Asymmetric Diels–Alder reactions with hydrogen bonding heterogeneous catalysts and mechanistic studies on the reversal of enantioselectivity

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Abstract—Chiral bis(oxazoline) complexes of Cu(II), Zn(II) and Mg(II) have been immobilized on silica support via hydrogen-bonding interactions. Up to 93% ee is obtained in the Diels–Alder reaction between 3-((E)-2-butenoyl)-1,3-oxazolin-2-one and cyclopentadiene at room temperature with the heterogeneous bis(oxazoline) complexes, and the catalysts can be recycled without losing enantioselectivity. Experimental and theoretical studies show that the reversal of the absolute product configuration upon immobilization of the PhBOX-Cu(II) catalyst is triggered by the anion dissociation from Cu(II) onto the surface of the support.
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1. Introduction

Enantioselective reactions catalyzed by chiral Lewis acid complexes are of great importance for the production of enantiopure pharmaceuticals and chemicals.[1] Among various chiral Lewis acid catalysts, those containing the chiral bis(oxazoline) (BOX) ligands have shown many applications in the last decade or so.[1,2] Particularly, excellent enantioselectivities have been obtained in DA reactions using this type of the complexes.[2,3] However, relatively large amounts of the chiral catalysts (1–10 mol%) are generally required, which makes recovery and recycling of the catalyst necessary. A number of strategies have therefore been designed and employed to immobilize and recycle the complexes of BOX ligands;[4] these include covalent bonding to organic polymers and inorganic supports,[5,6] non-covalent immobilization by the interaction between cationic BOX-based metal complexes and anionic supports,[7,8] and the use of solvents of special properties such as ionic liquids.[9]

Non-covalent immobilization is usually a convenient and also an industrially relevant method.[10] However, few examples of non-covalently immobilized BOX systems have been reported or known to be effective for the DA reactions at present. Mayoral et al. exchanged the BOX-M(II) (M=Cu, Mg, Zn) complexes onto laponite clays and nafion–silica nanocomposites for a benchmark DA reaction; but the ee was low ($\leq 11\%$).[8a] Hutchings et al. exchanged zeolite and mesoporous materials (MCM-41, Al-SBA-15, MSU-2) with $Cu(OAc)_2$ to obtain Cu(II)-exchanged materials, then modified the exchanged materials with chiral BOX ligands for a hetero-DA reaction. The resulting PhBOX-CuH-zeolite Y catalyst gave a higher enantio-selectivity (41% ee) compared to the homogeneous analogue (20% ee) although the activity was relatively low.[8b] More recently, the immobilization of homogeneous catalysts by hydrogen bonding has been reported.[11] Parallel to our research in immobilizing BOX complexes by hydrogen bonding for the DA reactions, Klein Gebbink and co-workers reported the same strategy for similar reactions.[12] A surprising observation from these studies is that the configuration of the product changed on going from the homogeneous to the heterogeneous system. This is of both fundamental and practical significance, as it indicates that immobilization alters the active catalytic species, and both enantiomers of a product may be accessible by choosing a suitable support. However, the origin of the
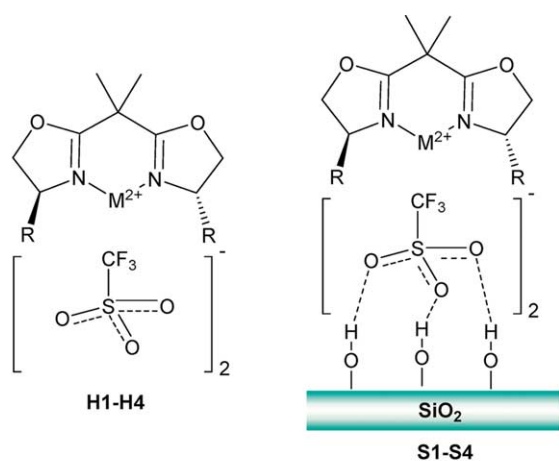
observed reversal is not yet clear, although it may be attributed to the interactions of the immobilized complexes with support surface.[8b,12] Herein we describe our results of the DA reaction of dienophile **5** with diene **6** using hydrogen bond-immobilized BOX-M(II) catalysts [Eq. 1] and the insight we gained both experimentally and computationally into the reversal of product configuration.

