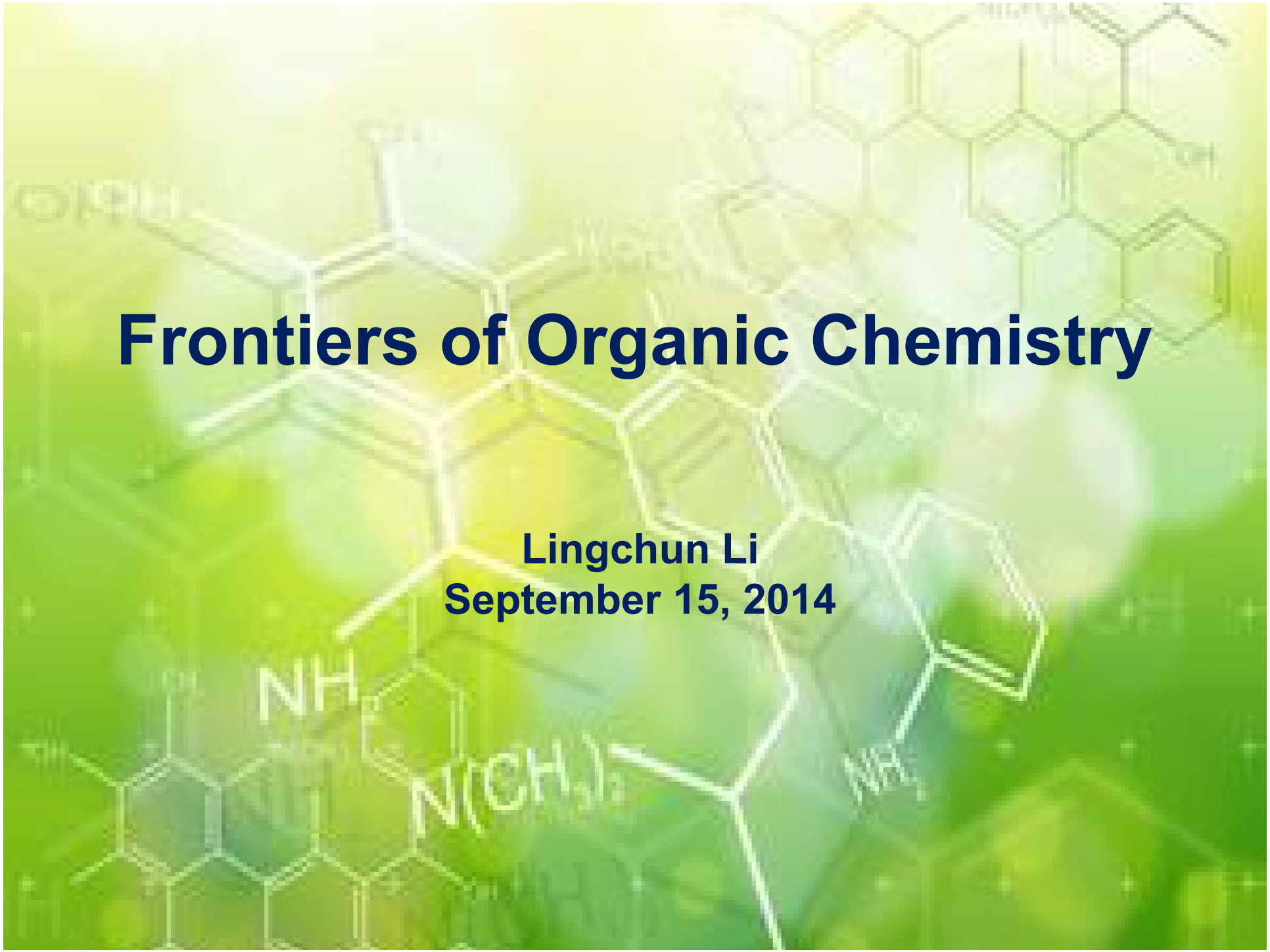


# Frontiers of Organic Chemistry

Lingchun Li

September 15, 2014

# Contents

# C-H Activation

## Why is C-H activation such big news?

Natural gas, for example, a vast, lowcost feedstock of hydrocarbons that remains untapped as a raw material, simply because there has been no easy way of turning it into synthetically useful compounds. This could be about to change.

C–H activation allows chemical groups to be placed directly in a molecule where none existed before, a process that previously often needed several steps. So it makes chemists to exploit organic compounds in previously unimaginable ways.

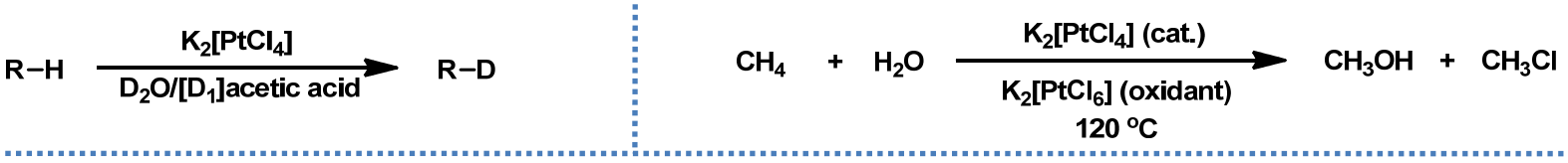
**The Holy Grail of Organomentallic Chemistry**

Bergman, R. G. *Nature* **2007**, *446*, 391.

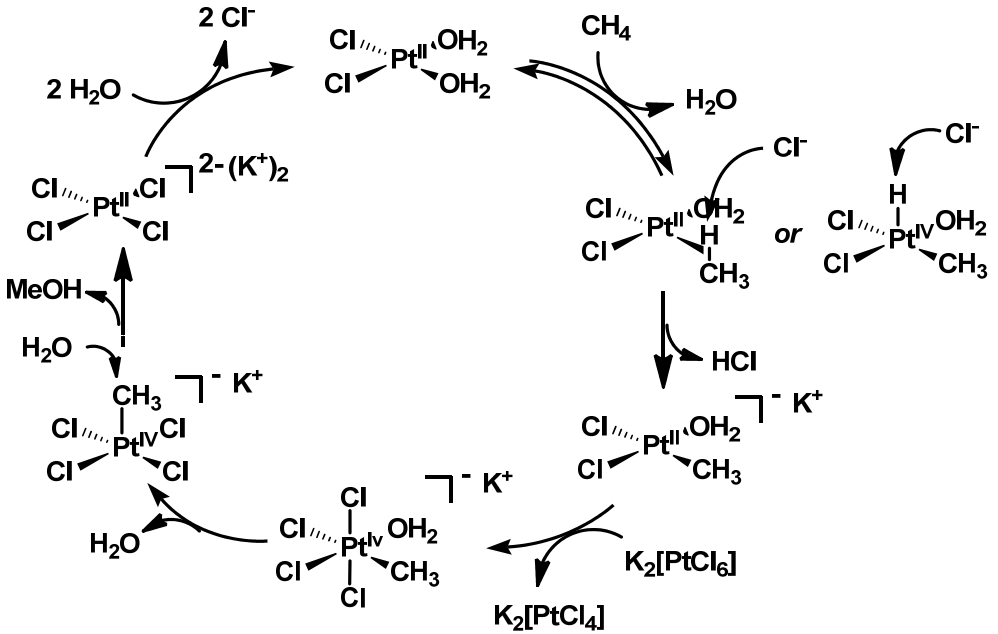
# C-H Activation

## The birth of C-H activation

The origins of the field lie in the 1960s and 1970s




Proposed mechanism:



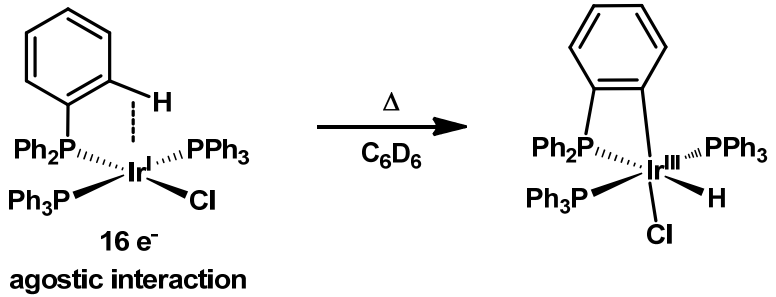


Goldshleger, N. F.; Tyabin, M. B.; Shilov, A. E.; Shteinman, A. A. *Zh. Fiz. Khim. (Engl. Transl.)* **1969**, *43*, 1222.

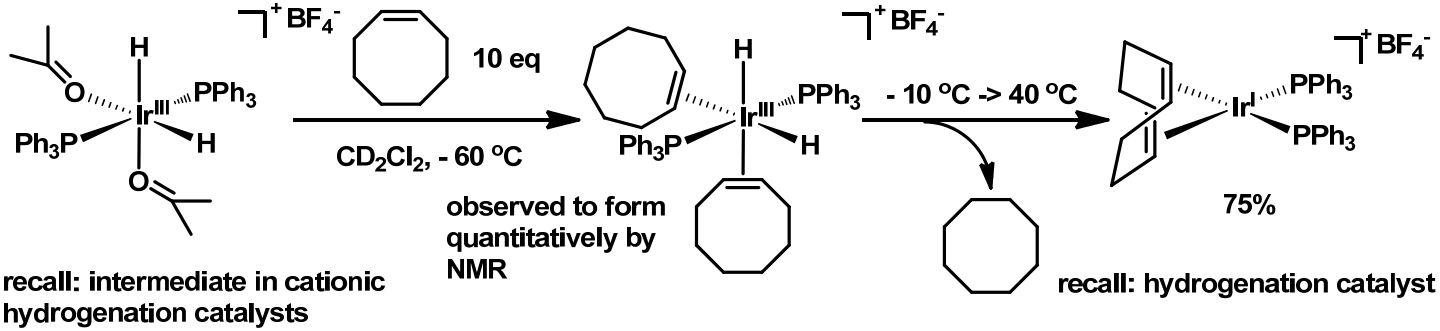
Goldshleger, N. F.; Eskova, V. V.; Shilov, A. E.; Shteinman, A. A. *Zh. Fiz. Khim. (Engl. Transl.)* **1972**, *46*, 785.

# C-H Activation

## The birth of C-H activation




Bennett, M. A.; Milner, D. L. *J. Am. Chem. Soc.* **1969**, *91*, 6983.

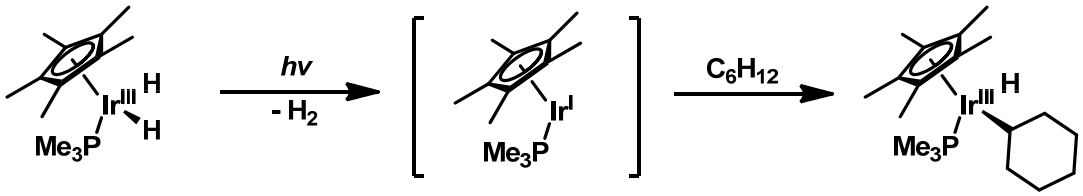



Crabtree, R. H.; Mihelcic, J. M.; Quirk, J. M.
*J. Am. Chem. Soc.* **1979**, *101*, 7738.

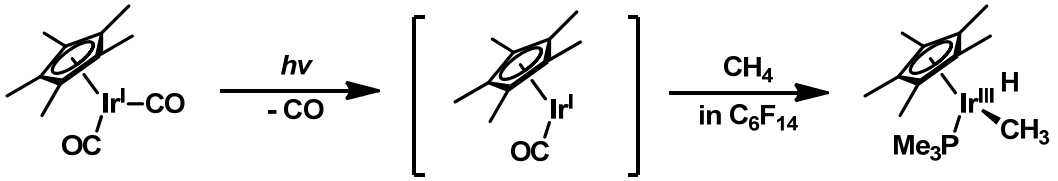
# C-H Activation

## The birth of C-H activation

The field really came alive in the early 1980s




Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 352.




Hoyano, J. K.; McMaster, A. D.; Graham, W. A. G.
*J. Am. Chem. Soc.* **1983**, *105*, 7190.

