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Axially chiral bidentate ligands in asymmetric catalysis

Mary McCarthy and Patrick J. Guiry*

Department of Chemistry, Conway Institute of Biomolecular and Biomedical Sciences, University College Dublin, Belfield, Dublin 4, Ireland

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1. Introduction

The preparation of enantiomerically pure compounds is an important and challenging area of contemporary synthetic organic chemistry.[1] The need for access to chiral compounds of a given absolute configuration stems from the relationships between the absolute configuration of organic compounds and their biological properties. There are numerous well-documented cases which highlighted the necessity for the preparation of enantiopure compounds and the development of chiral analytical techniques. Legislation was introduced in 1988 and implemented by the Food and Drug Administration (FDA), who require any company wishing to license a novel active ingredient as a racemic mixture to establish the activity of both enantiomers and also to show that the unwanted enantiomer does not cause any adverse effects. Two thirds of the 1200 drugs in development in 1996 were chiral and 51% were being developed as single enantiomer drugs. The market for

* Corresponding author. Tel.: +353-1-7062309; fax: +353-1-7062127; e-mail: p.guiry@ucd.ie

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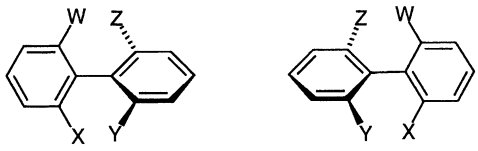


Figure 1.

dosage forms of single enantiomer drugs increased from $73 billion in 1996 to above $96 billion in 1998 and is estimated to rise above $100 billion by the end of this year.[2] Therefore, the search for efficient syntheses of enantiomerically pure compounds is an active area of research in both academic and industrial laboratories.

There are three main approaches to obtaining pure enantiomers, namely synthesis using compounds from the chiral pool, resolution of a racemic mixture and asymmetric synthesis. Asymmetric synthesis may be accomplished by the use of chiral reagents or auxiliaries and a plethora of well-developed examples of both approaches have been reported.[3] The asymmetric catalysis approach has obvious advantages over the reagent and auxiliary approach since a small amount of enantiomerically pure material can produce large quantities of enantiomerically enriched or enantiopure material. This research area includes the use of enzymes,[4] non-metal-based catalysts[5] and metal catalysts.[6] It is the application of man-made metal complexes for homogeneous catalysis that is pertinent to the present review.

The catalytic activity of a metal catalyst originates from the metal and the asymmetry of the metal-catalysed process is almost always induced by the organic ligands attached to that metal. These organic ancillaries, which may be viewed as a chiral scaffolding, control the binding of reactants and their subsequent reaction paths through steric and electronic interactions. Commonly used donor atoms, which include phosphorus, nitrogen, oxygen and sulfur, help to electronically tune the metal. A vast number of mono-, bi- and polydentate ligands have been successfully applied in asymmetric catalysis.[6]

Typically, once novel ligands have been prepared, their metal complexes are tested for their catalytic activity and enantiodifferentiating ability in standard transformations. These 'test' reactions include (among others) hydrogenation of olefins and carbonyl groups, allylic substitution and the addition of diethylzincs to aldehydes, whilst the oxidative transformations of epoxidation, hydroboration and hydrosilylation are also important. The ligands employed in these metal-catalysed processes possess elements of central, planar and axial chirality and/or combinations of these.[6] The research to date highlights the difficulty in finding a 'universal' ligand suitable for a wide spectrum of reactions. More commonly, there is a need for the tailoring of ligands within each transformation for each substrate used.

Axial chirality (atropisomerism) results from restricted rotation about single bonds, where the rotational barrier is sufficient to allow isolation of the enantiopure species. Biaryl isomerism, especially with respect to the substitution required for restricted rotation, has been extensively studied.[7] Oki arbitrarily defined the condition for the existence of atropisomerism as one where the enantiomers can be isolated and have a half-life of at least 1000 s.[8] The required free energy barrier is, however, temperature dependent: it is 61.5 kJ/mol at −73°C, 93.3 kJ/mol at 27°C and 109.6 kJ/mol at 77°C. Most tetra-*ortho*-substituted biphenyls (Fig. 1, W, X, Y, Z≠H) are resolvable and are stable to racemisation provided that at least two of the groups are not fluorine or methoxy. Tri-*ortho*-substituted biphenyls are readily racemised, especially when one of the the substituents is a fluorine or methoxy and otherwise the process is slow. Di-*ortho*-substituted biphenyls are only resolvable if the substituents are large, e.g. 1,1′-binaphthyl was found to readily racemise with a half-life of ca 0.5 s at 160°C.[9] An important note on nomenclature is that the descriptors a*R* and a*S* are sometimes used to distinguish axial chirality from other types. Alternatively, chiral axes may be viewed as helices and using helix nomenclature, *M* corresponds to a *R* and *P* corresponds to a *S*, where *M* and *P* originate from helix nomenclature.

2,2′-Substituted 1,1′-binaphthyls are particularly good examples due to their highly stable configuration and are good candidates as chiral ligands for asymmetric catalysis. Their conformational flexibility about the binaphthyl C(1)–C(1′) pivot allows a range of bite angles to accommodate a wide variety of transition metals.

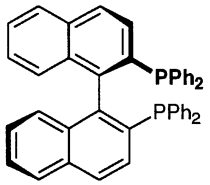
The use of atropisomeric binaphthyls as chiral auxiliaries in asymmetric synthesis has previously been reviewed by Salvadori in 1992 and Pu has reviewed atropisomeric binaphthyl dimers, oligomers and polymers in molecular recognition, asymmetric catalysis and novel materials in 1998.[10,11] Apart from these excellent reviews the application of atropisomeric biaryls solely to asymmetric catalysis has not been the focus of any single review.

In this review, which covers the literature up to the end of 1999, we attempt to systematise the role which bidentate, axially chiral ligands play in asymmetric catalysis. The ligands will be classified, not by the reactions to which their metal complexes have been applied, but by the biaryl and other groups present which induce chirality. Within this sub-classification the ligands will be described, where feasible, in the chronological order in which they were reported so that the development of ligand architectural design can be more easily monitored. The review is not meant to be comprehensive but the more relevant ligands and applications, in the opinions of the authors, will be described. The use of axially chiral 1,1′-binaphthol-type ligands in Lewis acid chemistry is not included as this is a topic which has been reviewed recently.[12]

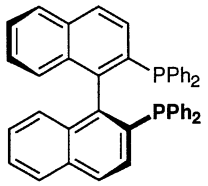
2. Diphosphine ligands

2.1. BINAP in asymmetric catalysis

The most well-known example of an axially chiral ligand is the diphosphine, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) **1**, a C_2-symmetric triaryldiphosphine (Scheme 1), the synthesis and first application of which



1 (*R*)-BINAP



1 (*S*)-BINAP

Scheme 1.

were reported by Noyori and Takaya in 1980.[13] This ligand very effectively induces asymmetry by intra-complex steric interactions between the bulky triarylphosphine system and the reactants bound to the metal. Its application in asymmetric catalysis has been reviewed in 1990[14] and 1992[10] and subsequently its use has been well documented in numerous textbooks.[6] Only a summary of its applications before 1992 will therefore be detailed here and an emphasis will be placed on its more recent successes.

Up to and including 1992, ruthenium complexes of BINAP **1** had proved to be successful in inducing high to excellent enantioselectivities in the hydrogenation of olefinic substrates, such as a range of α,β-unsaturated carboxylic acids **2**[15] (Scheme 2). *N*-acylaminoacrylic acids **3** were successfully reduced using Ru(II)–BINAP and Rh(I)–BINAP complexes in high to excellent enantioselectivities (Scheme 3).[13,16] The scope of Rh(I)–BINAP catalysis is, however, limited to a small range of suitably functionalised olefin substrates, whereas Ru(II)–BINAP chemistry has a broad utility.

Highly enantioselective reduction of the substituted allylic alcohols **4** has also been achieved (Scheme 4). With the latter substrates, the sense and extent of asymmetric induction are highly dependent on the substitution pattern and the reaction conditions, in particular the hydrogen pressure employed.[17]

Racemic allylic secondary alcohols, e.g. 4-hydroxy-2-cyclopentenone **5**, were successfully resolved by a kinetic resolution process using BINAP–Ru-catalysed hydrogenation[18] (Scheme 5).

As with olefin hydrogenations, the application of BINAP–Ru complexes to the enantioselective reduction of carbonyl groups had reached a high level of success by 1992. α-Keto acid derivatives **6** were reduced in quantitative yields with enantioselectivities of up to 89% (Scheme 6).[19]

Similarly, excellent reactivities and enantioselectivities were obtained with β-keto esters **7** as the substrates (Scheme 7).[20] The asymmetric reduction of 1,3-dicarbonyl systems with Ru-biarylphosphine catalysts was reviewed by Ager in 1997.[21]

The hydrogenation of γ-keto esters **8** and *o*-acylbenzoic esters **9** by BINAP–Ru complexes affords the corresponding γ-lactones or *o*-phthalides in excellent enantioselectivities (Scheme 8).[22]

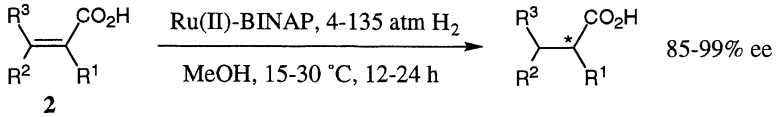
Other successful substrates for BINAP–Ru catalysed enantioselective reduction include amino and hydroxy ketones **10** (Scheme 9).[19,23]

A particularly efficient dynamic kinetic resolution of the α-substituted β-keto esters **11** using BINAP–Ru catalysts has also been developed, where >95% yield of one of the four possible diastereomeric hydroxy esters is obtained in excellent enantiomeric and diastereomeric excess (Scheme 10).[24]

The BINAP–Rh catalysed enantioselective isomerisation of the allylamines **12** and **13** to optically active enamines proceeds with high chemoselectivity and excellent enantioselectivity (96–99% ee). In this asymmetric isomerisation there is an excellent correlation between the substrate geometries, product (*E*)-enamine configurations and the BINAP chirality (Scheme 11).[25]

The enantioselective substitution of allylic acetates is the most studied asymmetric carbon–carbon bond forming process catalysed by transition metal complexes of palladium.[26] It is an important transformation and has proved to be a useful testing ground for the design and testing of novel ligands and for gaining mechanistic insights into organopalladium chemistry. Pd complexes of BINAP were applied with some success to the standard test reaction of malonates and 1,3-diphenylpropenyl acetate **14**. The reaction times were relatively long and enantioselectivities and chemical yields were moderate to good (Scheme 12).[27]

A second carbon–carbon bond forming reaction to which palladium complexes of BINAP have been studied is the Heck reaction.[28] In the intermolecular variant, the test reaction is between 2,3-dihydrofuran **15** and the aryl triflates **16**. Hayashi reported that this reaction, which proceeded in the presence of a base and a palladium catalyst generated in situ from $Pd(OAc)_2$ and (*R*)-BINAP, gave the (*R*)-2-aryl-2,3-dihydrofuran **17** and a small amount of the (*S*)-2-aryl-2,5-dihydrofuran **18** (Scheme 13).[29] The base affected the enantiomeric purity of (*R*)-**17** and the sterically demanding 1,8-bis(dimethylamino)naphthalene



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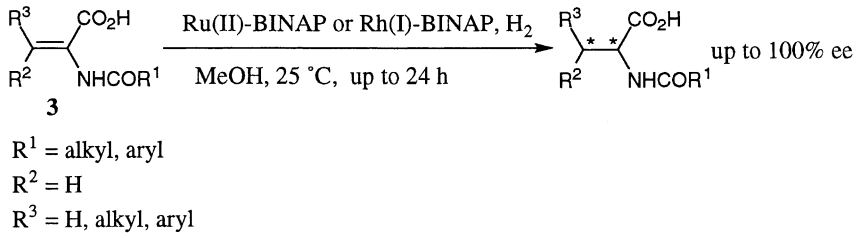
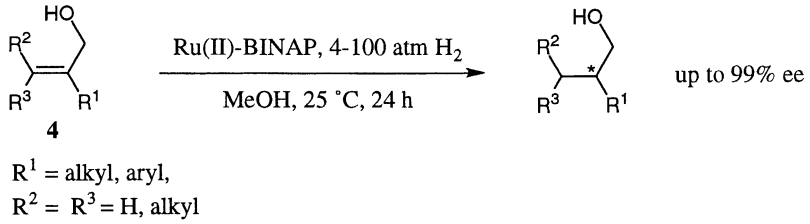
R^1 = alkyl, aryl, hydroxycarbonylalkyl
R^2 = H, hydroxyalkyl
R^3 = H, alkyl

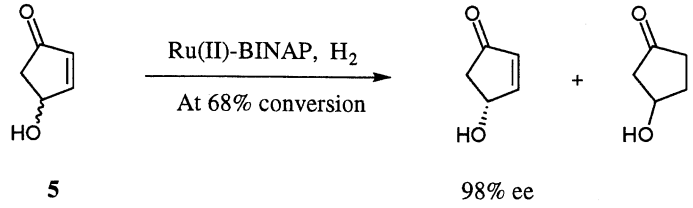
Scheme 2. Reduction of α,β-unsaturated carboxylic acids.



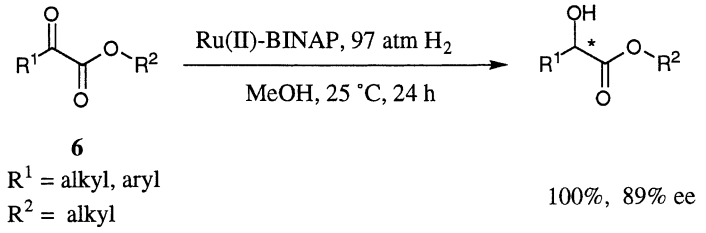
Scheme 3. Reduction of *N*-acylaminoacrylic acids.



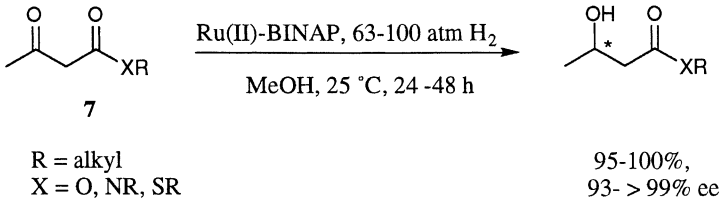
Scheme 4. Reduction of allylic aclohols.



Scheme 5. Kinetic resolution of allylic alcohols.



Scheme 6. Asymmetric reduction of α-keto acid derivatives.



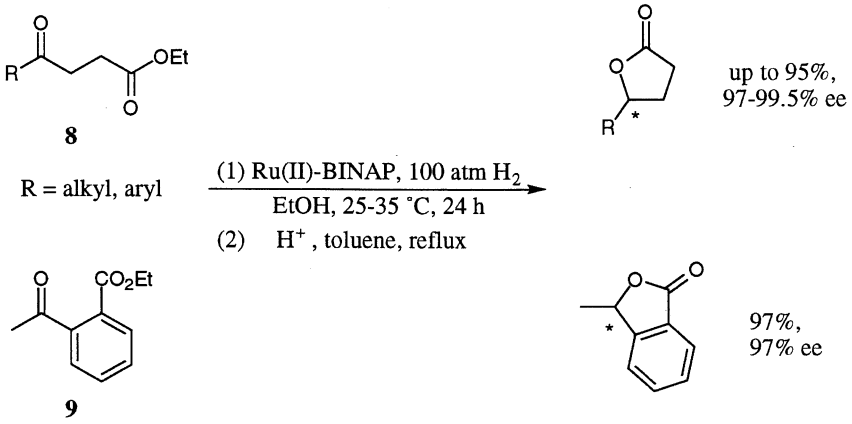
Scheme 7. Asymmetric reduction of β-keto esters.

(proton sponge) afforded the best results for a range of aryl triflates (Table 1).

