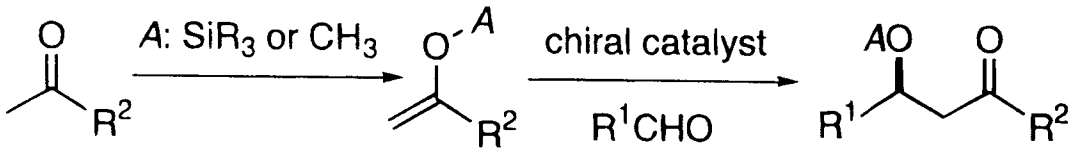
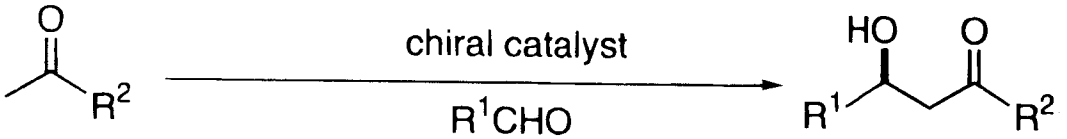
Catalytic Asymmetric Direct Aldol Reactions

(a) Mukaiyama-type Reactions



(b) Direct Reactions



- Unlike the "classic" aldol reactions, most asymmetric variants require pre-formation of enolate, enol, or equivalent
- Development of catalysts to promote this reaction directly can overcome the need to use stoichiometric amounts of base and reagents involved in enolate formation

Designing Such a System

Catalyst be capable of coordinating both reaction partners together in an asymmetric environment
Must turn-over effectively:
bind products less tightly than starting materials
active catalyst must be rapidly regenerated

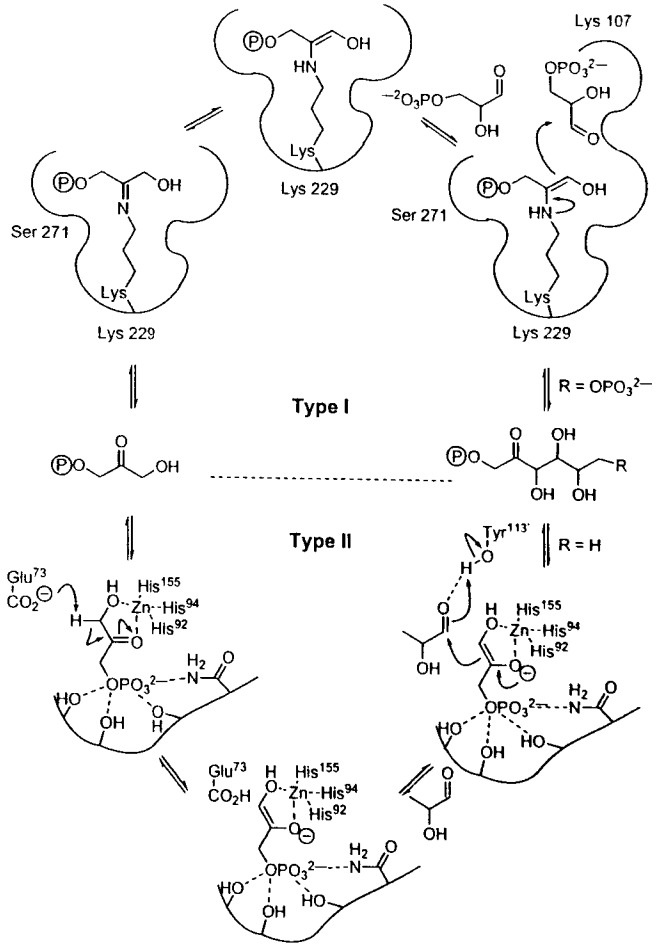
1. Biological inspiration:

Adolases:
Type I : found in animals and higher plants (enamine mechanism)
Type II: found in bacteria and fungi (utilize zinc cofactor)

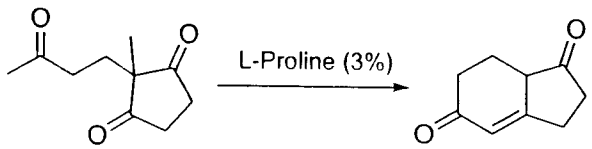
Catalytic antibodies:

Works by developing transition-state mimics of aldolase enzymes. The resultant antibodies that are produced catalyze aldol reactions themselves.

