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# Ionic Liquid Effect on the Reversal of Configuration for the Magnesium(II) and Copper(II) Bis(oxazoline)-Catalysed Enantioselective Diels–Alder Reaction

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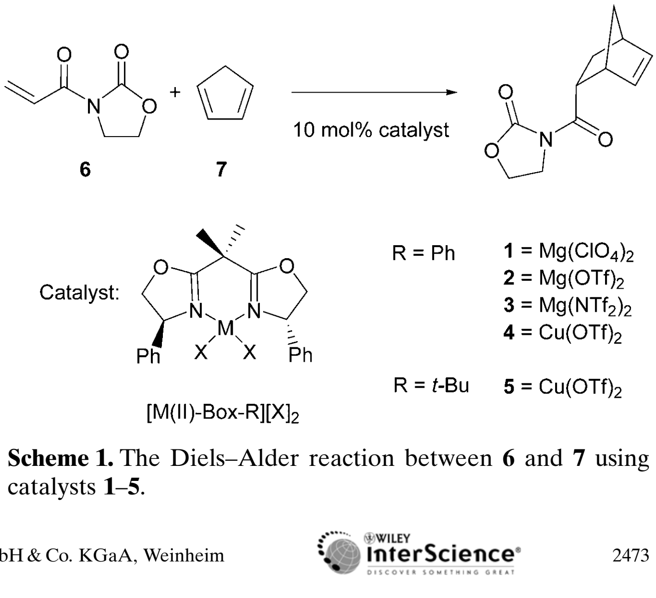
**Abstract:** Ionic liquids have been used to support a range of magnesium- and copper-based bis(oxazoline) complexes for the enantioselective Diels–Alder reaction between *N*-acryloyloxazolidinone and cyclopentadiene. Compared with reaction performed in dichloromethane or diethyl ether, an enhancement in *ee* is observed with a large increase in reaction rate. In addition, for non-sterically hindered bis(oxazoline) ligands, that is, phenyl functionalised ligands, a reversal in configuration is found in the ionic liquid, 1-ethyl-3-methylimidazolium bis[(trifluoromethanesulfonyl)imide], compared with molecular solvents. Supported ionic liquid phase catalysts have also been developed using surface-modified silica which show good reactivity and enantioselectivity for the case of the magnesium-based bis(oxazoline) complexes. Poor *ee*s and conversion were observed for the analogous copper-based systems. Some drop in *ee* was found on supporting the catalyst due a drop in the rate of reaction and, therefore, an increase in the contribution from the uncatalysed achiral reaction.

**Keywords:** asymmetric catalysis; Diels–Alder reaction; ionic liquids; oxazolines

The development of heterogeneous catalysts able to promote enantioselective organic reactions is a field of growing interest. A common method of heterogenisation is to covalently attach the homogeneous catalyst onto a support; however, this method often leads to changes in catalytic performance.[1] In order to alleviate these issues, immobilisation without covalent bonds has been developed. For example, supported ionic liquid phase (SILP) catalysis has been reported to be able to immobilise homogeneous catalysts for use in hydroformylations and carbonylations.[2] This method utilises a thin film of ionic liquid containing the homogeneous catalyst supported on a high surface area material. The resulting catalyst behaves similarly to that found under homogeneous reaction conditions due to the solvation of the metal complex by the ionic liquid with the reaction taking place in the thin liquid film. SILPs have also been used to immobilise achiral homogeneous catalysts for Heck and Suzuki–Miyaura reactions[3] and Knoevenagel condensations.[4] To date, asymmetric SILP-mediated reactions have been limited to cyclopropanations[5] and the Mukaiyama-aldol[6] reactions using bis(oxazoline)-Cu(II) catalysts supported on silica. In both cases, comparable enantioselectivities and conversions as under homogene-



**Scheme 1.** The Diels–Alder reaction between **6** and **7** using catalysts **1**–**5**.

**Table 1.** Homogeneous Diels–Alder reaction between **6** and **7** at 20 °C in diethyl ether, dichloromethane and [$C_2$mim] [$NTf_2$].[a] Enantioselectivities were determined from the *endo* isomer.

