Synthesis of a Novel Chiral Ionic Liquid and Its Application in Enantioselective Aldol Reactions

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A novel chiral ionic liquid, compound **1**, based on camphorsulfonic acid, was prepared. A catalytic amount of **1** readily promotes L-proline-catalyzed aldol reactions, with good chemoselectivity, both in H_2O and in organic solvents. Further, the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde afforded 2-[hydroxy(4-nitrophenyl)methyl]cyclohexanone (**6**) in 98% yield with high enantioselectivity (94% ee) when large amounts of **1** (5 equiv.) were used as promoter.

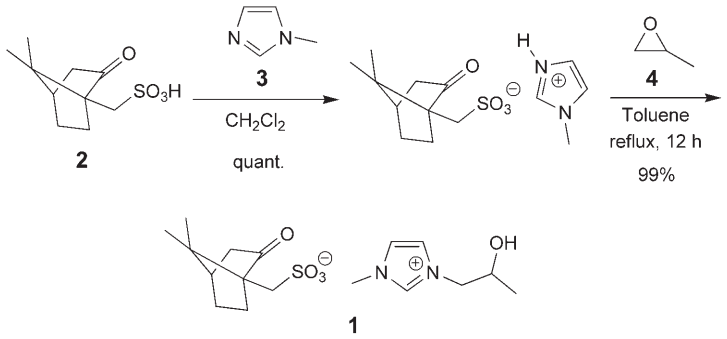
Introduction. – Recently, ionic liquids have attracted great interest among synthetic organic chemists because they have been shown to function as novel reaction media and promoters due to their unique properties such as a wide liquid range, good solvating ability, tunable polarity, high thermal stability, negligible vapor pressure, and ease of recyclability [1][2]. Since the first example of a ionic liquid with a chiral anion (lactate), reported in 1999 by *Seddon* and co-workers [3], many novel chiral ionic liquids have been prepared [4]. However, up to now few convincing examples in asymmetric catalysis have been reported, and the enantioselectivities achieved have been low to moderate in most cases [4a–d]. The best results so far were obtained by *Leitner* and co-workers [5] using a chiral anion-containing ionic liquid for the aza-type *Baylis–Hillman* reaction [5]. In this specific case, enantioselectivities of up to 84% ee (enantiomeric excess) were achieved, and an ionic transition state was postulated in which the chiral *Brønsted*-acidic anion is incorporated as a kind of organocatalyst.

In order to study the functionality of ionic liquids in asymmetric catalysis, we wanted to prepare a novel chiral ionic liquid and study its special functionality in aldol reactions. Herein, we report our findings concerning bifunctional activation with the novel chiral ionic liquid **1** in the presence of catalytic amounts of L-proline in H_2O or organic solvent.

Results and Discussion. – The synthesis of the chiral ionic liquid **1** is shown in *Scheme 1*. Strating from D-camphor-10-sulfonic acid (=(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-sulfonic acid; **2**) and 1-methyl-1*H*-imidazole (**3**), the corresponding salt was prepared, and then reacted with an epoxide (2-methyloxirane; **4**) to afford the target structure **1**. The synthetic procedure and workup were quite simple

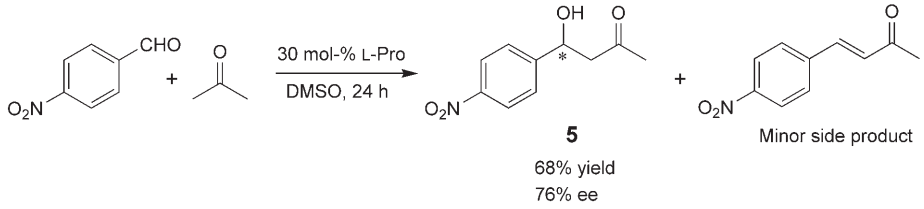
and practical, and afforded the product in excellent yield (> 99%). Compound **1** was obtained as a viscous liquid at room temperature, being soluble in moderately to highly polar solvents such as $CHCl_3$, CH_2Cl_2, acetone, AcOEt, DMF, H_2O, and MeOH, but insoluble in less polar solvents such as Et_2O, toluene, and hexane. These properties, together with the simple synthesis, suffice to practical applications in asymmetric synthesis.

