Synergistic Catalysis

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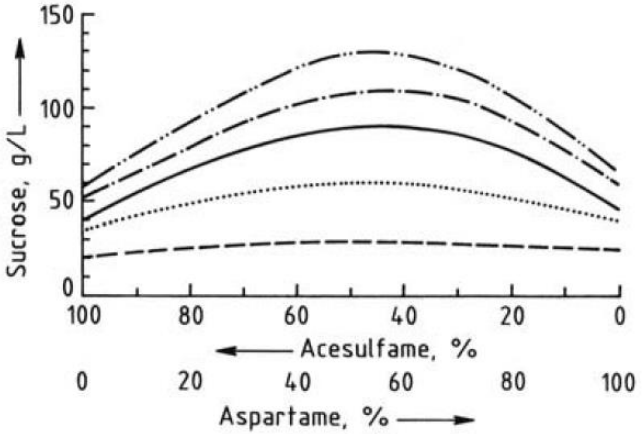
SED Group Meeting

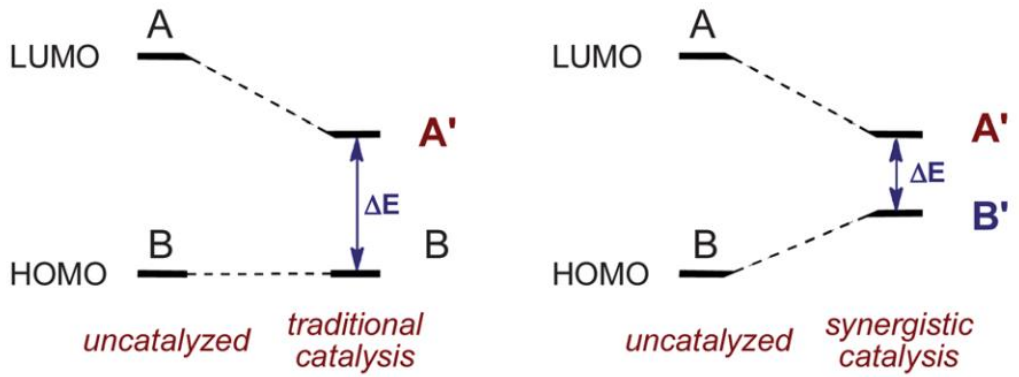
March 31, 2015

Synergy

- synergy (*n*), “the interaction of elements that when combined produce a total effect that is greater than the sum of the individual elements, contributions, etc.”

- synergistic catalysis (*n*), “the concurrent activation of both a nucleophile and an electrophile using distinct catalysts”





- also called “cooperative” or “dual” catalysis
- combining two distinct catalyst systems allows access to reactivity unattainable by either system individually

MacMillan, D. W. C. *et al*. *Chem. Sci*. **2012**, 3(3), 633-658

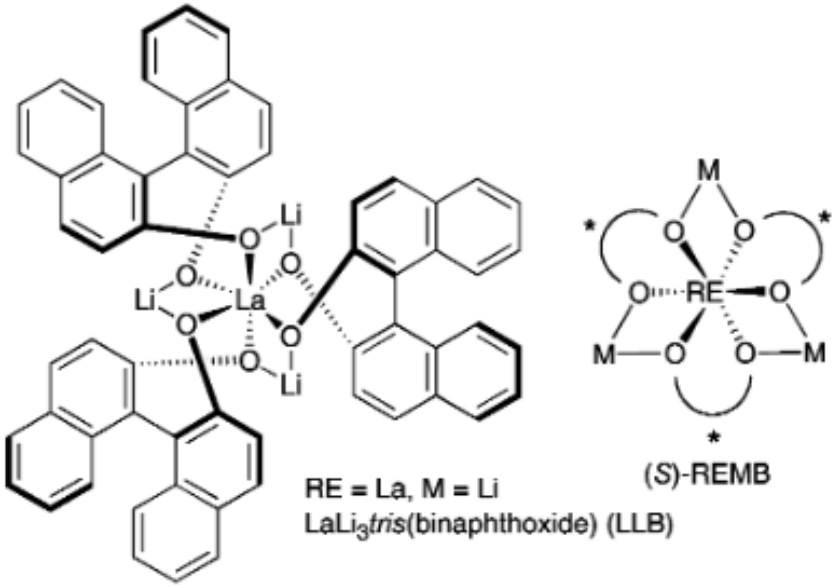
“Synergy.” dictionary.com Accessed 30 March 2015

Von Rymon Lipinski, G.-W. Sweeteners. In *Ullmann’s Encyclopedia of Industrial Chemistry*, Wiley-VCH: Weinheim, 2000. pp. 543-564

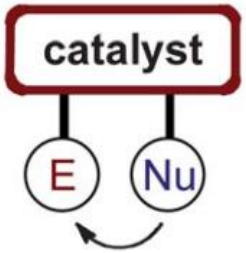
Some terminology

- synergistic catalysis has been differentiated from other forms of multicatalysis

- bifunctional catalysis
  - the nucleophile and electrophile are activated by different groups on the *same catalyst*
  - example: Shibasaki rare earth-alkali metal-BINOL (REMB) catalysts



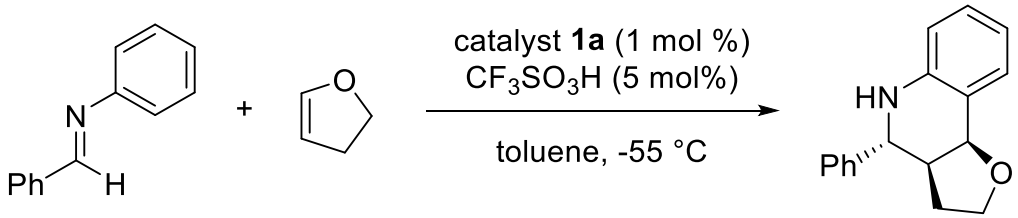
- Lewis acidic site (rare earth metal) for activation of electrophile)
- Bronsted basic sites for activation of nucleophile
- highly effective catalysts for asymmetric aldol reactions, Michael additions, etc.



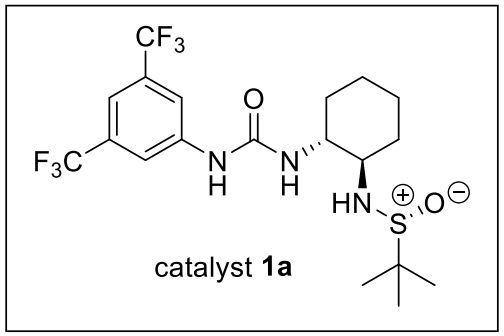
MacMillan, D. W. C. *et al*. *Chem. Sci*. **2012**, 3(3), 633-658
Shibasaki, M. *et al*. *Acc. Chem. Res*. **2009**, 42(8), 1117-1127

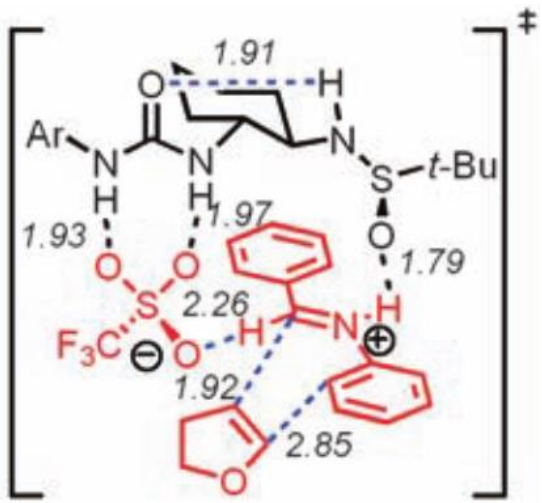
Some terminology

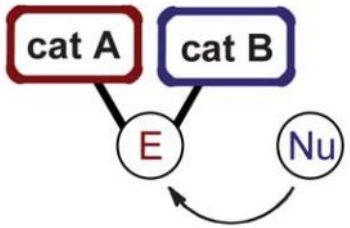
- Double activation catalysis
  - Two separate catalyst systems working together to activate *one reactive partner*
  - Jacobsen, 2010: cycloadditions promoted by a Brønsted acid and chiral urea



- 92% yield, dr = 4:1 (exo:endo), er = 95.5:4.5 (exo)



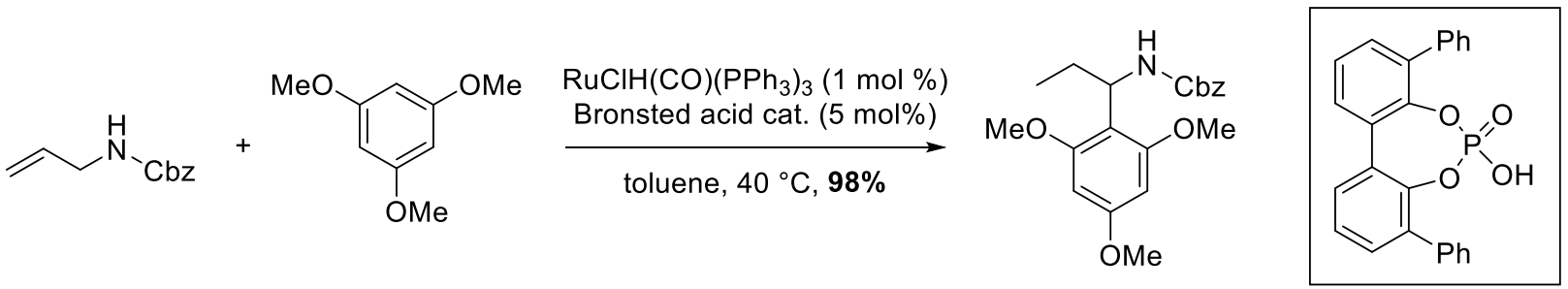


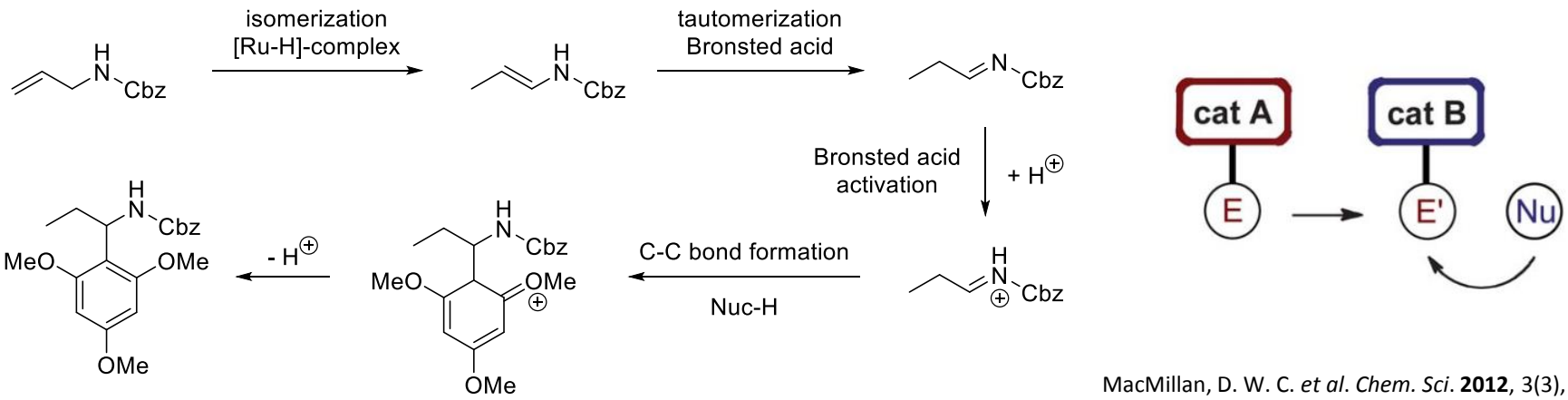


MacMillan, D. W. C. *et al*. *Chem. Sci*. **2012**, 3(3), 633-658
Jacobsen, E. N. *et al. Science* **2010**, 327, 986

Some terminology

- Cascade catalysis (sequential catalysis)
  - Two separate catalyst systems work in sequence to activate *one reactive partner*
  - Terada, 2008, tandem isomerization/C-C bond formation





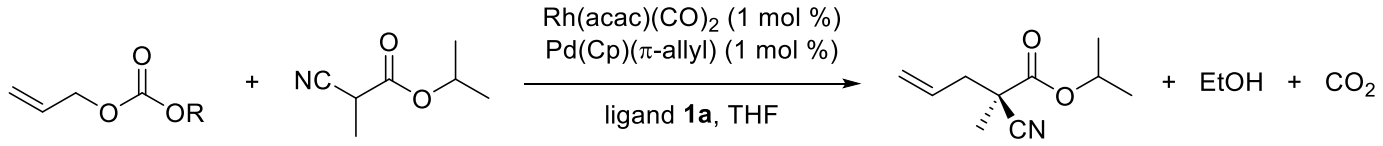
MacMillan, D. W. C. *et al*. *Chem. Sci*. **2012**, 3(3), 633-658
Terada, M. *et al*. *J. Am. Chem. Soc*. **2008**, 130, 14452