Advantages over aldolases is that they have much greater susbtrate generality

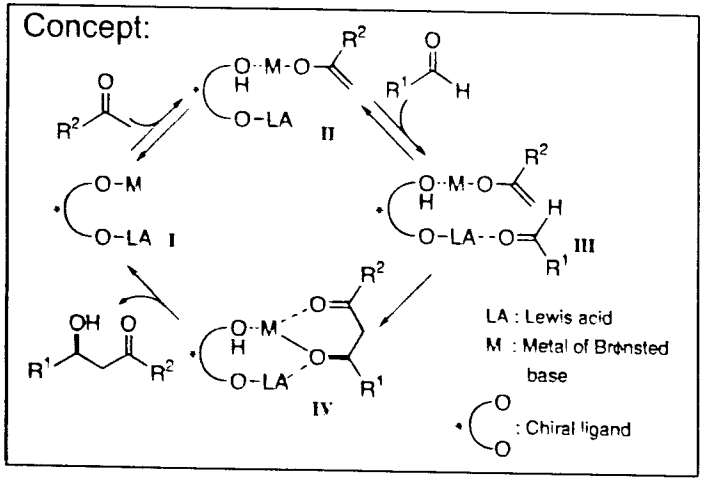


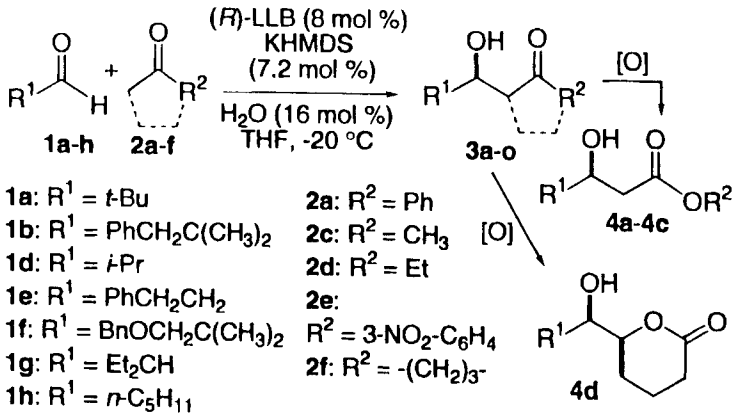
2. The Hajos-Parrish reaction:



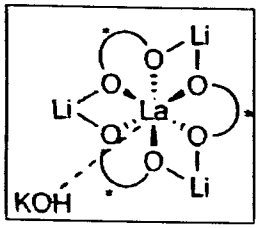
Use of Heterobimetallic Asymmetric Catalysts

Concept:





active catalyst

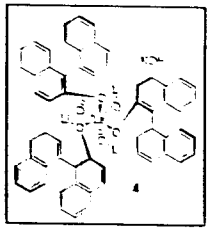


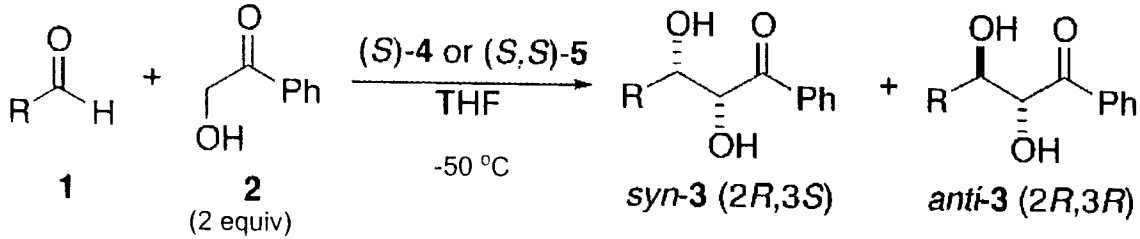
entry	aldehyde (R^1)	ketone[a] (R^2) (equiv)	aldol	time (h)	yield (%)	ee (%)
1	**1a**	**2a** (5)	**3a**	15	75	88
2	**1b**	**2a** (5)	**3c**	28	85	89
3	**1b**	**2c** (10)	**3g**	20	62	76
4[f]	**1b**	**2d** (15)	**3i**	95	72	88
5	**1f**	**2a** (5)	**3j**	36	91	90
6[e]	**1f**	**2a** (5)	**3j**	24	70	93
7[g]	**1d**	**2a** (5)	**3e**	15	90	33
8[h]	**1d**	**2e** (3)	**3k**	70	68	70
9[i]	**1g**	**2e** (3)	**3l**	96	60	80
10[h,j]	**1h**	**2e** (5)	**3m**	96	55	42
11[f]	**1e**	**2e** (3)	**3n**	31	50	30
12	**1b**	**2f** (5)	**3o**	99	95	76/88
					(*syn*/*anti* = 93/7)	(*syn*/*anti*)

[a]"Acetone and 2-butanone are widely used as solvents and are much cheaper than the corresponding enol silyl ethers and methyl enol ethers…The use of large excesses of ketone can thus be justified."

Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871.
Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.

