

Enantioselective Organo-Cascade Catalysis

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

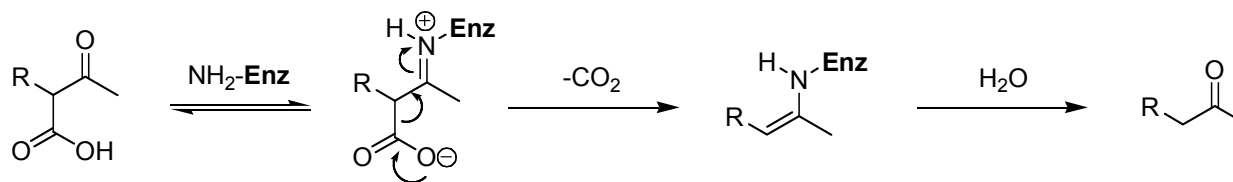
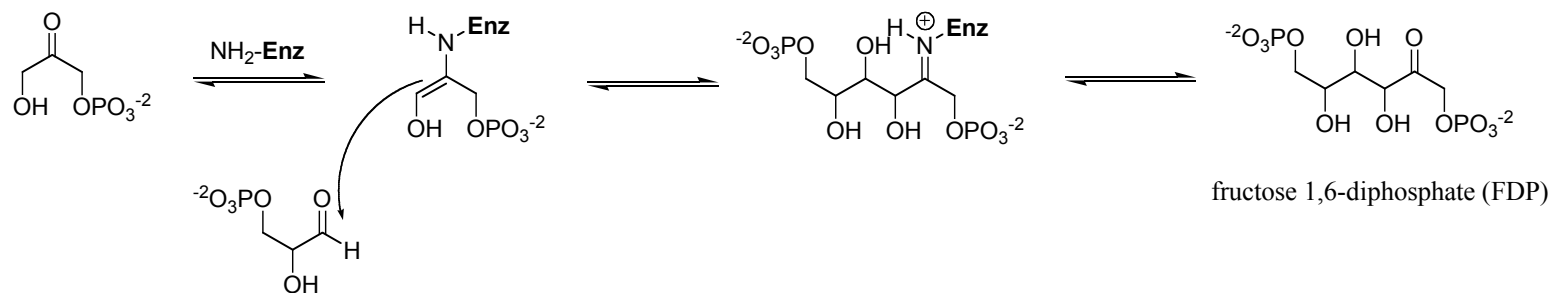
Erick B. Iezzi, PhD
Current Literature
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Why are these articles significant?

- 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

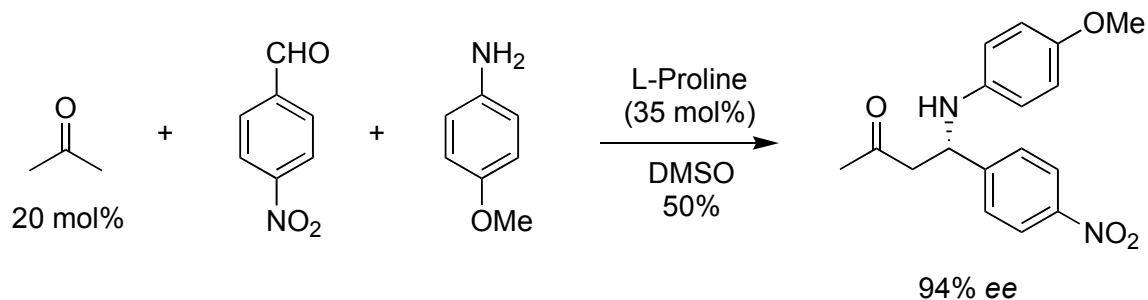
Asymmetric Aminocatalysis

- 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)



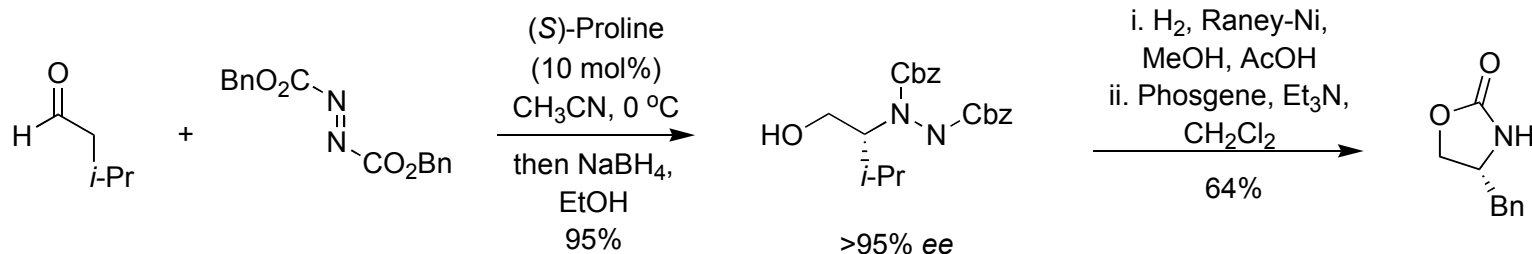
List, et al. *Synlett*. **2001**, *11*, 1675; Lerner, et al. *Science* **1997**, *278*, 2085

