David W.C. MacMillan: Career-in-Review

Yan Xu
Dong Group Meeting
Jan. 2, 2014

David W.C. MacMillan: *A Brief Introduction*

Career

1968 *Born in Bellshill, **Scotland.***

1987-1991 *Undergraduate degree in chemistry at **the University of Glasgow.***

1991-1996 *Doctoral studies with Professor **Larry E. Overman** at the **University of California, Irvine.***

1996-1998 *Postdoctoral studies with Professor **David Evans** at the **Harvard University.***

July 1998 *Dave began his **independent research career** at **the University of California, Berkeley.***

June 2000 Joined the department of chemistry at ***CIT***

June 2006 Appointed as the A. Barton Hepburn Professor of Chemistry at ***Princeton University.***

Title

- ***James S. McDonnell Distinguished University Professor*** of Chemistry at Princeton University.
- ***Chairperson*** of the Department of Chemistry at Princeton University.
- ***Director*** of the Merck Center for Catalysis at Princeton University.

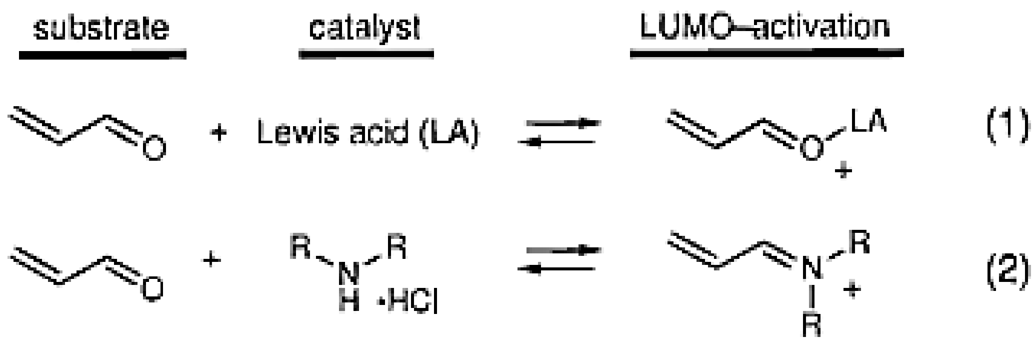
2010 - Present *Chemical Science*
[**Editor-in-Chief**]

Content

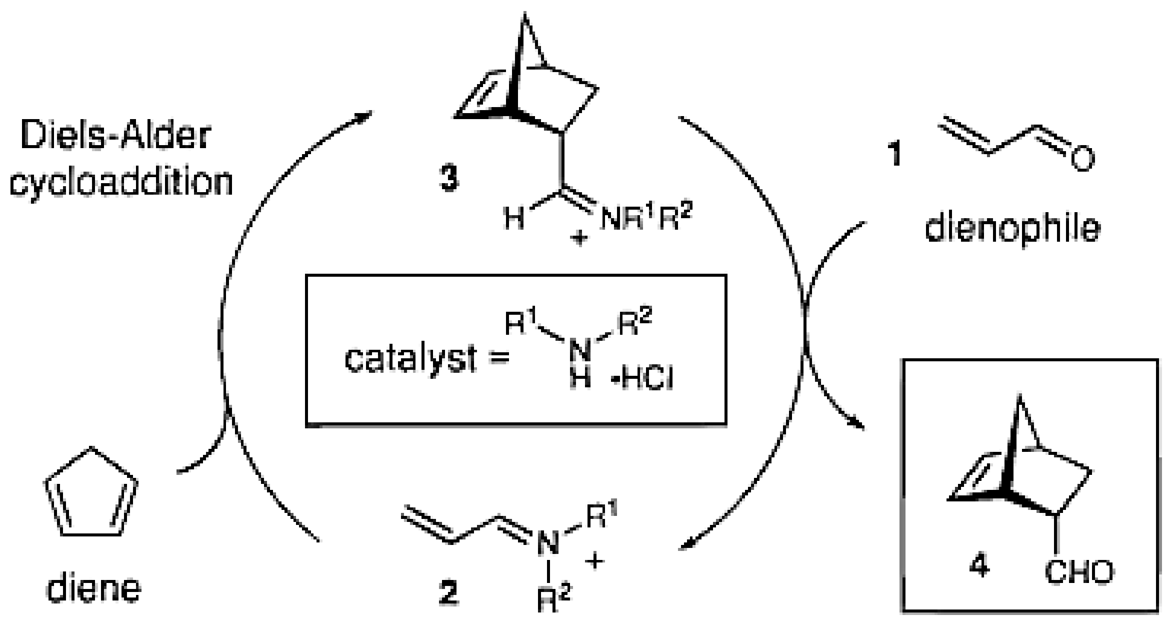
Content

The First Highly Enantioselective Organocatalytic Diels-Alder Reactions

- two way to lower the LUMO of the enal system

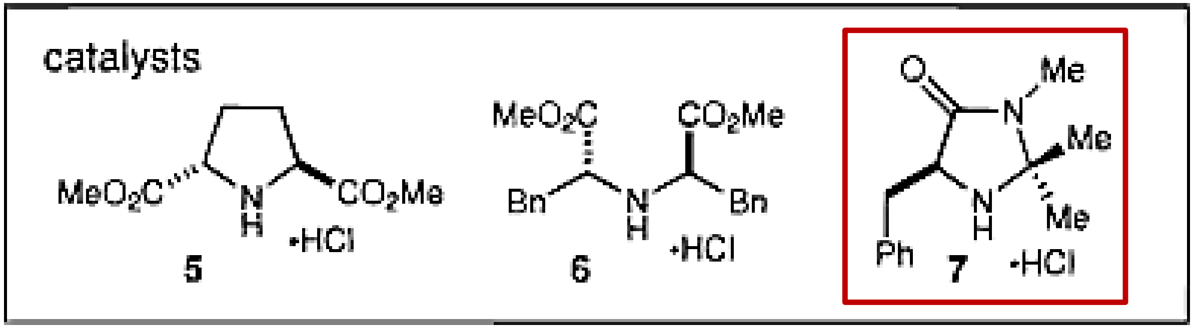


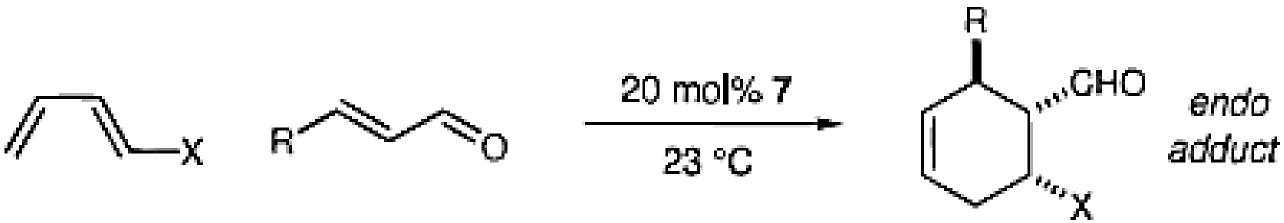
- designed reaction cycle



J. Am. Chem. Soc. **2000,** *122,* 4243-4244

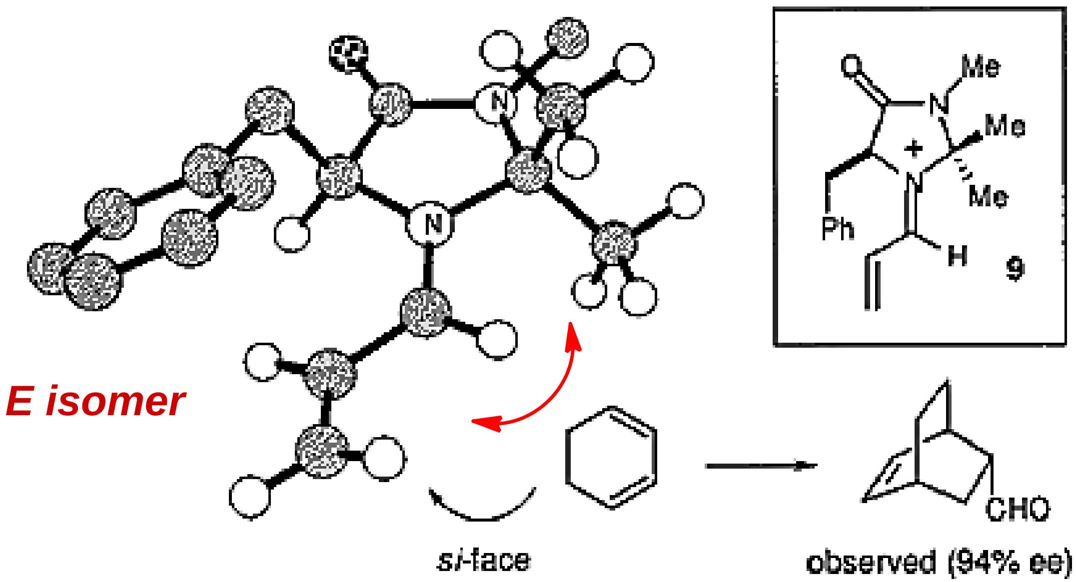
The First Highly Enantioselective Organocatalytic Diels-Alder Reactions





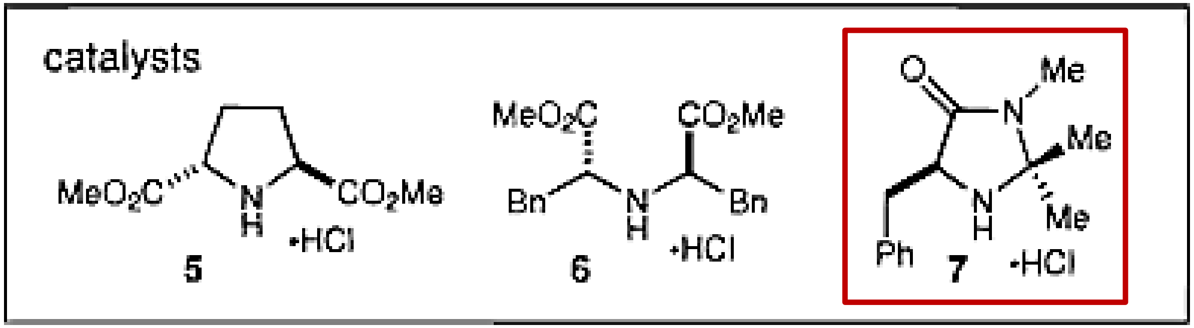
12 examples,
85-96% ee,
72-99% yield

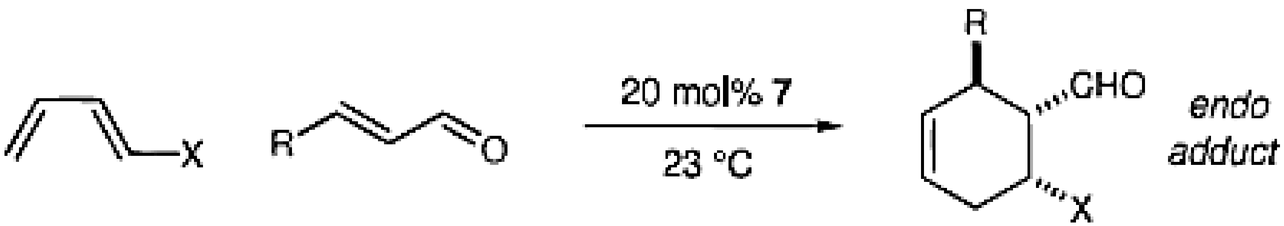
- origin of chiral control



J. Am. Chem. Soc. **2000,** *122,* 4243-4244

The First Highly Enantioselective Organocatalytic Diels-Alder Reactions



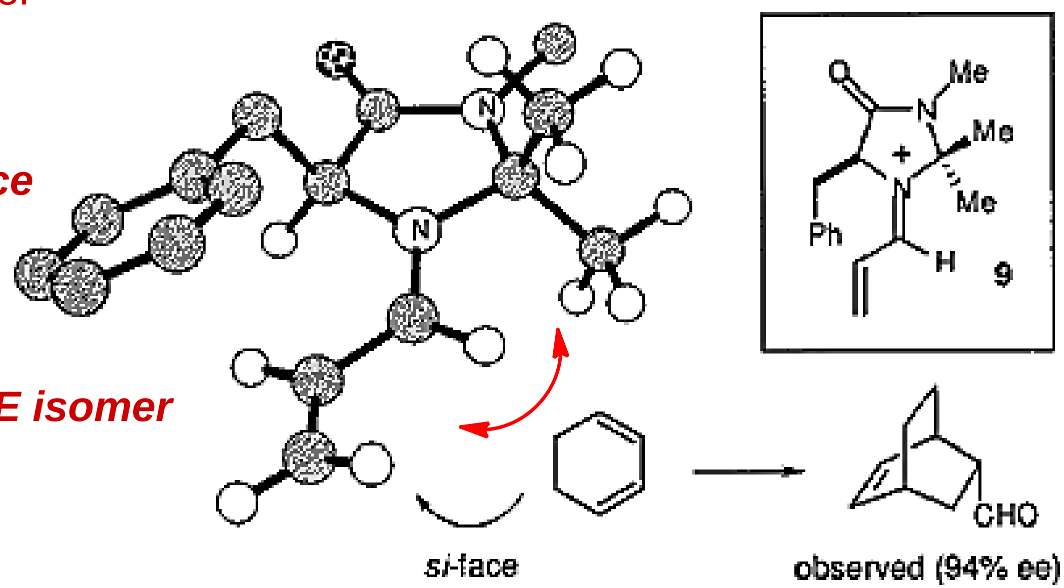


12 examples,
85-96% ee,
72-99% yield

- origin of chiral control

Shield the Re face

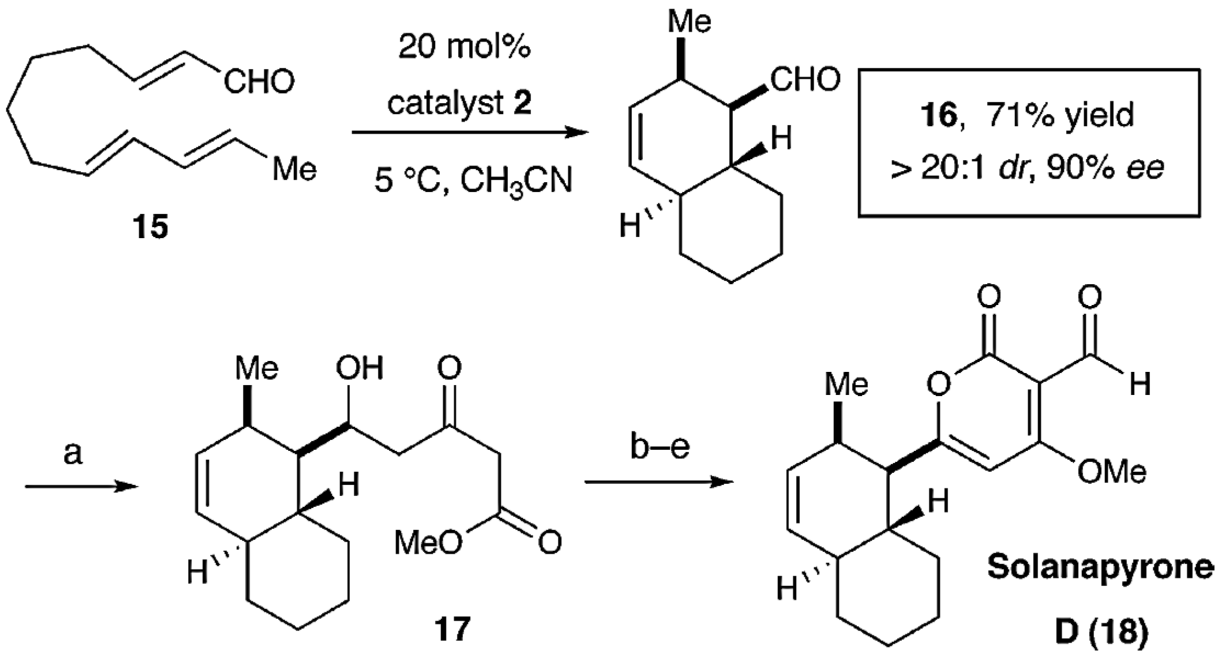
E isomer

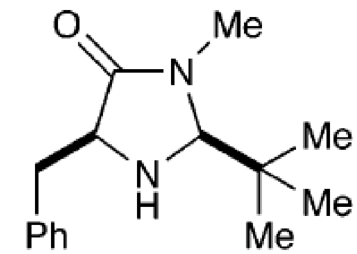


J. Am. Chem. Soc. **2000,** *122,* 4243-4244

The First Highly Enantioselective Organocatalytic Diels-Alder Reactions

- synthesis of *Solanapyrone*





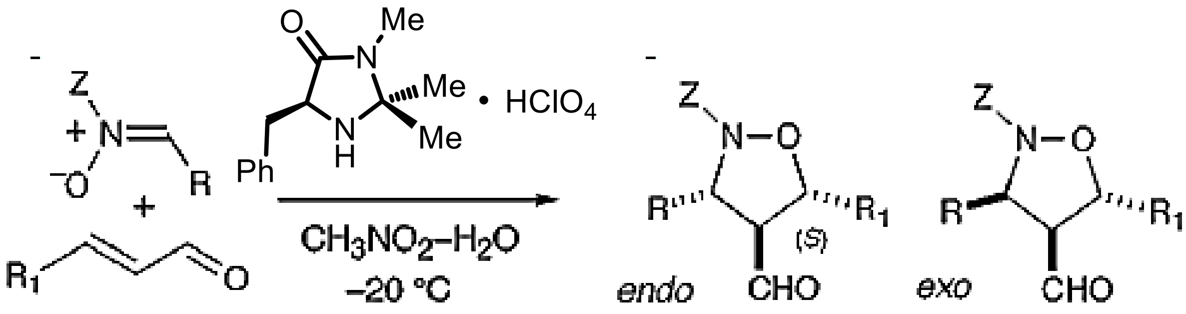
catalyst **2**

[a] Key: (a) Methyl acetoacetate bis(trimethylsilyl) enol ether, $TiCl_4$, CH_2Cl_2, −78 °C, 75%. (b) Dess−Martin Periodinane, CH_2Cl_2, 71%. (c) DBU, benzene, 60 °C, 87%. (d) Methyl *p*-toluenesulfonate, K_2CO_3, DMF, room temperature, 81%. (e) LDA, THF, −78 °C to 0 °C; methyl formate, −78 °C, 57% (91% based on recovered starting material).

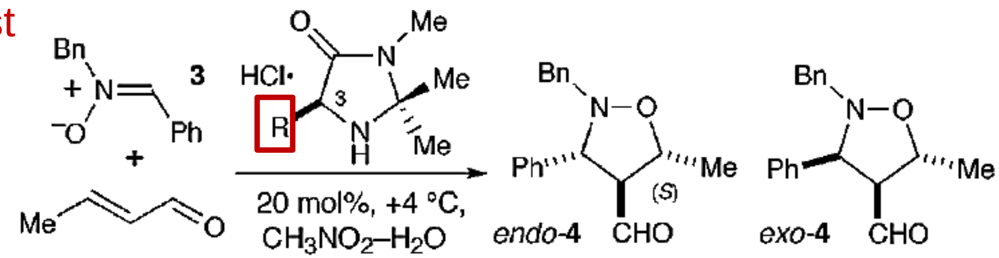
J. Am. Chem. Soc., **2005**, *127*, 11616-11617

Highly enantioselective [3+2] cycloaddition reaction

■ nitrone as the sustrate



■ screening of catalyst



entry	R–(catalyst)	Time (h)	% yield	*exo*:*endo*	% ee (*endo*)[a,b]
1	CH_2Ph (**1a**)	72	70	88:12	93
2	Ph (**1b**)	70	73	78:22	44
3	*i*-Pr (**1c**)	60	68	58:32	42
4	*t*-Bu (**1d**)	70	45	33:66	20
5	CH_2-2-napthyl (**1e**)	48	62	78:22	86
6	$CH_2C_6H_4OMe$-4 (**1f**)	48	77	79:21	89
7	CH_2CH_2Ph (**1g**)	48	72	50:50	69

J. Am. Chem. Soc. **2000,** *122,* 9874-9875

Highly enantioselective [3+2] cycloaddition reaction

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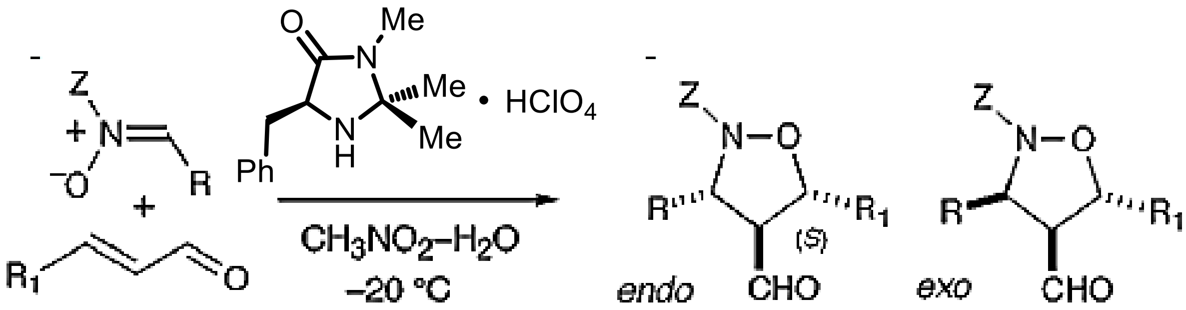

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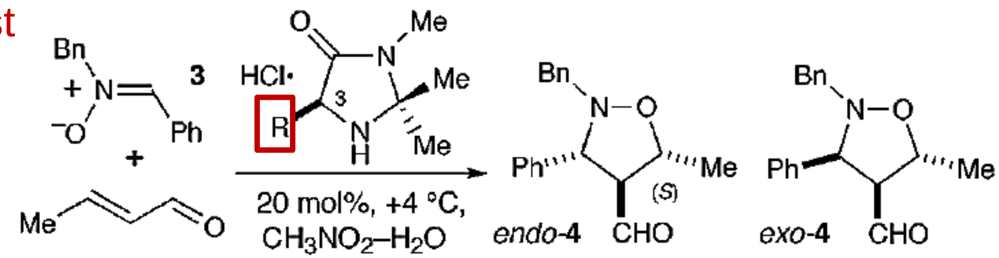

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J. Am. Chem. Soc. **2000,** *122,* 9874-9875

Highly enantioselective [3+2] cycloaddition reaction

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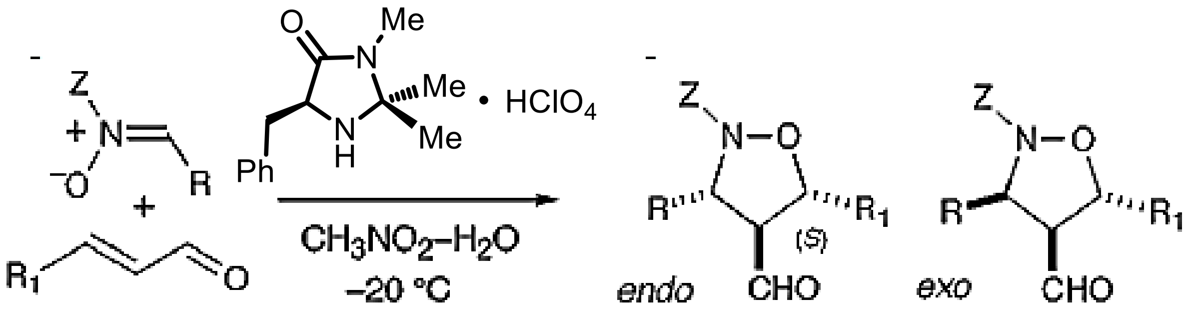
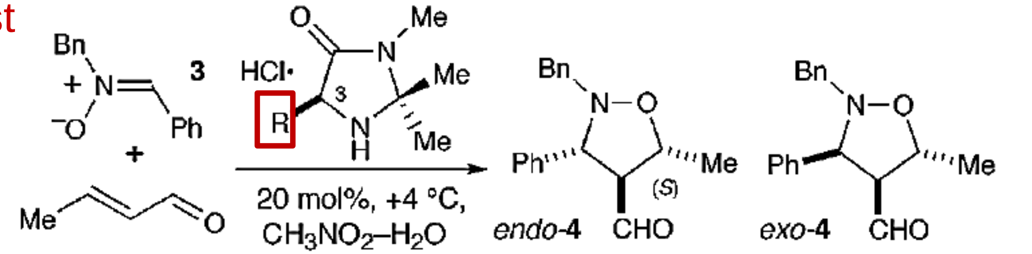


- screening of catalyst



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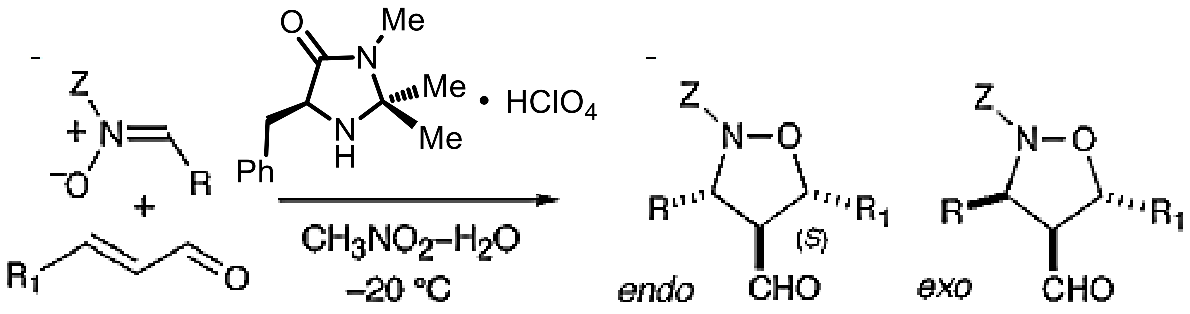
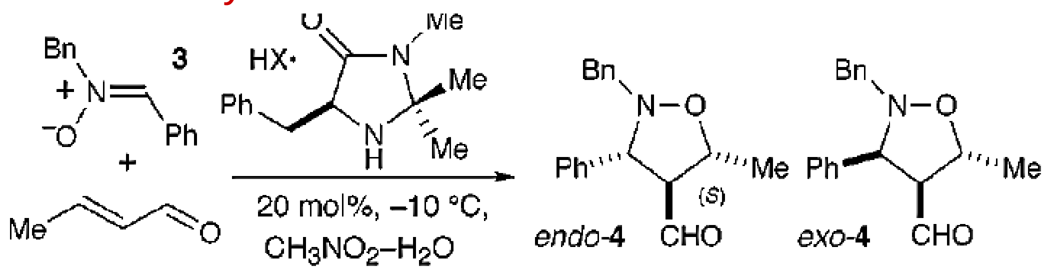
J. Am. Chem. Soc. **2000,** *122,* 9874-9875

Highly enantioselective [3+2] cycloaddition reaction

- nitrone as the sustrate



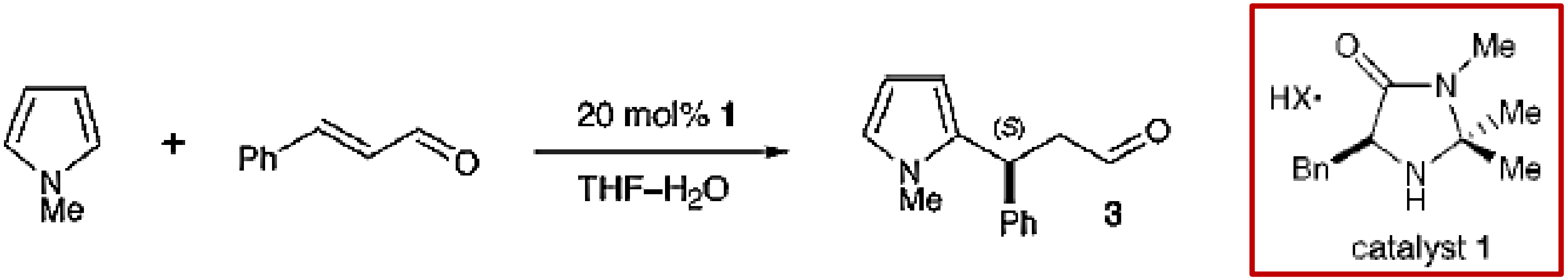
- screening of the acid cocatalyst



entry	HX co-catalyst	Time (h)	% yield	*endo*:*exo*	% ee (*endo*)[a]
1	HCl (**1a**)	108	70	88:12	95
2	TfOH (**5**)	101	88	89:11	90
3	TFA (**6**)	80	65	72:28	86
4	HBr (**7**)	80	77	94:6	93
5	$HClO_4$ (**8**)	80	86	94:6	90
6	$HClO_4$ (**8**)	100	98	94:6	94[b]

J. Am. Chem. Soc. **2000,** *122,* 9874-9875

The First Enantioselective Organocatalytic Friedel-Crafts Alkylation

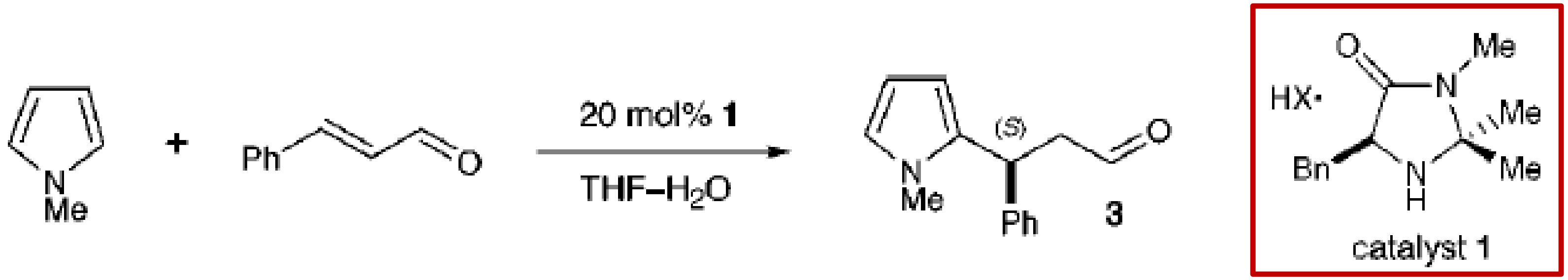


- very sensitive to the cocatalyst

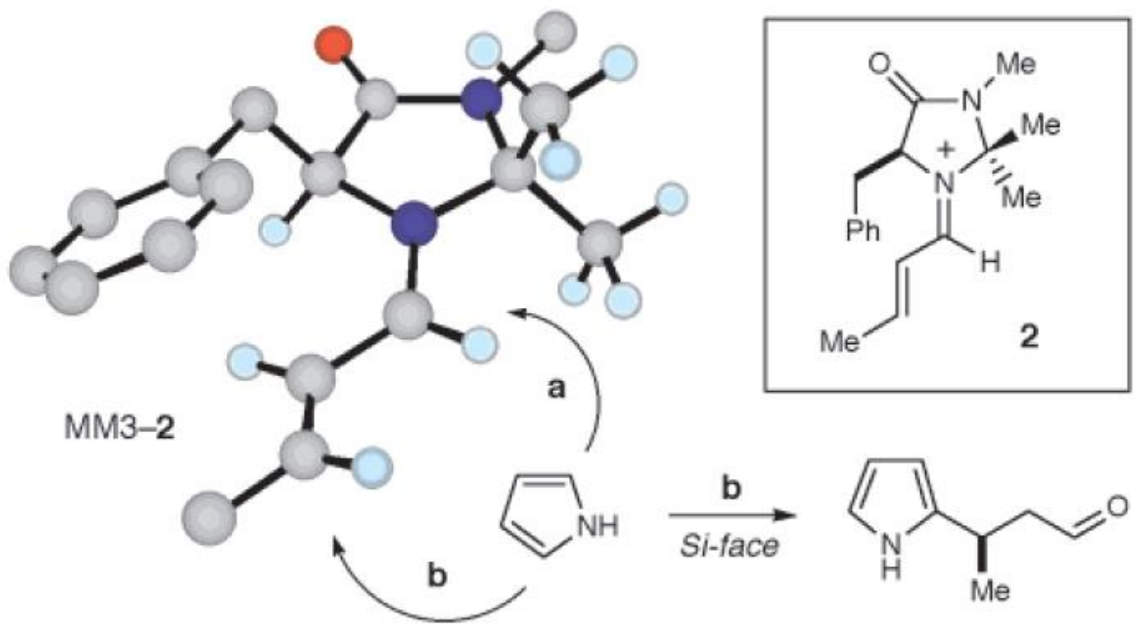
entry	H–X cocatalyst	Temp (°C)	Time (h)	% yield[a]	% ee[b,c]
1	$NCCH_2CO_2H$ (**1a**)	23	32	10	80
2	Cl_2CHCO_2H (**1b**)	23	32	62	80
3	Cl_3CCO_2H (**1c**)	23	3	64	81
4	TFA (**1d**)	23	3	78	81
5	TFA (**1d**)	–30	42	87	93

J. Am. Chem. Soc. **2001,** *123,* 4370-4371

The First Enantioselective Organocatalytic Friedel-Crafts Alkylation



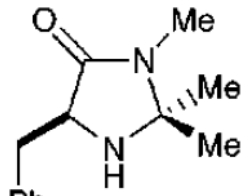
- 1,2-addtion is highly prohibited by the catalyst



calculated iminium ion model

J. Am. Chem. Soc. **2001,** *123,* 4370-4371

Enantioselective Indole Alkylation



catalyst **1**

cocatalysts =

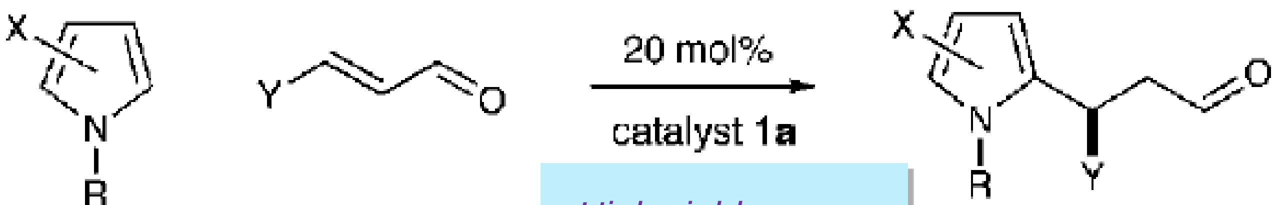
a = TFA

b = *p*-TSA

c = 2-NO_2PhCO_2H

- previous reaction

Pyrrole Alkylation

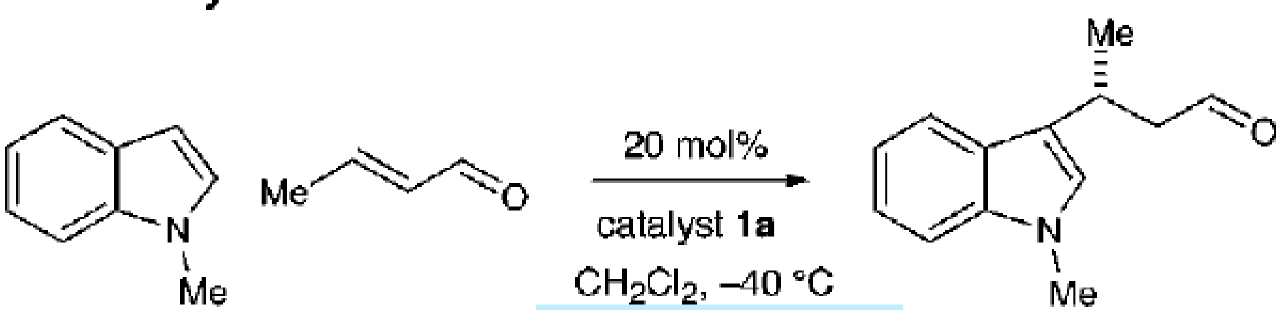


High yield
Good ee value

J. Am. Chem. Soc. **2001,** *123,* 4370-4371

- initial trial

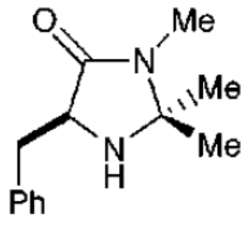
Indole Alkylation



Sluggish reaction
Poor ee value

J. Am. Chem. Soc., **2002,** *124*, 1172-1173

Enantioselective Indole Alkylation



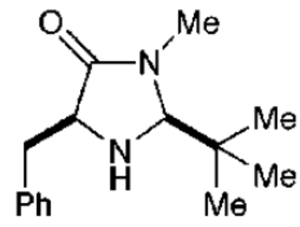
catalyst **1**

cocatalysts =

a = TFA

b = *p*-TSA

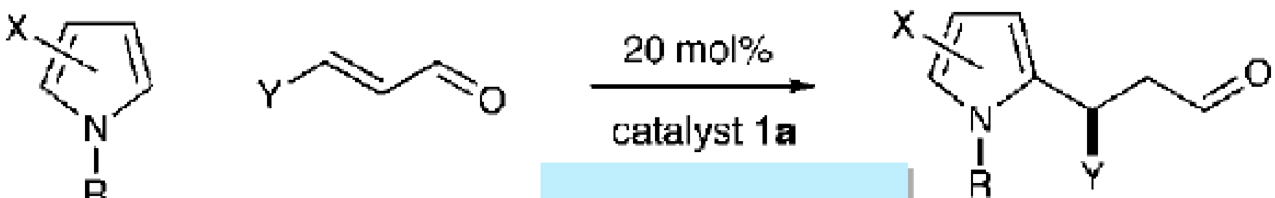
c = 2-NO_2PhCO_2H



catalyst **2**

■ previous reaction

Pyrrole Alkylation

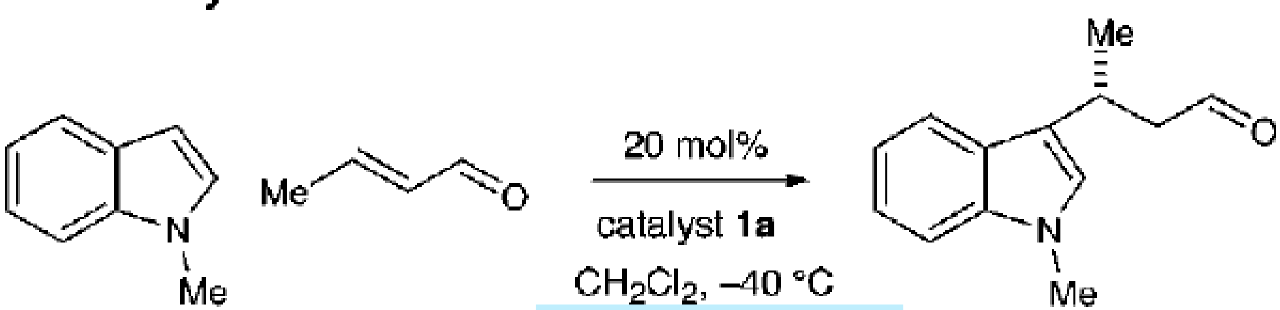


High yield
Good ee value

J. Am. Chem. Soc. **2001,** *123,* 4370-4371

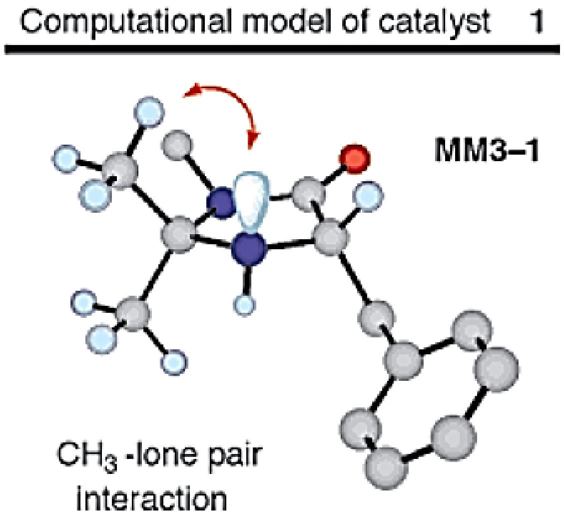
■ initial trial

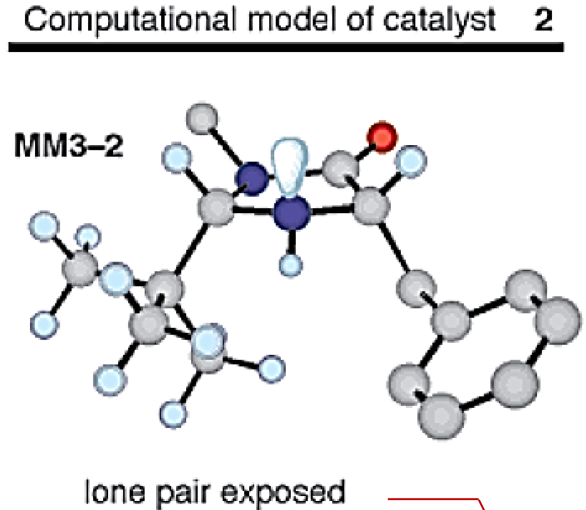
Indole Alkylation

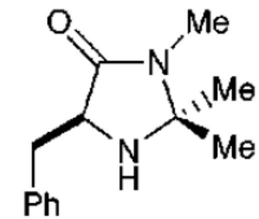


Sluggish reaction
Poor ee value

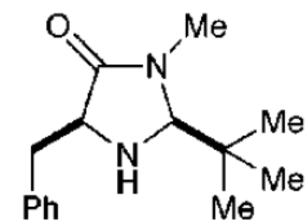
J. Am. Chem. Soc., **2002,** *124*, 1172-1173







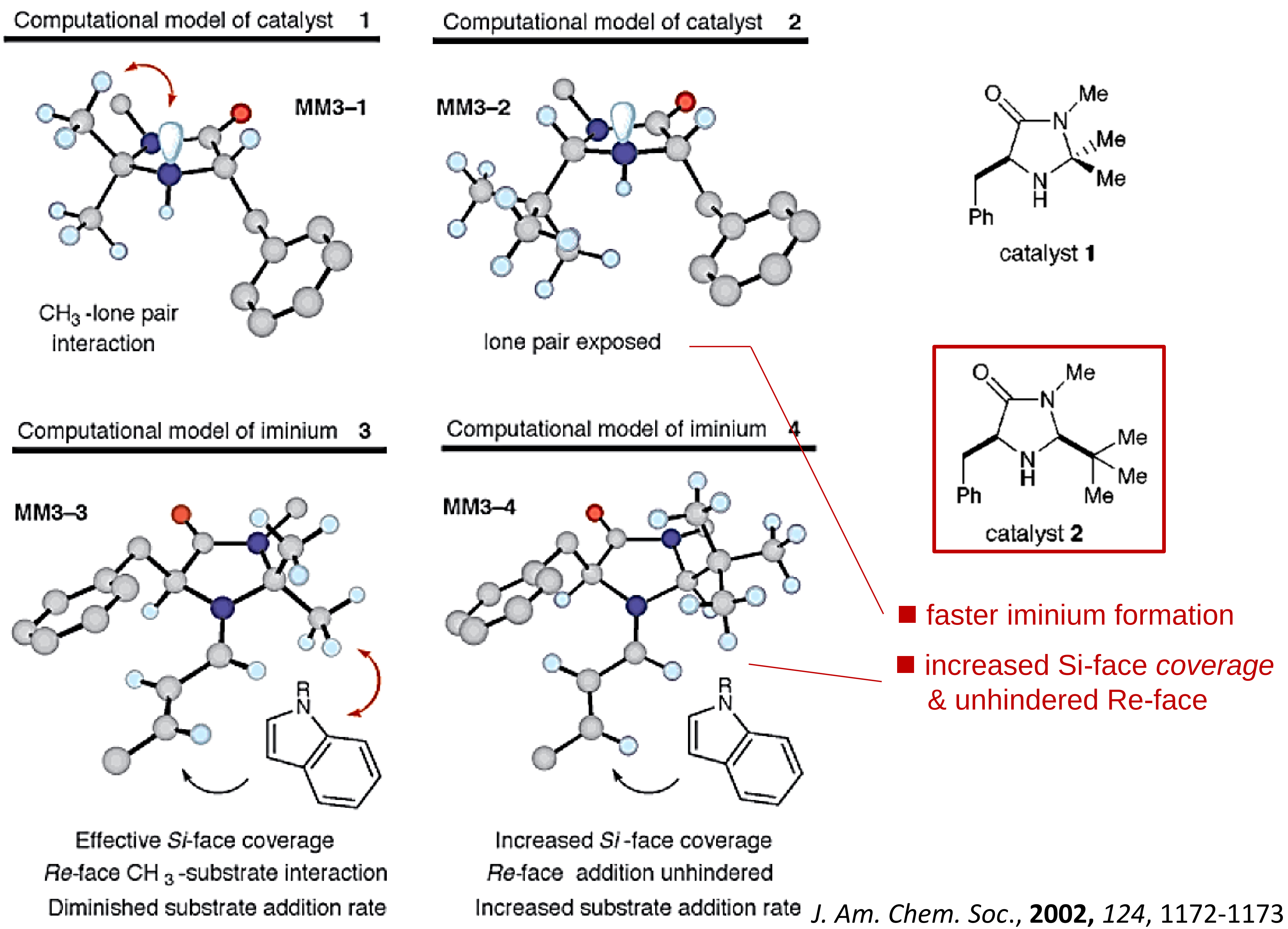
catalyst **1**



catalyst **2**

- faster iminium formation

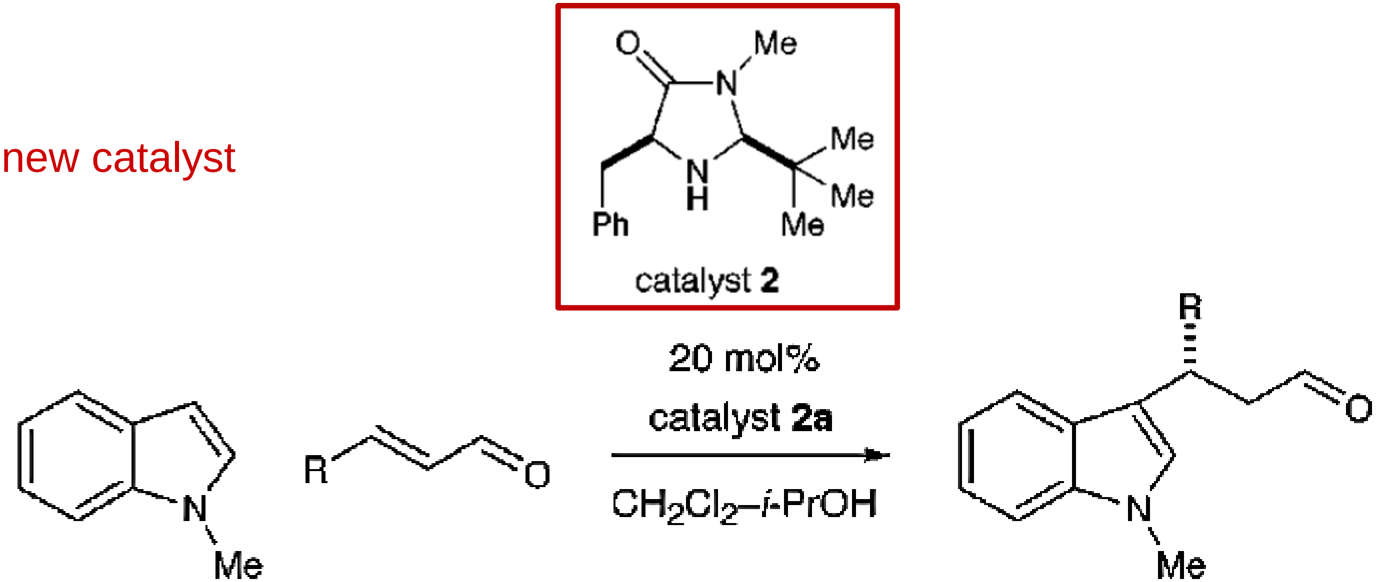
J. Am. Chem. Soc., **2002,** *124*, 1172-1173



