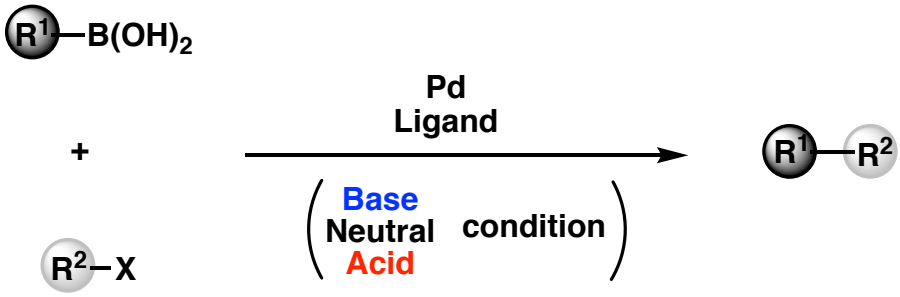
Suzuki-Miyaura cross coupling

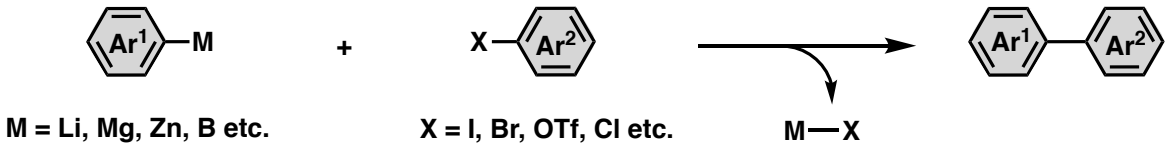


2024/ 11/ 1 (Fri)
Haruki Matsuda

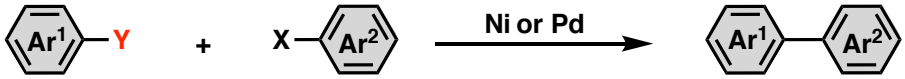
Contents

1. Introduction

1-1) C(sp^2)-C(sp^2) bond formation



Representative Ar-Ar coupling reaction



Kumada-Tamao-Corriu Cross Coupling (1972)[1)]

Y = MgX'
- ○ ArMgX' is highly reactive
- × ArMgX' is sensitive to water
- × Unable to use substrates react with ArMgX' (carboxylic acid, ketone, ester etc.)

Makoto Kumada

Negishi Cross Coupling (1977)[2)]

Y = ZnX'
- ○ Similar reactivity to Kumada coupling and wide substrate application range
- × ArZnX' is sensitive to water
- × Unable to use highly acidic hydrogen and highly reactivefunctional groups as substrates (carboxylic acid, aldehyde, hydroxy group etc.)

Ei-ichi Negishi

Suzuki-Miyaura Cross Coupling (1979)[3)]

Y = Boronic acid or ester
- ○ Boronic acid is stable in water and acid ⇨ Easy to handle
- ○ React even in air

Akira suzuki

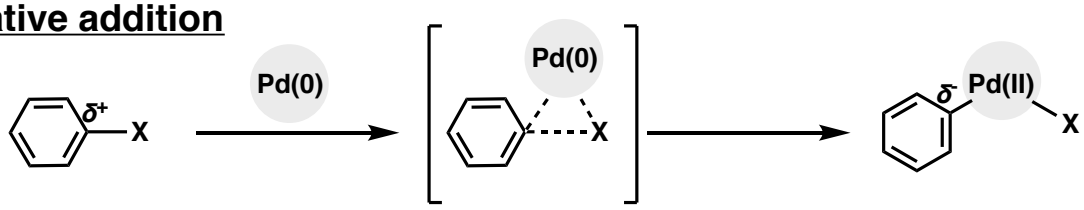
Norio Miyaura

Refference
1) Kumada, M. *et al*, *J. Am. Chem. Soc.* **1972**, 94, 4374
2) Negishi, E. *et al*, *J. Chem. Soc., Chem. Commun.* **1977**, 683
3) Suzuki, A., Miyaura, N., *J. Am. Chem. Soc.* **1979**, 866

1. Introduction

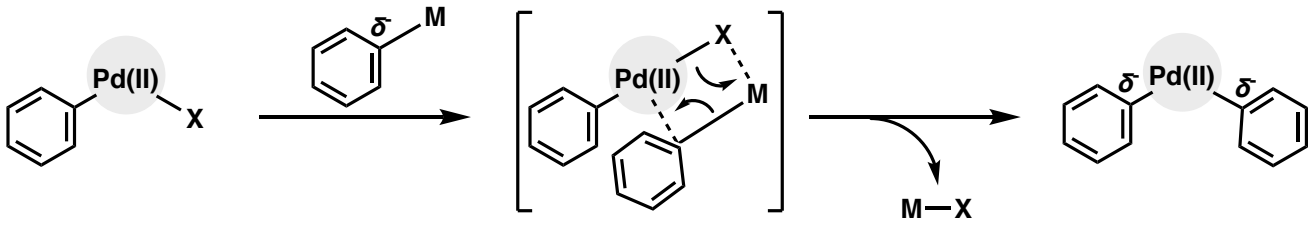
1-2) Reaction mechanism[4)]

