Conclusion

Our results clearly show the ease with which two photon processes can be induced in the photochemistry of **1** and presumably in many other systems. Interestingly, while laser applications have increased dramatically in the last few years, only a few rather isolated studies of transient photochemistry have been carried out. Perhaps more worrying than our lack of knowledge in this area is our lack of awareness that processes of this type may play a crucial role in many laser applications.

The study reported herein includes one of the first determinations of the lifetime of an excited biradical in fluid solution and a rather dramatic example of the differences in products between one- and two-photon processes (compare **3** and **4** with **9**). It also provides considerable insight into the sorts of measurements that can be used to examine processes of this type.

Experimental Section

Infrared spectra were recorded on a Digilab FTS-11 infrared spectrometer. A Perkin-Elmer 8320 gas chromatograph equipped with a 12-m BP1 on vitreous silica capillary column was used for all GC analysis. GC–MS spectra were recorded on a Hewlett-Packard 5995 instrument equipped with a 10-m Ultra 1 (OV-101) capillary column. Both ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer. A Perkin-Elmer Series 10 liquid chromatograph equipped with a Lobar Silica Gel 60 prepacked column (Merck, Size A, 1 cm × 24 cm) was used for all liquid chromatographic separations.

2,2,6,6-Tetraphenylcyclohexanone[10] was a generous gift from Professor D. H. R Barton. 2,5-Dimethyl-2,4-hexadiene (Aldrich) was distilled before use. β-Carotene was recrystallized from diethyl ether/petroleum ether. Benzene and methanol (Aldrich, Gold Label) and di-*tert*-butyl nitroxide were used as received.

Laser Flash Photolysis. Samples of **1**, 0.001–0.003 M in the appropriate solvent, were contained in 7 × 7 mm^2 quartz cells and were deaerated by nitrogen purging. A Lumonics TE-860-2 excimer laser (Xe-HCl, 308 nm, ~5-ns pulses; ≤80 mJ/pulse) and a Molectron nitrogen laser (~8-ns pulses, 337 nm, ≤10 mJ/pulse) or a PRA LN 1000 nitrogen laser (0.6-ns pulses, ≤1.5 mJ/pulse) were used for excitation. Further details of the laser flash photolysis facility[26] and the modifications required for two laser experiments[5] have been described. An Optical Multichannel Analyzer with an E.G.&G. 1420 detector recently has been incorporated in the laser system.

Preparative Photolysis of 1. A degassed sample of **1** (24 mg in 25 mL of benzene) was irradiated in a two-laser experiment with the excimer laser pulse followed ca. 100 ns later by the Molectron nitrogen laser pulse and with both lasers operating at 2 Hz. The sample was stirred by bubbling nitrogen through the cell during the irradiation period. The progress of the reaction was followed by GC analysis of a small aliquot of the solution. A total of 9000 shots, delivered in units of 1000 with 10–20 min intervals between units, was required to obtain ca. 90% conversion. Preliminary experiments indicated that inadequate sample mixing and >90% conversion led to decreased yields of the biphotonic product.

The irradiated reaction mixture was concentrated to 0.5 mL and separated by liquid chromatography with CH_2Cl_2/hexane solvent mixtures. The biphotonic product had a retention time of 22 min and was isolated in >90% purity as determined by GC analysis of the isolated material (ca. 1 mg). The material was an oil, and several attempts to crystallize it were unsuccessful.

Structure **9** was assigned to the isolated material on the basis of the following spectral data and as discussed above. MS, *m/e* 375 ($M^+ + 1$), 32.8%; 374 (M^+), 100.0%; 297, 17.3%; 253, 23.1%; 181, 17.4%. IR (thin film deposited from $CHCl_3$) 3085, 1640, 1600, 910, 760, 740, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.26–7.23 (m, 14 H), 6.06 (ddd, $J_{A,C}$ = 10.3 Hz, $J_{B,C}$ = 16.5 Hz, $J_{C,D}$ = 10.8 Hz, 1 H), 5.74 (dd, $J_{C,D}$ = 10.8 Hz, $J_{D,E}$ = 10.6 Hz, 1 H), 5.02 (d, $J_{B,C}$ = 16.5 Hz, 1 H), 4.92 (d, $J_{A,C}$ = 10.3 Hz), 4.84 (dd, $J_{D,E}$ = 10.6 Hz, $J_{E,F}$ = 10.4 Hz, 1 H), 4.08 (d, $J_{E,F}$ = 10.4 Hz, 1 H), 2.66–2.50 (m, 3 H), 2.36–2.31 (m, 1 H), 1.70–1.55 (m, 2 H).[27] ^{13}C NMR ($CDCl_3$) δ 132.4, 130.1, 129.8, 129.3, 127.9, 127.3, 126.8, 125.9, 125.1, 123.6, 118.3, 116.8, 50.25, 39.7, 22.6, 18.1. Proton decoupling experiments for protons A–F were used to establish the coupling patterns of the olefinic protons. A ^{13}C DEPT experiment confirmed the presence of one $=CH_2$ (116.8), one C–H (50.2), and three CH_2 (18.1, 22.6, 39.7) carbon atoms.

