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Process-scale preparation of enantiomerically pure γ-lactones by asymmetric hydrogenation of γ-ketoesters and comparative tests of the sensory properties of some antipodes

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Abstract—A reliable methodology, applicable on a process-scale level, for producing enantiomerically pure chiral γ-lactones by enantioselective hydrogenation of γ-ketoesters, followed by cyclisation of the resulting γ-hydroxyesters, has been developed. The multi-step procedure was transformed into a one-pot reaction. A very efficient chiral Ru-complex, based on the biheteroaromatic diphosphine ligand tetraMe-BITIOP, was developed as a catalyst, capable of coupling fast kinetics with high stereoselection levels. Its structure was fully elucidated through ^{31}P NMR, EPR and X-ray single-crystal analyses. The optimal experimental conditions are as follows: hydrogen pressure = 30 psi, S/C ratio = 2000, 30% in weight substrate concentration. Yields are quantitative and enantiomeric excesses in the range 98–99.9%. Sensorial tests on the antipodes of two γ-lactones demonstrated the very different properties of the enantiomers.

1. Introduction

The importance of chiral γ-lactones, in which the carbon atom bearing the alcohol moiety is stereogenic, has been recognised since the 19th century.[1] Their occurrence as components of natural products and their utility as synthons in the preparation of a great variety of alkaloids, terpenoids and biologically active compounds is amply documented in the literature. Many chiral γ-lactones are common flavour components,[2] hence employed as additives in the perfume and food industries, mostly as racemates, which are inexpensive bulk intermediates. As expected, however, the sensory properties of chiral γ-lactones depend on the absolute configuration of the stereogenic carbon; it is well known that enantiomeric γ-lactones exhibit flavours, which are very different both in quality and intensity.[3] Thus, the advantages of a reliable, robust and industrially scalable synthetic methodology capable of producing a single enantiomer are evident.

The most popular enantioselective synthetic approaches to this class of molecules have been recently highlighted.[4] The large-scale preparation of enantiopure γ-lactones has been attempted according to a great variety of strategies. To date, however, there has not been a stereoselective method available, which would couple both chemical and economical advantages, so as to be considered applicable to the industrial production of these intermediates.

The requirements for a scalable method are: the accessibility of inexpensive starting materials; the simplicity of the synthetic scheme, which should be the most direct

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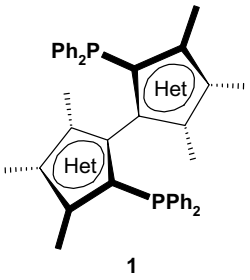
possible (possibly a one-pot synthesis); the high levels of chemical and stereoselection yields; the high productivity; the technological simplicity; the safety of the process and its environmental respect. It is quite evident that the resolution procedures of racemates are inapplicable. Successful attempts to accede to enantiopure γ-lactones have been performed through enzymatic methods[5] starting from a great variety of prochiral substrates: all these methodologies suffer breakdowns related to the low concentration levels, which are strongly limiting for productivity, to the cleaning and draining of process water, to the disposal of the exhausted enzyme masses.

The most promising approaches are based on chemical enantioselective catalysis. Noyori first applied the high-pressure hydrogenation (100 bar) of γ-ketoesters mediated by BINAP-Ru-X_2 complexes to the preparation of γ-hydroxyesters, which could be cyclised to lactones in good yields and remarkable enantiomeric excesses.[6] This methodology undoubtedly exhibits some positive points: starting materials are easily available and very inexpensive; high pressure technology is well-established today, even though large volume autoclaves equipped with the appropriate safety fittings are economically very onerous; the procedure does not involve pollution problems, since the products are volatile compounds and can be easily separated from the metal catalyst by distillation under reduced pressure. However, some negative aspects must be considered: productivity is low, since five days are required to carry the reactions to completion, and the turnover number is low. Much better results can be obtained when the $[NH_2–Me_2]$ $[\{RuCl\ (SEGPHOS)\}_2(\mu\text{-}Cl)_3]$ complex was employed as the catalyst, even though the experiments were limited to ethyl levulinate as the sole substrate.[7] The reaction times were reduced to 20 h when working at 50 bar hydrogen pressure, with 10^3 as a Substrate/Catalyst (S/C) ratio, at 50 °C in methanol solution. Conversion was quantitative and the enantiomeric excess of ethyl 4-hydroxypentanoate found to be 99.0%.

The target of the present work was the development of a general synthetic method of γ-lactones in high enantiomeric purity, based on the enantioselective catalytic hydrogenation of γ-ketoesters, successfully tested on different substrates, which would be economically acceptable and scalable to an industrial level. The driving force for this work was the availability of several members of an electronically tunable class of diphosphine ligands, characterised by an atropisomeric biheteroaromatic backbone, having the general structure **1** (Scheme 1) we had designed previously.[8]

The electronic availability of the phosphorus atoms can be modulated either by changing the five-membered aromatic heterocyclic system, or the position of the diphenylphosphino group on it. The Ru and Rh complexes of some of these ligands have been found so successful in the hydrogenation reactions of the carbon–oxygen double bond of α- and β-ketoesters and of carbon–carbon double bond of prostereogenic acrylic acid derivatives and in some carbon–carbon bond forming reaction, that they are now produced on an industrial scale level.



