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A Pioneering Career in Catalysis: Henri B. Kagan

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ABSTRACT: In this invited paper, we highlight the enormous scholarly scope of our mentor and colleague, Professor Henri B. Kagan, and the impact that his research has had on numerous fields of chemistry. It extends from the development of asymmetric oxidation, asymmetric reduction, unique features in lanthanide chemistry, issues of nonlinear effects, and the question of the origin of chirality on earth.



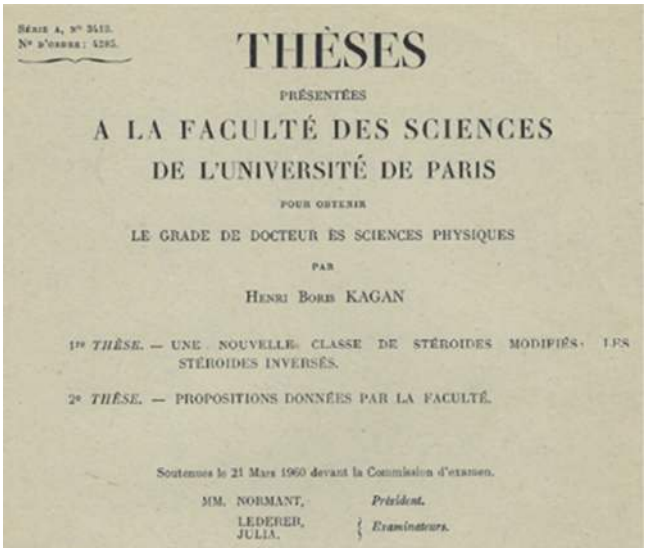
KEYWORDS: *asymmetric hydrogenation, asymmetric oxidation, nonlinear effects in asymmetric catalysis, origin of chirality, samarium iodide*

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1. EARLY CONTRIBUTIONS

The passion of Henri Kagan toward chirality makes him a true heir of Louis Pasteur, one of the fathers of stereochemistry who first isolated the enantiomers of tartaric acid in the early 19th century. To understand this attraction for chirality more thoroughly, the influence of his early mentors, Jean Jacques and Alain Horeau, was pivotal toward this field. Henri Kagan was first hired by Jean Jacques at the Collège de France to work in the field of steroids (Figure 1). During his Ph.D., he first came up with the idea of preparing the so-called inversed steroids (Figure 2).

The different biological activities of enantiomers were well-known at that time, and the idea of Henri Kagan was that inversed steroids might present antihormone activities. Thus, during his Ph.D., which he presented in March 1960, he devised several syntheses to prepare such compounds. For instance, the first example was a model of an inversed cortisone, prepared in about 12 steps from dehydroepiandrosterone.[1] Despite the lack of biological activities, this first entry in the field of chirality was the foundation of his love for stereochemistry. This was further consolidated by his interactions with Alain Horeau (one of the pioneers in the field of resolution and in the determination of absolute configurations by chemical methods), who hired Henri Kagan in 1962 as a vice-director of the Laboratoire de Chimie Organique des Hormones, with the offer to start his own research projects. His work with Alain Horeau on organometallic reagents (e.g., Reformatsky reagents) and partial resolution led Henri Kagan to start to develop novel ideas for the construction of stereocenters using chiral reagents and/or


THÈSES

PRÉSENTÉES

A LA FACULTÉ DES SCIENCES

DE L'UNIVERSITÉ DE PARIS

POUR OBTENIR

LE GRADE DE DOCTEUR ÈS SCIENCES PHYSIQUES

PAR

HENRI BORIS KAGAN

1re THÈSE. — UNE NOUVELLE CLASSE DE STÉROIDES MODIFIÉS: LES STÉROIDES INVERSÉS.

2e THÈSE. — PROPOSITIONS DONNÉES PAR LA FACULTÉ.

Soutenues le 21 Mars 1960 devant la Commission d'examen.

MM. NORMANT, *Président.*

LEDERER, JULIA, *Examinateurs.*

Figure 1. Title page of Henri Kagan's Ph.D. thesis.

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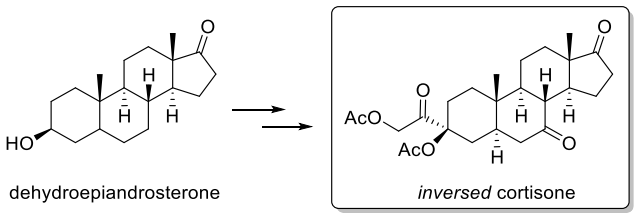


Figure 2. Inversed steroids.

chiral substrates. Some representative examples of his early achievements are presented in Figure 3:

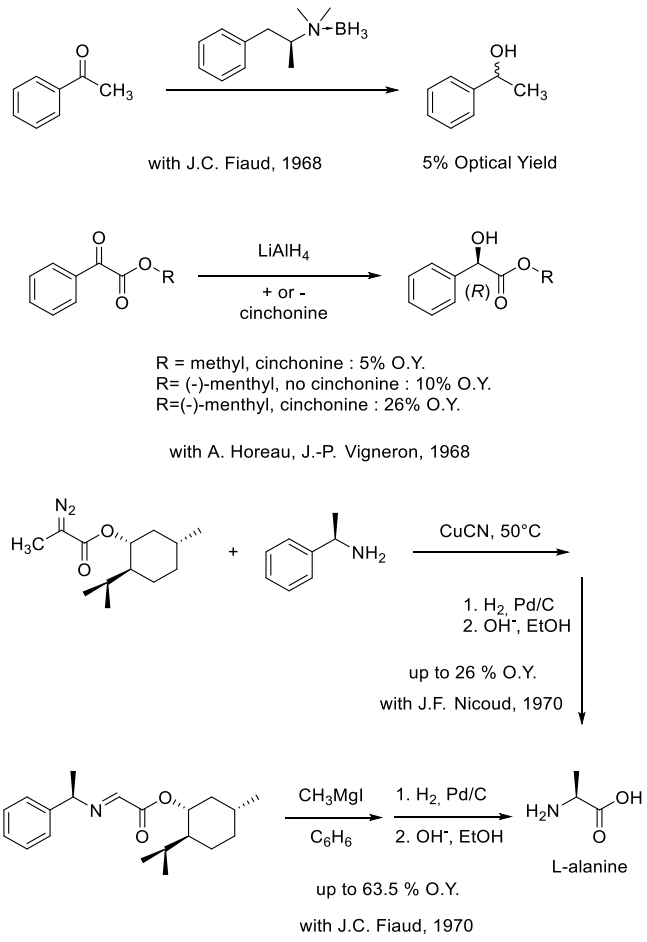


Figure 3. Novel ideas for the construction of stereocenters using chiral reagents or chiral substrates.

A first attempt was reported in 1968, with one of his Ph.D. students, as they attempted to reduce acetophenone with chiral amines/borane adducts.[2] Although the optical yields were at this time very modest, this could be regarded as an early attempt at reagent activation by a chiral base. The diastereoselective reduction of glyoxylate esters was also studied with a lithium aluminum hydride reagent modified by cinchonine, with a modest optical yield of 5%.[3] However, the positive effect of combining a chiral menthyl ester and the chirally modified reducing agent led to an improvement to 26%, while the unmodified hydride reagent gave only a 10% optical yield on the chiral ester, and this was later recognized as the Match-Mismatch effect in asymmetric synthesis. This idea was later applied to the preparation of enantiomerically enriched amino acids, using either substrates bearing two chiral fragments (addition of Grignard reagents on activated imines[4]) or the combination of two chiral substrates (carbene insertion onto an N−H bond[5]). In each case, the influence of the Match-Mismatch effect was confirmed.

Henri Kagan is now widely recognized as being the pioneer in many fields related to asymmetric catalysis and lanthanide chemistry, but some earlier works dealing with various aspects of photochemistry could also be considered as equally important, although less recognized.

