

# **Cobalt(II) Catalysts – Their Use in the Enantioselective Ring-opening of 1,2-Dioxines**

A thesis submitted for the Degree of Doctor of Philosophy in the Faculty of  
Science

By

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## **Declaration of Originality**

This work contains no material which has been accepted for the award of any other degree or diploma in any other university or other tertiary institution and, to the best of my knowledge and belief, this thesis contains no material previously published or written by any other person, except where due reference has been made in the text.

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## Abstract

A series of new cobalt(II)  $\beta$ -keto iminato complexes and cobalt(II) salens have been made and the effect of chirality in the northern, southern and peripheral quadrants of these catalysts, with respect to induced enantiomeric excess, during the ring-opening of 1,2-dioxines has been determined.

Synthesis of a series of cobalt  $\beta$ -keto iminato complexes was achieved after modification of literature procedures used for the synthesis of manganese  $\beta$ -keto iminato complexes and this procedure was applied to generate ligands with ethyl, *t*-butyl, (-)-bornyl, (+)-menthyl and (-)-menthyl esters and a methyl side chain. Synthesis of the cobalt salens was also achieved using a modified literature procedure, in respect to the more complex aldehydes made.

It was ascertained that chirality in the northern quadrant of these catalysts, obtained by the use of optically pure diamines, was of greatest importance in introducing enantiomeric excess into the products of ring-opening of 1,2-dioxines; namely  $\gamma$ -hydroxy enones, and chirality in the southern and peripheral quadrants was of lesser, although still significant, importance.

The reaction conditions were optimised and the conditions under which the highest enantiomeric excess was introduced were determined. The ideal solvent for the ring-opening was found to be THF with a catalyst concentration between 5 and 10 mol% at a temperature of  $-15^{\circ}\text{C}$ . These conditions were found to be applicable to all catalysts and 1,2-dioxines tested.

Enantiomeric excess as high as 76 % could be introduced when the optimised reaction conditions were used in large scale syntheses of cyclopropane (**61**).

LC-MS studies indicate the presence of a solvent chelated species present in the reaction mixture when the solvent used is THF, however, the use of non-chelating solvents, such as dichloromethane, did not exhibit this same solvent chelated species. Catalyst dimers were also present in the mixture when analysed by LC-MS.

The presence of oxygen in the reaction mixture was found to inhibit rearrangement of the dioxine with catalyst oxygen dimers (two molecules of catalyst bound to a single molecule of oxygen) present when analysed by LC-MS, however, the catalyst could be 're-activated' by de-aeration of the solution and was able to introduce the same enantiomeric excess, as prior to the addition of oxygen was unaffected.

It was found that not only cobalt(II) tetradentate complexes were useful in the ring-opening of *meso* 1,2-dioxines. Achiral iron(II) salen and ruthenium(II) salen were also made and shown to be capable of ring-opening the dioxine. A purchased chiral manganese(III) salen was also shown to be capable of ring-opening the 1,2-dioxine, however, the time taken for the rearrangement to occur led to ring closure of the  $\gamma$ -hydroxy enone and dehydration of the cyclic hemiacetal.

The catalysts were also applied to the enantioselective ring-opening of epoxy-1,2-dioxines for the first time with a high level of success with enantiomeric excesses of between 60 and 90 % introduced with most of the catalysts.

To show that these catalysts have the potential for use in the synthesis of potentially bioactive cyclopropyl amino acids, amines, acids and alcohols a small number were prepared, including both racemic and optically enriched or optically pure cyclopropanes.



## Abbreviations

Anal. Calculated	analysis calculated
Bn	benzyl
Bor	bornyl
Bu	butyl
Bu <sup>t</sup> , <i>tert</i> -Bu, <i>t</i> -Bu	<i>tert</i> -butyl
DCM	dichloromethane
<i>de</i>	diastereomeric excess
DMAP	4-( <i>N,N</i> -dimethylamino)pyridine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i> )-pyrimidone
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
<i>ee</i>	enantiomeric excess
EH	2,3-epoxy-4-hydroxynonanal
Et	ethyl
HPLC	high-performance liquid chromatography
IR	infra red
LC-MS	liquid chromatography – mass spectroscopy
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
MHz	megahertz

Mn	menthyl
NMR	nuclear magnetic resonance
Pd/C	Palladium on carbon
Ph	phenyl
R <sub>f</sub>	retention factor
TBDPS	<i>tert</i> -butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC, t.l.c.	thin layer chromatography
TMS	tetramethyl silane