# New Chiral Complexes of Platinum(II) as Catalysts for the Enantioselective Baeyer−Villiger Oxidation of Ketones with Hydrogen Peroxide: Dissymmetrization of *meso*-Cyclohexanones

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The synthesis and characterization of a number of chiral complexes of the type $[(P-P)Pt(\mu\text{-}OH)]_2^{2+}$ (P−P = (*R*)-binap, (*S*,*S*)-diop, (*R*,*R*)-pyrphos, (*R*,*R*)-norphos, (*R*,*R*)-Me-duphos, (*S*,*S*)-bppm) are reported. These are used for the enantioselective Baeyer−Villiger oxidation of substituted *meso*-cyclohexanones using 35% hydrogen peroxide as oxidant. The reaction is performed at 0 °C with moderate yields, showing in some cases ee higher than 50%. Best catalysts are those containing atropoisomeric ligands possessing $C_2$ symmetry and/or capable of making seven-membered chelate rings with the metal. The results represent the first example of dissymmetrization of achiral cyclohexanones obtained via the Baeyer−Villiger oxidation using a transition metal catalyst.

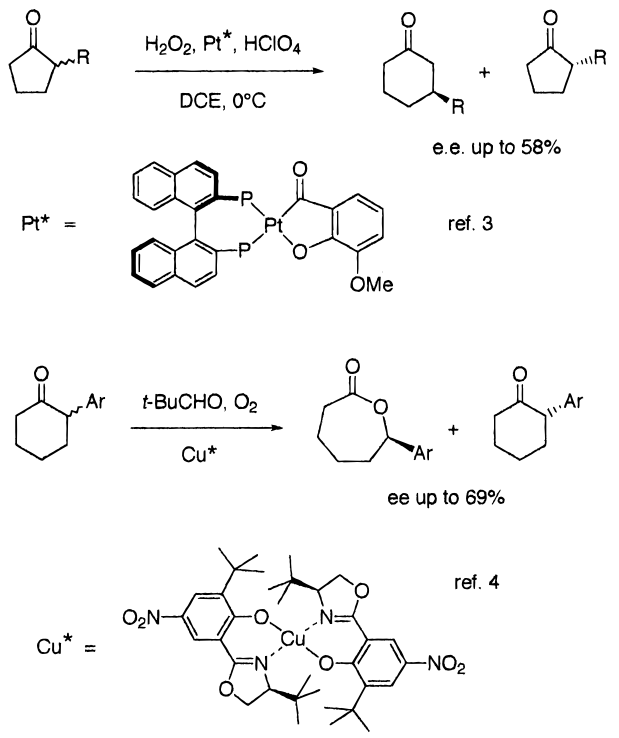


## Introduction

The Baeyer−Villiger oxidation of ketones is a reaction of large synthetic utility[1] for which a number of transition metal complexes have been recently identified as possible soluble catalysts.[2] While organic peroxy acids are the oxidants of choice in the organic reaction, the most notable oxidants used in association with catalysts are either hydrogen peroxide or dioxygen in the presence of an aldehyde as cocatalyst. An additional advantage of using a catalyst is that it can be easily modified with chiral ligands, thereby allowing in principle the achievement of an asymmetric transformation starting from achiral reagents.

Some years ago, we[3] and Bolm and co-workers[4] reported independently the first example of catalytic, asymmetric Baeyer−Villiger oxidation in the conversion of a series of racemic, substituted cyclic ketones into enantiomerically enriched lactones (Scheme 1). Although the catalytic systems were different, the principle was the same, i.e., the kinetic resolution of a racemic mixture by preferential conversion of one of the enantiomers in the presence of a chiral catalyst. This principle has recently found a spectacular application by the group of Jacobsen in the hydrolytic resolution of racemic epoxides, where almost enantiomerically pure epoxides and glycols could be obtained.[5]

**Scheme 1**




The first example of genuine asymmetric induction in a catalyzed Baeyer−Villiger oxidation was reported by Bolm et al. in the conversion of substituted cyclobutanones to the corresponding butyrolactones with an asymmetric induction up to 91% ee.[6] Unfortunately, the catalyst did not seem to possess a wide applicability, as it is unable to oxidize ketones other than cyclobutanones; therefore the scope of the reaction remained

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(1) Krow, G. C. *Org. React.* **1993**, *43*, 251, and references therein.

(2) (a) Strukul, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1198. (b) Bolm, C.; Beckmann, O.; Khan Luong, T. K. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley VCH: Weinheim, 1998; Vol. 2, Chapter 2.4, p 213. (c) Bolm, C. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, 1997; Vol. 2, p 43.

(3) (a) Gusso, A.; Baccin, C.; Pinna, F.; Strukul, G. *Organometallics* **1994**, *13*, 3442. (b) Strukul, G.; Varagnolo, A.; Pinna, F. *J. Mol. Catal.* **1997**, *117*, 413.

(4) Bolm, C.; Schlingloff, G.; Weickardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1848.

(5) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

(6) (a) Bolm, C.; Schlingloff, G.; Bienewald, F. *J. Mol. Catal.* **1997**, *117*, 347. (b) Bolm, C.; Luong, T. K. K.; Schlingloff, G. *Synlett* **1997**, 1151.

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**Scheme 2**

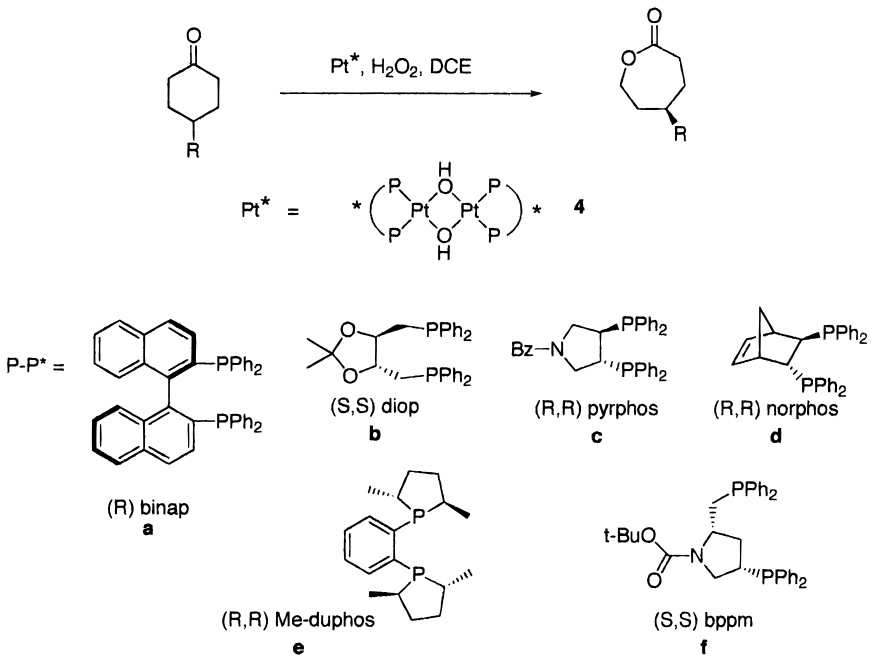
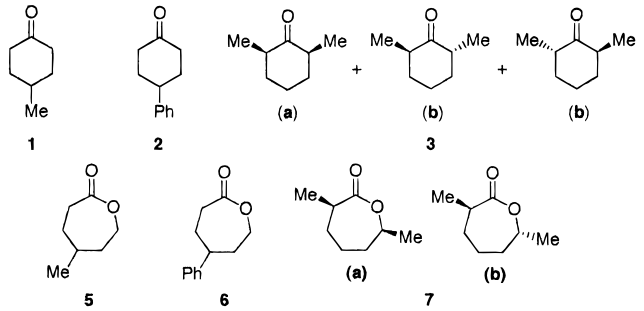



