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Application of high pressure, induced by water freezing, to the direct asymmetric aldol reaction

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Abstract—High pressure, induced by water freezing, has been successfully applied to the direct catalytic asymmetric aldol reaction, in which higher yield and better enantioselectivity can be realized than in the reaction at room temperature under 0.1 MPa.

High pressure is one of the indispensable tools in organic synthesis,[1] because many reactions are known to be accelerated under high pressure. In spite of its usefulness, it is not widely used in the average laboratory due to the need for special apparatus. Recently we have developed a new method for the generation of high pressure using an autoclave and a household electric refrigerator. As the volume of water increases by about 10% on freezing, a high pressure, up to 200 MPa, can be easily created when water is frozen in a sealed autoclave at −20 °C. Hayakawa et al. elegantly employed this high pressure for the inactivation of microorganisms.[2] As a first application of this high pressure to organic synthesis, we have developed a high-yield Michael reaction of alcohols and α, β-unsaturated ketones in the presence of a catalytic amount of DMAP and $LiClO_4$.[3] The Baylis–Hillman reaction was also found to be accelerated under this high pressure.[4]

High pressure induced by water freezing has two unique features: one is that a high pressure of up to 200 MPa can be easily obtained, and the other is that low temperature (−20 °C) experiments under high pressure can be carried out. We applied our high pressure system to the direct catalytic asymmetric three-component List–Barbas–Mannich reaction, in which higher yield and better enantioselectivity can be realized than in the reaction at room temperature under 0.1 MPa, due to the high pressure and low temperature.[5]

The direct asymmetric catalytic aldol reaction is one of the most important carbon–carbon bond forming reactions, and excellent results for it have recently been published;[6,7] one of which is an elegant, proline-mediated aldol reaction between acetone and aldehydes, by List and co-workers[7] As the reaction is synthetically useful, we applied our high pressure system to it, expecting a higher enantioselectivity due to the lower reaction temperature, which will be disclosed in this paper.

A reaction of *p*-nitrobenzaldehyde and acetone was selected as a model. First, we carried out the reaction under the same conditions as used by List, Barbas and co-workers[7a,c] (room temperature, 0.1 MPa, 68%, 76% ee, Table 1, entry 1), our results giving slightly decreased yield and enantioselectivity (63%, 69% ee, entry 2). As pointed out by List, Barbas and co-workers[7a,c] the dehydration product of the aldol, 4-(*p*-nitrophenyl)-3-butene-2-one, was the side product, which we isolated in 15% yield. When the same reaction was carried out at −20 °C and ambient pressure, the enantioselectivity was increased by up to 75% ee with a slight decrease of yield (57%) and without formation of α, β-unsaturated ketone (entry 3).

Induced pressure by water freezing, however, accelerates the reaction to provide the aldol at a good yield (75%) and with good enantioselectivity (75% ee), with a small amount of formation of α, β-unsaturated ketone (entry 4). As the reaction temperature decreases, a higher the

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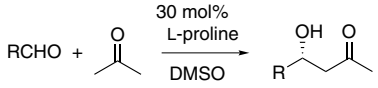
Table 1. The aldol reaction of various aldehyde and acetone catalyzed by L-proline at ambient pressure and high pressure induced by water freezing[a]

Entry	Aldehyde	Pressure (MPa)	Temperature (°C)	Time (h)	Aldol[b] (%)	Ee of aldol (%)	α, β-Enone[c] (%)	SM[d] (%)
1[e]	*p*-Nitrobenzaldehyde	0.1	23		68	76[f]		
2	*p*-Nitrobenzaldehyde	0.1	23	19	63	69[f]	15	<2
3	*p*-Nitrobenzaldehyde	0.1	−20	19	57	75[f]	<2	30
4	*p*-Nitrobenzaldehyde	200	−20	19	75	75[f]	3	20
5[e]	*o*-Chlorobenzaldehyde	0.1	23		94	69[g]		
6	*o*-Chlorobenzaldehyde	0.1	23	18	95	65[g]	<2	<2
7	*o*-Chlorobenzaldehyde	0.1	−20	17	95	72[g]	<2	<2
8	*o*-Chlorobenzaldehyde	200	−20	18	96	70[g]	<2	<2
9[e]	*p*-Bromobenzaldehyde	0.1	23		75	65[g]		
10	*p*-Bromobenzaldehyde	0.1	23	19	53	70[g]	15	<2
11	*p*-Bromobenzaldehyde	0.1	−20	19	41	76[g]	4	49
12	*p*-Bromobenzaldehyde	200	−20	19	65	75[g]	5	20
13[e]	Benzaldehyde	0.1	23		62	60[g]		
14	Benzaldehyde	0.1	23	24	62	69[g]	28	<2
15	Benzaldehyde	0.1	−20	24	40	78[g]	8	46
16	Benzaldehyde	200	−20	24	78	75[g]	15	5
17[e]	2-Naphthaldehyde	0.1	23		54	77[h]		
18	2-Naphthaldehyde	0.1	23	24	51	74[h]	27	<2
19	2-Naphthaldehyde	0.1	−20	22	32	82[h]	4	60
20	2-Naphthaldehyde	200	−20	24	67	80[h]	8	21
21	*p*-Anisaldehyde	0.1	23	24	33	65[g]	48	18
22	*p*-Anisaldehyde	0.1	23	45	31	59[g]	65	<2
23	*p*-Anisaldehyde	0.1	−20	49	6	77[g]	<2	92
24	*p*-Anisaldehyde	200	−20	24	12	82[g]	2	80
25	*p*-Anisaldehyde	200	−20	66	30	76[g]	11	40
26[e]	Cyclohexanecarboxaldehyde	0.1	23		68	76[g]		
27	Cyclohexanecarboxaldehyde	0.1	23	16	46	88[g]	32	<2
28	Cyclohexanecarboxaldehyde	0.1	−20	72	6	90[g]	<2	90
29	Cyclohexanecarboxaldehyde	200	−20	72	21	96[g]	<2	70

