3,3′-Bis(diphenylphosphino)-1,1′-disubstituted-2,2′-biindoles: Easily Accessible, Electron-Rich, Chiral Diphosphine Ligands for Homogeneous Enantioselective Hydrogenation of Oxoesters

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Racemic (±)-3,3′-bis(diphenylphosphinyl)-1,1′-dimethyl-2,2′-biindole (**1c**) (N-Me-2-BINPO) and (±)-3,3′-bis(diphenylphosphinyl)-1,1′-bis(methoxymethyl)-2,2′-biindole (**1d**) (N-MOM-2-BINPO) were synthesized in satisfactory yields following a three-step reaction sequence, starting from indole. Resolution of racemic **1c** and **1d** was achieved through fractional crystallization of their diastereomeric adducts with optically active dibenzoyl tartaric acids, followed by alkaline decomplexation of the diastereomerically pure salts. Their trichlorosilane reduction gave enantiopure phosphines (+)- and (−)-(**1a**) (N-Me-2-BINP) and (+)- and (−)-(**1b**) (N-MOM-2-BINP). The electrochemical oxidative potential of **1a** and **1b** was found to be 0.52 and 0.60 V, respectively. Both the enantiomers of (**1a**) were tested as ligands of Ru(II) in asymmetric hydrogenation reactions of α- and *β*-oxoesters. Reactions were found to be outstandingly fast and enantioselection quite good. Comparative kinetic experiments on the hydrogenation reaction of methyl acetoacetate carried out with **1a**, **1c**, BINAP, and other biheteroaromatic diphosphines as ligands of Ru(II) demonstrated that all the reactions follow a first-order kinetic. A linear relationship was found between the kinetic constant log and the electrochemical oxidative potential of the diphosphine ligand.

Introduction

The search for easily accessible chiral ligands for transition metals, showing high enantioselection ability in homogeneous catalysis, is an ongoing challenge in chemical research. Chelating diphosphines, supported by an atropisomeric biaryl scaffold, are currently rated as very efficient chiral inducers in many asymmetric transformations, and BINAP[1] and BIPHEMP[2] are the prototypes of this family. A few years ago we presented a class of chiral diphosphines structurally characterized by an atropisomeric backbone consisting of two interconnected, five-membered, heteroaromatic units.[3] The advantages of these ligands over the more traditional biaryl carbocyclic systems are numerous: (a) It was possible to accede to a highly modular, homogeneous class of diphosphine ligands having different electronic properties at phosphorus. In fact, it is possible to modulate electronic phosphorus availability through the inherent electron-releasing capacity of the heterocyclic system constituting the backbone. This strategy provides a viable alternative to the introduction of electron-donating or electron-withdrawing groups on the biaryl backbone[4] or on the nonstereogenic substituents at phosphorus.[5] This traditional approach is synthetically very demanding, particularly in C_2 symmetry systems. (b) It is possible to vary the steric properties of the ligands by introducing suitable substituents on the biaryl backbone. (c) The synthetic routes to five-membered biheteroaryl systems are simpler and more flexible than those available for the six-membered carbocyclic biaryls.

The examples of biheteroaromatic diphosphines we have published so far have 3,3′-bibenzo[*b*]thiophene (BITIANP) and 4,4′,6,6′-tetramethyl-3,3′-bibenzo[*b*]thiophene (tetraMe-BITIANP),[3,6] 3,3′-bibenzo[*b*]furan (BICUMP),[6] 3,3′-dimethyl-2,2′-biindole (BISCAP),[7] 1,1′-bibenzimidazole (BIMIP),[7] and 2,2′,5,5′-tetramethyl-3,3′-

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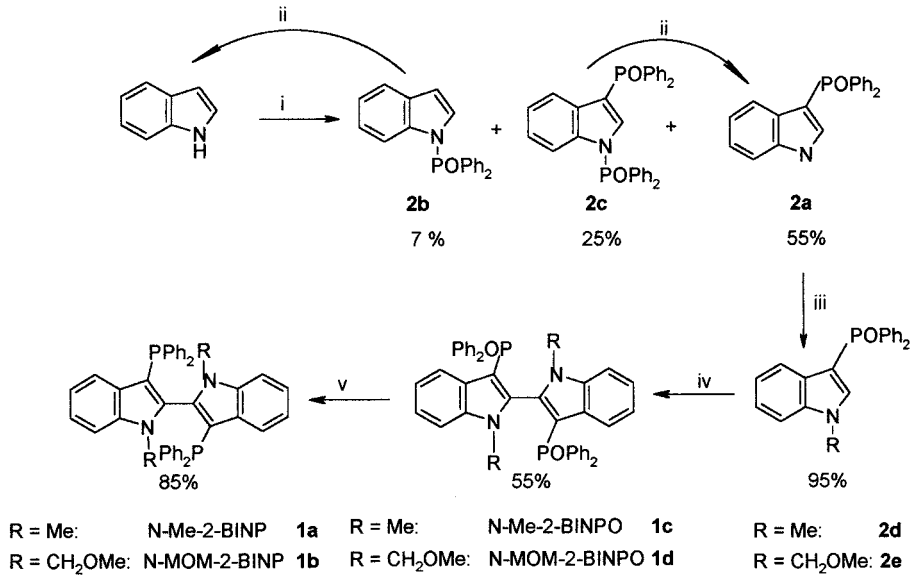
Scheme 1



[a] Reagents and conditions: (i) MeMgCl, Ph_2PCl, THF, rt, 12 h; H_2O_2, CH_2Cl_2, rt, 30 min; (ii) KOH, EtOH, reflux, 2.5 h; (iii) RX, NaH, THF, rt, 1 h; (iv) BuLi, TMEDA, THF, $CuCl_2$, 3 h, rt; (v) $HSiCl_3$, TEA, xylene, 100−140 °C, 5 h.

