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Synthesis of a New Water-Soluble C_2-Symmetric Chiral Diamine: Preliminary Investigation of Its Catalytic Properties for Asymmetric Hydrogenation under Biphasic Conditions

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A water-soluble version of *N*,*N*′-dimethyl-1,2-diphenylethane-1,2-diamine was prepared by introduction of phosphonic acid moieties on the para position of the aromatic rings. Preliminary investigation of the catalytic properties of the iridium complex of this ligand under biphasic conditions showed that this system compared well with the homogeneous counterpart for the asymmetric hydrogenation of ketones but with noticeably higher reaction rates for the biphasic system.

Introduction

The use of water-soluble organometallic catalysts for chemical reactions is one successful solution to the major problem of homogeneous catalysis, i.e., the expensive separation of catalyst from products and possible unconverted reactants. The best evidence is given by the variety of large-scale industrial processes parallel to academic research.[1] Aqueous two-phase catalysis is located between heterogeneous and homogeneous catalysis, and in this context, there is a steady demand for water-soluble and water-stable metal complexes. Despite the broad range of polar groups employed to achieve water solubility, sulfonated derivatives have proven to be the most efficient, as illustrated by the famous tris(*m*-sulfonatophenyl)phosphine[2] associated to rhodium for biphasic aqueous hydroformylation or hydrogenation. Very close in nature to sulfonate is the phosphonate PO_3Na_2 group that can also confer an outstanding solubility in water. Curiously, however, the use of these polar units to prepare water-soluble ligands is rather limited in the literature,[3] probably because of the well-known ability of phosphonic acids to strongly coordinate most of the metals at various oxidation states.[4] However, we and others have shown that in the case of phosphines[3a−c,e−h] or diamines[3d] functionalized by PO_3Na_2 moieties, soft metals such as Pd^{II}, Rh^{I}, Ru^{II}, or Ir^{I} preferably bind to the phosphine or nitrogen centers, thus opening the way to their potential use in biphasic catalysis. This approach was successfully developed by us with new iridium and rhodium bisphosphonato-2,2′-bipyridine complexes, efficient for the hydrogenation of substituted acetophenones in water under hydrogen pressure.[3d] Encouraged by these good results, and as a logical extension of this work, we were interested in knowing if this methodology might be applicable to chiral series. For this purpose, we describe in this paper a water-soluble version of enantiomerically pure (1*R*,2*R*)- and (1*S*,2*S*)-*N*,*N*′-dimethyl-1,2-diphenylethane-1,2-diamines **2a**, functionalized by phosphonic acid units on the phenyl rings. The corresponding iridium complexes were tested for the asymmetric hydrogenation of various aromatic ketones under hydrogen pressure in a water−methanol mixture. The following justified this choice: (i) the facile large-scale preparation of C_2-symmetric diamine **2a** reported in the literature[5] that should be easy to transpose to parent functionalized

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(1) For a detailed review, see: (a) *Aqueous Phase Organometallic Catalysis*: Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, 1998. (b) Cornils, B.; Herrmann, W. A.; Eckl, R. W. *J. Mol. Catal. A: Chem.* **1997**, *116*, 27−33.

(2) See, for example: (a) Rhône-Poulenc Recherche (Kuntz, E.). FR Patent 2.314.910, 1975. Kuntz, E. G. *Chem. Technol.* **1987**, 570−575. (b) Sheldon, R. A. *C. R. Acad. Sci. Paris, Série IIc, Chem.* **2000**, *3*, 541−551. (c) Grosselin, J. M.; Mercier, C.; Grass, F. *Organometallics* **1991**, *10*, 2126−2133.

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(4) See, for example: Clearfield, A. In *Progress in Inorganic Chemistry* Karlin, K. D., Ed.; Wiley & Sons: New York, 1998; pp 371−510.

