The Career of Gregory C. Fu

Eric Welin

MacMillan Group Meeting

May 9, 2012

Greg Fu: Biography

- Born 1963 in Galion, Ohio
- Graduated from MIT, 1985

  K. Barry Sharpless
- Ph.D. from Harvard, 1991

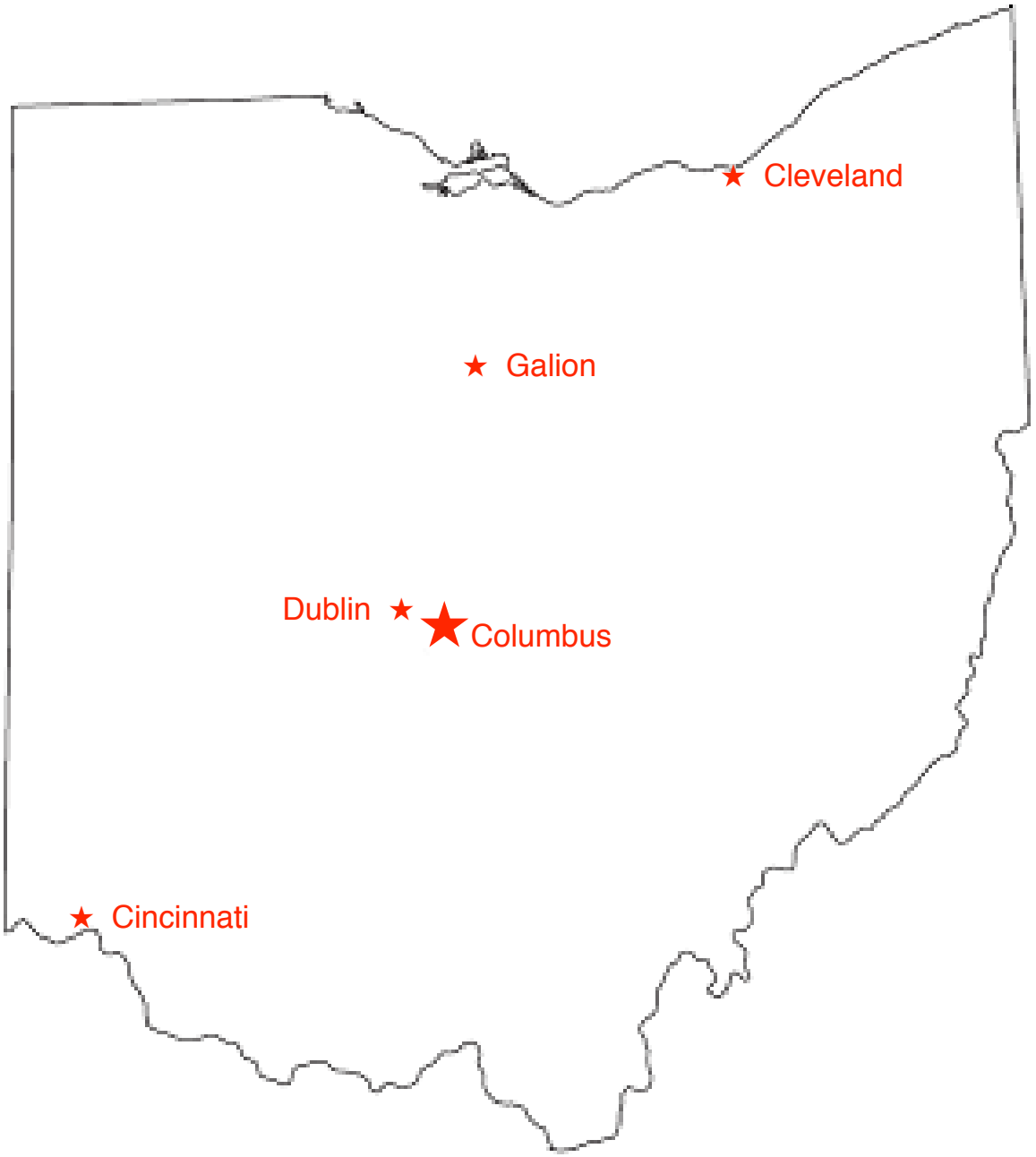
  David A. Evans – Rh/Ir catalyzed hydroborations
- Postdoctoral Fellow at CalTech, 1993

  Robert H. Grubbs – ring closing metathesis
- Assistant Professor at MIT, 1993-1998

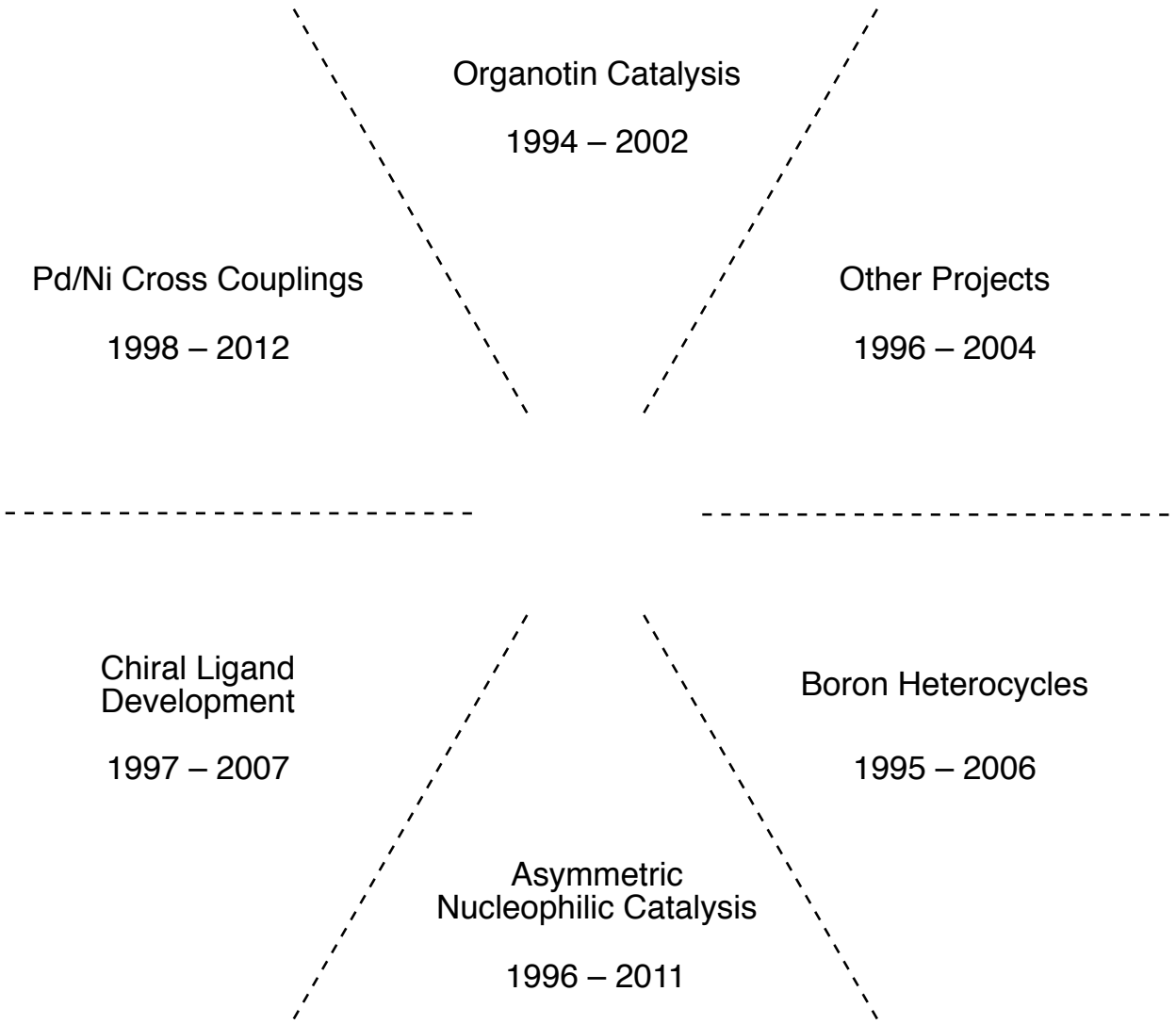
  Promoted to Associate Professor in 1998, Professor in 1999, Firmenich Professor of Chemistry in 2007
- Altair Professor of Chemistry, CalTech 2012

- NSF Young Investigator Award
- ACS Cope Scholar Award
- Fellow, Royal Society of Chemistry
- Fellow, American Academy of Arts and Sciences
- ACS Award for Creative Work in Synthetic Organic Chemistry

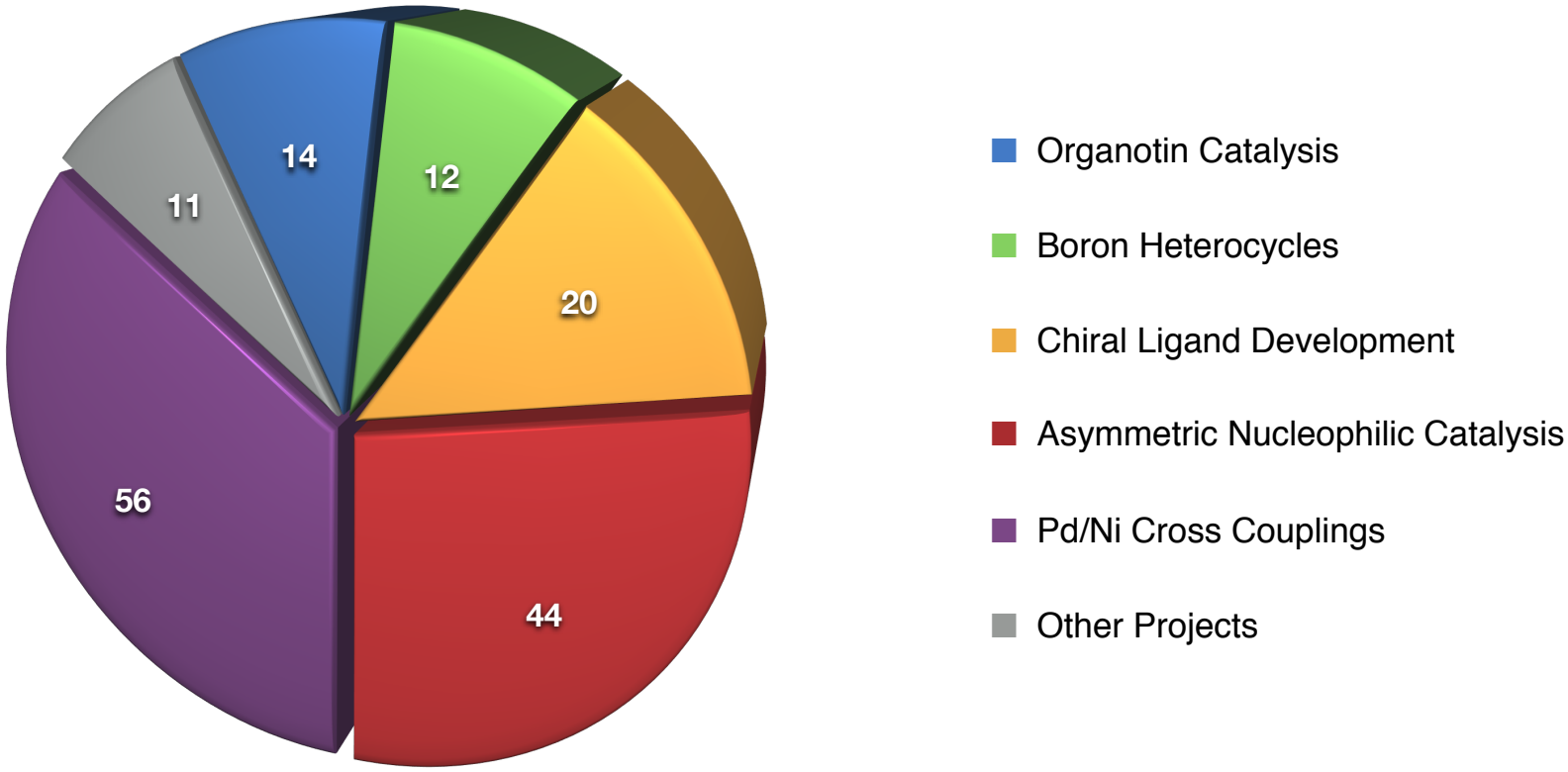
Ohio: A Geography Lesson



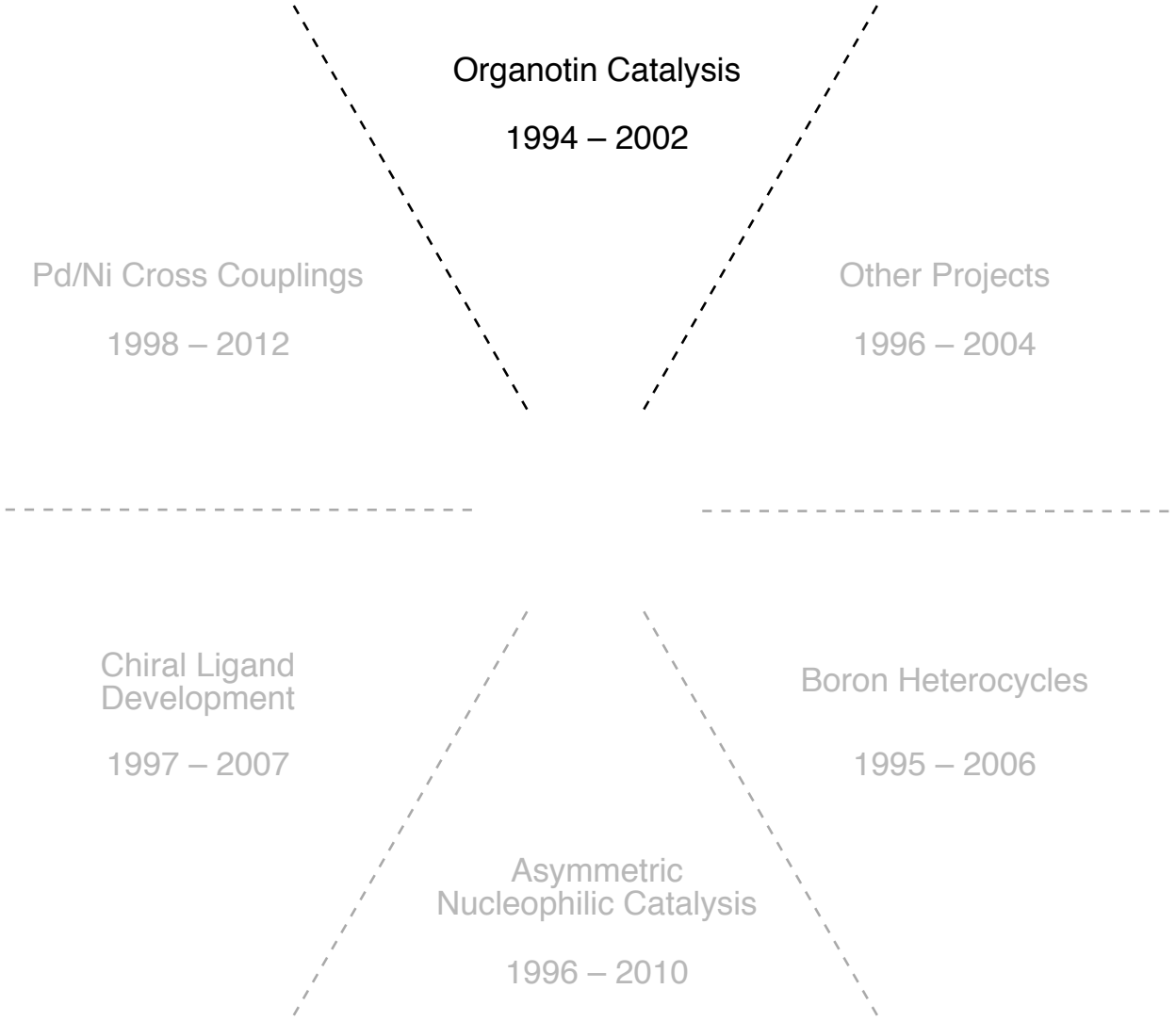
Greg Fu: Significant Research Areas



Publications by Research Area

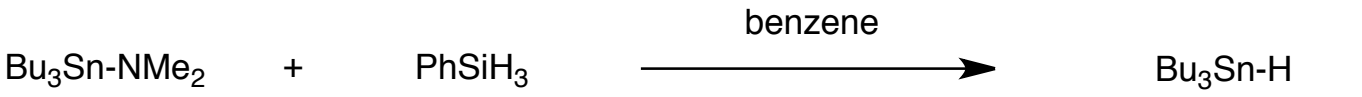


Greg Fu: Significant Research Areas



Organotin Catalysis: Reductions

- Regeneration of Sn-H (with $PhSiH_3$ or PMHS) allows use of catalytic quantities of alkyl tin



