Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 639–645

4,4′ and 5,5′-DiamBINAP as a hydrosoluble chiral ligand: syntheses and use in Ru(II) asymmetric biphasic catalytic hydrogenation

Mikaël Berthod,[a] Christine Saluzzo,[a] Gerard Mignani[b] and Marc Lemaire[a,*]

[a]*Laboratoire de Catalyse et de Synthèse Organique, UMR 5181, UCBL, CPE Bat. 308, 43, Boulevard du 11 Novembre 1918, 69622 Villeurbanne Cedex, France*
[b]*Rhodia, Centre de recherches de Lyon, 85, avenue des Frères-Perret, BP 62, 69192 Saint-Fons Cedex, France*

Received 21 October 2003; revised 10 December 2003; accepted 11 December 2003

Abstract—4,4′ and 5,5′-DiaminomethylBINAP were prepared in five steps from enantiomerically pure BINAP. Their synthesis involves, as key steps, the regioselective bromination of BINAP and the chemoselective efficient reduction of a dicyano, diphosphine oxide into the corresponding dicyano, diphosphine by a mixture of $HSiCl_3/PhSiH_3$. The ruthenium complexes of these new ligands were tested for the homogeneous and water/organic solvent biphasic asymmetric hydrogenation of β-ketoesters leading to 100% conversion with an enantiomeric excess greater than 97% in water. Catalysts can be recycled several times by extraction of the product with pentane.

1. Introduction

Although asymmetric catalysis is without doubt one of the most promising methods for the synthesis of chiral compounds,[1] its industrial applications remain rare, even if a wide variety of reactions have been performed with both high enantioselectivities and conversions.[2] The lack of employment of asymmetric catalysis is partly due to the problems of separation and recovering of the expensive chiral catalyst. To overcome this drawback, two types of enantioselective heterogeneous catalysts have emerged: heterogeneous catalysts with demonstrated catalytic activities that are rendered chiral by modification with a chiral auxiliary[3] and homogeneous catalysts with demonstrated enantioselectivity and activity modified in such a way as to become heterogeneous.[4] Thus, the catalyst can be recovered from the reaction mixture by filtration, precipitation or extraction.

Since the industrial application of the rhodium-TPPTS system by Hoechst AG in Oberhausen, Germany, the development of water-soluble organometallic catalysis has expanded significantly. The recovery of catalysts from products by phase separation has become a very active field of research.[5,6] In the case of asymmetric catalysis, substantial efforts have been made to prepare water-soluble chiral catalysts for biphasic applications. Most of the reported water-soluble chiral ligands have been prepared by the incorporation of anionic groups such as sulfonate or carbonate cationic groups such as quaternary ammonium ions, or neutral hydrophilic groups such as polyethers. In many cases, chiral catalysts in aqueous or organic two-phase systems led to a lower stereoselectivity and/or reactivity than in the homogeneous organic phase, due to several factors such as the solvent effect, the reaction kinetics and mass transport in the two solvents.[7]

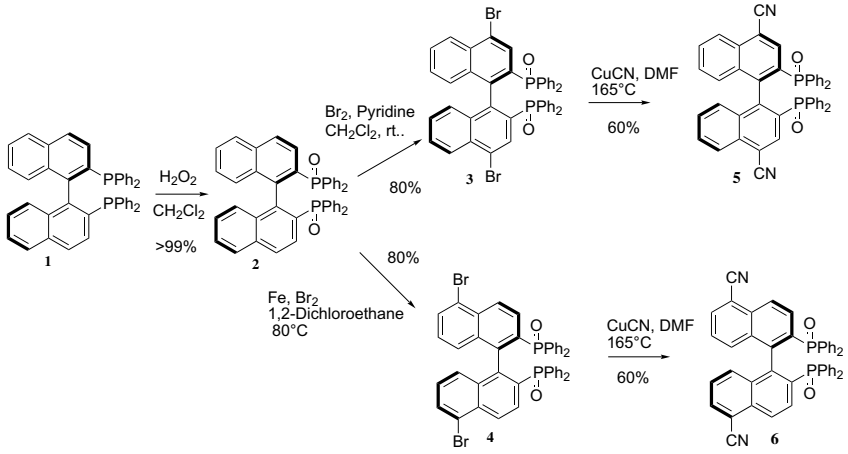
Recently, we reported the synthesis of a BINAP derivative bearing two amine functions: 6,6′-dimethylamino-BINAP (diamBINAP).[8] This modified BINAP was then involved in the synthesis of insoluble catalysts and water-soluble catalysts,[9] which were shown to be as efficient and selective as BINAP itself for the hydrogenation of β-ketoesters. Nevertheless, the synthesis of 6,6′-diamBINAP equates careful chromatographic purification, which rendered its manufacture difficult. Thus in order to overcome these drawbacks, we chose to functionalize directly and regioselectively BINAP at the 4,4′- and 5,5′-positions.