**Chart 1**

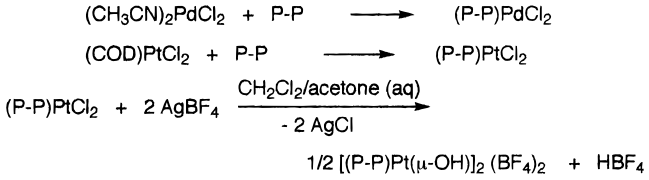



rather limited. In this work we now report a more general example of asymmetric induction in the case of some prochiral *meso*-cyclohexanones (Chart 1). The reaction is catalyzed (Scheme 2) by a class of bridging hydroxo complexes of Pt(II) that have been recently recognized to be the most active catalysts for the Baeyer−Villiger oxidation.[7] These catalysts have been modified with commercially available chiral diphosphines (Scheme 2) and therefore have a significant potential for applications in organic synthesis.

## Results and Discussion

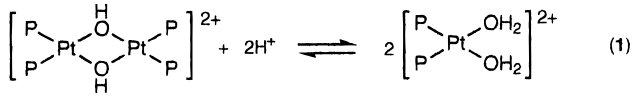
**Synthesis of the Catalysts.** The chiral catalysts were prepared according to a general method already known in the literature[8] and already experienced in the preparation of the catalysts reported in ref 7 for the Baeyer−Villiger oxidation of cyclic and acyclic ketones (Scheme 3). The addition of the appropriate diphosphine to $(COD)PtCl_2$ yields the corresponding diphosphine Pt dichloride complex, from which the bridging hydroxo species is obtained by addition of 2 equiv of silver tetrafluoroborate. Optimum results are obtained using

**Scheme 3**




a reagent grade $CH_2Cl_2$/acetone solvent mixture, where the trace water present is responsible for the formation of the bridging hydroxo ligand.

We have observed that upon precipitation some $HBF_4$ (Scheme 3) may be retained on the solid Pt($\mu$-OH) complexes. Since it is known that in solution the equilibrium depicted in eq 1 can arise in the presence of acid,[9] in order to avoid interference with the catalytic reactions all complexes of type 4 were dissolved in $CH_2Cl_2$ and extracted with water.




(1)

**Characterization.** Complexes **4a** and **4c** were already reported elsewhere.[3b] All the other complexes of type **4** and the corresponding dichlorides are new and have been characterized by IR, NMR, and molar conductivity measurements. A summary of their spectroscopic features is reported in Table 1.

The dichloro complexes display in the IR spectrum the typical symmetric and asymmetric Pt−Cl stretching modes in the region around 300 $cm^{-1}$. Their $^{31}P\{^1H\}$ NMR spectra are consistent with the presence of two equivalent (diop and duphos derivatives) or inequivalent (norphos and bppm derivatives) phosphorus nuclei with evidence for P−Pt coupling constants in the range 3500−3700 Hz, similar to other homologous complexes[7,8]

(7) Gavagnin, R.; Cataldo, M.; Pinna, F.; Strukul, G. *Organometallics* **1998**, *17*, 661.

(8) (a) Li, J. J.; Li, W.; Sharp, P. R. *Inorg. Chem.* **1996**, *25*, 604. (b) Bandini, A. L.; Banditelli, G.; Demartin, F.; Manassero, M.; Minghetti, G. *Gazz. Chim. Ital.* **1993**, *123*, 417.

(9) (a) Pisano, A.; Consiglio, G.; Sironi, A.; Moret, M. *J. Chem. Soc., Chem. Commun.* **1991**, 421. (b) Sperrle, M.; Grämlich, V.; Consiglio, G. *Organometallics* **1996**, *15*, 5196.

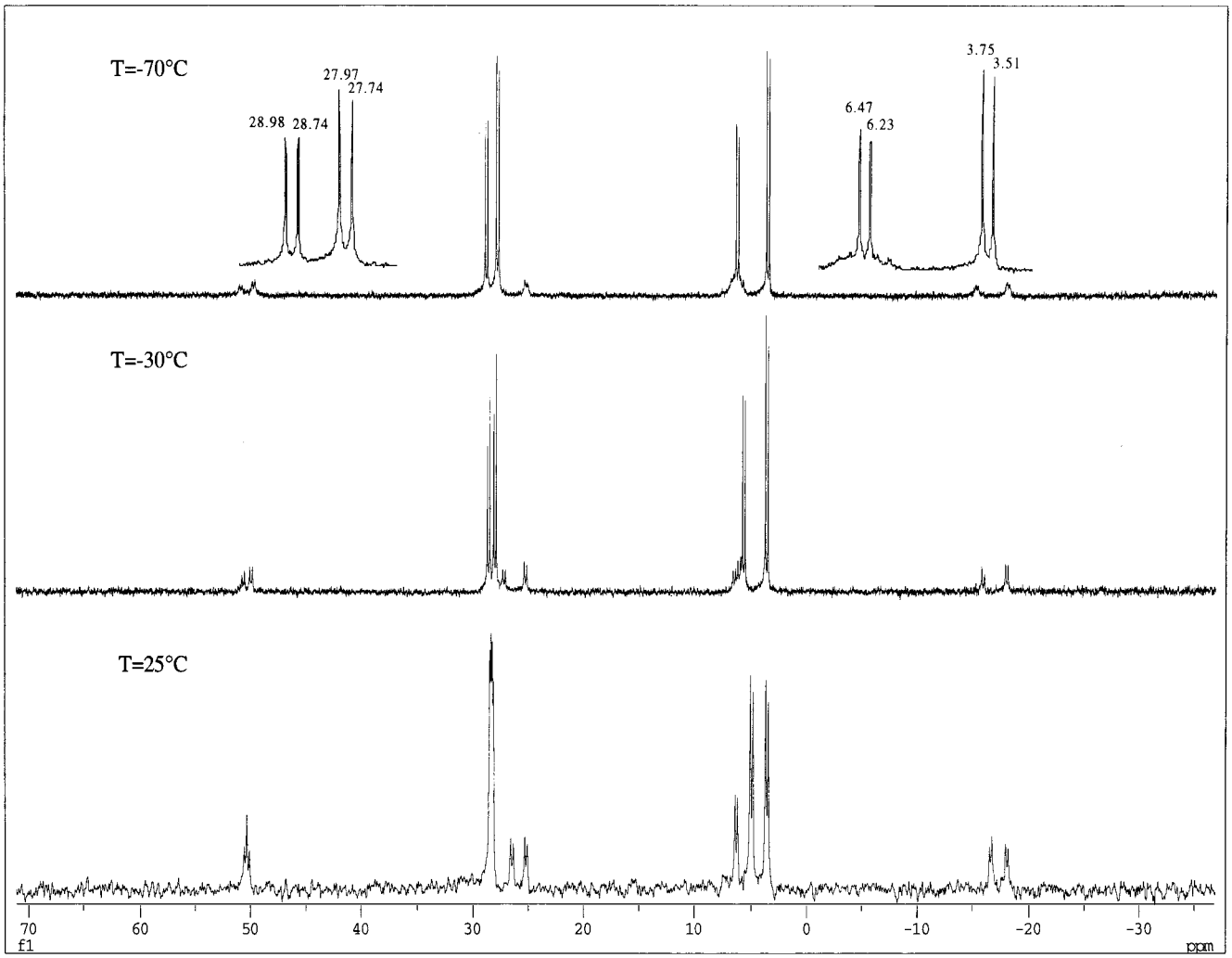
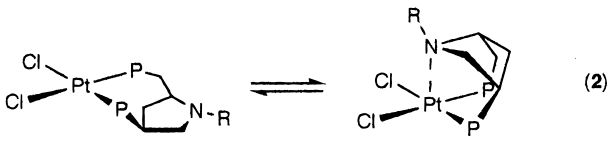