5   **6**   *(S)-endo*   *(R)-endo*   (1)
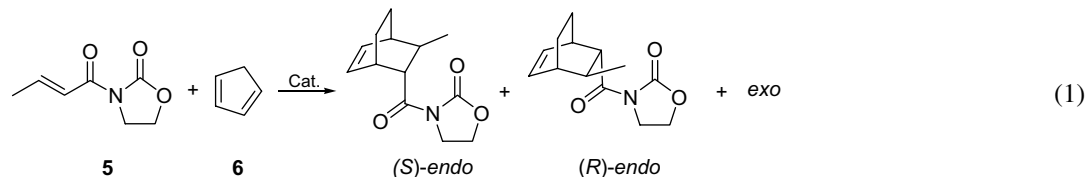
2. Results and discussion

2.1. Preparation and characterization of the catalysts

The homogeneous catalysts **H1–H4** were prepared in dichloromethane using metal triflates and 1 equiv of a BOX ligand. The corresponding supported catalysts **S1–S4** were prepared by the adsorption of complexes **H1–H4** to the surface of the silica (Fig. 1). The loading of the metal in the resulting heterogeneous catalysts is 1.0–1.1 wt% for copper and zinc, but only 0.03 wt% for magnesium. Anhydrous dichloromethane was used as the solvent for the preparation of the heterogeneous catalysts because of its dissolubility for BOX catalysts and aprotic nature (protic solvents would interfere with the adsorption).[13] Before the adsorption, the support was heated at 300 °C in order to remove the physisorbed water, which would otherwise complicate the interpretation of the results (vide infra).

The immobilization of the homogeneous catalysts **H1–H4** onto silica was assumed to derive from hydrogen bonding interactions between the triflate anions and surface silanol groups (Fig. 1). Direct evidence for the hydrogen bonding is obtained from IR studies. Before adsorption, the support displays a sharp peak at 3740 cm^{-1}, which can be ascribed to the stretching frequency of isolated silanols (Fig. 2a).[14] Upon adsorption of the homogeneous catalysts, the intensity of this IR band decreases considerably and only a shoulder at 3651 cm^{-1} is observed. In addition, the bending vibration of the Si–O in silanols characterized by the band at 975 cm^{-1} is red shifted to 946 cm^{-1} and becomes broad (Fig. 2b).[14] Pimentel et al. showed that hydrogen bonding results in red-shifts in the –OH stretching vibration frequency and the half-width of the band is broadened.[13] This has been confirmed by others.[11a,15] Support for the integrity of the BOX structures in **S1–S4** comes from the IR spectra (Fig. 3).
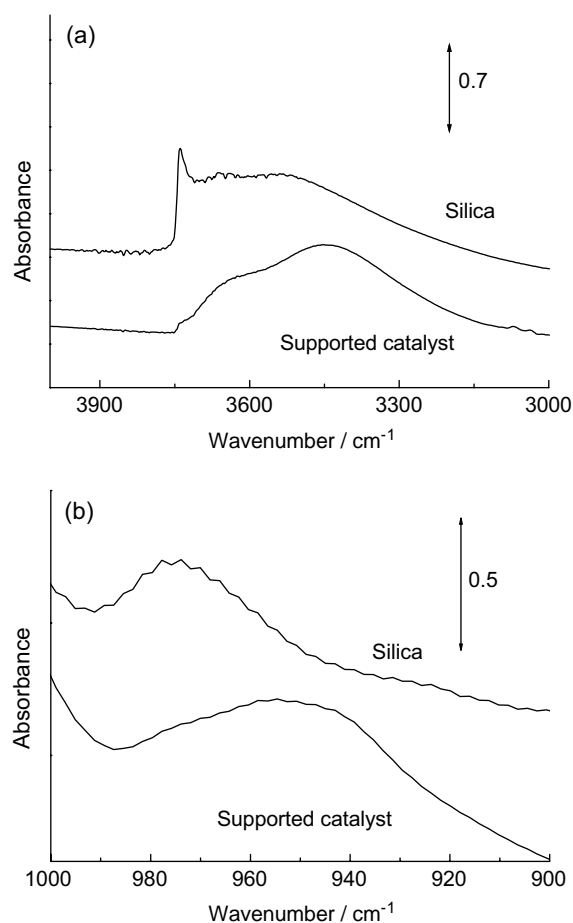
Figure 2. FTIR spectra of the stretching and the bending frequencies of the hydroxyl groups on silica before and after the immobilization of **H2**: (a) stretching frequencies of the hydroxyl groups; (b) the bending frequencies of the hydroxyl groups.

Homogeneous catalysts	Corresponding supported catalysts
H1: M = Cu, R = *t*Bu	**S1**
H2: M = Cu, R = Ph	**S2**
H3: M = Zn, R = Ph	**S3**
H4: M = Mg, R = Ph	**S4**

Figure 1. The precatalysts BOX-M(II) **H1–H4** and their immobilization by hydrogen-bonding interaction.

