Tetrahedron Letters 49 (2008) 4235–4238

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A recyclable non-immobilized siloxy serine organocatalyst for the asymmetric direct aldol reaction

Yong-Chua Teo [a,*], Guan-Leong Chua [b]

[a] Natural Sciences and Science Education, National Institute of Education, Nanyang Technological University, 1 Nanyang Walk, Singapore 637616, Singapore
[b] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371, Singapore

ARTICLE INFO

Article history:
Received 19 February 2008
Revised 25 April 2008
Accepted 30 April 2008
Available online 2 May 2008

Keywords:
Direct asymmetric aldol
Ionic liquid
Organocatalyst
Recyclable

ABSTRACT

A recyclable siloxy-L-serine organocatalyst has been developed to catalyze asymmetric direct aldol reactions in [bmim][BF_4], furnishing the β-hydroxy carbonyl scaffold in high enantio- and diastereoselectivities using a selection of aromatic aldehydes and cycloalkanes. The siloxy serine organocatalyst in the ionic liquid can be reused for up to four successive cycles with comparable enantioselectivities.

The direct catalytic asymmetric aldol reaction is a powerful carbon–carbon bond forming reaction and is used for the construction of enantiomerically enriched β-hydroxy carbonyl compounds and their derivatives. The intense demand for stereoselective syntheses of aldol products has been fuelled by its application in producing key synthons in numerous synthetic strategies for natural products synthesis, as well as in medicinal chemistry.[1]

The application of ionic liquids as 'green' alternatives to conventional solvents for a wide range of organic transformations has become increasingly important in recent years. Ionic liquids have the potential to have low human toxicities and eco-toxicities.[2] In addition, ionic liquids are nonvolatile, stable, and can be reused.[3] Furthermore, the development of efficient asymmetric organocatalytic protocols in ionic liquids is interesting since it provides an avenue for the recovery and reuse of the organocatalyst. This would make the reaction protocol economical and environmentally friendly.

The majority of recent strategies for the reuse of organocatalysts in ionic liquids have involved chemical functionalization of the ionic liquid with the purpose of attaching the chiral organocatalyst. In most, if not in all cases, proline was introduced to the side-chains of the ionic liquid.[4] This strategy, although ensuring the recyclability of the catalysts, might require time-consuming and uneconomical transformations, and the associated problems with manipulation of ionic liquids in multistep syntheses.

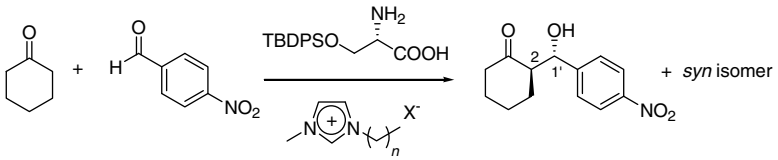
Our group thus investigated the possibility of immobilizing the organocatalysts in ionic liquids without any chemical transformations. For this early work, we employed the siloxy serine organocatalyst developed recently in our group. This siloxy serine was found previously to catalyze the asymmetric direct aldol reaction via a biphasic system, furnishing a wide variety of β-hydroxy carbonyl scaffolds in good yields and excellent enantioselectivities.[5] In this Letter, we describe the use, and reuse, of the acyclic TBDPS-L-serine catalyst that catalyzed efficiently asymmetric direct aldol reactions in the ionic liquid [bmim][BF_4]. Noteworthy is that prior chemical functionalization of the ionic liquid with the siloxy serine catalyst was not necessary for enabling recyclability. The ionic liquid containing the siloxy serine organocatalyst was recovered after a simple work-up of the reaction mixture.

In an initial study, we investigated the siloxy serine catalyzed reaction between cyclohexanone and 4-nitrobenzaldehyde in a series of ionic liquids, including both $[PF_6]^-$ and $[BF_4]^-$ type ionic liquids, using a standardized protocol. The organocatalyst (0.05 mmol) was added to a reaction vial containing 4-nitrobenzaldehyde (0.5 mmol), cyclohexanone (2.5 mmol), and ionic liquid (0.5 mL). The reaction was stirred at room temperature for 18 h. After the reaction was complete, the aldol product was isolated by a simple extraction using diethyl ether. The results evaluating the merits of the various ionic liquids are shown in Table 1. The desired products were obtained in good yields (>81%) and enantiomeric excesses (78–90% ee).

