Electronic Tuning in C_1-Symmetric Chelating Diphosphane Ligands Supported on Stereogenic Aryl–Heteroaryl Templates

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Abstract: The syntheses of a wide range of novel C_1-symmetric chelating diphosphanes with stereogenic axes are reported. These ligands feature identical or different phosphanyl groups supported on diverse atropisomeric templates based on the interconnection of five-membered heteroaromatic and six-membered carbocyclic rings. Easy synthetic accessibility, independent tunability of the electronic and steric properties of the two phosphane donors, the low cost and the good stereoselection ability of some of them obtained in an enantiopure state are the main advantageous features of this class of ligands.

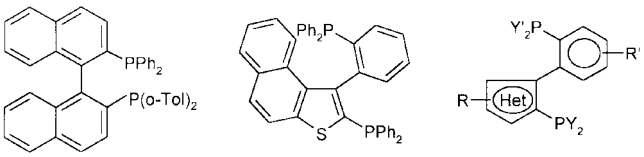
Key words: diphosphane ligands, heterocyclic diphosphanes, chiral ligands, C_1 ligands, asymmetric hydrogenation

Introduction

For a long time C_2-symmetry has been assumed to be a prerequisite for a chiral ligand to provide high enantioselectivity levels in asymmetric catalysis.[1] For this reason, and for the easier modeling of the ligands and of the reaction intermediates, until recently ligand design for asymmetric hydrogenation has been largely dominated by C_2-symmetric diphosphanes.[2] However, it has been pointed out[3] that C_2-symmetry does not necessarily need to be maintained in the relevant complexes and that the originally homotopic P-donors can play different roles in the catalytic cycle. Thus, ligand asymmetry may result in an advantage rather than a drawback in a stereoselective reaction and the stereochemical outcome of the process basically depends upon effective matching between the catalytic complex and the substrate, which is ultimately modulated by the steric and the electronic properties of the ligand. Thus, it is not a paradox that C_2-symmetric controllers are highly efficient since they produce C_1-symmetric catalysts, which are, in turn, the enantioselective origin for C_1-symmetric products.

This conclusion finds support in the results obtained with diphosphanes carrying constitutionally heterotopic chelating functions; the success of the ferrocenyl diphosphanes of the JOSIPHOS family is probably one of the most illustrative of this trend and has contributed to drawing attention to the aspects of asymmetric catalysis pertinent to the design of new ligands.[4] Also, it should be noted that metalloenzymes, which are all devoid of C_2-symmetry, are nevertheless highly efficient in the chirality transfer processes.

Atropisomeric chelating diphosphanes are among the most efficient chiral chelating ligands for asymmetric hydrogenation. The stereogenic axial cores of these derivatives are in general C_2-symmetric and they are built up by introducing the chelating phosphorus functions onto homotopic sites of a C_2-symmetric scaffold.[5] Atropisomeric C_1-symmetric diphosphanes have been prepared in the biphenyl[6] and in the binaphthyl families (BINAPP', Figure 1),[7] by stepwise introduction of two non equivalent phosphanyl groups. The BINAPP' ligand is a chiral inducer more efficient than the relevant C_2-symmetric counterpart, BINAP, in the Rh-catalyzed asymmetric hydrogenation of acrylic acid derivatives and in Pd-catalyzed allylic alkylation.[7] It should be stressed that the different substitution pattern at the phosphorus termini does not affect symmetry only, but induces substantial changes in the electronic properties and in the steric enviroment at the donor center as well. Thus, the performances of BINAPP' is the result of both of these effects which cannot be independently considered.



BINAPP' **1a**

Figure 1 Chemical structures of BINAPP' and new atropisomeric chelating diphosphanes

We have recently described the synthesis of the ligand **1a** featuring two identical constitutionally heterotopic phosphanyl substituents.[8] This was obtained by attaching two diphenylphosphane groups onto a C_1-symmetric scaffold constituted by a 3-phenylnaphtho[2,1-*b*]thiophene backbone (Figure 1).

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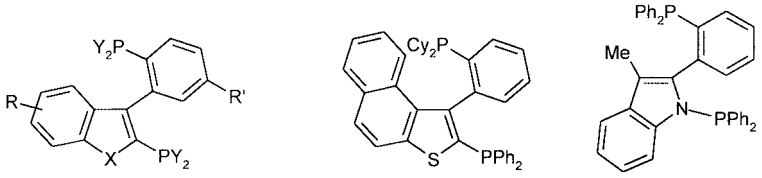
Ligand **1a** is the first diphosphane featuring a C_1-symmetric atropisomeric scaffold and it is the prototype of a new class of chiral ligands possessing the general structure schematically represented in Figure 1, in which the electronic properties of the donor centers are modulated by the inherently differentiated electronic demand or supply of the supporting heteroaromatic ring and of the phenyl system onto which suitable substituents can easily be introduced. This electronic fine-tuning possibility can be fruitfully combined with very easy synthetic accesses, which are merely reduced to the preparation of aryl substituted five-membered aromatic heterocycles. Furthermore, since the two phosphanyl groups are introduced through different methodologies (acid-base lithiation on the heterocyclic ring and transmetalation on the carbocyclic ring), it becomes easy to introduce two differently substituted phosphane groups on the two rings.

Since, the stereoselectivity obtained with ligand **1a** in asymmetric catalysis was often similar to those obtained with C_2-symmetric analogues,[8] we decided to pursue further efforts to increase the variety of the atropisomeric C_1-symmetric scaffolds for chelating diphosphanes. The new ligands described in this paper are reported in Figure 2, but it is evident that the choice for new scaffolds is unlimited.

They are naphthothiophene-, naphtho- and benzofuran- and indole-based ligands and express the structural potential connected with this class of ligands. Diphosphane **1b** was obtained in an enantiopure state and submitted to preliminary catalysis tests as a ligand of Ru (II) in the stereoselective hydrogenation of prostereogenic ketonic functions.

Synthesis of the Ligands

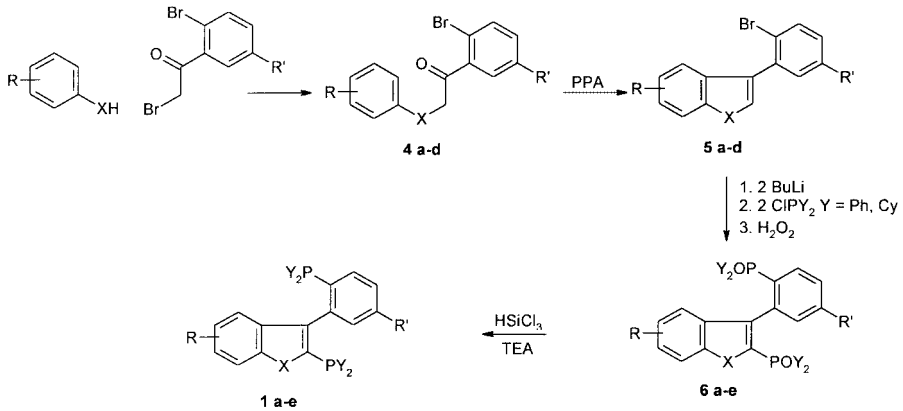
The synthetic approach to the heterocyclic-carbocyclic backbone of all the ligands is very simple; according to Scheme 1, syntheses of **1a**–**e** were easily achieved starting from inexpensive, commercially available, β-thionaphthol, β-naphthol or 3,5-dimethylphenol and the suitable ω,2-dibromoacetophenones. Compounds **4a**–**d** resulting from the nucleophilic substitution were cyclized to the corresponding arylthiophenes **5a**,**b** or furans **5c**,**d** in acid-



