Catalytic heterogeneous aziridination of alkenes using microporous materials

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Copper-exchanged zeolite Y is a highly active catalyst for the aziridination of alkenes; modification using bis(oxazolines) leads to preparation of the first heterogeneous enantioselective aziridination catalyst.

The design of asymmetric catalysts is of intense current interest,[1] and procedures making use of chiral transition metal complexes have been described for epoxidation, cyclopropanation, aziridination and hydrogenation of alkenes in homogeneous solution.[2–6] There is increasing recognition that heterogeneous catalysts have practical advantages over homogeneous ones.[6–8] We describe here a generic approach to the design of heterogeneous transition-metal catalysts by making use of the well-known ability of zeolites to undergo metal cation exchange,[9] together with their acid–base properties.[10] By constructing transition-metal complexes within the spatially restricted environment of the zeolite pores, enantioselective organic transformations can be catalysed with comparable or even greater efficiency than in the corresponding homogeneous process. We exemplify this approach with the first heterogeneous catalyst for asymmetric aziridination of alkenes.

We have found that CuHY zeolite is successful in catalysing the aziridination of a range of alkenes employing [*N*-(tolyl-*p*-sulfonyl)imino]phenyliodinane (PhI=NTs) as the nitrogen source. The results are shown in Table 1. The Cu-exchanged zeolite (CuHY) was prepared by conventional ion-exchange methods with aqueous $Cu(OAc)_2$ solution, the concentration of which was chosen so as to obtain the required exchange level (*ca.* 50–60% of available H^+). The cation-exchanged zeolite was then washed with distilled water and dried at 110 °C in air. CuHY was initially screened in the aziridination of styrene (Table 1, entries 1–3), since this alkene affords good yields of aziridine when copper triflate is used as a homogeneous catalyst.[4] Using a five-fold molar excess of styrene, the desired *N*-tosylaziridine was obtained in 90% yield (entry 1). These

initial results confirmed our contention that cations within zeolites could be used as heterogeneous counterparts of known homogeneous catalysts, and, to the best of our knowledge, this is the first example of an aziridination reaction catalysed heterogeneously.

In order to confirm the absence of homogeneously catalysed reaction, following reaction the zeolite catalyst was recovered by filtration and another aliquot of reactants (styrene:PhI=NTs = 5:1 molar ratio) was added to the recovered filtrate; no further product was observed. Further, the removed catalyst was reused with fresh reagents and solvent, and the zeolite demonstrated similar activity to when it was used initially.

It was noted in earlier studies that, in the homogeneously catalysed reaction,[4] the yield of aziridine decreased to 37% when the molar ratio of styrene:PhI=NTs = 1:1 was employed, due to the competing breakdown of the PhI=NTs reagent. This decrease was found to be less significant using our heterogeneous catalyst, where 87% yield was obtained when a styrene:PhI=NTs = 1:1 molar ratio was used (Table 1, entry 2) as compared to a yield of 90% when a styrene:PhI=NTs = 1:1 molar ratio was used (Table 1, entry 1).

CuHY was found to be successful in catalysing the aziridination of a range of alkenes (Table 1) in addition to styrene. It is observed that the catalyst gives best results with phenyl-substituted alkenes and lower yields are observed with cyclohexene and *trans*-hex-2-ene. Interestingly, for the aziridination of *trans*-stilbene no product could be observed. This was considered to be the due to the relatively bulky aziridine product being too large to be accommodated within the supercages of CuHY. However, the aziridination of *trans*-methyl cinnamate inside CuHY proceeded in 84% yield, despite being similar in structure type to the *trans*-stilbene product. We used molecular modeling to investigate the ease with which these two aziridines could be placed into the pore structure of zeolite Y. These calculations suggest that the *N*-tosylaziridine formed from *trans*-methyl cinnamate can adopt a conformation which can easily be accommodated in the pores of zeolite Y. The aziridine derived from *trans*-stilbene can be constructed within the supercages but is indeed too bulky to diffuse through the connecting channels of the zeolite. We consider this to be a crucial piece of evidence since it shows that the aziridination reaction with the CuHY catalyst occurs within the intracrystalline space. Furthermore, this exciting result illustrates the potential for a heterogeneous catalyst to possess size-specificity to a precise degree. Such a property could be exploited by constructing zeolites with a range of pore sizes, and could also be developed to achieve regioselectivity in a reagent containing two or more double bonds.

