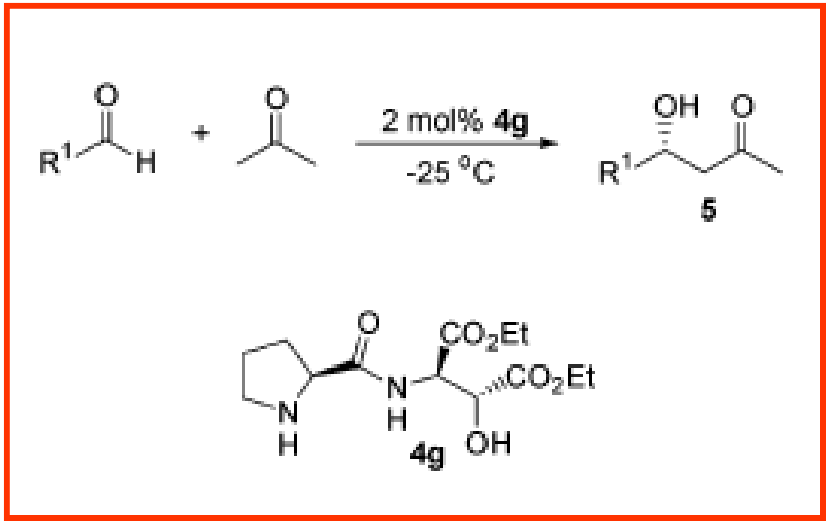
A Highly Efficient Organocatalyst for Direct Aldol Reactions of Ketones and Aldehydes

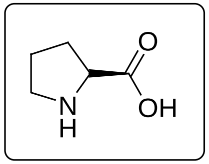


Zhuo Tang, Zhi-Hua Yang, Xiao-Hua Chen, Lin-Feng Cun, Ai-Qiao Mi, Yao-Zhong Jiang, and Liu-Zhu Gong

Contribution from the Key Laboratory for Asymmetric Synthesis and Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu,610041, China, and Graduate School of Chinese Academy of Sciences, Beijing, China

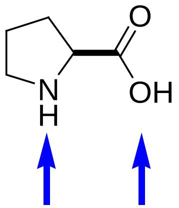
J. Am. Chem. Soc. **2005**, *ASAP*

Topic Outline

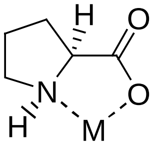


- *Introduction*: Proline as an asymmetric organocatalyst
- *Background*: Discovery of proline as an organocatalyst for asymmetric reactions
- Proline-catalyzed direct asymmetric intermolecular aldol reactions
- Scope and applications of proline-catalyzed direct asymmetric aldol reactions reactions
- *Title paper*: A highly Efficient Organocatalyst for Direct Aldol Reactions of Ketones with Aldehydes
- *Summary*

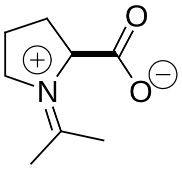
Introduction - Proline as a Universal Asymmetric Catalyst??



