Works by Prof. Bill Morandi
- Isofunctional Reactions -

Literature Seminar

2019/01/12 Koichi Hagiwara

Today’s contents

1. Introduction of "isofunctional reactions"

2. Shuttle reactions - (retro-)hydrocyanation -

3. Metathesis reations - C-S or C-P bond -

Prof. Bill Morandi

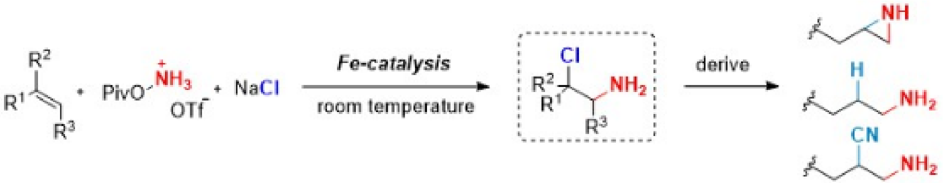
2006 BS; at the ETH Zurich in Biology
2008 MS; at the ETH Zurich in Chemical Biology
2012 Ph. D; at the ETH Zurich in Organic Chemistry (under Prof. Erick M. Carreira)
2012-2014 Postdoctoral fellow; at California Institute of Technology (under Prof. Robert H. Grubbs)
2014-2018 Group leader at Max-Planck-Institut fur Kohlenforschung
2018- Associate Professor (with tenure) at the ETH Zurich

3 topics are described in his home page (http://morandi.ethz.ch/research.html)

1. Shuttle Catalysis

2. Aliphatic C-O Bond Activation

3. Direct Catalytic Synthesis of Unprotected Amines

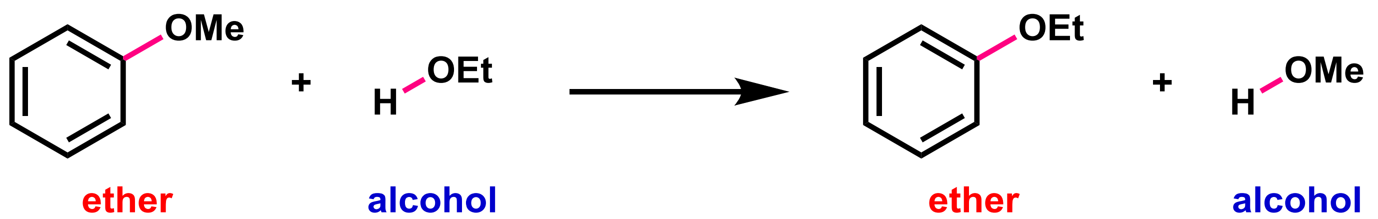


Aminochlorination (Science 2018)

Concept of “Isofunctional Reactions”

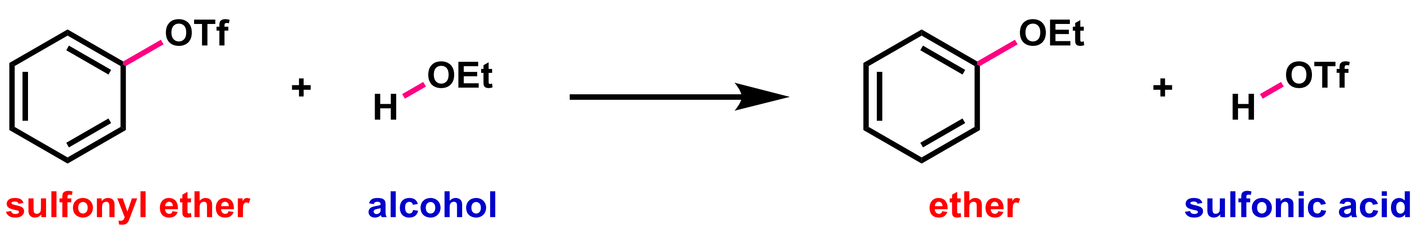
•definition of "isofunctional reactions" by Morandi
→ the number and type of functional groups are conserved throughout the reaction.
(one of the reversible isodesmic reactions)

•illustrative example of an isofunctional, isodesmic reaction



same bonds and same functional groups

•illustrative example of a non-isofunctional, isodesmic reaction



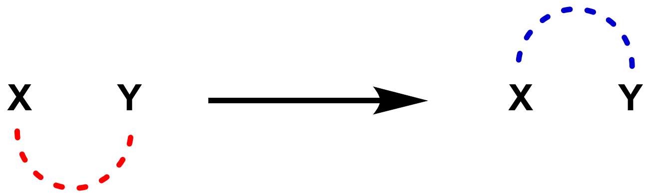
same bonds but different functional groups

Bhawal, B. N. ; Morandi, B. *Angew. Chem. Int. Ed. Accepted Article* doi: 10.1002/anie.201803797

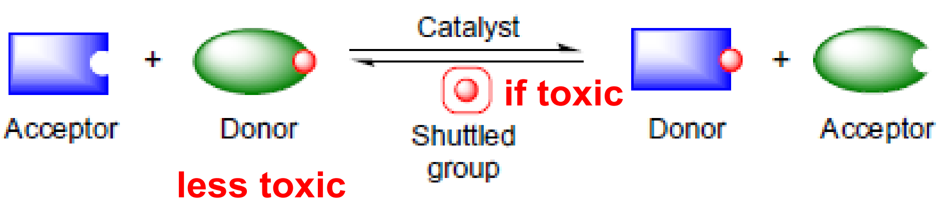
Classification of "Isofunctional Reactions"

•definition of "isofunctional reactions" by Morandi
→ the number and type of functional groups are conserved throughout the reaction.
(one of the reversible isodemic reactions)
→ classified in 3 groups

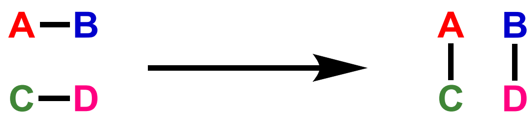
1. isomerization and rearrangement reaction (unimolecule)



2. shuttle reaction (more than 2 molecules)



3. metathesis reaction (more than 2 molecules)

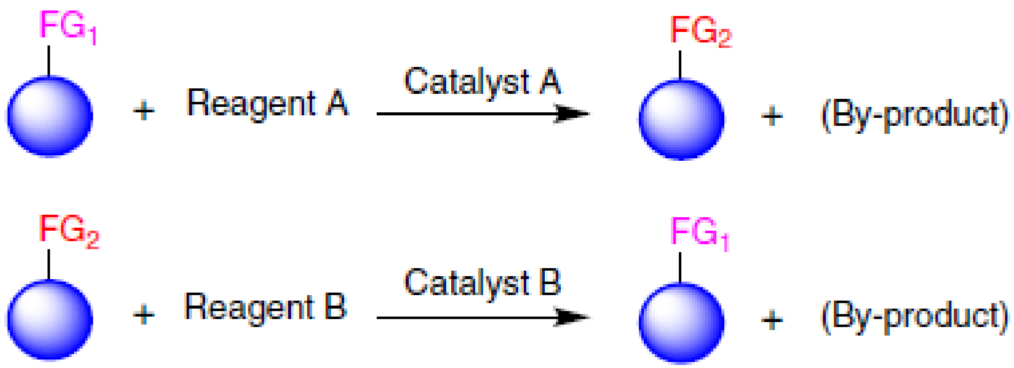


Bhawal, B. N. ; Morandi, B. *Angew. Chem. Int. Ed. Accepted Article* doi: 10.1002/anie.201803797

Advantage of “Isofunctional Reactions”

•traditional approach for functional group interconversion

a

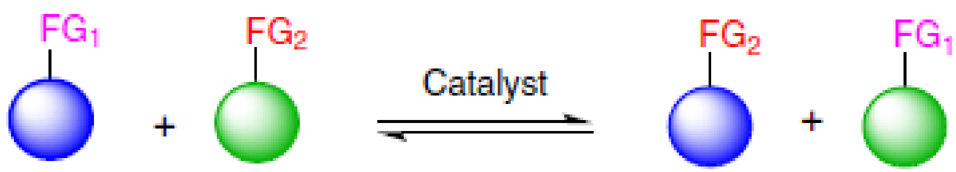


ΔG<<0→irreversible process

completely diffrerent reaction conditions

unstable reactive reagent→toxic

•functional group metathesis



ΔG≈0→reversible process

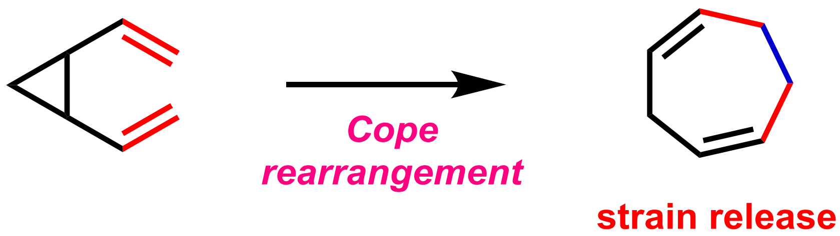
similar reaction conditions

less toxic

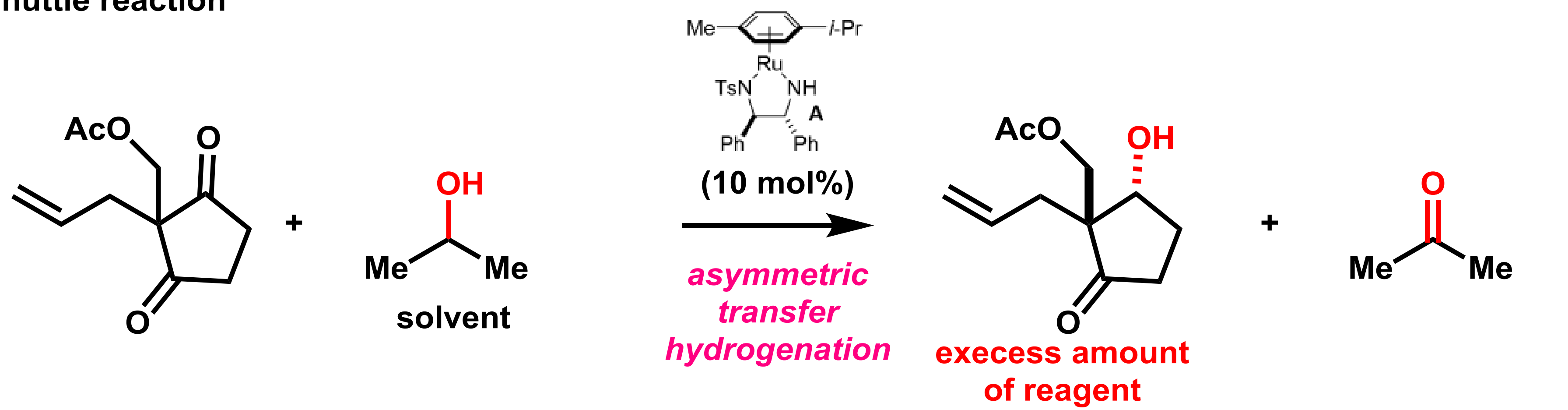
Lee, Y. H.; Morandi, B. *Nat. Chem.* **2018**, *10*, 1016.

Driving Force of "Isofunctional Reactions"

1. **isomerization** and **rearrangement** reaction

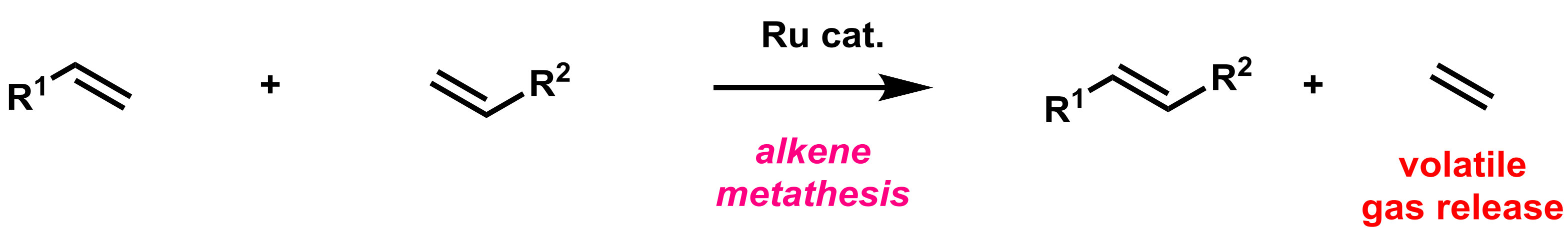


2. shuttle reaction



Noyori, R. et al. *J. Am. Chem. Soc.* **1995**, *117*, 7562.
Inoue, M. et al. *Org. Lett.* **2018**, *20*, 130.

3. metathesis reaction



Bhawal, B. N. ; Morandi, B. *Angew. Chem. Int. Ed. Accepted Article* doi: 10.1002/anie.201803797

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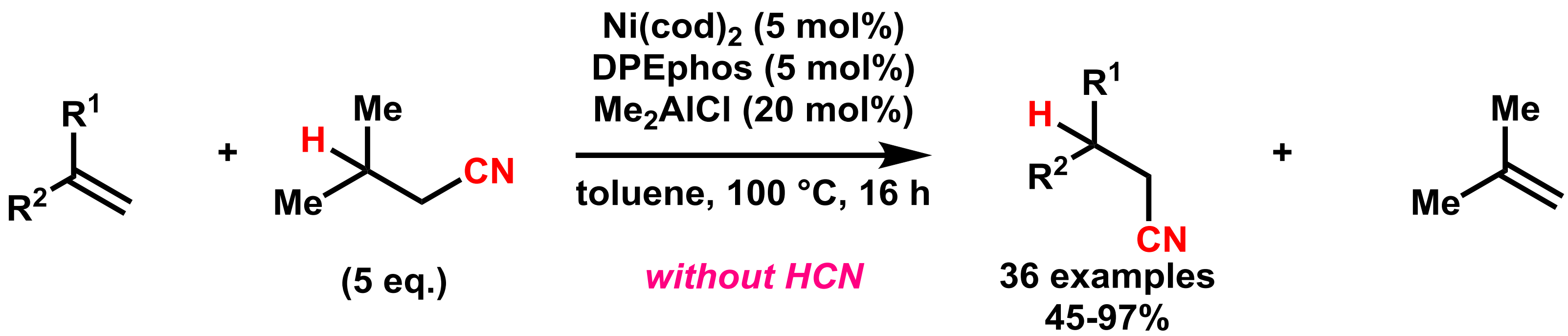
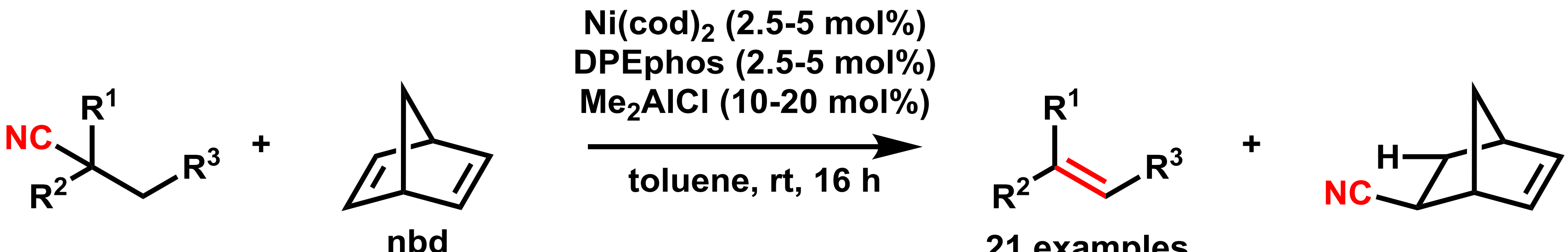
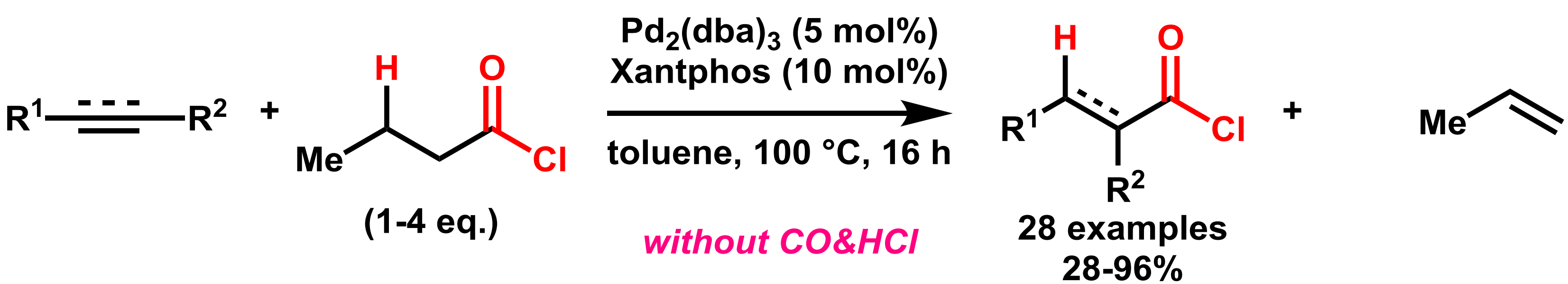
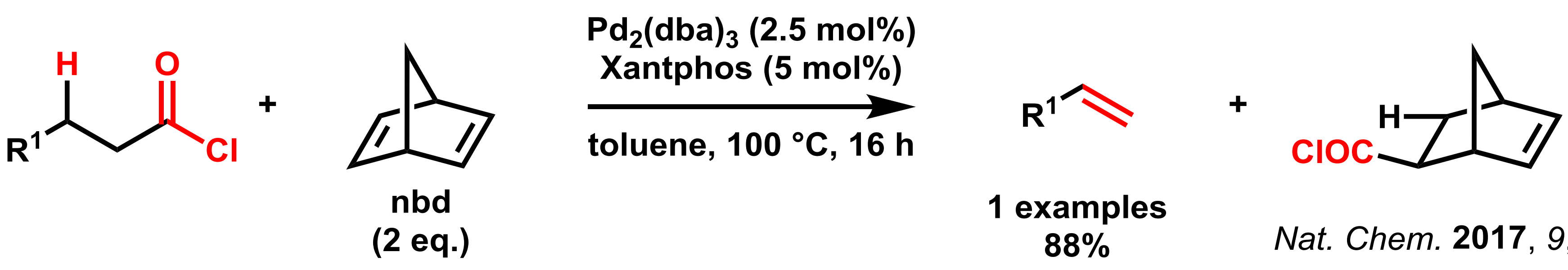
Successful Results of "Shuttle Reaction"





Science **2016**, *351*, 832.

