Free Design of Chiral Diphosphine Chelating Ligands for Stereoselective Homogeneous Catalysis by Assembling Five-membered Aromatic Heterocycles

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Introduction.

Stereoselective homogeneous catalysis represents a methodology for producing chiral enantiopure compounds from prochiral substrates, which is in perfect alignment with the current direction organic synthesis development is taking today, that is synthetic efficiency, which is mainly related to chemo-, regio- and stereoselectivity, and atom economy. It goes without saying that it is also environmentally benign by design.

The hydrogenation reactions of olefinic and carbonyl (Pro)[1] chiral and configurationally labile chiral substrates are today widely applied even on an industrial scale [1]. Also the single and cascade stereoselective Heck reaction has recently attracted a great deal of attention, thanks to its versatility and efficiency in carbon-carbon bond formation, even though a few regioselectivity problems remain to be solved [2]. Stereoselective hydroformylation and hydrosilylation reactions have also attained sufficient maturity levels [3].

However, it was found that each reaction and substrate requires that steric and electronic properties of the metal complex be tailored according to their needs. Since the steric and electronic properties of the complex (the metal being the same) are determined by the scaffold supporting the chelating groups, it can be easily understood why chemists have designed numerous ligands provided with many highly diversified structures, both in terms of their geometric and electronic properties (Figure 1).

For example, electron-rich, C_2 symmetry diphosphines, like Burk's Alkyl-DuPHOSes are known to be very active as Rh(I) and Ru(II) ligands in functionalized carbon-carbon double bond hydrogenation of enamidoacids [4].

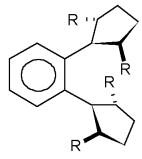
Electron-poor C_2 symmetric bis(diphenylphosphino)-benzamides of *trans*-1,2- diamminocyclohexane introduced by Trost, produce Pd complexes with high enantiofacial selection ability in allylation reactions [5].

Evans' electron-poor C_2 dissymmetric bis-oxazolines give Cu(I) complexes which are very active and enantioselective in olefin cyclopropanation, [6] while their Mg complexes behave successfully in stereoselective Diels-Alder cycloadditions [7].

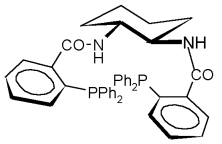
Noyori's BINAP is probably the most heralded C2 symmetry diphosphine ligand and deserves its fame thanks to its great versatility and historical priority [8].

The presence of electronically diverse and poor phosphorus atoms in a C_1 chirotopic environment, like that shown in BINAPHOS, is the best choice in olefin hydroformylation [9].

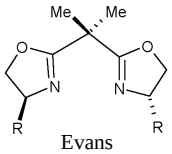
Analogously, Togni's C_1 symmetry ferrocenyl diphosphines, having electronically highly diversified chelating functions, are reported as very efficient ligands in oxo-ester hydrogenation reactions [10].



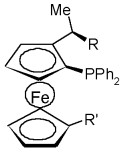
DuPHOS - Burk



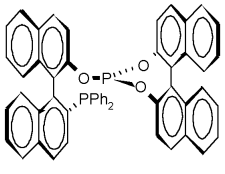
Trost



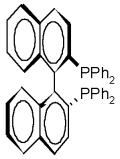
Evans



JosiPHOS - Togni



BINAPHoS - Nozaki, Takaya

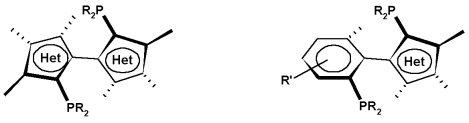


BINAP - Noyori

Figure 1

It is evident that a company working in the field of asymmetric homogeneous catalysis should possess a complete series of different ligands, each one working efficiently in a specific reaction.

The basic idea of the present research was to build C_2 [11] and C_1 [12] symmetry diphosphines having the general formula reported below.



C_2 C_1

The C_2 symmetry ligands are characterized by an atropisomeric biaryl backbone constituted by two interconnected five-membered heteroaromatic rings.

The C_1 symmetry diphosphines are characterized by the presence of an atropisomeric backbone deriving from the junction of a five-membered heteroaromatic ring to a six-membered carbocyclic unit.

The advantages offered by the biheteroaromatic diphosphines having C_2 symmetry are the following:

a) It was possible to accede to a homogeneous series of ligands rather than to a single ligand.

b) They should display, at least in principle, rather similar geometry, but very different electronic properties on their phosphorus atoms. In fact, five-membered aromatic heterocycles can be very electron-rich or electron-poor and it is evident that the electronic availability of the phosphorus groups must be directly influenced by the electronic properties of the supporting heterocycle. Furthermore, given the same heterocycle, the position in which the phosphorus atom is carried is important, since electronic density varies from position to position on the same ring. Thus it was possible to modulate the electronic properties of phosphorus either by changing the supporting heterocycle or its position on it. In accordance with this strategy, a vast series of bis(diphenylphosphino) chelating ligands, endowed with differently tuned phosphine groups, could be prepared.

c) It was possible to vary the steric properties of the ligands either by introducing different substituents on the backbone or by changing the non-stereogenic substituents at phosphorus.

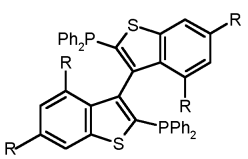
d) The greater synthetic accessibility of biheteroaromatic systems in comparison to those currently available. In fact, the five-membered aromatic heterocycles, unlike carbocyclic systems, can be directly and regioselectively metallated through a simple acid-base process in α position. This reaction was, in principle, very useful both for building the biaryl backbone and for introducing the phosphine groups.

Results and Discussion.

C_2 Symmetry Ligands.

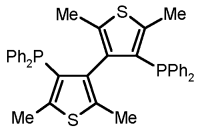
The C_2 symmetry diphosphine ligands, prepared and resolved to an enantiopure state and on a preparative scale so far, are reported in Figure 2.

The acronyms assigned to all the ligands were coined by adding the suffix P, meaning Phosphine, to a contraction of the current name of the heterocyclic system characterizing the backbone, with BI as a prefix, indicating the biaryl nature of the ligand. Symbols of the substituents on the backbone precede the acronym. Thus, the ligands belonging to the bithianaphthene series were called BITIANP and tetraMe-BITIANP, where BITIANP means bi-thianaphthene-phosphine.

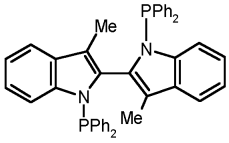


R = H BITIANP

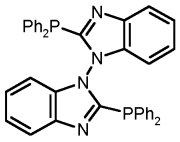
R = Me tetraMe-BITIANP



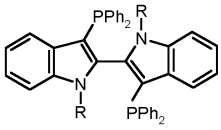
tetraMe-BITIOP



BISCAP

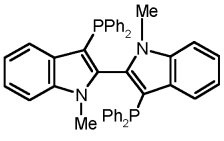


BIMIP



R = CH_2OCH_3 N-HOM-2-BINP

R = CH_2OH N-HOM-2-BINP



N-Me-2-BINP

Figure 2

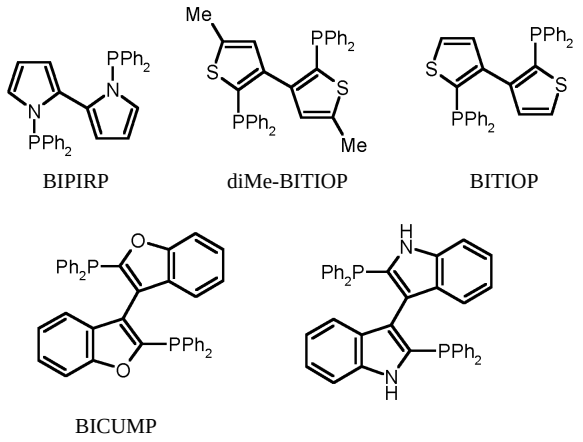


Figure 3

In the case of tetraMe-BITIANP, [13] which is the very first ligand synthesized in the biheteroaromatic series, the two methyl groups in 4 and 4' position had to confer configurational stability to the ligand through considerable steric hindrance to rotation around the interanular bond. However, it was found that this kind of substitution is not necessary to attain configurational stability, since the unsubstituted ligand, BITIANP, does not racemize even at 140 °C in DMF solution.