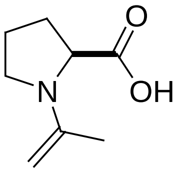
Bifunctional Acid/Base Catalysis



Metal Catalysis



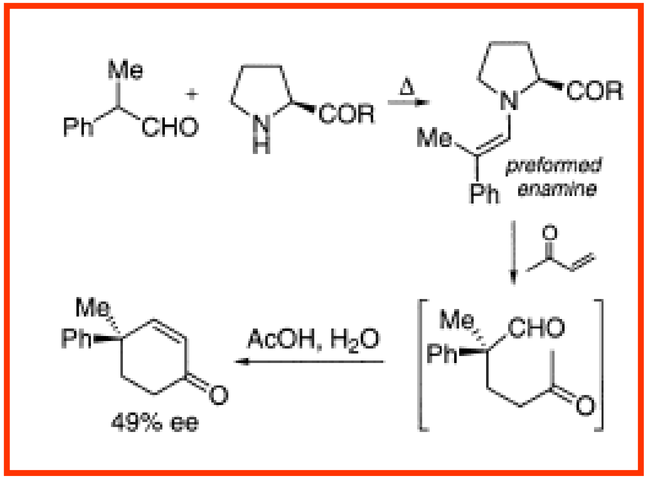
Iminium Catalysis



Enamine Catalysis

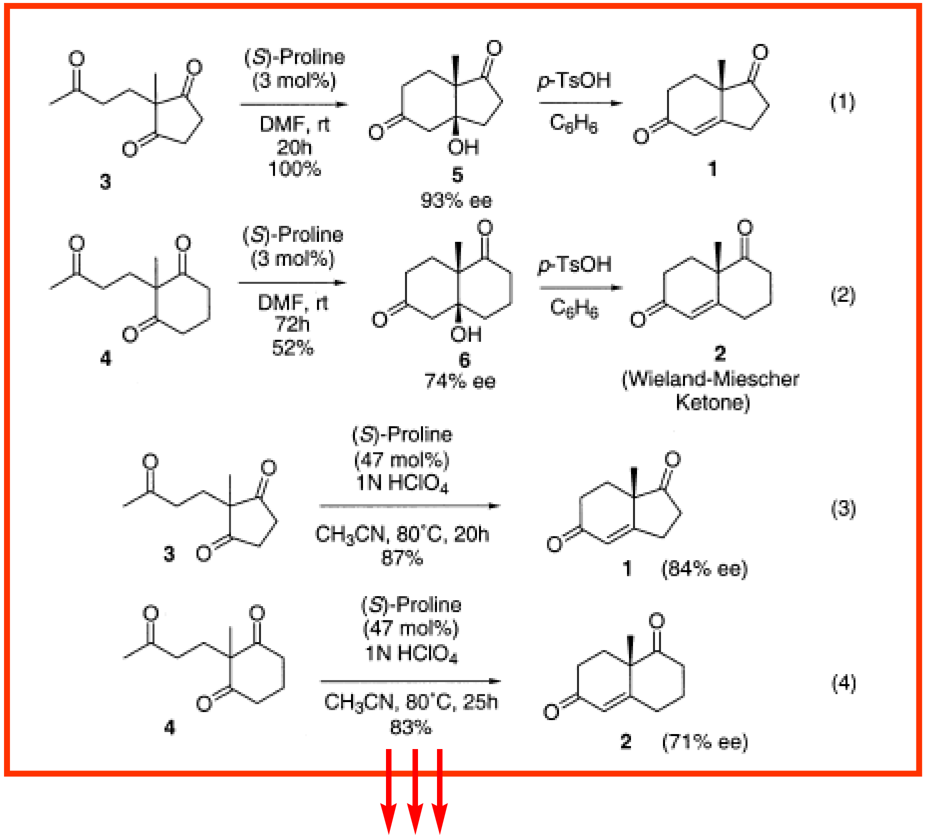
- Proline is an abundant chiral molecule
  a) nontoxic and inexpensive
  b) readily available in both enantiomeric forms
  c) comfortable reaction conditions and recyclable
- A bifunctional, with a carboxylic acid and an amine functional groups
- A ligand in asymmetric transition-metal catalysis
- A chiral modifier
- An effective organocatalyst, such as the aldol, Mannich, and Michael reactions
- An ideal compromise between small rigid organocatalysts and enzymes

Discovery of Proline as an Organocatalyst for Asymmetric Reactions



- Yamada's asymmetric Robinson-annulation was developed based on the proline-derived enamines.

Yamada, S.; Otani, G. *TL* **1969**, 4237-4240.



- Hajos-Parrish-Eder-Sauer-Wiechert reactions: The proline-catalyzed asymmetric intramolecular aldol reactions of triketones were discovered by two industrial groups.

Hajos, Z. G. *J. Org. Chem.* **1974**, *39,* 1615.
Eder, U. *ACIEE.* **1971**, *10,* 496.
Cohen, N. *Acc. Chem. Res.* **1976**, *9,* 412.

leads to numerous asymmetric synthesis of steriods and terpenoids
Eg. Baccatin III and Taxol

Danishefsky, S. J. *JACS* **1996**, *118*, 2843.