J. Am. Chem. Soc., **2002,** *124*, 1172-1173

Enantioselective Indole Alkylation

- with new catalyst

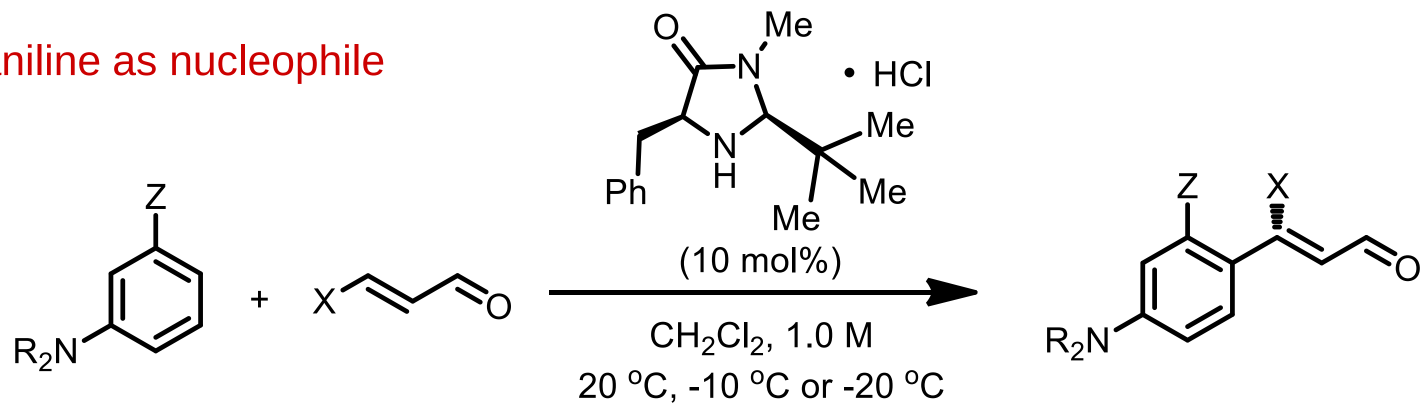


entry	R	temp °C	time (h)	% yield	% ee[a]
1	Me	−83	19	82	92[b]
2	Pr	−60	6	80	93
3	*i*-Pr	−50	32	74	93
4	CH_2OBz	−83	18	84	96[b]
5	Ph	−55	45	84	90
6	CO_2Me	−83	21	89	91

J. Am. Chem. Soc., **2002,** *124*, 1172-1173

Other Enantioselective Friedel-Crafts Type Alkylations

- aniline as nucleophile

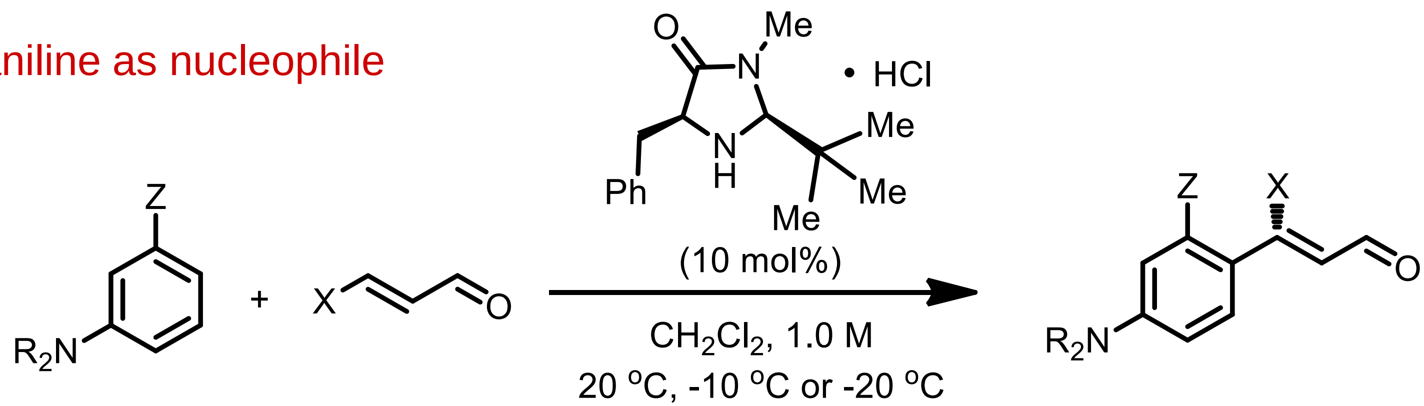


25 examples, 66-97% yield, 84-97 % ee

J. Am. Chem. Soc., **2002**, *124*, 7894-7895

Other Enantioselective Friedel-Crafts Type Alkylations

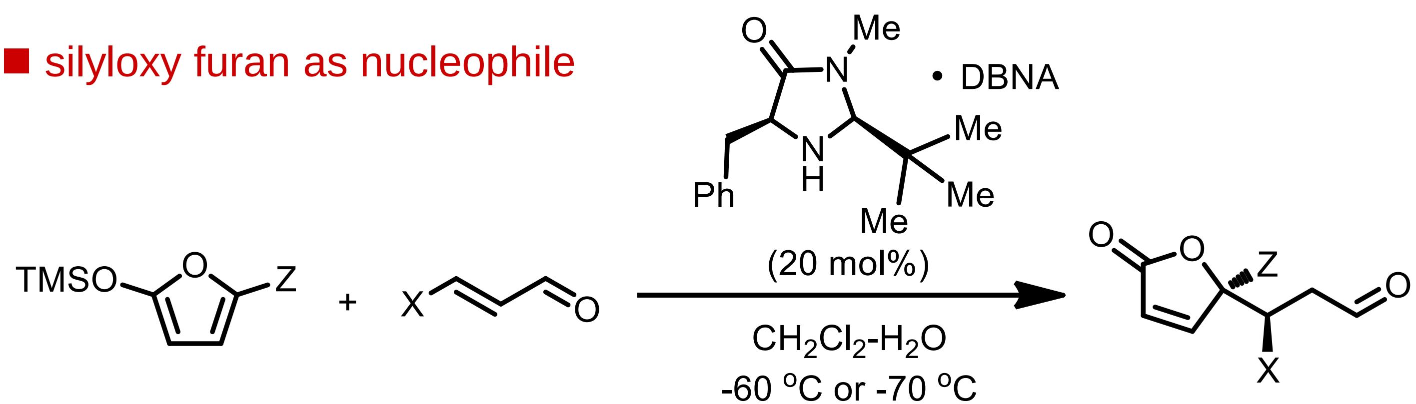
■ aniline as nucleophile



25 examples, 66-97% yield, 84-97 % ee

J. Am. Chem. Soc., **2002**, *124*, 7894-7895

■ silyloxy furan as nucleophile



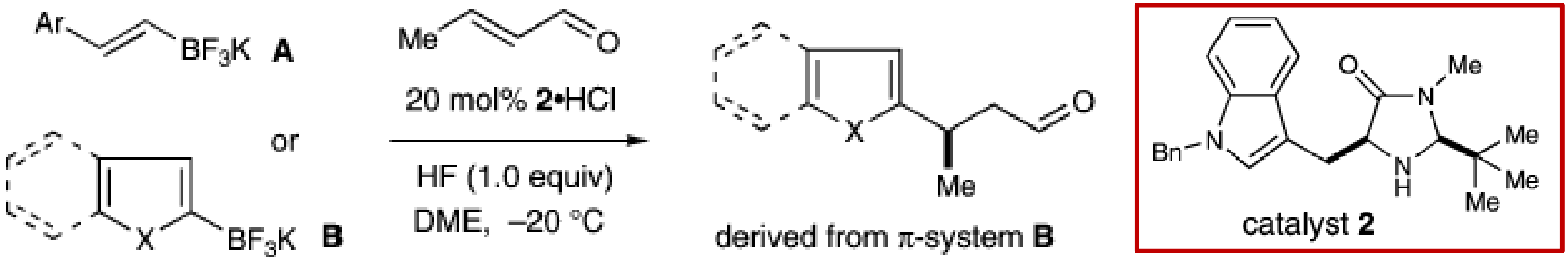
DBNA = 2,4-dinitrobenzoic acid (DBNA)

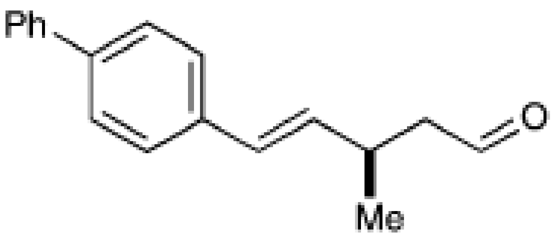
12 examples, 80-93% yield, 90-99 % ee

J. Am. Chem. Soc., **2003**, *125*, 1192-1194

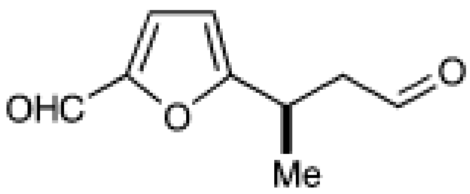
Other Enantioselective Friedel-Crafts Type Alkylations

- Trifluoroborate salts (Molander reagent) as nucleophile





91 % yield, 95 % ee

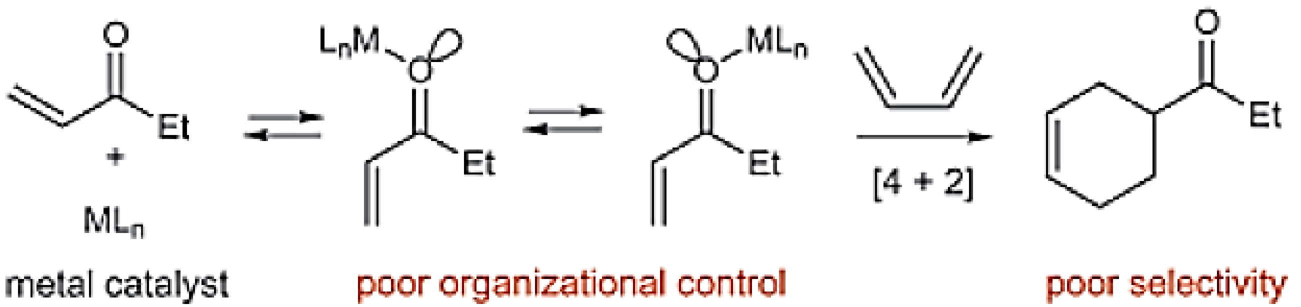


85 % yield, 95 % ee

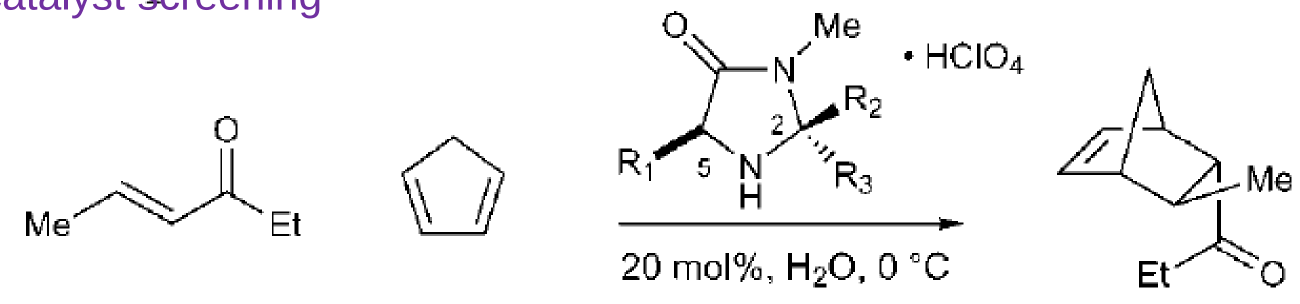
J. Am. Chem. Soc., **2007**, *129*, 15438-15439

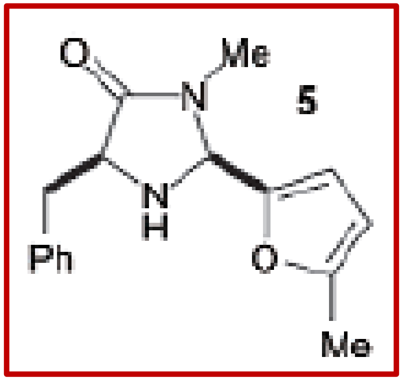
The First General Enantioselective Catalytic Diels-Alder Reaction with Simple α,β-Unsaturated Ketones

- regular chiral metal catalyst is difficult to distinguish the two asymmetric lone pair



- catalyst screening





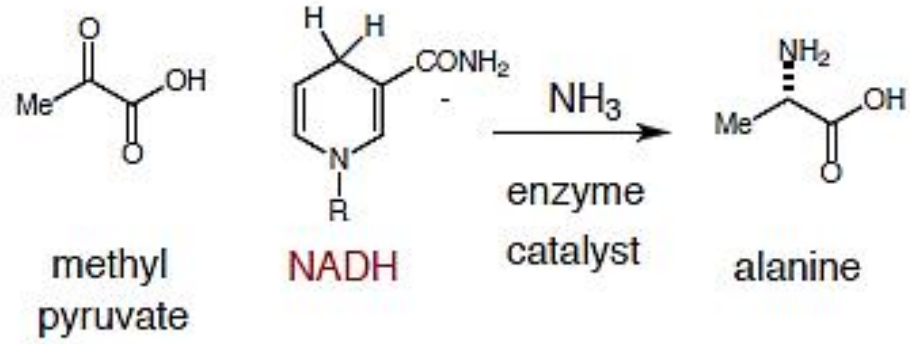
entry	cat.	R_1	R_2 (R_3)	time (h)	% yield	*endo:exo*	% ee[a,b]
1	**1**	Bn	Me (Me)	48	20[c]	7:1	0
2	**2**	Bn	*t*-Bu (H)	48	27[c]	9:1	0
3	**3**	Ph	Ph (H)	22	88	21:1	47
4	**4**	Bn	Ph (H)	42	83	23:1	82
5	**5**	Bn	5-Me-furyl (H)	22	89	25:1	90

78-92 % yield, 85-98 % ee

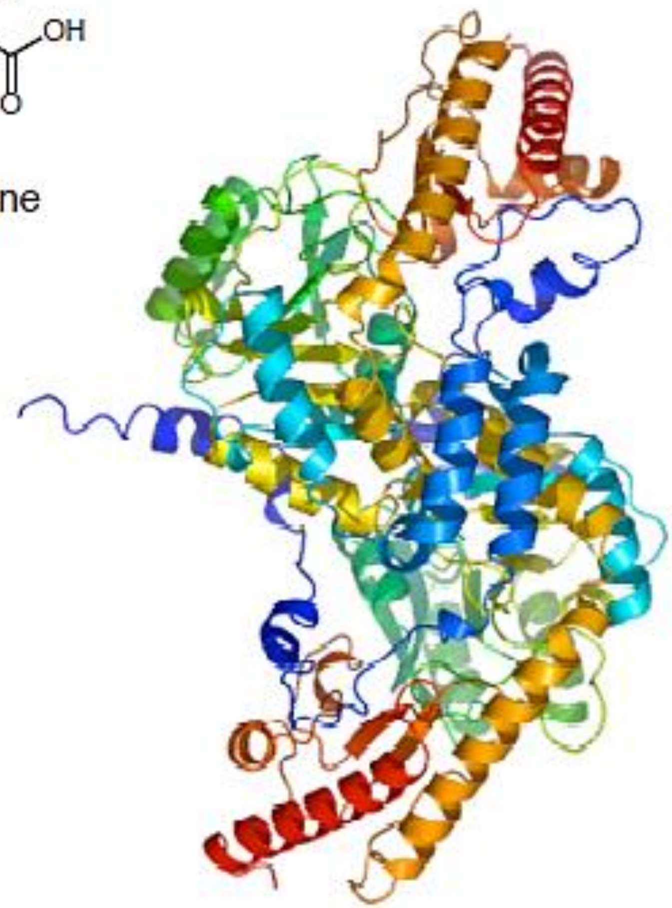
J. Am. Chem. Soc., **2002**, *124*, 2458-2460

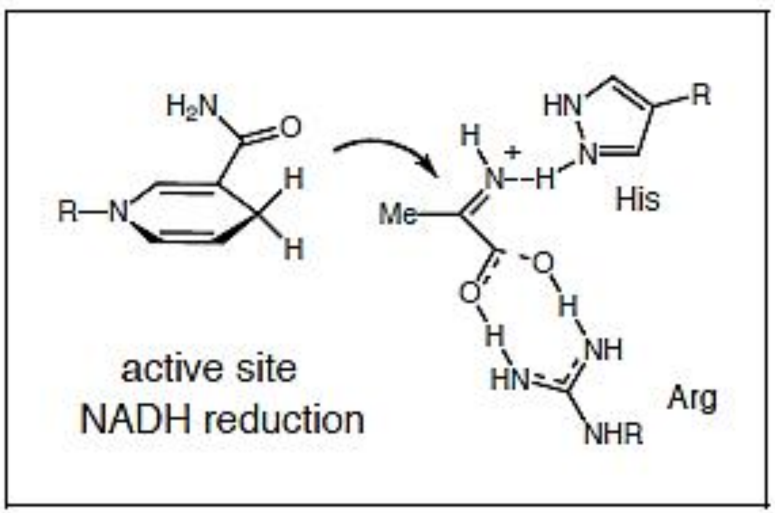
Organic Catalyzed Reduction in Biological Systems

■ NADH: Natures Reduction (Hydrogenation) Reagent (Coenzyme)



alanine transferase





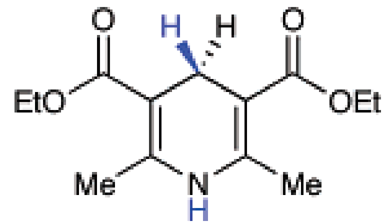
Selective reduction of pyruvate imines to create amino acids

Could this organocatalytic sequence be utilized in the redution of carbon–carbon double bonds

J. Am. Chem. Soc., **2005**, *127*, 32-33

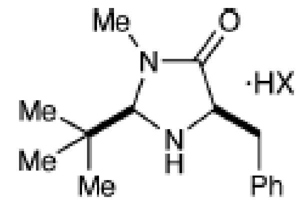
Enantioselective Organocatalytic Hydride Reduction

- Hantzsch ester: analogue of NADH

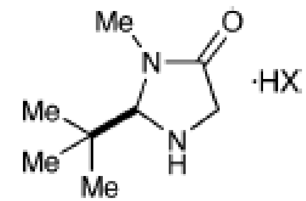


Hantzsch ester
hydride source

- LUMO lowing amine catalyst: analogue of enzyme



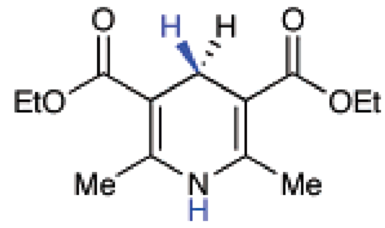
catalyst **1**



catalyst **2**

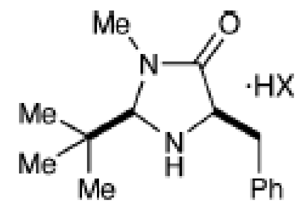
Enantioselective Organocatalytic Hydride Reduction

- Hantzsch ester: analogue of NADH

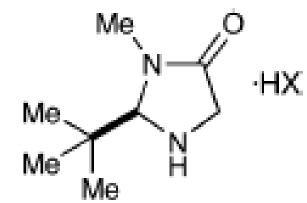


Hantzsch ester
hydride source

- LUMO lowing amine catalyst: analogue of enzyme

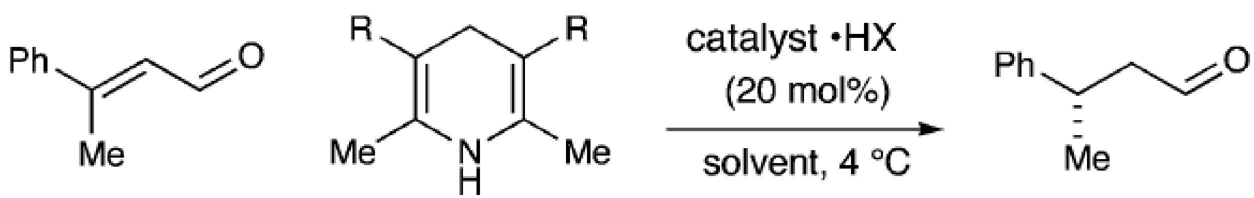


catalyst **1**



catalyst **2**

- catalyst screening



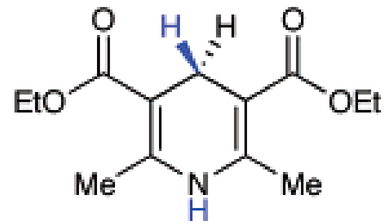
(1)

entry	catalyst	HX	solvent	time (h)	% conversion[b]	% ee[c]
1	L-proline	TFA	toluene	5	47	15
2	**1**	TFA	toluene	1	96	75
3	**2**	TFA	toluene	1	95	88

J. Am. Chem. Soc., **2005**, *127*, 32-33

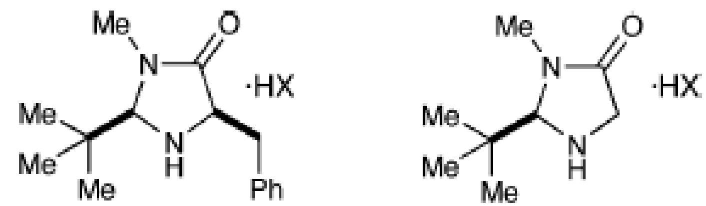
Enantioselective Organocatalytic Hydride Reduction

- Hantzsch ester: analogue of NADH



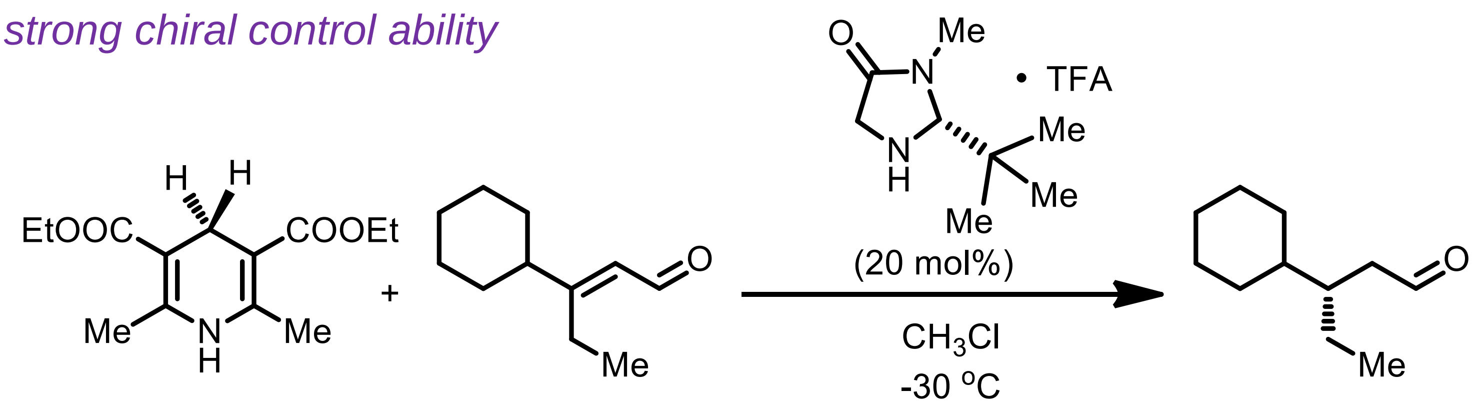
Hantzsch ester
hydride source

- LUMO lowing amine catalyst: analogue of enzyme



- substrate scope research:

strong chiral control ability

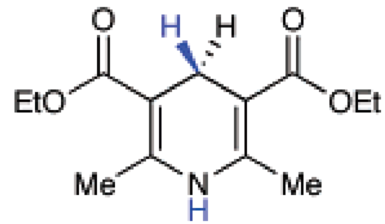


95 % yield, 91 % ee

J. Am. Chem. Soc., **2005**, *127*, 32-33

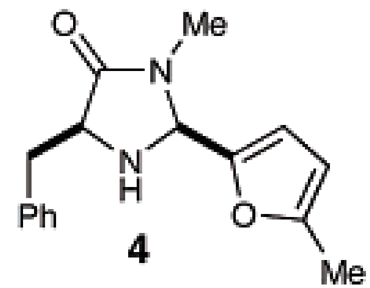
Enantioselective Organocatalytic Hydride Reduction

- Hantzsch ester: analogue of NADH



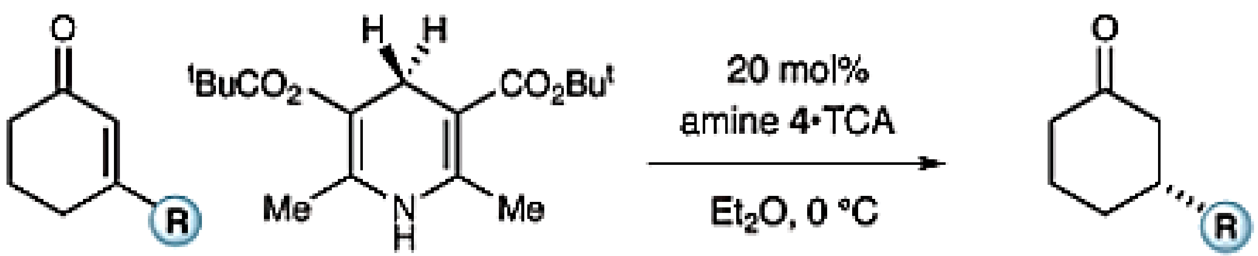
Hantzsch ester
hydride source

- LUMO lowing amine catalyst: analogue of enzyme



4
enone catalyst

- In 2006, further expanded to cyclic enone substrate!

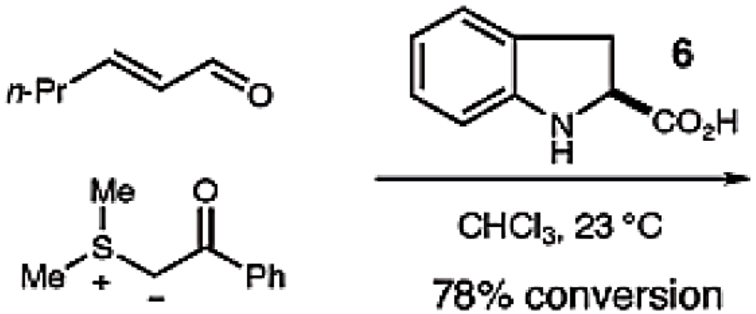


1 equiv 1.1 equiv product

12 examples (5-7 member rings)
70-89 % yield, 88-96 % ee

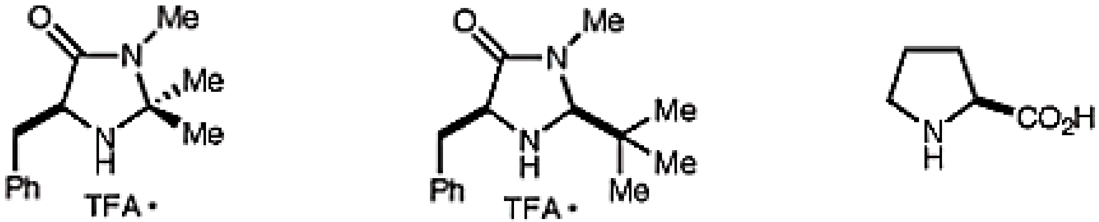
J. Am. Chem. Soc., **2006**, 128, 12662-12663

Enantioselective Cyclopropanation Reaction



78% conversion 94% ee, 27:1 dr

- Catalyst screening:

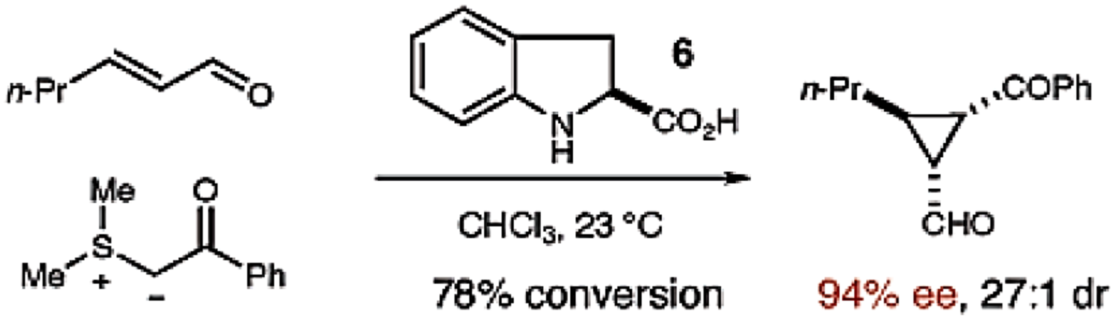


imidazolidinone **2**	imidazolidinone **3**	L-proline (**4**)
0% conversion	0% conversion	72% conversion (46% ee)

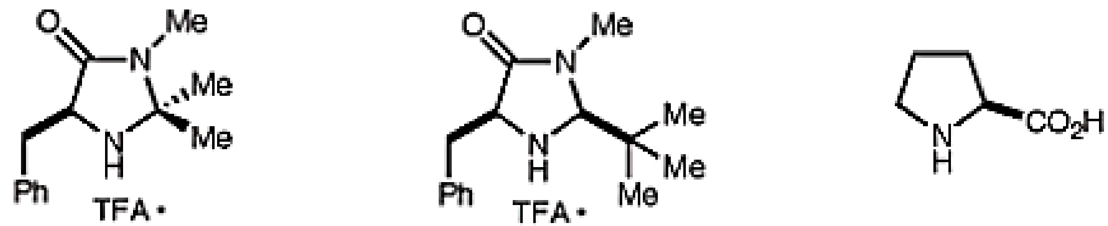
***only** L-proline gives the desired product! Why?*

J. Am. Chem. Soc., **2005**, *127*, 3240-3241

Enantioselective Cyclopropanation Reaction



- Catalyst screening:



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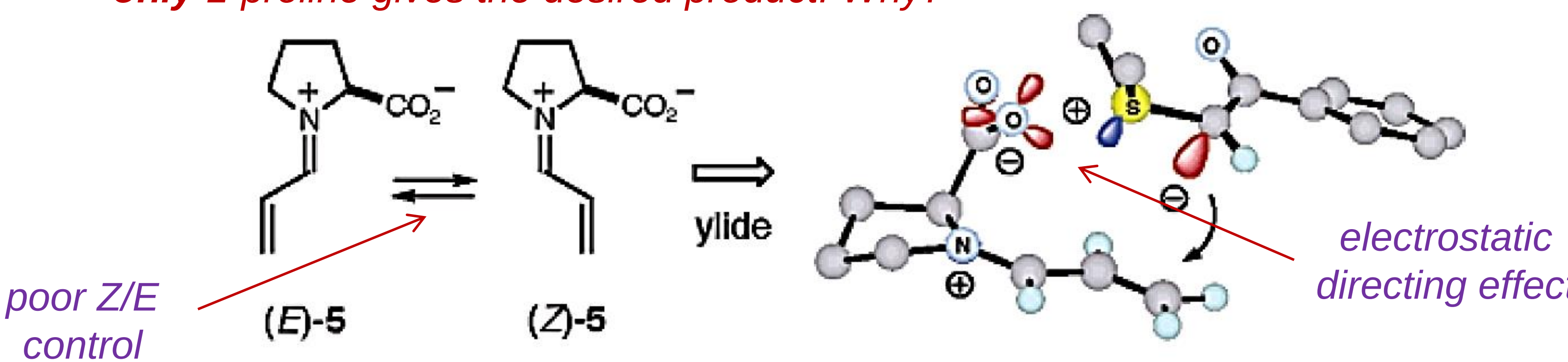
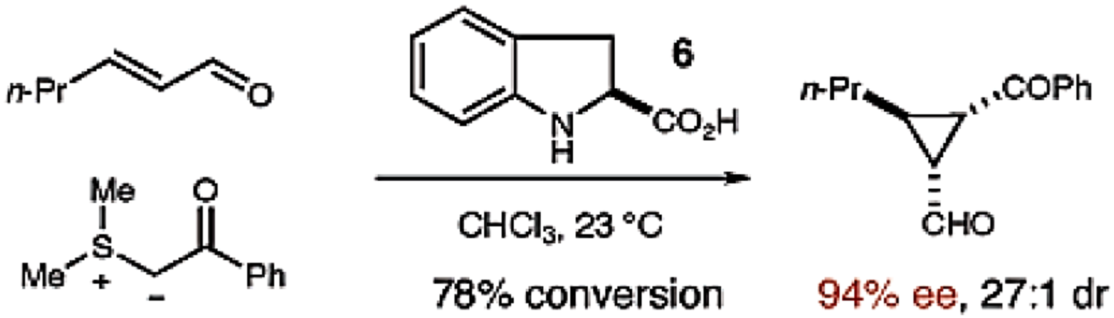


zwitterionic iminium
poor iminium control

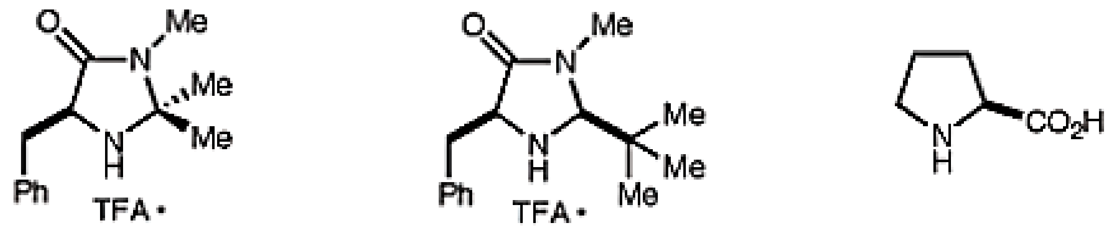
directed electrostatic activation
good reactivity, low % ee

J. Am. Chem. Soc., **2005**, *127*, 3240-3241

Enantioselective Cyclopropanation Reaction



- Catalyst screening:



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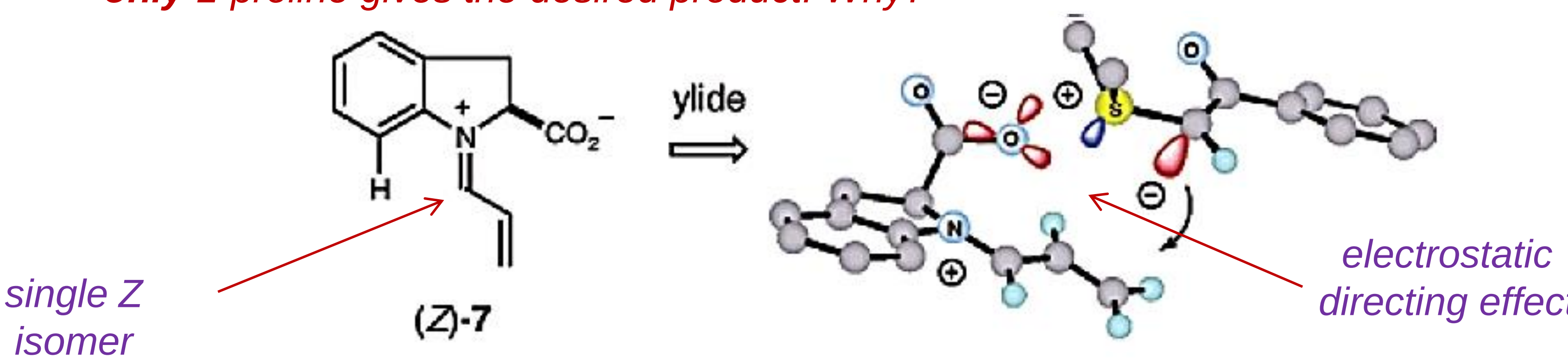
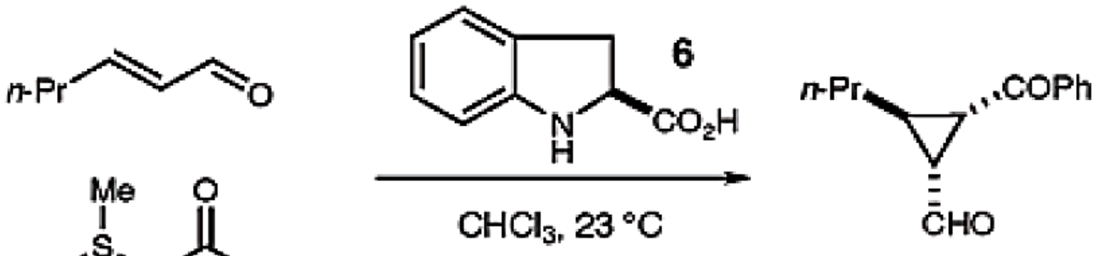


van der Waals forces lead to selective (Z)-iminium formation

retain electrostatic activation good reactivity, high % ee

J. Am. Chem. Soc., **2005**, *127*, 3240-3241

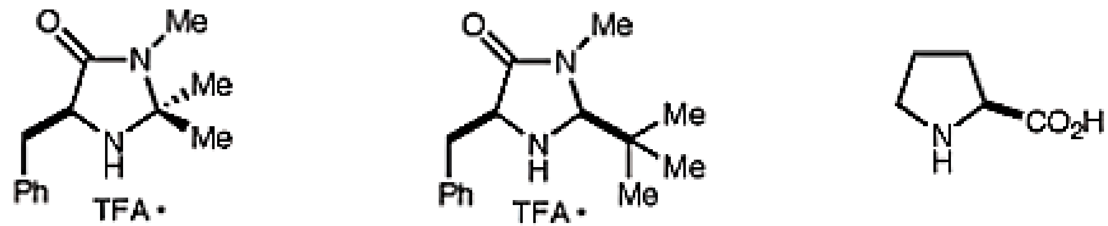
Enantioselective Cyclopropanation Reaction



78% conversion   94% ee, 27:1 dr

solvent	%conv	%ee
DMF	20	–30
acetone	16	28
THF	25	77
$CHCl_3$	85	95

- Catalyst screening:



imidazolidinone **2**	imidazolidinone **3**	L-proline (**4**)
0% conversion	0% conversion	72% conversion (46% ee)

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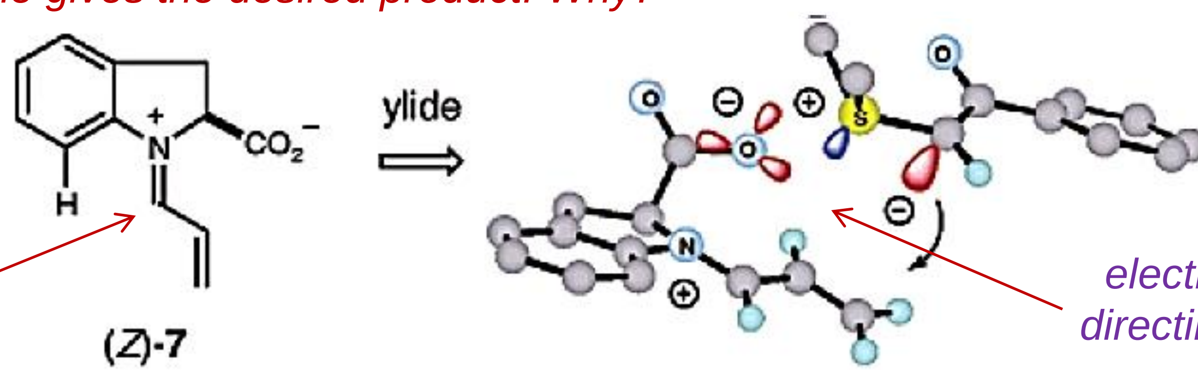


(*Z*)-**7**

single Z isomer

electrostatic directing effect

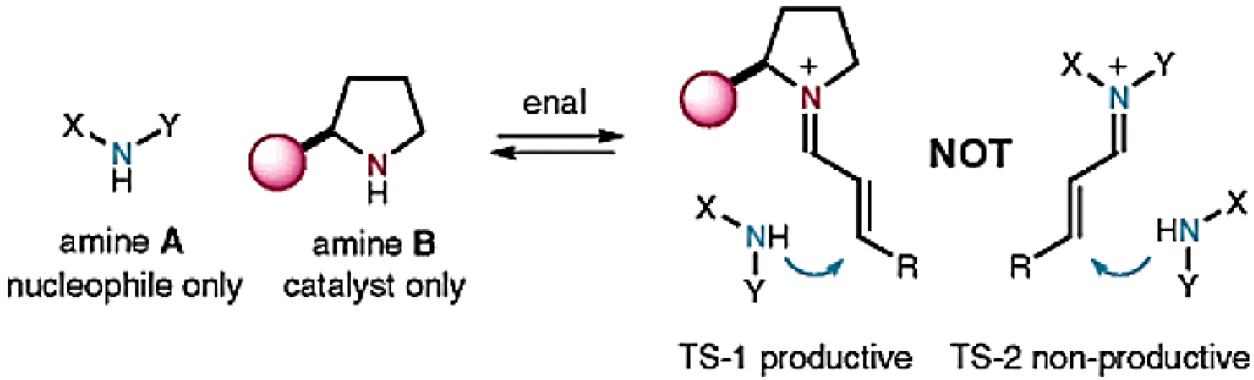
van der Waals forces lead to selective (*Z*)-iminium formation

retain electrostatic activation good reactivity, high % ee

J. Am. Chem. Soc., **2005**, *127*, 3240-3241

Enantioselective Amination Reaction

- Iminum catalyzed amination requires selective amine partition

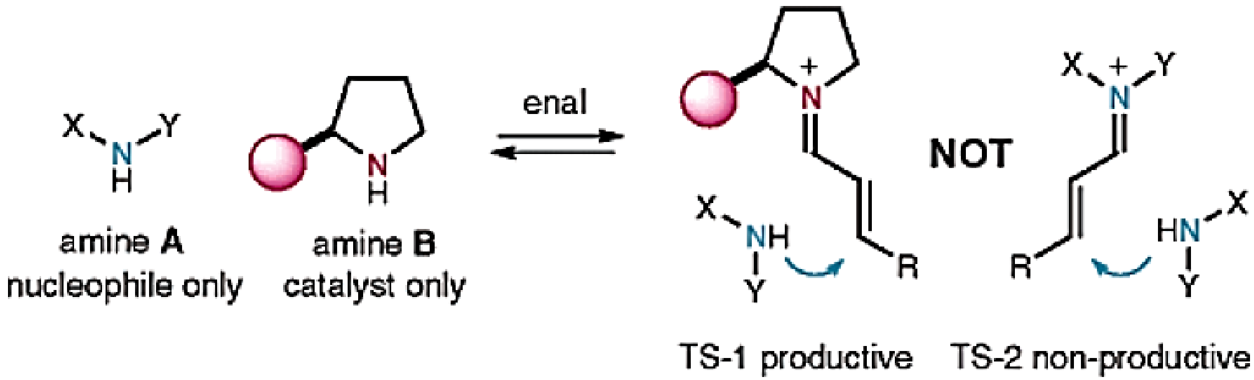


- Carbamate is good, but with poor nucleophilicity

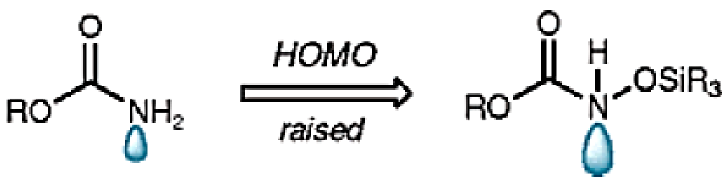
J. Am. Chem. Soc., **2006**, *128*, 9328-9329

Enantioselective Amination Reaction

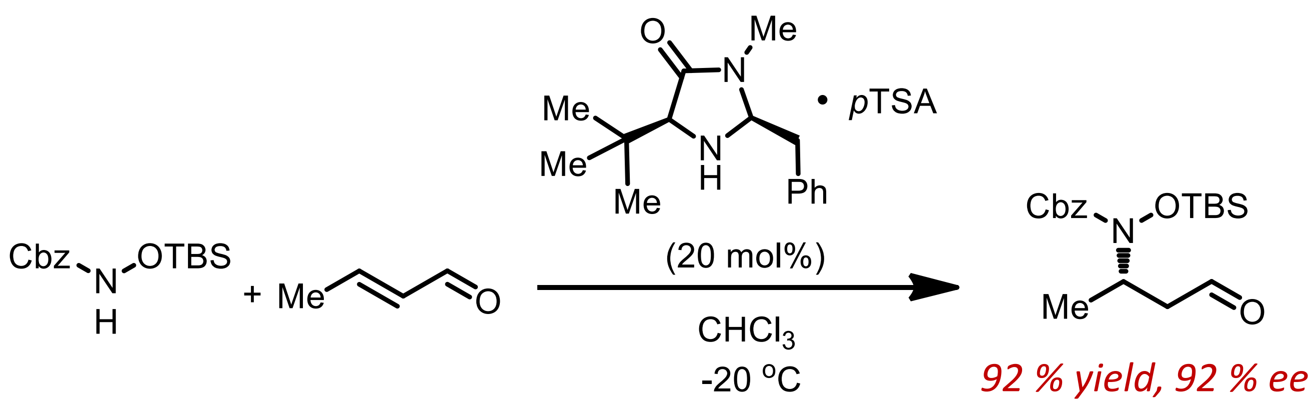
- Iminum catalyzed amination requires selective amine partition



- Carbamate is good, but poor nucleophilicity
- Carbamate nucleophilicity enhanced by *α*-effect



- Enhanced nucleophilicity
- (N–H) pK_a ~ 9.0



J. Am. Chem. Soc., **2006**, *128*, 9328-9329

Content

1 *LUMO Catalysis*

2 *HOMO Catalysis*

3 *Cascade LUMO-HOMO Catalysis*

4 *SOMO Catalysis*

5 *Photoredox Organo Catalysis*

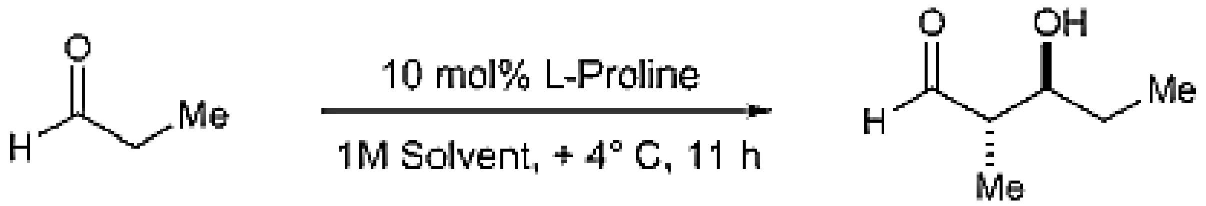
6 *Photoredox Organo Catalysis (Type II)*

