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Observation of the enhancement in enantioselectivity with conversion for the aziridination of styrene using copper bis(oxazoline) complexes†

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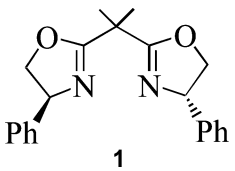
During the aziridination of styrene using copper bis(oxazoline) complexes the ee increases with conversion due to further reactions of the product.

The design of effective asymmetric catalysts remains important as chiral intermediates are crucial in the agrochemical and pharmaceutical industries.[1,2] Most success has been achieved with homogeneous catalysis. In recent years, we have studied the aziridination of alkenes using Cu–bis(oxazoline) complexes pioneered by Evans *et al*.[3] and we have shown that electrostatic immobilisation of the complex within zeolite HY can produce a heterogeneous catalyst that gives higher enantioselection than the corresponding homogeneous non-immobilised complex.[4] Most studies of asymmetric reactions report only the yields and ee at the conclusion of the reaction. In the aziridination reaction we have found that, surprisingly, the ee increases with conversion. We have found that this is due to interaction of the aziridine with sulfonamide, which is a breakdown product of the nitrene donor. Our findings show that the aziridine is not stable in the presence of the copper–bis(oxazoline) catalyst and, in this communication, we present our initial results.

During our work on the heterogeneous copper bis(oxazoline) **1** catalysed enantioselective aziridination of styrene we observed that the ee obtained increased with conversion. As this observation is difficult to rationalise using conventional models for the origin of enantioselectivity in catalytic reactions, we further investigated the effect in both the heterogeneous (CuHY) and homogeneous ($Cu(OTf)_2$) cases. Fig. 1 illustrates the typical magnitude of this effect which is also observed over a range of reaction conditions.[5,6] We have concentrated on the heterogeneous reaction as the reaction is slower and thus easier to study.



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There are two likely explanations for an increase in ee during the reaction, either the catalyst is being modified by the product, and thus the ee is enhanced in an autocatalytic manner (*i.e.* catalyst + product form a new catalyst which is more selective) or the initial product is being selectively converted between enantiomers. Addition of further reagents after the maximum ee has been achieved gives no change in ee and hence it seems likely that the enhancement with conversion is due to changes in the catalyst. CuHY is difficult to dry completely and to eliminate the possibility that water was implicated in the enhancement we ran control experiments in which small quantities of water were added at the end of the reactions and observed a small decrease in ee indicating that the involvement of water cannot account for this effect. To determine if the enhancement could be explained by reaction of first-formed aziridine with catalyst, two authentic samples of aziridine (*R*)-*N*-(*p*-tosylsulfonyl)-2-phenyl aziridine (76% ee) and (*R*)-*N*-(*p*-nosylsulfonyl)-2-phenyl aziridine (85% ee) were treated with bis(oxazoline)/CuHY under standard conditions with the addition of nitrene donors. In all cases (and in the $Cu(OTf)_2$ homogeneous case) a decrease in the amount of aziridine coupled to an increase in ee was observed (Scheme 1),[6] indicating that preferential consumption of the minor enantiomer could play a role in the enhancement observed. Crucially, this would appear to be a very minor role as these effects were small and the timescale (24 h) means that during the reaction

