Effect of surface modification on the reactivity of MCF-supported IndaBOX†

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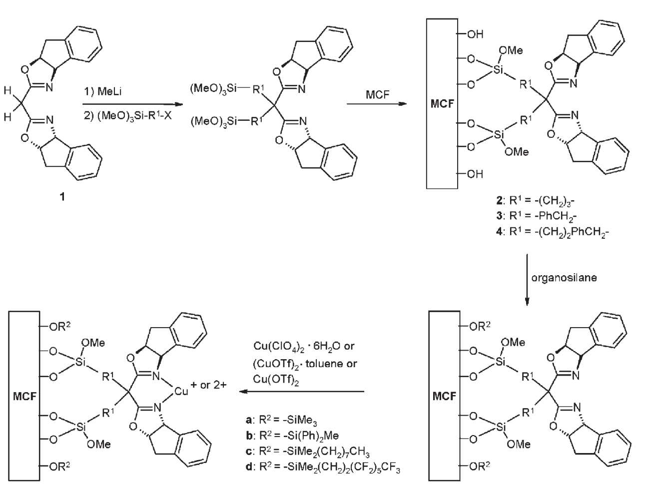
MCF-immobilized indaBOX–copper complexes, which show high enantioselectivities in asymmetric Diels–Alder and cyclopropanation reactions and have reactivities strongly affected by their environment, were prepared using various linker groups and silanol capping agents.

Chiral organometallic catalysts are important for the synthesis of pharmaceuticals and fine chemicals. It is of great interest to immobilize these homogeneous catalysts onto solid supports to allow them to be easily recovered and reused. The key to generating successful heterogenized catalysts is to avoid catalyst leaching during recycling, while retaining the excellent activity and enantioselectivity of the organometallic complexes. Various supports have been considered for such applications. In particular, silica supports have been found to be more promising than polymeric supports with regard to stability and reusability; they also provide for the flexible control of catalyst environment through surface modification with organosilanes. However, due to difficulties in the covalent linking of chiral ligands to silica supports and in the removal of reactive surface silanol groups, many of the reported heterogenized chiral catalysts involved polymeric supports instead of silica supports.[1–3] While some studies have focused on immobilizing chiral ligands on silica supports,[4–9] little work has been devoted towards modulating the catalyst environment near the active sites.

In this study, bisoxazoline ligands were immobilized onto mesocellular foam (MCF), whose synthesis has been described elsewhere.[10–12] MCF was templated by triblock copolymers in the presence of mesitylene. We have chosen this silica support for its high surface area (814 $m^2 g^{-1}$), and open, ultralarge pores of 25 nm, which were interconnected by windows of 11 nm. Such a pore structure would prevent any steric issues associated with the immobilization of bulky ligands, and minimize any diffusion limitation of large substrates. Experiments were conducted to assess the effect of free silanol groups, and the impact of modifying the environment around the catalytic sites. Specifically, different capping agents were introduced to the support surface, and various linker groups were employed for the fixation of the bisoxazoline ligands onto the MCF support.

IndaBOX **1**[13] was modified by the method illustrated in Scheme 1. It was first treated with MeLi at −50 °C. Lithiation of the two protons at the bridged carbon was followed by reaction with organosilanes containing electrophilic halide functionalities. The resulting trimethoxysilane-modified indaBOX ligands were then immobilized onto MCF by heat treatment in toluene. Solid state ^{13}C MAS NMR and ^{29}Si MAS NMR spectra of the immobilized indaBOX ligand **2** showed characteristic peaks corresponding to *C*=N (167 ppm) and Si-O*Si*(OR′)$_2$R (−65 to −51 ppm), while FT-IR illustrated the characteristic C=N vibration at 1643 cm^{-1}. The surface silanol groups on the silica support were capped with various trialkylsilanes, providing different hydrophobic environments around the MCF-anchored indaBOX ligands. FT-IR spectra illustrated a decrease in free Si–OH stretching (3400 cm^{-1}) after silanol capping. Elemental analysis also confirmed an increased carbon content on the MCF after silanol capping.