2. Results and discussion

Most of the BINAP derivatives were usually prepared from BINOL or protected BINOL with a phosphination

* Corresponding author. Tel.: +33-4-7243-1407; fax: +33-4-7243-1408; e-mail: marc.lemaire@univ-lyon1.fr

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.12.033

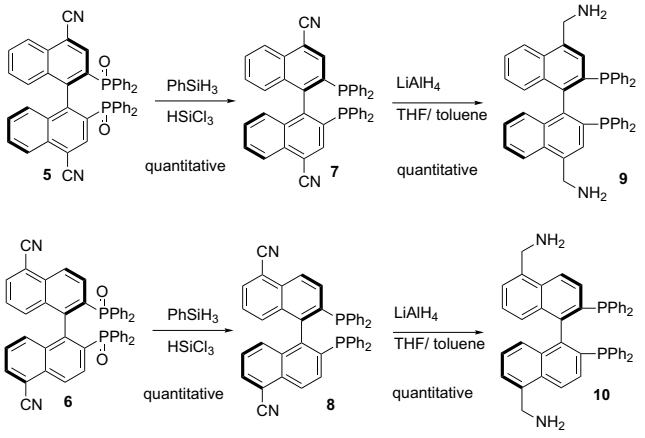


Scheme 1. Synthesis of 4,4′ and 5,5′-dicyanoBINAPO (**5** and **6**).

reaction at the end of the synthesis.[10] In order to prepare 4,4′- and 5,5′-diamBINAP **9** and **10**, we chose a five step synthesis strategy starting from optically active BINAP. As depicted in Scheme 1, (*R*)- or (*S*)-BINAP were transformed into their corresponding dioxide **2** followed by a regioselective bromination. The 4,4′-positions were brominated in the presence of pyridine[11] according to Köckritz and co-workers while the 5,5′-positions were brominated in the presence of iron as catalyst. In both cases, brominations were regioselective, with only a trace of monobrominated by-products being detected. The dibrominated phosphines **3** and **4** were obtained in 80% isolated yield. The 4,4′- and 5,5′-positions were brominated with an electron withdrawing group, with a phosphine oxide group at the 2,2′-position.[12] In the literature the only way (except cross-coupling reactions) to reach the 5,5′-position is by nitration[13] and sulfonation.[14] Our method was not as acidic but required a strong Lewis acid. Phosphine oxides are Lewis bases[15] and may be complexed during electronic substitution in presence of Lewis acid. Although the 4,4′-position was the most reactive, the presence of a Lewis acid seemed to deactivate this position by complexing the phosphine oxide; Br_2 (activated by the presence of Fe) would brominate the less deactivated 5,5′-position. To our knowledge, this method is the first report, which leads to a dibrominated BINAP at the 5,5′-position.

Dicyanation of these molecules with CuCN in DMF at 150 °C gave 4,4′ and 5,5′-dicyanoBINAPO **5** and **6** in 60% yield after recrystallization from ethanol. This key step is much easier than the same one for the 6,6′-diamBINAP synthesis, where a difficult chromatographic purification was involved.

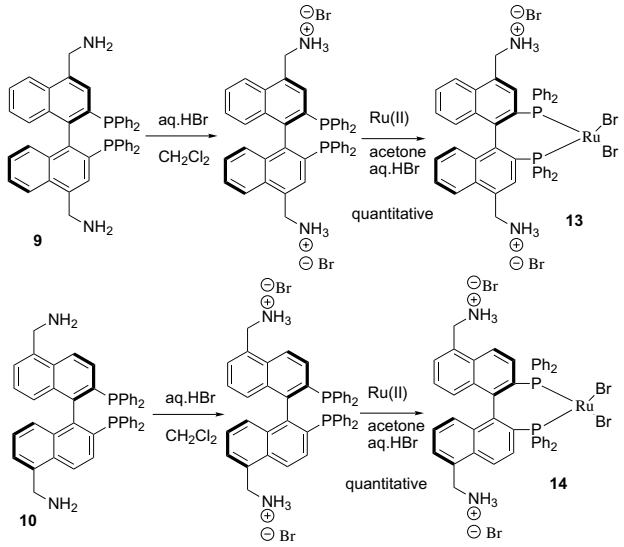
Reduction of the phosphine oxide did not succeed using normal reducing agents, such as $HSiCl_3$,[16] $LiAlH_4$ and $PhSiH_3$,[17] which gave partly reduced phosphine oxide and numerous nondetermined by-products. More complex methods such as Imamoto's ($MeOTf + LiAlH_4$)[18] failed too. For that reason, we optimized a new reducing system consisting of a mixture of $PhSiH_3$ and $HSiCl_3$ at 120 °C.



Scheme 2. Synthesis of 4,4′ and 5,5′-diamBINAP.

