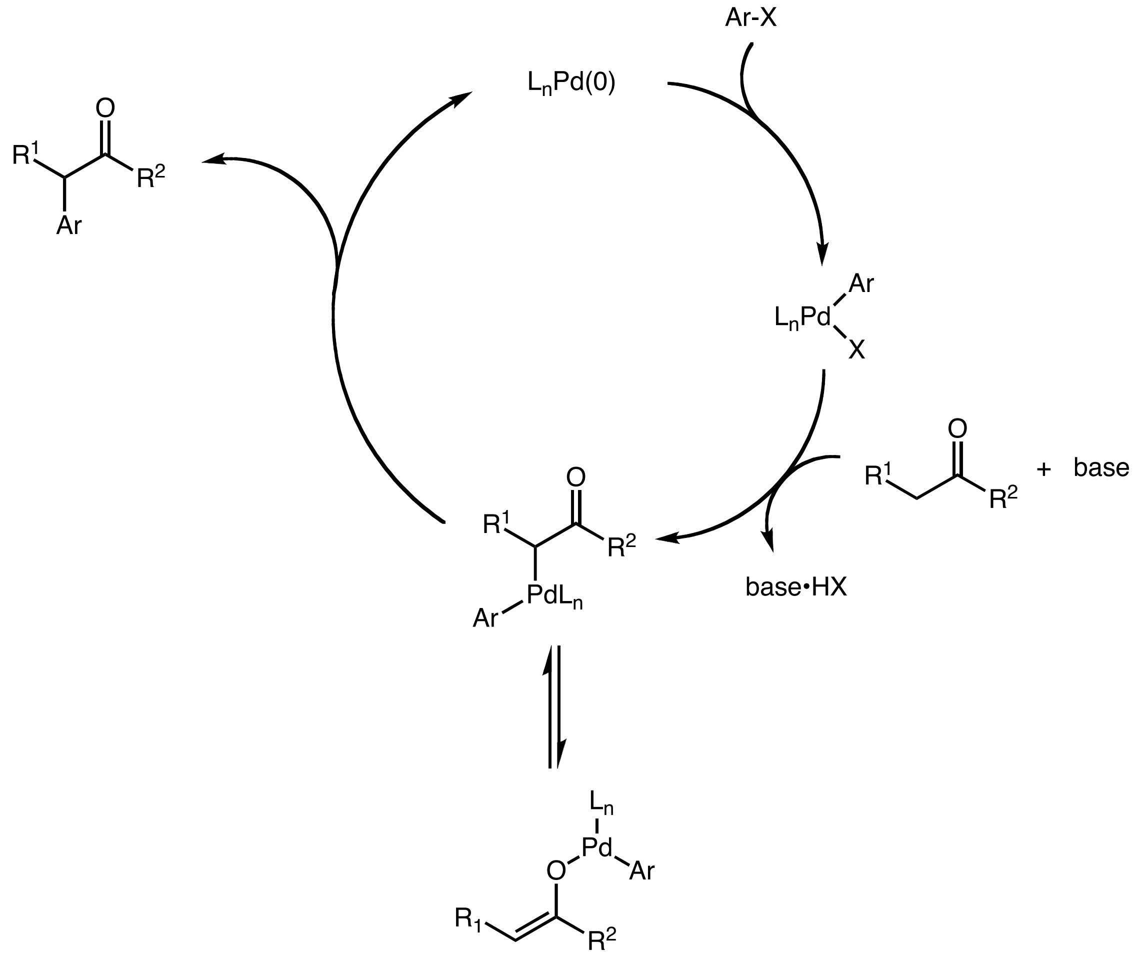
Buchwald-Hartwig C-C Bond Formation



Group Meeting Presentation

Andrew Dilger

April 21st, 2010

Csp^3-Csp^2 C-C Bond Formation

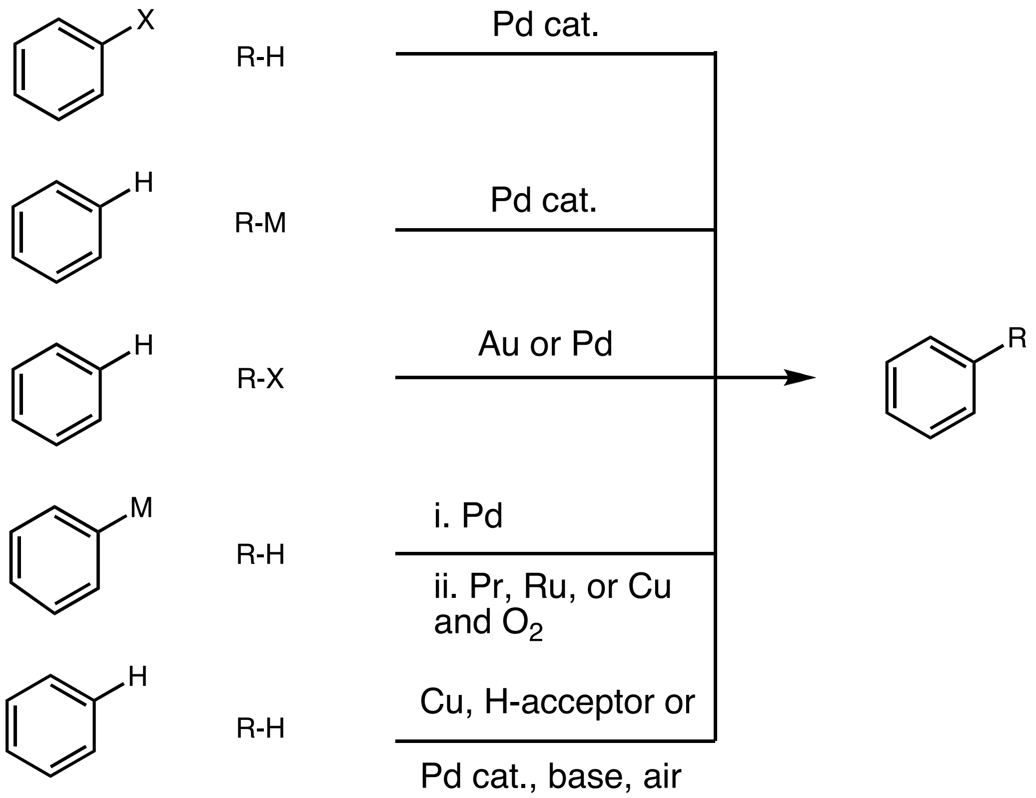
unactivated sp^3 C-H
aryl halide

aryl C-H
alkyl metals

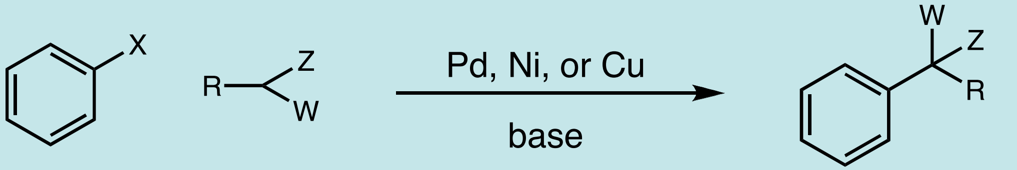
aryl C-H
alkyl halide

unactivated sp^3 C-H
aryl metals

dehydrogenation
aryl C-H/sp^3 C-H



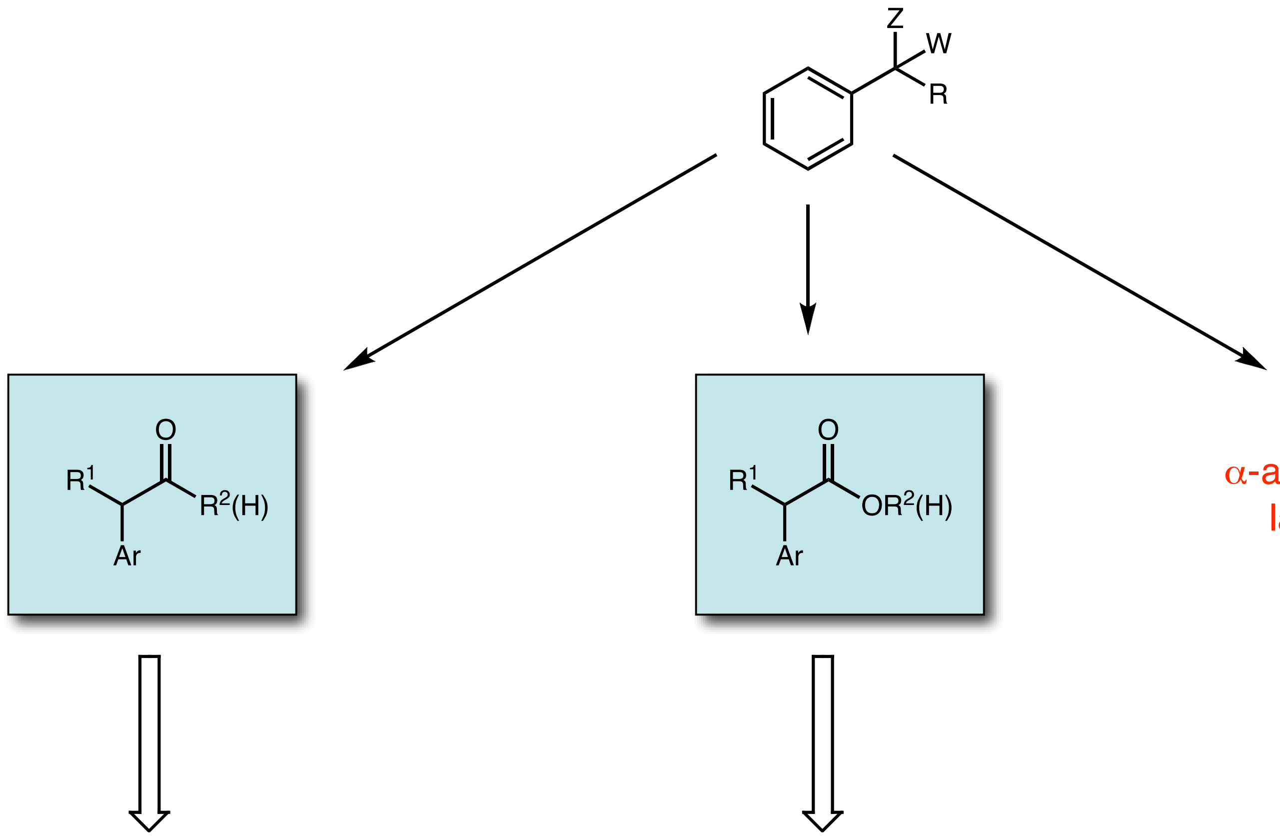
aryl halide
acidic sp^3 C-H



Z, W = electron withdrawing group

Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.

Scope of This Presentation



ketone enolates
silyl enol ethers
aldehydes
enol esters
ketimines

ester enolates
silyl ketene acetals

α-arylated nitriles, amides
lactams, dicarbonyls

Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.

Buchwald-Hartwig C-C Bond Formation

Presentation Outline

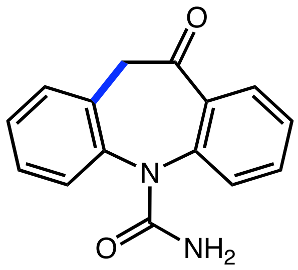
- ■ Introduction
- ■ α-Arylated ketones
  - Discovery and optimization studies
  - Direct arylations of ketones and enones; including asymmetric variants
  - Arylation of silyl enol ethers
- ■ α-Arylated aldehydes, esters, and carboxylic acids
  - Intra- and intermolecular arylation of aldehydes
- ■ Conclusions

Relevant review articles:

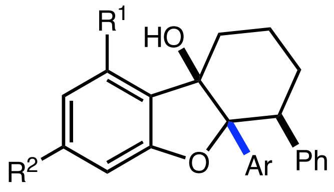
Bellina, F.; Rossi, R. *Chem. Rev*. **2010**, *110*, 1082.
Burtoloso, A. C. B. *Synlett* **2009**, 320.
Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.
Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 953.

