



Asymmetric hydrogenation of α -keto acid derivatives by rhodium–{amidophosphine–phosphinite} catalysts

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Abstract: The enantioselective hydrogenation of several α -keto esters (**3a–f**, **5a–j**), α -keto amides (**7a–e**) and isatine derivatives (**9a–d**) with a set of four representative neutral homogeneous rhodium–amidophosphine–phosphinite catalysts has been investigated. Trifluoroacetato–Rh–AMPP catalytic precursors promoted the rapid, efficient synthesis of aliphatic α -hydroxy esters **4a–f** in moderate to high enantioselectivities (66–95% ee), in contrast to most aromatic α -hydroxy esters **6a–j** (8–81% ee). Best enantioselectivities for α -hydroxy amides **8a–e** (85–95% ee) and dioxindoles **10a–d** (80–94% ee) were obtained with chloro–Rh–AMPP precursors. It is proposed that, contrary to α -keto amides, α -keto esters do not chelate onto the rhodium center and that, in such circumstances, the asymmetric induction is mainly controlled by the steric hindrance around the C=O function. © 1997 Elsevier Science Ltd

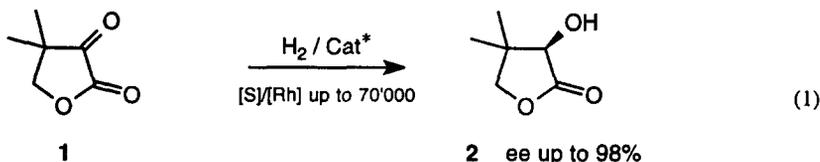
Introduction

Enantiomerically pure α -hydroxy acid derivatives are important chiral building blocks for the synthesis of a wide variety of natural products and biologically active molecules.¹ One of the most valuable direct routes to enantiomerically-enriched α -hydroxy acid derivatives is through asymmetric hydrogenation of corresponding α -keto acid compounds, and several highly enantioselective catalyst systems have been developed for this purpose. The latter include heterogeneous platinum catalysts modified with cinchona alkaloids which have proved to be efficient (up to 90% ee) in the hydrogenation of pyruvic and phenylglyoxylic esters,² as well as of ethyl benzylpyruvate in the large scale synthesis of an intermediate towards the ACE inhibitor Benazepril.³

The other alternatives are homogeneous rhodium and ruthenium complexes. Almost all of the ruthenium-based catalysts which have been used for the hydrogenation of α -keto acid compounds are associated to atropisomeric bisphosphines like the outstanding BINAP,⁴ BICHEP,⁵ BIPHEMP and MeO–BIPHEP,⁶ as well as other new atropisomeric ligands.⁷ Despite relative low activities, which usually require quite severe reaction conditions, these catalytic systems perform very well in terms of enantioselectivity and afforded acyclic α -hydroxy esters in 80–93% ee, as well as mandelamide derivatives in up to 96% ee.⁵ The hydrogenation of the cyclic α -keto ester 2-oxo-3,3-dimethyl- γ -butyrolactone **1** in (*R*)-pantolactone **2** (eqn 1), a key intermediate in the synthesis of vitamin B and co-enzyme A, is catalysed sluggishly by RuX₂(DIPAMP) catalysts (80% ee),^{6,8} or better with Ru-complexes associated to BINAP related diphosphines (90% ee).⁴ In fact, the best catalysts for this reaction remain rhodium-based systems. Since its discovery in 1977 by means of a Rh(BPPM)Cl catalyst,^{9a} the hydrogenation of **1** has been progressively improved by variation of the structure of the ligand,^{9,10a,b} and even more importantly by variation of the anionic Rh-ligand.^{10b,c} These new systems thus afforded **2** in 90–92% ee at substrate/catalyst ratios (S/C) up to 200 000. Equally interesting, we have reported that the new, readily available amino(do)phosphine–phosphinites (AMPP),¹¹ are efficient ligands for the rhodium-catalysed enantioselective hydrogenation of activated keto compounds. As a

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matter of fact, these systems afforded asymmetric inductions for **2** of 95–98% ee at S/C ratios of up to 70 000.^{11b,c} The corresponding Ru–AMPP catalysts are less efficient in terms of enantioselectivity and above all of activity.¹²

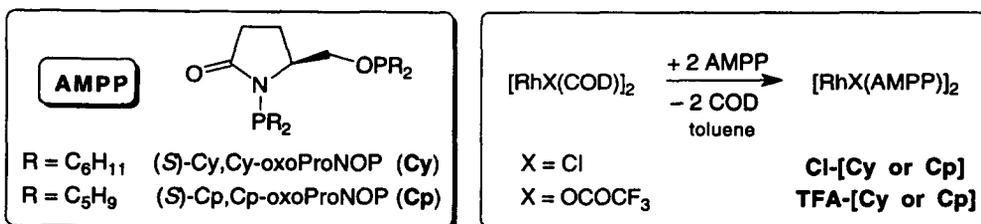


Investigations conducted on rhodium catalysts associated to other ligands demonstrated that very high enantioselectivities (up to 96% ee) could also be achieved for the hydrogenation of ethyl benzylpyruvate with NORPHOS, while 'classical' diphosphines like DIOP-type ligands or BINAP and its homologues proved to be much less efficient.^{2a} More recently, the use of optically active diamines as ligand in the rhodium-catalysed hydrogenation of methyl phenylglyoxylate has been investigated with a moderate success (up to 50% ee);¹³ It is noteworthy that the same systems under hydrogen transfer conditions led to much better results (up to 99% ee for ethyl mandelate), but the scope of their utilisation seems rather limited as only 5% ee was obtained for the reduction methyl pyruvate.¹⁴

In a general way, the enantioselective hydrogenation of α -keto acid derivatives has been much less investigated than that of simple and functionalized β -keto esters.^{4,15} Moreover, most efforts in this field have been concentrated on substrate **1**, especially for rhodium-based systems. This article describes studies which are concerned with the asymmetric hydrogenation of a variety of aliphatic and aromatic α -keto esters and amides by neutral rhodium–AMPP catalysts. In a first section, we report the catalytic performances (i.e. activity and enantioselectivity) of selected catalysts and the synthesis of various optically active α -hydroxy esters and amides, some of them new, in up to 96% ee. A second section is devoted to a mechanistic analysis of these results.

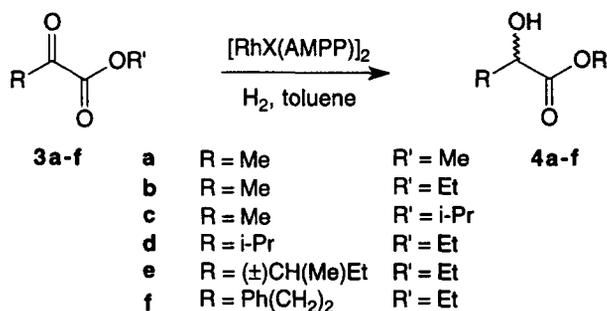
Results

Our earlier studies on AMPP have shown that the best ligands, in terms of enantioselectivity and activity of the corresponding rhodium catalytic species, are most often derived from cyclic amino alcohols and bear alkyl substituents at their phosphorus moieties.^{11a,c} For these reasons, two representative AMPP ligands derived from oxoprolinol ((*S*)-2-(hydroxymethyl)-5-pyrrolidinone) and bearing either cyclohexyl (Cy) or cyclopentyl (Cp) groups at the P(N) and P(O) moieties were selected for this study (Scheme 1). Concerning rhodium catalyst precursors, our efforts were focused on neutral chloro- and trifluoroacetato- complexes, respectively prepared from chloro- and trifluoroacetato(1,5-cyclooctadiene)rhodium dimeric complexes (Scheme 1), and which proved to have marked different catalytic properties.^{11b,c}



Scheme 1. Ligands and catalyst precursors used in this study.

First, the ability of the chosen catalysts was evaluated in the asymmetric hydrogenation of a set of aliphatic acyclic α -keto esters, **3a–f** (Scheme 2). Experiments were carried out under standard conditions (S/C=200, 50 atm, 20°C, toluene) in order to compare both activities and selectivities.



Scheme 2.

The results, summarized in Table 1, show that all the aliphatic α -keto esters tested were readily hydrogenated under the standard reaction conditions. The influence of pressure was examined in the case of ethyl pyruvate **3b** and was shown to only affect the catalytic activity (entries 6–8); Although all the reactions could be carried out under atmospheric pressure, activities were significantly increased (3 times) since 5 atm. As a general trend, trifluoroacetato-precursors led to better or at least equivalent catalytic activities and enantioselectivities than the corresponding chloro-complexes. The influence of the chiral AMPP ligand on the enantioselectivity was variable upon the nature of the substrate, so that each substrate required an individual screening. Namely, for methyl pyruvate **3a**, the best results were obtained with the trifluoroacetato-rhodium complex of Cp,Cp-oxoProNOP, but for the other α -keto esters **3b–f**, the Cy,Cy-oxoProNOP complex proved to be more efficient. It is noteworthy that for pyruvate esters **3a–c**, the nature of the achiral anionic ligand X did not affect the ee values (entries 1–6), contrary to higher α -keto esters for which marked differences appeared between chloro- and trifluoroacetato-precursors (compare entries 14 and 15, 17 and 18, 19 and 20).

