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Chiral P,N-ligands with pyridine-nitrogen and phosphorus donor atoms. Syntheses and applications in asymmetric catalysis

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1. Introduction

Since the design of chiral ligands plays a key role in the development of metal-catalysed asymmetric reactions, many recent studies have addressed the development of novel chiral ligands.[1]

To date, a large number of chiral ligands having hetero-donor atoms with nitrogen and phosphorus functional moieties (P,N-ligands) has been prepared and their usefulness for asymmetric reactions has been investigated.[2] The success in metal-catalysed asymmetric reactions of these mixed donor ligands arises from the fact that they are a class

Keywords: pyridine-phosphorus ligands; metal complexes; asymmetric catalysis.

Abbreviations: Ac, acetyl; acac, pentane-2,4-dione; anisyl, 2-methoxyphenyl; Ar, aromatic; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene; COD, 1,5-cyclooctadiene; Cp, 1,5-cyclopentadienyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; DCC, 1,3-dicyclohexylcarbodiimide; DME, 1,2-dimethoxyethane; DMF, dimethylformamide; DMPA, 4-dimethylaminopyridine; DMPP, 3,4-dimethy-1-phenylphosphole; dppb, 1,4-bis(diphenylphosphino)butane; dppe, 1,2-bis(diphenylphosphino)ethane; dppp, 1,3-bis(diphenylphosphino)propane; DMSO, dimethylsulphoxide; EDCI, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide chloride; HOBT, 1-hydroxybenzotriazole; Ms, methanesulfonyl; PHENAP, 6-(2′-diphenylphosphino-1′-naphthyl)phenanthridine; PYDIPHOS, (−)-(4*S*,5*S*)-4-(2-pyridyl)-5-(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dixolane; Pyr-phos, pyridine-phosphines; QUINAP, 1-(2′-diphenylphosphino-1-naphthyl)isoquinoline; QUIPHOS, (2*R*,5*S*)-3-phenyl-2-(8-quinolinoxy)-1,3-diaza-2-phosphabicyclo[3.3.0]octane; THF, tetrahydrofuran; Ts, 4-methylbenzenesulfonyl.

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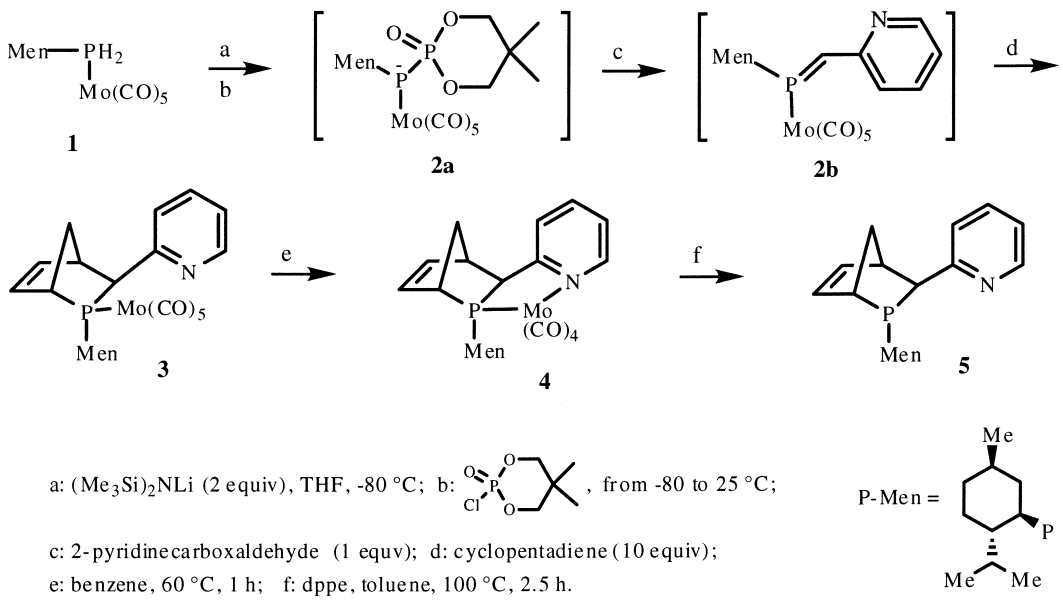


Scheme 1.

of hemilabile ligands possessing a combination of hard and soft donor atoms. Therefore, the different features associated with each donor atom provide a unique reactivity to their metal complexes.[3] The hard ends weakly coordinate to soft metal centres and easily dissociate in solution to afford a vacant site whenever demanded, whereas their chelate effect confers stability to the catalyst precursor in the absence of substrate.[4] Moreover, a further advantage of P,N-ligands over regular phosphine-based ligands is that the former can be separated from the organic products via phase separation under acidic conditions.

In the context of P,N-ligands, a prominent position is occupied by those with pyridine N-donors. In 1993, Newkome overviewed the syntheses, reactions and catalytic properties of pyridine-phosphines. This review, however, contained only one reference on chiral derivatives of such ligands.[5] More recently, an excellent review has covered the structure, reactivity and catalytic behaviour of complexes containing P,N-ligands, the N atom being included in a pyridine ring. A section of this review focused on the structure of complexes with asymmetric ligands.[6]

In recent years, chiral pyridine-phosphine ligand-metal complexes have received a great deal of attention and an increasing number of reports on their synthesis and use in various catalytic processes have been published.

The present account is intended to focus on recent developments in the syntheses and metal-catalysed asymmetric reactions of not only chiral pyridine-phosphines, but also of other chiral P,N-ligands in which the pyridine framework is part of more complex heterocycles, such as quinolines, isoquinolines, phenanthridines, etc. and the phosphorus atom belongs not only to simple phosphine functionalities, but also to other groups, such as phosphites, phosphoramides, etc. (denoted as (pyr-phos)-ligands).

This review not only updates the previous reviews but also reports the synthetic schemes followed for the preparation of chiral ligands, the syntheses of which have already mentioned been, but not sufficiently described.

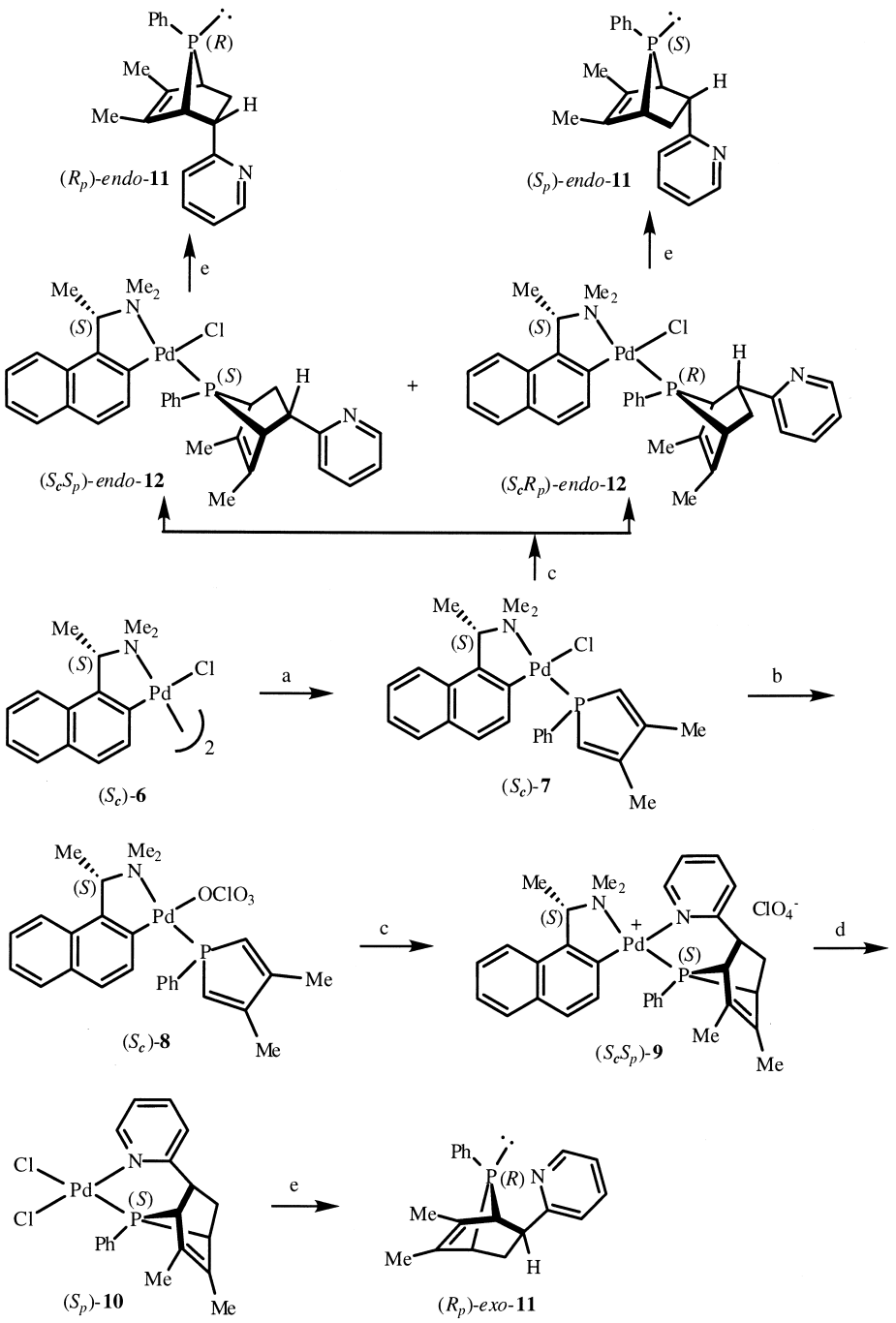
This article is organised into two sections. The first section is dedicated to the synthetic procedures used to prepare chiral (pyr-phos)-ligands, with particular attention to those ligands which have found application as chiral promoters in asymmetric processes. The second section is devoted to a discussion of the enantioselective processes which utilise such ligands.

2. Syntheses

2.1. Pyridine-phosphorus ligands with central chirality

The first preparation of a chiral non-racemic pyridine-phosphine was reported in 1992 by Mathey's group as part of a study on the reactivity of prochiral phosphoalkenes.[7] They devised a two-step procedure for the conversion of the molybdenum complex **1** into an optically pure phosphine (Scheme 1). In the first step, the primary phosphine complex **1** was phosphorylated and the resulting phospha-Wittig reagent **2a** was allowed react with 2-pyridinecarboxaldehyde. The phosphaalkene complex **2b** thus formed was not isolated, but was trapped with cyclopentadiene to give the cycloaddition product **3**. This complex was unstable and readily lost one CO to give the stable chelate **4**. The decomplexation of **4**, carried out by heating with 1,2-diphenylphosphino ethane (dppe), afforded the chiral pyridine-phosphine **5** in 27% overall yield from **1** as a pure diastereomer.

Another type of stereochemically controlled asymmetric Diels–Alder reaction to obtain (pyr-phos)-ligands has been developed by Leung et al.[8] They carried out the reaction between 2-vinylpyridine and the 3,4-dimethyl-1-phenylphosphole (DMPP) unit of a chiral palladium complex derived from (−)-di-μ-chlorobis[(*S*)-dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]dipalladium(II) ((*Sc*)-**6**), which is

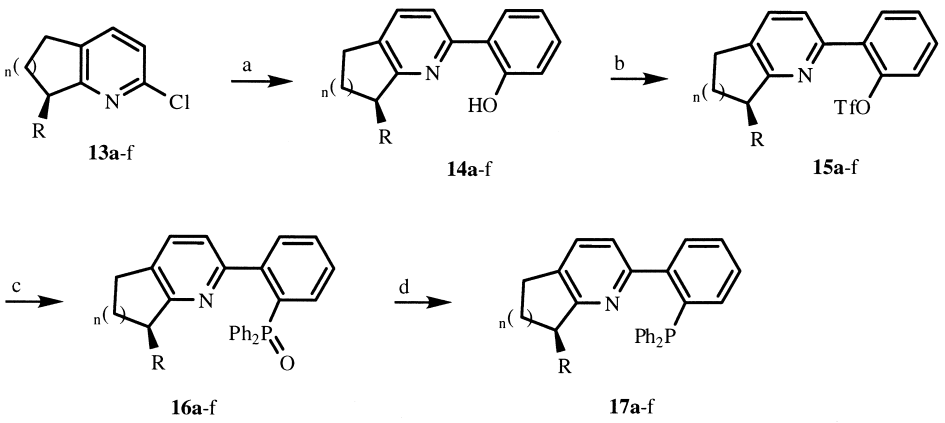


Scheme 2.

used as both the reaction promoter and stereochemical controller (Scheme 2).

By the reaction of (*Sc*)-**6** with DMPP, the chloro complex (*Sc*)-**7** was obtained regiospecifically in quantitative yield, because of the *trans*-directing effects originating from the σ-donating nitrogen and π-accepting aromatic carbon atom of the *ortho*-metallated naphthylamine chelate (Scheme 2). The cyclic diene in (*Sc*)-**7** reacted smoothly with 2-vinylpyridine to give a 1:1 mixture of two *endo*-cycloaddition products (*ScSp*)- and (*ScRp*)-*endo*-**12**, where the *endo*-cycloadducts are coordinated to palladium as monodentate ligands via their phosphorus donor atoms only (Scheme 2, top). These complexes were separated by fractional crystallisation and converted into the corresponding free pyridine-phosphine ligands (*Sp*)- and (*Rp*)-*endo*-**11**, by decomplexation with potassium cyanide.

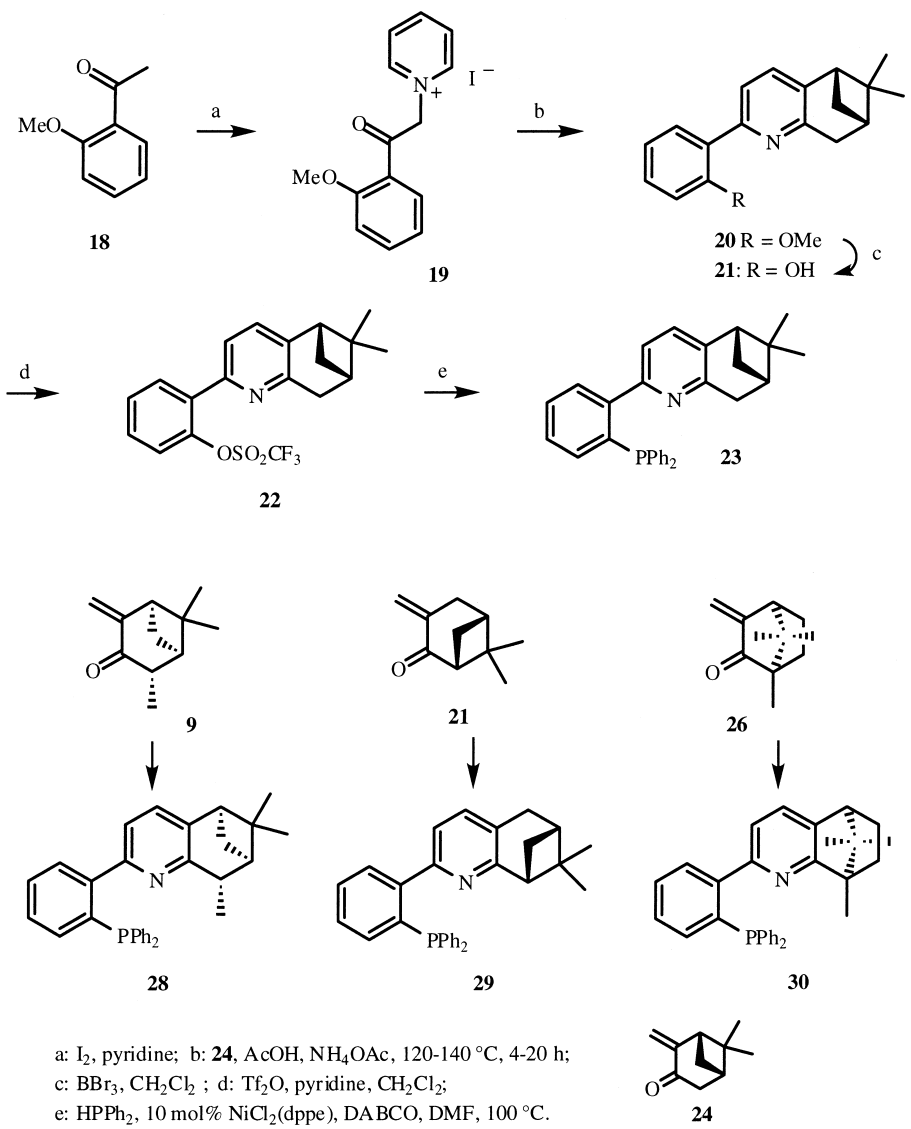
On the other hand, when the kinetically-labile perchlorate complex (*Sc*)-**8**, generated by treatment of (*Sc*)-**7** with silver



(n = 1): **a**: R = Ph; **b**: R = *i*-Pr; **c**: R = CMe_2OTBS
(n = 2): **d**: R = Ph; **e**: R = *i*-Pr; **f**: R = CMe_2OTBS

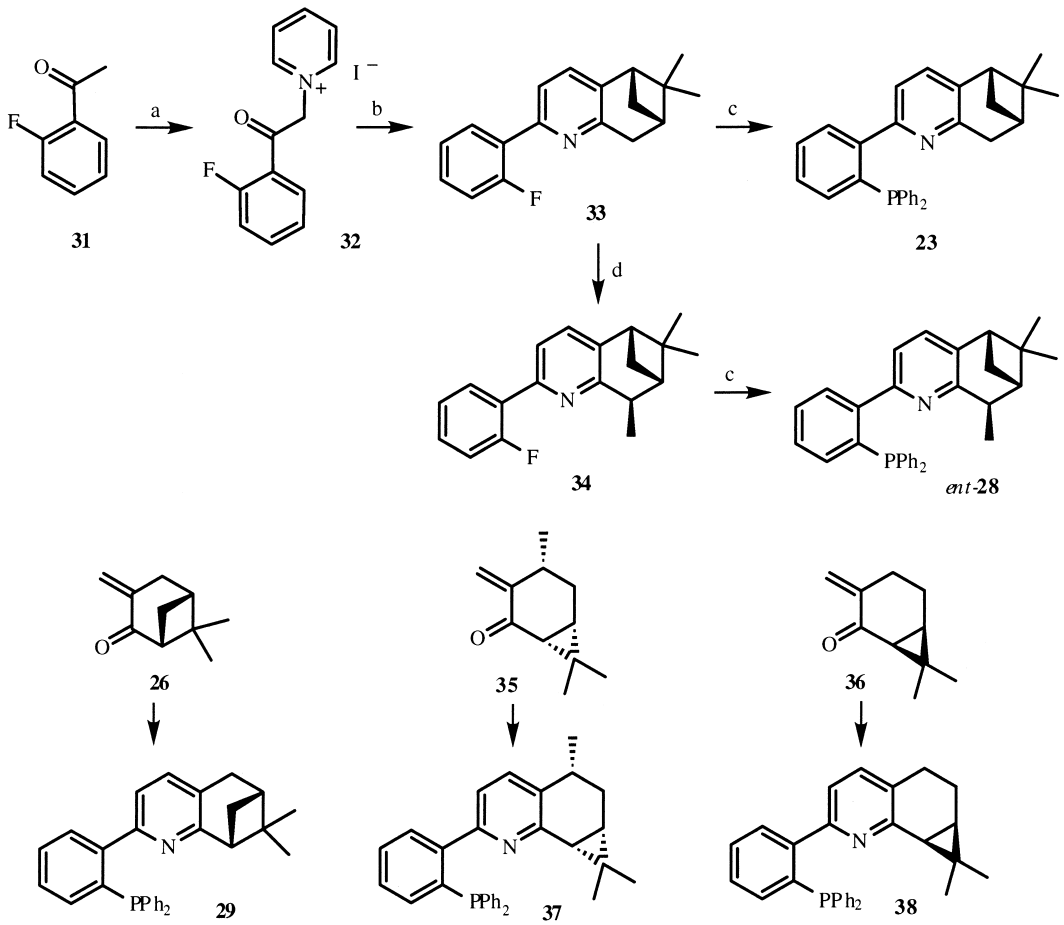
a: 2-hydroxyphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane/H_2O (6/1); b: Tf_2O, 2,6-lutidine; c: $HPOPh_2$, $Pd(OAc)_2$, dppb, *i*-Pr_2NEt, DMSO; d: $HSiCl_3$, NEt_3, toluene.

Scheme 3.



a: I_2, pyridine; b: **24**, AcOH, NH_4OAc, 120-140 °C, 4-20 h; c: BBr_3, CH_2Cl_2 ; d: Tf_2O, pyridine, CH_2Cl_2; e: $HPPh_2$, 10 mol% $NiCl_2$(dppe), DABCO, DMF, 100 °C.

Scheme 4.



Scheme 5.

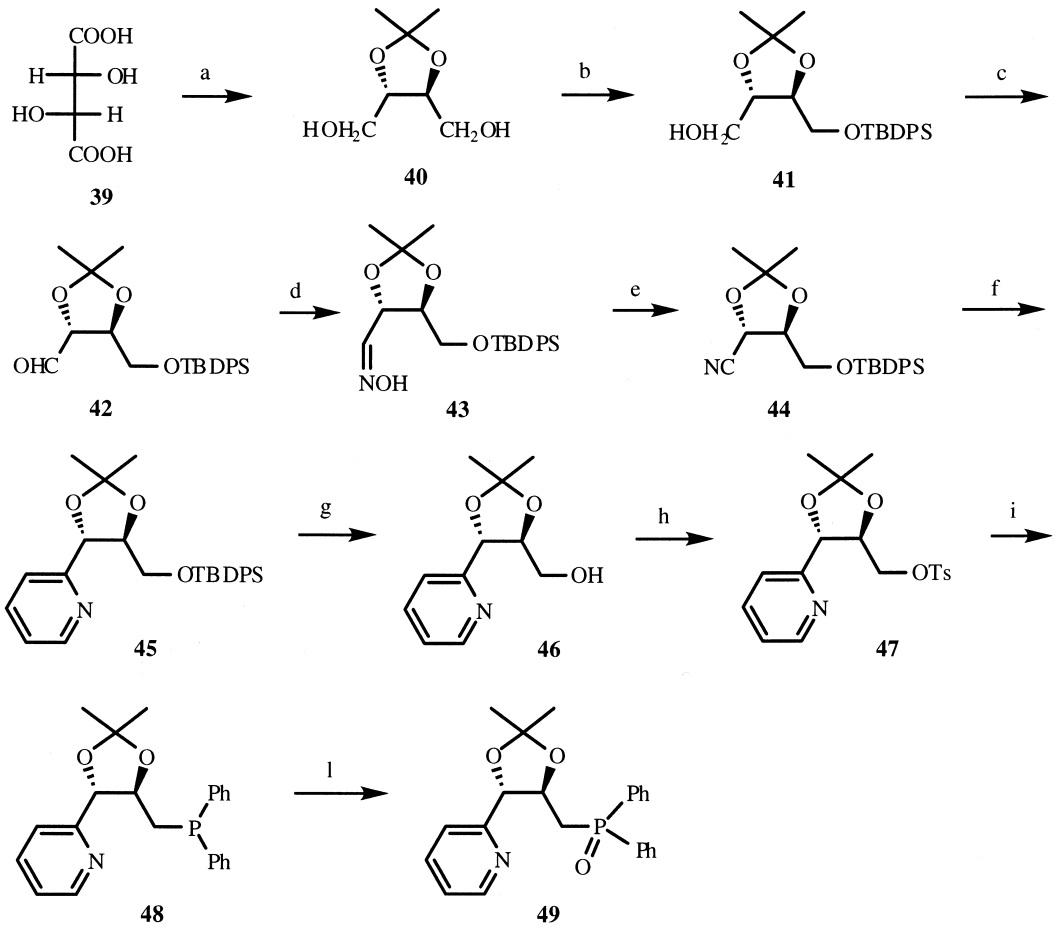
perchlorate, was treated with an excess of 2-vinylpyridine at 75°C, only the cycloaddition product (*ScSp*)-*exo*-**9** was produced stereoselectively (Scheme 2, bottom). In contrast to the *endo*-complexes, the pyridine-phosphine forms a metal chelate via both the pyridine-nitrogen and phosphorus atoms.

Treatment of the perchlorate salt (*ScSp*)-*exo*-**9** with concentrated sulphuric acid at room temperature removed the naphthylamine auxiliary chemoselectively to give an unisolated intermediate that, upon addition of an excess of lithium chloride, gave the dichloro complex (*Sp*)-**10**. Finally, liberation of (*Rp*)-*exo*-**11** from (*Sp*)-**10** was achieved by treatment with aqueous potassium cyanide.

A new class of chiral 2-(phosphinoaryl)pyridines has been introduced by Katsuki.[9] The synthesis of these chiral ligands **17a–f** (Scheme 3) started with the corresponding chiral chloropyridines **13a–f** which were previously used as intermediates for the synthesis of chiral bipyridines.[10] Suzuki cross-coupling of **13a–f** with 2-hydroxyphenylboronic acid gave the pyridylphenols **14a–f**, which were converted into the trifluoromethanesulphonates **15a–f** with $(CF_3SO_2)_2O$ and 2,6-lutidine. Palladium-catalysed cross-coupling of **15a–f** with diphenylphosphine oxide afforded the phosphine oxides **16a–f**, which were finally converted into 2-(phosphinoaryl)pyridines **17a–f** by reduction with trichlorosilane and triethylamine.

Although the 2-(phosphinoaryl)pyridines prepared by Katsuki afforded very good results in asymmetric allylic alkylations,[9] their use is limited, because only small amounts of these ligands are available. In fact, the preparation of the intermediate chloropyridines **13a–f** requires a rather elaborate synthesis or the separation of a racemic mixture by preparative chiral HPLC.[10] With the aim of obtaining similar ligands more easily, Kocovsky[11] and the present authors[12] have independently prepared a series of 2-(phosphinoaryl)pyridines from terpenes (Schemes 4 and 5). Both methods have as a key step the construction of the tetrahydroquinoline skeleton by following the Kröhnke annulation which involves the reaction of an α,β-unsaturated ketone with a pyridinium salt.[13]

Scheme 4 illustrates our approach to the phosphinoquinolines **23** and **28–30**.[12] The pineno fused tetrahydroquinoline **20** was prepared by the reaction of (−)-pinocarvone (**24**) with 1-phenacylpyridinium iodide **19**, which was, in turn, synthesized by the reaction of 2-methoxyacetophenone (**18**) with iodine in pyridine. Demethylation of the methyl ether



a: literature; b: NaH (1 equiv), *t*-BuPh$_2$SiCl (TBDPSCl), 75%; c: (COCl)$_2$, DMSO, Et$_3$N, -78 °C, 89%; d: NH$_2$OH·HCl, 10% K$_2$CO$_3$; e: N,N'-carbonyldiimidazole, 89%; f: CpCo(COD), acetylene, toluene, 120 °C, 14 atm, 94%; g: Bu$_4$NF, THF, 83%; h: TsCl, Et$_3$N, DMPA, CH$_2$Cl$_2$; i: Ph$_3$P, Na/K, dioxane, 67%; l: 5% H$_2$O$_2$, 96%.

Scheme 6.