A rather intense band at $\sim 1630 \text{ cm}^{-1}$ is observed, which corresponds to the C=N bond stretching and is similar to that of the homogeneous complexes ($\sim 1633 \text{ cm}^{-1}$). We can therefore conclude that upon adsorption of the triflates complexes **H1**–**H4** to silica, hydrogen-bonding interactions take place between silanols and sulfonate oxygen atoms, and the BOX-M(II) cations are immobilized primarily via ionic interaction.
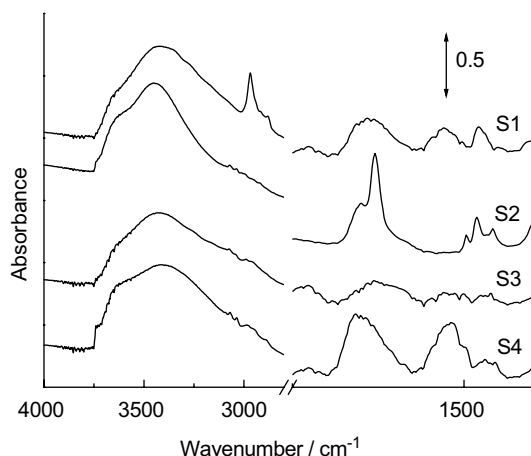
Figure 3. FTIR spectra of the supported catalysts: *t*BuBOX-Cu(II)-SiO$_2$ (**S1**), PhBOX-Cu(II)-SiO$_2$ (**S2**), PhBOX-Zn(II)-SiO$_2$ (**S3**), and PhBOX-Mg(II)-SiO$_2$ (**S4**).

2.2. Homogeneous versus heterogeneous DA reactions

For homogeneous DA reactions, better enantioselectivities are usually obtained at lower temperatures. However, practical applications of heterogeneous catalysts often need relatively high temperatures. With this in mind, the frequently used homogeneous catalysts **H1** and **H2** were initially immobilized for the DA reaction of dienophile **5** with diene **6** at room temperature [Eq. 1]. Table 1 summarizes the results obtained with **S1**, and for comparison those obtained with **H1** in homogeneous reactions are also included. As we can see, the supported catalyst displays a lower activity and enantioselectivity compared to the homogeneous analogue in dichloromethane (entries 1 and 2). This is at least partially due to leaching of copper cations into the solution, which contained 79.8 ppm copper at the time when the reaction was terminated. Nevertheless,

the percentage of leaching was only 0.8%. A homogeneous experiment was carried out in which 0.8% amount of the catalyst was added and no more than 15% of conversion was observed, indicating a heterogeneous process. In contrast, an excellent enantioselectivity and enhanced activity were observed with **S1** when the less polar toluene was used as the solvent (entries 3 and 4) in which the copper leaching is reduced to 4.9 ppm. The introduction of additional substrate to the filtrate before separating the product resulted in no obvious reaction, indicating that the DA reaction we observed is heterogeneous. However, a decreased activity was observed when the heterogeneous catalyst was reused (entries 5 and 6). Based on a study by Evans et al., who showed that the hydration of **H1** brought about a detrimental effect on its activity and 3 Å molecular sieves proved effective in reactivating the catalyst,[3c] we deduced that the activity decrease could arise from the effects of moisture or copper leaching in the subsequent reactions. 3 Å molecular sieves were therefore added to the heterogeneous system and we were delighted to find that **S1** could be reused. After 3 runs, the enantioselectivity remained unchanged, although the activity decreased slightly (entries 7–9). The *endo/exo* ratios of **H1** and **S1** are comparable in both solvents.

The phenyl-substituted BOX ligand is known to be less enantioselective in Cu(II) catalyzed DA reactions than its *t*Bu analogue. This is also true with **S2**, as seen from Table 2. However, **S2** provides higher enantioselectivities than **H2** in all three solvents examined (Table 2, entries 1–4). This might be attributed to geometric constrains imposed on the PhBOX-Cu(II) catalyst by the silica surface.[8b,11b,c] It may also arise from the reaction occurring at the liquid–solid interface, as the enantioselectivities of related reactions are known to be solvent-dependent.[3c,16] The lower ee values observed with **H2** in toluene (3%) and ether (6%) may be also resulted from the lower solubility of the complex in the two solvents. In the case of **S1**, better enantioselectivity is obtained when toluene is used as the solvent in the heterogeneous catalysis (Table 2, entry 4). In contrast to **S1**, the phenyl-substituted **S2** affords product with the configuration opposite to that obtained with its counterpart **H2**. This is interesting, as it suggests that the DA reaction with **S2** is a heterogeneous process and more importantly, the active catalytic species are different on going from the homogeneous solution to the solid surface (vide infra).