Proposed Mechanism of Proline Catalyzed Intramolecular Aldol Reaction

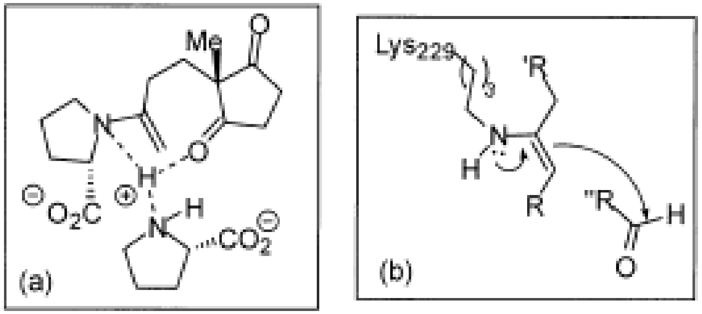
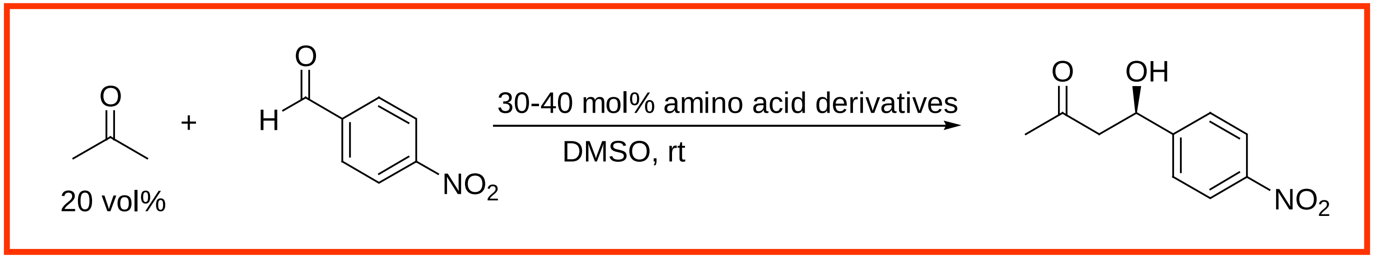


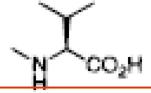
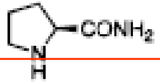
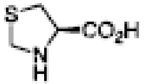
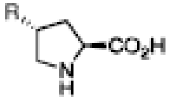
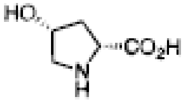
Figure 1. Proposed enamine intermediates in (a) proline catalyzed intramolecular aldol and (b) Type I aldolase.

- Proposed mechanism of the proline catalyzed intramolecular aldol reaction involved an enamine intermediate
- Both the secondary amine and the carboxylic acid moieties were involved in the catalysis
- Proton transfer is facilitated by a bifurcated H-bond between the enamine, the ketone and the amine of a second molecule of the proline
- This mechanism is analogous to the mode of action of Type I aldolase by activating the ketone by enamine formation

Agami, C. *TL* **1986**, *27*, 1501. Agami, C. *Bull. Soc. Chim. Fr.* **1988**, *3*, 499. Wong, C. –H. *Enzymes in Synthetic Organic Chemistry*; Elsevier: Oxford, UK, 1994.

First Example of Proline-Catalyzed Direct Asymmetric Intermolecular Aldol Reactions

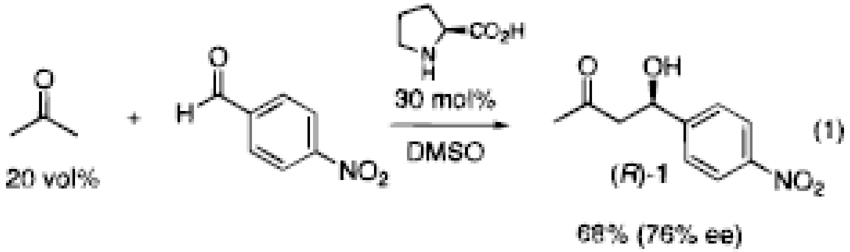


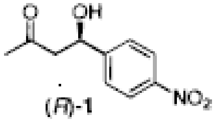
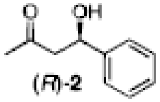
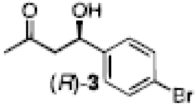
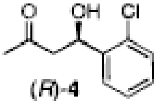
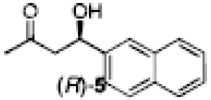
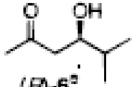
Compound	Entry	Yield	ee[a]
(*L*)-His, (*L*)-Val (*L*)-Tyr, (*L*)-Phe	1	< 10%	n. d.[b]
	2	< 10%	n. d.
	3	55%	40%
	4	68%	76%
	5	< 10%	n. d.
	6	< 10%	n. d.
	7	67%	73%
	8a R = OH 8b R = OtBu 8c R = OAc	85% > 50%[c] 70%	78% 62% 74%
	9	> 50%[c]	62%[d]

- Primary amino acids and acyclic amino acids failed to afford desired product
- Both the pyrrolidine ring and the carboxylate are crucial for efficient catalysis

List, B. *JACS* **2000**, *122,* 2395.