Evans *et al.*[4] have shown that modification of the copper homogeneous catalysts using chiral bis(oxazoline) ligands induces enantioselectivity. We have examined modification of the CuHY catalyst with a range of oxazolines and have observed *N*-tosylaziridine products with up to 61% ee. The optimum conditions for racemic heterogeneous aziridination of alkene, in

Table 1 CuHY-catalysed aziridination of representative alkenes

Entry	Alkene[a]	Cu (mol%)	Yield (%)[b]
1	Styrene	25	90 (92)
2	Styrene[c]	25	87 (35)
3	Styrene	5	62
4	α-Methylstyrene	25	33
5	*p*-Chlorostyrene	25	76
6	*p*-Methylstyrene	25	66
7	Cyclohexene	25	50 (60)
8	Methyl cinnamate	25	84 (73)
9	*trans*-Stilbene	25	0 (52)
10	*trans*-Hex-2-ene	25	44

[a] Unless otherwise specified reaction conditions were: MeCN, 25 °C, styrene:PhI=NTs = 5:1. [b] Isolated yield of aziridine based on PhI=NTs. Values in parentheses indicate yields obtained from homogeneous reactions. [c] styrene:PhI=NTs = 1:1 molar ratio.

the absence of bis(oxazoline), was observed to be at 25 °C using MeCN as solvent. As expected, for the enantioselective reaction, the use of lower reaction temperatures was found to give the highest enantioselectivities. We have found that a temperature of −10 °C provides the highest enantioselectivity of 42% ee without compromising yield when using MeCN solvent and 2,2-bis{2-[(4R)-1-phenyl-1,3-oxazolinyl]}propane **1** as the chiral modifier. It would be reasonable to assume that one chiral modifier would be required per zeolite supercage to obtain maximum enantioselectivity. We have, however, found that very low levels of the expensive modifier can be used without resulting in decreases in yield or enantioselectivity. An

1 R^1 = Ph, R^2 = H, R^3 = Me
2 R^1 = Bu^t, R^2 = H, R^3 = Me
3 R^1 = Ph, R^2 = R^3 = H
4 R^1 = R^2 = Ph, R^3 = H

5
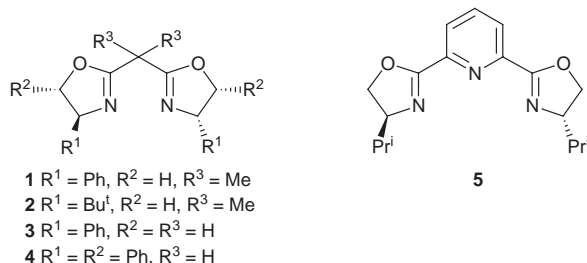
excess of **1** significantly reduces the yield of aziridine, due to pore-blocking, but both yield and enantioselectivity were maximized with a molar ratio of only PhI=NTs : **1** = 1 : 0.05. This corresponds to a molar ratio of Cu^{2+} : **1** of 2 : 1, indicating that not all the Cu^{2+} cations are modified in our experiments. In a subsequent experiment, an excess of **1** was stirred with CuHY (Cu^{2+} : **1** = 1 : 60) in MeCN. The zeolite was filtered and washed with acetonitrile, then used as the catalyst in fresh solvent and reactants. Both yield and enantioselectivity observed were identical to that obtained when **1** was added directly to the reaction mixture (molar ratio of PhI=NTs : **1** = 1 : 1.05). It is clear that very low levels of the modifier are required to obtain the enantioselectivities reported.

