Breaking the Base Barrier

-Rational design of Pd and Ni catalyst for the efficient C-N bond formation reaction-

2020. 4. 25. Literature Seminar

D2 Tsukasa Shimakawa

Contents

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Article

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Breaking the Base Barrier: An Electron-Deficient Palladium Catalyst Enables the Use of a Common Soluble Base in C−N Coupling

Joseph M. Dennis,[†] Nicholas A. White,[†] Richard Y. Liu, and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

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Article

The Quest for the Ideal Base: Rational Design of a Nickel Precatalyst Enables Mild, Homogeneous C−N Cross-Coupling

Richard Y. Liu,[†] Joseph M. Dennis,[†] and Stephen L. Buchwald*

Prof. Stephen, L. Buchwald / Introduction

Education and academic career:

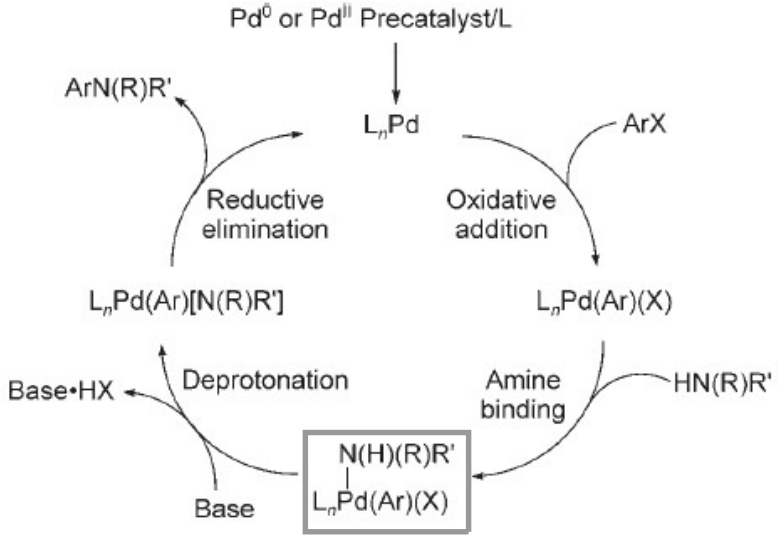
1977. B.S.c @Brown University (Parker, K. A. and Cane, D. E.)
1982. Ph. D. @Harvard University (Prof. Knowles, J. R.)
1982-1984. Posdoc, @Caltech (Prof. Grubbs, R. H.)
1984-1993 Assistant and Associate professor, @MIT
1993- Professor, @MIT

Research area:

1. Cross-coupling 2. Bioconjugation
3. Continuous flow synthesis 4. Copper-hydride chemistry

Anionic nucleophilic base
NaO*t*-Bu, $LiN(TMS)_2$,,,
1. incompatible with many functional group (CF_3, halogen, etc)

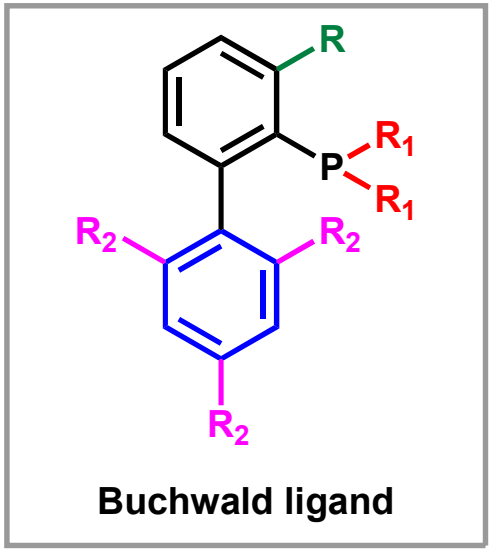
Inorganic insoluble base
K_3PO_4, K_2CO_3, Cs_2CO_3,,,
1. difficult to stir onscale
2. particle size affects reactivity



O Design of ligand and Pd precatalyst → well studied
X Require strong base → longstanding problem

a) https://chemistry-buchwald.mit.edu/ b) Surry, D. S. and Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27.
c) Surry, D. S. and Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.

Buchwald ligand (1)



Buchwald ligand

Pd^0–L
monoligated
12e⁻ Pd(0)

active specie

large R_1 and R_2

L—Pd^0—L
14e⁻ Pd(0)

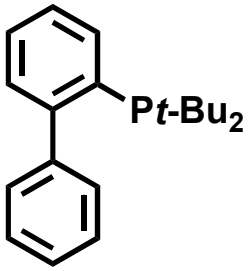
large R_1

R_1: e⁻ donation

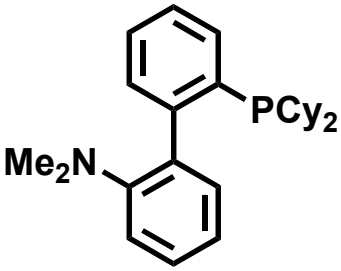
Ar
L-Pd^{II}–X

amine coordination ; deprotonation

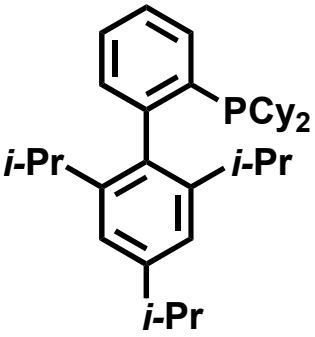
Ar
R_1
L—Pd^{II}–N
R_2



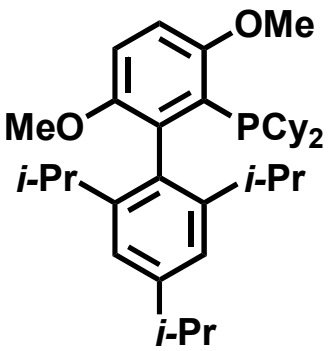
JohnPhos



DavePhos



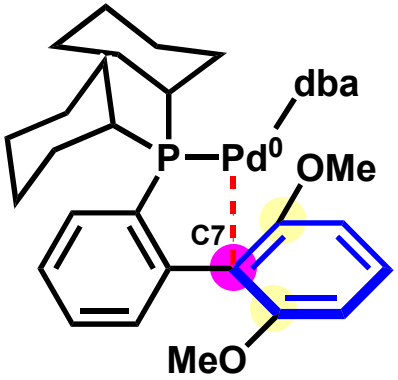
XPhos



BrettPhos

Surry, D. S. and Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.
Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem*. **2003**, *68*, 2861.

Buchwald ligand (2) -Pd-arene interaction-



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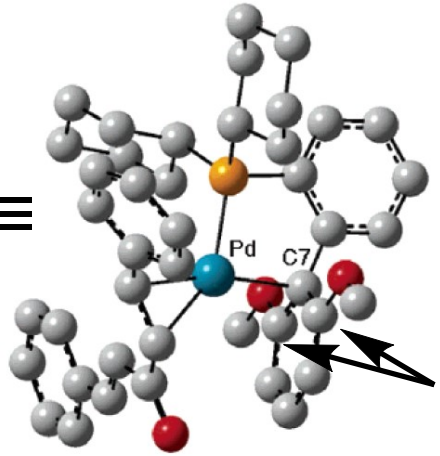
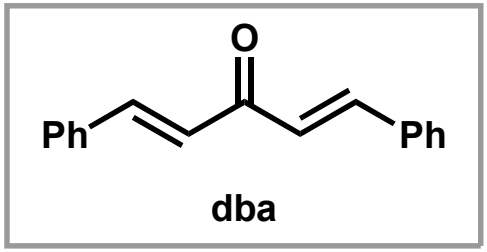
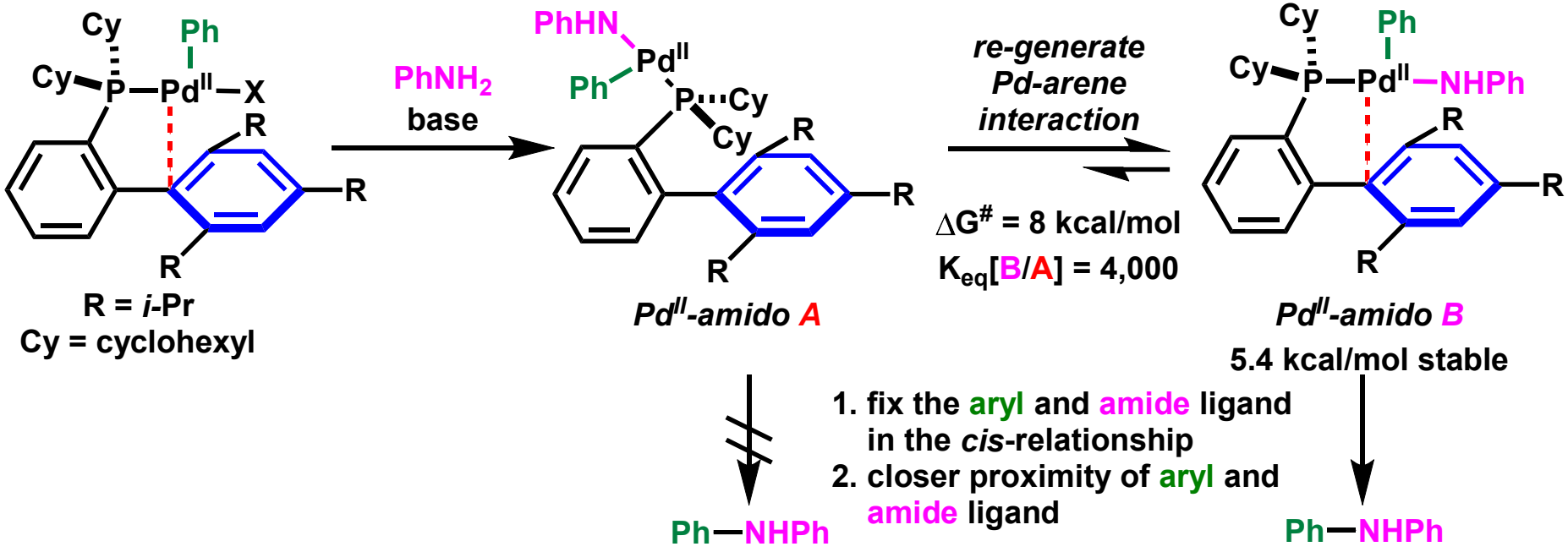


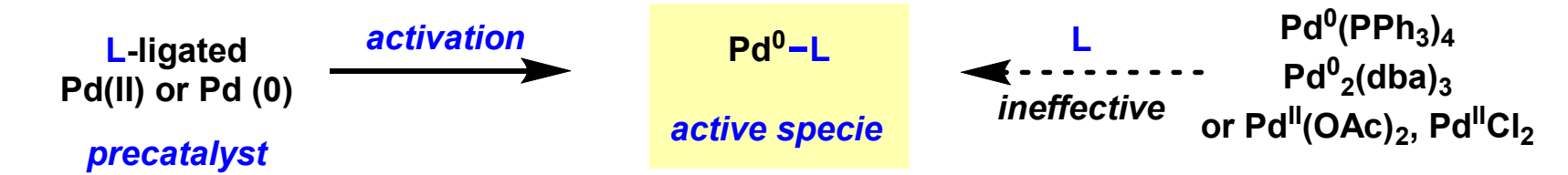
Pd-C7: 2.374 Å
Pd-*ortho carbon:* 2.696, 2.788 Å
→ donation to Pd (η1 interaction)

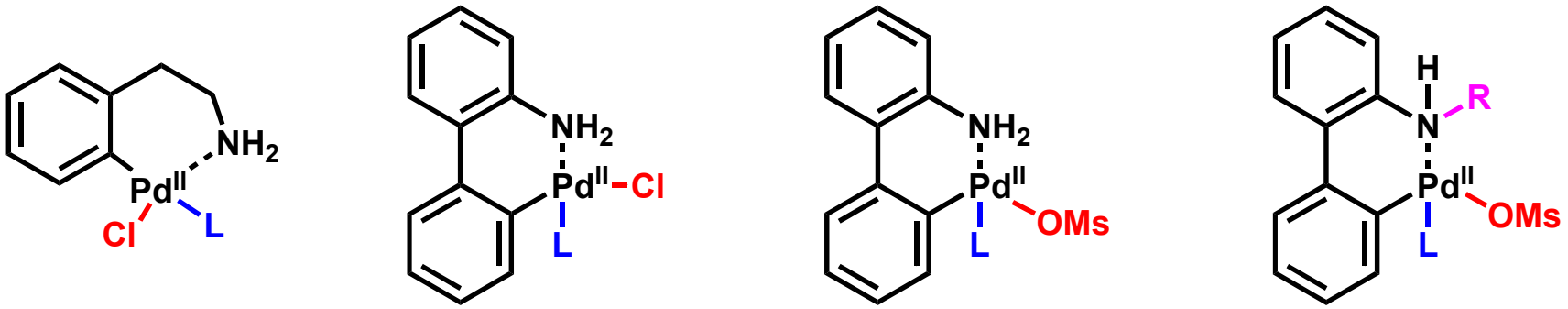




Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.
Barder, T. E. and Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 12003.

