1 - Introduction

Asymmetric catalysis has become one of the most powerful methods to produce a single-enantiomer drug and now provides one of the most cost-effective and environmentally responsible methods for the production of a vast array of structurally diverse, enantiomerically pure compounds. Since a small amount of chiral catalyst can, in principle, produce a large amount of optically active product. Transition metal enantioselective catalysis is certainly among the most challenging and widely investigated area in modern organometallic chemistry. In 1971, H. B. Kagan and T. P. Dang discovered the Diop ligand or (2,3-O-isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane[1], the first C2-symmetric diphosphane that allowed asymmetric hydrogenation of dehydroamino acids, when complexed with rhodium. The basic idea was that a suitable functionality and skeletal rigidity of the phosphine ligand would contribute to the differentiation of transition states needed to accomplish enantioselective catalysis. The rhodium (I)-DIOP catalyst was superior to monophosphines catalysts in asymmetric hydrogenation of dehydro amino acids. It is interesting to note that Pr. H. B. Kagan’s 1970 initial patent also includes the structure of an atropisomeric ligand, a potential candidate for asymmetric catalysis, which is now developed by Roche under the name Biphemp.

This new idea showed that the chirality of phosphorous atom wasn’t necessary to obtain good selectivity, complex rigidity between the metal and the bidentate ligand allowed a better discrimination of the transition states needed to achieve an efficient asymmetric catalysis. This concept, using Rh-dipamp as catalyst unable Monsanto to be
the primary supplier of L-DOPA, a compound used in the stabilizing the effects of Parkinson’s disease\cite{2}. Numerous C2 symmetric ligands have since been described, the best example being the Binap, synthesized ten years after by the team of R. Noyori and H. Takaya\cite{3}. This master discovery generated intense activity in the new field of asymmetric catalysis. H. B. Kagan, in collaboration with C. Agami have made another important discovery when they revealed the non-linear effects of asymmetric catalysis\cite{4-6}. The present article contains some French contributions in the field asymmetric catalysis.

2 - Asymmetric Hydrogenation

Following Wilkinson’s work\cite{7} on alkene’s hydrogenation with the complex RhCl(PPh3)3, L. Horner\cite{8} and W. S. Knowles\cite{9} teams, showed that with the replacement of triphenylphosphane by a chiral monophosphane, the hydrogenation of atropic acid led to a low 15% enantioselectivity. The first meaningful results in asymmetric hydrogenation (63% ee) came from the H.B. Kagan team using the bidentate chiral ligand Diop associated with a rhodium complex. The first enantioselective hydrogenation of dehydroamino acids using the Diop ligand as chiral ligand\cite{10}, have also been described. The realization of meaningful enantioselectivity with the Diop ligand was a great breakthrough in the field of asymmetric hydrogenation.

Numerous examples of asymmetric catalytic reduction such as enamides hydrogenation\cite{11}, and the imines hydrosilylation\cite{12}, have been realized using the Diop ligand and a rhodium complex\cite{13}. In 1973 the Diop ligand was linked on a Merrifield resin. It was the first example of solid supported asymmetric catalysis\cite{14}. H.B. Kagan and his collaborators studied the asymmetric reduction of original substrates such as mono-dehydropeptides\cite{15}, mono-dehydroenkephalines\cite{16} and bis-dehydrodipeptides\cite{17}.

\begin{center}
\includegraphics[width=0.8\textwidth]{chemical_diagram.png}
\end{center}

Catalysis in France: an Adventure 2007, July 2 / 30
with excellent diastereoselectivities. After the Diop ligand, the Orsay team turned to the synthesis of other types of original ligand. They designed Diop ligand analogues\(^ {18}\) which are efficient in both hydrogenation and hydrosilylation. The synthesis of Phellanphos, Nopaphos\(^ {19}\) or Norphos analogues such as 6-endo-hydroxy Norphos\(^ {20}\) and its acyclic analogue\(^ {21}\) have been realized and their properties in catalysis have been assessed. A general synthesis of 2-hydroxyalkyl diphenylphosphanes has been described\(^ {22}\) as well as the synthesis of a multidentate ligand\(^ {23}\).

Following these pioneer discoveries, enantioselective hydrogenation through homogenous catalysis has become a core technology to generate stereogenic tertiary carbon. J.-C. Fiaud’s team evaluated the catalytic activity of chiral 2,5-disubstituted phospholanes as ligand for rhodium-catalyzed asymmetric hydrogenation of dehydroamino acids\(^ {24}\). The hydrogenation of (Z)-N-acetamidocinnamate methyl yielded up to 93% of enantioselectivity\(^ {24}\). Chiral 1,2,5-triphenylphospholanium tetrafluoroborate salt\(^ {24}\), chiral secondary diphenylphospholane\(^ {24}\) and a series of enantiopure phosphinites were synthesized and used in asymmetric hydrogenation of functionalized alkenes\(^ {24}\).