The level of performance of the chosen catalysts is noticeable: turnover frequencies up to 35 min⁻¹ were attainable under relatively smooth conditions, and best enantioselectivities ranged from 65 to 95% ee. As a matter of fact, lactate esters **4a–c** were obtained in 81–90% ee at room temperature, and the synthesis of almost enantiomerically pure products (94–95% ee) could be performed by carrying out the hydrogenation at -20°C with *ca.* 0.3 mol% of catalyst (entries 9 and 13).¹⁶ Higher α -keto esters were reduced with poorer enantioselectivities, which could not be significantly improved by lowering the temperature. Noteworthy, the presence of a stereogenic center in the substrate did not affect the asymmetric induction of the catalyst, as hydrogenations of racemic α -keto ester **3e** yielded both corresponding diastereomers (50:50 mixtures) with the same ee's (entries 19–21). More, all α -hydroxy esters **4a–f** exhibited the same absolute configuration for the predominant enantiomer.

We next investigated the enantioselective hydrogenation of a set of aromatic α -keto esters, **5a–i** (Scheme 3, Table 2). The reactivity of this kind of substrate was most comparable to that of aliphatic α -keto esters; A sole exception was found for ethyl (2,4-dimethylphenyl)glyoxylate (**5g**) which, surprisingly, required longer times for the reactions to go to completion (entries 37–39). Undoubtedly, the most interesting feature comes from the striking dependence of enantioselectivity on the nature of the substrate. As a matter of fact, simple phenylglyoxylates like the ethyl and benzyl esters (**5a** and **5j**, respectively) gave very low ee's, whatever the catalyst used (entries 24–27). The same trend was found for *para*- and *meta*-chloro- or methoxy-substituted derivatives **5b**, **5c** and **5e** (entries 28–30, 33–34). However, *ortho,para*-disubstituted phenylglyoxylates led to somewhat higher ee's as the 2,4-dimethyl derivative **5g** was hydrogenated in up to 51% ee (entries 37–39). This effect was even more pronounced for the 2,4-dimethoxy compound **5f** (up to 74% ee, entries 35, 36), and the 2,4-dichloro derivative **5d** (up to 81% ee, entries 31, 32). The results obtained from 2-thienyl and 2-furylglyoxylate ethyl esters (**5h** and **5i**) were intermediate and illustrated, once again, the marked influence of the anionic

Table 1. Asymmetric hydrogenation of aliphatic α -keto esters **3a-f**^a

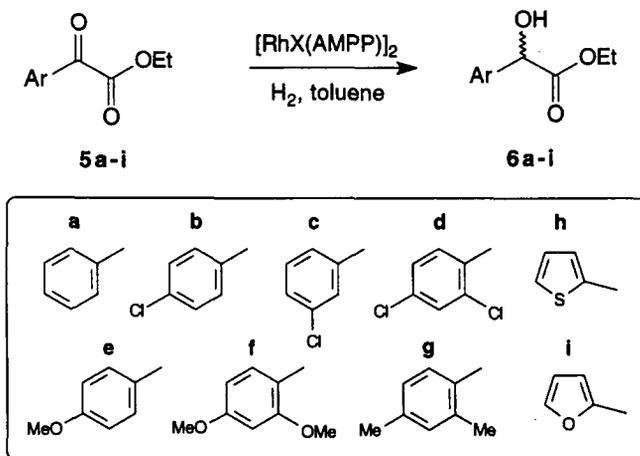
entry	substrate	catalyst	time ^b (min)	convers. ^c (mol %)	$t_{1/2}$ ^d (min)	ee of 4e (%) (conf)
1	3a	Cl-[Cy]	40	100	15	74 (R)
2	"	TFA-[Cy]	30	100	4	76 (R)
3	"	Cl-[Cp]	30	100	4	80 (R)
4	"	TFA-[Cp]	30	100	4	81 (R)
5	3b	Cl-[Cy]	25	100	18	85 (R)
6	"	TFA-[Cy]	45	100	6	89 (R)
7 ^f	"	"	150 ^f	96	25	88 (R)
8 ^g	"	"	20 ^g	100	9	89 (R)
9 ^h	"	"	120 ^h	100	30	95 (R)
10	"	Cl-[Cp]	10	99	4	82 (R)
11	"	TFA-[Cp]	30	100	4	82 (R)
12	3c	Cl-[Cy]	60	100	10	86 (R)
13 ⁱ	"	TFA-[Cy]	60 ⁱ	75	25	94 (R)
14	3d	Cl-[Cy]	180	99	8	36 (R)
15	"	TFA-[Cy]	25	97	3.5	61 (R)
16 ^j	"	"	430 ^j	99	150	67 (R)
17	"	Cl-[Cp]	10	95	5	36 (R)
18	"	TFA-[Cp]	20	98	5	55 (R)
19	3e	Cl-[Cy]	120	99	25	42 (R) ^k
20	"	TFA-[Cy]	20	99	6	66 (R) ^k
21	"	TFA-[Cp]	30	100	3	61 (R) ^k
22	3f	TFA-[Cy]	90	100	< 10	77 (R)
23	"	TFA-[Cp]	30	100	5	58 (R)

^a Reaction conditions unless otherwise stated: Substrate/Rh = 200, ca. 4 mmol of substrate in 10 mL of toluene, 20 °C, $P(\text{H}_2)$ = 50 atm. See Experimental Section for typical procedure. ^b Reaction times were not necessarily optimized. ^c Determined by quantitative GLC analysis. ^d Time for 50% conversion. ^e Enantiomeric excesses were determined by GLC analysis (see Experimental Section). ^f $P(\text{H}_2)$ = 1 atm. ^g $P(\text{H}_2)$ = 5 atm. ^h $T = -20$ °C, [S]/[Rh] = 350. ⁱ $T = -20$ °C. ^j $T = -20$ °C, [S]/[Rh] = 450. ^k Indicates the absolute configuration of the new stereogenic center produced at C-2; **4e** was obtained as a 50:50 mixture of diastereomers 2*R*,3*R* and 2*R*,3*S*, both with the same ee.

achiral ligand X both on catalytic activity and enantioselectivity, and the aforementioned superiority of trifluoroacetato-rhodium precursors for the hydrogenation of α -keto esters (entries 40–47).

Due to the wide disparity of the above results and the general, poor ability of Rh-AMPP catalysts to promote the enantioselective synthesis of *aromatic* α -hydroxy esters, we turned our attention to the asymmetric hydrogenation of the related *aromatic* α -keto amides **7a–e** (Scheme 4). *N*-Benzyl amides were prepared in 33–90% yield by reaction of the corresponding α -keto ethyl esters with benzylamine following the reported procedure¹⁷ (see Experimental Section). As expected from our previous work,¹¹ much better results were obtained from this class of substrate (Table 3).

The screening of different reaction parameters conducted on *N*-benzylphenylglyoxamide (**7a**, entries 48–54) revealed typical features which proved to apply systematically for the asymmetric hydrogenation of aryl α -keto amides **7**. The most important characteristic is that, contrary to aliphatic and aromatic α -keto esters, chloro-rhodium catalyst precursors led to better ee values than the corresponding trifluoroacetato-complexes. However, the latter produced significantly more active



Scheme 3.

catalytic species than chloro-Rh complexes, as indicated by the 4–6 times decrease of the half-reaction times (entries 48 and 52, 53 and 54). It has to be mentioned that this drop in reactivity in going from TFA to chloro-Rh catalysts remains relative, as notable turnover frequencies up to 20 min^{-1} were obtained with $[\text{RhCl}\{(S)\text{-Cp,Cp-ProNOP}\}]_2$ at 20°C , 1 atm (79% ee).^{11a} Carrying out hydrogenations under moderate pressure allowed both catalytic activities and enantioselectivities to be increased. Thus, α -keto amides **7a–e** were hydrogenated under 50 atm, with a [substrate]/[Rh] ratio up to 1000, yielding quantitatively products **8a–e** in 85–92% ee. None of these reactions were really optimized and it has to be noticed that enantioselectivities up to 95% ee were observed for **8a** by combining the effect of pressure and that of temperature (entry 51). Anyway, enantiomerically pure *N*-benzyl- α -hydroxy amides were easily obtained in high yields through recrystallization of crude samples (see Experimental Section).

The asymmetric hydrogenation of the cyclic α -keto amide isatine **9a** and some of its derivatives **9b–d** was next investigated (Scheme 5). The resulting dioxindoles **10a–d** are recognized antihypoxic compounds but their biological activity has been evaluated only as racemates.¹⁸ The synthesis of enantiomerically pure α -hydroxy amides **10a** and **10c** via enzymatic reduction of the isatine derivatives has been reported,¹⁹ but we cast doubt on the enantiomeric purity of the obtained products (*vide infra*). Hydrogenations of isatine derivatives **9a–d** were conducted under the same reaction conditions as those used for α -keto amides **7**, except that toluene/methanol (1:1 v/v) was used as the solvent because of the very low solubility of compounds **9a–d** in pure toluene (Table 4).

As expected, chloro-Rh-AMPP complexes proved to be efficient catalyst precursors in terms of enantioselectivity, at least when associated to Cy,Cy-oxoProNOP since the performances of the two selected ligands varied in a wide range (compare entries 59 and 62, 65 and 66). Reactions were sluggish under 1 atm and were best conducted under 50 atm. Under these conditions, dioxindoles **10a–d** were obtained in quantitative yields in 80–90% ee. Lowering the temperature once again led to an increase in the ee (up to 94% for **10a**), but the catalytic activity was so reduced that the reaction did not go to completion after 13 h (entry 61); No drop of the ee was observed by using a [S]/[Rh] ratio up to 1000.

