Enantioselective Organo-Cascade Catalysis

Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C.
JACS, 2005, ASAP

and

Catalytic Asymmetric Reductive Michael Cyclization

Yang, J. W.; Hechavarria Fonseca, M. T.; List, B.
JACS, 2005, ASAP

Erick B. Iezzi, PhD
Current Literature
October 15, 2005

Why are these articles significant?

- Use chiral amines as enantioselective catalysts (iminium and enamine intermediates) to rapidly assemble complex structures

- MacMillan and co-workers use amine catalysts to mimic an enzymatic 'cascade catalysis' that controls product stereochemistry via intermolecular reactions

- List and co-workers use a single amine catalyst to generate complexity via an intramolecular tandem sequence

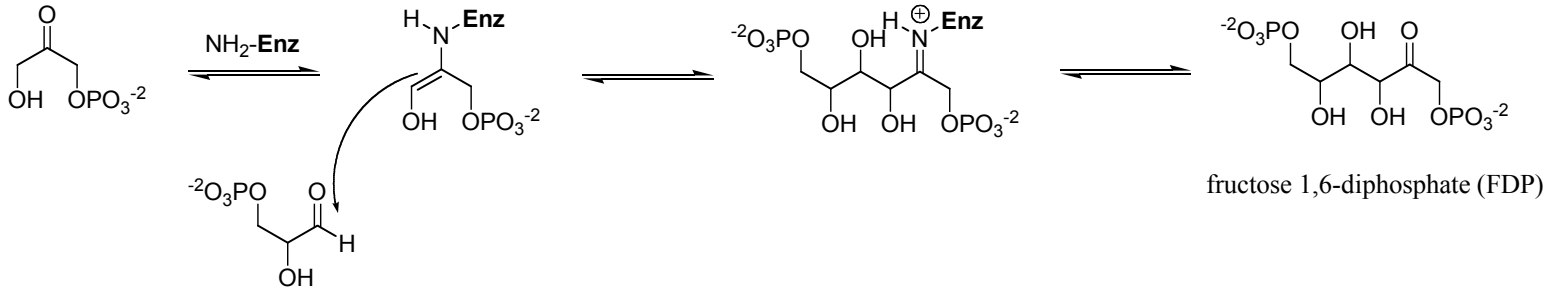
- Both achieve products with high yields and selectivities (diastereo- and enantioselectivity) under user-friendly conditions with safe and simple starting materials

Asymmetic Aminocatalysis

- Amines can activate carbonyl groups (i.e., acetone) as do Lewis or Brønsted acids
  - Iminium ion enhances both electrophilicity and α-C-H-acidity

- Two aminocatalytic pathways:
  1. Iminium catalysis - Knoevenagel-type condensations, cyclo- and nucleophilic additions
  2. Enamine catalysis - Electrophilic addition and pericyclic reactions

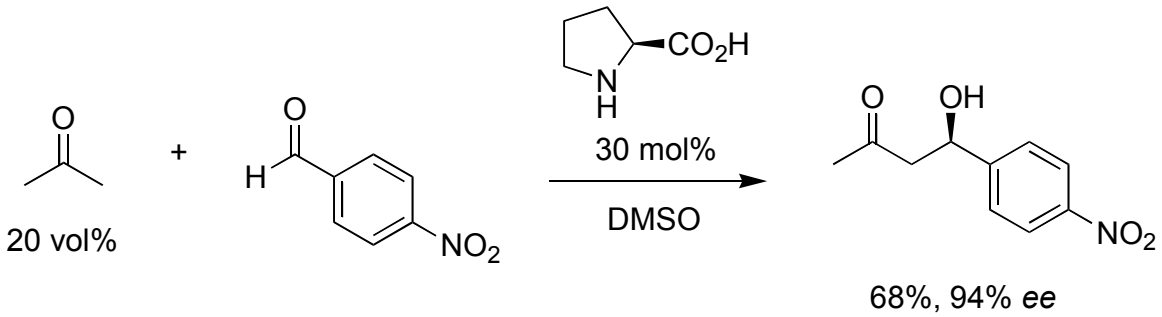
- Aminocatalysis is a biomimetic strategy used by important enzymes such as class I aldolases (enamine catalysis) and ketoacid decarboxylases (iminium catalysis)

