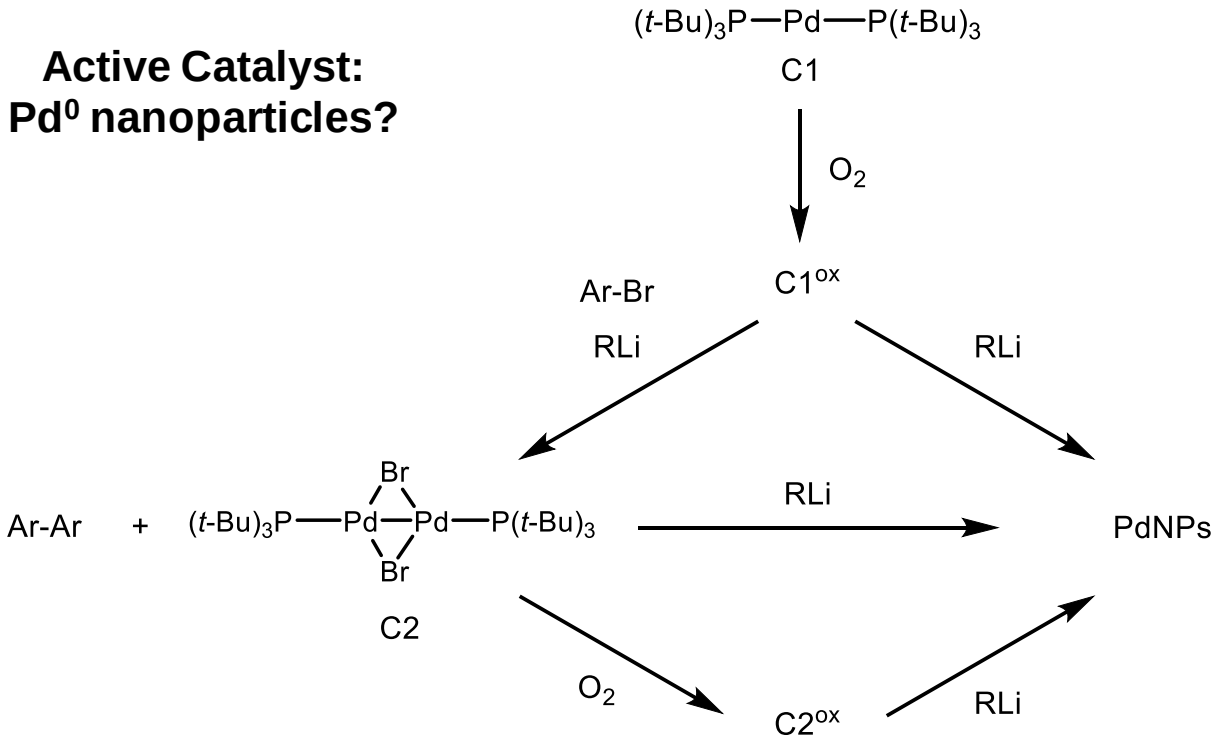


Pd(I) bridged di-nuclear catalyst shows similar activity with or without O_2 activation.

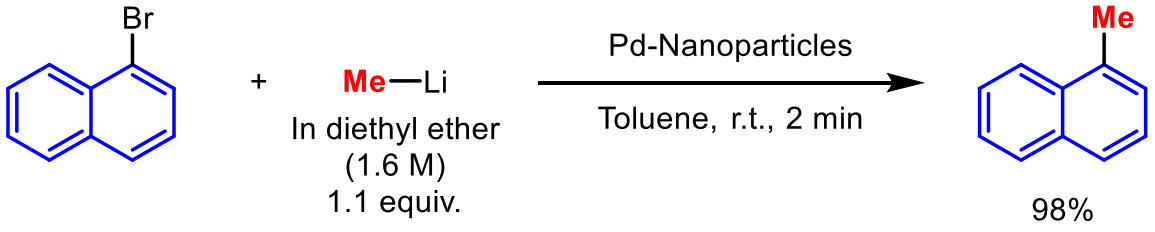
Feringa et. al., *Angew. Chem. Int. Ed.,* **2017**, 56, 3354-3359.

$Pd(P(t\text{-}Bu)_3)_2$ Conversion Into Active Catalyst

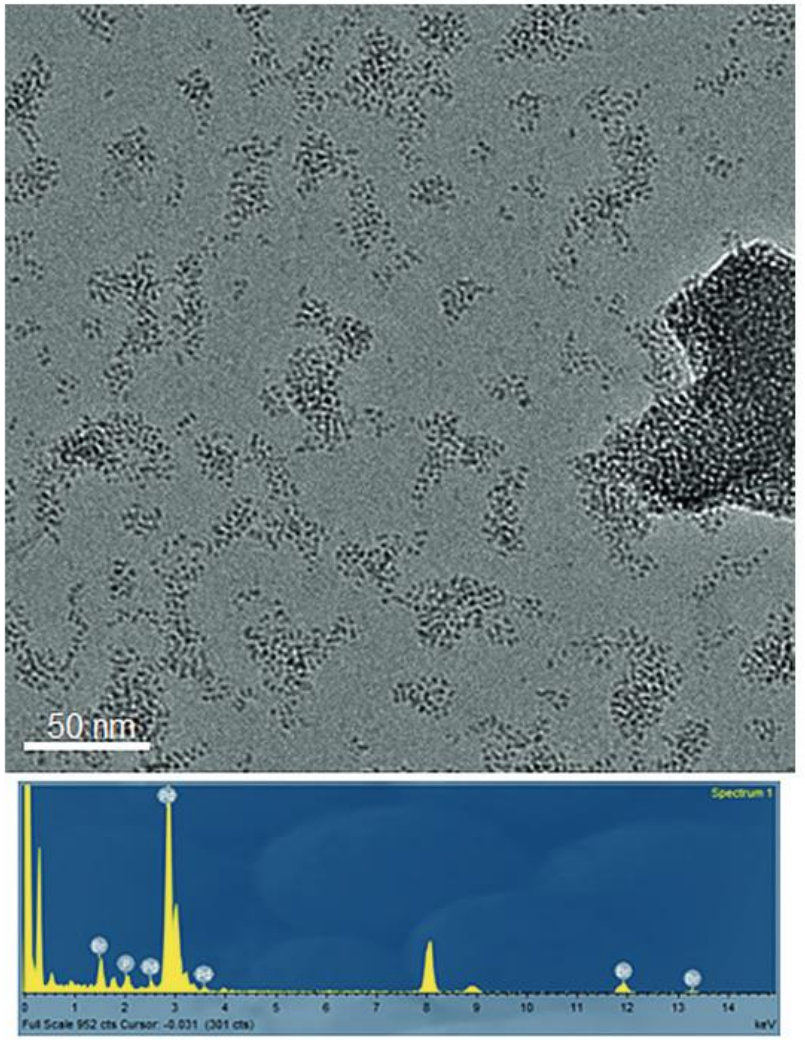
Active Catalyst:
Pd^0 nanoparticles?



Isolated Pd-nanoparticles resubjected to reaction conditions:

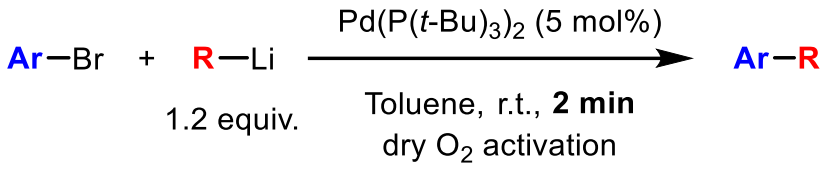


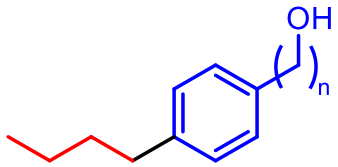
Pd-nanoparticles isolated after a catalytic reaction:



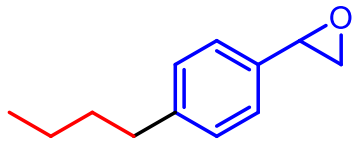
Feringa et. al., *Angew. Chem. Int. Ed.,* **2017**, 56, 3354-3359.