7 *Summary*

Content

Enantioselective Aldol Reaction

- Aldehyde dimerization

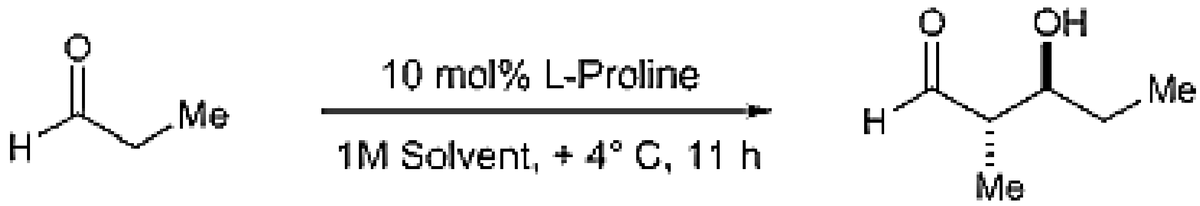


91 % yield, 3:1 dr, 99 % ee

J. Am. Chem. Soc., **2002**, *124*, 6798-6799

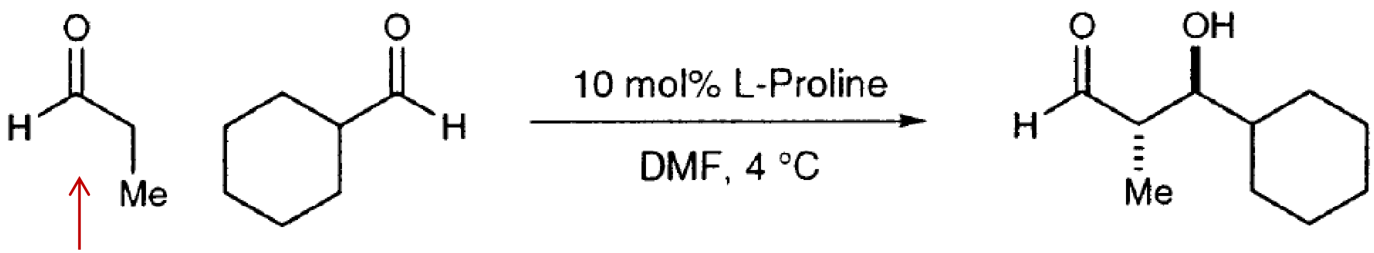
Enantioselective Aldol Reaction

- Aldehyde dimerization



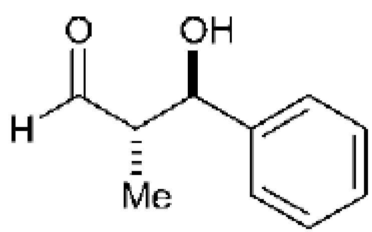
91 % yield, 3:1 dr, 99 % ee

- Aldehyde cross-aldol reaction: *with non-enaminizable aldehyde*

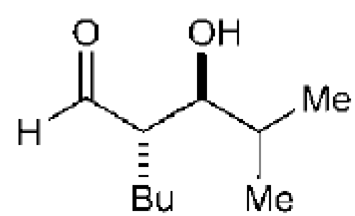


syringe pump addition

87 % yield, 14:1 dr, 99 % ee



81 % yield, 3:1 dr, 99 % ee

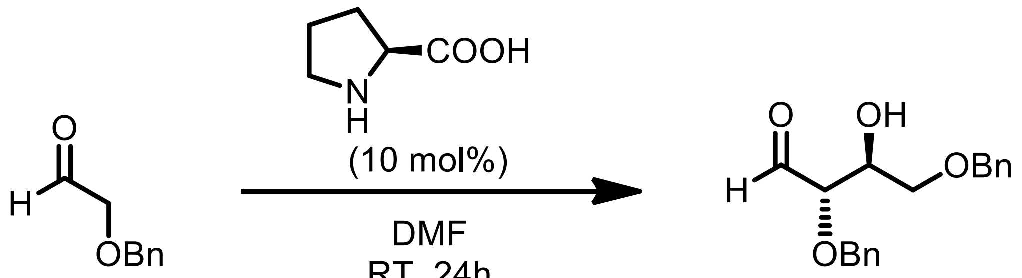


80 % yield, 24:1 dr, 98 % ee

J. Am. Chem. Soc., **2002**, *124*, 6798-6799

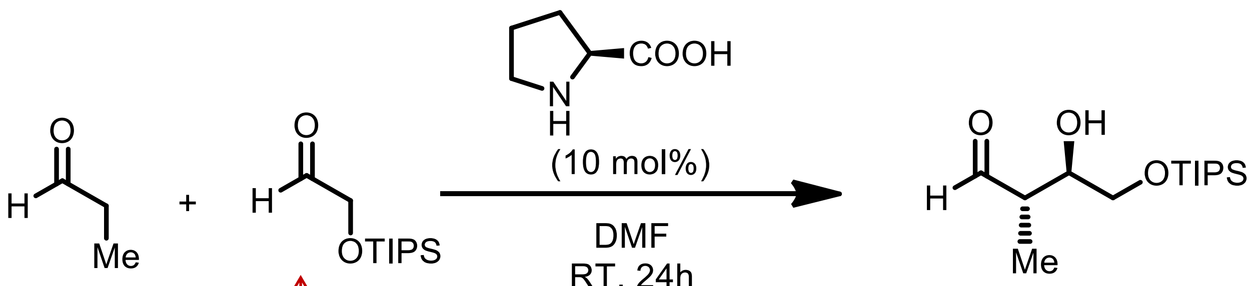
Enantioselective Aldol Reaction：Further Expansion

- α-Oxy-aldehyde dimerization



73 % yield, 4:1 dr, 98 % ee

- Cross-aldol reaction: *with non-enaminizable aldehyde*



75 % yield, 4:1 dr, 99 % ee

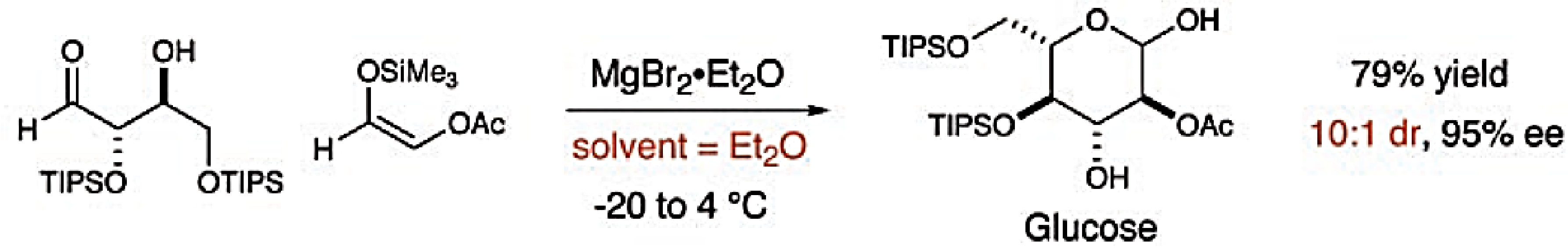
*Here as **Aldol acceptor***
Differs with metal mediated reaction

Angew. Chem. Int. Ed. **2004**, *43*, 2152 –2154

Angew. Chem. Int. Ed. **2004**, *43*, 6722-6724

Enantioselective Aldol Reaction：Further Expansion[2]

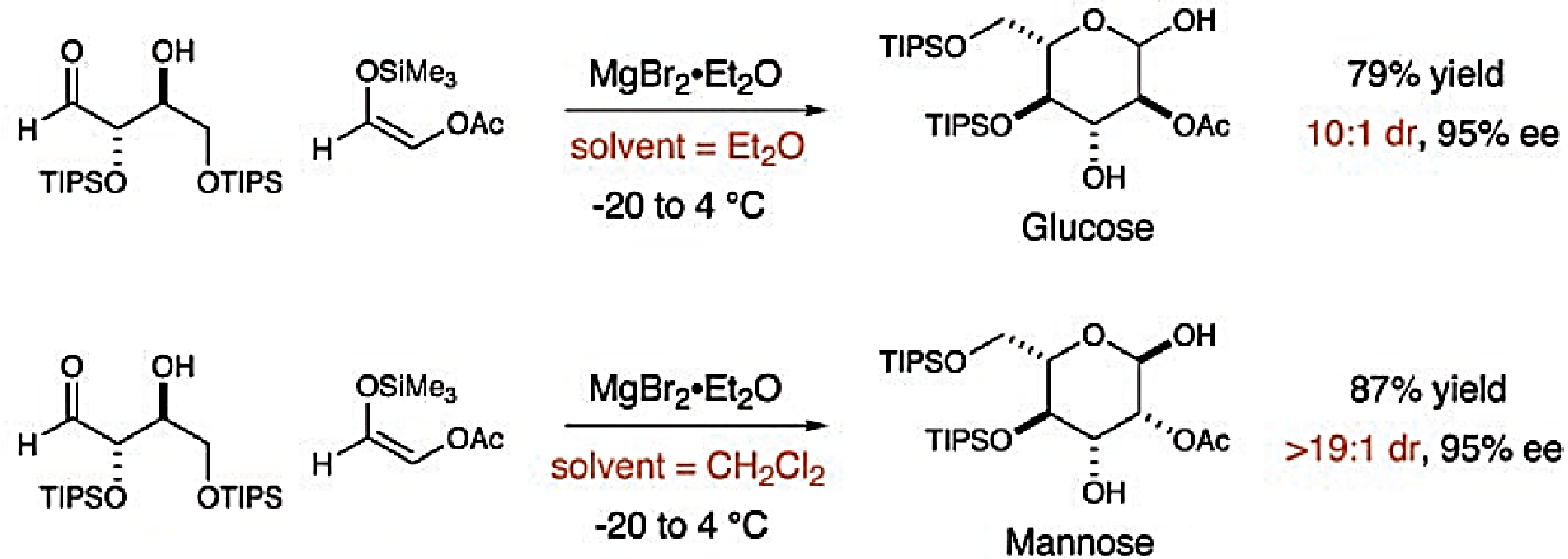
- monosaccharide synthesis!



Science, **2004**, *305*, 1752-1755

Enantioselective Aldol Reaction：Further Expansion[2]

- monosaccharide synthesis!



Science, **2004**, *305*, 1752-1755

Enantioselective Aldol Reaction：Further Expansion[2]

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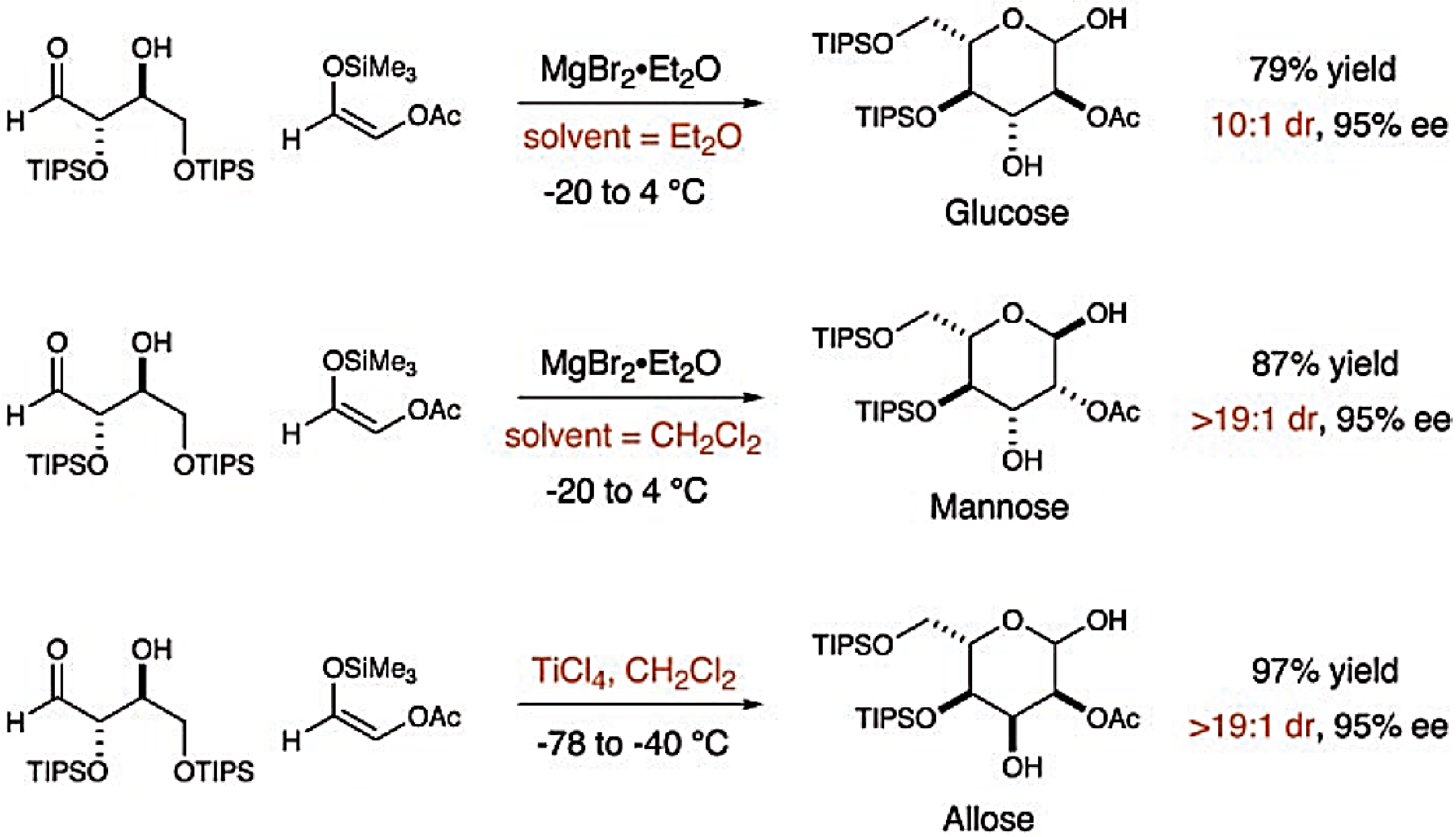
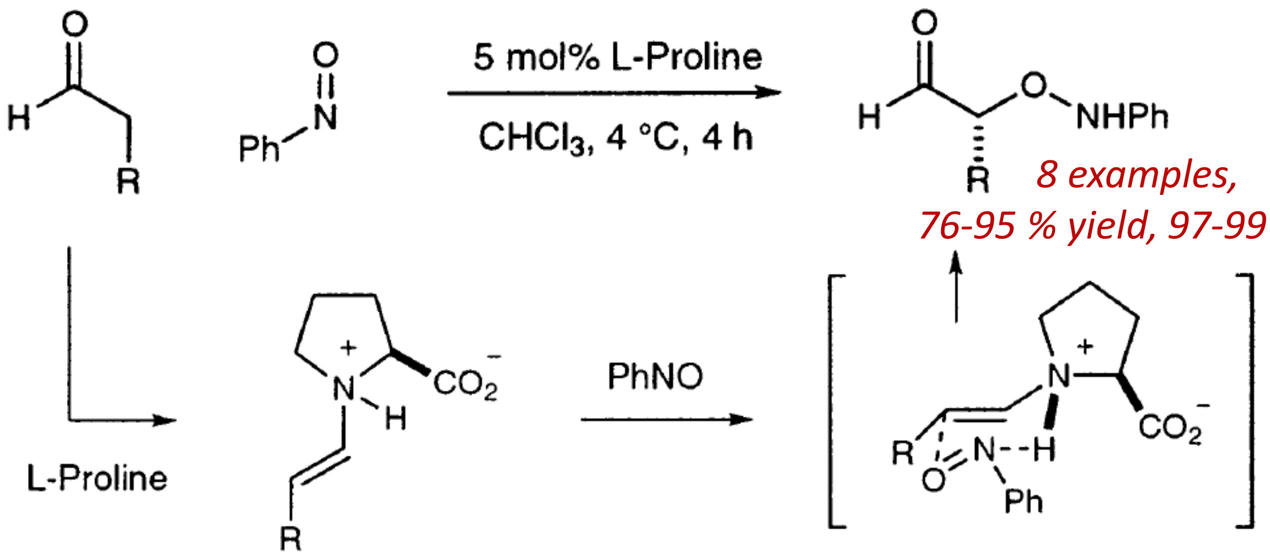


Science, **2004**, *305*, 1752-1755

HOMO Catalysis: other than Aldol

α-Oxidation of Aldehydes

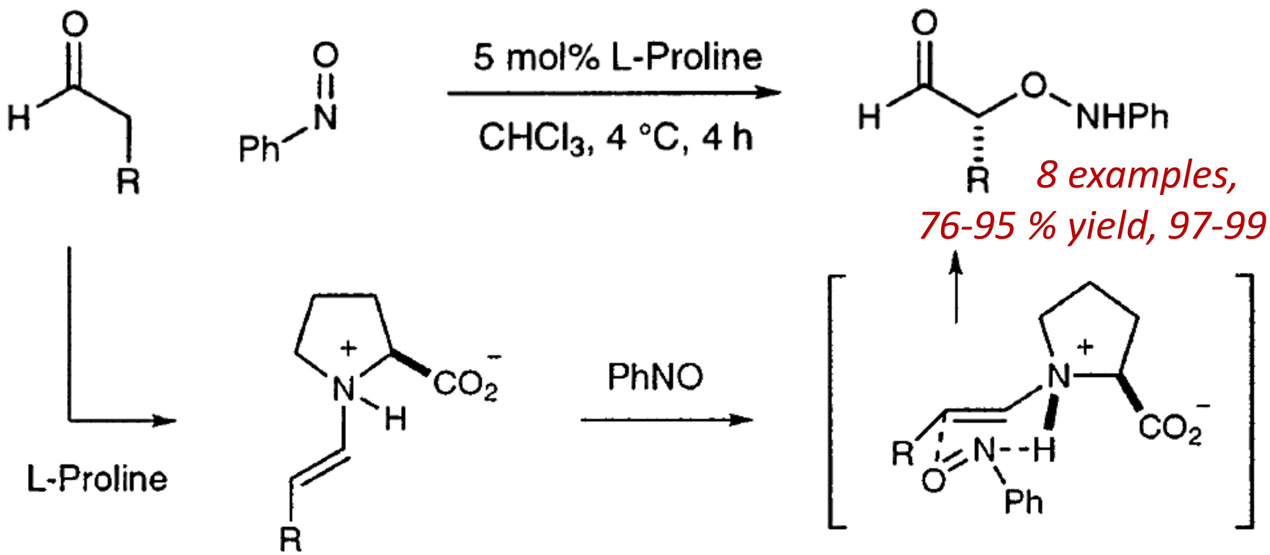


8 examples,
76-95 % yield, 97-99 % ee

J. Am. Chem. Soc., **2003**, *125*, 10808-10809

HOMO Catalysis: *other than Aldol*

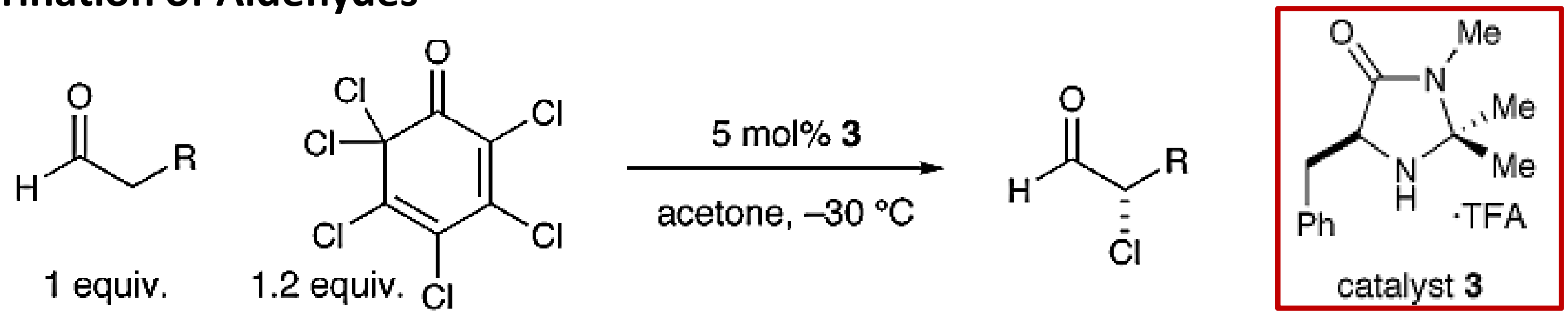
α-Oxidation of Aldehydes



8 examples,
76-95 % yield, 97-99 % ee

J. Am. Chem. Soc., **2003**, *125*, 10808-10809

α-Chlorination of Aldehydes



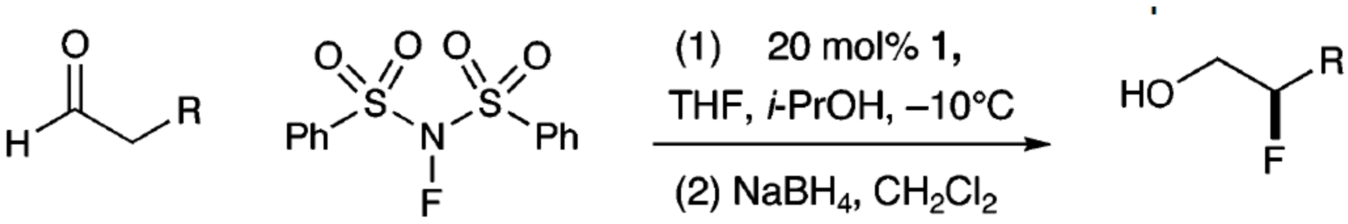
the Leckta quinone

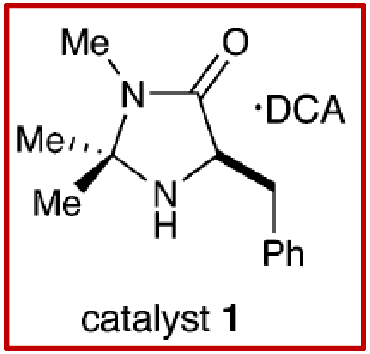
7 examples,
71-92 % yield, 87-95 % ee

J. Am. Chem. Soc., **2004**, *126*, 4108-4109

HOMO Catalysis: other than Aldol

α-Fluorination of Aldehydes

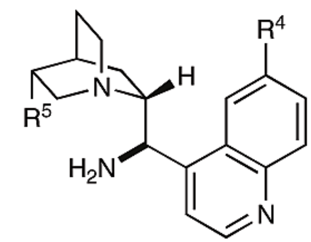




54-96% yield, 91-99% ee

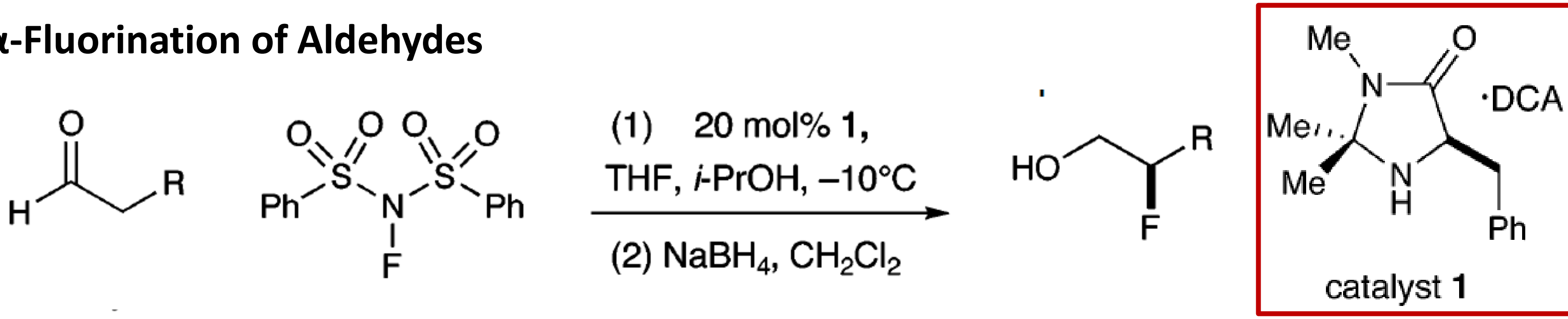
J. Am. Chem. Soc., **2005**, *127*, 8826-8828

*For the **α-Fluorination of cyclic ketone** using cinchonine-type catalyst, see:*
J. Am. Chem. Soc., **2011**, *133*, 1738-1741



HOMO Catalysis: other than Aldol

α-Fluorination of Aldehydes



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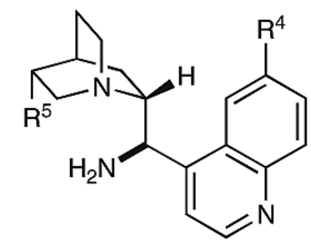
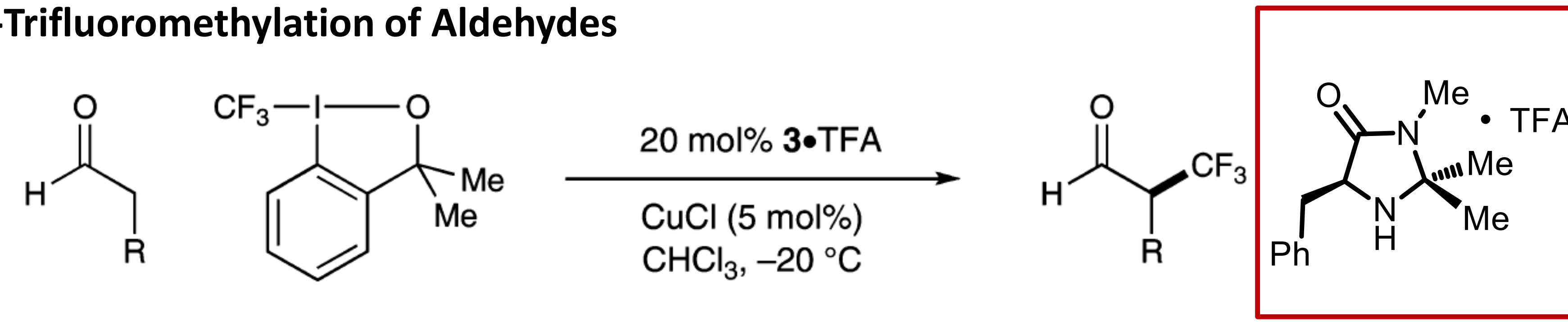


α-Trifluoromethylation of Aldehydes



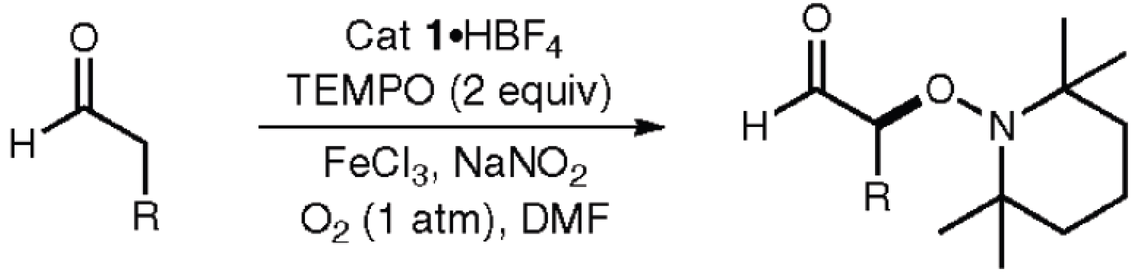
Togni reagent

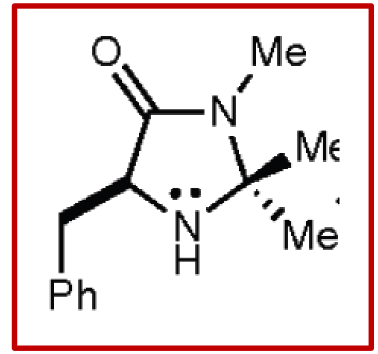
70-87% yield, 93-97% ee

J. Am. Chem. Soc., **2010**, *132*, 4986-4987

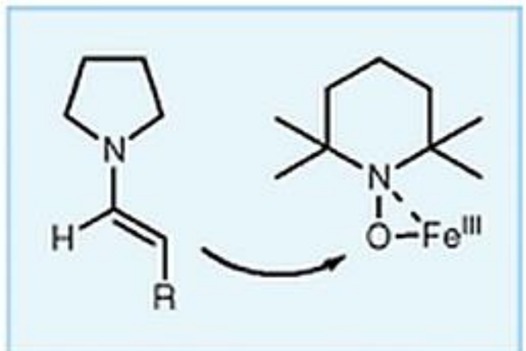
HOMO Catalysis: *other than Aldol*

α-Oxidation of Aldehydes



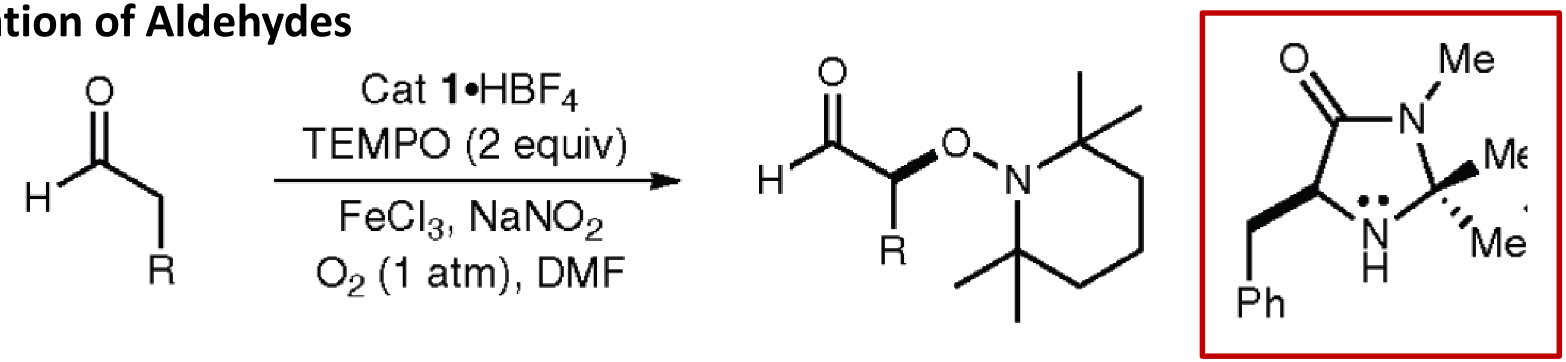


49-80% yield, 32--90% ee



HOMO Catalysis: *other than Aldol*

α-Oxidation of Aldehydes



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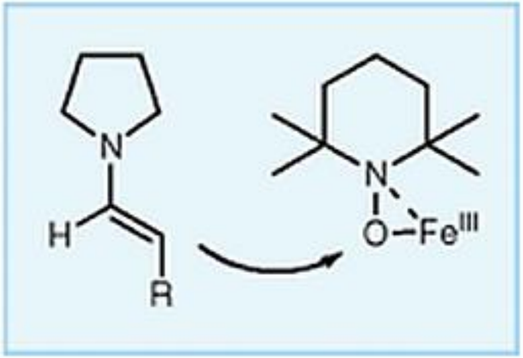
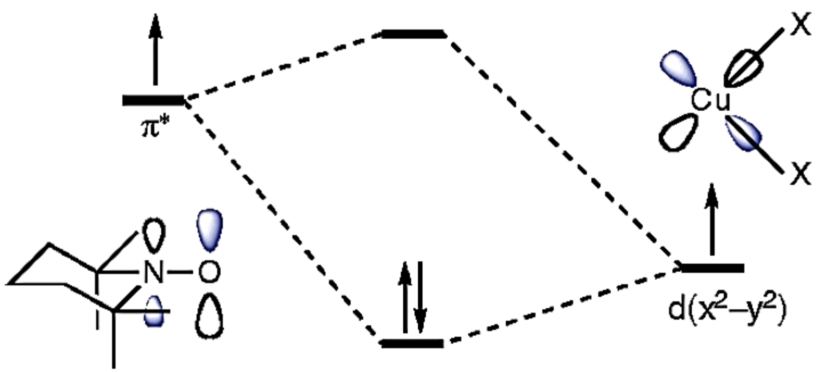




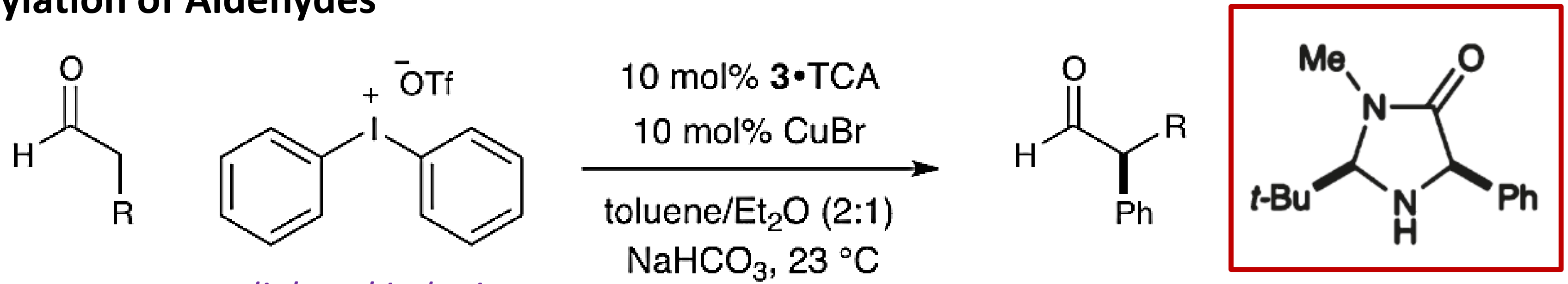
Complex formation: LUMO centered on TEMPO oxygen

Baerends, E. *J. Inorg. Chem*. **2009**, *48*, 11909

J. Am. Chem. Soc., **2010**, *132*, 10012-10014

HOMO Catalysis: other than Aldol

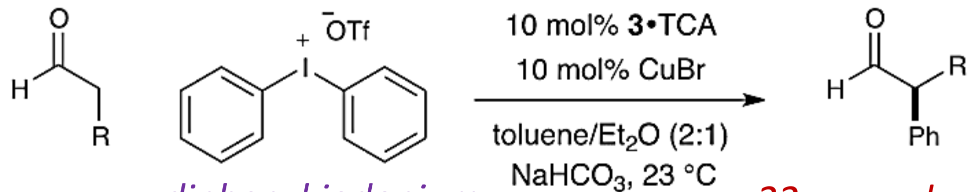
α-Arylation of Aldehydes



diphenyl iodonium

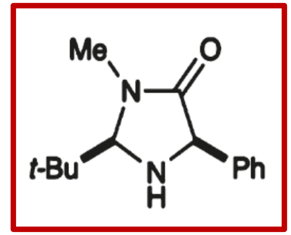
22 examples, 90-94% ee

J. Am. Chem. Soc., **2011**, *133*, 4260-4263

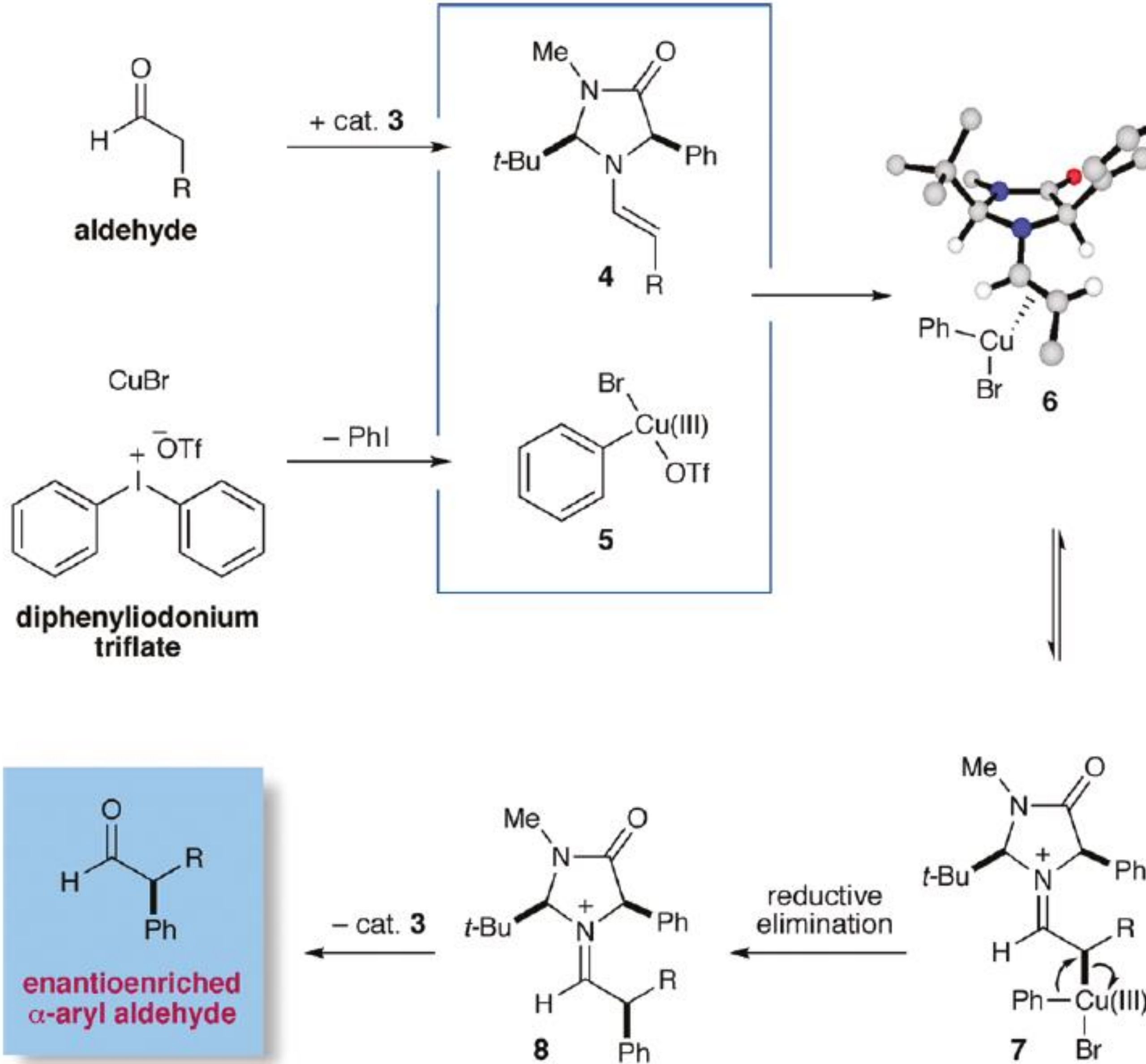


diphenyl iodonium

22 examples, 90-94% ee



■ proposed mechanism

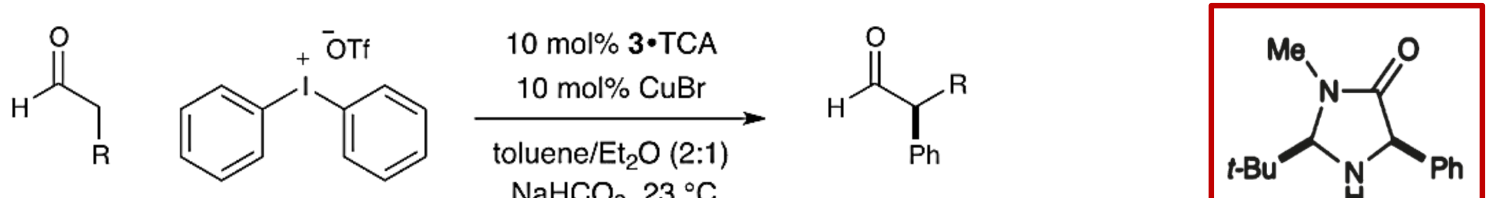


For studies on the mechanism of copper-catalyzed arylation, see:

(a) Lockhart, T. P. J. Am. Chem. Soc. ***1983****, 105, 1940.*

(b) Beringer, F. M.; Geering, E. J.; Kuntz, I.; Mausner, M. J. Phys. Chem. ***1956****, 60, 141.*

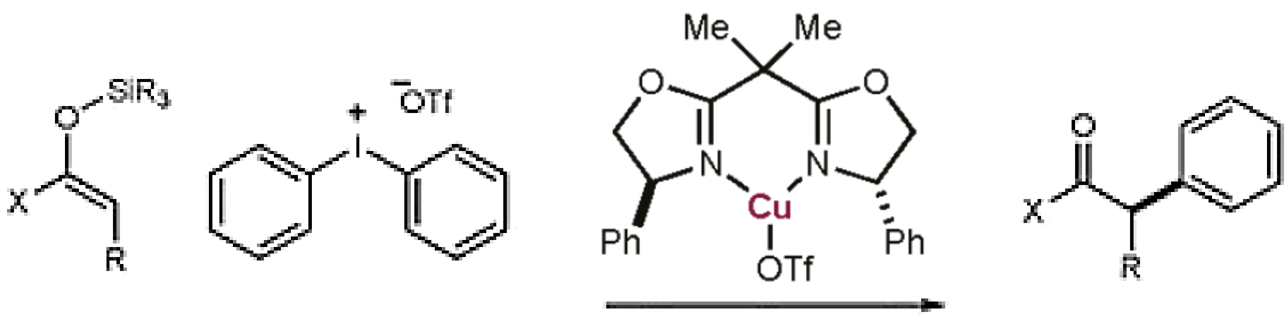
J. Am. Chem. Soc., **2011**, *133*, 4260



diphenyl iodonium

22 examples, 90-94% ee

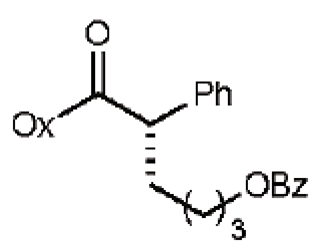
■ Further expansion to **ester** and **amide** substrate: *the use of enolsilane*



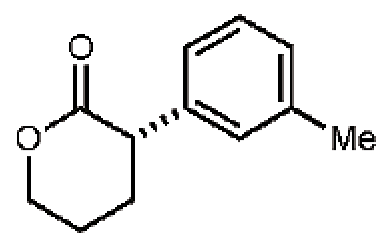
enolsilane
X = OR, NR_2

chiral Cu(I) salt

no chiral amine catalyst



94% yield, 93% ee

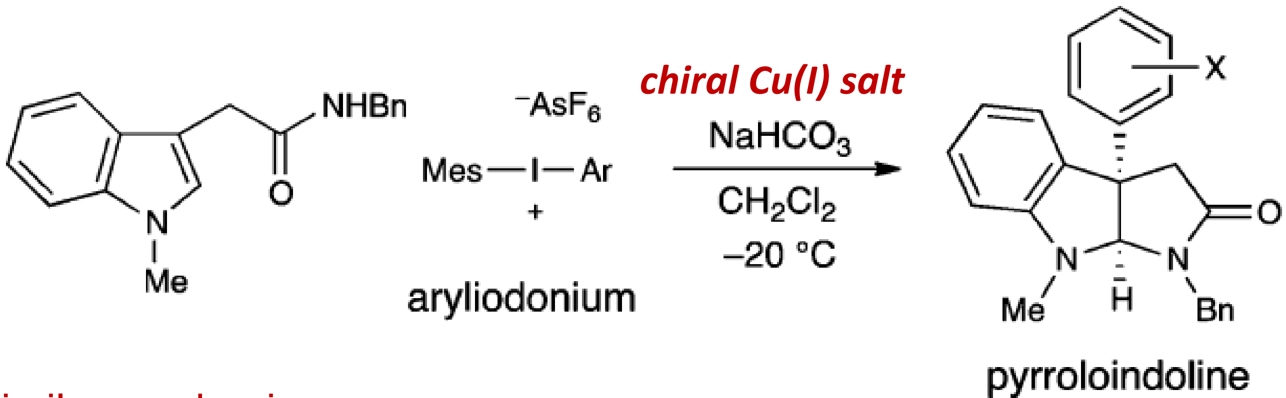


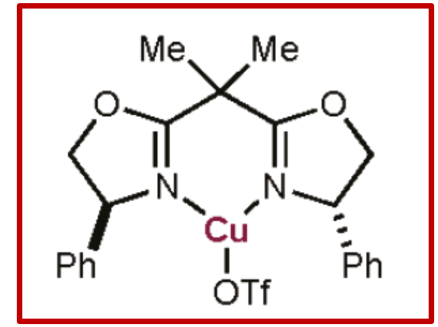
79% yield, 90% ee

J. Am. Chem. Soc., **2011**, *133*, 13782-13785

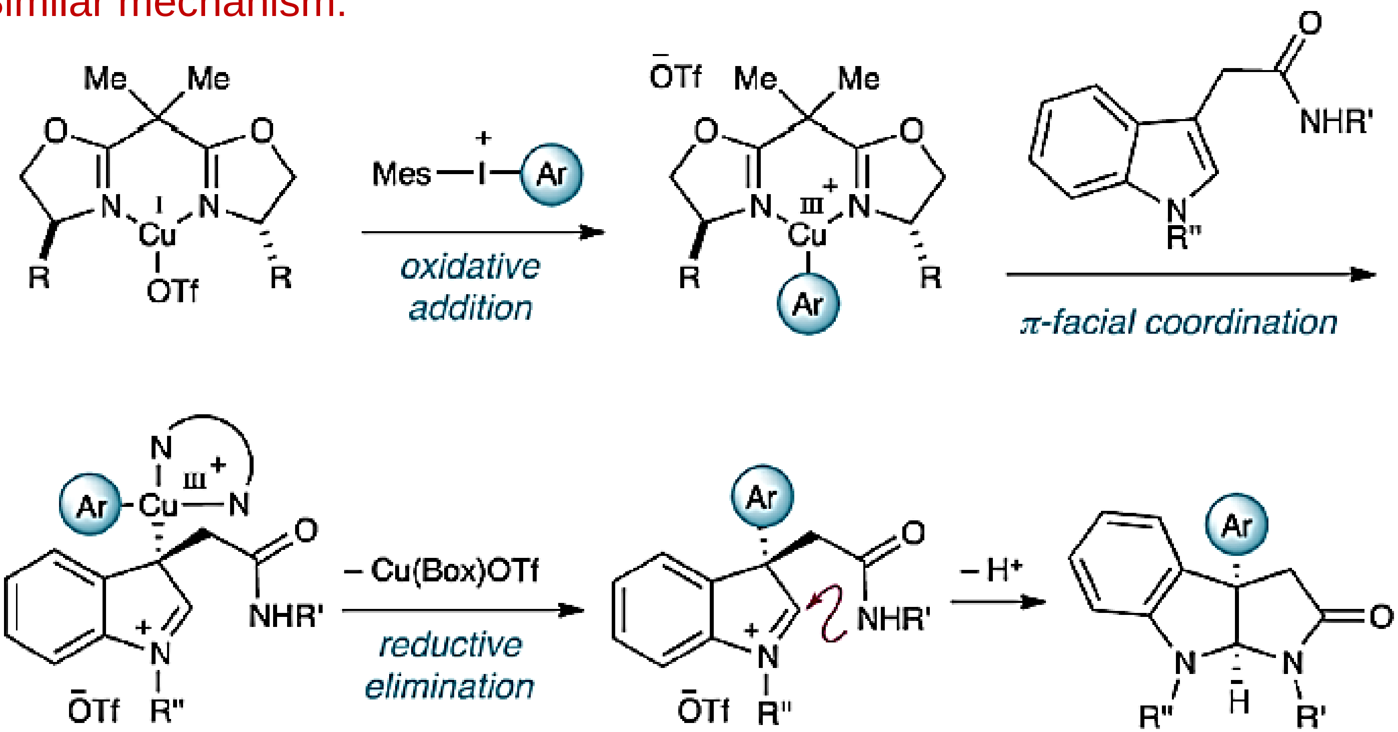
Not belong to the HOMO catalysis, but stongly related:

- using ***indole*** as the nucleophile instead of ***enolsilane***





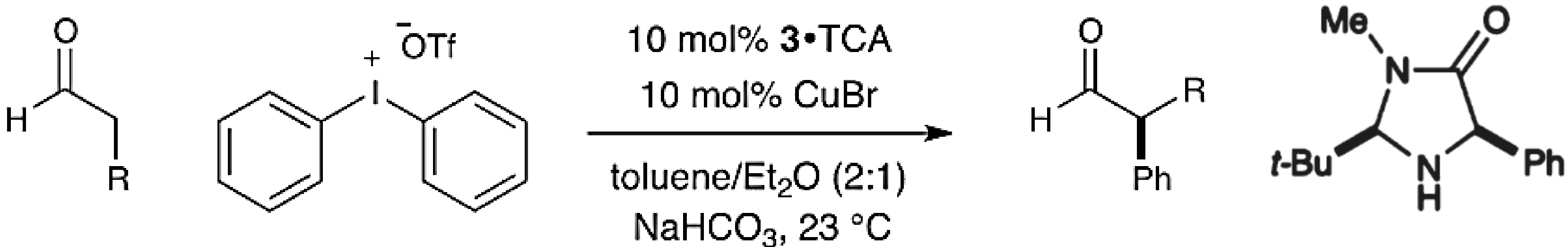
- Similar mechanism:



J. Am. Chem. Soc., **2012**, *134*, 10815-10818

HOMO catalysis: Further development

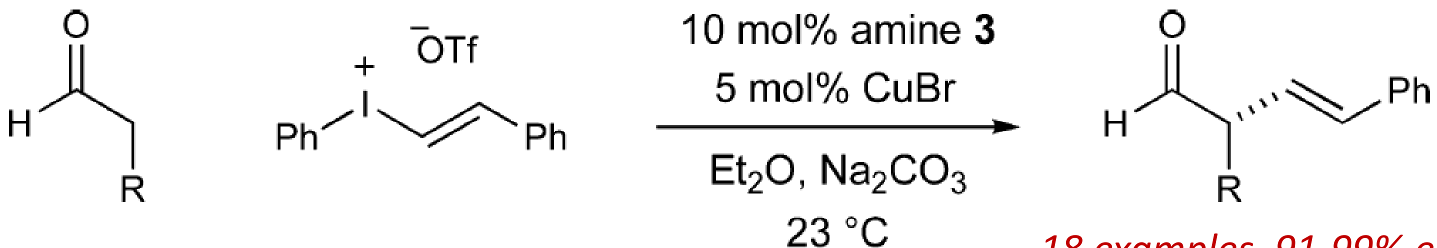
α-Arylation of Aldehydes



diphenyl iodonium

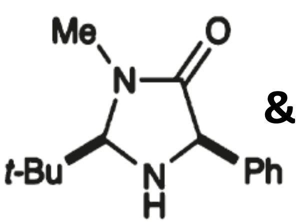
22 examples, 90-94% ee

α-Vinylation of Aldehydes



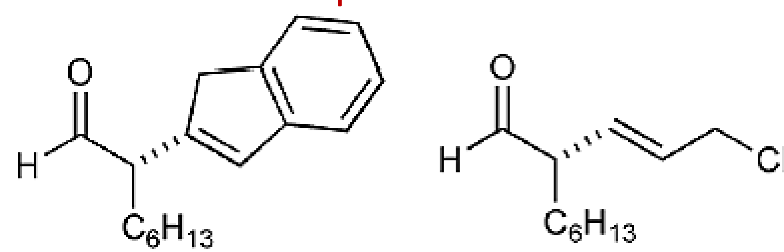
18 examples, 91-99% ee

- Identical catalyst combination



& **CuBr**

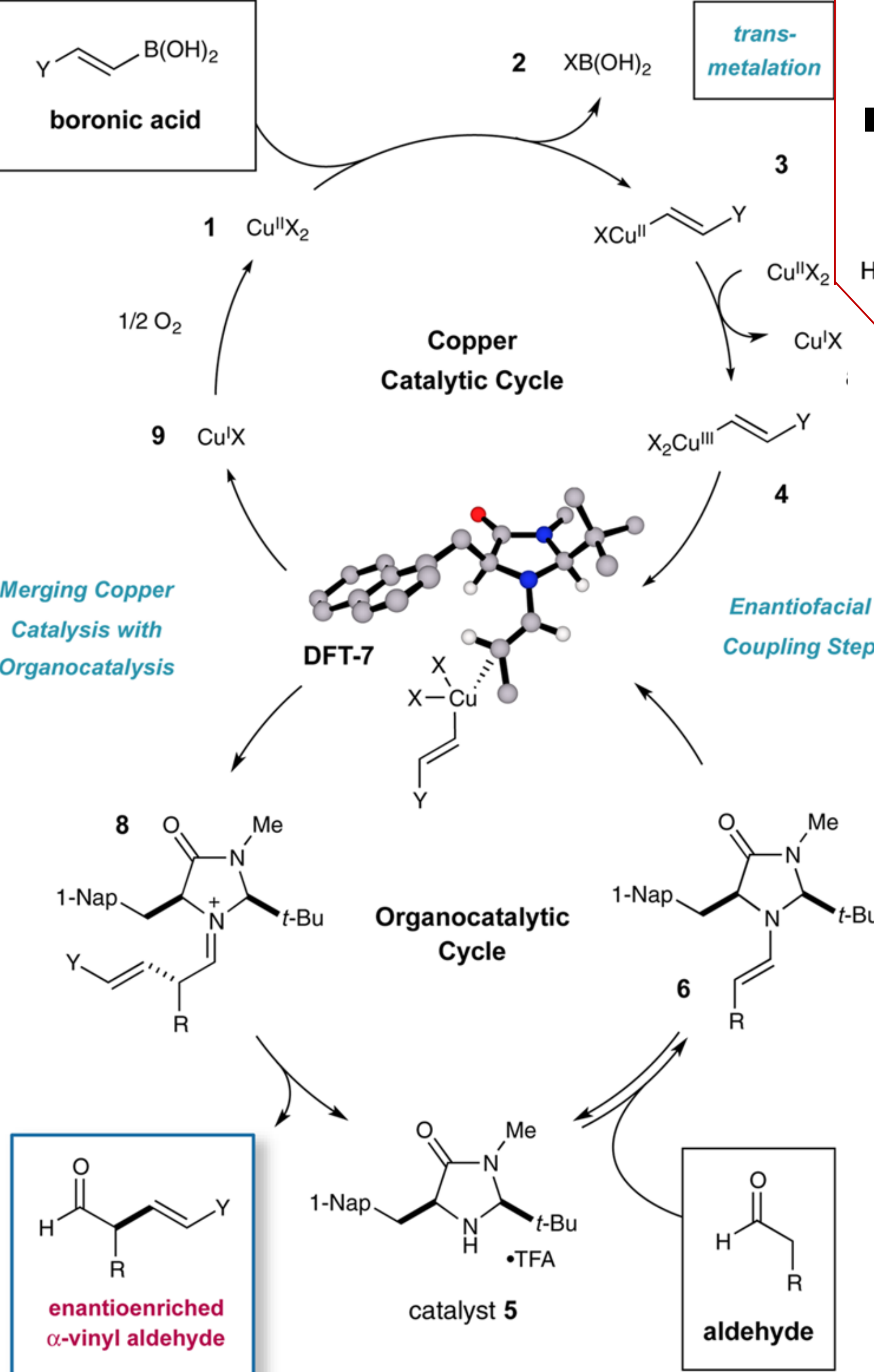
- Substrate scope



71% yield, 96% ee   91% yield, 94% ee

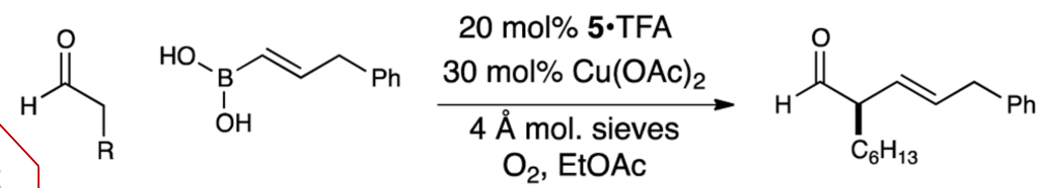
- Vinyl hypervalent iodide

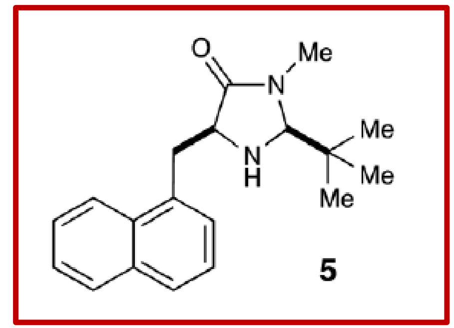
J. Am. Chem. Soc., **2012**, *134*, 9090-9093

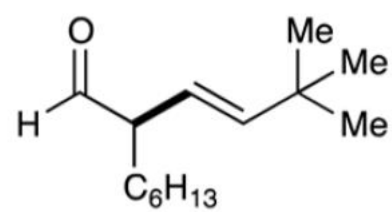


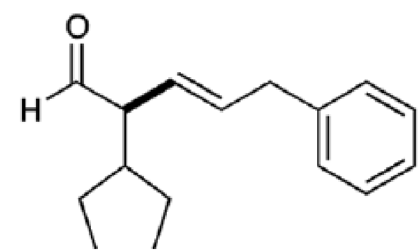
HOMO catalysis: Further development

- Combination of ***vinyl boronic acid*** and O_2









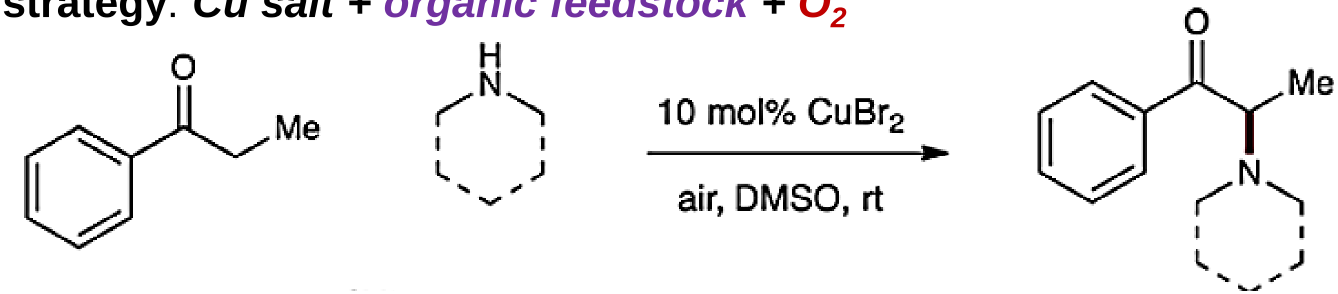
80% yield, 95% ee

73% yield, 90% ee

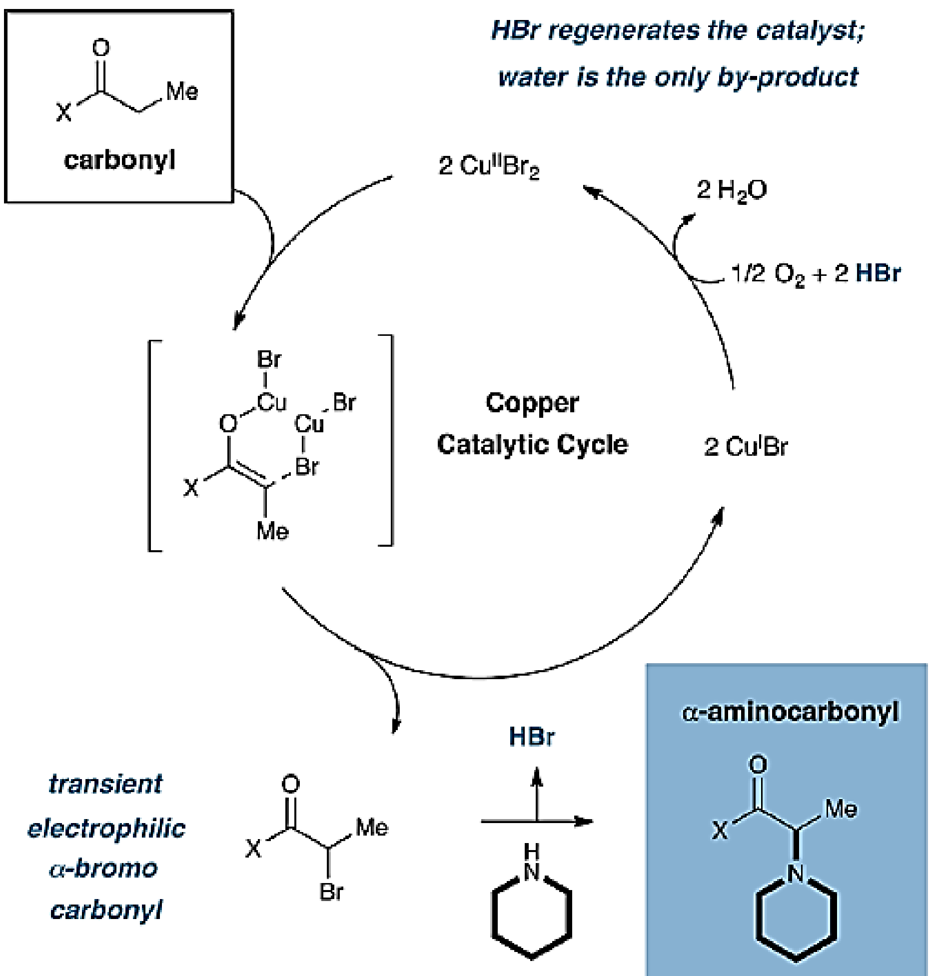
J. Am. Chem. Soc., **2013**, *135*, 11756-11759

Not belong to the HOMO catalysis, but stongly related:

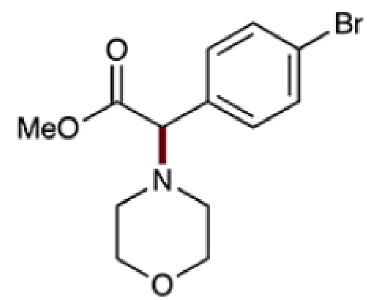
- **Same strategy**: ***Cu salt* + *organic feedstock* + *O_2***



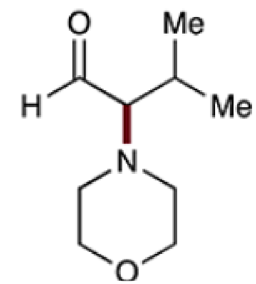
Proposed Mechanism:



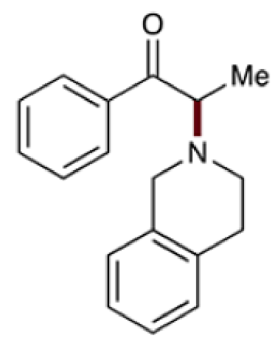
Substrate scope



91% yield



67% yield



90% yield

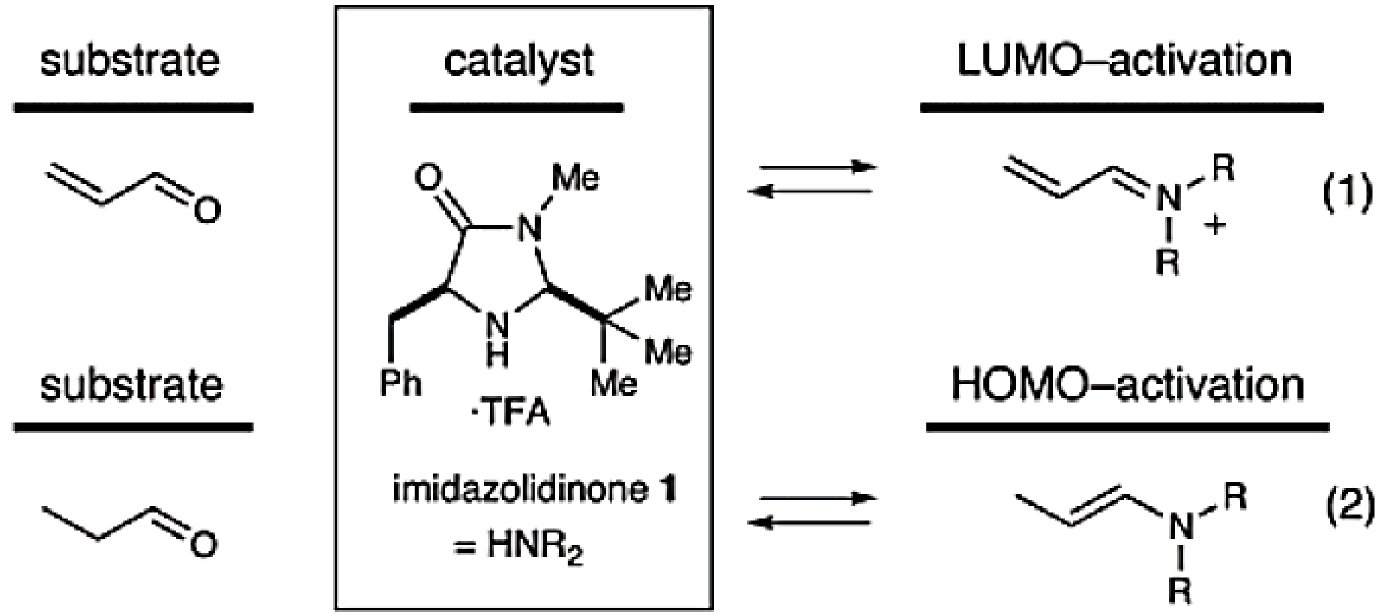
J. Am. Chem. Soc., **2013**, *135*, 16074-16077

Content

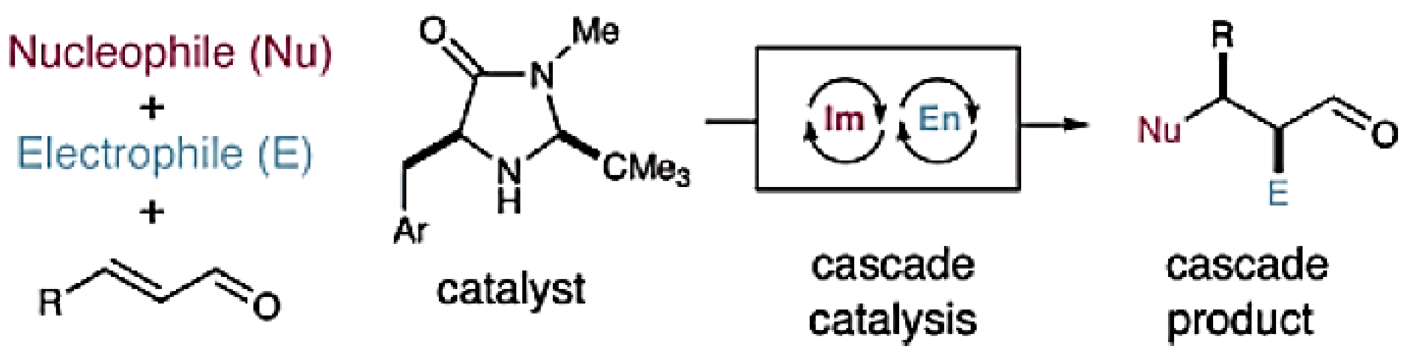
Content

Cascade Catalysis: Merging HOMO and LUMO Activation

- Imidazolldinones: Organocatalysts for HOMO or LUMO Activation



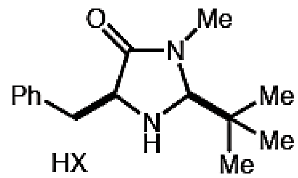
- Cascade Catalysis: **Merging HOMO and LUMO Activation with one catalyst**



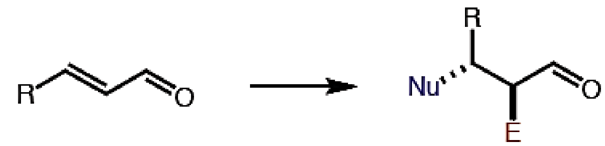
J. Am. Chem. Soc., **2005**, *127*, 15051-15053

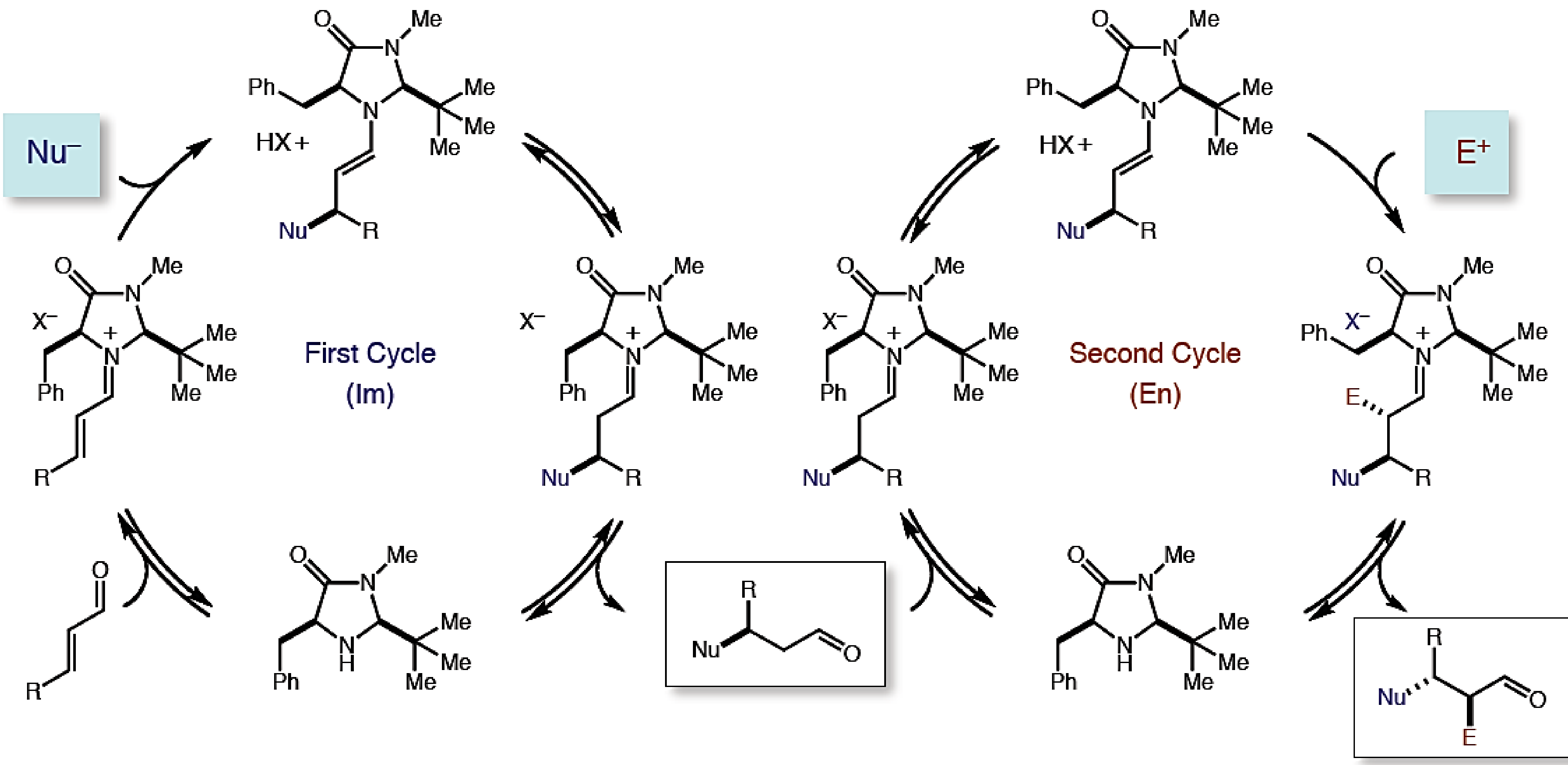
Cascade Catalysis: Merging HOMO and LUMO Activation

- **First step:**
  Iminium catalysis
- **Second step:**
  Enamine catalysis



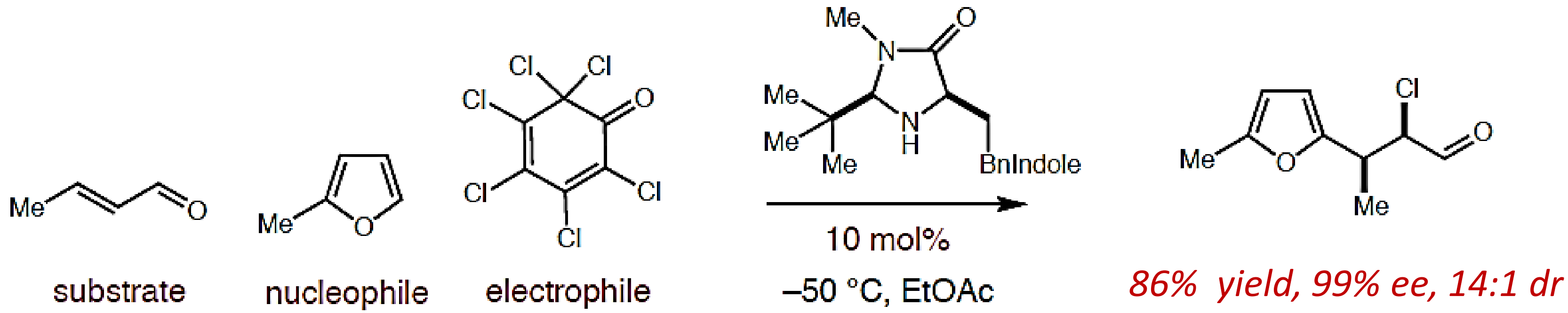
imidazolidinone



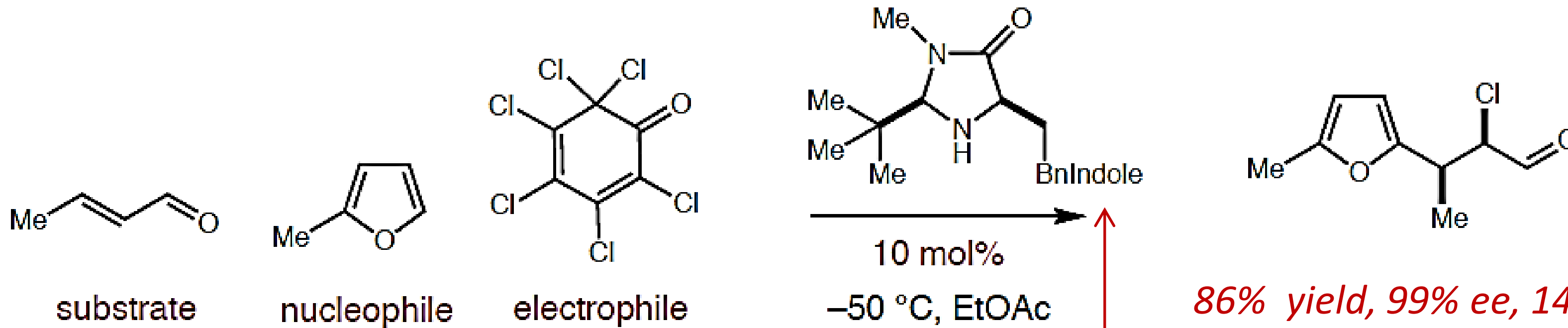


J. Am. Chem. Soc., **2005**, *127*, 15051-15053

Cascade Catalysis: Enantioselective β-aryl-α-chlorination



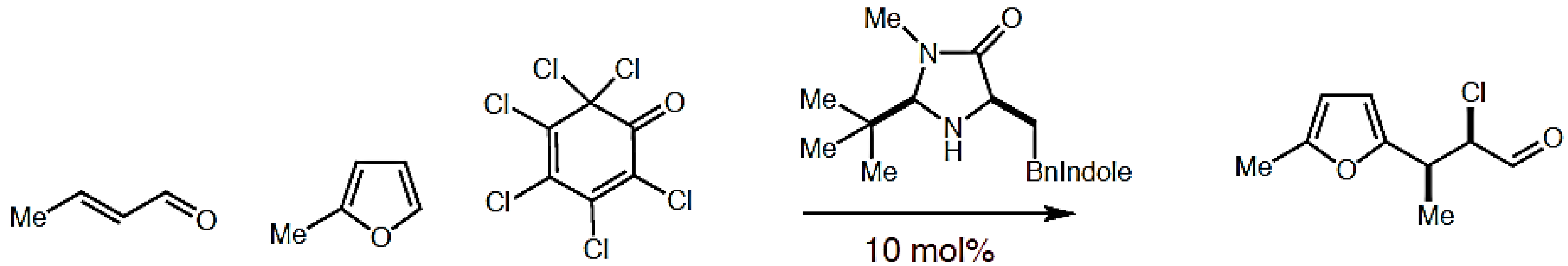
Cascade Catalysis: Enantioselective β-aryl-α-chlorination



86% yield, 99% ee, 14:1 dr

Large Bn-indole side chain:
Higher shield of the upward side
overcome the substrate control in the second catalytic circle

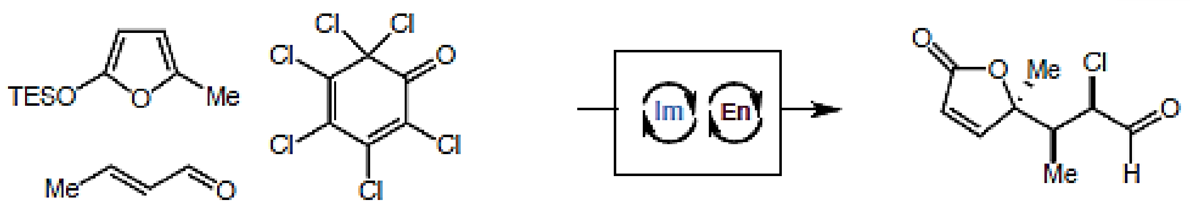
Cascade Catalysis: Enantioselective β-aryl-α-chlorination



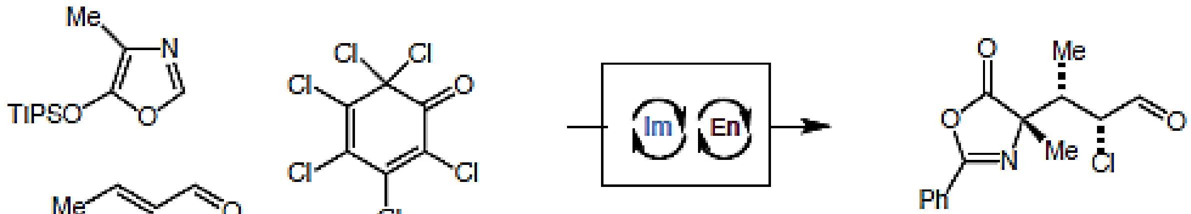
substrate nucleophile electrophile

86% yield, 99% ee, 14:1 dr

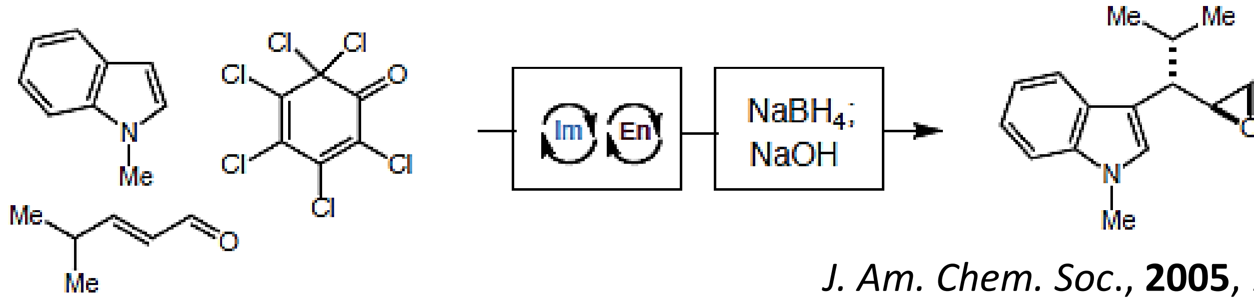
- Substrate scope



71% yield
syn:anti 25:1
99% ee



97% yield
syn:anti 9:1
99% ee

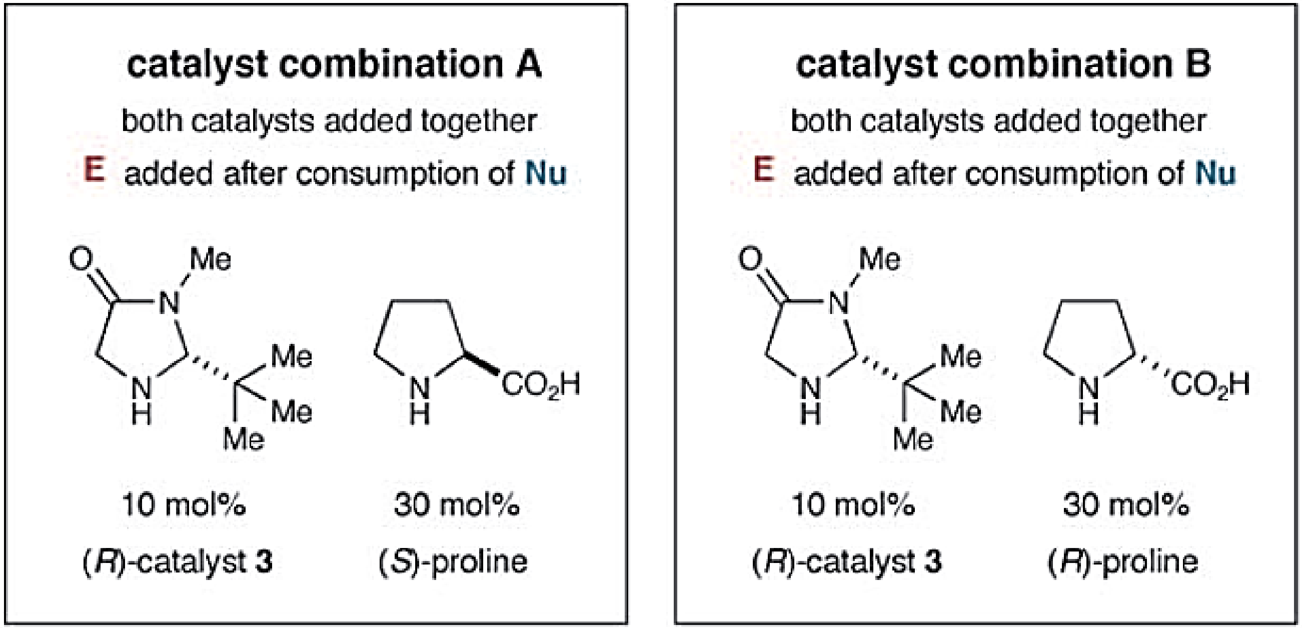


75% yield
syn:anti 12:1
99% ee

J. Am. Chem. Soc., **2005**, *127*, 15051-15053

Cascade Catalysis: More reaction types

- Modular combination of ***proline*** and ***Macmillan amine***

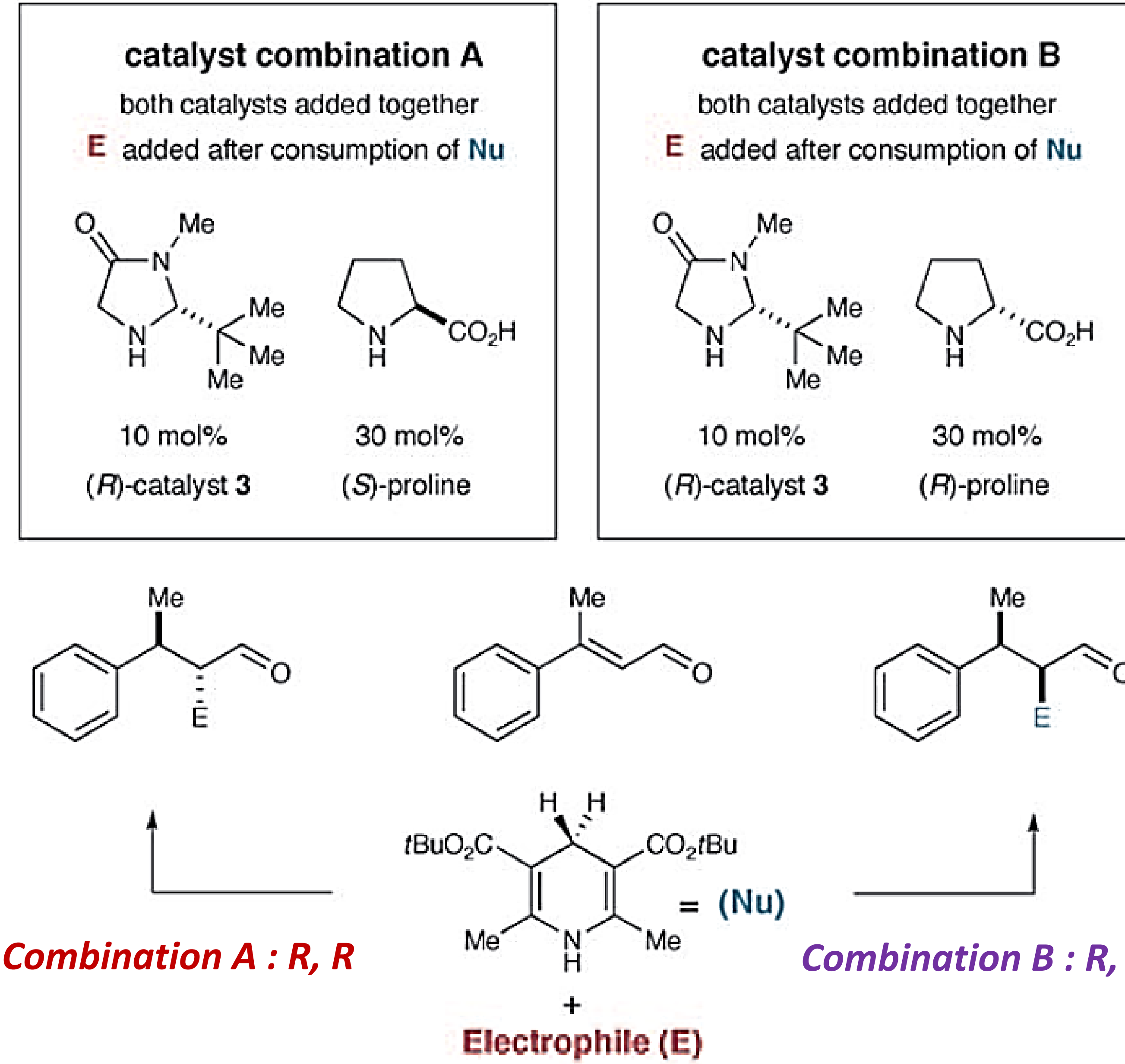


- ***Macmillan amine: Iminium catalyst***
- ***Proline: Enamine catalyst***

Angew. Chem. Int. Ed., **2009**, *48*, 4349-4353

Cascade Catalysis: More reaction types

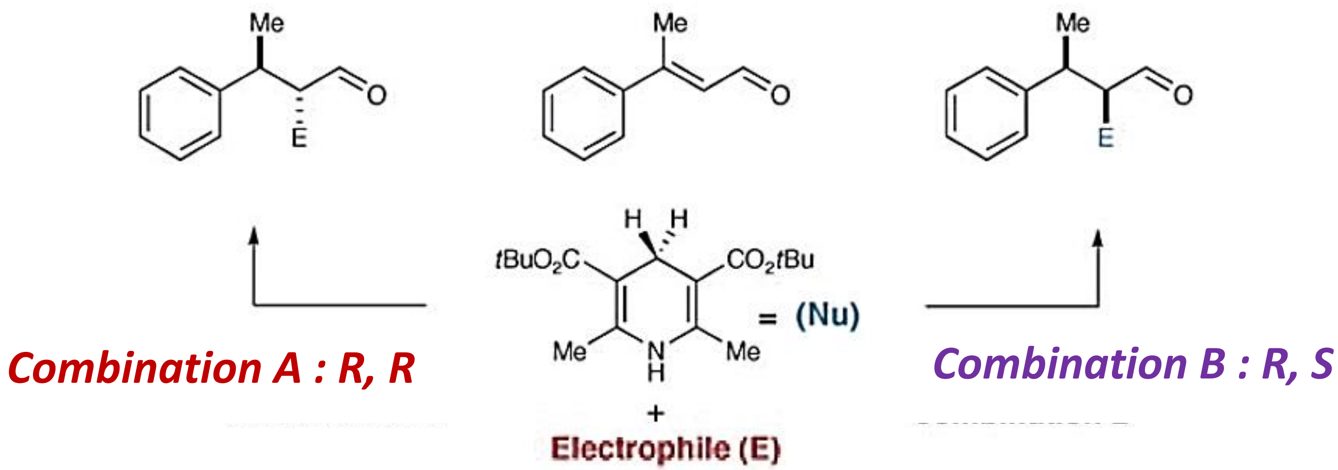
- Modular combination of ***proline*** and ***Macmillan amine***



Combination A : R, R

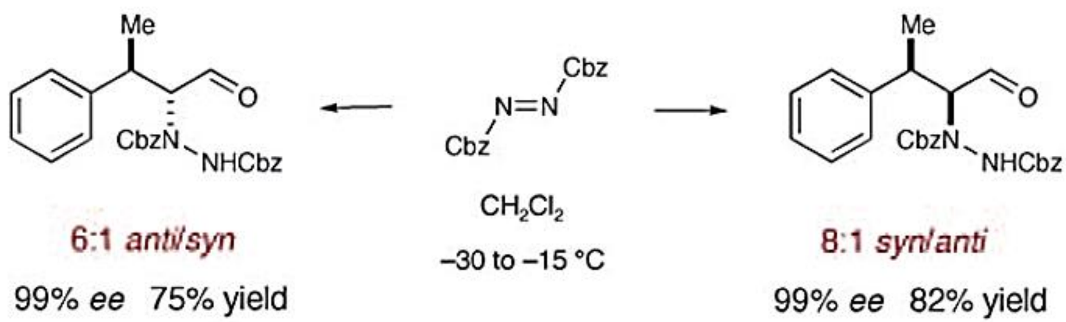
Combination B : R, S

Angew. Chem. Int. Ed., **2009**, *48*, 4349-4353

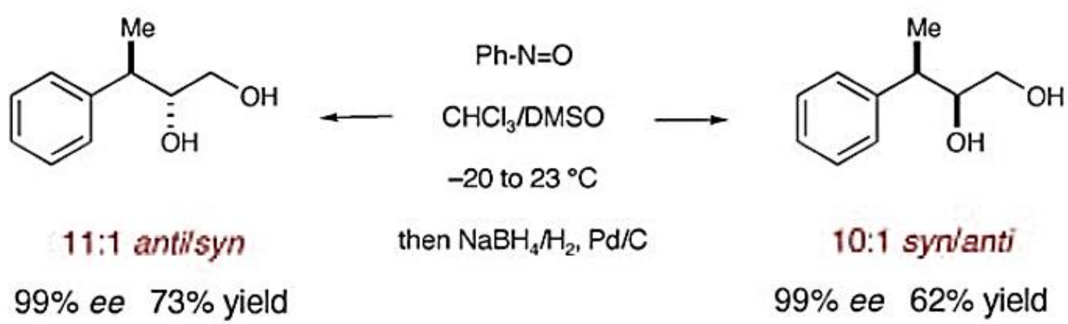


Combination A	E + conditions	Combination B

Enantioselective Hydro-Amination:



Enantioselective Hydro-Oxidation:



Angew. Chem. Int. Ed., **2009**, *48*, 4349

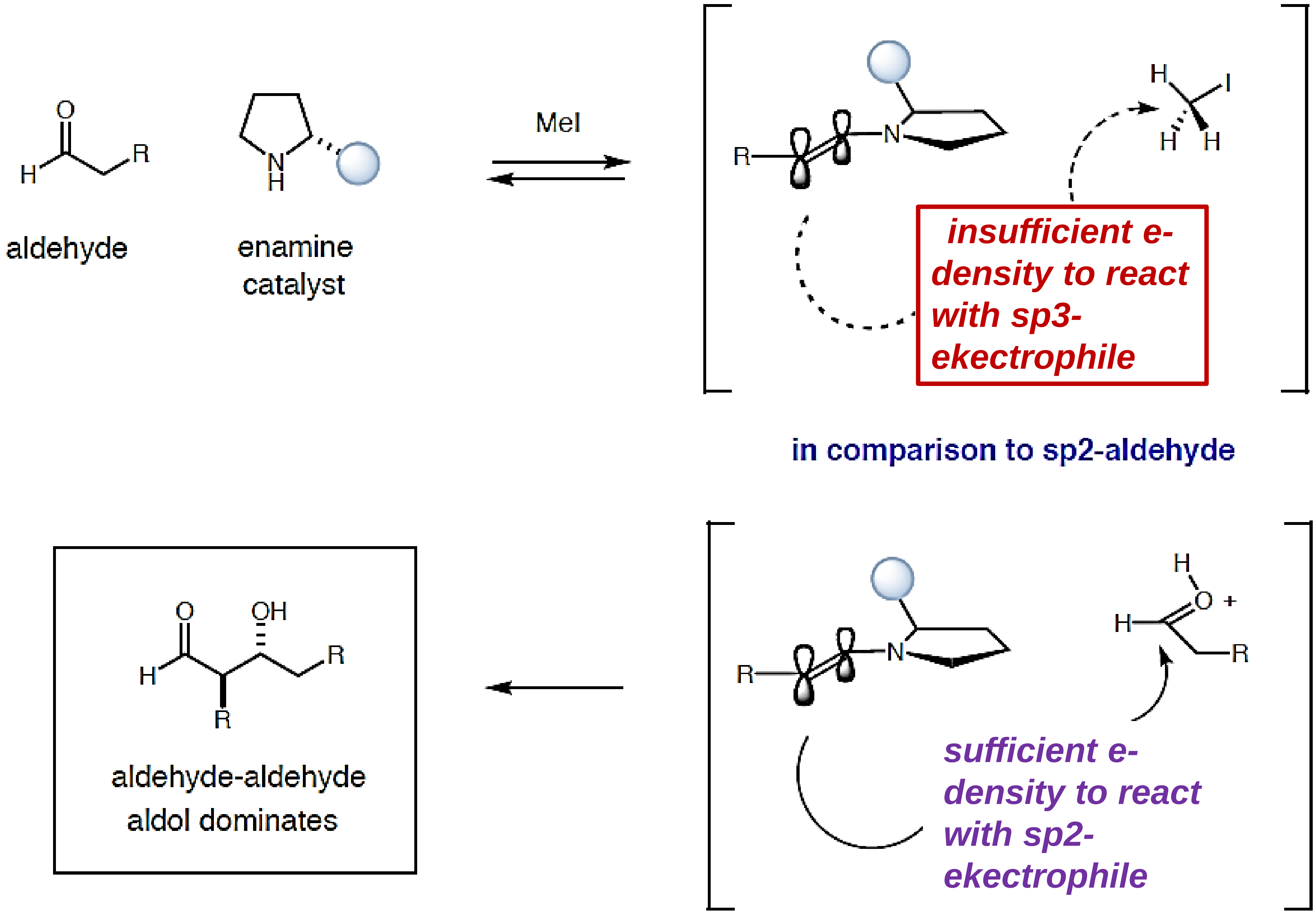
Content

1. *LUMO Catalysis*
2. *HOMO Catalysis*
3. *Cascade LUMO-HOMO Catalysis*
4. *SOMO Catalysis*
5. *Photoredox Organo Catalysis*
6. *Photoredox Organo Catalysis (Type II)*
7. *Summary*

