

Immobilized Catalysts

Heterogeneous Enantioselective Catalyzed Carbonyl- and Imino-Ene Reactions using Copper Bis(Oxazoline) Zeolite Y**

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The current high demand in the pharmaceuticals industry for efficient and economical routes to enantiomerically pure α -hydroxy and α -amino carbonyl compounds has focused interest on carbonyl-ene and imino-ene reactions as a potential source of these compounds.^[1] Homogeneously catalyzed carbonyl-ene reactions have been reported using a chiral methyl–aluminum–binaphthol complex,^[2] but the scope of this catalyst was very limited. Subsequently, the scope of

the reaction was widened to the use of 1,1-disubstituted alkenes with titanium–binol (binol = 2,2'-dihydroxy-1,1'-binaphthyl) homogeneous catalysts.^[3] Recently, interest has focused on the use of soluble copper(II) bis(oxazoline) complexes as catalysts for the reaction of a range of glyoxylate and pyruvate esters and substituted alkenes to generate α -hydroxy carbonyl compounds in high yields and with high *ee* values.^[4a] In contrast, there is only a single example of a homogeneously catalyzed imino-ene reaction involving copper binap (binap = [1,1'-binaphthalene]-2,2'-diylbis(diphenylphosphane)) complexes.^[5] These catalysts and processes remain, however, limited in their economic efficiency because of the inability to recover the catalysts from the reaction medium. Previously, bis(oxazoline) bound to soluble poly(ethylene glycol) has been used to generate a recyclable catalyst which is recovered by precipitation at the end of each reaction cycle, but the enantioselection decreased with each reuse.^[6]

Herein, we present the first heterogeneously catalyzed, efficient enantioselective carbonyl- and imino-ene reactions using a readily recyclable catalyst. Our approach to designing highly enantioselective heterogeneous catalysts uses electrostatic immobilization of cations within zeolites and mesoporous materials. Previously, we have shown that heterogeneous catalysts for the enantioselective aziridination of alkenes, with *ee* \geq 95 %, can be designed on this basis.^[7] In addition, we have shown that the copper bis(oxazoline) complex, when constrained within the zeolite structure,^[8] gives substantially higher enantioselection than the homogeneous catalysts.^[7,9] Similar effects have been noted for other immobilized catalysts.^[10] We have now found that bis(oxazoline)-modified CuH zeolite Y catalysts are extremely effective catalysts for asymmetric carbonyl- and imino-ene reactions and, furthermore, these catalysts can be readily recovered and reused without loss of catalyst performance.

The reaction of ethyl glyoxylate with a range of alkenes has been investigated using the immobilized copper–zeolite Y (Cu-HY) bis(oxazoline) catalyst and the results are shown in Table 1. In the absence of the bis(oxazoline), negligible reaction was observed. The results show that the reactions proceed with good yields and, in many cases, high enantioselection. Interestingly, the use of (*S,S*)-**2** as the ligand with α -methylstyrene leads to significantly higher *ee* value (93 %) than the use of (*S,S*)-**1** (77 %). Even removal of the methyl groups on the bridging carbon atom, that is, using (*S,S*)-**3** gives a higher *ee* value under the same conditions. This result shows that, by further fine tuning of the ligand, improved enantioselection can be expected. Of particular note is the reaction of 2-methylhept-2-ene using (*R,R*)-**1** which gave a major and minor product in a molar ratio of 3.2:1 (ca. 76:24). The *anti:syn* diastereoselectivity of the major product was 5:1 (i.e. ca. 83:17). However, the observation of reaction with this substrate, albeit with a low yield, shows the advantages of using the heterogeneous catalysts, since previous studies^[4b] have shown that enantioselective reactions with 1,2-disubstituted alkenes are not catalytic with the homogeneous copper bis(oxazoline) complex catalysts.

