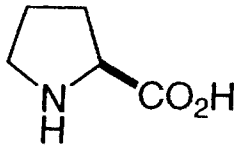
Literture Seminar (2007. Jun. 16th) Hisashi Mihara D2

Enantioselective Organocatalysis Using HOMO, LUMO and SOMO Activation

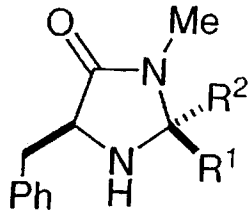
Introduction.

Benjamin List



L-proline

Professor D. W. C. MacMillan



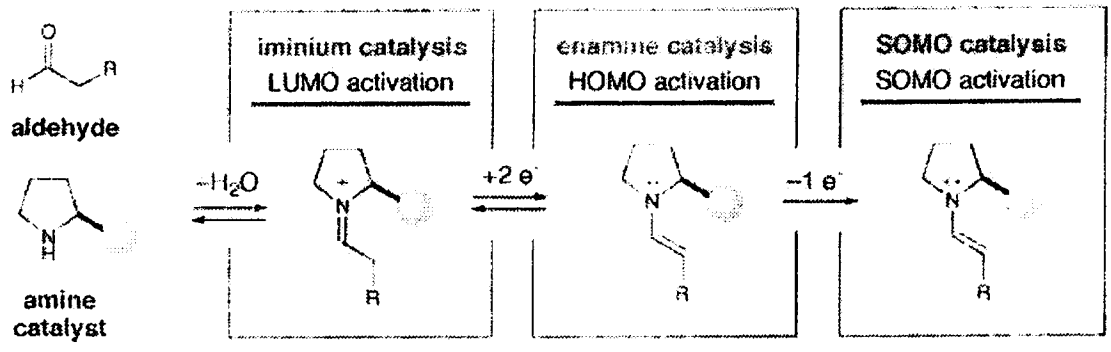
imidazolidinone

In 2000

L-proline

catalyst was published out.

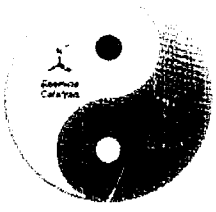
Imidazolidinone



- enamine ⟷ imine

like the "ying and yang"

「陰 陽」



- radical cation

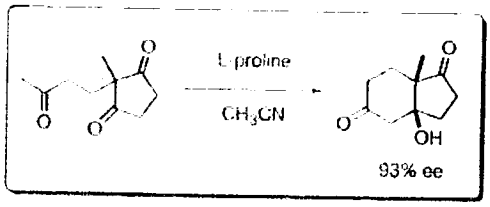
↓

「New Concept」

- Contents
  - The history of Amino catalysis
  - Enamine catalyst (HOMO activation)... Using L-proline, imidazolidinone catalyst
  - Iminium catalyst (LUMO activation)
  - Tandem Iminium - Enamine Catalyst
  - Radical catalyst (SOMO activation)

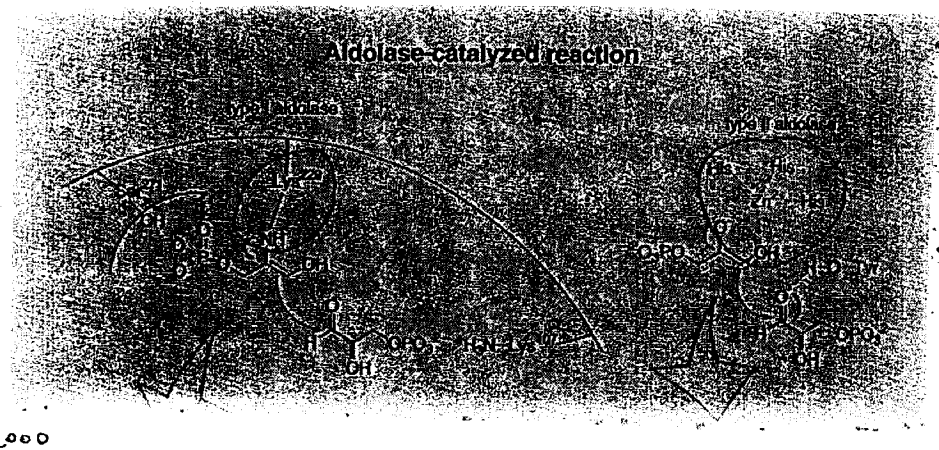
◦ The History of Amino catalysis

· First example catalytic Asymmetric Aldol Reaction Using L-proline



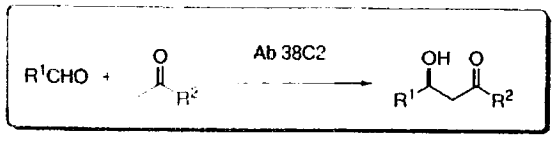
Sauer, Wiechert *Angew. Chem. Int. Ed.* 1971, *10*, 496.

Hajos, Parrish *J. Org. Chem.* 1974, *39*, 1615



- Type I aldrase exist in universal. (including human being)
- Type II aldrase exist in mold and algae etc

Before 2000



List, Barbas, et al

Direct Catalytic Asymmetric Aldol Reactions of Aldehydes with Unmodified Ketones

Yoichi M. A. Yamada, Naoki Yoshikawa, Hiroaki Sasai, and Masakatsu Shibasaki*

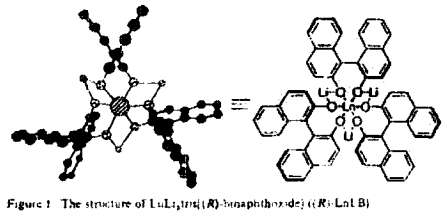
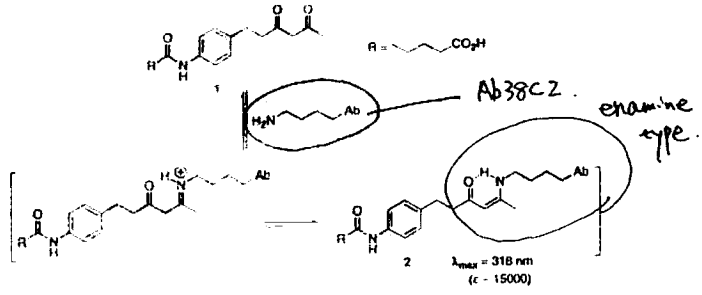
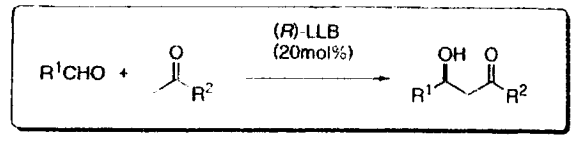


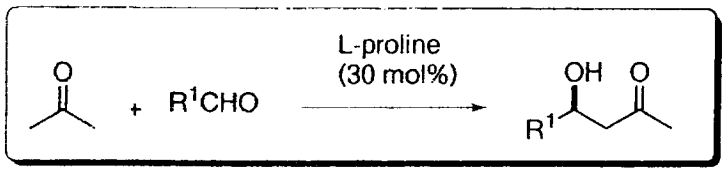
Figure 1. The structure of LuLi3tris(R)-binaphthoxide] ((R)-LnLB)



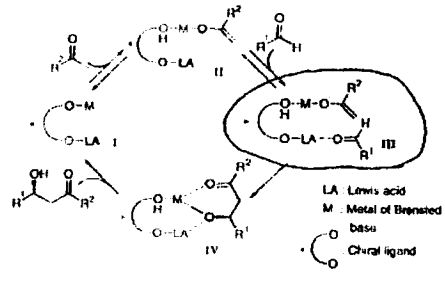


Shibasaki et al *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871.