| Entry | Catalyst | Diethyl ether | | Dichloromethane | | [$C_2$mim] [$NTf_2$] | |
|---|---|---|---|---|---|---|---|
| | | % *endo* | % *ee* (config.) | % *endo* | % *ee* (config.) | % *endo* | % *ee* (config.) |
| 1 | **1** | 85 | 3 (*S*) | 85 | 62 (*S*) | 92 | 76 (*R*) |
| 2 | **2** | 80 | 22 (*S*) | 80 | 51 (*S*) | 94 | 79 (*R*) |
| 3 | **3** | 87 | 31 (*R*) | 87 | 65 (*S*) | 92 | 66 (*R*) |
| 4 | **4** | 80 | 19 (*R*) | 80 | 15 (*R*) | 86 | 20 (*S*) |
| 5 | **5** | 86 | 15 (*S*) | 86 | 78 (*S*) | 86 | 90 (*S*) |

[a] All selectivities recorded at 100% conversion (reaction time: 1 h in diethyl ether and dichloromethane; 2 min in [$C_2$mim] [$NTf_2$]).

ous reaction conditions were found. This paper reports on the optimisation and comparison of homogeneous and heterogenised (*S*)-bis(oxazoline) complexes of Mg(II) and Cu(II) for the asymmetric Diels–Alder reaction between *N*-acryloyloxazolidinone (**6**) and cyclopentadiene (**7**) (Scheme 1).

Table 1 summarises the results of the Diels–Alder reaction using catalysts **1–5** in 1-ethyl-3-methyl imidazolium bis[(trifluoromethanesulfonyl)imide] ([$C_2$mim] [$NTf_2$]), diethyl ether and dichloromethane. High conversions were achieved within 2 min at room temperature using all the catalysts in the ionic liquid with enantioselectivities higher than reactions conducted in dichloromethane or diethyl ether with the latter showing very poor *ee*s. Interestingly, for the Mg(II)-based catalysts **1** and **2** a reversal of configuration was found in dichloromethane and diethyl ether compared with in [$C_2$mim] [$NTf_2$] (Table 1, entries 1 and 2). For catalyst **3**, the ionic liquid and diethyl ether showed the same configuration whilst the opposite enantiomer was found in the case of dichloromethane (Table 1, entry 3).

Desimoni reported that addition of a coordinating solvent such as water to a solution of (*R*)-**1** in $CH_2Cl_2$ resulted in a change in catalyst geometry and a switch in product configuration.[7] In contrast, addition of water to a $CH_2Cl_2$ solution of (*R*)-**2**, i.e., where the catalyst contained a more coordinating anion, resulted in no change in product configuration. Herein, the change in product configuration from (*S*)- to (*R*)-enantiomer is observed with catalysts **1** and **2** when switching between the molecular solvents and the ionic liquid (Table 1, entries 1 and 2) irrespective of the coordination ability of the anion. Furthermore, a change in product configuration was also observed using catalyst **4** on changing the reaction media from diethyl ether or dichloromethane to [$C_2$mim] [$NTf_2$] (Table 1, entry 4). In contrast, replacing the BOX-Ph ligand with a more sterically hindered BOX-*t*-Bu ligand decreases the ability of catalyst geometry to change and the (*S*)-enantiomer is produced in all the solvents examined using catalyst **5** (Table 1, entry 5). The change in configuration observed for catalysts **1**, **2** and **4** in the ionic liquid compared with the molecular solvents may be due to anion exchange with the catalyst anion. Although Sibi and Matsunaga reported that changing the anion from $[OTf]^-$ to $[NTf_2]^-$ led to a change in configuration for this Diels–Alder reaction catalysed by Mg(II) in $CH_2Cl_2$,[8], in the present study no change in product configuration is noted when changing metal anion in dichloromethane; however, a change was observed on switching the catalyst anion from $[ClO_4]^-$/$[OTf]^-$ to $[NTf_2]^-$ in diethyl ether (Table 1, entries 1–3). The solvent-dependent configuration is likely to be strongly affected by solvation and the stability of the anion coordination in each solvent which influences the active catalyst geometry. In [$C_2$mim] [$NTf_2$], the high concentration of $[NTf_2]^-$ anions encourage chelation to the metal centre, whereas in $CH_2Cl_2$ a weaker attachment occurs leading to all the catalysts forming the same enantiomeric configuration. Since catalyst **3** in diethyl ether results in a change in configuration compared with catalysts **1** and **2** and matches that found in the ionic liquid, this supports the fact that it is the presence of $[NTf_2]^-$ which controls catalyst geometry and hence the predominant enantiomer produced. In contrast to the Mg(II) bis-oxazoline complexes, Cu(II) bis-oxazoline complexes commonly show a decrease in enantioselectivity in the presence of a coordinating solvent.[9] However, in the present study, both catalysts showed an increase in enantioselectivity when carried out in the ionic liquid compared with dichloromethane or diethyl ether.

