Modified BINAP: The How and the Why

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1. Historical Introduction

More than 35 years after the discovery of practical asymmetric catalysis by Knowles[1] and Kagan,[2] BINAP appears to be both the most used and the most useful ligand for asymmetric catalysis. Indeed, hydrogenation of many substrates can be carried out with metal complexes of this ligand with very high ee and turnover. Many other reactions giving rise to the formation of a C−C bond can also be obtained with high ee since this particular ligand exhibits atropoisomery. Since the discovery of BINAP by Noyori in 1980,[3] the successful applications of this ligand for asymmetric catalysis are scientific as well as economic. More than 750 papers, including several reviews, deal with the use or the synthesis of BINAP itself. Possibly even more important are the 244 patents claiming new synthesis or particular uses of BINAP.[4]

BINAP itself is one of the rare chiral ligands produced on an industrial scale,[5] and several large-scale asymmetric syntheses are now carried out with BINAP. Among them, the Takasako synthesis of L-menthol by asymmetric isomerization could be considered as the first demonstration of large-scale industrial feasibility of asymmetric catalysis.

BINAP has been available commercially for several years now, but research is still being conducted to find easier and cheaper synthetic methods for this important molecule. Nonetheless, many modifications of the structure of BINAP have been made to increase efficiency (turnover) and selectivity (ee), but also to facilitate separation from the bulk of the reaction. With this latter objective in mind, and taking into account BINAP's industrial potential, it is not surprising that all modern technologies aiming for easy separation and recycling are currently explored with BINAP. Homogeneous supported catalysts with BINAP grafted onto organic or inorganic supports have been described, and polymers including the BINAP structure in the main chain have been proved to be efficient as well as selective catalytic precursors. Successful modifications have also been performed to obtain catalysts soluble in water, ionic liquids, perfluorinated solvents, supercritical CO_2, and so on.

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Mikaël Berthod was born in 1977 in Annecy, France. He performed a six-month internship in organic synthesis (*P*-chiral ligand syntheses) at the University of Montreal (Canada) in the laboratory of Professor Helene Lebel in 2000. He obtained his DEA in 2001 from Joseph Fourier University (Grenoble, France), where he worked in the laboratory of Doctor Andrew Green (total syntheses of azulenes). He received his Ph.D. degree from the University of Lyon in 2004 for studies concerning the syntheses of new BINAP derivatives and their uses in asymmetric catalysis. He is currently pursuing postdoctoral studies at the University of Montreal in the area of enantioselective cyclopropanation with Professors Andre Charette and Helene Lebel.

Gérard Mignani studied chemistry at the Orsay and Rennes Universities (Lavoisier Medal in 1977), where he received his Ph.D. (Docteur Ingénieur) in 1980 and his Thèse d'Etat in 1982 in the field of organometallic chemistry and homogeneous catalysis, specializing in steroid chemistry (Rhône-Poulenc Grant), with the Professor Dabard team. He joined the Rhône-Poulenc research group in Lyon in 1980, where he developed new processes in organic chemistry and terpene chemistry and in homogeneous and heterogeneous catalysis. Thereafter he performed postdoctoral research with Professor Seyferth at the Massachusetts Institute of Technology (Cambridge, MA) on ceramic precursors and organosilicon chemistry. He came back to Rhône-Poulenc, where he developed new ceramic precursors, new nonlinear optic derivatives, polymers, and homogeneous catalysis processes. He spent 10 years as Group Leader in Silicon Chemistry. His research interests were the polyfunctionalization of polysiloxanes, new organometallic catalysis for organosilicon applications, and the functionalization of mineral charges. Now, his research interests are new processes and scaleup in organic chemistry, organometallic catalysis (homogeneous and heterogeneous), and new methodology in chemistry synthesis. He received the Prix de la Recherche in 1995, in 2001 the Prix Rhodia Group, and in 2004 the Prix Centre de Recherches-Rhodia. Dr. Mignani has contributed to about 60 international scientific publications and more than 120 patents.

The availability and the versatility of BINAP have allowed research in many areas, and we believe that now is an appropriate moment to collect all these results and to organize current data on "Modified BINAP: The How and the Why".

Gary Woodward was awarded his PhD in 1989 from Bristol University working for Dr. Martin Murray. His Ph.D. thesis was in the area of phosphorus–nitrogen ring system chemistry. He then began his career in industry in 1989 with the Albright and Wilson chemical company as a research chemist working on the synthesis and scaleup of new organophosphorus-based scale and corrosion inhibitors. This work resulted in the launch of a new system of non-heavy-metal-containing all-organic corrosion inhibitors, BRICORR288. Gary Woodward has held several roles in research and development at Albright and Wilson and now the Rhodia chemical company. His research work in industry has been in organophosphorus chemistry; this has been the design, scaleup, and industrialization of new products in the application areas of water treatment, flame retardants, organophosphines, and organophosphorus intermediates for the pharmaceutical industry. He is the author of 14 patents covering new organophosphorus chemistry applied in a wide range of applications, scale and corrosion inhibitors, phosphorus-containing polymers, flame retardancy, pharmaceutical intermediates, and phosphine ligands. His current role is Research and Development Manager for Rhodia's Phosphorus Performance Derivatives business based at Oldbury in the West Midlands, U.K.

Marc Lemaire was born in 1949 in Paris. He was employed several years in the pharmaceutical industry as a technician, and then he obtained the engineer level (CNAM Paris, 1979) and his Ph.D. degree at the Paris VI University (Professor J. P. Guetté, "New chlorinating reagent"). In 1983 he obtained a postdoctoral position at the University of Groningen (The Netherlands; Professor F. M. Kellog, "Thiamacrocycles as ligand for asymmetric catalysis"). He returned to Paris and obtained an assistant position at CNAM and then he became a professor at the University of Lyon. His group is working in five main areas: (1) heterogeneous catalysis in fine chemistry, (2) asymmetric catalysis, (3) separation science, including new ligands for liquid–liquid extraction, new ionoselective materials, and new complexing agents of nanofiltration–complexation systems, (4) organic conductors, including poly(thiphenes) and poly(pyrroles), and (5) deep desulfurization of gas oil.

The diverse approaches applied to BINAP modification may be useful and inspiring for the chemistry of other ligands and applications in asymmetric synthesis.

2. Industrial Methods To Produce BINAP

There are four methods which may be used for the large-scale production of BINAP, which will be discussed in chronological order of invention. For convenience these methods are named after their inventors or the companies that filed the patent, even where the ownership of that patent has since changed hands. For example, Monsanto filed the "Monsanto method" in 1997, but the ownership then passed through NSC Technologies to Great Lakes Chemical Corp., who have awarded an exclusive license of the technology to Rhodia, who implements it now.

2.1. Noyori/Takasago Method

The first synthesis of BINAP was reported by Noyori[3,6] and its use patented by Takasago[7,8] (a Japanese flavors and fragrances manufacturer) in 1984−85. Takasago maintained the patent and kept the use of BINAP in-house, so the method has not been used elsewhere except for the production of small research samples.

As with all the industrial methods for BINAP synthesis, the starting point is 1,1′-binaphthol (BINOL); in this case the racemate is used. This is then converted under harsh conditions to dibromide with at best a moderate yield (45% reported) (Figure 1). Once this bromide is available, process efficiency

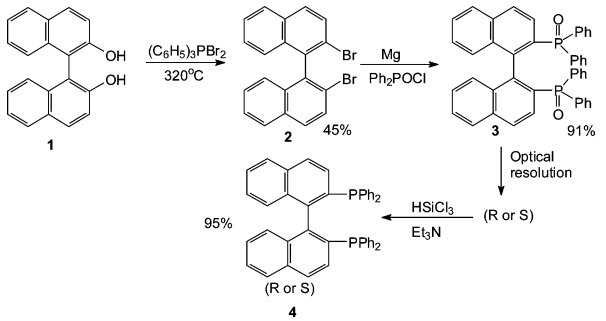

Figure 1. Noyori/Takasago synthesis of BINAP.

improves, with a Grignard coupling to form the bis-(phosphine oxide). This is then resolved by fractional crystallization with camphorsulfonic acid or 2,3-di-*O*-benzoyltartaric acid into its optically pure isomers. A silane reduction then produces BINAP itself.

The major advantage of this route is simply that it was the first to succeed and allow BINAP to be available on a moderate scale. However, from a production point of view it is relatively long-winded compared to more recent methods (see below). Also, the loss of more than half of the BINOL backbone in the bromination step means that the overall yield is poor. Similarly, the optical resolution near the end of the synthetic sequence implies that the yield is halved again if only one optical isomer is desired commercially (it is highly unlikely that the demand for each isomer will always be equal!).

Thus, the Noyori/Takasago process has survived due to early implementation and patent protection, but is unlikely to survive open competition from the next generation of synthetic methods.

The best known of Takasago's industrial uses of BINAP is the manufacture of (−)-menthol from myrcene (see Figure 2). In this case the catalyst [(*S*)-BINAP]$_2$Ru·ClO_4^- (**11**) is used for the asymmetric isomerization of diethylgeranylamine to 3-(*R*)-citronellal enamine before classical conversion to menthol. More recently, however, Takasago's manufacture of menthol has switched to the use of SEGPHOS.[9]

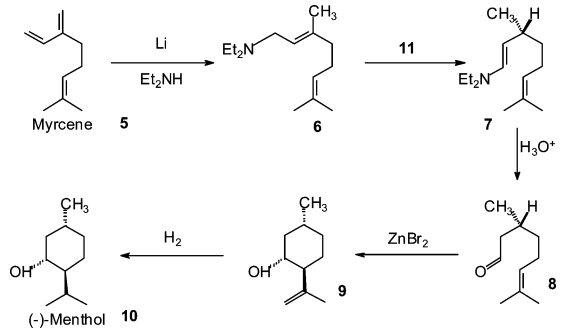

Figure 2. Takasago synthesis of menthol.

2.2. Merck Inc. Method

The second route was developed by Merck Inc. in the U.S. in 1994.[10] It was the first route to offer a short synthetic sequence from fairly readily available materials with good yields.

Again, the route starts from BINOL, but in this case the BINOL can be resolved prior to derivatization by the Toda method[11] and the stereochemistry preserved throughout the synthetic sequence. The (*R*)- or (*S*)-BINOL is then esterified with triflic anhydride and a base in almost quantitative yield (Figure 3). The BINOL ditriflate (2,2′-di(trifluoro-

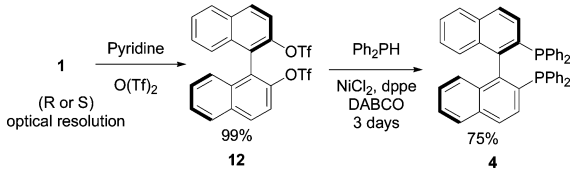

Figure 3. Merck Inc. synthesis of BINAP.

methylsulfonyl)-1,1′-binaphthyl) is then coupled with diphenylphosphine using a nickel chloride catalyst. It is reported that excess diphenylphosphine acts as a reducing agent to generate a Ni^0 species in situ which is the active catalyst.

Obviously, the synthetic sequence is now much shorter, only two steps from commercially available resolved BINOL, and the yields are very good (indeed the highest of all the methods discussed here). There are, however, two key disadvantages to the coupling step: (i) The use of diphenylphosphine is highly hazardous; it is pyrophoric and toxic and has a notorious stench. (ii) The duration of the coupling step (72 h) is extensive and reduces the reactor efficiency of the process compared to, e.g., the Monsanto process.

There are no publications that the authors are aware of which indicate that the Merck process is used by any other manufacturer under license. However, it does bear inclusion in this industrial production section of the review as it is likely to be actively considered by any potential producer.

2.3. Monsanto Method

A third process was invented by a group of researchers from Monsanto[12] and has the advantage of using industrially available diphenylchlorophosphine as a starting material.

In this case zinc metal is used as a reductant to generate the active nickel(0) catalyst. The diphenylchlorophosphine is then reacted with chiral BINOL ditriflate in the presence of excess zinc to give the desired BINAP (Figure 4).

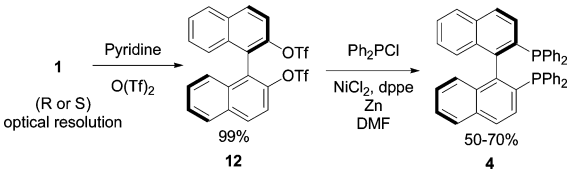

Figure 4. Monsanto synthesis of BINAP.

The major advantage of the Monsanto process is the availability and ease of handling of the raw materials. They can all be handled with only simple precautions in a general-purpose plant. The batch time is also shorter than that of the Merck Inc. route. The disadvantage of the system is that the yield is reportedly slightly lower than that of the Merck Inc. route. However, the efficiency and safety advantages outweigh these disadvantages, to make Rhodia's implementation of this method the largest scale route to BINAP.

As mentioned above this route has been exclusively licensed to Rhodia for the production of large quantities of BINAP. It has recently been launched onto the commercial market with hundreds of kilograms available.

2.4. Merck Gmbh Method

The Merck Gmbh route[13] is a recent variation on the Monsanto route, but exploits the omission from Monsanto's patent of longer chain homologues of the triflate group. Thus, the substrate of the coupling reaction is no longer BINOL ditriflate but BINOL dinonaflate (where nonaflate = $-S(O)_2CF_2CF_2CF_2$-CF_3) (Figure 5). The remainder of the process is

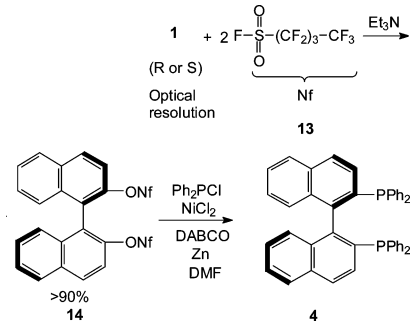

Figure 5. Merck Gmbh synthesis of BINAP.

extremely similar to that of Monsanto, with the sole difference being the addition of DABCO base as in the Merck Inc. method.

The same arguments apply to this process as to the Monsanto method (see above). However, there may be queries concerning the dependence of the Merck Gmbh patent on the Monsanto patent; a discussion of the legal precedence of these patents is beyond the scope of this review, but should be borne in mind by the reader.

As with the Merck Inc. patent, this has not to our knowledge been operated industrially. However, it does bear consideration by anyone wishing to make BINAP.

3. Modification of the Phenyl Moiety of BINAP

Since the first practical synthesis of BINAP was reported in 1986,[6] various industrial syntheses have been developed. This ligand has been found to have remarkable chiral recognition ability and broad applicability in various transition-metal-catalyzed asymmetric reactions[14] such as hydrogenation,[15] hydrosilylation,[16] 1,3-hydrogen migration,[17] etc. BINAP–ruthenium catalysts are well recognized to be highly efficient catalysts for asymmetric hydrogenation of various functionalized olefins and ketones such as α-(acylamino)acrylic acids,[18] α,β-unsaturated carboxylic acids,[19] enamides,[20] allylic and homoallylic alcohols,[21] alkylidene lactones,[22] alkenyl ethers,[14] β-keto esters,[23] and β-hydroxy ketones and β-amino ketones.[24] But even if BINAP has shown excellent efficiency, its use in industrial applications remains relatively rare (approximately 20 applications).[25] This is principally due to the cost of the metals and the ligand. To avoid this drawback, different approaches have been developed to increase catalyst activity and recycling. In most cases, these approaches need BINAP functionalization to modify its steric and electronic properties and/or to heterogenize the catalyst. Many possibilities have been envisaged to functionalize BINAP. Both the phenyl groups and the naphthyl skeleton have been modified. Although using phenyl groups has led to success with increasing activity and selectivity, the naphthyl skeleton was mainly used to obtain easy separation and recycling of the catalysts from the bulk of the reaction.

Since the discovery of BINAP in 1980[3] and its use as a ligand, no derivatives were synthesized before 1986 with the first practical synthesis of Noyori et al. The interest in modifying phenyl substituents generally results in the modification of the electronic properties of the phosphorus ligand. Both electronic effects (i.e., basicity of the phosphorus) and steric hindrance could be modified.

Genet et al. have compared BINAP, MeO-BIPHEP, SYNPHOS, and SEGPHOS (which have similar electronic properties) under exactly the same reaction conditions for the same hydrogenation substrate. The different selectivities obtained with these four ligands could be explained mainly by the differences of the dihedral angle.[26] Atropoisomery is one of the most powerful tools for enantioselection; this type of ligand allows the formation of catalytic sites in which the chiral environment is controlled by classical steric and electronic factors, but also by the dihedral angle between the two aromatic cycles of the binaphthyl moiety. One of the most important electronic factors is the σ-basicity (or the π-acidic character) of the phosphine group. Electronic donor–acceptor properties of these diphosphines have been investigated by

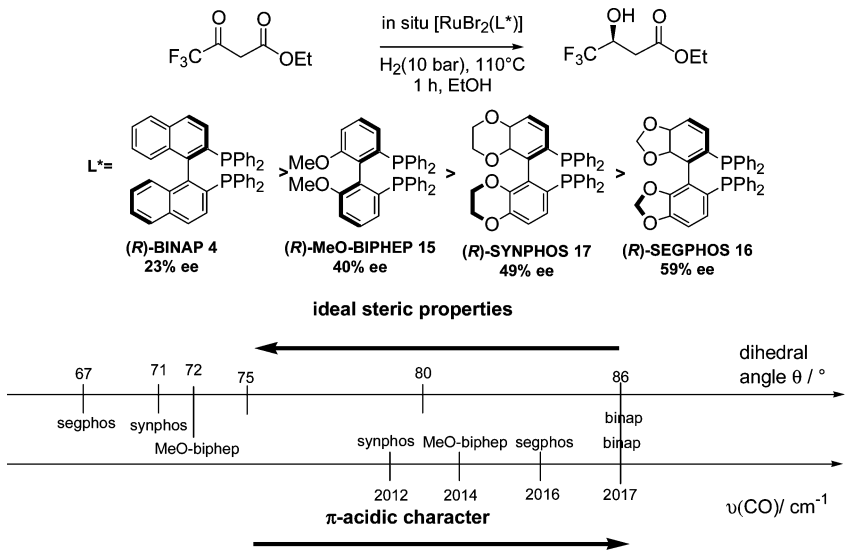

Figure 6. Comparative study of BINAP, MeO-BIPHEP, SYNPHOS, and SEGPHOS in ruthenium-catalyzed hydrogenation of ethyl trifluoroacetate on steric and electronic scales.

studying the carbonyl stretching frequencies of [RhCl(diphosphine)(CO)] complexes which were prepared by the reaction of [(RhCl(CO)$_2$)$_2$] with diphosphine ligands.[27,28] The higher the carbonyl stretching frequency, the higher the π-acidic character of the diphosphine. As described by Allen and Taylor,[29] another way to assess the σ-donor ability of a phosphine group is to measure the magnitude of ^1J(P−Se) in the ^{77}Se isotopomer of the corresponding phosphine−selenide. An increase in this coupling constant indicates an increase in the s character of the phosphorus lone pair orbital (i.e., a less basic phosphine) (see section 3.2). The dihedral angle, which is the second, but nonetheless important, parameter, can be evaluated either using X-ray structure or by molecular modeling.[30]

The ligand with the narrowest dihedral angle gave the best enantioselectivities (Figure 6). BINAP derivatives with narrow dihedral angles should be more selective than BINAP itself; indeed some of the modifications of the BINAP structure, for example, the increase of the bulkiness of the phenyl substituents on phosphorus, could modify this dihedral angle.

3.1. Modification of Phenyl Groups

3.1.1. Via Nucleophilic Substitution onto the Phosphorus Derivatives

The first (*R*)- or (*S*)-BINAP derivatives were obtained from 2,2′-dibromo-1,1′-binaphthyl and diarylphosphinyl chloride (Figure 7). This method is similar to the first industrial way of synthesizing BINAP (Figure 1). But with this method Noyori described the synthesis of two new BINAP analogues, *p*-Tol-BINAP (**18**) and the *p*-*t*-Bu-BINAP (**19**). These new derivatives were tested with ruthenium metal complexes and gave excellent results in the hydrogenation of citronellol with the same selectivity and better activity than BINAP.[31] On one hand, increasing the overall steric hindrance on the phenyl group bound to phosphorus should decrease the dihedral angle, whereas, on the other hand, the electron-donating effect of the alkyl group should increase the electronic density on the phosphorus atom.

No other derivatives were described before a Japanese patent from Takasago International Corp., claiming the synthesis of the *p*-MeO-BINAP derivative (Figure 8).[32] This new analogue was prepared

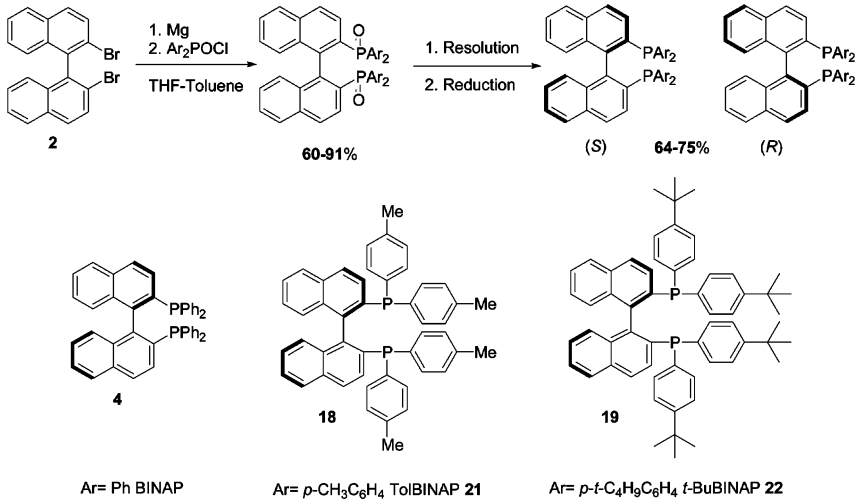

Figure 7. First synthesis of BINAP derivatives by Noyori.

using the same method as Figure 7. It was described as enhancing the conversion rate in asymmetric synthesis when used with metal complexes such as rhodium or ruthenium. It seems that electron-rich groups on phenyl increase the reactivity of the catalysts. Nevertheless, neither experimental data nor theoretical studies explaining this result were published at that time.

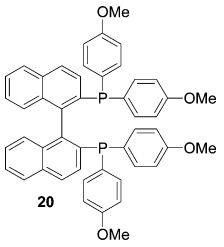

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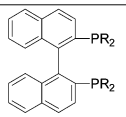
Figure 8. *p*-Methoxy-BINAP.

The influence of phenyl substituents was studied a few years later, once again by a Takasago team. Many new derivatives were synthesized and compared to BINAP and other analogues[28,33] (Figure 9).



	R
18 *p*-Tol-BINAP	4-$CH_3C_6H_4$
20 *p*-MeO-BINAP	4-$CH_3OC_6H_4$
21 *m*-Tol-BINAP	3-$CH_3C_6H_4$
22 3,5-Xylyl-BINAP	3,5-$(CH_3)_2C_6H_3$
23 3,5-(tBu)$_2$-BINAP	3,5-(tBu)$_2C_6H_3$
24 *p*-F-BINAP	4-FC_6H_4
25 *p*-Cl-BINAP	4-ClC_6H_4
26 Cy-BINAP	cyclohexyl

Figure 9. BINAP derivatives with substituents on the four phenyl rings.