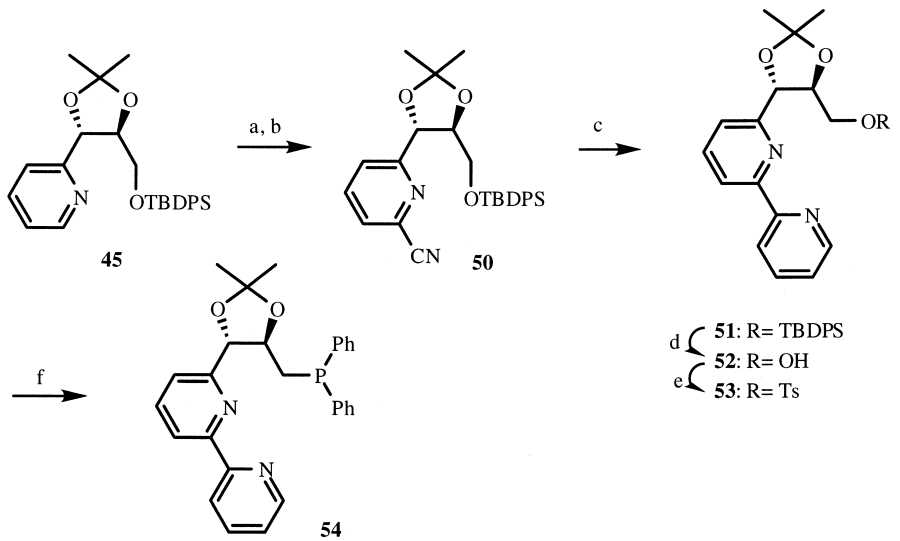
20 with boron tribromide occurred in good yield (79%) to give the phenol **21**, which was converted into the trifluoromethanesulphonate **22** with $(CF_3SO_2)_2O$ in pyridine (88%). Finally, treatment of the triflate **22** with diphenylphosphine in the presence of 10 mol% of $NiCl_2$(dppe) and two equivalents of 1,4-diazabicyclo[2.2.2]octane (DABCO) in DMF at 100°C gave the corresponding phosphinoquinoline ligands **23** (20%) with the corresponding *P*-oxide (20%) and the phenyl derivative (16%). The last compound results from the reduction of the trifluoromethanesulphonate group.

Having obtained the desired phosphinoquinoline **23**, this protocol was extended to other α-methylene ketones (Scheme 4), the ketones **25**, **26** and **27**, obtained from (−)-isopinocampheol, (−)-β-pinene and (+)-camphor, respectively, giving the corresponding phosphinoquinoline ligands **28**, **29** and **30**.

Kocovsky and co-workers examined an alternative synthetic method to obtain this class of compounds.[11] They considered that a convenient approach could involve the nucleophilic substitution of an electrophilic aryl fluoride with potassium diphenylphosphide. The fluoro derivative **33** was prepared by the reaction of (−)-pinocarvone (**24**) with the pyridinium iodide **32**, synthesised in turn by the reaction of 2-fluoroacetophenone **31** with iodine in pyridine (Scheme 5). Treatment of the fluoropyridine **33** with $KPPh_2$ in the presence of 18-crown-6 afforded the desired phosphine **23** in 55% yield. This successful procedure was applied to other chiral building blocks, the α-methylene ketones **35** and **36**, being prepared from (+)-3-carene and (+)-2-carene, respectively, and affording the phosphinoquinolines **37** and **38**, respectively. Finally, the ligand *ent*-**28**, which is the methyl derivative of **23**, was prepared by stereospecific methylation of the fluoro derivative **33**, followed by introducing the diphenylphosphino group, from **34**, in the usual way (Scheme 5).

The present authors have described the preparation of PYDIPHOS (**48**) as the first representative member of chiral pyridine-phosphines using L-(+)-tartaric acid (**39**) as the starting point[14,15] (Scheme 6).

The synthesis started from the aldehyde **42** which was

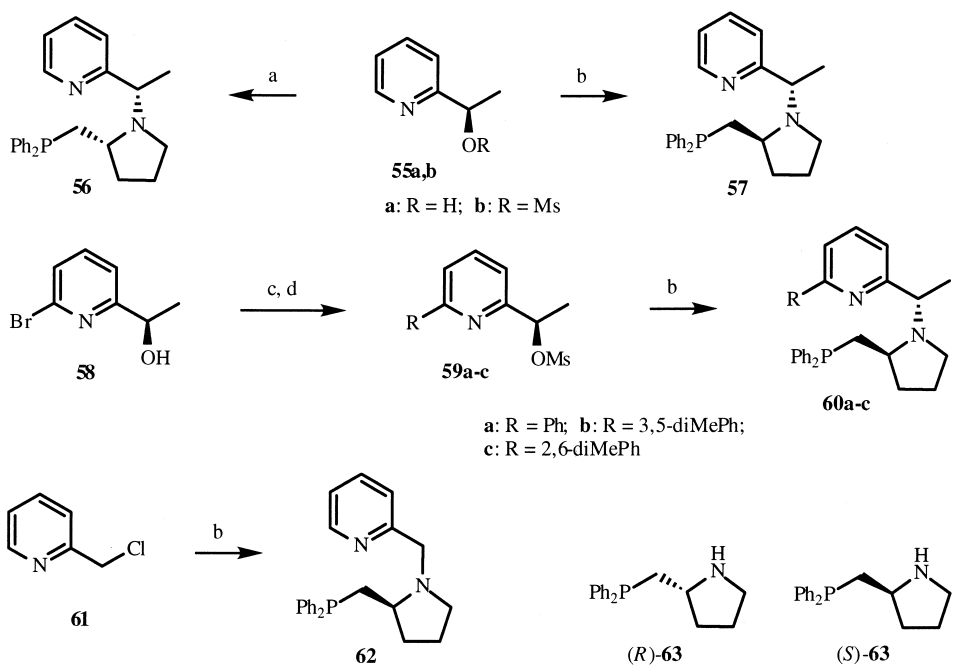


a: MCPA, $CHCl_3$, 24 h; b: $(CH_3)_2NCOCl$, $(CH_3)_3SiCN$, CH_2Cl_2, rt, 6 d, 83%;
c: CpCo(COD), acetylene, toluene, 120 °C, 13 atm, 86%; d: Bu_4NF, THF, 97%;
e: TsCl, Et_3N, DMPA, CH_2Cl_2, 75%; f: Ph_3P, Na/K, dioxane, 15%.

Scheme 7.

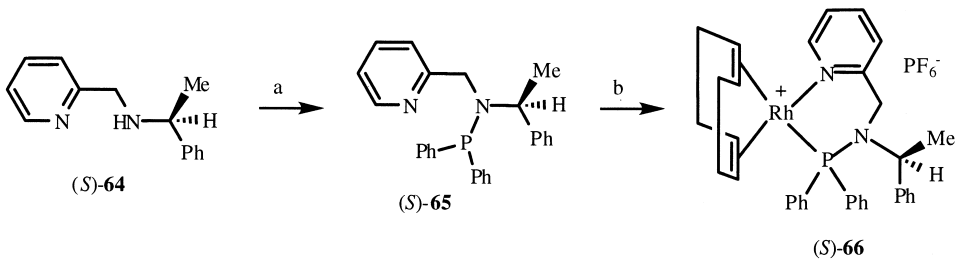
prepared by selective protection of the known diol **40**[16] with *tert*-butyldiphenylsilyl chloride, followed by Swern's oxidation of **41**. The aldehyde **42**[17] was converted into the nitrile **44** via the formation of the corresponding oxime **43**, followed by dehydration with *N*,*N*′-carbonyldiimidazole. The cobalt-catalysed cocyclotrimerisation of the nitrile **44** with acetylene[18] afforded the pyridine **45** in 62% overall yield based on **42**. The hydroxy group was then easily deprotected using a 0.1 M solution of Bu_4NF in THF to give the alcohol **46** which was converted into the tosylate **47**. Finally, nucleophilic displacement of the tosyl group with Na/K diphenylphosphide mixture gave PYDIPHOS (**48**) in 29% overall yield based on **40**. A similar result was obtained using a commercial solution of potassium diphenylphosphide in THF. Treatment of **48** with diluted hydrogen peroxide gave the *P*-oxide **49** in 96% yield.

With compound **48** in hand, the present authors examined



a: (*R*)-**63**, *i*-Pr_2NEt, MeCN, 60 °C; b: (*S*)-**63**, *i*-Pr_2NEt, MeCN, 60 °C;
c: MsCl, DMPA, CH_2Cl_2; d: $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, THF.

Scheme 8.

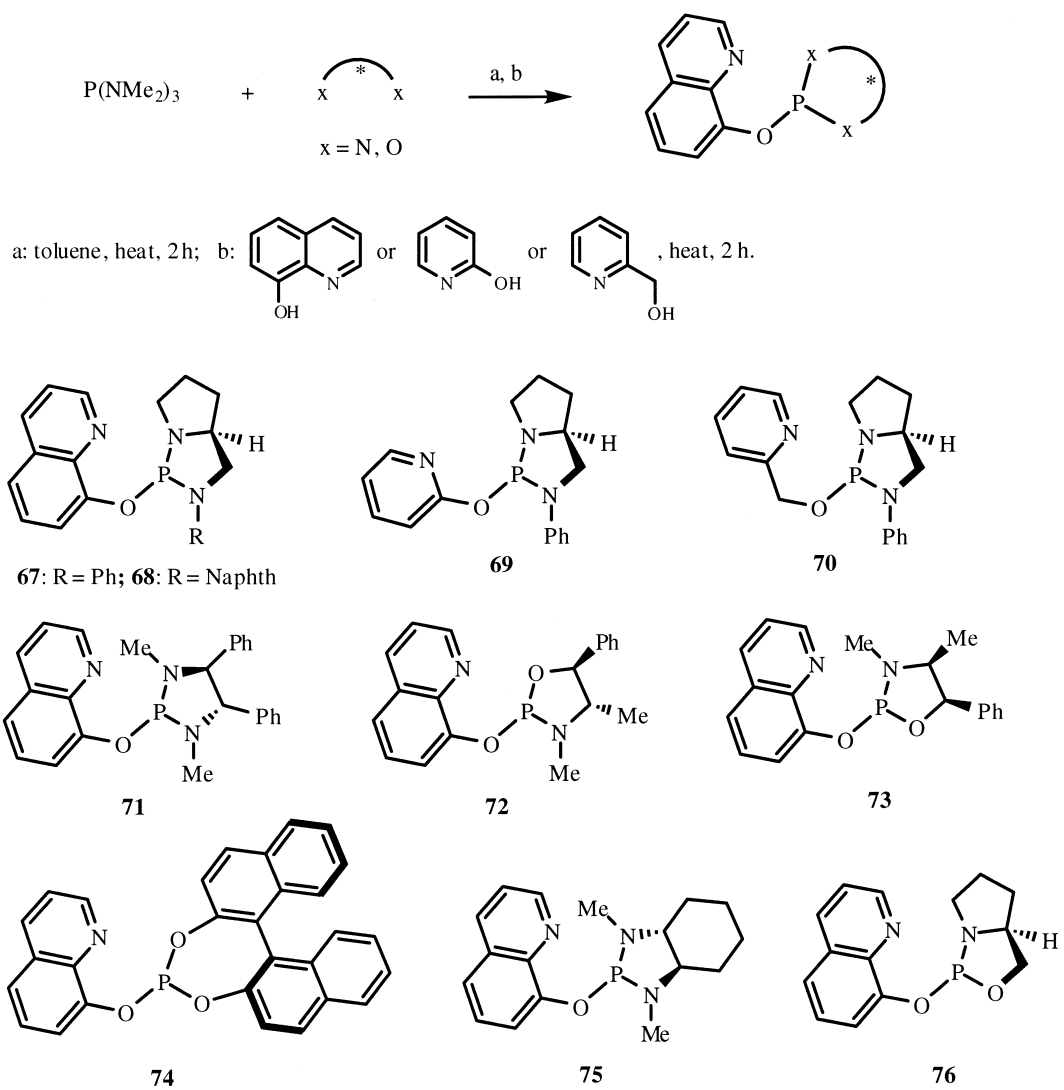


a: *n*-BuLi, Et_2O, -78°C then PPh_2Cl, 82%; b: $[Rh(COD)Cl]_2$, MeOH, NH_4BF_4.

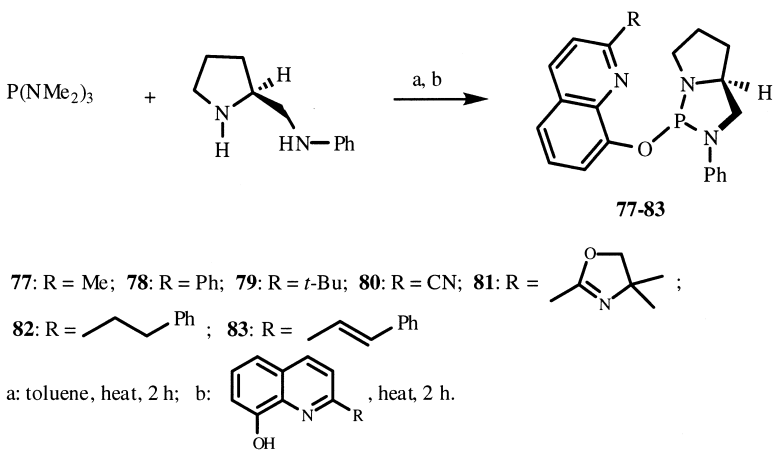
Scheme 9.

the possibility of preparing its pyridyl derivative **54**. This new bipyridine-phosphine was obtained starting from the pyridine **45** and following the reaction sequence reported in Scheme 7. Regiospecific introduction of a cyano group into the 6-position of the pyridine **45** was obtained by treatment of its *N*-oxide derivative with trimethylsilylcarbonitrile and dimethylcarbamyl chloride in CH_2Cl_2 for 6 days (83% yield based on **45**).[19] Cocyclotrimerisation of the cyanopyridine **50** with acetylene in the presence of CpCo(COD) afforded the dipyridine **51** in 86% yield. From this intermediate, the bipyridine-phosphine **54** was obtained in three steps using an experimental procedure analogous to that described for the compound **1**. In this case, however nucleophilic displacement of the tosyl group of **53** with Na/K diphenylphosphide gave a complex mixture from which **54** was recovered in low yield (15%) after three repeated chromatographic separations.

Chiral (pyr-phos)-ligands having 1-(pyridin-2-yl)ethyl and 2-(diphenylphosphinomethyl)-pyrrolidin-1-yl moieties were synthesised and used in asymmetric allylic alkylation reactions (Scheme 8).[20]



Scheme 10.

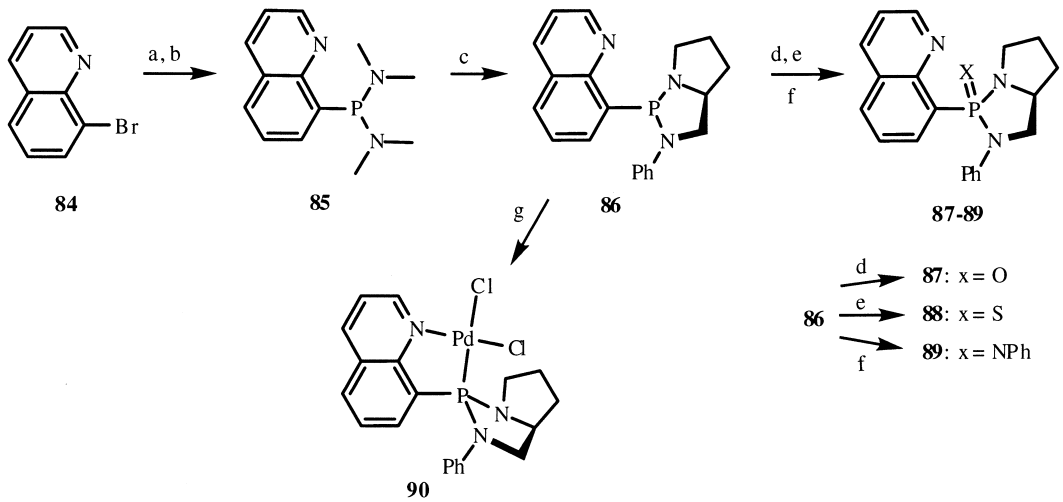


Scheme 11.

The ligands **56** and **57** were prepared in satisfactory yields (67–70%) by the stereospecific substitution of enantiomerically pure 1-(pyridin-2-yl)ethyl methanesulfonate (**55b**) with (*S*)- or (*R*)-2-(diphenylphosphino)methylpyrrolidine ((*S*)- or (*R*)-**63**),[21], respectively. Following the same protocol, the series of ligands **60a–c** were obtained (78–91% yields) starting from the mesylates **59a–c** that were, in turn, prepared by Suzuki cross-coupling of the 6-bromopyridine **58** with arylboronic acids (69–97% yields). Finally, the ligand **62**, bearing only one stereogenic centre, was obtained in 68% yield by the nucleophilic substitution of 2-(chloromethyl)pyridine (**61**) with (*S*)-**63**. The enantiomerically pure pyridine alcohols **55a** and **58** were prepared by lipase-catalyzed kinetic acetylation with vinyl acetate.[22]

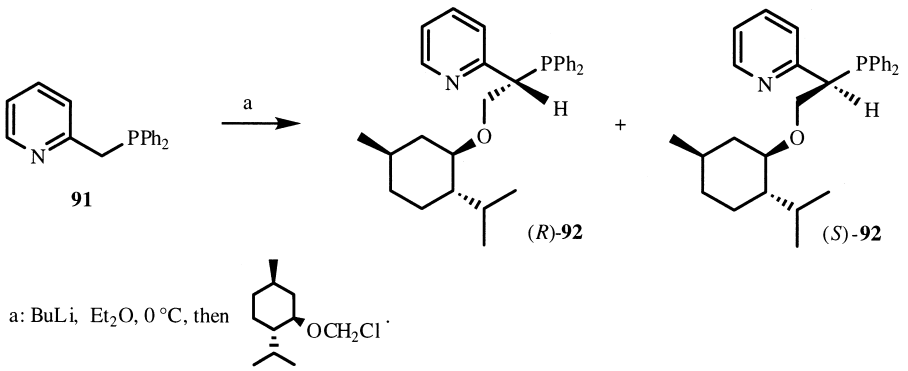
Brunner has reported the synthesis of the chiral aminophosphane–pyridine (*S*)-**65** and the corresponding rhodium complex (*S*)-**66** that was used in hydrosilylation and cross-coupling reactions. This ligand was prepared in good yield (82%) by treatment of the aminopyridine (*S*)-**64** with *n*-BuLi at −78°C, followed by chlorodiphenylphosphine (Scheme 9).[23]

Buono's group[24] reported, in a sequence of papers, the application in asymmetric catalysis of a number of non-symmetric chiral pyridine- and quinoline-phosphine ligands bearing the chirality at the phosphorus atom. Initially, they prepared the pyridine derivatives **68**,[24b] **69**[24a] and **70**[24a] and the (2*R*,5*S*)-3-phenyl-2-(8-quinolinoxy)-1,3-diaza-2-phosphabicyclo[3.3.0]octane (QUIPHOS, **67**),[24a,e] which is the most well-known exponent of the series (Scheme 10). These ligands were obtained by an exchange reaction between tris(dimethylamino)phosphine and (*S*)-2-anilinomethylpyrrolidine, followed by addition of 2-hydroxypyridine, 2-hydroxymethylpyridine or 8-hydroxyquinoline, respectively (Scheme 10). They, successively modified the structure of the chiral moiety attached to the phosphorus atom of QUIPHOS using a diamine, diol or an aminoalcohol the auxiliaries. The compounds **71–76**[24h] were easily obtained in workable yields, varying from 48 to 62% (Scheme 10). Next, using this protocol a number of



a: *s*-BuLi, THF, -78 °C; b: $PCl(NMe_2)_2$, THF, -78 to 25 °C; c: (*S*)-2-anilinomethylpyrrolidine, toluene, reflux, 61% (2 steps); d: *t*-BuOOH, toluene (85%); e: S_8, toluene (95%); f: PhN_3, toluene (100%); g: $PdCl_2(MeCN)_2$, CH_2Cl_2, 100%.

Scheme 12.



Scheme 13.

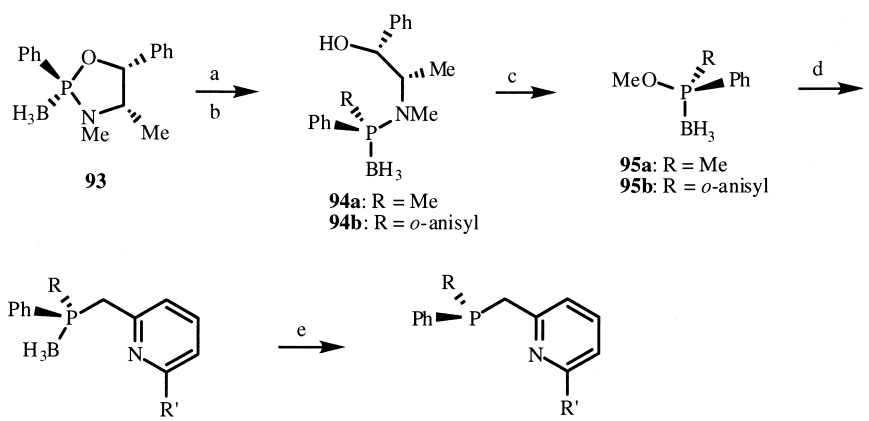
QUIPHOS derivatives (**77**–**83** in Scheme 11) were prepared employing 2-substituted 8-hydroxyquinolines as the starting point.[24h]

In order to evaluate the electronic differentiation and bite angle effects of QUIPHOS in different asymmetric catalytic reactions catalysed by transition metal complexes, Buono has recently prepared the new P,N-ligand **86** analogue to QUIPHOS (Scheme 12).[25] This ligand, which forms a five-membered chelate ring, was expected to have increased stability because the hydrolysable P–O bond was replaced by a stable P–C fragment. The ligand **86** was obtained from 8-bromoquinoline (**84**), the lithio derivative of which was trapped by chlorobis(dimethylamino)-phosphine to form **85**, and a total diastereoselective exchange reaction between **85** and (*S*)-anilinomethylpyrrolidine then afforded **86**. From **86**, its derivatives **87**–**89** were easily prepared (Scheme 12). The structure of **86** and its bidentate chelating ability were confirmed by the X-ray structure of the palladium(II) complex **90**, which was obtained in quantitative yield by mixing an equimolar amount of $PdCl_2(MeCN)_2$ and **86** in CH_2Cl_2 (Scheme 12).

Mathieu's group investigated the asymmetric transfer hydrogenation reaction by using ruthenium complexes bearing optically active tridentate ligands with P,N,O-donor atoms.[26,27] They reported the synthesis of (*R*)- and (*S*)-1-(diphenylphosphino)-2-((1*R*,2*S*,5*R*)-menthoxy)-1-(2-pyridyl)ethane ((*R*)- and (*S*)-**92**) (Scheme 13)[27] and of the series of ligands **97a**–**d** in which the chiral centre is on the phosphorus atom (Scheme 14).[27,28]

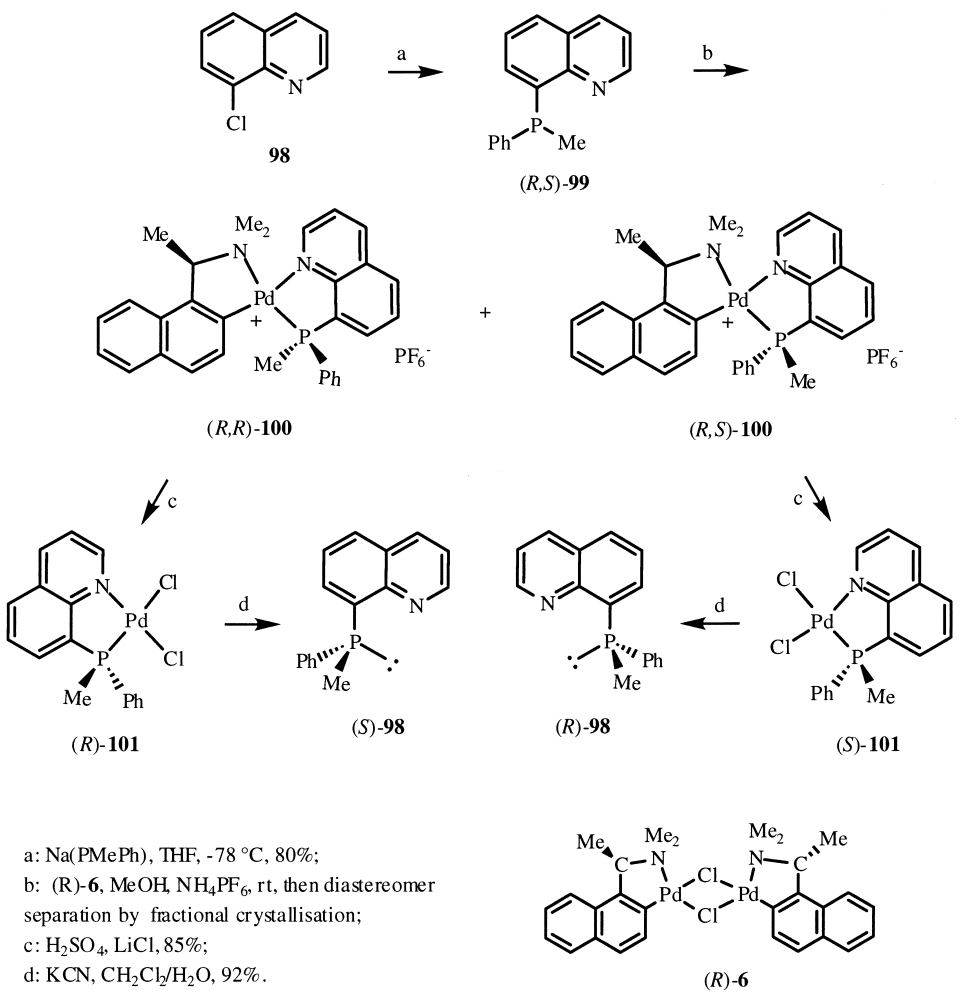
Successive addition of BuLi and chloromethyl (1*R*,2*S*,5*R*)-menthyl ether to the phosphinopyridine **91** led to **92** (70% yield) as a mixture of diastereomers (1:1 ratio) which it was possible to separate only after complexation with borane. The absolute configuration of these ligands was deduced from the X-ray structure determination of a ruthenium–(*S*)-**92** complex (Scheme 12).

The ligands **97a**–**d** were synthesised as depicted in Scheme 14.[27,28] The addition of methyllithium or 2-anisyllithium to (2*R*,4*S*,5*R*)-3,4-dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine[29] (**93**) afforded the aminophosphine–borane complexes **94a** and **94b**, respectively. A subsequent acid methanolysis at room temperature of **94a** and **94b** gave the phosphinite–borane complexes **95a** and **95b** which by reaction with 2-(lithiomethyl)pyridine or



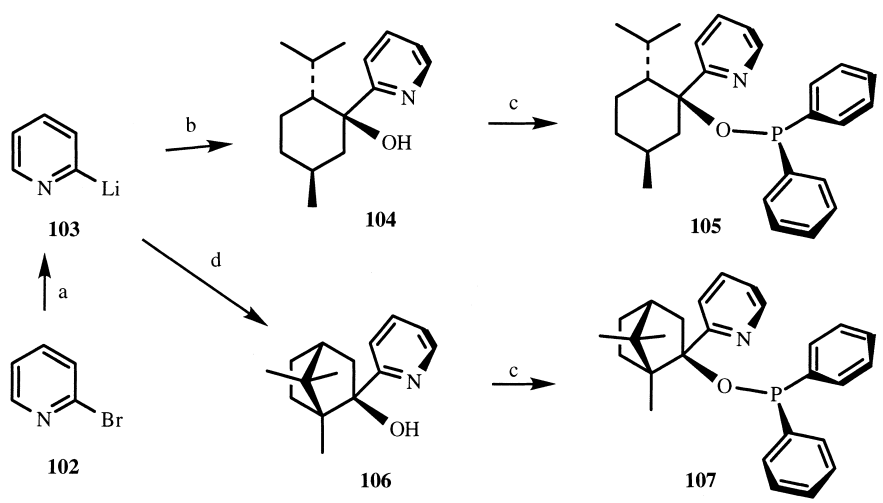
a: RLi, -78 to 0 °C; b: H_2O, 0 °C; c: $MeOH/H_2SO_4$, 25 °C, 80%; d: 2-(lithiomethyl)pyridine or 2-(lithiomethyl)-6-methylpyridine, THF, -20 °C, 55-77%; e: morpholine, 70 °C, 2 h, 85-96%.

Scheme 14.