The scope of the reactions using the immobilized catalyst was extended and the reaction of α -methylstyrene with methyl pyruvate was investigated (Scheme 1). These results,

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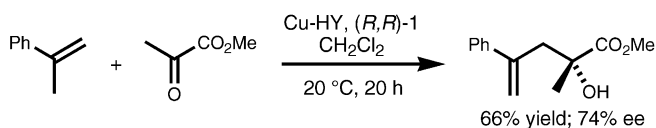
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Table 1: Enantioselective carbonyl-ene reactions catalyzed by bis(oxazoline) Cu-HY.

1 R_{brg} = CH₃, R_{ox} = Ph
2 R_{brg} = CH₃, R_{ox} = C(CH₃)₃
3 R_{brg} = H, R_{ox} = C(CH₃)₃

Bis(oxazoline)	Alkene	Enophile	Product	T [h]	Yield [%]	ee config. [%]
(S,S)-1	α -methylstyrene	$\text{H}-\text{C}(=\text{O})-\text{CO}_2\text{Et}$		20	85	77 S
(S,S)-1	methylene cyclohexane	$\text{H}-\text{C}(=\text{O})-\text{CO}_2\text{Et}$		100	65	94 S
(S,S)-1	methylene cyclopentane	$\text{H}-\text{C}(=\text{O})-\text{CO}_2\text{Et}$		100	71	93 S
(R,R)-1	2-methylheptene	$\text{H}-\text{C}(=\text{O})-\text{CO}_2\text{Et}$		150	69	72 R
(R,R)-1	2-methylhept-2-ene	$\text{H}-\text{C}(=\text{O})-\text{CO}_2\text{Et}$	 major minor	150	23	77 R
(S,S)-2	α -methylstyrene	$\text{H}-\text{C}(=\text{O})-\text{CO}_2\text{Et}$		12	87	93 R
(S,S)-3	α -methylstyrene	$\text{H}-\text{C}(=\text{O})-\text{CO}_2\text{Et}$		12	91	85 R
(R,R)-1	α -methylstyrene	$\text{H}-\text{C}(=\text{O})-\text{CO}_2\text{Et}$		20	66	80 R
(S,S)-1	α -methylstyrene			10	87	90 R
(S,S)-2	α -methylstyrene			5	83	92 R

along with those in Table 1, show that the heterogeneous copper catalysts are active for the carbonyl-ene reactions across a range of alkene substrates and carbonyl compounds. The scope was further extended to imino-ene reactions (Table 1). The results demonstrate that both α -carboxyl imine (ethyl-*N*-benzhydryliminoethanoate) and alkylimine (*N*-benzyl isovalerimine) compounds readily react with α -methylstyrene giving high yields and enantioselectivity with

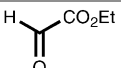
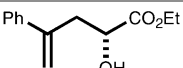
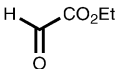
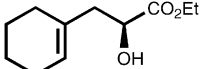
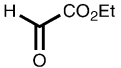
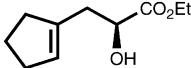


Scheme 1. Cu-HY = Immobilized copper-zeolite Y catalyst.

the immobilized copper catalyst. Previous studies involving homogeneous catalysts^[5] have used imine compounds that have an electron-withdrawing substituent, usually a carbonyl or carboxyl group, adjacent to the imine carbon atom to enhance its reactivity. Our preliminary study using *N*-benzyl isovalerimine shows that these groups are not necessary with the immobilized heterogeneous catalyst.

The reaction of the immobilized copper-bis(oxazoline) zeolite Y catalyst was compared with a homogeneous copper catalyst, Cu(OTf)₂ in the presence of the bis(oxazoline), under comparable conditions (Table 2). Although the homogeneous catalyst gave a higher yield, the *ee* values observed for α -methyl styrene and methylene cyclohexane were comparable for the two catalysts. However, the *ee* values observed with the heterogeneous catalyst for methylene cyclopentane

Table 2: Comparison of the immobilized catalyst (Cu-HY) with the homogeneous catalyst for the carbonyl-ene reaction.

