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Asymmetric cyclopropanation in ionic liquids: effect of anion and impurities

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Abstract—Cyclopropanation of styrene with ethyl diazoacetate catalysed by copper triflate and a bis(oxazoline) occurs with good yield and enantioselectivity in a variety of ionic liquids. The catalyst solution can be recycled four times with little drop in yield or selectivity. The purity of the ionic liquid has a marked effect on the yield and enantioselectivity.
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Ionic liquids have negligible vapour pressure and hence have attracted much study recently as replacements for organic solvents for synthetic chemistry as part of a strategy to reduce emissions of VOC's.[1] Ionic liquids may also give benefits in terms of increased selectivity and in separation and recycling of metal-containing catalysts when the system is biphasic.[2] The catalyst remains in the ionic liquid phase and in some cases can be reused several times with little reduction in activity. This approach has also been applied in asymmetric catalysis including epoxidation[3] and dihydroxylation[4] of alkenes, ring opening of epoxides,[5] allylic substitution[6] and particularly in hydrogenation of alkenes.[7]

A problem that can arise in the use of ionic liquids for immobilisation of transition metal based catalysts is that at low catalyst concentrations impurities in the ionic liquids, particularly halide ions, can have a significant effect by coordinating to the metal and hence blocking an active site. For example, the rate of rhodium catalysed biphasic hydrogenation of pent-1-ene in [BMIM][BF_4] (BMIM = 1-butyl-3-methylimidazolium) was significantly lower than in [BMIM][PF_6] due to the presence of chloride impurity in the [BMIM][BF_4] ionic liquid.[8] Chloride impurities in [BMIM][BF_4] also had a marked effect on the metal catalysed Michael addition of acetylacetone to methylvinyl ketone.[9]

Bis(oxazolines) in conjunction with various copper salts catalyse a wide range of reactions with good to excellent enantioselectivity.[10] Amongst these, the cyclopropanation of styrene was studied by Evans et al. who demonstrated that the catalytic activity and enantioselectivity was dependent on the nature of the anion associated with the copper.[11] Similar effects on activity and selectivity of changing the anion and the solvent have been observed by other workers.[12] The use of weakly coordinating anions was shown to be crucial in Diels–Alder catalysis with copper bis(oxazoline) complexes.[13]

Various strategies have been investigated for immobilisation and recycling of the copper oxazoline catalysts,[14] including covalent attachment to an organic polymer,[15,16] ion-pairing with an anionic support[15,17] and covalent attachment to silica.[18] During the course of our work the use of imidazolium based ionic liquids for immobilisation of bis(oxazoline) copper catalysts and their use in cyclopropanation of styrene has been reported and it was found that the nature of the cation and anion of the ionic liquid effected the performance of the catalysts.[19] However, our results differ from those published particularly in the case of ionic liquids containing the BF_4 anion. We report here the copper bis(oxazoline) catalysed asymmetric cyclopropanation of styrene in four different ionic liquids, attempts to reuse the catalyst, and a reinterpretation of some of the results described previously.

Evans et al. reported that cyclopropanation of styrene with ethyl diazoacetate in chloroform catalysed by the complex of bis(oxazoline) **1** with copper(I) triflate (Scheme 1) gave the *trans* and *cis* cyclopropanes in a

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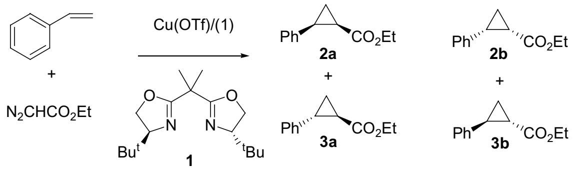

Scheme 1.

