## Catalysis Science & Technology

### PAPER

Cite this: DOI: 10.1039/c3cy00352c

# Towards heterogeneous organocatalysis: chiral iminium cations supported on porous materials for enantioselective alkene epoxidation<sup>†</sup>

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Enantiomerically pure iminium cations have been supported on a microporous support (zeolite Y) and on a mesoporous support (Al-MCM-41). These materials are effective asymmetric catalysts for the epoxidation of a range of aryl alkenes, giving high conversions quickly and with enantioselectivities similar to or in some cases even higher than are achievable using the corresponding iminium tetraphenylborates under homogeneous conditions. The catalysts can be simply recycled by filtration and washing. The methodology is illustrated in the synthesis of two natural products, (-)-(3'S)-lomatin and (+)-(3'S,4'R)-trans-khellactone, showing the general efficacy of our approach.

### Received 20th May 2013, Accepted 14th June 2013 DOI: 10.1039/c3cy00352c

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### Introduction

Catalytic methods have the potential to transform the production of chemicals across a very broad range of applications. Indeed, catalytic methods are used routinely in bulk chemical manufacture, but these simple methods, employing heterogeneous catalysts, often supported metals, are not generally applicable for the production of chiral products, which are now commonly required in the pharma, agrochemical, and fine chemical sectors. Asymmetric homogeneous catalysis, where chiral compounds are generated in solution with high enantiomeric purity, has been the subject of intense research over a number of years, and resulted in the award of the Nobel prize for chemistry to Noyori, Sharpless, and Knowles in 2001. There are difficulties, however, in adapting this type of process for commercial purposes.

In recent years, organocatalysis has become increasingly used in enantioselective synthetic processes, where it has proved very successful, achieving rapid reactions leading to

high enantiomeric excesses. Organocatalysis is the term used to describe the acceleration of (organic) reactions by the presence of catalytic species derived only from carbon, hydrogen, and other non-metallic elements, such as nitrogen, oxygen and sulfur. Metal atoms, if present in the reaction system, are not involved in the transition state for the reaction, although organocatalysis has been combined with other types of catalysis, including that by metals.<sup>1</sup> Catalysis arising from simple proton transfers to or from organic catalysts is not usually included in the canon, which requires direct bonding of the organocatalyst with one or more of the reactants during the catalyst turnover. Thus proline is an organocatalyst for aldol reactions not because of its basic nitrogen atom but rather because of its nucleophilic reaction with carbonyl groups to generate reactive iminium intermediates.<sup>2</sup> Almost invariably, organocatalytic reactions are conducted in the liquid phase (homogeneous or two-phase), and this limits their application in commercial fine chemicals production because of the problems associated with separation of the (often expensive) catalyst from the products and its subsequent reuse. There is a clear need for the adaptation of organocatalysts so as to render them heterogeneous, thereby permitting separation of products and catalyst by simple filtration in batch reactions and permitting the development of processes using flow reactors. In this paper we describe an approach to heterogenization of organocatalysts, which is applicable to iminium salt catalysis of alkene epoxidation.

Oxidation is one of the most important types of transformation in chemistry. Selective oxidation is an important requirement for wide range of processes, and is particularly problematic in the

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<sup>†</sup> Electronic supplementary information (ESI) available: Full tables of results, figures, full experimental detail. See DOI: 10.1039/c3cy00352c

#### Paper

production of pharmaceutical and agrochemical actives and intermediates. Existing processes, both stoicheiometric and catalytic, suffer from a range of deficiencies, including limited substrate specificity, scale-up issues, catalytic activity and turnover, and the generation of considerable waste streams derived from the bulk or co-oxidant. For example, in the pharmaceutical industry, typically 10–1000 kg of chemical waste are produced per kg of product on a scale of 100–1000 tons per year of product.<sup>3</sup> A considerable amount of this waste is unrecoverable inorganic waste produced by using oxidation or reduction reagents. For these reasons, many oxidation procedures successful on the laboratory scale have found very limited industrial application to date. Use of such stoicheiometric oxidizing reagents, with the concomitant production of inorganic by-products, necessarily brings inherent environmental disadvantages and other hazards.

Chiral epoxides are extremely useful building blocks for asymmetric synthesis,<sup>4</sup> and the development of effective systems for the asymmetric epoxidation of alkenes has received considerable attention.<sup>5</sup> Catalysts for enantioselective epoxidation in particular, however, are few, and, while successful systems are known, they were all developed as homogeneous systems.<sup>6</sup> The goal of devising a reusable heterogeneous catalyst for asymmetric oxidation, particularly alkene epoxidation, has been achieved in recent years.<sup>7</sup>

All the heterogeneous epoxidation catalysts developed hitherto have contained metals as key components, active in the transition state for reaction. Our aim was to develop a heterogeneous organocatalyst for epoxidation. Oxaziridinium salts generated, for example, by oxidation of iminium salts are useful electrophilic oxidants for alkene epoxidation, and the precursor iminium salts may be used catalytically under homogeneous conditions. Building on the original discovery by Lusinchi of epoxidation using iminium salt catalysis,<sup>8</sup> we and others9 have had considerable success over the past decade in elaborating a range of iminium salts that are effective catalysts at low loadings for enantioselective epoxidation using Oxone (2KHSO<sub>5</sub>·KHSO<sub>4</sub>·K<sub>2</sub>SO<sub>4</sub>) as the stoicheiometric oxidant. We have shown that oxaziridinium salts based on dihydroisoquinolines and dibenzazepines, generated transiently from iminium ions in the presence of a range of stoicheiometric oxidants, including Oxone, hydrogen peroxide,<sup>10</sup> bleach,<sup>11</sup> and even electrochemical oxidation,<sup>12</sup> can be used to generate epoxides with very high enantioselectivities of up to 97% ee. All these reactions are generally taken to involve conversion of the chiral iminium cation into a chiral oxaziridinium intermediate capable of transferring an oxygen atom directly to a prochiral alkene substrate (Scheme 1), hence the role of the iminium salt is as a catalyst. The chirality of our iminium salts is provided by the attachment of an asymmetric exocyclic group to the key iminium nitrogen atom, with an asymmetric centre directly bonded. Examples are shown below  $(1, {}^{13}2, {}^{14}$  and  $3^{15}$ ). Epoxidation reactions are typically conducted in aqueous acetonitrile (which forms a two-phase system under the reaction conditions in all cases when the oxidant is added). The counter-ions investigated also proved to modulate the enantioselectivity: tetraphenylborate and periodate ions gave the highest ee, while hexafluorophosphate and