![Chemical structure](image)

The F. Mathey’s team\(^ {25}\) worked on the bridged phosphorous phosphanes of the 1-phosphanorbornadiene family. In this family, Bipnor (bis-phosphanorbornadiene) gave excellent results for the hydrogenation of dehydroamino acids with rhodium as catalyst (>98% ee). Recently, an easy accessible analogue of Bipnor known as C\(_2\)-Bipnor was reported and showed a wider range of applications than Bipnor\(^ {25}\). Other types of structures derived from the phosphanorbornadiene backbone\(^ {26}\) are being developed by Rhodia. In the same way, the G. Balavoine and J.-C. Daran’s team used chiral phospholes in asymmetric hydrogenation catalyzed by rhodium and iridium complexes\(^ {27}\).
Asymmetric hydrogenation application fields have been widened by the use of chiral ruthenium complexes. Asymmetric hydrogenation using chiral complexes of ruthenium through the dynamic kinetic resolution of α-substituted β-cetoesters was discovered in 1989[28-29]. A general method for the synthesis of chiral ruthenium catalysts was developed by J.P. Genet, V. Vidal and co-workers[30]. This method is compatible with a large range of chiral diphosphines such as Dipamp which was synthesized on large scale by the team of S. Jugé[31], phosphetanes[32], chiral phosphetanoferrocenes[33], dissymmetric atropisomeric diphosphanes such as MeO-NAPhePHOS[34] and triMe-NAPhePHOS[35] or symmetric such as SYNPHOS®[36] and DIFLUORPHOS®[37], the last two being industrially made by Synkem SAS. These ligands were used in the rhodium and ruthenium-catalyzed asymmetric hydrogenation of a wide range of functionalized ketones and alkenes with high level of selectivities. Moreover, the Ru-Synphos catalyst has been successfully used in the synthesis of some industrially relevant key intermediates and bioactive molecules[38] through dynamic kinetic resolution[39]. The synthesis of precursors of the liposidomycins and RA-IV derivative was described via asymmetric hydrogenation of β-ketoesters[40]. Recently, a new generation of chiral iridium catalysts was developed in collaboration with a Japanese group[41].
Some modified Binap ligands\cite{42} were reported and 4,4’ and 5,5’-Binap derivatives were used for catalytic asymmetric hydrogenation of ethyltrifluoroacetoacetate\cite{43}. Helicene derivatives\cite{44}, \(\beta\)-chirogenic \(\beta\)-aminophosphine and amino-phosphane phosphinite ligands were synthesized\cite{45}. Cyclic \(\beta\)-iminophosphine were used for the asymmetric hydrogenation of ketones\cite{46} and aminophosphine-oxazoline for iridium-catalyzed enantioselective hydrogenation of arylimines\cite{47}.

P. Dixneuf’s team has also studied the hydrogenation of carbon-carbon double bonds of cyclic cyclic carbonates\cite{48} and acyloxazolidinones\cite{49} with Binap and DuPHOS ruthenium catalysts. This study has been extended to the tetralone enamides hydrogenation\cite{50}. P. Dixneuf and C. Bruneau used this catalytic system in the enantioselective hydrogenation of tetrasubstituted double bond of enamides with an enantioselectivity up to 72\%\cite{51}. C. Bruneau and coll. reported that chiral rhodium complexes bearing monophosphites
ligands were found to be efficient catalysts for asymmetric hydrogenation of β-acylaminoacrylates with ee values up to 94\%\textsuperscript{[52]}. A. Mortreux and co-workers\textsuperscript{[53]} demonstrated that aminophosphine-phoshinite derivatives (AMPP) were very efficient in asymmetric hydrogenation of functionalized ketones with ee up to 99\%. These RhAMPP-catalysts together with Ru-MeO-Biphemp were used respectively in Rh and Ru-mediated hydrogenation reactions of chloroketone (up to 96\% ee) and enamide (up to 98\% ee), which were used as key steps for the synthesis of SR58611A\textsuperscript{[54]}. F. Agbossou and J. F. Paul performed a density functional study of hydrogenation of ketones catalysed by neutral rhodium-diphosphane complexes\textsuperscript{[55]}.

Today, numerous industrial processes use an enantioselective hydrogenation step in the creation of asymmetric centers. In this context, the team of J.-P. Genet in collaboration with Firmenich company, discovered an efficient catalytic system for the hydrogenation of tetra-substituted bonds. This reaction is used for the large-scale production of (+)-cis-dihydrojasmonate, under the trade name as Paradisone\textsuperscript{®}\textsuperscript{[56]}, which is one of the components of the perfumes of Christian Dior (Dolce vita) and Ralph Lauren (Romance).
The fundamental field of asymmetric hydrogenation has been recognized in 2001 with the award of the Chemistry Nobel Price to professors R. Noyori\(^{[57]}\) and W. S. Knowles\(^{[58]}\) together with professor K.B. Sharpless for his work on asymmetric oxidation.