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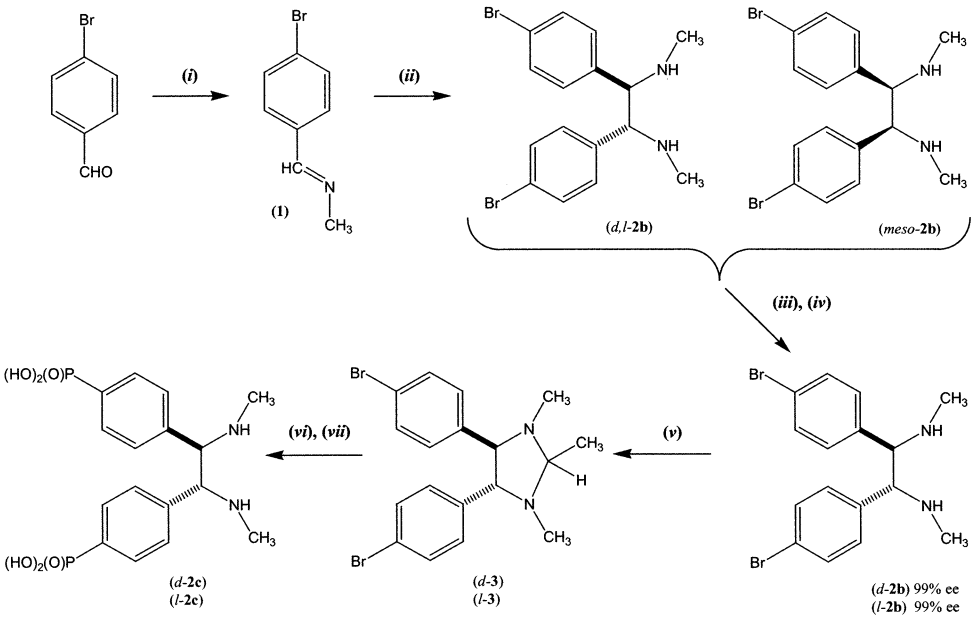
SCHEME 1[a]



[a] Reaction conditions: (i) aqueous CH_3NH_2 (96%). (ii) (a) Zinc/Me_3SiCl, THF; (b) DL-tartaric acid, 95% EtOH (63%). (iii) SiO_2 chromatography eluting with EtOH/Et_2O saturated with NH_3 (1/9) (80%). (iv) L- or D-tartaric acid, 95% EtOH (85% for *d*-**2b**; 90% for *l*-**2b**). (v) Acetaldehyde, Et_2O, 4 Å MS (97.5%). (vi) Pd_2dba_3, $HP(O)(OEt)_2$, Et_3N, Ph_3, toluene, 105 °C (81%). (vii) Me_3SiBr, CH_2Cl_2, then MeOH (81%).

diamines; (ii) beside phosphines that have proved to be highly efficient ligands for asymmetric catalysis,[6a,b] nitrogen-based ligands are also good candidates in this field and offer several advantages such as air stability and ease of preparation and handling;[6c] (iii) iridium complexes of diamine **2a** have been reported for the asymmetric reduction of α-keto-esters with molecular hydrogen with ee values up to 72%,[7a] and the rhodium analogue performed the reduction of acetophenone under hydride transfer conditions with 67% ee (KOH/*i*-PrOH) and 56% ee (tBuOK/*i*-PrOH).[7b]

Results and Discussion

The desired chiral bisphosphonato diamine **2c** (Scheme 1) was prepared starting from the enantiomerically pure *d* and *l* forms of C_2-symmetric diamine **2b** synthesized by adapting the procedure described by Alexakis et al.[5] for the preparation of *N*,*N*′-dimethyl-1,2-diphenylethane-1,2-diamine **2a**. Imine **1** was prepared by condensation of 4-bromobenzaldehyde with an aqueous solution of methylamine. The reductive dimerization of **1** on a 0.25 mol scale using the combination of zinc and chlorotrimethylsilane afforded the mixture of racemic *d*,*l* and *meso* diamines **2b** in a 1:1 ratio. In our hands, THF was found to be the best solvent compared to acetonitrile, which is usually recommended in the literature but led, in our case, to the formation of large amounts of 4-bromobenzylmethylamine. The separation of the *d*,*l*-**2b** and *meso*-**2b** isomers by crystallization in various solvents or by treatment of the crude mixture with racemic tartaric acid in ethanol failed, but the latter treatment was efficient for isolation of the pure mixture of the *d*,*l* and *meso* compounds, the separation of which was then easily performed by chromatography on silica eluting with ethanol gradients in diethyl ether saturated with ammonia.[8] Then, the resolution of the *d*,*l* diamine **2b** was carried out using L-(+)-tartaric acid and D-(−)-tartaric acid successively, according to an optimized protocol derived from Alexakis et al.,[5] to give the (*R*,*R*)- and (*S*,*S*)-diamines in good yields. At this stage, the introduction of the phosphonate groups was investigated via a Pd-catalyzed cross-coupling reaction of the bromoaryl units and diethyl phosphite, as described by Hirao et al.[9] Very poor results were obtained using the standard conditions, probably because of the ability of the diamine to coordinate palladium. This problem was overcome by using a large excess of triphenylphosphine (10-fold excess with respect to the diamine) as previously reported by us[10] for a similar reaction in the case of bipyridines. Moreover, cleaner reactions were observed when $Pd((P(C_6H_5)_3)_4$ was replaced by Pd_2dba_3 as the palladium(0) source. Nevertheless, under our best conditions, the yield did not

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(7) (a) Tommasino, M. L.; Thomazeau, C.; Touchard, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1999**, *10*, 1813−1819. (b) Bernard, M.; Guiral, V.; Delbecq, F.; Fache, F.; Sautet, P.; Lemaire, M. *J. Am. Chem. Soc.* **1998**, *120*, 1441−1446.