Products **18**−**26** were synthesized using the same method as described in Figure 9. Six derivatives were new (**21**, **22**, **23**, **24**, **25**, **26**), and for the first time electron-withdrawing groups such as halogens were introduced. Also for the first time, substituents on the meta position of the aryl group were introduced. The authors investigated the electronic donor−acceptor properties of BINAP and its derivatives by the spectral data of the carbonyl stretching frequencies of [RhCl(BINAP)(CO)] complexes. They found υ_{CO} values for the complexes of BINAP and its derivatives to be higher than those of the alkyl-substituted diphosphine ligand Cy-BINAP. Moreover, they observed almost linear relationships between the values of υ_{CO} and Hammet σ-values and Kabachnik's σ^{Ph}-values of BINAP derivatives. The results indicate that *p*-F-BINAP and *p*-Cl-BINAP have more π-acidic character than BINAP itself. They also performed the asymmetric hydrogenation of methyl (±)-2-(benzamidomethyl)-3-oxobutanoate with cationic ruthenium(II) complexes as catalysts. Complexes with BINAP derivatives substituted by a methyl or methoxy group at the para position were used as catalysts for this hydrogenation in methanol. No remarkable changes in catalytic activity and stereoselectivity were observed with electron-donating substituents, while introduction of electron-withdrawing substituents in the para position resulted in decreased catalytic activity and stereoselectivity. They also observed that in dichloromethane−methanol an iodoruthenium complex of meta-disubstituted BINAP derivatives brought about remarkable changes in the diastereoselectivities. This shows that substituents at the meta positions are effective for high diastereoselectivity. Finally in 1994 a U.S. patent from Takasago[34] again described 3,5-dimethyl-BINAP (**22**).

In 1995, a European patent[35] from Hoffmann-La Roche AG described water-soluble BINAP derivatives, but for the first time using a method different from Noyori's (Figure 11). An aqueous biphasic system represents a very attractive and powerful technology if catalyst separation and recycling are required. Since the first industrial application of the rhodium−TPPTS (trisulfonated triphenylphosphine) system by Hoechst AG in Oberhausen, Germany, the development of water-soluble organometallic catalysis has expanded significantly.[36] In the case of asymmetric catalysis, substantial effort has been made to prepare water-soluble chiral catalysts for biphasic applications. High turnover and easy recycling render this technology of particular interest from an economic point of view.

First they synthesized (1,1′-binaphthalene)bis(phosphonic dichloride) (**27**) by analogy with compound **29** described in another Hoffman-La Roche AG patent[37] (Figure 10).

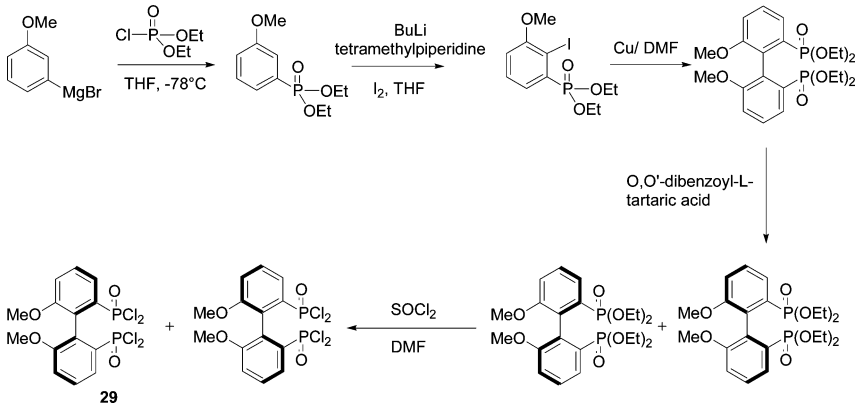


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Figure 10. Synthesis of (*R*)- or (*S*)-(6,6′-dimethoxybiphenyl-2,2′-diyl)bis(phosphonic acid dichloride).

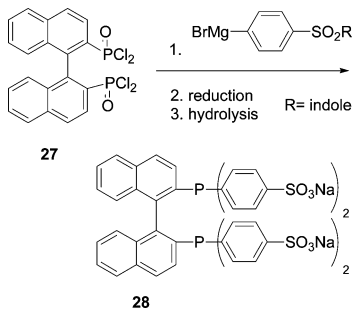


Figure 11. Synthesis of water-soluble *p*-sulfonato-BINAP.

This analogue **29** of 2,2′-bis(phosphonic acid dichloride)-1,1′-binaphthyl (**27**) was synthesized in six steps from the 3-bromoanisole. No yields are given for this synthesis in the patent. The key step was the Ullmann coupling reaction, which easily produced the substituted biphenyl. To our knowledge the full description of this original and promising strategy has not yet been published.

The new derivative **28** was synthesized as follows. In the first step an optically active derivative of **27** is reacted under Grignard conditions with at least 4 equiv of an aromatic Grignard reagent containing a protected sulfonato group in the para position. Subsequently, the resulting bis(phosphine oxide) is reduced, and the protecting group of the sulfonate is removed. This method uses a new strategy compared to Noyori's but first of all requires the introduction of the dichlorophosphine via a nucleophilic addition. To our knowledge this strategy has not been applied in an industrial synthesis of BINAP or BINAP derivatives.

3.1.2. Use of Nucleophilic Phosphorus Derivatives

In 1994 a real breakthrough in the synthesis of BINAP and BINAP derivatives was made when Cai et al. proposed the synthesis of chiral BINAP via a novel nickel-catalyzed phosphine insertion[10,38] (Figure 5). For the first time BINAP was not synthesized by a nucleophilic substitution on phosphorus atoms. Noyori's method requires a high temperature in bromination of binaphthol, and requires a special reaction vessel because of the generation of hydrobromic acid during bromination. Furthermore, this method can be applied for the preparation of modified BINAP on phenyl moieties. It also requires optical resolution of racemic modified BINAP, and therefore, the cost will be high when only one of the enantiomorphic isomers is desired. Cai's method avoids these drawbacks even if diphenylphosphine is hardly usable in large quantities (Figure 5). No resolution and no reduction of phosphine oxide were required with this method, and optically pure BINAP was obtained with a good yield of 75% using relatively cheap chiral BINOL as a starting material.

We have already mentioned that diphenylphosphine is not suitable for industrial uses in a large quantity in view of the stability, stench, and toxicity. As a result of these drawbacks this method has not been used, to our knowledge, to synthesize BINAP derivatives. In 1997, Takaya et al. conducted investigations to solve the above-mentioned problems. They improved Cai's method following the discovery that an optically active 2,2′-bis(disubstituted phosphino)-1,1′-binaphthyl (**4**) could be synthesized by introducing 2,2′-bis(trifluoromethanesulfonyloxy)-1,1′-binaphthyl (**12**) into reaction with disubstituted phosphine oxide in the presence of a transition-metal−phosphine complex (Figure 13). This new approach was used to prepare many BINAP derivatives previously claimed in a patent.[39] The key step of this method (and its limitation) was the synthesis of disubstituted phosphine oxide. The authors reported the phosphine oxide could be synthesized according to the methods proposed by Saunders et al.[40] and Hays et al.[41] An aryl Grignard reagent, prepared by reaction between magnesium and bromo or iodoaryl, reacted with diethyl phosphate to give the desired disubstituted phosphine oxide (Figure 12) in yields from 72% to 91%.

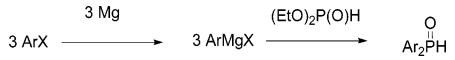


Figure 12. General synthesis of disubstituted phosphine oxide.

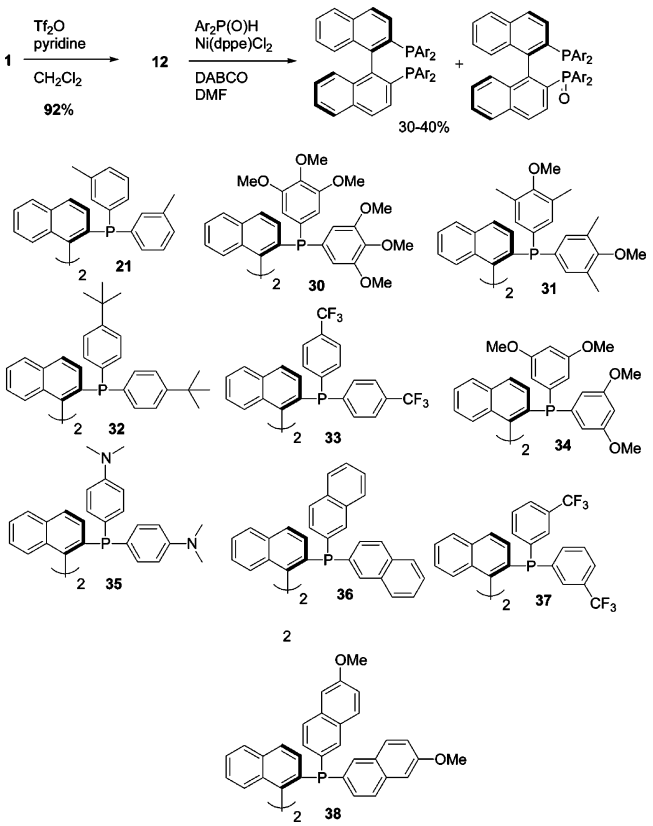


Figure 13. Takasago's method to synthesize BINAP derivatives.

Moreover, BINAP derivatives **18**, **22**, **23**, **24**, and **25** were also synthesized with this method. An optically active diphosphine monoxide compound was also obtained and could be easily reduced to synthesize BINAP using the classical method for reducing phosphine oxide, such as trichlorosilane, for example. These derivatives were described in the patent, but to our knowledge have not been tested.

Recently a Japanese patent[42] and a European patent[43] from Takeda Chemical Industries Ltd. proposed a new process for the preparation of BINAP

and BINAP derivatives. The new method is similar to both Cai's and Takasago's, but they react an activated binaphthyl (**12**) with a phosphine−borane complex in the presence of an amine (DABCO) and a nickel catalyst ([$NiCl_2$(dppe)]) in dimethylformamide. The phosphine−borane complexes were synthesized by reaction with cerium chloride, sodium borohydride, lithium aluminum hydride (Figure 14),

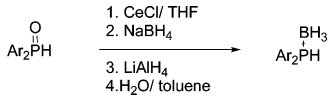


Figure 14. General synthesis of disubstituted phosphine−borane complexes.

and the corresponding phosphine oxide (which were synthesized as described in Figure 12). The yields are from 20% to 76%.

This approach avoids the possible oxidation of the phosphine during the phosphination. The phosphine−borane complexes are stable and easy to handle and can be suitable for industrial mass production. The phosphination conditions are quite similar to those of Cai's method, and deprotection of the phosphine−borane complexes occurs in situ. Many BINAP derivatives were synthesized by this new method, such as compounds **18**, **19**, **20**, **21**, **22**, **23**, **24**, **25**, **31**, **34**, and **35** and those described in Figure 15 with yields between 24% and 79%.

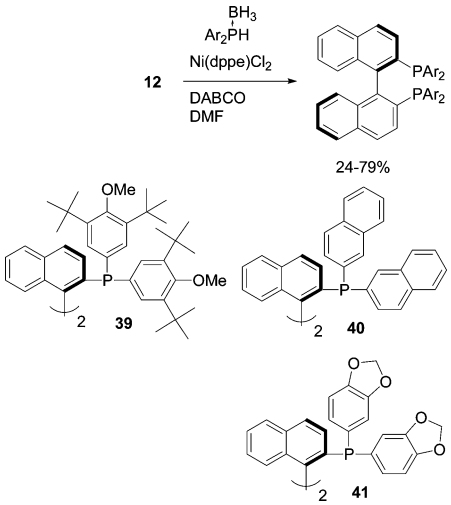


Figure 15. Takeda's method to synthesize BINAP derivatives.

Compound **175** has been tested in the hydrogenation of (*Z*)-α-acetamide cinnamate with $Rh(COD)_2OTf$ complex at 100 bar in methanol at 25 °C for 24 h. Total conversion and 91.4% ee were obtained, whereas BINAP in the same conditions gave total conversion but only 15.3% ee.

In 1997, the Takasago group proposed a variation of this method to synthesize chiral unsymmetric BINAP derivatives[44] (Figure 16).

This approach allows the syntheses of BINAP derivatives with no C_2 chirality. For example, the (*S*)-2-di(2-naphthyl)phosphino-2′-diphenylphosphino-1,1′-binaphthyl was used with a Ru(II) metal complex for the hydrogenation of ketopantolactone and gives a good selectivity of 50% ee. Moreover, this type of

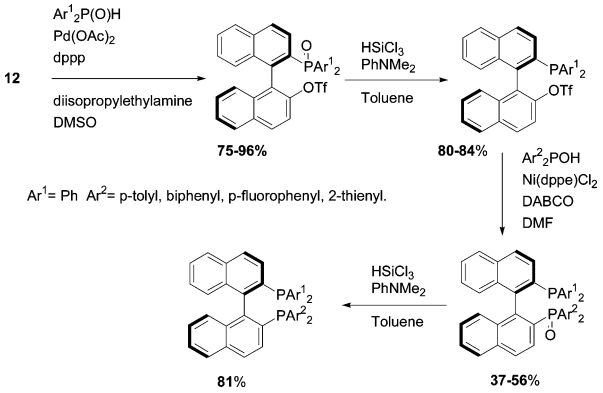


Figure 16. Takasago's method to synthesize chiral unsymmetric BINAP derivatives.

ligand exhibited an excellent performance in asymmetric hydroformylation of olefins.[45]

In the same year Kohlpaintner et al. synthesized a water-soluble BINAP derivative, 2,2′-bis(di-*p*-(3-*p*-sulfonatophenylpropyl)phenyl)phosphino-1,1′-binaphthalene (**42**) (Figure 17).[46]

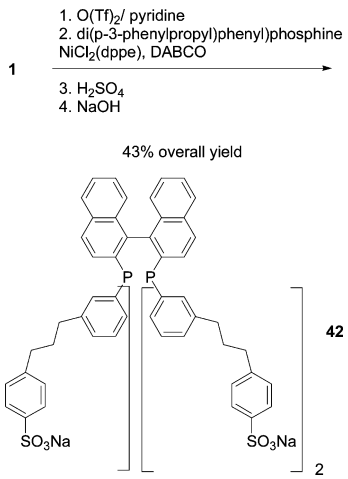


Figure 17. 2,2′-Bis(di-*p*-(3-*p*-sulfonatophenylpropyl)phenyl)phosphino-1,1′-binaphthalene.

The synthesis was carried out by using Cai's strategy with di(*p*-(3-phenylpropyl)phenyl)phosphine, synthesized by the reaction of *p*-(3-phenylpropyl)-phenyllithium with PCl_3. The resulting phosphine was selectively sulfonated to yield highly water-soluble BINAP derivatives in 43% overall yield. This ligand was tested in the two-phase water/ethyl acetate hydrogenation of acetophenone *N*-benzylimine

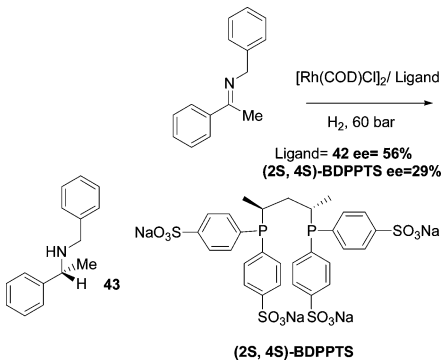


Figure 18. Asymmetric reduction of acetophenone *N*-benzylimine.

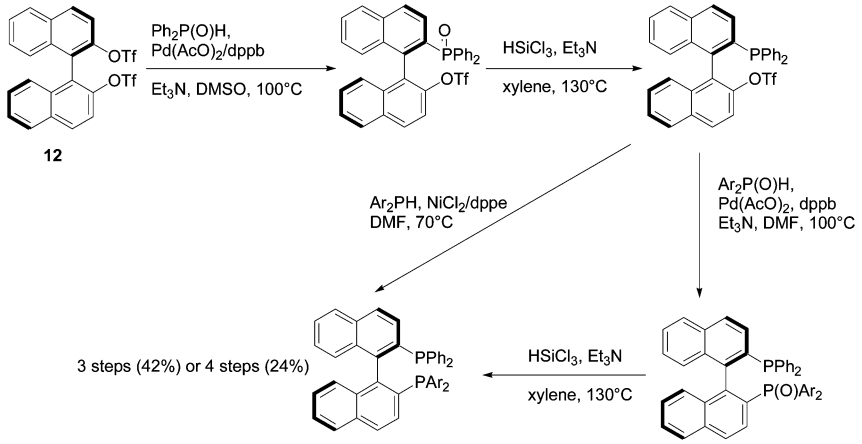


Figure 19. Synthesis of *P,P′*-heterotopic binaphthyldiphosphanes (BINAPP′).

with a Rh metal complex and gave compound **43** with 98% yield and 56% ee. Compared to Rh−BDPPTS catalyst (45% yield, 29% ee), rhodium catalyst with this BINAP derivative offers higher activity and selectivity (Figure 18) (BDPPTS = bis(diphenylphosphino)pentane).

Kohlpaintner et al. claimed the use of this amphiphilic phosphine ligand **42** for asymmetric hydrogenation and asymmetric hydroformylation.[47] The sulfonate groups were separated from phosphine functional groups by a spacer; this possibly reduced the supposed negative influence of the electron-withdrawing sulfonates.

Recently Gladiali et al. published a synthesis of *P,P′*-heterotopic binaphthyldiphosphanes (BINAPP′)[48] from 2,2′-binaphthol. In fact, they used the method described by Takasago (Figure 13) in 1997 to prepare BINAP and other ligands which were claimed in the patent[44] but not described. With this method they obtained ligands **44** and **45** having on one hand two phenyl substituents on the phosphorus atom and on the other hand two tolyl substituents (Figure 19).

Both ligands (*S*)-**44** and (*S*)-**45** have been compared with (*S*)-BINAP in the Pd-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (**46**) and in the Rh-catalyzed hydrogenation of acetamidoacrylic acid derivatives **47** (Figure 20).

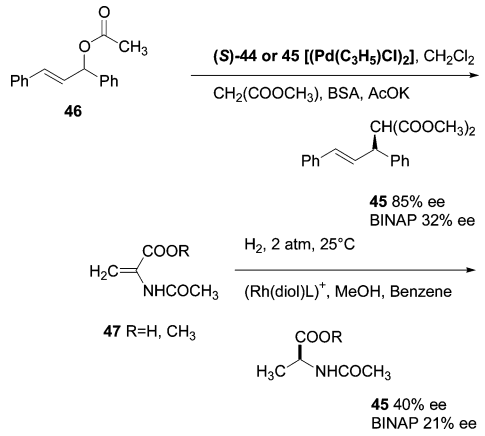


Figure 20. Asymmetric allylic alkylation of **46** and asymmetric hydrogenation of **47** using BINAPP′.

44 gave results similar to those of (*S*)-BINAP, while **45** was more selective than its C_2 counterpart in both processes. The improvement was particularly pronounced in the allylic alkylation with dimethyl malonate, where the alkylated malonate was obtained in 85% ee with (*S*)-**45** compared to 32% ee obtained with (*S*)-BINAP. In the hydrogenation, the in situ Rh catalysts obtained from **45** were also more efficient, but the ee improvement over BINAP was less significant and the catalytic activity was definitely lower than expected. Preliminary evidence showed that differentiation of the donor centers in binaphthalene-template-chelating diphosphane can result in higher selectivity.

The introduction of perfluoroalkyl groups onto the ligand is interesting in the use of either perfluorinated solvent[49] or supercritical CO_2.[50] In the case of fluorinated solvent, over 60% in weight of fluorine is generally required to ensure a sufficient solubility. This is difficult to obtain in the case of BINAP, which already has a molecular weight of 623. Recently, Sinou et al. prepared chiral fluorous BINAP derivatives. They were synthesized by modification of Takasago's method (Figure 13). The required fluorous ponytails were introduced through *O*-alkylation of preformed polyhydroxy chiral phosphines[51] (Figure 21).

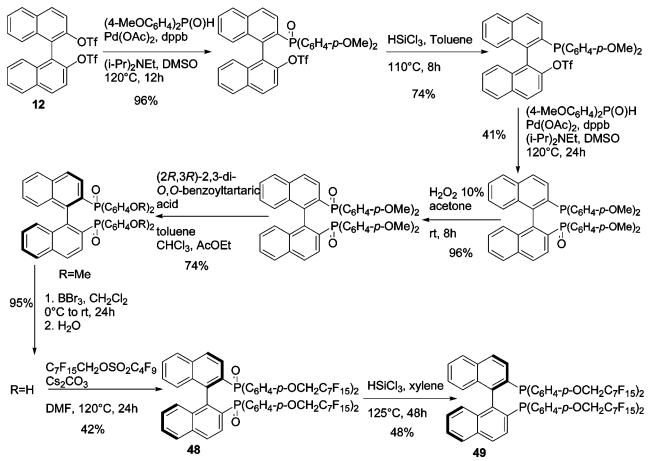


Figure 21. Synthesis of chiral fluorous BINAP.

Fluorous BINAP was obtained in eight steps from bis(trifluoromethanesulfonate) of binaphthol **12** with an overall yield of 4%. To compare the new fluorinated BINAP analogue **49** to the examples in the

literature, the asymmetric Heck reaction between 2,3-dihydrofuran (**50**) and aryl triflates **51** with Pd(OAc)$_2$/**49** catalyst was tested (Figure 22).

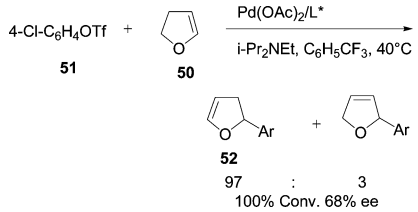


Figure 22. Asymmetric Heck reaction of 2,3-dihydrofuran with 4-chlorophenyl triflate.

The reaction was quantitative using 4-chlorophenyl triflate (**51**), 2-(4-chlorophenyl)-2,3-dihydrofuran (**52**) being formed with a very high selectivity (97%) and 68% enantiomeric excess. These results compare favorably to those obtained using the parent BINAP ligand in the same solvent (yield 67%, selectivity 92%, ee 76%), but the observed ee was lower than that achieved using a fluorous BINAP ligand bearing fluorous ponytails in the 6,6′-positions of the binaphthyl moiety (yield 59%, selectivity 88%, ee 90%).[52] This could be ascribed to the lower electron-withdrawing effect of the naphthyl moiety compared to the phenyl counterpart.

Recently Erkey and Dong synthesized a fluorinated analogue of BINAP with OCF_3 substitution of the aryl groups in the BINAP skeleton (*p*-OCF_3-BINAP) (Figure 23).[53]

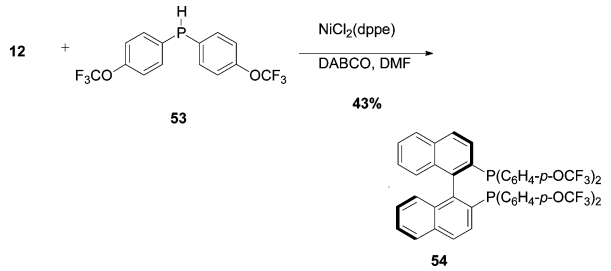


Figure 23. Synthesis of a fluorinated analogue of BINAP.