* Corresponding author. Tel.: +65 6790 3846; fax: +65 6896 9414.
E-mail address: yongchua.teo@nie.edu.sg (Y.-C. Teo).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.159

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



Entry	Ionic liquid	Yield[b] (%)	*anti*/*syn*[c] (%)	ee[d] (%)
1	[bmim][PF_6], $n = 3$	82	78:22	86
2	[hmim][PF_6], $n = 5$	81	80:20	80
3	[omim][PF_6], $n = 7$	86	77:23	78
4	[bmim][BF_4], $n = 3$	86	82:18	90
5	[hmim][BF_4], $n = 5$	84	77:23	84
6	[hmim][PF_6], $n = 5$	85	73:27	86[e]
7	[bmim][BF_4], $n = 3$	<5	—	—[f]

[a] Unless otherwise noted, the reaction was performed with aldehyde (0.5 mmol), ketone (2.5 mmol), and siloxy serine organocatalyst (0.05 mmol) in ionic liquid (0.5 mL) at room temperature for 18 h.
[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 *anti* isomer and was determined by HPLC analysis on a chiral phase.
[e] Reaction was carried out in 0.25 mL of [hmim][PF_6].
[f] Reaction was carried out using L-serine as the organocatalyst with a reaction time of 72 h.

Interestingly, it was observed that the enantiomeric excess obtained in the above mentioned two classes of ionic liquids decreased with increasing chain length of the alkylated imidazole moiety. In the case of [PF_6]-type ionic liquids, the best enantiomeric excess was achieved using [bmim][PF_6] (86% ee, Table 1, entry 1), whereas [omim][PF_6] afforded the aldol product with a moderate enantiomeric excess (78% ee, entry 3). The same trend was also observed for the [BF_4]-type ionic liquids. Among the ionic liquids investigated, the direct aldol reaction carried out in [bmim][BF_4] was the best, affording the aldol product with a good yield of 86% and an enantiomeric excess of 90% (entry 4). Moreover, the reaction carried out using a reduced amount of ionic liquid led to a significant decrease in both diastereo- and enantioselectivities (entry 6). It is also worth noting that the direct aldol reaction carried out using unprotected L-serine as the organocatalyst afforded the product in very poor yield after 72 h (entry 7). This result illustrated that the hydrophobic OTBDPS moiety in the serine-derived organocatalyst was essential, probably for the formation of a reaction core within the ionic liquid thus channeling the direct aldol reaction in an enantioselective fashion.[6]

Having optimized the reaction conditions, the siloxy serine catalyzed direct aldol reaction in [bmim][BF_4] was extended to a series of aldehydes to explore the generality of this catalytic system. The results are summarized in Table 2.

In most cases, the β-hydroxy carbonyl compounds were obtained in good yields and high enantioselectivities. The more reactive aldehydes underwent the catalytic process to afford the products in excellent enantioselectivities and with good *anti*-selectivity (Table 2, entries 1–4). The direct aldol reaction of neutral aldehydes catalyzed by the siloxy-L-serine catalyst also afforded the products in high enantio- and diastereoselectivities (entries 5 and 6). Moreover, the enantioselectivity obtained for a representative electron rich aldehyde gave good enantioselectivity, although the yield was moderate (entry 7). Good enantioselectivities were also obtained when cyclopentanone was employed as the donor albeit with low diastereoselectivities (entries 8 and 9). Although the aldol reaction of acetone and 4-nitrobenzaldehyde proceeded in the ionic liquid, the enantioselectivity and yield obtained were only moderate (entry 10). The stereochemistry of the β-hydroxy group of the aldol adducts **1** was determined to have *S* configuration by chiral-phase HPLC analysis in comparison with reported data.[7]

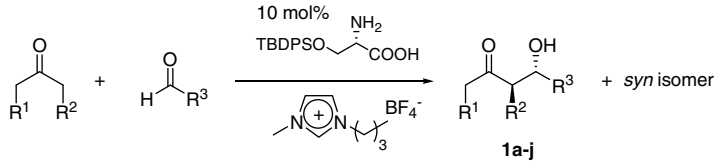
Next, we continued our study by exploring the recyclability of the siloxy serine organocatalyst. The reaction of 4-nitrobenzaldehyde (0.5 mmol) and cyclohexanone (2.5 mmol) in [bmim][BF_4] (0.5 mL) was selected in this model study. After the reaction was complete, the reaction mixture was extracted with ether (6 mL × 3) to give the ionic liquid residue.