Synergistic Catalyst Systems

- General Classes:
- Metal-metal systems
- Metal-nonmetal systems
  - Enamine organocatalysis + metal catalysis
  - Other systems not involving enamines
- Photoredox organocatalysis

Rh/Pd synergistic catalysis

- Enantioselective allylation of alpha-cyano carbonyls
  - Ito, 1996

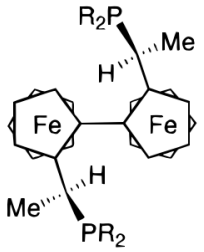


3a: R = Et
3b: R = $CH(CF_3)_2$

2

4

entry	3	Pd[b]	Rh[b]	ligand	temp (°C)	time (h)	yield[c] (%)	ee[d] (%)
1	**3a**	+	+	**1a**	0	4	98	32 (*R*)
2	**3a**	+	−	**1a**	0	5	97	0
3	**3a**	−	+	**1a**	0	24	0	
4	**3b**	+	+	**1a**	−25	5	91	93 (*R*)



(*S*,*S*)-(*R*,*R*)-TRAP

R = Ph: PhTRAP (**1a**)

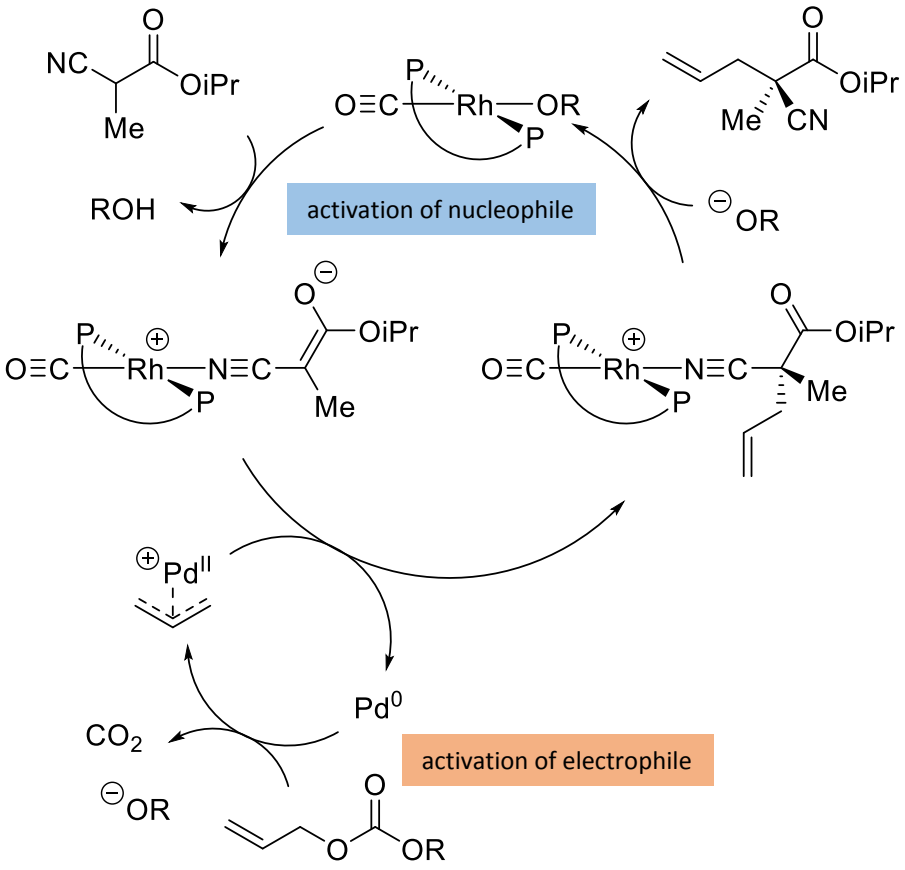
trans- coordinating ligand

- chiral environment around Pd has no effect on enantioselectivity
- inclusion of Rh is necessary
- R group on the allyl carbonate has a large effect on er

Ito, Y. *et al*. *J. Am. Chem. Soc*. **1996**, 118(13), 3309-3310

Rh/Pd synergistic catalysis

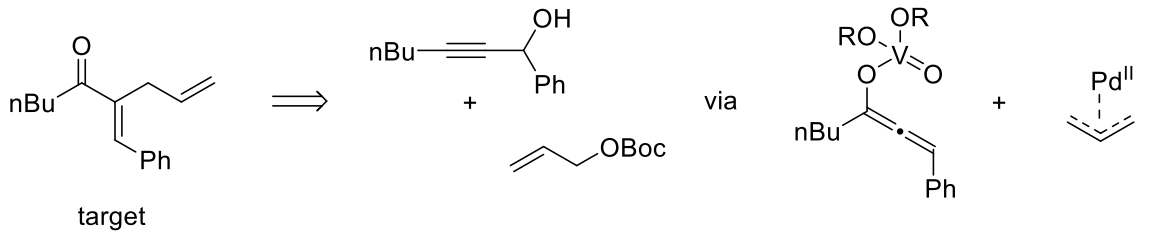
- Proposed catalytic cycle:
  - Pd cycle: generation of π-allyl Pd^{II} species accompanied by ejection of CO_2 and alkoxide
  - Rh cycle: alkoxide ligand displaced by α-cyano ester accompanied by deprotonation
  - activated Rh-bound cyano enolate attacks π-allyl species forming C-C bond
  - presence of a less basic alkoxide ensures that cyano enolate is actually bound to Rh during bond-forming step



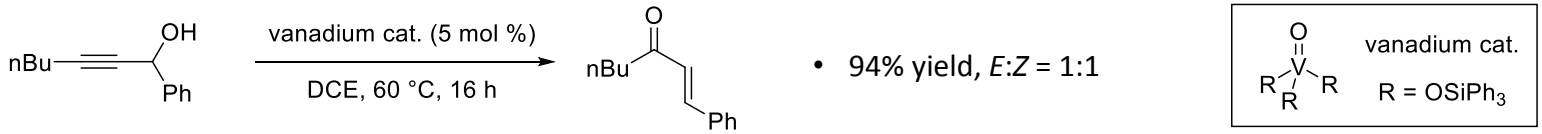
Ito, Y. *et al*. *J. Am. Chem. Soc*. **1996**, 118(13), 3309-3310
MacMillan, D. W. C. *et al*. *Chem. Sci*. **2012**, 3(3), 633-658

V/Pd synergistic catalysis

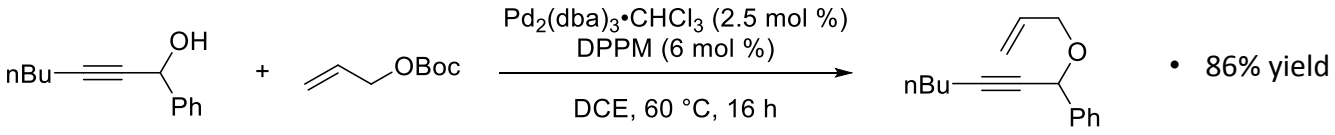
- Trost, 2011
  - investigating the α-allylation of unsaturated carbonyl compounds



  - vanadium-catalyzed 1,3-transpositions of propargyl alcohols (Meyer-Schuster rearrangement)



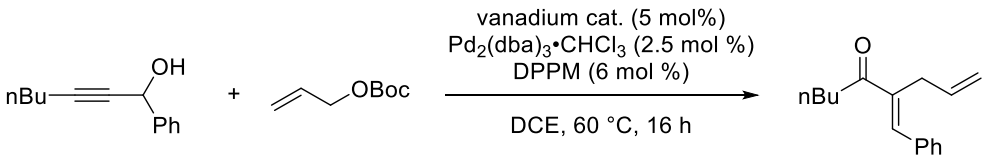
  - palladium-catalyzed Tsuji-Trost allylation



Trost, B. M. *et al*. *J. Am. Chem. Soc*. **2011**, 133(6), 1706-1709

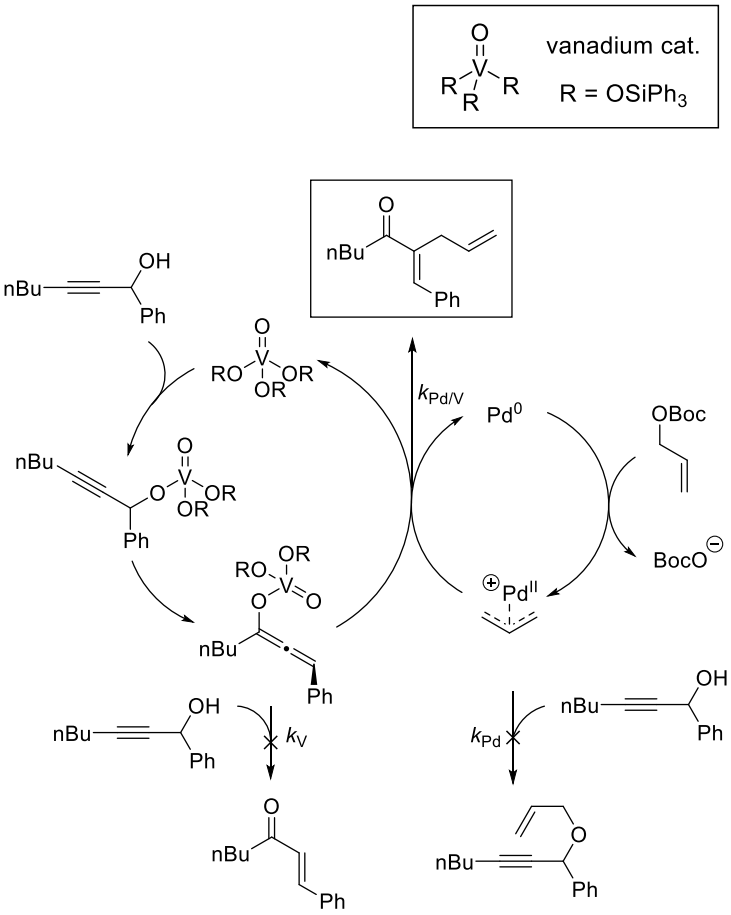
V/Pd synergistic catalysis

- Combination of the two catalyst systems leads to different reactivity:



- 98% yield, *E*:*Z* = 5:1

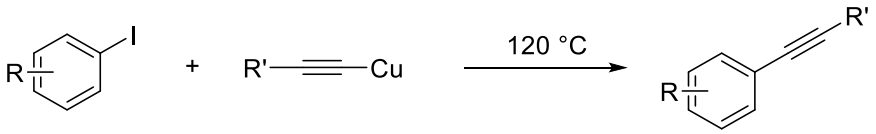
- Proposed mechanism:
  - normal reactivity modes of individual catalyst systems are completely repressed
  - concentration of propargyl alcohol in solution is still large; the chance of an intermediate encountering an alcohol is far greater than both intermediates encountering each other
  - therefore: rate of reaction between two activated intermediates is *exceptionally fast*



Trost, B. M. *et al*. *J. Am. Chem. Soc*. **2011**, 133(6), 1706-1709
MacMillan, D. W. C. *et al*. *Chem. Sci*. **2012**, 3(3), 633-658

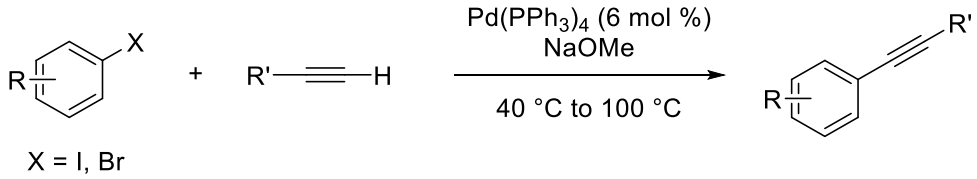
Cross-Couplings as Synergistic Reactions

- arene-alkyne couplings: initial investigations
  - Stephens and Castro (1963)



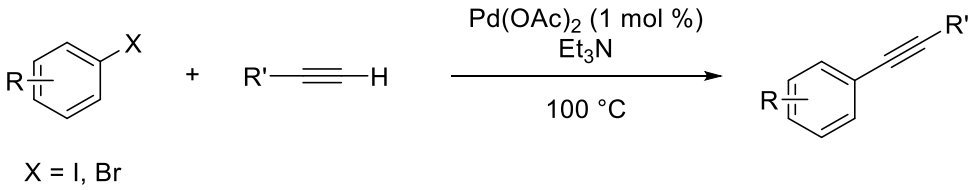
- requires preparation of stoichiometric copper acetylides, high temperatures