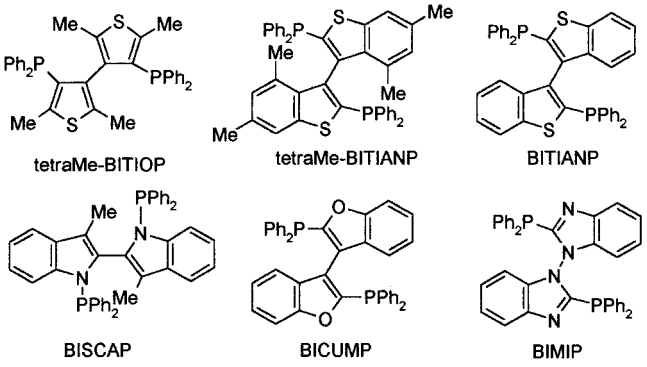


Figure 1. Some biheteroaromatic diphosphines.

bithiophene (tetraMe-BITIOP)[8] backbones (Figure 1). Very successful results have been obtained so far in the hydogenation of prostereogenic functionalized ketonic and olefinic double bonds and in the Heck synthesis by employing the first and the last ligands of this series.[9]

We found electrochemical oxidative potential ($E°$), determined by voltammetry, to be a very significant probe of the electronic availability of the phosphorus atoms in these compounds: the higher its value, the more electron-poor the phosphine.[7] Oxidative potential increases along the series in the following order: tetraMe-BITIOP ($E° =$ 0.57 V), tetraMe-BITIANP ($E° = 0.76$ V),[10] BITIANP ($E°$ = 0.83 V), BISCAP ($E° = 0.90$ V), BICUMP ($E° = 1.03$ V), BIMIP ($E° = 1.15$ V).[10]

This order is in accordance with the expected decrease in the electronic availability of the supporting heterocycle and with a decrease in the electronic density of the position in which the diphenylphosphino group is carried. Since high electronic density at phosphorus is known, though only qualitatively, to be a favorable parameter in ruthenium-catalyzed hydrogenation reactions of ketonic carbonyl of ketoesters,[8,11] we decided to focus our attention on the synthesis of 3,3′-bis(diphenylphosphino)-1,1′-dimethyl-2,2′-biindole (**1a**) (N-Me-2-BINP) and 3,3′-bis(diphenylphosphino)-1,1′-bis(methoxymethyl)-2,2′-biindole (**1b**) (N-MOM-2-BINP), where the phosphino groups are located in β position, the most electron-rich position, of the indole ring which is, per se, one of the most electron-rich heterocycles. The structure of N-MOM-2-BINP appeared attractive, since cleavage of the methoxymethyl group would afford 3,3′-bis(diphenylphosphino)-2,2′-biindole, an excellent scaffold upon which to attach functions capable of conferring special properties to the catalytic metal complexes.

Furthermore, to gain quantitative evidence of the influence of the electronic availability of phosphorus on the kinetics of hydrogenation of oxoesters, we considered the comparison of kinetic data drawn from the hydrogenation of ethyl acetoacetate promoted by the ruthenium(II) complexes of the biheteroaromatic diphosphines cited above and BINAP, taken as a reference ligand.

Results and Discussion

Syntheses of racemic diphosphines N-Me-2-BINP (**1a**) and N-MOM-2-BINP (**1b**) and of the corresponding phosphine oxides N-Me-2-BINPO (**1c**) and N-MOM-2-BINPO (**1d**) were achieved through a straightforward reaction sequence, starting from indole (Scheme 1).

Preferential introduction of phosphorus in position 3 on the indole ring was performed by reaction of *N*-indolylmagnesium iodide with diphenylchlorophosphine

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in THF solution.[12] We found that harder reactants, such as *N*-indolylsodium or diphenylphosphinyl chloride, exclusively orient the attack of phosphorus at the nitrogen atom.

Evaluation of product distribution was performed by careful column chromatography of the phosphine oxides obtained by oxidation of the crude reaction mixture with 33% hydrogen peroxide, in dichloromethane solution, at 0 °C. 3-(Diphenylphosphinyl)indole (**2a**) was obtained in a 55% yield, together with *N*-(diphenylphosphinyl)indole (**2b**) and 1,3-bis(diphenylphosphinyl)indole (**2c**) in 7% and 25% yields, respectively. Treatment of the mixture of crude phosphine oxides **2a**, **2b**, and **2c** with the calculated amount of alcoholic sodium hydroxide produced cleavage of the phosphorus−nitrogen bond in **2b** and **2c**, converting **2b** into indole, and the useless diphosphine oxide **2c** into the desired monophosphine oxide **2a**. Following this procedure, the latter was isolated in a pure state in a 78% overall yield.

Methylation of the anion of **2a** with methyl iodide in THF solution gave 3-(diphenylphosphinyl)-1-methylindole (**2d**) in a quantitative yield. The oxidative coupling reaction ($CuCl_2$) of the 2-lithium derivative of **2d** gave racemic (±)-3,3′-bis(diphenylphosphinyl)-1,1′-dimethyl-2,2′-biindole, (±)-N-Me-2-BINPO (**1c**) in a 51% yield.

Alternative quenching of the anion of **2a** with chloromethoxymethane gave 3-(diphenylphosphinyl)-1-methoxymethylindole (**2e**) in an 89% yield. The oxidative coupling reaction of its 2-lithium derivative, under the same experimental conditions employed for the synthesis of **1c**, gave racemic (±)-3,3′-bis(diphenylphosphinyl)-1,1′-bis(methoxymethyl)-2,2′-biindole, (±)-N-MOM-2-BINPO (**1d**), again in a 51% yield. Overcrowding around the incipient interannular bond probably is the yield-limiting factor impeding these coupling reactions. However, owing to the availability of inexpensive starting materials and the simplicity of the experimental procedures, we were able to scale-up both the reaction sequences, so as to prepare more than 10-g batches of racemic **1c** and **1d**. They could be converted into the corresponding racemic phosphines **1a** and **1b**, in an about 90% isolation yield, by reaction with trichlorosilane, in the presence of triethylamine, in refluxing xylene solution.

We first checked the electronic availability at phosphorus in N-Me-2-BINP (**1a**) and N-MOM-2-BINP (**1b**). Voltammetric experiments showed the anodic peak, corresponding to a nonreversible monoelectron abstraction, at 0.52 and 0.60 V, respectively.[10] The value found for **1a** is the lowest observed for a bis(diphenylphosphino) chelating ligand, including all our biheteroaryl diphosphines, BINAP ($E°$ = 0.63 V) and other popular ones, like DIOP ($E°$ = 0.97 V), CHIRAPHOS ($E°$ = 0.97 V), NORPHOS ($E°$ = 0.83 V), and BPPM ($E°$ = 0.99 V). MeDuPHOS was found to be, as expected, the most electron-rich diphosphine ($E°$ = 0.39 V).