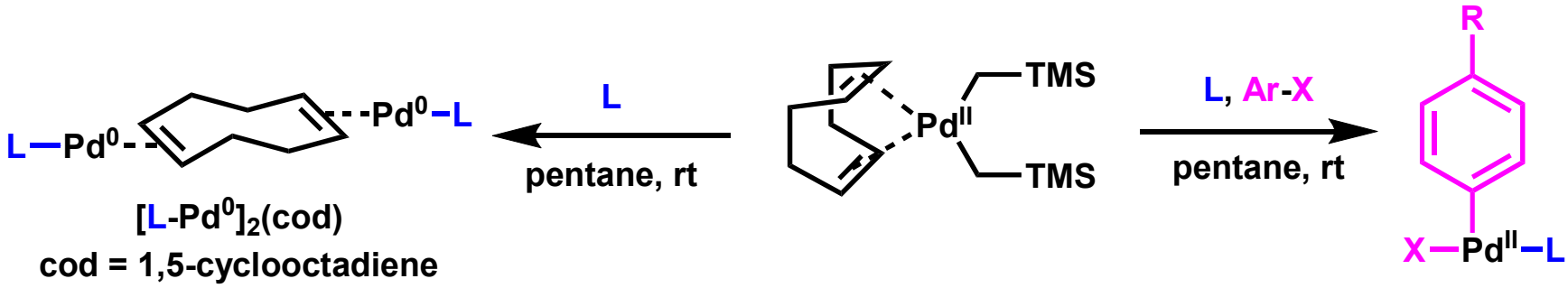
Pd precatalyst from Buchwald's group





♣ electron deficient Pd center
♣ dissociation of OMs ligand

R = Me or Ph



a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686. b) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci*. **2013**, *4*, 916. c) Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. *J. Org. Chem*. **2014**, *79*, 4161. d) Lee, H. G.; Milner, P. J.; Buchwald, S. L. *Org. Lett*. **2013**, *15*, 5602. e) Lee, H. G.; Milner, P. J.; Colvin, M. T.; Andreas, L.; Buchwald, S. L. *Inorg. Chim. Acta*. **2014**, *422*, 188. f) Ingoglia, B. T. and Buchwald, S. L. *Org. Lett*. **2017**, *19*, 2853.

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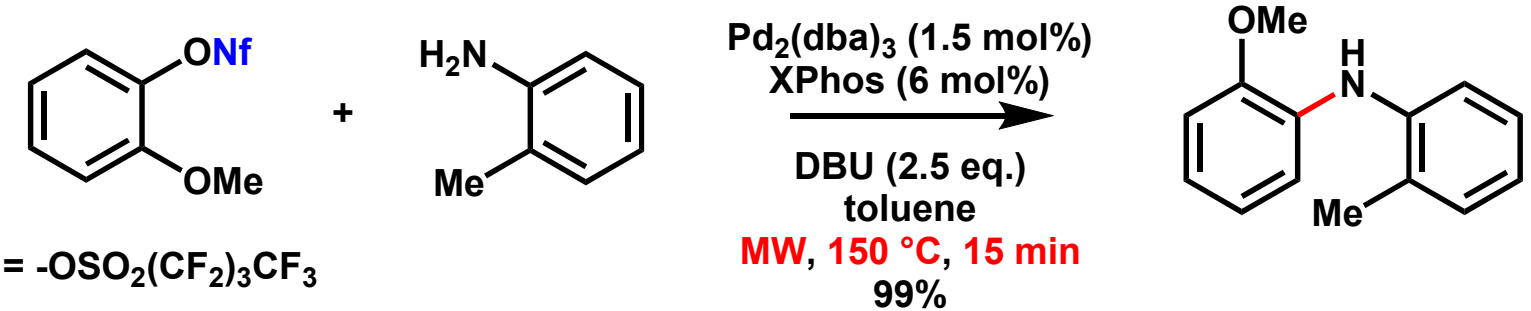
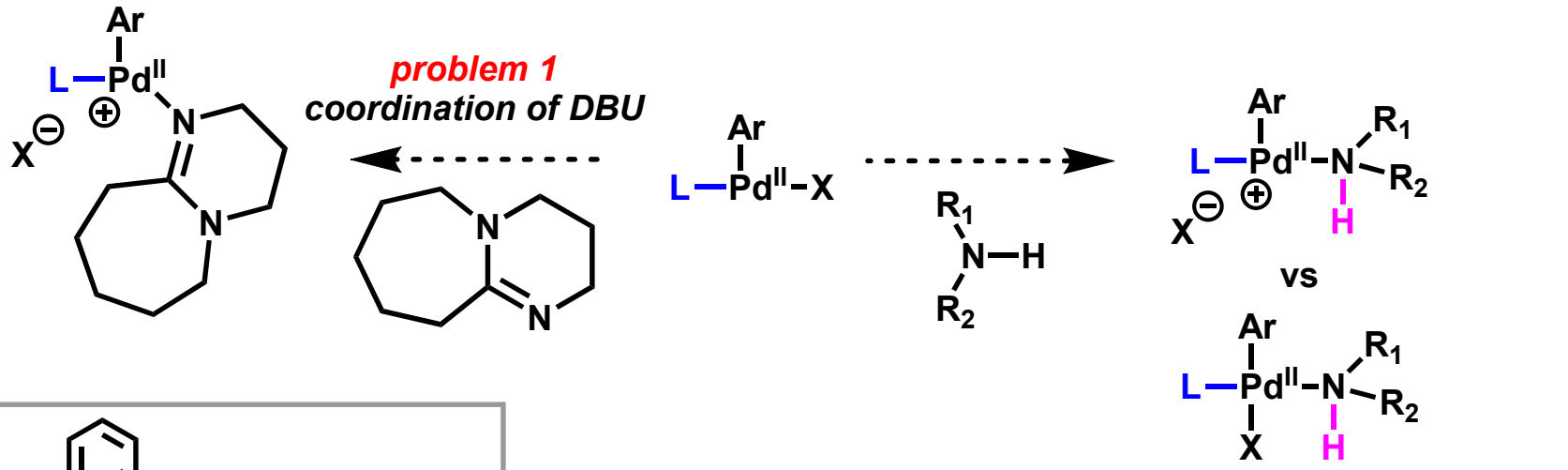
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Base barrier and assumed problems



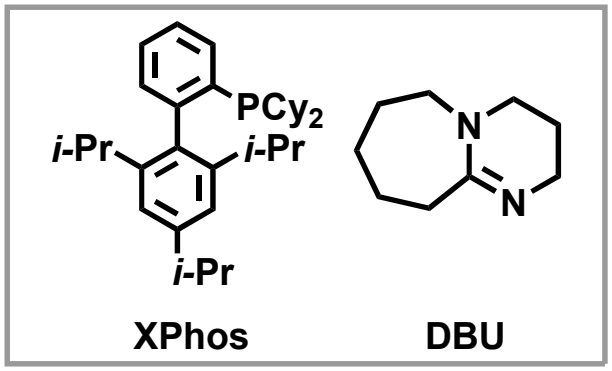
Nf = $-OSO_2(CF_2)_3CF_3$



problem 2

pK_{BH+} of N-H

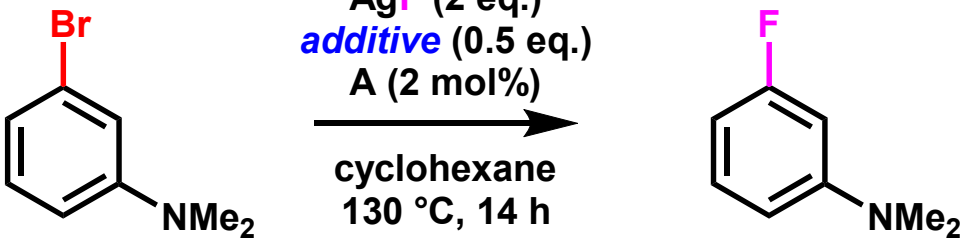
pK_{BH+} : alkyl amine > aryl amine



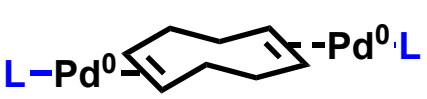
1. Require **Nf** group
2. Harsh condition
3. 1° aryl amine

Tundel, R. E.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2006**, *71*, 430.
Norrby, P-O. et al. *J. Org. Chem.* **2014**, *79*, 11961.

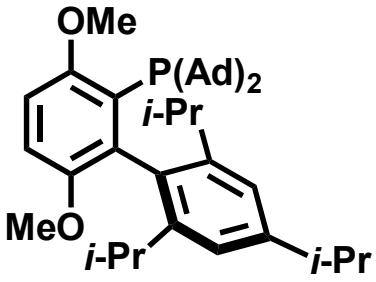
Base effect in Pd catalyzed fluorination



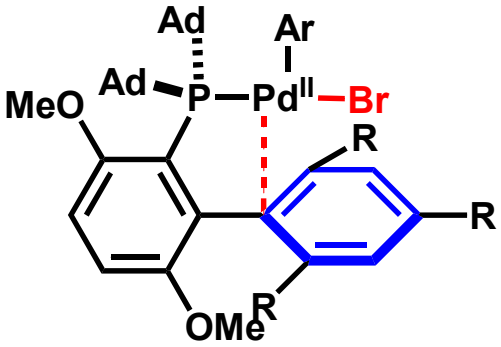
entry	*additive*	NMR yield
1	none	0%
2	K_2CO_3	11%
3	CsF	65%
4	KF	71%