Proline-Catalyzed Direct Asymmetric Aldol Reactions

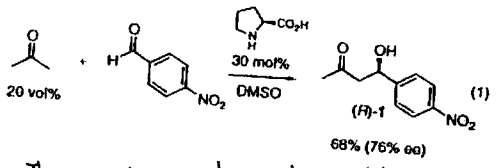


List, Barbas, et al *J. Am. Chem. Soc.* **2000**, *122*, 2395.



° Enamine catalysis (HOMO activation) using L-proline

··· Proline-Catalyzed Direct Asymmetric Aldol Reaction. J.A.C.S. 2000, 122, 2395

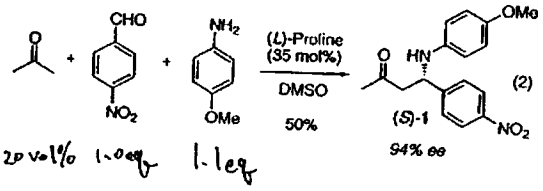


·· primary amino acid and secondary acyclic amino acid fail to give desired product

→ The reaction with isobutylaldehyde gave aldol product in 97% yield 96% ee.

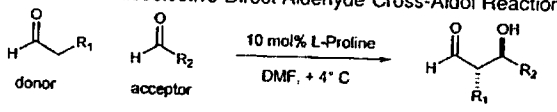
↓

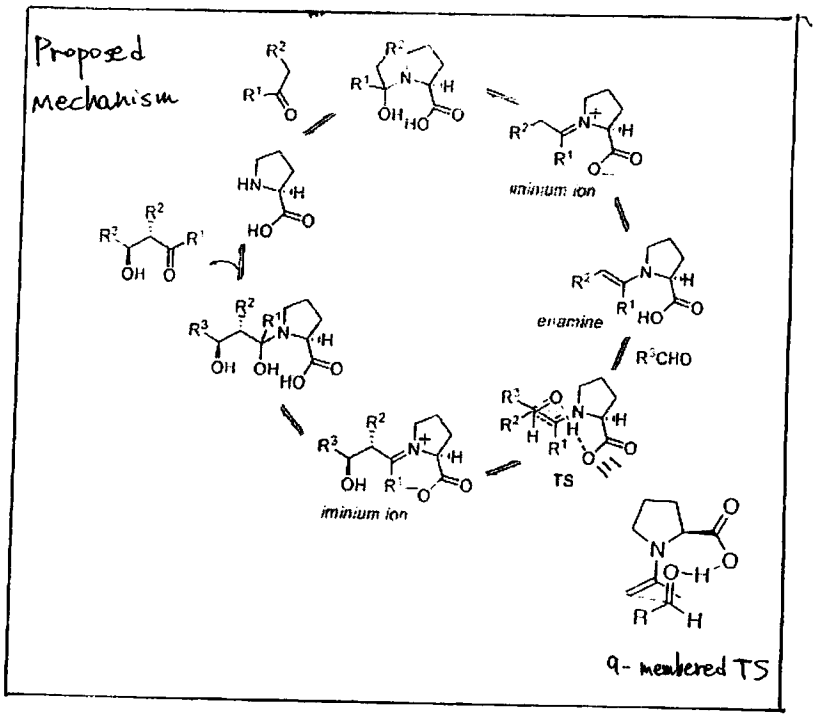
J.A.C.S. 2000, 122, 9336



J.A.C.S. 2002, 124, 6798

Enantioselective Direct Aldehyde Cross-Aldol Reaction



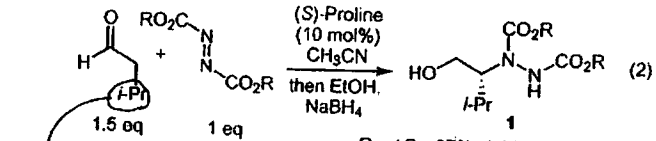


→ Nucleophilic addition.

Direct Catalytic Asymmetric α-Amination of Aldehydes

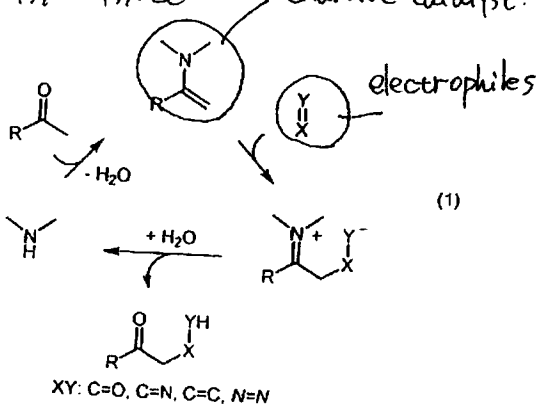
List

J.A.C.S. 2002, 124, 5657



R = t-Bu: 97% yield, 92% ee (20°C)
R = Bn: 99% yield, 86% ee (20°C)
99% yield, 96% ee (0°C)

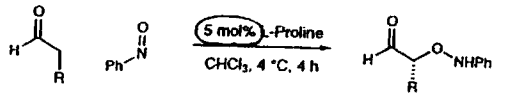
nPr	93%	95% ee
nBu	94%	97% ee
Me	97%	95% ee
Bn	95%	95% ee



The Direct and Enantioselective Organocatalytic α-Oxidation of Aldehydes

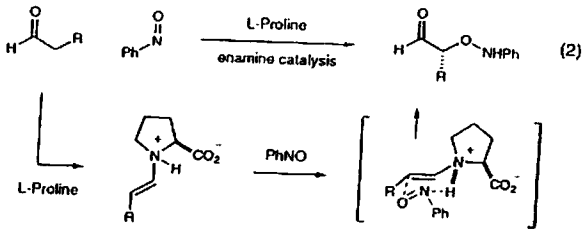
MacMillan et al.

J.A.C.S. 2003, 125, 10808



→ 5 mol% 45 min 86%, 97% ee
2 mol% 2h 88%, 97% ee
0.5 mol% 18h 68%, 94% ee

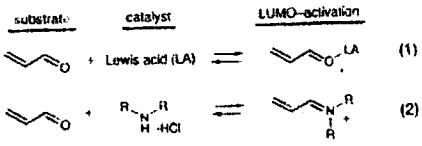
Organocatalyzed Direct α-Oxyamination



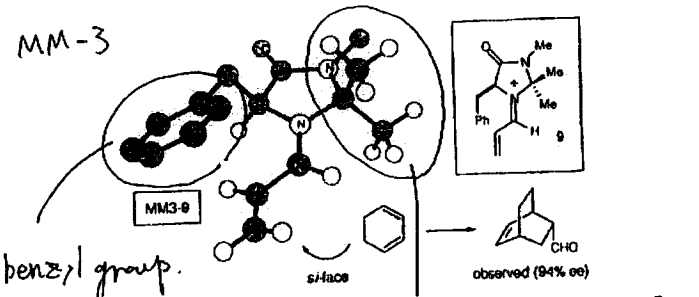
◦ Iminium Catalyst (LUMO activation)

New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels–Alder Reaction

J. Am. Chem. Soc. 2000, 122, 4243.



↓ LUMO lowering activation like Lewis acids.



benzyl group effectively shields the re face

selective formation of (E)-iminium isomer to avoid nonbonding interaction

Scheme 1

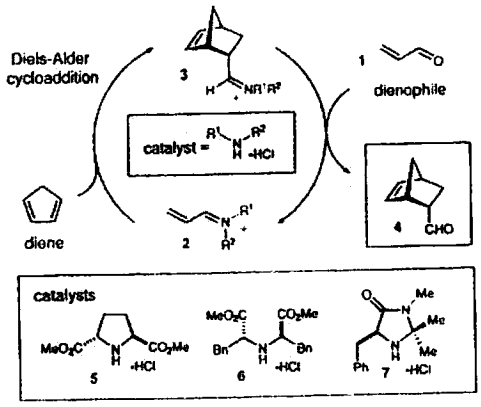
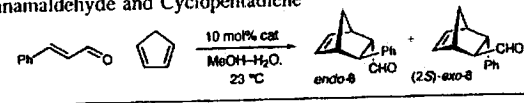


