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A mild and efficient procedure for asymmetric Michael additions of cyclohexanone to chalcones catalyzed by an amino acid ionic liquid

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ABSTRACT

A mild and efficient procedure for Michael additions of cyclohexanone to chalcones has been developed. In the presence of amino acid ionic liquid [EMIm][Pro] (200 mol %), cyclohexanone reacted with various chalcones to afford Michael adducts in high yields (85–98%) and moderate to good enantioselectivities (16–94% ee), accompanied by an unexpected solvent-dependent inversion of the enantioselectivity.

1. Introduction

Over the past few years, searching for new solvents and materials based on chiral ionic liquids (CILs) has become a research focus of increasing importance; a growing number of CILs have been designed for and utilized in potential applications, such as asymmetric synthesis, stereoselective polymerization and chiral resolution.[1] With the rapid development of CILs, these new solvents have the potential to play a key role in enantioselective organic chemistry, and their impact in this field is expected to be enhanced.

Among the newly developed CILs, those derived from amino acids have attracted increasing interest in the chemical community,[2] particularly in asymmetric synthesis. Due to their convenient chemical modification, CILs with chiral cations derived from natural amino acids can be successfully used as highly enantioselective organocatalysts,[3] while there are much less CILs modified on the anion structure.

Since Fukumoto et al.[4] succeeded in synthesizing amino acid ionic liquids from 20 natural amino acids, studies on the properties of amino acid ionic liquids have intensified.[5] However, their applications as solvents or catalysts have yet to be reported, which drove us to research the properties of amino acid ionic liquid used as chiral solvents and catalysts for asymmetric synthesis.

We chose the Michael addition reaction as a model reaction, which constitutes as one of the most important classes of new carbon–carbon bond-forming reactions for the preparation of organic target products in synthetic organic chemistry.[6] There are also publications reporting Michael addition reactions catalyzed by CILs,[3,7] all of which are modified on the cations to provide a chiral group. However, these reactions employ highly activated Michael acceptors, such as nitroalkenes.[8] Enantioselective catalytic conjugate addition of ketones with enones remains a challenging reaction; this issue has not been well studied except by Wang et al.,[9] who used a chiral pyrrolidinylmethylsulfonamide as a catalyst. Herein, for the first time, we used an anion-modified CILs 1-ethyl-3-methylimidazolium-(*S*)-2-pyrrolidinecarboxylic acid salt [EMIm][Pro] as a catalyst, and have developed a mild and efficient procedure for the asymmetric Michael additions of cyclohexanone to chalcones. The products could be obtained in much less time, with high yields and moderate to good enantioselectivities, accompanied by an unexpected solvent-dependent inversion of the enantioselectivity which to the best of our knowledge has not been reported before.

2. Results and discussion

Initially, encouraged by the dramatic catalytic activity of the amino acid proline, we decided to research the properties of [EMIm][Pro] **1** (Fig. 1) in a Michael addition. Catalyst **1** could be easily obtained according to the literature (Scheme 1).[4] *N*-Methylimidazole was employed as a starting material to react with excess bromoethane in ethyl acetate to give 1-ethyl-3-methylimidazolium bromide in good yield (80%). Then, 1-ethyl-3-methylimidazolium hydroxide could easily be obtained by an anion exchange reaction of 1-ethyl-3-methylimidazolium bromide with 201 × 7 Styrene-DVB. Lastly, L-proline was used to neutralize 1-ethyl-3-methylimidazolium hydroxide with the desired product CILs in 70% yield.

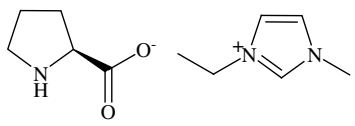

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Figure 1. 1-Ethyl-3-methylimidazolium-(*S*)-2-pyrrolidinecarboxylic acid salt ([EMIm][Pro]).