With the optimum conditions established for the enantioselective aziridination of styrene, other bis(oxazolines) and alkenes were screened with CuHY as the catalyst (Table 2). *trans*-β-Methylstyrene was found to show similar degrees of enantioselectivity to styrene. However, *trans*-methyl cinnamate gave a much higher result of 61% ee, albeit in poorer yield. The *tert*-butyl substituted bis(oxazoline) **2**, when used in MeCN, gave racemic aziridine. We suggest this is because MeCN, a ligand for Cu^{2+}, binds more strongly to the active sites than does

this bis(oxazoline). Support for this interpretation comes from our observation that, by carrying out the reaction using styrene as the solvent, enantioselectivity was restored, although both yield and ee were then lower than for the homogenous reaction. To provide further evidence that the reaction is proceeding within the supercages of the zeolite, reactions were carried out using a simple phenyl-substituted bis(oxazoline) **3**, which is known to fit inside the zeolite, and using a diphenyl substituted analogue **4**, which was considered as the result of molecular simulations to be too bulky to fit inside the zeolite pores. At 25 °C the smaller bis(oxazoline) **3** gave 10% ee for both the heterogeneous and homogeneous reactions. However, for the heterogeneously catalysed reaction, using CuHY as catalyst, the bulky diphenyl bis(oxazoline) **4** gave racemic product, despite inducing 15% ee for the equivalent homogeneously catalysed reaction. This is again evidence that the reaction is truly heterogeneous and is occurring within the pores of the zeolite. Further modification of the bis(oxazaline) has shown that the pyridine-bridged bis(oxazoline) **5** gives the highest enantioselectivity of 61% ee for the aziridination of styrene (Table 2). We consider that these initial results are encouraging and that careful optimization of the chiral ligand will result in further improvements in ee and yield.

The major advantage of the use of CuHY as a catalyst for this reaction is the ease with which it can be recovered from the reaction mixture by simple filtration if used in a batch reactor (alternatively it can be used in a continuous flow fixed bed reactor). We have carried out the heterogeneous asymmetric aziridination of styrene until completion, filtered and washed the zeolite then added fresh styrene, PhI=NTs and solvent, without further addition of bis(oxazoline) **1**, for several consecutive experiments and have found that both yield and enantioselectivity are retained. After each consecutive experiment a portion of CuHY was retained to determine the concentration of copper still present in the zeolite. For each experiment we found that only traces of the copper were removed from the catalyst ($< 0.5\%$ of the total Cu^{2+} is lost from the catalyst). Filtrate containing trace Cu^{2+} has been used in a reaction and was not found to catalyse aziridination. We have noted that adsorbed water can build up within the pores of the zeolite on continued use and this can lead to some loss of activity. However, full enantioselectivity and yield can be recovered if the catalyst is simply dried in air prior to reuse. We are therefore confident that this catalyst system can form the basis of a commercial heterogeneous catalyst for the aziridination of alkenes.

Table 2 Representative bis(oxazolines) for the enantioselective aziridination of alkenes

Oxazoline	Alkene^a	T/°C	Yield (%)^b	Ee (%)^{b,c}
1	*trans*-Methyl cinnamate	−10	8 (21)	61 (70)
1	*trans*-β-Methylstyrene	−10	74	36
1	Styrene	−10	82	44
1	Styrene	25	87	29
2	Styrene	−20	64	0
2	Styrene^d	−20	15 (89)	18 (63)
3	Styrene	25	78 (75)	10 (10)
4	Styrene	25	73 (74)	0 (15)
5	Styrene	−10	4	61

^{a} Unless otherwise specified, reaction conditions were: MeCN, alkene : PhI=NTs = 5 : 1. ^{b} Values in parentheses indicate yields obtained from homogeneous reactions. ^{c} Enantioselectivity determined by chiral HPLC. Absolute configurations of major products, determined by optical rotation, are (*S*) for *trans*-β-methylstyrene and *trans*-β-methyl cinnamate, (*R*) for styrene. ^{d} Styrene was used as solvent.

Notes and References

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