ChemComm

Cr(salen) catalysed asymmetric ring opening reactions of epoxides in room temperature ionic liquids

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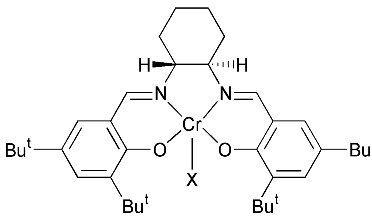
Received (in Cambridge, UK) 12th June 2000, Accepted 31st July 2000
First published as an Advance Article on the web 25th August 2000

Cr(salen) catalysed asymmetric ring opening reactions of epoxides with $TMSN_3$ proceed readily in the room temperature ionic liquid 1-butyl-3-methylimidazolium salts ([bmim][X]) with easy catalyst/solvent recycling.

Optically pure β-amino alcohols are important structural elements in many biologically active molecules as well as the starting point in the design of many chiral ligands. Among many other methods, asymmetric ring opening reactions (ARO)[1] of epoxides with $TMSN_3$ catalysed by Cr(salen) complex **1** has been recognised as an attractive approach to the synthesis of optically pure β-amino alcohols.[2] Especially, the Cr(salen) catalyst exhibits indefinite stability under catalytic conditions which allows for its repeated recycling. Jacobsen reported that this reaction can be run without solvents and the catalyst can be recycled a number of times without loss of activity and enantioselectivity.[2a] However, this catalyst recycling procedure involves the potentially hazardous distillation of the neat liquid azides, which may prove a limitation for large scale applications.

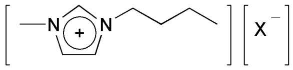


(*R*,*R*)-**1a**; X = Cl
(*R*,*R*)-**1b**; X = N_3

For catalyst recycling,[3] homogeneous chiral catalysts can be immobilised either by anchoring the catalyst on a solid support[3a] or by use of a two-phase system.[3b] All of these approaches are interesting but usually require additional modification of the catalyst. Moreover, such approaches frequently lead to partial loss of activity and/or enantioselectivity. Recently, a new approach has been adopted for catalyst separation and recycling in a few types of catalytic reaction involving the use of ionic liquids,[4] *i.e.* a salt mixture with a melting point below ambient temperature. Air and moisture stable room temperature ionic liquids consisting of 1,3-dialkylimidazolium cations and their counter anions, in particular, have attracted growing interest in the last few years.[5] In these solvents, catalysts having polar or ionic character can be immobilised and thus the ionic solutions containing the catalyst can be easily separated from reagents and products. For example, we reported recently a practical method for recycling a chiral Mn(salen) epoxidation catalyst by using this type of ionic liquid.[5g]

Herein we report a new and highly practical recycling procedure of Cr(salen) catalyst involving the use of air and moisture stable ionic liquids based on 1-butyl-3-methylimidazolium [bmim] salts **2a–d**.[6]

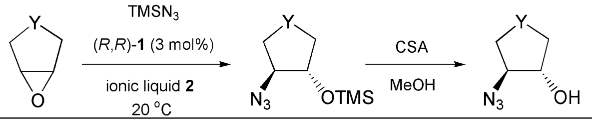
To compare the effect of ionic liquids on both reactivity and enantioselectivity, we first examined the asymmetric ring opening reactions of cyclopentene oxide with $TMSN_3$ which were carried out in the presence of 3 mol% of (*R*,*R*)-**1a** in four different ionic liquids, [bmim][X] **2** {X = PF_6 (**2a**),[6a] SbF_6 (**2b**),[6b] BF_4 (**2c**)[6a] and OTf (**2d**)[6c]} at 20 °C. After completion of the reaction, hexane (15 mL in 2 mmol scale experiment) was added and the reaction mixture stirred for 10 min. The hexane phase (upper phase) was then separated from the ionic liquid phase containing the Cr(salen) complex (*R*,*R*)-**1b**[7] by simple decantation and analysed by chiral GC to determine ee values.† After removing the hexane under reduced pressure, methanol and camphorsulfonic acid were added to the residue, and the mixture was allowed to stir at room temperature for 30 min. The methanol was evaporated off and the residue was purified by column chromatography on silica gel with ethyl acetate–hexane to afford the pure azido alcohol.



[bmim][X] (**2**); X = PF_6 (**2a**)
SbF_6 (**2b**)
BF_4 (**2c**)
OTf (**2d**)

As shown in Table 1 (entries 1–4), both reactivity and enantioselectivity were strongly influenced by the nature of the anion [X]. When the hydrophobic ionic liquid [bmim][PF_6] **2a** was used, the desired azido silyl ether was obtained with the same degree of yield and enantiomeric excess (94% ee) as those[2a] obtained under homogeneous conditions reported by Jacobsen *et al.* (Table 1, entry 1). Using the other hydrophobic ionic liquid [bmim][SbF_6] (**2b**), the reaction was run with similar conversion, although in slightly lower ee (Table 1, entry 2). In sharp contrast to these results, in the hydrophilic ionic liquids, [bmim][BF_4] (**2c**) or [bmim][OTf] (**2d**), the reaction hardly occurred (Table 1, entries 3 and 4). In the case of using the BF_4 salt (**2c**), only a 5% yield of product was obtained in nearly racemic form (3% ee). More dramatically, in the OTf salt **2d** the reaction did not proceed at all. Although this counter ion

