The Direct and Enantioselective Organocatalytic α-Oxidation of Aldehydes

Sean P. Brown, Michael P. Brochu, Christopher J. Sinz, and

David W. C. MacMillan.

JACS, 2003, *125*, 10808-10809

Asymmetric Organocatalysis

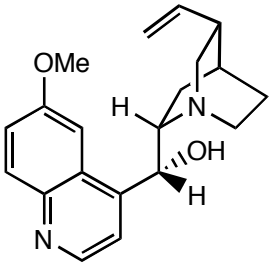
The use of chiral organic molecules to catalyse an enantioselective transformation

An alternative to organometallic mediated asymmetric processes

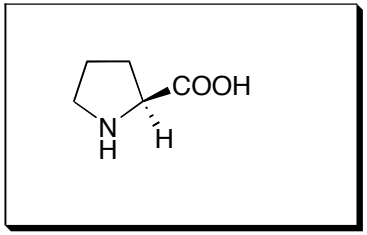
<u>Advantages include</u>

- Easy manipulation
- Enviromentally friendly
- Tolerates aerobic conditions
- Does not require dry solvents
- Amenable to a variety of solvents
- Amenable to solid phase

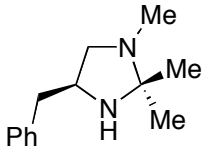
