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Platinum-Catalyzed Oxidations with Hydrogen Peroxide: Enantiospecific Baeyer–Villiger Oxidation of Cyclic Ketones

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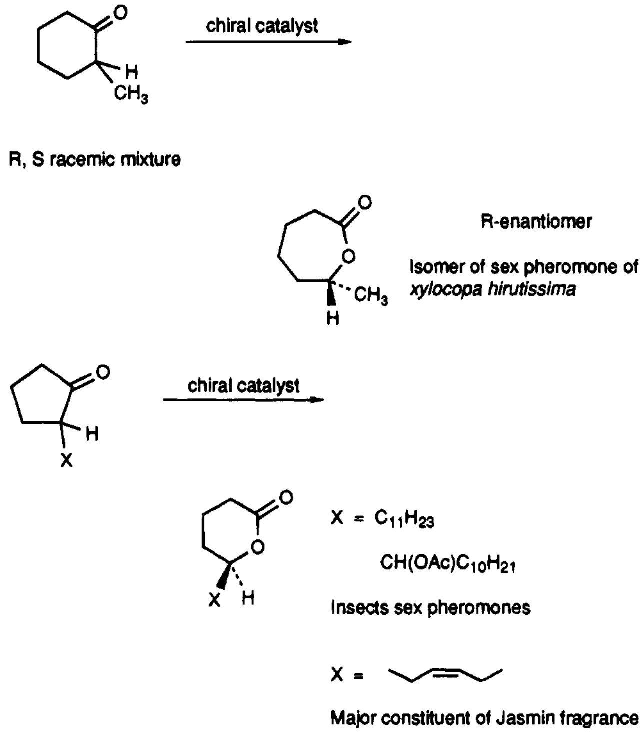
The Baeyer–Villiger oxidation of some cyclic ketones as a potential entry to naturally occurring lactones is reported in the presence of a variety of platinum(II) complexes as catalysts. The reaction is accomplished using hydrogen peroxide as oxidant and is tested in a discontinuous and semicontinuous fashion. The stereochemistry of the catalyzed transformation has been determined, and it is found that the reaction proceeds with retention of configuration at the migrating carbon atom. Chiral catalysts of the type $[(P\text{-}P^*)Pt(CF_3)(solv)]^+$ and $(P\text{-}P^*)Pt(2\text{-van})$ ($P\text{-}P^*$ = various chiral diphosphines; 2-van = the dianion of 2-vanillin) have been synthesized and characterized. While the mechanism of action of the former complexes is already known, the latter require 1 equiv of $HClO_4$ to become catalytically active. This reaction has been investigated synthetically and spectroscopically by $^{31}P\{^1H\}$ NMR and IR and results in the formation of a new cationic Pt–carbonyl species. The asymmetric Baeyer-Villiger oxidation of a variety of racemic mixtures of chiral ketones results in a kinetic resolution leading to chiral lactones with ee up to 58%.

Introduction

Chiral lactones are an important class of organic compounds, the use of which is widespread in a variety of biochemical applications. For example, they are used as intermediates in the synthesis of some antibiotics,[1] as biogenetic precursors of steroids and terpenes,[2] or simply as natural products. In the last category, even some simple chiral lactones may find practical applications either in agrochemistry[3] or in the fragrance industry.[4] Some examples are presented in Scheme 1. The most direct synthetic route for this class of compounds involves the Baeyer–Villiger oxidation[5] of the corresponding ketones that are normally easily available as racemic mixtures. Under standard synthetic conditions this will lead to the formation of a racemic lactone and require the separation of the enantiomers.

Recently, a microbiological process based on the use of *Acinetobacter chalcoaceticus* has been reported,[6] with which chiral lactones with optical purities up to 74% have been obtained. As is indicated in Scheme 1, asymmetric catalysis might be an attractive alternative based on the same principle. In fact, similarly to microorganisms, a chiral catalyst would lead to a kinetic resolution of the starting racemic ketone through the preferential conversion into the (hopefully) desired lactone enantiomer.

Scheme 1



Over the past decade, we have been studying the catalytic properties of a class of Pt(II) complexes of the type $P_2Pt(CF_3)(X)$ (P_2 = various diphosphines, X = solvent, –OH) in a variety of oxidation reactions. These include the selective[7] (even enantioselective[8]) epoxidation of olefins, the ketonization of olefins,[9] the oxidation

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[1] Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984,** *49,* 576 and references therein.

[2] (a) Eliel, E. L.; Soai, K.; Kennan, W. R. *Tetrahedron Lett.* **1981,** *22,* 2859. (b) Eliel, E. L.; Lynch, J. E. *Tetrahedron Lett.* **1981,** *22,* 2855.

[3] (a) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979,** *44,* 2169. (b) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1978,** *43,* 378. (c) Wheeler, J. W.; Evans, S. L. *Tetrahedron Lett.* **1976,** 4029. (d) Ko, K.-Y.; Eliel, E. L. *J. Org. Chem.* **1986,** *51,* 5353.

[4] (a) Demole, E.; Lederer, E.; Mercier, D. *Helv. Chim. Acta* **1962,** *45,* 685. (b) Demole, E.; Winter, M. *Helv. Chim. Acta* **1962,** *45,* 1256. (c) Dubs, P.; Stüssi, R. *Helv. Chim. Acta* **1962,** *61,* 990. (d) Kondo, K.; Saito, E.; Tunemoto, D. *Tetrahedron Lett.* **1975,** 2275.

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[6] (a) Alphand, V.; Archelas, A.; Furstoss, R. *J. Org. Chem.* **1990,** *55,* 347. (b) Alphand, V.; Furstoss, R. *Tetrahedron*: *Asymmetry* **1992,** *3,* 379 and references therein.

of carbon monoxide,[10] the oxidation of alcohols to ketones,[11] the direct hydroxylation of aromatics,[12] and the Baeyer–Villiger oxidation of cyclic ketones,[13] the last process representing the only unambiguous example of transition-metal catalysis of this reaction.[14] All these processes utilize hydrogen peroxide as the primary oxidant. The advantages of using hydrogen peroxide as an oxidant for synthetic organic chemistry have been pointed out by some authors,[17] and the whole subject of catalytic oxidations involving H_2O_2 has been recently reviewed.[18]

The facile modification of the above complexes with chiral diphosphines seems to open a possible access to an enantioselective version of the Baeyer–Villiger oxidation. In this work we wish to report a study of the stereochemistry of this reaction in the presence of platinum(II) catalysts and our attempts to synthesize chiral lactones that might be of interest for the synthesis of some natural products.

Results and Discussion

Productivity of the Reaction. In a previous paper,[13b] it was observed, in the conversion of a variety of cyclic ketones, that the productivity of the Baeyer–Villiger oxidation catalyzed by Pt complexes was limited by the partial decomposition of the oxidant H_2O_2. On the basis of some mechanistic similarities with the classical organic reaction with peroxyacids, it was suggested[13b] that this decomposition was possibly due to the involvement of elusive dioxirane products capable of interacting further with H_2O_2 and leading to its decomposition.

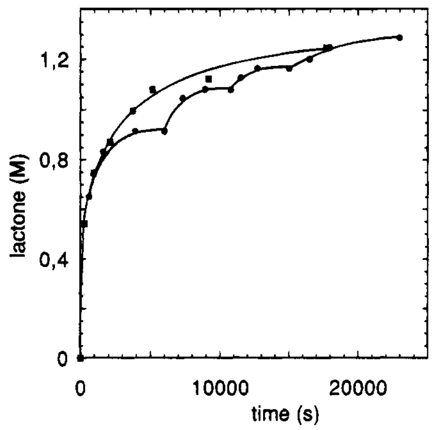


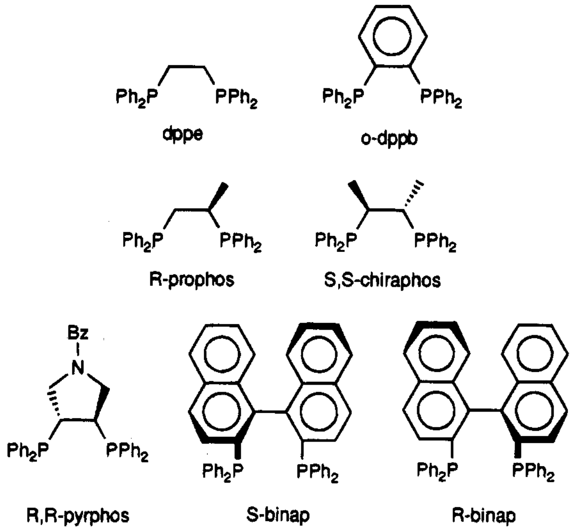
Figure 1. Comparison between the discontinuous (squares) and semicontinuous (circles) methods in the lactonization of 2-methylcyclohexanone catalyzed by [o-dppb)Pt(CF_3)(CH_2Cl_2)]BF_4.