(8) For very large-scale preparations, a limiting step is the separation of *meso*-**2b** and *d*,*l*-**2b** by column chromatography. To overcome this problem, this mixture can be treated by acetaldehyde to form *meso*-**3** and *d*,*l*-**3**. The aminal *d*,*l*-**3** was selectively crystallized out of acetonitrile, and after hydrolysis under acidic conditions, *d*,*l*-**2b** was recovered and used for the separation of the *d* and *l* isomers (yield of *d*,*l*-**2b** isolated from a *meso*-**2b** and *d*,*l*-**2b** mixture on a 30 g scale: 79%). See Supporting Information.

(9) Hirao, T.; Masunage, T.; Yoshiro, O.; Agawa, T. *Synthesis* **1981**, 56−57.

(10) Penicaud, V.; Odobel, F.; Bujoli, B. *Tetrahedron Lett.* **1998**, *39*, 3689−3692.

TABLE 1. Experimental Data for the Asymmetric Hydrogenation of Acetophenone under H_2 Pressure Using Ligand 2b in Methanol and Ligand 2c in 1/1 Water/Methanol[a]

entry	conditions	metal/ligand/substrate	alcohol yield (%)	ee[f] (%)
1[b]	(*R*,*R*)-**2b** + $[Ir(COD)Cl]_2$	1/2/40	31	58
2[b]	(*R*,*R*)-**2b** + $[Ir(COD)_2]BF_4$	1/2/40	>99	60
3[b]	(*R*,*R*)-**2c** + $[Ir(COD)_2]BF_4$	1/2/40	93	55
4[b]	(*R*,*R*)-**2c** + $[Ir(COD)_2]BF_4$	1/2/200	28	47
5[b,c]	(*R*,*R*)-**2c** + $[Ir(COD)_2]BF_4$	1/2/200	>99	34
6[d] cycle 1	(*R*,*R*)-**2c** + $[Ir(COD)_2]BF_4$	1/2/200	>99	50
7[d] cycle 2	(*R*,*R*)-**2c** + $[Ir(COD)_2]BF_4$	1/2/200	>99	54
8[d] cycle 3	(*R*,*R*)-**2c** + $[Ir(COD)_2]BF_4$	1/2/200	>99	52
9[d] cycle 4	(*R*,*R*)-**2c** + $[Ir(COD)_2]BF_4$	1/2/200	>99	51
10[d]	(*R*,*R*)-**2c** + $[Ir(COD)_2]BF_4$	1/2/1000	38	52
11[d,e]	(*R*,*R*)-**2c** + $[Ir(COD)_2]BF_4$	1/2/1000	>99	53
12[d]	(*R*,*R*)-**2c** + $[Ir(COD)_2]BF_4$	1/1/200	15	50
13[d]	(*R*,*R*)-**2c** + $[Rh(COD)_2]BF_4$	1/2/200	formation of Rh metal	
14[d]	(*R*,*R*)-**2c** + $[Ru(p\text{-cym.})(Cl)_2]_2$	1/2/200	37	16

[a] General conditions: [Ir, Rh, or Ru] = 2×10^{-3} M, 1/2/10 metal/ligand/NaOH, 45 atm, 50 °C, 21 h. [b] Catalyst prepared under air. [c] OH^- (6 equiv) added with respect to iridium. [d] Catalyst prepared under argon. [e] Reaction time: 62 h. [f] (*S*)-Enantiomer. Enantiomeric excesses were measured either by GC on a Machery-Nagel LIPODEX E column (length, 25 m; diameter, 250 μ; flow, 2 mL/mn; carrier gas, helium; 86 °C isotherm) or by HPLC on a Chiracel OD-H column (eluent, 98/2 hexane/*i*-PrOH; flow, 0.5 mL/min; pressure, 14 atm) with similar results.

exceed 70% of a mixture of the desired bisphosphonate diamine contaminated with its monofunctionalized analogue. Protection of the diamine was thus necessary, and for this purpose, the two enantiomers of **2b** were easily converted into the corresponding *d* and *l* aminals **3** by reaction with acetaldehyde. An X-ray crystallographic study clearly indicates that the *d* form of **3** corresponds to the (*R*,*R*)-enantiomer. On substrate **3**, the palladium-catalyzed phosphonation of the aryl rings proceeded well. In the workup of the reaction, the major part of the triphenylphosphine was recovered by crystallization and an acid treatment step was introduced, allowing the removal of the aminal protecting group. The phosphonate ester form of diamines *d*- and *l*-**2c** was thus obtained in good yields, and the corresponding phosphonic acid analogues were obtained by their deprotection using Mc Kenna's method.[11]

