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Highly Efficient AILs/L-Proline Synergistic Catalyzed Three-Component Asymmetric Mannich Reaction

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Abstract: A three-component asymmetric Mannich reaction of isovaleraldehyde, methyl ketones, and aromatic amines was efficiently synergistic catalyzed by amide-task-specific ionic liquids (AILs)/L-proline under mild conditions. The corresponding asymmetric Mannich reaction adducts were obtained in moderate to high yields and stereo selectivity in all the cases tested. The product was easily isolated, and the

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remaining catalysis system can be readily recovered and reused at least three times without significant loss of catalytic activity and selectivity.

Keywords: amide-task-specific ionic liquids (AILs), L-proline, Mannich reaction, synergistic catalysis

INTRODUCTION

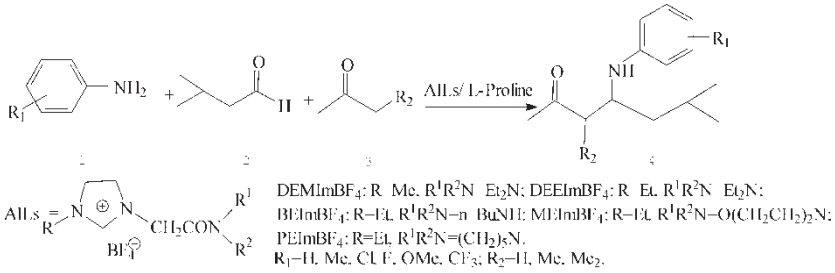
The Mannich reaction is a very important carbon–carbon bond-forming reaction in synthetic organic chemistry and a classic method for the preparation of β-amino carbonyl compounds. The three-component asymmetric Mannich reaction of aldehydes, ketones, and amines, however, generally requires complicated, expensive, and highly toxic metal catalysts and harmful organic solvents such as dimethyl sulfone (DMSO),[1,2] *N*,*N*-dimethyl formamide (DMF),[3] and H_2O/tetrahydrofuran (THF).[4] Commercially available, efficient, economic, and environmentally friendly catalysts and solvents are still urgent. Fortunately, L-proline, an inexpensive and readily available biomimetic, has become a mostly promising catalyst in many asymmetric reactions,[5,6] and high yields and ees have always been reported for the Mannich reaction in normal solvents.[7] At the same time, task-specific ionic liquids (TSILs), because of their useful properties such as high thermal stability, excellent solubility, efficient catalytic activity, and ease of product isolation,[8] are becoming promising alternative solvents to traditional organic solvents. So, establishing a novel catalytic system of TSILs/proline in an asymmetric Mannich reaction seems an ideal solution to the traditional method.

Noticing that DMF had been used as an effective solvent and showed excellent dual catalytic effects in the Mannich reaction, we intended to link the similar structure to ionic liquids, prepare a series of the amide-task-specific ionic liquids (AILs), and explore the asymmetric Mannich reaction of a series of isovaleraldehyde, methyl ketones, and aromatic amines to form β-amino ketones catalyzed by AILs/L-proline (Scheme 1). To the best of our knowledge, this is the first report on the AILs/L-proline synergistic catalyzed organic reaction.

EXPERIMENTAL

Typical Reaction Procedure for 4-p-Tolylamino-6-methyl-2-heptanone (4a)

All ILs were synthesized according to the literatures.[9–11] Isovaleraldehyde (0.43 g, 5 mmol), acetone (0.29 g, 5 mmol), p-tolylamine (0.54 g, 5 mmol), $DEMImBF_4$ (2 mL), L-proline (5% mmol) were added successively to a 20-mL round-bottomed flask under stirring. The reaction proceeded for 2 h at 20°C. Then reaction mixture extracted with isopropyl ether (5 mL × 3); the



Scheme 1. AILs/L-proline synergistic catalyzed asymmetric Mannich reaction of isovaleraldehyde, methyl ketones, and aromatic amines.

organic phases were combined, washed with water (5 mL), dried with anhydrous magnesium sulfate, and distilled to remove the solvent. The product was obtained as a light yellowish oil (1.091 g, yield 96%), and the pure product was obtained by column chromatography (eluent, ethyl acetate–hexane, 3 : 1). Satisfactory spectrometric data characterized the structure.