**Figure 1.** Variable-temperature $^{31}P\{^1H\}$ NMR spectrum of [(bppm)$PtCl_2$].

and consistent with the presence of a *trans* chloride ligand.[10]

Some odd features are observed in the case of the bppm derivative. In fact, at room temperature (Figure 1) the spectrum seems to show the existence of two different species, which is evident upon lowering the temperature. As shown in Figure 1, at −70 °C the spectrum clearly shows four main signals with evidence for P−P coupling and the respective $^{195}Pt$ satellites, consistent with the presence of two species with the same symmetry of [(bppm)$PtCl_2$] in slightly different concentrations. The close values found for both the chemical shift of the homologous phosphorus donors and the coupling constants (Table 1) seem to suggest that the species are most likely isomers. A possible interpretation suggested by molecular models is shown in eq 2, in which a possible equilibrium is presented between two conformers: one with an open structure and another one in which the diphosphine heterocycle can rotate and position the N donor above the square coordination plane as a possible fifth axial ligand.




(2)

**Table 1. IR and $^{31}P\{^1H\}$ NMR Characterization of New Complexes**

| complex | IR ($cm^{-1}$)[a] | $^{31}P\{^1H\}$ NMR[b] |
|---|---|---|
| [(diop)$PtCl_2$] | 320, 296 (PtCl) | $\delta$ −0.93 s; $^1J_{P-Pt}$ 3519 |
| [(norphos)$PtCl_2$] | 315, 292 (PtCl) | $\delta$ −11.58 d; $^2J_{P-P}$ 4.8, $^1J_{P-Pt}$ 3685<br>$\delta$ −10.75 d; $^2J_{P-P}$ 4.8, $^1J_{P-Pt}$ 3678 |
| [(duphos)$PtCl_2$] | 315, 286 (PtCl) | $\delta$ 67.2 s; $^1J_{P-Pt}$ 3126 |
| [(bppm)$PtCl_2$][c] | 318, 295 (PtCl) | $\delta$ 28.41 d; $^2J_{P-P}$ 18.3, $^1J_{P-Pt}$ 3549<br>$\delta$ 28.26 d; $^2J_{P-P}$ 18.3, $^1J_{P-Pt}$ 3549<br>$\delta$ −4.96 d; $^2J_{P-P}$ 18.5, $^1J_{P-Pt}$ 3475<br>$\delta$ −3.58 d; $^2J_{P-P}$ 18.5, $^1J_{P-Pt}$ 3502 |
| [(diop)Pt($\mu$-OH)]$_2$($BF_4$)$_2$ (**4b**) | 3590 (OH)<br>1060 ($BF_4$) | $\delta$ −3.98 s; $^1J_{P-Pt}$ 3558 |
| [(norphos)Pt($\mu$-OH)]$_2$($BF_4$)$_2$ (**4d**) | 3593 (OH)<br>1064 ($BF_4$) | $\delta$ 5.81 m; $^1J_{P-Pt}$ 3679 |
| [(duphos)Pt($\mu$-OH)]$_2$($BF_4$)$_2$ (**4e**) | 3594 (OH)<br>1060 ($BF_4$) | $\delta$ 64.04 s; $^1J_{P-Pt}$ 3474 |
| [(bppm)Pt($\mu$-OH)]$_2$($BF_4$)$_2$ (**4f**) | 3554 (OH)<br>1054 ($BF_4$) | $\delta$ 43.79 m; $^1J_{P-Pt}$ 3115<br>$\delta$ 41.5 m; $^1J_{P-Pt}$ 3128 |

[a] In KBr disk; O−H modes determined in DCE solutions. [b] $\delta$ in ppm, coupling constants in Hz. [c] NMR data taken at −70 °C.

As to hydroxo complexes, their IR spectra show a strong broad band in the 900−1100 $cm^{-1}$ range corresponding to a noncoordinated $BF_4^-$ anion and a

(10) Appleton, T. G.; Bennett, M. A. *Inorg. Chem.* **1979**, *17*, 739.