The enantiomeric purity of dioxindoles **10a–d** was determined by several methods, giving consistent results (NMR spectroscopy of the pure product in the presence of chiral shift reagent (+)-Eu(hfc)₃ and of derivatization products with chiral reagents; polarimetry; see Experimental Section). The specific rotations of our products were much higher than those previously reported¹⁹ (for instance, for **10a**: $[\alpha]^{25}_{\text{D}} (c 1, \text{MeOH}) = +36$ (94% ee, this work) vs +7 (claimed to be >99% ee)¹⁹), thus indicating a problem of purity for the products obtained via enzymatic reduction.

Table 2. Asymmetric hydrogenation of aryl α -keto esters **5a-j**^d

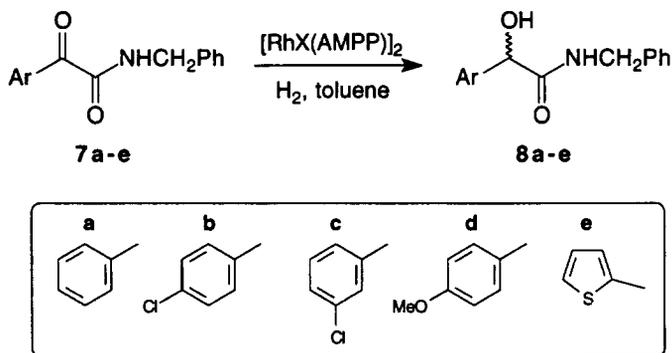
entry	substrate	catalyst	time ^b (h)	convers. ^c (mol %)	$t_{1/2}$ ^d (min)	ee of 6 ^e (%) (conf)
24	5a	Cl-[Cy]	0.8	97	10	8 (S)
25	"	TFA-[Cy]	0.5	100	11	8 (S)
26	"	TFA-[Cp]	1.5	100	nd	5 (S)
27	5j ^f	TFA-[Cy]	3	100	nd	29 (S)
28	5b	Cl-[Cp]	21	90	nd	8 (-)
29	"	TFA-[Cp]	17	100	nd	<1 (-)
30	5c	TFA-[Cy]	2	100	nd	20 (S)
31	5d	TFA-[Cy]	2	100	nd	81 (S)
32 ^g	"	TFA-[Cp]	21 ^g	100	nd	81 (S)
33	5e	Cl-[Cy]	18	100	nd	21 (-)
34	"	TFA-[Cy]	17	100	nd	16 (-)
35	5f	TFA-[Cy]	7	100	nd	70 (-)
36	"	TFA-[Cp]	3.3	100	nd	74 (-)
37	5g	Cl-[Cy]	46	100	nd	46 (-)
38	"	TFA-[Cy]	23	38	nd	51 (-)
39	"	TFA-[Cp]	25	70	15h	35 (-)
40	5h	Cl-[Cy]	5	81	30	24 (S)
41	"	TFA-[Cy]	4	97	10	36 (S)
42	"	Cl-[Cp]	1.2	100	nd	25 (S)
43	"	TFA-[Cp]	1	100	8	48 (S)
44	5i	Cl-[Cy]	5	85	nd	22 (S)
45	"	TFA-[Cy]	1	50	60	35 (S)
46	"	Cl-[Cp]	3	100	nd	23 (S)
47	"	TFA-[Cp]	3	100	nd	42 (S)

^a Reaction conditions unless otherwise stated: Substrate/Rh = 200, ca. 4 mmol of substrate in 10 mL of toluene, 20 °C, $P(\text{H}_2)$ = 30 atm; see Experimental Section for typical procedure. ^b Reaction times were not optimized. ^c Determined by quantitative GLC and/or ¹H NMR analysis. ^d Time for 50% conversion; nd: not determined. ^e See Experimental Section for the determination of ee and absolute configuration of prevailing enantiomer. ^f **5j**: benzyl phenylglyoxylate. ^g $T = -20$ °C, [S]/[Rh] = 500.

Discussion

The efficiency of neutral Rh-AMPP complexes to promote the enantioselective hydrogenation of α -keto esters appears strictly dependent on the substrate structure. To our knowledge, the enantioselectivities and the activities obtained for the hydrogenation of pyruvate esters (Table 1) are among the best ones reported in the literature, and are comparable to the performances of neutral Rh-BPPM type systems.^{9f} Also, the hydrogenation of ethyl benzylpyruvate **3e**, which is of industrial interest, proceeded with a high activity and excellent catalytic productivity to afford the desired α -hydroxy ester in a noteworthy ee (77%).³ Unfortunately, this is not the case for the hydrogenation of most *aromatic* α -keto esters; Such a specificity of neutral Rh-AMPP catalysts for the hydrogenation of *aliphatic* α -keto esters is rather surprising, but it is in line with recent results obtained with the *in situ* [Rh(NBD)Cl]₂/(2*S*,3*S*)-NORPHOS) system.³

The mechanism of rhodium-catalysed hydrogenation of keto compounds is much less documented than that of olefins. As a matter of fact, all attempts from our and other groups have failed up to now

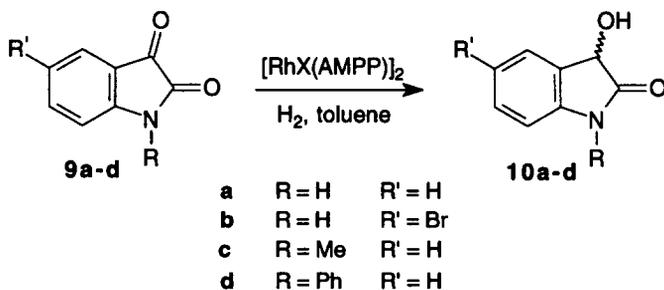


Scheme 4.

Table 3. Asymmetric hydrogenation of aryl α -keto amides **7a–e**^a

entry	substrate	catalyst	$P(\text{H}_2)$ (atm)	time ^b (h)	$t_{1/2}$ ^c (min)	ee of 8 ^d (%) (conf)
48	7a	Cl-[Cy]	1	18	58	87 (S)
49 ^e	"	"	1	5	-	-
50 ^f	"	"	50	18 ^f	nd	92 (S)
51 ^g	"	"	50	8.5 ^g	nd	95 (S)
52	"	TFA-[Cy]	1	1.5	10	61 (S)
53	"	Cl-[Cp]	1	2.3	30	80 (S)
54	"	TFA-[Cp]	1	0.5	8	67 (S)
55	7b	Cl-[Cy]	50	17	nd	87 (S)
56	7c	Cl-[Cy]	50	1	nd	87 (S)
57	7d	Cl-[Cy]	50	2	nd	85 (S)
58	7e	Cl-[Cy]	50	24	nd	86 (S)

^a Reaction conditions unless otherwise stated: Substrate/Rh = 200, ca. 4 mmol of substrate in 10 mL of toluene, 20 °C; see Experimental Section for typical procedure. Results for the hydrogenation of **7a** taken in part from ref 11b. ^b Not optimized reaction times for 100% conversion of **7** as determined by ¹H NMR analysis. ^c Time for 50% conversion; nd: not determined. ^d See Experimental Section for the determination of ee. ^e $T = -22$ °C. ^f [S]/[Rh] = 1'000. ^g $T = -15$ °C, [S]/[Rh] = 50.



Scheme 5.

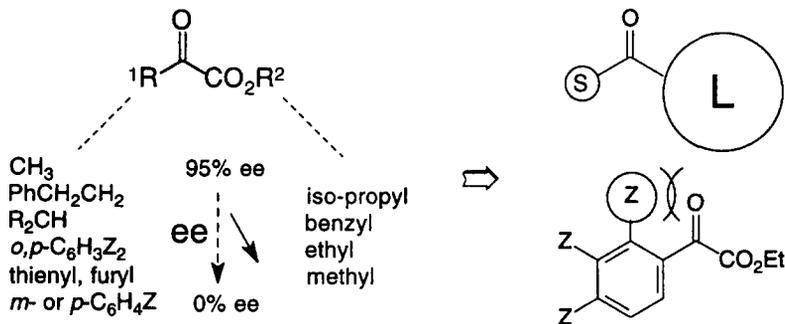
to isolate or even identify catalytic intermediates formed from *neutral* rhodium complexes and various keto derivatives. A starting point generally adopted is to assume that, as with olefins, the mechanism

Table 4. Asymmetric hydrogenation of isatine derivatives **9a-d**^d

entry	substrate	catalyst	time ^b (h)	conv. 9 ^c (mol %)	ee of 10 ^d (%) (conf)
59 ^e	9a	Cl-[Cy]	24 ^e	100	90 (+)
60 ^f	"	"	7	25 ^f	90 (+)
61 ^g	"	"	17	63 ^g	94 (+)
62	"	Cl-[Cp]	7 ^h	100	68 (+)
63	9b	Cl-[Cy]	18	100	86 (+)
64	9c	Cl-[Cy]	20	100	80 (+)
65	9d	Cl-[Cy]	24	100	88 (+)
66	"	Cl-[Cp]	20	100	67 (+)

^a Reaction conditions unless otherwise stated: Substrate/Rh = 200, *ca.* 2 mmol of substrate in 20 mL of toluene/methanol (1:1), 20 °C, $P(\text{H}_2) = 50$ atm. ^b Reaction times were not optimized. ^c Conversion of **9** as determined by ¹H NMR analysis. ^d See Experimental Section for the determination of ee. ^e [S]/[Rh] = 1'000. ^f $P(\text{H}_2) = 1$ atm. ^g $T = -20$ °C. ^h $t_{1/2} = 20$ min.

involves formation of a ketone complex followed by oxidative addition of hydrogen.^{20,21} Nonetheless, several questions remain of fundamental interest, as the way the keto compound coordinates onto the metal centre. In this regard, a possible explanation for the large disparity of enantioselectivities with α -keto esters can be proposed considering that such substrates *do not* chelate onto the rhodium centre of catalytic species and that asymmetric discrimination comes from steric hindrance around the C=O function to be hydrogenated. The observed trend of optical yields for the hydrogenation of aliphatic α -keto esters $\text{R}^1\text{COCO}_2\text{R}^2$ (Table 1) supports this hypothesis: the bigger the R^2 group at the alkoxy carbonyl moiety and the smaller the R^1 α -substituent at C=O, the better the ee (Scheme 6).