Indeed, in the early 1970s, as was the case for many scientists, Henri Kagan was searching for new theories on the appearance of chirality on earth (homochirality), and his work on the determination of absolute configurations of nonracemic molecules led him to investigate the influence of circularly polarized light (CPL) on the course of a stereoselective reaction. The formation of helicenes was chosen as a model, and Kagan and co-workers studied the photocyclization of stilbenes into [6]helicene by CPL (Figure 4). The measurement of the optical

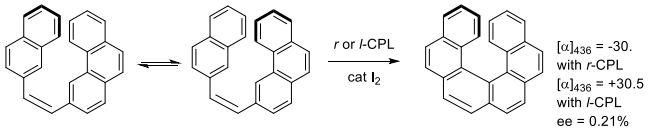


Figure 4. Stereoinduction by circularly polarized light.

rotation of the products was in full agreement with an asymmetric induction by the right- or left-CPL, with enantioselectivities of around 0.21%. Even if this enantioselectivity appears very modest (it was shown later that enantioselectivities are ultimately limited by the Kuhn anisotropic factors g), this result, along with the work of Calvin,[6] paved the way for a fascinating area of research which is still very active now to explain the phenomenon of chirality on earth.[7] In a later publication, Kagan and co-workers investigated a complementary pathway for generating chirality by CPL photodegradation of racemic compounds. Although such reactions required almost full conversions (>99%), of the starting material, significant enantiomeric excesses (up to 36%) were obtained for the photodecomposition of racemic camphor into α-campholenic aldehyde, via a Norrish Type I cleavage mechanism.[8]

The group continued some research in the field of photochemistry and published in 1973 one of the very first examples of an enantioselective reaction enabled by Triplet Energy Transfer via a chiral photosensitizer. Indeed, the photoderacemization of a racemic sulfoxide by a chiral naphthylamide led to a photoequilibrium of around 4% ee.[9] Similarly, Kagan et al. investigated photochemical transformations, such as the photoequilibration of sulfoxides, in chlolesteric crystal media, albeit with low to negligible ees.[10] Finally, it should be noted that his visionary thinking led, in 1978 (around the same time as that of leading scientists such as J.-M. Lehn and J. P. Sauvage), to the description of one of the first examples of hydrogen photoproduction, using $Ru(bipy)_3^{2+}$ as a photocatalyst.[11]

Because of his long-standing interest in the field of asymmetric hydrogenation, Henri Kagan was also regularly involved in the design of chiral ligands for such applications (Figure 5). This was the opportunity to become involved in the field of the conception of ferrocenyl derivatives with planar chirality, and

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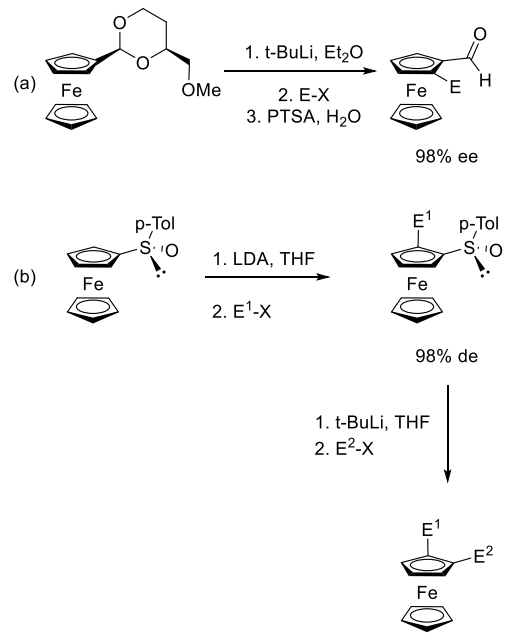


Figure 5. Ferrocenyl derivatives with planar chirality.

he designed two efficient methods based on ortho lithiation strategies.

The first method (a), starts from a chiral actetal, easily prepared from ferrocene carboxaldehyde and a chiral triol auxiliary.[12] Diasteroselective ortho lithiation was carried out with *tert*-butyllithium in diethyl ether at −78 °C, followed by electrophilic capture of the lithio-intermediate. After removal of the chiral auxiliary by hydrolysis of the acetals, the planar chiral ferrocenyl aldehydes were obtained in high yields with 98% ees. A second method was even more efficient to introduce two different groups on two ortho positions of a ferrocene structure, starting with either enantiomer of ferrocenyl-*p*-tolyl sulfoxide, easily prepared in one step from ferrocene through the Andersen method. The ortho lithiation was here carried out with LDA in THF and delivered, after electrophilic capture, the ortho-substituted aldehydes with high des (98%).[13] The sulfoxide was then easily replaced by sulfur−lithium exchange with *tert*-butyllithium and electrophilic capture of the lithio intermediates.[14] Those methods were widely used by Kagan and other groups for the preparation of chiral metallocene derivatives with planar chirality, including chiral ligands.[15]

Early in his carrier, Henri Kagan investigated the use of reagents and catalysts supported or inserted into solid supports, as potentially convenient systems for reagent handling and recovery, but also to evaluate the influence of the support on the reaction outcome. Graphite was the support of choice in such studies, which included graphite bisulfate as a catalyst for Fischer esterification and aromatic nitration, antimony pentachloride-graphite for halogenation reactions, and xenon hexafluoride-graphite for fluorination reactions.[16] After the discovery of 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane (DIOP), Kagan, Setton and co-workers immobilized a DIOP analog on oxidized graphite and studied the performance of the corresponding rhodium catalyst in enantioselective dehydroamino acid- hydrogenation.[17]

2. CONTRIBUTIONS TO ASYMMETRIC HYDROGENATION AND HYDROSILYLATION

The homogeneous asymmetric hydrogenation of prochiral unsaturated compounds catalyzed by transition metal complexes is undoubtedly one of the most efficient and straightforward methods to access enantiomerically enriched molecules. The seminal work of Professor Kagan played a crucial role with outstanding discoveries in this arena that contributed to the explosive flurry of activities and paved the way for global research and the implementation of asymmetric hydrogenation methods. The pioneering developments of Knowles[18] and Horner[19] in 1968 demonstrated that a chiral version of soluble Wilkinson-type rhodium complexes[20] containing optically active tertiary phosphine ligands enabled enantioselective hydrogenations of unsaturated olefins, albeit with low enantioselectivities (<15% ee). In 1971, Morrison and co-workers reported the hydrogenation of atropic acids and (*E*)-*α*-methylcinnamic acid using a Rh(I)-diphenylneomenthylphosphine (NMDPP) catalyst system with up to 61% ee.[21] Only a few reports related to asymmetric hydrogenation using soluble rhodium complexes were reported when H. B. Kagan started to work in this area in 1971, looking for a rational approach to prepare a chiral catalyst and to demonstrate the usefulness of a chiral diphosphine Rh(I) complex. Professor Kagan postulated that the ligand conformation should possess maximum rigidity and that the ligands must stay bound to the metal to avoid epimerization equilibria to reach a high level of stereoselectivity. Phosphines such as R*-$P(C_6H_5)_2$, where R* is chiral, were chosen to increase the steric control introduced by the R* group with the idea of decreasing the flexibility around the R*-P bond. In this context, ligands with a 2-fold axis of symmetry were prepared from inexpensive, readily available tartaric acid enantiomers after protection of the diol derivatives. This major contribution anticipated the success of bidentate diphosphines, which involved chelation of the ligand as a prerequisite to achieve a high level of enantioselectivities.

Because ((2*R*,3*R*)-2,3-dimethoxybutane-1,4-diyl)bis-(diphenylphosphine) was not an efficient asymmetric catalyst, the idea was to reduce the flexibility of the seven-membered chelate ring with the rhodium by introducing a dioxolane ring. From this was created (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenyl-phosphinobutane [(−)-DIOP], which was prepared as a crystalline diphosphine from (+)-tartaric acid.[22] (−)-DIOP was easy to synthesize, purify and store, and thus represented the first chiral bidentate phosphine ligand—a major breakthrough in asymmetric catalysis that demonstrated Kagan's exceptional creativity in the field of stereochemistry (Figure 6).

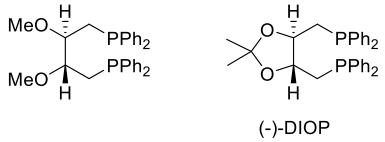


Figure 6. First diphosphines with C2-symmetry.

(−)-DIOP provided among the best results in asymmetric hydrogenation achieved at this time (Figure 7). The Rh(I) chiral complex was synthesized *in situ* starting from $[RhCl(Olefin_2)_2]$ obtained from $RhCl_3$ by adding the chiral phosphine ligands to provide a displacement of olefins. The Rh-DIOP-catalyzed asymmetric hydrogenation of olefins was usually performed under extremely mild conditions using a catalyst ratio of S/C =

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Figure 7. Samples of DIOP that were synthesized in Professor Kagan's laboratory and are preserved to this day in Professor Kagan's office.

100. Pioneering experiments were carried out on atropic acids and their derivatives (Figure 8), albeit with moderate enantioselectivities up to 25% ee.

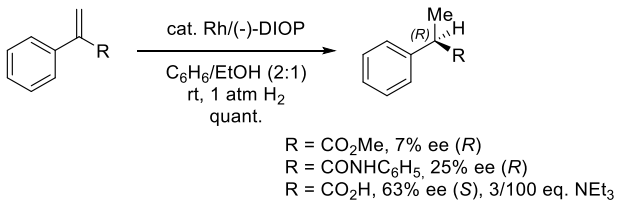


Figure 8. Asymmetric hydrogenation of conjugated esters, amides, and acids.