Table 1. Homogeneous versus heterogeneous DA reactions catalyzed by the catalysts **H1** and **S1**, respectively[a]

Entry	Catalyst	Solvent	Time (h)	Conv. (%)[b]	*endo/exo*[c]	ee (%)[c]	Config.[d]
1	**H1**	CH$_2$Cl$_2$	8	>97[e]	89:11	90	*S*
2	**S1**	CH$_2$Cl$_2$	8	43	89:11	85	*S*
3	**H1**	Toluene	8	70	92:8	88	*S*
4	**S1**	Toluene	8	83	91:9	93	*S*
5	**S1** (1st)	Toluene	22	98	89:11	91	*S*
6	**S1** (2nd)	Toluene	22	76	92:8	92	*S*
7[f]	**S1** (1st)	Toluene	22	98	90:10	91	*S*
8[f]	**S1** (2nd)	Toluene	22	92	92:8	91	*S*
9[f]	**S1** (3rd)	Toluene	22	83	90:10	91	*S*

[a] Reactions were performed at room temperature with the ratio of catalyst/substrate=1/10.
[b] The conversion was determined by ^{1}H NMR (400 MHz).
[c] The *endo/exo* ratio and the ee value of the *endo* isomer were analyzed by chiral HPLC.
[d] The configuration of the product was confirmed by comparing with the literature.[3c]
[e] There was no peak of the substrate in the ^{1}H NMR spectrum.
[f] The reaction was carried out in the presence of 3 Å molecular sieves.

Table 2. Homogeneous versus heterogeneous DA reactions catalyzed by the catalysts **H2** and **S2**, respectively[a]

Entry	Catalyst	Solvent	Conv. (%)	endo/exo	ee (%)	Config.
1	**H2**	CH_2Cl_2	100	89:11	15	S
2	**S2**	CH_2Cl_2	100	83:17	31	R
3	**S2**	Et_2O	100	90:10	21	R
4	**S2** (1st)	Toluene	100	83:17	42	R
5	**S2** (2nd)	Toluene	100	82:18	46	R
6	**S2** (3rd)	Toluene	98	84:16	40	R
7	**S2**[b]	Toluene	100	79:21	21	R
8	**S2**[c]	Toluene	100	83:17	36	R

[a] The reaction time was 22 h under the conditions the same as those given in Table 1.
[b] The silica support was calcinated at 550 °C for 4 h.
[c] The silica was firstly calcinated at 550 °C for 4 h, then refluxed in 1 M HNO_3 for 2 h and finally washed with deionized water until neutrality.

We also attempted the reuse of **S2**. Following the first run of the DA reaction in toluene, the catalyst was firstly recovered by centrifugation and then dried for the next run. However, the activity and enantioselectivity of the catalyst decreased significantly. We have tried to improve reaction by working-up under an argon atmosphere. No significant change in selectivity is found when **S2** is reused this way in toluene (Table 2, entries 4–6).

Previous results show that covering the free silanol groups on the silica increases the enantioselectivity in the DA reaction,[17] revealing the importance of the support effect. In our studies, different results are obtained. The silica involved was calcinated at 300 °C for 3 h to remove the physisorbed water. However, when the silica was calcinated at 550 °C for 4 h (corresponding to partial dehydroxylation thus less silanol groups),[14] a significant decrease in ee was observed (Table 2, entries 4 and 7). Interestingly, when the silica calcinated at 550 °C was refluxed with 1 M HNO_3 for 2 h and washed with deionized water until neutral, the resulting catalyst gave an significant improved ee value (Table 2, entry 8). By treating with the HNO_3 for 2 h, the dehydroxylated surface of silica would be partially rehydroxylated and the silanol groups regenerated,[14] and hence the ee was improved again (Table 2, entries 7 and 8). These observations suggest that the change of the silanol groups on the surface of the support can influence the enantioselectivity. This is not surprising, as the closely related DA reaction of ethyl glyoxylate with 1,3-cyclohexdiene catalyzed by **H2** has given ees depending on solvent dielectric constants.[16a] The calcination of the support alters the density of surface silanol groups and so may affect their interaction with or the 'solvation' of the BOX complex.

2.3. Mechanistic studies on the reversal of enantioselectivity

Being interested in the observed reversal of the enantioselectivity (Table 2), we decided to undertake further studies. As aforementioned, the recent reports from the groups of Hutchings and Klein Gebbink have revealed similar observations.[8b,12] However the cause for this reversal at the molecular level is still to be delineated. Such reversals in product configuration have also been noted in related homogeneous DA reactions on going from (S)-tBuBOX-Cu(II) to (S)-PhBOX-Cu(II) complexes.[3d,18a,19] This was a result from the BOX-Cu(II)-dienophile complexes adopting a square planar vs. a tetrahedral geometry or from π-stabilization involving the PhBOX ligand. More recently, Jørgensen has

demonstrated that, a number of factors such as solvents with different dielectric constants, may have subtle influence on the geometries of the BOX-Cu(II)-dienophile intermediates.[16a]