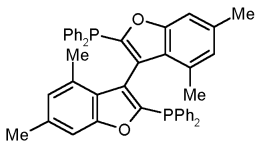
The tetramethyl-bithiophene diphosphine, tetraMe-BITIOP, is the only non-benzo-condensed, configurationally stable, diphosphine prepared so far and is also one of the most successful ligands of the series [14].

BIMIP, having a 1,1'-bibenzimidazole backbone, is the first chiral atropisomeric diphosphine with hindered rotation around a nitrogen-nitrogen bond [15].

The so-called 2-BINPs have a 2,2'-biindole backbone; *N*-Me 2-BINP features *N*-Me-substituted nitrogen atoms, while N-MOM-2-BINP, is protected at nitrogen by the methoxymethyl [16] group. Partial cleavage of this group with perchloric acid gave the hydroxymethyl functionalized diphosphine. Proper functionalization of the hydroxy group of this ligand could make the complex water-soluble or bond the catalyst to a polymer, in order to facilitate recovery of the catalyst once the reaction is terminated.

Skatole is the structural and synthetic precursor of BISCAP, which is the first diphosphine ligand having the phosphorus atom bonded to an aromatic nitrogen atom. It is interesting to note that BISCAP and N-Me-2-BINP, are constitutional isomers, differing only in the exchanged positions of the methyl and phosphine groups on the 2,2'-biindole backbone. They should possess, at least in theory, quite similar geometric features, but very different electronic properties on their phosphorus atoms.

The sole configurationally stable ligand which was not resolved in an enantiopure state on a preparative scale so far is tetraMe-BICUMP. The acronym is derived from Cumaron, which is the former name for benzo[*b*]furan.

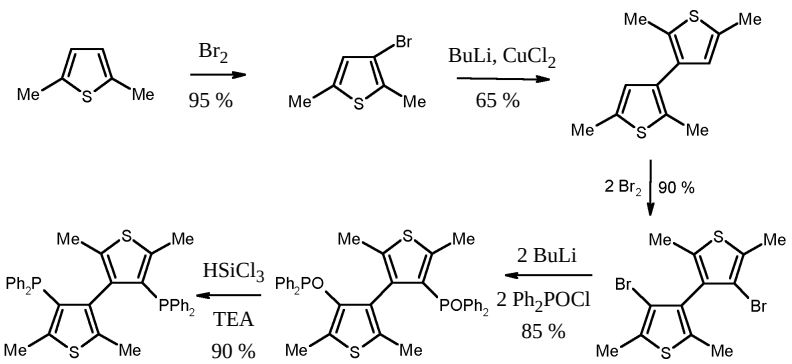


The ligands reported in Figure 3 were found not to be configurationally stable at room temperature.

The 2,2'-dipyrrolic and the 3,3'-bithiophenic systems cannot be configurationally stable, since they are not supplied with the *ortho*-substituents necessary to hinder rotation around the interanular bond. They were prepared to discover how phosphorus electronic availability changed when the heterocyclic system constituting the backbone, the position of the phosphine groups on it, and the substituents were varied.

It was, instead, rather surprising to find that the unsubstituted benzofuran-based system, BICUMP, was not configurationally stable at room temperature, while the analogous benzothiophene-based derivative, as anticipated, was stable at 140 °C.

Scheme 1



This observation fits with the low configurational stability reported for the ligand with a 3,3'-biindole structure [17]. It is evident that the geometric features of the three bithianaphthene-, biindole- and bibenzofuran-based systems must be quite different. Configurational stability decreases in the order along the series.

Synthesis of the C_2 Symmetry Ligands.

As for the synthesis of the ligands, the synthetic route for tetraMe-BITIOP and the 2-BINPS can be taken as a general guide.

Synthesis of tetraMe-BITIOP is carried out in four steps, starting from commercially available 2,5-dimethylthiophene (Scheme 1).

Bromination of 2,5-dimethylthiophene followed by lithiation of the bromoderivative and oxidative coupling of the resulting anion afford the backbone. Dibromination, double α lithiation, followed by quenching of the dianion with two equivalents of diphenyl-phosphinylchloride, produced the diphosphine-oxide in good yields.

Reduction to phosphine is generally carried out after resolution of racemic phosphine-oxide. It is carried out with trichlorosilane, in toluene solution, in the presence of an organic tertiary base as hydrogen chloride acceptor and leads to phosphines in good yields.

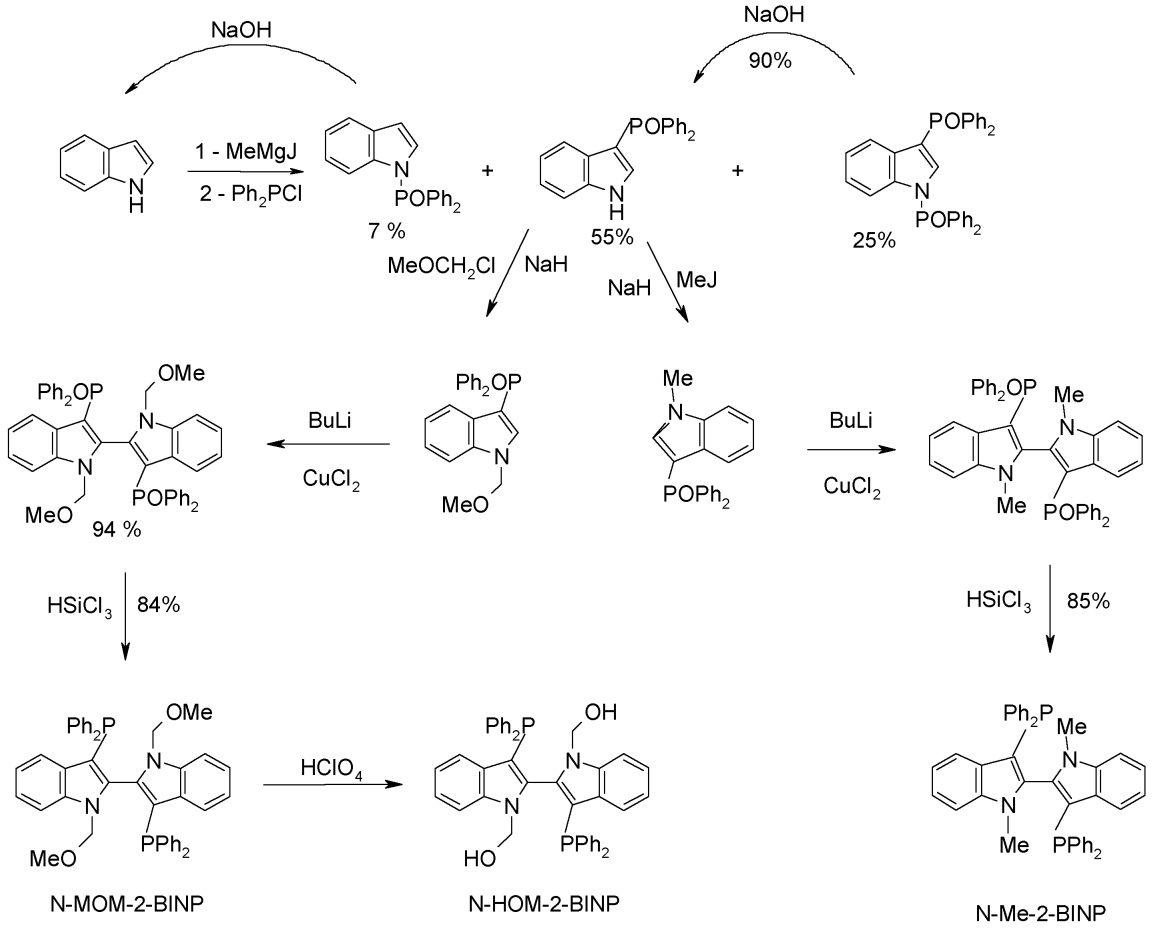
When the resolution process is carried out on racemic diphosphine, the sequence can be relieved of the reduction step by using diphenyl-chlorophosphine in place of diphenyl-phosphinylchloride.