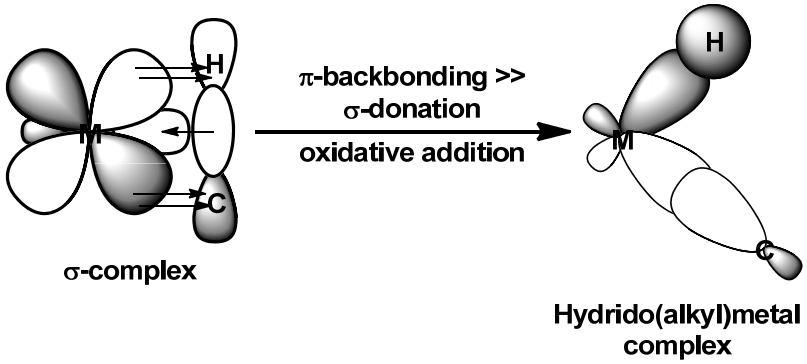
# C-H Activation

## Bergman type

VS

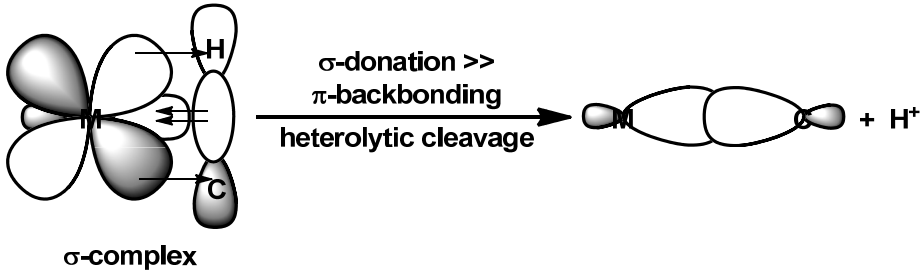
## Shilov type

### C-H Activation via Late, Nucleophilic Complexes




- formal 2e$^-$ oxidation state increased
- nucleophilic metal complexes are used in their low stable oxidation states
- very sentitive to oxidants

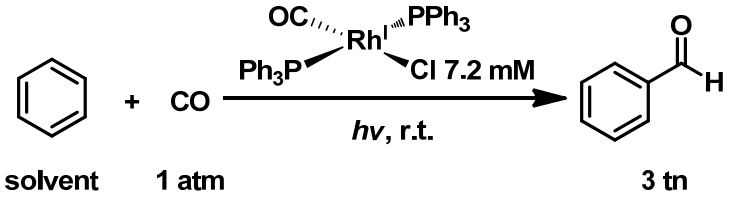
### C-H activation via late, electrophilic complexes



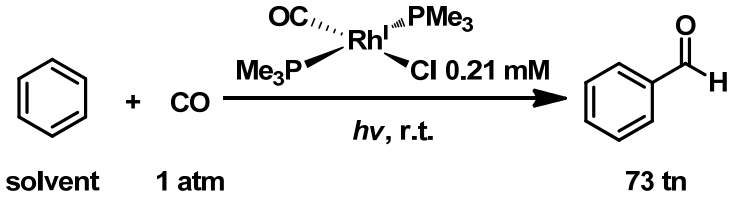

- no oxidation state change
- electrophilic metal complexes are used in their highest stable oxidation states
- compatable with oxidants

# C-H Activation

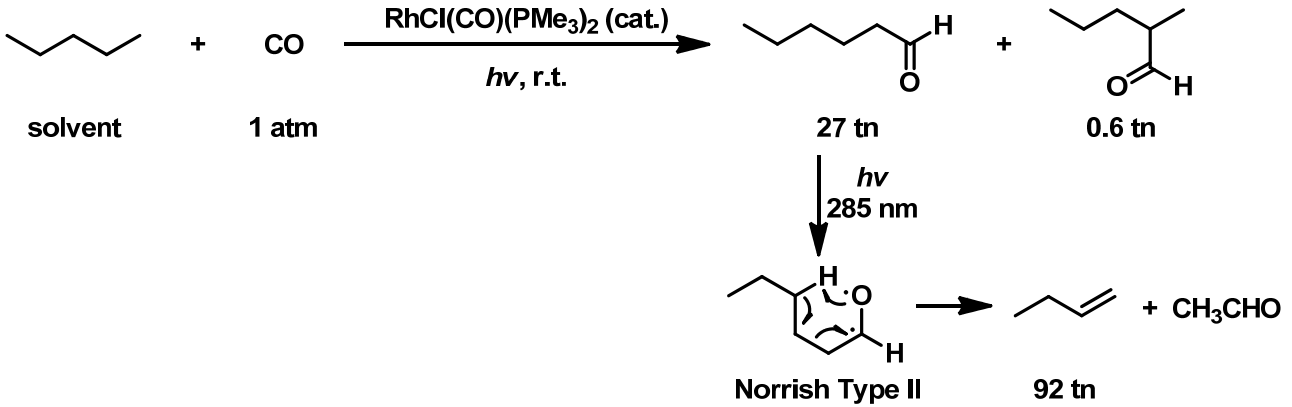
## Direct carbonylation of benzene and alkanes




Kunin, A. J.; Eisenberg, R.
*J. Am. Chem. Soc.* **1986**, *108*, 535.



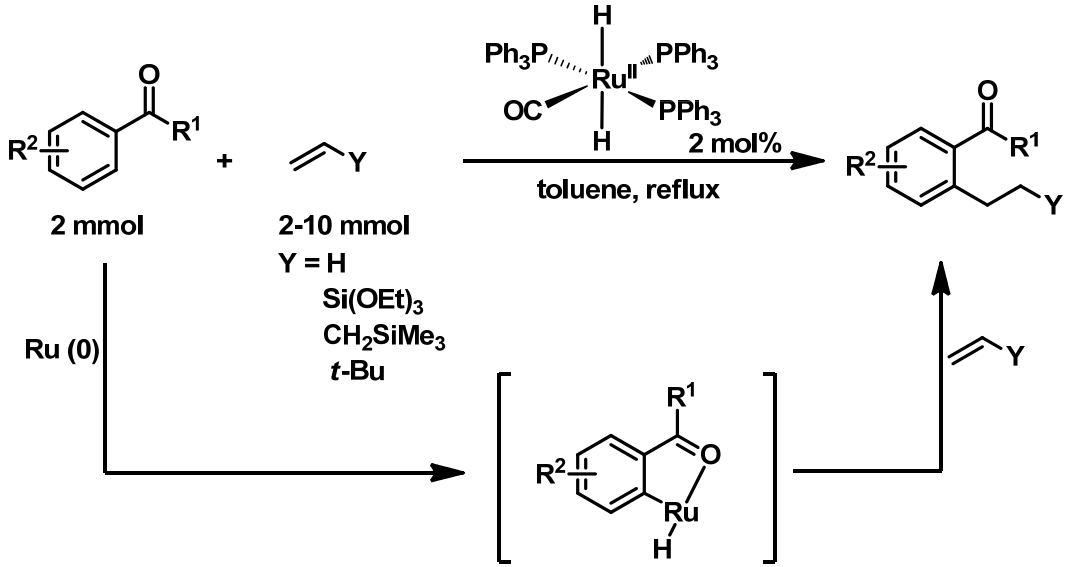

Sakakura, T.; Tanaka, M.
*Chem. Lett.* **1987**, 249.




Sakakura, T.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1987**, 758.

# C-H Activation

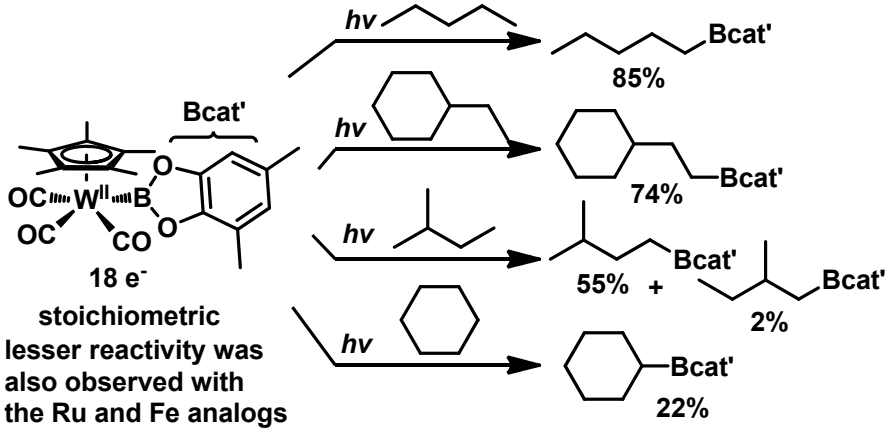
## Oxygen chelate assisted $C_{sp2}$-H-olefin reductive coupling



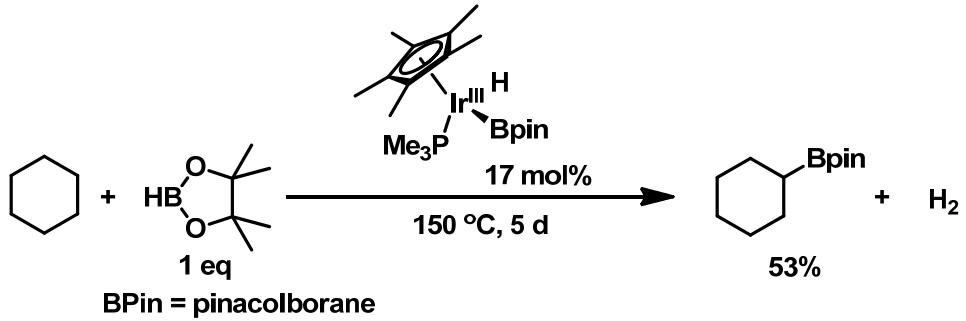

Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529

# C-H Activation

## Direct Borylation of Alkanes



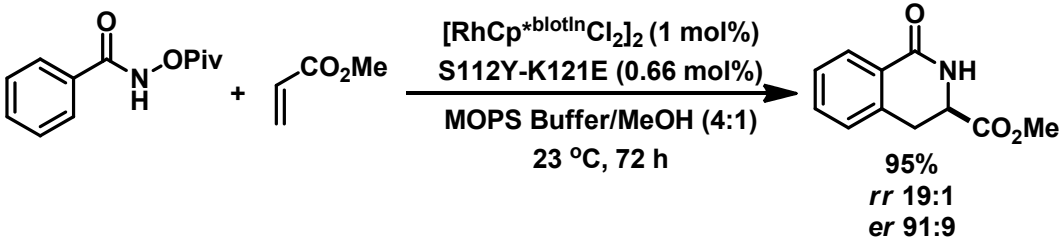

Waltz, K. M.; Hartwig, J. F. *Science* **1997**, *277*, 211.

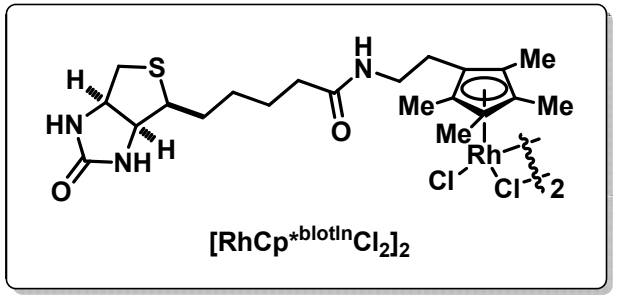



Iverson, C. N.; Smith, M. R. III. *J. Am. Chem. Soc.* **1999**, *121*, 7696.

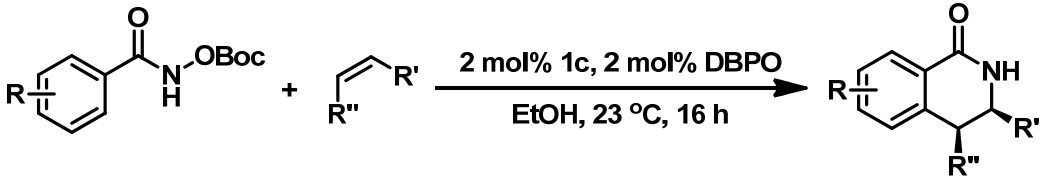
# C-H Activation

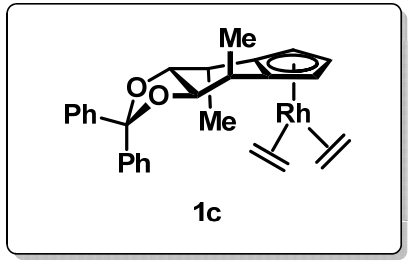
## Asymmetric C–H activation




Hyster, T. K.; Knörr, L.; Ward, T. R.; Rovis, T. *Science*, **2012**, *338*, 500.

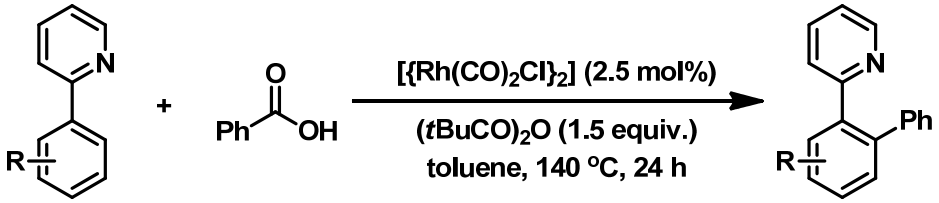


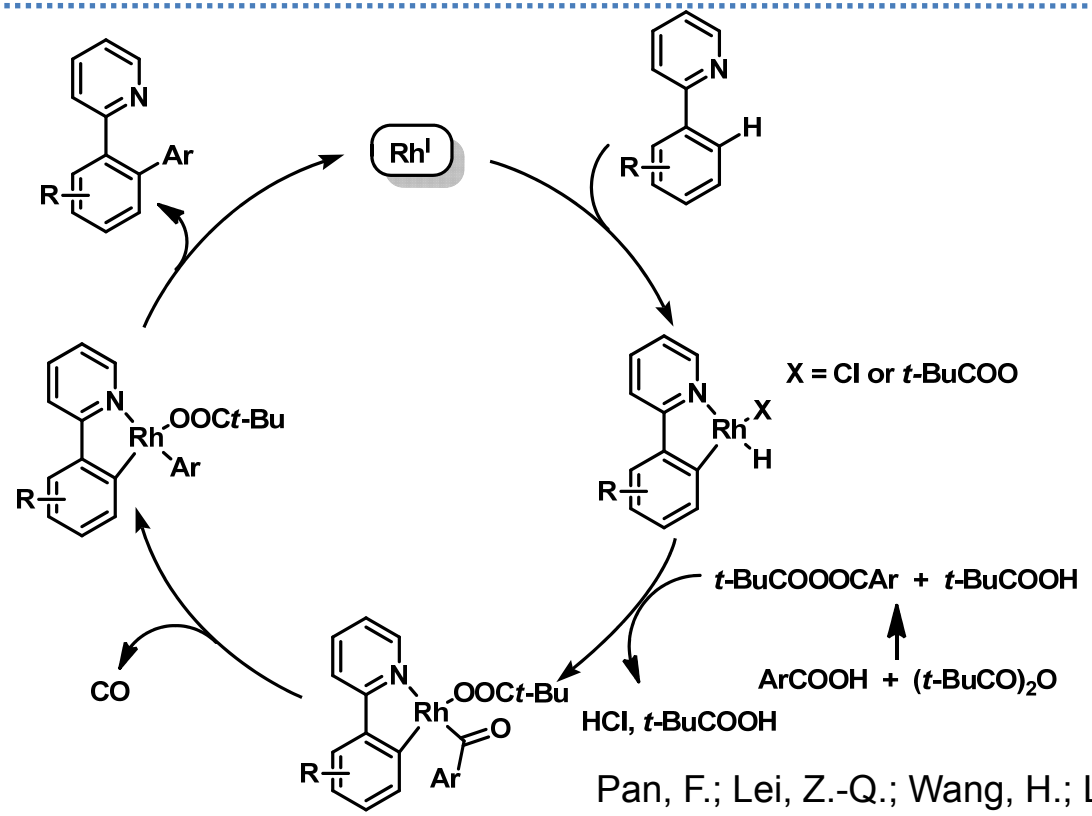




Ye, B.; Cramer, N. *Science*, **2012**, *338*, 504.