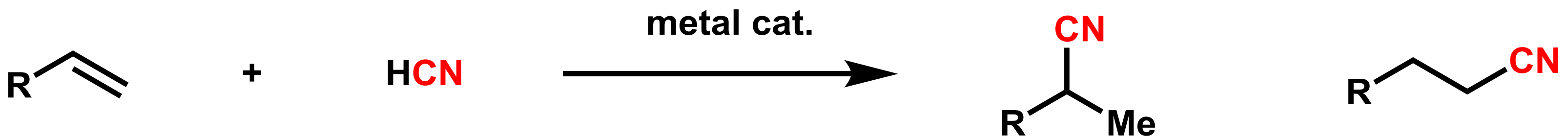




Nat. Chem. **2017**, *9*, 1105.

Problems of Transformation of Alkenes to Nitriles

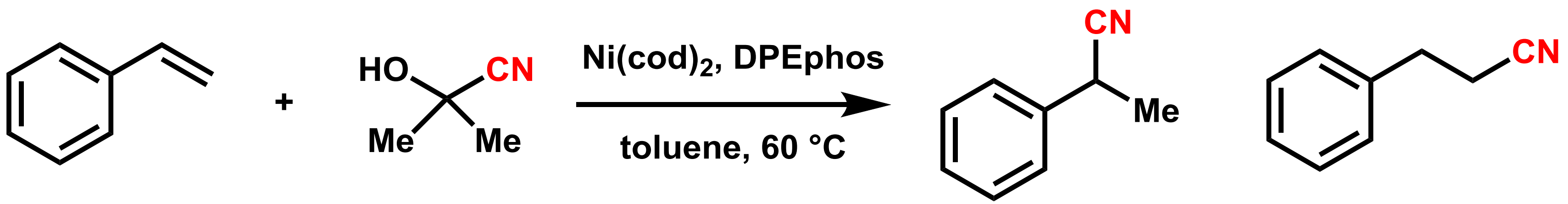
•traditional approach from alkenes to nitriles



•problems

1. HCN is a toxic and explosive gas

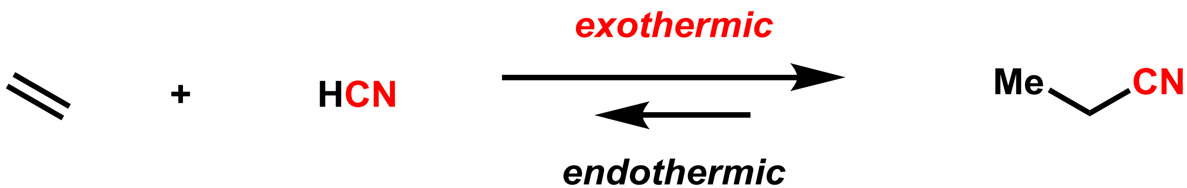
   → replaced to less volatile surrogates (ex. TMSCN, acetone cyanohydrin), but still toxic



93% 1%

de Greef, M.; Breit, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 551.

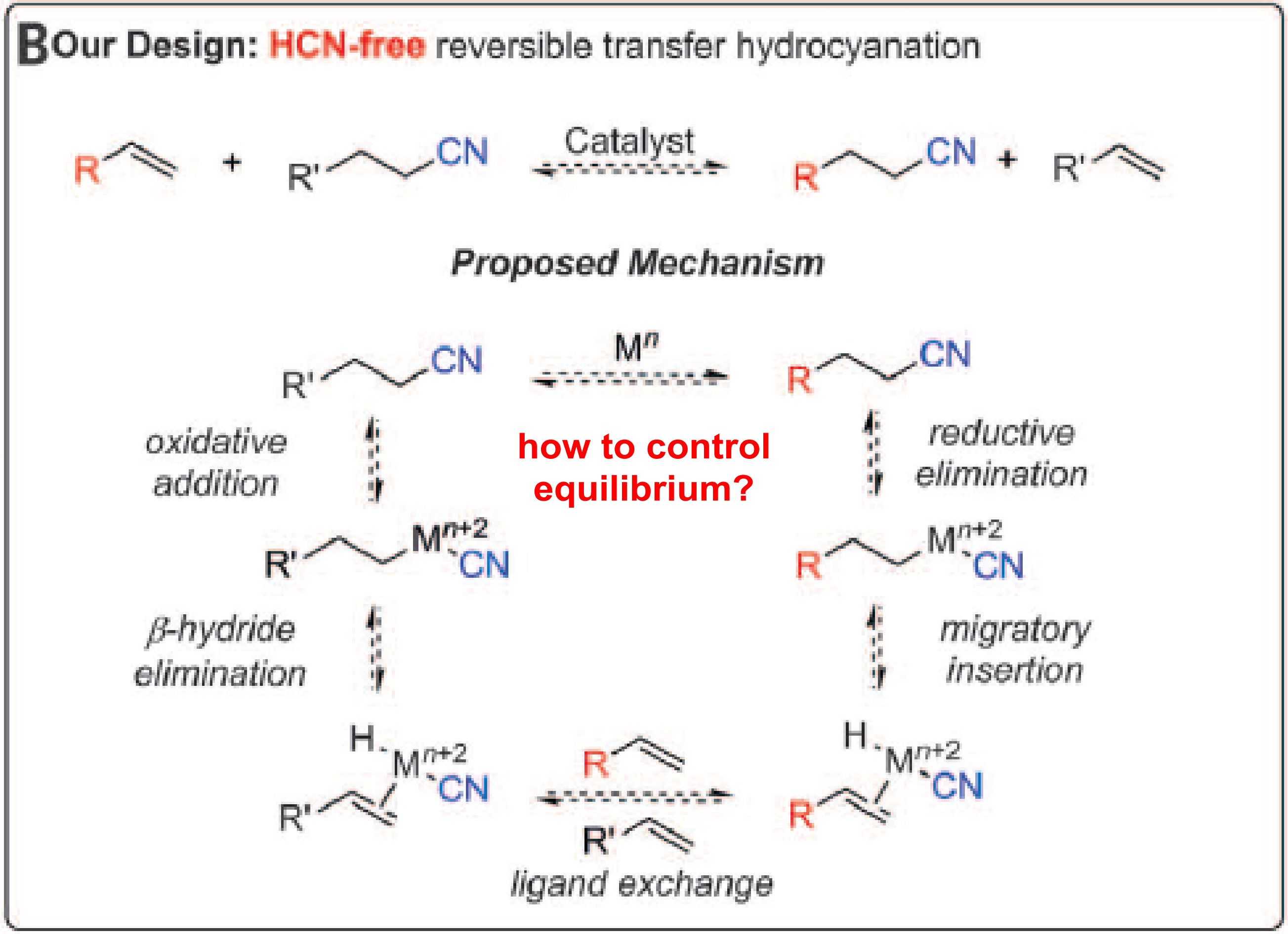
2. retro-hydrocyanation is difficult (therodynamically uphill)



heat of formation (kJ/mol) 52.4 135.1 51.7

D. R. Lide, Ed., *CRC Handbook of Chemistry and Physics, Internet Version 2005* (CRC Press, Boca Raton, FL,**2005**)

Design of HCN-free Reversible Transfer Hydrogenation

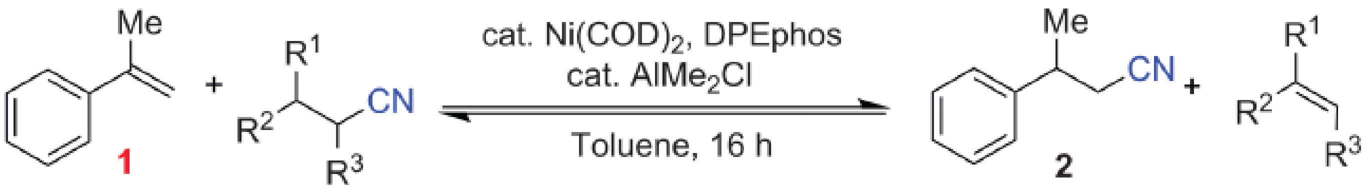


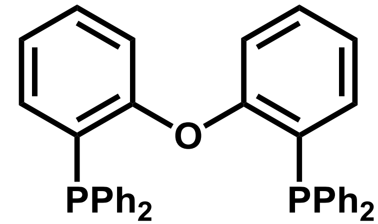
oxidative addition to aliphatic C-CN bond is somewhat difficult
→Ni(0) was used in the presence of Lewis acid

Fang, X.; Yu, P.; Morandi, B. *Science* **2016**, *351*, 832.

Optimization of Reaction Conditions

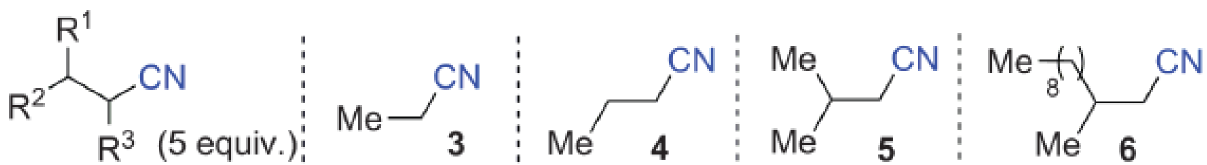
A Thermodynamic Challenge: How can we drive the equilibrium to obtain **1** or **2** selectively ?





DPEphos

B Hydrocyanation: Formation of gaseous disubstituted alkene best driving force



	3	4	5	6
yield **1** -> **2** (100 °C)	3%	26%	69%	60%
open system	—	41%	86%	67%

driving force:
using large excess of reagent
volatile alkene formation
(Le Chatelier's priciple)

C Retro-Hydrocyanation: Strained alkenes best driving force

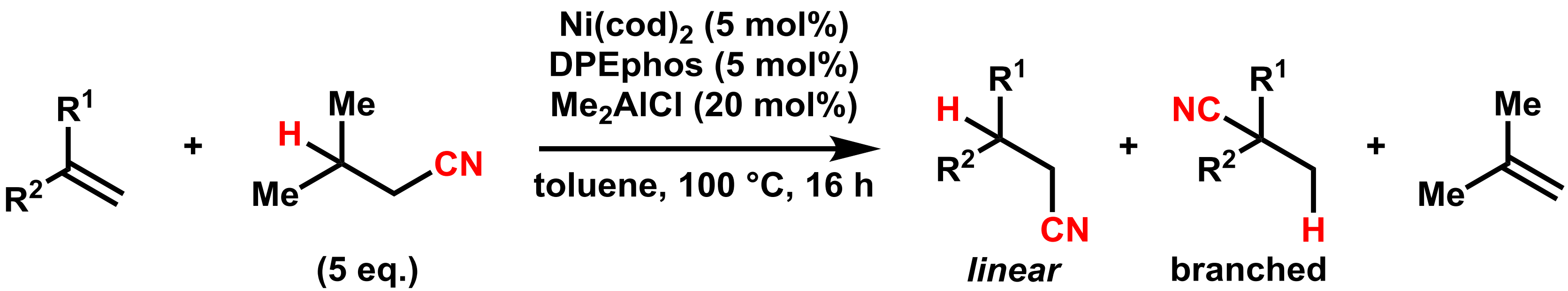
	no acceptor	7	8
yield **2** -> **1** (28 °C)	<5%	46%	99%

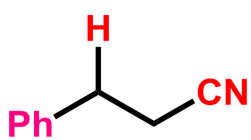
driving force:
strain release of norbornene and norbornadiene

cf. Murphy, S. K.; Park, J.-W.; Cruz, F. A.; Dong, V. M. *Science* **2015**, *347*, 56.
See also Fujino-kun's LS on 181027.

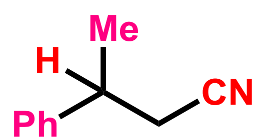
Fang, X.; Yu, P.; Morandi, B. *Science* **2016**, *351*, 832.

Substrate Scope - Hydrocyanation -

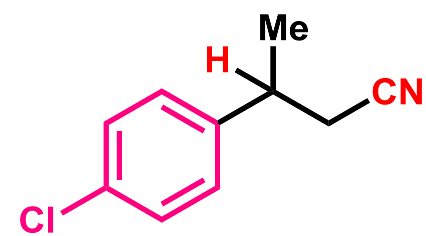




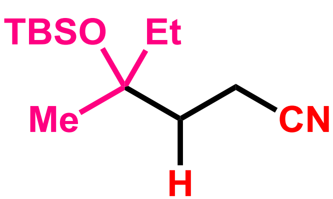
86% (*l*:*b* = 81:19), 100 °C
73%* (*l*:*b* = 81:19), 100 °C
*1.5 eq of hydrocyanide donor



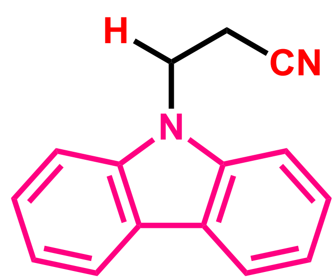
91% (*l*:*b* > 95:5), 130 °C



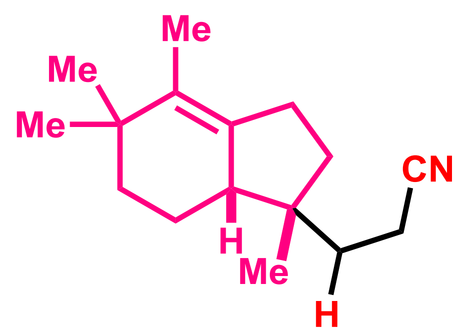
84% (*l*:*b* > 95:5), 130 °C



97% (*l*:*b* > 95:5), 130 °C



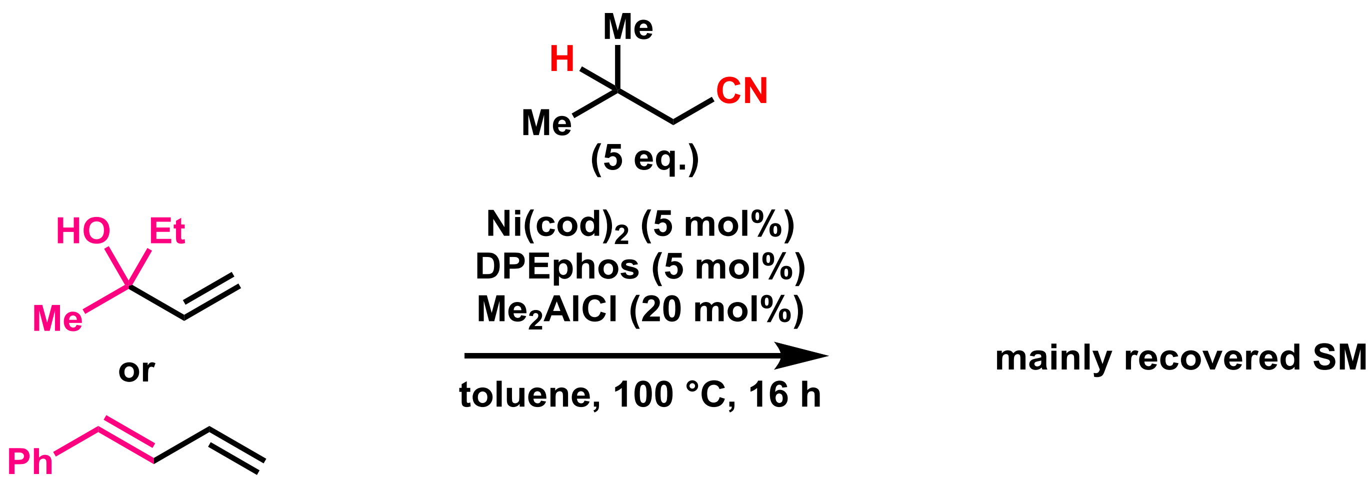
65%, 130 °C



95% (*l*:*b* > 95:5), 130 °C

Fang, X.; Yu, P.; Morandi, B. *Science* **2016**, *351*, 832.

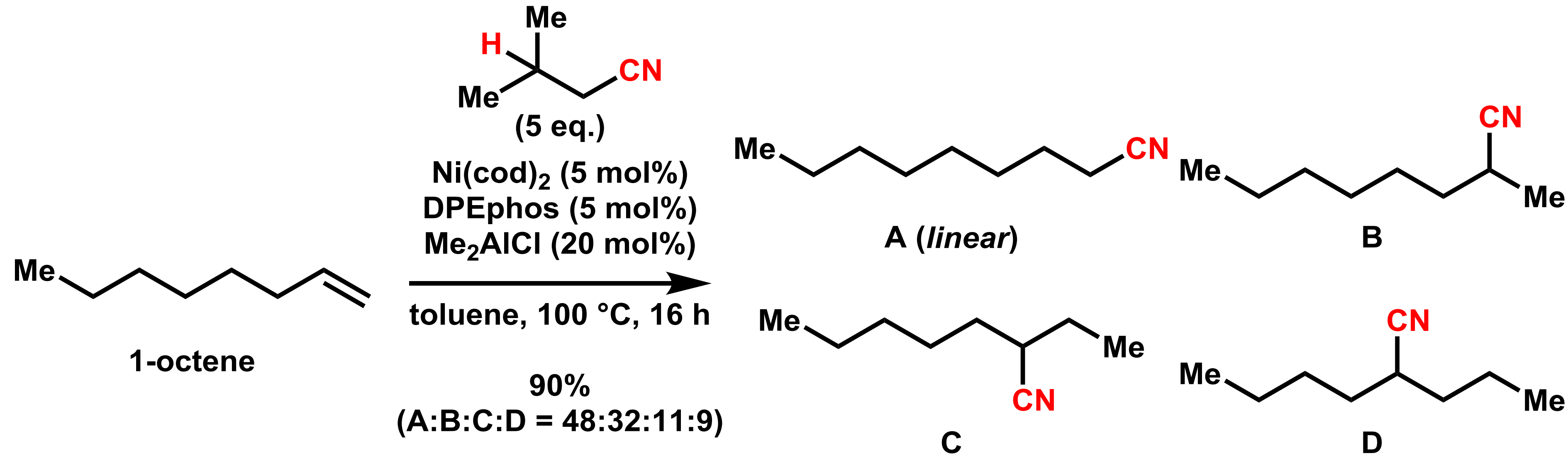
Limitations
- Compatibility with Functional Groups -

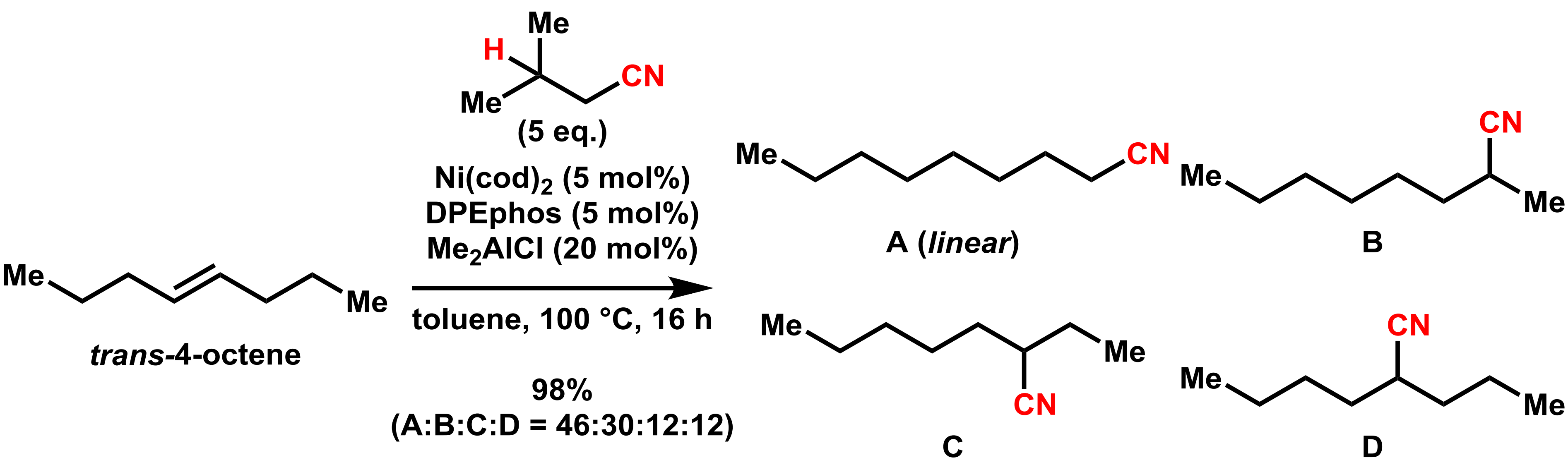


free OH groups and dienes are not compatible with these conditions

Fang, X.; Yu, P.; Morandi, B. *Science* **2016**, *351*, 832.

