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Highly Enantioselective Direct Aldol Reaction Catalyzed by Organic Molecules

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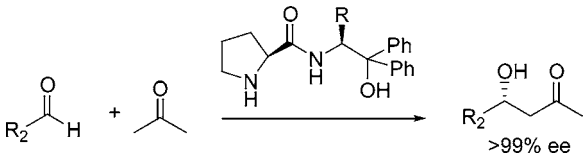
ABSTRACT



We have demonstrated that a new class of L-proline-based organic compounds catalyzed the direct aldol reaction between aldehydes and acetone to provide *β*-hydroxy ketones in good yields. The reaction is efficient, and 5–10 mol % of the catalyst and excellent enantioselectivities (97–99% ee) were obtained in both aromatic and aliphatic aldehydes. The presence of a *gem*-diphenyl group at the *β*-carbon is necessary for high enantioselectivity.

An enantioselective C−C bond formation reaction catalyzed by chiral organic molecules (asymmetric organocatalysis)[1] has become an important area of research in organic synthesis. Aldol is one such reaction where a great emphasis has been given to the design of new chiral organocatalysts[2] where, besides avoiding transition metals, the reaction can directly be done by taking an aldol donor and acceptor.[3] In this direct aldol reaction, there is no need for preactivation of carbonyl compounds as is done in the Mukaiyama aldol reaction.[4,5] The major breakthrough came from a finding by List,[6] Barbas III,[7] and co-workers that L-proline could act as a catalyst in intermolecular direct aldol reaction where L-proline functions as a "microaldolase" similar to the Type I aldolase enzyme.[8] Since then, L-proline[9] and its derivatives[10] have been evaluated for use in enantioselective direct aldol reaction. The reaction is presumed to proceed via an enamine intermediate. Initially, the enantiofacial selectivity was explained with a metal-free version of the Zimmerman−Traxler-type transition-state model having a tricyclic hydrogen-bonded framework.[6a] Later, on the basis of computational study, it was postulated that the nitrogen of L-proline may not participate in hydrogen bonding with the carboxylic hydrogen.[11] According to the model for proline and its

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derivatives, the transition state is stabilized through other hydrogen bondings. Therefore, a small change in the pK_a value of organic compounds will affect its catalytic activity and selectivity. It is a great challenge to organic chemists to find a suitable compound with an optimal pK_a so that excellent enantioselectivity can be obtained. We have designed a small class of L-proline-based chiral organic molecules having a *gem*-diphenyl group which played a key role in realizing the goal. Herein, we report that these organic compounds can be used with low catalyst loading (5 mol %) to give an excellent enantioselectivity (>99% ee) in the direct aldol reaction.

The organic molecules **1a**−**1m** (Figure 1) were synthesized from L-proline and corresponding β-amino alcohols

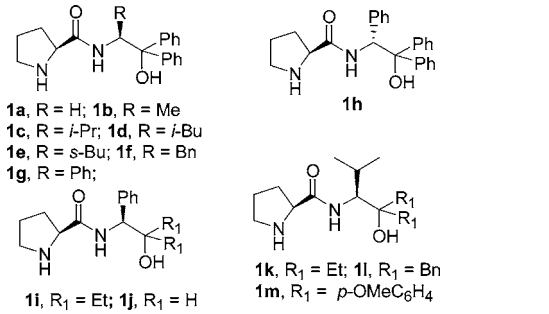


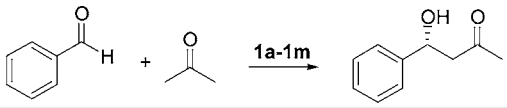
Figure 1. Organocatalysts evaluated in the direct aldol reaction.