This scheme, in which the first steps are devoted to the formation of the interanular bond, while the phosphorus groups are introduced at the end of the synthesis, is the one we followed most frequently.

The exception to this synthetic strategy is the synthesis of the 2-BINPs, which requires that the sequence be inverted (Scheme 2).

This synthetic scheme takes advantage of the exclusive property of the unsubstituted magnesium indolyl anion to undergo attack by soft electrophilic species, in this case diphenyl-chlorophosphine, in position 3, and not at nitrogen, under special experimental conditions. If either

Scheme 2



diphenyl-phosphinic acid chloride as electrophilic reagent, or sodium as a cation are used, the attack occurs exclusively at nitrogen.

Strong alkaline hydrolysis easily converts the product resulting from concurrent double electrophilic substitution into the mono C-substituted product, which can be obtained in a 75% overall yield. Alkylation at nitrogen is a very simple process and can be effected with different electrophilic species, such as methyl iodide and chloromethoxymethane.

Oxidative coupling of the anions, which are formed by acid-base exchange with butyl lithium, builds the biheteroaromatic scaffold, affording the two diphosphine-oxides in acceptable yields. After resolution, they could be converted into the corresponding racemic phosphines in an about 90% isolation yield, by reaction with trichlorosilane.

The product resulting from partial cleavage of the hydroxymethyl group was easily obtained in an enantiopure state starting from enantiopure N-MOM-2-BINP by reaction with perchloric acid.

Resolution of C_2 Symmetry Ligands.

Large-scale resolution was performed through two known procedures.

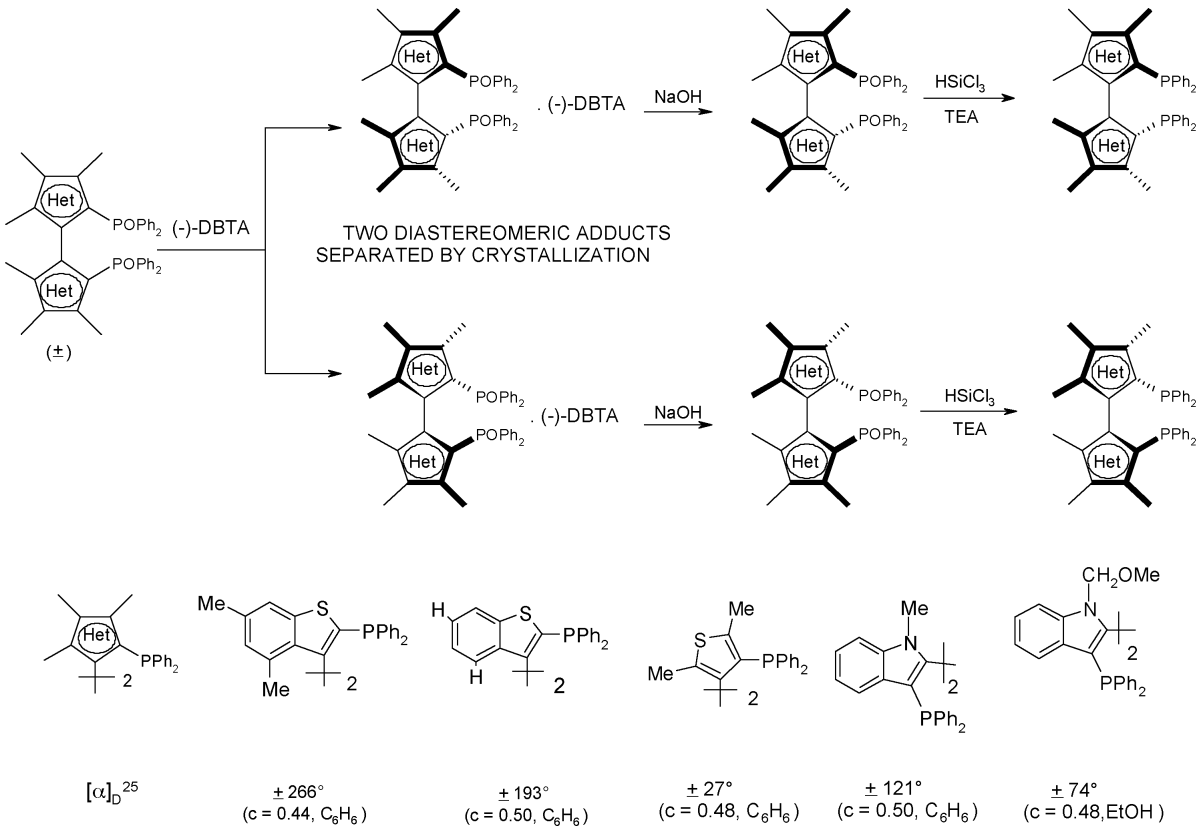
The simplest resolution system involves fractional crystallization of the diastereomeric adducts which are formed by reaction of racemic diphosphine-oxides with optically active acids, generally dibenzoyltartaric acids (Scheme 3). In all cases one crystallization is enough to give diastereomerically pure adducts. Alkaline decomplexation of the adducts afforded enantiopure phosphine-oxides which had to undergo reduction to phosphines with trichlorosilane.

This procedure only works with electron-rich phosphine-oxides. It was followed for resolution of the two bithianaphthene-based ligands, BITIANP and tetraMe-BITIANP, of the bithiophene-based diphosphine, tetraMe-BITIOP, and of the 2-BINPs.