[a] The molar ratio, aldehyde/acetone/L-proline = 1:27:0.3, DMSO was used as a solvent.
[b] Yield of aldol.
[c] Yield of the dehydrated α, β-unsaturated ketone.
[d] Yield of the recovered starting material.
[e] Data of Ref. 7c.
[f] Chiral HPLC: Chiralcel AD-RH, CH_3CN/H_2O = 30:70.
[g] Chiral HPLC: Chiralcel AD-H, hexane/^{i}PrOH = 30:1.
[h] Chiral HPLC: Chiralcel AD-H, hexane/^{i}PrOH = 12:1.

enantioselectivity is realized. At lower temperatures, the reaction does not proceed smoothly, reducing the chemical yield. Under our high-pressure conditions, however, the reaction still proceeds efficiently at lower temperatures, due to the high pressure, affording the same chemical yield with higher enantioselectivity than those for the reactions carried at room temperature and ambient pressure. Moreover, the side reaction of dehydration is suppressed, thereby giving a better conversion yield at −20 °C (Scheme 1).

The model reaction of *p*-nitrobenzaldehyde indicates the effectiveness of the high pressure induced by water freezing, and the generality of this finding is examined with a variety of aldehydes, which are summarized in Table 1. As *o*-chlorobenzaldehyde is found to be an exceptionally reactive aldol acceptor, it reacts with acetone at ambient pressure, both at room temperature and at −20 °C, affording the adduct in excellent yield with high enantioselectivity (entries 5–8). It is not necessary to employ the high pressure method with this substance. As for *p*-bromobenzaldehyde, an electron-deficient aldehyde, better enantioselectivity and yield under high pressure were obtained as those for the reaction at room temperature and ambient pressure (entries 9–12). While α, β-unsaturated ketones were formed in substantial amounts in the reactions of benzaldehyde and 2-naphthaldehyde at room temperature and ambient pressure, the formation of these side products was reduced with an increase of enantioselectivity under high pressure (entries 13–20). Cyclohexanecarboxaldehyde, an aliphatic aldehyde, reacts very slowly at −20 °C under 0.1 MPa, affording the aldol in only 6% yield with high optical purity (entry 28). Under high pressure, the yield was increased to 21% with excellent enantioselectivity (96% ee) (entry 29), in which dehydration, a major side reaction at room temperature and ambient pressure, was completely suppressed.

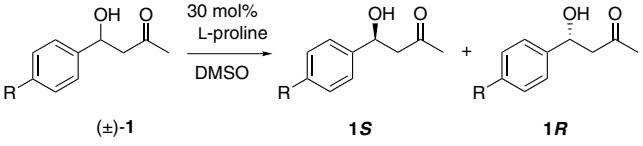


Scheme 1. Proline catalyzed direct asymmetric aldol reaction.

As for *p*-anisaldehyde, an electron-rich aldehyde, dehydrated ketone is the major product at room temperature

and ambient pressure, and the reaction scarcely proceeds at −20 °C and ambient pressure (entries 21–23). On the other hand, the reaction is clean under high pressure, affording the aldol in 30% yield with 76% ee, with recovery of the starting material at 40%, indicating a good conversion yield (entry 25). As for the enantioselectivity, the largest difference (11% ee) between the reactions at ambient and high pressure was observed (entries 21 and 25). In this aldol reaction of *p*-anisaldehyde at ambient pressure, a marked decrease in the optical purity of the aldol was observed when the reaction was carried out for a longer time, and there was an increase in the dehydrated product (entries 21 and 22). As these results strongly suggest kinetic resolution of the aldol, the kinetic resolution of racemic aldol derived from nitrobenzaldehyde, benzaldehyde, and *p*-anisaldehyde was investigated (Scheme 2).

