DOI: 10.1002/adsc.200700388

Siliceous Mesocellular Foam-Supported Aza(bisoxazoline)-Copper Catalysts

Jaehong Lim,[a] Siti Nurhanna Riduan,[a] Su Seong Lee,[a,*] and Jackie Y. Ying[a,*]

[a] Institute of Bioengineering and Nanotechnology, 31 Biopolis Way, The Nanos, Singapore 138669
Fax: (+65)-6478-9020; e-mail: sslee@ibn.a-star.edu.sg or jyying@ibn.a-star.edu.sg

Received: August 5, 2007; Revised: December 30, 2007; Published online: May 13, 2008

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Aza(bisoxazoline) was easily immobilized on siliceous mesocellular foam (MCF) in a systematic approach. It was found that silanol precapping, linker group flexibility, ligand loading, and silanol postcapping were important factors to consider in optimizing silica-supported aza(bisoxazoline) catalysts. The optimized MCF-supported aza(bisoxazoline)-copper catalyst offered the same enantioselectivity as its homogeneous counterpart, and excellent recyclability. The heterogenized catalyst showed a much higher chemoselectivity in a short reaction time. The heterogenized aza(bisoxazoline)-copper(I) catalyst was successfully applied to a circulating flow-type packed bed reactor with excellent productivity and enantioselectivity. The circulating flow-type reactor was found to be very useful for gas-generating catalytic reactions such as cyclopropanation reaction.

Keywords: asymmetric catalysis; cyclopropanation; immobilization; packed bed reactor; siliceous mesocellular foam

Introduction

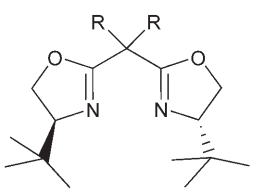
Chiral bisoxazoline-metal complexes are of great value in various asymmetric catalytic reactions.[1] However, these catalysts require high catalyst-to-substrate ratios to achieve high enantioselectivity and high turnover frequency (TOF). Thus, there is a great deal of interest to immobilize these catalysts on various types of supports.[2–4]

Although inorganic supports[5] have advantages due to physical strength and chemical inertness, polymer supports[6] are preferred to covalently fixate homogeneous catalysts due to their facile immobilization. However, the polymer support tends to swell in the organic reaction medium. To avoid this issue, high polymer cross-linking can be used, which gives rise to problem such as brittleness and increased portion of embedded catalysts.[7] The embedded catalysts are inaccessible to substrates, leading to an inefficient system.

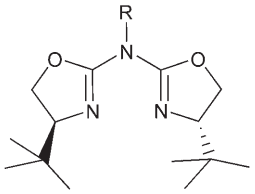
Mesoporous silica has attracted substantial interest as a catalytic support due to its ultrahigh surface area and well-defined pore structure.[8] The large internal surface area associated with the pores could provide a high dispersion of catalytic sites. Some of the resulting site-isolated catalysts offered enhanced reactivity.[9] Mesoporous silica with a 3-dimensional pore structure can be an attractive catalytic support by providing more effective diffusion of substrates. Siliceous mesocellular foam (MCF), with its ultralarge pores of >10 nm, is particularly useful for reactions involving large substrates.[10]

Since chiral bisoxazoline-metal catalysts have strong interactions with silica surface, most silica-supported chiral bisoxazoline-metal catalysts showed lower enantioselectivities in asymmetric catalytic reactions, compared to their homogeneous counterparts. There have only been a few reports on silica-supported chiral bisoxazoline-metal catalysts, which showed poor enantioselectivities, particularly in asymmetric cyclopropanation.[3b,f] It was reported that postcapping of the residual silanol groups on the silica support with trimethylsilyl (TMS) groups after catalyst immobilization improved the enantioselectivity of the silica-supported catalysts. However, the enantioselectivity was still lower than that exhibited by the homogeneous catalysts.[11] Recently, our group reported a novel precapping method, which might reduce the interaction of immobilized bisoxazoline (box) ligands with silica surface during the immobilization step.[12] It might lead to more efficient complexation of the box ligand with copper, resulting in a higher enantioselectivity.

Aza(bisoxazoline) (azabox) has a nitrogen atom instead of a carbon atom at the center of the box. This



bisoxazoline (box)



aza(bisoxazoline) (azabox)

nitrogen atom leads to a particularly strong interaction between azabox and silica support, and more flexibility after immobilization. This may make it difficult to achieve high enantioselectivity and recyclability with silica-supported azabox. Fraile et al. reported that azabox has a stronger binding affinity to copper.[13] The strong coordination can lead to less leaching of copper from the heterogenized azabox-copper catalysts, resulting in better recyclability. Recently, several heterogenized azabox catalysts have been reported.[4] However, most of them were supported on polymers. Covalent immobilization of azabox on silica has not been reported to date.

Conventionally, most asymmetric reactions involve batch processing. In contrast, the flow-type reactor has numerous advantages including more on-stream time, less maintenance, more consistent product stream, less solvent wastage, and less catalyst attrition/loss.[14] Despite these benefits, there have been very few accounts of continuous systems for asymmetric catalysis.[15] Recently, continuous flow reaction systems for asymmetric cyclopropanation have been reported.[16] Some reactions can be quite complicated for continuous flow reactor applications due to the generation of side-products that are rate-inhibiting and/or gaseous in nature. Such side-products must be removed quickly from the reactor to achieve an efficient reaction process.

Herein, we report the immobilization of azabox on MCF for asymmetric cyclopropanation. By examining the effect of support precapping, catalyst linker group, ligand loading, and support postcapping, we were able to significantly improve the enantioselectivity and regioselectivity of silica-supported azabox catalysts. We also successfully applied the heterogenized catalyst to a circulating flow-type packed bed reactor to rapidly remove the nitrogen gas that was generated inside the reactor during the catalytic reaction.

Results and Discussion

Preparation of Catalyst Support

MCF is a stable mesoporous silica with ultralarge cell-like pores (24–42 nm) interconnected by windows of 9–22 nm.[10] This novel support material is well-suited for fixating bulky complexes, and for catalyzing reactions with large substrates. Conventional MCF has irregular particle morphology and a particle size of tens of microns. For more effective packed bed applications, we have recently synthesized spherical MCF microparticles of ~5 μm.[10f,g,12] Their ultralarge pore size and 3-dimensional pore structure could minimize the diffusion limitations, and reduce the back pressure in a packed bed reactor even at high flow rates.

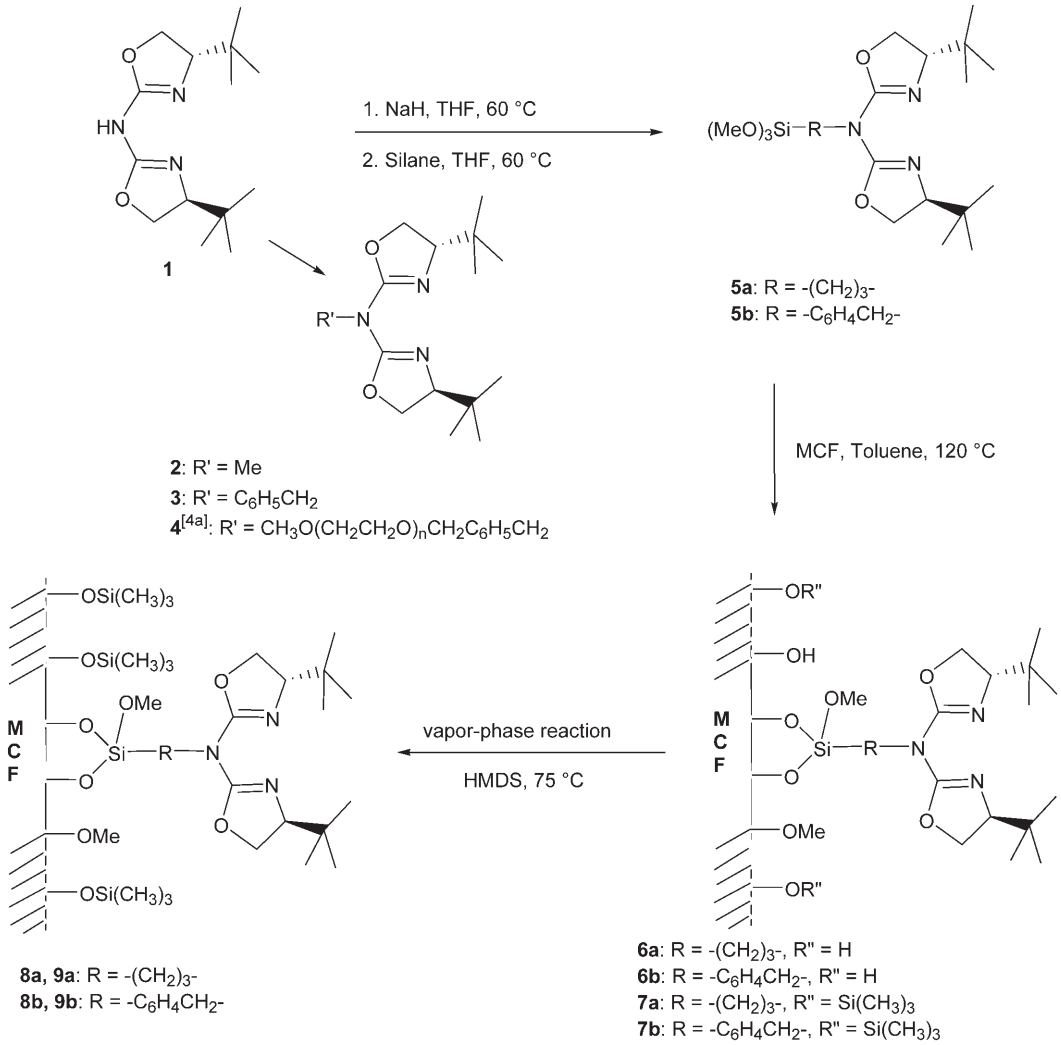
The spherical MCF microparticles were precapped with TMS groups by the reaction with hexamethyldisilazane (HMDS) in toluene. To achieve uniform distribution of TMS groups on the support, MCF particles were well dispersed in toluene, and then HMDS was slowly added to the mixture at room temperature. Heating the mixture at 60 °C overnight allowed both TMS groups of HMDS to react with the silanol groups of the support. This partially TMS-precapped MCF was used for immobilization of azabox.