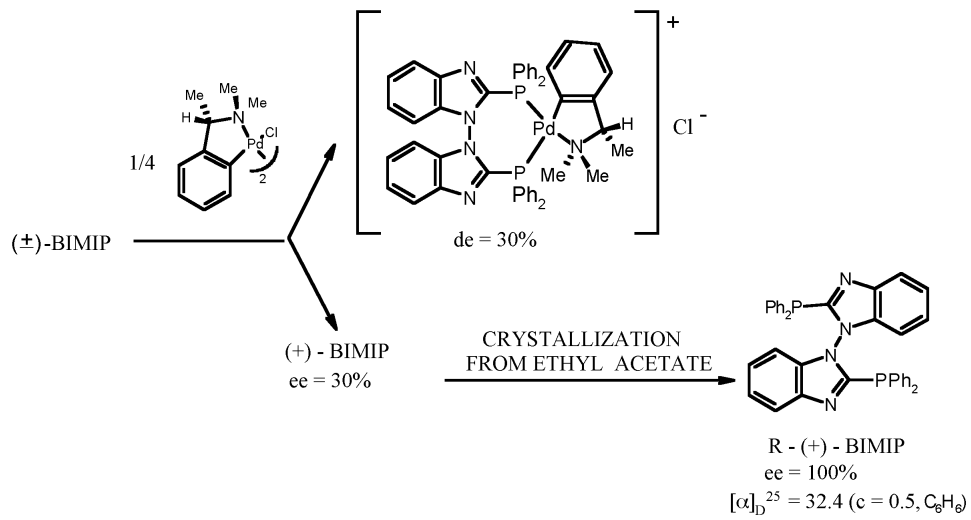
It was not possible to apply this method of resolution to bibenzofuran-, biskatole- and to bibenzimidazole-based diphosphine-oxides, which are too electron-poor to give adducts with carboxylic or sulphonic acids.

In order to resolve these racemates, a technique was utilized which calls for a combination of kinetic resolution and fractional crystallization of the diastereomeric complexes which are formed by reaction of racemic diphosphine with an aminopalladium chiral derivative,

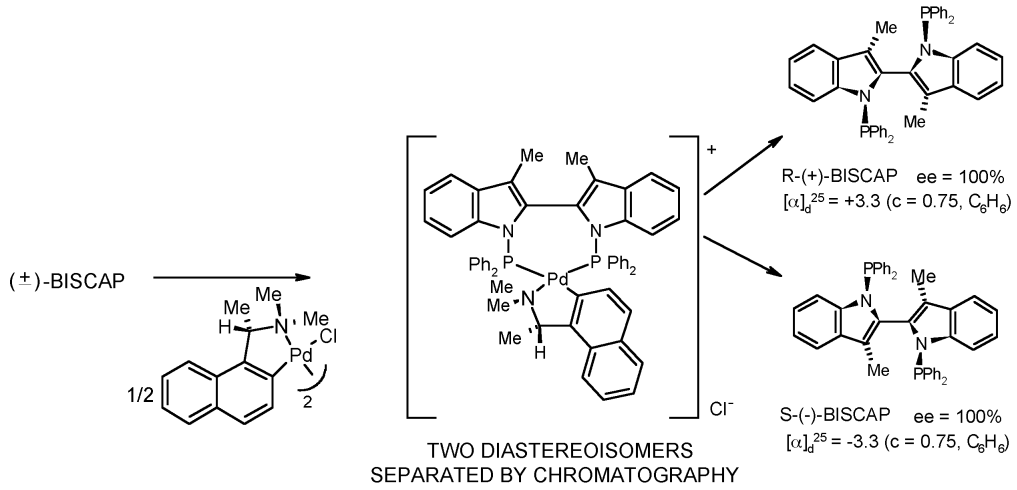
Scheme 3



Scheme 4



Scheme 5



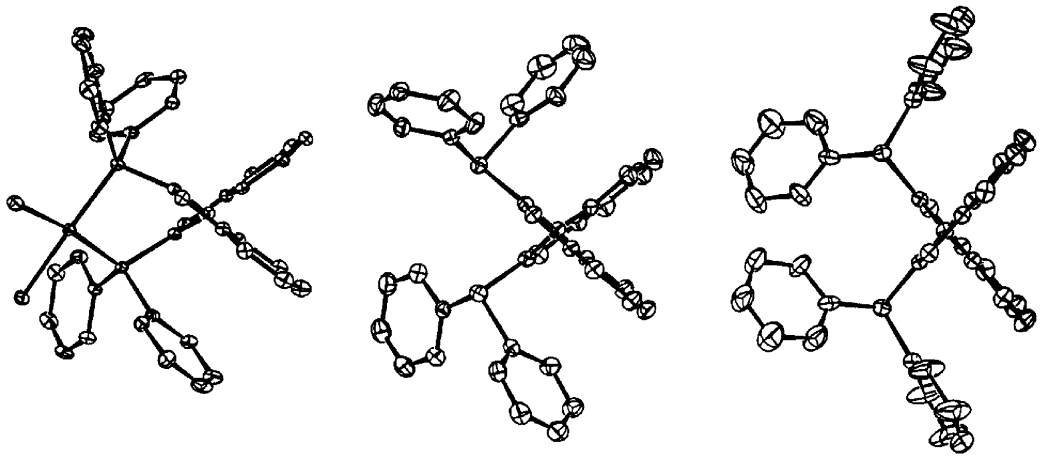
as resolving agent, easily prepared from 1-phenyl-ethylamine, commercially available in both the enantiomerically pure forms.

This resolution scheme, which was followed in the case of BIMIP, which is the electron-poorest ligand of the series, is reported in Scheme 4 [19].

If one fourth of a mole of the chiral complexing reagent for one mole of diphosphine is used, both a 30% diastereomeric enrichment in the complexed, as well as a 30% enantiomeric enrichment in the uncomplexed diphosphine were produced. Once this unbalanced state has been reached, it is easy to accede to enantiopure BIMIP by careful crystallization from ethyl acetate. Less soluble racemate precipitate first, then large crystals of the pure enantiomer separate, which is the dextrorotatory antipode when the complexation reagent has S as absolute configuration.

The same procedure worked successfully also in the case of BISCAP, the skatole-based diphosphine (Scheme 5).

In this case, the aminopalladium chiral complex was prepared starting from a naphthyl-ethylamine whose specific rotatory power value was found definitely higher than that reported in literature [20]. The diastereomeric complexes were separated by column chromatography and their decomplexation was accomplished with sodium cyanide.



(±) -BIMIP-$PdCl_2$ (±) -BIMIP (S) - (+) - BIMIP

Figure 4

Enantiomeric purity of the ligands was checked by chiral hplc, effected on the corresponding phosphine-oxides obtained by their hydrogen peroxide treatment.

Characterization of C_2 Symmetry Ligands.

As for structural characterization, X-ray diffractometric analysis is now available for most of the ligands. X-ray diffractometric analysis was generally performed on the complexes of the ligands with transition metals and, in the case of BIMIP, [18] also on the free ligand and not only on the racemate, but also on the dextrorotatory enantiomer. In this case the absolute *R* configuration was inferred by Flack's method (Figure 4).

X-ray diffractometric analysis has also clearly explained why BITIANP, the ligand having a bithianaphthene backbone, is configurationally stable at 140 °C temperature, while the analogous ligand having a bibenzofuran backbone, BICUMP, is not stable even at room temperature.

Figure 5 illustrates the structures of the dichloropalladium complexes of these two ligands.