Synthetic Interest in α-Arylated Carbonyls

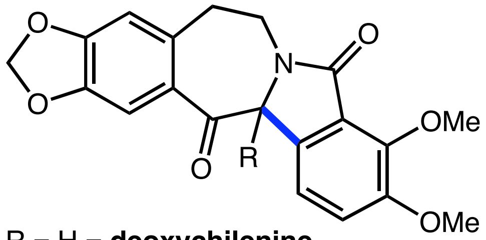
■ Natural products and pharmaceuticals



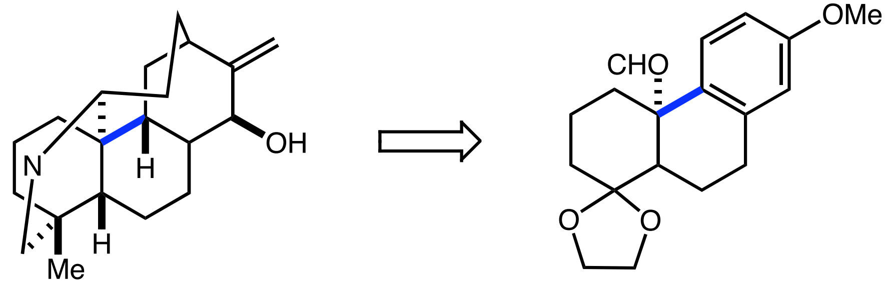
Trileptal



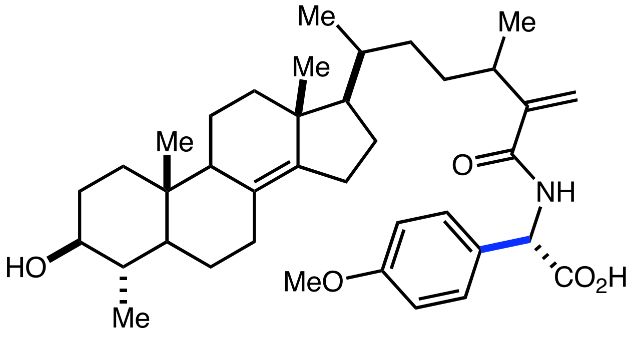
rocaglaols



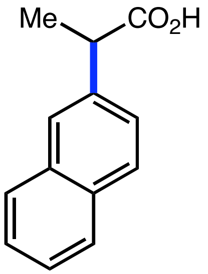
R = H = **deoxychilenine**
R = OH = **chilenine**



nominine



polimastamide A

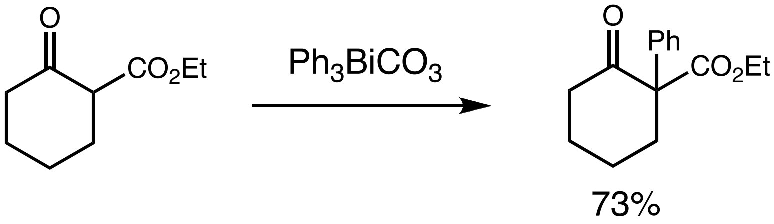


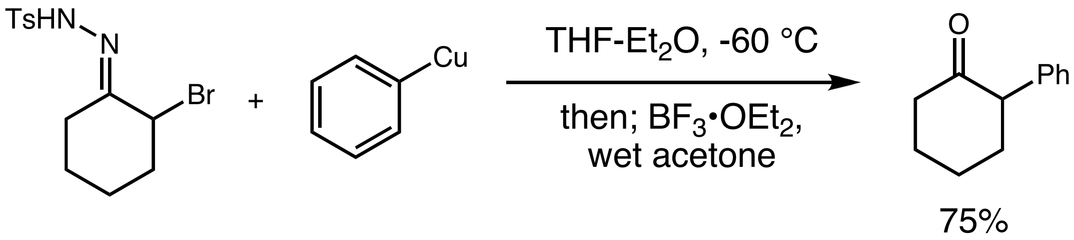
Naproxen

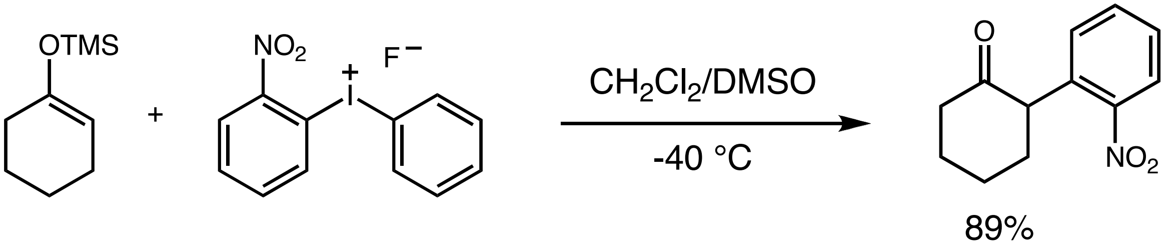
Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.

Selected Methods for α-Arylation of Carbonyls

- Stoichiometric, pre-activated aryl and/or carbonyl substrates



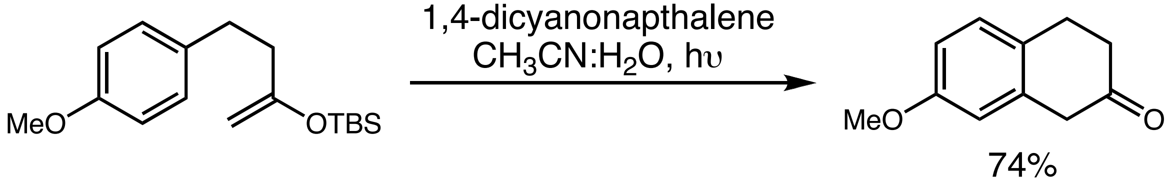




Aryl bismuth: Abramovitch, R. A.; Barton, D. H. R.; Finet, J.-P. *Tetrahedron*, **1988**, *44*, 3039.
Aryl copper: Sacks, C. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7372.
Diaryl iodonium: Iwama, T.; Birma, V. B.; Kozmin, S. A.; Rawal, V.H; *Org. Lett.* **1999**, *1*, 673.

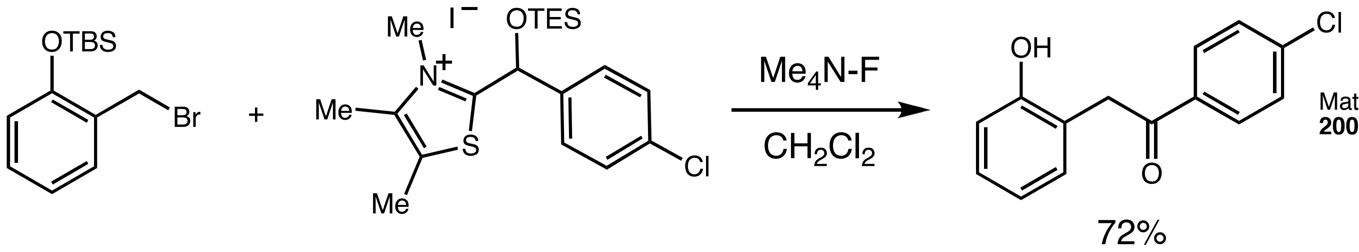
Selected Methods for α-Arylation of Carbonyls

■ Photoinduced electron transfer



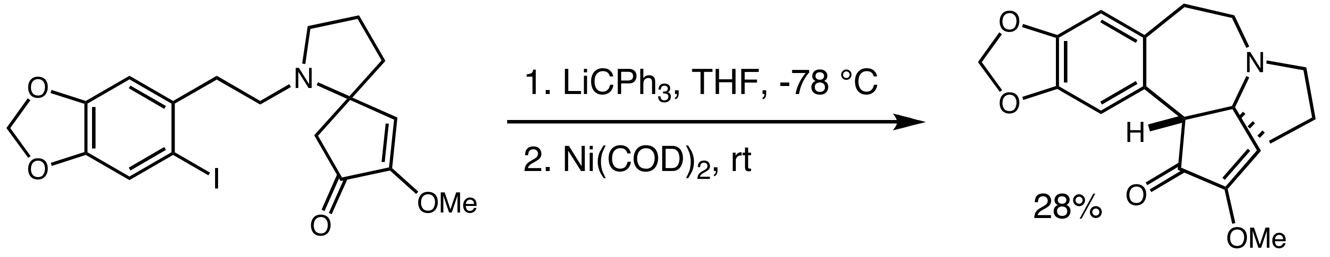
Pandey, G.; Krishna, A.; Girija, K.; Karthlkeyan, M. *Tetrahedron Lett*, **1993**, *34*, 6631.

■ Acyl anion addition to *o*-quinone methide



Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 4508.

■ Ni-catalyzed coupling of enolate with aryl halide



Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507

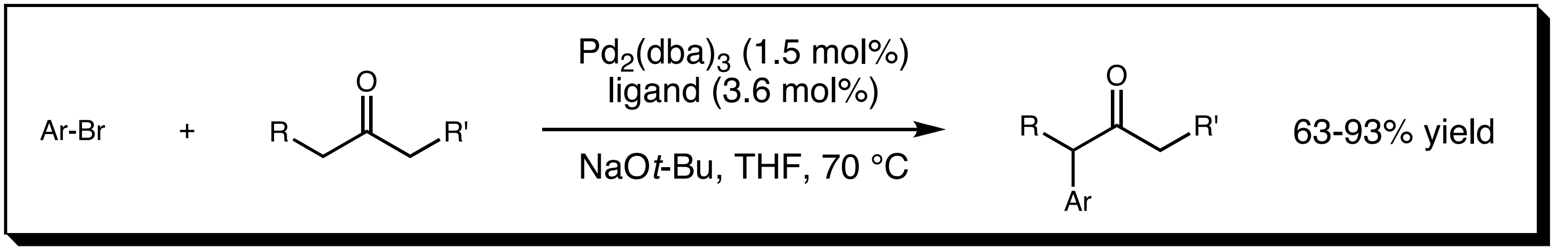
Transition Metal-Catalyzed α-Arylation of Carbonyls

> *"The observation of phenylacetone as a side product of an aryl halide amination in acetone solvent inspired the development of a practical synthetic method for the α-arylation of a variety of ketones and carboxylic acid derivatives."*

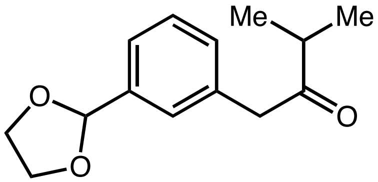
Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