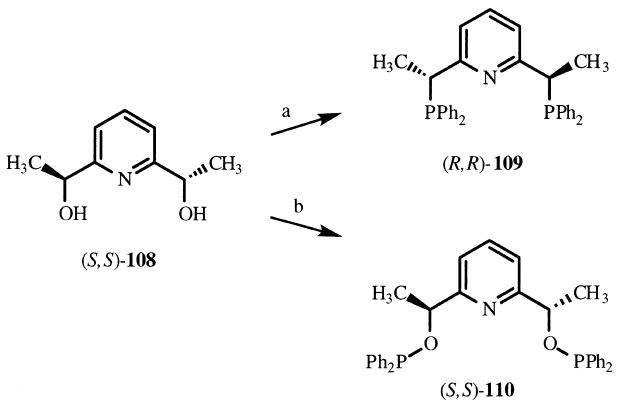


Scheme 15.

2-(lithiomethyl)-6-methylpyridine at −20°C led to the phosphine–borane complexes **96a–d**. The trifunctional ligands **97a–d** were finally liberated from their borane complexes by morpholine at 70°C. Examining the bonding properties of these ligands toward $[Rh(cod)]^+$, it emerged that an increase of the steric hindrance of the 2-position of the pyridine ring (R′=Me vs. H) favours a labile character of the Rh–N bond. In this event, an additional potentially hemilabile center (R=*o*-anisyl) is likely to compete for bonding to Rh(I).



Scheme 16.



a: MsCl, NEt_3, CH_2Cl_2, 0 °C, 90%, then $KPPh_2$, benzene, 6 °C, 30%.
b: BuLi (2.4 equiv), THF. -78 °C, 1 h, then Ph_2PCl (2 equiv), 0 °C, 8 h, 48%.

Scheme 17.

Wild's group have described a direct and efficient synthesis of (*R*,*S*)-methylphenyl-8-quinolylphosphine (**99**) and its resolution (Scheme 15).[30] Comprising the treatment of the 8-chloroquinoline (**98**) with Na(PMePh) in THF at −78°C to give (*R*,*S*)-**99** in good yield (80%). This racemic phosphine was resolved by fractional crystallisation of a pair of internally diastereoisomeric palladium(II) complexes (*R*,*R*)- and (*R*,*S*)-**100** derived from the chiral chelating ligand and (*R*)-**6**. The liberation of the tertiary phosphine from (*R*,*R*)- and (*R*,*S*)-**100** was accomplished by treatment with sulfuric acid and lithium chloride (85%). The resulting square-planar complexes (*R*)- and (*S*)-**101** were finally converted into the optically pure enantiomers (*S*)- and (*R*)-**99** with aqueous potassium cyanide (92%).

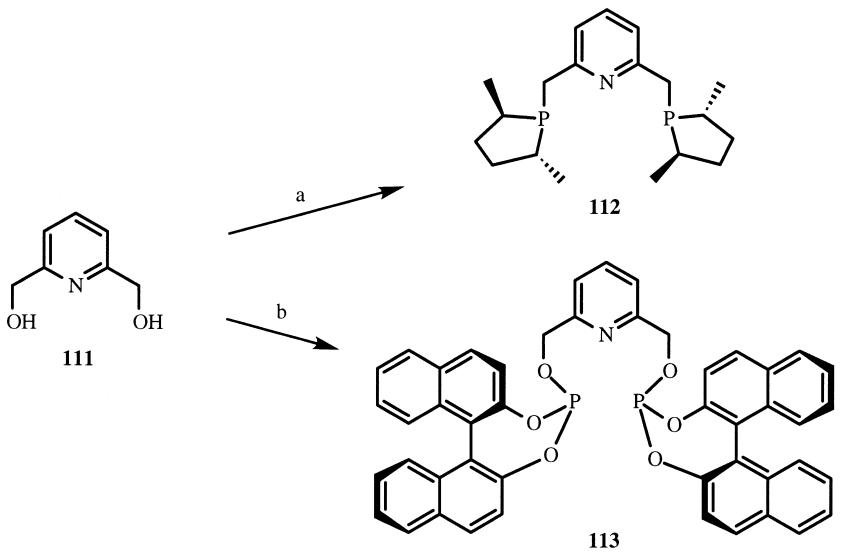
Faraone and the present authors have prepared cationic rhodium(I) complexes containing the P,N-chelate ligands [(1*S*,2*S*,5*R*)-1-diphenylphosphinyl-2-(2-methylethy)-5-methylcyclohexyl]pyridine[31] (**105**) and 2-{(1*R*,2*R*,4*R*)-2-diphenylphosphinyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}pyridine[32] (**107**) (Scheme 26) which were used in the enantioselective hydroformylation of olefinic substrates. These ligands were easily obtained in a two-step sequence based on the stereospecific addition of 2-pyridyllithium (**103**) to (−)-menthone and (+)-camphor.[33] The pyridyl-alcohols **104** and **106** thus obtained were deprotonated with BuLi and then treated with Ph_2PCl to give the desired ligands **105** and **107**, respectively (Scheme 16).

Osborn's group described the synthesis of four examples of a family of chiral ligands possessing the mixed donor set P−N−P, based on 2,6-disubstitution of the pyridine nucleus.[34] These ligands possess C_2-symmetry where the chirality can be placed either on the backbone α to the pyridine nucleus (**109** and **110**, Scheme 17) or on the pendant phosphine arm (**112** and **113**, Scheme 18).

The synthesis of **109** and **110** started from the known chiral pyridinediol (*S*,*S*)-**108**[35] which was prepared in a different manner by asymmetric reduction of the 2,6-diacetylpyridine derivative using Brown's chiral borane reduction reagent (−)-Dip-Cl.[36] The preparation of **109** was carried out by conversion of the diol (*S*,*S*)-**108** to the corresponding dimesylate, followed by treatment with $KPPh_2$ (Scheme 17). This tridentate phosphine was also prepared by Zhang using a slightly different procedure.[37]

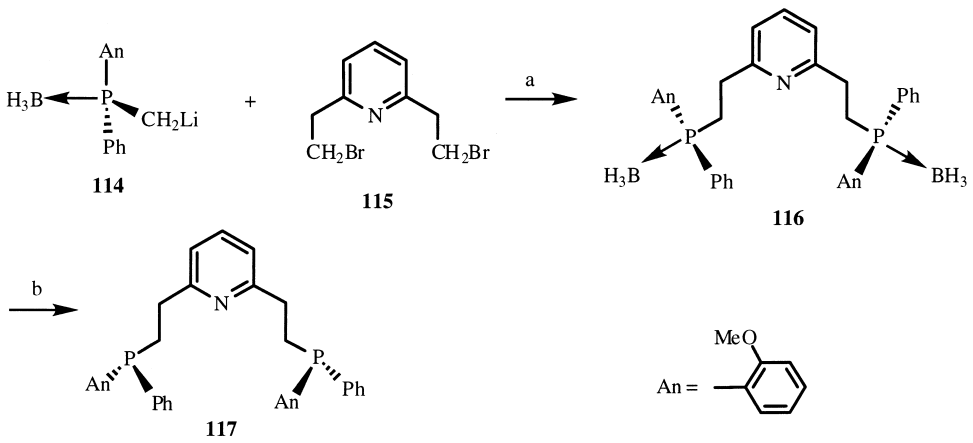
Treatment of the diol (*S*,*S*)-**108** with BuLi followed by addition of Ph_2PCl led to the phosphinite **110**.

Scheme 18 illustrates the synthesis of the phosphines **112** and **113** from the achiral diol **111**. The preparation of **112** involves the conversion of this diol to the corresponding dichloro derivative followed by treatment with a THF



a: $SOCl_2$, 0 °C, then reflux, 6 h, then Na_2CO_3, then Li^+ salt of (2R,5R)-dimethylphospholanate (2 equiv), THF, 25 °C, 1 h; b: (R)-naphtholatochlorophosphite (2 equiv), THF, -40 °C, then NEt_3, 65%.

Scheme 18.



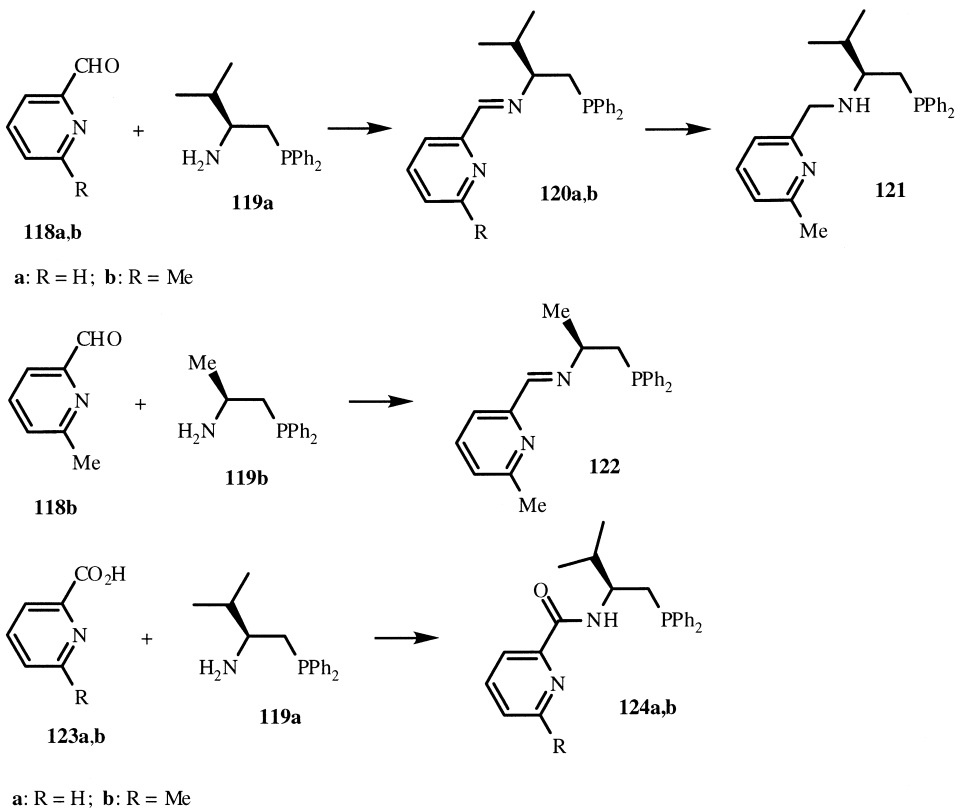
a: THF, -78 °C, 68%; b: $HNEt_2$, 70%.

Scheme 19.

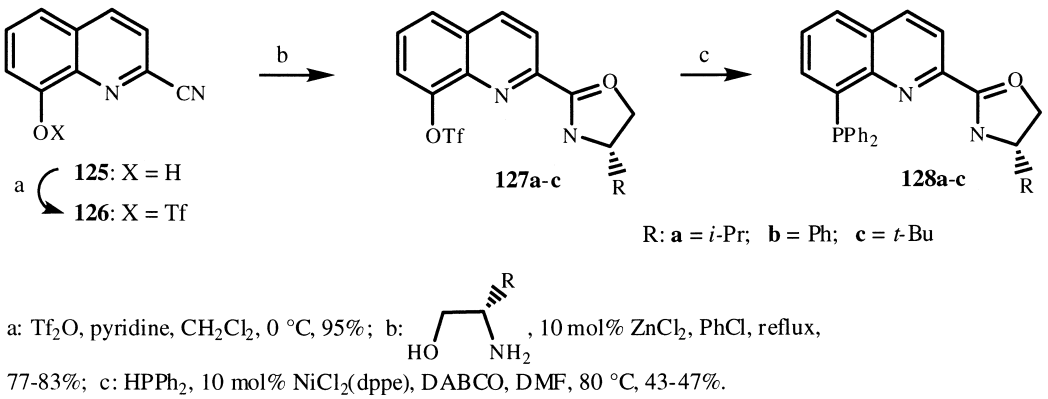
solution of the lithium salt of (2*R*,5*R*)-dimethylphospholanate. The phosphite **113** was easily prepared from the (*R*)-naphtholatochlorophosphite and the pyridinediol **111** in the presence of NEt_3.

Zhang and co-workers[38] reported another type of tridentate P–N–P ligands (Scheme 19), based on 2,6-disubstituted pyridine, which differs from the previous ligands by the presence of two stereogenic phosphorus atoms. The synthesis of **117** was achieved by the reaction of the lithium salt of the optically pure phosphine **114**[39] with the 2,6-bis-(bromomethy)pyridine (**115**), followed by removal of the borane groups from **116**.

Morimoto's group developed new tridentate chiral ligands bearing α-substituted pyridines and aminoethylphosphines as the chiral unit and optimised their use in the enantioselective conjugate addition of diethylzinc to enones.[40] The arylidene derivatives **120a**,**b** and **122** were obtained quantitatively by condensation of the pyridinecarboxaldehydes **118a**,**b** and the (*S*)-2-alkyl-2-aminoethylphosphines **119a**,**b** and **124**.[41,42] (Scheme 20). Reduction of **120b** with lithium aluminium hydride gave **121**. The picolinamide derivatives **124a**,**b** were prepared by acylation of (*S*)-2-isopropyl-2-aminoethylphosphine (**119a**) with the corresponding pyridinecarboxylic acids **123a**,**b** in the presence of a condensing agent (EDCI, HOBT or NEt_3).



Scheme 20.



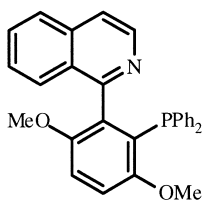
Scheme 21.

Ahn et al. reported the synthesis of N,N,P-chelates based on the quinoline or oxazoline framework.[43] They proposed that, for the preparation of **128a–c** (Scheme 21), 2-cyano-8-hydroxyquinoline (**125**) would be an adequate staring material. In fact, the oxazoline moiety could be introduced by $ZnCl_2$-catalysed condensation of the nitrile group of **126** and the corresponding aminoalcohols, and the diphenylphosphino group by a Ni(0)-catalysed coupling reaction between the triflate group of **127** and diphenylphosphine. This synthetic plan was indeed realised and the results are summarised in Scheme 21.

2.2. Pyridine-phosphorus ligands with axial chirality

To date, surprisingly few axially-chiral (pyr-phos)-ligands have been reported and the group of Brown has been at the forefront in the design, preparation and application of their metal complexes in asymmetric catalysis.

Brown and co-workers, in a study aimed at the synthesis of axially chiral chelate ligands for catalysis which do not correspond to the diphosphine model, addressed their efforts to obtain atropisomerically chiral P,N-ligands based on a biaryl linkage between isoquinoline and arylphosphines through the 1- and 2-positions, respectively. They initially prepared 1-(2-diphenylphosphino-3,6-dimethoxyphenyl)-isoquinoline (**129**) and attempted its resolution. Unfortunately, this compound was found to racemise quite easily with an estimated half-life of ca. 1 h at room temperature and therefore precludes its application in asymmetric catalysis.[44]



129

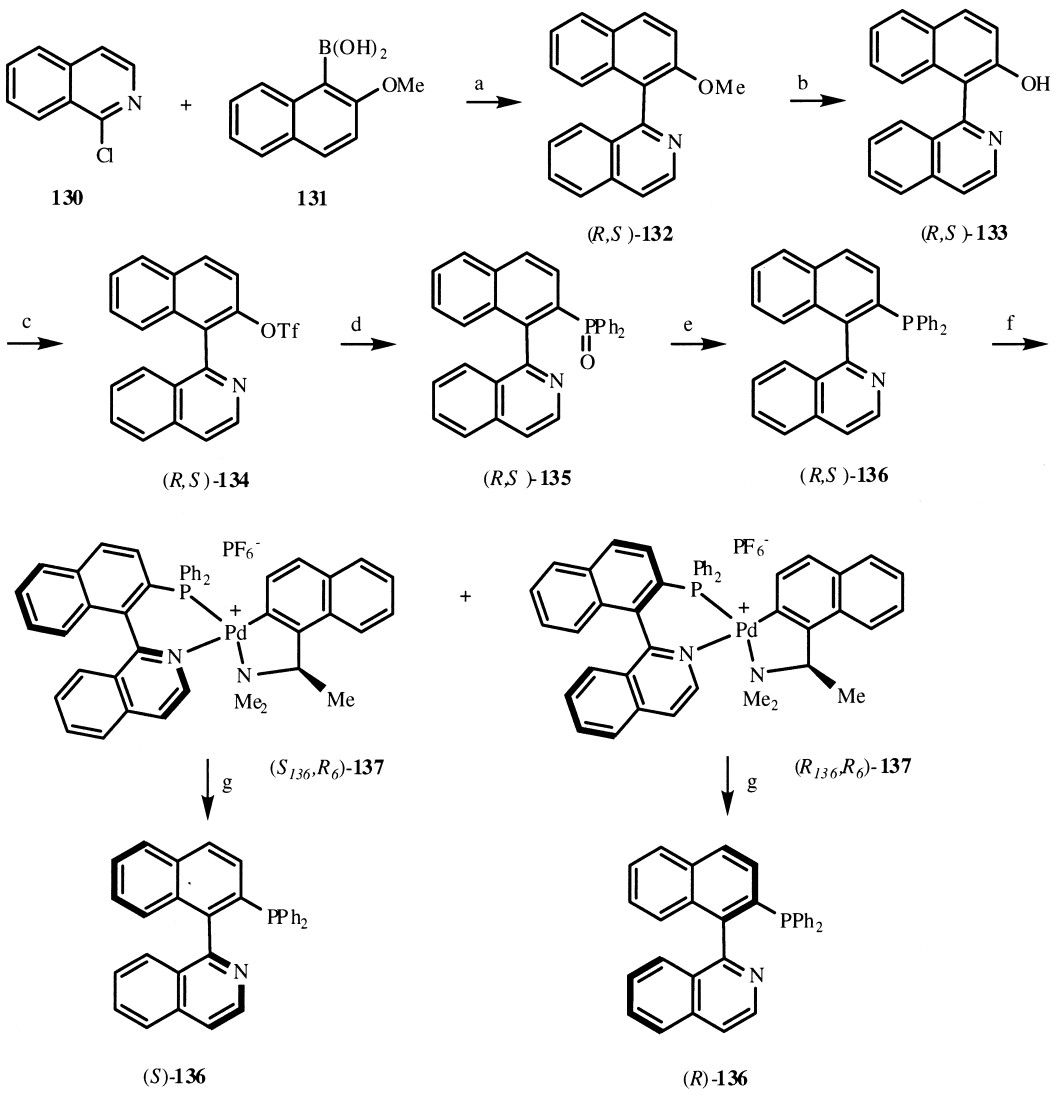
With the object of forming an optically active stable analogue of ligand **129**, the same authors focused centered their attention on the 1-(2-diphenylphosphino-1-naphthyl)-isoquinoline (QUINAP, **136**).[45] The synthesis of this compound was accomplished as described in Scheme 22. The arylboronic acid **131**, prepared by reacting the Grignard reagent from 1-bromo-2-methoxynaphthalene with trimethylborate in THF at −78°C, was cross-coupled with 2-chloroisoquinoline (**130**) in the presence of 3% $Pd(PPh_3)_4$ and Na_2CO_3 in dimethoxyethane at reflux temperature to give **132** in high yield (96%). Cleavage of the methyl ether with BBr_3 gave the phenol **133** (86%) which was converted into the trifluoromethanesulphonate **134** with Tf_2O (84%). Palladium-catalysed coupling of the triflate **134** with diphenylphosphine oxide afforded the phosphine oxide **135** (60%) which was finally reduced to the phosphine **136** with $HSiCl_3/NEt_3$ (84%).

After several unsuccessful attempts to resolve the racemic phosphine using tartaric acid and related compounds, chiral Pd complexes which have been successfully utilised for phosphine and diphosphine resolutions were employed. The reaction of (*R*,*S*)-**136** and (*R*)-**6** in CH_2Cl_2 produced the pair of diastereomeric complexes (S_{136},R_6)- and (R_{136},R_6)-**137**. These diastereomers showed different stability[46] and solubility and were therefore readily separated and were then converted to the free phosphine by treatment with 1,2-bis(diphenylphosphino)ethane. The resolved QUINAP was enantiomerically stable on heating to 65°C for 24 h.

The very interesting results acquired by QUINAP in asymmetric catalysis prompted the group of Brown to modify the basic structure of this ligand to study the effects of changing certain parameters on the enantioselectivity. These changes include the electronic and steric character of both the nitrogen and phosphorus donor atoms, besides the variation of the bite angle by modifying the ring size either of the isoquinoline or of the naphthalene.

Initially, Brown modified the structure of QUINAP by introducing a benzo-fuse ring on the 3,4-positions of the isoquinoline framework. This idea stemmed from a mechanistic study on the use of QUINAP in Pd-catalysed allylic alkylation that suggested the importance of the role of the 3-H of the isoquinoline in determining the steric course of the reaction.[47] Therefore, in the hope of increasing the catalytic and enantioselective ability of QUINAP, Brown et al. prepared and resolved the 6-(2′-diphenylphosphino-1′-naphthyl)phenanthridine[48] (PHENAP, **140** (Scheme 23).

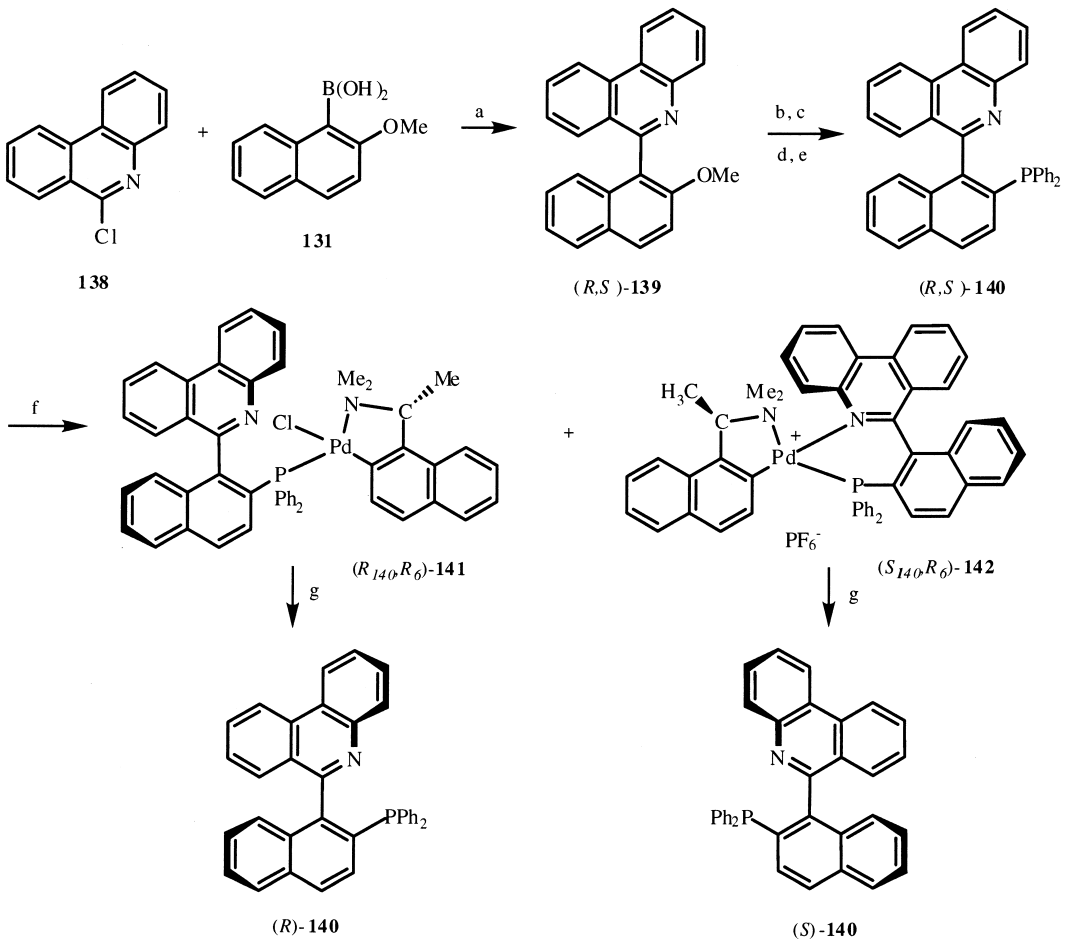
PHENAP was prepared following the methodology used for QUINAP, employing 6-chlorophenanthridine (**138**) as the



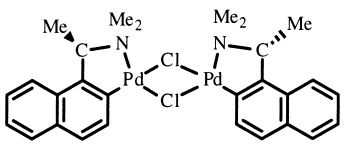
Scheme 22.

starting material (Scheme 23). A very different behaviour between PHENAP and QUINAP was, however, observed during the resolution procedure via the formation and separation of diastereomeric palladium-complexes. In this case, resolution via the C,N-palladocycle derived from (*R*)-*N*,*N*-dimethyl-α-methyl-1-naphthylamine led to the formation of the two defined complexes (R_{140},R_6)-**141** and (S_{140},R_6)-**142** with the (*S*,*R*)-form possessing a chelated ligand and the (*R*,*R*)-form open with only the phosphine coordinated. From both of these complexes, enantiopure (*S*)- and (*R*)-**140** were obtained.

Brown and co-workers,[49] in order to study the effects of the variation of ligand bite angle on reactivity and the selectivity of a catalytic reaction, successively modified the basic structure of QUINAP, replacing the naphthalene ring with that of indole. They synthesised the 1-methyl-2-diphenylphosphino-3-(1′-isoquinolyl)indole (**146**) according to Scheme 24. Pd-catalysed cross-coupling of 1-chloroisoquinoline (**130**) with the boronic acid **143**, prepared from the corresponding bromide, afforded **144** in high yield (84%). After deprotection and *N*-methylation, the key phosphinylation step was optimally carried out by using Schlosser's base to give the racemic phosphine **146** (85%). Attempts to resolve **146** by the previously described method used for QUINAP, led to the isolation of a single



a: $Pd(PPh_3)_4$, Na_2CO_3, DME reflux; 12 h, 89%;
b: BBr_3, CH_2Cl_2, 12 h, 81%;
c: Tf_2O, DMAP, CH_2Cl_2, 1 h, 72%;
d: $Pd(OAc)_2$, dppp, $Ph_2P(H)O$, $NaHCO_3$, DMSO, 80 °C, 20 h, 88%;
e: $HSiCl_3$, NEt_3, C_7H_8, reflux, 2.5 h, 81%;
f: (*R*)-**6**, MeOH, rt. then KPF_6, H_2O;
g: 1,2-bis(diphenylphosphino)ethane, CH_2Cl_2

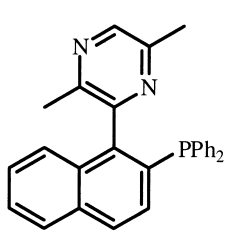


(*R*)-**6**

Scheme 23.

diastereomer in 99% yield. It was, therefore, apparent that both enantiomers of the ligand were able to form the same product, indicating that the new phosphinamine is stereochemically labile at ambient temperature and so is of little use in asymmetric catalysis.

