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The first asymmetric ring-expansion carbonylation of *meso*-epoxides†

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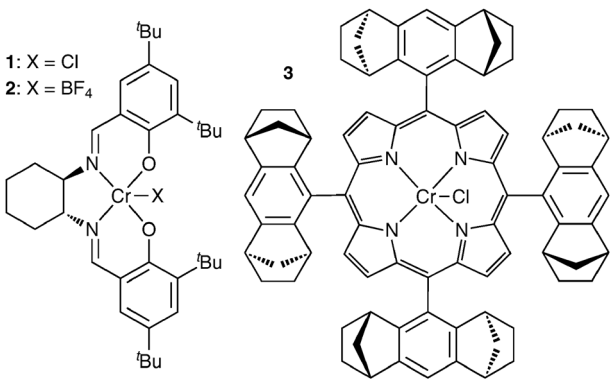
The first asymmetric ring-expansion carbonylation of *meso*-epoxides to β-lactones is reported. Two structurally diverse chiral Cr(III) chloro complexes in conjunction with $Co_2(CO)_8$ were shown to be competent catalytic systems for this transformation, displaying significant levels of asymmetric induction of up to 56% ee.

β-Lactones represent an important class of biologically active, naturally occurring compounds with broad utility in organic synthesis and as precursors for polymeric materials.[1] The first direct enantioselective synthesis of β-lactones was described by Wynberg and Staring employing a cinchona alkaloid catalysed asymmetric intermolecular [2 + 2] cycloaddition between ketene and activated aldehydes.[2] Over the past 30 years, this pioneering study inspired intensive research into this reaction resulting in various innovative modifications and ever more widening substrate scope. At present, the chiral Lewis base (LB*),[3] chiral Lewis acid[4] (LA*) or cooperative LB*–LA[5] catalysed intermolecular [2 + 2] cycloaddition between ketenes (mostly generated *in situ*) and carbonyl compounds delivers β-lactones with various substitution patterns in high enantio- and diastereoselectivities.[6] An elegant intramolecular variant of this reaction has also been developed leading to bi- and tricyclic β-lactones in high enantioselectivities.[7]

The ring-expansion carbonylation of epoxides to β-lactones is an attractive alternative to the above strategy as epoxides are more readily available than ketenes.[8] However, with the exception of two reports on the carbonylative asymmetric kinetic resolution of *trans*-2-butene oxide by Coates *et al.*[9] and propylene oxide by Bildstein *et al.*,[10] the *asymmetric* carbonylation of epoxides remains unexplored. Surprisingly, to the best of our knowledge, there has been no report on the asymmetric carbonylation of *meso*-epoxides in spite of the clear synthetic benefits of such a transformation.

We recently reported an efficient catalytic system for the carbonylation of epoxides comprised of commercially available (TPP)CrCl (TPP = tetraphenylporphyrinato) and $Co_2(CO)_8$.[11] This offers a distinct practical advantage over the previously reported seminal systems of Coates *et al.*[8c–h] With this study as our basis, and taking into account that Cr-derived systems are the most active,[8d] we sought to explore a stereoselective variant of this transformation employing chiral Cr(III) chloro complexes, and disclose herein our preliminary investigations.

Chiral Cr(III) chloro complexes **1** and **3** were chosen for evaluation in the asymmetric carbonylation of *meso*-epoxides. Our choice of the former was guided by the fact that Jacobsen's catalyst, (*R*,*R*)-(salen)CrCl **1**, and related Schiff base catalysts have been shown to induce high levels of stereocontrol in the asymmetric ring-opening of *meso*-epoxides.[12] The D_4-symmetric Cr(III) chloro complex **3** derived from Halterman's porphyrin,[13] which has been shown to induce high levels of stereocontrol in the asymmetric hetero Diels–Alder reaction,[14] was chosen as a chiral analogue of (TPP)CrCl.[15]



2,3-Benzyloxymethyl ethylene oxide was selected as the test substrate as the enantiomeric excess of the resulting β-lactone product could be determined directly by chiral HPLC analysis. For the initial experiment, 5.0 mol% of **1** and 5.0 mol% of $Co_2(CO)_8$ were used as co-catalysts in THF under our previously optimised conditions (500 psi of CO, 70 °C, 16 h).[11] We were pleased to find that this catalytic system proved active delivering the *trans*-β-lactone product in 65% conversion and in 54% isolated yield. Moreover, chiral HPLC analysis indicated that this desymmetrative carbonylation had occurred with 12% enantiomeric excess (Table 1, entry 1).