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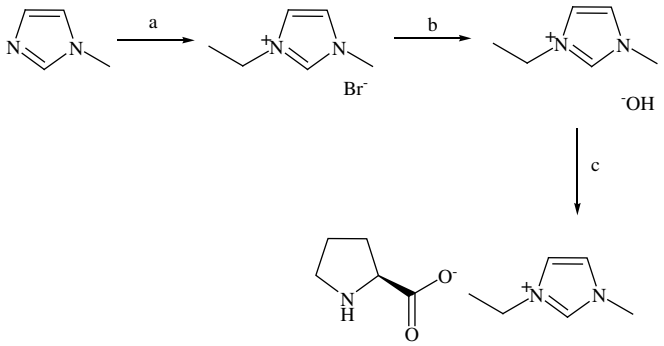
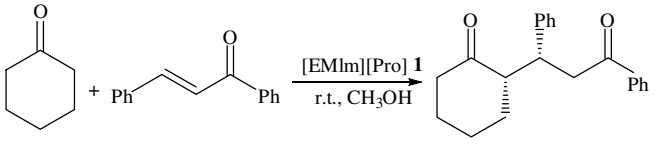


Scheme 1. Synthesis of chiral amino acid ionic liquid: 1-ethyl-3-methylimidazolium-(*S*)-2-pyrrolidinecarboxylic acid salt ([EMIm][Pro]). Reagents and conditions: (a) CH_3CH_2Br, $CH_3CO_2C_2H_5$, 80%; (b) 201 × 7 Styrene-DVB; (c) (*S*) proline, 70%.

The experiments were first conducted by screening [EMIm][Pro] as a catalyst in various ratios with chalcone **3** to promote the Michael reaction (Table 1). The initial conditions were with the reaction performed in CH_3OH at room temperature with cyclohexanone **2** and the chalone **3** in a 3.5:1 ratio. When using 10 mol % catalyst loading (Table 1, entry 1), the Michael addition product **4a** was obtained in 30% yield with moderate (23:77) dr value but low enantioselectivity (17%). Surprisingly, when 50 mol % of **1** was added (Table 1, entry 2), the yield soared to 75% in 20 h along with a 6:94 diastereoselectivity and a 40% ee value. Encouraged by this result, we screened the amount of the catalyst under similar reaction conditions, finding that 200% of **1** had the right properties to achieve good product formation (Table 1, entry 6) with an excellent yield (98%) in 4 h and a high ee value up to 86%. The addition of more catalyst did not give better results but a decrease of the ee value. (Table 1, entry 7–10). Figure 2 gives an outline view of the result.

Table 1
The effect of [EMIm][Pro] catalyst in the asymmetric Michael addition of cyclohexanone with chalcone in CH_3OH



2 **3a** **4a**

Entry	Cat. (mol %)	*t* (h)	Yield[a] (%)	dr[b]	ee[b] (%)
1	10	20	30	23:77	17
2	50	20	75	6:94	40
3	100	10	85	17:83	59
4	150	4	86	8:92	64
5	190	4	90	14:86	70
6	200	4	98	20:80	86
7	210	4	96	13:87	78
8	270	4	93	9:91	75
9	300	4	94	8:92	67
10	350	4	96	8:92	59

[a] Isolated yields after column chromatography.
[b] Determined by HPLC analysis on a chiral AD-H column.

In the presence of 200 mol % of **1**, the addition of cyclohexanone with chalcone was examined in different solvents. Table 2 summarizes the results. A substantial change of the solvent had a significant effect on the yield and stereoselection. When performed in toluene, THF or dichloromethane (Table 2, entries 1–3), the reaction produced **4a** in moderate yield and poor selectivity. Good results were attained when methanol, ethanol or DMSO (Table 2, entries 4–6) were used, accompanied by an unexpected solvent-dependent inversion of the enantioselectivity. Determined by HPLC analysis on a chiral AD-H column, the product obtained from DMSO had an inverse configuration when compared with that obtained from methanol or ethanol. The same reaction carried out in ionic liquids [BMIm]BF_4 and [BMIM]PF_6 provided the adduct with 31% and 44% ee values, both in good yield (Table 2, entries 7 and 8). There was a small ee value decrease when using cyclohexanone as a solvent, while a 60% ee value was obtained in 91% yield when the catalyst **1** was used as a solvent (Table 2, entries 9 and 10).