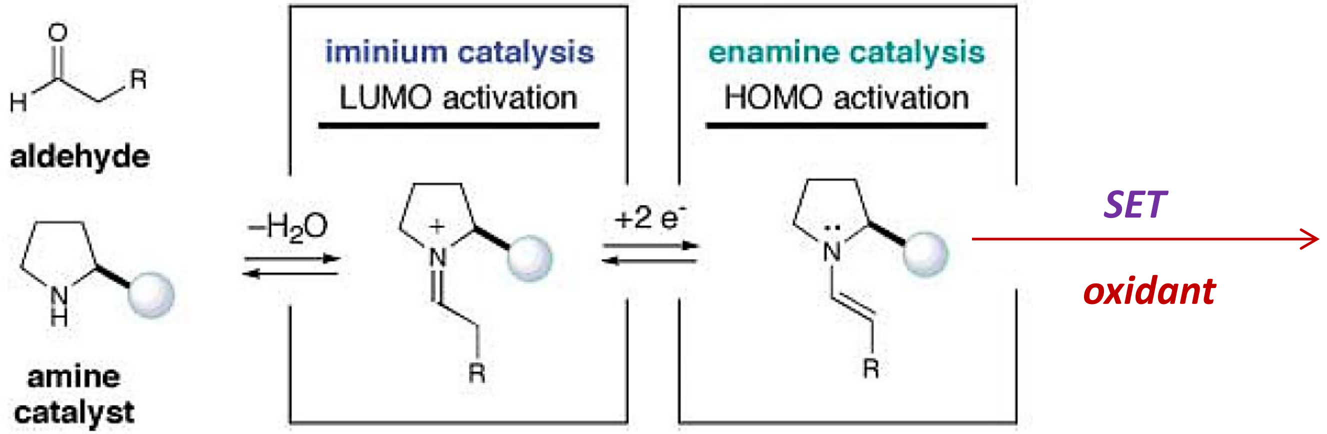
Content

HOMO catalyst: inefficient with some nucleophile

- Potential issues for enantioselective alkylation using HOMO catalysis

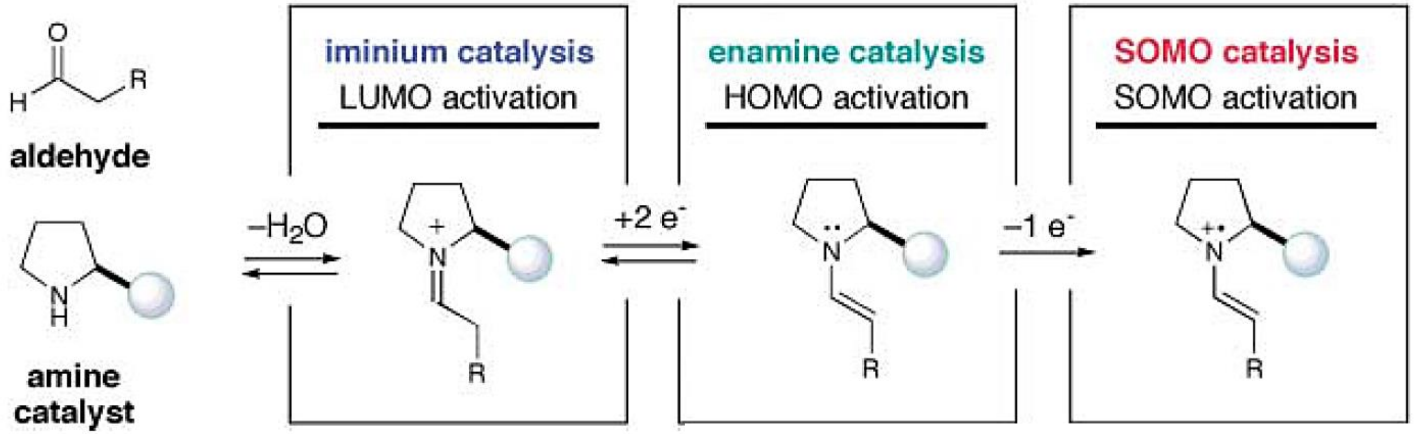


New Idea: *SOMO catalysis after a SET process*



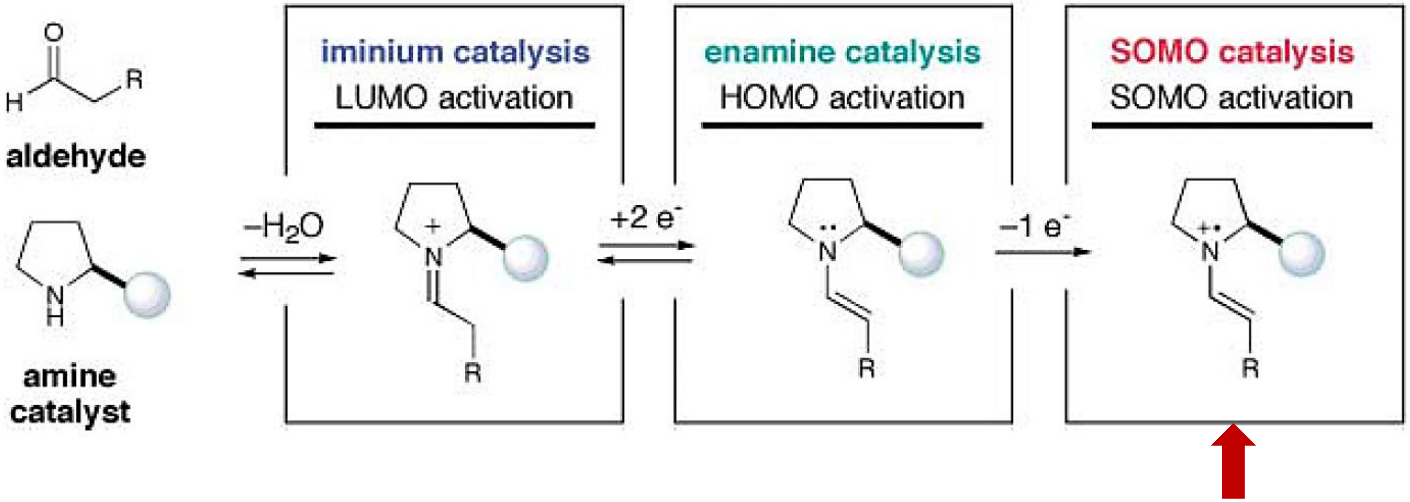
Science, **2007**, *316*, 582-585

New Idea: SOMO catalysis after a SET process



Science, **2007**, *316*, 582-585

New Idea: SOMO catalysis after a SET process

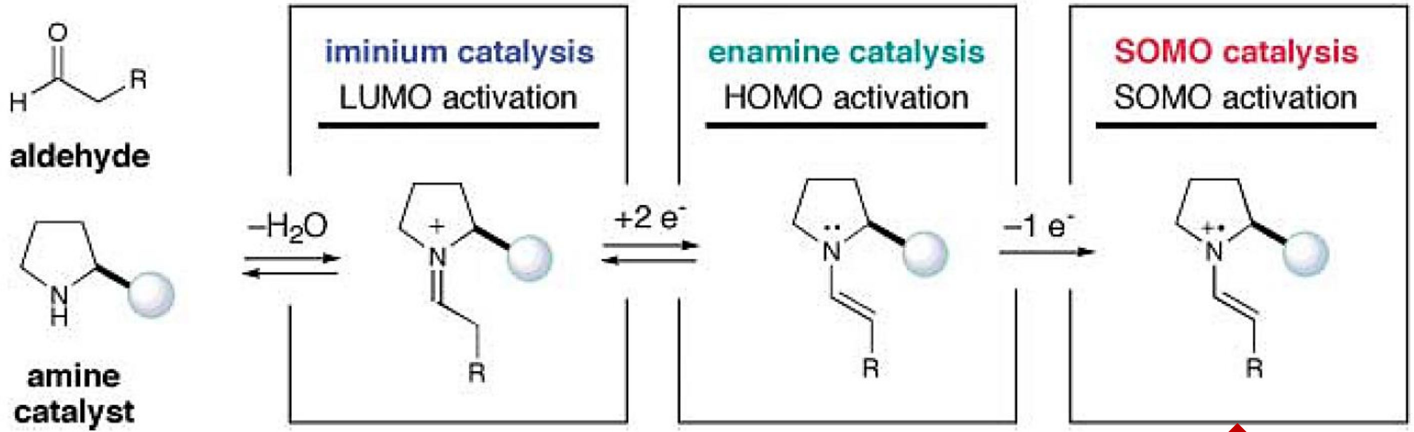


HOMOphile
(allyl bromide)

SOMOphile
(allyl silane)

Science, **2007**, *316*, 582-585

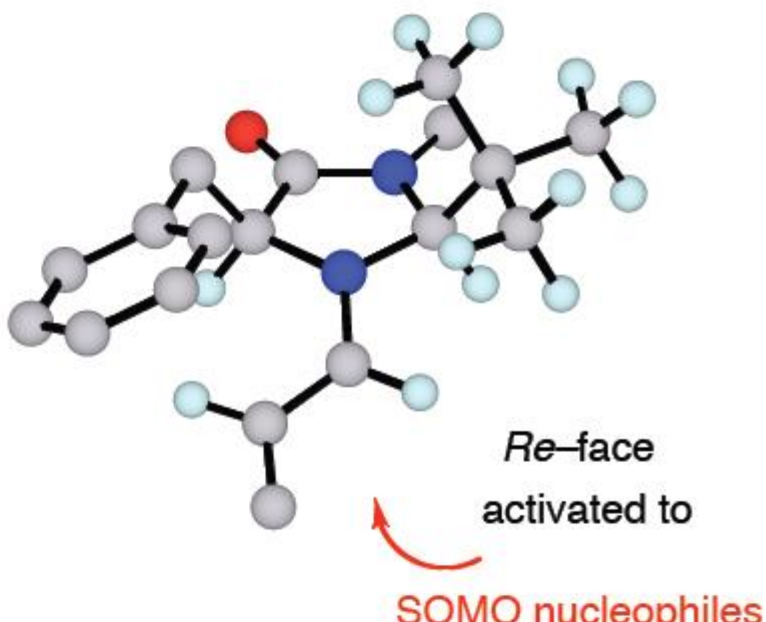
New Idea: SOMO catalysis after a SET process



HOMOphile (allyl bromide)

SOMOphile (allyl silane)

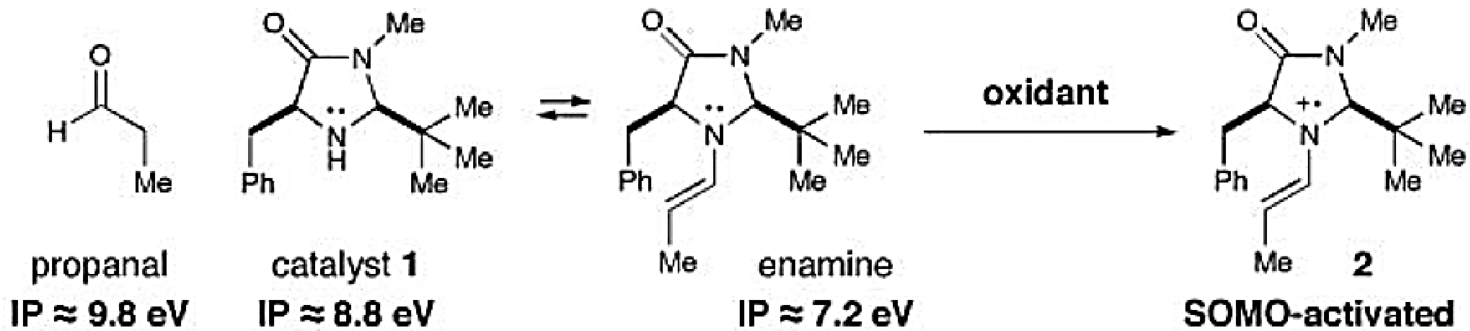
- SOMO intermediate: same chiral control as HOMO intermediate



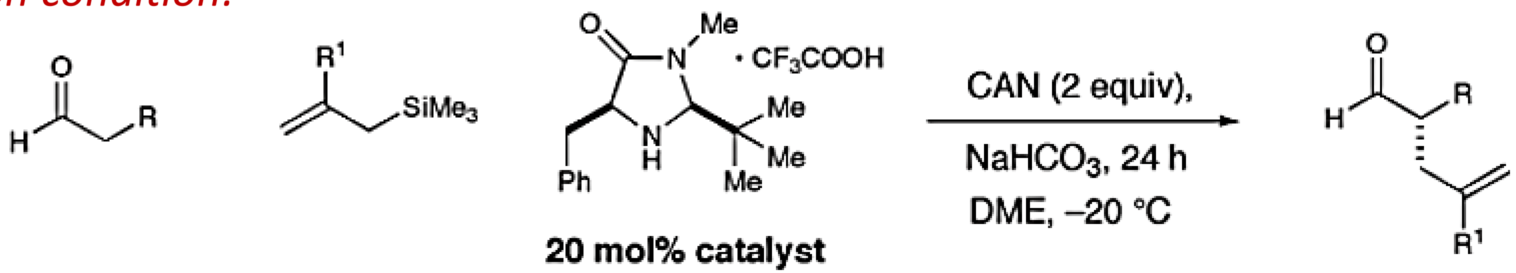
Science, **2007**, *316*, 582-585

SOMO catalysis: Enantioselective Aldehyde α-Allylation

- *CAN: selective oxidant*



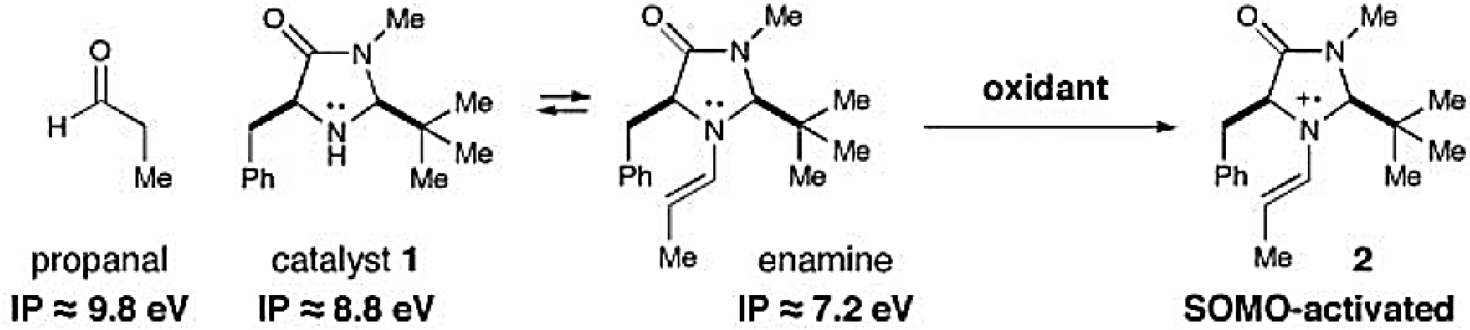
- *Reaction condition:*



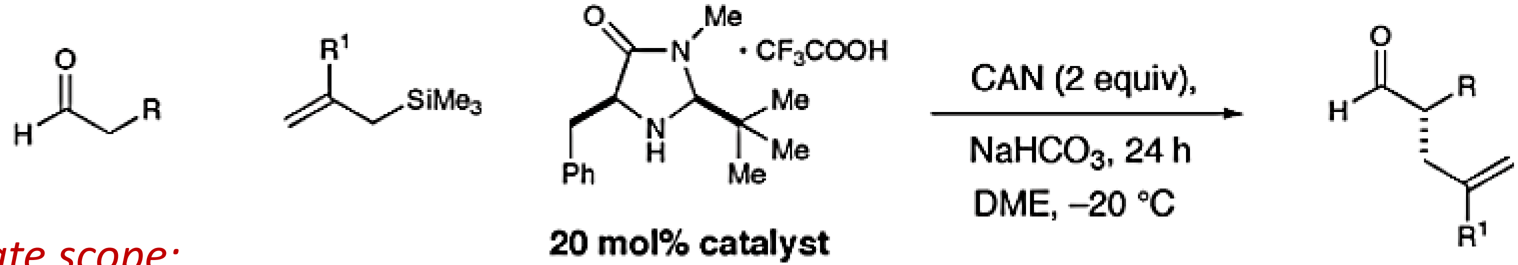
Science, **2007**, *316*, 582-585

SOMO catalysis: Enantioselective Aldehyde α-Allylation

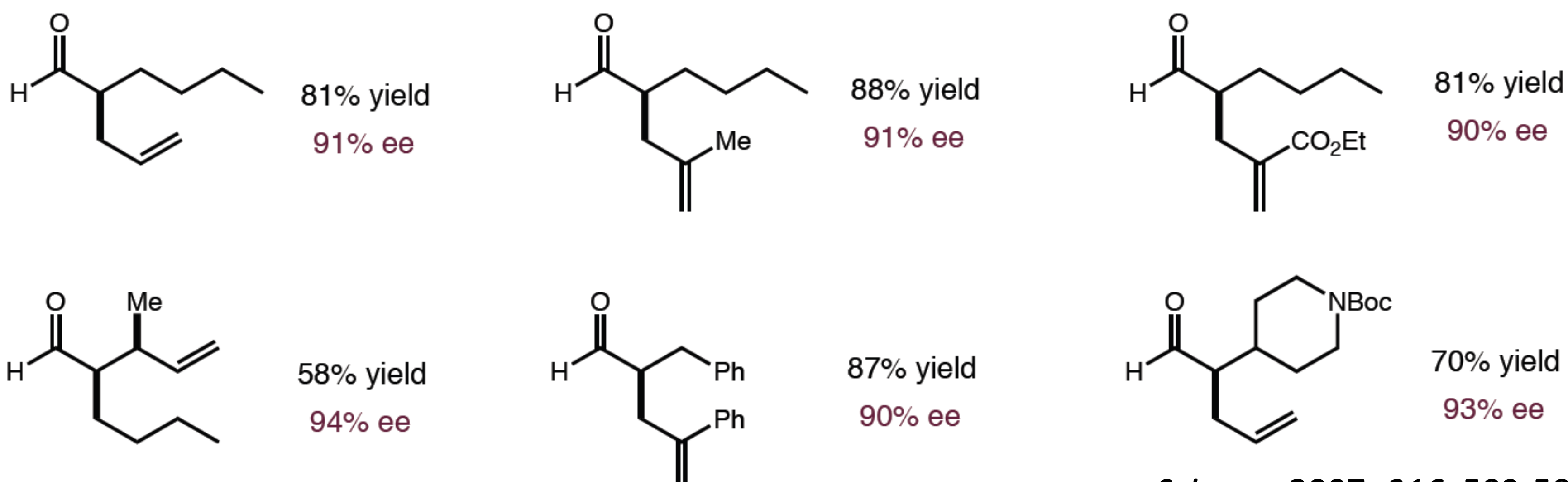
CAN: selective oxidant



Reaction condition:

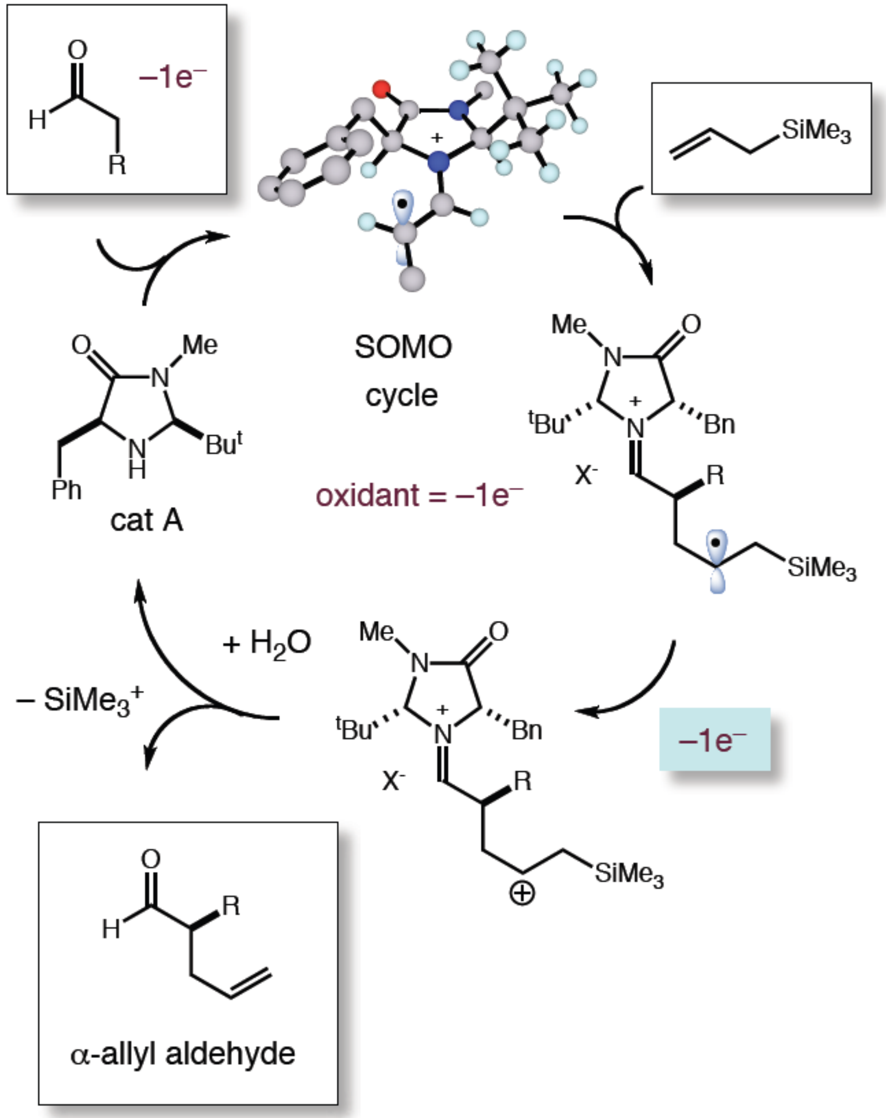


Substrate scope:

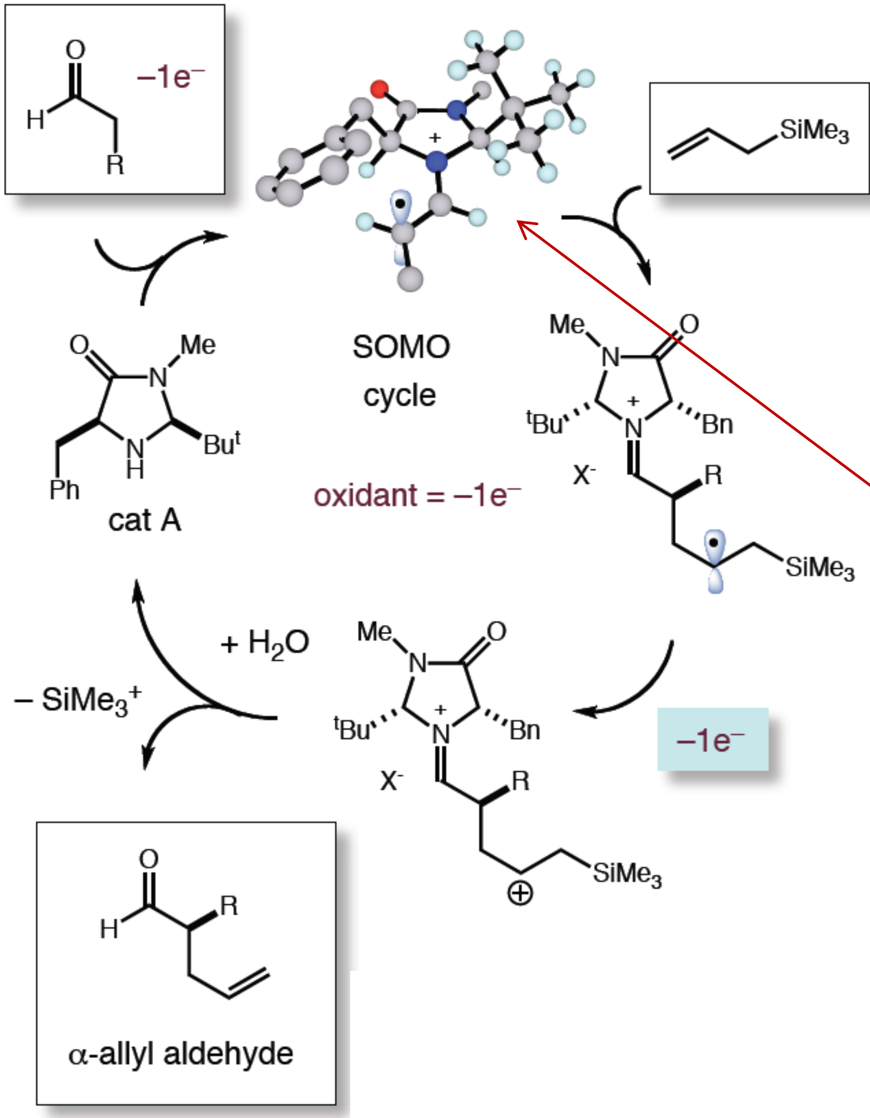


Science, **2007**, *316*, 582-585

SOMO catalysis: the proof of the machenism

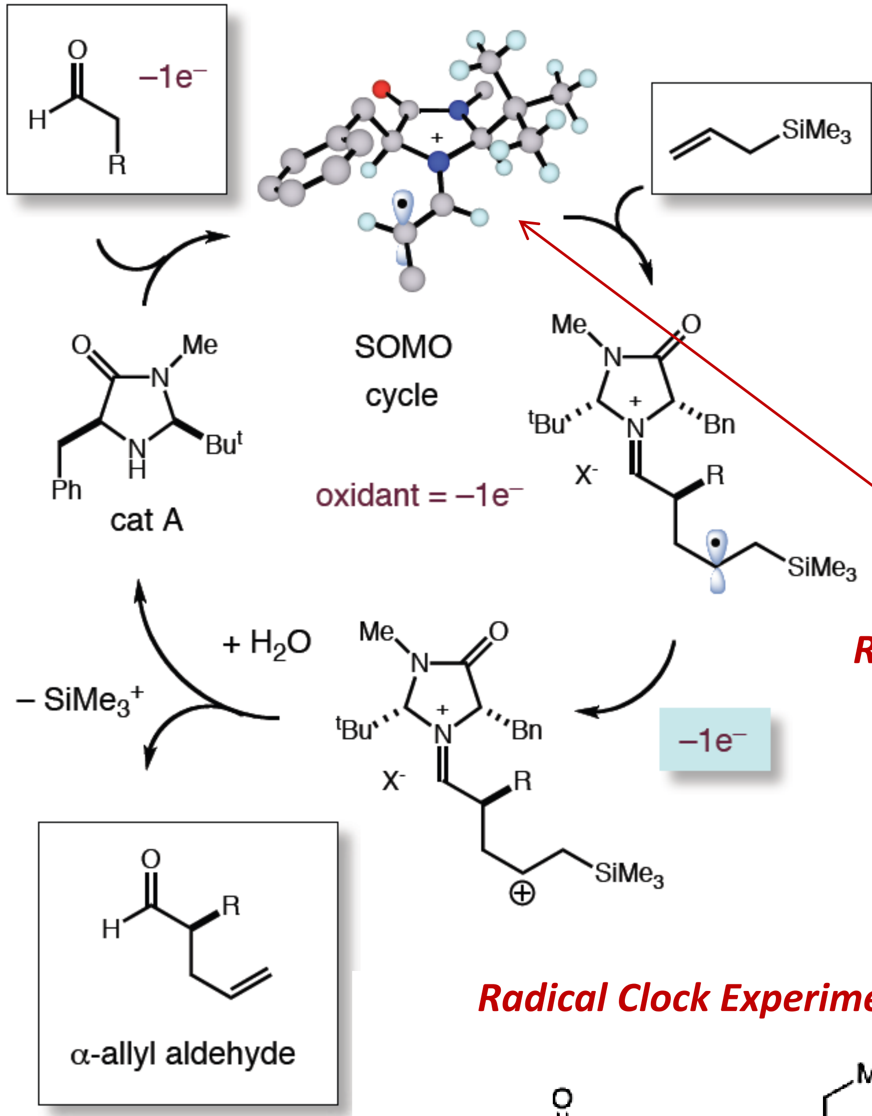


SOMO catalysis: the proof of the machenism



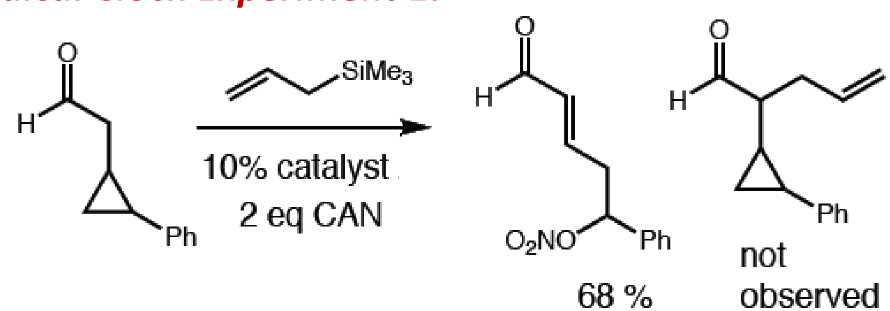
■ ***Radical-Cation Intermediate**?*

SOMO catalysis: the proof of the machenism

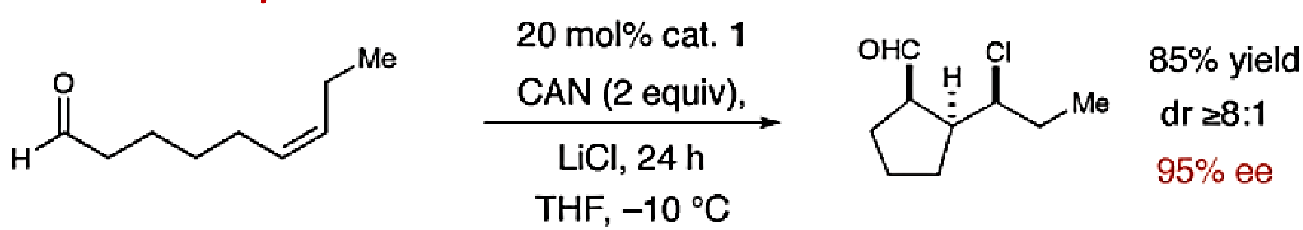


■ ***Radical-Cation Intermediate***?

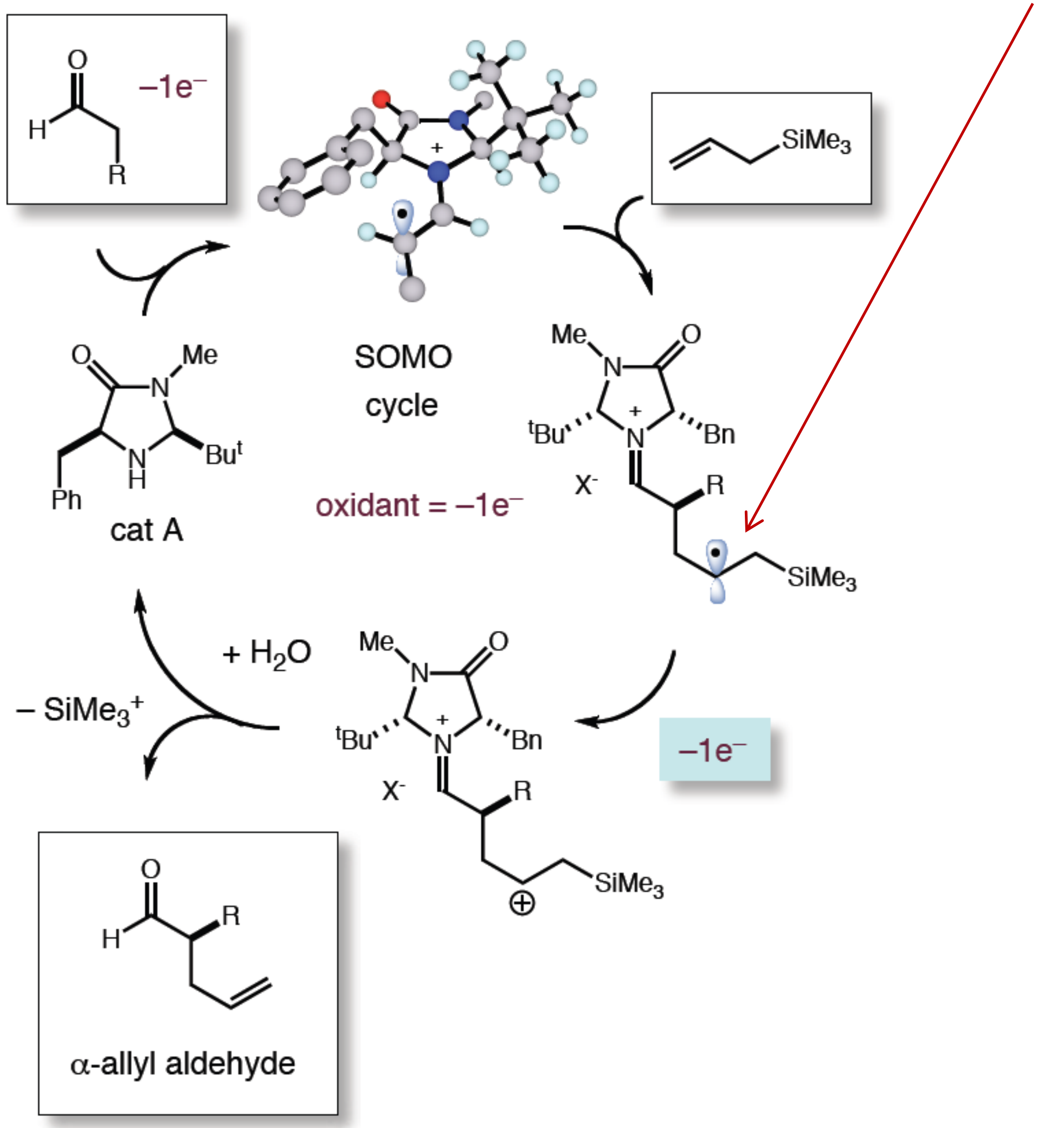
Radical Clock Experiment 1:



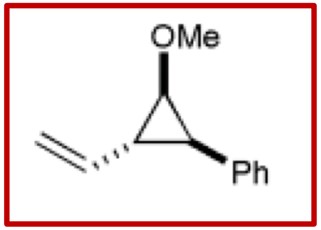
Radical Clock Experiment 2:



SOMO catalysis: the proof of the machenism

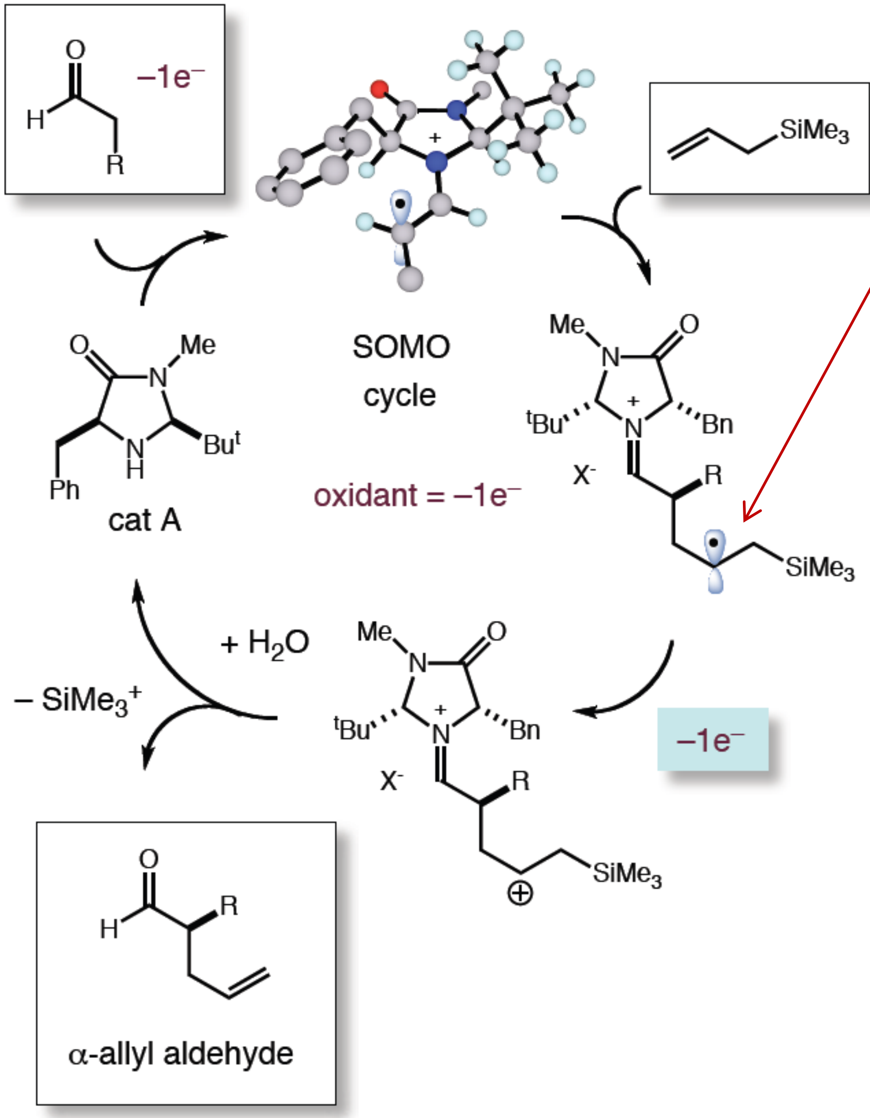


■ ***Radical or Carbocation?***

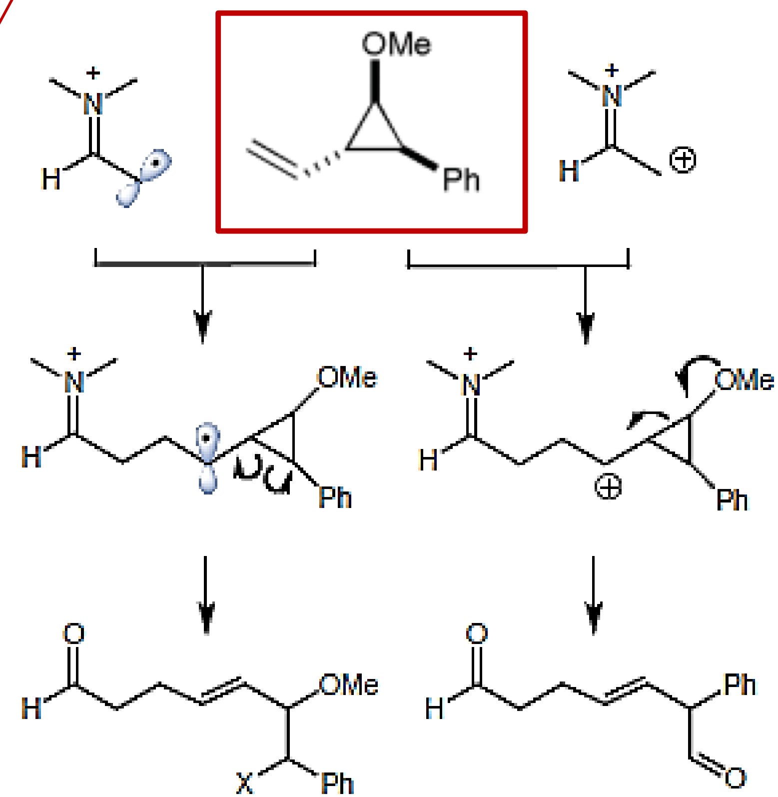


radical clock & "cation clock"

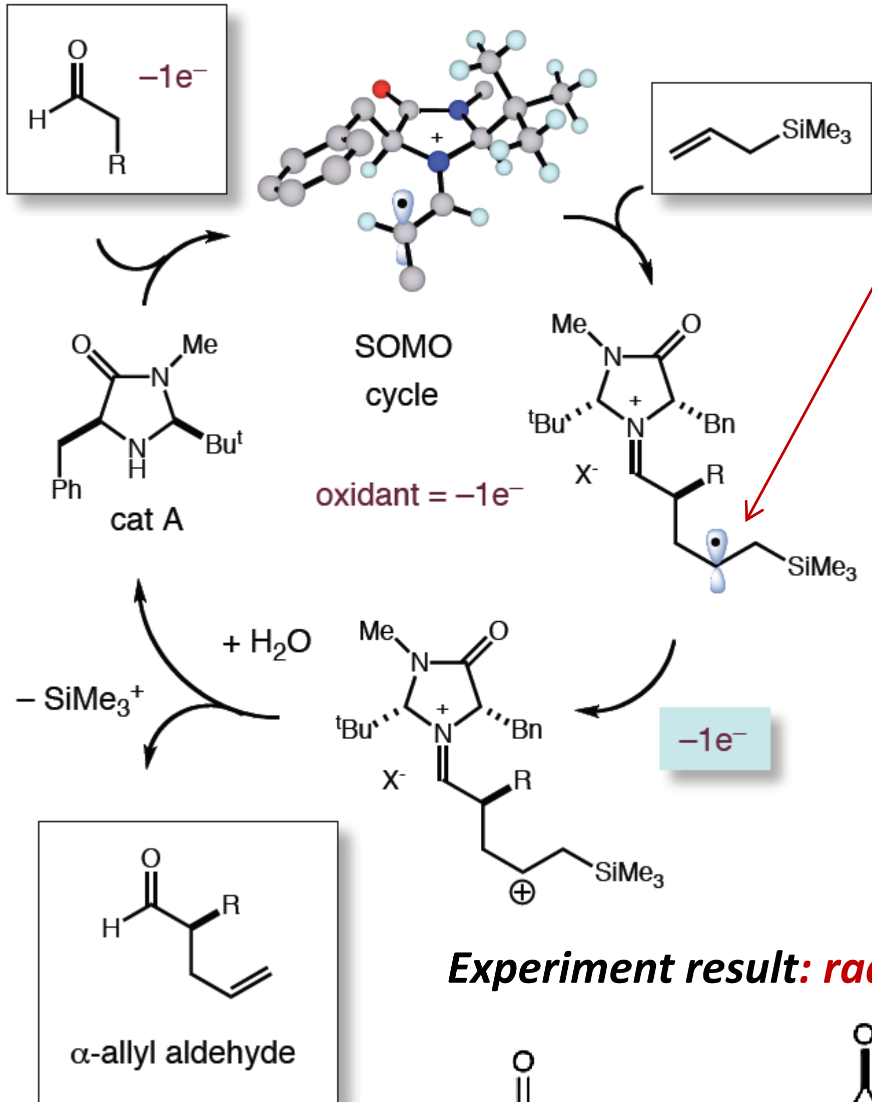
SOMO catalysis: the proof of the machenism



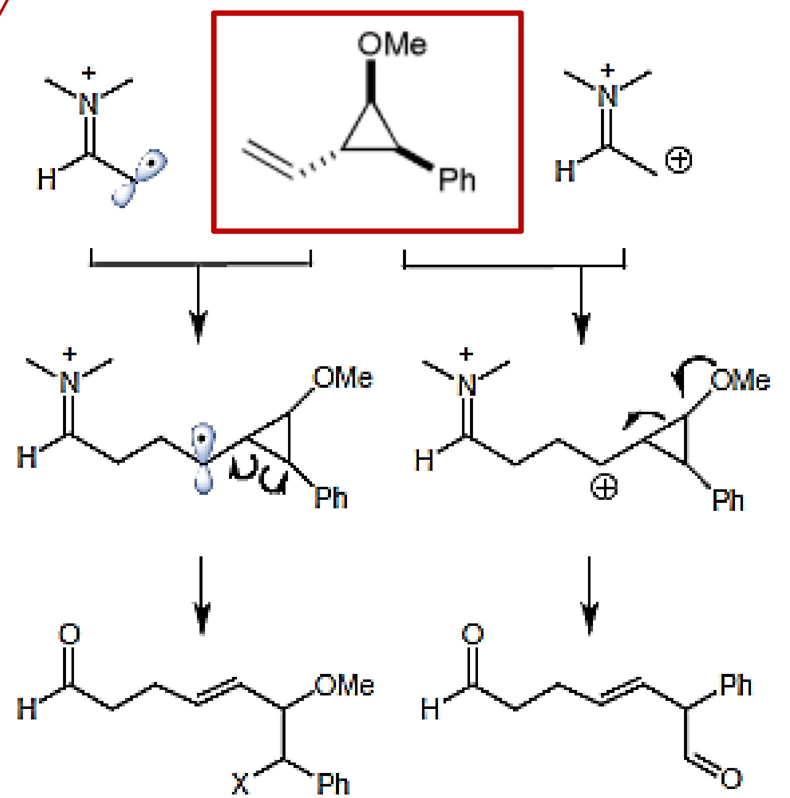
■ ***Radical or Carbocation?***



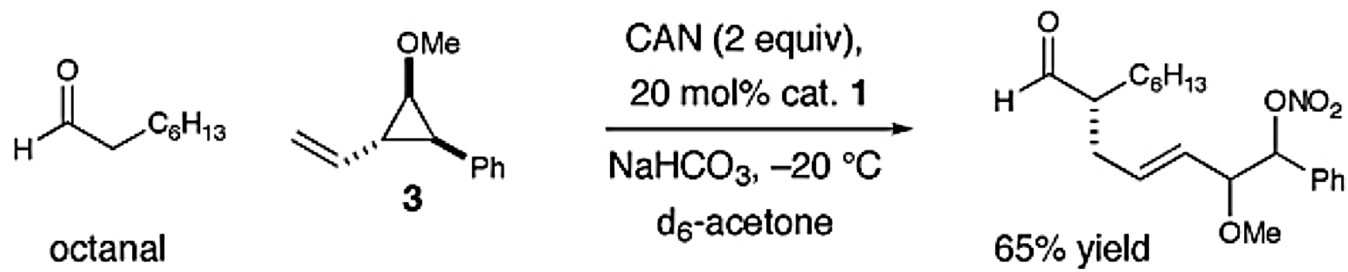
SOMO catalysis: the proof of the machenism



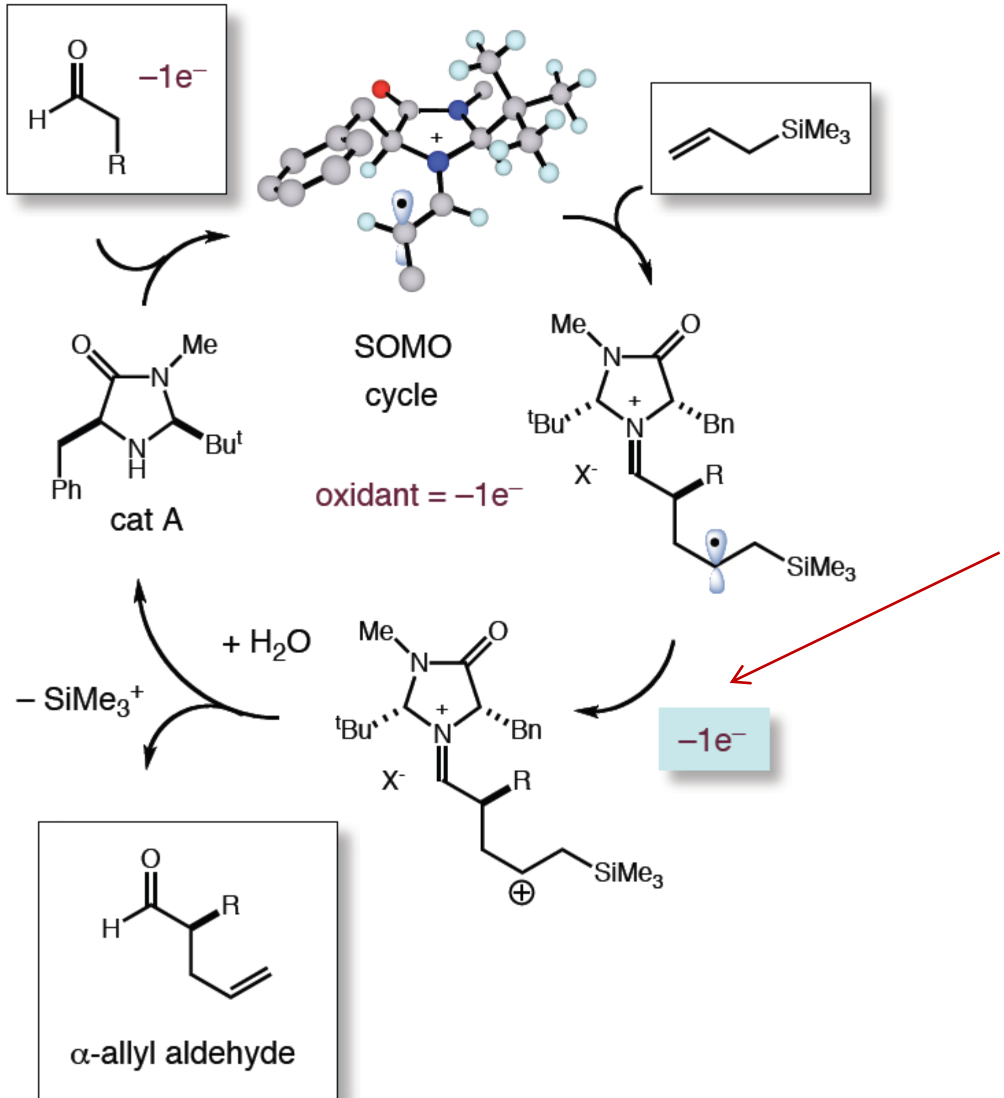
■ *Radical or Carbocation?*



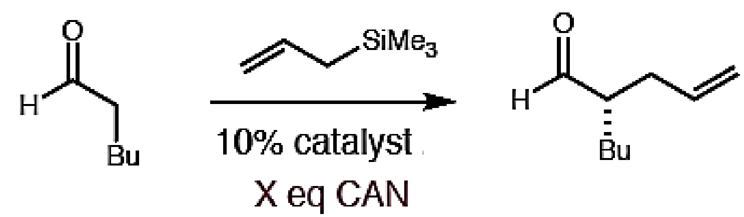
Experiment result: radical-pathway product