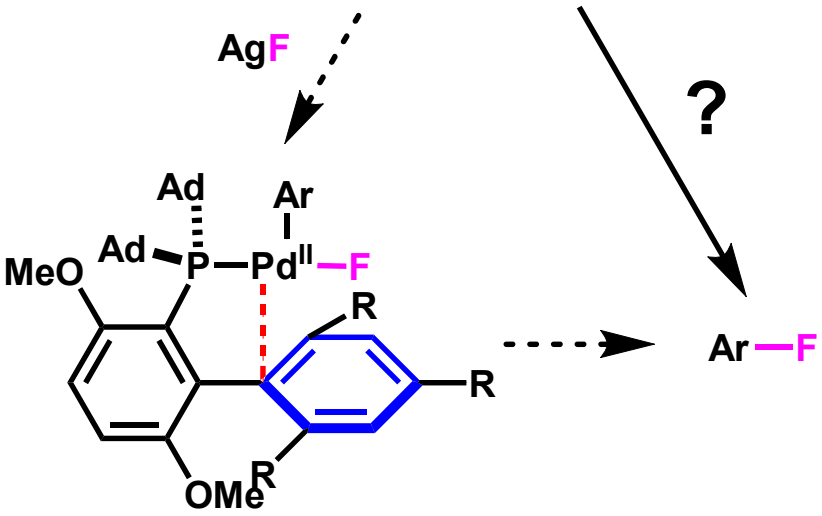


A
L = AdBrettPhos



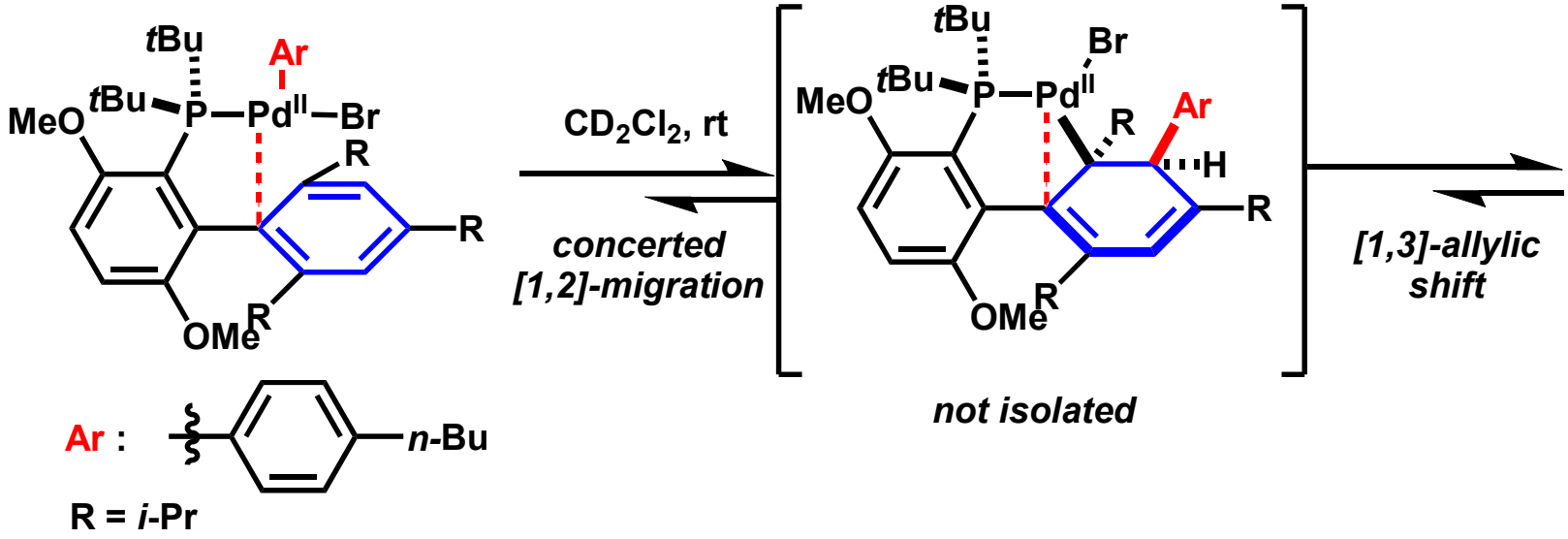
AdBrettPhos

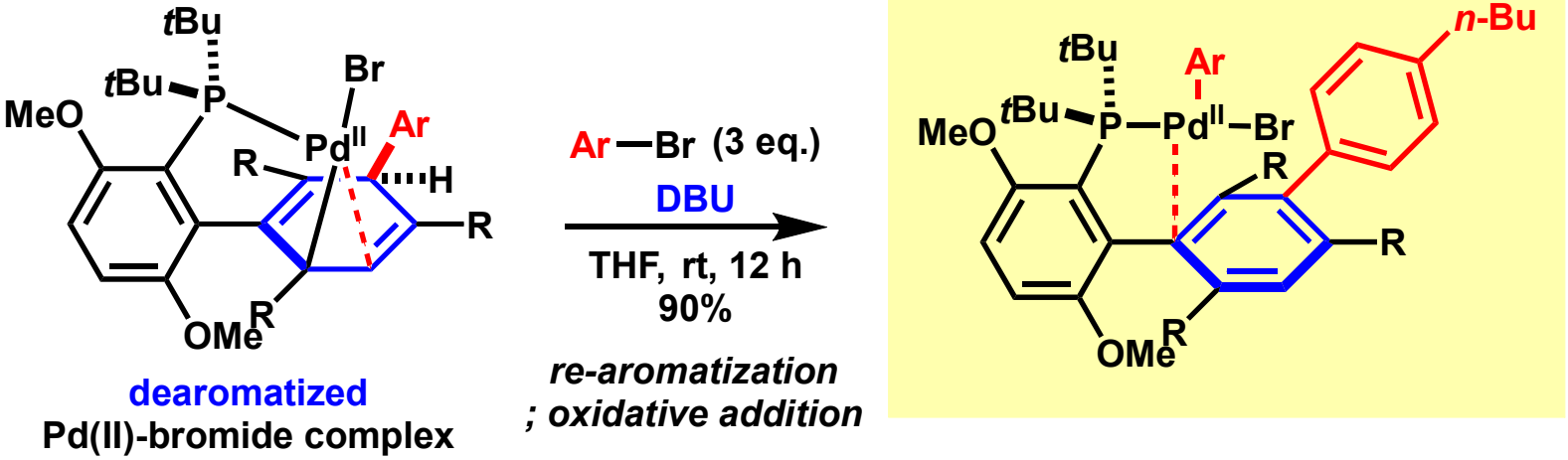




R = *i*-Pr

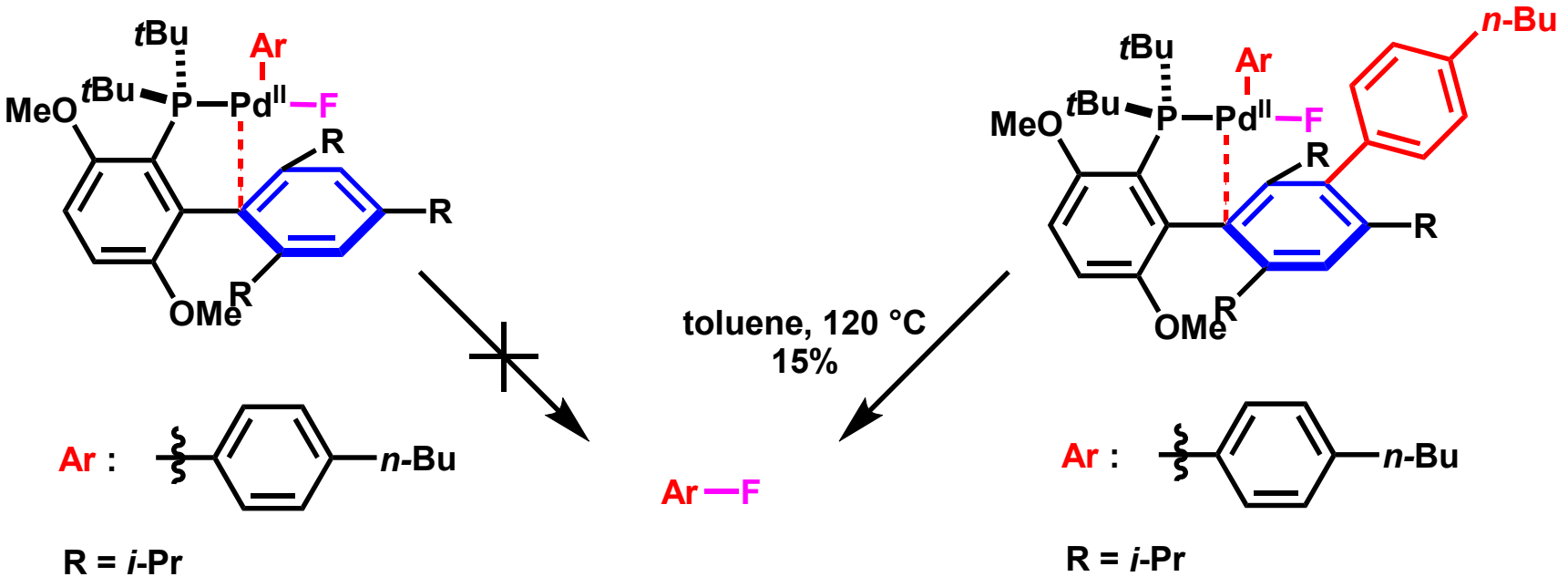
In situ modification of the catalyst

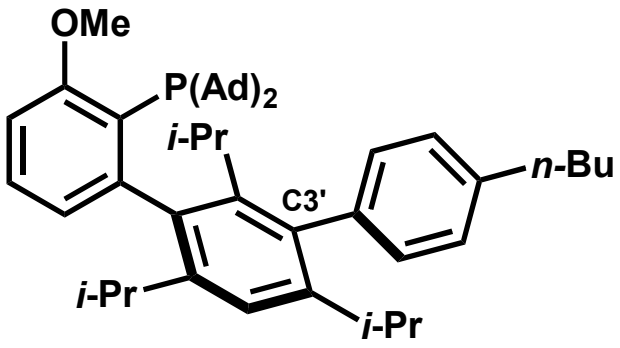




Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 18106.

AlPhos -efficient Buchwald ligand-



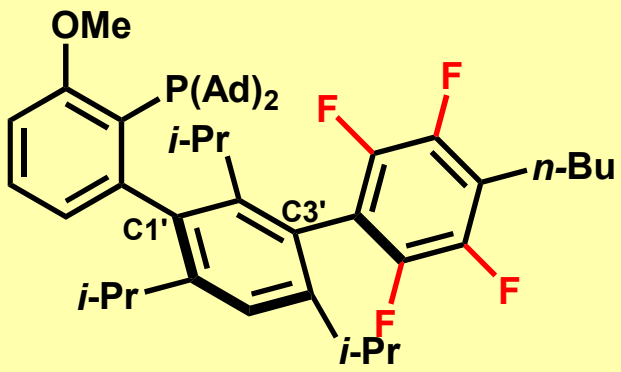


HGPhos

electron-withdrawing group at C3'

↓ Pd-arene interaction

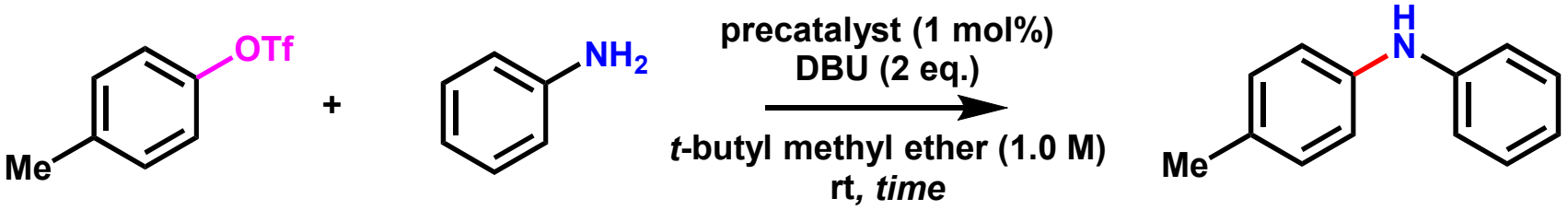
↑ three coordinate character



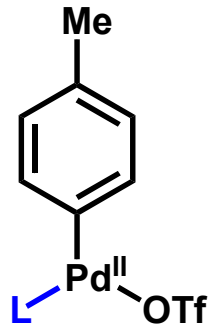
AlPhos

a) Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**,*133*, 18106. b) Sather, A. C.; Lee, H. G.; De La Rosa, V. Y.; Yang, Y.; Muller, P.; Buchwald, S. L. *J. Am. Chem. Soc*. **2015**, *137*, 13433.