They used Cai's method and replaced diphenylphosphine by *p*-trifluoromethoxydiphenylphosphine (**53**), which was synthesized via its oxide as described in Figure 12, and then reduced by trichlorosilane. They obtained *p*-OCF_3-BINAP (**54**) with a 43% yield.

The properties of the corresponding fluorinated ruthenium catalyst in tiglic acid hydrogenation reactions were investigated in conventional solvent, methanol, as well as in dense carbon dioxide. In the past decade, the use of supercritical carbon dioxide ($scCO_2$) has provoked increasing interest as a nontoxic and environmentally benign solvent for metal-catalyzed processes.[54] Supercritical CO_2 has been used as an alternative medium for a number of asymmetric hydrogenations,[50] although catalyst solubility, especially with metal complexes, has been a problem.[55] The effects of fluorous groups incorporated onto conventional BINAP have also been investigated, with the following conclusions. In methanol, the reaction rate constant with Ru[*p*-OCF_3-BINAP] was lower than that with BINAP itself due to the electron-withdrawing property of incorporated OCF_3 groups. At low hydrogen pressures, enantioselectivity with Ru[*p*-OCF_3-BINAP] was almost the same as with Ru−BINAP. At higher hydrogen pressures, enantioselectivity was much higher for fluorinated BINAP. The modified fluorinated catalyst had a much higher solubility in dense CO_2 than the conventional catalyst. CO_2 had a great influence on both the activity and enantioselectivity. Addition of methanol to CO_2 was found to increase the enantioselectivity.

3.2. Introduction of Aliphatic and Heterocyclic Substituents

Due to the relatively easier access to the aryl derivative of phosphine, the synthesis of analogues of BINAP with alkyl and heterocyclic substituents was developed. Nevertheless, a few examples of 2,2′-disubstituted phosphino-1,1′-binaphthyl, with a substituent different from phenyl, have also been described. The use of 2,2′-bis(dicyclohexylphosphino)-1,1′-binaphthyl (Cy-BINAP, **26**) was reported in 1985 by Inoue et al.,[56] although the synthesis was described later in 1991.[57] The asymmetric hydrogenation of nerol in the presence of a rhodium complex containing **26** gave citronellol (**58**) with an optical purity of 66% ee (Figure 25).

The same year, in an attempt to provide complexes with an improved performance as catalysts for asymmetric synthesis reactions, Kumobayashi et al. from Takasago once again synthesized 2,2′-bis(dicyclopentylphosphino)-1,1′-binaphthyl (cP-BINAP, **56**).[58] This can be prepared through the reaction shown in Figure 24.

2,2′-Dibromo-1,1′-binaphthyl (**2**) is reacted with magnesium to prepare a bis Grignard reagent, which is then reacted with the dicyclopentylphosphonyl chloride to synthesize cP-BINAP oxide. Resolution with dibenzoyltartaric acid and reduction with trichlorosilane gave the pure **56** in 4% overall yield. cP-BINAP has been used with rhodium metal complexes to perform the asymmetric hydrogenation of nerol (**57**) (Figure 25). (*S*)-(−)-Citronellol (**58**) at a conversion of 99% and a selectivity of 99% with 70% ee was obtained.

Under these specific conditions, the cyclopentyl group introduced in place of the phenyl group of BINAP exhibits greatly improved selectivity and conversion in asymmetric syntheses, as compared with complexes having BINAP, **18**, or **26** as a ligand, which gave, respectively, 52%, 50%, and 66% ee with 60−90% conversion in similar conditions.

Despite the interesting results obtained with **26** and **56**, no other derivatives were studied before 2001. A Canadian group, Keay et al., synthesized 2,2′-bis(di-2-furylphosphino)-1,1′-binaphthalene (TetFu-BINAP, **59**). This time the two phosphorus atoms were less electron rich than in BINAP.[59] It was demonstrated by comparing the $^1J(^{31}P-^{77}Se)$ coupling values for selenium derivatives of BINAP (**4**) (738 Hz) and **59** (767 Hz). Allen and Taylor reported[29] that an increase in the $^1J(^{31}P-^{77}Se)$ coupling constant of phosphine selenides indicates an increase in the s character of the phosphorus lone pair orbital (i.e., less basic phosphine). Clearly, phosphorus atoms in TetFu-

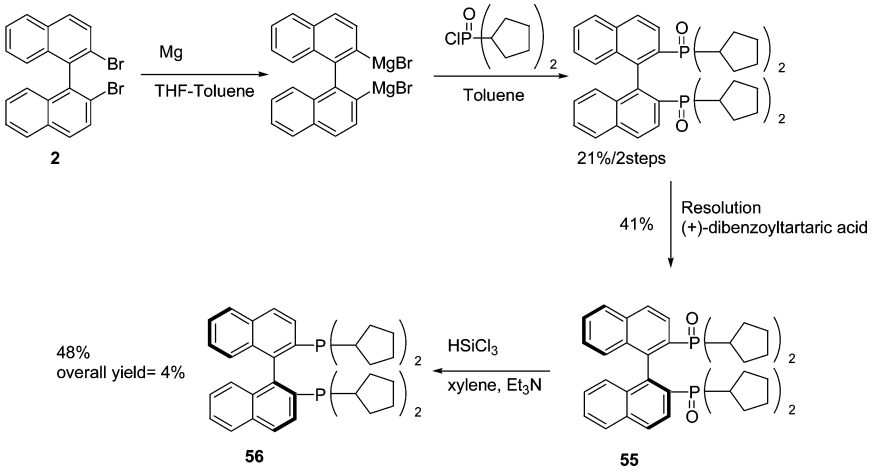


Figure 24. Synthesis of 2,2′-bis(dicyclopentylphosphino)-1,1′-binaphthyl (**56**).

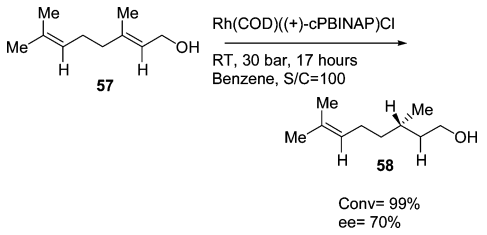


Figure 25. Asymmetric hydrogenation of nerol with Rh(COD)((+)-cP-BINAP)Cl.

BINAP are less basic than those in BINAP, and are therefore less electron rich. **2** was treated with magnesium metal in refluxing THF and the resulting Grignard reagent treated with chloro(di-2-furyl)-phosphine to provide racemic TetFu-BINAP in 55% yield. It was treated with (1*S*)-camphorsulfonyl azide derivative in refluxing THF to provide a mixture of diastereomers which were easily separated on a column of silica gel. Hydrolysis of the phosphinimines followed by reduction of the resulting phosphine oxides provided (−)- and (+)-TetFu-BINAP in 38% overall yield (Figure 26).

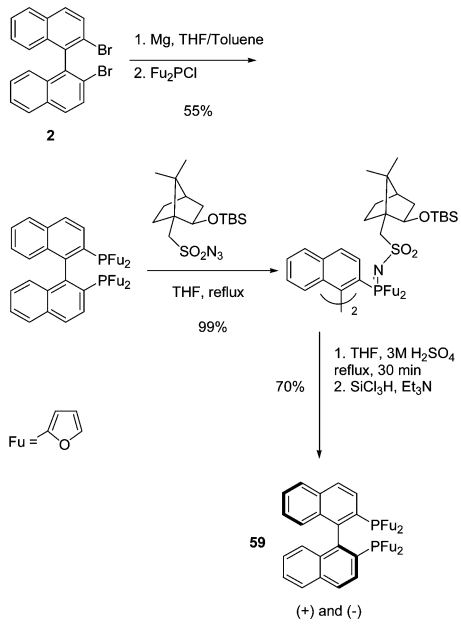
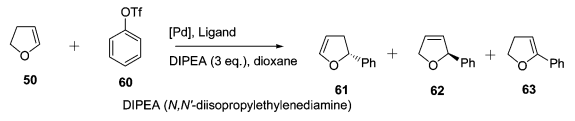


Figure 26. Synthesis and resolution of TetFu-BINAP.

They also determined for the complex [TetFu-BINAP]$PdCl_2$ a bite angle value of 91.7° smaller but similar to that measured for the [BINAP]$PdCl_2$ structure (92.7°). Therefore, any change in activity observed between TetFu-BINAP and BINAP should be mainly due to the reduction in the size of a furan ring relative to a benzene ring, or due to electronic effects caused by the presence of the furan rings. They tested their new ligand in the asymmetric Heck arylation of **50** with phenyl triflate (**60**) (Figure 27).



Entry	Pd source	Ligand	Conditions	Conv. (%)	Ratio **61/62**	%Yield (%e.e.) (*R*)-**61**	**63**	(*S*)-**62**
1	$Pd_2(dba)_3$	(*R*)-TetFuBINAP	50°C, 7 days	22	3.4	17 (89)	0	5 (63)
		(*R*)-BINAP		56	27	53 (66)	1	2 (15)
2	$Pd_2(dba)_3$	(*R*)-TetFuBINAP	100°C, 7 days	100	2.3	60 (19)	14	26 (2)
		(*R*)-BINAP		100	4.1	73 (41)	9	18 (26)
3	$Pd(OAc)_2$	(*R*)-TetFuBINAP	100°C, 7 days	100	2.5	64 (49)	10	26 (16)
		(*R*)-BINAP		100	7.2	86 (57)	2	12 (79)

Figure 27. Application of (*R*)-TetFu-BINAP in the Heck arylation of 2,3-dihydrofuran.

TetFu-BINAP ligand formed a less active Pd catalyst than the corresponding BINAP, and it provided a lower level of isomer selectivity. TetFu-BINAP provided the highest enantioselectivity at 50 °C, so it follows that incorporation of the four furyl moeities into the ligand design did not compromise the phosphine's ability to discriminate between the two enantiotopic faces of 2,3-dihydrofuran. However, it is clear that reduced phosphine donor capacity has an adverse effect upon the rate and conversion.

Finally in 2003, Pregosin et al. described ruthenium(II) alkyl-BINAP complexes.[60] They synthesized 2,2′-bis(diisopropyl)-1,1′-binaphthalene (*i*-Pr-BINAP, **64**) by treating **2** with *t*-BuLi followed by an addition of chlorodiisopropylphosphine. i-Pr-BINAP was obtained with a 68% yield (Figure 28).

They also synthesized the already known **26** using this method. To our knowledge, these ligands were not obtained in an optically pure form and no catalytic test was carried out. But the authors studied the reaction of these ligands with some ruthenium metal complexes. They concluded that, compared to

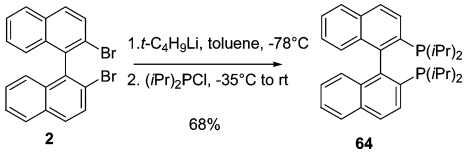


Figure 28. Synthesis of *i*-Pr-BINAP.

their phenyl counterparts, ruthenium−isopropyl- and −cyclohexyl-BINAP analogues display some similar bonding properties; however, these are housed in rather different molecular structures.

4. Modification of the Binaphthyl Moiety

Generally, but not always, the modification of the binaphthyl moiety was performed to facilitate separation, probably because the large conjugated naphthyl rings are less sensitive to the electronic effect of the substituent. Conveniently modification of the phenyl substituent directly bonded to the phosphorus should influence more strongly both the electronic density on the phosphorus atom and the steric hindrance around this coordinating atom (vide supra). For this purpose, the modification of the naphthyl group can be obtained by three main strategies. First, BINAP could be used as a starting material and is usually protected in the form of its oxide or by other common methods to protect phosphine. These protected BINAPs are finally functionalized either by electrophilic reaction or by deprotonation. In fewer cases, other precursors such as BINOL have been used as the starting material and the phosphine group has been introduced after the functionalization of the binaphthyl moiety. Cai's method allows an easy route to modified BINAP from modified BINOL. This review deals with BINAP derivatives, and modified BINOL is not exhaustively described here (for a review on BINOL derivatives see Chen et al.[61]). Finally, oxidative coupling of substituted naphthol followed by phosphination could give the desired product. As will be seen, several positions of BINAP can be modified, and different strategies have already been developed. The 3,4,5,6-positions have been the subject of most of the research described so far, probably because introducing substituents in positions 7 and 8 is more difficult than in other positions (Figure 29). Moreover, introducing substituents on

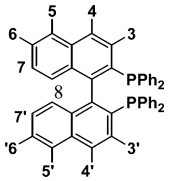


Figure 29. BINAP numbering.

position 7 or 8 of BINAP would modify the dihedral angle and therefore the ligand properties. Most of the modifications on the naphthyl moiety of the BINAP aim for an easier separation and recycling. Therefore, it is not surprising that the positions least susceptible to modifying the ligand properties are privileged, such as positions 4−6 and, to a lesser extent, position 3.

4.1. Functionalization in the 3,3′-Positions

3 and 3′ are the positions for which modifications could most influence both the electronic density on the phosphorus atom and the steric hindrance around the catalytic site thanks to the strong ortho-directing effect[62] of the phosphine group. The 3,3′-positions were directly obtained by the deprotonation of BINAP oxide (**3**) with butyllithium or LDA[63] (Figure 30).

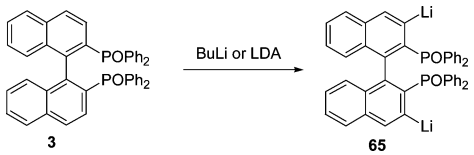


Figure 30. Deprotonation of BINAP oxide.

The lithium derivatives **65** can be halogenated by reaction with bromine or iodine or alkylated with alkyl iodide (Figure 31). Suzuki coupling with the halogenated BINAP oxide gives the arylated derivatives. 3,3′-Disubstituted BINAP is finally obtained by reduction of the phosphine oxide with $LiAlH_4$ (LAH) or silane. No description of the products and no yields were given in the patent.

To our knowledge, no applications have as yet been described for these 3,3′-derivatives.

In the same patent, Zhang Xumu described a new access to BINAP derivatives by synthesizing 3,3′-disubstituted chiral phosphinite. The 3,3′-positions of BINOL were substituted by various groups such as methyl, phenyl, etc. thanks to the ortho-directing effect of alcohol according to known literature methods.[64] A phosphination gave the BINAP derivatives. In this particular case an oxygen atom is present between the binaphthyl moiety and the phosphorus atoms (Figure 32).

The substituted BINOL was then deprotonated with *n*-BuLi in THF, and a chlorodiarylphosphine was then added to reach the desired molecule. To examine the effectiveness of the new chiral ligands, hydrogenation of a typical dehydroamino acid derivative and an enamide was carried out with the rhodium−phosphine complex prepared by mixing $Rh(COD)_2PF_6$ and a chiral phosphine ligand (Figure 33).

The 3,3′-disubstituted bisphosphinite ligands **71**−**74** are more effective than unsubstituted bisphosphinite **75**. The authors conclude that the introduction of 3,3′-substituted groups can restrict the rotation of phenyl groups adjacent to phosphines, and therefore, a well-defined chiral pocket around the transition metal is formed. Conformational rigidity is crucial for achieving high enantioselectivity for a number of asymmetric reactions.

4.2. Functionalization in the 4,4′-Positions

Due to the sensitivity of the phosphine group to oxidation reagents, and especially to dihalide such as Cl_2 or Br_2, no synthesis described the possibility to functionalize 4,4′-positions before that of the Köckritz and Kant group. They presented a simple method using Br_2 and pyridine in dichloromethane to brominate BINAP oxide in positions 4 and 4′.[65] This reaction is extremely regioselective, and only

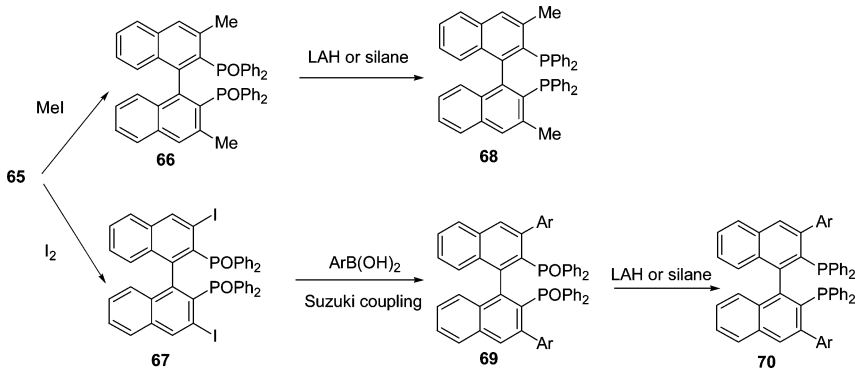


Figure 31. BINAP functionalization in positions 3 and 3′.

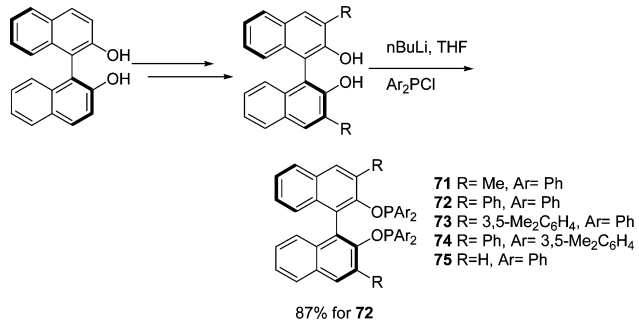


Figure 32. Synthesis of 3,3′-disubstituted chiral phosphinite from BINOL.

Entry	Ligand	Substrate	
		NHAc, COOMe	NHAc, Ph
1	**71**	95% ee	67% ee
2	**72**	>99% ee	94% ee
3	**73**	95% ee	89% ee
4	**74**	93% ee	90% ee
5	**75**	73% ee	28% ee

The reaction was carried out at rt under 3 atm of H_2 for 12h in THF (3 mL) with complete conversion (S/C=100).

Figure 33. Rh(I)-catalyzed asymmetric hydrogenation with **71**, **72**, **73**, **74**, and **75**.

monobromo (**76**) and dibromo (**77**) BINAPO in the 4,4′-positions were formed. Moreover, the optical purity of the initial BINAPO was conserved in the reaction (Figure 34). Nevertheless, the slow rate of the reaction appears to be a limiting factor.

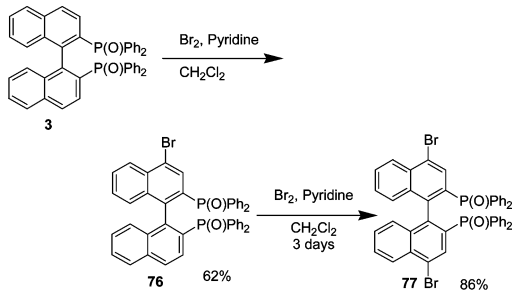


Figure 34. Selective bromination of BINAPO in positions 4 and 4′.

4.2.1. Phosphonic Acid Derivatives

The Köckritz group used this 4,4′-dibromo intermediate to introduce phosphonate groups with modified palladium-catalyzed reactions of bromo products with diethyl phosphite. Finally they reduced BINAPO with phenylsilane and then hydrolyzed the dialkyl phosphonate with bromotrimethylsilane (Figure 35).

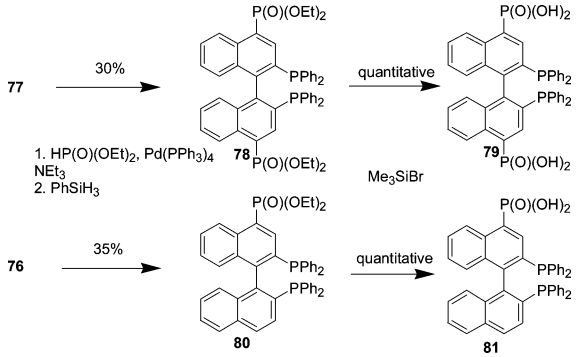


Figure 35. Synthesis of phosphorylated 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyls.

In situ generated rhodium complexes of mono- and bisphosphorylated enantiopure BINAP ligands have been used for the asymmetric hydroformylation of styrene (**83**) and vinyl acetate (**82**).[66] In the latter case, while using homogeneous conditions, a slight increase of the enantioselectivity (6−9%) compared to that of BINAP was observed although only 27% ee was obtained for the biphasic aqueous hydroformylation of styrene[67] (Figure 36).

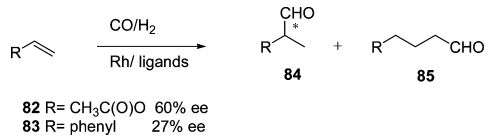


Figure 36. Hydroformylation of vinyl acetate and styrene.

Homogeneous and biphasic asymmetric hydrogenations of dimethyl itaconate have also been performed with the corresponding Ru complexes. A reduced product has been obtained with good yields and 93% ee in homogeneous conditions and 79% ee in an aqueous biphasic system[68] (Figure 37).

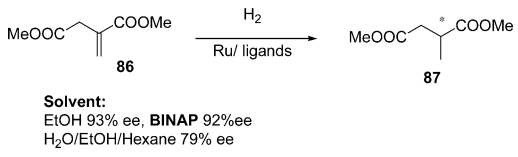
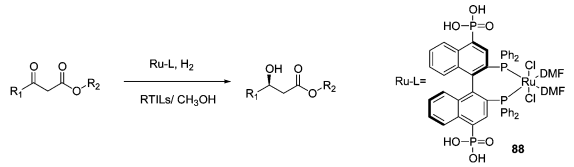


Figure 37. Hydrogenation of dimethyl itaconate.

Compared to BINAP, the complex of bisphosphonic acid **79** showed a slight increase of the enantiomeric excess, while the bisphosphonate **78** was less enantioselective. Obviously, the substitution in the fourth position of the binaphthyl skeleton does not significantly disturb the enantioselection step during the catalytic cycle. Nevertheless, in aqueous biphasic systems the enantiomeric excess was diminished.

Room temperature ionic liquids (RTILs) are emerging as excellent alternatives to toxic, volatile, and/or inflammable organic solvents in homogeneous and biphasic processes.[69] Inert ionic liquids with counteranions such as tetrafluoroborate, hexafluorophosphate, or bis(trifluoromethylsulfonyl)imide have been used as catalyst supports in biphasic processes for a wide range of reactions.[70] Today, many examples of hydrogenation in RTILs are known, and in most cases, good results are obtained and recycling is often possible.[71,72] With the same 4,4′-bis(phosphonic acid)-BINAP (**79**), Lin et al. have tested the hydrogenation of β-keto esters in RTILs with Ru(II) catalysts.[73] The Ru(ligand)$(DMF)_2Cl_2$ precatalysts were synthesized by treating the 4,4′-bis(phosphonic acid)BINAP with $[Ru(benzene)Cl_2]_2$ in DMF at 100 °C. The utility of such a catalyst has been examined for the asymmetric hydrogenation of β-keto esters with various RTILs such as 1-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$), 1-butyl-3-methylimidazolium hexafluorophosphate ($BMImPF_6$), and 1-propyl-2,3-dimethylimidazolium bis(trifluoroethylsulfonyl)amide (DMPIIm) (Figure 38).



		Ru-L				Ru-BINAP
Entry	Substrate	MeOH	DMPIIm	$BMIBF_4$	$BMIPF_6$	DMPIIm
1	89	98.3	99.0	98.4	99.3	98.9
2		98.6	99.3	99.1	99.1	99.1
3		94.2	98.1	98.9	98.9	98.1
4		96.7	97.5	98.5	97.5	96.9
5		91.7	95.1	96.3	94.9	98.1

Figure 38. Ee values for asymmetric hydrogenation of β-keto esters in RTILs.