1b: X = S R' = OMe R = 3,4-benzo Y = Ph
1c: X = O R' = H R = 3,4-benzo Y = Ph
1d: X = O R' = H R = 3,5-diMe Y = Ph
1e: X = S R' = H R = 3,4-benzo Y = Cy

2 **3**

Figure 2 Chemical structures of new atropisomeric chelating diphosphanes synthesized in the present study



a: X = S R = 3,4-benzo R' = H Y = Ph
b: X = S R = 3,4-benzo R' = OMe Y = Ph
c: X = O R = 3,4-benzo R' = H Y = Ph
d: X = O R = 3,5-diMe R' = H Y = Ph
e: X = S R = 3,4-benzo R' = H Y = Cy

Scheme 1

ic medium. Introduction of the phosphinyl groups in **6a**–**e** was performed by lithiation of the α-position of the thianaphthene or benzofuran system and simultaneous transmetalation of the *ortho*-bromine atom with butyllithium, followed by quenching of the bis-anion with diphenyl- or dicyclohexylchlorophosphane and oxidation in situ with hydrogen peroxide. Reduction with trichlorosilane of diphosphine oxides **6a**–**e** produced the corresponding diphosphanes **1a**–**e** in high yields.

For the preparation of **2** (Scheme 2), the 3-(2-bromophenyl)naphtho[2,1-*b*]thiophene (**5a**)[8] was selectively metalated with LDA in the α-position of the thiophene ring and the resulting anion quenched with chlorodiphenylphosphane and the crude product oxidized to the 3-(*o*-bromophenyl)-2-(diphenylphosphinyl)naphthothiophene (**7**) in 82% isolated yields. Introduction of the dicyclohexylphosphinic group on the aromatic carbocyclic ring was performed by lithiation with *t*-BuLi, followed by quenching of the resulting anion with chlorodicyclohexylphosphane. Oxidation of the reaction mixture, followed by column chromatography allowed isolation of 3-(2-dicyclohexylphosphinyl)phenyl-2-(diphenylphosphinyl)[2.1-*b*]naphthothiophene (**8**) in 74% yield. Reduction with trichlorosilane of diphosphine oxide **8** produced the corresponding diphosphane **2** in satisfactory yields (Scheme 2).

Straightforward is also the synthesis of the indole-based ligand **3** involving a simple Fischer indolization to produce the backbone. Double metalation followed by reaction with two equivalents of diphenylphosphinyl chloride affords diphosphine oxide **10**, which was reduced to diphosphane **3** in the usual way (Scheme 3).

Evaluation of the Electronic Availability of the Ligands at Phosphorus

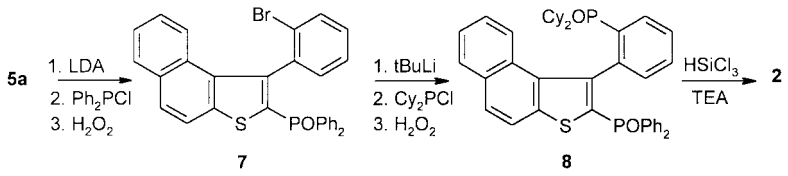
We evaluated the different electronic properties of the phosphanyl groups of all the ligands by voltammetry[9] through their electrochemical oxidative potential E°. Only in the case of diphosphane **2** were two oxidation peaks found, while in all the others, voltammetric experiments showed only one peak, since degradative evolution of the radical cation took place before a further electron could be abstracted from the second phosphane group. The peak is attributable to the more electron-rich phosphane group, namely the one located on the phenyl ring. In these cases, the oxidation potential values of the diphenylphosphane groups on the heterocyclic moieties were inferred from those shown by structurally similar monophosphanes.[9a] The electrochemical oxidative potentials of all the ligands described are reported in Table 1.

Table 1 Electrochemical Oxidative Potentials E° of the Ligands

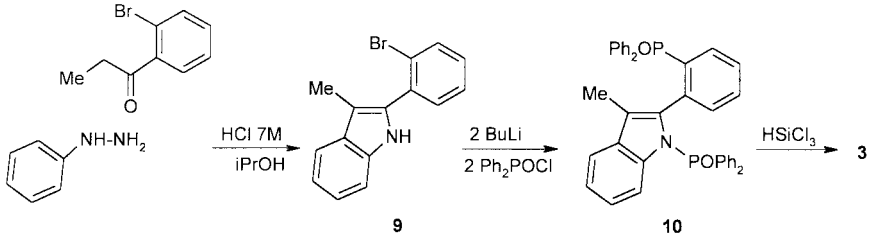
Ligand	E° of Hetaryl P (V)	E° of Aryl P (V)
1a	0.91[a]	0.74
1b	0.91[a]	0.75
1c	-	0.68
1d	0.9–0.95[b]	0.72
1e	-	0.67
2	1.01	0.64
3	0.90[c]	0.70

[a] E° (V) of 2-diphenylphosphino-3-phenylnaphto[2,1-*b*]thiophene.[8,]
[b] E° (V) of 2,2'-bis(diphenyl)phosphino-4,4',6,6'-tetramethyl-3,3'-bibenzo[*b*]furan.[10,]
[c] E° (V) of 1,1'-bis(diphenyl)phosphino-3,3'-dimethyl-2,2'-biindole.[9a]

E° values for the phosphane groups located on heteroaromatic rings are in good agreement with those we have found for diphenylphosphino groups in α-position of a 3,3'-bithianapthene system (BITIANP).[11] E° values for the phosphane groups on the phenyl moiety are comparable to those shown by BIPHEP and BINAP. The E° values



Scheme 2



Scheme 3

of heterocyclic phosphane groups are also influenced by the nature of the heterocyclic scaffold and by their position on it.

As expected, dicyclohexyl substituted phosphane groups are more electron-rich than the diphenylsubstituted ones, as demonstrated by their constantly lower E° values.

Interestingly, the presence of the electron-releasing methoxy substituent on the phenyl ring in **1b** does not influence the oxidative potential value shown by **1a**. This observation is in agreement with the observation that the methyl groups present in 4-Tol-BINAP (E° = 0.65 V)[10] do not exert any effect on the electrochemical oxidative potential of BINAP (E° = 0.63 V).[9a] A possible interpretation of these data involves conformational effects in solution which do not allow the phosphorus lone pair to conjugatively align and overlap the π-system of the substituted phenyl ring.

Evaluation of Configurational Stability of the Ligands

Configurational stability of naphthofuran-based ligand **1c** was evaluated through a ^{31}P NMR experiment carried out in parallel with diphosphane **1a** for which high configurational stability had been previously demonstrated through successful resolution. We took advantage of the spectra of the complexes which are formed by reaction of racemic diphosphanes with an excess of enantiopure (+)- or (−)-di-μ-chloro-bis[(*S*)-dimethyl(α-methylbenzyl)amminato-C^2N] palladium(II) (Scheme 4).