  - Cassar (1975)



- high temperatures required, esp. for bromoarenes and substituted iodoarenes

  - Heck (1975)

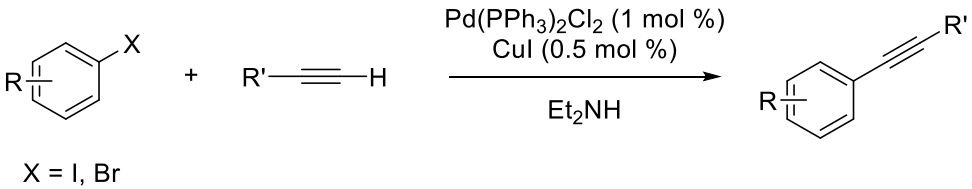


- high temperatures required

Stephens, R. D.; Castro, C. E. *J. Am. Chem. Soc.* **1963**, 28(12), 3313-3315
Cassar, L. *J. Organomet. Chem*. **1975**, 93(2), 253-257
Heck, F. R. et al. *J. Organomet. Chem*. **1975**, 93(2), 259-263

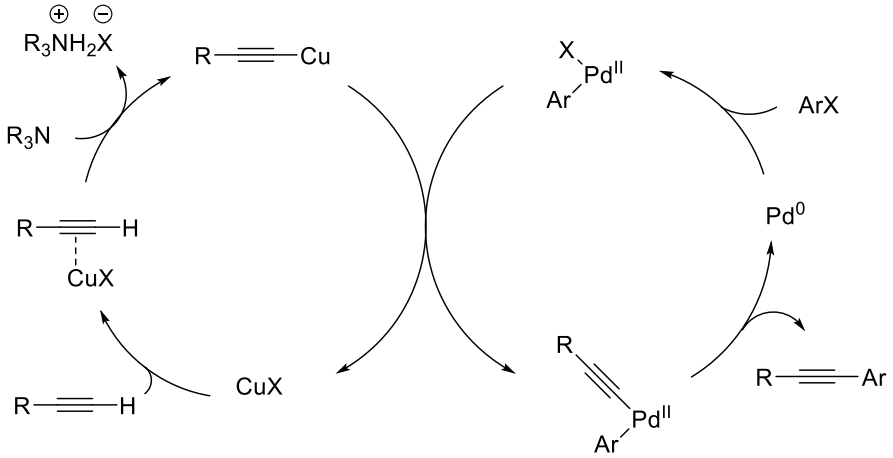
Cross-Couplings as Synergistic Reactions

- Sonogashira (1975)



- all couplings proceed at room temperature
- no reaction observed in the absence of catalytic copper iodide at room temperature

- activation of alkyne in Cu system generates the copper acetylide catalytically under mild conditions



A CONVENIENT SYNTHESIS OF ACETYLENES : CATALYTIC SUBSTITUTIONS OF ACETYLENIC HYDROGEN WITH BROMOALKENES, IODOARENES, AND BROMOPYRIDINES

Kenkichi Sonogashira, Yasuo Tohda, and Nobue Hagihara

Scientific and Industrial Research, Osaka University, Yamadakami, Suita, Osaka 565, Japan

(Received in Japan 4 October 1975; received in UK for publication 4 November 1975)

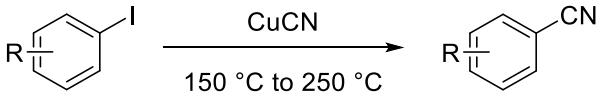
Stephans-Castro coupling of copper(I) arylacetylenes with iodoarenes[1] or iodoalkenes[2] is a useful reaction for the synthesis of acetylenes in laboratories, its scope being sometimes limited by the violent reaction conditions and by the difficulties in preparations of cuprous acetylides.

We now report that an acetylenic hydrogen can be easily substituted by iodoarenes, bromoalkenes or bromopyridines in the presence of a catalytic amount of bis(triphenylphosphine)palladium dichloride - cuprous iodide in diethylamine under a very mild condition. Very recently, Cassar[3] and Heck[4] reported independently the same substitution reaction catalyzed by similar catalysts. In our method, the reaction proceeds under a milder condition in the presence of a co-catalyst, cuprous iodide, and gives more satisfactory results for the direct synthesis of symmetrically disubstituted acetylenes from acetylene gas.

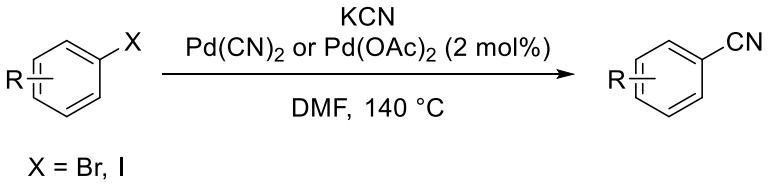
Sonogashira, K. *et al*. *Tetrahedron Lett*. **1975**, 16(50), 4467-4470

Cyanation of Aryl Halides

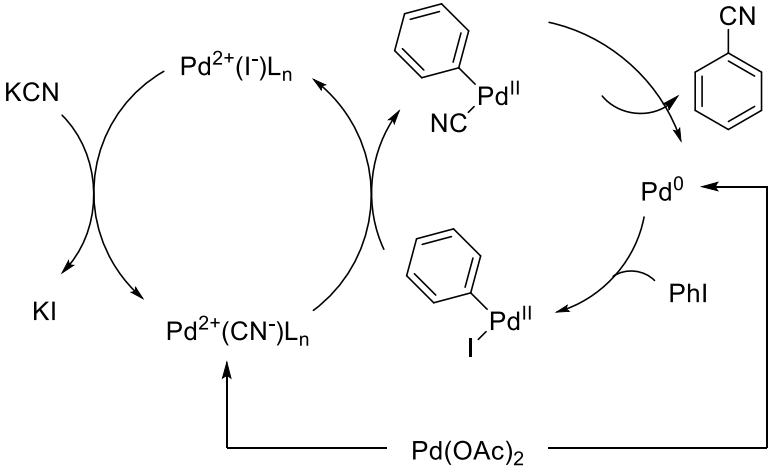
- began as a stoichiometric reaction
  - Rosenmund-von Braun reaction



- developed into a catalytic reaction
  - Pd-catalyzed cyanation, Takagi, 1973



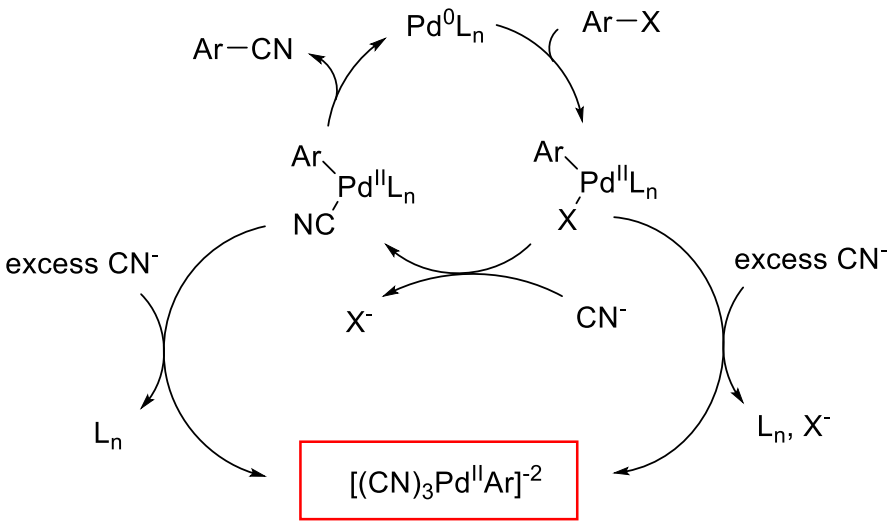
- proposed catalytic cycle
  - Pd plays two different roles in two different cycles
  - traditional OA - transmetallation - RE
  - cyanide shuttle



Beller, M. *et al*. *Chem. Soc. Rev*. **2011**, 40(10), 5049-5067
Takagi, K. *et al*. *Chem. Lett*. **1973**, 2(5), 471-474

Cyanation of Aryl Halides

- problems with Pd-only system:
  - cyanide ions deactivate the catalyst!
  - large concentrations of cyanide compete with transmetallation and reductive elimination to form inactive complexes
- solutions:
  - stoichiometric additives (reducing agents) which can reactivate the catalyst
  - use of stoichiometric copper or zinc cyanides (more covalent species) which reduce the concentration of free cyanide ion in solution



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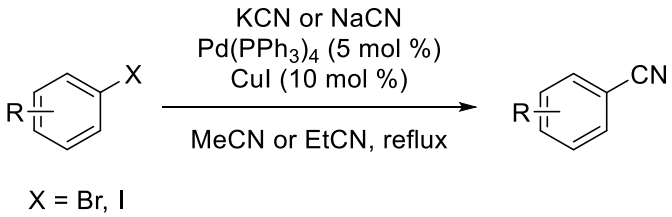
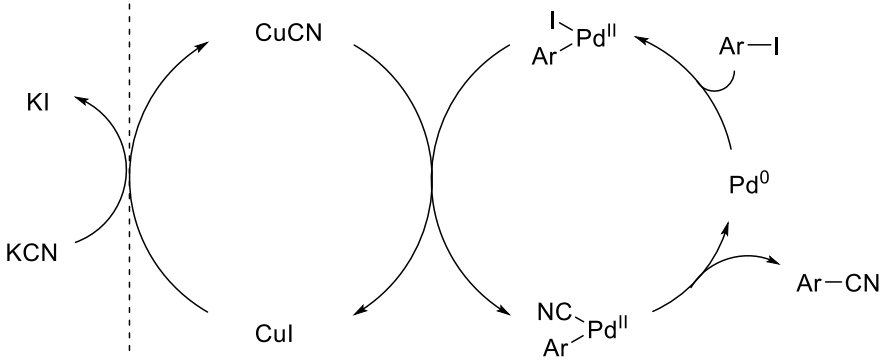
Cyanation of Aryl Halides

- Problem was solved most effectively by using a Pd- and Cu- synergistic system
  - Anderson, Eli Lilly, 1998



- Proposed cycle:
  - catalytic copper acts as a shuttle for sparingly soluble cyanide ion
  - prevents poisoning of Pd- coupling cycle



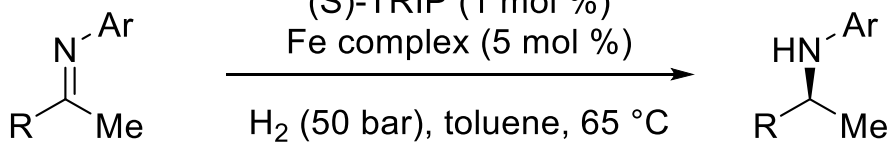
MacMillan, D. W. C. *et al*. *Chem. Sci*. **2012**, 3(3), 633-658
Anderson, B. A. *et al*. *J. Org. Chem*. **1998**, 63(23), 8224-8228

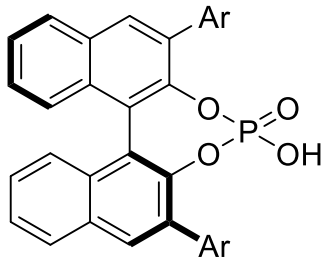
Synergistic Catalyst Systems

- General Classes:
- Metal-metal systems
- Metal-nonmetal systems
  - Enamine organocatalysis + metal catalysis
  - Other systems not involving enamines
- Photoredox organocatalysis

Case study 1

- iron hydrogenation catalyst + Brønsted phosphoric acid
  - Beller, 2011:

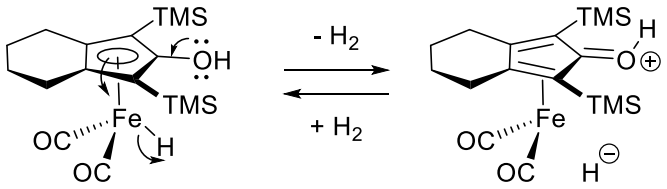


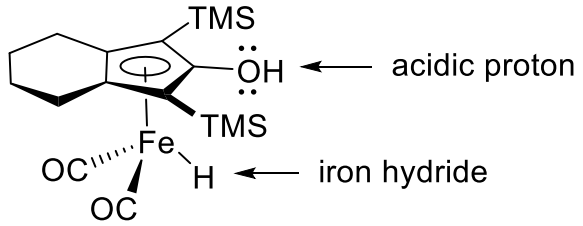


(S)-TRIP
Ar = 2,4,6-$iPr_3C_6H_2$

- 20 examples, 60-94% yield, er ≥ 83:17
- R = alkyl, aryl

- Mechanism of action of Knölker's complex:
  - Does not involve oxidation state change at Fe