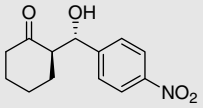
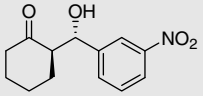
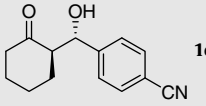
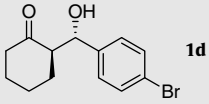
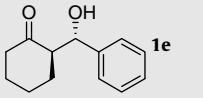
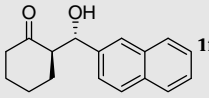
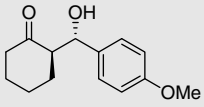
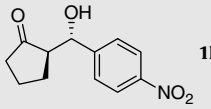
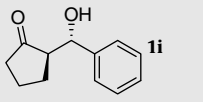
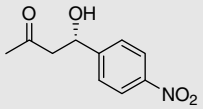
However, treatment of the resultant residue with the aldehyde and cyclohexanone did not afford any products after 60 h. Investigations into this problem revealed the presence of the siloxy serine catalyst in the ether extracts as evident in the crude ^{1}H NMR. This suggested that the siloxy serine organocatalyst exhibited preferential solubility in the ether layer as opposed to the ionic liquid. Henceforth, a modification of the extraction protocol was initiated to ensure that the siloxy serine catalyst remained in the ionic liquid residue.

In this modified protocol, water (0.25 mL) was added to the reaction mixture prior to the extraction step. The ionic liquid and water mixture was then extracted with ether (6 mL × 3) to afford the organic extracts containing the crude product. This was then immediately purified by flash chromatography. The water residue in the ionic liquid was then removed under reduced pressure until a constant weight was achieved. The resulting ionic liquid residue was then used for the next run. It was demonstrated that identical reactivities and stereoselectivities were observed using this recycled ionic liquid residue and the biphasic property of the ionic liquid was maintained. Some loss of activity was observed for the third and fourth reuse of the siloxy serine organocatalyst in the ionic liquid but good yields and enantioselectivities could still be achieved. The results of the recyclability studies are shown in Table 3.

In conclusion, we have demonstrated the first efficient asymmetric direct aldol reaction catalyzed by a recyclable siloxy-L-serine organocatalyst in an ionic liquid[8] without prior chemical functionalization. Noteworthy features of this system are (1) the direct aldol reaction proceeded in [bmim][BF_4] using simple procedures; (2) prior chemical attachment of the siloxy serine catalyst to the ionic liquid was not necessary for the catalytic activity and recyclability; (3) the siloxy serine catalyst can be prepared easily

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

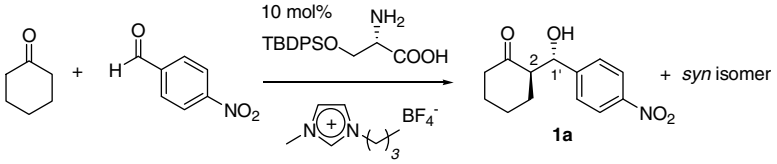


Entry	Product	*t* (h)	Yield[b] (%)	*anti*/*syn*[c] (%)	ee[d] (%)
1	 **1a**	18	86	82:18	90
2	 **1b**	16	85	83:17	92
3	 **1c**	16	83	81:19	88
4	 **1d**	18	78	82:18	90
5	 **1e**	16	52	83:17	90
6	 **1f**	18	62	86:14	90
7	 **1g**	22	40	88:12	88
8	 **1h**	18	69	52:48	84
9	 **1i**	18	62	62:38	86
10	 **1j**	23	42	—	41

[a] Unless otherwise noted, the reaction was performed with aldehyde (0.5 mmol), ketone (2.5 mmol), and siloxy serine organocatalyst (0.05 mmol) in [bmim][BF_4] (0.5 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 *anti* isomer and was determined by HPLC analysis on a chiral phase.

and economically from commercially available sources, with both enantiomers readily available; (4) the siloxy serine organocatalyst in [bmim][BF_4] can be recycled for up to four times with comparable enantioselectivities and; (5) 10 mol % of catalyst was sufficient to furnish the aldol products in excellent yields and enantioselectivities. Further work on broadening the scope of this siloxy serine organocatalyst and the use of other amino acid derivatives is ongoing in our laboratory.

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



Cycle	*T* (h)	Yield[b] (%)	*anti*/*syn*[c] (%)	ee[d] (%)
1	18	86	82:18	90
2	18	84	82:18	88
3	48	72	81:19	86
4	60	68	82:19	86

[a] Unless otherwise noted, the reaction was performed with aldehyde (0.5 mmol), ketone (2.5 mmol), and siloxy serine organocatalyst (0.05 mmol) in [bmim][BF_4] (0.5 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 *anti* isomer and was determined by HPLC analysis on a chiral phase.