Examples of Organocatalysts



Cinchona Alkaloids



L-Proline

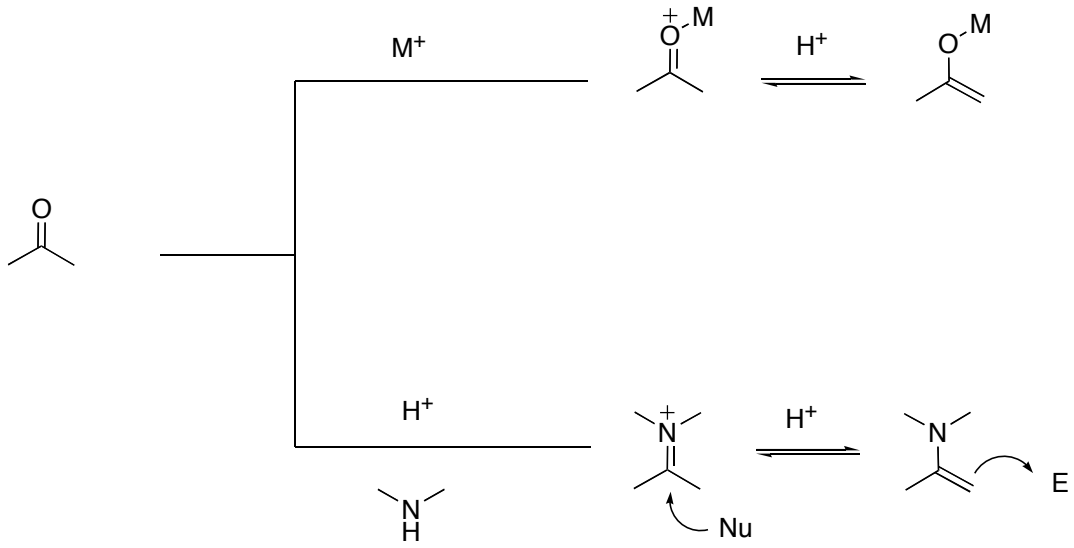


Amino Acid Derivatives

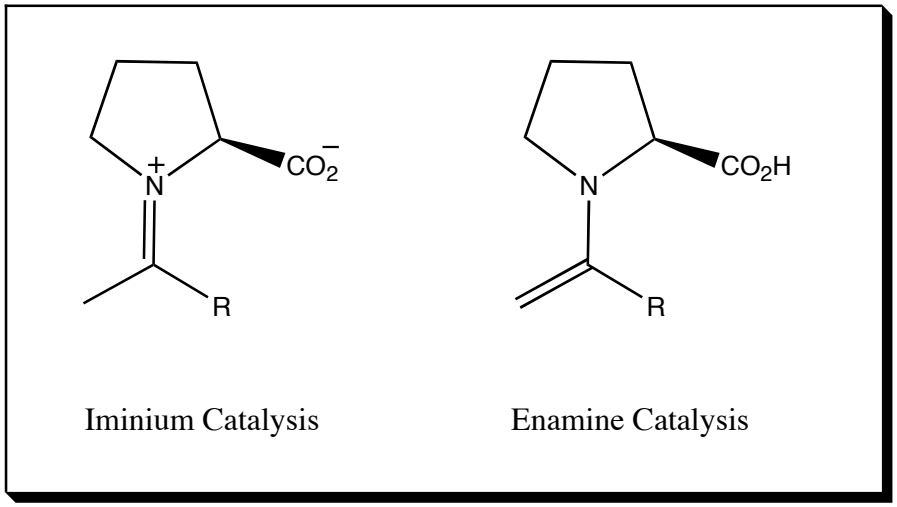
Peptide based catalysts

Aminocatalysis

(A Biomimetic strategy used by enzymes such as class I aldolases.)



Organocatalysis with L - Proline

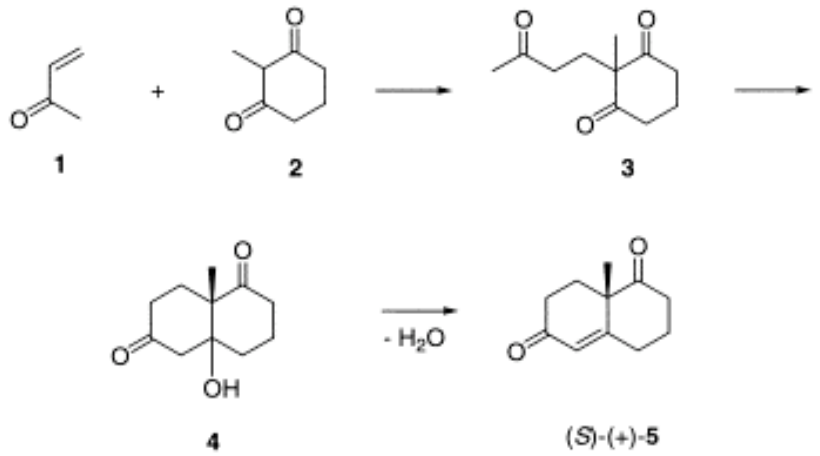


Iminium Catalysis

Enamine Catalysis

The First Enantioselective Organocatalytic Reaction:

Robinson Annulation

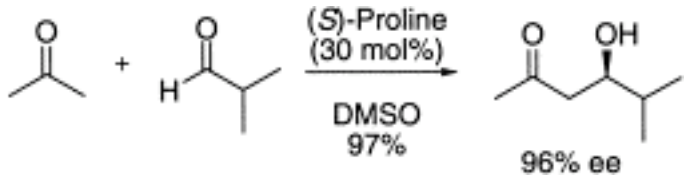


Using D- or L- Proline

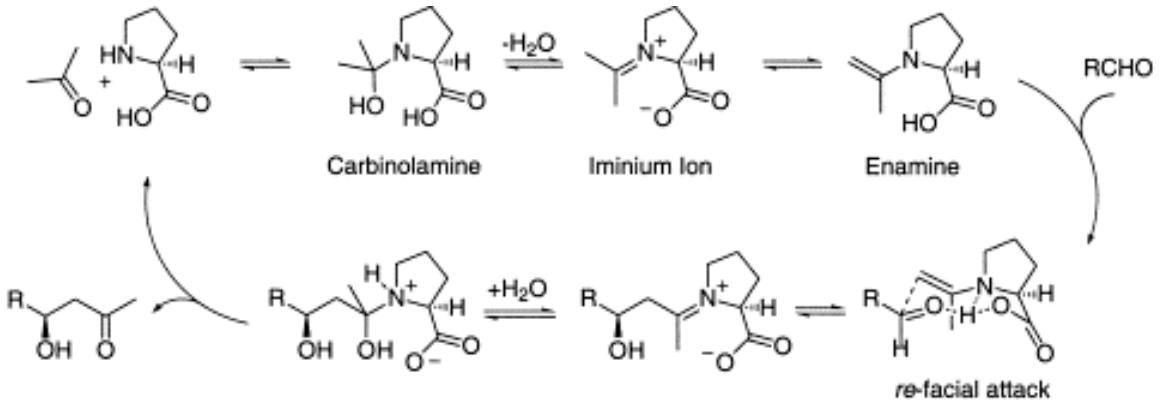
Two step: Intramolecular aldol step catalysed by (L)-Proline high yield (100%) and ee (93%)
J. Org. Chem, **1974**, *39*, 1615-1621.