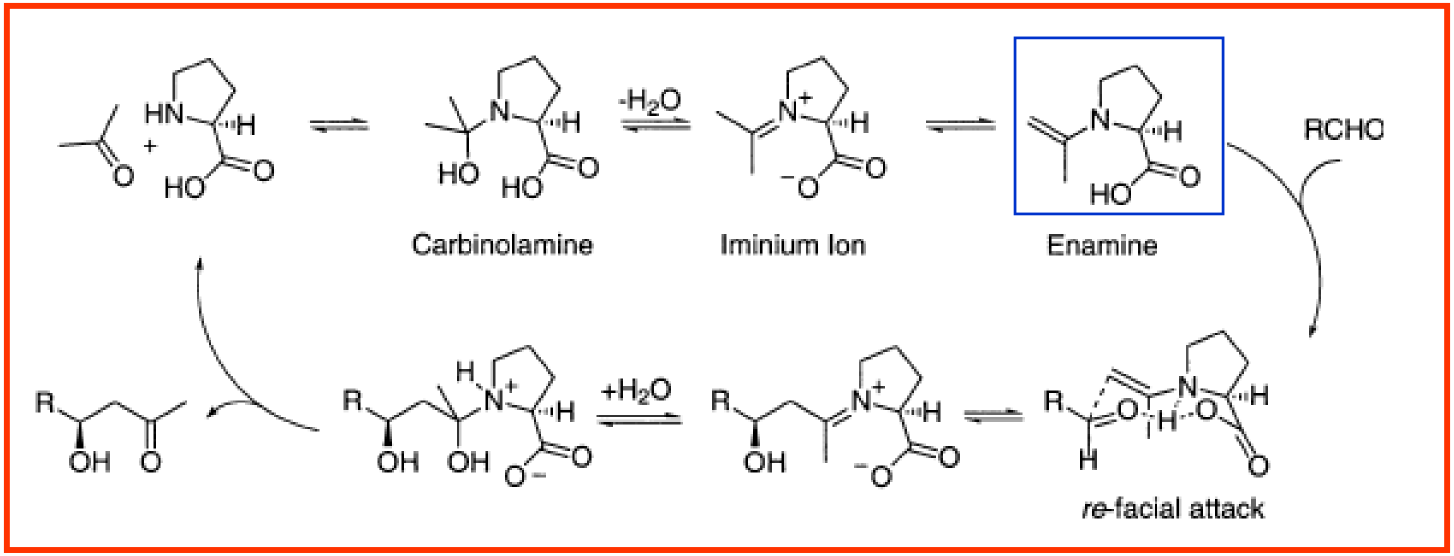
First Example of Proline-Catalyzed Direct Asymmetric Intermolecular Aldol Reactions



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}

List, B. *JACS* **2000**, *122,* 2395.

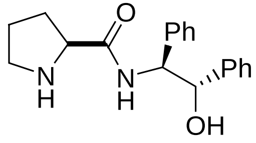
Proposed Mechanism for the Directed Intermolecular Aldol Reaction



- Proline as a “micro-aldolase” which provides both the nucleophilic amino group and an acid/base cocatalysis in the form of the carboxylate
- Enamine intermediate is involved
- Enantiofacial selectivity is determined by Zimmerman-Traxler type TS

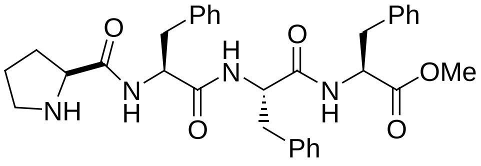
List, B. *JACS* **2000**, *122,* 2395.

Proline Analogues Used in Asymmetric Catalytic Direct Aldol Reactions

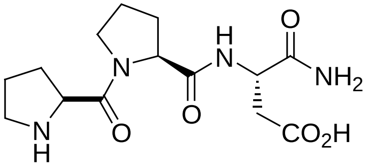


(**1**) Gong, L,-Z. *JACS* **2003**, *125*, 5262.
(5 mol %, 44->99% ee)

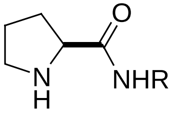
Proline containing di- and tripeptides:
Pro-Ala, Pro-Asp, Pro-Trp, Pro-Glu, Pro-Ser
Pro-Gly-Gly, Pro-His-Ala
List, . *SYNLETT* **2003**, *12*, 1901.
(30 mol %, 31-76% ee)