Acknowledgment

We thank the National Institute of Education (Grant No. RP5/06 TYC), Nanyang Technological University, for their generous financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.159.

References and notes

1. For recent reviews, see: (a) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595; (b) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65; (c) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506; (d) Mukherjee, S.; Yang, J.-W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
2. For a recent review, see: (a) Ranke, J.; Stolte, S.; Strömann, R.; Arning, J.; Jastorff, B. *Chem. Rev.* **2007**, *107*, 2183; For examples, see: (b) Stolte, S.; Matzke, M.; Arning, J.; Böschen, A.; Pitner, W. R.; Welz-Biermann, U.; Jastorff, B.; Ranke, R. *Green Chem.* **2007**, *9*, 1170.
3. (a) Jacques, M. *Adv. Synth. Catal.* **2006**, *348*, 275; (b) Chen, S.-L.; Chua, G.-L.; Ji, S.-J.; Loh, T.-P. Ionic Liquid: A Green Solvent for Organic Transformations I, in Ionic Liquids in Organic Synthesis. In *ACS Symposium Series 950*; Malthotra, S. V., Ed.; American Chemical Society, 2007; p 161; (c) Chen, S.-L.; Chua, G.-L.; Ji, S.-J.; Loh, T.-P. Ionic Liquid: A Green Solvent for Organic Transformations II, in Ionic Liquids in Organic Synthesis. In *ACS Symposium Series 950*; Malthotra, S. V., Ed.; American Chemical Society, 2007; p 177; (d) Parvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615; (e) Afonsa, C. A. M.; Branco, L. C.; Candeias, N. R.; Gois, P. M. P.; Lourenco, N. M. T.; Mateus, N. M. M.; Rosa, J. N. *Chem. Commun.* **2007**, 2669.
4. (a) Kotrusz, P.; Kimentova, I.; Gotov, B.; Toma, S.; Solcaniova, E. *Chem. Commun.* **2002**, 2510; (b) Loh, T. P.; Feng, L.-C.; Yang, H. Y.; Yang, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 8741; (c) Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 3949; (d) Miao, W.; Chan, T.-H. *Adv. Synth. Catal.* **2006**, *348*, 1711; (e) Ni, B.; Zhang, Q.; Headley, A. D. *Green Chem.* **2007**, *9*, 737; (f) Zhou, L.; Wang, L. *Chem. Lett.* **2007**, *36*, 628.
5. (a) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586; (b) Zou, W.; Ibrahem, I.; Dziedzic, P.; Sundén, H.; Córdova, A. *Chem. Commun.* **2005**, 4946; (c) Dziedzic, P.; Zou, W.; Hafrén, J.; Córdova, A. *Org. Biomol. Chem.* **2006**, *4*, 38; (d) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383; (e) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801; (f) Limbach, M. *Tetrahedron Lett.* **2006**, *47*, 3843; (g) Deng, D.-S.; Cai, J. *Helv. Chim. Acta* **2007**, *90*, 119; (h) Wu, X.; Jian, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812; (i) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 288; (j) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2007**, *46*, 5572; (k) Teo, Y.-C. *Tetrahedron: Asymmetry* **2007**, *18*, 1155.
6. (a) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809; (b) Breslow, R. *Acc. Chem. Res.* **2004**, *37*, 471; (c) Lindstrom, U. M.; Anderson, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 548.
7. Hayashi, Y.; Sumiya, T.; Takashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958.
8. General procedure for the asymmetric direct aldol reaction in ionic liquids. *Preparation of (2R,1′S)-2-[hydroxy-(4-nitrophenyl)-methyl]-cyclohexanone* **1a**: A catalytic amount of siloxy serine catalyst (0.0172 g, 0.05 mmol, 0.1 equiv) was added to a vial containing 4-nitrobenzaldehyde (0.0760 g, 0.5 mmol, 1.0 equiv), cyclohexanone (0.26 mL, 2.5 mmol, 5 equiv), and [bmim][BF_4] (0.5 mL) under air in a closed system. The reaction mixture was stirred at room temperature for 18 h and subsequently extracted with diethyl ether (6 mL × 5). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The crude aldol product was purified by silica gel column chromatography (hexane/ethyl acetate 4:1) to afford **1a** as a white solid (0.107 g, 86% yield). The diastereomeric *anti*–*syn* ratio was determined by ^{1}H NMR analysis of the reaction mixture: δ 5.48 (d, 1H, J = 1.8 Hz, *syn*, minor), 4.89 (d, 1H, J = 8.8 Hz, *anti*, major). Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 254 nm, 20 °C): t_R = 26.3 min (minor) and 34.9 min (major).