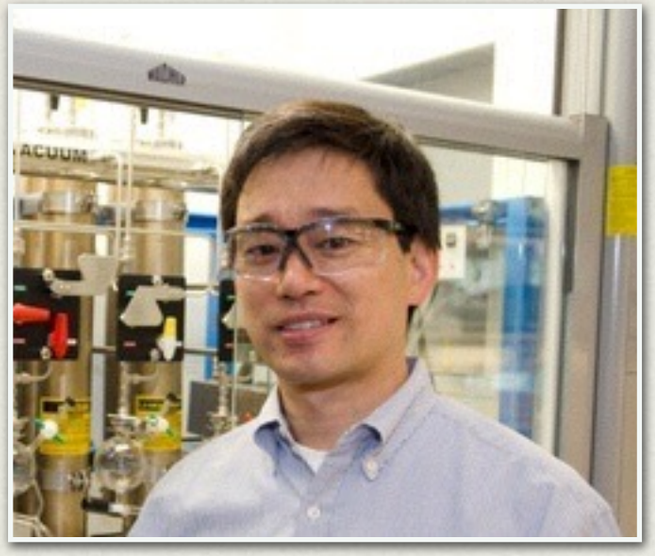
Mini-Career review of Gregory C. Fu

Reporter: Lin Deng
Advisor: Prof. Guangbin Dong
Date: June 3rd, 2015

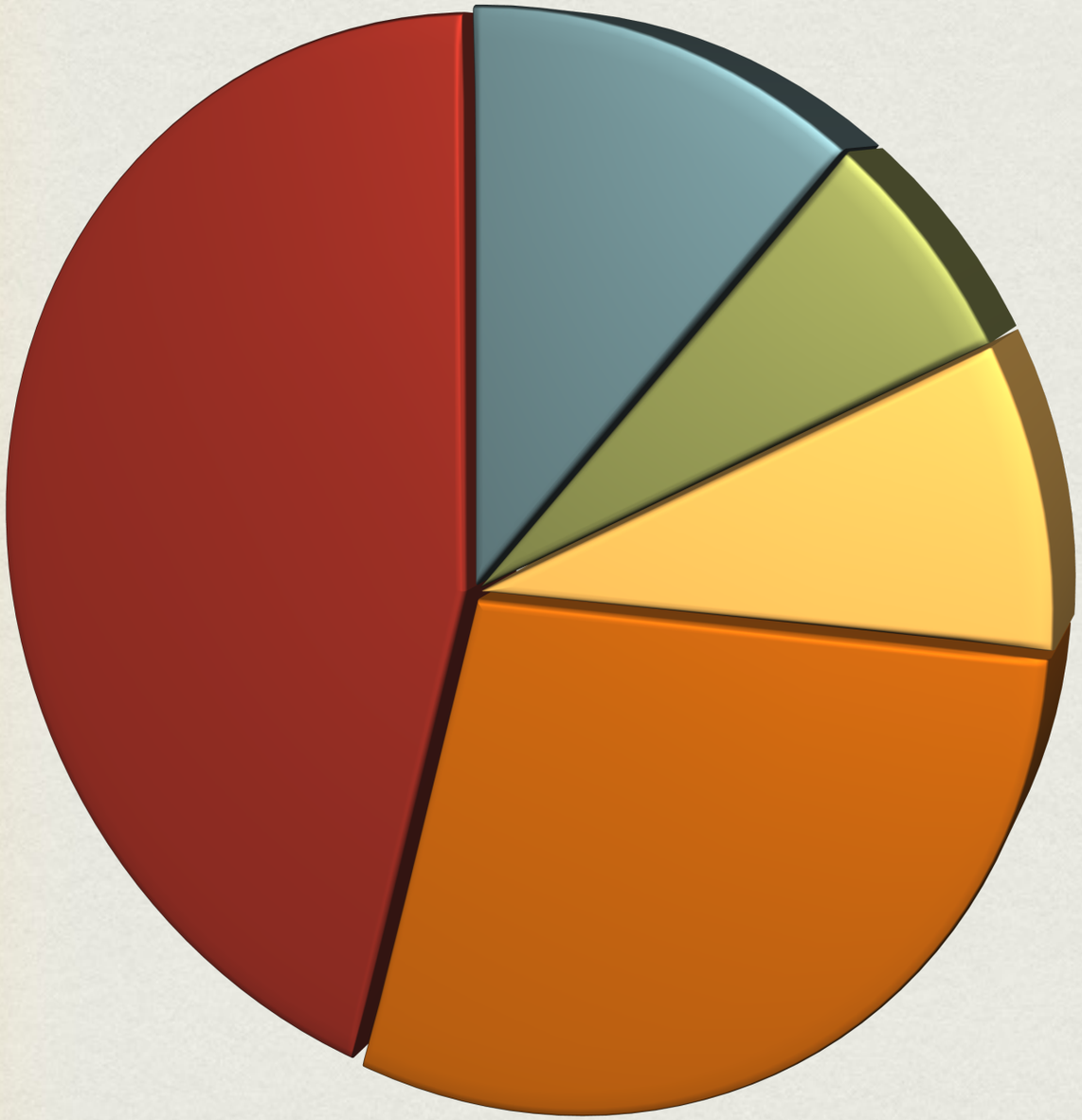
About Greg Fu



22 years
independent career
210 publications

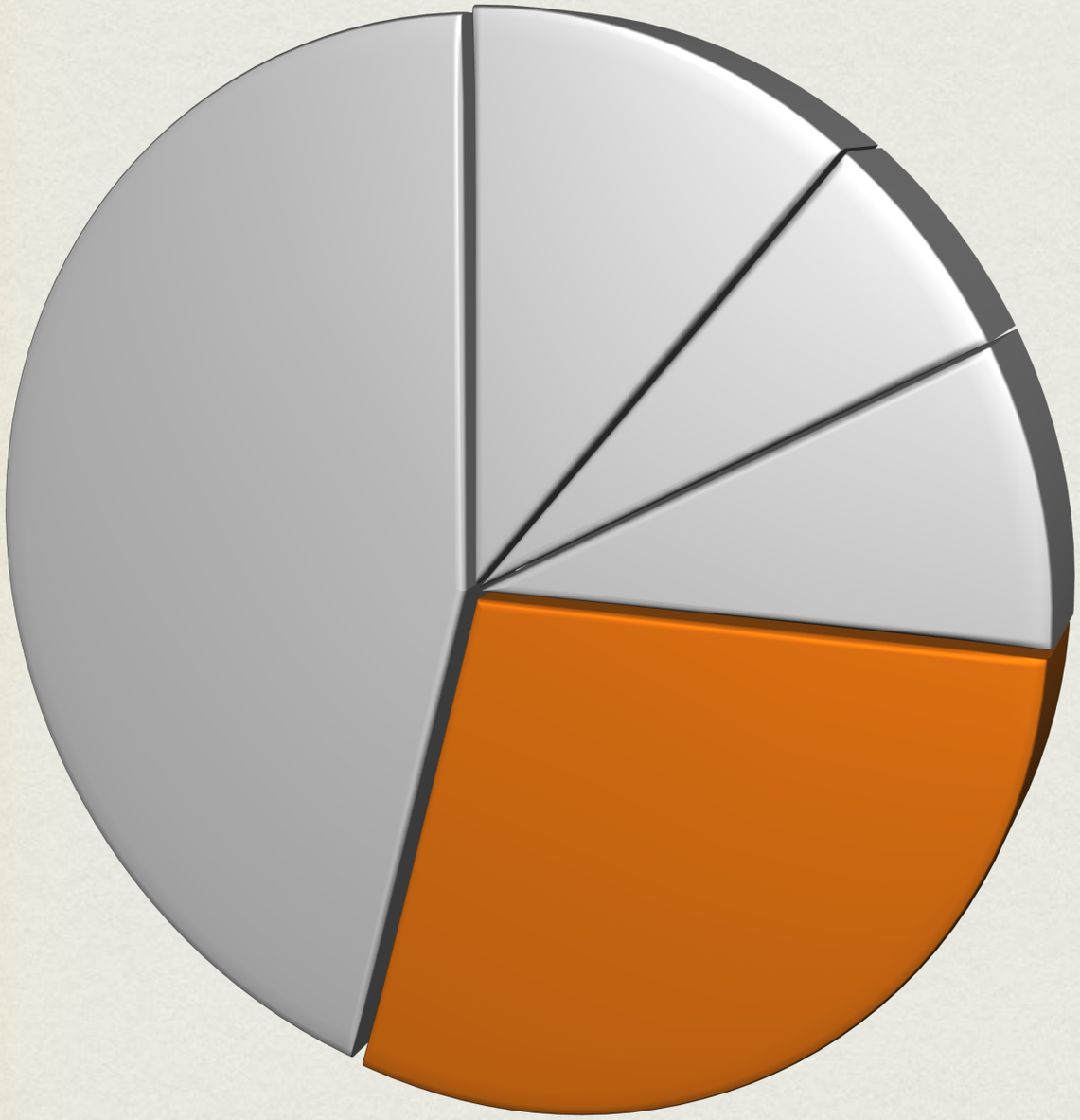
- Born 1963 in Galion, Ohio
- Undergraduate Student with Prof. K. Barry Sharpless, MIT, 1985
- Graduate Student with Prof. David A. Evans, 1991
- Postdoctoral Fellow with Prof. Robert H. Grubbs, 1993
- Assistant Professor of Chemistry, MIT, 1993-1998
- Associate Professor of Chemistry, MIT, 1998-1999
- Professor of Chemistry, MIT, 1999-2007
- Firmenich Professor of Chemistry, MIT, 2007-2012
- Altair Professor of Chemistry, Caltech, 2012-present

Significant research area of Gregory C. Fu



- Chiral ligand development
- Boron heterocycles
- Organotin Catalysis
- Asymmatric Nucleophilic catalysis
- Pd/ Ni/Cu catalyzed cross-coupling

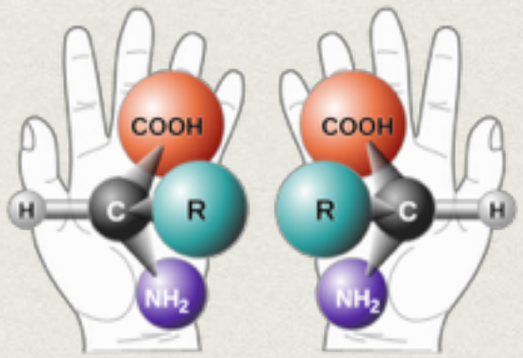
Asymmetric Nucleophilic catalysis



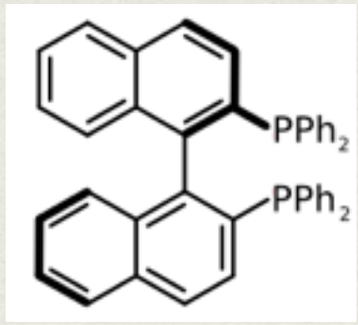
- Chiral ligand development
- Boron heterocycles
- Organotin Catalysis
- Asymmetric Nucleophilic catalysis
- Pd/ Ni/Cu catalyzed cross-coupling

Asymmetric Nucleophilic catalysis

- **Types of chirality**

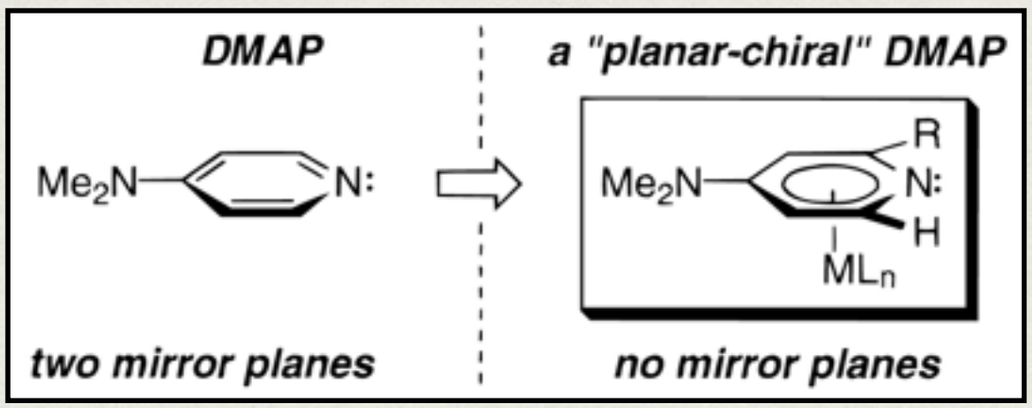


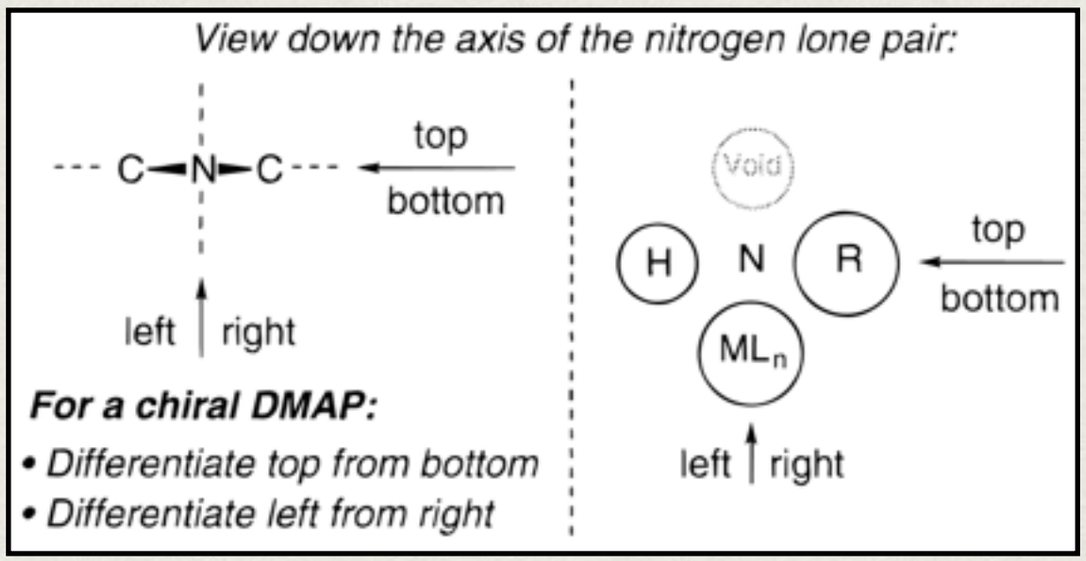
From a stereocenter



Axial chirality

- **"Planar-chiral" Heterocycles**



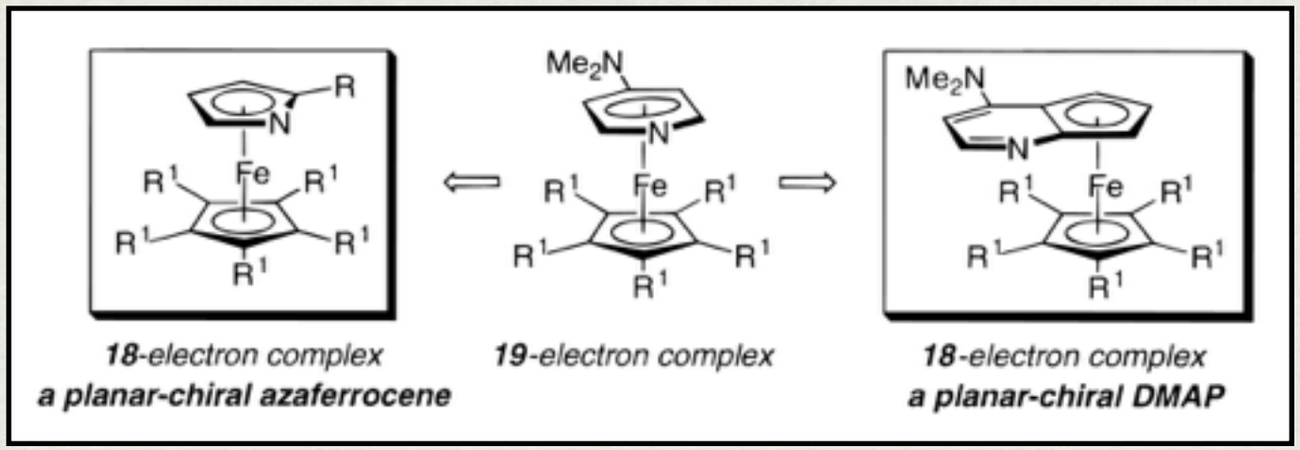


Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412.

Asymmetric Nucleophilic catalysis

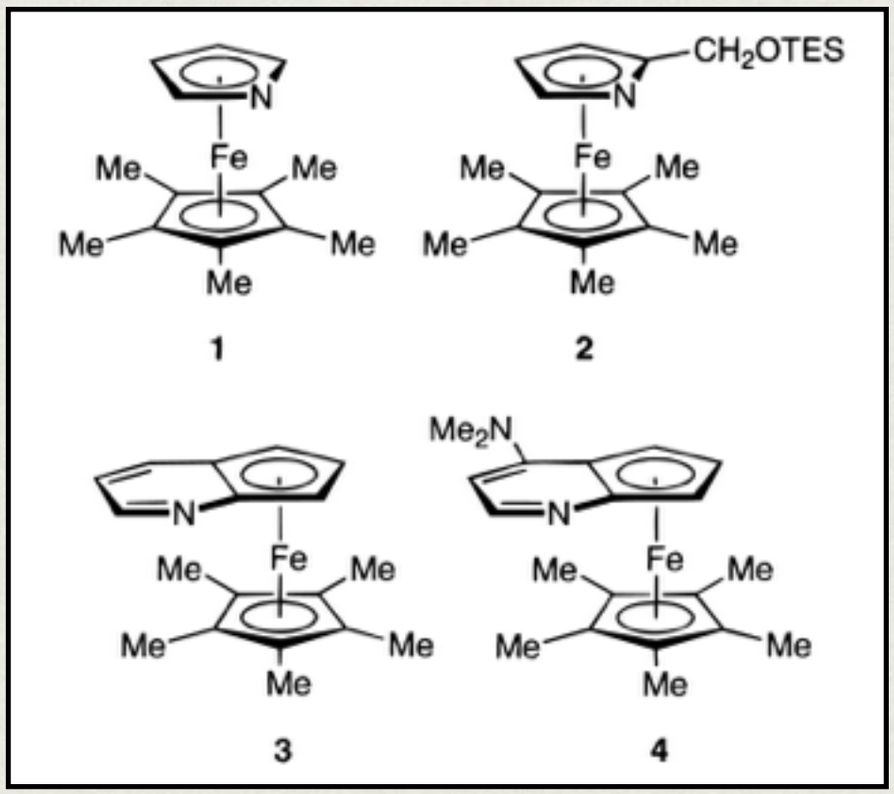
- **Design principles**
  - **Electron-rich**
  - **tunable steric environment**
  - **Robust enough for catalysis**
- **How they discover the privileged catalyst**
  - **DMAP— widely used as nucleophilic catalyst**
  - **Derivatives of DMAP is of great interest**

First synthesize the racemic catalyst to test reactivity



Analogues of imidazole

Move the ferrocene away

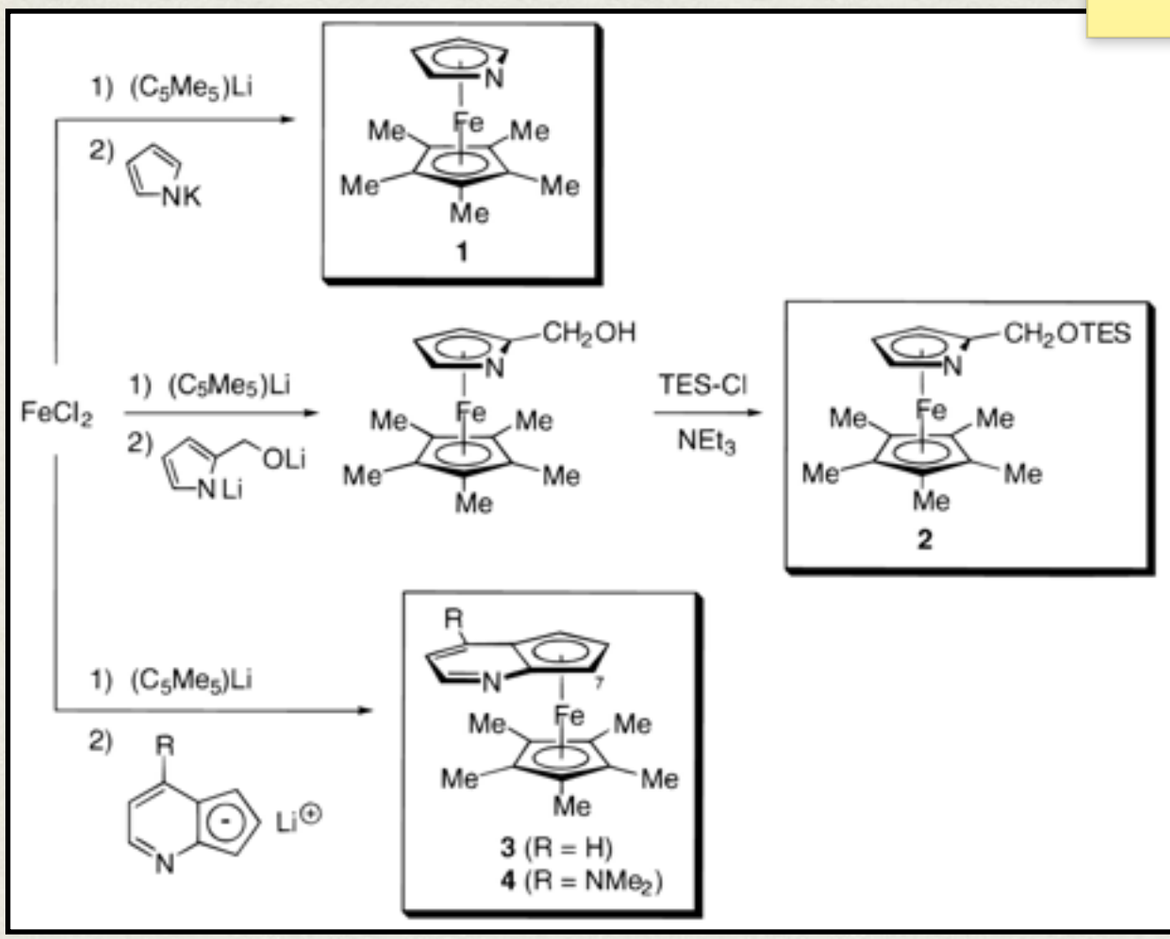


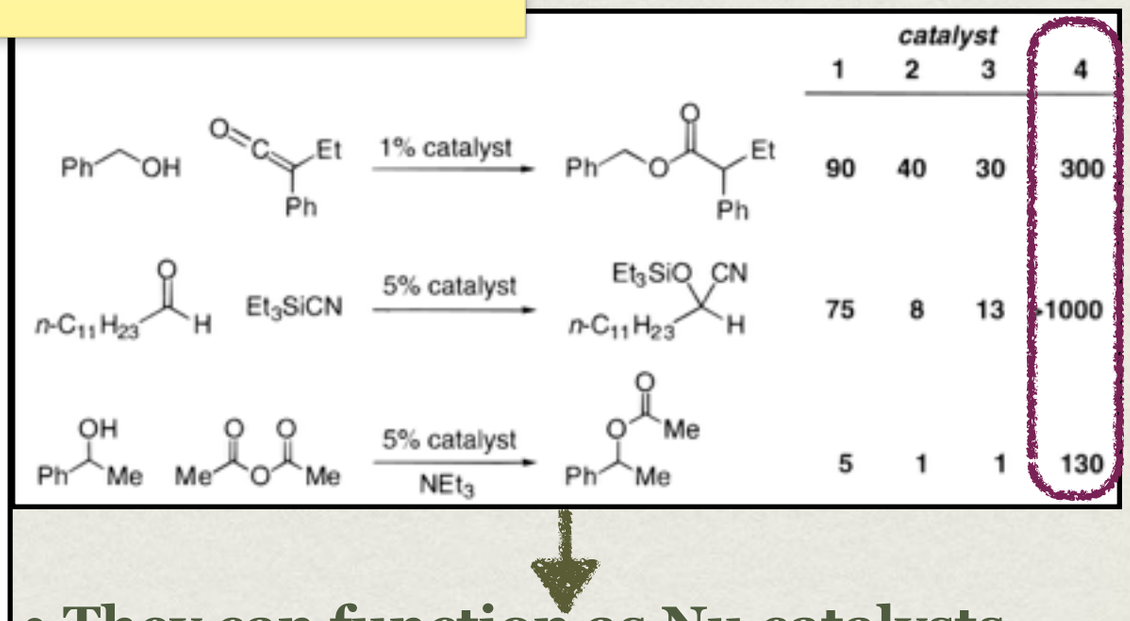
Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412.
Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230.