### 3 - Hydrogen transfer

Several French teams worked on asymmetric reductions by hydrogen transfer. In 1990, inspired by the examples of Rh(I) catalyzed hydrogen transfers, the team of R. Chauvin replaced the hydrogen by isopropanol in basic medium with a ruthenium(II)-Diop complex\(^{[59]}\). Significant selectivity was obtained (62% ee) by the team of J.P. Genet and V. Vidal for the reduction of acetophenone and its derivatives, by using several ruthenium complexes\(^{[60]}\). In 1993, M. Lemaire and co-workers\(^{[61]}\) showed that nitrogenous ligands like diamines could be an interesting alternative to diphosphanes. They have used amides, ureas and thioures in asymmetric catalysis by hydrogen transfer reaction catalyzed by rhodium and ruthenium complexes with excellent selectivities\(^{[62]}\). Theoretical studies on the diamine-rhodium complex structure were also conducted\(^{[63]}\). Asymmetric hydrogen transfer reductions of prochiral ketones catalyzed by ruthenium or iridium complexes with chiral bis(oxazolines)\(^{[64]}\) and enantiopure β-aminoborals have been reported\(^{[65]}\). Chiral polyaminoborals and polyamino thiols were shown to be effective in the Ru-promoted asymmetric hydrogen transfer reduction of acetophenone\(^{[66]}\).

\[
\begin{align*}
\text{R}^*\text{O} & \quad \text{R} \\
\text{R} & \quad \text{R'} \quad \text{OH} & \quad \text{R'} \\
\text{[Ru]/[Rh] cat./L*} & \quad \text{i-PrOH, base} & \quad \text{L*} = \\
\text{X=O, S} & \quad \text{Ph} & \quad \text{Ph} \\
\text{R1} & \quad \text{N-C-N} & \quad \text{N-C-N} \\
\text{RCH2NH} & \quad \text{HO} & \quad \text{OBn} \\
\text{R=Ar} & \quad \text{R=Ar} & \quad \text{R=Arle} 
\end{align*}
\]

F. Mathey et al. used a Bipnor ruthenium complex in the hydrogenation of acetophenone\(^{[25]}\). The team of A. Mortreux described the reduction of β-ketoesters and other ketones by chiral diamines\(^{[67]}\) or ephedrine\(^{[68]}\) Ru-complexes and a variety of β-aminoborals has been used for the reduction of aromatic ketones\(^{[69]}\). The team of R.
Chauvin tested a rhodium-methyldiopium complex for hydrogen transfer reactions\cite{70}. C. Mioskowski and his collaborators have described the dynamic kinetic resolution of α-amino-β-ketoesters in a formic acid /triethylamine mixture with a chiral perfluorosulfonated diamine and obtained good enantio- and diastereoselectivities\cite{71}. The team of J. Cossy studied the reduction of symmetric and dissymmetric diketones-1,3\cite{72}, and C-2 substituted\cite{73} allowing syn diastereoisomers with good enantioselectivities.

4 - Asymmetric hydrosilylation and hydroamination

In the early 70’s, the team of H.B. Kagan developed the first examples of imines hydrosilylation catalyzed by Diop-rhodium complex\cite{12}. In 1989, G. Balavoine and his colleagues described the first use of chiral oxazolines as ligand for asymmetric hydrosilylation\cite{74}. Recently, the team of R. Chauvin used chiral phosphonium ylures which catalytic potential had not been explored. In particular not stabilized binapium ylures ligand\cite{75} and chiral sulfinylphosphoniophosphides ylures\cite{76} led to very fast rhodium(I) complexes with good activity. J. F. Carpentier and A. Mortreux reported zinc–diamine-catalyzed asymmetric hydrosilylation of ketones with ee up to 99%\cite{77}.

\[ \text{RhP} \text{Y} \text{P = PPh}_2 \text{CH}_2 \text{PPh}_2 \text{CPh}_2 \text{P} \text{S O} \text{••} \text{p-Tol} \text{H} \text{NH Ar} \text{HN Ar} \text{R}_1 \text{R}_2 \text{R}_1 \text{R}_2 \]

\( \text{R}_1=\text{H, Me} \)
\( \text{R}_2=\text{Ph, 2-MeO-C}_6\text{H}_4, \text{pCl-C}_6\text{H}_4, \text{Cyclohexyl...} \)
\( \text{Ar=C}_6\text{H}_4 \)

J. Collin, E. Schultz and co-workers achieved an enantioselective intramolecular hydroamination catalyzed by lanthanide ate complexes coordinate with \( N \)-substituted \((\mathcal{R})-1,1'\)-binaphthyl-2,2’ diamido ligands\cite{78} with ee up to 78%.
5 - PN and PO ligands in homogenous catalysis

In the beginning of the 80’s, the teams of A. Mortreux and F. Petit, in collaboration with the teams of G. Buono et G. Peiffer, developed a new generation of PN, PO and AMPP (Aminophosphanes Phosphinites) chiral ligands, very useful for the formation of C-C and C-H\(^{[79]}\). For instance, these ligands proved to be efficient in the hydrovinylation of cyclohexa-1,3-diene catalyzed by Ni ; the ThreoNOOP ligand gives 93% ee on vinylcyclohex-3-ene due to its tridentate capacity\(^{[80]}\).