This new catalyst is highly active for catalytic asymmetric hydrogenation in homogeneous RTIL−MeOH systems. Complete conversions have been achieved, and interestingly, highly enantioselective hydrogenation of β-keto esters in all three RTILs with ee values higher than those obtained from homogeneous reactions in MeOH were obtained. All β-keto esters were hydrogenated in the homogeneous RTIL−MeOH systems to give β-hydroxy esters in quantitative yields and ee values ranging from 94.9% to 99.3%. These ee values compare favorably with those obtained with Ru−BINAP catalysts in the homogeneous DMPIIm−MeOH system. Catalyst **88** was better than the same BINAP catalyst in all cases (entries 1−4) except for the last substrate (entry 5). Nevertheless, although the differences are not large, the rationalization of the results does appear to be difficult.

Lin et al. also demonstrated that both RTILs and catalyst can be recycled and reused several times for asymmetric hydrogenation of methyl acetoacetate (**89**). They carried out recycling by extracting the mixture with degassed hexane. The IL phase was washed twice more with degassed hexane. After being dried under vacuum, the RTIL phase was fitted with methyl acetoacetate and MeOH and then subjected to hydrogenation conditions (Figure 39).

	88/$BMImPF_6$		**88**/DMPIIm	
Run	Conversion (%)	ee (%)	Conversion (%)	ee (%)
1	99	99.3	99	98.5
2	98	97.3	99	98.9
3	89	95.2	99	98.3
4	84	89.7	99	97.5
5	62	74.9	77	95.9
6	50	66.7	44	81.9

All reactions were carried out with 1 mol% catalyst under 100 bars of H_2 for 22 h.

Figure 39. Recycling of catalyst **88** for hydrogenation of methyl acetoacetate in RTIL−MeOH.

The first three runs of hydrogenation reactions gave almost the same conversion and enantioselectivity. Subsequent runs led to only a slight deterioration of enantioselectivity but a significant drop in activity. The authors give no explanation for this loss of activity.

They also explored the synthesis of chiral porous zirconium phosphonates for enantioselective hydrogenation of unfunctionalized aromatic ketones.[74] Remarkably, BINAP-derived porous zirconium phosphonates provide enantioselectivity superior to that of their homogeneous parent counterpart Ru−BINAP−DPEN (DPEN is 1,2-diphenylethylenediamine) system developed by Noyori et al.[75]

Treatment of (*R*)-4,4′-bis(phosphonic acid)BINAP with $[Ru(benzene)Cl_2]_2$ followed by (*R*,*R*)-DPEN afforded the phosphonic acid-substituted Ru−BINAP−DPEN intermediate **90**, which was directly reacted with Zr(O-*t*-Bu)$_4$ under reflux conditions to give chiral porous zirconium phosphonates **91** of the approximate formula $Zr[Ru(L)(DPEN)Cl_2]\cdot 4H_2O$ (Figure 40).

Acetophenone was hydrogenated to 1-phenylethanol with complete conversion and 96.3% ee in 2-propanol with a 0.1 mol % loading of Zr−Ru−L solid. This level of enantioselectivity is significantly higher than that observed for the parent Ru−BINAP−DPEN homogeneous catalyst, which typically gives ~80% ee for the hydrogenation of acetophenone under similar conditions. The recycling of the Zr−Ru−L system was successful for asymmetric hydrogenation of 1-acetonaphthone with no deterioration of enantioselectivity (Figure 41).

The Zr−Ru−L system was used for eight cycles of hydrogenation without loss of enantioselectivity. The conversion did not decrease for the first six runs, but began to drop at the seventh reuse. The authors explain that the loss of activity may not reflect the

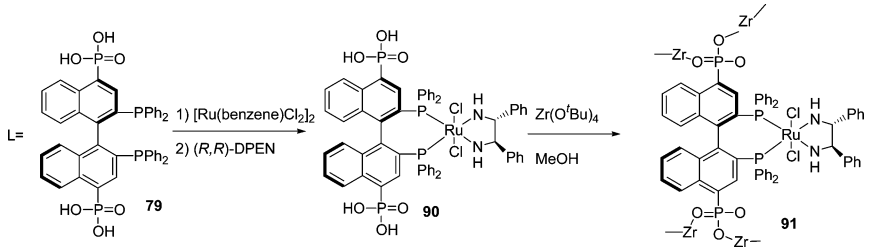
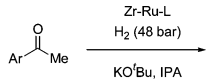


Figure 40. Synthesis of chiral porous zirconium phosphonate.



Entry	Reuse	Conv. (%)	ee (%)
1		100	99.0
2	First	100	99.0
3	Second	100	99.1
4	Sixth	95	99.1
5	Seventh	85	99.0

The reactions were carried out with 0.1 mol% solid loading and 1% KO^{t}Bu under 48 bars H_2 pressure for 20 h.

Figure 41. Use and reuse of Zr−Ru−L for hydrogenation of acetophenone and 1-acetonaphthone.

intrinsic instability of the Zr−Ru−L solid catalyst. They conducted the experiments without rigorous exclusion of air, and they thought oxygen sensitivity of the ruthenium hydride complexes may have contributed to the loss of activity after multiple runs.

Very recently Lin et al. developed recyclable and reusable mesoporous-silica-anchored Ru catalysts based on 4,4′-substituted BINAPs and used for the hydrogenation of β-alkyl β-keto esters with up to 95.2% ee.[76]

4.2.2. Aminomethyl Derivatives

Introduction of two amino groups is potentially interesting for two types of application: on one hand, water-soluble catalysts can be obtained, and on the other hand, it is possible to prepare material thanks to the formation of polyamide or polyurea. Using 4,4′-dibromo-BINAPO (**77**), 4,4′-diam-BINAP (**93**) was obtained in a three-stage sequence.[77] Reaction with copper cyanide gave the 4,4′-dicyano-BINAPO. Reduction of the phosphine oxide is not successful when using common reducing agents, such as $HSiCl_3$, $LiAlH_4$, and $PhSiH_3$, which gave partly reduced phosphine oxide and numerous nondetermined byproducts. More complex methods such as Imamoto's ($MeOTf + LiAlH_4$) also failed. For that reason, a new reducing system consisting of a mixture of $PhSiH_3$ and $HSiCl_3$ at 120 °C was successfully used. This method permitted the chemoselective reduction of phosphine oxide without reducing cyano groups. This rapid and efficient method gave 4,4′-dicyano-BINAP (**92**), which was reduced with lithium aluminum hydride to obtain 4,4′-diam-BINAP[78] (Figure 42) with

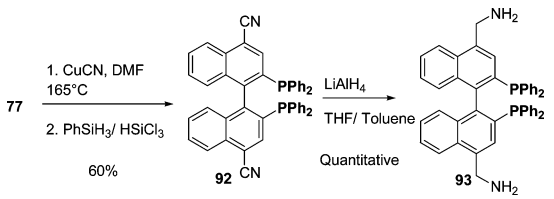
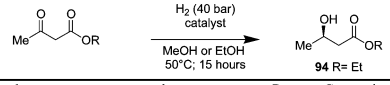


Figure 42. Synthesis of 4,4′-diaminomethyl-BINAP.

an overall yield of 60% from BINAP oxide without any requirement of tedious liquid chromatography.

To evaluate this new ligand, the corresponding ruthenium complexes were prepared by reaction of [(COD)Ru(2-methallyl)$_2$] according to the general procedures described by Genet et al.[79] The catalytic activities of these ruthenium complexes in the hydrogenation of methyl or ethyl acetoacetate were tested, respectively, in methanol and ethanol, with a substrate:catalyst ratio (S:C) of 1000, at 50 °C and under 40 bar of hydrogen. The same ruthenium complexes were prepared with (*R*)-BINAP to compare the activity and selectivity of the ligands (Figure 43).



Entry	ligand	complex	R	Conversion (%)	ee (%)
2	(*R*)-4,4'-*diam*BINAP	[(COD)Ru(2-methyallyl)$_2$]	Et	100	98
3	(*R*)-BINAP	[(COD)Ru(2-methyallyl)$_2$]	Et	100	98

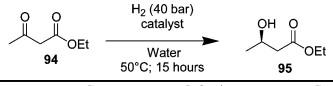
[2] &

Figure 43. Ruthenium-catalyzed reduction of keto esters with 4,4′-diam-BINAP.

93 proved to be as efficient as the BINAP complex, which gave total conversion for the reduction of ethyl acetoacetate in 99% ee. The aminomethyl groups have no major influence on either activity or selectivity.

The bromohydrate form of ligand **93** and the corresponding Ru(II) catalysts were prepared in situ from [Ru(COD)(2-methylallyl)$_2$] and aqueous hydrobromic acid according to the usual procedures.[79,80] Hydrosoluble catalyst was obtained in quantitative yield.

To evaluate these hydrosoluble catalysts, the hydrogenation was carried out using ethyl acetoacetate (**94**) as substrate (Figure 44). Water and ethyl aceto-



Entry	Reuse	Cat.	Subst/cat.	Conv.[a] (%)	ee[a] (%)
1	1st	**(*R*)-4,4'**	1000	100	98
2	8 th	**(*R*)-4,4'**	1000	100	97
3		**(*R*)-BINAP**	1000	100	98[a]

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

Figure 44. Recycling of hydrosoluble catalyst in the hydrogenation of ethyl acetoacetate.

acetate were added to obtain a biphasic mixture where the catalysts were only in the aqueous phase and the substrate was in both phases. 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, and the homogeneous solution obtained was extracted three times with pentane. Fresh substrate was added to the resulting aqueous phase, and a new hydrogenation could be carried out.

In catalytic hydrogenation of this substrate this 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′-diam-BINAP had no influence on catalytic activity and selectivity, which were similar to those of BINAP itself. The decrease of activity and selectivity observed after eight runs was probably due to catalyst oxidation despite taking the utmost care.

4.2.3. Polyfluorinated Derivatives

The introduction of a perfluoroalkyl chain could be performed to obtain a catalyst that is usable in supercritical CO_2 and/or perfluorinated solvent (see section 3.1.2 and Figure 21). The latter, nevertheless, requires a high percentage of fluorine in the molecule to reach a significant solubility. The introduction of a polyfluorinated chain is not an easy task. In many cases this is done by using linkers such as ester, ether, amide, and other hydrophilic functional groups.[50,81] This strategy has two drawbacks, the first being the number of steps required to introduce such linkers and the other being the hydrophilic properties of these functional groups. The latter is hardly compatible if high hydrophobicity is required. The use of organometallic derivatives of polyfluorinated chains is not easy, but Chen and Tamborski have demonstrated that an unsymmetrical Ullman reaction could be achieved between an aromatic halide and perfluoroalkyl iodides.[82] Attachment of the fluoroalkyl chain to the BINAP oxide was directly available via a copper-mediated cross-coupling reaction between perfluoroalkyl iodide and the (*R*)- or (*S*)-4,4′-dibromo-BINAPO. Products were then reduced with the $PhSiH_3/HSiCl_3$ system to give 4,4′-perfluoroalkyl-BINAP in 85% overall yield (Figure 45). Moreover,

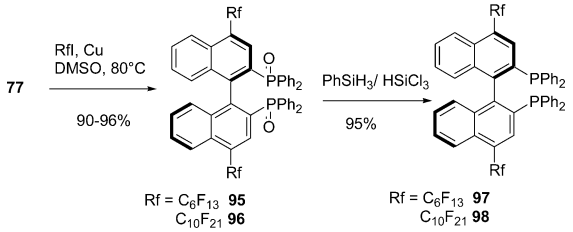
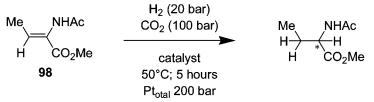


Figure 45. 4,4′-Perfluoroalkyl-BINAP synthesis.

no symmetric cross-coupling products were observed even when only a slight excess of perfluorinated reagents were used.[83]

This ligand was tested in homogeneous hydrogenation of ethyl acetoacetate in ethanol. The 4,4′-perfluoroalkyl-BINAP showed the same activities and enantioselectivities as 4,4′-diam-BINAP and BINAP itself. Perfluoroalkyl groups seem to have no influence compared to BINAP, and the length of the perfluoroalkyl chains changes neither the activity nor the selectivity.

The perfluoroalkyl-BINAP was also tested in the hydrogenation of methyl 2-acetamidoacrylate (**98**) in $scCO_2$. [(COD)Ru(2-methallyl)$_2$] was used as the metal complex. The use of supercritical fluids as reaction media offers the opportunity to replace conventional organic solvents and also to optimize and potentially allow a broader solvent compatibility and therefore solvent effect on the reaction selectivities[84] (Figure 46).



Entry	Subst/ cat	Ligand	Complex	Co-solvent (ml)	Conv [a] %	ee[a] %
1	500	(*R*)-BINAP	[(COD)Ru(2-methallyl)$_2$]	0.5	100	60
2	500	(*R*)-**97**	[(COD)Ru(2-methallyl)$_2$]	0.5	100	74
3	500	(*R*)-**98**	[(COD)Ru(2-methallyl)$_2$]	0.5	100	72

[a] Conversion and enantioselectivity were determined by GC on a Supelco beta-DEX (60m, 0.25mm) capillary column. Co-solvent: trifluorotoluene.

Figure 46. Hydrogenation of methyl 2-acetamidoacrylate with 4,4′-perfluoro-BINAP in $scCO_2$ with trifluorotoluene as cosolvent.

Perfect conversions were obtained, and good selectivities were observed. 4,4′-Perfluorohexyl-BINAP (**97**) gave an enantiomeric excess 14% higher compared to BINAP. The presence of the perfluoroalkyl groups increased the solubility and gave a more effective catalyst. Moreover, an effect of the acidity of the solvent has been observed: a decrease of acidity as a result of increasing selectivity.

4.2.4. Other Derivatives

Recently, Lin et al. synthesized a family of 4,4′-substituted BINAP derivatives from 4,4′-dibromo-BINAPO by two different approaches.[85] In the first, the BINAP derivatives were synthesized by halogen metathesis, Suzuki coupling, or a Pd-catalyzed phosphonation reaction followed by Ti(O-*i*-Pr)$_4$-mediated reduction with triethoxysilane or reduction with phenylsilane as already described by Köckritz et al. (Figure 47).

In the second approach, 4,4′-dibromo-BINAPO was reduced to 4,4′-dibromo-BINAP (**107**) by Ti(O-*i*-Pr)$_4$-mediated reduction with triethoxysilane. The BINAP derivatives were then obtained with good yields by lithiation with *n*-butyllithium followed by treatment with various electrophiles (Figure 48). The lithiation could not be performed directly with **77** because of the ortho-directing effect of the phosphine oxide, which influences the selectivity of this reaction.

These derivatives were used to study the substituent effect on BINAP. Ruthenium precatalysts were prepared by mixing 4,4′-disubstituted BINAP ligands and [$RuCl_2$(benzene)]$_2$ in hot DMF, and were used for catalysis without further purification. The asymmetric hydrogenation of ethyl benzoylacetate (**108**) was studied.

Although all these Ru−4,4′-BINAP catalysts showed similar activities, their enantioselectivities varied from 72% to 99%. It seems that bulky and electron-donating groups enhanced the enantioselectivity

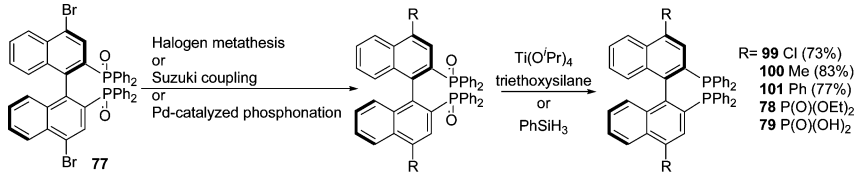


Figure 47. Synthesis of 4,4′-disubstituted BINAP derivatives from 4,4′-dibromo-BINAPO via the substitution reduction strategy.

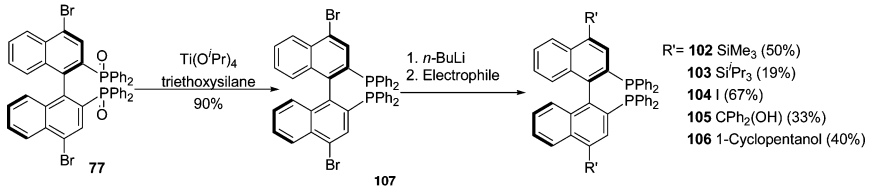
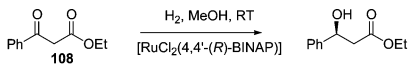


Figure 48. Synthesis of 4,4′-disubstituted BINAP derivatives from 4,4′-dibromo-BINAPO via the reduction substitution strategy.

(Figure 49) while electron-withdrawing groups decreased the ee values obtained (Figure 50).



Entry	Ligand	4,4'-Substituent groups	ee (%)
1	**100**	R=Me	85.0
2	**101**	R=Ph	71.8
3	**78**	R=P(O)(OEt)$_2$	98.8
4	**79**	R= P(O)(OH)$_2$	97.2
5	**102**	R'=SiMe$_3$	99.5
6	**103**	R'=Si^{i}Pr$_3$	98.6
7	**105**	R'=CPh$_2$(OH)	99.3
8	**106**	R'=1-cyclopentanol	99.2

All reactions were carried out under 96 bars of H_2 in methanol at room temperature for 20 h with 1 mol% catalyst loading. All reactions were judged to have > 98% conversions.

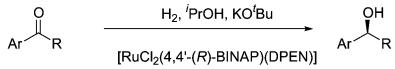
Figure 49. Asymmetric hydrogenation of ethyl benzoylacetate with bulky and electron-donating 4,4′-substituted BINAP derivatives as the ligand.

Entry	Ligand	4,4'-Substituent groups (σ_m)	ee (%)
1	**BINAP**	None	85.0
2	**107**	R=Br (0.39)	80.8
3	**99**	R=Cl (0.37)	77.0
4	**104**	R'=I (0.35)	86.5

All reactions were carried out under 96 bars of H_2 in methanol at room temperature for 20 h with 1 mol% catalyst loading. All reactions were judged to have > 98% conversions. σ_m values indicate an electron-withdrawing capability of the substituent. The higher σ_m the higher electron-withdrawing capability.[1]

Figure 50. Asymmetric hydrogenation of ethyl benzoylacetate with 4,4′-halogen-substituted BINAP derivatives as the ligand.

The highest enantiomeric excess was obtained with the Ru catalyst based on 4,4′-TMS-BINAP (**102**) with 99.5% ee, which is better than that of BINAP itself. **102** was chosen to hydrogenate a variety of β-aryl keto esters. Complete conversion and very high ee values of 97.8−99.6% were obtained by using 1 mol % Ru catalyst derived from ligand **102** (Figure 51). A decrease in enantiomeric excess was observed when an electron-withdrawing substituent was placed in the ortho position of the aryl group of the substrate, but all products were obtained with high or very high ee values. The authors explain this enhancement of ee values by molecular modeling studies. They show that unlike analogous β-alkyl keto esters, the aryl group on the β-aryl keto esters can form $\pi-\pi$ stacking interactions with one of the phenyl groups on BINAP



Ar, R	BINAP	99	100	102	105	79
Ph, Me	83.0	85.7	89.9	96.0	91.5	97.1
1-naphthyl, Me	96.9	97.9	98.0	99.0	98.5	99.0
4-^{t}Bu-Ph, Me	94.0	91.4	90.9	99.0	95.4	99.1
4-Me-Ph, Me	83.1	79.0	77.5	95.4	83.8	97.4
4-Cl-Ph, Me	60.0	66.9	60.9	90.5	88.4	95.8

All the reactions were carried out at room temperature with 0.1 mol% catalyst and 1 mol% KO^{t}Bu additive under 10 bar hydrogen pressure in 20 h. The ee values were determined by GC on a Supelco β-dex 120 column. All conversions were >99% as judged by the integrations of GC peaks.

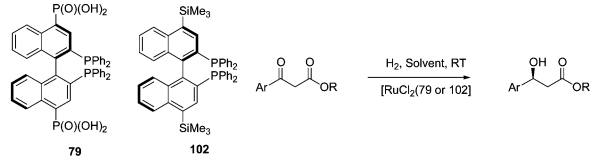
Figure 51. Asymmetric hydrogenation of ketones with [RuCl$_2$(4,4′-(*R*)-BINAP)(DPEN)].

in the disfavored transition state, which will stabilize this transition state and lead to a deterioration in the enantiomeric excess. In contrast, bulky substituents at the 4,4′-positions will have significant repulsive interactions with the aryl group, cause destabilization of the disfavored transition state, and thus enhance the enantioselectivity drastically.

Moreover, very recently Lin et al. used these ligands to synthesize a family of tunable precatalysts, [Ru(4,4′-BINAP)(chiral diamine)Cl$_2$], and used them for enantioselective hydrogenation of aromatic ketones (Figure 51).[87]

Noyori et al. have already used the chiral [Ru(diphosphine)diamine)Cl$_2$] system for hydrogenation of simple ketones and obtained the most remarkable enantioselectivity and activity characteristics.[88] Subsequent mechanistic studies by Noyori et al. and Morris et al. also established a catalytic pathway in which the key step involves simultaneous transfer of a hydride on the Ru center and a proton of the RNH$_2$ ligand to the carbonyl group via a six-membered pericyclic transition state to afford chiral secondary alcohols.[89] The result obtained by Lin et al. differs from that of previous chiral diphosphines that rely on the bis(xylyl)phosphino groups to control enatioselectivity. An X-ray structural study reveals that the bulky substituents on the 4,4′-positions of BINAP can effectively create a suitable chiral pocket in the transition state and thus provide a new mechanism for the enantiocontrol in such a remarkable asymmetric process. They also immobilized Ru catalysts based on **79** and **102** in RTILs. These catalysts are highly active for catalytic asymmetric

hydrogenation of a wide range of β-aryl keto esters in the homogeneous $BMImBF_4$−methanol system (Figure 52).



Ar	R	102 MeOH	102 RTIL/MeOH	79 MeOH	79 RTIL/MeOH
Ph	Et	99.5	98.9	97.2	99.3
4'-MeO-Ph	Et	99.5	94.4	94.0	95.9
4'-F-Ph	Me	99.3	98.1	97.1	98.9
4'-Cl-Ph	Me	99.1	97.8	97.6	98.3
2'-Cl-Ph	Me	99.6	98.9	97.2	99.8
4'-CF_3-Ph	Me	99.0	98.4	97.2	98.9
3'-CF_3-Ph	Me	98.4	98.9	98.4	98.8
2'-CF_3-Ph	Me	97.8	96.7	97.3	97.5

All reactions were carried out under 96 bars of H_2 in methanol at room temperature for 20 h with 1 mol% catalyst loading. All reactions were judged to have > 98% conversions.

Figure 52. Ru-catalyzed asymmetric hydrogenation of β-aryl keto esters with **79** and **102** as the ligands.

The authors concluded that the polarity of the complex used as the asymmetric catalyst can enhance performances in RTILs. They recycled the catalysts, but the ee's and conversions decrease slightly after each reuse. This is not surprising considering the solubility factor of a silane derivative. No oxidation of the catalyst was observed during workup.

In conclusion, it is interesting to note that the 4,4′-substituent effects can enhance enantioselectivity as well as favor separation during recycling.

