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Application of High Pressure Induced by Water-Freezing to the Direct Catalytic Asymmetric Three-Component List–Barbas–Mannich Reaction

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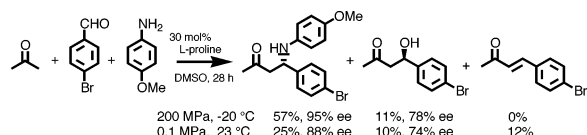
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High pressure is one of the factors that can effectively accelerate many organic transformations,¹ although its use in organic synthesis is rather limited owing to the necessity for special high-pressure apparatus. A new and easy method for generating high pressure is desirable. We have been investigating the novel method of high pressure induced by water-freezing, in which the high pressure (ca. 200 MPa) is easily achieved simply by freezing water (−20 °C) in a sealed autoclave.² The Michael reaction of alcohols with α,β -enones^{2a} and the Baylis–Hillmann reaction^{2b} have been effectively accelerated by this high pressure.

The Mannich reaction, on the other hand, is synthetically useful for the construction of nitrogen-containing molecules.³ Recently many excellent results have appeared describing catalytic asymmetric variants of this reaction,^{4–6} among which is an elegant, asymmetric, three-component Mannich reaction catalyzed by proline reported independently by List⁴ and Barbas.⁵ Despite the high enantioselectivity, there are limitations to List's reaction: Yields are generally insufficient when acetone is used as the Mannich donor, while the Mannich acceptor should be electron-deficient and highly reactive.

In this communication, we describe how our newly developed, high-pressure method has been applied to the List–Barbas–Mannich reaction, in the expectation that the effects of both high pressure and low temperature would play pivotal roles; i.e. that the yield and enantioselectivity would be improved due to the negative activation volume of the three-component coupling reaction and the lower temperature, respectively.

The Mannich reaction of *p*-bromobenzaldehyde, *p*-anisidine, and acetone was investigated under high-pressure induced by water-freezing, and it was found that the Mannich and aldol adducts were obtained in 57% yield with 95% ee, and in 11% yield with 78% ee, respectively.⁷ When the same reaction was performed under ambient pressure at room temperature, the reaction proceeded slowly, affording the Mannich adduct in 25% yield with 88% ee, the aldol product in 10% yield with 74% ee, and 4-(*p*-bromophenyl)-3-butene-2-one, the dehydrated product, in 12% yield.



As the reaction under high pressure gave the Mannich product in better yield and enantioselectivity without concomitant formation of the α,β -enone, the present high-pressure method has been applied to other aldehydes to investigate the generality of the reaction, the results being summarized in Table 1. As some of the Mannich

Table 1. Mannich Reaction of Various Aldehydes, *p*-Anisidine, and Acetone Catalyzed by L-Proline under Ambient Pressure and High Pressure Induced by Water-Freezing^a

entry	aldehyde	MPa	°C	h	% ^b	%ee
1 ^c	<i>p</i> -nitrobenzaldehyde	0.1	23		50 ^d	94
2	<i>p</i> -nitrobenzaldehyde	0.1	23	12	20 ^d	90 ^f
3	<i>p</i> -nitrobenzaldehyde	0.1	−20	12	5 ^d	98 ^f
4	<i>p</i> -nitrobenzaldehyde	200	−20	12	58 ^d	91 ^f
5	<i>p</i> -bromobenzaldehyde	0.1	23	28	25 ^e	88 ^g
6	<i>p</i> -bromobenzaldehyde	200	−20	28	57 ^e	95 ^g
7	benzaldehyde	0.1	23	72	12 ^e	79 ^g
8	benzaldehyde	200	−20	72	99 ^e	93 ^g
9	1-naphthaldehyde	0.1	23	48	14 ^d	86 ^f
10	1-naphthaldehyde	200	−20	48	67 ^d	93 ^f
11 ^c	2-naphthaldehyde	0.1	23		35 ^d	96
12	2-naphthaldehyde	0.1	23	24	15 ^d	89 ^f
13	2-naphthaldehyde	200	−20	24	64 ^d	91 ^f
14	<i>o</i> -anisaldehyde	0.1	23	24	25 ^e	92 ^g
15	<i>o</i> -anisaldehyde	200	−20	24	61 ^e	97 ^g
16	<i>m</i> -anisaldehyde	0.1	23	96	14 ^e	63 ^g
17	<i>m</i> -anisaldehyde	200	−20	96	83 ^e	97 ^g
18	<i>p</i> -anisaldehyde	0.1	23	96	0	
19	<i>p</i> -anisaldehyde	0.1	40	4	20 ^e	54 ^g
20	<i>p</i> -anisaldehyde	200	−20	96	99 ^e	94 ^g
21	3,4-dimethoxybenzaldehyde	0.1	23	96	0	
22	3,4-dimethoxybenzaldehyde	200	−20	96	65 ^e	95 ^g
23	<i>N</i> -acetyl-(4-formyl)aniline	0.1	23	24	0	
24	<i>N</i> -acetyl-(4-formyl)aniline	200	−20	24	82 ^d	92 ^f
25	2-furalaldehyde	0.1	23	41	65 ^d	95 ^f
26	2-furalaldehyde	200	−20	41	95 ^d	>99 ^f
27	cyclohexylcarbaldehyde	0.1	23	40	23 ^d	4 ^f
28	cyclohexylcarbaldehyde	200	−20	40	90 ^d	84 ^f

^a The molar ratio of aldehyde:*p*-anisidine:L-proline = 1:1.1:0.3, DMSO was used as solvent. ^b Isolated yield. ^c Data of ref 4b. ^d The yield of the Mannich adduct. ^e The two-step yield of the amino alcohol derived from LiAlH₄-reduction of the labile Mannich adduct, see Supporting Information for details. ^f Enantiomeric excess was determined by chiral HPLC analysis of the Mannich adduct. ^g Enantiomeric excess was determined by chiral HPLC analysis of the *anti*-1,3-aminosilyl ether derived from the Mannich adduct by the following procedure: (1) reduction with LiAlH₄, (2) silylation with TBSOTf and 2,6-lutidine, (3) separation of the *anti*- from the *syn*-isomer. See the Supporting Information for details.

adducts are prone to racemize during purification, they were isolated as the corresponding amino alcohols after reduction with LiAlH₄.