To obtain fully TMS-capped MCF, a vapor-phase grafting method was used. An excess amount of HMDS was injected into a flask with MCF under a closed, high vacuum system, and then the flask was heated to vaporize HMDS for reaction with the silanol groups of MCF.

Effect of Silanol Groups

Azabox **1** was prepared by the reported method in moderate yield.[17] Compound **2** was readily synthesized by reaction of **1** with methyl iodide (Scheme 1). To investigate the effects of free silanol groups, homogeneous azabox-Cu(II) catalyst [**2**:Cu(II)] was physically mixed with bare MCF (**2a**) and fully TMS-capped MCF (**2b**), respectively, in dichloromethane (Figure 1). When the two mixtures were centrifuged, the precipitates showed that all the copper complexes in **2a** were adsorbed on bare MCF, whereas the majority of the copper moiety in **2b** remained in the solution.

Cu(II) was reduced to Cu(I) by phenylhydrazine prior to asymmetric cyclopropanation of styrene. **2a** showed 13% and 21% lower enantioselectivities for *trans* (**12**) and *cis* (**13**) products, respectively, compared to **2b** (Table 1). Compound **2a** showed similar results in the second run with slightly increased enantiomeric excess (*ee*) values. However, **2b** gave very low yield (2%) in the second run, and turned pale yellow in color. Photoacoustic Fourier-transform infrared (PA-FTIR) spectra confirmed that **2a** retained most of the organometallic catalysts after 2 runs, and **2b** contained very little organometallic catalysts after 2 runs. Each run was followed by thorough washing with dichloromethane. These results indicated that TMS capping successfully reduced the interaction between the catalyst and support surface, leading to



Scheme 1. Immobilization of azabox on MCF.

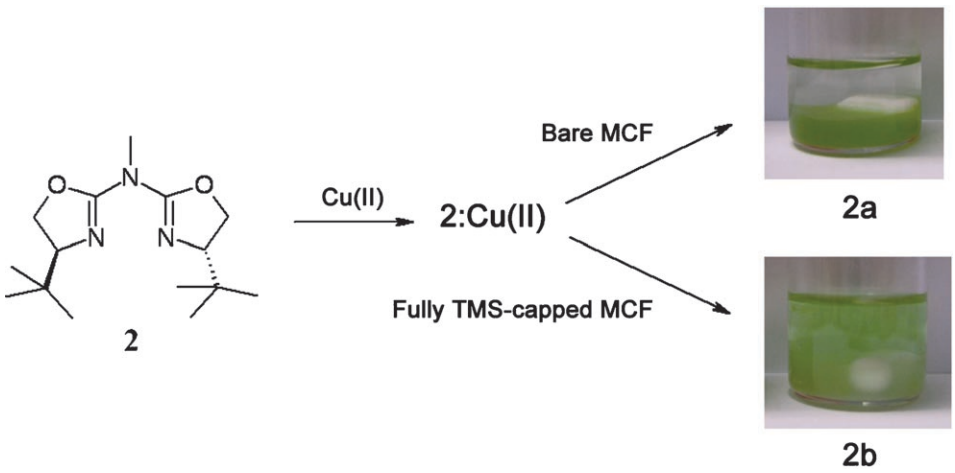
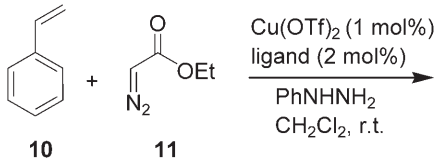
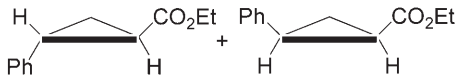


Figure 1. Mixing of homogeneous azabox-Cu(II) with calcined bare MCF (**2a**) and fully TMS-capped MCF (**2b**). The white bar is a magnetic stir bar.

Table 1. Asymmetric cyclopropanation of styrene over **2a** and **2b** after reduction of copper.[a]



10 11



12 13

Ligand	Run no.	Yield [%][b]	**12/13** ratio[c]	*ee* [%] of **12**[d]	*ee* [%] of **13**[d]
2a	1	73	64/36	78	66
	2	67	66/34	82	72
2b	1	78	74/26	91	87
	2	2	71/29	86	81

[a] All reactions were carried out under argon at 25 °C for 7 h (dropwise addition of EDA for 5 h, followed by stirring for an additional 2 h), styrene/EDA ratio = 1.5.
[b] Calculated from a gas chromatography (GC) calibration curve between n-dodecane and the products.
[c] Determined by GC.
[d] Determined by GC with a Chiraldex-B column.

high enantioselectivity. However, if the support was fully precapped by TMS, then it would only allow for the catalyst to be weakly adsorbed onto its surface; such a weak interaction would result in major catalyst leaching. This study suggested that it would be useful to have partial precapping of MCF with TMS, followed by covalent reaction of the catalyst with the residual silanol groups of the surface-treated MCF.

Preparation of Heterogenized Azabox-Cu(I) Catalysts

Azabox **1** was easily deprotonated with sodium hydride in tetrahydrofuran (THF), and the resulting anion was reacted with electrophilic trialkoxysilanes (3-iodopropyltrimethoxysilane and *p*-(chloromethyl)-phenyltrimethoxysilane) to give T-silyl-functionalized azabox **5** (Scheme 1). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra confirmed the complete T-silyl functionalization of **1**. Different amounts of ligand **5** were immobilized onto uncapped bare MCF and partially TMS-precapped MCF (0.8 mmol TMS g^{-1}) by heating in toluene to give **6** and **7**, respectively. The remaining silanol groups were postcapped with TMS groups by vapor-phase treatment with HMDS to yield **8** and **9**. ^{13}C and ^{29}Si cross-polarization magic angle spinning (CPMAS) NMR spectra revealed that the azabox ligand **5** was well-immobilized on the MCF surface. Starting with **1**, the overall yield of the final postcapped heterogenized azabox **8** or **9** was over 80%.

Complexation of Cu(II) with the immobilized ligands was achieved by adding a Cu(II) triflate solution in THF to a THF suspension of **8** or **9**. After stirring for 1 h, the suspension was filtered, washed with THF thoroughly, and dried under vacuum. Elemental analysis showed that most of the copper (> 99%) remained on the box-functionalized MCF. Cyclopropanation was performed over Cu(I) complexes, which were generated *in situ* by reducing Cu(II) complexes with phenylhydrazine.

Asymmetric Cyclopropanation of Styrene over MCF-Supported Azabox-Cu(I) Catalysts with a Propyl Linker

The immobilized azabox with a flexible propyl linker group showed a great improvement in enantioselectivity and regioselectivity (*trans*/*cis* ratio) by using the partially precapped MCF. While **8a** with a catalyst loading of 0.240 mmol g^{-1} offered 32% *ee* for the *trans* isomer **12** and a *trans*/*cis* ratio of 63/37, **9a** with a catalyst loading of 0.262 mmol g^{-1} gave 88% *ee* for the *trans* isomer **12** and a *trans*/*cis* ratio of 71/29 in the asymmetric cyclopropanation of styrene (Table 2). The enantioselectivity and recyclability of **9a** also depended largely on the ligand loading density. When the ligand loading was increased from 0.120 mmol g^{-1} to 0.262 mmol g^{-1}, the enantioselectivity increased considerably from 68% *ee* to 88% *ee* for the *trans* isomer **12**, and the recyclability improved significantly as well.

The low enantioselectivity of **8a** with the propyl linker group might be caused by incomplete TMS postcapping, followed by incomplete complexation of the immobilized ligands with the copper sources. This incomplete TMS postcapping might have stemmed from the strong interactions between the immobilized azabox and the support surface, or the large cone angle of the immobilized azabox ligands with the flexible propyl linker group.