The drawings show very different situations: in fact the first has C_2 symmetry, while the second has C_1 symmetry. Assuming that the variations in bond angles and distances are not substantial on passing from the coordinated ligand to the free one, two limit conformations, corresponding to

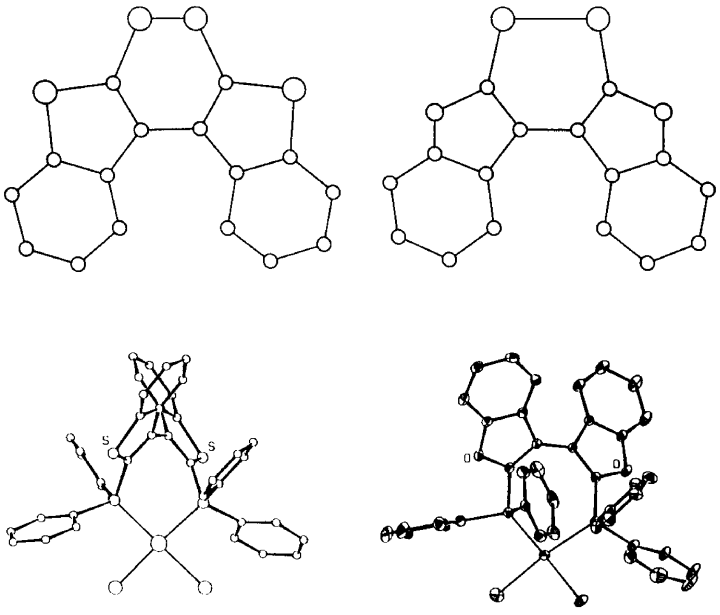


Figure 5

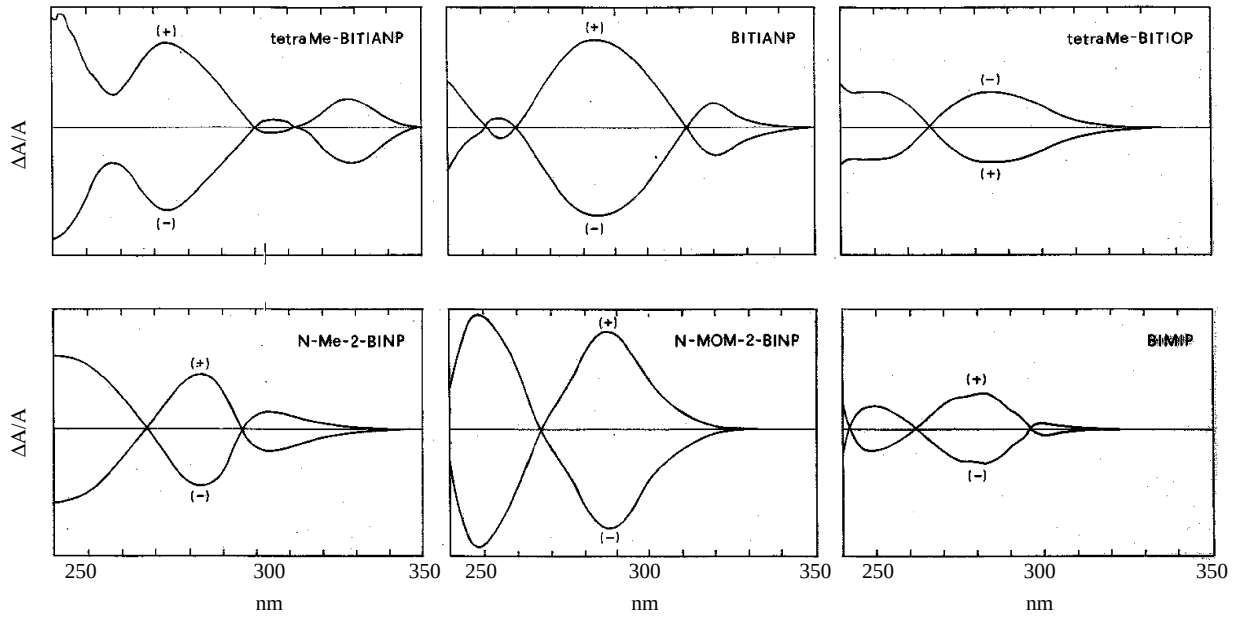


Figure 6

the enantiomerization transition states of the ligands can be computed. Only the syn-periplanar conformation for both of the ligands is reported in the figure, but the same observations are also valid for the anti-periplanar arrangements. Contrary to what occurs in BITIANP, both these conformations lead to such great phosphorus-phosphorus and peri carbon-carbon distances in the analogous oxygenated structures that rotation can be expected.

As for the chiroptical properties of the ligands isolated in an enantiomerically pure state, the Circular Dicroism curves of six of them are reported in Figure 6.

The enantiomers which exhibit curves with similar shape should have the same absolute configuration.

Configurational assignment to enantiopure ligands was made by comparison of their CD curves with those shown by (+)- and (−)-BIMIP, for which the absolute configuration was known from X-ray analysis. All the *R* enantiomers are dextrorotatory at 589 nm, except for tetraMe-BITIOP, the sole non-benzocondensed diphosphine, whose *R* enantiomer is levorotatory at this wavelength. These assignments were found to be in agreement with the stereoselection results.

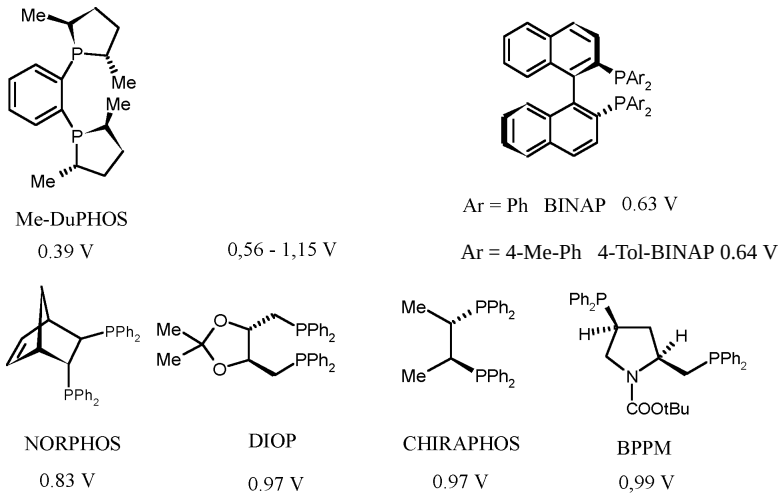


Figure 7

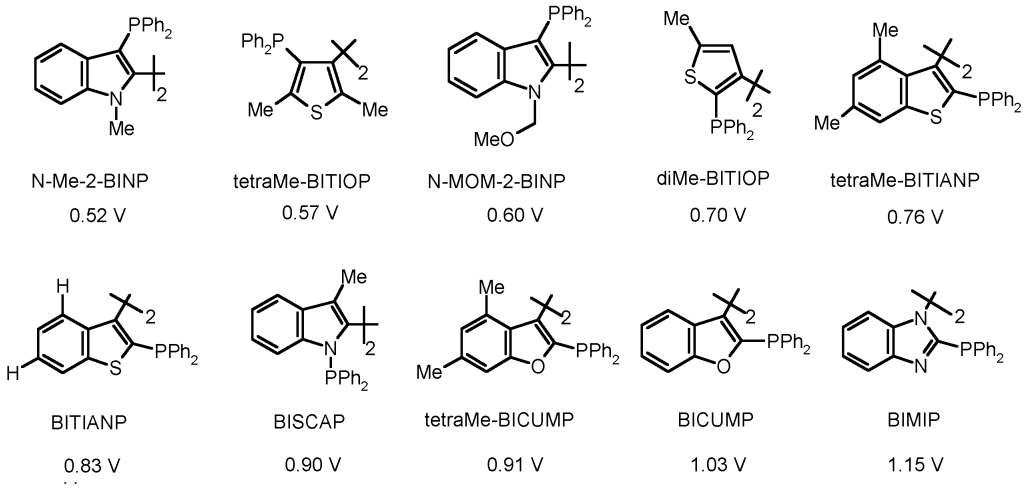


Figure 8

As for the evaluation of the electronic properties of the ligands, from the various parameters available, the electrochemical oxidative potential, determined by cyclic voltammetry, was used. This parameter is related to the energy required to remove an electron from the system, and, in the case of the biheteroaromatic diphosphines, the electron is usually removed from the phosphorus atom. The higher its value is, the more electron-poor the diphosphine. The lower its value, the easier the mono-electron abstraction and the more electron-rich the phosphine.