For homogeneous asymmetric DA reactions, solvents, counterions and additives, for example, achiral ancillary ligands and molecular sieves, often influence the enantioface selection.[16a,18,20a,21] The asymmetric induction with BOX-M(II) catalysts is also dependent on the coordination geometry of the metal center,[3c,18,20] with square planar and octahedral coordination favoring α-Si face addition while the tetrahedral arrangement favoring α-Re face reaction (Fig. 4). A distorted square pyramidal geometry is expected to give the same face selection as a square planar or octahedral species.
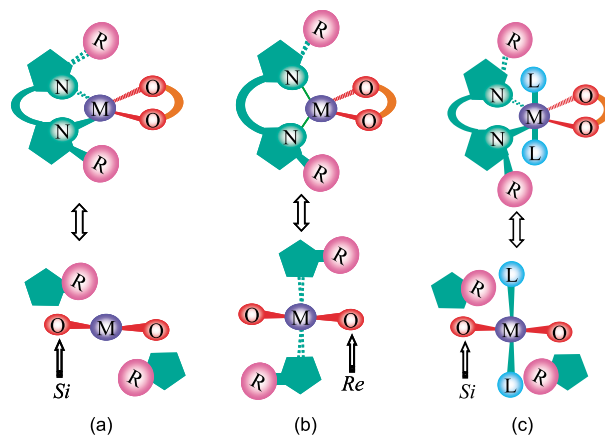
Figure 4. Effect of the BOX-M(II)-dienophile geometries on asymmetric induction: (a) planar, (b) tetrahedral, and (c) octahedral. M: metal, R: substituted group on the ring of BOX, L: coordinated anions or molecules.

Bearing solvent effects in mind, we first examined the reaction of the dienophile **5** with the diene **6** in solvents with diverse dielectric constants. As seen from Table 3, there is

Table 3. Homogeneous DA reactions catalyzed by the catalyst **H2** in different solvents at room temperature[a]

Entry	Solvent	Dielectric constant[22]	ee (%)	Config.
1	Et_2O	4.27	6	S
2	THF	7.52	21	S
3	CH_2Cl_2	8.93	15	S
4	MeOH	33.00	40	S
5	MeCN	36.64	35	S
6	$MeNO_2$	37.27	24	S

[a] The reaction time was 22 h under the conditions the same as those given in Table 1.

a correlation between the ees and the dielectric constants. Higher dielectric constants generally favor higher ees. Unlike the reaction of ethyl glyoxylate with 1,3-cyclohexadiene,[16a] there was no reversal in the product configuration. This indicates that the reversal we observed with **H2** and **S2** is less likely to be attributed solely to the change in the solvating media on going from homogeneous solution to solid surface. Because IR measurements of **S2** indicate the presence of hydrogen bondings between the triflate anions and surface silanol groups, we suggest that the reversal could simply be resulted from the dissociation of the triflate ions from Cu(II) to the surface. This hypothesis implies that the triflate is coordinated to the PhBOX-Cu(II) complexes in homogeneous reactions. However, whilst there is evidence of one triflate coordination to Cu(II) at the solid state as well as suggestion of the association of triflate with Cu(II) in catalysis,[3c,23] the literature has generally assumed that the PhBOX-Cu(II)-dienophile intermediates adopt a distorted square planar configuration with OTf$^-$ playing little role.

To shed more light on the hypothesis that the reversal we observed resulting from the dissociation of OTf$^-$ from the PhBOX-Cu(II) catalyst, we investigated the DA reaction catalyzed by the analogous BOX-Zn(II) and BOX-Mg(II) complexes derived from the corresponding triflates. In the absence of a coordinating ligand or counterion, the BOX-M(II)-dienophile (M=Zn, Mg) intermediates assume a tetrahedral geometry because of the lack of crystal field stabilization.[20] However, the homogeneous DA reactions catalyzed by the triflate complexes of BOX-Zn(II) and BOX-Mg(II) are consistent with OTf$^-$ coordination, forming octahedral BOX-M(II)-dienophile intermediates.[18,20a] Thus, if immobilization leads to the removal of OTf$^-$ from BOX-M(II) onto the surface, the heterogeneous BOX-M(II) catalysts would furnish products of opposite configuration. Table 4 summarizes the results we obtained with the catalysts **H3**, **H4** and the corresponding immobilized catalysts **S3** and **S4**. It is interesting to find that the

immobilization of **H3** and **H4** did result in the reversal of enantioselectivity, providing strong support for our hypothesis above that the reversal in product configuration between **H2** and **S2** is a result of OTf$^-$ dissociation from Cu(II) due to hydrogen bonding with the surface silanols. The lower activity observed with **S4** is due to the lower loading of magnesium in comparison with that of zinc (0.03 vs 1.0 wt%).