Asymmetric Nucleophilic catalysis

- **Synthesis & Reactivity of Thos**

addition of alcohol to ketene;
cyanosilylation of carbonyl group
Rates



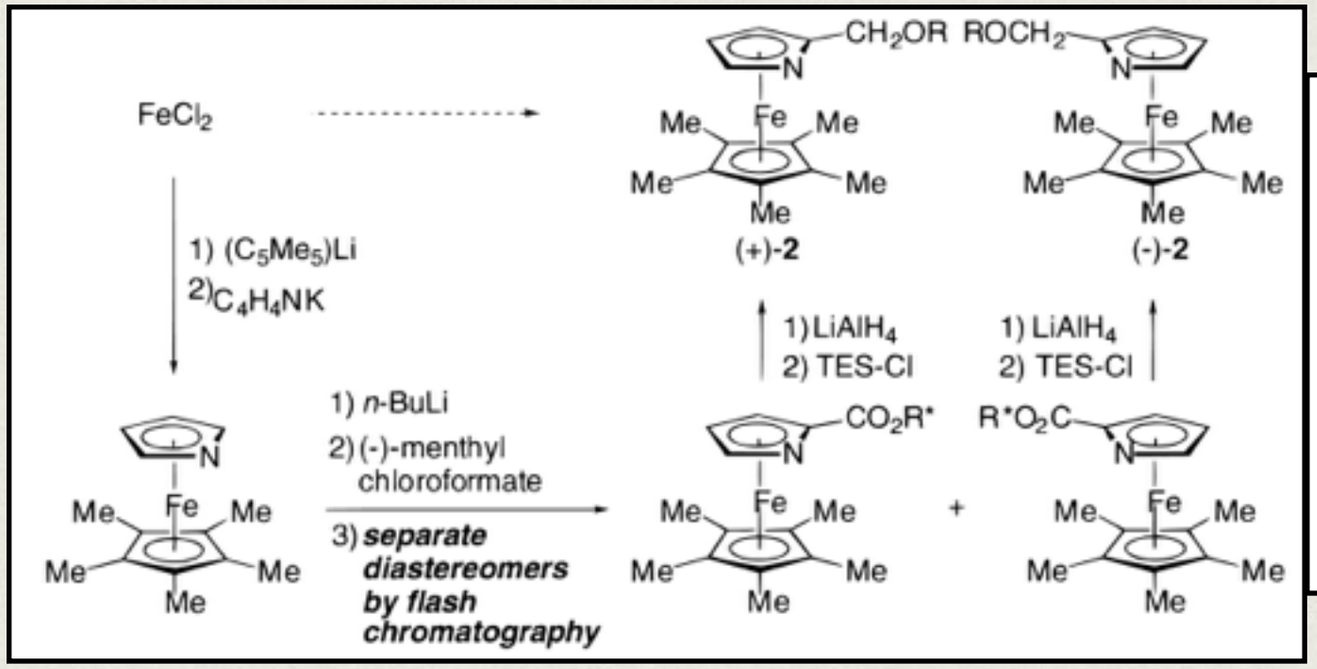


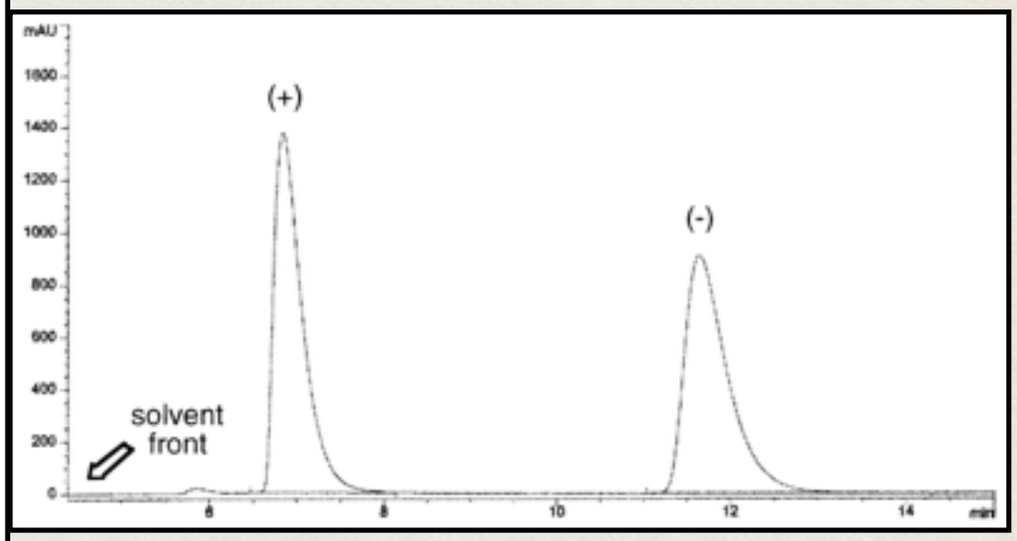
- **They can function as Nu catalysts**
- **1 vs 2———Steric effects**
- **3 vs 4———electronic effects**
- **4 is most active catalyst**

Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412.
Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230.
Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492.

Asymmetric Nucleophilic catalysis

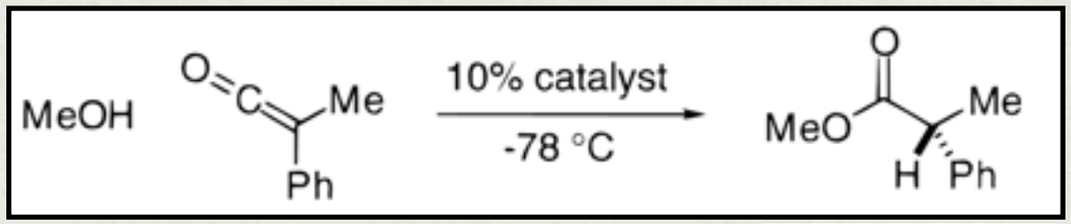
- **Move forward to asymmetric catalysis**
  - **How to obtain enantiopure complexes**



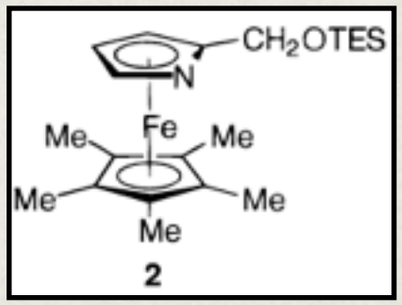


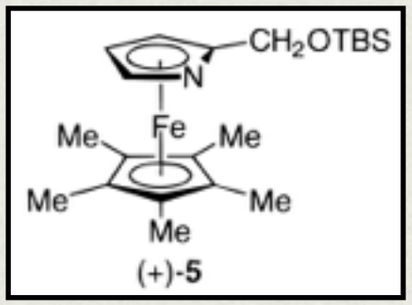
- **Catalytic enantioselective addition of alcohols to ketene**

Previous examples all require stoichiometric quantity of a chiral alcohol



(+)-2	*50% ee*
(+)-5	*56% ee*





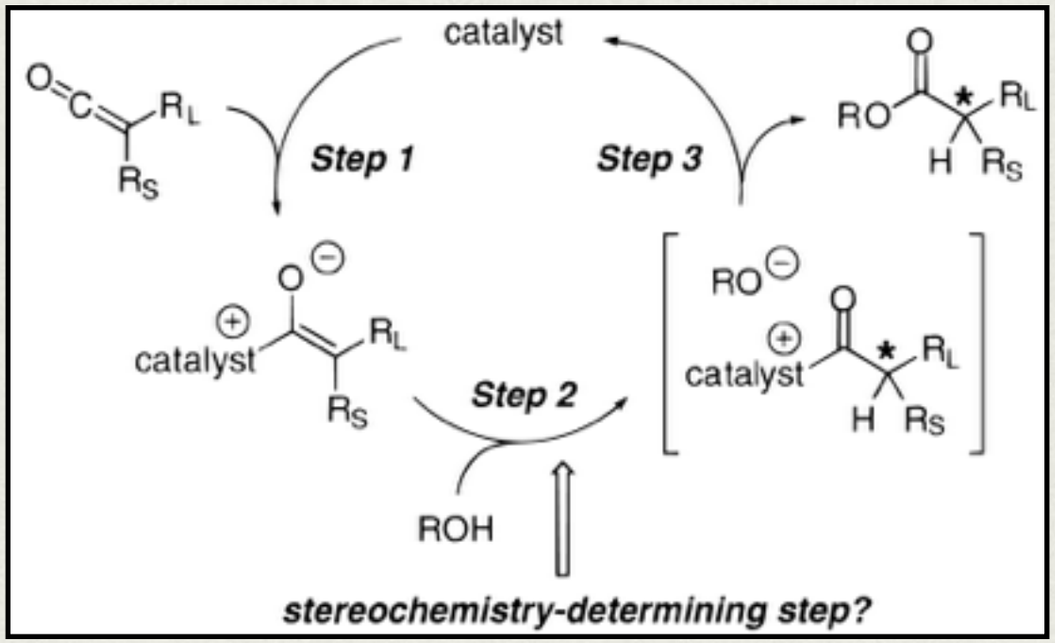
Steric matters

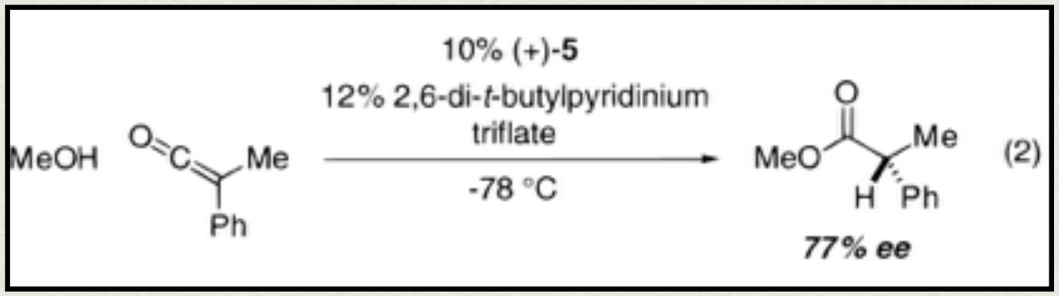
Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412.
Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637.

Asymmetric Nucleophilic catalysis

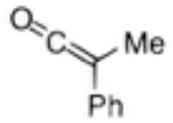
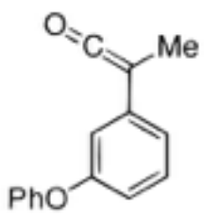
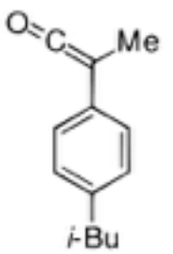
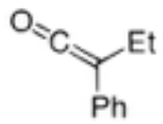
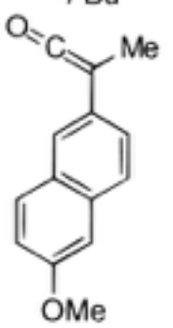
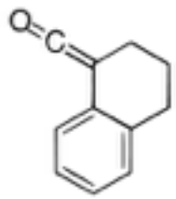
- **Catalytic enantioselective addition of alcohols to ketene**

  Proposed mechanism and condition optimization





External proton source might be beneficial

Entry	Substrate	% ee	% Yield	Entry	Substrate	% ee	% Yield
1		77	87	4		74	96
2		77	88	5		68	92
3		75	80	6		80	97

Steric affects ee

Mechanism:

- **One molecule of catalyst involved in stereochemistry-determining step**
- **Proton transfer in the R.D.S.**

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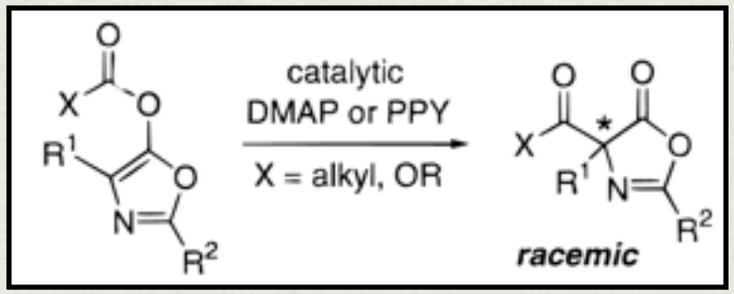
Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637.

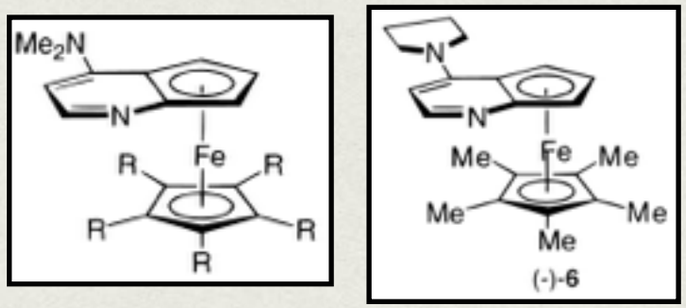
Asymmetric Nucleophilic catalysis

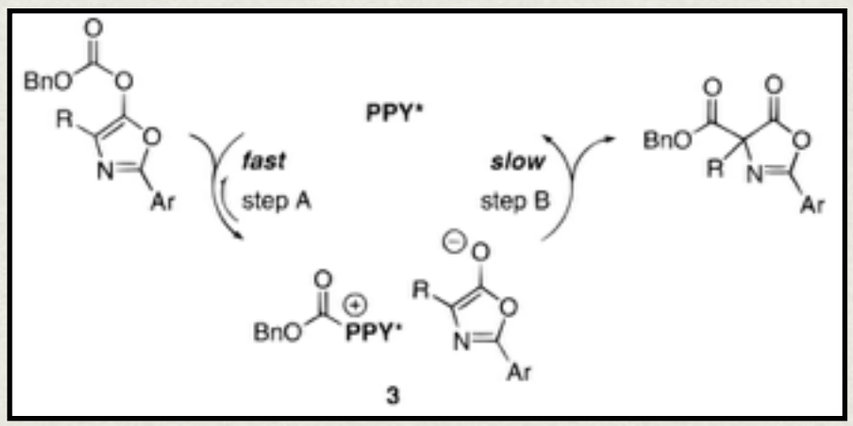
- **Catalytic enantioselective rearrangement of O-acylated azlactones**

Steglich rearrangement

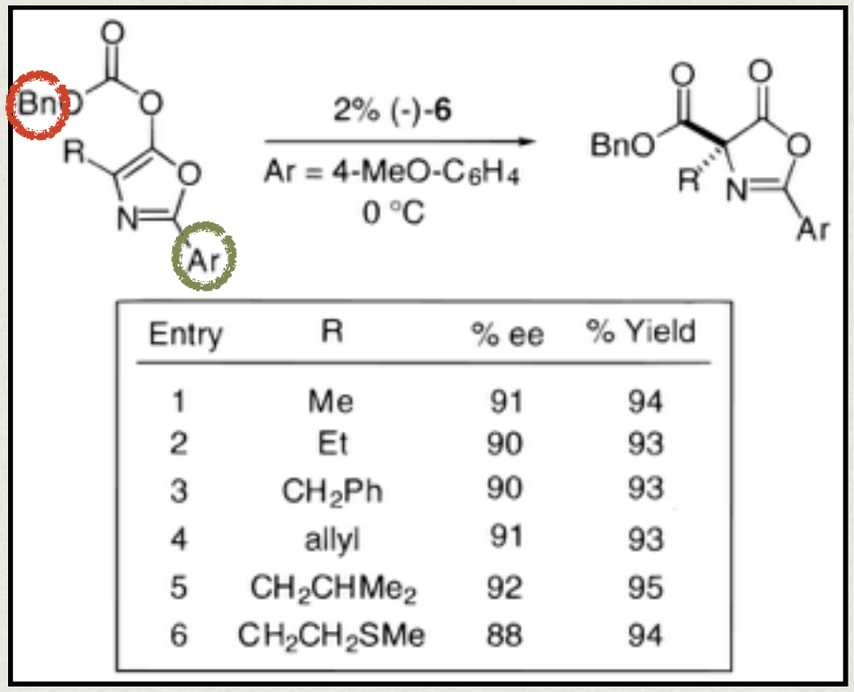


Bn- and 4-MeO-C6H4 proved to give best ee and yield on the other 2 sites.





Upon openning of the lactone, provide protected α-alkylated α-amino acids



Entry	R	% ee	% Yield
1	Me	91	94
2	Et	90	93
3	CH_2Ph	90	93
4	allyl	91	93
5	CH_2CHMe_2	92	95
6	CH_2CH_2SMe	88	94

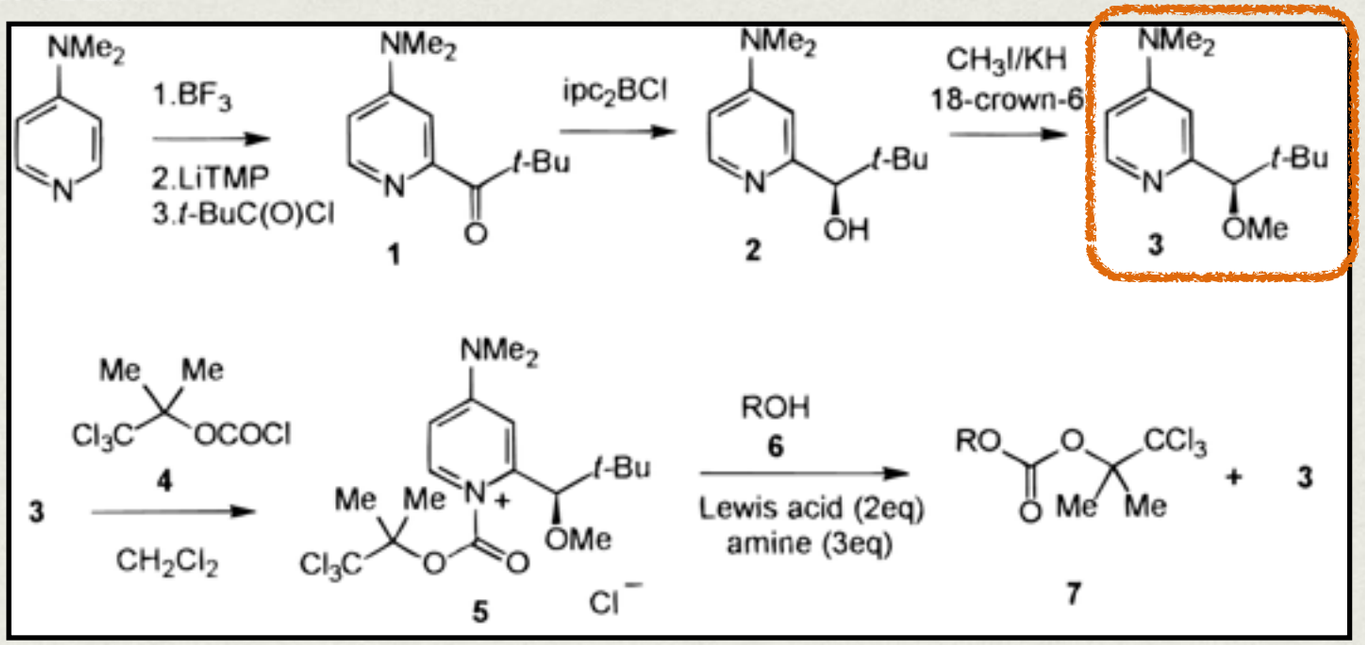
Mechanism:

- **Ion pair 3 as resting state—zero order in substrate and independent of concentration**
- **Step A reversible— cross over experiment**
- **Product is conformationally stable**

Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412.
Steglich, W.; Hofle, G. *Tetrahedron Lett.* **1970**, 4727.
Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532.

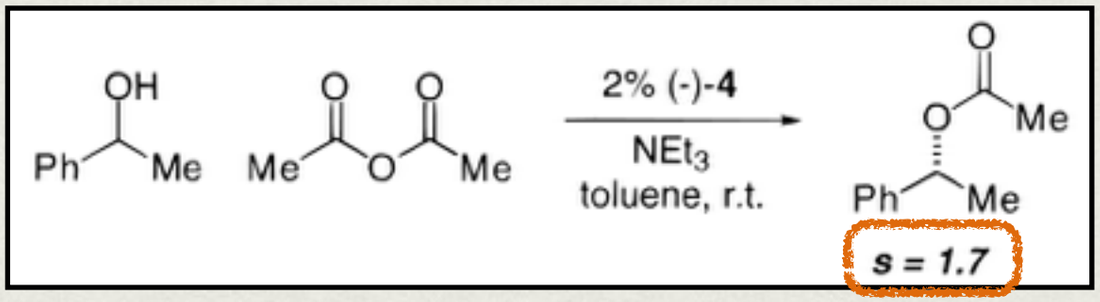
Asymmetric Nucleophilic catalysis

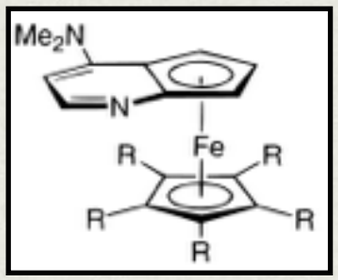
- **Kinetic resolutions of secondary alcohols**
  - **Factor s——characterize the enantioselection**
    s=k(fast-reacting enantiomer)/k(slow-reacting enantiomer); s>10 is required for resolution to be synthetically useful
  - **An inspiring work:**



Through the DMAP-derivatives catalyzed acylation—realize kinetic resolution of secondary alcohols —s: 11~44; 20-40% Y, 90% ee of PD

- **Given that 4 is active for catalyze acylation rxn of alcohol**





4: R=Me

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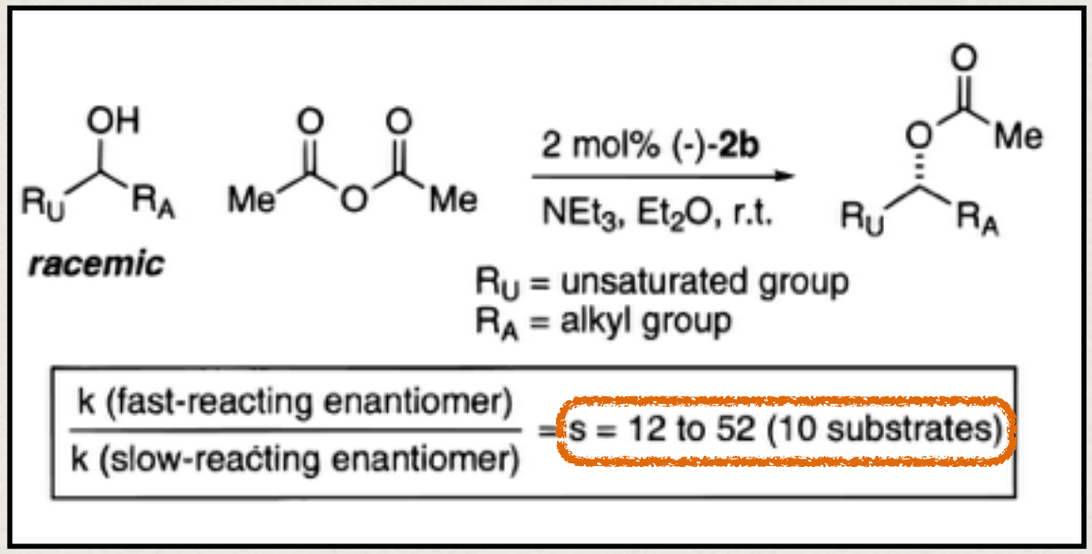
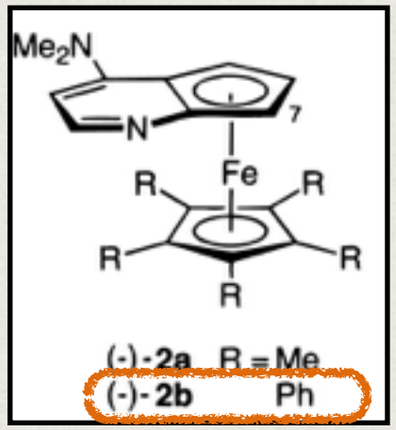
Ruble, J. C.; Latham, H. A.; Fu, G. C.*J. Am. Chem. Soc.* **1997**, *119*, 1492.

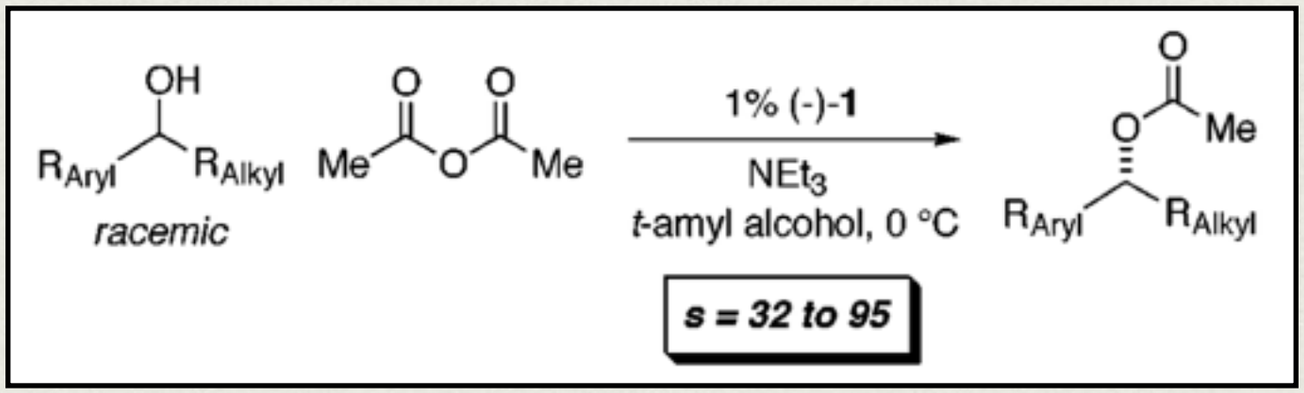
Asymmetric Nucleophilic catalysis

- **Kinetic resolutions of secondary alcohols**
  - **Solution to the low s——increase the *left-to-right* or *bottom-to-up* difference for the ligand**
    - ***left-to-right:* add a methyl group at 7-position ——*lose activity***
    - ***bottom-to-up:* Change the R group to Ph——*improve the s***





- **Solvent plays an important role—why *tert*-amyl alcohol?**
  - ***enhanced rate—decrease the temp.; also lower catalyst loading***



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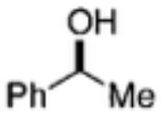
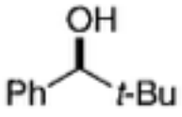
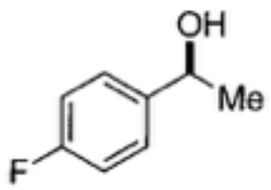
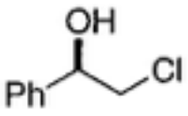
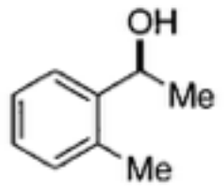
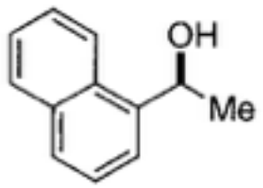
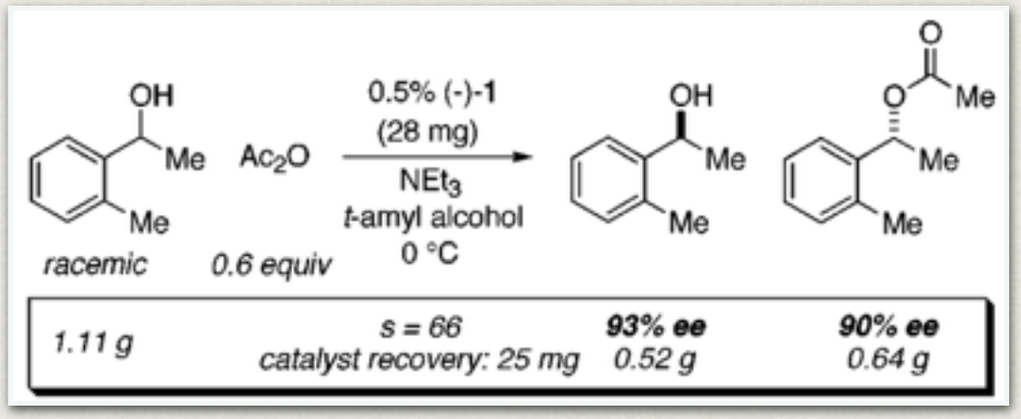
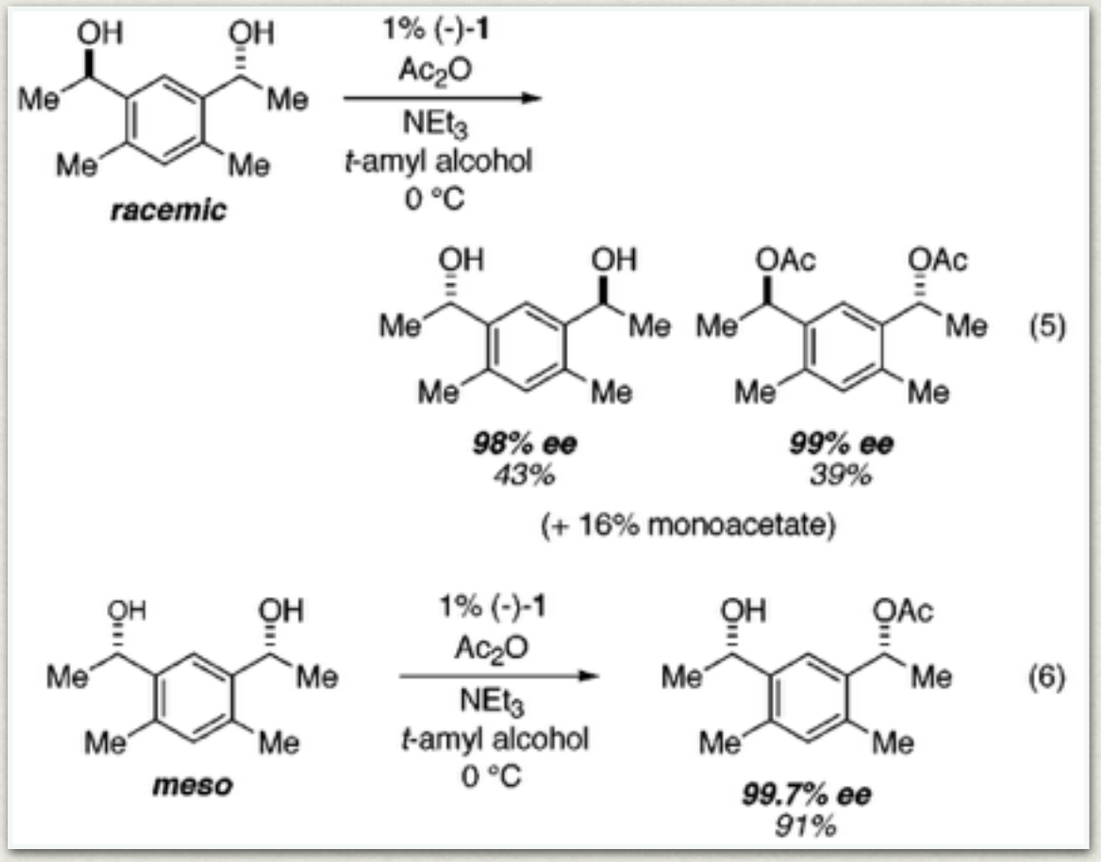
Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998,** *63*, 2794.