N-MOM-2-BINP (**1b)**, was found to be slightly more electron-poor than N-Me-2-BINP (**1a)**, on account of the electron-withdrawing inductive effect exerted by the oxygen atom of the methoxymethyl group on the indole ring.

Resolution of N-Me-2-BINPO **(1c)** and N-MOM-2-BINPO **(1d)** was successfully achieved following a known resolution methodology.[13] Fractional crystallization of the diastereomeric adducts produced by reaction of (±)-**1c** and (±)-**1d** with equimolar amounts of enantiopure (−)-*O*,*O*′-dibenzoyl-L-tartaric acid gave, in both cases, the dextrorotatory diastereoisomer as the less-soluble adduct. [Adduct from **1c**: mp = 233 °C ($CHCl_3$); $[\alpha]^{25}_D$ = +6.2 (*c* = 0.50, EtOH); (yield: 60% of the theoretical amount). Adduct from **1d**: mp = 234 °C ($CHCl_3$/AcOEt 3:1); $[\alpha]^{25}_D$ = +18.5 (*c* = 0.51, EtOH); (yield: 57% of the theoretical amount)]. The mother liquors were treated with 0.75 M sodium hydroxide solution to effect the decomplexation of the soluble adduct and to remove the resolving agent. The residue was treated in turn, with (+)-*O*,*O*′-dibenzoyl-D-tartaric acid, according to the procedure described above, to give the levorotatory adduct [Adduct from **1c**: mp = 236 °C; $[\alpha]^{25}_D$ = −6.0 (*c* = 0.51, EtOH) (yield: 86% of the theoretical amount). Adduct from **1d**: mp = 236 °C; $[\alpha]^{25}_D$ = −17.6 (*c* = 0.51, EtOH) (yield: 86% of the theoretical amount)].

Repetition of this procedure on the crystallization residues allowed quantitative resolution of the racemates.

Alkaline decomplexation of the dextrorotatory complex obtained from **1c** gave dextrorotatory phosphine oxide (+)-N-Me-2-BINPO, (+)-**1c**, [mp = 301 °C ($MeOH/H_2O$ 13:5); $[\alpha]^{25}_D$ = +67,6 (*c* = 0.50, EtOH)]; the levorotatory adduct correspondingly gave levorotatory (−)-N-Me-2-BINPO, (−)-**1c** [mp = 302 °C; $[\alpha]^{25}_D$ = −65.6 (*c* = 0.51, EtOH)].

In the case of the adducts obtained from **1d**, alkaline treatment of the dextrorotatory complex afforded the dextrorotatory phosphine oxide (+)-N-MOM-2-BINPO, (+)-**1d**, [mp = 351 °C (2-propanol/H_2O-1:1); $[\alpha]^{25}_D$ = +77.1 (*c* = 0.51, EtOH)]. The levorotatory adduct analogously gave levorotatory (−)-N-MOM-2-BINPO, (−)-**1d** [mp = 351 °C; $[\alpha]^{25}_D$ = −76.6 (*c* = 0.52, EtOH)].

Enantiomeric purity of (+)- and (−)-**1c** and **1d** was confirmed by chiral HPLC analysis (Supelcosil LC-(*R*)-phenylurea, eluant: hexane:2-propanol:CH_2Cl_2 50:5:45 (v/v/v), 0.5 mL.min^{-1}).[14] The CD spectra of the antipodes were also perfect mirror images (Figure 2 and Figure 3).

Reduction of (+)-**1c** to (+)-N-Me-2-BINP, (+)-**1a** [mp = 321 °C; $[\alpha]^{25}_D$ = +119.5 (*c* = 0.51, C_6H_6)] was performed with trichlorosilane in excess, in the presence of triethylamine, in a refluxing xylene solution, under argon atmosphere. Analogous reduction of (−)-**1c**, gave (−)-N-Me-2-BINP, (−)-**1a** [mp = 322 °C; $[\alpha]^{25}_D$ = −121 (*c* = 0.50, C_6H_6)].

Parallel results were obtained in the reduction of (+)- and (−)-**1d** which respectively gave (+)-N-MOM-2-BINP, (+)-**1b** [mp = 179 °C; $[\alpha]^{25}_D$ = +133 (*c* = 0.42, C_6H_6)] and (−)-N-MOM-2-BINP, (−)-**1b** [mp = 179 °C; $[\alpha]^{25}_D$ = −135 (*c* = 0.42, C_6H_6)] in 90% yields.

Enantiomeric purity of all the optically pure diphosphines was confirmed by oxidation with hydrogen peroxide which gave enantiopure diphosphine oxides (HPLC). This result demonstrates that the ligands are configurationally stable up to 140 °C, which is the reaction temperature at which they are prepared by reduction of the corresponding diphosphine oxides.

The CD spectra of enantiomeric diphosphines showed perfectly specular shapes (Figure 2 and Figure 3).

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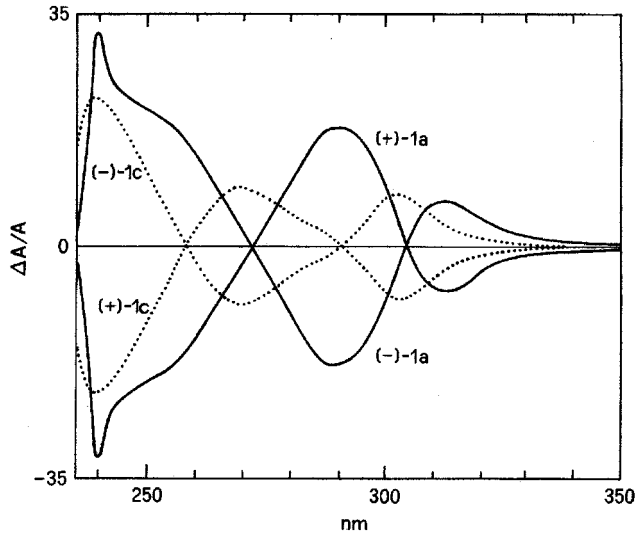