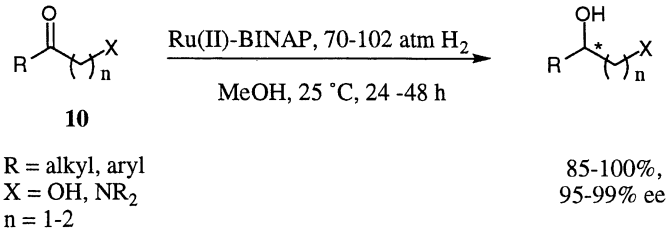
The first successful intramolecular asymmetric Heck reactions using BINAP–Pd complexes were reported in 1989 by Shibasaki who focused on the preparation of the *cis*-decalin derivatives **19** from the prochiral alkenyl iodides or triflates **20** and obtained enantioselectivities of up to 92% in moderate chemical yields of 60% (Scheme 14).[30]

Overman showed that, despite using the same hand of BINAP, the sense of enantioselection could be opposite in the Heck cyclisations of aryl iodides depending on the careful choice of reaction conditions.[31] The aryl iodide **21**, for example, afforded either the spirooxoindole (*R*)-**22** or spirooxoindole (*S*)-**22** in reasonable enantioselectivities in palladium-catalysed cyclisations carried out in the presence or absence of silver salts (Scheme 15).

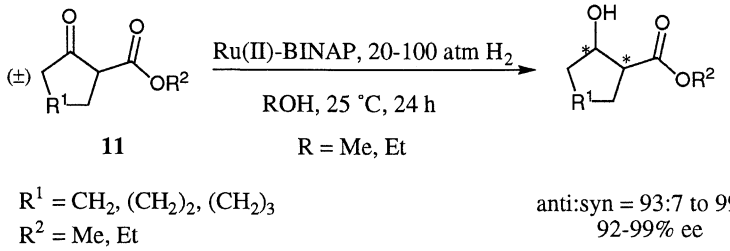
The hydroboration of vinylarenes, catalysed by cationic



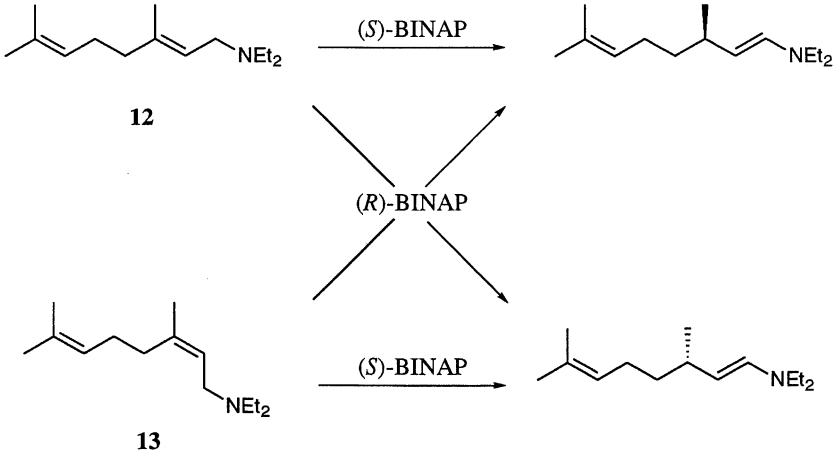
Scheme 8. Reduction of γ-keto esters and *o*-acylbenzoic esters.



Scheme 9. Reduction of amino and hydroxy ketones.

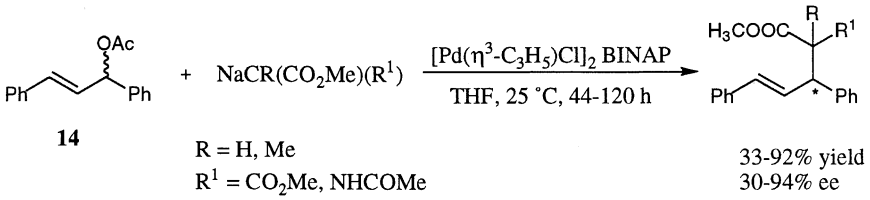


Scheme 10. Dynamic kinetic resolution of α-substituted β-keto esters.

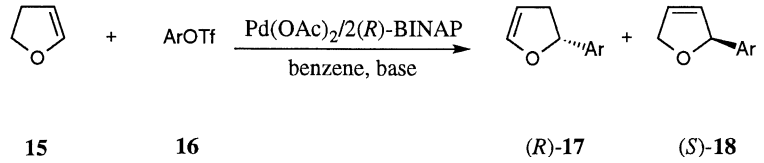


Scheme 11. Enantioselective isomerisation of allylamines.

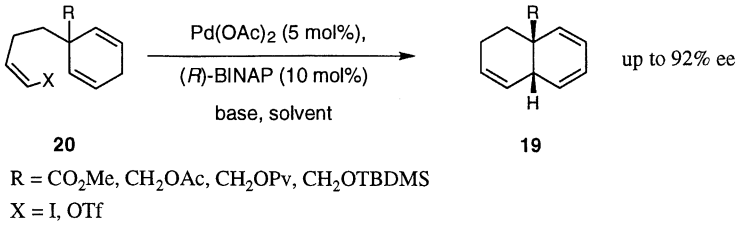
rhodium(I)–phosphine complexes, has become a transformation of significant importance.[32] One of the first enantioselective variants was developed by Hayashi who employed rhodium–BINAP complexes for hydroboration of the styrenes **23** in ees of up to 96% (Scheme 16).[33] Cyclic vinylarenes, such as indene **24** and dihydronaphthalene **25**, were poor substrates as only 19% ee was obtained with **24**, whereas no reaction was reported for **25**.



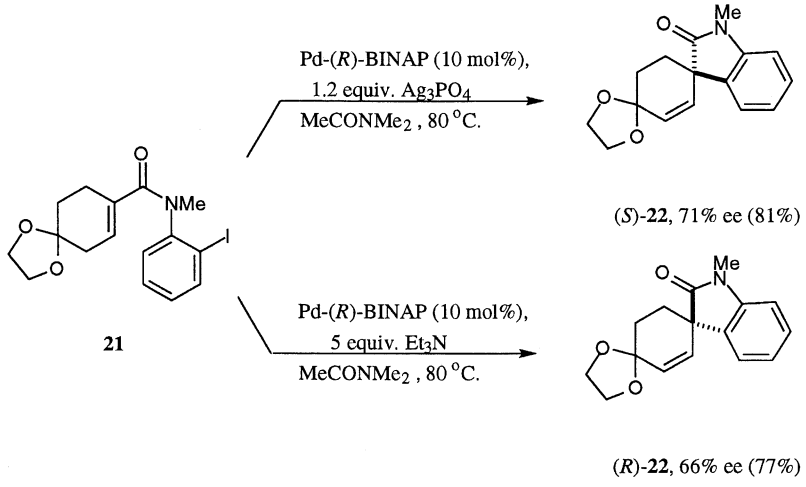
Scheme 12. Enantioselective allylic alkylation.



Scheme 13. Intermolecular asymmetric Heck reaction.



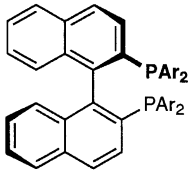
Scheme 14. Intramolecular asymmetric Heck reaction.



Scheme 15.

2.2. BINAP analogues in asymmetric catalysis

Taking the above summary of applications of metal complexes of BINAP as being representative of its success in inducing such high levels of asymmetry, it is not surprising that the synthesis and design of other atropisomeric diphosphines became an active area of research in the late 1980s and continues to the present day. The electronic properties at phosphorus were the first variation to be investigated and this led to the preparation and application of a series of BINAP analogues **26**–**31**, which retain the 1,1′-binaphthyl backbone but differ in the bis-arylphosphine group.[13b,34]



26: Ar = 3-MeC_6H_4
27: Ar = 4-MeC_6H_4
28: Ar = 4-$MeOC_6H_4$
29: Ar = 3,5-$(Me)_2C_6H_3$
30: Ar = 4-ClC_6H_4
31: Ar = 4-FC_6H_4

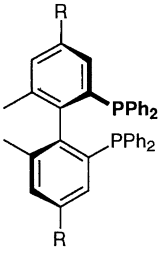
These modified BINAP analogues have been applied to

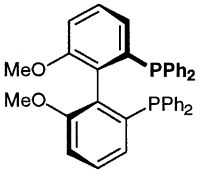
Table 1. Enantioselective palladium-catalysed Heck reaction with (*R*)-BINAP

ArOTf (Ar)	ee (%), (% yield)	
	(*R*)-17	(*S*)-18
p-ClC_6H_4	>96 (54)	6 (21)
m-ClC_6H_4	>96 (66)	39 (22)
o-ClC_6H_4	92(53)	53 (21)
p-AcC_6H_4	>96 (50)	7 (24)

ruthenium-catalysed hydrogenation processes and there are examples where reaction rates and selectivities are improved compared to the parent BINAP catalyst system, e.g. in the hydrogenation of the β-keto ester **32**, Ru-(**28**) complexes gave the product in 99% ee after 27 h using a higher substrate/catalyst (*S*/*C*) ratio (Scheme 17).[35,36] Use of [RuI(*p*-cymene)(bisphosphine)]I catalysts prepared from ligands **27**, **29** and **31** results in loss of enantioselectivities in the reduction of **32** compared to BINAP (97, 93 and 97% vs 99%, respectively).[34]

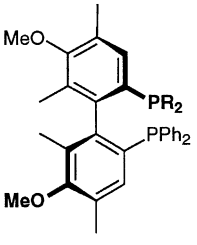
The biphenyl system is easier to modify geometrically, sterically or electronically than the binaphthyl system, leading to the synthesis of a variety of atropisomeric biphenyl diphosphines and the application of their metal complexes in asymmetric catalysis. The groups of Schmid and Frejd have independently prepared 2,2′-bis(diphenylphosphino)-6,6′-dimethyl biphenyl (BIPHEMP) **33** and the related analogues **34**–**35**.[37,38] As the biphenyl group, like the binaphthyl group, is not completely rigid it can form a variety of stable chelate complexes with many transition metals. It was, however, necessary to substitute the 6,6′-positions in order to prevent racemisation.

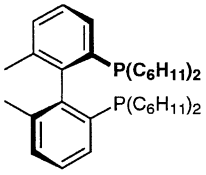




R = H **33** (BIPHEMP)
R = Me **34**
R = NMe_2 **35**

36 (MeO-BIPHEP)

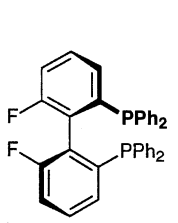




R = C_6H_5 **37** (BIMOP)
R = C_6H_{11} **38** (MOC-BIMOP)

39 (BICHEP)

MeO-BIPHEP **36**, an analogue of BIPHEMP **33**, was also reported by Schmid and is an example in which the electronic properties at phosphorus have been varied.[39] The related ligands BIMOP **37** and MOC-BIMOP **38** have been described by Achiwa.[40] The dialkylmonoarylphosphine, BICHEP **39**, reported by Takaya is particularly electron rich.[41] The diphosphine **40**, prepared by Jendralla, is the first example of an electron-poor biphenyl-type ligand.[42] Similar electron-deficient biarylphosphines, FUPMOP **41** and BIFUP **42**, were also reported by Achiwa.[40a]



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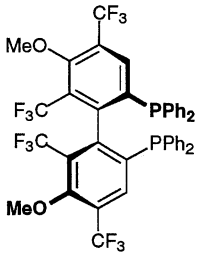
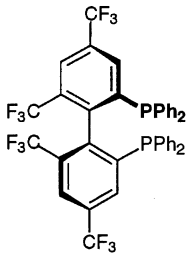
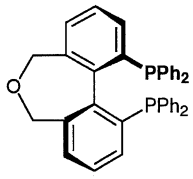


41 (FUPMOP)



42 (BIFUP)



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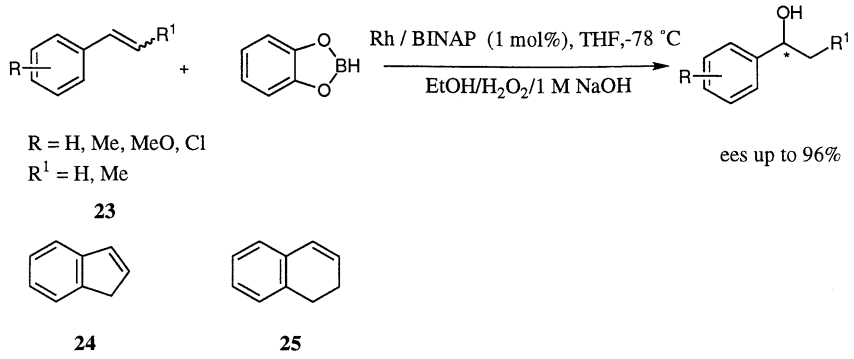
[RuI(*p*-cymene)(bisphosphine)]I catalysts prepared from the majority of the ligands **33**–**42** were applied in the reduction of β-keto esters and gave similar reactivities and enantioselectivities compared to BINAP as long as the ligand employed contained at least one electron-donating substituent, regardless of whether the ligand also possessed electron-withdrawing substituents. The reactivity was deleteriously affected by the presence of only electron-withdrawing groups on the biphenyl backbone and the enantioselectivities were lowered slightly.[21,40a]

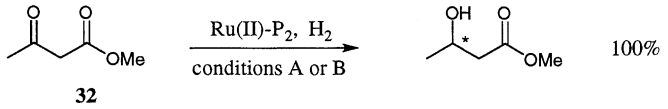
The dihedral angle of a ligand (for seven-membered chelates, the angle between the carbon atoms bearing the donor atoms) is directly related to its natural bite angle. Changes in this dihedral angle, which may be controlled by varying the steric bulk of the 6,6′-substituents, can lead to enhanced asymmetric induction. The angle can also be held within a limited range by bridging the 6,6′-positions, e.g. in the diphosphine **43**.[39a] Here, the torsional mobility is restricted and **43** is, therefore, more rigid than BIPHEMP **33**.

Table 2. Rh-catalysed asymmetric isomerisation of *N*,*N*-diethylnerylamine **12**[37]

Rh((*R*)-L)(cod)BF_4 ligand	Yield (%)	ee (%) Configuration
1	97	96 (*R*)
33	95	98 (*R*)
34	90	98 (*R*)
35	60	98 (*R*)
36	90	98 (*R*)
43	89	98 (*R*)



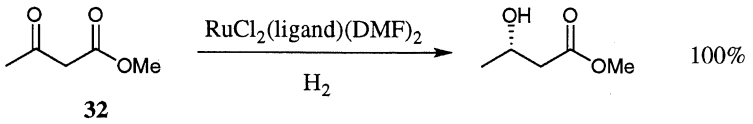
Scheme 16.



A; Ligand **1**, MeOH, 1500 psi H_2, 50 °C, S/C 1,000, 48 h, 98% ee

B; Ligand **28**, MeOH/CH_2Cl_2, 1500 psi H_2, 30 °C, S/C 4,000, 27 h, 99% ee

Scheme 17.

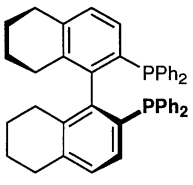


Ligand (*S*)-**1**, S/C 1150, 99% ee

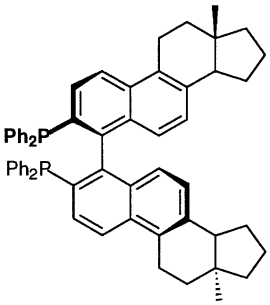
Ligand (*S*)-**45**, S/C 1260, 99% ee

Scheme 18.

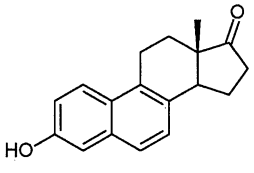
Many of the ligands (**33**–**43**) have been applied in the rhodium-catalysed asymmetric isomerisation of *N*,*N*-diethylnerylamine **12** (Scheme 11) and a comparison of the results, shown in Table 2, is useful. Each of the ligands tested gave slightly higher enantioselectvities than BINAP.