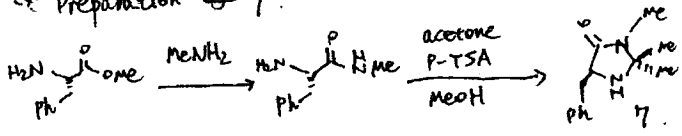
Table 1. Organocatalyzed Diels–Alder Reaction between Cinnamaldehyde and Cyclopentadiene

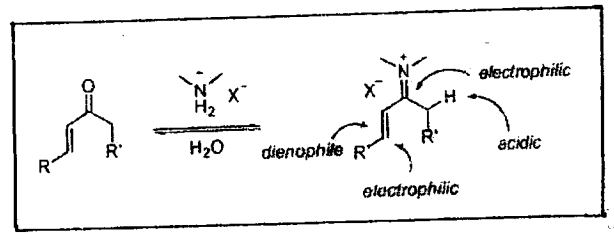


entry	catalyst	time (h)	yield (%)	*exo*:*endo*	*exo* ee (%)[a,b]
1	(*S*)-Pro-OMe·HCl	27	81	2.7:1	48 (2*R*)
2	(*S*)-Abr-OMe·HCl	10	80	2.3:1	59 (2*S*)
3	5	23	92	2.6:1	57 (2*R*)
4	6	84	82	3.6:1	74 (2*R*)
5	7	8	99	1.3:1	93 (2*S*)[c]

[a] Product ratios determined by GLC using a Bodman Γ-TA or β-PH column. [b] Absolute and relative configurations assigned by chemical correlation to a known compound (Supporting Information). [c] Using 5 mol % catalyst.

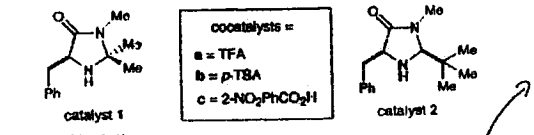
* Preparation of 7.





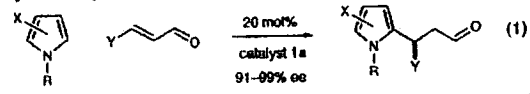
Enantioselective Organocatalytic Indole Alkylations. Design of a New and Highly Effective Chiral Amine for Iminium Catalysis

... J.A.C.S. 2002, 124, 1172

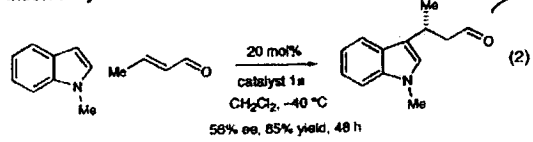


T.A.C.S. 2001, 123, 4370

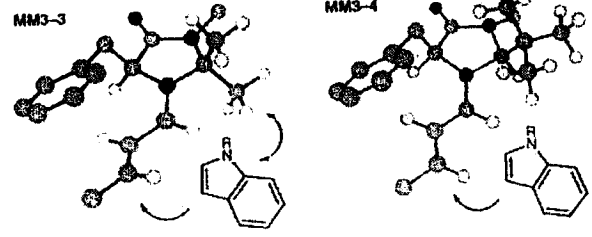
Pyrrole Alkylation

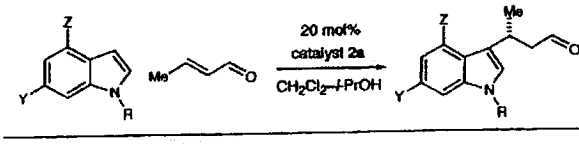


Indole Alkylation



→ Development of New imidazolidinone catalyst 2

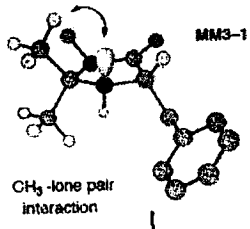




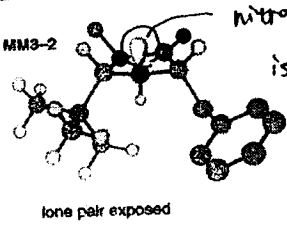
entry	indole substituents R	Y	Z	temp (°C)	time (h)	% yield	% ee[a]
1	Me	H	H	−87	19	82	92[b]
2	H	H	H	−60	22	72	91[b]
3	allyl	H	H	−72	20	70	92
4	CH_2Ph	H	H	−60	120	80	89[b]
5	H	H	Me	−60	3	94	94[c]
6	Me	H	OMe	−87	19	90	96[c]
7	H	Cl	H	−60	13	73	97[c]

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration determined by chemical correlation. [c] Reaction conducted with (*E*)-BzOCH$_2$CH=CHCHO.

Computational model of catalyst 1



Computational model of catalyst 2



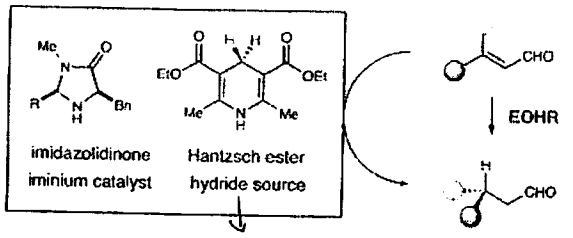
nitrogen lone pair is positioned away from structural impediment

CH3– lone pair eclipsing orientation.

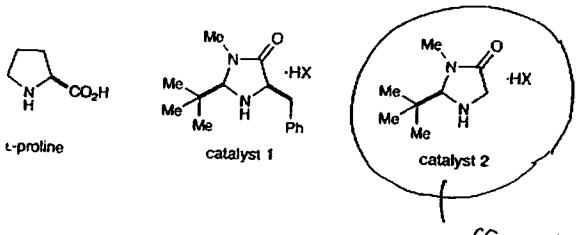
Enantioselective Organocatalytic Hydride Reduction

J. A. C. S. 2005, 127, 32 MacMillan et al.

Enantioselective Organocatalytic Hydride Reduction (EOHR)

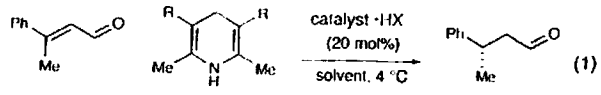


like NADH. (shown below).



most effective.

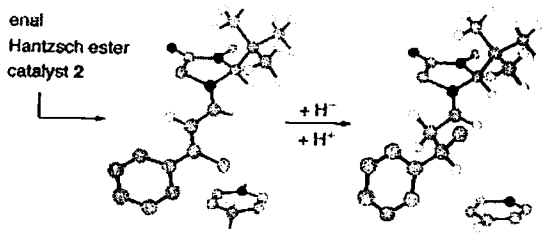
Table 1. Effect of Catalyst and Solvent on EOHR[a]



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
4	1	HCl	toluene	8	70	81
5	2	HCl	toluene	31	19	87
6	2	TFA	$CHCl_3$	1	99	85
7	2	TFA	$CHCl_3$	24	90[d]	93
8	2	TCA	$CHCl_3$	23	91[d]	93

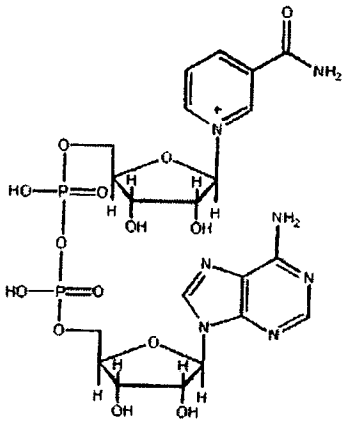
[a] R = CO_2Et. [b] Conversion determined by GLC analysis. [c] Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA). [d] At −30 °C.