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



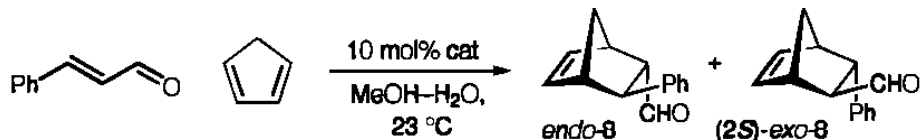
List, et al. *J. Am. Chem. Soc.* **2000**, *122*, 9336-9337

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



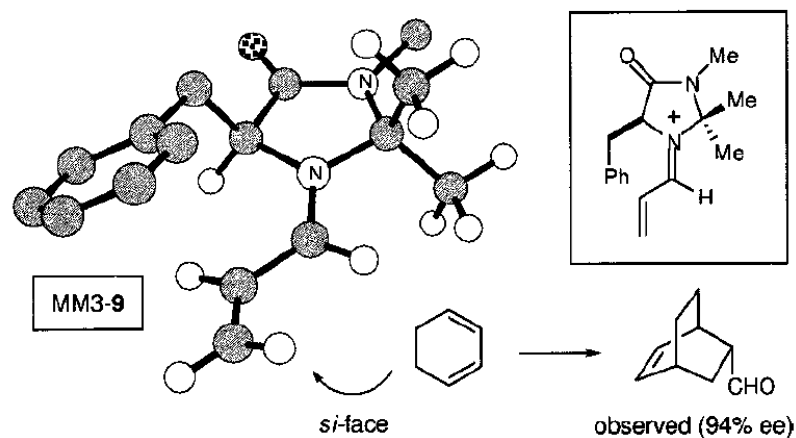
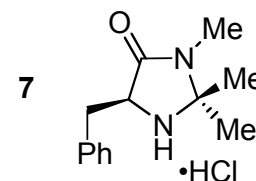
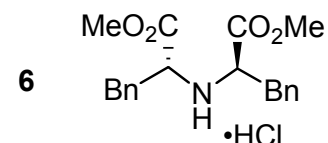
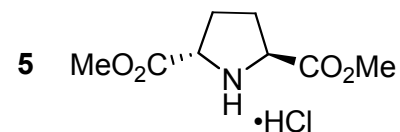
List, et al. *J. Am. Chem. Soc.* **2002**, *124*, 5656-5657

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



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

Catalysts



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

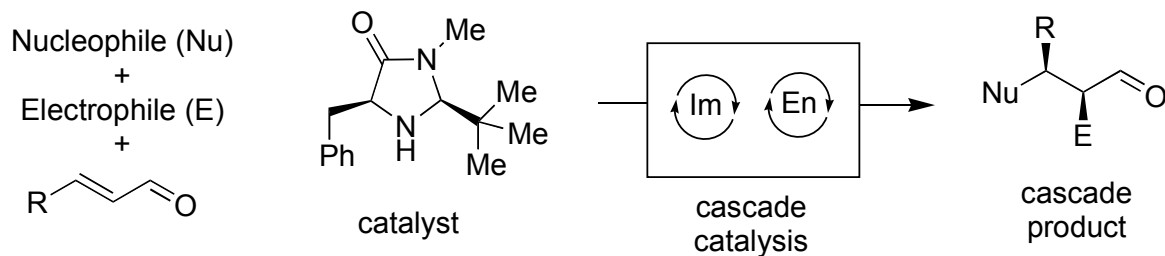
Enantioselective Organo-Cascade Catalysis (ASAP Article, MacMillan and co-workers)

- 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 actinomycetes) are assembled by polyketide synthases, which perform a successive decarboxylative condensations of simple precursors

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

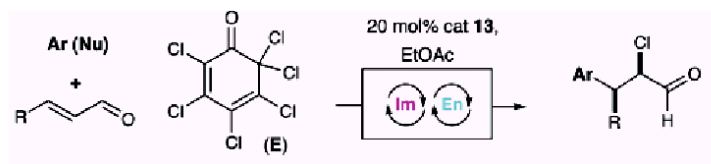
- Imidazolidinone-based catalytic cycles are used to generate complex structures without catalyst-catalyst interactions