Oxidative addition

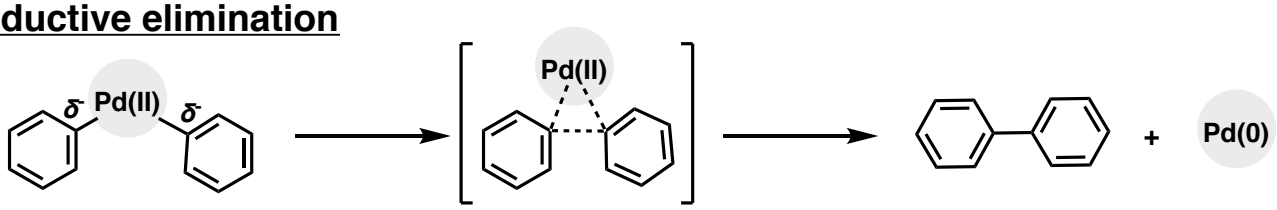


Electron rich Pd promotes oxidative addition

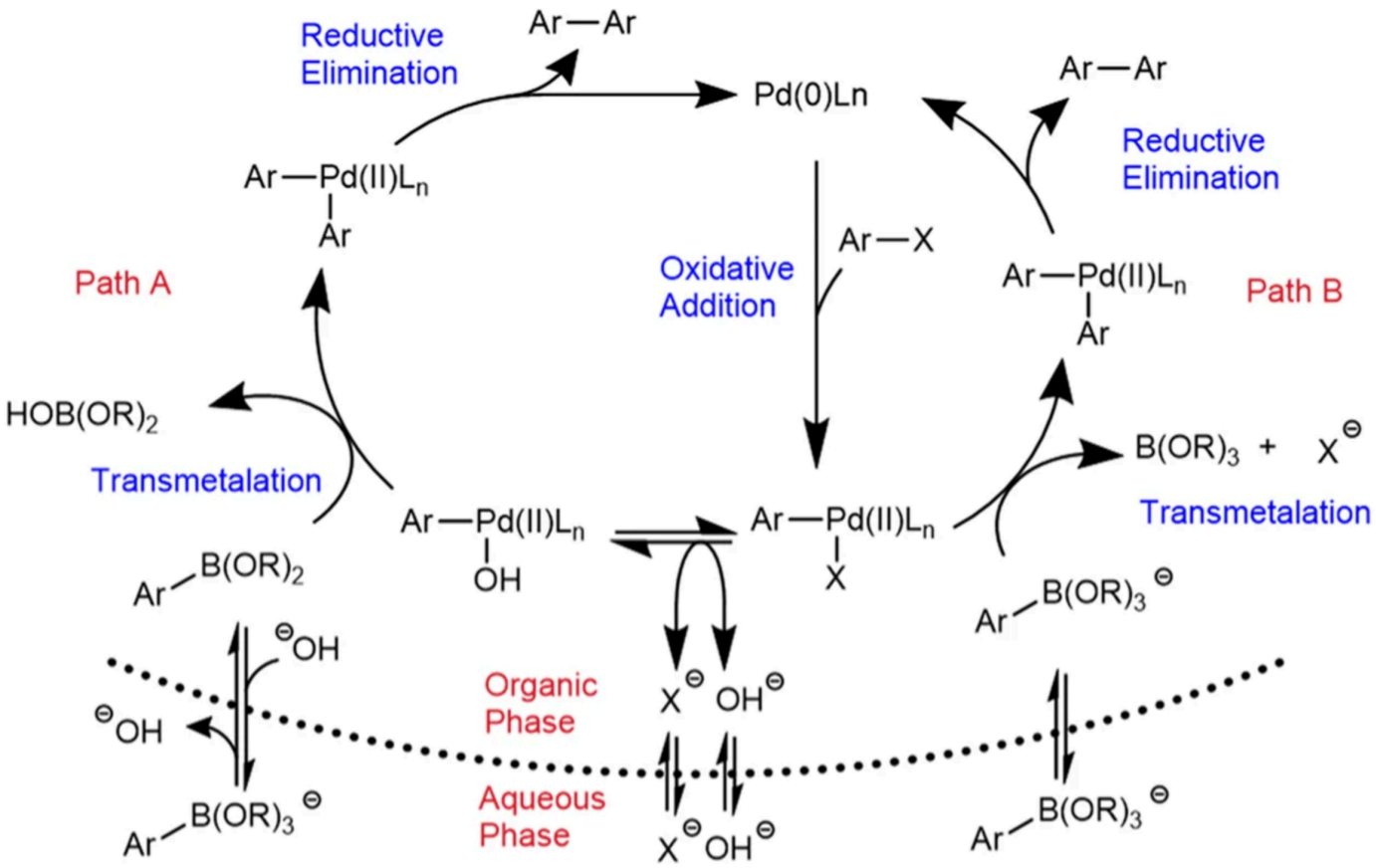
Transmetalation



Reductive elimination



Bulky ligands promote reductive elimination

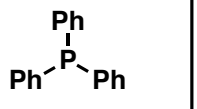


Refference

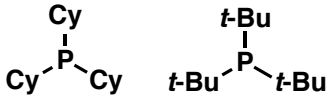
4) Hein, J. *et al*, *Nature Communications* **2024**, 15, 5436

2. Examples of the catalyst based on key structure

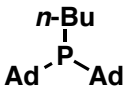
Triaryl phosphine



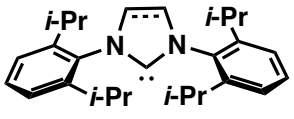
Trialkyl phosphine

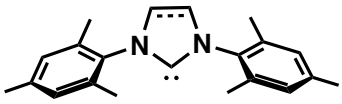


CatacXium

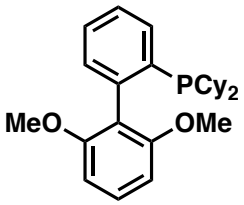


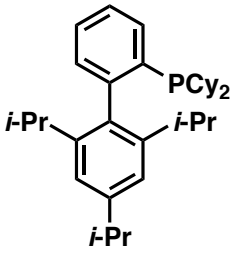
NHC(N-Heterocyclic Carbene)

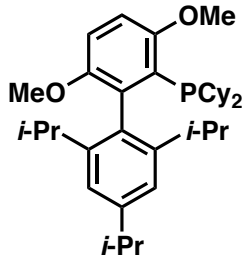




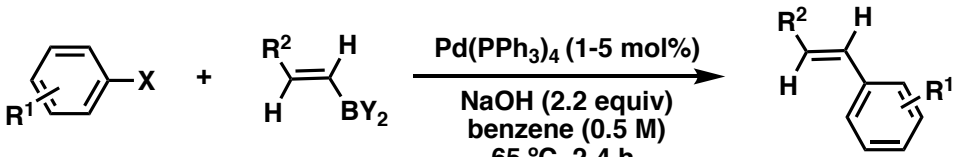
Buchward-type phosphine







2-1) Triaryl Phosphine[3)]

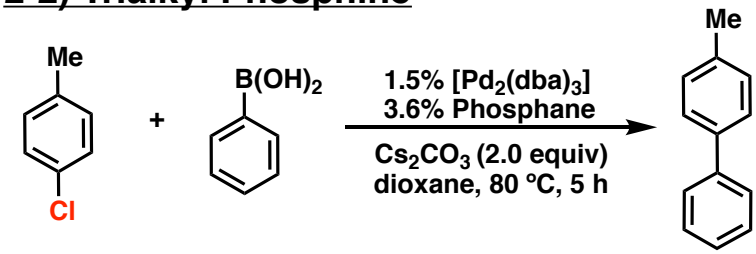


5.0 mmol
X = I, Br, Cl

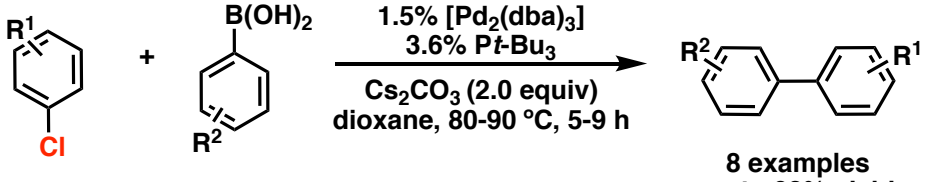
1.1 equiv

14 examples
up to 100% yield
※ X = Cl, <5% yield

2-2) Trialkyl Phosphine[5)]



Entry	Phosphane	Yield [%] (GC)
1	–	0
2	PPh_3	0
3	BINAP[a]	0
4	dppf[b]	0
5	$P(o\text{-tol})_3$	10
6	$Ph_2P(CH_2)_3PPh_2$	0
7	$Cy_2P(CH_2)_2PCy_2$	0
8	PCy_3	75
9	$PtBu_3$	86



8 examples
up to 92% yield

Guregory C. Fu

The ability of electron donating
Trialkyl phosphine > Triarylphosphine

Steric hinder
Trialkyl phosphine > Triarylphosphine

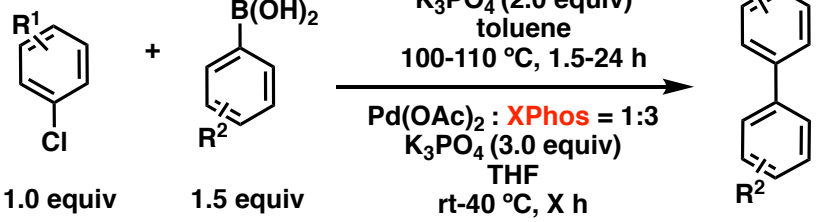
⇨ oxidative addtion and reductive elimination are promoted

※ Trialkyl ligands are easily oxidized in the air so it is difficult to handle

Refference
3) Suzuki, A. *et al*, *J. Am. Chem. Soc.* **1979**, 19, 866
5) Fu, G. C. *et al*, *Angew. Chem. Int. Ed.* **1998**, *37*, 3387

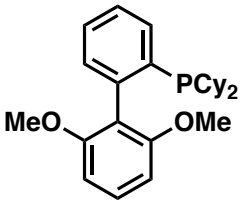
2. Examples of the catalyst based on key structure

2-3) Buchwald-type phosphines[6)]

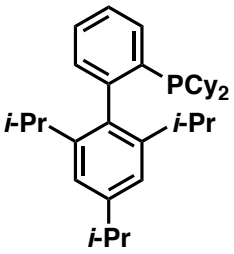


1.0 equiv

1.5 equiv

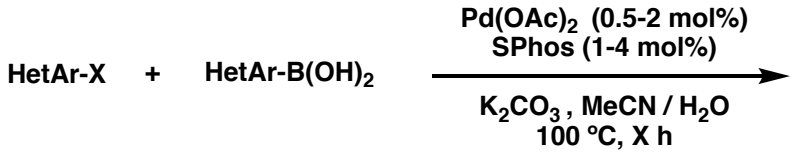


SPhos
5 examples
up to 99% yield



XPhos
16 examples
up to 99% yield

Heteroaryl substrates[7)]

