

# Efficient Heterogeneous Asymmetric Catalysis of the Mukaiyama Aldol Reaction by Silica- and Ionic Liquid-Supported Lewis Acid Copper(II) Complexes of Bis(oxazolines)

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**Abstract:** Lewis acid complexes based on copper(II) and an imidazolium-tagged bis(oxazoline) have been used to catalyse the asymmetric Mukaiyama aldol reaction between methyl pyruvate and 1-methoxy-1-trimethylsilyloxypropene under homogeneous and heterogeneous conditions. Although the *ees* obtained in ionic liquid were similar to those found in dichloromethane, there was a significant rate enhancement in the ionic liquid with reactions typically reaching completion within 2 min compared with only 55 % conversion after 60 min in dichloromethane. However, this rate enhancement was offset by lower chemoselectivity in ionic liquids due to the formation of 3-

hydroxy-1,3-diphenylbutan-1-one as a by-product. Supporting the catalyst on silica or an imidazolium-modified silica using the ionic liquid or in an ionic liquid-diethyl ether system completely suppressed the formation of this by-product without reducing the enantioselectivity. Although the heterogeneous systems were characterised by a drop in catalytic activity the system could be recycled up to five times without any loss in conversion or *ee*.

**Keywords:** asymmetric synthesis; heterogeneous catalysis; ionic liquids; Mukaiyama aldol; recyclable catalyst

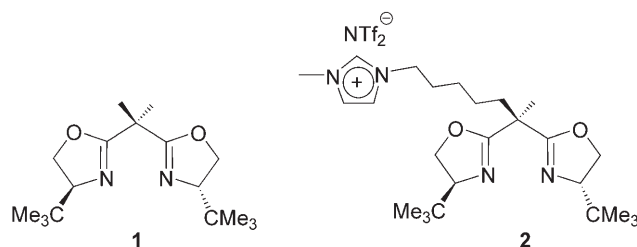
## Introduction

The asymmetric Mukaiyama aldol reaction<sup>[1]</sup> is a highly versatile and powerful tool for the construction of new C–C bonds in organic synthesis. In this reaction, enantiomerically enriched secondary and tertiary  $\beta$ -hydroxy esters are formed by coupling silyl enolates or silylketene acetals with aldehydes and activated ketones, respectively.<sup>[2]</sup> While a host of Lewis acid complexes based on the transition metals and main group elements including titanium<sup>[3]</sup> zirconium,<sup>[4]</sup> scandium,<sup>[5]</sup> boron,<sup>[6]</sup> tin<sup>[7]</sup> and silver<sup>[8]</sup> in combination with a chiral multidentate ligand, have been used to affect stereocontrol of this transformation, systems based on copper(II) and a bis(oxazoline) are among the most efficient.<sup>[9]</sup> However, the use of such homogeneous catalysts has several disadvantages, most notably their low to moderate stability at ambient temperature, air sensitivity and poor recyclability. Heterogenisation of homogeneous catalysts has been investigated in an attempt to overcome these limitations and common im-

mobilisation strategies include anchoring the catalyst to a polymer<sup>[10]</sup> or grafting it onto silica.<sup>[11]</sup> In general, these approaches have met with limited success primarily due to significant leaching of the ligand during the extraction process.<sup>[12]</sup> One promising approach involves the use of azabis(oxazolines) which bond to copper more strongly than their bis(oxazoline) counterparts which should result in reduced leaching. In this regard, phosphorus dendrimer-immobilized azabis(oxazolines) form highly efficient catalysts for the asymmetric benzoylation of *rac*-diols with excellent recyclability.<sup>[13]</sup> In addition to the problem of leaching, the activity of an immobilized catalyst can be strongly influenced by the environment around the metal on the surface and as a result, many reactions are mass transfer limited and suffer from significant catalyst instability as well as a reduction in enantioselectivity.<sup>[14]</sup>

Ionic liquids have been attracting increasing interest as a medium for catalysis as their low volatility and immiscibility with non-polar organic solvents makes them ideal candidates for catalyst immobilisa-

tion and recycling.<sup>[15]</sup> Additional benefits associated with the use of ionic liquids for asymmetric catalysis have also been identified including significant enhancements in rate as well as marked improvements in enantioselectivity compared with the same transformation in conventional organic solvents.<sup>[16,17]</sup> Even though the use of an ionic liquid enables the catalyst to be recycled, leaching of the ligand or catalyst into the extracting solvent often causes a gradual reduction in enantioselectivity and/or conversion with successive cycles. One potential solution to this problem involves the use of a task-specific ionic liquid in which an imidazolium fragment is attached to the ligand, remote from the active centre, to improve retention of the catalyst in the ionic liquid during extraction of the product. In this regard, we have recently reported that Lewis acid copper(II) complexes of 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] **1** gave significant enhancements in rate and enantioselectivity for Diels–Alder reactions in ionic liquids compared with dichloromethane and its imidazolium-tagged counterpart **2** can be recycled ten times without any loss in activity or enantioselectivity (Figure 1).<sup>[18]</sup> As expected, the imidazolium-tagged