Table 1 Enantioselective ring opening of *meso* epoxides in ionic liquids **2a–d**[a]



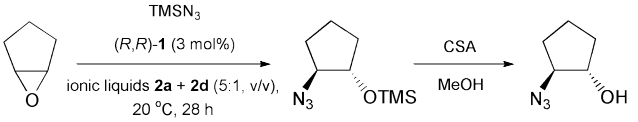
Entry	Substrate (Y)	Ionic liquid **2**	*t*/h	Yield[b] (%)	% ee[c]
1	CH_2	**a**	28	76	94
2	CH_2	**b**	28	75	87
3	CH_2	**c**	28	5	3
4	CH_2	**d**	28	trace	—
5	$(CH_2)_2$	**a**	18	86	85
6	O	**a**	18	74	97

[a] All reactions were run on 2 mmol scale of epoxide at 20 °C using 3 mol% of (*R*,*R*)-**1** in 1 mL of ionic liquid **2**. [b] Isolated yield of azido alcohol. [c] All ee's correspond to those of azido silyl ether and were determined by chiral GC: see footnote†.

DOI: 10.1039/b004645k

effect can not be explained easily, it is apparent that the different hydrophobic character of **2** depending on the anion plays a decisive role in this reaction. Thus, we examined the ARO of other epoxides in the hydrophobic ionic liquid **2a**. All the yields and enantiomeric excesses were quite comparable to those[2a] obtained under homogeneous conditions (Table 1, entries 5 and 6). Although, as mentioned above, excellent results were achieved using the ionic liquid **2a**, the catalyst existed in a suspended form in the ionic liquid **2a** when hexane was added to the reaction mixture after reaction. On the other hand, although the reaction hardly occurred in the ionic liquids **2c** and **2d**, the catalyst was immobilised more efficiently in these solvents after reaction than in **2a**, and thus formed a clear red–brown solution phase, which can make its separation from the hexane phase more easy. We expected that a system combining the hydrophobic and hydrophilic ionic liquids might provide beneficial effects on the catalyst immobilisation. As we expected, in the mixture of **2a** and **2d** with a volume ratio of 5:1, the reaction proceeded with comparable yield and enantiomeric excess to those[2a] obtained under homogeneous conditions (Table 2, entry 1). Moreover, the catalyst could be much better immobilised in this mixture after reaction than in the ionic liquid **2a** alone, and thus the ionic liquid phase containing the catalyst was almost quantitatively recovered from the hexane phase.[8] The recovered ionic liquid phase containing the catalyst was reused several times without any loss of activity and enantioselectivity even after the fifth use (Table 2).

Table 2 Enantioselective ring opening of cyclopentene oxide with catalyst recycling using a mixture of ionic liquids **2a** and **2d**[a]



Entry	Recycle no.	Yield (%)	%ee
1	0	68	94
2	1	72	93
3	2	85	93
4	3	75	94
5	4	76	93

[a] All reactions were run on 2 mmol of epoxide at 20 °C using 3 mol% of (*R*,*R*)-**1** in 1.2 mL of the ionic liquid mixture (1 mL of **2a** and 0.2 mL of **2d**).

In summary, we have developed a new and highly practical recycling procedure of Cr(salen) catalyst by using the air and moisture stable ionic liquids **2**. This procedure does not include hazardous work-up stages such as distillation of the azide product, and moreover, provides not only simple recycling of catalyst but also the additional advantage that the catalyst can be used without any modification of the structure. The catalytic activity and enantioselectivity were strongly dependent on the nature of the anion [X] in the ionic liquids [bmim][X] **2**. Detailed studies for the optimisation of this process and the extension of this methodology to other ARO's are currently in progress.

This research was supported by a grant from the Korea Institute of Science and Technology.

Notes and references

† The ee values of products were determined by chiral GC: for 1-azido-2-(trimethylsiloxy)cyclopentane: Chrompak Chiralsil-dex CB, 95 °C isothermal, 25.1 min (1*R*,2*R*), 27.3 min (1*S*,2*S*). For 1-azido-2-(trimethylsiloxy)-cyclohexane; Chrompak Chiralsil-dex CB, 110 °C isothermal, 24.3 min (1*R*,2*R*), 27.1 min (1*S*,2*S*). For 3-azido-4-(trimethylsiloxy)tetrahydrofuran; Chrompak Chiralsil-dex CB, 75 °C for 10 min, then 2 °C min^{-1}, 34.4 min (3*R*,4*S*), 35.2 min (3*S*,4*R*).

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6 Preparation of ionic liquids: (*a*) For **2a** and **2c**: P. A. Z. Suarez, J. E. L. Dullius, S. Einloft, R. F. de Souza and J. Dupont, *Polyhedron*, 1996, **15**, 1217; (*b*) The synthesis of **2b** was similar to that of **2a** and **2c** with the exception that $NaSbF_6$ was used in place of $NaPF_6$ or $NaBF_4$; (*c*) For **2d**: P. Bonhôte, A.-P. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Grätzel, *Inorg. Chem.*, 1996, **35**, 1168. All ionic liquids used in this paper were pre-dried under reduced pressure (0.5 mmHg) at 50 °C for 24 h.

7 The recovered catalyst displayed a strong IR absorbance at 2058 cm^{-1}; see ref. 2(*a*).

8 The Cr(salen) catalyst **1** is slightly soluble in hexane. However, in this case, the amount of catalyst dissolved in the hexane phase is negligible.