To examine the above postulate, T-silyl-functionalized azabox was first complexed with copper triflate, and then immobilized on bare MCF by stirring in dichloromethane for 4 days (Scheme 2). Compound **14**, prepared by phenylhydrazine reduction, offered higher enantioselectivity for the *trans*-isomer **12** (86% *ee*) (Table 3) than the mixture of homogeneous **2a**:Cu(I) and bare MCF (78% *ee*) (Table 1). It is noteworthy that the enantioselectivity was much higher than that of **8a**:Cu(I) (~30% *ee*) (Table 2). This implied that if the immobilized ligand **8a** was fully coordinated with the copper, the heterogenized catalyst should give a high enantioselectivity of > 80% *ee* for

Table 2. Asymmetric cyclopropanation of styrene over the MCF-supported azabox-Cu(I) catalysts with a propyl linker.[a]

Ligand	Loading [mmol g^{-1}]	Run #	Yield [%][c]	**12/13** ratio[d]	*ee* [%] of **12**[e]	*ee* [%] of **13**[e]
2[f]		1	69	71/29	91	87
3		1	82	74/26	93	90
4[f]		1	69	71/29	91	87
9a	0.120	1	68	70/30	68	64
		2	40	67/33	40	38
8a[b]	0.176	1	68	62/38	24	19
		2	65	62/38	37	27
8a[b]	0.240	1	69	63/37	32	27
		2	67	63/37	57	47
9a	0.262	1	69	71/29	88	83
		2	81	71/29	91	87
		3	85	71/29	92	88
		4	80	72/28	92	89
		5	83	71/29	92	89
		6	83	71/29	92	89

[a] All reactions were carried out under argon at 25 °C for 7 h (dropwise addition of EDA for 5 h, followed by stirring for an additional 2 h), styrene/EDA ratio = 1.5.
[b] Styrene/EDA = 3.
[c] Calculated from a GC calibration curve between *n*-dodecane and the products.
[d] Determined by GC.
[e] Determined by GC with a Chiraldex-B column.
[f] Taken from ref.[3a]

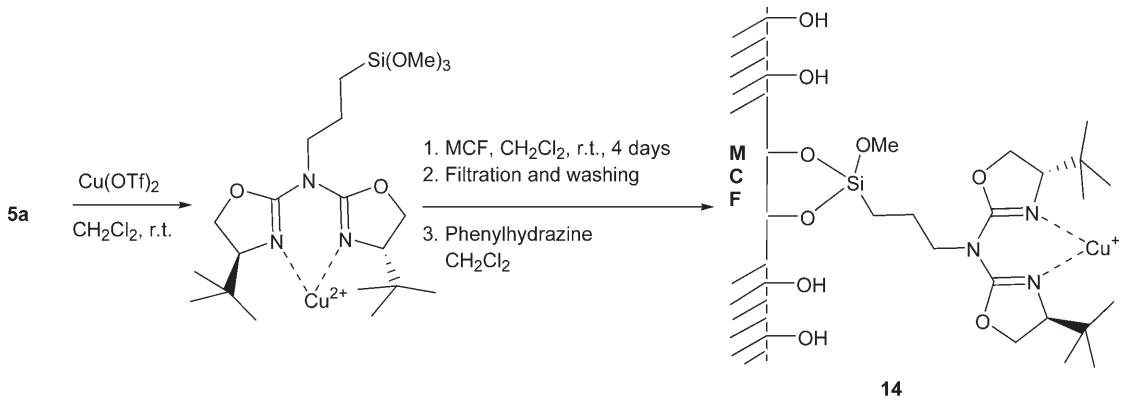
Table 3. Asymmetric cyclopropanation of styrene over **14**.[a]

Run #	Yield [%][b]	**12/13** ratio[c]	*ee* [%] of **12**[d]	*ee* [%] of **13**[d]
1	75	62/38	86	78
2	79	64/36	87	78
3	76	65/35	87	79

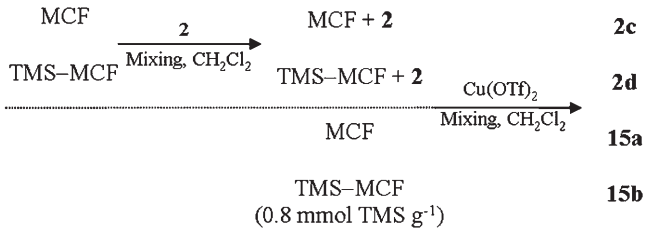
[a] All reactions were carried out under argon at 25 °C for 7 h (dropwise addition of EDA for 5 h, followed by stirring for an additional 2 h), styrene/EDA ratio = 2.
[b] Calculated from a GC calibration curve between *n*-dodecane and the products.
[c] Determined by GC.
[d] Determined by GC with a Chiraldex-B column.

the *trans*-isomer, even with the strong interaction between the catalysts and the support surface. Therefore, the low enantioselectivity of **8a**:Cu(I) might be caused mostly by the incomplete complexation of the immobilized ligands with the copper sources.

To investigate the relationships between the strong interaction of the ligand with the support surface and the effective complexation with copper, azabox **2** was first mixed with bare MCF and fully TMS-capped MCF, respectively, in dichloromethane, and then the copper triflate was added to each mixture to give **2c** and **2d** (Scheme 3). Compound **2c** gave similar enantioselectivity (77% *ee* for the *trans*-isomer **12**) (Table 4) as **2a** (the mixture of homogeneous catalyst **2**:Cu(II) and bare MCF) (78% *ee*) (Table 1). This implied that the strong interaction between the free



Scheme 2. Immobilization of T-silyl-functionalized azabox-Cu(II) catalyst.



Scheme 3. Mixing of the azabox ligand **2** with bare MCF and fully TMS-capped MCF prior to complexation with the copper sources, and mixing of the copper sources with bare MCF and partially precapped MCF without the azabox ligand **2**.

Table 4. Asymmetric cyclopropanation of styrene over **2c**, **2d**, **15a**, and **15b** after reduction of Cu(II) to Cu(I).[a]

Catalyst	Run #	Yield [%][b]	**12/13** ratio[c]	*ee* [%] of **12**[d]	*ee* [%] of **13**[d]
2c	1	65	64/36	77	63
2d	1	81	74/26	89	82
15a	1	58	57/43	-	-
15b	1	45	63/37	-	-
	2	53	63/37	-	-
	3	49	67/33	-	-

[a] All reactions were carried out under argon at 25 °C for 7 h (dropwise addition of EDA for 5 h, followed by stirring for an additional 2 h), styrene/EDA ratio = 1.5.
[b] Calculated from a gas chromatography (GC) calibration curve between *n*-decane and the products.
[c] Determined by GC.
[d] Determined by GC with a Chiraldex-B column.

azabox ligand **2** and the support surface did not affect the complexation of the ligand with copper. In contrast, **2d** led to superior yield (81%) and enantioselectivity (89% *ee* for the *trans* isomer **12**), illustrating the importance of TMS capping of MCF.

It is also noteworthy that (i) the mixture of Cu(II) and bare MCF (**15a**) catalyzed the cyclopropanation of styrene with a moderate yield (58%) after reduction to Cu(I), and (ii) the mixture of Cu(II) and partially TMS-capped MCF (0.8 mmol TMS g^{-1}) (**15b**) also catalyzed the cyclopropanation of styrene with slightly higher *trans*/*cis* ratio and lower chemoselectivity probably due to the presence of the TMS groups (Table 4). This study showed that free copper ions could be coordinated with the support surface to result in low selectivities. When the azabox ligands were anchored on the support surface, their mobility would be restricted to movements within the cone angle of the immobilized ligand. If copper ions coordinated very strongly to the support surface through silanol groups, they would not be able to complex with the immobilized ligands. This was different from the case of **2c**. Therefore, it would be critical to remove the sites on the support surface with which copper could coordinate in order to enhance the enantioselectivity.

The precapping process for **9a** might facilitate the postcapping of the silanol groups by reducing interactions between the azabox ligands and the support surface at the anchoring step. Therefore, **9a**:Cu(I) gave higher enantioselectivity than **8a**:Cu(I). MCF of **9a** was precapped with 0.8 mmol of TMS g^{-1} prior to the ligand immobilization. Thus, **9a** with a lower ligand loading would have more possibility for interactions between the immobilized ligands and the residual silanol groups. High ligand loading could reduce such undesired interactions since there would be fewer residual silanol groups after the ligand immobilization. This would also improve the chance for copper to complex with the immobilized ligands, resulting in enhanced enantioselectivity. Thus, for azabox immobilized by a flexible linker group, high enantioselectivity and good recyclability could be achieved via partial precapping of MCF and high ligand loading. **8a**:Cu(I) showed slightly increased enantioselectivity in the second run probably due to more complexation of the immobilized ligands with free copper ions staying on the support surface during the catalytic reaction.

Asymmetric Cyclopropanation of Olefins by MCF-supported Azabox-Cu(I) Catalysts with a Methylphenyl Linker

When the catalyst was immobilized through a rigid methylphenyl linker group, the ligand loading had a greater effect on enantioselectivity than support precapping. The rigidity of the methylphenyl linker group might considerably reduce the interaction between the immobilized ligand and MCF surface even at a low ligand loading and in the absence of support precapping. **8b**:Cu(I) without precapping offered high enantioselectivity (90% *ee* for *trans*-isomer **12**) and high *trans*/*cis* ratio (69/31) (Table 5). Precapping increased the *trans/cis* ratio from 69/31 to 72/28. And **9b**:Cu(I) with precapping and a high ligand loading (0.245 mmol g^{-1}) achieved excellent recyclability and the same enantioselectivity (93% *ee* for *trans*-isomer **12**) (Table 5) as its homogeneous counterpart **3**:Cu(I) (Table 2). Elemental analysis showed that leaching of copper after 8 runs was negligible (~0.30 ppm in run #1, and ~0.23 ppm on the average for runs #2 to #8), which could be attributed to the strong binding of copper to azabox.[13] The small cone angle of the immobilized ligand with a methylphenyl linker or the reduced interaction of this rigid ligand with the support surface might lead to the more effective postcapping of silanol groups, followed by effective complexation of the anchored ligands with the copper sources.