RESULTS AND DISCUSSION

To select a suitable AIL, the solubility of synthesized AILs with common solvents was first tested. The results showed that they are easily soluble in high-polarity solvents and partly soluble or immiscible in moderates or weak-polarity solvents. The solubility in water is greatly affected by the substitution structure of amide; $DEMImBF_4$, $DEEImBF_4$, and $BEImBF_4$ are miscible in water whereas $MEImBF_4$ and $PEImBF_4$ are partly miscible. Considering ease of product isolation, we thought the water-miscible AILs might

Table 1. AILs/L-proline synergistic catalyzed asymmetric Mannich reaction of isovaleraldehyde, acetone, and p-tolylamine in different solvents[a]

Entry	Solvents	Time (h)	Conversion (%)[b]	Selectivity (%)	Ee (%)
1	$DEMImBF_4$	2	98.8	>99.0	>99.0
2	$BEImBF_4$	2	98.7	97.4	>99.0
3	$DEEImBF_4$	2	98.1	97.6	>99.0
4	$BMImBF_4$	6	94.8	94.6	91.2
5	DMF	6	76.0	—	—
6	DMF	24	95.0	92.7	>99.0

[a]Reaction conditions: substrate (5 mmol), 5% mol L-proline, solvent 3 mL, rt. Conversion and selectivity were detected by GC/MS. Ee were based on GC or HPLC (chiral column, comparison was made to racemic standards); the absolute configuration of the major product was R type.

[b]Based on p-tolylamine.

be the choice for the Mannich reaction. We explored the reaction of the isovaleraldehyde, acetone, and p-tolylamine catalyzed by L-proline in three water-miscible AILs to compare their efficiency. The results listed in Table 1 show that AILs/L-proline have good catalytic activity and selectivity as compared with the nonfunctional counterpart ($BMImBF_4$). $DEMImBF_4$ is found to be the best medium for the reaction; almost quantitative conversion and selectivity within 2 h were found. The aldol condensation side product in DMF/L-proline, which is the main side product characterized by GC-MS, was effectively suppressed under the AILs/L-proline catalytic system. The results indicated that the new catalytic system significantly shortened the reaction time in ionic liquids as compared to the reactions run in DMF (entries 1–3 and 6), improved regioselectivity over the $BMImBF_4$/L-proline system, and showed an apparently synergistic catalysis effect.

With these results in hand, various substrates were employed in the $DEMImBF_4$/L-proline system, and the results are listed in Table 2. Acetone, various aromatic amines, and isovaleraldehyde were almost smoothly converted to the corresponding β-amino ketones with high ee value (entries 1, 4–11). However, when the asymmetric methyl ketones were selected as starting materials, the objective Mannich products were hardly obtained (entries 2, 3). Using acetone as a starting material, the space obstacle effect of aromatic amines has also a great effect on the reaction, so reactions involving p, m-aromatic amines showed better conversion and selectivity than those involving o-aromatic amines (entries 1, 4, 6–8). The new catalytic system could be recycled after simple product isolation and reused three times without significant loss of catalytic activity (Table 3). Although the further exploration of substrate scope and synergistic catalytic mechanism is still needed, the primary research results had suggested that the new catalytic system would be a more suitable one for the asymmetric Mannich reaction.

SELECTED CHARACTERIZATION DATA

4-p-Tolylamino-6-methyl-2-heptanone (4a)

IR (film): 3310 (NH), 1720 (C═O), 1600, 1500 (Ar), 1376, 1285, 1120 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.03 (d, $J = 8.0$ Hz, 2H), 6.44 (d, $J = 8.0$ Hz, 2H), 3.76 (s, 1H, CH-N), 3.44 (s, broad, 1H, NH), 2.62–2.45 (m, 2H, CH_2CO), 2.15 (s, 3H, Me-Ar), 2.04 (s, 3H, MeCO), 1.67 (m, 1H), 1.41 (m, 1H), 1.27 (m, 1H), 0.84 (m, 6H, Me_2C); MS: m/z, 233 (M^+), 176 (100), 160, 134, 118, 106, 91; ES calculated for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00; found: C, 77.20; H, 9.97; N, 6.01.

4-p-Tolylamino-3,6-dimethyl-2-heptanone (4b)

MS: m/z, 247(M^+), 190 (100), 176, 160, 133, 118, 106, 91, 85, 77, 69, 55.