EOHR: Origins of Enantiocontrol with Catalyst 2

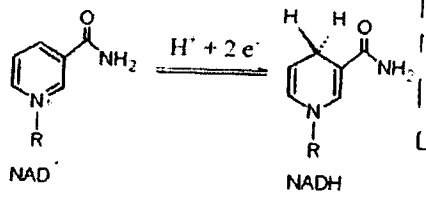


→ ∴ NADH was not a viable reagent in this reaction. ↳ same reaction reported

List et al
Angew 2005, 44, 108.

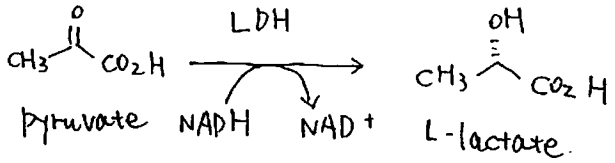


Nicotinamide Adenine Dinucleotide
(NAD⁺)

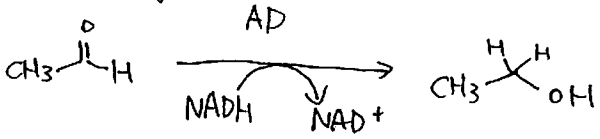


in the body

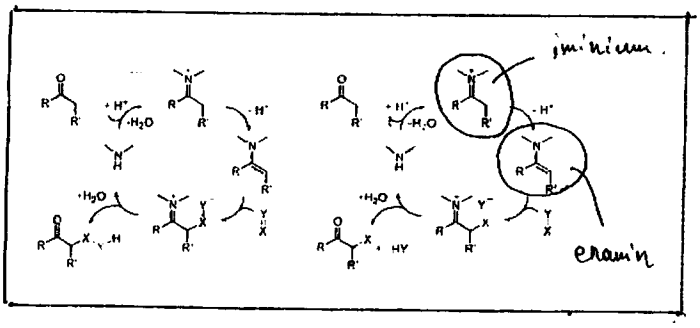
- lactate dehydrogenase (LDH)

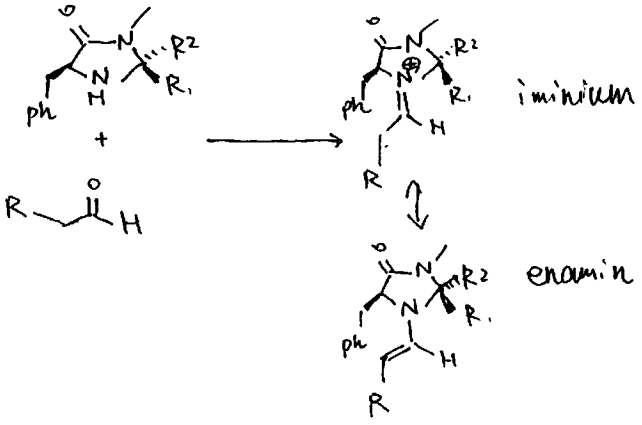


- alcohol dehydrogenase



- Application to Enamin Catalyst.

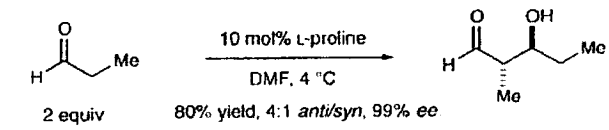




6/12

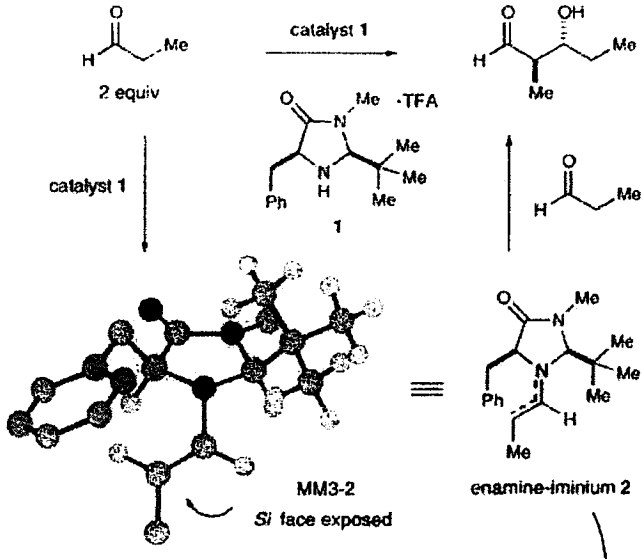
The Importance of Iminium Geometry Control in Enamine Catalysis: Identification of a New Catalyst Architecture for Aldehyde–Aldehyde Couplings**

... Angew. Chem. Int. Ed 2004, 43, 6722.



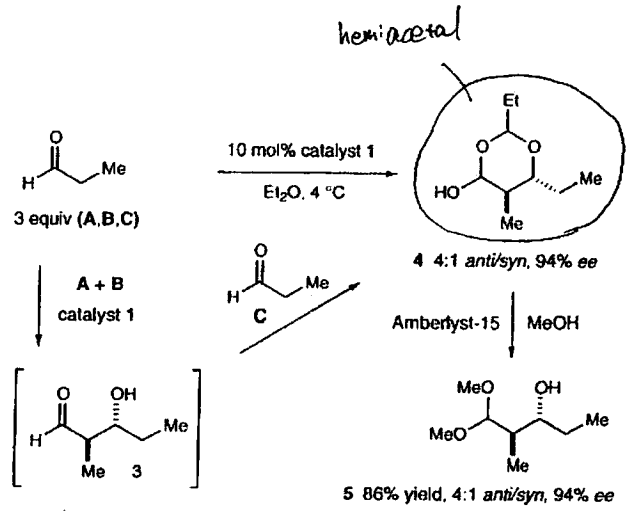
Scheme 1. Proline-catalyzed aldehyde–aldehyde aldol reaction.

→ J.A.C.S. 2002, 124, 6798



Scheme 2. Imidazolidinone-catalyzed aldehyde–aldehyde aldol reaction.

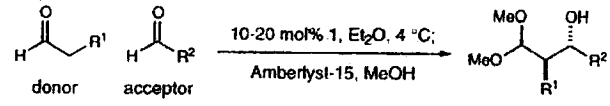
transition state.



Scheme 3. Imidazolidinone-catalyzed aldol reaction: initial results.

α-methylenealdehyde donors by means of a syringe pump to acceptor → prevent homodimerization

Imidazolidinone-catalyzed direct aldol condensation: reaction scope.



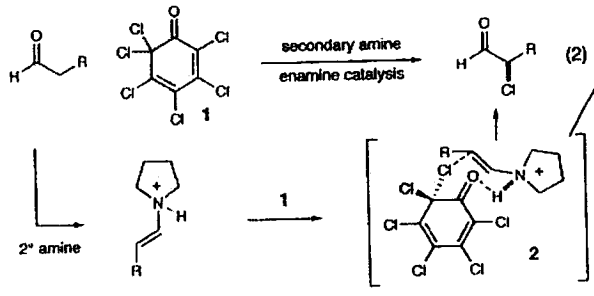
(Table shows >90% ee

anti/syn 4:1 ~ 11:1)

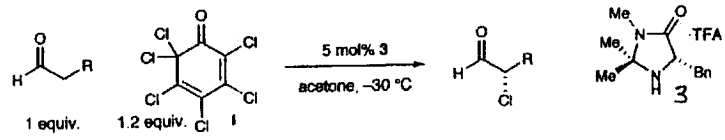
Direct and Enantioselective Organocatalytic α-Chlorination of Aldehydes

J.A.C.S. 2004, 126, 4108

Organocatalyzed Direct α-Chlorination



Proton-mediated cyclic transition state.