# C-H Activation

## Decarbonylative C-H bond arylation of arenes

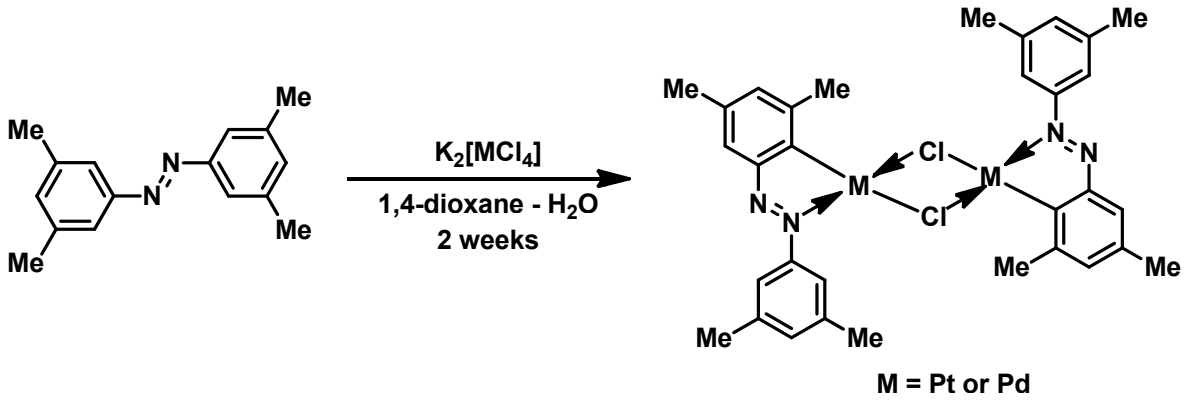


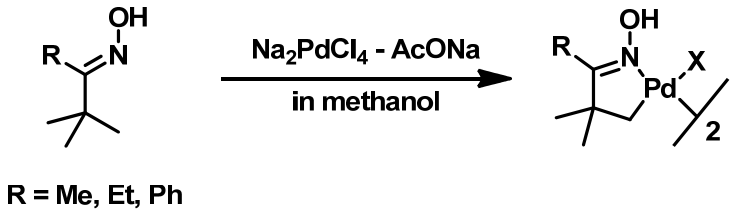

Pan, F.; Lei, Z.-Q.; Wang, H.; Li, H.; Sun, J.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2013**, *52*, 2063.

# C-H Activation

## Cyclopalladation Reaction



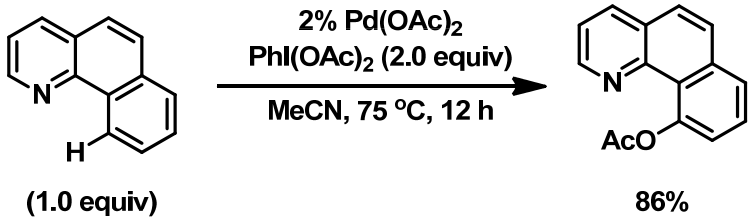

Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272.



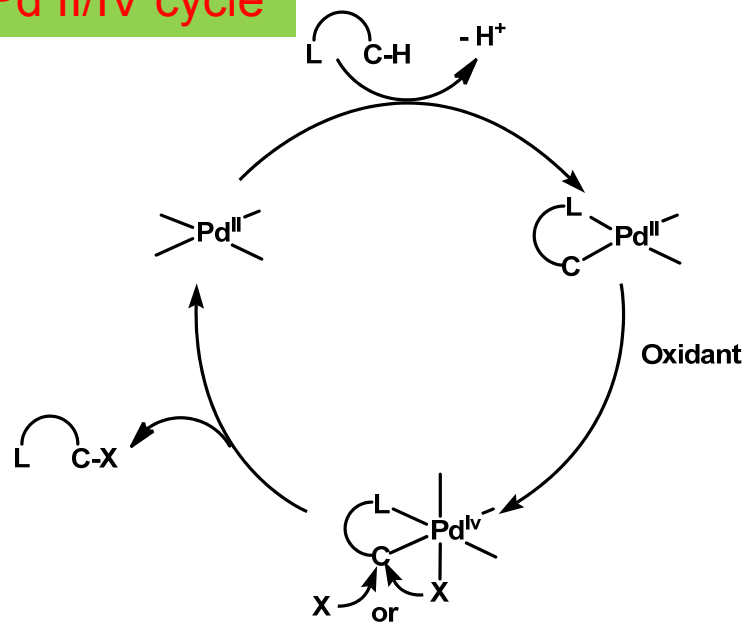

Constable, A. G.; McDonald, W. S.; Sawkins, L. C.; Shaw, B. L.
*J. Chem. Soc., Dalton Trans.* **1980**, 1992.

# C-H Activation

## Ligand directed, palladium-catalyzed C–H bond functionalization




Pd II/IV cycle

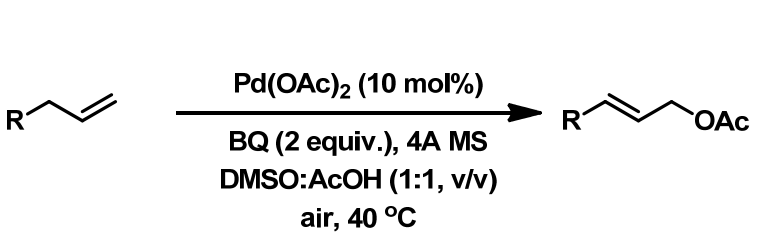


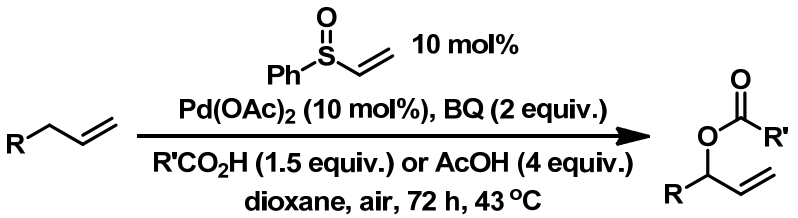

- Directing groups including amides, imines and oximes have been explored and demonstrate generally high yields.
- C-C, C-F, C-$CF_3$ and C-X were all constructed.


Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.
Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45, 936.*

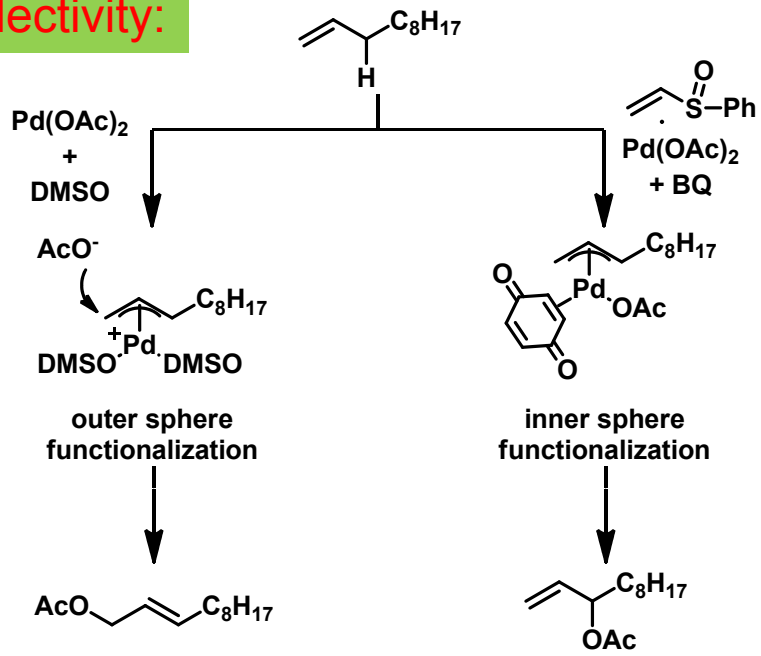
# C-H Activation

## Catalytic Functionalization of Allylic C-H Bonds

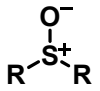



Site-selectivity:




**Weak, ambidentate ligands**



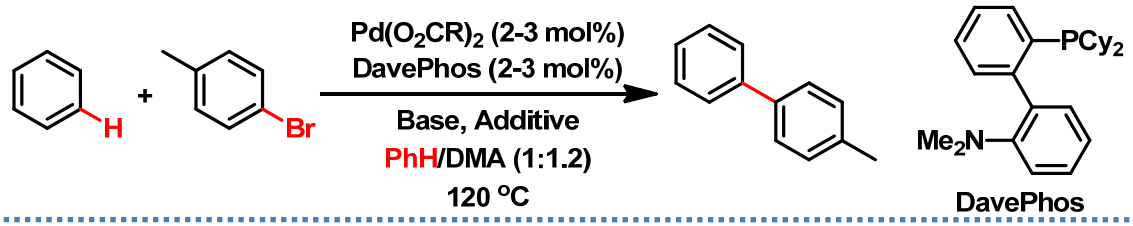

- ambidentate (O or S)
- σ donor (O)
- π acceptor (S)
- supports dicationic Pd
- activates π-allylPd

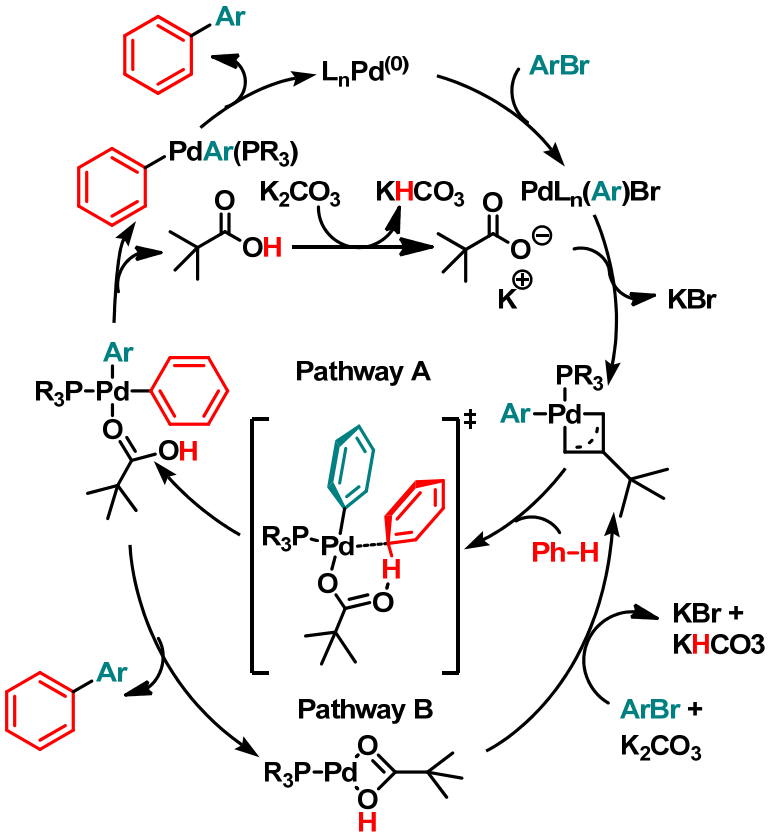

Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.

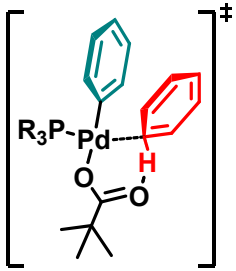
Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.

# C-H Activation

## Intermolecular, non-directed C–H cross-coupling



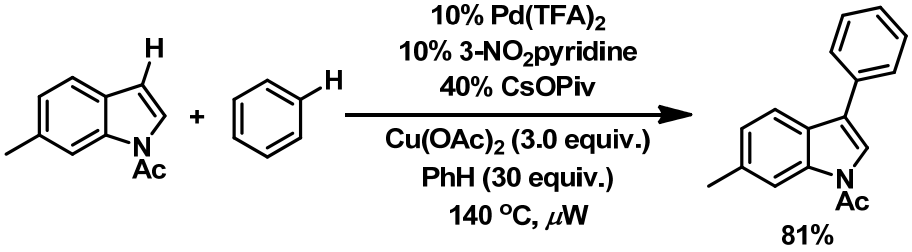

C-H Activation via Concerted Metallation Deprotonation (CMD) Pathway

- Direct arylation of unactivated arenes
- Unprecedented reactivity from a palladium-pivalic acid co-catalyst system
- Pivalic acid as a catalytic proton shuttle and a key element in catalyst design

Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

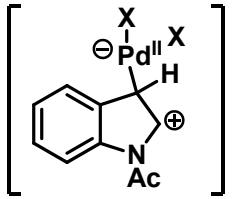
# C-H Activation

## Intermolecular, non-directed C–H cross-coupling

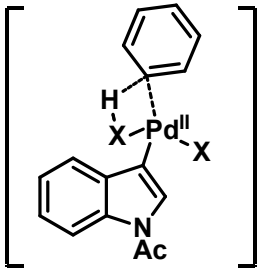



Challenge is to activate selectively 1 arene 1st and then only the other arene 2nd. No homo coupling observed. Mechanistic divergence.

Electron rich heteroarene reacts via a $S_EAr$ mechanism selectively first.