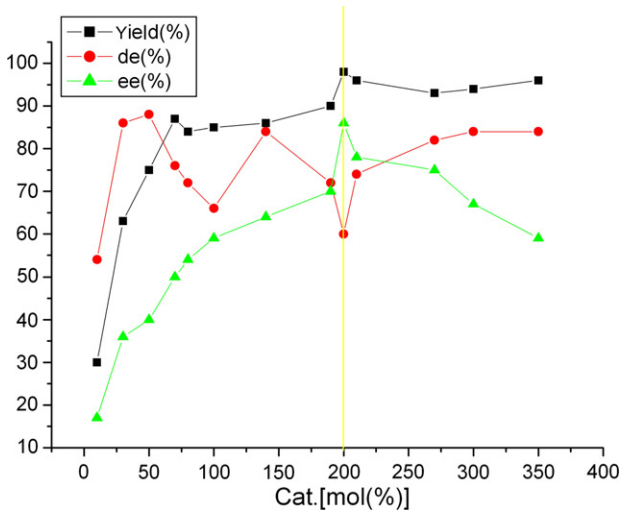
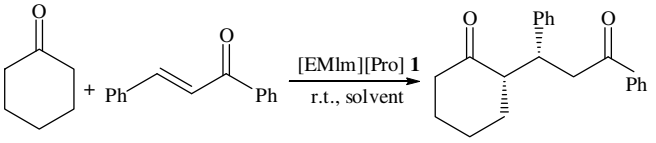


Figure 2. The effect of [EMIm][Pro] catalyst in the asymmetric Michael addition of cyclohexanone with chalcone in CH_3OH.

Table 2
Investigation of different kinds of solvents in the asymmetric Michael addition of cyclohexanone with chalone



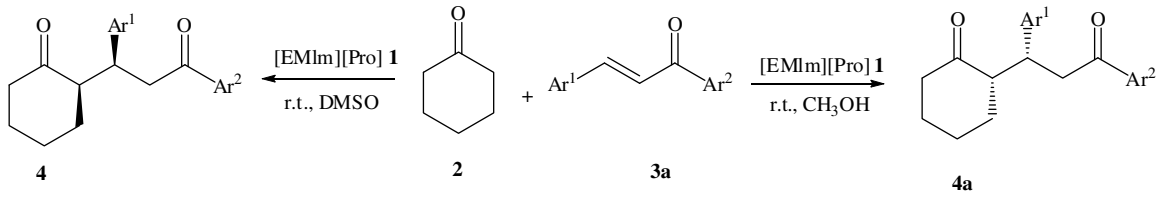
2 **3a** **4a**

Entry	Solvent	*t* (h)	Yield[a] (%)	dr[b]	ee[b] (%)
1	Toluene	15	50	11:89	27
2	THF	5	50	8:92	41
3	CH_2Cl_2	15	45	29:71	6
4	CH_3OH	4	98	20:80	86
5	C_2H_5OH	4	90	15:85	69
6	DMSO	4	95	12:88	−78[c]
7	$BMIBF_4$	4	70	22:78	31
8	$BMIPF_6$	4	75	20:80	46
9	Cyclohexanone	4	89	14:86	62
10	[EMIm][Pro]	4	91	21:79	60

[a] Isolated yields after column chromatography.
[b] Determined by HPLC analysis on a chiral AD-H column.
[c] An inversed configuration determined by HPLC analysis on a chiral AD-H column.