Limitation - Alkene Isomerization -

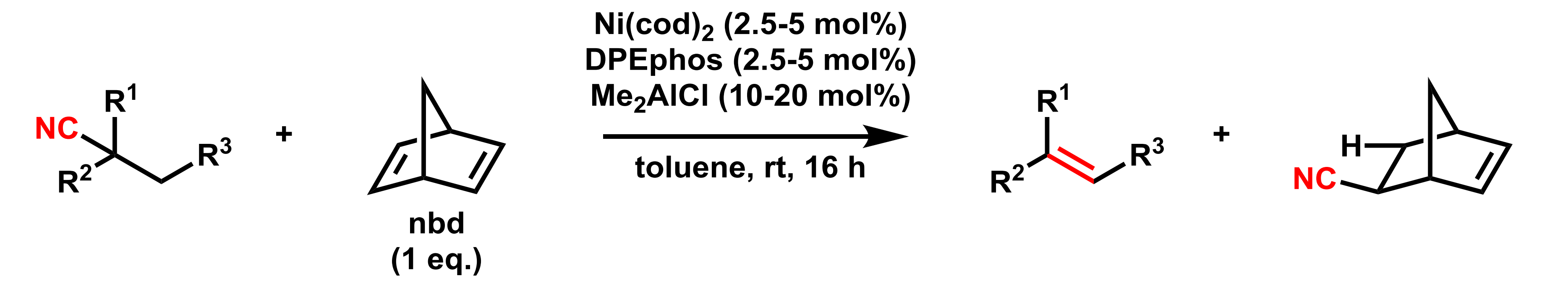


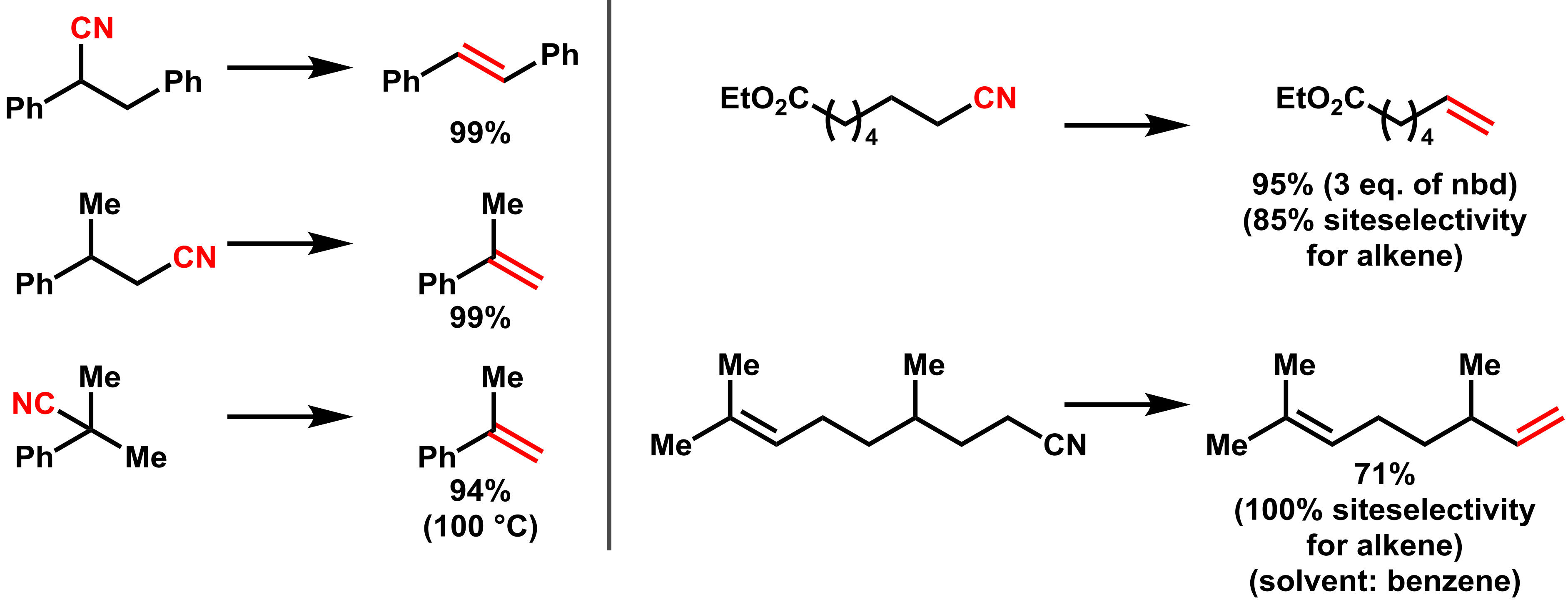


Ni^{II}-H mediated alkene isomerization competed.

Fang, X.; Yu, P.; Morandi, B. *Science* **2016**, *351*, 832.

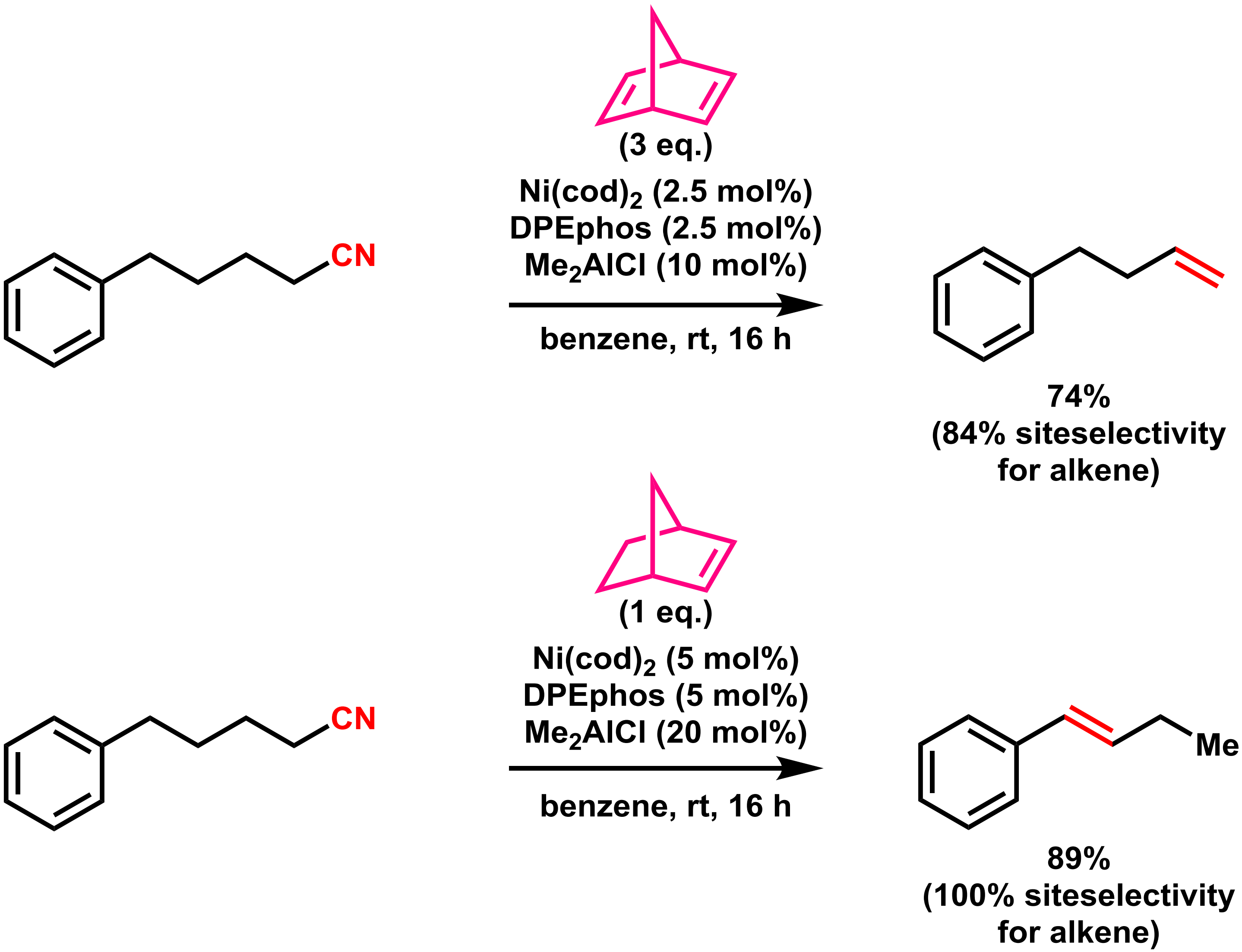
Substrate Scope - Retro-hydrocyanation -





Fang, X.; Yu, P.; Morandi, B. *Science* **2016**, *351*, 832.

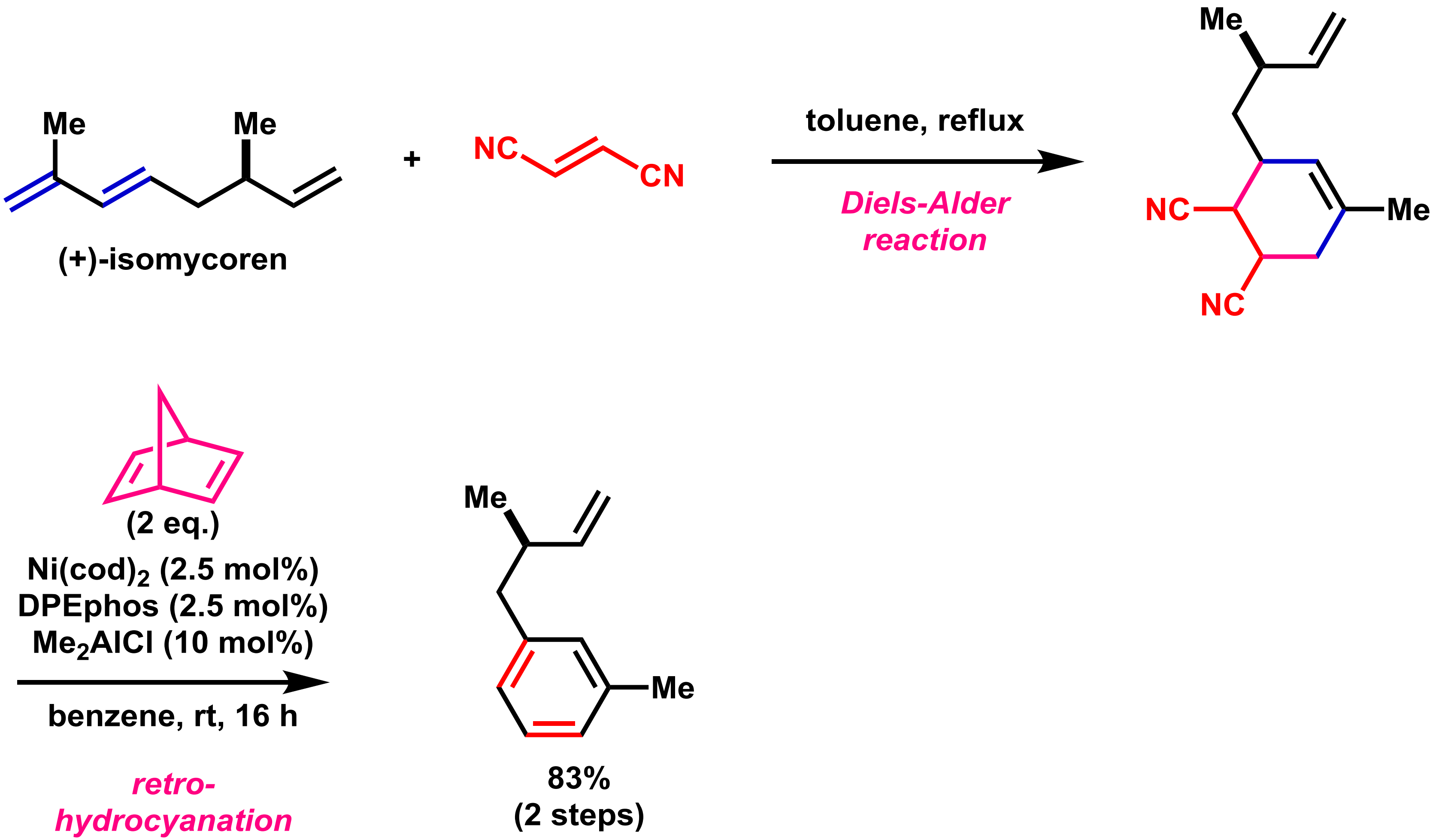
Control over Isomerization



isomerization was controlled by acceptor alkene (and equivalents?)

Fang, X.; Yu, P.; Morandi, B. *Science* **2016**, *351*, 832.

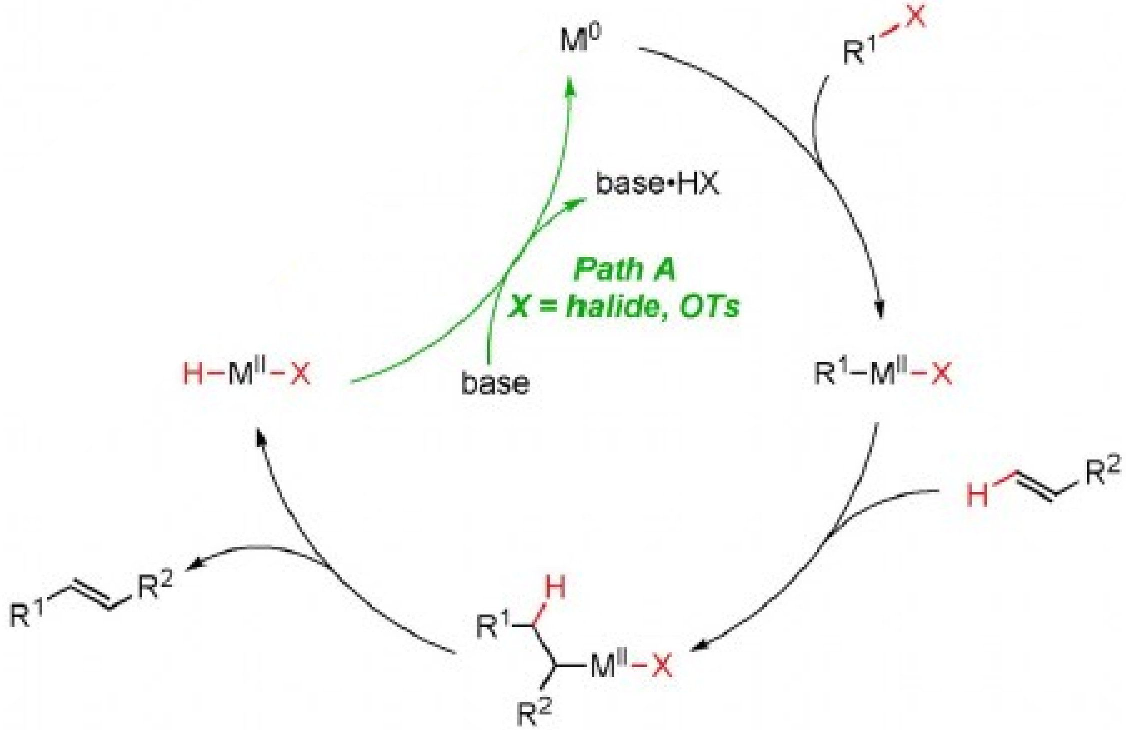
Application to Aromatic Ring Formation



Fang, X.; Yu, P.; Morandi, B. *Science* **2016**, *351*, 832.