1

Scheme 1.

A further aim of this work was checking the sensory differences exhibited by the antipodes of some phenyl substituted γ-lactones, in order to evaluate the effects of the presence of a phenyl ring in the system on aroma.

2. Results and discussion

2.1. Choice of the substrates

The substrates we considered were ethyl levulinate **2a**, methyl 4-oxooctanoate **2b**, methyl 4-oxododecanoate **2c**, the methyl 4-oxo-6-phenylhexanoate **2d**, methyl 4-oxo-7-phenylheptanoate **2e**, methyl 3-methyl-4-oxooctanoate **2f** and methyl 3-methyl-4-oxononanoate **2g**. The racemic β-methyl substituted γ-ketoesters **2f** and **2g** were also considered in order to investigate the diastereoselectivity of the process (Scheme 2).

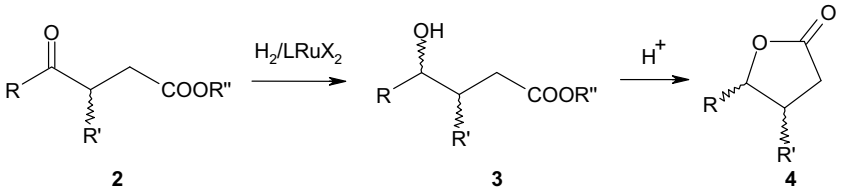
The hydrogenation of commercially available ethyl levulinate was chosen as the bench reaction to perform the preliminary comparative experiments.

2.2. Choice of the chiral ligand

We have been able to demonstrate that the Ru complexes produced from electron-rich ligands, are kinetically much more efficient than those resulting from electron-poorer diphosphines in the hydrogenation of α- and β-ketoesters.[9] Opposite results were observed in the inter- and intramolecular Heck reaction, where the palladium complexes of medium rich diphosphines, such as BITIANP **1b**, exhibit the highest catalytic activity.[10]

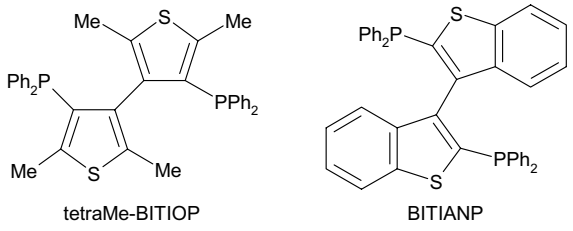
According to our quantitative classification of the electronic availability of the diphosphines, based on their electrochemical oxidative potential $E°$ (V) (the lower the $E°$, value the electron richer is the phosphine),[11] tetra-Me-BITIOP **1a** is a very electron-rich ligand ($E° = 0.57$ V), while BITIANP **1b** displays much more limited electron-releasing properties ($E° = 0.83$ V).

Thus, the most obvious strategy was to test the electron-rich diphosphine **1a** as a ligand of Ru in the γ-ketoester hydrogenations under the experimental conditions previously described in Noyori's paper.[6] It must be pointed out, however, that BINAP is a rather electron-rich ligand as well ($E° = 0.63$ V). Furthermore, we found that the $E°$ of SEGPHOS is fully comparable to that shown by **1a** ($E° = 0.56$ V) (Scheme 3).



a	R = Me	R' = H	R" = Et
b	R = *n*-Bu	R' = H	R" = Me
c	R = *n*-Oct	R' = H	R" = Me
d	R = Ph-$(CH_2)_2$-	R' = H	R" = Me
e	R = Ph-$(CH_2)_3$-	R' = H	R" = Me
f	R= *n*-Bu	R' = Me	R" = Me
g	R= *n*-Pent	R' = Me	R" = Me

Scheme 2.



Scheme 3.

As for the structural characterisation of the metal complexes of **1a**, we were able to prepare crystals of (tetraMe-BITIOP)$PdCl_2$ and (tetraMe-BITIOP)$PtCl_2$ suitable for X-ray diffractometric analysis. We found that the crystal structures of the Pd and Pt complexes were nearly superimposable: the former is reported in Figure 1.

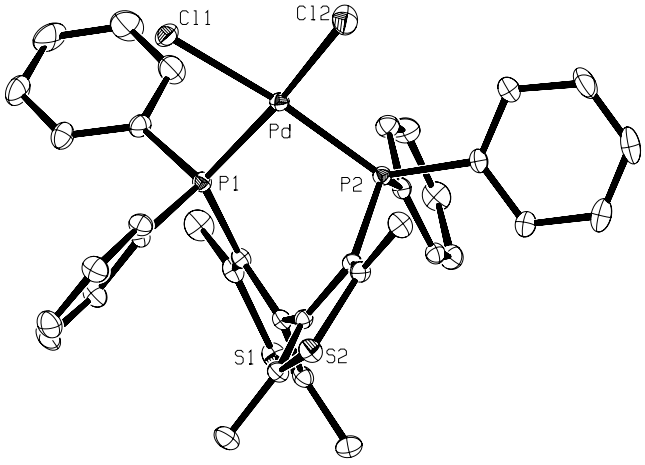


Figure 1. X-ray structures of (tetraMe-BITIOP)$PdCl_2$.