$t_{1/2} < 1$ min, 99%

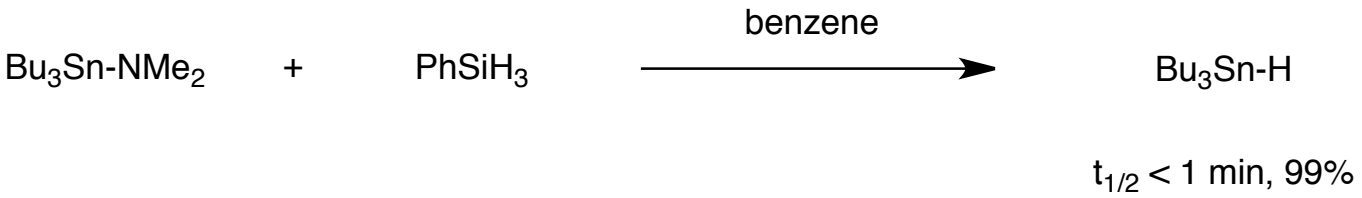
- will affect conjugate reduction of enones, reduction of *N*-benzyl imines, azides, nitroalkanes (to alkanes)

- unactivated olefins are not reduced under these conditions

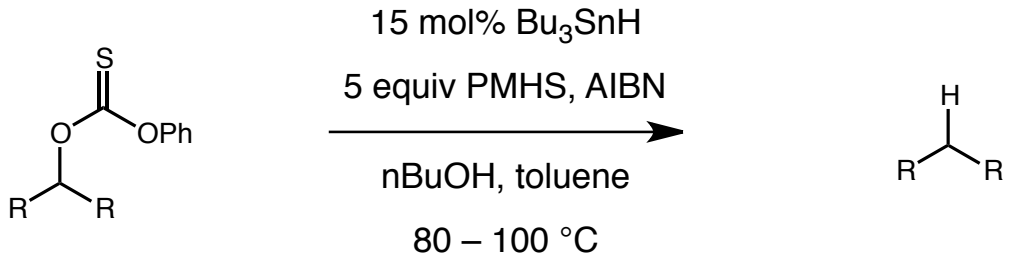
Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1997**, *62,* 7070
Hays, D. S.; Scholl, M.; Fu, G. C. *J. Org. Chem.* **1996**, *61,* 6751
Lopez, R.; Fu, G. C. *Tetrahedron.* **1997**, *53,* 16349
Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63,* 2796
Tormo, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1997**, *62,* 7070

Organotin Catalysis: Reductions

- Regeneration of Sn-H (with $PhSiH_3$ or PMHS) allows use of catalytic quantities of alkyl tin



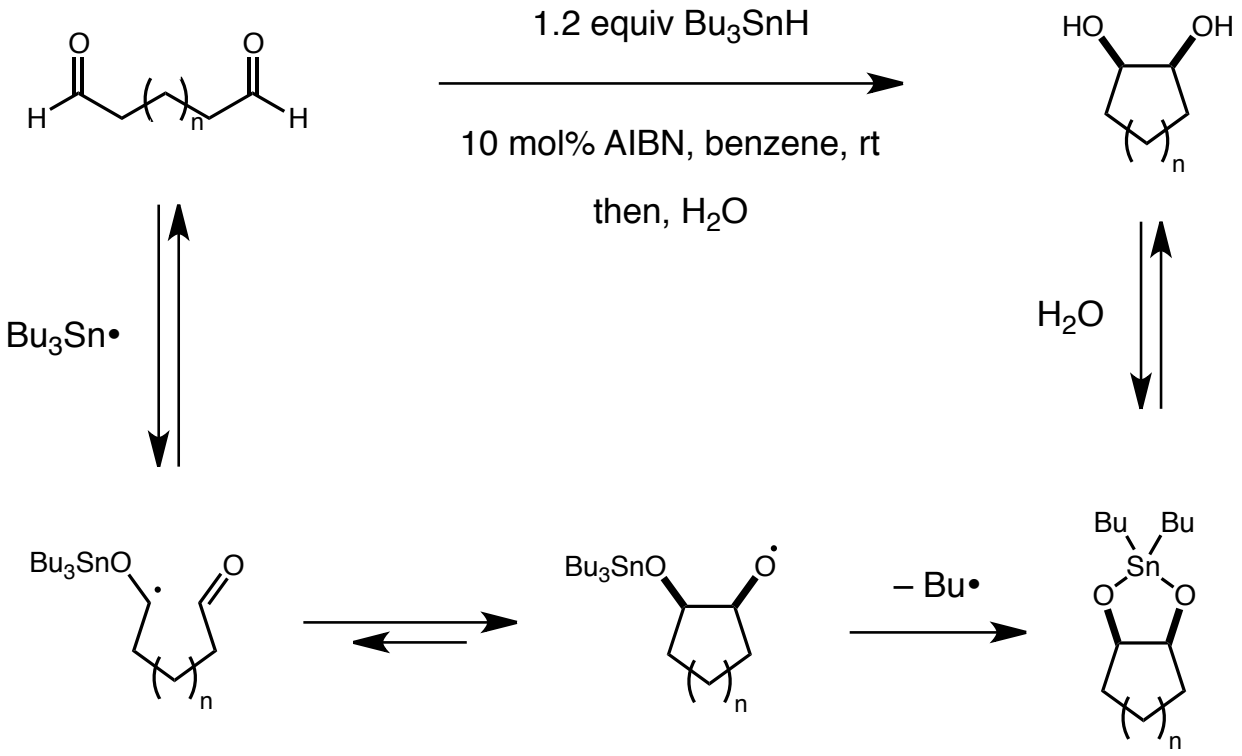
- catalytic Barton-McCombie deoxygenation



Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119,* 6949

Organotin Mediated Reductive Cyclizations

- tin ketyl radical cyclization of dialdehydes

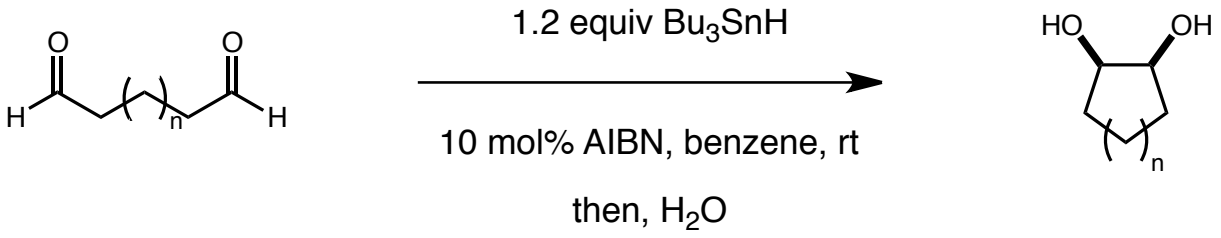


- reaction is very cis-selective in closing 5-membered rings; not selective with 6-membered rings
- reaction is more efficient for 6-membered rings (84-88%); less so for 5-membered rings (46-64%)

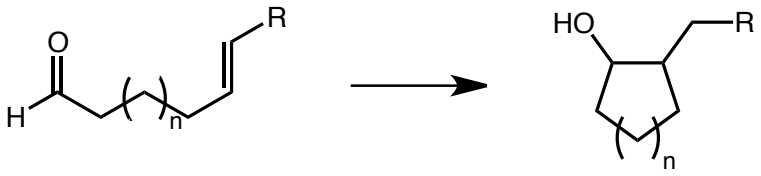
Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117,* 7283

Organotin Mediated Reductive Cyclizations

- tin ketyl radical cyclization of dialdehydes



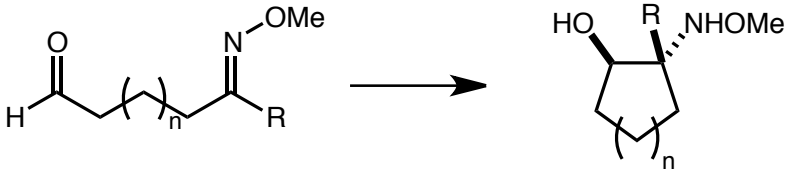
- olefin substrates (catalytic Sn + $PhSiH_3$)



66-85%

poor selectivity

- *O*-methyl oxime substrates (catalytic Sn + $PhSiH_3$)

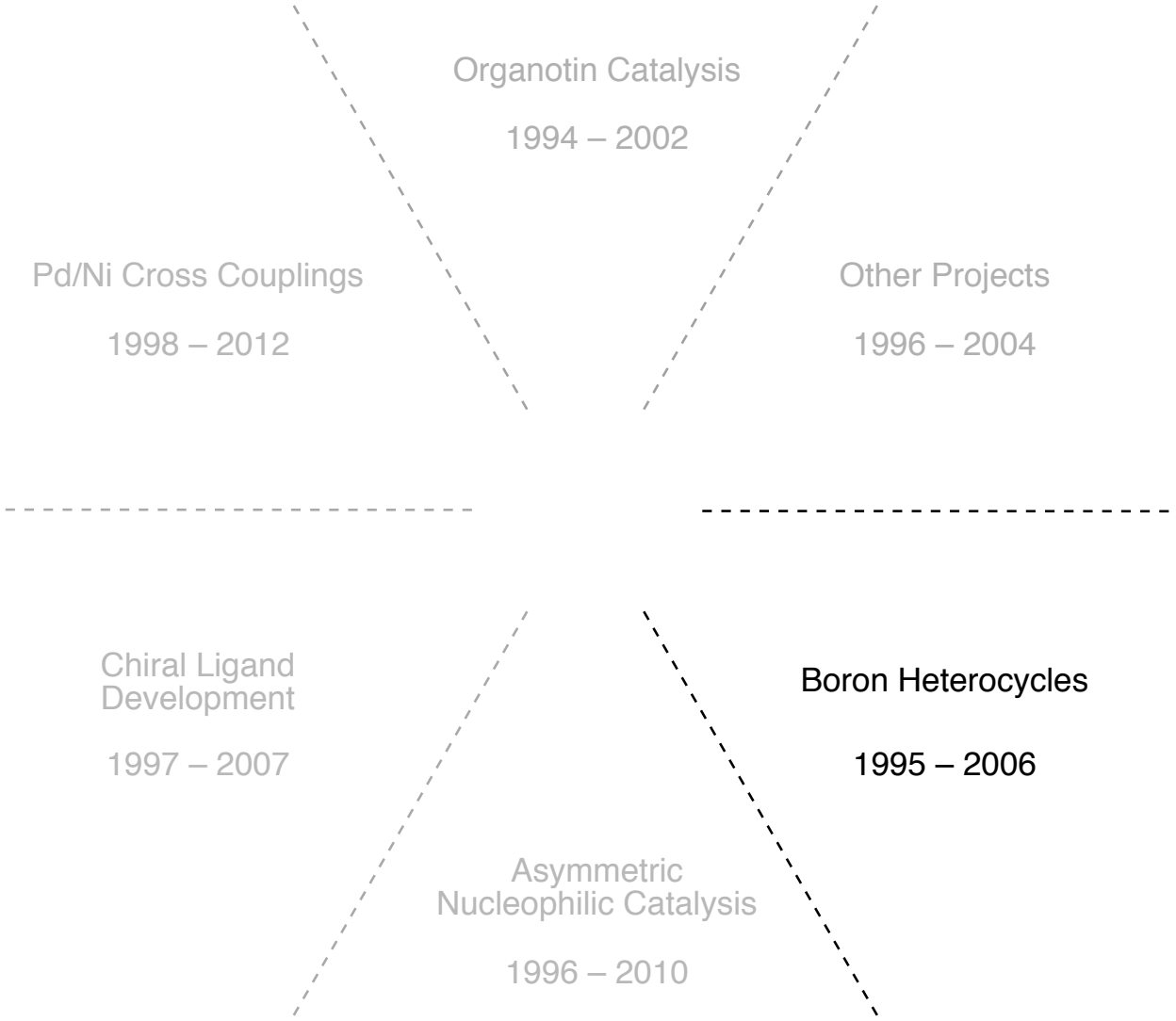


44-84%

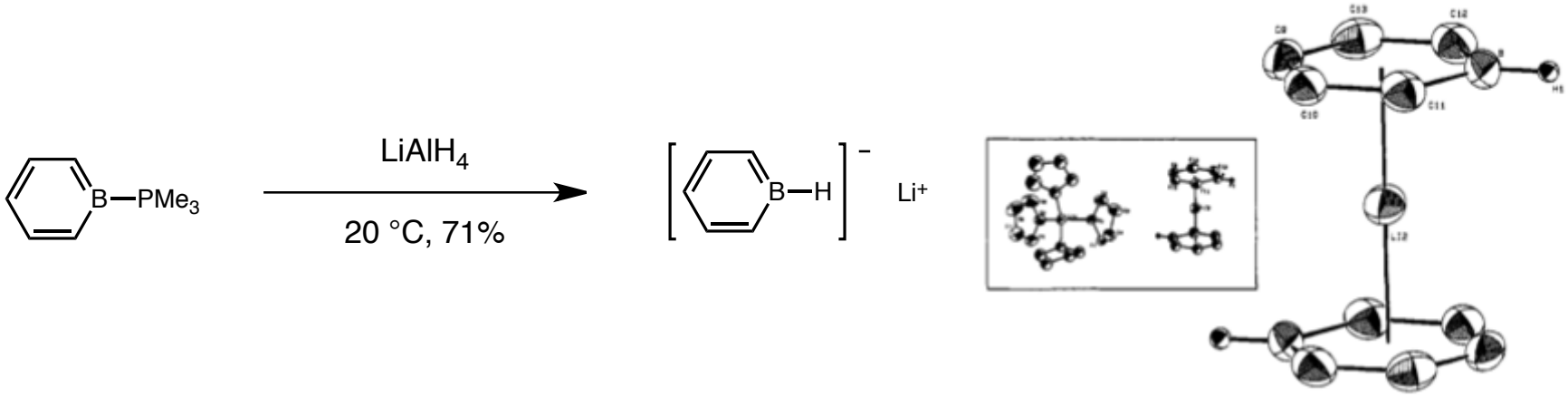
trans selective (2-180:1)

