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Heterogenization of a Chiral Bis(oxazoline) Catalyst by Grafting onto Silica

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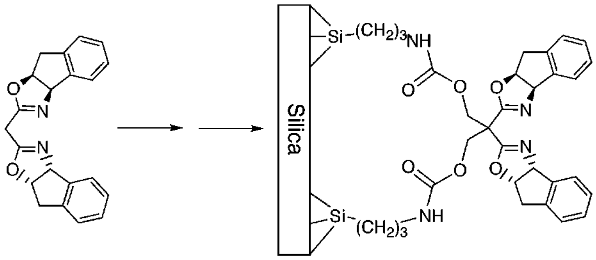
ABSTRACT



We report here the first heterogenization of a bis(oxazoline) ligand on an inorganic (silica) surface. The activity and enantioselectivity of this new material as a catalyst for the Diels–Alder reaction were checked, and it was shown that under certain conditions enantioselectivities similar to those of the homogeneous catalyst are reached. It was also shown that under these conditions the catalyst can be recycled without loss of activity or selectivity.

Chiral bis(oxazoline) (BOX) ligands and their application as catalysts have been the subject of extensive research during the past decade. Ligands of this type give high enantioselectivities for a wide range of reactions.[1] In particular, they show excellent enantioselectivities (of up to 90−99% ee) for Diels−Alder reactions.[2]

One of the disadvantages of the BOX catalysts, however, is that a large catalyst-to-substrate ratio is needed to accomplish most reactions. It is clear that for such catalysts to be practically useful they should be recycled, and this can best be done by their heterogenization. A successful heterogenization will also lead to a cleaner process, which will not leave any catalyst (ligand or metal) contamination in the products of the reaction.

When we started working on the subject, bis(oxazoline) ligands had not yet been heterogenized. Recently, however, a few papers concerning their heterogenization have appeared: Reiser and Glos introduced poly(ethylene glycol) chains on the nitrogen bridge of aza-bis(oxazolines),[3] and Mayoral et al. polymerized BOX ligands through functionalization of the carbon bridge with polymerizable double bond groups, followed by homopolymerization or copolymerization with DVB.[4] Both papers are interested in cyclopropanation reactions. Very recently Cozzi et al. reported the use of poly(ethylene glycol)-supported bis(oxazoline) ligands as catalysts for cyclopropanation reactions, ene-reactions, and a Diels−Alder reaction.[5] They obtain good enantioselectivities for the first two reaction types, with up to 95% ee, but get no more than 45% ee for the Diels−Alder reaction. Noncovalent heterogenizations were performed even earlier. Mayoral et al. report the immobilization of BOX ligands by cationic exchange on clays and on nafion or nafion−silica nanocomposites and their use in cyclopro-

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(1) For review see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45.

(2) (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728−729. (b) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461. (c) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815−3818.

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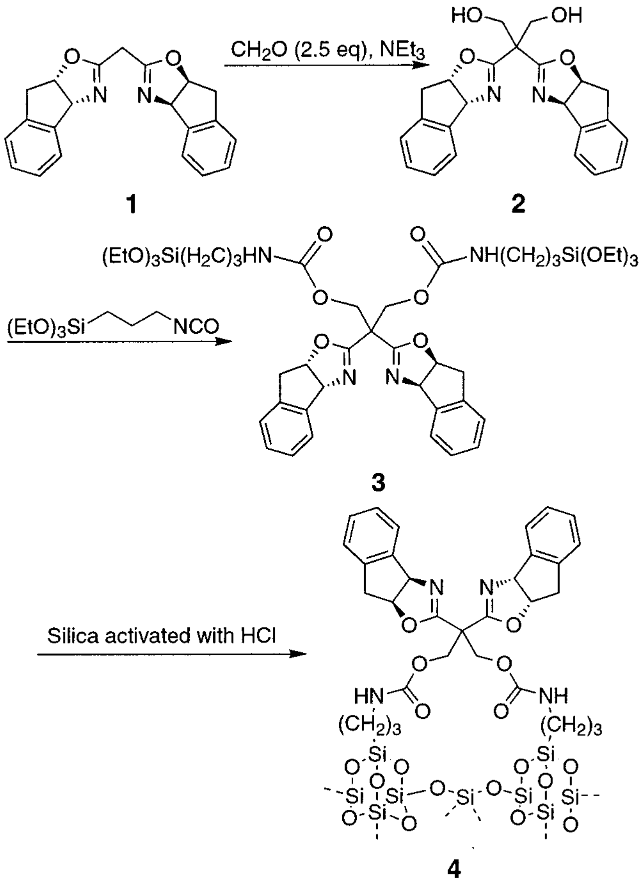
panation reactions, but recycling is often difficult, probably as a result of leaching of the active species.[6] Similar catalysts have also been used more recently by this group as catalysts for the Diels–Alder reaction, but the enantioselectivities obtained were low (up to 11% ee).[7] Hutchings et al. report a modification of copper-exchanged zeolite Y with bis(oxazoline) ligands that gives only moderate enantioselectivities in aziridination of alkenes.[8]