To examine the effect of silanol groups on the copper(II) bisoxazoline catalysts, homogeneous catalyst **1** was physically mixed with the calcined MCF and with the MCF capped with trimethylsilyl (TMS) species. At 25 °C, the mixture containing the calcined MCF showed only 71% ee, while that containing the TMS-capped MCF gave 84% ee, which was exactly the same enantioselectivity obtained by pure homogeneous catalyst **1**.[13] The results showed that the presence of silanol groups from the silica support adversely affected the enantioselectivity of homogeneous catalyst **1**.



Scheme 1 Immobilization of indaBOX onto MCF.

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† Electronic supplementary information (ESI) available: general synthesis, preparation of **2**, **2a**, **2b**, **2c**, **2d**, **3**, **3a**, **4**, **4a** and **9**, typical Diels–Alder reaction, kinetic experiments, and typical cyclopropanation of styrene. See http://www.rsc.org/suppdata/cc/b5/b506205e/

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Table 1 Diels–Alder reaction of cyclopentadiene and dienophile **5** or **6** over homogeneous catalyst **1**, MCF-supported catalysts **2**, **2a**, **3a** and **4a**, and colloidal silica-supported catalyst **9**[a,14]

Catalyst	Dieno-phile	Mol% of Catalyst	Temp[b] (°C)	Reaction time (h)	Conversion (%)	% *endo*	% ee[c] (*endo*)
1	**5**	10	25	1	100	90	84
			0	2	100	93	88
			−30	4	100	95	92
			−78	24	100	97	95
2	**5**	10	25	1	100	91	47
			0	1	100	92	56
			−30	2	100	94	76
			−78	8	100	94	77
2a	**5**	10	25	1	100	91	70
			0	1	100	93	76
			−30	2	100	95	84
			−78	8	100	96	88
3a	**5**	10	25	1	100	91	69
			0	1	100	93	77
			−30	2	100	95	84
			−78	8	100	96	88
4a	**5**	10	25	1	100	91	74
			0	1	100	93	79
			−30	2	100	95	85
			−78	8	100	96	90
		2	0	1	100	94	75
4a	**6**	10	25	24	98	86	86
		30	25	6	78	87	85
9	**5**	10	25	1	100	93	68
			0	2	100	94	72
			−30	8	100	96	77
			−78	24	100	96	80

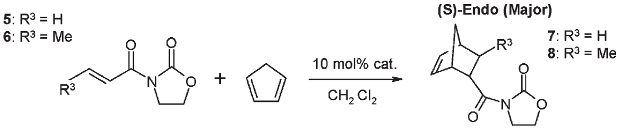
[a] Ligand:Cu molar ratio = 1.1. [b] Reactions at −78 °C took place over 4 h, and were then warmed to room temperature. [c] Determined by HPLC on Chiralcel OD-H column.

Capping of silanol groups in MCF also greatly enhanced the enantioselectivity of the heterogenized catalysts. Table 1 illustrates that heterogenized catalyst **2** has only 47% ee, while the same catalyst capped with TMS (heterogenized catalyst **2a**) gave 70% ee at room temperature. In fact, **2a** achieved 88% ee at −78 °C, and provided a high *endo* regioselectivity for product **7** over all temperatures examined (Table 1).

Catalysts **2a**, **3a** and **4a** were compared to determine the effect of the propyl, methylphenyl and methylphenylethyl linker groups on catalyst performance. An excellent *endo* regioselectivity was obtained over all three TMS-capped MCF-supported catalysts for the temperature range examined. Catalyst **4a** exhibited the highest enantioselectivity (90% ee at −78 °C).

The above studies illustrated that capping of the silanol groups was critical towards achieving high selectivities in silica-supported indaBOX catalysts.

The heterogenized catalyst, **4a**, retained its high enantioselectivity and activity even at a substrate-to-catalyst ratio as high as 50, achieving 75% ee and 100% conversion in just 1 h at 0 °C. It also displayed a high selectivity for the reaction between cyclopentadiene and dienophile **6** to give product **8** (see Table 1). Homogeneous catalyst **1** with $Cu(ClO_4)_2$ has been reported to give 84% ee and 94% *endo* at 23 °C for this reaction.[15] A separate account of a complex of $Cu(ClO_4)_2 \cdot \mathbf{1}$ immobilized onto silica gave 70% ee and 96% *endo* for the same reaction at room temperature.[5,6] In contrast, catalyst **4a** showed a lower *endo* regioselectivity of 86% at room temperature, but attained a higher enantioselectivity (86% ee).