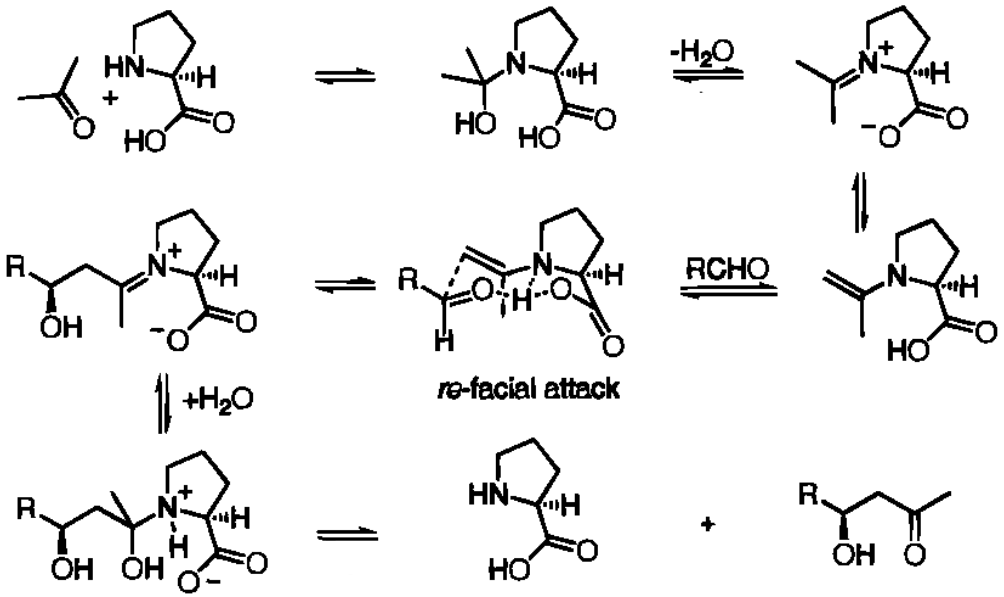


fructose 1,6-diphosphate (FDP)

List, et al. *Synlett.* **2001**, *11*, 1675; Lerner, et al. *Science* **1997**, *278*, 2085

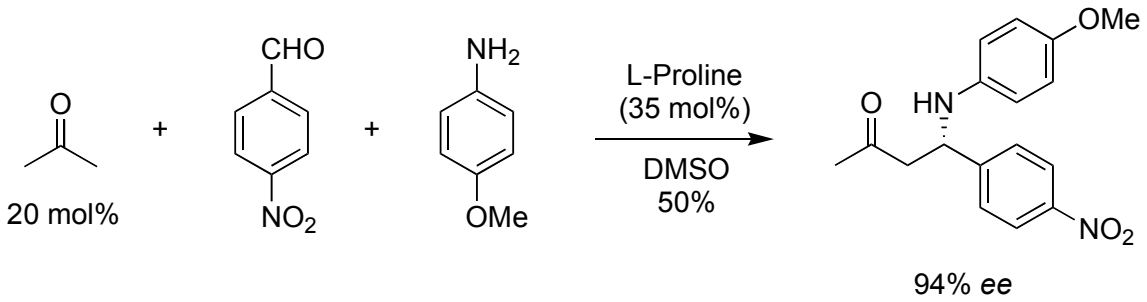
Proline-Catalyzed Direct Asymmetric Aldol Reaction (List and co-workers)





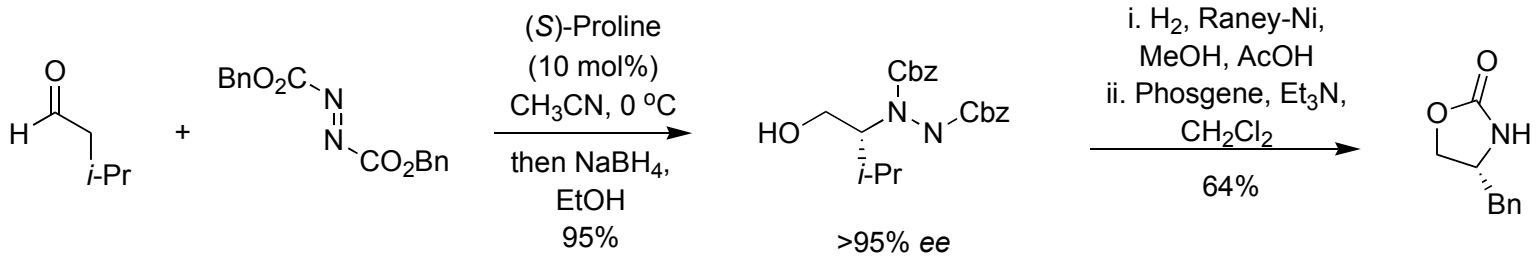
List, et al. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396

Direct Catalytic Asymmetric Three-Component Mannich Reaction (List and co-workers)



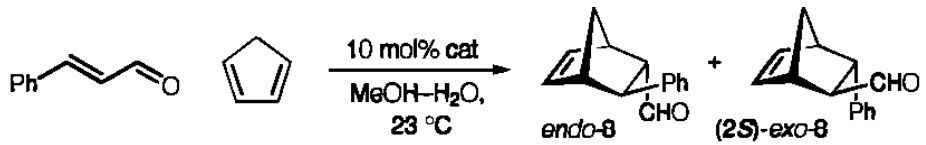
List, et al. *J. Am. Chem. Soc.* **2000**, *122*, 9336-9337