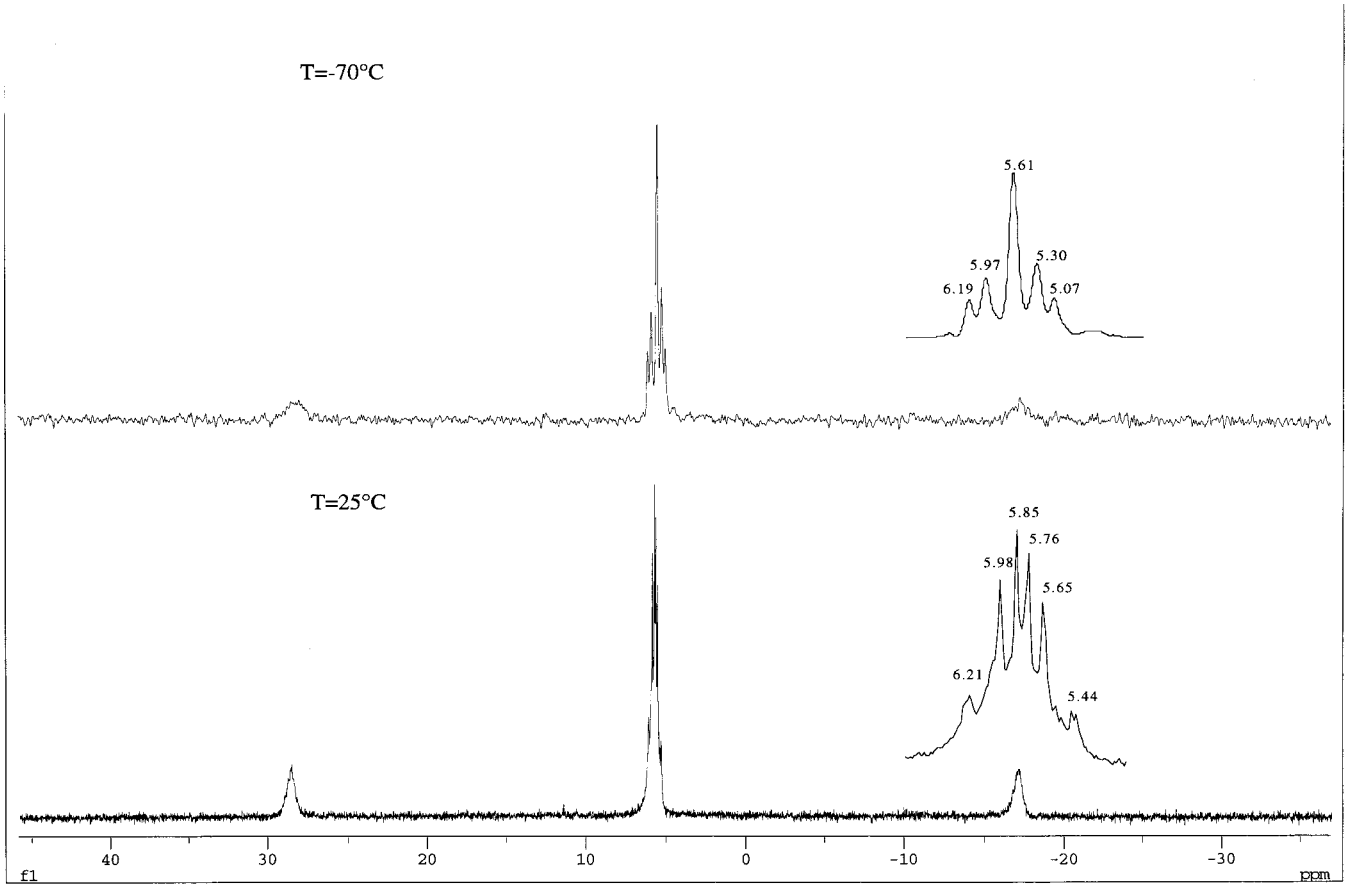
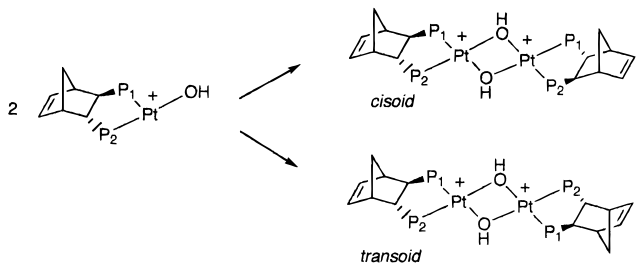



**Figure 2.** Variable-temperature $^{31}P\{^1H\}$ NMR spectrum of **4d**.

**Scheme 4**




medium intensity band in the 3550−3590 $cm^{-1}$ range, typical of the O−H stretching mode in bridged type complexes.[3b,7,8,11] The $^{31}P\{^1H\}$ NMR features are in agreement with the formulation proposed for complexes **4b** and **4e**, as are the P−Pt coupling constants (3100−3600 Hz for a P *trans* to a hydroxo ligand[3b,7,8,10,11]) for all complexes. The spectrum of **4d** is different from expected (Figure 2). Theoretically, with norphos having two nonequivalent phosphorus nuclei, upon hydroxo bridge formation two different isomers may form, namely, a *cisoid* isomer and a *transoid* isomer (Scheme 4), each giving rise to two doublets with P−Pt coupling and $^{195}$Pt satellites. As shown in Figure 2 the spectrum of **4d** appears as an incompletely resolved multiplet, probably arising from overlapping of signals, that does not split into its components even upon lowering the temperature to −70 °C. The situation for **4f** is even more complex. Here the isomerism depicted in eq 2 is coupled with the *cisoid*/*transoid* isomerism, leading to a total of at least six different species. As can be seen from Figure 3, the spectrum is very complex with overlapping of signals at least in the case of the main ones, the features of which are reported in Table 1.

Evidence for the cationic nature of these complexes was gained from molar conductivity measurements. Data are collected in Table 2 and refer to $10^{-3}$ M solutions in MeOH. The values observed are in agreement with previous data for this class of compounds[3a,7,8] and fall in the range foreseen for 2/1 electrolytes.[12]

**Substrates and Products.** The substrates tested are commercially available products and are summarized in Chart 1. As can be seen, they are all prochiral *meso* ketones from which chiral lactone enantiomers are formed depending on which one of the carbon atoms adjacent to the carbonyl group migrates on the peroxy oxygen in the lactone formation step. The mechanism of the catalyzed Baeyer−Villiger oxidation as suggested by a study[7] with the homologous $[(dppb)Pt(\mu\text{-}OH)]_2^{2+}$ complex (dppb = 1,4-bis(diphenylphosphino)butane) is shown in Scheme 5. Indeed, as indicated in Chart 1, ketone **3** is commercially available as a mixture of two different isomers: a *meso* isomer (**3a** 79%) and a chiral racemic isomer (**3b** 21%) for which the enantioselective conversion into lactones (**7a** and **7b**, respectively) is a kinetic resolution process.

Product mixtures for all the substrates indicated in Chart 1 were obtained by stoichiometric conversions

(11) (a) Longato, B.; Corain, B.; Bonora, G. M.; Pilloni, G. *Inorg. Chim. Acta* **1987**, *137*, 75. (b) Trovò, G.; Bandoli, G.; Casellato, U.; Corain, B.; Nicolini, M.; Longato, B. *Inorg. Chem.* **1990**, *29*, 4616. (c) Bandini, A. L.; Banditelli, G.; Cinellu, M. A.; Sanna, G.; Minghetti, G.; Demartin, F.; Manassero, M. *Inorg. Chem.* **1989**, *28*, 404. (d) Li, J. J.; Sharp, P. R. *Inorg. Chem.* **1994**, *33*, 183.

(12) Geary, W. J. *Coord. Chem. Rev.* **1971**, *7*, 81.