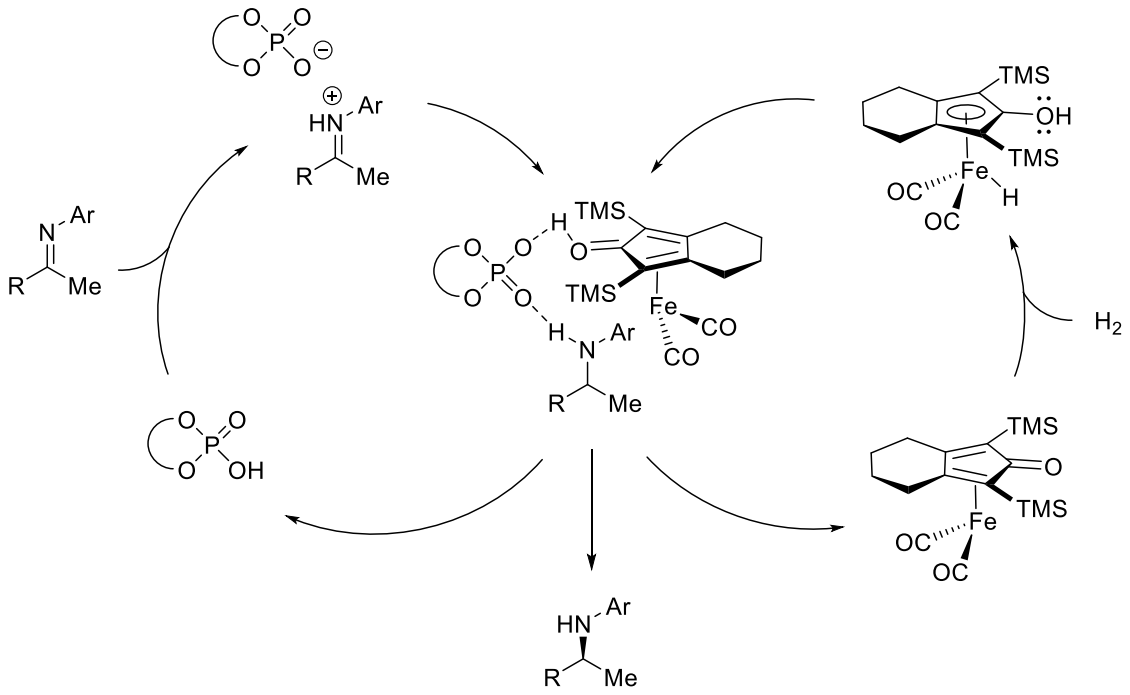


Knölker's complex

Beller, M. *et al*. *Angew. Chem. Int. Ed*. **2011**, 50(22), 5120-5124
MacMillan, D. W. C. *et al*. *Chem. Sci*. **2012**, 3(3), 633-658

Case Study 1

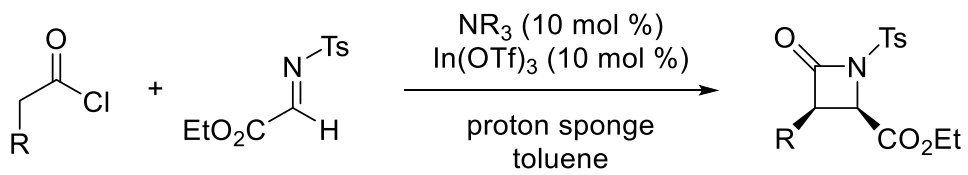
- iron hydrogenation catalyst + Brønsted phosphoric acid
  - proposed catalytic cycle:
    - protonation of imine generates chiral ion pair which is activated towards hydride delivery
    - proton transfer regenerates acid catalyst; Knölker's complex reactivated by H_2

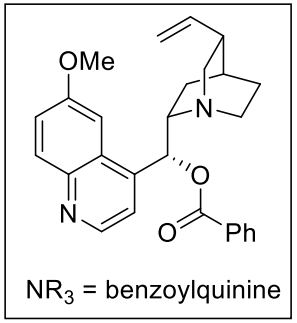


Beller, M. *et al*. *Angew. Chem. Int. Ed*. **2011**, 50(22), 5120-5124

Case Study 2

- Lewis acid metal catalysis + organic Lewis base catalysis
  - Lectka, 2002, hetero [2 + 2] cycloadditions
  - synthesis of β-lactams from acyl chlorides and N-tosyl imines



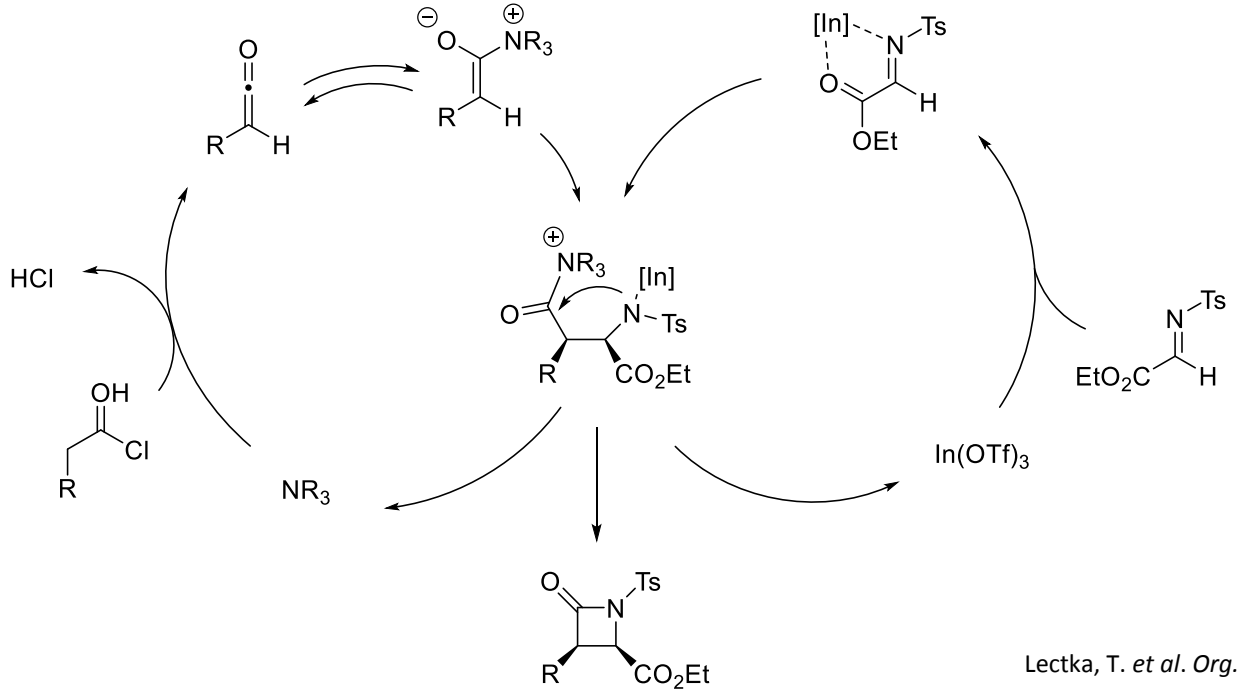


  - 6 examples, 92-98% yield, R = Ph, Bn, OPG
  - 9:1 dr, 96-98% ee

Lectka, T. *et al*. *Org. Lett*. **2002**, 4(9), 1603-1605

Case Study 2

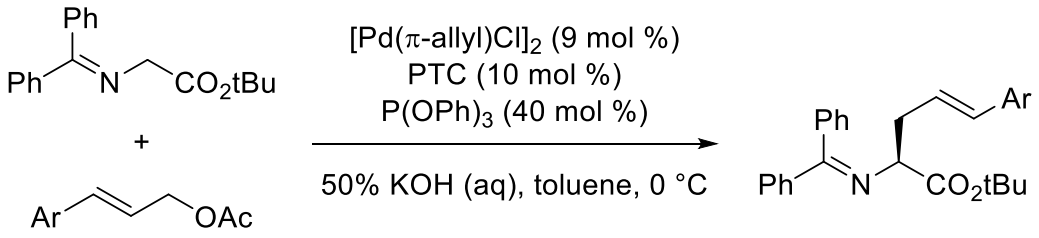
- Lewis acid metal catalysis + organic Lewis base catalysis
  - Lectka, 2002, hetero [2 + 2] cycloadditions
  - Proposed mechanism:
    - Lewis base facilitates elimination of HCl to form ketene, which is in equilibrium with zwitterionic species
    - enolate adds to N-tosyl imine which has been activated by LA
    - final ring closing step regenerates both catalysts

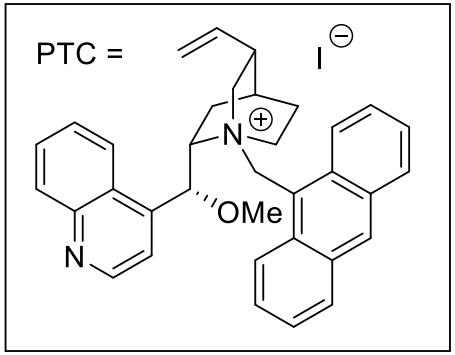


Lectka, T. *et al*. *Org. Lett*. **2002**, 4(9), 1603-1605

Case Study 3

- Pd Tsuji-Trost catalysis + chiral ammonium phase transfer catalysis
  - Takemoto, 2001, enantioselective Tsuji-Trost allylation of glycine-imine Schiff bases



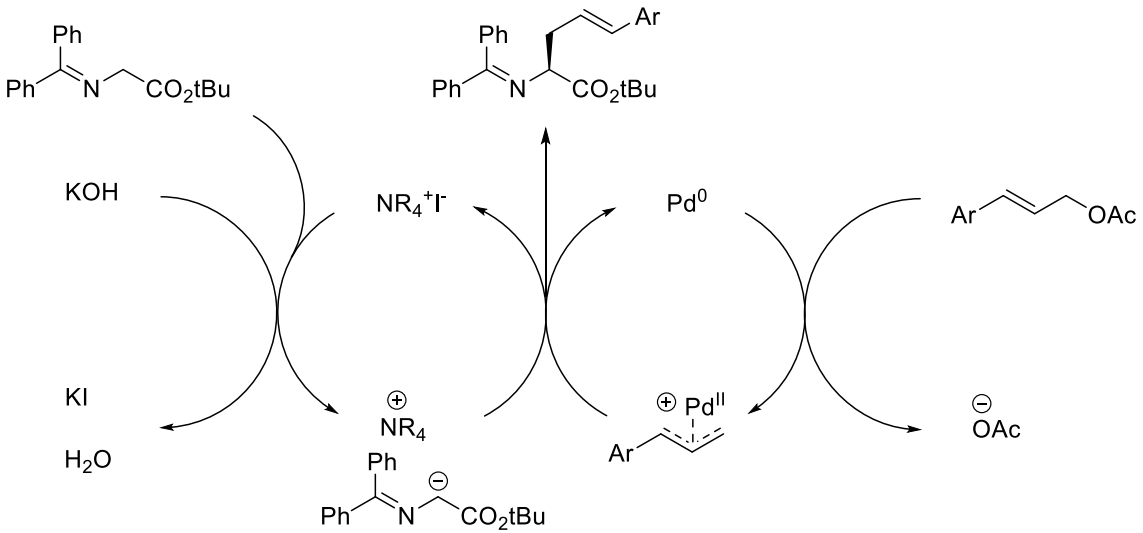


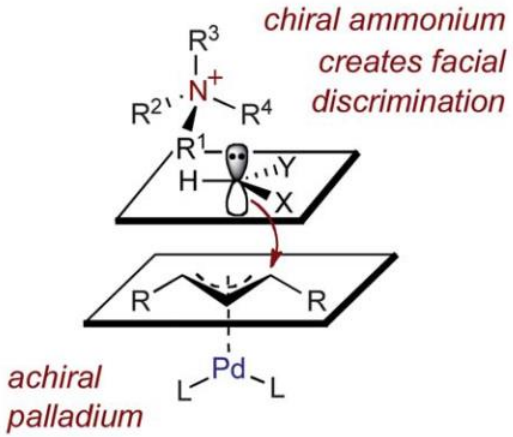
- 6 examples, 39-89% yield, er > 95:5
- Ar = electron rich, electron poor

Takemoto, Y. *et al*. *Org. Lett*. **2001**, 3(21), 3329-3331

Case Study 3

- Pd Tsuji-Trost catalysis + chiral ammonium phase transfer catalysis
  - Takemoto, 2001, enantioselective Tsuji-Trost allylation of glycine-imine Schiff bases
  - Proposed mechanism:
    - enolate forms chiral ion pair with ammonium PTC, which determines stereochemical course of allylation