The proposed change in catalyst geometry which results in the change in *ee* is observed in the $^1$H NMR spectrum of the complex in the presence of **6**. The acryloyl and oxazolidinone ring protons of the complexed imide are deshielded in the ionic media compared with those in dichloromethane and this occurs when the oxazolidinone ring is close to a phenyl group. The NMR data are consistent with the ionic liquid stabilising an octahedral geometry around the magnesium whereas a tetrahedral geometry is found in dichloromethane. Similar data have also been observed on addition of 2 equiv. of MeOD to the cata-

**Table 2.** Comparison of SILP immobilised Mg(II) and Cu(II) catalysts for the Diels–Alder reaction between **6** and **7** (20 °C, 1 h) in diethyl ether. Enantioselectivities determined from the *endo* isomer.

| Entry | Catalyst | % conv. | % *endo* | % *ee* (config.) |
|---|---|---|---|---|
| 1[a] | – | 50 | 83 | |
| 2[b] | – | 17 | 84 | |
| 3[b,c] | – | 8 | 81 | |
| 4[b,c] | **1** | 0 | | |
| 5[b] | **1** | 39 | 87 | 2 (*R*) |
| 6[c] | **5** | 0 | | |
| 7[c] | **1** | 100 | 88 | 64 (*R*) |
| 8 | **1** | 100 | 92 | 66 (*R*) |
| 9 | **2** | 100 | 91 | 67 (*R*) |
| 10 | **3** | 100 | 88 | 7 (*R*) |
| 11 | **4** | 13 | 92 | 3 (*S*) |
| 12 | **5** | 32 | 87 | 12 (*S*) |

[a] Uncatalysed homogeneous reaction in diethyl ether.
[b] No ionic film present.
[c] Untreated silica used.

lyst in $CDCl_3$[7b] which also resulted in a reversal in configuration.

Copper(II) and Mg(II) bis(oxazoline) catalysts immobilised in ionic liquid were supported on untreated silica or surface-modified silica in which the silanol groups were reacted with pH 7 buffer.[10] Table 2 compares the catalytic performance as a function of preparation for the DA reaction in diethyl ether. Poor *ee*s and conversions were found for **1** adsorbed on untreated silica or surface-modified silica in the absence of a supporting ionic liquid film (Table 2, entries 4 and 5). On untreated silica, no conversion was obtained due to the polymerisation of **7**.[11] In contrast, **1** and **2** (Table 2, entries 7–9) adsorbed on the surface-modified or untreated silica *via* an ionic liquid film showed high conversion and comparable or higher *ee*s than those obtained in dichloromethane under homogeneous reaction conditions and much higher than found in diethyl ether for the analogous reactions. Importantly, the configurations observed for the SILP catalysts are the same as found in the ionic liquid and not those found in diethyl ether indicating that the reaction is proceeding in the ionic liquid film and not in the solvent phase. As found for the homogeneous reactions in ionic liquids, a reduction in *ee* was observed on using catalyst **3** (Table 2, entry 10) compared with catalysts **1** and **2** (Table 2, entries 8 and 9). In all cases, a reduction in the rate of reaction was also found compared with the corresponding homogeneous ionic liquid reactions (Table 1, entries 1–3) as has been observed for other SILP catalysts.[6] This may be the cause of the lower *ee*s found on heterogenisation compared with the homogeneous reactions in the ionic liquid. The lower rate of the metal-catalysed reaction allows the uncatalysed reaction or silica-catalysed polymerisation of **7** to compete leading to a reduction in the overall *ee*. Despite significant competing achiral rates of reactions (Table 2, entries 1–3) complete conversions with good *ee*s are achievable for Mg(II)-based catalysts. Contrasting behaviour was found for the Cu(II) catalysts **4** and **5** which both showed a marked decrease in conversion and *ee* upon immobilisation compared with the homogeneous catalysed reactions conducted in all the the solvents examined (Table 2, entries 6, 11, and 12). As found for the homogeneous reactions, a reversal in product configuration was noted for the SILP-mediated reactions using catalysts **1**, **2** and **4** compared with the analogous homogeneous reactions in dichloromethane and diethyl ether and for catalyst **3** in dichloromethane.

