Self-assembled organic–inorganic hybrid silica with ionic liquid framework: a novel support for the catalytic enantioselective Strecker reaction of imines using $Yb(OTf)_3$–pybox catalyst†

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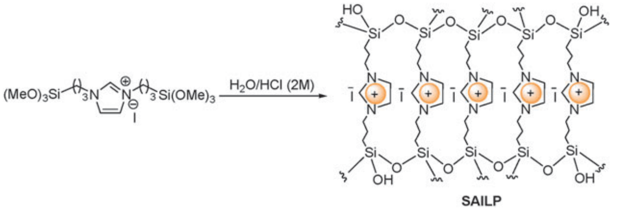
$Yb(OTf)_3$–pybox is immobilized in a novel self-assembled ionic liquid hybrid silica and has been successfully applied as a catalyst for the asymmetric Strecker hydrocyanation of aldimines. This catalytic system can be reused for at least 6 times without any significant loss of activity and enantioselectivity.

The catalytic asymmetric Strecker reaction provides a straightforward and facile approach for the preparation of chiral α-aminonitriles, which are important structural motifs for construction of both natural and unnatural α-aminoacids.[1] The development of efficient chiral catalysts continues to be one of the most challenging aspects of this and a number of either metal-based chiral Lewis acid catalysts[2] or organocatalysts[3] have been introduced for the activation of the carbon = nitrogen double bond of imines followed by the enantioselective addition of cyanide ion sources. While significant progress has been made, the majority of reported catalysts are homogeneous where separation of the expensive chiral catalysts from products and their reuse can be problematic.[4] This is an especially serious problem in the pharmaceutical industry because the level of metallic impurities in active pharmaceutical intermediates is closely regulated. In this regard, immobilized catalysts offer advantages over non-immobilized systems and in some instances heterogeneous catalysts can lead to higher enantiomeric excess than their homogeneous counterparts.[5] However, despite the attractiveness of using immobilized enantioselective catalysts, to the best of our knowledge, there are only two reports on the application of supported chiral catalysts in the asymmetric Strecker reaction through the pioneering work of Jacobsen and Shibasaki.[6] The main strategy in these is to immobilize chiral catalysts through the formation of a covalent bond between the solid support (polymeric or inorganic) and the chiral catalyst. While this strategy is the most popular method for the immobilization of chiral homogeneous catalysts, it often needs an additional functionalization step of the chiral ligands, which may increase the total catalyst preparation cost. Therefore, in many applications it is more desirable to use non-covalent immobilization strategies in which no further modification of the commercially available chiral ligands (or catalysts) is necessary.[7]

Ionic liquids (ILs) have attracted significant attention over the last decade, and their applications as green reaction media have been widely explored.[8] However, since ionic liquids are very expensive and their environmental impact due to wasteful preparation procedures or toxicity can be high, their widespread practical applications are very limited, where the properties of ILs offer particular value it is desirable to keep the amount of ionic liquids required to a minimum and here immobilization on solid supports is a viable option.[9] Although, these supported ionic liquid catalysis (SILC) systems significantly reduce the amount of IL in a typical process, loading of the chemically immobilized IL can mean very high solids loading in the reaction and ILs commonly leach from the support. Moreover, there is no precedent on the use of this strategy in the catalytic asymmetric Strecker reaction of imines. Very recently, we have explored a highly enantioselective Strecker hydrocyanation of a wide variety of aldimines giving good to excellent yields and enantioselectivities using homogeneous $Yb(OTf)_3$–pybox complexes.[10] Despite the significant utility of this catalyst system in asymmetric Strecker reaction, the catalysts could not be recycled.