Table 2. DEMImBF$_4$/L-proline synergistic catalyzed Mannich reaction of isovaleraldehyde, methyl ketones, and aromatic amines[a]

Entry	Product	Ketone	Amine	Time(h)	Yield (%)	Ee/dr
1	**4a**	CH_3COCH_3	p-Tolylamine	2	96	>99
2	**4b**	CH_3COEt	p-Tolylamine	2	79	3.1/1[b]
3	**4c**	$CH_3COC_3H_5$	p-Tolylamine	24	Trace	—
4	**4d**	CH_3COCH_3	o-Tolylamine	6	82	28
5	**4e**	CH_3COCH_3	p-Anisidine	2	95	99
6	**4f**	CH_3COCH_3	p-Chloroaniline	2	83	96
7	**4g**	CH_3COCH_3	m-Chloroaniline	4	93	82
8	**4h**	CH_3COCH_3	o-Chloroaniline	2	72	33
9	**4i**	CH_3COCH_3	p-Fluoroaniline	2	94	97
10	**4j**	CH_3COCH_3	Aniline	2	90	93
11	**4k**	CH_3COCH_3	m-Trifluoromethylaniline	4	78	78

[a]Reaction conditions: substrate (5 mmol), DEMImBF$_4$/L-proline, 3 mL, 5% mol, rt. The conversion (based on amine) and yields were calculated by GC/MS; ee detection was based on GC or HPLC (chiral column, comparison was made to racemic standards).

[b]Diastereomeric ratio (*syn:anti*) was based on ^{1}H NMR analysis of crude products and GC/MS.

[c]Detected by GC/MS, not further isolated or characterized.

Table 3. Recycle of the catalysis system

Entry	Test	Isovaleraldehyde	Acetone	p-Tolylamine	Yield (%)	Ee (%)
1	Fresh	5 mmol	5 mmol	5 mmol	96	>99
2	Recycle 1	5 mmol	5 mmol	5 mmol	92	>99
3	Recycle 2	5 mmol	5 mmol	5 mmol	89	>99
4	Recycle 3	5 mmol	5 mmol	5 mmol	85	>99

4-o-Tolylamino-6-methyl-2-heptanone (4d)

IR (film): 3370 (NH), 1710 (C═O), 1600, 1500 (Ar), 1480, 1435, 1400, 1018 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm 7.12 (m, 1H), 7.04 (m, 1H), 6.65 (d, $J = 8$ Hz, 2H) 3.95 (m, 1H), 3.58 (s, 1H), 2.74–2.71 (m, broad, 1H) 2.64 (m, 1H), 2.12 (m, 6H), 1.75–1.74 (m, broad, 1H) 1.53 (m, 1H), 1.39 (m, 1H), 0.98 (m, 6H); MS: m/z, 233 (M^+), 176 (100), 168, 160, 144, 134, 127, 118, 107, 100, 91, 84, 77, 69, 55; ES calculated for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00; found: C, 77.17; H, 9.96; N, 6.03.

4-[(p-Methoxyphenyl)amino]-6-methyl-2-heptanone (4e)
CAS:306776-15-8

IR (film): 3348 (NH), 1712 (C═O), 1600, 1502 (Ar), 1220 (Ar-O-C), 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm 6.69 (d, $J = 8$ Hz, 2H), 6.52 (d, $J = 8$ Hz, 2H), 3.74 (m, 3H), 3.66 (m, 3H), 2.61 (m, 2H), 2.04 (m, 3H), 1.64 (m, 1H), 1.39 (m, 1H), 1.23 (m, 1H), 0.87 (m, 6H); MS: m/z, 249 (M^+), 192 (100), 176, 160, 150, 134, 123, 117, 108, 102, 92, 80, 69, 63, 55.

4-[(p-Chlorophenyl)amino]-6-methyl-2-heptanone (4f)

IR (film): 3340 (NH), 1710 (C═O), 1600, 1500 (Ar), 1290, 810 (Ar-Cl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm 7.10 (d, $J = 8$ Hz, 2H), 6.53 (d, $J = 8$ Hz, 2H), 4.31 (s, 1H, CH-N), 3.84 (m, 1H, NH), 2.67 (m, 2H, CH_2CO), 2.12 (s, 2H), 1.72 (m, 1H), 1.50 (m, 3H), 0.90 (m, 6H), MS: m/z, 253 (M^+), 196 (100), 180, 154, 140, 127, 118, 111, 99, 91, 84, 75, 65, 55; ES calculated for $C_{14}H_{20}NOCl$: C, 66.26; H, 7.94; N, 5.52; found: C, 66.20; H, 7.91; N, 5.50.