Asymmetric Nucleophilic catalysis

- **Kinetic resolutions of secondary alcohols**
  - **Impressive selectivity makes the reaction useful**

entry	unreacted alcohol, major enantiomer	s (selectivity factor)[a] Et_2O 2% catalyst r.t.	s (selectivity factor)[a] *t*-amyl alcohol 1% catalyst 0 °C
1		14	**43** *99% ee @ 55% conv.*
2		52	**95** *96% ee @ 51% conv.*
3		18	**68** *99% ee @ 54% conv.*
4		12	**32** *98% ee @ 56% conv.*
5		22	**71** *99% ee @ 53% conv.*
6		22	**65** *95% ee @ 52% conv.*





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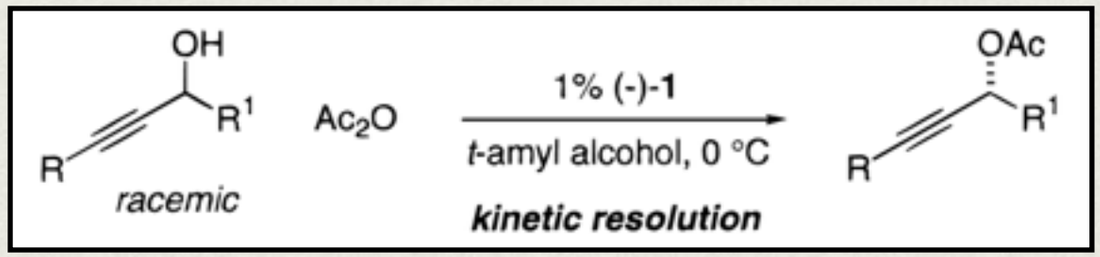
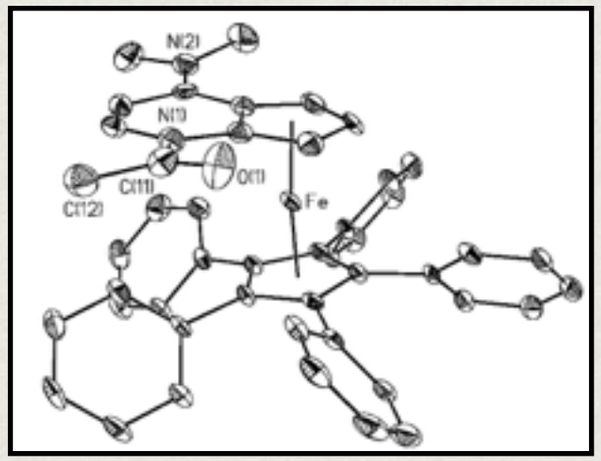
Asymmetric Nucleophilic catalysis

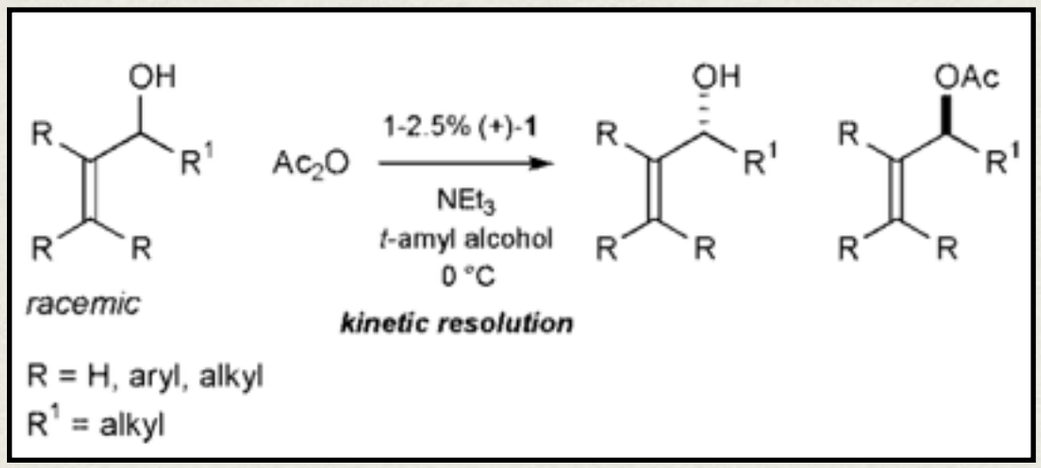
- **Kinetic resolutions of secondary alcohols**
  - **Apply on other substrates**
    - **Propargylic Alcohols——s: 4 to 20**

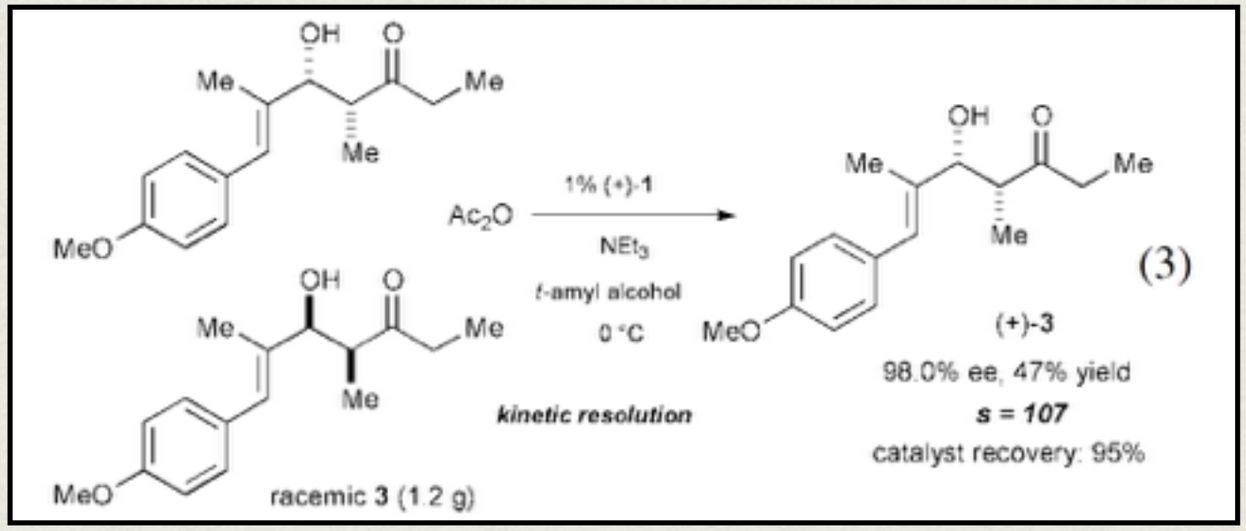




Crystal structure of the adduct confirms the expanded conjugation and significantly increased steric bulky because of the phenyl ring

  - **Allylic alcohols (s: 5 to 80)& application to natural product synthesis**





Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* ***1999****, 121, 5091.*
Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chemical Communications* ***2000****, 1009.*

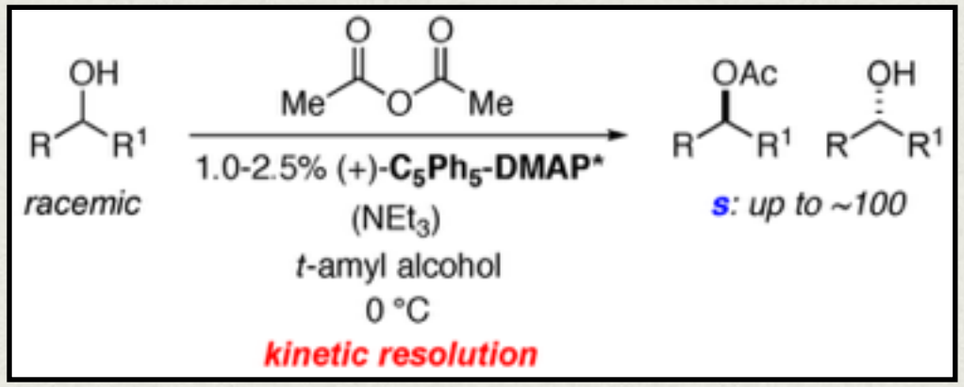
Asymmetric Nucleophilic catalysis

- **After more than 10 years—— Dynamic kinetic resolution of secondary alcohol**

  An idea always in mind, wait until a powerful racemization method appears

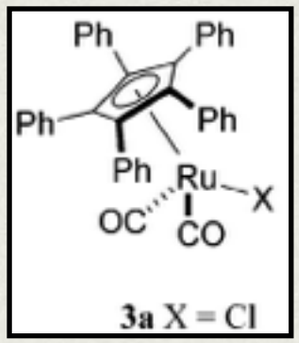
  - **Dynamic kinetic resolution:**

    Allows stereo-convergent transformation of racemic substrate into a single enantiomer conquer the 50% yield limitation

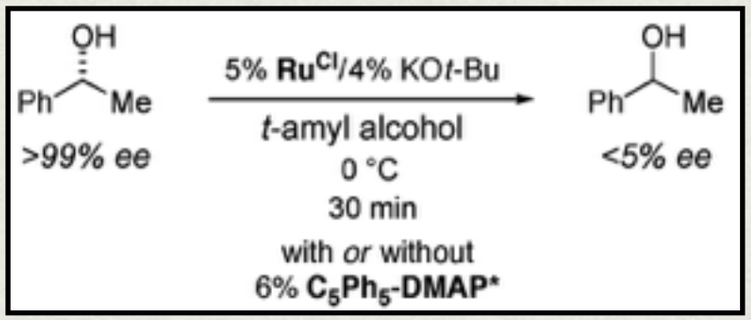


Requests of the catalyst:

- **Highly active**
- **Compatible with the reaction condition**



Great for dynamic kinetic resolution of secondary alcohol with enzyme.

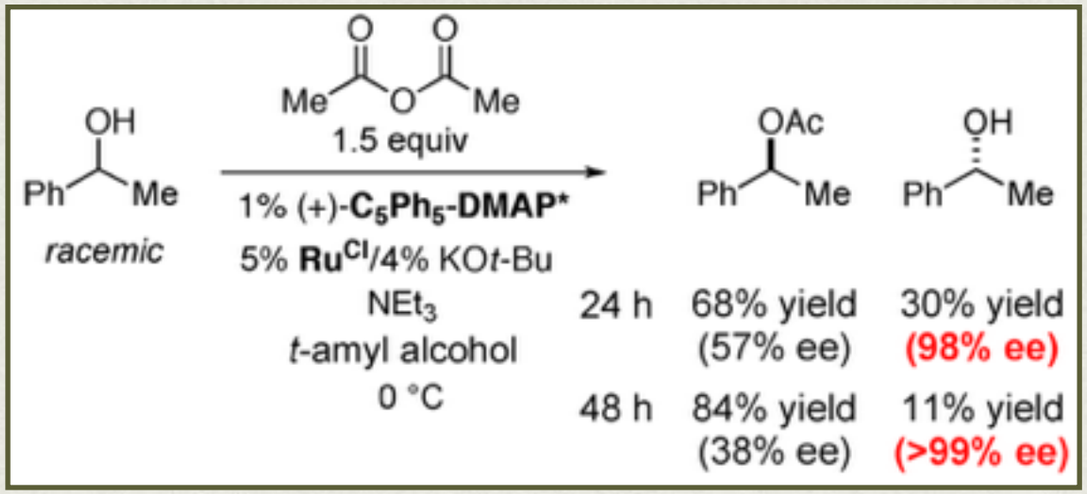


racemization happens smoothly in the solvent and the existence of ligand for kinetic resolution

Lee, S. Y.; Murphy, J. M.; Ukai, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15149.
Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817.

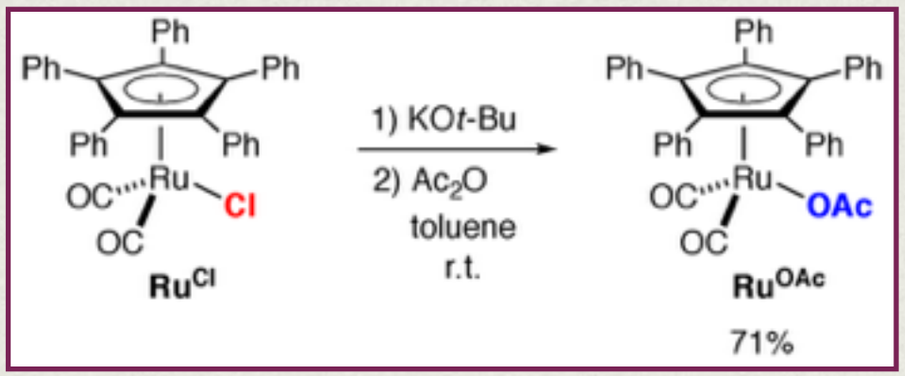
Asymmetric Nucleophilic catalysis

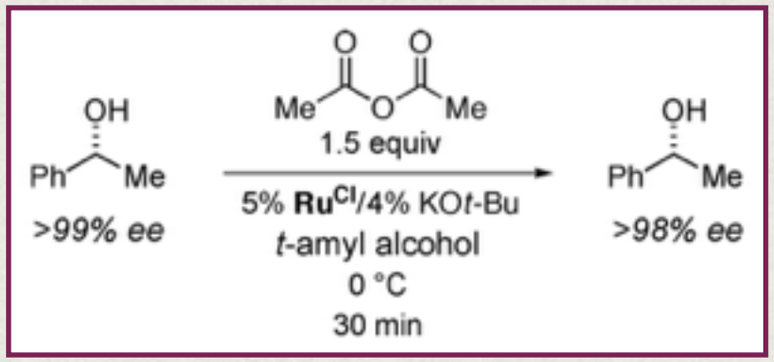
- **After more than 10 years—— Dynamic kinetic resolution of secondary alcohol**

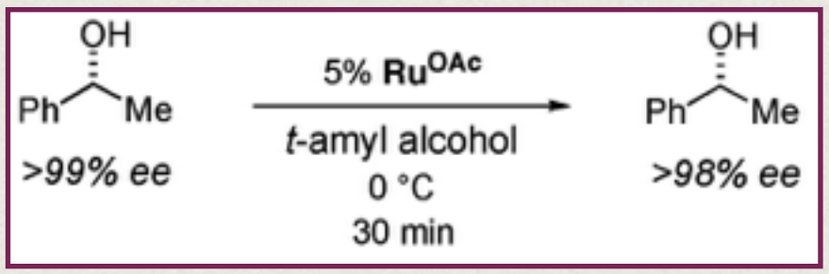


Dynamic kinetic resolution didn't happen.

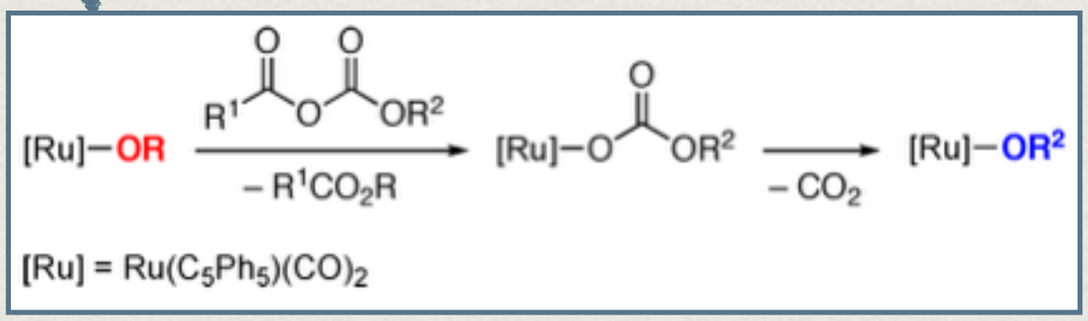
Ac_2O deactivates the racemization catalyst







Actual active species



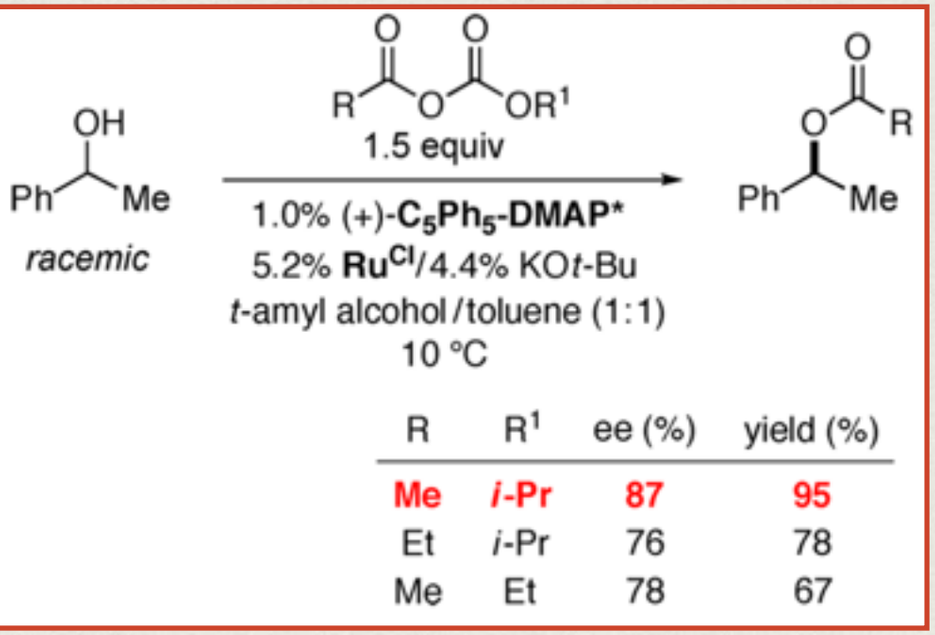
Find a way out

Lee, S. Y.; Murphy, J. M.; Ukai, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15149.
Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817.

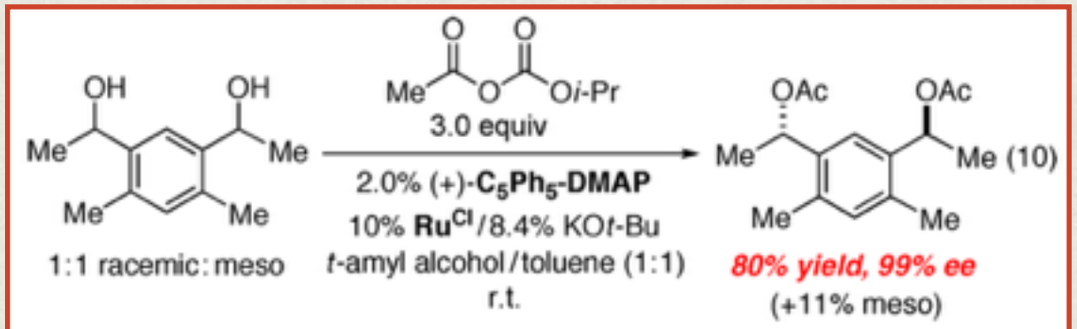
Asymmetric Nucleophilic catalysis

- **After more than 10 years—— Dynamic kinetic resolution of secondary alcohol**

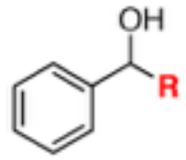
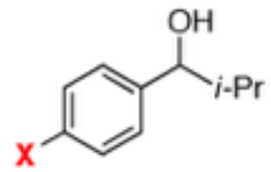
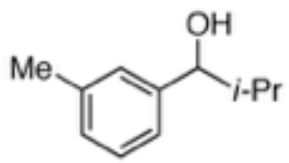
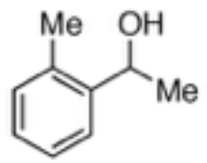
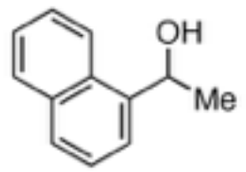
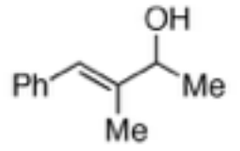
Acyl carbomate works very well



R	R^1	ee (%)	yield (%)
Me	*i*-Pr	87	95
Et	*i*-Pr	76	78
Me	Et	78	67



Q2: Mechanism understanding

entry	alcohol		ee (%)	yield (%)[b]
1		R = Me	87	95 (85)
2		Et	90	96 (95)
3		cyclopentyl	82	90 (86)
4		*i*-Pr	91	98 (95)
5		X = Cl	85	89 (88)
6		OMe	88	93 (92)
7			91	97 (96)
8			93	97 (92)
9			90	99 (94)
10			88	97 (90)

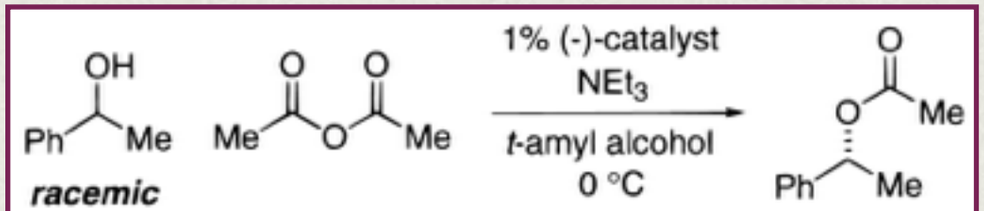
Works well for branch alkyl group ——doesn't work in enzyme case

Allylic also works

Lee, S. Y.; Murphy, J. M.; Ukai, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15149.
Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817.

Asymmetric Nucleophilic catalysis

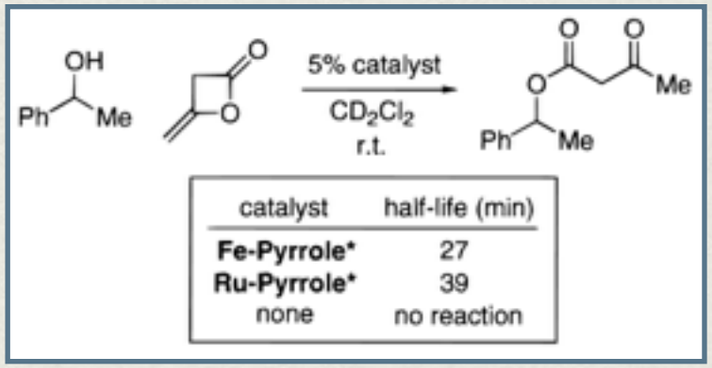
- **Is Ion the Only choice?**



catalyst	selectivity factor
Fe-DMAP*	2
Fe-C_5Ph_5-DMAP	43

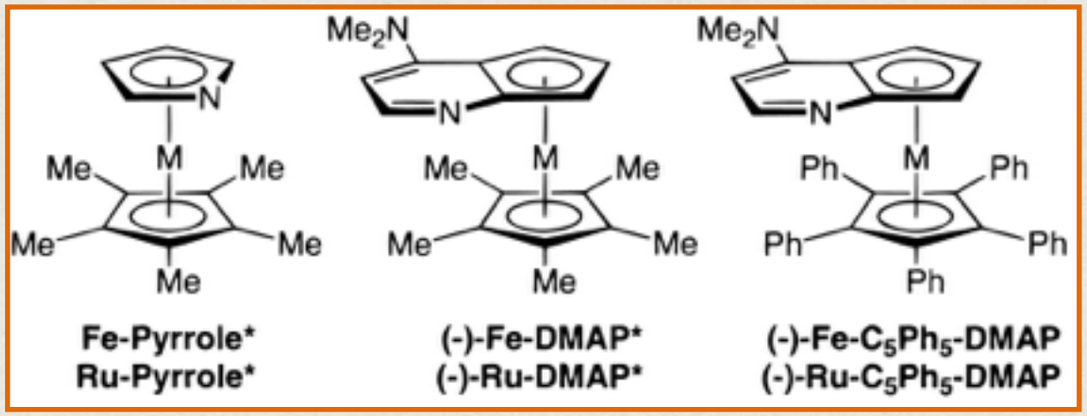
Will Ruthenium also function well?