Scheme 1



The asymmetric aldol reaction of an aldehyde and a modified or unmodified ketone is one of the most-important methods for the stereoselective construction of C–C bonds [6]. This reaction yields β-hydroxy carbonyl compounds, which have great potential in organic synthesis [7]. Even though many *Lewis* acid catalysts have been reported for this transformation, more emphasis has recently been given to chiral metal-free catalysts (organocatalysts), as they are more efficient and environmentally friendly [8]. L-Proline is one such representative organic molecules, which has showed good catalytic activity and high stereoselectivity in aldol reactions (*Scheme 2*). However, some of the protocols reported to date involve high-boiling solvents such as DMSO or DMF, or toxic $CHCl_3$ [9], which limits the industrial application of this reaction. Recent work has attempted to overcome this drawback by using a recyclable ionic liquid, H_2O, and polyethyleneglycol (PEG) as solvent [10]. However, it was reported that the aqueous aldol reaction of acetone with 4-nitrobenzaldehyde is difficult to carry out in the presence of catalytic amounts of L-proline (40 mol-%) in pure H_2O without additives [11].

Scheme 2. *Classical* L*-Proline-Catalyzed Aldol Reaction*



Initially, we tried to use the chiral ionic liquid **1** as catalyst proper (at 10 mol-%), without addition of proline in the above model reaction between acetone and 4-

nitrobenzaldehyde, but no addition product was detected after 17 h. However, when L-proline and **1** (10 mol-%) in an aqueous mixture of the reactants were used, the reaction proceeded at room temperature and gave rise to an excellent yield (up to 98%) within only 5 h, which indicated that the presence of **1** efficiently promotes the L-proline-catalyzed aldol reaction.

We next tested the catalytic effect of different amounts of **1** in the above aldol reaction (*Fig. 1*). When 1 mol-% of **1** was used, 25% ee was achieved. Interestingly, however, the *racemic* product was obtained when 3 mol-% (or more) of **1** were used. These results show that the chiral ionic liquid plays an important role in this reaction. Although the yield was excellent, H_2O did not prove to be a suitable solvent for the asymmetric aldol reaction of acetone and 4-nitrobenzaldehyde.

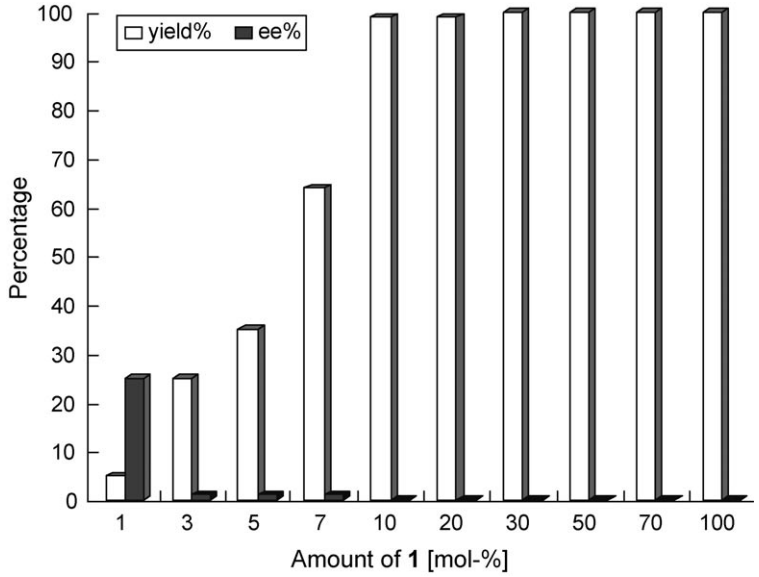


Fig. 1. L-*Proline-catalyzed aldol reaction in the presence of* **1**. Conditions: 10 mol-% L-Pro, 1 – 100 mol-% **1**, 1 mmol of 4-nitrobenzaldehyde, acetone/H_2O 1 : 4 (2 ml), r.t, 5 h.

On the basis of above results, we tested the above L-proline-catalyzed aldol model reaction in different organic solvents, except for DMSO [9]. As shown in *Table 1*, in most of the solvents, excellent yields of the corresponding aldol product **5** were obtained in the presence of 10 mol-% of **1** after 5 h, with enantioselectivities of 63 – 74% ee.

We also conducted experiments to assess the effect of varying the relative amount of **1**, using acetone as solvent. As shown in *Fig. 2*, the enantioselectivities of the aldol product **5** decreased dramatically by increasing the concentration of the ionic liquid, *racemic* **5** being obtained in the presence of 5 equiv. (500 mol-%) of **1**. Interestingly, though, the reaction tolerates a small amount of **1** ($\leq$20 mol-%) without affecting the enantiomeric excess of the aldol product.

Table 1. L-*Proline-Catalyzed Aldol Reaction of Acetone with 4-Nitrobenzaldehyde in the Presence of the Chiral Ionic-Liquid Promoter* **1**. Conditions: 4-nitrobenzaldehyde (1 mmol), L-proline (10 mol-%), acetone/solvent 1 : 4 (*v*/*v*), total volume 3 ml, r.t.