$S_EAr$



CMD Pathway

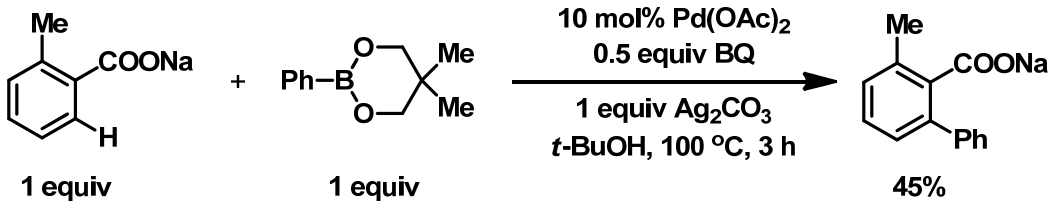
Pd(Ar) intermediate now prefers to react via a concerted proton transfer mechanism and selects for the arene.

Fagnou's work significantly extended the utility of C–H and dehydrogenative cross-couplings as well as provided evidence for and popularized the concerted metallation deprotonation (CMD) mechanism.

Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172.

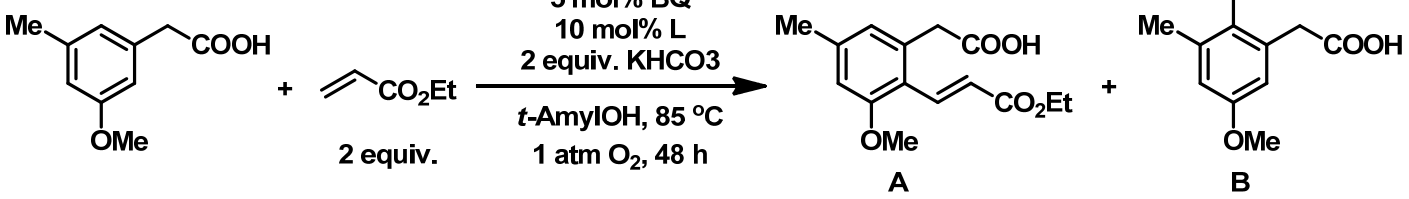
# C-H Activation

## Ligand directed, palladium-catalyzed C–H bond functionalization




Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.

Pd 0/II cycle



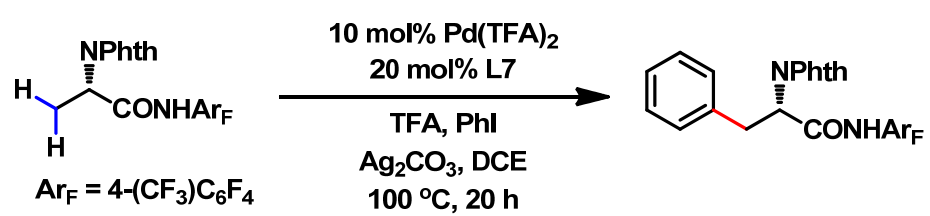

| L | A : B |
|---|---|
| no ligand | 1.4 : 1 |
| Boc-Leu-OH | 7 : 1 |
| Formyl-Leu-OH | 13 : 1 |
| Boc-Ile-OH | 8 : 1 |
| Ac-Ile-OH | 10 : 1 |
| Formyl-Ile-OH | 20 : 1 |

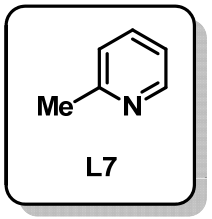
- Addition of an amino acid ligand can improve the position selectivity based on sterics of the sides of the aryl ring.
- Yu's work has vastly expanded the variety of substituents and directing groups that can be installed and Employed in aryl C–H activations

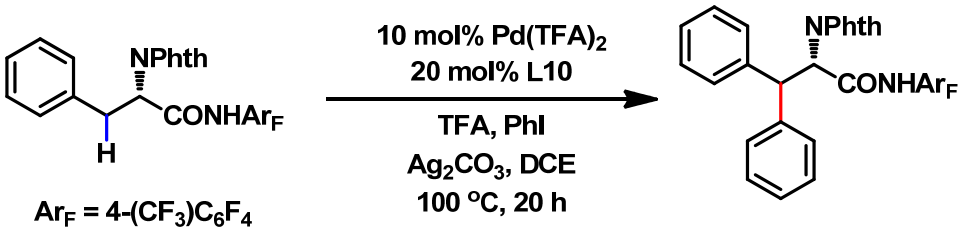
Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science*, **2010**, *327*, 315.

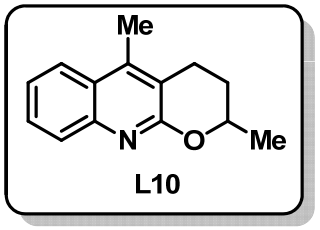
# C-H Activation

## Ligand-Controlled C($sp^3$)–H Arylation




- Use of ligands to tune the reactivity and selectivity
- Catalyst-controlled $C_{sp3}$–H arylation
- Both configurations of the β-chiral center can be accessed

He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216.

# C-H Activation

## Summary

The field of metal-catalyzed C-H functionalization has clearly seen a flurry of activity over the past decades, and huge advances have been made in both the development of novel reactions and the mechanistic study of these transformations.

## Outlook

- Expand the scope of directing groups (aldehydes, ketones, alcohols, and oxygen heterocycles …)
- Mechanistic investigations
- Asymmetric C-H functionalization

# Organocatalysis

## What is Organocatalysis?

Organocatalysis: the use of small organic molecules to catalyze organic transformations

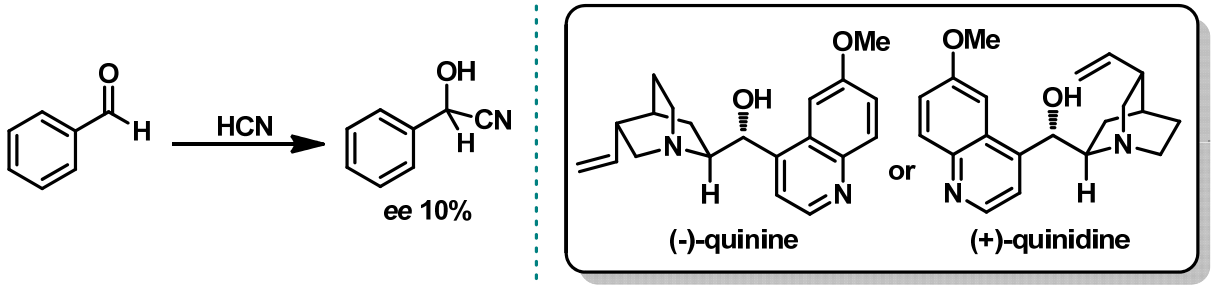
## Factors to the birth and rapid growth of organocatalysis

- The conceptualization of the field
- The advantages of organocatalytic research
- The advent of generic modes of catalyst activation, induction and reactivity.

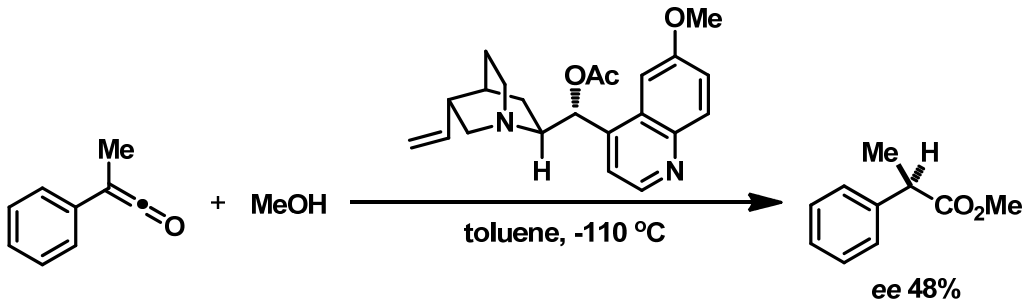
MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

# Organocatalysis

## The birth of organocatalysis




Bredig, C. *Chemiker-Zeitung* **1912**, *35*, 324.

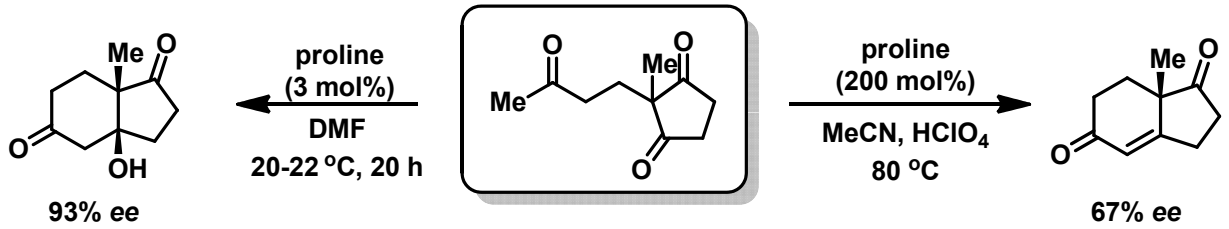



Pracejus, H. *Justus Liebigs Annalen der Chemie* **1960**, 9.

# Organocatalysis

## The birth of organocatalysis

Hajos-Parrish-Eder-Sauer-Wiechart: Asymmetric Breakthrough

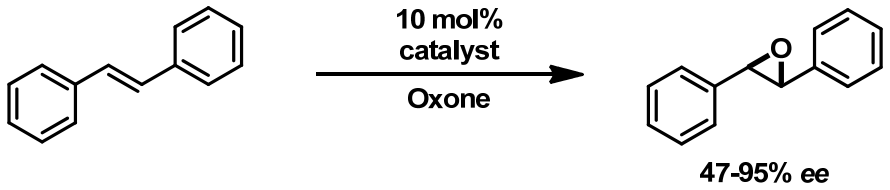


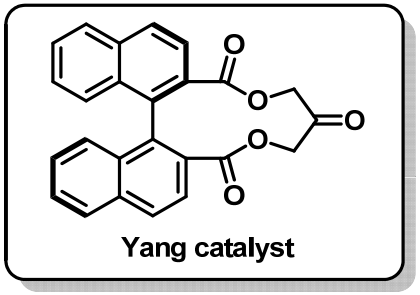

- Extraordinary result that was well received by the chemical synthesis community
- Viewed as a unique chemical reaction, not part of a larger interconnected field
- Manuscript emphasis never placed on the benefits of organocatalysts or new catalysis concepts
- General lessons were never extrapolated thereby stalling potential application over multiple reaction types
- The value of a general over-arching field that used organic catalysts was never recognized

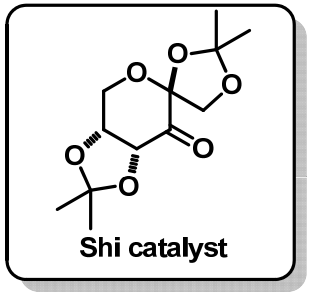

Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496.

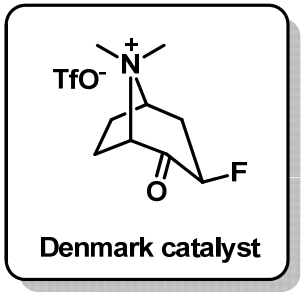
# Organocatalysis

## The birth of organocatalysis




- Employed ketones as enantioselective catalysts
- Demonstrated that organic catalysts could be employed to solve major chemical problems
- Did not conceptualize the field or define the benefits of organocatalysis
- Involved the invention of a single catalyst for a single reaction type


Yang, D.; Yip, Y-C.; Tang, M-W.; Wong, M.-K.; Zheng, J-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491.

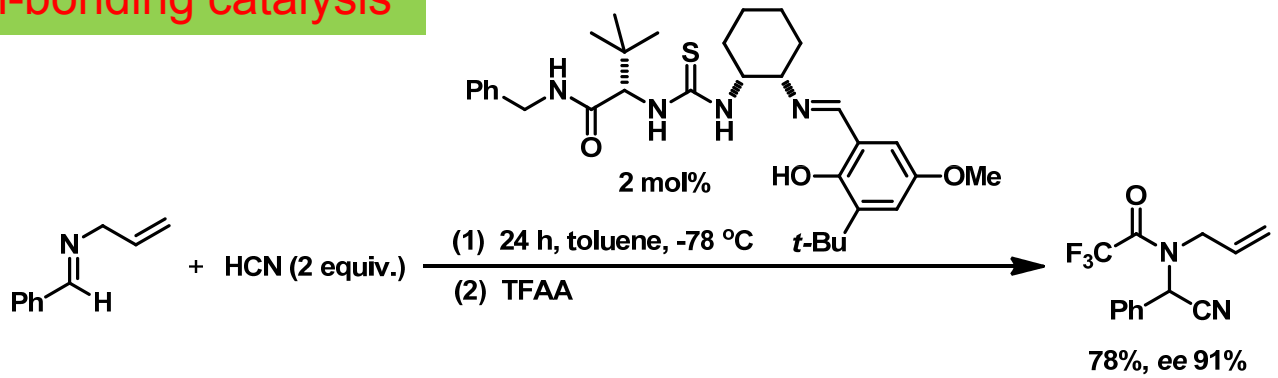
Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.

Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288.