SOMO catalysis: *the proof of the machenism*

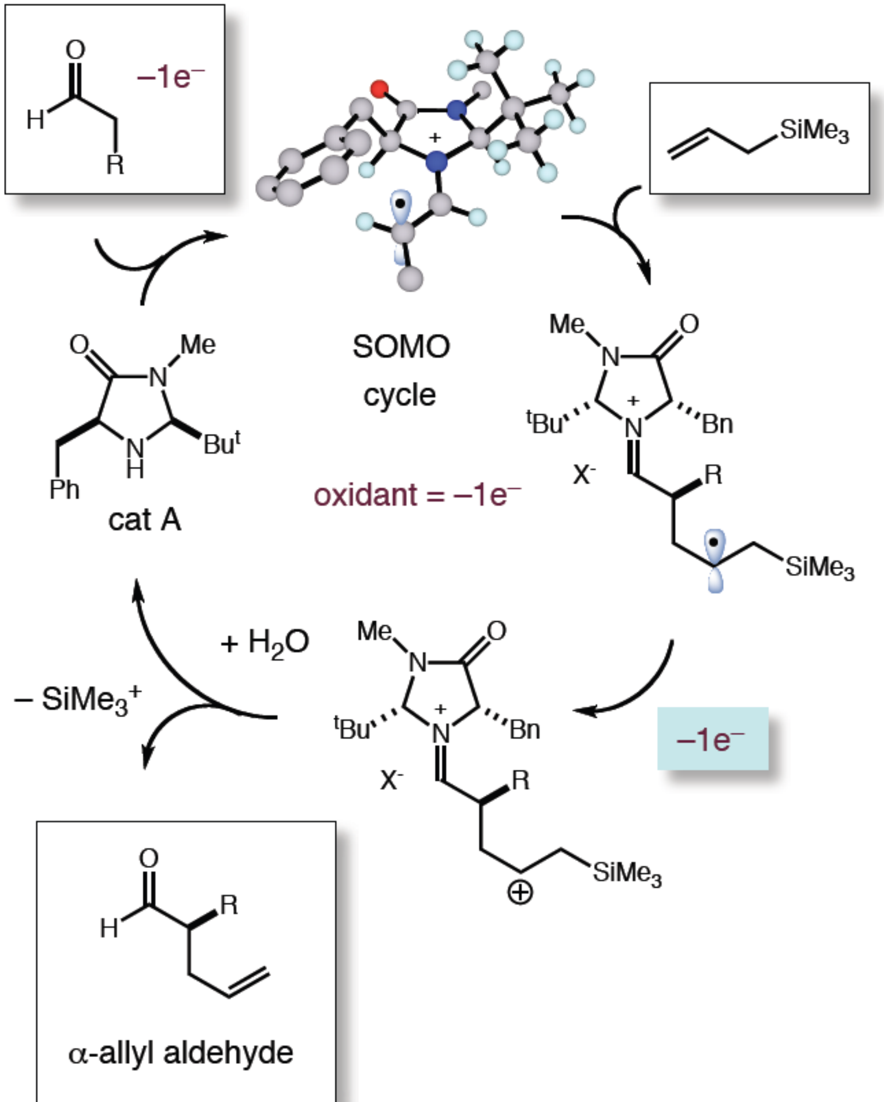


■ ***Second SET oxidation?***



X eq CAN	% Yield
1.0	37%
1.5	61%
2.0	88%
3.0	87%

SOMO catalysis: the proof of the machenism



SOMOphile:
electron rich nucleophile with the ability to stablized a new generated radical

many noncatalytic C–C, C–O, C–N, C–S, and C–X (where X is a halogen) bond formations (*15–19*). Our analysis reveals the attractive prospect of applying asymmetric SOMO catalysis to important problems such as direct and enantioselective allylic alkylation, enolation, arylation, carbo-oxidation, vinylation, alkynylation, or intermolecular alkylation of aldehydes.
To test this activation concept, we selected

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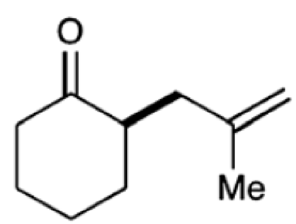
*For the **intramolecular version**, see:*
Chem. Sci., **2011**, *2*, 1470-1473

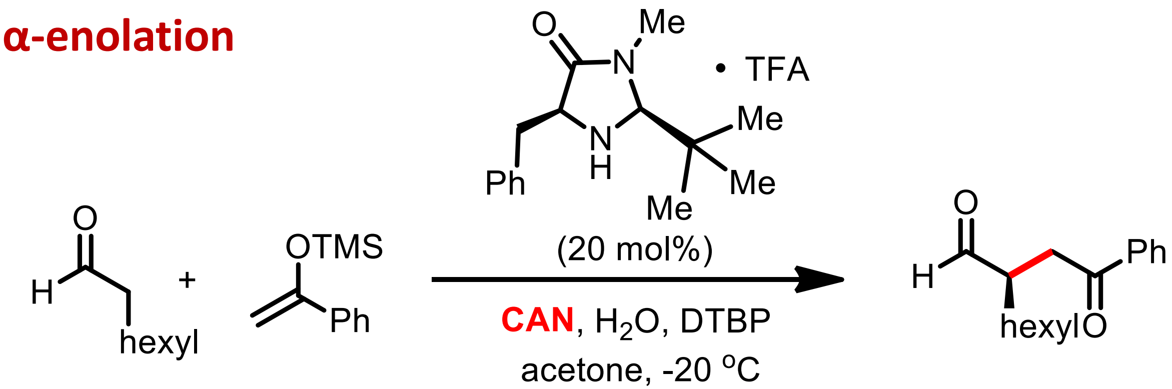
*For the SOMO allylation of **cyclic ketone**, see:*



Proc. Nat. Acad. Sci. USA, **2010**, *107*, 20648-20651

SOMO catalysis: More than allylation

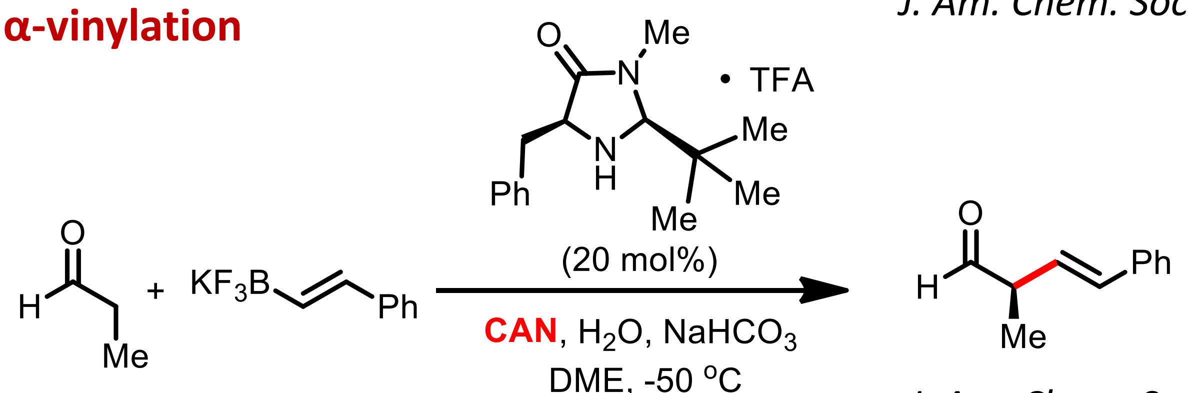
Aldehyde α-enolation



85% yield, 90% ee

J. Am. Chem. Soc., **2007**, *129*, 7004-7005

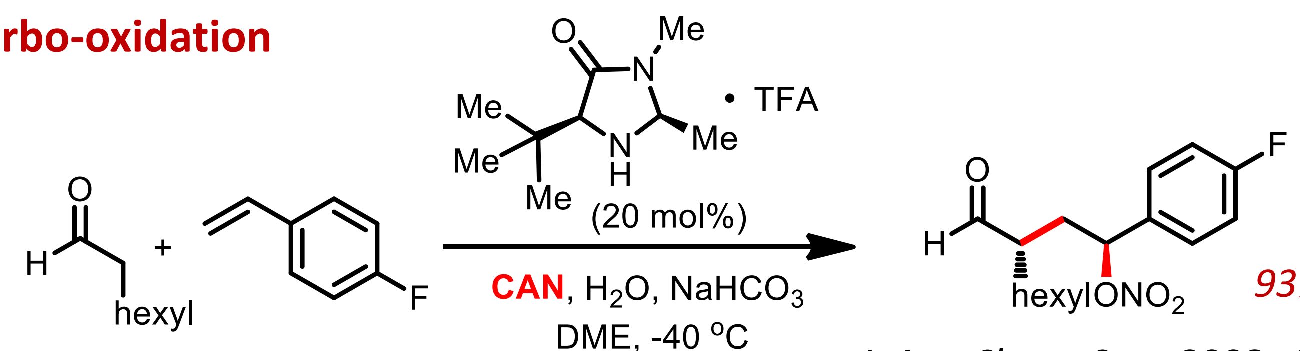
Aldehyde α-vinylation



72% yield, 94% ee

J. Am. Chem. Soc., **2008**, *130*, 398-399

Styrene carbo-oxidation



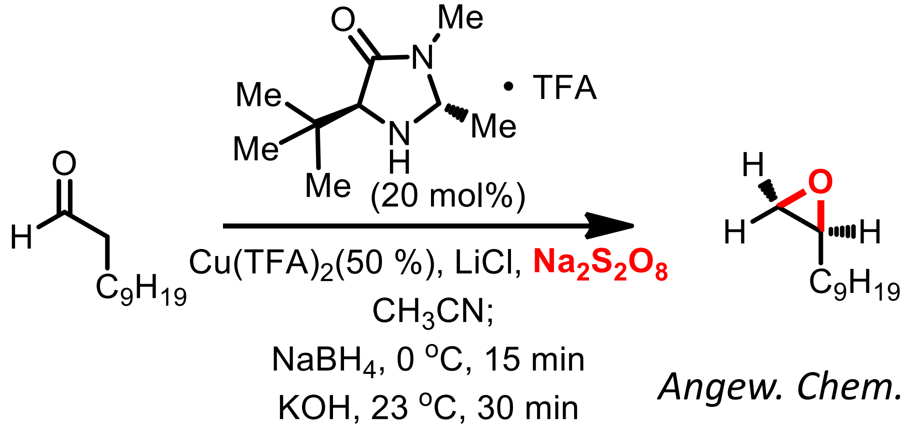
93% yield, 96% ee

J. Am. Chem. Soc., **2008**, *130*, 16494-16495

*For the styrene **carbo-amination**, see*: *J. Am. Chem. Soc.*, **2012**, *134*, 11400-11403

SOMO catalysis: More than allylation

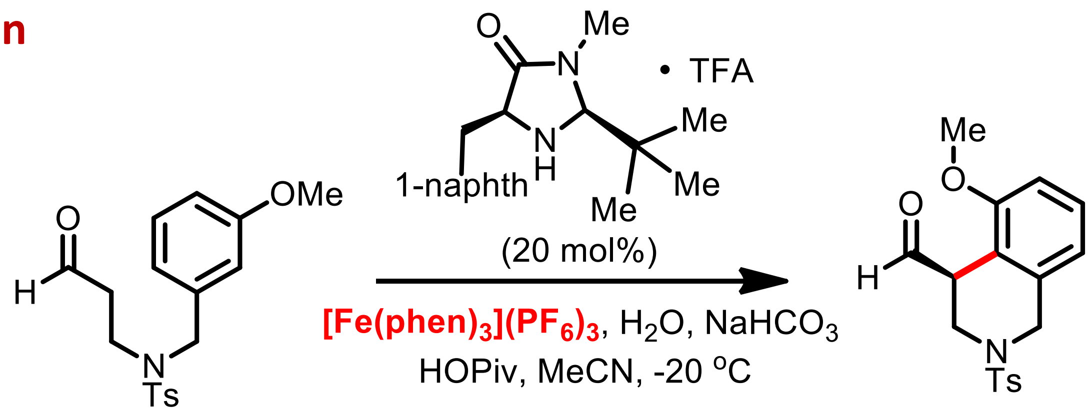
Epoxidation



85% yield, 95% ee

Angew. Chem. Int. Ed., **2009,** *48*, 5121-5124

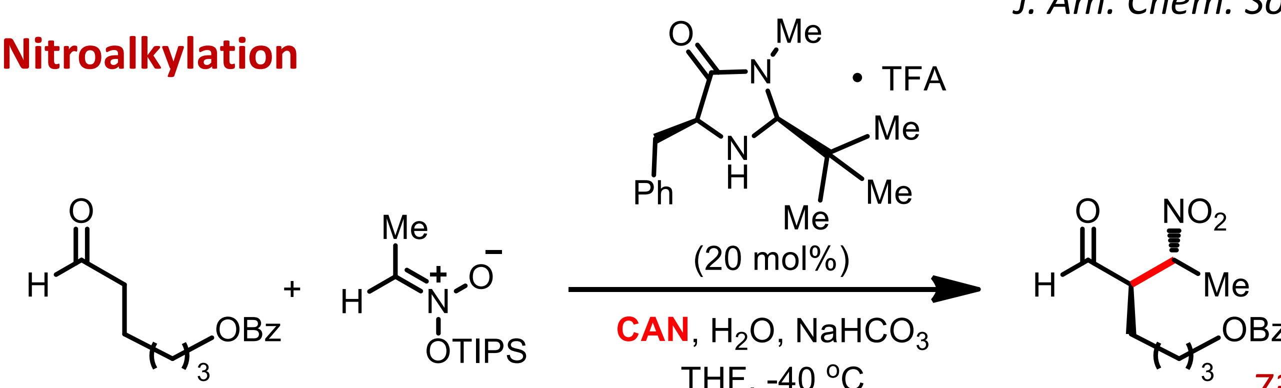
α-Arylation



86% yield, 95% ee

J. Am. Chem. Soc., **2009**, *131*, 11640-11641

α-Nitroalkylation

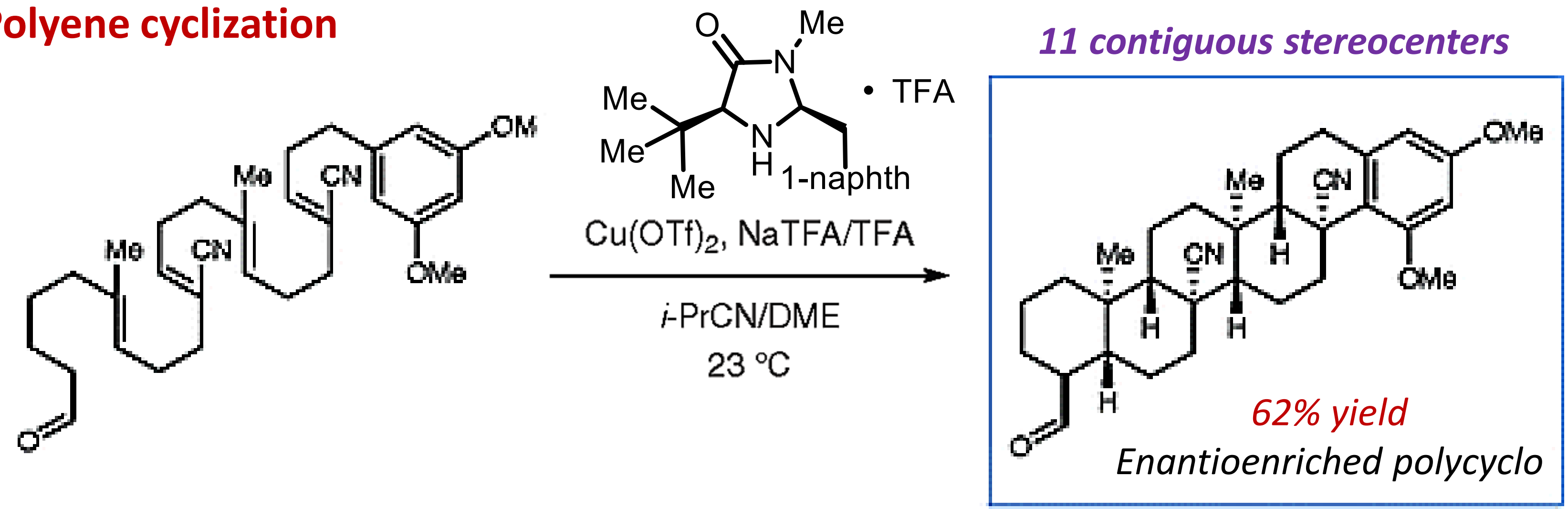


73% yield, 87% ee, dr = 6:1

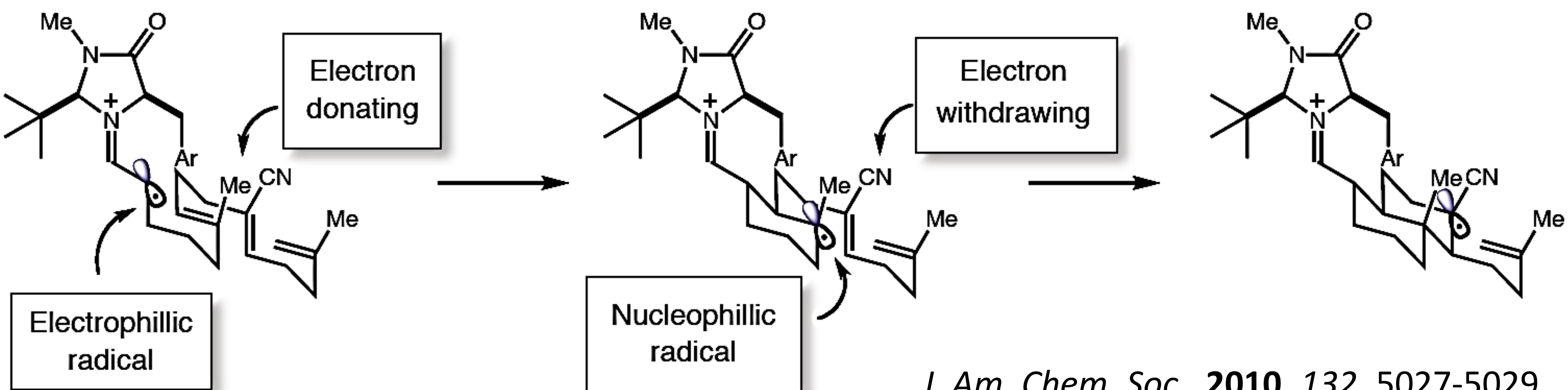
J. Am. Chem. Soc., **2009**, *131*, 11332-11334

SOMO catalysis: More than allylation

Polyene cyclization



- Propagating species is radical: alternating polarity favors cyclization

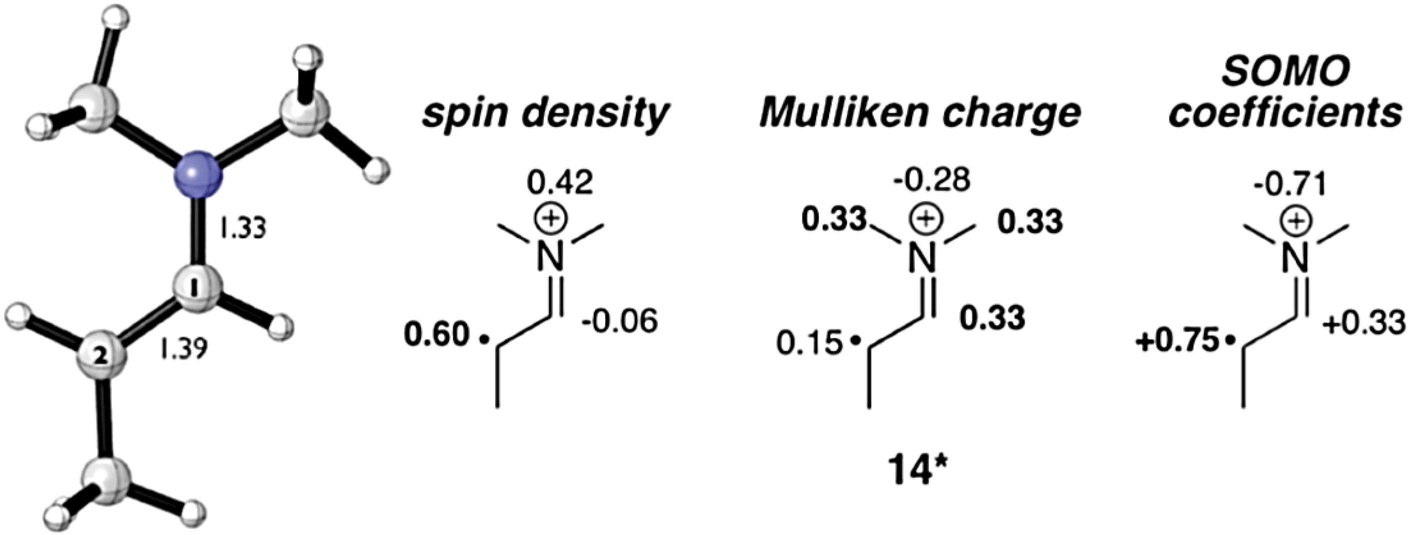


J. Am. Chem. Soc., **2010**, *132*, 5027-5029

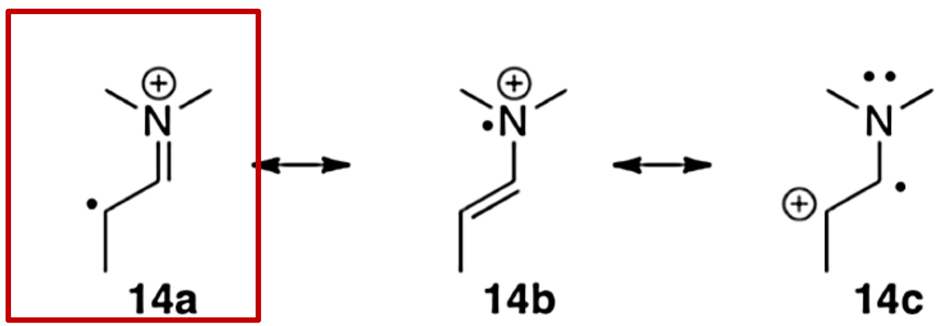
For an extremely similar intramolecular homo-ene reaction of aldehyde, see:
J. Am. Chem. Soc., **2013**, *135*, 9358-9361

SOMO catalysis: Nature of Intermediates in Organo-SOMO Catalysis

- Calculation study



14*

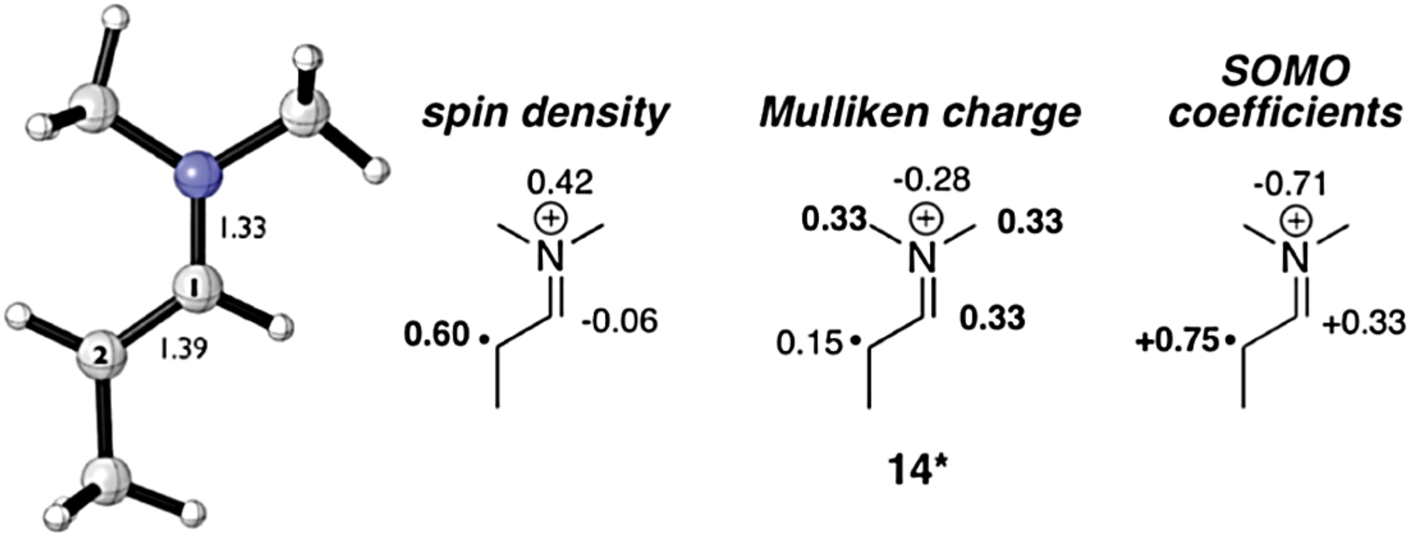


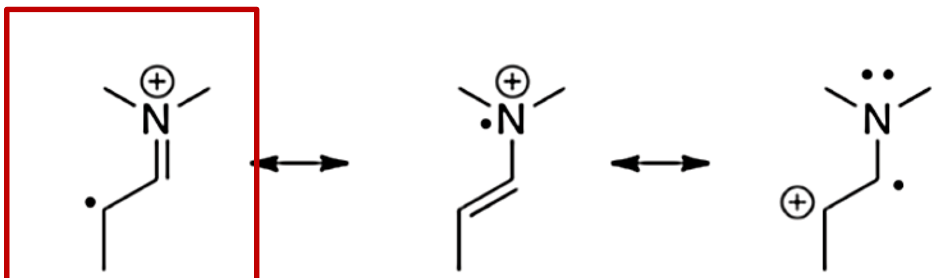
- *SOMO orbital is* ***mainly on the β-carbon***

J. Am. Chem. Soc., **2010**, *132*, 6106-6110

SOMO catalysis: Nature of Intermediates in Organo-SOMO Catalysis

- Calculation study



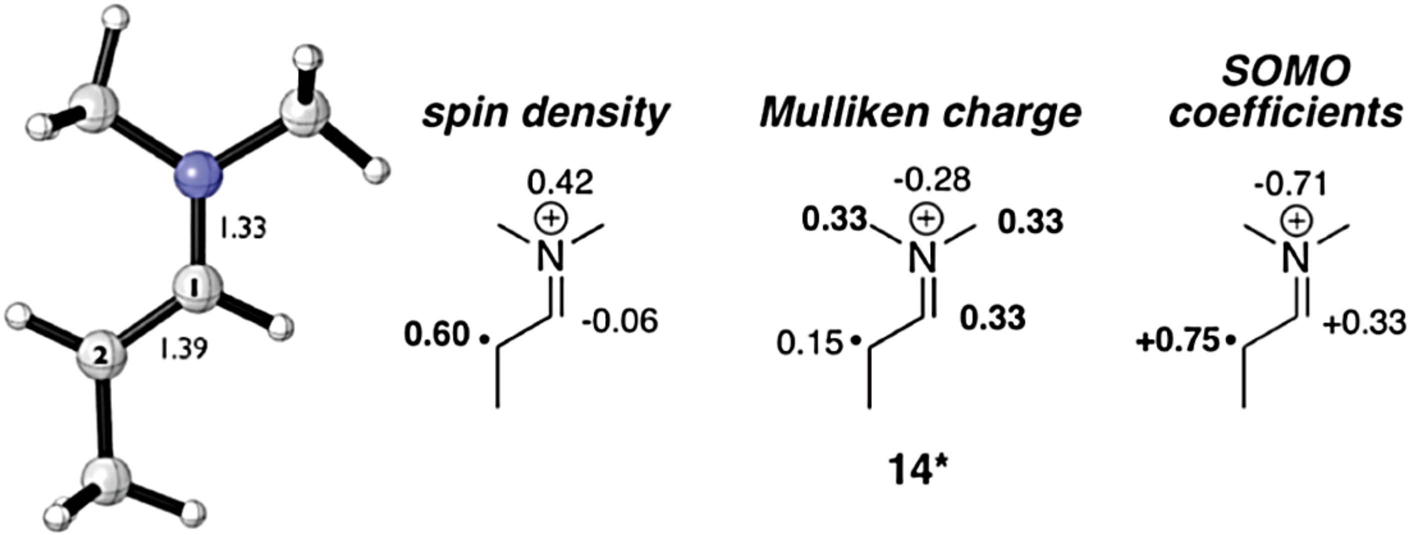


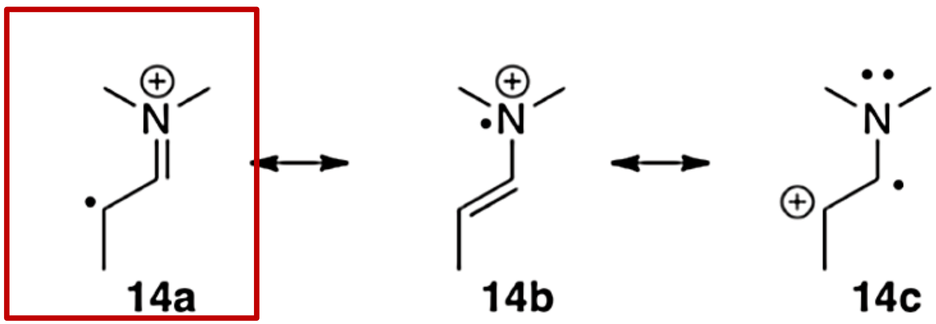
- *SOMO orbital is* ***mainly on the β-carbon***
- *can be best characterized as an* ***alkyl radical conjugated to an iminium cation***

J. Am. Chem. Soc., **2010**, *132*, 6106-6110

SOMO catalysis: *Nature of Intermediates in Organo-SOMO Catalysis*

- Calculation study





- *SOMO orbital is* ***mainly on the β-carbon***
- *can be best characterized as an* ***alkyl radical conjugated to an iminium cation***
- ***consistent with the previous mechanism hypothesis***

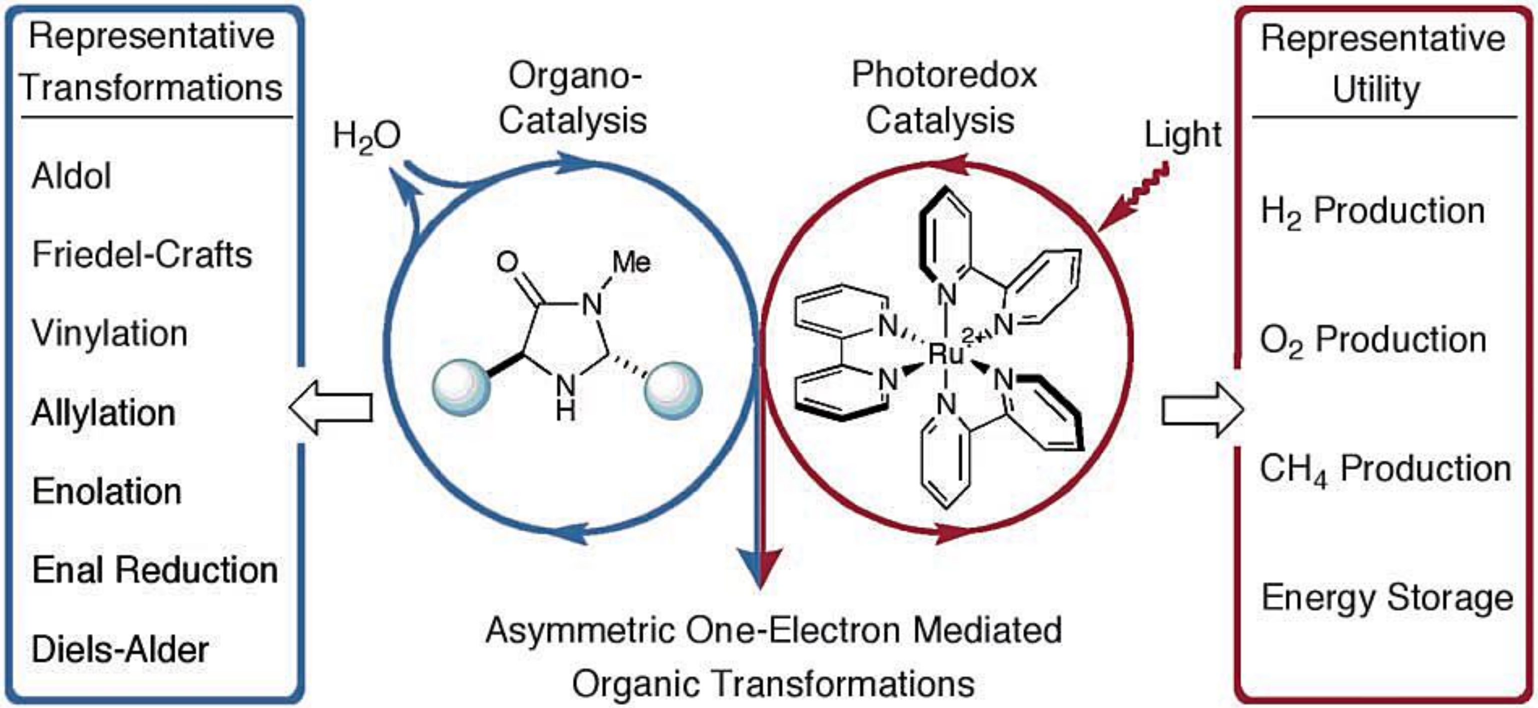
J. Am. Chem. Soc., **2010**, *132*, 6106-6110

Content

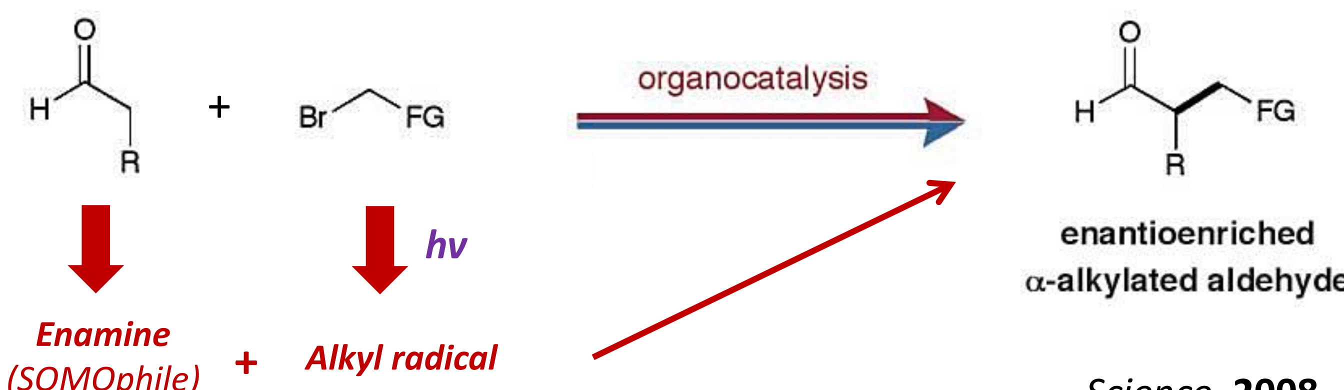
1. *LUMO Catalysis*
2. *HOMO Catalysis*
3. *Cascade LUMO-HOMO Catalysis*
4. *SOMO Catalysis*
5. *Photoredox Organo Catalysis*
6. *Photoredox Organo Catalysis (Type II)*
7. *Summary*

Content

New Catalysis：Merge the Organo Catalyst and the Photo Redox Catalyst

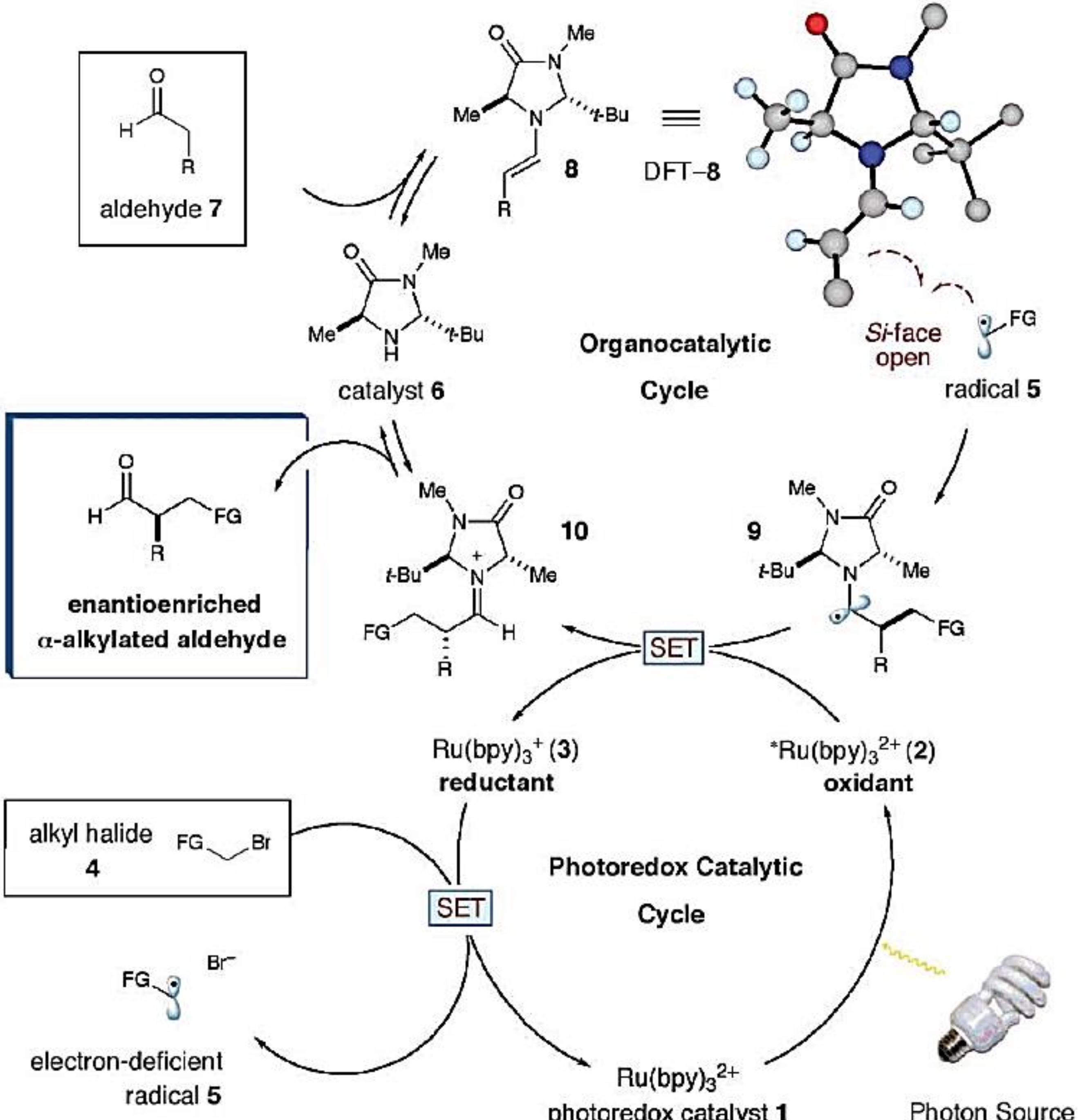


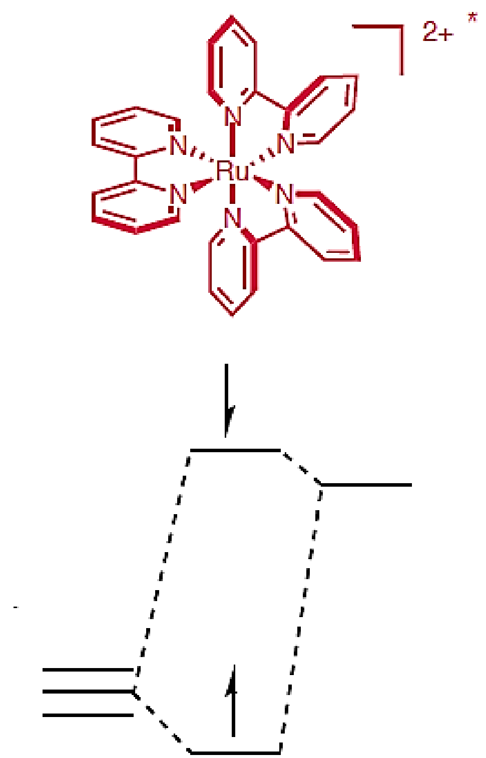
■ *Enantioselective Catalytic Carbonyl α-Alkylation:* ***A brief design***



Science, **2008**, *322*, 77-80

New Catalysis：Merge the Organo Catalyst and the Photo Redox Catalyst





Ligand-centered orbital (π^*)

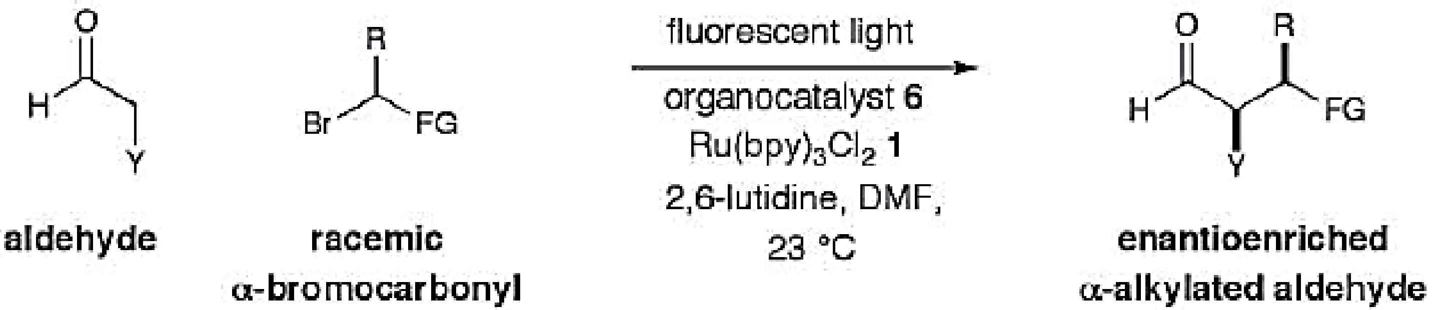
$Ru(bpy)_3^{2+*}$

excited ligand-based state

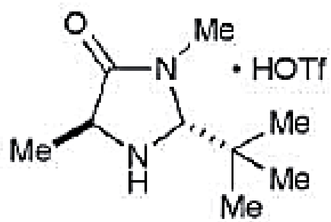
Science, **2008**, *322*, 77-80

New Catalysis：Merge the Organo Catalyst and the Photo Redox Catalyst

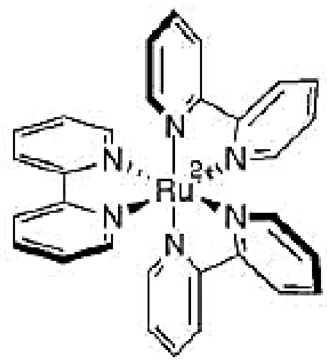
- Enantioselective Catalytic Carbonyl α-Alkylation



Catalyst Combination



organocatalyst **6** (20 mol%)

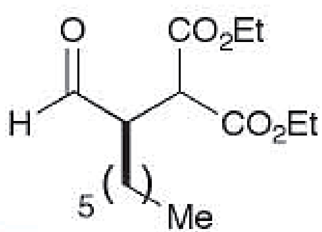


Ru(bpy)$_3$Cl$_2$ **1** (0.5 mol%)

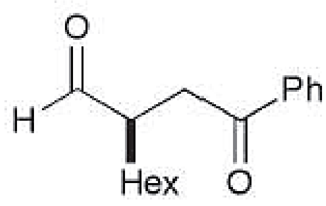
Photon Source

15 W fluorescent light bulb

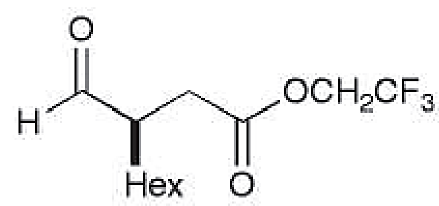
- Substrate scope



93% yield, 90% ee



84% yield, 96% ee

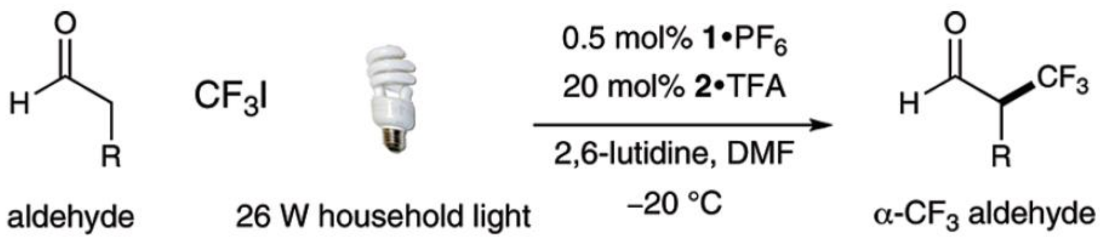


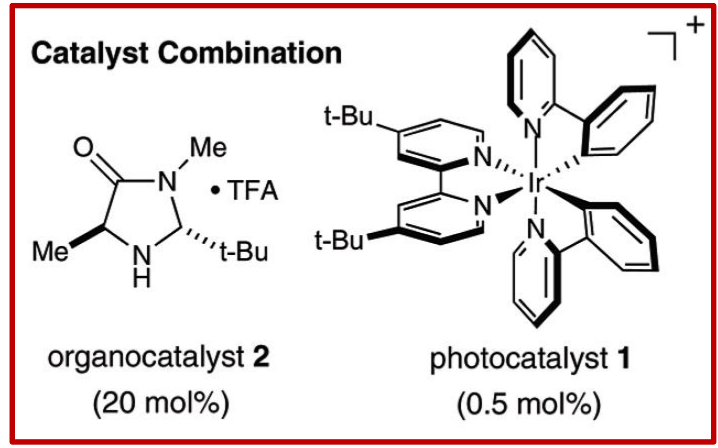
80% yield, 92% ee

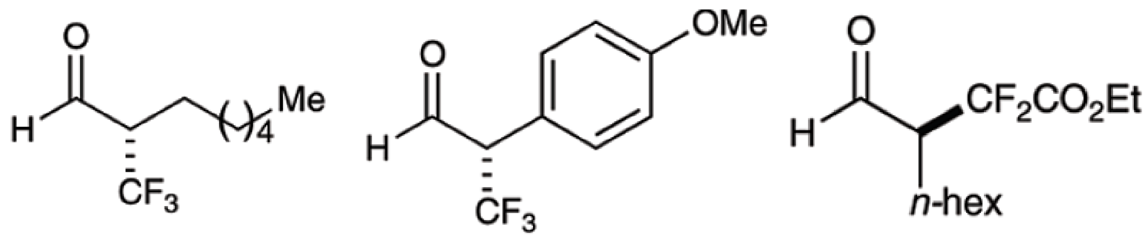
Science, **2008**, *322*, 77-80

Enantioselective Photo-redox Organo Catalysis

Enantioselective α-trifluoromethylation





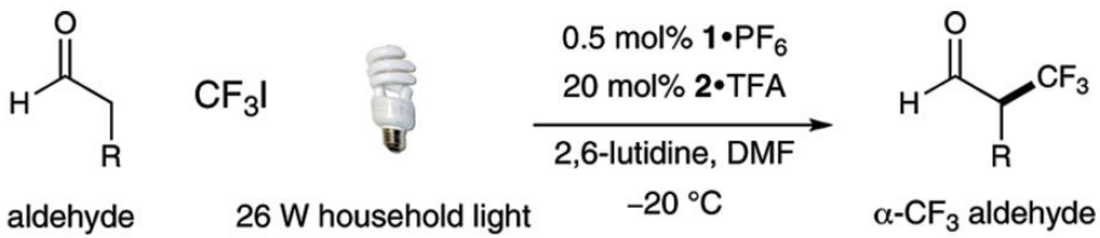


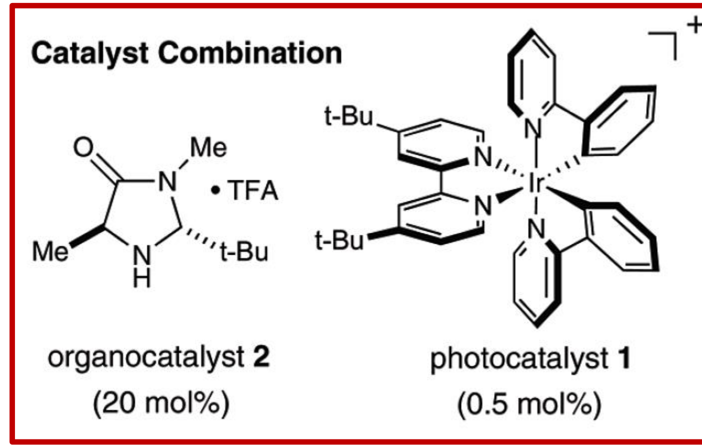
79% yield, 99% ee *61% yield, 93% ee* *89% yield, 99% ee*