Access to syn- and anti-α,β-Dihydroxyketones





1 2 (2 equiv) *syn*-3 (2*R*,3*S*) *anti*-3 (2*R*,3*R*)

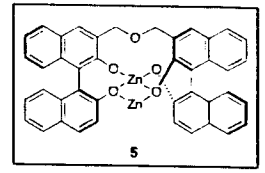


Table 1. Aldol Reaction Using Heterobimetallic Catalyst 4[a]

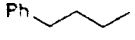
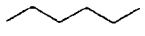
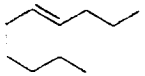
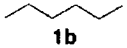
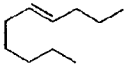
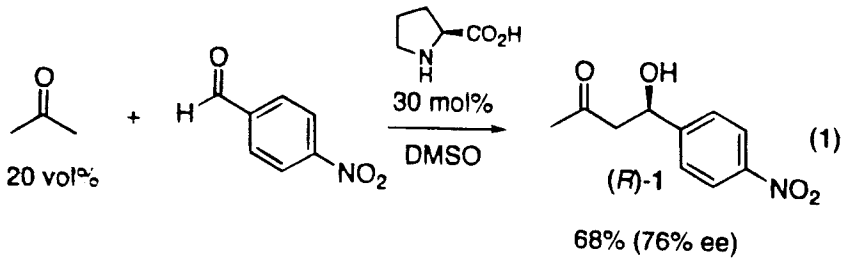
entry	R	product	catalyst (mol %)	time (h)	yield[b] (%)	dr[c] (*anti*:*syn*)	ee[d] (*anti*/*syn*)
1	 1a	3a	10	24	87 (84)	5:1	95 / 74
2[e]	1a	3a	5	40	78 (78)	4:1	92 / 70
3	 1b	3b	10	24	90 (84)	3:1	94 / 84
4	 1c	3c	10	28	92 (90)	3:1	94 / 83
5	 1d	3d	10	24	92 (86)	2:1	90 / 83
6	 1e	3e	10	24	89 (89)	2:1	95 / 87

Table 2. Aldol Reaction Using Zn–Zn-linked-BINOL Complex 5[a]

entry	R	product	catalyst (mol %)	time (h)	yield[b] (%)	dr[c] (*anti*:*syn*)	ee[d] (*anti*/*syn*)
1	 1f	3f	10	36	92	1:5	67 / 86[e]
2	 1g	3g	10	48	89	1:6	78 / 85[e]
3	 1h	3h	10	48	79	1:7	72 / 79
4	 1b	3b	10	60	80	1:2	73 / 77
5	 1c	3c	10	60	81	1:2	75 / 79
6	 1d	3d	10	36	80	1:2	79 / 83
7	 1e	3e	10	48	89	1:3	81 / 81

Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466.

Proline-Catalyzed Direct Asymmetric Aldol Reaction



Product	Yield	ee[a]	$[\alpha]_D$[b]
(*R*)-1	68%	76%	
(*R*)-2	62%	60%	+ 41.8° (c = 1.1)[c]
(*R*)-3	74%	65%	
(*R*)-4	94%	69%	
(*R*)-5	54%	77%	
(*R*)-6[e]	97%	96%	+ 61.7° (c = 0.6)[d]

A variety of other amino acids were tested
All were inferior to proline

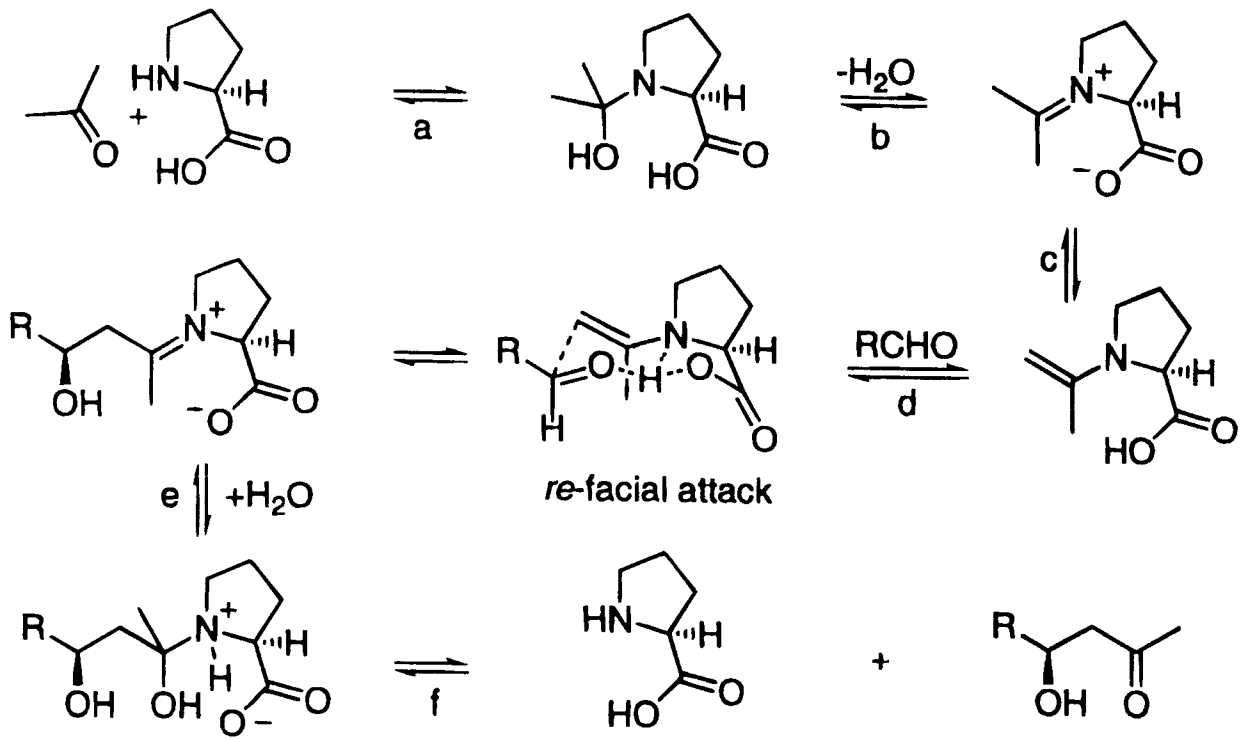
Pyrrolidine ring *and* carboxylate are essential