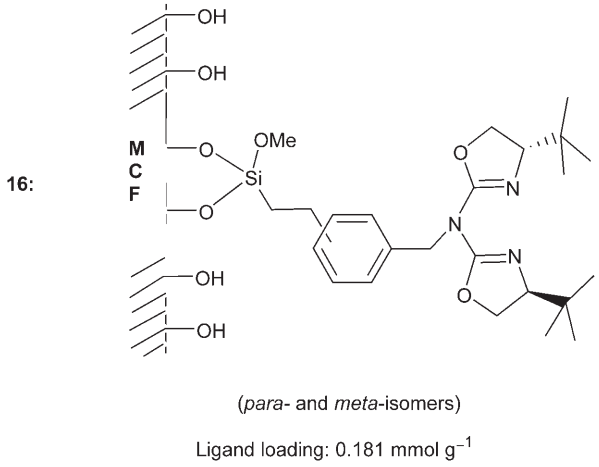
Table 5. Asymmetric cyclopropanation of styrene over MCF-supported azabox-Cu(I) catalysts with a methylphenyl linker.[a]

Ligand	Loading [mmol g^{-1}]	Run #	Yield [%][c]	**12/13** ratio[d]	*ee* [%] of **12**[e]	*ee* [%] of **13**[e]
9b	0.148	1	55	72/28	84	80
		2	60	72/28	88	84
8b[b]	0.157	1	79	69/31	90	85
		2	80	69/31	90	85
		3	79	68/32	89	83
		4	81	67/33	87	80
9b	0.245	1	83	72/28	93	91
		2	84	72/28	93	91
		3	86	72/28	93	91
		4	86	72/28	93	91
		5	87	72/28	93	91
		6	80	72/28	93	91
		7	80	72/28	93	91
		8	80	72/28	93	91

[a] All reactions were carried out under argon at 25 °C for 7 h (dropwise addition of EDA for 5 h, followed by stirring for an additional 2 h), styrene/EDA ratio = 1.5.
[b] Styrene/EDA = 3.
[c] Calculated from a GC calibration curve between *n*-dodecane and the products.
[d] Determined by GC.
[e] Determined by GC with a Chiraldex-B column.

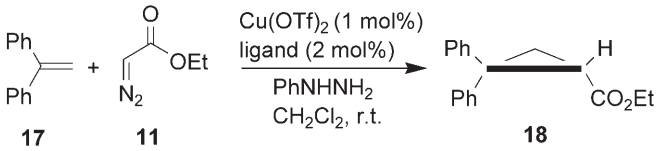
Azabox catalyst was also immobilized on bare MCF by a methylphenylethyl linker group (-$CH_2C_6H_4CH_2CH_2$-, *para*- and *meta*-isomers). The species **16**:Cu(I) (Scheme 4) gave a higher enantioselectivity (55% *ee* for *trans*-isomer **12**) than **8a**:Cu(I) (24% *ee*) and a lower enantioselectivity than **8b**:Cu(I) (90% *ee*). The flexibility of the methylphenylethyl linker lies between the propyl and the methylphenyl linkers. This showed that the rigidity of the linker group played an important role in reducing the interaction between the immobilized ligands and the support surface, and/or facilitating the complexation of the immobilized ligands with copper sources through the effective postcapping of surface silanol groups.

Catalyst **9b**:Cu(I) offered high enantioselectivity (93% *ee*) also in the asymmetric cyclopropanation of 1,1-diphenylethylene (Table 6). Catalyst **9b**:Cu(I) showed a lower yield than the polymer-supported catalyst **4**:Cu(I)[4a] probably due to the lower substrate/ethyl diazoacetate (EDA) ratio (2 instead of 3) and shorter reaction time. However, **9b**:Cu(I) offered slightly higher enantioselectivity than **4**:Cu(I).



Scheme 4. MCF-supported azabox with methylphenylethyl linker group.

Table 6. Asymmetric cyclopropanation of 1,1-diphenylethylene over **9b**:Cu(I).[a]

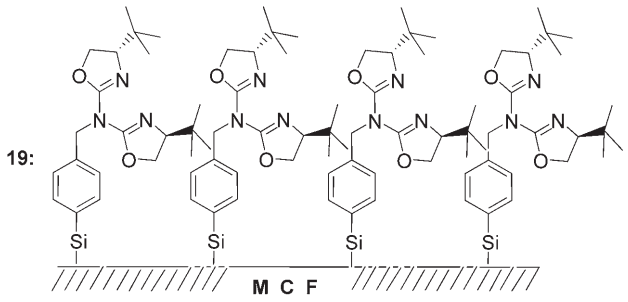


Ligand	Run #	**17/11** ratio	Yield [%][c]	*ee* [%] of **18**[d]
4[b]	1	3	78	90
9b	1	2	62	93
	2	2	60	93

[a] All reactions were carried out under argon at 25 °C for 7 h (dropwise addition of EDA for 5 h, followed by stirring for an additional 2 h).
[b] Taken from ref.[4a] Total reaction time was 11 h.
[c] Isolated yield.
[d] Determined by HPLC (Chiralcel OD-H column, hexane:2-propanol = 99.4:0.6).

Maximization of Azabox Loading Density on MCF

To maximize the loading of azabox, an excess of T-silyl-functionalized azabox was reacted with dried MCF without precapping. 0.507 mmol g^{-1} of ligand loading was achieved (Scheme 5), which translated to 0.641 mmol of azabox being anchored onto 1.0 g of bare MCF. Therefore, azabox ligands were located very close to each other, and might be suffering from steric hindrance. The steric effect led to lower chemoselectivity and yield as the reaction time was reduced. For example, when the reaction time was decreased from 420 min to 180 min, **19**:Cu(I) showed a large reduction in yield from 81% to 61%, although EDA was almost consumed (Table 7). More by-products (such as diethyl maleate and fumarate, and their oligomers derived from carbene dimerization) were generated when the chemoselectivity was decreased. The lower chemoselectivity at a shorter reaction time could be attributed to the high packing density of bulky azabox catalysts on the support surface.



Scheme 5. Maximization of azabox loading density on MCF.

It is noteworthy that the catalyst **9b**:Cu(I) with a high ligand loading (0.245 mmol g^{-1}) achieved high chemoselectivity even when the reaction time was reduced to 75 min (Table 7). This could lead to superior productivity. In contrast, the homogeneous counterpart **3**:Cu(I) showed significantly lower chemoselectivity over 75 min of reaction time (Table 7). This illustrated a further benefit of the covalent immobilization of azabox on MCF.

Circulating Flow-Type Reactor

The optimal catalyst **9b** (ligand loading = 0.245 mmol g^{-1}) was initially applied to a continuous flow reactor [Figure 2, **a**)]. **9b**:Cu(OTf)$_2$ microparticles were packed into a small empty HPLC column (50 mm × 4.6 mm I.D.) by a commercial slurry packer, and Cu(II) was readily reduced to Cu(I) by flowing phenylhydrazine solution in CH_2Cl_2 through the HPLC system. After washing away the excess phenylhydrazine by flowing CH_2Cl_2, EDA was diluted in CH_2Cl_2 (0.33 M), and continuously mixed with an equal volume of styrene solution (0.67 M) in CH_2Cl_2 by the HPLC mixer. The resulting solution was slowly supplied into the packed bed reactor at a flow rate of 0.2 mL min^{-1} by using the HPLC system to obtain full conversion at the initial reaction time. This generated a large amount of nitrogen gas as a by-product, which was trapped within the packed bed reactor system for a relatively long time at the low flow rate before elution. Both conversion and enantioselectivity decreased steadily with reaction time. Although the conversion and enantioselectivity were slightly improved

Table 7. Asymmetric cyclopropanation of styrene over MCF-supported azabox-Cu(I).[a]

Ligand	Run #	Reaction time [min]	Yield [%][b]	**12/13** ratio[c]	*ee* [%] of **12**[d]	*ee* [%] of **13**[d]
19	1	420	81	69/31	94	90
	2	420	77	68/32	94	90
	3	420	82	68/32	94	90
19	1	180	61	70/30	93	91
	2	180	63	70/30	94	91
9b	1	75	82	72/28	94	90
	2	75	83	72/28	94	90
	3	75	84	72/28	94	90
	4	35	79	72/28	94	90
	5	35	77	72/28	94	90
	6	15	61	72/28	94	90
	7	15	54	72/28	94	90
3	1	75	52	74/26	94	91
3	1	35	35	74/26	94	91

[a] All reactions were carried out under argon at 25 °C for 7 h (dropwise addition of EDA for 5 h, followed by stirring for an additional 2 h), styrene/EDA ratio = 2.
[b] Calculated from a gas chromatography (GC) calibration curve between *n*-dodecane and the products.
[c] Determined by GC.
[d] Determined by GC with a Chiraldex-B column.

