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Asymmetric Mannich Reaction of Malonates with Aldimines Using Yb^{III}-Pybox Complexes Supported on Self-Assembled Organic–Inorganic Hybrid Silica with an Imidazolium Framework

Babak Karimi,*[a] Ehsan Jafari,[a] and Dieter Enders[b]

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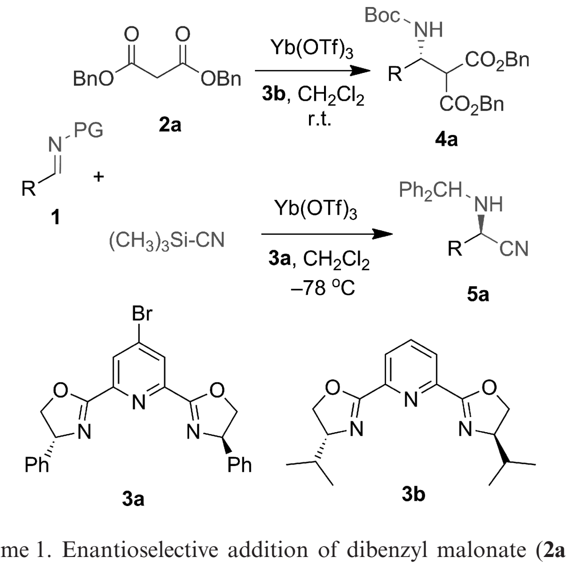
$Yb(OTf)_3$/*i*Pr-pybox (**3b**) immobilized on a self-assembled organic–inorganic hybrid silica with ionic liquid phase (SAILP) (Catalyst **A**) behaves as an efficient and recyclable catalyst in the enantioselective Mannich reaction of malonate esters with *N*-Boc aldimines to afford the corresponding products in good yields and enantioselectivities. In particular, it has been shown that the use of catalyst **A** resulted in much superior enantioselectivities in comparison with either 1:2 $Yb(OTf)_3$/**3b** on a periodic mesoporous organosilica with 10 percent imidazolium framework (catalyst **C**) or a catalyst comprising 1:1 $Yb(OTf)_3$/**3b** on SAILP under the same reaction conditions. Catalyst **A** could be recycled and reused at least four times with only a slight decrease in either catalytic activity or enantioselectivity.

Introduction

Catalytic asymmetric Mannich reactions constitute highly useful and efficient methods for the preparation of chiral β-amino carbonyl compounds through C–C bond formation. This is an important organic transformation because the prepared β-amino carbonyl compounds are significant chiral building blocks in the skeleton of important pharmaceutical and agrochemical molecules and they are vital intermediates of organic chemistry.[1,2] In particular, the use of malonate derivatives as nucleophiles in the Mannich reaction of imines has attracted much attention because the products of this reaction can be easily decarboxylated to give the corresponding β-amino acid derivatives.[3] In this respect, despite the fact that much attention has been dedicated to the development of new and efficient organocatalytic Mannich protocols by employing malonate-type nucleophiles,[4] catalysis based on chiral metal complexes remains very limited.[5] In addition, to our knowledge, there has been no precedent example of asymmetric Mannich reactions using malonate derivatives in the presence of supported and recyclable metal catalysts. Adding to this appeal, in contrast to the relatively well-developed enantioselective Mannich reaction with a variety of chiral metal complexes based on Al, Ti, Zr, or Cu etc.,[6] only one report of employing Yb^{III} chiral complexes has been identified for this transformation.[7] Therefore, it seems that there is still much room to develop new variations of these catalysts in asymmetric Mannich reaction.[8]

In this context, we recently disclosed a highly efficient and enantioselective Strecker hydrocyanation of a wide range of *N*-benzhydryl aldimines by utilizing a chiral $Yb(OTf)_3$/**3a** complex, whereby the corresponding α-aminonitriles were obtained in excellent yields and with enantiomeric excess (*ee*) values of up to 98% (Scheme 1).[9] This powerful catalyst in the form of $Yb(OTf)_3$/**3b** complex has subsequently been employed as an efficient and highly enantioselective catalyst in the Mannich reaction of malon-



Scheme 1. Enantioselective addition of dibenzyl malonate (**2a**) to *N*-Boc imine or TMSCN to *N*-benzhydryl imines in the presence of homogeneous chiral $Yb(OTf)_3$/**3b** complex.