The team of A. Mortreux and F. Petit developed further the use of these ligands for C-C bonds forming reactions\(^{[81]}\). Thus, AMPP were used for asymmetric hydroformylation with the first identification of a rhodium hydride complex\(^{[82]}\). A. Mortreux studied the applications of AMPP ligands in hydrosilylation, hydroformylation, ethylene-diene hydrovinylation, conjugated diolefin dimerization and allylic nucleophilic substitution\(^{[83]}\).

The team of G. Buono developed new chiral monophosphanes, in which the phosphorous atom is chiral, such as oxazaphospholines\(^{[84]}\) or o-hydroxyarylphosphide derivative\(^{[85]}\) for enantioselective reductions of ketones. A. Alexakis, L. Micouin and co-workers demonstrated that monodentate ligands such as phosphoramidites and phosphites could be used for the enantioselective iridium-catalyzed hydroboration of meso-bicyclic hydrazines\(^{[86]}\).
Another ligand developed by this team, the PN type Quiphos, proved to be efficient in enantioselective catalysis\cite{87} so were chiral iminodiazaphospholidines with basic properties, efficient in Cu-catalyzed asymmetric cyclopropanations\cite{88}.

6 - Ferrocenyle type chiral ligands

In the field of ferrocenyle chiral ligand chemistry, the team of H.B. Kagan also developed new ways for asymmetric synthesis avoiding resolution methods\cite{89}. Thus, several planar chiral ferrocenes were prepared by diastereoselective deprotonation of chiral sulfoxides\cite{90} or chiral acetals\cite{91}. It was then possible to efficiently get 1,2-bis(phosphane)\cite{92}, 1,3-bis(phosphane)\cite{93} and 1,1′-bis(phosphetano)ferrocenes\cite{33} that were very efficient ligand for the asymmetric hydrogenation of dehydroamino acids and allylic substitution.

7 - Palladium, Iridium, Copper and Ruthenium in metal-catalyzed allylation and etherification

The asymmetric allylation of stabilized carbanions, catalyzed by chiral palladium complexes is a very efficient way to obtain C-C bonds. The team of H. B. Kagan and J.-C. Fiaud described the first asymmetric induction in the late 70’s\cite{94}. Thus, β-diketones and β-ketoesters allylation with the Diop ligand open the way for palladium η³-allyle complexes in chemistry.
This research has been extended by the team of J.-C. Fiaud, setting up the first enantioselective reaction allowing the creation of axial chiral compounds\[95\]. The reaction of malonates on 1-vinylcyclohexanol 4-substituted carboxylates led to an excellent enantioselectivity by using palladium complexes and the Binap ligand. The allylic substitution of esters of 1-arylethanol type compounds was also asymmetrically set up for the first time with \((R,R)-\text{Me-DuPHOS}\)[96]. The enantioselectivities of this Pd-catalyzed benzylic reaction were recently improved and reached 90\% by using an isopropyl analogue of DuPHOS ligand\[97\].

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

The team of J.-P. Genet also worked on stereoselective reactions catalyzed by palladium complexes. The first glycine derivative imines’ allylation was performed with the Diop ligand leading to 68\% enantiomeric excess\[98\].

\[
\begin{align*}
\text{N} & \quad \text{MeO}_2\text{C} \\
\text{Ph} & \quad \text{Ph} \\
\text{MeO}_2\text{C} & \quad \text{H}
\end{align*}
\]

Inter and intramolecular substitution reaction by functionalized carbonated nucleophiles, was applied to the synthesis of alkaloids\[99\], optically active cyclopropanes\[100\] and \(\beta\)-lactams\[101\]. The synthesis of (-)-chanoclavine I was accomplished via this technology in the presence of Pd/Binap system in 60\% yield and 95\% enantiomeric excess\[99\].
The alkylation of prochiral aryl cyano esters has also recently been investigated by F. Agbossou-Niedercorn’s group\textsuperscript{[102]}. The use of the chiral pocket ligands of Trost’s group allowed the formation of quaternary stereogenic centers in ee up to 63%.

Nitrogenated and oxygenated nucleophiles have also been used in this type of reaction to prepare key intermediates of natural or pharmacologically active products. The teams of J. Muzart\textsuperscript{[103]} and D. Sinou\textsuperscript{[104]} have thus described the efficient access to the backbone of vinylic heterocycles or chiral alkylidenes. The cyclization of benzene-1,2-diol with various racemic propargylic carbonates in the presence of Binap ligand afforded the corresponding 2-benzylidene-3-methyl-2,3-dihydro-1,4-benzodioxine derivatives in ee ranging from 40 to 97\%\textsuperscript{[105]}.

The catalytic properties of the newly synthesized ligands such as the bis(oxazolines) or the phospholes of the G. Balavoine’s team\textsuperscript{[106]} has been evaluated in allylic alkylations. D. Sinou and his collaborators have recently shown that the use of surfactants associated with the Binap ligand allowed to carry out this reaction in water\textsuperscript{[107]}.