We considered it worth comparing the geometrical properties of the dichloropalladium complexes of **1a** and BINAP in order to investigate possible structural influences on the catalytic behaviour of their ruthenium complexes. Unfortunately, no single-crystal X-ray structures are available for the metal complexes of SEGPHOS.

Some notable differences are evident in the structures of the metal dichloride complexes of BINAP and tetraMe-BITIOP, as evidenced in Figure 2, reporting the results of their superimposition, in which the metal and phosphorus atoms are coincident.

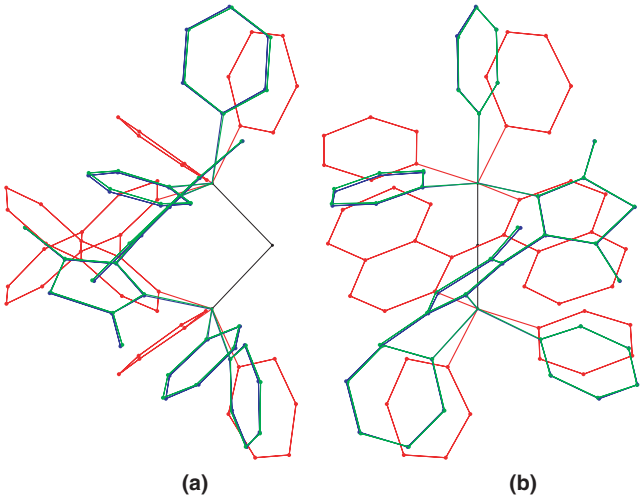


Figure 2. Superimposition of the X-ray structures of (BINAP)$PdCl_2$ (in red), (tetraMe-BITIOP)$PdCl_2$ (in green) and (tetraMe-BITIOP)$PtCl_2$ (in blue). Metal and phosphorus atoms are made to coincide. (a): view perpendicular to the plane individuated by metal and phosphorus atoms. (b): view aligned to the same P-metal-P plane.

Some points deserve special mention: (i) (BINAP)$PdCl_2$ complex is C_2 symmetric, while (tetraMe-BITIOP)$PdCl_2$ displays some distortion, which makes the model asymmetric (the same situation is found in the Pt complex); (ii) The P–Pd–P angle (natural bite angle) is nearly identical in all the complexes [92.7° in (BINAP)$PdCl_2$, and 92.0(2)° in (tetraMe-BITIOP)$PdCl_2$]; (iii) A substantial difference was found in the torsion angle around the interanular bond, which is 68.4° in (BINAP)$PdCl_2$ and 60.4(2)° in (tetraMe-BITIOP)$PdCl_2$. This quite large difference in the dihedral angle could play a relevant role in

the stereoselective process, since it has been documented that the lower the value of this angle, the higher the performances of the catalyst in hydrogenation reactions;[7,12] (iiii) A further difference was found in the steric encumbrance generated by the different biaryl backbone in the backside of the stereogenic core, which should influence stereoselectivity. The biphenyl moiety seems to produce a more overcrowded situation than the bithiophene unit.

2.3. Optimisation of the experimental procedure

The experimental conditions for the preliminary test hydrogenation experiments were standardised as follows: 100 bar hydrogen pressure, ethanol as solvent, at about 0.1 M substrate concentration, a 500 S/C ratio, 4×10^{-4} M dry HCl as co-catalyst (as suggested by Noyori), 50 °C temperature.

We found that the kinetic improvement produced by (tetraMe-BITIOP)Ru$(CF_3COO)_2$ in comparison with (BINAP)Ru$(CH_3COO)_2$ under analogous experimental conditions, was appreciable, even though too modest to be considered satisfactory: about 10 h were saved over a nearly five day reaction time required to drive the reaction catalysed by BINAP-based promoters to completion. The enantiomeric excess was found satisfactory (higher than 98%).

The same experimental conditions were applied in the hydrogenation of substrates **2b–e** and, in all the cases studied, enantioselectivities were quite high. However the problem of very long reaction times remained. The results are summarised in Table 1.

Table 1.

Substrate	Product[a]	Ee (%)	Reaction time (h)
2a	(+)-(*R*)-**4a**	98[b]	76
2b	(+)-(*R*)-**4b**	97[c]	168
2c	(+)-(*R*)-**4c**	98[b]	168
2d	(+)-(*R*)-**4d**	98[d]	168
2e	(+)-(*R*)-**4e**	>99.9[e]	168

[a] Configuration data refer to reactions promoted by the (−)-(*R*)-tetraMe-BITIOP ruthenium complex.
[b] Ee evaluated by polarimetric analysis.
[c] Ee evaluated by chiral hplc with a Chiralpak AD, flow rate 0.8 mL/min, λ 215, hexane/EtOH 95:5.
[d] Ee evaluated by chiral hplc with a Chiralcel OJ, flow rate 0.8 mL/min, λ 210, hexane/EtOH 88:12.
[e] Ee evaluated by chiral hplc with a Chiralcel OB, flow rate 0.8 mL/min, λ 210, hexane/EtOH 75:25.

Very poor results were obtained in the hydrogenation of substrates **2f** and **2g** as precursors of Cognac and Whisky lactones: *syn*:*anti* diastereoselectivity was about 3:1, the enantioselection levels were very low and the reaction rates unsatisfactory.