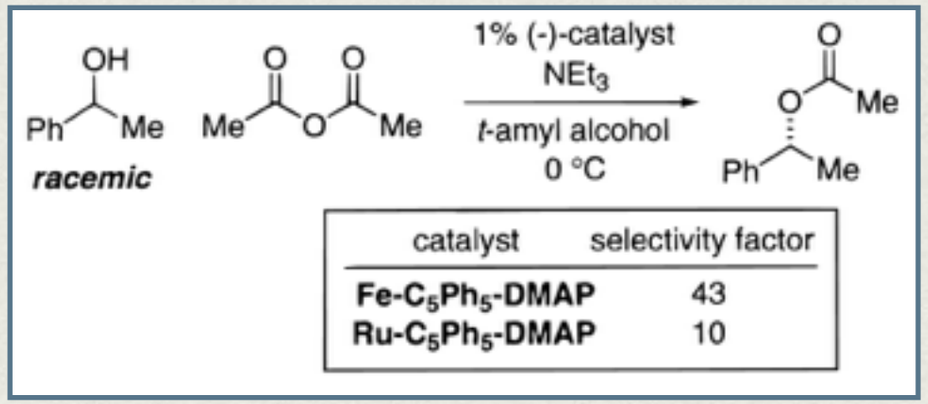
- **same d-electron number**



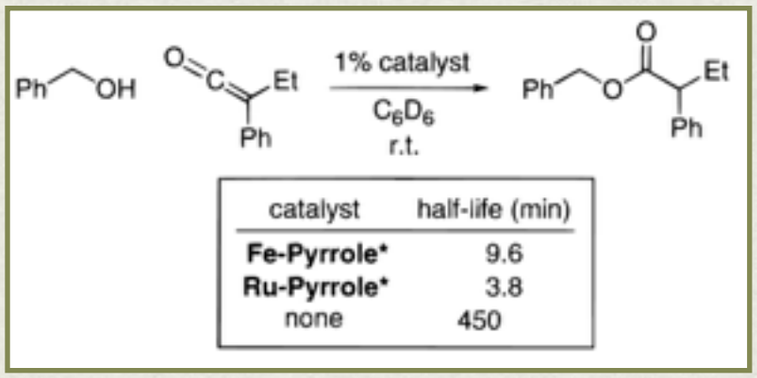
catalyst	half-life (min)
Fe-Pyrrole*	27
Ru-Pyrrole*	39
none	no reaction

Using similar synthetic method

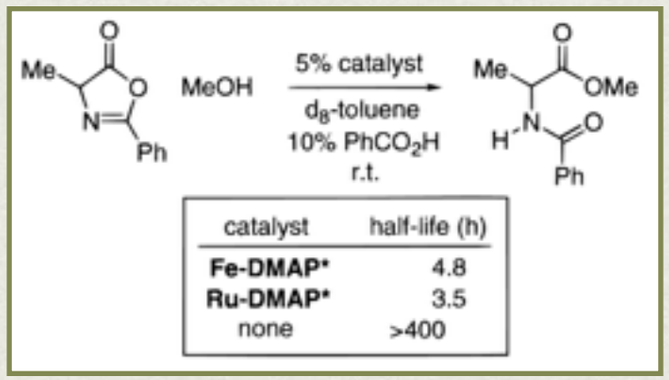




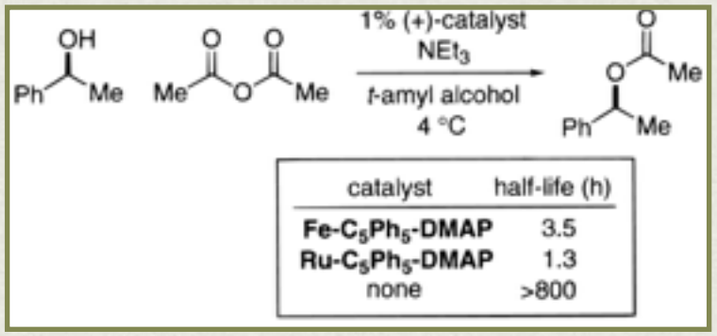
catalyst	selectivity factor
Fe-C_5Ph_5-DMAP	43
Ru-C_5Ph_5-DMAP	10



catalyst	half-life (min)
Fe-Pyrrole*	9.6
Ru-Pyrrole*	3.8
none	450



catalyst	half-life (h)
Fe-DMAP*	4.8
Ru-DMAP*	3.5
none	>400

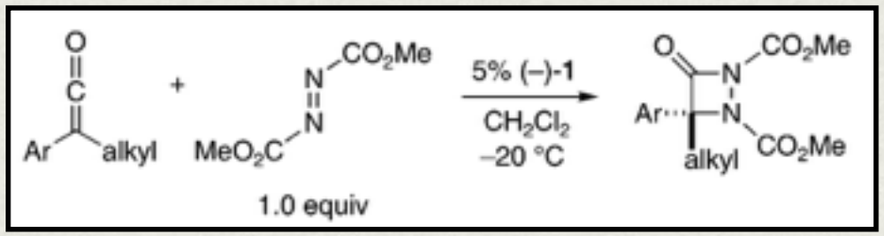


catalyst	half-life (h)
Fe-C_5Ph_5-DMAP	3.5
Ru-C_5Ph_5-DMAP	1.3
none	>800

Garrett, C. E.; Fu, G. C. *J. Am. Chem. Soc.* **1998,***120*, 7479.

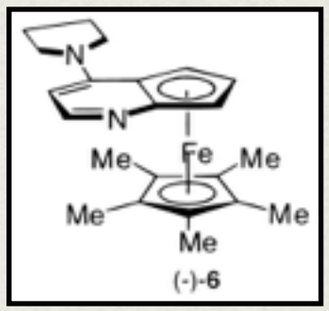
Asymmetric Nucleophilic catalysis

- **For enantioselective [2+2] ketene addition**
  - **C=N bond:** Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002,** *124*, 1578
  - **C=O bond:** Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed*. **2004**, *43*, 6358
  - **C=N bond:** Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc*. **2005**, *127*, 11586
  - **N=N bond:** Berlin, J. M.; Fu, G. C. *Angew. Chem. Int. Ed*. **2008**, *47*, 7048
  - **N=O bond:** Dochnahl, M.; Fu, G. C. *Angew. Chem. Int. Ed*. **2009**, *48*, 2391



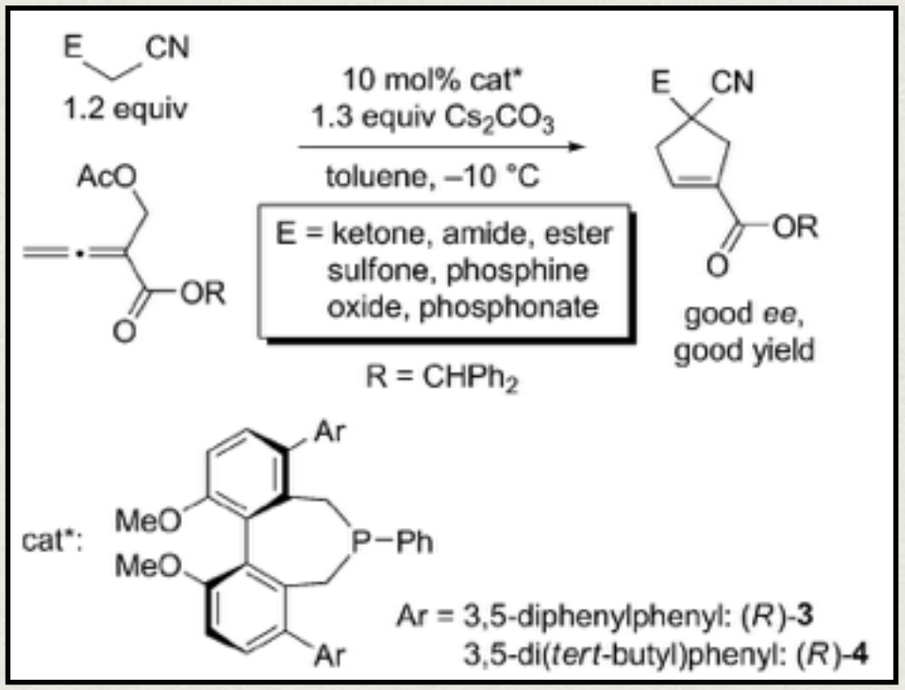
- **For enantioselective other ketene addition**
  - **Hydrazoic acid (HN_3):** Dai, X.; Nakai, T.; Romero, J. A. C.; Fu, G. C. *Angew. Chem., Int. Ed*. **2007**, *46*, 4367.
  - Lee, E. C.; McCauley, K. M.; Fu, G. C. *Angew. Chem., Int. Ed*. **2007**, *46*, 977.
  - Schaefer, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4606.
  - **Amines:** Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc*. **2002**, *124*, 10006.

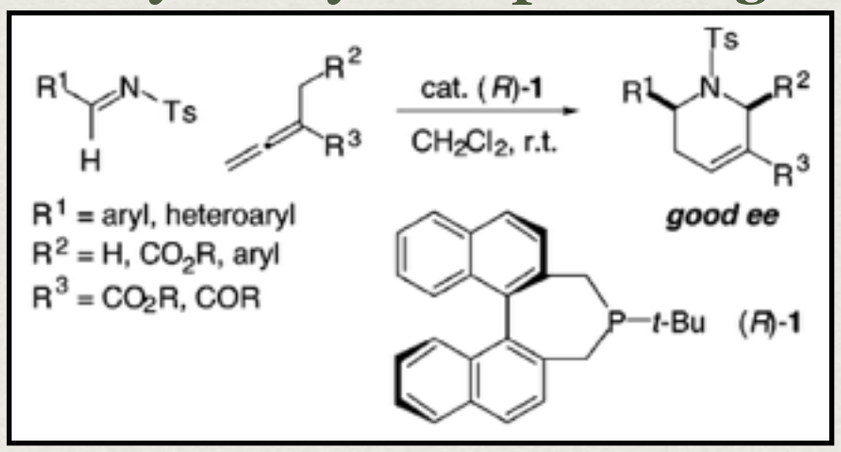
- **For kinetic resolution of amines**
  - Ie, Y.; Fu, G. C. *Chem. Commun.* **2000,** 119
  - Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed*. **2001**, *40*, 234
  - Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264

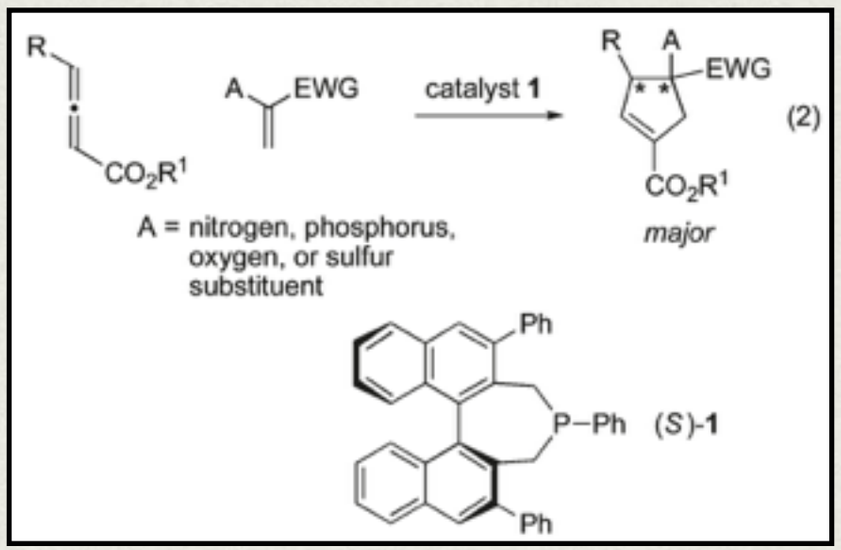


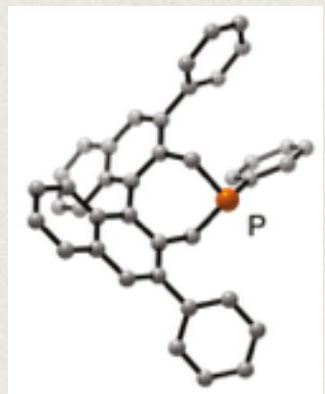
Asymmetric Nucleophilic catalysis

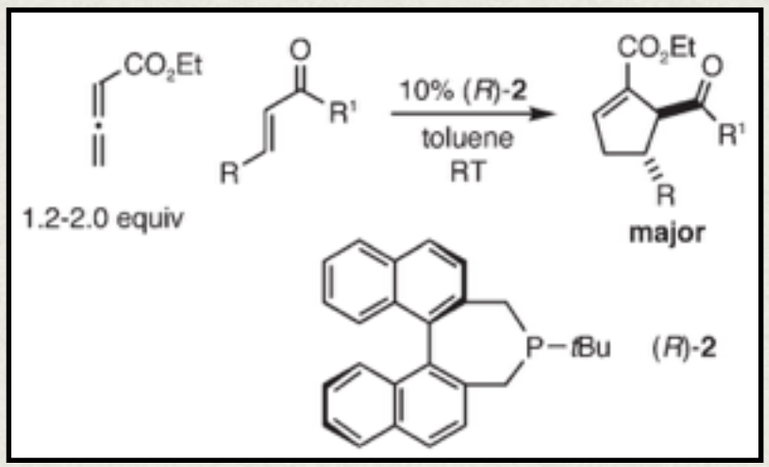
- **Enantioselective allene addition catalyzed by Phosphine-ligands**

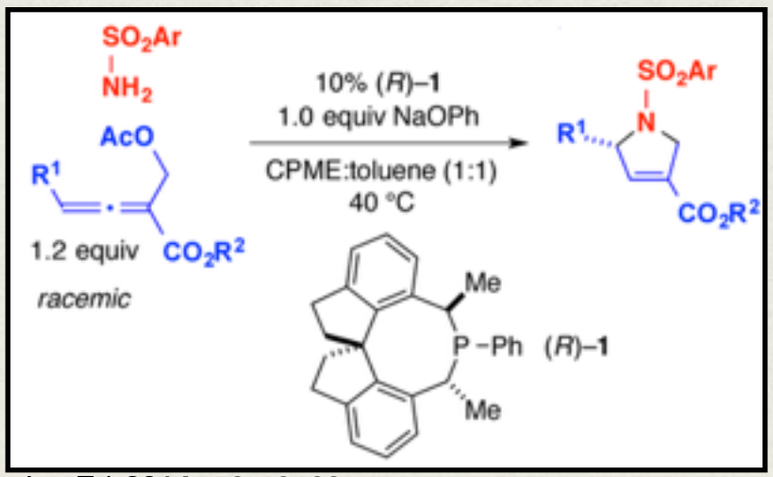












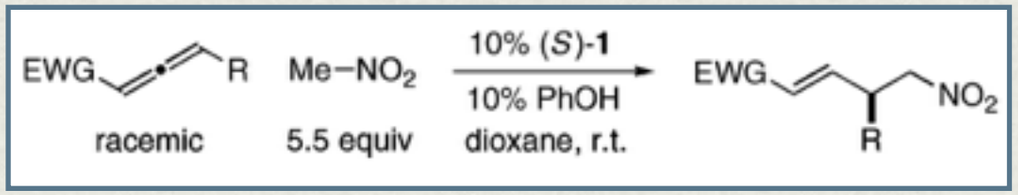
Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234.
Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1426.
Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293.
Ziegler, D. T.; Riesgo, L.; Ikeda, T.; Fujiwara, Y.; Fu, G. C. *Angew. Chem. Int. Ed.* **2014**, *53*, 13183.
Kramer, S.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 3803.

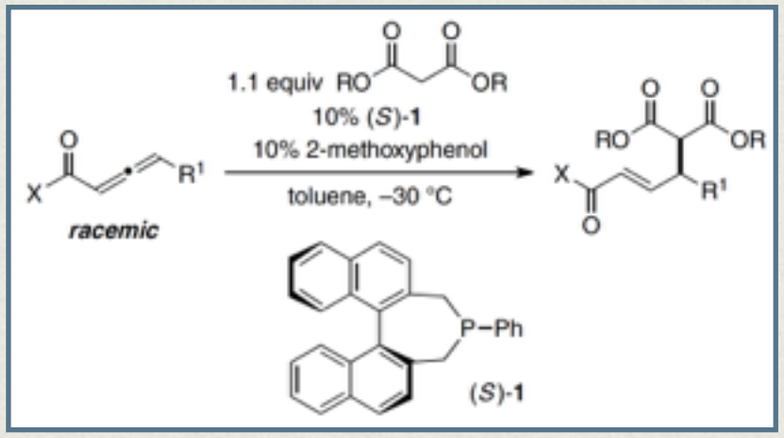
Asymmetric Nucleophilic catalysis

- **Enantioselective ketene addition catalyzed by Phosphine-ligands**

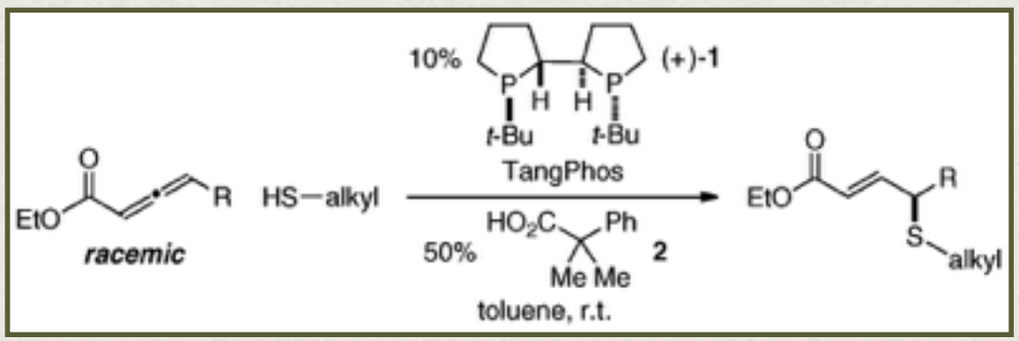
enatioselective functionalization of the γ position of carbonyl group is of interest

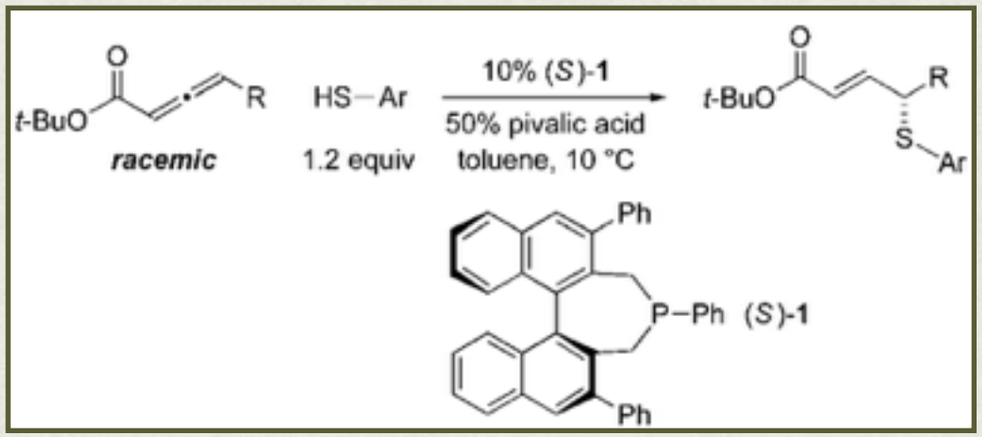
- **Carbon nucleophile**



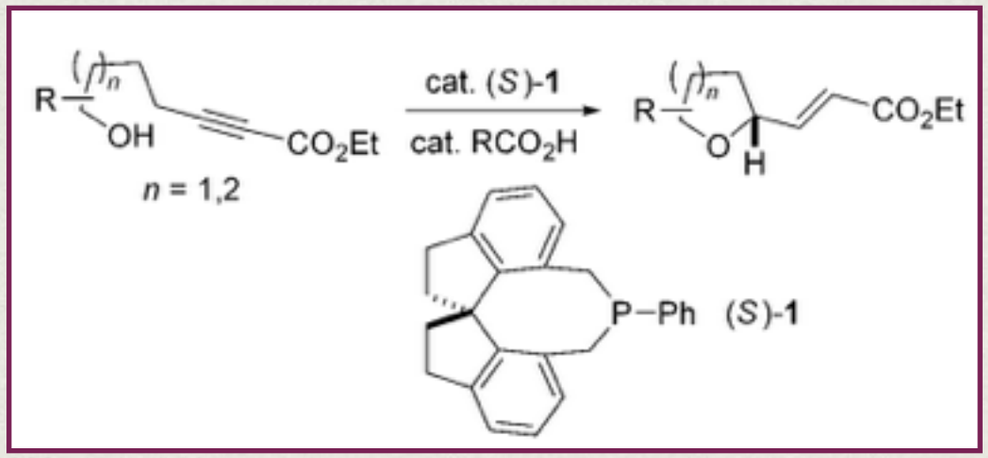


- **Sulfur nucleophile**





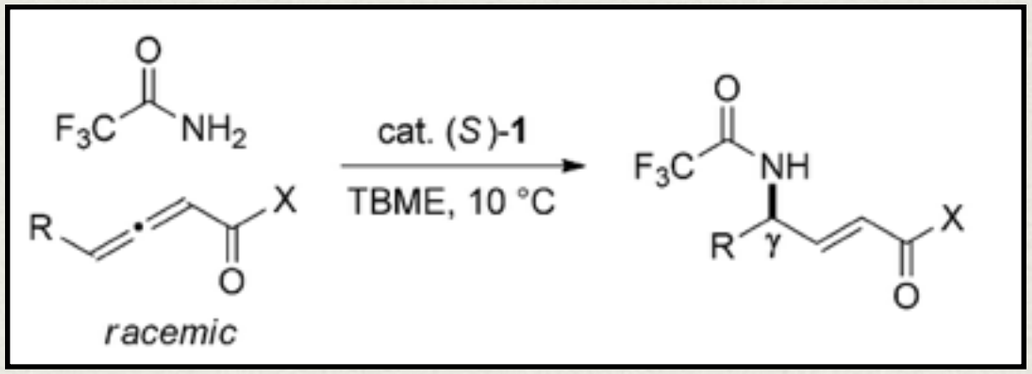
- **Oxygen nucleophile**

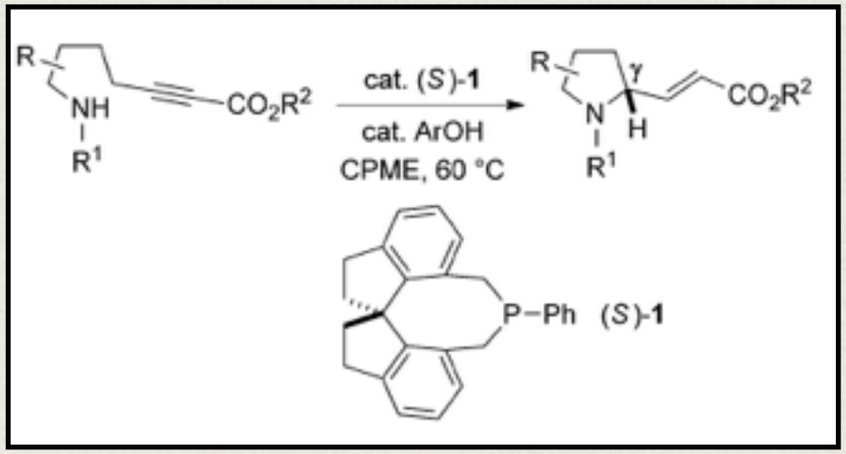


Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231.
Sinisi, R.; Sun, J.; Fu, G. C. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20652.
Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 4568.
Fujiwara, Y.; Sun, J.; Fu, G. C. *Chem. Sci.* **2011**, *2*, 2196.
Chung, Y. K.; Fu, G. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 2225.

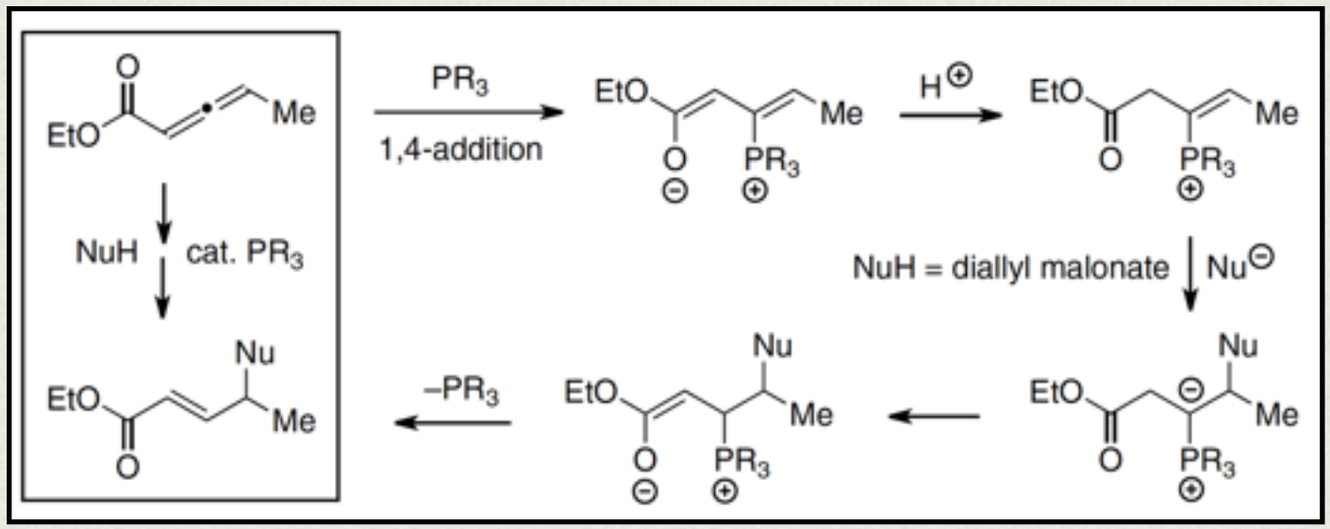
Asymmetric Nucleophilic catalysis

- **Enantioselective ketene addition catalyzed by Phosphine-ligands**
  - **Nitrogen nucleophile**





  - **General mechanism understanding**

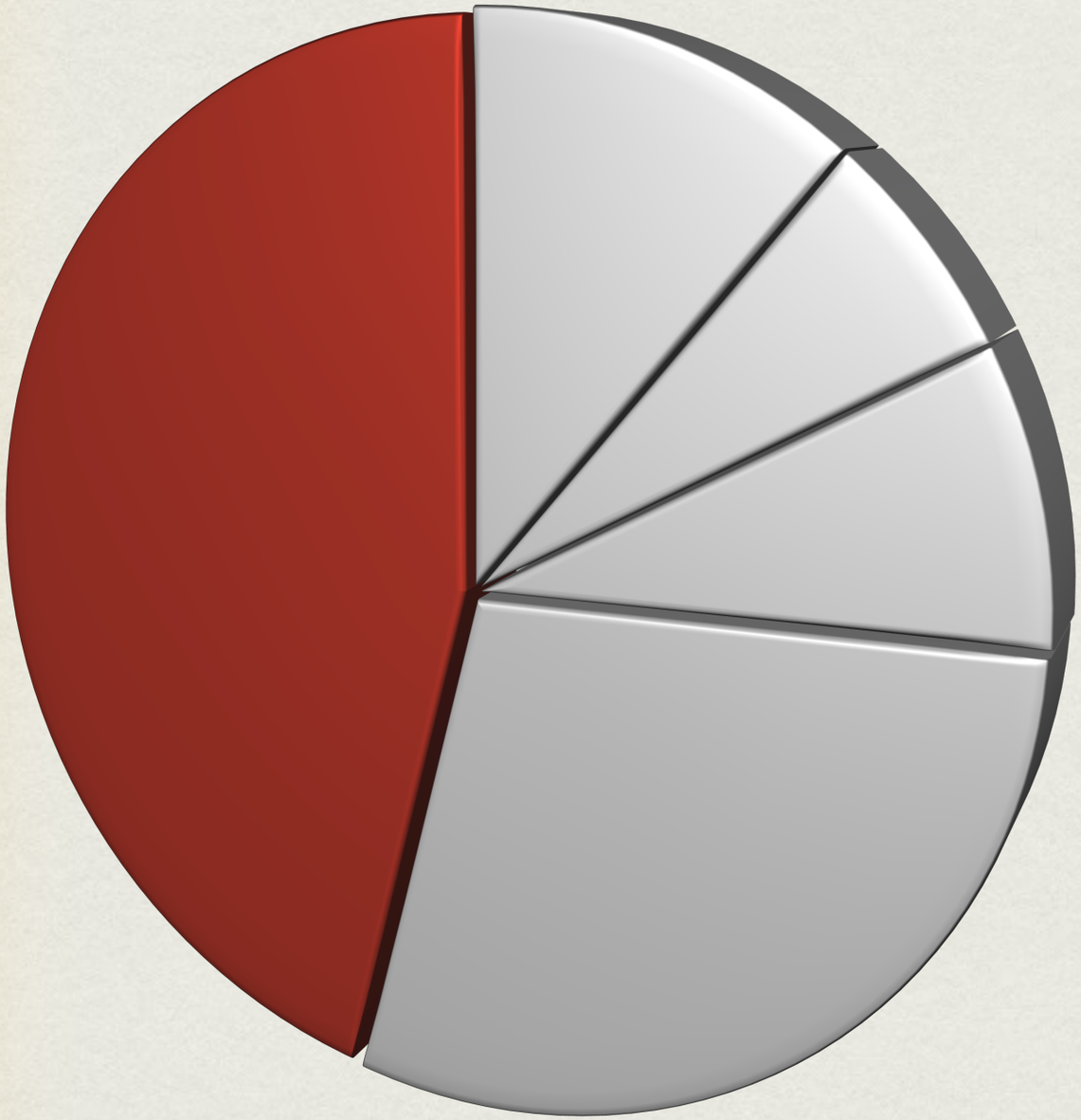


- **Resting state of catalyst is the phosphine itself**
- **Rate law: 1st order in catalyst and allene, 0 order in mlonate**
- **the ee of the PD correlates linearly with the ee of catalyst**

First step is turnover-limiting

Lundgren, R. J.; Wilsily, A.; Marion, N.; Ma, C.; Chung, Y. K.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 2525.
Sinisi, R.; Sun, J.; Fu, G. C. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20652.