Application to Mizorogi-Heck-type Reaction

•machanism of Mizorogi-Heck reaction

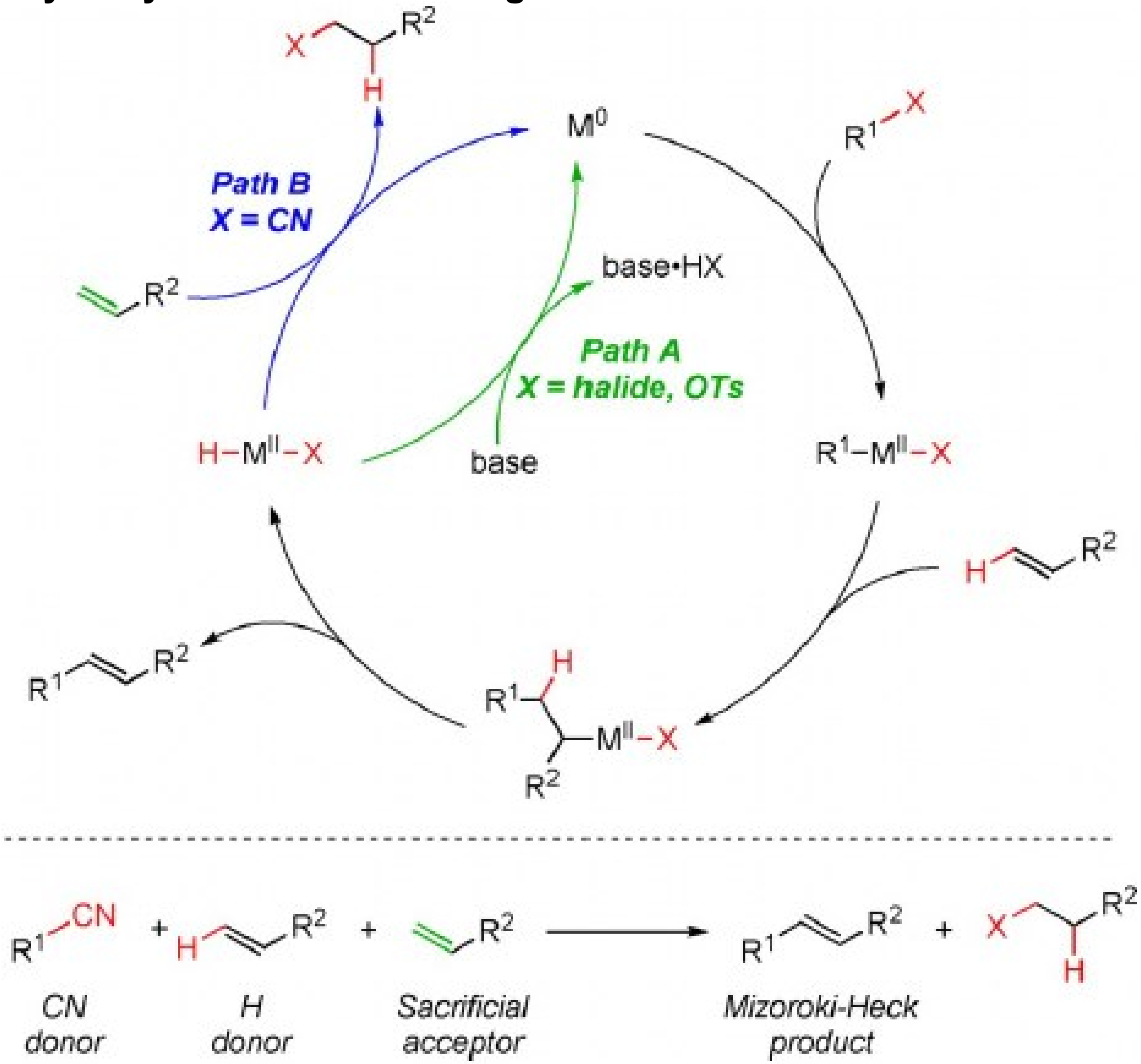


when X = CN, a Lewis acid needs for the efficient oxidative addition.
→ might not be compatible with base-assisted M^0 regeneration.

Fang, X.; Yu, P.; Cerai, G. P.; Morandi, B. *Chem. Eur. J.* **2016**, *22*, 15629.
Bhawal, B.; Morandi, B. *Chem. Eur. J.* **2017**, *23*, 12004. (Review)

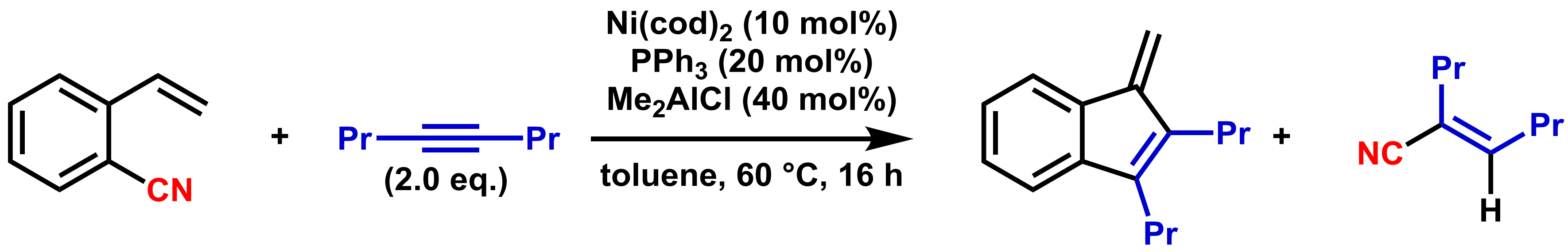
Application to Mizorogi-Heck-type Reaction

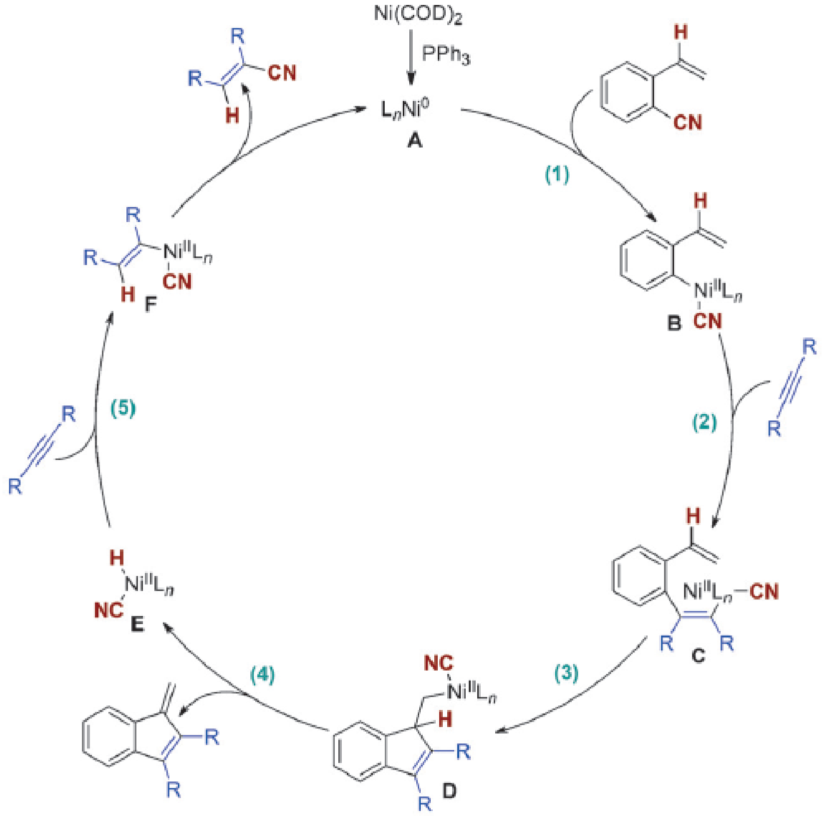
- combination of hydrocyanation with Mizorogi-Heck reaction



Fang, X.; Yu, P.; Cerai, G. P.; Morandi, B. *Chem. Eur. J.* **2016**, *22*, 15629.
Bhawal, B.; Morandi, B. *Chem. Eur. J.* **2017**, *23*, 12004. (Review)

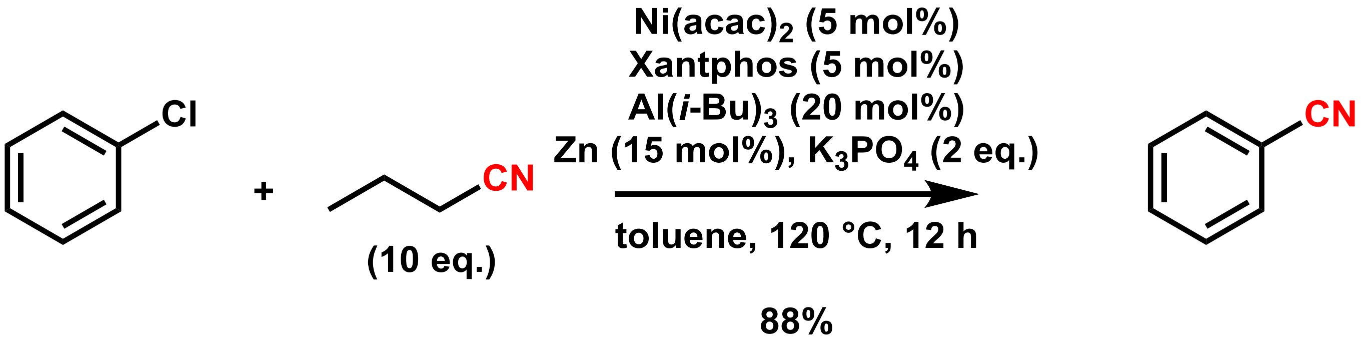
Application to Mizorogi-Heck-type Reaction

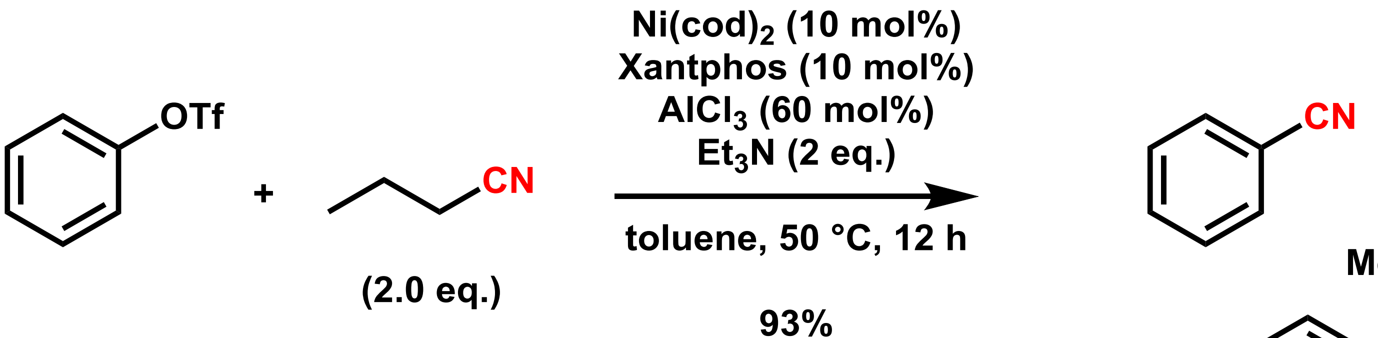


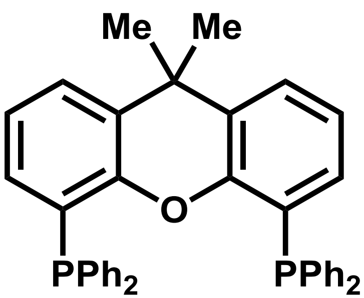


Fang, X.; Yu, P.; Cerai, G. P.; Morandi, B. *Chem. Eur. J.* **2016**, *22*, 15629.

Application to Cross-Coupling Reaction







Xantphos

Yu, P.; Morandi, B. *Angew. Chem. Int. Ed.* **2017**, *56*, 15693.

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3. Metathesis reations - C-S or C-P bond -

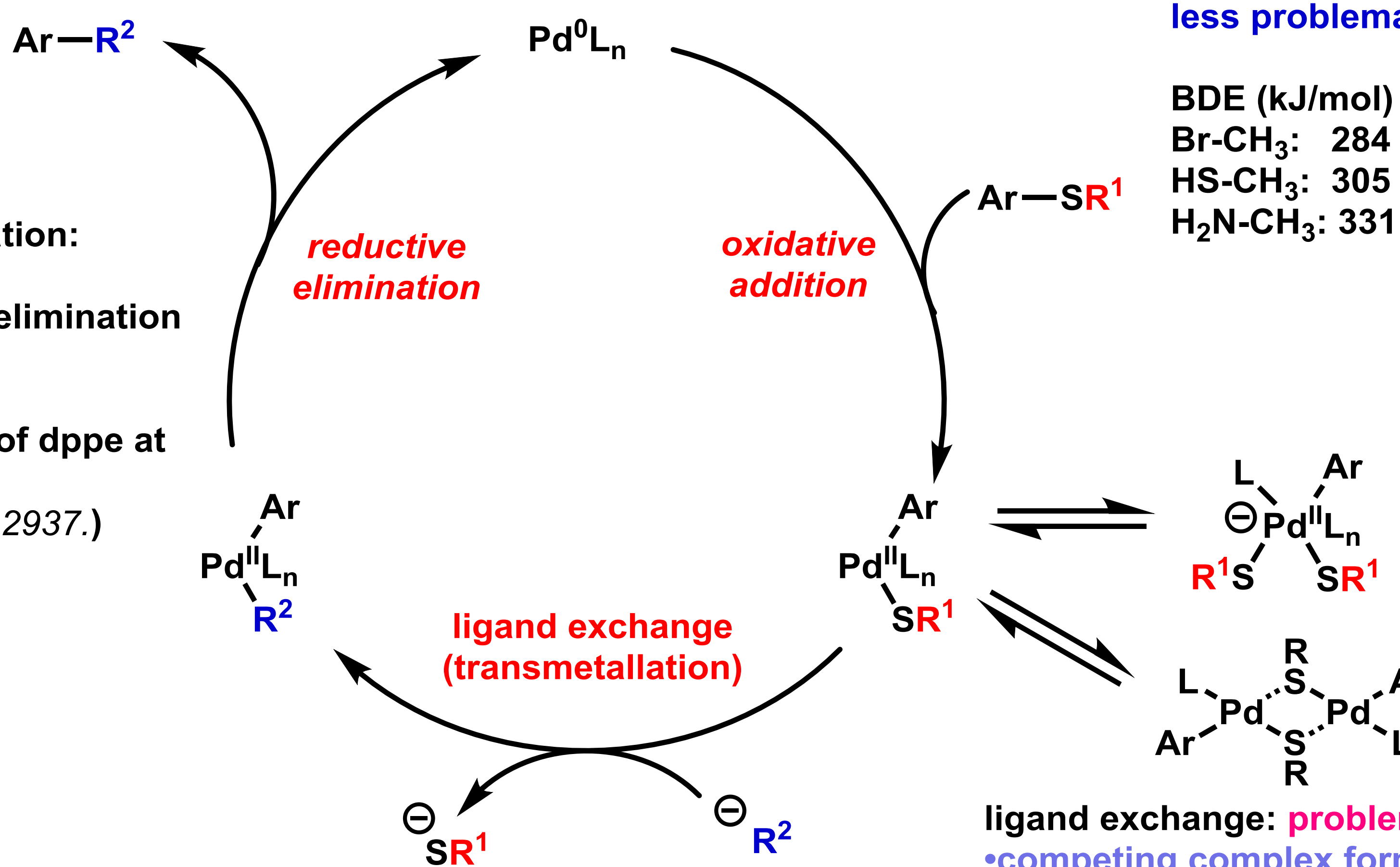
Problems of Transition Metal-Catalyzed Reaction of Ar-SR

oxidative addition:
less problematic

BDE (kJ/mol)
$Br\text{-}CH_3$: 284
$HS\text{-}CH_3$: 305
$H_2N\text{-}CH_3$: 331

reductive elimination:
less problematic
easier reductive elimination of ArSR

(in the presence of dppe at >50 °C
JACS, **1995**, *117, 2937.*)



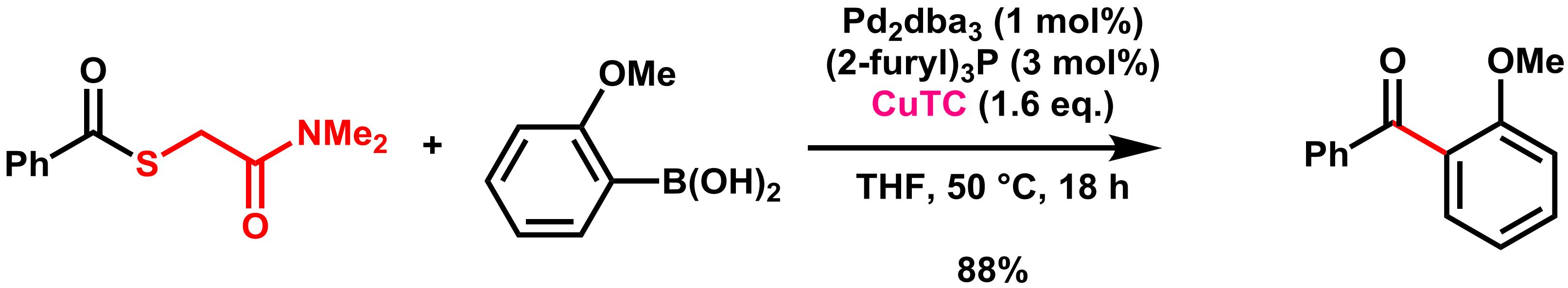
ligand exchange: problematic
•competing complex formation
•relatively strong interaction of S (soft) and transition metal

poisoning of transition metal:
ploblematic (R^2 = RS)

Hartwig, J. F. et al. *Chem. Eur. J.* **2006**, *12*, 7782.

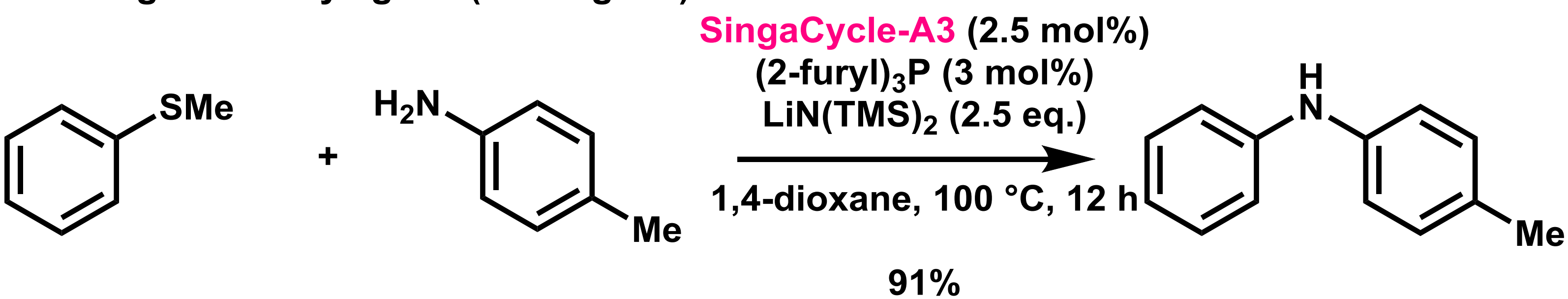
Successful Examples

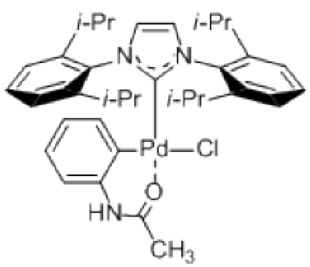
•transmetallation is accelerated by CuTC



Liebeskind, L. S.; Srogl, J. *J. Am. Chem Soc.* **2000**, *122*, 11260.