Simultaneous Reports of Practical Pd-Catalyzed α-Arylations

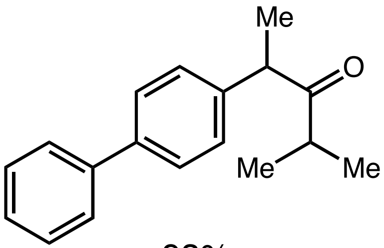
Buchwald's initial conditions



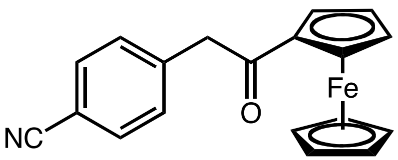
ligand = BINAP or Tol-BINAP



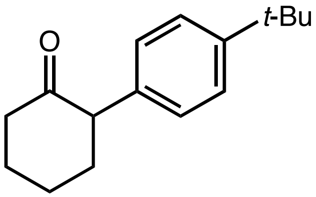
76%



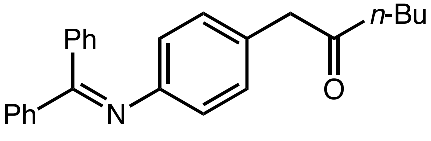
93%



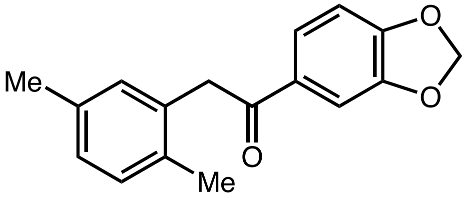
75%



83%



64%

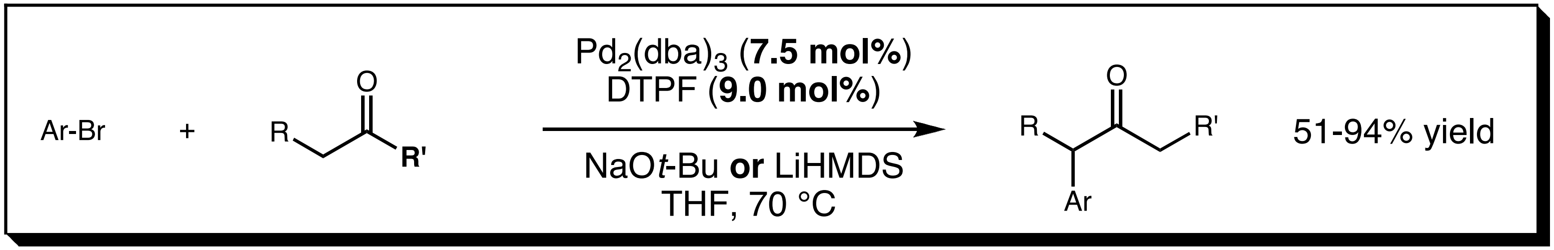


84% (3% Pd)

Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

Simultaneous Reports of Practical Pd-Catalyzed α-Arylations

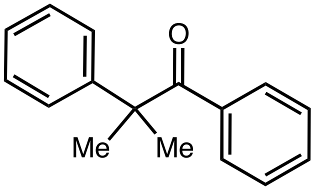
- Hartwig's initial conditions



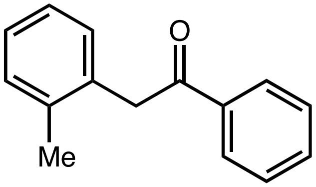
$Pd_2(dba)_3$ (**7.5 mol%**)
DTPF (**9.0 mol%**)

NaO*t*-Bu **or** LiHMDS
THF, 70 °C

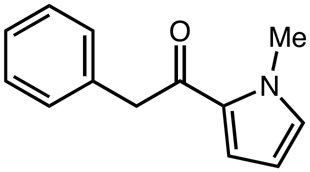
51-94% yield



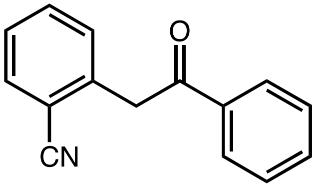
55% (10% Pd)



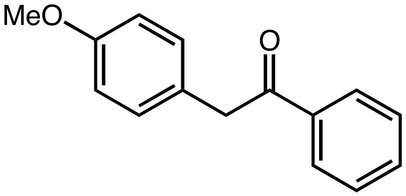
94%



79%

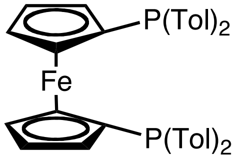


73% (NaO*t*-Bu)



69% (LiHMDS)

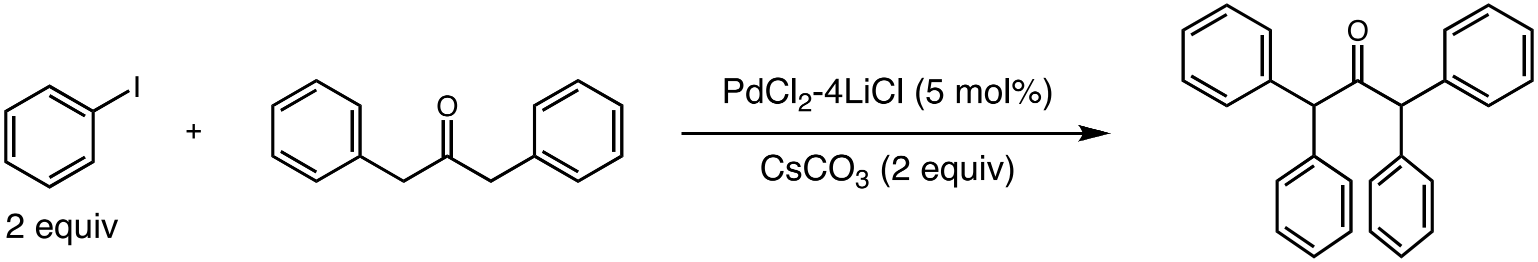
DTPF =



Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

Simultaneous Reports of Practical Pd-Catalyzed α-Arylations

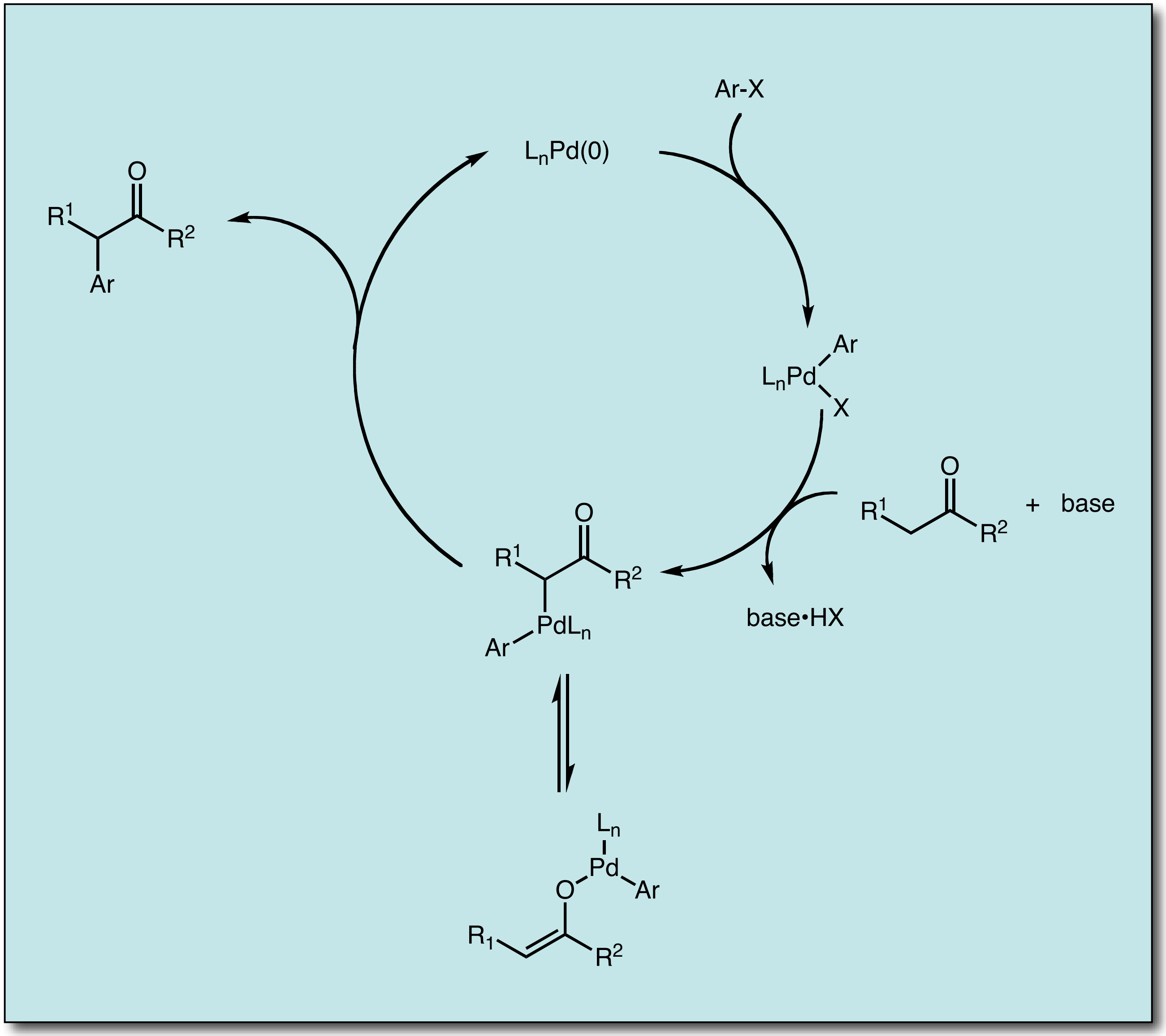
Miura's initial report



- This publication’s primary focus is the arylation of phenols

Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M.
Angew. Chem. Int. Ed. **1997**, *36*, 1740.

Accepted Mechanism for Ketone α-Arylation



Observations and Rationale From Initial Investigation

- Buchwald observed selective arylation at least hindered site
  - Deprotonation probably occurs prior to Pd coordination

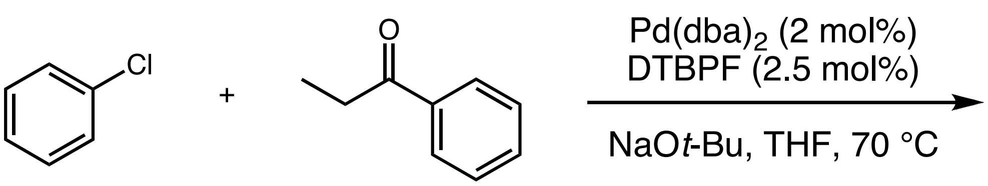
- Both groups noted the lack of competing β-hydride elimination
  - Chelating bis(phosphine) ligand renders Pd square planar with no open coordination site

- Hartwig observed mono vs. bis arylation selectivity trend
  - Electron-rich or electron-neutral aryl substrates only selective with LiHMDS
  - Electron-poor aryl substrates selective with NaO*t*-Bu

- Hartwig observed intermediate through ^{1}H and ^{31}P NMR with a metal-bound methylene
  - Enolate is C-bound, reductive elimination probably occurs via this coordination state

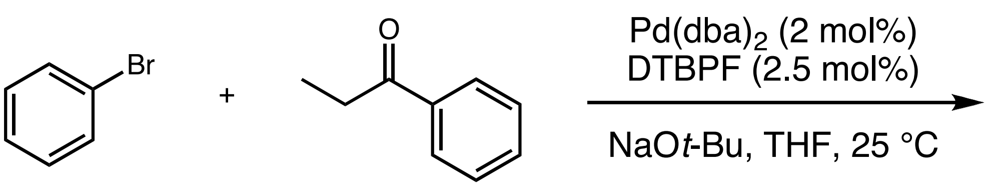
Hartwig's Elaboration of Initial Protocol

- New catalyst system enabled first use of aryl chlorides...

