The Direct and Enantioselective, One-Pot, Three-Component, Cross-Mannich Reaction of Aldehydes**

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Organocatalytic enantioselective reactions[1] have received great attention in recent years since the discovery by List and Barbas et al. of aldol reactions using proline as an organocatalyst.[2] These reactions are intermolecular variants of the Hajos–Parrish–Eder–Sauer–Wiechert reaction.[3] Such catalysts have now been successfully applied to other synthetically important transformations such as the Mannich[4–6] and Michael reactions,[7] α-aminations,[8] etc.[9]

The catalytic, asymmetric Mannich reaction is one of the most powerful methods for the construction of chiral nitrogen-containing molecules. Recently several excellent results were reported, some of which are based on catalytic asymmetric additions of a preformed enolate to aldimines.[10] Unlike such Mannich reactions of preformed enolates, the research groups of Shibasaki,[11] Jørgensen,[12] Trost,[13] List,[4] and Barbas[5] have developed direct, catalytic asymmetric Mannich reactions. The former three research groups used chiral organometallic catalysts, while the latter two employed proline as an organocatalyst: List et al. developed a three-component, asymmetric Mannich reaction between an aldehyde, 4-methoxyaniline (*p*-anisidine), and a ketone,[4] while Barbas and co-workers reported a Mannich reaction of *N*-PMP-protected[14] α-imino ethyl glyoxylate and an aldehyde.[5] Although proline-mediated reactions are synthetically useful, and afford Mannich products with excellent enantioselectivity, aldehydes were not employed as the Mannich donor in the reaction performed by List et al., while *N*-PMP-protected α-imino ethyl glyoxylate was the only Mannich acceptor examined in the reaction performed by Barbas and co-workers. The development of a direct and enantioselective, one-pot, three-component cross-Mannich reaction of two different aldehydes is desirable to expand the scope of these powerful asymmetric Mannich reactions; such a system would comprise a Mannich reaction in which one aldehyde is

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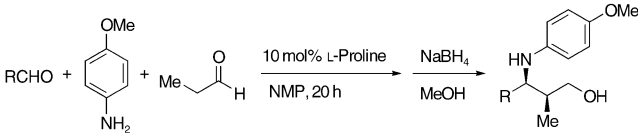
employed as the Mannich donor and the other aldehyde is utilized as a component of the Mannich acceptor to afford a synthetically versatile intermediate, a β-amino aldehyde.

Our initial attempt gave a disappointing result. We chose propanal as the Mannich donor and benzaldehyde as a component of the Mannich acceptor. Following the conditions used by List et al.[4] benzaldehyde, 4-methoxyaniline, and propanal were stirred in DMSO in the presence of a catalytic amount of L-proline at room temperature, but less than 10% yield of the cross-Mannich product was obtained, together with several unidentified products. As the formed β-amino aldehyde decomposed during purification by column chromatography on silica gel, it was isolated and characterized after reduction with $NaBH_4$ to the corresponding β-amino alcohol. As the cross-aldol condensation between benzaldehyde and propanal is a possible side reaction, propanal was added to a solution of aldimine generated in situ from benzaldehyde and 4-methoxyaniline at room temperature, but with no improvement in the yield. After several experiments, it was found that the reaction temperature is very important for this transformation. As shown in Table 1, the amino alcohol was obtained in less than 10 and 15% yield at room temperature and 0°C, respectively, together with several unidentified products (entries 1 and 2), when *N*-methyl-2-pyrrolidinone (NMP) was used as a solvent (see below). The yield increased to 50% when the reaction was performed at −10°C (entry 3), and a good yield and high enantioselectivity (90%, 98% *ee*) were obtained at −20°C (entry 4). The *syn* isomer (see below) was selectively generated, and no *anti* isomer could be detected by ^1H NMR spectroscopy (400 MHz). Possible side reactions are the self-aldol and cross-aldol condensations, which have been reported to proceed at 4°C by Northrup and MacMillan.[2j] The fact that the Mannich reaction proceeds at lower temperature (−20°C) than the aldol reaction (4°C) indicates that the aldimine is more electrophilic than the parent aldehyde. This is contrary to the generally accepted notion that an aldimine is less reactive toward nucleophilic addition than its corresponding aldehyde.[15] Recently $Yb(OTf)_3$,[16] $[PdCl_2(PPh_3)_2]$,[17] and the combination of $BF_3{\cdot}OEt_2$ and water[18] have been reported to be catalysts for the chemoselective activation of aldimines in preference to aldehydes, and the present catalyst also belongs to this rare class.