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[a] Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS),
Zanjan 45137-6731, Iran
E-mail: karimi@iasbs.ac.ir
http://www.iasbs.ac.ir/~karimi/karimi.htm
[b] Department of Chemistry, Institute for Organische Chemie, RWTH Aachen University,
Landoltweg 1, 52074 Aachen, Germany

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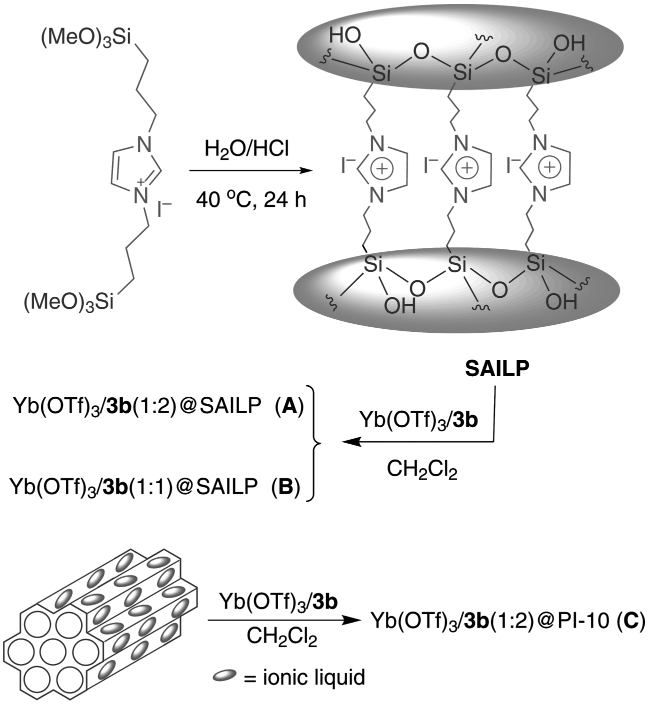
ate esters with *N*-Boc imines at room temperature, and this has led to the formation of the corresponding Mannich adducts with excellent yields and enantioselectivities in most cases (Scheme 1).[7] Meanwhile, to address the recyclability issue, we have found that immobilization of this chiral $Yb(OTf)_3$/**3a** catalyst system on a novel self-assembled organic-inorganic silica with ionic liquid phase (SAILP) can result in a recoverable and heterogeneous catalyst system, which consistently showed even higher selectivities in the enantioselective Strecker reaction as compared with its homogeneous analogues,[9] at higher reaction temperature (–60 to –40 °C vs. –78 °C) in six successive reaction runs.[10]

Results and Discussion

The consistently better catalytic performance of $Yb(OTf)_3$/**3a**@SAILP in the asymmetric Strecker reaction of imines,[10] and the fact that there is no example of Mannich reaction using supported chiral catalysts, made us ask if this chiral supported catalyst system might be favorably employed in the enantioselective Mannich reaction of malonates with imines. To do this, SAILP was prepared according to the our previously reported procedure using 1,3-bis(3-trimethoxysilylpropyl) imidazolium iodide (BTMSPI) as the ionic liquid precursor through its hydrolysis and co-condensation under mildly acidic conditions (Scheme 2).



Scheme 2. Synthesis of self-assembled ionic liquid phase (SAILP), $Yb(OTf)_3$/**3b**@SAILP (**A**, **B**), and $Yb(OTf)_3$/**3b**@PMO-IL (**C**).

The resulting yellow powder of SAILP was first characterized by simultaneous thermal analysis (STA), solid state ^{13}C and ^{29}Si NMR, FTIR and N_2 sorption analysis to establish the textural and structural features of the materials.

Thermal gravimetric (TG) analysis (Figure 1) of SAILP indicated no significant weight loss from room temperature to 300 °C, showing that the materials have thermal stability up to approximately 300 °C, but around 70% decrease in weight was observed in the range of 300 to 700 °C for the SAILP, which could be related to the organic moieties of the materials. The structure of the prepared materials was further verified by using FTIR spectroscopy. As can be seen in Figure 2, characteristic SAILP peaks for Si–OH at 3400 cm^{-1} and Si–O–Si at 1100 cm^{-1} confirmed the successful incorporation of the inorganic silica segment in the materials. In addition, the observed peaks for the aromatic and aliphatic C–H (2933 cm^{-1}), C=C (1571 cm^{-1}), and C=N (1635 cm^{-1}) absorbtion bands for the materials proved the presence of imidazolium moieties in their structure.