**Figure 1.** Bis(oxazolines) ligands **1** and **2**.

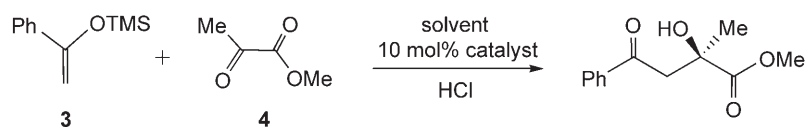
catalyst showed a much higher affinity for the ionic liquid phase during the recycle procedure than the analogous uncharged ligand. Recently, supported ionic liquid phase catalysis (SILPC) has emerged as potentially practical approach to immobilising homogeneous catalysts for use in continuous flow-operated fixed-bed reactors.<sup>[19]</sup> This technique also overcomes the problem of catalyst/ligand leaching associated with liquid-liquid biphasic systems as it combines the advantages of ionic liquids with those of heterogeneous support materials. In this approach a thin film of ionic liquid containing the homogenous catalyst is immobilised on the surface of a high area porous sup-

port material and the resulting system behaves much like a homogeneous catalyst. Although this technique has been applied to a number of reactions including rhodium-catalysed hydroformylation and carbonylations,<sup>[20]</sup> palladium-catalysed Heck and Suzuki–Miyaura reactions<sup>[21]</sup> and base-catalysed Knoevenagel condensations,<sup>[22]</sup> there is only a single example of its use in an asymmetric transformation.<sup>[23]</sup>

Having established that ionic liquids impart significant enhancement in rate and enantioselectivity in the copper catalysed Diels–Alder reaction,<sup>[17]</sup> the use of ionic liquids to develop a heterogeneous Lewis acid catalyst for the asymmetric Mukaiyama aldol reaction between 1-phenyl-1-trimethylsiloxyethene (**3**) and methyl pyruvate (**4**) (Scheme 1) was investigated. Although the aldol reaction has been studied extensively in ionic liquids<sup>[24]</sup> only one study has focused on the Mukaiyama aldol reaction. Therein, Loh et al. noted that 1-methyl-3-octylimidazolium chloride catalyses the Mukaiyama aldol reaction of a range of aliphatic and aromatic aldehydes with 1-methoxy-1-trimethylsilyloxypropene, to give yields ranging between 50–74%.<sup>[25]</sup> Herein, we report that comparable *ees* are obtained for the reaction between **3** and **4** under homogeneous conditions in ionic liquids and under heterogeneous conditions with the catalyst and ionic liquid supported on silica. Furthermore, the heterogeneous system based on an imidazolium-tagged catalyst can be recycled up to five times with no loss in enantioselectivity and only a slight reduction in conversion.

## Results and Discussion

Table 1 summarises the results of a comparative study of the Mukaiyama aldol reaction between 1-phenyl-1-trimethylsiloxyethene (**3**) and methyl pyruvate (**4**) catalysed by copper(II) complexes of bis(oxazolines) **1** and **2** in a range of bis[(trifluoromethyl)sulfonyl]imide ([NTf<sub>2</sub>]<sup>−</sup>)-based ionic liquids and in dichloromethane at room temperature. Typically, complete conversions were achieved within 2 min at room temperature in all the ionic liquids examined, whereas in dichloromethane moderate to good conversions (55–90%) were only achieved after 1 h. Interestingly, while the catalyst based on bis(oxazoline) **1** gave a markedly higher *ee* in [C<sub>2</sub>mim][NTf<sub>2</sub>] (90%) compared with dichloromethane (82%) the corresponding imidazolium-tagged catalyst gave similar *ees* in both



**Scheme 1.** The Mukaiyama aldol reaction.

**Table 1.** Homogeneously catalysed Mukaiyama aldol reaction between 1-phenyl-1-trimethylsiloxyethene (**3**) and methyl pyruvate (**4**) in a range of bis[(trifluoromethyl)sulfonyl]imide ([NTf<sub>2</sub>]<sup>−</sup>)-based ionic liquids and in dichloromethane at room temperature, unless otherwise stated. [Substrate] = 0.0575 M.