Table 1: Three-component Mannich reaction with various acceptor aldehydes.[a]



Entry	Aldehyde	*T* [°C]	Yield [%][b]	*syn*:*anti*	*ee* [%][c]
1	benzaldehyde	23	<10	n.d[d]	n.d
2	benzaldehyde	0	15	>95:5	n.d
3	benzaldehyde	−10	50	>95:5	90
4	benzaldehyde	−20	90	>95:5	98
5	benzaldehyde[e]	−20	71	>95:5	96
6	*p*-nitrobenzaldehyde	23	<10	n.d	n.d
7	*p*-nitrobenzaldehyde	0	89	>95:5	95
8	*p*-nitrobenzaldehyde	−10	93	>95:5	99
9	*p*-bromobenzaldehyde	−10	85	>95:5	95
10	*p*-bromobenzaldehyde	−20	33	>95:5	98
11	*p*-chlorobenzaldehyde	−20	91	>95:5	98
12	2-naphthaldehyde	−20	59	>95:5	96
13	*p*-tolualdehyde[e]	−20	95	>95:5	86
14	furfural	−20	87	>95:5	84
15	*p*-pyridinecarbaldehyde	−20	84[f]	>95:5	>99

[a] Reaction conditions: aldehyde:4-methoxyaniline:propanal:proline = 1.0:1.1:3.0:0.1, NMP was used as the solvent except in entries 5 and 13. Reaction time: 20 h. [b] Yield of the isolated amino alcohol. [c] The *ee* values were determined by chiral HPLC analysis (CHIRAPAK AD-H or AS-H). [d] Not determined. [e] DMF was used as the solvent. [f] Yield of the corresponding amino *tert*-butyldimethylsilyl ether, see text.

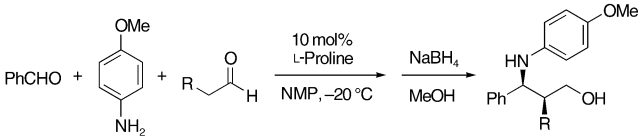
The same effect of the temperature on the yield was also observed with *p*-nitrobenzaldehyde: While at room temperature the reaction afforded several products, with the desired amino alcohol being formed in less than 10% yield, good results were obtained at 0°C and −10°C (entries 6–8).

Solvent effects were examined next. Unlike the elegant enantioselective cross-aldol reaction of aldehydes by Northrup and MacMillan,[2j] in which a wide variety of solvents can be employed, the reaction scarcely proceeded in CH_3CN, CH_2Cl_2, THF, and toluene. Good yields and high enantioselectivities were obtained in DMF and NMP (entries 4 and 5).[19]

