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# Proline catalyzed two-component, three-component and self-asymmetric Mannich reactions promoted by ultrasonic conditions

M. Lakshmi Kantam,[a,*] Ch. V. Rajasekhar,[a] G. Gopikrishna,[a] K. Rajender Reddy[a] and B. M. Choudary[b,*]

[a]*Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b]*Ogene Systems(I) Pvt. Ltd., Hyderabad 500 037, India*

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**Abstract**—The proline catalyzed two-component and three-component asymmetric Mannich reaction with hydroxyacetone and self-Mannich reaction with propanal were performed successfully under ultrasonic conditions in 1 h to afford Mannich products in 90–98% isolated yields and 81–99% ees with excellent diastereoselectivities.


The development of new stereoselective methods for the synthesis of optically pure molecules is important due to the increased interest in enantiopurity for drug candidates. In this context, the Mannich reaction is synthetically useful for the construction of nitrogen-containing molecules.[1] A catalytic diastereo- and enantioselective Mannich reaction is desirable because the chirality controlling element is used in limited quantities. Metal-containing and metal-free catalysts have led to a breakthrough in the diastereo- and enantioselective Mannich reactions.[2] Readily available metal-free organocatalysts are often preferred over chiral metal-based catalysts[3] even though yields as well as diastereo- and enantioselectivities are lower. L-proline is a commonly used metal-free organocatalyst and has been extensively studied in various reactions involving enamine intermediates.[4] An important proline catalyzed three-component Mannich reaction was developed by List et al.[5] Enolizable aldehydes and ketones were treated with in situ generated imines or preformed imines to afford the Mannich products with good yields and excellent enantioselectivities.[6] Barbas and co-workers used this strategy for direct Mannich reaction with preformed iminoglyoxylates.[7] Later, Hayashi et al. reported high pressure induced three-component asymmetric Mannich reactions with excellent stereoselectivities.[8]

The use of protected dihydroxyacetone in asymmetric Mannich reaction was first reported by Cordova and co-workers and subsequently Westermann reported rapid Mannich reactions using protected dihydroxyacetone and various imines, initially under normal conditions, and later under microwave conditions.[9] Enders has described the synthesis of selectively protected amino sugars via asymmetric three-component Mannich reactions.[10]

Despite the high enantioselectvity, there is a limitation to List's reaction where the yields are moderate with electron-rich aldehydes when hydroxyacetone was used as the ketone donor. Generally, chemical reactions are invariably accelerated in ionic liquids, and under microwave and ultrasonic conditions using both transition metal complexes and heterogeneous catalysts.[11] Noteworthy advances have been made in proline catalyzed reactions using ionic liquids in terms of reusability, improved stereoselectivity and reaction time.[12] Similarly, microwave assisted proline catalyzed asymmetric Mannich reactions have been reported with good yields and selectivities in short reaction times.[9,13] However, to the best of our knowledge there are no reports on the use of ultrasound promoted organocatalytic reactions. Here we report efficient and rapid two-component

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* Corresponding authors. Tel.: +91 40 2719 3510; fax: +91 40 2716 0921 (M.L.K.); e-mail: mlakshmi@iict.res.in

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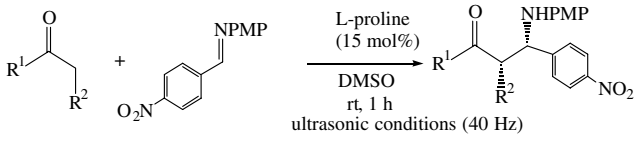
and three-component asymmetric Mannich reactions and a self-Mannich reaction with propanal and *p*-anisidine under normal ultrasonic conditions catalyzed by proline.

In an initial experiment, a 4:1 mixture of DMSO/acetone (10 mL), L-proline (17 mg) and preformed *N*-(*p*-nitrobenzylidene)-*p*-anisidine was reacted under ultrasonic conditions for 1 h, to afford the Mannich product in 50% yield (Table 1, entry 1). Under normal conditions at room temperature, 50% of the corresponding product was obtained after 24 h. No other side product was observed. We also employed 2-butanone and cyclohexanone, however, the yields were poor (Table 1, entries 2 and 3). With hydroxyacetone as the donor, the reaction was complete in 1 h with 98% yield (Table 1, entry 4). Lower conversion of the product was observed when we reduced the reaction time (Table 1, entry 5).

We next examined the optical purity, using acetone as the donor, the Mannich product was obtained with 36% ee (Table 1, entry 1). Notably, with hydroxyacetone, we obtained >99% ee (Table 1, entry 4). Based on the above experiments, it can be reasoned that the hydroxyl function in the ketone donor leads to formation of the enamine rapidly which subsequently attacks the electrophile to produce the Mannich product under ultrasonic conditions. With this high yielding and highly stereoselective process in hand, we further investigated the generality of the reaction with various preformed imines to broaden the scope of the reaction (Table 2).