Significant research area of Gregory C. Fu



- Chiral ligand development
- Boron heterocycles
- Organotin Catalysis
- Asymmatric Nucleophilic catalysis
- Pd/ Ni/Cu catalyzed cross-coupling

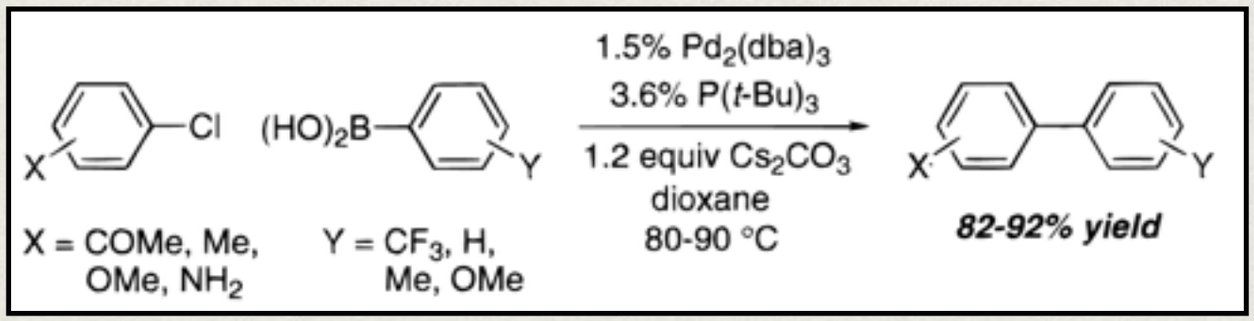
Pd/Ni/Cu catalyzed cross-coupling reaction

- **Palladium Catalyzed cross-coupling reaction**
  - **Arylchloride substrates—— more available and less expensive**

    Why coupling with iodide and bromide is much more common than chloride?

    - **Bond strength (BDE): C-Cl (95 kcal/mol) is stronger than C-Br (80 kcal/mol) and C-I (65 kcal/mol) bonds————————sluggish O.A.**
    - **If we consider the O.A. step, Pd (2.20) is electronegative, which is bad for O.A.**
    - **How to promote the O.A. step?**

    ————We need powerful Ligands to help the reaction: electron-rich & large ligands



Make Pd a better reductant

single ligated Pd —more free coordination site

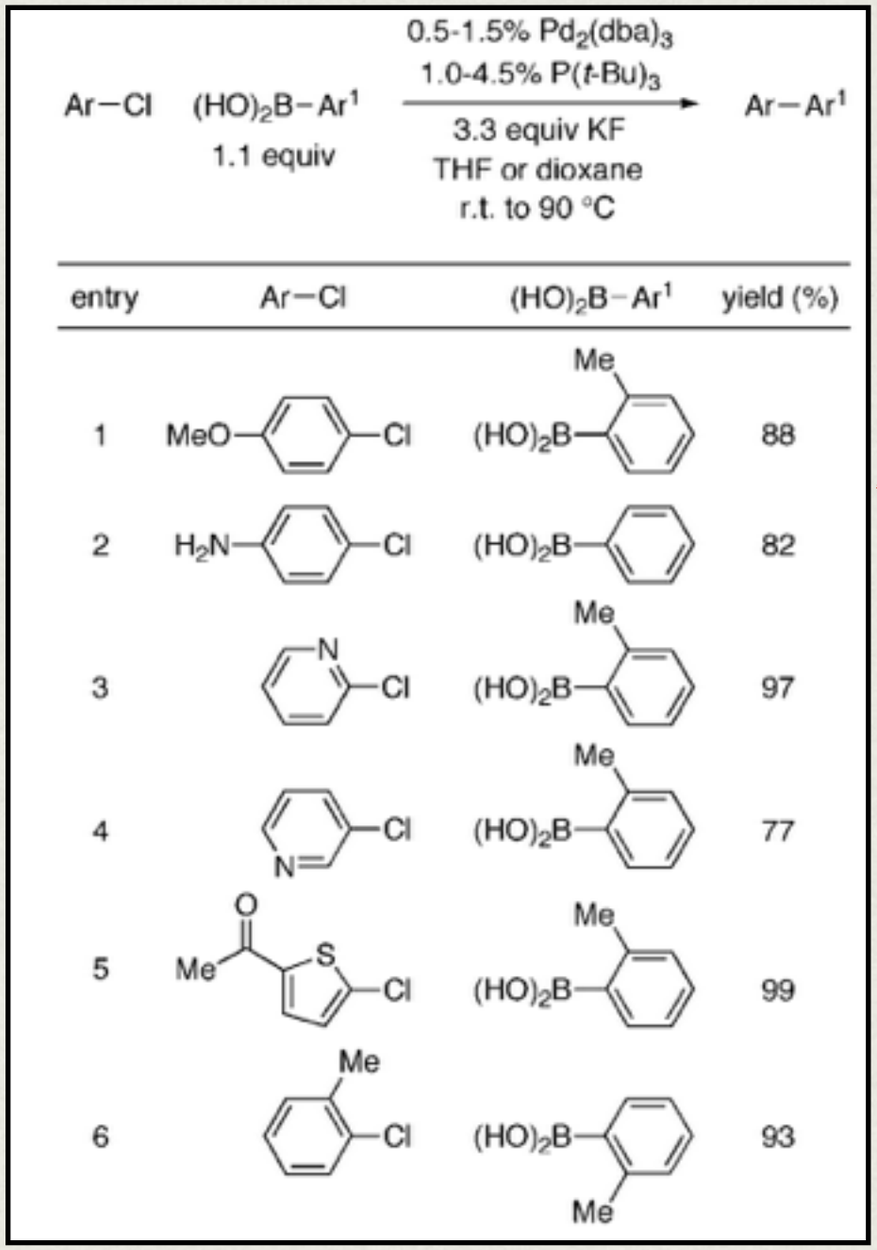
$P(tBu)_3$ is the ligand of choice: e-rich & with big cone angle (182°)

Fu, G. C. Acc. Chem. Res. **2008**, 41, 1555.
Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998,** *37*, 3387.

Pd/Ni/Cu catalyzed cross-coupling reaction

- **Palladium Catalyzed cross-coupling reaction**
  - **Arylchloride substrates—— more available and less expensive**

Using KF as base can lower the reaction temperature and it is much cheaper

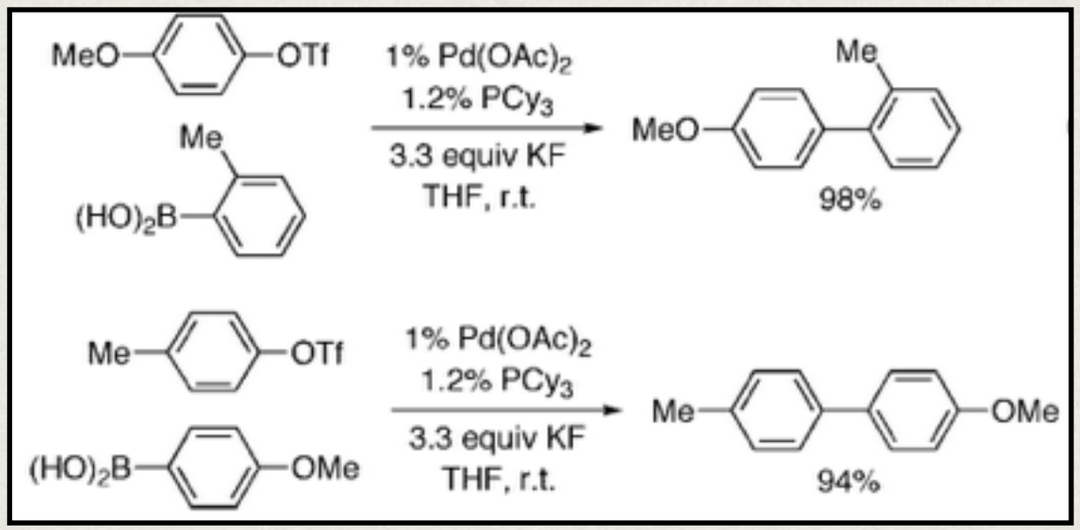


the ortho substituted substrates are difficult in other conditions

Works well for bromide and iodide @ r.t.

Unactivated chloride need 70-90; all others r.t.

PCy_3 is better for OTf substrates—less steric-hindered

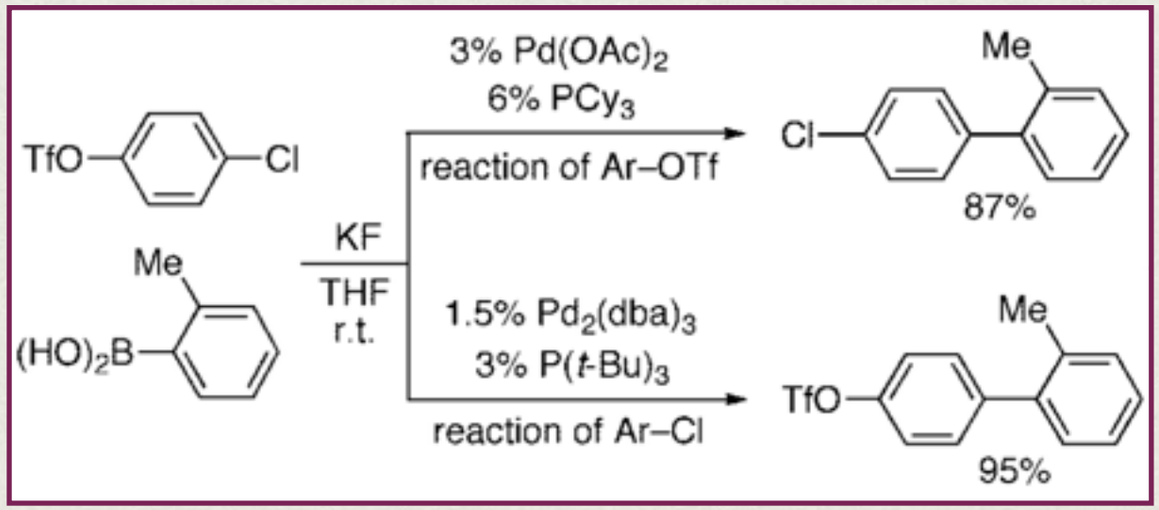


Fu, G. C. Acc. Chem. Res. **2008**, 41, 1555.
Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

Pd/Ni/Cu catalyzed cross-coupling reaction

- **Palladium Catalyzed cross-coupling reaction**
  - **Arylchloride substrates—— more available and less expensive**

Site-selective functionalization

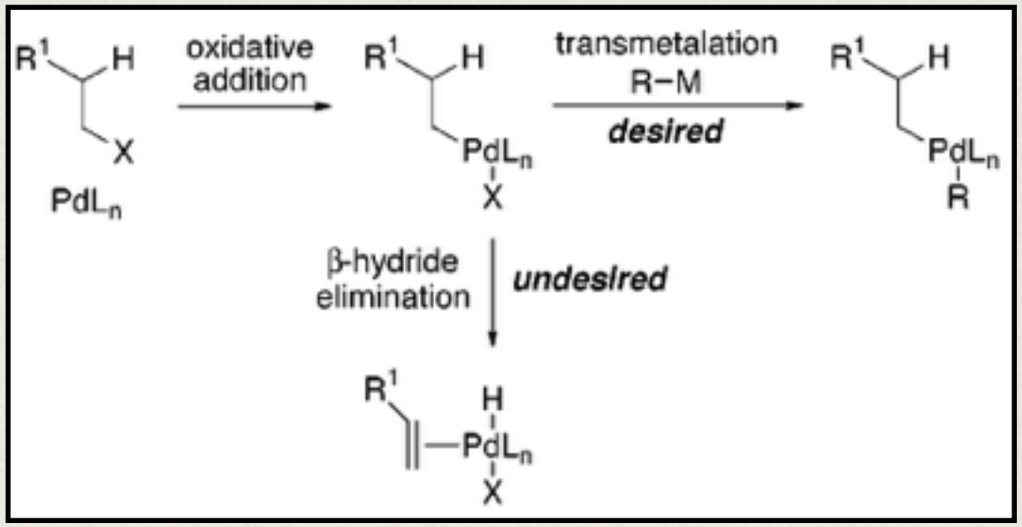


- **A general procedure for Suzuki coupling with aryl/vinyl halides/triflates**
- **General conditions for Heck, Stille, Sonogashira, Negishi couplings**
- **$Pd(PtBu_3)_2$ is commercially available and air stable for 1 month**
- **Usage of air-stable phosphonium salt (e.g. $[HPtBu_3]BF_4$) makes the reaction more practical**

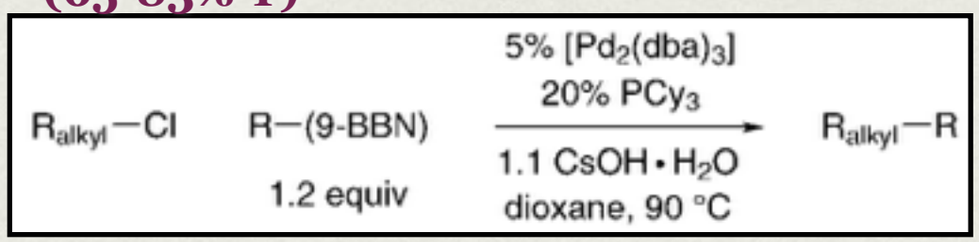
Fu, G. C. *Acc. Chem. Res*. **2008**, *41*, 1555.
Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**,*123,* 6989
Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**,*124*, 6343
Hundertmark, T.; Littke, A. F.; 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

Pd/Ni/Cu catalyzed cross-coupling reaction

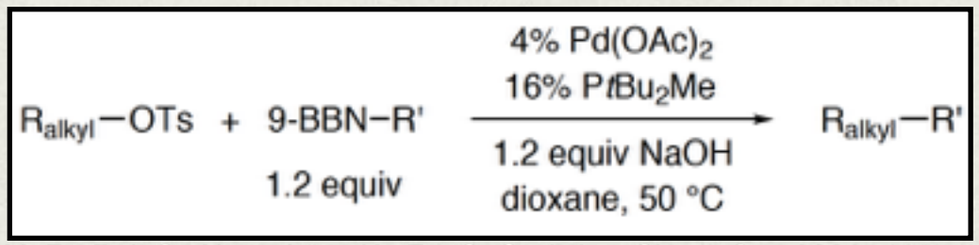
- **Palladium Catalyzed cross-coupling reaction**
  - **Primary alkyl bromide as coupling partners**
    - **sp^3 halides undergo slow O.A.**
    - **Quick β-Hydride elimination**

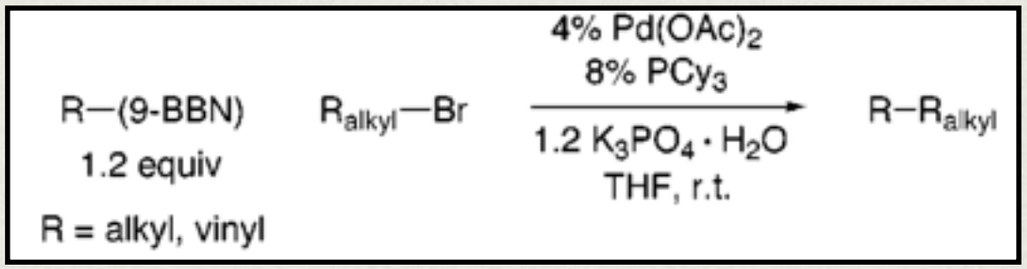


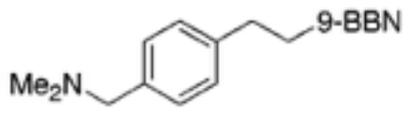
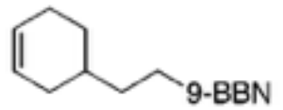
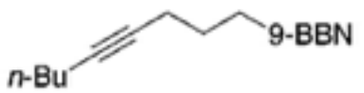
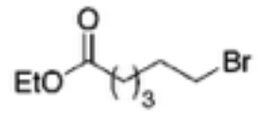
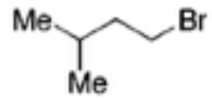
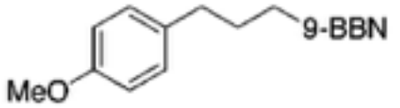
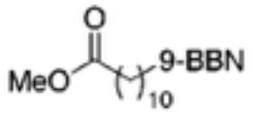
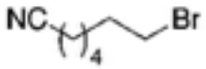
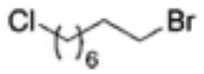
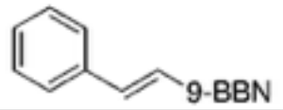
- **Also works for primary alkyl chloride (65-83% Y)**



- **With optimized ligand—for OTs (55-80% Y)**



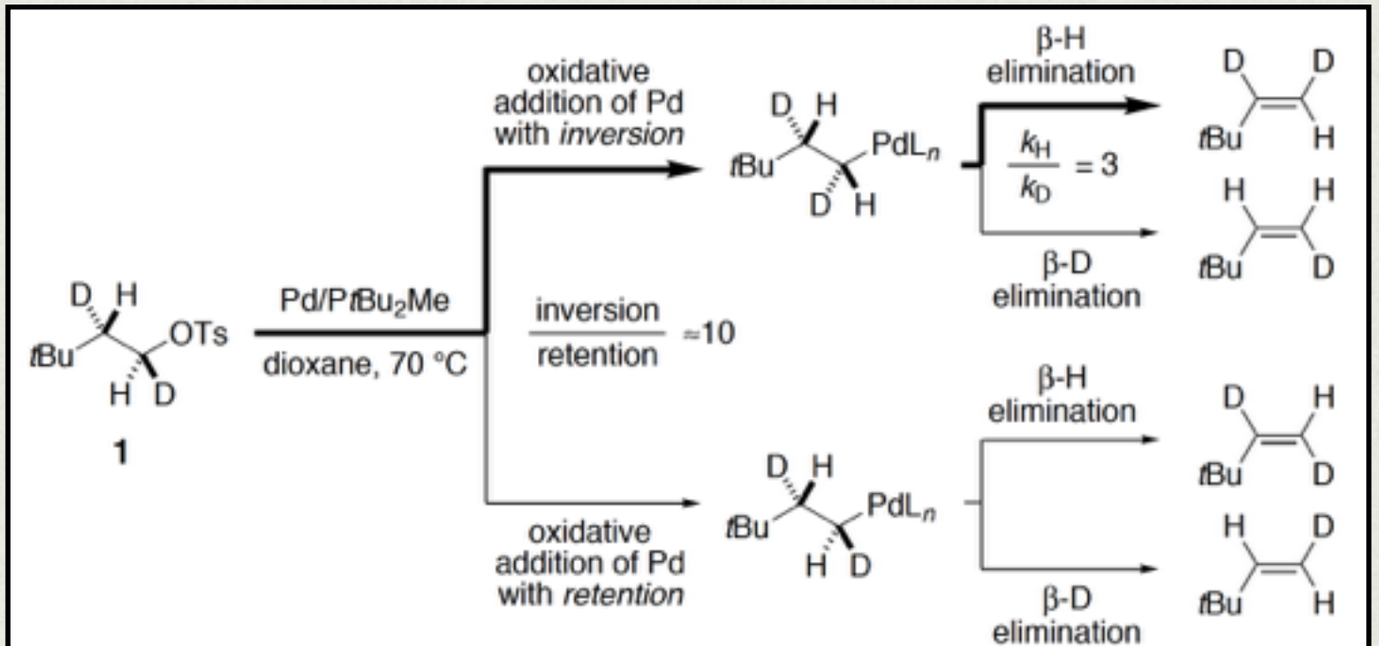


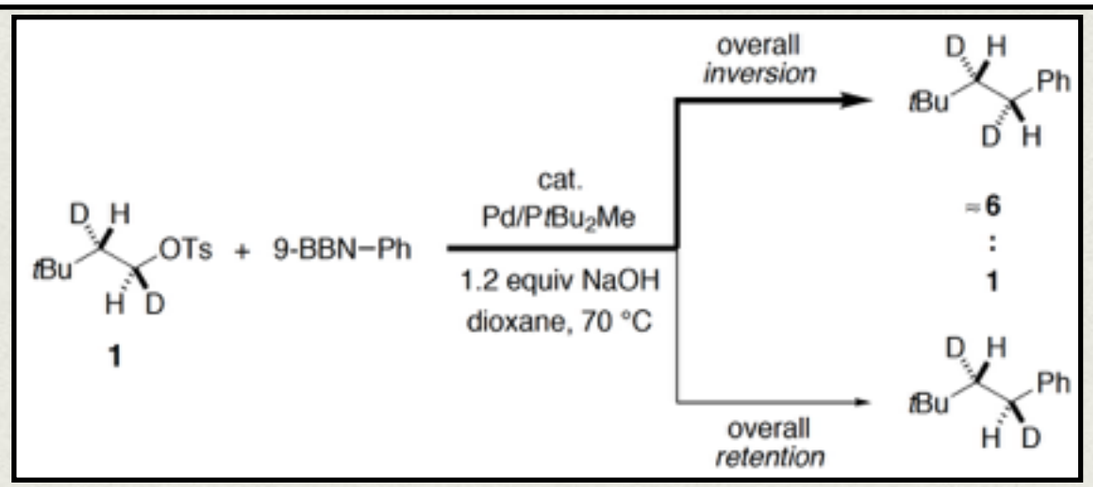
entry	R–(9-BBN)[a]	R_{alkyl}–Br	yield (%)[b]
1	*n*-Hex–(9-BBN)	*n*-Dodec–Br	93
2		*n*-Dodec–Br	78[c]
3		*n*-Dodec–Br	85
4			58
5			72
6		*n*-Hex–Br	80
7			81
8			81
9		*n*-Dodec–Br	66

Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.
Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1945.
Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 3910.

Pd/Ni/Cu catalyzed cross-coupling reaction

- **Palladium Catalyzed cross-coupling reaction**
  - **Mechanism understanding for OTs substrates**



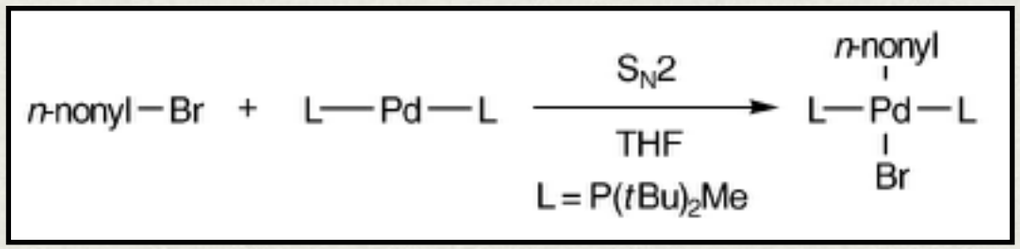


- **Predominant Inversion during O.A.**
- **Well-precedented retention of configuration during R.E.**

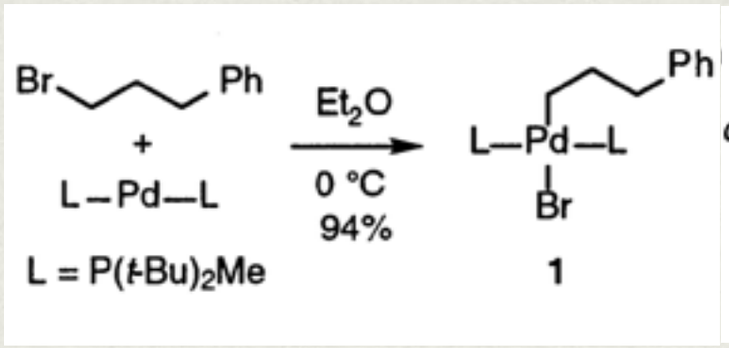
Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 3910.