Once the best reaction conditions had been established, the generality of this one-pot, three-component cross-Mannich reaction of aldehydes was examined (Table 1). Not only benzaldehyde, but 2-naphthaldehyde and *p*-tolualdehyde are also suitable Mannich acceptor aldehydes and afford adducts in good yield with high *syn*-diastereo- and enantioselectivities (entries 12 and 13). Electron-deficient aldehydes such as *p*-nitrobenzaldehyde and *p*-chlorobenzaldehyde react smoothly, also providing Mannich products with good yields and enantioselectivities (entries 8 and 11). Although the yield of the reaction using *p*-bromobenzaldehyde at −20°C is only 33%, because of the low solubility of the aldimine, a good yield was obtained when the reaction was performed at −10°C (entries 9 and 10). In addition to aromatic aldehydes, heteroaromatic aldehydes are also good Mannich acceptor aldehydes: Furfural and *p*-pyridinecarbaldehyde react with propanal to afford the adducts in good yield with high *syn*-diastereo- and enantioselectivity (entries 14 and 15). The product from the reaction of *p*-pyridinecarbaldehyde was characterized after conversion into the corresponding *tert*-butyldimethylsilyl ether, and the yield was 84% over three steps. It is noteworthy that the basic pyridine moiety has no detrimental effect on the proline catalyst. However, under the same reaction conditions aliphatic aldehydes such as cyclohexylcarbaldehyde gave a complex mixture, while the desired product was obtained in very low yield in the reaction of electron-rich aldehydes such as *p*-anisaldehyde.

In addition to propanal, *n*-butanal can also be successfully employed as the Mannich donor and affords the Mannich products in good yield with high diastereo- and enantioselectivity (Table 2, entries 1 and 2). When *n*-pentanal was used as the Mannich donor, however, the yield and the enantioselectivity were decreased to 55% and 71% *ee*,

Table 2: Three-component Mannich reaction with various donor aldehydes.[a]

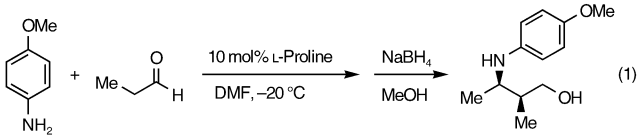


Entry	R	Yield [%][b]	*syn*:*anti*	*ee* [%][c]
1	Me	90	>95:5	98
2	Et	85	>95:5	97
3	*n*Pr	55	>95:5	71

[a] Reaction conditions: benzaldehyde:4-methoxyaniline:aldehyde:proline = 1.0:1.1:3.0:0.1 [b] Yield of the isolated amino alcohol. [c] *ee* values were determined by chiral HPLC analysis (CHIRAPAK AD-H).

respectively (entry 3). At present it is not clear why *n*-pentanal is a poor Mannich donor.

The self-Mannich reaction of propanal also proceeds effectively to afford the *syn*-3-amino-2-methylbutan-1-ol derivative in 70% yield and 96% *ee*. In this reaction, all three components (propanal, 4-methoxyaniline, and L-proline) are mixed together at −20°C without preformation of the aldimine. The success of this procedure indicates that the aldimine was formed even at −20°C, and that the reaction between the aldehyde and aldimine is faster than the self-aldol reaction. The high diastereoselectivity (*syn*:*anti* = >95:5) is in strong contrast to the self-aldol reaction of propanal, for which low diastereoselectivity (*syn*:*anti* = 4:1) is observed [Equation (1)].[2j]



A good-quality single crystal of the reduction product of the Mannich adduct of *p*-chlorobenzaldehyde, propanal, and 4-methoxyaniline was obtained and the relative and absolute configurations have been determined by X-ray crystallographic analysis.[20] The 2*S*,3*S* configuration of the 3-amino-2-methylpropan-1-ol unit (Figure 1) was determined by refinement of the Flack parameter, which converged at −0.2(4) for the configuration shown, and at 1.2(4) for the centrosymmetrically inverted structure. This result indicates that L-proline catalyzes a *si*-facial attack on the aldimine generated in situ (Figure 2), which is in good agreement with the transition-state model[21] for proline-catalyzed Mannich reactions with ketones proposed by List et al.[4] and Barbas and co-workers.[5] The present reaction gave the *syn*-β-amino-α-alkyl aldehyde with high diastereoselectivity, which is complementary to the asymmetric catalytic Mannich reactions of Kobayashi et al.[10e] and Lectka and co-workers,[10i,k] in which *anti*-β-amino-α-alkyl esters and ketones are selectively formed.