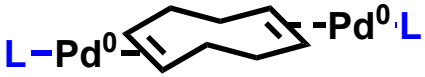
Screening of the catalyst



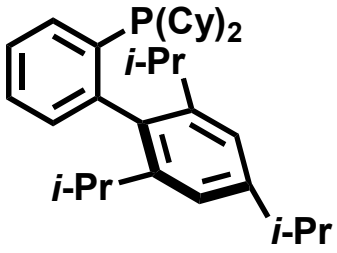
entry	precatalyst	*time*	NMR yield
1	P1 (L = XPhos)	20 min	0%
2	P2 (L = *t*-BuXPhos)	20 min	30%
3	P3 (L =AlPhos)	20 min	99%
4	P4 (L =AlPhos)	3 h	99%



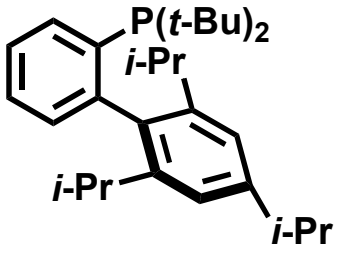
P1~P3



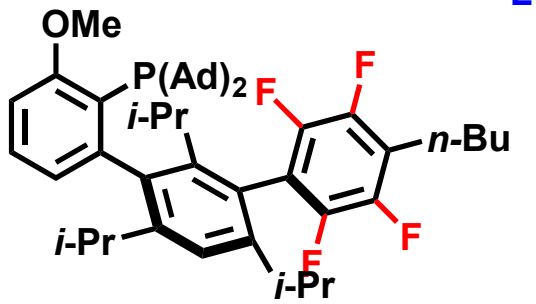
P4



XPhos

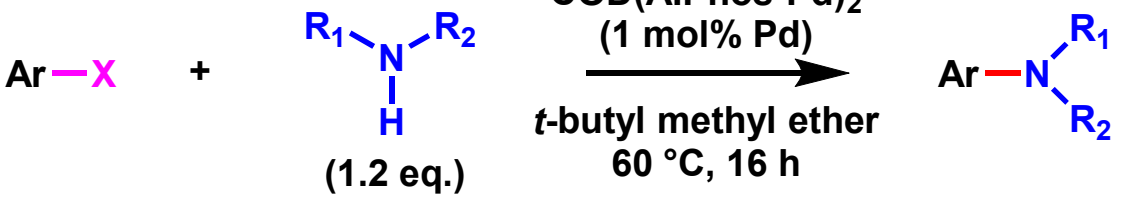


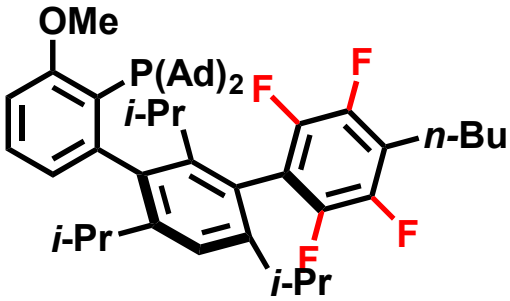
t-BuXPhos



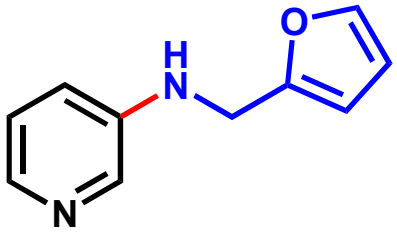
AlPhos

Substrate scope

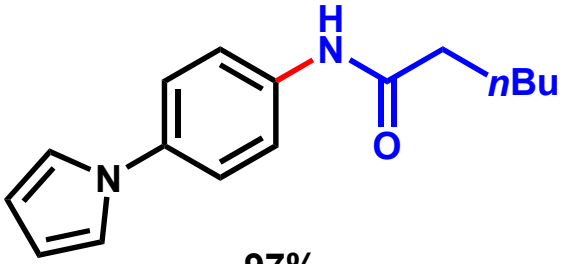




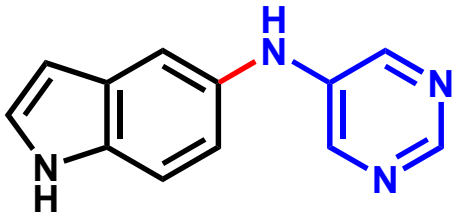
AlPhos



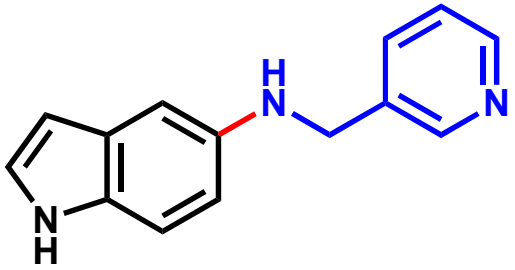
97%
X = OTf



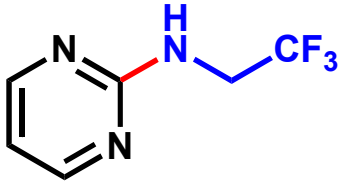
97%
X = OTf



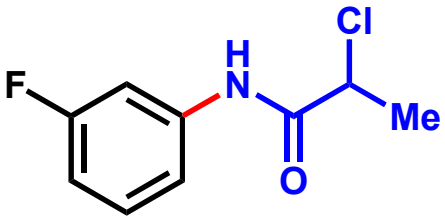
99%
X = Br



97% (DBU: 4 eq., Pd: 2 mol%)
X = Br



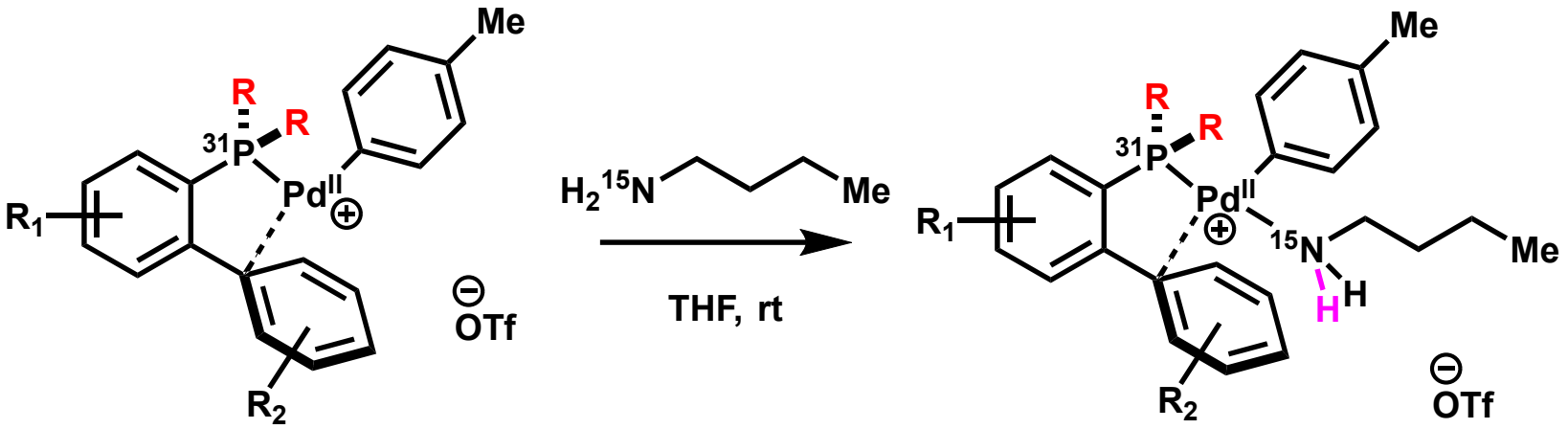
74% (rt)
X = Br



90% (rt)
X = OTf

Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2018**, *140*, 4721.

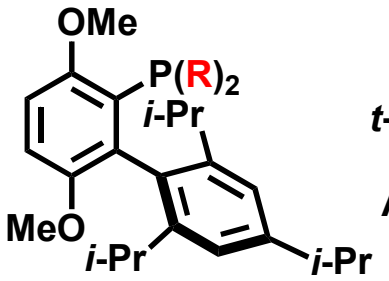
Correlation between Buchwald ligand and Pd-charge



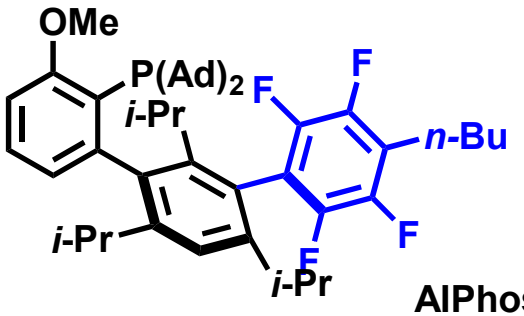
entry	ligand	R	Hirshfeld charge at Pd[a)]
1	Brettphos	Cy	186 x 10^{-3} e
2	*t*-BuBrettPhos	*t*-Bu	191 x 10^{-3} e
3	AdBrettPhos	Ad	195 x 10^{-3} e
4	AlPhos	Ad	203 x 10^{-3} e

a) B3LYP/6-31G(d)-SDD/SMD(THF)

1. Large R group and 2. electron-deficient aromatic ring increases the acidity of N-H proton



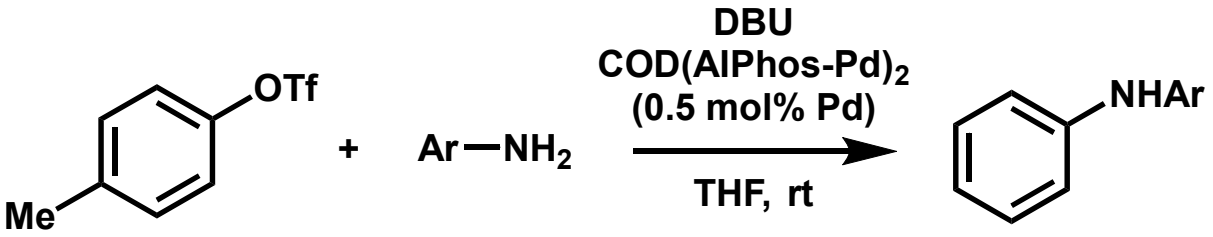
BrettPhos (R = Cy)
t-BuBrettPhos (R = *t*-Bu)
AdBrettPhos (R = Ad)



AlPhos

Norrby, P-O. et al. *J. Org. Chem.* **2014**, *79*, 11961.
Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2018**, *140*, 4721.

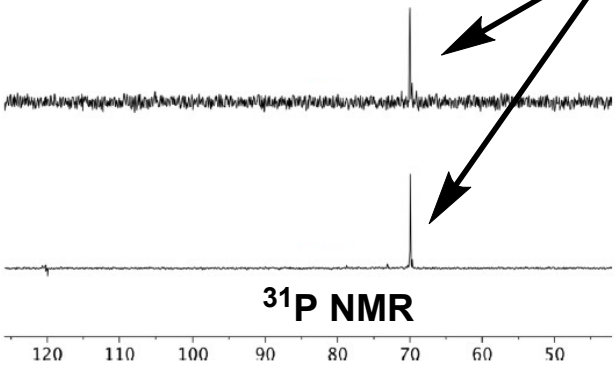
Mechanistic study



the same peak !