J. Am. Chem. Soc., **2009**, *131*, 10875-10877

Enantioselective Photo-redox Organo Catalysis

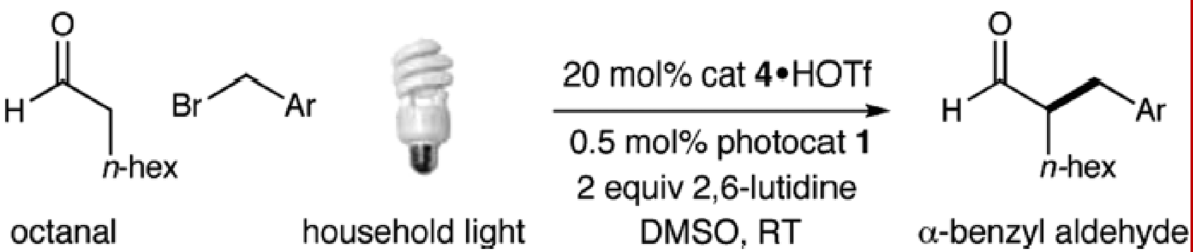
Enantioselective α-trifluoromethylation

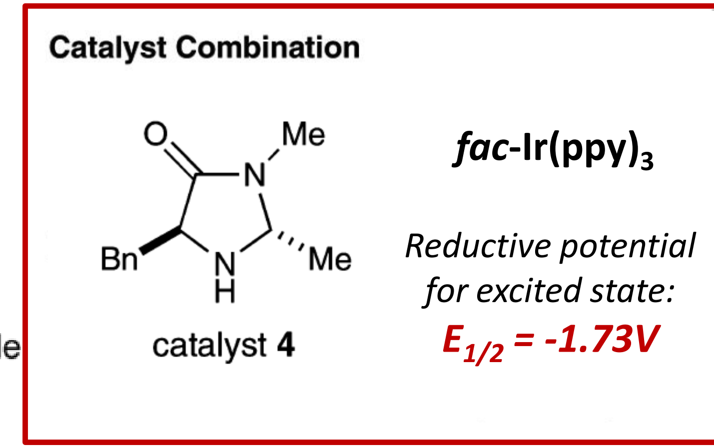




J. Am. Chem. Soc., **2009**, *131*, 10875-10877

Enantioselective α-benzylation





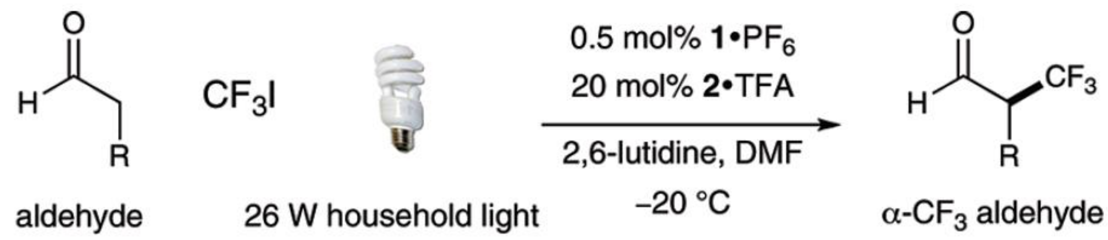
- substrate: only electron deficient aromatic compound

entry	Ar	catalyst	% yield[a]	% ee[b]
1	Phenyl	9	0	ND
2	2,4-$(NO_2)_2C_6H_3$	9	74	97

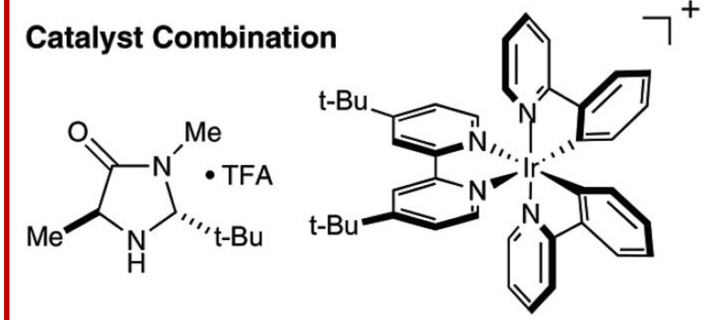
J. Am. Chem. Soc., **2010**, *132*, 13600-13603

Enantioselective Photo-redox Organo Catalysis

Enantioselective α-trifluoromethylation



Catalyst Combination

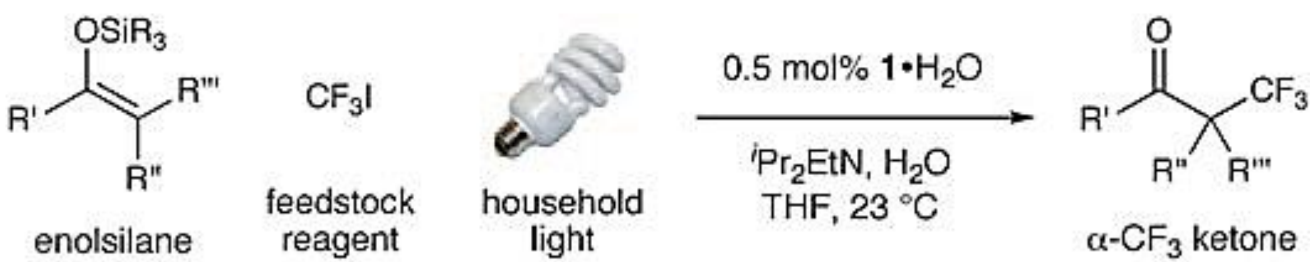


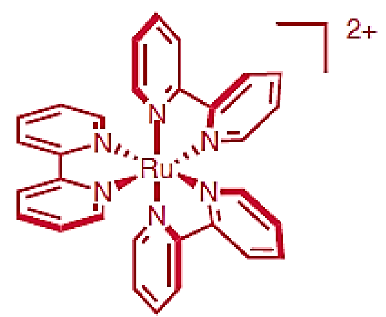
organocatalyst **2** (20 mol%)

photocatalyst **1** (0.5 mol%)

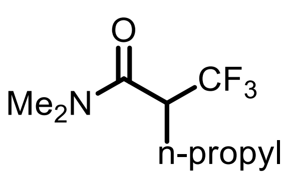
J. Am. Chem. Soc., **2009**, *131*, 10875-10877

Racemic α-trifluoromethylation: *Start from enolsilane*

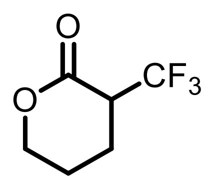




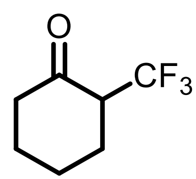
amide | *ester* | *ketone*



76 %



85 %

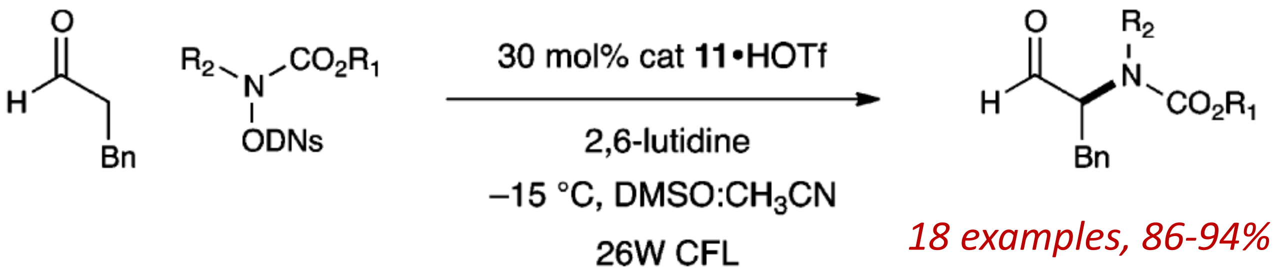


72 %

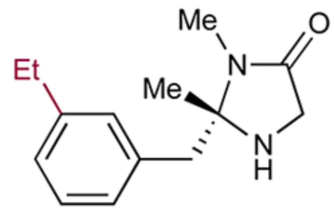
Angew. Chem. Int. Ed., **2011,** *50*, 6119-6122

Enantioselective Photo-redox Organo Catalysis

Enantioselective α-amination

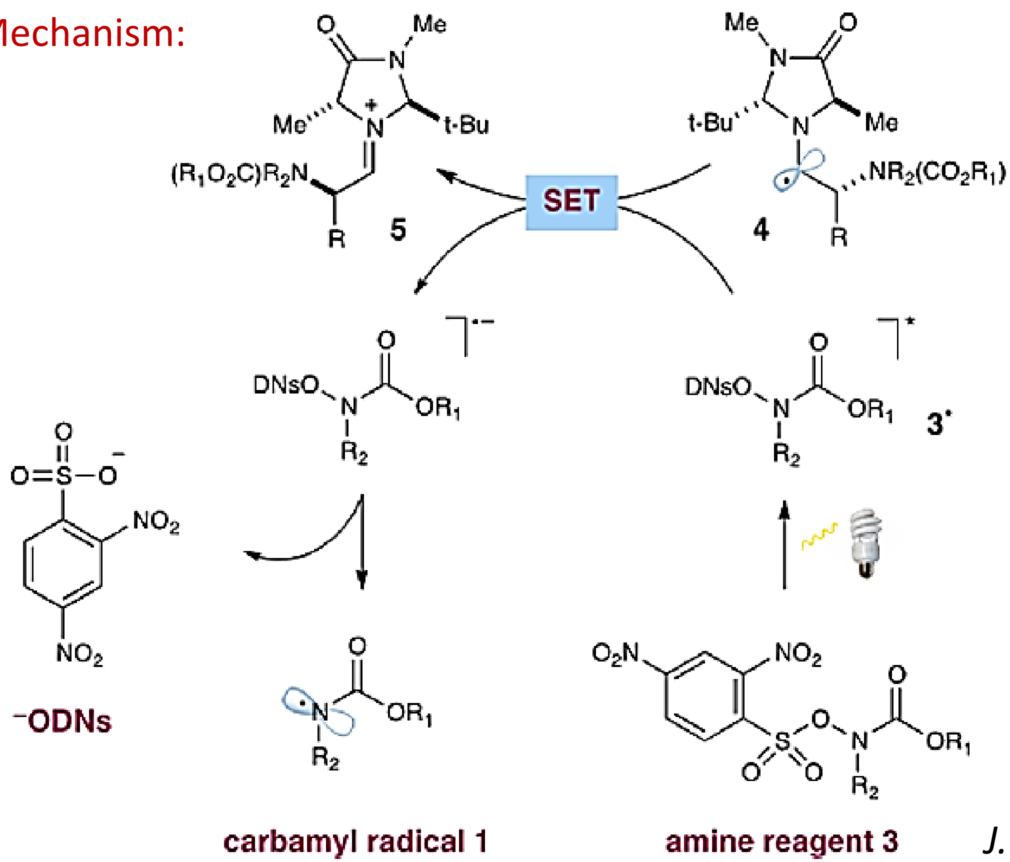


18 examples, 86-94% ee



Catalyst **11**

- *ODNs = 2,4-dinitrophenylsulfonyloxy*, ***a photolabile LG***
- *CO_2R_1 =* ***CO_2Me, CBz, Boc***
- Mechanism:



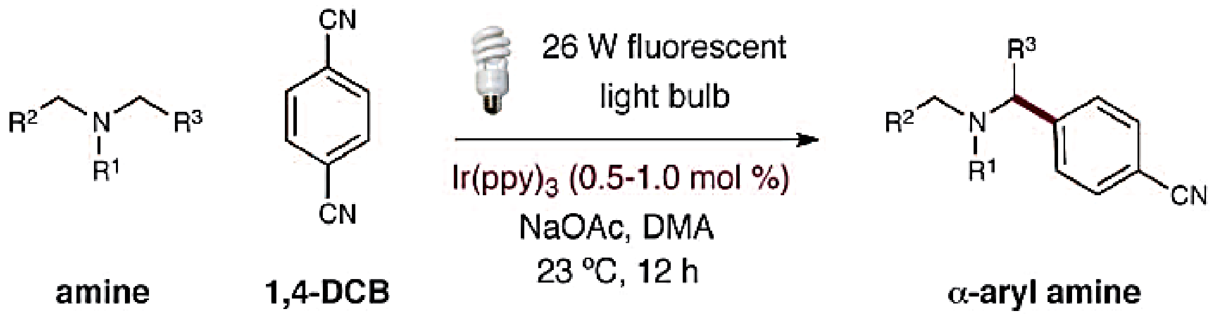
For the direct Coupling of α-Carbonyls with Functionalized Amines, see:
J. Am. Chem. Soc., **2013**, *135*, 16074-16077

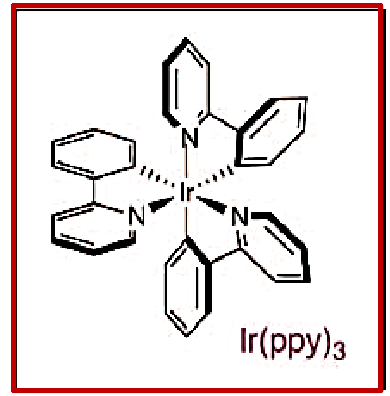
J. Am. Chem. Soc., **2013**, *135*, 11521-11524

Content

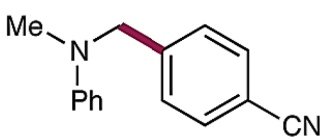
Content

Photo-redox Catalysis: a different type & via high throughput screening





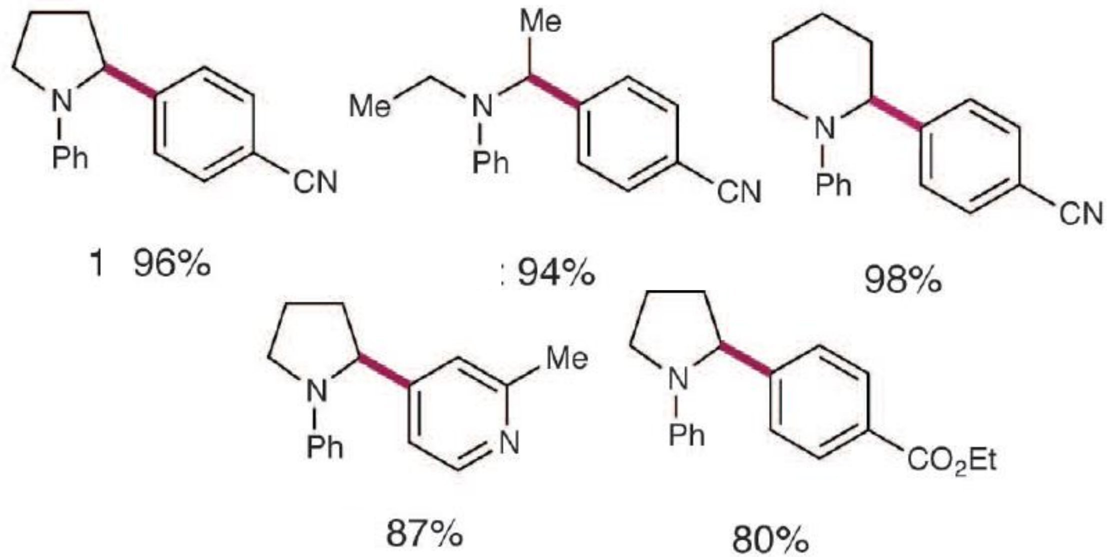
Initial Result



2, 11%

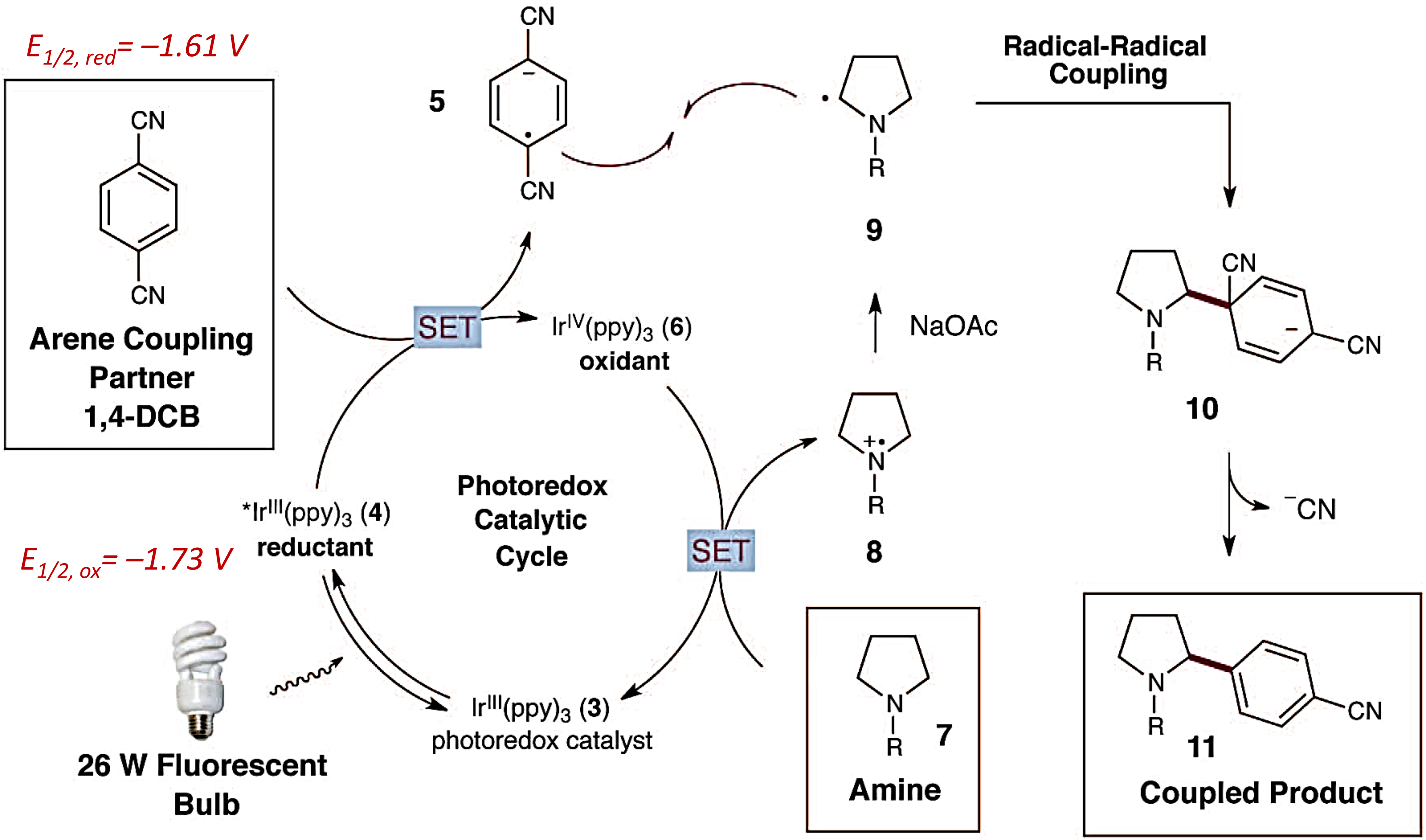
$Ir(ppy)_2(dtbbpy)PF_6$ - 0.5 mol%

Na_2CO_3, DMF, 23 ºC, 26 W Lamp



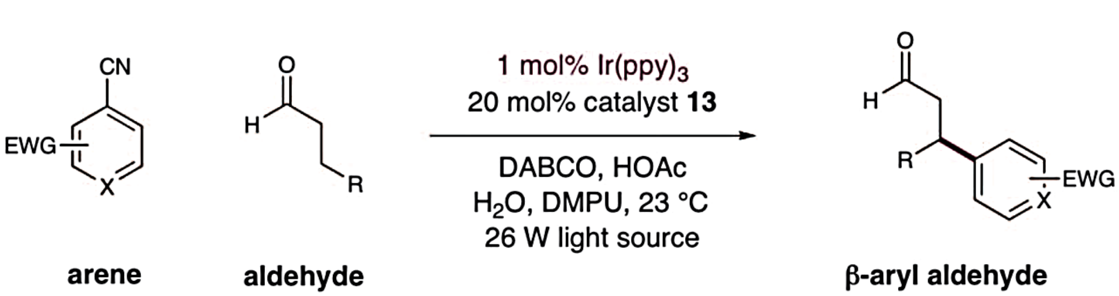
Science, **2011 ,** *334*, 1114-1117

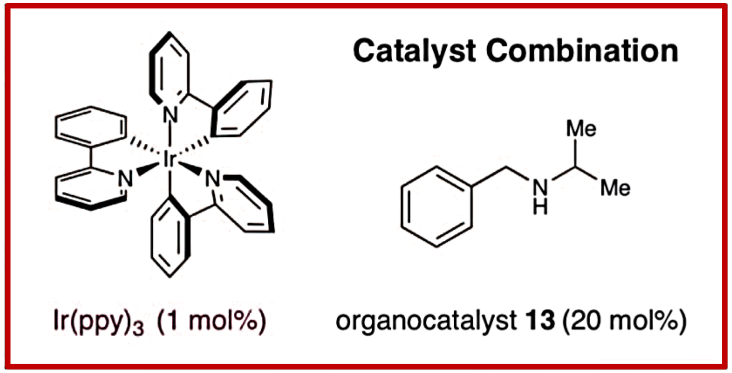
Photo-redox Catalysis: a different type & via high throughput screening

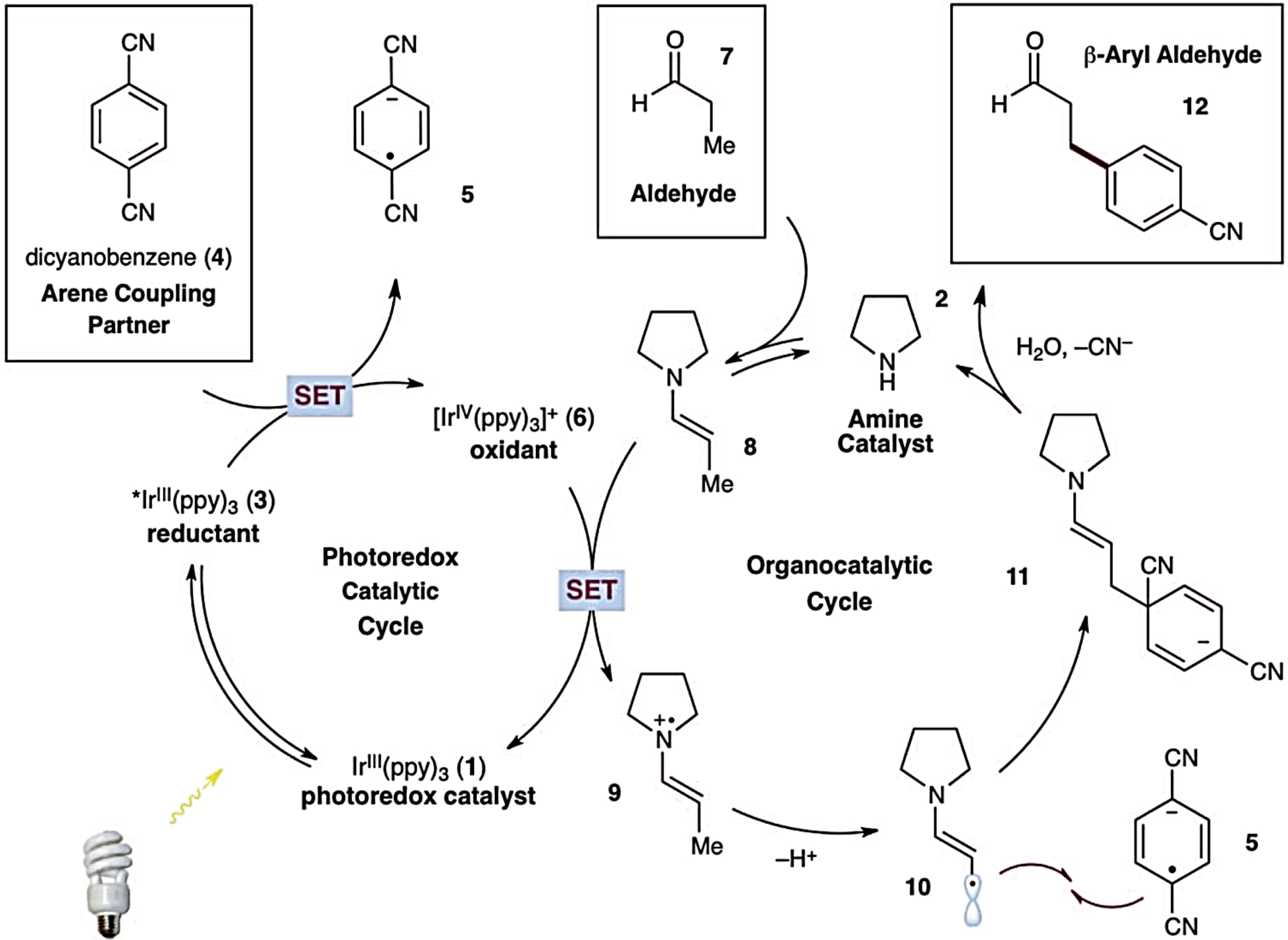


Science, **2011** , *334*, 1114-1117

Photo-redox Catalysis: for β-functionalization

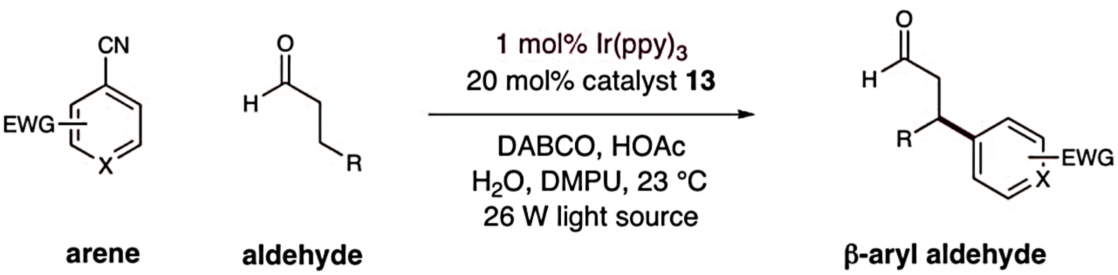


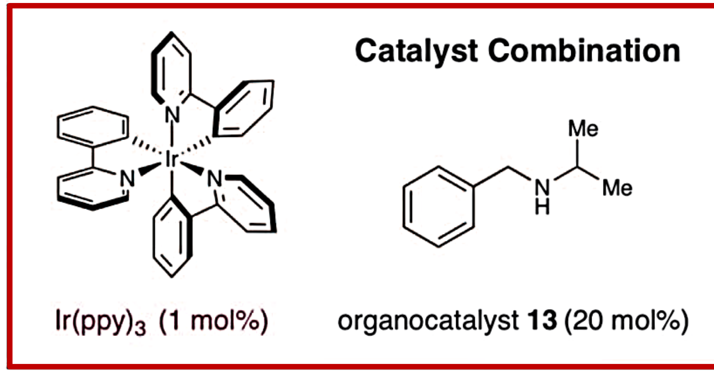


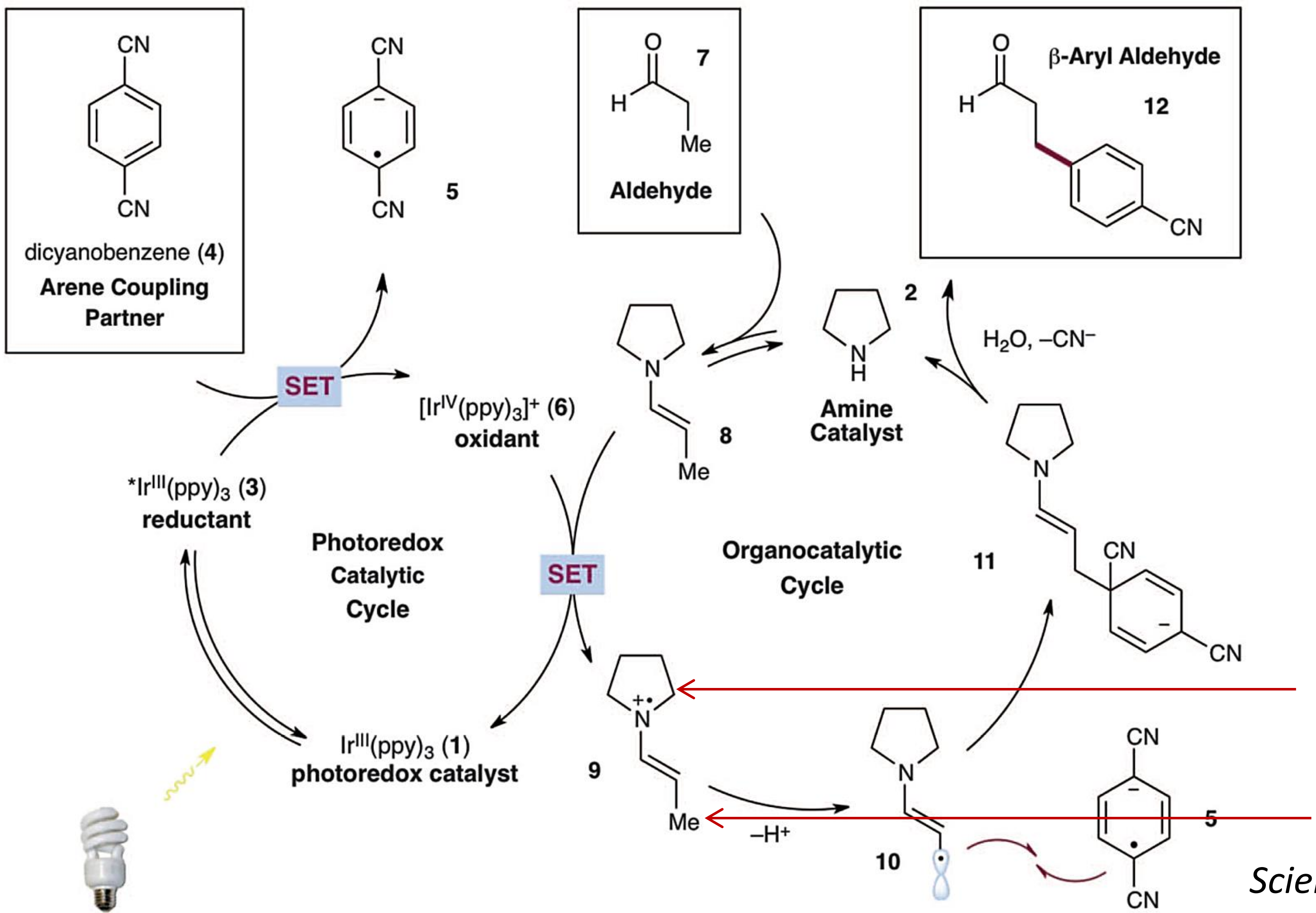


Science, **2013**, *339*, 1593-1596

Photo-redox Catalysis: for β-functionalization



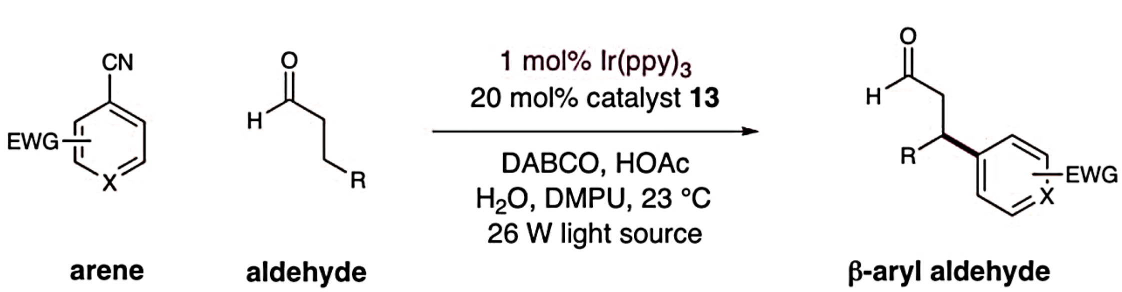




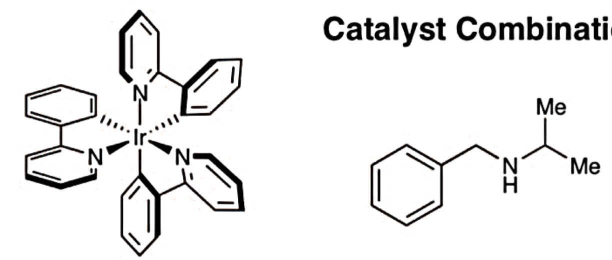
deprotonation prefer the ***allyl position*** *rather than the α-position*

Science, **2013**, *339*, 1593-1596

Photo-redox Catalysis: for β-functionalization

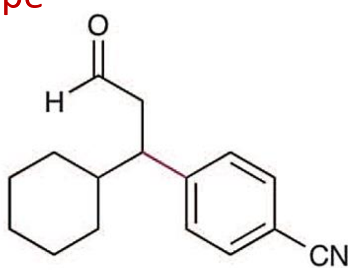


Catalyst Combination

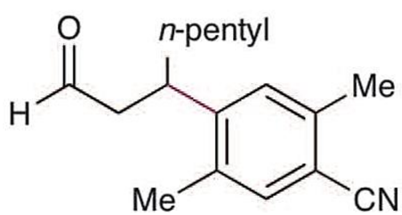


Ir(ppy)$_3$ (1 mol%) organocatalyst **13** (20 mol%)

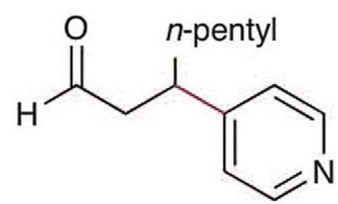
- Substrate scope



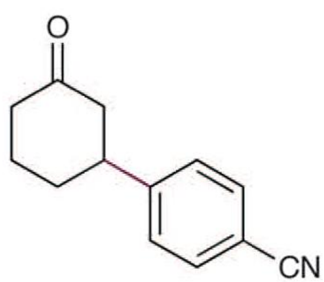
79 %



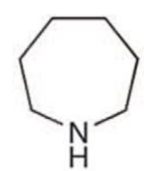
78 %



70 %



(±)-36: 88%

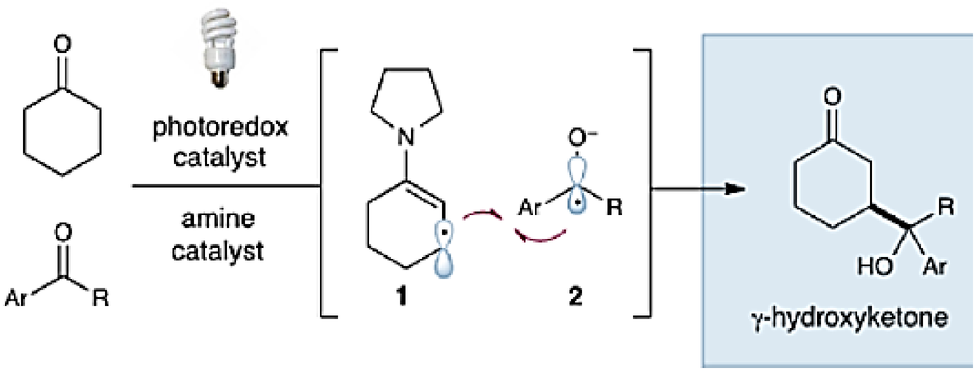


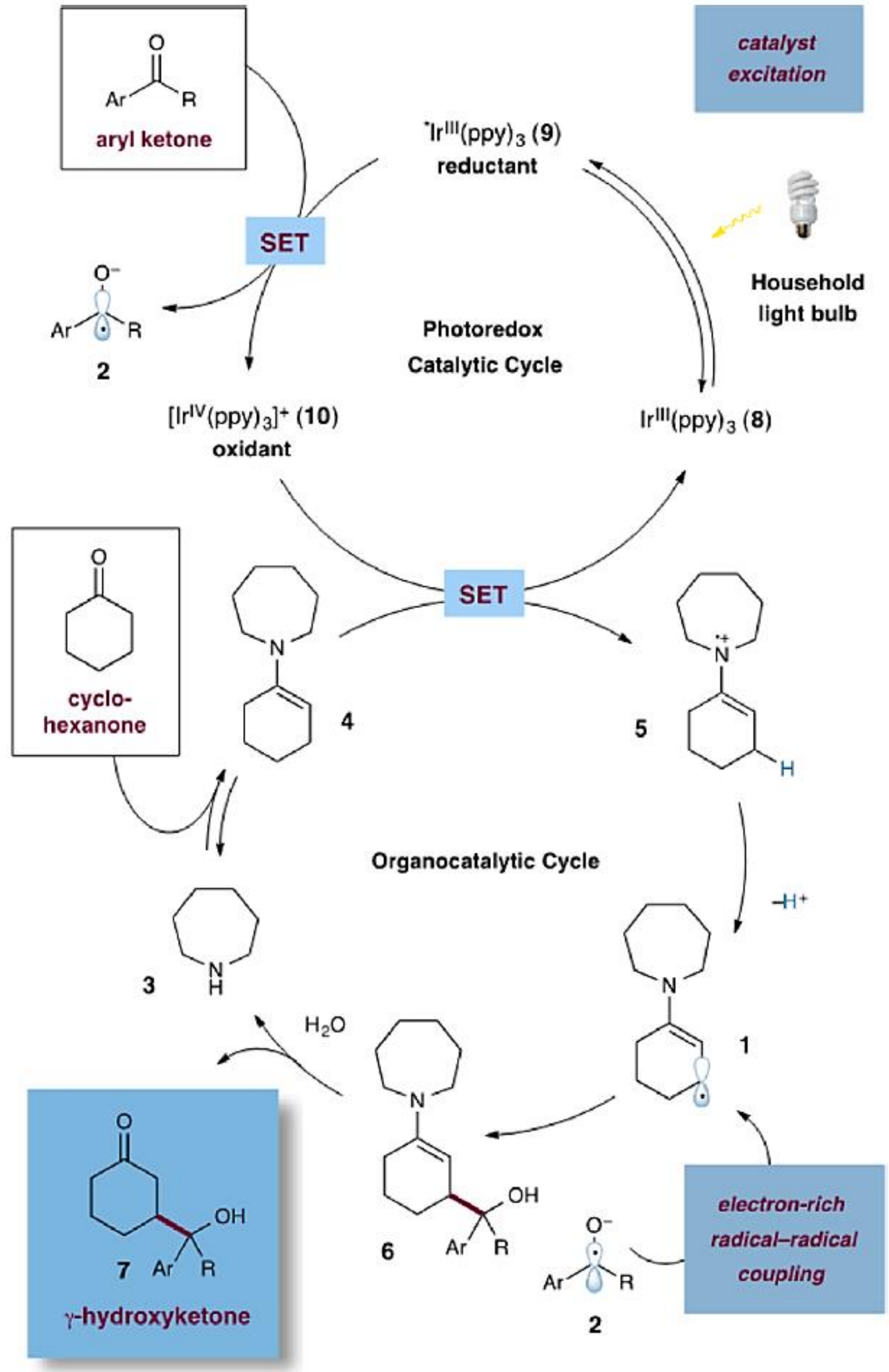
For cyclic ketone

azepane
(20 mol%)

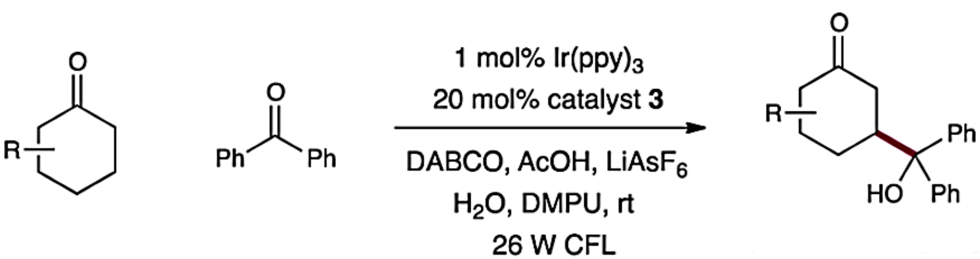
Science, **2013**, *339*, 1593-1596

Photo-redox Catalysis: β-functionalization

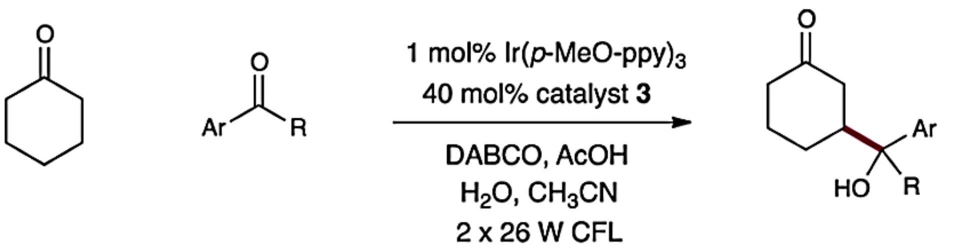




For benzophenone substrate

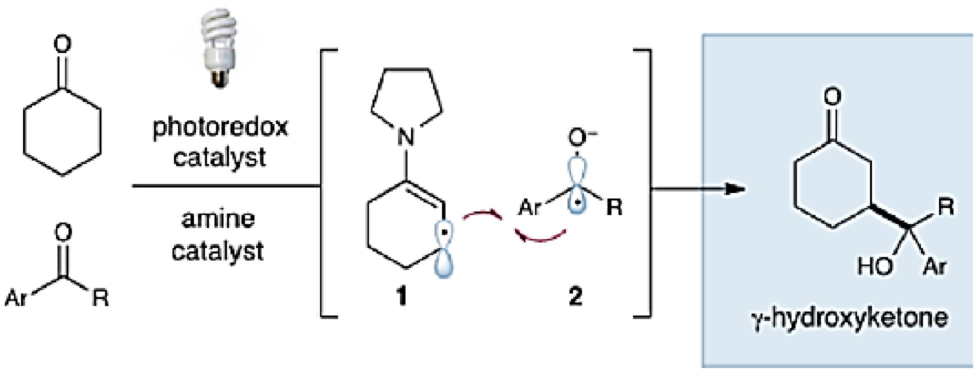


For arylalkylketone substrate

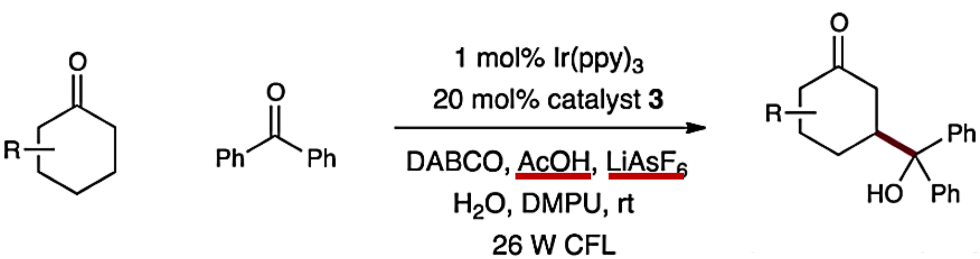


J. Am. Chem. Soc. **2013**, *135*, 18323−18326

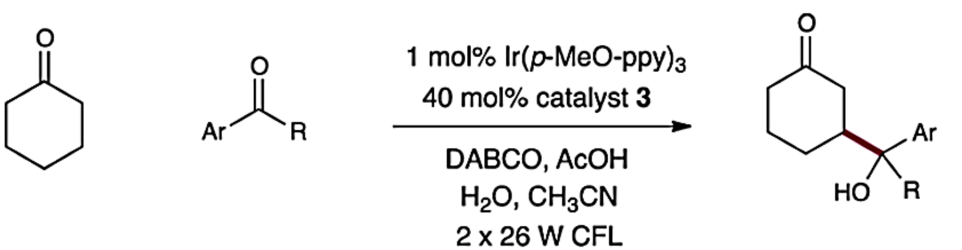
Photo-redox Catalysis: β-functionalization



For benzophenone substrate



For arylalkylketone substrate



J. Am. Chem. Soc. **2013**, *135*, 18323−18326

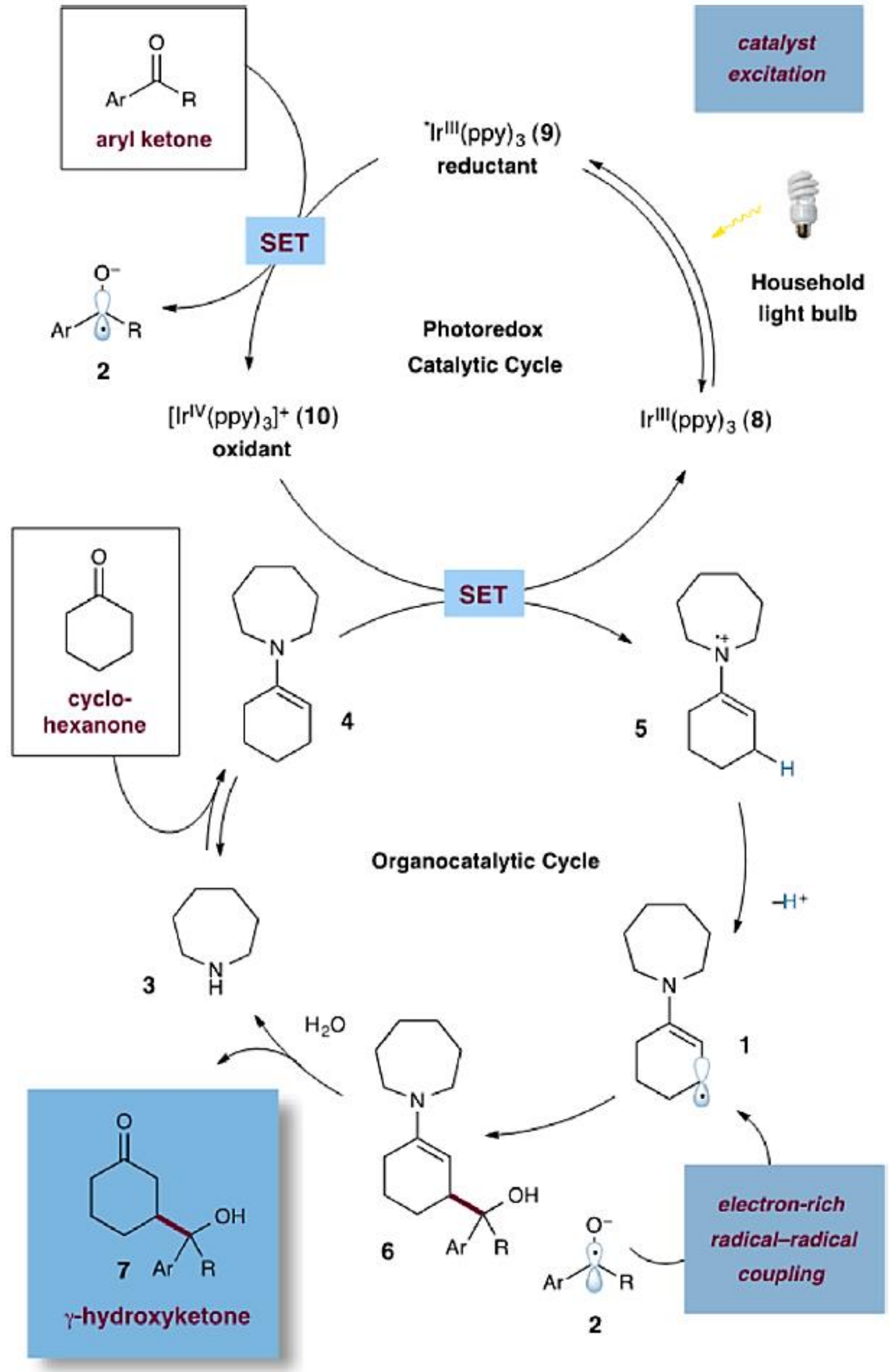
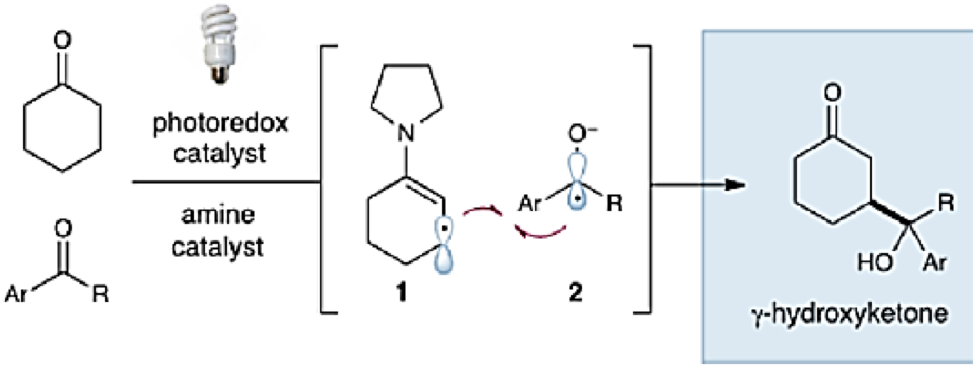
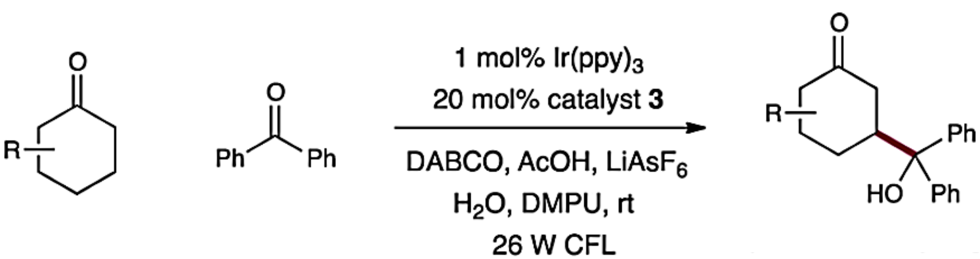