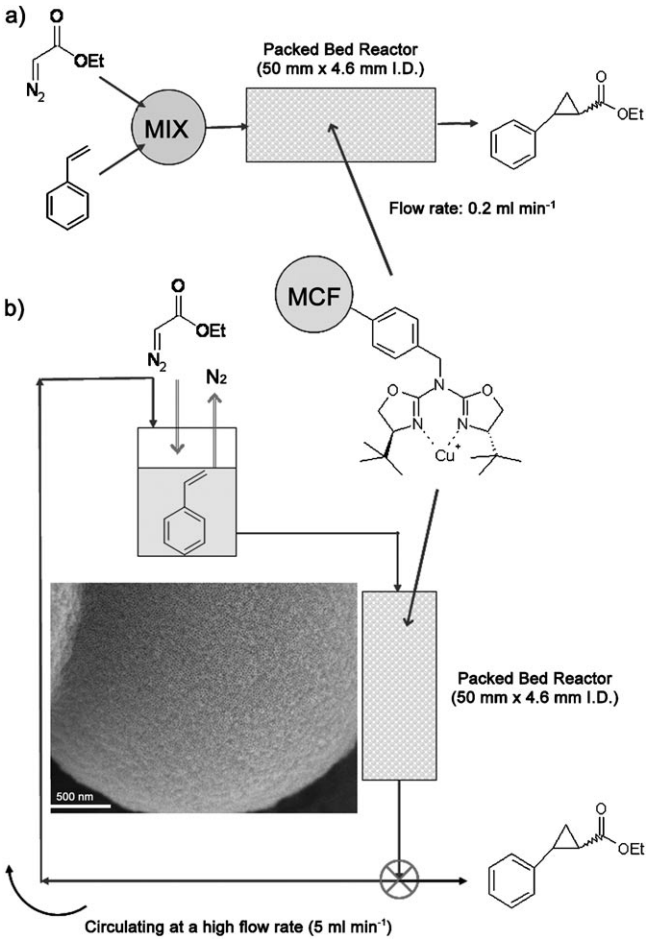


Figure 2. Experimental set-up for (**a**) the continuous flow reactor, and (**b**) the circulating flow-type reactor using a HPLC pump system (inset: high magnification SEM micrograph of spherical MCF).

with an increased amount of styrene (up to 10 equivalents of EDA), those values also decreased with reaction time. The nitrogen gas generated inside the packed bed reactor might have greatly damaged the efficiency of the catalytic system. These results did not agree with that for a monolithic mini-flow reactor with immobilized PhGli-box-Cu(OTf)$_2$,[16a] which did not show any noticeable changes after 5 h of continuous run. This might be due to the differences in support materials and box ligands employed.

In the modified reactor system, a styrene solution in CH_2Cl_2 was circulated through the packed bed reactor from a reservoir at a high flow rate (5 mL min^{-1}), and EDA was added slowly into the circulating solution [Figure 2, **b**)]. The high flow rate was applied to remove the nitrogen byproduct quickly from the packed bed reactor, giving a slightly high back pressure (up to 4.48 MPa). This circulating flow-type reactor showed excellent performance, attaining the same enantioselectivity (93% *ee* for the *trans*-isomer) and high yield (up to 80%) during 20 cycles (Figure 3).

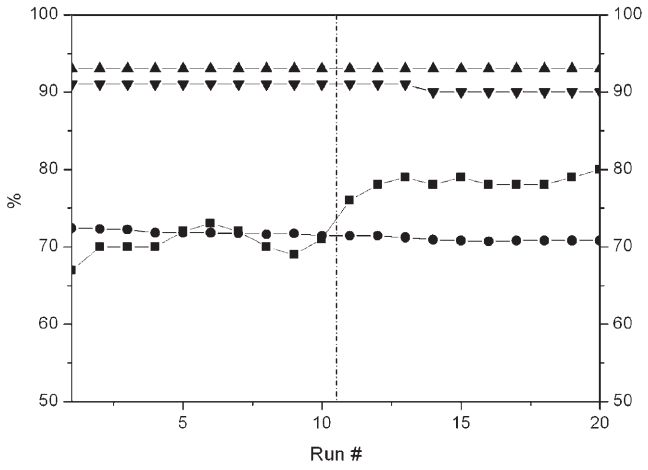


Figure 3. Asymmetric cyclopropanation of styrene by the circulating flow-type reactor (50 mm × 4.6 mm I.D.) with **9b**:Cu(I) (total amount of catalyst: 230 mg). (▲) % *ee* for the *trans* isomer, (▼) % *ee* for the *cis* isomer, (●) % *trans* isomers, and (■) yield. Total amount of reaction medium: 18 ml for runs #1 to #10, 14 mL for runs #11 to #20.

When the total volume of solvent decreased from 18 mL to 14 mL at the start of run #11, the yield was increased by ~10%. The reaction time of one cycle was reduced to 75 min for higher productivity; it was 5.6 times shorter than the typical reaction time in a batch reactor (420 min). TOF of the reaction (mmol of cyclopropanation products/mmol copper/h) was almost 68, which was 15 times higher than that by pybox-Ru monolithic mini-flow reactors, and similar to that by PhGli-box-copper monolithic mini-flow reactors using supercritical solvents.[16] However, the enantioselectivity achieved with our circulating flow-type reactor was much higher than that by the box-copper monolithic mini-flow reactors (59% *ee* for the *trans* isomer). In fact, similar enantioselectivity was attained by **9b**:Cu(I) in the circulating flow-type reactor as in the batch reactor (Table 7). The circulating flow-type reactor could be regarded as a hybrid between a batch reactor and a continuous flow reactor. It retained the benefits of a continuous flow reactor (such as more on-stream time and less catalyst attrition/loss), as well as the benefits of a batch reactor (such as quick removal of gaseous byproducts).

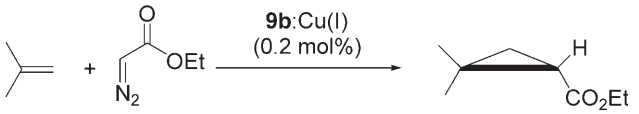
The ultralarge pore size of MCF microparticles provided the packed bed system with a relatively low back pressure. Scale-up of the reactor system could be optimized by increasing the particle size and/or pore size of the support to further reduce the back pressure.

Asymmetric Cyclopropanation of 2-Methylpropene

The circulating packed bed reactor did not work in the asymmetric cyclopropanation of 2-methylpropene

because the HPLC pump was not appropriate for eluting such a volatile substrate. Instead, the catalyst collected from the previous packed bed reactor study was used to catalyze the cyclopropanation of 2-methylpropene. The reused **9b**:Cu(I) catalyst (0.2 mol%) showed excellent enantioselectivity (91% *ee*) and high yield (90%) in a shorter reaction time (3 h) and at a higher reaction temperature (10 °C) (Table 8), compared to the reaction conditions from the literature (0.1 mol% homogeneous bisoxazoline catalysts, 19 h, 0 °C; 0.2 mol% heterogeneous bisoxazoline catalyst, 22 h, 0 °C). Elemental analysis showed that the leaching of copper after the catalytic reaction (TON = 3,500) was ~8% of the initial copper content.

Table 8. Asymmetric cyclopropanation of 2-methylpropene[a] over **9b**:Cu(I) recovered from the packed bed reactor after 20 cycles.



20 **11** **21**

Run #	**20/11** ratio	Chemoselectivity [%]	Yield [%][b]	*ee* [%] of **21**[c]
1	7	98	90	91
2	7	98	89	90
3	7	97	89	90

[a] All reactions were carried out under argon for 3 h (dropwise addition of EDA at 10 °C for 2 h, followed by warming up to room temperature over 1 h).
[b] Isolated yield.
[c] Determined by GC (Chiraldex G-TA, 50 m × 0.25 mm I.D.).

Table 9. Asymmetric cyclopropanation of 2-methylpropene by fresh **9b**:Cu(I) (0.1 mol%).

Run #	**20/11** ratio	Yield [%][c]	*ee* [%] of **21**[e]
1[a]	7	90	92
2[a]	7	86[d]	92
3[a]	7	86[d]	91
4[b]	7	86[d]	91
5[b]	7	86[d]	91

[a] Dropwise addition of EDA at 0 °C for 5 h, followed by warming up to room temperature over 14 h.
[b] Dropwise addition of EDA at 5 °C for 2 h, followed by warming up and stirring at 10 °C for 1.5 h, and warming up to room temperature over 0.5 h.
[c] Isolated yield.
[d] Overall yield from runs #2 to #5.
[e] Determined by GC (Chiraldex G-TA, 50 m × 0.25 mm I.D.).

A fresh **9b**:Cu(I) catalyst achieved 92% *ee* and 90% yield (Table 9) under the reaction conditions reported in the literature (0.1 mol%, 19 h, 0 °C). With a shortened reaction time and an increased reaction temperature, comparably high yield and high enantioselectivity were still obtained.