Careful experiments demonstrated the beneficial role of Et_3N in these transformations, with the best asymmetric induction achieved with the hydrogenation of atropic acid, providing the reversed (S)-configuration of the reduced product (with up to 63% ee). Several *α*-*N*-acylamino-*α*-acrylic acids and their derivatives were hydrogenated using the Rh-(−)-DIOP catalytic system, delivering the corresponding *α*-amino acids (Figure 9). The S/C ratio showed no influence on the stereochemical course of the hydrogenation. Alternatively, the natural (S)-amino acids were accessible by using (+)-DIOP enantiomer. This paper provided an extensive study of the hydrogenation of various precursors of alanine, phenylalanine, tyrosine, Dopa, and leucine using the Rh-(−)-DIOP catalyst system and detailed the parameters that influenced both the enantioselectivities and the rate of the hydrogenation.[23] As a demonstration of its significance, the publication highlighting these achievements has been cited over 1,100 times and viewed over 4,100 times.

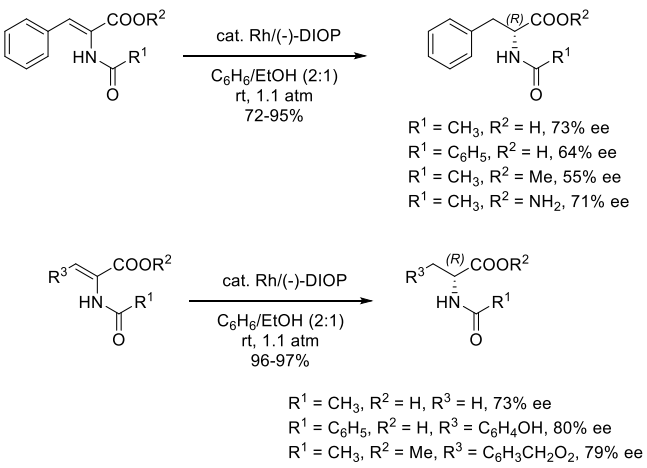


Figure 9. Asymmetric hydrogenation of *α*-*N*-acylaminoacrylic acid derivatives.

Surprisingly, substituents on the phenyl ring of the *α*-acetamidocinnamic acid derivatives seemed to increase the enantioinductions in the hydrogenation reactions. The meticulous work of Professor Kagan showed an effective enantioinduction of 83% (not shown) vs 73% (Figure 9) for the reduction of an *N*-acetyl phenylalanine precursor measured by v.p.c. analysis with a clean separation of the two enantiomers of the *N*-acetyl phenylalanine.[24] Kagan also studied the catalytic activity of Wilkinson's rhodium complexes with various diphosphines in the hydrogenation of *α*-acetamidocinnamic acid and styrene, demonstrating the influence of the chain linking the diphenylphosphino groups in changing the selectivity of the catalyst.[25]

Professor Kagan anticipated very early the crucial role of steric parameters in the Rh-catalyzed homogeneous hydrogenation of olefins. The group followed up this chemistry by designing novel ligands with the idea of evaluating the influence of steric parameters on the reduction (Figure 10). Various modified

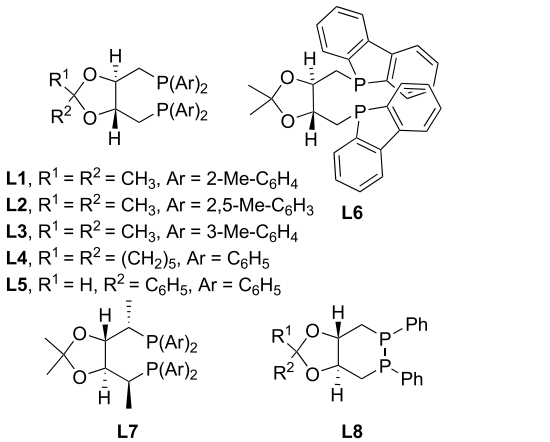


Figure 10. Chiral diphosphines related to (+)- and (−)-DIOP.

DIOP ligands **L1**−**L3** bearing methyl substitutions at different positions on the phenyl ring were developed as well as **L4**−**L5** with modifications on the dioxolane part to evaluate their catalytic properties compared to the parent (−)-DIOP ligand.[26] Notably, the influence of methyl substitutions on the phenyl ring of the DIOP was investigated for the Rh-catalyzed hydrogenation of *N*-acetyl phenylalanine precursor, demonstrating that substitution of a methyl group at the *meta* position of the aryl ring of the (−)-DIOP such as in **L3** increased both the enantiomeric excess and the rate of the hydrogenation reaction (up to 88% ee vs 82% ee), although **L1** bearing a methyl group at the *ortho* position of the phenyl ring as well as 2,5-disubstituted methyl groups in **L2** led to lower enantioinductions compared to the (−)-DIOP parent ligand. Enantioselective synthesis of phenylalanine derivatives has been accomplished with [Rh-(+)-DIOPCl], demonstrating that the enantioselectivity was influenced by the stereochemistry of the double bond, the *para*-

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substituent on the *N*-benzoyl group, and the esterification of the carboxylic acid group.[27]

Notably, the synthesis of the precursor of DOPA, a useful drug against Parkinson's disease, was also improved to 90% ee (vs 86% ee) using **L3** (Figure 11), although asymmetric hydrogenation performed with **L6** as a chiral ligand having the phenyl ring *ortho*-linked to form a phosphole system afforded low ee, interestingly with a reversed (*S*)-configuration.

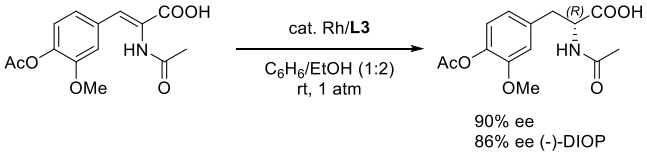


Figure 11. Asymmetric synthesis of DOPA intermediates.

Together with J. C. Fiaud at Paris-Sud University, H. B. Kagan designed a novel ligand derived from DIOP **L7** bearing two methyl groups on the alkyl side chain next to the phosphorus atom.[28] Similar results were obtained with the asymmetric synthesis of *N*-acetyl alanine with good enantioselectivity, although *N*-acetyl phenylalanine was produced with the opposite configuration in comparison to DIOP itself. They postulated that the conformation of the seven-membered-ring chelate involving the rhodium and phosphorus atoms must be modified by introduction of two methyl substituents. Later, Cyclodiop **L8**[29] with a P−P bond was prepared and catalyzed the reduction of (*Z*)-Ph═C(NHAc)COOH into (*R*)-*N*-acetylphenylalanine with 71% ee.

In a somewhat related contribution and to confirm the influence of the oxygen atom, a cyclopentane analogue of (−)-DIOP **L9** prepared from *trans*-cyclopentane-1,2-dicarboxylic acid was used in the reduction of acetamido cinnamic acid derivatives, exhibiting lower enantiofacial discrimination to deliver the corresponding (*R*)-*N*-acetyl phenylalanine (63% ee vs 82% ee), although a comparable level of enantioinduction was attained with ligand **L10** (Figure 12). These results clearly showed that steric factors played a key role in the asymmetric hydrogenation.

In addition to the development of related DIOP diphosphines, Professor Kagan contributed to the development of various novel chiral diphosphines, demonstrating his continuing research interests in stereochemistry and asymmetric catalysis.

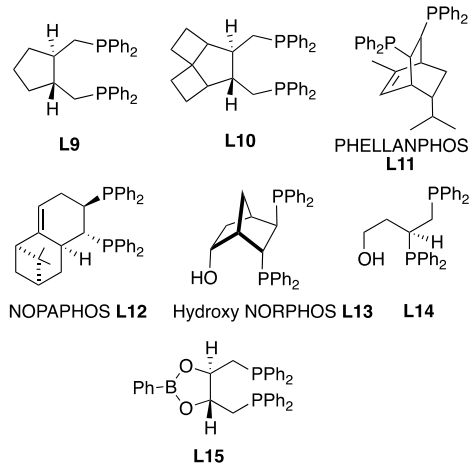


Figure 12. Other diphosphine ligands.