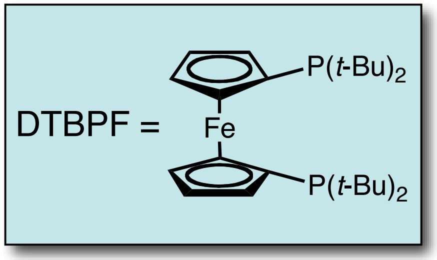


86%

- ...and room temperature coupling of aryl bromides



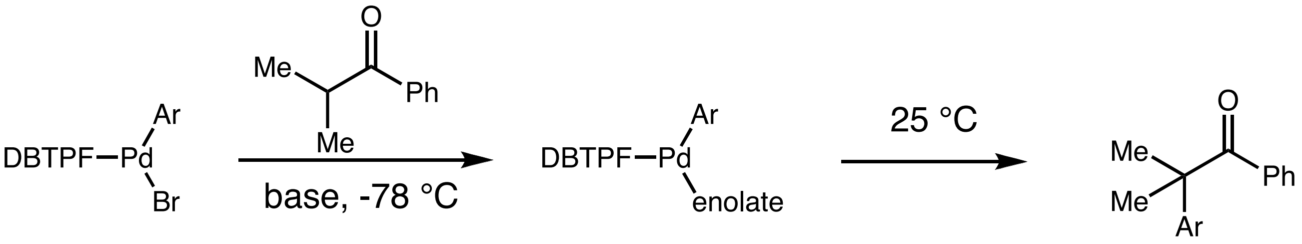
99%



Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

Hartwig's Elaboration of Initial Protocol

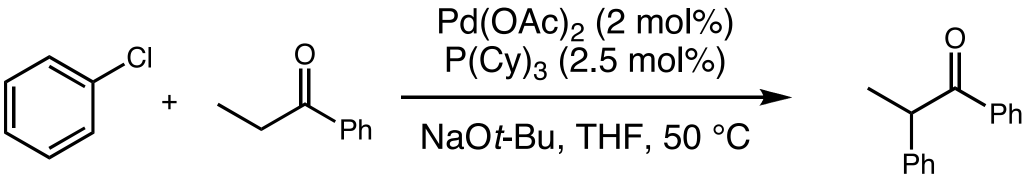
Qualitative mechanistic study shed light on binding mode of DTBPF enolate complex



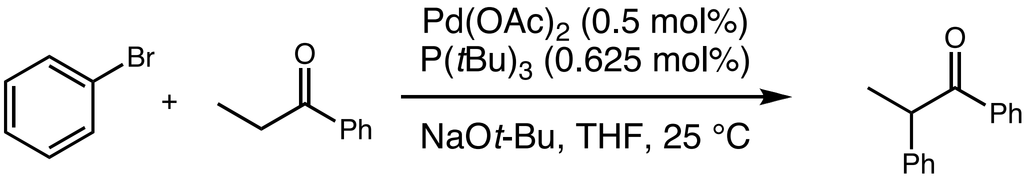
quantitative conversion

- DPPF bound enolate reductively eliminated in ~10%
- NMR showed ligand is bound to metal by only 1 phosphorous

Coordination number prompted the investigation of monodentate, bulky phosphine ligands



93%



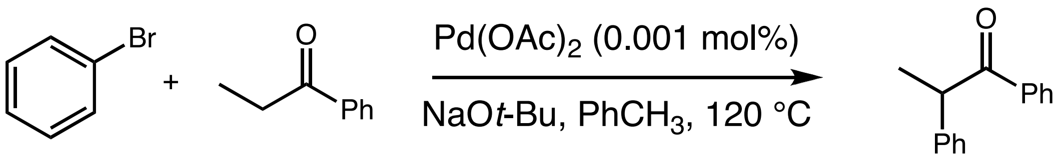
97%

- Extremely high turnover numbers (~20,000)
- Efficient reaction does not require chelation

Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

Buchwald's Elaboration Studies

High turnover numbers with bulky phosphines may have nothing to do with ligands

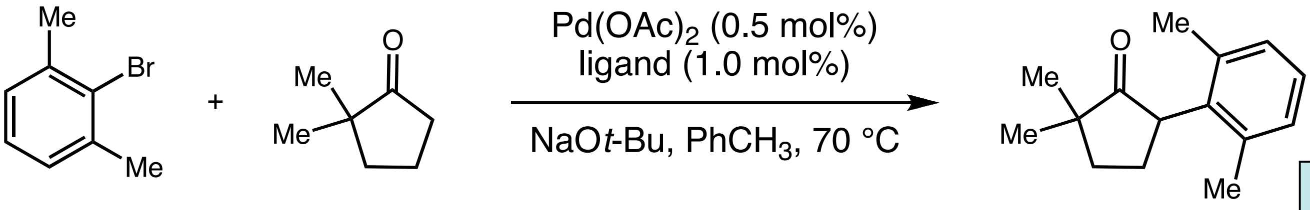


74%

- Turnover number = ~100,000

> *"These results exemplify the danger of drawing conclusions about the activity of a catalytic system when only one reaction is studied at low catalyst loadings."*

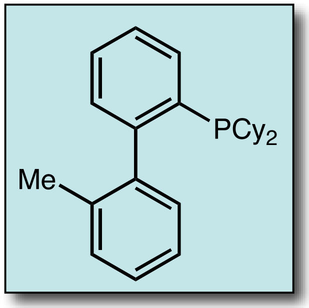
Also found success using bulky monodentate phosphine ligands



64%

- Wide substrate scope, including electron-rich/poor chlorides
- Acidic methyl and methylene (2-pentanone) not selective
- Xantphos (bidentate) and Pd(dba)$_2$ work well for those cases

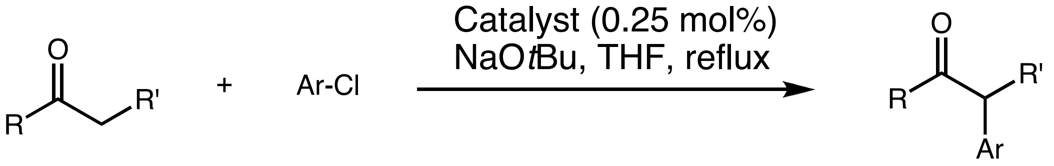
ligand =



Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L.
J. Am. Chem. Soc. **2000**, *122*, 1360.

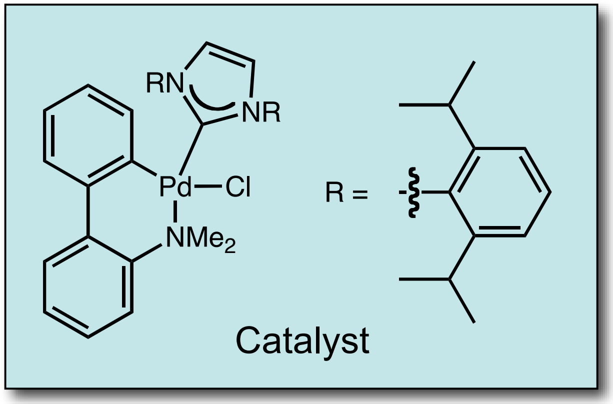
Arylation of Ketones

Nolan's use of NHC ligands on Pd



15 examples
72-99%

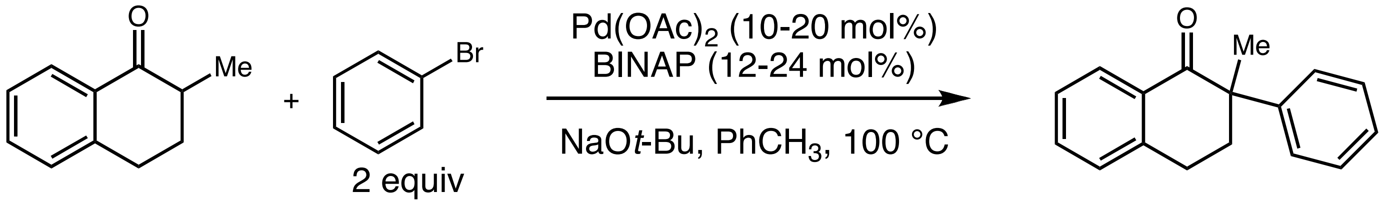
- Incredibly efficient catalyst
- Arene scope includes electron-poor, rich, and neutral



Navarro, O.; Marion, N.; Oonishi, Y.; Kelly III, R. A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685.

Head-to-Head Comparison of Catalytic, Enantioselective Methods

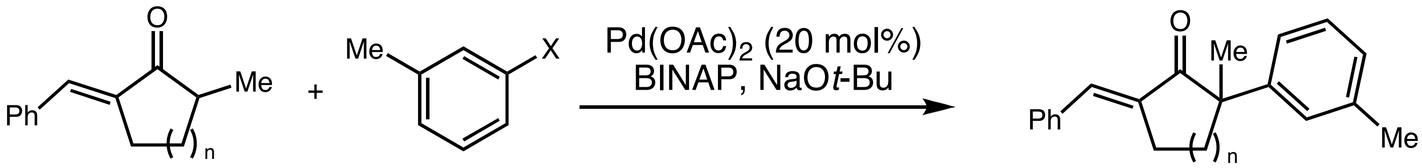
Buchwald's initial conditions



66%, 73% ee

- *Para*-substituted arenes yielded racemic products

"Enigmatic" results with phenylidene substituted substrates

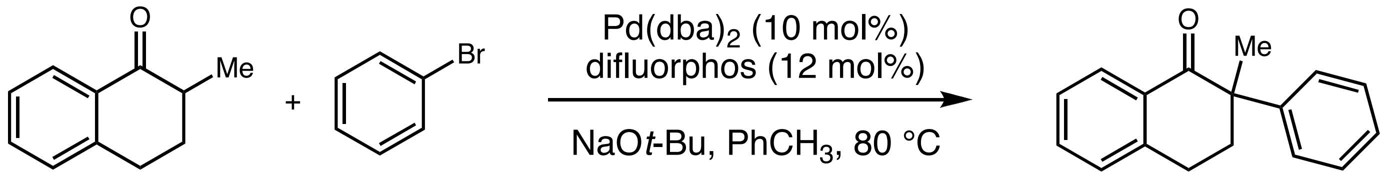


n = 1 = 80%, 94% ee
n = 2 = very low ee

Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918.

Head-to-Head Comparison of Catalytic, Enantioselective Methods

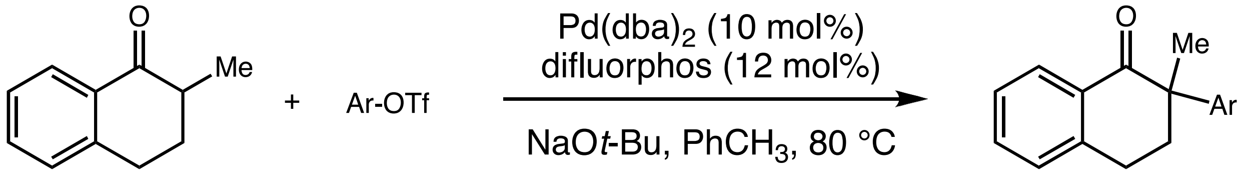
■ Hartwig's result



80%, 85% ee

- *Para*-substituted arenes well-tolerated

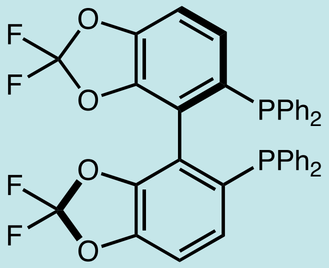
■ Expanding the scope to incorporate triflates



79-85%, 90-95% ee
(5 examples)

- Analogous indanone reactions (4 examples) proceed in 77-84% yield, 70-89% ee

difluorphos =

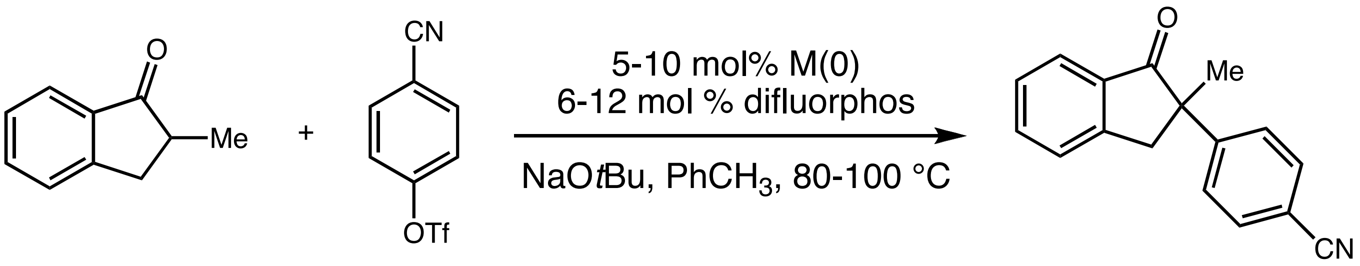


Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195.