Direct Catalytic Asymmetric α-Amination of Aldehydes (List and co-workers)



List, et al. *J. Am. Chem. Soc.* **2002**, *124*, 5656-5657

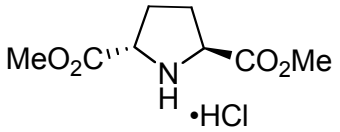
New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction (MacMillan and co-workers)



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]

Catalysts

5



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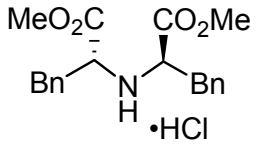

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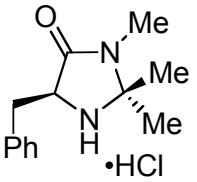
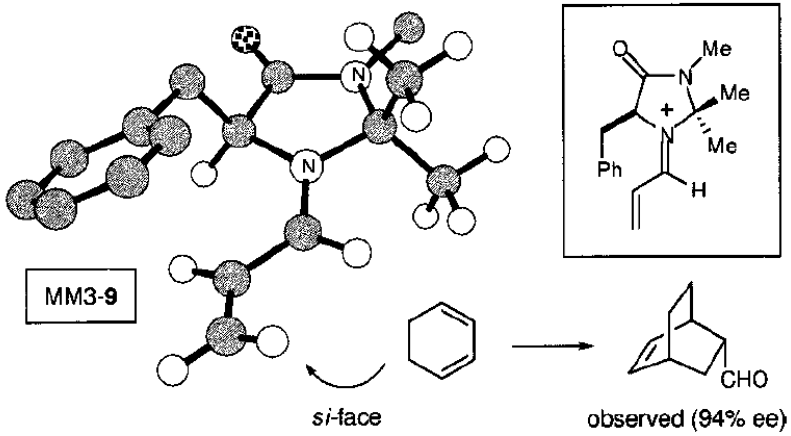
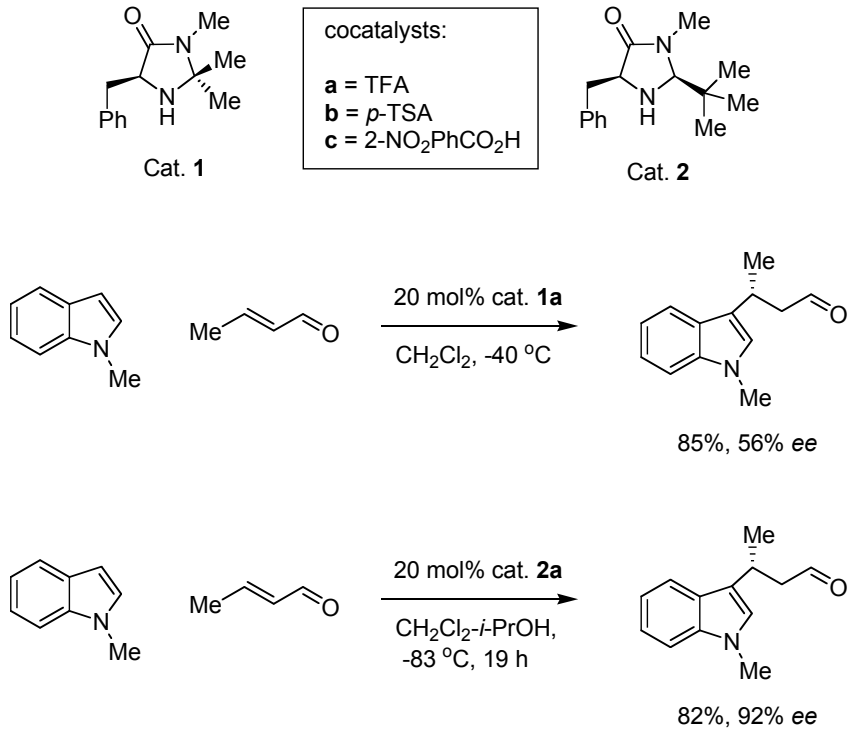