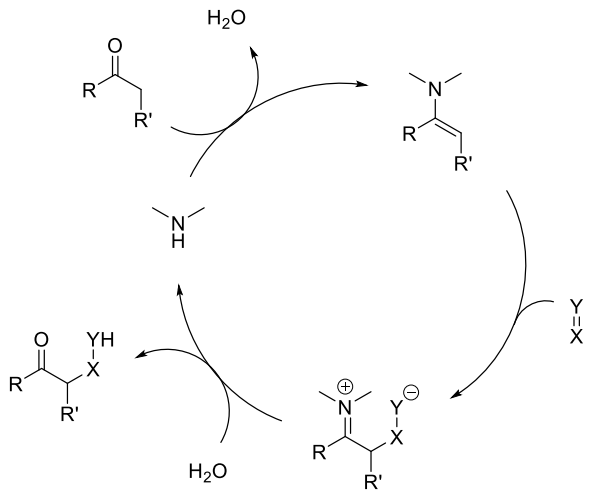




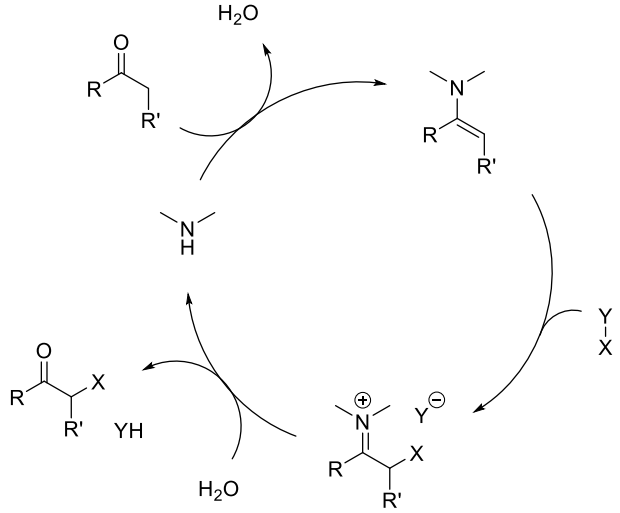
Lectka, T. *et al*. *Org. Lett*. **2002**, 4(9), 1603-1605
MacMillan, D. W. C. et al. *Chem. Sci*. **2012**, 3(3), 633-658

Enamine Organocatalysis

- General features
  - formation of enamine in situ from a catalytic amount of amine (activation of nucleophile)
  - attack on electrophile (addition or substitution)
  - hydrolysis of iminium ion to regenerate catalyst



nucleophilic addition
(e.g. aldol, Michael, Mannich)

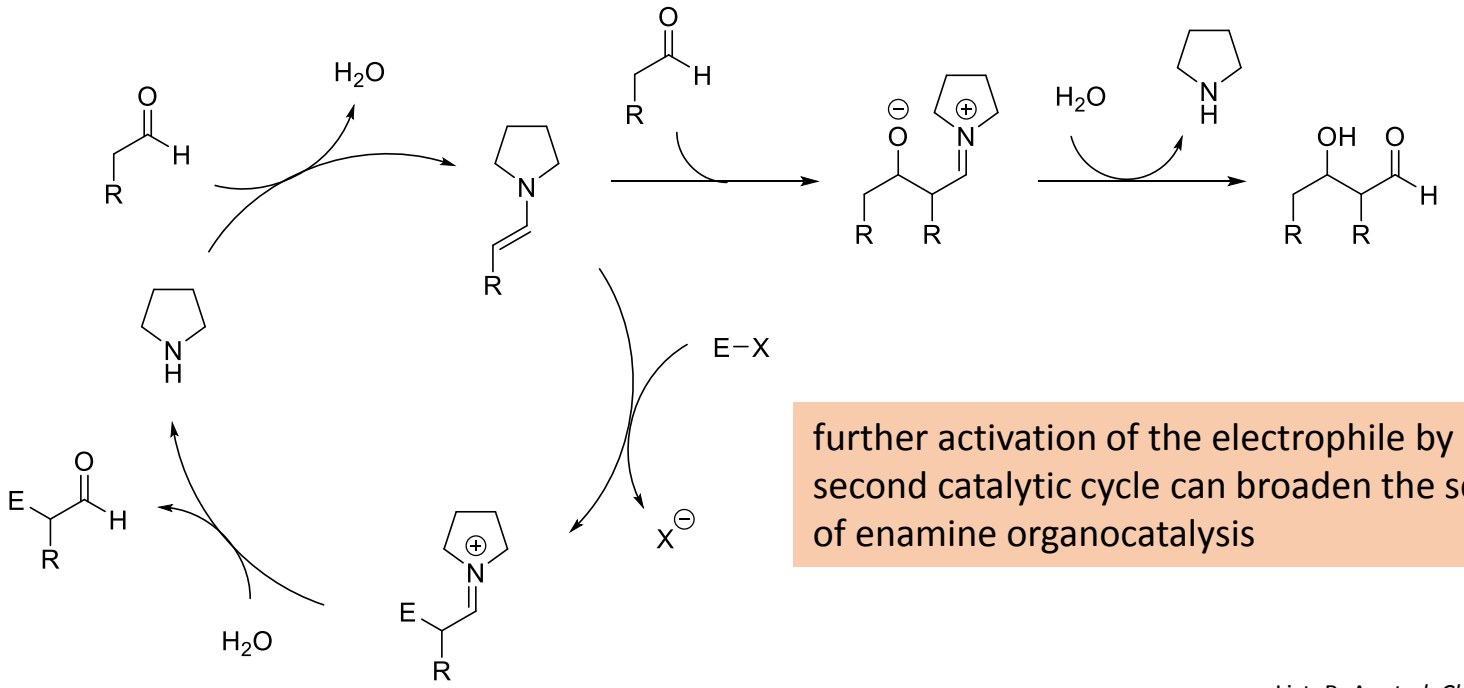


nucleophilic substitution
(e.g. fluorination with Selectfluor)

List, B. A. *et al. Chem. Rev*. **2007**, 107, 5471-5569

Enamine Organocatalysis

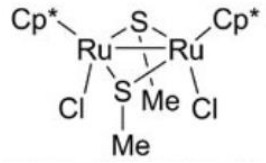
- Main problem:
  - Substrate scope is limited (carbonyls, imines, enals, electrophilic heteroatom sources)
  - Due to the fact that the initial carbonyl compound being activated by enamine catalysis is also a good electrophile
  - Leads to side-products, mainly self-aldol

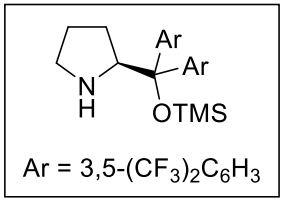


further activation of the electrophile by a second catalytic cycle can broaden the scope of enamine organocatalysis

List, B. A. *et al. Chem. Rev*. **2007**, 107, 5471-5569
MacMillian, D. W. C*. et al. Chem. Sci*. **2012**, 3(3), 633-658

Activation of propargyl alcohols



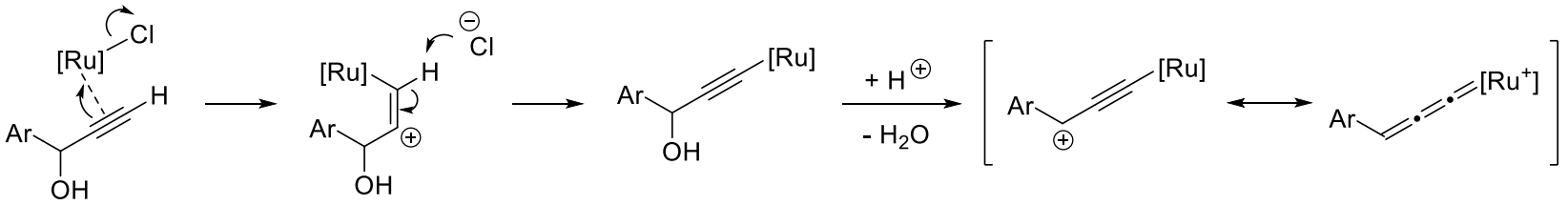


- α-propargylation of aldehydes
  - Nishibayashi, 2011

propargyl alcohol

- Ar = electron rich/poor
- R = alkyl, aryl
- 85-96% following $NaBH_4$ reduction
- modest dr (3.3:1) *syn*
- good er (most > 92:8)

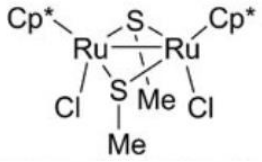
- mechanism involves formation of allenylidene complex from propargyl alcohol to generate the activated electrophile (ruthenium allenylidene)



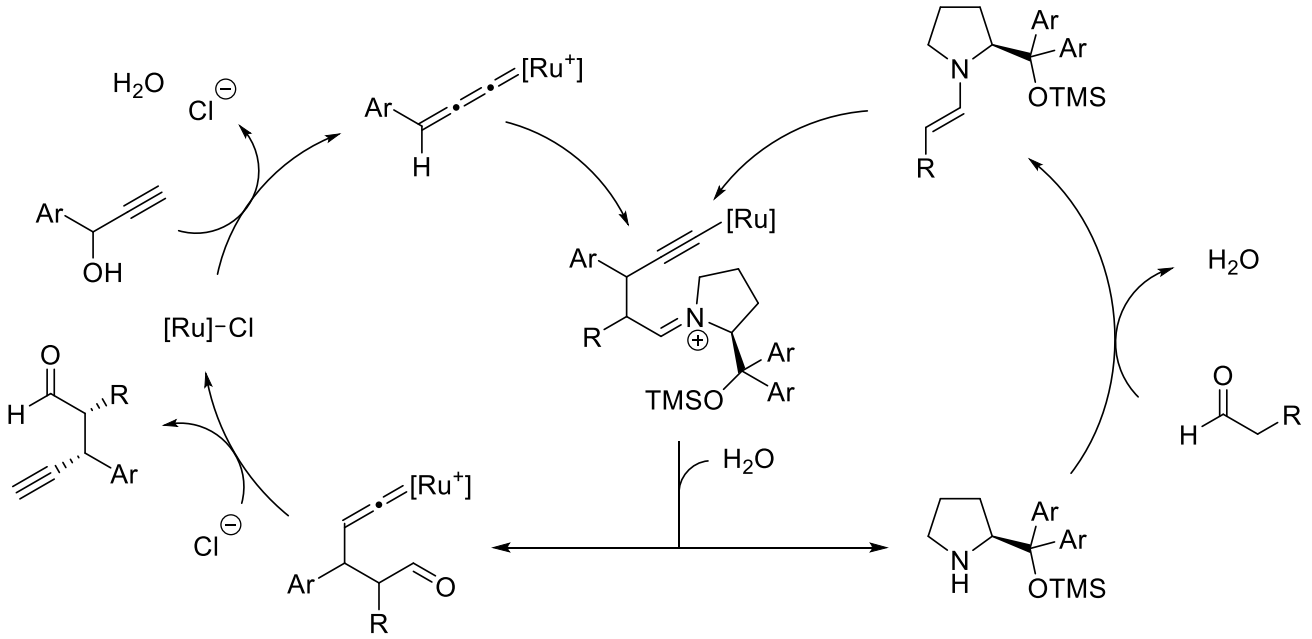
Nishibayashi, Y. *et al*. *Angew. Chem. Int. Ed*. **2010**, 49(40), 7289-7293

Activation of propargyl alcohols

- α-propargylation of aldehydes
  - proposed mechanism:
  - activated Ru-allenylidene is attacked by enamine
  - iminium hydrolysis followed by ligand displacement yields product