Unbranched aldehydes gave very low yields

- room temp, metal-free reactions
- 2-8 h (last entry 48 h)
- catalyst is nontoxic, inexpensive, and available in both enantiomers
- catalyst can be easily removed by aqueous extraction
- reaction doesn't require inert atmosphere

List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

Mechanism of Proline-Catalysis

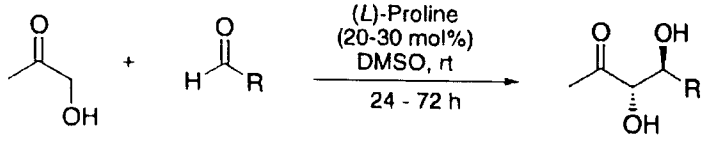


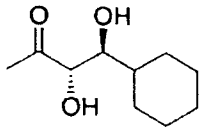
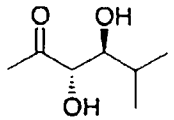
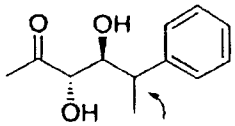
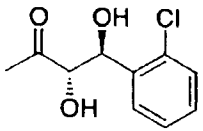
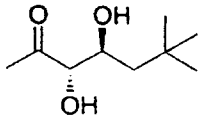
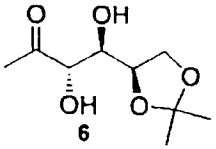
"Proline, perhaps, functions as a "micro-aldolase" that provides both the nucleophilic amino group and an acid/base cocatalyst in the form of the carboxylate"

Proline Catalyzed Synthesis of anti-1,2-Diols

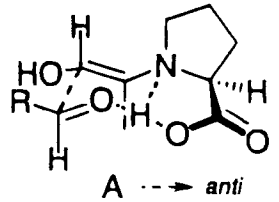
- Accessing anti-1,2-diols via Sharpless AD of *Z*-olefins generally give lower ee's than corresponding
- *E* olefins.

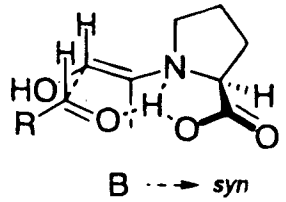
- The direct aldol is potentially more useful since both adjacent stereocenters are created via C-C bond formation



Entry	Product	Yield	dr[a]	ee[b]
(1)	 **1**	60%	>20 : 1	>99%
(2)	 **2**	62%	>20 : 1	>99%
(3)	 **3a + 3b** (2 : 1)	51%[c]	>20 : 1[d]	>95%[d]
(4)	 **4**	95%[c]	1.5 : 1[e]	67%
(5)	 **5**	38%[c]	1.7 : 1	>97%
(6)	 **6**	40%[c]	2 : 1	>97%[f]

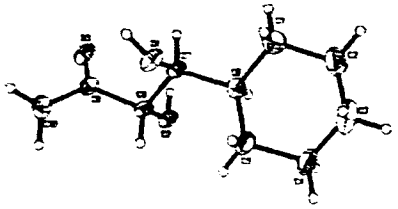
Stereochemical rationale:





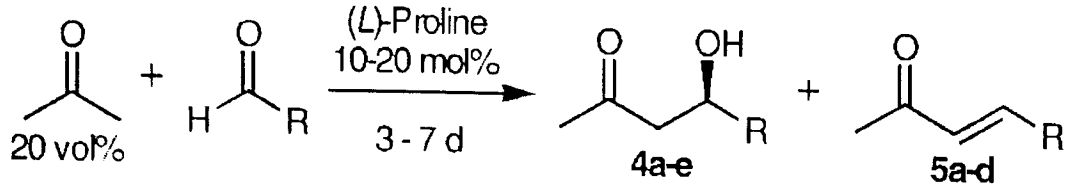
Drawback: 15 equiv of hydroxyacetone

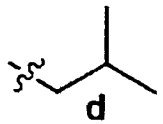
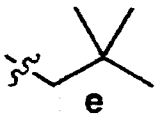
Absolute configurations assigned from crystal structure of **1**:



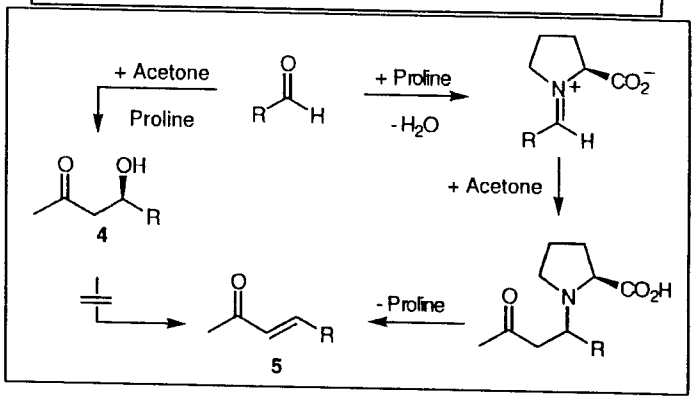
Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

Reactions with α-Unsubstituted Aldehydes

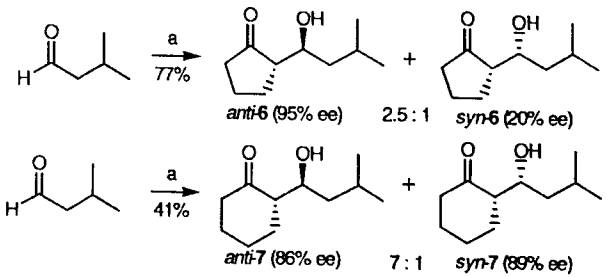


R =	yield of 4 (5)	ee[a]	solvent
 **a**	31% (38%) 29%	67% 70%	Acetone $CHCl_3$
 **b**	35% (40%)	73%	Acetone
 **c**[b]	34% (35%)	72%	$CHCl_3$
 **d**	34% (42%) 23% (46%)	73% 61%	Acetone $CHCl_3$
 **e**	22% (50%)	36%	$CHCl_3$

Independent experiments establish that elimination products do not arise from proline-catalyzed dehydration of aldols **4**



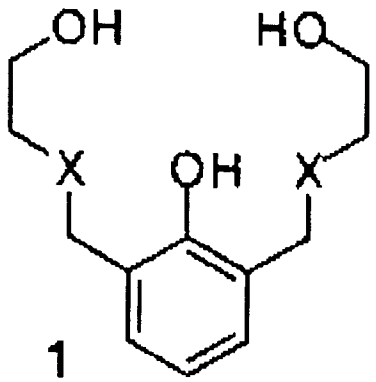
Cyclic ketones, w/ 20 mol% proline:



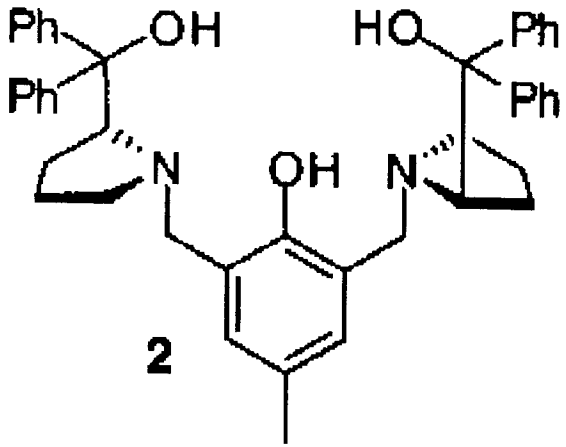
"Although the method is limited by modest yields and long reaction times, we feel the accessibility of both enantiomeric forms of proline, as well as the operational simplicity of this process, make it comparable to other methods for the direct catalytic asymmetric aldol reaction"

List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573.

Crown Organometals as Catalysts



1



2

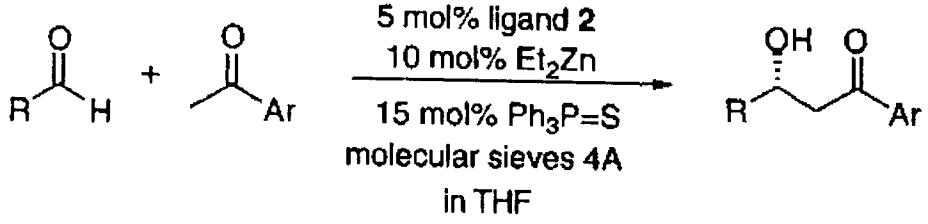
The use of crown compounds is attractive due to

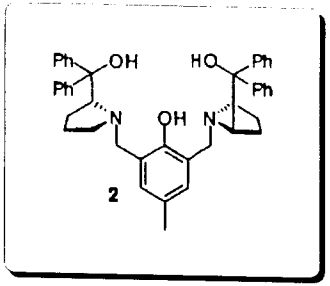
1. ability to tightly bind metal ions
2. high level of molecular recognition in binding events

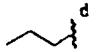
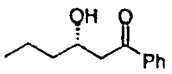
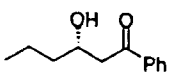
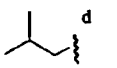
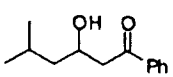
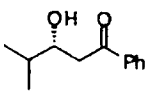
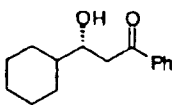
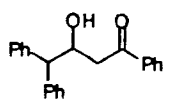
Therefore, should be highly suitable for asymmetric catalysis.