There is still a strong need of novel and original chiral ligands. Recently several French teams (F. Agbossou-Niedercorn’s, A. Alexakis’, N. Avarvari’s, E. Framery’s, J. Muzart’s, D. Sinou’s teams) have worked on this area and prepared new chiral ligands that were tested in standard reactions and more specifically in the Pd-catalyzed asymmetric allylic alkylation\textsuperscript{[108]}.

B. Chaudret’s group recently demonstrated that the Pd-catalyzed allylic alkylation reaction may also operate differently depending on the nature of the catalyst\textsuperscript{[109]}. Novel palladium nanoparticles stabilized by chiral diphosphite showed spectacular activity and were selective to one enantiomer of the substrate (rac- 3-acetoxy-1,3-diphenyl-1-propene), hence demonstrating a very high degree of kinetic resolution. This constitutes the first report of an asymmetric C-C coupling reaction catalyzed by nanoparticles with
a high enantiomeric excess and, moreover, the first nanoparticle-catalyzed reaction outside hydrogenation with the Pt/cinchonidinium system leading to high enantioselectivity.

Allylic substitution reactions have still attracted much attention as the control of the regio- and enantioselectivities are crucial in catalysis. Other metals such as iridium, copper and ruthenium have been identified as excellent catalysts for allylic substitution. The group of A. Alexakis has developed highly efficient systems implying the use of chiral phosphoramidite ligands. In the case of iridium catalyst, the addition of malonate type or amine as nucleophiles afforded the corresponding branched derivatives in good to excellent enantioselectivities \[^{[110]}\]. The use of copper is also highly challenging as it allows the addition of hard non-stabilized nucleophiles such as small alkyl or vinyl magnesium derivatives\[^{[111]}\].

The ruthenium-catalyzed allylic etherification reaction was described by the team of C. Bruneau and J.-L. Renaud. Regio- and enantioselective substitutions of cinnamyl chloride by various phenols have been achieved in the presence of a Ru/bisoxazoline ligand\[^{[112]}\].

8 - Michael type additions

In the field of C-C bond creation with simultaneous control of asymmetric centers, several French groups developed innovative methodologies and original chiral ligands. The addition of organometallic derivatives on Michael's acceptors is a fundamental
reaction in organic synthesis allowing the creation of C-C bond in β position of an activated unsaturated substrate. The team of A. Alexakis and J.-F. Normant was the first to describe the enantioselective conjugated addition of organocuprates on enones in the presence of a stoechiometric chiral ligand\cite{113}. This new concept has been quickly developed in catalysis with the conjugated addition of organozinc compound in the presence of chiral copper catalysts, leading to enantiomeric excess higher than 99% on various substrates\cite{114}. Trimethyl aluminium has also been employed in copper-catalyzed Michael addition to various nitroalkenes ee up to 93% using a chiral phosphoramidite. The synthesis of (+)-ibuprofen was achieved with 82% ee\cite{115}.

\[ \text{Et}_2\text{Zn} + \text{CuX cat.} \rightarrow \text{L* cat.} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{P} \]

\[ \text{N} \]

\[ \text{Ph} \]

\[ \text{R} \]

\[ \text{R'} \]

\[ \text{L*} = \]

\[ \text{R}_1 \]

\[ \text{GEA} \]

\[ \text{CuX} \]

\[ \text{Et} \]

\[ \text{R} \]

\[ \text{Ph} \]

\[ \text{O} \]

\[ \text{Me} \]

\[ \text{H} \]

\[ \text{2 mol. % Cu(CH}_3\text{Cn})_4\text{PF}_6 \]

\[ \text{L*} \]

\[ \text{Et}_2\text{O} \]

\[ 1.5 \text{ Me}_3\text{Al} \]

A. Alexakis et al. have also recently described an interesting copper-catalyzed conjugate addition-cyclization in the presence of chiral phosphoramidite cyclic products were obtained with high diastereoselectivity and 94% ee\cite{116}.

\[ \text{Ph} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{OMe} \]

\[ \text{CuX/L*} \]

\[ \text{Et}_2\text{Zn} + \text{Et}_2\text{O} \]

\[ -30^\circ\text{C} \]

\[ \text{r.t.} \]

\[ \text{e.e. up to 92%} \]

A. Alexakis in collaboration of S. Gladiali’s research group have reported the use of P, O-bidendate arylphosphine ligand for the asymmetric copper-catalyzed conjugate addition of dialkylzinc and trialkyl aluminium with the enantiomeric excess reaching 91%. A synthesis of enriched (R)-muscone (77% ee) was achieved using this procedure\cite{117}.

\[ \text{O} \]

\[ \text{2 mol. % Cu(CH}_3\text{Cn})_4\text{PF}_6 \]

\[ \text{L*} \]

\[ \text{Et}_2\text{O} \]

\[ 1.5 \text{ Me}_3\text{Al} \]

\[ \text{L*} = \]

\[ \text{PPh}_2 \]

\[ \text{P(O)} \]

\[ \text{Ph}_2 \]
A. Alexakis and the group of S. Roland in Paris have established that stable chiral N-heterocyclic carbenes (NHC) are particularly efficient in copper conjugate addition to a variety of Michael acceptor. Enantioselectivities reaching 93% were obtained\cite{118}.

