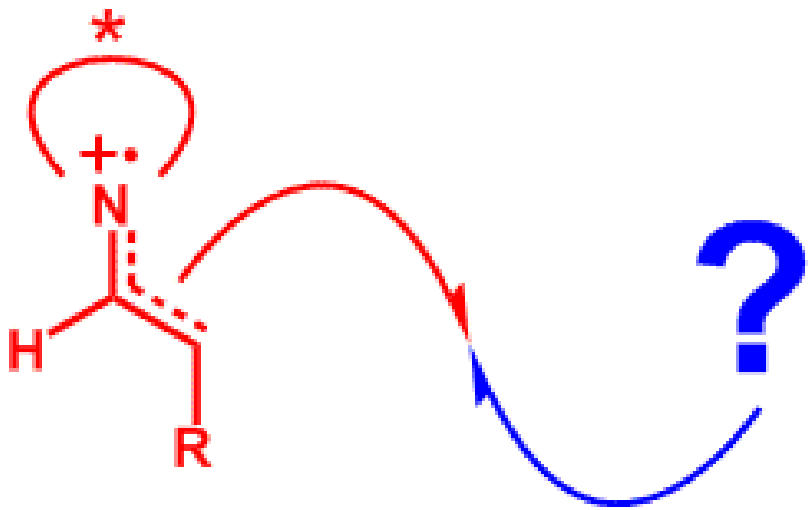
Singly Occupied Molecular Orbital Organocatalysis



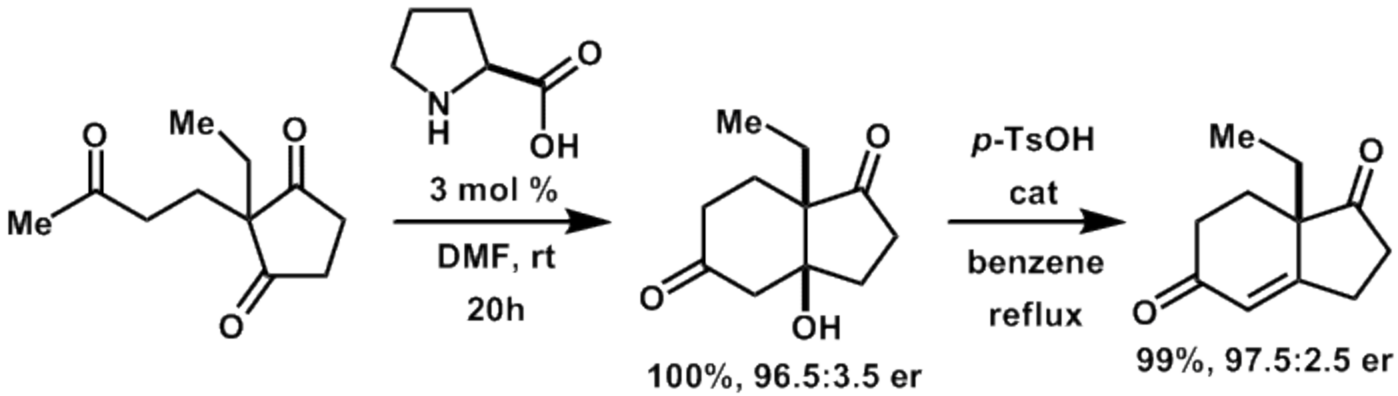
Nathan Werner

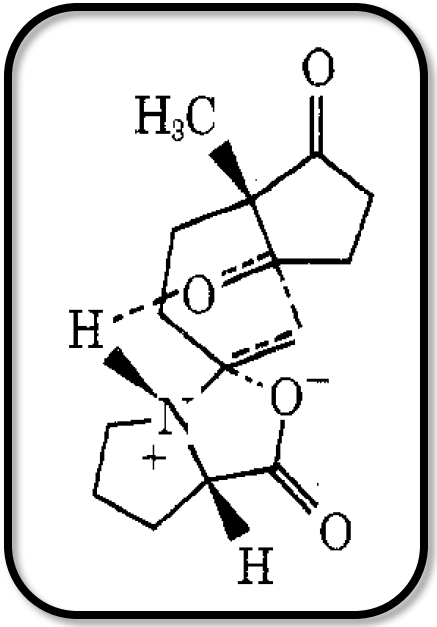
Denmark Group Meeting

February 10th, 2009

Overlooked Potential

- The use of small organic molecules to catalyze asymmetric transformations has been known since the early 1970's (e.g. the Hajos-Parrish-Eder-Sauer-Wiechert Reaction)





- However, the recognition of this reaction's mechanism as a general mode of carbonyl activation was overlooked

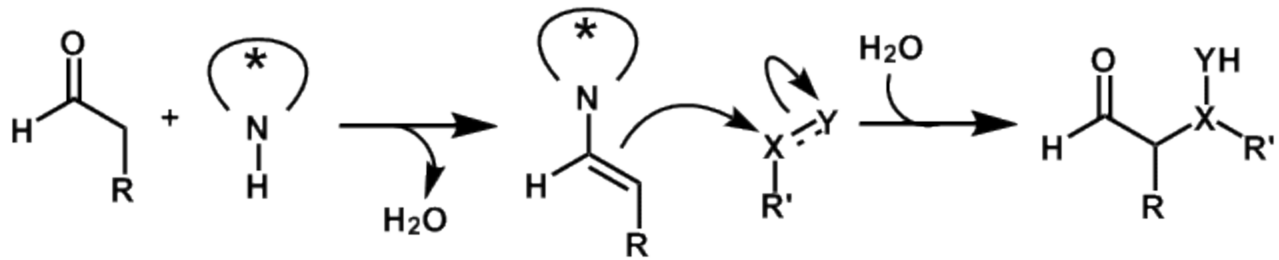
Hajos, Z. G. ; Parrish, D. R. *German patent DE 2102623* **1971**
Eder, U.; Sauer, G. R.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496-497
Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974,** *39*, 1615-1621

The Advent of Modern Organocatalysis

- In 2000, general modes of activation using small organic molecules (secondary amines) were introduced, namely enamine and iminium ion catalysis

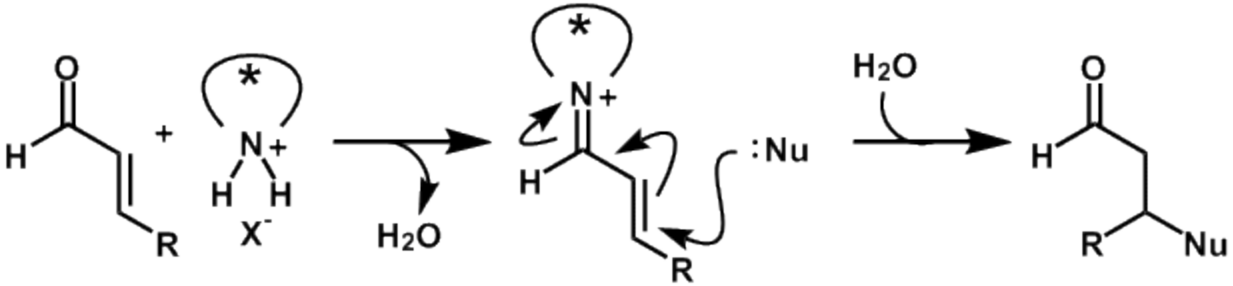
Enamine Catalysis

Activation Mode



HOMO activation
(25 new reactions)

Iminium Catalysis



LUMO activation
(50 new reactions)

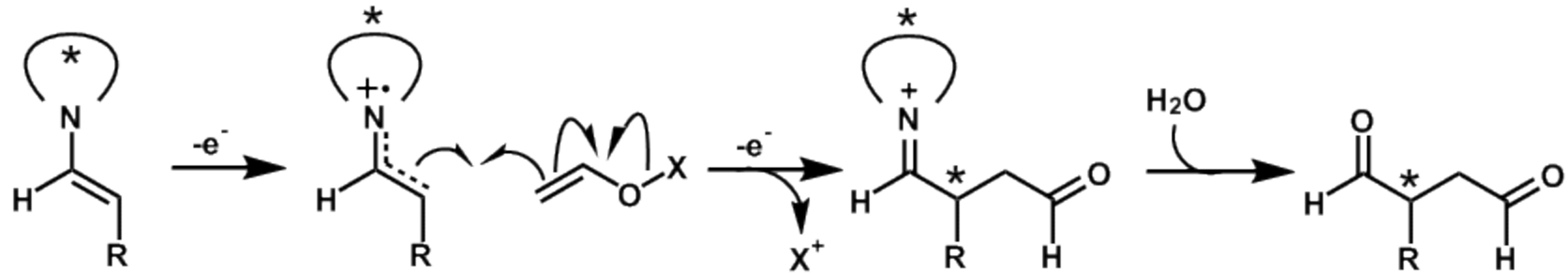
Limited to addition reactions by way of two electron transfers