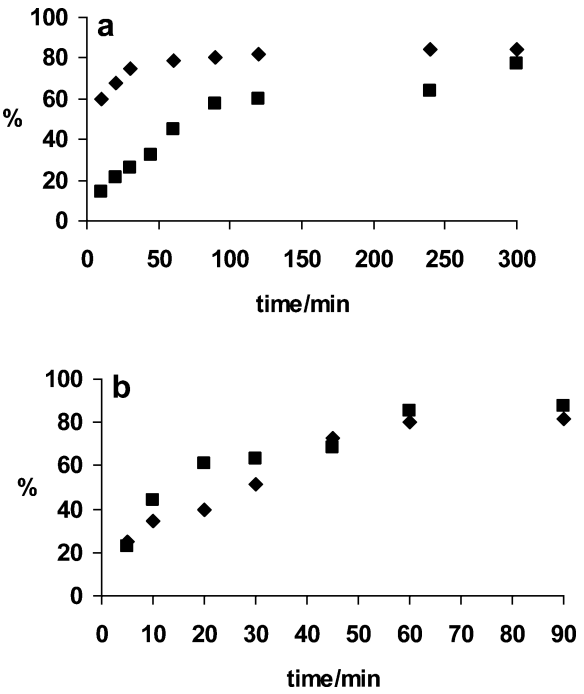
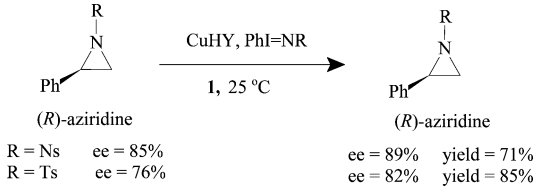


Fig. 1 Effect of reaction time on yield and ee of (*R*)-aziridine [styrene (1 mmol) reacted with CuHY (0.3 g) or $Cu(OTf)_2$ (0.015 g), nitrene donor (1.5 mmol) with (*R*,*R*)-bis(oxazoline) **1** in CH_3CN at 25 °C]. (a) CuHY with PhI=NNs; (b) $Cu(OTf)_2$ with PhI=NNs; ■ aziridine yield, ◆ ee.



Scheme 1

† Electronic supplementary information (ESI) available: further data. See http://www.rsc.org/suppdata/cc/b3/b309507j/

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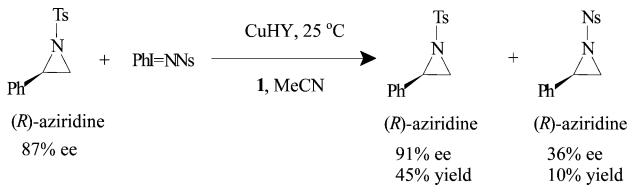
time (≤5 h) this effect could not explain the observed enhancement with conversion.

Significantly, however, when (*R*)-*N*-(*p*-tosylsulfonyl)-2-phenyl aziridine (84% ee) was reacted with PhI=NNs and bis(oxazoline) CuHY in addition to any decomposition of *N*-tosyl aziridine, a small amount (*ca*. 10%) of (*R*)-*N*-(*p*-nosylsulfonyl)-2-phenyl aziridine was recovered in a lower (36%) ee (Scheme 2). The entirely unexpected finding demonstrated by this crossover reaction, that under the reaction conditions product aziridine is continually reacting with nitrene donor, must bring a certain amount of question to conventional transition state models for the enantioselectivity of aziridination which consider only the approach of nitrenoid to styrene, and ignore further reactions of aziridines.

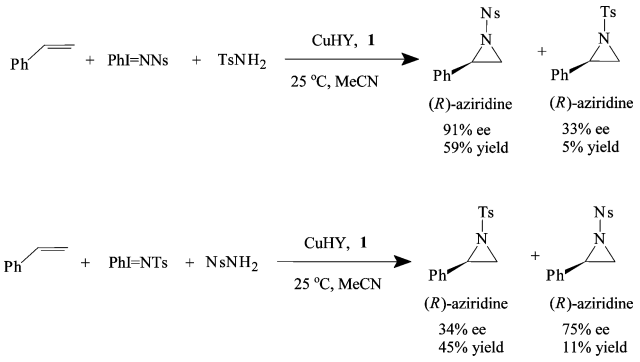
Additionally, experiments were carried out in which styrene was reacted with mixtures of nitrene donors and differently *N*-substituted sulfonamides (sulfonamides are an unavoidable by-product in these reactions) and both *N*-substituted aziridine products were formed, which as styrene and sulfonamide are unreactive, indicates that in the presence of the catalyst and nitrene donor, aziridine reacts with sulfonamide in a metathesis reaction to form crossover products (Scheme 3).[6] Control experiments showed that, as expected, the nitrene donors did not react with sulfonamide under these reaction conditions.