Comparison of the data obtained in the case of substrates **2f** and **2b**, differing only in the presence of the methyl group in position α to the ketonic carbonyl function, demonstrates that this kind of substitution is solely responsible for the dramatic worsening of kinetic activity and stereoselection ability of the Ru complex.

2.3.1. One-pot procedure. A good improvement of the synthetic procedure was realised by the simple observation that the primary product of the hydrogenation was a mixture of hydroxyester **3a** and lactone **4a**, and that the latter was the sole reaction product, if the reaction mixture was shortly refluxed after venting the hydrogen from the vessel. Thus, the synthetic scheme was reduced to a one-pot synthesis.

2.3.2. The 'bromoalkane effect'. An unexpected remarkable progress arose from a fortuitous observation. We found that the hydrogenation rates of several experiments carried out on the methyl 4-oxododecanoate **2c** were not reproducible and we discovered that the crucial parameter influencing kinetics was the purity of the starting material. In particular, small impurities of *n*-octyl bromide were found responsible for a remarkable reaction rate enhancement effect. Since substrate **2c** is prepared by reaction of *n*-octylmagnesium bromide with the *mono*-methyl ester-monochloride of succinic acid and purified by fractional distillation at reduced pressure, it was not surprising that traces of unreacted high-boiling bromooctane would have been retained in the final product.

We applied this trick to the hydrogenation procedure of other substrates and found that the addition of a 1-bromo-*n*-alkane (bromoalkane/substrate molar ratio = 0.16) invariably strongly reduced the reaction times, as shown in Table 2, while keeping the reaction enantioselectivities unchanged. Volatile 1-bromobutane can be employed in place of high-boiling 1-bromooctane in order to make the purification of the lactones easier.

Table 2.

Substrate	Bromo-alkane	Ee (%)	Reaction time (h)
2a	1-Bromobutane	98	43
2b	1-Bromooctane	>99.9	48
2c	1-Bromooctane	98	48
2d	1-Bromooctane	97	48

To explain this surprising rate enhancement, we carried out the hydrogenation of **2a** in the presence of 1-iodobutane instead of bromobutane, under the experimental conditions described in Table 2. An increase in the reaction rate would have supported the hypothesis that the insertion of the metal in the halogen-metal bond could occur to produce a catalytically more active species responsible for the observed rate enhancement. We found that the reaction rate was the same in both cases, thus ruling out mechanisms involving direct participation of the haloalkane in the production of the catalytic species.

A ^{31}P NMR investigation was carried out in order to detect any possible transformation of the starting (tetra-Me-BITIOP)Ru$(CF_3COO)_2$ complex (Fig. 3a) by sub- sequent additions of two equivalents of dry hydrogen chloride and *n*-butylbromide.

We found that a very complex mixture followed the addition of two equivalents of hydrogen chloride to the chloroform solution of pure bis(trifluoroacetate) complex, while no further modification of the spectrum occurred by addition of an excess of 1-bromobutane. A strong modification of the spectrum was observed, instead, by further addition of five equivalents of dry hydrogen chloride, which made the signals collapse into two clean, doublets, indicating the formation of a new single species (Fig. 3b).

When we employed the new, red-coloured, complex in the hydrogenation of ethyl levulinate under standard experimental conditions, we obtained kinetic data, which were fully comparable to those drawn from the reactions carried out in the presence of bromoalkanes.

These results suggest that at the origin of the outstanding rate enhancement produced by bromoalkanes is their partial hydrogenolysis, which supplies the starting complex the acidity necessary to be transformed into the new more active species.

As for the structure of the new complex, we knew that it was not the tetraMe-BITIOP-Ru-dichloride complex, since the latter was found scarcely active in the hydrogenation reactions of γ-ketoesters. Single-crystal X-ray diffraction analysis assigned to the deep red coloured complex, the diruthenium structure reported in Figure 4.

Thrichloro-bridged dinuclear face-sharing bioctaedral complexes of ruthenium with phosphines, in which the metal displayed average formal oxidation states in the range +2 to +3 are well known in the literature.[13] The point we had to clarify first was, therefore, the oxidation states of the metal atoms, which, in principle, were expected to be +2 for both of them, since no oxidising

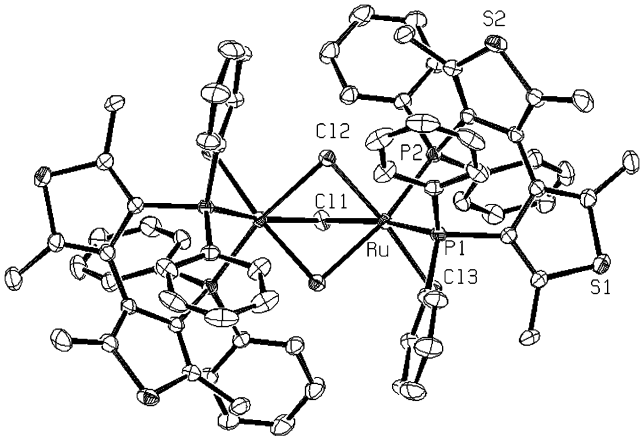


Figure 4. ORTEP projection along an interanular 3,3′-bithiophene bond.

reagents were involved in the formation of the new complex from the (tetraMe-BITIOP)Ru(CF_3COO)$_2$. In order to have evidence of the absence of a trivalent ruthenium in the dinuclear complex, we carried out comparative EPR experiments on the latter and on its mononuclear precursor in degassed frozen CH_2Cl_2–toluene solution. As expected, the (tetraMe-BITIOP)Ru(CF_3COO)$_2$ complex did not produce EPR signals, thus confirming that divalent ruthenium was only present. Somewhat more intriguing data were obtained in the case of the dinuclear complex. The freshly prepared sample gave only very minor signals but, after several minutes at room temperature, an axial signal ($g_\perp = 2.45$ and $g_\parallel = 1.70$) developed (Fig. 5).