MacMillan, D. W. C. *Nature* **2008**, *455*, 304-308

SOMO Catalysis

•Recently, catalysis based on single-electron oxidation of transiently produced, electron-rich enamines has introduced a new mode of activation termed SOMO organocatalysis

Singly Occupied Molecular Orbital Catalysis



Activation Mode

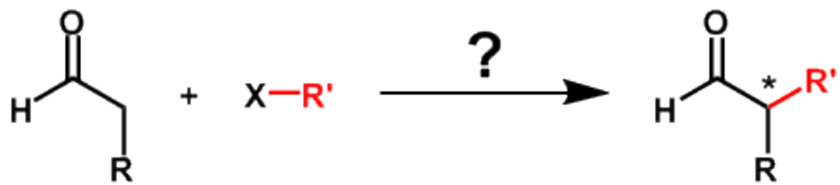
SOMO activation (6 new reactions)

•Activation by this method allows for reaction with a variety of weakly nucleophilic substrates incompatible with previous methods

MacMillan, D. W. C. *Nature* **2008**, *455*, 304-308

Impact: Solving the Unsolved

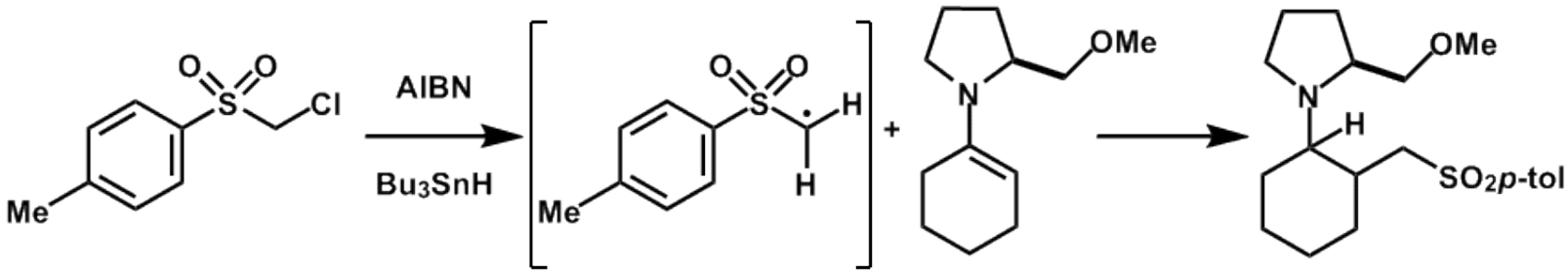
- The asymmetric α-alkylation of simple aldehydes has long been an unsolved problem in organic synthesis



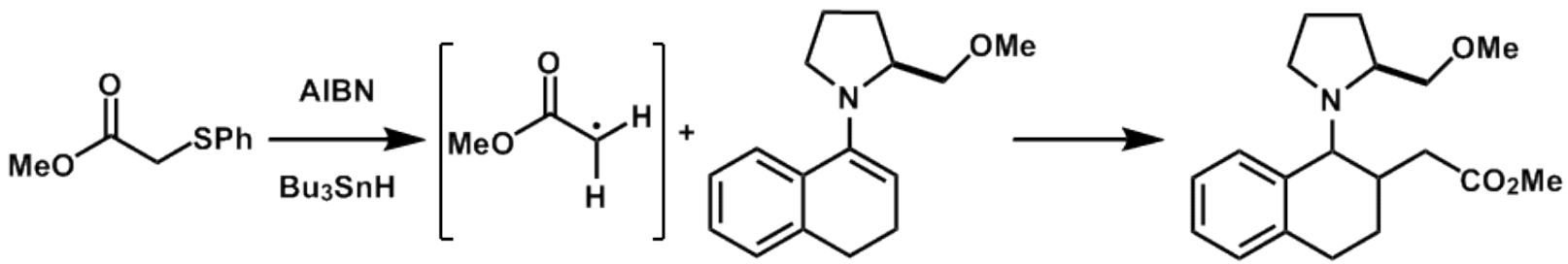
- Fundamental Problems
  - *N*-(enamine), *O*-(enolate) alkylation
  - Multiple alkylations
  - Self-condensation
  - Cannizzaro reaction
  - Tishchenko reaction
- Problems with asymmetric versions:
  - Chiral auxiliaries
  - Stoichiometrically preformed metalloenolates

For a notable exception:
Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450

Early Asymmetric Radical α-Alkylations



78%, 95:5 *cis/trans*
cis (1:1 *Re/Si*)



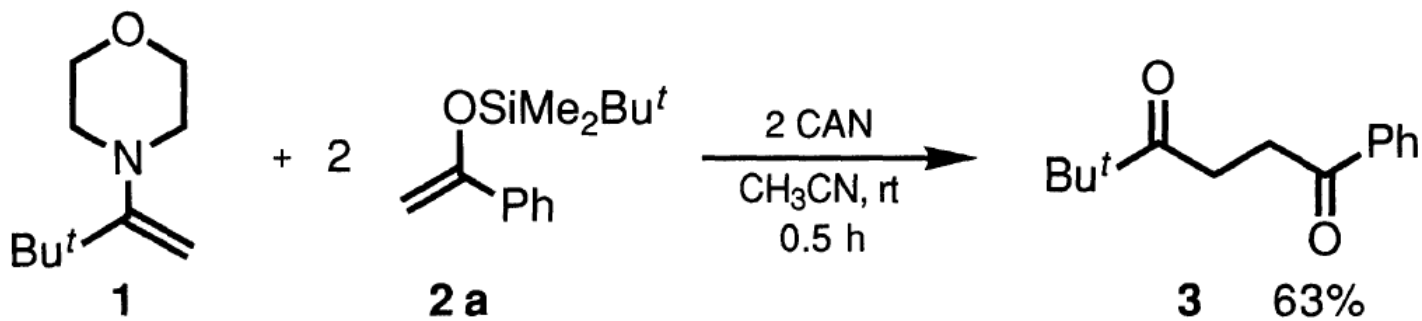
69%, 70:30 *cis/trans*
cis (89:11 *Re/Si*)

Group Question:

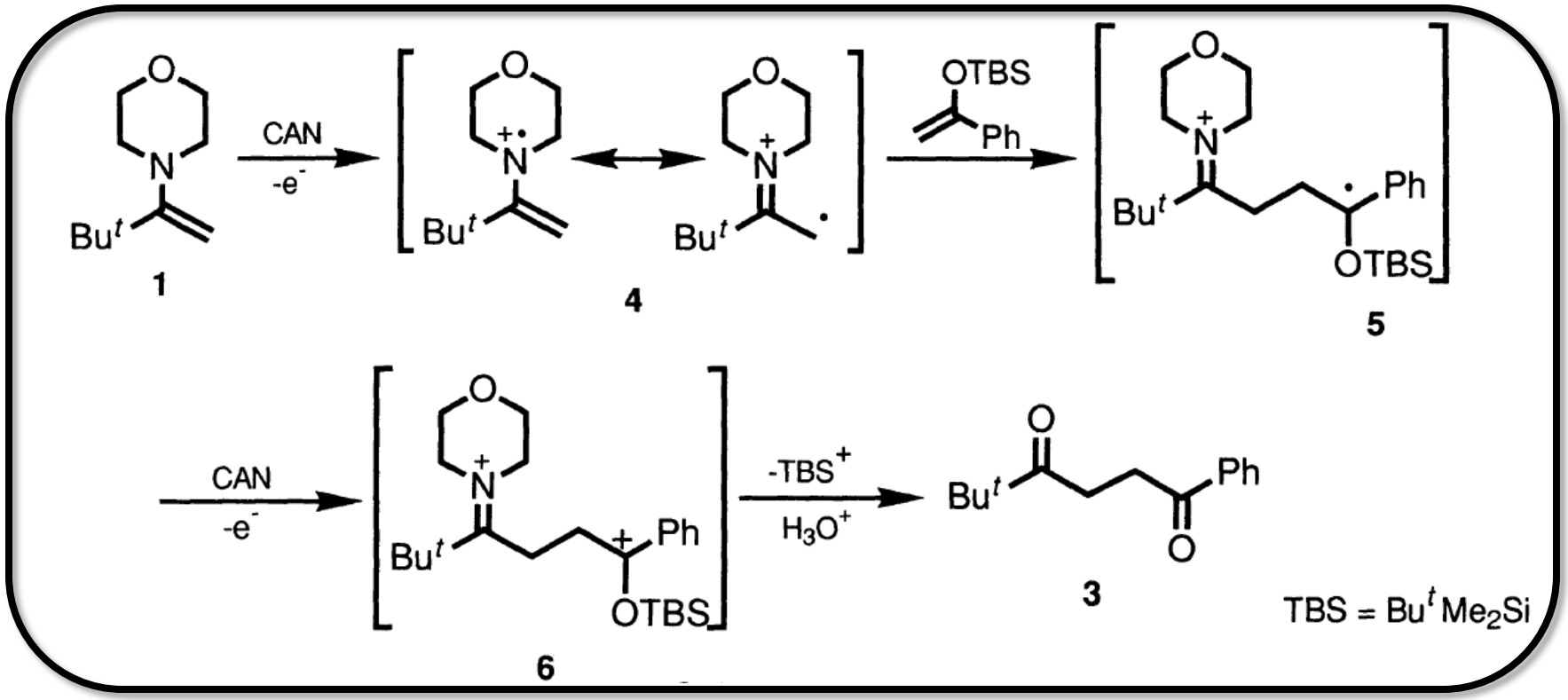
1. Propose stereochemical rational for the observed results
2. Use this rational to design an amine substituent to improve asymmetric control