A 500-MHz NMR spectrum of the photolysis mixture showed conclusively that **9** was present in the original mixture and was therefore not formed during the chromatographic separation. The NMR spectrum also showed the presence of additional olefinic signals which were not due to **9** or **4**; these are presumably due to the two minor products of the biphotonic reaction.

Acknowledgment. We are grateful to Professor D. H. R. Barton for a gift of **1**. Thanks are due to Dr. D. Meisel and Professors M. A. Fox and R. W. Fessenden for sharing their results prior to publication. Thanks are also due to S. E. Sugamori for technical assistance, to Dr. J. R. Brisson for recording the ^{1}H and ^{13}C NMR spectra, and to Dr. H. Casal for his help with the infrared spectra. The authors also acknowledge many valuable suggestions during the 1985 Gordon Conference on Organic Photochemistry.

Registry No. 1, 83576-30-1; **2**, 95935-53-8; **9**, 100858-14-8.

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(26) Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7747.

(27) Subscripts refer to the butadiene group:

$$H_AH_BC{=}CH_C{-}CH_D{=}CH_E{-}CH_F{<}$$

Nonlinear Effects in Asymmetric Synthesis. Examples in Asymmetric Oxidations and Aldolization Reactions

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Received August 1, 1985

Abstract: It has been shown in three experiments that there is a strong departure from the linear relationship usually assumed between the enantiomeric excess of a chiral auxiliary and the extent of the asymmetric synthesis. This gives useful information on the reaction mechanisms. Asymmetric oxidation of methyl *p*-tolyl sulfide or asymmetric epoxidation of geraniol in the presence of various chiral titanium complexes, as well as the proline-catalyzed Hajos–Parrish reaction, is investigated in detail.

Horeau and Guetté[1] discussed the importance of diastereomeric interactions of a mixture of enantiomers in the liquid phase. These interactions are responsible for some *unusual physical properties* of mixtures of enantiomers such as the nonequivalence of the enantiomeric excess and the optical purity[2] or the different NMR spectra for a racemic mixture or a pure enantiomer.[3–6] The

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[†] Université Paris VI.

[‡] Université Paris-Sud.

(1) Horeau, A.; Guetté, J. P. *Tetrahedron* **1974**, *30*, 1923–1931.

(2) Horeau, A. *Tetrahedron Lett.* **1969**, 3121–3124.

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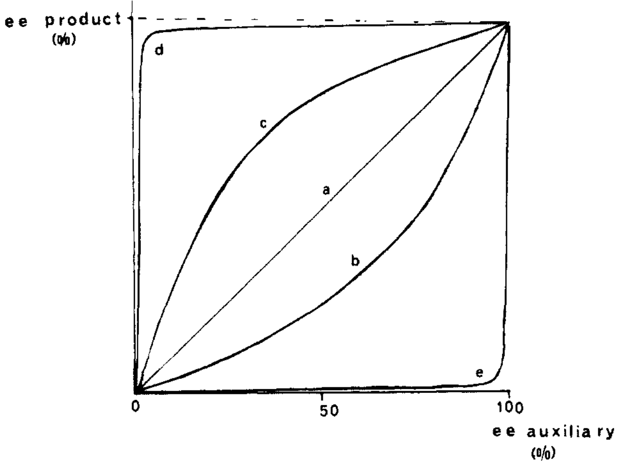
Scheme I. Some Correlations between the Enantiomeric Excess of the Product of an Asymmetric Synthesis and the Enantiomeric Excess of the Chiral Auxiliary



separation of enantiomers of a partially resolved compound by chromatographic methods in achiral conditions was also related to diastereomeric interactions.[7]

Wynberg and Feringa[8] in a pioneering work established the possibility of *different chemical behaviors* (rates and product distributions) of an enantiomerically pure compound and the corresponding racemic mixture in the absence of chiral reagents. Additional related examples were recently published.[9-11] We may now ask ourselves the following question: *what is the correlation between the enantiomeric excess (ee) of a compound and the value of one of its chemical properties?*

We wish to discuss the specific case where the "property" is the asymmetric induction produced by a chiral compound used as an auxiliary in an asymmetric synthesis.