Table 1. Lactonization of Different Ketones with [(P-P)Pt(CF_3)(solv)]$^+$ Catalysts: Comparison between the Semicontinuous and the Discontinuous Oxidation Methods[a]

catalyst	ketone	T (°C)	max amt of lactone (mmol) semicon	max amt of lactone (mmol) discon
[(o-dppb)Pt(CF_3)(CH_2Cl_2)]BF_4	menthone	50	1.50	0.75
[(dppe)Pt(CF_3)(CH_2Cl_2)]BF_4		50	1.00	0.63
[(o-dppb)Pt(CF_3)(CH_2Cl_2)]BF_4	2-methylcyclohexanone	25	4.50	3.75
[(pyrphos)Pt(CF_3)(CH_2Cl_2)]BF_4		0	0.75	0.50
		25	1.00	1.00
		50	1.50	1.25
	2-methylcyclopentanone	25	1.75	0.75

[a] Reaction conditions: Pt, 0.025 mmol; ketone, 25 mmol; N_2, 1 atm; 35% H_2O_2, 12.5 mmol (semicon, 5 × 2.5 mmol aliquots; discon, 1 × 12.5 mmol aliquot).

Chart 1



To see whether it was possible to improve the efficiency of the catalytic system and increase the amount of useful products, we tested the effect of dividing in different aliquots the amount of hydrogen peroxide used (semicontinuous method), with the hope that a constantly low H_2O_2 concentration would affect differently the rate of oxidation of the substrate with respect to the rate of decomposition of the oxidant. This methodology was compared to the more traditional one, which consisted of adding the amount of hydrogen peroxide all in one shot (discontinuous method). A comparison of the results obtained is reported in Figure 1 and Table 1. As shown in the case of the oxidation of 2-methylcyclohexanone catalyzed by [(o-dppb)Pt(CF_3)(CH_2Cl_2)]BF_4 (for definitions of the diphosphine acronyms, see Chart 1), the semicontinuous method (Figure 1) results in a reaction profile consisting of different steps corresponding to the different aliquots of H_2O_2 introduced. Of course, the initial rate of the individual steps decreases because of the increasing dilution of the

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(7) (a) Strukul, G.; Michelin, R. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1538. (b) Strukul, G.; Michelin, R. A. *J. Am. Chem. Soc.* **1985**, *107*, 7563. (c) Zanardo, A.; Pinna, F.; Michelin, R. A.; Strukul, G. *Inorg. Chem.* **1988**, *27*, 1966. (d) Zanardo, A.; Michelin, R. A.; Pinna, F.; Strukul, G. *Inorg. Chem.* **1989**, *28*, 1648.

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(14) Previous work on catalysis on Mo(VI) complexes[15] has been recently severely questioned.[16]

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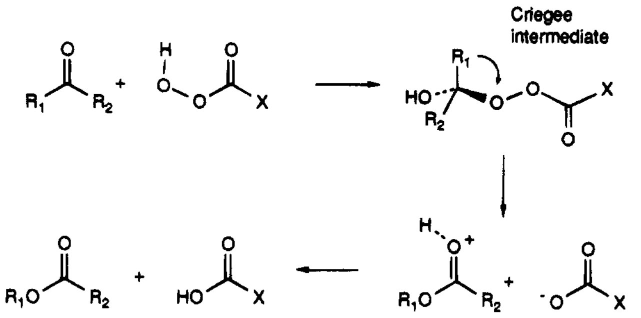
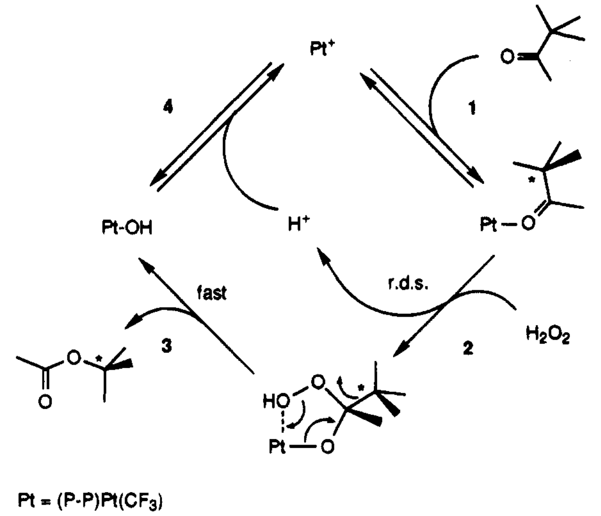
(17) (a) Sheldon, R. A. *Stud. Surf. Sci. Catal.* **1990**, *55*, 1. (b) Sheldon, R. A. *CHEMTECH* **1991**, 566. (c) Strukul, G. In *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Strukul, G., Ed.; Kluwer: Dordrecht, The Netherlands, 1992; Chapter 1, p 1.

(18) Strukul, G., Ed. *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Kluwer: Dordrecht, The Netherlands, 1992.

Scheme 2



Scheme 3



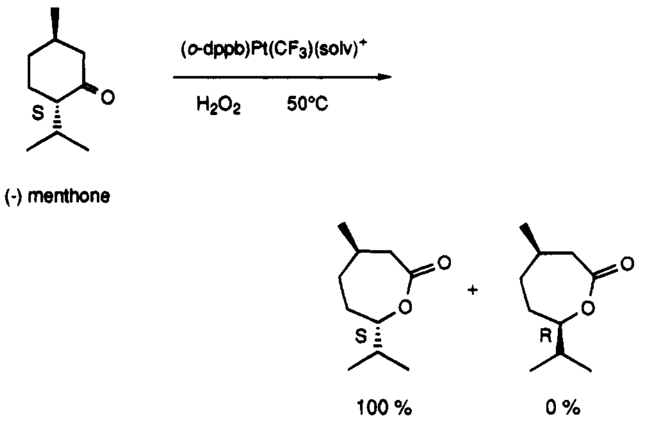
subsequent H_2O_2 aliquots. However, when this reaction profile is compared with that observed for the discontinuous method (Figure 1), it appears that the former is neither significantly more productive nor faster. These results are essentially confirmed from the data in Table 1, where a moderate increase in productivity is observed for the semicontinuous method. Since the latter does not appear to provide significant advantages, all the following catalytic experiments were carried out with the traditional discontinuous method.

Stereochemistry of the Reaction. As stated in the Introduction, the process depicted in Chart 1 is actually a kinetic resolution of a racemic mixture of enantiomers. In trying to develop an asymmetric transformation of this type, a prior study of the stereochemical course of the reaction is an essential requirement.

The Baeyer–Villiger oxidation with peroxy acids has long been recognized[19] to proceed with complete retention of configuration at the migrating carbon atom, in agreement with the mechanistic assumption that the rearrangement in the intermediate Criegee adduct is intramolecular[5,20] (Scheme 2).