When a C_2-symmetric diphosphane is employed, two diastereomeric complexes are produced in which the originally homotopic phosphorus atoms of the free ligand become diastereotopic (anisochronous). If the starting ligand is configurationally stable, a couple of double doublets is produced (generally after chloride for perchlorate anion exchange) with identical integrals. Different integrals indicate a diastereomeric excess in solution which is compatible only with a kinetic resolution process of configurationally labile antipodes.[9a]

A much more complex pattern is expected in the case of C_1-symmetric diphosphanes displaying constitutionally heterotopic phosphorus atoms. In these cases either of the antipodes produces two diastereoisomers, generally in different amounts. Thus, four couples of doublets are expected. If the free ligand is configurationally stable, the sum of the integrals of the signals attributable to the complexes formed from one enantiomer must be equal to the sum of the integrals of the signals related to the complexes formed from the antipode. The ^{31}P NMR spectrum of the mixture of diastereomeric complexes generated from naphthothiophene-based diphosphane (±)-**1a** is reproduced in Figure 3.

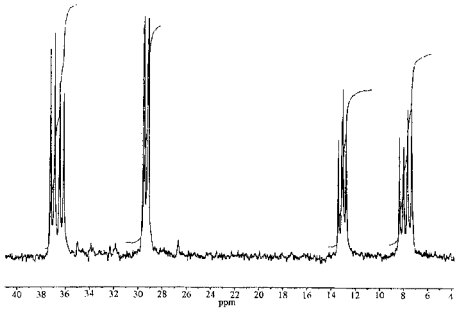
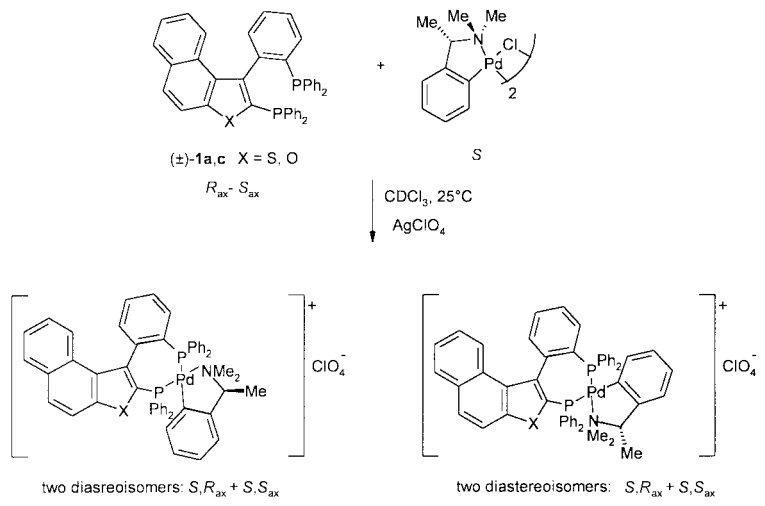


Figure 3 ^{31}P NMR spectrum of the mixture of the four diastereomeric amminopalladium complexes generated from (±)-**1a**

The ^{31}P NMR spectra of the diastereomeric complexes obtained from enantiopure (+)-**1a** and (–)-**1a** are reported in Figures 4 and Figure 5, respectively. They demonstrate that enantiopure (+)-**1a** affords two complexes in a 1.1:1 ratio, while two diastereoisomers in very different amounts (1:2.2 ratio) are formed from (–)-**1a**.



Scheme 4

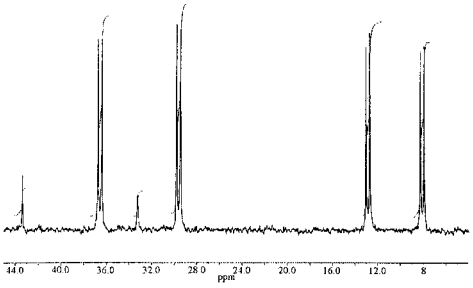


Figure 4 ^{31}P NMR spectrum of the mixture of the two diastereomeric amminopalladium complexes generated from (+)-**1a**

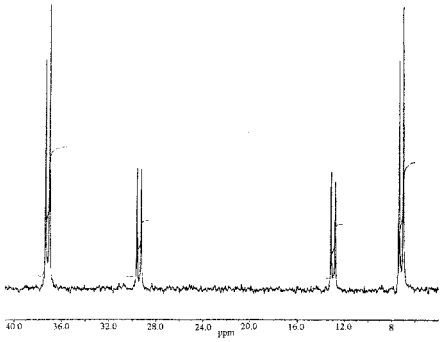


Figure 5 ^{31}P NMR spectrum of the mixture of the two diastereomeric amminopalladium complexes generated from (–)-**1a**

Careful integration of the signals present in the spectrum of the mixture of the four diastereomeric amminopalladium complexes generated from (±)-**1a** demonstrates that the two diastereomeric couples generated from (+)-**1a** and (–)-**1a** are present in a nearly perfect 1:1 ratio, thus giving clear support to the configurational stability of the ligand.

A mixture of four diastereomeric amminopalladium complexes was generated also from (±)-**1c** and its ^{31}P NMR spectrum (Figure 6) was found very similar to that just discussed for the analogous complexes obtained from racemic (±)-**1a**.

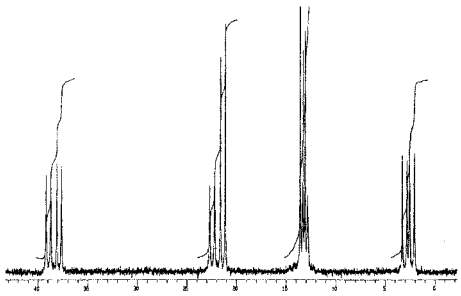


Figure 6 ^{31}P NMR spectrum of the mixture of four diastereomeric amminopalladium complexes generated from (±)-**1c**

In this case, it is difficult to assign the signals to the diastereomeric couples arising from the same enantiomer, even though it is rather evident that one enantiomer generates two complexes in very similar amounts, while the other one gives a rather unbalanced diastereomeric couple.

It was, however, impossible to find any combination of signals, which could be assigned to two diastereomeric couples in a good 1:1 ratio. This situation suggests that ligand **1c** is not configurationally stable at the complexation temperature (25 °C). In agreement with this conclusion, all the attempts performed to resolve the corresponding phosphane oxide **6c** by crystallization of its' adducts with different chiral acids and from several solvents failed.

This result matches a previous observation about the configurational stability of analogous bi-benzofuran- and bi-thianaphthene-based atropisomeric diphosphanes: the former was found configurationally labile at room temperature, while the latter did not racemize up to 150 °C.

No changes were observed in all the above reported spectra by heating the solution of the complexes at 80 °C for 3 hours.