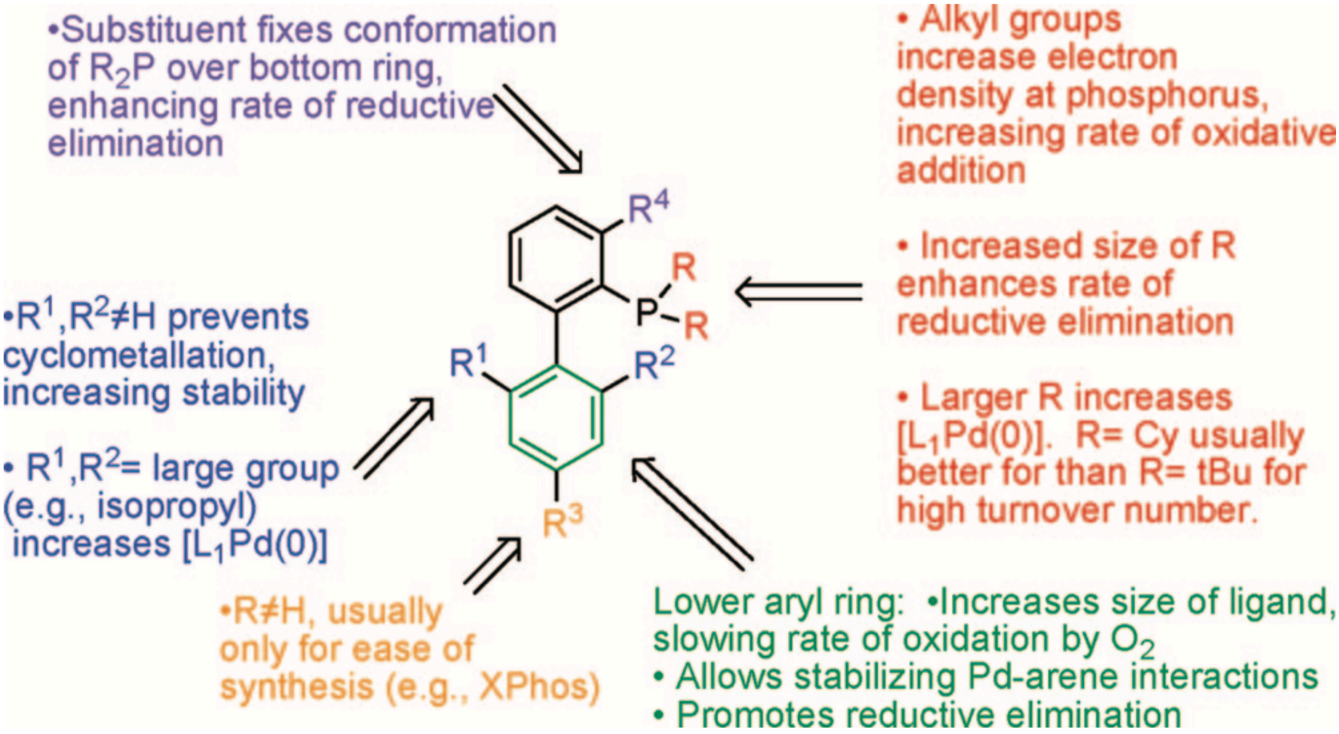


X = Br, Cl

7 examples
up to 99% yield

Stephen L. Buchwald

Structural features of the dialkylbiarylphosphines and their impact on the efficacy of catalysts using these ligands[7)]



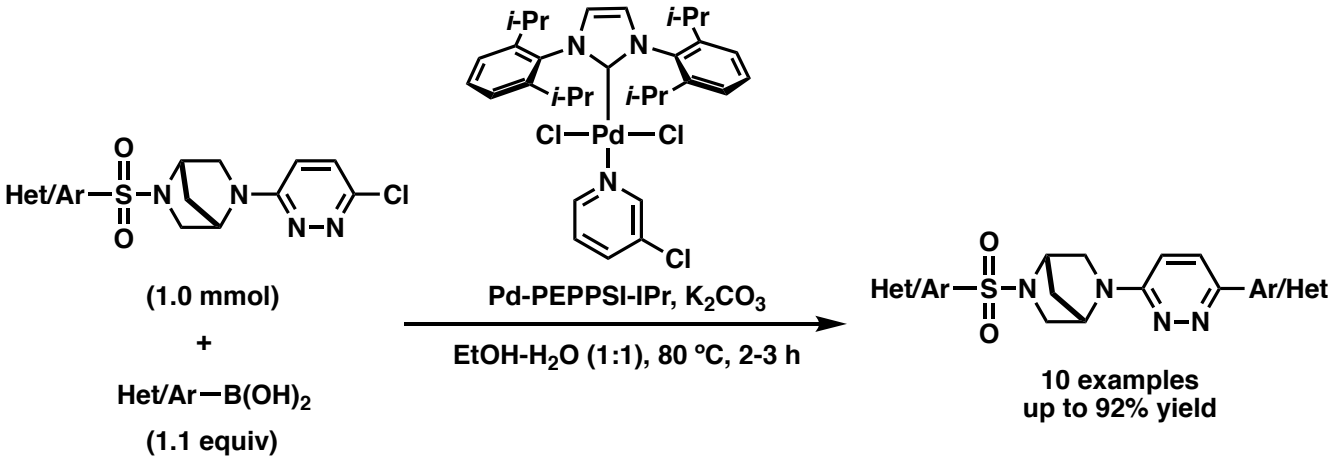
Refference

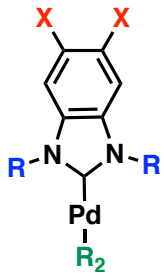
6) Buchwald, S. L. *et al. J. Am. Chem. Soc.* **2005,** *127,* 4685.

7) Buchwald, S. L. *et al. Acc. Chem. Res.* **2008**, 41, 1461.

2. Examples of the catalyst based on key structure

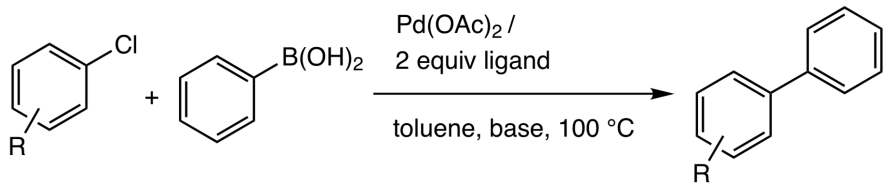
2-4) NHC (N-Heterocyclic carbene) catalyst[8)9)]

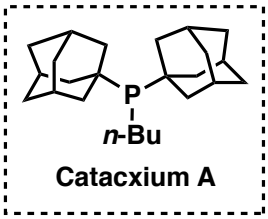




X : Electronic effect influences the rate of oxidative addition
R : Bulky groups facilitate reductive elimination
R_2 : Throw-away ligand

2-5) Catacxium A[10)]





ligand : Catacxium A
12 examples
up to 100% yield

Entry	PR_3	Pd [mol %]	Yield [%]	TON
1	PPh_3	0.1	5	50
2	$PhPCy_2$	0.1	23	230
3[a]	(*o*-tol)PCy_2	0.1	49	490
4[a]	(*o*-anisyl)PCy_2	0.1	42	420
5[12b]	(*o*-biph)PCy_2	0.05	93	1 860
6	(*o*-biph)PCy_2	0.01	47	4 700
7	PCy_3	0.1	23	230
8	P*t*Bu_3	0.01	92	9 200
9	P*t*Bu_3	0.005	41	8 200
10	$BuPAd_2$	0.01	94	9 400
11	$BuPAd_2$	0.005	87	17 400

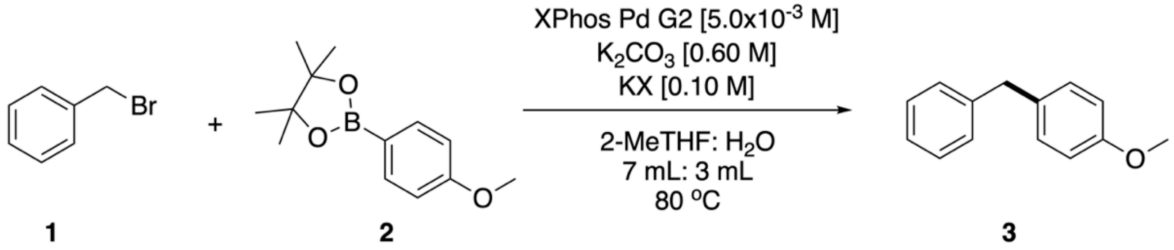
[a] P/Pd = 4:1.