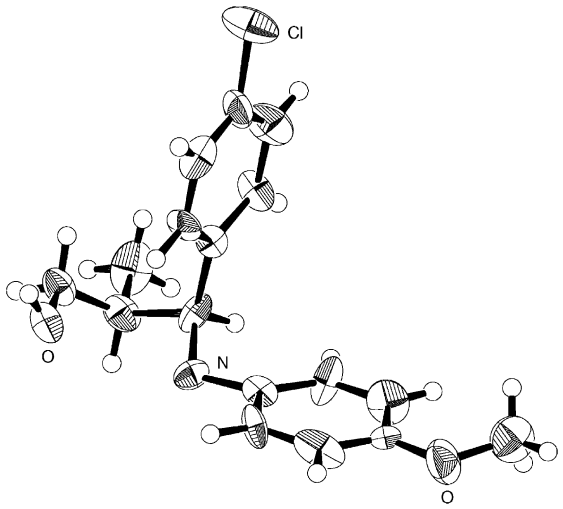


Figure 1. ORTEP diagram of the amino alcohol derived from *p*-chlorobenzaldehyde.

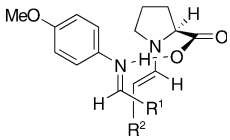


Figure 2. Transition-state model.

In summary, the one-pot, direct cross-Mannich reaction of two different aldehydes has been realized for the first time with high *syn*-diastereo- and enantioselectivities by the catalytic use of L-proline as an organocatalyst. The success of this process lies in the low reaction temperature (−20°C), at which side reactions, such as the aldol condensation, can be suppressed. There are several noteworthy features of this reaction: Proline is found to be one of the rare catalysts that activate aldimines preferentially to aldehydes. The present method for the selective formation of *syn*-β-amino-α-alkyl aldehydes is complementary to the organometal-mediated asymmetric catalytic Mannich reactions, in which the *anti*-β-amino-α-alkyl ester or ketone is selectively produced. The β-amino-α-alkyl aldehydes generated are versatile intermediates, the aldehyde portion of which can be further transformed into other functional groups.[5] The present method will be useful for the synthesis of nitrogen-containing chiral molecules.

Experimental Section

Typical experimental procedure (Table 1, entry 4): After stirring a solution of benzaldehyde (1.0 mmol), 4-methoxyaniline (1.1 mmol), and L-proline (0.1 mmol) in NMP (1.0 mL) for 2 h at RT, propanal (3.0 mmol) was added to the reaction mixture at −20°C, and stirring was continued for 20 h at this temperature. The reaction was quenched with phosphate buffer (pH 7.0), and the organic materials were extracted with ethyl acetate (×3), and the organic phases were combined and washed with brine, and dried over Na_2SO_4. After removal of the volatile materials under reduced pressure, the residue was dissolved in MeOH (3.0 mL), and then $NaBH_4$ (3.0 mmol) was added at 0°C. After stirring the mixture for 30 minutes, the reaction was quenched with phosphate buffer (pH 7.0), and the organic materials were extracted with ethyl acetate (×3). The organic phases were then combined and dried over Na_2SO_4. After removal of the volatile materials under reduced pressure, the residue was purified by thin-layer chromatography and afforded the β-amino alcohol in a

yield of 244 mg (90%) with 98% *ee*, as determined by HPLC analysis on a chiral stationary phase.[22]

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[20] Crystal data: $C_{17}H_{20}ClNO_2$, monoclinic, space group $P2_1$, $a = 10.206(4)$, $b = 6.187(2)$, $c = 12.962(5)$ Å, $\beta = 97.838(6)°$, $V = 810.8(5)$ Å^3, $Z = 2$, $R1 = 0.1427$, $wR2 = 0.4094$ (refined on F^2 using SHELXL97). CCDC-212084 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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