Philippe, R. and Schubert, S. *Synlett* **1990**, 624-626

Stoichiometric Enamine SOMO α-Enolation



CAN = $(NH_4)_2Ce(NO_3)_6$

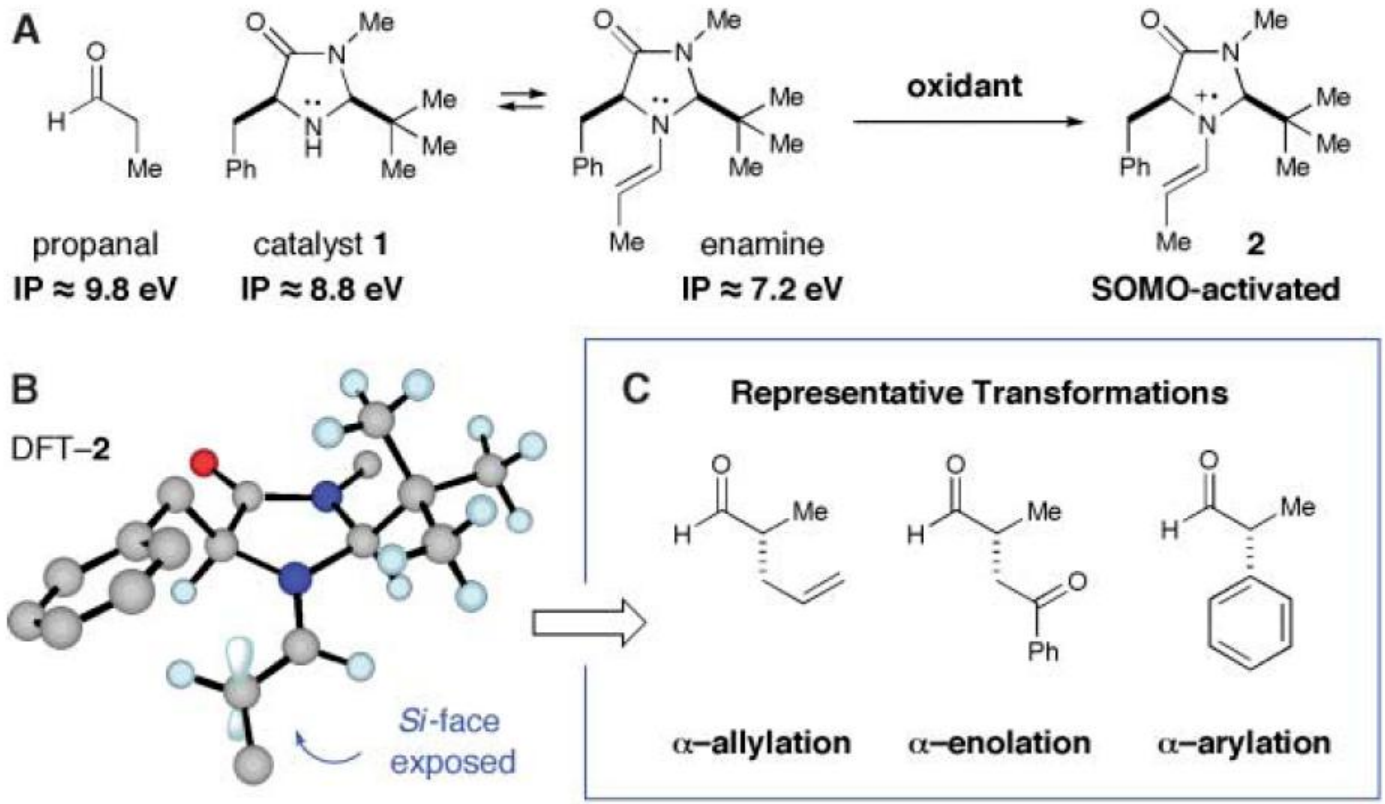


Narasaka, K. et al. *Chem. Lett.* **1992**, 2099-2102

Mechanistic Considerations

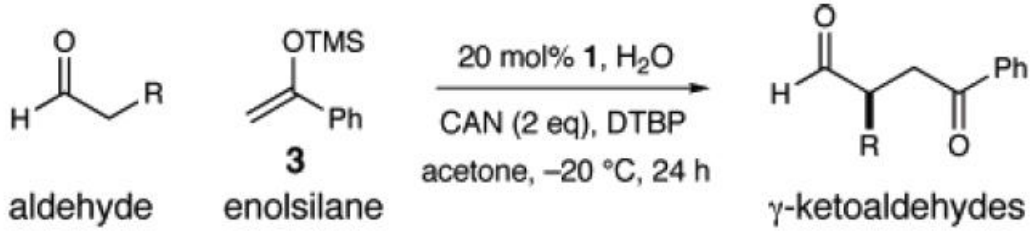
For Successful SOMO Organocatalysis:

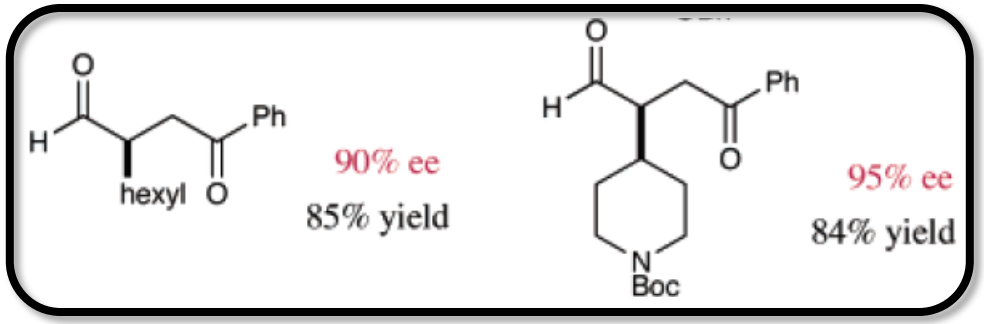
A. An equilibrium population of enamine must undergo preferential oxidation
B. The amine catalyst must generically enforce high levels of enantiocontrol in the coupling of the radical cation with nucleophiles
C. General reactivity mode useful in other enantioselective reaction