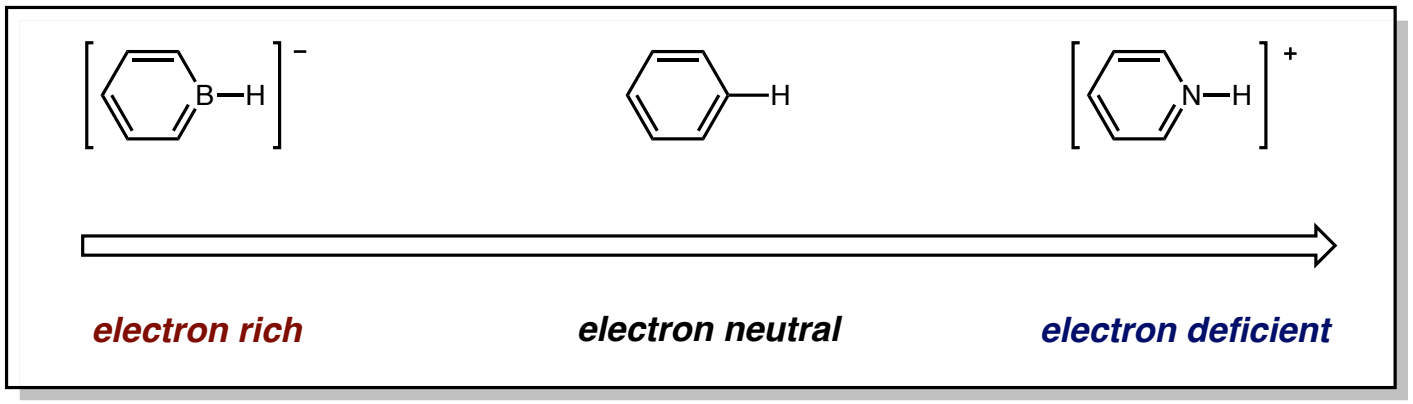
Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4
Tormo, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 201

Greg Fu: Significant Research Areas



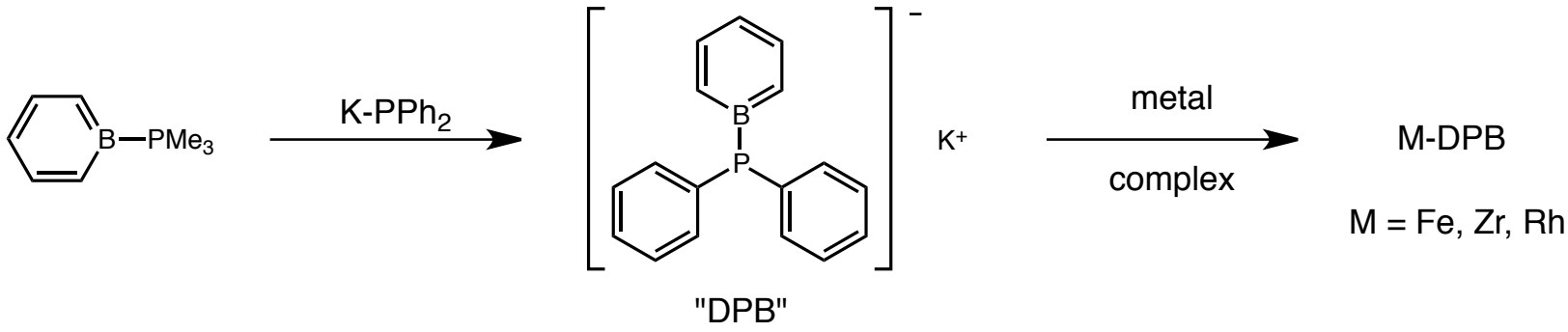
*Synthesis of 1-*H*-boratabenzene*





Hoic, D. A.; Davis, W. M.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117*, 8480

DPB: A boron analogue of PPh_3



"DPB"

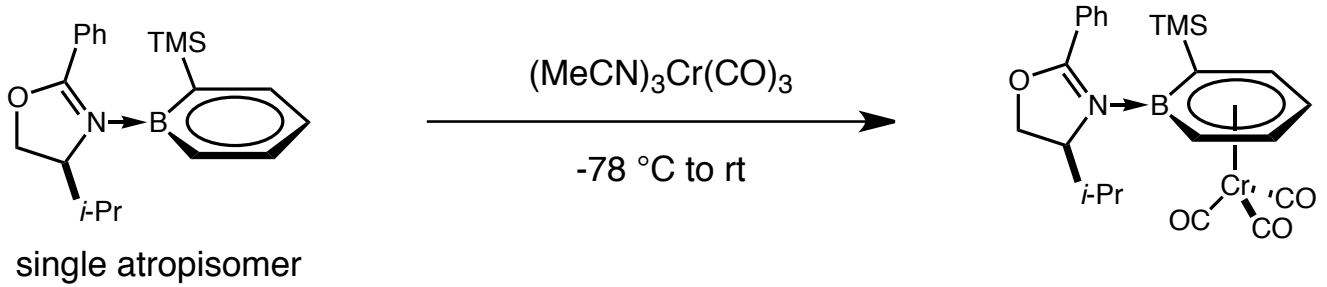
monodentate, electron-rich

entry	DPB complex	ν_{CO} (cm^{-1})
1	$[CpFe(CO)_2(\mathbf{PPh_3})]^+$	2025, 2070
2	$CpFe(CO)_2(\mathbf{DPB})$	1989, 2035
3	$CpFe(CO)_2(\mathbf{PPh_2})$	1966, 2015

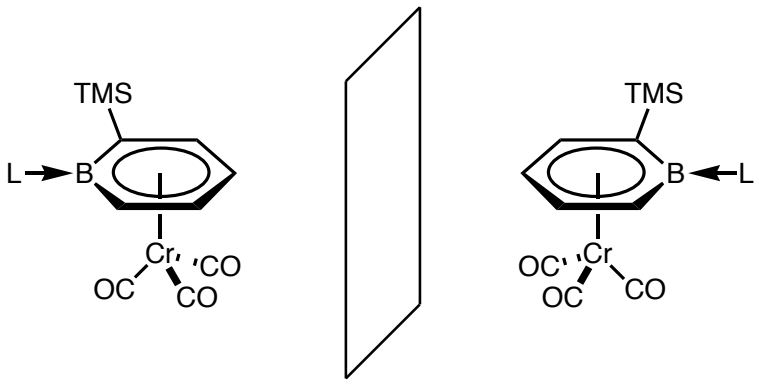
- IR stretches of CO bonds can be used to determine relative electron-richness
- more electron rich ligands = more M→CO donation = lower stretching frequency
- $(PPh_2)^-$ > DPB > PPh_3

Qiao, S.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1996**, *118*, 6329
Hoic, D. A.; Davis, W. M.; Fu, G. C. *J. Am. Chem. Soc.* **1996**, *118*, 8176

The first enantiopure planar-chiral Lewis acid complex

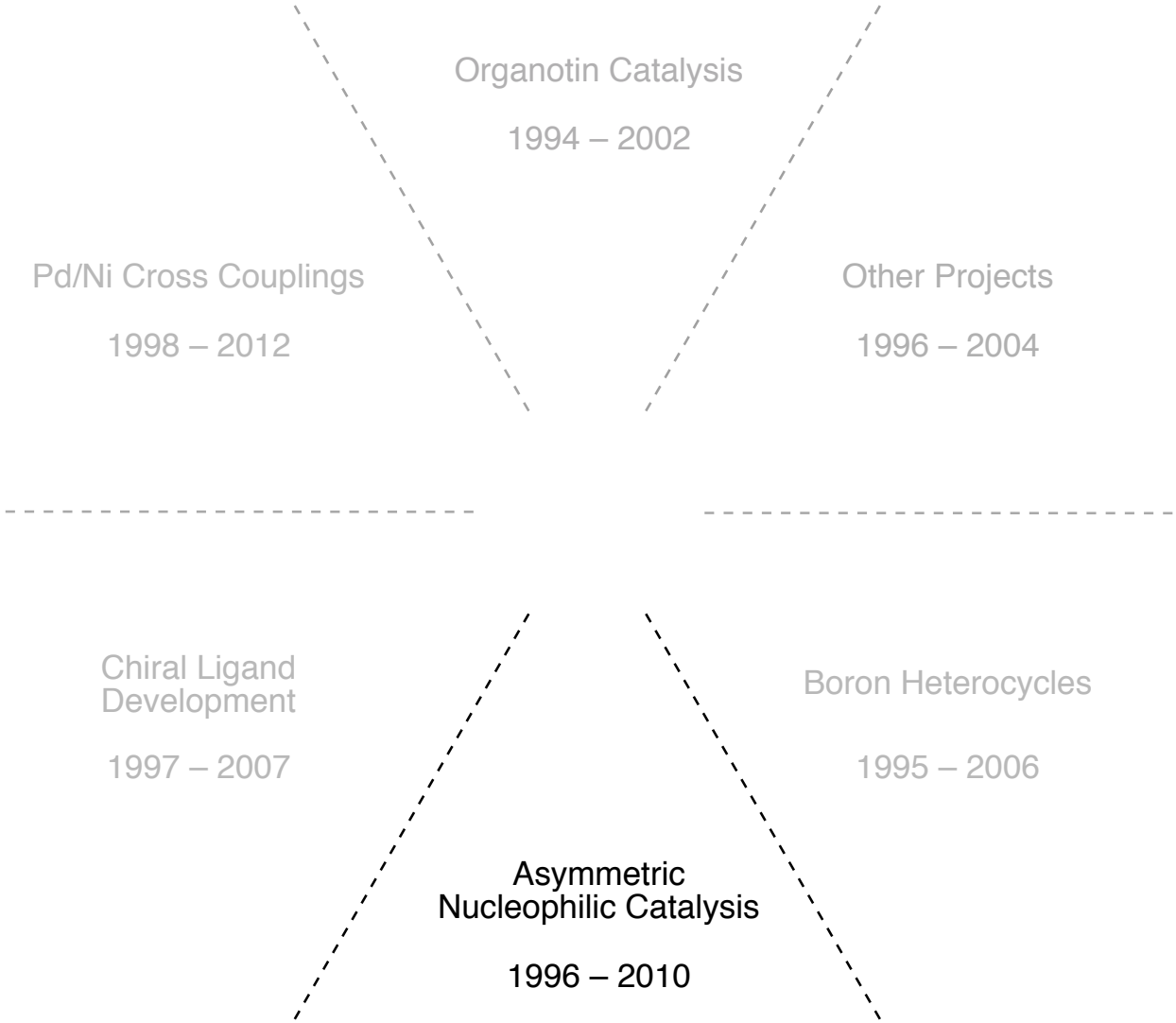


single atropisomer

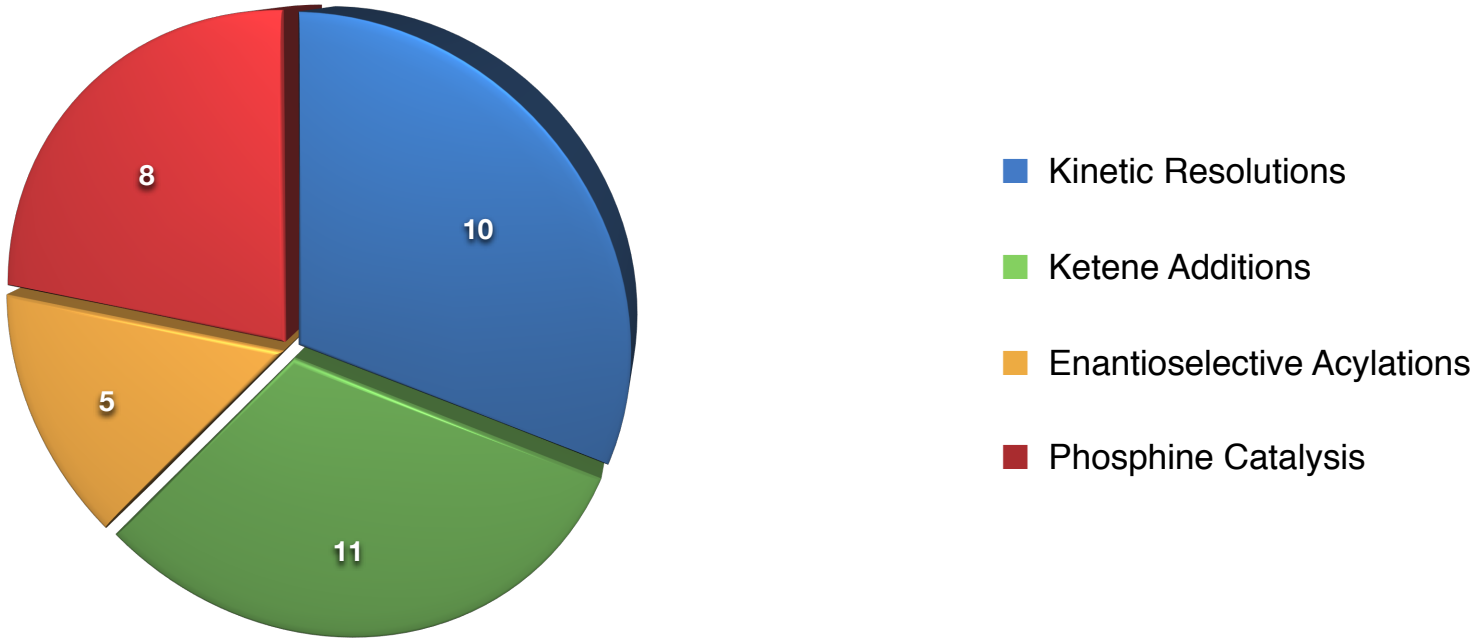


Tweddell, J.; Hoic, D. A.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 8286

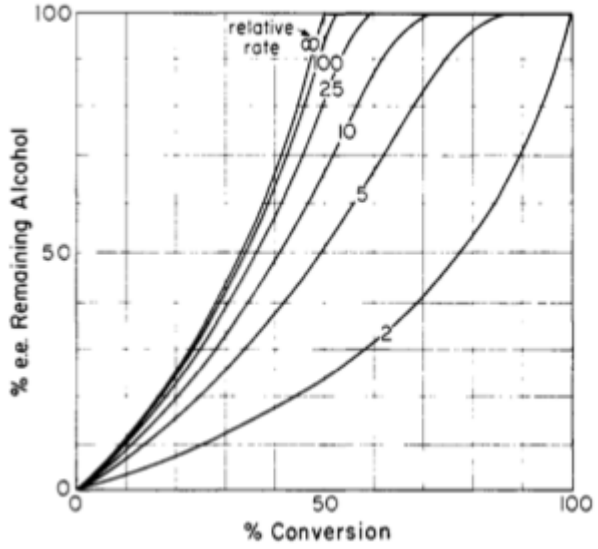
Greg Fu: Significant Research Areas



Asymmetric Nucleophilic Catalysis



Asymmetric Nucleophilic Catalysis: Kinetic Resolutions

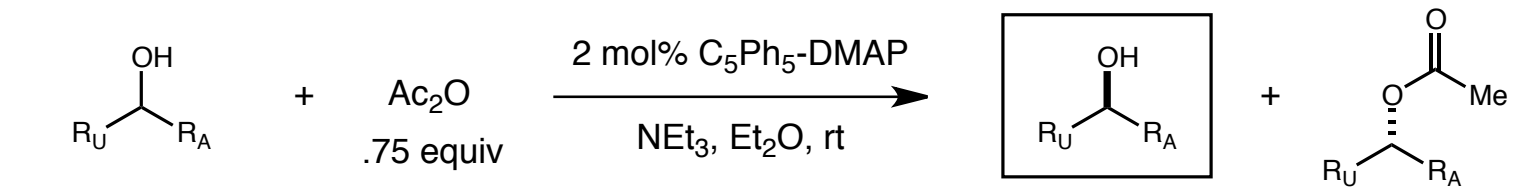


$$s = \frac{\text{rate of fast-reacting enantiomer}}{\text{rate of slow-reacting enantiomer}}$$

Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237

Asymmetric Nucleophilic Catalysis: Kinetic Resolutions

- acylation of racemic allylic/benzylic alcohols

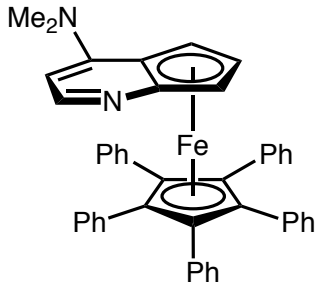


R_U = unsaturated

R_A = alkyl

s = 12-52

C_5Ph_5-DMAP =



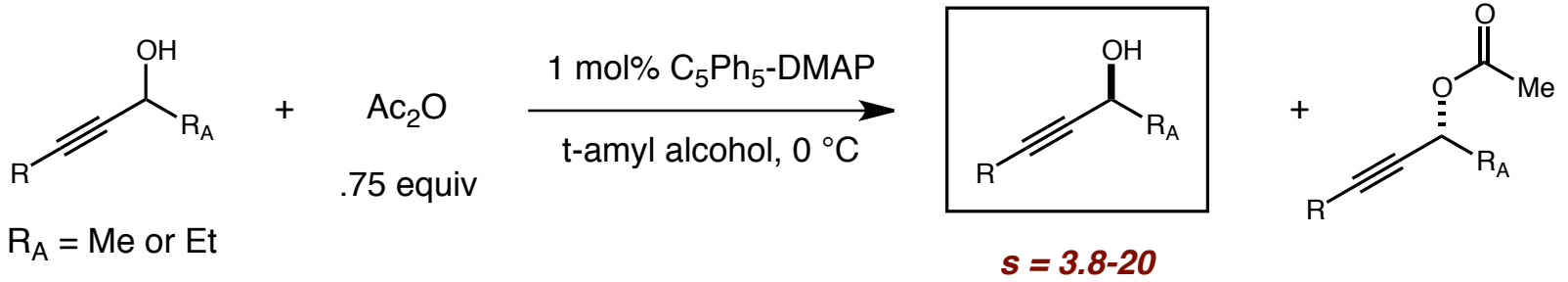
- s is rather independent of R_U; increases with steric bulk of R_A
- previous best catalytic, non-enzymatic kinetic resolution of allylic/benzylic alcohols had s ≤ 7
- chaning solvent to t-amyl alcohol provides increased selectivity (s = 32-95)

$$s = \frac{\text{rate of fast-reacting enantiomer}}{\text{rate of fast-reacting enantiomer}}$$

Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249
Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492
Ruble, C. J.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794

Asymmetric Nucleophilic Catalysis: Kinetic Resolutions

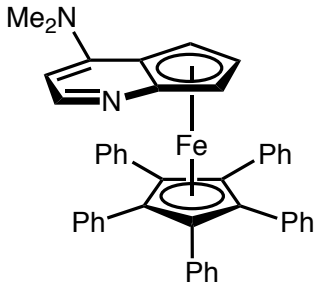
- acylation of racemic propargylic alcohols

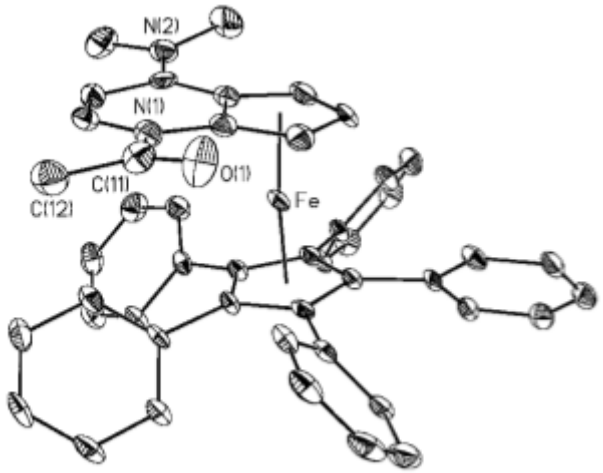


R_A = Me or Et

***s* = 3.8-20**

C_5Ph_5-DMAP =

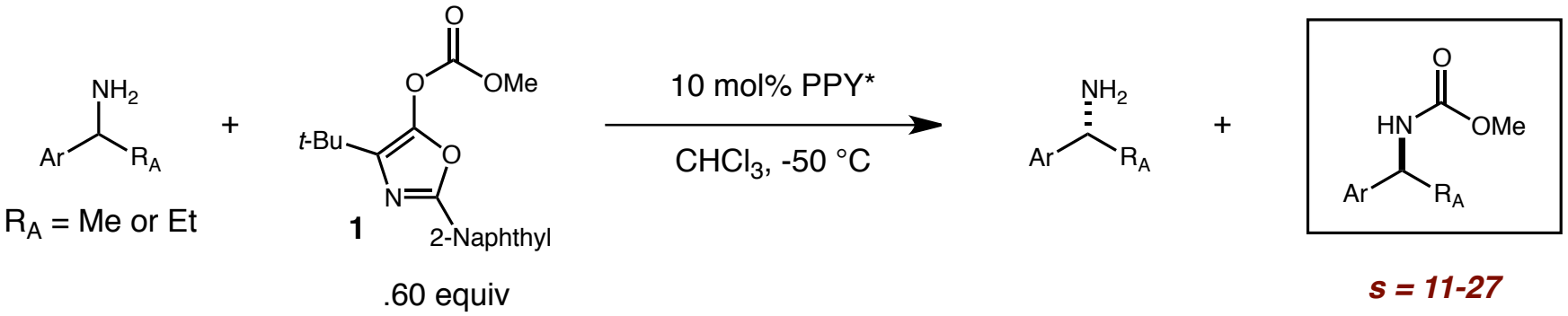




Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091

Asymmetric Nucleophilic Catalysis: Kinetic Resolutions

- acylation of racemic benzylic amines



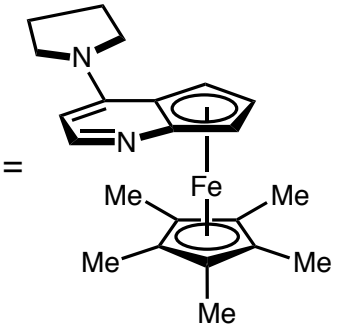
R_A = Me or Et

1

.60 equiv

***s* = 11-27**

PPY* =

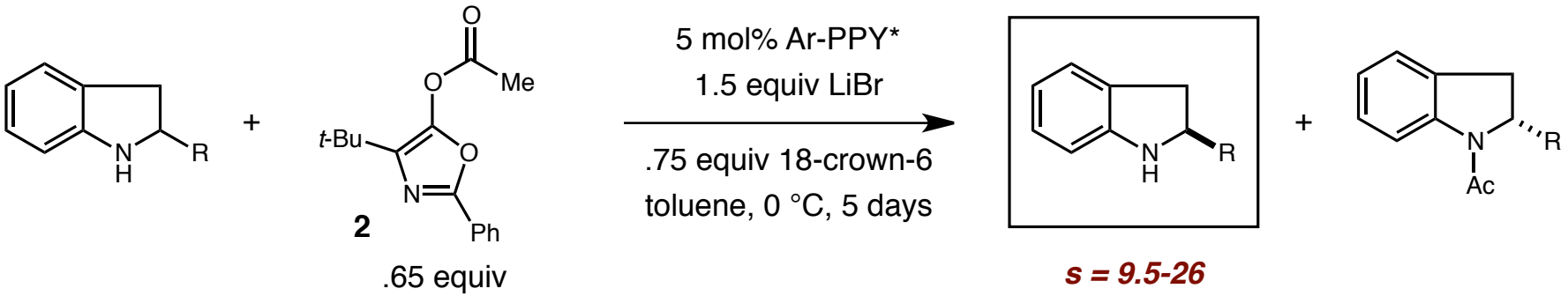


- amines are very challenging substrates due to their nucleophilicity → background
- earlier acylation studies showed that acyloxy oxazole **1** selectively and rapidly acylates the PPY* catalyst
- use of pre-acylated PPY* also accomplishes the acylation (non-catalytic)

Ie, Y.; Fu, G. C. *Chem. Commun.* **2000**, 119
Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234

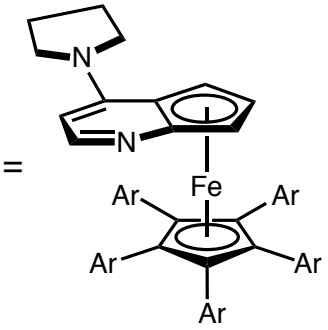
Asymmetric Nucleophilic Catalysis: Kinetic Resolutions

- acylation of racemic 2-substituted indolines



s = 9.5-26

Ar-PPY* =



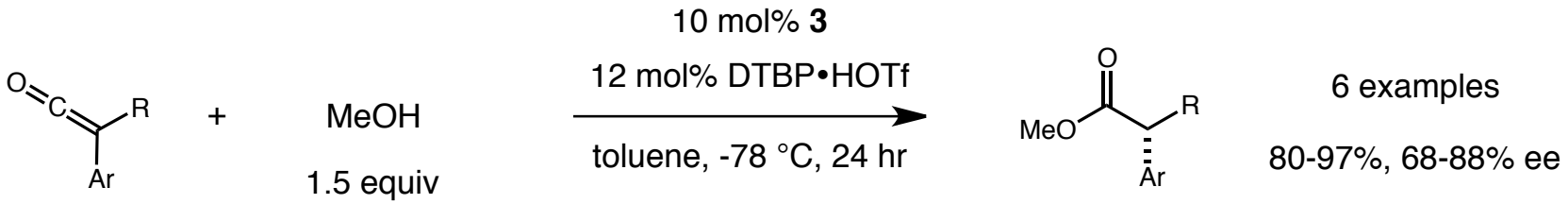
Ar = 3,5-Me_2Ph

- no previous method existed for kinetic resolution of indolines
- selectivity factor is strongly ion dependent

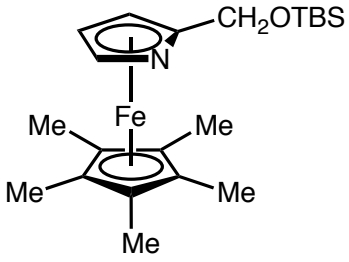
Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264

Asymmetric Nucleophilic Catalysis: Ketene Additions

- addition of methanol shows moderate enantioselectivity



3 =

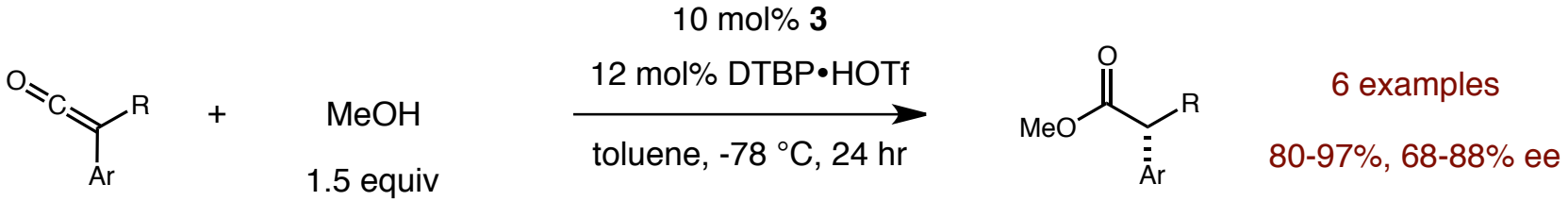


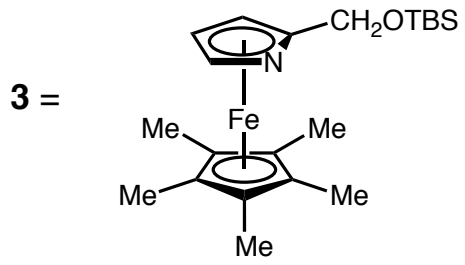
- 56% ee observed without DTBP•HOTf, 77% with
- strong KIE observed (3.2) with CH_3OD

Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637

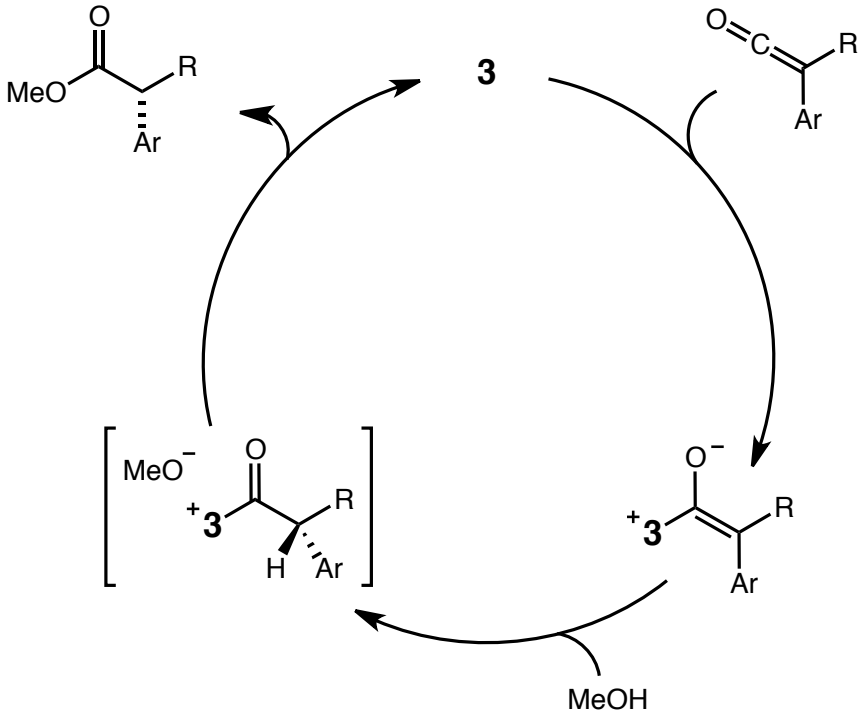
Asymmetric Nucleophilic Catalysis: Ketene Additions

