Heterogeneous enantioselective synthesis of a dihydropyran using Cu-exchanged microporous and mesoporous materials modified by bis(oxazoline)

Ya Wan[a], Paul McMorn[a], Frederick E. Hancock[b], and Graham J. Hutchings[a,*]

[a]*Department of Chemistry, Cardiff University, P.O. Box 912, Cardiff CF10 3TB, UK*
[b]*Synetix Chiral Technologies, Cambridge Science Park, Cambridge CB4 0FP, UK*

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The formation of dihydropyran from the Diels–Alder reaction between *E*-ethyl-2-oxo-3-pentenonate and vinyl ethyl ether is investigated using copper (II) bis(oxazoline) as catalyst. The homogeneously and heterogeneously catalyzed reactions are contrasted. Immobilization using mesoporous materials (Cu-MCM-41, Cu-AlSBA-15, Cu-MSU-2) and zeolite Y is found to produce an effective heterogeneous catalyst. Although the level of enantioselection is not high in this initial study, the CuH-zeolite Y/bis(oxazoline) catalyst gives the highest ee (41% ee), which is significantly higher than that observed for the $Cu(OTf)_2$ homogeneous catalyst (20% ee) under comparable conditions. In addition, with the heterogeneously catalyzed reaction, the enantioselection changes from the initial 2*R*,4*S* product to the 2*S*,4*R* diastereoisomer. This behavior is not observed with the homogeneously catalyzed reaction, which always yields the 2*R*,4*S* product. These results are discussed in terms of the confinement of the catalyst complex within the pores of the heterogeneous catalyst.

KEY WORDS: Diels–Alder reactions; dihydropyran synthesis; enantioselective reactions.

1. Introduction

There remains an immense interest in the synthesis of chiral molecules as they are important intermediates in the synthesis of many pharmaceuticals and agrochemicals. There has been significant progress in recent years concerning the design of homogeneous enantioselective catalysts [1]. However, in spite of these advances, the contribution of chiral catalysis to the overall production of chiral molecules remains much less than could be expected from the wide research interest. One obvious reason for this is that homogeneous catalysts can be difficult to recover and reuse. The identification of suitable enantioselective heterogeneous catalysts would overcome this difficulty and this has prompted considerable research in the use of immobilized chiral catalysts supported on polymers [2] or inorganic materials [3].

To date, most effort has been concentrated on asymmetric reduction. For example, considerable effort has been given to cinchona-modified platinum catalysts for the asymmetric reduction of α, β-ketoesters [4–6] but, recently, there has been considerable interest in the synthesis of chiral catalysts immobilized by covalent attachment for hydrogenation reactions [3]. These catalysts have been shown to give significantly higher enantioselection when compared with their nonanchored homogeneous counterparts [7]. These constrained chiral catalysts have provided a useful route to the synthesis of a number of compounds [8].

Of particular interest has been the use of copper bis(oxazoline) complexes as catalysts for a wide range of reactions [9]. Evans and coworkers have shown that these complexes are highly effective enantioselective homogeneous catalysts for carboxylic and hetero Diels–Alder, Aldol, Michael, ene and amination reactions [10], as well as aziridination [11,12]. Diels–Alder reactions are usually catalyzed by Lewis acids [13] and, often, excessive quantities of chiral Lewis acid (5–100 mol%) have to be employed. For this reason, immobilization of these catalysts is seen as being particularly useful. However, there are very few examples of supported chiral Lewis acid catalysts [14–19], and mostly polymer supports have been utilized and, as yet, inorganic supports have not been extensively utilized [18,19]. Recently, Corma *et al.* [20] have shown that copper bis(oxazoline) complexes can be covalently anchored to silica and MCM-41. We have adopted a different approach to immobilization in which the copper bis(oxazoline) complex is electrostatically bound within microporous and mesoporous materials [21]. We have shown that these catalysts can give a high yield and ee ($\geq$95%) for the aziridination of alkenes [22,23] and, furthermore, these catalysts are stable under reaction conditions and can be reused [24]. Recently, we have extended the use of these catalysts to carbonyl- and imino-ene reactions [25]. Previously, Evans and coworkers have shown that copper bis(oxazoline)

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[*] To whom correspondence should be addressed.

complexes are effective homogeneous catalysts for Diels–Alder reactions [26,27]. In this paper, we extend the use of our immobilized copper bis(oxazoline) catalysts to the synthesis of a dihydropyran, a prevalent structural subunit in many natural products, via an α-keto Diels–Alder cycloaddition.