Abridged Substrate Scope

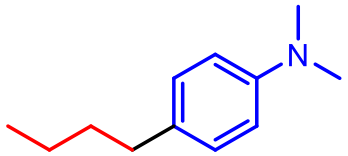




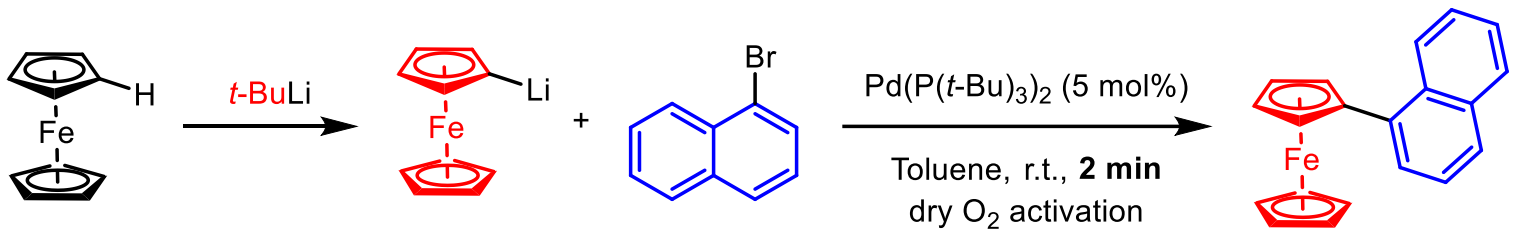
n=0, 83%
n=1, 71%
n=2, 52%



58%

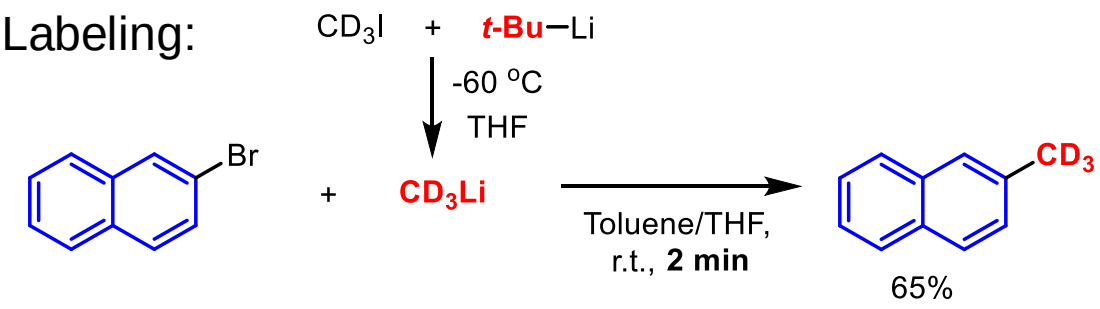


85%

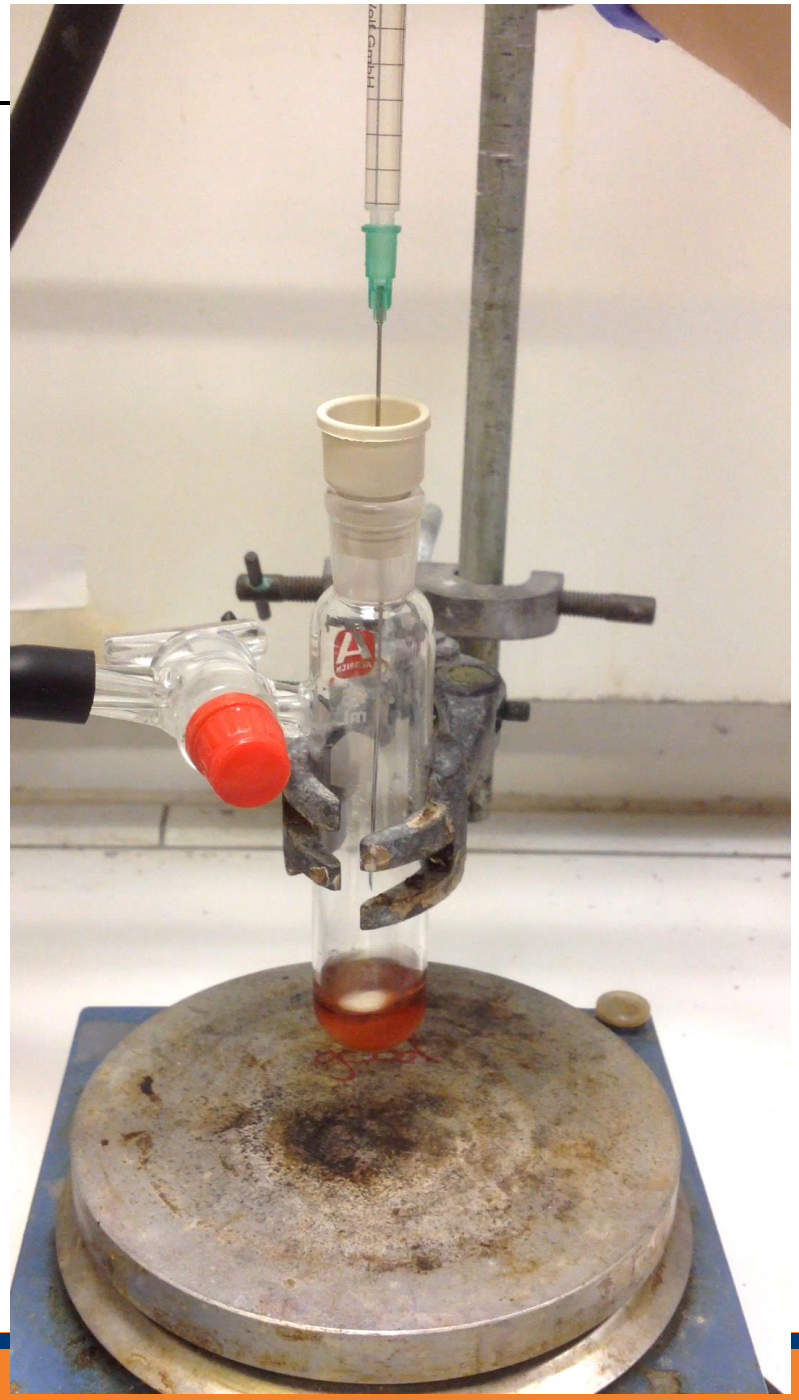


40%

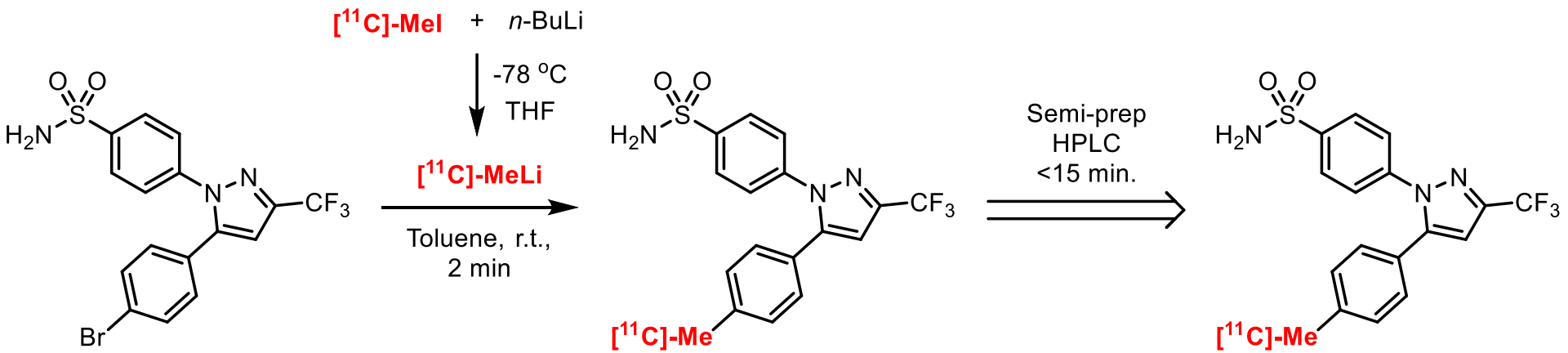
D$_3$C-Labeling:



65%



Rapid Coupling Enables Isotopic Labeling



Crude

65% decay-corrected radiochemical yield (average of three runs)

^{11}C Half-Life: 20.4 min

Pros:

Rapid C(sp^3)-C(sp^2) couplings at room temperature in minutes

Functional group tolerance expanded with acidic and electrophilic moieties

Cons:

Reactions still require dilute conditions with aprotic solvents

All reactions are moisture sensitive

Protic media as a reaction solvent?

Feringa et. al., *Angew. Chem. Int. Ed.,* **2017**, 56, 3354-3359.

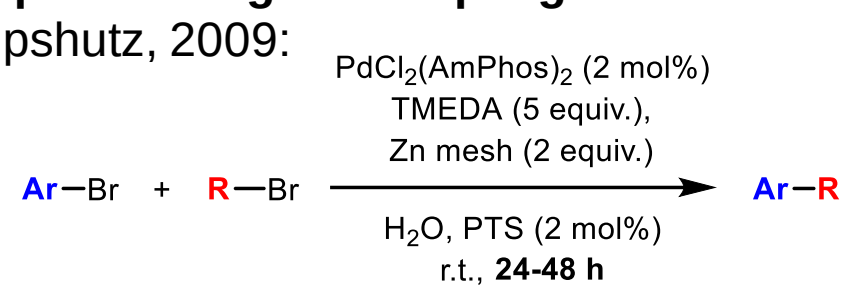
Polar Organometallic Reagents “On Water”

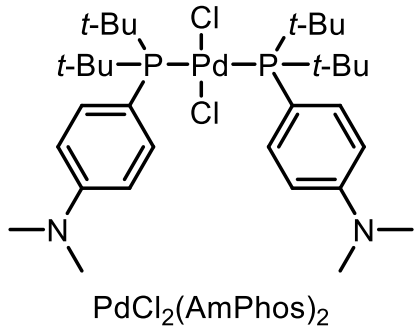
Sharpless et. al.

“We present several examples that illustrate a remarkable phenomenon: substantial rate acceleration when insoluble reactants are stirred in aqueous suspension, denoted here as “on water” conditions…”

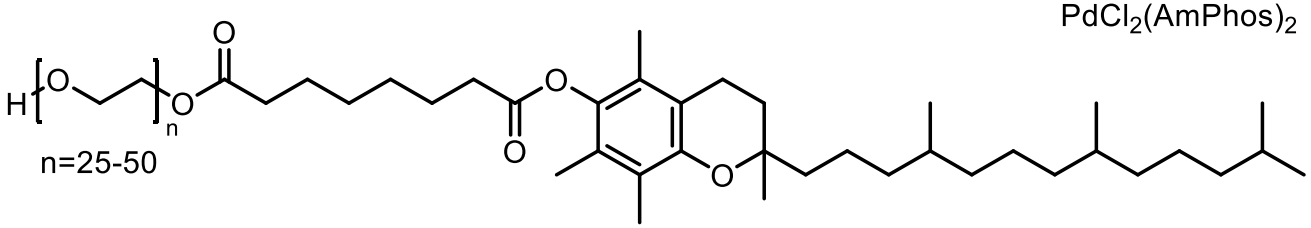
Aqueous Negishi couplings:

Lipshutz, 2009:



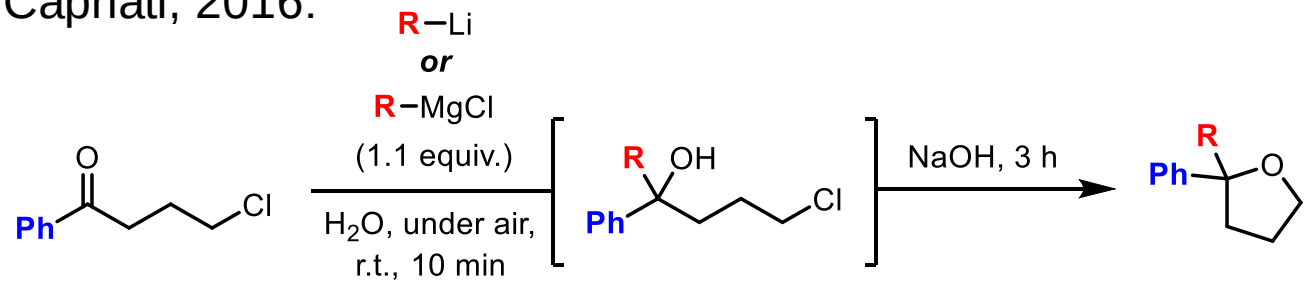


$PdCl_2(AmPhos)_2$



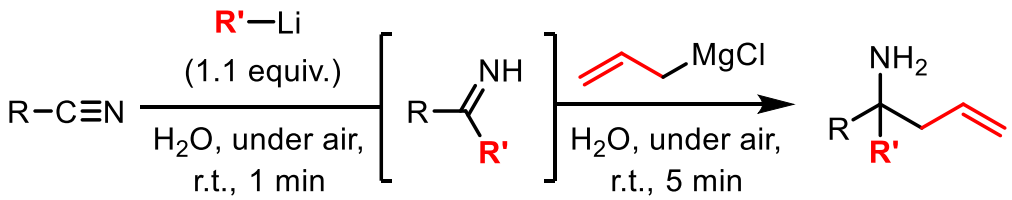
Rapid 1,2-addition open to air:

Capriati, 2016:



Rapid 1,2-addition then allylation:

Capriati, 2017:

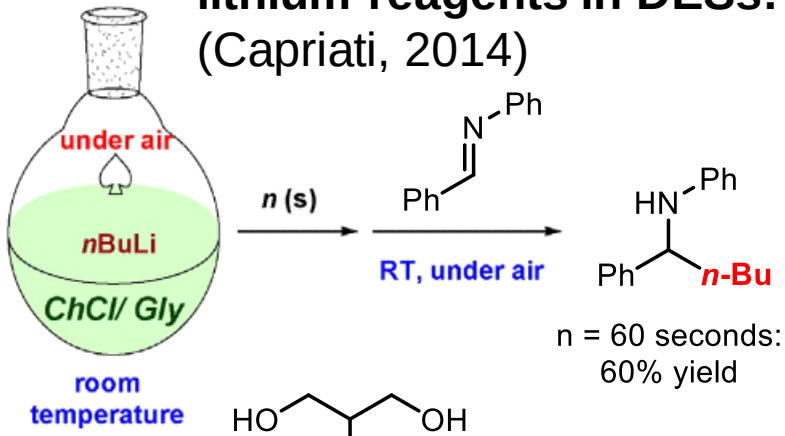


Lipshutz et. al., *J. Am. Chem. Soc.*, **2009**, 131, 43, 15593-15596., V. Capriati et. al., *Chem. Sci.*, **2016**, 7, 1192-1199., V. Capriati et. al., *Angew. Chem. Int. Ed.*, **2017**, 129, 10334-10337.