Entry	Ligand	Solvent	Time [min]	Conversion [%] <sup>[a,b]</sup>	Chemoselectivity [%] <sup>[a]</sup>	ee [%] <sup>[b,c]</sup>
1	<b>1</b>	CH <sub>2</sub> Cl <sub>2</sub> (−78 °C)	60	80	100	86
2	<b>1</b>	CH <sub>2</sub> Cl <sub>2</sub>	60	55	100	82
3	<b>1</b>	[C <sub>2</sub> mim][NTf <sub>2</sub> ]	2	100	93	90
4	<b>1</b>	[C <sub>4</sub> mpyrr][NTf <sub>2</sub> ]	2	100	95	81
5	<b>1</b>	[N <sub>3336</sub> ][NTf <sub>2</sub> ]	2	100	90	83
6	<b>2</b>	CH <sub>2</sub> Cl <sub>2</sub>	60	90	100	90
7	<b>2</b>	[C <sub>2</sub> mim][NTf <sub>2</sub> ]	2	100	95	91

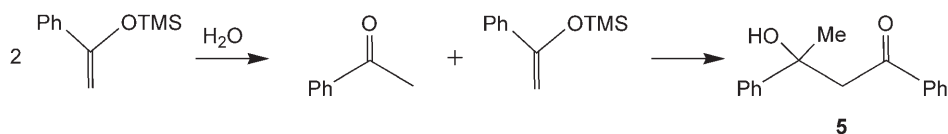
<sup>[a]</sup> Determined by <sup>1</sup>H NMR spectroscopy.<sup>[b]</sup> Average of three runs.<sup>[c]</sup> Enantiomeric excess determined by HPLC (Daicel Chiralcel OD-H).

solvents: 91 and 90 %, respectively. However, it should be noted that an improvement in *ee* was not obtained in all ionic liquids tested with [C<sub>4</sub>mpyrr][NTf<sub>2</sub>] and [N<sub>3336</sub>][NTf<sub>2</sub>] giving *ees* of 81 and 83 %, respectively. In addition, the *ee* of 86 % obtained with bis(oxazoline) **1** in CH<sub>2</sub>Cl<sub>2</sub> at −78 °C was still slightly lower than that of 90 % obtained in [C<sub>2</sub>mim][NTf<sub>2</sub>] at room temperature. Although high conversions were obtained in all the ionic liquids studied, a by-product, identified by <sup>1</sup>H NMR spectroscopy as 3-hydroxy-1,3-diphenylbutan-1-one (**5**), was consistently formed in approx. 10–15 % yield. Interestingly, **5** is only generated during reactions conducted in the ionic liquid and there was no evidence for its formation in dry dichloromethane. Moreover, **5** was obtained in near quantitative yield in the ionic liquid in the absence of copper triflate. This by-product is the result of a Mukaiyama aldol reaction between 1-phenyl-1-trimethylsiloxyethene, **3**, and acetophenone (Scheme 2), the latter of which is generated *via* hydrolysis of **3**. In this regard, acetophenone has been identified as a by-product in 30 % yield from the zinc chloride-mediated reaction between silylketene acetals and phosphorus trichloride in tetrahydrofuran<sup>[26]</sup> as well as the *O*- and *C*-acylation of **3** with acetyl chloride in the presence of antimony trichloride.<sup>[27]</sup>

In order to establish the likely origin of **5**, the role of water in the ionic liquids was further investigated by conducting a copper-catalysed reaction in undried [C<sub>2</sub>mim][NTf<sub>2</sub>] containing 0.057 wt % water which increased the by-product formation to 39 % whereas the corresponding reaction in dried [C<sub>2</sub>mim][NTf<sub>2</sub>], which contained 0.007 wt % water, gave only 7 % of

the by-product (Table 1 entry 3). Moreover, in dichloromethane containing 0.12 wt % water, 3 % conversion to **5** was also observed. This change in the selectivity associated with the water in the ionic liquid compared with the molecular solvent may be associated with the structure of the water in the ionic liquid. Hydrolytically unstable reagents are stabilised in wet ionic liquids due to the fact that the water is in the form of isolated molecules rather than aggregates as found in molecular solvents.<sup>[28]</sup> For the Mukaiyama aldol, this molecular state of the water may result in the hydrolysis of **3** to afford the by-product. In contrast, extended structures of water, as found in bulk water or in dichloromethane, do not lead to the formation of acetophenone and the by-product, as shown by the fact that the reaction does not occur in pure water or to the same extent in dichloromethane. The main selectivity issues associated with the Mukaiyama aldol reaction have been reported as being due to acid-catalysed hydrolysis. In molecular solvents the yield of aldol product formed is shown to be dependent on catalyst concentration,<sup>[29]</sup> silyl ether geometry<sup>[30]</sup> and concentration of water.<sup>[31]</sup> However, in these cases, even though the product yields were diminished there was no report of the formation of the self-condensation product that was obtained in ionic liquid, as described above.