Conclusions

Azabox was successfully immobilized on MCF. It was found that support precapping, linker group flexibility, ligand loading, and support postcapping were important factors to consider in achieving an excellent heterogenized catalyst. The optimal MCF-supported azabox-Cu(I) catalyst offered as high enantioselectivity and yield as the homogeneous counterpart, and excellent recyclability. This study demonstrated that silica-supported catalysts could achieve comparable enantioselectivity and yield as their homogeneous counterparts through proper design. In addition, the heterogenized catalyst with the optimal ligand loading density could attain superior chemoselectivity in a short reaction time with increased productivity. The optimal heterogenized catalyst was successfully applied to a circulating flow-type packed bed reactor, while retaining the attractive enantioselectivity, yield and recyclability. The circulating flow-type reactor was more suitable than the conventional continuous flow reactor for gas-generating processes, such as the cyclopropanation reaction.

Experimental Section

Spherical MCF was synthesized according to the literature procedure.[12] Other chemicals were purchased from commercial suppliers, and were used without further purification. L-*tert*-Leucine, anhydrous THF, toluene, anhydrous CH_2Cl_2, styrene, phenylhydrazine and EDA were purchased from Aldrich. Azabox was prepared according to the literature procedure.[16] 3-Bromopropyltrimethoxysilane, *p*-(chloromethyl)phenyltrimethoxysilane and [(chloromethyl)phenylethyl]trimethoxysilane (*para*- and *meta*-isomers) were purchased from Gelest Inc. PA-FTIR spectra were recorded on a Bio-rad FTS-60 A spectrometer with an MTEC Model 300 photoacoustic cell. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker spectrometer at ambient temperature. ^{13}C and ^{29}Si CPMAS NMR spectra were recorded on a 400 MHz Bruker spectrometer. Elemental analyses were performed with a CE440 CHN Analyzer (Exeter Analytical).

Preparation of Precapped MCF

MCF (5.0 g) was dried under vacuum at 120 °C overnight before use, and then well dispersed in toluene (60 mL). HMDS (422 μL, 2.0 mmol) was slowly added into the suspension. The mixture was stirred for 1 h at room tempera-

ture, and heated at 60 °C overnight. The suspension was filtered, washed with toluene, and dried under vacuum. Elemental analysis (%): C 2.86, H 0.94; loading of TMS: 0.794 mmol g^{-1}.

Preparation of Fully TMS-Capped MCF

MCF (2.0 g) was placed in a flask, and dried under vacuum at 120 °C overnight. Excess HMDS (1.0 mL) was added to the flask under the closed vacuum conditions. The flask was cooled with liquid N_2 under high vacuum. It was sealed and then warmed to room temperature. The flask was then placed in the oven at 75 °C for 5 h. After reaction, excess HMDS was removed under vacuum to yield fully TMS-capped MCF. Elemental analysis (%): C 5.35, H 1.35; loading of TMS: 1.486 mmol g^{-1}.

Preparation of 3

THF (5 mL) was added to NaH (22 mg, 0.92 mmol) and azabox **1** (200 mg, 0.75 mmol). The resulting solution was stirred for 6 h at 60 °C to give a clear solution. Benzyl chloride (103 μL, 0.9 mmol) was added and stirred at 60 °C overnight, giving a white precipitate (NaCl). After stirring overnight, aqueous NH_4Cl was then added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, and then dried over $MgSO_4$, filtered, and rotary-evaporated to give the crude product. The crude product was purified by flash column chromatography to give product **3**; yield: 247 mg (92%); $[\alpha]_D^{23}$: −8.23 (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 7.41$ (d, $J = 7.2$ Hz, 2H, Ph), 7.28 (td, $J = 7.2$, 1.2 Hz, 2H, Ph), 7.21 (td, $J = 7.2$, 1.2 Hz, 1H, Ph), 5.14 (d, $J = 15.2$ Hz, 1H, CH_2PhSi), 4.96 (d, $J = 15.2$ Hz, 1H, CH_2PhSi), 4.31 (td, $J = 9.2$, 1.2 Hz, 2H, CH_2CH), 4.20 (td, $J = 6.4$, 1.2 Hz, 2H, CH_2CH), 3.78 (ddd, $J = 9.2$, 6.4, 1.2 Hz, 2H, CH_2CH), 0.78 [s, 18H, $C(CH_3)_3$]; ^{13}C NMR ($CDCl_3$): $\delta = 157.2$, 137.8, 128.1, 127.1, 73.4, 70.1, 53.2, 33.9, 25.4; elemental analysis: calcd. (%) for $C_{21}H_{31}N_3O_2$: C 70.55, H 8.74, N 11.75; found: C 70.50, H 8.87, N 11.54.

Preparation of 6a

THF (5 mL) was added to NaH (22 mg, 0.92 mmol) and azabox **1** (200 mg, 0.75 mmol). The resulting solution was stirred for 6 h at 60 °C to give a clear solution. 3-Bromopropyltrimethoxysilane (141 μL, 0.75 mmol) was added and stirred at 60 °C overnight. White precipitates (NaBr) were formed and removed using centrifugation. The clear solution portion was added to MCF (2.5 g or 3.0 g) in toluene (40 mL), and heated to 120 °C overnight. The suspension was filtered through a filter funnel, and washed with toluene (20 mL × 3), CH_2Cl_2 (20 mL × 3), water (20 mL × 10), methanol (20 mL × 3) and CH_2Cl_2 (20 mL × 3). After drying in vacuum, the desired product (**6a**) was obtained. ^{1}H NMR (CD_2Cl_2) of **5a**: $\delta = 4.25$ (ddd, 2H, $J = 9.6$, 8.8, 1.2 Hz, CH_2CH), 4.16 (ddd, 2H, $J = 8.8$, 7.2, 2.4 Hz, CH_2CH), 3.75 (m, 4H, CH_2CH and $CH_2CH_2CH_2$Si), 3.53 (s, 9H, Si-OCH_3), 1.78 (m, 2H, $CH_2CH_2CH_2$Si), 0.86 [s, 18H, $C(CH_3)_3$], 0.61 (t, 2H, $J = 8.4$ Hz, $CH_2CH_2CH_2$Si); ^{13}C NMR (CD_2Cl_2) of **5a**: $\delta = 157.6$, 75.0, 69.8, 53.5, 34.2, 25.4, 21.4, 7.9, 6.5; PA-FT-IR of **6a**: $\nu = 2960$, 1666, 1090, 845, 806, 758 cm^{-1}.

With 2.5 g of MCF: elemental analysis (%) of **6a**: C 5.57, H 0.99, N 1.08; loading of **1**: 0.257 mmol g^{-1}. With 3.0 g of MCF: elemental analysis (%) of **6a**: C 3.71, H 0.82, N 0.82; loading of **1**: 0.195 mmol g^{-1}.

Preparation of 6b

The same procedure described for **6a** was followed, except that *p*-(chloromethyl)phenyltrimethoxysilane (162 μL, 0.75 mmol) was used instead of 3-bromopropyltrimethoxysilane. ^{1}H NMR ($CDCl_3$) of **5b**: $\delta = 7.58$ (d, $J = 8.0$ Hz, 2H, Ph), 7.44 (d, $J = 8.0$ Hz, 2H, Ph), 5.18 (d, $J = 14.9$ Hz, 1H, CH_2PhSi), 4.96 (d, $J = 14.9$ Hz, 1H, CH_2PhSi), 4.31 (dd, $J = 9.5$, 8.4 Hz, 2H, CH_2CH), 4.19 (dd, $J = 8.4$, 6.8 Hz, 2H, CH_2CH), 3.76 (dd, $J = 9.5$, 6.8 Hz, CH_2CH), 3.59 (s, 9H, Si-OCH_3), 0.75 [s, 18H, $C(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) of **5b**: $\delta = 157.3$, 140.7, 134.9, 134.7, 127.8, 73.6, 70.4, 53.5, 50.9, 34.1, 25.8; PA-FT-IR of **6b**: $\nu = 2960$, 1666, 1090, 845, 806, 758 cm^{-1}; elemental analysis (%) of **6b**: C 3.71, H 0.82, N 0.82; loading of **1**: 0.195 mmol g^{-1}.

Preparation of 7a

The same procedure described for **6a** was followed, except that 2.0 g or 4.0 g of TMS-precapped MCF was used as the support. With 2.0 g of TMS-precapped MCF: PA-FT-IR: $\nu =$ 2960, 2912, 2876, 2852, 1701, 1656, 1540, 1076, 811 cm^{-1}; elemental analysis (%): C 7.45, H 1.50, N 1.15; loading of **1**: 0.274 mmol g^{-1}.

With 4.0 g of TMS-precapped MCF: PA-FT-IR: (cm^{-1}) $\nu = 2960$, 2858, 1708, 1662, 1535, 1072, 811 cm^{-1}; elemental analysis (%): C 5.85, H 1.10, N 0.61; loading of **1**: 0.145 mmol g^{-1}.

Preparation of 7b

The same procedure described for **6b** was followed, except that 2.0 g or 4.0 g of TMS-precapped MCF (0.8 mmol TMS g^{-1}) was used as the support. With 2.0 g of TMS-precapped MCF: PA-FT-IR: $\nu = 3080$, 2960, 2912, 2875, 2851, 1701, 1653, 1478, 1080, 811 cm^{-1}; elemental analysis (%): C 9.07, H 1.58, N 1.09; loading of **1**: 0.260 mmol g^{-1}.

With 4.0 g of TMS-precapped MCF: PA-FTIR: $\nu = 3079$, 2959, 2852, 1701, 1665, 1523, 1077, 812 cm^{-1}; elemental analysis (%): C 7.26, H 1.33, N 0.68; loading of **1**: 0.162 mmol g^{-1}.