The mechanism proposed for the platinum-catalyzed oxidation[13b] is shown in Scheme 3. As shown, the possible enantiodifferentiating step is undoubtedly the first (step 1), i.e. the complexation of the ketone. In fact, when a chiral Pt catalyst is used in the presence of a racemic mixture of ketones, step 1 leads to the formation of two different diastereomeric Pt(ketone)$^+$ species, which in principle should form with different rates. However, in order to accomplish an overall asymmetric transformation, all the rest of the catalytic cycle (in particular step 3, where the migration of the chiral carbon of the ketone occurs) will have to proceed in a stereospecific fashion. In order to check this crucial point, we carried out the oxidation of an enantiomerically pure ketone (menthone) with the achiral catalyst [(*o*-dppb)Pt(CF_3)(CH_2Cl_2)]BF_4. The reaction was carried out at 50 °C using 0.025 mmol of catalyst, 25 mmol of menthone, and 12.5 mmol of 35% H_2O_2 and was monitored with GLC using a chiral β-cyclodextrin capillary column. The results are summarized in Scheme 4 and indicate that the reaction proceeds with complete retention of configuration at the migrating carbon atom. They also indicate that lactone formation results from a concerted rearrangement, providing strong support to the mechanism proposed[13b] for the catalytic reaction and shown in Scheme 3.

Scheme 4



Preparation of the Chiral Catalysts. As stated above, the preparation of chiral catalysts of the type [(P-P*)Pt(CF_3)(solv)]$^+$ can be easily accomplished according to the reaction sequence indicated in eqs 1–4 by

$$Pt(PPh_3)_4 + CF_3Br \rightarrow 2PPh_3 + (PPh_3)_2Pt(CF_3)Br \qquad (1)$$

$$(PPh_3)_2Pt(CF_3)Br + Ag^+ + Cl^- \rightarrow (PPh_3)_2Pt(CF_3)Cl \qquad (2)$$

$$(PPh_3)_2Pt(CF_3)Cl + P\text{-}P^* \rightarrow (P\text{-}P^*)Pt(CF_3)Cl + 2PPh_3 \qquad (3)$$

$$(P\text{-}P^*)Pt(CF_3)Cl + Ag^+ \rightarrow (P\text{-}P^*)Pt(CF_3)(solv)^+ + AgCl \qquad (4)$$

introducing the appropriate diphosphine in eq 3, an exchange reaction that takes advantage of the chelating effect of the diphosphine and is normally carried out in a benzene suspension.[8] In the past, this method has allowed the facile synthesis of complexes containing chiral diphosphines such as chiraphos, prophos, diop, and pyrphos.[8] Conversely, when binap was used in eq 3, the reaction led invariably to the recovery of the starting platinum complex even when the reaction time

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[19] (a) Berson, J. A.; Suzuki, S. *J. Am. Chem. Soc.* **1959**, *81*, 4088. (b) Gallagher, T. F.; Kritchevsky, T. H. *J. Am. Chem. Soc.* **1950**, *72*, 882. (c) Turner, R. B. *J. Am. Chem. Soc.* **1950**, *72*, 878. (d) Mislow, K.; Brenner, J. *J. Am. Chem. Soc.* **1953**, *75*, 2318.

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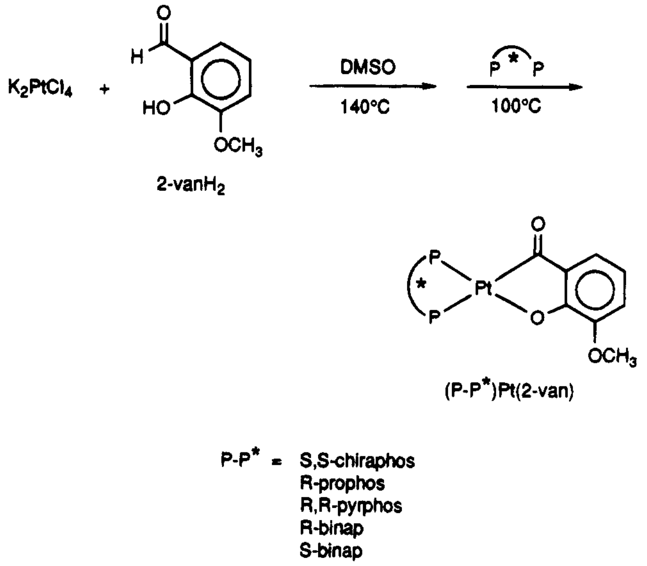
Scheme 5



was increased (24−72 h) or the solvent was changed (benzene, toluene, heptane).

Since binap has proved extremely successful as a chiral auxiliary in a wide variety of asymmetric transformations catalyzed by transition metals,[21] we thought of a different synthetic strategy in order to include this ligand among the chiral modifiers for Pt(II) complexes.

An important feature of the successful $[(P\text{-}P)Pt(CF_3)(solv)]^+$ catalysts, which determines their catalytic properties, is the ability of the CF_3 ligand to withdraw negative charge from the metal, thereby increasing its ability to activate the substrate toward nucleophilic attack.[22] In principle, a similar effect can be obtained also by other ligands such as, for example, the acyl ligand. For this reason we turned our attention to a class of chelate complexes of platinum(II) derived from salicylaldehyde and reported some years ago by Pregosin and co-workers.[23] According to the general procedure outlined by these authors, we synthesized a variety of (P-P*)Pt(2-van) complexes (2-van = dianion of 2-vanillin) as indicated in Scheme 5.

These complexes were characterized by IR and $^{31}P\{^1H\}$ NMR spectroscopy, and the relevant data are reported in Table 2. The IR spectra show in all cases a typical carbonyl stretching band at about 1605 cm^{-1},[23] two medium-intensity bands at about 1630 and 1580 cm^{-1} characteristic of a substituted phenyl ring,[24] and two strong bands around 1235 and 1100 cm^{-1} that can be attributed to the C—O—C vibration[12] of the methoxy substituent of the vanillinate ligand. Finally, a weak band typical of the Pt—O stretching[25] is observed at about 520 cm^{-1}.

Table 2. Spectroscopic Features of New (P-P*)Pt(2-van) Complexes

complex	IR (cm^{-1})[a]	$^{31}P\{^1H\}$ NMR[b]
(*R,R*-pyrphos)Pt(2-van)	1613 s (C═O) 1634 m, 1579 s (Ph) 1241 s, 1103 s (C—O) 527 m (Pt—O)	12.80 d (trans to O), $^2J_{P-P} = 12.1$, $^1J_{P-Pt} = 4327$ 25.51 d (trans to C), $^2J_{P-P} = 12.1$, $^1J_{P-Pt} = 1445$
(*S,S*-chiraphos)Pt(2-van)	1619 s (C═O) 1635 m, 1675 s (Ph) 1239 s, 1100 s (C—O) 510 m (Pt—O)	34.36 d (trans to O), $^2J_{P-P} = 2.9$, $^1J_{P-Pt} = 4176$ 45.41 d (trans to C), $^2J_{P-P} = 2.9$, $^1J_{P-Pt} = 1489$
(*R*-prophos)Pt(2-van)	1609 s (C═O) 1631 m, 1577 s (Ph) 1241 s, 1101 s (C—O) 528 m (Pt—O)	38.62 d (trans to O) (**A**), $^2J_{P-P} = 2.8$, $^1J_{P-Pt} = 4250$ 30.20 d (trans to C) (**A**), $^2J_{P-P} = 2.8$, $^1J_{P-Pt} = 1485$ 24.82 d (trans to O) (**B**), $^2J_{P-P} = 6.5$, $^1J_{P-Pt} = 4228$ 48.34 d (trans to C) (**B**), $^2J_{P-P} = 6.5$, $^1J_{P-Pt} = 1450$
(*R*-binap)Pt(2-van)	1609 s (C═O) 1637 m, 1581 s (Ph) 1240 s, 1097 s (C—O) 520 m (Pt—O)	18.80 d (trans to O), $^2J_{P-P} = 10.8$, $^1J_{P-Pt} = 4562$ 23.43 d (trans to C), $^2J_{P-P} = 10.8$, $^1J_{P-Pt} = 1488$
(*S*-binap)Pt(2-van)	1605 s (C═O) 1630 m, 1575 s (Ph) 1234 s, 1296 s (C—O) 520 m (Pt—O)	18.79 d (trans to O), $^2J_{P-P} = 10.9$, $^1J_{P-Pt} = 4561$ 23.42 d (trans to C), $^2J_{P-P} = 10.9$, $^1J_{P-Pt} = 1483$

[a] IR in Nujol mull, CsI windows; s = strong, m = medium. [b] Solvent $CDCl_3$; δ in ppm, J in Hz; d = doublet.