(a) Ar-OTf + Pd precat. + Ph-NH_2 + DBU

(b) Ar-OTf + Pd precat. + DBU

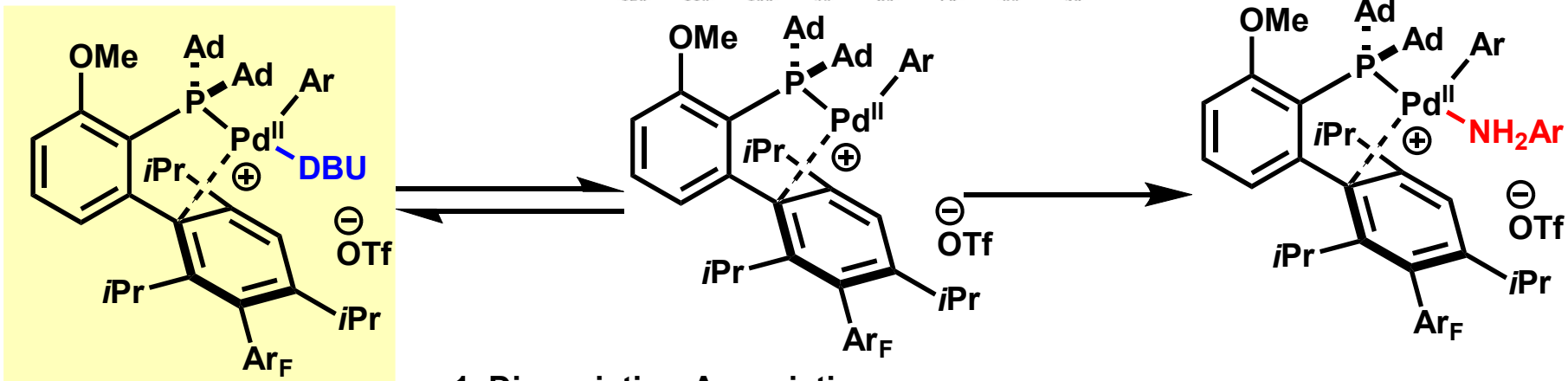


Kinetic data

zeroth order on [Ar-OTf]

positive first order on [Ar-NH_2]

negative first order on [DBU]



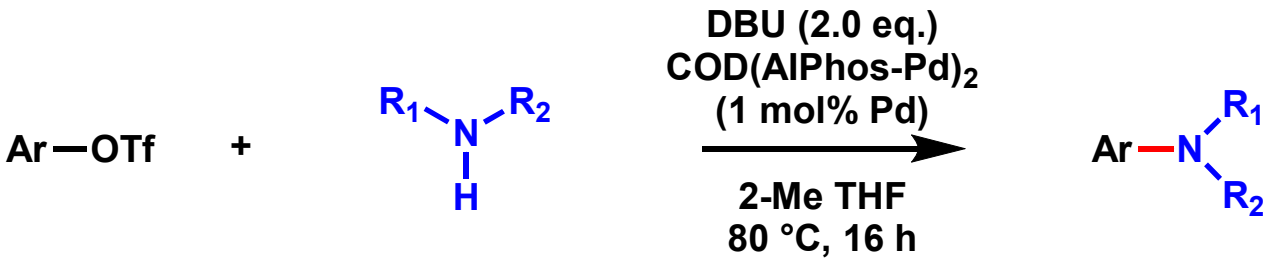
resting state

= species present in the highest concentration

1. Dissociation-Association
2. Rate Limiting Steps involves ligand substitution

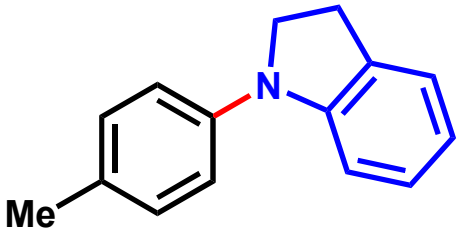
Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. *ACS. Catal*. **2019**, *9*, 3822.
Norrby, P-O. et al. *J. Org. Chem.* **2014**, *79*, 11961.

Enhanced reactivity



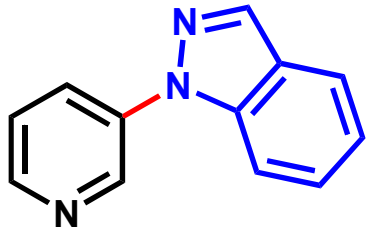
A: DBU was added at once

B: DBU was slowly added over 12 h



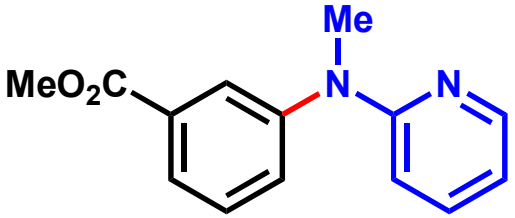
10% (A, 1.2 eq. of DBU, 60 °C)

99% (B, 60 °C)



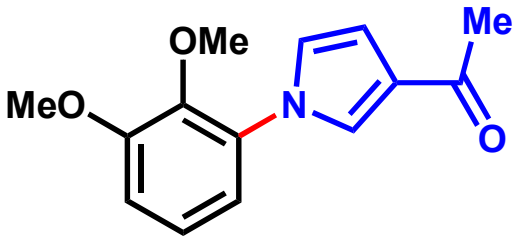
46% (A)

98% (B)



11% (A)

69% (B)



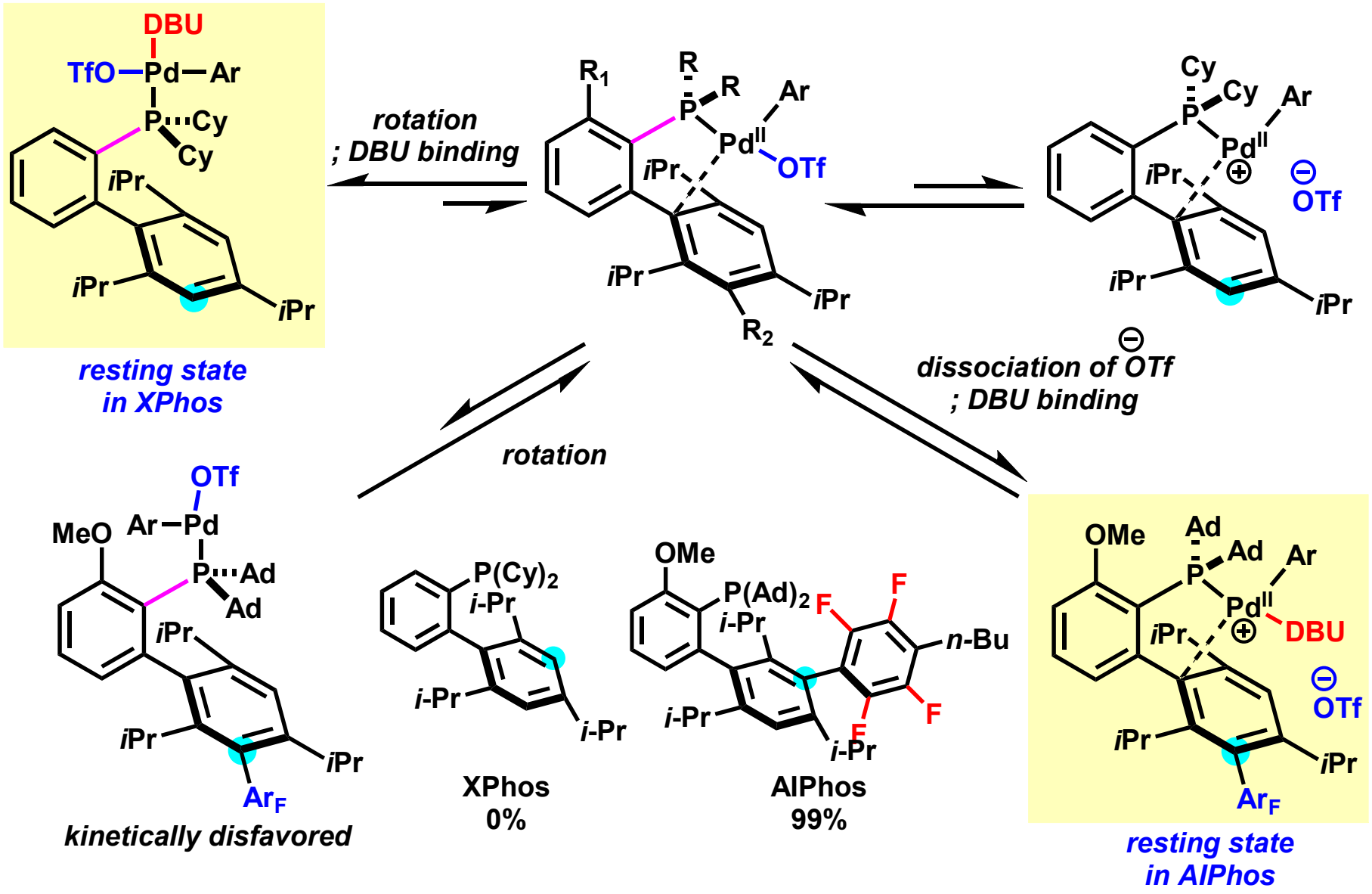
41% (A)

96% (B)

realize the coupling with 2° aryl amine

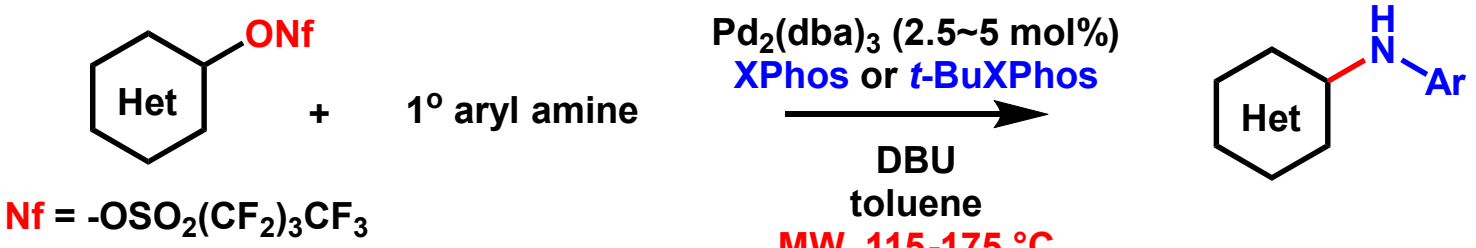
Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. *ACS. Catal*. **2019**, *9*, 3822.

The role of C3' substituent in AlPhos



Kim, S-T.; Pudasaini, B.; Baik, M-H. *ACS. Catal.* **2019**, *9*, 6851.
Barder, T. E. and Buchwald, S. L. *J. Am. Chem. Soc*. **2007**, *129*, 12003.

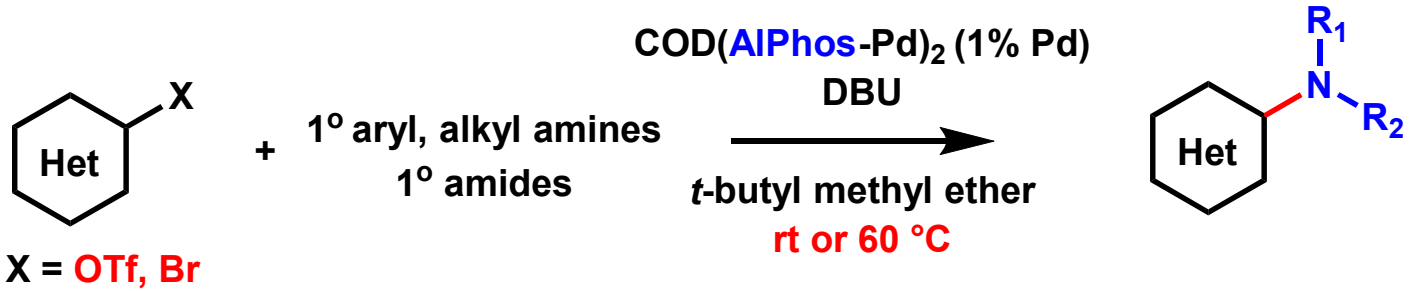
Short summary



rational modification of Buchwald ligand

1. large alkyl group at phosphine
2. substituent at C3'

1'. generation of cationic Pd^{II}-amine complex
2'. DBU/amine substitution



mechanistic investigation

elucidation of the resting state

slow addition of DBU enhanced the reactivity

O coupling with 2° aryl amine

a) Tundel, R. E.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2006**, *71*, 430. b) Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2018**, *140*, 4721. c)Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. *ACS. Catal*. **2019**, *9*, 3822.