More recently, in order to investigate the effect on the enantioselectivity of both the variation of the basicity of the nitrogen donor atom and the presence of a bulky substituent on C3 of QUINAP, Guiry has reported the synthesis and resolution of 2-(2-diphenylphosphine-2-naphthyl)-3,6-dimethylpyrazine (**148**). This compound, however, had an insufficient barrier to racemisation at room temperature, which precluded its application to asymmetric catalysis.[50]



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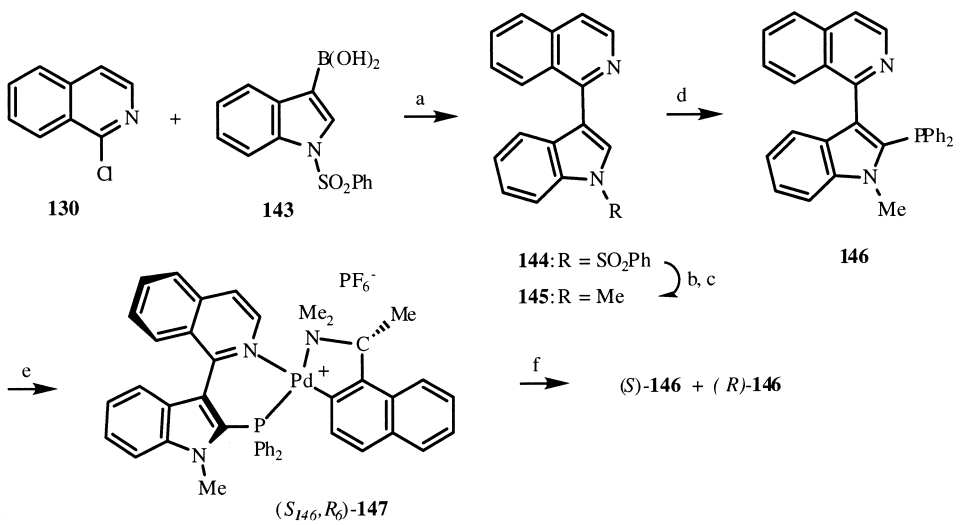
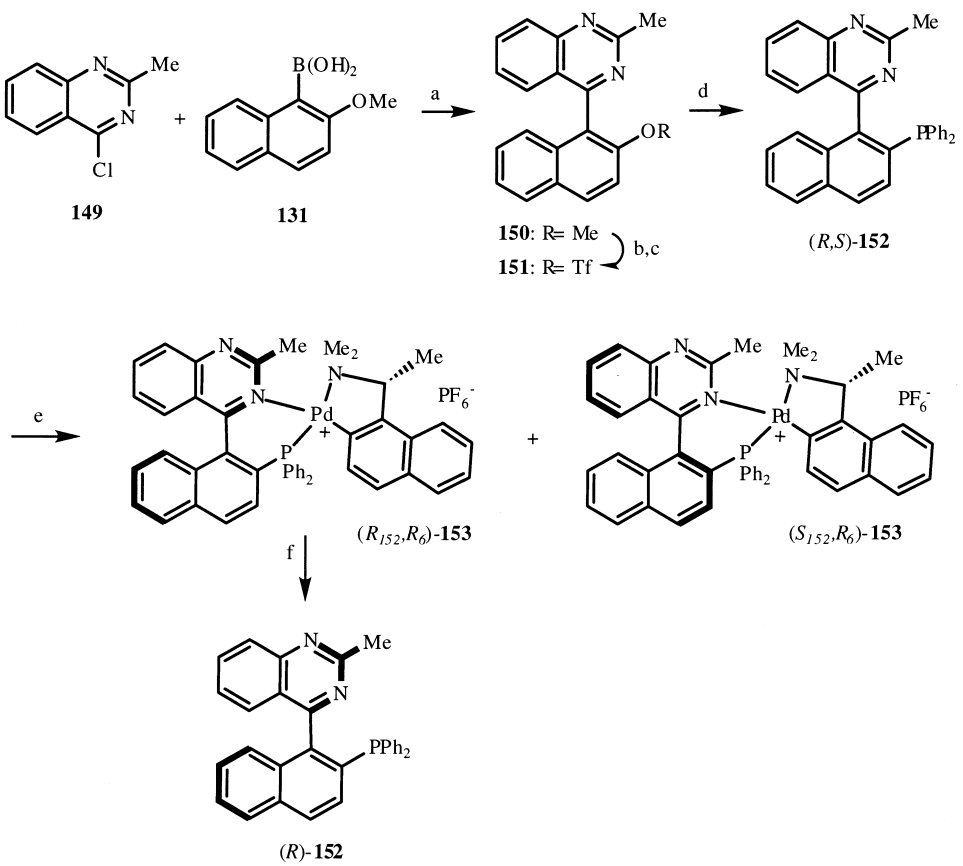
Next, 2-methyl- and 2-phenyl-4-(2-diphenylphosphine-1-naphthyl)quinazoline (2-methyl-quinazolinap **152**[51] and 2-phenyl-quinazolinap **157**[52]) (Schemes 25 and 26) were designed as efficient alternatives. The synthesis of these two axially-chiral ligands was similar to that previously reported for QUINAP and PHENAP, except for the metal-catalysed formation of the naphthyl-phosphorus bond. The 2-substituted 4-chloroquinazolines **149** and **154** were cross-coupled under Suzuki conditions with the boronic acid **131** to give the biaryls **150** and **155**, which were transformed into the triflates **151** and **156** in the usual way. Nickel(II)-catalysed coupling of **151** and **156** with diphenylphosphine directly



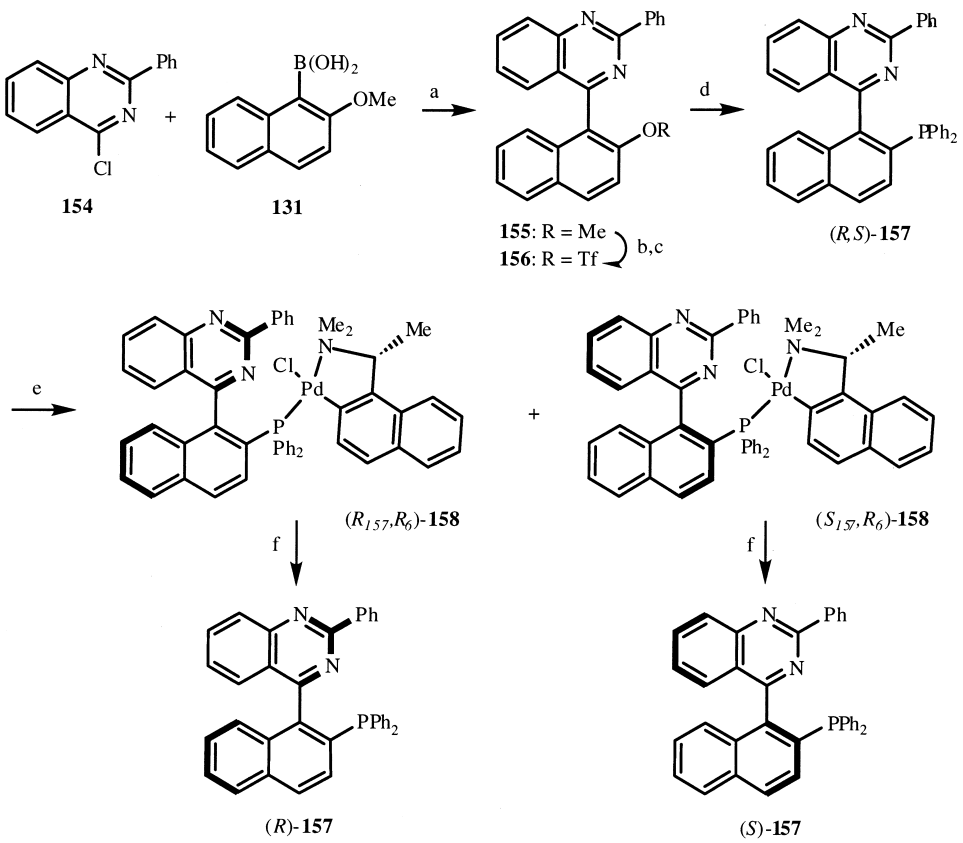
a: $Pd(PPh_3)_4$, Na_2CO_3, DME, MeOH, 84%; b: NaOH, MeOH, reflux, 84%; c: NaH, THF, MeI, 94%; d: BuLi, pentane, *t*-BuOK, THF, $ClPPh_2$, 85%; e: (*R*)-**6**, MeOH, rt. then KPF_6; f: 1,2-bis(diphenylphosphino)ethane, CH_2Cl_2.

Scheme 24.



a: $Pd(PPh_3)_4$, Na_2CO_3, DME, reflux, 72 h, 79%; b: BBr_3, CH_2Cl_2, 71%; c: Tf_2O, DMAP, CH_2Cl_2, 1 h, 79%; d: $HPPh_2$, $NiCl_2$(dppe), DABCO, DMF, 63%; e: (R)-**6**, MeOH, KPF_6, then fractional crystallisation; f: 1,2-bis(diphenylphosphino)ethane, CH_2Cl_2.

Scheme 25.

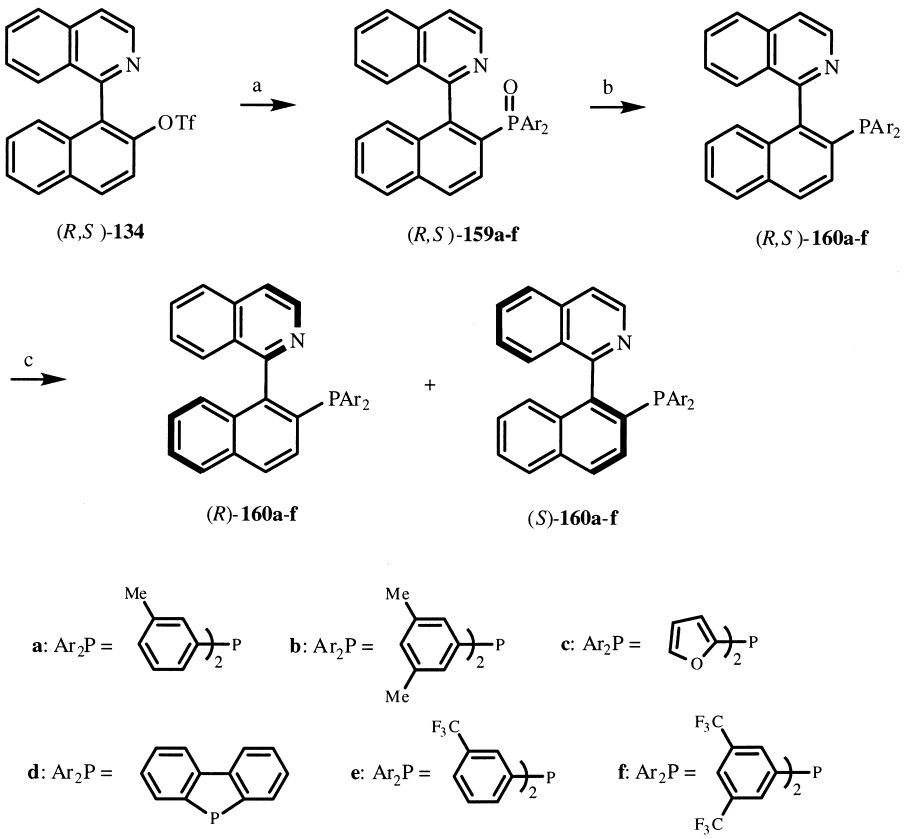


Scheme 26.

afforded **152** (63%) and **157** (74%), avoiding the formation of the intermediate *P*-oxide, which is produced when the Pd complex and diphenylphosphine oxide system is used.[53] Finally, the resolution of **152** and **157** was performed via the preparation and separation of diastereomeric Pd complexes derived from the ligands and (*R*)-**6**. A different behaviour was, however, observed for the two ligands because of their different steric demand. The performance of 2-methyl-quinazolinap was similar to that observed with QUINAP and it formed diastereomeric cationic Pd complexes (R_{152},R_6)- and (S_{152},R_6)-**153** (Scheme 25), which were separated by fractional crystallisation. The enantiopure ligand (*R*)-**152** was obtained by decomplexation of (R_{152},R_6)-**153** with dppe. The behaviour of 2-phenyl-quinazolinap resembled that of PHENAP due to their similar steric demand, treatment of 2-phenyl-quinazolinap with (*R*)-**102** affording a pair of neutral diastereomeric complexes (R_{157},R_6)- and (S_{157},R_6)-**158** (Scheme 26) in which only the phosphorus atom is coordinated to the palladium in the *trans* position with respect to the nitrogen donor atom of the resolving agent. These diastereomers were easily separated and then converted to the free phosphines in the usual way.

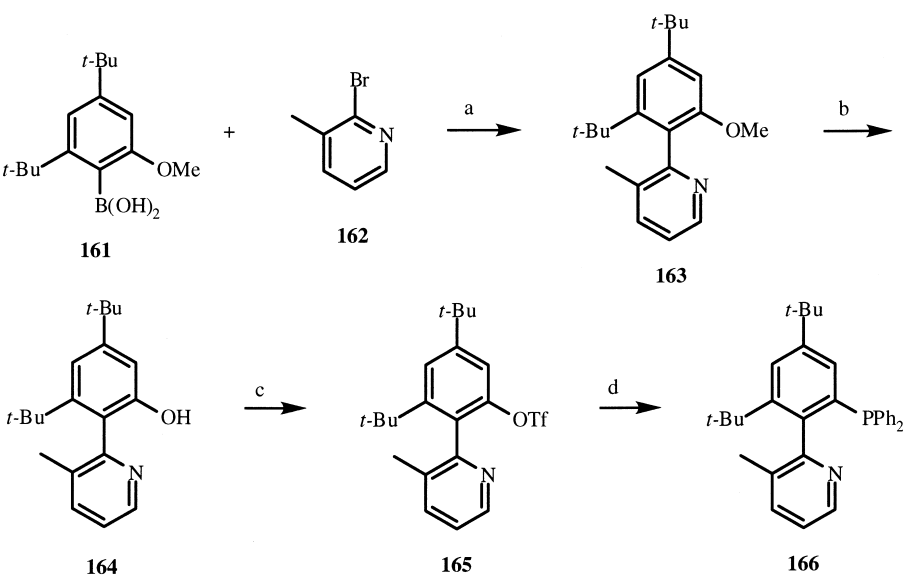
Brown modified the structure of BINAP in order to discover the effects of variation in the *P*-aryl substituents on catalysis.[54] The series of ligands **160a–f** were prepared by Pd-catalysed cross-coupling of the triflate **134** with the appropriate secondary phosphine oxide, followed by reduction with trichlorosilane (Scheme 27). For the phosphinylation step, considerable efforts were made to find an optimum procedure and it was found that diisopropylamine as the base and DMSO as the solvent afforded the best results. The resolution step was carried out by fractional crystallisation of diastereomeric C,N-palladocycle cationic complexes formed by the ligands with (*R*)-**102**, as previously described for BINAP. The order of crystallisation, however, was not predictable and, in the case of the furylphosphine **160c**, the specific rotation of the derived phosphine was anomalous, although the CD spectrum in the 220–350 nm region was as expected by comparison with the parent compound. This resolution procedure was unsuccessful with the phosphines **160e**,**f**.

In this account, the present authors wish to report a synthesis of the racemic compound **166**[55] that could be a very interesting ligand for asymmetric catalysis if resolved into enantiomers (Scheme 28). Racemic **163** was obtained by Suzuki cross-coupling of 2-bromo-6-methylpyridine (**162**) and the boronic acid **161** using $Pd(PPh_3)_4$ as the catalyst and potassium *tert*-butoxide as the base (83%).[56] Next, the triflate **165**, prepared in the usual way from **163**, underwent palladium-catalysed phosphination with triphenylphosphine which was used as the phosphinating reagent. This method



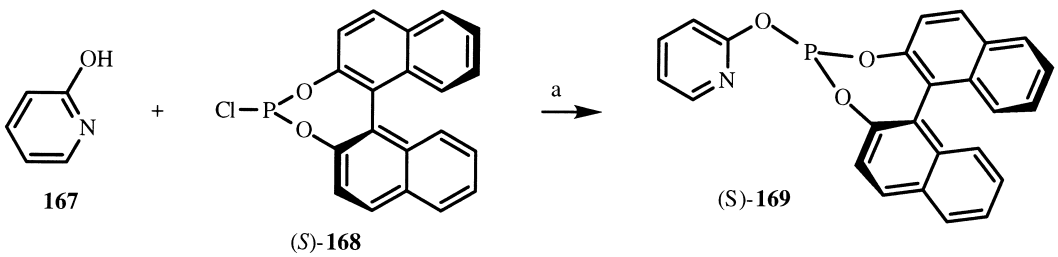
a: $Pd(OAc)_2$, dppe or dppp, $Ar_2P(H)O$, *i*-Pr_2NEt, DMSO, 90 °C, 20 h; b: $HSiCl_3$, NEt_3, toluene, reflux, 4 h, 43-73% yield in two steps; c: (*R*)-**6**, MeOH, KPF_6, rt, then diastereomer separation by fractional crystallisation, finally, 1,2-bis(diphenylphosphino)ethane, CH_2Cl_2.

Scheme 27.

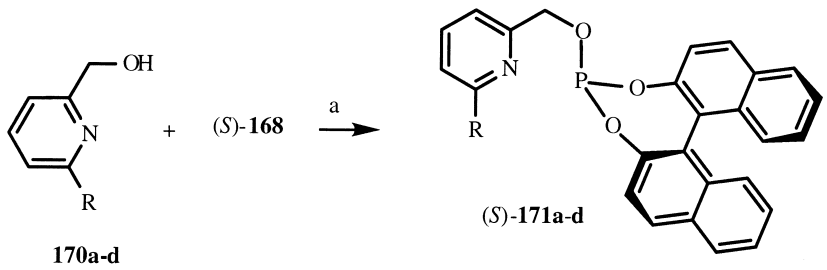


a: $Pd(PPh_3)_4$, KO'Bu, DME, reflux, 83%; b: PyHCl, 200 °C, 83%; c: Tf_2O;
d: $Pd(OAc)_2$, PPh_3, DMF, 110 °C, 4.5 d, 68%.

Scheme 28.

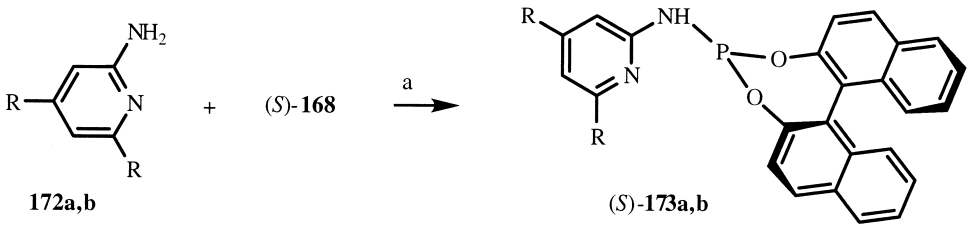


a: NEt_3,THF, 0 °C, 35%.



a: R = H; **b**: R = Me; **c**: R = Br; **d**: R = Ph

a: NEt_3, toluene, 0 °C, 78-80%.



a: R = H; **b**: R = Me

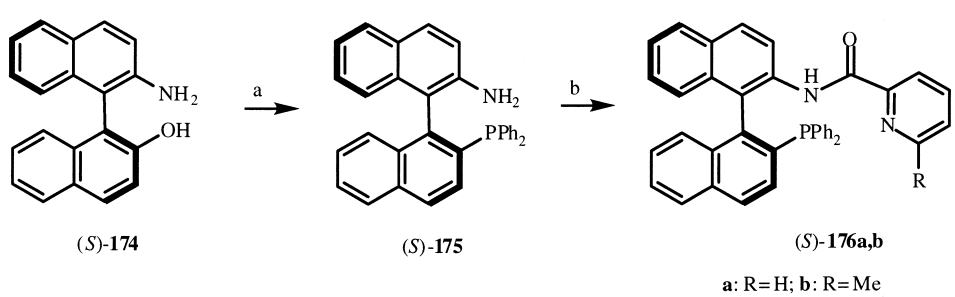
a: toluene, -10 °C, 58-77%.

Scheme 29.

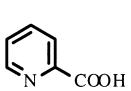
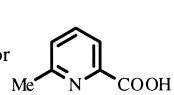
was developed by Chan et al., who also reported the synthesis of an array of atropisomeric P,N-ligands, related to **166**, possessing different dihedral angles and electronic properties.[55]

Faraone et al.[57,58] have reported the preparation of the atropisomeric P,N-ligands **169**, **171** and **173**, by the reaction of (*S*)-2,2′-binaphthol phosphorochloridite ((*S*)-**168**) with 2-pyridinone (**167**), the (6-substituted pyridin-2-yl)methanols **170a–d** and 2-aminopyridines **172a**,**b** (Scheme 29).

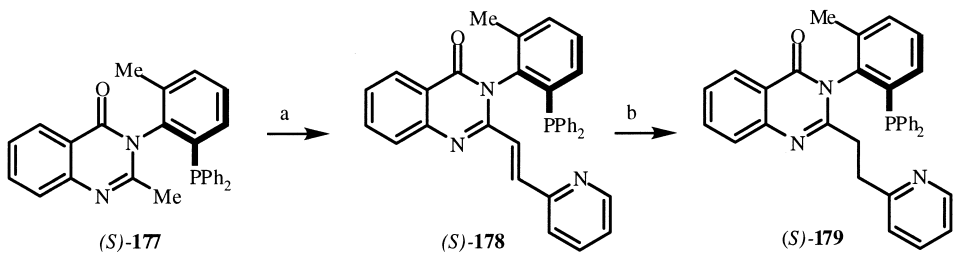
Zhang and co-workers investigated the application of the Cu-catalysed enantioselective conjugate addition of diethylzinc to enones using a new family of chiral P,N-ligands obtained by the combination of a diarylphosphane group with a substituted pyridine in a chiral binaphthyl backbone (Scheme 30).[59] The two ligands (*S*)-(+)-2-(2-pyridinylcarboxamido)-2′-(diphenylphosphanyl)-1,1′-binaphthyl (**176a**) and (*S*)-(+)-2-(6-methyl-2-pyridinylcarboxamido)-2′-(diphenylphosphanyl)-1,1′-binaphthyl (**176b**) were prepared in high yields (85–90%) by the reaction of 2-pyridinecarboxylic acid or 6-methyl-2-pyridinecarboxylic acid with the aminophosphine (*S*)-**175**, which was, in turn, synthesized from (*S*)-**174** according to a known procedure.[60]



a: R=H; **b**: R=Me

a: literature; b: DCC, DMAP, CH_2Cl_2,  or 

Scheme 30.

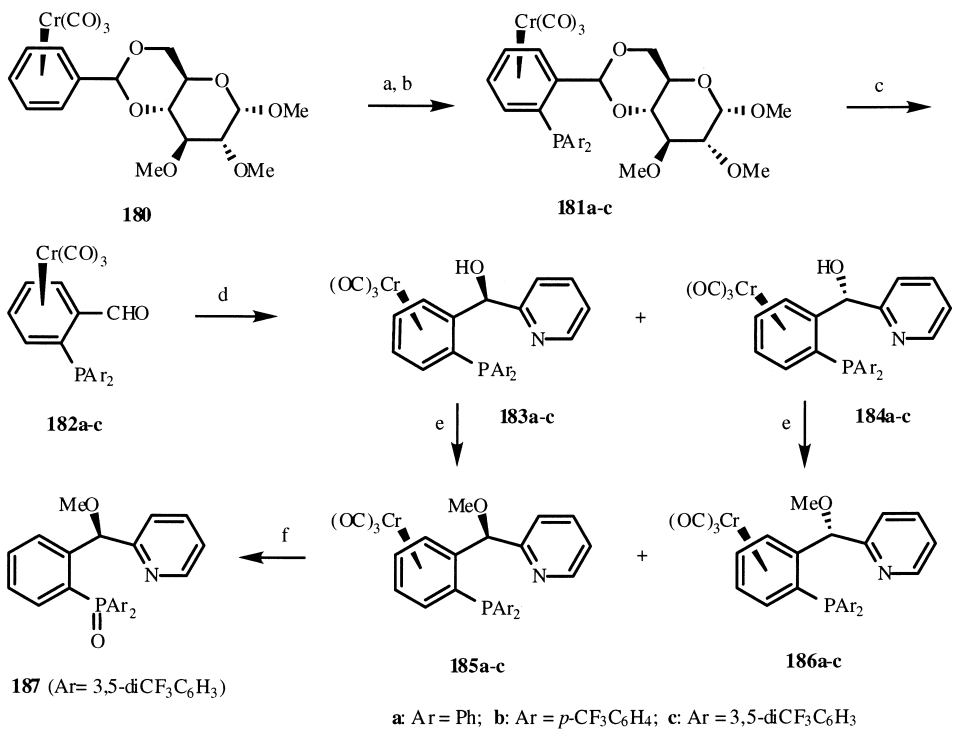


a: BuLi, THF, -78 °C, then 2-pyridinecarboxaldehyde, 78%; b: H_2, 10% Pd/C, 95%.

Scheme 31.

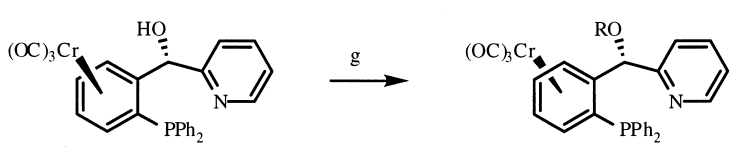
The major feature of these ligands is their relatively large bite angle when binding to transition metals. The rigid amide linker in **176** provides conformational rigidity of the biaryl ligand, which may be important for effective chiral induction.

Dai's group used the (*S*)-2-methyl-3-(2-diphenylphosphino-6-methylphenyl)-4(3*H*)-quinazolinone ((*S*)-**177**)[61] as the starting point for the synthesis of the atropisomeric chelate quinazolinone phosphine ligands (*S*)-**178** and (*S*)-**179** that are used in asymmetric allylic alkylation[62] (Scheme 31). The 2-methyl group of (*S*)-**177** was easily deprotonated with *n*-BuLi in THF at −78°C and subsequent treatment with 2-pyridinecarboxaldehyde afforded the bidentate ligand (*S*)-**178** in 78% yield after aqueous workup. Only the more thermodynamically favoured isomer with the *trans* double bond was formed. Finally, the saturated ligand (*S*)-**179** was easily obtained by hydrogenation of (*S*)-**178** in 95% yield.



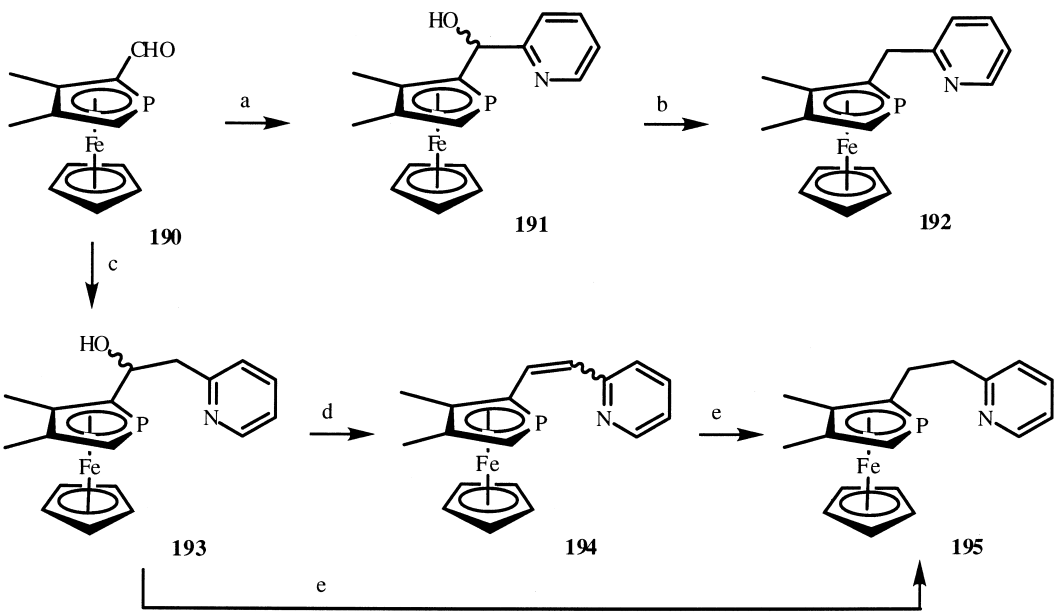
a: Ar = Ph; **b**: Ar = *p*-$CF_3C_6H_4$; **c**: Ar = 3,5-di$CF_3C_6H_3$

a: BuLi, Et_2O; b: Ar_2PCl; c: 50% H_2SO_4, THF or toluene, reflux; d: 2-pyridyllithium, Et_2O, - 78 °C; e: NaH, MeI, THF; f: I_2, THF.



g: NaH, BnBr or 4-$MeOC_6H_4CH_2Cl$, THF.

Scheme 32.