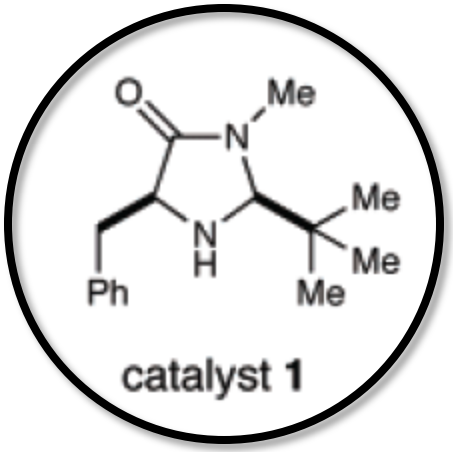


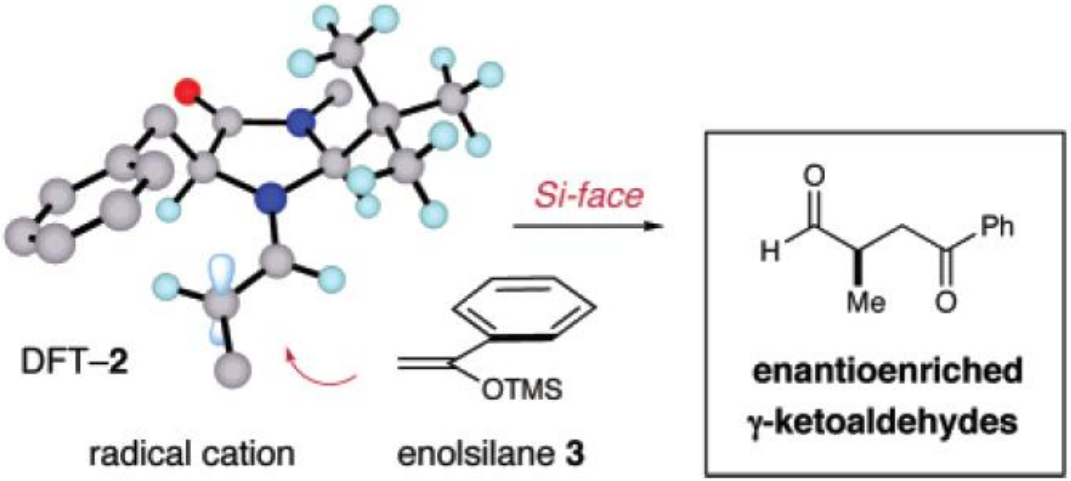
MacMillan, D. W. C.; et al. *Science* **2007**, 316, 582-585

Organocatalytic SOMO α-Enolation



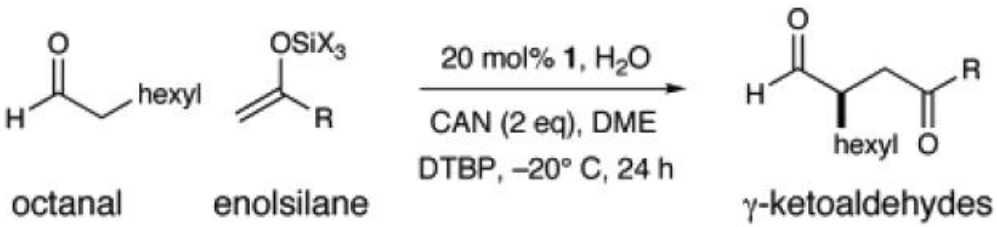


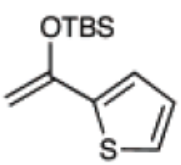
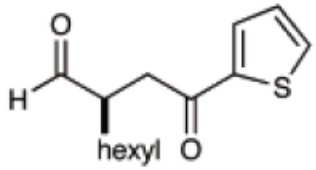
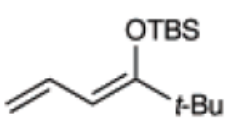
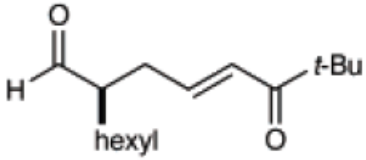




MacMillan, D. W. C.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 7004-7005

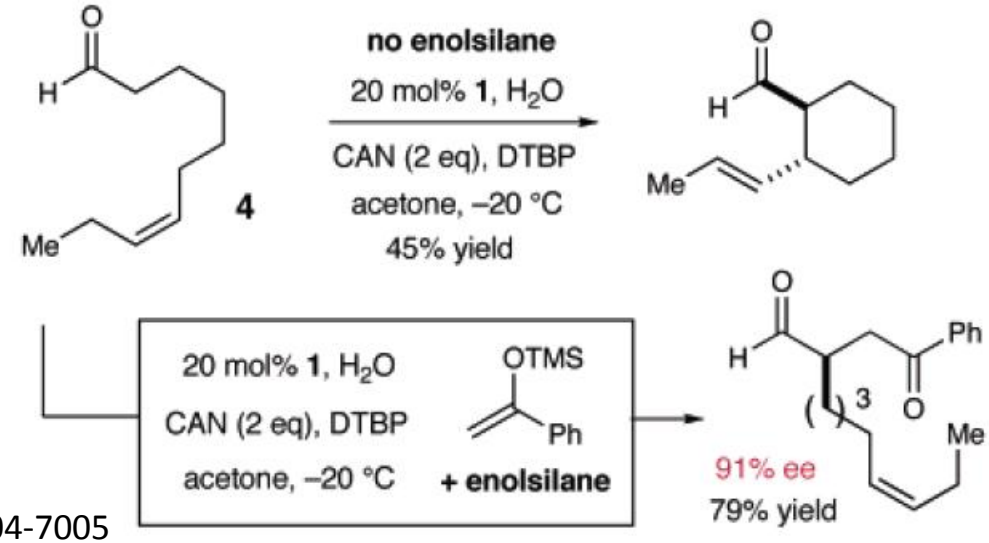
Enolsilane Scope and Chemoselectivity



enolsilane	product	% yield	% ee[a,b]
		70	93
		74	96

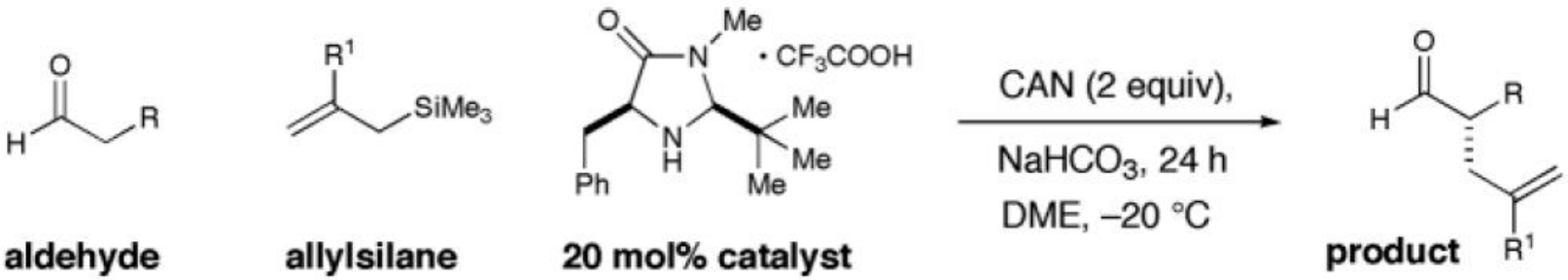
- Oxidation sensitive electron-rich heteroaromatic enolsilanes are compatible
- Dienes react exclusively at the γ-carbon with excellent enantioselectivity

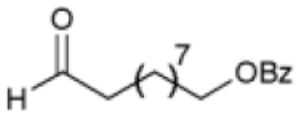
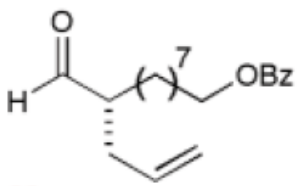
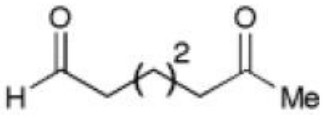
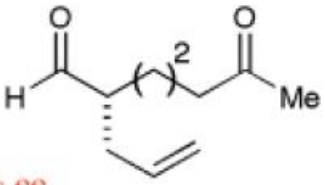
- Intermolecular reaction with enolsilanes is preferred over intramolecular reaction with π-neutral olefins



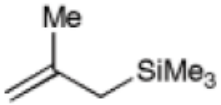
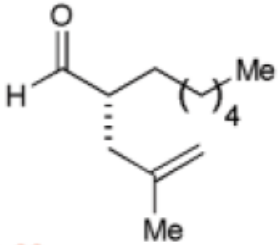
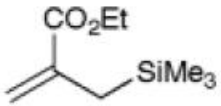
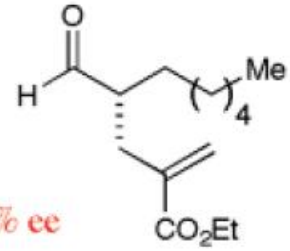
MacMillan, D. W. C.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 7004-7005

Organocatalytic SOMO α-Allylation



aldehyde	product*
	
72% yield, 95% ee	
	
72% yield, 87% ee	

*Reactions performed with allylsilane ($CH_2{=}CHCH_2SiMe_3$)

