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(*S*,*S*,*S*)-Perhydroindolic acid: efficient catalyst for direct asymmetric aldol reaction from aromatic aldehydes

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Abstract—Enantioselective addition of ketones to aromatic aldehydes has been achieved with up to 88% enantiomeric excess, using the commercially available (*S*,*S*,*S*)-perhydroindolic acid catalyst.

1. Introduction

β-Hydroxycarbonyl and 1,3-diol units are frequently found in complex polyol substructures of natural products and have attracted much attention from organic chemists. The aldol reaction, which is considered as one of the most important carbon–carbon bond-forming reactions in organic synthesis, can lead to these units by reacting a ketone and an aldehyde. Its usefulness for building up natural products[1] has promoted the rapid evolution of efficient chiral catalysts.[2,3] An organocatalytic approach utilizing L-proline as a catalyst for an intramolecular aldol cyclization was reported around 30 years ago.[4] Recently List et al. demonstrated that L-proline could also mediate the intermolecular aldol reaction directly from ketones and aldehydes.[5] Since then, L-proline and its structural analogues[6–9] have been evaluated in asymmetric catalytic direct intermolecular aldol reactions. Although impressive results were observed for branched aliphatic aldehydes, only fair enantioselectivities were observed for the reaction of aromatic aldehydes with acetone either by L-proline[5] or its derivatives and structural analogues,[6–9] with the exception of some prolinamide derivatives,[13] a N-substituted proline amide derived from (1*S*,2*S*)-1,2-diphenylaminoethanol,[14] and a proline-derived *N*-sulfonylcarboxamine.[15] Moreover, fine tuning of the catalytic properties of proline is difficult as both the secondary amine and the acidic proton are essential for efficient catalysis. Aiming at exploring the potential of new amino acids in organocatalysis, we herein report (*S*,*S*,*S*)-perhydroindolic acid **1** as an efficient catalyst in aldol reaction between aromatic aldehydes and ketones.

2. Results and discussion

We initially studied the reaction of acetone with 4-nitrobenzaldehyde as a benchmark reaction with different perhydroindole derivatives **1**, **3**–**4** or indoline **2** (Scheme 1).

The reaction of **1** (10 mol %) in DMSO/acetone (2/5) with 4-nitrobenzaldehyde at room temperature for 43 h furnished the aldol product in 27% isolated yield (30% conversion by NMR analysis). After aqueous work-up, extraction and purification on silica gel, an enantiomeric excess of 80% in favor of the (*R*)-ketoalcohol was determined by HPLC analysis. Increasing the amount of catalyst to 30 mol % improved the isolated yield to 69% without changing the enantioselectivity. In the presence of only 2 mol % of amino acid **1**, the hydroxyketone was isolated in 81% ee but in a poor 13% isolated yield. These results show for the first time that a 4,5-disubstituted proline type derivative, the (*S*,*S*,*S*)-perhydroindolic acid **1**, can be an efficient organocatalyst for the asymmetric aldol reaction, which provides better enantioselectivities than proline itself.[5–12] In fact, under the same reaction conditions (i.e., 30 mol % of catalyst in DMSO at room temperature) with proline itself, the aldol product was observed in 68% conversion and 76% ee. Under the same reaction conditions, neither the (*S*)-indolic acid **2** nor the modified