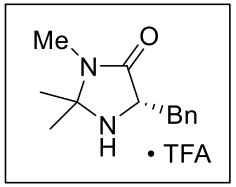
= [Ru]−Cl

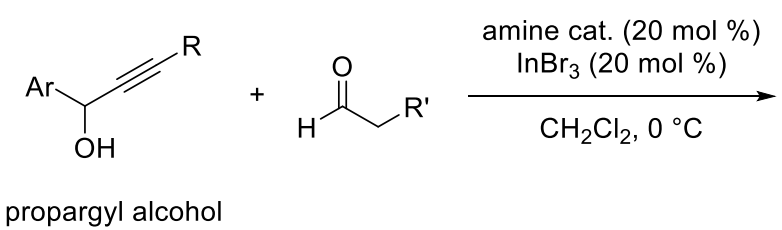


Nishibayashi, Y. *et al*. *Angew. Chem. Int. Ed*. **2010**, 49(40), 7289-7293

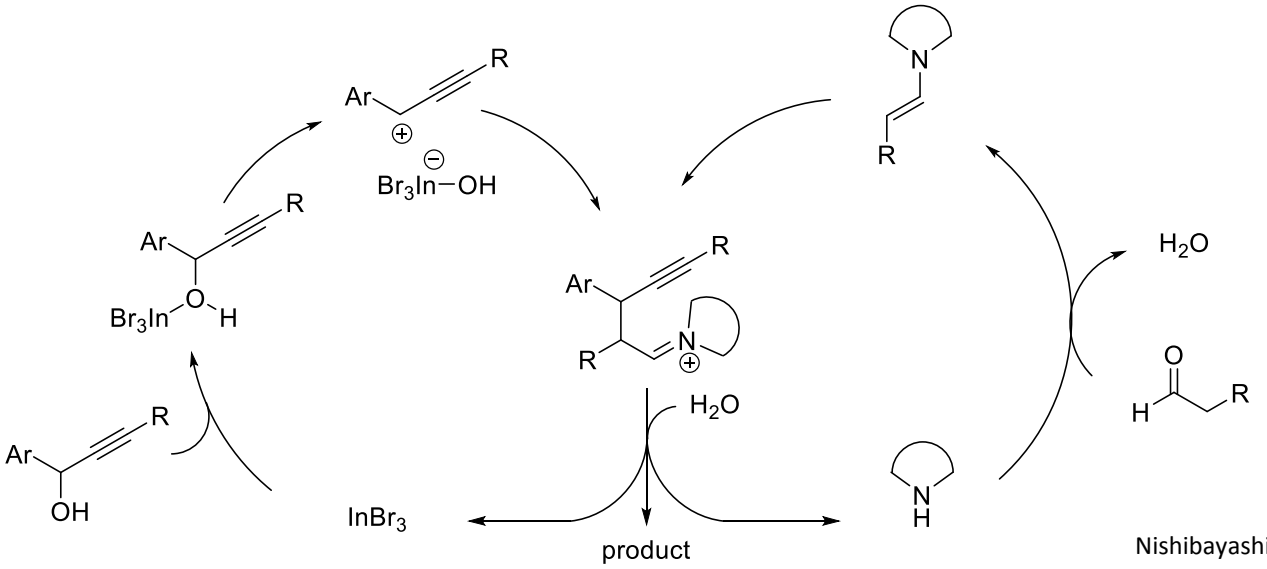
Activation of propargyl alcohols

- α-propargylation of aldehydes
  - internal alkynes are also accessible via synergistic catalysis
  - proceeds through a different mechanism requiring Lewis acid indium catalysis





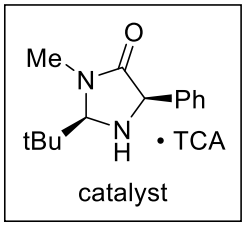
- R = benzyl, alkyl
- Ar = electron-rich
- 18-94% following $NaBH_4$ reduction
- er > 90:10

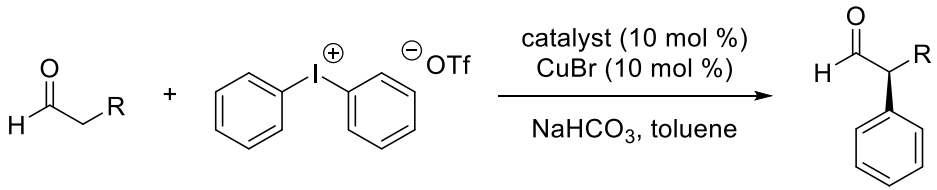


Nishibayashi, Y. *et al*. *Eur. J. Org. Chem*. **2011**, 12, 2239-2246

Activation of high-valent iodine electrophiles

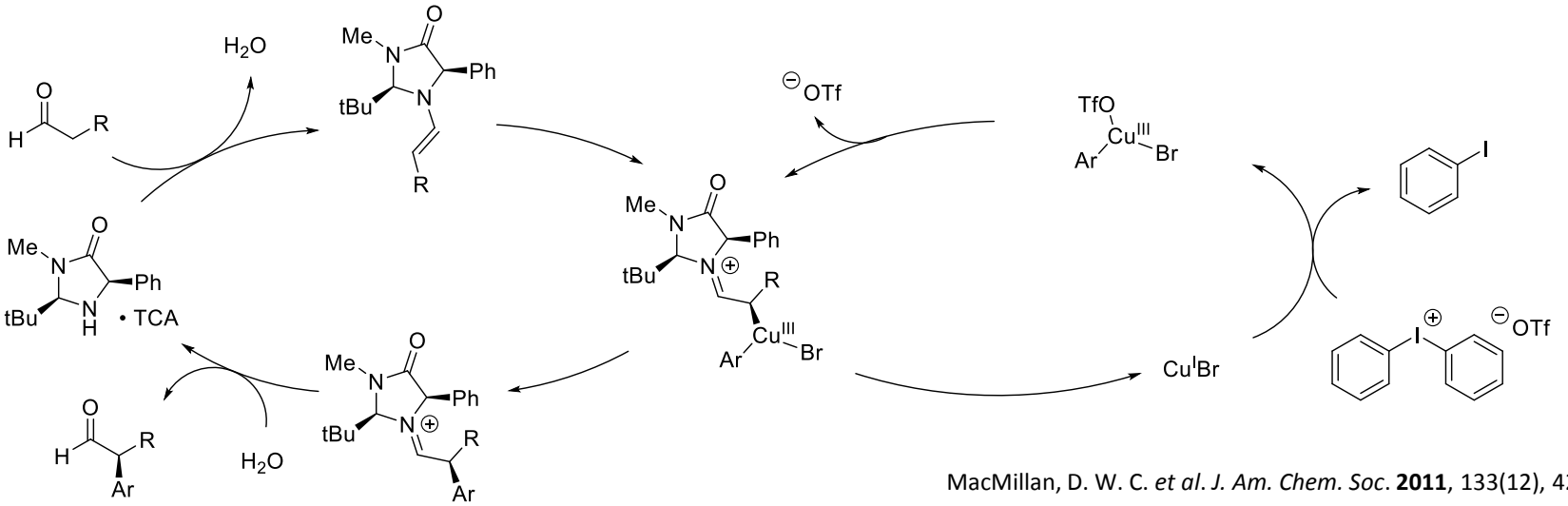
- α-arylation of aldehydes
  - MacMillan, 2011





- 67-95% yield, 22 examples
- ≥ 95:5 e.r. in all cases

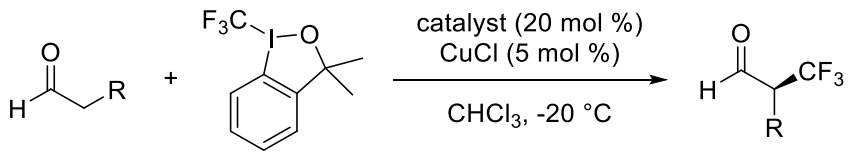
  - chiral amine generates nucleophilic enamine in one cycle
  - diaryliodonium salts oxidatively add to Cu in a second cycle



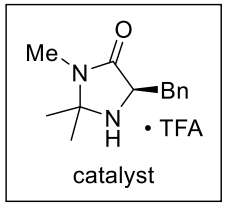
MacMillan, D. W. C. *et al*. *J. Am. Chem. Soc*. **2011**, 133(12), 4260-4263

Activation of high-valent iodine electrophiles

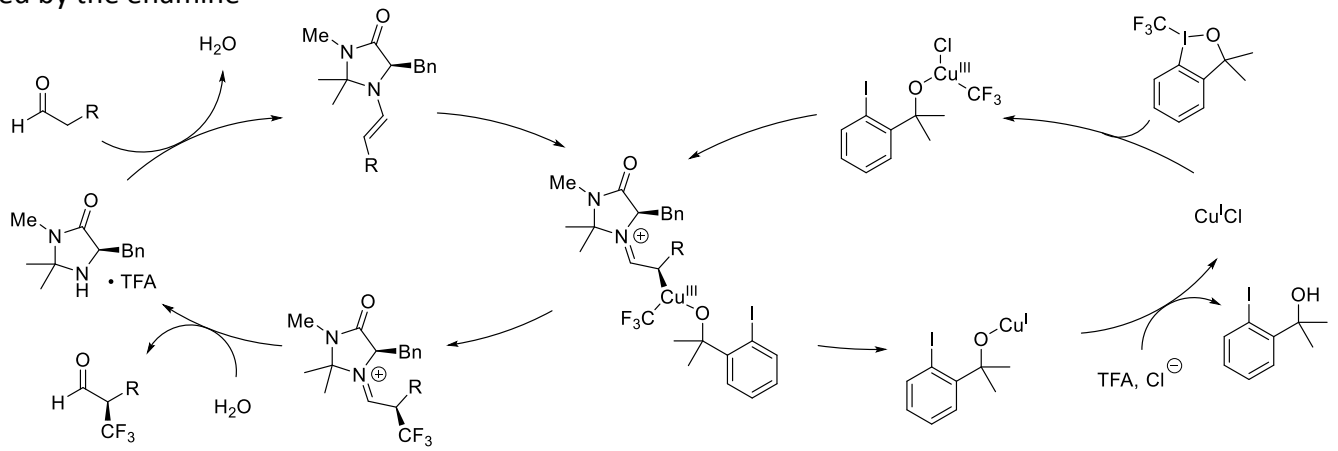
- enantioselective α-trifluoromethylation of aldehydes
  - MacMillan, 2010



- 12 examples, 70-87% yield
- ≥ 96:4 e.r.



  - in the absence of copper, the reaction proceeds with excellent e.r. (96:4) but low yield (14%)
  - original proposal suggested that Lewis acidic copper(I) coordinates oxygen of Togni's reagent, making iodine(III) more electrophilic
  - more likely, oxidative addition of Togni's reagent to copper(I) generates highly electrophilic copper(III) species which is attacked by the enamine



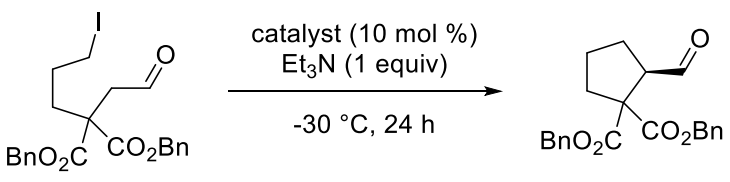
MacMillan, D. W. C. *et al*. *J. Am. Chem. Soc*. **2010**, 132(14), 4986-4987

Synergistic Catalyst Systems

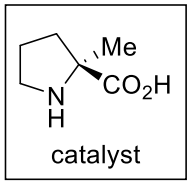
- General Classes:
- Metal-metal systems
- Metal-nonmetal systems
  - Enamine organocatalysis + metal catalysis
  - Other systems not involving enamines
- Photoredox organocatalysis

α-alkylation of aldehydes

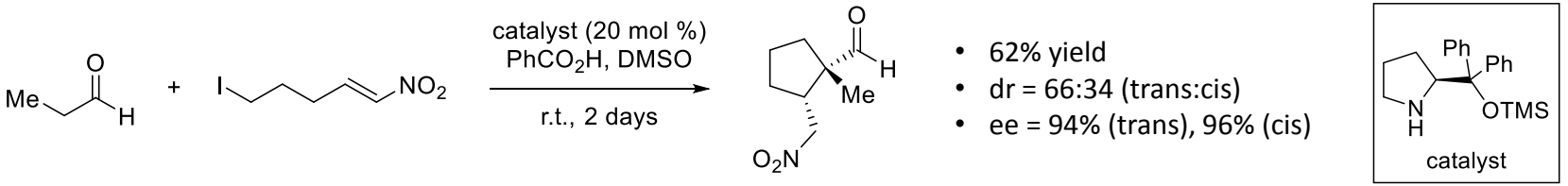
- Preamble: a difficult reaction!
  - List, 2004



- 94% yield, 97.5:2.5 e.r.