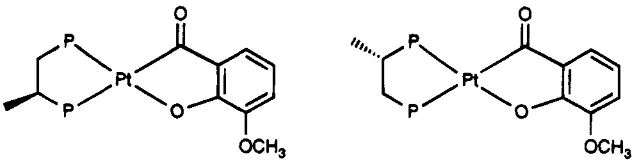


Figure 2. The two possible structural isomers of (*R*-prophos)Pt(2-van).

The $^{31}P\{^1H\}$ NMR spectra show in all cases the presence of two nonequivalent phosphorus nuclei with evidence of P—P coupling and the presence of ^{195}Pt satellites, in agreement with the proposed structure. The individual P—Pt coupling constants are strongly influenced by the ligand in trans position and are about 1450−1500 Hz for P trans to C and 4200−4500 Hz for P trans to O, similar to what was already observed for homologous complexes[23] and in agreement with the general work reported by Appleton and Bennett[26] some years ago in a systematic study of a homologous series of Pt diphosphine complexes of this type. A further comment on the spectrum of (prophos)Pt(2-van) is appropriate. As shown in Table 2, the spectrum indicates the presence of two different species (A and B) with similar spectroscopic properties in the approximate ratio A/B = 3/2. Similar to what was already observed for other prophos complexes of Pt(II),[8] this result is consistent with the existence of two nonequivalent structural isomers, which differ in the relative positions of the 2-van donor atoms with respect to the methyl group of the diphosphine (Figure 2).

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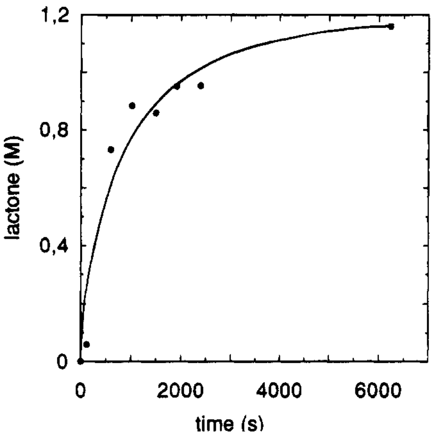
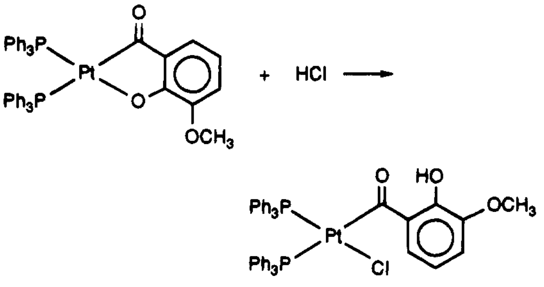


Figure 3. Typical reaction profile for the lactonization of 2-methylcyclohexanone catalyzed by (dppe)Pt(2-van) in the presence of an equimolar amount of $HClO_4$.

Catalytic Activity of New Complexes. The catalytic properties of (P-P)Pt(2-van) complexes in oxidation reactions are completely unknown, although it seems likely that, due to the chelating nature of the ligands surrounding the metal, catalysis could hardly be observed. In fact, when (dppe)Pt(2-van) or the other chiral diphosphine modified complexes were tested in the Baeyer–Villiger oxidation of 2-methylcyclohexanone, no reaction was observed.

It is known from the work of Pregosin[23] that the phenolic oxygen can be easily protonated in the presence of hydrogen chloride (eq 5). The new chloro derivative



(5)

is not catalytically active either. However, if the same reaction indicated in eq 5 is carried out with a strong noncoordinating acid ($HClO_4$) instead of HCl, it seems likely that a new species would form having a vacant coordination site and, at least in principle, catalysis might be possible. Therefore, we have studied the catalytic activity of the complex (dppe)Pt(2-van) in the Baeyer–Villiger oxidation of 2-methylcyclohexanone in the presence of an equimolar amount of $HClO_4$, added to the reaction mixture before starting the reaction (see Experimental Section). A typical reaction profile is shown in Figure 3, and a summary of the results obtained under different experimental conditions is reported in Table 3. As can be seen, the best productivity is observed when the medium is two-phase (DCE as solvent or neat ketone) and the initial rate can even be very high and be limited by the diffusion of H_2O_2 from the aqueous to the organic layer. In fact, in previous reactions we have observed that initial rates above $(3-4) \times 10^{-4}$ M s^{-1} are usually diffusion-controlled.[7c,13b] To maximize the amount of lactone in the asymmetric transformations, all reactions were carried out in neat ketone. In order to check the possible contribution to the catalysis of the H^+ introduced, a blank reaction was carried out in neat ketone without the Pt complex but in the presence of an equivalent amount of $HClO_4$ (Table 3). Indeed, a slow formation of methylcaprolactone takes place that stops after about 3 h. This would suggest that when the Pt complex is present, the contribution to the overall catalytic process from the residual H^+, not reacting with the complex, is only marginal.

Table 3. Oxidation of 2-Methylcyclohexanone with Hydrogen Peroxide Catalyzed by (dppe)Pt(2-van) under Various Conditions[a]

solvent	temp (°C)	initial rate (10^4 M s^{-1})	max amt of lactone (mmol)	time (min)
MeOH	50	1.8	0.88	24
THF	50	2.4	0.82	56
DCE	0	0.5	2.92	10078
	25	5	2.45	103
	50	7	2.58	186
ketone[b]	50	>10	5.10	20
ketone[b,c]	50	0.3	0.84	180

[a] Reaction conditions: Pt, 0.034 mmol; $HClO_4$, 0.034 mmol; 2-methylcyclohexanone, 6.8 mmol; 35% H_2O_2, 3.4 mmol; solvent, 2.2 mL; N_2, 1 atm. [b] Reaction carried out in pure ketone (34.0 mmol) and 35% H_2O_2 (17.0 mmol). [c] No Pt added.

Evolution of New Complexes. In order to investigate the evolution of the new (P-P)Pt(2-van) complexes in the presence of $HClO_4$, the reaction was monitored with $^{31}P\{^1H\}$ NMR spectroscopy. The complex (dppe)-Pt(2-van) (0.006 g, 0.008 mmol) was dissolved in acetone-d^6 (0.5 mL), and spectrum 1, shown in Figure 4, was recorded (δ 39.91 ppm (d), $^3J_{P-P} = 9.3$ Hz, $^1J_{P-Pt} = 1489$ Hz; δ 31.76 ppm (d), $^3J_{P-P} = 9.3$ Hz, $^1J_{P-Pt} = 4204$ Hz). The choice of the solvent is due to the fact that, as said above, catalytic reactions are carried out in neat ketone. An equimolar amount of 70% $HClO_4$ was added, and the new spectrum after 30 min showed (Figure 4, spectrum 2) the full formation of the new species **A** (δ 50.71 ppm (d), $^3J_{P-P} = 8.4$ Hz, $^1J_{P-Pt} = 1704$ Hz; δ 47.11 ppm (d), $^3J_{P-P} = 8.4$ Hz, $^1J_{P-Pt} = 3216$ Hz), still showing two inequivalent P nuclei, that appeared to be stable for at least 90 min.