by a standard reaction sequence (see Supporting Information). These were evaluated for direct aldol reaction between benzaldehyde and acetone (Table 1). The compounds **1a**−**1g** had different substituents (R) with (*S*)-configuration at the α-carbon while keeping a *gem*-diphenyl group constant at the β-carbon. These organic compounds were used in 10 mol %, and the reaction was studied at different temperatures. The compound **1a** (R = H), devoid of chirality at both the α- and β-carbon atoms, catalyzed the aldol reaction quite effectively, and 89% ee was obtained at −40 °C (entry 1). The catalyst **1b** (R = Me) induced higher enantioselectivity (92% ee) under the same conditions (entry 3). However, at room temperature, although the reaction was complete in 3 h, the ee was slightly lower (entry 2). The catalyst **1c** (R = *i*-Pr) was found to be insensitive to temperature as the ee's did not vary much (89−93% ee) from room temperature to −40 °C (entries 4−6). The catalyst **1d** (R = *i*-Bu) was found to be superior as the reaction was complete in 3 h at room temperature (entry 7) with modest yield (68%) and high enantioselectivity (93% ee).

At 0 °C, the same reactions took 14 h for completion, but the yield and ee of both could be improved (entry 8; 72% yield, 98% ee). On lowering the temperature further to −40 °C, more than 99% ee was obtained in the same reaction (entry 9). The enantioselectivity was moderate with the compound **1e** (R = *s*-Bu; entries 10 and 11) and high with **1f** (R = Bn; entries 12 and 13). The compound **1g** (R = Ph) catalyzed the reaction very efficiently and gave the aldol product in 77% yield and 99% ee at −40 °C (entry 16). The advantage of this catalyst is that it is effective even with low catalyst loading (5 mol %).

It is worth mentioning here that when the configuration of the phenyl substituent at the α-carbon was changed to (*R*) as in the case of **1h** and the reaction was compared with **1g** at room temperature, the enantioselectivity dropped from 84% to 24% (entry 14 vs entry 17). To see the effect of *gem*-diphenyl groups (R_1) at the β-carbon of **1g**, it was replaced by ethyl (**1i**) and H (**1j**) and then evaluated for the aldol reaction. These turned out to be poor in inducing asymmetric induction in the reaction (entries 18 and 19, 64% ee with **1i**; 42% ee with **1j**). The importance of *gem*-diphenyl groups at the β-carbon is further seen in compounds **1k** (R_1 = Et) and **1l** (R_1 = Bn) which gave poor asymmetric induction (entries 20−23; 36−43% ee) compared to **1c** (R_1 = Ph) that gave 89−93% ee (entries 4−6) in the same reaction. On having an electron-donating group in the para position of the phenyl groups as in the case of **1m**, the

Table 1. Direct Aldol Reaction Catalyzed by Organocatalysts **1a**−**1m**[a]



entry	catalyst	temp (°C)	time (h)	yield (%)	ee (%)[b]
1	**1a**	-40	48	64	89
2	**1b**	rt	03	72	88
3	**1b**	-40	48	52	99
4	**1c**	rt	03	65	89
5	**1c**	0	07	65	93
6	**1c**	-40	26	62	92
7	**1d**	rt	03	68	92
8	**1d**	0	14	72	98
9	**1d**	-40	48	52	>99
10	**1e**	rt	03	65	65
11	**1e**	-40	24	55	79
12	**1f**	rt	03	69	92
13	**1f**	-40	48	53	95
14	**1g**	rt	06	71	84
15	**1g**	0	08	76	91
16	**1g**	-40	22	77	99
17	**1h**	rt	06	65	24
18	**1i**	-40	30	57	64
19	**1j**	-40	26	67	42
20	**1k**	rt	07	63	36
21	**1k**	-40	48	51	46
22	**1l**	rt	05	67	36
23	**1l**	-40	45	57	43
24	**1m**	0	06	67	59

[a] The reaction was carried out in neat acetone (1 M conc.) using 10 mol % of the catalyst except for the catalysts **1g**, **1i**, and **1j** which were used in 5 mol %. [b] The ee was determined by HPLC on chiral columns.

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effectiveness of the catalyst is lost (entry 24; 59% ee). These results indicate that it is not essential that phenyl groups at the β-carbon atom should have any particular stereochemistry to obtain high enantioselectivity.