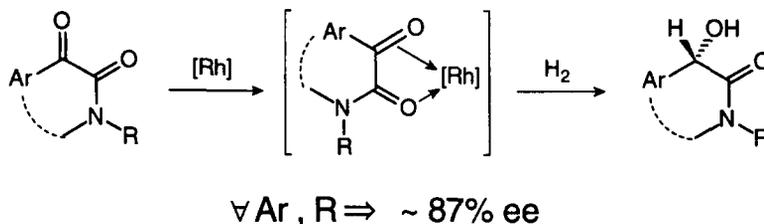


Scheme 6. Steric dissymmetry of the ketone as a possible source of enantiodifferentiation for α -keto esters.

A similar analysis can be made from the results obtained with *aromatic* α -keto esters by considering that phenyl and ethoxycarbonyl groups have comparable bulkiness. Thus, ethyl phenylglyoxylate and its *para*-substituted derivatives could be regarded as sterically symmetric ketones, but introduction of a *meta*-, and above all, an *ortho*-substituent breaks this symmetry. The steric nature, at least in part, of this effect of *ortho*-substituents in phenylglyoxylate esters appears clearly with the 2,4-dimethyl derivative, for which chelation of substrate via the *ortho* substituent is strongly unlikely. Such a chelation could hardly account for our results, particularly the low ee's observed for simple phenylglyoxylate esters.²²

The behaviour of α -keto amides is probably different because of the recognized, higher coordinating ability of amido versus alkoxy carbonyl groups. Chelation of the substrate onto the rhodium centre of catalytic species has already been proposed from spectroscopic investigations with *cationic* rhodium complexes and *N*-benzylphenylglyoxamide.^{17,20b} It is therefore a hypothesis that must be taken into

account also for *neutral* species. Noteworthy in this regard is the similarity of the optical yields obtained from *N*-benzylphenylglyoxamide derivatives **7a–e** (85–92% ee, Cl-[Cy] cat., 20°C, 50 atm) and isatine derivatives **9a–d** (80–90% ee); this indicates that structural features in α -keto amides are much less important for enantioface differentiation than in α -keto esters. More, it suggests that *N*-benzylphenylglyoxamide derivatives most probably adopts for the diketo moiety the same cisoid conformation than the blocked one in isatine derivatives (Scheme 7), which is in line with a probable chelation of the substrate.



Scheme 7. Cisoid diketo chelate as a possible reason for similar enantioselectivities with α -keto amides.

Although no optimization was attempted, the overall performances of neutral Rh–AMPP catalysts for the asymmetric hydrogenation of α -keto amides combine rather high activities, catalytic productivities and enantioselectivities. As the above properties are significantly affected by the nature of the anionic ligand X (Cl, TFA), this could mean either that the anionic ligand X remains coordinated onto the Rh centre throughout the catalytic cycle,^{11,21} or that it is displaced by the product alkoxide, with the case of displacement depending on X.²³ However, its contribution is still unclear and, in particular, no definitive explanation can be proposed for the superiority of chloro versus trifluoroacetato–Rh–AMPP precursors in terms of enantioselectivity.

To summarize, we assume that the alkoxy carbonyl moiety in α -keto esters acts more as a bulky group which breaks the symmetry of the carbonyl compound and facilitates enantioface differentiation, rather than as a coordinating moiety which allows the chelation of the substrate, as probably does the amido function in α -keto amides.

Experimental section

General considerations

NMR spectra were recorded on a AC-300 Brüker spectrometer (¹H: 300.1 MHz, ¹³C: 75.0 MHz, ¹⁹F: 282.4 MHz); Chemical shifts are reported in ppm downfield from TMS. Elemental analyses were carried out at the Department of Analytical Chemistry, University of Lille. Mass spectra were performed at an ionizing voltage of 70 eV. Melting and boiling points are uncorrected. Optical rotations were measured on a Perkin Elmer polarimeter in a 1 dm cell. IR spectra are expressed by wavenumber (cm⁻¹).

Materials

Except the following products, all other reagents are commercially available and were used as received. 2-Propyl pyruvate **3d** was obtained by esterification of pyruvoyl chloride.²⁴ (\pm) Ethyl 3-methyl-2-oxovalerate **3e** was prepared in 67% yield by alkylation with EtI of the sodium carboxylate salt in acetone.²⁵ Ethyl (3-chlorophenyl)glyoxylate **5c** was synthesized through reaction of diethyl oxalate with 3-chlorophenylmagnesium bromide.^{10d} Ethyl (2-furan)glyoxylate **5i** was obtained by esterification of the carboxylic acid with *p*-toluenesulfonic acid as a catalyst.

Ethyl (3-chlorophenyl)glyoxylate **5c**

Yield: 41%. Pale yellow oil. Eb: 120–130°C (0.1–0.2 mm Hg). NMR ¹H (CDCl₃): δ 1.33 (t, 3H, *J*=7.1 Hz, CH₃), 4.36 (q, 2H, OCH₂), 7.36 (m, 1H, *J*=7.9 and 1.3 Hz, H-5), 7.51 (m, 1H, *J*=8.0 and

1.0 Hz, H-4), 7.81 (m, 1H, $J=7.8$ and 1.1 Hz, H-6), 7.89 (m, 1H, $J=1.7$ Hz, H-2). NMR ^{13}C (CDCl_3): δ 13.8 (CH_3), 62.4 (OCH_2), 128.0, 129.5, 130.0 (CH aro), 133.8 (C aro), 134.5 (CH aro), 134.9 (C aro), 162.8 (COO), 184.6 (CO). IR (CHCl_3): ν 1738 (vs), 1685 (vs), 1196 (vs). MS (EI): 212/214 ($\text{M}^{+35}\text{Cl}/^{37}\text{Cl}$, 10%), 186/188 (15%), 139/141 ($\text{M}-\text{COOEt}$, 100%), 111/113 (40%).

Other substituted arylglyoxylate ethyl esters **5** were prepared by Friedel-Crafts acylation of the corresponding arene using a stoichiometric amount of AlCl_3 and ethyl chloroglyoxylate. Generally, a mixture of the desired α -keto ester and the related α -keto acid was obtained and the latter was converted into the desired ester by alkylation with EtI/KF in DMF.²⁶ The product was finally purified by distillation.

Ethyl (2,4-dichlorophenyl)glyoxylate 5d

Overall yield: 15%. Yellow oil. NMR ^1H (CDCl_3): δ 1.31 (t, 3H, $J=7.1$ Hz, CH_3), 4.34 (q, 2H, OCH_2), 7.30 (dd, 1H, J (H_3-H_5)=2.0 Hz, J (H_6-H_5)=8.3 Hz, H-5), 7.37 (d, 1H, H-3), 7.64 (d, 1H, H-6). NMR ^{13}C (CDCl_3): δ 13.6 (CH_3), 62.7 (OCH_2), 127.6 (C-5), 130.2 (C-3), 131.4 (C-2), 132.4 (C-6), 134.5 (C-1), 140.0 (C-4), 162.5 (COO), 185.1 (CO). IR (CHCl_3): ν 1738 (s), 1704 (s), 1584 (s). MS (EI): 246/248 ($\text{M}^{+35}\text{Cl}/^{37}\text{Cl}$, 5%), 201/203 (15%), 173/175 ($\text{M}-\text{COOEt}$, 100%), 145 (20%), 109 (20%).

Ethyl (2,4-dimethoxyphenyl)glyoxylate 5f

Overall yield: 81%. Yellow oil. Eb: 180°C (0.2 mm Hg). NMR ^1H (CDCl_3): δ 1.32 (t, 3H, $J=7.1$ Hz, CH_3), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.30 (q, 2H, OCH_2), 6.37 (d, 1H, J (H_3-H_5)=2.2 Hz, H-3), 6.52 (dd, 1H, J (H_5-H_6)=8.8 Hz, H-5), 7.81 (d, 1H, H-6). NMR ^{13}C (CDCl_3): δ 13.9 (CH_3 OEt), 55.5 (OCH_3), 55.7 (OCH_3), 61.3 (OCH_2), 97.8 (C-3), 106.7 (C-5), 115.4 (C-1), 132.4 (C-6), 162.1 (C-4), 165.7 (COO), 166.6 (C-2), 184.8 (CO). IR (CHCl_3): ν 1738 (s), 1661 (s), 1602 (vs). MS (EI): 238 (M^+ , 5%), 165 (M^+-COOEt , 100%), 122 (10%), 107 (8%).