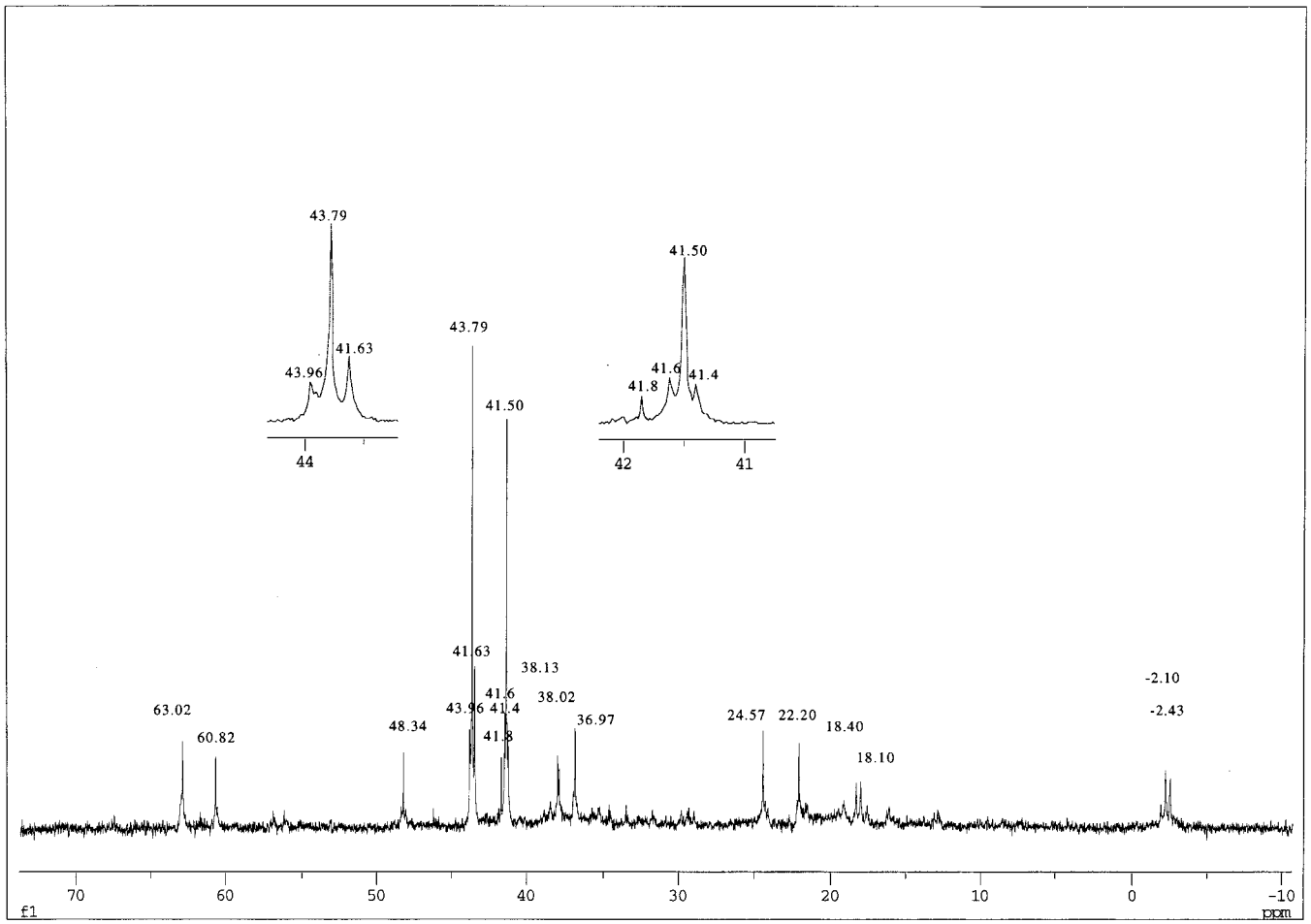


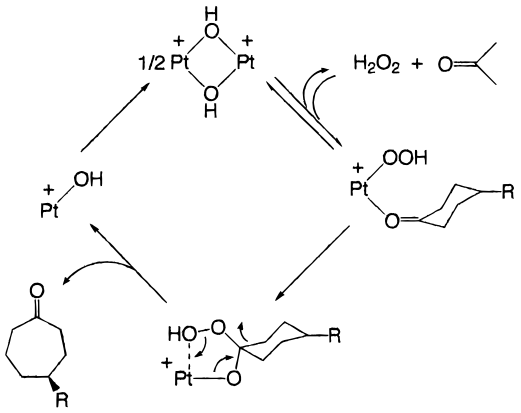

**Figure 3.** Room-temperature $^{31}P\{^1H\}$ NMR spectrum of **4f**.

**Table 2. Molar Conductivity Data of New [(P−P*)Pt(μ-OH)]$_2$ (BF$_4$)$_2$ Complexes**[a]

| complex | $\Lambda_M$ ($\Omega^{-1}$ mol$^{-1}$ cm$^2$) |
|---|---|
| [(diop)Pt(μ-OH)]$_2$(BF$_4$)$_2$ (**4b**) | 183 |
| [(norphos)Pt(μ-OH)]$_2$(BF$_4$)$_2$ (**4d**) | 171 |
| [(duphos)Pt(μ-OH)]$_2$(BF$_4$)$_2$ (**4e**) | 170 |
| [(bppm)Pt(μ-OH)]$_2$(BF$_4$)$_2$ (**4f**) | 147 |

[a] $10^{-3}$ M solutions in MeOH.

**Scheme 5**




using *m*-chloroperbenzoic acid (MCPBA) as oxidant. Separation of **3b** and the lactone products into the individual enantiomers was performed by GC using commercially available chiral columns. In Figure 4 a summary of the separations is given, while the conditions for the analysis are reported in the Experimental Section. The peak corresponding to ketone **3b** was identified in the GC analysis because it can be split into the two enantiomers. Figure 4 shows that the separations were always excellent with the only exception of lactones **7b**, for which moderate overlapping was observed. Since enantiomerically pure products were not available, in the evaluation of the individual ee's arising from the enantioselective reactions the prevailing enantiomer could not be established. The rotation of the catalyst-free crude product was determined by direct polarimetric analysis of a solution in DCE. In the case of lactones **5** and **6** this corresponds also to the rotation of the prevailing enantiomer; however, lactone **7** is a mixture and therefore the overall rotation is of no significance. For this reason, in the individual cases we termed **I** the enantiomer eluting first in the GC analysis and **II** the enantiomer eluting second. This rule is applied in the analysis of the catalytic reactions reported below.

**Catalytic Reactions.** Preliminary catalytic tests on substrates **1**−**3** were performed at room temperature using [(dppb)Pt(μ-OH)]$_2$(BF$_4$)$_2$ as the catalyst and 35% $H_2O_2$ as the oxidant. A summary of the profiles of the reactions (mmol product vs time) is shown in Figure 5. As can be seen, the reactions are relatively fast at the beginning and tend to level off rather quickly probably because of deactivation of the catalyst arising from reaction with trace amounts of free hydroxyacid produced by hydrolysis of the product.[7] The amount of