•electron-donating and bulky ligand (NHC ligand)

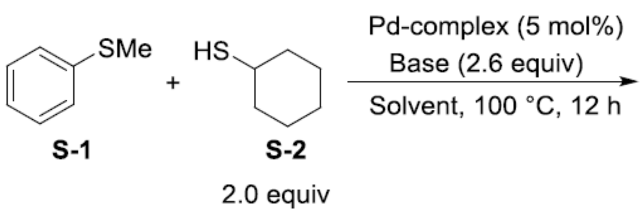


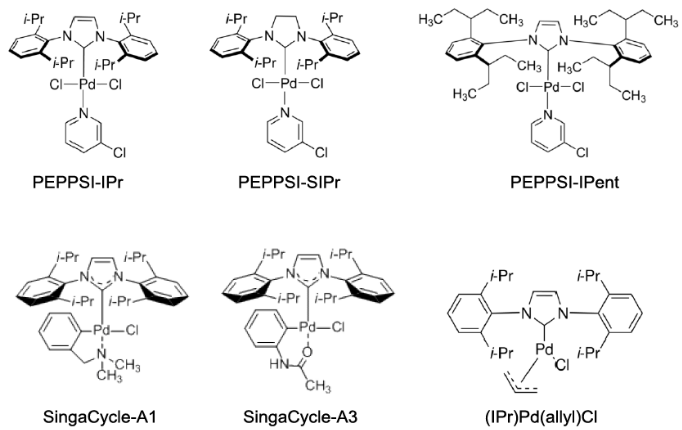


SingaCycle-A3

Sugahara, T.; Murakami, K.; Yorimitsu, H.; Osuka, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 9329.

Optimization of Reaction Conditions





Entry	Pd-complex	Base	Solvent	Yield (**31**)*
1	PEPPSI-IPr	K_2CO_3	toluene	0
2	PEPPSI-IPr	KO*t*-Bu	toluene	18%
3	PEPPSI-IPr	KOAc	toluene	0
4	PEPPSI-IPr	K_3PO_4	toluene	0
5	PEPPSI-IPr	KHMDS	toluene	68%
6	PEPPSI-IPr	NaHMDS	toluene	45%
7	PEPPSI-IPr	LiHMDS	toluene	81%
8	PEPPSI-IPr	LiHMDS	*o*-xylene	78%
9	PEPPSI-IPr	LiHMDS	dioxane	66%
10	PEPPSI-IPr	LiHMDS	THF	21%
11	PEPPSI-IPr	LiHMDS	DMF	trace
12	PEPPSI-IPr	LiHMDS	DMSO	trace
13	PEPPSI-IPr	LiHMDS	DCE	trace
14	PEPPSI-IPr	LiHMDS	acetonitrile	trace
15	PEPPSI-SIPr	LiHMDS	toluene	87%
16	PEPPSI-IPent	LiHMDS	toluene	63%
17	SingaCycle-A1	LiHMDS	toluene	92%
18	SingaCycle-A3	LiHMDS	toluene	85%
19	(IPr)Pd(allyl)Cl	LiHMDS	toluene	81%
20†	SingaCycle-A1	LiHMDS	toluene	91%
21‡	SingaCycle-A1	LiHMDS	toluene	90%
22§	***SingaCycle-A1***	***LiHMDS***	***toluene***	***90%***

*GC yield using dodecane as internal standard. †Pd-complex (1 mol%). ‡Pd-complex (0.5 mol%). §Pd-complex (0.4 mol%). ||Pd-complex (0.3 mol%). ¶1.5 equiv CySH. #2.5 equiv CySH.

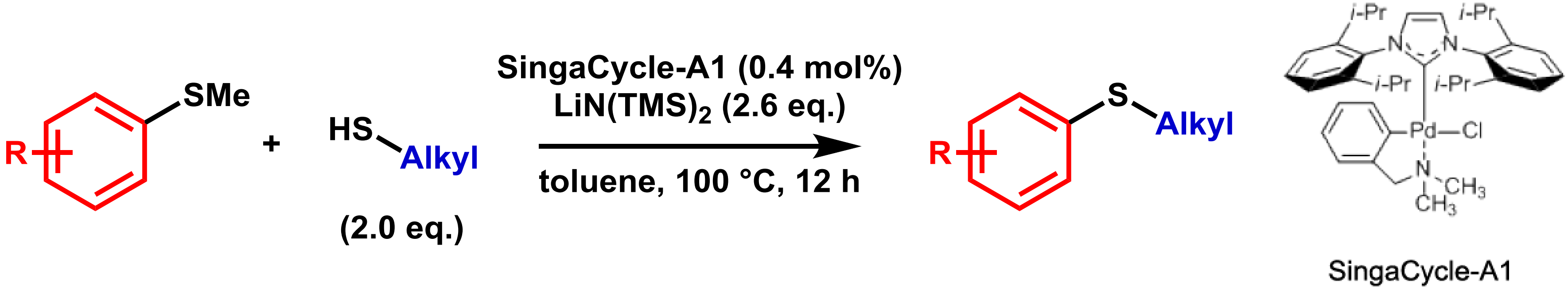
← **0.4% of Pd cat.**

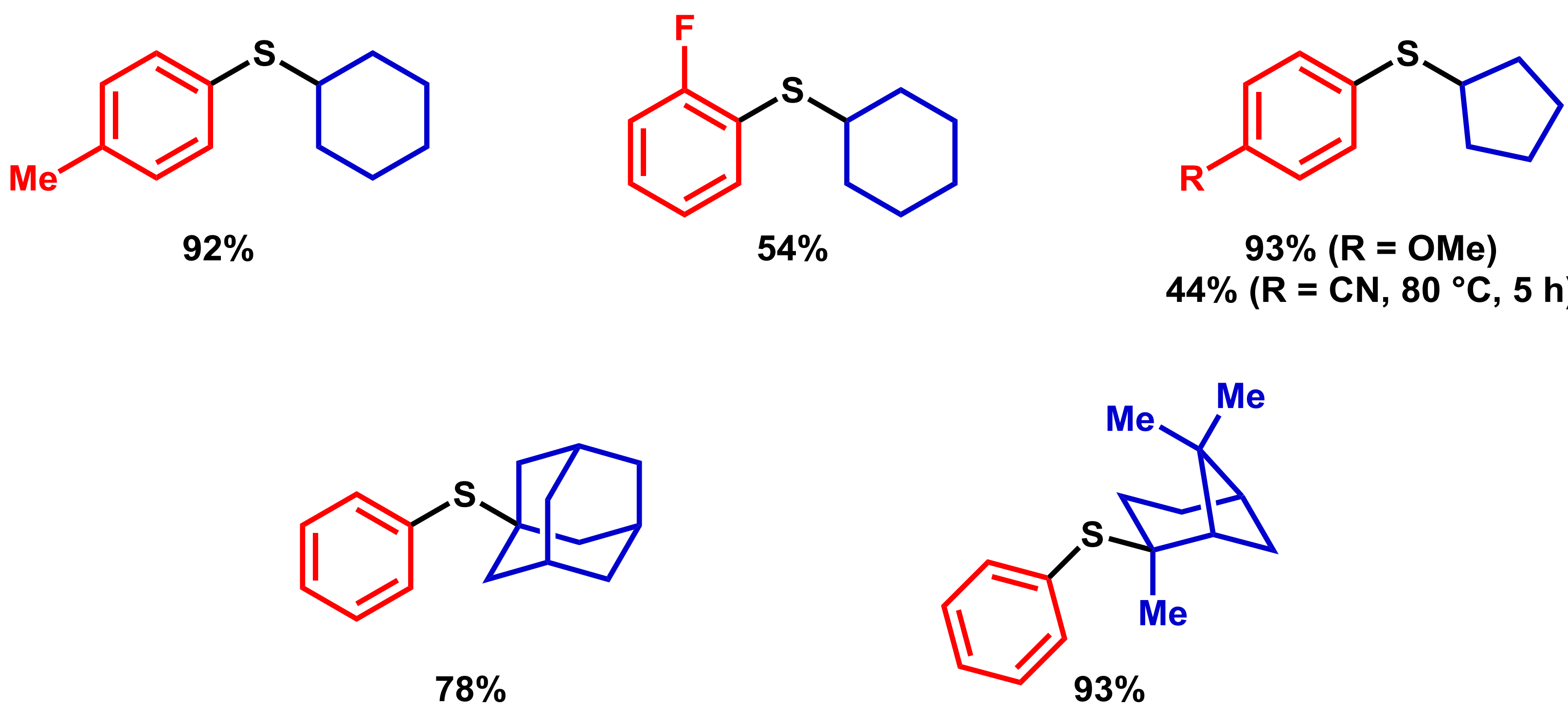
$LiN(TMS)_2$ was effective.

1. **strong base**
   →fast transmetallation
2. **resulting LiSMe has poor solubility in toluene.**

Liang, Z.; Bhawal, B. N.; Yu, P.; Morandi, B. *Science* **2017**, *356*, 1059.

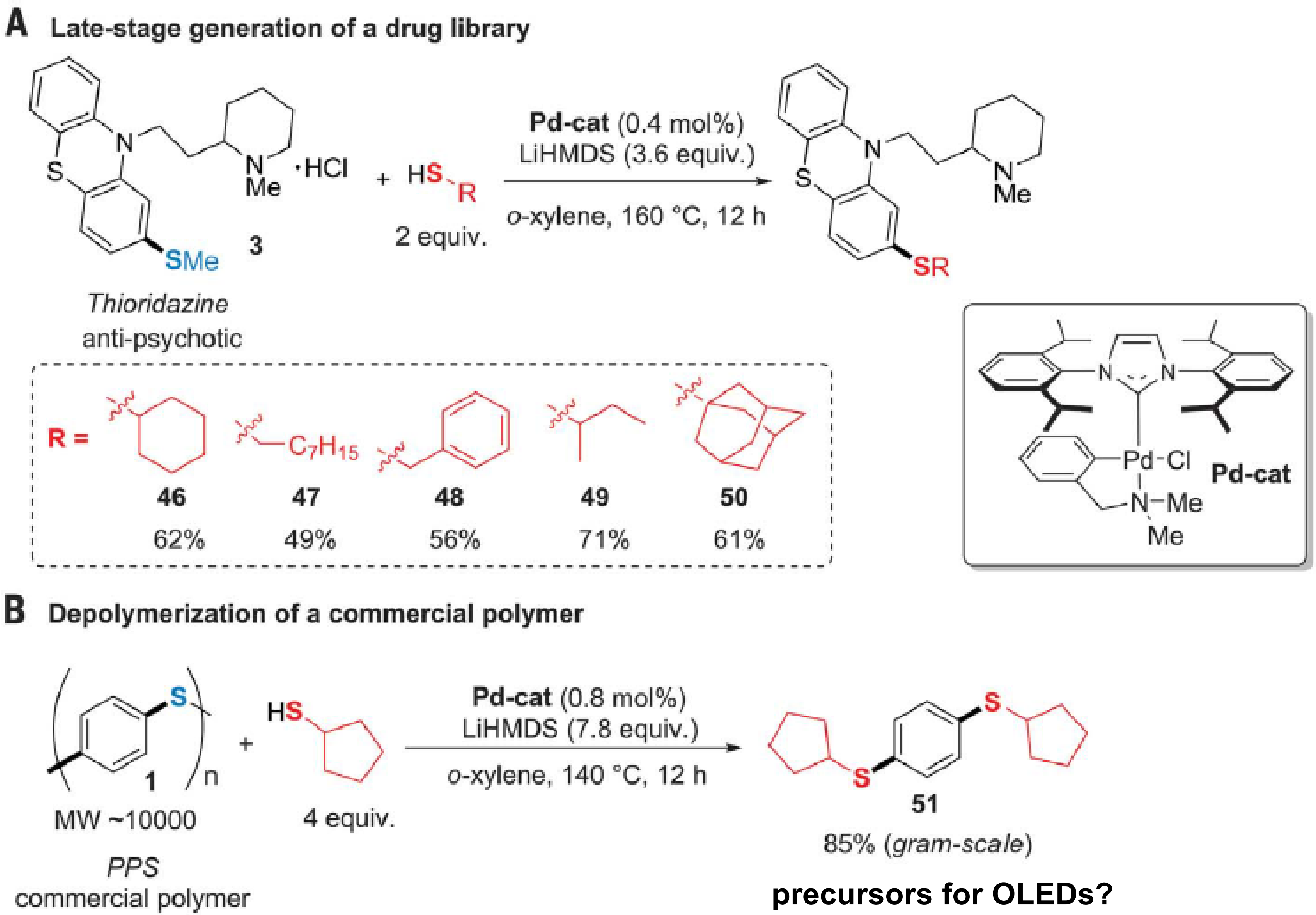
Substrate Scope Using Ar-SMe





Liang, Z.; Bhawal, B. N.; Yu, P.; Morandi, B. *Science* **2017**, *356*, 1059.

Further Application



precursors for OLEDs?

Liang, Z.; Bhawal, B. N.; Yu, P.; Morandi, B. *Science* **2017**, *356*, 1059.

Thermal Equilibrium

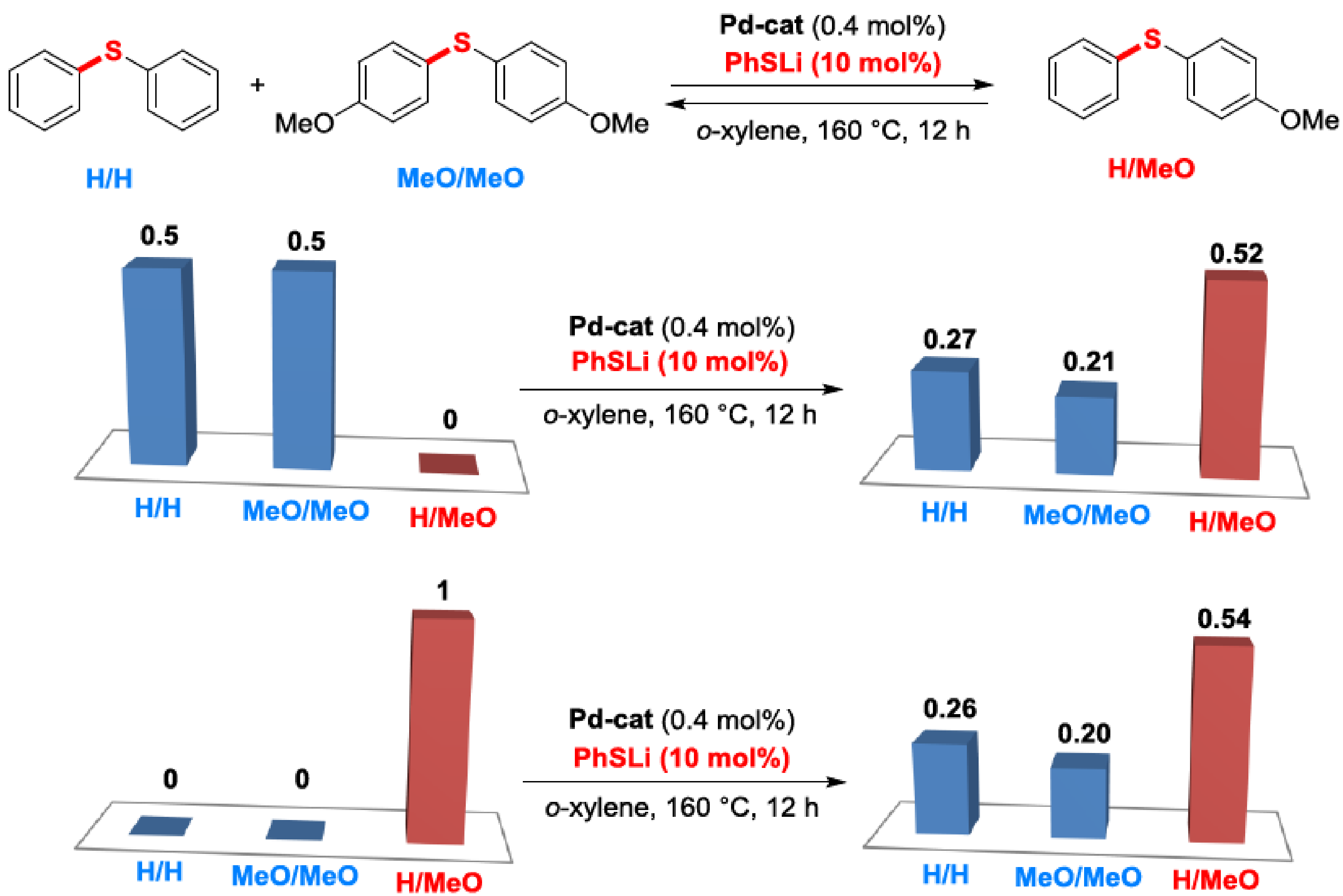
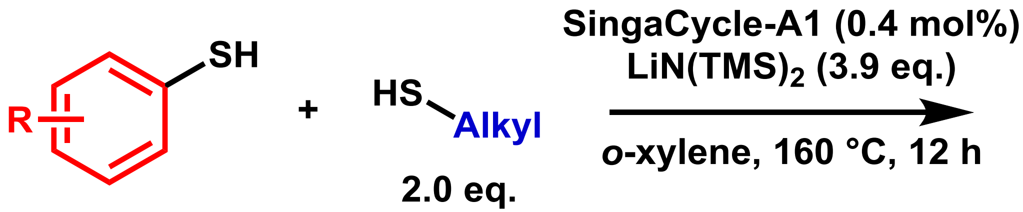
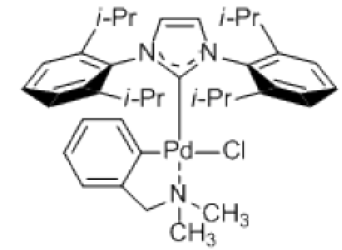


Figure S1 C–S/C–S metathesis using co-catalytic RS⁻.

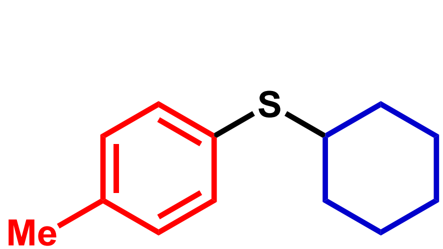
Liang, Z.; Bhawal, B. N.; Yu, P.; Morandi, B. *Science* **2017**, *356*, 1059.