A reversal in *ee* when changing from a homogeneous to a heterogeneous system has been previously reported[12,13] and was thought to be due to the dissociation of the catalyst anion on the support resulting in a change in catalyst geometry. For the SILP-mediated reactions where the catalysis takes place in a solid supported thin ionic liquid film, it is more likely that the change in catalyst geometry is induced by the large concentration of anions in an analogous manner to that found under homogeneous reaction conditions. The effect of the ionic liquid is also supported by results reported by Wang et al.[14] who observed a reduction in *ee* on immobilisation of catalysts **2** or **5** onto silica *via* hydrogen bonding.

Although the non-covalent immobilisation of bis(oxazoline) complexes, e.g., using supported ionic liquid phase catalysis, is believed to reduce conformational differences between the homogeneous and heterogeneous systems, this is not always found. Little or no reaction was observed, herein, using either BOX-Ph or BOX-*t*-Bu coupled with Cu(II) using the silica-supported ionic liquid system. Interestingly, for the Mukaiyama-aldol reaction using Cu(II) catalyst **5**, no erosion in *ee* was observed upon switching from a ionic liquid to a supported ionic liquid system and only a reduction in rate was seen due to mass transfer effects.[6]

Recycle experiments were performed using catalyst **1** supported on surface modified silica and untreated silica *via* an ionic liquid (Table 3). The use of catalyst **1** on untreated silica resulted in a dramatic drop in conversion upon recycle due to the polymerisation of **7** on the silica surface (Table 3, entry 1).

While the dimerisation of **7** is unavoidable under these reaction conditions, immobilisation of **1** on the surface-modified silica showed improved recyclability achieving complete conversion with a gradual erosion of *ee* on reuse (Table 3, entry 2). Again this is due to the accumulation of dimer on the catalyst surface. This proposal is supported by the fact that on doping of a reaction mixture using a SILP-based on catalyst **1** with **7** dimer complete conversion was achieved but

**Table 3.** Recycle of SILP-immobilised Mg(II)-BOX-Ph (20 °C, 1 h). Enantioselectivities determined from the *endo* isomer.

| Entry | Catalyst | Run | % conv. | % *endo* | % *ee* (config.) |
|---|---|---|---|---|---|
| 1[a] | **1** | 1 | 100 | 92 | 66 (*R*) |
| | | 2 | 17 | 92 | 61 (*R*) |
| 2 | **1** | 1 | 100 | 91 | 67 (*R*) |
| | | 2 | 100 | 92 | 54 (*R*) |
| | | 3 | 100 | 91 | 29 (*R*) |

[a] Untreated silica used.

with a drop in *ee* from 66 to 55%. No significant leaching of the metal or ligand was observed in the diethyl ether phase.

In summary, we have observed a reversal in product configuration associated with the ionic liquid systems, in both homogeneous and heterogeneous media, compared with those reactions performed in dichloromethane which may be associated with the formation of a strongly bound $[NTf_2]^-$ chelated catalyst. This is supported by reactions in diethyl ether which show that using the $[NTf_2]^-$-based Mg(II) catalyst resulted in a change in configuration compared with either the $[OTf]^-$- or $[ClO_4]^-$-based Mg(II) catalysts. Efficient SILP catalysis with recyclability has been achieved with Mg(II)-based bis(oxazoline) catalysts whereas immobilisation of the equivalent Cu(II) catalysts did not result in significant *ee*s or conversion.

## Experimental Section

### Representative Procedure

A flame-dried Schlenk flask was charged with ligand (0.011 mmol), metal salt (0.01 mmol) and solvent (2 cm$^3$) or silica-supported catalyst (0.6 g) and diethyl ether (5 cm$^3$). For the homogeneous reactions, the solution was stirred for 3 h when using molecular solvents and for 5 min using the ionic liquid to prepare the active catalyst.The resulting solution was stirred at 20 °C and **6** (0.1 mmol) was added followed by freshly distilled **7** (0.58 mmol). The reaction was stirred for the required time and then either diluted with 1:1 ethyl acetate:hexane for the dichloromethane/diethyl ether reactions or extracted with diethyl ether for ionic liquid reactions. The solution was filtered through a short column of silica gel to afford unpurified product which was analysed directly by HPLC. The SILP catalysts were prepared by adding untreated or surface-modified silica (0.5 g) and ionic liquid (0.1 cm$^3$) to a $CH_2Cl_2$ solution containing the catalyst. Thereafter, the $CH_2Cl_2$ was removed under vacuum leaving the solid catalyst.

Detailed information is supplied in the Supporting Information.

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