Preparation of Enantiopure Diphosphanes (+)- and (–)-1b

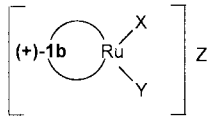
Resolution of racemic (±)-3-(2-diphenylphosphinyl-5-methoxyphenyl)-2-(diphenylphosphinyl)naphtho[2,1-*b*]thiophene [(±)-(**6b**)] was achieved following a known methodology involving fractional crystallization of its diastereomeric adducts with chiral dibenzoyltartaric acids (DBTA).[12]

Alkaline decomplexation of the diastereomerically pure complexes gave enantiopure phosphane oxides (+)- and (–)-**6b**, which were reduced with trichlorosilane to the corresponding enantiopure diphosphanes (–)-and (+)-**1b**, respectively. The enantiomeric purity of resolved phosphane oxides was checked by HPLC chromatography on a chiral stationary phase, while the enantiomeric purity of diphosphanes was controlled under the same analytical conditions after their reoxidation to phosphane oxides with hydrogen peroxide.

Preliminary Catalytic Experiments with Ru(II) Complexes of Enantiopure Diphosphane (+)-1b

Preliminary catalysis experiments on enantiopure (+)-**1b** were carried out on substrates, which are in standard use for the evaluation of stereoselection ability and catalytic activity of all new ligands presented in literature. Ru(II) complexes **11a**,**b** (Figure 7) were employed in catalytic hydrogenation of β-keto esters **12a**,**b** to hydroxyesters **13a**,**b** (Figure 8).

As expected, the ^{31}P NMR spectroscopy showed that the complex **11b** consists of a mixture of two diastereomeric species in a ratio of ca 3:1.



11

a X = Y = Cl Z = dmf_n

b X = Cl Y = *P*-cymene Z = I

Figure 7 Chemical structures of Ru(II) complexes of **11a**,**b**

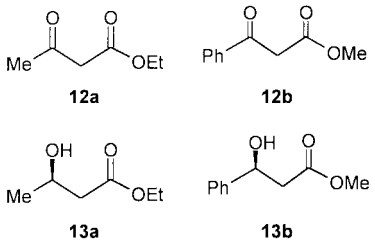


Figure 8 Chemical structures of β-keto esters **12a**,**b** and hydroxy esters **13a**,**b**

Table 2 summarizes stereoselection data and some characteristic experimental parameters. The enantiomeric excesses are quite high and comparable to those obtained with diphosphane **1a**[8] and with some efficient C_2-symmetric ligands.[9a] There is a rather negative temperature effect in the hydrogenation of **12a** with complex **11a**, which is, however, overcome by using complex **11b**.

Comparison of the catalytic efficiency of the Ru(II) complexes produced from **1a** and **1b** clearly demonstrated that the latter gives kinetically more active catalysts. The reaction time required to complete the hydrogenation reaction of acetoacetic ester **12a**, with **11a** as a catalyst, at 40 °C (110 min), was about one half of the time required to complete the same reaction (210 min) when the catalyst was prepared from **1a**, under identical experimental conditions. This holds true also in benzoylacetic ester **12b** hydrogenation: the reaction requires 3.75 hours when promoted by **11b**, while 6 hours are necessary when an analogous **1a** Ru(II)-complex is employed. Since it is well documented that electron-rich ligands foster the hydrogenation reaction of β-keto esters,[13] it appears that diphosphane **1b** behaves as a more electron rich promoter than **1a**, even though the E° values of these ligands are nearly the same. A tentative interpretation of these findings hypothesizes that the conjugative electron-releasing effect of the methoxy group to phosphorus, which is inhibited by conformational barriers in the free ligand, is activated by metal complexation, which reasonably involves a consistent conformational rearrangement.

We considered it important to verify the kinetic behavior of catalytic complex **11a** in the hydrogenation reaction of two different substrates, namely the acetoacetic and the benzoylacetic esters **12a** and **12b**, in order to obtain any possible information on the reaction mechanism.

We found that acetoacetic ester hydrogenation (Figure 9) follows a zero order kinetic in the substrate (linear dependence of substrate concentration upon time, $k = 11.57 \times 10^{-2}$ m·l^{-1}·sec^{-1}), while benzoylacetic ester reduction (Figure 10) follows a first order kinetics in the substrate ($k = 4.63 \times 10^{-5}$ sec^{-1}). These results demonstrate that in these multi-step reactions the reactants are involved in different steps of the whole sequence. In particular, **12a** is involved in the late step, which does not restrict the overall rate.

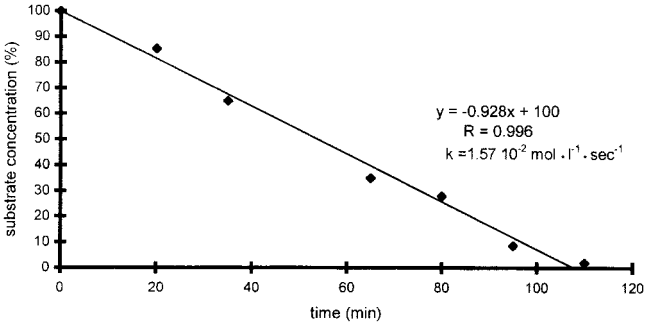


Figure 9 Hydrogenation of ethyl acetoacetate **12a** in the presence of **11a** as a catalyst (100 atm, 40 °C, S/C 300)

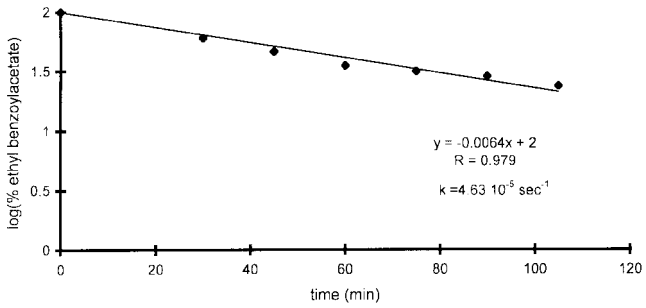


Figure 10 Hydrogenation of methyl benzoylacetate **12b** in the presence of **11a** as a catalyst (100 atm, 55 °C, S/C 240)

Table 2 Hydrogenation of β-Keto Esters with Ru(II) Complexes of (+)-**1b** as Catalysts

Substrate	Catalyst	Substrate/Catalyst	P (Atm)	T (°C)	T (h)	ee(%)[a]	Conf.	k (sec^{-1})
12a	**11a**	300	100	40	1.8	84	R	1.57×10^{-2}
12a	**11a**	300	100	25	5	>99.9	R	-
12a	**11b**	300	100	40	40	>99.9	R	6.18×10^{-4}
12b	**11a**	240	100	55	3.75	70	S	4.63×10^{-5}

[a] Evaluated by chiral HPLC.

Conclusions

Research developed in this work has produced a series of C_1-symmetric ligands for homogeneous stereoselective catalysis belonging to a new class of diphosphanes displaying a mixed aryl–heteroaryl atropisomeric backbone. The synthetic access to these systems is very simple being reduced to that of an aryl-substituted aromatic heterocycle.

Electrochemical characterization of the ligands has proved the flexibility that these systems offer in tuning the electronic properties at phosphorus, which ranges from modest to high electron availability.

Naphthofuran-based diphosphane **1c** has been found to be configurationally unstable at room temperature, while the analogous naphthothiophene-based diphospanes **1a** and **1b** were obtained in an enantiopure form on a preparative scale and they did not racemise even at 130 °C temperature. They have been successfully experimented as Ru(II)-ligands in the homogeneous stereoselective hydrogenation of keto esters, displaying good face-selection capacity and remarkable kinetic activity.