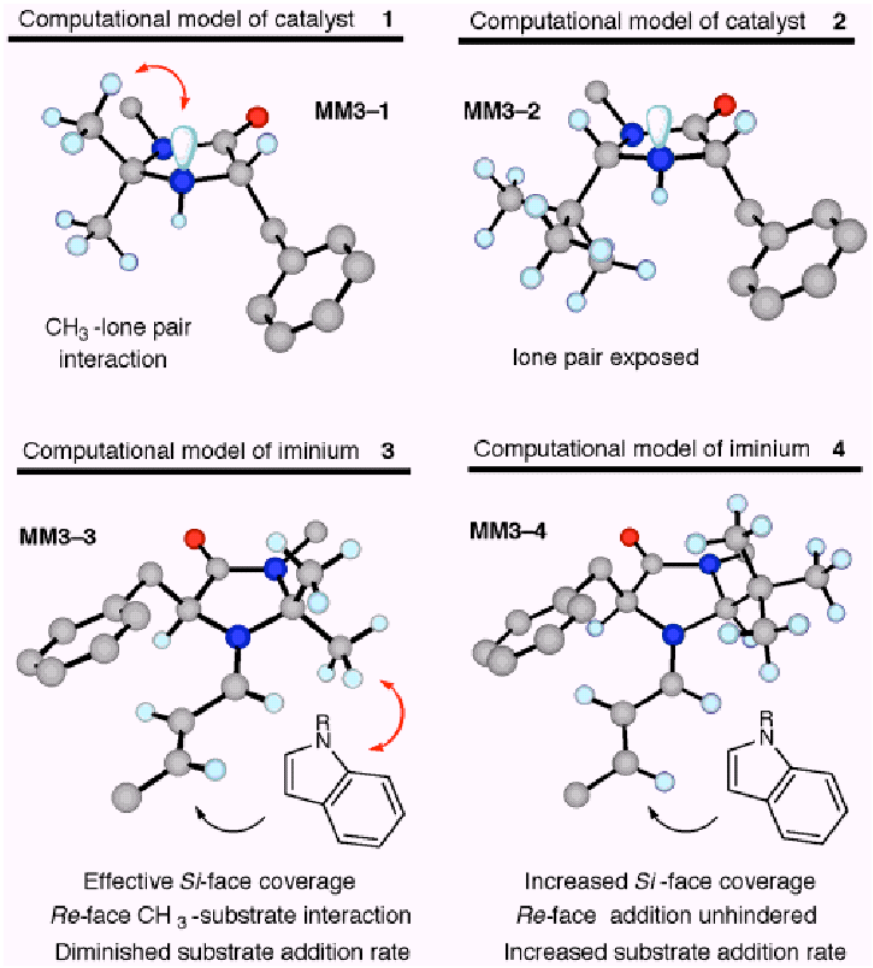


MacMillan, et al. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244

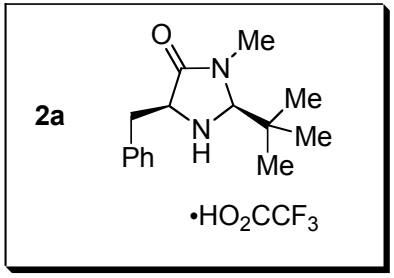
Enantioselective Organocatalytic Indole Alkylations. Design of a New and Highly Effective Chiral Amine for Iminium Catalysis (MacMillan and co-workers)

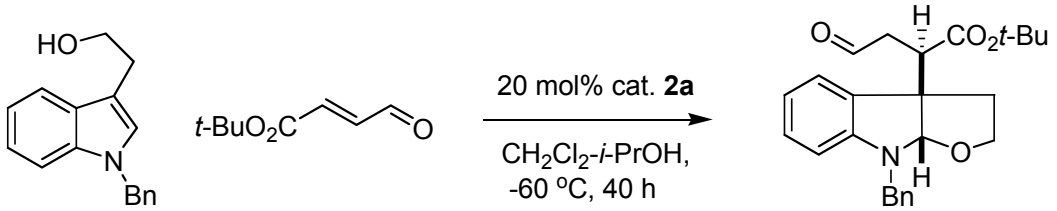


MacMillan, et al. *J. Am. Chem. Soc.* **2002**, *124*, 1172-1173

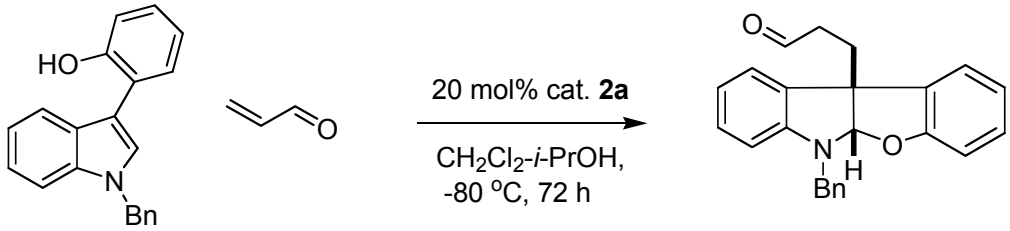


Enantioselective Organocatalytic Indole Alkylations: Furanoindole Construction (MacMillan and co-workers)