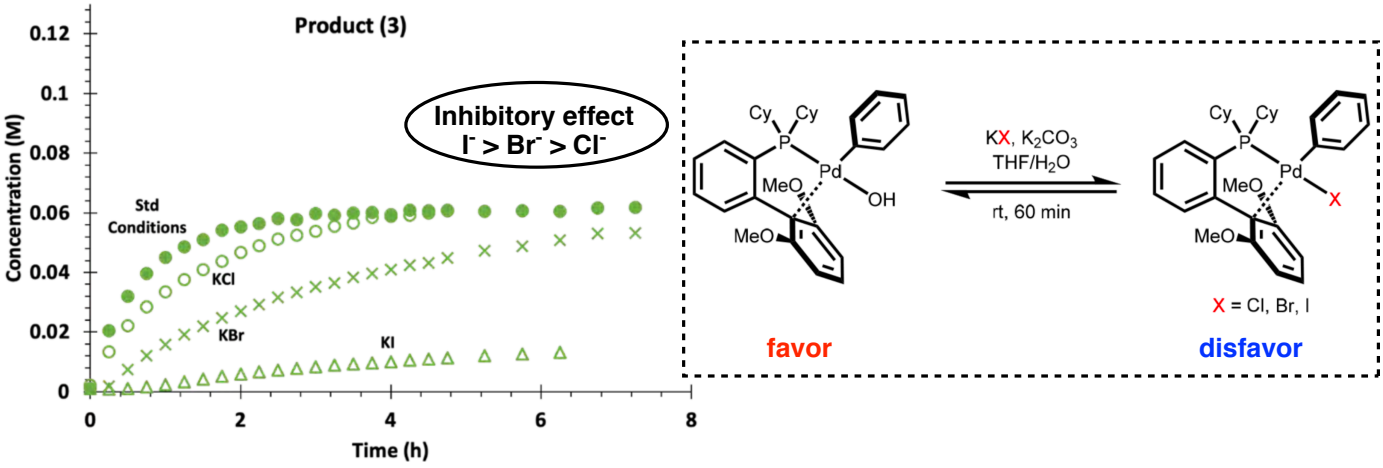
TON : Turnover number

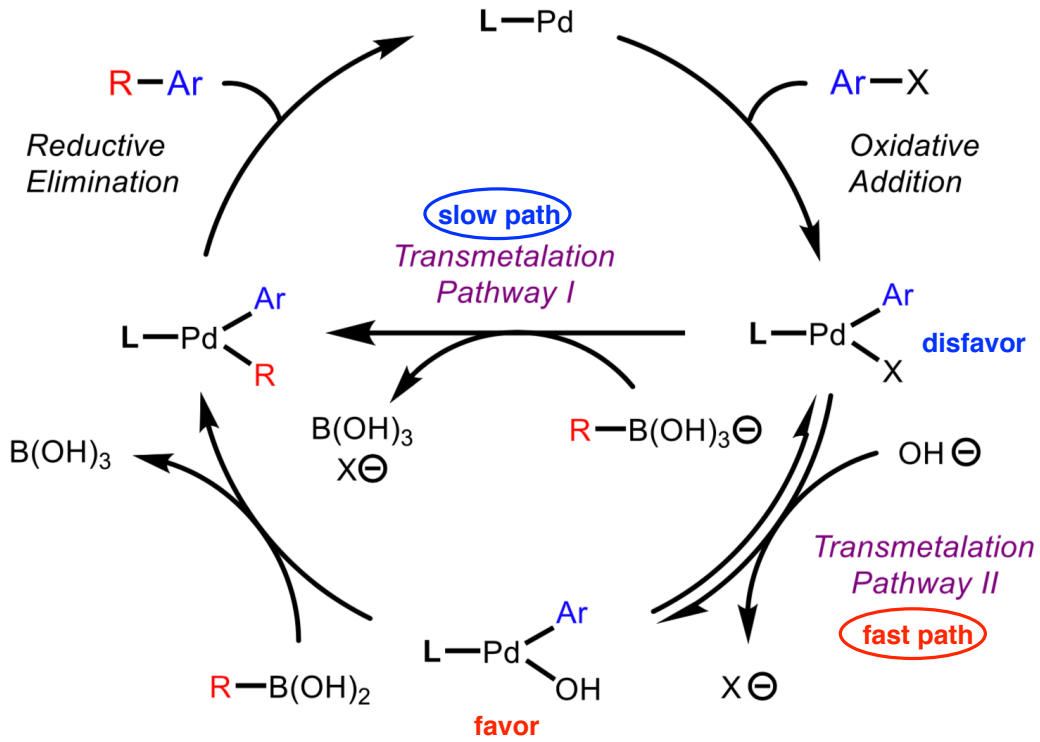
Refference
8) Peddiahgari, V. G. L., *et al. Organometal Chem.* **2018**, 32, e4068.
9) Organ, M. G., *et al. Angew. Chem. Int. Ed.* **2007**, 46, 2768.
10) Beller, M., *et al. Angew. Chem. Int. Ed.* **2000**, 39, 4153.

3. Improvement of reactivity

3-1) Effect of halide ion[11)]







Path II is revesible

⇩

As reaction proceeds, LPd(Ar)OH is converted to LPd(Ar)X and reaction slow down

⇩

Reducing X^- in the organic layer improves reactivity

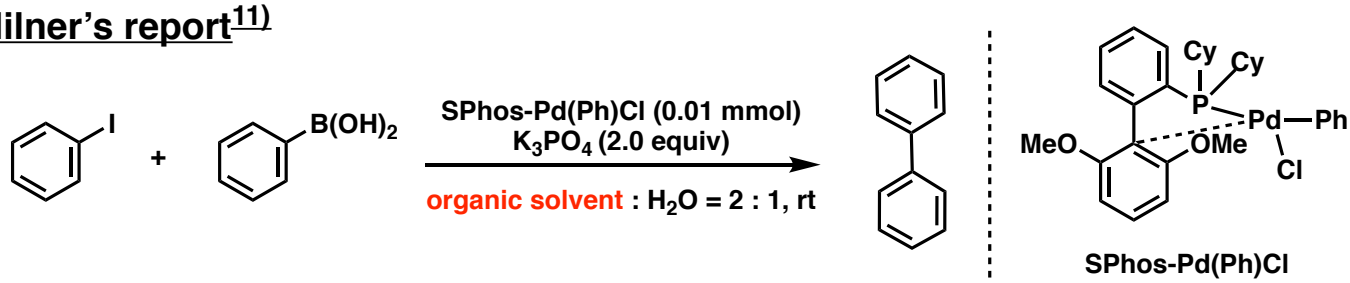
Refference

11) Milner, P. J. *et al. Org. Process Res. Dev.* **2019**, 23, 1631

3. Improvement of reactivity

Removal of Halogen ions in organic layer

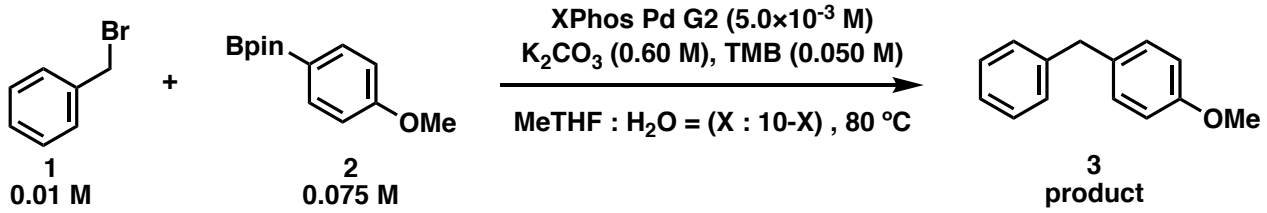
Milner's report[11)]



Organic Solvent	% PhI remaining after 16 h
THF	71
Et_2O	41
Toluene	0

⇒ KX is less soluble in non-polar solvent

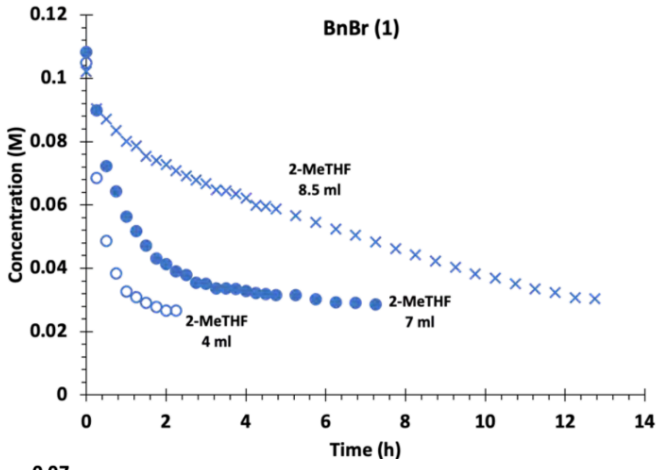
Hein's report[12)]