A concluding consideration involves the economic advantages related to this class of ligands for which the preliminary cost estimate is about one tenth of DuPHOS, one fifth of BINAP and one third of tetraMe-BITIOP[13] and, in some cases, even less. Thus diphosphanes **1a** and **1b** deserve consideration for a immediate application also on an industrial scale level.

Chiral HPLC analyses were performed with a DAICEL CHIRACEL OD column (210 nm). Electrochemical experiments were performed in a three-electrode cell at 25 °C under N_2. The working electrode was a platinum microelectrode (0.003 cm^2); the counter electrode was platinum; the reference electrode was silver/0.1 M $AgClO_4$ in MeCN (0.34 V vs. SCE). The voltammetric apparatus (Amel, Italy) included a 551 potentiostat modulated by a 568 programmable function generator. MeCN for voltammetric measurements was distilled twice over P_2O_5 and once over CaH_2. Et_4NClO_4 was dried at 70 °C under vacuum before use. All other chemicals were reagent grade and were used as such.

Hydrogenation reactions were carried out in a stirred (550 rpm) and thermostated 100 mL, Hastelloy Parr autoclave, equipped with a sampling pipe, which extended to the bottom of the vessel.

1-(2-Bromo-5-methoxy)phenyl-2-(2-naphthylthio)ethanone (4b)

A solution of 1-(2-bromo-5-methoxyphenyl)-2-bromoethanone[14] (7.05 g) in EtOAc (7 mL) was added dropwise into a mixture of H_2O (10 mL), EtOH (30 mL), KOH (1.28 g, 23 mmol) and 2-thionaphthol (3.67 g, 23 mmol), keeping the temperature below 25 °C. The mixture was stirred for 12 h and then concentrated under reduced pressure. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was dried (Na_2SO_4), concentrated to dryness and the residue was chromatographed (SiO_2, eluant: $CHCl_3$–hexane, 6:4 v/v). The last fractions were evaporated to dryness to give **4b** (5.48 g, 62%) as an oil.

^{1}H NMR ($CDCl_3$): δ = 7.72 (m, 4 H), 7.48 (m, 4 H), 6.78 (dd, 1 H, *J* = 8.72, 3.07 Hz, 3-H of the phenyl ring), 6.73 (d, 1 H, *J* = 3.07 Hz, 6-H of the phenyl ring), 4.4 (s, 2 H), 3.6 (s, 3 H).

3-(2-Bromo-5-methoxy)phenylnaphtho[2,1-*b*]thiophene (5b)

Compound **4b** (5.48 g, 14 mmol) was added under stirring to polyphosphoric acid (PPA, 45 g) at 80 °C. The mixture was stirred for 1 h, then poured onto ice, neutralized with 20% NH_4OH solution and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give **5b** as a solid, which was purified by triturating with diisopropyl ether (5.18 g, 94%).

^{1}H NMR ($CDCl_3$): δ = 7.68 (m, 6 H), 7.37 (s, 1 H, 2-H of thianaphthene ring), 7.28 (m, 1 H, 3-H of phenyl ring), 7.05 (d, 1 H, 6-H of phenyl ring), 6.94 (dd, 1 H, 4-H of phenyl ring), 3.8 (s, 3 H).

3-[2-(Diphenylphosphinyl-5-methoxy)phenyl]-2-(diphenylphosphinyl)naphtho[2,1-*b*]thiophene (6b)

BuLi (1.6 M in hexane, 19.5 mL, 31 mmol) was added dropwise to a solution of **5b** (5.18 g, 14 mmol) and TMEDA (5 mL) in THF (130 mL) at –70 °C under N_2. The temperature was allowed to warm to 20 °C, then diphenylphosphinous chloride (6.2 mL) was added and the mixture stirred for 12 h. The solvent was evaporated under reduced pressure, the residue treated with CH_2Cl_2 (140 mL) and 35% H_2O_2 solution (38 mL), and then stirred for 2 h. The organic layer was separated, dried (Na_2SO_4), and the residue obtained after evaporation of the solvent was chromatographed (SiO_2, eluant: EtOAc–CH_2Cl_2, 3:7, v/v). The last fractions eluted were evaporated under reduced pressure to give **6b** (2.9 g, 30%); mp 360 °C.

^{1}H NMR ($CDCl_3$): δ = 7.9–6.5 (m, 29 H), 3.35 (s, 3 H).

^{31}P NMR ($CDCl_3$): δ = 28.02 (s, 1 P), 20.42 (s, 1 P).

MS: *m*/*z* = 690 (M^+).

3-[2-(Diphenylphosphino-5-methoxy)phenyl]-2-(diphenylphosphino)naphtho[2,1-*b*]thiophene (1b)

In a three-necked flask equipped with a thermometer and a reflux condenser connected to an argon inlet tube were placed **6b** (0.2 g, 0.32 mmol), anhyd xylene (10 mL), Et_3N (0.45 mL, 3.32 mmol) and trichlorosilane (0.36 mL, 3.6 mmol). The mixture was stirred for 3 h at 110 °C. The solvent was removed under reduced pressure, then a 10% aq NaOH solution (18 mL) wad added to the residue and the mixture stirred at 60 °C for 15 min. The organic layer was extracted with degassed CH_2Cl_2, washed with degassed H_2O, dried (Na_2SO_4) and evaporated to dryness to give a solid which was triturated with MeOH to give **1b** (0.16 g, 85%); mp 243 °C.

^{1}H NMR ($CDCl_3$): δ = 8–6.6 (m, 32 H), 3.4 (s, 3 H)

^{31}P NMR ($CDCl_3$): δ = 6.3 (s, 1 P), –2.6 (s, 1 P).

1-(2-Bromo)phenyl-2-(2-naphthyloxy)ethanone (4c)

A solution of 1-(2-bromophenyl)-2-bromoethanone[15] (21 g, 75.5 mmol) in DMF (50 mL) was rapidly added to a DMF solution of anhyd sodium 2-naphtholate [from 2-naphthol (15 g, 104 mmol) and NaOMe]. The mixture was stirred for 3 d and concentrated under reduced pressure. The residue was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness to give a residue, which was chromatographed (SiO_2, eluent: $CHCl_3$). The last fractions eluted were evaporated to dryness to give **4c** (16 g, 62%) as an oil.

^{1}H NMR ($CDCl_3$): δ = 7.39 (m, 11 H), 5.22 (s, 2 H).

3-(2-Bromo)phenyl-naphtho[2,1-*b*]furan (5c)

Compound **4c** (16 g, 47 mmol) was added under stirring to PPA (100 g) at 80 °C. The mixture was stirred for 1.5 h, then poured onto ice, neutralized with 20% NH_4OH solution and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give **5c** (11g, 72%) as a viscous oil.

^{1}H NMR ($CDCl_3$): δ = 7.96 (d, 1 H, *J* = 8 Hz), 7.77 (m, 3 H), 7.48 (m, 7 H).

MS: *m*/*z* = 644 (M^+).