73:27 ratio and 99% and 97% ee, respectively.[11] Under our conditions the *trans*:*cis* selectivity remains the same, though the ee's, 89% and 96%, respectively, are slightly lower. The only variation to the literature conditions has been to add the ethyl diazoacetate to the styrene and catalyst at 10 °C instead of 0 °C before warming to 25 °C and to use a lower excess of styrene (1.5 equiv with respect to diazoacetate rather than 5 equiv). These changes were introduced to allow a direct comparison with the reactions carried out in ionic liquids. Styrene is not appreciably soluble in the ionic liquids, hence these reactions are biphasic and at 0 °C the viscosity of the ionic liquids makes magnetic stirring rather inefficient, however, much better mixing occurs at 10 °C. The catalyst solutions were prepared in chloroform before dissolution in the ionic liquid and then removal of the chloroform under vacuum. After the reaction the products were extracted from the ionic liquid with ether and filtered through silica. The yield and stereoselectivity were analysed by GC and the enantiomeric excess was determined by GC–MS after conversion to the (*R*)-1-phenylethylamides.[11]

The results of the cyclopropanation are shown in Table 1. As can be seen, the yields are generally similar in all the ionic liquids and in chloroform. The stereoselectivity and enantioselectivity are similar in all the ionic liquids and in chloroform, though the stereoselectivity is somewhat less in the NTf$_2$ liquid. A reduction in the stereoselectivity in [EMIM][NTf$_2$] (EMIM = 1-ethyl-3-methylimidazolium) was noted previously.[19] However, the yields and enantioselectivities are significantly higher than those (3–50% yield, 0–85% ee) observed previously[19] for the same reaction and catalyst[20] in [EMIM][BF$_4$], [EMIM][NTf$_2$] and [Oct$_3$NMe][NTf$_2$]. Notably in the previous study use of [EMIM][BF$_4$] led to very low yields and no enantioselectivity (see below). In that case the authors noted that when bis(oxazoline) copper complexes (chloride or triflate) were added to [EMIM][BF$_4$] the solution became a deep red colour and some solid precipitated. In our hands addition of [(Cu(*s,s*)^{t}Bu-box)OTf] to [BMIM][BF$_4$] gives a clear blue homogeneous solution as with all the other ionic liquids. Halide anions are expected to coordinate more strongly to copper than triflate and hence reduce or even stop catalytic activity. Similar adverse effects of halide impurity on catalysis in ionic liquids have been noted previously.[8,9] To investigate this possibility we examined the effect of added [BMIM]X (X = Cl, Br) on the catalysis. Addition of the catalyst to a solution of [BMIM][BF$_4$] with 5% [BMIM][Cl] added gave a homogeneous yellow-green solution, which was inactive as a cyclopropanation catalyst though it did lead to decomposition of the ethyl diazoacetate. If 5% [BMIM][Br] was used a deep red/brown solution was formed when the catalyst was added, this was also catalytically inactive for cyclopropanation. Thus, we suggest that the poor results observed previously for copper catalysed cyclopropanation in [EMIM][BF$_4$] are due to the presence of [EMIM][Br] impurity in the ionic liquid. The [EMIM][BF$_4$] used was made from [EMIM][Br] and NaBF$_4$ and filtered through Celite to remove the NaBr formed.[19] Seddon et al. have shown, at least for chloride salts that this procedure is inefficient at removing all the unreacted dialkylimidazolium halide.[21] We have extracted [BMIM][BF$_4$] with chilled water (5 °C), which gives much lower levels of halide impurity.

Another important issue with the use of ionic liquids is the possibility of recycling the catalyst solution. It was noted that using the less polar [BMIM][OTf] and [BMIM][NTf$_2$] liquids some leaching of the catalyst occurred in extraction of the products as judged by the colour transferred to the ether layer, there was also a faint blue spot on the baseline of the TLC plates used in purification. [BMIM][BF$_4$] and [BMIM][PF$_6$] showed minimal leaching and since the yields were better in the BF$_4$ liquid we chose that for experiments on recycling and reusing the catalyst.

To optimise the yield we wished to minimise the levels of diethyl maleate and fumarate formed by carbene dimerisation. This is often done by increasing the concentration of the styrene. However due to the limited solubility of styrene in the ionic liquids we chose to

Table 1. Cyclopropanation of styrene with ethyl diazoacetate catalysed by Cu(OTf)/**1**

Solvent	Yield (%)[a]	*trans*:*cis*	
		Selectivity (%)	Enantioselectivity (%)[b]
CHCl$_3$	59	73:27	89:96
BMIM[OTf]	53	76:24	97:95
BMIM[PF$_6$]	47	75:25	95:91
BMIM[NTf$_2$]	45	63:37	94:93
BMIM[BF$_4$]	61	75:25	95:89
BMIM[BF$_4$]/[Cl][c]	<1	—	—
BMIM[BF$_4$]/[Br][c]	<1	—	—

[a] Detemined by GC using decane as an internal standard.