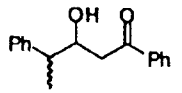
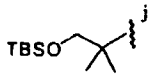
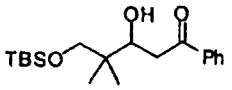
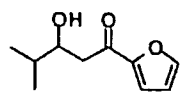
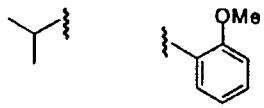
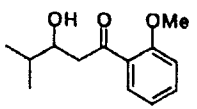
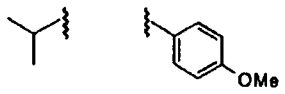
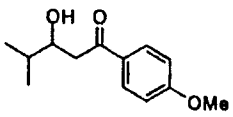
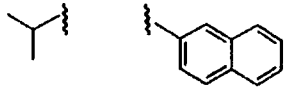
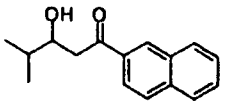
Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

Use of Aryl-Methyl Ketone





RCHO		Product[b]	yield %	ee[c] %
 [d]	-Ph		33	56
 [e]	-Ph		24	74
 [d]	-Ph		49	68
	-Ph		62[f]	98
	-Ph		60	98
	-Ph		79	99

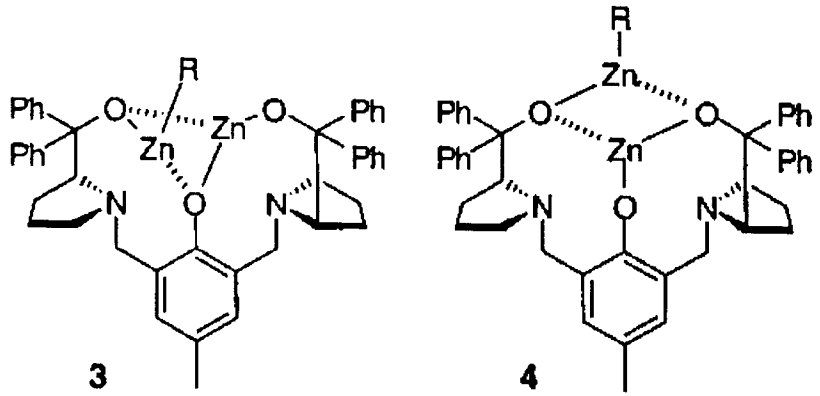
	-Ph		67[g] (2:1)	94[h] (98)[i]
 [j]	-Ph		61	93
			66	97
			48	97
			36[k]	98
			40[k]	96

Reactions conducted at 5 °C for 48h. aldehyde / ketone ratio 1:10

What is the Active Catalyst in Solution?

- presence of three active protons in ligands suggests involvement of more than 1 zinc
- two equiv of $ZnEt_2$ (rel. to ligand) liberates 3 equivalents of ethane gas
- one alkyl metal bond remains intact. *(This is verified by liberation of another molecule of ethane gas upon addition of water)*