44 (H_8-BINAP)



45

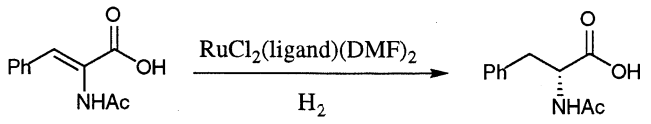


46

Ruthenium(II) complexes of H_8-BINAP **44** have been reported to be more effective catalysts for the asymmetric hydrogenation of α,β-unsaturated carboxylic acids than various ruthenium(II) complexes of BINAP **1**.[43,44] X-ray crystallography of the cationic Rh(I) complex, [Rh((*S*)-H_8–BINAP)(COD)]ClO_4, showed that the dihedral angle between the two aromatic rings is larger than that in the analogous complexes of BINAP and BIPHEMP. This increase in dihedral angle probably contributes to the enhanced enantioselective induction by H_8-BINAP by making the area available to the substrate at the metal smaller.

In 1997, Mohr reported the preparation of the diphosphine **45**, a variant of BINAP. This approach has the advantage of the non-requirement for resolution as it originates from the enantiomerically pure steroidal precursor, equilenine **46**, although the initial copper-promoted biaryl coupling proceeded with only moderate diastereoselectivities (20% de favouring *R*-axial chirality).[45] Ru complexes of **45** were applied in the reduction of methyl acetoacetate **32** and similar activities to BINAP were observed (Scheme 18).

Differences between **45** and BINAP were, however, observed in the reduction of α-acetamidocinnamic acid **47**, with **45** giving a higher ee (86 vs 77%) (Scheme 19). It is not clear what role the extra chiral centre of the ligand plays in inducing such a different enantiomeric excess.

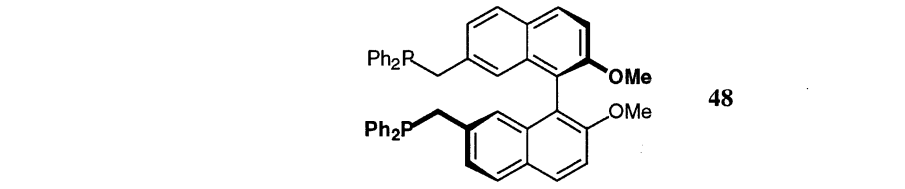


47

Ligand (*R*)-**1**, S/C 340, 7 atm H_2, 72 h, 90%, 77% ee

Ligand (*R*)-**45**, S/C 605, 7 atm H_2, 48 h, > 98%, 86% ee

Scheme 19.



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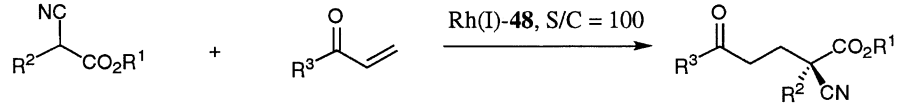


49

R^1 = Et, *i*-Pr, *t*-Bu

R^2 = Me

R^3 = Me, OMe

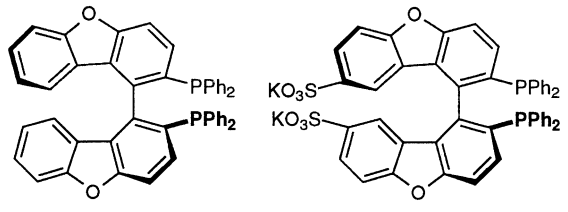
86-98% yield

11-73% ee

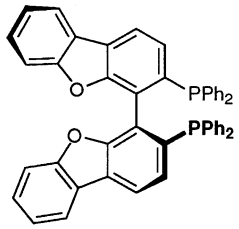
Scheme 20. Enantioselective Michael reactions.

Takaya, also in 1997, reported the preparation of 7,7′-bis(diphenylphosphinomethyl)-2,2′-dimethoxy-1,1′-binaphthyl **48**, a diphosphine ligand which possesses the axial chirality of a 1,1′-binaphthyl unit and has a sufficiently large bite angle to form *trans*-chelating organometallic complexes.[46] Rh(I) complexes of other *trans*-chelating diphosphines have been applied in asymmetric Michael reactions[47] of the 2-cyano esters **49** and Rh(I) complexes of **48** were applied in a similar test reaction, affording enantioselectivities from 11 to 73% in chemical yields of up to 98% (Scheme 20).

In 1999, Hiemstra reported the preparation and application of the dibenzofuran-based ligand BIFAP **50** and its sulfonated derivative BIFAPS **51**,[48] which are related to the analogous ligand BIBFUP **52**, developed by Laue and co-workers at Bayer in 1995, but for which no applications in catalysis have been reported.[49]

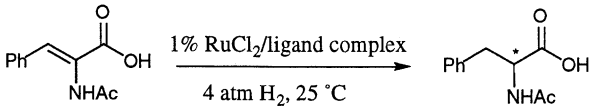


50 (BIFAP) **51**



52 (BIBFUP)

Ru–BIFAP and BIFAPS complexes were applied to the reduction of (*Z*)-acetamidocinnamic acid **47** and both showed somewhat lower enantioselectivities compared to BINAP **1** (Scheme 21).



47

Ligand (*R*)-**1**, 24 h, 100%, 87% ee (*R*)

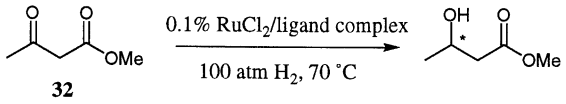
Ligand (*S*)-**50**, 100 h, 100%, 82% ee (*S*)

Ligand (*R*)-**51**, 48 h, 100%,72% ee (*R*)

Scheme 21.

Ru–BIFAP and BIFAPS complexes were also used for the reduction of methyl acetoacetate **32** and ligand **50** afforded excellent enantioselectivities similar to BINAP **1**. Under identical reaction conditions, the ruthenium complexes of ligand **51** gave 82% conversion after a prolonged reaction time of 68 h and only 11% ee. With the addition of 1% sulfuric acid, however, the results increased dramatically to rival those of ligand **50** (Scheme 22).

The first example of a diphosphine ligand **53**, where the biaryl system was replaced by a bi-heteroaryl system, was



32

Ligand (*R*)-**1**, MeOH, 2 h, 100%, 99% ee (*R*)

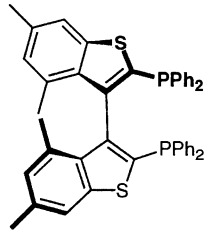
Ligand (*S*)-**50**, MeOH, 2 h, 100%, 100% ee (*S*)

Ligand (*R*)-**51**, MeOH, 68 h, 82%, 11% ee (*R*)

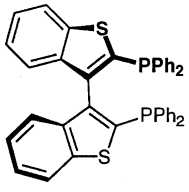
Ligand (*R*)-**51**, MeOH +1% H_2SO_4, 2 h, 100%, 100% ee (*R*)

Scheme 22.

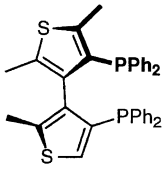
reported by Sannicolo and Cesarotti in 1995.[50] In designing this ligand, they wanted to compare the novel geometry of the interconnected five-membered rings with well-known six-membered ring biaryl systems. In addition, the electronic density at phosphorus should be increased relative to BINAP. Subsequently, the same group reported the preparation of the related BITIANP and TMBTP ligands **54** and **55**, respectively, but only the ruthenium complex of the former ligand **53** was applied in catalysis.[51] It reduced β-keto esters in ees up to 99%, kinetically resolved α-substituted β-keto esters with ees >99% and in 86% de (see Scheme 10), and reduced α-keto esters in 88% ee (see Scheme 6) and a range of olefinic substrates in 86–94% ee, these results being practically identical to those obtained using BINAP **1**.



53



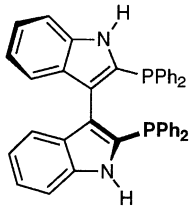
54 (BITIANP)



55 (TMBTP)

Palladium complexes of the ligands **54** and **55** were applied in the asymmetric intermolecular Heck reaction of aryl and alkenyl triflates with 2,3-dihydrofuran **15** (Scheme 23).[52] In contrast to BINAP which affords a mixture of regioisomers, the ligand **54** gave the 2-substituted 2,3-dihydrofuran in almost complete regioselectivity in high enantioselectivities (80–91%) and good yields. Even better results were obtained in the cyclohexenylation of **15**, with enantioselectivities of between 86 and 96% and yields of 76–93%.

A further example of a diphosphine ligand containing a biheteroaryl backbone is 2,2′-bis-diphenylphosphino-[3,3′]biindolyl **56** which was reported by Brown but applications of this ligand in catalysis have not been reported to date.[53]



56

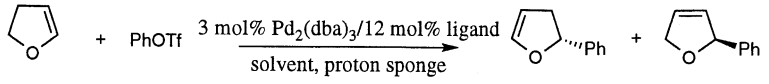
2.3. Recent applications of BINAP and analogues

In tandem with the preparation and application through the 1990s of novel axially chiral diphosphine ligands described above, new applications of metal complexes of diphosphines were also developed. In this section, we attempt to summarise some of the more important of these new transformations.

2.3.1. Hydrogenation. Impressive advances in the chemoselective reduction of carbonyls, e.g. the α,β-unsaturated substrate benzylidene acetone **57**, were developed by Takaya who employed BINAP–Ir(I)–aminophosphine complexes (Scheme 24).[54] Enantioselectivity of 65 and 97% carbonyl selectivity at 72% conversion was obtained.

Similar catalyst systems were successfully applied to the enantioselective reduction of the cyclic aromatic ketones **58** (Scheme 25).[55] Such substrates had proved difficult for conventional chiral phosphine catalysts but these novel mixed systems afforded yields of up to 95% and enantioselectivities of between 84 and 95%.

The alkyl phenyl ketones **59** were also tested and the enantioselectivity was highly dependent on the steric bulk of the alkyl group (Scheme 26).[56] The highest enantioselectivities were obtained when the alkyl groups were *i*-Pr



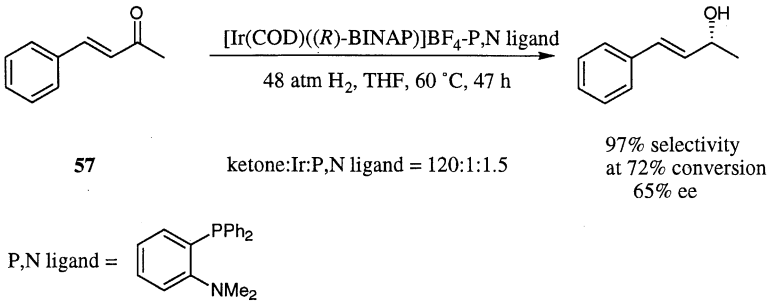
15 (*R*)-**17** (*S*)-**18**

Ligand (*R*)-**1**, DMF, 18 h, **17**:**18** = 7:1, 80% ee (**17**)

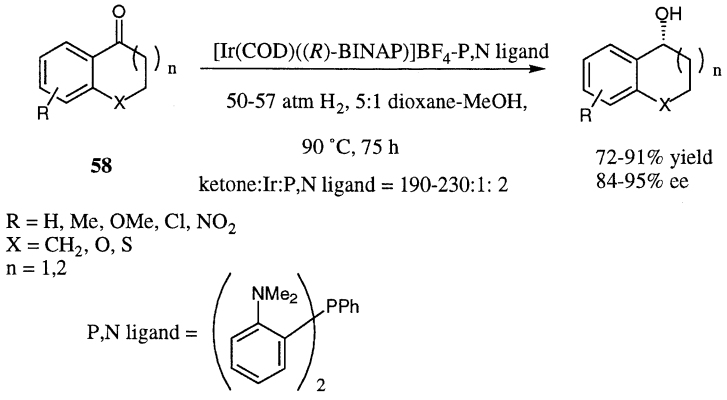
Ligand (*R*)-**54**, DMF, 20 h, **17**:**18** =100:< 1, 90% ee (**17**)

Ligand (*R*)-**55**, DMF, 3 d, **17**:**18** = 1:1, 4% ee (**17**), 2% ee (**18**)

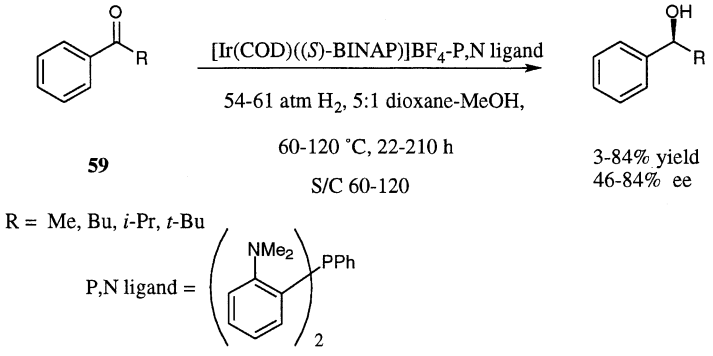
Scheme 23. Intermolecular Heck reactions with biheteroaryl diphosphine ligands.



Scheme 24. Carbonyl-selective reduction of **57**.



Scheme 25. Enantioselective reduction of aromatic ketones.



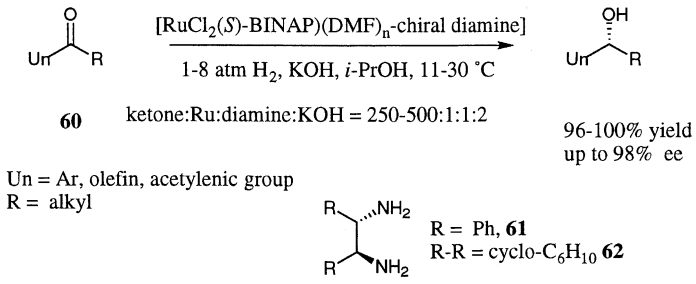
Scheme 26. Enantioselective reduction of acyclic aromatic ketones.

(84%). Complexes of H_8-BINAP **44** were applied to cycloalkyl aromatic ketones and gave increased enantioselectivity relative to the analogous BINAP-derived catalyst (80 vs 76%, respectively).

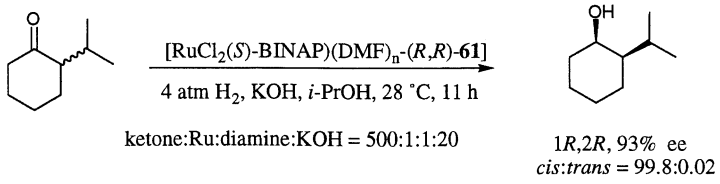
As the use of diphosphine–metal–aminophosphine catalyst systems proved to be so effective, further research ensued in which a diamine additive was tested. Particular success was obtained by Noyori in the enantioselective hydrogenation of a wide variety of aromatic and unsaturated ketones **60** using BINAP–Ru-chiral diamine-inorganic base catalyst systems (Scheme 27).[57] H_2 pressures of only 1–8 atm at ambient temperature were required for the quantitative preparation of secondary alcohols in up to 98% ee. The combination of (*S*)-BINAP and the (*S*)-diamines **61** (DPEN) and **62** gave the best results.

Diastereoselective reduction of racemic 2-*i*-propylcyclohexanone by a dynamic kinetic resolution is promoted by a catalyst combination of (*S*)-BINAP–Ru-(*R*,*R*)-**61** and quantitatively afforded the 1*R*, 2*R* alcohol in 93% ee with a *cis*/*trans* ratio of 99.8:0.02 (Scheme 28).[58]

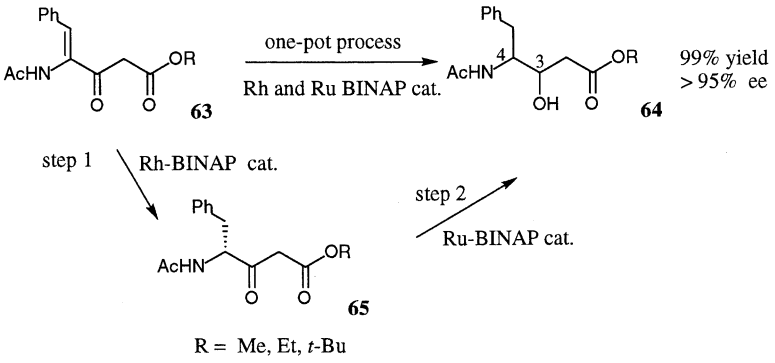
Takahashi has reported a one-pot, sequential asymmetric hydrogenation process utilising Rh(I)–BINAP and Ru(II)–BINAP catalysts as a direct method for the conversion of **63** into the core units of the four stereoisomers of the statine analogues **64** in practically enantiomerically pure form (Scheme 29).[59] The combination of Rh(I)–(*S*)-BINAP and Ru(II)–(*S*)-BINAP afforded (3*R*,4*R*)-**64** as Rh(I)–(*S*)-BINAP induced (*R*)-stereochemistry in the olefin reduction and Ru(II)–(*S*)-BINAP induced (*R*)-stereochemistry in the ketone reduction of **65**. This represents one of the first



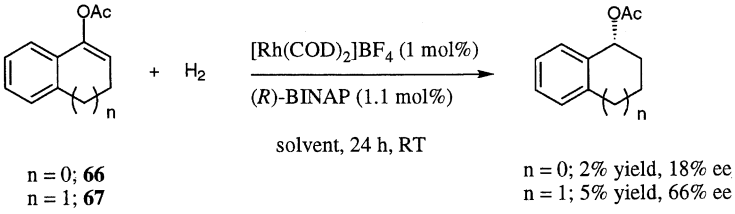
Scheme 27. Enantioselective reduction of ketones using BINAP–Ru-chiral diamine catalysts.