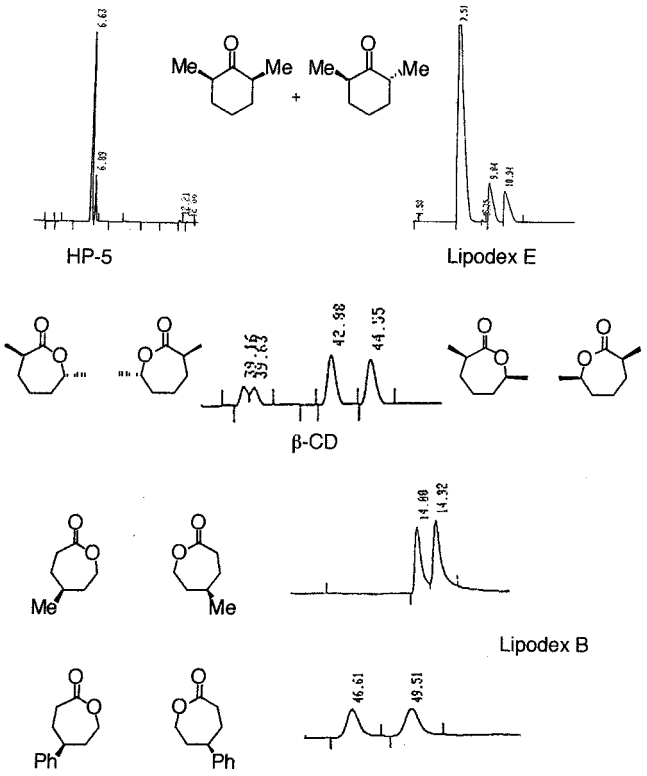



**Figure 4.** Summary of the GC separations of the chiral ketone and lactones.

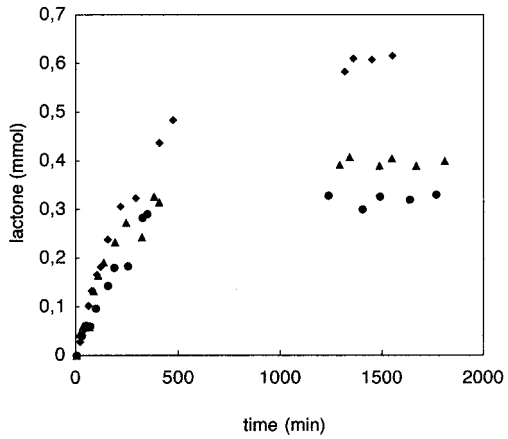
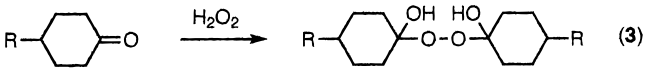



**Figure 5.** Reaction profiles for the Baeyer−Villiger oxidation of cyclohexanones with hydrogen peroxide catalyzed by [(dppb)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$. Reaction conditions: catalyst 1.7 $\mu$mol, ketone 1.7 mmol, $H_2O_2$ 1.7 mmol, solvent DCE, *T* 25 °C; (diamonds) lactone **7**; (triangles) lactone **5**; (circles) lactone **6**.

ketone converted in the individual cases was determined with the use of an internal standard (1,3-dimethoxybenzene).

The oxidation of **1** and **2** is complicated by a side reaction leading to the formation of a product that precipitates out of solution when the reaction mixture is brought to 0 °C. The solid was identified as a peroxide generated by spontaneous reaction of $H_2O_2$ with the ketone according to eq 3 according to a process that was




(3)

identified many years ago by Kharasch and Sosnovsky[13]

**Table 3. Enantioselective Oxidation of 1 with Hydrogen Peroxide Catalyzed by [(P−P*)Pt($\mu$-OH)]$_2^{2+}$ Complexes**[a]

| catalyst | lactone (mmol)[b] | ee (%)[c] |
|---|---|---|
| [(binap)Pt($\mu$-OH)]$_2$ (BF$_4$)$_2$ (**4a**) | 0.17 | 53 (−) **I** |
| [(diop)Pt($\mu$-OH)]$_2$ (BF$_4$)$_2$ (**4b**) | 0.12 | 8 (−) **I** |
| [(pyrphos)Pt($\mu$-OH)]$_2$ (BF$_4$)$_2$ (**4c**) | 0.081 | 4 (+) **II** |
| [(norphos)Pt($\mu$-OH)]$_2$ (BF$_4$)$_2$ (**4d**) | 0.13 | 13 (+) **II** |
| [(duphos)Pt($\mu$-OH)]$_2$ (BF$_4$)$_2$ (**4e**) | 0.19 | 18 (+) **II** |
| [(bppm)Pt($\mu$-OH)]$_2$ (BF$_4$)$_2$ (**4f**) | 0.085 | 50 (+) **I** |

[a] Experimental conditions: catalyst 8.5 $\mu$mol, ketone 1.7 mmol, $H_2O_2$ 1.7 mmol, *T* 0 °C. [b]After 72 h from GC analysis. [c]From GC analysis using Lipodex B chiral column (160 °C isotherm).

**Table 4. Enantioselective Oxidation of 2 with Hydrogen Peroxide Catalyzed by [(P−P*)Pt($\mu$-OH)]$_2^{2+}$ Complexes**[a]

| catalyst | lactone (mmol)[b] | ee (%)[c] |
|---|---|---|
| [(binap)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4a**) | 0.15 | 68 (−) **I** |
| [(diop)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4b**) | 0.068 | 17 (−) **I** |
| [(pyrphos)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4c**) | 0.016 | 13 (−) **I** |
| [(norphos)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4d**) | 0.030 | 7 (+) **II** |
| [(duphos)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4e**) | 0.022 | 21 (−) **I** |
| [(bppm)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4f**) | 0.042 | 34 (+) **II** |

[a] Experimental conditions: catalyst 8.5 $\mu$mol, ketone 1.7 mmol, $H_2O_2$ 1.7 mmol, *T* 0 °C. [b]After 72 h from GC analysis. [c]From GC analysis using Lipodex B chiral column (190 °C isotherm).

**Table 5. Enantioselective Oxidation of 3 with Hydrogen Peroxide Catalyzed by [(P−P*)Pt($\mu$-OH)]$_2^{2+}$ Complexes**[a]

| | lactone (mmol)[b] | | ee (%)[c] | |
|---|---|---|---|---|
| catalyst | **7a** | **7b** | | |
| [(binap)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4a**) | 0.20 | 0.14 | 79 (**I**) | 37 (**II**) |
| [(diop)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4b**) | 0.15 | 0.11 | 5 (**I**) | 5 (**II**) |
| [(pyrphos)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4c**) | 0.050 | 0.014 | 8 (**II**) | 13 (**II**) |
| [(norphos)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4d**) | 0.16 | 0.10 | 31 (**II**) | 8 (**II**) |
| [(duphos)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4e**) | 0.15 | 0.10 | 80 (**I**) | 11 (**II**) |
| [(bppm)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (**4f**) | 0.12 | 0.069 | 10 (**II**) | 3 (**I**) |

[a] Experimental conditions: catalyst 8.5 $\mu$mol, ketone 1.7 mmol, $H_2O_2$ 1.7 mmol, *T* 0 °C. [b]After 96 h from GC analysis. [c]From GC analysis using Chrompack $\beta$-CD chiral column (100 °C isotherm).

and that was reproduced in the present case. Although in the original work[13] the reaction requires an acid as catalyst, the reaction occurs spontaneously with the commercial $H_2O_2$ employed, probably because of the acidity (apparent pH ∼2) necessary to stabilize hydrogen peroxide. The side reaction may, in some cases, be quite significant since amounts as high as about 50% of the starting ketone are converted in peroxide (vide infra).

**Asymmetric Transformations.** Chiral complexes **4** were tested as catalysts for the asymmetric conversion of ketones **1**−**3** into the corresponding substituted $\epsilon$-caprolactones. Reactions were performed at 0 °C, and the reaction profiles were similar to that reported in Figure 2, although the time scale was longer because of a slower rate. A summary of the results is presented in Tables 3−5.

In the case of ketone **1**, Table 3 indicates that satisfactory results in terms of ee can be obtained with catalysts modified with binap (**4a**) and bppm (**4f**) chiral diphosphines, for which values around 50% could be observed. Better results in the oxidation of the same

(13) Kharasch, M. S.; Sosnovsky, G. *J. Org. Chem.* **1958**, *23*, 1322.