\[
\text{O}
\text{L*}, \text{Cu(OAc)}_2 \text{Et}_2\text{Zn} (1.5 \text{ eq.}) \text{Et}_2\text{O}, -78^\circ\text{C}, 16 \text{ h.}, \text{ e.e.} = 93\%
\]

This approach, employing monodentate ligands is now widely used among people working on copper based asymmetric synthesis\cite{119}. The asymmetric addition to $\alpha$-halo enones was also recently described in excellent yields and selectivites\cite{120}. Enantiomerically enriched 2-substituted 1,2-dihydroquinolines were obtained by A. Alexakis and co-workers using enantioselective addition of organolithium reagents to quinoline. 1,2-diamines or sparteine were used as external ligands and enantiomeric excesses up to 79% were obtained\cite{121}.

Asymmetric conjugate addition to $\beta$-disubstituted enones has received increasing interest during the last five years. However, one of the main drawbacks is the lack of reactivity of $\beta$-trisubstituted enones. A. Alexakis and co-workers have designed two efficient systems for the construction of carbon quaternary chiral centers using copper chiral diamino carbene ligands with Grignard reagent and alkylaluminium in the presence of phosphoramidites\cite{122}.

\[
1.2 \text{ R-MgBr, Et}_2\text{O} \quad 3\% \text{ CuOTf}_2, 4\% \text{ ImH}^+ \\
0^\circ \text{ or} -30^\circ\text{C}, 30 \text{ min.} \\
96\% \text{ e.e.} \\
\text{R} = \text{Butyl}
\]

A. Alexakis and co-workers have developed a new method of kinetic resolution of 1,3-cyclohexadiene monoepoxide with Grignard reagents leading to good yields, excellent regioselectivity through $\text{S}_\text{n}\text{2}$ pathway and enantioselectivity up to 90% ee\cite{123}.
The 1,4-addition of organometallic reagents to unsaturated compounds is one of the most versatile reactions in organic synthesis. In that context, it has been shown that trivalent organoboronic acids can efficiently add to unsaturated substrates in the presence of catalytic amount of rhodium catalysts and have proved to be a very good alternative to copper catalysts. J.-P. Genet, V. Michelet and co-workers have shown that the atropoisomeric ligand Digm-Binap\textsuperscript{147} in ethylene glycol gave Michael adducts with excellent enantioselectivities up to 98%. This reaction proceeded with high turn over number (TON 13200)\textsuperscript{124}.

\[
\begin{align*}
\text{O} & \quad \text{L* cat., ethylene glycol} \\
\text{(CH}_2\text{n)} & \quad \text{Rh cat.} \\
\text{RB(OH)_2} & \quad \text{NH}_2\text{Cl} \\
n = 1, 2 & \quad \text{R = Aryl} \\
\text{90-98\% ee}
\end{align*}
\]

The trivalent organoboron reagents have low toxicity, however many organoboranes are not highly stable. In contrast, potassium organotrifluoroborates have shown exceptional stabilities. J.-P. Genet and S. Darses have reported an efficient \textit{in situ} preparation of aryl, alkynyl, alkenyl potassium trifluoroborates\textsuperscript{125}. An asymmetric version of this 1,4-addition of potassium organotrifluoroborates to enones have been described by S. Darses and J.-P. Genet\textsuperscript{126}. Optimization of the conditions revealed that high yields and enantiomeric excesses could be achieved using cationic Rh(cod)\textsubscript{2}PF\textsubscript{6} complexed with atropoisomeric Binap, (R,S)-Josiphos and (R)-MeO-Biphep ligands in a toluene/water mixture as solvent.

\[
\begin{align*}
\text{O} & \quad \text{L* cat.} \\
\text{R = aryl, alken-1-yl} & \quad \text{e.e. up to 98\%} \\
\text{e.} & \quad \text{Cond a) or b)} \\
\text{R} & \quad \text{PPh}_2 \\
\text{MeO} & \quad \text{PCy}_2 \\
\text{MeO} & \quad \text{PPh}_2 \\
\text{MeO} & \quad \text{PPh}_2
\end{align*}
\]

Compared to Miyaura-Hayashi conditions using organoboronic acids derivatives this reaction using organopotassium trifluoroborates generally required lower amounts of the organometallic reagent. Using potassium vinyltrifluoroborate, high yields of vinylated Michael adducts were obtained.
These conditions proved to be general for the functionalization of other Michael acceptors like $\alpha,\beta$-unsaturated amides$^{[127]}$ and esters$^{[128]}$.

$$\begin{align*}
R^1 & \text{EWG} + R^2 \text{BF}_3 & \text{K} & \text{Rh(cod)}_2\text{PF}_6 & 3 \text{ mol}\% \\
(\text{R})\text{-binap} & \text{tol}/\text{H}_2\text{O}, 110^\circ\text{C} & \text{yld: } > 70\% & \text{ee: } 87-99\%
\end{align*}$$

$R^1 = \text{alkyl}$

$R^2 = \text{aryl, alken-1-yl}$

$\text{EWG} = \text{keto, ester, amide}$

9 - **Enolates in enantioselective catalysis**

The enolate enantioselective protonation allows a good control of the asymmetric center $\alpha$ of a carbonyl function. The French team of J.-C. Plaquevent and L. Duhamel first introduced this concept$^{[129]}$.