We present here the first covalent heterogenization of BOX ligands on an inorganic surface. We applied this heterogenized catalyst to the Diels–Alder reaction. This is the first time good enantioselectivities have been obtained for the Diels–Alder reaction using a heterogeneous chiral BOX ligand.

We chose to heterogenize indaBOX (**1**), which, because of its rigidity, gives especially good enantioselectivities for several reactions. It was prepared from commercially available 1*R*,2*S*-1-amino-2-indanol and diethyl malonimidate dihydrochloride according to a known procedure.[2c] To achieve heterogenization, the ligand was functionalized on the carbon bridge between the two oxazoline moieties, in a way that will neither disturb the C_2 symmetry of the ligand nor interfere with the catalytic site. The simplest way to introduce polymerizable functional groups seemed to be the double addition of formaldehyde to the active carbon, as shown in Scheme 1. We were inspired for this reaction by Guzaev,[9] who reported that the reaction of *β*-diketones with formaldehyde gives the same functionalization. We obtained **2** in 75–85% yield (Scheme 1) by a facilitated version of his procedure, using solid formaldehyde instead of a freshly prepared 20% formaldehyde solution in water.

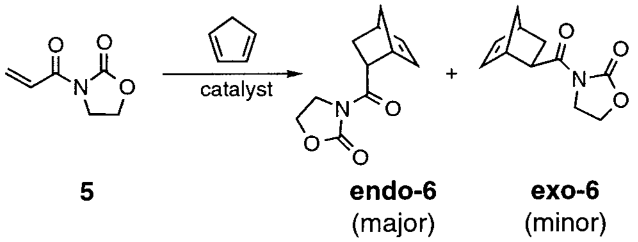
Scheme 1. Grafting of IndaBOX **1** onto Silica



Grafting on silica was then performed by the reaction of 3-(isocyanatopropyl)triethoxysilane with **2**.[10] The resulting **3** was not purified; it was reacted directly with a silica[11] to obtain **4**, with a degree of functionalization of 0.25 mmol of ligand per gram of **4** (Scheme 1). The overall yield for the last two steps is 71–75%.[12]

The heterogenized **4** was tested as a catalyst of the well-known Diels–Alder reaction of 3-acryloyl-2-oxazolidinone **5**[13] with cyclopentadiene (CPD), shown in Scheme 2.[2,14] Silica-grafted **4** (8 mol % relative to **5**) was mixed with $Cu(OTf)_2$ in CH_2Cl_2 for 1–4 h and then cooled to the desired temperature. 3-Acryloyl-2-oxazolidinone and freshly cracked CPD were then added one after the other. Samples were taken and injected on GC, and the reaction was stopped when no increase in conversion could be observed.

Scheme 2. Model Diels-Alder Reaction



Good enantioselectivities were obtained for the first three reaction cycles (65–73% ee), but the enantioselectivity went down on the fourth reaction cycle (Table 1). At −78 °C we obtain 87% ee. It is interesting to compare these results with those of Davies et al.,[15,16] who obtain 82% and 92% ee at

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(11) Matrex Si-60 from Millipore, particle size 70–200 *μ*m activated previously with HCl.

(12) Determined by microanalysis. Calculated according to nitrogen percentages.

(13) Prepared according to procedures from: (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256. (b) Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271–2273.