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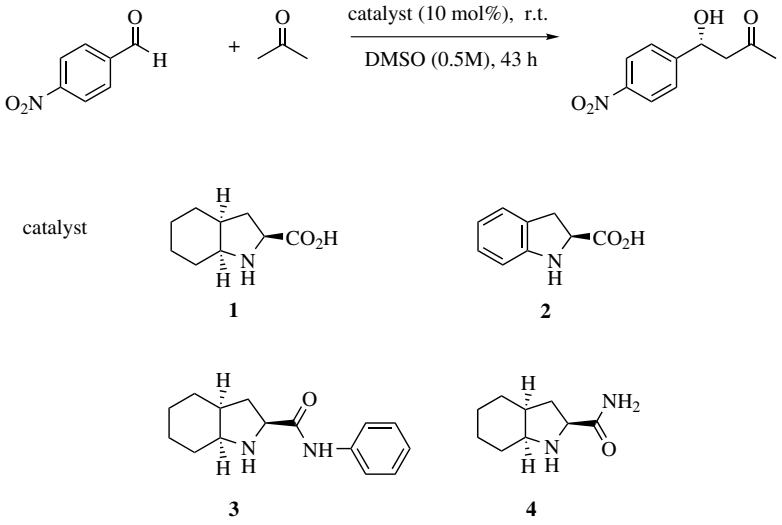
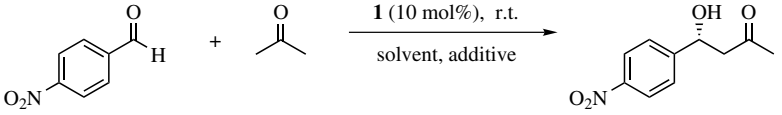


Scheme 1.

Table 1. Effect of solvents and additives in the aldol reaction[a]



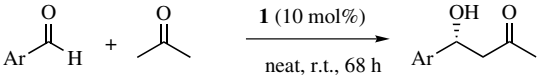
Entry	Time (h)	Solvent (M)	Additive (equiv)	Conversion[b] (%)	Yield[c] (%)	ee[d] (%)
1	75	—	—	**57**	**45**	**81**
2	67	DMSO (1)	—	35	33	**80**
3	43	DMSO (0.5)	—	30	27	**80**
4	68	DMSO (0.5)	H_2O (3)	34	32	74
5	68	DMSO (0.5)	H_2O (15)	67	50	50
6	43	THF (0.5)	—	23	14	69
7	68	THF (0.5)	H_2O (3)	18	17	61
8	68	THF (0.5)	H_2O (15)	46	25	13
9	68	DMF (0.5)	H_2O (15)	51	28	44
10	68	—	TFA (0.1)	21	19	61

[a] Conditions: 2 mmol of aldehyde, 56 mmol of acetone (28 equiv, 4 mL), 0.02 mmol of **1** at room temperature for 68 h.
[b] As determined by ^{1}H NMR spectroscopy.
[c] Isolated yield.
[d] Determined by HPLC analysis after purification.

perhydroindolic acid derivatives **3** and **4** led to the desired aldol compound.

In order to improve this catalytic system based on the activity of **1** (reactivity and selectivity), several solvents and additives were screened (Table 1). Throughout this study, we used 10 mol % of catalyst and 28 equiv of acetone. As reported in Table 1, DMSO was the solvent of choice in this reaction as it avoided the formation of by-products such as the α,β-unsaturated ketones (see conversion versus isolated yield in all the entries), and provided the best enantioselectivities (Table 1, entries 2 and 3). An alternative was to carry out the aldol reaction without any solvent. The enantioselectivity remained similar and the reactivity was slightly improved (Table 1, entries 1 and 2). Recently, Pihko,[16] Ward,[17] Yamamoto,[18] and Arvidsson[19] reported that water could bring a positive effect in the aldol reaction promoted by proline type deriva-

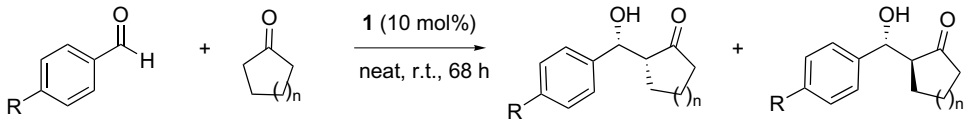
Table 2. Aldol reaction of acetone with various aromatic aldehydes[a]



Ar	Conversion[b] (%)	Yield[c] (%)	ee[d] (%)
C_6H_5	17	13	38
4-Me–C_6H_4	5	5	69
4-Br–C_6H_4	27	23	80
4-F–C_6H_4	30	27	73
4-CN–C_6H_4	69	56	77
4-NO_2–C_6H_4	57	45	81
4-CF_3–C_6H_4	64	52	85
2-NO_2–C_6H_4	74	73	87

[a] Conditions: 2 mmol of aldehyde, 56 mmol of acetone (28 equiv, 4 mL), 0.02 mmol of **1** at room temperature for 68 h.
[b] As determined by ^{1}H NMR spectroscopy.
[c] Isolated yield.
[d] Determined by HPLC analysis after purification.