※ R = cHex y. 87% 94%ee.

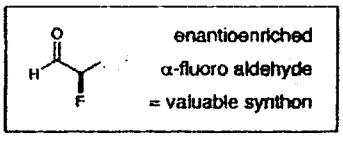
NCS was used y. 20%. 19%ee

L-proline gave almost racemic product.

Enantioselective Organocatalytic α-Fluorination of Aldehydes

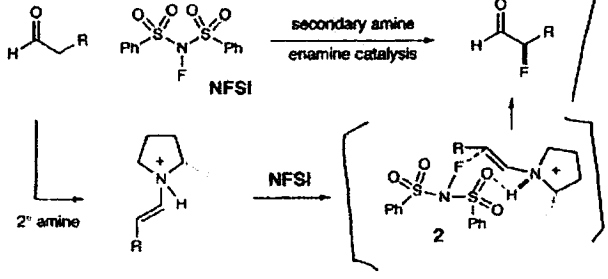
J.A.C.S. 2005, 127, 8826

Scheme 1

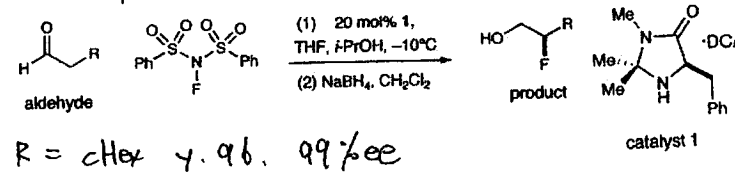


- C–F = metabolic stability in drug development
- Enantioselective access via enamine catalysis

Proposed Organocatalytic Direct α-Fluorination and Mechanism



sulfone-proton bonding transition state



R = cHex y. 96. 99%ee

addition of 10% i-Pr-OH improved ee.

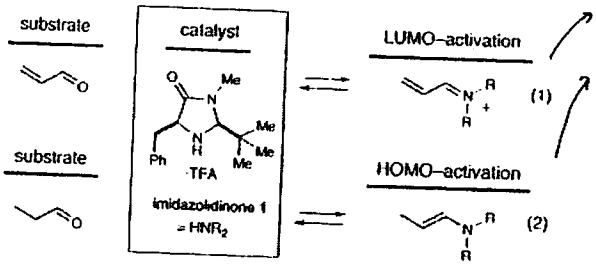
° Tandem Iminium - Enamine Catalysis

7/12

Enantioselective Organo-Cascade Catalysis

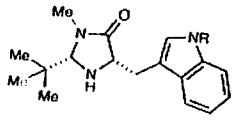
J.A.C.S. 2005, 127, 15051. MacMillan et al.

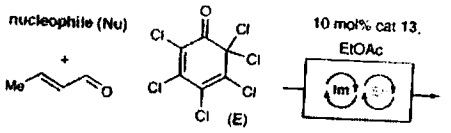
Imidazolidinones: Organocatalysts for HOMO or LUMO Activation



Diels-Alder, Friedel-Crafts etc.

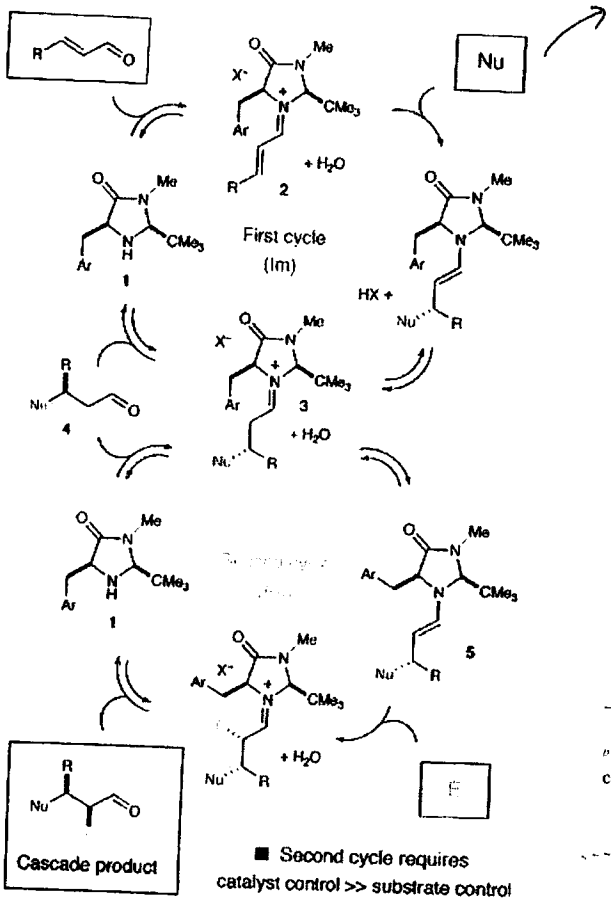
Aldol, α-halonation etc.

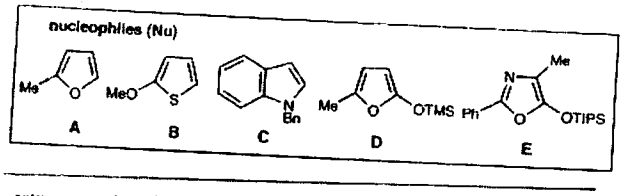


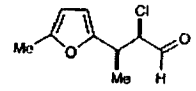
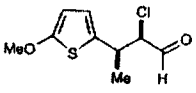
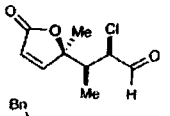
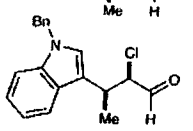
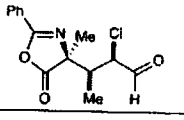


R = Bn, catalyst 13

Scheme 1. Cascade Catalysis: Merged Iminium–Enamine Activation





entry	nucleophile	product	temp (°C)	% yield	dr[a]	% ee
1	A		−50	86	14:1	99
2	B		−50	77	11:1	99
3[b]	D		−55	71	>25:1	>99
4	C		−60	75	12:1	>99
5	E		−40	97	9:1	>99

[a] Absolute and relative configuration assigned by chemical correlation. [b] Superior yields were obtained when the electrophile was added after consumption of the silyloxy furan.

··· Nu ·· aromatic π-nucleophile

E ··· chlorinated quinone.

··· entry 4, 5 ·· First cycle is Organocatalytic Mukaiyama Michael Reaction.

···· MacMillan et al J.A.C.S. 2003, 125, 1192.

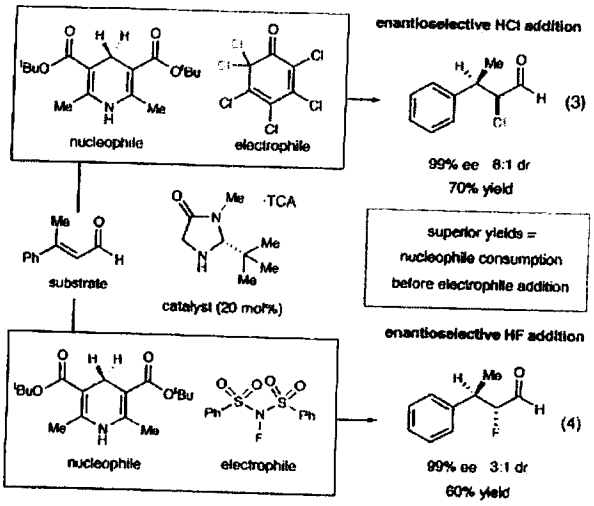
← Hantzsch ester was used as 「Nu」.