Asymmetric Synthesis with a Partially Resolved Chiral Auxiliary

If the chiral auxiliary material has, for example, an enantiomeric excess of 50% ($ee_{auxiliary} = 50\%$), the usual procedure to evaluate the theoretical optical yield of the reaction (ee_{max}) with an optically pure reagent or catalyst would be to double the enantiomeric excess of the reaction product ($ee_{product}$). More generally, ee_{max} is calculated according to the formula (1). This equation gives a linear correlation between $ee_{product}$ and $ee_{auxiliary}$ (Scheme I, curve a).

$$ee_{max} = ee_{product}/ee_{auxiliary} \qquad (1)$$

This method should, however, be applied with caution. Let us assume that an asymmetric reaction is catalyzed by a chiral catalyst. If this catalyst is of the type (M)L*, the above calculation perfectly applies. In this formulation, L* stands for a monodentate chiral ligand or for a bidentate chiral ligand (for example, a chiral diphosphine) and [M] stands for the rest of the complex. The situation is more complicated for the common case of complexes of the type $(M)L^*_2$.[12] If L* is not enantiomerically pure, three complexes of structures $(M)L_RL_R$, $(M)L_SL_S$, and $(M)L_RL_S$ may be formed, as already pointed out,[8,16,17] where L_R and L_S stand for both configurations of L*. When the "meso"-type catalyst $(M)L_RL_S$ is more reactive than the two other catalysts, the optical yield found for the asymmetric synthesis will be lower than the one expected from the formula (1) (Scheme I, curve b). If the meso-type catalyst is less active than $(M)L_RL_R$ or $(M)L_SL_S$, then the optical yield will be higher (Scheme I, curve c) than the one calculated from the formula (1). We shall confine the discussion on these qualitative arguments; however, a quantitative treatment by taking a simplified kinetic scheme will highlight later the importance of the composition of different stereoisomeric catalysts (assumed to be formed kinetically or to be in fast interconversion).

An analogous situation arises in reactions where the chiral auxiliary material is part of a chiral reagent.[18] We wish to report a detailed investigation on the relationship between the enantiomeric excess of the chiral auxiliary and the enantiomeric excess of the product formed in three different asymmetric reactions.

We first selected the asymmetric oxidation of sulfide **1** into sulfoxide **2** (eq 2) by a reagent which we have been studying,[21,22] a modification of the Sharpless reagent[23] for the asymmetric epoxidation of allylic alcohols. Our reagent is prepared by adding

(eq. 2)

1 2

successively 2 equiv of (+)-diethyl tartrate (DET) and 1 equiv of water to a solution containing 1 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ in CH_2Cl_2 at room temperature.[21] The resulting complex is presumably a μ-oxotitanium dimer containing chelated tartrate ligands on each titanium. The oxidant, *tert*-butyl hydroperoxide, as well as the corresponding sulfide, is then added to this complex and the oxidation is performed at −20 °C.

A now classical asymmetric synthesis, the epoxidation of allylic alcohols by the Sharpless reagent[23] ($Ti(O\text{-}i\text{-}Pr)_4$/(+)-DET = 1:1),

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[3] Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871–1872.

[4] (a) Harger, M. J. P. *Chem. Commun.* **1976**, 555–556. (b) Harger, M. J. P. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1882–1887.

[5] Kabachnik, M. I.; Mastrywkova, T. A.; Fedin, E. I.; Vaisberg, M. S.; Morozov, L. I.; Petrovsky, P. V.; Shipov, A. E. *Tetrahedron* **1976**, *32*, 1719–1728.

[6] Thong, C. M.; Marraud, M.; Neel, J. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1975**, *281*, 691–693.

[7] (a) Cundy, K. C.; Crooks, P. A. *J. Chromatogr.* **1983**, *281*, 17–23. (b) Charles, R.; Gil-Av, E. *J. Chromatogr.* **1984**, *298*, 516–520.

[8] Wynberg, H.; Feringa, B. *Tetrahedron*, **1976**, *32*, 2831–2834.

[9] Rautenstrauch, V. *Helv. Chim. Acta* **1982**, *65*, 402–406.

[10] Okada, M.; Sumitomo, H.; Atsumi, M. *J. Am. Chem. Soc.* **1984**, *106*, 2101–2104.

[11] Grassi, M.; Di Silvestro, G.; Farina, M. *Tetrahedron* **1985**, *41*, 177–181.

[12] Complexes of the type $(M)L^*_2$ are frequently used as active species in asymmetric catalysis, such as in modified Wilkinson hydrogenation catalysts $RhCl(PR^*_3)_2$, where PR_3^* is a chiral monophosphine,[13] or in cyclopropanation catalysts such as Co(camphoquinone oximate)$_2$.[14] When the chiral ligand is obtained by a resolution step, partially resolved samples are often used. Thus, $PhP(Me)CH_2Ph$ (16% ee) is the chiral ligand L* in the rhodium complex $RhClL_2^*$, to catalyze the asymmetric hydrogenation of a silyl enol ether.[15] The optical yield, ee_{max}, of the reaction was estimated by using eq 1 for the "correction" of the enantiomeric excess of the product taking into account the phosphine optical purity.

[13] Knowles, W. J. *Acc. Chem. Res.* **1983**, *16*, 106–112.

[14] Nakamura, A.; Konishi, A.; Tatsuno, Y.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3443–3448.

[15] Tanaka, M.; Watanabe, Y.; Mitsudo, T.-A.; Yasunori, Y.; Takegami, Y. *Chem. Lett.* **1974**, 137–140.

[16] Izumi, Y.; Tai, A. In "Stereodifferentiating Reactions"; Academic Press: New York, 1977; p 244.