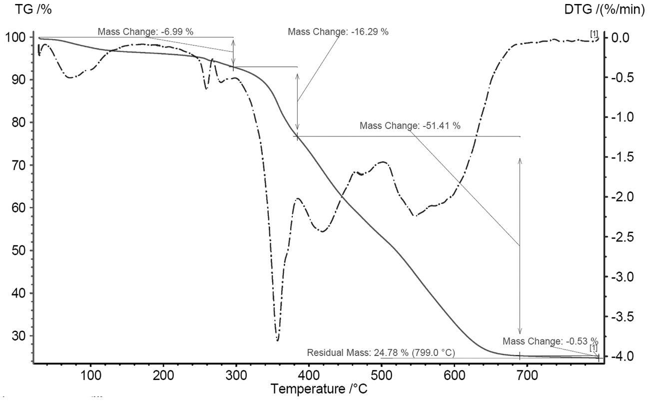


Figure 1. Thermal gravimetric analysis for SAILP.

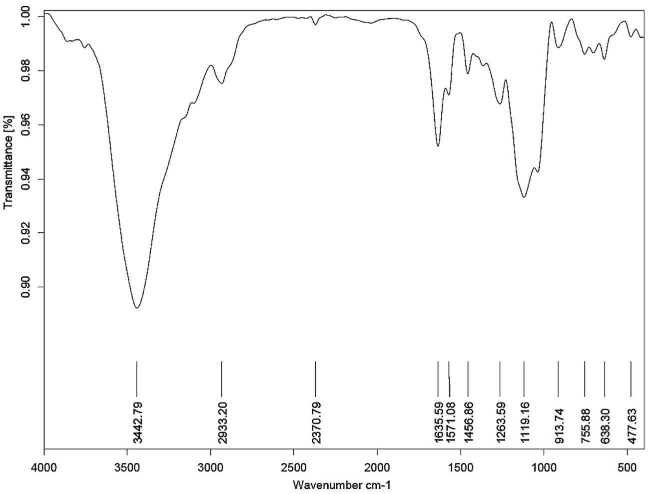


Figure 2. FTIR spectrum of the pristine SAILP.

The ^{13}C CP-MAS NMR spectrum of pristine SAILP, shown in Figure 3, clearly reveals three intense peaks at δ = 10.5, 24.7, and 52.8 ppm corresponding to carbon C-1 attached to Si, middle carbon C-2 of the bridge propyl group, and carbon C-3 bound to the imidazolium nitrogen, respectively.[10]

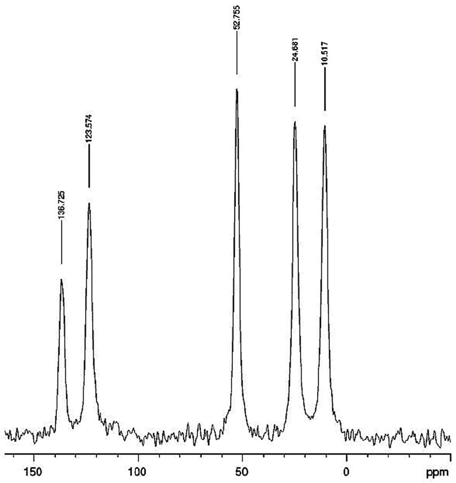


Figure 3. Solid-state ^{13}C CP-MAS NMR spectrum of the pristine SAILP.

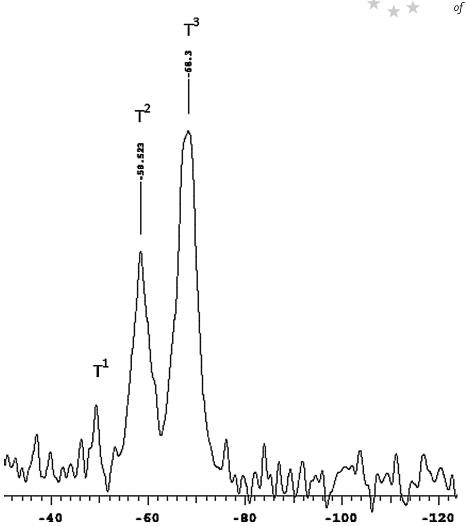


Figure 4. Solid-state ^{29}Si CP-MAS NMR spectrum of pristine SAILP.