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Scheme 1 Mediation of alkene epoxidation by oxaziridinium cations.

tetrafluoroborate were less selective, though more so than perchlorate. Subsequently, we demonstrated that use of tetraphenylphosphonium peroxymonosulfate (TPPP), which is soluble in organic solvents, as oxidant allows reactions to be conducted in homogeneous solution at low temperatures and in the absence of water.<sup>16</sup>



The aim of the present investigation was to heterogenize some of our iminium salts by immobilization in porous solids; by using microporous zeolite Y and mesoporous AlMCM-41, which are both acids, anion exchange could take place, and the original counter-anions could be replaced by the polyanionic solid. We now show that such supported iminium salts are effective as heterogeneous catalysts for the epoxidation of alkenes; in general, rates of reaction are somewhat reduced below those achieved in solution phase reactions, but enantioselectivities are usually similar, and in some cases are even higher, presumably as a result of confinement and conformational restriction within the pores of the support. We also report on the separation and reusability of the supported catalysts, and we describe the application of one of the catalysts in the highly enantioselective synthesis of two natural products.

### **Results and discussion**

#### Preparation and characterization of supported iminium cations

In this paper we describe the use of cation exchange to introduce iminium cations into porous materials and to retain them there. We have previously employed such a general procedure to introduce copper( $\pi$ ) cations into zeolite Y to produce heterogeneous catalysts used for enantioselective alkene aziridination.<sup>17</sup>

The iminium cations used in the present work have been previously used in standard two phase or homogeneous liquid phase conditions.<sup>9–11</sup> They fall into three structural groups: (i) dihydroisoquinolinium cations, *e.g.* **1**; (ii) dibenzazepinium

cations, *e.g.* **2**; and (iii) dinaphthazepinium salts, *e.g.* **3**. In all three categories, chirality is incorporated *via* the N-substituent, but cations in the third category have an additional axial chiral element in that the synthesis started from (R)-1,1'-binaphthalene-2,2'-diol. All were prepared first as the bromide salts but were purified and characterized, after anion exchange, as their tetraphenylborate salts, before use in epoxidations under the standard homogeneous or two-phase liquid conditions as indicated above. For incorporation into heterogeneous catalysts, the bromide salts were used directly.

In the present investigation, initial experiments to support the iminium cations involved the use of ammonium zeolite Y (faujasite; pore diameter 7.4 Å, cavity size 12 Å). This was stirred for 24 hours in ethanol with an equal weight of the appropriate, freshly prepared iminium bromide in order to allow cation exchange to occur. The cation-exchanged zeolite was filtered from the mixture, washed successively with ethanol and diethyl ether until the washings were free of bromide ions, and then dried at room temperature under vacuum for at least four hours. Thereafter it was stored before use in a vacuum desiccator. Such catalysts are designated Yn, where Y indicates the support and n represents the iminium salt from which the cation was obtained. Characterization of these materials was by conventional elemental analysis for carbon, hydrogen and nitrogen. It was observed that the ratios of the three elements did not correspond to that expected if the iminium cations were their only source, nor could the figures be fitted on the assumption that the original ammonium ions had been incompletely exchanged. It was concluded that some solvent (assumed to be ethanol) remained trapped in the zeolite and, on this basis, the composition of the solid could be uniquely assigned from the analytical figures. Supported iminium catalysts prepared in this way contained typically 0.6-0.8 mmol iminium cation per gram of solid (12-15% by weight), a roughly equivalent molar amount of ammonium cation and around twice the molar amount of ethanol. Amounts of the supported catalyst required to simulate the concentrations used in homogeneous and two-phase liquid systems were calculated from these analyses.

In subsequent experiments, a mesoporous aluminosilicate material Al MCM-41 (made with cetyltrimethyl ammonium bromide, ratio Si/Al = 12, N<sub>2</sub> physisorption surface area: 912 m<sup>2</sup> g<sup>-1</sup>, diameter of pore (BJH): 29.0 Å) was used to support the iminium cations; these catalysts are designated Mn. The procedure was similar to that used for zeolite Y, the aluminosilicate being calcined prior to use, and the mixture of iminium bromide in ethanol and the support mixed in a Schlenk tube. The mixture was subjected to three cycles of freezing in a liquid nitrogen bath under vacuum followed by thawing under nitrogen. Such temperature cycling aids degassing of solvent and solid support to minimize bubble formation at the liquid/solid interface, and helps to facilitate the ingress of the iminium cations to the pores. After filtration, and washing with ethanol and diethyl ether, the solid catalyst was dried under vacuum, usually at room temperature, before storage in a desiccator. The catalysts were routinely characterized by microanalysis for carbon, hydrogen and nitrogen, with nitrogen values now providing a crucial measure of maximum iminium incorporation. Iminium contents appeared generally somewhat lower than found with zeolite Y. In one instance the presence of the iminium cation was confirmed by solid-state <sup>13</sup>C NMR spectroscopy on the supported catalyst (see ESI<sup>†</sup>).

#### Catalytic enantioselective epoxidation

In initial experiments, directed towards establishing that epoxidation using the heterogeneous catalysts was feasible and was not adversely affected by considerations of mass transport, zeolite Y was used as the support for a group of eight different iminium cations having the dihydroisoquinolinium structure but with a range of chiral N-substituents (Fig. 1).