Herein, we present the first use of a **S**elf-**A**ssembled organic–inorganic hybrid silica with **I**onic **L**iquid **P**hase (SAILP) as a novel support for chiral $Yb(OTf)_3$–pybox catalyst system in which the catalyst remains active, and highly selective, over extended periods in catalytic asymmetric Strecker reactions of imines. We have found that not only SAILP hybrid silica is a superb support for $Yb(OTf)_3$–pybox, but also the resulting immobilized material catalyzes the Strecker reaction in a heterogeneous pathway, without leaching of the catalyst into solution under the described reaction condition. The self-assembled ionic liquid phase (SAILP) was prepared by hydrolysis and co-condensation of 1,3-bis(3-trimethoxysilylpropyl)-imidazolium iodide (BTMSPI)[11] under mild acidic conditions (Scheme 1).

The resulting yellow solid was characterized by simultaneous thermal analysis and solid-state NMR. The uniform



Scheme 1 Preparation of SAILP material.

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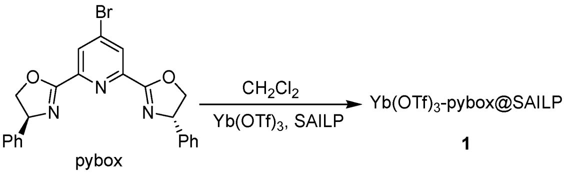
distribution of alkyl imidazolium group in the silica framework of the material was confirmed by ^{29}Si- and ^{13}C-CP–MAS NMR spectroscopy. The ^{29}Si spectrum of SAILP displays three signals at −49.1, −58.52 and −68.36 ppm corresponding, respectively, to T^1 [C–Si(OSi)$(OH)_2$], T^2 [C–Si$(OSi)_2$(OH)], and T^3 [C–Si–$(OSi)_3$] sites for Si species which are covalently attached to carbon atoms (see ESI†, Fig. S1). In addition, the absence of any resonance at −90 to −115 ppm which are related to Q^n sites of the silica framework clearly shows that no carbon–silicon bond cleavage of the BTMSPI molecules occurred in the synthesis conditions of SAILP.

The solid state ^{13}C CP–MAS NMR spectrum of SAILP was also determined to clarify the characteristic signals of the IL bridging moieties (see ESI†, Fig. S2). This spectrum illustrates carbon signals of ionic liquid moieties as follows: δ (ppm) = 10.5 (SiCH_2), 24.7 ($CH_2CH_2CH_2$), 52.8 (CH_2N), 123.6 ($CHCH$), and 136.7 (NCHN). These data show that the ionic liquid groups were indeed well incorporated intact into the material network. Moreover, the absence of any other carbon signal confirms that almost all of the Si–C bonds survived intact under the synthesis conditions. Thermogravimetric analysis of the SAILP composite was conducted from room temperature to 900 °C (see ESI†, Fig. S3). A loss of 2–5 wt% below 120 °C is due to the loss of residual methanol and water. This is followed by a second large main weight loss of ∼39% between 350–450 °C due to decomposition of alkyl imidazolium groups inside the SAILP framework. The amount of ionic liquid incorporated into the framework of the materials was estimated from the TGA to be ∼85% of the ionic liquid in the initial gel. This was further confirmed by elemental analysis of the material.

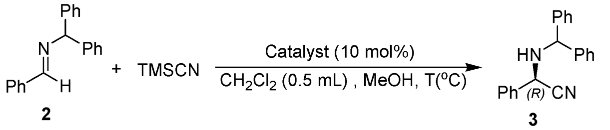
In the next stage, the ability of this self-assembled ionic liquid to immobilize $Yb(OTf)_3$–pybox catalyst and its use in the Strecker reaction was examined (Scheme 2).