The electrochemical oxidative potentials found for the most popular commercially available chiral diphosphines are reported in Figure 7.

Methyl-DUPHOS is the most electron-rich diphosphine, as expected, considering that it is the only ligand carrying dialkyl-substituted phosphine groups. All the other ligands are diphenylphosphino compounds and exhibit rather electron-poor phosphorus atoms. The group of the bis(diphenylphosphino)-biheteroaryls covers a rather ample field, ranging from the 0.52 V of the most electron-rich to the 1.15 V of the most electron-poor diphosphine. The detailed situation of this group is reported in Figure 8.

Upon analysis of this data, it is evident that both the electronic availability of the supporting heterocyclic system and the electronic density of the position where the diphenylphosphino group is carried are crucial. In fact, the

Table 1

Enantioselective hydrogenation of (*E*)-2-Methyl-2-propenoic acid (tiglic acid)

Catalyst	S/C	H_2 Kg/cm^2	Time h	% ee	Conf	Yield
[Ru((*S*)-tetraMe-BITIANP))(p.cym)l]l	500	10	88	92	S	quant
[Ru((*S*)-BINAP(C_6H_6)Cl]BF_4	1000	4	92	89	S	89
[Ru((*R*)-tetraMe-BITIOP(Me-allyl)$_2$]	3000	10	11	94	R	quant

T = 25 °C

Table 2

Enantioselective hydrogenation of Methyl Phenylglyoxlate Enantioselective hydrogenation of Benzoylacetate

Catalyst	S/C	H_2 Kg/cm^2	Temp °C	Time h	% ee	Conf	Yield
[RuCl((*S*)-BINAP)(C_6H_6)]Cl aq HBF_4	540	100	30	99	89	S	quant
[RuCl((*S*)-tetraMe-BITIOP)(C_6H_6)]Cl aq HBF_4	520	100	25	72	90	S	quant
[RuCl((*R*)-N-Me-2-BINP)(C_6H_6)]Cl aq HBF_4	200	100	30	26	89	R	quant

Table 3

Enantioselective Hydrogenation of Benzylacetate

Catalyst	S/C	H_2 Kg/cm^2	Temp °C	Time h	% ee	Conf	Yield
[$RuCl_2$(*R*)-tetraMe-BITIANP)(dmf)]$_n$	1000	100	25	100	90	S	92
[$RuCl_2$(*R*)-BINAP)(dmf)]$_n$	760	91	30	106	85	S	quant
[$RuCl_2$(*R*)-N-MOM-2-BINP)(C_6H_6)]	250	100	45	3	93	S	98
[$RuCl_2$(*S*)-N-Me-2-BINP)(dmf)]$_n$	251	100	45	0.8	93	R	quant

Table 4

Enantioselective Hydrogenation of Methyl Pyruvate

Catalyst	S/C	H_2 Kg/cm^2	Temp °C	Time h	% ee	Conf	Yield
[$RuCl_2$(*S*)-N-tetraMe-BITIANP)(dmf)]$_n$	600	100	25	100	8	S	quant
[RuCl((*S*)-BINAP)(C_6H_6)]Cl	580	100	30	95	88	S	quant

Table 5

Enantioselective Hydrogenation of Ethyl Acetoacetate

Catalyst	S/C	H_2 Kg/cm^2	Temp °C	Time h	% ee	Conf	Yield
[$RuCl_2$((*S*)-BITIANP)(dmf)]$_2$	1000	100	70	2	>99	S	91
[$RuCl_2$((*R*)-BINAP)(dmf)]$_2$	1950	100	100	0.5	98	R	97
[$RuCl_2$((*R*)-tetraMe-BITIOP)(dmf)]$_2$	1000	100	70	2	97	R	quant
[$RuCl_2$((*S*)-N-Me-2-BINP)(dmf)]$_2$	1114	50	10	30	95	S	quant

most electron-rich diphosphine is N-Me-2-BINP, where the phosphorus resides in the position having the highest electronic density of the electron-excessive indole ring. BISCAP, which is a constitutional isomer of it, differing only in the exchanged positions of the methyl and phosphine groups on the same 2,2'-biindole backbone, is a rather electron-poor ligand. Electronic demand progressively increases from indole to thiophene, to thianaphthene and then to benzofuran with parallel increases in oxidative potential. BIMIP is, as expected, the most electron deficient ligand of the series. The influence of the position of the phosphorus atom on the same heterocycle is also clearly demonstrated in the series of thiophene-based diphosphines. The phosphine groups located in α position are definitely more electron-poor than those bonded to β carbons. The electron releasing effect of methyl groups also works along the expected lines.

Catalytic Experiments.

The reactions which were studied most in depth are the hydrogenation of prostereogenic functionalized olefinic and carbonyl double bonds and the Heck reaction. Tiglic acid was used to test the activity in carbon-carbon double bond reduction and α-ketoesters and β-ketoesters to test activity in carbon-oxygen double bond hydrogenation.

Hydrogenation Reactions.

A selection of the most significant data is reported in the following tables.

Data regarding industrial application of tetraMe-BITIOP in substituted acrylic acid and β-ketoester hydrogenation are summarized in Figure 9. These data refer to hydrogenation procedures developed by CHEMI, which is the company who acquired all the patents on the biheteroaromatic diphosphines from the University of Milan.

These reactions are currently carried in CHEMI's plant on three hundred kilogram batches, under moderate hydrogen pressure, with very high substrate/catalyst ratios, very high substrate concentration in the first example and no solvent at all in the second case.

Chemical yields, enantiomeric excesses and reaction rates are in any case highly satisfactory.

To gain quantitative evidence of the influence of the electronic availability of phosphorus on kinetics, we considered a comparison of kinetic data drawn from the hydrogenation of ethyl acetoacetate using different biheteroaromatic diphosphines and BINAP as Ru ligands, under the same experimental conditions.