**Table 6. Enantioselective Oxidation of 1−3 with Hydrogen Peroxide under Different Conditions[a]**

| catalyst | ketone | ket/catal | lactone (mmol)[b] 7a | 7b | ee (%) |
|---|---|---|---|---|---|
| **4a** | **3** | 100 | 0.25 | 0.23 | 75 (**I**) 32 (**II**) |
| **4e** | | 100 | 0.20 | 0.17 | 73 (**I**) 7 (**II**) |
| **4a** | | 50 | 0.27 | 0.25 | 75 (**I**) 28 (**II**) |
| **4a** | | 25 | 0.35 | 0.28 | 75 (**I**) 21 (**II**) |
| **4a** | **1** | 100 | 0.29[c] | | 50 (−) **I** |
| **4a** | **2** | 100 | 0.16[c] | | 69 (−) **I** |

[a] Experimental conditions: ketone 1.7 mmol, $H_2O_2$ 1.7 mmol, *T* 25 °C. [b]After 96 h from GC analysis. [c]After 72 h.

substrate can be obtained only using a microbiological method, as was observed recently by Stewart et al.[14] Cyclohexanone monooxygenase from *Acinetobacter* was expressed in baker's yeast through a cloning technique to create a general reagent for asymmetric Baeyer−Villiger oxidations. Whole cells were used by these authors to produce the lactone **5** with >98% ee.

As to ketone **2** (Table 4), best results (ee 68%) are observed again with **4a** as catalyst and to a minor extent with **4e** and **4f** (ee 34% and 21%, respectively). Interestingly, in the case of both **1** and **2**, catalysts **4a** and **4f** produce preferentially opposite enantiomers.

In the case of ketone **3** two asymmetric transformations occur at the same time: the asymmetric induction on **3a**, producing the pair of enantiomers **7a**, and the kinetic resolution of racemic **3b**, producing the pair of enantiomers **7b**. As can be seen from Table 5, the asymmetric induction is generally more selective than the kinetic resolution, and some notable results (ee respectively 79% and 80%) are obtained with catalysts **4a** and **4e**.

To improve the productivity of the reaction, some tests were performed at 25 °C mostly using **4a** as the catalyst, which appeared to be the best one in all previous tests. Data are collected in Table 6. As can be seen, increasing the temperature results in a significant increase of the amount of product in the case of **5** and **7**, whereas no differences are observed in the case of **6**. At the same time, only a slight decrease in the ee's is observed in all cases. An increase in the catalyst concentration (i.e., a lower mol ketone/mol catalyst ratio) makes the system more productive. Interestingly, in the conversion of **3b**, the ee of **7b** decreases significantly with increasing productivity. This is not surprising if one considers that the amounts observed are well beyond 50% conversion (0.18 mmol) with respect to the initially present **3b**. In kinetic resolution of racemates conversions higher than 50% result in the occurrence of compensation effects.

**Origin of the Enantioselectivity.** On the basis of Scheme 4, it is clear that in the case of *meso* compounds the only possible enantiodifferentiating step is the rearrangement of the quasi-peroxometallacyclic intermediate, i.e., the migration of either enantiotopic carbon onto the nearby peroxygen. Clearly, the discrimination will depend on the energy associated with the two possible diastereomeric transition states (Figure 6a). On this simple basis a rationalization of the results reported in Tables 3−6 is very difficult, particularly because the

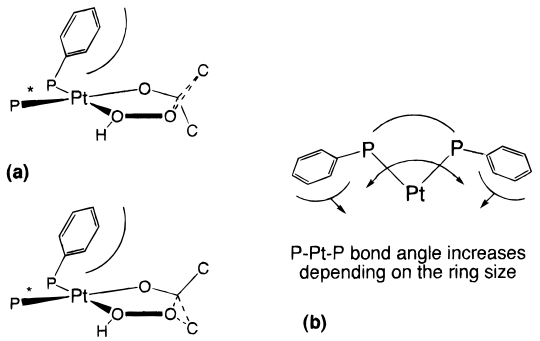



**Figure 6.** (a) Possible transition states for the rearrangement leading to lactone formation in Scheme 5. (b) Effect of the increase in the P−Pt−P bite angle in seven-membered chelate diphosphine−Pt rings.

side of the molecule in which the rearrangement occurs is relatively remote from the chiral pocket located on the diphosphines (in this respect the only exception may be duphos). The diphosphines bearing the highest enantioselectivity are binap, bppm, and duphos. Two of these (binap and duphos) are atropoisomeric and possess $C_2$ symmetry, and since the seminal work of Noyori,[15] $C_2$ symmetry auxiliaries have been recognized to play an important role in asymmetric catalysis and more generally in asymmetric synthesis.[16] On the other hand, two other diphosphines used in the present work (binap and bppm) make with the metal seven-membered rings, for which it is conceivable that the P−Pt−P bite angle is larger than 90°, as was observed in ref 8a for 1,4-diphenylphosphinobutane derivatives. It may be suggested that this structural feature will bring the phenyl substituents present on the two phosphorus atoms closer to the side of the rearrangement (Figure 6b), and this may influence the activation energies for the transition states depicted in Figure 3a, amplifying the differences. Although this view seems reasonable, it is clearly speculative and not exhaustive, as is demonstrated by the fact that the diop derivative (**4b**), which contains a $C_2$ symmetry auxiliary capable of making a seven-membered diphosphine−metal ring, always yields modest results.

## Conclusions

The study reported in this work represents the first example of dissymmetrization of *meso*-substituted cyclohexanones via enantioselective Baeyer−Villiger oxidation using hydrogen peroxide as oxidant and a chiral transition metal complex as catalyst. The results are quite encouraging, as in some cases ee's above 50% are observed. Best catalysts have proved to be those complexes in which the ligands bearing the chiral information possess $C_2$ symmetry and/or are capable of making with the metal seven-membered rings. These structural features result in an amplification of the enantioselectivity. Although catalysis with microorganisms may yield better ee's, the expression of the proper enzyme into a recombinant yeast through cloning[14] is not an easily available, straightforward synthetic pro-

(14) Stewart, J. D.; Reed, K. W.; Martinez, C. A.; Zhu, J.; Chen, G. *J. Am. Chem. Soc.* **1998**, *120*, 3541.

(15) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

(16) See for example: (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH: Weinheim, 1993. (b) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

cedure, as it requires biochemical expertise and specialized equipment not found in typical organic laboratories. In this respect traditional catalysis with transition metal complexes seems to be more amenable for scaling up into standard organic synthesis, as the access to the catalyst is certainly easier, in particular those catalysts (like the present ones) containing commercially available chiral diphosphines.

## Experimental Section

**Apparatus.** IR spectra were taken on a Nicolet FTIR Magna 750 and on a Digilab FTS 40 interferometers either in solid (KBr pellets) or in $CH_2Cl_2$ solution using $CaF_2$ windows. $^1H$ and $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker AC 200 spectrometer operating in FT mode, using as external references TMS and 85% $H_3PO_4$, respectively. Negative chemical shifts are upfield from the reference. Conductivity measurements were performed on a Radiometer instrument using $10^{-3}$ M solutions in MeOH at 25 °C. GC measurements were taken on a Hewlett-Packard 5790A gas chromatograph equipped with a 3390 automatic integrator. The following commercial columns were used: HP-5 (from Hewlett-Packard), $\beta$-CD (from Chrompack), and Lipodex B and Lipodex E (from Macherey-Nagel). GC−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 GC or GC−MS by comparison with authentic samples.