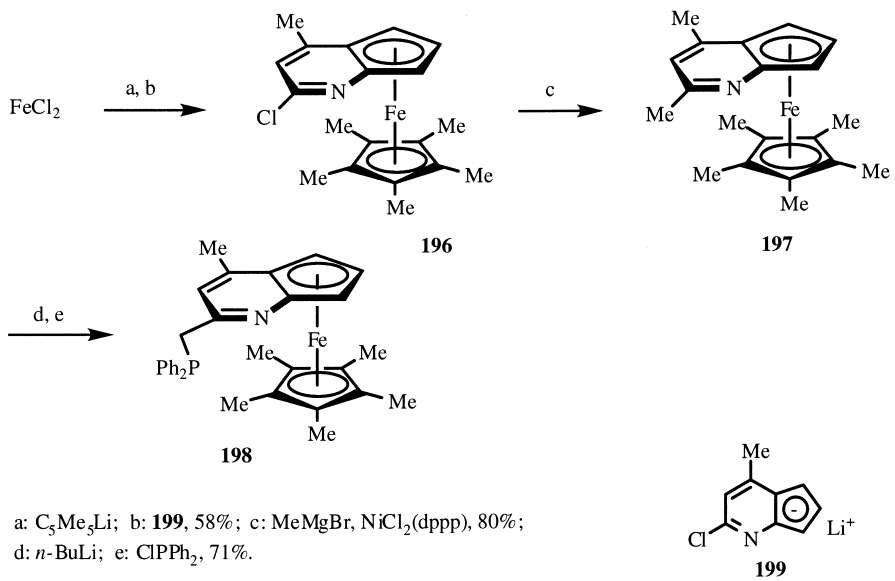
a: 2-pyridyllithium, Et_2O, 55%; b: $NaBH_4$, CF_3CO_2H, 64%; c: 2-(lithiomethyl)pyridine, THF, 77%; d: aqueous acidic conditions; e: $NaBH_4$, CF_3CO_2H, CH_2Cl_2, 80%.

Scheme 33.

2.3. Pyridine-phosphorus ligands with planar chirality

Three examples of (pyr-phos)-ligands with planar chirality have been reported. Chung et al.[63,64] described the synthesis of the planar chiral P,N-ligands **183**–**187**, bearing aryl-chromium tricarbonyl, phosphine and pyridine (Scheme 32). The synthesis of these ligands was based on the addition of 2-pyridyllithium to the optically active benz-aldehyde derivative **182** that was accessible from **181**, starting from the planar chiral known compound **180**.[65] The diastereomeric ratio of **183** and **184** was slightly dependent upon the substituent in the aryl phosphine moiety. As the number of electron-withdrawing substituents at phosphorus increases, the relative amount of **183** increases. The complexes **185** and **186** were obtained by deprotonation of **183** and **184** with NaH in THF, followed by the addition of MeI.[63] The *O*-benzyl and *O*-4-methoxybenzyl derivatives (**188** and **189**, respectively) of the complex **184a** were prepared by deprotonation of this complex, followed by treatment with benzyl bromide or 4-methoxybenzylchloride.[64]

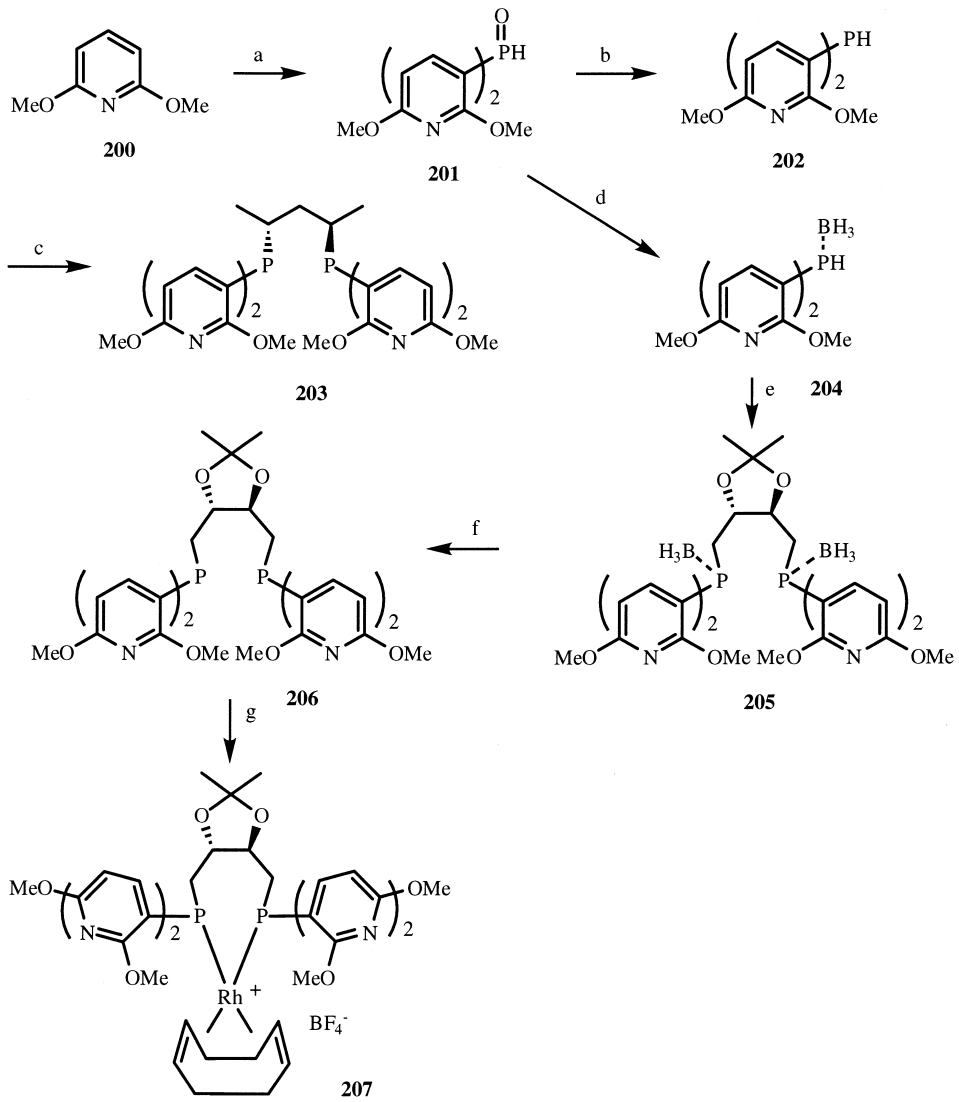
In order to understand the role of the $Cr(CO)_3$ moiety in the planar chiral ligand, Chung et al. carried out the demetallation of **185c**. Treatment of **185c** with an oxidising reagent, however, led to the isolation of the phosphine oxide **187** (Scheme 32).[63]



a: C_5Me_5Li; b: **199**, 58%; c: MeMgBr, $NiCl_2$(dppp), 80%; d: *n*-BuLi; e: $ClPPh_2$, 71%.

199

Scheme 34.

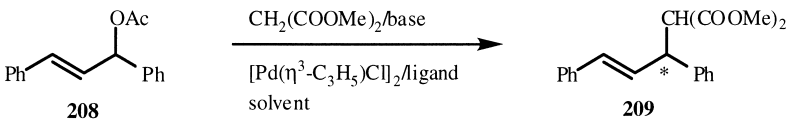


a: BuLi, THF, -40 °C, then $(EtO)_2POLi$, 80%; b: $HSiCl_3$, NEt_3, toluene, reflux, 76%;
c: LDA, THF, -78 °C, then (2S,4S)-pentanediol ditosylate, rt, 24 h, 39%; d:$LiAlH_4$-$NaBH_4$-$CeCl_3$, THF, then 2 N HCl, 54%; e: BuLi, THF, - 78 °C, then (2R,4R)-1,4-ditosyl-2,3-O-isopropylidenethreitol, rt, 12 h, 70%; f: DABCO, toluene, 40 °C, 4 h, 87%;
g: $[Rh(COD)_2]BF_4$, THF, 83%.

Scheme 35.

Ganter's group reported the synthesis of the pyridyl-substituted phosphaferrocenes **192** and **195**, as well as the coordination behaviour of these ligands toward transition-metal fragments.[66] As depicted in Scheme 33, the synthesis of the pyridyl ligands **192** and **195** was carried out starting from 2-formyl-3,4-dimethylphosphaferrocene (**190**),[67] which already proved to be a versatile building block for the synthesis of phosphaferrocene ligands.[68] Treatment of the aldehyde **190** with 2-pyridyllithium led to the alcohol **191** (83% de), which was deoxygenated with $NaBH_4$ and trifluoroacetic acid to yield the pyridylmethyl ligand **192**. The homologous pyridylethyl ligand **195**, with its backbone extended by a methylene unit, was obtained in an analogous reaction sequence when 2-(lithiomethyl)pyridine was employed as the nucleophilic reagent. If the work-up procedure for the preliminary alcohol **193** (60% de) was carried out under slightly acidic conditions, the formation of the olefin **194** (as a mixture of *E* and *Z* isomers) was observed by the elimination of water. The olefin can, however, be successfully transformed into the desired saturated ligand **195** by treatment with $NaBH_4$ and trifluoroacetic acid.

Fu and co-workers described the synthesis of the planar-chiral P,N ligand **198** (Scheme 34).[69] Treatment of $FeCl_2$ with C_5Me_5Li and then with 2-chloro-4-methyl-7*H*-cyclopenta[*b*]pyridinyllithium (**199**) afforded the ferrocene derivate **196**. Kumada coupling of **196** with MeMgBr



Scheme 36.

furnished **197**, which was lithiated and then quenched with $ClPPh_2$ to provide **198**, the enantiomers of which were readily resolved by chiral HPLC.

Finally, the present authors wish to report the synthesis of **203** and **206** that Chan's group employed in a study on hydrogenation.[70] Although these ligands behave as P,P-ligands, they incorporate the non-coordinating (2,6-dimethoxy)pyridin-3-yl group in their chiral skeleton.[71,72]

The synthetic route for the preparation of **203** is shown in Scheme 35.[71] The lithiation of 2,6-dimethoxypyridine (**200**) with BuLi at −40°C in THF followed by addition of lithium diethylphosphide gave the *P*-oxide **200** in 80% yield. The reduction of this compound with trichlorosilane in the presence of triethylamine afforded the phosphine **201** in good yield (76%). The air-stable ligand **203** was finally obtained in 39% yield by the reaction of the lithium salt of **202** with (2*S*,4*S*)-pentanediol ditosylate.

The adoption of this procedure for the preparation of the analogous ligand **205**[72] (Scheme 35) by the reaction of the lithium salt of **202** with (2*R*,4*R*)-1,4-ditosyl-2,3-*O*-isopropylidenethreitol, afforded very poor results (<5% yield). To overcome this problem, the phosphine borane-complex **204** was prepared through the reduction of the *P*-oxide **201** with the $LiAlH_4/CeCl_3/NaBH_4$ system (54%). Deprotonation of **204** with BuLi at low temperature, followed by the addition of the ditosylate, gave a high yield (70%) of the borane-complex **205** that by deboranation with DABCO was converted to the free ligand **206**. As the final step the rhodium-complex **207** was prepared by mixing **206** with 1 equiv. of $[Rh(COD)_2]BF_4$ in THF (83%).

3. Applications in asymmetric homogeneous catalysis

3.1. Allylic substitution

Palladium-catalysed asymmetric allylic substitution reactions have recently been the subject of a great deal of interest from the synthetic community due to their wide synthetic scope, practical simplicity and potential for asymmetric synthesis through the use of chiral ligands.[73] In this context, a number of P,N-ligands have now achieved high levels of stereocontrol.[2]

The alkylation of *rac*-1,3-diphenylprop-2-enyl acetate (**208**) with dimethyl malonate is used as the model reaction to compare the ability of new ligands to provide asymmetric induction in palladium-catalysed allylic substitutions (Scheme 36). This reaction is generally carried out using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as the procatalyst and sodium dimethyl malonate as the nucleophile in tetrahydrofuran solution. An alternative condition for the generation of the nucleophile entails the in situ treatment of dimethyl malonate with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in methylene chloride (Trost's procedure).[74]

In Table 1 are reported the results obtained in the reaction of *rac*-1,3-diphenylprop-2-enyl acetate with dimethyl malonate catalysed by palladium(0)-complexes of (pyr-phos)-ligands.

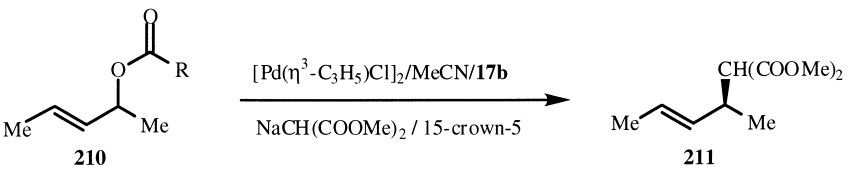
The palladium complexes of 2-(phosphinoaryl)pyridines **17a–f** were examined by Katsuki et al. in the alkylation of **208** with dimethyl malonate using Trost's procedure.[9] All ligands afforded the 1,3-diphenylprop-2-enyl malonate (**209**) in <3 h at room temperature and in quantitative yields. Enantiomeric excesses from 64 to 97% were recorded (Table 1). The most effective ligand was **17b**,

Table 1. Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate (**208**) catalysed by palladium(0) complexes of (pyr-phos)-ligands[a]

Ligand	Method[b]	Yield (%)	ee (%)	Config.	Reference
67	A	100	85	*R*	24a
69	A	100	87	*R*	24a
70	A	85	76	*R*	24a
71	A	78	12	*S*	24h
72	A	86	35	*S*	24h
74	A	91	33	*S*	24h
78	A	100	72	*S*	24h
82	A	83	78	*S*	24h
83	A	100	75	*S*	24h
48	A	99	7	*R*	14
17b	B	100	98	*S*	9
17d	C	100	96	*S*	9
29	B	96	71	*S*	12
28	C	95	68	*S*	12
23	C	87	37	*S*	12
30	C	92	50	*S*	12
192	D	65	19	*S*	66
195	D	80	11	*S*	66
183	C	91	90	*R*	63
184	C	86	69	*S*	63
185	C	95	89	*R*	63
186	E	83	93	*S*	63
(*S*)-**178**	F	65	87	*R*	62
(*S*)-**179**	F	68	78	*R*	62
(*S*)-**169**	C	94	0	-	57
(*S*)-**171b**	C	91	11	*S*	58
(*S*)-**173a**	C	93	37	*S*	58
117	A	97	75	*R*	75
56	D	85	26	*S*	20
57	D	81	58	*R*	20
60b	D	74	86	*R*	20
62	D	93	51	*R*	20
(*S*)-**136**	B	95	98	*R*	47
(*R*)-**140**	B	65	95	*S*	48

[a] Only representative examples are reported; for further examples, see the references cited in the table. The best stereochemical result obtained by each ligand is reported.

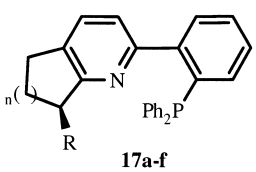
[b] Method A: $[Pd(C_3H_5)Cl]_2$, $CH_2(CO_2Me)_2$, BSA, KOAc, toluene; Method B: $[Pd(C_3H_5)Cl]_2$, $CH_2(CO_2Me)_2$, NaH, MeCN, 15-crown-5; Method C: $[Pd(C_3H_5)Cl]_2$, $CH_2(CO_2Me)_2$, BSA, AcOK, CH_2Cl_2; Method D: $[Pd(C_3H_5)Cl]_2$, $CH_2(CO_2Me)_2$, NaH, THF; Method E: $[Pd(C_3H_5)Cl]_2$, $CH_2(CO_2Me)_2$, NaH, DMF; Method F: $[Pd(C_3H_5)Cl]_2$, $CH_2(CO_2Me)_2$, NaH, CH_2Cl_2, 15-crown-5.



210 **211**

Scheme 37.

the Pd complex of which showed a very high enantioselectivity (97% ee) and good catalytic activity (reaction time: 30 min). An light improvement in the enantioselectivity (98% ee) was obtained when the reaction of the Pd-**17b** complex was carried out in acetonitrile at 0°C in the presence of 15-crown-5 by using NaH as the base instead of BSA.



17a-f

(n = 1): **a**: R = Ph; **b**: R = *i*-Pr; **c**: R = CMe_2OTBS
(n = 2): **d**: R = Ph; **e**: R = *i*-Pr; **f**: R = CMe_2OTBS

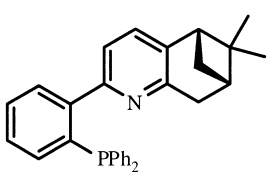
The same group next examined the allylic alkylation of 3-penten-2-yl acetate (**210**, R=Me), which is an unmanageable substrate among 1,3-dialkyl-substitued allyl acetates, using **17b** as the chiral source (Scheme 37). Several reaction conditions were explored, varying base, solvent and temperature. The best enantioselectivity (88% ee) was obtained by performing the reaction in acetonitrile at −15°C using NaH as the base in the presence of 15-crown-5 (Table 2). Although a good enantioselectivity was obtained under these reaction conditions, the chemical yield (36%) of the desired product **211** was unsatisfactory. In order to increase the yield, 1,3-dimethyl-substitued allyl substrates bearing alkyl carbonyloxy groups that are less potent leaving groups than the acetoxy group (**210**, R=OMe, OPr-*i* or OPh), were considered. When the phenyl carbonate was used as the substrate, an enantioselectivity of 93% ee in 85% yield was achieved (Table 2).

Although the 2-(phosphinoaryl)pyridines used by Katsuki afforded very good results in asymmetric allylic alkylations, their use is somewhat limited due to the difficulty of their preparation. With the aim of obtaining similar ligands more easily, the present authors prepared the related pyridine-phosphines **23** and **28**–**30** which assessed in the alkylation of **208** with dimethyl malonate.[12] Following Trost's procedure, these ligands were able to provide effective palladium catalysts and to give **209** in good yield and in low to moderate enantiomeric excess (37 to 70% ee). In an effort to increase the enantioselectivity of the reaction, two other methods for the generation of the malonate anion were checked using the most effective ligand **29**. When the reaction was carried out in acetonitrile with sodium malonate, generated using NaH, in the presence of 15-crown-5, a rapid reaction was observed (reaction time: 20 min), but the enantioselectivity remained unchanged (71% ee). On the other hand, the use of CH_2Cl_2 and tetrabutylammonium malonate, generated from dimethyl malonate and with the BSA/tetrabutylammonium fluoride system as the base, depressed both the reaction rate and enantioselectivity (66% ee).

Table 2. Allylic alkylation of **210** with dimethyl malonate catalysed by palladium–**17b** complex[a]

Substrate (R)	Temperature (°C)	Time	Yield (%)	ee (%)
Me	rt	40 min	66	82
Me	−15	72 h	36	88
Ome	rt	20 min	82	78
OPr-*i*	rt	25 min	75	81
Oph	−25	48 h	85	93

[a] Only representative examples are reported; for further examples, see Ref. 9.



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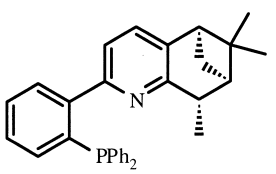

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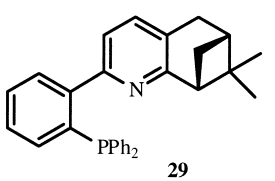

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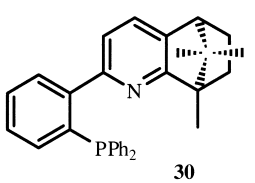
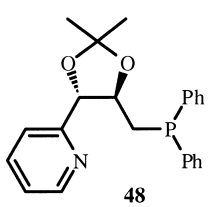


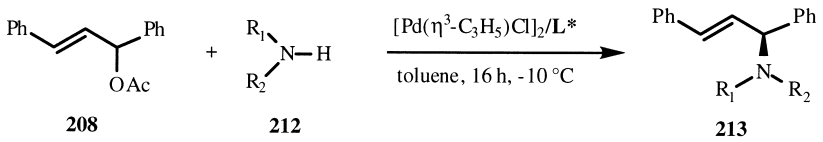
30

The present authors have assessed the ligand PYDIPHOS (**48**) in the allylic alkylation of **208**. A very good yield was obtained (99%), but the enantioselectivity (7% ee) was insignificant.[14]

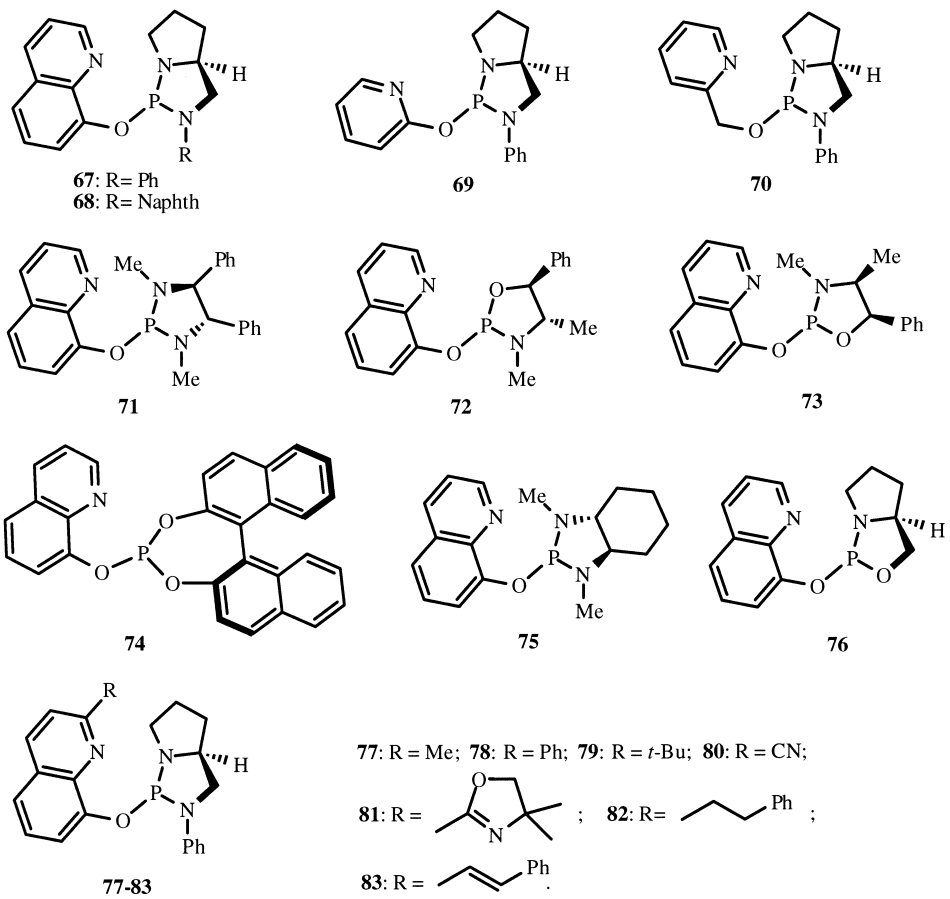


48

Buono's group evaluated the potential utility of (pyr-phos)-ligands as chiral controllers for enantioselective palladium-catalysed allylic substitutions.[24a] Initially, they examined the alkylation of **208** with dimethyl malonate using QUIPHOS (**67**) and a variety of solvents, temperatures and ratios of ligand to palladium. Under the best conditions (toluene, −10°C, **67**/Pd=4/1), a conversion of 100% and enantioselectivity of 85% ee were achieved (Table 1). These reaction conditions, employed with the ligands **69** and **70**, provided a level of enantioselectivity comparable to that obtained with the ligand **67** (Table 1).



Scheme 38.



These preliminary results prompted Buono to prepare and evaluate in this process a number of the quinoline–phosphine ligands (**71**–**83**) analogous to QUIPHOS, obtained by varying the nature of the chiral moiety and/or the substituents attached to the quinoline group.[24h]

The ligands **71**–**76**, obtained by replacement of the (*S*)-2-anilinomethylpyrrolidine moiety of **67** with other groups, led to a significant decrease in both the catalytic activity and stereodifferentiating ability (Table 1). On the other hand, the enantioselectivity recorded with ligands **77**–**83**, bearing a substituent on the C8 of the quinoline ring, was less than that seen with the parent QUIPHOS (Table 1).

The asymmetric allylic amination of 1,3-diphenylprop-2-enyl acetate **208**, to the desired product **213**, with primary or secondary amines **212** (Scheme 38) was carried out with the palladium-phosphine complex **67**–**70** catalysts by Buono's group.[24b] High enantioselectivities of up to 94% were observed using benzylamine, veratrylamine or morpholine as the nucleophiles (Table 3).

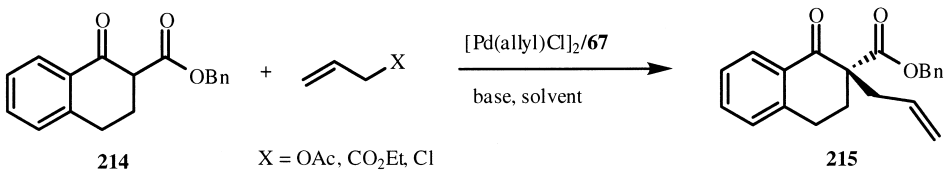
On the basis of these results, the same group next evaluated in this process the quinoline–phosphine ligands **71**–**83** using benzylamine as the nucleophile.[24h] The ligands **71**–**76**, however, produced a dramatic decrease in both the yield and enantiomeric excesses, with the best result being obtained with ligand **75** (56% yield, 29% ee) (Table 3). No improvement in the enantioselectivity was obtained with the QUIPHOS derivatives **77**–**83** (Table 3).

Buono's group investigated the asymmetric formation of

Table 3. Enantioselective palladium-catalyzed allylic amination alkylation of 1,3-diphenylprop-2-enyl acetate (**208**) with various amines **212**[a]

Ligand	Amine	Conv. (%)	ee (%)	Config.	Reference
67	$PhCH_2NH_2$	95	93	*S*	24b
68	$PhCH_2NH_2$	36	78	*S*	24b
69	$PhCH_2NH_2$	70	92	*S*	24b
70	$PhCH_2NH_2$	95	93	*S*	24b
67	Veratrylamine	97	94	*S*	24b
67	Morpholine	88	88	*S*	24b
75	$PhCH_2NH_2$	56	29	*R*	24h
77	$PhCH_2NH_2$	100	42	*R*	24h
78	$PhCH_2NH_2$	100	64	*R*	24h
80	$PhCH_2NH_2$	95	74	*R*	24h

[a] Only representative examples are reported; for further examples, see the references cited in the table.



Scheme 39.

quaternary centres by alkylation of allylic acetates with prochiral β-ketoesters using the palladium(0) complex with QUIPHOS as the catalyst.[24f]

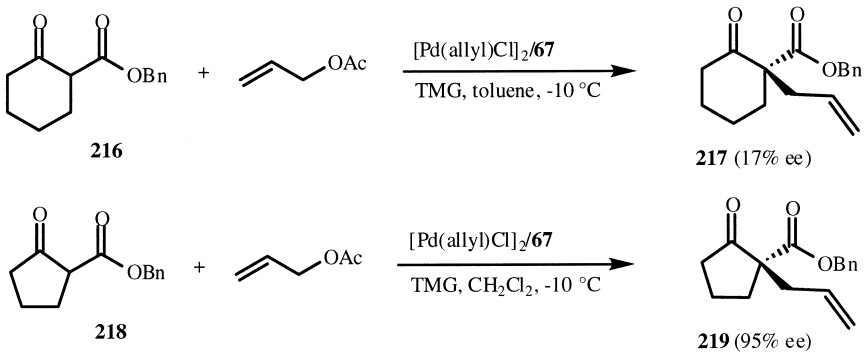
The reaction of 2-benzyloxycarbonyl tetralone (**214**) with allyl acetate was initially investigated (Scheme 39). Several experiments were explored and under the optimum conditions (toluene, −10°C and 1,1,3,3-tetramethylguanidine (TMG) as the base) the compound **215** was obtained in 89% yield and 54% ee.

Next, Buono et al. examined the alkylation of the β-ketoesters **216** and **218** (Scheme 40). Whereas, the six-membered cyclic β-ketoester **216** afforded **217** with disappointing results, the five-membered cyclic β-ketoester **218** produced **219** in 75% yield and 95% ee.