[17] Pasquier, M. L.; Marty, W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 315–316.

[18] In some cases, three different reagents may be formed as well, in principle of type RR, SS, and RS. Equation 1 will not necessarily give the extent of the asymmetric synthesis for reasons similar to those of the previous example. This phenomenon can occur especially if the reagent is in excess, allowing a selection between the meso-type reagent and its diastereomers or if there is a fast interconversion between the stereoisomeric reagents. An example is the modification of $LiAlH_4$ by introduction of chiral alcohols ROH*, leading to species of the type $LiAlH_{4-n}(OR^*)_n$ (n = 2 or 3).[19] The reduction by $Al(R^*)_3$ is also relevant to the present discussion;[20] in this case, the authors found a good linear correlation between $ee_{product}$ and $ee_{auxiliary}$.

[19] Grandbois, E. R.; Howard, S. I.: Morrison, D. J. *in* "Stereodifferentiating Addition Reactions"; Academic Press: New York, 1983; Vol. 2, Part A, pp 71–90.

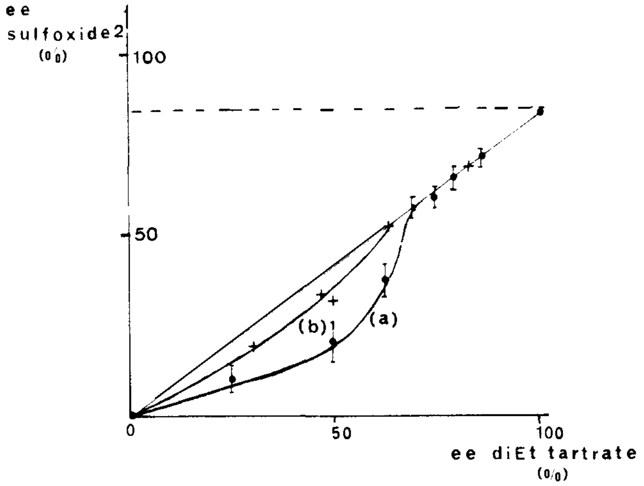
[20] Giacomelli, G.; Manicagli, R.; Lardicci, L. *J. Org. chem.* **1973**, *13*, 2370–2376.

[21] Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193.

[22] Duñach, E.; Kagan, H. B. *Nouv. J. Chim.* **1985**, *9*, 1–3.

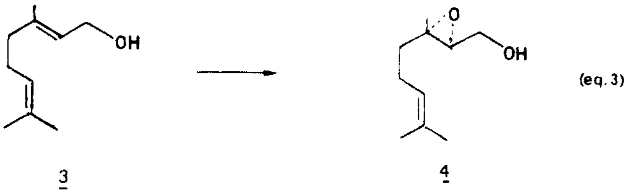
[23] Katsuki, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

Scheme II. Nonlinear Effect in the Asymmetric Oxidation of Sulfide **1** (Equation 2) and Enantiomeric Excess of (*R*)-**2** as a Function of the Enantiomeric Excess of (+)-DET[a]

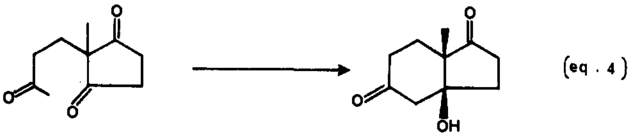


[a] (a) Stoichiometric conditions: $Ti(O\text{-}i\text{-}Pr)_4/DET/H_2O/t\text{-}BuOOH/\mathbf{1}$, 1:2:1:0.5 or 1:1:1:1.1. (b) Catalytic conditions: $Ti(O\text{-}i\text{-}Pr)_4/DET/H_2O/t\text{-}BuOOH/\mathbf{1}$, 0.5:1:0.5:1:1.

was also investigated in the specific case of (*E*)-geraniol (**3**) (eq 3).



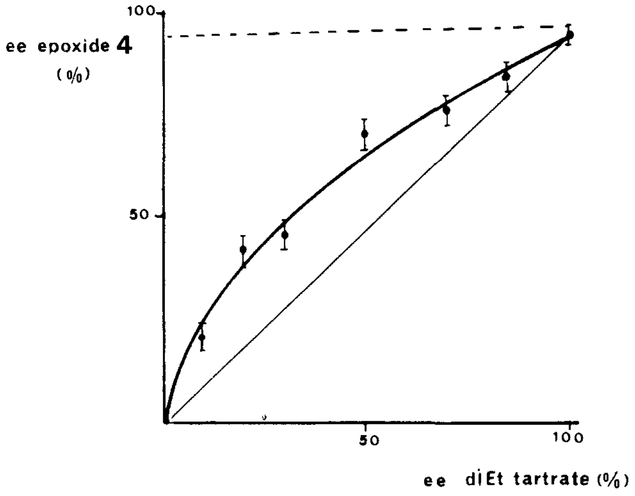
Finally, we studied a catalytic system dealing with an asymmetric Robinson annulation. The Hajos–Parrish reaction is a useful asymmetric synthesis which allows, for example, to transform the triketone **5** into *cis*-ketol **6** (ee 92%) in DMF under the influence of a catalytic amount of pure (*S*)-proline[24,25] (eq 4). Two of us are currently investigating extensively the mechanism of this reaction.[26,27]