2. Experimental

Zeolite Y (Union carbide, LZY84) was obtained commercially. Mesoporous materials MCM-41 [28], Al-SBA-15 [29] and MSU-2 [30] were prepared according to standard literature methods and the structures were confirmed using powder X-ray diffraction and solid-state NMR spectroscopy. The materials were treated with an aqueous solution of Cu(II) acetate (Aldrich) to prepare Cu^{2+}-exchanged materials. All materials were dried (110 °C, 16h) and calcined (550 °C, 3 h) prior to use as catalysts.

E-ethyl-2-pentenonate was prepared by the method of Sugimura and Yoshida [28] and Evans *et al.* [27] and involved the reaction of ethyl 2-(trimethylsiloxy)acrylate with acetaldehyde dimethylacetal. α-Keto Diels–Alder cycloaddition reaction of *E*-ethyl-2-oxo-3-pentenonate with ethyl vinyl ether was carried out in CH_2Cl_2 using a Schlenk tube. The catalyst (5 mol% Cu, either copper (II) triflate (Aldrich) or Cu-exchanged microporous or mesoporous material) was stirred in CH_2Cl_2 (2.5 mL) with the bis(oxazoline) **1** (6 mg) for 15 min and the mixture was stirred at the specified temperature. Following this, the ketoester (0.38 mmol) and the vinyl ether (10 mmol) were added. Reaction samples were analyzed by HPLC using a chiralpack OD-H column. The mobile phase was 1.0% ethanol/99.0% hexane with a flow rate of 1 mL/min. A UV detector was used, monitoring the signal at 254 nm.

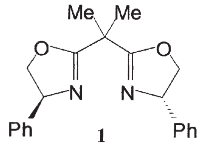

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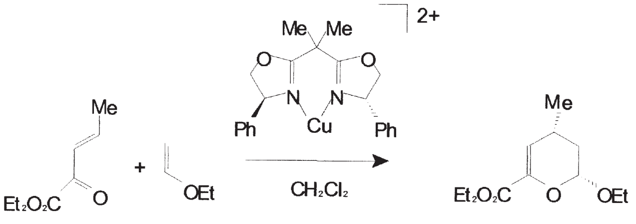
Table 1
Dihydropyran formation using $Cu(OTf)_2$ as catalyst[a]

Time (min)	Conversion[b] (%)	Selectivity[c] (%)	ee (%)	Configuration
15	35.8	30.7	19	2*R*,4*S*
40	94.4	94.2	21	2*R*,4*S*

[a] −3 °C, standard reaction conditions.
[b] Conversion of *E*-ethyl-2-oxo-3-pentenonate, results based on isolated yields.
[c] Selectivity to **2**.

3. Results and discussion

The Cu^{2+}-catalyzed reaction of *E*-ethyl-2-oxo-3-pentenonate with vinyl ethyl ether was investigated for the formation of the dihydropyran **2**.



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Initial experiments were carried out using $Cu(OTf)_2$ as a homogeneous catalyst, and the results are shown in table 1. The reaction was fairly rapid at −3 °C and a high yield of the product was obtained (88.9%). The ee for the 2*R*,4*S* product was ca. 20% and did not change with conversion or increasing reaction time.

Subsequent experiments were carried out using the Cu-exchanged zeolite Y, MCM-41, SBA-15 and MSU-2 catalysts, and the results are summarized in table 2. In general, the reactions with the heterogeneous catalysts were much slower, under comparable conditions, than the $Cu(OTf)_2$ homogeneously catalyzed reactions. Adding 3A molecular sieves during the reaction did not lead to any significant improvement. Slower reactions using the heterogeneous catalysts have been observed in our previous studies for the aziridination of styrene [24], although the effect was not so marked as in

Table 2
Dihydropyran formation with heterogeneous catalysts

Catalyst	Reaction time (h)	Temperature (°C)	Dihydropyran yield[a] (%)	ee (%)	Configuration
Cu-AlSBA-15	0.75	2	4.7	11.7	2*R*,4*S*
	46	2	66.3	4.0	2*S*,4*R*
Cu-MCM-41	0.02	4	25	6.9	2*R*,4*S*
	192	4	81	5.9	2*S*,4*R*
Cu-MSU-2	0.83	−7	4.4	3.4	2*R*,4*S*
	3	−5	30.9	2.1	2*S*,4*R*
CuH-Y	1.5	−5	1.4	4.1	2*R*,4*S*
	72	−5	16	41	2*S*,4*R*

[a] Isolated yields.