Bis-oxazoline	Alkene	Enophile	Catalyst	Product	T [h]	Yield [%]	ee config. [%]
(R,R)-1	α -methylstyrene		Cu-HY		20	66	80 R
(R,R)-1			Cu(OTf) ₂		20	94	66 R
(S,S)-1	methylene cyclohexane		Cu-HY		100	65	94 S
(S,S)-1			Cu(OTf) ₂		100	92	99 S
(S,S)-1	methylene cyclopentane		Cu-HY		100	71	93 S
(S,S)-1			Cu(OTf) ₂		100	94	57 S

was significantly higher than that observed with the homogeneous catalyst. This is considered to be due to the confinement of the heterogeneous catalyst within the zeolite pores, and we have also observed this in our previous studies on aziridination.^[7]

Following the reaction of methyl pyruvate and α -methylstyrene (Scheme 1), the catalyst was recovered, dried, and reused giving the same results. The aqueous phase from the crude-product washing step was analyzed, and it was determined that only approximately 1 % of the copper added with the heterogeneous catalyst leached, under the reaction conditions, into the reaction mixture. Further experiments showed that this level of copper was not an active homogeneous catalyst for the carbonyl- and imino-ene reactions. Hence, the copper-bis(oxazoline) zeolite Y catalyst is acting as a heterogeneous catalyst. A further series of experiments were carried out to demonstrate the facile reuse of this immobilized catalyst (Table 3). A large scale reaction of ethyl glyoxylate with α -methylstyrene was carried out (Entry 1, Table 3). Following the reaction, the catalyst was isolated by filtration and pretreated according to three different methods (Table 3). The pretreated, used catalyst was then used for subsequent reactions with either ethyl glyoxylate or methyl pyruvate. Our initial experiments were based on simply recovering the catalyst by filtration and vacuum drying before reusing (Entry 2, Table 3). Although the catalyst could be reused, the yield increased while the *ee* value decreased. This effect was due to product being retained from the initial

reaction (Entry 1, Table 3) which was then washed out into the reaction mixture during the subsequent reaction. For this reason, subsequent experiments on catalyst reuse involved a washing procedure (Entries 3–5, Table 3) to ensure product was not retained in the reused catalyst. The results show that, following washing, even without the further addition of bis(oxazoline), the washed, reused catalysts give comparable yields and *ee* values to those expected from a fresh catalyst (Entries 3–5, Table 3).

In addition, it is possible to use the catalyst for different reactions in successive experiments (Entries 1, 3–5, Table 3), which fully demonstrates the flexibility of the heterogeneous catalyst. If the reused catalyst is retreated with bis(oxazoline) prior to use, then improved enantioselection is observed (experiment 6, Table 3), but such a retreatment is not considered essential.

We have previously shown, using detailed EPR spectroscopy,^[8] that the bis(oxazoline) chelates to the copper within the supercages of the zeolite to form a square-planar complex. In the present study, we consider this is the active site for the catalyzed reaction, since the experiments reported clearly demonstrate the material is acting as a heterogeneous catalyst.

In conclusion, we have demonstrated the first heterogeneously catalyzed, enantioselective carbonyl-ene and imino-ene reactions, which provide a simple pathway for the synthesis of α -hydroxy and α -amino carbonyl compounds with good yields and high enantioselection.

Experimental Section

Cu-exchanged zeolite Y was prepared by ion-exchange of zeolite HY (50 g) with a solution of copper(II) acetate (7.85 g, 39.3 mmol in deionized water (150 mL)) for 16 h at 20 °C with periodic adjustment of the pH value to 7.5. The material was recovered by filtration, dried (110 °C), and calcined (550 °C). Using inductively coupled plasma (ICP) analysis, the zeolite was found to contain 3.1 wt % Cu.