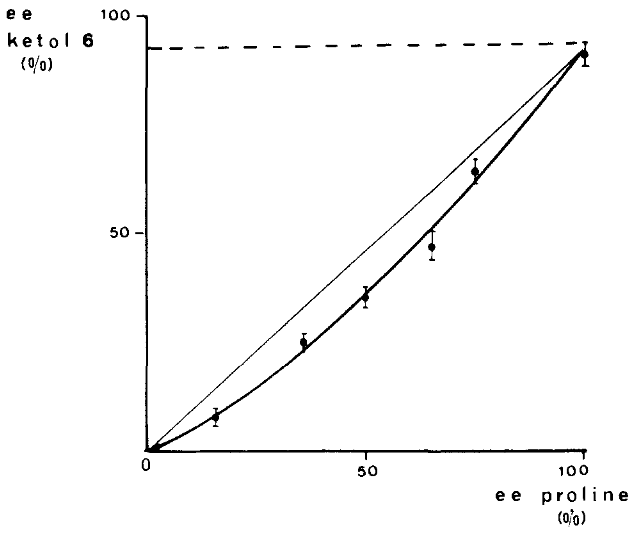
Results

A. The asymmetric oxidation of sulfide **1** (eq 2) was studied in the presence of the complex $Ti(O\text{-}i\text{-}Pr)_4/DET/H_2O$ (1:2:1), by using (+)-diethyl tartrate of different enantiomeric purities. In order to favor the formation of all the possible diastereomeric complexes, we first used stoichiometric conditions (1 equiv of complex with respect to sulfide) but carried out the reaction by addition of only 0.5 mol equiv of *t*-BuOOH. Under these circumstances, the yield of sulfoxide is quantitative with respect to the oxidant in all the experiments. Sulfide **1** and sulfoxide **2** are easily separated and recovered by flash chromatography, and the enantiomeric excess of **2** is measured. The results obtained are plotted in Scheme II. A strong departure from linearity is clearly observed (curve a). Unexpectedly, the linearity is recovered in the oxidations by using diethyl tartrate of optical purity higher than 70%. Experiments using 1 mol equiv of *t*-BuOOH were performed, in order to operate in the standard conditions for this asymmetric oxidation. The same strong departure from linearity was again observed, and curve a (Scheme II) could be reproduced.

Scheme III. Nonlinear Effect in the Epoxidation of Geraniol **3** (Equation 3) and Enantiomeric Excess of (−)-**4** as a Function of the ee of (+)-DET with $Ti(O\text{-}i\text{-}Pr)_4/DET/t\text{-}BuOOH/\mathbf{3}$, 1:1:2:1



Scheme IV. Nonlinear Effect in the Hajos–Parrish Reaction (Equation 4) and Enantiomeric Excess of Ketol **6** as a Function of the ee of (*S*)-Proline under Catalytic Conditions (See Experimental Section)



Recently, we found that the reaction **1** → (*R*)-**2** can be catalytic with a turnover of 2. We repeated the oxidation procedure by using diethyl tartrate of different enantiomeric purities, in the following conditions: (Ti complex)/(sulfide)/(*t*-BuOOH) = 0.5:1:1. The curve b of Scheme II was obtained.

B. The epoxidation of geraniol **3** by 1 equiv of the Sharpless reagent[23] $Ti(O\text{-}i\text{-}Pr)_4/(+)\text{-}DET/t\text{-}BuOOH$ (1:1:2) (eq 3) was consequently investigated under the described[23] conditions but with diethyl tartrate of various optical purities. Epoxygeraniol (**4**) was recovered with an excellent yield and with enantiomeric excesses which are not at all linearly correlated with the enantiomeric purity of the diethyl tartrate (Scheme III).

C. A kinetic study[27] has recently shown that the enantioselective Robinson annulation (Hajos–Parrish reaction)[24–26] catalyzed by (*S*)-proline (eq 4) involves two amino acid molecules in the transition state of the enantiodifferentiating step.