Figure 2. CD spectra (CH_2Cl_2) of (+)- and (−)-**1a** and (+)- and (−)-**1c**

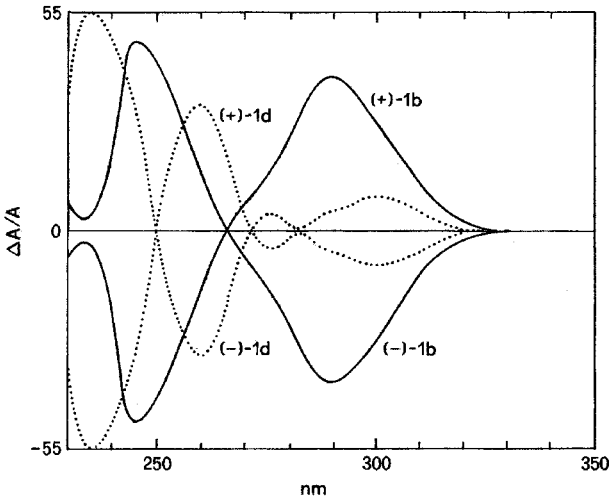
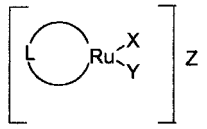


Figure 3. CD spectra (CH_2Cl_2) of (+)- and (−)-**1b** and (+)- and (−)-**1d**

We focused our tests of enantioselection ability and catalytic activity of the ruthenium (II) complexes **3** of (+)- and (−)-**1a**,**b** on the hydrogenation of Pro[1]-chiral α- and β-ketoesters **4a**−**e** and Pro[0]-chiral β-ketoester **6**, which has a configurationally labile stereocenter.

These reactions were chosen as reference reactions for two main reasons: first of all they are well described in the literature in tests employing the ruthenium complexes of many popular chiral diphosphines as catalysts.[15] Second, as anticipated, it had been previously observed that the kinetic behavior of these reactions is strongly influenced by the electronic availability of the ligand at phosphorus. These reactions appeared therefore to be a very good testing ground for evaluating the above-mentioned effects. The experimental results are summarized in Table 1.

The relationship between the configuration of the hydrogenation products and the rotatory power sign of the ligand was found to be identical to that observed in



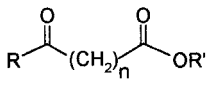
3

a : L = N-Me-2-BINP X = Y = Cl

b : L = N-Me-2-BINP X = p-cymene Y = Cl Z = J

c : L = N-Me-2-BINP X = C_6H_6 Y = Z = Cl

d : L = N-MOM-2-BINP X = Y = Cl



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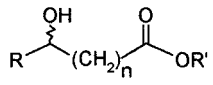
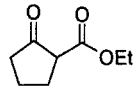
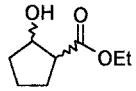


5

a : R = Me R' = Et n = 1
b : R = Ph R' = Et n = 1
c : R = Ph R' = Me n = 0
d : R = $Ph(CH_2)_2$ R' = Et n = 0



6



7

the case of BITIANP and BINAP.[6] This observation provides support for the following configurational assignment: (−)-N-Me-2-BINP, (−)-**1a**, and (−)-N-MOM-2-BINP, (−)-**1b**, should be the *S* enantiomers and dextrorotatory (+)-N-Me-2-BINP, (+)-**1a**, and (+)-N-MOM-2-BINP, (+)-**1b**, the *R* antipodes. Consequently, dextrorotatory (+)-N-Me-2-BINPO, (+)-**1c**, and (+)-N-MOM-2-BINPO, (+)-**1d**, should have *R* configuration, while *S* configuration should be assigned to levorotatory (−)-N-Me-2-BINPO, (−)-**1c**, and (−)-N-MOM-2-BINPO, (−)-**1d**. Comparison of the shape of the CD curves with those shown by BINAP[13] and by the only biheteroaromatic diphosphine with known configuration BIMIP[16] lends further support to these conclusions.

As for the enantioselection levels observed in acetoacetic ester (**4a**) (entries 1 and 9) and benzoylacetic (**4b**) (entries 4 and 10) hydrogenation, they were found to be rather good (92−93%) and comparable to those obtained with many popular commercially available chiral diphosphines.[5a,15] In the case of substrate **4a**, enantiomeric excess does not decrease when hydrogen pressure is halved (entry 2) and when the substrate-catalyst ratio is more than doubled (entry 3).

The ligands exhibited satisfactory enantioselection ability also in the carbonyl hydrogenation of α-oxoesters, such as phenylglyoxylic (**4c**) (entry 5 ee = 76%) and benzylpyruvic (**4d**) (entries 6 and 7) esters. In the former case enantiomeric excess was improved by employing a lower substrate-catalyst ratio value (entry 7; ee = 89%). Very good diastereo- (92%), but unsatisfactory enantioselectivity (64%), were found in the case of ethyl cyclopentanonecarboxylate **6** (entry 8) hydrogenation.

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Table 1. Asymmetric Hydrogenation of α- and β-Ketoesters

entry	cat.[a]	sub	solvent	*S/C*	H_2 (kg/cm^2)	*T* (°C)	*t* (h)	de (%)	ee (%)	conf
1	(−)-**3a**	**4a**	MeOH−H_2O	1000	100	10	25	−	93[b]	*S*
2	(−)-**3b**	**4a**	MeOH−H_2O	1000	50	10	30	−	95[b]	*S*
3	(−)-**3b**	**4a**	MeOH−H_2O	2490	100	32	4.5	−	94[b]	*S*
4	(−)-**3a**	**4b**	MeOH−H_2O	251	100	45	0.80		93[b]	*R*
5	(−)-**3c**	**4c**	MeOH−HBF_4	245	104	35	24	−	76[c]	*S*
6	(−)-**3c**	**4d**	MeOH−HBF_4	560	100	30	12		81[b]	*S*
7	(+)-**3c**	**4d**	MeOH−HBF_4	200	100	30	26	−	89[b]	*R*
8	(+)-**3a**	**6**	MeOH−H_2O	1000	100	45	3	92	64[b]	1*R*,2*R*
9	(−)-**3d**	**4a**	MeOH−H_2O	1000	100	40	2.7		92[b]	*S*
10	(−)-**3d**	**4b**	MeOH−H_2O	250	100	45	3		93[b]	*R*

[a] The optical rotatory power sign refers to that of the corresponding diphosphine. [b] HPLC analysis (CHIRACEL OD, eluant: hexane/2-propanol 90:10, 1 mL/min). [c] HPLC analysis (CHIRACEL OJ, eluant: hexane/ethanol 90:10, 1 mL/min).