The ionic liquid-catalyst system was also effective where only a small volume of ionic liquid was present. A reaction performed using 0.2 cm<sup>3</sup> [C<sub>2</sub>mim][NTf<sub>2</sub>] suspended in a dry, immiscible organic solvent (5.0 cm<sup>3</sup> diethyl ether) gave complete conversion with both catalysts derived from **1** and **2** after 2 min afford-

**Scheme 2.** Self-Mukaiyama aldol reaction of 1-phenyl-1-trimethylsiloxyethene resulting in the formation of by-product **5**.

ing *ees* of 91 % and 93 %, respectively. Importantly, these biphasic conditions appeared to completely suppress the formation of **5**; both  $^1\text{H}$  NMR and GC analyses of the reaction mixture showing no evidence for this by-product. Similarly, Kobayashi reported that silica-scandium-ionic liquid composites catalyse the Mukaiyama aldol reaction in water without causing hydrolysis of the hydrolytically sensitive silylketene acetals.<sup>[32]</sup> The biphasic system reported herein also showed potential for scale-up using continuous extraction. A scale-up of this reaction with 1 mol % catalyst generated from **2** under biphasic liquid-liquid conditions gave the desired  $\beta$ -hydroxy ester in 94 % isolated yield with an *ee* of 93 %.

The use of a biphasic system based on an ionic liquid and an immiscible organic solvent should allow the catalyst to be recycled, provided it is efficiently retained in the ionic liquid during the extraction process. Recycle experiments (Table 2) showed that although the ionic liquid allows for the recovery of the metal to >99.99 % per extraction, significant ligand leaching was observed. This is most evident in the case of ligand **1**, where up to 11.2 % of the ligand leaches during extraction, which results in a significant decrease in conversion after the first recycle. Interestingly, even with this level of leaching the very high activity of the catalyst in the ionic liquid resulted in conversions of 100 and 85 % for the first and second recycles, respectively, compared with a conversion of 55 % in dichloromethane after 60 min. As expected, the catalyst based on **2** showed a much higher affinity for the ionic liquid during extraction as evidenced by the recycle experiment which consistently gave 100 % conversion and excellent *ees* over the first three reactions. For reactions using ligand **2** with the ionic liquid, analysis of the extractant layer showed leaching of the ligand to be below the detectable limit by HPLC analysis.

**Table 2.** Recycle of the Mukaiyama aldol reaction between 1-phenyl-1-trimethylsiloxyethene (**3**) and methyl pyruvate (**4**) using a biphasic liquid-liquid reaction mixture containing  $[\text{C}_2\text{mim}][\text{NTf}_2]$  and diethyl ether.

Entry <sup>[a]</sup>	Ligand	Experiment number		
		Conversion [%] <sup>[b,c]</sup> and ( <i>ee</i> [%]) <sup>[c,d]</sup>		
		<b>1</b>	<b>2</b>	<b>3</b>
1	<b>1</b>	100 (91)	100 (93)	85 (91)
2	<b>2</b>	100 (93)	100 (94)	100 (93)

<sup>[a]</sup> An IL:diethyl ether ratio of 1:10 was used at room temperature and sampled after 2 min. All reactions were 100 % chemoselective.

<sup>[b]</sup> Determined by  $^1\text{H}$  NMR spectroscopy.

<sup>[c]</sup> Average of three runs.

<sup>[d]</sup> Enantiomeric excess determined by HPLC (Daicel Chiralcel OD-H).

With the aim of developing an improved catalyst system for use in a continuous process, catalysts based on **1** and **2** were supported on silica and imidazolium-modified silica (silica-IM) and their performance as heterogeneous catalysts compared for the Mukaiyama aldol reaction between **3** and **4** performed in diethyl ether as the solvent, details of which are presented in Table 3. When catalysts based on **1** and **2** were adsorbed onto unmodified silica and the reaction per-

**Table 3.** Mukaiyama-Aldol reaction between 1-phenyl-1-trimethylsiloxyethene (**3**) and methyl pyruvate (**4**) using catalyst supported on a pure or surface modified silica in the presence and absence of a supported ionic liquid performed in diethyl ether at room temperature.