80%, 93% *ee*, 12:1 dr



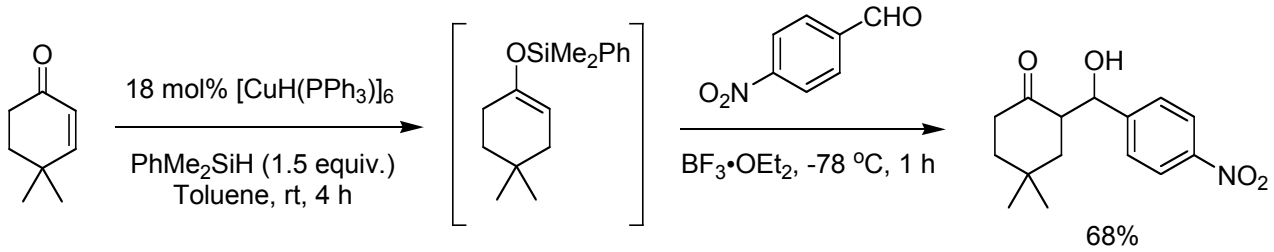
90%, 82% *ee*

-for construction of Diazonamide A core

MacMillan, et al. *PNAS* **2004**, *101*, 5482-5487

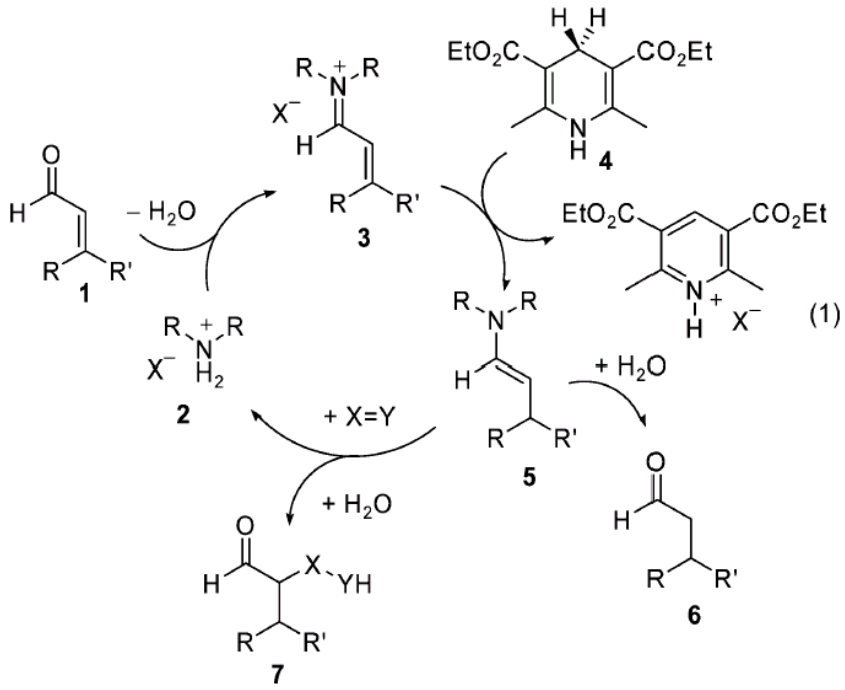
Catalytic Asymmetric Reductive Michael Cyclization (ASAP Article, List and co-workers)

- Use an amine catalyst to carry out a tandem sequence of events, which is similar to the metal-mediated reductive enolate generation-electrophile trapping process



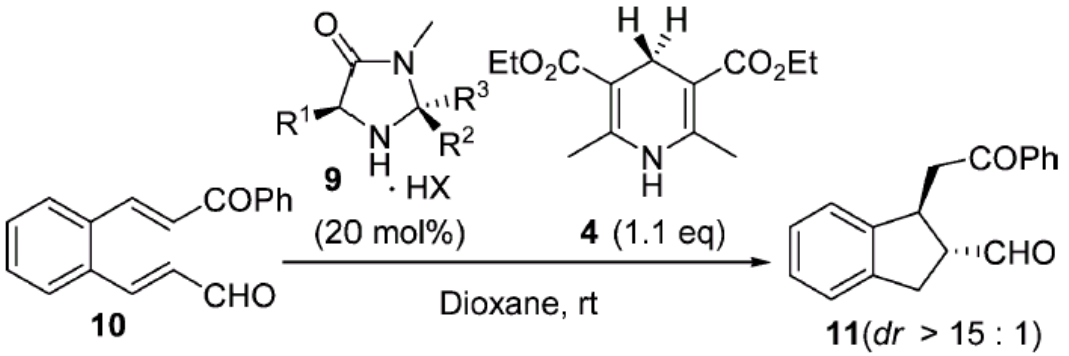
Lipshutz, et al. *Tetrahedron* **2000**, *56*, 2779-2788

- Use reductively generated (via Hantzsch ester) enamine intermediate (5) to react with in situ electrophiles