Heterogeneous catalyzed carbonyl-ene reactions using ethyl glyoxylate: The Cu-exchanged zeolite Y (0.360 g, 0.15 mmol Cu) was dried in a Schlenk flask under high vacuum (150 °C, 2 h) and then cooled (20 °C). CH₂Cl₂ (5.0 mL) and the bis(oxazoline) (0.025 g, 0.075 mmol) were added to the dried catalyst by syringe. Filtration at this point yielded an air stable catalyst with the same performance as that prepared and used in situ, this material was stable when stored in air at room temperature for up to 6 months. The suspension was stirred for 3 h at 20 °C and then alkene (0.149 mmol) and ethyl glyoxylate solution in toluene (1.02 g, 80 % solution in toluene, 7.47 mmol) were added by syringe. The reaction mixture was stirred at 20 °C and the reaction was monitored periodically by thin-layer chromatography (TLC). After the reaction, the catalyst was separated by filtration and the product was purified by flash column chromatography.

Homogeneously catalyzed carbonyl-ene reactions: Copper(II) triflate (Cu(OTf)₂, 0.054 g, 0.15 mmol) and bis(oxazoline) (0.056 g, 0.15 mmol) were added to a dry Schlenk flask under argon and CH₂Cl₂ (5 mL) was added by syringe. The solution was stirred for 3 h at 20 °C and then alkene (1.90 mmol) and ethyl glyoxylate (1.17 g,

Table 3: Reuse of the heterogeneous catalyst.^[a]

Entry	Reuse	Pretreatment ^[a]	Carbonyl compound	Yield [%]	ee config. [%]
1	–	–	ethyl glyoxylate	66	80 R
2	2nd use	(a)	ethyl glyoxylate	85	65 R
3	2nd use	(b)	methyl pyruvate	85	83 R
4	3rd use	(b)	methyl pyruvate	91	89 R
5	4th use	(b)	ethyl glyoxylate	89	82 R
6	2nd use	(c)	methyl pyruvate	79	80 R

[a] See Experimental Section for method definition.

80% solution in toluene, 9.51 mmol) were added by syringe. The reaction mixture was stirred at 20°C and the reaction was monitored periodically by TLC. After the reaction, the product was purified by flash chromatography.

Imino-ene reactions: Cu-exchanged zeolite Y (0.423 g, 0.17 mmol Cu) was dried in a Schlenk flask under high vacuum (150°C, 2 h) and then cooled (20°C). CH₂Cl₂ (5.0 mL) and bis(oxazoline) (0.025 g, 0.075 mmol) were added to the dried catalyst by syringe. The suspension was stirred for 3 h at 20°C and then α -methylstyrene (194 μ L, 1.49 mmol) and the imino(ethyl-*N*-benzhydryliminoethanoate (1.2 mmol)), or *N*-benzyl isovalerimine (2.55 mmol) were added by syringe. The reaction mixture was stirred at 20°C and monitored periodically by TLC. After complete reaction, the catalyst was separated by filtration. The crude product was purified by flash column chromatography.

Large scale reuse experiment: Vacuum-dried Cu-exchanged zeolite Y (3.1 wt % Cu, 1.44 g, 0.60 mmol Cu) pretreated with (*R,R*)-**1** (0.10 g, 0.40 mmol) was treated with ethyl glyoxylate (4.08 g, 29.88 mmol) and α -methylstyrene (0.708 g, 5.95 mmol) for 20 h at 20°C in CH₂Cl₂ (20 mL). The catalyst was separated by filtration and the product recovered and purified by flash column chromatography. Subsequent reactions of the used catalyst were carried out at a quarter of this scale. Prior to reuse, the catalyst was pretreated according to one of the following methods:

- vacuum drying only (60°C, 12 h; 150°C, 3 h);
- washed with ethylacetate (5 \times 5 mL) before vacuum drying and repeating the whole procedure twice more;
- washed and dried as in method (b), calcined (550°C, 6 h), and retreated with (*R,R*)-**1** (0.025 g, 0.075 mmol).

The *ee* value was determined using chiral HPLC using a Daicel Chiralpak OD column and yields of isolated products are reported.

The IUPAC name for 1,3-oxazoline is 4,5-dihydro-1,3-oxazole

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