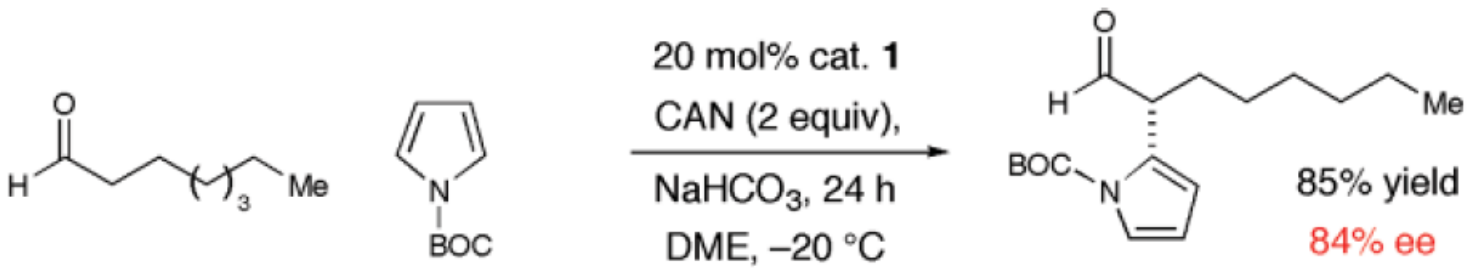
allylsilane	product‡
	
88% yield, 91% ee	
	
81% yield, 90% ee	

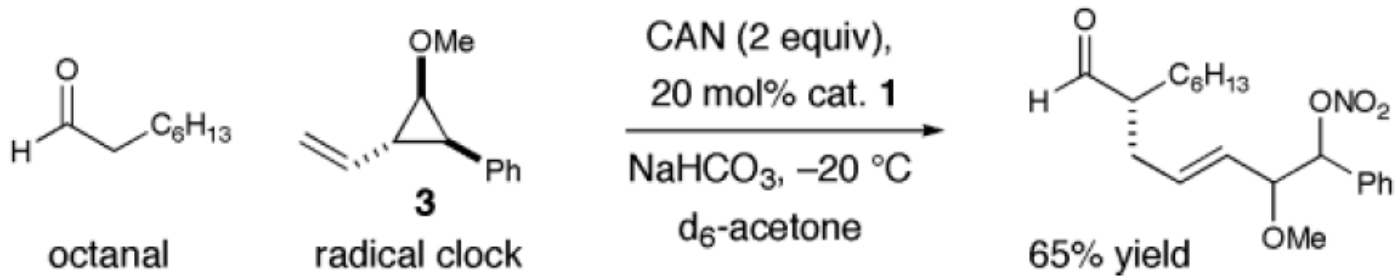
‡Reactions performed with octanal.

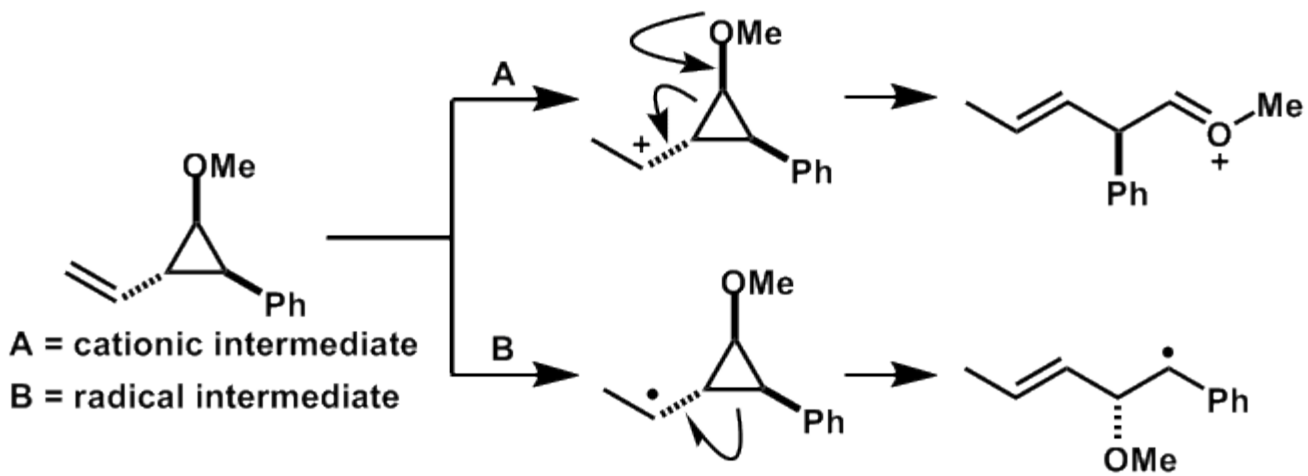
Many sensitive functional group are compatible with these conditions