List, et al. *J. Am. Chem. Soc.* **2005**, ASAP

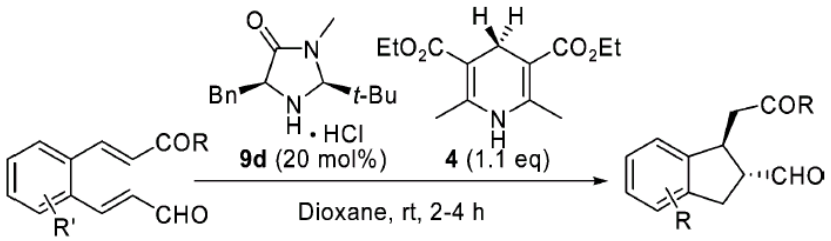
Catalyst Screening for the Reductive Michael Cyclization

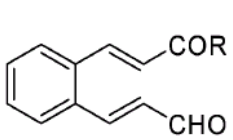
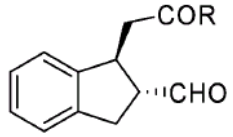
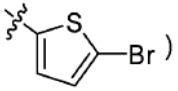
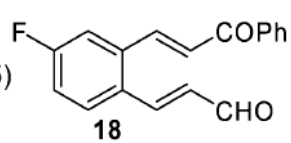
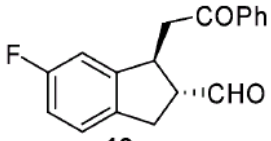
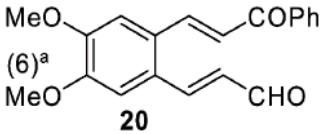
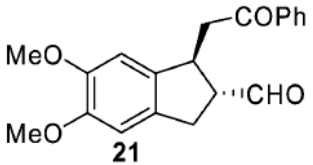
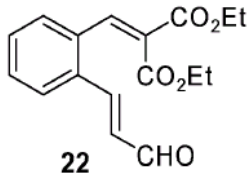
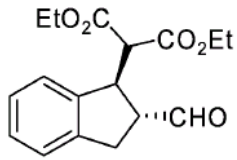


catalyst	R^1	R^2	R^3	X	time [h]	yield [%]	ee [%]
9a	H	*t*-Bu	H	CF_3CO_2	2	82	93
9b	H	*t*-Bu	H	Cl	12	90	95
9c	H	2,6-Ph_2Ph	H	Cl	12	75	16
9d	Bn	*t*-Bu	H	Cl	3	98	96
9e	*p*-BnOBn	*t*-Bu	H	Cl	6	91	95
9f	*p*-*t*-BuOBn	*t*-Bu	H	Cl	6	90	95
9g	Bn	Me	Me	Cl	24	<10	

List, et al. *J. Am. Chem. Soc.* **2005**, ASAP

Substrate Variation in the Reductive Michael Cyclization



Entry	Starting Material	Product	Yield [%]	*dr*	*ee* [%]
					
(1)	**10** (R = Ph)	**11**	98	15:1	96
(2)	**12** (R = 2-Naphthyl)	**13**	94	50:1	94
(3)	**14** (R = )	**15**	91	40:1	92
(4)	**16** (R = Me)	**17**	91	>50:1	91
(5)	 **18**	 **19**	95	21:1	97
(6)[a]	 **20**	 **21**	88	23:1	96
(7)[b]	 **22**	 **23**	86	>50:1	86

[a] Using catalyst **9a**. [b] Using catalyst **9c**.

List, et al. *J. Am. Chem. Soc.* **2005**, ASAP

Enantioselective Organo-Cascade Catalysis (ASAP Article, MacMillan and co-workers)

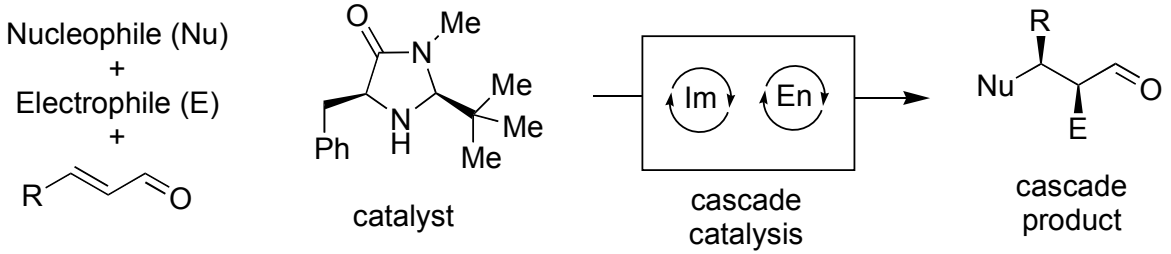
- Use amine catalysts to perform a 'cascade catalysis' of discrete events that mimic a biocatalytic assembly line, as opposed to the traditional 'stop and go' sequences

  - Specifically, polyketide natural products (i.e., erythromycin and actinomyces) are assembled by polyketide synthases, which perform a successive decarboxylative condensations of simple precursors