As such, PHELLANPHOS **L11**[30] and NOPAPHOS **L12**, which chelated with the rhodium with a rigid conformation, were prepared and their structures were confirmed by X-ray analysis.[31,32] (*S*,*S*)-**L11** and(*R*,*R*)-**L12** gave δ and λ chelated rings. The cationic [Rh(COD)-PHELLANPHOS]$^+PF_6^-$ (COD = 1,5-cyclooctadiene) complex exhibited excellent catalytic properties in asymmetric hydrogenation to access (*R*)-*N*-acetyl phenylalanine and (*R*)-*N*-acetyl alanine in quantitative yields and 95% enantioselectivities. Later, together with J. Ward and A. Börner at Paris-Sud University and Rostock University, H. B. Kagan explored the catalytic performances of alkyldiphenylphosphine-rhodium complexes having as an additional ligating functional group a hydroxyl substituent in a rigid (hydroxy NORPHOS, **L13**)[33] or a flexible framework [(*S*)-1,2 bis-(diphenylphosphino)butane-4-ol **L14**] from L-ascorbic acid.[34] Lower enantioselectivities and reaction rates were observed with the cationic complex prepared from acyclic analogue **L14** during the hydrogenation of *N*-acetyl dehydrophenylalanine and its methyl ester compared to the rigid catalyst derived from hydroxy NORPHOS **L13**. H. B. Kagan and A. Börner hypothesized that a prochiral substrate having a C═C double bond should be able to interact with the ligand both at the catalytic center and with the pendant Lewis acid. During the course of the group investigations, they also prepared the first chiral bimetallic complex based on a boron analogue of DIOP **L15**.[35] The corresponding neutral [RhCl**L15**] and cationic [Rh(COD) **L15**]$^+BF_4^-$ catalysts were less stereoselective than (-)-DIOP for the reduction of *N*-acetyl dehydrophenylalanine, but comparable enantioselectivities were achieved for the reduction of ketopantolactone (Figure 12).

Enamides[36,37] are exceptional prochiral substrates to access enantiomerically enriched amides and amines, which are biorelevant targets and valuable building blocks of synthetic interest. After the discovery in 1971 of the seminal Rh(I)-DIOP-catalyzed asymmetric hydrogenation of *N*-acyl dehydroamino acid and of a nonfunctionalized enamide,[23] Kagan's group investigated the hydrogenation of a range of enamides with up to 85% enantioselectivities and (*R*) or (*S*) inverted configurations, demonstrating the crucial role of solvents used for the transformation (Figure 13).[38]

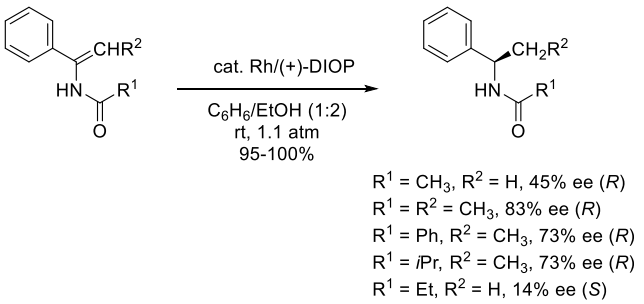


Figure 13. Asymmetric hydrogenation of enamides using Rh-(+)-DIOP.

A stable cationic [Rh(COD)(+)DIOP]$^+ClO_4^-$ complex successfully achieved the asymmetric hydrogenation of *N*-acetyl-1-phenyl-1-aminopropene with up to 92% ee.[39] Stereoselective syntheses of dipeptides[40−44] were also efficiently obtained using neutral [RhCl(−)-DIOP] and cationic [Rh-(COD)(+)-DIOP]$^+BF_4^-$ catalysts, as well as the Rh/DIPAMP complex.

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H. B. Kagan was not only interested in transition metal catalysis involving rhodium complexes, but he also designed and characterized the structure of a novel [IrCOD(+)-DIOPCl] catalyst, which was confirmed by X-ray analysis.[45] Because very little attention had been paid to the utilization of optically active hydrocarbon ligands, H. B. Kagan used titanium(IV) complexes containing menthyl (M)- and neomenthyl (NM) η^5-cyclopentadienyl ligands, $(\eta^5\text{-MCp})_2TiCl_2$ and $(\eta^5\text{-NMCp})(\eta^5\text{-Cp})TiCl_2$ to hydrogenate simple olefins such as 2-phenyl-1-butene.[46]

H. B. Kagan is also recognized for exceptional creativity in the development of an insoluble chiral polymer-supported rhodium complex related to the soluble Rh(I)-DIOP complex using a Merrifield resin.[47] The phosphinated resin obtained from $P(C_6H_5)_2Li$ was stirred for 21 h under argon at room temperature in a solution of $[RhCl(C_2H_4)_2]_2$ in benzene to provide the insoluble complex suspended in benzene, which enabled the catalytic heterogeneous asymmetric hydrogenation of α-ethylstyrene and methylatropate, albeit with a lower efficiency than in solution. As a demonstration of its significance, the publication highlighting this magnificent discovery has been cited over 310 times.

With the idea of avoiding the use of a polystyrene support sensitive to solvent effects and to use a rigid and solvent-insensitive surface, Professor Kagan and his group in collaboration with R. Setton at the University of Orléans reported the first graphite-supported chiral catalyst used in the enantioselective hydrogenation of (*Z*)-PhCH═C(NHAc)-COOH to afford (*S*)-*N*-acetyl phenylalanine having the configuration opposite to that observed in the Rh-catalyzed homogeneous hydrogenation using (−)-DIOP as ligand, albeit with low enantioselectivities. Nevertheless, the enantioinductions obtained clearly demonstrated that graphite functionalized with a chiral diphosphine was developed for the first time.[17]

Next to early ligand developments and their applications in asymmetric hydrogenation, the Kagan group studied the mechanism of the Rh-catalyzed reduction of (*E,Z*)-α-acylaminocinnamic acids[48] with important mechanistic implications and conclusions. The stereochemistry of various α-acylaminocinnamic acids was studied in the presence of the Rh-DIOP complex. Deuterium was used to investigate *E-Z* isomerization during the catalytic process. Catalytic deuteration of the *Z* isomer indicated a *cis*-addition, although the *E* isomer led to a mixture of d_2 diastereoisomers, demonstrating that some *E-Z* isomerization occurred prior to the reduction. The *Z* isomer is reduced much faster than the *E* isomer. Some *E-Z* isomerization occurred when the *E* isomer was reduced, indicated by the fact that there was no incorporation of deuterium at the vinylic position in the presence of the Rh-DIOP catalyst. Knowles at Monsanto independently reported similar mechanism studies.[49]

In addition to asymmetric hydrogenations, Kagan and his group investigated enantioselective hydrosilylations, which provide access to chiral amines and alcohols as well. After the pioneering examples of homogeneous hydrosilylation of olefins catalyzed by Ni(I) and Pt(II) complexes (albeit with low enantioselectivities),[50,51] Ojima and Kagan developed in 1973 the Rh-catalyzed hydrosilylation of ketones.[52,53] Specifically, the Rh-DIOP-catalyzed homogeneous and heterogeneous hydrosilylation of acetophenone was carried out using phenylnaphthylsilane, with 58% ee.[47] As part as his outstanding discoveries, Professor Kagan, in collaboration with R. Setton, was the first to develop the asymmetric hydrosilylation of ketones by a graphite-supported catalyst with configurations opposite to that observed for the less-enantioselective homogeneous hydrogenation.[47,17] He also carried out unprecedented studies on the Rh-DIOP-catalyzed hydrosilylation of imines, demonstrating that the reactions were at this time more efficient compared to the related ketones,[54] and found that the enantioinductions strongly depended on the nature of the silane used for the transformations. The process proceeded effectively under very mild conditions, generating enormous interest in this method. Finally, H. B. Kagan and his co-workers published many influential reviews and chapters[55] involving asymmetric hydrogenation[56−58] and hydrosilylation.[59,60]

Professor Henri Kagan is recognized for his exceptional creativity, making outstanding contributions to the field of asymmetric hydrogenation. The concept of C_2 symmetric bidentate diphosphines, with the first report of the DIOP ligand,[61] has inspired numerous chemists with a major influence on the development of asymmetric catalysis as demonstrated by noting that over 460 publications have appeared that include DIOP both in the titles and abstracts. Moreover, 14 patents related to DIOP and their derivatives have been filed by universities and companies (e.g., Mitsubishi Chem Corp, Johnson Matthey, Ajinomoto). Through these many contributions, Professor Kagan has left a legacy of unmatched excellence and scientific impact.

3. CONTRIBUTIONS TO ASYMMETRIC OXIDATION

Professor Kagan was a true polymath, interested in all types of reactivity, and for each of them, he was a key player in major discoveries: this is also the case for asymmetric oxidation reactions.

From the very outset of his career, Professor Kagan was always interested in oxidation reactions, beginning as a Ph.D. student investigating steroid synthesis with Pr Jean Jacques at the Collège de France. As mentioned previously, his first foray into *asymmetric* oxidative catalysis was the photocyclization reaction induced by circularly polarized light he described in 1971.[7a] Albeit with low optical activities, an enantioenriched hexahelicene was isolated in high yield by this method.