Scheme 28. Asymmetric hydrogenation via dynamic kinetic resolution.



Scheme 29. Sequential asymmetric hydrogenation using Rh(I)– and Ru(II)–BINAP catalysts.



Scheme 30.

one-pot uses of two metal catalysts in tandem, where the product of the first metal-catalysed reaction is the substrate for the second reaction.

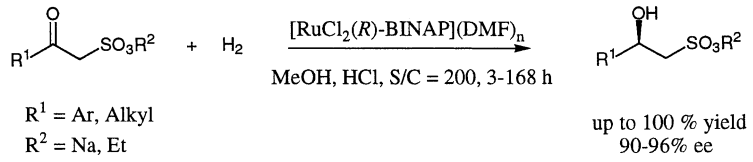
Other substrates to which the more conventional BINAP–Rh catalyst systems have recently been applied include the cyclic enol acetates (Scheme 30).[60] Very poor conversions and enantioselectivities were obtained with substrate **66**, although the enantioselectivity with substrate **67** improved to 66%, albeit with only a 5% conversion.

Ru–BINAP complexes catalyse the enantioselective hydrogenation of sodium β-keto sulfonates **68** in acidic methanol under atmospheric pressure of H_2 at 50°C to quantitatively give the corresponding β-hydroxy sulfonates with up to 96% ee (Scheme 31).[61]

Dixneuf and Bruneau have recently reported the use of Ru–BINAP complexes as catalysts for the enantioselective reduction of the ene carbamates **69** (Scheme 32).[62] Chemical yields of between 50 and 95% and enantioselectivities of up to 92% were obtained in a novel route to saturated carbamates.

Burk has increased the range of substrates for asymmetric hydrogenation by investigating γ,δ-dienamide esters **70** with Ru–BINAP and Rh–BINAP complexes (Scheme 33).[63] With the former complex as catalyst the conversion was 55% and the enantioselectivity was 83%, whereas the latter complex was active but not selective.

2.3.2. New applications. In 1994, Bosnich reported the use of Rh(I)–BINAP complexes in asymmetric intramolecular hydroacylation of the 4-pentenals **71** to the corresponding



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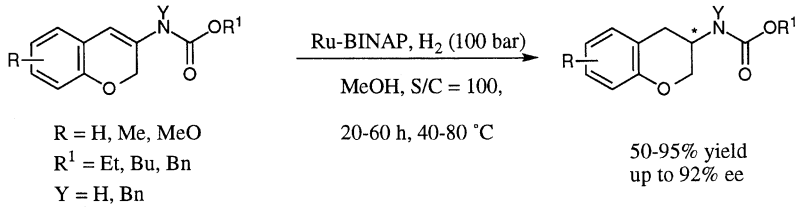
Scheme 31. Asymmetric hydrogenation of β-keto sulfonates.



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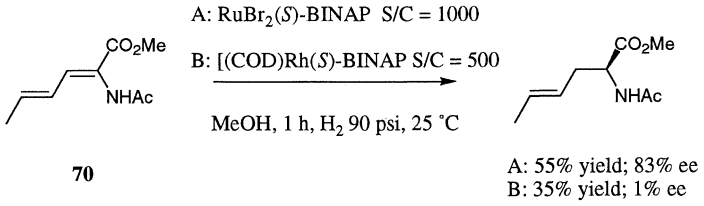
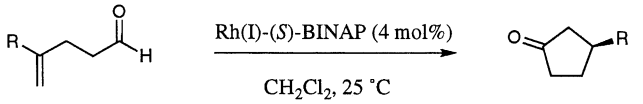
Scheme 32. Asymmetric hydrogenation of ene carbamates.



70

Scheme 33. Asymmetric hydrogenation of γ,δ-dienamide esters.



71

R = Me, *i*-Pr, *t*-Bu, Ar, CO_2Et, CO_2i-Pr

Scheme 34. Asymmetric intramolecular hydroacylation.

cyclic ketones (Scheme 34).[64] The optimal enantioselectivites were obtained with 4-pentenal substrates bearing 4-substituted tertiary substituents and esters.

The arylation of ketone enolates is a process which has received considerable attention, and Buchwald recently reported the first catalytic asymmetric variant using Pd–BINAP complexes and the α-methylcycloalkanones **72**–**73** (Scheme 35).[65] A range of substituted aryl bromides arylated **72** in yields of 40–73% and enantioselectivities of between 61 and 88%. The 2-methylcyclopentanone derivatives **73** were more successful substrates as the chemical yields were up to 86% and enantioselectivities were in the range 94–98%.

Hayashi reported an enantioselective Rh–BINAP-catalysed 1,4-addition of 2-alkenyl-1,3,2-benzodioxaboroles **74** to the α,β-unsaturated ketones **75** (Scheme 36).[66] The reactions afforded β-alkenylketones in high yields and in enantioselectivities of between 91 and 99%.

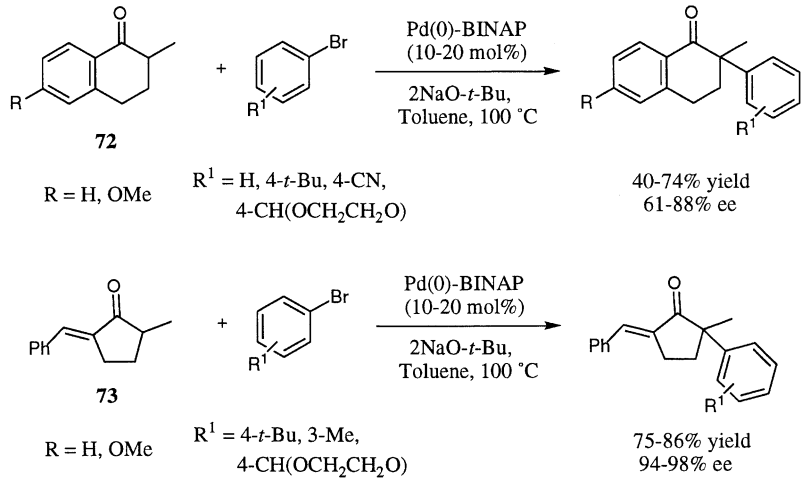
The application of Pt(II)–BINAP complexes as catalysts for the Baeyer–Villiger oxidation of ketones with hydrogen peroxide was reported by Strukul.[67] The enantioselective oxidation of the 4-substituted cyclohexanones **76** proceeded in good yields and enantioselectivities of 53–68% (Scheme 37).

A catalyst system based on $Pd(OTf)_2$–(*S*)-BINAP affected asymmetric carbonylative cyclisation of the *o*-allylaryl and 2-allylalkenyl triflates **77** with carbon monoxide to give high yields of the cyclopentenones in up to 95% ee.[68] The efficiency of the process for alkenyl triflates was significantly improved by the use of (*S*)-Tol-BINAP (in some examples the enantioselectivities were increased from 32 to 78%) and PMP (1,2,2,6,6-pentamethylpiperidine) was also a necessary additive for high enantioselectivities (Scheme 38).

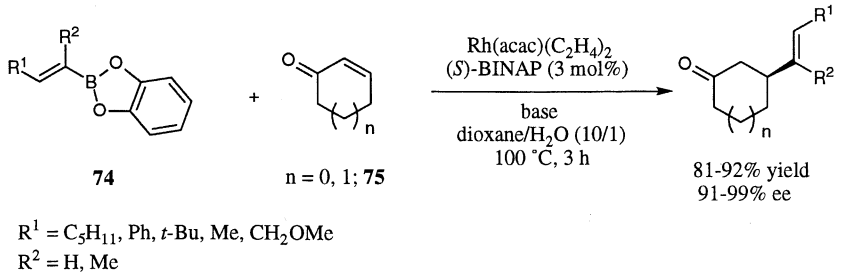
Ito reported that the asymmetric allylation of α-acetamido-β-ketophosphonates **78** was promoted, in the presence of potassium *t*-butoxide as base, by a catalyst prepared from $[Pd(\pi\text{-allyl})COD]BF_4$ and (*R*)-BINAP and gave the corresponding α-alkyl-α-aminophosphonic acid derivatives with 65–88% ee (Scheme 39).[69]

Jacobs used BINAP–Rh(I) for the asymmetric hydroformylation of vinyl acetate **79** and obtained product in moderate yields with enantioselectivities of up to 60% and regioselectivities of up to 99% (Scheme 40).[70]

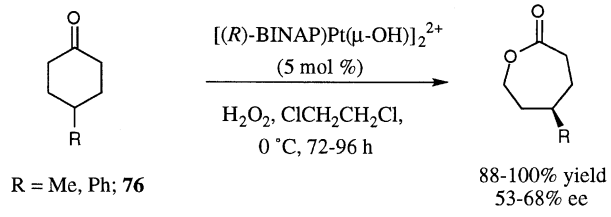
The scope of the previously described Rh(I)–BINAP-catalysed hydroboration of vinylarenes[33] has recently



Scheme 35. Asymmetric α-arylation of ketone enolates.



Scheme 36.

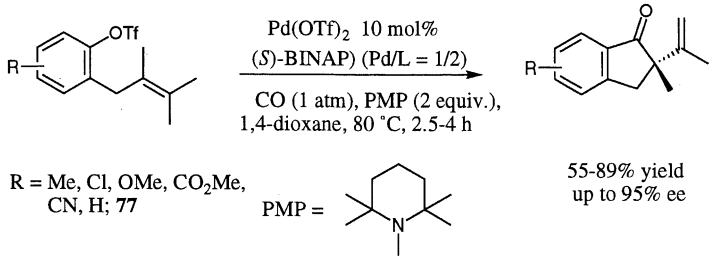


Scheme 37.

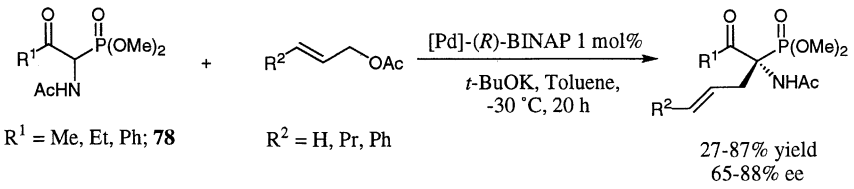
expanded by transforming the boronate esters **80** by homologation into the corresponding primary alcohols and carboxylic acids (Scheme 41).[71] This hydroxymethylation and hydrocarboxylation of vinylarenes uses a strategy in which the enantioselective step is separated from the carbon–carbon bond-forming step.

Yamamoto and co-wokers initiated a new area for metal–BINAP complexes with their report in 1996 of a highly enantioselective allylation of aldehydes with allyltributyltin catalysed by Ag(I)–BINAP complexes.[72] In their initial work, they employed allyltributyltin and a range of aldehydes **81** and obtained the corresponding homoallylic alcohols in moderate to high yield (25–95%) and with impressive enantioselectivities (88–97%) (Scheme 42). The Ag(I)–BINAP complex was proposed to act as a chiral Lewis acid catalyst rather than an allylsilver reagent.

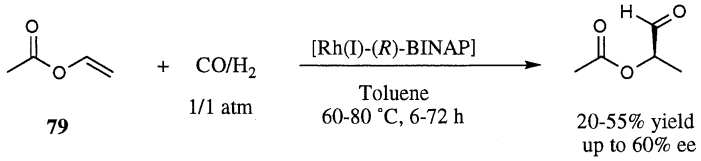
Subsequently, Yamamoto extended the range of allyltin reagents employed in this Ag(I)–BINAP-catalysed addition to aldehydes to include methallyl- and crotyltributyltin **82** and **83** (Scheme 43).[73] The enantioselectivities for the addition of **82** were high (70–98%) and the yields poor to high (22–96%), with the lowest yields and enantioselectivities obtained, as in Scheme 42, when alkyl aldehydes were tested. Regardless of the crotyltin geometry, *anti*-selectivity was preferred in a ratio of 85:15 in moderate to good yield



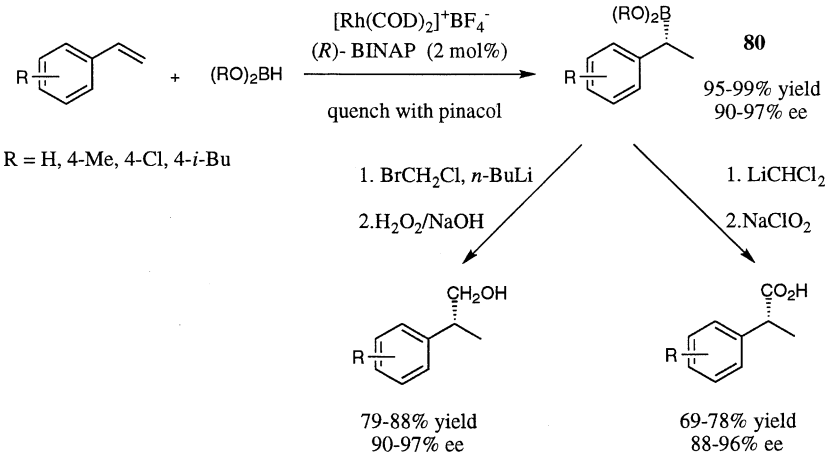
Scheme 38.



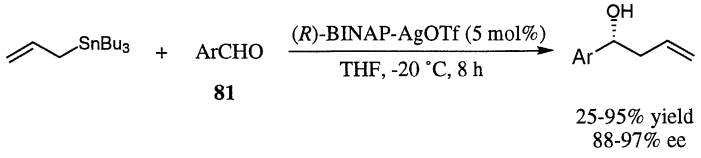
Scheme 39.



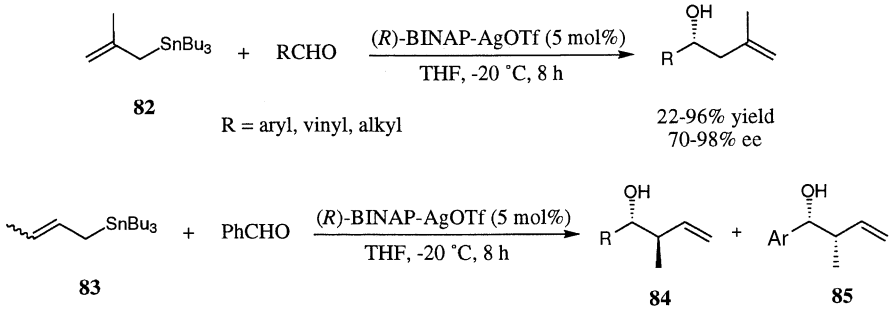
Scheme 40.



Scheme 41.