Head-to-Head Comparison of Catalytic, Enantioselective Methods

Factors controlling enantioselectivity

- Smaller dihedral angle in segphos and difluorphos than related ligands
- More active catalyst and triflate reactant allow for lower temp.
- P-C bond stability in ligand
- Pd for electron-rich/neutral, Ni for electron poor

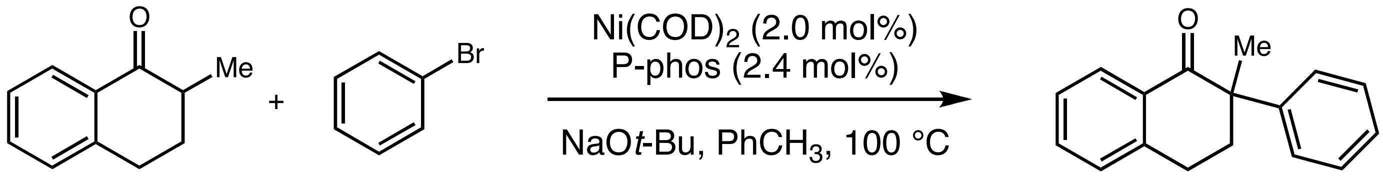


M = Pd = 65%, 55% ee
M = Ni = 75%, 95%ee

Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195.

Head-to-Head Comparison of Catalytic, Enantioselective Methods

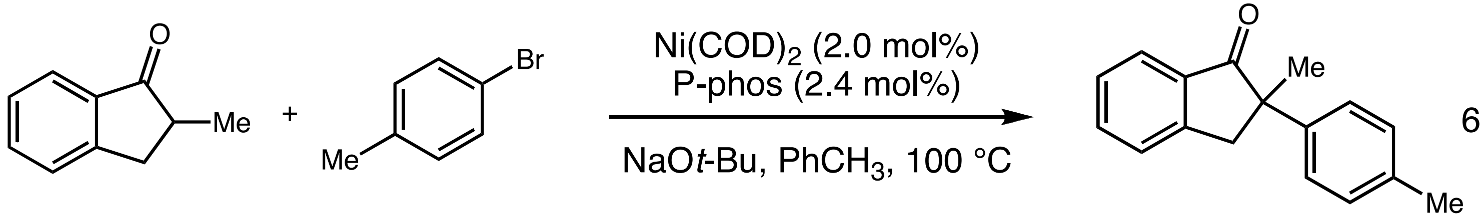
Kwong and Chan's Ni-catalyzed process



Ni(COD)$_2$ (2.0 mol%)
P-phos (2.4 mol%)

NaO*t*-Bu, PhCH$_3$, 100 °C

85%, 92% ee



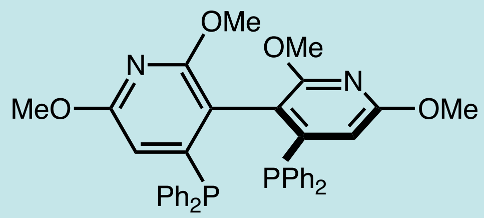
Ni(COD)$_2$ (2.0 mol%)
P-phos (2.4 mol%)

NaO*t*-Bu, PhCH$_3$, 100 °C

69%, 87% ee

- Compare above reaction to Pd/BINAP, which provided racemic products

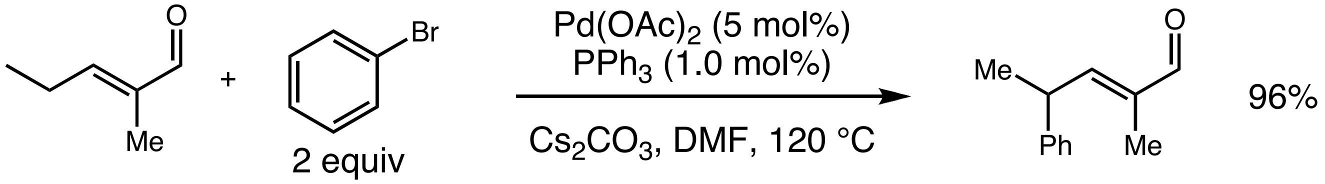
P-phos =



Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 195.

γ-Arylation of Enones

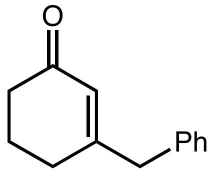
First report by Miura



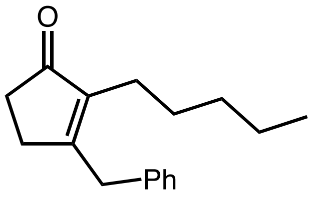
Pd(OAc)$_2$ (5 mol%)
PPh$_3$ (1.0 mol%)
Cs$_2$CO$_3$, DMF, 120 °C

96%

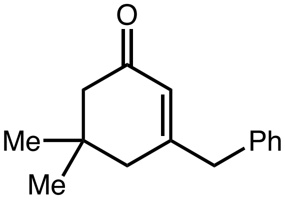
Also...



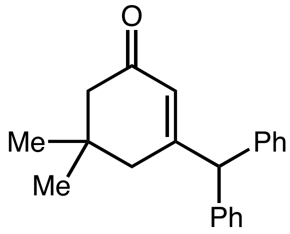
56%



58%



71% (60 °C)



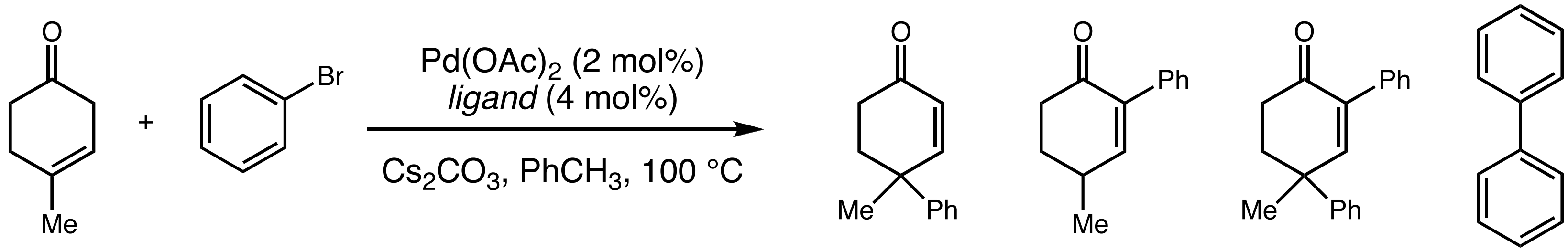
79% (80 °C)

- Limited by inability to generate quaternary centers

Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203.

γ-Arylation of Enones

- Buchwald's arylation of α,β- and β,γ-unsaturated ketones; ligand selection



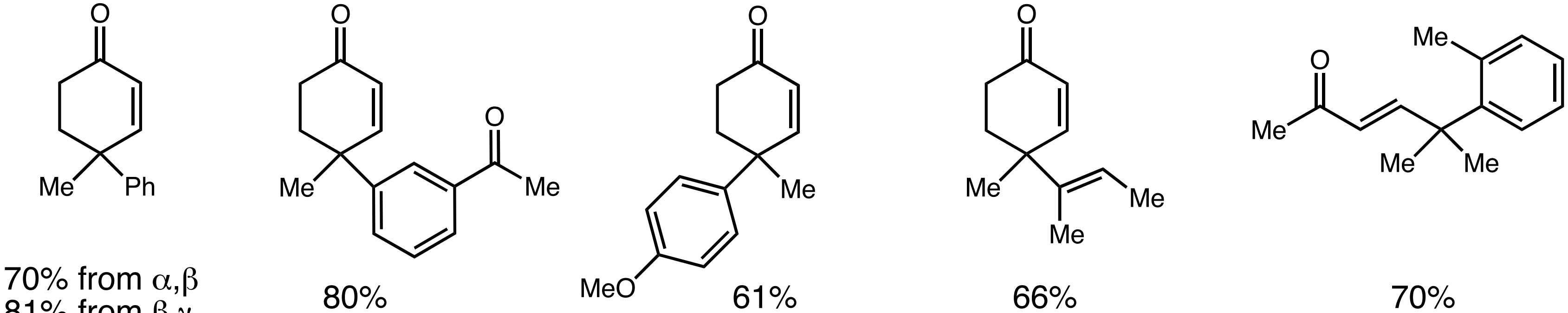
1 **2** **3** **4**

Entry	Ligand	**1**	**2**	**3**	**4**
1	P(*o*-tol)$_3$	35%	0	23%	26%
2	Xantphos	11%	12%	49%	0
3	CyJohnPhos	41%	7%	17%	14%
4	Xphos	0	4%	50%	0
5	**dppe**	**84%**	**0**	**0**	**0**
6	dppp	56%	0	0	5%
7	dppb	50%	2%	7%	0
8	BINAP	50%	7%	32%	0
9	dppf	28%	25%	53%	0
10	P(*t*Bu)$_3$	7%	0	27%	0

Hyde, A. M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 177.

γ-Arylation of Enones

Scope of reaction



70% from α,β
81% from β,γ

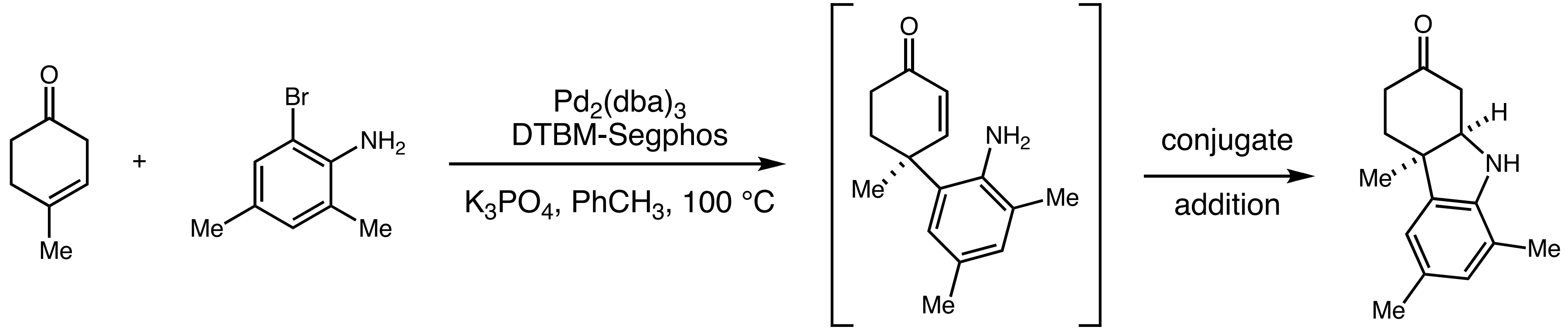
80%

61%

66%

70%

One-pot asymmetric domino reaction accesses ketoindoline skeleton



50%, 90% ee

Hyde, A. M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 177.