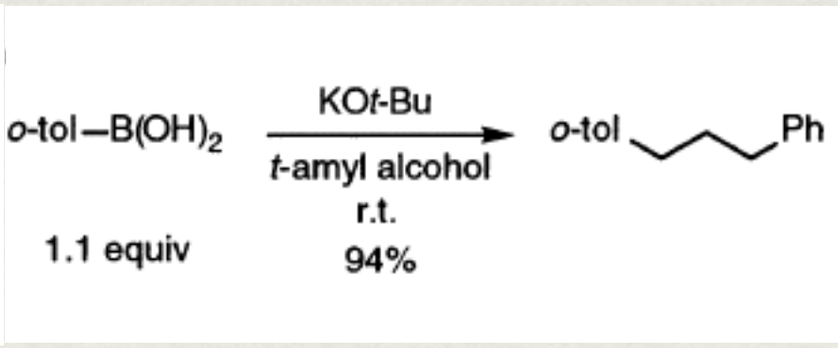
Pd/Ni/Cu catalyzed cross-coupling reaction

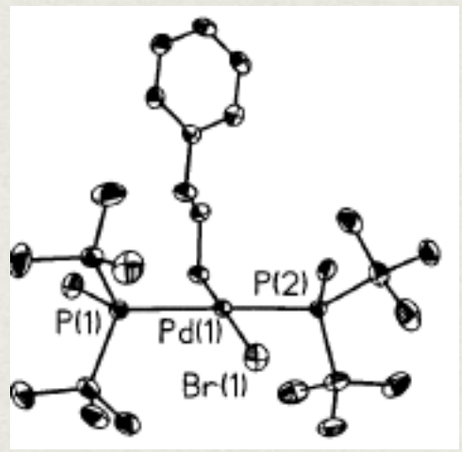
- **Palladium Catalyzed cross-coupling reaction**
  - **Mechanism understanding**



- **The activation parameters show a very large negative ΔS(activation)~-63eu————consistent with a Sn2 pathway**







- **With the $P(tBu)_2Me$, the O.A. happens quickly at 0 °C**
- **The O.A. can generate 1 under mild conditions that β-hydride elimination does not occur**

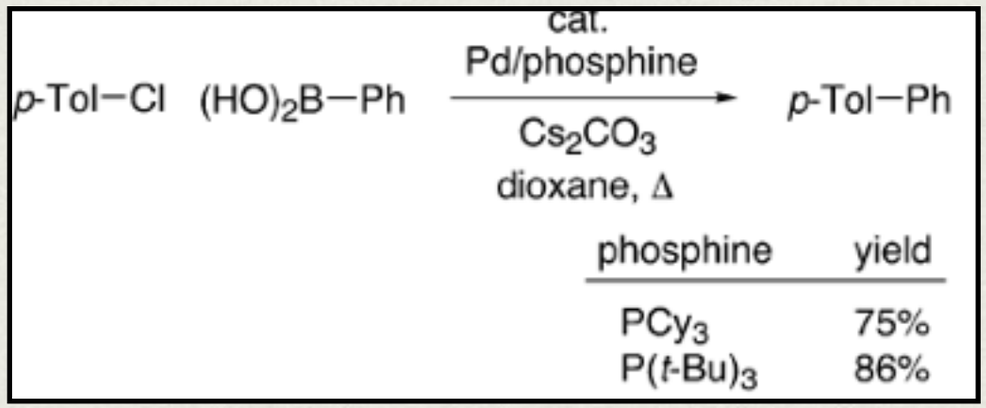
Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 5749.
Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

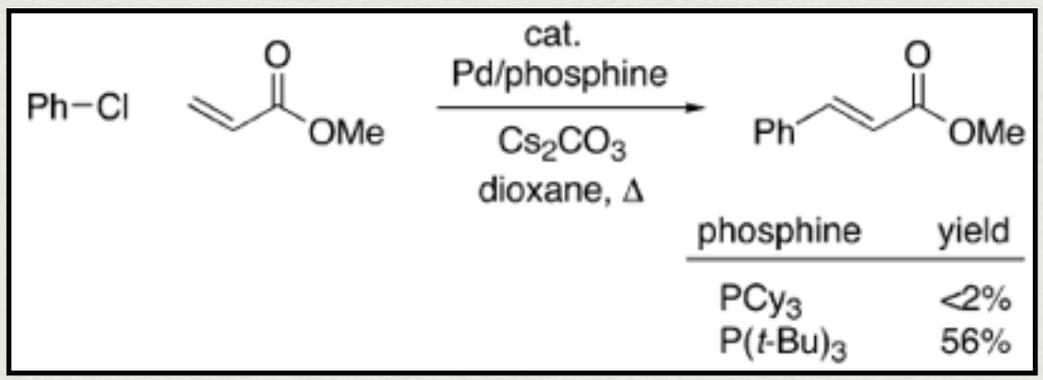
Pd/Ni/Cu catalyzed cross-coupling reaction

- **Palladium Catalyzed cross-coupling reaction**
  - **Mechanism understanding**

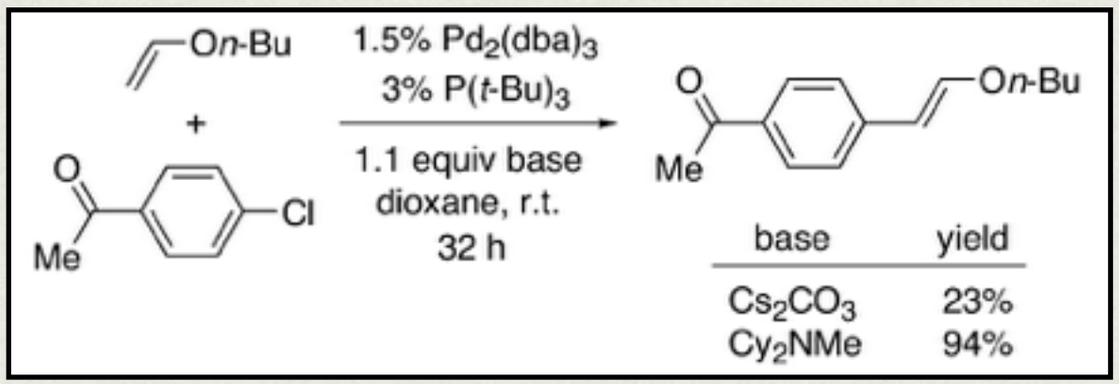
    Is the O.A. the only barrier for chloride substrate?

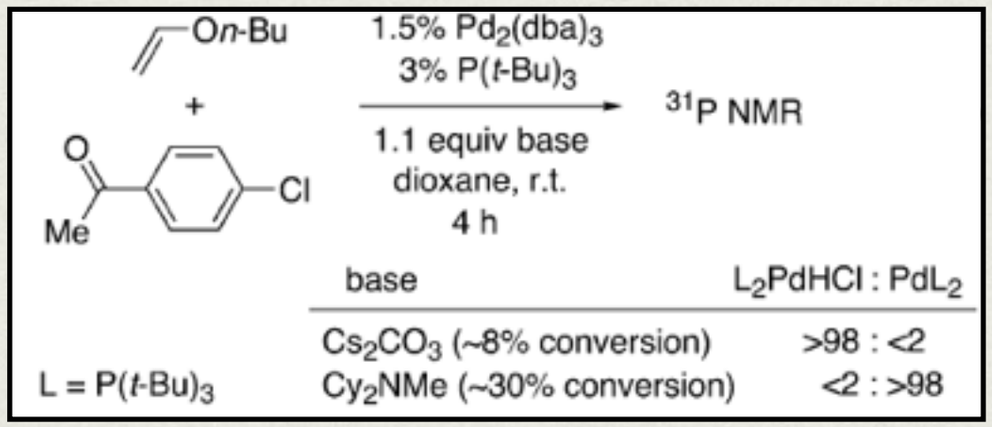
    - **Why is the difference between the two ligands?**





- **About the regeneration of Pd(0) species— effects of the base**



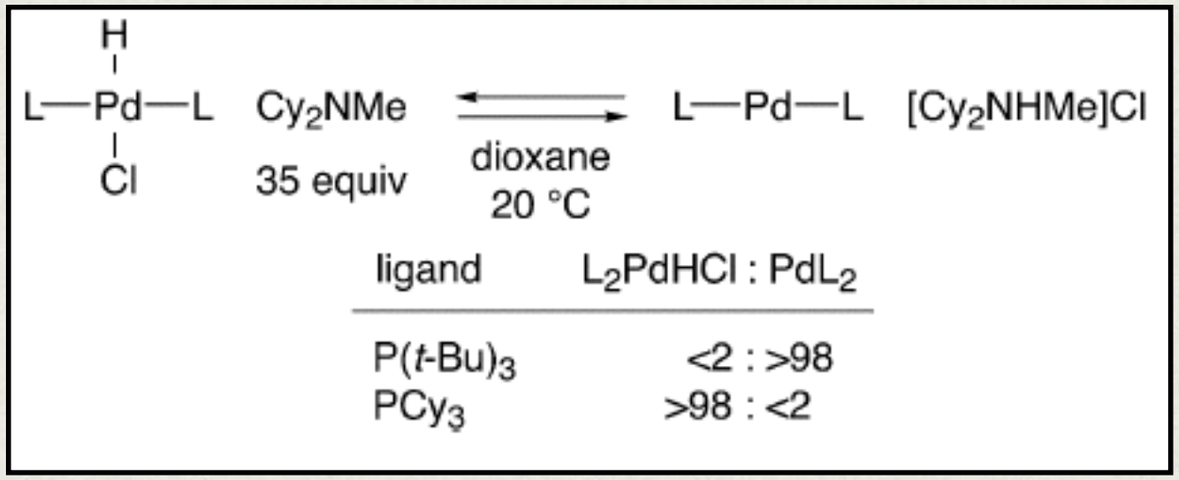


Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788.

Pd/Ni/Cu catalyzed cross-coupling reaction

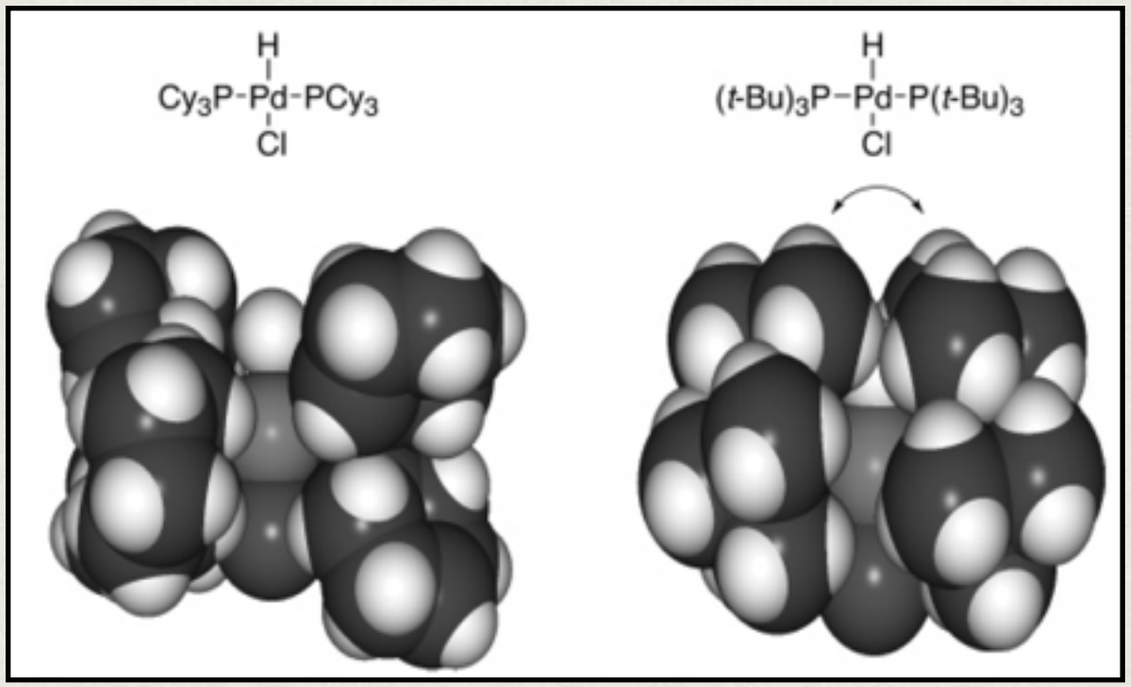
- **Palladium Catalyzed cross-coupling reaction**
  - **Mechanism understanding**

- **Equilibrium favors L_2PdHCl for PCy_3!**



ligand	$L_2PdHCl : PdL_2$
$P(t\text{-}Bu)_3$	<2 : >98
PCy_3	>98 : <2

- **Due to the reluctance of reductive elimination**



P-Pd-P: 180°
P-Pd-P: 161°——help the reductive elimination

Another possible insight: The sluggish Ligand dissociation may also help slow down the β-Hydride elimination

Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788.

Pd/Ni/Cu catalyzed cross-coupling reaction

- **Palladium Catalyzed cross-coupling reaction**

  - 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

- **Ni-Catalyzed cross-coupling reaction**

  - **Ni is much cheaper than Pd**
  - **Due to smaller orbital size, the activation energy of β-hydride elimination is 10-12 kcal/mol higher than Pd**

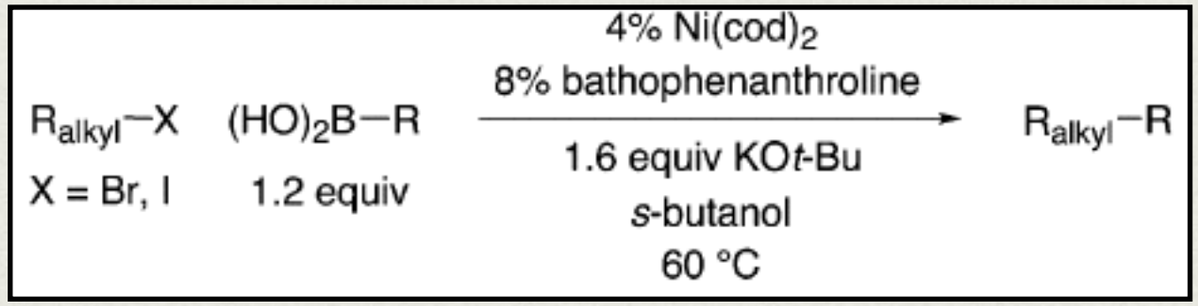
  - **Great for Alkyl-Alkyl coupling**

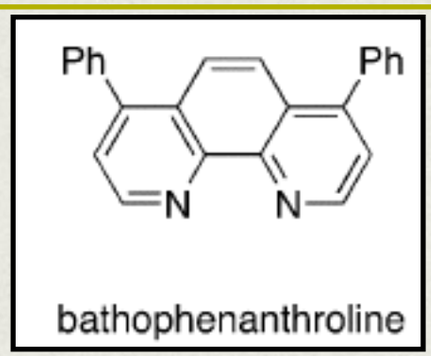
  - **However, usually sensitive to oxygen and mechanism is often unclear**

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

Pd/Ni/Cu catalyzed cross-coupling reaction

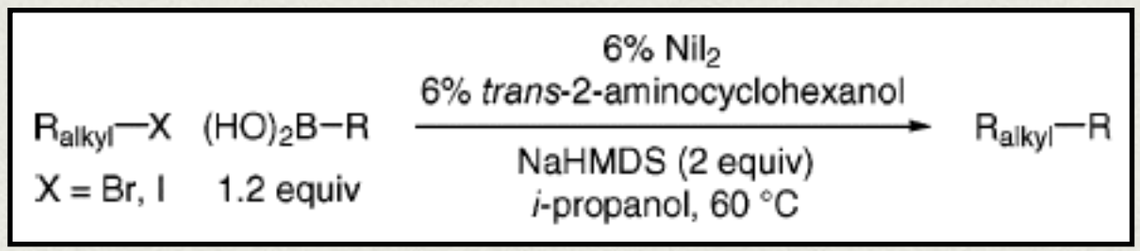
- **Ni-Catalyzed cross-coupling reaction**
  - **Suzuki coupling of unactivated secondary alkyl Halides with aryl or vinyl boron compounds**



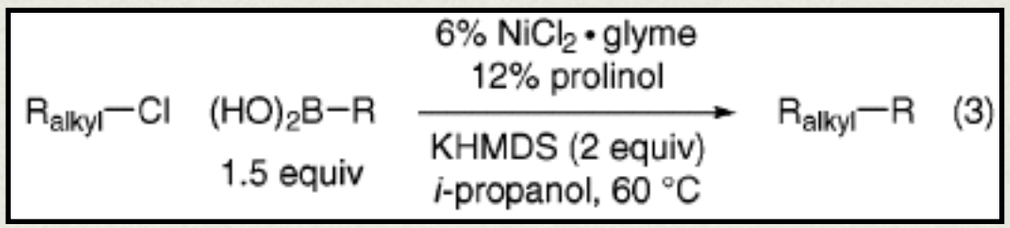


44-75% Y

Amino alcohols as ligand

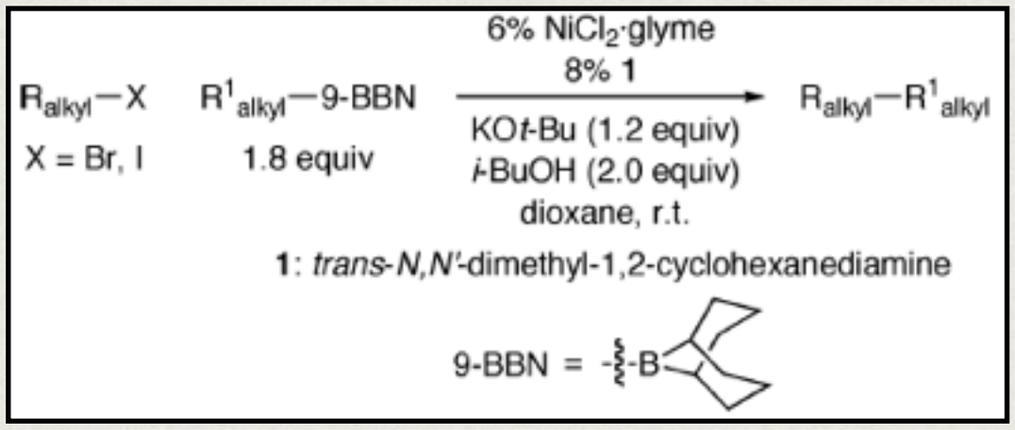


66-92% Y



46-87% Y

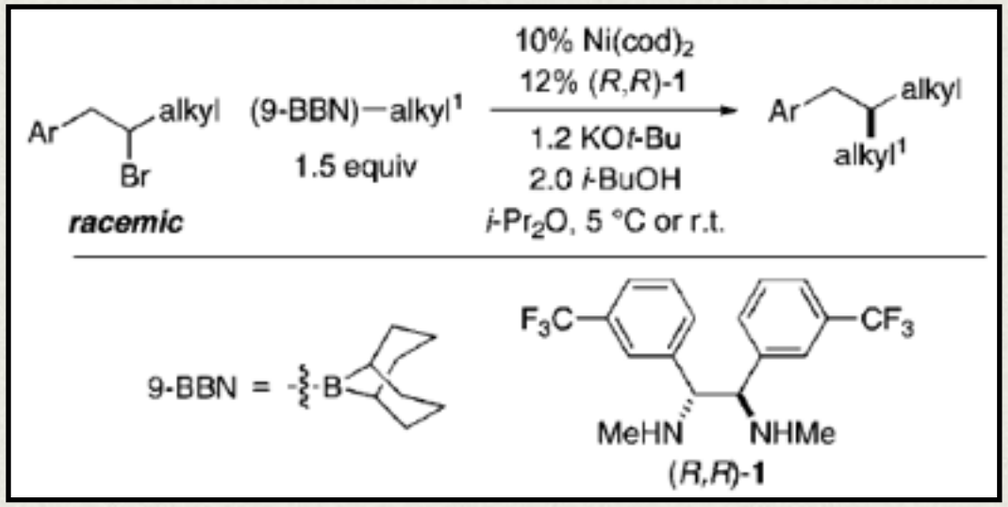
- **Suzuki coupling of unactivated secondary alkyl Halides with alkyl boron compounds**

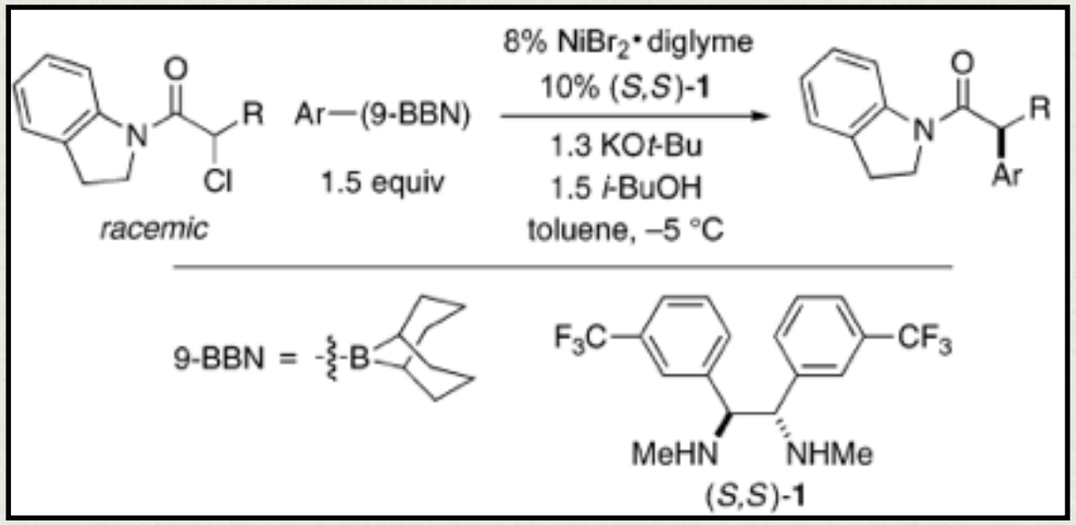


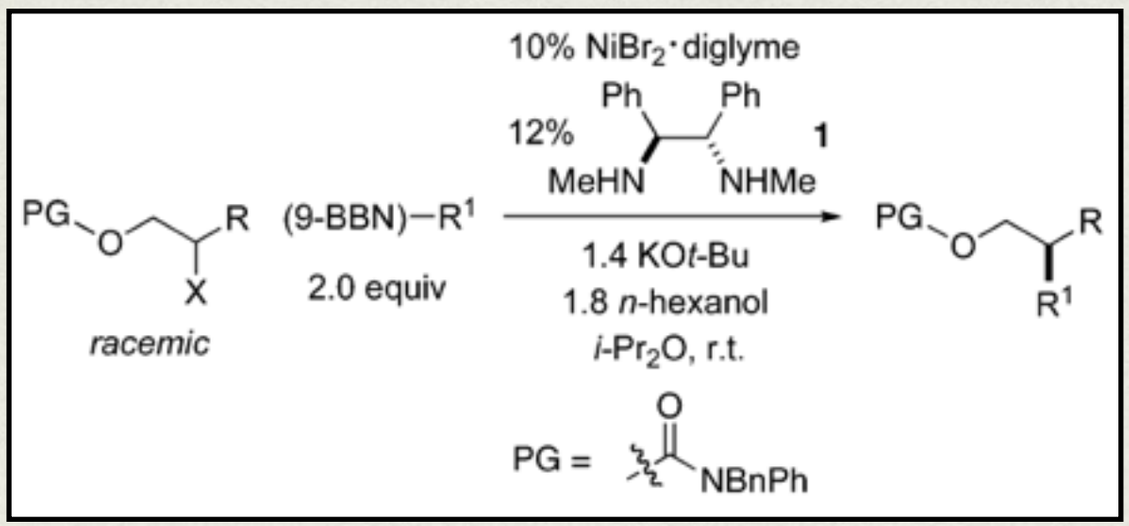
Zhou, J. S.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340.
González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360.
Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602.

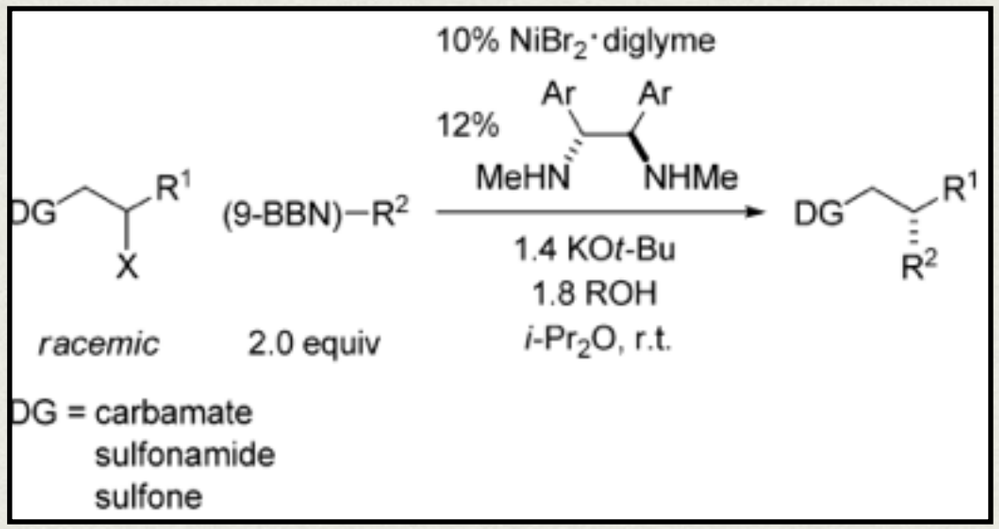
Pd/Ni/Cu catalyzed cross-coupling reaction

- **Ni-Catalyzed cross-coupling reaction**
  - **Enantioselective alkyl-alkyl Suzuki coupling——Utilizing different directing group**





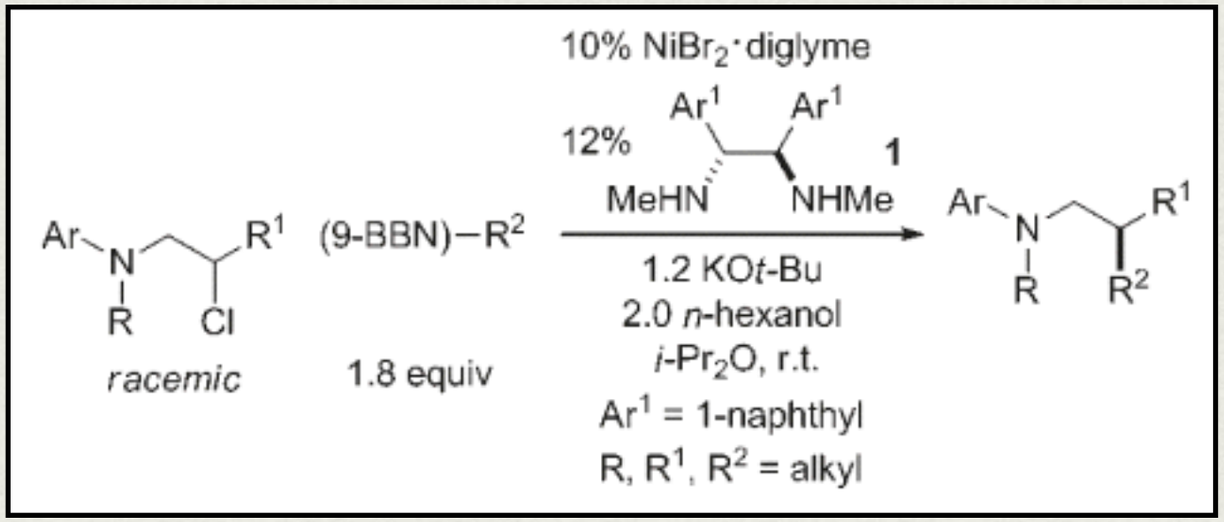




Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694.
Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027.
Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908.
Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794.