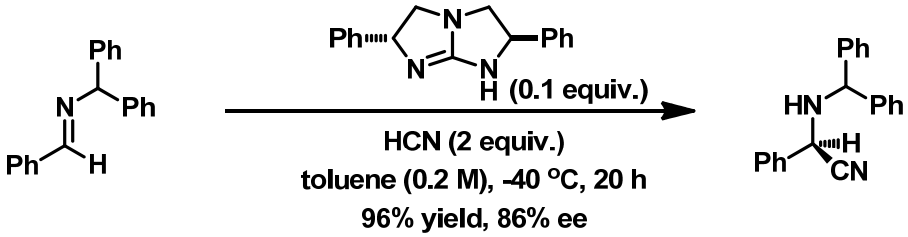
# Organocatalysis

## The birth of organocatalysis

Hydrogen-bonding catalysis



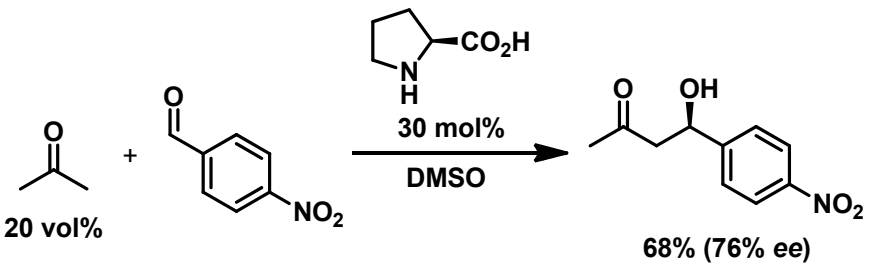

Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.




Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.

# Organocatalysis

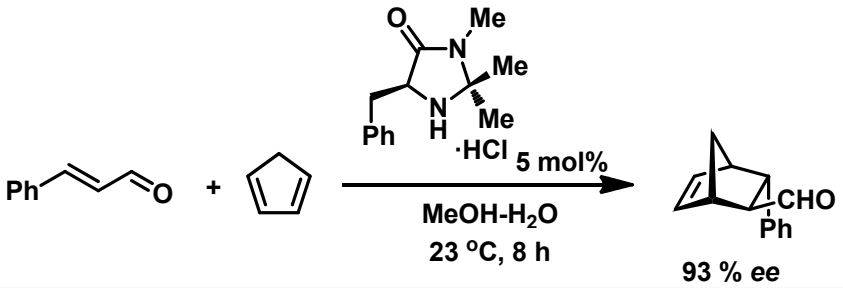
## The field of organocatalysis was effectively launched in 2000




- Proline is nontoxic, inexpensive, and readily available
- No prior modification of the carbonyl substrates is required.
- The catalyst can be readily removed by aqueous extraction.
- This is the first example of a nonmetallic small-molecule catalyst for direct intermolecular asymmetric aldol reactions.

… …

List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

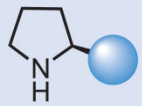
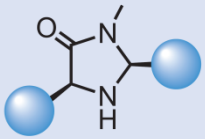
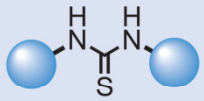
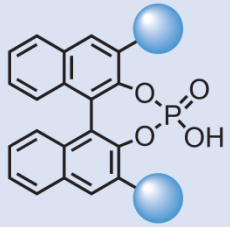
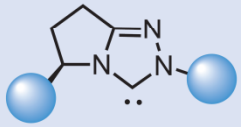



- Outlined the potential benefits of organic molecules as asymmetric catalysts
- Introduced the concept of a generic mode of activation for organic catalysis that could be used over many reaction types
- Introduced for the first time, the terminology organocatalysis, organic catalysis and organocatalytic

Ahrendt, K. A.; Borths, C. J. MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

# Organocatalysis

## Overview of organocatalysis

| Catalysts | Activation modes | Typical reaction steps | |
|---|---|---|---|
|  | ■ Enamine activation of aldehydes and ketones (HOMO raising) | EN | Aldol reaction<br>α-Functionalization<br>Michael reaction<br>Mannich reaction |
|  | ■ Iminium activation of α,β-unsaturated aldehydes (LUMO lowering) | IM | Michael reaction<br>Diels–Alder reaction<br>Friedel–Crafts reaction |
|  | ■ Hydrogen bonding (LUMO lowering) | H⋯Do | Michael reaction<br>Henry reaction<br>Mannich reaction<br>Strecker reaction |
|  | ■ Protonation (LUMO lowering) (counterion catalysis) | $H^+$ | Reduction<br>Mannich reaction<br>Friedel–Crafts reaction<br>Michael reaction |
|  | ■ Umpolung Breslow intermediate | NHC | Nucleophilic acylation<br>Benzoin reaction<br>Stetter reaction |

List, Barbas…

MacMillan…

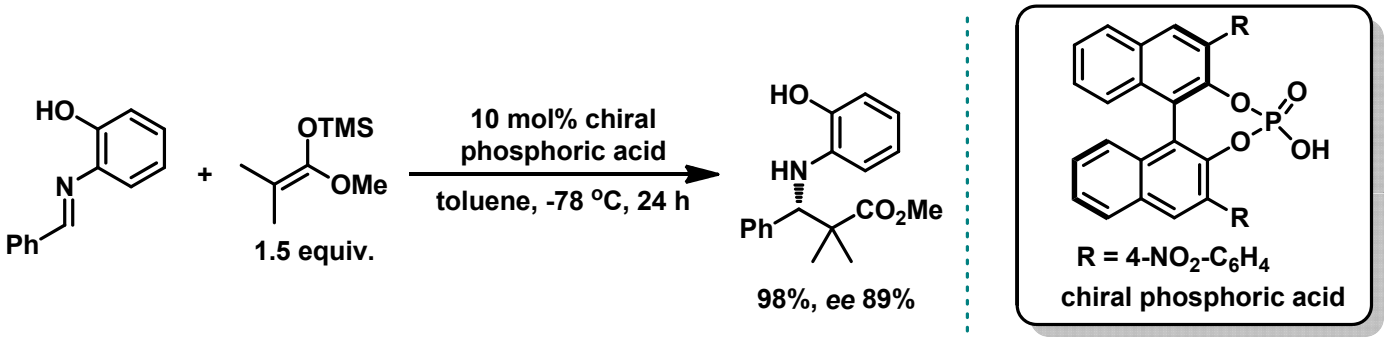
Jacobsen…

Akiyama，Terada…

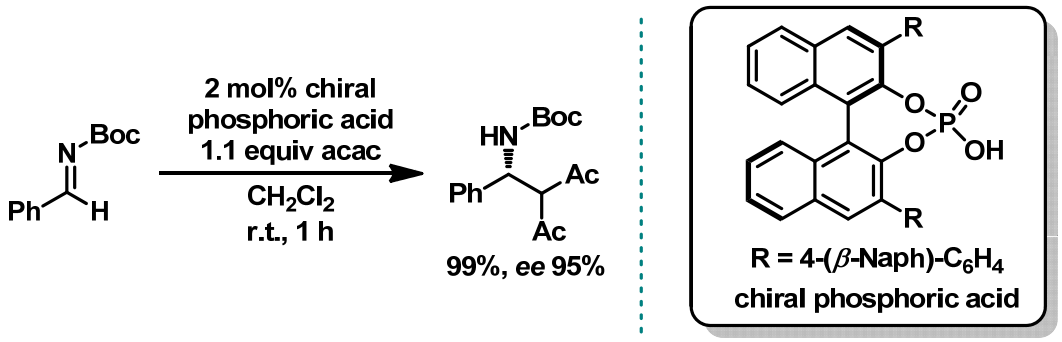
Enders, Rovis, Bode, Glorius …

# Organocatalysis

## Chiral Brønsted Acid-Catalyzed Mannich Reactions



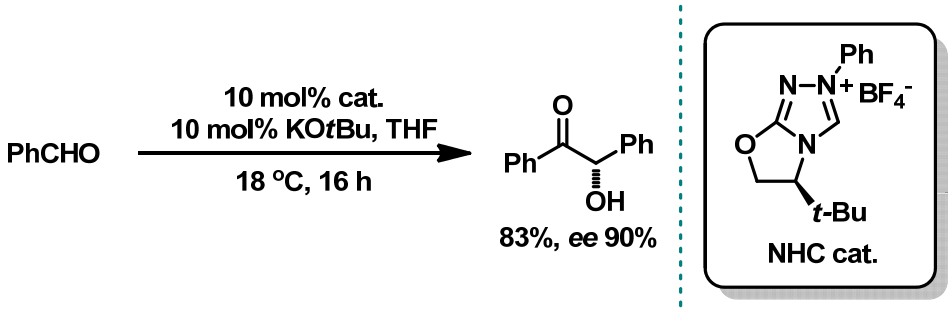

Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.



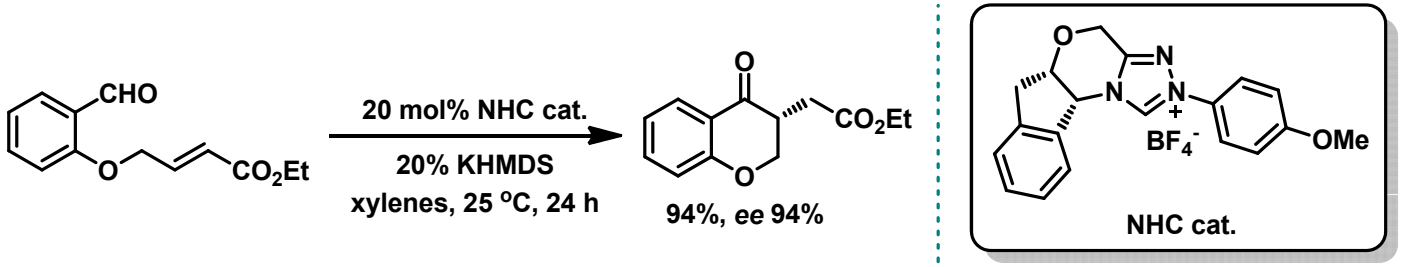

Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

# Organocatalysis

## NHC-Catalyzed Asymmetric reactions



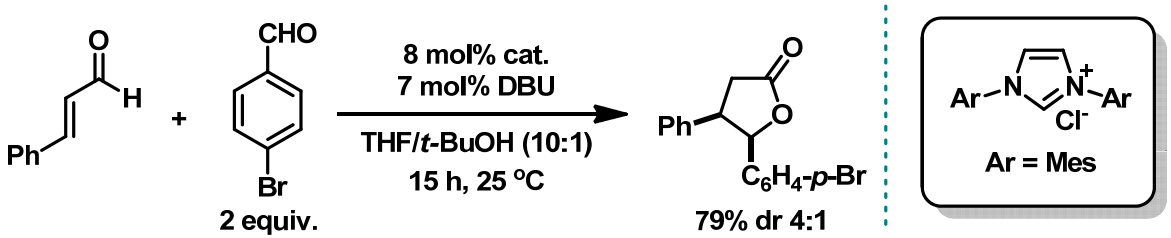

Enders, D.; Kallfass U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743.



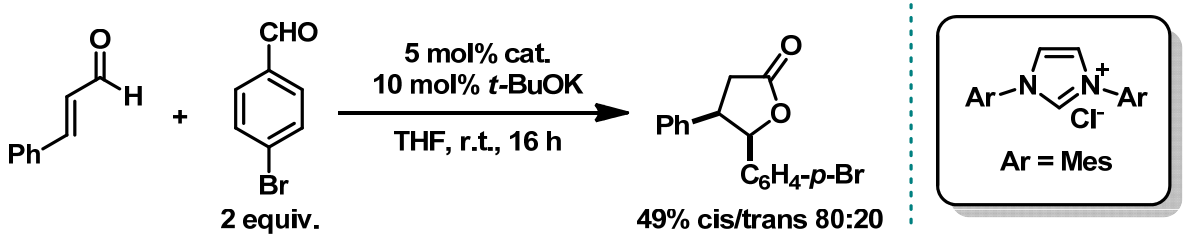

Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298.

# Organocatalysis

## NHC-Catalyzed Direct Annulations of Enals and Aldehydes



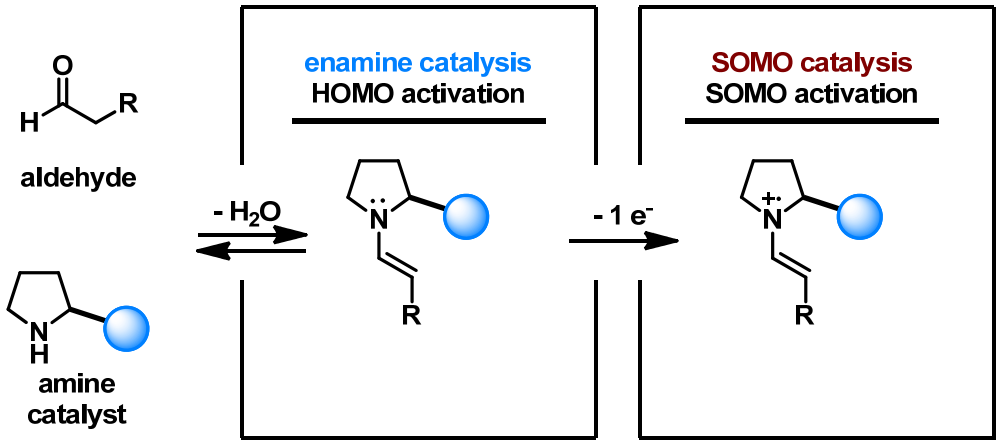

Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370.



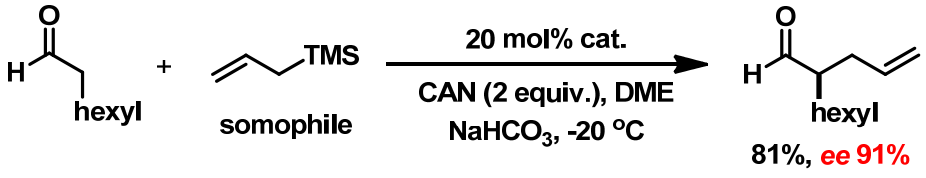

Burstein, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 6205.