Overview of Ketone Arylation

General trends

- Bulky phosphine or NHC ligands increase reaction rates by:
  -raising ground-state energy of high coordinate Pd catalyst
  -stabilizing energy of low coordinate Pd(0) complex
  -promoting reductive elimination

- Preferential arylation at least hindered site

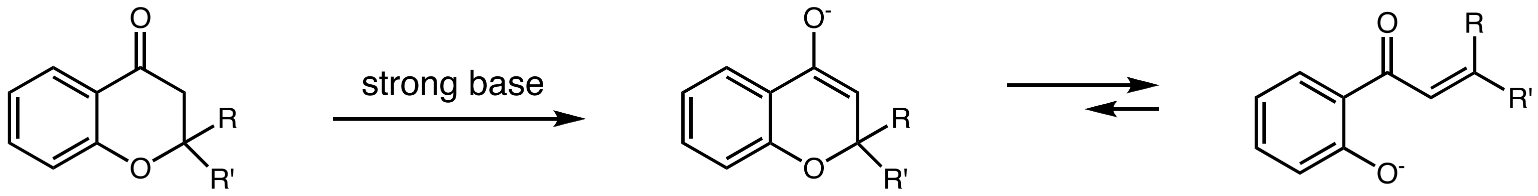
- Mono- vs. disubstitution
  -Monodentate ligands yield poor selectivity for ketones with two enolizable centers
  -Bidentate ligands yield better results in these cases

Simple starting point for arylation chemistry

- $Pd(OAc)_2$ or $Pd(dba)_2$ pre-catalysts
- *t*-butoxide or disilazide bases
- Commercially-available ligands (BINAP, $P\textit{t}Bu_3$, DPPF)
- $PhCH_3$ or THF

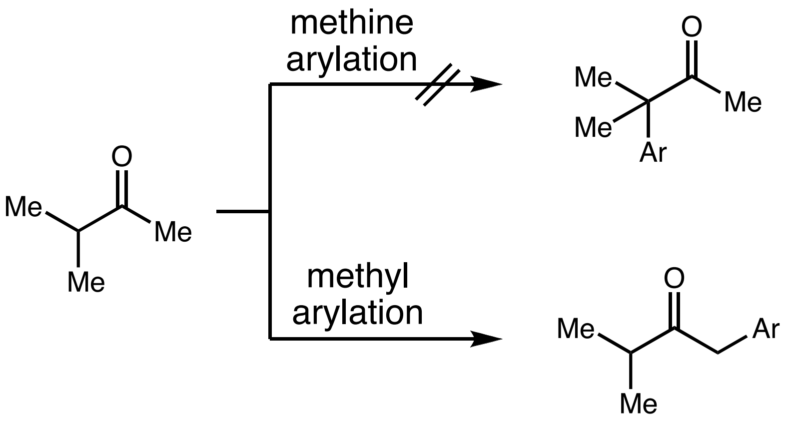
Limitations of Direct Arylation of Ketones

Require strongly basic conditions



- Also, acidic tertiary centers not amenable to enantioselective formation under these conditions

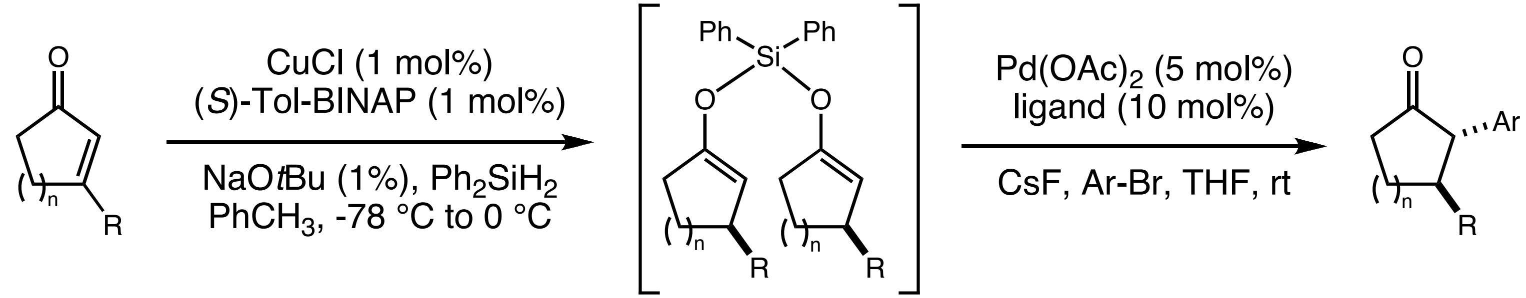
Preferential, if not exclusive, arylation at least hindered site



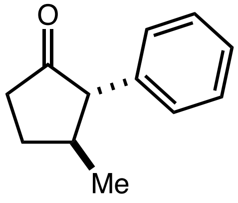
- Arylation of silyl enol ethers overcomes these limitations

Arylation of Silyl Enol Ethers

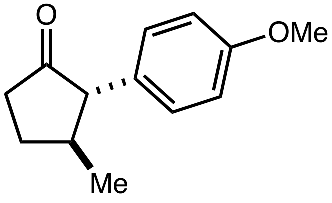
Buchwald's one-pot conjugate reduction/arylation



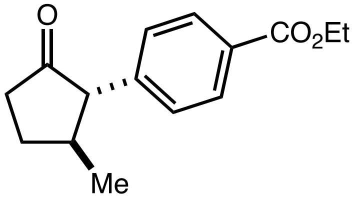
- Stoichiometry of BINAP and ligand crucial



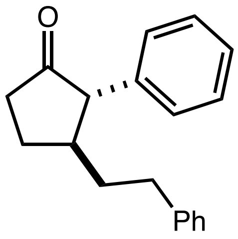
72%, 93% ee



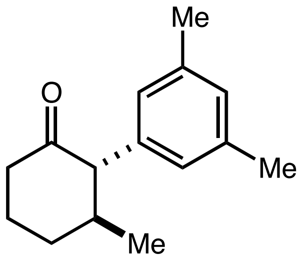
71%, 94% ee



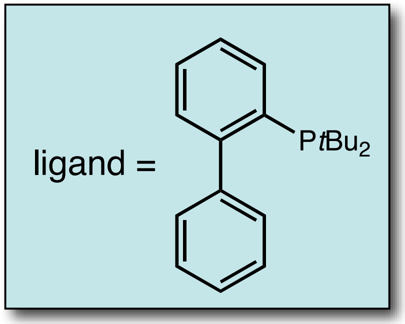
54%, 95% ee



75%, 96% ee



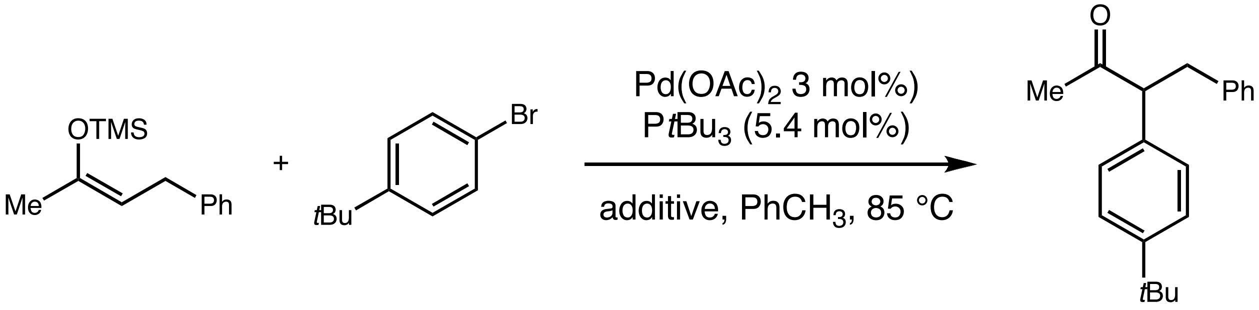
52%, 94% ee



Chae, J.; Yun, J.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 4809.

Arylation of Silyl Enol Ethers

- Hartwig's synergistic combination of metal fluorides

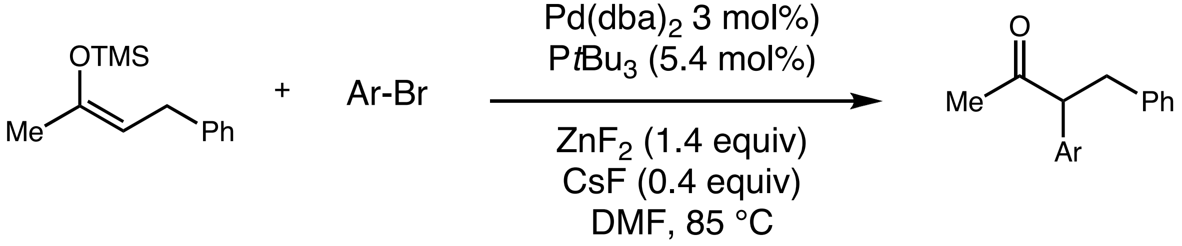


Entry	Additive	Yield
1	none	0
2	Bu_3SnF	34%
3	CsF	18%
4	Bu_3SnF, CsF	98%
5	ZnF_2	38%
6	Me_4NF	0

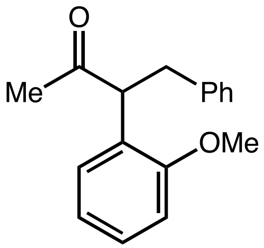
Su, W.; Raders, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2006**, *45*, 5852.

Arylation of Silyl Enol Ethers

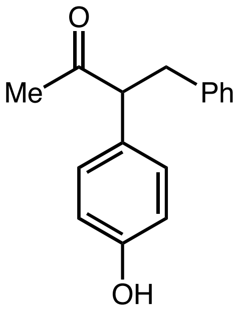
- Hartwig's synergistic combination of metal fluorides; tin free



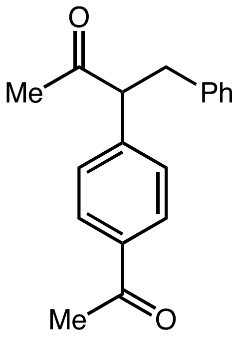
- Select examples



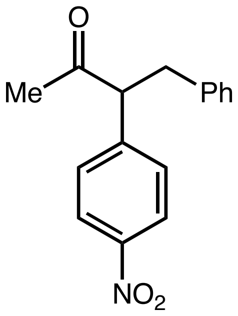
87%



53%



71%

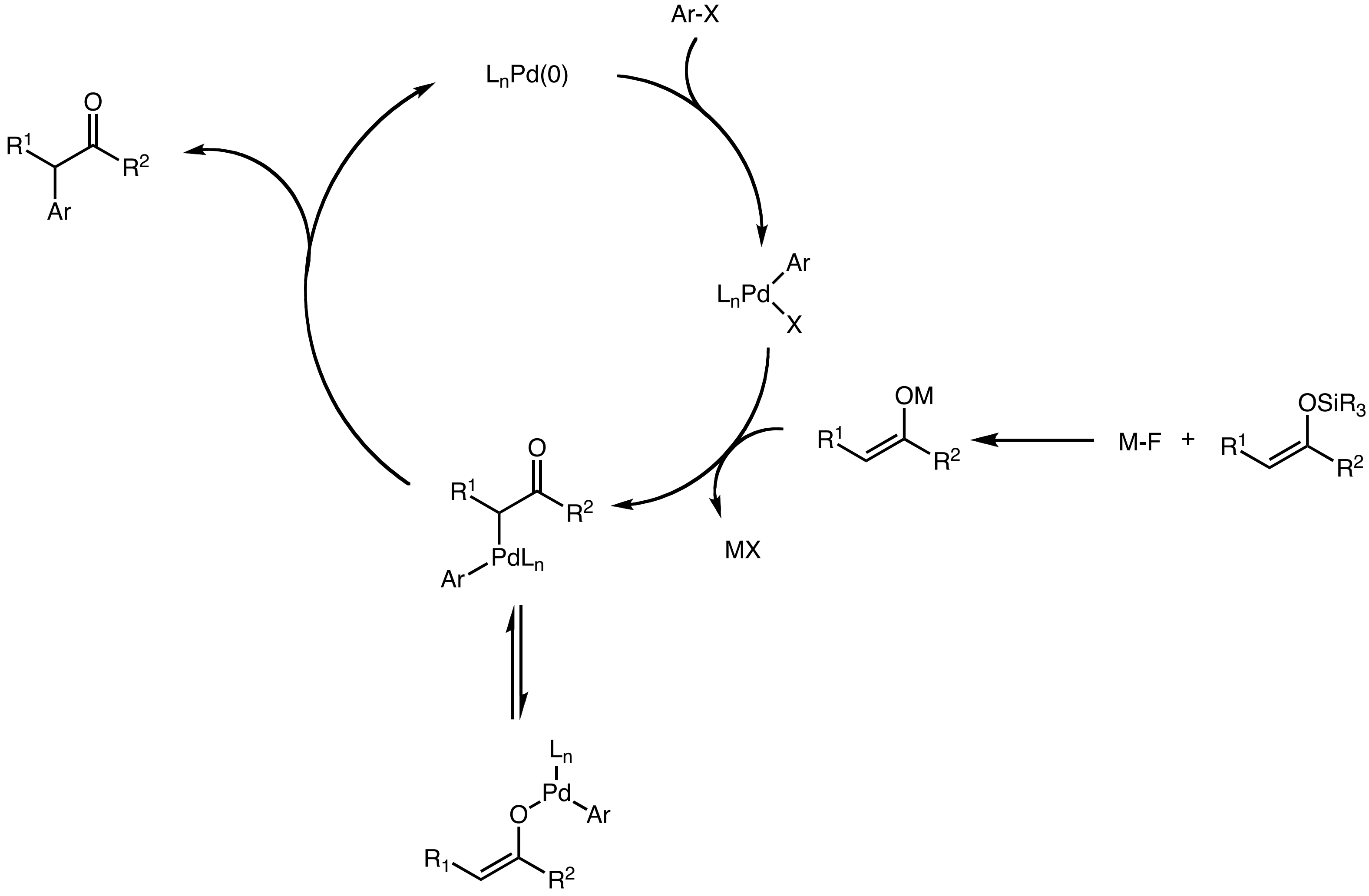


64%

Su, W.; Raders, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2006**, *45*, 5852.