Here again, experiments show that there is a nonlinear relationship between the (*S*)-proline enantiomeric purity and the enantioselectivity of the annulation product **6** (Scheme IV): in all cases, the observed enantiomeric excess is smaller than the values calculated by assuming a linear dependency between the

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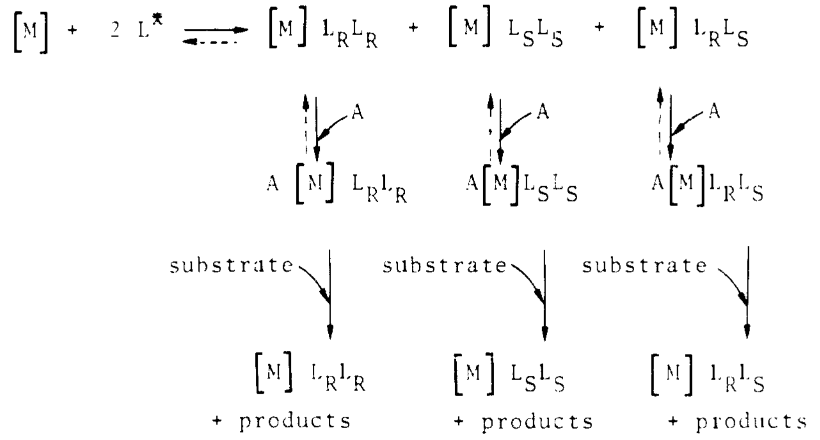
[24] Hajos, Z. G.; Parrish, D. *J. Org. Chem.* **1974**, *39*, 1615–1621.

[25] Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412–417.

[26] Agami, C.; Sevestre, H. *J. Chem. Soc., Chem. Commun.* **1984**, 1385–1386.

[27] Agami, C.; Levisalles, J.; Puchot, C. *J. Chem. Soc., Chem. Commun.* **1985**, 441–442.

Scheme V



L_R, L_S = chiral ligand or chiral auxiliary ; A = reactant (H_2, ROOH..)

M = metallic complex

proline and ketol enantiomeric excesses.

Discussion

The above examples clearly demonstrate that there is not always the possibility to calculate the optical yield of a reaction which uses a partially resolved ligand. The pronounced convexity of the curves of Schemes II and III with respect to a linear correlation affords a useful information: it completely excludes a complex involving only one tartrate ligand at the reaction center of the active oxidant species. The small but definite convexity of the curve in Scheme IV gives also a good evidence that more than one proline molecule mediates the Hajos–Parrish reaction.

Scheme V is a general presentation of an asymmetric synthesis with a chiral organometallic compound as the reagent or catalyst. As a simplification, Scheme V uses only two chiral ligands in the reagent or catalyst. The relative concentrations and the relative reactivities of the three possible complexes $A(M)L_RL_R$, $A(M)L_SL_S$, and $A(M)L_RL_S$ will regulate the overall stereoselectivity of the reaction. The first two enantiomeric complexes have the same reactivity and give products of the same enantiomeric excess but of opposite configuration. The meso-type complex $A(M)L_RL_S$ is a diastereoisomer of the first two ones. The reaction products obtained from this last complex will necessarily be of racemic composition (in some very specific situations, this may not be the case, for example, when the metal is itself an asymmetric center whose configuration depends on the sequence of the ligand fixation).

The stereoselectivity of the reaction will be first discussed for a *stoichiometric asymmetric* synthesis in which all the steps of Scheme V are irreversible. If the reagent $A(M)L^*_2$ is in excess with respect to the prochiral substrate, it may happen that the enantiomeric excess of the product does not linearly correlate with the enantiomeric excess of L*. This is because the meso-type complex reacts differently from the two chiral complexes or because all the complexes have the same reactivity but the ligand distribution is not the statistical one.

If the chiral reagent is in a stoichiometric amount with respect to the substrate and is fully consumed, the relative reactivity and/or the ligand distribution rates between the three complexes become unimportant. This results in a strict proportionality between the enantiomeric excess of the ligand L* vs. the enantiomeric excess of the product.

Asymmetric catalysis is more difficult to discuss without calculations based on a kinetic scheme. As an oversimplification (Scheme V), let us take a steady-state concentration of complexes $A(M)L_RL_R$, $A(M)L_SL_S$, and $A(M)L_RL_S$ (at the relative concentrations x, y, and z), with a first-order dependence on products R and S with respect to these complexes and with zero order with respect to the substrate in the various competing pathways. Calculations show that the enantiomeric purity of the product obtained and the enantiomeric excess of L* are correlated by

$$ee_{product} = ee_{max}ee_{auxiliary}f \tag{5}$$

where ee_{max} stands for the enantiomeric excess of the product when an enantiomerically pure ligand is used (eq 1) and f is a correction factor such as

$$f = (1 + \beta)/(1 + g\beta)$$

β is the relative amount $[z/(x + y)]$ of the meso- to the chiral-type catalysts and g is the relative reactivity of the meso-type complex with respect to that of the chiral catalyst (reactivities being expressed by the apparent rate constants which include absolute rate and equilibrium constants). The f factor depends on the enantiomeric excess of the ligand and is not constant. The classical linear correlation occurs only when $f = 1$, giving back (1). The value $f = 1$ occurs when $\beta = 0$ or $g = 1$. The value $\beta = 0$ means the absence of a meso-type complex. If $g = 1$, the reactivity of the meso-type complex is equal to the reactivity of the two chiral complexes.