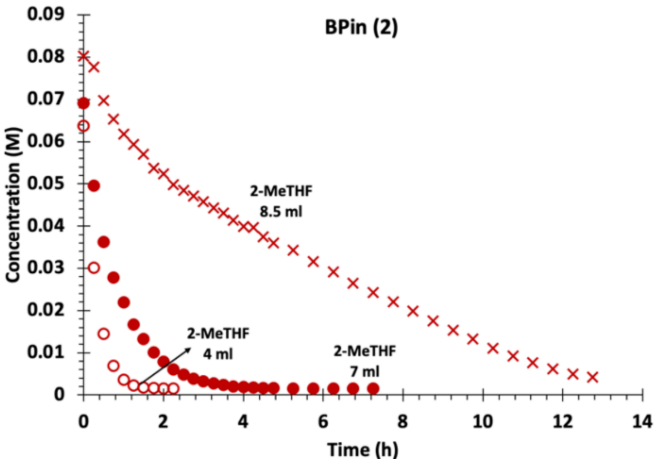


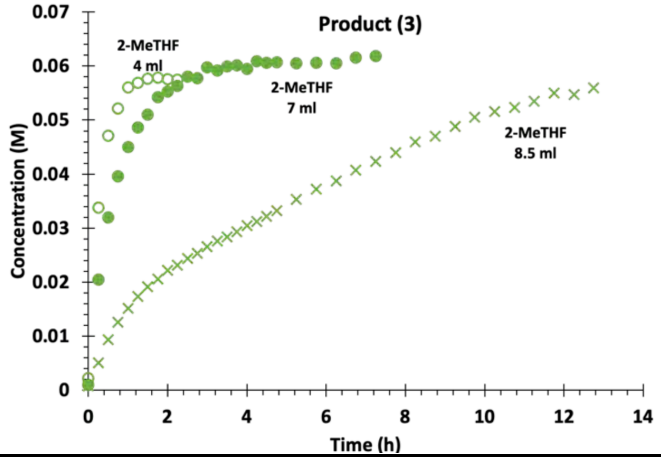
1
0.01 M

2
0.075 M

3
product





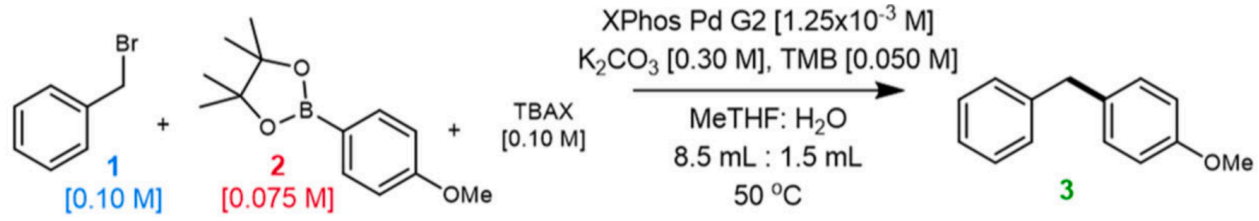


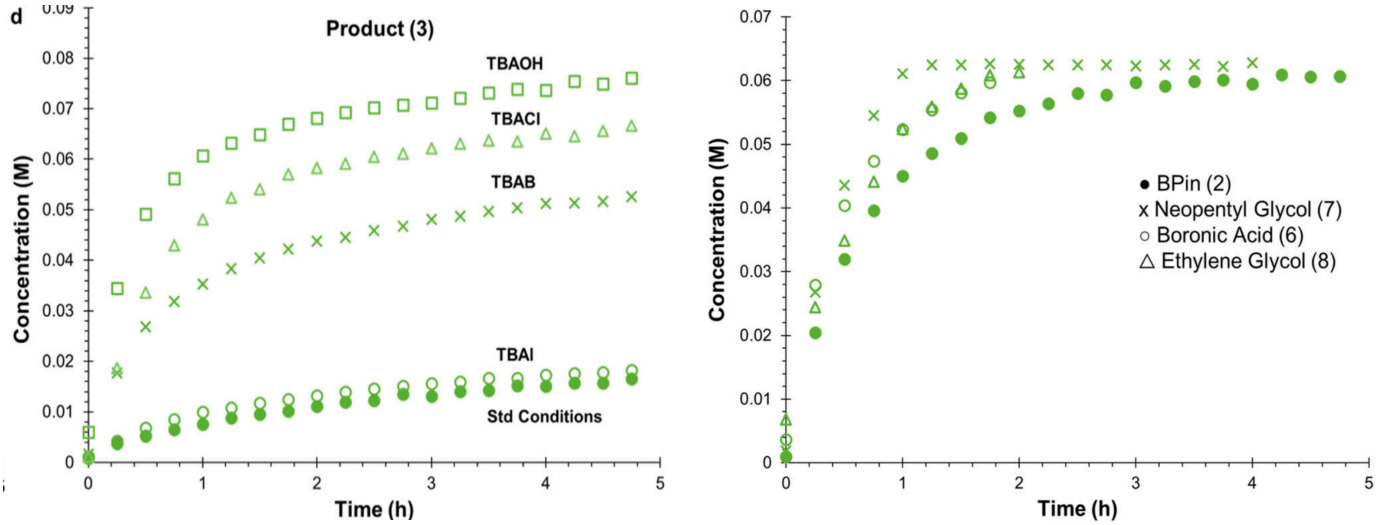
Refference

12) Hein. J. E. *et al. Nature Communication.,* **2024**, 15, 5436

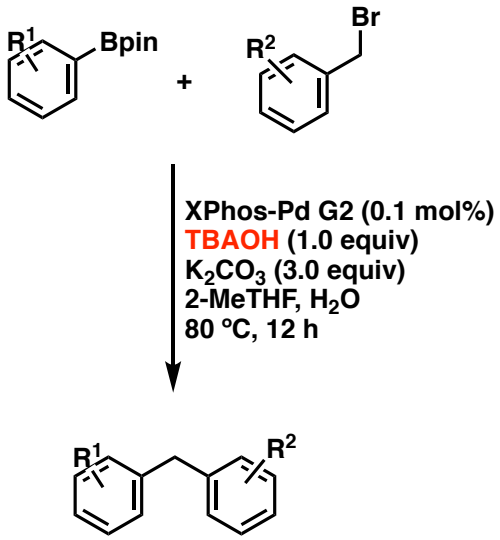
3. Improvement of reactivity

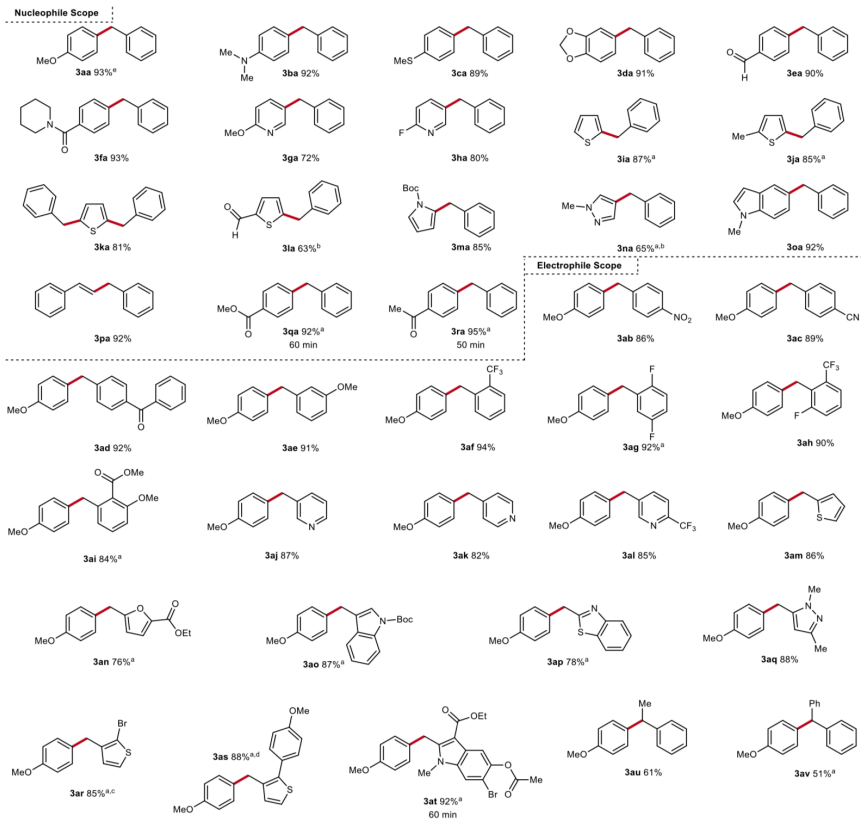
3-2) Phase-transfer catalyst[12)]





Substrate scope





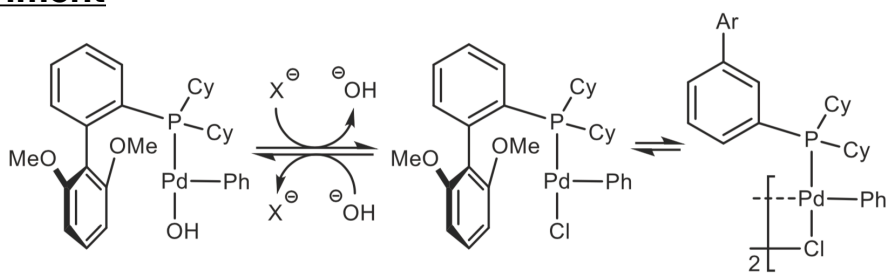
Refference

12) Hein. J. E. *et al. Nature Communication.,* **2024**, 15, 5436

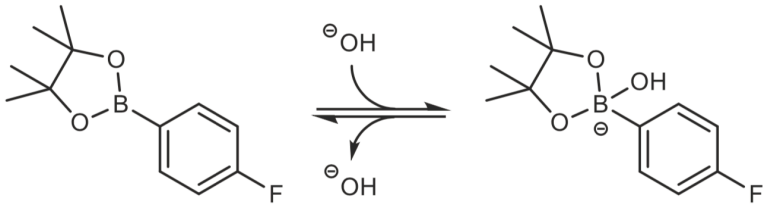
3. Improvement of reactivity

3-3) Reaction mechanism when Phase-transfer catalyst is used[12)]