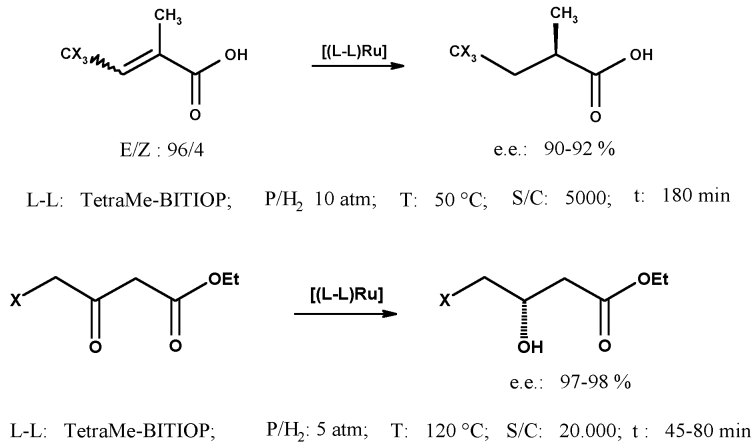
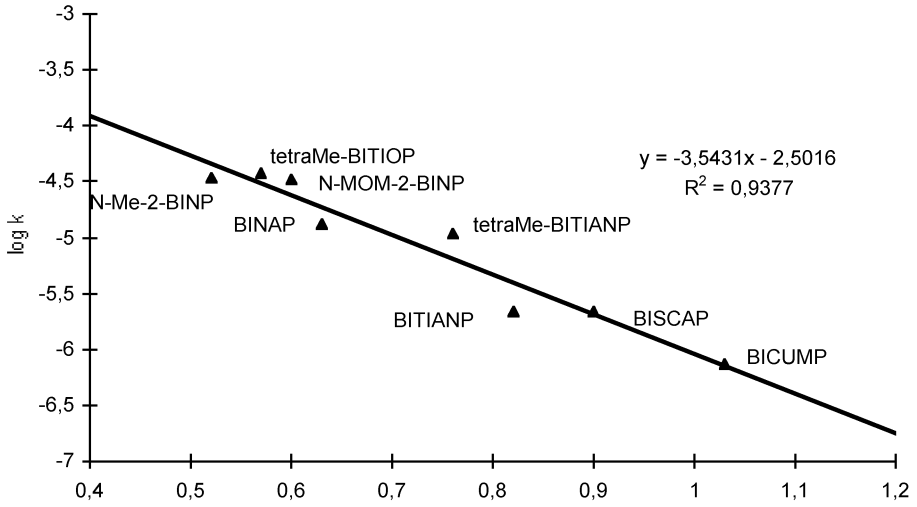


Figure 9



Kinetic experiments demonstrated that the reaction rate always follows a first-order kinetic in all cases, suggesting a common reaction mechanism, thus making the comparison of kinetic data acceptable. Furthermore, we found that rate constants can differ by as much as nearly two orders of magnitude.

We have demonstrated that this outstanding difference in reaction rate is mainly due to the different electronic properties of the ligand and we were able to give quantitative demonstration of that.

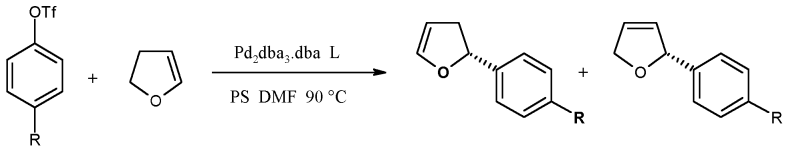
We found a strong linear relationship between the electrochemical oxidative potential values of the ligands and the catalytic activity of their ruthenium complexes, expressed in terms of kinetic constant logarithm [16]. This relationship is fully comparable to a Hammet-type relationship, valid since the activity of systems with different electronic properties and rather similar geometry is being compared. In the case in point, electron-rich phosphines facilitate the reaction.

It could be inferred that the ratios between the activation energies involved in electrochemical mono-electron abstraction from the phosphine group of the free ligands are maintained at the level of their Ru-complexes in the rate-determining step of the hydrogenation reaction of acetoacetic ester.

Heck Reaction.

An opposite situation was found in the case of the Heck-Cassar reaction.

The results reported here are the fruit of a cooperation with prof. L. Tietze. Research was carried out at Göttingen University.



R	time (h)	LIGAND	Yields	ee %	Yields
H	18	(R)-BINAP	67	96	28
H	18	(R)-BITIANP	84	91	-
H	72	(S)-tetraMe-BITIOP	58	20	42
Cl_2, OMe, CN, COMe	18-24	(R)-BITIANP	84-93	90-99	-

YIELD 76%
ee 86%

Preliminary experiments were devoted to check the enantioselection ability of our biheteroaromatic ligands in intermolecular Heck reaction [21].

Dihydrofuran and aryl- or alkenyltriflates were used, since these are the substrates in standard use for this kind of tests.

BITIANP, a moderately electron-poor, bithianaphthene-based ligand, and tetraMe-BITIOP, the electron-rich, bithiophene-based diphosphine were used, in parallel with BINAP.

The enantioselection data obtained with BITIANP are comparable to those obtained when using BINAP. It is worth noting that our ligand orients the reaction path toward the formation of the rearranged product in an exclusive way, while BINAP affords a mixture of both possible constitutional isomers.

On the contrary, electron-rich tetraMe-BITIOP behaves poorly in these reactions under many respects, such as regio- and stereo-selection ability and kinetic efficiency.

Interesting results have been obtained also in intramolecular Heck reaction tests [22].

In this case, the best enentiomeric excesses (ees) are obtained when tetraMe-BITIOP is employed, while very modest results follow the use of BITIANP, just the opposite of what seen before.

It is worth noting, however, that electron-poor phosphines produce the most active catalysts from a kinetic point of view.

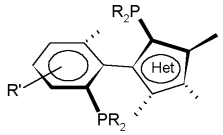
Electronic availability at phosphorus, evaluated again through the electrochemical oxidative potential, increases from top to bottom of this five-membered series and reaction rate undergoes a parallel decrease along the sequence.

Interestingly, the most enantioselective catalyst is also the kinetically less efficient one.

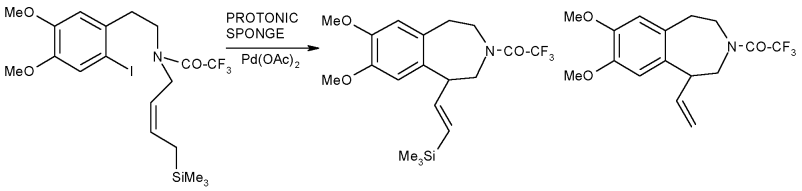
We are strongly convinced that, in a homogeneous series of chelating ligands, the electron-donor capacity of the ligand mainly influences its kinetic behavior, while its shape and geometric properties mainly influence its stereoselection ability.

C_1 Symmetry Ligands.

Recent developments in research are aimed at preparation of diphosphine ligands that are slightly more economical than those currently available. One must remember that BINAP, to cite one ligand in production for more than 15 years, still costs about $ 20,000 per kilogram and that Me-DUPHOS costs five times as much; even tetraMe-BITIOP, which is the ligand that Chemi uses most, though definitely less expensive than BINAP, has a rather high production cost. We attribute such high costs to the problems connected with the construction of C_2 symmetry systems. Thus the new project was to construct C_1 symmetry ligands, having the general structure reported below, without, however, giving up the advantages offered by five-membered aromatic heterocycles.



The project is again very simple: to construct ligands with an atropisomeric backbone, featuring a mixed structure, that is, derived from the interconnection of a five-membered heterocyclic system and a six-membered aromatic carbocyclic system.



LIGAND	t (h)	T (°C)	yield	% ee	yield	% ee
PPh_3	6	80	4		70	0
BITIANP	19	80	2	-	42	20
BINAP	40	80	7	18	72	64
MeO-BIPHEP	65	80	15	5	42	25
tetraMe-BITIOP	58	80	-	-	71	92

The advantages of this design are evident:

a) From a synthetic point of view, synthesis is reduced to that of an aryl heterocycle.

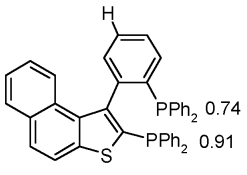
b) The variety of systems imaginable belonging to this new class of ligands is countless.

c) The advantages of being able to modulate the electronic availability of the two phosphine groups are maintained. The strategies for modulating electronic availability of the phosphorus bonded to the heterocyclic moiety are the same as those discussed before for C_2 symmetry systems. In regards to the phosphine group bonded to the aryl ring, it is possible to introduce suitable substituents on it.

d) Since the two phosphine groups are introduced on the backbone through different methodologies (acid-base lithiation on the heterocyclic ring and transmetallation on the carbocyclic ring), it becomes easy to introduce two differently substituted phosphine groups on the two rings.