Apart from these special two cases, eq 5 shows that there should always be a departure from the linear correlation. An interesting limiting situation in a catalytic reaction occurs when the meso-type complex is preferentially and irreversibly formed from a ligand L* having an enantiomeric excess, $ee_{auxiliary}$. In this case, one of the two chiral complexes $(M)L_RL_R$ or $(M)L_SL_S$ will not be obtained. In addition, if there is no catalytic activity for the meso-type complex ($g = 0$), f will be equal to $1/ee_{auxiliary}$ and eq 5 indicates that $ee_{product} = ee_{max}$ whatever the enantiomeric excess of the ligand. This paradoxical situation arises from the disappearance and/or the nonreactivity of the racemic part of the chiral ligand from the active catalytic cycle, giving a concomitant loss of catalytic activity but leading to an optical yield corresponding to the one obtained with the optically pure ligand (curve d, Scheme I). Of course, a more realistic situation is the intermediate one, represented by curve c of Scheme I, which reflects the advantage of working with the lowest concentration and (or) the lowest reactivity of the meso-type catalyst ($f > 1$).

When the meso-type complex is much more reactive than the chiral complexes ($g \to \infty$), f will vanish ($f \to 0$) and the enantiomeric purity of the product remains equal to zero whatever is the enantiomeric excess of the chiral ligand or the β value (curve e, Scheme I). Here also, a more realistic situation is the curve b in Scheme I, which shows the higher reactivity and (or) the larger concentration of the meso-type complex.

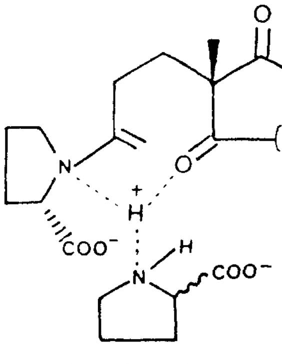
The same conclusions are retained if there is a fast ligand exchange between all the complexes. In this case, the complex of higher reactivity will determine the type of curve to be obtained.

Coming back to our experiment on the asymmetric oxidation of sulfide **1** (eq 2), we can make the following remarks. For the stoichiometric reactions where $[Ti/DET/H_2O] = [\mathbf{1}] = [t\text{-}BuOOH]$, the experimental curve a of Scheme II excludes the preferential formation of chiral-type complexes, unless there is fast ligand exchange. This is supported by the fact that the same curve is obtained when only half an equivalent of *t*-BuOOH was used for the oxidation. The results exclude a selection process between stable diastereomeric complexes but show that the active site for oxidation has at least two tartrate ligands in its vicinity.

The location of curve a (below the straight diagonal line of Scheme II) indicates a higher reactivity ($g > 1$) of the meso-type complex (whose concentration can be restored in a stoichiometric reaction by virtue of a fast tartrate exchange). A similar experimental curve was found in the catalytic reaction (curve b, Scheme II). The results are again in agreement with a kinetic scheme in which the meso-type catalyst reacts faster ($g > 1$) than the diastereomeric chiral catalysts $(M)L_RL_R$ or $(M)L_SL_S$. An unexpected finding remains: after 70% ee for the (+)-diethyl tartrate, the linear correlation is recovered. A kinetic model is under investigation for the analysis of this behavior.

The asymmetric epoxidation of geraniol (eq 3 and Scheme III) clearly shows that more than one tartrate unit plays an active role in the asymmetric induction. This is in agreement with the Sharpless observation that the reagent $Ti(O\text{-}i\text{-}Pr)_4$/(+)-DET (1:1) is a dimeric species in solution.[30] The strong departure from linearity is indicative of some proximity or cooperation of the two tartrate units during the asymmetric epoxidation. Since the optical yield of the reaction product is much higher than what is expected from a linear relationship ($f < 1$ in eq 5), it is reasonable to assume a better chiral efficiency of the homochiral dimeric reagent.

The Hajos–Parrish reaction will not be presently discussed in detail. This example is thoroughly different from the above ones. In this catalytic reaction the enantioselectivity is directed by the first ligand molecule (proline). It is believed[27] that enantiodifferentiation occurs on a three-center hydrogen-bonded structure **7** involving (i) the most reactive *pro-R* ring carbonyl, (ii) an enamine moiety resulting from the reaction between (*S*)-proline and the carbonyl chain (nucleophilic base catalysis), and (iii) a second proline molecule (general base catalysis). The observed deviation from linearity arises from diastereomeric interactions between the enamine intermediate and the second proline molecule. Therefore, the kinetic process of this catalytic reaction (substrate/catalyst molar ratio 33:1) is complicated to such an extent that it would not be wise to draw any definite conclusion as regards the homo or heterochiral nature of the favored diastereomeric transition state. Nevertheless, it still remains that this nonlinear relationship is an additional support to the multiple catalytic effect recently proposed[27] for the amino acid catalyst.



7

Conclusion

We discovered and studied the first cases of nonlinear correlation between the enantiomeric excess of a chiral auxiliary and the optical yield of an asymmetric synthesis (in a stoichiometric or a catalytic mode). Great caution is needed in interpreting the results of an asymmetric synthesis not using enantiomerically pure reagents or catalysts. If it is not possible to get the optically pure ligands, it becomes then necessary to use samples of chiral ligands with different enantiomeric excesses, in order to check the absence of any nonlinear relationship as those described above.