Substrate Scope Using Ar-SH

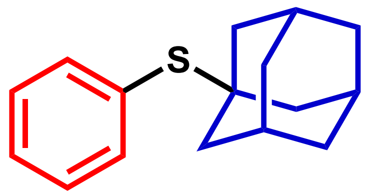




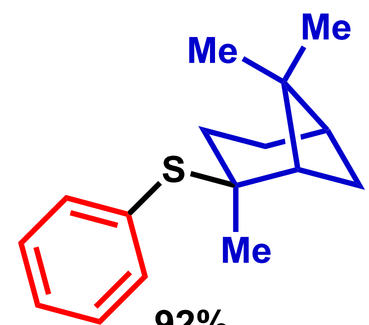
SingaCycle-A1



87%

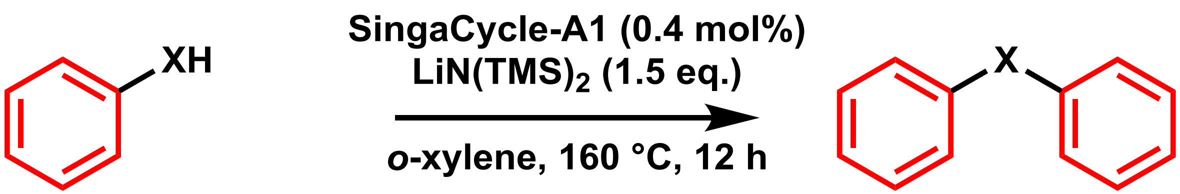


70%



92%

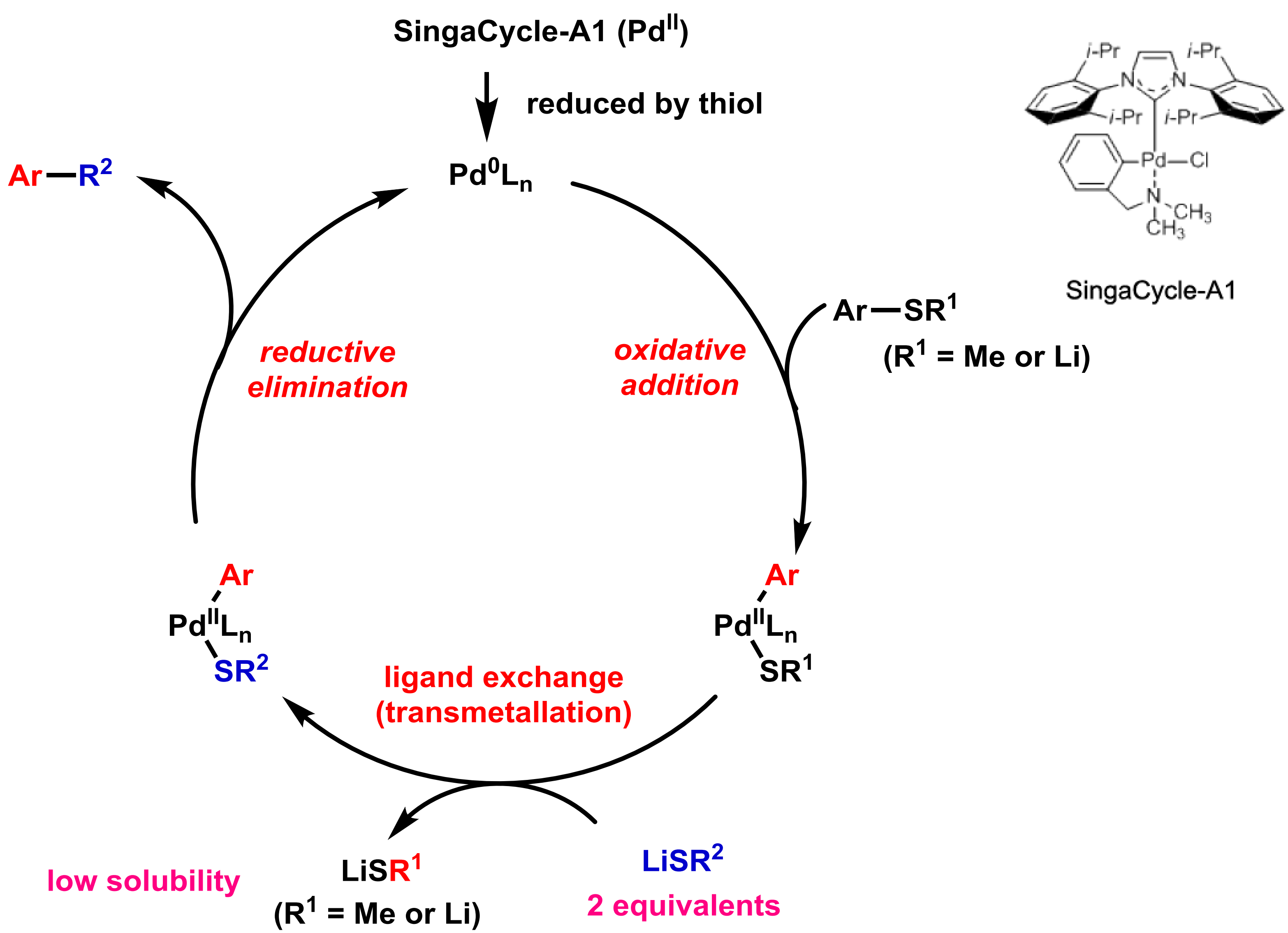
•homodimerization



76% (X = S)
96% (X = Se)

Liang, Z.; Bhawal, B. N.; Yu, P.; Morandi, B. *Science* **2017**, *356*, 1059.

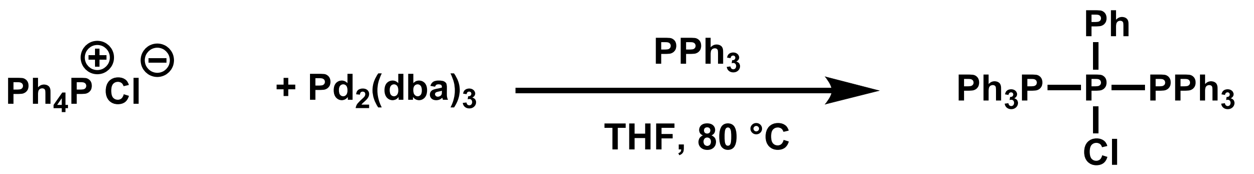
Proposed Mechanism



Liang, Z.; Bhawal, B. N.; Yu, P.; Morandi, B. *Science* **2017**, *356*, 1059.

Working Hypothesis

- oxidative addition to $C(sp^2)$-$P^{\oplus}Ph_3$

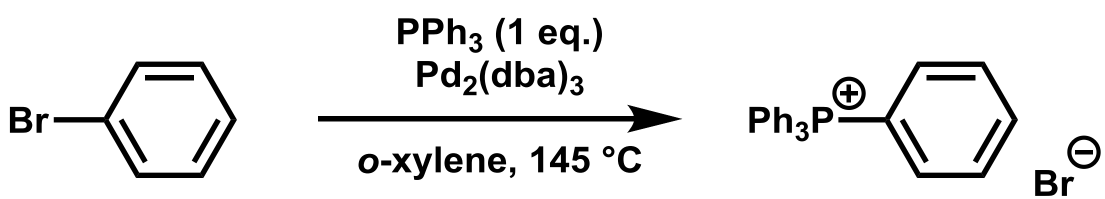


54%

confirmed by X-ray

Chang, S. et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 6166.

- reductive elimination to form phosphonium salt

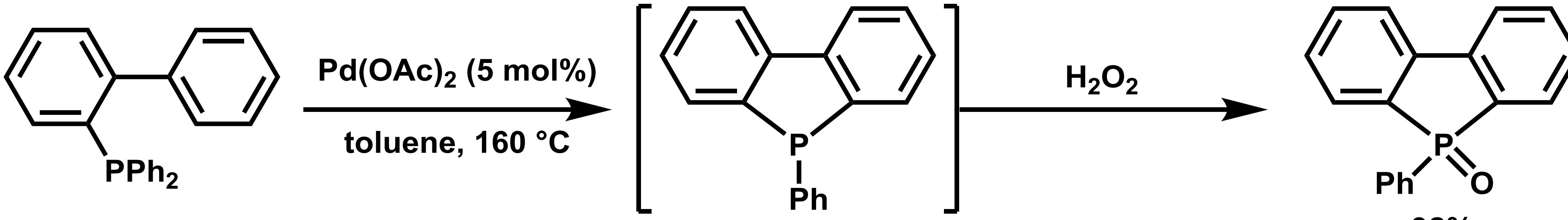


95%

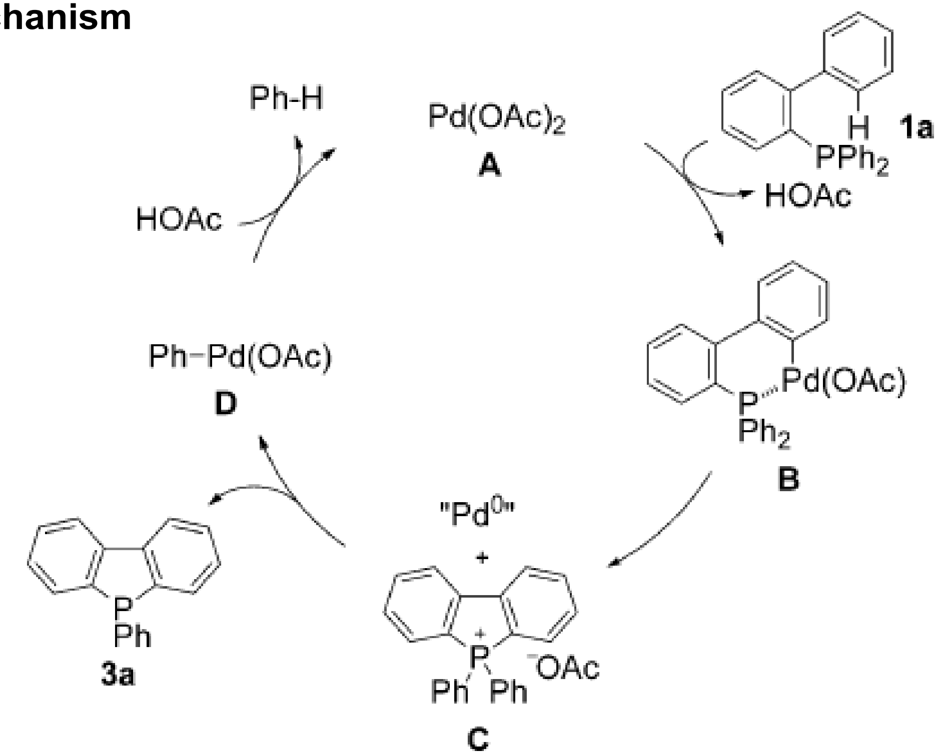
Marcoux, D.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 590.

→ **By combining these results, "C-P/C-P cross metathesis" would be realized.**

Examples of C-P/C-H Coupling

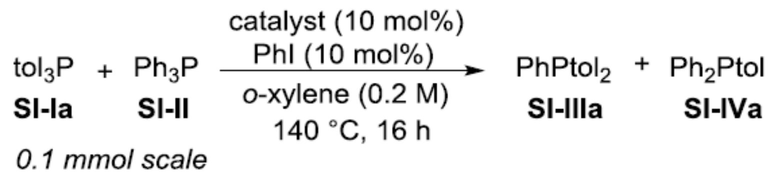


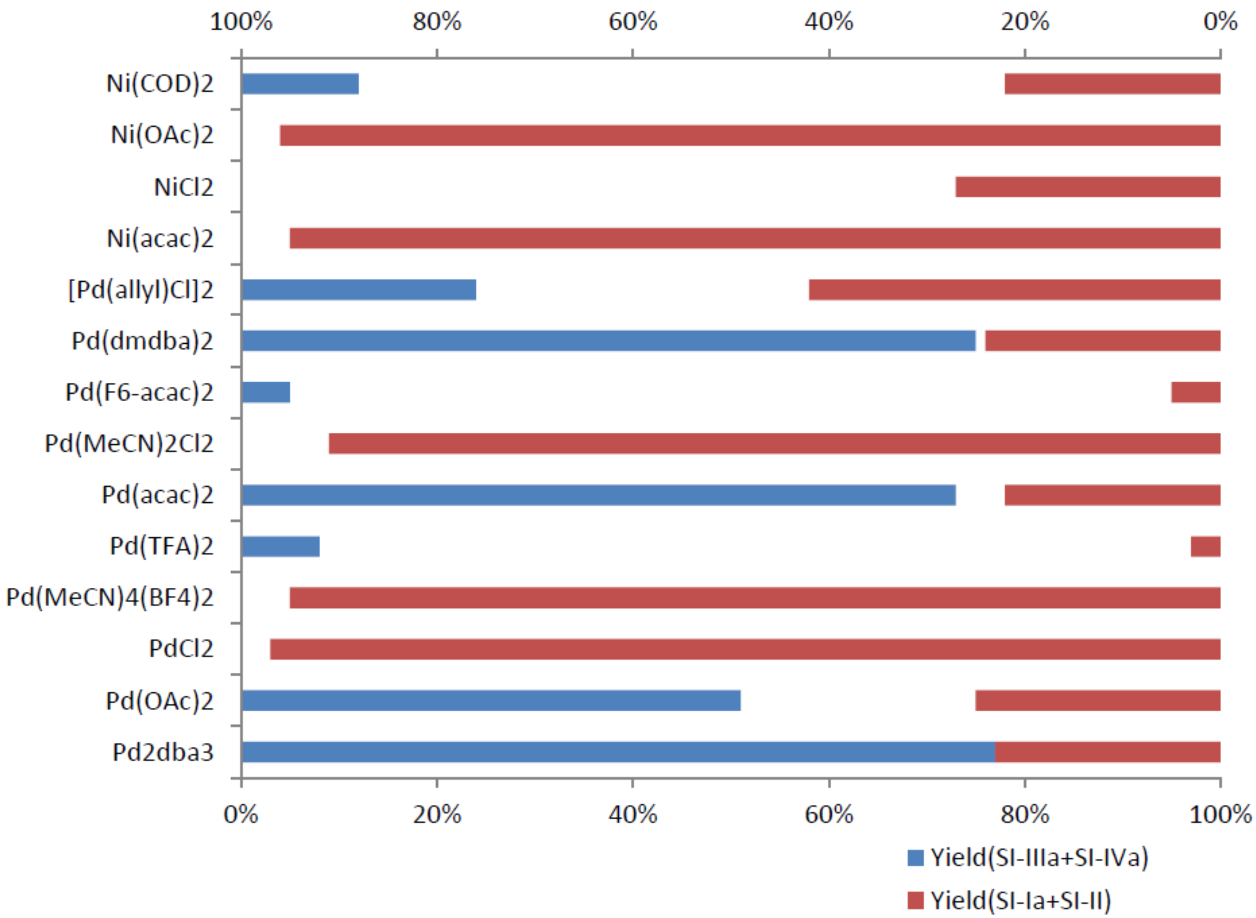
•proposed mechanism



Baba, K.; Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11892.

Screening the Catalyst





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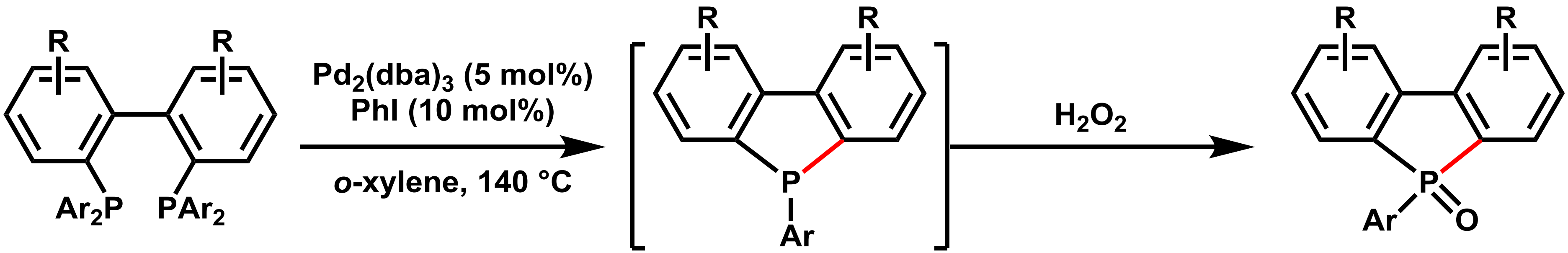
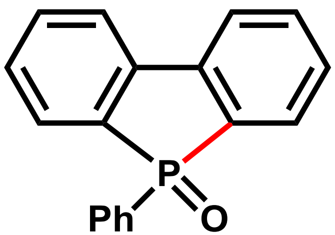
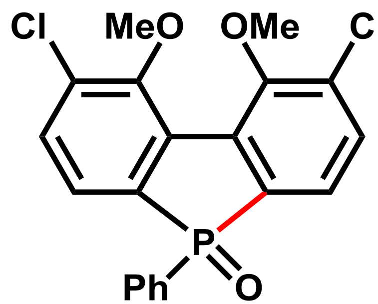
Application to Phosphorus Ring Formation