The team of J. Muzart showed that in the presence of a catalytic amount of palladium, it was possible to generate *in situ* an enolic specie from several substrates, which is protonated in an asymmetric and catalytic way by using an aminoalcohol$^{[130]}$.

The use of ketoesters and enol ethers led to ketones via a deprotection/decarboxylation/enantioselective protonation sequence, when the hydrogenation of $\alpha,\beta$-unsaturated ketones implies 1,4 addition of hydrogen. Previously, this team became famous for the dienols asymmetric protonation produced by Norrish II type photorearrangement of carbonylated $\alpha,\beta$-unsaturated compounds$^{[131]}$.

J.-P. Genet, S. Darses and co-workers have developed recently a new reaction of 1,4-addition/tandem enantioselective protonation allowing a direct access to amino acids$^{[132]}$.

Thus, the Michael type addition of organometallics on dehydroamino esters with chiral rhodium catalyst, generates catalytic species of rhodium enolates that are protonated by 2-methoxyphenol (guaiacol), an achiral proton source. Indeed the conjugate addition of potassium aryl and alkenyl-trifluoroborates to $N$-acylamidoacrylate furnishes a variety of $\alpha$-amino acid derivatives with good enantioselectivities. Under these conditions, boronic acids gave low conversion and modest enantiomeric excesses (40%).
10 - Enantioselective deprotonations

Asymmetric reactions under the influence of a chiral base, were the object of intense research in the last decades. The French team of J.-C. Plaquevent and L. Duhamel for the amino acid deracemization did the first description of the use of a stoechiometric chiral base. The same team also developed the first enantioselective catalytic deprotonation by using a chiral base.

\[
\begin{align*}
\text{NHAc} + R\text{-BF}_3 K & \rightarrow [\text{Rh(cod)}_2][\text{PF}_6] 3 \text{ mol}\% \\
\text{Guaiacol, Tol, 110°C} & \rightarrow R\text{-NHAc} \text{ CO}_2\text{Me} \\
\text{R} & = \text{aryl, alkenyl}
\end{align*}
\]

68–96 % yield
81–90% ee

11 - Asymmetric oxidation reactions

Among the numerous oxidation reactions, the French chemists’ works are mainly distinguished in the field of sulfide asymmetric oxidation into sulfoxides and the enantioselective allylic oxidation. In 1984, the team of H.B. Kagan set up for the first time a system derived from the Sharpless reagent by water addition allowing the asymmetric oxidation of sulfides into chiral sulfoxides, with ee over 90%.

This method developed between 1984 and 1996, has been modified by the firm Astra-Zeneca to produce Esomeprazole, used for the treatment of ulcers. The metallocenes sulfoxides have appeared as excellent ligands for asymmetric catalysis.

The team of M. Fontecave get also interest to the sulfide oxidation into sulfoxide with iron and ruthenium complexes.

The teams of J. Muzart and D. Sinou worked on cupro-catalyzed allylic oxidation of several cycloalkenes. The unsaturated ester are obtained by using enantiopure amino
acids as chiral ligands\textsuperscript{(138)} or fluorated bis(oxazolines)\textsuperscript{(109)}. Oxidation reaction of non functional olefin are also of main interest. The groups of D. Mansuy\textsuperscript{(140)}, B. Meunier\textsuperscript{(141)} and E. Rose\textsuperscript{(142)} have developed ingenious oxidation methods using metallic catalysts derived from salens and porphirins. The asymmetric epoxidation of alkenes was recently reported by the group of Muzart in the presence of a ruthenium\textsuperscript{(143)} or manganese\textsuperscript{(144)} catalysts containing sugar based ligands.

12 - Recycling in asymmetric catalysis

One of the challenge of asymmetric catalysis is the development of new processes allowing easier separation and recycling of the catalyst. A seducing solution for industrial processes is the use of two-phase systems, either liquid / liquid or liquid / solid where the catalyst and the product remain in different phases. One of the approach to make these two-phase systems is to prepare ligands with a strong affinity for one of the phase. The pioneer work of H.B. Kagan on the Diop ligand immobilization on polymer\textsuperscript{(14)}, have undoubtedly inspired the later research in this field. Some contributions were developed in France by the teams of J.-P. Genet, M. Lemaire, D. Sinou and J. Collin in the field of perfluorinated or hydrosoluble ligands for liquid/liquid systems, and also for liquid / solid systems with the preparation of supported ligands. Several families of ligands known for their efficiency in homogeneous C-H, C-C and C-O bonds formations, have been functionalized by hydrosoluble, perfluorinated, polyethylene glycol groups or incorporated in matrices to form new materials. Hydrosoluble sulfonated phosphanes derived from chiral ligands such as Cyclobutanediop, Skewphos, and Chiraphos, associated with rhodium or palladium, allowed the reduction of amino acids and imines precursors and the hydrocarboxylation of styrene derivatives, in two-phase systems\textsuperscript{(145)}.