If anion coordination and dissociation is the cause for the product configuration reversal on going from **H2**–**H4** to **S2**–**S4**, a similar reversal is also expected when the triflate counterion of **H2**–**H4** is replaced with a non- or much less-coordinating anion. This is indeed the case with the PhBOX-Zn(II) and PhBOX-Mg(II) catalysts, as shown in Table 5. Thus, whilst the DA reaction catalyzed by **H3** affords the *S endo* adduct with 22% ee (entry 1) which is consistent with a octahedral Zn(II) with axial triflate coordination, the product obtained by the (S)-PhBOX-Zn(SbF$_6$)$_2$ complex has the *R* absolute configuration with 64% ee (entry 2). In the latter case, the SbF$_6^-$ counterion is believed to be fully dissociated, giving rise to a tetrahedral Zn(II).[20c] Likewise, with less coordinating perchlorate ion, (R)-PhBOX-Mg(II) furnished the product with configuration opposite to that observed with the triflate complex (Table 5, entries 3 and 4).[18]

In the case of the (S)-*t*BuBOX catalyst **H1**, the *S endo* enantiomer is always obtained regardless of the counterion, for example, SbF$_6^-$ (non-coordinating) or OTf$^-$ (coordinating).[3c] Thus, on the basis of the above analysis, the catalyst **S1**, in which OTf$^-$ dissociates due to hydrogen bonding, should give the same (S) *endo* enantiomer as the homogeneous **H1** does. The results obtained are fully in accordance with this prediction (Table 1, entries 1 and 2).

Applying the same argument to the (S)-PhBOX-Cu(II) complex, we were surprised to find that replacing the coordinating OTf$^-$ anion with SbF$_6^-$ and ClO$_4^-$ did not result in the expected configuration reversal and in the case of (S)-PhBOX-Cu(SbF$_6$)$_2$, a *racemic* product was obtained (Table 5, entries 5, 6 and 8). The results obtained with (S)-PhBOX-Cu(ClO$_4$)$_2$ could be accounted for perchlorate coordination, leading to a square pyramidal or octahedral Cu(II) species and hence an adduct with *S* configuration. Although the 21-electron octahedral Cu(II) species not expected to be stable, there are a number of 5- and 6-coordinated Cu(II) complexes involving coordinated

Table 4. Comparison of the immobilized catalysts **S3** and **S4** with the homogeneous analogues **H3** and **H4** for the DA reactions, respectively[a]

Entry	Catalyst	Solvent	Conv. (%)	*endo/exo*	ee (%)	Config.
1	**H3**	CH$_2$Cl$_2$	>97	89:11	22	S
2	**S3**	CH$_2$Cl$_2$	95	85:15	24	R
3	**H4**	CH$_2$Cl$_2$	95	75:15	60	S
4	**S4**	CH$_2$Cl$_2$	46	85:15	30	R

[a] The reaction time was 22 h under the conditions the same as those given in Table 1.

Table 5. The DA reactions of dienophile **5** with diene **6** catalyzed by BOX-M(II) catalysts[a]

Entry	Catalyst	Time (h)	Conv. (%)	*endo/exo*	ee (%)	Config.
1	(S)-PhBOX-Zn(OTf)$_2$	22	>97	89:11	22	S
2[b]	(S)-PhBOX-Zn(SbF$_6$)$_2$	8	100	86:14	64	R
3[c]	(R)-PhBOX-Mg(OTf)$_2$	48	94	81:19	84	R
4[c]	(R)-PhBOX-Mg(ClO$_4$)$_2$	48	100	85:15	28	S
5	(S)-PhBOX-Cu(OTf)$_2$	22	100	89:11	15	S
6	(S)-PhBOX-Cu(SbF$_6$)$_2$	9	100	88:12	racemic	
7	(S)-PhBOX-Cu(SbF$_6$)$_2$ + 2 equiv H$_2$O	9	100	86:14	10	S
8	(S)-PhBOX-Cu(ClO$_4$)$_2$	2	100	86:14	28	S

[a] The reactions were run in CH$_2$Cl$_2$ with other conditions the same as those given in Table 1.
[b] The results were reported by Evans et al.[3c]
[c] The reactions were performed at −15 °C and were reported by Desimoni et al.[18c]

perchlorate ions.[24] However this does not explain the loss of enantioface discrimination with (*S*)-PhBOX-Cu(SbF$_6$)$_2$.