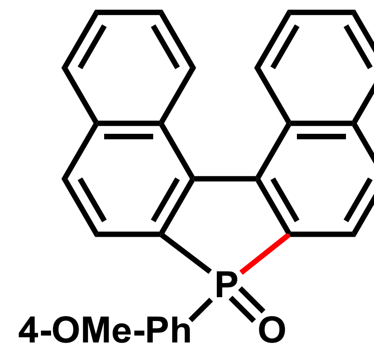




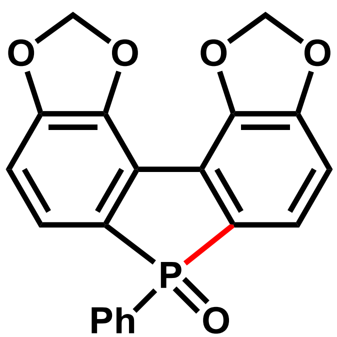
76%



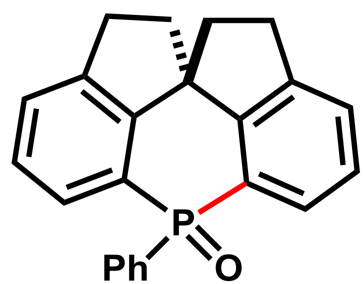
96%



99%



92%

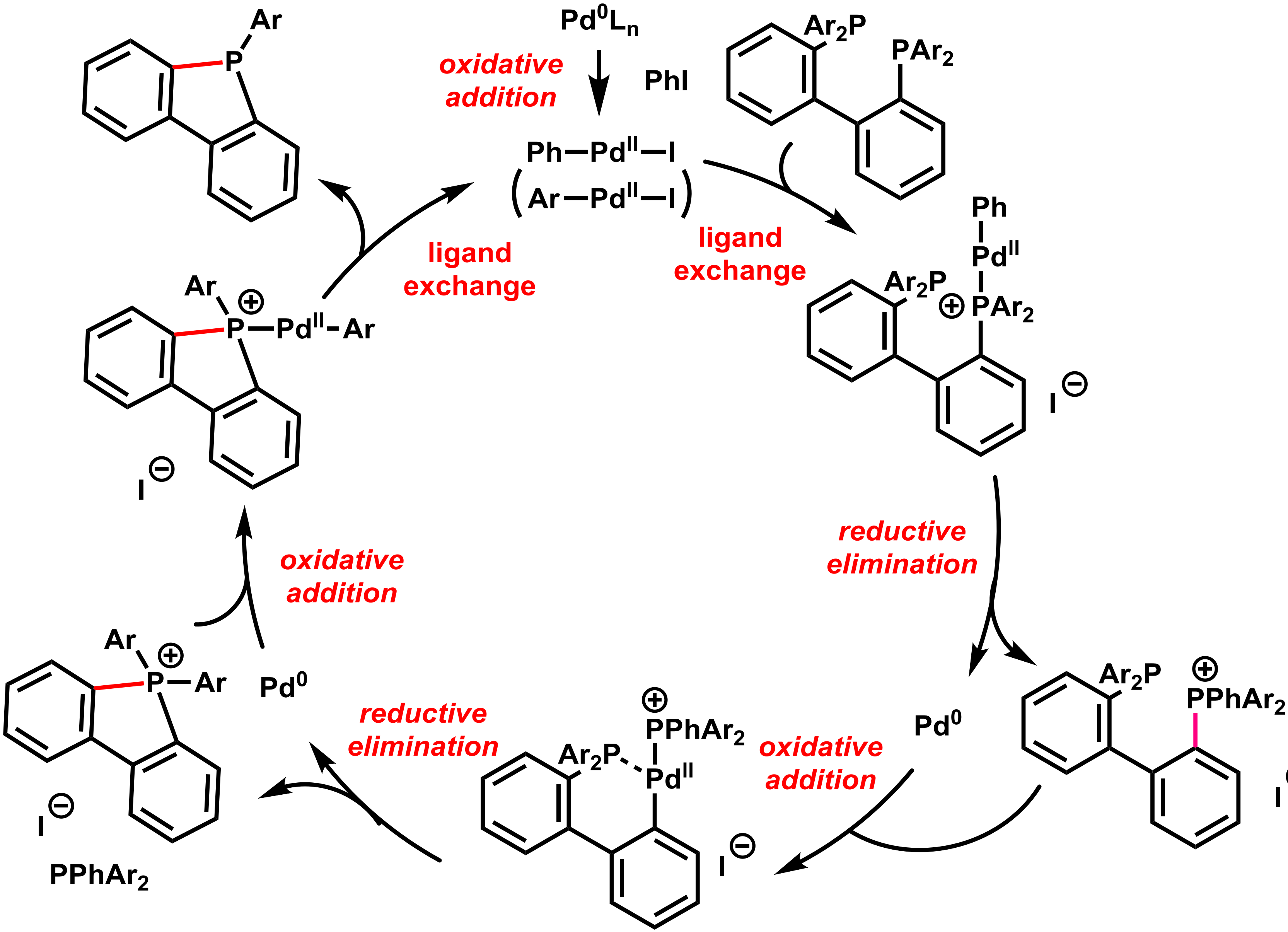


50%

>99%ee from >99%ee SM

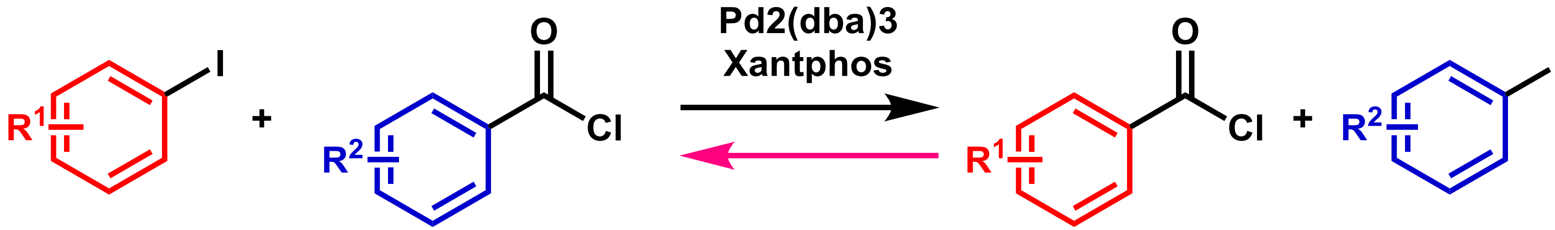
Liang, Z.; Bhawal, B. N.; Yu, P.; Morandi, B. *Science* **2017**, *356*, 1059.

Plausible Catalytic Cycle

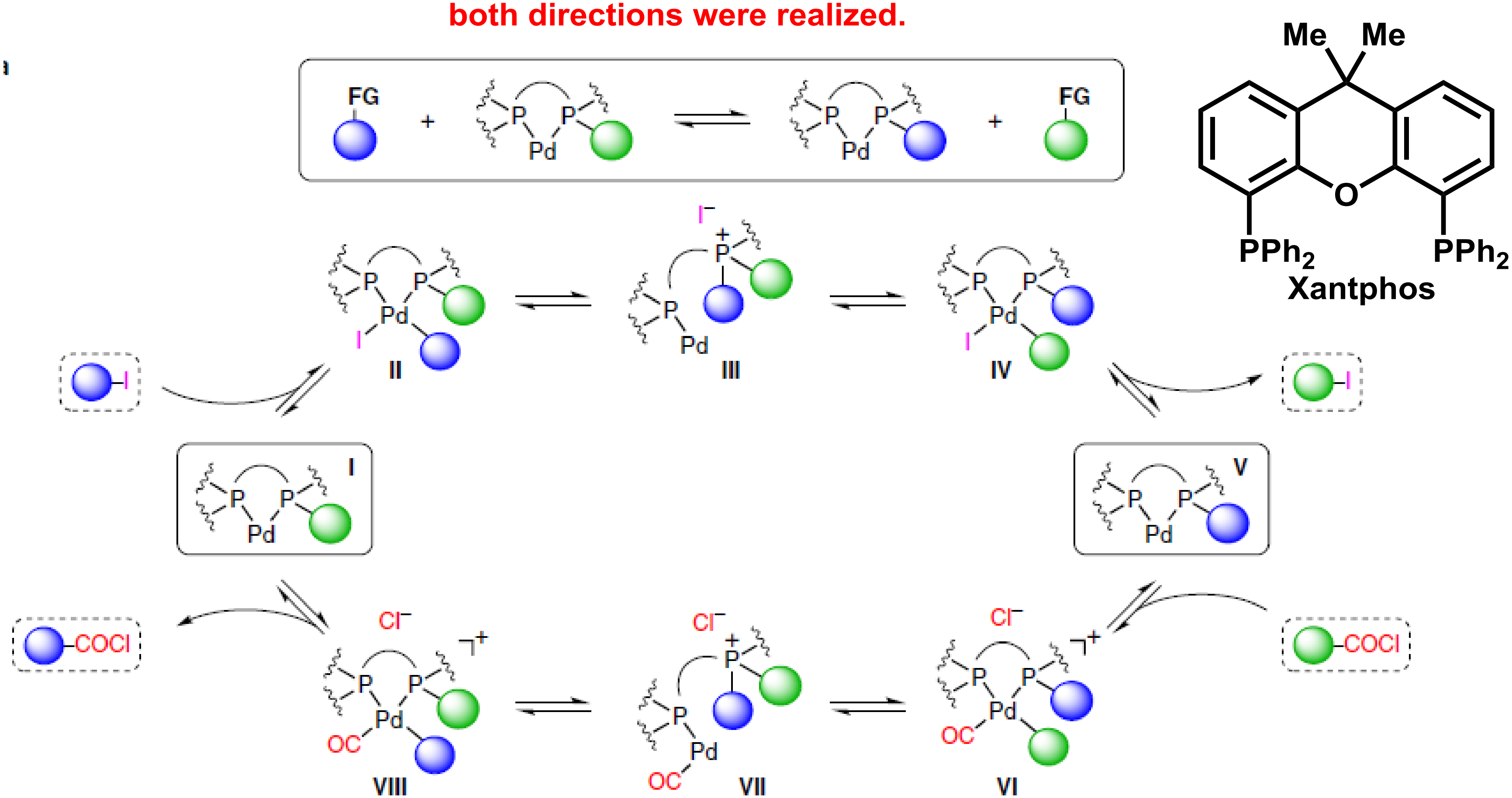


Liang, Z.; Bhawal, B. N.; Yu, P.; Morandi, B. *Science* **2017**, *356*, 1059.

“Functional Group Metathesis” - ArCOCl & ArI -



both directions were realized.

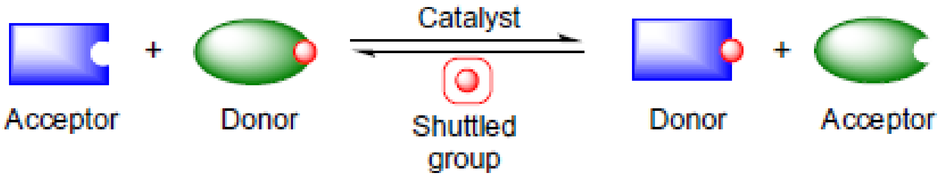


Xantphos

Lee, Y. H.; Morandi, B. *Nat. Chem.* **2018**, *10*, 1016.

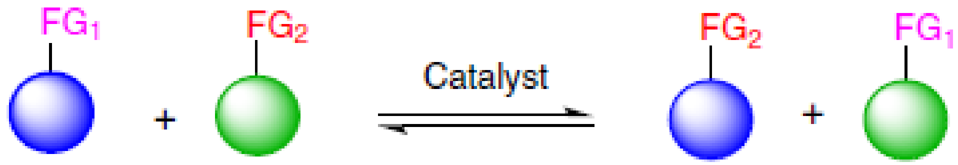
Summary

•shuttle reaction



combined with further catalytic reaction

•functional group metathesis

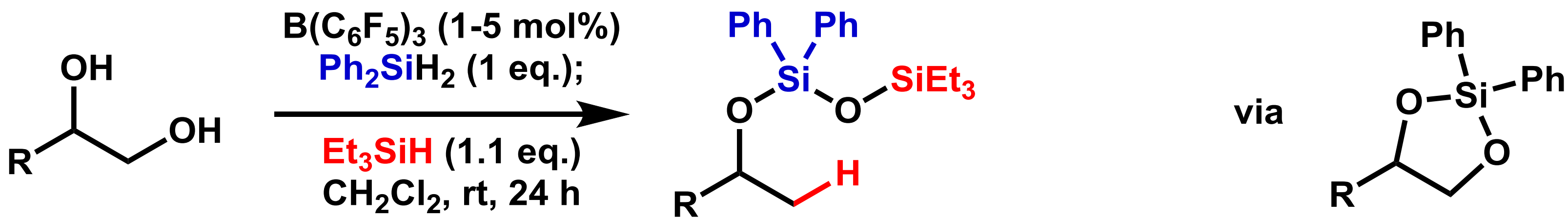


under developing
(in many cases: sp^2-X bond)

Appendix

Aliphatic C-O Bond Activation via Siloxane Intermediate

•primary position selective deoxygenation of terminal 1,2-diol

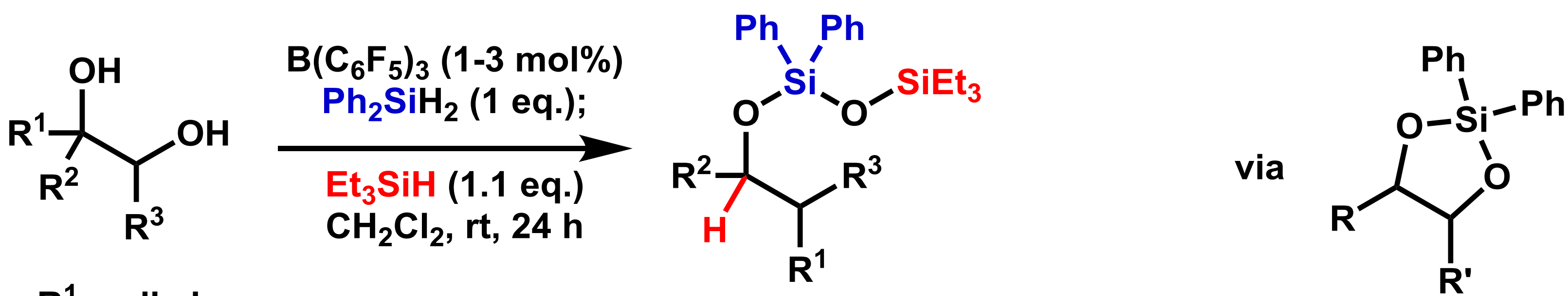


R = alkyl

11 examples
51-79% yield

Drosos, N.; Morandi, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 8814.
Cheng, G.-J.; Drosos, N.; Morandi, B.; Thiel, W. *ACS Catal.* **2018**, *8*, 1697.

•pinacol-type rearrangement

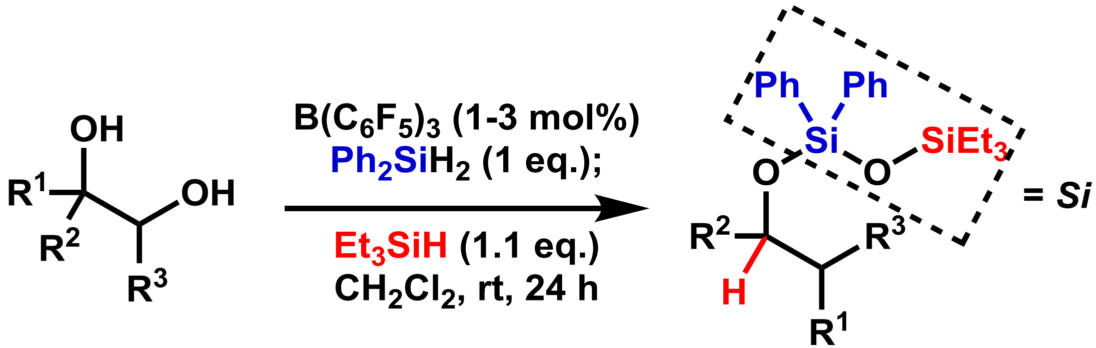


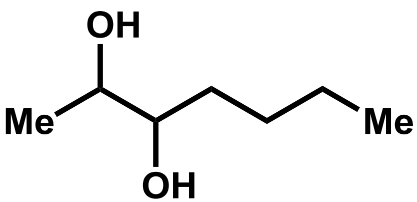
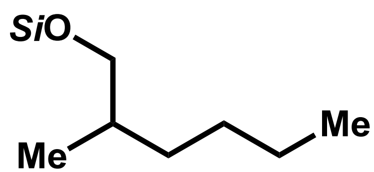
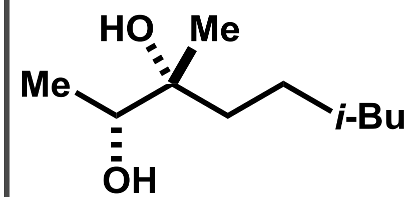
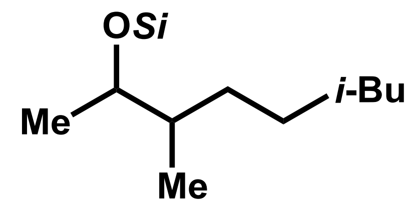
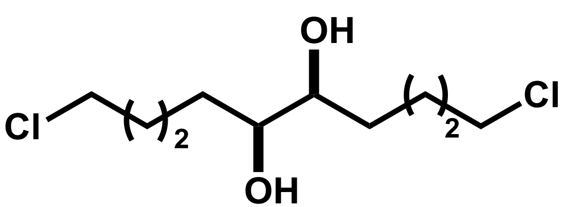
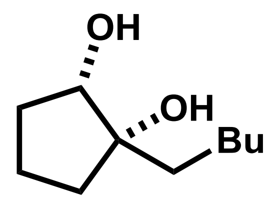
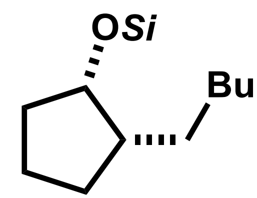
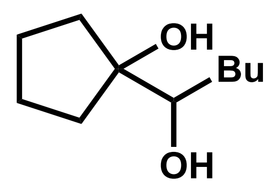
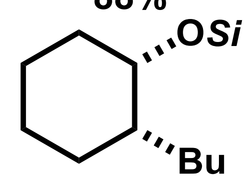
R^1 = alkyl
R^2 = H or alkyl

18 examples
39-91%

Drosos, N.; Cheng, G.-J.; Ozkal, E.; Cacherat, B.; Thiel, W.; Morandi, B. *Angew. Chem. Int. Ed.* **2017**, *56*, 13377.

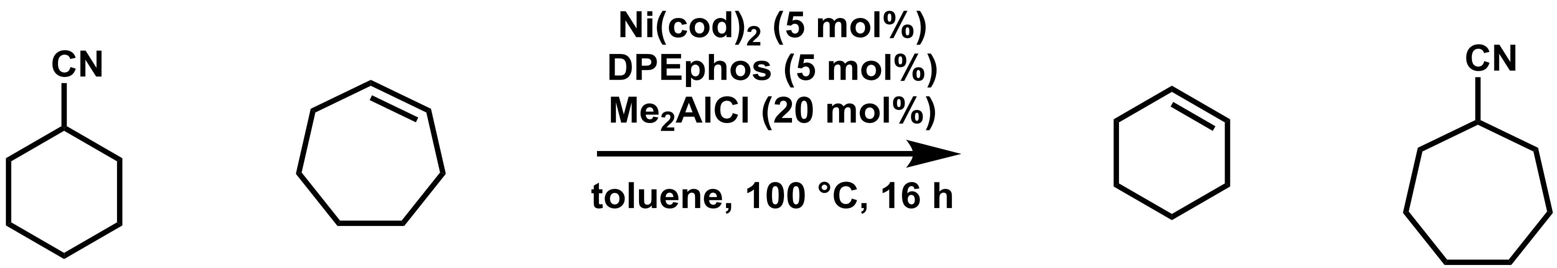
Substrate Scope



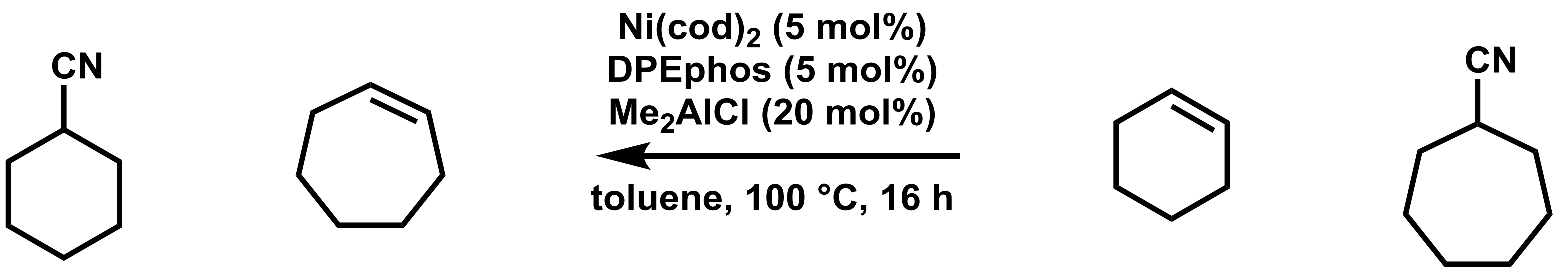
substrate	product	substrate	product
	 81% (from *syn* diol) 64% (from *anti* diol)		 82% (dr = 1:1)
	 64%		 88%
			 66%

Drosos, N.; Cheng, G.-J.; Ozkal, E.; Cacherat, B.; Thiel, W.; Morandi, B. *Angew. Chem. Int. Ed.* **2017**, *56*, 13377.