(**2**) Pro-Phe-Phe-Phe-OMe
Gong, L,-Z. *OL* **2004**, *6*, 2285.
(10-20 mol %, 84-96% ee)

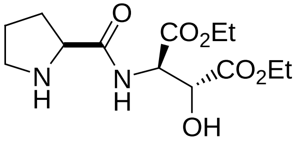


(**3**) H-L-Pro-L-Pro-L-Asp-NH_2
Wennemers, H. *OL* **2005**, *7*, 1101.
(1-5 mol %, up to 90% ee)



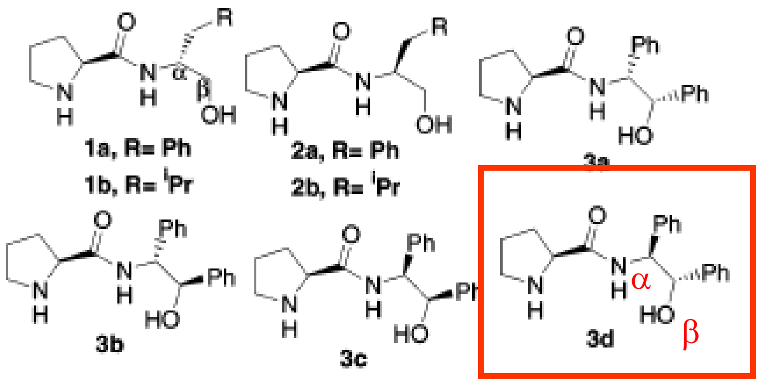
R = H, Bn, ^{t}Bu, Ar

(**4**) Gong, L,-Z. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755.

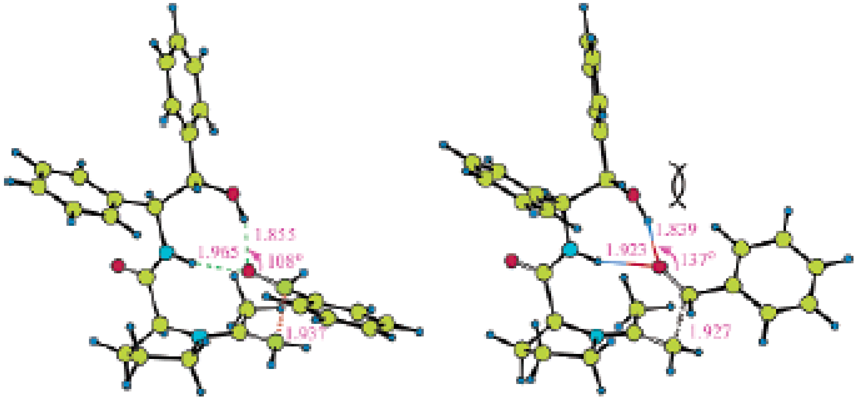


(**5**) Gong, L,-Z. *JACS* **2005**, *ASAP*
(2 mol %, 96-99% ee)

The Directed Intermolecular Aldol Reaction: Scope and Applications



1a, R= Ph
1b, R= ^{i}Pr
2a, R= Ph
2b, R= ^{i}Pr
3a
3b
3c
3d



TS1 (0.0) [0.0]   **TS2** (2.4) [3.0]

Figure 2. The calculated transition structure of the aldol reaction of benzaldehyde with acetone catalyzed by **3d**. The geometries were optimized with the HF/6-31G* method. The relative energies (kcal/mol) are with HF/6-31G* in ( ) and B3LYP/6-31G** in [ ].

Table 2. Direct Aldol Reactions of Acetone with Aldehydes by Chiral Organic Catalyst **3d**[a]

entry	product	R	yield (%)[b]	ee (%)[c]
1	4a	4-NO_2Ph	66	93
2	4b	4-BrPh	77	90
3	4c	4-ClPh	75	93
4	4d	2-ClPh	83	85
5	4e	Ph	51	83
6	4f	α-naphthyl	76	81
7	4g	*β*-naphthyl	93	84
8	4h	4-MePh	48	84
9	4i	3-NO_2Ph	63	87
10	4j	*c*-C_6H_{11}	85	97
11	4k	*i*-Pr	43	98
12	4l	*t*-Bu	51	>99
13	4m	*n*-Pr	17	87[d]
14	4n	*n*-Bu	12	86[d]
15	4j	*c*-C_6H_{11}	77	98[e]
16	4j	*c*-C_6H_{11}	48	98[f]

- (S)-configurations of C-α and C-β enhanced the enantioselectivity
- Decrease of the reaction temperature also increased the enantioselectivity

Gong, L.-Z. *JACS* **2003**, *125*, 5262.