When the same process was carried out in CD_2Cl_2, spectra 3–6, shown in Figure 4, were observed. The initial (Figure 4, spectrum 3) complex (δ 38.74 ppm (d), $^3J_{P-P} = 8.3$ Hz, $^1J_{P-Pt} = 1502$ Hz; δ 31.65 ppm (d), $^3J_{P-P} = 8.3$ Hz, $^1J_{P-Pt} = 4245$) was rapidly (10 min) substituted by three new Pt compounds (Figure 4, spectrum 4): **A** (δ 48.75 ppm (d), $^3J_{P-P} = 9.3$ Hz, $^1J_{P-Pt} = 1701$ Hz; δ 45.68 ppm (d), $^3J_{P-P} = 9.3$ Hz, $^1J_{P-Pt} = 3205$ Hz), the same compound observed in acetone-d_6, **B** (δ 44.17 ppm (d), $^3J_{P-P} = 11.1$ Hz, $^1J_{P-Pt} = 1487$ Hz; δ 39.67 ppm (d), $^3J_{P-P} = 11.1$ Hz, $^1J_{P-Pt} = 3318$ Hz), again showing two inequivalent P nuclei, and **C** (δ 47.65 ppm (d), $^1J_{P-Pt} = 3785$ Hz), displaying a rather broad singlet. Over about 90 min, species **A** transformed into **B** and **C** (Figure 4, spectrum 5), the latter being the final product (Figure 4, spectrum 6).

The same reaction was carried out on a preparative scale by starting from 0.10 g (0.14 mmol) of (dppe)Pt-(2-van) in dry acetone (50 mL) and 0.013 mL of 70% $HClO_4$. The material that was isolated after 0.5 h was a clear orange solid whose IR spectrum (Nujol) showed a characteristic strong band at 2112 cm^{-1}, the disappearance of the acyl band at 1610 cm^{-1}, the persistence of the CH_3O bands typical of vanillin at 1260 cm^{-1}, and a new, very strong, broad band in the 1100-cm^{-1} region

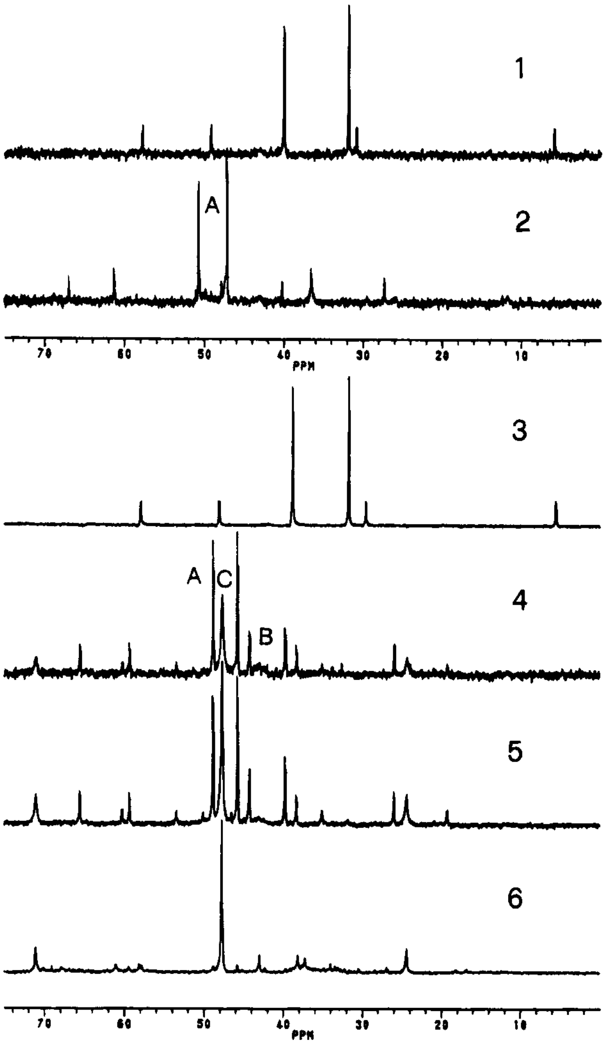


Figure 4. (1) $^{31}P\{^1H\}$ NMR spectrum (acetone-d_6) of (dppe)Pt(2-van). (2) Spectrum as in (1) when $HClO_4$ added, after 30 min. (3) $^{31}P\{^1H\}$ NMR spectrum (CD_2Cl_2) of (dppe)Pt(2-van). (4–6) Spectrum as in (3) when $HClO_4$ added (4) after 10 min, (5) after 40 min, and (6) after 90 min.

typical of the ClO_4^- anion. A material having the same IR features could also be obtained by treating (dppe)Pt(2-vanH)Cl with $AgClO_4$. The complex (dppe)Pt(2-vanH)Cl can be easily prepared from (dppe)Pt(2-van) by addition of a stoichiometric amount of HCl.[23]

These reactions are summarized in Scheme 6, where, consistent with the IR spectrum, the new compound is formulated as $[(dppe)Pt(Ph\text{-}2\text{-}OH\text{-}3\text{-}OCH_3)(CO)]ClO_4$. This compound is formed by intramolecular decarbonylation on the vacant coordination site of the intermediate $[(dppe)Pt(2\text{-}vanH)]ClO_4$, in agreement with previously reported examples of this reaction pathway for Pt(II) complexes.[27] The $^{31}P\{^1H\}$ NMR spectrum (acetone-d_6) of the material isolated from the above reaction is identical with that reported for species **A** in Figure 4, spectrum 2. The $^1J_{P-Pt}$ coupling constants observed in spectrum 2 of Figure 4 are typical for inequivalent phosphorus nuclei of (dppe)Pt-type complexes having in trans positions an aryl group (1704 Hz) and a CO molecule (3216 Hz), respectively.[26]

For the **B** and **C** species formed in the experiment carried out in CD_2Cl_2, it may be suggested that, due to the likely lability of the CO ligand in **A**, indicated by the relatively high stretching frequency (2112 cm^{-1}) and similar to that of other Pt(II) carbonyl complexes of the same type,[10,28] they arise from two subsequent hydrolytic steps ($HClO_4$ contains 30% H_2O). The first leads to the formation of a monohydroxy aryl complex (**B**) and the second to a symmetric dihydroxy complex (**C**) (Scheme 6), as is indicated by the relevant $^1J_{P-Pt}$ coupling constants.[7b,d,26]

In order to prove whether species **A** was actually involved as the catalyst in the Baeyer–Villiger oxidation, the product obtained from the preparative reaction was tested in the oxidation of 2-methylcyclohexanone in pure ketone at 25 °C under the conditions of Table 3, but without the addition of $HClO_4$. The reaction, whose initial rate cannot be measured, yielded a maximum amount of 7.2 mmol of lactone in 5 min. It may be inferred that in the catalytic reactions species **A** would evolve to either **B** or **C** due to the large amount of water or, more likely, that the coordinated CO is immediately oxidized by H_2O_2, as was previously observed in the case of the complex $[(diphoe)Pt(CF_3)(CO)]ClO_4$,[10] leaving the vacant coordination site necessary to carry out the catalysis. With reference to Table 3, in view of the above described solvent effect on the species formed after $HClO_4$ addition, it seems likely that the active species involved in the various cases may be different.

Asymmetric Oxidations. The substrates, products, and catalysts that were employed in the asymmetric Baeyer–Villiger oxidation are shown in Chart 2. Reactions have been carried out at 0, 25, and 50 °C using the neat substrate as solvent (two-phase medium) and the discontinuous method. Each case is considered separately.

a. 2-Methylcyclohexanone. This substrate can be easily oxidized with the Pt complexes to the corresponding lactone. The *R* enantiomer of this lactone constitutes the isomer of the sex pheromone of the carpenter bee *Xylocopa hirutissima*.[3a] The results obtained with the chiral catalysts under different experimental conditions are reported in Table 4. As can be seen, a good productivity is generally observed and a typical reaction profile evidences a rather high initial activity followed by a relatively rapid slowdown. An analysis of the residual hydrogen peroxide, after the maximum conversion has been reached, indicates that the oxidant has been almost completely consumed, suggesting that the system does not stop because the catalyst is deactivated but rather because there is a lack of oxidant. In fact, if a second aliquot of H_2O_2 is added, the reaction starts again, although with reduced activity.