In the atropoisomeric ligands family, Binap and Mop have been modified (ammonia, guanidinium, perfluorinated group).
These derivatives proved to be efficient for the asymmetric hydrogenation of alkenyl or carbonyl derivatives\textsuperscript{146-148} , allylic substitution\textsuperscript{149} , or allylic oxidation\textsuperscript{145} whether in water, in perfluorinated media, ionic liquids or supercritical CO\textsubscript{2} media. Chiral diamines (and diimines) functionalized by perfluorinated groups have also given good to excellent results in asymmetric hydrogenation by hydride transfer\textsuperscript{150} and promising enantiomeric excesses in allylic substitution and cyclopropanation reaction\textsuperscript{151}. Oxazolines were also efficient for Diels-Alder reactions\textsuperscript{152} , asymmetric allylic oxidation\textsuperscript{103-107} and cyclopropanation reaction\textsuperscript{153}. All these systems often led to the same efficiency and enantioselectivity that the ones obtained with a parent-ligand, but they have the benefit of being recyclable.

An original concept for recycling asymmetric bis(oxazoline)-type catalysts was reported by Schulz’ group\textsuperscript{154}. The formation of a charge-transfer complex between the chiral ligand and trinitrofluorenone that could be precipitated allowed the authors to recycle the catalyst several times in asymmetric Diels-Alder reactions.
Asymmetric C-C, C-O and C-N bond creation

The formation of carbo- and heterocycles is also a very promising research field to produce highly functionalized intermediates. The team of G. Balme\cite{155} has recently described the asymmetric version of the first cyclization of unsaturated derivatives with a Wacker type reaction. The group of D. Sinou has shown that the asymmetric arylation of 2,3-dihydrofuran with aryl triflates could be conducted in water in the presence of Binap and surfactants and afforded the thermodynamic alkene in ee up to 67%\cite{156}.

The formation of C-C bonds has also been well reported by the team of H. B. Kagan, using phase transfer conditions\cite{157}. Functionalized Schiff bases’ enantioselective alkylation, catalyzed by nickel complexes led to mono and disubstituted $\alpha$-amino acids. Other types of polyethylene glycol supported systems also led to the synthesis of $\alpha$-amino acids through glycine alkylation\cite{158}. Other French contributions to C-C bond forming reactions concern polymerization using palladium complexes and bisoxazolines\cite{159}, the cyclopropanation of styrene derivatives with bipyridine or terpyridine type of ligands\cite{160}, the allylation of aldehydes in the presence of an heterogeneous chromium catalyst\cite{161} or the methoxycarbonylation of alkene\cite{162}. The first example of a total axial chirality transfer was reported by the group of M. Malacria in the [2+2+2] cycloaddition of allendiynes\cite{163}. H. B. Kagan and Y. N. Belokon reported the asymmetric addition of TMSCN to benzaldehyde catalyzed by salens. They showed that a mixture of two salen derived $V^V$ and $Ti^{IV}$ complexes resulted in the formation of a mixed complex which exhibited catalytic properties derived from both organometallic species\cite{164}.

The group of J.-P. Genet and V. Michelet have conducted for the first time an asymmetric cycloisomerization of 1,6-ene, leading to a tandem formation of C-C and C-O bonds. Enantiomerically enriched functionalized carbo- and heterocycles were obtained in the presence platinum and a chiral monodentate atropisomeric ligand with ee up to 85%\cite{165}. The group of G. Buono described the first cobalt-catalyzed cycloaddition of cycloheptatriene with alkynes and therefore synthesized functionalized bicyclic derivatives in good yield and ee up to 74%\cite{166}. The formation of C-N bonds was achieved
via Sm-catalyzed reactions\textsuperscript{[167]}. The aza-Michael reactions of $\alpha,\beta$-unsaturated-$N$-acyloxazolidinone afforded the aspartic acid derivatives in ee up to 88%. The same catalyst was also efficient for the enantioselective ring opening of meso-epoxides by aromatic amines leading to amino alcohol derivatives in good yield and ee up to 93%.

14 - Asymmetric amplification and multi-substrate screening

H. B. Kagan and co-workers demonstrated asymmetric amplification in the addition of diethylzinc on aromatic aldehydes\textsuperscript{[168]} and by kinetic resolution using a racemic reagent in amine acetylation\textsuperscript{[168]}. The same group presented the principle of one-pot multi substrate screening which was successfully applied to several types of catalyzed enantioselective reactions\textsuperscript{[169]}.

15 - Conclusion

Asymmetric catalysis is a great tool for organic synthesis. Some of the systems compete with and sometimes match biological systems. It is more and more used worldwide for the production of chiral intermediates. This presentation, which doesn’t pretend to be complete, shows the intense activity of the French laboratories working in collaboration with the industrial world. This catalysis field contributes efficiently to the concept of green chemistry and sustainable development.

References