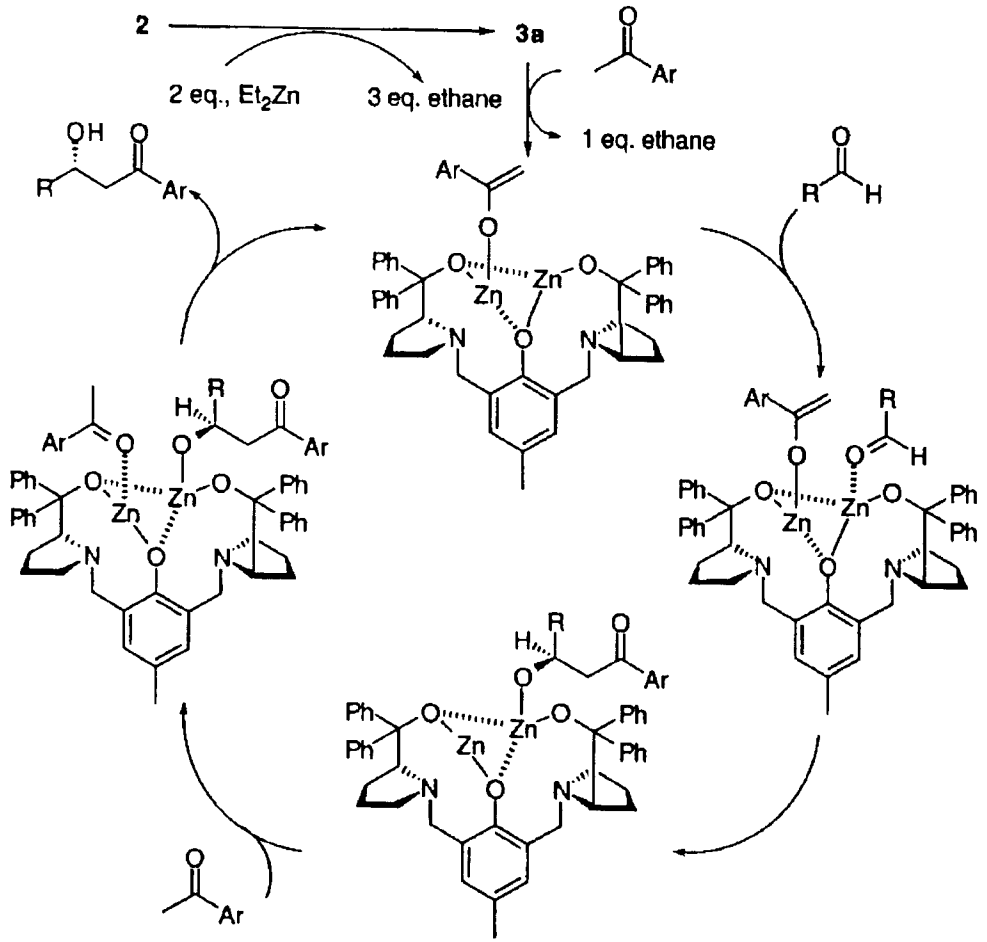
This suggests either 3 or 4 as active catalyst:



3 **4**

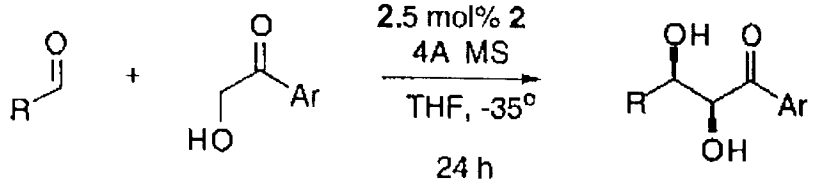
MM2 force field calculations indicate **3** is 7 kcal/mole more stable than **4**

Catalytic Cycle of Origin of Stereoselectivity



Selectivity controlled by enolate approaching *re* face of aldehyde

α-Hydroxyketones as Donors



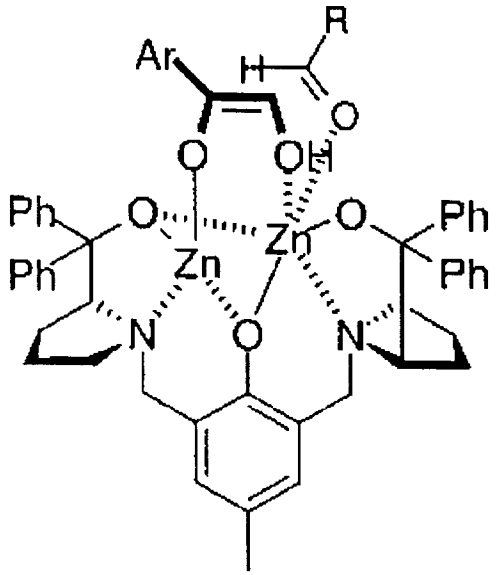
entry	R	Ar	Major Product[b]	isolated yield (%)	dr[c]	ee (%)[d]
1	a, b[e]	Ph		83 97	30:1 5:1	92 90
2a b[e] c[e,f]		Ph		89 93 72	13:1 5:1 6:1	93 86 93
3a b[e]		Ph		74 97	ONLY ONE 13:1	96 81
4a b[e] c[e,f]		Ph		65 96 79	35:1 3:1 4:1	94 88 93
5a b[e]		Ph		78 98	9:1 3:1	91 90
6[e,g]		Ph		62	3.5:1	96
7[e]		Ph		89	5:1	86
8[e]		Ph		91	5:1	87
9a[e,h] b[e,f]				90 77	6:1 6:1	96 98
10[e,h]				97	3.4:1	95

a: 2.5 mol% cat., 1.5 equiv hydroxyketone
b: 5.0 mol% cat.
c: 5.0 mol% cat., 1.1 equiv hydroxyketone

Absolute configuration of stereocenter derived from aldehyde is opposite to that obtained with acetophenone!

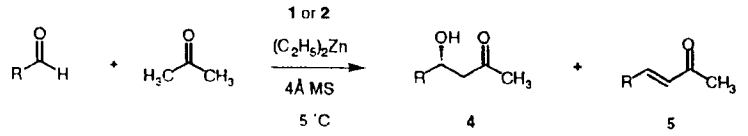
Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367.