Stimulated by the dramatic solvent effect, we tested a variety of chalones **3** with cyclohexanone **2** to investigate the generality of the solvent-dependence in this reaction, and the results are summarized in Table 3. All reactions were performed at room temperature in the presence of 200 mol % of **1** in CH_3OH or DMSO. It appeared that both electron-donating (entries 2 and 9) and electron-withdrawing (entries 3–5 and 10–12) groups led to similar yields but lower selectivities when compared with the unsubstituted substrate. The chalcone bearing an amine group provided the

Table 3
Catalytic asymmetric Michael addition reactions of cyclohexanone **2** with chalcone **3**[10,11]



Entry	Ar^1	Ar^2	Conditions[d]	t (h)	Yield[a] (%)	dr[b]	ee[b,c] (%)
1	Ph	Ph	A	4	98	20:80	86
2	4-MeC_6H_4	Ph	A	4	90	5:95	37
3	4-ClC_6H_4	Ph	A	4	98	4:96	60
4	Ph	4-ClC_6H_4	A	4	97	15:85	23
5	4-BrC_6H_4	Ph	A	4	80	23:77	44
6	Ph	4-$NH_2C_6H_4$	A	8	87	4:96	94
7	2-ClC_6H_4	4-MeC_6H_4	A	4	99	1:99	29
8	Ph	Ph	B	4	95	12:88	−78
9	4-MeC_6H_4	Ph	B	4	98	16:84	−72
10	4-ClC_6H_4	Ph	B	4	94	10:90	−65
11	Ph	4-ClC_6H_4	B	4	88	8:92	−72
12	4-BrC_6H_4	Ph	B	4	90	10:90	−39
13	Ph	4-$NH_2C_6H_4$	B	8	85	4:96	−91
14	2-ClC_6H_4	4-$MeOC_6H_4$	B	4	99	4:96	−16

[a] Isolated yields after column chromatography.
[b] Determined by HPLC analysis on a chiral AD-H column.
[c] An inverse configuration determined by HPLC analysis on a chiral AD-H column.
[d] Conditons A: reaction performed in CH_3OH; conditions B: reaction performed in DMSO.

adduct with excellent ee values both in CH_3OH and in DMSO (entries 6 and 13). We assumed that between catalyst **1** and the amine group there was probably a strong hydrogen-bond to anchor the substrate in a firm way (Fig. 3, State C). Substituents both at the Ar^1 and Ar^2 groups on the chalcone (entries 7 and 14) resulted in a small increase in diastereoselectivity, but an obvious decrease in enantioselectivity occurred.

Notably, the solvent-dependent inversion of the enantioselectivity took place in all reactions shown in Table 3. Products obtained from DMSO mostly displayed a higher ee value than those obtained from CH_3OH, each with a reverse enatioselectivity on an AD-H column after HPLC analysis.

With the success of the above reactions, we continued our study by exploring the recyclability of the catalyst which is important from an industrial point of view, especially when too much catalyst had been used compared with the result reported. We carried out our study by using the addition of cyclohexanone with chalcone in CH_3OH as a model reaction. After the reaction was complete, the reaction mixture was evaporated in vacuo and then extracted with ethyl acetate to give the ionic liquid residue. The residue was reused directly as a catalyst and this process was repeated five times. It was found that the desired adduct could still be obtained with a comparable yield but a small decrease of the ee value (Table 4).

To determine the configurations of the Michael adducts, we repeated the experiment in the literature[9] catalyzed by proline. After comparing the peak time on an AD-H column with our product **4** obtained from CH_3OH, the relative configurations were assigned as *syn*- and the absolute configurations were confirmed to be (2*S*,1′*R*).

Although attempts to detail the reaction mechanism have not yet been undertaken, we now propose a plausible transition state, representing the stereoselective and solvent-dependent of Michael addition reactions of cyclohexanone with chalcones. The reaction started with iminium activation of the cyclohexanone by the proline anion, together with an electrostatic interaction between chalcones and the imidazolium moiety of the catalyst (Fig. 3, State A).