The stereochemical outcome in the above direct aldol reaction catalyzed by **1** can be explained by a transition state (Figure 2), which is based on a previous model supported

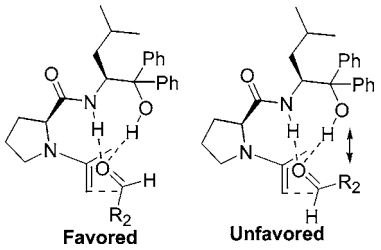
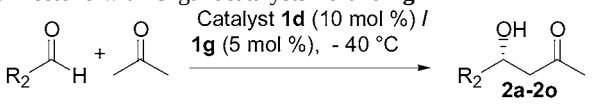


Figure 2. Transition-state models.

by DFT calculations.[10a] The aldehyde is activated by hydrogen bonding with the NH and OH of the catalyst in a manner that C−C bond formation takes place from its *re* face. The alternative *si* face is unfavored due to a nonbonding interaction between the R_2 group and the hydroxyl group. The presence of *gem*-diphenyl groups at the β-carbon restricts the conformation and makes the hydroxyl group a better hydrogen-bond donor. It also enhances solubility of the ligand in organic solvents.

From Table 1, it became clear that the organic compounds **1d** and **1g** are more efficient in inducing asymmetric induction in the aldol reaction of benzaldehyde and acetone. To increase the scope of the methodology, the aldol reaction was extended to several aromatic and aliphatic aldehydes and the results are summarized in Table 2. In all the cases, we got excellent enantioselectivities (97−99% ee). The catalyst **1d** appeared to be slightly superior to **1g** for inducing enantioselectivity in all the cases, especially in the case of an aliphatic aldehyde (entry 15).

Table 2. Direct Aldol Reaction between Various Aldehydes and Acetone with Organocatalysts **1d** and **1g**[a]



entry	R_2	product	yield (%)[b] 1d	yield (%)[b] 1g	ee (%)[c] 1d	ee (%)[c] 1g
1	Ph	**2a**	55	77	>99	99
2	4-ClC_6H_4	**2b**	62	88	>99	>99
3	4-FC_6H_4	**2c**	63	86	>99	96
4	3-ClC_6H_4	**2d**	62	78	>99	97
5	3-$OMeC_6H_4$	**2e**	59	70	>99	95
6	2-Cl-6-FC_6H_3	**2f**	67	72	>99	97
7	3-Cl-4-FC_6H_3	**2g**	65	72	99	97
8	4-$NO_2C_6H_4$	**2h**	70	78	99	85
9	3-MeC_6H_4	**2i**	61	71	99	97
10	3-FC_6H_4	**2j**	63	79	98	97
11	2,5-$F_2C_6H_3$	**2k**	69	73	98	95
12	2,3-$F_2C_6H_3$	**2l**	67	75	97	94
13	2-ClC_6H_4	**2m**	62	75	98	96
14	3-BrC_6H_4	**2n**	52	74	97	96
15	c-C_6H_{11}	**2o**	60	71	99	80

[a] The reaction was carried out in neat acetone with 1 M conc. at −40 °C for 24−48 h (see Supporting Information). [b] Isolated yield. [c] Determined by HPLC on chiral columns.

In summary, we have demonstrated that a new class of L-proline-based organic compounds catalyzed the direct aldol reaction between aldehydes and acetone to provide β-hydroxy ketones in good yields. The reaction is efficient with 5−10 mol % of the catalyst used, and excellent enantioselectivity (97−99% ee) was obtained in both aromatic and aliphatic aldehydes. The presence of a *gem*-diphenyl group at the β-carbon is necessary for high enantioselectivity. It is not essential to have a stereogenic center at the β-carbon atom as even unsubstituted catalyst **1a** gave high ee in the reaction. Other substituents (R) such as Me, *i*-Pr, *i*-Bu, *s*-Bu, Bn, and Ph with (*S*)-configuration did not show much difference in ee and chemical yield of the product. Among all these, **1d** (R = *i*-Bu) and **1g** (R = Ph) were found to give the best results.

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Note Added after ASAP Publication. The reference numbers were incorrectly cited in the text in the version published ASAP July 29, 2006; the corrected version was published ASAP August 2, 2006.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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