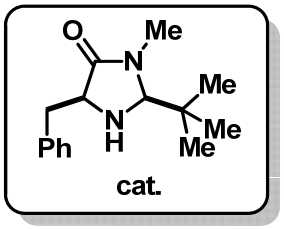
# Organocatalysis

## SOMO activation -- novel and powerful activatin mode




SOMO (Singly Occupied Molecular Orbital) catalysis was developed to allow for π-neutral or π-rich nucleophiles to add to the three-π electron radical cation species at the now electrophilic α-position of an aldehyde (via an *umpolung* of nucleophilic enamine catalysis)

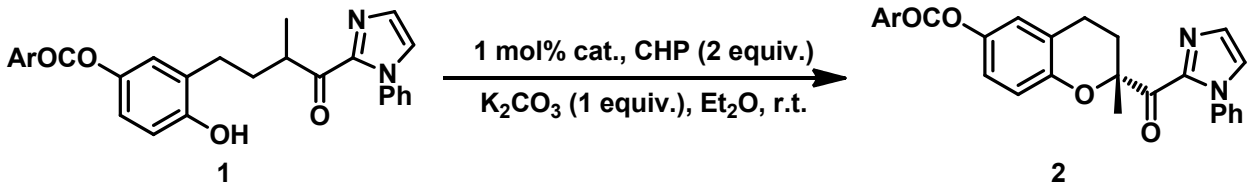


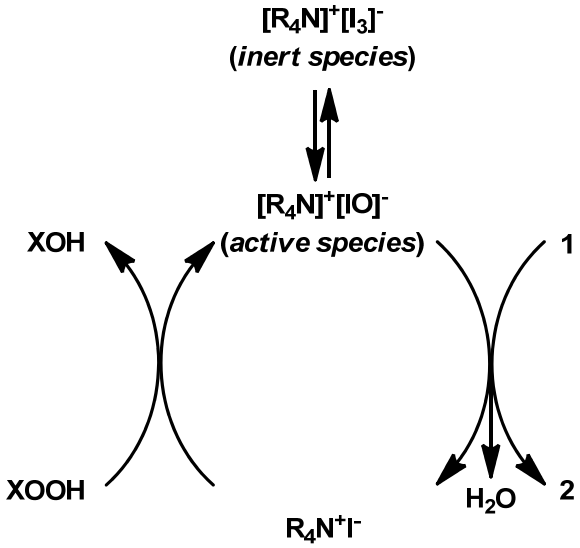



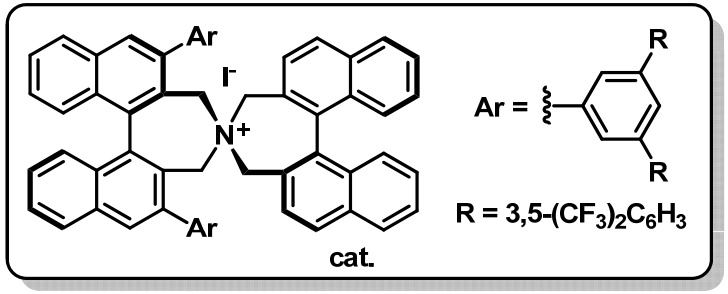

Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004.

# Organocatalysis

## High-turnover hypoiodite catalysis




Uyanik, M.; Hayashi, H.; Ishihara, K. *Science* **2014**, *345*, 291.

# Organocatalysis

## Summary

### Advantages VS Disadvantages

- Insensitive to mositure and air
- Inexpensive
- Readily available from bio-matter
- Operationally easy to handle
- Non-toxic, easily removed from waste streams
- Rich, new avenue for academic thought

- Low tunover number
- Hard to scale up
- No new reaction type (all reactions could be accomplished via metal catalysis)
- Narrow scope (for aldehyde or ketone substrates)

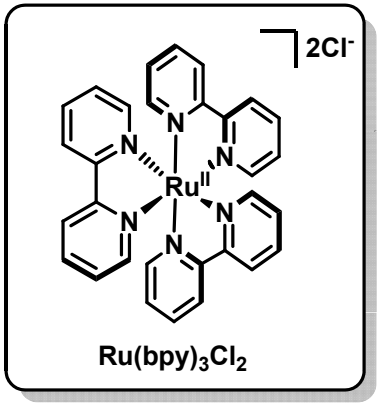
# Visible Light Photoredox Catalysis

## Overview of photoredox catalysis in organic synthesis

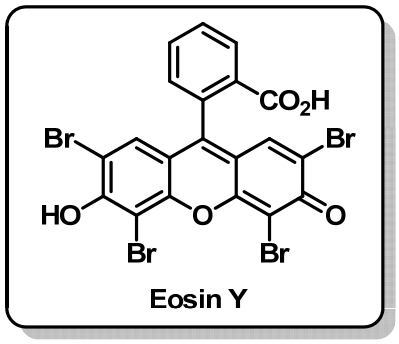
- As early as 1912, Ciamician recognized that light had the potential to serve as an inexpensive, abundant, renewable, and nonpolluting reagent for chemical synthesis
- In 1936, Burstall et al. synthesis the complex $[Ru(bpy)_3]Cl_2 \bullet H_2O$
- The ability of $Ru(bpy)_3^{2+}$ and related complexes to function as visible light photocatalysts has been recognized and extensively investigated for applications in inorganic and materials chemistry.
- In 1978, Kellogg et al. found light induced and dye or $Ru(bpy)_3^{2+}$ accelerated reductions of phenacyl sulfonium salts by 1,4-dihydropyridines
- In 1981, Pac et al. described the $Ru(bpy)_3^{2+}$-mediated reduction of electron-deficient olefins
- In 2008, concurrent reports about using $Ru(bpy)_3^{2+}$ as visible light photoredox catalyst from Yoon and MacMillan group

# Visible Light Photoredox Catalysis

**Why $Ru(bpy)_3Cl_2$ and its analogues, not organic dyes such as Eosin Y?**




VS




Higher energy visible light (400−475 nm) allows for the maximum potential energy gain without the possibility of undesired reactivity associated with direct excitation of organic substrates.

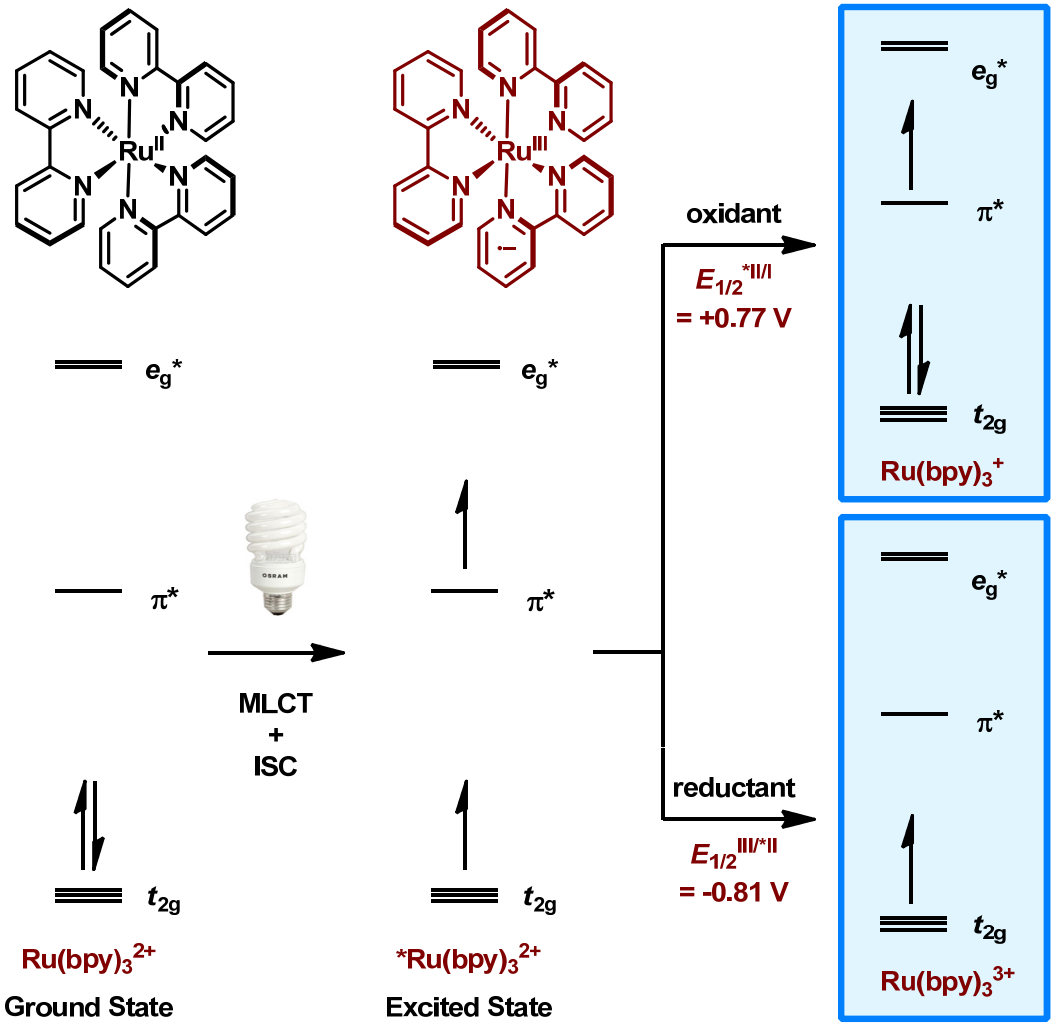
The maximum absorbance of $Ru(bpy)_3Cl_2$ is 452 nm.

The absorbance of organic dyes is significantly redshifted (e.g., $\lambda_{max}$(Eosin Y) = 522 nm).

Though advantageous that it avoids the use of precious metals, the excited state of Eosin Y has 0.37 eV less energy to potentially apply to reaction promotion.

# Visible Light Photoredox Catalysis

## Photochemistry of $Ru(bpy)_3^{2+}$



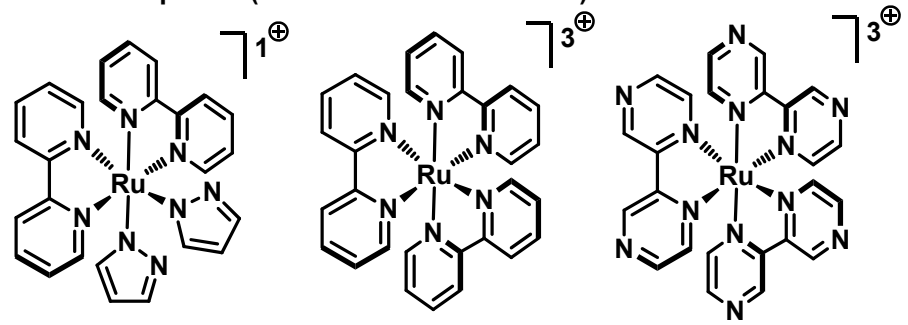

Photoredox catalysis may be employed to perform **overall redox neutral** reactions. As both oxidants and reductants may be transiently generated in the same reaction vessel

- Absorption at 452 nm (visible light)
- Stable, long-lived excited state ($\tau$ = 1100 ns)
- Single electron transfer (SET) catalyst
- Effective excited state oxidant and reductant

Prier, C. K.; Rankic, D. A.; MacMillan D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

# Visible Light Photoredox Catalysis

**Oxidized Complexes (Metal Centered Oxidation):**



$Ru(bpy)_2(pz)_2$ $E_{red}$ = 0.30 V

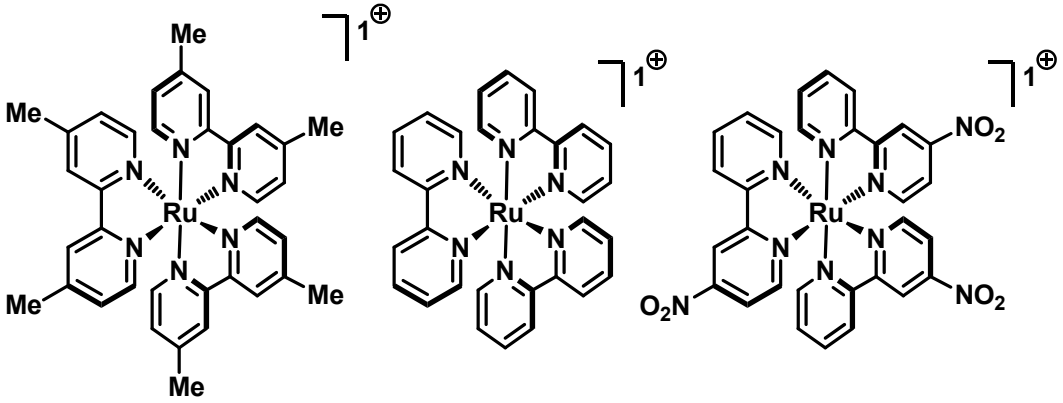
$Ru(bpy)_3$ $E_{red}$ = 1.26 V

$Ru(bpz)_3$ $E_{red}$ = 1.86 V

electron density of metal center

oxidative power of complex

**Reduced Complexes (Ligand Centered Reduction):**



$Ru(dmb)_3$ $E_{red}$ = -1.45 V

$Ru(bpy)_3$ $E_{red}$ = -1.35 V

*mer*-$Ru(4\text{-}O_2N\text{-}bpy)_3$ $E_{red}$ = -0.63 V

electron density of Ligand

reductive power of complex

**Ligand effects on ground-state redox properties of photocatalysts**

$Ox + e^{\ominus} \longrightarrow Red, E (V)$

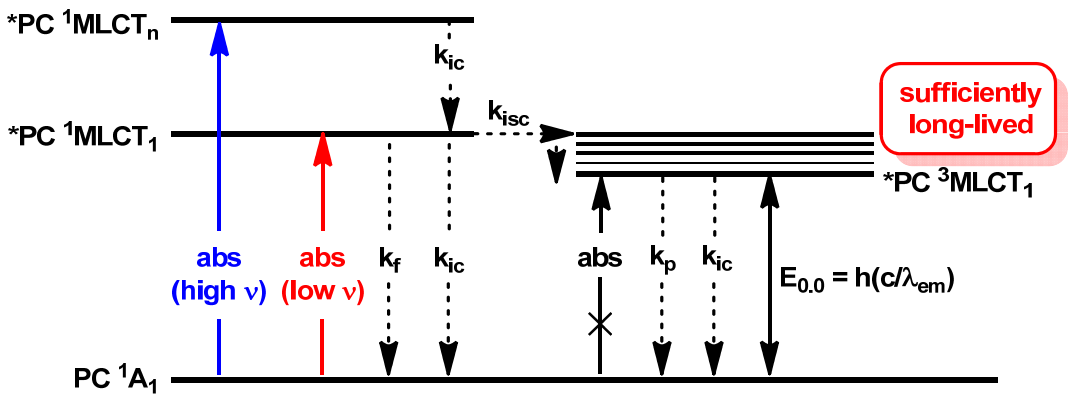
E > 0 : potent oxidant
E < 0 : potent reductant

+3 state : good oxidant
+2 state : stable ground state
+1 state : good redudant

Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617.