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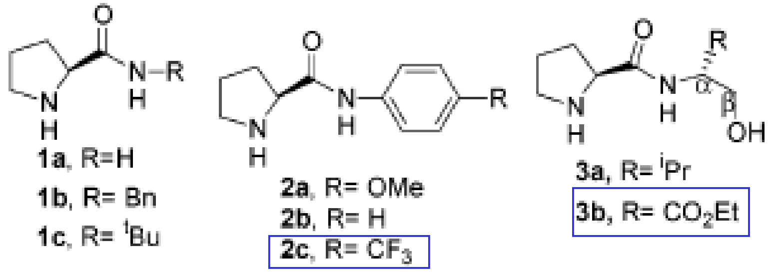

1a, R=H
1b, R= Bn
1c, R= ^{t}Bu

2a, R= OMe
2b, R= H
2c, R= CF_3

3a, R= ^{i}Pr
3b, R= CO_2Et

Figure 1. L-Proline amides used for direct Aldol reactions previously.[9b]

Table 1. The Direct Aldol Reaction of *p*-Nitrobenzaldehyde with Acetone Catalyzed by Organocatalysts **1**–**3**[9b]

entry	organo-catalyst	yield (%)[b]	ee (%)[c]	entry	organo-catalyst	yield (%)[b]	ee (%)[c]
1	**1a**	80	30	5	**2b**	88	37
2	**1b**	82	21	6	**2c**	88	45
3	**1c**	55	15	7	**3a**	78	33
4	**2a**	78	31	8	**3b**	63	61

[a] The reaction was carried out in neat acetone with a concentration of 0.5 M. [b] Isolated yield based on the aldehyde. [c] The ee values were determined by HPLC, and the configuration was assigned as *R* by comparison of retention times.

- Catalysts with strong electron withdrawing groups enhanced the enantioselectivity
- The enhancement is likely due to the electron-withdrawing nature that makes the N-H more acidic for the hydrogen bond in the transition state

Gong, L.-Z. *JACS* **2003**, *125*, 5262.
Gong, L.-Z. *JACS* **2005**, *ASAP*.

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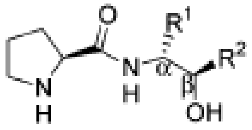
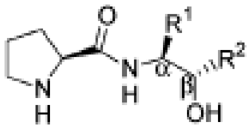
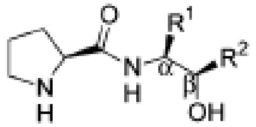


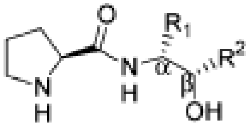
4a, R^1= R^2= *c*-C_6H_{11}
4b, R^1= R^2= Ph
4c, R^1= CO^{2}Et, R^2= Me
4d, R$_1$=R$_2$= CO_2Et



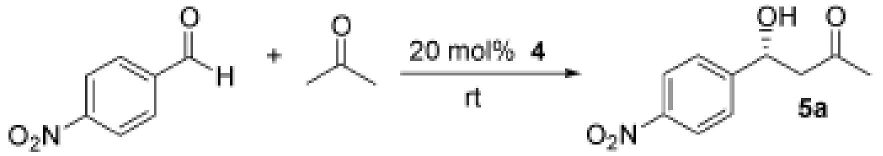
4e, R^1= R^2= *c*-C_6H_{11}
4f, R^1= R^2= Ph
4g, R$_1$=R$_2$= CO_2Et



4h, R^1= R^2= *c*-C_6H_{11}
4i, R^1= R^2= Ph
4j, R$_1$=R$_2$= CO_2Et



4k, R^1= R^2= *c*-C_6H_{11}
4l, R^1= R^2= Ph
4m, R$_1$=R$_2$= CO_2Et



entry	organo-catalyst	yield (%)[b]	ee (%)[c]
1	4a	51	15
2	4b	77	44[d]
3	4c	76	67[d]
4	4d	81	72[e]
5	4e	53	15
6	4f	89	69[d]
7	4g	85	87[e]
8	4h	59	12
9	4i	76	64[d]
10	4j	81	75[e]
11	4k	75	17
12	4l	63	49[d]
13	4m	80	67[e]
14	4g	60	95[e,f]
15	4g	62	99[e,g]

[a] Unless otherwise specified, the reaction was carried out in the presence of 20 mol % catalyst. [b] Isolated yield. [c] Determined by HPLC (see Supporting Information). [d] The result was reported in ref 9. [e] In the presence of 2 mol % catalyst. [f] The reaction was performed at 0 °C. [g] The reaction was performed at −25 °C.