Entry <sup>[a]</sup>	Ligand	Silica	Supported IL	Conversion [%] <sup>[b,c]</sup>	<i>ee</i> [%] <sup>[c,d]</sup>
1	<b>1</b>	Silica	-	81	7
2	<b>2</b>	Silica	-	85	10
3	<b>1</b>	Silica-IM	-	100	89
4	<b>2</b>	Silica-IM	-	100	92
5	<b>1</b>	Silica-IM	$[\text{C}_2\text{mim}][\text{NTf}_2]$	100	90
6	<b>1</b>	Silica-IM	$[\text{C}_4\text{mpyr}][\text{NTf}_2]$	100	94
7	<b>2</b>	Silica-IM	$[\text{C}_2\text{mim}][\text{NTf}_2]$	100	95
8	<b>1</b>	Silica	$[\text{C}_2\text{mim}][\text{NTf}_2]$	100	86
9	<b>2</b>	Silica	$[\text{C}_2\text{mim}][\text{NTf}_2]$	100	91

<sup>[a]</sup> Reactions were sampled after 20 min reaction and all reactions were 100 % chemoselective.

<sup>[b]</sup> Determined by  $^1\text{H}$  NMR spectroscopy.

<sup>[c]</sup> Average of three runs.

<sup>[d]</sup> Enantiomeric excess determined by HPLC (Daicel Chiralcel OD-H).

formed in diethyl ether in the absence of a supporting ionic liquid film, good conversions were obtained but both systems gave poor *ees* (entries 1 and 2). In stark contrast, the same catalysts immobilised on silica-IM gave complete conversions and excellent *ees* in diethyl ether with that based on **2** resulting in a slightly higher *ee* than **1** (entries 3 and 4). Importantly, the use of the ionic liquid grafted silica is not necessary for high conversions and *ees*, provided that a supporting ionic liquid film on the silica is used, since complete conversion and *ees* of 86–92 % were achieved with the unmodified silica systems (entries 8 and 9). However, it should be noted that slightly higher *ees* were consistently obtained with the imidazolium-modified supported system. This is in contrast with the results reported by Gruttadauria et al. where the

use of a covalently attached ionic liquid to silica was essential in order to obtain high enantioselectivity in the proline-catalysed chiral aldol reaction of a series of substituted benzaldehydes with acetone.<sup>[33]</sup> Interestingly, in some cases supporting the catalyst led to an increase in *ee* over the corresponding homogeneous reaction in the ionic liquid. For example, the catalyst based on **1** gave an *ee* of 81 % in [C<sub>4</sub>mpyrr][NTf<sub>2</sub>] under homogeneous conditions whereas the same catalyst immobilised on silica-IM in combination with a supported [C<sub>4</sub>mpyrr][NTf<sub>2</sub>] ionic liquid film gave a markedly higher *ee* (94 %). This highlights the subtle influence of reaction conditions on catalyst performance. As found for the liquid-liquid biphasic system, no by-product, **5**, was generated in the heterogenised catalyst system. In both the biphasic systems, liquid-liquid or liquid-solid, the increased selectivity may be the consequence of the silica/dry immiscible solvent drying the ionic liquid.

Since the catalysts supported on silica and silica-IM both gave complete conversions within 20 min and comparable enantioselectivities, exhaustive recycle experiments were performed in order to compare and assess the relative merits of these two systems, details of which are presented in Table 4. Although quantitative conversions were typically obtained after 20 min, as shown in Table 3, sampling the reaction after 5 min revealed that the heterogeneous systems are slower than the homogeneous reactions carried out in ionic liquid since complete conversions were routinely obtained within 2 min under these conditions (Table 1). However, these heterogeneous catalysts are at least as active as the corresponding homogeneous system in dichloromethane. For example, using a reagent concentration of 0.023 M, catalysts based on **1** and supported on silica-IM in combination with a film of [C<sub>2</sub>mim][NTf<sub>2</sub>] in diethyl ether (Table 3, entry 5) gave 100 % conversion to product after 20 min compared with 94 % conversion for the same catalyst under ho-

