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Organocatalytic Asymmetric *syn*-Selective Direct Aldol Reaction in Ionic Liquid

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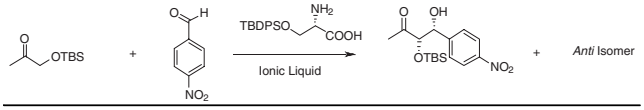
A practical and recyclable organocatalytic strategy is developed to provide *syn*-selective aldol products in ionic liquid. The siloxy serine organocatalyst mediates the direct aldol reaction of TBSO-protected hydroxyacetone with a variety of aldehyde to provide the β-hydroxycarbonyl scaffolds in good yields and enantioselectivities up to 94%.

Asymmetric organocatalysis has recently emerged as a powerful tool in organic synthesis[1] and excellent progress has been achieved following the discovery of the proline-catalyzed aldol reaction, which is the intermolecular variant of the Hajos–Parrish–Eder–Sauer–Wiechert reaction, reported by List, Lerner, and Barbas.[2] Among them, organocatalytic direct asymmetric aldol condensation[3,4] is one of the most effective carbon–carbon forming reactions used for synthesizing enantiomerically enriched β-hydroxycarbonyl structural units found in many biologically active compounds such as macrolide antibiotics and anti-cancer drugs.[5] The potential of this reaction to generate diversity and construction of useful building blocks for numerous pharmaceuticals and natural products have attracted attention from synthetic chemists and the pharmaceutical industry.[6]

In our endeavors toward the development of environmentally friendly organocatalytic strategies, we have developed a siloxy serine catalyst that can mediate the asymmetric aldol in water.[7] As an extension to this work, we have also recently reported the recyclability of this catalyst that uses cyclic ketone, predominantly cyclohexanone as the aldol donor, in [bmim][BF_4] to facilitate the synthesis of *anti*-configured β-hydroxycarbonyl scaffolds.[8] This work was the first report of an efficient recyclable primary amino acid for asymmetric reaction, furnishing a wide variety of aldol products in good yields and excellent enantioselectivities via biphasic system. Noteworthy is that prior chemical functionalization of the ionic liquid[9] with the siloxy serine organocatalyst was not necessary for enabling recyclability. The ionic liquid containing the siloxy serine organocatalyst was recovered after a simple workup of the reaction mixture. Based on this precedent and as part of our program to further develop recyclable organocatalytic strategy in ionic liquids, herein, we extend the protocol to the aldol reaction that install *syn*-selective configured 1,2-diols products.

In our initial experiment, we investigated the siloxy serine catalyzed aldol reaction between monoprotected TBSO–hydroxyacetone and 4-nitrobenzaldehyde in various ionic liquids using a standardized protocol. The results evaluating the merits of the various ionic liquid are shown in Table 1. The reaction catalyzed by 5 mol % of siloxy serine organocatalyst afforded the product in a good yield of 98% and moderate enantiomeric excess of 70% in [hmim][BF_4] (Table 1, Entry 1). An attempt to evaluate [PF_6] counter ions gave the product in a lower yield of 89% with comparable enantiomeric excess (Entry 2). Interestingly, it was observed that the presence of water as additive enhances the enantio-control of the reaction, affording the product with a higher enantiomeric excess of 90% in [hmim][BF_4] (Entry 3). In summary, the optimum conditions was achieved by using 10 mol % of the siloxy serine organocatalyst, ketone donor (2 equiv) in [bmim][BF_4] and water as additives at room temperature for 20 h whereupon the aldol product was isolated in an excellent yield of 93% and an enantiomeric excess of 90% (Entry 4). To enhance the atom economical aspect of this current synthetic approach, the optimized reaction was repeated with 1.1 equiv of the ketone donor. In this experiment, the aldol product was obtained in a good yield of 83% and excellent enantiomeric excess of 88% (Entry 5). Similarly, no chemical functionalization or derivatization was carried out to attach the siloxy serine organocatalyst to the ionic liquid.

Table 1. Optimization studies on the siloxy L-serine catalyzed enantioselective direct aldol reaction in ionic liquid[a]

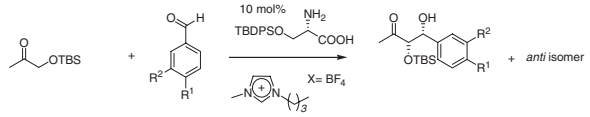


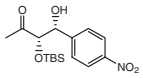
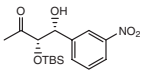
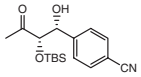
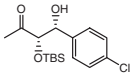
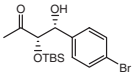
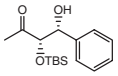
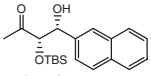
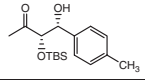
Entry	Ionic liquid	Catalyst /mol %	Additive	Yield[b] /%	*syn*/*anti*[c] /%	ee[d] /%
1	[hmim][BF_4]	5	—	98	70:30	70
2	[hmim][PF_6]	5	—	89	82:18	70
3	[hmim][BF_4]	10	H_2O	78	92:8	90[e]
4	[bmim][BF_4]	10	H_2O	93	92:8	90[e]
5	[bmim][BF_4]	10	H_2O	83	90:10	88[f]

[a]Unless otherwise noted, the reaction was performed with aldehyde (0.5 mmol), ketone (1.0 mmol), and siloxy serine organocatalyst (0.025 or 0.05 mmol) in ionic liquid (0.5 mL) at room temperature for 20 h. [b]Combined yield of isolated diastereomers. [c]Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Enantiomeric excess refers to the *syn*-isomer and was determined by HPLC analysis on a chiral phase. [e]The reaction was carried out using ionic liquid (0.4 mL) and water (0.1 mL) as additive. [f]The reaction was carried out with 1.1 equiv of ketone donor.