Deep Eutectic Solvents (DESs) with Polar Organometallic Reagents

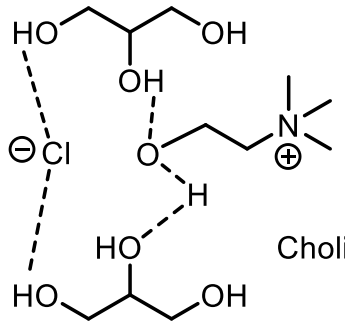
Ryder et. al.
"DESs contain large, nonsymmetric ions that have low lattice energy and hence low melting points. They are usually obtained by the complexation of a quaternary ammonium salt with a metal salt or hydrogen bond donor."

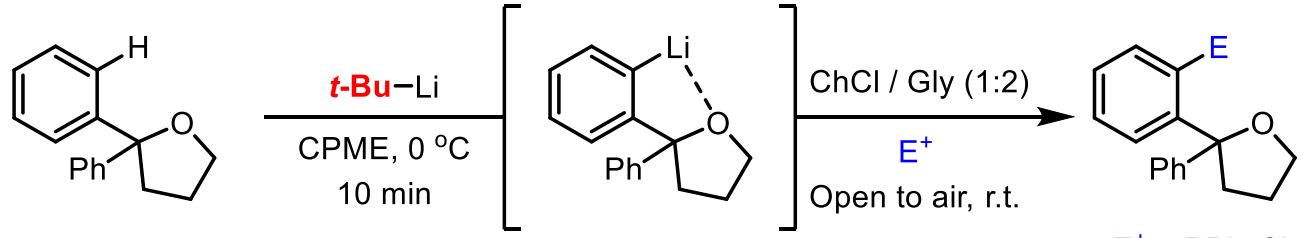
Extended stability of alkyl-lithium reagents in DESs:
(Capriati, 2014)



Vito Capriati, **2023**
(University of Bari Aldo Moro)

DESs enable similar reactivity to "on water" nucleophilic additions:
(Capriati, 2015)

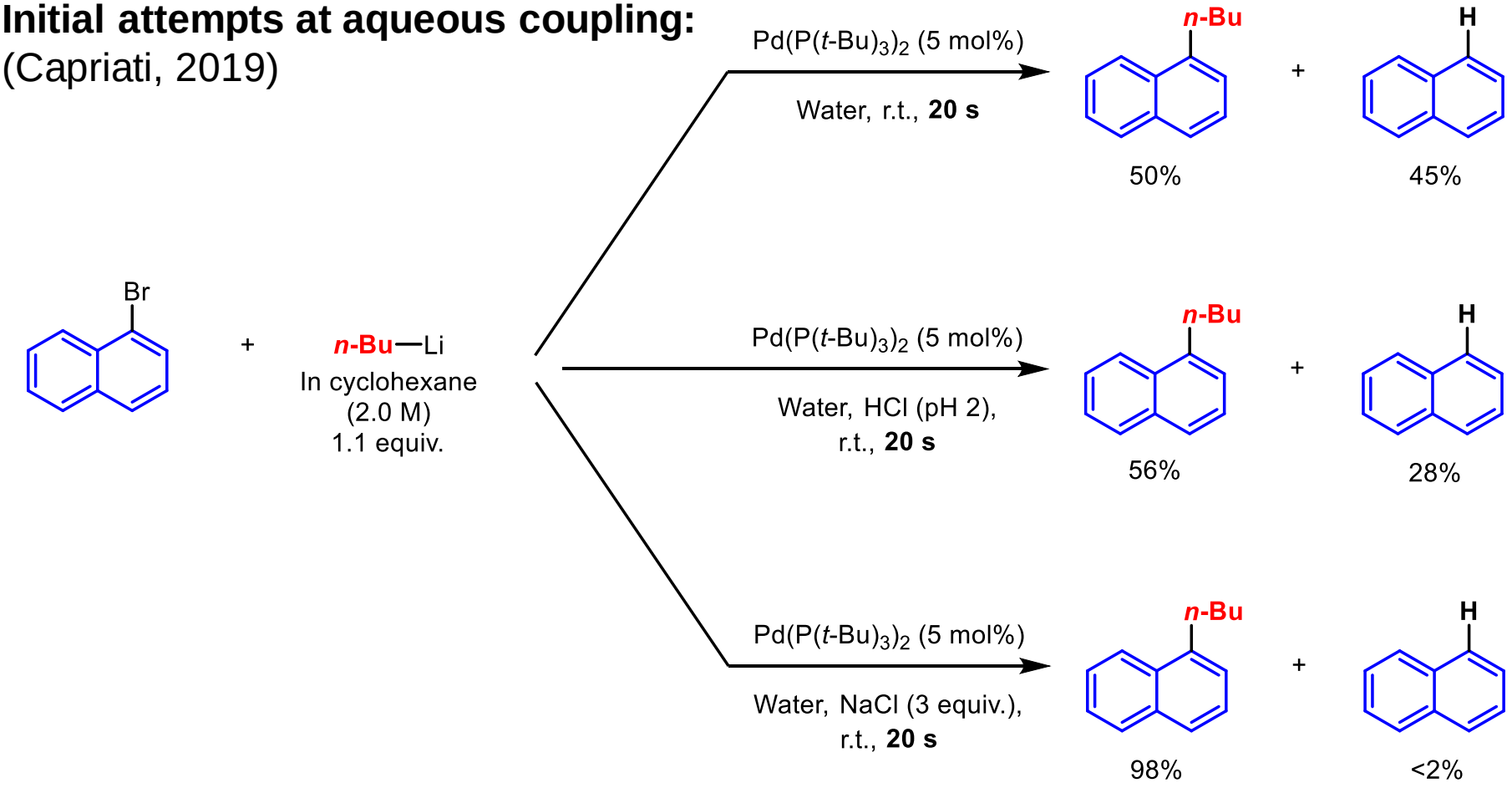




V. Capriati et. al., *Chem. Commun.*, **2014**, 50, 8655-8658., K. Ryder et. al., *Chem. Rev.* **2014**, 114, 21, 11060-11082. V. Capriati, *Chem. Commun.*, **2015**,51, 9459–9462.

Strategy: Aqueous Conditions with NaCl additive

Initial attempts at aqueous coupling:
(Capriati, 2019)

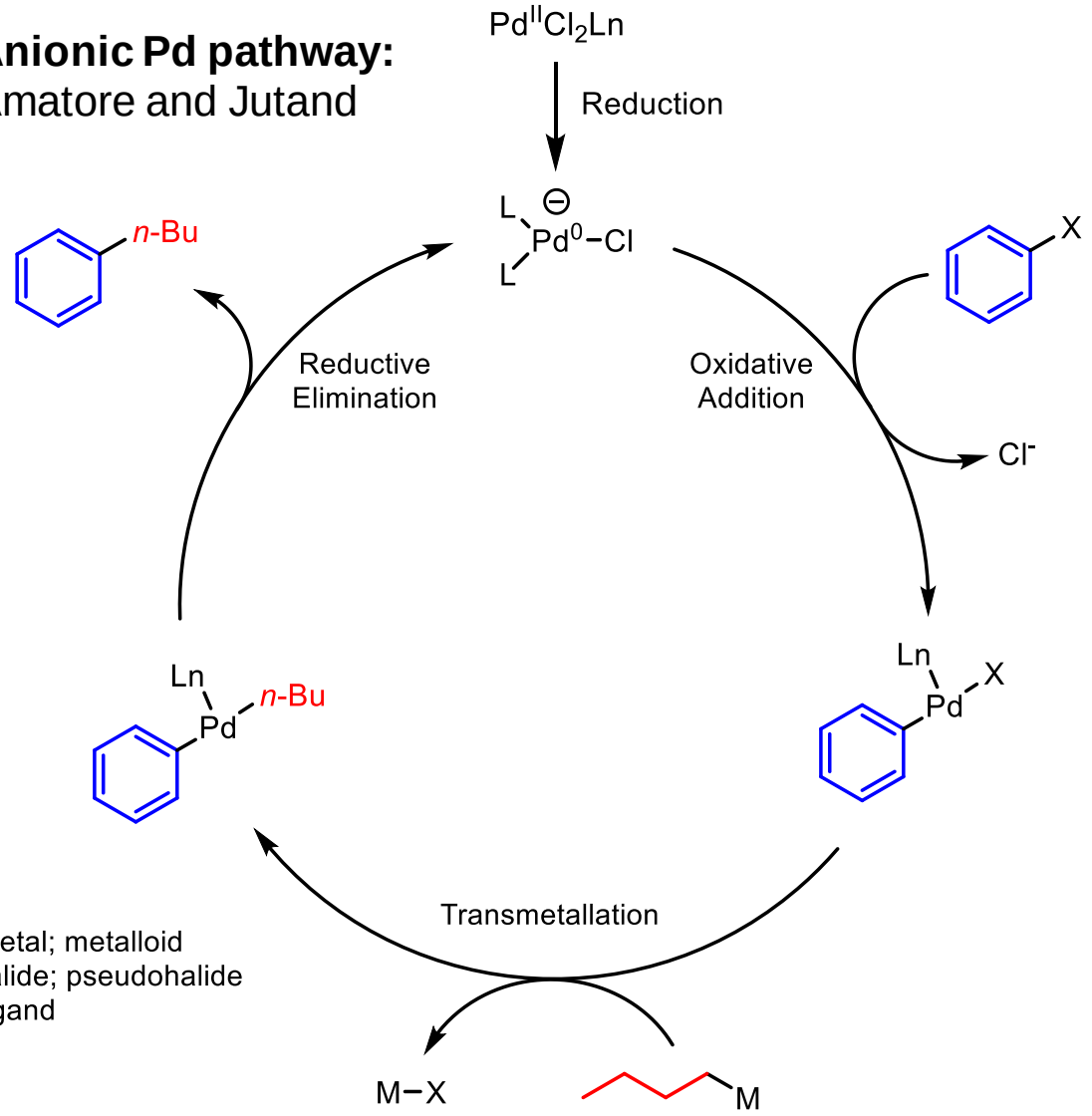


Role of the chloride additive?

Capriati et. al., *Angew. Chem. Int. Ed.*, **2019**, 131, 1813-1816.