4-[(m-Chlorophenyl)amino]-6-methyl-2-heptanone (4g)

IR (film): 3350 (NH), 1710 (C═O), 1600, 1500 (Ar), 1370, 1080, 790 (Ar-Cl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm 7.08 (m, 1H), 6.65 (m, 3H), 3.85 (m, 2H), 2.66 (m, 2H), 2.14 (m, 2H), 1.72 (m, 1H), 1.39 (m, 3H), 0.91 (m, 6H),

MS: m/z, 253 (M^+), 196 (100), 180, 154, 140, 127, 119, 111, 100, 91, 77, 69, 55; ES calculated for $C_{14}H_{20}NOCl$: C, 66.26; H, 7.94; N, 5.52; found: C, 66.21; H, 7.92; N, 5.48.

4-[(o-Chlorophenyl)amino]-6-methyl-2-heptanone (4h)

IR (film): 3346 (NH), 1715 (C═O), 1598, 1500 (Ar), 1404, 1180, 1020, 740 (Ar-Cl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm 7.25 (m, 1H), 7.14 (m, 1H), 6.73 (m, 1H), 6.60 (m, 1H), 4.12 (s, broad, 1H), 4.03 (m, 1H), 2.74 (d, 1H), 2.62 (d, 1H), 2.17 (s, 3H); 1.78 (m, 1H), 1.54 (m, 1H), 1.43 (m, 1H), 0.97 (m, 6H), MS: m/z, 253 (M^+), 200 (100), 184, 172, 158, 144, 132, 124, 117, 107, 99, 91, 77, 65, 55; ES calculated for $C_{14}H_{20}NOCl$: C, 66.26; H, 7.94; N, 5.52; found: C, 66.20; H, 7.96; N, 5.55.

4-[(p-Fluorophenyl)amino]-6-methyl-2-heptanone (4i)

IR (film): 3350 (NH), 1710 (C═O), 1600, 1500 (Ar), 1450, 1364, 1210 (Ar-F) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm 6.79 (m, $J = 8$ Hz, 2H), 6.47 (m, $J = 8$ Hz, 2H), 3.73 (m, 1H), 3.25 (s, broad 1H, NH), 2.56–2.46 (m, 2H), 2.05 (s, 3H), 1.63 (m, 1H), 1.41 (m, 1H), 1.24 (m, 1H), 0.84 (m, 6H), MS: m/z, 237 (25, M^+), 180 (100), 164, 138, 124, 111, 95, 83, 75, 55; ES calculated for $C_{14}H_{20}NOF$: C, 70.86; H, 8.49; N, 5.90; found: C, 70.90; H, 8.46; N, 5.91.

4-Phenylamino-6-methyl-2-heptanone (4j)

IR (film): 3350 (NH), 1710 (C═O), 1600, 1500 (Ar), 1370, 1308, 1250, 1140 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm 7.10 (m, 2H), 6.62 (m, 1H), 6.56 (m, 2H), 3.82 (m, 1H), 3.45 (m, 1H), 2.63 (m, 2H), 2.04 (s, 3H), 1.67 (m, 1H), 1.43 (m, 2H), 0.84 (m, 6H); MS: m/z, 219 (M^+), 162 (100), 146, 120, 106, 93, 77, 65; ES calculated for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39; found: 76.69; H, 9.60; N, 6.41.

4-[(m-Trifluorophenyl)amino]-6-methyl-2-heptanone (4k)

IR (film): 3352 (NH), 1709 (C═O), 1600, 1500 (Ar), 1320, 1158, 1120(C-F) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm 7.25 (m, 1H), 6.91 (m, 1H), 6.76 (d, $J = 8$ Hz, 2H) 3.90 (s, 1H, CH-N), 3.88 (s, 1H, NH), 2.63–2.61 (m, 2H, CH_2CO), 2.15 (s, 3H), 1.72 (m, 1H), 1.49 (m, 1H), 1.36 (m, 1H), 0.97 (m, 6H, MeC); MS: m/z, 303 (M^+), 220 (100), 206, 192, 178, 164, 140, 127, 111, 97, 83, 69, 55; ES calculated for $C_{15}H_{20}NO_2F_3$: C, 59.40; H, 6.65; N, 4.62; found: C, 59.32; H, 6.61 N, 4.63.

CONCLUSION

In summary, DEMImBF$_4$/L-proline has been demonstrated to be an excellent catalytic system for the Mannich reaction of a series of isovaleraldehyde, methyl ketones, and aromatic amines. The adducts, β-amino ketones, were obtained by simple manipulation in moderate to high yields (up to 96%) and enantioselectivities (up to $>$99% ee) under mild conditions. The catalysis system is easily to be recycled at least three times with a slightly activity loss.

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