Preparation of 8a

Catalyst **6a** (1.0 g) was dried at 80 °C for 1 day. Excess HMDS (0.75 mL) was added to the solid under vacuum. The flask was cooled under vacuum with liquid N_2. It was sealed and then warmed to room temperature. The flask was then placed in the oven at 75 °C for 5 h. After reaction, excess HMDS was removed under vacuum to yield the desired product **8a**.

With 2.5 g of MCF: elemental analysis (%): C 7.83, H 1.33, N 1.01; loading of **1**: 0.240 mmol g^{-1}. With 3.0 g of MCF: PA-FT-IR: $\nu = 2961$, 1664, 1087, 843, 807, 758 cm^{-1}; elemental analysis (%): C 6.69, H 1.22, N 0.74; loading of **1**: 0.176 mmol g^{-1}.

Preparation of 8b

The procedure described above was followed using **6b**. PA-FT-IR: $\nu = 2960$, 2929, 2859, 1709, 1664, 1089, 844, 801, 760 cm^{-1}; elemental analysis (%): C 10.35, H 1.60, N 0.74; loading of **1**: 0.176 mmol g^{-1}.

Preparation of 9a

The procedure described for **8a** was followed using **7a**. With 2.0 g of TMS-precapped MCF: ^{13}C CPMAS NMR (100 MHz): $\delta = 162.5$, 73.5, 67.9, 44.5, 33.0, 23.6, 8.8, −0.8; ^{29}Si CPMAS NMR (79.5 MHz): $\delta = 13.5$ [$Si(CH_3)_3$], −51.9 (T^1), −57.5 (T^2), −65.2 (T^3), −101.5 (Q^3), −108.6 (Q^4); PA-FT-IR: $\nu = 2959$, 2908, 2874, 2852, 1670, 1521, 1081, 845, 811, 758 cm^{-1}); elemental analysis (%): C 9.49, H 1.96, N 1.10; loading of **1**: 0.262 mmol g^{-1}.

With 4.0 g of TMS-precapped MCF: PA-FT-IR: $\nu = 2959$, 2907, 2852, 1672, 1523, 1076, 846, 810, 758 cm^{-1}; elemental analysis (%): C 7.79, H 1.53, N 0.53; loading of **1**: 0.126 mmol g^{-1}.

Preparation of 9b

The procedure described for **8a** was followed using **7b**. With 2.0 g of TMS-precapped MCF: ^{13}C CPMAS NMR (100 MHz): $\delta = 159.5$ (*C*=N), 142.6, 136.0, 129.2, 75.6, 70.4, 51.9, 34.9, 25.7, 1.7; ^{29}Si CPMAS NMR (79.5 MHz): $\delta = 14.6$ [$Si(CH_3)_3$], −62.1 (T^1), −68.9 (T^2), −77.4 (T^3), −101.5 (Q^3), −106.9 (Q^4); PA-FT-IR: $\nu = 3076$, 2958, 2907, 2874, 2850, 1648, 1479, 1395, 1079, 846, 812, 758 cm^{-1}; elemental analysis (%): C 11.21, H 1.94, N 1.03; loading of **1**: 0.245 mmol g^{-1}.

With 4.0 g of TMS-precapped MCF: PA-FT-IR: $\nu = 3077$, 2960, 2906, 2851, 1683, 1519, 1077, 840, 811, 758 cm^{-1}; elemental analysis (%): C 8.93, H 1.69, N 0.62; loading of **1**: 0.148 mmol g^{-1}.

Preparation of 14

THF (5 mL) was added to NaH (15 mg, 0.62 mmol) and azabox **1** (150 mg, 0.56 mmol). The resulting solution was stirred for 6 h at 60 °C to give a clear solution. 3-Bromopropyltrimethoxysilane (105 μL, 0.56 mmol) was added and stirred overnight at 60 °C. White precipitates (NaBr) were formed and removed using centrifugation. THF was evaporated in vacuum and CH_2Cl_2 was added. $Cu(OTf)_2$ was introduced to the dichloromethane solution to give a green solution. The resulting solution was stirred for 1 day at room temperature, and was added to MCF (2.5 g) in dichloromethane. The suspension was stirred for 4 days at room temperature, filtered through a filter funnel, and washed with dichloromethane (20 mL × 5). After drying in vacuum, the desired product (**14**) was obtained. PA-FT-IR: $\nu = 3741$, 2966, 1676, 1627, 1088, 809 cm^{-1}; elemental analysis (%): C 4.34, H 0.80, N 0.72, Cu 0.42; loading of Cu complexes: 0.066 mmol g^{-1}.

Preparation of 16

The same procedure described for **6a** was followed to give MCF-supported azabox, except that ((chloromethyl)phenylethyl)trimethoxysilane (*para*- and *meta*-isomers) (282 μL, 1.12 mmol) was used instead of 3-bromopropyltrimethoxysilane. ^1H NMR (CD_2Cl_2) of T-silyl-functionalized azabox (major *para* isomer): $\delta = 7.2$ (m, 4H, Ph), 5.05 (d, 1H, $J =$ 14.8 Hz, $CH_2PhCH_2CH_2Si$), 4.98 (d, 1H, $J = 14.8$ Hz, $CH_2PhCH_2CH_2Si$), 4.27 (m, 2H, CH_2CH), 4.18 (m, 2H, CH_2CH), 3.76 (ddd, 2H, $J = 9.2$, 6.8, 2.0 Hz, CH_2CH), 3.54 (s, 9H, Si-OCH_3), 2.67 (m, 2H, $CH_2PhCH_2CH_2Si$), 0.94 (m, 2H, $CH_2PhCH_2CH_2Si$), 0.79 [s, 18H, $C(CH_3)_3$]; ^{13}C NMR (CD_2Cl_2): $\delta = 158$, 144, 139, 128, 127, 73, 70, 34, 29, 25, 11; PA-FT-IR of MCF-supported azabox: $\nu = 2960$, 1666, 1090, 845, 806, 758 cm^{-1}.

With 3.0 g of MCF: elemental analysis (%): C 3.71, H 0.82, N 0.82; loading of **1**: 0.195 mmol g^{-1}.

Post-capping: The procedure described for **8a** was followed using the MCF-supported azabox. PA-FT-IR: $\nu =$ 3728, 2963, 1706, 1660, 1084, 796 cm^{-1}; elemental analysis (%): C 9.58, H 1.37, N 0.76; loading of **1**: 0.181 mmol g^{-1}.

Maximizing Azabox Loading on MCF (19)

MCF (2.0 g) was dried under vacuum at 120 °C overnight, and then well dispersed in toluene. The excess of the T-silyl-functionalized azabox was added to the reaction mixture, and then heated at 120 °C overnight. The suspension was filtered through a filter funnel, and washed with toluene (20 mL × 3), CH_2Cl_2 (20 mL × 3), water (20 mL × 10), methanol (20 mL × 3) and CH_2Cl_2 (20 mL × 3). After drying in vacuum at room temperature, the desired product was dried in vacuum at 80 °C. The remaining silanol groups were capped by the reaction with an excess of HMDS in the vapor phase. The excess HMDS was removed in high vacuum to give the final product (**19**). ^{13}C CPMAS NMR (100 MHz): $\delta = 157.3$ (*C*=N), 140.4, 133.9, 127.2, 73.6, 68.5, 49.8, 32.9, 23.7, −0.2; ^{29}Si CPMAS NMR (79.5 MHz): $\delta =$ 13.8 ($Si(CH_3)_3$), −62.1 (T^1), −69.6 (T^2), −77.4 (T^3), −101.5 (Q^3), −108.6 (Q^4); PA-FT-IR: $\nu = 3076$, 2958, 2907, 2874, 2850, 1648, 1479, 1395, 1079, 846, 812, 758 cm^{-1}; elemental analysis (%): C 17.01, H 2.40, N 2.13; loading of **1**: 0.507 mmol g^{-1}.

Typical Asymmetric Cyclopropanation

$Cu(OTf)_2$ (3.6 mg, 0.01 mmol) was dissolved in THF (2 mL), and then added to the MCF-immobilized bisoxazolines (0.022 mmol) well-dispersed in THF (2 mL). The mixture was stirred for 5 h, and filtered. The powder was thoroughly washed with THF, and then dried under vacuum. The catalyst was dispersed in CH_2Cl_2 (4 mL), and phenylhydrazine (25 μL of a 5% solution) was added. After addition of styrene (172 μL, 1.5 mmol), a solution of EDA (1.0 mmol, diluted with 2 mL of CH_2Cl_2) was introduced dropwise over 5 h using a syringe pump. The mixture was stirred for 2 h, and centrifuged. The solution portion was collected, and the *trans*/*cis* ratio and yield were determined by GC. The *ee* was determined by GC using a Chiraldex-B column. The precipitate was washed with CH_2Cl_2 (10 mL), and centrifuged 3 times. The recovered catalyst was reused directly for the next experiment.