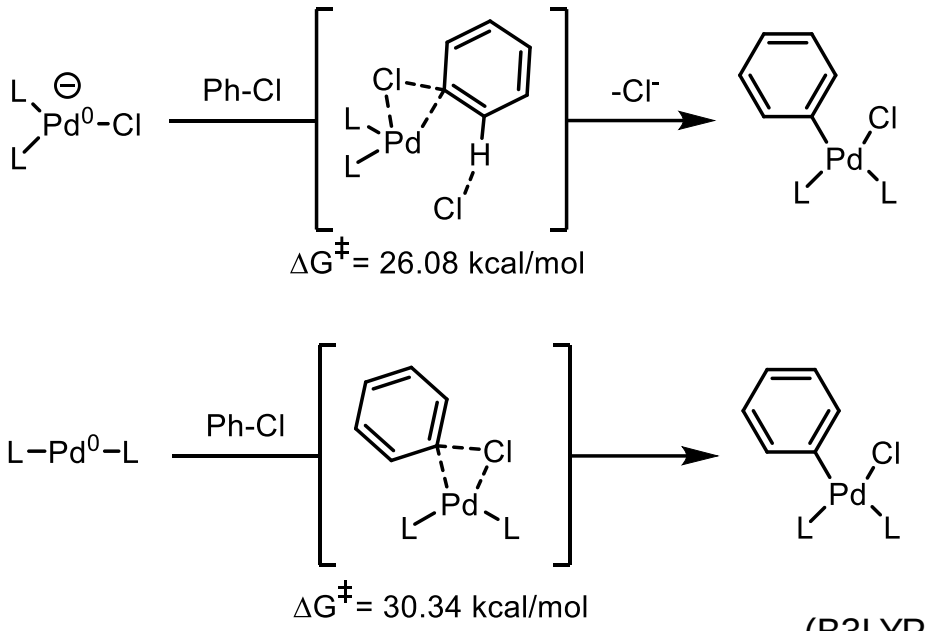
Seemingly Innocuous Chloride Additive

Anionic Pd pathway:
Amatore and Jutand



M=metal; metalloid
X=halide; pseudohalide
L=Ligand

DFT calculations from Amatore and Jutand:
When L = PPh_3:



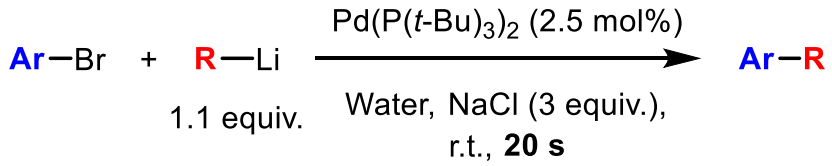
(B3LYP – LACVP)

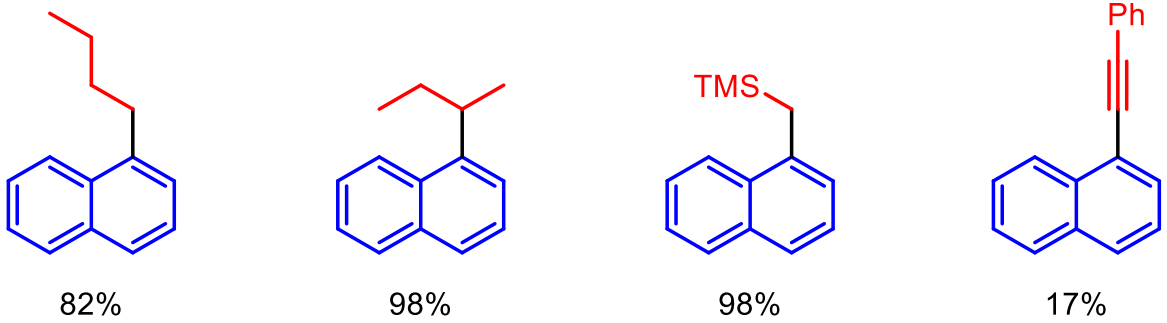
"The chloride additive effectively flattens the energy landscape of the cycle and thereby improves its turnover efficacy."
-Christian Amatore & Anny Jutand, 2005

Amatore, C. and Jutand, A. *J. Am. Chem. Soc.*, **1991**, 113, 8375-8384. Amatore, C. and Jutand, A., et. al., *J. Am. Chem. Soc.*, **1993**, 115, 9531-9541. Amatore, C. and Jutand, A. et. al., *J. Organomet. Chem.*, **1999**, 576, 254-278. Amatore, C. and Jutand, A. et. al., *J. Organomet. Chem.*, **2004**, 689, 3728-3734., C. Amatore, A. Jutand et. al., *Organometallics*, **2005**, 24, 10, 2319-2330.

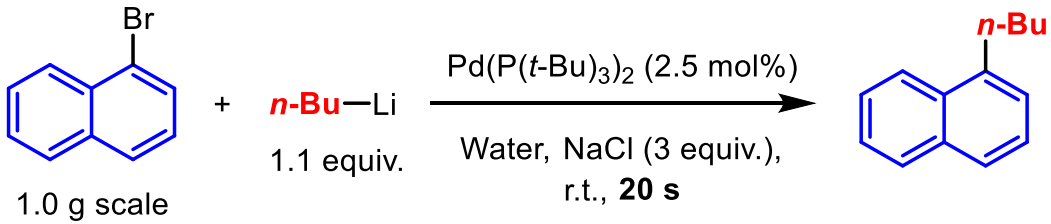
Scope of “On Water” Murahashi Couplings

Demonstration of C(sp^2)-C(sp) / (sp^2) / (sp^3) couplings:
(Capriati, 2019)





Gram-scale transformation:
Capriati, 2019:

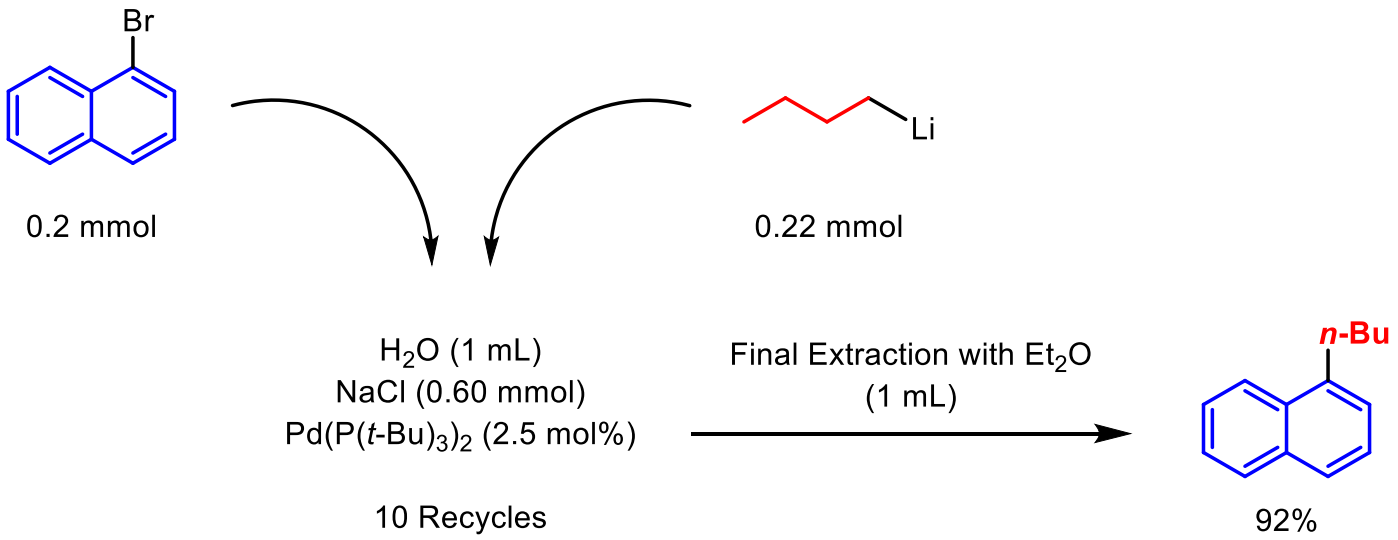


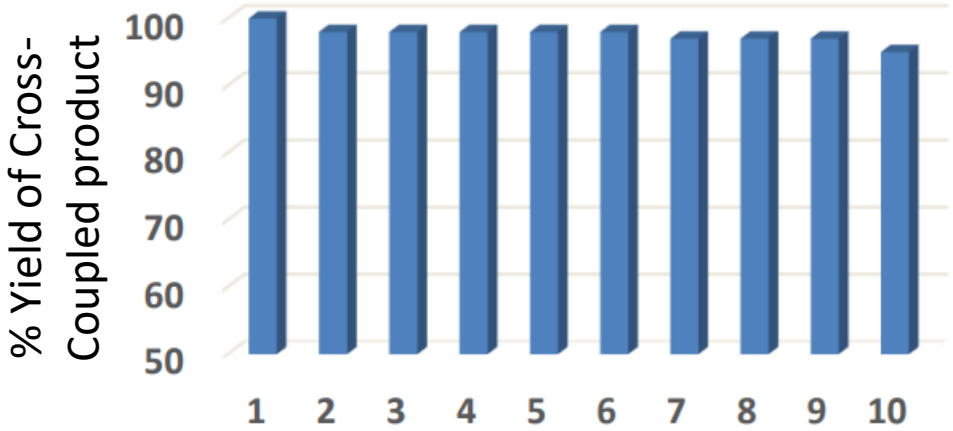
“Organolithiums are notoriously prone to ignition in air, and caution should be exercised in adopting the recommended procedure, especially on a larger scale.”

Capriati et. al., *Angew. Chem. Int. Ed.*, **2019**, 131, 1813-1816.

Recycled Catalyst Demonstrates Catalytic Activity

Batchwise recycling of catalyst allows for low E-factor:
(Capriati, 2019)





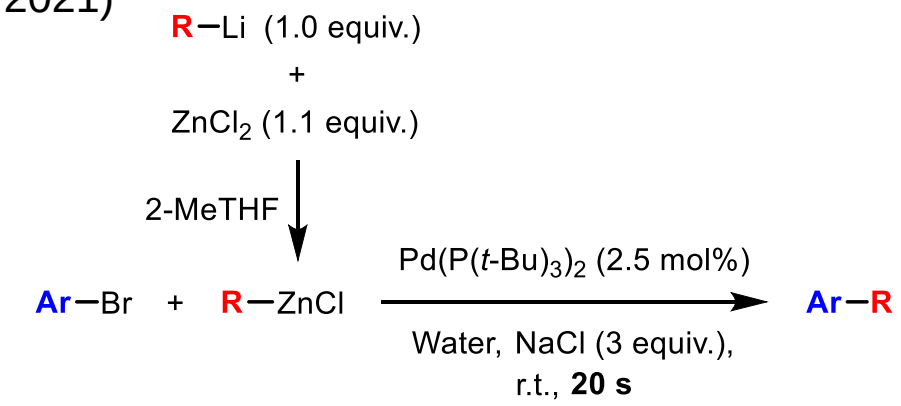
E-Factor = Mass of waste/Mass of product = **7.35** after 10 batches

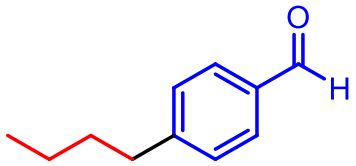
96% yield obtained for 10th batch of recycled catalyst

Capriati et. al., *Angew. Chem. Int. Ed.*, **2019**, 131, 1813-1816.