4.3. Functionalization in the 5,5′-Positions

BINAP derivatives substituted in the 5,5′-positions are the most exemplified. This is probably due to the possibility of electrophilic substitution onto this position of the BINAPO. Three major methods may be noted to synthesize 5,5′-substituted BINAP. Indeed nitration, sulfonation, and halogenation of the BINAPO permit the BINAP to be obtained directly in these positions when acidic (Brönsted or Lewis) media are used instead of neutral or basic media as described above.

4.3.1. Nitro and Amino Derivatives

Nitration of BINAPO (**3**) was first published in 1986 by Kumobayashi et al. and gave 5,5′-dinitro-BINAP dioxide (**108**), which was reduced to reach 5,5′-diamino-BINAPO and then 5,5′-diamino-BINAP (**109**)[90] (Figure 53).

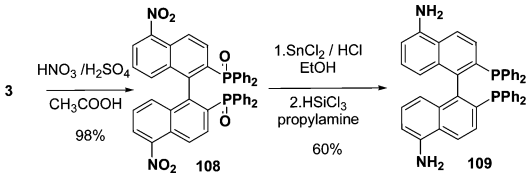


Figure 53. Synthesis of 5,5′-diamino-BINAP.

109 was used in the asymmetric isomerization of diethylgeranylamine using [Rh((+)-5,5′-diamino-BINAP)(nbd)]$^+ClO_4^-$. Excellent conversion to enamine was observed at 96%, whereas 83% conversion was observed with a comparative example using unsubstituted (+)-BINAP (Figure 54).

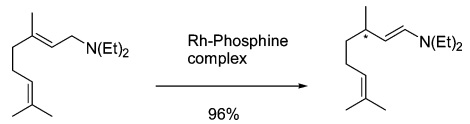


Figure 54. Asymmetric isomerization of diethylgeranylamine using [Rh((+)-5,5′-diamino-BINAP)(nbd)]$^+ClO_4^-$.

Many derivatives were obtained using **109** as the starting material. 5,5′-Diacetamido-BINAP (**110**) was prepared in one step from the diamino-BINAP by using acetic anhydride and tri-*n*-propylamine (Figure 55).

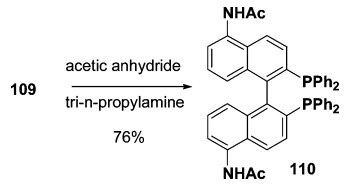


Figure 55. Synthesis of 5,5′-diacetamido-BINAP (**110**).

It was used in the same isomerization of diethylgeranylamine and gave 96% conversion. It can be seen from these results that the new phosphine forms complexes with metallic elements which exhibit high performances as catalysts. It is not specified if this increase in conversion compared to that of BINAP is due to the steric and/or electronic effects of the amino group. Nevertheless, this result could be compared to the effect of electron-withdrawing substituents on the 4,4′-positions (see above).

4.3.2. Polyester and PEG Derivatives

In another way Chan et al. developed several soluble polymer-supported catalysts for asymmetric hydrogenation. Contrary to BINAP itself, which cannot be easily attached to a polymer support, **109** could be easily used as a monomer for the formation of material for heterogeneous catalysis. Polymer-supported BINAP ligands[91] were synthesized by the polycondensation of the substituted BINAP, terephthaloyl chloride, and (2*S*,4*S*)-pentanediol to form soluble polyester-supported BINAP **111**[92] or poly(ethylene glycol) to form soluble PEG-supported BINAP **112**[93] (Figure 56).

MeO-PEG-supported BINAP **113** was also synthesized by the condensation of **109** with terephthaloyl chloride in the presence of triethylamine in DMAc followed by reaction with MeO-PEG-OH (M_w = 5000)[94] (Figure 57).

All these supported Ru(BINAP) complexes were tested in the hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid. The best results were obtained with the MeO-PEG-supported (**113**) Ru(BINAP)-$(acac)_2$, whereas PEG-supported (**112**) (Ru)BINAP was tested in homogeneous and two-phase conditions (Figures 58−60). Results in the last case appear to be significantly lower in terms of ee, but no clear explanation could be found for this observation. It is noticeable that polymer **113** possesses a catalytic site more clearly defined than that of the other material

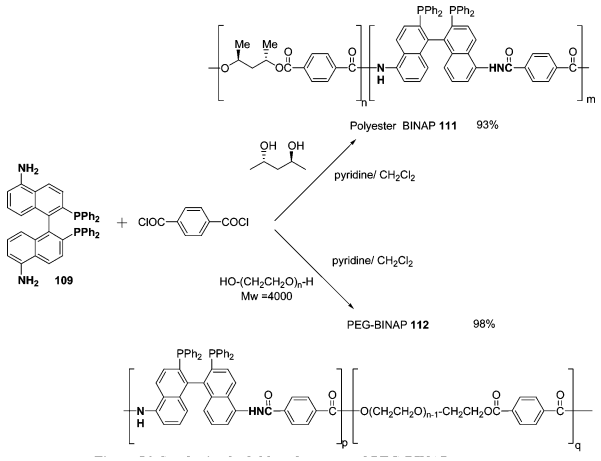


Figure 56. Synthesis of soluble polyesters and PEG-BINAP.

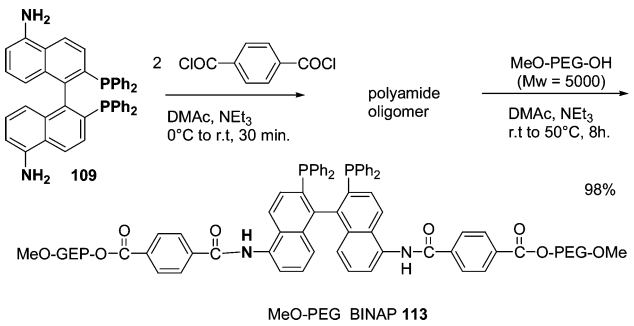


Figure 57. Synthesis of MeO-PEG-BINAP **113**.

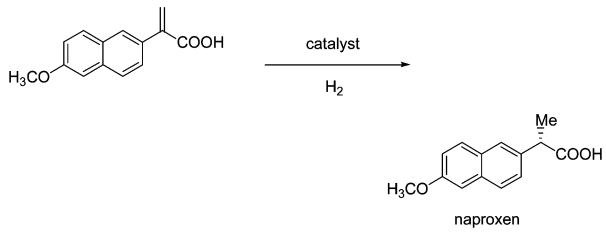


Figure 58. Synthesis of naproxen using supported BINAP.

Ligand	Reuse	Catalyst	Sub/cat.	Solvent	T° (°C)	Conv. (%)	ee (%)
BINAP		$Ru(acac)_2$	1000	MeOH	0-2	98.2	89.0
113		$Ru(acac)_2$	1000	MeOH	rt	100	90.2
113	2nd	$Ru(acac)_2$	1000	MeOH	rt	98.5	90.0
BINAP		$[Ru(cymene)Cl_2]_2$	100	MeOH	0-2	100	94.4
113		$[Ru(cymene)Cl_2]_2$	100	MeOH	0-2	100	96.0
113	3rd	$[Ru(cymene)Cl_2]_2$	100	MeOH	0-2	100	96.3

Figure 59. Hydrogenation of 2-(6′-methoxy-2′-naphthyl)-acrylic acid with MeO-PEG−Ru(BINAP).

Ligand	Catalyst	Sub/cat	Solvent	T° (°C)	Conv. (%)	ee (%)
112	$[Ru(cymene)Cl_2]_2$	50	MeOH	rt	74	87.2
112	$[Ru(cymene)Cl_2]_2$	50	Ethylacetate/ H_2O	rt	53.6	78.4

Figure 60. Hydrogenation of 2-(6′-methoxy-2′-naphthyl)-acrylic acid with supported Ru(BINAP).

for which the catalytic sites in the middle of the chain and at the extremity could be significantly different in terms of steric environment.

MeO-PEG-supported (**113**) Ru(BINAP) catalysts showed high catalytic activity and enantioselectivity, and in comparison to the parent monomeric Ru(BINAP) catalysts, slightly higher enantioselectivities were obtained. This soluble polymer was also used in biphasic systems. Although it gave rise to important selectivity (78% ee), the result was also significantly lower in terms of ee and conversion compared to that of the reaction performed in methanol.

MeO-PEG-supported $Ru(BINAP)(acac)_2$ catalyst is more active and maintains high enantioselectivity. In contrast to the chiral polyester-supported $[RuCl(BINAP)(cymene)]Cl$ catalyst, which also gives very good results, the MeO-PEG-supported catalyst realized hydrogenation reaction in methanol in a completely homogeneous manner, had higher catalytic activity, and induced higher enantioselectivity.

4.3.3. Dendritic Derivatives

Dendritic organometallic catalysts have become a very active field of research.[95] As well as increasing the molecular weight, which facilitates separation and recycling, the dendrimer architecture may offer a better means of controlling the disposition of catalytic species in soluble polymer-based catalysts. Fan et al. synthesized a series of soluble dendritic BINAP ligands from reaction of **109** with Frechet-type polyether wedges[96] (Figure 61). In situ catalyst

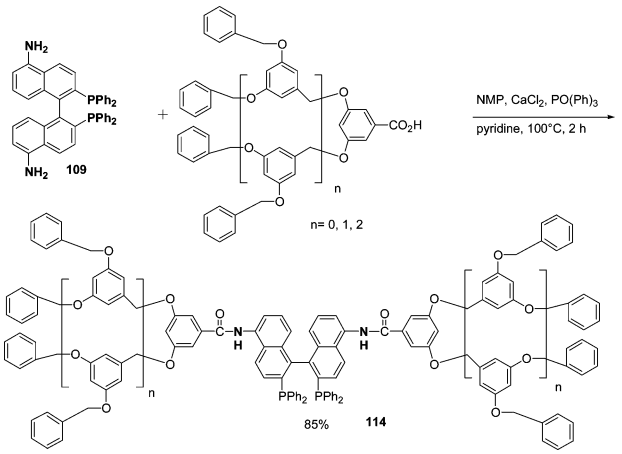
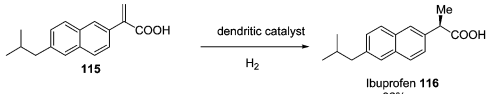


Figure 61. Synthesis of BINAP ligands with polyether dendritic wedges.

preparation was managed by mixing a dendritic BINAP ligand (**114**) with $[Ru(cymene)Cl_2)]_2$ in methanol−toluene (1:1, v/v). The complexes were used in the asymmetric hydrogenation of 2-[*p*-(2-methylpropyl)phenyl]acrylic acid (**115**).

Complete conversions were obtained with high enantioselectivities in 24 h. Ibuprofen (**116**) could be obtained with 92% ee and 100% conversion in 20 h (Figure 62).

Confirming the value of designing Ru(BINAP) catalysts with dendritic wedges, all of the dendritic catalysts performed better compared to the parent BINAP complex. These catalysts showed higher ee values than Ru(BINAP), although the highest generation catalyst ($n = 2$) gave slightly lower enantioselectivity. Most interestingly, the size of the dendritic wedges influenced the reactivity of these



Ligand	Catalyst	Sub/cat.	Solvent	Time	T° (°C)	TOF/h	Conv. (%)	ee (%)
(*S*)-BINAP	$[Ru(cymene)Cl_2]_2$	125	MeOH/toluene	2h	rt	6.3	10.2	89.8
N=0	$[Ru(cymene)Cl_2]_2$	125	MeOH/toluene	2h	rt	6.5	10.4	91.8
N=1	$[Ru(cymene)Cl_2]_2$	125	MeOH/toluene	2h	rt	8.3	13.2	92.6
N=2	$[Ru(cymene)Cl_2]_2$	125	MeOH/toluene	2h	rt	21.4	34.3	91.6
N=2 cycle 3	$[Ru(cymene)Cl_2]_2$	125	MeOH/toluene	5h	rt	16.6	66.6	90.9

Figure 62. Synthesis of ibuprofen using a dendritic ligand and $[Ru(cymene)Cl_2)]_2$.

catalysts; the rate of the reaction increased using higher generation catalysts. The authors proposed that the size effect is probably due to the steric bulk of the dendritic wedges, which affects the dihedral angle of the two naphthalene rings in the Ru(BINAP) complex, and thus leads to a faster rate and/or better enantioselectivity in the reaction. Moreover, the dendritic complexes could be quantitatively precipitated and recovered via filtration. The highest generation catalyst was recovered and reused for at least three cycles with the same activity and enantioselectivity.

4.3.4. Polymeric Bifunctional Derivatives of BINAP

Finally Fan et al. synthesized the soluble bifunctional polymeric ligand BINOL−BINAP **118** or BINOL−BINAPO by condensation of 3,3′-diformyl-1,1′-bi-2-naphthol (**117**) with **109** or the corresponding phosphine oxide in glacial acetic acid as solvent.[97] BINOL−BINAP copolymers have a molecular weight of 4251, although with a large dispersity coefficient (PDI = 2.7) and BINOL−BINAPO a molecular weight of 5083 (PDI = 3.7). They could be dissolved in common organic solvents such as dichloromethane, tetrahydrofuran, and toluene, but quantitatively precipitated by the addition of methanol (Figure 63).

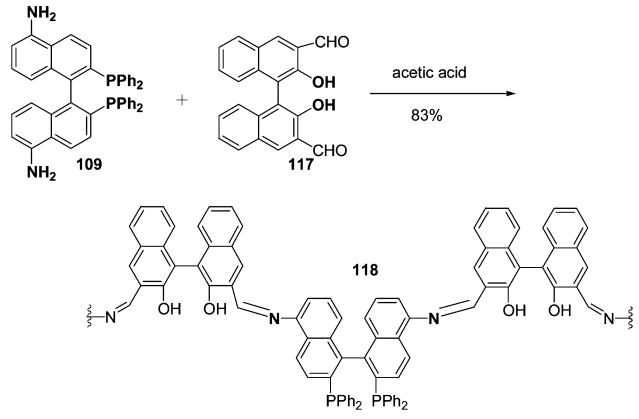
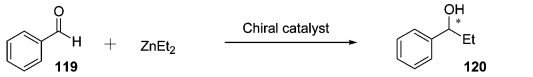


Figure 63. Synthesis of bifunctional BINOL−BINAP copolymers (idem for BINOL−BINAPO).

These soluble bifunctional polymeric chiral ligands were tested in the enantioselective addition of diethylzinc to benzaldehyde (**119**). 1-Phenyl-2-propanol (**120**) was synthesized in 99% conversion and 84% ee (Figure 64).



Entry	Catalyst	ee (%)	Conv. (%)
1	(*R*)-BINOL + $Ti(OPr^i)_4$	85	98
2	(R,R)-BINOL-BINAP + $Ti(OPr^i)_4$	84	95
3	Recycling of entry 2	84	99
4	(R,R)-BINOL-BINAPO + $Ti(OPr^i)_4$	48	100

Figure 64. Asymmetric addition of diethylzinc to benzaldehyde catalyzed by (*R*)-BINOL and (*R*,*R*)-BINOL−BINAP.

Both polymeric ligands were found to be active, while they showed notably different enantioselectivities. The BINOL−BINAP/Ti(IV) catalyst was found to have an efficiency similar to that of the parent catalyst BINOL/Ti(IV), while BINOL−BINAPO/Ti-(IV) gave the corresponding alcohol in only 48% ee. This was probably due to the different enantioselectivities of the two types of catalytically active centers. An important feature of the design of soluble polymeric catalysts is the easy and reliable separation of the chiral ligand based on its different solubilities in organic solvents. Upon completion of the reaction, polymer BINOL−BINAP was precipitated by the addition of methanol and recovered via filtration. The recovered ligand showed similar enantioselectivity and reactivity of a modest synthetic interest. This example is one of the first to define a macromolecular material with two distinct catalytic sites.

4.3.5. Sulfonic Acid Derivatives

Sulfonated phosphines are already employed in industry for several processes[98] such as the Ruhrchemie−Rhône Poulenc process, which is based on a rhodium−TPPTS catalyst for the hydroformylation of propene in water.[99] It is not surprising that in 1993 Davis et al. sulfonated BINAP. They reported the sulfonation of BINAP to obtain $BINAP(SO_3Na)_4$.[100] BINAP was dissolved in concentrated sulfuric acid, and fuming sulfuric acid (40% sulfur trioxide in concentrated sulfuric acid) was added. Three days later sulfonated BINAP was obtained in 85% yield (Figure 65).

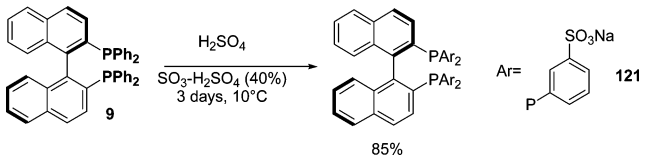


Figure 65. Synthesis of sulfonated 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

Only elemental analysis and ^{31}P NMR spectroscopy were carried out to identify the product. It seems that tetrasulfonated BINAP **121** was obtained, and a single major resonance at −11.1 ppm was observed. The authors proposed this structure because of the difference in π-stabilization energy; the phenyl rings in BINAP seem relatively more reactive toward electrophilic aromatic substitution by sulfur trioxide as compared to the naphthyl rings. Thus, they speculated that, in the major species obtained, only the four phenyl rings in BINAP are sulfonated under

their reaction conditions. Regarding the difference in reactivity of naphthyl rings compared to phenyl in electrophilic attack, this assumption appears, nevertheless, to be dubious.

The rhodium−BINAP(SO_3Na)$_4$ catalyst was prepared with [Rh(cod)Cl]$_2$ and sodium perchlorate. This catalyst was tested in the asymmetric hydrogenation of 2-acetamidoacrylic acid and its methyl ester **98** (Figure 66).

Substrate	Ligand	Solvent	Substrate/catalyst	E.e (%)
Acid	(*R*)-BINAP(SO_3Na)$_4$	H_2O	25	70.4, 68.0
Acid	(*R*)-BINAP	Ethanol	25	67.0
Ester	(*R*)-BINAP(SO_3Na)$_4$	H_2O	75	68.5

Figure 66. Hydrogenation of 2-acetamidoacrylic acid and its methyl ester at room temperature under 1 bar of H_2 using a rhodium complex with (*R*)-BINAP(SO_3Na)$_4$.

Results illustrate that the ee in water is approximately the same as that observed with the unsulfonated rhodium−BINAP complex in ethanol.[101]

To combine all the advantages of both homogeneous (high activity and high selectivity) and heterogeneous (ease in separating the catalyst from the product) catalysis, much work has been done with the aim of binding active metal centers to organic polymers or inorganic oxides. In this system it is convenient to include work done using silica with a thin film of water on its surface, called supported aqueous-phase catalysis (SAPC). Davis et al. reported the supported aqueous-phase asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid by the ruthenium complex of (*R*)-BINAP(SO_3Na)$_4$. The supported Ru−SAP−BINAP complex was prepared by mixing an aqueous solution of Ru−BINAP(SO_3Na)$_4$ complex with degassed CPG-240 (controlled-pore glass which bears an average pore size of 242 Å and is 120/200 mesh in size) followed by vacuum-drying at 40−50 °C. The dry supported Ru−SAP−BINAP could be rehydrated via water-saturated organic-phase treatment. Asymmetric hydrogenation with the SAP catalyst showed higher activity than that of the two-phase system. The larger interfacial surface area between the supported catalyst and the substrate was thought to be the cause of the high activity. Recovery of this supported catalyst seemed to be successful. Filtration of the reaction mixture yielded a colorless solution of product in ethyl acetate, and ruthenium leaching to the filtrate was below the instrumental detection limit. The SAP catalyst was further improved by using ethylene glycol in place of the water film on the glass beads.[102] Enantioselectivity as high as 96% was reported for the asymmetric catalytic hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid carried out in a mixture of chloroform/hexane (1:1) with a substrate-to-catalyst ratio of 300:1 and hydrogen pressure of 940−1010 bar.[103] The advantage of this heterogeneous catalyst was easier separation of the catalyst from the reaction system with no loss of catalyst in the organic phase.

Before Davis, Kumobayashi et al. reported in a patent the synthesis of 5,5′-disulfonato-BINAP (**122**) directly from BINAP[104] (Figure 67).

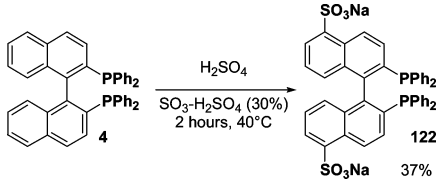


Figure 67. Synthesis of 5,5′-disulfonato-BINAP.

122 was obtained in 37% yield. This has been analyzed by ^{1}H NMR, ^{31}P NMR (−15.8 ppm), and elemental analysis. The authors proposed the 5,5′-disulfonato-BINAP even if (as in Davis' research) no study of the real structure has been made. This hypothesis is in contradiction with Davis' study, which claimed the presence of sulfonate on the phenyl rings and not on the naphthyl skeleton. Kumobayashi et al. reported a few years ago (see section 4.3.1) the nitration of BINAP and synthesized 5,5′-dinitro-BINAP. The position of the nitro group was determined by a ^{1}H−^{1}H COSY study. If nitration occurs in the 5,5′-positions, the sulfonation probably occurs in the 5,5′-positions too. Even if the protocol is not exactly the same between the two methods, the resulting product should bear at least two sulfonates in the 5,5′-positions.

This ligand was tested in the two-phase hydrogenation of ethyl acetoacetate in water with the [RuI_2-(*p*-cymene)$_2$]$_n$ complex. Good results were obtained, and ethyl 3-hydroxybutyrate was synthesized in 63% yield and 99% ee. Compared to that of BINAP in homogeneous conditions (conversion 99%, ee 99%), the conversion was lower, but very good selectivity was obtained. Moreover, the catalyst could be recycled with the same activity and enantioselectivity.

4.3.6. Aminomethyl Derivatives

Recently another approach to obtain 5,5′-disubstituted BINAP was found which allows a large family of 5,5′-BINAP derivatives to be prepared. Bromination of BINAP dioxide (**3**) with bromine and iron as the catalyst in 1,2-dichloroethane gave 5,5′-dibromo-BINAPO (**123**) (Figure 68).[77] The media used in this

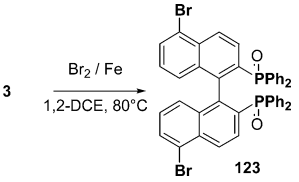


Figure 68. Synthesis of 5,5′-dibromo-BINAPO.

reaction were not as acidic in terms of Brönsted acidity as those in nitration or sulfonation, but this new approach uses a strong Lewis acid ($FeBr_3$). Phosphine oxides are strong Lewis bases[105] and may be complexed during electrophilic substitution in the presence of Lewis acid. Although the 4,4′-positions were the most reactive in basic conditions (see section 4.2.1), the presence of a Lewis acid seems to deactivate these positions by complexing the phosphine oxide. Br_2, activated by the presence of Fe, would brominate the less deactivated 5,5′-positions.

This intermediate was used to synthesize 5,5′-diam-BINAP (**124**) as described for 4,4′-diam-BINAP (Figure 69).

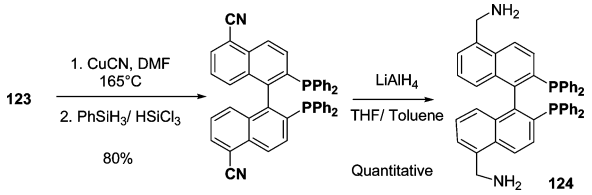


Figure 69. Synthesis of 5,5′-diam-BINAP.