The nonlinear relationship in asymmetric synthesis provides an additional and simple tool to get some insights into the reaction mechanisms. As previously developed, this allows us to discuss the structure of active species involved in the process (ligand exchange, aggregation, etc.) as well as the molecularity of the reaction with respect to the chiral reagent or catalyst.

Experimental Section

Apparatus. ^1H NMR spectra were recorded on Perkin-Elmer Model R-32 90-MHz, Bruker 400-MHz, and Bruker 250-MHz spectrometers. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Chemicals. CH_2Cl_2 was purified by treatment with basic alumina distillation and stored over molecular sieves under nitrogen. *t*-BuOOH solutions in toluene were prepared according to ref 23. Silica gel (Merck, Kieselgel 60, 230–400 mesh) was used for flash column chromatography. (+)- and (−)-diethyl tartrates were purchased from Janssen Co. The partially resolved diethyl tartrate samples were obtained by mixing weighted amounts of (+)- and (−)-diethyl tartrates. Methyl *p*-tolyl sulfide was prepared according to ref 29. $Ti(O\text{-}i\text{-}Pr)_4$ (Fluka) was distilled before use. $Eu(hfc)_3$ (Fluka) was used as such and stored under anhydrous conditions. (*R*)- and (*S*)-proline were purchased from Fluka.

Asymmetric Oxidation of Methyl *p*-Tolyl Sulfide. Stoichiometric oxidations were performed according to ref 21 on a 2.5 or 5 mmol scale. Sulfoxide (*R*)-**2** was isolated by flash column chromatography and its specific rotation measured in ethanol. Enantiomeric excess was calculated with respect to the following maximum specific rotation for a sample of enantiomerically pure **2**: $[\alpha]^{25}_D$ +151° (*c* 1.2, ethanol) (NMR measurement by a chiral shift reagent[30]). Proportionality between specific rotations and ee's was verified. Catalytic reactions were performed in the conditions of ref 23 by doubling the amount of sulfide.

Asymmetric Epoxidation of Geraniol 3. The epoxidation of geraniol **3** was carried out following the Katsuki–Sharpless detailed procedure.[23] The ee values were calculated from (i) the specific rotation of (2*S*,3*S*)-epoxygeraniol (**4**) (95% ee) ($[\alpha]_D$ −4.72° (*c* 1.5, $CHCl_3$) [lit.[23] −6.36°]), the difference between this value and our specific rotation value is unexplained; (ii) the specific rotation of the corresponding epoxyacetate ($[\alpha]_D$ −27.54° (*c* 1.1, $CHCl_3$)); and (iii) the ^1H NMR analysis ($CDCl_3$ solution) of the epoxyacetate in the presence of $Eu(hfc)_3$.

Asymmetric Aldolization Catalyzed by Proline. 2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (**5**) (250 mg) and (*S*)-proline (4.7 mg) were heated (50 °C) in dimethylformamide (1.4 mL), under an argon atmosphere, for 6.5 h. The mixture was then poured into water and extracted with methylene chloride; after being washed by water and dried over $MgSO_4$, the solvent was removed under reduced pressure. Silica gel column chromatography (petroleum ether/ether, 30/70) afforded (+)-(3a*S*,7a*S*)-3a,4,7,7a-tetrahydro-3a-hydroxy-7a-methyl-1,5(6*H*)-indanedione (**6**) (200 mg) in 80% yield. As already reported, no trace of diastereomer could be detected.[24]

The partially resolved (*S*)-proline samples were obtained by mixing enantiomerically pure (*S*)- and (*R*)-proline. The enantiomeric excess values of **6** were determined from the specific rotation of enantiomerically pure ketol **6** prepared following the Hajos–Parrish procedure[24] in $CHCl_3$ and the EtOH solutions: $[\alpha]^{20}_D$ +59.4° (*c* 0.6, $CHCl_3$) and + 50.1° (*c* 0.6, EtOH) [lit.[26] +60.4°, $CHCl_3$]. Proportionality between specific rotations and enantiomeric excesses was verified by using samples obtained from mixtures of racemic and enantiomerically pure ketols.

Acknowledgment. We are grateful to CNRS for financial support.

Registry No. 1, 4498-99-1; (*R*)-**2**, 1519-39-7; **3**, 106-24-1; **4**, 82188-73-6; **5**, 25112-78-1; **6**, 33879-04-8; (*S*)-proline, 147-85-3.

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(28) Sharpless, K. B.; Woodard, S. S.; Finn, M. C. *Pure Appl. Chem.* **1983**, *55*, 1823.

(29) Cooke, R. S.; Hammond, G. S. *J. Am. Chem. Soc.* **1970**, *92*, 2739–2745.

(30) Deshmukh, M.; Duñach, E.; Jugé, S.; Kagan, H. B. *Tetrahedron Lett.* **1984**, 3467; **1985**, 402.