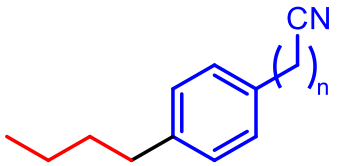
Expanded Scope Upon Switching to Zinc

Pre-formation of alkyl-zinc expands synthetic utility:
(Capriati, 2021)

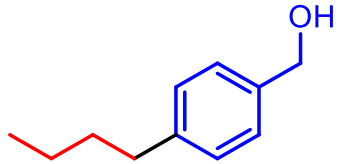




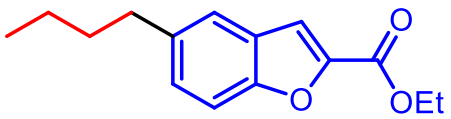
93%
5 gram scale



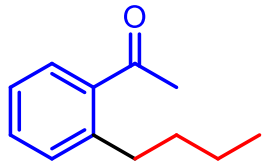
n=0, 98%
n=1, 70%



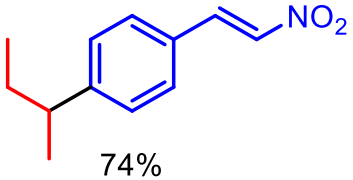
84%



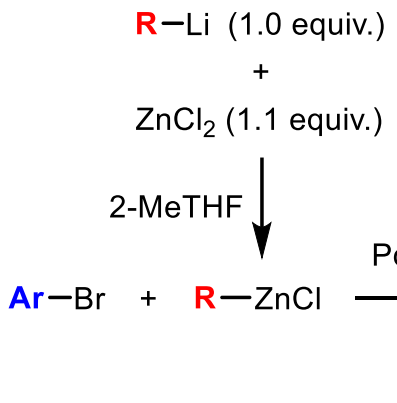
80%

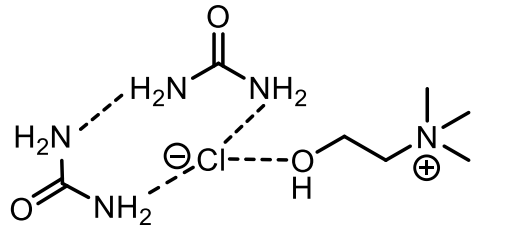


90%

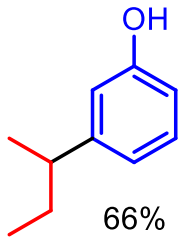


74%

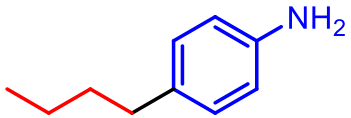




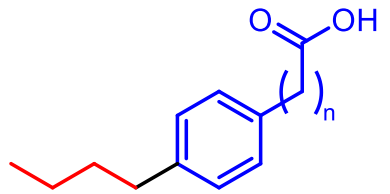
Choline Cl/Urea (1:2)



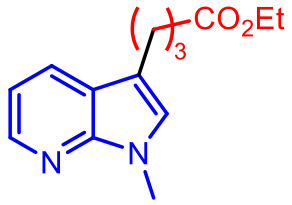
66%



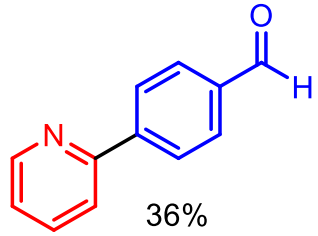
35%



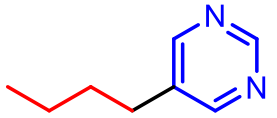
n=0, 35%
n=1, 38%



80%



36%

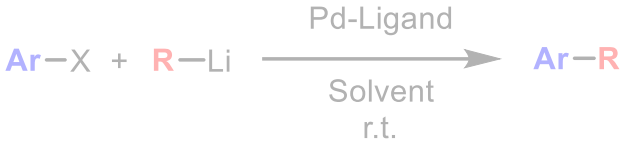


78%

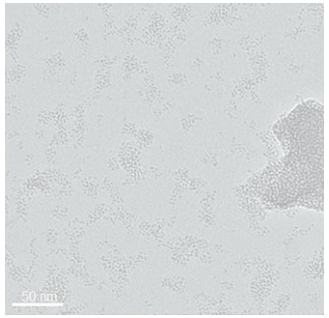
Capriati, *Angew. Chem. Int. Ed.*, **2021**, 60, 10632-10636.

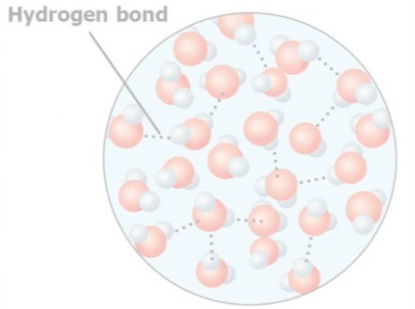
Presentation Overview

Initial Reports and Modern Revitalization

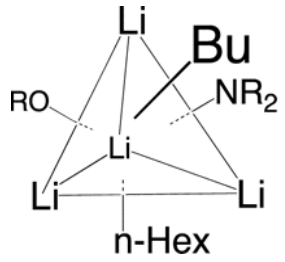


Mitigating Undesired Pathways: Two Strategies

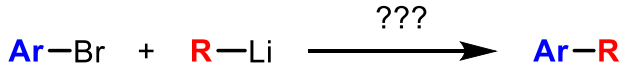




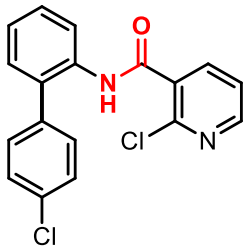
Conclusion and Outlook



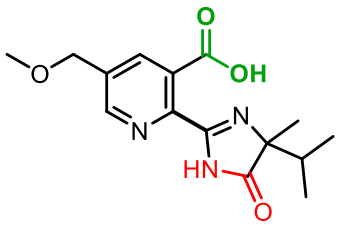
Pyrophoric?
Stable?
Soluble?



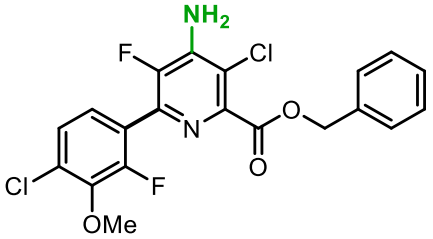
Conclusion and Outlook



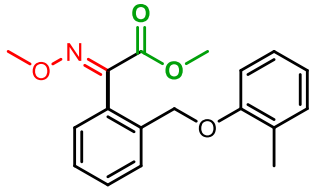
Boscalid



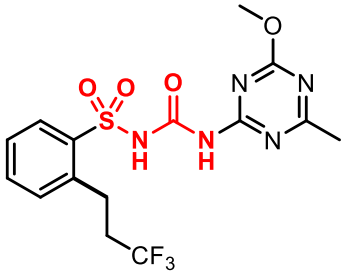
Imazamox



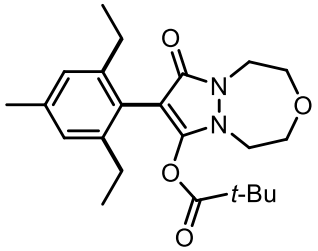
Florpyrauxifen-Benzyl Ester



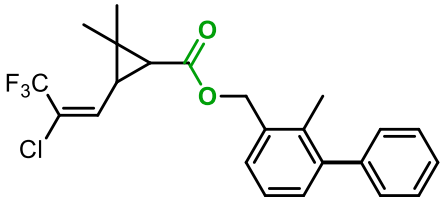
Bixafen



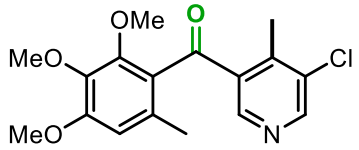
Prosulfuron



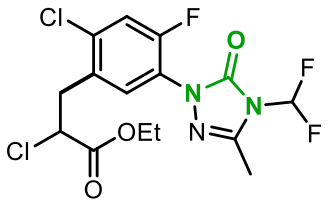
Pinoxaden



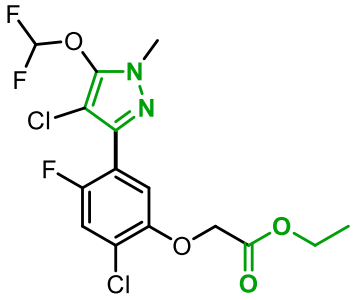
Bifenthrin



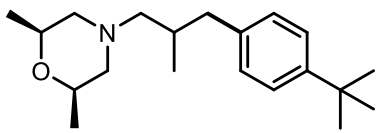
Pyrifenone



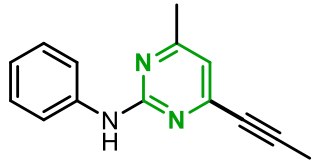
Carfenstrazone-Ethyl Ester



Pyraflufen-Ethyl Ester

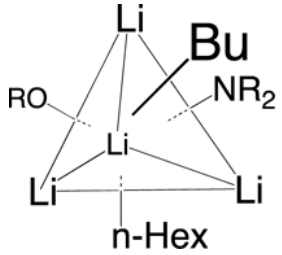


Fenpropimporh



Mepanipyrim

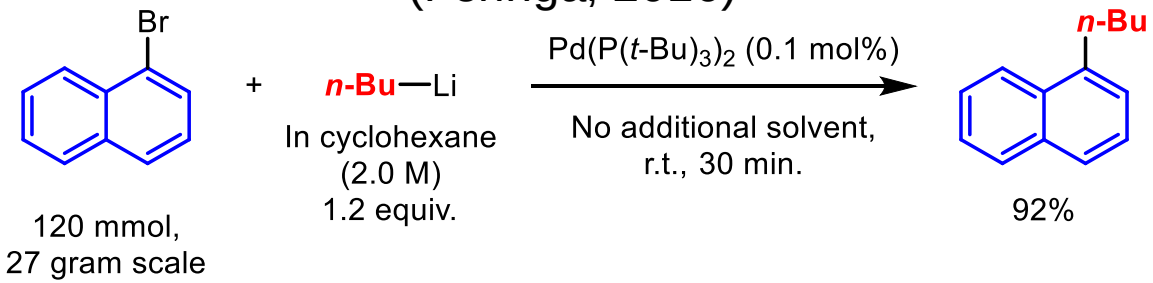
Conclusion and Outlook



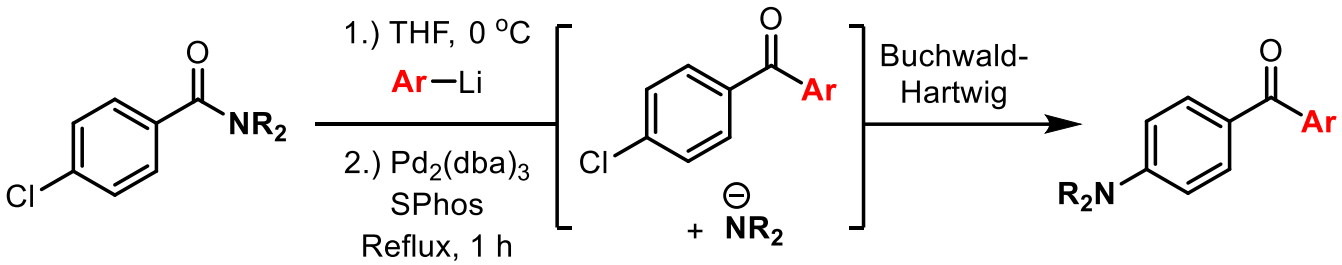
Pyrophoric?
Stable?
Soluble?

