Asymmetric Aldol Reactions in Caprolactam–Quaternary Ammonium Salt Coordination Ionic Liquid Catalyzed by L-Pro-L-Trp

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A direct asymmetric aldol reaction of aldehydes and acetone catalyzed by L-Pro-L-Trp was performed in β-caprolactam–quaternary ammonium salt coordination ionic liquid media in the presence of *N*-methylmorpholine (NMM) in high yield and with good enantioselectivity. The approach has the advantages of simple product isolation, and reusable catalyst and coordination ion liquids.

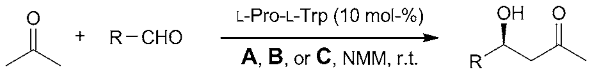
Introduction. – In recent years, ionic liquids have attracted a great deal of attention from synthetic chemists as novel reaction media [1–3]. This is mainly due to their nonvolatile nature, tunable polarity, and high thermal stability. The insolubility of ionic liquids in some solvents and their ability to dissolve catalysts, particularly transition-metal catalysts, has made them attractive with respect to both solvent and catalyst recycling. In the past decades, all kinds of ionic liquids have been found. *Zhao et al.* reported the properties of a new coordination ionic liquid, which was prepared with urea, thiourea as ligands and inorganic salts, by organic salts reaction, but their application in syntheses has been rarely reported [4].

Results and Discussion. – With focus on the coordination ionic liquid [4], we synthesized a series of β-caprolactam–quaternary ammonium salt coordination ionic liquids. Reaction of caprolactam as ligand and tetraalkylammonium halides according to a certain percentage (molar ratio 3:1), after heating in molten state, cooling, and drying, gave nonvolatile β-caprolactam (=4-propylazetidin-2-one)–Bu_4NCl (**A**), β-caprolactam–Bu_4NBr (**B**), and β-caprolactam–Et_4NCl (**C**) with, high thermal stability, low freezing point (0°, 0°, 6°), weak acidity (pH 6.27, 5.85, 6.22). They were soluble in polar solvents (such as DMF, EtOH, H_2O, and acetone) and insoluble in low-polarity solvents (such as Et_2O and AcOEt). Encouraged by the similar nature to ionic liquids, we attempted to perform an eco-friendly L-Pro-L-Trp-catalyzed direct asymmetric aldol reaction by making use of the coordination ionic liquid as solvent.

On the basis of our previous investigations of asymmetric aldol reactions [5], L-Pro-L-Trp, *N*-methylmorpholine (NMM), and a β-caprolactam–quaternary ammonium salt coordination ionic liquid were examined in the reactions.

First, the reaction feasibility was evaluated. Acetone (4 mmol), **A** (3 ml), L-Pro-L-Trp (10 mol-%), and 4-nitrobenzaldehyde (1 mmol), after adjusting the pH of the reaction solution to 8 with NMM, and stirring at room temperature for 12 h gave the corresponding aldol in a yield of 95% and with 67% ee (*Table*, *Entry 1*).

Table. *Reaction of Acetone with Various Aldehydes Catalyzed by* L-*Pro*-L-*Trp in Media* **A**, **B**, *or* **C**



Entry	R	Solvent	Time [h]	Yield [%]	ee [%][a])
1	4-O_2N–C_6H_4	**A**	12	95	67
		C	12	94	70
2	2-O_2N–C_6H_4	**A**	12	84	83
		B	12	80	81
3	3-O_2N–C_6H_4	**B**	12	89	67
		C	12	88	69
4	Ph	**A**	15	62	64
		B	15	60	65
5	4-Br–C_6H_4	**B**	20	85	64
		C	20	87	62
6	2-Cl–C_6H_4	**A**	24	87	59
		C	24	88	58
7	^{i}Pr	**B**	60	90	78
		C	60	90	80
8	Cyclohexyl	**A**	72	64	79
		B	72	63	77

[a]) The ee value was determined by HPLC analysis (*Daicel Chiralpak AD-H* column, hexane/^{i}PrOH 92 : 8; flow rate, 1.0 ml/min, λ 254 or 268 nm).

Furthermore, the generality of the transformation was examined with various aldehydes and acetone in coordination ionic liquids **A**, **B**, or **C** at room temperature, in the presence of NMM (*Table*). The yields were in the range of 60–95% with 58–83% ee, and an influence of the different solvents on the reaction was not noteworthy. In addition, compared with the method using DMSO as solvent [6], the yields and the ee values were of similar order.

Encouraged by this result, we studied the reusability of the catalyst and coordination ionic liquids. Using 4-nitrobenzaldehyde (1 mmol), acetone (4 mmol), L-Pro-L-Trp (10 mol-%), and NMM in **A** at room temperature as model reaction, the yields and ee values were good (93–95% and 67–68% ee, resp.) after ten cycles of reusing the catalyst and the coordination ionic liquids.

In conclusion, we have reported the direct asymmetric aldol reaction catalyzed by L-Pro-L-Trp in coordination ionic liquid **A**, **B**, and **C** in the presence of NMM, with the advantage of simple product isolations, and of reusability of catalyst and coordination ionic liquids. The reaction afforded β-hydroxy ketones in high yields and with good enantioselectivities. The detailed structures and properties of the coordination ionic liquids are currently under investigation.

Experimental Part

General. High performance liquid chromatography (HPLC): *Agilent 1100* liquid chromatograph. Optical rotations: *WZZ-2B* digital polarimeter. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance 400* spectrometer. Elemental analyses: *Vario EL III* instrument.

General Procedure for the Synthesis of Coordination Ionic Liquid. A mixture of the β-caprolactam (3 mol) and tetraalkylammonium halide (1 mol) was heated and stirred at the molten state for 1 h, followed by cooling and drying 24 h at 70° in vacuum, and storage in the drier.

General Procedure for the Synthesis of β-Hydroxy Ketones. Aldehyde (1 mmol), acetone (4 mmol), and L-Pro-L-Trp (10 mol-%) were mixed in the coordination ionic liquid (3 ml). After adjusting the pH of the soln. to 8 with NMM and stirring at r.t., the reaction was quenched with anh. Et_2O (3×5 ml). The combined org. extracts were concentrated, and the crude product was purified by column chromatography (SiO_2) to afford β-hydroxy ketone. The mother liquor (solvent + L-Pro-L-Trp) was retained for further runs.

This study was supported by the *China's Hebei Province Science and Technology Support Project* (No. 13964002D).

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Received August 14, 2012