Table 2

ligand (L)	*E*° (V)	k_{obs} (s^{-1})	$k_{obs}{}^i/k_{obs}{}^{BINAP}$	ee %
(+)-N-Me-2-BINP	0.52	3.47×10^{-5}	2.67	95
(+)-tetraMe-BITIOP	0.57	3.76×10^{-5}	2.89	98
(+)-N-MOM-2-BINP	0.60	3.33×10^{-5}	2,56	91
(+)-BINAP	0.63	1.3×10^{-5}	1	99
(+)-tetraMe-BITIANP	0.76	1.08×10^{-5}	0.83	99
(±)-BISCAP	0.90	2.17×10^{-6}	1.7×10^{-1}	−
(±)-BICUMP	1.03	2.17×10^{-7}	1.7×10^{-2}	−

The general conclusions which can be drawn regarding these results is that the stereoselection ability of N-Me-2-BINP and N-MOM-2-BINP does not stray from the limits of many good, commercially available diphosphines. On the other hand, catalytic activity, in terms of reaction times, shown by the complexes of N-Me-2-BINP, seems to be undeniably enhanced when compared with the data drawn from analogous reactions carried out with all the other bis(diphenylphosphino) chelating ligands which are more electron-poor.

To shed some light on this point, comparative kinetic experiments of the hydrogenation of ethyl 3-oxobutanoate (**4a**) were carried out with enantiopure (+)-N-Me-2-BINP (**1a**), (+)-N-MOM-2-BINP (**1b**), (+)-tetraMe-BITIOP, (+)-tetraMe-BITIANP, (+)-BINAP, and with racemic BISCAP and BICUMP (Table 2) as ligands of ruthenium(II), under identical experimental conditions (solvent: 95% aqueous ethanol; temperature: 40 °C; hydrogen pressure: 100 kg/cm^2; substrate−catalyst ratio: 1000; substrate concentration: 0.41 M). All the catalytic complexes were prepared according to the same experimental procedure.[18] Progress of the reaction was evaluated by GLC, after determination of the response factor between starting material and reaction product **5a**. In all the reactions where enantiopure ligands were used, we found that the enantiomeric excess of the product was constant throughout the entire reaction.

Kinetic data demonstrated that the reaction rate is first order in substrate in all cases. This homogeneity of kinetic behavior is a crucial prerequisite for comparison, since it suggests mechanistic homogeneity. A very good fitting was found when the reagent (or product) concentration log was plotted against time: straight lines were obtained (correlation coefficient *R* from >0.999 to 0.979), the slope of which gave the observed kinetic constant values (k_{obs}). These data demonstrate that the reaction rate found in the case of BINAP is nearly tripled when electron-rich diphosphines are used and reduced to about one twentieth when electron-poor ligands are employed. The k_{obs} value found in the case of the electron-richest diphosphine is about 50 times that observed in the case of the electron-poorest ligand.

We also found a strong linear correlation between the electrochemical oxidative potential value *E*° of the free ligands and the logarithm of k_{obs} of the reactions in which they are employed, as reported in Figure 4.

This relationship is fully comparable to a Hammet-type relationship, valid since the activity of systems with different electronic properties but rather similar geometry of the chelate core, is being compared. It could be inferred that the ratios between the energy differences involved in electrochemical monoelectron abstraction from the phosphine group of the free ligands in voltammetric experiments are maintained at the level of the catalytic complexes in the hydrogenation reaction of acetoacetic ester. The step of the catalytic cycle involving the displacement of the reaction product from the metal center, effected by ethyl acetoacetate, accounts for the observed first order in the substrate rate equation. The more basic the metal center, the easier the detachment of the ethyl hydroxybutyrate, which is removed as an anion.

Conclusions

The results reported above provide evidence of the crucial role played by the electronic properties of phosphorus in determining the hydrogenation rate of the ketonic function of ethyl acetoacetate. We found a free energy linear correlation between the electrochemical oxidative potentials of ligands exhibiting different electronic availability at phosphorus and the log of the observed rate constant (k_{obs}). In the case in point, electron-rich diphosphines facilitate the reaction, but we have recently given qualitative evidence that an opposite situation works in the intramolecular Heck reaction, which seems to be favored by electron-poor ligands.[17]

Easy synthesis, a simple resolution process, and successful application of the two BINPs as ruthenium ligands in hydrogenation reactions of α- and β-ketoesters all provide a convincing demonstration of the advantages offered by the biheteroaromatic scaffold. This simple architecture behaves effectively in tuning the electronic properties of the phosphorus atom bonded to it, while a proper substitution on it could afford chelating species endowed with suitable steric properties. This strategy looks very promising for tailoring synthetically accessible and efficient ligands, capable of satisfying all the stereoelectronic needs imposed by reaction and substrate.

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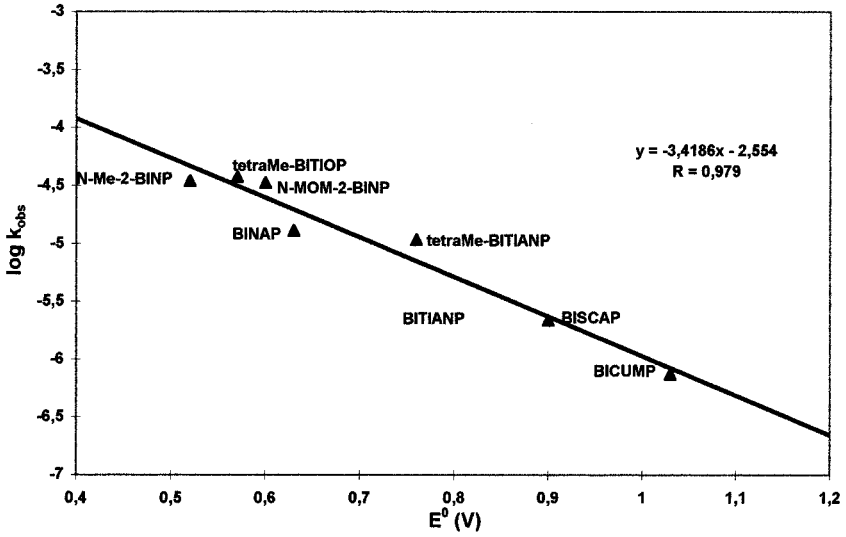

Figure 4. Ligand (L) electrochemical oxidative potential ($E°$)-observed kinetic constant (k_{obs}) relationship in ethyl acetoacetate hydrogenation catalyzed by [(L)$RuCl_2(DMF)_n$]

Experimental Section

General. Chiral HPLC analyses were performed with a DAICEL CHIRACEL OD (254 nm) column. The CD spectra were recorded in CH_2Cl_2 solution and plotted as mdeg/*A*, where *A* is the UV absorption of the same solution at 300 nm. Electrochemical oxidation potential of **1a** and **1b** were determined in a three-electrode cell, at 25 °C, under nitrogen in acetonitrile + 0.1 M Bu_4NClO_4. The working electrode was a platinum minidisk electrode (0.003 cm^2); the reference electrode was silver/0.1 M silver perchlorate in acetonitrile (0.34 V vs SCE). Phosphine solutions were 10^{-4} M, and the scan rate was 0.1 V s^{-1}. The voltammetric apparatus (AMEL, Italy) included a 551 potentiostat modulated by a 568 programmable function generator.