(Khosla, et al. *Annu. Rev. Biochem.* **1999**, *68*, 219)

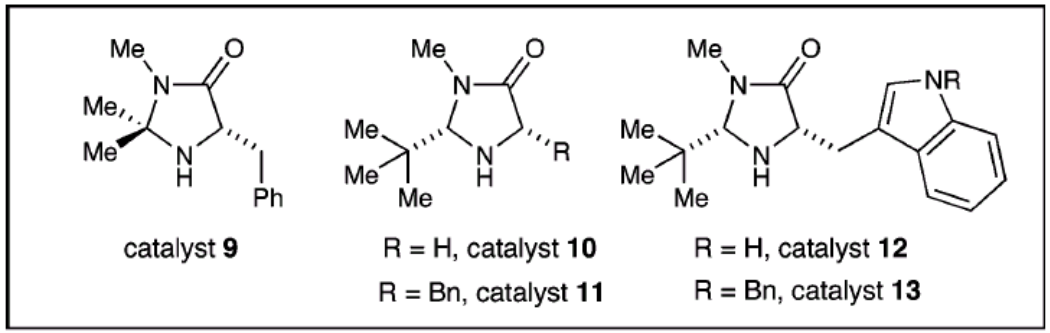
- Imidazolidinone-based catalytic cycles are used to generate complex structures without catalyst-catalyst interactions

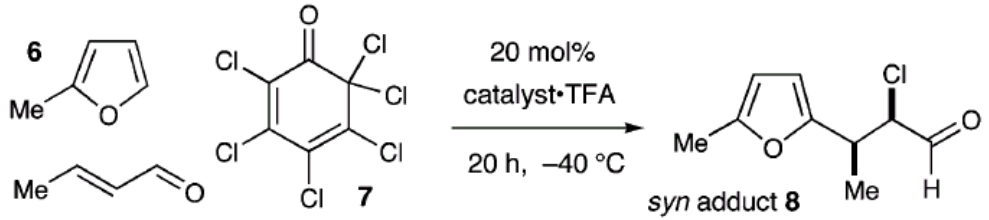
Cascade Catalysis: Merging Iminium (Im) and Enamine (En) Activation



MacMillan, et al. *J. Am. Chem. Soc.* **2005**, ASAP

Organo-Cascade Catalysis: Effect of Catalyst and Solvent

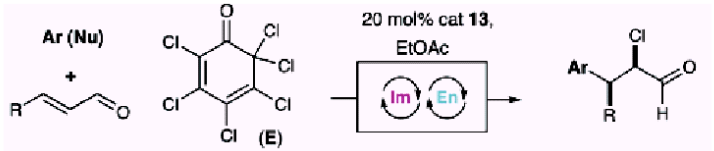


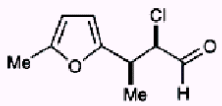
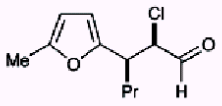
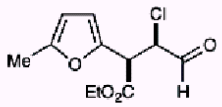
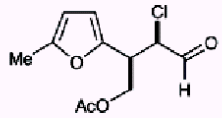
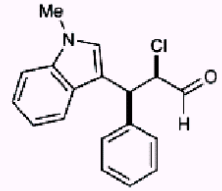
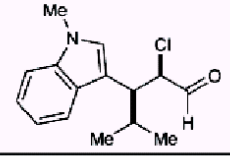


entry	catalyst	solvent	% conversion[a]	dr (*syn*:*anti*)[b]	% ee[c]
1	**9**	EtOAc	3	1:1	88
2	**10**	EtOAc	10	5:1	89
3	**11**	EtOAc	79	9:1	97
4	**12**	EtOAc	78	8:1	97
5	**13**	EtOAc	78	11:1	99
6	**13**	$CHCl_3$	54	8:1	94

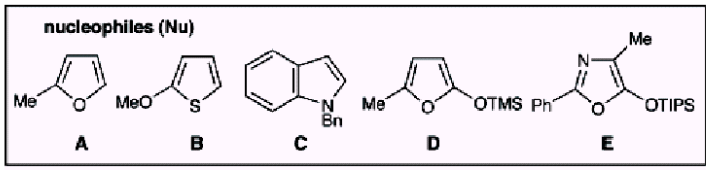
[a] Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). [b] Absolute and relative configuration assigned by chemical correlation. [c] Enantiomeric excess determined by chiral GLC analysis (Bodman β-DM).