Combining his interest in lanthanide chemistry, his laboratory reported the catalytic oxidation of benzoins to benzils with lanthanide nitrates in 1975,[62] and also the efficient employment of lanthanide alkoxides in the catalytic epoxidation of allylic alcohols and in Meerwein−Ponndorf−Verley−Oppenauer reactions.[63] He even explored heterogeneous catalysis by treating the cheapest source of Ce(IV), cerium dioxide, with a catalytic quantity of ruthenium chloride; the resulting CeO_2−Ru system promoted the efficient dioxygen oxidation of various alcohols and aldehydes, with the targeted products easily isolated by filtration and the heterogeneous catalyst regenerated in the presence of water and formaldehyde.[64]

Professor Kagan's seminal contributions in the field of asymmetric oxidation are indisputable. Together with Volker Schurig in Tübigen and Hubert Mimoun at the Institut Français du Pétrole, Henri Kagan first investigated this domain in 1979, at a time when the area was still in its infancy, even for the oxidation of activated carbon−carbon double bonds. He and his collaborators indeed described the use of an optically active molybdenum(VI) peroxo complex from an (*S*)-*N,N*-dimethyllactamide ligand to produce enantioenriched epoxides from simple unfunctionalized olefins in up to 34% ee.[65] In 1980, Katsuki and Sharpless reported their impressive epoxidation system [$Ti(OiPr)_4$, enantiopure diethyl tartrate (DET), and *tert*-butyl hydroperoxide (TBHP)], yielding highly enantioenriched

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2,3-epoxy alcohols from allylic alcohols.[66] Only a few years later, Kagan's group pointed out that although highly valuable building blocks, practical access to scalemic sulfoxides was still in demand by purely chemical oxidants. With Philippe Pitchen, he discovered that the addition of a molar equivalent of water to the Sharpless reagent led to the oxidation of sulfides to enantioenriched sulfoxides, whereas in the absence of water the reaction remained nonselective (Figure 14).[67] This

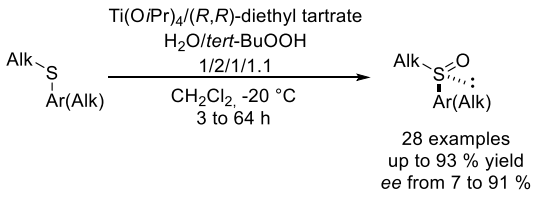


Figure 14. Asymmetric oxidation of sulfides to sulfoxides.

discovery is the result of a sharp optimization of the different parameters of the reaction, the quantity of the reagents, and their involvement in the mechanism of this oxidation.[68]

Indeed, the best sulfide oxidation system involved the use of two equiv of DET per titanium, and one equivalent of water, the absence of the latter or its presence in excess (i.e., 6 equiv) leading to racemic sulfoxides. At that time, infrared spectroscopic analyses led to the conclusion that similar oxidizing reagents arose from the 1:1:1 or 1:2:0 (Ti/DET/H_2O) stoichiometry; the Kagan group hypothesized that hydrolysis of the Ti−O-*i*Pr bonds formed species with μ-oxo bridges, leading to a polymeric active species. Hammett correlation measurements were performed to propose two mechanistic pathways for the reaction, i.e., an external attack by the chiral active species on the sulfur or prior coordination of sulfur to titanium before the oxidation. He even proposed that one or the other of these mechanisms was at play depending on the temperature at which the reaction was carried out. The usual thorough and meticulous work of Professor Kagan is still obvious in this study in which he furthermore proposed a model to predict the absolute configuration of the formed sulfoxides and argued about the inhibition effect of sulfoxides. It is so pleasant to read in these founding papers that Professor Kagan mentions in the acknowledgment part of the personal exchanges with Pr Sharpless on this subject; he also added an addendum to his 1984 article, pointing out that a similar study was published by Seraglia in Italy, just after the *Tetrahedron Letters*[67] preliminary account appeared.[69]

The Kagan group went further on to optimize and study in detail this efficient enantioselective transformation toward valuable sulfoxide derivatives.[70] Although he clarified the role of water in reactivity, he also studied the influence of the nature of the oxidant and discovered the beneficial use of cumene hydroperoxide on both the yield and the enantioselectivity values for many sulfoxides. At that time, he and his group furthermore demonstrated that the reaction could be performed with a catalytic quantity of the oxidation mixture in the presence of molecular sieves, without decreasing its activity, albeit with a loss in its selectivity. His charming stubbornness in providing extremely reproducible protocols is evidenced in a 1995 paper[71] in which one can read the perfect description of the procedure in terms of catalyst preparation, temperature, reaction time, order of addition, source of reagents, time, and storage conditions, etc. This allowed the synthesis of chiral sulfoxides with excellent enantiomeric excesses in a perfectly reproducible way, which is indisputable knowing that this article has been cited more than 170 times!

This precision in his way of carrying out his research enabled him to optimize at the same time the asymmetric oxidation process involving only catalytic quantities of the oxidizing system.[72] The replacement of water by 2-propanol in combination with cumyl hydroperoxide indeed allowed successful oxidation under catalytic conditions. A careful optimization of all reaction parameters led both to high yield and high ee for a wide range of aryl-, alkyl- or dialkylsulfides, provided one used a combination Ti(O*i*-Pr)$_4$/DET/*i*-PrOH with the exact 1:4:4 proportion in the presence of molecular sieves in an equivalent weight with respect to the sulfide (Figure 15). Enantiomeric excesses of more than 95% were measured,

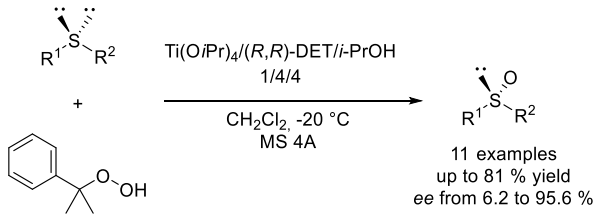


Figure 15. Catalytic asymmetric oxidation of sulfides to sulfoxides.

with the highest enantioselectivities achieved at that time in catalytic asymmetric sulfoxidations by nonenzymatic methods.

Pr Kagan very originally employed his method for the enantioselective oxidation of 1,3-dithianes[73] and for the synthesis of new optically active sulfoxides with chelating properties, in particular enantioenriched 8-(methylsulfinyl)-quinoline.[74]

In collaboration with industrial groups, Pr Kagan has proven the robustness of this method; the catalytic system was slightly modified with the use of an enantiopure amino alcohol as chiral ligand but led to the production of almost enantiomerically pure tenatoprazole, an irreversible proton pump inhibitor used for the prevention and treatment of gastric acid-related diseases (Figure 16).[75] This procedure was successfully implemented on scales that reached multiple kilograms.

A major application of this procedure has undoubtedly been its ability to yield ferrocenyl sulfoxides with high enantiomeric purity.[76] Again for these specific substrates, the method of preparation of the oxidant was carefully studied for a well-defined stoichiometry to achieve virtually complete enantiose-

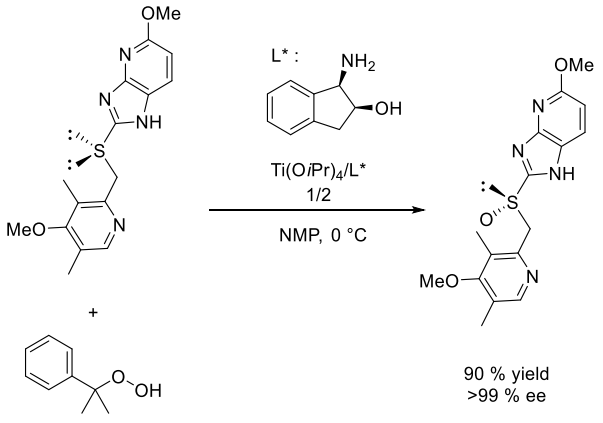


Figure 16. Asymmetric synthesis of (S)-tenatoprazole.

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lectivity in the case of some ferrocenyl aryl sulfides. These derivatives have served as valuable building blocks for their highly diastereoselective *ortho*-lithiation toward the synthesis of ferrocenyl derivatives with planar chirality.[13]

It is precisely by using this enantioselective oxidation reaction that the Kagan group investigated the question of understanding the influence of the enantiomeric excess of the catalyst used on the asymmetric induction that it produces.[77,78] This is another major discovery and advancement arising from the Kagan laboratory that is detailed elsewhere in this contribution.

Oxidation, and in particular asymmetric oxidation, are fields that Professor Kagan was able to lead so well with modesty, and in which one can only note the impressive results obtained.[79,80] His contributions come from an unfailing curiosity endowed with a creativity as rare as it is productive and a meticulousness in the exploration of reactivities that must remain inspiring for the community of asymmetric catalysis.

4. CONTRIBUTIONS TO LANTHANIDE CHEMISTRY

It is not at all obvious what sparked Professor Kagan's interest in lanthanide chemistry, but as with all the research he spearheaded, he was a true pioneer whose creative genius, instincts, and original thinking sparked a revolution in this domain. Thus, prior to the Kagan group's investigations, it is safe to say (as pointed out by Kagan himself) that the only interest shown by most organic chemists in lanthanides was the use of Ce(IV) reagents as oxidants or the role played by various lanthanide complexes as chiral shift reagents.