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

Preparation of 3-(Diphenylphosphinyl)indole (2a). A 3 M THF solution of MeMgCl (62.0 mL, 0.186 mol) was dropped into a solution of indole (20.0 g, 0.170 mol) in dry THF (150 mL) under N_2. After being refluxed 25 min, the mixture was cooled at −30 °C, and a solution of chlorodiphenylphosphine (36 mL, 0.170 mol) in THF (15 mL) was added.

The mixture was stirred at room temperature for 12 h and then concentrated in vacuo. The residue was dissolved into CH_2Cl_2 (500 mL), and H_2O_2 (100 mL, 30%) was added at 10 °C. After the mixture was stirred 30 min at room temperature, the organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The crude reaction product (45 g) was dissolved into ethanol (250 mL) and treated with an aqueous solution of KOH (35 g in 25 mL). The reaction mixture was refluxed for 2.5 h, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The crude reaction product was triturated with isopropyl ether to give **2a** (78%): mp 251 °C. ^1H NMR ($CDCl_3$) δ 6.94 (t, 1H), 7.04 (s, 1H), 7.09 (t, 1H), 7.28 (d, 1H), 7.34 (d, 1H), 7.40 (m, 4H), 7.51 (m, 2H), 7.72 (dd, 4H), 10.80 (s, 1H). ^{31}P NMR ($CDCl_3$) δ 23.90. Anal. Calcd for $C_{20}H_{16}NOP$: C, 75.69; H, 5.09; N, 4.41. Found: 75.86; H, 5.19; N, 4.43.

Column chromatography (SiO_2, eluant: CH_2Cl_2/MeOH 10:0.3) of the reaction mixture obtained from H_2O_2 oxidation, before alkaline hydrolysis, allowed isolation of *N*-(diphenylphosphinyl)indole (**2b**) and 1,3-bis(diphenylphosphinyl)-indole (**2c**) in a pure state. **2b**: mp 130 °C; ^1H NMR ($CDCl_3$) δ 6.58 (t, 1H), 6.78 (t, 1H), 7.10 (m, 2H), 7.41 (m, 4H), 7.58 (m, 8H); ^{31}P NMR ($CDCl_3$) δ 25.66. **2c**: mp 171 °C; ^1H NMR ($CDCl_3$) δ 6.95 (t, 1H), 7.95 (m, 2H), 7.42 (m, 14H), 7.63 (m, 11H); ^{31}P NMR ($CDCl_3$) δ 22.2 (1P, s), 26.8 (1P, s).

Preparation of 3-(Diphenylphosphinyl)-*N*-methylindole (2d). NaH (3.37 g, free-flowing powder, moistened with oil, 55−65%) was added portionwise to a suspension of **2a** (17.65 g) in dry THF (300 mL) under N_2. After the mixture was stirred 30 min, a solution of MeI (3.5 mL) in THF (50 mL) was added; the mixture was stirred for 1 h and then concentrated in vacuo. The residue was treated with water and CH_2Cl_2; the organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The crude reaction product was triturated with isopropyl ether to give **2d** (17.5 g, 95%): mp 218 °C. ^1H NMR ($CDCl_3$) δ 3.8 (s, 3H), 7.07 (t, 1H), 7.25 (m, 2H), 7.35 (m, 2H), 7.43 (m, 4H), 7.52 (m, 2H), 7.78 (dd, 4H); ^{31}P NMR ($CDCl_3$) δ 22.03. Anal. Calcd for $C_{21}H_{18}NOP$: C, 76.11; H, 5.47; N, 4.23. Found: 76.46; H, 5.49; N, 4.43.

Preparation of (±)-3,3′-Bis(diphenylphosphinyl)-*N*,*N*′-dimethyl-2,2′-biindole (1c). BuLi (0.048 mol, 1.6M solution in hexane) was dropped into a solution of **2d** (13.2 g) and TMEDA (7.2 mL) in dry THF (300 mL), at room temperature. After the mixture was stirred 1 h, $CuCl_2$ (8 g) was added; the mixture was stirred for 3 h, quenched with 2 N HCl solution, and stirred overnight. The mixture was concentrated in vacuo, the residue extracted with CH_2Cl_2, and the organic layer dried (Na_2SO_4) and concentrated in vacuo. The crude residue was treated with warm AcOEt, and the solid obtained was collected and crystallized (MeOH/H_2O 3:1) to give **1c** (6.7 g, 51%): mp 350 °C. ^1H NMR ($CDCl_3$) δ 3.40 (s, 6H), 7.68 (dd, 4H), 7.53 (dd, 4H), 7.13 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 21.9; mass spectrum *m*/*z* 660 (M^+). Anal. Calcd for $C_{42}H_{34}N_2O_2P_2$: C, 76.35; H, 6.81; N, 5.55. Found: 76.46; H, 6.77; N, 5.37.