Entry	System	Solvent	Time [h]	Yield [%][a])	ee [%]
1	L-Pro/**1**	acetone	5	99	72
2	L-Pro	acetone	11	80	73
3	L-Pro/**1**	toluene	5	53	70
4	L-Pro	toluene	11	25	69
5	L-Pro/**1**	THF	5	53	74
6	L-Pro	THF	11	27	73
7	L-Pro/**1**	CH_2Cl_2	5	93	63
8	L-Pro	CH_2Cl_2	11	59	65
9	L-Pro/**1**	MeCN	5	71	66
10	L-Pro	MeCN	11	55	66
11	L-Pro/**1**	Et_2O	5	62	68
12	L-Pro	Et_2O	11	10	71

[a]) Yields refer to isolated **5** (see *Scheme 2*).

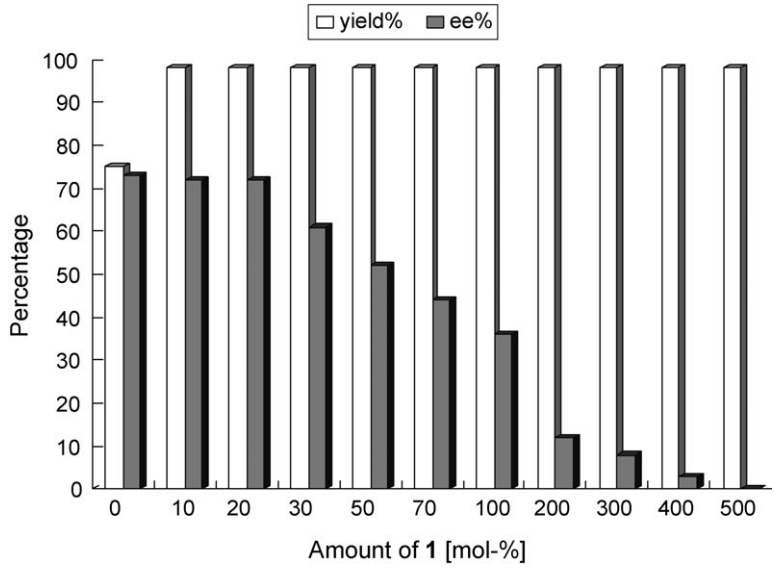
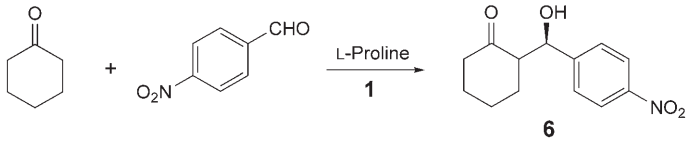


Fig. 2. L-*Proline-catalyzed aldol reaction in the presence of* **1**. Conditions: L-Pro (10 mol-%), 10–500 mol-% **1**, 1 mmol of 4-nitrobenzaldehyde, acetone (2 ml), r.t., 5 h.

Next, we investigated the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in the presence of L-proline and **1** in H_2O or in organic solvent (*Table 2*). To our delight, 10 mol-% of L-proline in the presence of 200 mol-% of **1** catalyzed the asymmetric formation of the desired aldol adduct **6** in 40% yield and 93% ee (*Table 2*, *Entry 21*). Furthermore, decreasing the amount of L-proline to 30 mol-% improved the conversion and stereoselectivity (*Entry 22*; 98% yield, 94% ee). It is clear, thus, that the

Table 2. *L-Proline-Catalyzed Aldol Reaction of Cyclohexanone with 4-Nitrobenzaldehyde in the Presence of* **1**. Conditions: At r.t. in the presence of 10 mol-% of L-Pro (unless otherwise noted).



6

Entry	**1** [mol-%]	Solvent	Time [h]	Yield [%][a])	*syn*/*anti*[b])	ee [%][c])
1	0 or 10	H_2O	10	trace	–	–
2	20	H_2O	10	11	68 : 32	2
3	30	H_2O	10	17	65 : 35	4
4	50	H_2O	10	47	63 : 37	3
5	70	H_2O	10	50	45 : 55	1
6	100	H_2O	10	87	36 : 64	3
7	200	H_2O	10	99	24 : 76	1
8	300	H_2O	10	99	24 : 76	1
9	400	H_2O	10	99	19 : 81	0
10	500	H_2O	10	99	19 : 81	0
11	200	MeCN	10	99	44 : 56	12
12	200	MeOH	10	60	39 : 61	41
13	200	PhMe	10	91	36 : 64	44
14	200	Et_2O	10	66	36 : 64	50
15	200	None	24	99	44 : 56	23
16	200	CH_2Cl_2	10	99	36 : 64	24
17	30	THF	24	34	47 : 53	89
18	50	THF	24	32	44 : 56	90
19	70	THF	24	35	42 : 58	86
20	100	THF	24	32	41 : 59	91
21	200	THF	24	40	39 : 61	93
22[d])	200	THF	10	98	29 : 71	94