A rhombic signal should be, however, expected for the EPR signals of complexes endowed with a C_2 symmetry axis, while axially symmetric EPR signals are typical of

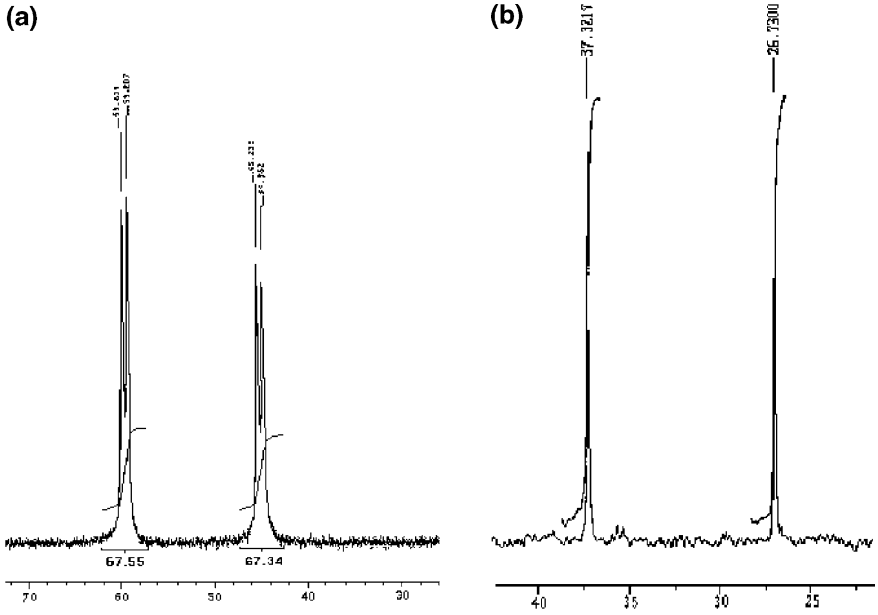


Figure 3. (a) ^{31}P NMR spectrum ($CDCl_3$) of (tetraMe-BITIOP)Ru(CF_3COO)$_2$; (b) ^{31}P NMR spectrum ($CDCl_3$) of (tetraMe-BITIOP)Ru(CF_3COO)$_2$ after addition of seven equivalents of dry hydrogen chloride.

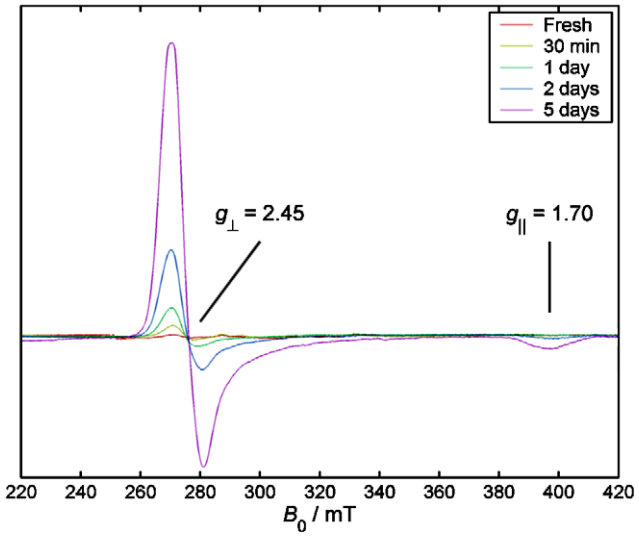


Figure 5. EPR spectra of the dinuclear ruthenium complex in dichloromethane/toluene 1:1 v/v at 77 K. The standing time at room temperature of the solution before EPR measurement is shown in the box.

binuclear complexes having connectivity L_3RuCl_3-$RuCl_2L$, where L is a monophosphine.[13] It is evident that the latter arrangement is compatible neither with the X-ray data nor with the geometry of bridged diphosphines. However, the above spectra are very similar to those observed in axially distorted octahedral low-spin $4d^5$ (t_{2g}^5) mononuclear Ru^{III} complexes.[14]

Furthermore, we found that the intensity of the axial EPR signal steeply increased over five days standing at room temperature under argon. The increase in EPR signal amplitude as a function of standing time is approximately parabolic. After 5 days, we observed an increase larger than 300-fold. This suggests that disruption of the dinuclear complex might have occurred, producing a mononuclear, paramagnetic Ru^{III} species, which was not present in the starting diamagnetic Ru^{II}–Ru^{II} complex.