Resolution of (±)-3,3′-Bis(diphenylphosphinyl)-*N*,*N*′-dimethyl-2,2′-biindole [(+)-1c] with (−)- and (+)-2,3-*O*,*O*′-Dibenzoyltartaric Acid [DBTA]. A mixture of (±)-**1c** (9 g) and (−)-DBTA monohydrate (5.1 g) was dissolved in $CHCl_3$ (50 mL), refluxed for a few minutes, and allowed to stand at room temperature for 24 h. The adduct between (+)-**1c** and (−)-DBTA was collected, and the filtrate was stored for the recovery of (−)-**1c**. The above complex (3.72 g) was further purified by treatment with warm $CHCl_3$. The solid collected [3.02 g, mp 233 °C, $[\alpha]^{25}_D = +6.2$ ($c = 0.50$, EtOH)] was treated with 0.75 N NaOH solution (57 mL), and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with water and then dried (Na_2SO_4). The solution, concentrated in vacuo, provided (+)-**1c** [1.5 g, mp 301.3 °C, $[\alpha]^{25}_D = +67.6$ ($c = 0.50$, EtOH)]. The mother liquors from the first resolution were concentrated to dryness to give a solid residue (11.7 g), which was treated with 0.75 N NaOH solution (230 mL) and extracted with two portions of CH_2Cl_2 (2 × 150 mL). The combined organic layers were washed with water and then dried (Na_2SO_4). The solution was concentrated

in vacuo to give a residue enriched in the levorotatory enantiomer. The recovered solid and (+)-DBTA (3.5 g) were dissolved in $CHCl_3$ (90 mL) and refluxed for a few minutes. After 24 h an adduct between (−)-**1c** and (+)-DBTA was collected and purified by treatment with warm $CHCl_3$. The complex [5.8 g, mp 236 °C, $[\alpha]^{25}_D = -5.9$ ($c = 0.50$ EtOH)] was treated with a 0.75 N NaOH solution (110 mL), and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with water and then dried (Na_2SO_4). The solution, concentrated in vacuo, provided (−)-**1c** [2.65 g, mp 301.9 °C, $[\alpha]^{25}_D = -65.6$ ($c = 0.50$, EtOH)].

Preparation of (−)-3,3′-Bis(diphenylphosphino)-1,1′-dimethyl-2,2′-biindole [(−)-1a]. (−)-**1c** (0.5 g), dry xylene (14 mL), trichlorosilane (0.6 mL), and triethylamine (0.8 mL) were placed in a three-necked flask equipped with thermometer and a reflux condenser, connected to an argon inlet tube. The mixture was heated at 100 °C under stirring for 1 h, at 120 °C for 2 h, and finally at 140 °C for 2 h. After being cooled to room temperature, the mixture was concentrated in vacuo; the residue was treated with 10% NaOH solution (35 mL) and stirred for 15 min at 60 °C. The mixture was extracted with CH_2Cl_2, and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was triturated with methanol (5 mL) to give (−)-**1a** [0.38 g, mp 322 °C, $[\alpha]^{25}_D = -121.05°$ ($c = 0.50$, C_6H_6)]. ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 6H), 6.94 (t, 2H), 7.07 (m, 8H), 7.24 (m, 12H), 7.43 (m, 6H); ^{31}P NMR ($CDCl_3$) δ −28.75. Anal. Calcd for $C_{42}H_{34}N_2P_2$: C, 80.23; H, 5.46; N, 4.46. Found: 80.36; H,5.73; N, 4.35.

(+)-**1c** was reduced to (+)-**1a** [mp 321 °C, $[\alpha]^{25}_D = +119.50°$ ($c = 0.50$, C_6H_6)] by following the same procedure.

Preparation of 3-(Diphenylphosphinyl)-*N*-methoxymethylindole (2e). NaH (5.6 g, free-flowing powder, moistened with oil, 55−65%) was added portionwise to a suspension of **2a** (36 g) in dry THF (450 mL) under N_2. After the mixture was stirred 25 min, a solution of methoxychloromethane (9 mL) in THF (100 mL) was added; the mixture was stirred for 1 h and then concentrated in vacuo. The residue was treated with water and CH_2Cl_2; the organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The crude reaction product was triturated with isopropyl ether to give **2e** (89%): mp 281 °C. ^{1}H NMR ($CDCl_3$) 3.25 (s, 3H), 5.5 (s, 2H), 7.1 (t, 1H), 7.27 (t, 1H), 7.38 (m, 2H), 7.45 (m, 4H), 7.52 (m, 2H), 7.76 (m, 4H); ^{31}P NMR ($CDCl_3$) δ 23.80. Anal. Calcd for $C_{22}H_{20}NO_2P$: C, 73.12; H, 5.58; N, 3.87. Found: 73.06; H, 5.49; N, 3.63.

Preparation of (±)-3,3′-Bis(diphenylphosphinyl)-1,1′-dimethoxymethyl-2,2′-biindole (1d). BuLi (40 mL, 1.6M solution in hexane) was dropped into a solution of **2e** (18 g) and TMEDA (9.2 mL) in dry THF (400 mL), at room temperature. After the mixture was stirred 30 min, $CuCl_2$ (10.3 g) was added; the mixture was stirred overnight, quenched with 2 N HCl solution, and concentrated in vacuo. The residue extracted with CH_2Cl_2, and the organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude residue was treated with AcOEt, and the solid obtained was treated with acetone to give **1d** (51%): mp 293 °C. ^{1}H NMR ($CDCl_3$) δ 3.15 (s, 3H), 5.3 (dd, 2H, $J = 10.4$ Hz), 7.0 (m, 3H), 7.15 (m, 2H), 7.25 (t, 1H, $J = 7.98$ Hz), 7.4 (m, 6H), 7.7 (m, 2H); ^{31}P NMR ($CDCl_3$) δ 21.96; mass spectrum m/z 660 (M^+). Anal. Calcd for $C_{42}H_{34}N_2O_2P_2$: C, 76.35; H, 6.81; N, 5.55. Found: 76.46; H, 6.77; N, 5.37.

Preparation of (±)-3,3′-Bis(diphenylphosphino)-1,1′-dimethoxymethyl-2,2′-biindole [(±)-1b]. (±)-**1d** (0.96 g), dry xylene (22 mL), trichlorosilane (1.06 mL), and triethylamine (1.48 mL) were placed in a three-necked flask equipped with thermometer and a reflux condenser, connected to an argon inlet tube. The mixture was heated at 80 °C under stirring for 90 min. After being cooled to room temperature, the mixture was concentrated in vacuo; the residue was treated with 10% NaOH solution (35 mL) and stirred for 15 min at 60 °C. The mixture was extracted with CH_2Cl_2, and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was triturated with methanol (5 mL) to give (±)-**1b** (90%): mp 248−250 °C. ^{1}H NMR ($CDCl_3$) δ 3.1 (s, 6H), 5.22 (dd,2H, $J = 10.48$ Hz), 6.98 (m, 2H), 7.11 (m, 3H), 7.28 (m, 3H), 7.43 (m, 2H), 7.6 (d, 1H, $J = 8.24$ Hz); ^{31}P NMR ($CDCl_3$) δ −29.30. Anal. Calcd for $C_{44}H_{38}N_2O_4P_2$: C,73.32; H, 5.31; N, 3.89. Found:73.36; H,5.73; N, 3.85.