Confirmation of Reversible Reactions



before	0.50 mmol	0.50 mmol	0 mmol	0 mmol
after	0.26 mmol	0.38 mmol	0.24 mmol	0.14 mmol

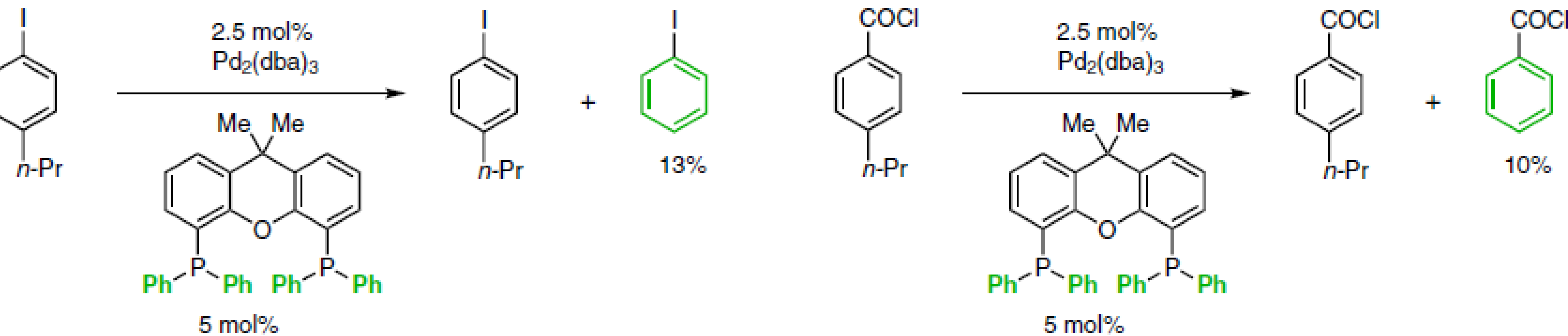


before	0 mmol	0 mmol	0.49 mmol	0.50 mmol
after	0.25 mmol	0.39 mmol	0.23 mmol	0.13 mmol

These reactions are reversible and thermodynamic equilibrium can be reached under these conditions.

Fang, X.; Yu, P.; Morandi, B. *Science* **2016**, *351*, 832.

b


I
n-Pr
2.5 mol%
Pd2(dba)3
Me Me
O
Ph P Ph Ph P Ph
5 mol%
I
n-Pr
+
I
13%
COCl
n-Pr
2.5 mol%
Pd2(dba)3
Me Me
O
Ph P Ph Ph P Ph
5 mol%
COCl
n-Pr
+
COCl
10%

c

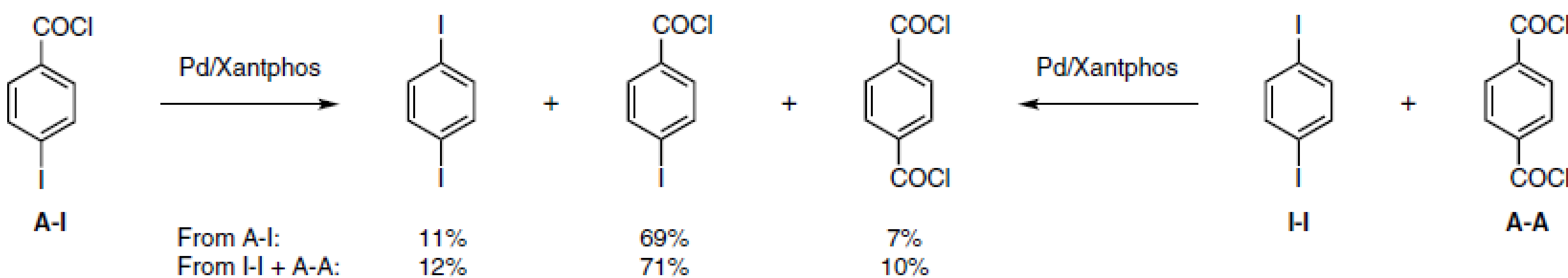
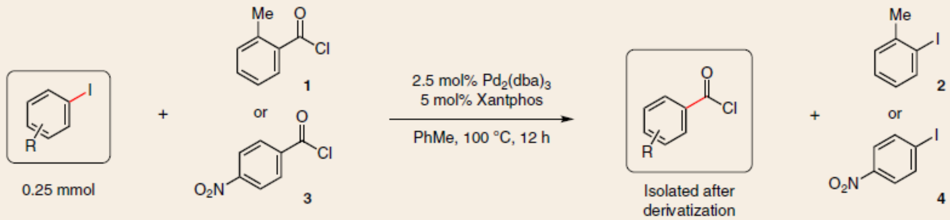
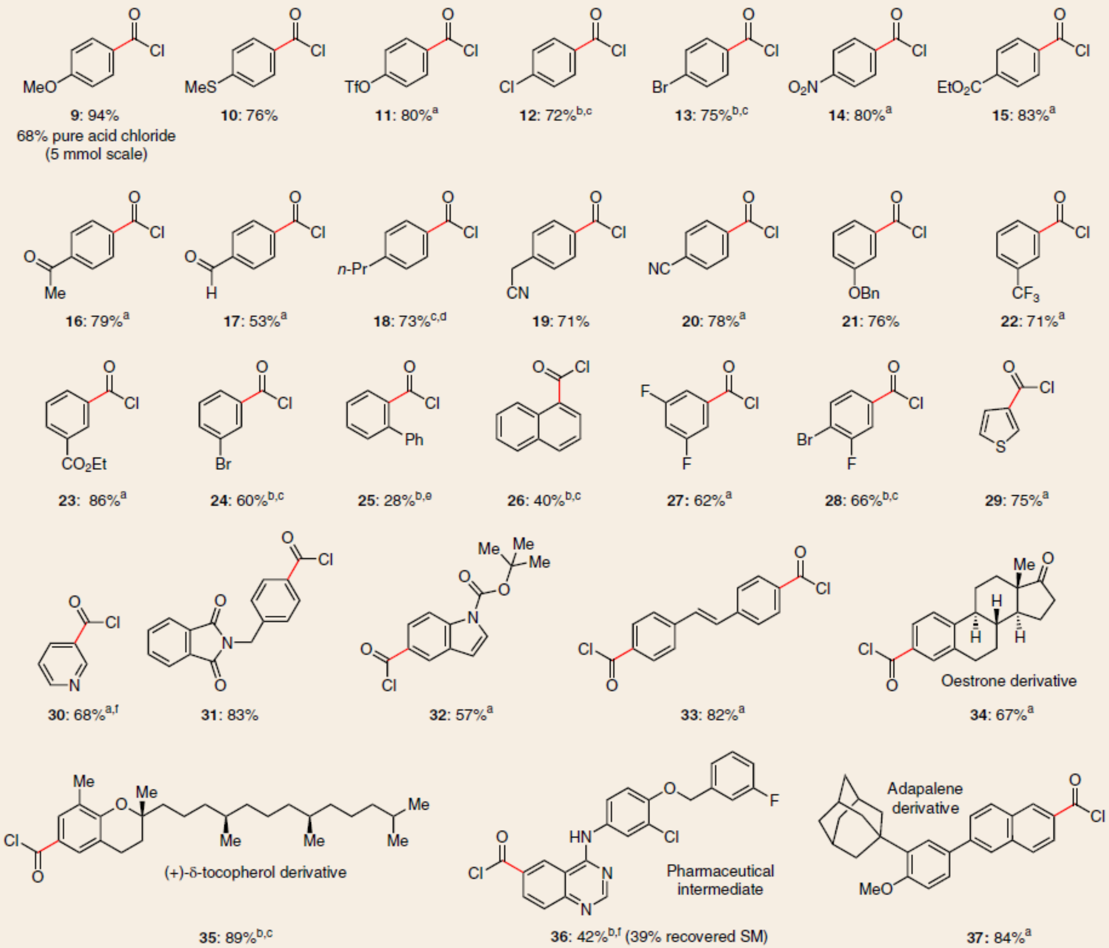

COCl
I
A-I
Pd/Xantphos
I
I
+
COCl
I
+
COCl
COCl
Pd/Xantphos
I
I
I-I
+
COCl
COCl
A-A
From A-I: 11% 69% 7%
From I-I + A-A: 12% 71% 10%

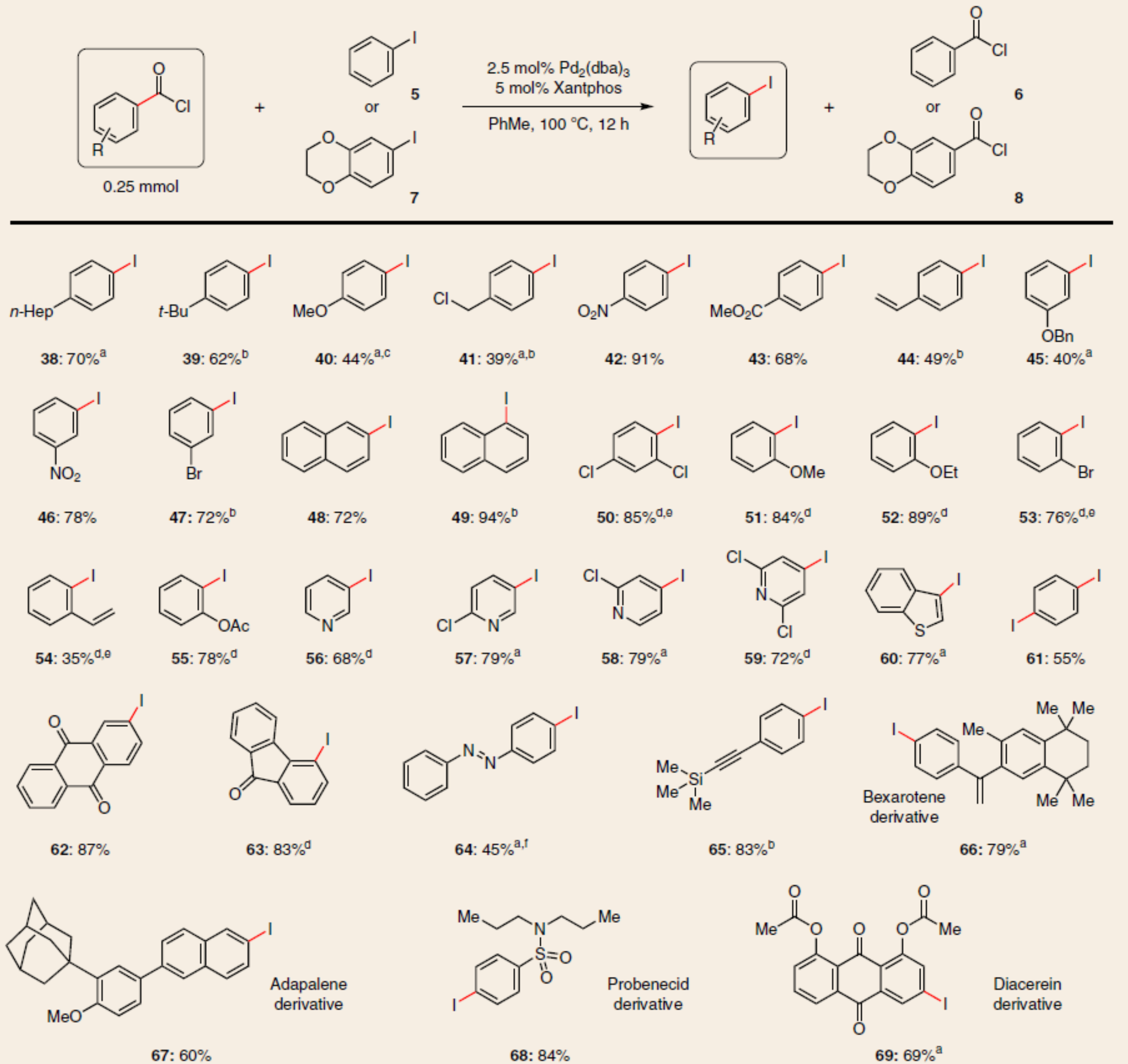
Table 1 | Substrate scope for the transformation of ArI into ArCOCl



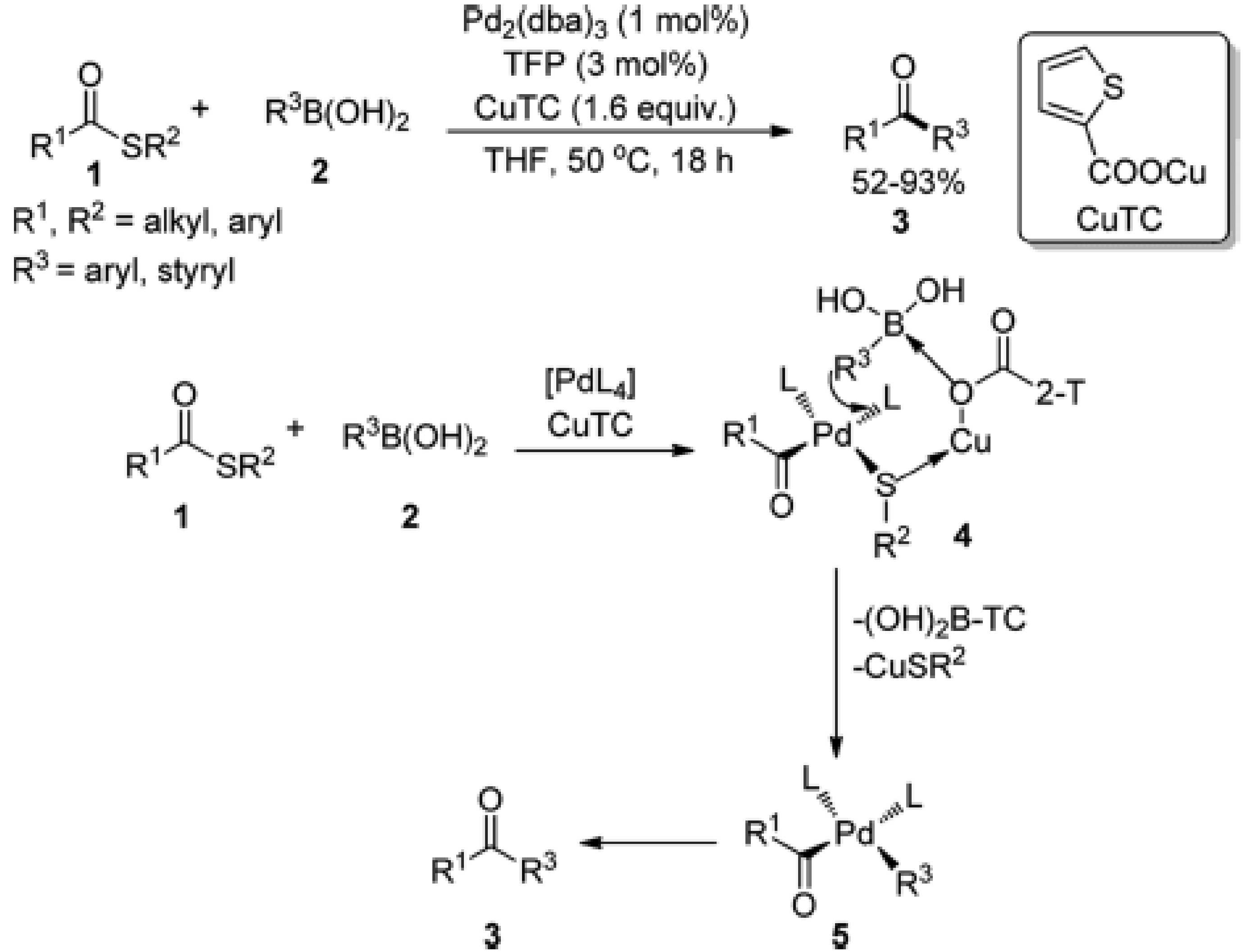


Yields (%) refer to isolated products after in situ derivatization of the ArCOCl product (Supplementary Section 9). Reaction conditions: ArI (0.25 mmol), **1** (1.5 equiv.), $Pd_2(dba)_3$ (2.5 mol%), Xantphos (5 mol%), toluene, 100 °C, 12 h. [a]**1** (3 equiv.). [b]**3** (1.3 equiv,). [c]125 °C. [d]**3** (1.1 equiv.). [e]Mesitylene, 180 °C. [f]o-xylene, 150 °C. For **9**, a pure acid chloride was isolated on a larger scale. TfO, trifluoromethanesulfonate; Bn, benzyl.

Table 2 | Substrate scope for the transformation of ArCOCl into ArI



All yields are isolated yields (%). Reaction conditions: ArCOCl (0.25 mmol), **5** (5 equiv.), $Pd_2(dba)_3$ (2.5 mol%), Xantphos (5 mol%), toluene, 100 °C, 12 h. [a]125 °C. [b]**7** (2 equiv.). [c]**7** (3 equiv.). [d]o-xylene, 150 °C. [e]**5** (2 equiv.). [f]**5** (10 equiv.). For **56**, a HCl salt of the substrate was used with DABCO (1,4-diazabicyclo[2.2.2]octane (0.5 equiv.)).


Pd2(dba)3 (1 mol%)
TFP (3 mol%)
CuTC (1.6 equiv.)
THF, 50 °C, 18 h
R1, R2 = alkyl, aryl
R3 = aryl, styryl
52-93%
COOCu
CuTC
[PdL4]
CuTC
-(OH)2B-TC
-CuSR2