Reactions were conducted using the heterogeneous catalysts, and the results compared with those for reactions under similar conditions using the corresponding soluble iminium tetraphenylborate as the catalysts in liquid phase, with several alkenes. In both types of reaction, the catalyst loading was nominally either 5 or 10% of the initial quantity of alkene, although uncertainties in the iminium content of the supported catalyst, arising from the imprecision of the elemental analyses, made the correspondence difficult to achieve exactly. Reactions were carried out with careful stirring in aqueous acetonitrile (1:1) at 0 °C with a twofold excess of Oxone<sup>™</sup> and followed to 100% alkene conversion by tlc. The work-up was extremely simple, requiring only addition of solvent and filtration. We were encouraged by the observation that in almost all cases epoxidation using the heterogeneous catalyst was comparable in rate to reactions in the homogeneous liquid phase. An exception was a catalyst incorporating one of the most bulky of the iminium cations investigated, Y1; compared to the homogeneous reaction, typically complete in 5 minutes at 0 °C, this catalyst led to much slower heterogeneous epoxidation of 1-phenylcyclohexene, although with an identical enantiomeric excess (40%) (Table 1). This catalyst was, however, inactive for the epoxidation of 1-phenyldihydronaphthalene,



Fig. 1 Iminium ions supported in zeolite Y.

 Table 1
 Catalytic asymmetric epoxidation of unfunctionalized alkenes

 mediated by dihydroisoquinolinium salts 1<sup>a</sup>



<sup>*a*</sup> Epoxidation conditions: iminium salt **1** (10 mol%), Oxone (2 eq.), Na<sub>2</sub>CO<sub>3</sub> (4 eq.), MeCN: H<sub>2</sub>O (1:1), 0 °C. <sup>*b*</sup> Enantiomeric excess determined by <sup>1</sup>H-NMR spectroscopy with Eu(hfc)<sub>3</sub> (0.1 eq.) as chiral shift reagent or by chiral HPLC on a Chiralcel OD Column. <sup>*c*</sup> Conversion evaluated from the <sup>1</sup>H-NMR spectra by integration of alkene *versus* epoxide peaks. <sup>*d*</sup> The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature. <sup>*e*</sup> No conversion after 6 h.

perhaps as a result of restriction by the small pore size of zeolite Y (see also Table S1, ESI<sup>†</sup>).

Despite the general success of iminium salts supported on zeolite Y as catalysts for alkene epoxidation, filtration of the heterogeneous catalyst **Y1** from the reaction mixture at the end of the reaction, washing with ethanol followed by diethyl ether and drying *in vacuo* at room temperature for 4 h, yielded a solid which showed no detectable catalytic activity. Possible reasons for this are (i) the catalyst was degraded under the reaction conditions; (ii) the catalyst, because its bulk prevents incorporation of **1** within the pores of zeolite Y, is held only on the outer surface from which it is detached during reaction and recovery. The latter explanation can, however, be regarded as unlikely, since removal by filtration of the catalyst from an epoxidation after partial reaction led to no further conversion of the alkene in the filtrate; there is therefore no evidence of leaching of the catalytic cations under the reaction conditions.

Further development of heterogeneous enantioselective epoxidation used the mesoporous aluminosilicate Al-MCM-41 in conjunction with iminium cations. This support, the framework of which is anionic as a result of the presence of incorporated aluminium, was chosen so as to ensure that there would be sufficient space within the pores to accommodate the bulkiest iminium cations. Because of our concern that leaching might occur from the larger pores of the support, one of the catalysts, M13, was stirred for 24 h in a range of solvents, and, after filtration, the filtrate was evaporated and the residue analysed by NMR spectroscopy. Cation 13 was found in residues from the following solvents, all water-miscible: acetonitrile, (1:1)aqueous acetonitrile, acetone and ethanol, we believe with a hydroxide counter-ion. No leaching was observed with toluene, chloroform or dichloromethane. Accordingly we sought to use the heterogeneous catalysts of the M-series under hydrophobic conditions. To this end we prepared tetraphenylphosphonium monoperoxysulfate, PPh<sub>4</sub><sup>+</sup> HSO<sub>5</sub><sup>-</sup>, from the triple salt Oxone and tetraphenylphosphonium chloride.<sup>18</sup> It was recrystallized from a mixture of dichloromethane and hexane to give a solid that, on analysis, was found to have a peroxide content of 85%. This material allowed epoxidation of a range of alkenes to be conducted in homogeneous dichloromethane solution using iminium tetraphenylborates as efficiently as those using Oxone,<sup>15</sup> and also in the presence of Al-MCM-41-supported iminium cations. Moreover it permitted epoxidations to be conducted at temperatures very much lower than were possible under the original Oxone/aqueous acetonitrile regime, with consequent advantages with respect to ee and peroxymonosulfate stability.



We illustrate the efficiency of heterogeneous epoxidation by the results shown in Table 2 for the reaction of a series of 6-substituted chromenes with tetraphenylphosphonium peroxymonosulfate as the stoicheiometric oxidant catalysed by M2 in dichloromethane at -20 °C. The very high ees induced in the corresponding homogeneous epoxidation system (shown in parentheses) were paralleled by the new heterogeneous MCM catalyst M2, with excellent conversions, and giving the same major enantiomers of the products, as indicated. For example, the MCM catalyst induces up to 99% ee in the epoxidation of chromenes, where the corresponding homogeneous catalytic system gives up to 97% ee. Particularly noteworthy is the fourth entry, where the M2 catalyst produced epoxide with 94% ee compared with the homogeneous system at only 74% ee; the considerable increase in ee under the heterogeneous conditions perhaps results from conformational restrictions in the transition state due to confinement in the MCM pores.