Encouraged by this result, we embarked on a screen of the reaction parameters. Switching to DME as the solvent gave comparable conversion and an increased ee of 19% (Table 1, entry 2). No reaction occurred when toluene or acetonitrile was used as the solvent and DME was adopted as the solvent of choice for all subsequent reactions. To investigate if reducing

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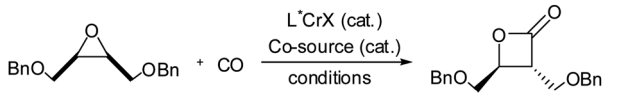
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data including HPLC traces, as well as the crystal structure of the cyclooctene derived β-hydroxy benzylamide. CCDC 895104. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc35596e

Table 1 Preliminary assessment of L*CrX **1–3** in the asymmetric ring-expansion carbonylation[a]



Entry	L*CrX (cat.)	Co-source (cat.)	Solv.	Temp/ °C	Time/ h	Conv[b] (%)	ee[c] (%)
1	**1**	$Co_2(CO)_8$	THF	70	16	65 (54)	12
2	**1**	$Co_2(CO)_8$	DME	70	16	62 (49)	19
3	**1**	$Co_2(CO)_8$	DME	45	48	41 (33)	12
4	**1**	$Co_2(CO)_8$	DME	rt	16	12	nd
5	**1**	$Na[Co(CO)_4]$	DME	70	16	23 (15)	9
6	**2**	$Co_2(CO)_8$	DME	70	16	Trace	nd
7	**2**	$Na[Co(CO)_4]$	DME	70	48	84 (56)	15
8	**3**[d]	$Co_2(CO)_8$[d]	DME	70	16	62 (56)	13

[a] Reaction conditions: epoxide (1.0 mmol), solvent (1.5 mL), CO (500 psi), L*CrX (5.0 mol%), Co-source (5.0 mol%). [b] Determined by ^{1}H NMR spectroscopy of the crude material; yield of isolated β-lactone is given in parentheses. [c] Determined by chiral HPLC analysis. [d] **3** (0.5 mol%), $Co_2(CO)_8$ (0.75 mol%).

the reaction temperature had a beneficial effect on the enantioselectivity, we conducted the carbonylation at 45 °C and at room temperature and found a decrease in both conversion and enantioselectivity (Table 1, entries 3 and 4).

In an attempt to explore if an *in situ* generated catalyst from **1** and $Na[Co(CO)_4]$ could deliver better results, equimolar amounts of **1** and $Na[Co(CO)_4]$ were subjected to the reaction conditions. In this case, a low conversion and a lower ee of 9% were observed (Table 1, entry 5).

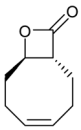
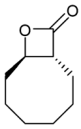
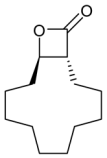
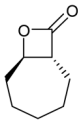
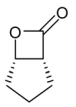
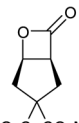
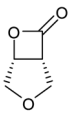
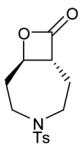
In order to investigate if an analogous of complex **1** with a weakly coordinating counterion would deliver higher enantioselectivities, [(*R*,*R*)-(salen)Cr]BF_4 **2** was synthesised and subjected to the reaction conditions.[16] Conducting the reaction with $Co_2(CO)_8$ as the cobalt source gave only traces of the product lactone, clearly indicating that the chloro ligand in **1** is necessary for the disproportionation of $Co_2(CO)_8$.[17] However, the **2**–$Na[Co(CO)_4]$ combination proved active affording the product in good conversion after 48 h and in comparable enantioselectivity (Table 1, entry 7 *vs.* entry 2).

The catalyst generated from 0.5 mol% of the chiral [(+)-porphyrin]CrCl **3** and 0.75 mol% of $Co_2(CO)_8$ showed a similar high activity to that generated from equimolar amounts of (TPP)CrCl and $Co_2(CO)_8$ delivering a 62% conversion to the product lactone with an ee of 13% (Table 1, entry 8).

Based on these results, we decided to evaluate the performance of catalysts generated from both, the **1**–$Co_2(CO)_8$ and the **3**–$Co_2(CO)_8$ systems for substrate screening according to reaction conditions in entries 2 and 8 of Table 1. Bicyclic epoxides that readily underwent ring-expansion carbonylation were chosen as substrates.[11]‡

A good conversion with both catalytic systems was obtained with cyclooctene oxide as the substrate, however with a low ee of the lactone product (Table 2, entries 1 and 2). Higher ee's of 11% and 6% were obtained with cyclooctane oxide as the substrate using complexes **1** and **3**, respectively (Table 2, entries 3 and 4). The enantiomeric excess remained low at 13 and 11% when moving to the 12-membered ring derived epoxide (Table 2, entries 5 and 6). A somewhat comparable

Table 2 L*CrCl–$Co_2(CO)_8$-catalysed asymmetric ring-expansion carbonylation of *meso*-epoxides[a]

