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First examples of the catalytic asymmetric ring-opening of *meso* 1,2-dioxines utilising cobalt(II) complexes with optically active tetradentate Schiff base ligands: formation of enantio-enriched cyclopropanes

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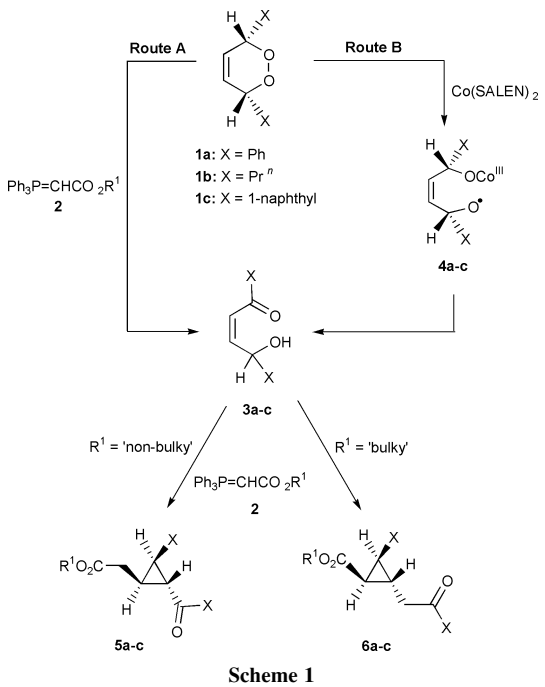
The combination of chiral cobalt β-ketoiminato or cobalt salen complexes and *meso* 1,2-dioxines leads to catalytic asymmetric ring-opening affording enantio-enriched *cis* γ-hydroxy enones; subsequent capture by an ylide affords enantio-enriched cyclopropanes.

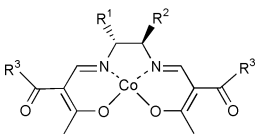
Functionalised cyclopropanes have proven to be exceedingly useful building blocks for the synthesis of natural and non-natural products.[1] Although there exists many excellent ways for the construction of the cyclopropyl core,[2,3] there is currently a deficiency in diastereoselectively efficient methods for the construction of diversely functionalised optically-pure cyclopropanes that contain greater than di-substitution. Our efforts have focussed on exploiting 1,2-dioxines **1** and stabilised phosphorus ylides **2** (*e.g.* R^1 = Me, Bn, Bu^t *etc.*) as precursors for the construction of diversely functionalised cyclopropanes **5** or **6**, Scheme 1. The ylides act as a mild base inducing ring-opening of the 1,2-dioxine **1** in a regiochemical fashion to produce the isomeric *cis* γ-hydroxy enones **3**, route A. Capture of this latter isomer by the ylide ultimately affords the observed cyclopropanes and is widely applicable to both symmetrical and non-symmetrical 1,2-dioxines.[4,5] We have also shown that cobalt salen can be utilised as a catalyst, which accelerates the ring-opening process affording *cis* γ-hydroxy enones **3** through the intermediacy of species **4**, route B.[4,5] This latter process is currently restricted to the ring-opening of symmetrical 1,2-dioxines **1** as only one regioisomer of enone **3** can be formed.

A logical extension to these latter findings was to investigate the use of cobalt(II) complexes with optically-active tetradentate Schiff base ligands. The hypothesis being that the chirality of the cobalt complex would induce enantioselectivity during the ring-opening process. We have previously shown that if the *cis* γ-hydroxy enone **3** is optically-pure then the resultant cyclopropanes formed on addition of ylide are also optically-pure.[6] We therefore report here the first examples of a catalytic asymmetric ring-opening of *meso* 1,2-dioxines which relies on the use of chiral cobalt β-ketoiminato or cobalt salen complexes; subsequent capture by an ylide affords enantio-enriched cyclopropanes.[7]

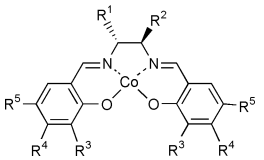


Scheme 1

Three *meso* 1,2-dioxines (**1a**–**c**)[4,5] and twelve chiral cobalt catalysts (**7a**–**h** and **8a**–**d**) were chosen to be evaluated. It is worthy of mention that while cobalt catalysts (**8a** and **b**) are