MacMillan, D. W. C.; et al. *Science* **2007**, 316, 582-585

α-Heteroarylation / Mechanistic Studies

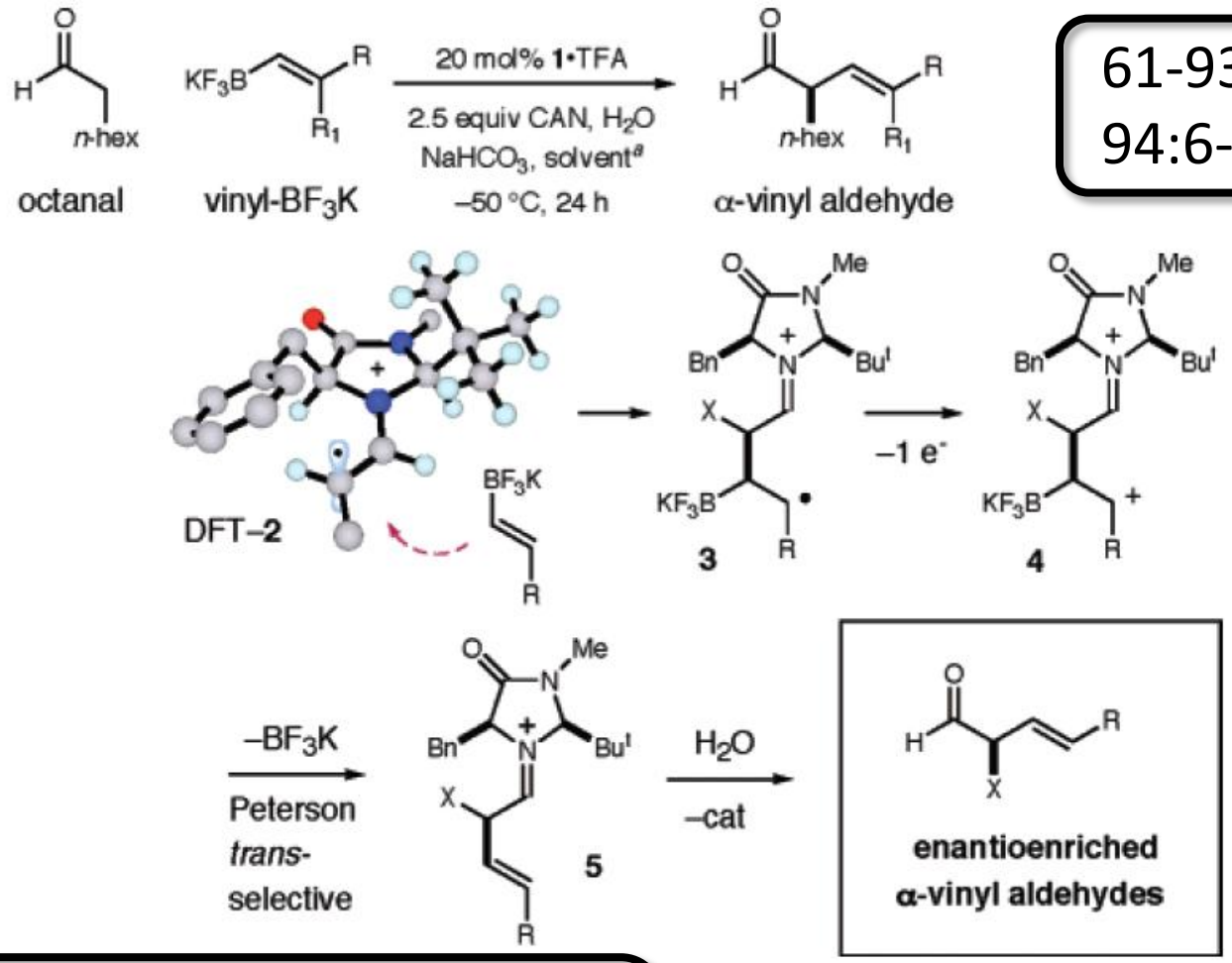






MacMillan, D. W. C.; et al. *Science* **2007**, 316, 582-585

Organocatalytic SOMO α-Vinylation

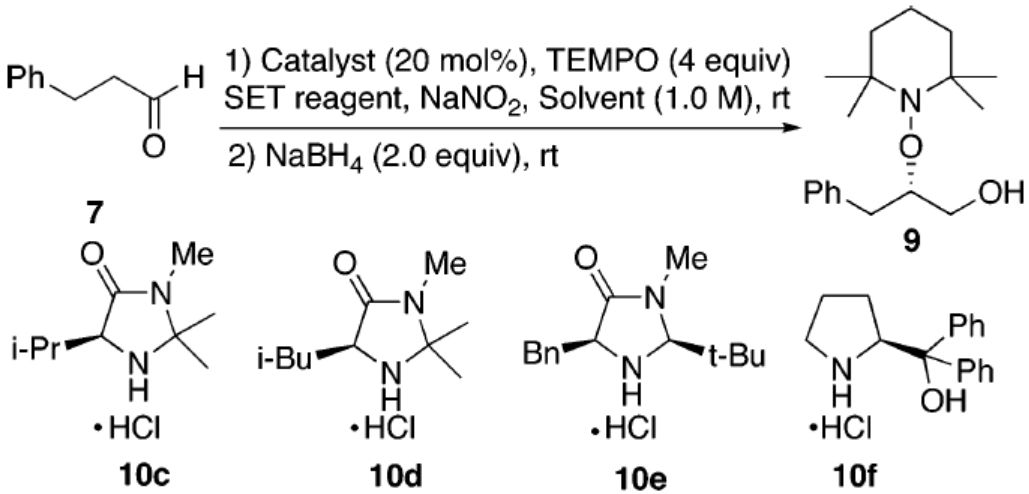


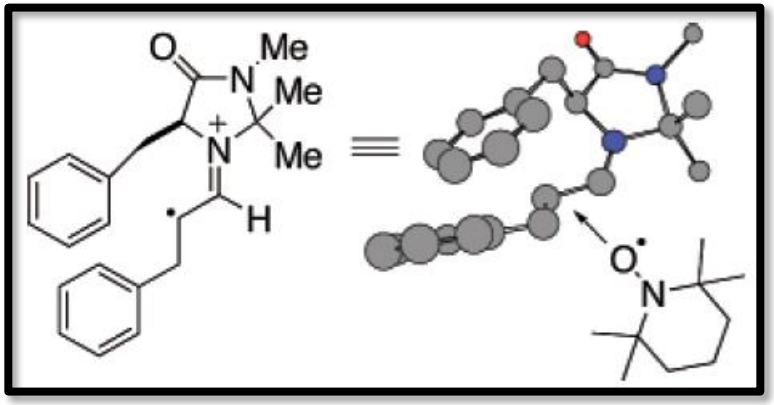
61-93% yield
94:6-98:2, er

SOMO organocatalysis appears a general mode of asymmetric activation

MacMillan, D. W. C.; et al. *J. Am. Chem. Soc.* **2008**, *130*, 398-399

Catalytic Single Electron Oxidation



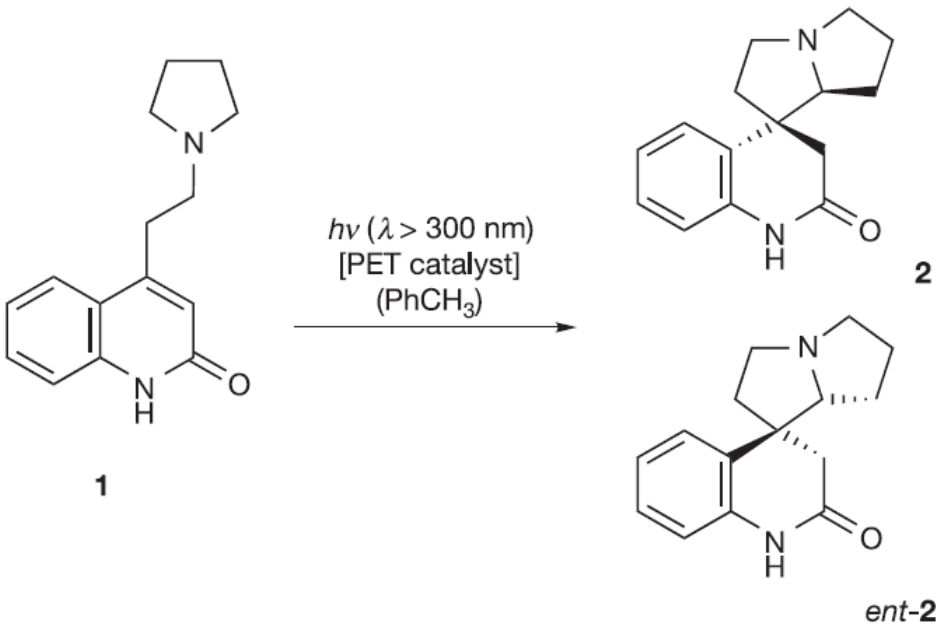


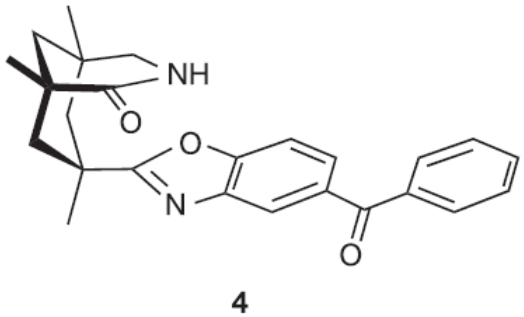
entry	SET reagent (mol %)	ligand	$NaNO_2$ (equiv)	solvent	yield (%)[b]	ee (%)[c]
1	Cp_2FeBF_4 (100)	**10b**	0	THF	87	80
2	Cp_2FeBF_4 (50)	**10b**	0	THF	40	74
3	$FeCl_3$ (100)	**10b**	0	THF	4	nd[d]
4	$FeCl_3$ (100)	**10b**	0	DMF	74	72
5[e]	$FeCl_3$ (30)	**10b**	0.3	DMF	82	75
6[e]	$FeCl_3$ (10)	**10b**	0.3	DMF	83	72

Catalytic single electron oxidation achieved using $FeCl_3/NaNO_2$ with O_2 as the stoichiometric oxidant

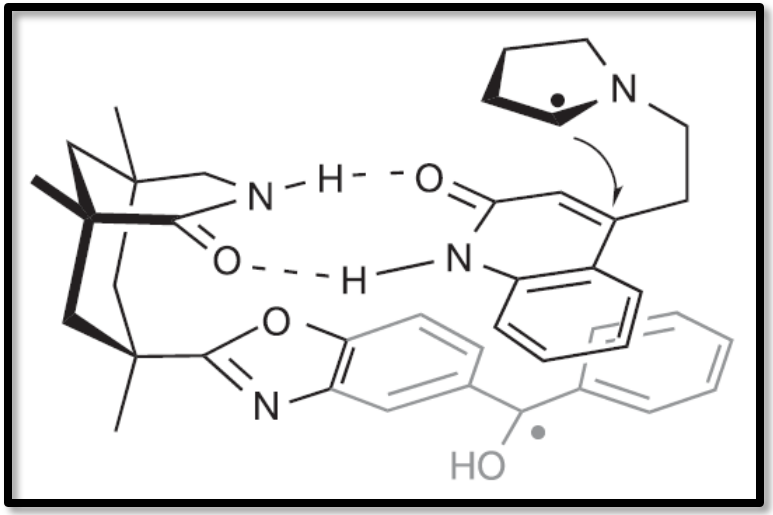
Sibi, M. P.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 4124-4125