Ethyl (2,4-dimethylphenyl)glyoxylate 5g

Overall yield: 64%. Yellow crystals. Mp: 59–60°C. NMR ^1H (CDCl_3): δ 1.38 (t, 3H, $J=7.1$ Hz, CH_3 OEt), 2.35 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 4.40 (q, 2H, OCH_2), 6.98 (m, 2H, H-3 and H-5), 7.58 (d, 1H, J (H_5-H_6)=8.3 Hz, H-6). NMR ^{13}C (CDCl_3): δ 12.8 (CH_3 OEt), 20.6 (CH_3), 20.8 (CH_3), 61.7 (OCH_2), 126.3 (C-5), 128.0 (C-1), 132.3, 132.8 (C-3, C-6), 141.1, 144.5 (C-2, C-4), 164.6 (COO), 188.1 (CO). IR (KBr): ν 1733 (vs), 1677 (vs), 1202 (s). MS (EI): 206 (M^+ , 5%), 161 (M^+-OEt , 3%), 133 (M^+-COOEt , 100%), 105 (25%). Rf (heptane/ Et_2O 50/50): 0.64.

α -Keto amides **7** were prepared by reaction of the corresponding α -keto ester with benzylamine following the reported procedure for **7a**.¹⁷

N-Benzyl-(4-chlorophenyl)glyoxamide 7b

Yield: 33%. Yellow crystals. Mp: 106–107°C. NMR ^1H (CDCl_3): δ 4.54 (d, 2H, $J=6.1$ Hz, CH_2), 7.25–7.40 (m, 5H, H aro), 7.44 (d, 2H, $J=8.5$ Hz, H aro), 8.34 (d, 2H, H aro). NMR ^{13}C (CDCl_3): δ 43.5 (CH_2), 127.9, 128.9 (CH aro), 131.6 (C aro), 132.7 (CH aro), 136.9, 141.2 (C aro), 161.1 (CONH), 186.1 (CO). IR (KBr): ν 3269 (m, NH), 1686 (m), 1650 (vs). MS (EI): 273/275 ($\text{M}^{+35}\text{Cl}/^{37}\text{Cl}$, 5%), 139/141 ($\text{M}-\text{CONHBz}$, 100%), 111 (30%), 106 (NHBz , 50%), 91 (Bz , 100%).

N-Benzyl-(3-chlorophenyl)glyoxamide 7c

Yield: 61%. Colourless crystals. Mp: 81–82°C. NMR ^1H (CDCl_3): δ 4.56 (d, 2H, $J=6.1$ Hz, CH_2), 7.30–7.50 (m, 6H, H Ph), 7.59 (ddd, 1H, $J=1.1$, 2.2, and 8.0 Hz, H aro), 8.28 (dt, 1H, H aro), 8.35 (dd, 1H, H aro). NMR ^{13}C (CDCl_3): δ 43.5 (CH_2), 127.9, 128.9, 129.4, 129.8, 131.1, 134.3, 134.7 (CH aro), 136.9 (C aro), 160.8 (CONH), 186.1 (CO). IR (KBr): ν 3299 (s, NH), 1679 (s), 1650 (vs). MS (EI): 273/275 ($\text{M}^{+35}\text{Cl}/^{37}\text{Cl}$, 7%), 139/141 ($\text{M}-\text{CONHBz}$, 65%), 106 (NHBz , 35%), 91 (Bz , 100%).

N-Benzyl-(4-methoxyphenyl)glyoxamide 7d

Yield: 90%. Colourless crystals. Mp: 91–92°C. NMR ^1H (CDCl_3): δ 3.87 (s, 3H, OCH_3), 4.55 (d, 2H, $J=6.1$ Hz, CH_2), 6.93 (d, 2H, $J=9.1$ Hz, H-3), 7.3–7.45 (m, 6H, H Ph), 7.5 (s broad, 1H, NH), 8.42 (d, 2H, H-2). NMR ^{13}C (CDCl_3): δ 43.4 (CH_2), 55.5 (OCH_3), 113.8 (C-3), 126.3 (C-1), 127.7, 127.8, 128.8 (C-2', C-3', C-4'), 133.9 (C-2), 137.2 (C-1'), 162.1 (CONH), 164.7 (C-4), 185.5 (CO). IR (KBr): ν 3242 (m, NH), 1673 (s), 1636 (vs), 1602 (s). MS (EI): 269 (M^+ , 5%), 135 ($\text{M}^+ - \text{CONHBz}$, 100%), 91 (40%), 77 (35%).

N-Benzyl-(2-thienyl)glyoxamide 7e

Yield: 87%. Colourless crystals. Mp: 92–93°C. NMR ^1H (CDCl_3): δ 4.55 (d, 2H, $J=6.5$ Hz, CH_2), 7.19 (dd, 1H, J (H3–H4)=3.9 Hz, J (H4–H5)=4.9 Hz, H-4), 7.3–7.4 (m, 6H, H Ph), 7.6 (s broad, 1H, NH), 7.83 (dd, 1H, J (H3–H5)=1.2 Hz, H-5), 8.42 (dd, 1H, H-3). NMR ^{13}C (CDCl_3): δ 43.5 (CH_2), 127.8, 128.2, 128.8, (C-2', C-3', C-4'), 136.7, 136.9, 138.1, 138.7 (C-1', C thienyl), 160.6 (CONH), 178.2 (CO). IR (KBr): ν 3370 (vs, NH), 1674 (s), 1635 (vs). MS (EI): 245 (M^+ , 10%), 111 ($\text{M}^+ - \text{CONHBz}$, 100%), 106 (BzNH, 50%), 91 (90%).

General procedure of asymmetric hydrogenation

All the reactions were performed under anaerobic conditions using standard Schlenk techniques. Hydrogenation solvents were distilled from sodium benzophenone ketyl (toluene) or magnesium methoxide (CH_3OH), and degassed. Rhodium–AMPP catalyst precursors were prepared as previously reported,¹¹ by mixing $[\text{Rh}(\text{COD})\text{X}]_2$ with 2 equiv of AMPP in toluene and evaporation of the solvent in vacuo. In a typical experiment, a solution of the α -keto acid derivative (4 mmol) in toluene (10 mL) was degassed by two freeze–thaw cycles and then transferred on the solid catalyst precursor (ca. 15 mg, 0.01 mmol). The resulting solution was transferred in a 100 mL stainless steel autoclave, hydrogen (99%, Air Liquide) was introduced (50 kg/cm²), and the reaction mixture was magnetically stirred at 20°C. After the desired reaction time or completion of the reaction (quantitative GLC monitoring), hydrogen was removed and the solution was concentrated in vacuo. The crude residue was analysed by NMR and/or GLC and then either distilled or chromatographed to give the hydrogenation product in 90–99% isolated yield (for 100% conversions).

Enantiomeric excesses of lactate derivatives **4a–e** were determined by GLC analysis of crude solutions (**4a–c**, **4e**: cyclodex β -I/P, 25 m \times 0.32 mm; **4d**: cyclodex G-TA, 25 m \times 0.32 mm). Ethyl mandelate **6a** was analyzed by HPLC (Chiralcel OD, hexane/2-propanol 95:5, 1 mL/min, UV detector 254 nm; t_{R} of (*S*)-**6a** and (*R*)-**6a**, 13.3 and 24.1 min). All the HPLC analyses were conducted under the same conditions, unless otherwise stated. Absolute configuration of the prevailing enantiomer was made by comparison with authentic samples and/or of the sign of optical rotation. The details for other products are given below.

Ethyl (R)-(-)-2-hydroxy-4-phenylbutanoate 4f ([90315-82-5])

Yellow oil. Anal. calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3$: C, 69.21; H, 7.74; Found: C, 69.50; H, 7.81. NMR ^1H (CDCl_3): δ 1.28 (t, 3H, $J=7.1$ Hz, CH_3 OEt), 1.97 and 2.10 (2m, 2 \times 1H, CH_2CH), 2.76 (m, 2H, CH_2Ph), 2.80 (s broad, 1H, OH), 4.20 (m, 3H, CH and OCH_2), 7.25 (m, 5H, H aro). NMR ^{13}C (CDCl_3): δ 14.0 (CH_3 OEt), 31.0 (CH_2), 36.0 (CH_2), (CH_3), 61.6 (OCH_2), 69.7 (CHOH), 125.9 (C-4), 128.3, 128.4 (C-2, C-3), 141.1 (C-1), 175.1 (COO). IR (CHCl_3): ν 1729 (vs). MS (EI): 208 (M^+ , 15%), 117 (10%), 104 (65%), 91 (100%). $[\alpha]_{\text{D}}^{25}$ (c 1, CHCl_3) = -15.8, 77% ee *R* (lit.²⁸ $[\alpha]_{\text{D}}$ (c 1, CHCl_3) = -22.1 for (*R*)-**4f**). Ee assayed by HPLC analysis; t_{R} of (*S*)-**4f** and (*R*)-**4f**, 9.8 and 15.6 min.

Ethyl (-)-2-hydroxy-2-(4'-chlorophenyl)acetate 6b ([13511-29-0] (\pm))

Greyish crystals. Anal. calcd for $\text{C}_{10}\text{H}_{11}\text{ClO}_3$: C, 55.96; H, 5.17; Found: C, 57.33; H, 5.11. NMR ^1H (CDCl_3): δ 1.21 (t, 3H, $J=7.1$ Hz, CH_3), 3.5 (s broad, 1H, OH), 4.1–4.3 (m, 2H, OCH_2), 5.12 (s, 1H, CH), 7.35 (m, 4H, H aro). NMR ^{13}C (CDCl_3): δ 14.0 (CH_3), 62.4 (OCH_2), 72.2 (CHOH), 127.8, 128.6 (C-2, C-3), 134.2, 136.8 (C-1, C-4), 173.2 (COO). IR (KBr): ν 3444 (s sharp), 1731 (vs). MS

(EI): 214/216 ($M^{+35}\text{Cl}/^{37}\text{Cl}$, 10%), 141/143 ($M-\text{COOEt}$, 100%), 113 (15%), 77 (80%). $[\alpha]_{\text{D}}^{25}$ (*c* 1, CHCl_3) = -14.7 (8% ee). Ee assayed by HPLC analysis; t_{R} of (+)-**6b** and (-)-**6b**, 9.9 and 11.8 min.