Fig. 2 provides a schematic illustration of iminium ion **13** in a 29 Å diameter MCM-41 channel. The channel structure is obtained from a supercell of the dense silica cristobalite phase into which 29 Å diameter channels have been cut with a wall thickness of 7 Å. The resulting dangling bonds have been capped with hydrogen atoms to represent the surface termination by hydroxylation that will occur during the synthesis procedure. Si atoms have then been randomly replaced by Al to give the experimental Si/Al ratio of 12. The porous structure has also been optimized using a molecular mechanics approach,

Table 2 Epoxidation of chromenes by MCM catalyst M2

	R	$\begin{array}{c} & \xrightarrow{\text{TPPP}(2 \text{ eq})} \\ & \xrightarrow{\text{CH}_2\text{Cl}_2} \end{array} \end{array} R$		
R	Conv./%	Temp./°C	Time/h	ee <sup>a</sup> /%
CN	100	-20	4.5	98 (96)
Cl	100	-20	4.5	92 (87)
$NO_2$	100	-20	9.8	99 (97)
Н	71	-20	4.5	94 (̈́74)́

<sup>*a*</sup> Values in parentheses indicate the ees obtained in the corresponding homogeneous reaction.

which reduced the crystallinity of the channel walls. This illustration gives an impression of the relative size of the organocatalyst and channel structure.

#### Reusability of the catalysts

After their first use, M-series catalysts were recovered by simple filtration and successive washing with dichloromethane, followed by drying under vacuum, usually at room temperature, for a minimum of 4 h. The dried solid was then used in a standard epoxidation with fresh alkene and TPPP. In a few experiments the drying temperature was raised to 60 °C in an effort to facilitate the removal of solvent and traces of water; this procedure seemed to lead to a small improvement in the conversion achieved on subsequent reuse of the catalyst. Table 3 shows a selection of representative results, which indicate that the catalysts are reusable, and, most importantly, enantiomeric excesses remained constant throughout. In general, however, declining epoxidation rates and conversions were observed upon reuse. In all the cases shown, further recycling of the catalyst resulted in conversions that were too low to be detectable (see also Table S3, ESI<sup>+</sup>).

We sought to understand the reasons for the reduced activity on reuse of the catalysts. Examination by MAS NMR spectroscopy of catalysts after use did not show the signals characteristic of residual iminium cation. There was, however,



Fig. 2 An illustration of iminium ion 13 in a MCM-41 channel.

evidence in the spectra of the presence of the iminium salts and/or tetraphenylphosphonium cations or their degradation products; clogging of the pores by these materials could clearly have an adverse effect on alkene epoxidation. The iminium cations (or the derived oxaziridinium cations) may undergo slow degradation under the epoxidation conditions, reactions slow enough to be undetectable in the original homogeneously catalysed conditions, which were generally complete within an hour, but becoming significant in the much lengthier reaction times used for the heterogeneous reactions. In this respect it is perhaps significant that in a series of successive reactions using catalyst M2 in the epoxidation of 1-phenylcyclohexene in  $CH_2Cl_2$  at -40 °C over 6 h, conversions were 56, 43 and 20%; successive reactions run for 24 h gave conversions of 100, 50 (increased to 63% when the catalyst was dried after recovery at 60 °C.) and 0%. We were therefore very pleased to observe that stirring the recovered catalyst for 24 h in dichloromethane prior to drying led to much more effective re-use, with both the first and second runs providing 100% conversion in the same reaction time. Although the third use led to a lower conversion of 53%, due possibly to catalyst losses, these promising results provide a proof of concept that our catalysts can be reused as well as providing enhanced enantioselection for the immobilized catalysts.

#### Application to total synthesis of natural products

One of the MCM-based catalysts, **M13**, was used in a short asymmetric synthesis of two simple pyranocoumarin natural products (Scheme 2). Coumarins are widely distributed in nature, both in linear and non-linear form, and have been shown to exhibit a broad range of pharmacological profiles,<sup>19</sup> including anti-bacterial,<sup>20</sup> anti-inflammatory,<sup>21</sup> anti-cancer,<sup>22</sup> and anti-HIV<sup>23</sup> activity. Naturally occurring pyranocoumarins

Table 3	Reusability of Al-MCM-41-supported catalyst M2					
	Ph	$ \begin{array}{c} \text{Cat M2} \\ \hline \text{TPPP (2 eq)} \\ \hline \text{CH}_2 \text{Cl}_2 \end{array} $	PhO			
Use <sup>b,c</sup>	Conv./%	Temp./°C	Time/h	ee <sup><i>a</i></sup> /%		
1	56	-40	6	32 (29)		
2	43	-40	6	32		
3	20	-40	6	32		
1	100	-40	24	32 (29)		
2	50	-40	24	32		
3	0	-40	24	_		
1	100	-40	24	32		
2	63	-40	24	32		
3	0	-40	24	_		
1	100	-40	24	31		
2	100	-40	24	32		
3	53	-40	24	32		

<sup>*a*</sup> Values in parentheses indicate the ees obtained in the corresponding homogeneous reactions. <sup>*b*</sup> Catalyst dried at 60 °C prior to re-use. <sup>*c*</sup> Catalyst stirred in dichloromethane for 24 hours prior to drying and re-use.



include seselin **14**, predominantly isolated from *Plumbago zeylanica*, *Naucleopsis caloneura*, *Carum roxburghianum*, and *Citrus grandis*;<sup>24</sup> and both enantiomers of lomatin **15**, isolated from *Lomatium nuttallii* and various Umbelliferae.<sup>25</sup> Seselin has shown cytotoxic activity against Vero monkey cells, with  $IC_{50}$  values of 12 µg mL<sup>-1</sup> and >20 µg mL<sup>-1</sup>.<sup>26</sup> (+)-*trans*-khellactone **16** shows cytotoxic activity against P-388 lymphocytic leukaemia systems (ED50 2.8 µg mL<sup>-1</sup>).