The first contribution to lanthanide chemistry from the Kagan Laboratory appears to be a report on the use of lanthanide nitrates for the catalytic oxidation of benzoins to benzils.[62] In this brief communication, five different lanthanide nitrates (Ln = La, Sm, Eu, Tm, and Yb) were used in the conversion of several substituted benzoins to benzils. Ytterbium nitrate was determined to be the most efficient catalyst in a process that was proposed to involve NO_3^- as the oxidizing agent, with oxygen serving as the stoichiometric oxidant (Figure 17). The

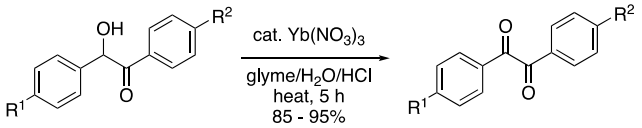


Figure 17. Oxidation of benzoins to benzils with lanthanide chemistry.

concluding statement of the contribution presciently proclaimed, "We are currently carrying out further studies of lanthanum salts as catalysts or modifiers for organic reactions since many are relatively cheap and safe reagents".

This exploration thus led to forays into other catalytic redox processes using various lanthanide complexes. For example, a serendipitous observation during the course of the group's investigations on SmI_2 chemistry (vide infra) led to a study on the preparation of lanthanide alkoxides and their use as catalysts in Meerwein-Ponndorf-Verley-Oppenauer reactions (Figure 18).[81] Thus, Barbier-type reactions of SmI_2 with various organic halides and aldehydes led to a class of samarium alkoxides that were found to participate in Oppenauer-type reactions with the aldehydes. The group followed up on this chemistry by developing a convenient synthesis of various lanthanide alkoxides and studying their role in the reversible hydride transfer processes between alcohol and carbonyl substrates. Further studies led to a convenient synthesis of Ln(O*i*-Pr)$_3$

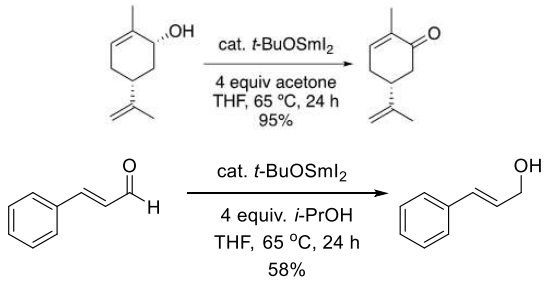


Figure 18. Lanthanide alkoxides and their use as catalysts in Meerwein−Ponndorf−Verley−Oppenauer reactions.

complexes (Ln = La, Ce, Sm, Yb) and their use in the catalytic epoxidation of allylic alcohols (Figure 19).[63]

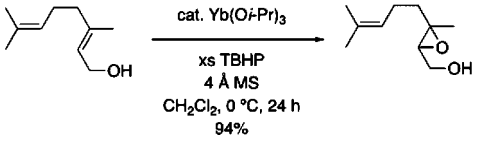


Figure 19. Ln(O*i*-Pr)$_3$ in the catalytic epoxidation of allylic alcohols.

Beyond the use of various lanthanide complexes in oxidation−reduction chemistry, the Lewis acid character of diverse lanthanide salts was exploited by the Kagan group in several domains. Among the first such studies, the selective rearrangement of terminal epoxides to methyl ketones was explored (Figure 20).[82] Serendipity again appears to have played a role in

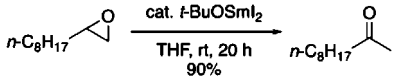


Figure 20. Selective rearrangement of terminal epoxides to methyl ketones.

the discovery of this transformation because in the exploration of the deoxygenation of epoxides by SmI_2 (vide infra), terminal epoxides unexpectedly provided methyl ketones as byproducts. Preparations of various iodo-containing samarium alkoxides were subsequently found to lead to excellent yields of the corresponding methyl ketones by a unique mechanism, a process that provided a convenient two-step (epoxidation/rearrangement) access to methyl ketones from terminal alkenes.

The Lewis acid character of lanthanide salts was exploited in other reactions of epoxides. For example, in the presence of thiols, various lanthanide complexes catalyzed the ring-opening of epoxides to generate α-hydroxy thioethers.[83] The method developed represented a very mild approach to the synthesis of such substructures (Figure 21).

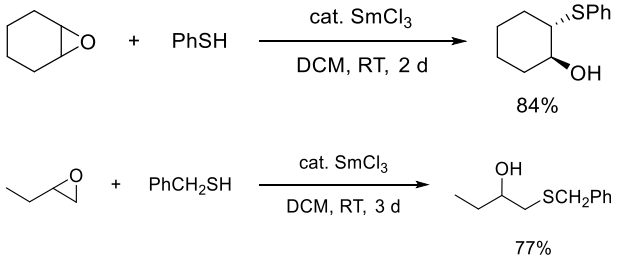


Figure 21. Ring-opening of epoxides with thiols.

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In addition to epoxides, lanthanide(III) chlorides as well as other complexes were found to serve as excellent Lewis acids for several carbonyl group transformations, including the promotion of aldol reactions with silyl enol ethers and addition of Me_3SiCN to aldehydes, forming cyanohydrin derivatives (Figure 22).[84]

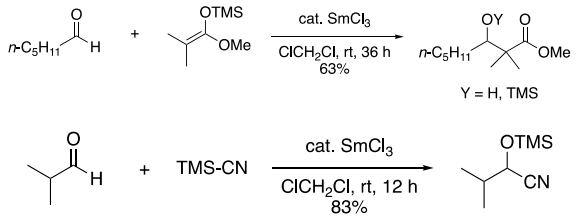


Figure 22. Aldol reactions with silyl enol ethers and the addition of Me_3SiCN to aldehydes.

As relatively mild Lewis acids, various Ln(III) salts were also found to induce ether- and thioether formation from allylic alcohol precursors (Figure 23).[85]

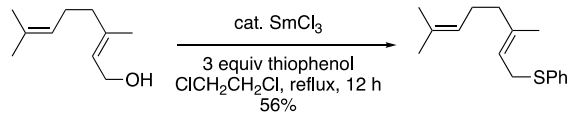


Figure 23. Thioether formation from allylic alcohol precursors.

Although simple in concept, design, and execution, these studies on the use of lanthanide complexes in catalysis provided the inspiration for others to delve into the potential of lanthanide catalysts for myriad transformations, including Diels–Alder reactions, Friedel–Crafts reactions, and beyond.

As important as Professor Kagan's contributions to lanthanide catalysis were to awaken the organic chemistry community to this field of research, it must be said that his single most remarkable contribution to lanthanide chemistry was the introduction and development of samarium diiodide (SmI_2). The initial incursion into this research was extremely unassuming, being revealed in a contribution describing a new and convenient synthesis of SmI_2 and YbI_2 (by the reaction of Sm or Yb metal with 1,2-diiodoethane), along with several seminal reactions using these reagents (e.g., reduction of conjugated carbonyl substrates, reduction of aldehydes and ketones, and the initial Barbier-type reactions).[86] Samarium diiodide had first appeared in the literature in 1930,[87] but received scant attention. The reasons were obvious: there was no practical synthesis of the material, and no one previously had the foresight to recognize that it could be useful in any way for organic synthesis. Consequently, the reagent languished away from the eyes of organic chemists for five decades, with fewer than a dozen mentions in the scientific literature. All of that changed in 1977 with the first report from the Kagan laboratory on the synthesis and utility of samarium diiodide (SmI_2) as a one-electron reducing agent.