Ethyl (S)-(+)-2-hydroxy-2(3'-chlorophenyl)acetate 6c

Yellow oil. Anal. calcd for $\text{C}_{10}\text{H}_{11}\text{ClO}_3$: C, 55.96; H, 5.17; Found: C, 55.63; H, 5.22. NMR ^1H (CDCl_3): δ 1.23 (t, 3H, $J=7.1$ Hz, CH_3), 3.4 (s broad, 1H, OH), 4.10–4.32 (m, 2H, OCH_2), 5.12 (s, 1H, CH), 7.29 (s, 3H, H aro), 7.43 (s, 1H, H aro). NMR ^{13}C (CDCl_3): δ 13.6 (CH_3), 62.0 (OCH_2), 72.0 (CHOH), 124.5, 126.4, 128.1, 129.5 (CH aro), 134.0 (C-3), 140.1 (C-1), 172.6 (COO). IR (CHCl_3): ν 1733 (vs). MS (EI): 214/216 ($M^{+35}\text{Cl}/^{37}\text{Cl}$, 7%), 141/143 ($M-\text{COOEt}$, 70%), 113 (30%), 77 (100%). $[\alpha]_{\text{D}}^{25}$ (*c* 1.315, CHCl_3) = +20.1 (20% ee *S*). Ee assayed by HPLC analysis; t_{R} of (*S*)-**6c** and (*R*)-**6c**, 9.9 and 12.3 min. For determining the absolute configuration of the prevailing enantiomer, an aliquot of **6c** was converted to ethyl mandelate: a solution of **6c** (100 mg, 0.36 mmol) and NEt_3 (0.4 mL, 2.8 mmol) in methanol (10 mL) was transferred in an hydrogenation flask containing Pd/C 10% (10 mg, 3 mol% cat). The atmosphere was replaced with H_2 and the suspension was agitated for 18 h. After filtration on neutral alumina to remove catalyst, the solution was evaporated in vacuo, and the crude solid extracted with $\text{H}_2\text{O}/\text{CHCl}_3$ (2:2 mL). The organic layer was dried from MgSO_4 and concentrated to afford pure ethyl mandelate which proved to contain mainly the *S* enantiomer (polarimetry, chiral HPLC).

Ethyl (S)-(-)-2-hydroxy-2(2',4'-dichlorophenyl)acetate 6d ((±) [41204-18-6])

Colourless oil. Anal. calcd for $\text{C}_{10}\text{H}_{10}\text{Cl}_2\text{O}_3$: C, 48.22; H, 4.05; Found: C, 50.42; H, 2.38. R_{f} (heptane/Et $_2\text{O}$ 50/50): 0.33. NMR ^1H (CDCl_3): δ 1.21 (t, 3H, $J=7.2$ Hz, CH_3), 3.63 (d, 1H, $J=4.7$ Hz, OH), 4.15–4.30 (m, 2H, OCH_2), 5.48 (d, 1H, CH), 7.25 (dd, 1H, $J(\text{H}_5-\text{H}_6)=8.3$ Hz, $J(\text{H}_5-\text{H}_3)=2.1$ Hz, H-5), 7.33 (d, 1H, H-6), 7.40 (d, 1H, H-3). NMR ^{13}C (CDCl_3): δ 14.0 (CH_3), 62.6 (OCH_2), 69.8 (CHOH), 127.4 (C-5), 129.7, 130.1 (C-3, C-6), 134.3, 134.8, 134.8 (C-1, C-2, C-4), 172.8 (COO). IR (KBr): ν 3435 (m broad), 1740 (vs). MS (EI): 248/250 ($M^{+35}\text{Cl}/^{37}\text{Cl}$, 10%), 213/233 ($M-\text{OH}$, 2%), 203/205 ($M-\text{OEt}$, 15%), 175/177 ($M-\text{COOEt}$, 100%), 147/149 ($M-\text{COCOOEt}$, 15%). $[\alpha]_{\text{D}}^{25}$ (*c* 1, CHCl_3) = -109.7 (81% ee *S*). Ee's were determined from ^1H NMR spectra of the isolated product in the presence of chiral shift reagent (+)-Eu(hfc) $_3$; $\delta_{\text{H-3R}}$ 7.85 (d, 8.3 Hz), $\delta_{\text{H-3S}}$ 7.93 (d, 8.3 Hz). An aliquot of **6d** (76% ee) was dechlorinated using the same procedure as described for **6c** (50% conversion in 39 h), yielding (*S*)-(+)-ethyl mandelate (73% ee, HPLC).

Ethyl (-)-2-hydroxy-2(4'-methoxyphenyl)acetate 6e ((±) [36141-66-9])

Yellowish oil. Anal. calcd for $\text{C}_{11}\text{H}_{14}\text{O}_4$: C, 62.85; H, 6.71; Found: C, 62.10; H, 6.95. NMR ^1H (CDCl_3): δ 1.21 (t, 3H, $J=7.1$ Hz, CH_3), 2.34 (s, 1H, OH), 3.79 (s, 3H, OCH_3), 4.15 and 4.25 (m, 2 \times 1H, OCH_2), 5.10 (s, 1H, CH), 6.88 (d, 2H, $J=6.7$ Hz, H-3 and H-5), 7.32 (d, 2H, H-2, H-6). NMR ^{13}C (CDCl_3): δ 14.0 (CH_3), 55.2 (OCH_3), 62.1 (OCH_2), 72.4 (CHOH), 113.9 (C-3, C-5), 127.8 (C-2, C-6), 130.6 (C-1), 159.6 (C-4), 173.8 (COO). IR (CHCl_3): ν 1731 (vs). MS (EI): 210 (M^+ , 7%), 137 ($M-\text{COOEt}$, 100%), 109 (7%), 94 (10%). $[\alpha]_{\text{D}}^{25}$ (*c* 1, CHCl_3) = -24.7 (21% ee). Ee assayed by HPLC; t_{R} of (+)-**6e** and (-)-**6e**, 15.0 and 30.5 min.

Ethyl (-)-2-hydroxy-2(2',4'-dimethoxyphenyl)acetate 6f ([120757-12-2])

Colourless oil. Anal. calcd for $\text{C}_{12}\text{H}_{16}\text{O}_5$: C, 59.99; H, 6.71; Found: C, 60.57; H, 6.51. Bp: 170°C (0.6 mm Hg). NMR ^1H (CDCl_3): δ 1.17 (t, 3H, $J=7$ Hz, CH_3), 2.3 (s, 1H, OH), 3.75 (s, 6H, 2 OCH_3), 4.17 (q, 2H, OCH_2), 5.18 (s, 1H, CH), 6.42 (m, 2H, H-3 and H-5), 7.14 (m, 1H, H-6). NMR ^{13}C (CDCl_3): δ 13.9 (CH_3), 55.1 and 55.2 (2 OCH_3), 61.4 (OCH_2), 69.5 (CHOH), 98.7 (C-3), 104.2 (C-5), 119.7 (C-1), 129.9 (C-6), 158.0 and 161.2 (C-2, C-4), 173.8 (COO). IR (CHCl_3): ν 3502 (s), 1737 (vs). MS (EI): 240 (M^+ , 10%), 167 ($M-\text{COOEt}$, 100%), 151 (10%), 137 (15%), 92 (15%). $[\alpha]_{\text{D}}^{25}$ (*c* 1, CHCl_3) = -74 (74% ee). Ee determined by ^{19}F NMR analysis of the (*R*)-MTPA ester ($\delta_{(-)}$ -70.2, $\delta_{(+)}$ -69.9); this technique gave consistent results with ee values based on the specific rotation.

Ethyl (-)-2-hydroxy-2(2',4'-dimethylphenyl)acetate 6g ((±) [20305-97-9])

Colourless oil. Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; Found: C, 69.92; H, 7.54. R_f (heptane/Et₂O 50/50): 0.37. NMR ¹H (CDCl₃): δ 1.21 (t, 3H, $J=7.1$ Hz, CH₃ OEt), 2.30 (s, 3H, CH₃), 2.39 (s, 3H, CH₃), 3.40 (d, 1H, $J=5.2$ Hz, OH), 4.10–4.32 (m, 2H, OCH₂), 5.30 (d, 1H, CH), 7.00 (m, 2H, H-3, H-5), 7.59 (d, 1H, $J(H_6-H_5)=8.4$ Hz, H-6). NMR ¹³C (CDCl₃): δ 14.0 (CH₃ OEt), 19.1 and 21.0 (CH₃), 62.6 (OCH₂), 70.2 (CHOH), 126.7, 126.9 (C-5, C-6), 131.5 (C-3), 133.9, 136.2, 138.0 (C-1, C-2, C-4), 174.3 (COO). IR (CHCl₃): ν 3527 (w, broad), 1729 (vs). MS (EI): 208 (M⁺, 10%), 190 (M–H₂O, 10%), 135 (M–COOEt, 100%), 107 (50%), 91 (50%). $[\alpha]_D^{25}$ (c 1, CHCl₃) = –67.7 (51% ee). Ee assayed by HPLC analysis; t_R of (+)-**6g** and (–)-**6g**, 9.5 and 14.3 min.