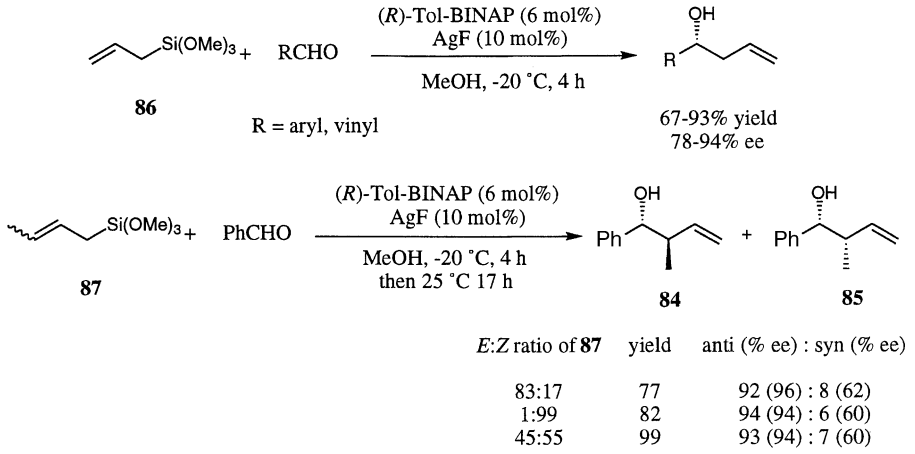


Scheme 42.

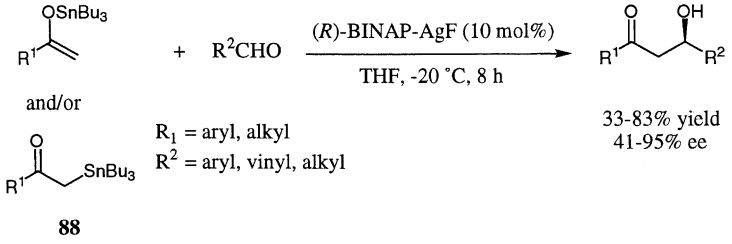


E:*Z* ratio of **83**	yield	anti (% ee) : syn (% ee)
95:5	56	85 (94) : 15 (64)
2:98	72	85 (91) : 15 (50)
53:47	45	85 (94) : 15 (17)

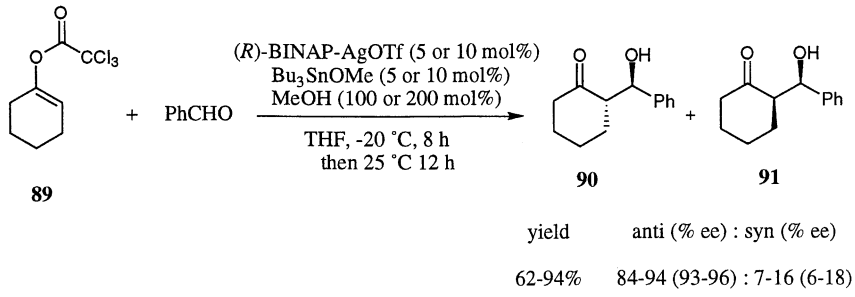
Scheme 43.



Scheme 44.



Scheme 45.



Scheme 46.

(45–72%) and the enantioselectivities for the *anti*-isomer **84** were up to 94% whilst those for the *syn*-isomer **85** were lower at 50–64%.

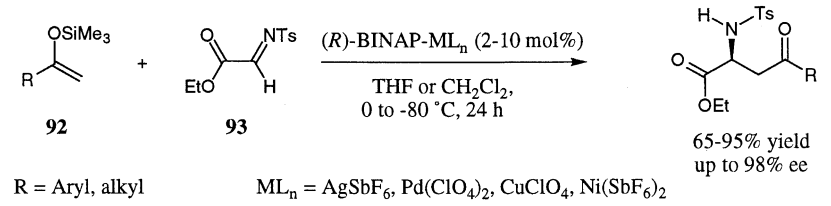
The related enantioselective addition of trimethoxysilanes **86** and **87** to aldehydes was reported to be catalysed by BINAP–AgF and Tol-BINAP–AgF complexes (Scheme 44).[74] The corresponding alcohols were obtained with high enantioselectivities (up to 96%) and *anti*-selectivity was again preferred (up to 94:6), irrespective of the double bond geometry of **87**.

In 1997, Yamamoto reported a highly enantioselective aldol reaction of aldehydes with tributyltin enolates **88** using BINAP–Ag(I) complexes as catalysts.[75] The additions to a range of aldehydes afforded the aldol products in moderate to high yield and up to 95% ee (Scheme 45).

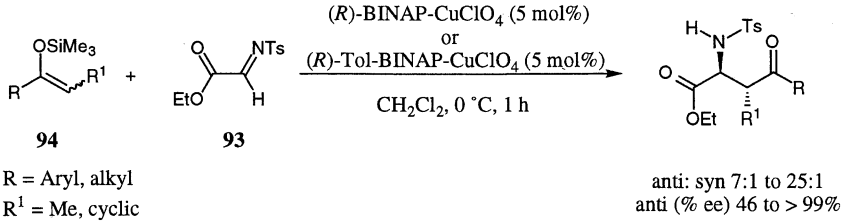
Subsequent to the aldol reaction of the tin enolate of cyclohexanone catalysed by a range of metal complexes,[76] the related enantioselective aldol reaction using a catalytic amount of tin enolate and BINAP–Ag(I) complexes has been reported.[77] The cyclohexanone-derived enol trichloroacetate **89** was reacted with benzaldehyde to afford the aldol products **90** and **91** in high *anti*/*syn* ratios and enantioselectivities of 93–96% for the *anti*-isomer **90** (Scheme 46).

Leckta developed a high-yielding, catalytic enantioselective alkylation of α-imino esters using BINAP and Tol-BINAP complexes of Ag(I), Cu(I), Ni(II) and Pd(II) as catalysts.[78] The enol silanes **92** were added to the tosyl imine **93** in 65–95% yield and in enantioselectivities of up to 98%, with enantioselectivities of >99% obtainable after recrystallisation (Scheme 47). Tol-BINAP–$CuClO_4(MeCN)_n$ gave the highest yield (91%) and enantioselectivity (98%) at 0°C.

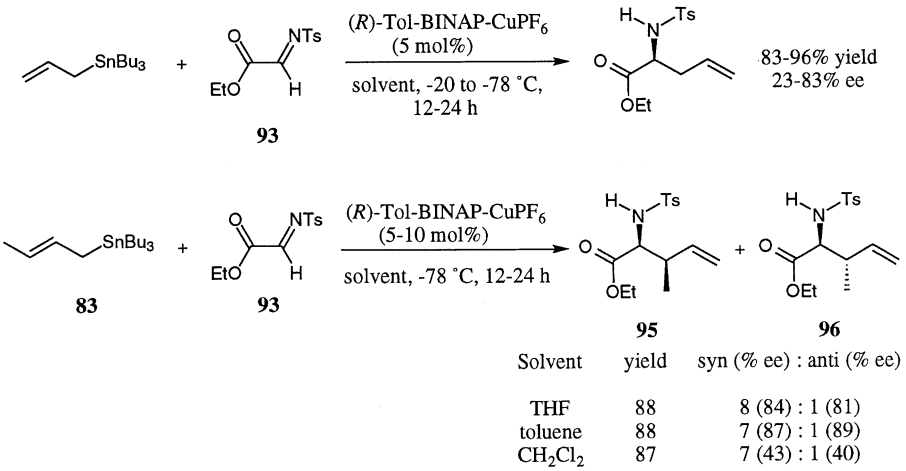
Having discovered an excellent catalyst system for such additions, Leckta extended the scope of the reaction to



Scheme 47.



Scheme 48.



Scheme 49.

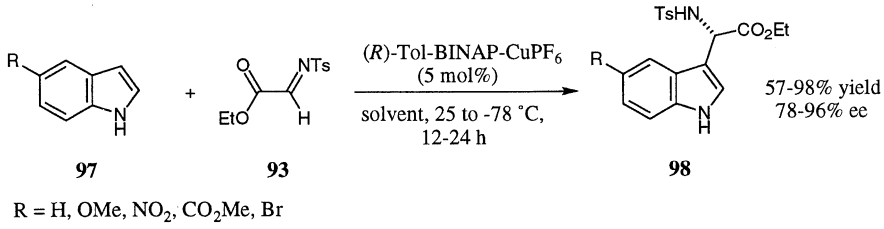
include diastereo- and enantioselective variants employing substituted enol silanes **94** (Scheme 48).[79] Regardless of the enol silane double bond geometry, excellent *anti*-diastereoselectivities and enantioselectivities (up to 99% ee) were obtained. Interestingly, the chiral ligands used are responsible for the diastereoselectivity observed and the results were explained by considering the catalyst to behave as a classical Lewis acid.

Jørgensen has reported similar copper-catalysed enantioselective additions of allylmetals to α-imino esters (Scheme 49).[80] The best results were obtained with allyltin reagents and Tol-BINAP–$CuPF_6$ catalysed the addition of allyltributyltin to **93** in high to excellent yield (83–96%) and up to 83% enantioselectivity. Crotyltributyltin **83** was additionally employed and the *syn*-isomer **95** was preferred to the *anti*-isomer **96** in ratios of up to 8/1, the optimal enantioselectivities obtained being *syn* (87%) and *anti* (89%).

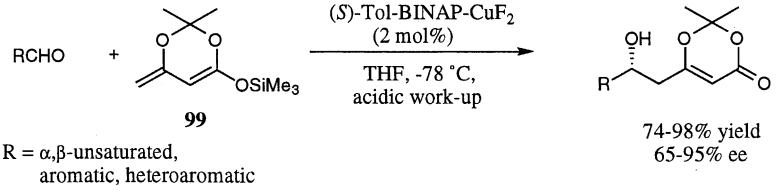
Johannsen extended the enantioselective addition to α-imino esters by using a range of indoles **97** and obtained the corresponding pyrrolyl *N*-tosyl α-amino acids **98** in up to 89% yield and up to 96% enantioselectivity using 1–5 mol% of a (*R*)-Tol-BINAP–$CuPF_6$ catalyst (Scheme 50).[81]

Carreira reported an apparent generation of chiral metal enolates in an enantioselective dienolate addition to aldehydes mediated by Tol-BINAP–CuF_2.[82] Using the silyl dienolate **99** as the nucleophile, the adducts were isolated for a range of aldehydes in good yields (74–98%) and up to 95% enantiomeric excess (Scheme 51). The use of BINAP–CuF_2 complexes gave reduced yields and enantioselectivities for a range of aldehydes, e.g. (90 vs 92%) and (88 vs 94%), respectively, for the benzaldehyde aldol product.

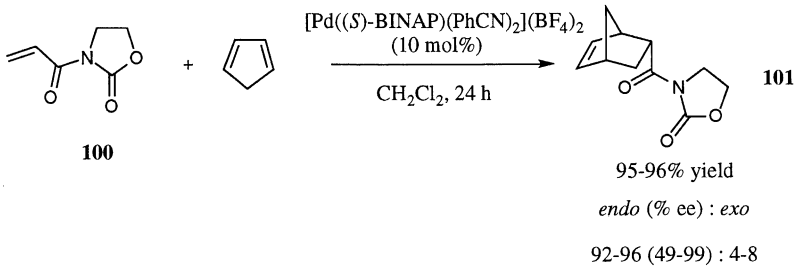
As the late transition metal complexes had shown such promise as chiral Lewis acid complexes it was clear that their application in Diels–Alder chemistry warranted investigation. Oi employed a cationic Pd(II) complex, [(*S*)-BINAP–$Pd(PhCN)_2$]BF_4, in a highly enantioselective reaction of cyclopentadiene with *N*-acryloyloxazolidinone **100** and obtained high *endo*/*exo* ratios of **101** and enantioselectivities of up to 99% (Scheme 52).[83]



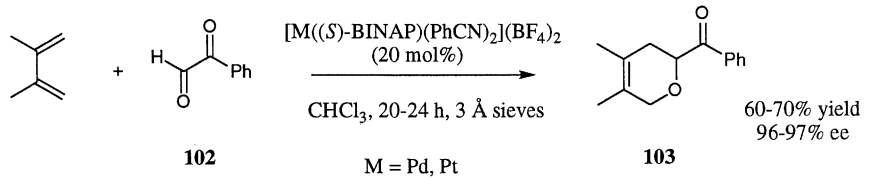
Scheme 50.



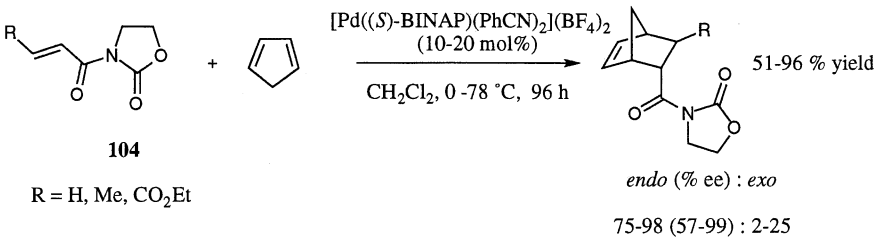
Scheme 51.



Scheme 52.



Scheme 53.



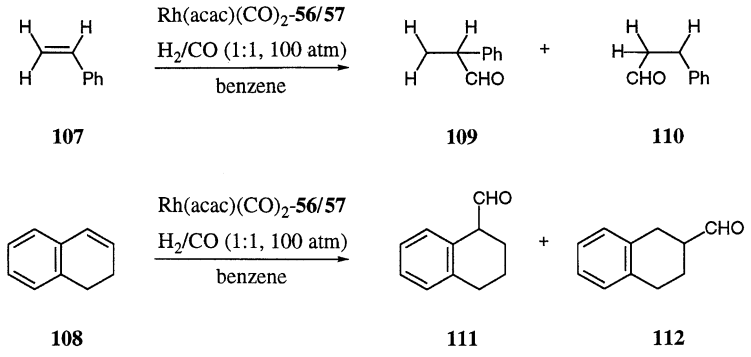
Scheme 54.

Oi's group subsequently employed similar Pd(II) and Pt(II) complexes in the hetero Diels–Alder reaction of non-activated dienes with the arylglyoxal **102** and glyoxylate esters **103** (Scheme 53).[84] High chemical yields and excellent enantioselectivities (up to 97%) for product **103** were obtained and 3 Å molecular sieves were found to be necessary as additives for optimal enantioselection.

Ghosh has also investigated the use of Pd(II)– and Pt(II)–BINAP complexes in the enantioselective Diels–Alder reaction of cyclopentadiene and substituted *N*-acryloyloxazolidinones **104** and the resultant adducts were obtained in excellent *endo*/*exo* selectivity as well as *endo* enantioselectivity (up to 99% ee) (Scheme 54).[85]

3. Phosphinephosphites

The non-C_2-symmetric phosphinephosphite ligands BINAPHOS **105**[86] and BIPHEMPHOS **106**[87] reported by

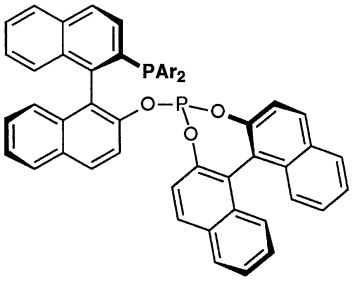


Scheme 55.

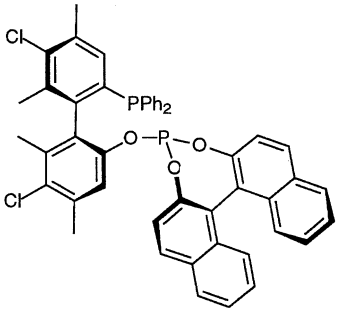
Table 3. Asymmetric hydroformylation of olefins

Entry	Ligand	Conv. (%)	**109/110**	**111/112**	ee (%)
1	(*S*,*R*)-**105**	>99	88/12		94
2	(*S*,*R*)-**106**	>99	90/10		94
3	(*R*,*R*)-**106**	95	92/8		16
4	(*S*,*R*)-**105**			95/5	97
5	(*S*,*R*)-**106**	74		95/5	96

Takaya each contain two sources of axial chirality and electronically different phosphorus donor atoms.