Thus, with this method 4,4′ and 5,5′-dicyanoBINAP **7** and **8** were obtained with up to 98% yield (Scheme 2). This efficient procedure permitted the chemoselective reduction of the phosphine oxide without reducing the cyano groups of **5** and **6**. Moreover, at the end of the reaction, products **7** or **8** crystallized from the reaction mixture and could be isolated in their pure form by filtration. Finally, the cyano groups were subsequently reduced with $LiAlH_4$ to give (*S*)- or (*R*)-4,4′ and 5,5′-diamBINAP, **9** and **10**, in 47% overall yield, starting from the enantiopure BINAP.

In order to evaluate ligands **9** and **10**, their corresponding ruthenium complexes were prepared via reaction of [(COD)Ru(2-methylallyl)$_2$] according to the general procedures described by Genêt et al.[19] The catalytic activities of these ruthenium complexes in the hydrogenation of methyl or ethyl acetoacetate were tested in methanol and ethanol, respectively, with a substrate/catalyst ratio (S/C) of 1000, at 50 °C and under 40 bar of hydrogen (Scheme 3). The same ruthenium complexes were prepared with the (*R*)-BINAP in order to compare the activity and selectivity of ligands (Table 1).

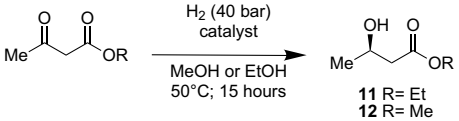


Scheme 3. Hydrosoluble catalysts from **9** and **10**.

Ligands **9** and **10** (Table 1, entries 2 and 4) were shown to be almost as efficient as the BINAP complex, which gave for the reduction of ethyl acetoacetate, total conversion and 98% ee (Table 1, entry 5). As we have already observed with 6,6′-diamBINAP[10] the aminomethyl groups do not have any influence either on the activity or on the selectivity. Moreover 4,4′ and 5,5′-diamBINAP exhibited the same efficiency as 6,6′-diamBINAP, which means that we do not change the geometry of the metal–ligand complex with the positions of the aminomethyl groups. Excellent conversions and ees were also observed for the reduction of methyl acetoacetate (Table 1, entries 1 and 3). The HBr salts of **9** and **10** and the corresponding Ru(II)-catalysts were prepared in situ from [Ru(COD)(2-methylallyl)$_2$] and aqueous hydrobromic acid according to the usual procedure.[20] Hydrosoluble catalysts **13** and **14** were obtained in quantitative yields (Scheme 3).

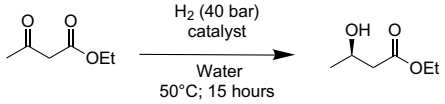
To evaluate these two hydrosoluble catalysts, hydrogenation was carried out using ethyl acetoacetate **11** as the standard substrate (Table 1). Water and ethyl acetoacetate were added to obtain a biphasic mixture where the catalysts were only in the aqueous phase. Complete conversion was obtained in all cases under 40 bar of hydrogen after 15 h at 50 °C. At the end of the reaction, the mixture was cooled down and the homogeneous solution obtained, extracted three times with pentane. Fresh substrate was added to the resulting aqueous phase the hydrogenation could be repeated under these conditions, **13** was recycled eight times with always more than 97% ee. Compound **14** was recycled six times with more than 97% ee (Table 2).

Table 1. Ruthenium catalyzed reduction of ketoesters with 4,4′ and 5,5′-diamBINAP



Entry	Ligand	R	Conversion (%)	Ee (%)
1	(*R*)-**9**	Me	100	99
2	(*R*)-**9**	Et	100	98
3	(*R*)-**10**	Me	100	99
4	(*R*)-**10**	Et	100	96
5	(*R*)-BINAP	Et	100	98

Table 2. Recycling of hydrosoluble catalysts in the hydrogenation of ethyl acetoacetate



Entry	Reuse	Catalyst	Substrate/ catalyst	Conversion[a] (%)	Ee[a] (%)
1		**13**	1000	100	99
2	First	**13**	1000	100	98
3	Eight	**13**	1000	100	97
4	First	**14**	1000	100	99
5	Sixth	**14**	1000	100	98
6		BINAP	1000	100	98[b]

[a] Conversion and enantioselectivity were determined by GC on a lipodex A (25 m × 0.25 mm) column.

[b] Hydrogenation was performed in homogeneous conditions in ethanol H_2 (40 bar), 50 °C, 15 h.

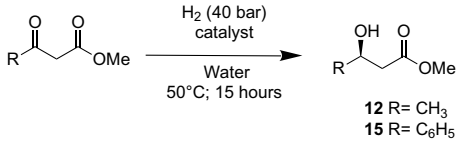
In the catalytic hydrogenation of this substrate our biphasic system was as good as BINAP itself with the advantage of recycling. As observed in homogeneous conditions, the presence of the two ammonium bromohydrate groups of hydrosoluble 4,4′ and 5,5′-diamBINAP had no influence on the catalytic activity and selectivity, which were similar to those of BINAP itself. The decrease in activity and selectivity observed after six or eight runs was due to the catalysts oxidation despite the utmost care taken.