Table 3
Dihydropyran formation using Cu-MCM-41^{a}

Time (min)	Conversion^{b} (%)	Selectivity^{c} (%)	ee (%)	Configuration
1	50.1	100	6.9	2*R*,4*S*
60	84.9	100	2.6	2*S*,4*R*
150	87.0	100	2.5	2*S*,4*R*
1 290	87.7	100	3.2	2*S*,4*R*
11 520	90.0	90.0	6.1	2*S*,4*R*

^{a}4 °C under standard conditions.
^{b}Based on *E*-ethyl-2-oxo-3-pentenonate.
^{c}Based on **2**.

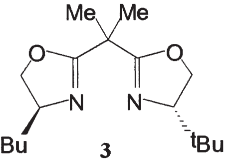
this case. Analysis of the solution following reaction indicated that ca. 1% of the Cu^{2+} present in these catalysts leached into solution. Experiments using these solutions did not reveal any significant activity and, hence, the reactions are considered to result from a heterogeneously catalyzed process. In addition, the catalysts could be recovered and reused without loss of catalyst. Further evidence confirming that the process is heterogeneously catalyzed is that the dihydropyran formed with the heterogeneous catalyst has the 2*R*,4*S* configuration, whereas the homogeneous catalyst produces the 2*S*,4*R* configuration exclusively.

An interesting effect was observed for the heterogeneously catalyzed reactions, which was not apparent in the homogeneously catalyzed process, namely, the reversal in enantioselectivity of the dihydropyran product. Initially, the 2*R*,4*S* product is observed and, subsequently, this switches to the 2*S*,4*R* product. More details of this for the Cu-AlSBA-15 and Cu-MCM-41 catalysts are given in tables 3 and 4. The effect is particularly significant for the reaction using Cu-SBA-15. The crossover occurs at around 20–23 h of reaction time under these conditions. Reversal in enantioselection during the course of a reaction is uncommon. In this case, for all the heterogeneous catalysts, there appears to be a very rapid initial reaction, followed by a very slow subsequent reaction. This is consistent with product inhibition of the heterogeneous catalysts, which has been observed in other zeolite-catalyzed reactions [29,30]. It is possible that the interaction of the reactants and products at the active site could influence the stereochemistry of the reaction. The effect is not observed in the homogeneous reaction under comparable conditions. However, interestingly, Evans *et al.* [31] has observed a reversal in enantioselectivity for the homogeneously catalyzed hetero Diels–Alder reaction for the *tert*-butyl-substituted bis(oxazoline) **3** versus phenyl-substituted bis(oxazoline) **1**.

Table 4
Dihydropyran formation using Cu-AlSBA-15^{a}

Time (h)	Conversion^{b} (%)	Yield^{c} (%)	ee (%)	Configuration
0.75	24.3	4.7	11.7	2*R*,4*S*
3	28.5	8.1	9.4	2*R*,4*S*
20.5	62.5	39.1	0.8	2*R*,4*S*
23	63.2	37.8	1.7	2*S*,4*R*
46	89.8	73.5	4.0	2*S*,4*R*
120	90.4	75.7	4.1	2*S*,4*R*

^{a}2 °C under standard conditions.
^{b}Based on *E*-ethyl-2-oxo-3-pentenonate.
^{c}Based on **2**, isolated yield.



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These findings suggest that the bulkiness of the ligand in the homogeneous complex can affect the outcome of the reaction with respect to enantioselection. In our case with the heterogeneous catalyst, the immobilized copper bis(oxazoline) complex is constrained within micropores and mesopores, and the interaction with the adsorbed product could lead to a similar increase in steric bulk associated with the active site. This is clearly an area that needs further investigation, since it will be necessary to contrast this effect of high enantioselection if Diels–Alder reactions using immobilized copper bis(oxazoline) complexes are to be achieved.

One further point requires discussion; namely, that the ee for the 2*S*,4*R* dihydropyran (41% ee) obtained using the zeolite Y immobilized complex is significantly higher than that obtained for the homogeneous catalyst (20% ee) under comparable conditions. This is further evidence that the steric bulk around the metal center influences the enantioselection. Although the degree of enantioselection in this study is not high (20–40% ee), the observation that the constrained immobilized complex gives a significantly enhanced ee represents a further example of where the heterogeneous catalyst gives superior results to the equivalent homogeneous catalyst. This effect has been noted by us for the copper bis(oxazoline) complex when immobilized in zeolite Y for the aziridination of styrene [23] and was observed earlier in the study of Thomas and coworkers [8].

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