Ethyl (S)-(+)-2-hydroxy-2(2'-thienyl)acetate 6h ((±) [62323-55-1]; (R) [61444-21-1])

Colourless oil which became oxidized over several weeks in air to a dark red oil. Anal. calcd for $C_8H_{10}O_3S$: C, 51.60; H, 5.41; S, 17.22; Found: C, 51.42; H, 5.51; S, 16.97. Eb: 130°C (0.6 mm Hg). NMR ¹H (CDCl₃): δ 1.27 (t, 3H, $J=7.1$ Hz, CH₃), 3.5 (s broad, 1H, OH), 4.26 (qd, 2H, $J=4.6$ and 7.1 Hz, OCH₂), 5.39 (d, 1H, $J=0.7$ Hz, CH), 6.97 (dd, 1H, $J=3.6$ and 5.1 Hz, H-4), 7.09 (dt, 1H, $J=1.1$ and 3.5 Hz, H-3), 7.26 (dd, 1H, $J=1.3$ and 5.1 Hz, H-5). NMR ¹³C (CDCl₃): δ 14.0 (CH₃), 62.5 (OCH₂), 69.0 (CHOH), 125.3, 125.6, 126.9 (C-3, C-4, C-5), 141.5 (C-2), 172.4 (COO). IR (neat): ν 1737 (vs). MS (EI): 186 (M⁺, 7%), 141 (M–OEt, 20%), 113 (M–COOEt, 100%), 85 (50%). $[\alpha]_D^{25}$ (c 2, CHCl₃) = +40.0 (48% ee S). Ee assayed by HPLC analysis; t_R of (+)-**6h** and (–)-**6h**, 12.7 and 18.1 min.

Ethyl (S)-(+)-2-hydroxy-2(2'-furyl)acetate 6i ((±) [19377-72-1])

White needles. Anal. calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92; Found: C, 56.41; H, 6.00. NMR ¹H (CDCl₃): δ 1.25 (t, 3H, $J=7.1$ Hz, CH₃), 3.5 (s broad, 1H, OH), 4.27 (m, 2H, $J=2.9$, 4.2 and 7.2 Hz, OCH₂), 5.17 (s, 1H, CH), 6.35 (m, 2H, H-3 and H-4), 7.38 (dd, 1H, $J=0.9$ and 1.7 Hz, H-5). NMR ¹³C (CDCl₃): δ 13.7 (CH₃), 62.3 (OCH₂), 66.7 (CHOH), 108.4, 110.3 (C-3, C-4), 142.7 (C-5), 151.0 (C-2), 171.2 (COO). IR (neat): ν 3451 (s), 1738 (vs). MS (EI): 170 (M⁺, 15%), 97 (M–COOEt, 100%). $[\alpha]_D^{25}$ (c 2, CHCl₃) = +39 (42% ee S). Ee assayed by HPLC analysis; t_R of (+)-**6i** and (–)-**6i**, 12.3 and 15.0 min.

Benzyl (S)-(+)-2-hydroxy-2-phenylacetate 6j

White powder. Anal. calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82; Found: C, 74.25; H, 5.56. Mp: 95–96°C. NMR ¹H (CDCl₃): δ 5.10–5.30 (m, 3H, CH₂+CH), 7.15–7.5 (m, 10H, H aro). NMR ¹³C (CDCl₃): δ 67.6 (CH₂), 72.9 (CHOH), 126.6, 127.9, 128.4, 128.5, 128.5, 128.6 (CH aro), 135.0, 138.1 (C aro), 173.5 (COO). IR (KBr): ν 3448 (s), 3409 (s), 1742 (m), 1723 (vs). MS (EI): 242 (M⁺, 0.2%), 107 (M–COOBz, 100%), 91 (40%). $[\alpha]_D^{25}$ (c 1.03, CHCl₃) = +57.5 (>99 ee S). Ee assayed by HPLC analysis; t_R of (S)-**6j** and (R)-**6j**, 18.5 and 39.8 min.

(S)-(+)-N-Benzyl-2-hydroxy-2-phenylacetamide 8a

White crystals. Anal. calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80; Found: C, 74.70; H, 6.22; N, 5.71. Mp: 136°C. NMR ¹H (CDCl₃): δ 4.39 (m, 2H, CH₂, $J=5.6$ and 5.9 Hz), 5.00 (s, 1H, CH), 6.64 (s broad, 1H, NH), 7.16 (m, 2H, H aro), 7.3–7.5 (m, 8H, H aro). NMR ¹³C (CDCl₃): δ 43.4 (CH₂), 74.1 (CHOH), 126.8, 127.5, 128.6, 128.7, 128.8 (CH aro), 137.6, 139.4 (C aro), 172.1 (CONH). IR (KBr): ν 3390 (m, broad), 3175 (m), 1635 (vs), 1440 (s), 1060 (s). MS (EI): 241 (M⁺, 15%), 223 (8%), 135 (M–NHbz, 20%), 107 (M–CONHBz, 100%), 91 (100%), 79 (90%). $[\alpha]_D^{25}$ (c 1.09, CHCl₃) = +82.2 (>99% ee, S). Ee determined by polarimetry based on the aforementioned value (obtained by recrystallization of a scalemic sample until constant optical rotation) and checked by ¹H and ¹³C NMR analysis after derivatization with chloroformic acid (1*R*,2*S*,5*R*)-(–)-methyl-2-(1-methylethyl)cyclohexanol ester²⁷ (selected values: ¹H NMR, $\delta_{(-)}$ 5.97 (s, CHOCO₂R*), $\delta_{(+)}$ 5.98; ¹³C NMR $\delta_{(-)}$ 153.3 (s, CHOCO₂R*), $\delta_{(+)}$ 153.1).

(S)-(+)-N-Benzyl-2-hydroxy-2(4'-chlorophenyl)acetamide 8b

White crystals. Anal. calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08; Found: C, 65.21; H, 5.24; N, 5.21. Mp: 108–110°C. NMR 1H ($CDCl_3$): δ 4.33 (d, 2H, $J=4.8$ Hz, CH_2), 4.95 (s, 1H, CH), 6.9 (s broad, 1H, NH), 7.15 (m, 2H, H aro), 7.25 (m, 7H, H aro). NMR ^{13}C ($CDCl_3$): δ 43.3 (CH_2), 73.4 (CHOH), 127.5, 127.6, 128.0, 128.7, 128.8 (CH aro), 134.3, 137.4, 137.9 (C aro), 171.9 (CONH). IR (KBr): ν 3405 (m), 3247 (m), 1661 (vs), 1621 (vs). MS (EI): 275/277 ($M^{+35}Cl/^{37}Cl$, 11%), 257/259 (5%), 141/143 (M–CONHBz, 65%), 113 (15%), 91 (Bz, 85%), 77 (100%). $[\alpha]^{25}_D$ (c 1, $CHCl_3$)=+64.4 (87% ee, S). Ee determined by polarimetry after dechlorination to **8a** using the same procedure as described for **6c** (100% conv in 17 h, 90% isolated yield).

(S)-(+)-N-Benzyl-2-hydroxy-2(3'-chlorophenyl)acetamide 8c

White crystals. Anal. calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08; Found: C, 65.53; H, 4.94; N, 5.01. Mp: 73–74°C. NMR 1H ($CDCl_3$): δ 4.36 (d, 2H, $J=5.9$ Hz, CH_2), 4.97 (s, 1H, CH), 6.8 (s broad, 1H, NH), 7.10–7.40 (m, 9H, H aro). NMR ^{13}C ($CDCl_3$): δ 43.2 (CH_2), 73.3 (CHOH), 124.8, 126.7, 127.5, 128.5, 128.7, 129.8 (CH aro), 134.3 (C-3), 137.4 (C-1'), 141.4 (C-1), 171.8 (CONH). IR (KBr): ν 3413 (m, broad), 1656 (vs), 1625 (vs). MS (EI): 275/277 ($M^{+35}Cl/^{37}Cl$, 20%), 257/259 (5%), 141/143 (M–CONHBz, 40%), 113 (25%), 91 (Bz, 100%). $[\alpha]^{25}_D$ (c 1, $CHCl_3$)=+56.3 (87% ee, S). Ee determined by polarimetry after dechlorination to **8a** using the same procedure as described for **6c** (100% conversion in 18 h, 81% isolated yield).

(S)-(+)-N-Benzyl-2-hydroxy-2(4'-methoxyphenyl)acetamide 8d

White powder. Anal. calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16; Found: C, 69.47; H, 7.16; N, 5.01. Mp: 105–106°C. NMR 1H ($CDCl_3$): δ 3.4 (s broad, 1H, OH), 3.79 (s, 3H, OCH_3), 4.42 (m, 2H, CH_2), 5.00 (s, 1H, CH), 6.50 (s broad, 1H, NH), 6.87 (m, 2H, H aro), 7.10–7.45 (m, 7H, H aro). NMR ^{13}C ($CDCl_3$): δ 43.5 (CH_2), 55.3 (OCH_3), 73.8 (CHOH), 127.6, 128.2, 128.7 (C-2, C-2', C-3', C-4'), 131.5 (C-1), 137.7 (C-1'), 159.9 (C-4), 172.3 (CONH). IR (KBr): ν 3400 (m, broad), 3284 (m), 1657 (s), 1613 (vs), 1515 (s). MS (EI): 271 (M^+ , 7%), 137 (M–CONHBz, 100%), 109 (20%), 91 (60%), 77 (55%). $[\alpha]^{25}_D$ (c 1, $CHCl_3$)=+66 (>98% ee, S). Ee determined by polarimetry based on the aforementioned value (obtained by recrystallization of a 85% ee product until constant optical rotation).