To evaluate this new ligand, the corresponding ruthenium complex was prepared by reaction of [(COD)Ru(2-methallyl)$_2$].[79] Catalytic activities of this ruthenium complex in the hydrogenation of methyl or ethyl acetoacetate were tested, respectively, in methanol and ethanol, with a S:C ratio of 1000, at 50 °C and under 40 bar of hydrogen. The same ruthenium complexes were prepared with (*R*)-BINAP to compare the activity and selectivity of the ligands. **124** proved to be as efficient as the BINAP complex, which gave total conversion and 98% ee in the reduction of ethyl acetoacetate. The aminomethyl groups have little or no influence on either activity or selectivity. Moreover, **124** exhibited the same efficiency as **93**, which means that substitution at these two positions has little influence on the general properties of BINAP. Excellent conversions and ee's were also observed for the reduction of methyl acetoacetate.

4,4′-Diam-BINAP could be transformed into bromohydrate by adding hydrobromic acid, and this new ligand proved to be soluble in water. The hydrosoluble catalyst was tested using the benchmark reaction, i.e., reduction of **94** (Figure 70). The bromohydrate form of this ligand 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.[79,80] The hydrosoluble catalyst was obtained in quantitative yield.

Entry	Reuse	Cat.	Subst/cat.	Conv. (%)	ee (%)
1	1st	**(*R*)-5,5'**	1000	100	99
2	6 th	**(*R*)-5,5'**	1000	100	98
3		**(*R*)-BINAP**	1000	100	98[a]

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

Figure 70. Recycling of hydrosoluble catalyst in the hydrogenation of ethyl acetoacetate.

Water and ethyl acetoacetate were added to obtain a biphasic mixture where the catalyst was 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, and the homogeneous solution obtained was extracted three times with pentane. Fresh substrate was added to the resulting aqueous phase, and the new hydrogenation could be carried out.

The reduction of ethyl acetoacetate using the aqueous biphasic system was as good as that of BINAP itself in ethanol with the advantage of recycling. As observed in homogeneous conditions the presence of the two ammonium bromohydrate groups of hydrosoluble 5,5′-diam-BINAP had no influence on the catalytic activity and selectivity, which were similar to those of BINAP itself. The decrease of activity and selectivity observed after six runs could probably be avoided by more careful protection from air.

4.3.7. Perfluoroalkylated Derivatives

Similar to the **77**, **123** was used to form 5,5′-perfluorooctyl-BINAP and -perfluorohexyl-BINAP[83] (**125**) (Figure 71).

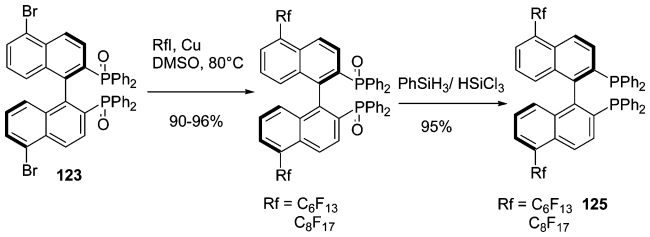
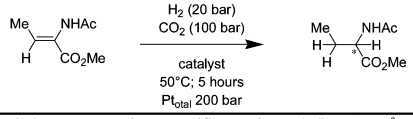


Figure 71. 5,5′-Perfluorohexyl-BINAP synthesis.

The 5,5′-perfluoroalkyl-BINAP showed the same activities and enantioselectivities as 4,4′- and 5,5′-diam-BINAP and BINAP itself. Perfluoroalkyl groups seem to have no influence compared to BINAP, and the length of the perfluoroalkyl chains does not change either activity or selectivity.

125 was tested in the hydrogenation of methyl 2-acetamidoacrylate in scCO_2. [(COD)Ru(2-methallyl)$_2$] was used as the metal complex (Figure 72).



Entry	Subs/ cata	Catalyst	trifluorotoluene (ml)	Conv [a] %	Ee[a] %
1	500	(*R*)-BINAP	0.5	100	60
2	500	(*R*)-**125**	0.5	100	74

[a] Conversion and enantioselectivity were determined by GC on a Supelco beta-DEX (60m, 0.25mm) capillary column.

Figure 72. Hydrogenation of methyl-2-acetamidoacrylate with **125** in scCO_2 with trifluorotoluene as cosolvent.

Good enantioselectivity and perfect conversion were obtained. The perfluorohexyl-BINAP gave 14% better selectivity than BINAP. The perfluorohexyl groups increased solubility and gave a more effective catalyst as was previously observed with the 4,4′-derivatives. Moreover, an acidity effect of the solvent has been observed. A decrease of acidity has the result of increasing selectivity.

4.4. Functionalization in the 6,6′-Positions

The 6,6′-positions of BINAP or BINAP oxide are not accessible via electrophilic substitution. These positions cannot be substituted directly as was shown for the 3,3′-, 4,4′-, and 5,5′-positions. Nevertheless, these are the positions which have been most frequently studied, because of the reactivity of the BINOL precursor. Contrary to those of BINAP, the 6,6′-positions are more reactive in BINOL and protected BINOL, and many electrophilic substitutions

can be conducted such as Friedel−Crafts acylation or bromination. A phosphination step is then necessary to prepare the BINAP derivatives. Jedlinski et al.[106] first reported the preparation of high-purity bis(6-bromo-2-hydroxy-1-naphthyl) in a single-stage process by bromination of BINOL in 1976 (Figure 73).

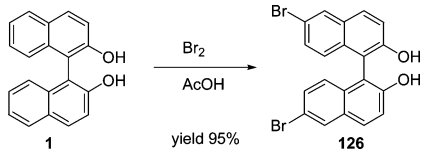


Figure 73. Bis(6-bromo-2-hydroxy-1-naphthyl) synthesis.

They conducted the synthesis in acetic acid and obtained a very good yield of 95%. In this synthesis the bromo product obtained was racemic, and a resolution was necessary to reach the enantiopure form. Performing the reaction at −20 °C, Cram[107] improved this method to reach enantiopure bis(6-bromo-2-hydroxy-1-naphthyl) directly from enantiopure BINOL. In 1994 Cai et al.[10] synthesized BINAP via a novel nickel-catalyzed phosphine insertion from the ditriflate of binaphthol (see section 3.2). Therefore, this new method permitted the transformation of BINOL derivatives into BINAP derivatives.

4.4.1. Monofunctionalization

To immobilize BINAP, two strategies are proposed. The first is to introduce a linker onto the naphthyl structure and then graft the BINAP derivative onto a support. The second implies bisfunctionalization to transform BINAP into a monomer which can be copolymerized. A strategy using electrophilic substitution was applied in 1996 by Bayston et al.[108] and the Oxford Asymmetry Ltd. company. They developed a selective Friedel−Crafts acylation to BINOL protected as ethers. The protecting group was removed using BBr_3 (Figure 74), and the ditriflate of the BINOL derivative was then phosphinated.

This BINAP derivative was used to reach aminomethylpolystyrene-supported BINAP.[109] Saponification of the ethyl ester with lithium hydroxide produced acid-functionalized BINAP **129**, which was ready to attach to a polymeric support such as aminomethylated polystyrene. Coupling of BINAP monomer to 0.21 mmol/g aminomethylated polystyrene was achieved using the standard peptide coupling reagents DIC (diisopropylcarbodiimide) and HOBt (hydroxybenzotriazole). A quantitative acylation giving a loading of 0.18 mmol/g was observed by mass balance (Figure 75). Today this ligand **130** is available commercially.

The supported BINAP **130** was tested in the hydrogenation of both olefins and β-keto esters (Figure 76).

The hydrogenation catalyst was prepared by mixing diphosphine, [Ru(COD)(2-methylallyl)$_2$], and HBr in acetone for 1 h. The polymer-supported catalyst showed high activity, giving the β-hydroxy ester in 97% ee. This indicates that loss of C_2 symmetry is not detrimental to enantioselectivity. Moreover, the catalyst can be reused. Following the successful application of the Ru−BINAP−diamine system in the asymmetric catalytic hydrogenation of simple ketones, Noyori et al. further prepared an immobilized catalyst (**175**) for the same reaction[110] (Figure 77). While the conversion decreased slightly after more than 10 cycles of reuse, the enantioselectivity of the reaction remained almost unchanged, and the result compared favorably with that of the free BINAP catalyst system.

Recently another BINAP was supported on a polystyrene−poly(ethylene glycol) copolymer (PS−PEG) resin and was used successfully for the rhodium-catalyzed asymmetric 1,4-addition of phenylboronic acid to σ,β-unsaturated ketones in water. For more information about this work from Hayashi see ref 111.

The Bayston group gave many other examples of the powerful strategy of the functionalized and then phosphinated BINOL. They brominated BINOL in the 6,6′-positions with Br_2 and then substituted bromine with different methods such as aromatic nucleophilic substitution with copper cyanide or Suzuki coupling, Stille coupling, or a Friedel−Crafts alkylation on protected BINOL (Figure 78). Few or no results concerning the use of these new BINAP derivatives are available at this time.

In the year 2000 a group from Takasago International Corp. with Kyoko and Noboru developed a new BINAP derivative to polymerize diphosphine.[112] They synthesized a monomer having a vinyl group at the 6-position of BINAP and prepared a copolymer including the BINAP derivative monomer, a styrene derivative, and divinylbenzene (Figure 79).

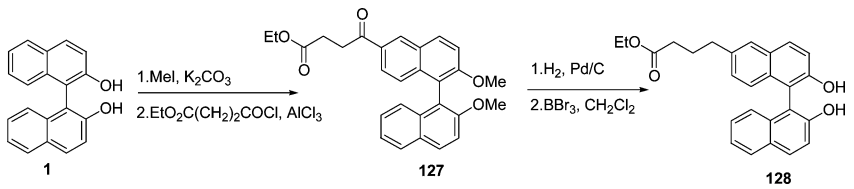


Figure 74. Synthesis of BINAP derivatives by acylation of BINOL.

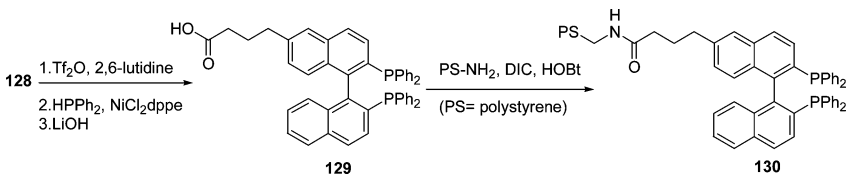
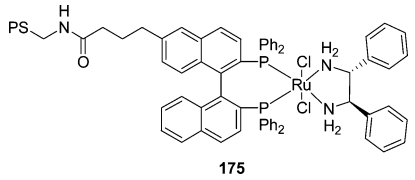


Figure 75. Synthesis of aminomethylpolystyrene-supported BINAP.

131 132

Entry	Phosphine	Substrate	Solvent	T (°C)	Time (h)	Yield (%)	ee (%)
1	(*R*)-BINAP	**131**	CH_2Cl_2	40 (20 bar)	16	100	>99
2	(*R*)-PS-BINAP	**131**	THF/MeOH	70	24	99	97
3	(*R*)-BINAP	**132**	THF/EtOH	50 (3 bar)	48	100	98
4	(*R*)-PS-BINAP	**132**	THF	50	18	95	56

Figure 76. Enantioselective hydrogenation of substrates with supported BINAP (2 mol % catalyst used; all hydrogenations were carried out at 10 bar unless otherwise stated).



175

Figure 77. Immobilized catalyst **175**.

They conducted a monophosphination of the ditriflate of BINOL. They were therefore able to brominate regioselectively in the 6′-position without modifying the 6-position. This experiment highlights the clear difference between the reactivity of the BINOL moiety and BINAP or BINAP oxide. The 6,6′-positions of BINOL are more reactive than the other positions in BINAP oxide. After this step, a Suzuki coupling gave the vinyl in the 6-position, and the second phosphine was introduced. With 6-vinyl-BINAP (**137**) a copolymer was synthesized by stirring the phosphine with styrene and divinylbenzene in the presence of poly(vinyl alcohol) at 80 °C. A rhodium complex was prepared, and the system was tested in the hydrogenation of methyl (*Z*)-α-benzamidocinnamate. The conversion was found to be 92%, and the optical purity was 56% ee, lower than that obtained with BINAP itself. The catalyst could be reused several times without loss of activity or selectivity.

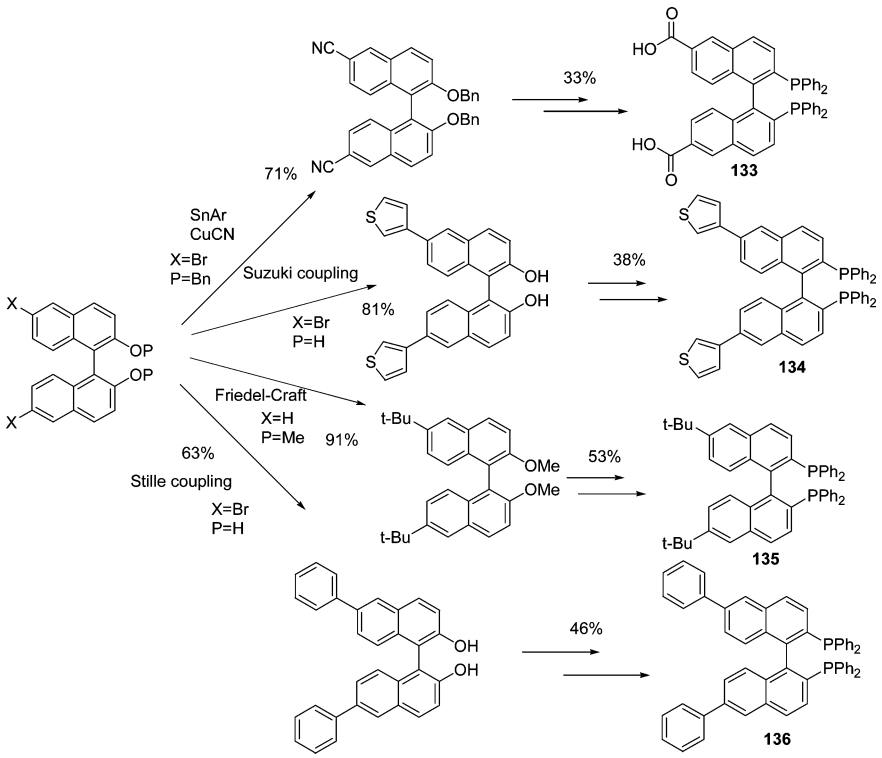


Figure 78. BINAP derivatives from bis(6-bromo-2-hydroxy-1-naphthyl).

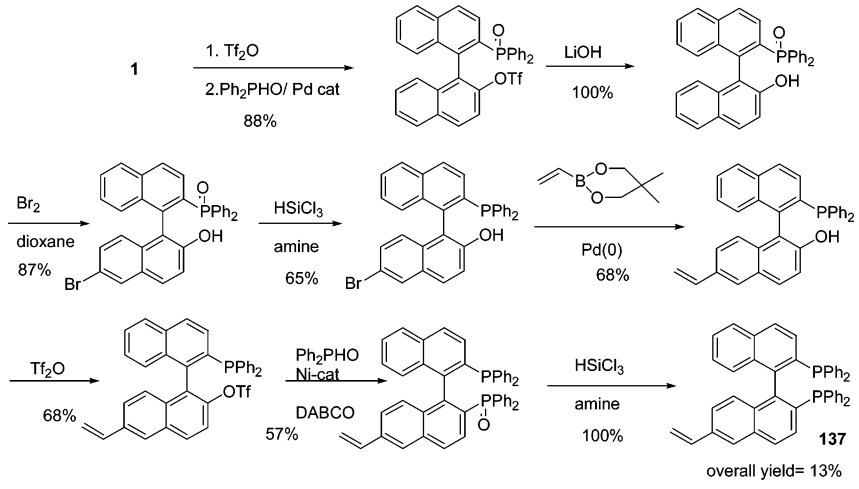


Figure 79. Synthesis of 6-vinyl-BINAP.

4.4.2. Bisfunctionalization

The advantage in using a bisfunctionalized BINAP is to maintain a pseudo-C_2 axis, which was proved to be an important factor in several, but not all, catalytic reactions. Many recyclable catalysts with 6,6′-disubstituted BINAP as a ligand[113] have been described recently. This synthetic method was to reach 6,6′-diaminomethyl-BINAP and use it to heterogenize BINAP itself. 6,6′-Dibromo-BINOL was obtained with Cram bromination,[107] and then the bromine was substituted by a cyano group via an aromatic nucleophilic substitution using copper(I) cyanide. Phosphination with Cai's method and reduction of the nitrile to aminomethyl using lithium aluminum hydride gave the desired product **138** (Figure 80). This synthesis was patented[114] and subsequently published.[115]

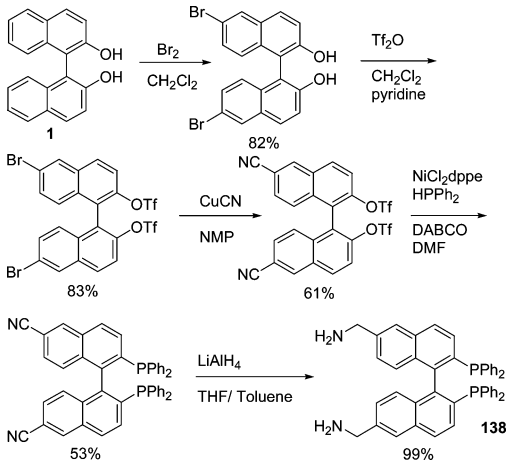
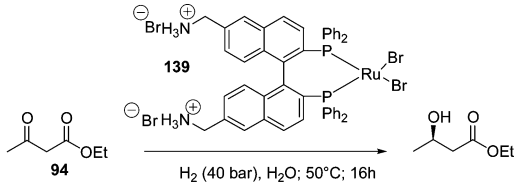


Figure 80. Synthesis of 6,6′-diam-BINAP.

4.4.3. Water-Soluble Derivatives

6,6′-Diam-BINAP (**138**) is a really useful ligand allowing the synthesis of hydrosoluble BINAP and insoluble polyBINAP. In the first approach, a water-soluble PEG derivative of 6,6′-diam-BINAP (number of PEG units 110−113, $M_n = 5000$) was synthesized according to the procedure by Veronese et al.[116] Their corresponding ruthenium complexes were synthesized from the $[RuCl_2(benzene)]_2$ precursor according to Noyori's procedure.[117] The reduction of ethyl acetoacetate by this ruthenium complex mixture affords, after careful extraction of the water-soluble product with pentane, 100% conversion and 75% ee and, after recycling, only 20% conversion and 56% ee. Second, the bromohydrate form **139** of 6,6′-diam-BINAP was synthesized. The formation of the ammonium salt was easily performed with aqueous hydrobromic acid in dichloromethane in 96% yield. The corresponding complex was prepared from the [Ru(η^3-2-methallyl)$_2$(η^2-COD)] precursor according to the Genet et al. procedure.[79] The catalyst was tested in the hydrogenation of ethyl acetoacetate[80] (Figure 81).

The modification of 6,6′-diam-BINAP provides a water-soluble BINAP analogue, such as the ammonium derivative, suitable for asymmetric biphasic catalytic hydrogenation of ethyl acetoacetate. From



Run	Reuse	Substrate/catalyst	Conversion (%)	Ee (%)
1		1000	100	94
2	1st	1000	97	91
3	2nd	1000	100	94
4	3rd	1000	100	83

Figure 81. Ruthenium-catalyzed reduction of ethyl acetoacetate with hydrosoluble BINAP.

the first to the third recycling catalyst **139** shows no loss of activity, but a slight decrease of enantioselectivity from 91% to 83% ee was observed.

Genet et al. described the synthesis of two substituted BINAPs in the 6,6′-positions, a diguanidinium-BINAP (**140**) and a PEG-BINAP (**141**), from **138**.[118] It was synthesized[119] as described above, except for two steps of protection/deprotection of the phosphine with borane before and after nitrile reduction. This protection appears to be unnecessary for the approach detailed above. The guanidinium phosphine was prepared in a two-step sequence by reaction of 6,6′-diam-BINAP with 2.5 equiv of *N*,*N*′-di-boc-*N*″-trifliguanidine and triethylamine in dichloromethane at 50 °C for 24 h followed by the addition of a solution of 3 N HCl in methanol. The poly(ethylene glycol) methyl ether (MeO-PEG, $M_n = 5000$) was acylated using glutaric anhydride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to provide the corresponding carboxylic acid. 6,6′-Diam-BINAP reacted with 0.9 equiv of the acid in dichloromethane at room temperature in the presence of dicyclohexylcarbodiimide and DMAP to afford quantitatively the monosubstituted PEG-Am-BINAP (Figure 82).

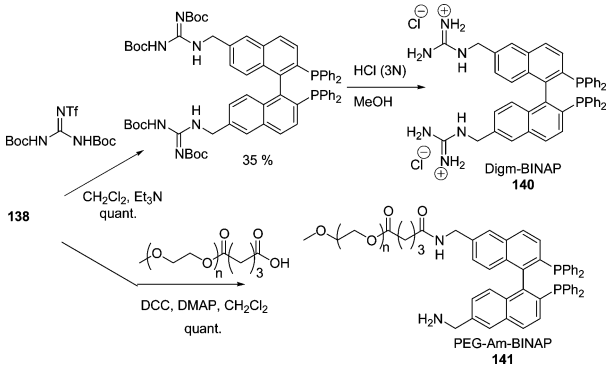


Figure 82. Synthesis of Digm-BINAP (**140**) and PEG-Am-BINAP (**141**).

These ligands were tested using a ruthenium catalyst in the asymmetric hydrogenation of methyl acetoacetate (Figure 83).

Each of these catalysts showed very good activities and selectivities. (*R*)-Digm-BINAP−$RuBr_2$ and PEG-(*R*)-Am-BINAP−$RuBr_2$ were recycled three and four times, respectively, and 3-hydroxybutyrate was easily

Entry	Catalyst	Solvent	T (°C)	ee (%)
1	(*R*)-diamBINAPRuBr$_2$	Ethylene glycol	Rt	96
2	(*R*)-digmBINAPRuBr$_2$	Ethylene glycol	Rt	96
3	PEG-(*R*)-*Am*-BINAPRuBr$_2$	MeOH	50	98

Figure 83. Ruthenium-catalyzed hydrogenation of methyl acetoacetate.

separated from the catalysts. The reactivity of some cationic rhodium complexes containing the (*R*)-digm-BINAP−RhBr$_2$ and PEG-(*R*)-Am-BINAP−RhBr$_2$ were also examined. Acetamidoacrylic acid was reduced under 2 bar of hydrogen at 50 °C quantitatively with excellent enantiofacial discrimination, leading to (*S*)-*N*-acetylalanine with 94% and 95% ee, respectively.

4.4.4. Phosphonic Acid Derivatives

Lin et al. synthesized 6,6′-bis(phosphonic acid)-BINAP (**143**) starting from 6,6′-dibromo-BINOL (**126**) in six steps and 42% overall yield. The key step involves nickel-catalyzed phosphonation of 2,2′-bis-(triflato)-1,1′-binaphthyl bis(diethylphosphonate) (**142**) (Figure 84).