Preliminary experiments were then run for the evaluation of the catalytic properties of aqueous solutions of **2c** for the asymmetric reduction of ketones (i) under hydrogen pressure and (ii) under hydride transfer conditions. Two homogeneous catalytic runs in methanol were first performed under H_2 pressure (45 atm, 50 °C, 21 h) using ligand **2b** treated with two iridium sources: $[Ir(COD)Cl]_2$ and $[Ir(COD)_2]BF_4$ (Ir/acetophenone molar ratio = 2.5%). Comparable ee values (~58%) were obtained, with a significantly higher reaction rate for the cationic complex (Table 1, entries 1 and 2), and hence the fluoroborate salt was chosen to study the catalytic properties of **2c** under biphasic conditions. Ligand **2c** was soluble in water after addition of 5 equiv of sodium hydroxide. Due to the very poor solubility of $[Ir(COD)_2]BF_4$ in water, a cosolvent had to be added. Consequently, the iridium precursor was first dissolved in methanol and the resulting solution was mixed with the same volume of ligand **2c** in water as prepared above. The mixture was stirred at ambient temperature for 4 days; at shorter times, some problems of stability were observed, with the formation of a small amount of black precipitate, resulting in a pollution of the reactor as evidenced by blank experiments that were not correct after a catalytic run. Under the former conditions, ligand **2c** compared fairly well with the homogeneous system (entry 3 versus entry 2). Attempts to run tests in pure water (by evaporation of the complex prepared in a water/methanol mixture and redissolution in water) resulted in lower ees (~35%).

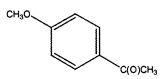
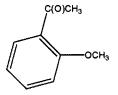
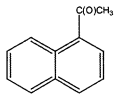
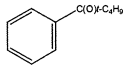
Whereas a lower iridium/substrate loading (0.5%) led to low conversion in 21 h (entry 4), the addition of sodium hydroxide in the reaction medium allowed higher reaction rates but with a decrease of the enantioselectivity (entry 5). A significant ee improvement was achieved by preparing the complex under an inert atmosphere since a quantitative yield and stable ees (average ca. 52%) were observed in a recycling experiment (entries 6−9). Completion of the reduction with similar ees was also obtained even with a further decrease of the catalyst loading (0.1%), although a longer reaction time was required (entries 10 and 11). A decrease of the ligand/iridium ratio slowed the reaction rate (entry 12), while attempts to use rhodium or ruthenium instead of iridium resulted in an unstable catalyst in the former case and lower conversion and ee in the latter case (entries 13 and 14).

The biphasic system was then tested for the reduction of other ketones, leading to ee values somewhat lower than those recorded with the homogeneous system based on **2b** (Table 2, entries 1−4) but showing higher yields.

The validity of these data was confirmed (i) by repeating the test corresponding to entry 3 satisfactorily and (ii) by measuring the initial reaction rates for the homogeneous system **2b** (TOF ≈ 10 h^{-1}; ee 75%) and the biphasic system **2c** (TOF ≈ 19 h^{-1}; ee 71%), used for the hydrogenation of 2-methoxyacetophenone (Ir/substrate = 0.1%). Interestingly, a significantly higher reaction rate was observed with diamine **2c**, consistent with data from entry 2. It is also worth noting that in the case of the bulky *tert*-butylphenyl ketone (entry 4), (i) the opposite enantiomers of 2,2-dimethyl-1-phenyl-1-propanol were formed using ligand **2b** versus **2c** and (ii) better results were obtained compared to the Ru-[(*S*)-BINAP/(*S*,*S*)-

(11) McKenna, C. E.; Higa, M. T.; Cheung, N. H., McKenna, M. C. *Tetrahedron Lett.* **1977**, 155−158.

TABLE 2. Compared Values for the Asymmetric Hydrogenation of Various Ketones under H_2 Pressure, Using Ligand (*S,S*)-2b in Methanol and Ligand (*S,S*)-2c in 1/1 Water/Methanol[a]

entry	substrate	alcohol yield using **2c** (%)	ee (%)	alcohol yield using **2b** (%)	ee (%)
1		> 99	50 (*R*)	78	65 (*R*)
2		> 99	70 (*R*)	32	74 (*R*)
3		98 93 93	69 (*R*) 64 (*R*) 64 (*R*)	53 49 49	77 (*R*) 79 (*R*) 72 (*R*)
4		> 99	72 (*S*)	27	84 (*R*)

[a] General conditions: [Ir] = 2 × 10^{-3} M, 1/2/10 Ir/ligand/NaOH, 45 atm, 50 °C, 21 h, Ir/substrate = 0.5%. Catalyst: (*S,S*)-**2c** + $[Ir(COD)_2]BF_4$ in 1/1 MeOH/water prepared under argon.