(+)-N-Benzyl-2-hydroxy-2-thienylacetamide 8e

White powder. Anal. calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66; S, 12.96; Found: C, 63.06; H, 5.23; N, 5.59; S, 12.69. Mp: 115–116°C. NMR 1H ($CDCl_3$): δ 4.05 (s broad, 1H, OH), 4.43 (m, 2H, CH_2), 5.31 (s, 1H, CH), 6.75 (s broad, 1H, NH), 6.95 (dd, 1H, $J=3.7$ and 4.8 Hz, H thienyl), 7.08 (d, 1H, $J=3.1$ Hz, H thienyl), 7.10–7.40 (m, 6H, H aro). NMR ^{13}C ($CDCl_3$): δ 43.3 (CH_2), 70.1 (CHOH), 125.7, 126.7, 127.5, 127.8, 128.6 (CH aro), 137.5, 138.1, 138.7, 142.5 (C aro), 171.5 (CONH). IR (KBr): ν 3409 (m, broad), 1650 (vs), 1538 (s). MS (EI): 247 (M^+ , 5%), 135 (15%), 113 (M–CONHBz, 100%), 91 (80%). $[\alpha]^{25}_D$ (c 1, $CHCl_3$)=+27.4 (>98% ee). Ee determined by polarimetry based on the aforementioned value (obtained by recrystallization of a 86% ee sample until constant optical rotation).

(+)-Dihydro-3,3-dioxindole 10a ((±) [61-71-2], [124508-45-8] (R))

Pale brown powder. Anal. calcd for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39; Found: C, 64.86; H, 4.73; N, 9.32. Mp: 168°C (dec). R_f (toluene/EtOH 85/15): 0.34 (dioxindole: 0.44). NMR 1H (acetone- d_6): δ 4.93 (d, 1H, $J=5.1$ Hz, CH), 5.2 (d, 1H, OH), 6.87 (d, 1H, $J=7.8$ Hz, H aro), 6.99 (dt, 1H, $J=1$ and 7.5 Hz, H aro), 7.21 (m, 1H, $J=7.7$ Hz, H aro), 7.35 (d, 1H, $J=7.4$ Hz, H aro), 9.2 (s broad, 1H, NH). NMR ^{13}C (methanol- d_4): δ 71.2 (CHOH), 111.1, 123.6, 126.0 (CH aro), 130.1 (C aro), 130.5 (CH aro), 143.2 (C aro), 180.0 (CONH). IR (KBr): ν 3350 (s, broad), 1732 (s), 1705 (vs), 1671 (m), 1626 (s), 1474 (s). MS (EI): 149 (M^+ , 20%), 148 (50%), 118 (15%), 92 (100%). $[\alpha]^{25}_D$ (c 1, EtOH)=+42.5 (>98% ee), $[\alpha]^{25}_D$ (c 1, MeOH)=+36 (94% ee) (lit.¹⁹ $[\alpha]^{25}_D$ (c 1, MeOH)=+7 for a sample claimed

to be optically pure, see text). Ee determined from ^1H NMR spectrum of the isolated product in the presence of chiral shift reagent (+)-Eu(hfc) $_3$; $\delta_{\text{H}(-)}$ 6.79 (d, 7.9 Hz), $\delta_{\text{H}(+)}$ 6.83 (d, 7.9 Hz). This technique gave consistent results with polarimetry based on our aforementioned value (obtained by recrystallization of a scalemic sample until constant optical rotation) and with ^1H NMR analysis of the derivatization product with chloroformic acid (1*R*,2*S*,5*R*)-(-)-methyl-2-(1-methylethyl)cyclohexanol ester²⁷ (selected values: $\delta_{\text{H}(-)}$ 5.77 (s, CHOCO $_2\text{R}^*$), $\delta_{\text{H}(+)}$ 5.79).

(+)-3,3-Dihydro-5-bromodioxindole **10b** ((\pm) [99304-37-7])

Yellowish powder. Anal. calcd for C $_8\text{H}_6\text{BrNO}_2$: C, 42.14; H, 2.65; N, 6.14.; Found: C, 42.74; H, 3.14; N, 6.03. Mp: 175–180°C. R $_f$ (toluene/EtOH 85/15): 0.48 (5-bromodioxindole: 0.53). NMR ^1H (acetone- d_6): δ 4.95 (d, 1H, $J=7$ Hz, CH), 5.4 (d, 1H, OH), 6.85 (d, 1H, $J=8$ Hz, H-3), 7.40 (dd, 1H, $J=1.5$ and 8 Hz, H-4), 7.48 (d, 1H, $J=0.5$ Hz, H-6), 9.35 (s broad, 1H, NH). NMR ^{13}C (methanol- d_4): δ 71.0 (CHOH), 112.8 (CH aro), 115.9 (C aro), 129.1 (CH aro), 132.4 (C aro), 133.4 (CH aro), 142.4 (C aro), 180.0 (CONH). IR (KBr): ν 3340 (s, broad), 1710 (vs), 1623 (m), 1478 (s). MS (EI): 227/229 (M $^{+79}\text{Br}^{81}\text{Br}$, 15%), 199/201 (10%), 171/173 (50%), 148 (M–Br, 45%), 92 (100%). $[\alpha]^{25}_{\text{D}}$ (c 1, EtOH)=+32 (85% ee). Ee determined from ^1H NMR spectrum of the derivatization product with chloroformic acid (1*R*,2*S*,5*R*)-(-)-methyl-2-(1-methylethyl)-cyclohexanol ester.²⁷

(+)-3,3-Dihydro-1-methyldioxindole **10c** ((*R*) [124508-46-9])

Yellowish powder. Anal. calcd for C $_9\text{H}_9\text{NO}_2$: C, 66.25; H, 5.56; N, 8.58; Found: C, 66.22; H, 5.67; N, 8.40. Mp: 126°C. R $_f$ (toluene/EtOH 85/15): 0.45 (1-methyldioxindole: 0.52). NMR ^1H (acetone- d_6): δ 3.11 (s, 3H, NMe), 4.96 (d, 1H, $J=5.1$ Hz, CH), 5.25 (d, 1H, OH), 6.92 (d, 1H, $J=7.8$ Hz, H aro), 7.05 (dt, 1H, $J=1.0$ and 7.3 Hz, H aro), 7.31 (tq, 1H, $J=0.5$, 0.7 and 7.8 Hz, H aro), 7.38 (d, 1H, $J=7.3$ Hz, H aro), 9.35 (s broad, 1H, NH). NMR ^{13}C (acetone- d_6): δ 26.0 (NMe), 70.1 (CHOH), 108.9, 123.0, 125.4 (CH aro), 129.1 (C aro), 130.0 (CH aro), 145.1 (C aro), 176.6 (CONH). IR (KBr): ν 3340 (s, broad), 1701 (vs), 1617 (s), 1470 (m), 1382 (m), 1350 (m). MS (EI): 163 (M $^+$, 50%), 135 (10%), 118 (10%), 106 (100%). $[\alpha]^{25}_{\text{D}}$ (c 1, EtOH)=+28 (80% ee) (lit.¹⁹ $[\alpha]^{25}_{\text{D}}$ (c 1, MeOH)=+3 for a sample claimed to be optically pure, see text). Ee determined from ^1H NMR spectra of the isolated product in the presence of chiral shift reagent Eu(hfc) $_3$ ($\delta_{\text{H}(-)}$ 6.90 (d, 7.6 Hz), $\delta_{\text{H}(+)}$ 6.99 (d, 7.8 Hz)) and of the derivatization product with chloroformic acid (1*R*,2*S*,5*R*)-(-)-methyl-2-(1-methylethyl)cyclohexanol ester.²⁷

(+)-3,3-Dihydro-1-phenyldioxindole **10d**

Yellowish powder. This compound rapidly became oxidized in air, particularly in solution, to give back **9d**. Mp: 86°C (dec). Anal. calcd for C $_{14}\text{H}_{11}\text{NO}_2$: C, 74.65; H, 4.92; N, 6.22; Found: C, 72.81; H, 5.17; N, 5.68. R $_f$ (toluene/EtOH 85/15): 0.60 (1-phenyl-dioxindole: 0.78). NMR ^1H (acetone- d_6): δ 5.15 (d, 1H, $J=6.7$ Hz, CH), 5.4 (d, 1H, OH), 6.75 (d, 1H, $J=7.5$ Hz, H aro), 7.0–7.35 and 7.4–7.7 (m, 8H, H aro). NMR ^{13}C (acetone- d_6): δ 70.3 (CHOH), 109.8, 123.6, 126.0, 127.3, 128.6 (CH aro), 129.0 (C aro), 130.0, 130.3 (CH aro), 144.8 (C aro), 176.0 (CONH). IR (KBr): ν 3408 (s, broad), 1715 (vs), 1615 (s), 1482 (s), 1455 (s), 1374 (s). MS (FAB/NBA): 225 (M $^+$, 100%), 208 (M–OH, 70%), 196 (50%). $[\alpha]^{25}_{\text{D}}$ (c 1, EtOH)=+21 (88% ee). Ee determined from ^1H NMR spectrum of the isolated product in the presence of chiral shift reagent (+)-Eu(hfc) $_3$ ($\delta_{\text{H}(-)}$ 5.35 (d, $J=6$ Hz), $\delta_{\text{H}(+)}$ 5.40 (d, $J=6$ Hz)) and by ^{19}F NMR analysis of the (*R*)-MTPA ester ($\delta_{(-)}$ –69.9, $\delta_{(+)}$ –69.7).

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