3-[2-(Diphenylphosphinyl)phenyl]-2-(diphenylphosphinyl)-naphtho[2,1-*b*]furan (6c)

BuLi (1.6 M in hexane, 25 mL, 40 mmol) was added dropwise into a solution of **5c** (5.78 g, 18 mmol) and TMEDA (6 mL) in THF (100 mL) at –70 °C under N_2. The temperature was allowed to warm to 20 °C and the mixture stirred for 30 min. Diphenylphosphinous chloride (7.4 mL, 39.9 mmol) was added and the mixture stirred for 1 h. The solvent was evaporated under reduced pressure, the residue treated with CH_2Cl_2 (100 mL) and 35% H_2O_2 solution (20 mL), and then the mixture was stirred for 2 h. The organic layer was separated, dried (Na_2SO_4) and the residue was chromatographed (SiO_2, eluant: EtOAc–CH_2Cl_2, 3:7, v/v). The last fractions eluted were evaporated under reduced pressure to give **6c** (6.0 g, 52%) as a crystalline solid; mp 162–165 °C.

^{1}H NMR ($CDCl_3$): δ = 7.78 (m, 8 H), 7.35 (m, 20 H), 6.63 (m, 2 H).

^{31}P NMR ($CDCl_3$): δ = 31.85 (s, 1 P), 18.90 (s, 1 P).

3-[2-(Diphenylphosphino)phenyl]-2-(diphenylphosphino)-naphtho[2,1-*b*]furan (1c)

In a three-necked flask equipped with a thermometer and a reflux condenser connected to an argon inlet tube were placed **6c** (6.0 g, 9.3 mmol), anhyd xylene (50 mL), Et_3N (12.5 mL, 92 mmol) and trichlorosilane (10.6 mL, 106 mmol) and the mixture was stirred for 4 h at 140 °C. The organic layer was separated, washed with degassed H_2O, dried and evaporated to dryness to give a solid which was triturated with MeOH to give **1c** (4.2 g, 72%).

^{1}H NMR ($CDCl_3$): δ = 7.91(d, 2 H, *J* = 8.4 Hz), 7.75 (d, 1 H, *J* = 9 Hz), 7.62 (d, 2 H, *J* = 9 Hz), 7.32 (m, 25 H), 6.93 (t, 2 H, *J* = 7.5 Hz).

^{31}P NMR ($CDCl_3$): δ = –13.72 (d, 1 P, *J* = 7.8 Hz), –32.10 (d, 1 P, *J* = 7.8 Hz).

1-(2-Bromo)phenyl-2-(3,5-dimethyl)phenoxyethanone (4d)

A solution of 1-(2-bromophenyl)-2-bromoethanone[15] (10 g, 36 mmol) in DMF (30 mL) was rapidly added to a DMF solution of anhyd sodium 3,5-dimethylphenolate [from 3,5-dimethylphenol (4.39 g, 36 mmol) and NaOMe]. The reaction mixture was stirred for 3 d at 25 °C and concentrated under reduced pressure. The residue was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was dried (Na_2SO_4), concentrated to dryness and the residue was chromatographed (SiO_2, eluent: hexane–CH_2Cl_2, 6:4 v/v) to give **4d**, which was triturated with diisopropyl ether (0.7 g, 61%); mp 74 °C.

^{1}H NMR ($CDCl_3$): δ = 7.61 (d, 1 H, *J* = 7.2 Hz, 3-H of the phenyl ring), 7.48 (td, 1 H, *J* = 4.36 Hz, 5-H of the phenyl ring), 7.4 (t, 1 H, *J* = 5.45 Hz, 4-H of the phenyl ring), 7.35 (dd, 1 H, *J* = 7.2 Hz, 6-H of the phenyl ring), 6.63 (s, 1 H, 4-H of the xylyl ring), 6.52 (s, 2 H, 2-H and 6-H of the xylyl ring), 5.1 (s, 2 H, CH_2), 2.26 (s, 6 H, 2 CH_3).

3-(2-Bromo)phenyl-4,6-dimethylbenzo[*b*]furan (5d)

Compound **4d** (1.3 g, 4.08 mmol) was added under stirring to PPA (13 g) at 80 °C. The mixture was stirred for 30 min, then poured onto ice, neutralized with aq 20% NH_4OH solution and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give a residue, which was chromatographed (SiO_2, eluent: hexane) to give **5d** (1.1g, 89%).

^{1}H NMR ($CDCl_3$): δ = 7.68 (d, 1 H, *J* = 7 Hz, 3-H of the phenyl ring), 7.47 (s, 1 H, 2-H of the benzofuran ring), 7.29 (m, 4 H), 6.82 (s, 1 H, 5-H of the benzofuran ring), 2.43 (s, 3 H), 2.1 (s, 3 H).

3-[2-(Diphenylphospinyl)phenyl]-2-(diphenylphosphinyl)-4,6-dimethylbenzo[*b*]furan (6d)

BuLi (1.6 M in hexane, 5.2 mL, 8.3 mmol) was added dropwise to a solution of **5d** (1.15 g, 5.7 mmol) and TMEDA (1.2 mL) in THF (100 mL) at −70 °C under N_2. The temperature was allowed to warm to 20 °C, then diphenylphosphinous chloride (2.16 mL, 11.6 mmol) was added and the mixture stirred for 3 h. The solvent was evaporated under reduced pressure, the residue treated with CH_2Cl_2 (100 mL) and 35% H_2O_2 solution (5 mL) and the mixture was stirred for 2 h at 25 °C. The organic layer was separated, dried (Na_2SO_4) and the residue chromatographed (SiO_2, eluent: EtOAc–CH_2Cl_2, 3:7, v/v). The last fractions eluted were evaporated under reduced pressure to give **6d** in a pure state(1 g, 42%); mp 218 °C.

^{1}H NMR ($CDCl_3$): δ = 7.89 (m, 4 H), 7.7 (m, 6 H), 7.48 (m, 14 H), 7.02 (s, 1 H, 7-H of the benzofuran ring,), 6.61 (s, 1 H, 5-H of the benzofuran ring), 2.17 (s, 3 H), 1.97 (s, 3 H).

^{31}P NMR ($CDCl_3$): δ = 31.31 (s, 1 P), 17.72 (s, 1 P).

3-[2-(Diphenylphospino)phenyl]-2-(diphenylphosphino)-4,6-dimethylbenzo[*b*]furan (1d)

In a three-necked flask equipped with a thermometer and a reflux condenser connected to an argon inlet tube were placed **6d** (1g, 1.76 mmol), anhyd xylene (23 mL), Et_3N (1.7 mL, 12.5 mmol) and trichlorosilane (1.22 mL, 12 mmol). The mixture was stirred for 2 h at 140 °C. The organic layer was separated, washed with degassed H_2O, dried (Na_2SO_4) and evaporated to dryness to give a solid which was triturated with degassed EtOAc to give **1d** (0.66 g, 70%); mp 320 °C (dec.).

^{31}P NMR ($CDCl_3$): δ = –13.55 (s, 1 P), –30.86 (s, 1 P).