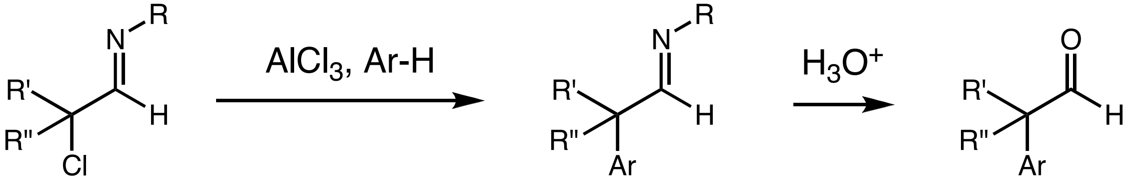
Arylation of Silyl Enol Ethers

- Mechanism analogous to ketone arylation



Arylation of Aldehydes

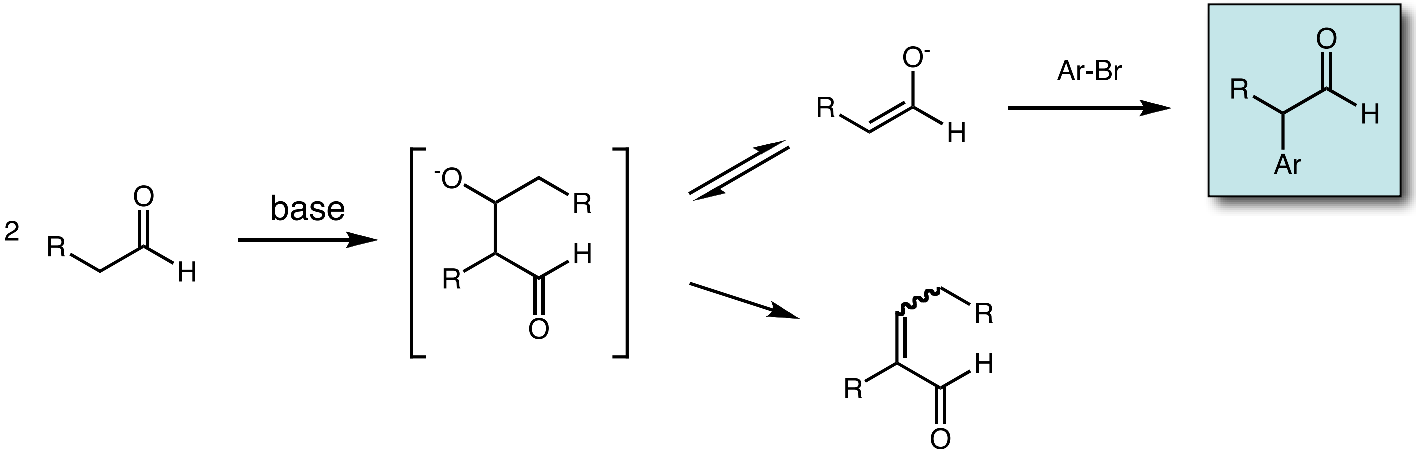
Previous syntheses of arylated aldehydes



7 examples, 26-82% yield

Challenge associated with aldehyde arylation

- Strongly basic conditions - aldol condensation

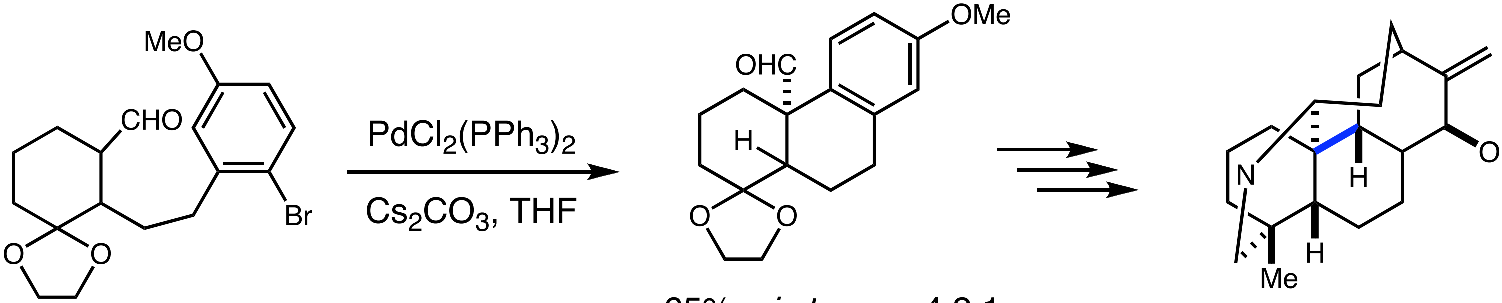


De Kimpe, N.; Verhe, R.; De Buyck, L. Schamp, N. *Tetrahedron Lett.* **1982**, *23*, 2853.

Arylation of Aldehydes

Intramolecular variants

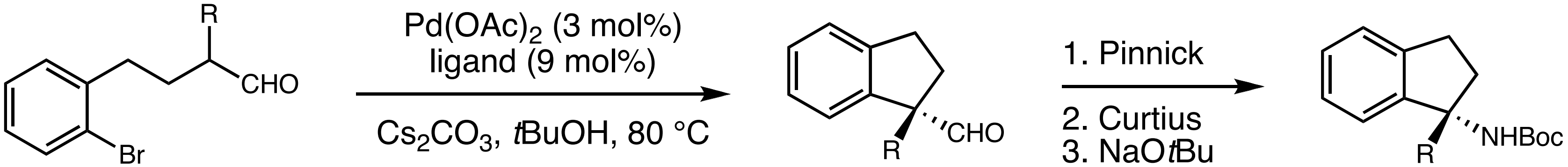
Initial reports by Muratake and Natsume



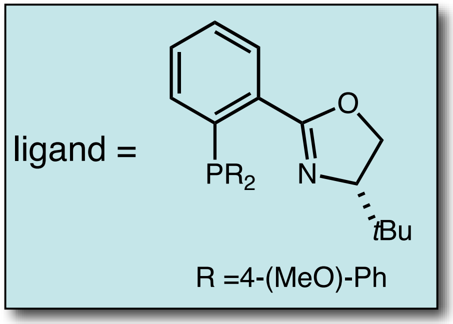
65%, *cis*:*trans* = 4.2:1

nominine

Asymmetric method developed by Buchwald



10 examples
27-88%, 53-98% ee

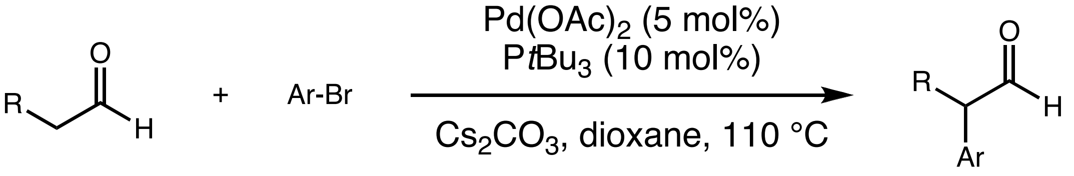


Muratake, H.; Natsume, M. *Tetrahedron Lett.* **2002**, *43*, 2913.
Garcia-Fortanet, J.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47, 8108.*

Arylation of Aldehydes

Intermolecular variants

Miura's approach

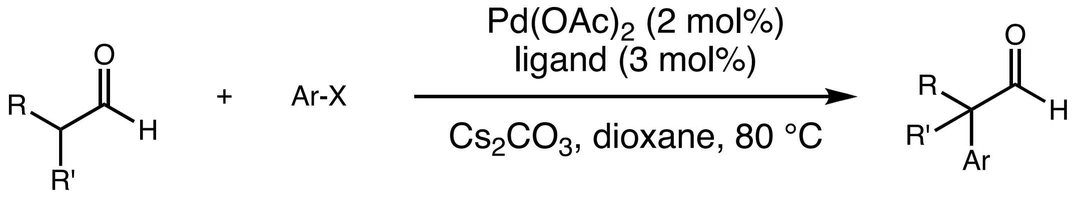


$Pd(OAc)_2$ (5 mol%)
P*t*Bu_3 (10 mol%)
Cs_2CO_3, dioxane, 110 °C

10 examples
50-82%

- Somewhat limited reaction scope; only linear aldehydes
- Undesirably high temperatures

Buchwald's first reported conditions; confirmation of reversible aldol hypothesis



$Pd(OAc)_2$ (2 mol%)
ligand (3 mol%)
Cs_2CO_3, dioxane, 80 °C

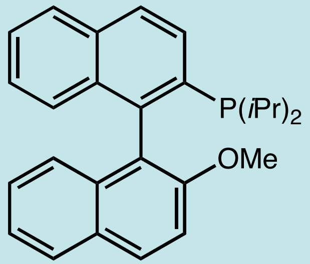
12 examples (R' = H), 66-86%
8 examples (R' = alkyl), 57-89%
(mostly electron-poor arenes)

R = alkyl, R' = alkyl or H

X = Cl or Br

- Product of hexanal self-condensation thermodynamically and kinetically competent in reaction (~same rate as hexanal)

ligand =

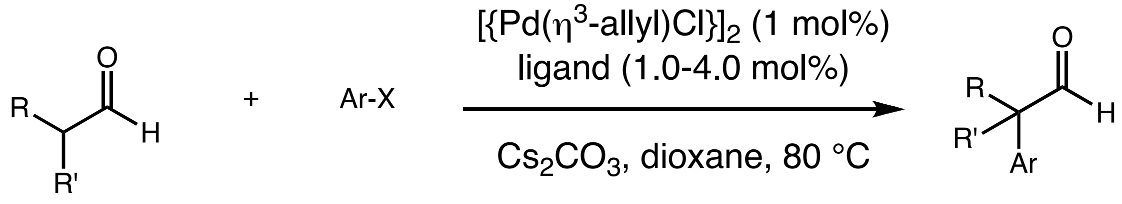


Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, T.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101.
Martin, R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 7236.