It is worth noting that binuclear anionic complexes of this kind have been prepared starting from electron-rich diphosphines, such as achiral bis(dicyclohexyl)-1,4-phosphinobutane[15a] and chiral 2,2′-bis[bis(4-methoxyphenyl)-phosphino]-1,1′-binaphthyl (*p*-MeO-BINAP)[15b] and SEGPHOS.[7] In both the latter examples the counter ion is an ammonium cation, while it should be a proton in our case.

Some geometric features of the binuclear complex deserve special comment. The P–Ru–P angle value is very similar to that shown by the mononuclear Pd and Pt complexes described above. Very different is, instead, the value of the torsional angle of the bithiophene backbone, which undergoes a relevant reduction by passing from the mononuclear complexes (60.4°) to the dinuclear system (56.1°). This behaviour was not observed in the BINAP series, where both mononuclear and dinuclear Ru complexes display very similar torsional angles.

The extremely low value of the dihedral angle of the diruthenium complex of tetraMe-BITIOP is suggested as the main reason for the kinetic enhancements and improvements in enantioselectivity observed when it was used as the catalyst instead of the mononuclear complexes, such as (tetraMe-BITIOP)$Ru(CF_3COO)_2$ or (tetraMe-BITIOP)$RuCl_2$.

At this point, the experimental method for the catalytic γ-lactone synthesis was considered acceptable for scaling the process. However, two more parameters had to be investigated in detail; the concentration of the substrate and the S/C ratio.

2.3.3. Optimisation of the substrate/catalyst ratio. The maximisation of the S/C ratio represents a crucial point in any investigation directed towards producing an industrially valuable catalytic synthetic methodology.

Once more, the hydrogenation reaction of **2a** was taken as a model. Experiments were carried out with 1000:1 and 2000:1 S/C ratios, under identical experimental conditions. As expected, a decrease in the S/C ratio was followed by a parallel decrease in the reaction rate (48 and 67 h, respectively, were required for the complete conversion), while the enantiomeric excesses did not seem to be influenced at all by this parameter. We considered the reaction time required when the 2000/1 S/C ratio was employed still acceptable.

2.3.4. Concentration. It is evident that the more concentrated the reaction solution, the higher the productivity of the process. Thus, we considered unsatisfactory about 5% substrate concentration employed in the preliminary experiments and carried out some hydrogenation experiments on **2e** with much higher substrate concentrations (6 g of substrate for 20 mL of solvent). This concentration increase was found beneficial for reaction kinetics, since a one-week reaction time was surprisingly reduced to only two days.

2.3.5. Hydrogen pressure. Several experiments were performed in order to evaluate the effects of the hydrogen pressure on kinetics and stereoselectivity. (TetraMe-BITIOP)$Ru(CF_3COO)_2$ modified by the addition of seven moles of dry hydrogen chloride, was employed as catalyst in all the experiments.

Ethyl levulinate was first used as a substrate. Hydrogen pressure was progressively decreased from 100 to 2 atm according to the following sequence: 50, 25, 10, 2 atm. No substantial variations in kinetics were observed at different pressures, since 48 h were required to drive the reaction to completion in all cases. This result opens up the possibility to perform the synthesis at low pressure and less expensive reactors. Also the enantiomeric excesses in the final product were found to be unaffected by pressure.

The extension of these findings to substrate **2e** did not give the same highly satisfactory results, since both reaction rate and enantioselectivity were reduced by lowering the hydrogen pressure: five days were found

necessary to drive the reaction to completion when hydrogen pressure was reduced to 30 psi, and analogous was the reaction time when 50 atm pressure was used. In the latter case, the enantiomeric excess was 95%, while it decayed to 80% in the former.

3. Sensory differences between enantiomeric γ-lactones (+)- and (−)-γ-lactones 4d and 4e

The triangle method was performed in accordance with the UNI 11073 standard[16] to detect whether there were significant sensory differences (i.e., aromatic intensity) between (+)-, (−)- and (±)-γ-lactones **4d** and **4e**.

Evaluations were carried out in three sessions by 30 selected assessors, namely students and staff, at the University of Milan (men and women aged between 25 and 30), on an empty stomach for one hour before the evaluation for both the experiments. Assessors were requested to smell three samples and to locate the odd sample in a set of three, of which two samples were identical, even if a difference was not perceptible (forced-choice method). Samples were coded and presented in random order from judge to judge and from session to session. Two samples were evaluated in each session for the first and second experiment. Within each session the design was balanced for order and carryover effects.[16] Table 3 shows the results of the comparison between the three samples of lactone **4e** and the critical number of correct responses (one-tailed, $p = 1/3$) at different levels of significance.[17]

From Table 3, it can be observed that there was a significant difference both between (−)- and racemic γ-lactone ($p < 0.001$) and between (+)- and (−)-γ-lactone ($p < 0.001$). Conversely, no significant difference was detected between (+)- and racemic **4e**.

In addition, the following descriptions were obtained from assessors who correctly identified the odd sample: (+)-, (−)- and (±)-γ-lactone were found to be floral and fruity (red fruits) while (−)-γ-lactone showed a higher overall aromatic intensity than (+)-γ-lactone.