In order to extend the validity of our system, other β-ketoesters were tested in the same conditions of hydrogenation (Table 3). Methyl acetoacetate **12** and ethyl benzoylacetate **15** were both hydrogenated with excellent activity and ee.

3. Conclusion

Herein, we have reported that ruthenium complexes of 4,4′ and 5,5′-diamBINAP exhibit excellent efficiency in the catalytic hydrogenation of β-ketoesters (total conversions and ees greater than 96%). As with 6,6′-diamBINAP, the presence of the two aminomethyl groups of 4,4′ and 5,5′-diamBINAP had no influence on the catalytic activity, which was similar to those of the BINAP itself. Moreover, an efficient regioselective synthesis

Table 3. Biphasic heterogeneous hydrogenation of **12** and **15**



Entry	Reuse	Substrate	Catalyst	Substrate/catalyst	Conversion[a](%)	Ee[a] (%)
1		**12**	**13**	1000	100	99
2	First	**12**	**13**	1000	100	98
3		**12**	**BINAP**	1000	100	98[b]
4		**15**	**13**	1000	100	98
5	First	**15**	**13**	1000	100	99
6		**15**	**BINAP**	1000	100	97[b]

[a] Conversion and enantioselectivity were determined by GC on a lipodex A (25 m × 0.25 mm) column.
[b] Hydrogenation was performed in homogeneous conditions in ethanol H_2 (40 bar), 50 °C, 15 h.

from BINAPO have been developed to reach 4,4′ and 5,5′-diaminomethylBINAP. This synthesis is easier than WITH 6,6′-diamBINAPs and can be performed on a larger scale. Moreover, we have demonstrated that quaternarization of 4,4′ and 5,5′-diamBINAP provides a water-soluble BINAP analogue, suitable for asymmetric biphasic catalytic hydrogenation of several β-ketoesters. The use of such a ligand is interesting because high conversions and attractive enantioselectivities were obtained. In addition, it allows easy separation of the catalyst from the reaction product by extraction. The reuse of the ruthenium complex is effective without any loss of either conversion or enantioselectivity.

4. Experimental

4.1. General methods

Solvents were dried with 4 Å molecular sieves and distilled under an argon stream on $LiAlH_4$ or purchased anhydrous (Aldrich or Acros). For catalytic use, solvents were deoxygenated by repeated evacuation and argon purging. NMR spectra were recorded on a Bruker AC 200 and DRX 300. Chemical shifts are given in ppm using tetramethylsilane as the internal standard for ^1H and ^{13}C NMR spectra, and ^{31}P NMR from H_3PO_4. Coupling constants are reported in Hz. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. For the air-sensitive compounds, elemental analyses were not performed. Mass spectra were recorded on LCQ Advantage Thermofinnigan. Conversions and enantioselectivities were determined by GC on a lipodex A (25 m × 0.25 mm) column. All the yields are isolated yields.

4.2. (*R*) or (*S*)-BINAPoxide 2

In a 250 mL round-bottomed flask were placed either (*R*)- or (*S*)-BINAP (3 g, 4.81 mmol) and 100 mL of CH_2Cl_2. The mixture was cooled to 0 °C and 10 mL of hydrogen peroxide (35%) then added. The mixture was stirred for 4 h. Then 100 mL of water was added. Aqueous phases were extracted with 50 mL of CH_2Cl_2. The organics phases were washed with 50 mL of aqueous sodium hydrogen sulfite solution, dried over Na_2SO_4 and evaporated to obtained a white solid (3.14 g, 4.8 mmol, quantitative yield). ^1H NMR (300 MHz, $CDCl_3$): 6.80 (d, 4H, $J = 3.7$), 7.2–7.3 (m, 8H), 7.3–7.5 (m, 12H), 7.6–7.7 (m, 4H), 7.8–7.9 (m, 4H). ^{31}P NMR (81 MHz, $CDCl_3$): 28.67. Mp: 256–258 °C $[\alpha]_D = +198.1$ (*c* 1, Benzene).