  - Enders, 2008

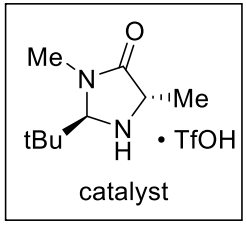


- 62% yield
- dr = 66:34 (trans:cis)
- ee = 94% (trans), 96% (cis)

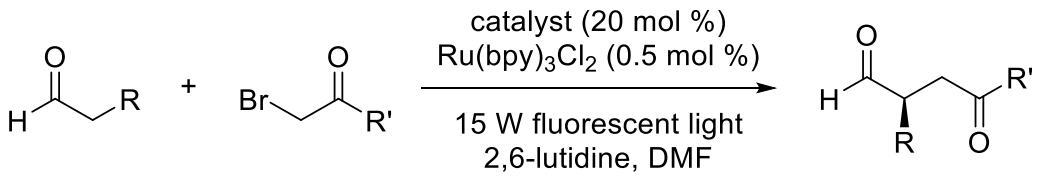
- substrate scope is severely limited
  - only intramolecular alkylations are possible under enamine organocatalysis
  - catalyst alkylation and self-aldol condensation products are typically observed in intermolecular alkylations

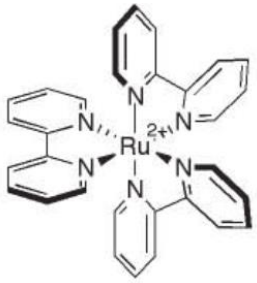
List, B. *et al*. *J. Am. Chem. Soc*. **2004**, 126(2), 450-451
Enders, D. *et al*. *Angew. Chem. Int. Ed*. **2008**, 47(39), 7539-7542

α-alkylation of aldehydes



- solved by synergistic catalysis
  - MacMillan and Nicewicz, 2008



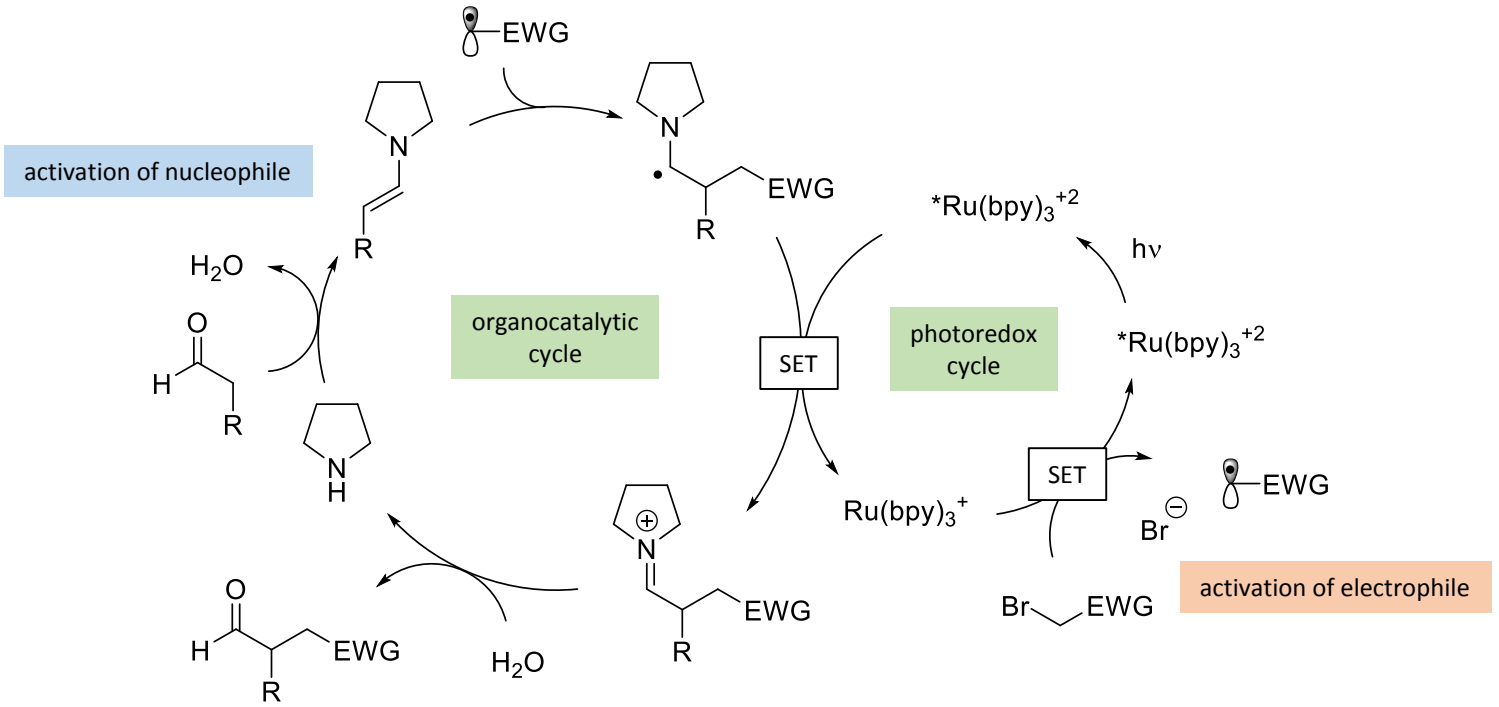


  - 12 examples, 63-93% yield, e.r. ≥ 95:5
  - employ a one-electron pathway rather than a two-electron pathway
  - activate electrophile by generating an electron-deficient radical via photocatalysis

Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, 322(5898), 77-80

Photoredox organocatalysis

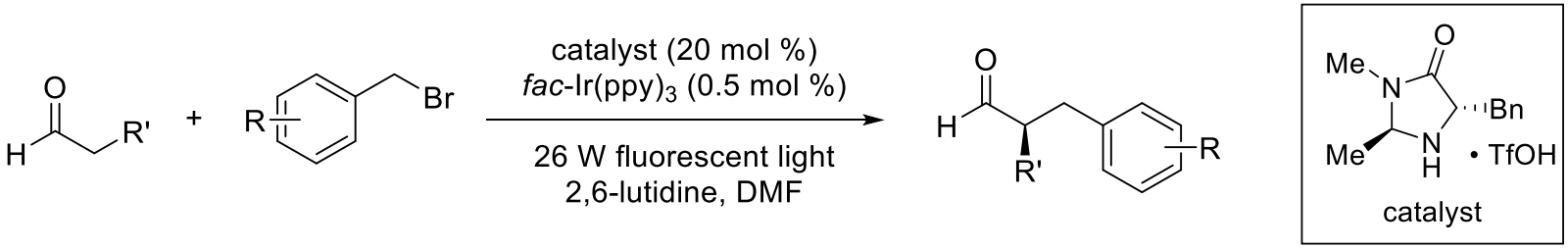
- proposed mechanism:
  - formation of electron-deficient radical by reductive cleavage of C-X bond
  - photoredox cycle serves two purposes: activation of the electrophile, and oxidation of the α-amino radical to the iminium ion in the organocatalytic cycle



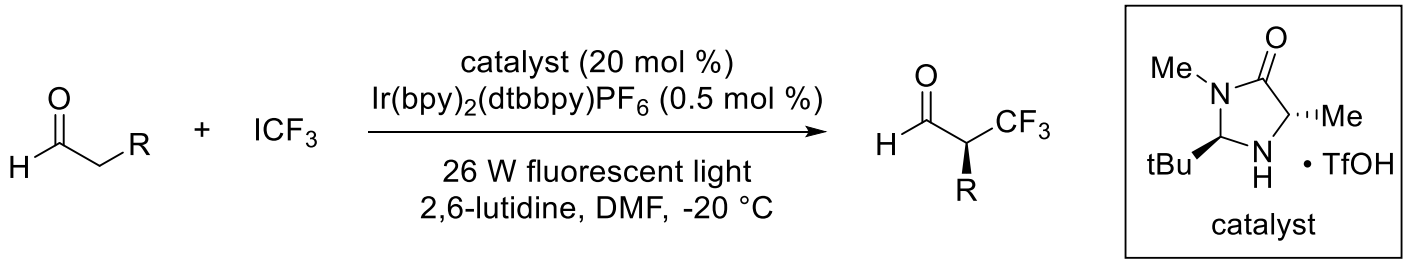
Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, 322(5898), 77-80

Photoredox-viable substrates

- Any species which can generate an electron-deficient radical can serve as the electrophilic reaction partner
  - alpha-benzylation (via benzyl radical)



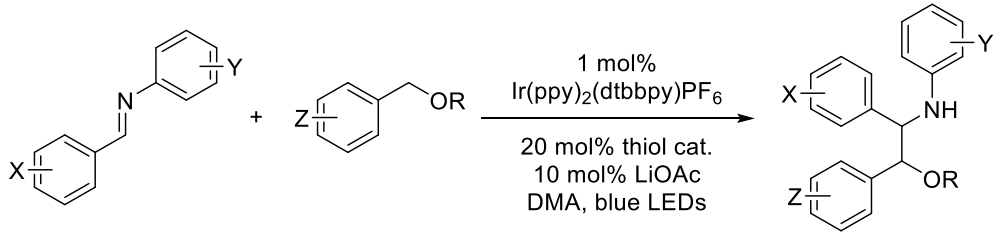
  - alpha-trifluoromethylation (via trifluoromethyl radical)



MacMillan, D. W. C. *et al*. *J. Am. Chem. Soc.* **2009**, 131(31), 10875-10877
MacMillan, D. W. C. et al. *J. Am. Chem. Soc*. **2010**, 132(39), 13600-13603

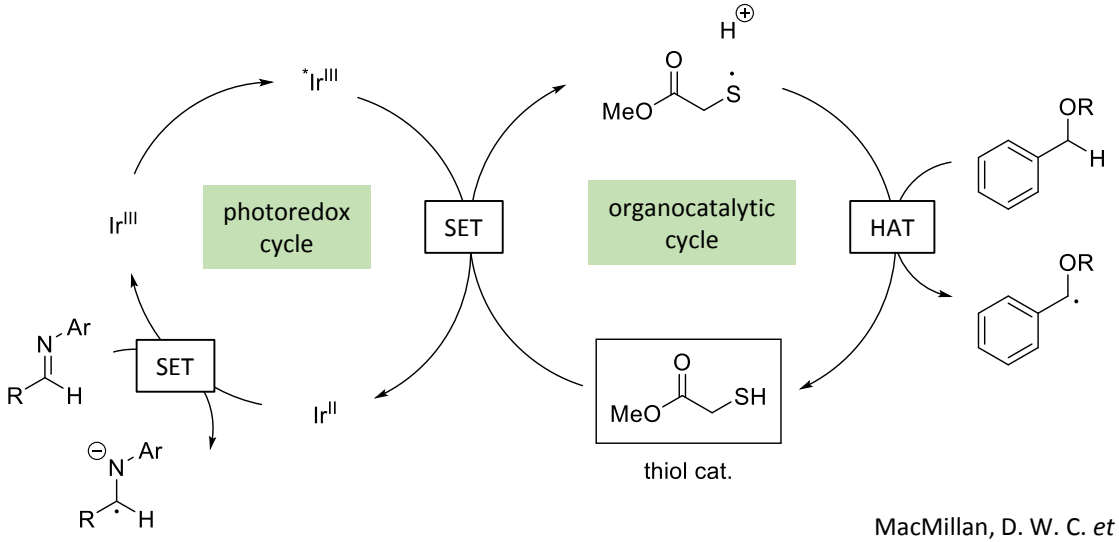
Photoredox with other organocatalysts

- Synthesis of β-amino alcohols from imines and benzyl ethers
  - MacMillan, 2014



- 28 examples
- 45-85% yield
- R = Me, Bn, TBS
- X,Y = EDG, EWG
- Z = EDG

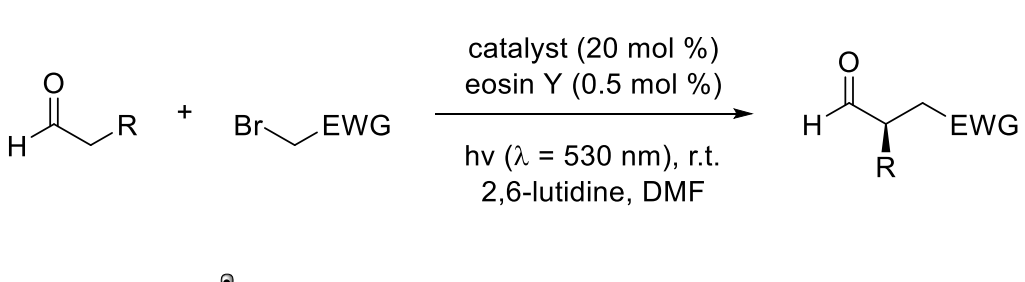
  - Proposed mechanism involves the generation of a thiyl radical by SET oxidative cleavage
  - Hydrogen atom transfer (HAT) between thiyl radical and benzyl alcohol generates reactive species