Repeating the procedure they had already used for 4,4′-bis(phosphonic acid)BINAP, Lin et al. explored the synthesis of chiral porous zirconium phosphonates based on **143** for enantioselective hydrogenation of unfunctionalized aromatic ketones.[69]

Treatment of (*R*)-6,6′-bis(phosphonic acid)BINAP with [Ru(benzene)Cl$_2$]$_2$ followed by (*R*,*R*)-DPEN afforded the phosphonic acid-substituted Ru−BINAP−DPEN intermediate **144**, which was directly reacted with Zr(O-*t*-Bu)$_4$ under reflux conditions to give chiral porous zirconium phosphonates **145** of the approximate formula Zr[Ru(L)(DPEN)Cl$_2$]·4H$_2$O (Figure 85).

Acetophenone was hydrogenated to 1-phenylethanol with complete conversion and 79% ee in 2-propanol with 0.1 mol % loading of Zr−Ru−L solid. This level of enantioselectivity is significantly the same as that observed for the parent Ru−BINAP−DPEN homogeneous catalyst, which typically gives ∼80% ee for the hydrogenation of acetophenone under similar conditions. Although the Zr−Ru−6,6′-bis-(phosphonic acid)BINAP material **145** is as active as the equivalent 4,4′-bis(phosphonic acid)BINAP **91** for the hydrogenation of aromatic ketones, the enantioselectivity is lower than but similar to that of the parent Ru−BINAP−DPEN homogeneous catalyst.[73] The authors believe that very different ee values observed between the 4,4′ and the 6,6′ systems are the results of the substituent effects on BINAP.

With a similar system they carried out the heterogeneous asymmetric hydrogenation of β-keto esters. The [Ru(6,6′-bis(phosphonic acid)BINAP)(dmf)$_2$Cl$_2$] = [Ru(L)(dmf)$_2$Cl$_2$] intermediate was synthesized by treating **143** with [(Ru(benzene)Cl$_2$)$_2$] in DMF at 100 °C. Chiral porous zirconium phosphonate with approximate formula [Zr{Ru(L)(dmf)$_2$Cl$_2$}]·2MeOH (Zr−Ru−L) was synthesized by refluxing Zr(OtBu)$_4$ and 1 equiv of [Ru(L)(dmf)$_2$Cl$_2$] in methanol. These heterogeneous catalysts are highly active for the asymmetric hydrogenation of β-keto esters. Several β-keto esters were hydrogenated with complete conversion and ee values ranging from 91.7% to 95.0% with the same enantioenrichment as the parent homogeneous BINAP−Ru catalyst (Figure 86).

Zr−Ru−L gave a turnover frequency (TOF) of 364 h^{-1} with a 0.1% solid loading, in comparison with a TOF of 810 h^{-1} for the homogeneous BINAP−Ru catalyst under identical conditions. This is a remarkably small difference between homogeneous and supported homogeneous reactions.

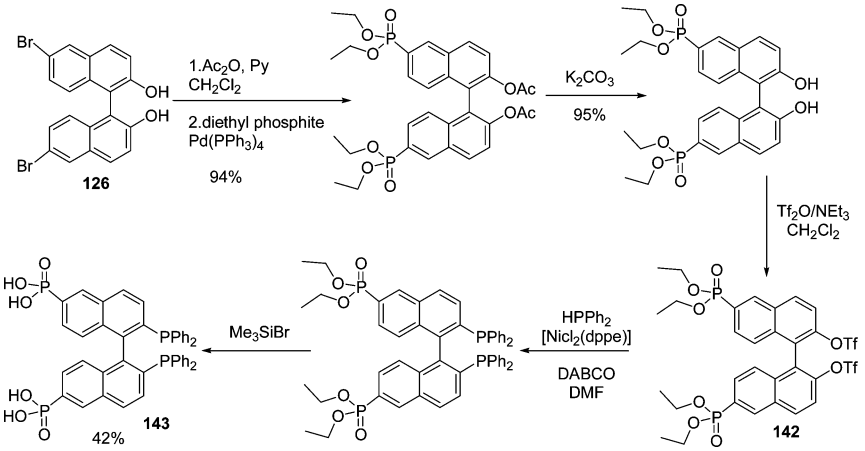


Figure 84. Synthesis of 6,6′-bis(phosphonic acid)BINAP.

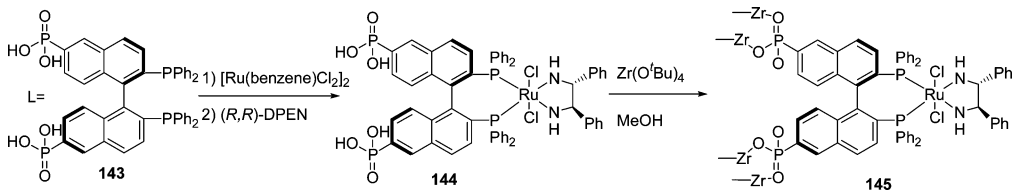


Figure 85. Synthesis of chiral porous zirconium phosphonate.

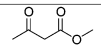
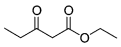
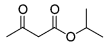
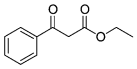
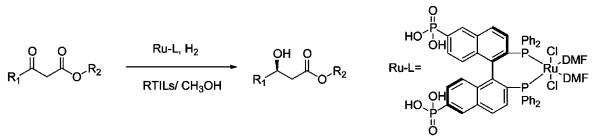
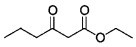
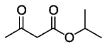
Substrate	Catalyst loading (%)	H_2 pressure (bar)	Temperature (°C)	ee (%)
	1	96	RT	95.0
	0.1	48	60	93.3
	1	96	RT	92.0
	1	96	RT	91.7
	1	96	RT	69.6
	1	96	RT	93.3

Figure 86. Heterogeneous asymmetric hydrogenation of β-keto esters.

Repeating the procedure they had already used for **79**, Lin et al. tested the hydrogenation of β-keto esters in RTILs with 6,6′-bis(phosphonic acid)BINAP−Ru(II) catalysts.[120] The $[Ru(ligand)(DMF)_2Cl_2]$ precatalysts were synthesized by treating **143** with $[Ru(benzene)Cl_2]_2$ in DMF at 100 °C. The efficiency in selectivity of such a catalyst has been examined for the asymmetric hydrogenation of β-keto esters with various RTILs such as $BMImBF_4$, $BMImPF_6$, and DMPIIm (Figure 87).



Substrate	Ru-**143** MeOH	DMPIIm	$BMIBF_4$	$BMIPF_6$	Ru-BINAP DMPIIm
	98.9	93	98.3	93.9	98.9
	98.7	98.5	98.9	98.7	99.1
	98.3	93	97.5	93.5	98.1

All reactions were carried out with 1 mol% precatalyst in a H_2 pressure of 100 bars at a 50:50 mixture of RTIL and MeOH at rt for 22 h and had complete conversions.

Figure 87. Ee values for asymmetric hydrogenation of β-keto esters in RTILs.

This new catalyst is highly active for asymmetric hydrogenation in the homogeneous RTIL−MeOH systems. Although complete conversions have been achieved with three different RTILs for all the β-keto esters, the enantioselectivity is quite sensitive to the nature of the RTILs. Clearly, with the catalyst used, $BMImBF_4$ is the best choice of RTILs and affords ee values comparable to those obtained from homogeneous reactions in MeOH (except that of 2,2-dimethylacetoacetate). Nevertheless, **143** gave lower enantioselectivities than those obtained in the same conditions with the 4,4′ equivalent.

Lin et al. also demonstrated that both the RTILs and catalyst can be recycled and reused several times for asymmetric hydrogenation of methyl acetoacetates. They performed the recycling by extracting the mixture with degassed hexane. The IL phase was washed two more times with degassed hexane. After being dried under vacuum, the RTIL phase was recharged with methyl acetoacetate and MeOH and then subjected to hydrogenation conditions (Figure 88).

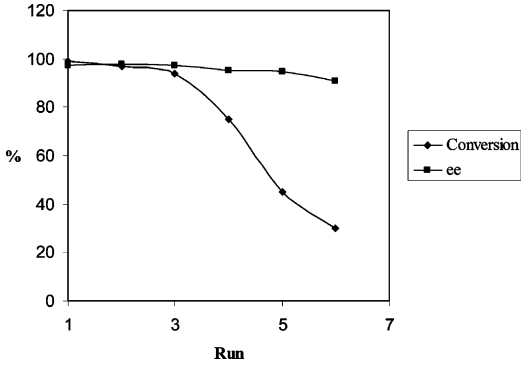


Figure 88. Recycling and reuse of Ru−L catalysts for hydrogenation of methyl acetoacetate in $BMImBF_4$−MeOH.

The first three runs of hydrogenation reactions gave the same level of activity and enantioselectivity. Subsequent runs led to a slight deterioration of enantioselectivity but a significant drop in activity. The authors give no explanation for this loss of activity.

4.4.5. Perfluoroalkylated Derivatives

Stuart et al. developed two simple efficient routes to perfluoroalkylated arylphosphines.[121,122] The direct attachment of a C_6F_{13} group to the aryl ring is feasible via a copper-mediated cross-coupling reaction between a perfluoroalkyl iodide and an aryl iodide or bromide, while the incorporation of an additional C_2H_4 spacer group is possible via a Heck coupling of aryl halides with $CH_2{=}CHC_6F_{13}$, followed by reduction of the resultant double bond. Both of these methodologies have been applied to the derivation of the protected (*R*)-6,6′-dibromo-BINOL for the preparation of the 6,6′-fluoroalkylated BINAP **148** and **149** ligands[123] (Figure 89).

According to Noyori, catalysts were prepared from the reaction of $[RuCl_2(benzene)]_2$ with the ligands in DMF. Then the hydrogenation of dimethyl itaconate was carried out in MeOH, at room temperature under 20 bar of H_2 for 15 min (substrate:catalyst = 2000, 1.0 μmol of catalyst, 2 mL of solvent) (Figure 90).

Fluorous ponytails impose no detectable effets on the enantioselectivity during reduction of prochiral olefins such as dimethyl itaconate, but affect the rates of hydrogenation, as can be judged by the excellent ee obtained with the three ligands and the lower conversion observed with Ru−(*R*)-C_6F_{13}-BINAP. These results indicate that the electronic effects arising from 6,6′-fluoroalkylation of BINAP only impact the hydrogenation activity of the Ru−BINAP catalysts.

4.4.6. Polymer with BINAP in the Main Chain

If homogeneous asymmetric catalysis is seldom used, it is probably and essentially due to problems of separation and recycling of the expensive chiral catalyst. To overcome these drawbacks, very soon after the discovery of homogeneous asymmetric catalysis, heterogeneous catalysis methods were used, particularly polymer-supported homogeneous cataly-

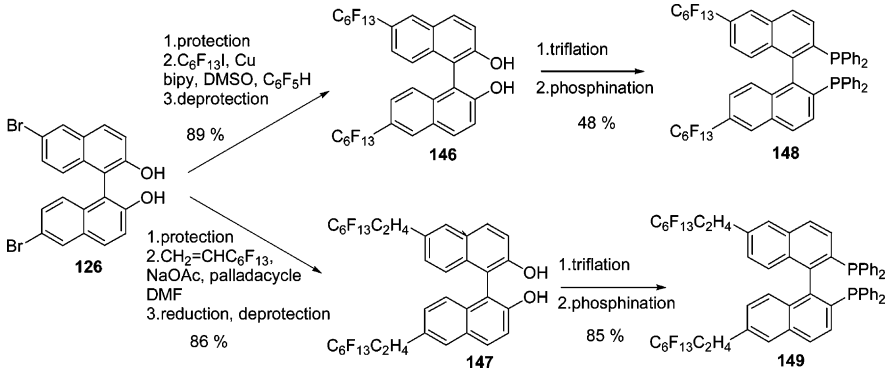


Figure 89. Synthesis of fluoroalkyl-derivatized BINAP ligands.

Entry	Catalyst	Conversion (%)	ee (%)
1	Ru-(*R*)-BINAP	86	95.4
2	Ru-(*R*)-C_6F_{13}-BINAP	42	95.3
3	Ru-(*R*)-$C_6F_{13}CH_2CH_2$-BINAP	83	95.7

Figure 90. Hydrogenation of dimethyl itaconate by ruthenium catalysts.

sis. This methodology was developed by Kagan et al.[124] and Stille et al.[125] in the 1970s and used for reactions such as hydroformylations,[126] dihydroxylations,[127] epoxidation,[128] and hydrogenation.[129] To obtain an insoluble, easily separable, and recyclable catalyst, Lemaire et al. studied several structural parameters.[130] The use of cross-linked polymers was shown to give rise to an inefficient and nonselective catalytic system. Therefore, the concept developed with polyNAP is the use of polymer chains of a molecular weight sufficiently high to avoid solubilization but without cross-linking to allow swelling and chain mobility. Low accessibility of the catalytic sites is obviously the main limitation of heterogeneous supported catalysis; therefore, low molecular weight non-cross-linked material was used. On the other hand and contrary to the approach of Bayston, heterogenization of BINAP was conducted with the conservation of a pseudo-C_2 or C_2 symmetry. Various types of linkers and spacers were used. In addition, well-defined BINAP derivatives with high molecular weight and low solubility in methanol were also synthesized.

The polyamide **151** was obtained with 60% yield by polycondensation of (*S*)-6,6′-diam-BINAP with terephthaloyl chloride in dimethylacetamide (DMA) (Figure 91).

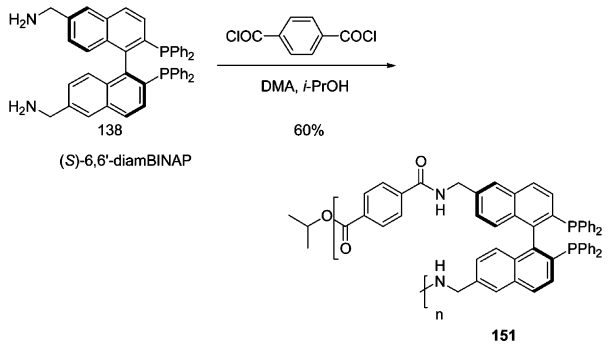


Figure 91. Synthesis of polyamide derivatives of 6,6′-diam-BINAP.

Ureas and polyureas were prepared by the addition of 6,6′-diam-BINAP with mono- or diisocyanate in dichloromethane. Diureas **152** and **153** were obtained in 80% and 61% yields, respectively, by the addition of 2 equiv of octadecylisocyanate or 2-naphthylisocyanate (Figures 91 and 92).

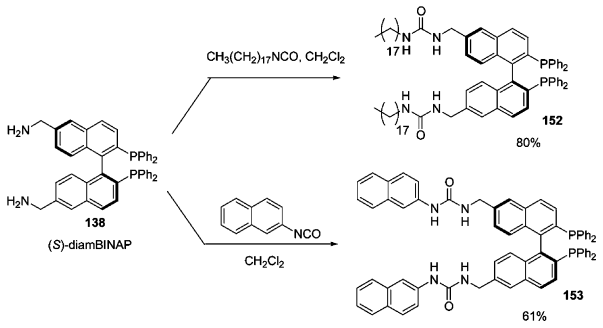


Figure 92. Synthesis of urea derivatives of 6,6′-diam-BINAP.

For polyurea, the addition of diisocyanatohexane led to the expected polyurea **154** with 96% yield. Other less flexible diisocyanates such as di(4-isocyanatophenyl)methane were involved. This solution produces polymers **155** with 76% yield[131] (Figure 93).

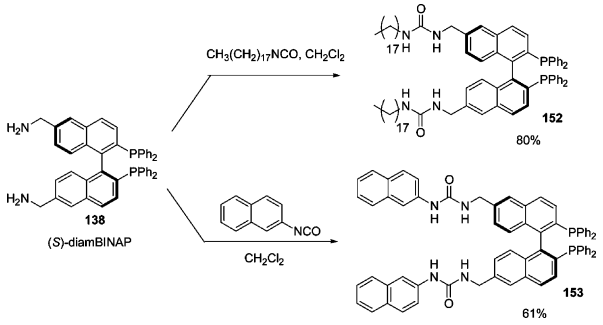


Figure 93. Synthesis of polyurea derivatives of 6,6′-diam-BINAP.

Unlike diurea **152**, which is soluble in all organic solvents, polyamide **151**, diurea **153** and polymers **154** and **155** are insoluble in dichloromethane, toluene, and methanol but soluble in dipolar nonprotic solvents such as dimethylformamide or dimethyl sulfoxide.

All these new ligands were tested in the hydrogenation of methyl acetoacetate. The neutral ruthenium complexes of polyamide **151** and ureas **152**, **154**, and **155** and the cationic ruthenium complexes of com-

pounds **151**, **152**, **153**, **154**, and **155** were synthesized from the $[RuCl_2(benzene)]_2$ precursor. The catalytic activities of these ruthenium complexes were tested in methanol with a substrate:catalyst ratio of 1000 (Figure 94).

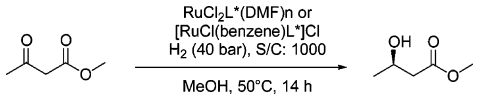


Figure 94. Reduction of methyl acetoacetate with neutral or cationic complexes of **151**, **152**, **153**, **154**, and **155**.

The results are summarized in Figures 95 and 96. Ruthenium complexes **151**, **153**, **154**, and **155** insoluble in methanol were used for heterogeneous reduction. In contrast, the Ru−**152** complex is soluble in methanol and was used as a homogeneous catalyst.

Run	Ligand	Use	Conv. (%)[a]	ee (%)[a]
1	**151**	1st	100	78
2	**151**	2nd	4	99
3[b]	**152**		36	48
4	**154**		46	88
5	**155**		100	97
6[b]	**BINAP**		100	99

[a]Conversion and ee were determined by chiral GC analysis on a Lipodex A column

[b]Homogeneous catalysis

Figure 95. Ruthenium neutral complex ($RuCl_2L^*(DMF)_n$) catalyzed asymmetric hydrogenation of methyl acetoacetate.

Run	Ligand	Use	Conv. (%)[a]	ee (%)[a]
1[b]	**BINAP**		100	>99
2[b]	**6,6'-*diam*BINAP**		100	>99
3[b]	**152**		100	>99
4	**153**	1st	100	>99
5	**153**	2nd	99	97
6	**153**	3rd	54	33
7	**154**	1st	52	88
8	**154**	2nd	3	30
9	**155**	1st	97	99
10	**155**	2nd	53	99

[a]Conversion and ee were determined by chiral GC analysis on a Lipodex A column

[b]Homogeneous catalysis

Figure 96. Diurea and polyurea ruthenium cationic complex ([RuCl(benzene)L*]Cl) catalyzed asymmetric hydrogenation of methyl acetoacetate.

For neutral ruthenium complexes, rigid polymeric systems are more efficient, leading to 100% conversion with 97% ee (run 5). Diurea **152** or polymer **154** with a flexible spacer chain gives rise to conversions of 50% and ee's of 48% and 88%, respectively (runs 3 and 4). For the ligand **155** having diphenylmethyl as a spacer, although the first run was really encouraging (complete conversion and 97% ee), a poor conversion with low ee was observed after reuse. Polyamide **151** led to 100% conversion and 78% ee (run 1). Unfortunately the conversion in this case also failed after recycling, probably due to leaching (run 2). Reduction was also performed using cationic (more active) complexes prepared using $[RuCl_2(benzene)]_2$ in ethanol/benzene (8:1) as precursor, and results obtained in this case are generally higher in terms of ee (Figure 96).

Diurea−ruthenium cationic complexes Ru−**153** are the most active in heterogeneous conditions, leading to complete conversion and product with >99% ee. It has been shown to be as efficient as BINAP, 6,6′-diam-BINAP, or diurea **152** (runs 1−3) in homogeneous conditions. But after two reuses of the catalyst both the activity and enantioselectivity decrease. This is probably due to partial solubilization of the ruthenium complex in methanol.

The most effective of the polymeric ligands is that formed with polymer **155**, which presents 97% conversion and 99% ee (run 9). In contrast, polymer **154** having a flexible spacer (run 7) is less selective (88% ee) than ligand **155**. It is worth noting that, for polyureas **154** and **155**, the more rigid the polymer, the better the conversion and ee (runs 7 and 9). The reuse of these catalysts was not a success.

Compared to neutral complexes, the corresponding cationic complexes have been shown to give higher conversion and ee.

In conclusion, this study showed that the more rigid the spacer, the more efficient the catalyst. In other words, the conformation of those catalysts must be as stable as possible.[132] This theory was verified, and the best results were achieved with another polymer, 6,6′-polyNAP. The monomer **138** was polymerized by polyaddition with a diisocyanate to yield quantitatively 6,6′-polyNAP **150**[133] (Figure 97). This

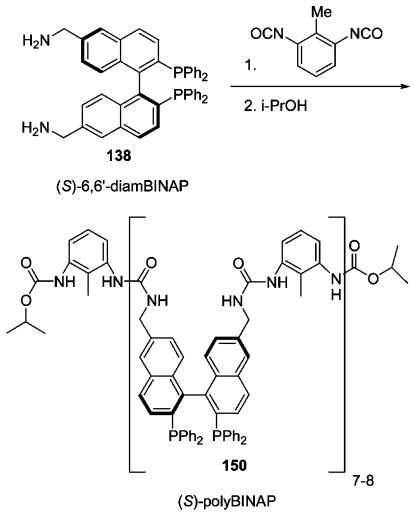
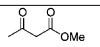


Figure 97. Synthesis of polyNAP from diam-BINAP.

new polymer was more rigid than the others described above. In addition the methyl group on the diisocyanate moiety affords a competitive coordination with the urea functional group.

Gel permeation chromatography analysis for polymer **150** gave an average molecular weight of 8400, and a degree of polymerization of 10 was found, although the index of polydispersity was rather large. It was used as a ruthenium ligand in asymmetric hydrogenation of C=O and C=C bonds.[134] Comparative results with BINAP are presented in Figures 98 and 99. In the case of the β-keto esters (runs 1 and 2, Figure 98), similar activity and selectivity (99%) were observed. An attempt to reuse 6,6′-polyNAP−$RuBr_2$ was performed with this substrate, and after four times, no loss of either selectivity or activity was

Run	Substrate	Catalyst	Solvent	Time (h)	S/C	Conv. (%)	ee (%)
1		BINAP-$RuBr_2$	MeOH	14	1000	100	99
2		6,6'-PolyNAP-$RuBr_2$	MeOH	14	1000	100	99
3		(*S*)-BINAP-$RuCl_2$ dmf[a] + (*S,S*)-DPEDA	*i*-PrOH-KOH	18	500	99	87
4		(*S*)-6,6'-polyNAP-$RuBr_2$ + (*S,S*)-DPEDA	*i*-PrOH-*t*-BuOK	18	1000	100	68

[a]Hydrogen pressure: 4 bar.

Figure 98. Reduction of carbonyl compounds with H_2, at 50 °C under 40 bar, with BINAP and 6,6′-polyNAP **150**.

Run	Substrate	Catalyst	Solvent	Time (h)	S/C	Conv. (%)	ee (%)
1		BINAP-$RuCl_2$-dmf	MeOH	14	100	95	78
2		(*S*)-6,6'-polyNAP-$RuCl_2$-dmf	MeOH	14	100	95	70

Figure 99. Hydrogenation of olefinic substrates at 50 °C under 10 bar with BINAP and 6,6′-polyNAP **150**.

observed. The reduction of acetophenone in the presence of DPEDA was carried out to use the synergetic effect of the amine described by Noyori et al. in 1995.[135] The reaction conditions employed with 6,6′-polyNAP (run 4), even though different from Noyori's conditions (run 3), yielded total conversion (100%) and an interesting enantioselectivity (68%). For this reaction the catalytic system was filtered and reused four times. Only a slight loss of enantioselectivity was observed (from 68% to 61%).