Circulating Flow-Type Reactor

Catalyst **9b**:$Cu(OTf)_2$ (230 mg, 0.03 mmol) was packed into an empty HPLC column (50 mm × 4.6 mm I.D.). A pump system of HPLC was used to flow a solution into the

column. Phenylhydrazine (3.5 μL, 0.036 mmol) solution in CH_2Cl_2 (5 mL) was passed through the column to reduce Cu(II) to Cu(I), and the column was washed by flowing CH_2Cl_2. Styrene (688 μL, 6.0 mmol) solution in CH_2Cl_2 (9 mL) was flowed from a reservoir flask to the column at 5 mL min^{-1}, and then EDA (315 μL, 3.0 mmol) and dodecane (342 μL, 1.5 mmol) in CH_2Cl_2 (9 mL) were added into the reservoir flask over 55 min. The solution of the reservoir was further circulated for 20 min to give a clear solution, which was then collected at the end of the column. The yield and *trans*/*cis* ratio were determined by GC. The *ee* was determined by GC using a Chiraldex-B column. The column was washed by flowing CH_2Cl_2 (15 mL), and then a further cycle of the reaction was performed with the same procedure without further reduction of the catalyst with phenylhydrazine. From run #11, the amount of CH_2Cl_2 for dilution of styrene was reduced from 9 mL to 5 mL.

Acknowledgements

This work was funded by the Institute of Bioengineering and Nanotechnology (Biomedical Research Council, Agency for Science, Technology and Research, Singapore).

References

[1] a) A. K. Gosh, P. Mathivanan, J. Capiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; b) A. Pfaltz, *Synlett* **1999**, 835–842; c) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325–335; d) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159–2232.

[2] D. Rechavi, M. Lemaire, *Chem. Rev.* **2002**, *102*, 3467–3494.

[3] a) M. I. Burguete, J. M. Fraile, J. I. García, E. García-Verdugo, S. V. Luis, J. A. Mayoral, *Org. Lett.* **2000**, *2*, 3905–3908; b) M. I. Burguete, J. M. Fraile, J. I. García, E. García-Verdugo, C. I. Herrerías, S. V. Lui, J. A. Mayoral, *J. Org. Chem.* **2001**, *66*, 8893–8901; c) R. Annunziata, M. Benglia, M. Cinquini, F. Cozzi, M. J. Pitillo, *J. Org. Chem.* **2001**, *66*, 3160–3166; d) S. Orlandi, A. Mandoli, D. Pini, P. Salvadori, *Angew. Chem.* **2001**, *113*, 2587–2589; *Angew. Chem. Int. Ed.* **2001**, *40*, 2519–2521; e) E. Díez-Barra, J. M. Fraile, J. I. García, E. García-Verdugo, C. I. Herrerías, S. V. Luis, J. A. Mayoral, P. Sánchez-Verdú, J. Tolosa, *Tetrahedron: Asymmetry* **2003**, *14*, 773–778; f) R. J. Clarke, I. J. Shannon, *Chem. Commun.* **2001**, 1936–1937; g) A. Lee, W. Kim, J. Lee, T. Hyeon, B. M. Kim, *Tetrahedron: Asymmetry* **2004**, *15*, 2595–2598; h) J. G. Knight, P. E. Belcher, *Tetrahedron: Asymmetry* **2005**, *16*, 1415–1418.

[4] a) M. Glos, O. Reiser, *Org. Lett.* **2000**, *2*, 2045–2048; b) J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, O. Reiser, M. Vaultier, *Tetrahedron Lett.* **2004**, *45*, 6765–6768; c) H. Werner, C. I. Herrerías, M. Glos, A. Gissibl, J. M. Fraile, I. Pérez, J. A. Mayoral, O. Reiser, *Adv. Synth. Catal.* **2006**, *348*, 125–132; d) J. M. Fraile, I. Pérez, J. A. Mayoral, O. Reiser, *Adv. Synth. Catal.* **2006**, *348*, 1680–1688.

[5] C. E. Song, S. Lee, *Chem. Rev.* **2002**, *102*, 3495–3524.

[6] a) N. E. Leadbeater, M. Marco, *Chem. Rev.* **2002**, *102*, 3217–3274; b) C. A. McNamara, M. J. Dixon, M. Bradley, *Chem. Rev.* **2002**, *102*, 3275–3300; c) D. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345–3384; d) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401–3429.

[7] A. Mandoli, S. Orlandi, D. Pini, P. Salvadori, *Chem. Commun.* **2003**, 2466–2467.

[8] a) J. Y. Ying, C. P. Mehnert, M. S. Wong, *Angew. Chem.* **1999**, *111*, 58–82; *Angew. Chem. Int. Ed.* **1999**, *38*, 56–77; b) E. D. V. Dirk, M. Dams, B. F. Sels, P. A. Jacobs, *Chem. Rev.* **2002**, *102*, 3615–3640; c) C. Li, *Catal. Rev.* **2004**, *46*, 419–492; d) A. Tafuchi, F. Schüth, *Micropor. Mesopor. Mater.* **2005**, *77*, 1–45; e) X. S. Zhao, X. Y. Bao, W. Guo, F. Y. Lee, *Materials Today* **2006**, *9*, 32–39.

[9] a) J. M. Thomas, R. Raja, D. W. Lewis, *Angew. Chem.* **2005**, *117*, 6614–6641; *Angew. Chem. Int. Ed.* **2005**, *44*, 6456–6482; b) J. Jarupatrakorn, T. D. Tilley, *J. Am. Chem. Soc.* **2002**, *124*, 8380–8388; c) C. Nozaki, C. G. Lugmair, A. T. Bell, T. D. Tilley, *J. Am. Chem. Soc.* **2002**, *124*, 13194–13203.

[10] a) D. Zhao, J. Feng, Q. Huo, N. Melosh, G. H. Fredrickson, B. F. Chmelka, G. D. Stucky, *Science* **1998**, *279*, 548–552; b) P. Schmidt-Winkel, W. W. Lukens, Jr., D. Zhao, P. Yang, B. F. Chmelka, G. D. Stucky, *J. Am. Chem. Soc.* **1999**, *121*, 254–255; c) P. Schmidt-Winkel, W. W. Lukens, Jr., P. Yang, J. S. Lettow, J. Y. Ying, G. D. Stucky, *Chem. Mater.* **2000**, *12*, 686–696; d) J. S. Lettow, Y. J. Han, P. Schmidt-Winkel, P. Yang, D. Zhao, G. D. Stucky, J. Y. Ying, *Langmuir* **2000**, *16*, 8291–8295; e) J. S. Lettow, T. M. Lancaster, C. J. Glinka, J. Y. Ying; *Langmuir* **2005**, *21*, 5738–5746; f) Y. Han, S. S. Lee, J. Y. Ying, *Chem. Mater.* **2006** *18*, 643–649; g) Y. Han, S. S. Lee, J. Y. Ying, *Chem. Mater.* **2007**, *19*, 2292–2298.

[11] a) D. Rechavi, M. Lemaire, *Org. Lett.* **2001**, *3*, 2493–2496; b) D. Rechavi, M. Lemaire, *J. Mol. Catal. A* **2002**, *182–183*, 239–247; c) D. Rechavi, B. Albela, B. Laurent, M. Lemaire, *Tetrahedron* **2005**, *61*, 6976–6981; d) T. M. Lancaster, S. S. Lee, J. Y. Ying, *Chem. Commun.* **2005**, 3577–3579; e) S. S. Lee, J. Y. Ying, *J. Mol. Catal. A: Chem.* **2006**, *256*, 219–224.

[12] S. S. Lee, S. Hadinoto, J. Y. Ying, *Adv. Synth. Catal.* **2006**, *348*, 1248–1254.

[13] J. M. Fraile, J. I. García, C. I. Herrerias, J. A. Mayoral, O. Reiser, A. Socuellamos, H. Werner, *Chem. Eur. J.* **2004**, *10*, 2997–3005.

[14] G. Jas, A. Kirschning, *Chem. Eur. J.* **2003**, *9*, 5708–5723.

[15] a) A. J. Sandee, D. G. I. Petra, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. Leeuwen, *Chem. Eur. J.* **2001**, *7*, 1202–1208; b) N. Künzle, J.-W. Solèr, A. Baiker, *Catal. Today* **2003**, *79*, 503–509; c) A. Mandoli, S. Orlandi, D. Pini, P. Salvadori, *Tetrahedron: Asymmetry* **2004**, *15*, 3233–3244; d) D. A. Annis, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 4147–4154; e) M. I. Burguete, E. Garcia-Verdugo, M. J. Vicent, S. V. Luis, H. N. Pennemann, N. G. Keyserling, J. Martens, *Org. Lett.* **2002**, *4*, 3947–3950; f) B. Altava, M. I. Burguete, E. García-Verdugo, S. V. Luis, M. J. Vicent, *Green Chem.* **2006**, *8*, 717–726.

[16] a) M. I. Burguete, A. Cornejo, E. García-Verdugo, J. García, M. J. Gil, S. V. Luis, V. Martínez-Merino, J. A. Mayoral, M. Sokolova, *Green Chem.* **2007**, *9*, 1091–1096; b) M. I. Burguete, A. Cornejo, E. García-Verdugo, M. J. Gil, S. V. Luis, J. A. Mayoral, V. Martínez-Merino, M. Sokolova, *J. Org. Chem.* **2007**, *72*, 4344–4350.
[17] H. Werner, R. Vicha, A. Gissibl, O. Reiser, *J. Org. Chem.* **2003**, *68*, 10166–10168.