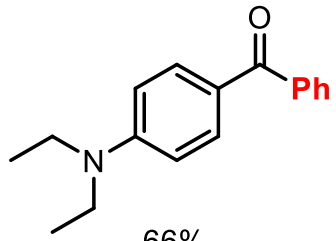
"Preparation, Properties, and Safe Handling of Commercial Organolithiums"
T. Rathman and J. A. Schwindeman, 2014

Neat, gram scale coupling:
(Feringa, 2016)

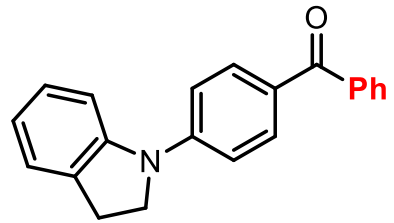


One-pot 1,2-addition/ Buchwald-Hartwig coupling
(Feringa, 2019)

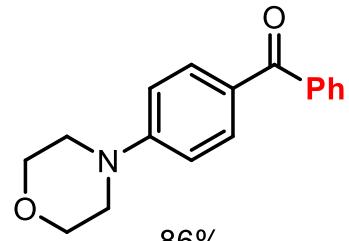




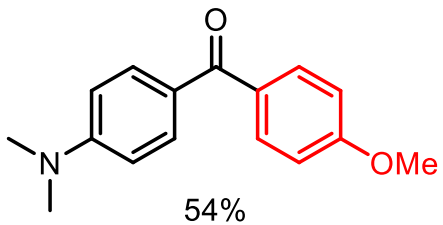
66%



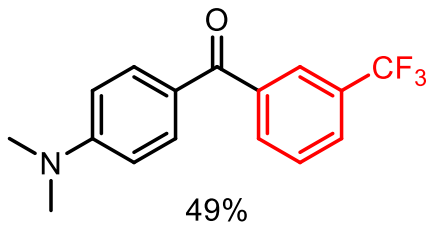
85%



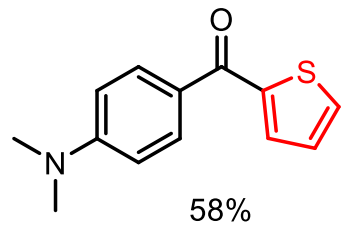
86%



54%



49%



58%

Schwinderman and Rathman, *Org. Process Res. Dev.*, **2014**, 18, 10, 1192–1210., Feringa et. al., *Nat. Commun.*, **2016**, 7, 11698-11705. Feringa et. al., *Chem. Commun.*, **2019**, 55, 2908-2912.

Additional Readings

1.) “The Resurrection of Murahashi Coupling after Four Decades”

Colacot et. al., *ACS Catal.* **2021**, 11, 21, 13188–13202.

2.) “The Future of Polar Organometallic Chemistry Written in Bio-Based Solvents and Water”

Capriati et. al., *Chem. Eur. J.*, **2018**, 24, 14854-14863.

3.) “Advances in deep eutectic solvents and water: applications in metal- and biocatalyzed processes, in the synthesis of APIs, and other biologically active compounds”

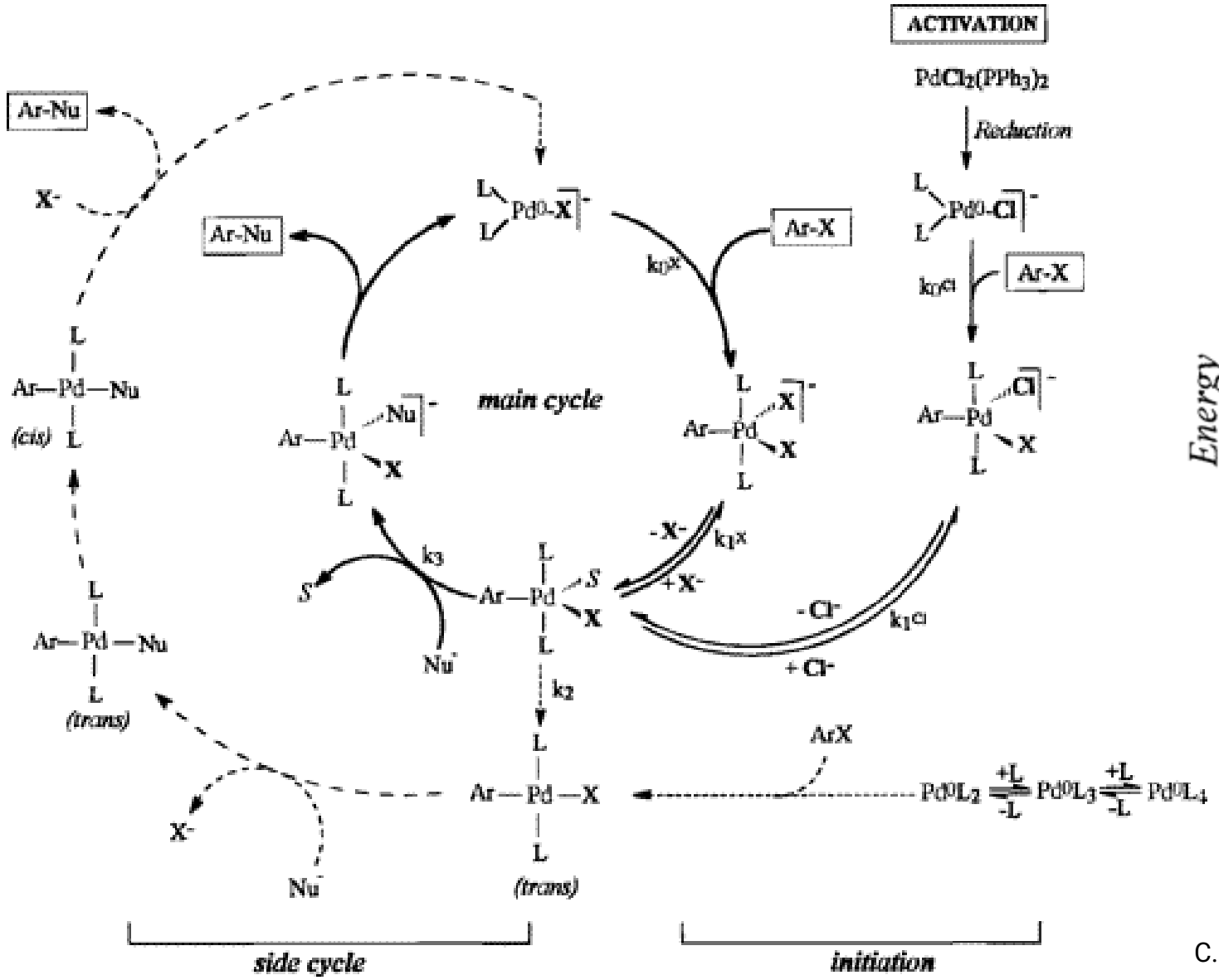
Capriati et. al., *Org. Biomol. Chem.*, **2021**, 19, 2558–2577.

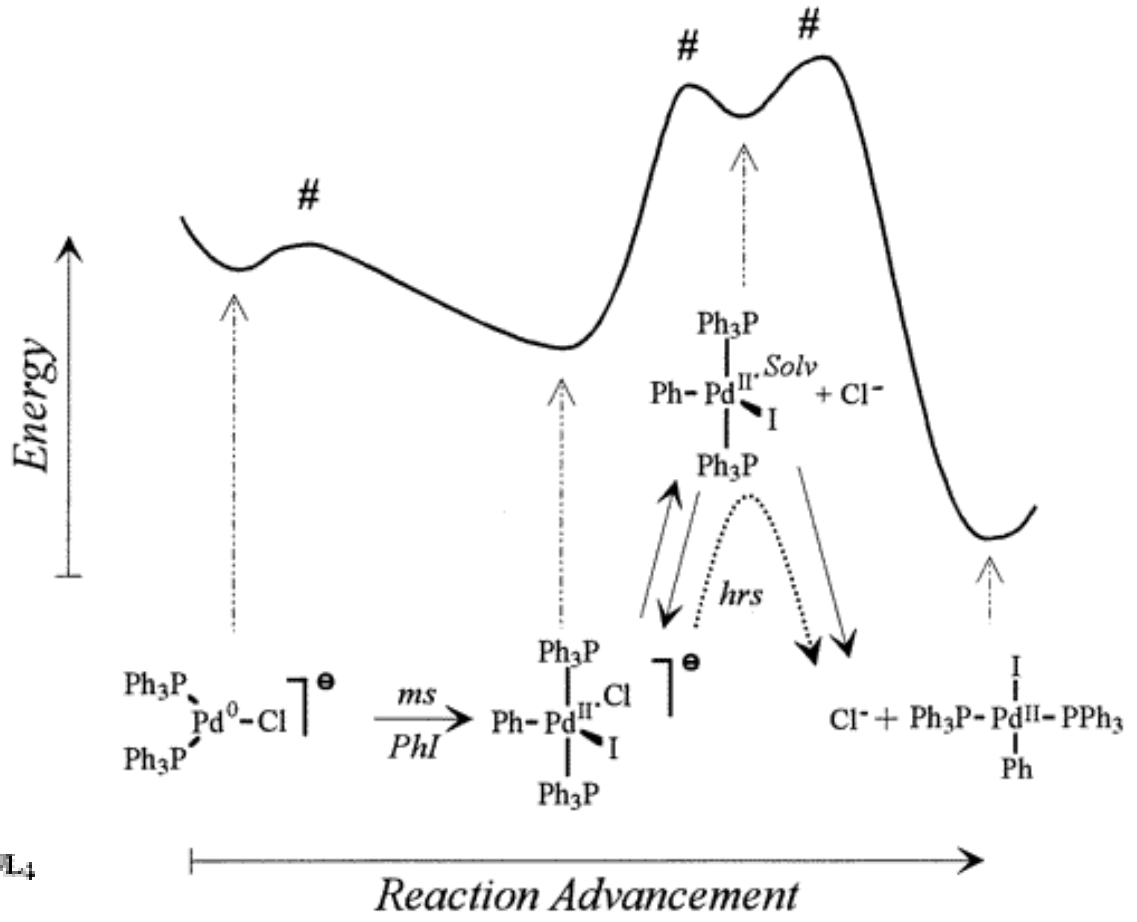
4.) “Selectivity in micellar catalyzed reactions: The role of interfacial dipole, compartmentalization, and specific interactions with the surfactants”

Beverina et. al., *Current Opinion in Colloid & Interface Science*, **2023**, 64, 101681-101697.

Questions?

Backup Slide – Amatore and Jutand Proposed Anionic Pathway

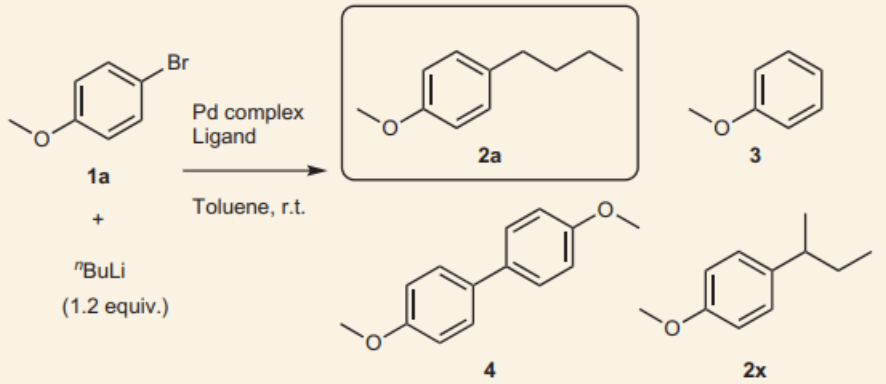




C. Amatore, A. Jutand et. al., *Acc. Chem. Res.* **2000**, 33, 5, 314–321.

Backup Slide – Feringa reaction optimization

Table 1 | Cross-coupling of *n*-BuLi and 4-methoxy-bromobenzene.