mogeneous conditions in dichloromethane. The disparate rates of these two ionic liquid systems is consistent with previous studies<sup>[34]</sup> and is most likely to be due to reduced mass transport at the solid-liquid interface compared with the efficient mass transport in the homogeneous system. However, this lower activity is mitigated by the ease of recycle and Table 4 compares the enantioselectivity and conversion as a function of the number of recycles for heterogenised catalysts based on **2** under a range of conditions. The catalyst immobilised on silica-IM in the absence of an additional ionic liquid film recycled only poorly in diethyl ether and conversions decreased after the first recycle (entry 1). However, improved recyclability was obtained in the presence of a supporting film of [C<sub>2</sub>mim][NTf<sub>2</sub>] with conversions beginning to decrease after three recycles (entry 2). Surprisingly, the combination of *unmodified* silica with ionic liquid adsorbed onto the silica resulted in the most efficient recycling and gave stable conversions and enantioselectivities over six reactions (entry 3). As expected, the recycle efficiency of the cationic ligand, **2**, was much higher than that of its uncharged counterpart **1**, which gave a significantly reduced conversion on the first recycle due to the leaching of the ligand (entry 4). As found for the homogeneous reactions, ligand leaching of **2** was below the detectable limit whereas 19.1 % of **1** was found to leach after the first recycle and was a major factor in the drop in conversion on the first recycle. Analysis of the solvent phase after extraction by suppressed ion chromatography (IC) was performed for all the samples and this showed that the leaching of [C<sub>2</sub>mim][NTf<sub>2</sub>] into the diethyl ether layer was below the detection limit, i.e., <1 ppm. In all cases, no significant change in the enantioselectivity was observed as a function of recycle. The drop in conversion on recycle for reactions using ligand **2** was determined to be due to aggregation of the silica particles during recycle experiments which is possibly

**Table 4.** Recycle of the Mukaiyama-aldol reaction between 1-phenyl-1-trimethylsiloxyethene (**3**) and methyl pyruvate (**4**) using silica-supported catalyst performed in diethyl ether at room temperature and sampled after 5 min.

Entry <sup>[a]</sup>	Silica	Experiment number							
		Conversion [%] <sup>[b,c]</sup> ( <i>ee</i> [%] <sup>[c,d]</sup> )							
		1	2	3	4	5	6	7	8
1	Silica-IM	40 (90)	39 (89)	32 (90)	10 (89)	4 (86)	-	-	-
2	Silica-IM + [C <sub>2</sub> mim][NTf <sub>2</sub> ]	44 (92)	46 (90)	42 (91)	40 (89)	29 (92)	13 (90)	-	-
3	Silica + [C <sub>2</sub> mim][NTf <sub>2</sub> ]	52 (92)	50 (90)	50 (93)	53 (90)	49 (90)	45 (89)	33 (92)	20 (91)
4	Silica + [C <sub>2</sub> mim][NTf <sub>2</sub> ] <sup>[e]</sup>	48 (87)	31 (85)	9 (82)	-	-	-	-	-

<sup>[a]</sup> Unless otherwise stated the reaction was catalysed by a combination of ligand **2** and Cu(OTf)<sub>2</sub>. All reactions were 100 % chemoselective.

<sup>[b]</sup> Determined by <sup>1</sup>H NMR spectroscopy.

<sup>[c]</sup> Average of three runs.

<sup>[d]</sup> Enantiomeric excess determined by HPLC (Daicel Chiralcel OD-H).

<sup>[e]</sup> Catalyst generated from **1** and Cu(OTf)<sub>2</sub>.



due to a build up of polyhydroxylated products on the silica surface.<sup>[35]</sup>

## Conclusions

Ionic liquids have been shown to significantly increase the rates of the homogeneously Cu(II)-catalysed Mukaiyama aldol reaction compared with the conventional solvent, dichloromethane. However, although the homogeneous system in ionic liquids produced high activity and excellent product enantioselectivity, lower chemoselectivity was observed due to the formation of a by-product resulting from the Mukaiyama aldol reaction of 1-phenyl-1-trimethylsiloxyethene and acetophenone. Formation of this by-product was suppressed, without any reduction in the enantioselectivity, by supporting the catalyst on silica using ionic liquid or in an ionic liquid-diethyl ether system. Although the heterogenised system was slightly less active than the corresponding homogeneous system, the catalyst based on **2**, immobilised on unmodified silica and impregnated with ionic liquid could be recycled five times without loss in conversion or *ee*.