Although exceedingly important as the ground-breaking report of viable and convenient SmI_2 chemistry, this *Nouveau Journal de Chimie* communication paled in comparison to the blockbuster paper that followed in the *Journal of the American Chemical Society* three years later, where the full scope of the processes outlined above were detailed.[88] In this epic contribution, the Kagan group outlined a series of transformations that set the stage for all SmI_2 chemistries to follow (Figure 24). Through this initial research, the power of SmI_2 to

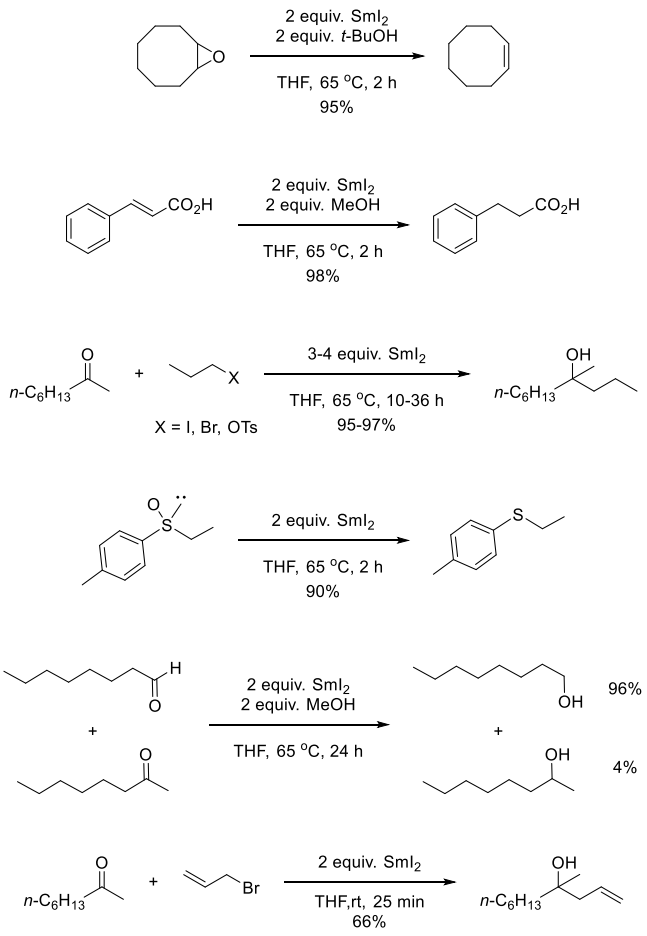


Figure 24. Key transformations discovered in Kagan's seminal SmI_2 methods paper.

carry out essential reductions and reductive coupling reactions was revealed: a virtual cornucopia of transformations. Deoxygenation reactions of both epoxides and sulfoxides were described, most with very high yields. The reduction of conjugated carbonyl substrates demonstrated that while α,β-unsaturated carboxylic acids and -esters could be cleanly converted to their saturated congener, unsaturated aldehydes and -ketones were problematic owing to competitive over-reduction. As expected based on these results, isolated aldehydes and ketones were cleanly reduced to the corresponding alcohols, while carboxylic acids and -esters were unreactive. Aldehydes could be reduced with excellent chemoselectivity in the presence of ketones. Alkyl iodides, -bromides, and even -tosylates were reduced to the corresponding alkanes, but perhaps most importantly, the group demonstrated that SmI_2-promoted Barbier-type reactions could be carried out in exceptionally high yields.

As a demonstration of its significance, the article outlining these results has now been viewed over 10,000 times and cited over 1,300 times, and although virtually no research on SmI_2 was published during the first 50 years of its initial description, now nearly 2000 papers describing various aspects of SmI_2 have been published, speaking volumes about the profound influence of this contribution.

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The Kagan group then explored other important aspects of synthetic chemistry related to SmI_2. For example, the use of this reagent for the formation of pinacols from both aldehydes and ketones was outlined (Figure 25).[89] The remarkable rapidity of

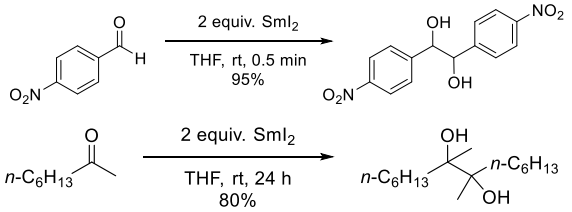


Figure 25. Formation of pinacols.

this reaction with aromatic aldehydes and its tolerance of relatively sensitive functional groups (e.g., nitro and cyano) made it a useful addition to the synthetic organic chemistry toolbox.

In a somewhat related contribution, the group discovered that α-ketols could be generated from the reaction of acid chlorides and SmI_2 or dicyclopentadienylsamarium (Cp_2Sm).[90] Aromatic acid chlorides were found to provide clean conversion to symmetrical α-diketones in the presence of these reducing agents, while aliphatic acid chlorides provided reasonable yields of α-ketols in the presence of either ketones or aromatic aldehydes. Mechanistic investigations indicated that the acyl chlorides reacted with the Sm(II) species to generate unusual acylsamarium(III) intermediates, which subsequently underwent addition to the carbonyl electrophiles to generate the observed products. A later investigation revealed that these transformations were best carried out in THP rather than THF,[91] presumably because the former solvent provided greater stabilization of the key acylsamarium intermediate (Figure 26).

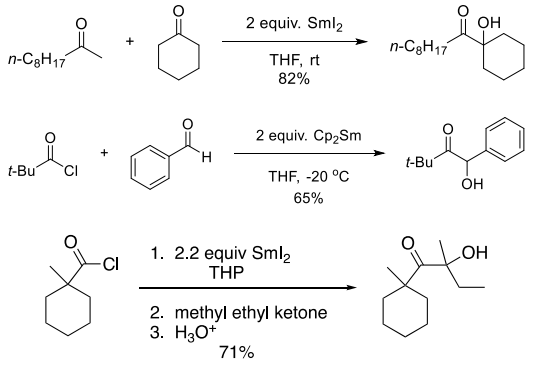


Figure 26. Synthesis of α-hydroxy carbonyl compounds.

Getting back to catalysis, the Kagan group discovered that many of the protocols outlined above for stoichiometric SmI_2 chemistry were improved upon by using various transition metal catalysts.[92] Thus, Barbier-type reactions, deoxygenation of epoxides, reduction of ketones, and the generation of α-ketols by reaction of acid chlorides with nitriles all benefitted in terms of yield and rate of reactions in the presence of catalytic NiI_2.

At this point in time, more than 45 years after the first report from the group at Orsay, applications of lanthanides to challenges in organic synthesis continue unabated, and they range from attempts to develop catalytic transformations of Sm(II) species[93] to the burgeoning area of photoredox chemistry.[94] Nearly all of this activity can be ultimately traced directly back to the profound vision and commanding intellect of its progenitor, Professor Henri Kagan.

5. CONTRIBUTIONS TO NONLINEAR EFFECTS IN ASYMMETRIC CATALYSIS

The beauty of chemistry is that accidents can provide mankind with new knowledge and breakthrough technologies. A scientist who painstakingly conducts an experiment and carefully analyzes its results can change the world. At the same time, there are discoveries in chemistry that are difficult to make by chance and require a genius mind. Such discoveries include nonlinear effects in asymmetric catalysis (Figure 27). Anticipating, understanding, explaining, and at the same time finding experimental evidence yourself are extremely rare examples.

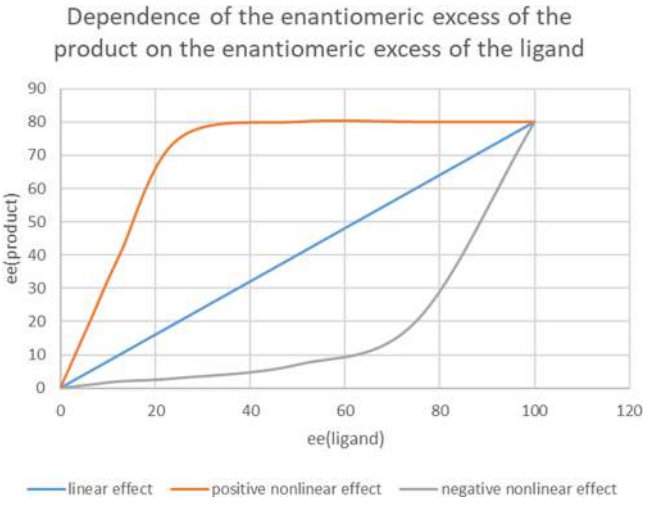


Figure 27. Linear and nonlinear effects in asymmetric catalysis.

In the late 1960s, when Professor Kagan became involved in asymmetric synthesis, he wondered about the mechanisms and possibility of nonlinear effects. At that time, there were very few enantiomerically pure ligands. The ligands on which he was able to test such an effect showed no evidence of nonlinear behavior.[95] However, he, understanding the importance of the possibility of the existence of nonlinear effects, did not give up and kept looking. Almost two decades later, his first article proving the existence of nonlinear effects was published. The first paper was published in 1986 and immediately included not only a conjecture, but also three fundamentally different examples and even an explanation of the phenomenon.[77] As we can see in many of Professor Kagan's discoveries, there is a trend to show the breadth of the idea by fundamentally different examples at once.