Asymmetric catalysis using the supported chiral catalyst **1** (equivalent to 10 mol% of $Yb(OTf)_3$–pybox) was investigated in the reaction of *N*-benzylidenediphenylmethanamine **2** with trimethylsilyl cyanide (TMSCN) under our previously reported condition at −78 °C (Table 1, entry 1).[10] Although high yields and enantioselectivity were obtained under homogeneous conditions (Table 1, entry 2), using the heterogeneous chiral catalyst **1** gave disappointing results (Table 1, entry 1). In light of the above observation, and based on the assumption that the aldimine **2** is less prone to reaction at −78 °C, we examined the Strecker reaction of **2** at higher temperatures. We found that by increasing the reaction temperature to −50 °C, the Strecker reaction started and proceeded smoothly at this temperature using **1** as catalyst, and the desired α-aminonitrile **3** was isolated in an excellent yield of 95% after 36 h with high enantioselectivity of 80% (Table 1, entry 3). It is important to note that while the same reaction using homogeneous $Yb(OTf)_3$–pybox under identical reaction conditions went to completion within 36 h, the enantiomeric excess of **3** was only 53% (Table 1, entry 4). In a separate experiment, the use of 1,3-bis(3-trimethoxysilylpropyl)imidazolium iodide (BTMSPI) instead of the solid support was shown to give much worse results further confirming the beneficial role of SAILP in obtaining acceptable enantioselectivities (Table 1, entry 5). These results clearly show the existence of a synergistic effect between the SAILP and that of immobilized $Yb(OTf)_3$–pybox catalyst system.



Scheme 2 Preparation of heterogeneous chiral catalyst **1** and its application in the asymmetric Strecker reaction.

Table 1 Enantioselective Strecker reaction of *N*-benzylidenediphenylmethanamine catalyzed by $Yb(OTf)_3$–pybox catalyst system[a]



Run	Catalyst	T/°C	Time/h	Yield (ee)[b,c] [%]
1[d]	$Yb(OTf)_3$–pybox@SAILP	−78	48	<5 (ND)
2	$Yb(OTf)_3$–pybox	−78	30	95 (97)
3[d]	$Yb(OTf)_3$–pybox@SAILP	−50	36	95 (80)
4	$Yb(OTf)_3$–pybox	−50	36	93 (53)
5	$Yb(OTf)_3$–pybox/IL[e]	−50	36	97 (39)

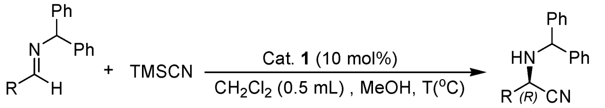
[a] $Yb(OTf)_3$ (10 mol%)/pybox (20 mol%), TMSCN (2 equiv.), MeOH (2 equiv.). [b] Yields refer to isolated products. [c] Enantiomeric excesses were determined by HPLC analysis on a CHIRALPAK AD column. [d] 0.6 g of SAILP was used. [e] BTMSPI was used as ionic liquid.

Under the optimized reaction conditions (Table 1, entry 3), we then investigated the generality of our method with respect to the aldimine structure (Table 2). A range of aromatic aldimines, including substituted aromatic (entries 2–9, 12 and 13), heteroaromatic (entries 10 and 11), α,β-unsaturated (entry 14), and aliphatic aldehyde-derived aldimines (entry15), were tested in the asymmetric Strecker hydrocyanation using our new catalyst, giving α-aminonitriles in good to excellent yields with modest to high level of enantioselectivity. Remarkably, the imines derived from pyridine-3-carbaldehyde and thiophene-2-carbaldehyde are effective substrates, affording the respective products in 71% and 82% ee, respectively (Table 2, entries 10 and 11). However, when more challenging α-unbranched aliphatic aldimines were used, the enantioselectivities were not complete even under a modified three-component procedure (Table 2, entries 15 and 16).

We attribute the low enantioselectivities in the case of aliphatic aldimines to isomerization of the imine to the corresponding enamine and also to α-racemization of the corresponding α-aminonitriles under the reaction conditions. However, considering the significant difficulty of this type of reaction, we believe that the enantioselectivities are still in a synthetically useful range. To further clarify the advantages of our heterogeneous chiral ytterbium catalyst, Table 2 also summarizes both the catalytic activity and enantioselectivity of our previous homogeneous system[10] for the same reaction conditions at −50 °C (entries 17–24). These results clearly confirm that ee values were consistently higher when using **1** rather than its homogeneous analogue under the described reaction conditions (temperature range −60 °C to −40 °C).