Arylation of Aldehydes

Intermolecular variants

■ Hartwig's conditions; easily reducible Pd precatalyst



$[\{Pd(\eta^3\text{-allyl})Cl\}]_2$ (1 mol%)
ligand (1.0-4.0 mol%)

Cs_2CO_3, dioxane, 80 °C

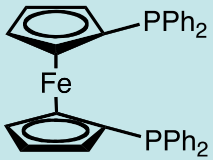
11 examples (R' = H), 61-93%
16 examples (R' = alkyl), 67-91%

R = alkyl, R' = alkyl or H

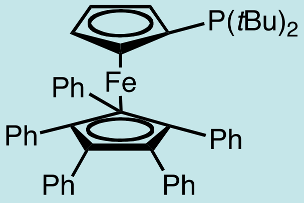
X = Cl or Br

- Comprehensive scope with respect to arene electronics
- Enhanced reactivity compared to Buchwald's BINAP-derived ligand
- Getting pre-catalyst into cycle faster helps to outcompete aldol

ligand for
linear aldehydes



ligand for
branched aldehydes



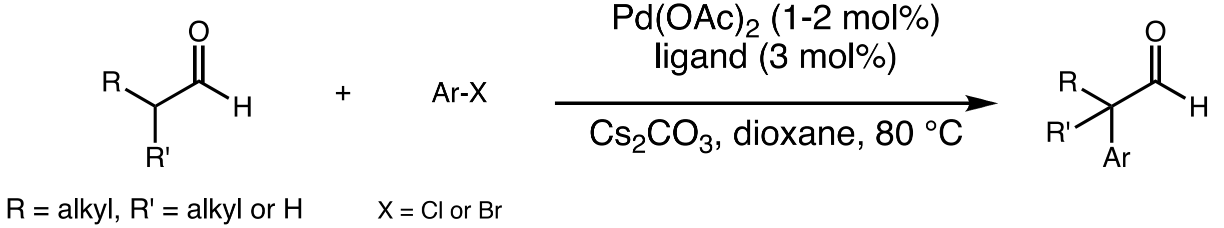
Vo, G. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 2127.

Arylation of Aldehydes

Intermolecular variants

■ Buchwald's second report; harnessing the power of water-mediated preactivation

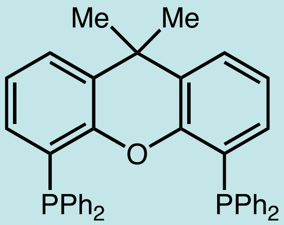
- Pre-generate $L_nPd(0)$ by heating $Pd(OAc)_2$ (1 mol%), H_2O (4 mol%), and ligand (3 mol%) for 1 minute at 80 °C in dioxane



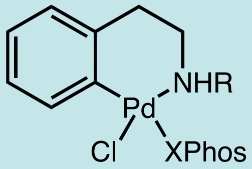
12 examples (R' = H)
X = Cl; 51-75%, X = Br; 56-84%

6 examples (R' = alkyl)
X = Cl; 51-60%, X = Br; 54-68%

ligand for aryl bromides



one-component precatalyst for aryl chlorides



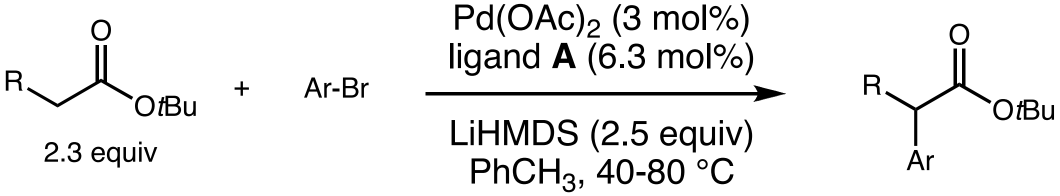
- Method stands up to more challenging electron-rich arenes (all arenes electron-rich)

"*According to the known -I effect of a methoxy group in the meta position, 3-chloroanisole cannot be considered electron-neutral*"

Catalyst pre-activation: Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505.
Aldehyde arylation: Martin, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561.

α-Arylation of Esters

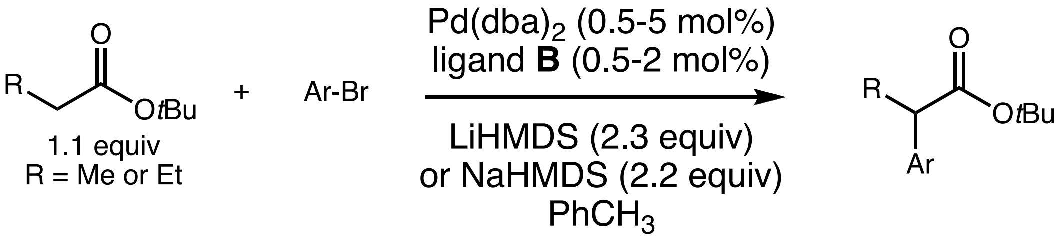
Buchwald's system based on *o*-biphenyl phosphines



propionate esters: 48-92%
acetate esters: 66-90%
phenylacetate esters: 71-90%

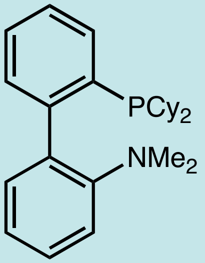
- LiHMDS essential for complete conversion
- *t*-Butyl esters necessary in most cases to minimize Claisen products

Hartwig's system based on NHC ligand

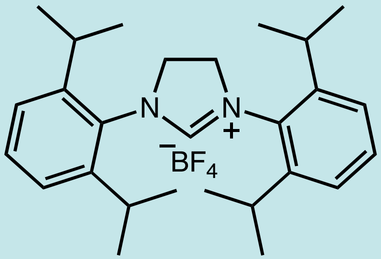


propionate esters: 66-88%
acetate esters: 60-98%

ligand **A**



ligand **B**

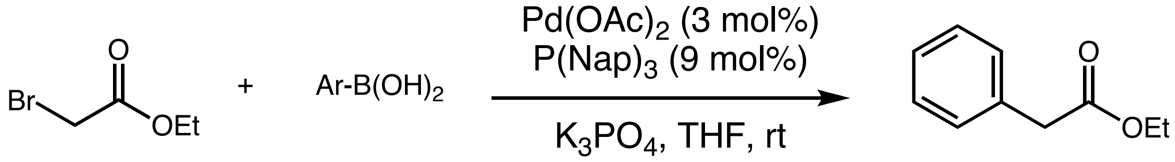


Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996.
Jorgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557.

α-Arylation of Esters

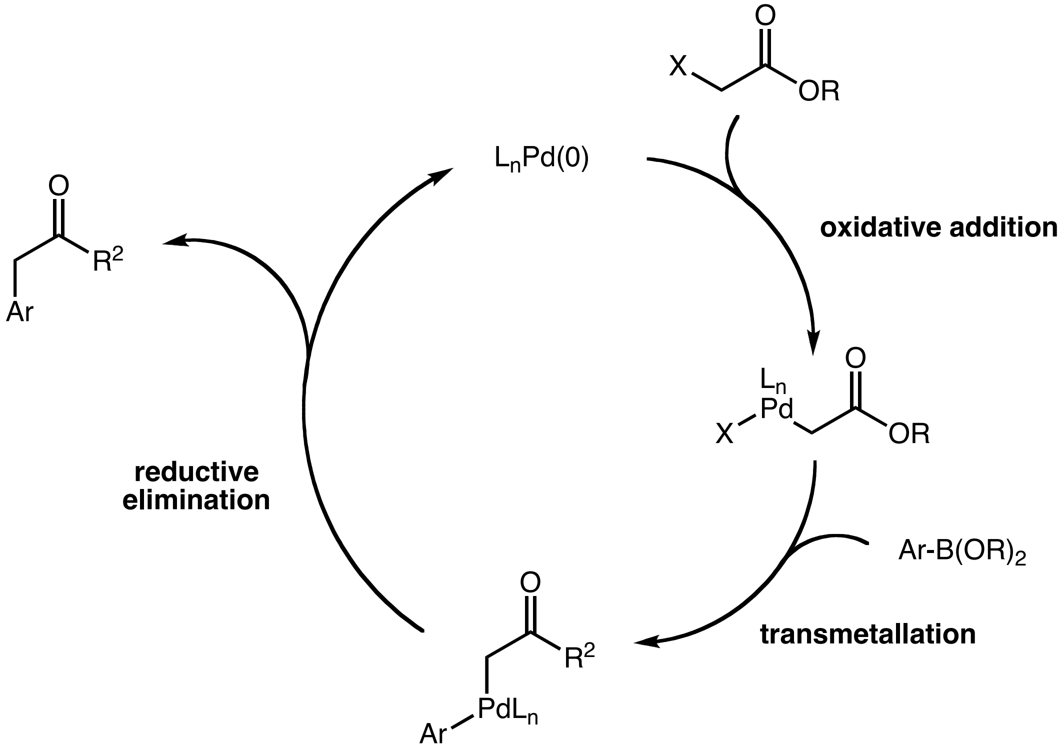
Gooβen's complementary method

Coupling of arylboronic acids and bromoacetic acid derivatives



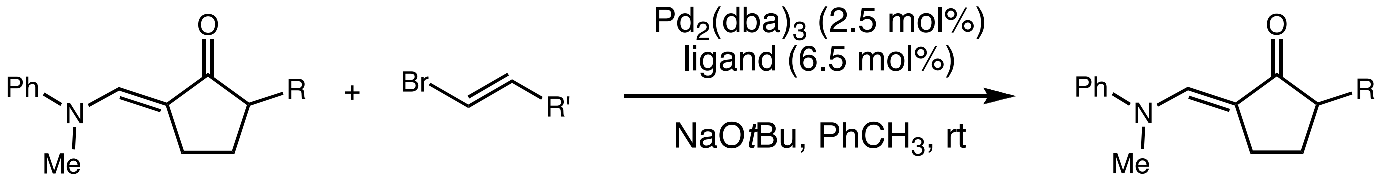
63-90%

Probable mechanism



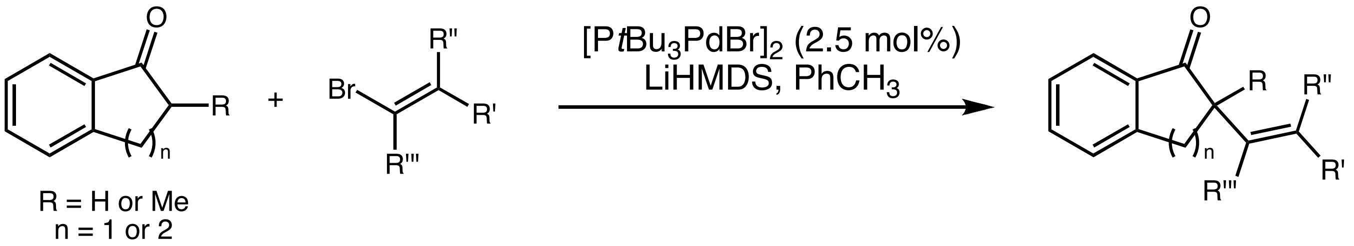
α-Vinylation of Ketones

Buchwald's catalytic, enantioselective method

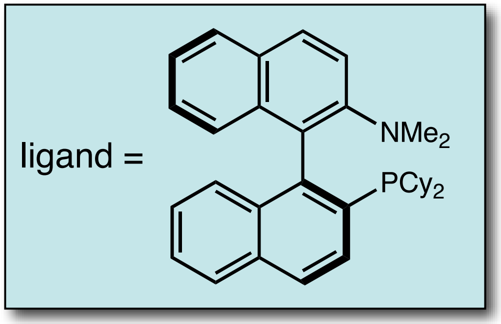


76-95%, 71-92% ee

Amgen's vinylation



62-95%



Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897.
Huang, J.; Bunel, E.; Faul, M. M. *Org. Lett.* **2007**, *9*, 4343.

Summary/Conclusions

Competition or checks & balances extremely beneficial

- Having two premier research groups working in the same area promotes rapid advancement in that field

Lessons learned (or re-learned for some...)

- Highly active catalysts are those which:
  - stabilize the Pd(0) intermediate
  - simultaneously promote oxidative addition and reductive elimination
  - contain bulky, electron-rich phosphines or NHCs

- Ultimately, reaction efficiency is highly-dependent upon:
  - carbonyl and halide (or pseudohalide) substrates
  - Pd source
  - ligand choice
  - solvent and base

- Asymmetric reactions are possible, though mostly confined to generation of quaternary centers