Enlightened by the work of Jørgensen and co-workers,[16a] and aiming to gain further insight into the observations made above and particularly into the configuration reversal encountered with **S2**, we undertook HF (Hartree–Fork) modeling of the cationic BOX-M(II)-**5** intermediates. For simplicity, the influence of the counter ions or the silanols was not considered during the calculation. The *t*BuBOX-Cu(II)-**5** and PhBOX-Zn(II)-**5** are believed to prefer square planar and tetrahedral geometry, respectively, as aforementioned. Figure 5 shows the total energies of the two cations alongside that of PhBOX-Cu(II)-**5** against the dihedral angle θ. As clearly seen, the Zn(II)-dienophile intermediate is indeed highly in favor of a tetrahedral geometry with the most stable configuration at θ = 80. The energy cost on going to the perfect square planar coordination is 12.4 kcal mol^{-1} and to the tetrahedral arrangement is only 0.4 kcal mol^{-1}. In contrast, the most stable configuration for *t*BuBOX-Cu(II)-**5** is found at θ = 39°, and it is significantly less energy-costly to change to the perfect square planar than to the tetrahedral geometry, 4.7 versus 9.3 kcal mol^{-1}. Thus the results from modeling confirm the speculations aforementioned, that is, the dienophile intermediate of *t*BuBOX-Cu(II) preferring square planar, and that of PhBOX-Zn(II) preferring tetrahedral in the absence of coordinating anions.
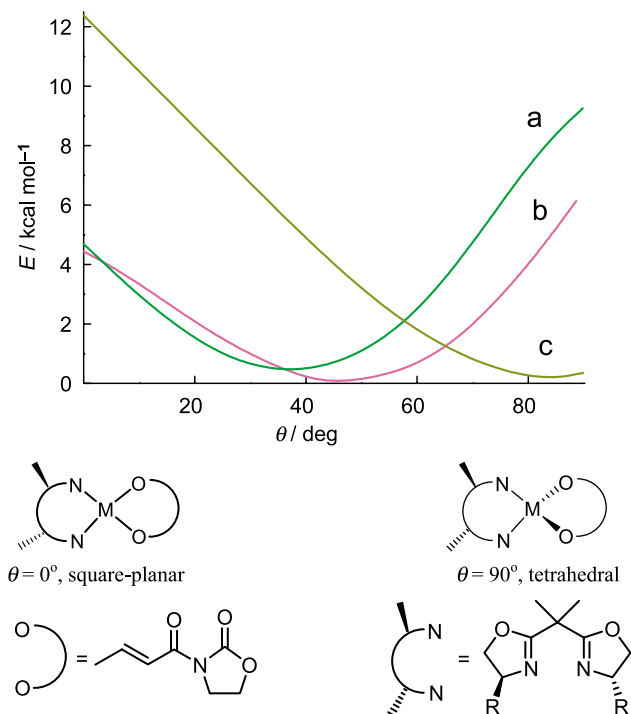
Figure 5. Calculated intermediate energies: (a) *t*BuBOX-Cu(II)-dienophile, (b) PhBOX-Cu(II)-dienophile, and (c) PhBOX-Zn(II)-dienophile. The dihedral angel θ refers to the angle between the plane of N–M–N and that of O–M–O.

Unlike those two intermediates, (*S*)-PhBOX-Cu(II)-**5** has the most stable configuration at θ = 46°, right in the middle of a square planar and tetrahedral arrangement. More interestingly, the energy difference between going from

the most stable state to the extreme planar and tetrahedral geometry is small, only about 1.7 kcal mol^{-1}. The energy needed for changing the dihedral angle from 46 to 80°, the most stable configuration for the tetrahedral PhBOX-Zn(II)-**5** which yields the *R endo* adduct, is 3.9 kcal mol^{-1}. This is only 0.5 kcal mol^{-1} difference from that required for a change to the square planar geometry. Such a small energy difference makes us believe that (*S*)-PhBOX-Cu(II)-**5** is flexible in configuration and is involved in a dynamic equilibrium between planar and tetrahedral geometries. This explains why the cyclization leads to a *racemic* product when the anion is non-coordinating and points to the enantioselection observed with the triflate salt of PhBOX-Cu(II) in the homogeneous DA reaction being a result of OTf$^-$ coordination to the PhBOX-Cu(II)-dienophile species. When 2 equiv H$_2$O was added to the reaction catalyzed by the SbF$_6^-$ salt, the *S endo* adduct was obtained albeit with a low 10% ee (Table 5, entry 7). This is consistent with water coordination, forming square pyramidal or octahedral Cu(II) intermediates and hence giving rise to the addition at the α-*Si* face of **5**. This may also explain the effect of support on the ees discussed earlier (Table 2, entries 7 and 8).

In the case of **S2**, in which evidence suggests that the OTf$^-$ is dissociated, the DA reaction of **5** with cyclopentadiene **6** furnished the *R endo* adduct in 42% ee in toluene (Table 2, entry 4) instead of a *racemic* product as expected. This could be due to weak interactions between the surface Lewis acidic groups and the oxazolidinone ring oxygen of the substrate, and/or restrictions imposed by the surface on the conformations adoptable by the two phenyl rings. The formation of the *R* adduct is less likely to be purely a 'solvent' effect for an interfacial reaction, as solvents of widely different polarity did lead to the same face selection, although Jørgensen et al. found that face selection in the DA reaction of ethyl glyoxylate and 1,3-cyclohexadiene could be altered by solvents of different dielectric properties.[16a]

3. Conclusions

A series of the silica-supported heterogeneous BOX-M(II) catalysts have been successfully prepared for the DA reaction of 3-((*E*)-2-butenoyl)-1,3-oxazolin-2-one and cyclopentadiene at room temperature. The supported BOX-Cu(II) catalysts show enhanced enantioselectivities in toluene compared to their homogeneous counterparts, and it can be recycled without losing enantioselectivity. Spectroscopic evidence suggests that the immobilization of the homogeneous catalysts results from the hydrogen-bonding interactions between the triflate counterions and the surface silanol groups. Thus, as also shown by others,[11,12] hydrogen bonding can provide a simple way for the immobilization of homogeneous catalysts, which requires neither modification of the catalysts nor functionalization of the surface.