One step: Lower yield (49%) and ee (76%) obtained (requires more catalyst)
Tett. Lett., **2000**, 6951-6954.
JACS, **2000**, *122*, 2395-2396.

Aldol Reaction

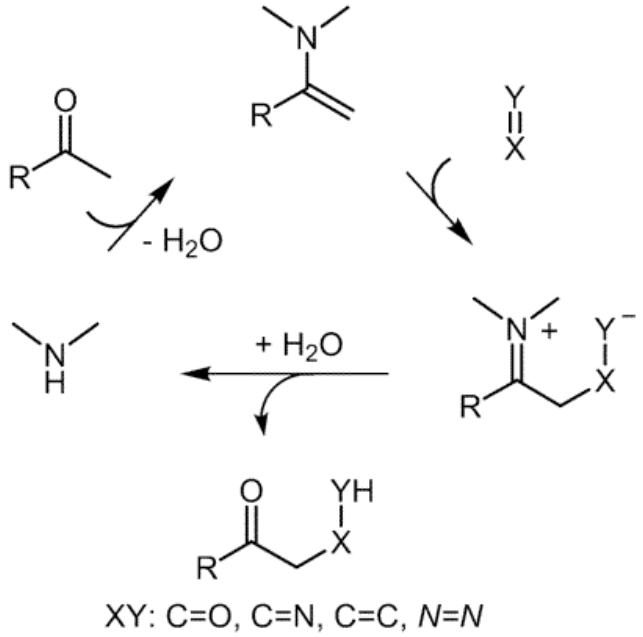


Highly enantioselective proline catalysed direct intermolecular aldol reaction.
JACS, **2000**, *122*, 2395-2396.



Mechanism of the proline catalysed aldol reaction
Synlett, **2001**, 1675-1686.

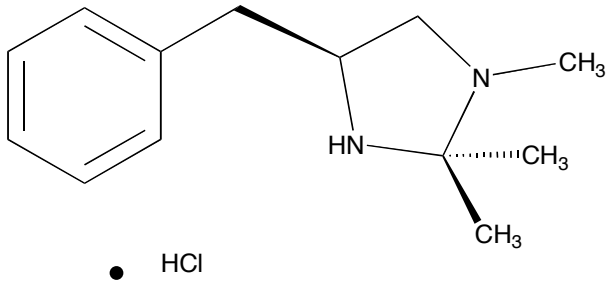
Enamine Catalysis Cycle



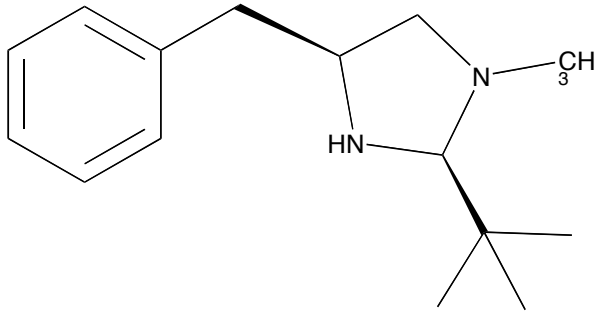
(1)

JACS, **2002**, *124*, 5656-5657.