The appearance of another two intense peaks with approximately 2:1 ratio at δ = 123.5 and 136.7 ppm correspond to –CH=CH- and –N–CH–N– moieties of the imidazolium ring, respectively, and the absence of any additional carbon signal clearly proves that all BTMSPI groups were well consolidated in the framework of the material.

In addition, the ^{29}Si CP-MAS NMR spectrum of SAILP showed an intense peak at δ = –68.4 ppm corresponding to T^3 sites [C-Si(OSi)$_3$] and another signal at δ = –58.5 ppm with lower intensity for T^2 Si sites [C-Si(OH)(OSi)$_2$] (Figure 4). The Si resonance related to partially condensed T^2 and complete condensed T^3 sites, are significantly more intense than observed for incomplete condensed T^1 [C-Si-(OH)$_3$] sites, evidencing the presence of organic moieties inside the framework of the material and confirming a high degree of condensation of the silanol groups. Moreover, the absence of signals concerning Q silicon sites [Q_n, Si(OSi)$_n$ (OH)$_{4-n}$] below δ = –100 ppm clearly demonstrate that no significant hydrolytic Si–C bond cleavage had occurred and that the bridge-bonded organic group survived intact in the hybrid silica network under the synthetic conditions. Moreover, N_2-sorption analysis of SAILP materials showed typically an isotherm very similar to type II, which is in most cases characteristic of nonporous or macroporous materials according to the IUPAC classification.[11]

Finally, the resulting SAILP was used as a support for the immobilization of chiral Yb(OTf)$_3$/**3b** complex. To do this, the supported catalysts were generated by simply exposing Yb(OTf)$_3$ (10 mol-%) to either 2 or 1 equivalent of isopropyl-pybox ligand in anhydrous CH_2Cl_2 followed by treatment with SAILP (200 mg) and evaporation of the solvents to give catalyst A or B, respectively (Scheme 2). For the purpose of comparison, we also prepared another chiral supported catalyst (catalyst **C**) by immobilizing a 1:2 Yb(OTf)$_3$/**3b** on a periodic mesoporous organosilica with 10 percent imidazolium framework (PMO-IL) by following our previously reported procedure.[12] Catalyst **C** was also characterized by N_2-sorption analysis (Figure S8) and by transmission electron microscopy (TEM) (Figure 5). As can be clearly seen, 2D hexagonal channels with pore diameter of approximately 7–8 nm remained almost unchanged after immobilizing the Yb(OTf)$_3$/**3b** complex. This value is in good agreement with the average pore diameter estimated from the Barrett–Joyner–Halenda (BJH) method from the adsorption branch of the N_2-sorption isotherm (Figure S10).

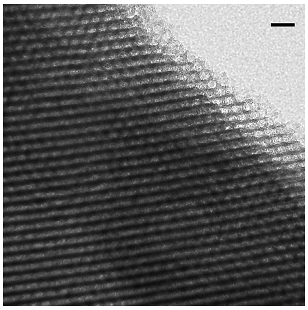


Figure 5. TEM image of 1:2 Yb(OTf)$_3$/**3b** complex supported on a periodic mesoporous organosilica with 10 percent imidazolium framework (PMO-IL) (Catalyst **C**); scale bar: 20 nm.

The total metal loading of the material was then measured by atomic absorption spectroscopy through a standard addition protocol. Moreover, Yb(OTf)$_3$/**3b**@SAILP catalyst was further characterized by using TGA, FTIR, and TEM analysis.