- The electron nature of the catalyst substituent affects the enantioselectivity of the reactions

- The enantioselectivity is significantly increased by lowering the reaction temperature (rt vs 0 ^oC vs –25 ^oC, entries 7, 14, and 15, respectively)

Gong, L.-Z. *JACS* **2005**, *ASAP*.

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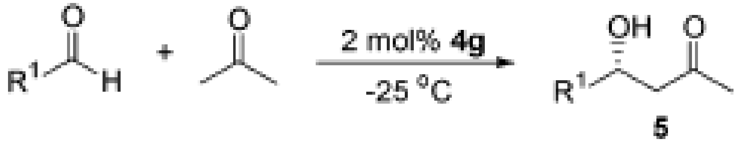
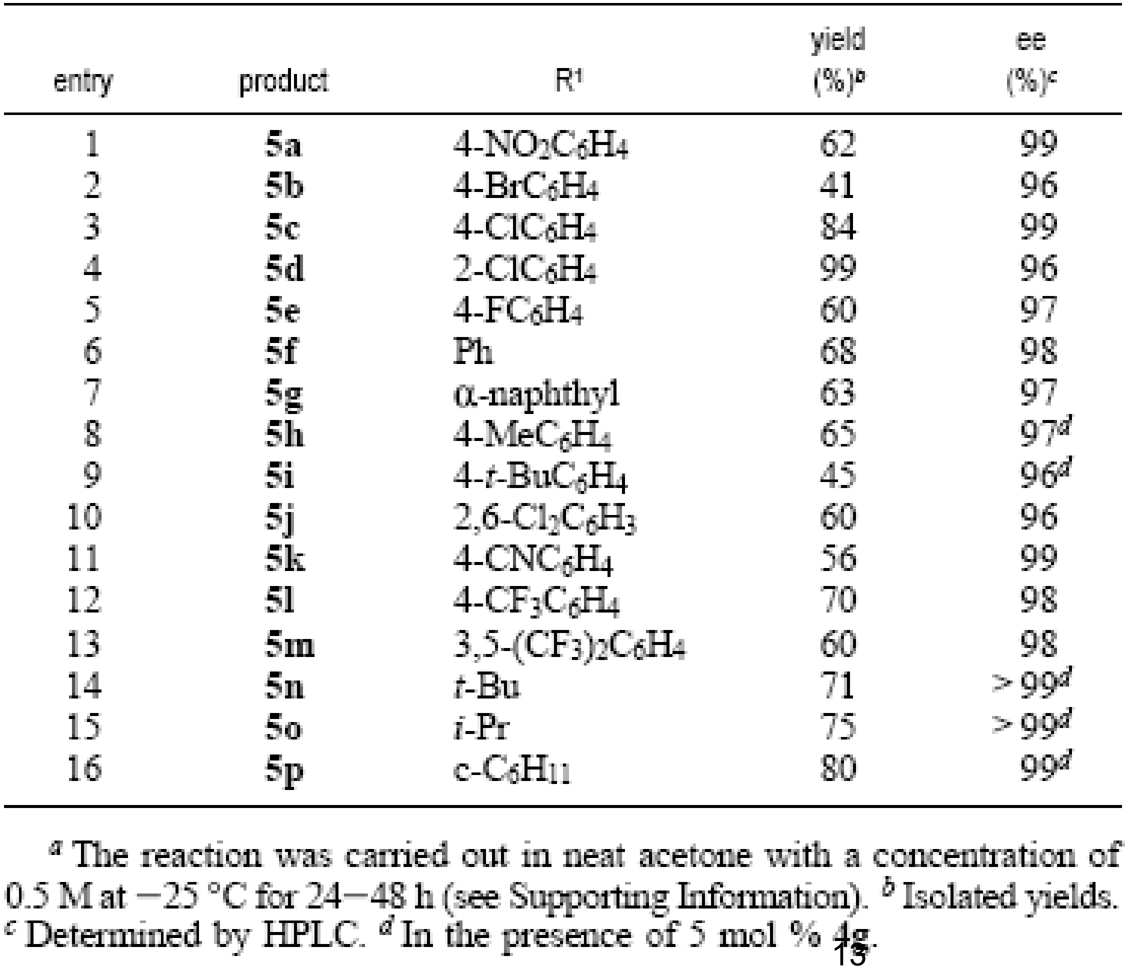
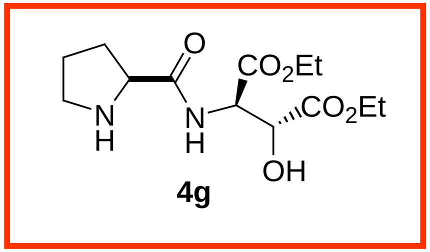