MacMillan's Organocatalysts (Available from Sigma Aldrich)



derivative of phenylalaine
catalyses asymmetric Diels Alder
1,3-dipolar additions
Pyrrole alkylations



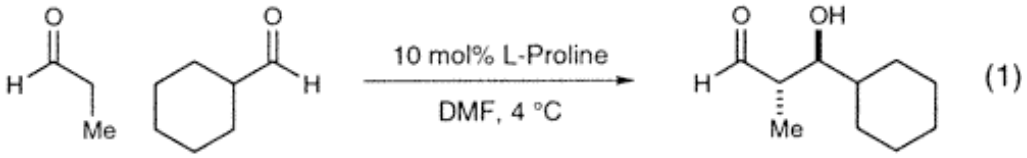
Asymmetric indole alkylations
Friedel-Crafts Alkylations
Conjugate additions

Macmillan prepared optically active 1,2-diols with the enantiselective organocatalytic □-oxidation of aldehydes as the key step.

Using proline as the catalyst and nitrosobenzene as the oxygen source

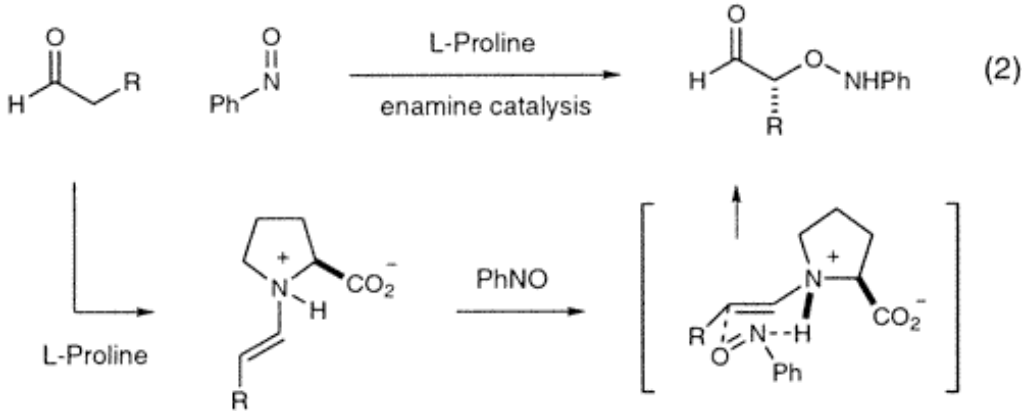
Previously reported the proline catalysed cross aldol reaction of aldehydes *JACS*, **2002**, *124*, 6798.

Proline Catalyzed Cross Aldol Addition



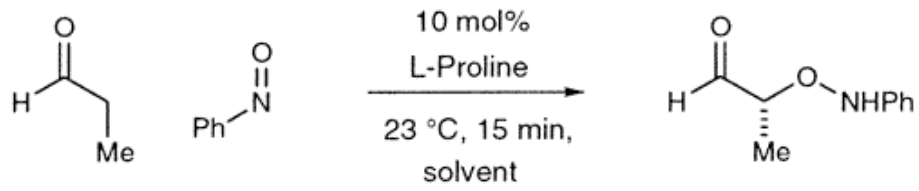
87% yield, 14:1 *anti:syn*, 99% ee

Organocatalyzed Direct α-Oxyamination



Examined •Solvent effects• Catalyst loading• Substrate scope

Effect of Solvent on the Asymmetric α-Oxyamination



entry	solvent	%yield	%ee
1	dioxane	8	97
2	EtOAc	18	95
3	THF	24	97
4	DMSO	35	94
5	DMF	46	97
6	NMP	50	98
7	CH_3CN	67	96
8	PhH	67	97
9	$CHCl_3$	78	96

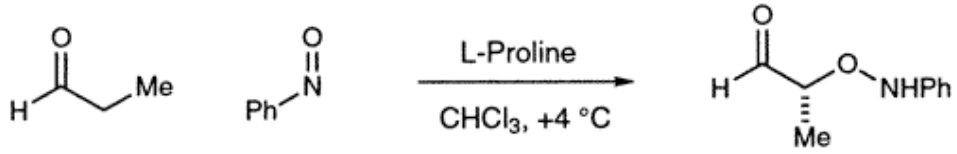
Isolated yields at arbitary 15-min time point. Yields were calculated after conversion to the corresponding primary alcohol