Control experiment

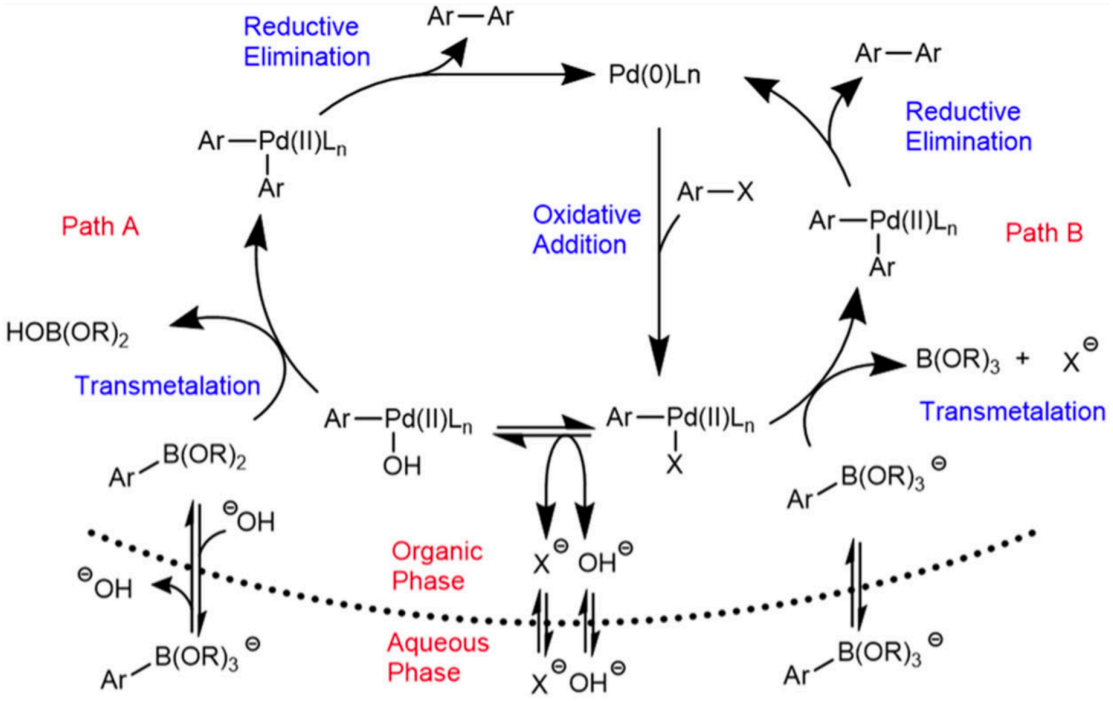


	Concentration	Concentration	Concentration
w/o TBACl	0.79 mM	0.52 mM	1.14 mM
w/ TBACl	0.02 mM	0.66 mM	2.30 mM



	Concentration	Concentration
w/o TBACl	46.03 mM	0 mM
w/ TBACl	4.17 mM	20.6 mM

Plausible mechanism



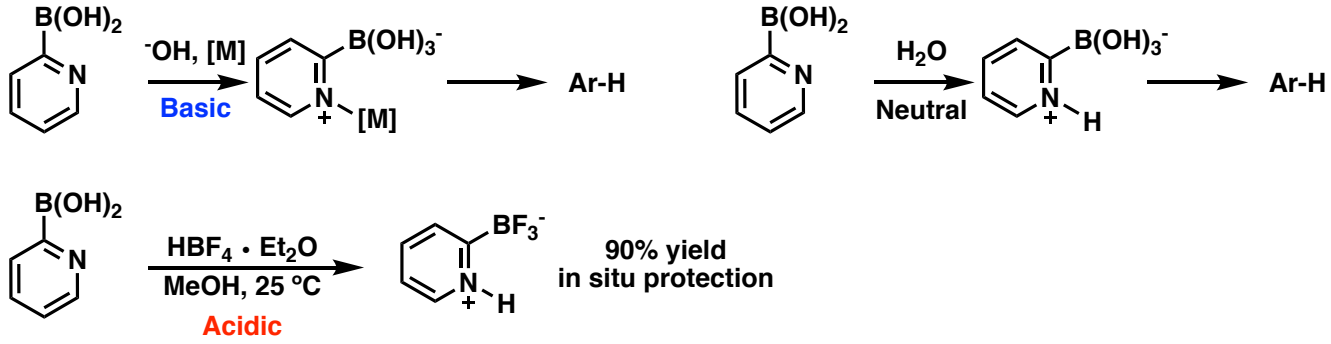
When a phase transfer catalyst is added, the reaction proceeds on Path B

Refference

12) Hein. J. E. *et al. Nature Communication.,* **2024**, 15, 5436

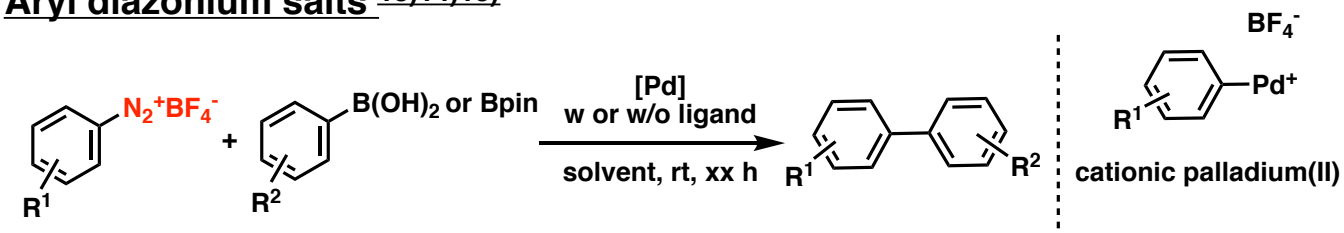
4. Non-basic conditions

protodeboronation



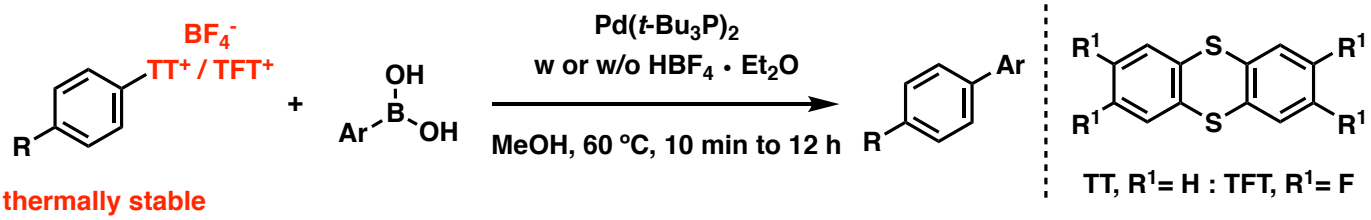
4-1) Cationic intermediate

Aryl diazonium salts [13)14)15)]



thermally instable

Aryl thianthrenium salts [16)]