Seselin was prepared in 94% yield from 7-hydroxycoumarin by reaction with 3-methylbut-2-enal diethyl acetal in the presence of 3-picoline under microwave irradiation.<sup>27</sup> Epoxidation of seselin under our standard conditions using the **M13** catalyst at -20 °C gave the (3'*S*,4'*S*)-epoxide in 93% ee in a conversion of 74% over 4.5 h. The isolated yield was 64%. This compares quite well with epoxidation using the corresponding homogeneous catalyst containing iminium ion **2**, at 95% ee, and with epoxidation using the homogeneous catalyst containing iminium ion **1**, at 97% ee.<sup>27</sup> We have also shown that subsequent reductive ring-opening of the epoxide with sodium cyanoborohydride gave the alcohol (–)-(3'*S*)-lomatin in 92% yield, while acid-catalysed hydrolytic ring-opening of the epoxide gave (+)-(3'*S*,4'*R*)-trans-khellactone in 95% yield, in each case without loss of enantiopurity.

### Conclusions

We have successfully produced enantiomerically pure iminium cations supported on a microporous support (zeolite Y) and on a mesoporous support (Al-MCM-41) and have shown that such materials are effective catalysts for the asymmetric epoxidation of a range of aryl alkenes, giving high conversions quite quickly and with enantioselectivities close to or in some cases even higher than are achievable using the corresponding iminium tetraphenylborates under homogeneous conditions. The best results are obtained using dichloromethane as the liquid phase and tetraphenylphosphonium monoperoxysulfate as the stoicheiometric oxidant, since this combination allows reactions to be carried out at low temperatures. We have demonstrated that the catalysts can be simply recycled by filtration and washing and can then be successfully reused for epoxidation. In general, however, at the present stage of development, the recycled catalysts lead to falling conversions on each reuse for reasons that are at present unclear. Nevertheless we believe that we have the prototype of a reusable heterogeneous iminium catalyst for alkene epoxidation, using peroxymonosulfate as the stoicheiometric oxidant, that can in favourable cases deliver high enantioselectivities.

### **Experimental section**

### Al-MCM-41

The variant of MCM-41 used throughout this research is Al-MCM-41, which contains a high alumina content. Al-MCM-41 was prepared by adding tetraethylorthosilicate to a solution of hexadecyltrimethylammonium bromide containing aluminium isopropoxide. Following static heating at 110 °C for 96 h and calcination at 550 °C, Al-MCM-41 was obtained in 66% yield.

### General procedure for the synthesis of dihydroisoquinolinium zeolite-Y salts from 2-(2-bromoethyl)benzaldehyde and primary amines

A solution of amine (5–10 mmol) in ethanol (10 mL per g of amine) was added dropwise to an ice-cooled solution of 2-(2-bromoethyl)benzaldehyde (1.1 eq.) in ethanol (10 mL per g of amine). The reaction mixture was stirred overnight at ambient temperature. Ammonium zeolite-Y (1:1 wt/wt with respect to amine) was added in one portion and the reaction stirred at ambient temperature overnight. The zeolite-Y catalyst was washed with ethanol (3 × 15 mL) and diethyl ether (3 × 15 mL) and dried under vacuum at room temperature for at least 4 hours. The catalyst was stored in a desiccator at room temperature.

### General procedure for the synthesis of dihydroisoquinolinium Al-MCM-41 salts from 2-(2-bromoethyl)benzaldehyde and primary amines

A solution of amine (5-10 mmol) in ethanol (10 mL per g of amine) was added dropwise to an ice-cooled solution of 2-(2bromoethyl)benzaldehyde (1.1 eq.) in ethanol (10 mL per g of amine). The reaction mixture was stirred overnight at ambient temperature and transferred to a Schlenk tube. Al-MCM-41 (1:1 wt/wt with respect to amine) was added in one portion and the mixture stirred, followed by the evacuation of air from the Schlenk tube. The mixture was cooled in liquid nitrogen until the solution attained freezing point. After 10 min at this temperature the solution was allowed to thaw under a nitrogen atmosphere. The evacuation, freezing and thawing process was repeated twice more, and the Al-MCM-41 catalyst recovered by filtration. The Al-MCM-41 catalyst was washed with ethanol  $(3 \times 15 \text{ mL})$  and diethyl ether  $(3 \times 15 \text{ mL})$  and dried under vacuum at room temperature for at least 4 hours. The catalyst was stored in a desiccator at room temperature.

### General procedure for the synthesis of biphenyl azepinium Al-MCM-41 salts from 2-[2-(bromoethyl)phenyl]benzene carbaldehyde and primary amines

A solution of amine (5-10 mmol) in ethanol (10 mL per g of amine) was added dropwise to an ice-cooled solution of 2-(2bromoethyl)benzaldehyde (1.1 eq.) in ethanol (10 mL per g of amine). The reaction mixture was stirred overnight at ambient temperature and transferred to a Schlenk tube. Al-MCM-41 (1:1 wt/wt with respect to amine) was added in one portion and the mixture stirred, followed by the evacuation of air from the Schlenk tube. The mixture was cooled in liquid nitrogen until the solution attained freezing point. After 10 min at this temperature the solution was allowed to thaw under a nitrogen atmosphere. The evacuation, freezing and thawing process was repeated twice more, and the Al-MCM-41 catalyst recovered by filtration. The Al-MCM-41 catalyst was washed with ethanol  $(3 \times 15 \text{ mL})$  and diethyl ether  $(3 \times 15 \text{ mL})$ , and dried under vacuum at room temperature for at least 4 hours. The catalyst was stored in a desiccator at room temperature.