(*S,S*)-**7a**: $R^1 = R^2$ = Ph, R^3 = (-)-bornoxy
(*R,R*)-**7b**: $R^1 = R^2$ = Ph, R^3 = (-)-bornoxy
(*R,R*)-**7c**: R^1, R^2 = -$(CH_2)_4$-, R^3 = (-)-bornoxy
7d: $R^1 = R^2$ = H, R^3 =(-)-bornoxy
(*S,S*)-**7e**: $R^1 = R^2$ = Ph, R^3 = ethoxy
(*R,R*)-**7f**: $R^1 = R^2$ = Ph, R^3 = ethoxy
(*R,R*)-**7g**: R^1, R^2 = -$(CH_2)_4$-, R^3 = ethoxy
(*S,S*)-**7h**: $R^1 = R^2$ = Ph, R^3 = methyl



(*R,R*)-**8a**: R^1, R^2 = -$(CH_2)_4$-, R^3 = *t*-Bu, R^4 = H, R^5 = *t*-Bu
(*R,R*)-**8b**: R^1, R^2 = -$(CH_2)_4$-, $R^3 = R^4 = R^5$ = H
(*R,R*)-**8c**: R^1, R^2 = Ph, R^3 = (*S*)-PhEtCH-, $R^4 = R^5$ = H
(*S,S*)-**8d**: R^1, R^2 = Ph, R^3 = (*S*)-PhEtCH-, $R^4 = R^5$ = H

known, only the synthesis of the chiral ligands for some of the remaining catalysts have previously been reported.[8] In particular, chiral cobalt β-ketoiminato complexes of types (**7a–h**) represent a new class of chiral cobalt complexes.

Table 1 contains examples of the formation of optically-enriched cyclopropane **5a**[9] utilizing 1,2-dioxine **1a**, catalyst **7a** (5 mol%) and the benzyl ester ylide.[10] The results confirm our hypothesis that the chirality of the cobalt complex would induce enantioselectivity during the ring-opening process of *meso* 1,2-dioxines. Additionally, it can be seen that the solvent of choice for this particular ring-opening process from those currently trialled is THF. The effect of temperature on observed *ee* in both CH_2Cl_2 (entries 1–5) and THF (entries 11–14) was also probed and revealed that ee is maximized for the ring-opening of **1a** by the catalyst **7a** at *ca.* −15 to −20 °C. Based on these initial observations it is now possible to highlight the practical potential of this new catalytic asymmetric cyclopropanation reaction under semi-optimized conditions. Thus, a solution of 1,2-dioxine **1a** 0.5 g in THF 20 mL and a solution of catalyst **7a** 120 mg in THF 5 mL were equilibrated at −15 °C for 0.5 h after which time the two solutions were combined whilst maintaining the temperature at −15 °C. The rearrangement of **1a** into **3a** was monitored by TLC and when complete, (0.5 h) benzyl ester ylide 1.0 g added and the reaction mixture allowed to attain ambient temperature overnight. Workup and measurement of ee resulted in cyclopropane **5a** being isolated in 78% yield and displaying a 76% ee.

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Table 1 Preparation of optically-enriched cyclopropane **5a** from *meso* 1,2-dioxine **1a** with chiral cobalt β-ketoiminato complex **7a**[a]

Entry	Solvent	Temp./°C)	Ee (%)[b]	Entry	Solvent	Temp./°C)	Ee (%)[b]
1	CH_2Cl_2	20	38	8	CCl_4	20	34
2	CH_2Cl_2	0	48	9	Acetone	20	52
3	CH_2Cl_2	−10	56	10	CH_3CN	20	52
4	CH_2Cl_2	−20	72	11	THF	20	68
5	CH_2Cl_2	−40	60	12	THF	0	74
6	Et_2O	20	34	13	THF	−15	76
7	Toluene	20	34	14	THF	−40	72

[a] Carried out utilising 20 mg **1a** in the appropriate solvent (1 mL) at the specified temperature. The catalyst **7a** (5 mol% with respect to 1,2-dioxine concentration) was then added and the ring-opening monitored by TLC. After complete rearrangement the benzyl ester ylide 1 equiv. was added and the mixture allowed to attain ambient temperature overnight. Cyclopropane **5a** was then isolated by column chromatography. [b] Determined according to ref. 9.