4.3. (*S*)-4,4′-DibromoBINAPO 3

In a 250 mL round-bottomed flask were placed (*S*)-BINAPO (5 g, 7.64 mmol) and 150 mL of CH_2Cl_2. Pyridine (0.62 mL, 7.64 mmol) and bromine (1.2 mL, 22.92 mmol, 3 equiv) were added. The mixture was stirred at room temperature for 20 h. The organic phase was extracted successively with 1 M aqueous sodium hydrogen sulfite solution, brine and saturated sodium hydrogen carbonate solution, dried and evaporated. To obtain the bis-brominated product **3**, the above described bromination procedure was repeated twice and the crude product of the preceding bromination used as starting materials. A white solid (4.74 g, 5,8 mmol, 76%) was obtained after recrystallization from ethanol. ^1H NMR (300 MHz, $CDCl_3$): 6.80 (d, 2H, $J = 8.3$), 6.85 (ddd, 2H, $J = 0.9$; 6.7; 15.1), 7.2–7.5 (m, 18H), 7.6–7.7 (m, 4H), 7.75 (s, 2H), 8.23 (d, 2H, $J = 8.4$). ^{13}C NMR (75 MHz, $CDCl_3$): 123.3, 123.5, 127.1, 127.5, 127.8, 128.3, 128.5, 128.7, 129.0, 130.3, 131.6, 131.7, 131.8, 131.8, 131.9, 131.9, 132.3, 132.4, 132.7, 132.8, 132.9, 133.0, 133.1, 133.3, 134.4, 134.7, 134.9, 142.2, 142.3, 142.4. ^{31}P NMR (81 MHz, $CDCl_3$): 27.60. $[\alpha]_D^{25} = -96.4$ (*c* 1, DMF). ESI^+: $MH^+ = 813.33$. Mp: >300 °C. Calcd. C 65.05, H 3.72, P 7.62, Br 19.67; found C 65.13, H 3.82, P 7.81, Br 19.42.

4.4. (*S*)-4,4′-DicyanoBINAPO 5

In a 50 mL round-bottomed flask fitted with a reflux condenser were placed (*S*)-4,4′dibromoBINAPO

(200 mg, 0.25 mmol) and copper cyanide (63 mg, 0.7 mmol, 2.8 equiv) in 3 mL of DMF. The mixture refluxed overnight then cooled. 1 mL of ethylenediamine and 1 mL of water were added. After stirring for 5 min, 5 mL of water and 10 mL of toluene were added. The aqueous phase was then extracted with 10 mL of toluene. The organic phases were washed with 5 mL of water, 5 mL of HCl (0.5 M, four times) 5 mL of brine and 5 mL of saturated sodium carbonate solution. The mixture was dried and evaporated and the residue recrystallized from methanol. A white solid was obtained (100 mg, 0.15 mmol, 60% yield). ^{1}H NMR (200 MHz, $CDCl_3$): 6.73 (d, 2H, $J = 8.4$), 6.90 (ddd, 2H, $J = 1.0$; 7.0; 14.3), 7.2–7.8 (m, 22H), 7.85 (d, 2H, $J = 11.3$), 8.28 (d, 2H, 8.3). ^{13}C NMR (75 MHz, $CDCl_3$): 110.8, 111.0, 117.9, 125.8, 127.6, 128.0, 128.6, 128.8, 129.0, 129.2, 129.7, 130.3, 130.7, 131.0, 132.1, 132.2, 132.3, 132.6, 132.8, 132.9, 133.0, 133.9, 134.5, 134.7, 147.3. ^{31}P NMR (81 MHz, $CDCl_3$): 27.77. $[\alpha]_D^{25} = -94.3$ (c 1, DMF). ESI$^+$: $MH^+ = 705.2$. Mp: >300 °C. Calcd. C 78.40, H 4.29, N 3.98, P 8.79; found C 77.99, H 4.33, N 3.74, P 8.2.

4.5. (*R*)-5,5′-DibromoBINAPO 4

A solution of (*R*)-BINAPO (4.8 g, 7.4 mmol) in 1,2-dichloroethane (45 mL) was added dropwise to a stirred refluxing solution of 1,2-dichloroethane (65 mL), Br_2 (7.6 mL, 148 mmol, 20 equiv) and Fe (622 mg, 11.1 mmol, 1.5 equiv). After addition was completed, the mixture was left at reflux overnight and then filtered to remove any iron. The organic layer was washed sequentially with H_2O, aqueous 1 M sodium hydrogen sulfite, saturated sodium hydrogen carbonate solution and brine. After drying over Na_2SO_4 the solvent was removed to obtain a white solid (4.85 g, 6 mmol, 80.7%). ^{1}H NMR (200 MHz, $CDCl_3$): 6.62 (t, 2H, $J = 15.0$), 6.72 (d, 2H, $J = 9.0$), 7.2–7.5 (m, 20H), 7.55 (dd, 2H, $J = 3.0$, 1.0), 7.6–7.8 (m, 2H), 8.3 (dd, 2H, $J = 1.7$, 9.0). ^{13}C NMR (75 MHz, $CDCl_3$): 123.2, 126.5, 127.1, 127.3, 128.5, 128.7, 129.9, 131.6, 131.8, 132.1, 132.3, 132.5, 132.8, 132.9, 133.4, 135.0. ^{31}P NMR (81 MHz, $CDCl_3$): 29.20. $[\alpha]_D^{25} = +97.7$ (c 1, DMF). ESI$^+$: $MH^+ = 813.32$. Mp: >300 °C. Calcd. C 65.05, H 3.72, P 7.62, Br 19.67; found C 65.34, H 4.05, P 7.46, Br 19.44.