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Table 1. Recycling of Catalyst **4**

entry	metal	cycle (°C)	% conv (h)	% endo	% ee[a]
1	$Cu(OTf)_2$[b]	1 (−78)	82 (48)	96	87
2		1 (0)	97 (1)	89	65
3		2 (0)	53 (1)	90	73
4		3 (0)	65 (1)	88	69
5		4 (0)	19 (1)	89	17
6	$Cu(ClO_4)_2\cdot 6H_2O$[c]	1 (0)	96 (1)	86	70
7		2 (rt)	97 (1)	85	65
8		3 (−15)	97 (1)	90	85
9		4 (0)	100 (1)	88	79

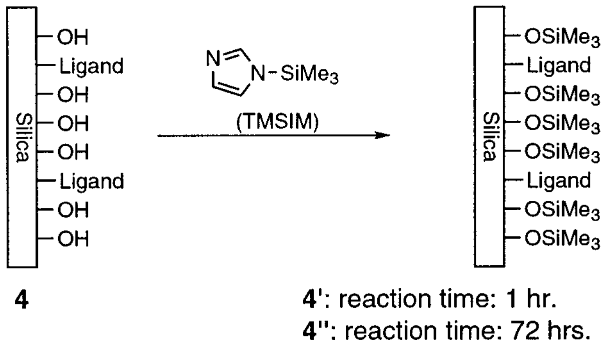
[a] The ee is given for the major product, the endo enantiomer. It was determined by HPLC on Chiralcel-OD column with 95% heptane/5% 2-propanol as the eluant. Absolute configuration: (+)-2*R*.[2a,18] [b] The reaction was conducted under argon, in dry CH_2Cl_2. The catalyst (8 mol %) was separated by centrifuge or by filtration. The catalyst was dried in vacuum before reuse. [c] The catalyst (10 mol %) was separated by centrifuge or by filtration and was used directly for the next cycle.

−50 and −65 °C, respectively, when using the homogeneous indaBOX ligand dimethylated on its bridge.

It occurred to us at this point that the reason for the unsatisfactory enantioselectivities after several recycling sessions may be the high sensitivity of the catalytic complex to water, combined with the hygroscopic nature of the silica. Ghosh has recently shown that, when $Cu(ClO_4)_2\cdot 6H_2O$ is used as the catalyst precursor, the catalytic species is not sensitive to water.[17] We therefore used this as the metal in our system. The silica-grafted **4** was mixed with the metal overnight at ambient temperature. The dienophile was added, and mixed with the catalyst for an hour, cooled to the desired temperature, and treated with freshly cracked CPD. As opposed to the previous experiments, no efforts were made to keep catalyst **4** dry; the reaction was conducted in CH_2Cl_2, not redistilled and not under inert atmosphere. At the end of the reaction the catalyst was washed with the same solvent and used directly for the next cycle, without prior drying. This system gave improved enantioselectivities, which did not diminish after 4 cycles (entries 6−9, Table 1).

It has previously been shown that in some cases protecting the free silanol groups of the silica with silanes increases the activity and the enantioselectivity of the reaction (e.g., for the addition of Et_2Zn to aldehydes catalyzed by amino alcohol ligands[19]). We therefore modified the silica surface using *N*-trimethylsilylimidazole (TMSIM)[20] to obtain the protected silica **4′** (Scheme 3). According to McMurtrey, a reaction of 1 h is sufficient to protect all silanol groups on a normal (not previously functionalized) silica. However,

Scheme 3 . Protection of the Hydroxyl Groups of the Silica



silica **4′** gave only a very small rise in enantioselectivity relative to **4** at room temperature. We tried reacting silica **4** with TMSIM for 72 h. The obtained silica **4″** gave indeed improved results. The enantioselectivity went up to 81% ee at room temperature (entry 3, Table 2) and reached 92% ee at −78 °C (entry 4, Table 2), which approaches the results of the homogeneous catalyst (98% ee).[2a] Microanalysis shows that the ratio of protecting TMS groups per ligand is 3.3 for **4′** and 6 for **4″**. IR of the modified silica shows a peak around 2970, typical of methyl groups. This peak is relatively stronger in the **4″** silica than in **4′**. Hence both IR and microanalysis indicate that a longer reaction time with TMSIM gives a better covering of the silanol groups. Logically, the silanol groups nearest to the ligands would be the most difficult to protect, since they are the most sterically hindered ones, and it is exactly these sites which can most interfere with the chiral catalytic sites. This explains why a significant rise in enantioselectivity is observed only when using the more protected silica **4″**.