+

chlorinated quinone or NFSI was used as 「E」.

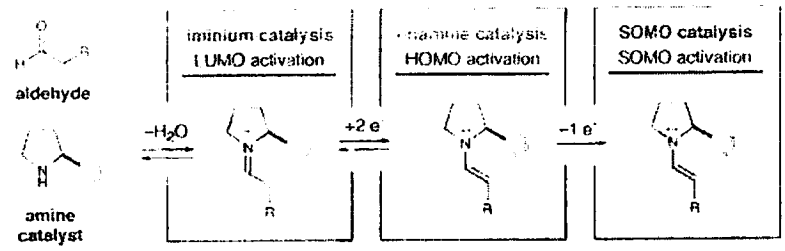
⇩

Asymmetric addition of HCl and HF



Enantioselective Organocatalysis Using SOMO Activation.

MacMillan et al. Science 2007, 316, 582.



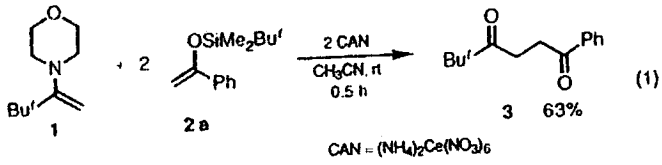
→ one-electron oxidation of transient enamine species should generate a 3-π-electron radical cation.

Fig. 1. SOMO catalysis via single-electron oxidation of a transiently formed enamine. LUMO, lowest unoccupied molecular orbital; R, an arbitrary organic substituent.

··· From these result. enamins and iminium ions rapidly interconverted.

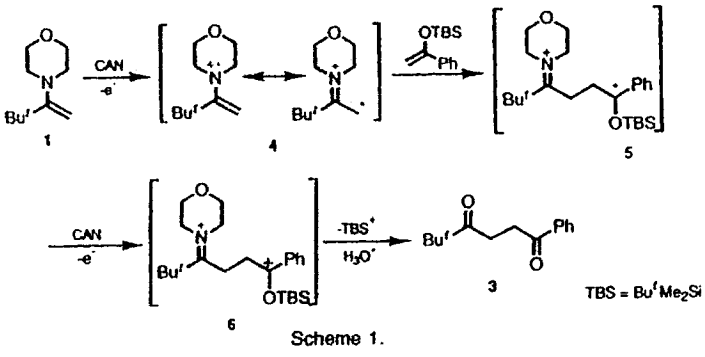
Generation of Cation Radicals from Enamines and Their Reactions with Olefins

Chem. Lett. 1992, 2099. Narasaka et al.



··· pinacolone enamin + 4-(t-butyldimethyl silloxy) styrene.

+ 2eq CAN → α-alkylation produce



Scheme 1.

· The enamine is oxidized to the cation radical 4 with CAN.

↓

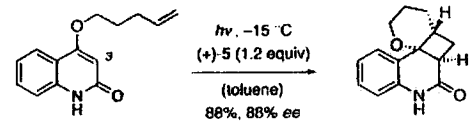
silylenol ether was reacted with 4.

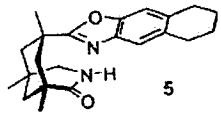
Catalytic enantioselective reactions driven by photoinduced electron transfer

Nature. 2005, 436, 1139. Bach et al.

Enantioselective Intramolecular [2+2]-Photocycloaddition Reaction in Solution.

Angew. Chem. Int. Ed. 2000, 39, 2302.

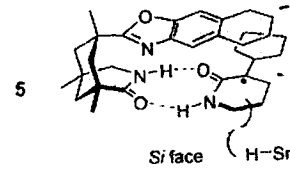




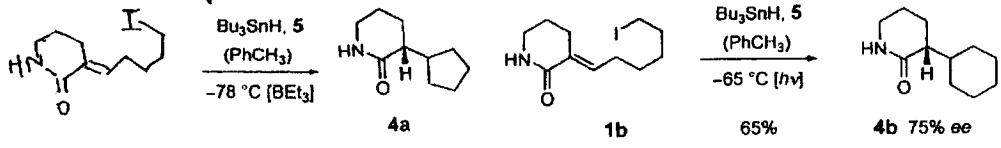
Scheme 3. The intramolecular [2+2]-photocycloaddition reaction of the prochiral substrate 6.

Hydrogen Bond Mediated Enantioselectivity of Radical Reaction

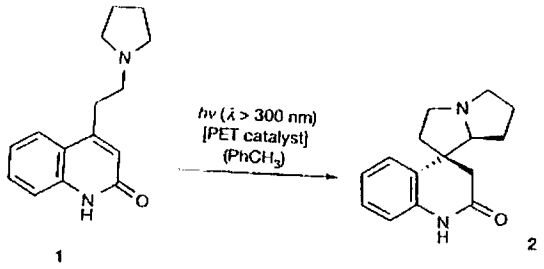
Angew. Chem Int. Ed 2004, 43, 5849

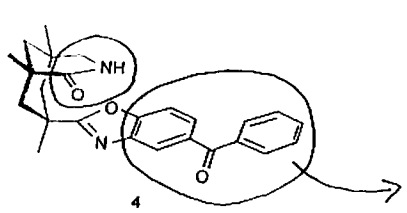


---- Re face is shielded linked by hydrogen bonding.



[BEt3] 20 mol% 5 2.5eq. Bu3SnH 2.0eq.





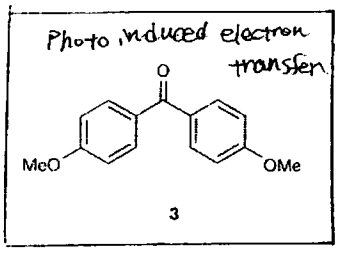


Figure 1 | PET-catalysed cyclization of the prochiral substrate 1 to the chiral pyrrolizidine 2 and its enantiomer *ent*-2.

3 as a PET catalyst, racemic reaction proceeded in good yeild (10 mol%, 71%)

chiral catalyse 4

→ · two hydrogen bonds at the bridgehead lactam.

· benzophenone unit.

... 30 mol% 1h, Y. 64% 17% ee,,

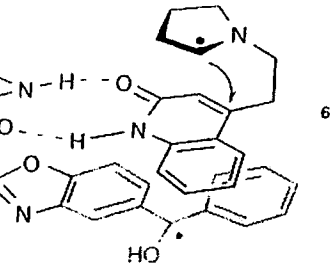
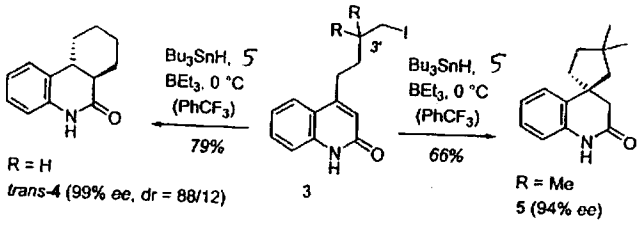


Figure 3 | Explanation for the facial differentiation in the PET-catalysed cyclization of the prochiral substrate 1 via radical intermediate 6.