In his first paper, Professor Kagan posed the question: '*what is the correlation between the enantiomeric excess (ee) of a compound and the value of one of its chemical properties?*'

Thus, the authors were able to show that the oxidation of asymmetric sulfide with *tert*-butyl hydroperoxide using diethyl tartrate and tetraisopropoxide produced enantiomerically enriched sulfoxide (Figure 28). A negative nonlinear effect was observed for such a system. This is because a dimeric complex consisting of two ligands and two titanium atoms is formed in the system. When using a mixture of ligand enantiomers in a ratio other than 50 to 50 or 100:0, combinations of RR, RS, SR, and SS pairs can be formed. The RR versus RS pairs are diastereomers and can exhibit different

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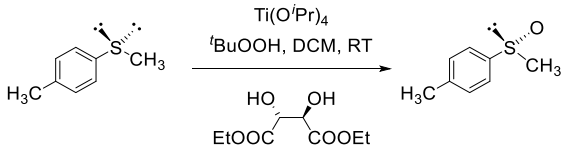


Figure 28. First example of a negative nonlinear effect.

reaction rates as well as different enantioselectivities in the reaction. In this case, the pair that loses enantioselectivity wins in terms of reaction rate. This results in a negative nonlinear effect.

As a second example, the authors used the same oxidation system but for geraniol. It seemed counterintuitive to expect the opposite of the situation for this case. However, a positive nonlinear effect is observed here (Figure 29).

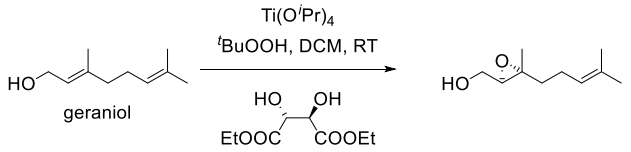


Figure 29. First example of positive nonlinear effect.

As a third example, the authors described the asymmetric intramolecular Hajos−Parrish−Eder−Sauer−Wiechert reaction (Figure 30). The authors found a small negative nonlinear effect.

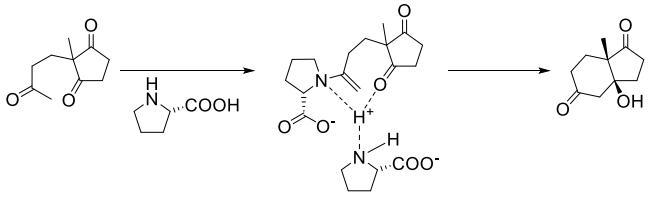


Figure 30. Proposed mechanism for the Hajos−Parrish−Eder−Sauer−Wiechert reaction proposed in 1986.

Later, when the era of asymmetric organocatalysis began, it became an urgent task to understand the mechanism regarding the presence of nonlinear effects in the aldol reaction catalyzed by proline and its analogues. This case turned out to be very interesting, because the possibility of a solid/liquid equilibrium turned out to be an essential factor.

What did the discovery of nonlinear effects in asymmetric catalysis lead to? A better understanding of what happens in asymmetric reactions. With a few simple experiments of mixing two enantiomers of a ligand or precatalyst, it became possible to obtain data on the structure of the active catalyst, a species that may be generated in such low concentration or so unstable that it is not possible to isolate.

The study of nonlinear effects made it possible to show the possibility of a reaction explaining the origin of chirality. Kagan's original work led to a flurry of work on the search for nonlinear effects. In 1988, Oguni showed a positive nonlinear effect in the reaction of the addition of diethylzinc to benzaldehyde (Figure 31).[96] In 1989, Noyori showed that in this reaction, the use of the ligand DAIB with an enantiomeric excess of only 15% allows access to a product with 95% ee (Figure 32).[97] This allowed Soai to discover his famous asymmetric self-catalytic reaction (Figure 33).[98]

Many attempts to engage in asymmetric catalysis resulted in a product with a low enantiomeric excess using an enantiomeric

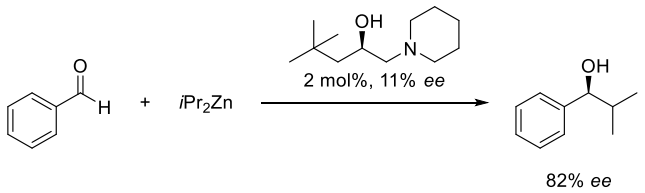


Figure 31. A positive nonlinear effect in the reaction of the addition of diethylzinc to benzaldehyde showed by Oguni et al.

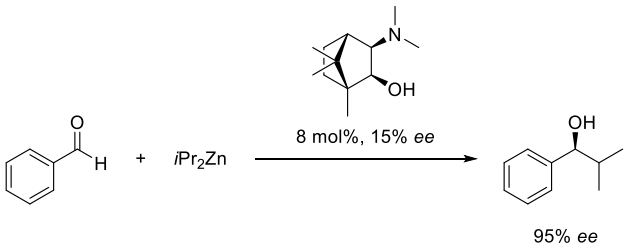


Figure 32. A positive nonlinear effect in the reaction of the addition of diethylzinc to benzaldehyde is shown by Noyori et al.

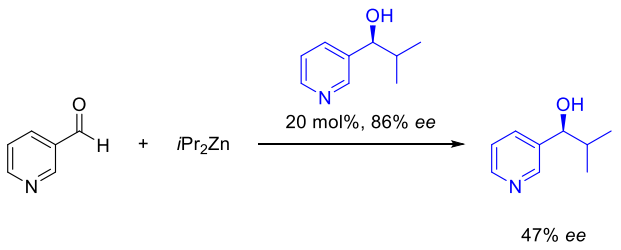


Figure 33. Asymmetric self-catalytic reaction shown by Soai et al.

pure catalyst. Who would have thought that the situation could be the opposite, that an impure substance could give an enantiomeric excess in a product exceeding its own purity? Henri Kagan was able not only to conceive of this concept but also to find evidence for its existence.

Here we have considered only giant milestones in Kagan's work. The fields of interest were very diverse. He was involved in heterogeneous asymmetric catalysis,[47] light energy storage in chemical systems (Figure 34),[11b] selective fluorination with such amazing reagents as $C_{19}XeF_6$ (Figure 35),[16] asymmetric phase transfer catalysis, and chiral shift reagents (Figure 36).[99]

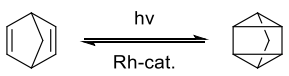


Figure 34. Light energy storage in chemical systems.

6. CONCLUSION

As is clear from the brief descriptions above outlining Professor Kagan's exceptional contributions to science, he is a gifted and extraordinarily creative individual with exceedingly broad interests and possesses a deep intellect and innate curiosity that allowed him to make those types of leaps of knowledge that establish him as a true genius. He created several entirely new fields of research that became pillars upon which substantial realms of exploration are now based (Figure 37).

From a personal point of view, those who know him recognize him as a quiet, thoughtful, caring, and self-effacing individual, not at all interested in self-promotion or hyping his remarkable

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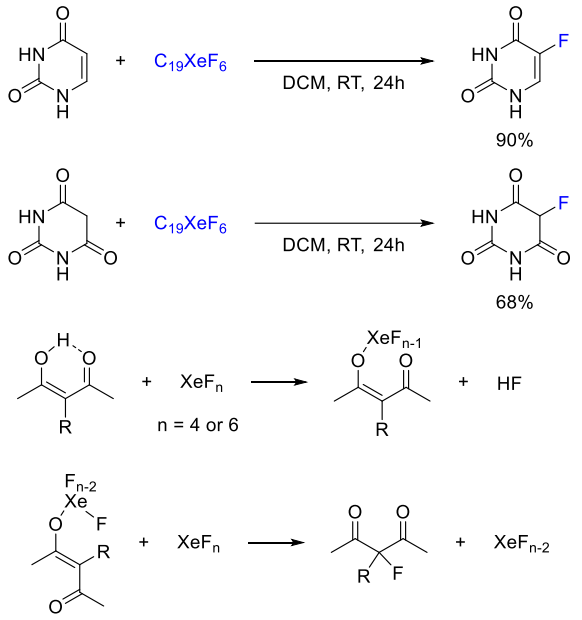


Figure 35. Selective fluorination by $C_{19}XeF_6$ and the proposed mechanism of action.

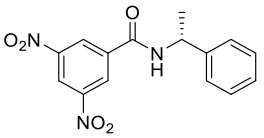


Figure 36. Chiral shift reagent suggested by Kagan et al.

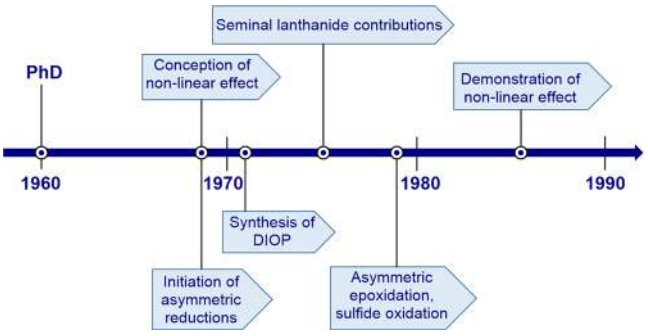


Figure 37. Timeline of Prof. Kagan's big breakthroughs.

contributions. In this regard, he truly deserves tremendous respect and admiration.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c02965.

Recollections from former students and colleagues about Professor Kagan (PDF)

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Notes

The authors declare no competing financial interest.

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