Having characterized all Yb(OTf)$_3$/**3b**@SAILP samples, we next proceeded to study and compare their catalytic performance in the enantioselective Mannich reaction of malonate esters with *N*-Boc imines. Since in our previous study it was realized that the highest *ee* values of Mannich adducts could only be obtained by employing *N*-Boc protecting imines and benzylmalonate under homogeneous conditions,[7] we began our investigation with catalyst **A** by employing essentially the same reaction constituents. Initially, we found that reacting benzaldehyde *N*-Boc imine (**2a**, 1 mmol), benzylmalonate (**3**, 1.1 mmol), MeOH (1 equiv.), and catalyst **A** (10 mol-%) at room temperature for 24 h afforded β-amino ester **4a** in high yield (93%) and moderate enantioselectivity (46%) (Table 1, entry 1). Given that the level of enantioselectivity in this reaction was much inferior to that obtained by using homogeneous $Yb(OTf)_3$/pybox[7] under the same catalyst loading, we hypothesized that the reaction temperature may be crucial to enhance the enantioselectivity. Indeed, when the reaction temperature was decreased to 0 and –18 °C, the enantioselectivity increased dramatically to 51 and 74%, respectively, under otherwise the same reaction conditions (Table 1, entries 2 3). However, further decreasing the reaction temperature to –40 °C resulted in a considerably lower enantioselectivity of 64% (Table 1, entry 4). It was also found that reducing the amount of catalyst to 5 mol-% while maintaining the temperature at –18 °C had a detrimental effect on both the yield and the enantioselectivity of the reaction (Table 1, entry 5). The ratio of Yb/ligand was also found to be critical to attain good enantioselectivity because the reaction in the presence of catalyst **B** (10 mol-%) resulted in inferior selectivity (Table 1, entries 6–9). It was also found that the use of PMO-IL instead of SAILP did not show any positive effect in improving the selectivity (Table 1, entry 10).

Table 1. Optimization of the reaction conditions.[a]

Entry	Cat.	Temp. [°C]	Yield [%][b]	*ee* [%][c][d]
1	A	r.t.	93	46
2	A	0	88	51
3	A	–18	82	74
4	A	–40	71	64
5[e]	A	–18	65	58
6	B	r.t.	77	34
7[f]	B	r.t.	95	22
8[f]	B	–18	90	63
9[f]	B	–40	79	55
10	C	r.t.	91	34

[a] Reaction conditions: Catalyst **A**–**C** (10 mol-%), **1a** (1 equiv.), **2a** (1.1 equiv.) unless otherwise stated. The reaction was performed in dichloromethane for 24 h. [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC analysis on a CHIRALPAK AS column. [d] Absolute configuration was determined to be *R* according to reported data.[13] [e] 5 mol-% catalyst **A** was used. [f] 10 mol-% NEt_3 was used.

Having optimized the reaction parameters (Table 1, entry 3), we then tested the scope and limitations of the asymmetric Mannich reaction of various *N*-Boc-imine derivatives and dibenzylmalonate in the presence of 10 mol-% catalyst **A** for 24 h at –18 °C (Table 2). As indicated in Table 2, a wide range of aromatic aldimins bearing either electron-withdrawing or electron-donating groups at the *ortho*, *meta* and *para* positions provided the corresponding β-amino carbonyl compounds in good yields and enantioselectivities (Table 2, entries 1–11). Remarkably, the position and electronic nature of the substituent on the aromatic ring had a very restricted effect on the *ee* values and yields. It is worth mentioning that the supported catalyst **A** gave high yield and good enantioselectivity for 2-furyl *N*-Boc imine as a heteroaryl compound in reaction with dibenzylmalonate (Table 2, entry 12), indicating that no poisoning of the supported Yb catalyst occurred with heteroatom-containing substrates. Interestingly, the present supported Yb catalyst also promoted the asymmetric Mannich reaction of aliphatic aldimins, albeit with relatively low *ee* and yield with respect to the aromatic substrates (Table 2, entry 13).

Table 2. Scope of the enantioselective heterogeneous Mannich reaction of dibenzylmalonate and *N*-Boc imine derivatives using ionic liquid supported pybox catalyst **A**.[a]

Entry	R	Yield [%][b]	*ee* [%][c][d]
1	Ph	82	74
2	2-BrC_6H_4	86	74
3	3-BrC_6H_4	88	70
4	4-BrC_6H_4	89	74
5	2-ClC_6H_4	87	70
6	4-ClC_6H_4	88	75
7	2-MeC_6H_4	81	73
8	3-MeC_6H_4	83	72
9	4-MeC_6H_4	82	75
10	4-isopropyl	82	73
11	1-naphthyl	81	77
12	2-furyl	87	78
13	cyclohexyl	71	55

[a] Reaction conditions: Catalyst **A** (10 mol-%), **1** (1 equiv.), **2a** (1.1 equiv.). The reaction was performed in dichloromethane for 24 h. [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC analysis on a CHIRALPAK AS column. [d] Absolute configuration was determined to be *R* according to the reported data.[13]