※ Org. Lett 2006, 8, 3145



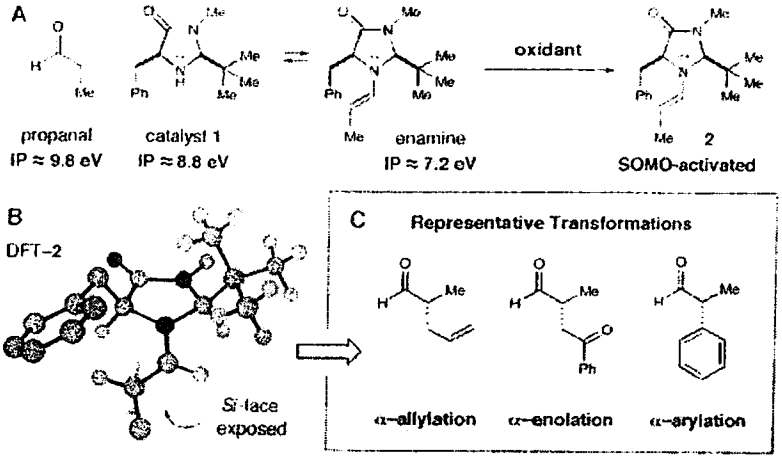
5 (2.5 eq) ... good result was obtain

but.

4 was obtained in 55%ee in the presence of 10 mol% 5.

→ It is difficult to proceed SOMO reaction.

MacMillan's proposal



→ Ionization potential.

The enamine is sufficiently more susceptible to oxidation.

→ · 3-π electron system away from the bulky t-Bu group.

radical-centered carbon selectively populates an E configuration.

· Benzyl group should effectively shield the re face.

Fig. 2. (A) Catalytic chemical steps leading to formation of the SOMO-activated intermediate. Me, methyl; Ph, phenyl. (B) DFT–calculated three-dimensional structure of the enantio-differentiated radical cation. (C) Possible transformations arising from enantioselective organocatalytic SOMO catalysis.

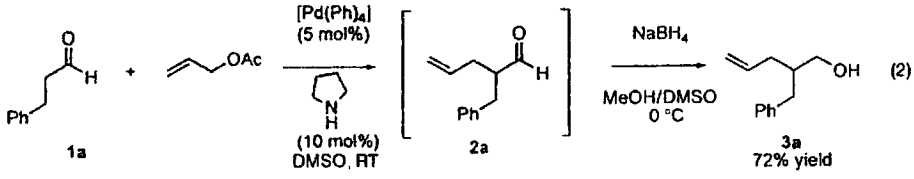
10/12

To test SOMO activation concept, they selected "direct and enantioselective allylic alkylation"

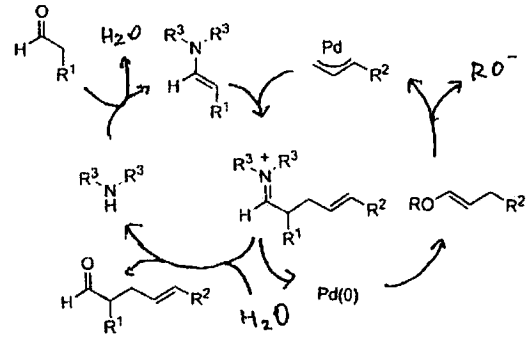
Direct Catalytic Intermolecular α-Allylic Alkylation of Aldehydes by Combination of Transition-Metal and Organocatalysis**

Angew. Chem. Int. Ed. 2006, 45, 1952

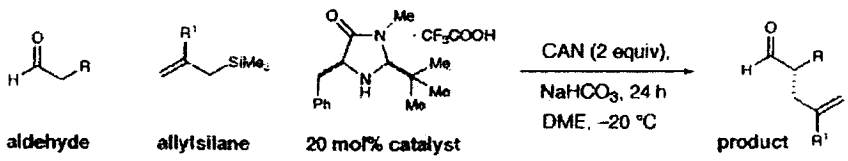
Cordova et al.



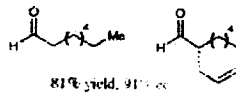
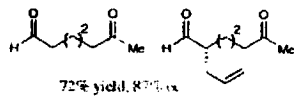
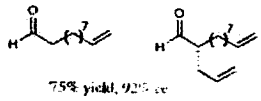
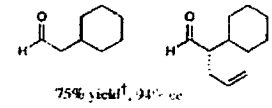
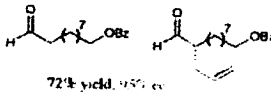
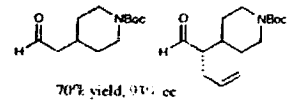
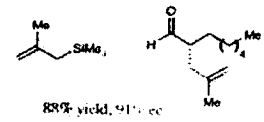
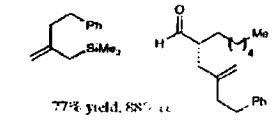
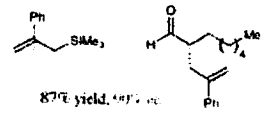
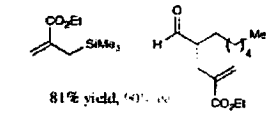
Proposed mechanism



↳ This is the example of intermolecular α-alkylation of aldehydes.



aldehyde allylsilane 20 mol% catalyst product

entry	aldehyde	product*	entry	aldehyde	product*
1		81% yield, 91% ee	4		72% yield, 87% ee
2		75% yield, 92% ee	5		75% yield†, 94% ee
3		72% yield, 95% ee	6		70% yield, 97% ee
entry	allylsilane	product‡	entry	allylsilane	product‡
7		88% yield, 91% ee	9		77% yield, 88% ee
8		87% yield, 90% ee	10		81% yield, 90% ee

*Reactions performed with allylsilane (CH_2=$CHCH_2SiMe_3$) †Yield determined by gas chromatographic analysis. ‡Reactions performed with octanal.

→ chemical functionalities appear to be inert under these mild oxidative conditions.

(olefin, ketone, ester, carbamate)

A ~ C. preliminary results broad scope of SOMO activation.

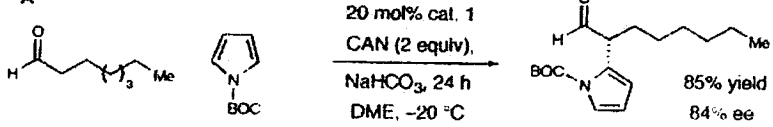
A ··· α-heteroarylation

B ··· cyclization with trapping of exogenous halide

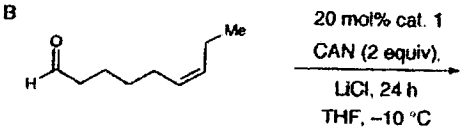
C ··· demonstrate radical passway.