Contents

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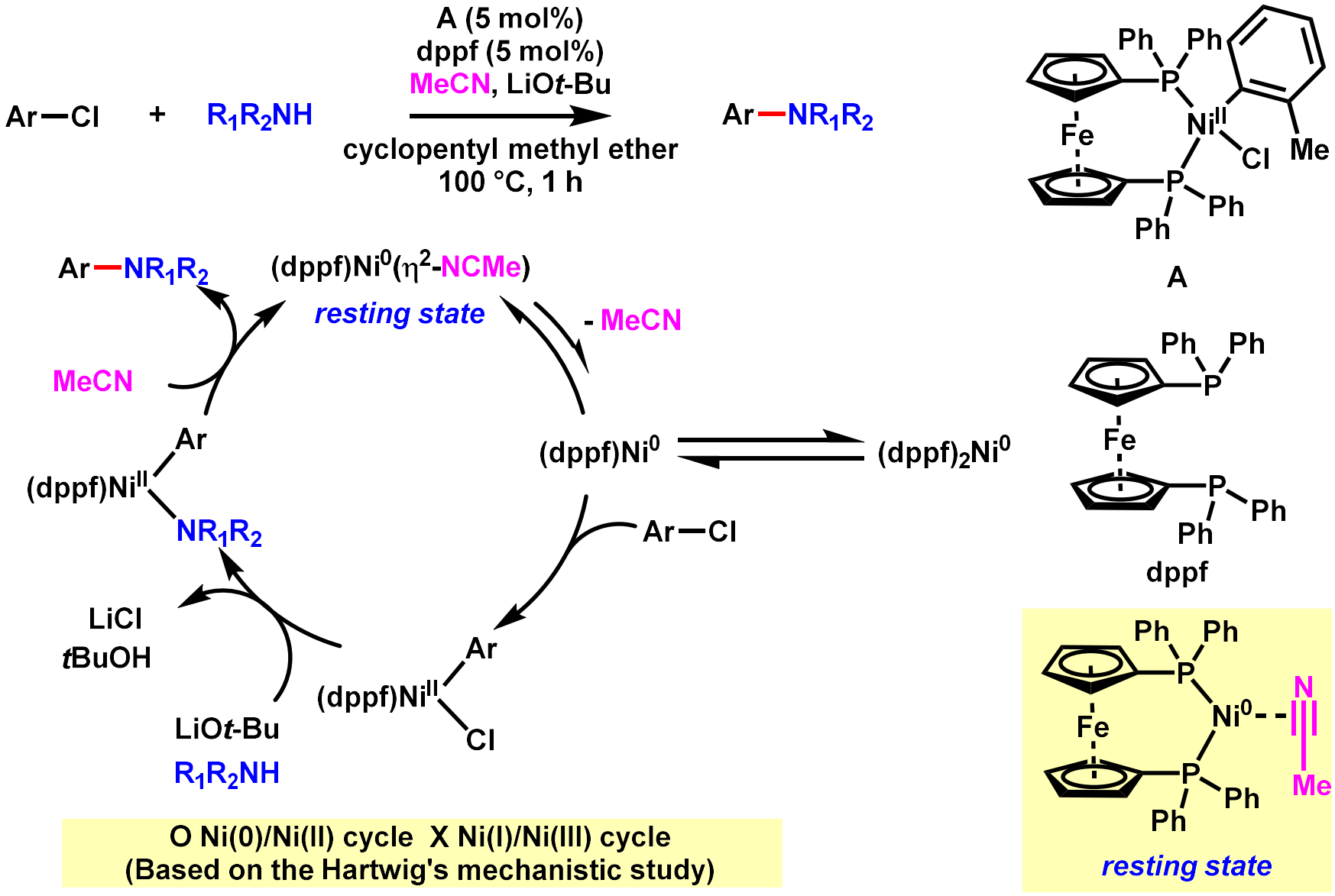
Article

The Quest for the Ideal Base: Rational Design of a Nickel Precatalyst Enables Mild, Homogeneous C–N Cross-Coupling

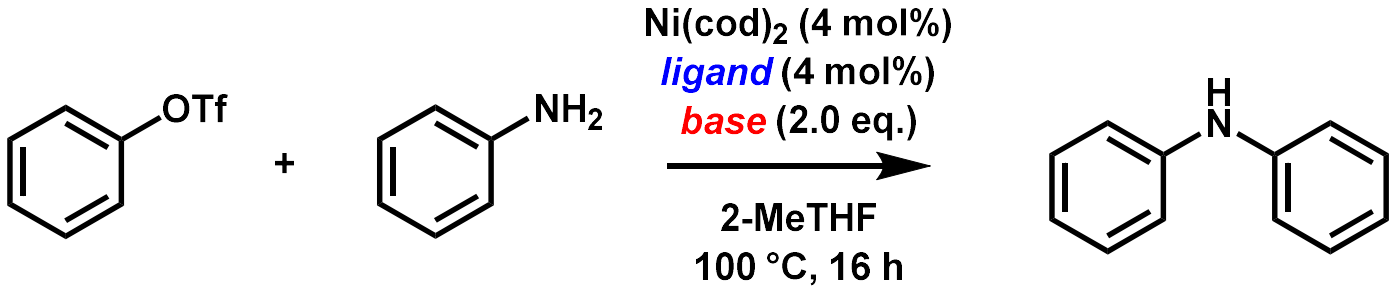
Richard Y. Liu,[†] Joseph M. Dennis,[†] and Stephen L. Buchwald*

Previous results in Buchwald's group

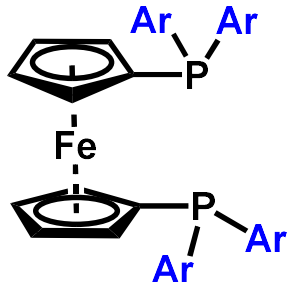


a) Park, M. H.; Teverovskiy, G.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 220. b) Ge, S. and Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 16330. c) Ge, S.; Green, R. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 1617.

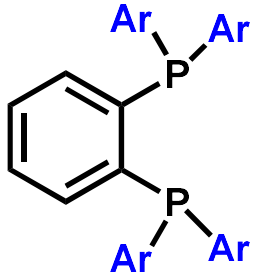
Initial attempts for Ni catalyzed C-N coupling



entry	*ligand*	*base*	GC yield
1	dppf	Et_3N	6%
2	$[CF_3]_4$-dppf	Et_3N	32%
3	$[CF_3]_8$-dppf	Et_3N	94%
4	$[CF_3]_8$-dppbz	Et_3N	23%
5	$[CF_3]_8$-dppf	*i*-Pr_2NEt	87%
6	$[CF_3]_8$-dppf	DBU	trace



dppf: Ar = Ph
$[CF_3]_4$-dppf: Ar = 4-CF_3
$[CF_3]_8$-dppf: Ar = 3,5-CF_3

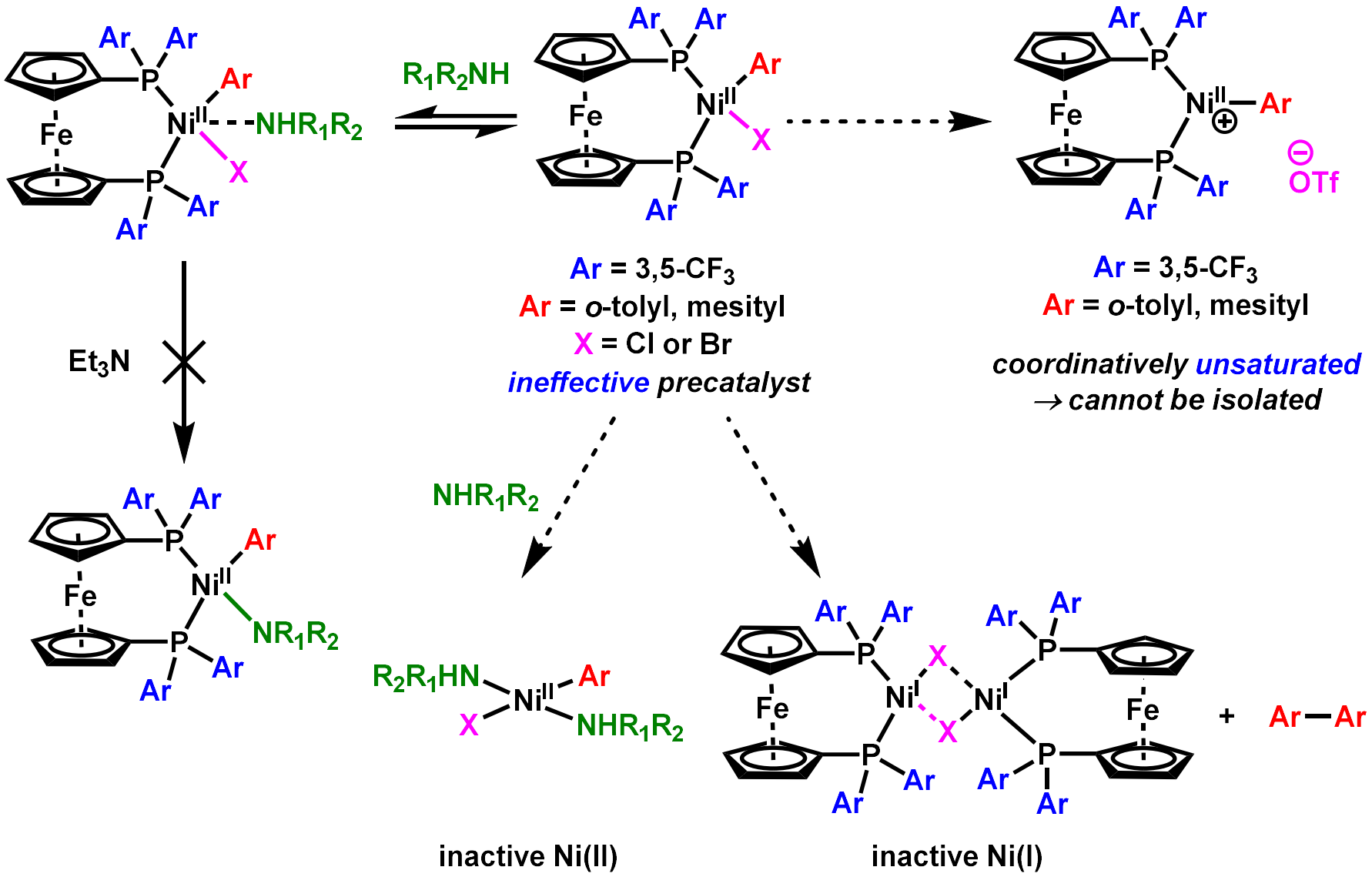


dppbz: Ar = Ph
$[CF_3]_8$-dppbz
: Ar = 3,5-CF_3

Key structure for the reaction
1. ferrocene backbone 2. electron-deficent Ar group