DPEN] system for which the substrate was surprisingly almost inert (6% yield, 61% ee even under 50 atm of H_2).[6b]

The case of 4-methylcyclohexanone was also examined, to compare the cis/trans ratios of the corresponding alcohol formed in biphasic (using **2c**) and homogeneous conditions (using **2b**). Similar results were obtained (conversion > 99%; cis/trans ≈ 25/75), but in the latter case, the final product was contaminated by 15% of 1,1-dimethoxy-4-methylcyclohexane.

It was also of interest to study the ability of ligand **2c** complexed to rhodium [precursor: $[Rh(COD)Cl]_2$] to catalyze asymmetric transfer hydrogenation in conditions similar to those described by Thorpe et al.[12] [*t*-BuOK, 1:1 water/*i*-PrOH] with water soluble aminosulfonamide ligands. The activity of our system for the reduction of acetophenone (46% ee for a 95% yield) was found to be similar to that reported with **2a** in homogeneous conditions (46% ee for a 98% yield),[13] using comparable experimental conditions (1:2:4:20 Rh/ligand/*t*-BuOK/substrate).

In conclusion, this work gives evidence that organometallic complexes functionalized by PO_3H_2 moieties can be advantageously used in biphasic catalytic processes, with an easy recovery of the metal complex in the aqueous phase. This is the first example of chiral nitrogen ligand derivatized using this strategy. The preliminary catalytic results show that the reported diamine-bisphosphonate **2c** allows the asymmetric reduction of ketones under hydrogen pressure or under hydride transfer conditions as well, with performances very close, or in some cases superior, to that observed with the homogeneous parent system using **2b**. As a consequence, phosphonates appears to be a valuable option, parallel to sulfonates, for the derivatization of homogeneous ligands to be used in aqueous media. Our future work will concentrate on the development of a supported version ligand **2c** that will be readily accessible, taking account of our successful experience using bipyridine-bisphosphonates.[14]

Experimental Section

Chemical analyses were performed by the C.N.R.S. Analysis Laboratory (Vernaison). The optical purity of compound **2b** was determined by HPLC analyses using a Chiracel OD-H column (flow = 0.5 mL/min, solvent = 95/5 hexane/*i*-propanol, detection = 254 nm, retention times: *meso*, 5.4 min; *d*, 6.7 min; *l*, 9.5 min).

X-ray crystal data for *d*-**3** (Figure 1): $C_{18}H_{20}Br_2N_2$; M = 424.2, monoclinic space group *C*2 (No. 5), *T* = 100 K, ρ_{calcd} = 1.593 g/cm^3, *Z* = 4, *a* = 22.9874(5) Å, *b* = 5.16190(10) Å, *c* = 15.9750(4) Å, β = 111.1200(10)°, *V* = 1768.24(7) Å^3, μ = 2.291 mm^{-1}. Final *R* [$F^2 > 2\sigma(F^2)$] = 0.0345, w*R*(F^2) = 0.0997 for 229 variables and 4896 data points. Full details can be found in Supporting Information.

***N*-Methyl-4-bromobenzimine (1).** 4-Bromobenzaldehyde (48 g, 0.26 mol) was added to an aqueous solution (40% w/w, 26 mL) of methylamine cooled to 0 °C. The resulting milky white emulsion was stirred at room temperature for 1 h. The crude mixture was then extracted with 150 mL of dichloromethane. The organic phase was separated, washed with 100 mL of water, dried over sodium sulfate, and filtered, and the solvent was evaporated under reduced pressure. The desired imine was obtained as a white solid (49.3 g) in 96% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.50 (3H, d, ^4J = 1.7 Hz), 7.55 (4H, m), 8.22 (1H, q, ^4J = 1.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 48.2, 124.9−129.3−131.8−135.1, 161.2.