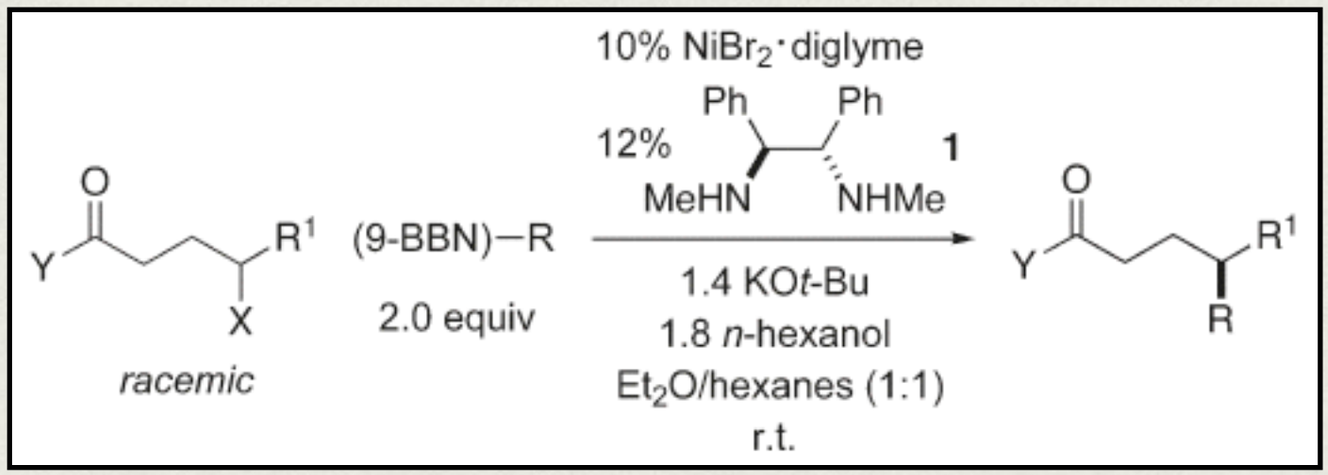
Pd/Ni/Cu catalyzed cross-coupling reaction

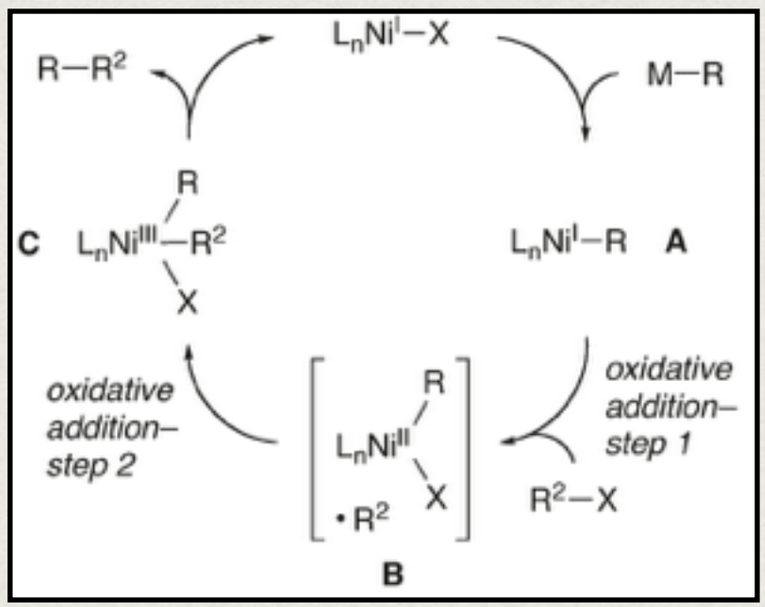
- **Ni-Catalyzed cross-coupling reaction**
  - **Enantioselective alkyl-alkyl Suzuki coupling——Utilizing different directing group**



Amine as directing group

- **Control @ γ-position**

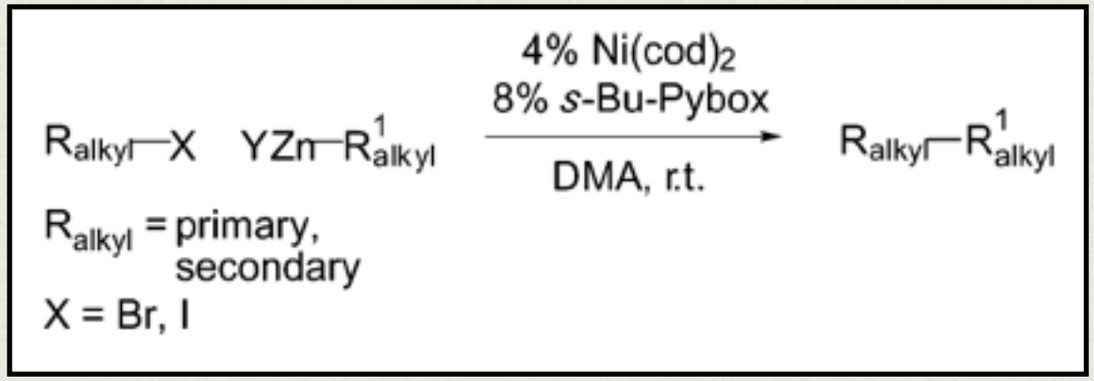


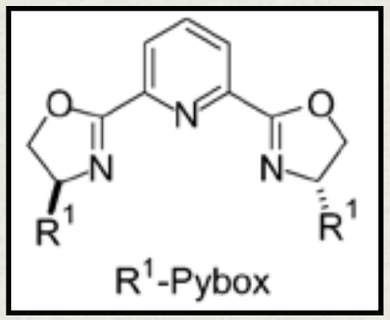


Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154.
Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362.

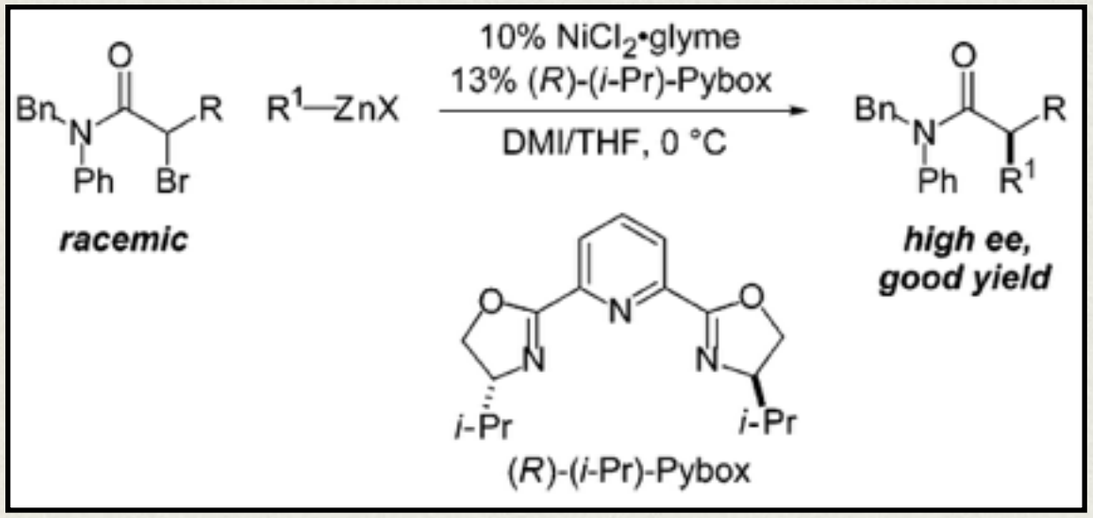
Pd/Ni/Cu catalyzed cross-coupling reaction

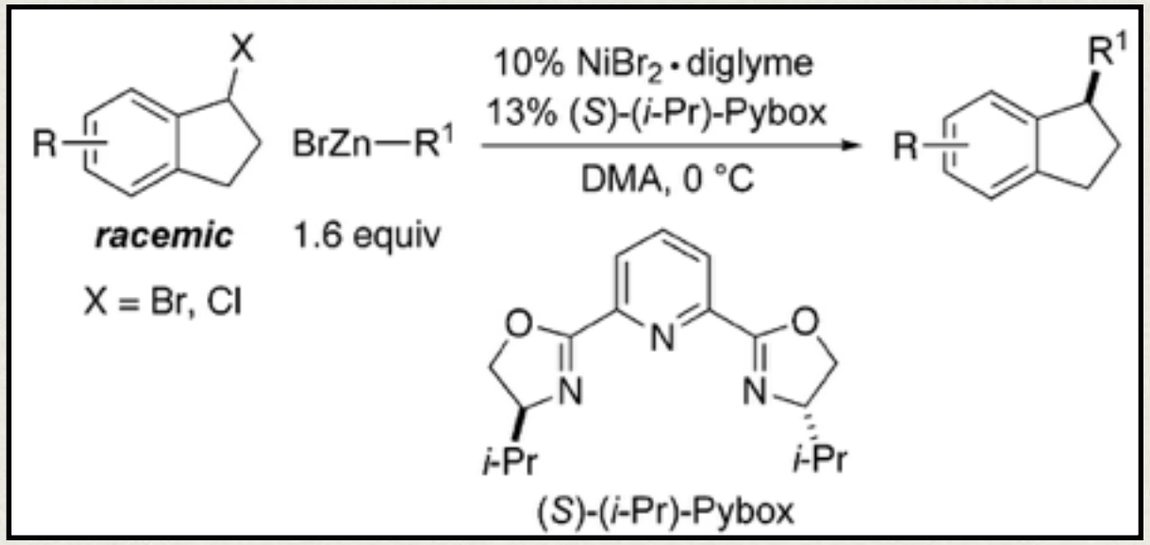
- **Ni-Catalyzed cross-coupling reaction**
  - **Negishi coupling of unactivated secondary alkyl Halides**





  - **Enantioselective Negishi coupling of unactivated secondary alkyl Halides**

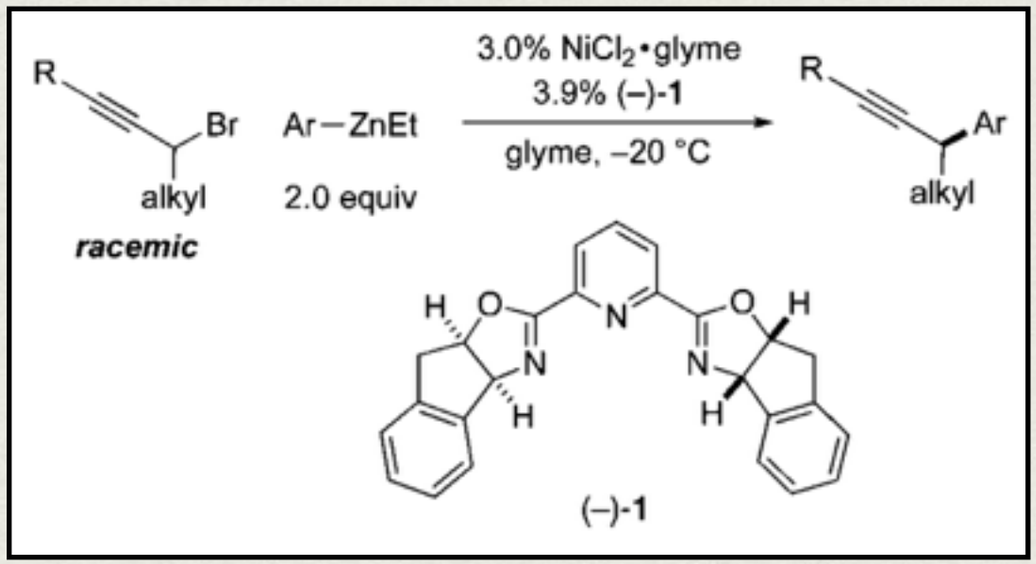


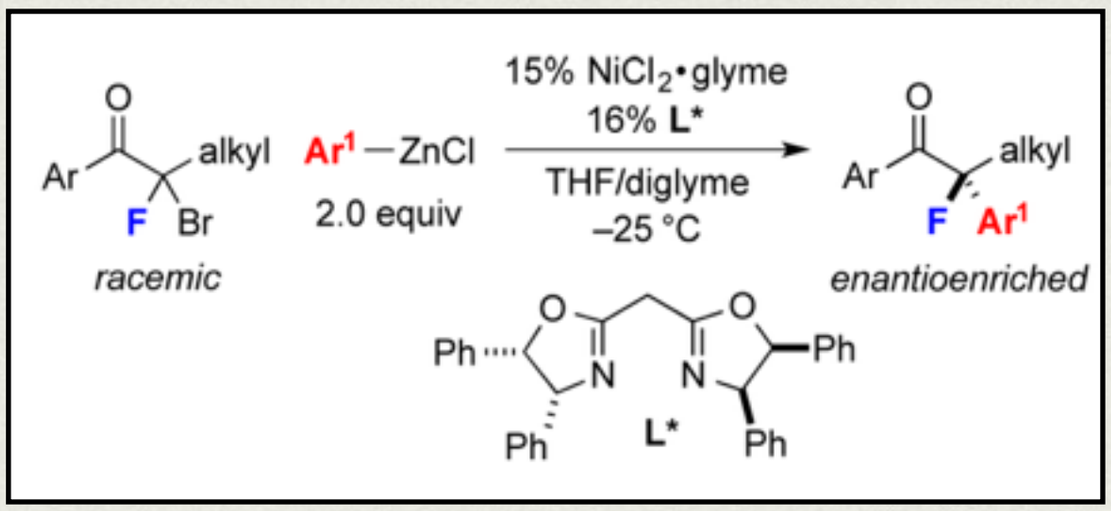


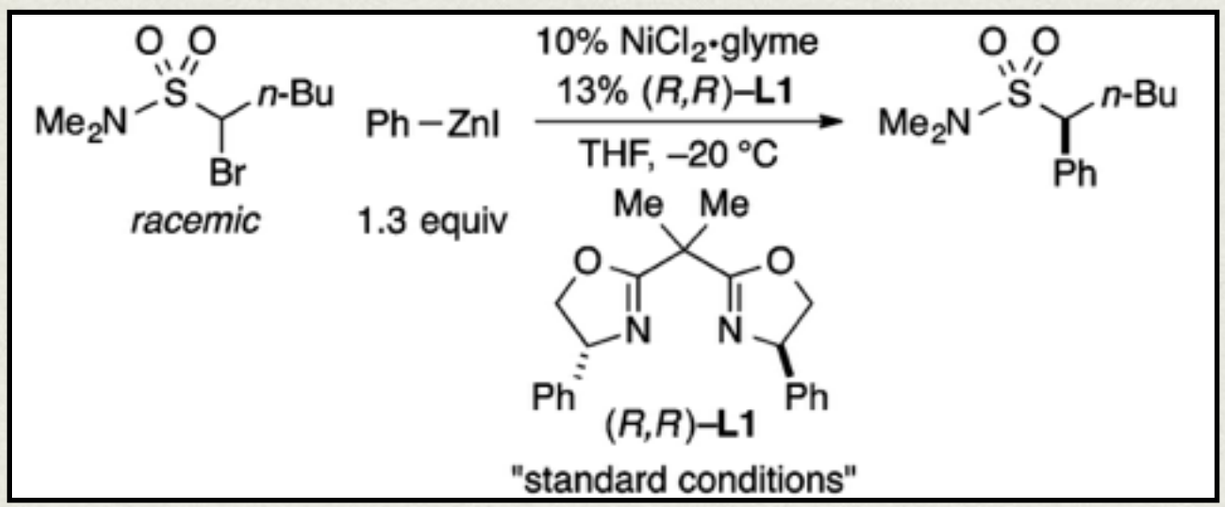
Zhou, J. S.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726.
Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.
Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482.

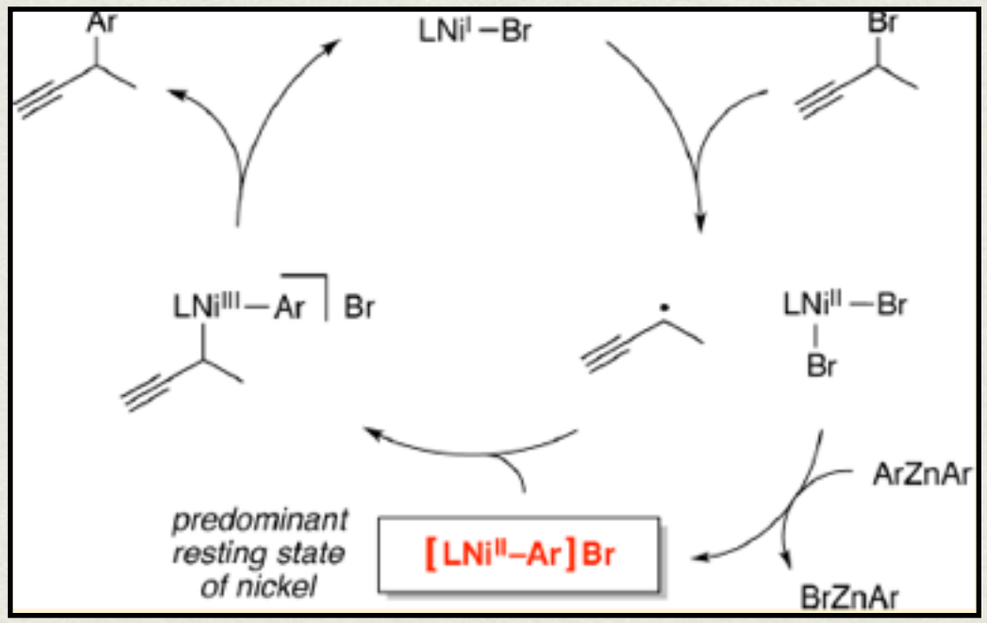
Pd/Ni/Cu catalyzed cross-coupling reaction

- **Ni-Catalyzed cross-coupling reaction**
  - **Enantioselective Negishi coupling of unactivated secondary alkyl Halides**







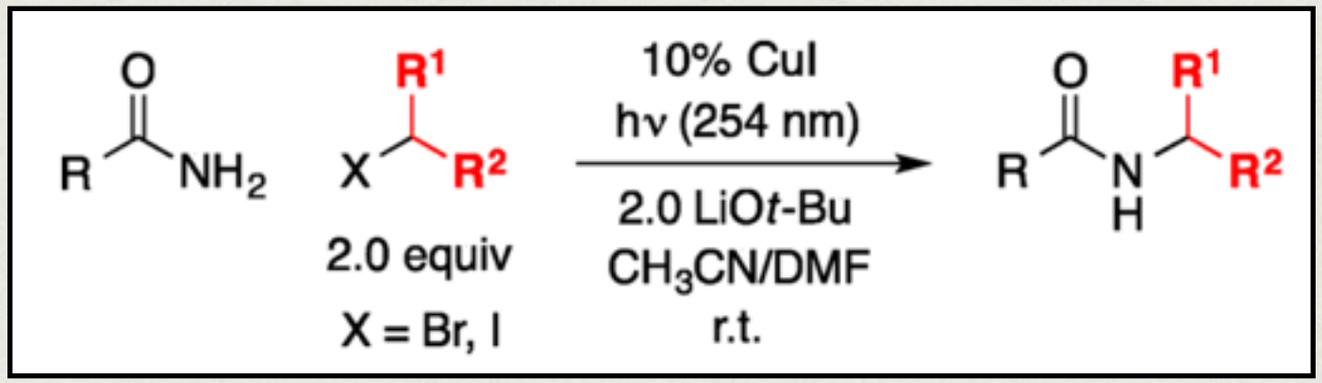


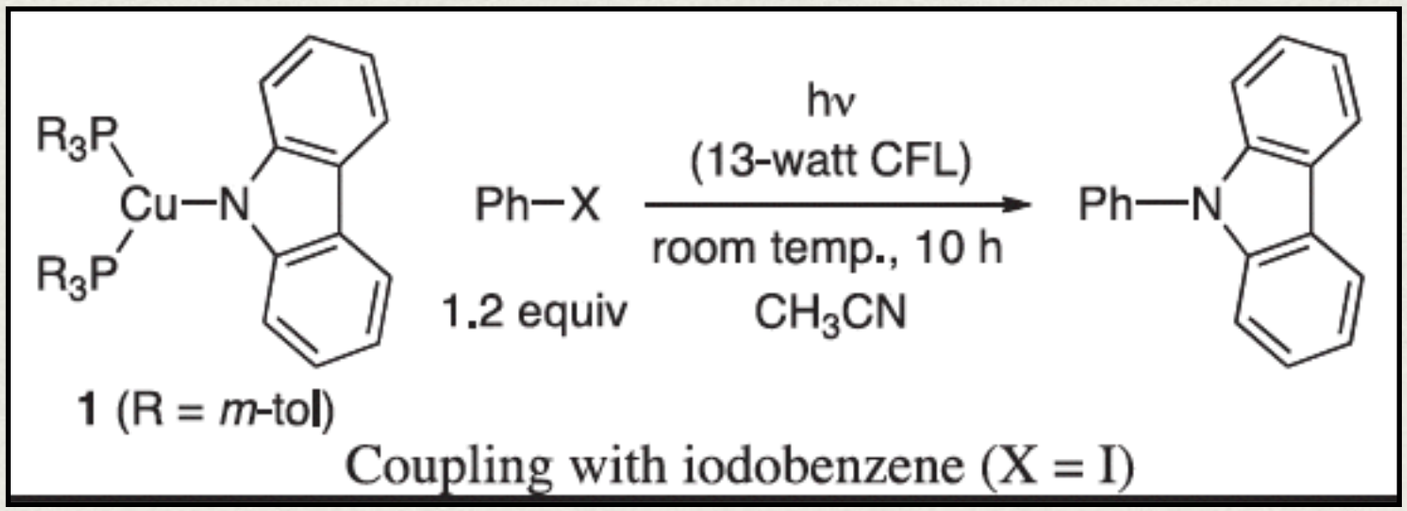
O.A. happens through a bimetallic mechanism

Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645.
Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 5520.
Choi, J.; Martín-Gago, P.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 12161.
Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588.

Pd/Ni/Cu catalyzed cross-coupling reaction

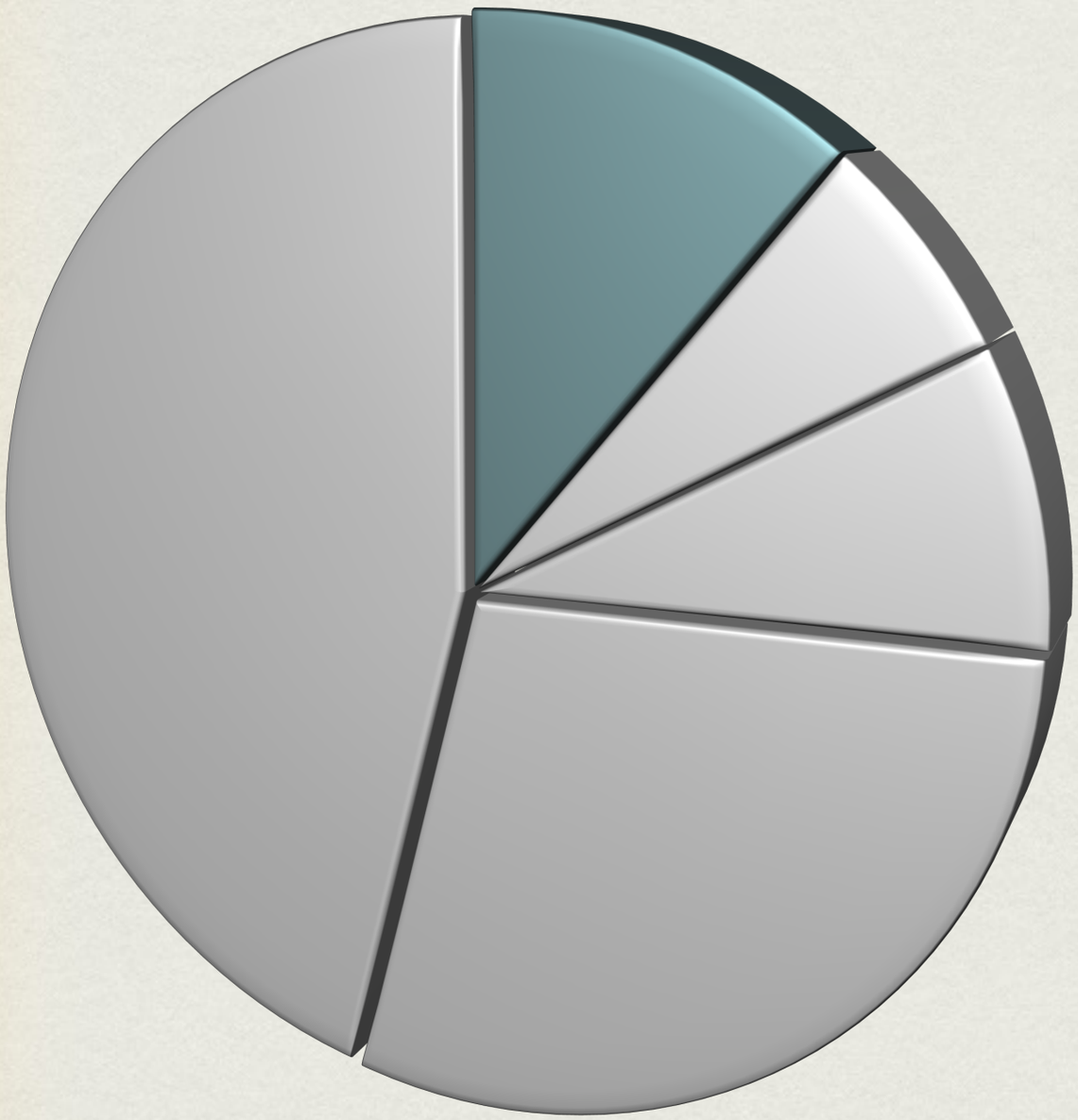
- **Cu-catalyzed Alkylation of amides**
  - Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 2162.
  - Lee, M. M.; Teuscher, J.; Miyasaka, T.; Murakami, T. N.; Snaith, H. J. *Science* **2012**, *338*, 643.