(*R*,*S*)-**105** BINAPHOS

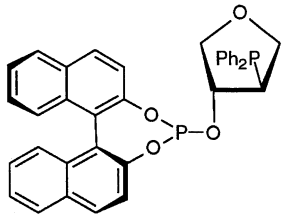


(*S*,*R*)-**106** BIPHEMPHOS

Rh(I)-complexes of (*R*,*S*)- and (*S*,*R*)-BINAPHOS **105** and (*R*,*S*)- and (*S*,*R*)-BIPHEMPHOS **106** have been applied to the asymmetric hydroformylation of monosubstituted and disubstituted olefins, **107** and **108**, respectively (Scheme 55). High enantioselectivities had previously been reported only for the hydroformylation of arylethenes and some functionalised olefins catalysed by chiral diphosphine–Pt(II)–$SnCl_2$ systems[88] but problems such as low reaction rates, competitive hydrogenation, unsatisfactory branched to normal product ratios and product racemisation remained. These problems, however, did not arise with either **105** or **106** (Table 3).

Conversions were excellent and were mostly >99%. The branched-to-normal ratio was generally very good, usually about 80–90% of the required branched product. No hydrogenation products were detected and enantioselectivities ranged from 80–97% ee. When Rh(I)-complexes of either (*R*,*R*)-**105** or (*R*,*R*)-**106** were used in hydroformylation the enantioselectivities obtained were much lower (entry 3). The enantioselectivities, therefore, depend on the structures of the phosphite moieties relative to that of the 2-(diphenylphosphino)-1,1′-binaphthyl backbone, i.e. (*S*,*R*)-**105** is matched whilst (*R*,*R*)-**105** is mismatched.

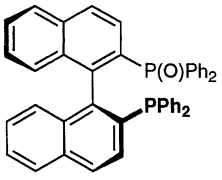
Börner has reported phosphinephosphite ligands which contain both axial and central chirality, (a*S*,3*R*,4*R*)-**113** representing the matched situation for this ligand. (a*S*,3*R*,4*R*)-**113** and the other diastereomers were tested in the Rh(I)-catalysed hydroformylation of allyl acetate, but the enantioselectivities obtained were low, the highest being 43% (Scheme 56).[89]



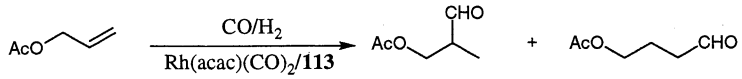
(a*S*,3*R*,4*R*)-**113**

4. Phosphorus–oxygen ligands

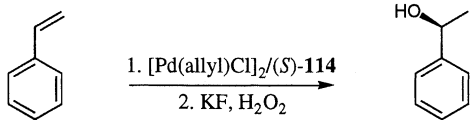
(*S*)-2-Diphenylphosphino-2′-diphenylphosphinyl-1,1′-binaphthalene BINAPO **114**, an axially chiral ligand with oxygen and phosphorus donor atoms, was reported by Gladiali in 1998.[90] He developed an efficient methodology for its synthesis by successive phosphinylation and phosphination on to the 2,2′-carbon atoms of the binaphthyl backbone.



114 (*S*)-BINAPO



Scheme 56.



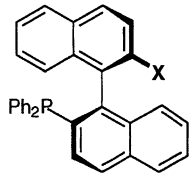
Scheme 57.

Table 4. Pd-catalysed hydrosilylation of alkenes with MOP

X in 115	Yield of **118** (%)	Ratio of **118**/**118′**	ee (%)
Ome	83	93/7	95
O-*i*-Pr	88	90/10	91
OCH_2Ph	85	80/20	95
Et	80	90/10	93

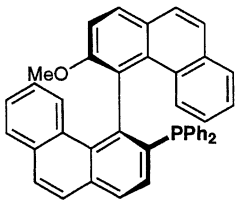
BINAPO **114** was tested and was shown to be an effective chiral inducer for the Pd-catalysed asymmetric hydrosilylation of styrene, giving enantioselectivity up to 72% (Scheme 57). P–O chelation to Pd was observed in solution and confirmed in the solid state by X-ray analysis. Subsequently, the Pt complex of this ligand was tested in the hydroformylation of styrene and afforded up to 30% ee of the branched aldehyde.[91]

In 1991, Hayashi developed an axially chiral phosphine ligand, 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl (MOP) (**115a**), which, when bound to Pd, exhibited a high catalytic activity, high regioselectivity giving 2-silylalkanes and high enantioselectivity.[92] Importantly, this was the first time that this regioselectivity had been reported. Although designed as a monodentate ligand, recent work by Kocovsky and Lloyd-Jones suggests possible P–C bidentate behaviour for these ligands and for this reason they are included in the present review.[93]



115 (*S*)-MOP

115a: X = OMe
115b: X = OCH_2Ph
115c: X = O-*i*-Pr
115d: X = Et (R)
115e: X = CN
115f: X = CH_2NMe_2
115g: X = COOMe
115h: X = COOH
115i: X = OH
115j: X = H (R)



116 (*R*)-MOP-phen

Access can easily be gained to various functional groups at the 2′-position from the triflate and, hence, many analogues **115b–j** with varying sizes of X were synthesised.[94] The monophosphine containing a biphenanthryl skeleton, MOP-phen **116**, where the 2′-OMe moiety was retained and the naphthyl group was increased in size to a phenanthryl group has been synthesised using the same reaction sequence as that for MOP **115a**.[94a,95]

MOP and its analogues have been successfully employed in many enantioselective catalytic reactions, including palladium-catalysed hydrosilylation of simple terminal olefins,[93] hydrosilylation of cyclic olefins,[96] reduction of allylic esters with formic acid[95,97] and reduction of allylic carbonates with formic acid.[98]

Pd-complexes of MOP and its analogues give enantioselectivities ranging from 91 to 95% ee for the hydrosilylation–oxidation of **117** to the secondary alcohol **120** (Scheme 58 and Table 4).[92] The catalyst is efficient, giving yields of (**118**+**118′**) of between 80 and 88% and requiring only 0.01 mol% of catalyst, and the regioselectivity ranged from 80 to 93% in favour of **118**.

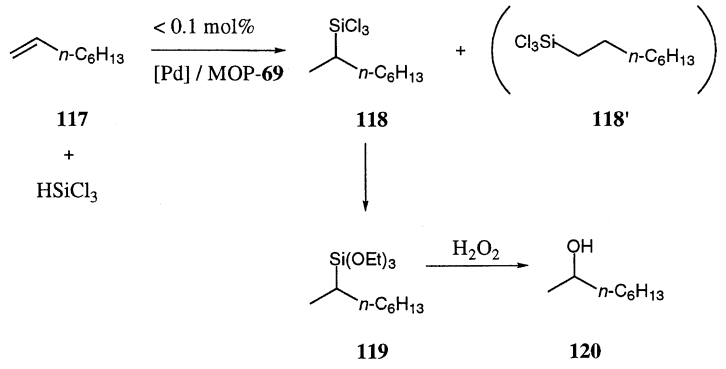
The hydrosilylation of norbornene **121** with trichlorosilane in the presence of 0.01 mol% of a MOP-Pd catalyst gave a quantitative yield of *exo*-2-(trichlorosilyl)norbornene **122** as the only product (Scheme 59), which was oxidised with hydrogen peroxide to give *exo*-2-norbornanol **123** in 96% ee as the 1*S*,2*S*,4*R* isomer.

Pd-catalysed reduction of allylic esters was also investigated using complexes of MOP and its derivatives which exhibited both high catalytic activity and regioselectivity to give less-substituted olefins (Scheme 60 and Table 5).[94,97]

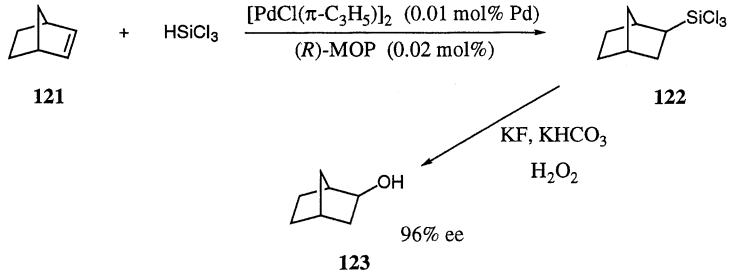
The reaction of geranyl methyl carbonate **124** with formic acid and 1,8-bis(dimethylamino)naphthalene in the presence of 1 mol% of a **115**-Pd catalyst proceeded regioselectively to give (*S*)-3,7-dimethyl-1,6-octadiene **125** in 76% ee. The same reaction proceeded with 85% ee when MOP-phen **116** was used. The reduction was very slow and not regioselective with the diphosphine BINAP **1**.

The observation that MOP-phen **116** gave greater enantioselectivities than MOP **115** may be explained by studying the X-ray crystal structure of *trans*-$PdCl_2(MOP)_2$. This showed that the ring of the naphthyl group on MOP which is substituted with the methoxy group is located close to the central metal atom on coordination. The high enantioselectivity observed in the catalytic asymmetric reactions is most likely due to steric interactions between the A ring and the substrate when coordinated to the metal. By increasing the bulk using a phenanthryl group, greater enantioselectivities should therefore be, and are attained. MOP **115** and MOP-phen **116** have proved to be very important and efficient catalysts in many Pd catalysed reactions, attaining high conversion with good regio- and enantioselectivity.

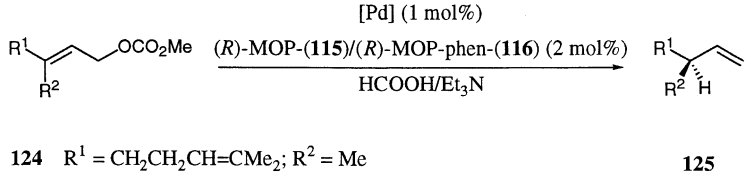
In 1998, Fuji reported a novel and related phosphine ligand,



Scheme 58.

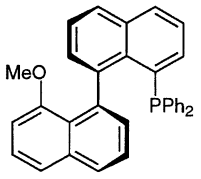


Scheme 59.



Scheme 60.

8-diphenylphosphino-8′-methoxy-1,1′-binaphthyl (8-MeO-MOP) **126**. Initial studies showed that the Pd-catalysed reduction of allylic carbonates with formic acid gave enantioselectivities of up to 82%.[99]



126 8-MeO-MOP

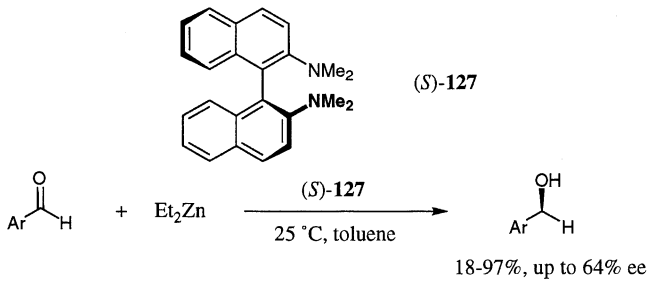
5. Bidentate nitrogen ligands

In comparison to axially chiral diphosphines, very few examples of axially chiral bidentate nitrogen ligands have been reported. *N,N,N′,N′*-tetramethyl-2,2′-diamino-1,1′-binaphthyl **127** was prepared in 1991 by the group of Salvadori.[100] Enantioselective alkylation of aromatic aldehydes by diethylzinc (Scheme 61) is mediated by a catalytic amount of **127** to give the corresponding ethyl aryl secondary alcohols in good yield and with enantioselectivities of up to 64%.

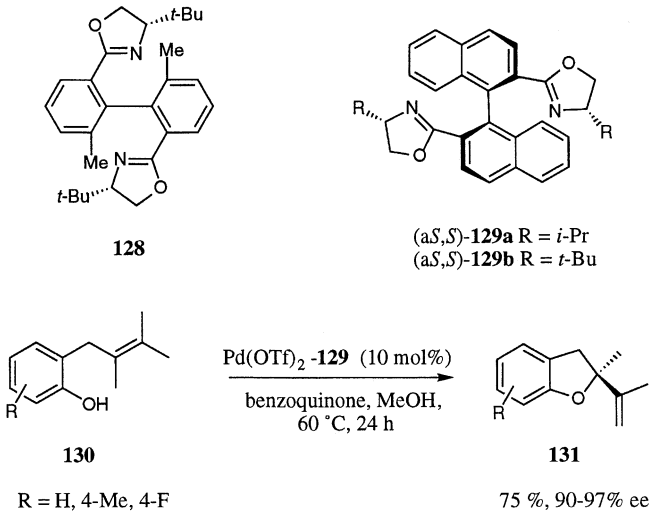
Table 5. Pd-catalysed reduction of allylic esters with formic acid

Ligand	Conditions	Yield (%)	ee (%)
MOP (**115**)	20°C, 16 h	95	76
MOP-phen (**116**)	20°C, 17 h	> 99	85
BINAP (**1**)	40°C, 4 days	30	–

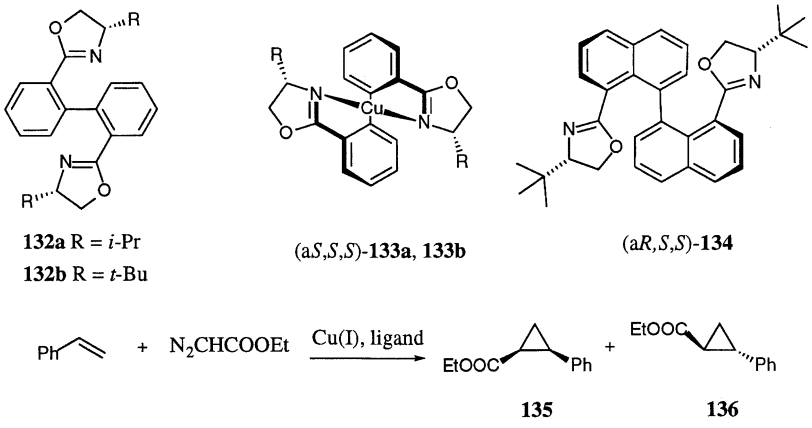
The oxazoline unit has been widely used in asymmetric catalysis due to its ease of preparation from amino alcohols, its modularity and its ability to induce asymmetry in a range of metal-catalysed reactions.[101] It was, therefore, of little surprise that bidentate nitrogen ligands containing both axial chirality, arising from hindered rotation of the biphenyl rings, and the central chirality of the oxazoline unit were prepared, the first example being the C_2-symmetric bisoxazoline ligand **128** bearing four *ortho*-substituents. Its Cu catalyst was applied to the preparation of the natural product, Sirenin, giving 90% ee in a cyclopropanation.[102] The analogous 1,1′-binaphthyl ligands **129a–b** were subsequently reported by the groups of Hayashi and Andrus.[103] The former group applied Pd complexes of **129** in a Wacker-type cyclisation of the substrates **130** (Scheme 62) affording dihydrobenzofurans **131** in yields of up to 75% and with enantioselectivities of up to 97%.[104]



Scheme 61.



Scheme 62.



Scheme 63.

As noted in Section 1, enantiomerically stable biphenyls require at least three *ortho*-substituents to avoid racemisation.[105] The di-*ortho*-substituted analogue of **128**, ligand **132**, was reported by Ikeda in 1997.[106] In solution, the diamine **132** should exist as two rapidly interconverting diastereomers, but when coordinated to Cu(I) only one diastereomeric form of the ligand, (a*S*,*S*,*S*)-**133**, was observed. The bisoxazoline ligand **134**, which contains oxazoline units in the 8-position on the naphthyl ring, was reported by Meyers in 1998.[107] The main metal-catalysed process to which these bisoxazoline ligands **129**, **132** and **134**, have been applied is the Cu-catalysed cyclopropanation of styrene (Scheme 63 and Table 6).

Within this series of bisoxazolines, the product cyclopropanes **135** and **136** were obtained in higher enantioselectivities when the *t*-butyl substituted oxazoline complex was used and, using diethyl diazoacetate, 90% ee was obtained with the ligand **134**.