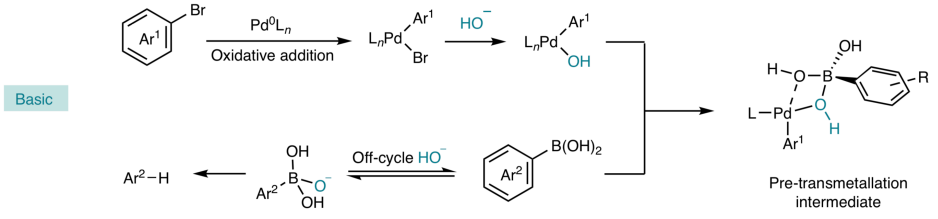
thermally stable

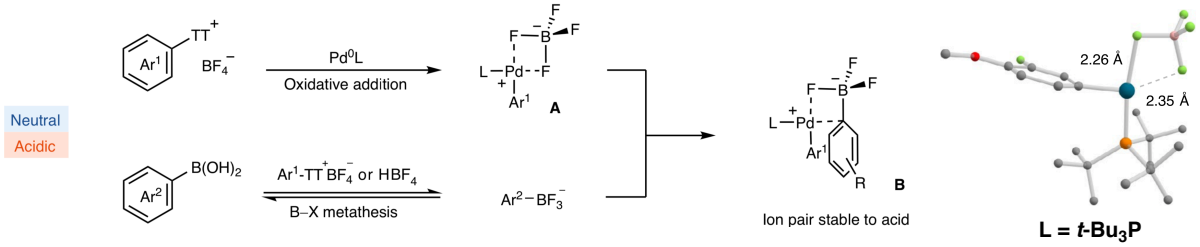
0.1 mmol or 0.2 mmol

1.1-2.0 equiv

Acidic condition
12 examples
up to 98% yield

Neutral condition
16 examples
up to 98% yield





Refference

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14) Demoute, J.-P. *et al. Tetrahedron Letters.* **1996**, 37, 3857.
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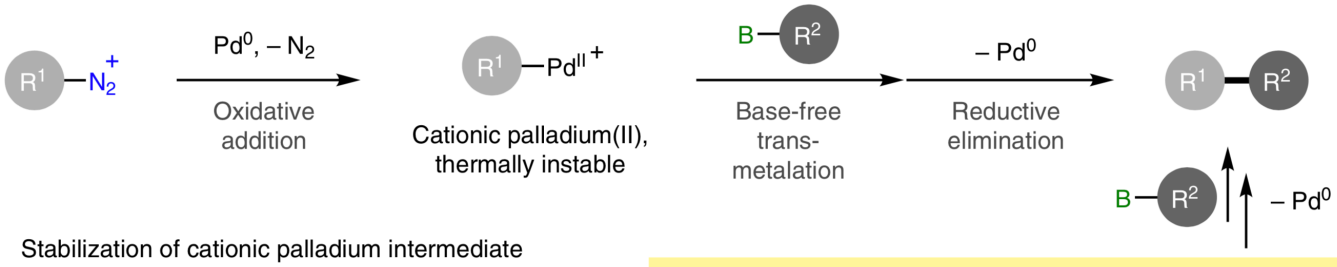
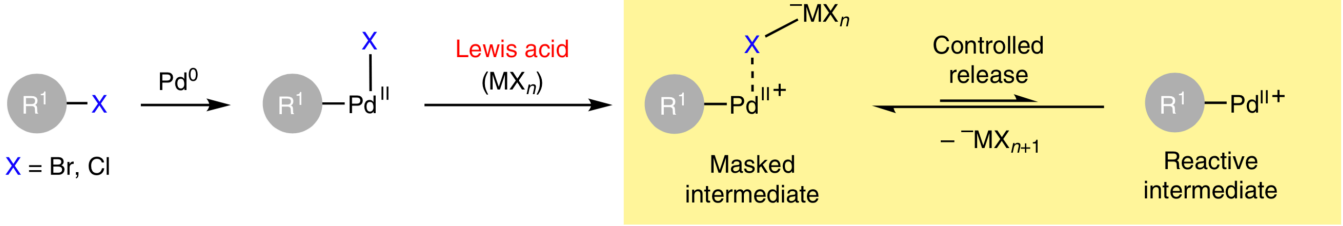
4.Non-basic conditions

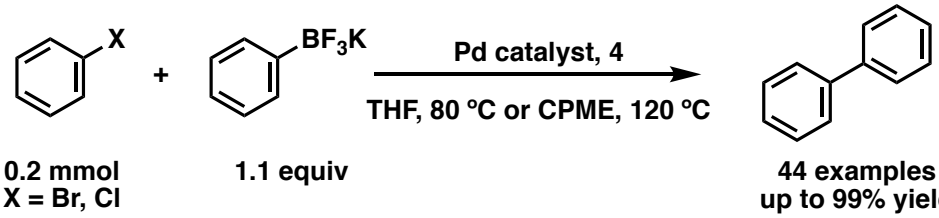
Leiws acidic condition by Hosoya[17)]

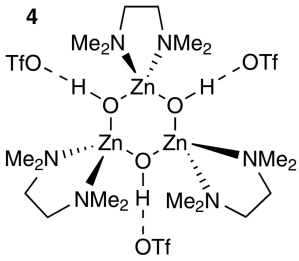
Via cationic palladium(II) intermediate at room temperature