When DMSO was used as a solvent, the oxygen atom from the DMSO had occupied the position of chalcone and blocked the

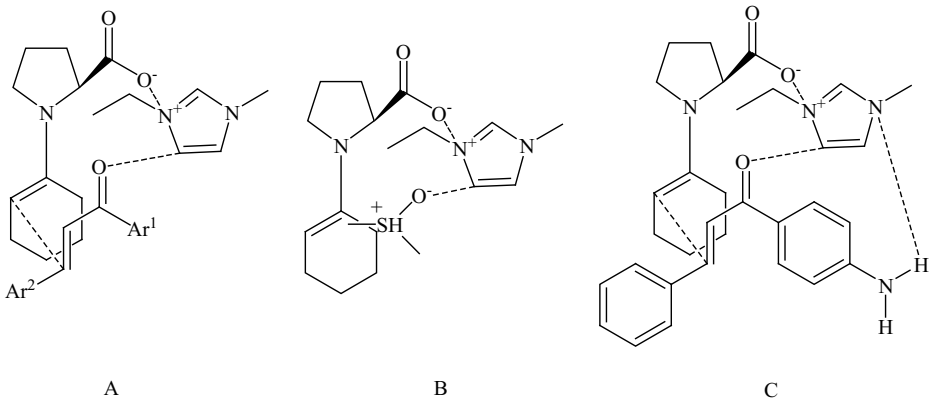


Figure 3. Proposed transition states A, B and C.

Table 4
Recycling study of the Michael addition catalyzed by an amino acid ionic liquid

Reuse	t (h)	Yield[a] (%)	dr[b]	ee[b] (%)
1	4	98	21:79	86
2	4	95	20:80	83
3	4	97	18:82	82
4	4	97	18:82	80
5	4	98	20:80	81

[a] Isolated yields after column chromatography.
[b] Determined by HPLC analysis on a chiral AD-H column.

proximity to the prochiral iminium from the side where chalcone had attacked in the other solvents. As a result, an inverse of the enantioselectivity was observed (Fig. 3, State B).

3. Conclusion

In conclusion, we have developed a new, mild and efficient procedure for Michael additions of cyclohexanone with chalcones. In the presence of amino acid ionic liquid [EMIm][Pro] (200 mol %), cyclohexanone could react with various chalcones to afford Michael adducts in high yields (85–98%) with moderate to good enantioselectivities (16–94% ee), accompanied by an unexpected solvent-dependent inversion of the enantioselectivity. Further investigations of this novel transformation and the synthetic applications of the [EMIm][Pro] are underway.