It is interesting to notice that the new catalysts derived from 2-vanillin are significantly more active and productive than the traditional catalysts derived from $-CF_3$. It may be suggested that, once species **A** has formed, the phenyl ring is disposed perpendicularly to the coordination plane, thereby leaving more space with respect to the $-CF_3$ ligand. A correlation between steric hindrance and catalytic activity has been previously observed in the epoxidation of simple olefins.[7d]

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Scheme 6

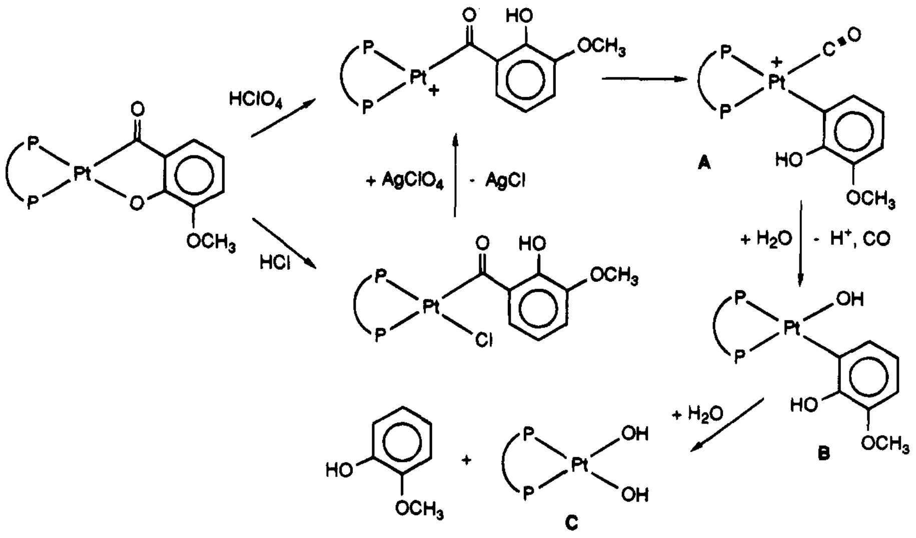
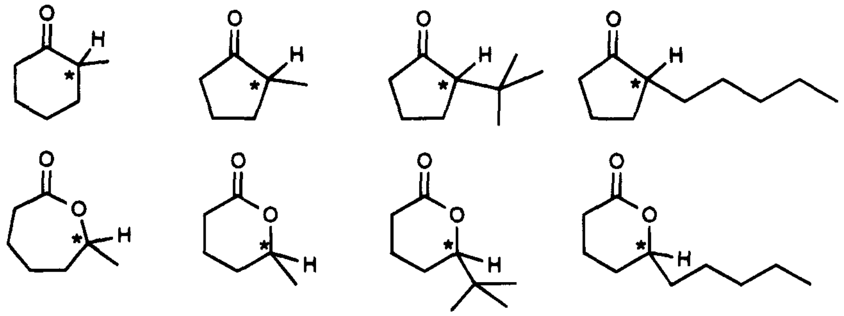


Chart 2



1	$[(S,S\text{-chiraphos})Pt(CF_3)(CH_2Cl_2)]\ BF_4$
2	$[(R,R\text{-pyrphos})Pt(CF_3)(CH_2Cl_2)]\ BF_4$
3	(S,S-chiraphos)Pt(2-van)
4	(R,R-pyrphos)Pt(2-van)
5	(R-prophos)Pt(2-van)
6	(R-binap)Pt(2-van)
7	(S-binap)Pt(2-van)

The enantiomeric excess was determined gas chromatographically with a chiral β-cyclodextrin column; it remains constant during each experiment (see for example Figure 5A) when catalysts **1** and **2** are employed. Since the reaction is a kinetic resolution, in principle, this would imply that the ee decreases with the conversion. Indeed, the low ee and low maximum conversion observed with catalysts **1** and **2** would probably prevent the observation of this compensation effect. However, when the ee vs conversion dependence was monitored using catalyst **6** at 0 °C, the curve shown in Figure 5B was observed. As can be seen, the initially low ee increases up to 48% for a conversion of ~3.5% and then remains constant until ~12% conversion, at which point the reaction stops. This amplification of the initial ee, which occurs only with the (P-P)Pt(2-van) catalysts, is a further indication of the uncertainty on the nature of the catalytically active species with the latter complexes (see the NMR experiment above) and suggests that the species initially present rapidly evolves into a different (more enantioselective) catalyst.

Assignment of the absolute configuration to the prevailing enantiomer was made by optical rotation after separation of the lactone from the reaction mixture and comparison to literature data.[3a] As can be seen from Table 4, the ee obviously depends on the experiment temperature and is normally below 15%, with the exception of the experiments carried out with the binap derivatives, where significantly higher values are observed. Moreover, the (*S*)-lactone is always obtained with derivatives of *R*,*R*-pyrphos, *R*-binap, and *R*-prophos, while the (*R*)-lactone is preferred with the catalysts modified with *S*,*S*-chiraphos. This tendency to produce the lactone with a configuration that is opposite to that of the chiral diphosphine is particularly evident when comparing the behavior of (*R*-binap)Pt(2-van) to that of (*S*-binap)Pt(2-van). As can be seen, both the reactivity and the ee are the same, but the (*S*)-lactone is obtained with the former and the (*R*)-lactone with the latter.

b. 2-Methylcyclopentanone. The results obtained in the lactonization of this ketone with the different catalysts are summarized in Table 5. The same considerations made for 2-methylcyclohexanone concerning (i) the dependence of the initial rate and ee on temperature, (ii) the excess H_2O_2 consumption, and (iii) the

Table 4. Lactonization of 2-Methylcyclohexanone with Hydrogen Peroxide Catalyzed by Chiral Pt(II) Complexes[a]

catalyst	temp (°C)	initial rate (10^4 M s^{-1})	max amt of lactone (mmol)	time (min)	ee (%)[b]	remaining H_2O_2 (%)
1	0	1.8	1.88	5831	11 (*R*)	
	25	4	1.90	1553	9 (*R*)	9
	50	6	1.38	208	8 (*R*)	
2	0	0.21	0.75	218	16 (*S*)	
	25	0.25	1.00	1432	3 (*S*)	12
3	0	1.5	3.50	5578	9 (*R*)	
	25	>10	4.25	956	7 (*R*)[c]	7
	50	≫10	4.00	26	5 (*R*)	
4	0	1.4	3.07	5576	15 (*S*)	
	25	0.2	3.52	2423	12 (*S*)	7
5	0	0.9	2.55	1105	7 (*S*)	10
6	0	1.0	2.25	1561	45 (*S*)	
	25	3	3.75	1223	37 (*S*)[c]	8
	50	>10	3.53	104	31 (*S*)	
7	25	3	3.70	1150	39 (*R*)	

[a] Reaction conditions: Pt, 0.025 mmol; ketone, 25 mmol; 35% H_2O_2, 12.5 mmol; N_2, 1 atm; with catalysts **3–7** $HClO_4$ (0.025 mmol) added. Remaining H_2O_2 (last column) refers to the amount introduced. [b] ee determined by gas chromatography. [c] Absolute configuration determined also by optical rotation.

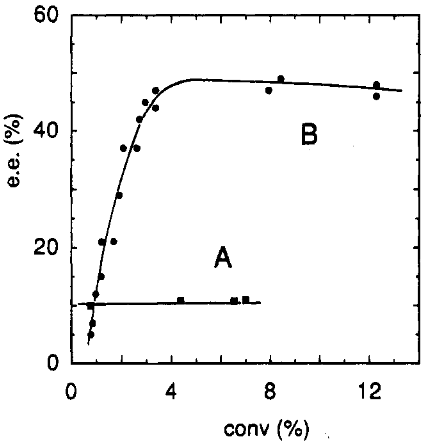


Figure 5. ee vs conversion plot for the lactonization of 2-methylcyclohexanone at 0 °C: (A) catalyst **2**; (B) catalyst **6**.