entry	product	R^1	yield (%)[b]	ee (%)[c]
1	**5a**	4-$NO_2C_6H_4$	62	99
2	**5b**	4-BrC_6H_4	41	96
3	**5c**	4-ClC_6H_4	84	99
4	**5d**	2-ClC_6H_4	99	96
5	**5e**	4-FC_6H_4	60	97
6	**5f**	Ph	68	98
7	**5g**	α-naphthyl	63	97
8	**5h**	4-MeC_6H_4	65	97[d]
9	**5i**	4-*t*-BuC_6H_4	45	96[d]
10	**5j**	2,6-$Cl_2C_6H_3$	60	96
11	**5k**	4-CNC_6H_4	56	99
12	**5l**	4-$CF_3C_6H_4$	70	98
13	**5m**	3,5-$(CF_3)_2C_6H_4$	60	98
14	**5n**	*t*-Bu	71	>99[d]
15	**5o**	*i*-Pr	75	>99[d]
16	**5p**	c-C_6H_{11}	80	99[d]

[a] The reaction was carried out in neat acetone with a concentration of 0.5 M at −25 °C for 24−48 h (see Supporting Information). [b] Isolated yields. [c] Determined by HPLC. [d] In the presence of 5 mol % **4g**.

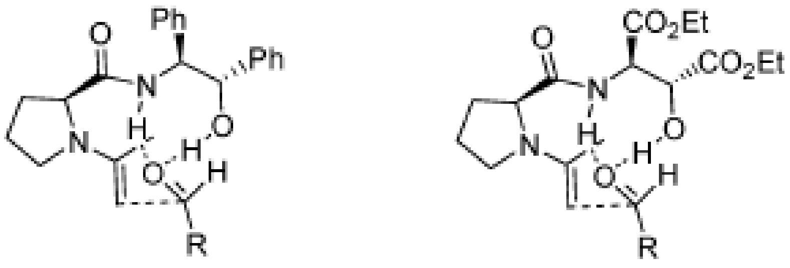


4g

- Aldol products were formed with very high enantioselectivities ranging from 96% to 99% ee under the optimal condition

Gong, L.-Z. *JACS* **2005**, *ASAP*.

Plausible Transition State



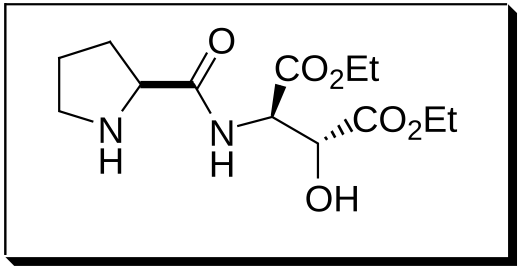
TS1 TS 2

- According to the DFT calculation, the double hydrogen bond of the TS2 is stronger than the one in TS1 might from due to the strong electron-withdrawing nature of the esters

Gong, L.-Z. *JACS* **2005**, *ASAP*.

Summary

- ⇨ A family of L-proline amides was screened for their ability to catalyze the direct aldol reactions
- ⇨ Catalysts with strong electron withdrawing groups showed enhanced catalytic activity and enantioselectivity
- ⇨ The direct aldol reactions of a wide range of aldehydes with acetone resulted excellent enantioselectivities (96-99% ee) in the presence of 2 mol % of optimized catalyst



Relevent reviews

Jarvo, E. R. and Miller, S. J. *Tetrahedron* **2002**, *58*, 2481.
List, B. Miller, S. J. *Tetrahedron* **2002**, *58*, 5573.
Miller, S. J. *Acc. Chem. Res*. **2004,** *37*, 601.