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



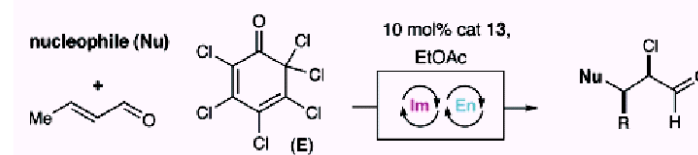
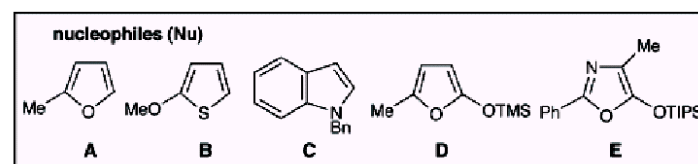
MacMillan, et al. *J. Am. Chem. Soc.* **2005**, ASAP

Organo-Cascade Catalysis: 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 ₂ Et		-60	80	22:1	99
4	CH ₂ OAc		-40	82	11:1	>99
5	Ph		-40	83	9:1	99
6	<i>i</i> -Pr		-40	67	12:1	>99

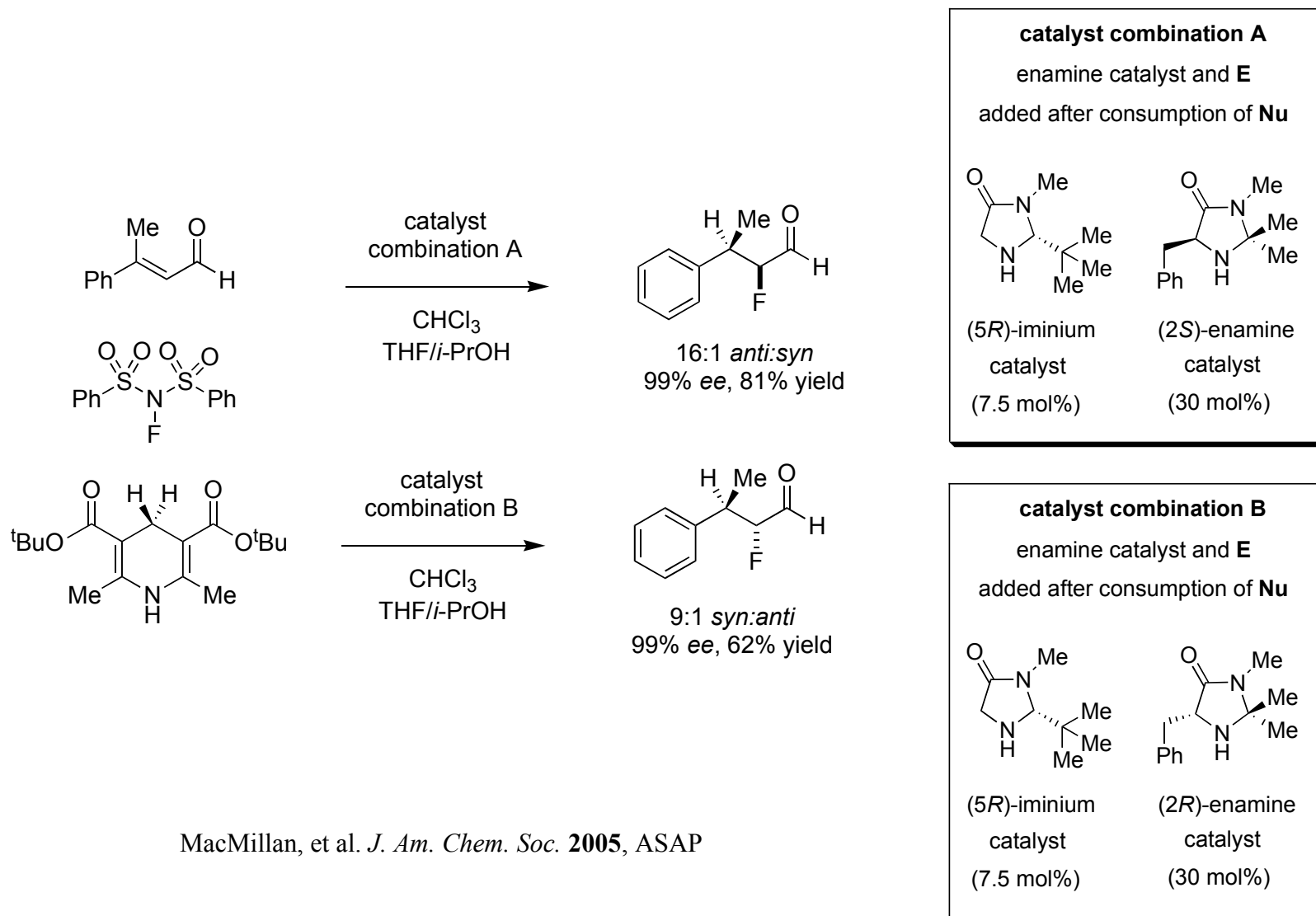
^a Absolute and relative configuration assigned by chemical correlation.
^b Enantiomeric excess determined by chiral GLC analysis.



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



Summary

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