One of the most interesting observations of this study is the reversal in product configuration when the homogeneous catalyst (*S*)-PhBOX-Cu(OTf)$_2$ is immobilized. Both the experimental results and theoretical calculations indicate that the triflate counterion coordinates to Cu(II) in homogeneous reactions and the configuration reversal

upon immobilization is triggered by the dissociation of the anion from the metal cation due to hydrogen-bonding interactions with the surface silanols. Since a geometric change is highly feasible of the PhBOX-Cu(II)-dienophile intermediate towards either square planar or tetrahedral configuration and a conformational rearrangement of the phenyl rings of BOX is not expected to be energy-costly, the face selection and hence the enantioselectivity can be subtly affected by a number of factors such as the surface Lewis acidic and basic groups and the restrictions imposed by the surface morphology on the conformations adoptable by the BOX ligands.

4. Experimental

4.1. General

The ^1H NMR spectra were recorded on a 400 MHz spectrometer with $CDCl_3$ as the solvent. Elemental analyses were carried out on an inductively coupled plasma emission spectrometer (ICP-AES). FTIR spectra of the catalysts ($4000–400\ cm^{-1}$) were recorded on a Thermo Nicolet Impact 470 FTIR spectrometer. Self-supporting wafers of 1.3 cm were placed in an IR cell with CaF_2 windows. The wafers were purged at 60 °C for 2 h under a controlled nitrogen atmosphere with a flow rate of 60 ml min^{-1}. The spectra were obtained by scans of 64 with a resolution of 4 cm^{-1}. Theoretical calculations were performed using the Gaussian 03 program package and were carried out at the HF (Hartree–Fork) Level with 3-21G* basis set for C, O, N, H and Lanl2dz basis set for Cu and Zn. All the optimized models were based on the known crystal structures.[3c,16a] The solvent was not included in the calculation model.

4.1.1. Preparation of the heterogeneous catalysts. A BOX-M(OTf)$_2$ complex was dissolved in dichloromethane (0.28 mmol, ~0.03 M), and the resulting solution was filtered onto the pretreated silica (530 mg) under an argon atmosphere. The suspension was stirred for 3 h at room temperature, filtered, washed with dichloromethane several times and dried in vacuum to remove the solvent.

4.1.2. Heterogeneous DA reactions. An appropriate solution of dienophile **5** (0.23 mmol, 0.23 M) was added to a supported BOX-M(II) catalyst (metal content: 0.023 mmol), and the suspension was stirred for 15 min. 12 equiv of cyclopentadiene (2.8 mmol, 182 mg) was then added. After a certain period of time the reaction was stopped, and the catalyst was separated by filtration, thoroughly washed with the same solvent and then used for the subsequent reactions. The product was isolated by filtration through silica. The conversion was determined by ^1H NMR. The *endo/exo* ratio and ee value of the *endo* isomer were analyzed by chiral HPLC [Chiralcel-OD column with hexane/ethanol (98/2) as the eluant]. The configuration of the products was confirmed by comparing with the literature.[3c]

4.1.3. Homogeneous DA reactions. An appropriate solution of dienophile **5** (0.4 mmol, ~0.23 M) was added to a solution of BOX-M(II) catalyst (0.04 mmol, ~0.03 M). The mixture was stirred at room temperature for 15 min, and

then 12 equiv of cyclopentadiene (4.8 mmol, 317 mg) was added. After a certain period of time, the reaction was stopped and the product was isolated by filtration through silica. The conversion, *endo/exo* ratio and ee of the *endo* isomer were determined as described above.

4.2. Materials

2,2′-Isopropylidenebis[(4S)-4-*tert*-butyl-2-oxazoline] (*t*Bu-BOX) and (*S*)-2,2′-isopropylidenebis(4-phenyl-2-oxazo-line) (PhBOX) were purchased from Aldrich. Cu(OTf)$_2$, Zn(OTf)$_2$ and Mg(OTf)$_2$ were purchased from Fluka. Amorphous silica (pore diameter: 9.7 nm, BET: 390 m^2 g^{-1}) was commercially obtained. 3-((E)-2-Butenoyl)-1,3-oxazolin-2-one and the homogeneous BOX-M(II) catalysts were prepared following the literature procedures.[3b,25] Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Amorphous silica was ground, washed with 1 M HNO_3 and then with distilled water to neutrality, and dried in vacuum at 80 °C. Before use, the silica was treated in air at 300 °C for 3 h to remove the physisorbed water.

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