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The Effect of Catalyst Loading and Donor Ligands in the Mn(III) Salen Catalysed Chiral Epoxidation of Chromenes: Synthesis of BRL 55834.

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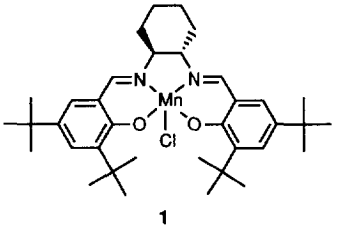
Abstract: In the absence of a donor ligand both the reaction rate and product e.e. of the manganese (III) salen catalysed epoxidation of 2,2-dimethyl-6-pentafluoroethylchromene were dependent on the catalyst loading. Isoquinoline N-oxide was the most effective donor ligand, affording highly efficient epoxidations with catalyst loadings of 0.1-0.4 mol%. These findings allowed the realisation of a concise, inexpensive synthesis of BRL 55834. Copyright © 1996 Elsevier Science Ltd

The discovery of chiral manganese (III) salen complexes as catalysts has for the first time allowed a convenient and inexpensive method for the efficient asymmetric epoxidation of unfunctionalised olefins.[1] Observed enantioselectivities are particularly high with *cis* or cyclic olefins, and chromenes are ideal substrates.[2] The *tert*-butyl substituted catalyst **1** is one of the most effective of those studied, and both enantiomers are commercially available.[3]

In order to effect an improved synthesis of the novel airways selective potassium channel activator **BRL 55834**,[4] we envisaged a chiral epoxidation of the pentafluoroethylchromene **3**, (prepared from the known iodochromene **2**, Scheme 1).[5] The most convenient method reported involves stirring a two-phase system of two equivalents of aqueous sodium hypochlorite buffered to pH 11.3 with a dichloromethane solution of the substrate and (*S,S*) catalyst **1**,[1b,d,3] normal catalyst loadings are 2-6.5 mol%.[1b,d,2,6] By following the stated conditions[1b] (catalyst loading 2 mol%) this reaction proceeded smoothly, and a 75% yield of the pure desired enantiomer **4** was obtained after recrystallisation from hexane. Chiral hplc analysis of the reaction mixture indicated that the crude product had an e.e. of 93%. The reaction appeared clean by hplc,[7] and the main function of the recrystallisation was to remove the unwanted enantiomer. We therefore expected that the yield could be optimised by adjusting the reaction conditions to allow the maximum product e.e.



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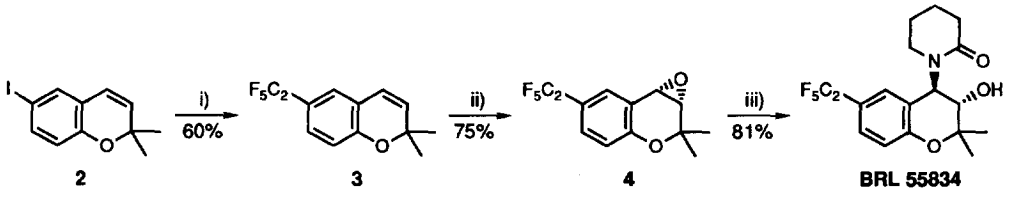


Reagents: i) $C_2F_5CO_2Na$, CuI, DMF, 140°C; ii) NaOCl, MDC, **1**; iii) 2-piperidone, KO^tBu, ^tBuOH

Scheme 1

We then undertook a series of experiments involving the epoxidation of **3** to compare the effect of different catalyst **1** loadings between 0.1 and 8 mol% on the reaction rate and product **4** e.e. Reactions were run at ambient temperature (22°C), and aliquots removed to check the progress of the reaction by hplc. On completion of the reaction, the catalyst degradation materials were removed by filtration through a silica pad, and the e.e. of the crude product determined by chiral hplc.

In practice, both the reaction rate and the product e.e. were dependent on the catalyst loading. Reactions were essentially complete after 30 minutes at 8 mol% to 24 hours at 0.75 mol%, and had progressed no further than 69% in 90 hours with 0.1 mol% catalyst loading. The product e.e. showed a range from 84% for 0.1 mol% to 97% for 8 mol%. Little improvement in product e.e. was seen above 2 mol% catalyst loading, but below 1 mol% both e.e. and reaction rate deteriorated rapidly, (Figures 1 and 2).

The dependence of product e.e. on catalyst loading is well known in the Sharpless epoxidation of allylic alcohols, but has not been reported for this system.[8] These findings are consistent with the observed degradation of the catalyst during the reaction, leading with low initial catalyst concentration, to its expiry, thereby preventing completion of the reaction. Examination of the product e.e. whilst reactions were partially complete showed a shallow decline with time, suggesting that there is an achiral or less enantioselective 'leakage' pathway, possibly catalysed by a catalyst breakdown material, which is operative.

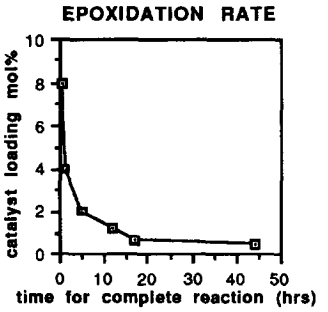


Figure 1

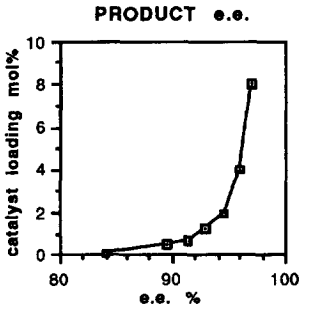


Figure 2

Epoxidation of pentafluoroethylchromene 3 using NaOCl and Mn(III) salen catalyst 1.