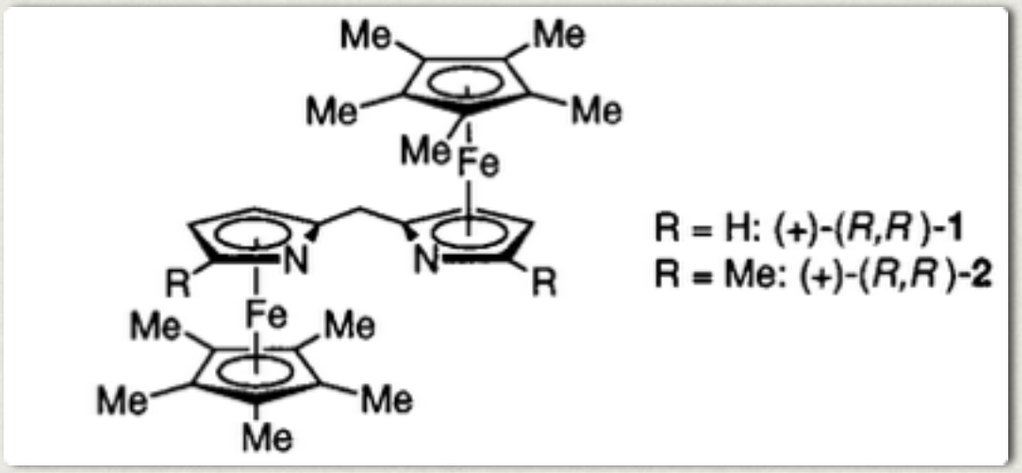
Coupling with iodobenzene (X = I)

Significant research area of Gregory C. Fu

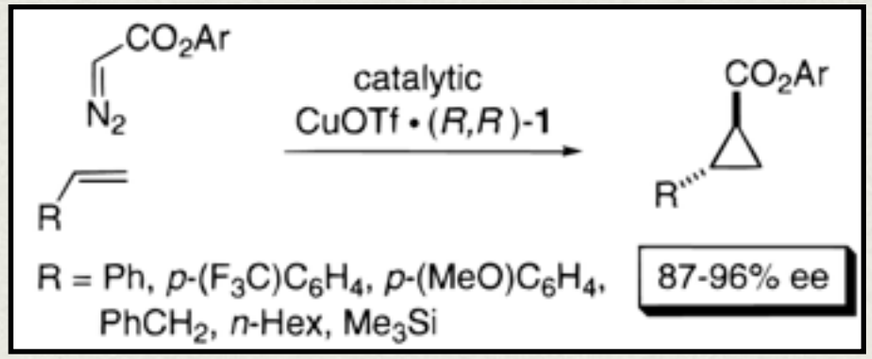


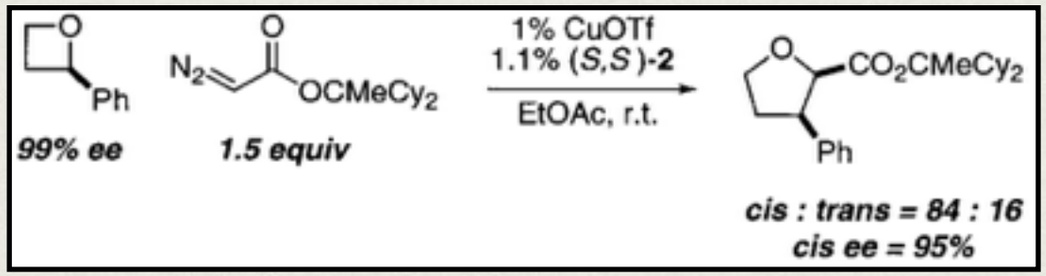
- Chiral ligand development
- Boron heterocycles
- Organotin Catalysis
- Asymmatric Nucleophilic catalysis
- Pd/ Ni/Cu catalyzed cross-coupling

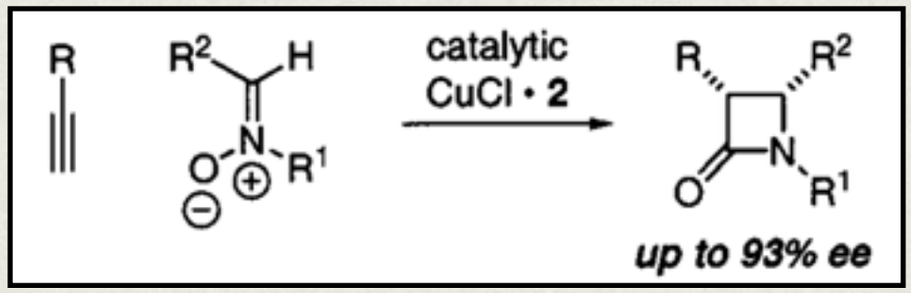
Chiral ligand development

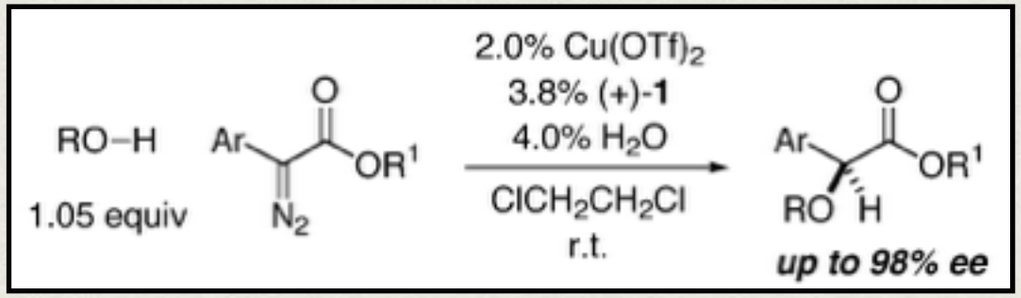


- A ligand with planar-chirality; similar to bisoxazoline ligands
- Find its use in Copper carbenoid chemistry
  - Cyclopropanation
  - oxetane insertion
  - OH insertion
- Coupling of alkynes with Nitrones





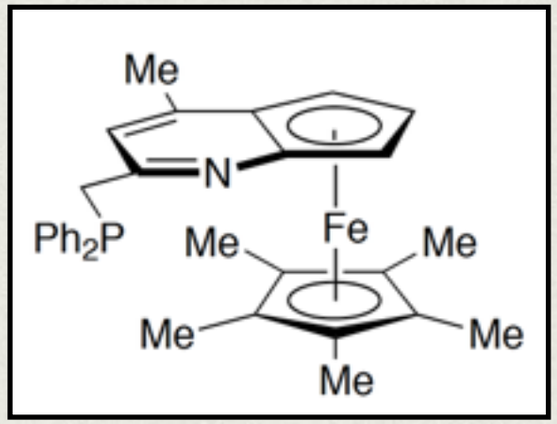




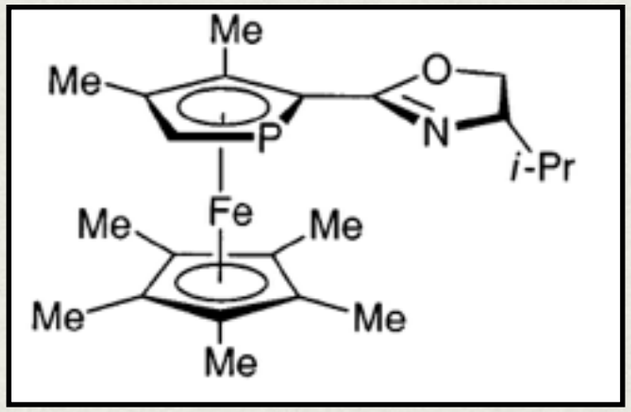
Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998,** *120*, 10270
Lo, M. M.-C.; Fu, G. C. *Tetrahedron* **2001**, *57*, 2621
Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572
Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594

Chiral ligand development

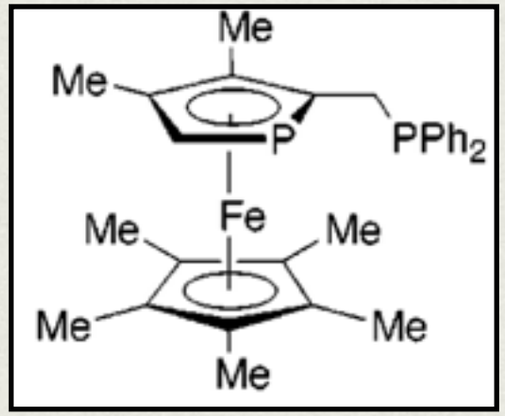
- **ligands with planar-chirality; several other types**



hydrosilylation of aryl alkyl or Dialkyl ketones



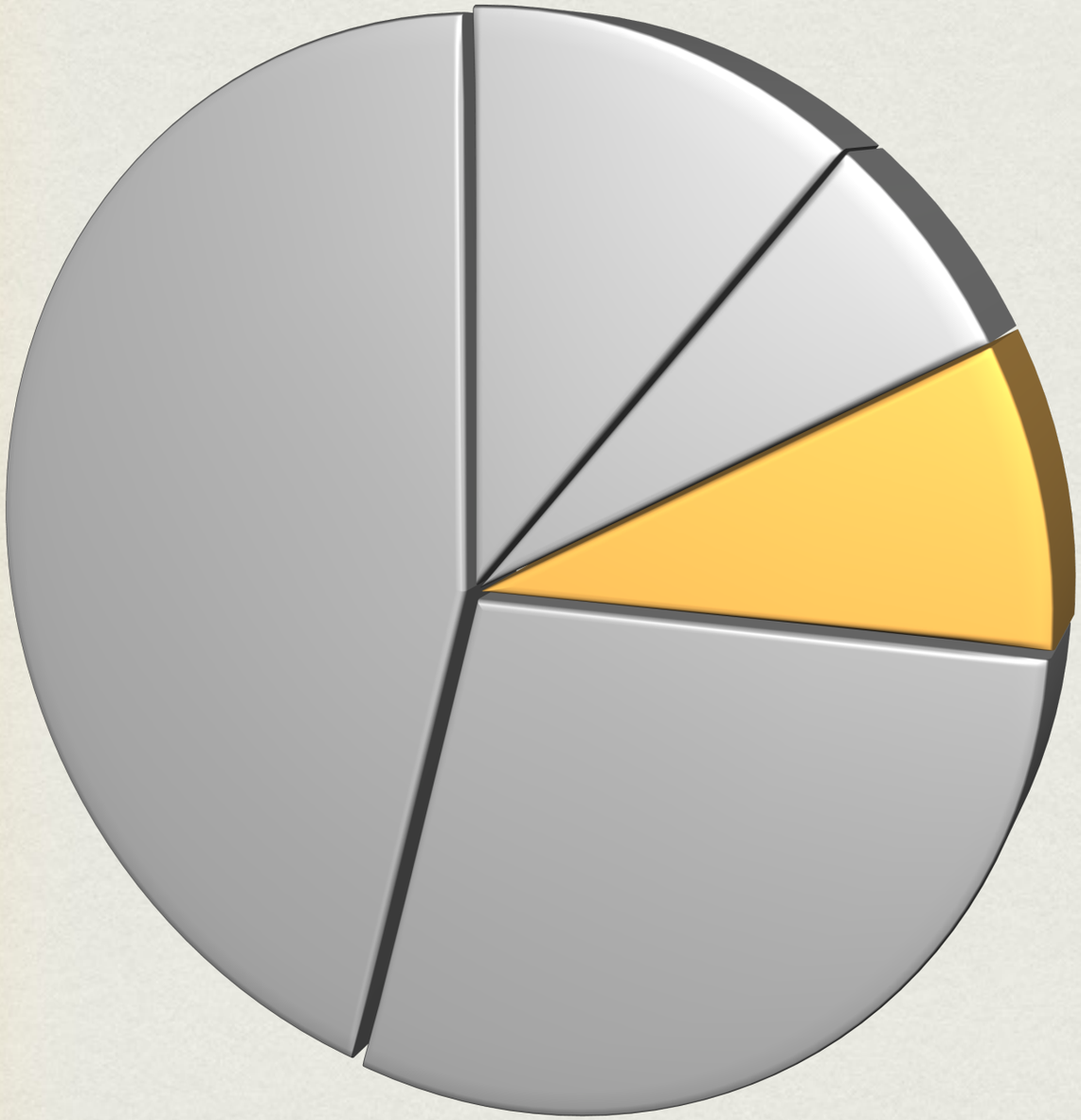
Cu-catalyzed [3+2] cycloaddition



Rh-cat. isomerization of allylic alcohols

- Qiao, S.; Fu, G. C. *J. Org. Chem*. **1998**, *63*, 4168
- 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
- Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699
- Tao, B.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3892.
- Shintani, R.; Fu, G. C. *J. Am. Chem. Soc*. **2003,** *125*, 10778

Significant research area of Gregory C. Fu



- Chiral ligand development
- Boron heterocycles
- Organotin Catalysis
- Asymmatric Nucleophilic catalysis
- Pd/ Ni/Cu catalyzed cross-coupling

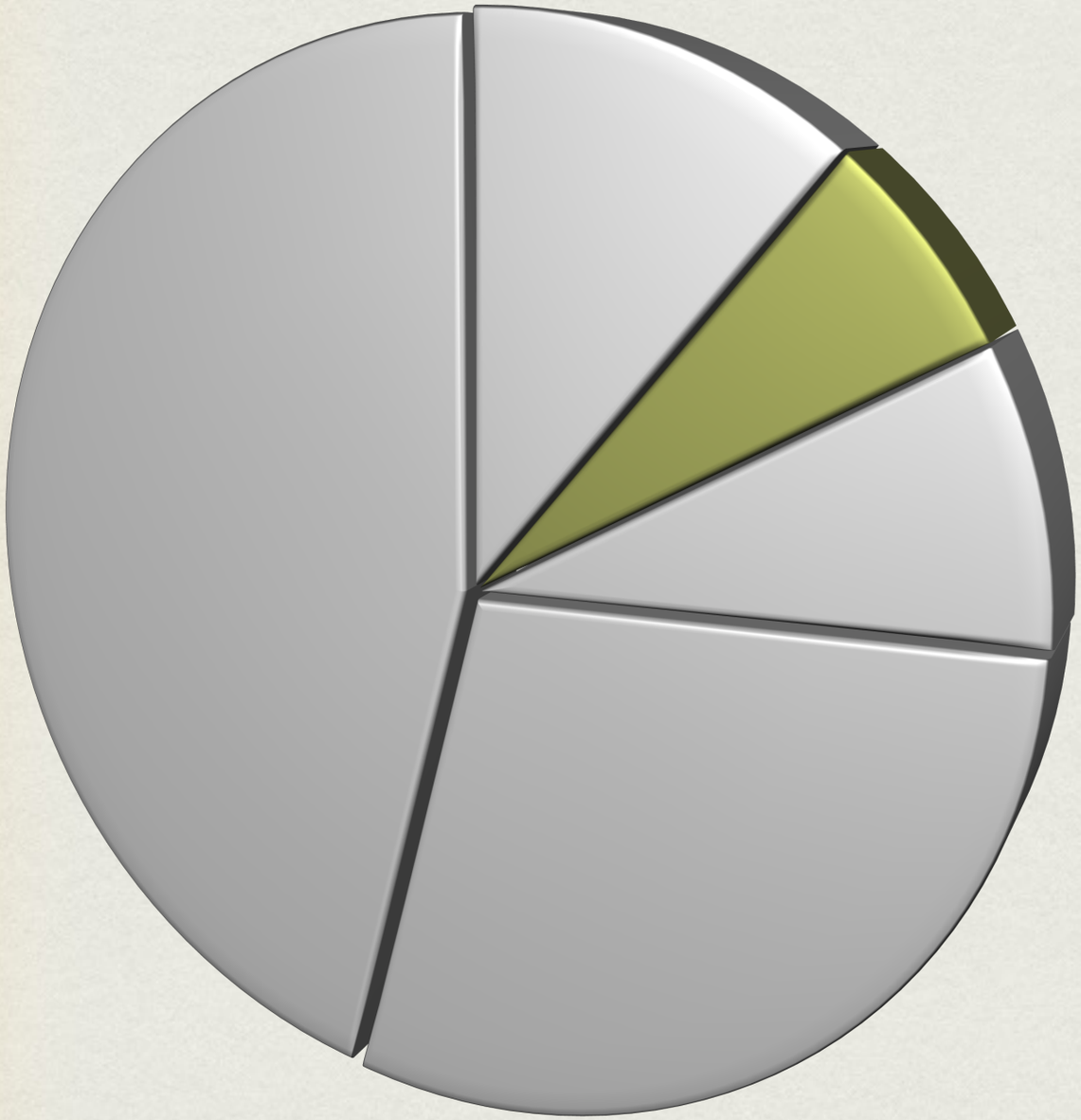
Organotin Catalysis

- **Catalytic usage of alkyl tin reagent**
  - 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

- **tin ketyl radical cyclization of dialdehydes**
  - Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc*. **1995**, *117,* 7283
  - 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

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

Significant research area of Gregory C. Fu



- Chiral ligand development
- Boron heterocycles
- Organotin Catalysis
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- Pd/ Ni/Cu catalyzed cross-coupling

Boron Heterocycles

- **Synthesis of 1-H-boratabenzene; DPB—boron analogue of PPh_3 ;**

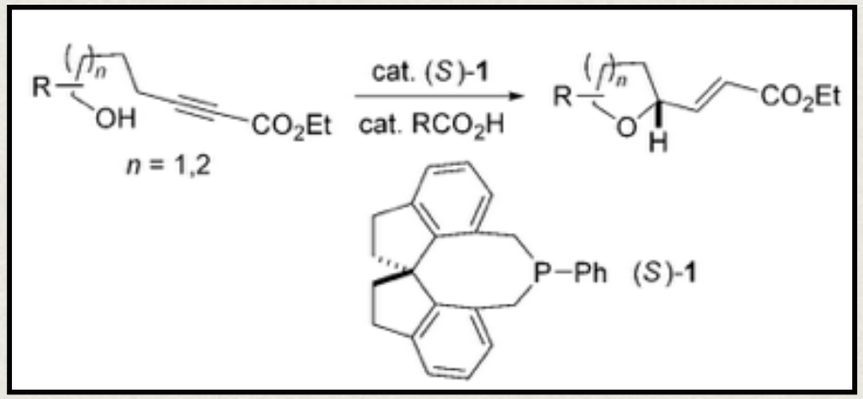
  - Hoic, D. A.; Davis, W. M.; Fu, G. C. *J. Am. Chem. Soc.* **1995,** *117*, 8480
  - Qiao, S.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1996**, *118*, 6329
  - Hoic, D. A.; Davis, W. M.; Fu, G. C. *J. Am. Chem. Soc.* **1996**, *118,* 8176

- **Synthesis of enantiopure planar-chiral Lewis acid complex**
  - Tweddell, J.; Hoic, D. A.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 8286
  - Liu, S.-Y.; Lo, M. M. C.; Fu, G. C. *Tetrahedron* **2006**, *62*, 11343.
  - Liu, S.-Y.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2005,** *127*, 15352–15353.

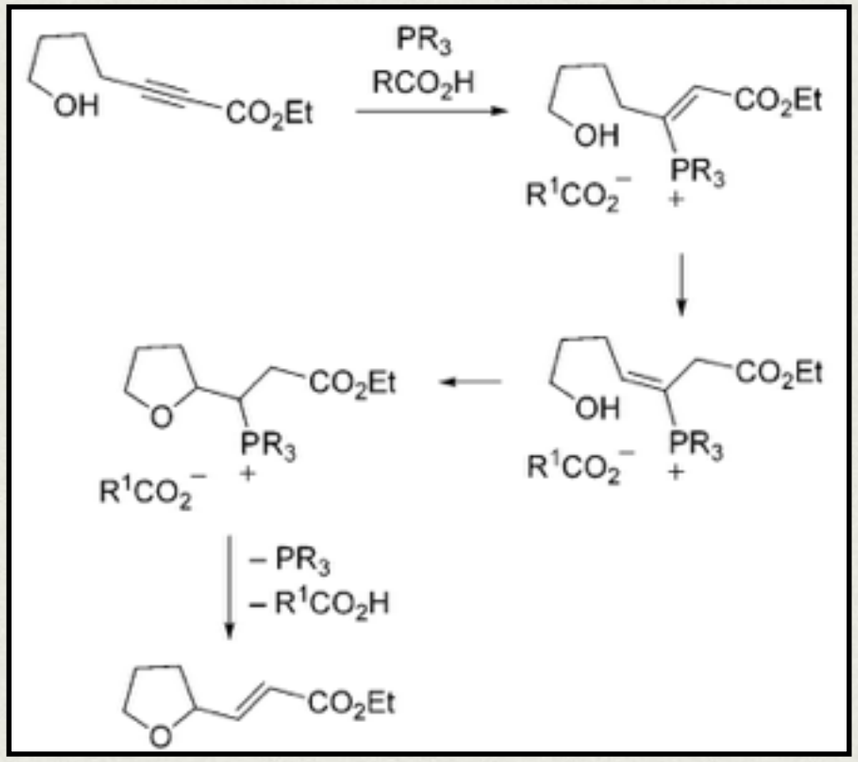
Thanks for your attention!

Question 1

Q1. we have talked about the addition of internal alcohol to alkynoates as shown below. The racemic version of this reaction is first reported by Prof. Trost. (J. Am. Chem. Soc, 1994, 116,10819). Please propose a plausible mechanism for this reaction.



Answer:



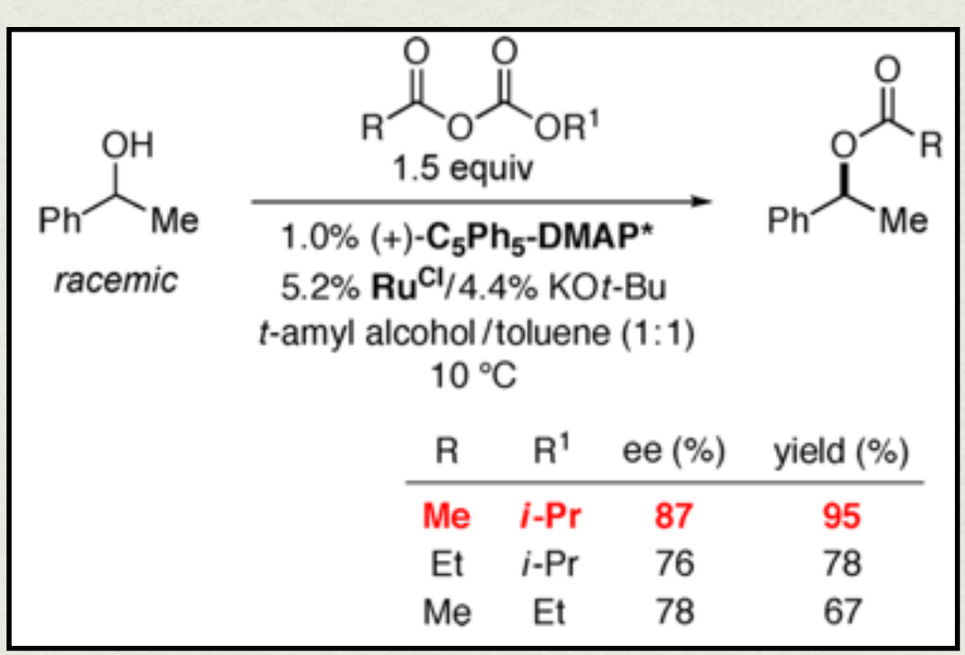
Question 2

Q2. In the mechanism investigation of dynamic kinetic resolution of secondary alcohols, they have several observations as listed below:

- **The rate law is first order in the alcohol; first order in the acylation catalyst; "fractional" order in acetyl isopropyl carbonate, and zeroth order in the racemization catalyst.**
- **The resting state of the planar-chiral DMAP derivative is a mixture of the free catalyst and the N-acylated catalyst**

2-1: please propose a posible mechanism for the reaction

2-1: design experiment to further confirm the mechanism you proposed



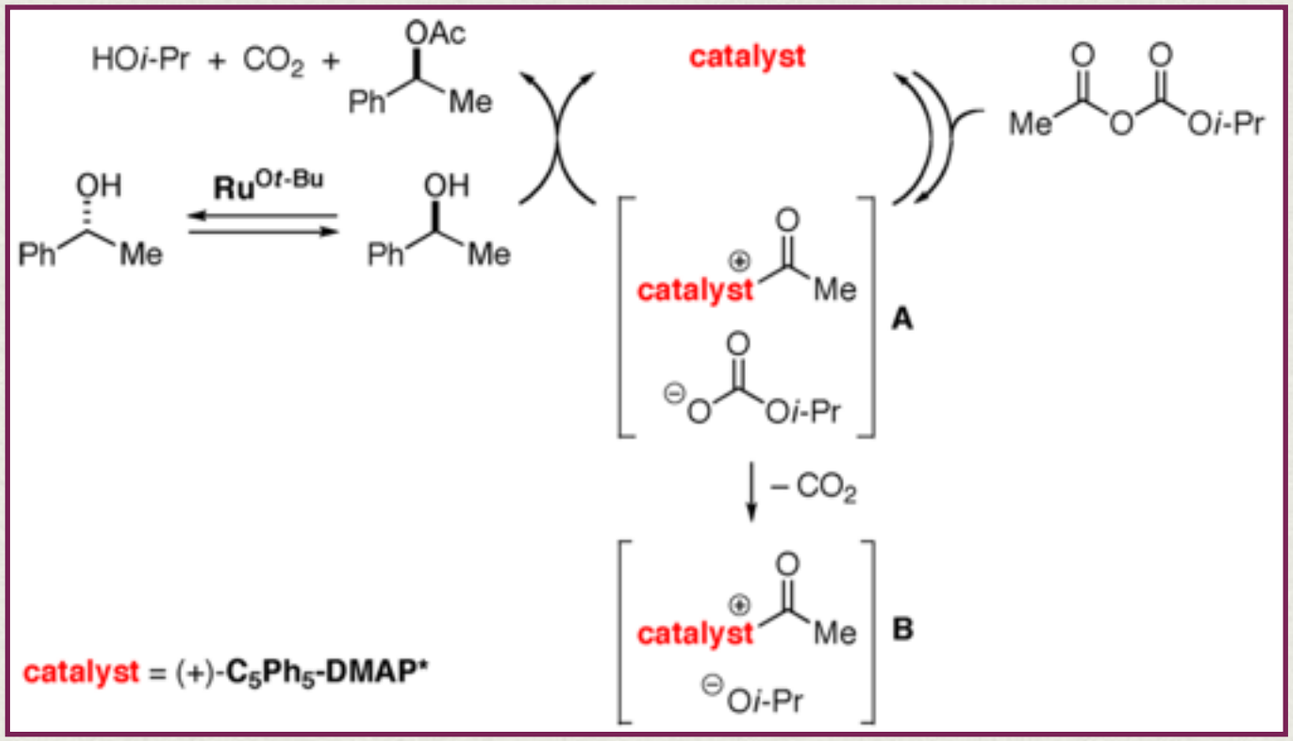
R	R^1	ee (%)	yield (%)
Me	***i*-Pr**	**87**	**95**
Et	*i*-Pr	76	78
Me	Et	78	67

Answer to Q2

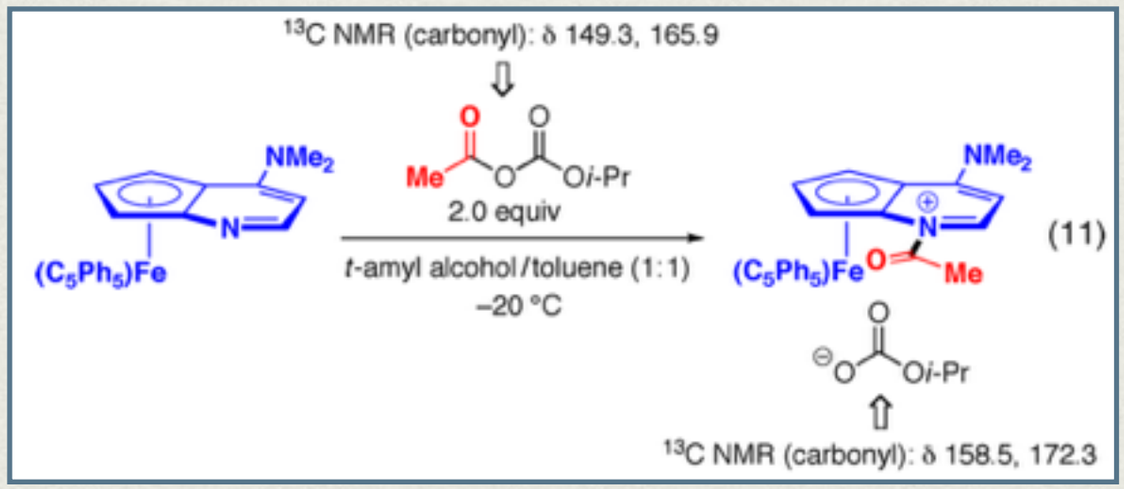
Mechanism understanding

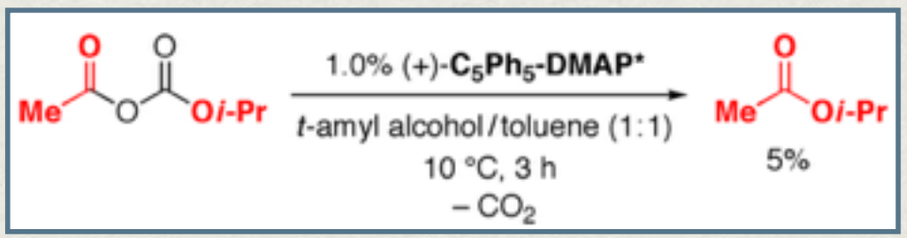
R.D.S

A is more reasonable decarboxylation is slow



- **Rate law**
- **Resting state of catalyst**





Lee, S. Y.; Murphy, J. M.; Ukai, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15149.
Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817.