3-[2-(Dicyclohexylphosphinyl)phenyl]-2-(dicyclohexyl-phosphinyl)naphtho[2,1-*b*]thiophene (6e)

BuLi (2.5 M in hexane, 2.6 mL, 6.5 mmol) was added dropwise into a solution of **5a**[8] (1.0 g, 2.9 mmol) and TMEDA (1 mL) in anhyd THF (40 mL) at –70 °C under N_2. The temperature was allowed to warm to 20 °C and the mixture stirred for 11 h. Then dicyclohexylphosphinous chloride (1.5 g, 6.5 mmol) was added and the mixture was stirred for 1 h. The solvent was evaporated under reduced pressure, the residue treated with CH_2Cl_2 (25 mL) and 35% H_2O_2 solution (10 mL), and the mixture was stirred for 2 h. The organic layer was separated, dried (Na_2SO_4) and the residue chromatographed (SiO_2, eluant: EtOAc–CH_2Cl_2, 1:1, v/v) to give **6e** (0.7 g, 35%); mp 274 °C.

^{1}H NMR ($CDCl_3$): δ = 7.84 (d, 1 H, *J* = 8.14 Hz), 7.82 (d, 1 H, *J* = 8.7 Hz), 7.72 (d, 1 H, *J* = 8.7 Hz), 7.5 (m, 4 H), 7.34 (m, 1 H), 7.06 (m, 2 H), 0.5–2.5 (m, 44 H).

^{31}P NMR ($CDCl_3$): δ = 44.90 (s, 1 P), 43.04 (s, 1 P).

MS: *m*/*z* = 684 (M^+).

3-[2-(Dicyclohexylphosphino)phenyl]-2-(dicyclohexyl-phosphino)naphtho[2,1-*b*]thiophene (1e)

In a three-necked flask equipped with a thermometer and a reflux condenser connected to an argon inlet tube were placed **6e** (0.13 g, 0.2 mmol), anhyd xylene (4 mL), Et_3N (0.25 mL, 1.8 mmol) and trichlorosilane (0.2 mL, 2 mmol). The mixture was stirred for 1 h at 120 °C and then for 2 h at 140 °C. The organic layer was separated, washed with degassed H_2O, dried and evaporated to dryness to give a solid which was triturated with degassed MeOH to give **1e** (0.01 g, 80%); mp 200 °C (dec.)

^{31}P NMR ($CDCl_3$): δ = –9.54 (d, 1 P, *J* = 11 Hz), –17.48 (d, 1 P, *J* = 11 Hz).

3-(o-Bromo)phenyl-2-(diphenylphosphinyl)naphtho[2,1-*b*]-thiophene (7)

LDA (1.5 M solution in THF, 7.5 mL, 0.0117 mol) was added dropwise dropped into a solution of **5a** (4.0 g, 11.6 mg) in anhyd THF (170 mL) at –70 °C under N_2. After stirring for 15 min, the temperature was allowed to warm at –40 °C and then diphenylphosphinous chloride (2.16 mL, 11.6 mmol) was added. The mixture was stirred for 30 min, then the solvent was removed under reduced pressure

and the residue treated with CH_2Cl_2 (80 mL) and 35% H_2O_2 solution (15 mL). The mixture was stirred for 2 h at r.t. and then diluted with H_2O. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo to give a solid, which was triturated with diisopropyl ether to give **7** in a pure state (1.26 g, 82%); mp 193 °C.

^{1}H NMR ($CDCl_3$): δ = 7.84 (m, 4 H), 7.68 (m, 2 H), 7.55 (m, 2 H), 7.45 (m, 4 H), 7.31 (m, 6 H), 7.18 (m, 2 H).

^{31}P NMR ($CDCl_3$): δ = 19.15 (s, 1 P).

MS: *m*/*z* = 539 (M^+).

3-[2-(Dicyclohexylphosphinyl)phenyl]-2-(diphenylphosphinyl)-naphtho[2,1-*b*]thiophene (8)

t-BuLi (1.5 M in pentane, 7.17 mL, 10.8 mmol) was added dropwise into a solution of **7** (5.02 g, 9.3 mmol) in anhyd Et_2O (150 mL) at –78 °C under N_2. After stirring for 15 min, the temperature was allowed to warm to 10 °C and dicyclohexylphosphinous chloride (2.5 g, 10.8 mmol) was added. The mixture was stirred for 3 h and the solvent was removed at reduced pressure. CH_2Cl_2 (150 mL) and 35% H_2O_2 solution (20 mL) were added and the mixture was stirred for 2 h. The organic layer was separated, dried (Na_2SO_4) and concentrated under vacuo to give a residue, which was chromatographed (SiO_2, elution with CH_2Cl_2–EtOAc, 3:7, v/v) to give **8.** This was further purified by trituration with diisopropyl ether (4.6 g, 74%); mp 242 °C.

^{1}H NMR ($CDCl_3$): δ = 7.84 (dd, 2 H, *J* = 8 Hz, 3.1 Hz), 7.58 (m, 9 H), 7.32 (m, 2 H), 7.22 (m, 1 H), 7.05 (m, 5 H), 6.77 (m, 1 H), 0.7–2.1 (m, 22 H).

^{31}P NMR ($CDCl_3$): δ = 44.16 (s, 1 P), 28.7 (s, 1 P).

MS: *m*/*z* = 672 (M^+).

3-[2-(Dicyclohexylphosphino)phenyl]-2-(diphenylphosphino)-naphtho[2,1-*b*]thiophene (2)

In a three-necked flask equipped with a thermometer and a reflux condenser connected to an argon inlet tube were placed **8** (0.2 g, 0.3 mmol), anhyd xylene (6 mL), Et_3N (0.35 mL, 2.6 mmol) and trichlorosilane (0.24 mL, 2.4 mmol). The mixture was stirred at 130 °C for 4 h. After cooling to r.t, the mixture was concentrated in vacuo, the residue treated with aq 10% NaOH solution (15 mL) and stirred at 60 °C for 15 min. Degassed CH_2Cl_2 was added (15 mL), the organic layer separated, dried (Na_2SO_4), evaporated to dryness to give a residue which was triturated with degassed MeOH to give **2** (0.12 g, 64%); mp 157 °C (dec.).

^{1}H NMR ($CDCl_3$): δ = 7.82 (d, 1 H, *J* = 8.7 Hz), 7.78 (d, 1 H, *J* = 7.4 Hz), 7.67 (d, 1 H, *J* = 8.7 Hz), 7.43 (m, 2 H), 7.34 (m, 2 H), 7.27 (m, 1 H), 7.11 (m, 5 H), 6.93 (m, 3 H), 6.82 (m, 2 H), 6.71 (m, 2 H), 0.7–2.0 (m, 22 H).

^{31}P NMR ($CDCl_3$): δ = –18.23 (s, 1 P), –16.31 (s, 1 P).

2-(2-Bromophenyl)-3-methylindole (9)

A solution of 2-bromopropiophenone phenylhydrazone (8.54 g, 42 mmol) in 7 M HCl in propan-2-ol (40 mL) was left to stand for 2 h at 25 °C. The solvent was evaporated and the residue dissolved into CH_2Cl_2, washed with aq 5% $NaHCO_3$ solution and with H_2O. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give a solid, which was triturated with hexane (5.8 g, 72%).