The hydrogenation reaction in the presence of 6,6′-polyNAP−ruthenium as catalyst was extended to ethylenic substrates (Figure 99). Comparable results, concerning activity and enantioselectivity, were obtained for 6,6′-polyNAP and BINAP for the reduction of α-acetamidoacrylic acid. Conversions are about 95% and ee's up to 70%, which is close to that observed in similar conditions with BINAP itself. 6,6′-polyNAP proved to be an efficient ligand for hydrogenation of β-keto esters, ketones, and ethylenic substrates.

Another polymer containing BINAP in the main chain was described by Pu et al. This polymer is soluble in classical organic solvents such as dichloromethane, toluene, or THF, but the catalyst is insoluble. They have carried out Suzuki coupling of a chiral binaphthyl monomer and a dibromophenyl followed by reduction of the phosphinoxy groups with trichlorosilane to prepare the polyBINAP **156**[136] (Figure 100).

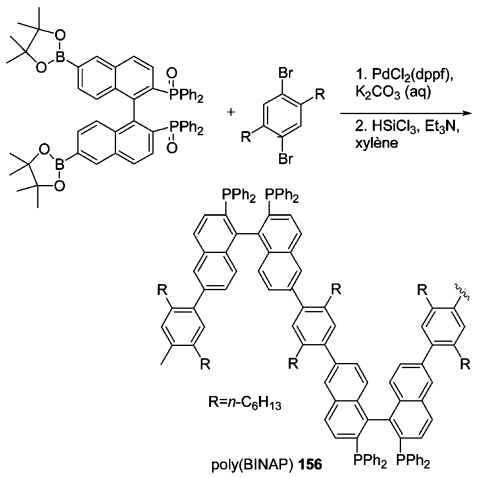


Figure 100. Synthesis of optically active polyBINAP.

Gel permeation chromatography analysis shows that its molecular weight is $M_w = 5800$ and $M_n = 4300$ (PDI = 1.35) relative to polystyrene standards. They used this material to prepare chiral polymeric rhodium and ruthenium complexes for the asymmetric hydrogenation of dehydroamino acid derivatives and methyl aryl ketones (Figure 101).

Substrates	catalysts	H_2 pressure (psi)	Conversion (%)	Ee (%)
(*Z*)-methyl α-(benzamido) cinnamate	$Rh(COD)_2BF_4$	30	>99	75
acetophenone	$[RuCl_2(benzene)]_2$ (*R,R*)-DPEN	60	100	80
1'-acetonaphtone	$[RuCl_2(benzene)]_2$ (*R,R*)-DPEN	200	>99	92

Figure 101. Asymmetric hydrogenation by the polyBINAP−Rh and −Ru complexes.

Enantioselectivity obtained with these catalysts was similar to that obtained with BINAP itself. This polymer catalyst **156** demonstrates once again that the catalytic properties of an enantioselective monomer catalyst can be preserved in a rigid and sterically regular polymer backbone. The use of the polymer-based material allows the easy recovery and reuse of these catalysts.

Pu also described the synthesis of a copolymer, BINOL−BINAP **157**.[137] They have used a triphenylene dibromide linker molecule to copolymerize with the optically active monomers of BINOL and BINAP in a 2:1:1 ratio. After several steps including Suzuki coupling, reduction of the phosphoryl groups, and hydrolysis of the BINOL protecting groups, a copolymer was obtained (Figure 102).

In this polymer, BINOL and BINAP are expected to be distributed randomly along the polymer chain. The polymer can be dissolved in common organic solvents such as dichloromethane, THF, toluene, and DMF. Its molecular weight is $M_w = 11600$ and $M_n = 7500$ (PDI = 1.55) as measured by gel permeation chromatography relative to polystyrene standards. The polymer was then converted to a polymeric ruthenium(II) complex and tested in the asymmetric hydrogenation of acetophenone. Very good conversion (>99%) and ee (84%) were obtained. They have also studied the use of the ruthenium complex in a tandem catalytic asymmetric diethylzinc addition and asymmetric hydrogenation of *p*-acetylbenzaldehyde to generate a chiral diol (Figure 103). Conversion of >99%, 94% ee, and 87% de were obtained.

This demonstrates that the rigid polybinaphthyl structure can preserve the catalytic properties of a monomer catalyst but can also allow distinctively different catalytic sites to function independently in the polymer chain to conduct two asymmetric reactions simultaneously.

4.4.7. Silyl Derivatives as Linker

Nakamura et al. reported the binaphthol substituted by a polyfluorinated chain (**159**) for the enantioselective addition of diethylzinc to aromatic aldehydes in a fluorous biphasic system.[138] The readily available tris(polyfluoroalkyl)silyl group was intro-

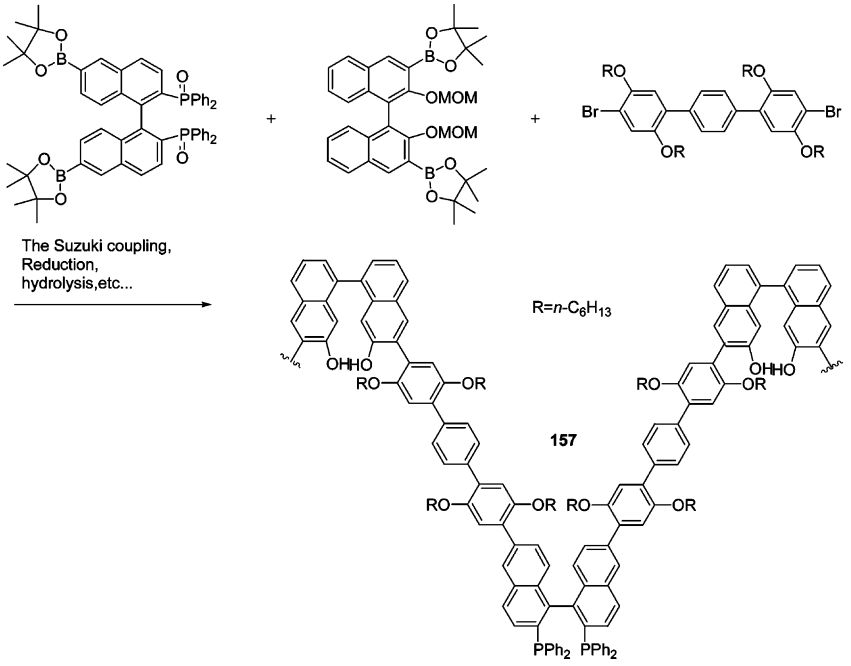


Figure 102. Synthesis of BINOL−BINAP copolymer.

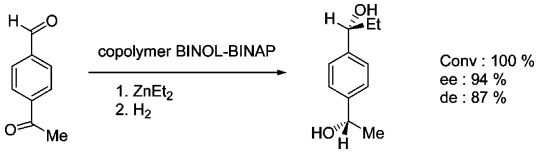


Figure 103. Use of copolymer BINOL−BINAP in asymmetric catalysis.

duced to the 6,6′-positions as a fluorous tag of methoxymethyl (MOM) protected 6,6′-dibromo-BINOL (**136**). The polyfluoroalkylsilylated BINOL derivatives **158** were obtained with 91% yield via lithiation at the 6,6′-positions of **136** and then reaction with $(C_6F_{13}CH_2CH_2)_3SiBr$ according to Curran's method.[139] The alcohol group of **158** was deprotected with hydrochloric acid in THF under reflux and vigorous stirring (Figure 104).

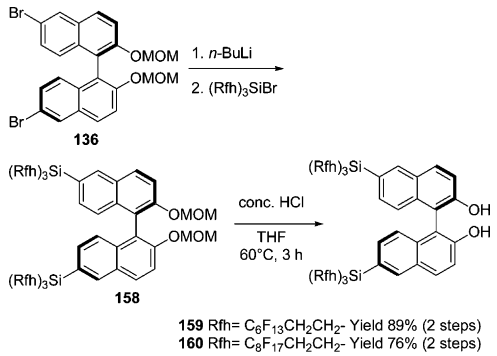


Figure 104. Synthesis of chiral fluorous BINOL.

When the bistriflate of (*R*)-F_{13}-BINOL (**161**) was phosphinated with $HPPh_2$ by using $NiCl_2$(dppe) in benzotrifluoride (BTF) at 100 °C for 3 days under argon, the desired product was obtained. Nevertheless, isolation of the product was impossible. The crude product was oxidized, purified, and then reduced to give the BINAP derivative **162**[140] (Figure 105).

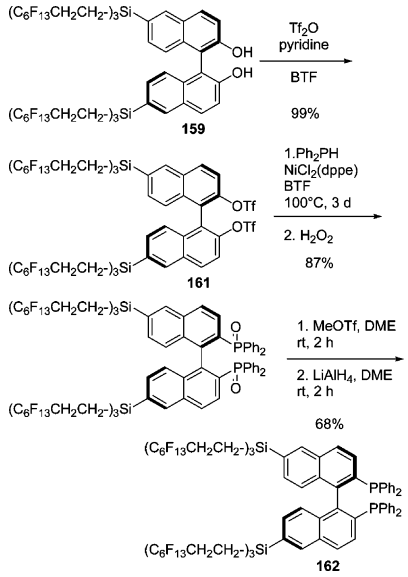
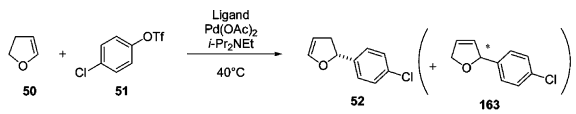


Figure 105. Synthesis of BINAP with a fluorinated chain and silyl as the linker.

The (*R*)-F_{13}-BINAP **162** was tested in an asymmetric Heck reaction between 2,3-dihydrofuran and 4-chlorophenyl triflate.[141] The results are summarized in Figure 106.



Entry	Ligand	Solvent	Time (h)	Yield			ee (%)	
				52	163	52/163	52	163
1	(*R*)-BINAP	BTF	24	67	6	92/8	76	nd
2	(*R*)-F_{13}BINAP	BTF	77	59	8	88/12	90	nd
3	(*R*)-F_{13}BINAP	Benzene	62	59	22	72/28	92	nd
4	(*R*)-F_{13}BINAP	Benzene/FC-72 (1:1, v/v)	62	39	18	69/31	93	nd
5	(*R*)-F_{13}BINAP	Benzene/FC-72 (1:1, v/v)	50	2	<1	62/38	93	nd

Figure 106. Asymmetric Heck reaction of 2,3-dihydrofuran with 4-chlorophenyl triflate.

The reaction rate is lower in the case of ligand **162** than in that of BINAP. BTF is a good solvent for (*R*)-F_{13}-BINAP (entry 2, 90% ee) but not for (*R*)-BINAP (entry 1, 76% ee). Benzene was also a good solvent for the fluorous BINAP (entry 3, 92% ee), although the chemical yield increased. Finally they performed the reaction in a benzene/FC-72 biphasic system (entries 4 and 5). The enantioselectivity was the same as that observed in benzene, but the conversion was lower (39%). Moreover, the recycling of the catalyst was not efficient (2% yield) because of inactivation of the catalyst by ligand oxidation in the FC-72 phase.

4.4.8. 6,6′-Diam-BINAP Grafted onto Silica

Lamouille[142] chose to immobilize 6,6′-diam-BINAP on silica gel. 6,6′-Diam-BINAP was bonded to a mineral support by a covalent bond. Moreau's method was used for the synthesis of this silyl derivative. 6,6′-Diam-BINAP was reacted with 3-(triethoxysilyl)-propylisocyanate to give the silyl product **164**. This compound was then anchored onto silica gel **165** (Figure 107).

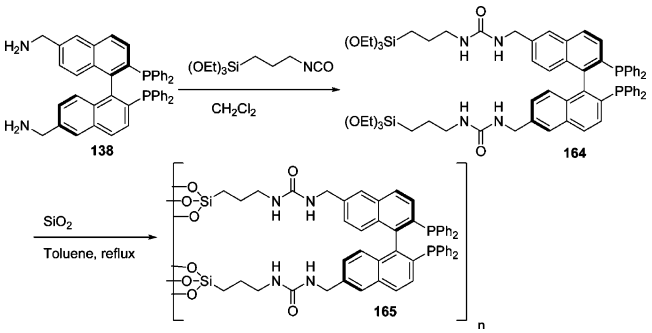
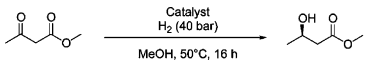


Figure 107. Synthesis of new inorganic material from 6,6′-diam-BINAP.

The cationic ruthenium complex of compound **165** was synthesized from the $[RuCl_2(benzene)]_2$ precursor.[135] This complex was tested in solid−liquid biphasic conditions for the hydrogenation of methyl acetoacetate (Figure 108). Pugin has shown with his



Entry	Mmol ligand/g of **165**	S/C	First use		Second use		Third Use	
			Conv(%)	Ee (%)	Conv(%)	Ee(%)	Conv(%)	Ee (%)
1	0.3	555	100	98	100	84	86	54
2	0.3	1000	48	48				
3	0.126	555	100	100	100	77	90	23
4	0.06	1000	100	94	70	65		

Figure 108. Reduction of methyl acetoacetate with the Ru−**165** complex.

study of the bisPPM ligand (PPM = (2*S*,4*S*)-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine) that the cationic catalyst was more active than a neutral catalyst[143] when using a catalyst grafted onto silica.

Good conversions and selectivities were obtained except for entry 2. Recycling was possible, but conversions and selectivities decrease after each use. Finally these results show that activity and selectivity increase when the material charge decreases. Pugin has already made the same observation.[144]

4.5. Functionalization in the 7,7′-Positions

The first BINAP substituted in the 7,7′-positions was described by Cai et al.[145] in 1996. They prepared 7,7′-bis(methoxy)BINAP (**169**) by phosphination of 7,7′-bis(methoxy)BINOL (**167**). BINOL substituted in the 7,7′-positons was prepared by an oxidative coupling of 7-methoxy-2-naphthol (**166**) with $CuCl_2$ and *tert*-butylamine. The binaphthol **167** was then protected as a ditriflate, and the classic phosphination was carried out (Figure 109). A resolution step was taken on compound **167** but was not given in the patent.

Later, in 2000 Keay et al. followed the same strategy.[146] They wished to determine how the methoxy group in the remote ring from the diphenylphosphino moeity would affect the basicity of the phosphorus atom and ultimately how the ee obtained would compare to that of BINAP. According to Koga and co-workers,[147] they prepared **167** by treating the **166** with a mixture of CuCl(OH)/TMEDA. They then applied the resolution procedure developed by Shan et al.,[148] using boronate complexes and proline, and separated the diastereomers formed. The diphenylphosphino groups were introduced using the procedure developed by Laneman et al.[149] in which the bistriflate was treated with Ph_2PCl (opposite $HPPh_2$ in Cai et al.'s procedure) in the presence of $NiCl_2$-(dppe) and zinc (Figure 110).

Three different asymmetric Heck reactions were performed to compare the efficiency of **169** to that of BINAP. The results indicate that the new ligand is a catalyst with efficiency and selectivity similar to those of BINAP. The two methoxy groups at the 7,7′-positions do not significantly lower the ee in palladium-catalyzed transformations.

Recently, Yokozawa and Saito from Takasago International Corp. described new BINAP derivatives substituted in positions 7 and 7′ and simultaneously on the phenyl group.[150] Substituted BINOL with a benzyloxy group was prepared by an oxidative coupling of 7-benzyloxy-2-naphthol (**170**) with $CuCl_2$ and *tert*-butylamine. The BINOL derivative was subjected to optical resolution using quinine to obtain an optically active isomer (**171**). This isomer was then protected with (MOM)Cl, debenzylated, and then reacted with *p*-xylyl dibromide. The alcohol was deprotected, and then (−)-DANP (**173**) was obtained with an overall yield of 13% by forming the BINOL triflate **172** and then reacting this compound with diphenylphosphine in the presence of palladium catalyst (Figure 111).

Using the same strategy, they also synthesized some derivatives with modifications of the phenyl moieties, such as dimethyl-DANP **174** (Figure 112).

These new ligands were tested in the hydrogenation of dehydronaproxen. Catalysts $[Ru(OAc)_2$((−)-DANP or DMDANP)] were prepared and then put in reaction in methanol at 15 °C with a hydrogen pressure of 50 bar (Figure 113).

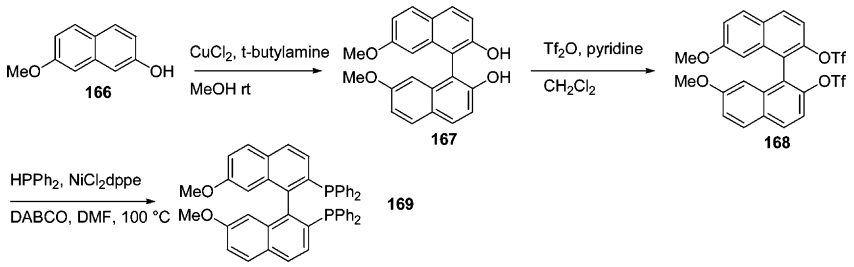


Figure 109. Synthesis of 7,7'-bis(methoxy)BINAP

Figure 109. Synthesis of 7,7′-bis(methoxy)BINAP.

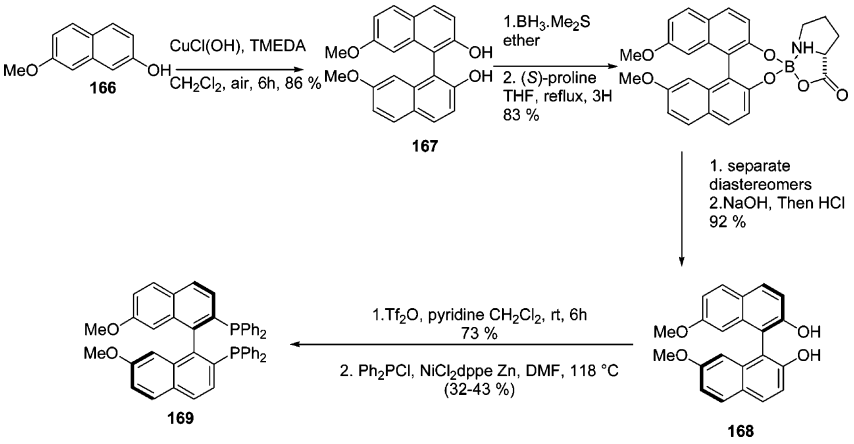


Figure 110. Synthesis of optically active 7,7′-bis(methoxy)BINAP.

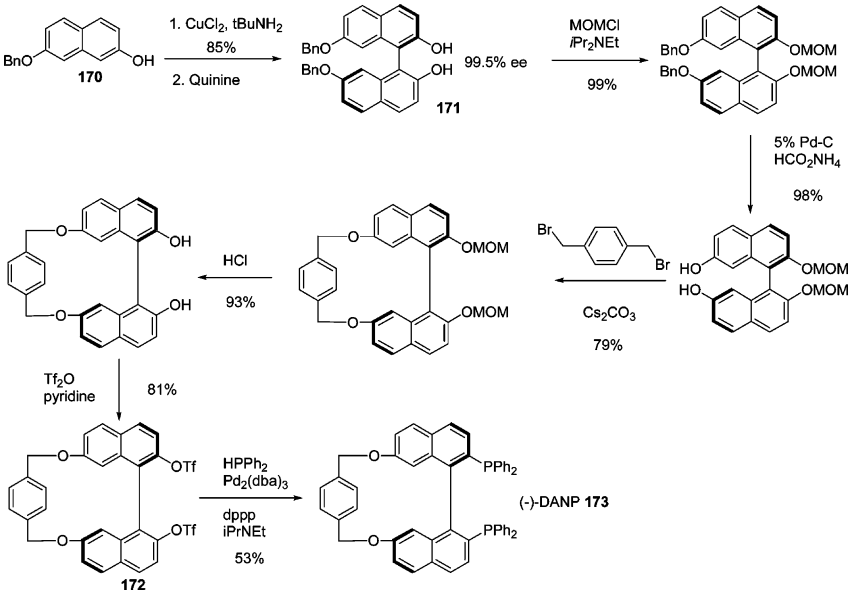


Figure 111. Synthesis of the 7,7′-BINAP derivative DANP.

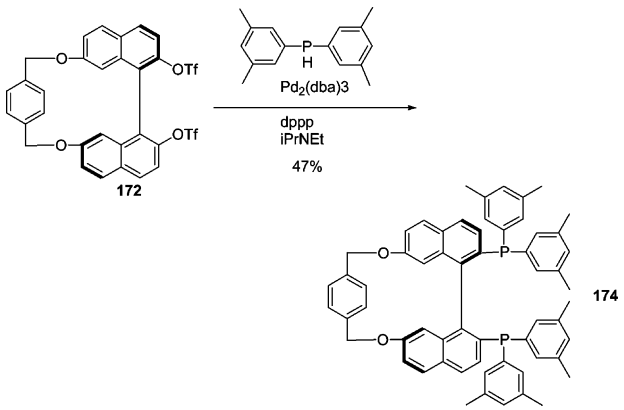


Figure 112. Synthesis of dimethyl-DANP (DMDANP).

Entry	Ligand	Time (hours)	Conv. (%)	Ee (%)
1	(-)-DANP	19	97	85.7
2	(-)-DMDANP	7	99	92.3
3	(*R*)-*p*-TolBINAP	19	93	87

Figure 113. Asymmetric hydrogenation of dehydronaproxen with 7,7′-BINAP derivatives.

These two new ligands were more active than Tol-BINAP. DANP was less enantioselective than Tol-BINAP; conversely DMDANP gave the higher enantioselectivity. Both substitutions on the binaphthyl moiety and on the phenyl moiety gave a positive effect for the asymmetric hydrogenation of the dehydronaproxen.

5. Conclusion

Asymmetric catalysis could be considered as one of the "high-tech" methods of the present-day chemical industry, with the high hopes (and potential disappointments) associated with such fast-growing technologies. Atropoisomery was originally considered to be a rather exotic form of chirality. Nevertheless, it has proved to be one of the most efficient, selective, and fruitful tools to induce asymmetric transformation and catalysis. Indeed BINOL and BINAP represent a real success story, from both an academic and an industrial point of view. This is of course thanks to the creative work of the Noyori group, and also to the many chemists who have explored the possibility of such catalyst complexes and improved their conditions of practical use. To our knowledge, no other asymmetric ligands have as yet found so many concrete applications in universities and in industry. Similarly, examples of the transformation of the BINAP structure have allowed the evaluation of most of the technologies able to separate and recycle the catalyst. Biphasic catalytic systems have been assessed using BINAP transformation to be soluble in water, in ionic liquid, in supercritical CO_2, or in perfluorinated solvents. In contrast, some modifications make BINAP soluble in nonpolar solvents but insoluble in polar solvents to permit separation by precipitation. Homogeneous supported catalysis with inorganic and organic supports was also used. Such material included BINAP, grafted onto the support or presented in the main chain as a copolymer.

By modifying the BINAP scaffold, chemists can easily and effectively tune both the steric and electronic characters of the chiral metal−BINAP complexes. Such modifications often allow a better activity and selectivity of the catalyst as was shown in many examples such as Noyori's invention of the [(Xyl-BINAP)Ru(diamine)Cl_2] system for the hydrogenation of aromatic ketones. The presence of the xylyl groups offers up to 15% ee enhancement.

6. References

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