***meso*- and *d,l*-1,2-Bis-(4-bromophenyl)-*N,N′*-dimethylethane-1,2-diamine (2b).** Zinc (325 mesh, 16.5 g, 0.25 mol) was suspended in anhydrous freshly distilled THF (75 mL) under argon. The zinc powder was activated by addition of 1,2-

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dibromoethane (2.2 mL) using a syringe while stirring, and the mixture was heated under mild reflux for 1 min. After the mixture was cooled to room temperature, chlorotrimethylsilane (4.5 mL) was added with a syringe and evolution of ethylene gas was observed. The reaction medium was stirred for 45 min, and the imine **1** (49.3 g in 150 mL of dry THF, 0.25 mol) was added in one portion. Chlorotrimethylsilane (48 mL, 0.38 mol) was then added dropwise over a 30 min period, while keeping the flask in an oil bath warmed at 35 °C. The mixture was then refluxed for 3 h and cooled to 0 °C. Under strong stirring, a solution prepared by mixing concentrated aqueous ammonium hydroxide (75 mL) and saturated aqueous ammonium chloride (225 mL) was carefully poured into the flask; after 45 min, the remaining zinc was removed by filtration over Celite. The organic layer was separated and the aqueous phase extracted with dichloromethane (3 × 300 mL). The combined organic phases were dried over sodium sulfate and evaporated after filtration to give an orange deliquescent residue. Ethanol (95%) was added (270 mL), and the crude mixture was refluxed, resulting in a clear yellow solution. Meanwhile, racemic tartaric acid (18.5 g, 0.123 mol) was dissolved in 95% hot ethanol (150 mL) and added to the clear diamine solution, and the resulting mixture was refluxed for 1 h. It was allowed to cool at room temperature and allowed to stand overnight. The precipitate formed was collected by filtration and washed with cold 95% ethanol (3 × 50 mL). This salt (72.5 g) was suspended in 445 mL of distilled water, and 37 mL of aqueous 50% (w/w) sodium hydroxide was added, followed by 370 mL of dichloromethane. After stirring for 1 h, the phases were separated and the aqueous phase was extracted using dichloromethane (3 × 230 mL). The combined organic phases were washed with 460 mL of saturated NaCl aqueous solution, dried over sodium sulfate, and evaporated to give the pure diamine **2b** (white powder, 31 g, 63% yield) as a 50/50 mixture of the *meso* and *d*,*l* isomers. The *meso* compound was isolated by column chromatography (SiO_2), eluting with diethyl ether saturated with ammonia, and then the *d*,*l* mixture was recovered eluting with EtOH/Et_2O saturated with NH_3 (1/9) with an 80% separation yield. *meso*-**2b** ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (2H, s), 2.11 (6H, s), 3.56 (2H, s), 7.11 (4H, d, ^3J = 8.4 Hz), 7.45 (4H, d, ^3J = 8.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.5, 70.1, 121.5−130.1−131.6−139.4. mp: 140 °C. *d*,*l*-**2b** ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.88 (2H, s), 2.22 (6H, s), 3.44 (2H, s), 6.88 (4H, d, ^3J = 8.4 Hz), 7.30 (4H, d, ^3J = 8.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.5, 70.5, 120.9−129.7−131.2−139.8. Mp: 118 °C.

***d*- and *l*-1,2-Bis-(4-bromophenyl)-*N*,*N*′-dimethyl-ethane-1,2-diamine (2b).** A mixture of pure *d*,*l* diamine **2b** (11.7 g, 0.0295 mol) and 257 mL of 95% ethanol was refluxed until the diamine dissolved. Meanwhile, 4.41 g of L-tartaric acid (0.0294 mol) was dissolved in boiling 95% ethanol (257 mL) and added to the diamine solution, and the resulting mixture was refluxed for 1 h, after the observation of salt formation. The reaction medium was allowed to cool to room temperature for 2 h, and the precipitate was collected by filtration and washed with cold 95% ethanol (3 × 50 mL). This salt was suspended in 100 mL of distilled water, and 9.4 mL of aqueous 50% (w/w) sodium hydroxide was added, followed by 90 mL of dichloromethane. After the mixture was stirred for 1 h, the phases were separated and the aqueous phase was extracted using dichloromethane (3 × 70 mL). The combined organic phases were washed with 70 mL of saturated NaCl aqueous solution, dried over sodium sulfate, and evaporated. This treatment was repeated twice to obtain the *d* diamine **2b** (5 g, ee = 99% [HPLC]; yield of separation = 85%) as a white deliquescent powder. $[\alpha]_D^{20}$ 84.5 (*c* 1, CH_2Cl_2). The three combined mother liquors obtained above were concentrated under vacuum, and the residue was stirred with 100 mL of distilled water and 9.4 mL of aqueous 50% (w/w) sodium hydroxide, followed by 90 mL of dichloromethane. After stirring for 1 h, the phases were separated and the aqueous phase was extracted using dichloromethane (3 × 70 mL). The combined organic phases were washed with 70 mL of saturated NaCl aqueous solution, dried over sodium sulfate, and evaporated. The resulting crude mixture (ee 67%) was treated once with D-tartaric acid, using a procedure identical to that described for the preparation of the *d* diamine **2b**. The *l* diamine **2b** (5.25 g, ee = 99%; yield of the separation = 90%) was finally obtained as a white deliquescent powder. $[\alpha]_D^{20}$ −84.5 (*c* 1, CH_2Cl_2). Anal. Calcd for $C_{16}H_{18}N_2Br_2$: C, 48.26; H, 4.56; N, 7.04. Found: C, 47.93; H, 4.58; N, 6.98.