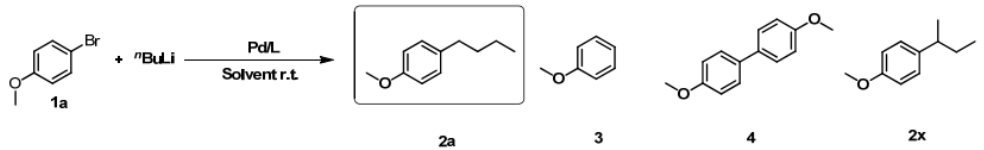


Entry	Pd complex	Ligand	Reaction time (h)	Conversion (%)	2a:3:4:2x*
1	$Pd_2(dba)_3$, 2.5 mol%	XPhos, 10 mol%	3	Full	80:5:10:5
2	-	-	3	25	-:>95:-:-
3	$Pd_2(dba)_3$, 2.5 mol%	-	3	22	23:48:29:-
4	$Pd_2(dba)_3$, 2.5 mol%	SPhos, 10 mol%	1	Full	89:5:6:-
5	$Pd_2(dba)_3$, 2.5 mol%	P(*t*-Bu)$_3$, 6 mol%	1	Full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

*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).
dba, dibenzylideneacetone; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; SPhos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

Backup Slide – Feringa reaction optimization

Table S1.



Entry[a]	L mol%	Pd mol%	^{n}BuLi	Reaction time	Solvent	Conversion	2a/3/4/2x
1	**XPhos 10%**	$Pd_2(dba)_3$ 5%	1.5 equiv	3h	toluene	Full	80/5/10/5
2	**XPhos 10%**	$Pd_2(dba)_3$ 2.5%	1.2 equiv	3h	toluene	Full	80/5/10/5
3	**XPhos 10%**	$Pd(OAc)_2$ 5%	1.2 equiv	3h	toluene	Full	80/5/10/5
4	**XPhos 5%**	$Pd_2(dba)_3$ 1.75%	1.2 equiv	3h	toluene	Full	80/5/10/5
5	**XPhos 15%**	$Pd_2(dba)_3$ 2.5%	1.2 equiv	3h	toluene	Full	80/5/10/5
6	**XPhos 10%**	$Pd_2(dba)_3$ 2.5%	1.2 equiv	3h	hexane	No conversion	-
7	**SPhos 10%**	$Pd_2(dba)_3$ 2.5%	1.2 equiv	3h	toluene	Full	89/5/6/-
8	**SPhos 10%**	$Pd_2(dba)_3$ 2.5%	1.2 equiv	6h	toluene	Full	88/6/6/-
9	**SPhos 10%**	$Pd_2(dba)_3$ 1.25% %CuBr·SMe_2 2.5%	1.2 equiv	3h	toluene	Full	82/5/13/-
10	**SPhos 10%**	$Pd_2(dba)_3$ 2.5%	1.2 equiv	1h	toluene	Full	89/5/6/-
11	**SPhos 20%**	$Pd_2(dba)_3$ 5%	1.2 equiv	1h	toluene	Full	89/5/6/-
12	**SPhos 10%**	$Pd_2(dba)_3$ 2.5%	1.2 equiv	1h	toluene/hexane 3:1	No conversion	-
13	**SPhos 10%**	$Pd(OAc)_2$ 5%	1.2 equiv	1h	toluene	Full	88/6/6/-
14	**DavePhos 10%**	$Pd_2(dba)_3$ 2.5%	1.2 equiv	1h	toluene	Full	80/10/10/-
15	**DavePhos 10%**	$Pd_2(dba)_3$ 2.5%	1.2 equiv	3h	toluene	Full	82/7/11/-
16	**P(^{t}Bu)$_3$ 6%**	$Pd_2(dba)_3$ 2.5%	1.2 equiv	1h	toluene	Full	90/6/4/-
17	-	$Pd[P(^tBu)_3]_2$ 5%	1.2 equiv	1h	toluene	Full	96/4/-/-
18	-	-	1.2 equiv	2h	THF	86%	Complex mixture

Backup Slide – Feringa active catalyst investigations

Active Catalyst Investigation

Testing of η^2-O_2-Pd(PCy_3)$_2$. In a dry Schlenk flask Pd(PCy_3)$_2$ (2,5 mol%, 0.015 mmol, 10 mg) and 1-Br-naphthalene (0.6 mmol) were dissolved in 4 mL of dry toluene at room temperature. The mixture was slowly purged with 10 ml of pure oxygen and stirred for 5 min, upon which the color changed from slightly yellow to dark green. MeLi (1.5 eq) was diluted with toluene to reach 2.0 mL; this solution was added over 2 min by the use of a syringe pump. After the addition was completed, the reaction was quenched with 0.5 mL of MeOH. The crude mixture was filtered over Celite and an aliquot was analized via GCMS. No desired cross-coupled product was obtained.

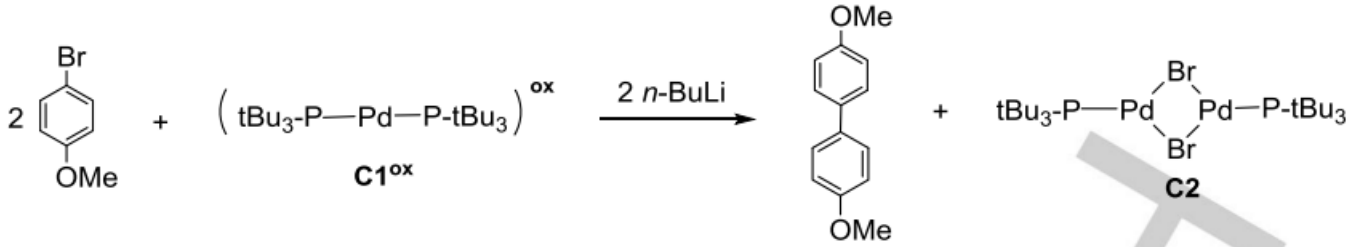
Testing of η^2-O_2-Pd(PPh_3)$_2$. In a dry Schlenk flask Pd(PPh_3)$_4$ (2,5 mol%, 0.015 mmol, 17.3 mg) and 1-Br-naphthalene (0.6 mmol) were dissolved in 4 mL of dry toluene at room temperature. The mixture was slowly purged with 10 ml of pure oxygen and stirred for 5 min, upon which the color changed from slightly yellow to dark green. MeLi (1.5 eq) was diluted with toluene to reach 2.0 mL; this solution was added over 2 min by the use of a syringe pump. After the addition was completed, the reaction was quenched with 0.5 mL of MeOH. The crude mixture was filtered over Celite and an aliquot was analized via GCMS. No desired cross-coupled product was obtained.

Testing of [PdBr(P*t*-Bu_3)]$_2$. In a dry Schlenk flask [PdBr(P*t*-Bu_3)]$_2$ (2,5 mol%, 0.015 mmol, 11.7 mg) and 1-Br-naphthalene (0.6 mmol) were dissolved in 4 mL of dry toluene at room temperature. MeLi (1.5 eq) was diluted with toluene to reach 2.0 mL; this solution was added over 2 min by the use of a syringe pump. After the addition was completed, the reaction was quenched with 0.5 mL of MeOH. The crude was filtered over Celite and an aliquot was analized via GCMS. The desired cross-coupled product was obtained with good conversion and selectivity.

Testing of [PdBr(P*t*-Bu_3)]$_2$ + O_2. In a dry Schlenk flask [PdBr(P*t*-Bu_3)]$_2$ (2,5 mol%, 0.015 mmol, 11.7 mg) and 1-Br-naphthalene (0.6 mmol) were dissolved in 4 mL of dry toluene at room temperature. The mixture was slowly purged with 10 ml of pure oxygen and stirred for 5 min, upon which the color changed from slightly yellow to dark green. MeLi (1.5 eq) was diluted with toluene to reach 2.0 mL; this solution was added over 2 min by the use of a syringe pump. After the addition was completed, the reaction was quenched with 0.5 mL of MeOH. The crude was filtered over Celite and an aliquot was analized via GCMS. The desired cross-coupled product was obtained with good conversion and selectivity.

Isolation and testing of PdNPs. In a dry Schlenk flask Pd(P*t*-Bu_3)$_2$ (2,5 mol%, 0.015 mmol, 7.66 mg) were dissolved in 2 mL of dry toluene at room temperature and exposed to dry oxygen atmosphere for 16 h, resulting in an intense red solution. To the solution was added MeLi (4 mol%) which resulted in the darkening of the solution and the formation of a black solid. The solution was centrifuged and washed with toluene (2 mL, 3 times), and the residue was analyzed *via* ^{1}H- and ^{31}P-NMR (tol-d_8), in which no homogeneous components were observed. To the solid, 2 mL of toluene and 1-Br-naphthalene (1 eq 0.6 mmol) were added. MeLi (1.5 eq) was diluted with toluene to reach 2.0 mL; this solution was added over 2 min by the use of a syringe pump. After the addition was completed, the reaction was quenched with 0.5 mL of MeOH. The crude mixture was filtered over Celite and an aliquot was analized via GCMS. The desired cross-coupled product was obtained with good conversion and selectivity.

Backup Slide – Feringa active catalyst investigations



Scheme 1 *In situ* formation of C2 from C1 during the reaction

SUPPORTING INFORMATION WILEY-VCH

IR characterization of C1^{ox}. To a flame dried Schlenk flask equipped with a magnetic stirrer 11 mg of Pd(P*t*-Bu$_3$)$_2$ were added. The compound was dissolved in dry, deoxygenated toluene, and exposed to dry O_2 atmosphere for 16 h. The solvent was then removed in vacuo, and the solid state IR spectrum was recorded and compared with the IR spectrum of the starting complex, Pd(P*t*-Bu$_3$)$_2$.