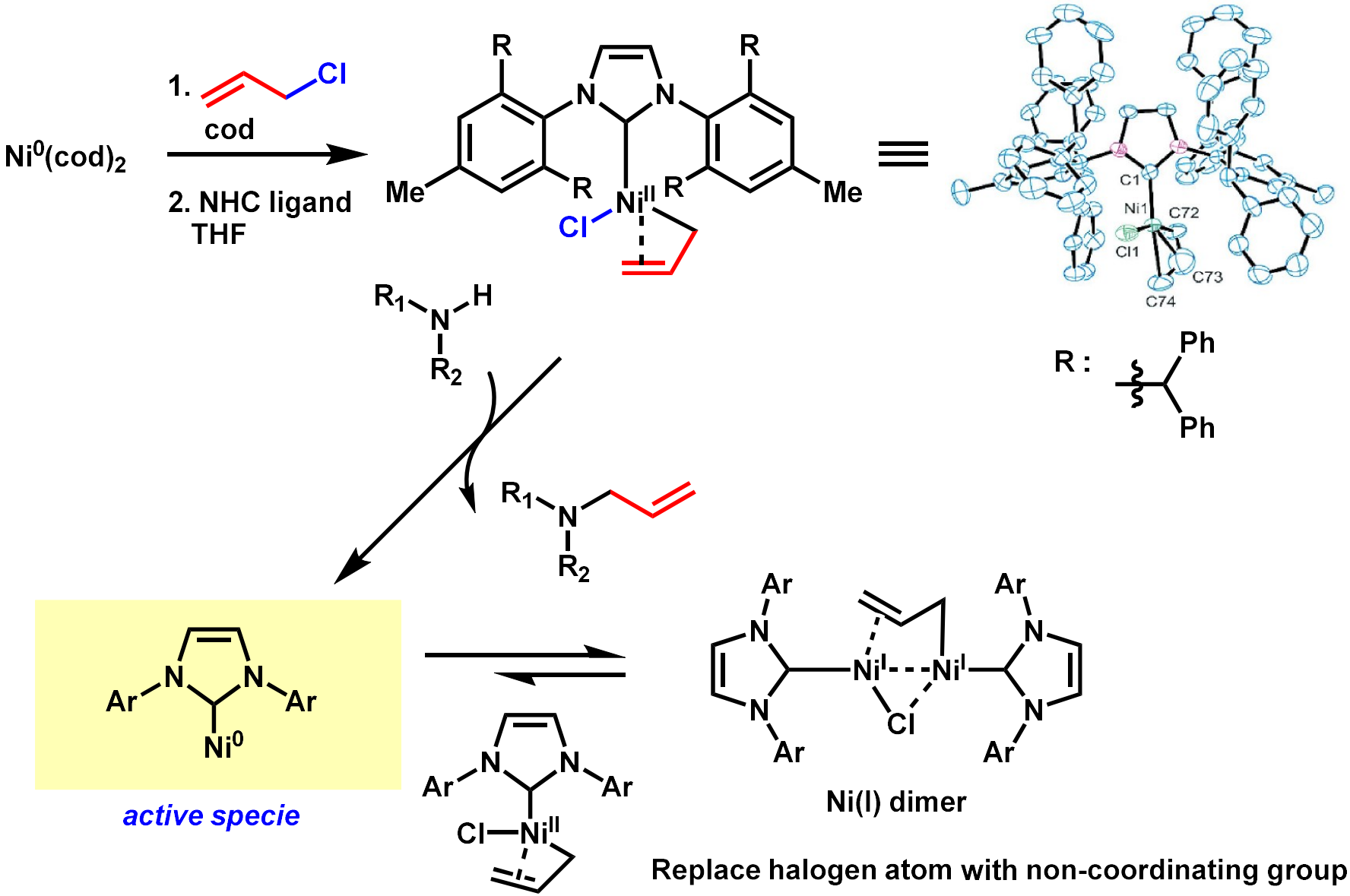
Liu, R. Y.; Dennis, J. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2020**, *142*, 4500.

Unsuccessful oxidative addition precatalyst



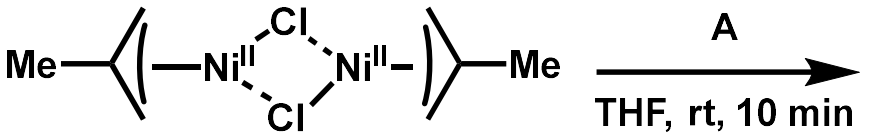
a) Liu, R. Y.; Dennis, J. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2020**, *142*, 4500.
b) Ge, S.; Green, R. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 1617.

η^3-allyl group in Ni(II) precatalyst



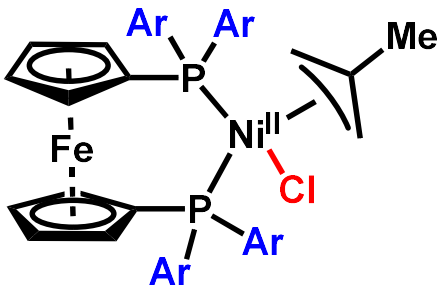
a) Martin, A. R.; Nelson, D. J.; Meiries, S.; Slawin, A. M. Z.; Nolan, S. P. *Eur. J. Org. Chem.* **2014**, 3127.
b) Hruszkewycz, D. P.; Balcells, D.; Guard, L. M.; Hazari, N.; Tilset, M. *J. Am. Chem. Soc.* **2014**, *136*, 7300.

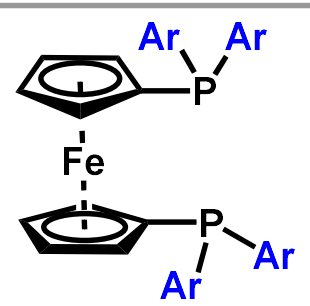
Preparation of Ni(II) precatalyst



A

THF, rt, 10 min



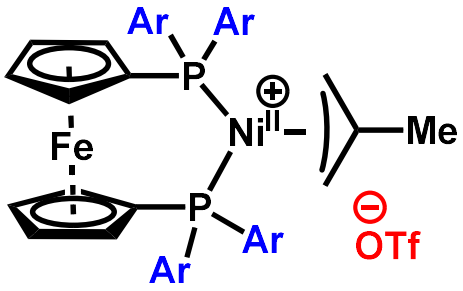


A
Ar = 3,5-CF_3

Ar = 3,5-CF_3

TMSOTf (2.0 eq.)

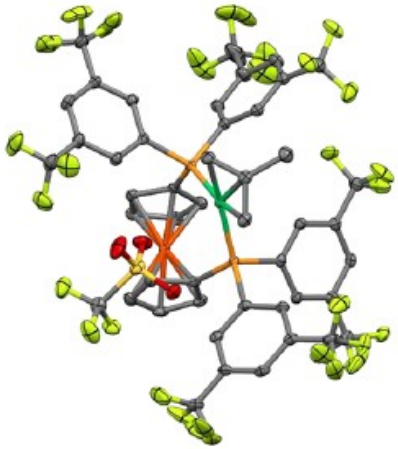
THF, 30 min, rt
70% (2 steps)

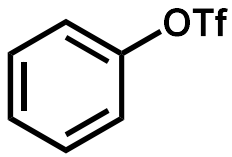


Ar = 3,5-CF_3

air-stable Ni^{II} precatalyst

≡





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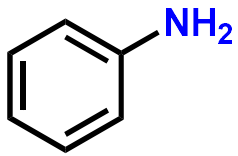
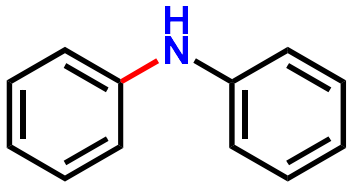


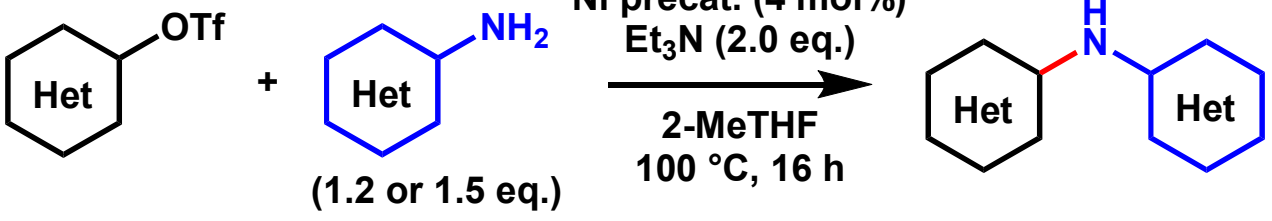
Ni precat. (4 mol%)
Et_3N (2.0 eq.)

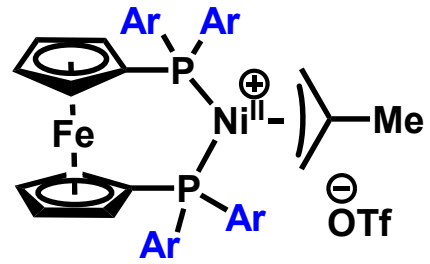
2-MeTHF
100 °C, 16 h
98% (GC yield)



Liu, R. Y.; Dennis, J. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2020**, *142*, 4500.
Standley, E. A. and Jamison, T. F. *J. Am. Chem. Soc.* **2013**, *135*, 1585.