We have also found that our catalyst demonstrated excellent reusability; after the first use of the catalyst **1** in the asymmetric

Table 2 Enantioselective Strecker reaction of aldimines catalyzed by Yb(OTf)$_3$–pybox@SAILP catalyst system[a]



Run	R	Time/h	T/°C	Yield (ee)[b,c] [%]
1	Ph	36	−50	95 (80)
2	2-Me–C_6H_4	48	−60	94 (79)
3	3-Me–C_6H_4	72	−50	93 (71)
4	4-Me–C_6H_4	72	−50	86 (77)
5	2-Br–C_6H_4	72	−40	81 (86)
6	3-Br–C_6H_4	72	−40	71 (53)
7	4-Br–C_6H_4	72	−40	88 (71)
8	2-Cl–C_6H_4	72	−40	58 (71)
9	2-Naphthyl	72	−60	92 (74)
10	3-Pyridyl	72	−50	95 (71)
11	2-Thenyl	96	−50	55 (82)
12	3-TBDMSO–ph	72	−50	89 (60)
13	2,4-Me_2–C_6H_3	48	−50	81 (72)
14	Ph–CH=CH	72	−50	97 (90)
15[d]	Ph–CH_2CH_2	48	−50	91 (44)
16[d]	$CH_3(CH_2)_5$	48	−50	85 (45)
17[e]	Ph	36	−50	95 (53)
18[e]	2-Cl–C_6H_4	72	−40	95 (46)
19[e]	2-Br–C_6H_4	72	−40	97 (70)
20[e]	4-Me–C_6H_4	72	−50	96 (50)
21[e]	2-Me–C_6H_4	48	−60	98 (62)
22[e]	Ph–CH=CH	72	−50	98 (62)
23[e]	3-Pyridyl	72	−50	72 (56)
24[d,e]	Ph–CH_2CH_2	48	−50	95 (34)

[a] Yb(OTf)$_3$ (10 mol%)/pybox (20 mol%), SAILP (0.6 g), TMSCN (2 equiv.), MeOH (2 equiv.) unless otherwise stated. [b] Yields refer to isolated products. [c] Enantiomeric excesses were determined by HPLC analysis on a CHIRALPAK AD column. [d] Reaction was performed under one pot conditions. [e] Yb(OTf)$_3$ (10 mol%)/pybox (20 mol%), TMSCN (2 equiv.), MeOH (2 equiv.) under homogeneous conditions.

Strecker reaction of **2** to give **3** in 95% yield and 80% ee, the catalyst was washed with *n*-hexane and the recovered catalyst was successfully used in 6 subsequent reaction runs and exhibited remarkably consistent enantioselectivities (Fig. 1). To rule out the contribution of homogeneous catalysis, the asymmetric Strecker reaction of **2** was attempted using the residue from the *n*-hexane extraction. No appreciable amount of enantioselectivity was observed even after prolonged reaction time (72 h) at −50 °C. This result clearly confirms that the reaction mainly occurs on the surface of the SAILP.[12]

Further studies to improve the reaction efficiency and to use this strategy for other enantioselective catalyst systems are in progress.

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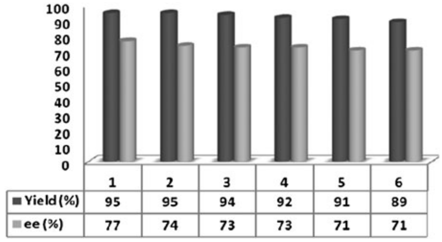

Fig. 1 Reusability of the Yb(OTf)$_3$–pybox@SAILP catalyst in the enantioselective Strecker reaction of *N*-benzylidenediphenylmethanamine.

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