- addition of methanol shows moderate enantioselectivity





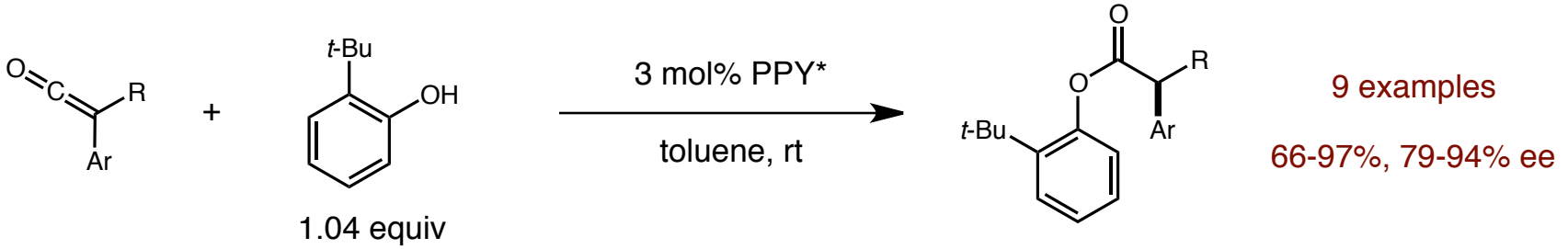
- initial mechanism involved enantioselective protonation of catalyst bound enolate



Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637

Asymmetric Nucleophilic Catalysis: Ketene Additions

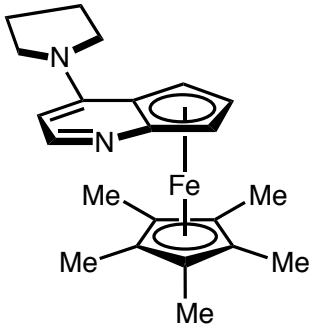
- use of a more acidic alcohol and a more basic catalyst improves ee



9 examples

66-97%, 79-94% ee

PPY* =

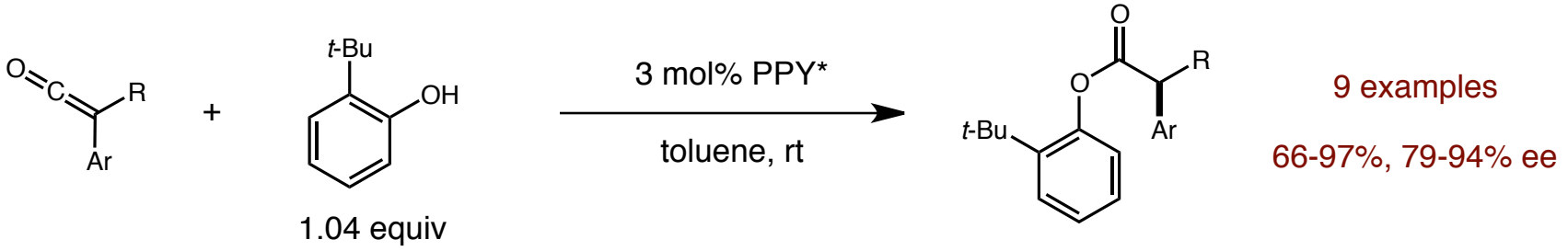


- resting state of catalyst is protonated ion pair with phenoxide anion
- highest ee's achieved in nonpolar solvent in dilute concentrations
- these observations suggest that PPY* is serving as a chiral Brønsted acid

Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006
Schaefer, C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2005,** *44*, 4606
Lee, E. C.; McCauley, K. M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2007,** *46*, 977
Dai, X.; Nakai, T.; Romero, J. A. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2007,** *46*, 4367

Asymmetric Nucleophilic Catalysis: Ketene Additions

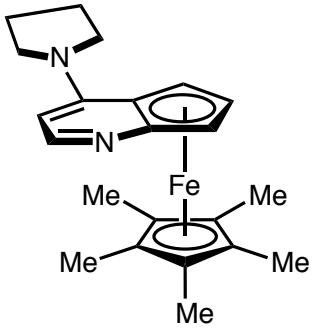
- use of a more acidic alcohol and a more basic catalyst improves ee

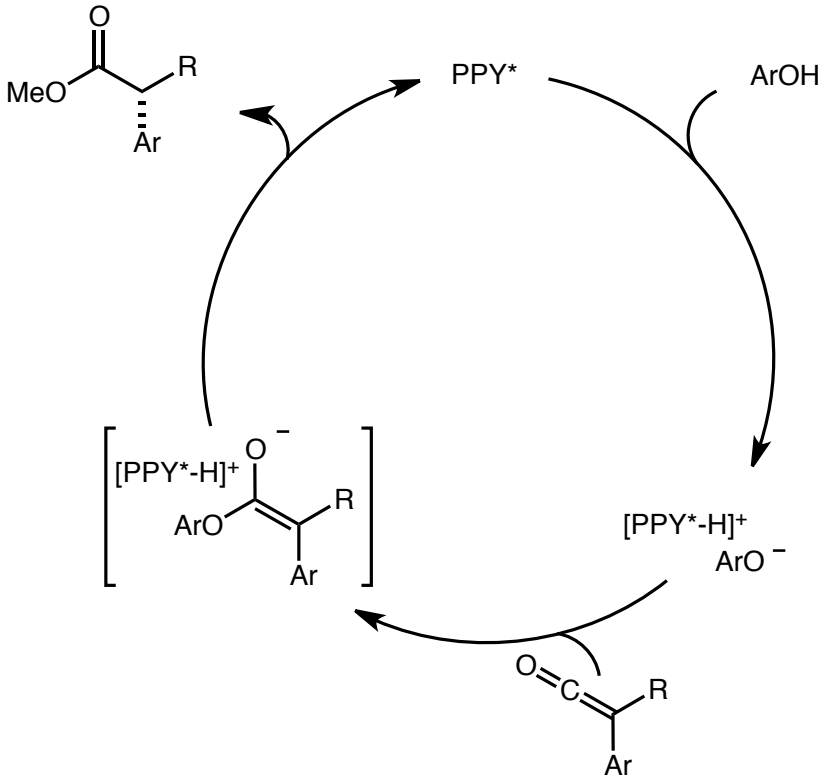


9 examples

66-97%, 79-94% ee

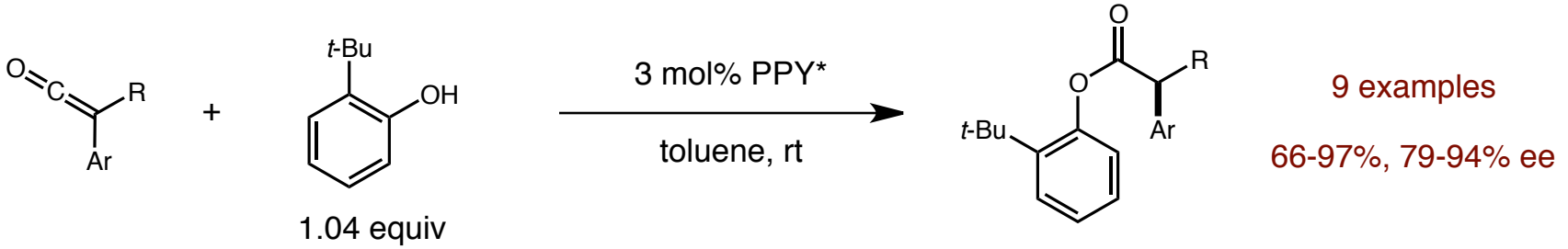
PPY* =





Asymmetric Nucleophilic Catalysis: Ketene Additions

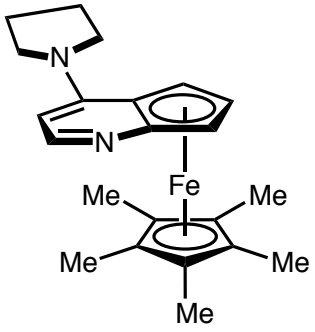
- use of a more acidic alcohol and a more basic catalyst improves ee



9 examples

66-97%, 79-94% ee

PPY* =



- this reaction manifold has been applied to addition of:
  - 2-cyanopyrrole
  - diphenylacetaldehyde
  - electrophilic chlorine (opposite enantiosense)
  - hydrazoic acid

Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006
Schaefer, C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2005,** *44*, 4606
Lee, E. C.; McCauley, K. M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2007,** *46*, 977
Dai, X.; Nakai, T.; Romero, J. A. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2007,** *46*, 4367

Asymmetric Nucleophilic Catalysis

- for references on enantioselective ketene [2+2] cycloadditions see:

Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578
Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6358
Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586
Berlin, J. M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 7048
Dochnahl, M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 2391

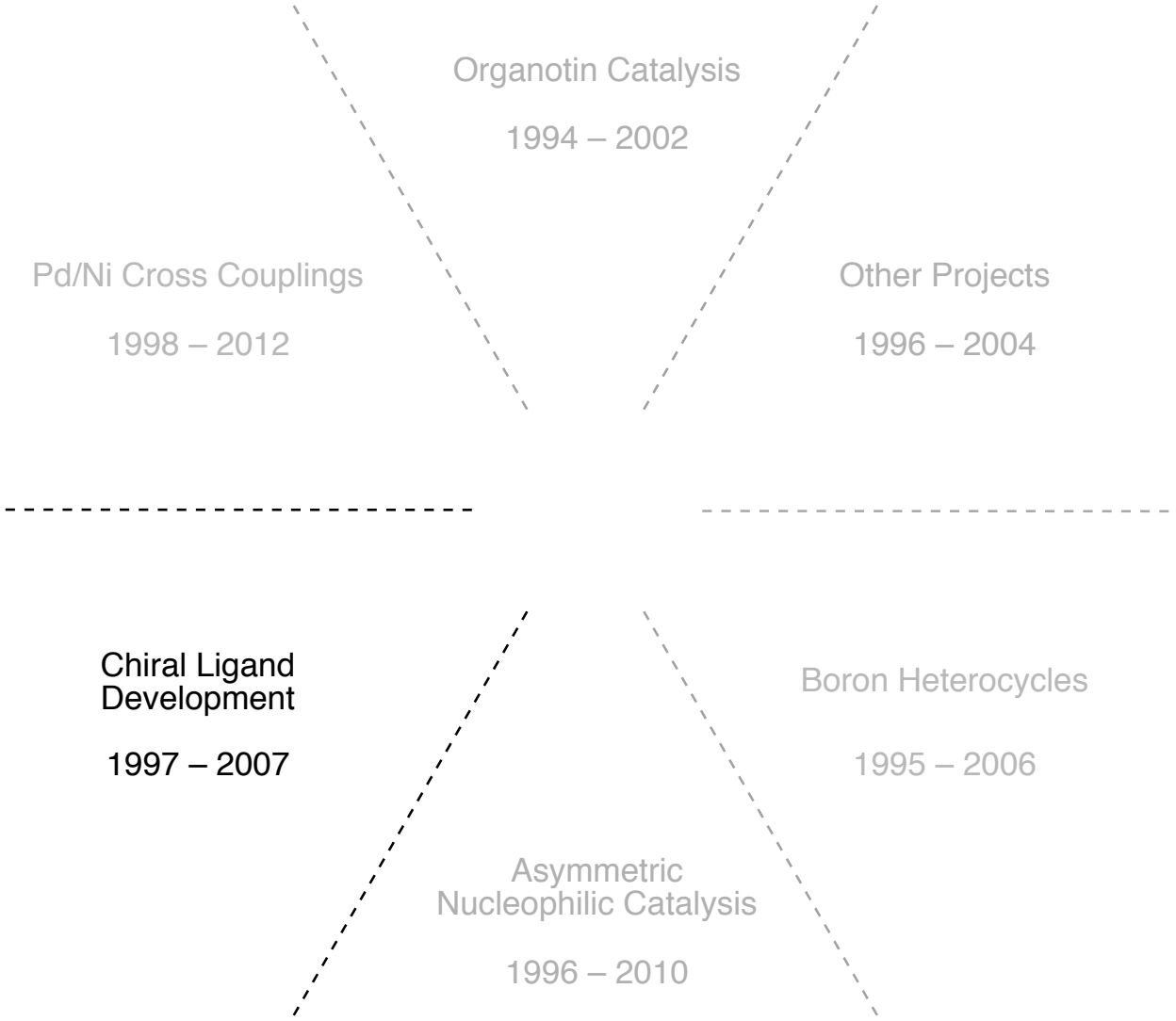
- for references on enantioselective acylations see:

Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532
Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050
Hills, I. D.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 3921
Mermerian, A. H.; Fu, G. C. *Angew. Chem. Int. Ed.* **2005**, *44*, 949
Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604

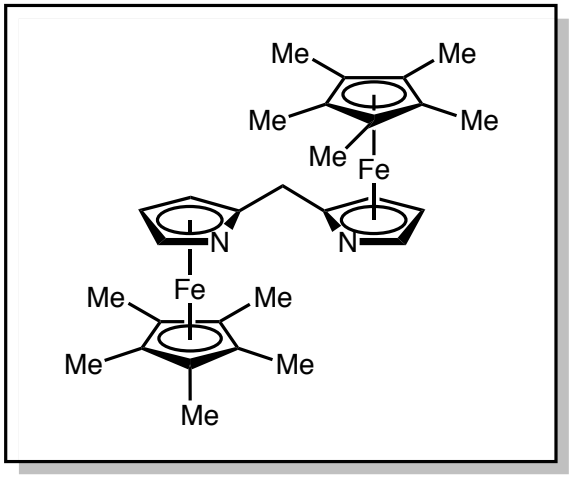
- for references on enantioselective phosphine catalysis

Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234
Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1426
Chung, Y. K.; Fu, G. C. *Angew. Chem.* **2009**, *121*, 2259
Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231
Wilson, J. E.; Sun, J.; Fu, G. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 161
Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 4568
Sinisi, R.; Sun, J.; Fu, G. C. *Proc. Nat. Acad. Sci. USA* **2010**, *107*, 20652
Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *133*, 12293

Greg Fu: Significant Research Areas



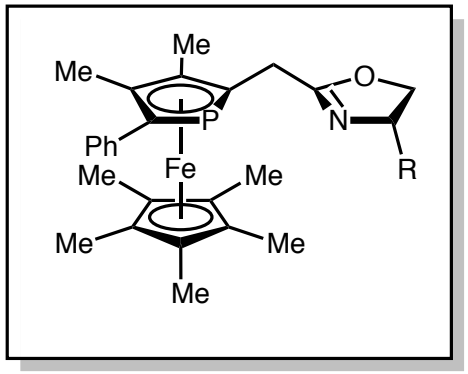
Bisazaferrocene: BISAF

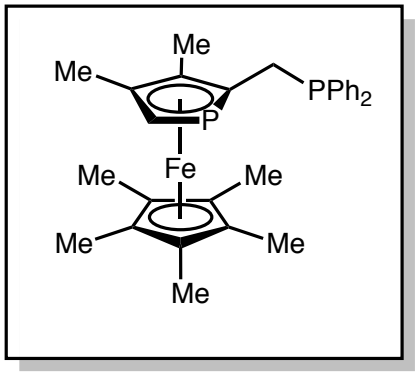


- structurally and electronically similar to bisoxazoline ligands
- has found use in copper carbenoid chemistry:
  - cyclopropanation
  - oxetane insertion
  - OH insertion
- also used in [3+2] cycloaddition between nitrones and alkynes

Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 10270
Lo, M. M.-C.; Fu, G. C. *Tetrahedron* **2001**, *57*, 2621
Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572
Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594