**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 Acros), *m*-chloroperbenzoic acid (MCPBA, 75% from Janssen), dppb, (*R*,*R*)-norphos, (*R*,*R*)-Me-duphos (from Strem), (*R*)-binap, (*S*,*S*)-diop, (*S*,*S*)-bppm (from Fluka), (*R*,*R*)-pyrphos (from Degussa), and most of the synthetic reagents were commercial products and used without purification.

The following compounds were prepared according to literature procedures: [(dppb)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$,[8] [(binap)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$,[3b] [(pyrphos)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$,[3b] [(COD)PtCl$_2$].[17]

**[(bppm)PtCl$_2$].** To a solution of the complex (COD)PtCl$_2$ (0.136 g, 0.363 mmol) in $N_2$-saturated $CH_2Cl_2$ (50 mL) was added solid bppm (0.200 g, 0.363 mmol). The resulting solution was stirred at room temperature for 24 h. Then it was concentrated to small volume under reduced pressure, and an identical amount of $Et_2O$ was added. The resulting pale yellow solid was filtered, washed with $Et_2O$, and dried in vacuo (yield 94%).

Anal. Calcd (found) for $C_{34}H_{37}NO_2Cl_2P_2Pt$: C, 49.83 (49.72); H, 4.55 (4.37).

**[(diop)PtCl$_2$].** This complex was prepared similarly to (bppm)PtCl$_2$ starting from (COD)PtCl$_2$ (0.150 g, 0.40 mmol) and diop (0.200 g, 0.40 mmol) (yield 98%).

Anal. Calcd (found) for $C_{31}H_{32}O_2Cl_2P_2Pt$: C, 48.70 (48.77); H, 4.22 (4.31).

**[(norphos)PtCl$_2$].** This complex was prepared similarly to (bppm)PtCl$_2$ starting from (COD)PtCl$_2$ (0.162 g, 0.42 mmol) and norphos (0.200 g, 0.42 mmol) (yield 90%).

Anal. Calcd (found) for $C_{31}H_{28}Cl_2P_2Pt$: C, 51.11 (51.20); H, 3.87 (3.72).

**[(Me-duphos)PtCl$_2$].** This complex was prepared similarly to (bppm)PtCl$_2$ starting from (COD)PtCl$_2$ (0.244 g, 0.653 mmol) and Me-duphos (0.200 g, 0.653 mmol) (yield 88%).

Anal. Calcd (found) for $C_{18}H_{28}Cl_2P_2Pt$: C, 37.77 (37.86); H, 4.93 (5.01).

**[(bppm)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (4f).** The complex (bppm)PtCl$_2$ (0.250 g, 0.305 mmol) was placed in a round-bottomed flask, to which $CH_2Cl_2$ (70 mL) and reagent grade acetone (55 mL) were added. After saturating with $N_2$, 0.415 mL (0.610 mmol) of a $AgBF_4$ solution in acetone was added. The mixture was stirred in the dark for 1 h, and then AgCl was filtered off. The resulting solution was concentrated to small volume under reduced pressure, and the addition of $Et_2O$ resulted in the precipitation of a white solid that was filtered, washed with $Et_2O$, and dried in vacuo (yield 65%).

Anal. Calcd (found) for $C_{68}H_{76}N_2O_6P_4Pt_2B_2F_8$: C, 47.90 (47.77); H, 4.49 (4.40).

**[(diop)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (4b).** This complex was prepared similarly to **4f** starting from (diop)PtCl$_2$ (0.250 g, 0.327 mmol) and the $AgBF_4$ solution (0.440 mL, 0.654 mmol) (yield 78%).

Anal. Calcd (found) for $C_{62}H_{66}O_6P_4Pt_2B_2F_8$: C, 46.69 (46.57); H, 4.17 (4.12).

**[(norphos)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (4d).** This complex was prepared similarly to **4f** starting from (norphos)PtCl$_2$ (0.250 g, 0.343 mmol) and the $AgBF_4$ solution (0.466 mL, 0.686 mmol) (yield 85%).

Anal. Calcd (found) for $C_{62}H_{58}O_2P_4Pt_2B_2F_8$: C, 48.90 (48.77); H, 3.84 (3.95).

**[(Me-duphos)Pt($\mu$-OH)]$_2$(BF$_4$)$_2$ (4e).** This complex was prepared similarly to **4f** starting from (Me-duphos)PtCl$_2$ (0.250 g, 0.350 mmol) and the $AgBF_4$ solution (0.476 mL, 0.700 mmol). The complex is moderately hygroscopic (yield 65%).

Anal. Calcd (found) for $C_{36}H_{58}O_2P_4Pt_2B_2F_8$: C, 35.72 (35.62); H, 4.83 (4.75).

**Synthesis of Lactones.** Lactones used as standards for gas chromatography 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 a few hours the solid MCBA was filtered off, and the solution containing the lactone was used for qualitative identification in the GC analysis.

**Catalytic Reactions.** These were carried out in a 25 mL round-bottomed flask equipped with a stopcock for vacuum/$N_2$ operations and a sidearm 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. Stirring was performed by a Teflon-coated bar driven externally by a magnetic stirrer. The concentration of the commercial $H_2O_2$ solution was checked iodometrically prior to use.

The following general procedure was followed: The required amount of catalyst was placed in solid form in the reactor, which was evacuated and filled with $N_2$. Purified, $N_2$-saturated ketone was added under $N_2$ flow, followed by the required amount of solvent. After thermostating at the required temperature for a few minutes, the $H_2O_2$ solution in the appropriate amount was injected through the septum and time was started.

All reactions were monitored with GC by direct injection of samples taken periodically from the reaction mixtures with a microsyringe. Separation of the products was performed on a 25 m HP-5 capillary column using a flame ionization detector. Conversion percentage was determined through the use of

**Table 7. Conditions for the GC Analysis of the Chiral Compounds[a]**

| compound | column | oven $T$ (°C) | retention time[b] (min) | $R_f$ |
|---|---|---|---|---|
| **3b** | Lipodex E | *c* | 9.84 | 1.11 |
| **5** | Lipodex B | 160 | 14.08 | 1.06 |
| **6** | Lipodex B | 190 | 46.61 | 1.06 |
| **7a** | $\beta$-CD | 100 | 39.16 | 1.01 |
| **7b** | $\beta$-CD | 100 | 42.88 | 1.04 |

[a] Injection temp 260 °C, detector (FID) temp 250 °C, column head pressure 10 psi, total (He) flow 100 mL/min, split ratio 100. [b] Referred to the peak eluting first. [c] 80 °C (6 min), then 80−120 °C (2 °C/min).

(17) McDermott, J. X.; White, J. F.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 6521.

calibration curves between the individual substrates and 1,3-dimethoxybenzene as internal standard.

The extent of the asymmetric induction (ee %) was determined with GC with the use of chiral columns. The analytical conditions for the separation of the different enantiomers are summarized in Table 7.

**Optical Rotations.** The reaction mixtures were treated with $Et_2O$ to precipitate the catalyst. The resulting solution was concentrated in vacuo to eliminate $Et_2O$ and analyzed with a polarimeter to determine the sign of rotation.

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