Scheme 2 Diels–Alder reaction of cyclopentadiene and dienophile **5** or **6**.

Catalyst **4a** was also investigated for its reusability, a major advantage of anchoring chiral catalysts onto insoluble supports.[16,17] To recycle the catalyst, the post-reaction solution was centrifuged. The recovered catalyst was washed several times with fresh dichloromethane, and then used directly in the next run. Table 2 showed that catalyst **4a** achieved 100% conversion over all 5 runs, and displayed high enantioselectivities of 79–90%, depending on the reaction temperature for each run. Interestingly, the enantioselectivity was also dependent on the nature of the solvent used in the reaction and the catalyst washes.[5,6] Lower enantioselectivities were associated with the use of anhydrous dichloromethane, and higher ee values were obtained when water-saturated dichloromethane (1850 ppm of H_2O) was used.[15] It should also be noted that after 5 runs, the enantioselectivity provided by **4a** at 25 °C with a hydrous solvent (80% ee) was actually higher than that achieved by a fresh catalyst at 25 °C with an anhydrous solvent (74% ee). Thus, the methylphenylethyl-linked and TMS-capped catalyst **4a** demonstrated high activity, enantioselectivity and *endo* regioselectivity over multiple reaction cycles.

Catalyst **2a** was investigated further to determine if its activity could be enhanced with changes in the catalyst environment on the MCF surface. Catalyst **2**, which contained a propyl linkage, was protected with different capping agents, trimethylsilyl, methyldiphenylsilyl, octyldimethylsilyl and perfluorooctyl-dimethylsilyl, to give catalysts **2a**, **2b**, **2c** and **2d**, respectively. The 1 h conversions of these MCF-supported catalysts were measured at −78 °C, −30 °C, 0 °C and 25 °C for the asymmetric Diels–Alder reaction of cyclopentadiene and **5**. Fig. 1 shows that the MCF-supported catalysts **2a**, **2b**, **2c** and **2d** possessed superior activity to the homogeneous catalyst **1** and the non-porous, colloidal silica-supported catalyst **9**, especially at low temperatures. For example, at −30 °C, the MCF-supported catalysts showed conversions of $\geqslant$90%, whereas catalysts **1** and **9** displayed 69% and 48% conversions, respectively. Like catalyst **2a**, catalyst **9** involved a propyl linker group and had its surface silanol groups capped with TMS.

Table 2 Diels–Alder reaction of cyclopentadiene and dienophile **5** over fresh and recycled MCF-supported catalyst **4a**[a,14]

Run #	Temp (°C)	Solvent (CH_2Cl_2)	Conversion[c] (%)	% *endo*	% ee (*endo*)
1	0	anhydrous	100 (87[d])	93	83
2	0	anhydrous	100	94	79
3	0	hydrous[b]	100	92	84
4	−46	hydrous[b]	100[e]	96	90
5	25	hydrous[b]	100 (85[d])	91	80
1[f]	25	anhydrous	100	91	74

[a] Ligand:Cu molar ratio of 1.1. Catalyst was used directly without washing and drying after $Cu(ClO_4)_2 \cdot 6H_2O$ was added. [b] Solvent was water-saturated (with 1850 ppm of H_2O). [c] Conversion after 1 h, unless otherwise noted. [d] Isolated yield. [e] Conversion after 3 h. [f] Fresh catalyst was used after drying.