Variation of solvents has a pronounced effect on reaction rates

Excellent levels of enantioselection observed for a diverse range of solvents

Improved selectivities were observed at lower temperatures

Effect of catalyst loading on Organocatalysed Oxidation



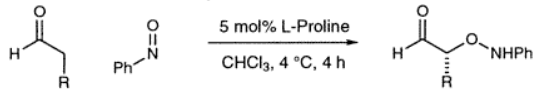
entry	mol%L-proline	time	%yield	%ee
1	10	20 min	88	97
2	5	45 min	86	97
3	2	2 h	88	97
4	1	8 h	83	97
5	0.5	18 h	68	94

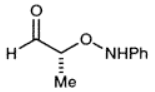
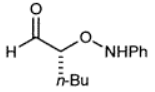
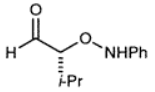
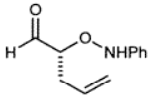
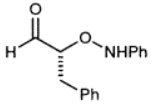
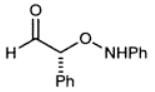
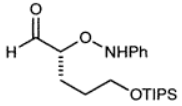
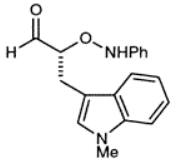
Yields based on the isolation of the corresponding primary alcohol.

Catalyst loadings as low as 0.5 mol% can be used

The operational use of 2 mol% L-proline ensures high reaction efficiency and enantioselectivity with favourable reaction times

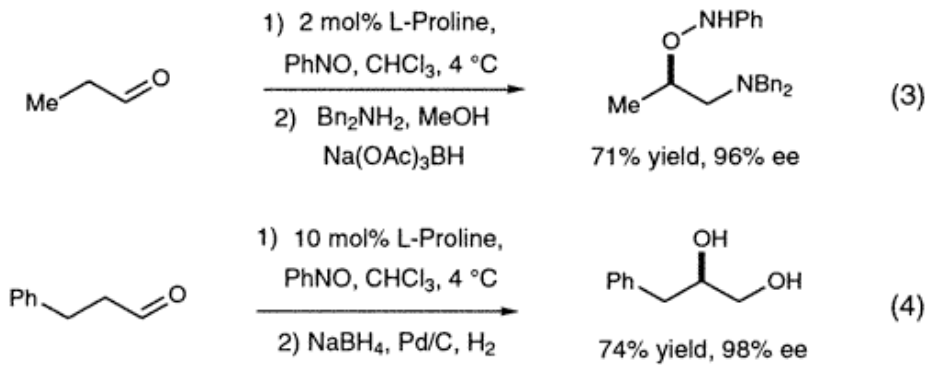
Enantioselective α-Oxyamination: Substrate Scope:



entry	R	Product	% yield[a]	% ee[b]
1	Me		88	97[c]
2	*n*-Bu		79	98
3	*i*-Pr		85	99
4	$CH_2CH{=}CH_2$		80	99[d]
5	CH_2Ph		95	97[d]
6	Ph		60	99
7	$(CH_2)_3OTIPS$		76	98
8	CH_2-(3'-*N*-methyl-indole)		83[e]	98

The □-oxyaldehyde products are oligomeric in solution and were isolated as the corresponding primary alcohols

(The oligomeric aldehydes undergo reactions typical of aldehydes)



Conclusions

•All reactions conducted in air using wet solvents-highly suitable for industry

•Enantioselective route to chiral 1,2-diol precursors

Future Work

•Useful building blocks for natural product synthesis

•Multi-component reactions

• Discovery of more organocatalysts

Incidentally, a paper published on similar work appeared at the same time in *Angewandte chemie Int*., **2003**, *42*, 4247-4250.