Table 5. Lactonization of 2-Methylcyclopentanone with Hydrogen Peroxide Catalyzed by Chiral Pt(II) Complexes[a]

catalyst	temp (°C)	initial rate (10^4 M s^{-1})	max amt of lactone (mmol)	time (min)	ee (%)[b]	remaining H_2O_2 (%)
1	0	1.2	0.98	3927	10 (*R*)	
	25	3.1	1.54	503	10 (*R*)	8.5
2	0	0.01	0.28	3935	21 (*S*)	
	25	0.03	0.56	2771	2 (*S*)	21
3	0	4	0.98	1381	26 (*R*)	
	50	>10	2.80	1212	9 (*R*)	
4	0	0.08	0.84	4159	12 (*S*)	
	25	0.95	1.26	1358	26 (*S*)	10
	50	4	2.80	1236	13 (*S*)	
5	0	2.3	0.84	1274	20 (*S*)	
	25	5	0.98	240	6 (*S*)	14
6	0	0.47	0.84	1213	16 (*S*)	
	25	3.2	1.26	1288	14 (*S*)	11
	50	4	1.40	1176	4 (*S*)	

[a] Reaction conditions: Pt, 0.028 mmol; ketone, 28 mmol; 35% H_2O_2, 14 mmol; N_2, 1 atm; with catalysts **3–6** $HClO_4$ (0.028 mmol) added. Remaining H_2O_2 (last column) refers to the amount introduced. [b] ee and absolute configuration determined by optical rotation.

Table 6. Lactonization of 2-*tert*-Butylcyclopentanone with Hydrogen Peroxide Catalyzed by Chiral Pt(II) Complexes[a]

catalyst	temp (°C)	initial rate (10^4 M s^{-1})	max amt of lactone (mmol)	time (min)	ee (%)[b]	remaining H_2O_2 (%)
1	25	0	0	4165		
	80	8	0.09	1513	0	
2	80	>10	0.16	2617	0	
3	80	3	0.03	1202	*c*	
4	80	4	0.03	1200	*c*	
5	50	7	0.06	3973	7	8.5
6	50	7	0.06	2805	12	6

[a] Reaction conditions: Pt, 0.0063 mmol; ketone, 6.3 mmol; 35% H_2O_2, 3.15 mmol; N_2, 1 atm; with catalysts **3–6** $HClO_4$ (0.0063 mmol) added. Remaining H_2O_2 (last column) refers to the amount introduced. [b] ee determined by gas chromatography. [c] Not determined.

Table 7. Lactonization of 2-*n*-Pentylcyclopentanone with Hydrogen Peroxide Catalyzed by Chiral Pt(II) Complexes[a]

catalyst	temp (°C)	initial rate (10^4 M s^{-1})	max amt of lactone (mmol)	time (min)	ee (%)[b]	remaining H_2O_2 (%)
1	0	0.02	0.39	3836	31 (+)	
	25	1.2	0.55	1370	23 (+)	17
2	0	0.003	0.06	3840	*c*	
	25	0.01	0.11	1400	*c*	16
	50	3.1	0.22	4053	*c*	
3	0	0.04	0.66	4301	27 (+)	
	25	1.3	0.88	1316	24 (+)	18
4	0	0.02	0.39	4326	44 (−)	
	25	0.54	0.72	1346	33 (−)	14
	50	1.7	0.72	1454	24 (−)	
5	0	0.03	0.44	4302	18 (−)	
	25	1.1	0.66	405	17 (−)	11
6	0	0.02	0.44	4305	58 (−)	
	25	0.32	0.61	1284	50 (−)	23
	50	2.4	1.65	3999	22 (−)	

[a] Reaction conditions: Pt, 0.011 mmol; ketone, 11 mmol; 35% H_2O_2, 5.5 mmol; N_2, 1 atm; with catalysts **3–6** $HClO_4$ (0.011 mmol) added. Remaining H_2O_2 (last column) refers to the amount introduced. [b] ee determined by optical rotation. [c] Not determined.

correlation between the absolute configuration of the lactone and that of the diphosphine apply even in this case. However, with this substrate separation of the two lactone enantiomers with the chiral β-cyclodextrin columns was not possible. Therefore, the lactone was always separated from the reaction mixture and analyzed polarimetrically. ee values were calculated by comparison with literature data.[3a]

c. 2-*tert*-Butylcyclopentanone. This substrate was studied in order to see whether the presence of a bulky substituent had some influence on the enantioselection of the catalyst, in comparison with the previous 2-methylcyclopentanone case. Unfortunately, under the usual temperature conditions, 2-*tert*-butylcyclopentanone is not very reactive, thereby confirming the reactivity dependence of this catalytic system on steric factors.[7d] In most cases a temperature of 80 °C had to be used in order to observe a modest catalytic activity (Table 6). Under these conditions ee could hardly be observed, also because of the low amount of lactone produced. In any case, no literature data are available for the determination of the absolute configuration. However, in two cases a slow reaction occurred even at 50 °C, but a modest ee was observed in both cases, the indication being that the effect of the steric hindrance of the substrate is more likely to depress the catalytic activity rather than to increase the enantioselectivity.

d. 2-*n*-Pentylcyclopentanone. This substrate is of synthetic interest since its lactone is closely related to δ-jasmolactone, i.e. the major constituent of the jasmine fragrance (Scheme 1). The results obtained in the Baeyer–Villiger oxidation of this substrate with the various catalysts are reported in Table 7. Similarly to 2-methylcyclopentanone, the ee was determined by optical rotation following the lactone separation from the reaction mixture. This was determined by comparison with literature data, where the specific rotation but not the absolute configuration could be found. In the case of catalyst **2**, the lactone product could not be separated from the starting ketone due to very low conversion.

A comparison with the data for 2-methylcyclopentanone shows that a longer side chain in the substrate leads to a slight decrease of the catalytic activity but to a significant increase of the optical purity. In fact, in this case fairly good ee's are observed with all catalysts, the results being particularly good in the case of (*R*,*R*-pyrphos)Pt(2-van) (**4**) and (*R*-binap)Pt(2-van) (**6**).

Conclusions

The results reported in this work represent the first example of an asymmetric Baeyer–Villiger transformation catalyzed by a transition metal through a kinetic resolution and leading to products of potential practical interest. This is made possible because there is easy access to chiral Pt(II) catalysts based on well-known and commercially available chiral diphosphines and because, as has been pointed out, the catalytic reaction with these complexes is stereospecific. As has been demonstrated, the stereospecificity is due to the concerted nature of the rearrangement leading to the lactone formation and emphasizes some additional similiarties between the metal-mediated reaction and classic organic chemistry.

Experimental Section

Apparatus. IR spectra were measured on a Perkin-Elmer 683 spectrophotometer and on a Digilab FTS 40 interferometer either in Nujol mulls using CsI plates or in CH_2Cl_2 solution using CaF_2 windows. $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker AC 200 spectrometer operating in the FT mode, using as external reference 85% H_3PO_4. Negative chemical shifts are upfield from the reference. GLC measurements were taken on a Hewlett-Packard 5790A gas chromatograph equipped with a 3390 automatic integrator. GLC–MS measurements were performed on a Hewlett-Packard 5971 mass selective detector connected to a Hewlett-Packard 5890 II gas chromatograph. Identification of products was made with GLC or GLC–MS by comparison with authentic samples. Optical rotation measurements were performed on a Perkin-Elmer 241 polarimeter operating at 589 nm.

Materials. Solvents were dried and purified according to standard methods. Ketone substrates were purified by passing through neutral alumina, prior to use. Hydrogen peroxide (35% from Fluka), *m*-chloroperbenzoic acid (90%; MCPBA, Janssen), dppe, *o*-dppb, *R*-prophos, and *S*,*S*-chiraphos (Strem), *R*,*R*-pyrphos (Degussa), *R*-binap and *S*-binap (Janssen), and most of the synthetic reagents were commercial products and were used without purification.