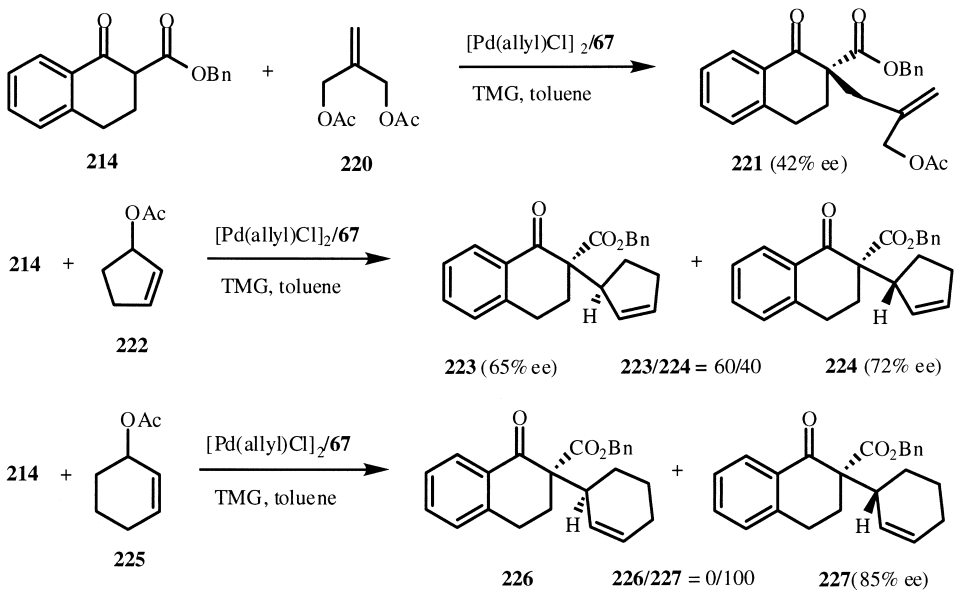
Finally, the same workers explored other allylating agents such as the bis-acetate **220** and the cyclic allyl esters **222** and **225** (Scheme 41). The diacetate **220** led to the formation of **221** in 79% yield and 42% ee. The cyclic ester **222** led to the formation of the diastereomers **223** and **224** (60:40 ratio) in quite good enantioselectivities (65 and 72% ee, respectively). In contrast, the ester **225** provided only the diastereomer **227** in 78% yield and 85% ee.

Buono's group have also investigated the desymmetrisation of 2,3-bis(acetoxymethyl)bicyclo[2.2.1]hepta-2,5-diene (**228**) using palladium(0)-catalysed amination (Scheme 42).[24d]

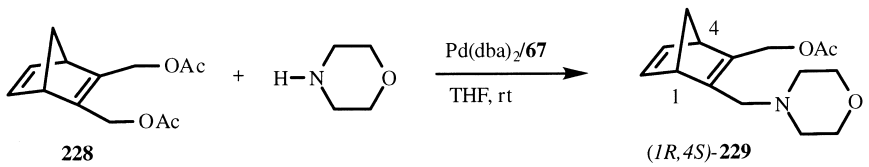
They initially determined the effect on the reaction of different secondary amines as nucleophiles, of various



Scheme 40.



Scheme 41.



228 (*1R,4S*)-**229**

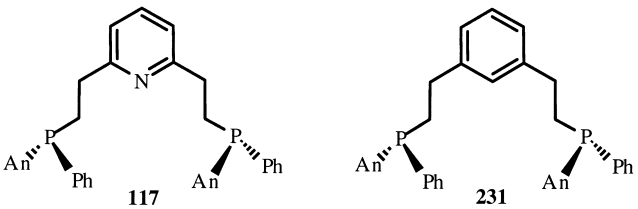
Scheme 42.

tertiary amines as acceptor bases and of a series of organophosphorus ligands complexed to the palladium. Among the ligands examined, the alkyl phosphites, alkylarylphosphites and aryl-aminophosphines were the most promising. Next, they investigated the enantioselective amination reaction of **228** with morpholine as the nucleophile using a number of chiral organophosphorus ligands. The best results were obtained with QUIPHOS, leading to the monoaminated product (1*R*,4*S*)-**229** in 93% yield and 89% enantiomeric excess, which was found to be independent of the presence or absence of the acceptor base (NEt_3). The absolute configuration was determined by chemical correlation from the corresponding known acetoxy derivative.

Two types of potentially tridentate ligands based on the pyridine framework have been applied in allylic alkylation reactions. These consist in a set of N,N,P-ligands bearing stereogenic centers on carbon atoms and of a P,N,P-ligand with two stereogenic phosphorus atoms.

The N,N,P-ligands **56**, **57**, **60a–c**, and **62**, assessed in the allylic alkylation of **208** following a standard procedure ($[Pd(C_3H_5)Cl]_2$, $NaCH(CO_2Me)_2$, THF), afforded low to moderate enantiomeric excesses (26–77%) at 0°C.[20] The ligands **56** (26% ee, (*S*)) and **57** (58% ee, (*R*)), differing from the configuration of the stereocentre in the pyrrolidine ring, gave opposite enantiomers of **209**, indicating that the absolute configuration of the product is controlled by the chirality of the pyrrolidine moiety. The introduction of an aryl group on the C6 of the pyridine ring increased the selectivity up to 75–77% ee. When the reaction was carried out at −40°C the selectivity was increased up to 86% ee (ligand **60c**). Interestingly, ligand **62** (51% ee) with only one stereogenic center gave a stereochemical outcome very similar to ligand **57**. These ligands possess three possible electron-donor atoms and different modes of coordination to the palladium are therefore possible. Unexpectedly, the phenyl ligand **230** afforded enantiomeric excess (73% ee) similar to **57**, indicating that the pyridine nitrogen is not necessary for a high selectivity. This suggests that the Pd-complex is formed with bonding via the phosphorus atom and nitrogen atom of the pyrrolidine and not the pyridine ring nitrogen.

Zhang et al. prepared the ligand **117** based on 2,6-disubstituted pyridine and examined its palladium complex in the allylic alkylation of **208**.[75] Although the reaction was carried out using a range of conditions, the enantioselectivity never exceeded 75% ee (BSA, KOAc, toluene, −40°C). The ligand **117** can adopt a tridentate (P,N,P-coordination) or bidentate (P,P- or P,N-coordination) chelate mode to afford a π-allylpalladium 18- or 16-electron species, respectively. In order to understand which coordination geometry is responsible for the enantioselective alkylation, the ligand **231**, where the pyridine group has been replaced by a benzene ring, was synthesised. This bidentate ligand afforded the same enantioselectivity as **117**, indicating that the π-allylpalladium with the potential tridentate ligand **117** prefers the coordination with two phosphine ligands to form a 16-electron species and that the pyridine does not coordinate to palladium in this intermediate. This deduction was supported by the ^{31}P NMR spectrum of the catalytic precursor ($[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and **117**) which showed a single signal, indicating that the two phosphine groups are in magnetically equivalent environments.

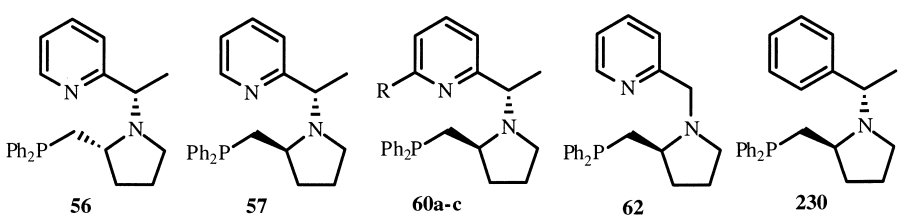


117 **231**

Two examples of (pyr-phos)-ligands with planar chirality have been synthesised and used in palladium-catalysed asymmetric allylic substitution.

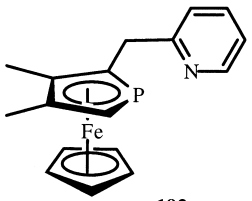
The alkylation of **208** with sodium dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and the ligands **192** and **195** in THF was complete after 3 h.[66] The reaction product **209** was isolated in 65–85% yields, but the enantiomeric excesses were only 19 and 11%, respectively.

More interesting results were obtained with the ligands **183–187**.[63] The allylic alkylations, carried out under Trost's protocol at 0°C, afforded high yields of **209**. The absolute configuration of the product was controlled by the

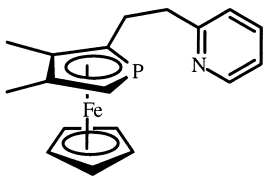


56 **57** **60a-c** **62** **230**

a: R = Ph; **b**: R = 3,5-diMePh;
c: R = 2,6-diMePh



192



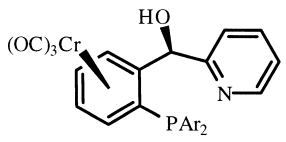
195

absolute configuration at the stereogenic centre of the benzylic carbon, so that the preferred formation of (*R*)-**209** resulted by using the ligands **183** and **185**, and that of (*S*)-**209** by using **184** and **186**. The enantioselectivities observed with **183** (up to 90% ee) and **185** (up to 89% ee) were greater than those for **184** (up to 69% ee) and **186** (up to 89% ee). In addition, an increasing enantioselectivity was generally recorded as the number of electron-withdrawing substituents in the arylphosphine increased. The effect of variation of both the solvent and base on the reaction with the ligands **183b** and **186b**,**c** was studied. Significant effects on the reaction time, yield and enantioselectivity were observed. An increasing of the enantioselectivity was recorded with **186b** (from 72 to 80% ee using THF as the solvent and NaH as the base) and **186c** (from 89 to 93% ee using DMF as the solvent and NaH as the base). Finally, in order to study the role of the $Cr(CO)_3$ moiety in the planar chiral ligand, the phosphine oxide **187** was assessed, but it was inactive in the allylic alkylation.

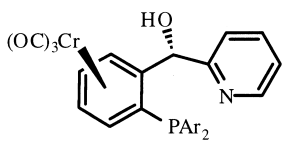
Examples of chiral (pyr-phos)-ligands, the chirality of which stems from the presence of an axis of chirality have been reported in allylic alkylation reactions.

Dai et al. have examined the atropisomeric ligands (*S*)-**178** and (*S*)-**179** in the allylic alkylation of **208** under a variety of conditions.[62] The optimised conditions were found by using NaH as the base in the presence of 15-crown-5 in CH_2Cl_2. Under these conditions, a moderate yield (65%) and a good enantiomeric excess (87%) were obtained with the ligand (*S*)-**178**. In contrast, with the ligand (*S*)-**179**, the product **209** was obtained in satisfactory yield (67%), but in a lower enantiomeric excess (78%). This result suggests that the palladocycle formed from the palladium centre and the ligand (*S*)-**179** is more flexible, decreasing the control of the enantiomeric excess.

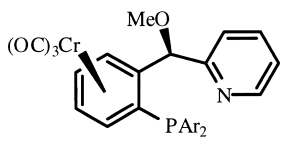
On the other hand, ligands (*S*)-**169**, (*S*)-**171a–d** and (*S*)-**173a**,**b**, based on the chiral 1,1′-binaphthol structure,



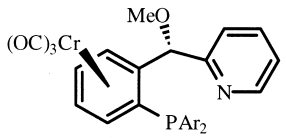
183a-c



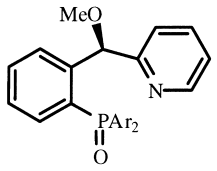
184a-c



185a-c

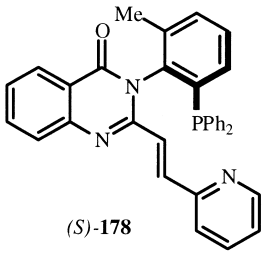


186a-c

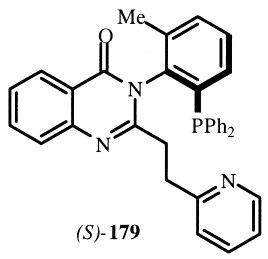


187 (Ar = 3,5-di$CF_3C_6H_3$)

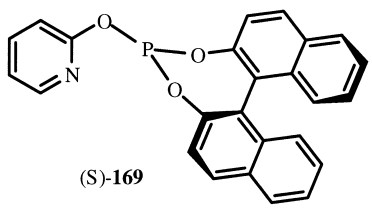
a: Ar = Ph;
b: Ar = *p*-$CF_3C_6H_4$;
c: Ar = 3,5-di$CF_3C_6H_3$



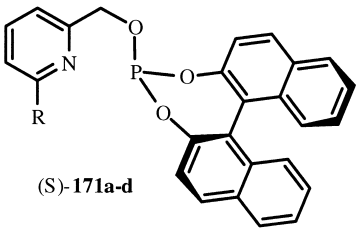
(*S*)-**178**



(*S*)-**179**

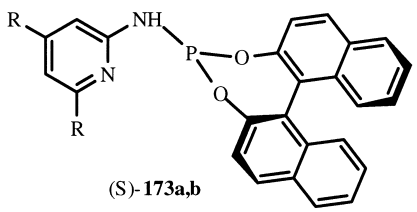


(S)-**169**



(S)-**171a-d**

a: R = H; **b**: R = Me; **c**: R = Br; **d**: R = Ph

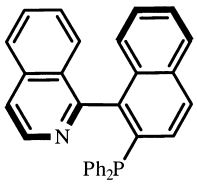


(S)-**173a,b**

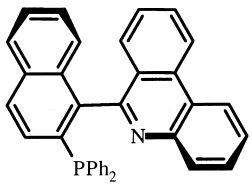
a: R = H; **b**: R = Me

gave **209** in good yield (90–95%), but with a low enantioselectivity (0–37% ee).[57,58]

Brown and co-workers applied the Pd complexes of 1-(2-diphenylphosphino-1-naphthyl)isoquinoline (QUINAP, **136**), an atropisomerically-chiral P,N-ligand based on a biaryl linkage between isoquinoline and 2-naphthylphosphine rings, in asymmetric allylic alkylation.[47]



(*S*)-QUINAP **136**



(*R*)-PHENAP **140**

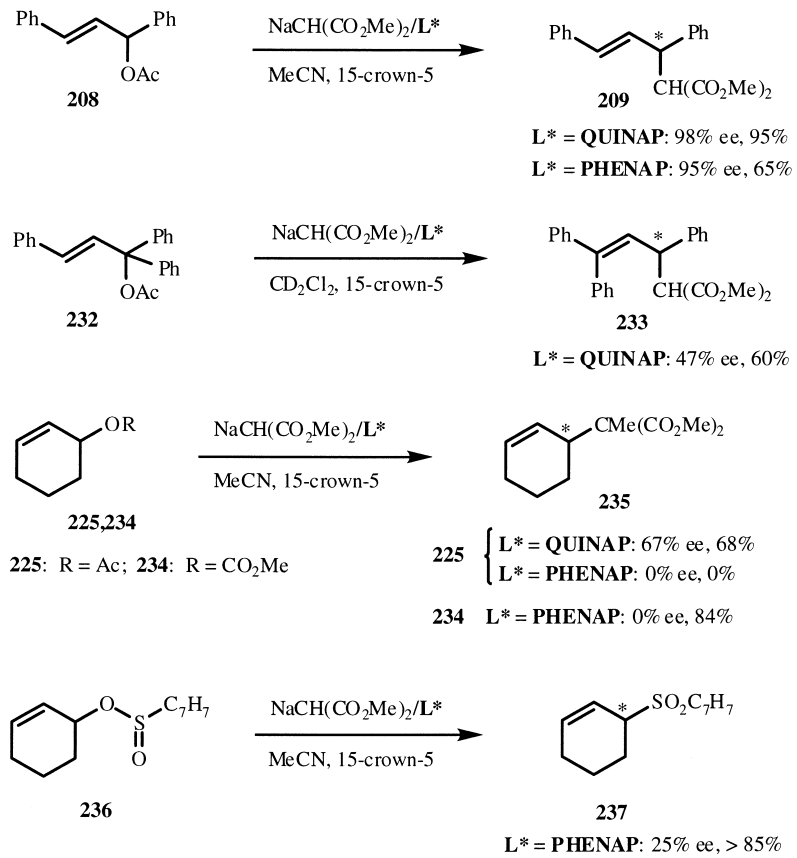
Tetrafluoroborate allylpalladium complexes of the ligand (*S*)-**136** with allylpalladium chloride and its mono-, 1,3-di- and 1,1,3-triphenyl analogues were prepared and used in the alkylation with dimethyl malonate. Initially, the alkylation was carried out of **208** using Trost's procedure and it was found that the level of asymmetric induction was essentially independent of the solvent, varying between 75 and 78% ee. A small effect on the enantiomeric purity of the product was also observed when the reaction was performed using the sodium or lithium salts of dimethyl malonate under a variety of solvents.

A significant enhancement in the enantioselectivity was, however, found when the reaction of **208** with NaCH$(CO_2Me)_2$ in MeCN was carried out in the presence of 15-crown-5 (95% ee at 20°C). A further improvement was finally effected by performing the reaction at −13°C (98.2% ee).

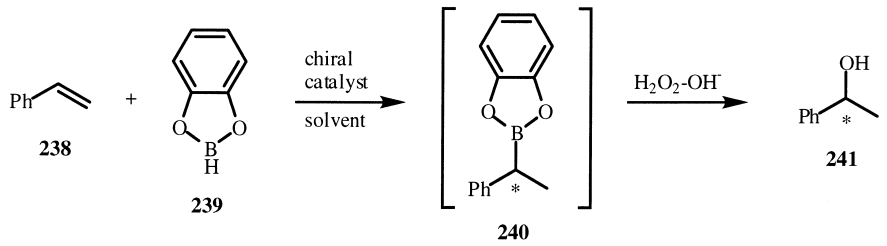
Under these optimised conditions, other substrates were then examined. The triphenylpropenyl acetate **232** afforded the product **233** (Scheme 43) in 60% yield and 47% ee, but the reaction rate was markedly slower than that of the diphenyl analogue, requiring 4 days to be complete.

Additionally, with 2-cyclohexenyl acetate **225** (Scheme 43), the reaction was rather slow (68% yield in 16 h) and the enantiomeric purity of the product was modest (67% ee).

The same group, after envisaging from a mechanistic study the importance of the role played by the 3-H of the isoquinoline of QUINAP in determining the steric course of the reaction, modified the structure of this ligand by replacing the 3-H with a larger substituent. The ligand 6-(2-diphenylphosphino-1-naphthyl)phenanthridine (PHENAP, **140**), bearing a benzo-fused ring on the 3,4-positions of the isoquinoline ring, was prepared and assessed in this process.[48] Under the previously-optimized conditions, PHENAP gave a slightly reduced enantioselectivity in the reaction of **209** with respect to QUINAP (95 vs. 98% ee), but it was more effective under the base-free conditions introduced by Trost (94 vs 76% ee). Unexpectedly, this ligand was unreactive towards the alkylation of **225** and, with the more reactive carbonate **234**, the desired



Scheme 43.



Scheme 44.

product **235** was produced in 84% yield as a racemate. The intramolecular palladium-catalysed rearrangement of the allylsulfinate **236** was also examined. No reaction was apparent at room temperature, but it was complete in few minutes at 60°C, giving the enantiomeric enriched sulfone **237**, albeit in moderate enantiomeric excess (25%) (Scheme 43).

3.2. Hydroboration

Catalysed asymmetric hydroboration of alkenes is becoming a valuable procedure for the synthesis of chiral secondary alcohols.[76] Catecholborane is the most useful borane and rhodium complexes are the most effective catalysts. The standard test reaction for comparing the

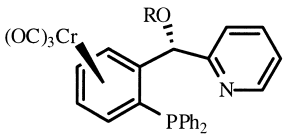
Table 4. Hydroboration of olefins catalysed by Rh complexes containing (py-phos)-ligands[a]

Catalyst	Substrate[b]	Temperature (°C)	*sec*-Alcohol[c] (%)	Yield[d] (%)	ee (%)	Configuration	Reference
[Rh(COD)2]BF4/**184a**	**257**	0	–	45	14	*S*	64
[Rh(COD)$_2$]BF$_4$/**186a**	**257**	0	–	72	84	*R*	64
[Rh(COD)$_2$]BF$_4$/**188**	**257**	−15	–	41	84	*R*	64
[Rh(COD)$_2$]BF$_4$/**189**	**257**	0	–	39	61	*R*	64
[Rh(COD)$_2$]BF$_4$/**188**	**263**	0	–	93	84	*R*	64
[Rh(COD)$_2$]BF$_4$/**188**	**259**	0	–	31	73	*R*	64
[Rh(COD)$_2$]BF$_4$/**188**	**258**	0	–	31	86	*R*	64
(*R*)-**243**	**250**	rt	93	81	92	*R*	79
(*R*)-**243**	**251**	rt	97	81	86	*R*	79
(*R*)-**243**	**252**	rt	97	75	89	*R*	79
(*S*)-**246**	**255**	rt	96	67	79	*S*	79
(*R*)-**223**	**257**	rt	96	82	94	*R*	79
(*S*)-**246**	**260**	rt	92	81	72	*S*	79
(*S*)-**246**	**261**	rt	95	80	77	*S*	79
(*R*)-**243**	**262**	rt	92	77	80	*R*	79
(*S*)-**246**	**267**	rt	97	82	83	*S*	79
(*S*)-**246**	**268**	rt	97	76	83	*S*	79
(*S*)-**246**	**269**	rt	92	82	74	*S*	79
(*R*)-**243**	**270**	rt	71	80	82	*R*	79
(*S*)-**246**	**271**	rt	61	77	89	*S*	79
(*R*)-**243**	**272**	rt	91	80	89	*R*	79
(*S*)-**246**	**274**	rt	91	72	75	*S*	79
(*R*)-**243**	**281**	rt	–	67	86	*R*	79
(*R*)-**243**	**282**	rt	99	78	96	*R*	79
(*S*)-**246**	**283**	rt	99	80	78	*S*	79
(*R*)-**243**	**284**	rt	96	82	90	*R*	79
(*R*)-**248**	**257**	rt	–	70	67	*R*	78
(*R*)-**248**	**282**	rt	–	69	84	*R*	78
(*R*)-**248**	**283**	rt	–	59	64	*R*	78
(*R*)-**248**	**284**	rt	–	57	74	*R*	78
(*R*)-**249**[e]	**238**	0	80	100[f]	79	*R*	80
(*R*)-**249**[e]	**257**	0	77	91[f]	81	*R*	80
(*R*)-**249**[e]	**266**	0	83	100[f]	49	*R*	80
(*R*)-**249**[e]	(*E*)-**277**	25	91	100[f]	94	*R*	80
(*R*)-**249**[e]	(*Z*)-**277**	25	92	100[f]	91	*R*	80
(*R*)-**249**[e]	(*E*)-**278**	0	89	72[f]	92	*R*	80
(*R*)-**249**[e]	(*E*)-**279**	0	91	65[f]	93	*R*	80
(*R*)-**249**[e]	(*E*)-**280**	25	–	0[f]	–	–	80
(*R*)-**249**[e]	(*Z*)-**280**	25	0	100[f]	62	*R*	80

[a] Only representative examples are reported; for further examples, see the references cited in the Table. The best stereochemical result obtained by each ligand is reported.
[b] For the related structures, see Scheme 46.
[c] Benzylic position.
[d] Benzylic *sec*-alcohol.
[e] (*R*)-**249** was prepared in situ by adding $CF_3SO_3SiMe_3$ to a solution of (1,5-cyclooctadiene)(2,4-pentanedionate)rhodium(I) and (*R*)-**157**.
[f] Conversion.

ability of new ligands to provide asymmetric induction in this process is that between styrene (**238**) and catechol borane (**239**) in the presence of a chiral catalyst followed by oxidation with alkaline hydrogen peroxide of the unisolated catecholborate ester **240** to form the alcohol **241** (Scheme 44).

The application of rhodium complexes containing chiral (pyr-phos)-ligands in the hydroboration of vinylarenes has furnished very good results in terms of regioselectivity, yield and enantioselectivity.



184a: R = H; **186a**: R = Me; **188**: R = Bn;
189: R = 4-MeOC$_6$H$_4$CH$_2$

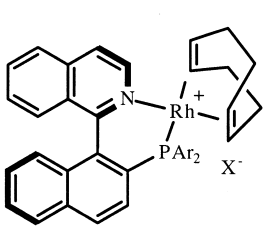
Rhodium complexes with the ligands **184a**, **186a**, **188** and **189** have been examined by Chung et al. with regard to the catalytic activity and enantioselectivity in the reaction of vinylarenes with catecholborane.[64] The reactions were carried out using 1.2 equiv. of catecholborane, 0.02 equiv. of [Rh(COD)$_2$]BF$_4$, 0.024 equiv. of the ligand in THF at 0°C for 18 h, followed by oxidation with alkaline hydrogen peroxide. Under these conditions, the hydroboration of 4-methoxystyrene with the ligands **186a** and **188** afforded the corresponding *sec*-alcohol in good yield and enantioselectivity (up to 84% ee), whereas the other two ligands were less effective (Table 4). On the basis of these results, the ligand **188** was used for the hydroboration of the other styrene derivatives, 4-bromostyrene, 3,4-dimethoxystyrene and 2,4-dimethylstyrene. All substrates afforded a good enantioselectivity (73–86% ee) that unexpectedly was not very sensitive to the electronic effect of the substituent on the styrene ring (Table 4). On the other hand, a very high yield was obtained only when 4-bromostyrene, was used.

Brown et al. in a series of papers demonstrated the potential of rhodium complex of QUINAP and its derivatives in the hydroboration of various alkenes with catecholborane.[77–79] In preliminary experiments, they prepared, by treatment of QUINAP with [Rh(COD)(acac)]–$CF_3SO_3SiMe_3$ or [Rh(COD)$_2$]BF$_4$, the Rh complexes **242** and **243** which were used in the hydroboration of a number of olefins[77] (Table 4). The hydroboration of 4-methoxystyrene with (*S*)-**242** afforded (*S*)-1-(4-methoxyphenyl)ethanol with very high regio- and chemoselectivity, 95% of the *sec*-alcohol and about 2% each of the primary alcohol and alkane being formed. The yield was moderate (57%), but the enantioselectivity was very good (94% ee). Attempts to optimise the reaction conditions showed that (a) lowering of the temperature did not enhance the ee, but reduced the chemoselectivity; (b) higher concentrations of catecholborane were deleterious; and (c) the ee was relatively insensitive to the solvent change. On this basis, other alkenes were examined, but only vinylarenes gave interesting results in terms of stereoselectivity.

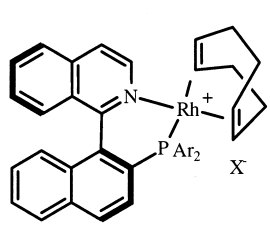
Next, Brown et al. changed the structures of the ligand QUINAP and the reactant in order to probe for the relative importance of electronic and steric effects. The Rh complexes **244**–**247** were prepared and used in the hydroboration of a large number of alkenes (for related structures, see Scheme 46). Both styrene derivatives bearing electron-releasing substituents **250**–**257** and those having electron-withdrawing substituents **260**–**262** and **264**–**269** were examined. Concerning the first type of substrates, the complex **243** usually afforded the highest ees (up to 94%). The results obtained for the two alkoxystyrenes **256** and **257** with the catalyst **243** (94% ee) indicated that an electronic-rich alkene is, to some extent, favoured for maximum stereoselectivity.

The ees (up to 89%) obtained with the second class of alkenes were generally lower than those obtained with the electron-rich alkenes. With the exception of *p*-fluorostyrene, the catalyst **246** (derived from furylphosphine) gave higher enantioselectivities than the catalyst **243** or any of the other catalysts employed.