Phosphaferrocenes

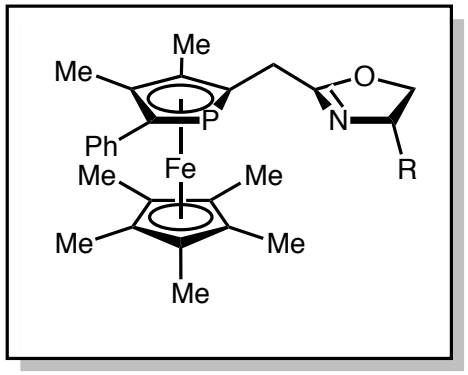


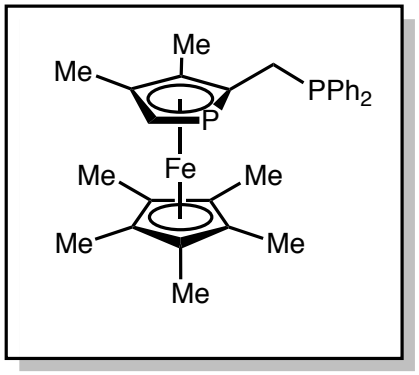


- also similar to bisoxazoline ligands, but somewhat more versatile:

Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699
Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778
Shintani, R.; Lo, M. M.-C.; Fu, G. C. *Org. Lett.* **2000**, *2*, 3695
Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M. C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870
Qiao, S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 4168

Phosphaferrocenes



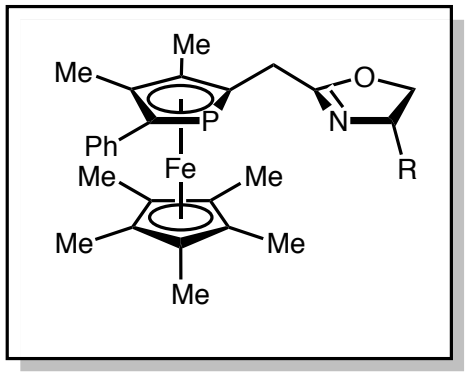


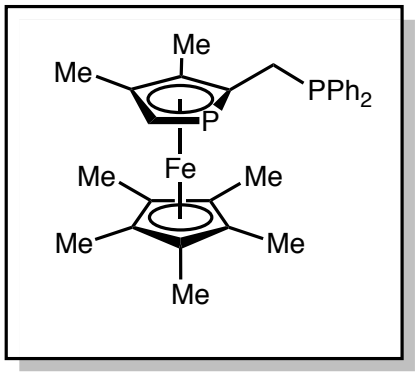
- also similar to bisoxazoline ligands, but somewhat more versatile:

- conjugate additions
- [3+2] cycloadditions
- Tsuji-Trost additions

Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699
Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778
Shintani, R.; Lo, M. M.-C.; Fu, G. C. *Org. Lett.* **2000**, *2*, 3695
Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M. C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870
Qiao, S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 4168

Phosphaferrocenes



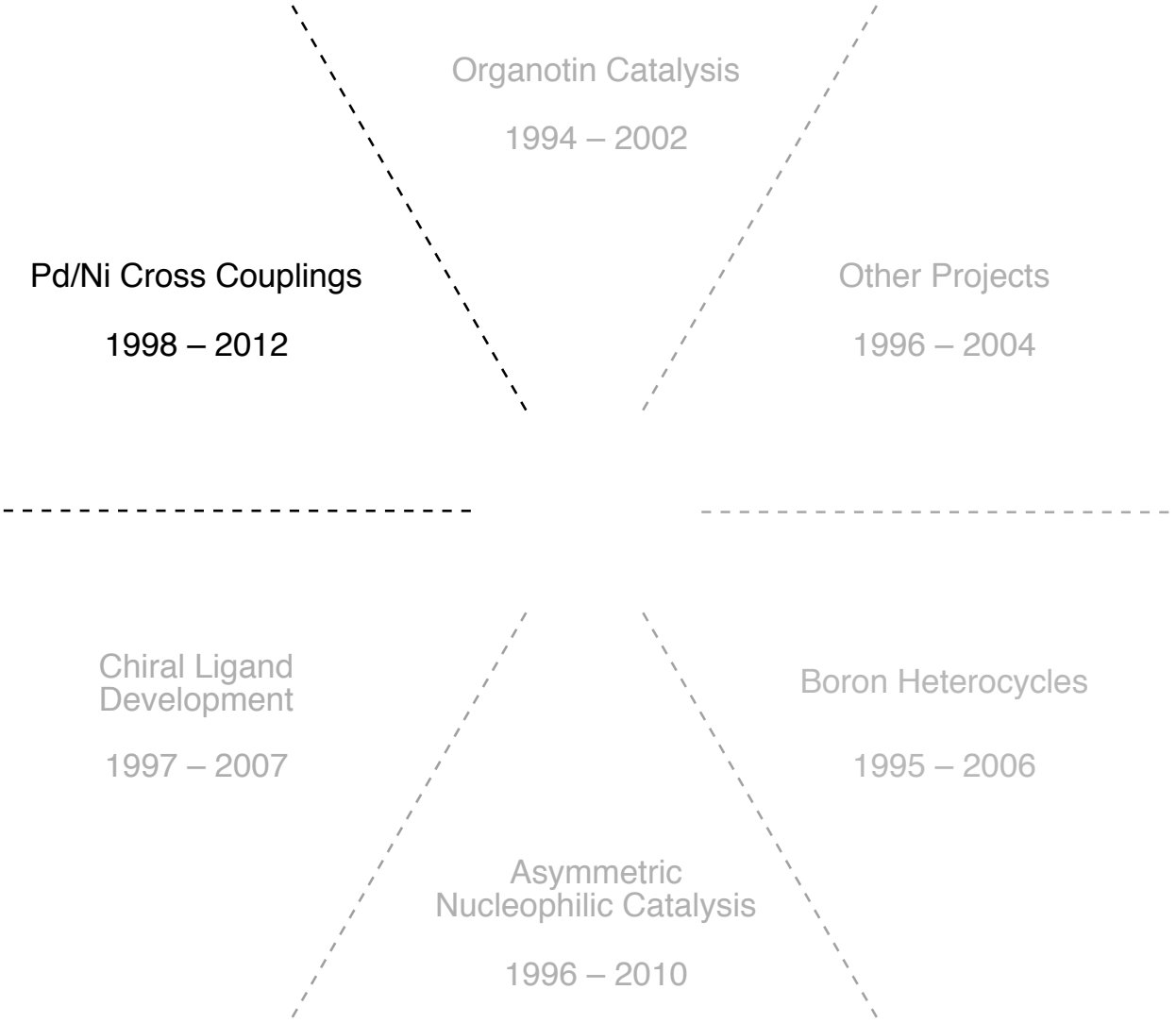


- also similar to bisoxazoline ligands, but somewhat more versatile:

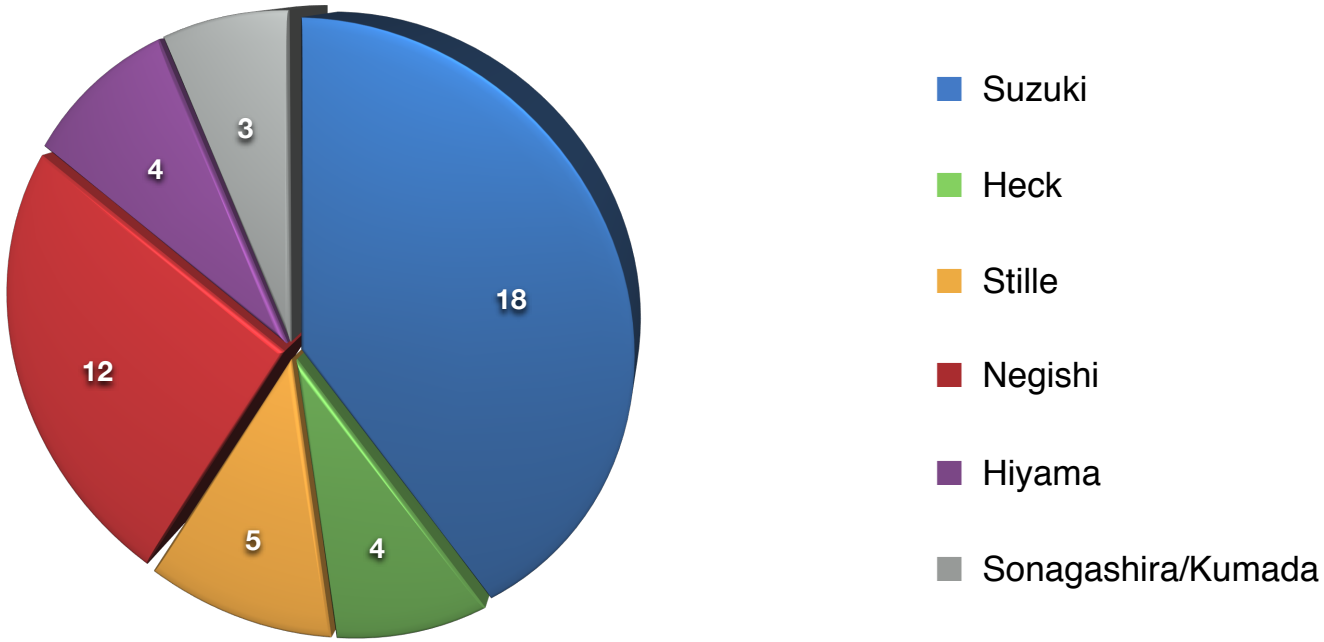
- conjugate additions
- [3+2] cycloadditions
- Tsuji-Trost additions
- allylic alcohol rearrangement
- asymmetric hydrogenation

Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699
Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778
Shintani, R.; Lo, M. M.-C.; Fu, G. C. *Org. Lett.* **2000**, *2*, 3695
Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M. C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870
Qiao, S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 4168

Greg Fu: Significant Research Areas

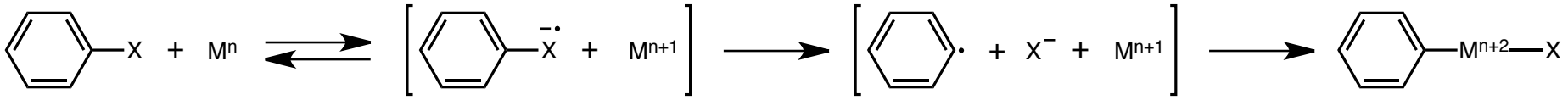


Pd/Ni Catalyzed Couplings



In the Beginning: Aryl Chlorides

- while cross couplings with aryl bromides and iodides were common, those with aryl chlorides were rare, despite being more readily available and less expensive
  - why? bond strength (Ar-I < Ar-Br < Ar-Cl)

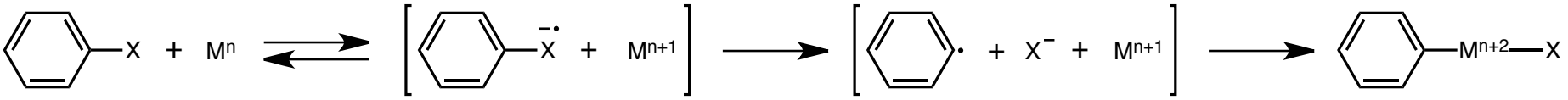


  - reversibility of first step requires a reasonably strong reductant to favor products
  - Pd is rather electronegative (2.20), so how can this process be favored?

Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319
Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387

In the Beginning: Aryl Chlorides

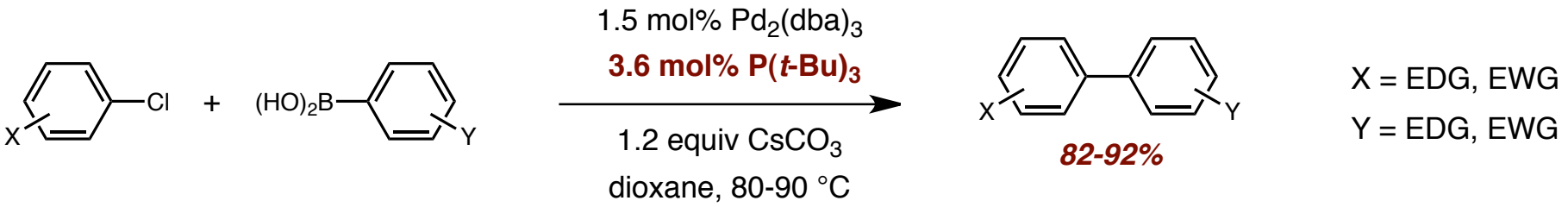
- while cross couplings with aryl bromides and iodides were common, those with aryl chlorides were rare, despite being more readily available and less expensive
  - why? bond strength (Ar-I < Ar-Br < Ar-Cl)



  - reversibility of first step requires a reasonably strong reductant to favor products
  - Pd is rather electronegative (2.20), so how can this process be favored?

ligands

  - nature of ligation is the most important factor determining the reactivity of a given metal (identity and stoichiometry)



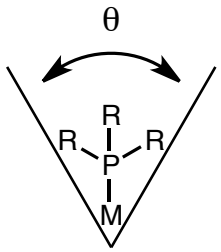
Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319
Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387

Why P(t-Bu)$_3$?

- extremely electron rich (makes Pd a stronger reductant)
  - how can we measure this? pK_a of conjugate acid

phosphine	pK_a
PPh_3	2.73
P(*n*-Bu)$_3$	8.43
PCy_3	9.70
P(*t*-Bu)$_3$	11.40

- extremely large (favors singly ligated species – more free coordination sites on Pd)
  - how can we measure this? cone angles (Tolman angles)

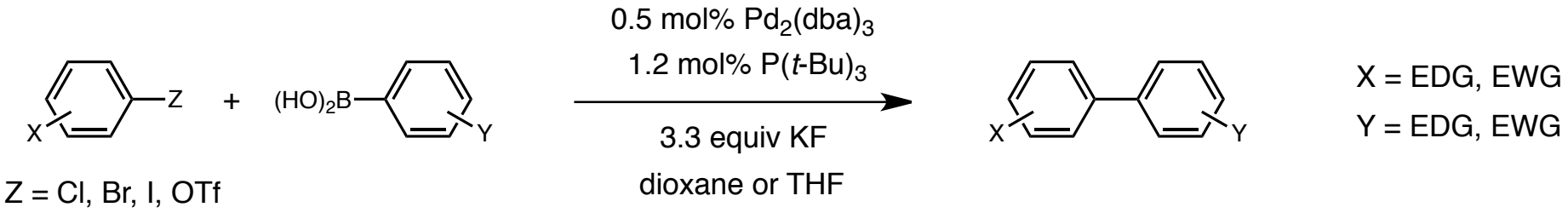


phosphine	θ
PPh_3	145°
P(*n*-Bu)$_3$	132°
PCy_3	170°
P(*t*-Bu)$_3$	182°

Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313
Rahman, M. M.; Liu, H. Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics*, **1989**, *8*, 1
Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295