***d*- and *l*-4,5-Bis-(4-bromophenyl)-1,2,3-trimethylimidazolidine (3).** The desired *d* or *l* diamine **2b** (4.38 g, 0.011 mol), 58 mL of dry diethyl ether, 4 Å molecular sieves (4.2 g), and acetaldehyde (1.22 mL, 0.022 mol) were charged in a flask, under argon. The mixture was stirred for 1.5 h, filtered, and evaporated to yield **3** as a white powder (4.54 g, 97.5% yield), which was crystallized from acetonitrile as colorless needles. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (3H, d, ^3J = 5.8 Hz), 2.20 (3H, s), 2.24 (3H, s), 3.24 (1H, d, ^3J = 8.6 Hz), 3.50 (1H, d, ^3J = 8.6 Hz), 3.90 (1H, q, ^3J = 5.8 Hz), 7.0 (4H, m), 7.37 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.0, 35.5, 38.3, 76.3, 77.9, 80.8, 121.3−129.8−131.4−138.7−139.0. *l*-(**3**) $[\alpha]_D^{20}$ −97.7 (*c* 1, CH_2Cl_2). Mp: 115 °C. *d*-**3**: $[\alpha]_D^{20}$ 97.7 (*c* 1, CH_2Cl_2). Mp: 115 °C. Anal. Calcd for $C_{18}H_{20}N_2Br_2$: Br, 37.67; C, 50.96; H, 4.75; N, 6.60. Found: Br, 37.69; C, 51.01; H, 4.81; N, 6.63.

***d*- and *l*-1,2-Bis-(4-dihydroxyphosphorylphenyl)-*N*,*N*′-dimethyl-ethane-1,2-diamine (2c).** Aminal **3** (0.5 g, 1.18 mmol), triphenylphosphine (3.09 g, 11.8 mmol), and $Pd_2(dba)_3$ (0.109 g, 0.118 mmol) were charged in a flask under argon. Toluene (14 mL), triethylamine (0.72 mL, 5.18 mmol), and diethyl phosphite (0.67 mL, 5.18 mmol) were added, and the mixture was degassed thoroughly using several vacuum/argon cycles. The reaction medium was stirred and heated at 102−105 °C for 15 h. After the mixture was cooled to room temperature, water (20 mL) and dichloromethane (20 mL) were added and the aqueous layer was extracted with dichloromethane (2 × 4 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine, dried over sodium sulfate, and evaporated under vacuum to obtain a yellow gummy mass. To this residue was added boiling 95% ethanol (15 mL) until complete dissolution, and the mixture was allowed to stand at room temperature for 1 h. The crystalline triphenylphosphine thus formed was filtered off (1.9 g), and the mother liquor was evaporated under reduced pressure. The crude product was dissolved in a mixture of methanol (8 mL) and dichloromethane (6 mL), and 12 M HCl (0.5 mL) was added. After stirring for 2 h, the solution was evaporated under vacuum and water (20 mL) and dichloromethane (20 mL) were added. The organic layer was extracted with water (2 × 4 mL), and the combined aqueous layers were washed with dichloromethane (6 × 10 mL). The resulting turbid aqueous phase was neutralized using a saturated sodium bicarbonate solution (pH 7−8) and then extracted with 20 mL of dichloromethane. The aqueous layer was further washed with dichloromethane (3 × 3 mL), and the combined organic extracts were washed with water (15 mL) and brine, dried using sodium sulfate, and evaporated to dryness to give the ester form of diamine **2c** as a colorless oil (0.43 g, yield 81%), which was used directly for the hydrolysis of the ester groups. If performed on a larger scale (2.3 g of starting **3**), the yield of this synthesis was about 70%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (12H, t, ^3J = 7 Hz), 2.27 (6H, s), 2.50 (2H, bs), 3.66 (2H, s), 4.1 (8H, m), 7.15 (4H, m), 7.45 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.2 (d, $^3J_{C-P}$ = 6.4 Hz), 34.4, 62.0 (d, $^2J_{C-P}$ = 5.3 Hz), 70.8, 127.0 (d, $^1J_{C-P}$ = 188 Hz), 128.0 (d, J_{C-P} = 15 Hz), 131.4 (d, J_{C-P} = 10 Hz), 145.4. ^{31}P NMR (81 MHz, $CDCl_3$): δ 18.4.