### General procedure for the synthesis of binaphthalene azepinium Al-MCM-41 salts from (*R*)-binaphthalene azepines

N-Bromosuccinimide (1.2 eq.) and azo-bis-isobutyronitrile (0.05 eq.) were added to a solution of the azepine in dichloromethane (5 mL per g of azepine), and the mixture heated to reflux for 2 h. The reaction mixture was allowed to cool and the solvent removed under reduced pressure. The residue was redissolved in ethanol and the mixture stirred overnight at ambient temperature, and transferred to a Schlenk tube. Al-MCM-41 (1:1 wt/wt with respect to amine) was added in one portion and the mixture stirred, followed by the evacuation of air from the Schlenk tube. The mixture was cooled in liquid nitrogen until the solution attained freezing point. After 10 min at this temperature the solution was allowed to thaw under a nitrogen atmosphere. The evacuation, freezing and thawing process was repeated twice more, and the Al-MCM-41 catalyst recovered by filtration. The Al-MCM-41 catalyst was washed with ethanol  $(3 \times 15 \text{ mL})$  and diethyl ether  $(3 \times 15 \text{ mL})$ , and dried under vacuum at room temperature for at least 4 hours. The catalyst was stored in a desiccator at room temperature.

### General procedure for the synthesis of binaphthalene azepinium Al-MCM-41 salts from (*R*)-2'-(bromomethyl)-[1,1']binaphthyl-2-carbaldehyde and primary amines

A solution of the amine in ethanol (10 mL per g of amine) was added dropwise to a solution of (*R*)-2'-bromomethyl-[1,1']binaphthalenyl-2-carboxaldehyde (1.10 equivalent with respect to the amine) in ethanol (10 mL per g of carboxaldehyde) at 40 °C. The mixture was maintained at 40 °C with stirring overnight. The yellow mixture was allowed to cool to ambient temperature. The residue was redissolved in ethanol and the mixture stirred overnight at ambient temperature, and transferred to a Schlenk tube. Al-MCM-41 (1:1 wt/wt with respect to amine) was added in one portion and the mixture stirred, followed by the evacuation of air from the Schlenk tube. The mixture was cooled in liquid nitrogen until the solution attained freezing point. After 10 min at this temperature the solution was allowed to thaw under a nitrogen atmosphere. The evacuation, freezing and thawing process was repeated twice more, and the Al-MCM-41 catalyst was recovered by filtration. The Al-MCM-41 catalyst was washed with ethanol ( $3 \times 15$  mL) and diethyl ether ( $3 \times 15$  mL), and dried under vacuum at room temperature for at least 4 hours. The catalyst was stored in a desiccator at room temperature.

### (+)-*N*-((4*S*,5*S*)-2,2-Dimethyl-4-(4-(methylsulfonyl)phenyl)-1,3dioxan-5-yl)-3,4-dihydroisoquinolinium Al-MCM-41

Prepared according to the general procedure from (4S,5S)-5amino-2,2-dimethyl-4-(4-(methylsulfonyl)phenyl)-1,3-dioxane (1.5 g, 5.26 mmol) to yield the product as a colourless powder (1.60 g from 1.50 g of Al-MCM-41); found C, 13.67; H, 1.66; N, 0.80 (ratio found C:H:N 13.7:1.7:0.8), C<sub>22</sub>H<sub>26</sub>NO<sub>4</sub>S requires C, 65.97; H, 6.54; N, 3.50% (ratio required C:H:N 13.7:1.4:0.7). Catalyst loading of Al-MCM-41 (15.8%).

### (S)-2-(3,3-Dimethylbutan-2-yl)-3,4-dihydroisoquinolinium zeolite-Y

Prepared according to the general procedure from (*S*)-3,3dimethylbutan-2-amine (1.5 g, 14.85 mmol) to yield the product as a colourless powder (1.59 g from 1.50 g of ammonium zeolite-Y); found C, 14.48; H, 2.60; N, 1.75 (ratio found C:H:N 14.5:2.6:1.8),  $C_{15}H_{22}N$  requires C, 83.28; H, 10.25; N, 6.47% (ratio required C:H:N 14.5:1.8:1.1). Catalyst loading of zeolite-Y (17.4%).

### (*R*)-2-(2-Hydroxy-1-phenylethyl)-3,4-dihydroisoquinolinium zeolite-Y

Prepared according to the general procedure from (*R*)-phenylglycinol (1.5 g, 10.95 mmol) to yield the product as a colourless powder (1.61 g from 1.50 g of ammonium zeolite-Y); found C, 15.38; H, 2.14; N, 1.68 (ratio found C:H:N 15.4:2.1:1.7),  $C_{17}H_{18}NO$  requires C, 80.92; H, 7.19; N, 5.55% (ratio required C:H:N 15.4:1.4:1.1). Catalyst loading of zeolite-Y (17.9%).

#### (S)-2-(2-Hydroxypropyl)-3,4-dihydroisoquinolinium zeolite-Y

Prepared according to the general procedure from (*S*)-1-aminopropan-2-ol (1.5 g, 19.95 mmol) to yield the product as a colourless powder (1.60 g from 1.50 g of ammonium zeolite-Y); found C, 12.28; H, 2.14; N, 1.72 (ratio found C:H:N 12.3:2.1:1.7),  $C_{12}H_{12}NO$  requires C, 75.75; H, 8.48; N, 7.36% (ratio required C:H:N 12.3:1.6:1.2). Catalyst loading of zeolite-Y (15.1%).

### (*S*)-2-(1-Hydroxy-3-methylbutan-2-yl)-3,4dihydroisoquinolinium zeolite-Y

Prepared according to the general procedure from (+)-(*S*)-valinol (1.5 g, 14.55 mmol) to yield the product as a colourless powder (1.55 g from 1.50 g of ammonium zeolite-Y); found C, 16.33; H, 2.52; N, 2.03 (ratio found C:H:N 16.3:2.5:2.0), C<sub>14</sub>H<sub>20</sub>NO requires C, 76.81; H, 8.43; N, 6.89% (ratio required C:H:N 16.3:1.9:1.4). Catalyst loading of zeolite-Y (19.6%).