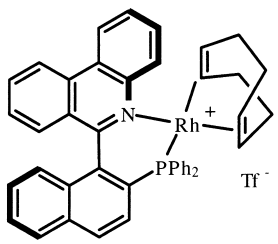
The hydroboration of the vinylarenes **270**–**275** indicated that, in general, an increase in the steric demand around the reaction site leads to a lower enantioselectivity. The example of hydroboration of 2-methoxy-1-vinylnaphthalene



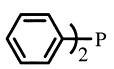
(*R*)-**242**,**243**,**247**

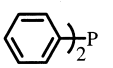


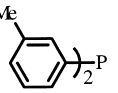
(*S*)-**242**,**244**,**245**,**246**

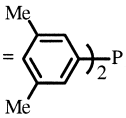


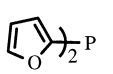
(*R*)-**248**

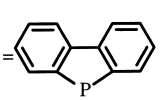
242: X$^-$ = Tf$^-$, Ar$_2$P = 

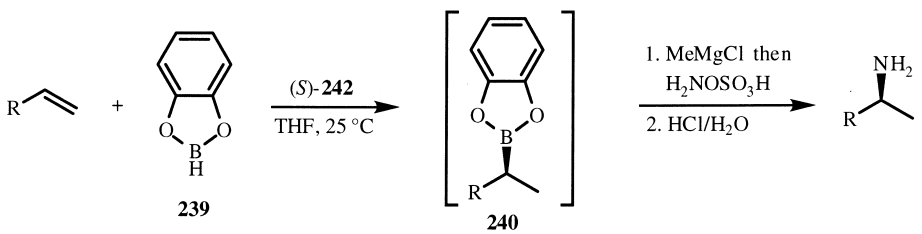
243: X$^-$ = BF$_4^-$, Ar$_2$P = 

244: X$^-$ = BF$_4^-$, Ar$_2$P = 

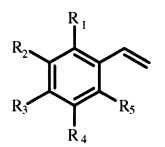
245: X$^-$ = BF$_4^-$, Ar$_2$P = 

246: X$^-$ = BF$_4^-$, Ar$_2$P = 

247: X$^-$ = BF$_4^-$, Ar$_2$P = 

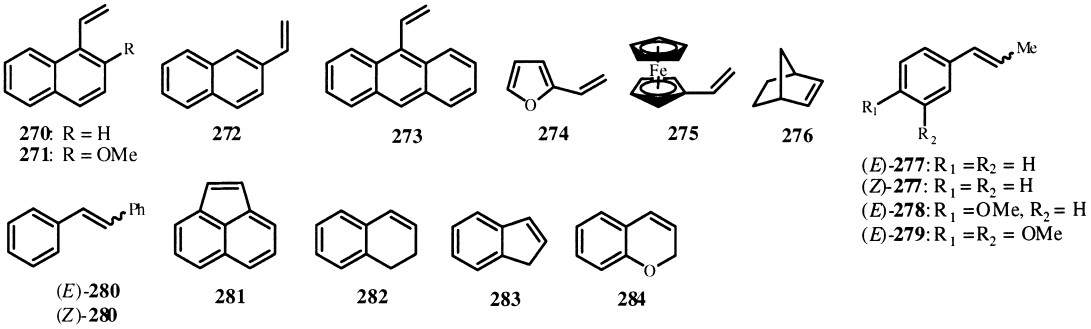


Scheme 45.



238, **250**-**269**

238: $R_1 = R_2 = R_3 = R_4 = R_5 = H$; **250**: $R_2 = R_3 = R_4 = R_5 = H$, $R_1 = Me$; **251**: $R_1 = R_3 = R_4 = R_5 = H$, $R_2 = Me$;
252: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = Me$; **253**: $R_2 = R_4 = R_5 = H$, $R_1 = R_3 = Me$; **254**: $R_2 = R_4 = H$, $R_1 = R_3 = R_4 = Me$
255: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = NMe_2$; **256**: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = OEt$; **257**: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = OMe$;
258: $R_2 = R_4 = R_5 = H$, $R_1 = R_3 = OMe$; **259**: $R_1 = R_4 = R_5 = H$, $R_2 = R_3 = OMe$; **260**: $R_2 = R_3 = R_4 = R_5 = H$, $R_1 = F$;
261: $R_1 = R_3 = R_4 = R_5 = H$, $R_2 = F$; **262**: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = F$; **263**: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = Br$
264: $R_2 = R_3 = R_4 = R_5 = H$, $R_1 = Cl$; **265**: $R_1 = R_3 = R_4 = R_5 = H$, $R_2 = Cl$; **266**: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = Cl$
267: $R_2 = R_3 = R_4 = R_5 = H$, $R_1 = CF_3$; **268**: $R_1 = R_3 = R_4 = R_5 = H$, $R_2 = CF_3$; **269**: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = CF_3$

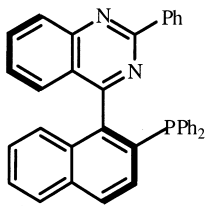


Scheme 46.

represents the limit of this methodology with existing ligands and, although the ee (89%) was reasonable with the catalyst **246**, only 61% of the secondary alcohol was obtained.

Brown examined also the hydroboration of β-substituted vinylarenes **277**–**284**. The hydroboration of (*Z*)- and (*E*)-propenylbenzene gave high and very similar ees indicating a rhodium-hydride driven isomerization. The symmetrical alkene acenaphthene (**273**) gave rise to the corresponding secondary alcohol with 86% ee. Consistently good results (96% ee) were obtained with 1,2-dihydronaphtalene (**282**) using catalyst **243**, while indene (**283**) gave the best result (78% ee) with catalyst **246**. The combination of the electron-rich β-substituted styrene (*E*)-**278** and catalyst **243** gave the higher enantiomeric excess (97%).

Brown and also Guiry, envisaging the important role played by the 3-H region of the isoquinoline of QUINAP in the ligand-reacting complex interactions leading to the enantioselection, assessed in this process two derivatives of QUINAP. Brown used PHENAP which is the 3,4-benzo-fused derivative of QUINAP, while Guiry synthesised 4-(2-diphenylphosphine-1-naphthyl)-2-phenylquinazoline (**157**), which has as the major structural difference with QUINAP and PHENAP the presence of the 2-phenyl substituent on the quinazoline ring.



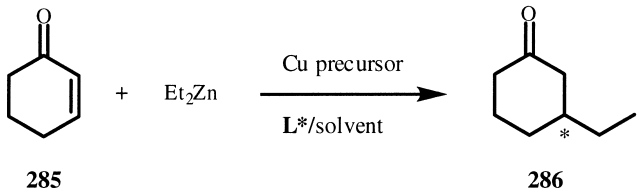
(*S*)-**157**

Brown prepared by treatment of PHENAP with [Rh(COD)(acac)]–$CF_3SO_3SiMe_3$ the rhodium complex **248** which

Table 5. Hydroboration-amination of vinylarenes using (*S*)-**242** as the catalyst[81]

Olefin[a]	Product	Regioselectivity (%)	Yield (%)	ee (%)
238	1-Phenylethylamine	>98	54	98
(*E*)-**277**	1-Phenylpropylamine	>98	50	90
257	1-(4-Methoxyphenyl)ethylamine	>98	56	98
284	Indan-1-ylamine	>98	61	77
283	1,2,3,4-Tetrahydronaphthalen-1-ylamine	96	51	97
272	1-(Naphthalen-2-yl)ethylamine	92	62	90
284	Chroman-4-ylamine	98	64	89

[a] For the related structures, see Scheme 46.



285 **286**

Scheme 47.

was used in the hydroboration of a number of vinylarenes with catecholborane (Table 4).[78] Using styrene, indene and 1-phenylpropene as the substrates, comparable yields (59–70%), but lower enantioselectivities, were obtained with the complex **248** with respect to the complex **243**. On the other hand, **248** was a more effective catalyst than **243** in the hydroboration of dihydronaphthalene and chromene, affording the corresponding alcohols in 84 and 74% ee, respectively. The striking differences between the two P,N-rhodium complexes indicated that the phenanthridine moiety participates to control the diastereoselectivity of the alkene coordination, or, more strictly, in the stereochemically defining transition state for hydride transfer from rhodium to carbon.

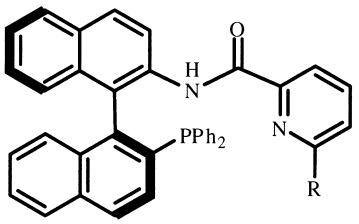
Guiry et al. carried out the reaction with catechol borane in THF using 1 mol% of the Rh-complex (*R*)-**249** prepared in situ by adding $CF_3SO_3SiMe_3$ to a solution of (1,5-cyclooctadiene)(2,4-pentanedionate)rhodium(I) and the ligand (*R*)-**157**.[80] This cationic rhodium catalyst was applied in the hydroboration of substituted arylethenes, β-substituted arylethenes and cyclic olefins, giving excellent conversions, good enantioselectivities and ees of up 97% (Table 4). For substituted arylethenes, the ligand **157** as with QUINAP and PHENAP afforded lower ees than BINAP. For β-substituted arylethenes and cyclic olefins, however, these axially-chiral phosphinamine ligands are far superior. This was explained by inferring that these less sterically-demanding ligands more easily accommodate the increased steric demand of the olefin.

Brown et al. developed a one-pot asymmetric synthesis of primary amines from vinylarenes.[81] The method is based on the hydroboration with catecholborane employing the rhodium complex (*S*)-**242**, followed, on completion of the hydroboration reaction, by treatment of the unisolated catechol borate ester with 2 equiv. of MeMgCl and after 30 min with 3 equiv. of H_2NOSO_3H (Scheme 45). The application of this procedure to several vinylarenes allowed the corresponding primary amines to be obtained in moderate yields (50–64%) and in good to very high enantioselectivities (77–98% ee) (Table 5). The ee values of the amines reflect the enantioselectivity of the catalytic hydroboration step, since the H_2O_2-OH^- oxidation of the intermediate boranes provided secondary alcohols with a quite similar enantiomeric purity (Scheme 46).

3.3. Conjugate addition of diethylzinc to enones

The conjugated addition of various organometallic reagents to α,β-unsaturated carbonyl or related compounds is one of the most widely-used synthetic methods for carbon–carbon bond formation.[82] High yields and enantioselectivities have been obtained by copper-complexes with (pyr-phos)-ligands.

Zhang et al. used the P,N-ligands (*S*)-**176a**,**b** in the copper-catalysed enantioselective conjugate ethyl transfer from diethylzinc to substituted enones.[59]



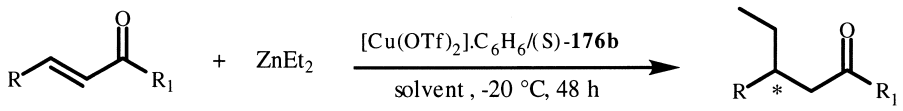
(*S*)-**176a,b** **a**: R = H **b**: R = Me

Initially, using 2-cyclohexen-1-one (**285**) as a substrate to develop the optimal reaction, conditions they found good yield (76%) and high asymmetric induction (91% ee) when the ligand **176a** was used at −20°C with $[Cu(OTf)_2]\cdot C_6H_6$

Table 6. Copper-catalysed enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one (**285**)[a]

Ligand	Cu precursor	Solvent	Temperature (°C)	Yield (%)	ee (%)	Configuration	Reference
176a	$[Cu(OTf)_2]\cdot C_6H_6$	Toluene	−20	76	91	*S*	59
176a	$[Cu(CH_3CN)_4]\cdot BF_4$	Toluene/$Cl(CH_2)_2Cl$	−20	95	85	*S*	59
176b	$[Cu(OTf)_2]\cdot C_6H_6$	toluene	−20	100	89	*S*	59
176b	$[Cu(CH_3CN)_4]\cdot BF_4$	Toluene/$Cl(CH_2)_2Cl$	−20	98	92	*S*	59
120a	$Cu(OTf)_2$	CH_2Cl_2	0	95	55	*S*	40
120b	$Cu(OTf)_2$	CH_2Cl_2	0	100	91	*S*	40
122	$Cu(OTf)_2$	CH_2Cl_2	0	94	36	*S*	40
124a	$Cu(OTf)_2$	Toluene	−20	85	52	*S*	40
124b	$Cu(OTf)_2$	Toluene	−20	90	40	*S*	40
121	$Cu(OTf)_2$	CH_2Cl_2	0	100	30	*S*	40
67	CuI/H_2O	CH_2Cl_2	−20	76	61	*R*	24g
67	$CuI/Zn(OH)_2$	CH_2Cl_2	−20	100	53	*R*	24g
71	$CuI/Zn(OH)_2$	CH_2Cl_2	−20	91	20	*R*	24h
77	$CuI/Zn(OH)_2$	CH_2Cl_2	−20	100	42	*R*	24h
78	$CuI/Zn(OH)_2$	CH_2Cl_2	−20	100	50	*R*	24h
79	$CuI/Zn(OH)_2$	CH_2Cl_2	−20	100	51	*R*	24h
80	$CuI/Zn(OH)_2$	CH_2Cl_2	−20	96	55	*R*	24h

[a] Only representative examples are reported; for further examples, see the references cited in the table.



287: R = R_1 = Ph;
288: R = Ph; R_1 = *p*-$MeOC_6H_4$
289: R = *p*-$MeOC_6H_4$; R_1 = Ph
290: R = Ph; R_1 = Me
291: R = *i*-Pr; R_1 = Me

292: R = R_1 = Ph, 85%, 96% ee
293: R = Ph; R_1 = *p*-$MeOC_6H_4$, 69%, 97% ee
294: R = *p*-$MeOC_6H_4$; R_1 = Ph, 97%, 98% ee
295: R = Ph, R_1 = Me, 70%, 90% ee
296: R = *i*-Pr, R_1 = Me, 53%, 86% ee

Scheme 48.

as the catalytic precursor in apolar non-coordinating solvents such as toluene (Scheme 47). Comparable or better results (up 92% ee) were obtained by replacing **176a** with the sterically-more-hindered ligand **176b** (Table 6).

Next, they extended this research to find an effective catalytic system for a variety of acyclic enones. In the conjugate addition to chalcone (**287**), an enantiomeric excess of 96% was obtained with the ligand **176b** by carrying out the reaction at −20°C in a toluene/1,2-dichloroethane (2/1) mixture and by using $[Cu(OTf)_2]\cdot C_6H_6$ as the procatalyst (Scheme 48).

Under these optimal conditions, several acyclic enones with aryl substituent groups were successfully converted into the corresponding chiral ketones (up to 98% ee) (Scheme 48), and, in addition a very interesting result was obtained with the acyclic enone **291** bearing only aliphatic substituents (86% ee).

Buono et al. in two successive papers reported their investigations dealing with the use of QUIPHOS **67** and other related ligands in the enantioselective copper catalysed 1,4-addition of diorganozinc to various enones[24g,h] (Table 6).

Using ligand **67** and 2-cyclohexen-1-one (**285**) as the test substrate, the effects on the enantioselectivity of several variables, such as the nature of the copper source (Cu(OTf), CuBr, CuI, etc.), the solvent, the reaction temperature, the presence of additives and the amount of the ligand were investigated.[24g]

A dramatic effect on the enantioselectivity was observed by varying the solvent (from 7 to 45% ee) and by performing the reaction in the presence of water. The best result was obtained using Cu/**67**/H_2O/Et_2Zn in a 0.005/0.01/0.5/2 molar ratio (with respect to the substrate) at −20°C in dichloromethane, leading to the expected product **286** in 61% ee and 76% yield. The outcome of the reaction was ascribed to the in situ formation of the $Zn(OH)_2$ species, which could act as a Lewis acid by complexation to the enone carbonyl, thereby increasing the enantiofacial differentiation, and enhancing the enantioselectivity of the reaction. As a confirmation of that proposal, replacement of the water by $Zn(OH)_2$ under the best experimental conditions led to the same results in terms of yield and enantioselectivity.

The optimal catalytic system was next applied to other enone substrates (2-cyclohepten-1-one, chalcone and 4-phenyl-3-buten-2-one) using diethyl- and dibutylzinc. In no example did the enantioselectivity exceed 49% ee.

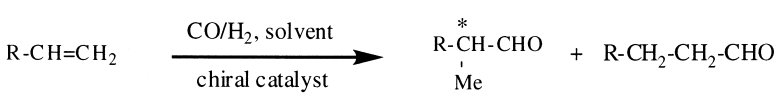
The same group, on the basis of the results obtained with QUIPHOS, assessed the ligands **71**–**76** and **77**–**83** in the copper-catalysed conjugated addition of diethylzinc to 2-cyclohexen-1-one.[24h]

Irrespective of the experimental conditions applied, good conversions (>90%) were noted in all cases (Table 6). A significant improvement in the enantiomeric excess of the product was observed when the reaction was completed in the presence of $Zn(OH)_2$. The ligands **71**–**76** gave poor enantioselectivities, varying from 2 to 25% ee. On the other hand, the ligands **77**–**83** led to enantioselectivities and yields which were lower or similar to those previously obtained with QUIPHOS, underlining the importance of the ligand structure on the stereochemical outcome of the reaction.

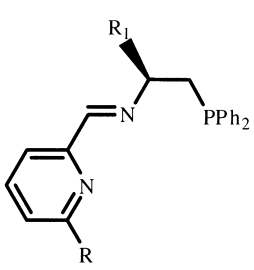
Morimoto et al. used tridentate ligands in the copper-catalysed conjugate addition of diethylzinc to enones, hoping to increasing the stereoselectivity of the reaction obtained with similar bidentate P,N-ligands, since the use of tridentate ligands could stabilise a possible monoalkyl-copper(I) intermediate by forming a more rigid chiral environment.[40]

The enantioselective 1,4-addition of diethylzinc to **285** with the ligands **120a**,**b**,**121**,**122** and **124a**,**b** was examined carrying out the reaction with $Cu(OTf)_2$ (1 mol%) and the ligand (2.5 mol%) at 0°C in dichloromethane (Table 6).

Among the analogue series **120a**,**b** and **122**, the highest enantioselectivity (91% ee) was afforded by the ligand **120b**. Lower enantioselectivities were obtained with the other ligands, indicating that the tridentate phosphino, imino



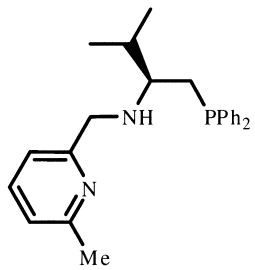
Scheme 49.



120a: R = H; R_1 = *i*-Pr

120b: R = Me; R_1 = *i*-Pr

122: R = R_1 = Me



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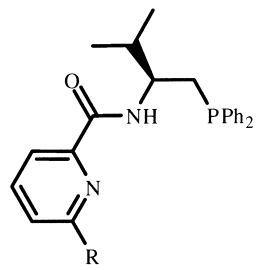


124a: R = H; **124b**: R = Me

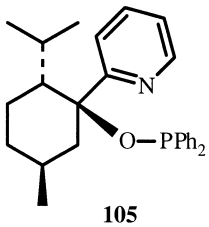
and pyridino groups play important roles in forming the desired chiral pocket around the Cu atom for alkylation with diethylzinc, followed by coordination with 2-cyclohexen-1-one. The conjugate addition to chalcone (**287**) was also examined with the ligand **120b** under typical reaction conditions. The corresponding β-ethylation product **292** was isolated in 90% yield and 71% ee (*R*).

3.4. Hydroformylation

The asymmetric hydroformylation of olefins is a useful synthetic method for preparing optically active aldheydes[83] (Scheme 49).

Some metal complexes containing (pyr-phos)-ligands have been applied in this process by Faraone and by the present authors.

Faraone et al. prepared the rhodium complexes [Rh(C_8H_{12})(**105**)]ClO_4 (**297**) and [Rh(CO)(PPh_3)(**105**)]ClO_4 (**298**) including the P,N-chelate ligand **105**. These catalysts were used in the hydroformylation of the olefinic substrates, styrene, 2-vinylnaphthalene, methyl acrylate and vinyl acetate (Table 7).[31] The hydroformylation of styrene proceeded easily with both catalysts **297** and **298**. The chemoselectivity of the reaction was very satisfactory, as well as the regioselectivity toward the branched aldehyde, but a very poor enantioselectivity was obtained (6% ee). The hydroformylation of 2-vinylnaphthalene with **298** afforded (*R*)-2-(2-naphthyl)propanal in 78% ee as the exclusive product (100% yield). Very good yields and regioselectivities were obtained in the methyl acrylate hydroformylation with both catalysts, but only **298** furnished a very high enantioselectivity (92% ee). Hydroformylation of vinyl acetate with **298** gave excellent regioselectivity and yield,



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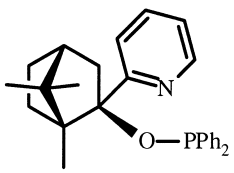

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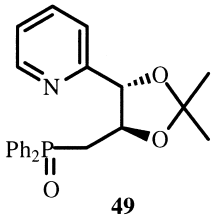

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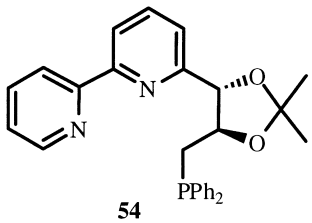


54

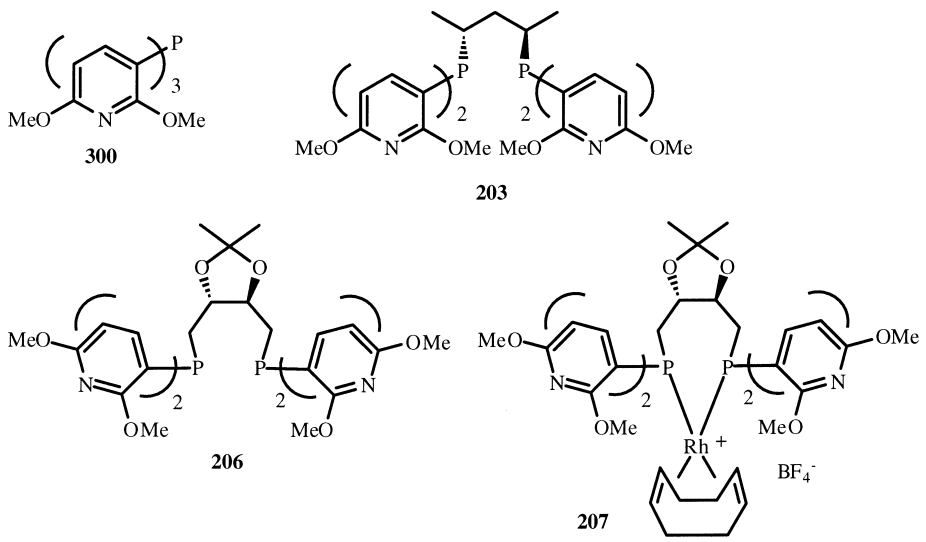
Table 7. Hydroformylation of olefins[a]

Catalytic precursor	Substrate	Conv. (%)	b/l[b]	ee (%)	Configuration	Reference
[Rh(C_8H_{12})(**105**)]ClO_4 (**297**)	Styrene	100	88/12	6	*R*	31
[Rh(CO)(PPh_3)(**105**)]ClO_4 (**298**)	Styrene	98	78/22	6	*R*	31
[Rh(CO)(PPh_3)(**105**)]ClO_4 (**298**)	2-Vinylnaphthalene	100	100/0	78	*R*	31
[Rh(CO)(PPh_3)(**105**)]ClO_4 (**298**)	Methyl acrylate	95	97/3	92	*R*	31
[Rh(CO)(PPh_3)(**105**)]ClO_4 (**298**)	Vinyl acrylate	50	100/0	12	*R*	31
[Rh(COD)(**107**)]BF_4 (**299**)	Styrene	95	80/20	9	*S*	32
[Rh(COD)(**107**)]BF_4 (**299**)	4-Isobutylstyrene	98	80/20	19	*S*	32
[Rh(COD)(**107**)]BF_4 (**299**)	3-Methoxystyrene	97	54/46	7	*S*	32
[Rh(COD)(**107**)]BF_4 (**299**)	2-Vinylnaphthalene	98	72/28	45	*S*	32
[Rh(COD)(**107**)]BF_4 (**299**)	6-Methoxy-2-vinylnaphthalene	93	78/22	14	*S*	32
(**48**)Rh(CO)Cl	Styrene	30	90/10	28	*R*	14
(**48**)Pt($SnCl_3$)Cl	Styrene	20	70/30	31	*R*	14
$Rh(CO)_2$(acac)/**48**[c]	Styrene	80	95/5	1	*R*	14
$Rh(CO)_2$(acac)/**49**[c]	Styrene	98	97/3	1	*R*	14
$Rh(CO)_2$(acac)/**49**[c]	Styrene	99	95/5	–	–	84
$Rh(CO)_2$(acac)/**48**[c]	Phenyl vinyl ether	95	96/4	~10	–	84
$Rh(CO)_2$(acac)/**49**[c]	1-Phenyl-1-(pyridin-2-yl)ethene	99	99/1	~10	–	84

[a] Only representative examples are reported; for further examples, see the references cited in the table. The best stereochemical result obtained by each ligand is reported.

[b] Ratio between branched and linear isomers.

[c] The catalyst was prepared in situ.



but a low enantiomeric excess (12% ee). Excellent regioselectivity and yield were recorded in the hydroformylation of vinyl acetate with **298**, but a low enantiomeric excess was acquired (12% ee).

The present authors used the catalyst [Rh(COD)(**107**)]BF_4 (**299**) containing the ligand **107** in the hydroformylation of the series of vinylaromatics, styrene, 4-isobutylstyrene, 3-methoxystyrene, 2-vinylnaphthalene and 6-methoxy-2-vinylnaphthalene (Table 7).[32] The complex **299** exhibited good catalytic activity, but moderate regioselectivities were observed, with the branched isomers prevailing. Low enantioselectivities were obtained and only with the 2-vinylnaphthalene was a moderate ee (45%) achieved.

The present authors reported the enantioselective hydroformylation of styrene with rhodium and platinum complexes containing the ligands **48**,**49** and **54**.[14] The (**48**)$Rh(CO)_2Cl$ catalyst afforded, under mild conditions, low yields of hydrotropaldehyde having 28% ee (Table 7). With the in situ formed $Rh(CO)_2$(acac)/**48** complex, a much higher catalytic activity was observed, but without asymmetric induction. Similar results were obtained with the in situ formed Rh(I)-complexes with the ligand **54** and the corresponding *P*-oxide **49**. It is possible that, in both cases, the concentrations of the catalytically active species bearing the chiral ligands are very low and cannot compete under oxo-conditions with the more effective unmodified Rh–carbonyl complexes present in the reaction medium. The hydroformylation reaction runs sluggishly in the presence of the preformed platinum(II) catalyst [(**48**)$Pt(SnCl_3)Cl$] giving only 31% ee. Contrary to expectations for Pt(II) complexes, the ligand **48** shifted the regioselectivity towards the formation of the branched aldehyde.

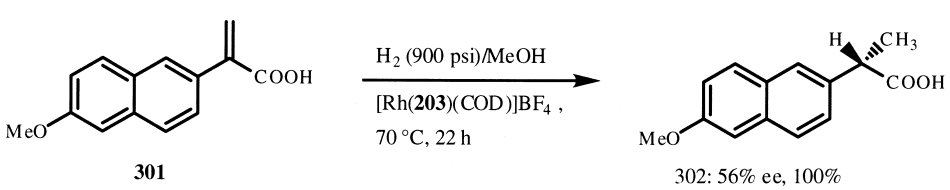
Next, during a more extensive investigation, the present authors assessed the Rh complexes of the ligands **48** and **49** in the hydroformylation of the functionalised olefins, styrene, vinyl acetate, 2-vinylpyridine, phenyl vinyl ether, 1,1-diphenylethene and 1-phenyl-1-(pyridin-2-yl)ethene (Table 7).[32] The reactions were performed using catalysts formed in situ from the ligands **48** and **49** and [$Rh(CO)_2$(acac)]. In most cases, good chemo- and regioselectivities, but unsatisfactory enantioselectivities, were obtained. The best ees (about 10%) were obtained in the hydroformylation of phenyl vinyl ether with **48** and 1-phenyl-1-(pyridin-2-yl)ethene with **49**. In the hydroformylation of styrene, vinyl acetate and phenyl vinyl ether, the Rh complex containing **49** was remarkably more active than the catalyst formed with **48**.