When racemic aldol (±)-**1** was treated with 30 mol% of L-proline in DMSO at room temperature and ambient pressure, not only dehydration reaction but also retro-aldol reaction proceeded, with the recovery of the starting material, the aldol, the optical purity of which is summarized in Table 2. Kinetic resolution occurred in all the aldols derived from both electron-rich and electron-deficient aldehydes, though the decomposition rate of the aldol was dependent on the substrate: The dehydration and retro-aldol reactions of aldol derived from *p*-anisaldehyde proceeded, affording 4-(*p*-methoxyphenyl)-3-butene-2-one and *p*-anisaldehyde, while the starting material was recovered in 74% yield with 15% ee in 1 h and in 57% yield with 27% ee in 3 h, in which an opposite enantiomer of the aldol product was predominantly recovered. On the other hand, the reaction of the aldol derived from *p*-nitrobenzaldehyde was very slow, and the aldol was recovered in 80% yield with 14% ee and 64% yield with 30.8% ee after 24 and 64 h, respectively, in which 2,3-di-(*p*-nitrophenyl)-hexahydropyrrolo[2,1-*b*]oxazole[8] was isolated as one of side products, formed by the reaction of proline and *p*-nitrobenzaldehyde generated via retro-aldol reaction. Though



Scheme 2. Kinetic resolution of (±)-**1**.

K_{fast}/K_{slow} is not high, it was found that the kinetic resolution proceeds in reactions of all aldols and that the predominantly generated enantiomer in the aldol reaction is more rapidly converted via retro-aldol and dehydration reactions, which decreases the optical purity of the aldol adduct with a longer reaction time.

Recently, Kotsuki and co-workers applied high pressure to the same L-proline-mediated aldol reaction, in which a modest improvement in enantioselectivity was achieved, compared with the literature value at ambient pressure.[9] As the high pressure reaction was performed in neat acetone, in spite of the List's reference experiment being conducted in DMSO solution at 0.1 MPa,[7a,c] the improvement of the enantioselectivity should be ascribed not only to the pressure effect but also to the solvent effect. As the same level of enantioselectivity is obtained between the reactions at high pressure (200 MPa) and at ambient pressure at −20 °C, the increase of the enantioselectivity under high pressure induced by water-freezing should be ascribed not to the high pressure but to the lower temperature in our case.

In summary, we found that high pressure induced by water-freezing (200 MPa, −20 °C) can accelerate the direct asymmetric aldol reaction catalyzed by L-proline, affording aldols with better enantioselectivity (5–11% ee increase) compared with the reaction performed at room temperature and ambient pressure. Optical purity is increased owing to the low reaction temperature, while the increase of the chemical yield is ascribed to the high pressure. Another advantage of the high pressure induced by water freezing is its low temperature, which suppresses side reactions such as dehydration, enabling a good conversion yield. It was also found that kinetic resolution by L-proline proceeds in the aldols derived from both electron-rich and electron-deficient aldehydes.

Typical experimental procedure

The reaction was performed as follows: To a 1.8 mL Teflon tube was added *p*-nitrobenzaldehyde (30.2 mg, 0.20 mmol), L-proline (7.0 mg, 0.06 mmol), acetone (400 μL), and DMSO (1.4 mL), and the tube was capped with exclusion of air. This tube was placed in an autoclave, the inner capacity of which is about 100 mL, and

Table 2. Kinetic resolution of (±)-**1** catalyzed by L-proline[a]

Entry	R	Time (h)	Yield (%)[b]	**1*S*:1*R***		K_{fast}/K_{slow}
1	NO_2	24	80	57.0[c]	43.0[c]	4.1
2	NO_2	64	64	65.4[c]	34.6[c]	4.6
3	H	5	75	53.5[d]	46.5[d]	1.6
4	H	7	65	57.5[d]	42.5[d]	2.0
5	OMe	1	74	57.5[d]	42.5[d]	2.9
6	OMe	3	57	63.5[d]	36.5[d]	2.7

[a] Racemic (±)-**1** was treated with 30 mol% of L-proline in DMSO at room temperature and ambient pressure.
[b] Recovered starting material **1**.
[c] Chiral HPLC:Chiralcel AD-RH, CH_3CN/H_2O = 30:70.
[d] Chiral HPLC:Chiralcel AD-H, hexane/^{i}PrOH = 30:1.

equipped with a pressure monitor. The autoclave was completely filled with water, sealed tightly, and left in a household electric refrigerator at −20 °C. It was found that the internal pressure reached about 200 MPa after 12 h. After 19 h, the autoclave was taken out of the refrigerator, and the Teflon tube was removed from the autoclave. The reaction was quenched with phosphate buffer and the organic materials were extracted with ethyl acetate three times. After drying the organic phase, volatile organic materials were removed under reduced pressure, after which purification by thin layer chromatography (hexane/ethyl acetate = 1:1) afforded the aldol product in 75% yield (31.3 mg) with 4-(*p*-nitrophenyl)-3-butene-2-one (3%) and recovered *p*-nitrobenzaldehyde (20%). The enantiomeric excess of the aldol is 75%, which was determined by chiral HPLC analysis.

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