Table 2 Effect of chiral cobalt β-ketoiminato complexes of type **7a–h** and cobalt salen catalysts **8a–d** on observed ee utilising 1,2-dioxines **1a–c**[a]

Entry	1,2-Dioxine	Catalyst	Ee (%)[b]	Entry	1,2-Dioxine	Catalyst	Ee (%)[b]
1	**1a**	**7a**	44	11	**1b**	**7h**	30
2		**7b**	34	12	**1c**	**7a**	44
3		**7c**	46	13	**1a**	**8a**	30
4		**7d**	14	14[c]			34
5		**7e**	46	15		**8b**	38
6		**7f**	46	16[c]			44
7	**1a**	**7g**	42	17		**8c**	34
8		**7h**	46	18		**8d**	50
9	**1b**	**7a**	34	19[c]			64
10		**7e**	32	20[cd]			78

[a] Reactions were carried out utilising 20 mg of 1,2-dioxine in CH_2Cl_2 (1 mL) at 20 °C except where noted. The appropriate amount of catalyst (entries 1–3, 7.5 mol%; entries 4–12, 10 mol%; entries 13–20, 5 mol% with respect to 1,2-dioxine concentration) was then added and the ring-opening monitored by TLC. After complete rearrangement the benzyl ester ylide 1 equiv. was added and the mixture left overnight. Cyclopropanes **5a–c** were then isolated by column chromatography and the isolated yields varied between 70–88%. [b] Determined according to ref. 9. [c] Performed in THF. [d] Performed at 4 °C.

A diverse range of chiral cobalt β-ketoiminato complexes **7a–h** and cobalt salen catalysts **8a–d** were prepared next in order to probe in which quadrant(s) sterics and/or chiral group positioning is important on observed ee, Table 2. In addition, these catalysts were examined for a range of di-alkyl and di-aryl *meso* 1,2-dioxines **1a–c** in order to probe the generality of this transformation. Overall, the results summarised within Table 2 indicate that useful enantioselectivities can be incorporated for a wide range of chiral cobalt β-ketoiminato catalysts **7a–h** (entries 1–12) and that the catalytic asymmetric cyclopropanation is widely applicable to a range of *meso* 1,2-dioxines. Comparison of entries 1 and 4 indicate that chirality located within the northern hemisphere of these β-ketoiminato complexes is important in inducing the high enantioselectivities. Moreover, analysis of the use of chiral cobalt salen catalysts **8a–d** (entries 13–20) also reveals that these catalysts induce useful ee's into the cyclopropanation sequence. Indeed, the matched salen catalyst **8d** led to an impressive 89 : 11 enantiomeric ratio when the reaction was carried out in THF at 4 °C (entry 20).

A full study encompassing a wide range of catalyst types is the focus of current studies and will be reported in full shortly along with a model depicting how the enantioselectivity is induced.

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7 The overall concept is by no means limited to cyclopropane formation. We will describe shortly the formation of enantio-enriched lactones which is also reliant on the catalytic asymmetric ring-opening of *meso* 1,2-dioxines by these chiral cobalt catalysts.

8 (*a*) For general procedures to prepare the β-ketoiminato ligands see: T. Nagata, K. Imagawa and T. Yamada, *Inorg. Chim. Acta*, 1994, **220**, 283; K. D. Sugi, T. Nagata, T. Yamada and T. Mukaiyama, *Chem.Lett*., 1997, 493; T. Nagata, K. Imagawa, T. Yamada and T. Mukaiyama, *Chem. Lett*., 1994, 1259; (*b*) For general procedures to prepare cobalt salen catalysts see: T. Fukuda and T. Katsuki, *Tetrahedron*, 1997, **53**, 7201; R. Irie, K. Noda, Y. Ito, N. Matsumoto and T. Katsuki, *Tetrahedron: Asymmetry*, 1991, **2**, 481.

9 Racemic **5a** has previously been characterized, see ref. 4. The ee was determined by dissolving cyclopropane **5a** (5 mg) in a 1 : 4 benzene-d_6 : CCl_4 solution and employing the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] complex. The benzyl protons at *ca.* δ 5.2 ppm displayed baseline separation.

10 It should be noted that a wide range of bulky and non-bulky ester ylides including chiral ester ylides can be employed. See refs. 4 and 5 for examples.