Preparation of [[(+)- and (−)-N-Me-2-BINP]RuCl$_2$-(DMF)$_n$] (3a). To a Schlenk tube charged with (*S*)-N-Me-2-BINP (2.9×10^{-2} mmol) and red brown $[RuCl_2(C_6H_6)]_2$ (1.25×10^{-2} mmol), prepared according to the procedure reported in the literature,[18] was added freshly distilled, argon-degassed, DMF (5 mL). The mixture was stirred at 100 °C for 10 min. The resulting orange-yellow solution was cooled to 50 °C and concentrated under reduced pressure. The ruthenium complex **3a** obtained as residue was left under vacuum for 1 h and then argon pressurized. It was utilized without further purification in the enantioselective reductions of α- and β-ketoesters. The ^{31}P NMR spectrum showed a complex set of signals, indicating that the crude catalyst was a mixture of $RuCl_2$ (N-Me-2-BINP)-$(DMF)_n$ with a different number of coordinated solvent molecules.[19] ^{31}P NMR ($CDCl_3$) δ 53.41 (d, $J = 37.9$ Hz), 50.79 (d, $J = 42.7$ Hz), 49.85 (d, $J = 39.8$ Hz), 49.10 (d, $J = 43.6$ Hz), 45.27 (d, $J = 38.2$ Hz), 44.09 (d, $J = 42.9$ Hz), 42.67 (d, $J = 43.42$ Hz), 40.67 (d, $J = 41.3$ Hz), 39.13 (d, $J = 36.5$ Hz), 36.04 (d, $J = 43.04$ Hz), 17.65 (d, $J = 43.37$ Hz).

Preparation of [RuI((+)- and (−)-N-Me-2-BINP)(*p*-cymene)]I (3b). (−)-N-Me-2-BINP (0.0207 g, 0.0325 mmol), $[Ru(p\text{-cymene})I_2]_2$ (0.0159 g, 0.0153 mmol), ethanol (6 mL), and CH_2Cl_2 (3 mL) were stirred in a Schlenk tube, under argon, at 50 °C, for 1.5 h. The resulting 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 36.79 (d, $J = 39.5$ Hz,), 27.61 (d, $J = 39.5$ Hz).

Preparation of [RuCl((+)- and (−)-N-Me-2-BINP)(C_6H_6)]-Cl (3c). (+)-N-Me-2-BINP (0.0218 g, 0.0342 mmol), $[RuCl_2(C_6H_6)]_2$ (0.007 g, 0.0280 mmol), ethanol (7 mL), and C_6H_6 (1 mL) were stirred in a Schlenk tube under argon at 55 °C for 1 h. The resulting 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 36.09 (d, $J = 42.9$ Hz), 17.62 (d, $J = 43.6$ Hz).

Preparation of [[(+)- and (−)-N-MOM-2-BINP]RuCl$_2$-(DMF)$_n$] (3d). To a Schlenk tube charged with (*S*)-N-MOM-2-BINP (1.3×10^{-2} mmol) and red brown $[RuCl_2(C_6H_6)]_2$ (0.6×10^{-2} mmol), prepared according to the procedure reported in the literature,[18] was added freshly distilled, argon-degassed, DMF (5 mL). The mixture was stirred at 100 °C for 15 min. The resulting orange-yellow solution was cooled to 50 °C and concentrated under reduced pressure. The ruthenium complex **3d** obtained as residue was left under vacuum for 1 h and then argon pressurized. It was utilized without further purification in the enantioselective reductions of α- and β-ketoesters. The ^{31}P NMR spectrum showed a complex set of signals clustered around 46 and 48 ppm, indicating that the crude catalyst was a mixture of $RuCl_2$ (N-MOM-2-BINP)$(DMF)_n$ with a different number of coordinated solvent molecules.[19]

Asymmetric Hydrogenation of Ethyl 3-Oxobutanoate (4a) with 3a. A 100 mL Hastelloy autoclave was purged five times with hydrogen; a solution of ethyl 3-oxobutanoate (7.69 mmol) and (+)-**3a** (0.00385 mmol) in a mixture of MeOH/H_2O (20 mL/1 mL), previously degassed for 15 min with argon, was loaded into the autoclave with a syringe. Hydrogen was introduced (105 kg/cm^2), and the solution was stirred at 45 °C for 30 min. The autoclave was cooled, the hydrogen pressure released, the solvent evaporated, and the residue distilled under vacuum (18 mmHg) to give ethyl (*R*)−(−)-3-hydroxybutanoate (**5a**) (100% yield).

Hydrogenation of ethyl benzoylacetate (**4b**) and 2-(ethoxycarbonyl)cyclopentanone (**6**) was carried out under the same conditions employed for ethyl 3-oxobutanoate, unless otherwise stated.

Asymmetric Hydrogenation of Methyl Phenylglyoxylate (4c). A 100 mL Hastelloy autoclave was purged five times

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with hydrogen, and then a solution of methyl phenylglyoxylate (3.085 mmol) and (+)-**3c** (0.028 mmol) in MeOH (20 mL) containing HBF_4 (0.152 mmol), previously degassed for 15 min with argon, was loaded into the autoclave with a syringe. Hydrogen was introduced (100 kg/cm^2), and the solution was stirred at 30 °C for 26 h. The autoclave was cooled, the hydrogen pressure released, and the solvent evaporated. Chromatography (SiO_2, eluant: hexane/AcOEt 7:3) provided (*R*)-(+)-2-hydroxy-2-phenylmethyl acetate (**5d**) (85% yield).

Asymmetric hydrogenation of ethyl 2-keto-4-phenylbutyrate (**4d**) was carried out under the same conditions as employed for methyl phenylglyoxylate.

Kinetic Experiments. At appropriate time intervals, stirring was stopped, and an aliquot of the solution was drawn out through the sampling pipe by exploiting internal pressure and GC-analyzed to evaluate conversion. After sampling, the hydrogen pressure was restored and stirring resumed.

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