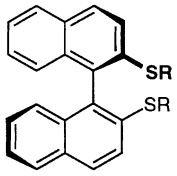
6. Sulfur-containing ligands

There are examples of axially chiral ligands containing sulfur as the donor atom in bidentate, heterobidentate and heterotopic sulfur-containing ligands. 1,1′-Binaphthalene-2,2′-dithiol (BINAS) **137** was synthesised in enantiopure form by De

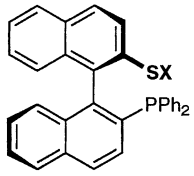
Table 6. Cu-catalysed cyclopropanation of styrene

Ligand	Catalyst (mol%)	Ratio **135/136**	% ee **135/136**
(a*S*,*S*,*S*)-**129a**	2.0	40/60	61/62
(a*S*,*S*,*S*)-**129b**	2.0	41/59	86/87
(a*S*,*S*,*S*)-**132a**	1.0	26/74	59/49
(a*S*,*S*,*S*)-**132b**	1.0	3/68	84/74
(a*R*,*S*,*S*)-**134b**	2.0	33/66	90/67

Lucchi via a Newman–Kwart rearrangement.[108] BINAS **137** and Me_2BINAS **138** were tested by Gladiali and Claver in the enantioselective Rh-catalysed hydroformylation of styrene (see Scheme 55).[109] The yields and regioselectivities were excellent but the enantioselectivities were low (up to 15%). The enantioselectivity was the highest to date, however, with ligands containing donor atoms other than phosphorus.



R = H BINAS **137**
R = Me Me_2BINAS **138**

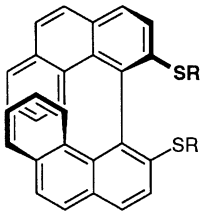


X = Me **139a**
X = *i*-Pr **139b**
X = H **139c**

The inherent electronic disparity in the heterobidentate and heterotopic ligand systems can give dual control of enantioselectivity by combining steric and electronic effects. Unsymmetrical disubstituted binaphthyls are more difficult to prepare than their symmetrical counterparts. They may be synthesised either by coupling of two different naphthalene derivatives, or by selective reaction at one of two identical groups on a binaphthyl. The first method is limited by the electronic demands of the reacting partners. The second route has proved to be useful for the introduction of phosphorus, employing Morgans' monophosphinylation[110] and for the introduction of sulfur by the previously mentioned Newman–Kwart rearrangement.[111] In 1994, Gladiali published the synthesis of the heterobidentate *S*-alkyl (*R*)-2-diphenylphosphino-1,1′-binaphthyl-2′-thiol derivatives **139a–c**, which were the first examples of axially chiral P–S ligands.[112] The ligand **139** was conveniently synthesised from the commercially available enantiopure diol. The ligands were obtained using Morgan's selective monophosphinylation without any loss of enantioselectivity.

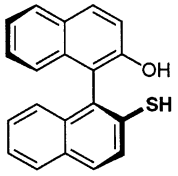
The ligands **139a–c** were tested in the enantioselective rhodium(I) catalysed hydroformylation (see Scheme 55) and hydrosilylation of styrene (see Scheme 57).[113] The reactions proceeded with high chemo- and regioselectivity with the highest enantioselectivity being 54% for the hydrosilylation and 10–25% for the hydroformylation.

Gladiali also reported the preparation of 4,4′-biphenanthrene-3,3′-dithiol (H_2 BIPHES) **140a** and its dithiomethylether Me_2BIPHES **140b**, the vaulted analogues of BINAS **137** and Me_2BINAS **138**, respectively.[114] Rhodium complexes of **140a** and **141b** were applied to the asymmetric hydroformylation of styrene and the extent of aldehyde conversion ranged from 53 to 100%, with selectivities for the branched product in the range 51 to 96%, although with low enantioselectivites (<20%).[115]

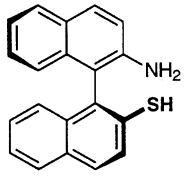


R = H H_2 BIPHES **140a**
R = Me Me_2 BIPHES **140b**

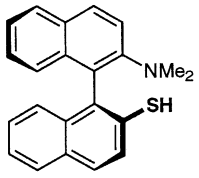
The ligands **141–143** have been prepared by Kocovsky[116] but their application in asymmetric catalysis has not yet been reported. Woodward has also reported an efficient synthesis of the ligand **141** in three steps from BINOL without the use of chromatography.[117]



(*S*)-**141**

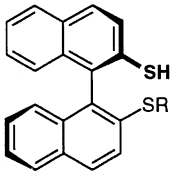


(*S*)-**142**

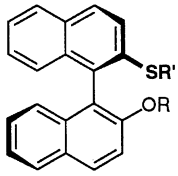


(*S*)-**143**

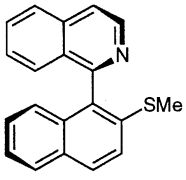
The heterotopic *S*,*S*′- and heterodonor *O*,*S*-chelating ligands **144–148** have been synthesised more recently by Gladiali by the desymmetrisation of the readily available C_2-symmetric 2,2′-disubstituted binaphthalene derivatives.[118]



R = Me **144**
R = *i*-Pr **145**

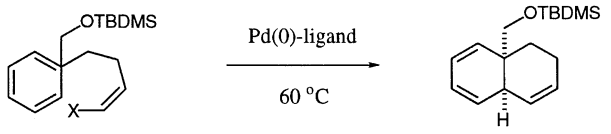


R = R' = H **146**
R = H; R' = Me **147**
R = Me; R' = H **148**



149

Chelucci reported the preparation of the *N*,*S*-chelating ligand **149** and applied it to palladium-catalysed allylic alkylation but obtained only 2% ee.[119]



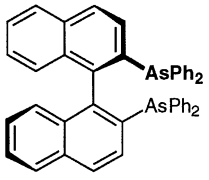
X = I **151a**
X = OTf **151b**

Scheme 64.

Many of the sulfur-containing ligands have only recently appeared in the literature and it is clear that their application in catalysis will undoubtedly appear in the near future.

7. Arsine-containing ligands

Triphenylarsine had proved to be an effective ligand for tandem Suzuki cross coupling–Heck reactions.[120] Shibasaki has developed axially chiral arsine-containing ligands and has recently reported 2,2′-bis(diphenylarsino)-1,1′-binaphthyl (BINAs) **150**.[121]



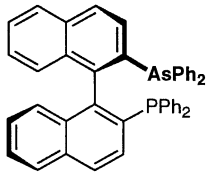
(*R*)-BINAs **150**

BINAs **150** was prepared in 34% yield (>95% ee) from the enantiopure ditriflate of BINOL using a modification of the method of Cai,[113] and was evaluated as a chiral ligand in the Pd-catalysed intramolecular asymmetric Heck reaction (Scheme 64 and Table 7). It was found to be a more effective ligand than BINAP **1** in intramolecular asymmetric Heck reactions of alkenyl iodides **151a**, giving higher yield and enantioselectivity (entries 1 and 2). BINAs was, however, not as good as BINAP in intramolecular asymmetric Heck reactions involving aryl triflates or alkenyl triflates (**151b**), in this case a lower yield and enantioselectivity being obtained for BINAs (entries 3 and 4).

From this work, it was clear that a phosphorus donor atom was required for better reactivity in the reaction of aryl triflates or alkenyl triflates. This led to the synthesis by Shibasaki of BINAPAs **152**, which like BINAs **150**, was synthesised in >95% ee from the enantiopure ditriflate of binaphthyl by successive selective reaction at one triflate group to introduce the phosphine followed by conversion of the other triflate to the arsine.[122]

Table 7. Pd-catalysed intramolecular Heck reaction with BINAP and BINAs

Entry	X	Ligand	Time (h)	Yield (%)	ee (%)
1	I	BINAs	24	90	82
2	I	BINAP	24	55	32
3	OTf	BINAs	24	5	82
4	OTf	BINAP	24	21	93



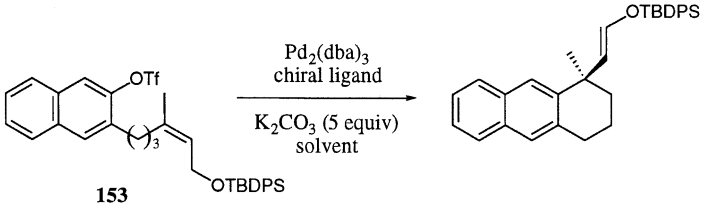
(*R*) - BINAPAs **152**

Pd complexes of BINAPAs **152** were then tested in the intramolecular asymmetric Heck reaction of the aryl triflates **153** (Scheme 65 and Table 8). The ligand **152** was shown to be more effective than BINAP **1** in terms of yield but not enantioselectivity and gave, for example, 91% yield and 88% ee when the reaction was carried out in toluene (entry 2). Under identical conditions, however, the Pd complexes of BINAP **1** gave a 74% yield and an enantioselectivity of 89% (entry 1). In general, the reactions proceeded faster when BINAPAs was used as the ligand, although with a decreased enantioselectivity compared to BINAP **1** (entries 3 and 4).

BINAs **150**, BINAPAs **152** and BINAP **1** can, therefore, be used as tailor-made ligands for a variety of asymmetric Heck reactions.

8. Phosphorus–nitrogen ligands

The ability of heterobidentate ligands to induce asymmetry by exerting a combination of steric and electronic effects on reactions occurring within the coordination sphere of the transition metal to which they are bound has led to the development of an active area of research in their design and application in asymmetric catalysis. Of the possible combinations of donor atoms, the phosphinamine class has received most attention and examples possessing different chiral elements and backbone scaffolding have been designed and applied with success in catalytic asymmetric synthesis.[6d] As there are numerous examples of axially chiral phosphinamines, it is necessary to sub-classify the different examples according to the axially chiral unit employed. In addition, the range of reactions to which this class of ligands has been employed is relatively small and,



153

Scheme 65.

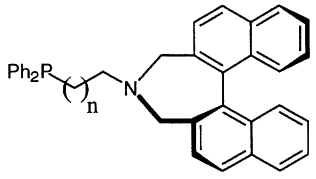
Table 8. Pd-catalysed intramolecular Heck reaction with BINAP and BINAPAs

Entry	Ligand	Solvent	Time (h)	Yield (%)	ee (%)
1	BINAP	Toluene	46	74	89
2	BINAPAs	Toluene	46	91	88
3	BINAP	1,2-Dichloroethane	48	76	88
4	BINAPAs	1,2-Dichloroethane	48	95	81

for direct comparative purposes, the majority of the results obtained are therefore tabulated together, where possible.

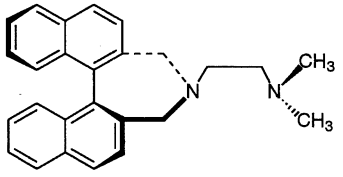
8.1. 3,5-Dihydro-4*H*-dinaphthazepine-containing ligands

8.1.1. Possessing axial chirality. In 1994, Koga et al. synthesised the axially chiral phosphinamine ligands **154** and **155** in high yield (~70%) in two steps from optically pure (+)-2,2′-bisbromomethyl-1,1′-binaphthyl and the corresponding amine.[123] The chiral inducing group in these ligands is the 3,5-dihydro-4*H*-dinaphthazepine unit in which the donor atoms are not directly linked to the 1,1′-binaphthyl group.

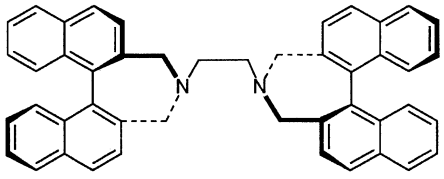


n = 1; **154**
n = 2; **155**

This unit was originally investigated by Cram and Mazaleyrat in 1981, who prepared the diamine ligands **156** and **157** which were only tested as stoichiometric modifiers and have not found use in catalysis.[124]



(*S*)-**156**

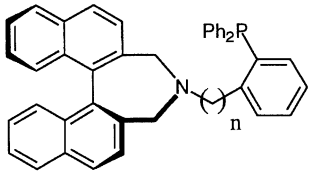


(*R*,*R*)-**157**

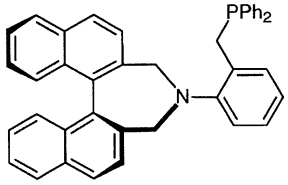
The enantioselective substitution of allylic acetates is the most extensively studied asymmetric carbon–carbon bond forming process catalysed by transition metal complexes of Pd.[125] This is an important transformation and it has proved to be a useful testing ground for the design and testing of new ligands and for gaining mechanistic insights into organopalladium chemistry. Excellent enantioselectivities have been attained using phosphinamine ligands which induce asymmetry through a combination of steric and electronic interactions.[126]

The ligands **154** and **155** were tested in asymmetric allylic alkylation by treatment of the allyl–Pd complex generated in situ and the standard test substrate, 1,3-diphenyl-2-propenyl acetate, with dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate (the BSA procedure) (Scheme 66 and Table 9). The ligand **154** gave enantioselectivities of up to 93%, and the ligand **155** gave up to 96% ee demonstrating that both a five-membered and six-membered chelate ring size induced high asymmetry.

Widhalm and co-workers subsequently reported the phosphinamine ligands **158**–**160**, which were also prepared from optically pure (+)-2,2′-bisbromomethyl-1,1′-binaphthyl.[127] These were similar to Koga's ligands **154** and **155** but possess a less flexible carbon backbone connecting the phosphorus and nitrogen atoms. The length and rigidity of the backbone determines the natural bite angle which can have a major influence on the enantioselectivity and catalytic activity of the complex. In addition, the donor atoms in these ligands were quite different electronically, as the phosphine in **158**–**159** is a triarylphosphine and that in **160** is a diarylalkylphosphine, whilst the amine in **158** and **160** is a dialkylaniline and that in **159** is a trialkylamine.



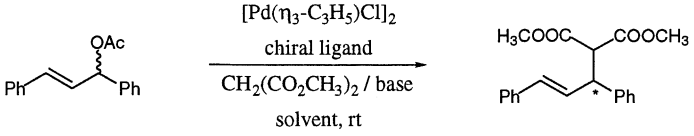
n = 0; **158**
n = 1; **159**



160

The ligands **158**–**160** were also tested in enantioselective Pd-catalysed allylic alkylation reactions using the preformed anion (reaction with NaH) of dimethylmalonate, where the nucleophile is preformed and added to the reaction mixture as its sodium salt (Table 9). The ligand **158** gave 96% ee and **159** afforded values up to 97% ee (entries 3 and 4). A much lower ee of 18% was obtained when the ligand **160** was employed (entry 5), which was explained by suggesting that the ligand became monodentate during the reaction.

8.1.2. Possessing axial and central chirality. Widhalm et



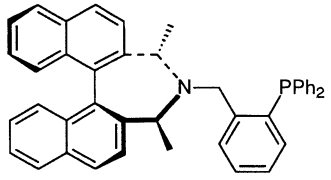
Scheme 66.

Table 9. Pd-catalysed allylic alkylation

Entry	Ligand	Base	Solvent	Time (h)	Yield (%)	ee (%) (configuration)
1	(*R*)-**154**	BSA	CH_2Cl_2	1.7	96	93 (*R*)
2	(*R*)-**155**	BSA	CH_2Cl_2	2.5	96	96 (*R*)
3	(*S*)-**158**	NaH	THF	4	95	96 (*S*)
4	(*S*)-**159**	NaH	THF	4	95	97 (*S*)
5	(*S*)-**160**	NaH	THF	4	97	18 (*S*)
6	(*S*)-**161**	BSA	CH_2Cl_2	4	76	55 (*S*)
7	(*S*)-**162**	BSA	CH_2Cl_2	52	85	34 (*S*)
8	(a*S*,*S*)-**163**	BSA	CH_2Cl_2	4	79	44 (*S*)
9	(*R*)-**164**	NaH	CH_2Cl_2	24	86	64 (*S*)
10	(*R*)-**164**	Mal[a]	CH_2Cl_2	24	87	71 (*S*)
11	(*R*)-**164**	BSA	CH_2Cl_2	24	87	64 (*S*)
12	(*R*)-**164**	Mal[a]	CH_2Cl_2	24	85	71 (*S*)
13	(*R*)-**169**	Mal[a]	CH_2Cl_2	24	85	73 (*S*)
14	(*R*)-**170**	Mal[a]	CH_2Cl_2	24	80	69 (*S*)
15	(*R*)-**171**	Mal[a]	CH_2Cl_2	24	77	68 (*S*)

[a] Cs_2CO_3 used as base instead of NaH.

al. proceeded to modify the phosphinamine **159** by introducing steric bulk in closer proximity to the N-coordination site.[128] These more crowded phosphinamines **161** and **162**, however, showed significantly lower reactivities and enantioselectivities in the allylic substitution reaction (Table 9, entries 6 and 7).