# Visible Light Photoredox Catalysis

## Calculations of approximate reduction potentials of *Ru(bpy)$_3^{2+}$




PC = photocatalyst, $^1A_1$ = ground state, *PC $^1$MLCT$_1$ = lowest spin-allowed metal to ligand charge transfer excited state, *PC $^1$MLCT$_n$ = numerous singlet excited states, $k_f$, $k_{ic}$, $k_{isc}$, and $k_p$ are the rate constants for fluorescence, internal conversion, intersystem crossing, and phosphorescence, respectively and $\lambda_{em}$ is the maximum emission wavelength of the photocatalyst.

**Figure :** Generalized Jablonski diagram of photocatalysts

***Oxidative Quenching:***

$E_{red}[PC^{+1} / *PC] = E_{red}[PC^{+1} / PC] - E_{0.0}$ *(1)*

$Ru(bpy)_3^{3+} + e^{\ominus} \longrightarrow *Ru(bpy)_3^{2+}$

77 K: $E_{red}[PS^{+1} / *PS]$ = 1.26 V - 2.13 V = **-0.87 V**

293 K: $E_{red}[PS^{+1} / *PS]$ = 1.26 V - 2.02 V = **-0.76 V**

***Reductive Quenching:***

$E_{red}[*PC / PC^{-1}] = E_{red}[PC / PC^{-1}] + E_{0.0}$ *(2)*

$*Ru(bpy)_3^{2+} + e^{\ominus} \longrightarrow Ru(bpy)_3^{1+}$

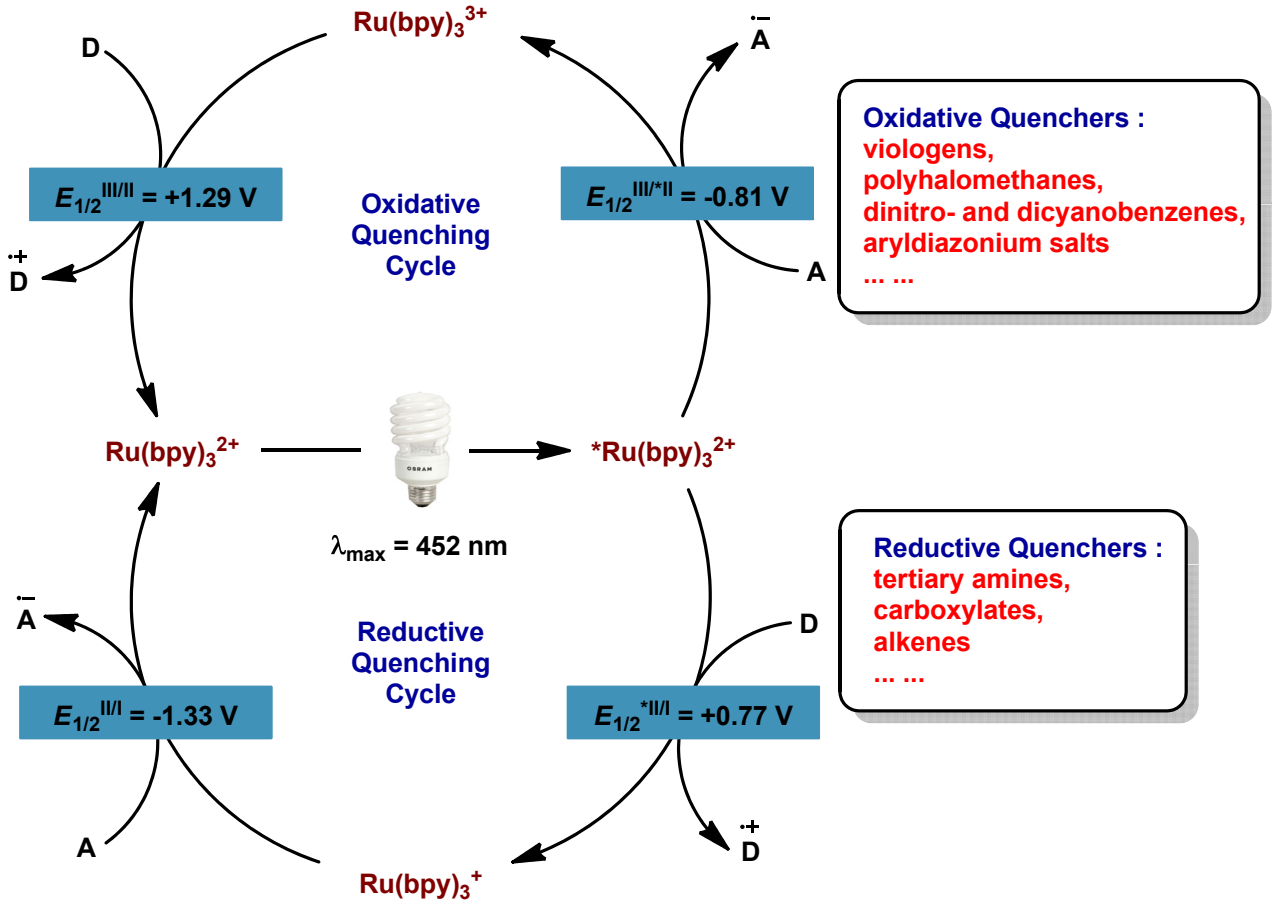
77 K: $E_{red}[*PS / PS^{-1}]$ = -1.35 V + 2.13 V = **0.78 V**

293 K: $E_{red}[*PS / PS^{-1}]$ = -1.35 V + 2.02 V = **0.67 V**

Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617.

# Visible Light Photoredox Catalysis

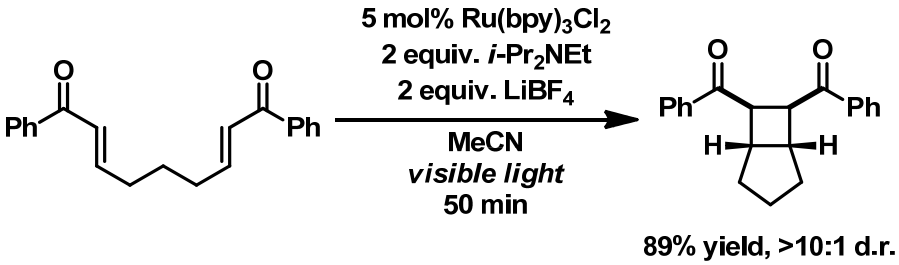
## Oxidative and reductive quenching cycle of $Ru(bpy)_3^{2+}$

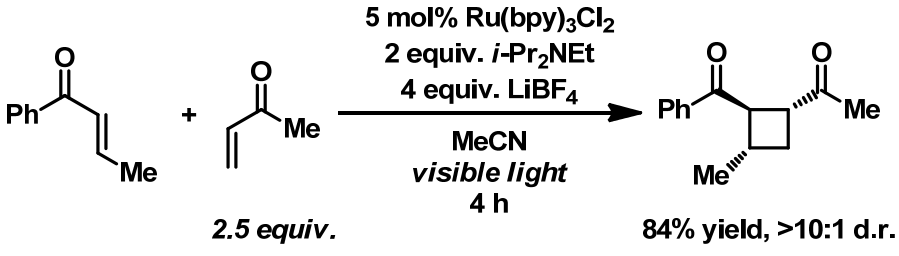


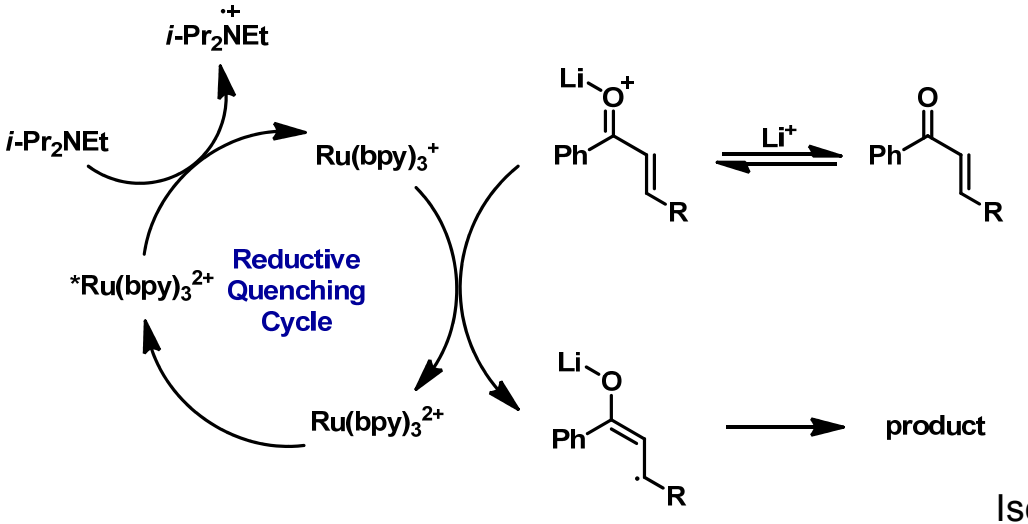

Prier, C. K.; Rankic, D. A.; MacMillan D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

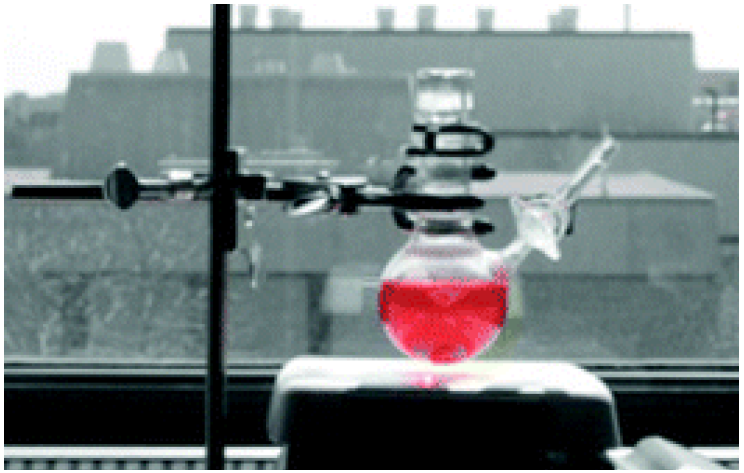
# Visible Light Photoredox Catalysis

## Visible light photocatalysis of [2+2] enone cycloadditions



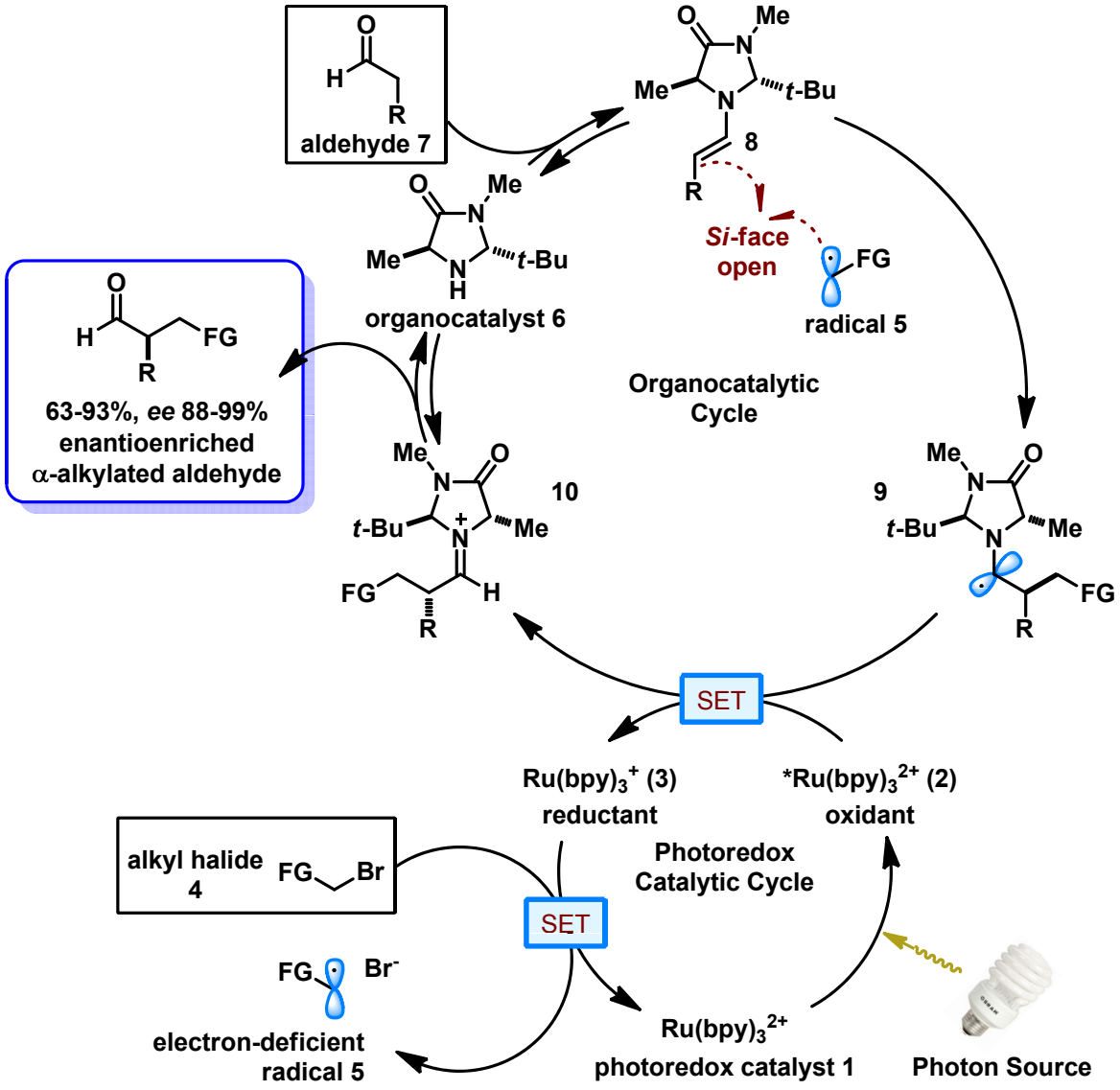



Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P.
*J. Am. Chem. Soc.* **2008**, *130*, 12886.
Du. J.; Yoon, T. P.
*J. Am. Chem. Soc.* **2009**, *131*, 14604.