Finally, racemic aziridine reacts with nitrene donor and bis(oxazoline) CuHY to give a slight ee which at lower temperatures increases to 38%.[6] This deracemisation and the earlier ee enhancements are consistent with the proposal that nitrene donor and catalyst react with aziridine in a pseudo-equilibrium process to form aziridine of different ee and/or different *N*-substituent to the original.

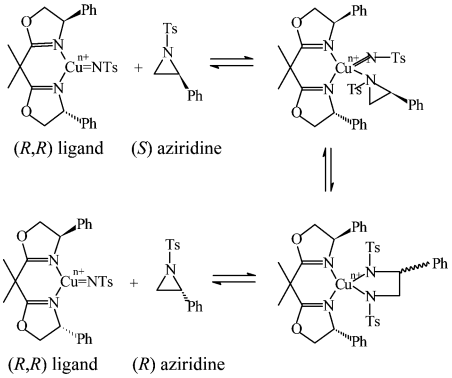
We propose that the interconversion occurs *via* the intermediacy of ring opened species, formed by reaction of the aziridine with a nitrogen nucleophile (derived from either nitrene donor or sulfonamide) mediated by aziridine *N*-coordination to a Cu^{2+} ion behaving as a Lewis acid, as recently demonstrated by Lin *et al*.[7] Little or no ring opened products



Scheme 2



Scheme 3



Scheme 4

were detected, however it seems likely that ring opened species are intermediate in the interconversion of enantiomers. This could be a 2-step SN1-type process which allows for loss of stereochemical integrity at the cation stage, or an SN2-type reaction in which case the loss of stereochemistry is dependent upon which sulfonamide fragment is eventually lost to reform the aziridine. The diamine intermediate may well exist as a chelate ring around the copper ion, in which case the formation of a 5-centred intermediate in the presence of the chiral bis(oxazoline) ligand (Scheme 4) may give improved control in the micropores of the zeolite catalyst, explaining why higher enantioselectivity can be observed with the heterogeneous system.[4]

In conclusion we have discovered a new reaction of aziridines with sulfonamides and nitrene donors which it appears plays an important role in the stereochemical outcome of the copper catalysed aziridination reaction *via* interconversion of aziridine enantiomers after the initial aziridination reaction has occurred.

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Notes and references

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5 $Cu(OTf)_2$, oxazoline **1** (2,2-bis[(4*R*)-4-phenyl-1,3-oxazoline-2-yl]), *p*-tosyl sulfonamide, *p*-nosyl sulfonamide and styrene were purchased from Aldrich. PhI=NTs, PhI=NNs and the CuHY catalyst were prepared as previously described.[4] In a typical reaction, styrene (0.101 g, 1.0 mmol), nitrene donor (1.5 mmol), CuHY (0.3 g) were stirred together in acetonitrile (2.5 ml) at 25 °C. The chiral bis(oxazoline) **1** (0.07 mmol, 98%) was added prior to the addition of the styrene and nitrene donor. Reaction times varied depending on the nitrene donor and were typically *ca.* 3 h for PhI=NTs and *ca.* 5 h for PhI=NNs, and the reaction was followed by dissolution of the nitrene donor and was considered complete once all the nitrene donor had dissolved. The reaction mixtures were then filtered through a plug of silica wool with ethyl acetate (50 ml) as eluent. Flash chromatography gave the aziridine as a white solid. Products were analysed by hplc and the ee was determined using chiral hplc on the isolated aziridine products.
6 See electronic supplementary information (ESI).
7 B. L. Lin, C. R. Clough and G. L. Hillhouse, *J. Am. Chem. Soc.*, 2002, **124**, 2890.