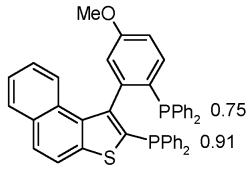
Without a doubt, the disadvantages of constitutional heterotopism of the two phosphine groups remains. We contemplated regulation of the regioselectivity of the approach of the prochiral substrate to the catalytic species in two different ways: by clearly differentiating the electronic properties of the two phosphine groups and by clearly differentiating their steric environment.

The first two ligand in this series obtained in an enantiopure state, on a preparative scale, are reported below [23]. In regards to the electronic properties of the two phosphorus atoms, cyclic voltammetry supplies interesting data. The oxidation peaks were found, at 0.74 V and 0.91 V, related to the phosphine group on the phenyl and on the heterocyclic rings respectively.



H.L

$[\alpha]_D^{25}$ = 172 (c = 0.38, C_6H_6)



MeO.L

$[\alpha]_D^{25}$ = 167 (c = 0.30, C_6H_6)

These values confirm that the two phosphorus atoms have different donicity, as desired, even though it was rather surprising to find that the methoxy group on the carbocyclic unit has no effect on the electrochemical oxidative potential of the phosphine group in the *para* position.

The syntheses of these ligands, reported in Scheme 6, are very simple and utilize commercially-available and inexpensive starting materials, like β-naphthalene thiol and *ortho*-bromoacetophenones; α-bromination of the acetophenones, followed by condensation with sodium naphthalenethiolate are very simple reactions. Cyclodehydration produces the backbone. Double metallation, followed by reaction with two equivalents of diphenylphosphinyl chloride, affords racemic diphosphine-oxides in satisfactory overall yields.

Resolution is also quite simple and was performed, as usual, at the level of the phosphine-oxides, through fractional crystallization of the diastereomeric adducts with optically active dibenzoyltartaric acids.

The stereoselection data obtained in the hydrogenation reactions, performed on keto-esters as reference substrates, are reported in Table 6. The preliminary results of enantioselection are not always as high as previously seen with C_2 symmetry ligands, but they are nonetheless, quite interesting.

On the basis of these data, when considering that a preliminary cost estimate for these ligands is less than one fifth of BINAP's cost, it appears that these ligand could already be employed either in many reactions in which the required enantiomeric excess is not 100%, or when the enantiomeric excess can be increased through simple techniques, like crystallization.

Scheme 6

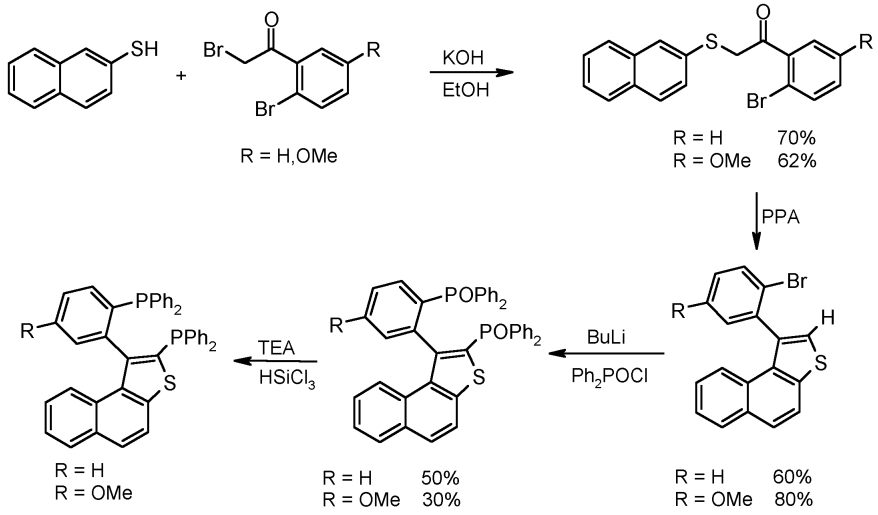


Table 6

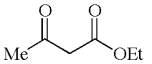
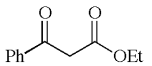
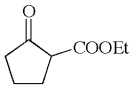
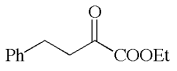
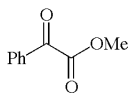
Substrate	Catalyst	S/C	P Atm	Temp °C	Time h	% ee	Conf
	[(+)-H.L•$RuCl_2$(dmf)]$_n$	1289	100	40	3.5	96	*R*
	[(+)-MeO.L•$RuCl_2$(dmf)]$_n$	1300	100	25	-	>99.9	-
	[(+)-H.L $RuCl_2$(dmf))]$_n$	1240	100	55	6	73	*S*
	[(+)-MeO.L•$RuCl_2$(dmf)]$_n$	1240	100	55	3.75	70	-
	[(-)-H.L•$RuCl_2$(dmf)]$_n$	1000	100	40	8	97 (de = 74%)	1*S*, 2*S*
	[(-)-H.L•$RuCl(C_6H_6)$]Cl (HBF_4)	1243	100	50	24	81	*S*
	[(-)-H.L•$RuCl(C_6H_6)$]Cl (HBF_4)	445	100	50	30	93	*S*

Figure 10 illustrates some other ligands we have synthesized in this series, which are currently in the resolution stage. They are naphthothiophene-, naphtho- and benzofuran-, and indole-based systems and express the structural potential connected with this class of ligands.

Conclusions.

Two very modular class of C_2 and C_1diphosphine atropisomeric chelating ligands were designed. The most interesting features of these ligands are related to the possibility of modulating the electronic properties at phosphorus through the inherent electronic availability of five-membered aromatic heterocycles constituting the backbone. This modular design is very useful to tailor the structure of the ligand according to the requirements imposed by the reaction typology and by the substrate.

Evidence was given for the strong relationship existing between the electronic availability at phosphorus of the free ligands and the kinetic behavior of their metal complexes when employed as homogeneous chiral

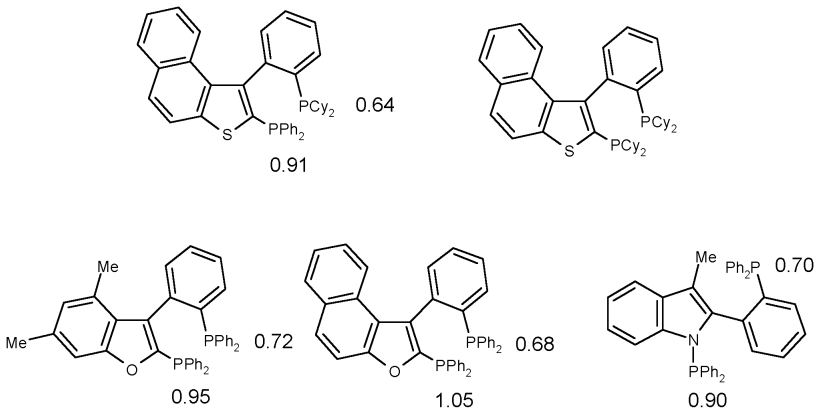


Figure 10

catalysts; the reaction rate of oxo-ester hydrogenation is enhanced by metal complexes produced from electron-rich diphosphines, while enantioselective Heck reaction prefers catalysts originating from electron-poor ligands.

Acknowledgement.

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