The key issue for all of the supported catalysts is their easy and efficient separation from the reaction mixture and having constant reactivity over repeated runs. In the next stage of this research we tested the reusability of catalyst **A** in the mentioned reaction. To do this, the catalyst was easily separated from the reaction mixture after each run by centrifugation and reused in the next cycle. The results indicated that the catalyst did not show a considerable loss in *ee* for the asymmetric Mannich reaction after reuse in thee consecutive runs (Table 3). These results reveal that the present supported system not only has superior activity in asymmetric Mannich reaction of a wide range of aldimins but also provides a highly recoverable heterogeneous Yb catalyst for this reaction.

Table 3. Asymmetric Mannich reaction with recyclable solid catalyst.[a]

Yield [%] (*ee* [%])[b][c]			
Run 1	Run 2	Run 3	Run 4
82 (73)	81 (72)	81 (72)	75 (68)

[a] Reaction conditions: Catalyst **A** (10 mol-%), **1** (1 equiv.), **2a** (1.1 equiv.). The reaction was performed in dichloromethane for 24 h. After completion, the catalyst was separated by centrifugation and reused in another run. [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC analysis on a CHIRALPAK AS column.

Conclusions

A series of heterogeneous chiral Yb^{III} supported systems have been prepared by physical immobilization of various ratios of $Yb(OTf)_3$/*i*Pr-pybox (**3b**) complexes on either a self-assembled organic–inorganic hybrid silica with ionic liquid phase (SAILP) (Catalyst **A** and **B**) or a periodic mesoporous organosilica with approximately 10% ionic liquid framework (PI-10) (Catalyst **C**) and characterized in detail by standard solid-state analytical techniques. Among the developed catalysts, it was found that catalyst **A**, which is denoted as $Yb(OTf)_3$/**3b**@SAILP is an efficient and recyclable chiral catalyst for the enantioselective Mannich reaction of malonates to *N*-Boc aldimines. The process is simple and applicable for a diverse range of *N*-Boc aldimines in good yields and enantioselectivities. This is the first heterogeneous catalyst for the asymmetric Mannich reaction in which the catalyst could be readily recovered and reused four times, thus making this procedure more environmentally acceptable and economically attractive.

Experimental Section

General Procedure for the Preparation of 1,3-Bis(3-trimethoxysilylpropyl)imidazolium Iodide (BTMSPI): 1,3-bis(3-trimethoxysilylpropyl)imidazolium iodide (BTMSPI) was synthesized as described in our previous synthetic reports.[12a] First, a suspension of sodium imidazolide in anhydrous THF was prepared from reaction between freshly dried imidazole (2 g) and NaH 95% (0.77 g) in a flame-dried two-necked flask containing anhydrous THF (60 mL) under an argon atmosphere. Then 3-iodopropyl-trimethoxysilane (5.8 mL) was added to the stirred suspension and the mixture was heated to reflux for 12 h. After cooling to room temperature, the solvent was removed under reduced pressure until the oil containing NaCl was obtained. Then 3-(iodopropyl)trimethoxysilane (5.8 mL) and anhydrous toluene (60 mL) was added and the mixture was heated to reflux for 24 h. After cooling the reaction mixture to room temperature, the toluene phase was separated by using a clean and dry syringe. The resultant mixture was first washed with absolute toluene (5 × 30 mL) to remove all unreacted starting materials and then CH_2Cl_2 (50 mL) was added to precipitate NaCl from reaction mixture. Dichloromethane solution was transferred into another well-dried flask. Pale-yellow IL (BTMSPI) was then obtained after removal of solvent and dried under vacuum at room temperature. ^1H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.00 (s, 1 H, NCHN), 7.46 (d, J = 1.7 Hz, 2 H, CHCH), 4.32 (t, J = 7.1 Hz, 4 H, NCH_2), 3.60 (s, 18 H, 6 OCH_3), 2.00 (m, 4 H, $CH_2CH_2CH_2$), 0.62 (t, J = 8.1 Hz, 4 H, $SiCH_2$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C, TMS): δ = 136.1 (NCHN), 122.2 (CHCH), 51.8 (NCH_2), 50.8 (OMe), 24.1 ($CH_2CH_2CH_2$), 5.8 ($SiCH_2$) ppm.