### (S)-2-(1-Hydroxypropan-2-yl)-3,4-dihydroisoquinolinium zeolite Y

Prepared according to the general procedure from (*S*)-2-aminopropan-1-ol (1.5 g, 19.95 mmol) to yield the product as a colourless powder (1.56 g from 1.50 g of ammonium zeolite-Y); found C, 14.16; H, 2.18; N, 1.92 (ratio found C:H:N 14.2:2.2:1.9),  $C_{12}H_{12}NO$  requires C, 75.75; H, 8.48; N, 7.36% (ratio required C:H:N 14.2:1.1:1.0). Catalyst loading of zeolite-Y (16.3%).

### 2-(2,4,6-Tribromophenyl)-3,4-dihydroisoquinolinium zeolite Y

Prepared according to the general procedure from 2,4,6-tribromoaniline (1.0 g, 3.03 mmol) to yield the product as a colourless powder (1.66 g from 1.50 g of ammonium zeolite-Y); found C, 19.96; H, 1.78; N, 1.93 (ratio found C:H:N 20.0:1.8:1.9),  $C_{15}H_{13}NBr_3$  requires C, 40.49; H, 2.49; N, 3.15% (ratio required C:H:N 20.0:1.4:1.6). Catalyst loading of zeolite-Y (23.0%).

### 2-(2,6-Dimethylphenyl)-3,4-dihydroisoquinolinium zeolite Y

Prepared according to the general procedure from 2,6-dimethylaniline (1.5 g, 12.45 mmol) to yield the product as a colourless powder (1.61 g from 1.50 g of ammonium zeolite-Y); found C, 15.10; H, 2.11; N, 1.75 (ratio found C:H:N 15.1:2.1:1.8),  $C_{15}H_{13}NBr_3$  requires C, 86.40; H, 7.68; N, 5.93% (ratio required C:H:N 15.1:1.8:1.2). Catalyst loading of zeolite-Y (18.1%).

### (*R*)-*N*-[(4*S*,5*S*)-5-(4-(4-Methanesulfonyl)phenyl)-2,2-dimethyl-1,3-dimethyl-1,3-dioxanyl)]-7*H*-dinaphtho[2,1-*c*;1'2'*e*]azepinium Al-MCM-41

Prepared according to the general procedure from (4S,5S)-5amino-2,2-dimethyl-4-(4-(methylsulfonyl)phenyl)-1,3-dioxane (1.5 g, 5.26 mmol) to yield the product as a colourless powder (1.62 g from 1.50 g of Al-MCM-41); found C, 6.84; H, 1.28; N, 0.74 (ratio found C:H:N 6.8:1.2:0.8), C<sub>35</sub>H<sub>32</sub>NO<sub>4</sub>S requires C, 74.71; H, 5.73; N, 2.49% (ratio required C:H:N 6.8:0.5:0.2). Catalyst loading of Al-MCM-41 (7.5%).

## (*R*)-*N*-[(4*S*,5*S*)-5-(4-Phenyl)-2,2-dimethyl-1,3-dioxanyl)]-7*H*-dinaphtho[2,1-*c*;1'2'-*e*]azepinium Al-MCM-41

Prepared according to the general procedure from L-acetonamine (1.5 g, 7.23 mmol) to yield the product as a colourless powder (1.63 g from 1.50 g of Al-MCM-41); found C, 6.61; H, 1.49; N, 0.37 (ratio found C:H:N 6.6:1.5:0.4),  $C_{34}H_{30}NO_2$ requires C, 84.27; H, 6.24; N, 2.89% (ratio required C:H:N 6.6:0.5:0.2). Catalyst loading of Al-MCM-41 (7.3%).

### (-)-*N*-{(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)phenyl]-1,3dioxan-5-yl}-5*H*-dibenzo[*c*,*e*]azepinium Al-MCM-41

Prepared according to the general procedure from (4*S*,5*S*)-5-amino-2,2-dimethyl-4-(4-(methylsulfonyl)phenyl)-1,3-dioxane (1.5 g, 5.26 mmol) to yield the product as a colourless powder (1.61 g from 1.50 g of Al-MCM-41); found C, 9.31; H, 1.59; N, 0.59 (ratio found C:H:N 9.3:1.6:0.6),  $C_{27}H_{28}NO_4S$  requires C, 70.10; H, 6.10; N, 3.03% (ratio required C:H:N 9.3:0.8:0.4). Catalyst loading of Al-MCM-41 (10.5%).

# (–)-2-[(4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl]-5H-dibenzo[c,e]azepinium Al-MCM-41

Prepared according to the general procedure from L-acetonamine (1.5 g, 7.23 mmol) to yield the product as a colourless powder (1.65 g from 1.50 g of Al-MCM-41); found C, 9.63; H, 1.49; N, 0.53 (ratio found C:H:N 9.6:1.5:0.5),  $C_{26}H_{26}NO_2$ requires C, 81.22; H, 6.82; N, 3.64% (ratio required C:H:N 9.6:0.8:0.4). Catalyst loading of Al-MCM-41 (10.9%).

### General procedure for catalytic asymmetric epoxidation of simple alkenes mediated by iminium salts using Oxone

Oxone (2 equivalents) was added to an ice-cooled solution of sodium carbonate (4 eq.) in water (12 mL per 1.50 g of sodium carbonate) with stirring. The resulting foaming solution was stirred for 5-10 minutes until the initial effervescence subsided. The iminium salt (10 mol% with respect to the alkene substrate) was added as a solution in acetonitrile (6 mL per 1.50 g of sodium carbonate), followed by the alkene as a solution in acetonitrile (6 mL per 1.50 g of sodium carbonate). The suspension was stirred at the same temperature until the substrate was completely consumed according to TLC analysis. The reaction mixture was diluted with ice-cooled diethyl ether (20 mL per 100 mg substrate) followed immediately by the same volume of water. The aqueous phase was washed four times with diethyl ether, and the organic fractions were combined, washed with brine, and dried. Subsequent filtration and removal of solvents under reduced pressure yielded a yellow or light brown residue. Column chromatography could be performed using ethyl acetate : light petroleum (1:99) to isolate the pure epoxide.