Table 4 shows a comparison between results for the three samples from the second experiment and the critical number of correct responses (one-tailed, $p = 1/3$) at different levels of significance.[18]

Results reported in Table 4 showed no significant differences between (−)-and racemic γ-lactone **4d**; on the other hand, a significant difference was observed both between (+)- and (−)-γ-lactone ($p < 0.01$) and between (−)- and (±)-5-(2-phenyl-ethyl)-dihydro-furan-2-one **4d** ($p < 0.001$).

In addition, the following descriptions were obtained from assessors who correctly identified the odd sample: (+)-, (−)- and (±)-γ-lactone samples were found to be fruity (red fruits and peach) while (−)-γ-lactone showed a lower overall aromatic intensity than (+)-γ-lactone.

4. Conclusion

The results reported herein demonstrate that the target of the research, namely to develop a process-scale route to enantiomerically pure chiral γ-lactones, has been attained.

The effects produced by several different reaction parameters on kinetics and stereoselectivity, like the nature of the chiral ligand and of the ancillary co-ligands, the hydrogen pressure and the S/C ratio have been carefully investigated and optimised. In some cases, the hydrogen pressure could be reduced to 2 atm, which is an incredibly low pressure value for the hydrogenation of oxoesters. Substrate concentration was also considered, since it is a crucial parameter for productivity. The isolation of the intermediate γ-ketoesters was found unnecessary and the synthesis thus reduced to one-pot reaction.

A very electron-rich diphosphine ligand for ruthenium must be employed in order to attain acceptable reaction rates. TetraMe-BITIOP **1a** satisfies this requirement. A new dinuclear face-sharing bioctaedral complex of tetraMe-BITIOP with outstanding catalytic activity was prepared and fully characterised.

Table 3. Results from a comparison between the three samples of (−)-, (+)- and (±)-5-(3-phenyl-propyl)-dihydro-furan-2-one **4e**

Samples	Number of assessors	Number of correct responses	Probability levels		
			$\alpha = 0.05$	$\alpha = 0.01$	$\alpha = 0.001$
(−)-**4e** versus (±)-**4e**	30	19	15	17	19
(+)-**4e** versus (−)-**4e**	30	23	15	17	19
(+)-**4e** versus (±)-**4e**	30	10	15	17	19

Table 4. Results from a comparison between the three samples of (−)-, (+)- and (±)-5-(2-phenyl-ethyl)-dihydro-furan-2-one **4d**

Samples	Number of assessors	Number of correct responses	Probability levels		
			$\alpha = 0.05$	$\alpha = 0.01$	$\alpha = 0.001$
(−)-**4d** versus (±)-**4d**	30	12	15	17	19
(+)-**4d** versus (−)-**4d**	30	17	15	17	19
(+)-**4d** versus (±)-**4d**	30	19	15	17	19

Preliminary cost evaluations indicate that this methodology is economically acceptable for the large-scale production of some enantiomerically pure γ-lactones.

5. Experimental

5.1. General

Unless otherwise specified, all solvents and reagents were reagent grade and used without purification. ^{1}H NMR were recorded as solutions in $CDCl_3$ on 200 or 300 MHz Bruker spectrometers. Hydrogenation reactions were carried out in a stirred (550 rpm), 100 mL, Hastelloy Parr autoclave equipped with a sampling pipe extending to the bottom of the vessel. To evaluate the reaction's conversion, stirring was stopped and an aliquot of the solution drawn out through the sampling pipe by exploiting internal pressure and GC or ^{1}H NMR analysed. After sampling, the hydrogen pressure was restored and stirring resumed.

5.2. γ-Ketoesters

Ethyl 4-oxopentanoate was purchased from Aldrich. Methyl 4-oxooctanoate and methyl 4-oxododecanoate were prepared by cross coupling between the monoester-monochloride of succinic and glutaric acids and the suitable Grignard compound in the presence of catalytic amounts of CuI. This procedure is described with Fe(acac) as catalyst.[19] Methyl 4-oxo-6-phenyl-exanoate and methyl 4-oxo-7-phenyl-eptanoate were supplied by Prof. Claudio Fuganti, Dipartimento di Chimica Organica, Politecnico di Milano, Centro CNR per la Chimica delle Sostanze Organiche Naturali.

5.3. Hydrogenation of γ-ketoesters: general procedure

A solution of (tetraMe-BITIOP)Ru$(CF_3COO)_2$ (15.8 mg, 0.017 mmol) in ethanol (2 mL), previously degassed for 15 min with argon, and a 5.75 M HCl solution in isopropanol (20 μL) were stirred in a Schlenk tube under argon at 45 °C for 30 min. A solution of **2a** in degassed ethanol (20 mL) was then added and the resulting solution loaded with a syringe into a 100 mL stainless-steel autoclave, previously purged three times with hydrogen. Hydrogen was introduced, and the solution stirred at 45 °C until ethyl levulinate disappeared. Hydrogen pressure was released and the reaction mixture refluxed to complete the lactonisation. The solvent was then removed under reduced pressure and **4a** recovered in a pure state after distillation in vacuo.

5.4. Lactones

Lactones **4a**,[20] **4b**,[21] **4c**[21] and **4d**[22] are already known in literature in both enantiopure antipodes. The dextrorotatory enantiomers displayed an (*R*)-configuration at the stereocentre. Only (+)-**4e** is described in the literature[23] to which an (*R*)-configuration can be reasonably assigned as well.