4.6. (*R*)-5,5′-DicyanoBINAPO 6

In a 250 mL round-bottomed flask fitted with a reflux condenser were placed (*R*)-5,5′dibromoBINAPO (4.7 g, 5.8 mmol) and copper cyanide (1.04 g, 16.24 mmol, 2.8 equiv) in 3 mL of DMF. The mixture was heated to reflux overnight. The mixture was then cooled and 25 mL of ethylenediamine and 25 mL of water added. After stirring for 5 min, 100 mL of water and 200 mL of toluene were added, the aqueous phase was then extracted with 100 mL of toluene. The organic phases were washed with 100 mL of water, 100 mL of HCl (0.5 M, four times) 100 mL of brine and 100 mL of saturated sodium carbonate solution. The mixture was dried and evaporated. A white solid was obtained (3.71 g, 5.5 mmol, 90.8%). The product was recrystallized from ethanol to yield 2.52 g, 61.7% of a white product. ^{1}H NMR (200 MHz, $CDCl_3$): 6.85 (dd, 2H, $J = 7.0$, 7.1), 6.97 (d, 2H, $J = 9.0$), 7.2–7.5 (m, 20H), 7.6–7.7 (m, 2H), 7.8 (dd, 2H, $J = 1.1$, 6.1), 8.33 (dd, 2H, $J = 1.9$, 7.1). ^{13}C NMR (75 MHz, $CDCl_3$): 110.4, 110.9, 117.8, 125.3, 125.4, 125.7, 128.5, 128.6, 128.7, 128.8, 128.9, 129.1, 129.4, 131.0, 131.2, 131.6, 131.9, 132.1, 132.2, 132.4, 132.8, 132.9, 133.0, 133.1, 133.3, 133.6, 134.2, 134.5, 138.3, 143.0. ^{31}P NMR (81 MHz, $CDCl_3$): 29.1. $[\alpha]_D^{25} = +95.3$ (c 1, DMF). ESI$^+$: $MH^+ = 705$. Mp: >300 °C. Calcd. C 78.40, H 4.29, N 3.98, P 8.79; found C 78.12, H 4.35, N 3.84, P 8.45.

4.7. (*S*)-4,4′-DicyanoBINAP 7

In a 25 mL round-bottomed flask under an inert atmosphere fitted with a reflux condenser was placed, (*S*)-4,4′-dicyanoBINAPO (420 mg, 0.6 mmol). Degassed phenylsilane (8 mL, 64.8 mmol) was added. The mixture was heated to 130 °C after which trichlorosilane was added in three portions (3 × 1 mL) after 1, 3 and 15 h. The solution was then stirred for 2 h, cooled and evaporated till a white solid was obtained. This latter was washed with cyclohexane, filtered on Millipore and dried. White crystals were obtained in quantitative yields (402 mg, >99%). ^{1}H NMR (300 MHz, $CDCl_3$): 6.64 (d, 2H, $J = 9$), 6.93–6.97 (m, 2H), 7.1–7.3 (m, 20H), 7.54 (t, 2H), 7.98 (s, 2H), 8.23 (d, 2H, $J = 8, 3$). ^{13}C NMR (75 MHz, $CDCl_3$): 111.6, 118.2, 125.4, 125.6, 127.8, 128.0, 128.8, 128.9, 129.0, 129.1, 129.12, 129.16, 129.2, 129.5, 129.8, 132.2, 132.8, 132.9, 133.0, 133.1, 133.2, 133.4, 134.6, 134.8, 134.9, 135.0, 135.1, 135.15, 135.2, 136.0, 136.1, 136.2, 136.7, 136.8, 136.9, 137.1, 148.3, 148.6, 148.9. ^{31}P NMR (81 MHz, $CDCl_3$): −13.30. $[\alpha]_D^{25} = -96.3$ (c 1, DMF). HRLSIMS: MH^+. Calcd 673.1884, found 673.1879.

4.8. (*R*)-5,5′-DicyanoBINAP 8

In a 25 mL round-bottomed flask under an inert atmosphere and reflux condenser was placed (*R*)-5,5′-dicyanoBINAPO (420 mg, 0.6 mmol). Degassed phenylsilane (8 mL, 64.8 mmol) was then added. The mixture was heated to 130 °C and trichlorosilane was added in three portions (3 × 1 mL) after 1, 3 and 15 h. The solution was stirred for 2 h, cooled and evaporated till a white solid was obtained. It was washed with cyclohexane, filtered on Millipore and evaporated. The product was obtained in quantitative yields (400 mg, >99%). ^{1}H NMR (300 MHz, $CDCl_3$): 6.6–6.8 (m, 4H), 7.04–7.3 (m, 20H), 7.4 (d, 2H, $J = 7.14$), 7.5 (d, 2H, $J = 8.85$), 8.3 (d, 2H, $J = 9.03$). ^{13}C NMR (75 MHz, $CDCl_3$): 110.2, 117.7, 124.9, 125.7, 128.3, 128.4, 128.5, 128.54, 128.6, 128.65, 129.1, 131.8, 132.4, 132.5, 132.6, 132.65, 132.7, 132.8, 132.9, 133.0, 133.1, 134.3, 134.5, 134.7, 135.0, 135.5, 136.5, 136.6, 139.1, 143.2, 143.6. ^{31}P NMR (81 MHz, $CDCl_3$): −13.99. $[\alpha]_D^{25} = +98.6$ (c 1, DMF). HRLSIMS: MH^+. Calcd 673.1884, found 673.1881.