The above-mentioned oil (1.108 g, 2.16 mmol) was dissolved in 15 mL of dichloromethane, and bromotrimethylsilane (2.9 mL, 21.6 mmol) was added in one portion and stirred at room temperature under inert atmosphere for 2 days. The reaction medium was evaporated under reduced pressure to obtain a foamy solid to which methanol (15 mL) was added, and the mixture was stirred for 1 day at ambient temperature.

Methanol was then evaporated, and the residue was dissolved in 10 mL of water. Upon addition of acetone, a white solid appeared, which was filtered, washed with acetone, and dried under vacuum to give 0.8 g of compound **2c** as a white powder (75% yield). ^{1}H NMR (200 MHz, D_2O): δ 2.60 (6H, s), 5.07 (2H, s), 7.20 (4H, m), 7.75 (4H, m). ^{31}P NMR (81 MHz, D_2O): δ 11.9. *l*-**2c**: $[\alpha]_D^{20}$ −62.7 (*c* 1, 1 M NaOH). Mp: 285 °C (dec.). *d*-**2c**: $[\alpha]_D^{20}$ 62.6 (*c* 1, 1 M NaOH). Mp: 285 °C (dec.). The compounds were isolated in the form of their hydrobromide monohydrate salt. Anal. Calcd for $C_{16}H_{22}N_2P_2O_6 \cdot HBr \cdot H_2O$: P, 12.41; C, 38.49; H, 5.05; N, 5.61. Found: P, 12.48; C, 38.43; H, 5.15; N, 5.57.

General Conditions for Hydrogenation under Hydrogen Pressure. Ligand **2c** (15 mg, 0.03 mmol) was suspended into 3.75 mL of distilled water, and 150 μL of 1 M sodium hydroxide (OH^-/**2c** 5 equiv) was added. The resulting clear mixture was thoroughly degassed using several vacuum/argon cycles, and 3.75 mL of a degassed 4×10^{-3} M $[Ir(COD)_2]BF_4$ solution in methanol was added. Then, the mixture was stirred at room temperature for 4 days under argon. The catalyst was then transferred into a 30 mL stainless steel glass-coated autoclave, and the substrate (with the desired iridium/substrate molar ratio) was then introduced. The autoclave was purged three times with argon, followed by three times with hydrogen, and the final H_2 pressure was adjusted to 45 atm and heated at 50 °C. After 21 h of stirring, the autoclave was allowed to cool and decompressed. The reaction mixture was extracted several times using petroleum ether for analysis. The compared reaction rates between the homogeneous (**2b**) and biphasic (**2c**) systems were measured using an autoclave (volume = 300 mL) equipped with a sampling valve, a tubular oven, an internal temperature probe, and a mechanical stirrer (set at 1000 rpm). For each test, 75 mL of the catalyst solution ([Ir] = 4×10^{-4} M) was used with a 0.1% iridium/substrate ratio.

General Conditions for the Hydride Transfer Hydrogenation. Ligand **2c** (28.5 mg, 0.057 mmol) was suspended into 2.3 mL of distilled water, and 285 μL of 1 M sodium hydroxide (5 equiv) was added. The resulting clear mixture was thoroughly degassed, and 2.3 mL of a 0.1 M degassed *t*-BuOK solution in isopropanol was added. Then, 7 mg [0.014 mmol] of $[Rh(COD)Cl]_2$ were introduced, and the mixture was stirred at 50 °C overnight. Finally, 67 μL of acetophenone [Rh/substrate 5%] was injected into this yellow solution with a syringe.

The reaction products obtained from the catalytic tests were analyzed by gas chromatography (using the internal standard method [nonane]) with a J & W Scientific DB-1701 column (*l* = 30 m, i.d. = 0.25 mm), equipped with a FID detector (N_2 as the carrier gas). The enantiomeric excesses of the various alcohols (Table 2) formed were measured using a Machery-Nagel LIPODEX E column (*l* = 25 m, i.d. = 0.25 mm, He as the carrier gas); the configuration of the major enantiomer formed was assigned by polarimetry, by comparison with literature data.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **1**, **2b**, **3**, and **2c** (ester and acid form); X-ray crystallographic data for compound *d*-**3** and an ORTEP drawing of the structure, corresponding to the (*R*,*R*)-enantiomer; and experimental procedure for the separation of *meso*-**2b** and *d*,*l*-**2b** on large-scale preparations. This material is available free of charge via the Internet at http://pubs.acs.org.

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