[a]) Yield of isolated **6**. [b]) Determined by ^{1}H-NMR. [c]) Enantiomeric excess in favor of the *anti*-isomers. [d]) In the presence of 30 (instead of 10) mol-% of L-Pro.

chiral ionic liquid **1** accelerates the reaction without negative effect on enantioselectivity.

Conclusions. – We have prepared the novel chiral ionic liquid **1** from D-camphor-10-sulfonic acid (CSA) and demonstrated that a catalytic amount of **1** readily promotes L-proline-catalyzed aldol reactions, with good chemoselectivity, both in H_2O and organic solvents. Our results indicate that H-bonding plays an essential role in this process by selectively stabilizing the transition state of aldol reactions. The aldol reaction of cyclohexanone with 4-nitrobenzaldehyde afforded 2-[hydroxy(4-nitrophenyl)methyl]cyclohexanone (**6**) in excellent yield (98%) and enantioselectivity (94% ee), when large amounts of the chiral ionic liquid were used. Our findings could open up a new avenue of the combination of chiral ionic liquids with organocatalysts for highly efficient asymmetric catalysis.

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Experiment Part

General. All reagents and solvents were used as received, without further purification. Flash chromatography (FC) was performed on silica gel (200–300 mesh). TLC was performed on silica-gel F_{254} plates, spots being visualized under UV light. IR Spectra were recorded on an FT-IR apparatus; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra were recorded at 400 and 100 MHz, resp., and chemical shifts δ (in ppm) were referenced to internal solvent signals.

*3-(2-Hydroxypropyl)-1-methyl-1*H*-imidazol-3-ium (1*S*,4*R*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptane-1-sulfonate* (**1**). L-Camphor-10-sulfonic acid (**2**; 23.2 g, 0.1 mol) was added in small portions to a soln. of 1-methyl-1*H*-imidazole (**3**; 8.2 g, 0.1 mol) in CH_2Cl_2 (250 ml) at r.t., and the mixture was stirred for 2 h. After removal of the solvent *in vacuo*, the corresponding imidazolium sulfonate salt, isolated as a colorless solid (quant.), was dissolved in toluene (200 ml), and 2-methyloxirane (**4**; 0.5 mol) was added. The flask was sealed under Ar gas and heated to reflux for 24 h. When the reaction was complete, the mixture had separated into two layers. The solvent was removed *in vacuo*, and **1** was obtained as a brownish, highly viscous material. IR (neat): 3423, 2962, 1738, 1643, 1575, 1454, 418, 1229, 1189, 1171, 1046. ^1H-NMR (400 MHz, $CDCl_3$; cationic part only): 1.20 (*d*, Me); 3.26 (*m*, C*H*OH); 3.99 (*s*, MeN); 4.21, 4.36 (2*t*, 2 × 1 H each of NCH_2); 7.44, 7.57 (2*s*, 2 × 1 H of Im); 9.46 (*s*, NC*H*N of Im). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.3; 19.5; 19.6; 25.0; 26.7; 36.5; 42.5; 42.7; 45.1; 48.0; 48.2; 50.1; 58.2; 121.7; 123.6; 136.4; 217.5.

Aldol Reaction. A cat. amount of L-proline was added to a vial containing 4-nitrobenzaldehyde (0.5 mmol), cyclohexanone (2.5 mmol), **1** (10–500 mol-%), and solvent (2 ml). The mixture was vigorously stirred at r.t. for the time indicated (see *Table 2*). The mixture was then poured into an extraction funnel containing brine, and diluted with dist. H_2O. The aq. layer was repeatedly extracted with AcOEt, the combined org. phases were dried (Na_2SO_4), and concentrated under reduced pressure. The crude was purified by FC (SiO_2) to furnish the desired aldol product **6**. The enantiomeric excess (ee) was determined by chiral-phase HPLC (*AD-H*; hexane/i-PrOH 80:20; 0.5 ml/min, detection at 254 nm). The following retention times were found: 21.767 and 23.733 min (*syn* isomers); 25.708 and 32.875 min (*anti* isomers).

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