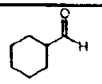
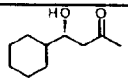
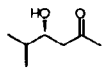
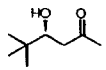
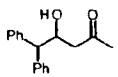
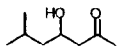
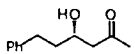
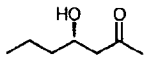
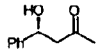
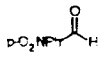
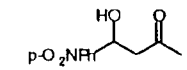
Stereochemical Rationale of Observed Selectivity

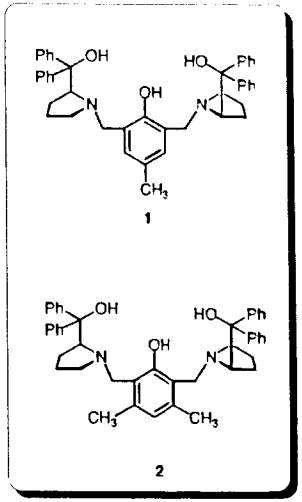


- Enolate of α-hydroxyketone now serves as a bidentate ligand bridging the two zincs
- Opposite face of aldehyde is then exposed to react upon binding

Second Generation Dinuclear Zinc



entry	aldehyde	catalyst	product	ratio 4 / 5[j]	yield 4 (%)[i]	*ee* (%)
1		1[e]		ONLY 4	62	87
		1[f]		ONLY 4	85	93
		2[f]		ONLY 4	89	92
2		1[e]		ONLY 4	80	87
		2[f]		ONLY 4	89	91
3		1[e]		ONLY 4	76	86
		2[f]		ONLY 4	72	94
4		1[e]		ONLY 4	79	82
		1[f]		ONLY 4	72	87
		2[f]		ONLY 4	84	91
5		1[e]		ONLY 4	24	76
		2[f]		ONLY 4	59	84
6		1[e]		6:1	59	89
		1[f]		1:3	24	89
		2[f]		15:1	76	82
7		1[e]		ONLY 4	56	84
		1[g]		15:1	55	87
		2[f]		ONLY 4	69	89
		2[h]		ONLY 4	72	84
8		1[e]		3:1	55	88
		1[g]		3:1	57	85
		2[e]		ONLY 4	78[b]	83
		2[f]		1:4	12	79
9		1[e]		2:1	36	74
		1[e]		ONLY 4	62[c]	78
		2[f]		8:1	54	76



Standard conditions:
0.5 mmol aldehyde
0.5 mL acetone
Catalyst added as
0.1M solution in THF

footnotes:
e : 5% cat.
f : 10% cat.
g : 5% cat. + PPh_3S (50%)
h : 10% cat. + PPh3S (50%)

Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497.

Summary

	Simple ketones	α-unbranched aldehydes	α-hydroxyketones
	Yields and reaction times variable, most examples use 5 equiv ketone	Yields and ee's are greatly attenuated in these cases	Can accesss both anti and syn products with good dr, great yields and ee's, using 2 equiv of ketone
	Both enantiomers of proline are readily accessible, stable, and cheap, ee's generally only moderate	Poor yields, moderate ee's	Yields are moderate, dr's and ee's are great. Anti product obtained. Need ~15 equiv ketone, however
	Yields not very high, but can be improved with 2nd generation catalyst. Ee's are excellent	Biggest effect of 2nd generation catalyst seen here, both yields and ee's are improved dramatically	Yields generally quite good, dr's and ee's excellent. Syn product obtained. Can use as little as 1.1 equiv of ketone.

Additional References

Use of a chiral barium complex for direct aldol (superior to LLB catalyst but inferior to LLB + KHMDS + H_2O system)

Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561.

Excellent review of different types of aldol reactions including

1. Aldolase catalyzed reactions
2. Antibody design and catalysis
3. Small-molecule catalysts

Machajewski, T. D.; Wong, C-H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.

Prior studies on antibody-catalyzed direct aldol reactions:

(a) Wagner, J.; Lerner, R. A.; Barbas, C. F., III *Science* **1995**, *270*, 1797.
(b) Barbas, C. F., III; Heine, A.; Zhong, G.; Hoffmann, T.; Gramatikova, S.; Bjo¨rnestedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, E. A.; Lerner, R. A. *Science* **1997**, *278*, 2085-2092.
(c) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **1998**, *120*, 2768-2779.
(d) List, B.; Shabat, D.; Barbas, C. F., III; Lerner, R. A. *Chem. Eur. J.* **1998**, 881-885.
(e) Zhong, G.; Shabat, D.; List, B.; Anderson, J.; Sinha, S. C.; Lerner, R. A.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **1998**, *37*, 2481-2484.
(f) Zhong, G.; Lerner, R. A.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **1999**, *38*, 3738-3741.
(g) Sinha, S. C.; Sun, J.; Miller, G.; Barbas, C. F., III; Lerner, R. A. *Org. Lett.* **1999**, *1*, 1623-1626.