Acknowledgements

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10. *Typical procedure*: chalcone **3** (17 mg, 0.081 mmol) was added to a vial containing cyclohexanone (2; 30 μL, 0.284 mmol) and catalyst **1** (37.0 mg, 0.0162 mmol) in CH_3OH (0.5 mL) at room temperature. The mixture was stirred vigorously and monitored by TLC. When the reaction was finished, the reaction mixture was directly purified by flash silica gel chromatography (ethyl acetate/hexane, 1:5) to afford the adduct as a white solid; yield: 25 mg (98%); 20: 80 dr (determined by HPLC) and 86% ee; Chiralpak AD-H column (*i*-PrOH/hexane 10/90, flow rate 0.9 mL/min, $\lambda = 254$ nm): $t_R = 26.3$ min (minor) and 31.4 min (major).
11. All new compounds gave satisfactory analytical and spectral data. (*S*)-2-((*R*)-1-(4-Bromophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (Table 3, entry 5) yield: 80%. Mp 115–118 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.91 (d, $J = 7.2$ Hz, 2H), 7.52 (t, $J = 7.3$ Hz, 1H), 7.43 (d, $J = 7.8$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 7.07 (d, $J = 8.4$ Hz, 2H), 3.70 (dt, $J = 9.8$, 9.8, 3.9 Hz, 1H), 3.50 (dd, $J = 16.4$, 3.9 Hz, 1H), 3.20 (dd, $J = 16.37$, 9.79 Hz, 1H), 2.69 (dt, $J = 10.0$, 10.0, 4.8 Hz, 1H), 2.52–2.33 (m, 2H), 2.03–1.97 (m, 1H), 1.81–1.62 (m, 4H), 1.29–1.26 (m, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 213.0, 198.4, 141.1, 136.9, 133.0, 131.6, 130.2, 128.5, 128.1, 120.4, 55.5, 43.8, 42.4, 40.6, 32.5, 28.5, 24.3; HPLC Chiralpak AD-H column (*i*-PrOH/hexane 10/90, flow rate 0.9 mL/min, $\lambda = 254$ nm): $t_R = 22.6$ min (minor) and 26.7 min (major). (*S*)-2-((*R*)-1-(4-Phenyl)-3-oxo-3-(4′-aminophenyl)-propyl)-cyclohexanone (Table 3, entry 6) yield: 87%. Mp 153–155 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.5 (s, 1H), 7.97–7.92 (m, 2H), 7.84–7.81 (m, 2H), 7.60–7.50 (m, 2H), 7.23–7.18 (m, 3H), 3.79 (dt, $J = 9.8$, 9.8, 4.0 Hz, 1H), 3.63 (dd, $J = 16.0$, 4.0 Hz, 1H), 3.34 (dd, $J = 15.9$, 9.6 Hz, 1H), 2.78 (dt, $J = 10.1$, 9.8, 4.8 Hz, 1H), 2.60–2.38 (m, 2H), 2.04–1.96 (m, 1H), 1.84–1.76 (m, 2H), 1.64–1.58 (m, 3H), 1.34–1.30 (m, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 213.6, 198.7, 142.0, 135.5, 134.4, 132.5, 129.9, 129.6, 128.5, 128.4, 128.2, 127.7, 126.6, 124.0, 55.9, 44.3, 42.3, 41.4, 32.5, 28.5, 24.1; HPLC Chiralpak AD-H column (*i*-PrOH/hexane 10/90, flow rate 0.9 mL/min, $\lambda = 254$ nm): $t_R = 35.1$ min (major) and 55.6 min (minor). (*S*)-2-((*R*)-1-(2-Chlorophenyl)-3-oxo-3-(4′-methoxyphenyl)-propyl)-cyclohexanone (Table 3, entry 7) yield: 99%. Mp 122–123 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.94 (d, $J = 8.8$ Hz, 2H), 7.30 (d, $J = 7.8$ Hz, 1H), 7.27–7.24 (m, 1H), 7.18 (t, $J = 7.4$, 7.4 Hz, 1H), 7.09 (t, $J = 7.5$, 7.5 Hz, 1H),7.436.89 (d, $J = 8.8$ Hz, 2H), 4.22 (dt, $J = 10.0$, 10.0, 3.8 Hz, 1H), 3.84 (s, 3H),3.52 (dd, $J = 15.9$,3.9 Hz, 1H), 3.30 (dd, $J = 16.0$, 9.9 Hz, 1H), 2.89 (dt, $J = 10.3$, 10.2, 5.0 Hz, 1H), 2.55–2.35 (m, 2H), 2.04–1.98 (m, 1H), 1.85–1.79 (m, 1H), 1.64–1.56 (m, 3H), 1.27–1.22 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 213.2, 197.1, 163.3, 139.7, 134.7, 130.5, 130.2, 129.9, 129.6, 127.6, 127.0, 113.6, 58.5, 55.4, 42.7, 42.6, 38.5, 32.6, 28.7, 24.7; HPLC Chiralpak AD-H column (*i*-PrOH/hexane 10/90, flow rate 0.9 mL/min, $\lambda = 254$ nm): $t_R = 41.0$ min (minor) and 84.1 min (major).