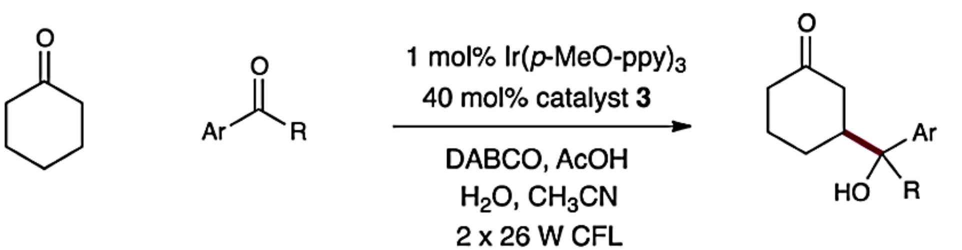
Photo-redox Catalysis: β-functionalization



For benzophenone substrate

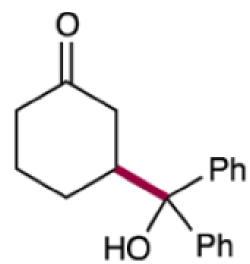


For arylalkylketone substrate

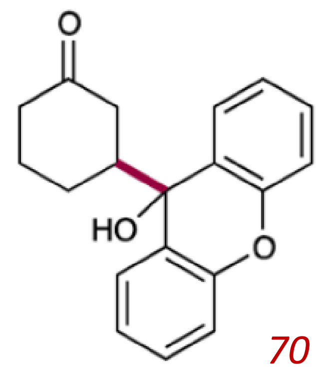


J. Am. Chem. Soc. **2013**, *135*, 18323−18326

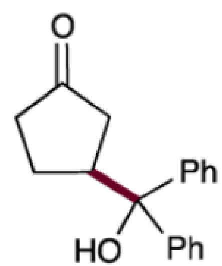
Substrate scope



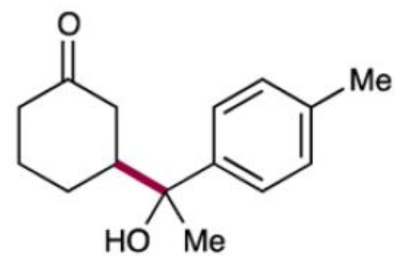
81 %



70 %

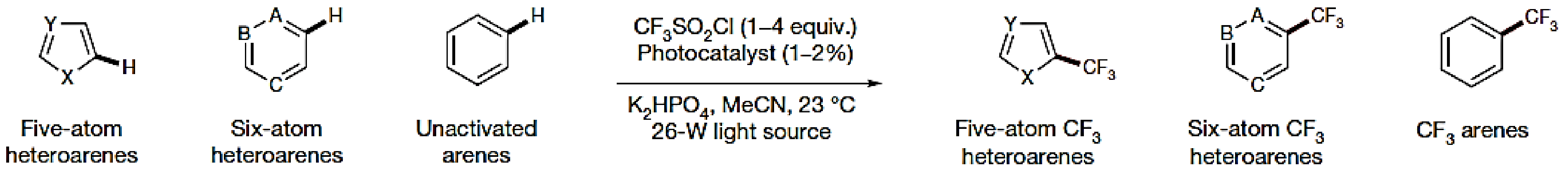


65 %



79 %

Photo-redox Catalysis: Arene Trifluoromethylation

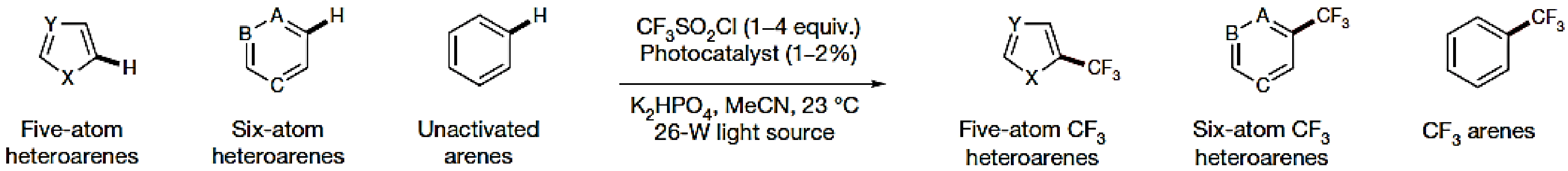


Photocatalyst = **$Ru(phen)_3Cl_2$**

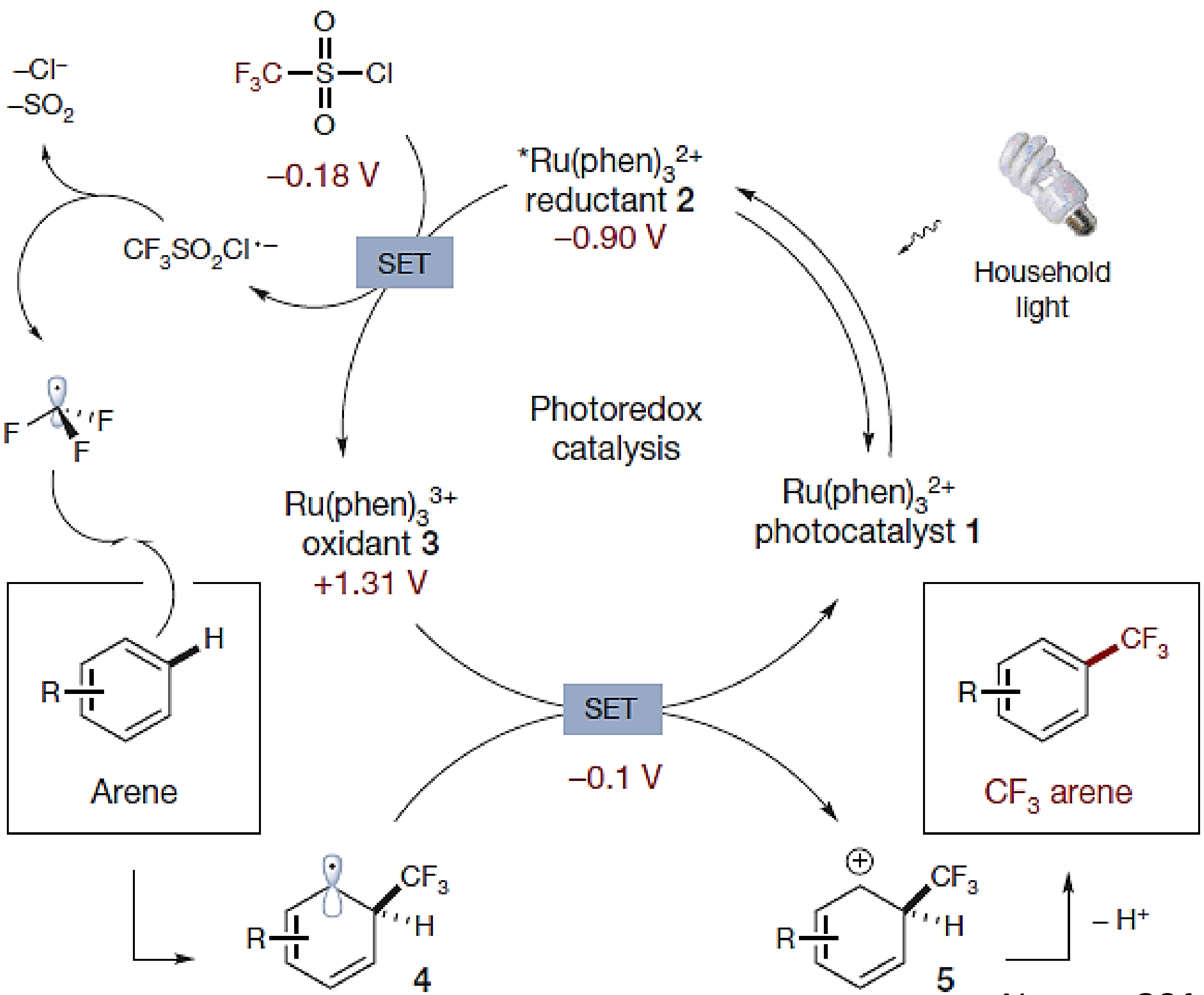
CF3 radical *comes from* **CF_3SO_2Cl**

Nature, **2011**, *480*, 224-228

Photo-redox Catalysis: Arene Trifluoromethylation

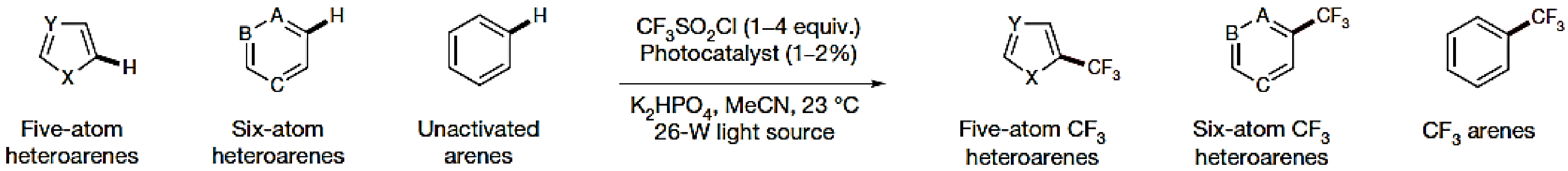


- Proposed mechanism:



Nature, **2011**, *480*, 224-228

Photo-redox Catalysis: Arene Trifluoromethylation



- Substrate scope: ***hetereo arene*** & ***electron-rich arene***

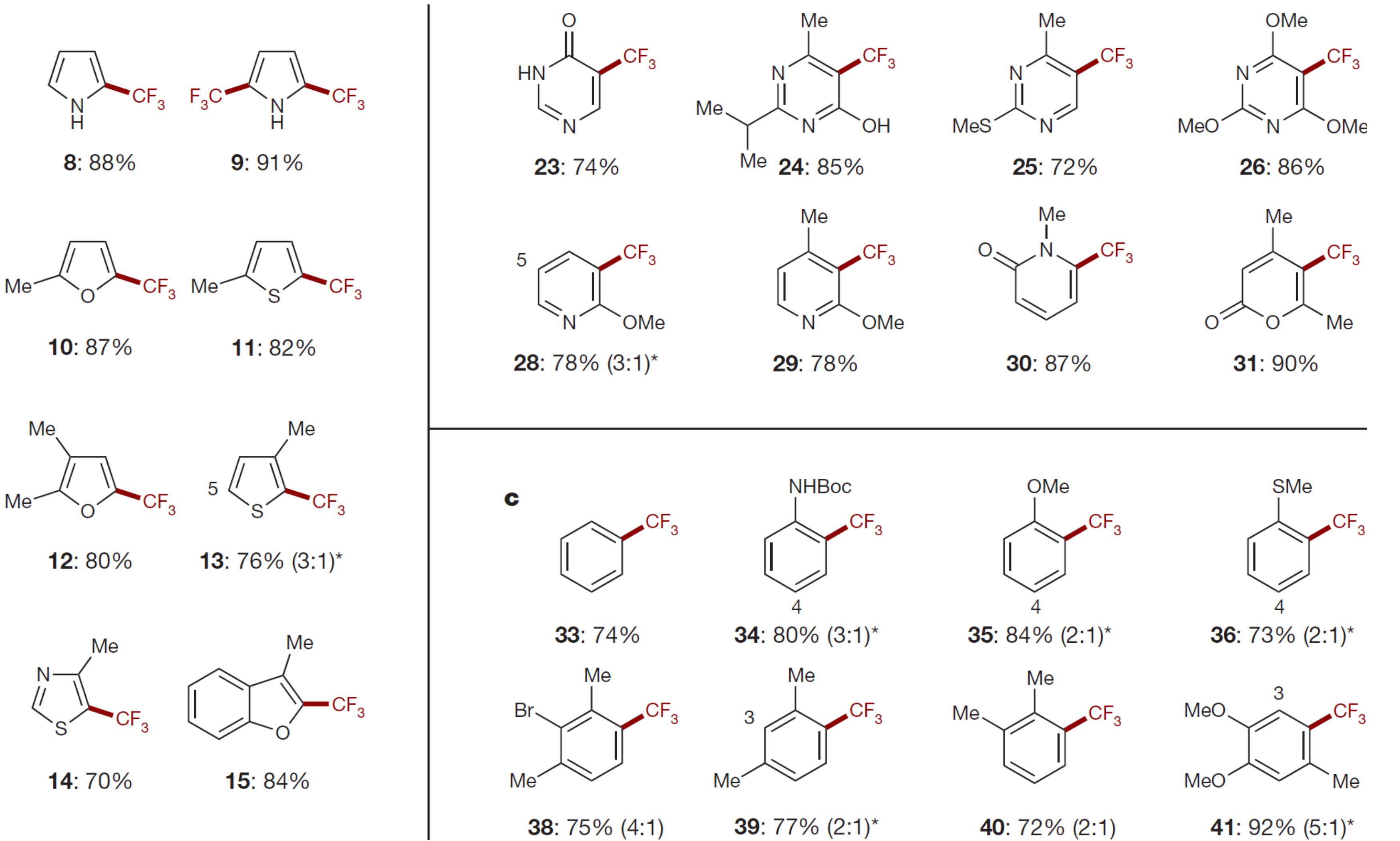
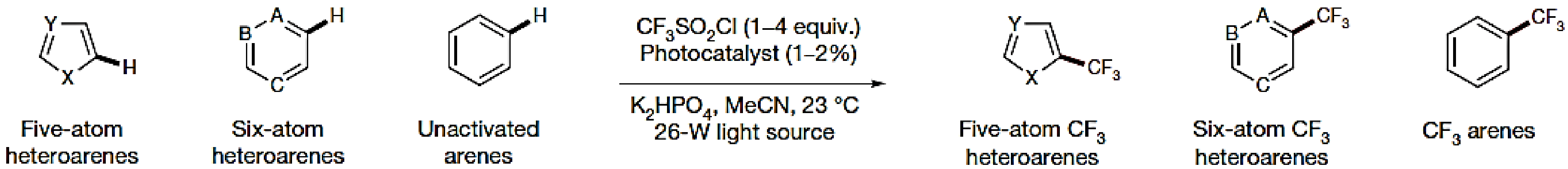


Photo-redox Catalysis: Arene Trifluoromethylation



■ Substrate scope: ***hetereo arene*** & ***electron-rich arene***

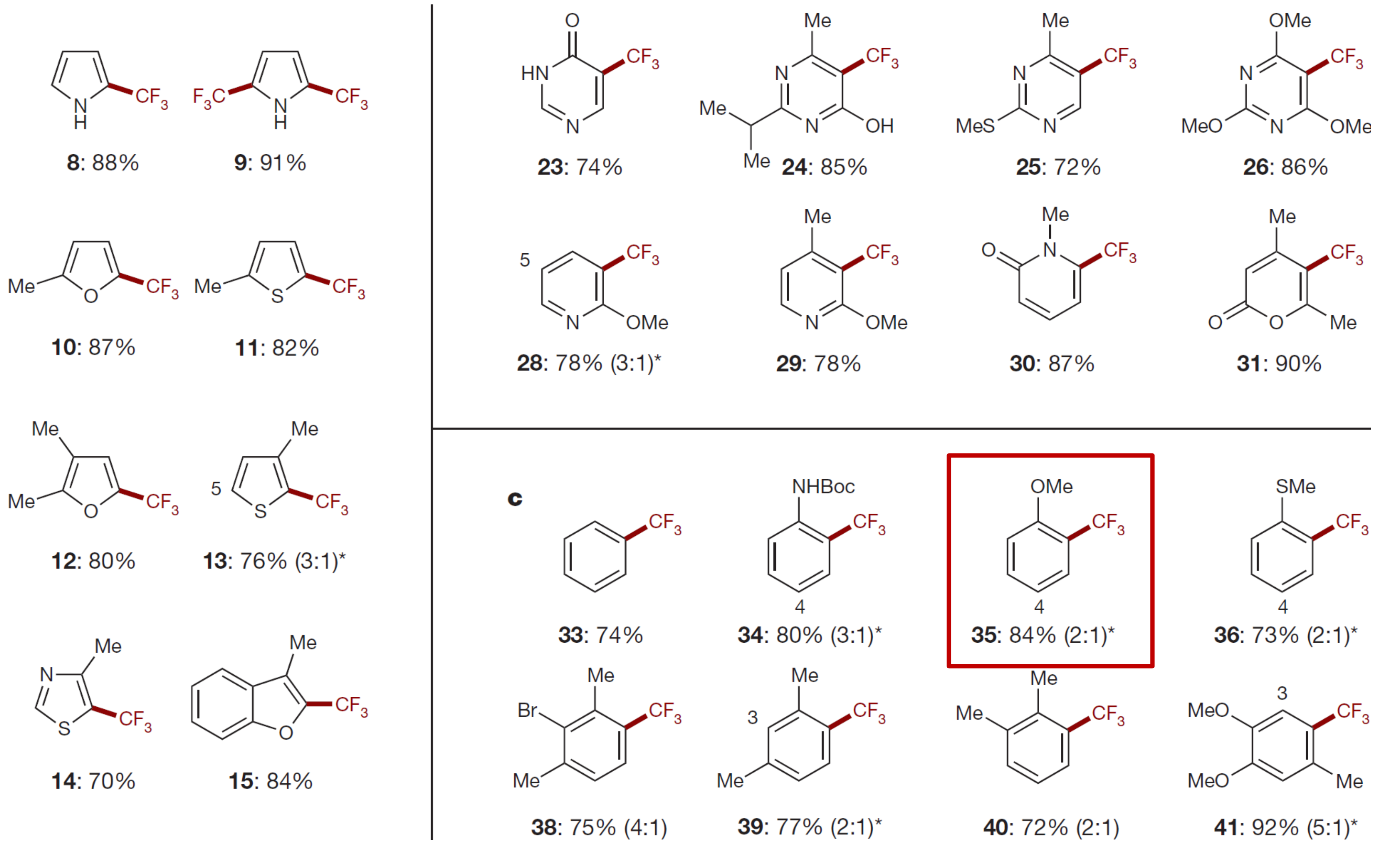
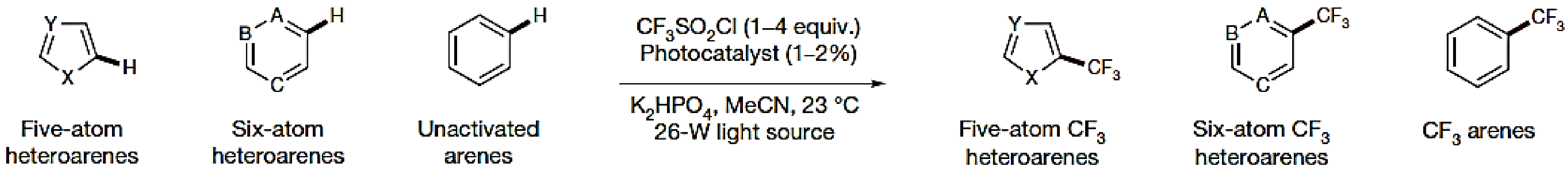
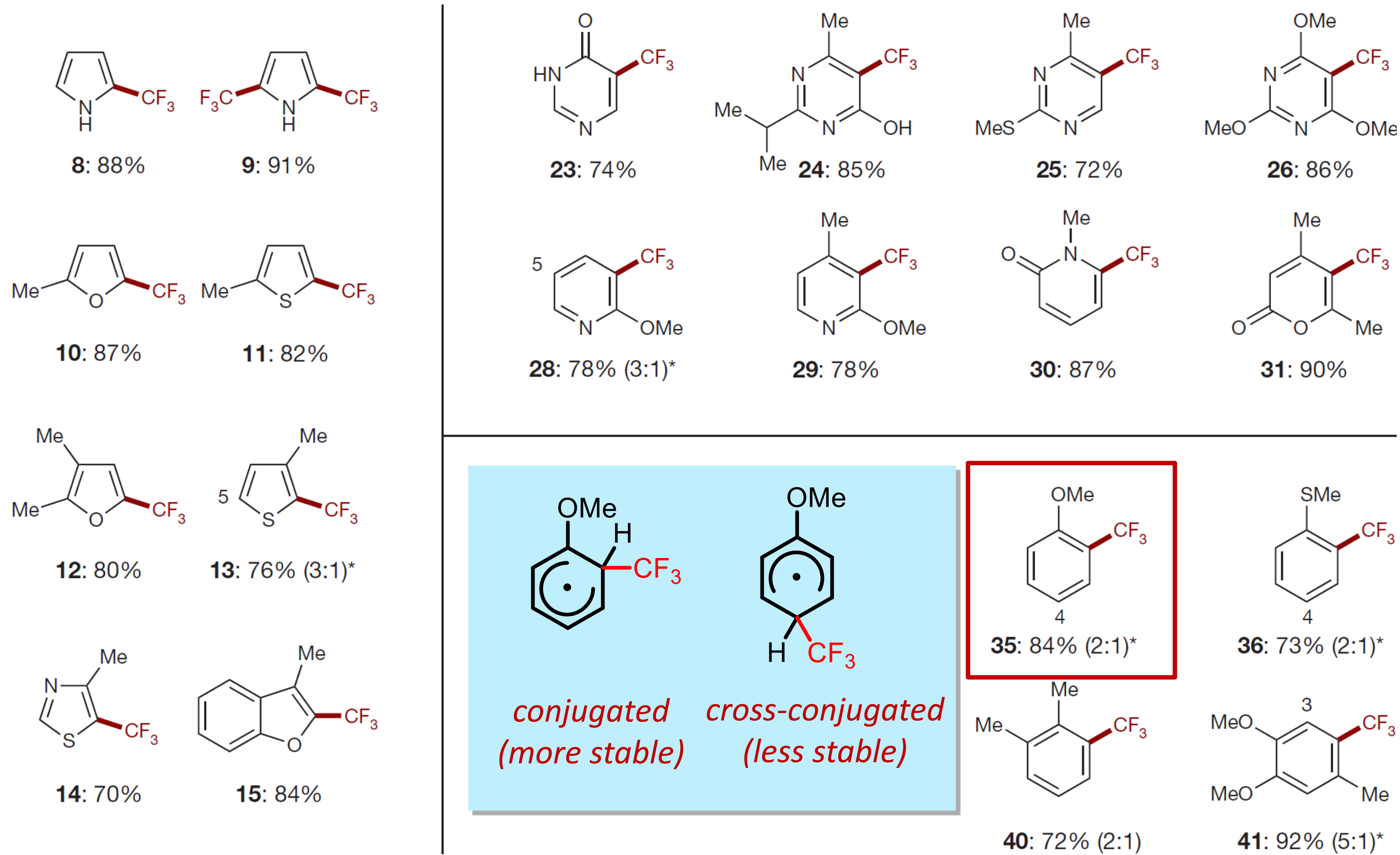


Photo-redox Catalysis: Arene Trifluoromethylation



■ Substrate scope: ***hetereo arene*** & ***electron-rich arene***



Content

Content

1 *LUMO Catalysis*

2 *HOMO Catalysis*

3 *Cascade LUMO-HOMO Catalysis*

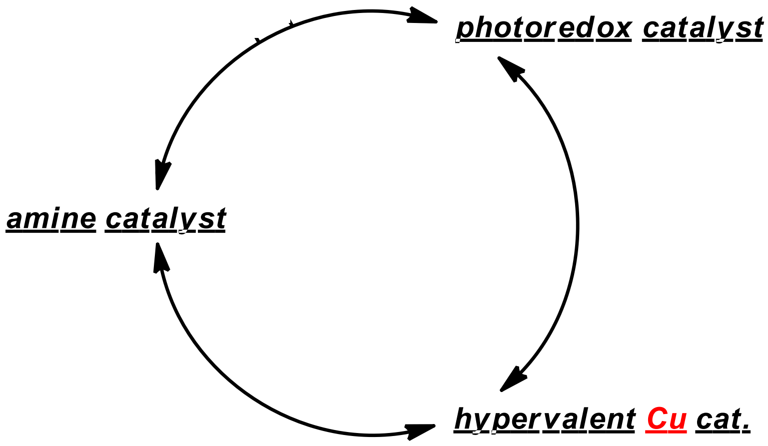
4 *SOMO Catalysis*

5 *Photoredox Organo Catalysis*

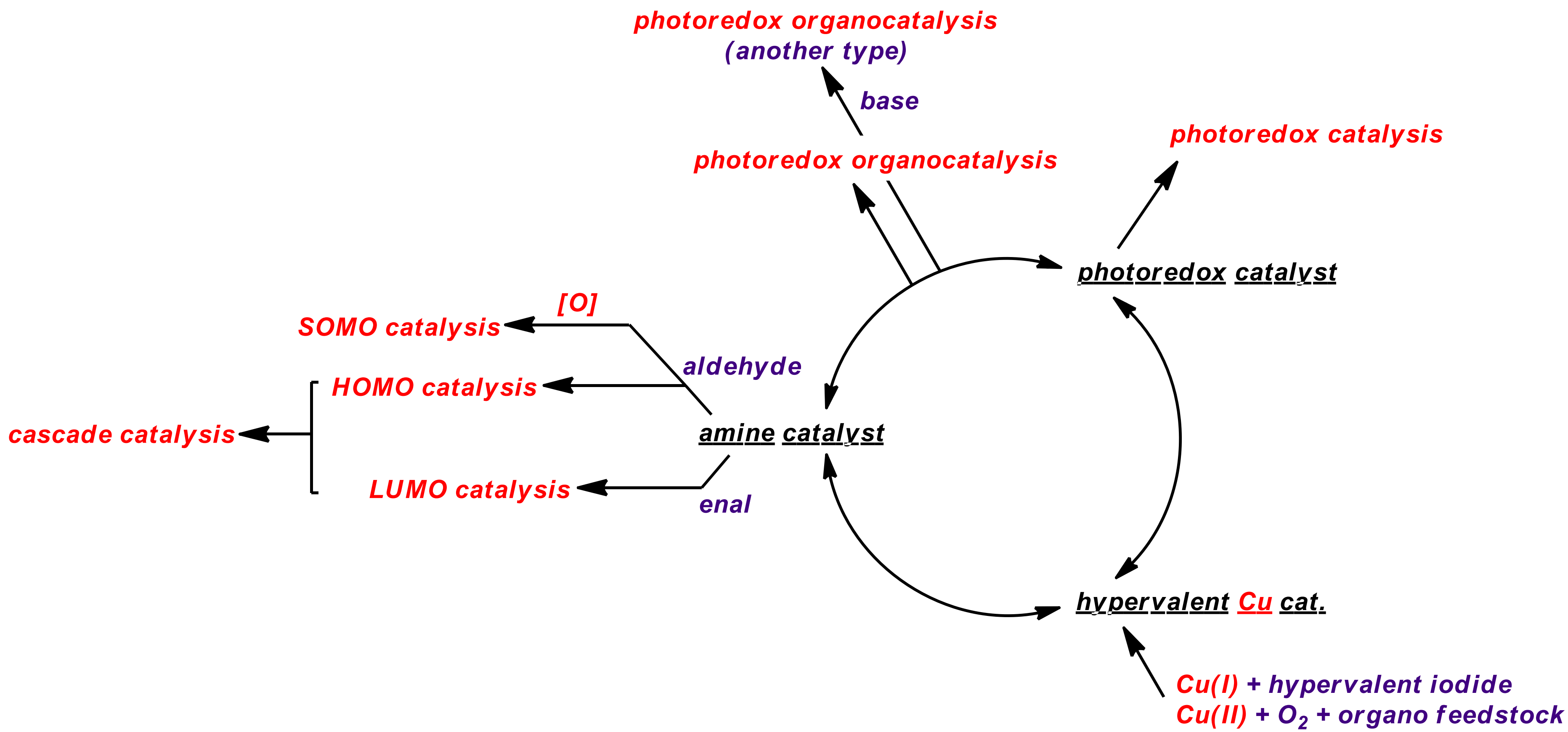
6 *Photoredox Organo Catalysis (Type II)*

7 ***Summary***

Summary

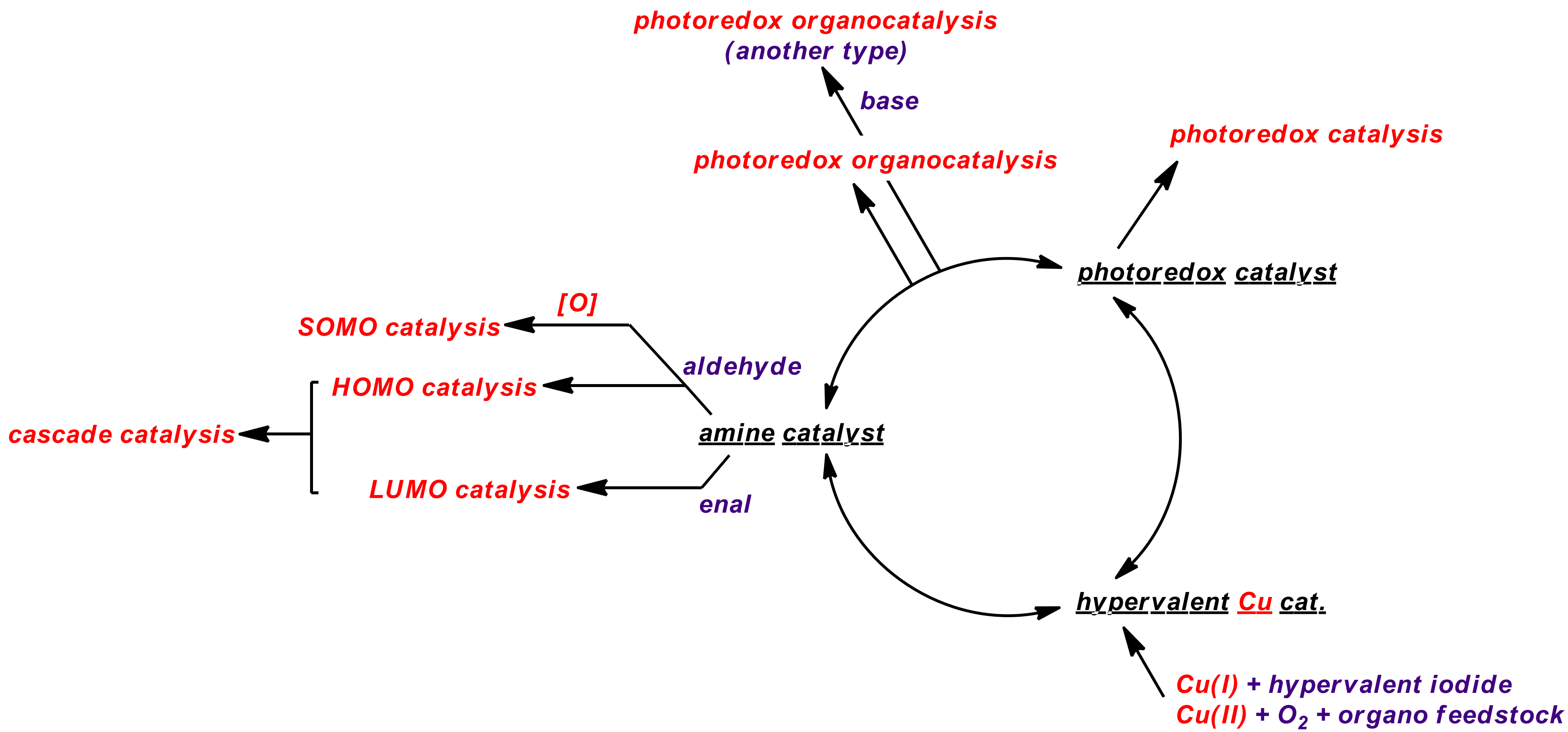


Summary



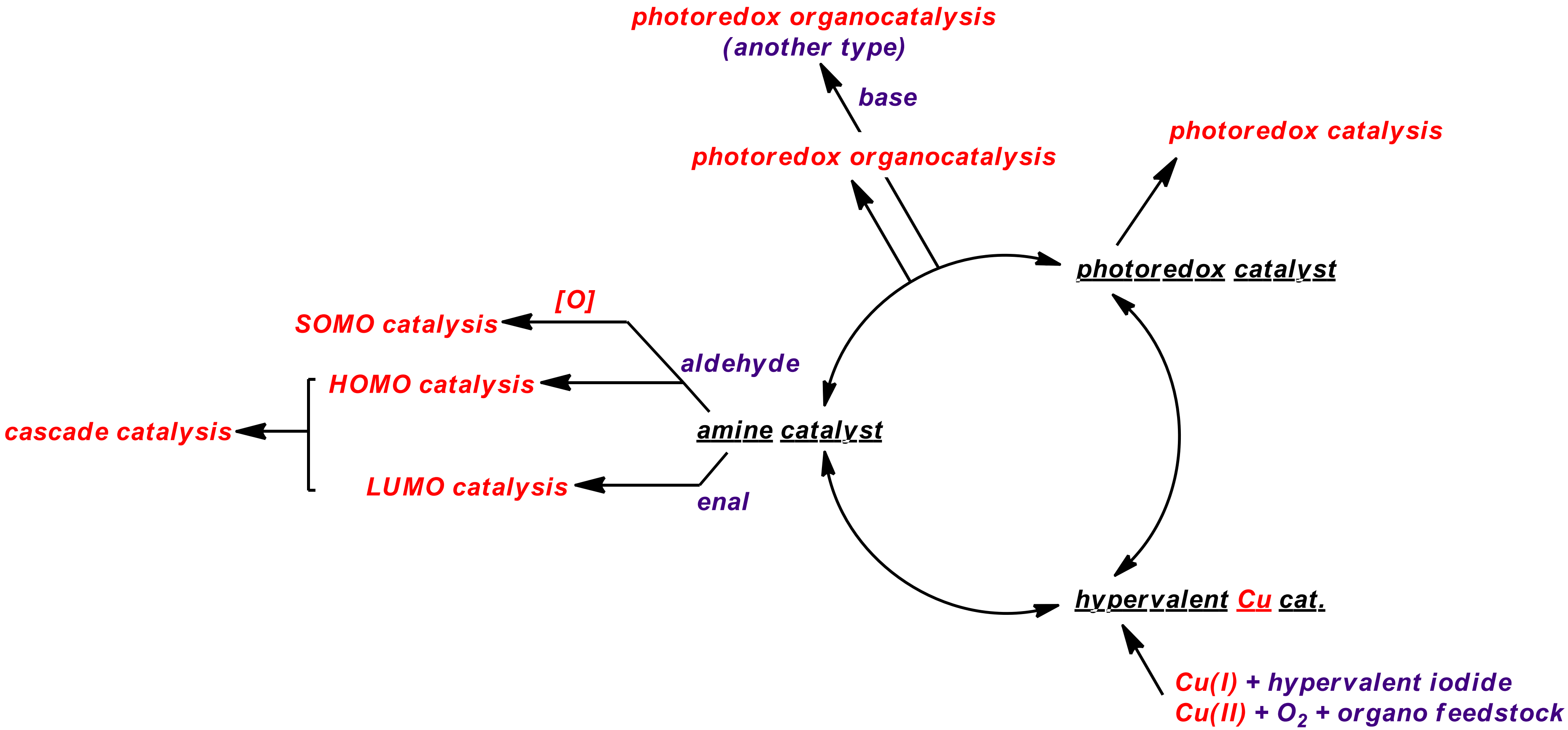
photoredox organocatalysis
(another type)
base
photoredox organocatalysis
photoredox catalysis
photoredox catalyst
[O]
SOMO catalysis
aldehyde
HOMO catalysis
cascade catalysis
amine catalyst
LUMO catalysis
enal
hypervalent Cu cat.
Cu(I) + hypervalent iodide
Cu(II) + O_2 + organo feedstock

Summary



- *New chiral amine catalyst family*
- *Merge different type of catalysis*
- *Deep-going mechanism study*

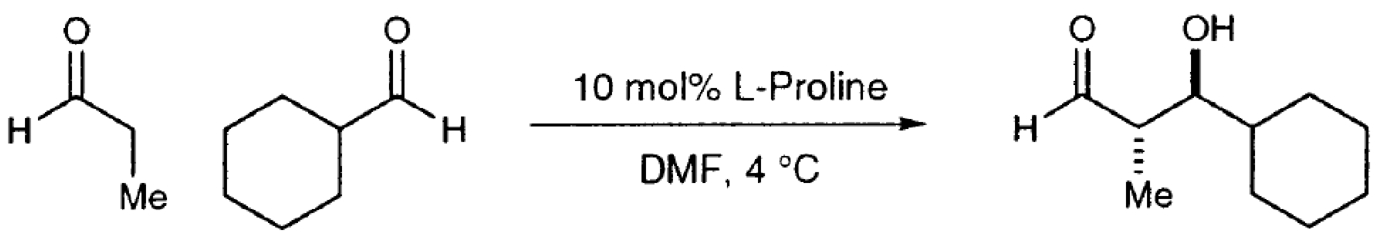
Summary

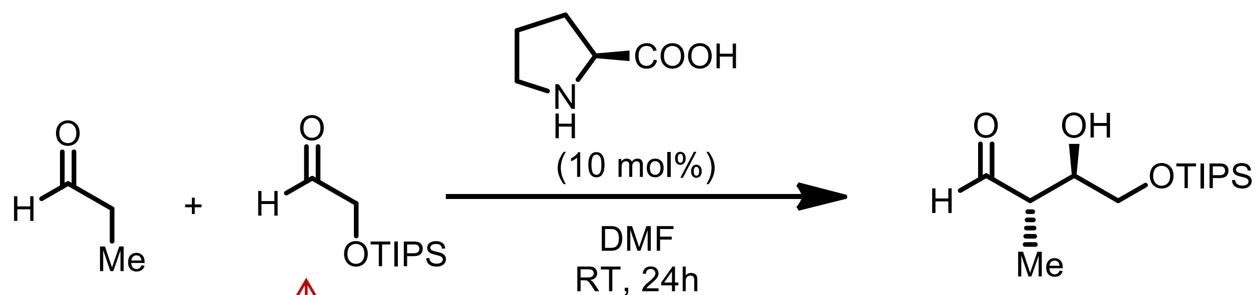


- New chiral amine catalyst family
- Merge different type of catalysis
- Deep-going mechanism study

Thank You !

Q1





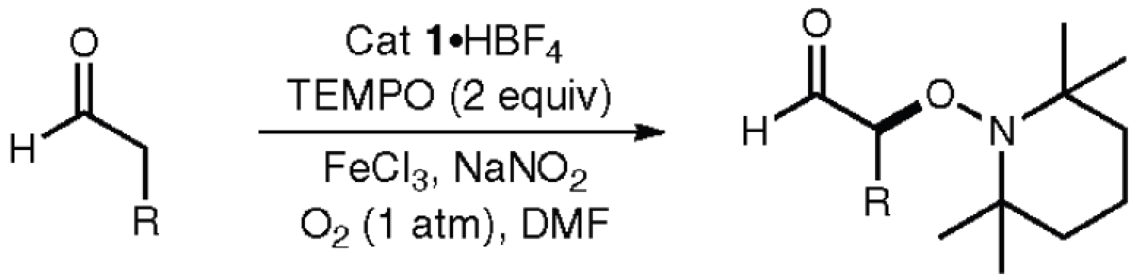
75 % yield, 4:1 dr, 99 % ee

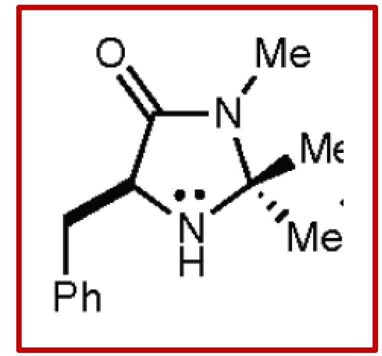
*Here as **Aldol acceptor***
Differs with metal mediated reaction

J. Am. Chem. Soc., **2002**, *124*, 6798-6799

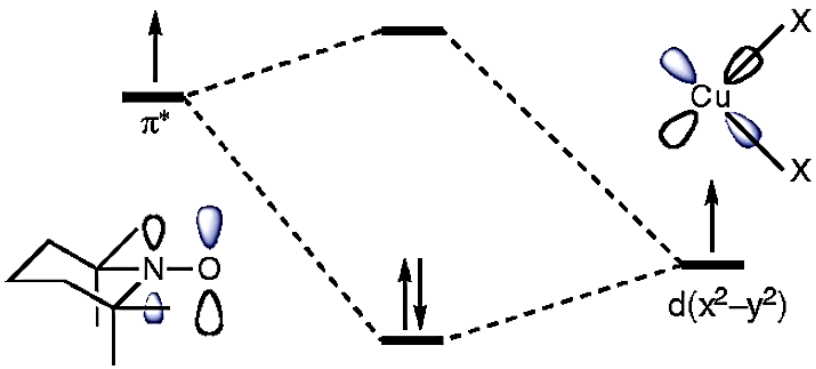
Q2

α-Oxidation of Aldehydes



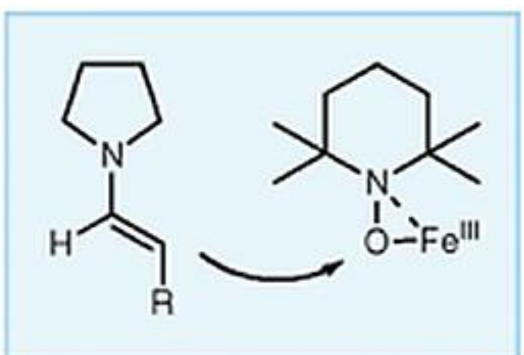


49-80% yield, 32--90% ee



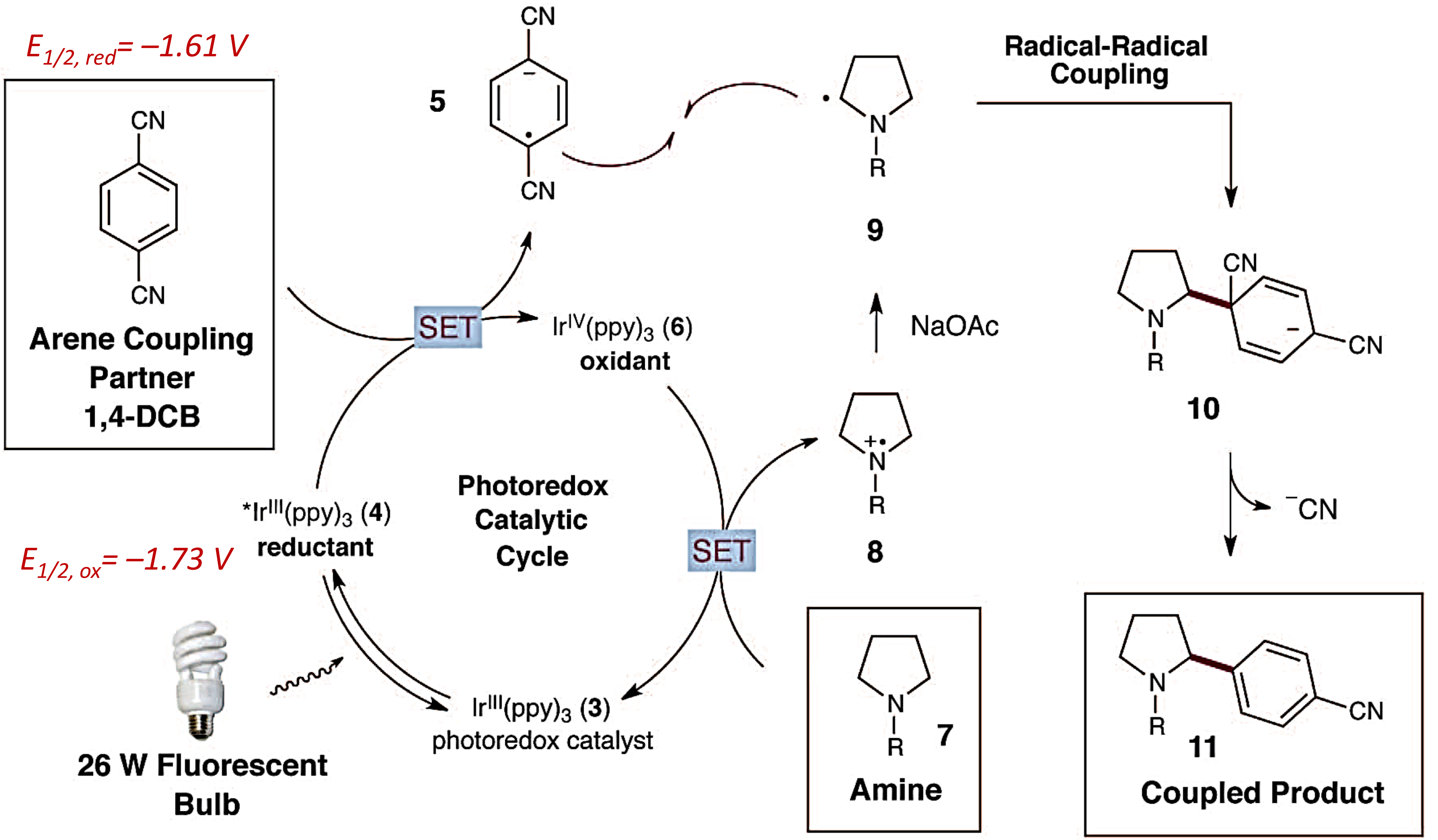
Complex formation: LUMO centered on TEMPO oxygen

Baerends, E. *J. Inorg. Chem*. **2009**, *48*, 11909



J. Am. Chem. Soc., **2010**, *132*, 10012-10014

Q3



Science, **2011** , *334*, 1114-1117