[b] Determined by GC–MS after conversion to the 1-phenylethylamide; **3a** was the major *trans* enantiomer and **2a** the major *cis* enantiomer based on retention times of the 1-phenylethylamides.

[c] Contains 5% [BMIM][X] (X = Cl, Br).

reduce the rate of addition of the ethyl diazoacetate (5 h) and to keep the reaction mixture at 10 °C throughout this period and lower the concentration of the catalyst by using twice the amount of ionic liquid. Using these conditions gave increased yields of products. The results of performing the reaction eight times in the same batch of ionic liquid are displayed in Table 2. As can be seen for the first four runs the yield and enantioselectivity are comparable. After the fourth run, the yield drops with a slight reduction in selectivity though the enantioselectivity generally remains high.

Table 2. Repeated cyclopropanation reactions of styrene with ethyl diazoacetate catalysed by Cu(OTf)/(**1**) in [BMIM][BF_4][a]

Run	Yield (%)	*trans*:*cis*	
		Selectivity (%)	Enantioselectivity (%)
1	88	75:25	97:94
2	88	75:25	95:93
3	90	73:27	93:91
4	85	72:28	98:98
5	69	65:35	76:77
6	71	66:34	81:78
7	55	69:31	76:72
8	51	69:31	77:78

[a] Yield, stereoselectivity and enantioselectivity measured as for Table 1.

In conclusion we have shown that copper catalysed cyclopropanation can be carried out in ionic liquids with high yield and enantioselectivity. The catalyst solution can be recycled at least four times before there is a significant drop in yield. The purity of the ionic liquids has a marked effect on the catalysis. Particular care should be taken in the purification of hydrophilic ionic liquids prepared by metathetical anion exchange to ensure that all the dialkyl imidazolium halide is removed.

1. Experimental

Ethyl diazoacetate and styrene were used as supplied. The ionic liquids were synthesised by anion exchange from [BMIM][Cl][22] according to literature procedures.[23] [BMIM][BF_4] was washed with chilled water to remove [BMIM][Cl] impurities,[21] and all the ionic liquids were dried under vacuum at 60 °C prior to use. Thin layer chromatography was carried out on silica gel plates Merck 60 F254 and flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm). GC was performed on a Perkin–Elmer XL gas chromatograph, using BP10 (SGE) capillary columns (30 m × 0.25 mm) with hydrogen as carrier. GC–MS analysis was performed on a Perkin–Elmer TurboMass GC–MS autosystem using a PE5 column (30 m × 0.25 mm).

The ionic liquid catalyst solutions were prepared from a stock solution of the copper triflate bis(oxazoline). The stock solution was prepared by stirring a mixture of $\{Cu(OTf)\}_2$·toluene, (0.0259 g, 0.07 mmol) and 2,2′-isopropylidenebis-[(4*S*)-4-*tert*-butyl-2-oxazoline] (0.0497 g 0.168 mmol) in chloroform (1.4 mL) for 3 h after which time the solution was filtered through glass wool. A measured portion (200 μL) of this solution was added to the ionic liquid (2 mL) and the bluish-green homogeneous solution was stirred for 30 min after which time the chloroform was removed under vacuum. Styrene (344 μL, 3 mmol) was added and the resultant biphasic system was stirred for 10 min before addition of the ethyl diazoacetate (210 μL, 2 mmol) over 2 h using a syringe pump. The reaction mixtures were allowed to equilibrate to 25 °C over 4 h and stirred for a further 10 h. The product was extracted using diethyl ether (6 × 3 mL), the combined extracts were filtered over silica and concentrated in vacuo to a pale yellow oil. The yields and *trans*:*cis* selectivity were determined at this stage by GC using decane as an internal standard. The esters were converted to the *R*-1-phenylethylamides by the literature method,[11] the amide fraction was separated by preparative TLC and this fraction was used to determine the enantioselectivity.

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