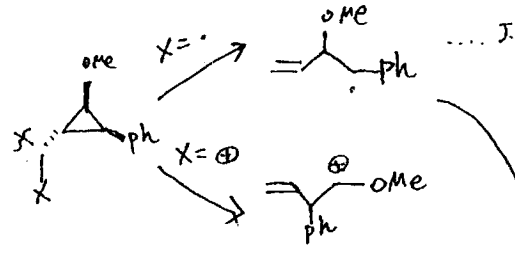
···· J.A.C.S. 1994, 116, 9753 etc

A

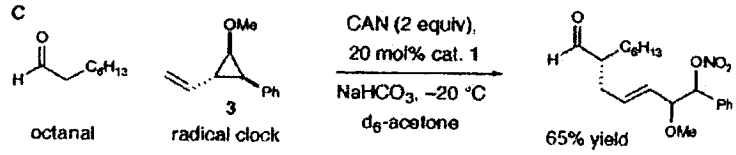


B





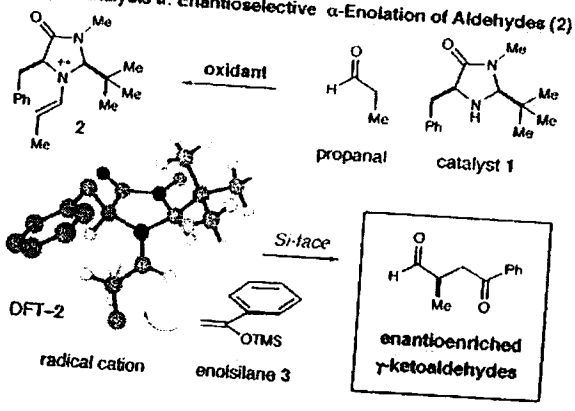
C

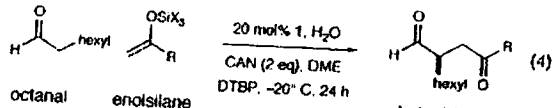


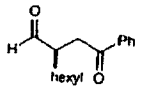
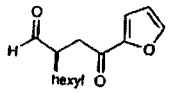
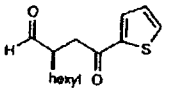
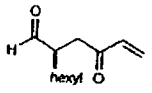
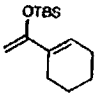
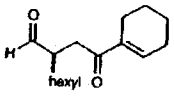
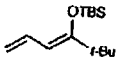
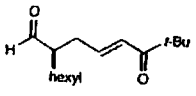
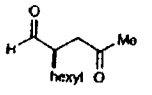
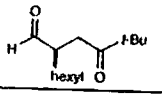
Enantioselective Organocatalytic Singly Occupied Molecular Orbital Activation: The Enantioselective α-Enolation of Aldehydes

J. A. C. S. 2007, 129, 7004. MacMillan et al.

SOMO Catalysis II: Enantioselective α-Enolation of Aldehydes (2)

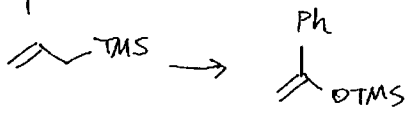




entry	enolsilane	product	% yield	% ee[a,b]
1[c]			85	90
2[d]			77	92
3[d]			70	93
4			61	90
5			71	92
6			74	96
7			67	86
8			55	92

[a] Enantioselectivity determined by GLC or SFC analysis. [b] Stereochemistry assigned by chemical correlation or by analogy. [c] Performed in acetone. [d] Performed at −50 °C.

→ somophile



※ This reaction is catalytic enantioselective version of Narasaka et al.

(See p.)

→ π-rich endsilanes will readily participate as somophiles.

(alkyl, vinyl and aryl)

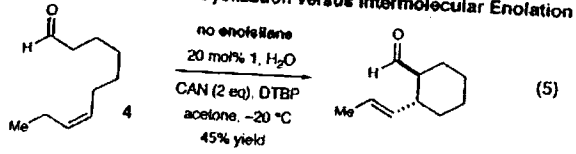
· bulky silyl groups to prevent substrat hydrolysis.

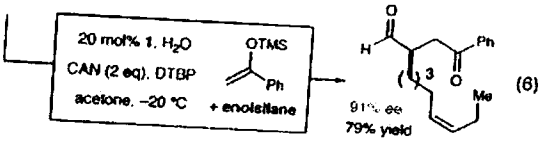
(entry 7, 8. the use of TMS enolethers γ. 39% 73%ee and ≤10%, 0%ee)

intramoleaure cydohexyl ring formation with π-neutral defin.

↓

Intramolecular Radical Cyclization versus Intermolecular Enolation





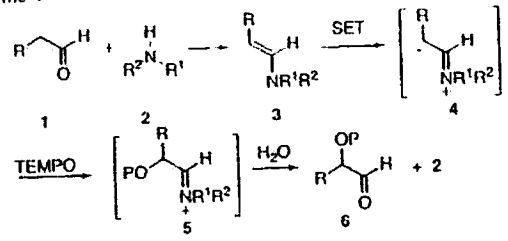
… Impressive as this work is, there are still limitations.

This reaction requires two equivalents of the oxidizing agent.

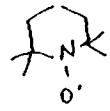
Organocatalysis in Radical Chemistry. Enantioselective α-Oxyamination of Aldehydes

T.A.C.S. 2007. 129. 4124. Sibi et al.

Scheme 1



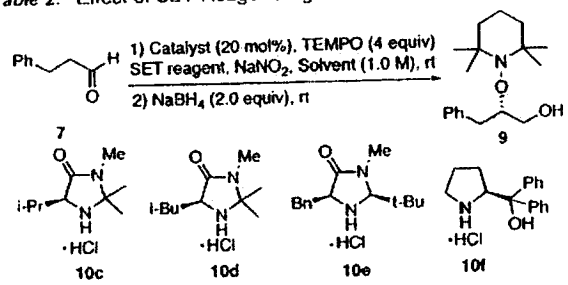
.... enamine could be oxidized using SET.
(like MacMillan's case)



TEMPO was used as a radical trap reagent

→ C-O bond forming reaction.

Table 2. Effect of SET Reagent, Ligand, and Solvent[a]

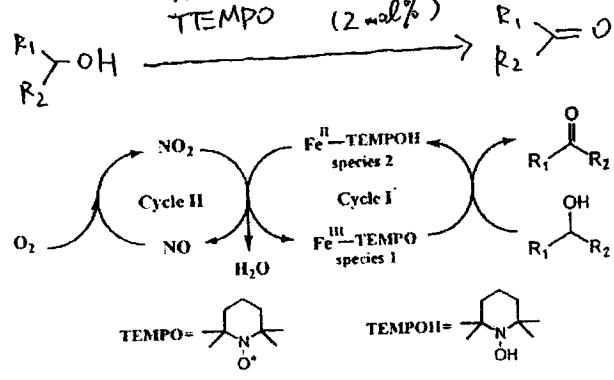


entry	SET reagent (mol %)	ligand	$NaNO_2$ (equiv)	solvent	yield (%)[b]	ee (%)[c]
1	Cp_2FeBF_4 (100)	**10b**	0	THF	87	80
2	Cp_2FeBF_4 (50)	**10b**	0	THF	40	74
3	$FeCl_3$ (100)	**10b**	0	THF	4	nd[d]
4	$FeCl_3$ (100)	**10b**	0	DMF	74	72
5[e]	$FeCl_3$ (30)	**10b**	0.3	DMF	82	75
6[e]	$FeCl_3$ (10)	**10b**	0.3	DMF	83	72
7[e]	$FeCl_3$ (10)	**10c**	0.3	DMF	75	5
8[e]	$FeCl_3$ (10)	**10d**	0.3	DMF	64	46
9[e]	$FeCl_3$ (10)	**10e**	0.3	DMF	26	0
10[e]	$FeCl_3$ (10)	**10f**	0.3	DMF	33	17

[a] For reaction conditions, see Supporting Information. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Not determined. [e] Reaction run using 2 equiv of TEMPO and oxygen as a co-oxidant.

→ $FeCl_3$ was cheaper than Cp_2FeBF_4.
$NaNO_2$ / O_2 was cooxidant.
--- Chem. Comm. 2005, 5322.

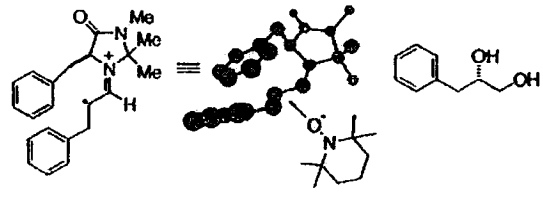
$FeCl_3 \cdot 6H_2O$ (5 mol%)
$NaNO_2$ (5 mol%)
TTEMPO (2 mol%)



Scheme 1 Proposed mechanism for the aerobic oxidation of alcohols.

↓ catalytic amount of the SET reagent could be used.

※ L-proline was used almost racemic.
(Y. 91%, -3% ee).



→ This model is consistent with MacMillan's model.

Figure 1. Stereochemical model.