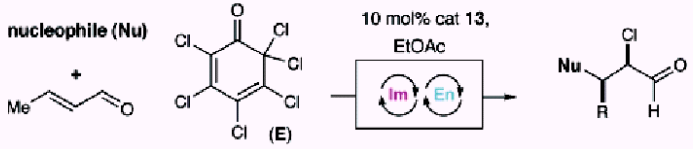
Organo-Cascade Catalysis: Scope of Enal Component and Representative Nucleophiles

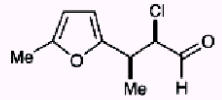
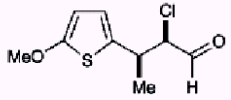
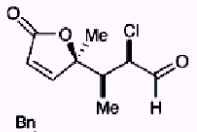
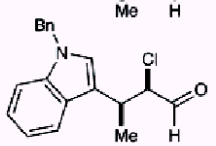
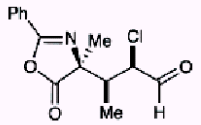


entry	R =	product	temp (°C)	% yield	dr[a]	% ee[b]
1	Me		–50	86	14:1	99
2	Pr		–50	74	13:1	99
3	CO_2Et		–60	80	22:1	99
4	CH_2OAc		–40	82	11:1	>99
5	Ph		–40	83	9:1	99
6	*i*-Pr		–40	67	12:1	>99

[a] Absolute and relative configuration assigned by chemical correlation.
[b] Enantiomeric excess determined by chiral GLC analysis.

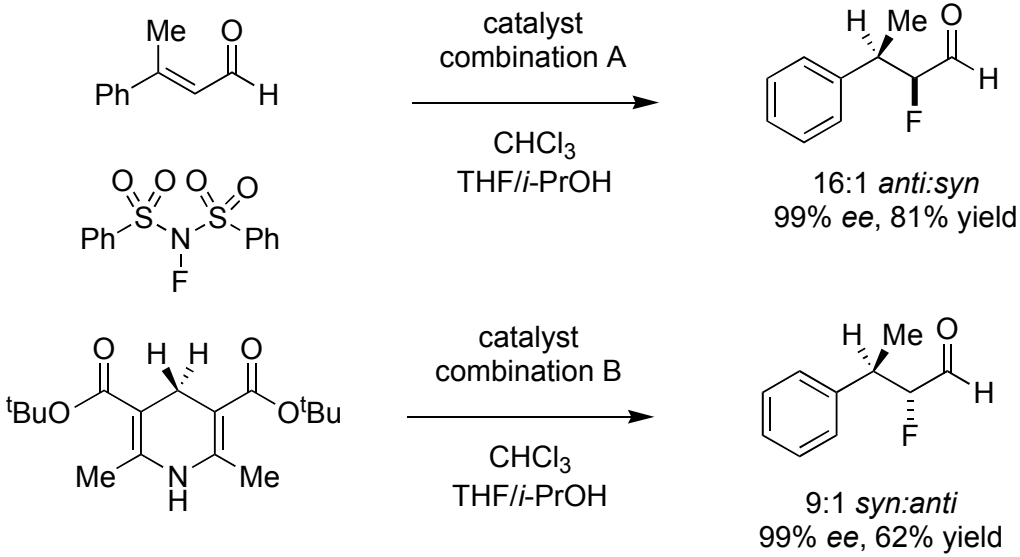




entry	nucleophile	product	temp (°C)	% yield	dr[a]	% ee
1	A		–50	86	14:1	99
2	B		–50	77	11:1	99
3[b]	D		–55	71	>25:1	>99
4	C		–60	75	12:1	>99
5	E		–40	97	9:1	>99

[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.

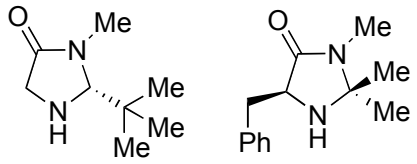
Organo-Cascade Catalysis: Employment of Discrete Amine Catalysts to Enforce Cycle-Specific Selectivities



catalyst combination A

enamine catalyst and **E**

added after consumption of **Nu**



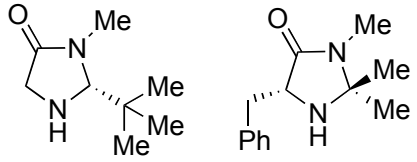
(5*R*)-iminium catalyst (7.5 mol%)

(2*S*)-enamine catalyst (30 mol%)

catalyst combination B

enamine catalyst and **E**

added after consumption of **Nu**



(5*R*)-iminium catalyst (7.5 mol%)

(2*R*)-enamine catalyst (30 mol%)

MacMillan, et al. *J. Am. Chem. Soc.* **2005**, ASAP

Summary

List and co-workers:

- Developed a highly enantioselective organocatalytic reductive Michael cyclization of enal enones
- Practical and user-friendly conditions
- Potential application in the synthesis of natural products

MacMillan and co-workers:

- Developed a new strategy for organo-catalysis based on the biochemical blueprints of cascade catalysis
- Rapid access to structural complexity while achieving exquisite levels of enantiocontrol (combining catalytic cycles leads to enantioenrichment)
- Studies in the area of triple cascade catalysis are underway