## Experimental Section

### General Procedures

Unless otherwise stated all reagents (*ex* Aldrich) were used as received. 1-Butyl-1-methylpyrrolidinium bis[(trifluoromethyl)sulfonyl]imide ([C<sub>4</sub>m<sub>pyrr</sub>][NTf<sub>2</sub>]), 1-ethyl-3-methylimidazolium bis[(trifluoromethyl)sulfonyl]imide ([C<sub>2</sub>mim][NTf<sub>2</sub>]) and *N,N,N,N*-tripropylhexylammonium bis[(trifluoromethyl)sulfonyl]imide ([N<sub>336</sub>][NTf<sub>2</sub>]) were prepared in house using standard literature methods.<sup>[36]</sup> In all cases prior to reaction the ionic liquids were dried under vacuum at 50 °C overnight. All ionic liquids contained <0.16 wt% water determined by Karl-Fischer analysis and <10 ppm halide by suppressed ion chromatography. The selectivity and conversions were determined by <sup>1</sup>H NMR and GC and the *ees* were calculated from the HPLC profile using a Chiralcel OD-H column (hexane:propan-2-ol, 96:4, flow rate 1 cm<sup>3</sup> min<sup>-1</sup>). The retention times of the enantiomers were minor (*R*)-enantiomer *t<sub>R</sub>* = 20.1 min and major (*S*)-enantiomer *t<sub>R</sub>* = 23.8 min. The absolute stereochemistry was assigned by comparison with that previously reported in the literature; (*S*)-enantiomer 99% *ee*  $[\alpha]_{\text{D}}^{25}$ : +84.4° (*c* 3.5, CHCl<sub>3</sub>).<sup>[8c]</sup>

### General Procedure for the Homogeneous Copper-Catalysed Mukaiyama Aldol Reaction between 1-Phenyl-1-trimethylsiloxyethene and Methyl Pyruvate in Dichloromethane

A flame-dried Schlenk flask was charged with ligand (0.0127 mmol, 11 mol%), copper(II) triflate (0.0042 g, 0.0115 mmol, 10 mol%) and dichloromethane (2 cm<sup>3</sup>) and the resulting solution stirred at room temperature for 3 h to

afford a clear green solution. After this time, freshly distilled methyl pyruvate (0.0117 g, 10.4 μL, 0.115 mmol) followed by 1-phenyl-1-trimethylsiloxyethene (0.0243 g, 26 μL, 0.126 mmol) were added. The reaction mixture was stirred at room temperature for the specified amount of time and then diluted with 5 cm<sup>3</sup> of 1:1 ethyl acetate:hexane. On concentrating the reaction mixture, the crude silyl ether was dissolved in 5 cm<sup>3</sup> of THF and treated with 1 M HCl. After stirring at room temperature for 2 h, the solution was diluted with 10 cm<sup>3</sup> water and extracted with ether (3 × 10 cm<sup>3</sup>). The ether layer was washed with 10 cm<sup>3</sup> of a saturated aqueous solution of NaHCO<sub>3</sub> and then dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated. This concentrate was filtered through a short column of silica gel to afford unpurified product.

### General Procedure for the Homogeneous Copper-Catalysed Mukaiyama Aldol Reaction between 1-Phenyl-1-trimethylsiloxyethene and Methyl Pyruvate in Ionic Liquids

A flame-dried Schlenk flask was charged with ligand (0.0127 mmol, 11 mol%), copper(II) triflate (0.0042 g, 0.0115 mmol, 10 mol%). To this was added dichloromethane (2 cm<sup>3</sup>) and ionic liquid (2 cm<sup>3</sup>) and the resulting solution stirred at room temperature for 5 min. After this time the dichloromethane was removed under vacuum and freshly distilled methyl pyruvate (0.0117 g, 10.4 μL, 0.115 mmol) was added followed by 1-phenyl-1-trimethylsiloxyethene (0.0243 g, 26 μL, 0.126 mmol). The resulting mixture was stirred at the desired temperature for the specified amount of time after which the ionic liquid was extracted with diethyl ether (3 × 5 cm<sup>3</sup>) in air. After hydrolysis and standard work-up, the crude product was filtered through a short column of silica gel to afford unpurified product which was analysed.

### Ionic Liquid Recycle Experiments

Following extraction with diethyl ether, the ionic liquid solution was subject to vacuum to remove traces of diethyl ether, flushed with inert gas, and charged with further portions of methyl pyruvate (0.0117 g, 10.4 μL, 0.115 mmol) and 1-phenyl-1-trimethylsiloxyethene (0.0243 g, 26 μL, 0.126 mmol) at room temperature.