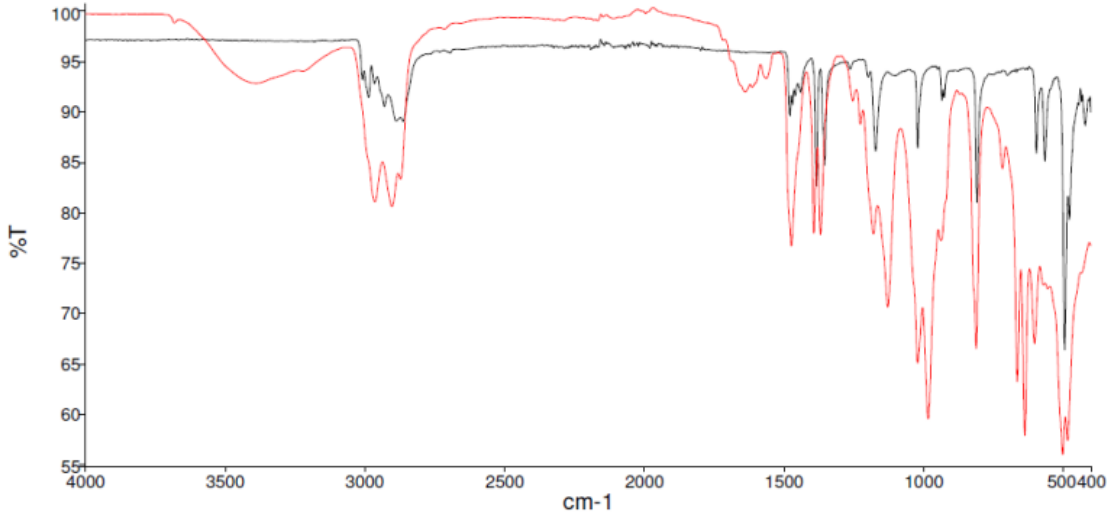


Figure 7 –IR spectra of C1 (black) and C1^{ox} (red)

Comment:
In case of formation of η^2-peroxo species, stretching of the O-O bond is normally observed in IR spectroscopy. For η^2-O_2Pd peroxo complexes such stretching is in the range of 800-915 cm^{-1}. In our case IR analysis was performed to see if such species could be present, but a signal corresponding to an η^2-peroxo complex could not be found.

Backup Slide – Radiolabeling Experimental Procedure

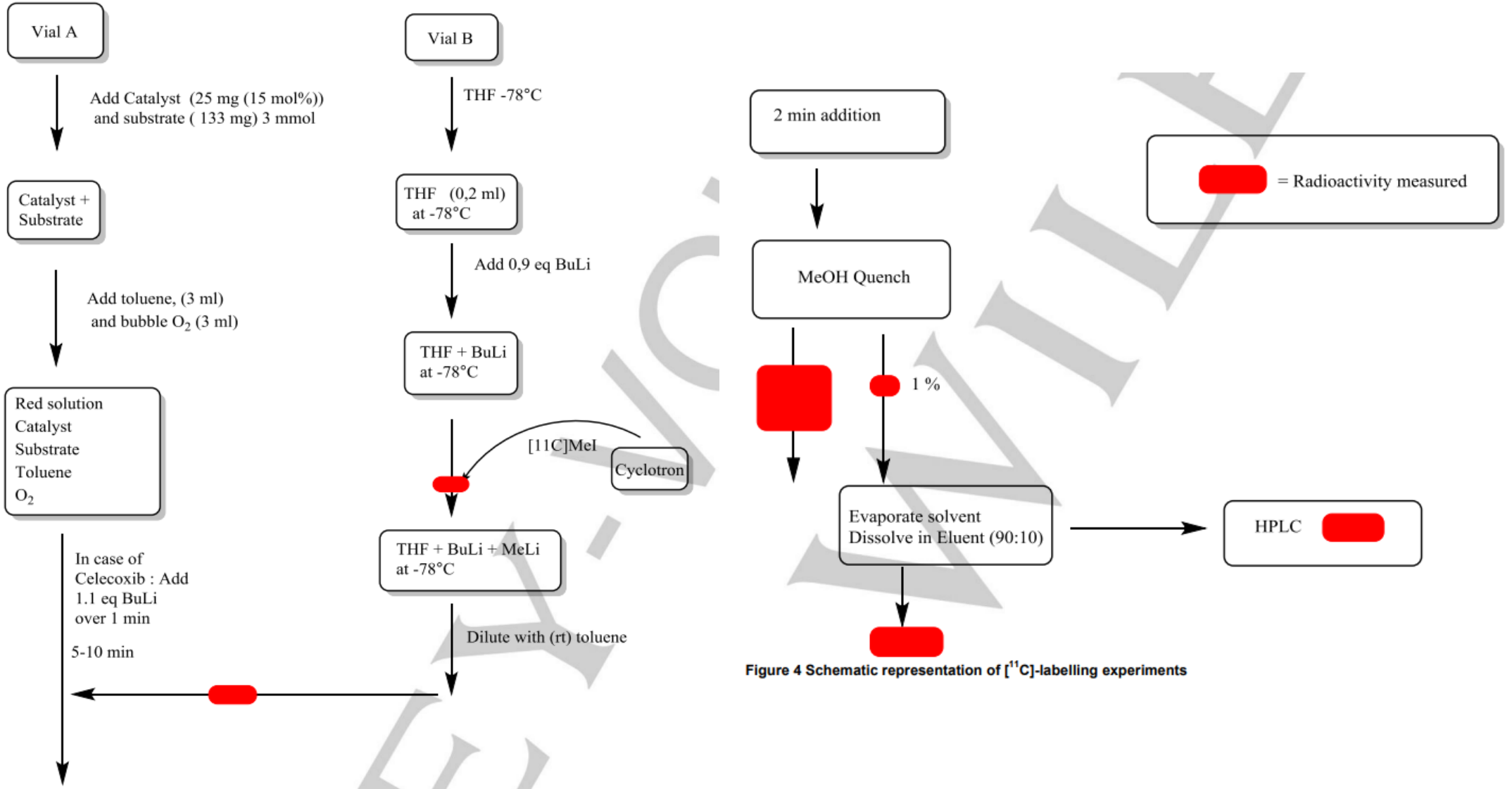
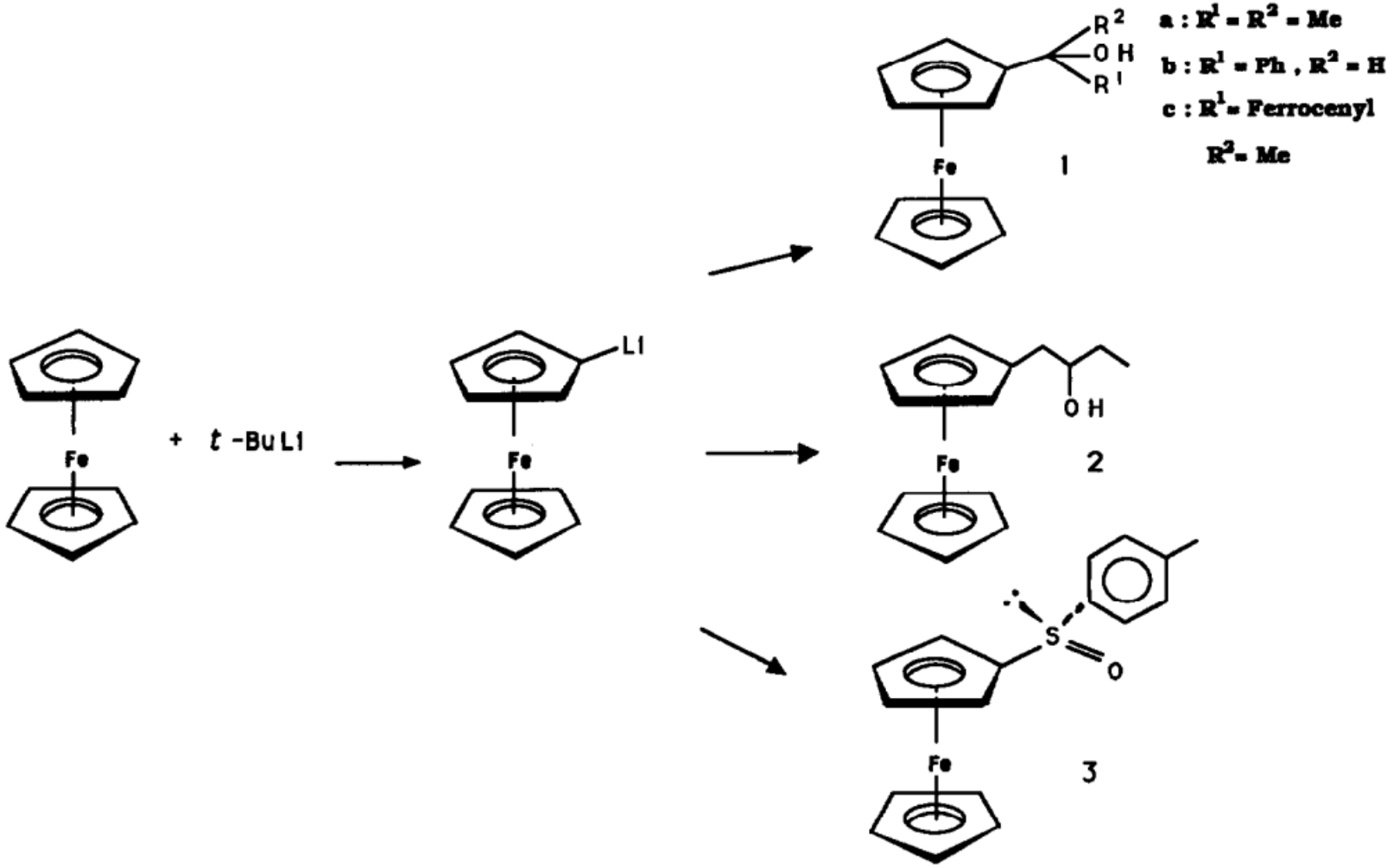


Figure 4 Schematic representation of [^{11}C]-labelling experiments

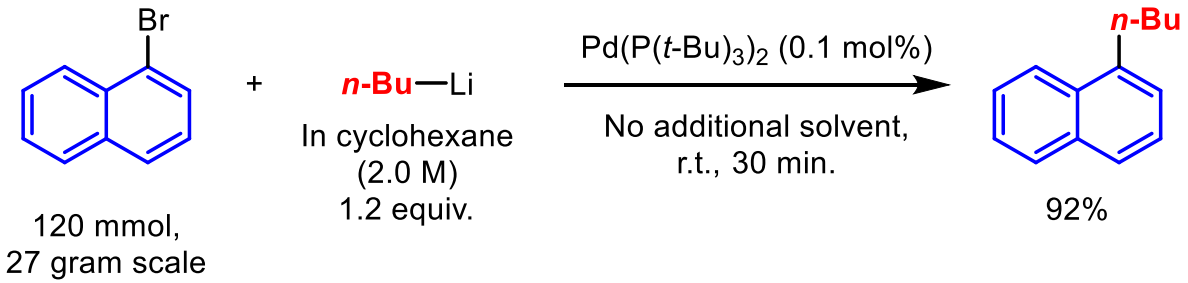
Backup Slide – Monolithiation of Ferrocene



Backup Slide – nBuLi addition to neat electrophile

Methods

The corresponding organolithium reagent (1.2 eq) was added over a mixture of substrate (1.0 eq) and catalyst (1.5–3 mol%) at RT for 10 min. After the addition was completed, a saturated solution of aqueous NH_4Cl was added and the mixture was extracted with AcOEt or Et_2O. The organic phases were combined and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product that was then filtered over a silica gel plug to afford the pure product. For NMR spectra of the compounds in this article, see Supplementary Figs 3–73.



Backup Slide – On water dangling H-bonds

On the cooperative formation of non-hydrogen-bonded water at molecular hydrophobic interfaces

Joel G. Davis, Blake M. Rankin, Kamil P. Gierszal and Dor Ben-Amotz*

B. Amotz et. al., *Nat. Chem.*, **2013**, 5, 796-802.