Photoinduced Electron Transfer





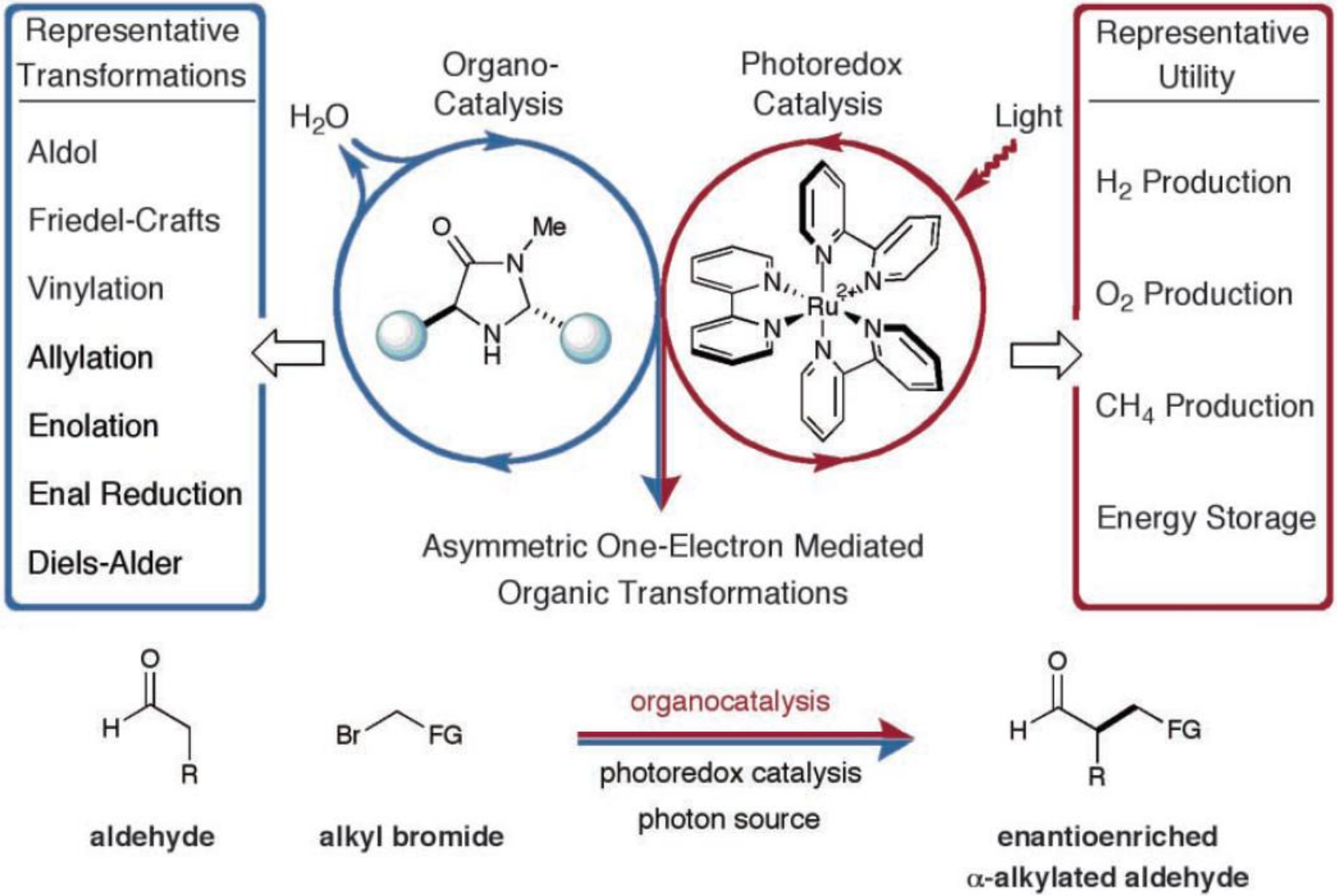
Catalyst	Equiv.*	Time (h)	Product	e.r.†	e.e.‡ (%)	Yields§ (%)
4	0.3	1	2	85/15	70	64



Photoinduced electron transfer can be used to form α-amino radicals competent in asymmetric catalysis

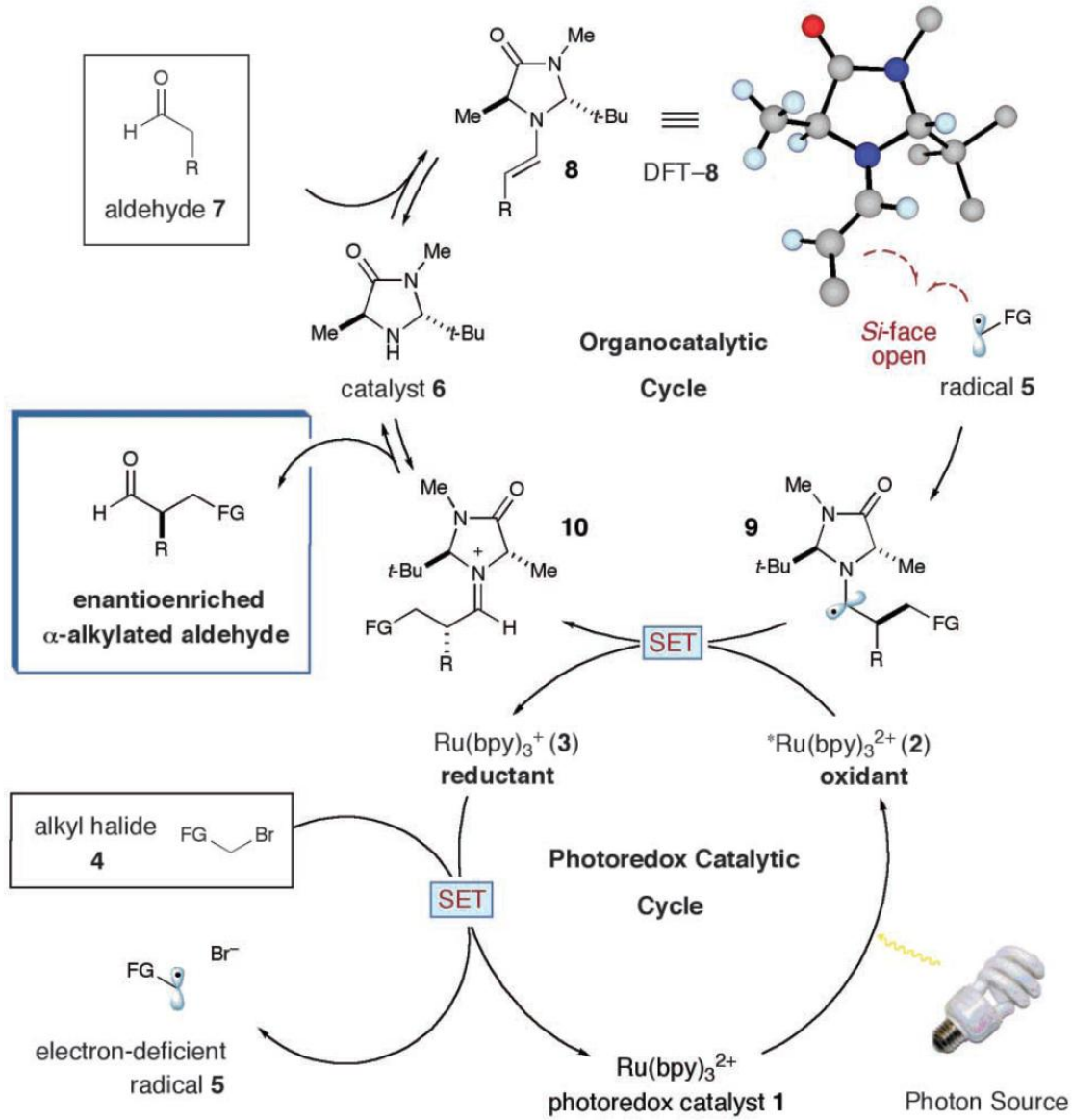
Bach, T.; et al. *Nature* **2005**, *436,* 1139-1140

Merging PET and SOMO Catalysis



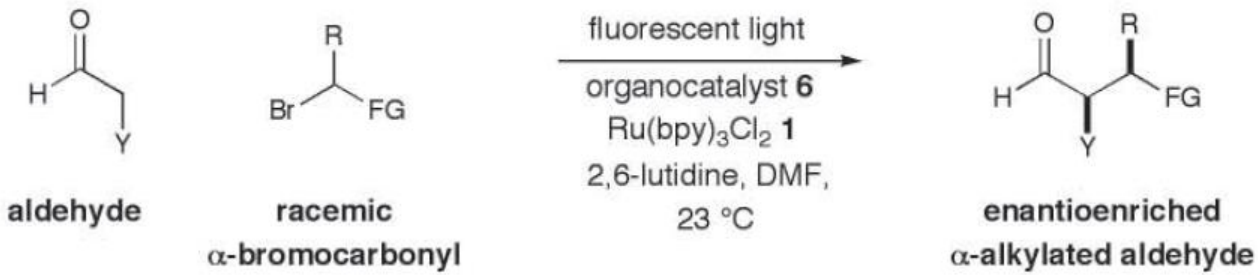
MacMillan, D. W. C.; et al. *Science* **2008**, *322,* 77-80