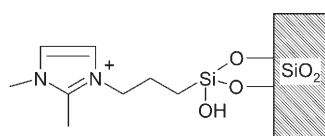
### Scaled-Up Homogeneous Copper-Catalysed Mukaiyama Aldol Reaction between 1-Phenyl-1-Trimethylsiloxyethene and Methyl Pyruvate in a Biphasic Ionic Liquid-Diethyl Ether System

A flame-dried Schlenk flask was charged with ligand (0.0127 mmol, 1.1 mol%), copper(II) triflate (0.0042 g, 0.0115 mmol, 1.0 mol%). To this was added dichloromethane (2 cm<sup>3</sup>) and ionic liquid (0.2 cm<sup>3</sup>) and the resulting solution stirred at room temperature for 5 min. The dichloromethane was removed under vacuum after which diethyl ether (10 cm<sup>3</sup>) was added followed by freshly distilled pyruvate (0.117 g, 1.15 mmol) and 1-phenyl-1-trimethylsiloxyethene (0.243 g, 1.26 mmol). The resulting mixture was stirred at room temperature for one hour after which time the ethereal layer was decanted and the ionic liquid further

extracted with diethyl ether ( $5 \times 10 \text{ cm}^3$ ) in air. After hydrolysis and standard work-up the crude product was purified through a column of silica (30% ethyl acetate-hexane) to afford the product as a pale yellow oil; yield: 0.239 g (94%; 93% ee).

### General Procedure for the Heterogeneous Copper-Catalyzed Mukaiyama Aldol Reaction between 1-Phenyl-1-trimethylsiloxyethene and Methyl Pyruvate

Both Davicat silica SP1500 (pore diameter 150 nm, BET surface area  $25 \text{ m}^2 \text{ g}^{-1}$ ) and a surface-modified silica were used to support the catalyst. The modified support was prepared by reacting the Davicat silica SP1500 with 1,2-dimethyl-3-(3-trimethoxysilylpropyl)imidazolium tetrafluoroborate to form a covalently attached surface ionic liquid phase as reported by Gruttadauria et al.<sup>[37]</sup> The resulting imidazolium-modified silica, silica-IM, (Figure 2) had a pore diameter



Silica-IM

**Figure 2.** Schematic structure of the ionic liquid modified silica, silica-IM.

of 90 nm and a BET surface area of  $17 \text{ m}^2 \text{ g}^{-1}$ .

A flame-dried Schlenk flask was charged with ligand (0.0127 mmol, 11 mol%), copper(II) triflate (0.0042 g, 0.0115 mmol, 10 mol%) and dichloromethane ( $5 \text{ cm}^3$ ) and the resulting solution stirred at room temperature for 3 h. To the resulting green solution was added silica (0.5 g) and, for catalysts using a supported ionic liquid film,  $0.1 \text{ cm}^3$  (ca. 0.14 g) of ionic liquid was also added. The dichloromethane was removed under vacuum for 2 h to afford a free-flowing blue powder after which the flask was charged with diethyl ether ( $5 \text{ cm}^3$ ) followed by freshly distilled methyl pyruvate (0.0117 g,  $10.4 \mu\text{L}$ , 0.115 mmol) and 1-phenyl-1-trimethylsiloxyethene (0.0243 g,  $26 \mu\text{L}$ , 0.126 mmol). The reaction mixture was stirred at the indicated temperature for the specified amount of time after which the silica was extracted with diethyl ether ( $3 \times 5 \text{ cm}^3$ ) in air. After hydrolysis and standard work up the crude product was filtered through a short column of silica gel to afford unpurified product which was analysed as described above.

### Procedure for Recycle of the Silica-Supported Catalyst

The silica/ether slurry solution was subject to filtration using a filter stick in order to separate the phases and the silica was further extracted with diethyl ether ( $2 \times 5 \text{ cm}^3$ ). After extraction fresh diethyl ether ( $5 \text{ cm}^3$ ) was added to the silica and the resultant slurry was charged with further portions of pyruvate (0.0117 g,  $10.4 \mu\text{L}$ , 0.115 mmol) and 1-phenyl-1-trimethylsiloxyethene (0.0243 g,  $26 \mu\text{L}$ , 0.126 mmol).

It should be noted that for reactions conducted in dichloromethane, prior to addition of reagents, the time re-

quired to form the active catalyst is critical to achieving reproducible catalyst performance. As reported by Evans et al.<sup>[38]</sup> and reported for similar copper-catalysed Diels-Alder reactions,<sup>[17]</sup> a 3-h complexation time is typically required to obtain consistent results. In contrast, for reactions conducted in the ionic liquid, the catalyst performance does not depend on the metal-ligand complexation time and reproducible ees and conversions were obtained after aging/complexation for only 5 min.

For all results reported, the selectivity with respect to *n* is defined as follows [Eq. (1)]:

$$\% \text{selectivity} = \frac{\%n}{\sum \% \text{products formed}} \times 100 \quad (1)$$

where % *n* is the percentage yield of the compound *n*. Throughout the text, the conversion refers to the % conversion of pyruvate.

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