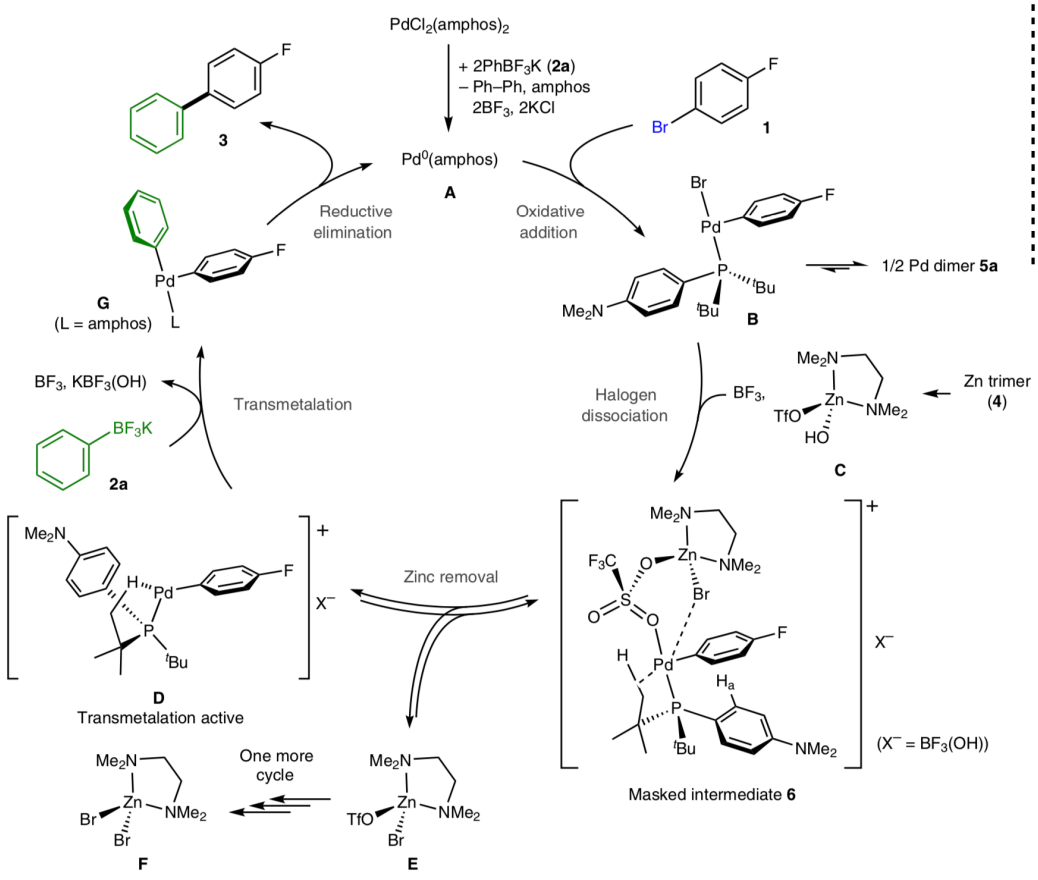


Stabilization of cationic palladium intermediate









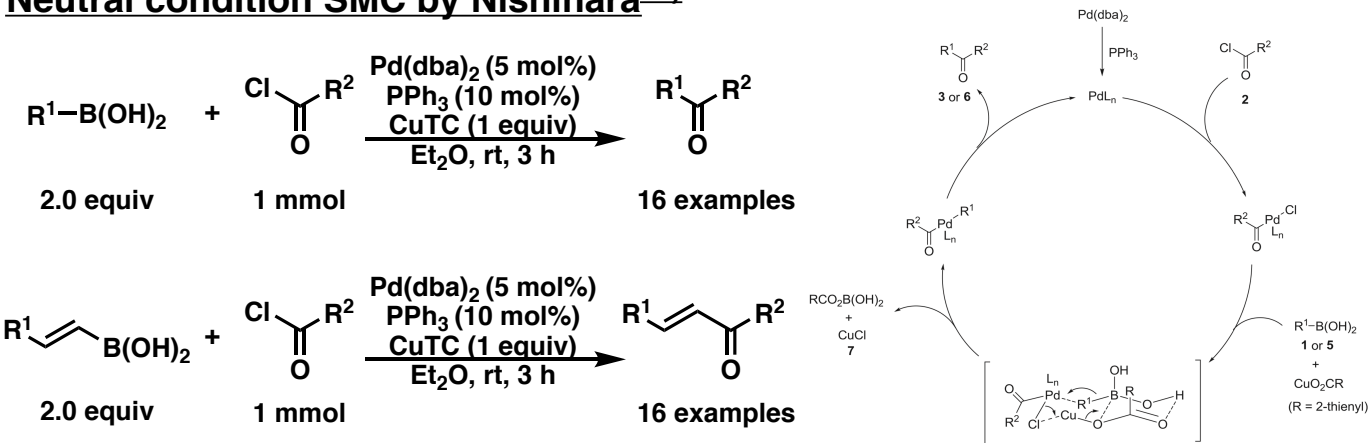
Refference

17) Niwa, T., Hosoya, T. *et al. Nature Catalysis*. **2021**, *4*, 1080

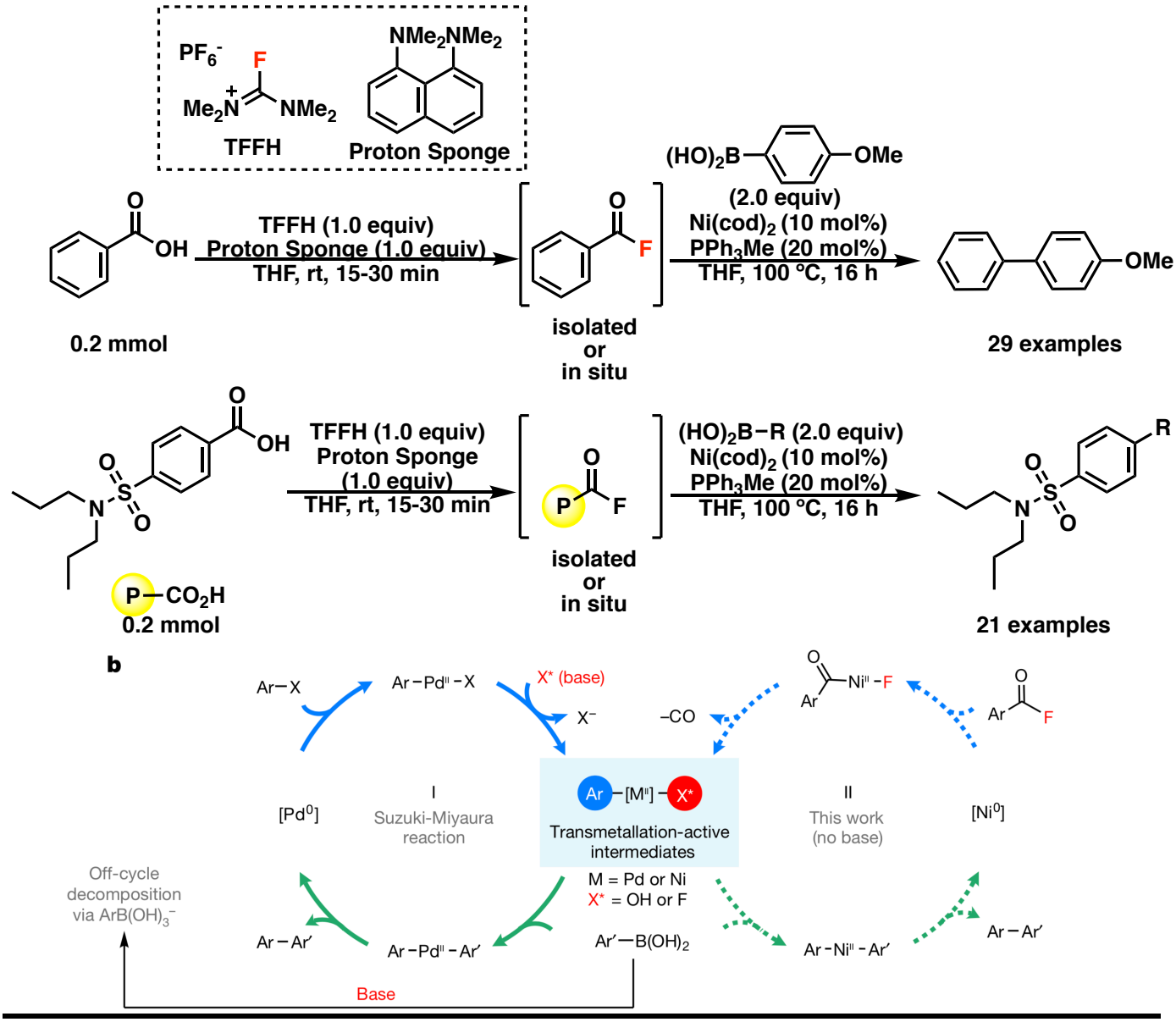
4.Non-basic conditions

4-2) Neutral condition

Neutral condition SMC by Nishihara[18)]



Neutral condition SMC by Sanford[19)]



Refference

18) Nishihara. Y. *et al. Tetrahedron* **2013**, 69, 2565.

19) Sanford. M. S. *et al. Nature* **2018**, 563, 100.

5. Proposal

C-X bond

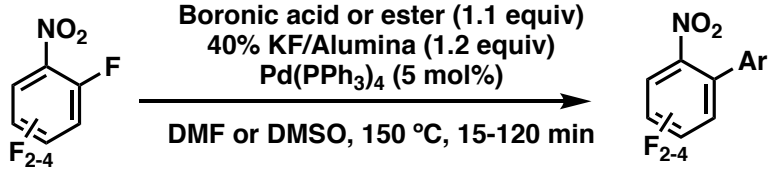
9	17	35	53
F	Cl	Br	I
Fuluorine	Chlorine	Bromine	Iodine

strong bond ← 460 kJ/mol | 350 kJ/mol | 294 kJ/mol | 239 kJ/mol → week bond

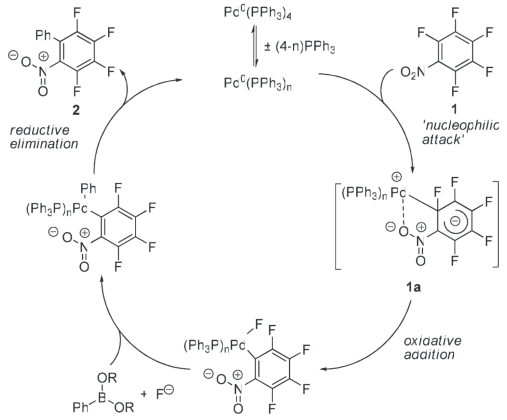
Bond energy

Previous work

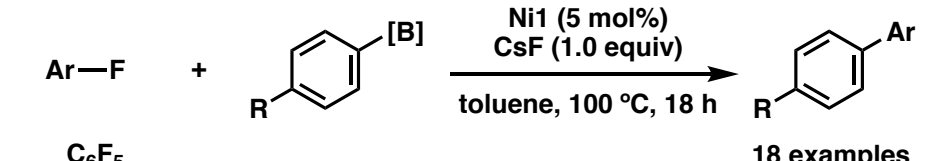
o-Nitro substrate[20)]



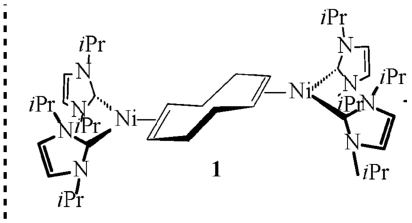
16 examples
up to 96% yield



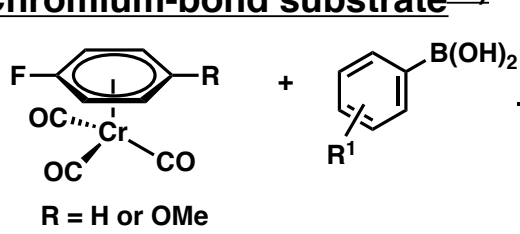
Perfluorinated subatrate[21)]



18 examples
up to 100% yield



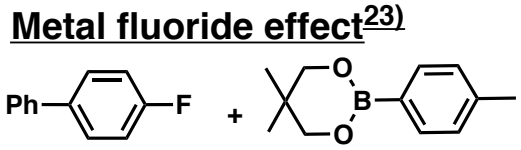
Chromium-bond substrate[22)]



7 examples
up to 87% yield

R = H or OMe

Metal fluoride effect[23)]

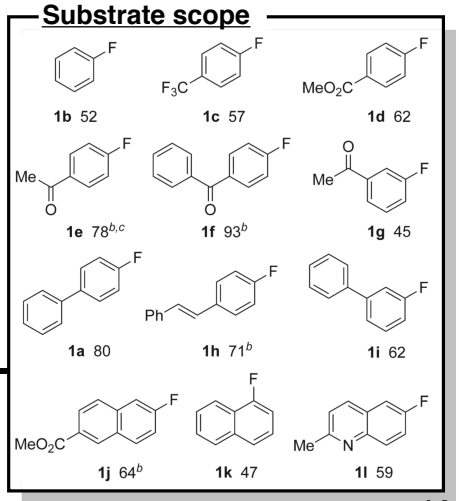


additive : ZnF_4
12 examples
up to 93% yield

(0.25 mmol) (3.0 equiv)

entry	additive	yield (%)[b]	entry	additive	yield (%)[b]
1	none	38	6	TiF_4	77
2	MgF_2	47	7	ZnF_4	80
3	ZnF_2	56	8	FeF_3	48
4	CeF_3	52	9	NiF_2	44
5	TiF_3	61	10	AlF_3	43

Substrate scope



Reference

20) Nelles, G. and Kilickiran, P. *et al. J. Org. Chem.* **2010**, 75, 5860
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