4.9. (*S*)-4,4′-DiaminomethylBINAP 9

In a 100 mL round-bottomed flask, under an inert atmosphere, (*S*)-4,4′-dicyanoBINAP (400 mg, 0.6 mmol) was dissolved in a mixture of 23 mL of toluene and 23 mL of tetrahydrofuran. $LiAlH_4$ (227.7 mg, 6 mmol) was then added portionwise. The mixture was heated to 105 °C and stirred for 2 h. The product was cooled and 0.5 mL of water and 0.5 mL of a 10 M sodium hydroxide solution were added and stirred for 5 min. Celite (1.5 g) was added and stirred for 5 min. Then the solution was filtered. The filtrate was dried and the solvent evaporated to yield a white solid (407 mg, 0.6 mmol, 100%). ^{1}H NMR (200 MHz, $CDCl_3$): 1.56 (s, 4H), 4.33 (s, 4H), 6.7–7.0 (m, 4H), 7.1–7.3 (m, 20H), 7.4–7.5 (m, 4H), 8.08 (d, 2H, $J = 8.5$)). ^{31}P NMR (81 MHz, $CDCl_3$): −14.62. ^{13}C NMR (50 MHz, $CDCl_3$): 44.3, 123.1, 125.6, 126.9, 127.6, 128.0, 128.1, 128.4, 128.6, 128.8, 129.1, 131.3, 132.7, 132.9, 133.0, 134.0, 134.4, 138.9. $[\alpha]_D^{25} = -102.4$ (*c* 1, DMF). $[\alpha]_D^{25} = +101.7$ (*c* 1, DMF). HRLSIMS: MH^+. Calcd 681.2588, found 681.2581.

4.10. (*R*)-5,5′-DiaminomethylBINAP10

In a 100 mL round-bottomed flask under an inert atmosphere, (*R*)-5,5′-dicyanoBINAP (400 mg, 0.6 mmol) was dissolved in a mixture of 23 mL of toluene and 23 mL of tetrahydrofuran. $LiAlH_4$ (227.7 mg, 6 mmol) was then added portionwise. The mixture was heated to 105 °C and stirred for 2 h. The reaction mixture was cooled and 0.5 mL of water and 0.5 mL of a 10 M sodium hydroxide solution were added and stirred for 5 min. Celite (1.5 g) was added and stirred for 5 min. Then the solution was filtered. The filtrate was dried and the solvent evaporated to yield a white solid (405 mg, 0.6 mmol, 100%). ^{1}H NMR (200 MHz, $CDCl_3$): 1.6 (s, 4H), 4.37 (s, 4H), 6.8–7.0 (m, 4H), 7.1–7.3 (m, 20H), 7.36 (d, 2H, $J = 6.58$), 7.5 (d, 2H, $J = 8, 82$), 8.15 (d, 2H, $J = 8, 82$). ^{31}P NMR (81 MHz, $CDCl_3$): −15.50. ^{13}C NMR (50 MHz, $CDCl_3$): 44.3, 122.2, 125.6, 125.9, 127.3, 128.1, 128.3, 128.4, 128.7, 129.0, 129.3, 130.0, 132.6, 132.9, 133.2, 133.8, 135.2, 139.4. $[\alpha]_D^{25} = -100.3$ (*c* 1, DMF). $[\alpha]_D^{25} = +101.4$ (*c* 1, DMF). HRLSIMS: MH^+. Calcd 681.2588, found 681.2587.

4.11. Typical reduction procedure of β-ketoesters

All experiments were performed under argon and all solvents were degassed by argon bubbling followed by three vacuum/argon cycles. Catalysts were prepared according to literature procedures.[9,10] A calculated amount of β-ketoesters in 2 mL of MeOH or EtOH was added to the above catalysts obtained in situ. This solution was put in a stainless steel hydrogenation vessel. After purging three times with argon and three times with hydrogen, the pressure was raised to 40 bar and the reaction mixture stirred at 50 °C for 15 h. The reaction mixture was filtered on Celite and analyzed by GC to determine both conversion and ee.