3.5. Hydrogenation

Catalytic asymmetric hydrogenation reactions of unsaturated compounds are a powerful tool for the preparation of chiral compounds.[85]

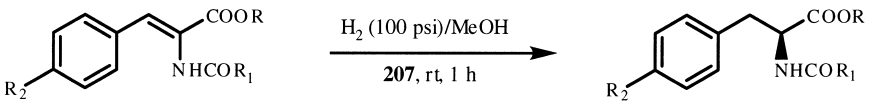
Unfortunately, the rhodium and ruthenium complexes containing pyridylphosphine ligands were found to be catalytically inactive in this reaction. The inactivity of the catalyst was attributed to the pyridyl group that by coordination to the metal centre renders the complex coordinately saturated.[86] Recently, Chan's group prepared the pyridylphosphine ligand **300** and found that, on preventing the coordination of the pyridyl group to the metal centre, the resulting complexes were active for the hydrogenation of olefins, aldehydes and imines.[70]

Continuing their research in this field, the same group



301 302: 56% ee, 100%

Scheme 50.



303a-i

304a-i

a: R = Me, R_1 = Me, R_2 = H; **b**: R = H, R_1 = Me, R_2 = H;
c: R = H, R_1 = Ph, R_2 = H; **d**: R = Me, R_1 = Ph, R_2 = H;
e: R = Me, R_1 = Ph, R_2 = Me; **f**: R = Me, R_1 = Ph, R_2 = Br;
g: R = Me, R_1 = Ph, R_2 = Cl; **h**: R = Me, R_1 = Me, R_2 = Cl;
i: R = Me, R_1 = Me, R_2 = OMe

a: 60% ee; **b**: 33% ee; **c**: 66% ee;
d: 83% ee; **e**: 80% ee; **f**: 78% ee;
g: 79% ee; **h**: 57% ee; **i**: 62% ee

Scheme 51.

prepared the chiral pyridine-phosphine ligands **203** and **206** incorporating the non-coordinating pyridyl group of **300** into chiral skeletons and examined the corresponding Rh complexes as catalysts in the asymmetric hydrogenation of prochiral olefins.[71,72]

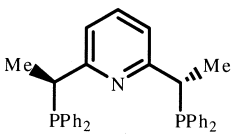
The hydrogenation of 2-(6-methoxy-2-naphthyl)propenoic acid (**301**), using the complex prepared in situ from $[Rh(COD)_2]BF_4$ and **203**, under 900 psi H_2 at 70°C in 12 h afforded naproxen (**302**) in 100% conversion and 28% ee (Scheme 50). The addition of 10 equiv. of phosphoric acid improved the enantioselectivity (56% ee, 100% conversion).[71] Interestingly, the ligand **203** gave substantially better results than the regular arylphosphine analogues.

Next, Chan and co-workers prepared the Rh complex **207** from the parent ligand **206** and determined the catalytic activity and stereodifferentiating ability of this catalyst in the asymmetric hydrogenation of prochiral olefins.[72]

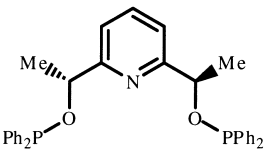
The complex **207** was found to be an effective catalyst for the asymmetric hydrogenation of α-amidoacrylic acid and its derivatives **303a–i** to form **304a–i** (Scheme 51). The rate and the enantioselectivity of the reaction were affected by the choice of solvent, H_2 pressure and the reaction temperature. When the hydrogenation of methyl α-acetamidocinnamate was carried out in methanol at 25°C and under 100 psi of H_2 for 1 h, the product was formed in 100% yield and 60% ee (64% ee was obtained at 0°C for 8 h). Under these conditions, the hydrogenation of aromatic α-(acylamino)acrylic acids afforded moderate to good enantiomeric excesses (up to 83%).

Good enantioselectivities were obtained in the hydrogenation of other prochiral olefins **305a–d** and **306a–e** (Scheme 52). Interestingly, a comparison of these results with those obtained with DIOP, revealed that the products of the two systems are of opposite configurations in the hydrogenation of amidoacrylic acids, enols and itaconic acid.

Osborn et al. reported the synthesis of rhodium(I)- and iridium(I)-complexes containing the tridentate ligands **109** and **110** and their application in the asymmetric hydrogenation of imines.[87]

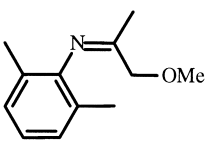


(*S,S*)-**109**

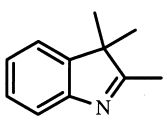


(*R,R*)-**110**

They used the series of catalysts reported in Table 8 in the asymmetric hydrogenation of the imines **307–309**. The imine **307** was readily converted by **310** into the chiral amine with modest enantioselectivity (40% ee). The complex **312** (prepared in situ) gave a higher enantiomeric excess (55% ee), but unfortunately deactivated more quickly. The rhodium complex **311** did not show catalytic activity, while **313** was slightly active, giving an ee of 41%. The reduction of the imine **308** with **310** and **312** (produced in situ as catalysts) was surprisingly quite efficient, but yielded only low enantioselectivities. The imine **309** gave



307



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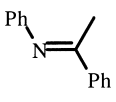
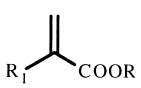
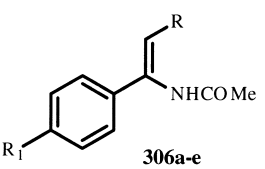


309



305a-d

a: R = Me, R_1 = NHCOMe, 48% ee (S)
b: R = Me, R_1 = OCOMe, 28% ee (S)
c: R = Et,, R_1 = OCOMe, 42% ee (S)
d: R = H, R_1 = CH_2COOH, 32% ee (R)



306a-e

a: R = Me, R_1 = H, 84% ee (S)
b: R = *n*-Pr, R_1 = H, 40% ee (S)
c: R = Me, R_1 = Me, 81% ee (S)
d: R = Me, R_1 = Cl, 81% ee (S)
e: R = H, R_1 = CF_3, 76% ee (S)

Scheme 52.

Table 8. Asymmetric hydrogenation of imines **307**–**309**.[87]

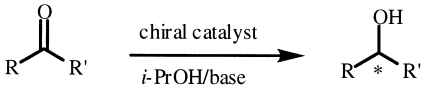
Catalyst	Imine	Yield (%)	ee (%)	Configuration
310=$\{Ir[(R,R)$-**109**$](COD)\}ClO_4$	**307**	87	40	*S*
310[a]=$[Ir(COD)Cl]_2/2ClO_4^-/2(S,S)$-**109**	**307**	65	34	*R*
	308	100	8	–
	309	6	26	*S*
311=$\{Rh[(R,R)$-**109**$](NBD)\}ClO_4$	**307**	0	–	–
312=$[Ir(COD)Cl]_2/(R,R)$-**110**	**307**	5	–	–
312[a]=$[Ir(COD)Cl]_2$/2 ClO_4^-/2 (R,R)-**110**	**307**	31	55	*S*
312[a]=$[Ir(COD)Cl]_2$/2 ClO_4^-/2 (S,S)-**110**	**307**	37	53	*R*
	308	88	7	–
313=$\{Rh[(R,R)$-**110**$](NBD)\}ClO_4$	**307**	9	41	*S*

[a] Catalyst prepared in situ.

both poor rates and ee values with all the catalysts tested. The hydrogenation rates of imines with these systems was very high, but the yields were limited in several cases by the deactivation of the catalyst, which was attributed to the irreversible formation of a dihydrido complex.

3.6. Transfer hydrogenation

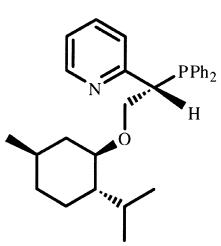
Transfer hydrogenation from 2-propanol to prochiral ketones **314** catalyzed by optically active transition metal complexes represents a method for asymmetric synthesis of alcohols **315**[88] (Scheme 53).



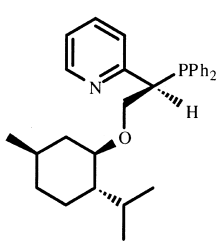
314 **315**

Scheme 53.

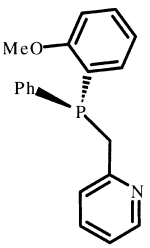
Mathieu et al.[26,27] applied the ruthenium complexes obtained by the reaction of an equimolar amount of $RuCl_2(PPh_3)$ and the tridentate P,N,O-ligands (*S*)-**92**, (*R*)-**92** and **97c** in the transfer hydrogenation of acetophenone, which is used as a model substrate for this reaction (Table 9). Different procedures were examined. The main differences in the runs resided in the temperature, concentration of the base (equiv with respect to Ru) and of the complex (substrate/catalyst). Under optimised conditions, the best stereochemical result was observed for the ligand (*S*)-**92** with an enantiomeric excess of 60%, but with a low catalytic activity. The other ligands afforded modest results.



(*R*)-**92**



(*S*)-**92**



97c

Zhang et al.[37] in a preliminary study examined the H-transfer enantio-differentiating reduction of aryl methyl ketones using $RuCl_2(C_6H_6)$ as a precursor with the tridentate P,N,P-ligand (*R*,*R*)-**109**. Conversions from 33 to 98% and enantioselectivities from 30 to 74% ee were obtained (Table 9).

3.7. Hydrosilylation

Asymmetric metal-catalysed hydrosilylation of prochiral ketones to furnish silyl ethers, and their subsequent hydrolysis provides an effective entry into secondary chiral alcohols.[89] Zhang et al. investigated the asymmetric hydrosilylation of aryl alkyl ketones with diphenylsilane catalysed by $[RuCl_2(C_6H_6)]_2$ with the chiral tridentate ligand **117** (Table 10).[38]

After optimisation of the reaction conditions, an enantioselectivity of 54% ee (97% yield) was obtained in the hydrosilylation of acetophenone (**316**) with diphenylsilane in the presence of AgOTf as additive and THF as solvent to form **318** via **317** (Scheme 54).

Table 9. Asymmetric transfer hydrogenantion of aryl methyl ketones[a]

Substrate	Catalyst	Base	Yield	ee (%)	Configuration	Reference
Acetophenone[b]	$RuCl_2(PPh_3)(R)$-**92**	*i*-PrOK	50	60	*R*	27
Acetophenone[c]	$RuCl_2(PPh_3)(S)$-**92**	NaOH	90	3	*R*	27
Acetophenone[d]	$RuCl_2(PPh_3)$(**97c**)	*i*-PrOK	30	12	*R*	27
Acetophenone[e]	$RuCl_2(C_6H_6)$/**109**	NaOMe	67	48	*R*	37
3,4-Dihydro-(2*H*)naphthalen-1-one[f]	$RuCl_2(C_6H_6)$/**109**	NaOMe	33	74	*R*	37
1-(Naphthalen-2-yl)ethanone[f]	$RuCl_2(C_6H_6)$/**109**	NaOMe	92	42	*R*	37
1-(Naphthalen-1-yl)ethanone[f]	$RuCl_2(C_6H_6)$/**109**	NaOMe	98	30	*R*	37

[a] Only representative results are reported; for further results, see the references cited in the table.
[b] Substrate/catalyst=200/1, base/catalyst=0.5, reaction time=60 min, temperature=45°C.
[c] Substrate/catalyst=1000/1, base/catalyst=240, reaction time=20 min, temperature=80°C.
[d] Substrate/catalyst=200/1, base/catalyst=1, reaction time=60 min, temperature=45°C.
[e] Substrate/catalyst=100/1, base equiv.=5, reaction time=24 h, temperature=25°C.
[f] Substrate/catalyst=100/1, base equiv.=25, reaction time=24 h, temperature=25°C.

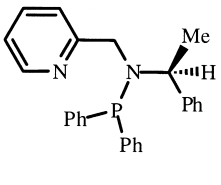
Table 10. Enantioselective hydrosilylation of alkyl aryl ketones with diphenylsilane catalysed by $[RuCl_2(C_6H_6)]_2$ with ligand **117**

Ketone	Time (h)	Yield (%)	ee (%)	Configuration
Acetophenone	24	97	54	*S*
1-(2-Bromophenyl)ethanone	72	87	57	*S*
1-(3-Bromophenyl)ethanone	72	92	62	*S*
1-(4-Bromophenyl)ethanone	48	93	55	*S*
3,4-Dihydro-(2*H*)naphthalen-1-one	60	91	47	*S*
1-(Naphthalen-2-yl)ethanone	24	98	66	*S*
1-(Naphthalen-1-yl)ethanone	30	85	48	*S*

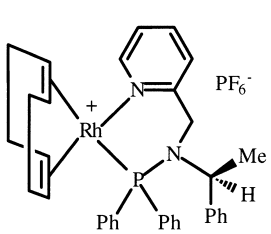
In order to understand the role that the pyridine-nitrogen plays in the catalytic process, the hydrosilylation of acetophenone was examined in the presence of the ligand **231**. Interestingly, no stereoselectivity was detected with this ligand, indicating that the pyridine in the tridentate ligand **231** is crucial for achieving a relatively high enantioselectivity in the hydrosilylation.

Moderate enantioselectivities (ranging from 47 to 66% ee) and excellent conversions (isolated yields from 85 to 98%) were observed using alkyl aryl ketones under optimum conditions (Table 10).

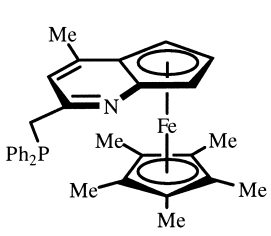
Brunner used the cationic rhodium complex (*S*)-**66**, containing the ligand (*S*)-**65**, in the enantioselective hydrosilylation of acetophenone with diphenylsilane. (*R*)-1-Phenylethanol was obtained in good yield (90%), but in very low enantioselectivity (3% ee).[23]



(*S*)-**65**



(*S*)-**66**



198

Fu's group applied the ligand **198** in the rhodium-catalysed asymmetric hydrosilylation of ketones. Initially, they examined the reduction of acetophenone using a silane and $[Rh(COD)Cl]_2$ as the procatalyst.[69] The stereoselectivity was highly dependent on the choice of silane and the best enantioselectivity (98% ee) was obtained using $MesPhSiH_2$. Excellent enantiomeric excesses (95 to 99%) and yields (74 to 99%) were also obtained when an array of electronically varied derivatives of aryl alkyl ketones and an aldehyde, (1-D)-benzaldehyde, were used (Table 11). In addition, the reduction of dialkyl ketones afforded good enantioselectivity (72 to 96% ee), but in this case the best stereoselectivity was obtained using *o*-Tol_2SiH_2 as the silane (Table 11).

Table 11. Enantioselective hydrosilylation of ketones catalysed by $[Rh(COD)Cl]_2$ with ligand **198** in THF solution

Ketone	Silane	Yield (%)	ee (%)
Acetophenone	$MesPhSiH_2$	94	98
1-(4-Methoxyphenyl)ethanone	$MesPhSiH_2$	97	97
1-(4-Trifluoromethylphenyl)ethanone	$MesPhSiH_2$	88	96
1-(Naphthalen-1-yl)ethanone	$MesPhSiH_2$	97	99
1-(2,4-Dimethylphenyl)ethanone	$MesPhSiH_2$	97	95
1-(2,4,6-Trimethylphenyl)ethanone	$MesPhSiH_2$	99	98
3,4-Dihydro-2*H*-naphthalen-1-one	$MesPhSiH_2$	95	98
1-Phenylpropanone	$MesPhSiH_2$	96	98
(1-D)-Benzaldehyde	$MesPhSiH_2$	74	95
Adamantyl methyl ketone	*o*-Tol_2SiH_2	92	96
Cyclohexyl methyl ketone	*o*-Tol_2SiH_2	91	94
4-Phenylbutan-2-one	*o*-Tol_2SiH_2	98	82
Octan-2-one	*o*-Tol_2SiH_2	81	72

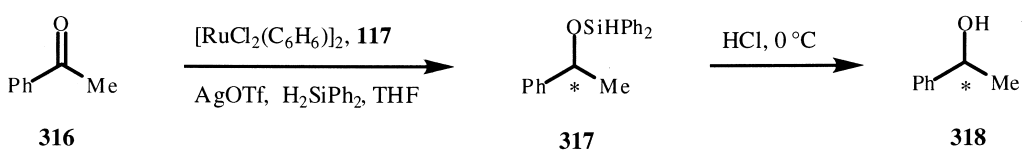
3.8. Other reactions

3.8.1. Diels–Alder reactions. The Diels–Alder reaction is one of the most important reactions in organic chemistry since it allows the building up of complex molecules in one step.[90]

Buono's group reported their preliminary results on the catalytic enantioselective Diels–Alder reaction of 3-acryloyl-1,3-oxazolidine-2-one (**320**) with cyclopentadiene (**319**) in the presence of copper(II)-catalysts prepared in situ from $Cu(OTf)_2$ and the pyridine-phosphine ligands **67** and **71** both bearing a stereogenic phosphorus atom[24c] (Scheme 55).

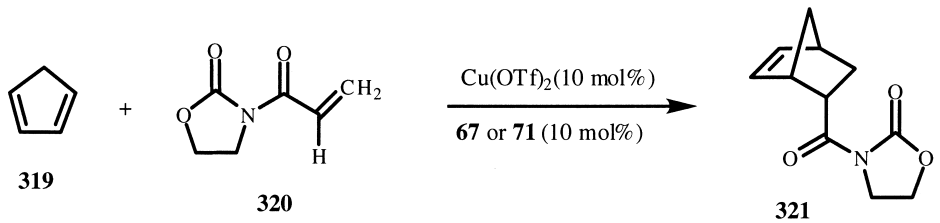
A number of experiments were carried out, varying both the solvent and the temperature. Under the best conditions (CH_2Cl_2, from −78°C slowly to room temperature), complete conversion to **321** was achieved after 24 h at 25°C. An *endo*–*exo* ratio of >98:2 was obtained with both ligands, but only **67** afforded a very high enantioselectivity (>99% ee) (36% ee with **71**). The steric course of the reaction was rationalised.

3.8.2. Heck reaction. Kocovsky's group assessed the efficacy of the ligands *ent*-**28**,**29**,**37** and **38** in the enantioselective Heck addition[91] of PhOTf to dihydrofuran **322** to form the 2-phenyl-2,5-dihydrofuran (**323**) (Scheme 56).[11]

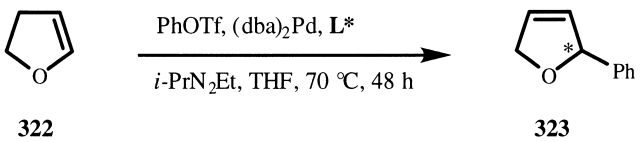


316 **317** **318**

Scheme 54.



Scheme 55.



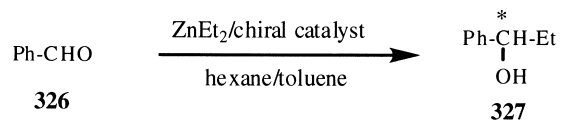
Scheme 56.

Using solvent and base variation, they identified *i*-Pr_2NEt in THF (70°C, 2 days) as the most suitable system for high enantioselectivity and which minimised the formation of the by-side products.

The ligand **29** induced the formation of (*S*)-**323** with 59% ee in 45% yield. The ligand **37** proved to be more enantioselective, giving (*S*)-**323** with 70% ee, while its quasi-enantiomer **38** produced the opposite enantiomer (*R*)-**323** with 69% ee, indicating that the presence of the methyl group on C5 of **37** is unimportant for the stereochemical outcome. Reversal of the product configuration was also observed for *ent*-**28**, which furnished (*R*)-**323** with 88% ee (68% yield). Only a slight isomerisation (~1%) of the more stable 4,5-isomer was observed.

3.8.3. Hydrocarboethoxylation. The present authors examined the asymmetric hydroesterification of styrene (**238**), to afford the esters **324** and **325**, with the palladium complexes of ligands **48** and **54** (Scheme 57).[15] The obtained data showed that using only preformed $PdCl_2$/**48** complex, the catalytic activity was satisfactory and the enantioselectivity appreciable (20% ee); the complexes formed in situ between $PdCl_2$ and the ligands **48** and **54** exhibited very poor activity (5–20% conv.) and enantioselectivity (2–3% ee). These results strongly suggested that complexation of these ligands to Pd(II) in a chelating manner is rather difficult under the reaction conditions used.

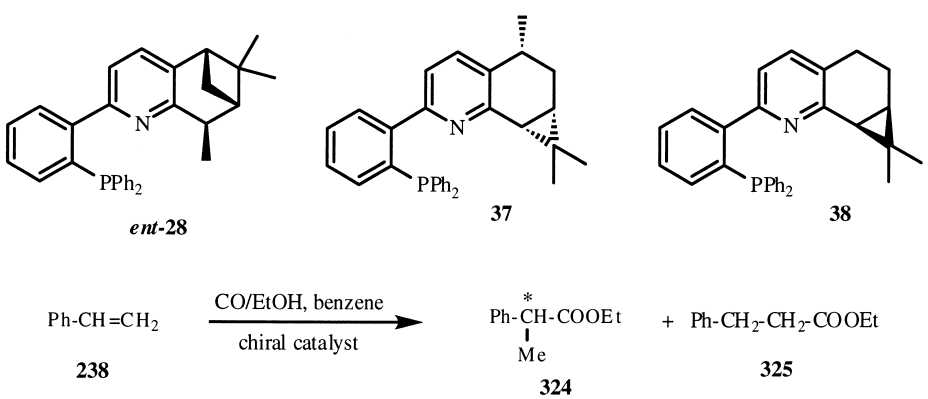
3.8.4. Asymmetric addition of diethylzinc to benzaldehyde. The enantioselective addition of diethylzinc to benzaldehyde (**326**),[92] to give the alcohol **327**, using the ligands **48** and **54** and the *P*-oxide of **48** was evaluated (Scheme 58).[14] All catalysts gave 1-phenyl-1-propanol in good yields (84–99%), but with low enantioselectivities (2–21% ee). It should be noted that this represents the sole example reported to date of the use of chiral phosphine derivatives in this catalytic process.



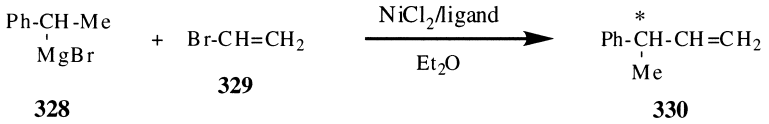
Scheme 58.

3.8.5. Cross coupling. Brunner and also the present authors have considered the enantioselective formation of 3-phenyl-1-butene (**330**) by the cross-coupling reaction[93] of 1-phenylethylmagnesium bromide (**328**) with vinyl bromide (**329**), catalysed by the complexes formed in situ from anhydrous $NiCl_2$ and the ligands (*S*)-**65** and **48** (Scheme 59). With the ligand **48**, the olefin **330** was obtained with both low enantioselectivity (26% ee) and yield (40%).[14] On the other hand, the ligand (*S*)-**65** afforded **330** in 90% yield, but in lower ee (3% ee).[94]

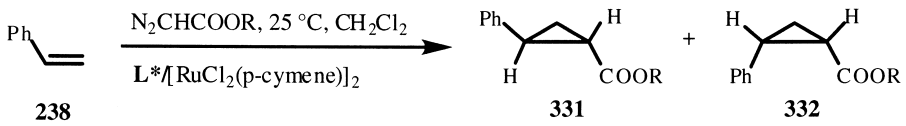
3.8.6. Cyclopropanation. The synthesis of optically active cyclopropane derivatives by the stereoselective addition of a carbenoid reagent to an alkene is an important reaction from a historical as well as a practical point of view.[95] To evaluate the efficiency of the N,N,P-chelate ligands **128a–c** in the asymmetric cyclopropanation, Ahn et al. examined the inter- and intramolecular Ru(II)-catalysed cyclopropanation of various olefins using $[RuCl_2(p\text{-cymene})]_2$ as the procatalyst[43] (Schemes 60–62).



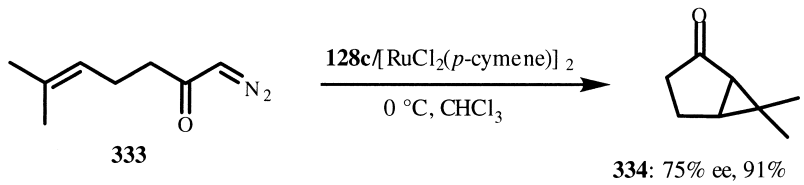
Scheme 57.



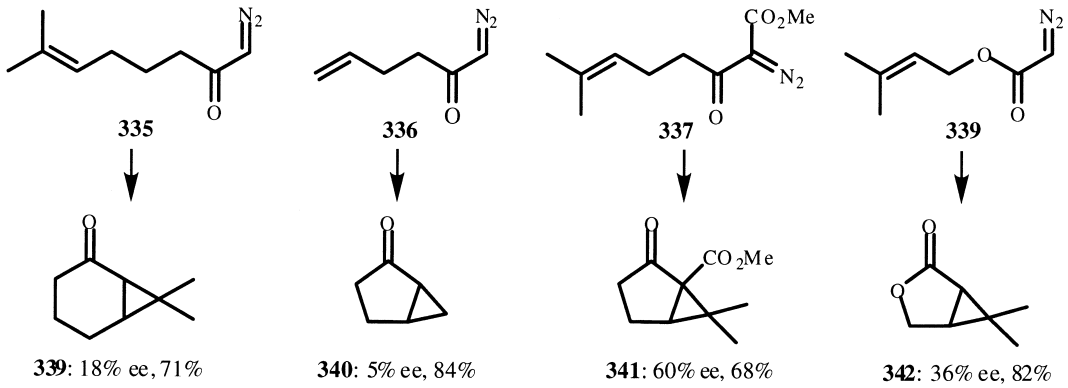
Scheme 59.



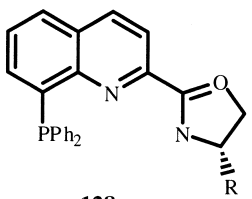
Scheme 60.



Scheme 61.



Scheme 62.



128a-c R: **a** = *i*-Pr; **b** = Ph; **c** = *t*-Bu

The reaction of styrene (**238**), to form the cyclopropanes **331** and **332** (Scheme 60), afforded a disappointingly low enantioselectivity, although it gave good yields (Table 12). In contrast, the catalyst exhibited good reactivity and high thermal stability and provided high yields in the intramolecular cyclopropanation. The optimal conditions were determined for the reaction of the diazo-ene **333** that afforded the cyclopropane **334** in 75% ee and 91% yield when the ligand **128c** was used (Scheme 61). Several other substrates **335**–**338**, to form the cyclopropanes **339**–**342**, were studied, but only a poor to moderate selectivity was observed, showing a large fluctuation in the enantioselectivity depending on the substrates used (Scheme 62).

Table 12. Enantioselective cyclopropanation of styrene with alkyl diazoacetates using Ru(II)–**128** complexes

Ligand	R	Yield (%) **331**+**332**	*trans*–*cis* **331**–**332**	ee (%)	
				331	**332**
128a	Et	59	68:38	4	7
128c	*l*-Menthyl	81	89:11	28	65

4. Conclusions

Although (pyr-phos)-ligands have been known for a long time and have been used largely in coordination chemistry, only in the last decade has an increasing number of chiral non-racemic derivatives of this type of ligands been prepared and their metal complexes applied in catalytic asymmetric synthesis.

Although the versatility of these ligands has been demonstrated in numerous catalytic asymmetric syntheses, new opportunities are yet to be explored.

It is hoped that this review will stimulate further research so

that new (pyr-phos)-systems can be designed and their metal complexes applied in other areas of organic synthesis.

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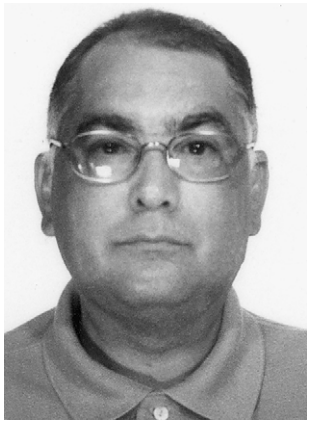
Biographical sketch



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