# Visible Light Photoredox Catalysis

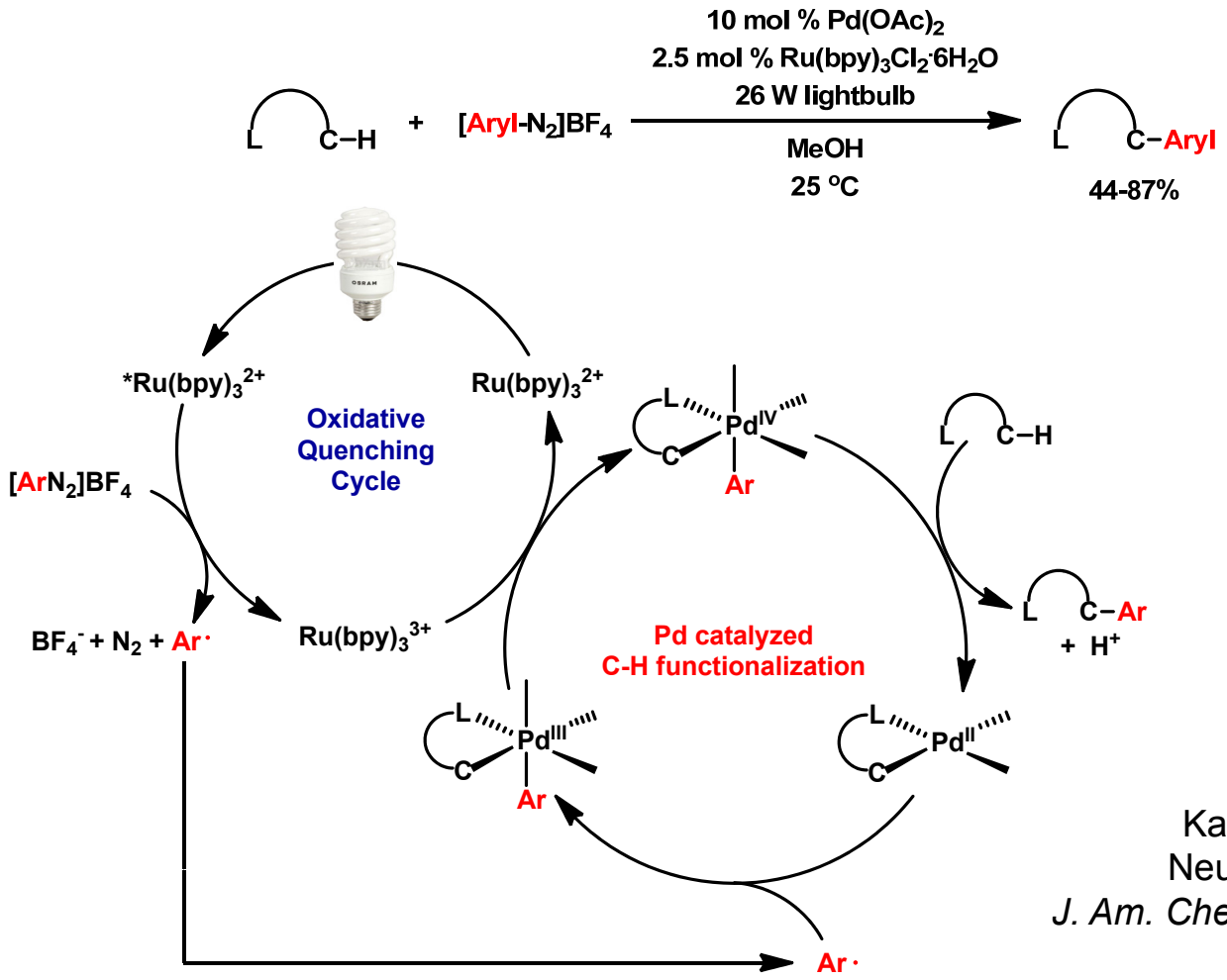
## Merging photoredox catalysis with organocatalysis




Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77.

# Visible Light Photoredox Catalysis

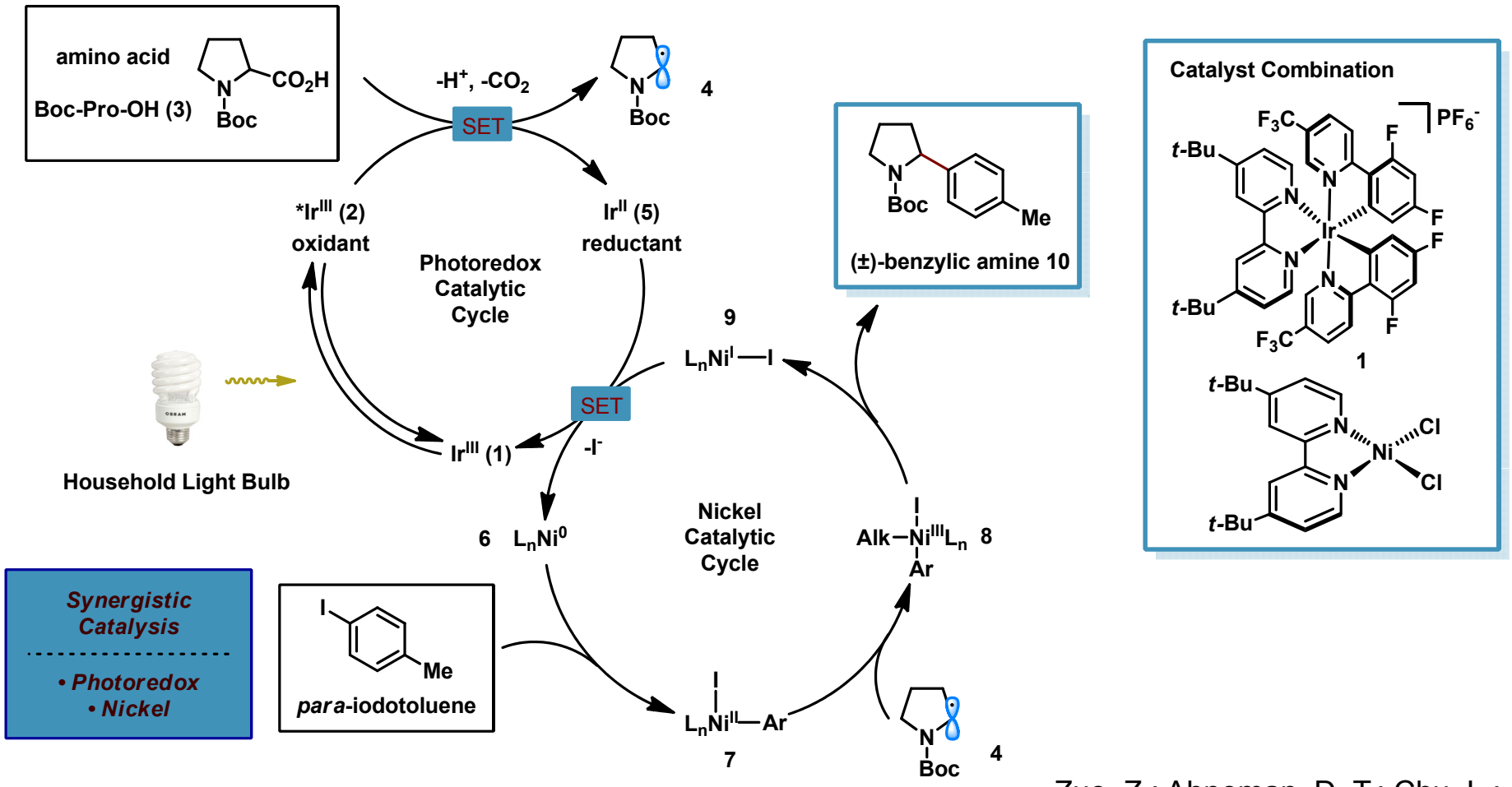
## Merging photoredox catalysis with highvalent Pd catalyzed C-H functionalization




Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566.

# Visible Light Photoredox Catalysis

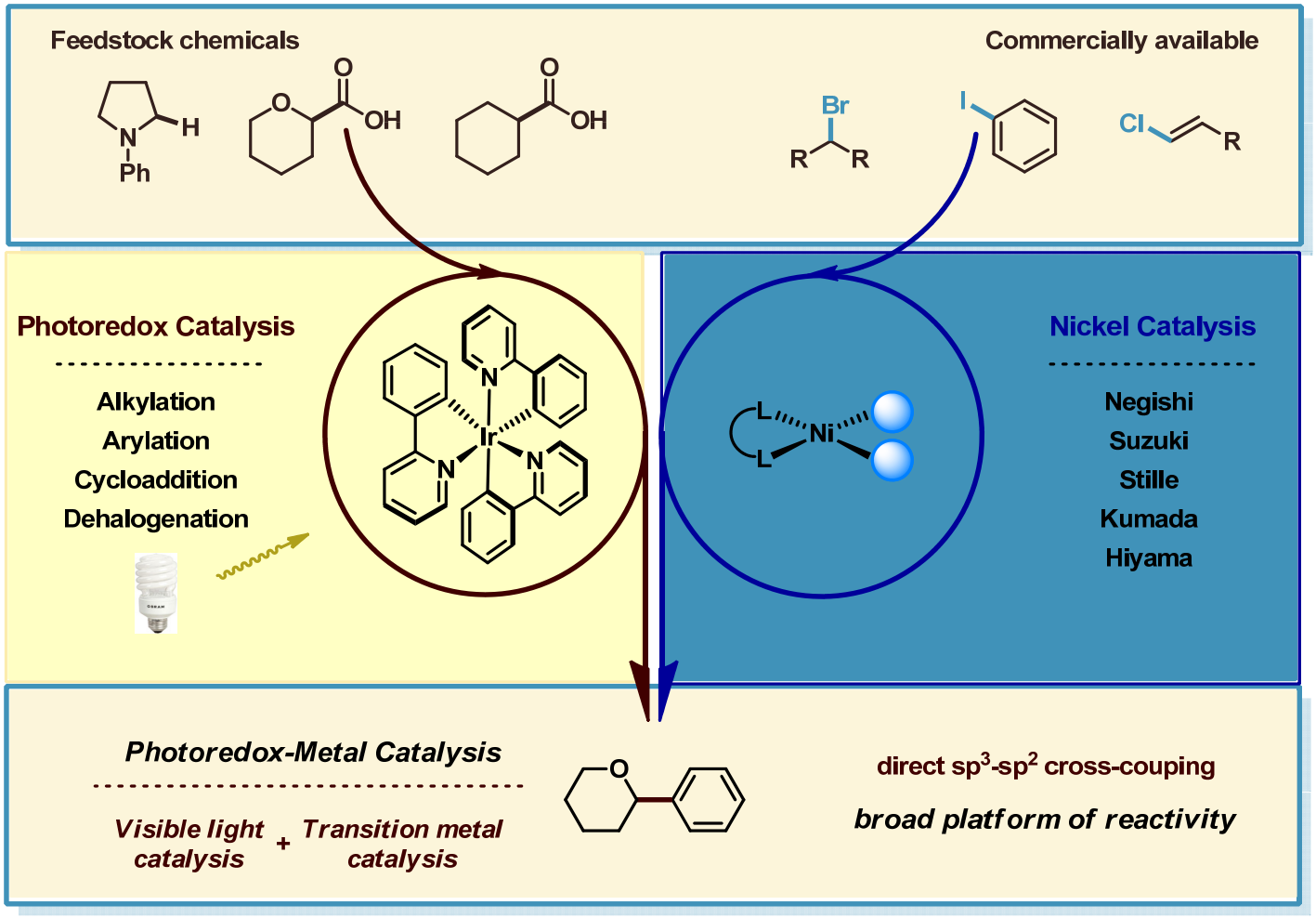
## Merging photoredox with nickel catalysis




Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437.

# Visible Light Photoredox Catalysis

## Merging photoredox with nickel catalysis yields access to direct $sp^3$-$sp^2$ crosscoupling



# Visible Light Photoredox Catalysis

## Summary

Although photoredox catalysis has only recently received widespread attention as a tool for synthetic organic chemists, it has already been applied to the development of a wide range of new carbon−carbon bond forming reactions under mild and environmentally benign conditions.

## Outlook

- Develop more efficient catalyst (Metal, Ligand ...)
- Merging with more other modes of catalytic activation systems (enamine catalysis, NHC catalysis, transition metal catalysis …)
- Perform efficiently on large scales