Table 2. Influence of Protection of Silanol Groups and of Temperature on Enantioselectivity When $Cu(ClO_4)_2\cdot 6H_2O$ Is Used to Form the Catalyst[a]

entry	catalyst	temp (°C)	time (h)	% endo	% ee
1	**4**	rt	1	85	65
2	**4′**	rt	1	86	71
3	**4″**	rt	1	86	81
4	**4″**	−78	3	86	92

[a] The conversion is 99−100% for all reactions.

We usually worked with 8−10 mol % catalyst to substrate (entry 1, Table 3). Using 20 mol % catalyst does not improve the enantioselectivity (entry 2, Table 3), but reducing it to 5 mol % surprisingly has almost no effect on the enantio-

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Table 3. Influence of Catalyst-to-Substrate Ratio on Enantioselectivity

entry	mol % of catalyst[a]	% conv	% endo	% ee
1	10	99+	86	71
2	20	99+	89	71
3	5	99+	88	68

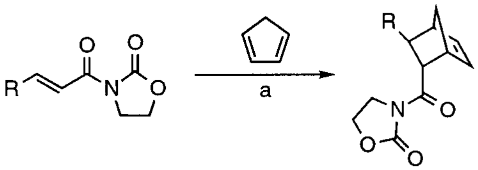
[a] Catalyst **4′** at room temperature.

selectivity (entry 3, Table 3). It can be concluded that the major impediment to an increase in the enantioselectivity of our system is the accessibility of the ligand on the silica. It is known that the homogeneous indaBOX ligand gives 98% ee (at −78 °C) for the same reaction as long as 10 mol % of the catalyst are used, but that it goes down to 92% ee when only 5 mol % of the catalyst are used.[17]

To show the general nature of the reaction, several other substrates were tried. The results are presented in Scheme 4. For substrate **7**[13a] an ee of 70% was observed, compared with 84% ee for the homogeneous ligand.[17] Substance **10**[13a] was formed with 61% ee (no experiments with the parallel homogeneous system are reported in the literature; however, when Cu(OTf)$_2$ was used with the homogeneous ligand only 35% ee were obtained[2c]).

In conclusion, we have shown that indaBOX **1** can be heterogenized by grafting onto silica. The obtained catalyst can then be efficiently recycled if Cu(ClO$_4$)$_2$·6H$_2$O is used as the metal precursor. In this case the catalyst is very robust. Best results were obtained when the silanol groups of this silica catalyst were protected by TMS groups. In this case we obtain 81% ee at room temperature and 92% ee at −78 °C. These results, although not quite as good as those of the homogeneous system, are better than any achieved so far with heterogeneous BOX ligands for the Diels−Alder reaction. Our system has the advantage of being compatible with air humidity, and reactions as well as filtrations can be easily performed with no need for special conditions. The catalyst is ready for reuse directly after filtration. Other ways of heterogenizing the functionalized ligand **2** as well as other applications of this system to reactions such as cyclopropanation and aziridination are currently being explored in our laboratory.

Scheme 4. Reacting Other Substrates



7: R = Me
9: R = Ph

8: R = Me (70% ee)[b]
10: R = Ph (61% ee)[c]

[a] 1 sili-indaBOX:1 Cu(ClO$_4$)$_2$·6H$_2$O (10 mol %); CH$_2$Cl$_2$, rt. [b] After 3 h: 70% yield (GC), 96% endo, 70% ee (2*R*) (HPLC on chiralcel OD, 10% 2-propanol in heptane). [c] Reacted for 50 h; isolated on silica column with 0−25% EA in pentane. 63% Isolated yield; 79% endo, 61% ee (2*S*), calculated according to α_D in CCl$_4$ (measured α_D = 109°), by comparison with the literature.[21,22]

Supporting Information Available: Experimental procedures for the synthesis of the catalysts and for the Diels−Alder reactions, as well as analytical data, are available.

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