For electron-deficient aldehydes such as *p*-nitro- and *p*-bromobenzaldehydes, the yield at room temperature under 0.1 MPa is only 20–25%, while it is 57–58% under water-freezing high-pressure conditions, when the optical purity is 91–95% ee (entries 2–6). At low temperature (−20 °C) under 0.1 MPa, the reaction proceeds very slowly, affording only a minute amount (5%) of the Mannich adduct in very high optical purity (98% ee) (entry 3). These results clearly indicate that high pressure decreases the optical purity⁸ but increases the reaction rate, while lowering the temperature decreases the reaction rate but increases the optical purity in the reaction of *p*-nitrobenzaldehyde.

The reactions of benzaldehyde, and 1- and 2-naphthaldehydes under water-freezing high-pressure conditions afford Mannich

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adducts in good yield (64–99%) with excellent enantiomeric excess (91–93% ee), in marked contrast to the reaction at room temperature under 0.1 MPa, in which low yields (12–15%) and decreased enantioselectivity (79–89% ee) are obtained (entries 7–13).

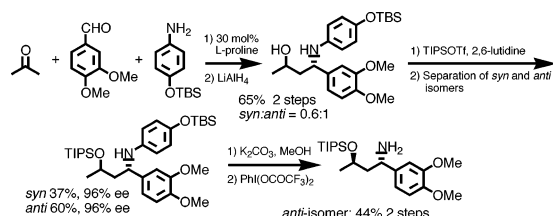
For electron-rich aldehydes, both yield and optical yield are low at room temperature under 0.1 MPa, and in particular, no reaction proceeds in the cases of *p*-anisaldehyde, 3,4-dimethoxybenzaldehyde, and *N*-acetyl-(4-formyl)aniline, while good yields (61–99%) and excellent enantioselectivities (92–97% ee) have been realized under water-freezing high-pressure conditions (entries 14–24). Higher temperature (40 °C) had no beneficial effect either on yield or enantioselectivity as the Mannich product of *p*-anisaldehyde was obtained in only 20% yield with lower enantiomeric excess (54% ee), along with several unidentified products (entry 19), while the Mannich adduct was obtained quantitatively and in 94% ee (entry 20), without any byproducts under our high-pressure conditions.

2-Furaldehyde and aliphatic aldehydes such as cyclohexylcarbaldehyde also react under water-freezing high-pressure conditions to give Mannich adducts in good yield and high optical purity (entries 25–28).

Generally a small amount of α,β -enone product was observed at ambient pressure, which was not formed at high pressure.

The predominant enantiomer formed is the same irrespective of pressure, and its absolute stereochemistry is expected to be the same as that determined by List and Barbas et al.^{4,5}

Next 4-*tert*-butyldimethylsiloxyaniline was employed instead of *p*-anisidine, because this *N*-substituent can be easily removed under mild oxidative conditions. 4-*tert*-Butyldimethylsiloxyaniline reacts even with highly electron-rich, unreactive, 3,4-dimethoxybenzaldehyde, affording the Mannich adduct with the same efficiency as does *p*-anisidine. After reduction with LiAlH_4 , protection of the hydroxyl group with TIPSOTf and 2,6-lutidine and separation of the *anti*- and *syn*-isomers, the *tert*-butyldimethylsiloxyphenyl moiety could be removed by our recently developed method using $\text{PhI}(\text{OCOCF}_3)_2$ ⁹ to afford the 1,3-amino alcohol, without affecting the electron-rich 3,4-dimethoxyphenyl moiety, while oxidative removal with CAN or DDQ gave complex mixtures.¹⁰ As selective reductions of 1,3-aminoketones to both *syn*- and *anti*-1,3-amino alcohols are known,¹¹ the present procedure is one practical method for the preparation of chiral 1,3-amino alcohols with either *syn*- or *anti*-stereochemistry.



In summary, the water-freezing induced-pressure method widens the scope and generality of the List–Barbas–Mannich reaction, giving both better yield and enantioselectivity, the increases of yield and optical purity being due to the high pressure and low temperature, respectively. High pressure and low temperature are both essential for the success of this asymmetric catalytic reaction; the former not only accelerates the reaction but also suppresses

side reactions such as the formation of α,β -enone. An especially noteworthy feature is that electron-rich, aromatic aldehydes, unreactive substrates under ambient pressure, can be successfully employed, affording the product in good yield. Moreover, by using 4-*tert*-butyldimethylsiloxyaniline, removal of the *N*-substituent can be successfully performed without affecting any other oxidatively labile, electron-rich aromatic groups, affording the *syn*- and *anti*-1,3-amino alcohols, both of which are synthetically useful, in high optical purity. Its high yield, excellent enantioselectivity, and operational simplicity, combined with the availability and low cost of the catalyst as well as the diversity of the accessible chemical structures, mean the present reaction will prove useful in synthesis.

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Supporting Information Available: Details of the experimental procedure and characterization and physical data of the products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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