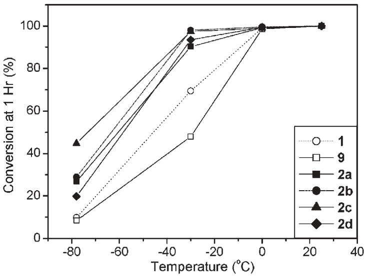


Fig. 1 Conversion of Diels–Alder reaction of cyclopentadiene and dienophile **5** over homogeneous catalyst **1**, MCF-supported catalysts **2a**, **2b**, **2c** and **2d**, and colloidal silica-supported catalyst **9**.[14]

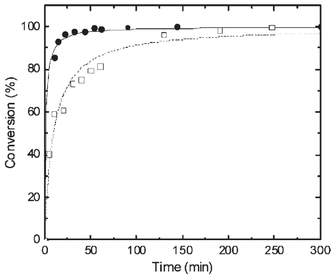


Fig. 2 Conversion of Diels–Alder reaction of cyclopentadiene and dienophile **5** as a function of time over (□) homogeneous catalyst **1** and (●) MCF-supported catalyst **3a** at −30 °C in CH_2Cl_2.[14]

In addition to demonstrating superior activities to **1** and **9**, the MCF-supported catalysts were able to retain a high enantioselectivity regardless of their capping moiety. This was especially clear at −78 °C, where the four MCF-supported catalysts **2a**, **2b**, **2c** and **2d** showed substantially different 1 h conversions, while their ee values remained remarkably similar (88%, 88%, 89% and 87%, respectively).

Kinetic studies conducted at −30 °C showed that catalyst **3a** has an apparent second-order kinetic rate constant of 10.6 $L \cdot mol^{-1} \cdot min^{-1}$. Fig. 2 illustrates that catalyst **3a** gave a much faster conversion than homogeneous catalyst **1**, which has a rate constant of 1.4 $L \cdot mol^{-1} \cdot min^{-1}$. Besides having a superior activity, catalyst **3a** demonstrated a high ee value of 84%.

The MCF-immobilized indaBOX catalyst also showed high enantioselectivity and reactivity in asymmetric cyclopropanation of styrene (Table 3). The heterogeneous catalyst showed high enantioselectivity up to 84% ee for *cis* isomer with excellent recyclability.

In summary, IndaBOX, a chiral bisoxazoline, was successfully immobilized onto MCF by a simple method. The heterogenized indaBOX catalysts showed high enantioselectivity and reactivity in asymmetric Diels–Alder reaction and asymmetric cyclopropanation with good recyclability. Surface modification gave rise to a different environment around the catalytic site, which had a great influence on the reactivity of the MCF-immobilized indaBOX.

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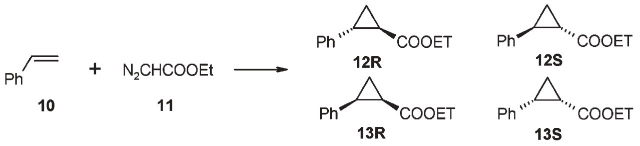
Table 3 Cyclopropanation of styrene with EDA catalyzed by the heterogenized catalysts[a]

Catalyst	Run #	Styrene/ EDA	% Yield[c]	*trans*/*cis*[d]	% ee *trans*[e]	% ee *cis*[e]
1:CuOTf	1	1.2	84	64/36	87	86
2a:CuOTf	1	3.0	93	51/49	78	80
	2	1.2	86	48/52	72	78
	3	1.2	86	46/54	66	76
2a:$Cu(OTf)_2$[b]	1	1.2	73	51/49	78	81
	2	1.2	84	47/53	75	80
	3	1.2	73	45/55	74	80
4a:CuOTf	1	3.0	91	51/49	82	81
	2	1.2	92	51/49	82	80
	3	1.2	88	49/51	80	76
4a:$Cu(OTf)_2$[b]	1	1.2	77	52/48	82	84
	2	1.2	84	50/50	81	83
	3	1.2	84	47/53	80	83

[a] 1 mol% Cu at room temperature for 7 h (dropwise addition of EDA for 5 h and stirring for an additional 2 h). [b] Reduced by phenylhydrazine before use. [c] Calculated from GC calibration curve between n-decane and product. [d] Determined by GC. [e] Determined by GC with a Cyclodex-B column. **12R** (*trans*) and **13R** (*cis*) are the main isomers.



Scheme 3 Cyclopropanation of styrene with ethyl diazoacetate (EDA).

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