Having established an acceptable catalyst loading for this reaction, we sought to determine the effect of adding donor ligands.[9] For this study a catalyst loading of 1 mol% and 1 eq. donor ligand were initially selected. All the donor ligands examined effected a small improvement in the product e.e., but only pyridine N-oxide (PyNO), 4-picoline N-oxide (PicNO), 4-phenylpyridine N-oxide (PPyNO), quinoline N-oxide (QNO) and isoquinoline N-oxide (IQNO) showed an improvement in reaction rate. Of these we found that PyNO and PicNO showed very similar properties. PPyNO, QNO and IQNO gave much faster reactions, but that mediated by QNO failed to proceed to completion. PPyNO and IQNO were selected for further evaluation, and the results are shown in Table 1.

Although the addition of either PPyNO or IQNO effected a highly significant increase in the rate of reaction, halving the catalyst loading and donor ligand concentration enabled a clear difference between the effectiveness of the two to be ascertained, favouring IQNO. Using IQNO, an efficient epoxidation of **3** was possible using as little as 0.1 mol% of the catalyst **1**. In addition, IQNO unlike PPyNO could be removed from the dichloromethane product solutions by washing with water, [experimentally determined $\log P_{(\text{dichloromethane/water})}$ IQNO = 0.29, PPyNO = 1.00].

In contrast to the reactions run in the absence of donor ligand, in the presence of IQNO there was no relationship between the catalyst loading and the enantioselectivity, indeed this parameter was remarkably constant for the range of catalyst loadings examined. This finding is in line with the proposal that catalyst lifetime is extended by the aromatic N-oxide binding to the Mn(III) complex, and thereby preventing irreversible reactions with substrate or epoxide product.[9c]

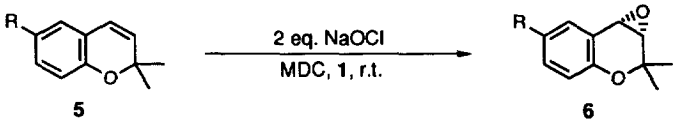
Simple work up of a reaction using 0.2 mol% catalyst and 0.1 eq. IQNO by filtration, twice washing with water, solvent evaporation and crystallisation of the residue from hexane (3 vols.) afforded pure **4** in a yield of 84%.

Table 1. Effect of donor ligands on the epoxidation of **3**.

1 loading mol%	Donor Ligand		e.e. %	Time for completion[a]
1.0	none		90	12 h.
1.0	DMSO	1.0 eq	95	63% in 7 h.
1.0	2-MeImid	1.0 eq	n.d.	6% in 8 h.
1.0	PyNO	1.0 eq	94	2.5 h.
1.0	PicNO	1.0 eq	94	2 h.
1.0	QNO	1.0 eq	93	96% in 10 min.
1.0	PPyNO	1.0 eq	93	<10 min.
1.0	IQNO	1.0 eq	94	<10 min.
0.5	PPyNO	0.5 eq	92	30 min.
0.5	IQNO	0.5 eq	93	<10 min.
0.2	IQNO	0.2 eq	94	30 min.
0.2	IQNO	0.1 eq	95	1 h.
0.1	IQNO	0.2 eq	94	3 h.
0.1	IQNO	0.1 eq	94	87% in 2 h.

a) Where incomplete, figures are corrected hplc conversions.

The epoxidation of a number of other 6-substituted chromenes was examined in the presence of 0.1 equivalents of IQNO, using the minimum catalyst loading allowing complete reaction within a reasonable time, (Scheme 2). For comparison, the same reactions were run in the absence of donor ligand, these results are shown in Table 2. It is noticeable that in the absence of donor ligand only the epoxidation of 6-nitro chromene proceeded to completion, and the enantioselectivity of these reactions was consistently inferior to those conducted in the presence of IQNO.



5 **6**

Scheme 2

Table 2. Effect of addition of IQNO on the epoxidation of chromenes **5.**

	No donor ligand			0.1 eq. IQNO		
R	Catalyst loading	e.e %	Extent of reaction[a]	Catalyst loading	e.e. %	Time for completion
H	0.1 mol%	80	77%	0.1 mol%	93	1 h.
I	0.1 mol%	81	89%	0.1 mol%	94	1 h.
Br	0.1 mol%	83	80%	0.1 mol%	92	2 h.
$COCH_3$	0.2 mol%	90	67%	0.2 mol%	94	1.5 h.
CN	0.2 mol%	80	71%	0.2 mol%	94	4 h.
NO_2	0.4 mol%	91	100%	0.4 mol%	93	1 h.

a) After 18 hours. Corrected hplc conversion.

In conclusion, isoquinoline N-oxide is an effective donor ligand for the Mn (III) salen catalysed asymmetric epoxidation of chromenes. The low concentration of donor ligand and similarly low catalyst loading required for efficient reaction makes this a particularly clean and inexpensive method, which should be applicable to a much wider range of substrates.

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