In the Mannich reaction of electron-deficient aromatic aldehydes (ρ-nitro, ρ-cyano and ρ-bromo) with hydroxyacetone, the yields, ees and des were very high. (Table 2, entries 1–3). The reaction with benzaldehyde afforded the product in very good yield, 94% and 98% ee with 10:1 diastereoselectivity (Table 2, entry 4). The increase in yields and optical purity is due to the high pressure, rapid heating and rapid cooling during ultrasonic irradiation. This method has wide applicability to afford

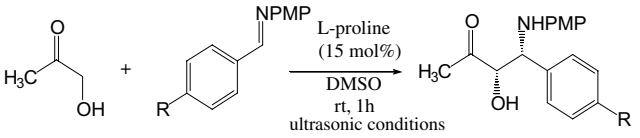
**Table 1.** Screening of ketone donors with aromatic aldimines under ultrasonic conditions




| Entry | $R^1$ | $R^2$ | Yield[a] | ee[b] (%) |
|---|---|---|---|---|
| 1 | $CH_3$ | H | 50 | 36 |
| 2 | $CH_3$ | $CH_3$ | 10 | nd |
| 3 | $(CH_2)_4$ | $(CH_2)_4$ | 15 | nd |
| 4 | $CH_3$ | OH | 98 | 99 |
| 5 | $CH_3$ | OH | 80[c] | 99 |

nd = not determined.
[a] Yields were determined by $^1$H NMR.
[b] Ees were determined by HPLC analysis (Chiralcel AD and AD-RH column).
[c] Yield after 45 min.

**Table 2.** Mannich reaction of various aldimines and hydroxyacetone catalyzed by L-proline at ambient temperature and induced by ultrasonic conditions




| Entry | R | Time (h) | Yield[a] (%) | *Syn*/*anti*[b] | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | $NO_2$ | 1.0 | 98 | 94:6 | 99 |
| 2 | CN | 1.0 | 98 | 96:4 | 99 |
| 3 | Br | 1.0 | 96 | 94:6 | 98 |
| 4 | H | 1.0 | 94 (93) | 90:10 | 98 (93) |
| 5 | Me | 1.0 | 90 (86) | 85:15 | 98 (85) |
| 6 | OMe | 1.0 | 91 (85) | 75:25 | 81 (65) |

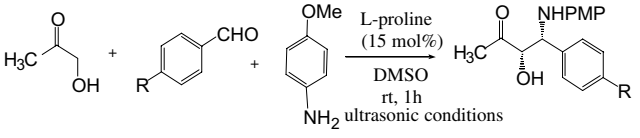
[a] Isolated yields after silica-gel column chromatography. (The values in parentheses are yields under conventional conditions).
[b] The *syn*/*anti* ratio was determined by $^1$H NMR spectroscopy.
[c] Enantiomeric excess was determined by HPLC analysis (Daicel AD-RH column). The values in parentheses are ees under conventional conditions.

various types of amino alcohols with high optical purity. In the case of the electron-rich aldehydes, the yields and ees are quite impressive in comparison to those reported under normal conditions (Table 2, entries 5 and 6).

After achieving high enantioselectivities in two-component reactions, we performed the reactions under three-component conditions. Three-component asymmetric Mannich reactions also produced very good results (Table 3) and it was noticed that ultrasonic conditions not only promoted the asymmetric Mannich reaction, but also promoted imine formation between the aromatic aldehydes and *p*-anisidine in very short intervals. However, three-component reactions produced slightly lower yields and enantioselectivities compared with the two-component reactions.

In addition, the use of aldehydes as nucleophilic donors offers a particularly attractive route to fuctionalized

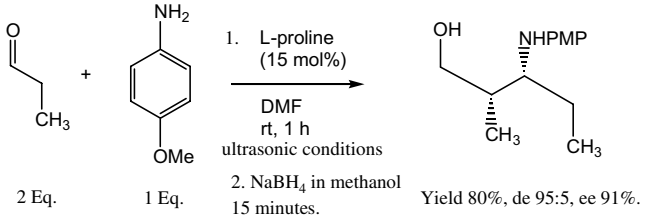
**Table 3.** Three-component asymmetric Mannich reaction of various aromatic aldehydes and *p*-anisidine with hydroxyacetone catalyzed by L-proline at ambient temperature under ultrasonic conditions




| Entry | R | Time (h) | Yield[a] (%) | *Syn*/*anti*[b] | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | $NO_2$ | 1.0 | 98 | 94:6 | 99 |
| 2 | CN | 1.0 | 98 | 96:4 | 98 |
| 3 | Br | 1.0 | 94 | 94:6 | 96 |
| 4 | H | 1.0 | 90 (93) | 90:10 | 85 (94) |
| 5 | OMe | 1.0 | 85 (91) | 75:25 | 66 (81) |

[a] Isolated yields after silica-gel column chromatography. (The values in parentheses are for two-component conditions).
[b] The *syn*/*anti* ratio was determined by $^1$H NMR spectroscopy.
[c] Enantiomeric excess was determined by HPLC analysis (Daicel AD-RH column). The values in parentheses are ees obtained under conventional conditions.

β-amino acids and their derivatives including β-lactams and amino alcohols. Not only does this strategy involve the creation of two contiguous stereocenters upon carbon–carbon bond formation, but also provides structural and functional diversity. Recently, self-Mannich reactions were reported at low temperature with excellent yields and enantioselectivity.[14] After the successful use of hydroxyacetone with imines, we proceeded with the enamine intermediates formed from aliphatic aldehydes as nucleophiles for stereoselective, amino acid-catalyzed self-Mannich reactions. We examined self-Mannich reactions of propanal with *p*-anisidine at room temperature under ultrasonic conditions and observed the formation of a single product, which upon $NaBH_4$ reduction gave *syn*-3-amino-2-methylbutane-1-ol derivatives in 80% yield and 91% ee. This is the first report on rapid self-Mannich reaction of propanol with high yield and ees at room temperature.




In conclusion, this ultrasonic method widens the scope and generality of the proline catalyzed asymmetric Mannich reaction with better yields and enantioselectivities. Both electron-rich and -deficient aldehydes worked well under these conditions. The high yield, high optical purity and operational simplicity make this present method potentially useful in organic synthesis.

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