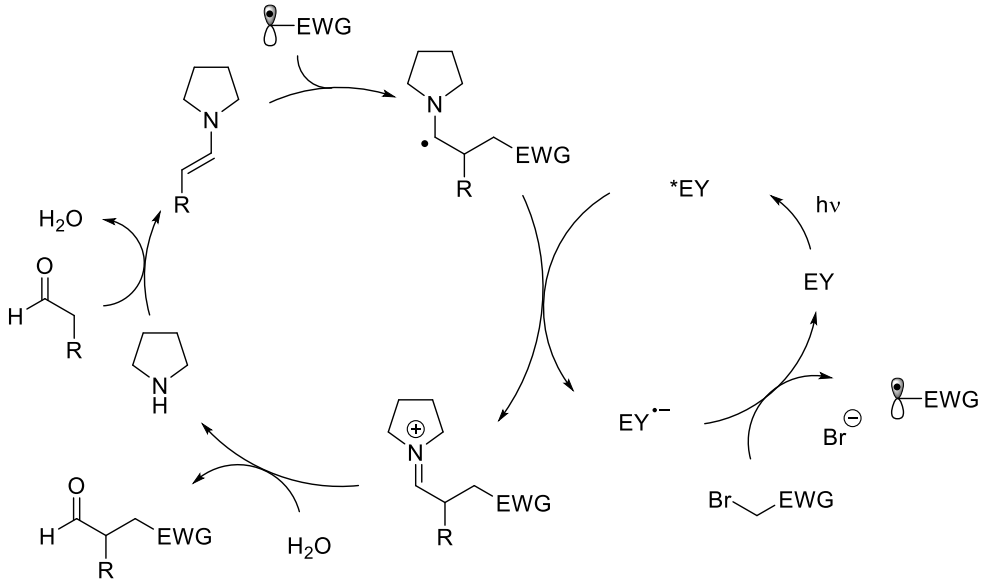


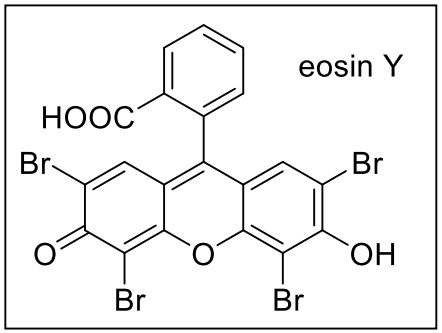
MacMillan, D. W. C. *et al*. *J. Am. Chem. Soc.*, **2014**, 136(49), 16986-16989

Metal-free photoredox

- organic dyes (eosin Y) can be used in place of Ir and Ru catalysts
  - Zeitler, 2011, α-alkylation of aldehydes



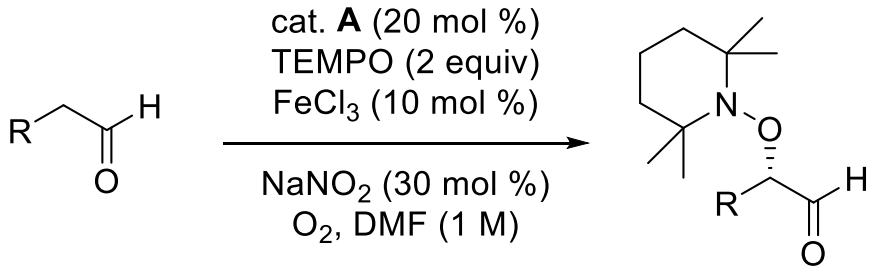




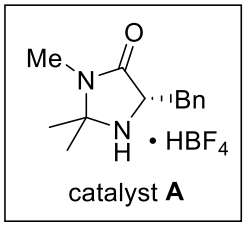
Zeitler, K. *et al*. *Angew. Chem. Int. Ed*. **2011**, 50(4), 951-954

Group Problem

- Sibi (in 2007) reported the following α-oxyamination reaction:



- R = alkyl, aryl, heteroaryl

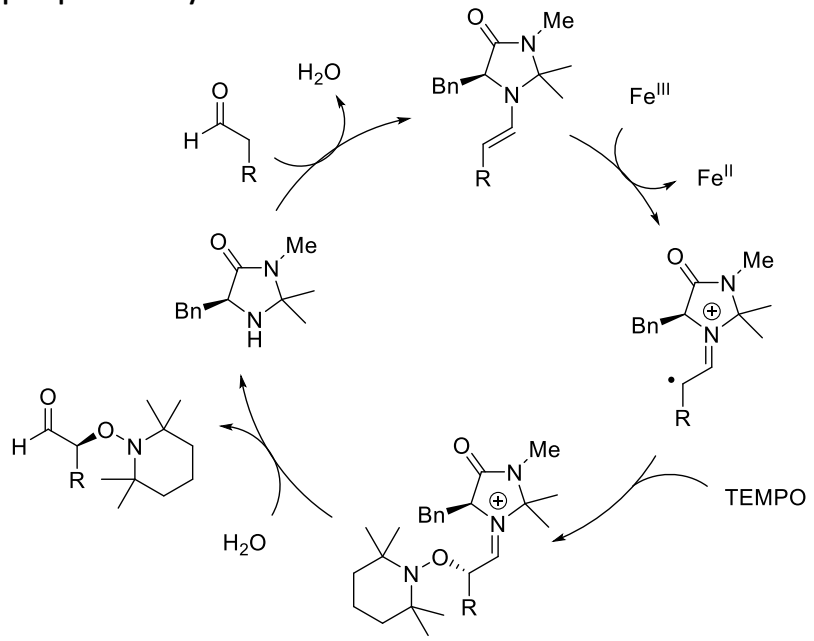


- Propose two mechanisms (catalytic cycles), one which invokes synergistic catalysis and one which does not
- Propose an experiment which would distinguish between the two mechanisms

Sibi, M. P. *et al*. *J. Am. Chem. Soc*. **2007**, 129(14), 4124-4125

Group Problem -- Solution

- Original mechanism proposed by Sibi:

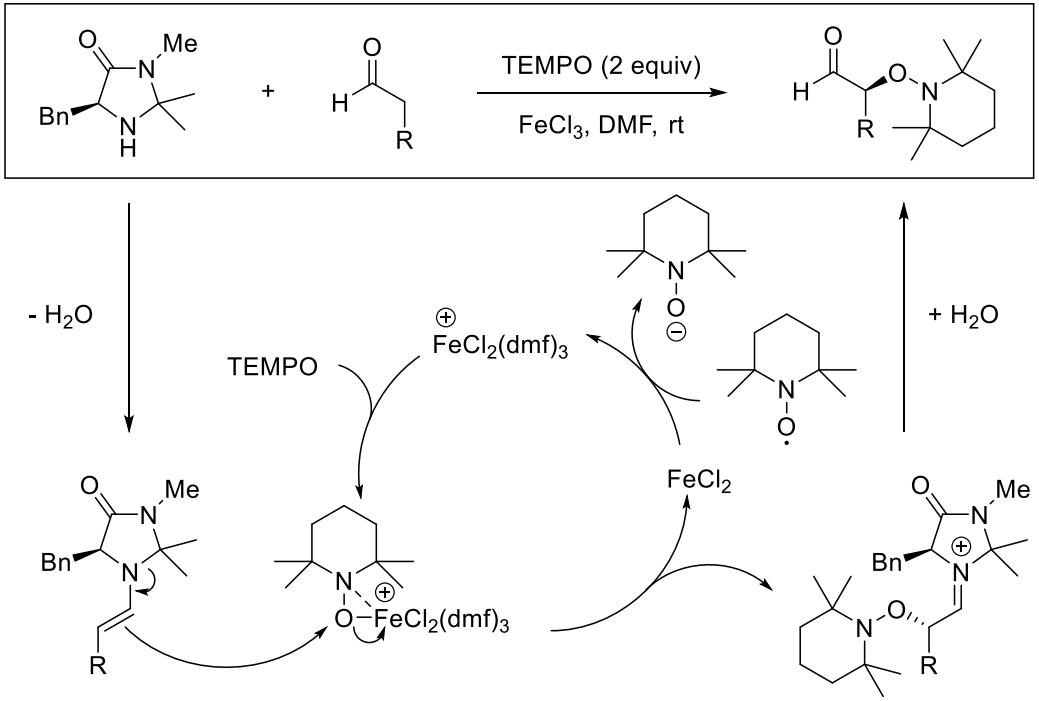


- function of iron is a SET oxidizing agent to form the iminium α-radical, which then combines with TEMPO to form the product
- iron is not activating TEMPO (not synergistic)

Sibi, M. P. *et al*. *J. Am. Chem. Soc*. **2007**, 129(14), 4124-4125

Group Problem -- Solution

- Revised mechanism proposed by MacMillan:

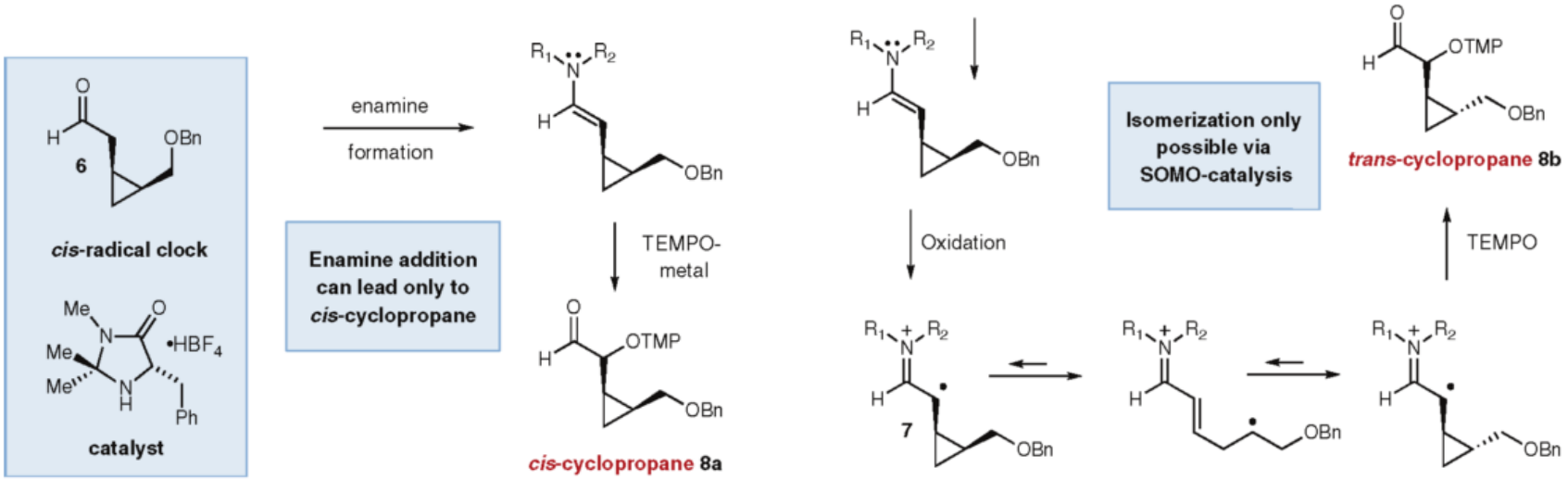


- iron acts as a Lewis acid to coordinate TEMPO, activating it towards a 2 electron nucleophilic attack (synergistic catalysis)

MacMillan, D. W. C. *et al*. *J. Am. Chem. Soc*. **2010**, 132(29), 10012-10014

Group Problem -- Solution

- Radical clock experiment:

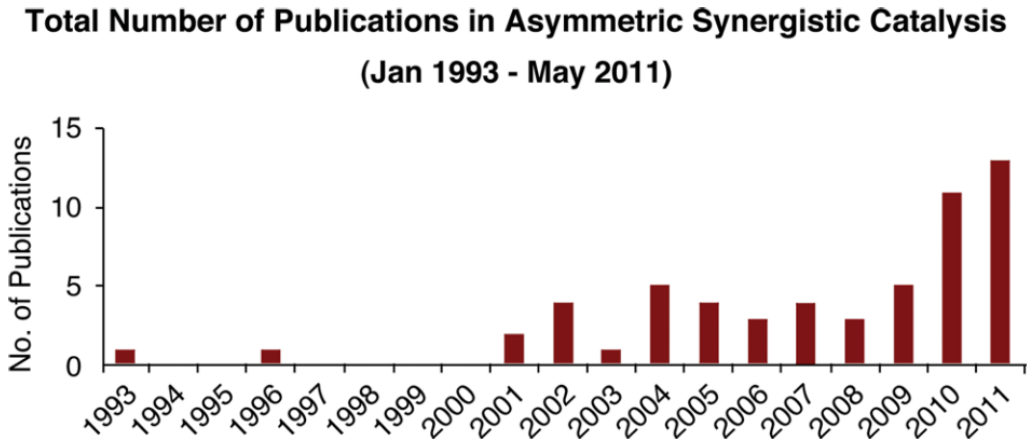


- *cis*-cyclopropane **8a** was the only product observed

MacMillan, D. W. C. *et al*. *J. Am. Chem. Soc*. **2010**, 132(29), 10012-10014

Concluding Remarks

- Synergistic catalysis, the combination of two distinct catalyst systems for simultaneous activation of the nucleophile and electrophile, can be used to enhance reactivity
- Still a growing field



- Regardless of what it's called, synergistic catalysis is a useful strategy for organic chemists

MacMillan, D. W. C. *et al*. *Chem. Sci*. **2012**, 3(3), 633-658

Key Reference

- Review:
  - MacMillan, D. W. C. *et al*. *Chem. Sci*. **2012**, 3(3), 633-658

- All other references are cited on the slides in which they appear