### Tetraphenylphosphonium monoperoxysulfate<sup>28</sup>

Oxone triple salt  $(2KHSO_5: KHSO_4: K_2SO_4)$  (15.00 g, 48.80 mmol with respect to KHSO5) was dissolved in deionised water (300 mL) and stirred at 10-15 °C. A solution of tetraphenylphosphonium chloride (15.00 g, 40.00 mmol) in distilled dichloromethane (300 mL) was added gradually over 5 minutes. After an additional 30 minutes, stirring was interrupted and the organic layer separated. The solvent was removed under reduced pressure at room temperature. The crude colourless salt was transferred to a sintered glass funnel and washed with distilled water (2  $\times$  75 mL), dissolved in dichloromethane (180 mL), and dried over magnesium sulfate. Hexane was added to the solution until cloudiness developed. The flask was placed at -20 °C overnight to produce a colourless solid (15.70 g, 71%), approximately 85% pure in peroxide.  $\delta_{\rm H}$  (400 MHz:  $CDCl_3$ ) 7.64 (8H, m, 8 × CH arom.), 7.78 (8H, m, 8 × CH arom.). 7.89 (4H, m 4 × CH arom., para to P), 8.92 (1H, br s, OH).

### General procedure for catalytic asymmetric epoxidation of simple alkenes mediated by iminium salts using tetraphenylphosphonium monoperoxysulfate

Tetraphenylphosphonium monoperoxysulfate (2 eq. with respect to the alkene substrate) was dissolved in the desired solvent (2 mL per 0.10 g oxidant) and cooled to the required

temperature. A pre-cooled solution of the iminium salt in the reaction solvent (0.50 mL per 0.10 g oxidant) at the same temperature was added dropwise over 15-20 minutes. The reaction vessel temperature was monitored to minimize temperature fluctuation during addition. The alkene was added as a solution in the reaction solvent (0.50 mL per 0.10 g oxidant) in the same manner as the catalyst. The mixture was stirred at the same temperature until the substrate was completely consumed according to TLC analysis. Diethyl ether (20 mL per 0.10 g oxidant), pre-cooled to the reaction temperature was added to precipitate the remaining oxidant. The solution was filtered through Celite, and the solvents removed under reduced pressure. Diethyl ether (40 mL) was added to the brown residue obtained, and the solution passed through a short pad of silica to remove catalyst residues. The solvent was again removed under reduced pressure to yield the epoxide. Column chromatography could be performed using ethyl acetate: light petroleum (1:99) to isolate the pure epoxide.

### General procedure for the formation of racemic epoxides for enantiomeric excess determinations

The alkene was dissolved in dichloromethane (10 mL per g of alkene) and cooled to 0 °C. A solution of *m*-CPBA (2 eq.) in dichloromethane (10 mL per g of alkene), pre-dried over MgSO<sub>4</sub>, was added. The reaction was allowed to attain ambient temperature and stirred until complete consumption of the substrate was observed by TLC analysis. Saturated aqueous NaHCO<sub>3</sub> (10 mL per g of alkene) was added. The organic layer was washed with saturated NaOH (1.0 M) (10 mL per g of alkene) and dried over MgSO<sub>4</sub>. The solvents were removed under reduced pressure to yield the crude epoxides. Analytically pure samples of the epoxides were obtained through column chromatography, typically eluting with ethyl acetate : light petroleum (1:99).

#### Seselin oxide

**Homogeneous.** Seselin (0.110 g, 0.5 mmol) was dissolved in dichloromethane (24 mL), and the solution cooled to -20 °C. Catalyst **13**, with a tetraphenylborate counter-ion, (0.036 g, 0.05 mmol) and TPPP (0.570 g, 1.00 mmol) were added, and the mixture was stirred at -20 °C for 24 hours. Diethyl ether was added (25 mL) to precipitate the remaining oxidant. The solution was filtered through Celite and the solvents removed under reduced pressure. Diethyl ether (20 mL) was added to the residue and the solution obtained was passed through a short pad of silica to remove the catalyst residues. The solvent was again removed under reduced pressure to yield seselin epoxide as a colourless solid (0.080 g, 71%) of 95% ee (HPLC conditions: hexane : isopropanol (90 : 10), oven temp. 20 °C, column Eurocel 01 250 × 4.6 mm, 5 µm particle size, flow rate 1 mL min<sup>-1</sup>).

**Heterogeneous.** Seselin (0.220 g, 1.0 mmol) was dissolved in dichloromethane (24 mL), and the solution cooled to -20 °C. Catalyst **M13** (0.380 g) and TPPP (1.14 g, 2.00 mmol) were added, and the mixture was stirred at -20 °C for 24 hours. Diethyl ether was added (50 mL) to precipitate the remaining oxidant. The solution was then filtered through Celite and the

solvents removed under reduced pressure. Diethyl ether (40 mL) was added to the residue and the solution obtained was passed through a short pad of silica to remove the catalyst residues. The solvent was again removed under reduced pressure to yield seselin epoxide as a colourless solid (0.150 g, 64%) of 93% ee (HPLC conditions: hexane:isopropanol (90:10), oven temp. 20 °C, column Eurocel 01 250 × 4.6 mm, 5  $\mu$ m particle size, flow rate 1 mL min<sup>-1</sup>).

### Acknowledgements

This investigation has enjoyed the support of the EPSRC, Loughborough University, the University of Cardiff, and the ERDF (ISCE-Chem & INTERREG IVa programme 4061). We acknowledge the support of The Royal Society (PCBP: Industry Fellowship). We are also indebted to the EPSRC Mass Spectrometry Unit, Swansea.

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