In the Beginning: Aryl Chlorides

- changing base leads to milder, general conditions for aryl halides



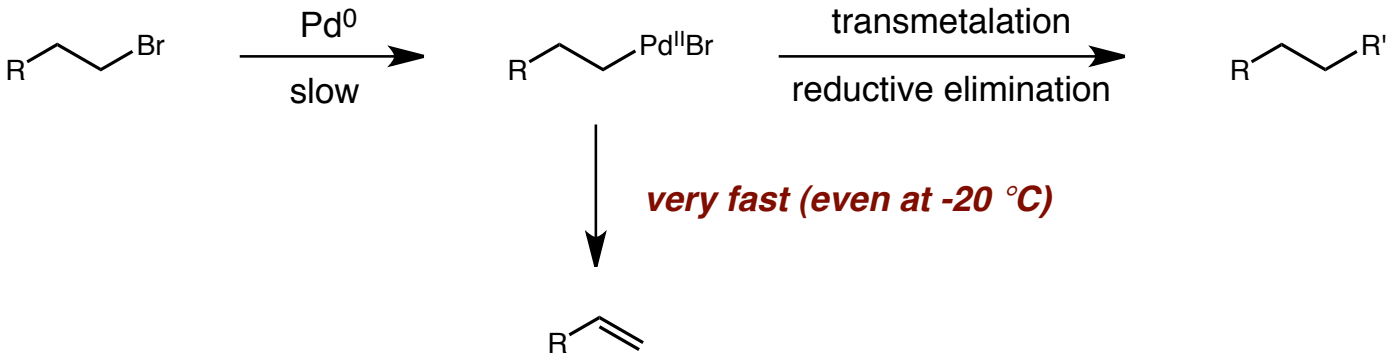
Z = Cl, Br, I, OTf

- electron rich chlorides require high temperatures; all others proceed at room temperature
- aryl triflates require less sterically hindered phosphine → 1 mol% $Pd(OAc)_2$, 1.2 mol% PCy_3
- this represents a general procedure for Suzuki couplings with aryl/vinyl halides/triflates
- similar, general conditions found for Heck, Stille, Sonagashira, and Negishi couplings
- $Pd[P(t\text{-}Bu)_3]_2$ is a stable, commercially available solid that can be stored in air ~1 month

Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020
Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989
Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343
Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729
Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719
Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1282

Primary Alkyl Bromides as Substrates

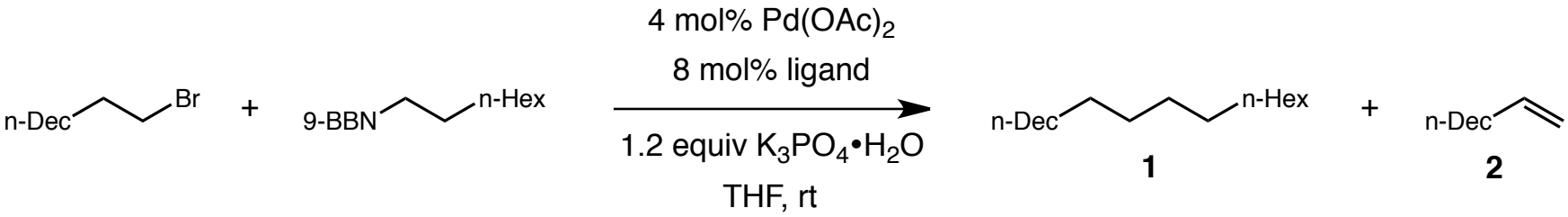
- sp^3 halides are slow to undergo oxidative addition and quickly β-hydride eliminate



- the authors had already shown that difficult oxidative additions can be achieved with the appropriate choice of ligand – why not try it?

Primary Alkyl Bromides as Substrates

- first attempts at alkyl-alkyl Suzuki couplings with β-hydrogens



	ligand	**1**	**2**
	PPh_3	--	--
	$P(o\text{-tol})_3$	--	14%
	$P(t\text{-Bu})_3$	--	21%
θ = 160°	$P(i\text{-Pr})_3$	68%	6%
	PCy_3	85%	--

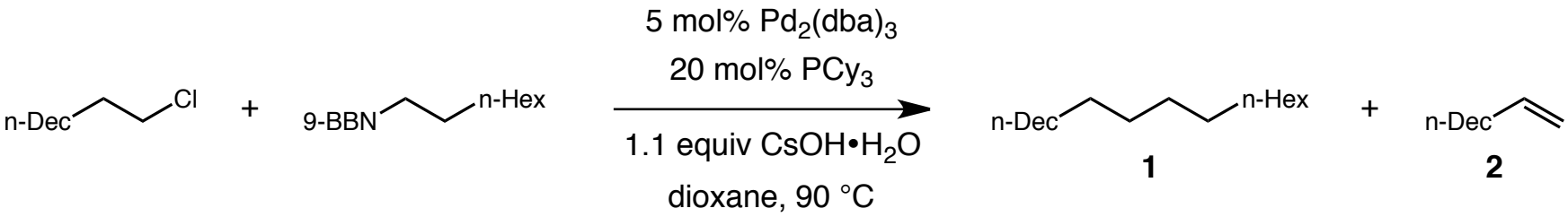
- 9 examples, ***58-93%***

- all partners have ≥ 2 methylene units adjacent to the terminus (1 vinyl borane)

Netherton, M. R.; Dai, C.; Neuschütz, Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099
Lou, S.; Fu, G. C. *Org. Synth.* **2010**, *87*, 299

Primary Alkyl Chlorides and Tosylates as Substrates

- similar conditions were developed for alkyl chlorides

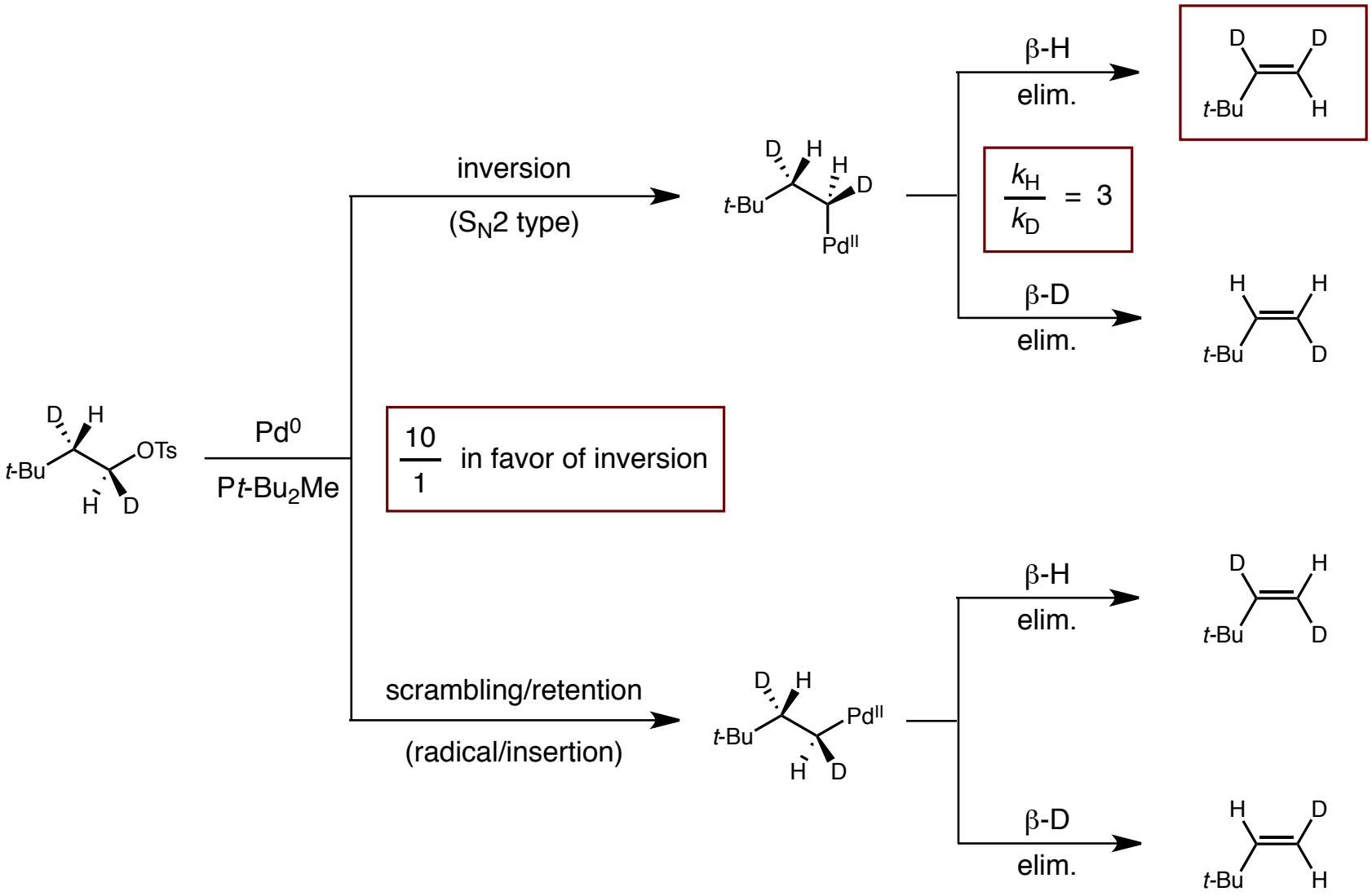


- further ligand optimization was required for alkyl tosylates:

	R =		
	i-Pr	Et	Me
PCy_2R	44%	70%	48%
P*t*-Bu_2R	--	--	**78%**

Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1945
Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910

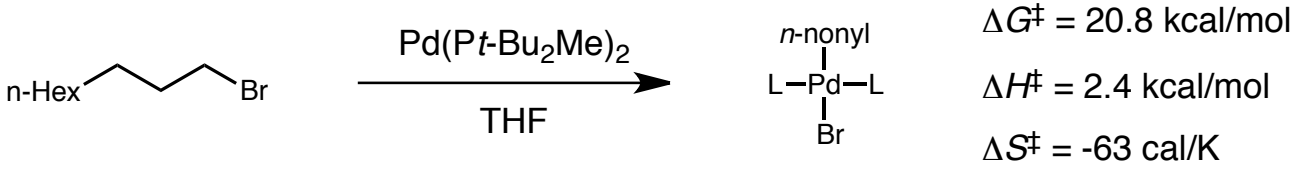
Labelling Study: Mechanism of Oxidative Addition



Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910

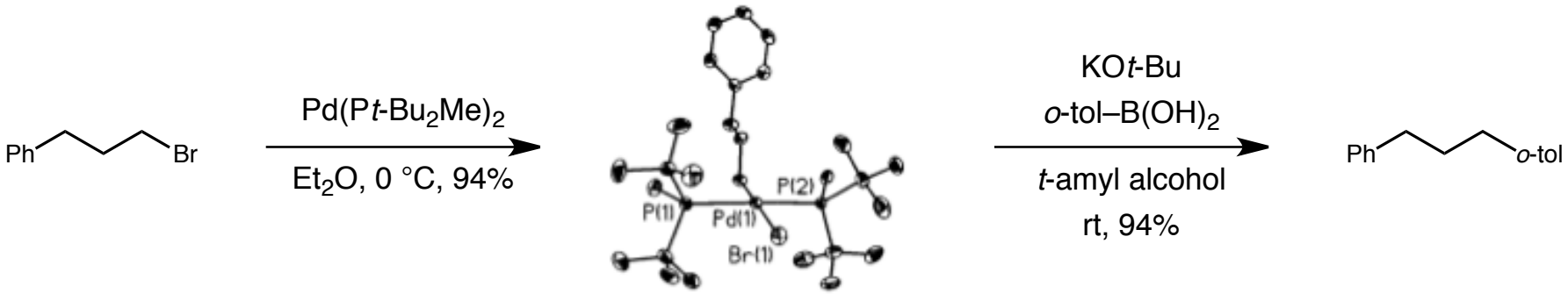
Further Oxidative Addition Studies

- kinetic studies reveal activation parameters:



- large negative entropy of activation is consistent with S_N2 type mechanism

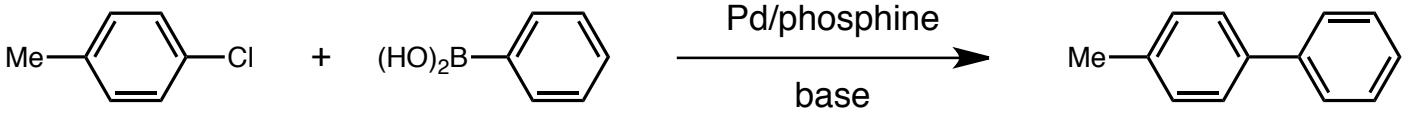
- crystal structure of oxidative addition product



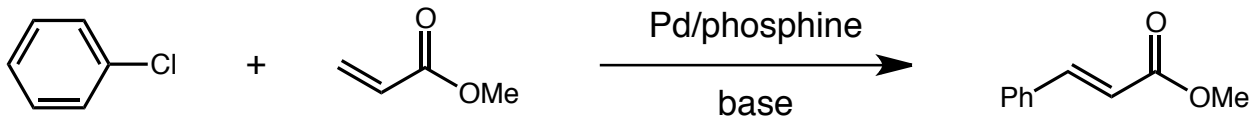
Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5749
Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662

What About β-Hydride Elimination?

- Heck reaction with aryl chlorides gives unexpected results:



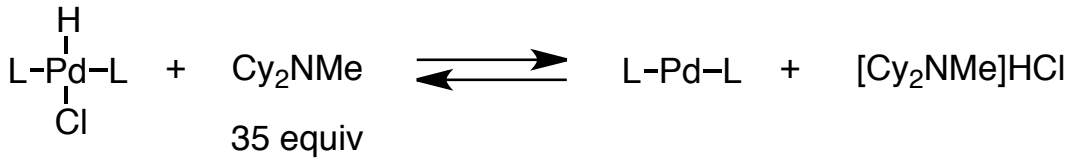
phosphine	yield
PCy_3	75%
$P(t\text{-}Bu)_3$	86%



phosphine	yield
PCy_3	--
$P(t\text{-}Bu)_3$	56%

- Why would PCy_3 shut down reactivity?

  - Stability of the L_2PdHCl complex after β-hydride elimination

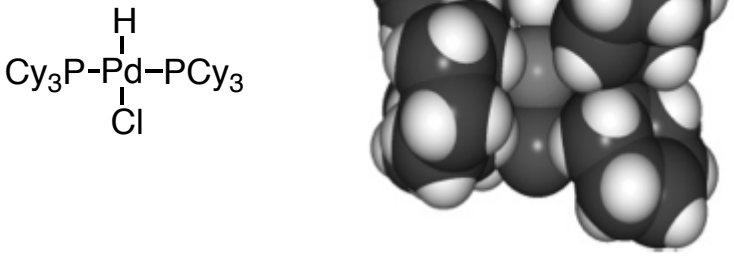


phosphine	$L_2PdHCl : L_2Pd$
PCy_3	>98 : <2
$P(t\text{-}Bu)_3$	<2 : >98

Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178

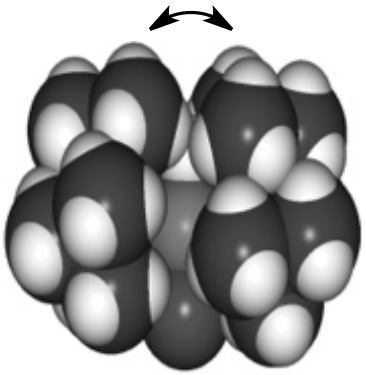
What About β-Hydride Elimination?