The following compounds were prepared according to literature procedures: [(dppe)Pt(CF_3)(CH_2Cl_2)]BF_4,[29] [(*o*-dppb)Pt(CF_3)(CH_2Cl_2)] BF_4,[7d] [(*S*,*S*-chiraphos)Pt(CF_3)(CH_2Cl_2)]BF_4,[8] [(*R*,*R*-pyrphos)Pt(CF_3)(CH_2Cl_2)] BF_4,[7d] (dppe)Pt(2-van),[23] and 2-*tert*-butylcyclopentanone.[30] 2-*n*-Pentylcyclopentanone was prepared from 2-phenyl-2-cyclopenten-1-one (Janssen) by hydrogenation on 5% Pd/C.

(*S*,*S*-chiraphos)Pt(2-van). In a round-bottomed flask equipped with a reflux condenser K_2PtCl_4 (0.75 g, 1.81 mmol), Na_2CO_3 (0.58 g, 5.47 mmol), and 2-vanillin (0.276 g, 1.81 mmol) were mixed in DMSO (25 mL) under N_2, heated to 140 °C with stirring, and maintained at that temperature for 30 min. The solution was slowly cooled down to 100 °C, and then solid *S*,*S*-chiraphos (0.77 g, 1.81 mmol) was added. Further cooling to 60 °C was followed by evaporation of the solvent in vacuo. The dry residue was extracted with CH_2Cl_2 and filtered, and the filtrate was treated with activated carbon. After 15 min the mixture was filtered and concentrated in vacuo to a few milliliters. Addition of EtOH (5 mL) resulted in the precipitation of a yellow powder, which was filtered, washed with Et_2O, and dried in vacuo (yield 57%). Anal. Calcd (found) for $C_{36}H_{34}O_3P_2Pt$: C, 56.03 (55.74); H, 4.44 (4.25).

(*R*,*R*-pyrphos)Pt(2-van). This complex was prepared similarly to (*S*,*S*-chiraphos)Pt(2-van) by starting from K_2PtCl_4 (0.95 g, 2.29 mmol), Na_2CO_3 (0.73 g, 6.88 mmol), 2-vanillin (0.35 g, 2.29 mmol), and *R*,*R*-pyrphos (1.21 g, 2.29 mmol) (yield 48%). Anal. Calcd (found) for $C_{42}H_{39}NO_3P_2Pt$: C, 58.47 (57.85); H, 4.55 (4.71).

(*R*-prophos)Pt(2-van). This complex was prepared similarly to (*S*,*S*-chiraphos)Pt(2-van) by starting from K_2PtCl_4 (0.51 g, 1.24 mmol), Na_2CO_3 (0.39 g, 3.72 mmol), 2-vanillin (0.19 g, 1.24 mmol), and *R*-prophos (0.51 g, 1.24 mmol) (yield 52%). Anal. Calcd (found) for $C_{35}H_{32}O_3P_2Pt$: C, 55.48 (55.22); H, 4.26 (4.13).

(*R*-binap)Pt(2-van). This complex was prepared similarly to (*S*,*S*-chiraphos)Pt(2-van) by starting from K_2PtCl_4 (0.29 g, 0.69 mmol), Na_2CO_3 (0.22 g, 2.07 mmol), 2-vanillin (0.10 g, 0.69 mmol), and *R*-binap (0.43 g, 0.69 mmol). Due to its higher solubility, the complex was precipitated from CH_2Cl_2 with hexane (yield 81%). Anal. Calcd (found) for $C_{52}H_{40}O_3P_2Pt$: C, 64.26 (64.52); H, 4.15 (4.31).

(*S*-binap)Pt(2-van). This complex was prepared similarly to (*S*,*S*-chiraphos)Pt(2-van) by starting from K_2PtCl_4 (0.29 g, 0.69 mmol), Na_2CO_3 (0.22 g, 2.07 mmol), 2-vanillin (0.10 g, 0.69 mmol), and *R*-binap (0.43 g, 0.69 mmol). Due to its higher solubility, the complex was precipitated from CH_2Cl_2 with hexane (yield 75%). Anal. Calcd (found) for $C_{52}H_{40}O_3P_2Pt$: C, 64.26 (64.07); H, 4.15 (4.35).

Reaction of (dppe)Pt(2-van) with $HClO_4$. The complex (diphos)Pt(2-van)(0.10 g, 0.13 mmol) was dissolved in dry acetone (30 mL) and stirred under N_2. A 10.93 N solution of $HClO_4$ (12 μL) was added with a microsyringe. The solution turned immediately from pale yellow to orange and returned to pale yellow in a few minutes. After 15 min the solution was rapidly evaporated to dryness in vacuo at room temperature to give a pale orange powder, which was redissolved in 1 mL of acetone and precipitated with Et_2O (20 mL). The solvent was decanted and the solid dried in vacuo.

Synthesis of Lactones. Lactones used as standards for gas chromatographic determinations in the individual catalytic reactions were synthesized from the starting ketone (20 mmol) in 25 mL of CH_2Cl_2 to which 20 mmol MCPBA was added under N_2 with stirring. After 24 h the solid MCBA was filtered off and the solution containing ~85% lactone was used for qualitative identification and for the determination of the separation conditions of the lactone enantiomers on the chiral β-cyclodextrin GC column.

Catalytic Reactions. These were carried out in a 25-mL round-bottomed flask equipped with a stopcock for vacuum/N_2 operations and a side arm fitted with a screw-capped silicone septum to allow sampling. Constant temperature (±0.1 °C) was maintained by water circulation through an external jacket connected with a thermostat. For reactions carried out at temperatures >25 °C the reaction vessel was equipped with a reflux condenser. Stirring was performed by a Teflon-coated bar driven externally by a magnetic stirrer. The absence of diffusional problems below 3×10^{-4} M s^{-1} initial rates was determined by the conversion vs time plot independence of the stirring rate in randomly selected catalytic experiments. The concentration of the commercial H_2O_2 solution was checked iodometrically prior to use.

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The following general procedure was followed. The required amount of catalyst was placed as the solid in the reactor, which was evacuated and filled with N_2. Purified, N_2-saturated ketone was added under N_2 flow, followed, if necessary, by the required amounts of solvent. After the system was thermostated at the required temperature with stirring for a few minutes, the H_2O_2 solution in the appropriate amount was injected through the septum and the time was started. When using (P-P)Pt(2-van) catalysts an amount of 70% $HClO_4$ equivalent to the amount of catalyst was added prior to H_2O_2 addition. The solution was stirred for 1 h, and then H_2O_2 was injected.

All reactions were monitored with GLC by direct injection of samples taken periodically from the reaction mixtures with a microsyringe. Initial rate data were determined from conversion vs time plots. Prior quenching of the catalyst with LiCl did not show any differences in randomly selected analyses. Separation of the products was performed on 25-m HP-5 capillary columns using a flame ionization detector.

The amount of residual H_2O_2 at different times was determined by sampling 10-μL aliquots from the aqueous phase. These were diluted in water and titrated iodometrically.

Determination of ee. The ee values at the maximum lactone conversion were determined by GC using a 25-m Chrompack CP-β-cyclodextrin-2,3,6-M-19 capillary column. Since even for racemic mixtures there is an apparent ee which depends on the peak area, a calibration curve of apparent ee/peak area was first determined using the racemic lactones synthesized according to the above procedure. The calibration curve was used to correct the experimental values obtained in the enantioselective reactions.

In some cases (2-methylcyclopentanone, 2-*n*-pentylcyclopentanone) the lactone enantiomers could not be separated by GC and therefore ee values were determined by optical rotation on solutions obtained according to the following separation procedure. The catalytic reaction mixture was quenched with the addition of an aqueous solution of LiCl. Addition of a few milliters of Et_2O resulted in the precipitation of the catalyst, which was filtered off. The organic layer was separated, and the residual ketone was eliminated as semicarbazone according to a known procedure.[31] The pure lactone product was isolated in CH_2Cl_2 solution, the concentration of which was determined by addition of a known amount of 1,3-dimethoxybenzene used as internal standard. This solution was analyzed polarimetrically.

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