Entry	L*CrCl (mol %)	$Co_2(CO)_8$ (mol %)	β-Lactone	Conv.[b] (%)	Yield[c] (%)	ee[d] (%)
1	**1** (5.0)	5.0		86	82	+6
2	**3** (0.5)	0.75		≥ 98	85	+2
3	**1** (5.0)	5.0		≥ 98	83	+11
4	**3** (0.5)	0.75		≥ 98	94	−6
5	**1** (5.0)	5.0		≥ 98	86	+13
6	**3** (0.5)	0.75		≥ 98	71	+11
7	**1** (5.0)	5.0		≥ 98	91	−4
8	**3** (0.5)	0.75		≥ 98	81	−16
9	**1** (5.0)	5.0		≥ 98	89	−40
10	**3** (0.5)	0.75	(1*S*,2*R*)[e]	≥ 98	83	−33
11	**1** (5.0)	5.0		≥ 98	78	+45
12	**3** (2.0)	3.0	MeO_2C CO_2Me (1*R*,2*S*)[f]	≥ 98	83	+41
13	**1** (5.0)	5.0		≥ 98	93	−56
14	**3** (0.5)	0.75	(1*R*,2*S*)[f]	≥ 98	86	−33
15	**1** (5.0)	5.0		54	47	+31[g]
16	**3** (2.0)	3.0	N Ts	75	56	−31[g]

[a] Reaction conditions: epoxide (1.0 mmol), DME (1.5 mL, 0.67 M), CO (500 psi), 70 °C, 16 h. [b] Determined by ^{1}H NMR spectroscopy of the crude material. [c] Yield of isolated β-lactone. [d] Determined by chiral HPLC analysis of the β-hydroxy benzylamides derivative. [e] Absolute configuration was assigned based on ref. 7*e*. [f] Absolute configuration is predicted based on analogy to that determined for the cyclopentane derived β-lactone. [g] Determined directly by chiral HPLC analysis.

enantioselectivity was obtained in the case of cycloheptane oxide with **1** affording the bicyclic β-lactone product in 4% ee, and in contrast to 16% ee when using complex **3** (Table 2, entries 7 and 8).

We were delighted to see a marked increase in asymmetric induction with cyclopentane and 2,5-dihydrofuran derived epoxides which, as reported previously, gave the expected

cis-β-lactone products.[11] Cyclopentane oxide was carbonylated with 40% and 33% ee using **1** and **3**, respectively (entries 9 and 10). Higher enantioselectivities of 45% and 41% ee were achieved with the diester substituted cyclopentane oxide. In the latter case, a higher loading of 2.0 mol% was necessary for complete conversion. Interestingly, the sense of chiral induction was reversed when compared with cyclopentane oxide (entries 11 and 12 *vs*. entries 9 and 10).

The carbonylation of 2,5-dihydrofuran derived epoxide using catalyst **1** gave 56% ee,[18] the highest enantioselectivity of the presented study, while catalyst **3** gave an enantiomeric excess of 33%, and equal to the value obtained with cyclopentane oxide (Table 2, entry 14 *vs*. entry 10).

The carbonylation of the slow-reacting[11] 1-tosyl-2,3,6,7-tetrahydro-1*H*-azepine derived epoxide using catalyst **1** gave a conversion of 54% and an isolated yield of 47%. The enantiomeric excess of the lactone product was determined to be 31% by chiral HPLC analysis. A higher loading of 2.0 mol% was required to achieve a good conversion with catalyst **3** and the corresponding β-lactone was isolated in 56% yield and in an enantiomeric excess of 31%.

In conclusion, we show for the first time that the *asymmetric* ring-expansion carbonylation of *meso*-epoxides to β-lactones is feasible. The active catalysts for this transformation were generated *in situ* from air stable components consisting of Jacobsen's catalyst **1** or the D_4-symmetric **3** and $Co_2(CO)_8$. Although enantioselectivities achieved in this study are moderate, we anticipate that a substantial improvement might be possible when evaluating rationally selected examples from the large number of literature-known chiral Cr(III) complexes.

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Notes and references

‡ β-Lactone products without a UV active chromophore were derivatised by the reaction with benzylamine to the corresponding β-hydroxy benzylamides, the enantiomeric excess of which was determined by chiral HPLC analysis (see ESI†). X-Ray analysis of the cyclooctene derived β-hydroxy benzylamide confirmed the expected *trans*-stereochemistry (see ESI†).

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18 The effect of the relative stoichiometry of **1** and $Co_2(CO)_8$ on the enantioselectivity was studied using the 2,5-dihydrofuran derived epoxide as the substrate. Under otherwise identical conditions to those in entry 13 of Table 2, decreasing the loading of **1** to 1.0 mol% gave a full conversion to the lactone (89% yield) with a comparable enantioselectivity of 53% ee. Increasing the loading of **1** to 10.0 mol% resulted in a diminished selectivity of 35% ee ($\geq$ 98%, 82% yield). These experiments indicate that an equimolar ratio or an excess of $Co_2(CO)_8$ to **1** is necessary to minimise non-enantioselective background reactions.