^{1}H NMR ($CDCl_3$): δ = 8.15 (s, 1 H, NH), 7.71 (d, 1 H, *J* = 8 Hz, 4-H of the indole ring), 7.62 (d, 1 H, *J* = 7.8 Hz, 7-H of the indole ring), 7.44 (dd, 1 H, *J* = 7.62, 2.1 Hz), 7.39 (2 superimposed t, 2 H, 5-H-and 6-H of the indole ring), 7.2 (m, 3 H), 2.3 (s, 3 H).

1-(Diphenylphosphinyl)-2-[(2-diphenylphosphinyl)phenyl]-3-methylindole (10)

BuLi (1.6 M in hexane, 2.5 mL, 6.5 mmol) was added to a solution of **9** (0.5 g, 1.75 mmol) and TMEDA (0.3 mL) in anhyd THF (40 mL) at –60 °C under N_2. The temperature was allowed to warm to r.t. and the mixture stirred for 1 h, then diphenylphosphinous chloride (0.74 mL, 3.99 mmol) was added and the mixture stirred for 1 h. The solvent was removed under reduced pressure and CH_2Cl_2 (50 mL) and 35% H_2O_2 solution (5 mL) were added. The solution was kept at r.t. for 2 h, then the organic layer was separated, dried (Na_2SO_4) and evaporated to dryness to give a residue which was chromatographed (SiO_2, eluant: EtOAc–CH_2Cl_2, 7:3, v/v). The last fractions eluted were collected and evaporated to give **10** (0.76 g, 72%); mp 137–140 °C.

^{1}H NMR ($CDCl_3$): δ = 8.05 (m, 1 H), 7.43 (m, 23 H), 7.06 (t, 1 H, *J* = 8.1 Hz), 6.95 (m, 1 H), 6.87 (m, 1 H), 6.58 (t, 1 H, *J* = 6.81 Hz), 1.38 (s, 3 H).

^{31}P NMR ($CDCl_3$): δ = 29.01 (s, 1 P), 25.31 (s, 1 P).

MS: *m*/*z* = 607 (M^+).

1-(Diphenylphosphino)-2-[(2-diphenylphosphino)phenyl]-3-methylindole (3)

In a three-necked flask equipped with a thermometer and a reflux condenser connected to an argon inlet tube were placed **10** (0.2 g, 0.34 mmol), anhyd xylene (5 mL), Et_3N (0.38 mL, 2.8 mmol) and trichlorosilane (0.27 mL, 2.7 mmol). The mixture was stirred for 2 h at 80 °C. After cooling to r.t., the mixture was concentrated under vacuo, the residue treated with aq 10% NaOH solution (15 mL) and stirred at 60 °C for 15 min. Degassed CH_2Cl_2 was added (15 mL), the organic layer separated, dried (Na_2SO_4) and evaporated to dryness to give a residue which was triturated with degassed MeOH to give **3** (0.12 g, 64%); mp 157 °C (dec.).

^{31}P NMR ($CDCl_3$): δ = 35.45 (d, 1 P, *J* = 11.69 Hz), –15.04 (d, 1 P, *J* = 11.69 Hz).

Optical Resolution of (±)-6b with (–)- and (+)-2,3-*O*,*O*'-Dibenzoyltartaric Acid (DBTA)

Crystallization of the diastereomeric adducts formed by the reaction of (±)-**6b** (2.9 g, 4.6 mmol) with (+)-DBTA (1.58 g, 4.4. mmol) from $CHCl_3$ (10 mL) gave the dextrorotatory diastereoisomer as the less soluble adduct; $[\alpha]_D^{25}$ +75.49 (*c* = 0.51, EtOH). Alkaline treatment with aq 0.75 N NaOH solution (10.6 mL) and extraction with CH_2Cl_2 (2 × 10 mL) gave (–)-**6b** (0.42 g); mp 260–265 °C; $[\alpha]_D^{25}$ –190.5 (*c* = 0.28, MeOH). The mother liquors from the first resolution step were concentrated to dryness to give a solid, which was treated with aq 0.75 N NaOH solution (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The resulting diphosphine oxide (0.85 g), treated in turn with (–)-DBTA (1.33 g) according to the procedure described above, gave the levorotatory adduct; $[\alpha]_D^{25}$ –75.49 (*c* = 0.51, EtOH). Alkaline treatment gave enantiopure (+)-**6b**; mp 260–265 °C; $[\alpha]_D^{25}$ +189.6 (*c* = 0.28, MeOH). Repetition of this procedure on the mother liquors allowed total resolution of the racemate.

3-[(2-Diphenylphospino-5-methoxy)phenyl)]-2-(diphenylphosphino)naphtho[2,1-*b*]thiophene [(+)-(1b) and (–)-1b]

Reduction of the enantiopure diphosphinoxides (+)-**6b** and (–)-**6b** to the corresponding enantiopure diphosphines (+)-**1b** and (–)-**1b** was performed following the procedure described above for the reduction of (±)-**6b.**

(+)-**1b**

Mp 243 °C; $[\alpha]_D^{25}$ +166 (*c* = 0.30, benzene).

(–)-**1b**

Mp 245 °C; $[\alpha]_D^{25}$ –166 (*c* = 0.30, benzene).

Preparation of 11a

To a Schlenk tube charged with (+)-**1b** (25.5 mg, 0.039 mmol) and red brown $[RuCl_2(C_6H_6)]_2$ (9.66 mg, 0.019 mmol) was added fresh-

ly distilled and argon-degassed DMF (12.3 mL). The mixture was stirred at 100 °C for 15 min, and the temperature was allowed to warm to 50 °C. The solution was concentrated under reduced pressure to give a residue, which was used as a catalyst in the enantioselective hydrogenation of β-keto esters without further purification.

Preparation of 11b

Compound (+)-**1b** (0.1 g, 0.15 mmol), $[Ru(p\text{-cymene})I_2]_2$ (9.66 mg, 0.01 mmol), EtOH (12.3 mL) and CH_2Cl_2 (30 mL) were stirred in a Schlenk tube under argon at 50 °C, for 1.5 h. The resulting red solution was concentrated under reduced pressure and the residue was used in the asymmetric catalytic reductions without further purification.

^{31}P NMR ($CDCl_3$): δ = 39.67 (d, 0.3 P, *J* = 56.5 Hz), 38.05 (d, 1 P, *J* = 62.4 Hz), 24.51 (d, 1 P, *J* = 62.4 Hz), 19.24 (d, 0.3 P, *J* = 56.5 Hz).

Hydrogenation Reactions; Ethyl (*R*)-(+)-3-Hydroxybutyrate (13a); Typical Procedure

In a typical experiment (Table 1, entry 1), a solution of **12a** (2.6 g, 20 mmol) and **11a** (0.068 g, 0.07 mmol) in MeOH (10 mL), previously degassed with argon, was loaded by syringe into an autoclave. H_2 was introduced (100 Kg/cm^2), and the solution was stirred at 40 °C for 110 min. The autoclave was cooled, the hydrogen pressure released, the solvent evaporated, and the residue distilled (17 mmHg) to give **13a** in a quantitative yield.

Kinetic Experiments

At appropriate time intervals, stirring was stopped and samples of the solution were drawn out through the sampling pipe by exploiting the internal pressure. Conversion was evaluated through GC analysis. After sampling operations, the H_2 pressure was restored and stirring resumed.

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