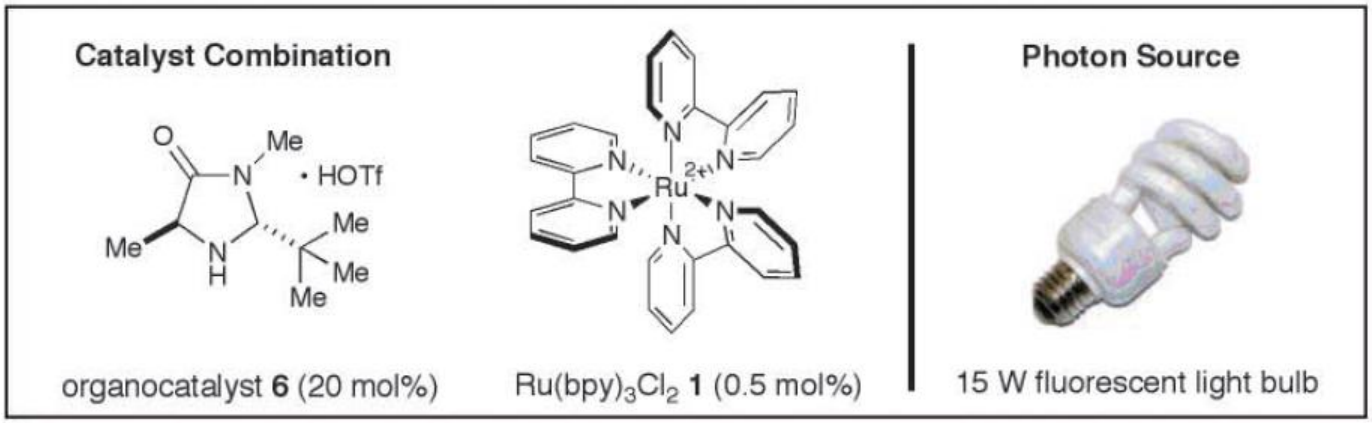
Method Design

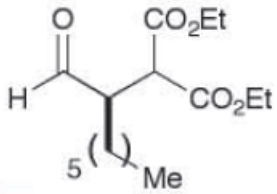


MacMillan, D. W. C.; et al. *Science* **2008**, *322,* 77-80

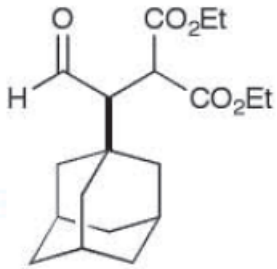
Optimized Reaction and Scope



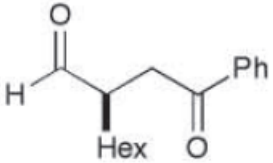




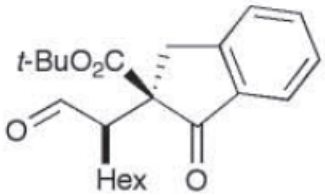
93% yield, 90% ee



63% yield†, 93% ee



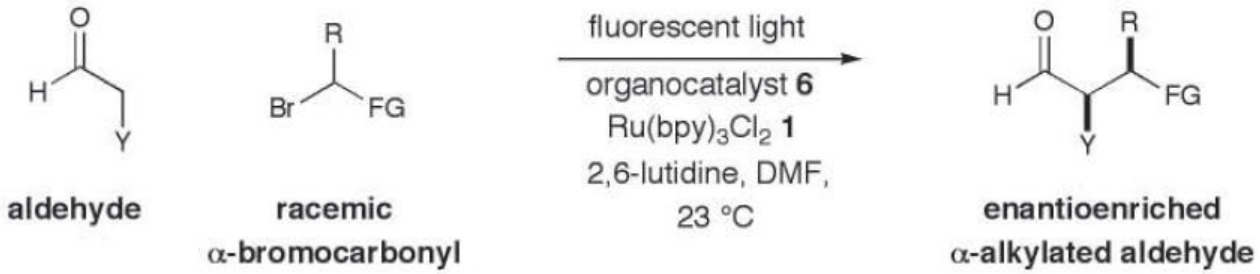
84% yield, 96% ee

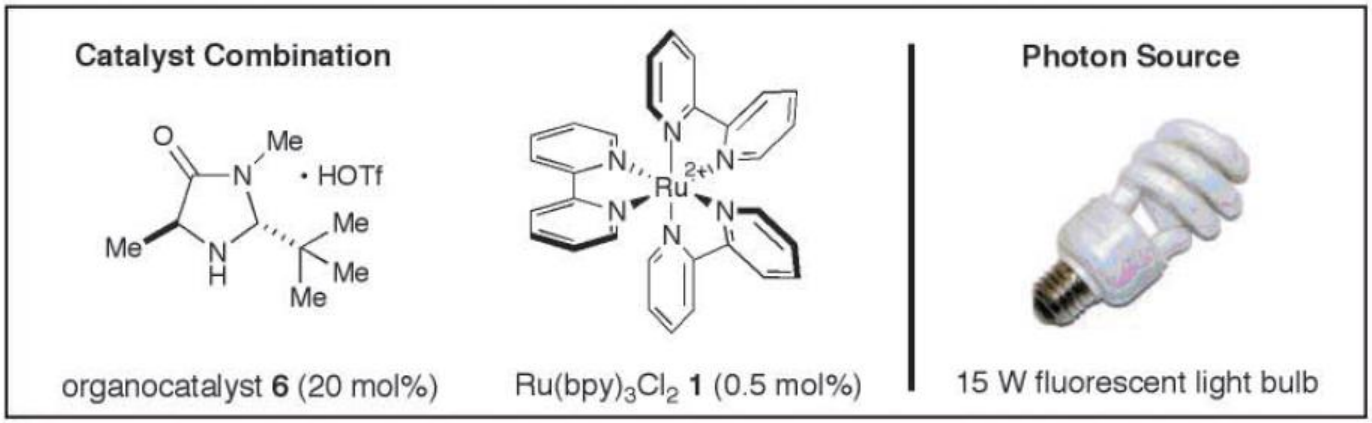


70% yield, 5:1 dr, 99% ee

MacMillan, D. W. C.; et al. *Science* **2008**, *322,* 77-80

Control Experiments



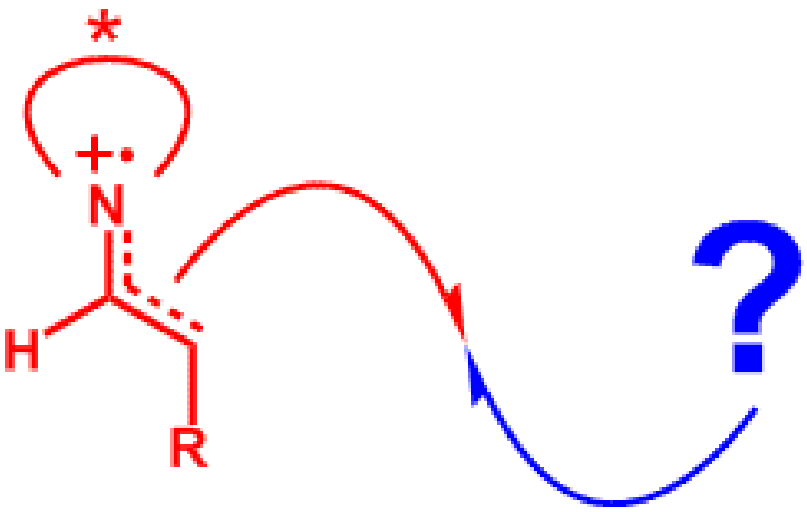


1. Rigorous exclusion of light = no product
2. Exclusion of $Ru(bpy)_3Cl_2$ = <10% product at 24 h
3. Exclusion of $Ru(bpy)_3Cl_2$ with high energy UV radiation (300-350 nm = >80% conversion
4. MLCT absorption band (465 nm) increased reaction rate to 90 min (6 h); with no $Ru(bpy)_3Cl_2$ <5% product

MacMillan, D. W. C.; et al. *Science* **2008**, *322,* 77-80

Conclusions

- Singly occupied molecular orbital organocatalysis offers a general mode of aldehyde activation
- These developments have, for the most part, solved limitations in the asymmetric α-alkylation of aldehydes
- Molecular oxygen can be used as the stoichiometric oxidant for SOMO catalysis
- In addition, photoinduced electron transfer can generate radical iminium cations used for asymmetric transformations



What is the next SOMOphile?

For additional commentary see:
Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48,* 1360-1363
Mukherjee, S.; List, B. *Nature* **2007**, *447,* 152-153
Jorgensen, K. A.; et al. *Angew. Chem. Int. Ed.* **2007**, 46, 7356-7359
Renaud, P.; Leong, P. *Science* **2008**, *322,* 55-56