Having optimized the reaction conditions, the direct aldol reaction was extended to a series of aromatic aldehydes as acceptors. The more reactive aromatic aldehydes with 3- or 4-nitro and 4-cyano substituents afforded the products in high yields, excellent enantioselectivities and *syn*-selectivity

Table 2. The catalytic asymmetric aldol reaction catalyzed by siloxy L-serine organocatalyst in [bmim][BF_4][a]



Entry	Product		Time /h	Yield[b] /%	*syn*/*anti*[c] /%	ee[d] /%
1		**1a**	24	93	91:9	90
2		**1b**	18	87	94:6	94
3		**1c**	20	89	89:11	90
4		**1d**	20	72	91:9	65
5		**1e**	24	70	90:10	86
6		**1f**	22 22	37 93[c]	90:10 87:13	91 81
7		**1g**	22 22	38 63[c]	86:14 82:18	81 84
8		**1h**	24	60[c]	81:19	78

[a]Unless otherwise noted, the reaction was performed with aldehyde (0.5 mmol), ketone (1.0 mmol), and siloxy serine organocatalyst (0.05 mmol) in ionic liquid (0.4 mL) and water (0.1 mL) at room temperature. [b]Combined yield of isolated diastereomers. [c]Diastereoselectivity was determined by ^{1}H NMR analysis of the reaction mixture. [d]Enantiomeric excess refers to the *syn*-isomer and was determined by HPLC analysis on a chiral phase. [e]Reaction was carried out with 20 mol % catalyst loading.

(Table 2, Entries 1–3). Moderate yields and enantiomeric excess were achieved in the case of 4-chloro- or 4-bromobenzaldehyde as acceptors (Entries 4 and 5). Neutral aldehydes such as benzaldehyde and naphthaldehyde afforded moderate to high yields with good enantio- and diastereoselectivities (Entries 6 and 7) using higher catalyst loading. The catalytic process using a representative aldehyde with a *para*-electron-donating group, afforded the product in good enantioselectivity in modest yield (Entry 8).

Having established the practicality of this reaction, attention was focused on the recyclability and reusability of this organocatalyst in the ionic liquid. After ether extraction of the product, the ionic liquid residue was dried with nitrogen and the catalytic system was reloaded with 4-nitrobenzaldehyde and TBSO–hydroxyacetone for the next run. As shown in Table 3, it was found that the solvent and catalyst system could be reused for up to 3 times with good yields and comparable enantioselectivities of **1a**. The significant decrease in the chemical yield of the product in the third cycle suggested that the lost of catalytic activity might be due to the leaching of the siloxy serine catalyst to the ether layer during the extraction procedure.

Table 3. Recycling studies[a] of the siloxy L-serine catalyzed direct aldol reaction in [bmim][BF_4]

Cycle	*T*/h	Yield[b] /%	*syn*/*anti*[c] /%	ee[d] /%
1	24	93	91:9	90
2	26	82	92:8	87
3	48	60	90:10	86

[a]Unless otherwise shown, the reaction was performed with aldehyde (0.5 mmol), ketone (1.0 mmol), siloxy serine organocatalyst (0.05 mmol) in [bmim][BF_4] (0.4 mL), and water (0.1 mL) at room temperature. [b]Combined yield of isolated diastereomers. [c]Diastereoselectivity was determined by ^{1}H NMR analysis of the reaction mixture. [d]Enantiomeric excess refer to the *syn*-isomer and was determined by HPLC analysis on a chiral phase.

In conclusion, we have developed an efficient and recyclable siloxy serine organocatalyst for asymmetric *syn*-selective aldol reaction in ionic liquid.[10] Features worth noting include: (1) the direct asymmetric aldol reaction proceeded efficiently in [bmim][BF_4] to afford a variety of valuable compounds from commercially available substrates; (2) the procedure is simple to perform and requires mild conditions; (3) the siloxy serine organocatalyst is prepared easily and economically from commercially available sources, with both enantiomers readily available; (4) the yields and enantioselectivities obtained for most of the products were similar, if not, higher as compared to using water as the solvent; and (5) prior chemical attachment of the siloxy serine catalyst to the ionic liquid was not needed for the catalytic activity and recyclability of the organocatalyst. Further extension of this catalytic system to other asymmetric reactions is ongoing in our laboratory and the results will be reported in due course.

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