General Procedure for the Preparation of Self-Assembled Silica with Ionic Liquid Framework (SAILP) under Acidic Conditions: SAILP was synthesized by using our previous synthetic report with slight modification.[10] Typically, 1,3-bis(3-trimethoxysilylpropyl) imidazolium iodide ionic liquid (10 mmol) was added to deionized water (5 g) and 2.0 M HCl solution (22.5 g) with stirring at 40 °C for 24 h under an argon atmosphere. The resulting mixture was then transferred into a Teflon-lined autoclave and heated at 100 °C for 72 h under static conditions. The obtained mixture was first thoroughly washed with deionized water/ethanol solvent and then a yellow powder was obtained after drying of the final material at room temperature.

General Procedure for Preparation of Periodic Mesoporous Organosilica with Approximately 10% Imidazolium Functions (PI-10) in the Framework: PMO-IL was synthesized according to our previous methods.[12a] Typicaly, a molar ratio 0.013 P123: 26.515 H_2O: 5.300 KCl: 4.200 HCl: 1.000 Si was used. Pluronic P123 (1.67 g) was dissolved in a mixture of H_2O (10.5 g) and HCl (2 M, 46.14 g), then KCl (8.8 g) was added and the system was stirred until a homogeneous solution was obtained. A pre-mixture of ionic liquid (0.95 g) and tetramethoxyorthosilicate (2.74 g) in anhydrous methanol was added to the solution and the mixture was stirred at 40 °C for 24 h. The resulting mixture was then aged without stirring at 100 °C for 72 h. The obtained PMO with surfactant was filtered, washed with deionized water, and dried at room temperature. The surfactant was extracted from the PMO-IL by a Soxhlet apparatus by using ethanol (100 mL) and concd. aqueous HCl (3 mL). In a typical extraction, as synthesized PMO (1 g) was washed four times with the above-mentioned acidic ethanol solution over 12 h.

General Procedure for the Preparation of Yb^{III} Triflate/Complex Followed by Immobilization of $Yb(OTf)_3$-pybox Complex onto SAILP (Catalyst A): A well-dried glass tube was charged with $Yb(OTf)_3$ (30 mg, 0.048 mmol) and the corresponding pybox ligand (29 mg, 0.096 mmol) under an argon atmosphere. After addition of CH_2Cl_2 (1.0 mL) to the mixture, it was stirred vigorously at room temperature for 1 h until the mixture became homogeneous. To the resulting clear complex solution were added SAILP (200 mg) and additional anhydrous CH_2Cl_2 (2 mL) under argon and the resulting mixture was stirred for 12 h at room temp. The excess of CH_2Cl_2 was slowly removed under reduced pressure and the resulting free-flowing yellow powder was then dried at 60 °C overnight to furnish the supported catalyst $Yb(OTf)_3$/**3b**@SAILP. The amount of Yb was further determined by atomic absorption spectroscopy through standard addition protocol after acid washing of a weighed sample of the catalyst. Catalysts B and C were prepared and characterized in the same way (see the Supporting Information for more details).

A Typical Catalytic Procedure for Asymmetric Mannich Reaction Using $Yb(OTf)_3$/3b@SAILP (Catalyst A): To a dispersion of $Yb(OTf)_3$/pybox@SAILP **A** (equivalent to 10 mol-% Yb) in CH_2Cl_2 (1 mL) under an argon atmosphere, *N*-Boc imine **1** (1 mmol) was added and the resulting mixture was cooled to –18 °C. After 30 min, dibenzyl malonate **2a** (neat, 0.312 g, 1.1 mmol) and methanol (1 mmol) were added to the flask in one portion. The reaction was maintained at the desired temperature until complete consumption of imine was observed by thin-layer chromatography. After completion of the reaction, *n*-hexane (20 mL) was added to the reaction mixture at the same temperature and then the products were separated from the heterogeneous catalyst by filtration or centrifugation. The excess of *n*-hexane was removed in vacuo and the products were purified by flash chromatography on silica gel using hexane/ethyl acetate.

Supporting Information (see footnote on the first page of this article): Further experimental details, FT-IR, and ^1H and ^{13}C NMR spectra of both starting Boc-imines and the products, HPLC chromatograms of the products, N_2 adsorption-desorption analysis and TEM images, and TGA analysis of the materials.

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