- what is causing this differential behavior?
  - not electronics
  - sterics? – examine crystal structures

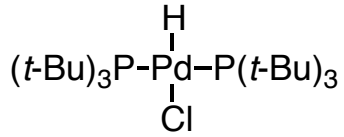


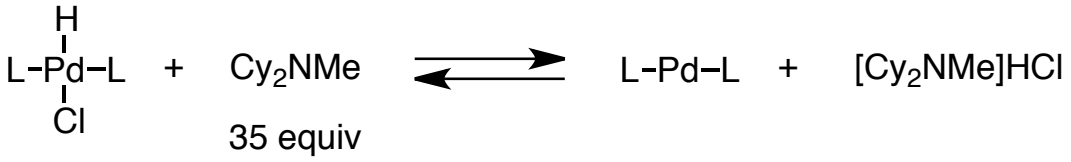
P–Pd–P = 180°

pushed together - destabilized



P–Pd–P = 161°



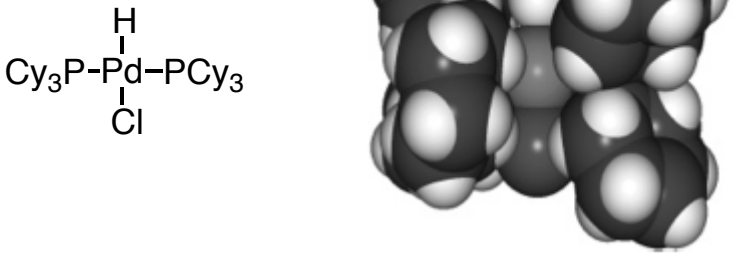


phosphine	$L_2PdHCl : L_2Pd$
PCy_3	>98 : <2
$P(t\text{-Bu})_3$	<2 : >98

Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178

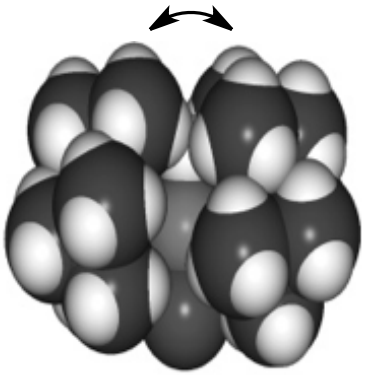
What About β-Hydride Elimination?

- what is causing this differential behavior?
  - not electronics
  - sterics? – examine crystal structures

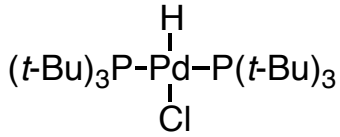


P–Pd–P = 180°

pushed together - destabilized



P–Pd–P = 161°



- must lose a ligand in order to undergo reductive elimination of HCl
  - this is accelerated when P(*t*-Bu)$_3$ is used, but the PCy$_3$ complex is stable to ligand loss

Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178

What About β-Hydride Elimination?

- PCy_3 ($\theta = 170°$) and P*t*-Bu_2Me ($\theta = 161°$) do not lose ligands rapidly
  - therefore, their complexes do not undergo rapid β-hydride elimination
  - if $k_{transmetalation} > k_{ligand\ loss}$, efficient cross coupling can be acheived

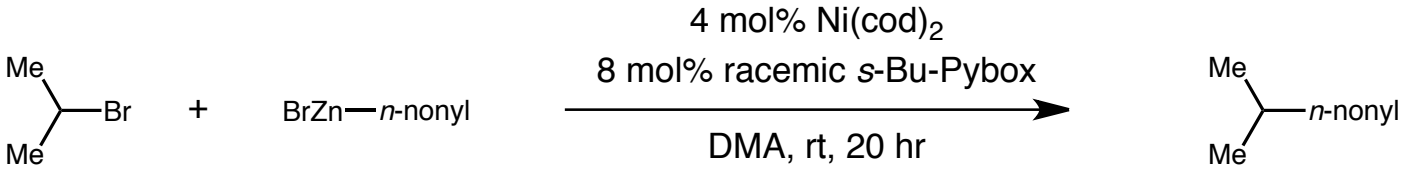
- For alkyl Stille coupling: Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718
- For alkyl Hiyama coupling: Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616
- For alkyl Negishi coupling: Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527
- For alkyl Sonagashira coupling: Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642
- For alkyl Heck coupling: Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340

Nickel Catalysis

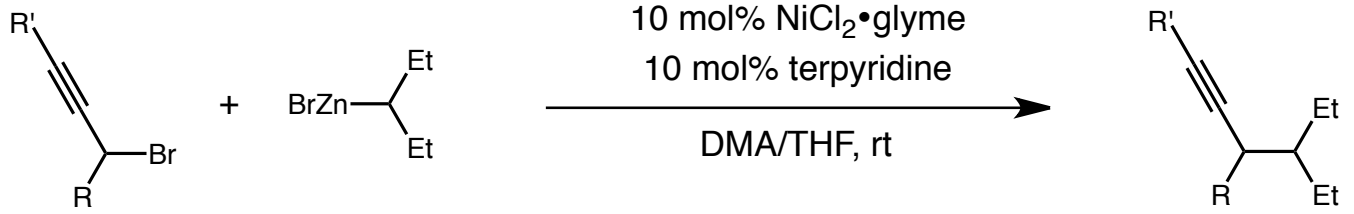
- Instead of palladium, nickel can also be used
  - obvious benefit is cost ($36/100 g Ni vs. $368/5 g Pd)
  - due to smaller orbital size, β-hydrogen elimination $TS^{\ddagger}$ is 10-20 kcal/mol than palladium
  - lends itself perfectly to alkyl-alkyl cross coupling
  - drawbacks include sensitivity to variable conditions, oxygen sensitivity, mechanistic ambiguity

Koga, N.; Obara, S.; Kitaura, K.; Morokuma, K. *J. Am. Chem. Soc.* **1985**, *107*, 7109

Nickel Catalysis: Negishi Couplings



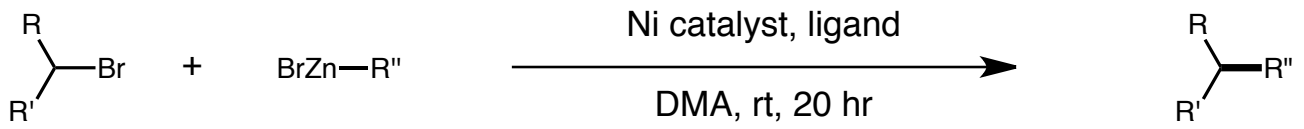
- initially reaction was limited to primary zinc bromides
- tolerates sterically hindered primary and secondary bromides and iodides

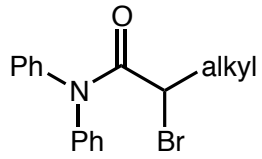


- propargyl bromides and chlorides couple to secondary zinc bromides

Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726
Smith, S. W.; Fu, G. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 9334

Nickel Catalysis: Asymmetric Negishi Couplings

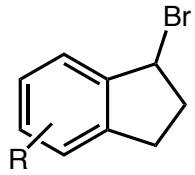




alkyl zinc bromides

$NiCl_2$•glyme, *i*-Pr–Pybox

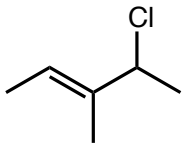
58-90%, 77-96% ee



alkyl zinc bromides

$NiBr_2$•diglyme, *i*-Pr–Pybox

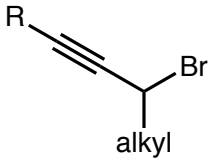
39-89%, 91-99% ee



alkyl zinc bromides

$NiCl_2$•glyme, $BnCH_2$–Pybox

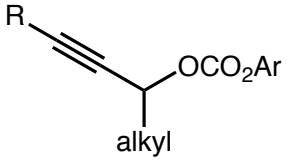
54-97%, 69-96% ee



aryl-ethyl zinc reagents

$NiCl_2$•glyme, indanyl–Pybox

39-92%, 77-96% ee



aryl zinc iodides

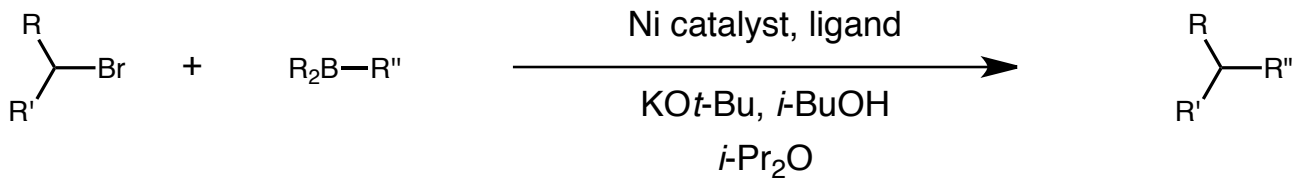
$NiCl_2(PCy_3)_2$, indanyl–Pybox

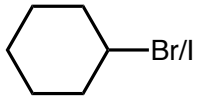
57-94%, 84-93% ee

- all halides are racemic – chirality derived from radical trapping on the metal during oxidative addition

Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594
Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10842
Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756
Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645
Oelke, A. J.; Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *133*, 2966

Nickel Catalysis: Suzuki Couplings

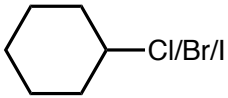




aryl boronic acids

$Ni(cod)_2$, bathophenanthroline

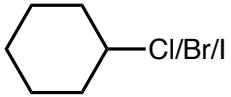
44-90%



aryl boronic acids

NiI_2, 2-aminocyclohexanol

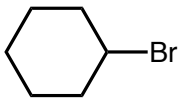
46-91%



alkyl boranes

$NiBr_2$•diglyme, **4**

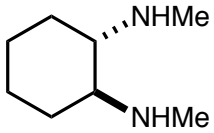
57-94%, 84-93% ee



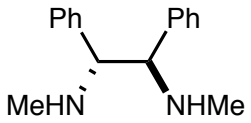
alkyl boranes

$NiCl_2$•glyme, **3**

64-93%



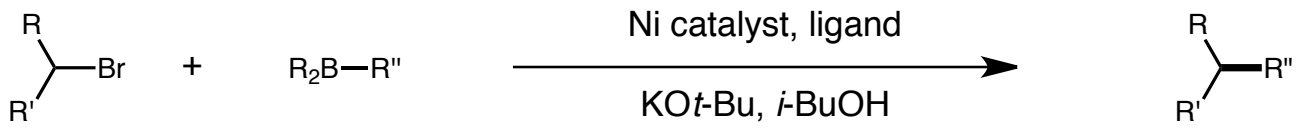
3 (racemic)

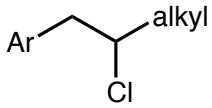


4 (racemic

Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340
Gonzalez-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360
Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602
Lu, Z.; Fu, G. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6676

Nickel Catalysis: Asymmetric Suzuki Couplings

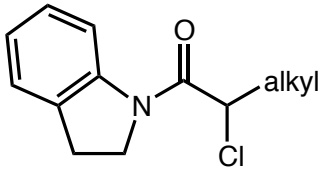




alkyl boranes

$Ni(cod)_2$, **5**

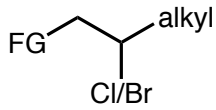
68-86%, 70-94% ee



aryl boronic acids

$NiBr_2$•diglyme, **5**

46-91%

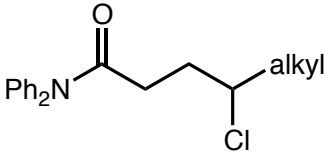


alkyl boranes

$NiBr_2$•diglyme, **5,6**

57-93%, 80-96% ee

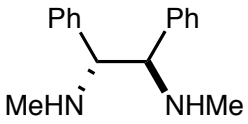
FG = carbamate,
sulfamate
amine



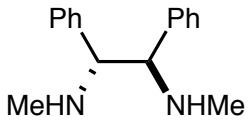
alkyl boranes

$NiBr_2$•diglyme, **6**

51-83%, 82-91% ee



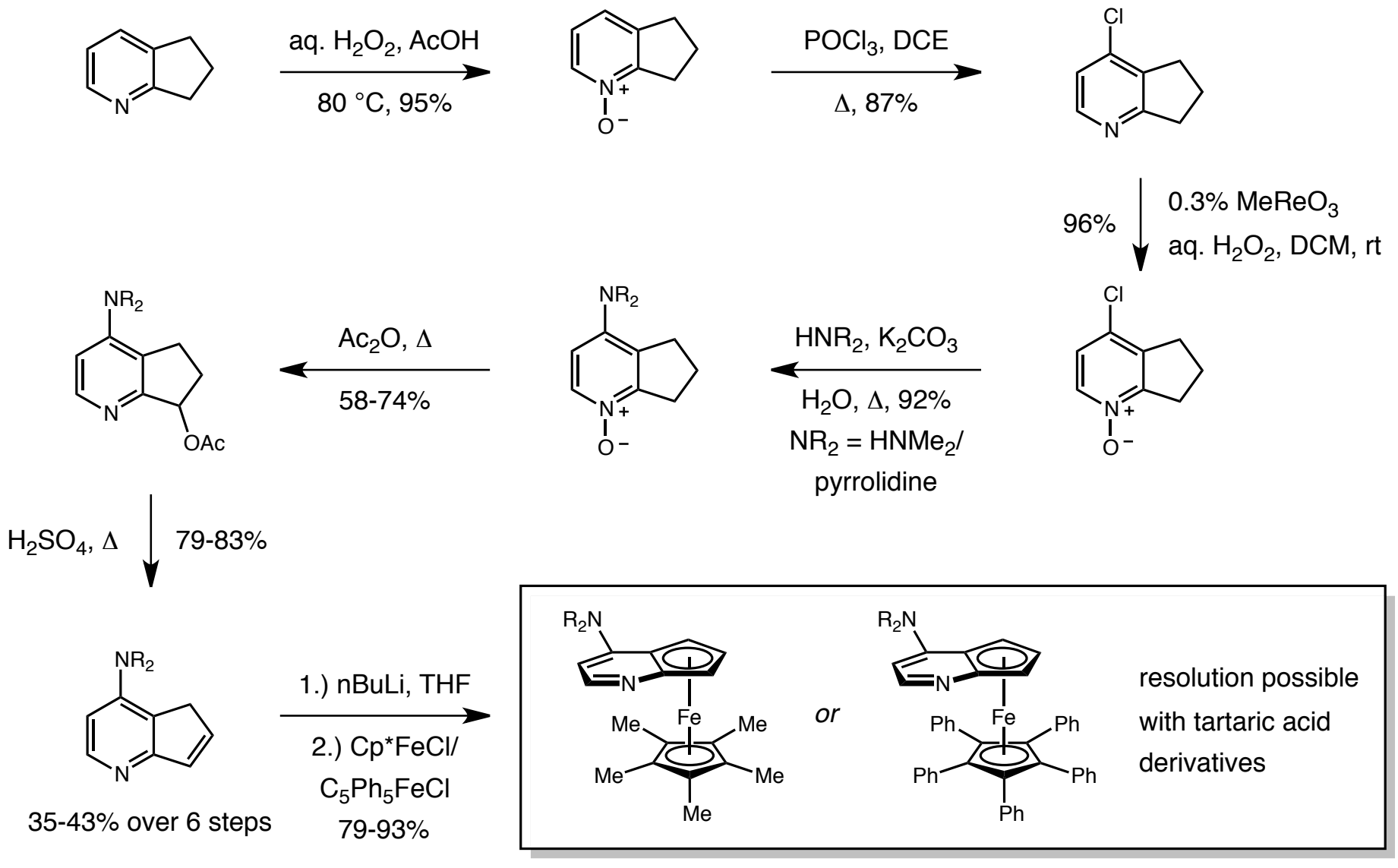
5



6 (chiral)

Saito, B; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694
Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027
Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908
Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362

Catalyst Synthesis



Wurz, R. P.; Lee, E. C.; Ruble, J. C.; Fu, G. C. *Adv. Synth. Catal.* **2007**, *349*, 2345