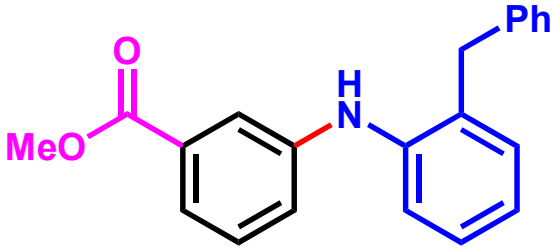
Substrate scope



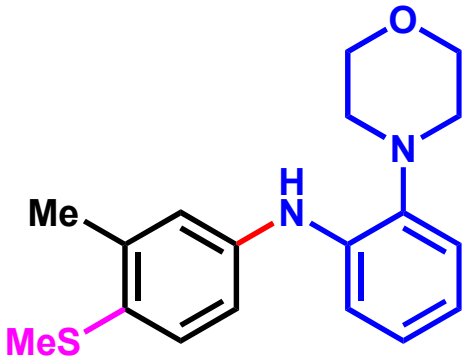


Ar = 3,5-CF_3

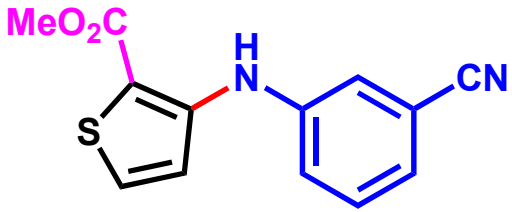
Ni precatalyst



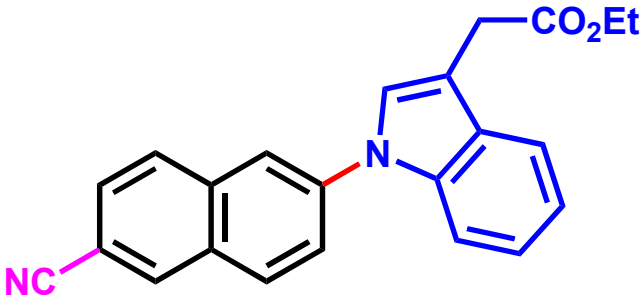
91%



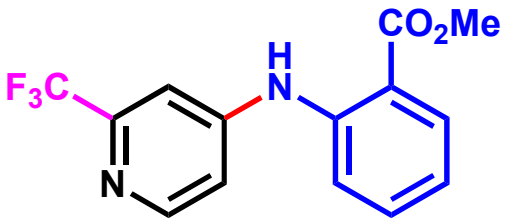
84%



94%



81%



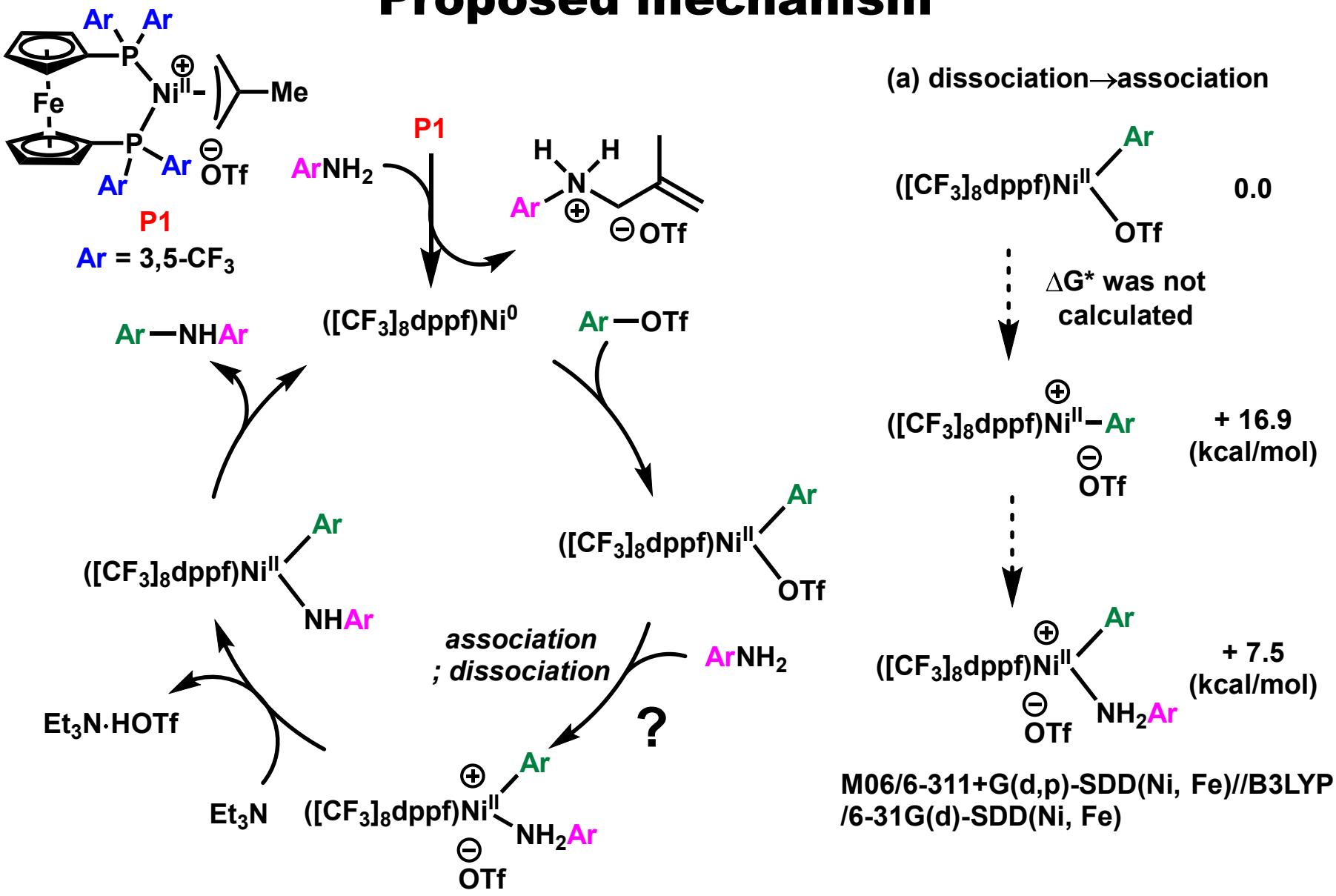
93%

X elecron rich Ar-OTf ?
X aliphatic amine
X 2 ° aryl amine

|||

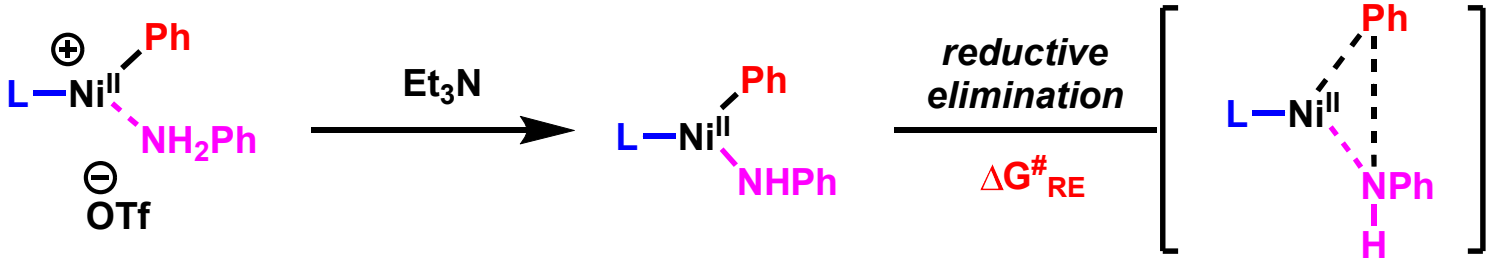
narrow substrate scope ?

Proposed mechanism

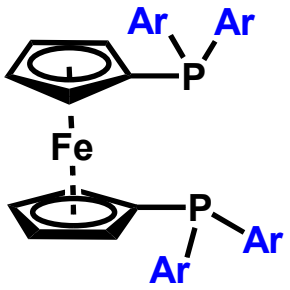


Liu, R. Y.; Dennis, J. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2020**, *142*, 4500.

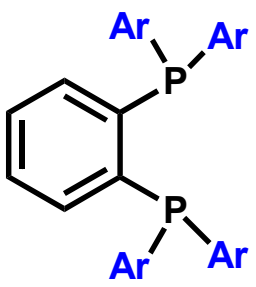
The character of bidendate phosphine ligand



entry	ligand	pK$_{BH+}$ of N-H	ΔG$^{\#}_{RE}$	yield
1	dppf	15.3	17.2	6%
2	[CF$_3$]$_4$-dppf	13.4	16.7	32%
3	[CF$_3$]$_8$-dppf	12.2	16.4	94%
4	[CF$_3$]$_8$-dppbz	13.0	17.9	23%



dppf: Ar = Ph
[CF$_3$]$_4$-dppf: Ar = 4-CF$_3$
[CF$_3$]$_8$-dppf: Ar = 3,5-CF$_3$



[CF$_3$]$_8$-dppbz
: Ar = 3,5-CF$_3$

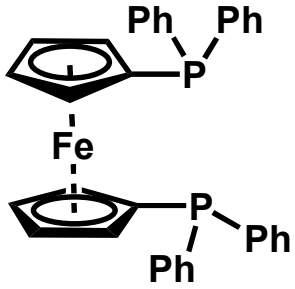
M06/6-311+G(d,p)-SDD(Ni, Fe)//B3LYP/6-31G(d)-SDD(Ni, Fe)

pKa of Et$_3$N•HOTf = 12.5
pK$_{BH+}$ of PhNH$_2$ = 28.5

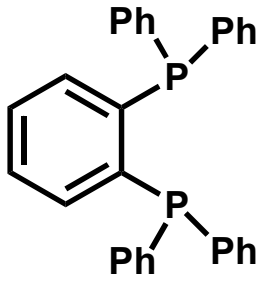
electrodeficient Ar group ⟹ More cationic Ni(II)-amine specie

Liu, R. Y.; Dennis, J. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2020**, *142*, 4500.

The role of ferrocene backbone -my opinion-



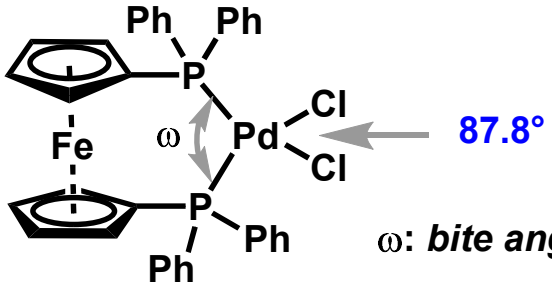
dppf



dppbz

ligand	*bite angle*
dppf	99.1°
dppbz	83°

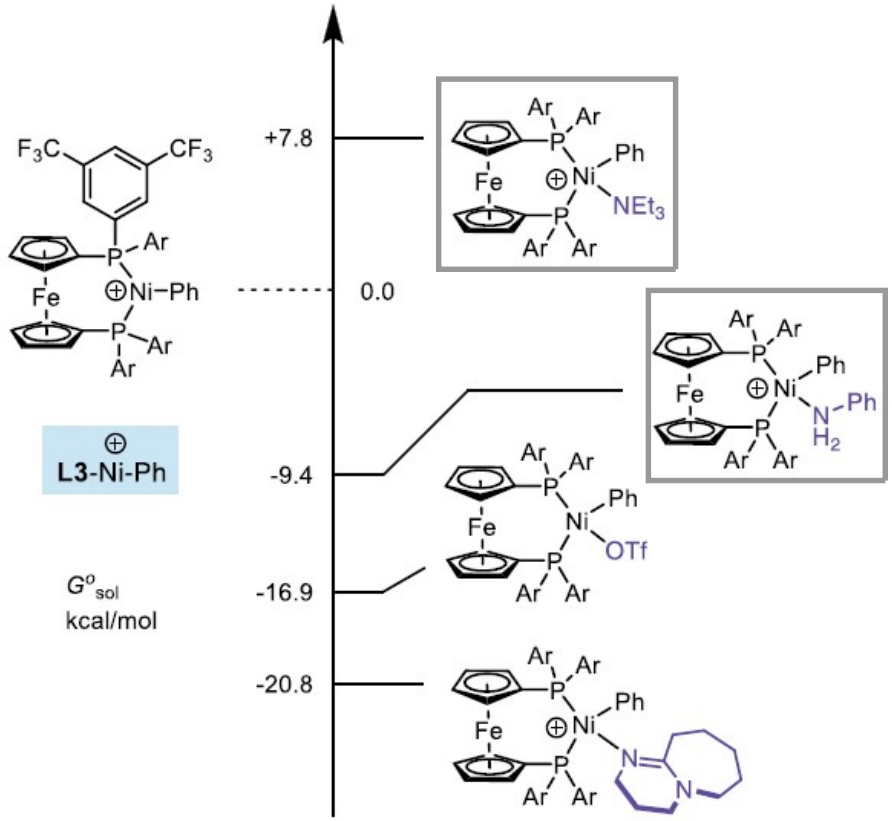
1. facilitate the reductive elimination
2. decrease the pK_{BH+} of N-H proton ?
3. low binding ability of Et_3N ?



87.8°

ω: *bite angle*

$Pd^{II}Cl_2$(dppf)



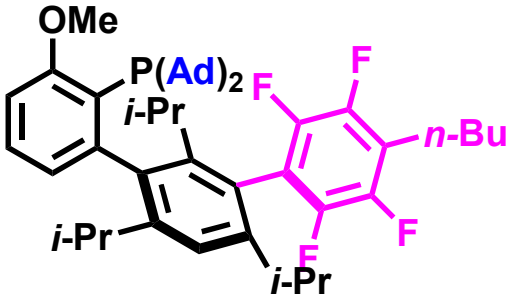
Relative binding energies to Ni(II) complex[a)]

a) M06/6-311+G(d,p)-SDD(Ni, Fe)//B3LYP/6-31G(d) -SDD(Ni, Fe)

a) Liu, R. Y.; Dennis, J. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **2020**, *142*, 4500. b) Hayashi, T. et al. *J. Am. Chem. Soc*. **1984**, *106*, 158. c) Mansell, S. M. *Dalton Trans*. **2017**, 46, 15157.

Summary

1. electron deficient Ar group at C3'
2. bulky Ad group at phosphine



AlPhos

base: DBU

Ar—X (X = OTf, Br)

+

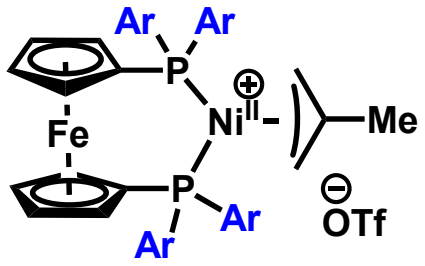
primary amine (alkyl, aryl)

primary amide

(2° aryl amine)

Realize the use of soluble and weak organic base like Et_3N and DBU

1. electron deficient Ar group
2. wide bite angle of dppf liigand
3. η^3-allyl group for the precatalyst



Ar = 3,5-CF_3

Ni^{II} precatalyst

base: Et_3N

Ar—X (X = OTf)

+

primary aryl amine

future work : Expansion of the substrate scope to 2° aliphatic amine

Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2018**, *140*, 4721.
Liu, R. Y.; Dennis, J. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **2020**, *142*, 4500.