4.12. Formation of the catalysts 13 and 14 (according to the literature[9])

Under Ar, at 25 °C, 8.4 μL of an aqueous HBr solution (48%) (0.05 mmol) was added to a stirred solution of (*R*) or (*S*)-4,4′ or 5,5′-diamBINAP (17 mg, 0.025 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was allowed to stir for 1 h after which the solvent was then removed. To the residue was added Ru[(2-methylallyl)2(COD)] (7.5 mg, 0.024 mmol) and 1 mL of acetone. Then 8.4 μL of an aqueous HBr solution (48%) (0.05 mmol) was added. The reaction mixture was allowed to stir for 0.5 h after which the solvent was removed. Catalysts were used immediately for the hydrogenation.

4.13. Typical biphasic reduction procedure of β-ketoesters

Under Ar, to the preceding catalysts dissolved in H_2O (1 mL), the water-insoluble β-ketoesters were added (substrate/catalyst: 1000). This biphasic mixture was allowed to stir and then stand overnight in a stainless steel hydrogenation vessel at 50 °C under 40 bar H_2. The resulting water-soluble reduced product was extracted three times with pentane. The aqueous phase containing the catalyst was reused as previously described.

GC conditions

Substrate	Conditions	Retention time
Methyl acetoacetate	Lipodex A	Starting material: 5.3 min
	45 °C (5 min)–1 °C/min–60 °C (5 min)	Enantiomers: 7.13; 7.93 min
Ethyl acetoacetate	Lipodex A	Starting material: 10.17 min
	40 °C (30 min)	Enantiomers: 26.3; 27.4 min
Ethyl benzoylacetate	Lipodex A	Starting material: 12.3 min
	90 °C (1 min)–1 °C/min–150 °C (1 min)	Enantiomers: 14.5; 15.2 min

References and notes

1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley Intersciences: New York, 1994.
2. Kumobayashi, H.; Miura, T.; Sayo, N.; Saito, T.; Zhang, X. *Synlett* **2001**, 1055.
3. Nakagawa, S.; Sugimura, T.; Tai, A. *Chem. Lett.* **1997**, 859; Kukula, P.; Cerveny, L. *J. Mol. Catal. A.* **2002**, *185*, 195–202; Welton, T. *Chem. Rev.* **1999**, *99*, 2071; Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3692; Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A.* **2002**, *182–183*, 419–437; Jessop, P. G.; Ikaria, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475–493.
4. For example see: Fan, Q. H.; Li, Y. M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385–3466.
5. Kuntz, E. G. *CHEMTECH* **1987**, 570; Herrmann, W. A.; Kohpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524.
6. *Aqueous-phase Organometallic Catalysis*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 1998.

7. Sinou, D. In *Aqueous-phase Organometallic Catalysis*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 1998; pp 432–439.
8. ter Halle, R.; Colasson, B.; Schulz, E.; Spagnol, M.; Lemaire, M. *Tetrahedron Lett.* **2000**, *41*, 643.
9. Lamouille, T.; Saluzzo, C.; ter Halle, R.; Le guyader, F.; Lemaire, M. *Tetrahedron Lett.* **2001**, *42*, 663.
10. (a) Kumobayashi, H.; Miura, T.; Sayo, N.; Saito, T.; Zhang, X. *Synlett* **2001**, 1055; (b) Birdsall, D. J.; Hope, E. G.; Stuart, A. M.; Chen, W.; Hu, Y.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 8551; (c) ter Halle, R.; Schulz, E.; Spagnol, M.; Lemaire, M. *C.R. Acad. Sci. Paris, Serie IIc, Chimie/ Chemistry* **2000**, *3*, 553.
11. Kant, M.; Bischoff, S.; Siefken, R.; Grundemann, E.; Kockritz, A. *Eur. J. Org. Chem.* **2001**, *3*, 477.
12. Schuster, B.; Kim, J.-I. *J.A.C.S.* **1992**, *114*, 9309.
13. Okano, T.; Shimano, Y.; Konishi, H.; Kiji, J.; Fukuyama, K.; Kumobayashi, H.; Akutagawa, S. *Takasago Perfumery Co., Ltd, Japan*, **1987**, JP 62178594.
14. Ishizaki, T.; Kumobayashi, H. *Takasago International Corp., Japan*, **1993**, EP 544455.
15. Reichardt, C. *Solvents and solvent effects in organic chemistry*. 2nd ed.; VCH: Cambridge; New York, NY, 1988. p 23.
16. Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.*, *Vol. 8*, 57.
17. Marsi, K. L. *J. Org. Chem.* **1974**, *39*, 265.
18. Imamoto, T.; Kikuchi, S.-I.; Miura, T.; Wada, Y. *Org. Lett.* **2001**, *3*, 87.
19. Genêt, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Cano de Andrade, M.; Laffite, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 665.
20. (a) Lamouille, T.; Saluzzo, C.; ter Halle, R.; Le Guyader, F.; Lemaire, M. *Tetrahedron Lett.* **2001**, *42*, 663–664; (b) Genêt, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Caño De Andrade, M. C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 665–674.