Table 3. Aldol reaction of cyclic ketones with aromatic aldehydes[a]



R = CN, NO_2 *syn* *anti*

Entry	*n*	R	Conversion[b] (%)	Yield[c] (%)	*syn*/*anti*[b]	ee *syn*[d] (%)	ee *anti*[d] (%)
1	2	CN	ND	40	13/87	22	78
2	2[e]	CN	ND	ND	ND	51	88
3	2	NO_2	ND	54	17/83	4	52
4	2[e]	NO_2	50	ND	ND	70	78
5	1	CN	100	100	72/28	52	77
6	1[e]	CN	100	ND	ND	46	80
7	1	NO_2	100	95	62/38	48	66
8	1[e]	NO_2	100	ND	ND	46	64

[a] Conditions: 2 mmol of aldehyde, 56 mmol of acetone (28 equiv, 4 mL), 0.02 mmol of **1** at room temperature for 68 h.
[b] As determined by ^{1}H NMR spectroscopy.
[c] Isolated yield.
[d] Determined by HPLC analysis.
[e] The crude reaction was directly analyzed by chiral HPLC.

tives. However, in our catalytic system, water had a detrimental influence. The reaction rate did not improve while the enantioselectivity decreased dramatically by increasing the amount of water (entries 4–5 and 7–8).

Recent computational studies by Houk and co-workers[20] suggested that although the enantioselectivity could be determined at the aldol addition step, the rate-determining step could also be the formation of the enamine from the ketone and the amino group of the organocatalyst. This raises the possibility that certain acid or base additives might improve the overall rate of the reaction by promoting enamine formation. However, by adding trifluoroacetic acid, we were unable to improve the enantioselectivity or the rate of the reaction (Table 1, entry 11).

To test the substrate generality of this amino acid catalyst, we studied the reaction of various aromatic aldehydes with acetone under neat conditions at room temperature for 68 h. The results (Table 2) show that aldehydes bearing an electron withdrawing group at the *meta*- or *para*-position provided better conversions and yields than aldehydes bearing an electron donating group. In the same way, the enantioselectivities were slightly lower with electron rich aromatic aldehydes than with halogenated, cyano-, trifluoromethyl-, and nitrobenzaldehydes. However, these enantioselectivities compete with those reported with L-proline[5] or other simple amino acids.[6–12]

Cyclohexanone and cyclopentanone were used in this aldol reaction. Cyclohexanone was reacted with *para*-cyanobenzaldehyde and *para*-nitrobenzaldehyde to generate the corresponding aldol adducts in moderate isolated yields. The diastereomeric ratios are comparable, according to NMR analysis. Surprisingly, such aldol products can epimerize during purification as shown in Table 3, entries 1–4. Thus, after purification on silica gel, the enantiomeric excess of the *anti* isomer, arising from cyclohexanone and 4-nitrobenzaldehyde, decreased from 78% to 52% and the enantiomeric excess of the corresponding *syn* isomer dropped from 70% to 4% (Table 3, entries 3 and 4).

The reaction of cyclopentanone provided higher conversions and yields. With this ketone, no epimerization occurred during purification on silica gel (entries 5–8). The diastereomeric ratios and the enantioselectivities are slightly lower than with cyclohexanone (entries 1–4 and 5–8). However, it is worth noting that these results are still better than those obtained with other organocatalysts.[16–18]

3. Conclusion

In conclusion, we have shown that perhydroindolic acid **1** is an efficient organocatalyst that leads to good enantioselectivities in aldol reactions of ketones and aromatic aldehydes. Although its catalytic efficiency is unsatisfactory at the moment, this new catalyst incorporating two more stereogenic centers in the backbone competes with other proline derivatives, and other types of organocatalysts, in terms of enantioselectivity, and opens up new perspectives in organocatalysis.

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