5.5. X-ray crystallographic analysis of (tetraMe-BITIOP)$PdCl_2$ and (tetraMe-BITIOP)$PtCl_2$

Single-crystal X-ray diffraction measurements were performed on a Bruker SMART-APEX diffractometer; graphite monochromator, Mo-Kα radiation ($\lambda = 0.71073$ Å), room temperature. The structures were solved by SIR-92[24] and refined by full-matrix least-squares on F^2 by SHELX-97.[25] All crystallographic data (excluding structure factors) were deposited to the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 235819 (tetraMe-BITIOP)$PdCl_2$ and CCDC 235818 (tetraMe-BITIOP)$PtCl_2$. Copies of the data can be obtained free of charge on application to CCDC, 2 Union Road, Cambridge CB2 1EZ, UK, e-mail deposit@ccdc.cam.ac.uk.

5.5.1. (TetraMe-BITIOP)$PdCl_2$. $C_{36}H_{32}Cl_2P_2PtS_2$, $M_r = 856.67$, orthorhombic, space group $P2_12_12_1$, $a = 11.5647(6)$, $b = 16.3399(9)$, $c = 17.3988(9)$ Å, $V = 3287.8(3)$ Å^3, $Z = 4$, $D_c = 1.734$ g cm^{-3}, μ(Mo-Kα) = 4.689 mm^{-1}; 75866 collected data ($2\theta \leqslant 65°$); 11771 unique [10636 with $I_o > 2\sigma(I_o)$], $R_{ave} = 0.0293$, absorption correction[26] based on multi-scan procedure ($T_{min}/T_{max} = 0.766$); final disagreement factors for all reflections: $R_w(F2) = 0.0532$ and $R = 0.0296$, goodness-of-fit = 0.942; minimum/maximum difference Fourier residues −0.37/1.75 e Å^{-3}.

5.5.2. (TetraMe-BITIOP)$PtCl_2$. $C_{36}H_{32}Cl_2P_2PdS_2$, $M_r = 767.98$, orthorhombic, space group $P2_12_12_1$, $a = 11.5729(6)$, $b = 16.3017(10)$, $c = 17.3736(10)$ Å, $V = 3277.7(3)$ Å^3, $Z = 4$, $D_c = 1.556$ g cm^{-3}, μ(Mo-Kα) = 0.980 mm^{-1}; 126246 collected data ($2\theta \leqslant 68°$); 12965 unique [10245 with $I_o > 2\sigma(I_o)$], $R_{ave} = 0.0375$, absorption correction[26] based on multi-scan procedure ($T_{min}/T_{max} = 0.961$); final disagreement factors for all reflections: $R_w(F2) = 0.0562$ and $R = 0.0432$, goodness-of-fit = 0.889; minimum/maximum difference Fourier residues −0.26/0.81 e Å^{-3}.

5.5.3. [{RuCl(tetraMe-BITIOP)}$_2$(μ^2-Cl)$_3$]H. A 6 M HCl solution in *i*-PrOH (19 μL) was added to a warm solution of (tetraMe-BITIOP)Ru$(CF_3COO)_2$ (14.6 mg, 0.016 mmol) in ethanol (4.5 mL), previously degassed 15 min with argon. The solution was left to stand overnight and deep red crystals of [{RuCl(tetraMe-BITIOP)}$_2$ (μ^2-Cl)$_3$]H·EtOH separated. Anal. Calcd: C, 55.28; H, 4.45; S, 7.98; P, 7.70; Cl, 11.03. Found: C, 55.69; H, 4.35; S, 8.14; P, 7.55; Cl, 11.21.

Crystallographic data have been already deposited to the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 237679.[27]

5.6. Electron paramagnetic resonance (EPR) spectroscopy

EPR experiments were performed on a Bruker ElexSys E560 spectrometer at 77 K. Weighted amounts of the ruthenium dinuclear complex were dissolved in oxygen free dichloromethane/toluene 1:1 v/v to obtain 10^{-2} M solutions, which were transferred and stored in

standard quartz EPR tubes under argon. Measurements were performed at 77 K by means of a cold finger filled with liquid nitrogen.

5.7. Preparation of the samples of racemic and enantiopure lactones for sensory evaluation

A dilution was selected for all the lactones, which would guarantee that the solutions submitted to testing in the two runs would display a similar aroma and could be differentiated only on the basis of a different aromatic intensity. The following dilutions were chosen under the expertise of seven trained judges, with the condition that they either would not be below the perception threshold or too much saturating. In the case of racemic 5-(3-fenilpropil)-tetrahydrofuran-2-one **4d** and the corresponding enantiopure antipodes, a 1:500.000 dilution ratio was chosen, while a 1:10.000 dilution was chosen in the case of lactone **4e**.

The test solutions of γ-lactone **4d** were prepared according to the following procedure: a solution of 50 μL of the lactone in 96% ethanol (2 mL, Merck analytical grade) was diluted to 50 mL with distilled water in a 50 mL volumetric flask. The resulting solution (1 mL) was further diluted to 500 mL with distilled water in a 500 mL volumetric flask. The test solutions of γ-lactone **4e** were prepared according to the procedure described above with the only difference being that whole solution (50 mL) obtained in the first dilution operation was diluted to 500 mL with distilled water in a 500 mL volumetric flask.

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