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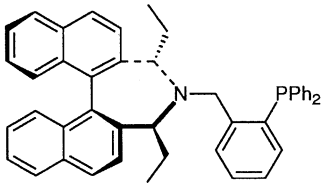
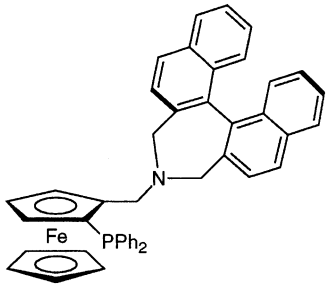


162

For one example, namely the allylic substitution of 3-penten-2-yl acetate, a much smaller substrate than 1,3-diphenyl-2-propenyl acetate, the enantioselectivity was 68% with the ligand **161** while it was 5% with the ligand **159**. This shows that increasing the bulk around the nitrogen donor atom facilitates increased ees for smaller substrates.

8.1.3. Possessing axial and planar chirality. Widhalm et al. extended this work by combining the axial chirality of the 3,5-dihydro-4*H*-dinaphthazepine unit with the planar chirality inherent in a 1,2-disubstituted ferrocene ring when designing the ligand **163**.[129]

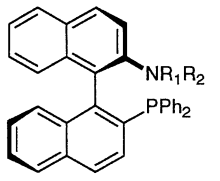


(a*S*,*S*)-**163**

As with the previous ligands in this series, it was tested in enantioselective Pd-catalysed allylic alkylations. With 1,3-diphenyl-2-propenyl acetate, the ees were much lower with the ligand **163** (44% ee) than for the related ligand **159** (97% ee) (Table 9, compare entries 4 and 8). As the chelate ring size is identical for each ligand, the decrease in ees may be attributed to a mismatch in chirality in the ligand **163** between the (*S*)-axial and (*S*)-planar chirality but this has not been investigated. As with the ligand **160**, monodentate coordination through the phosphorus atom was suggested to explain the low enantioselectivity obtained.

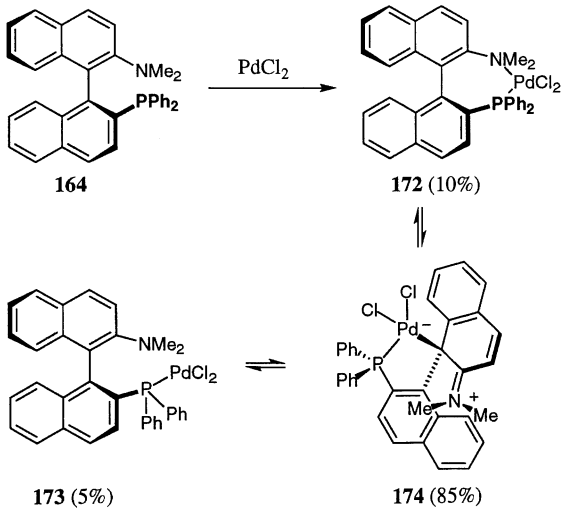
8.2. 1-Naphthyl-2-naphthylamine-containing ligands

8.2.1. Possessing axial chirality. In 1998, Kocovsky et al. reported the preparation of a series of 1-naphthyl-2-naphthylamine-containing ligands (**164**–**171**).[130] These ligands are analogous to Hayashi's ligand, MOP **115**, by replacing the oxygen atom with a nitrogen.[94]



164; $R_1 = R_2 = Me$
165; $R_1 = H$; $R_2 = Me$
166; $R_1 = H$; $R_2 = Et$
167; $R_1 = H$; $R_2 = i$-Pr
168; $R_1 = H$; $R_2 = Cy$
169; $R_1 = Me$; $R_2 = i$-Pr
170; $R_1 = Me$; $R_2 = Cy$
171; R_1-$R_2 = Cy$

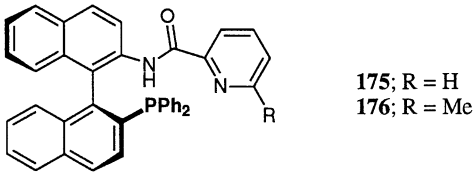
Four members of the series (**164**, **169**–**171**) were tested for their asymmetry-inducing ability in the Pd-catalysed substitution of 1,3-diphenylpropenylacetate and a summary of these results is given in Table 9 (entries 9–15). Pd complexes of the ligand **164** afforded between 64 and 71% ee, either using the pre-formed malonate with NaH or Cs_2CO_3 as base, or the BSA procedure. The highest ee (73%) was obtained using the ligand **169**, whereas the ligands **170** and **171** gave slightly lower ees of 69 and 68%, respectively. As with previous phosphinamine ligands, the preferred enantiomer is suggested to be derived from nucleophilic attack at the allyl terminus *trans* to the phosphorus donor atom in a chelated transition state. The $PdCl_2$ complex of **164**, however, was found by ^1H NMR spectroscopy to be an 85:10:5 mixture of three species (Scheme 67). In addition to the expected P,N-chelated complex **172** and the monodentate complex **173**, the



Scheme 67.

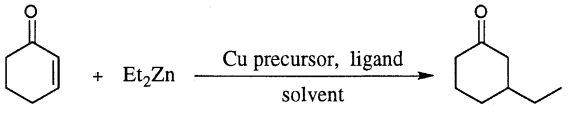
predominant species **174** showed that **164** acts as a P,C-ligand with an unusual C_σ–Pd bonding mode.[93]

Zhang et al. have also used the 1-naphthyl-2-naphthylamine framework in combination with a substituted pyridine system in the design of their ligands **175** and **176**.[131] These possess relatively large bite angles and a conformationally rigid amide linker.



175; R = H
176; R = Me

Once prepared the ligands were tested in the Cu-catalysed 1,4-addition of diethylzinc to cyclohexenone (Scheme 68 and Table 10). Using $[Cu(MeCN)_4BF_4]$ as the Cu precursor, the ligand (*S*)-**175** gave (*S*)-product in 95% yield in 85% ee when a mixture of toluene and dichloroethane (DCE) was employed as the solvent, whereas use of toluene alone afforded slightly lower ees. The methyl-substituted ligand **176**, however, gave ees up to 92% with excellent conversions.

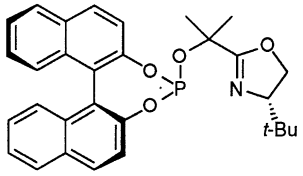


Scheme 68.

These ligands were also applied to the standard acyclic enone substrate, *trans*-chalcone (Scheme 69 and Table 11). Using $[Cu(OTf)_2{\cdot}C_6H_6]$ as the Cu precursor, the ligand (*S*)-**175** gave (*S*)-product in 92% yield in 83% ee. The more highly substituted ligand **176** again gave higher yields and ees (up to 96%) (entries 2–3 in Table 11). Indeed, the ee obtained (98%) for the conjugate addition to *p*-methoxy-substituted chalcone and those summarised in Table 11 are the highest reported to date for acyclic enones.

8.3. 1,1′-Biarylphosphiteoxazoline-containing ligands

8.3.1. Possessing axial and central chirality. Most of the Pd-catalysed allylic alkylations studied have used symmetrical substrates, e.g. 1,3-diphenylpropenyl acetate, 3-penten-2-yl acetate and cyclohexenyl acetate. A problem arises with monosubstituted allylic acetates as a lack of regiocontrol causes an achiral linear product to be formed (Scheme 70). Pfaltz showed that, by systematic modification of the electronic and steric properties of the ligand bound to Pd, the regioselectivity of allylic alkylations could be controlled.[132] They achieved the best results so far with the ligand (a*S*,*S*)-**177**, derived from axially chiral (*S*)-binaphthol and an oxazoline, the (a*R*,*S*)-diastereomer derived from (*R*)-binaphthol giving lower regio- and enantioselectivities.



(a*S*,*S*)-**177**

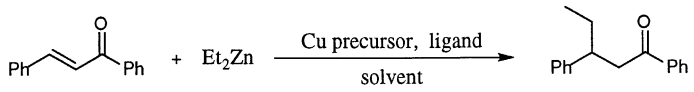
Using (a*S*,*S*)-**177** with 3-phenylpropenyl acetate **178** as the substrate, the best results achieved were in benzene at room temperature giving an enantioselectivity of 90% with regioselectivity **179**:**180**=76:24 (Scheme 70).

They achieved higher regio- and enantioselectivities using **181**, the 1-naphthyl allylic acetate as the substrate, e.g. 94%

Table 10. Cu-catalysed 1,4-addition of Et_2Zn to cyclohexenone

Entry	Ligand	Cu precursor	Solvent	Temperature (°C)	Yield (%)	ee (%) Configuration
1	(*S*)-**175**	$[Cu(MeCN)_4BF_4]$	Toluene	0	82	82 (*S*)
2	(*S*)-**175**	$[Cu(MeCN)_4BF_4]$	Tol/DCE[a]	−20	95	85 (*S*)
3	(*S*) **176**	$[Cu(MeCN)_4BF_4]$	Tol/DCE	−20	98	92 (*S*)
4	(*S*)-**176**	$Cu(OTf)_2$	Toluene	0	100	72 (*S*)
5	(*S*)-**176**	$[Cu(OTf)]_2{\cdot}C_6H_6$	Toluene	−20	76	91 (*S*)
6	(*S*)-**176**	$[Cu(OTf)]_2{\cdot}C_6H_6$	Toluene	−20	100	89 (*S*)
7	(a*S*,*S*)-**177**	$Cu(OTf)_2$	Toluene	−20	93	9 (*S*)
8	(a*R*,*S*)-**177**	$Cu(OTf)_2$	Toluene	−20	85	52 (*R*)
9	(a*R*,*S*)-**184**	Cu(OTf)[b]	Toluene	−20	99	82 (*R*)
10	(a*R*,*S*)-**184**	$Cu(OTf)_2$[b]	Toluene	−20	96	90 (*R*)

[a] DCE=1,2-dichloroethane.
[b] Ligand/Cu ratio=2:1 (otherwise 1:1).

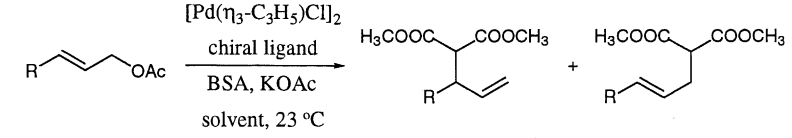


Scheme 69.

Table 11. Cu-catalysed 1,4-addition of Et_2Zn to *trans*-chalcone

Entry	Ligand	Cu Precursor	Solvent	Temperature (°C)	Yield (%)	ee (%) Configuration
1	(*S*)-**175**	$[Cu(OTf)]_2{\cdot}C_6H_6$	Tol/DCE[a]	−20	92	83 (*S*)
2	(*S*)-**176**	$[Cu(OTf)]_2{\cdot}C_6H_6$	Tol/DCE	−20	85	96 (*S*)
3	(*S*)-**176**	$[Cu(OTf)]_2{\cdot}C_6H_6$	Tol/DCE	−20	72	94 (*S*)
4	(*S*)-**176**	$Cu(OTf)_2$	Toluene	0	100	72 (*S*)
5	(*S*) **176**	$[Cu(OTf)]_2{\cdot}C_6H_6$	Toluene	−20	76	91 (*S*)
6	(*S*)-**176**	$[Cu(OTf)]_2{\cdot}C_6H_6$	Toluene	−20	100	89 (*S*)
7	(a*R*,*S*)-**177**	$Cu(OTf)_2$[b]	Toluene	−20	38	50 (*S*)
8	(a*R*,*S*)-**184**	$Cu(OTf)_2$[b]	Toluene	−20	48	43 (*S*)

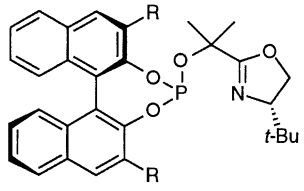
[a] DCE=1,2-dichloroethane.
[b] Ligand/Cu ratio=2:1 (otherwise 1:1).



R = Ph **178** **179** **180**
R = 1-naphthyl **181** **182** **183**

Scheme 70.

ee was obtained with regioselectivity **182**:**183**=95:5. This study clearly demonstrated that the mismatched ligand (a*R*,*S*)-**177** gave lower regio- and enantioselectivities. The preparation of analogues of **177** is relatively straightforward as the oxazoline unit is derived from amino acids and many biaryl diols are readily available. These modular ligands could therefore be tailored for a particular substrate and reaction.

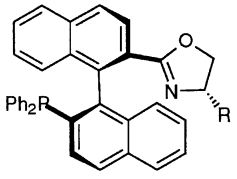


R = H; (a*R*,*S*)-**177**
R = Me; (a*R*,*S*)-**184**

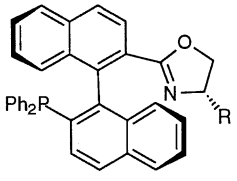
(a*R*,*S*)-(**177**) and its substituted analogue (a*R*,*S*)-(**184**) have been employed by Pfaltz et al. as chiral inducers in Cu-catalysed addition of diethylzinc to enones.[133] Enantioselectivities of up to 90% were obtained with the ligand (*R*,*S*)-(**184**) for the enantioselective 1,4-addition of diethylzinc to cyclohexenone (Table 10). Pfaltz's oxazoline-phosphites gave lower enantioselectivities for the acyclic enone, *trans*-chalcone, where the highest enantioselectivity obtained was 50% (Table 11). This again highlights that a general ligand/metal/substrate match is difficult to determine by empirical means and requires intensive studies to optimise each reaction. For Cu-catalysed 1,4-addition of enones, however, the cyclic substrates are generally best transformed using the Pfaltz phosphite-oxazolines whilst the ligands developed by Zhang are better for acyclic enones.

8.4. 1,1′-Binaphthyloxazoline-containing ligands

8.4.1. Possessing axial and central chirality. It was clear from the work of Pfaltz et al. in the preparation and application of the ligands (a*S*,*S*)- and (a*R*,*S*)-**177**, that the 1,1′-binaphthylphosphite backbone could be successfully used in combination with the oxazoline unit. In 1998, the groups of Hayashi and Ikeda independently reported the synthesis of the diastereomers (a*S*,*S*)-**185** and (a*R*,*S*)-**186** and the *t*-butyl analogue (a*R*,*S*)-**187**, which they applied in Pd-catalysed allylic substitution of 1,3-diphenyl-2-propenyl acetate.[134,135]



(a*S*,*S*)-**185**; R = *i*-Pr



(a*R*,*S*)-**186**; R = *i*-Pr
(a*R*,*S*)-**187**; R = *t*-Bu

The enantioselectivities observed ranged from 28 to 96%, Ikeda's bulkier *t*-butyl-substituted ligand (a*R*,*S*)-**187** giving the best result of 96% ee and 90% yield (Scheme 69 and Table 12, entry 6). The BSA method employed by Ikeda worked better than the malonate procedure tested by

Table 12. Pd-catalysed allylic alkylation

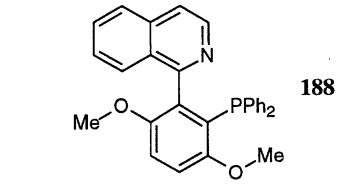
Entry	Ligand	Base	Solvent	Time (h)	Yield (%)	ee (%) Configuration
1	(a*S*,*S*)-**185**	NaH	THF	3.5	>99	28 (*S*)
2	(a*S*,*S*)-**185**	NaH	THF	5	60	50 (*S*)
3	(a*S*,*S*)-**185**	BSA	CH_2Cl_2	4	93	85 (*S*)
4	(a*R*,*S*)-**186**	NaH	THF	2	>99	86 (*R*)
5	(a*R*,*S*)-**186**	NaH[a]	THF	48	>99	91 (*R*)
6	(a*R*,*S*)-**187**	BSA[b]	CH_2Cl_2	7	90	96 (*R*)
7	(*S*)-**189**	NaH[c]	CH_3CN	1	95	98 (*R*)
8	(*R*)-**196**	NaH[d]	CH_3CN	1	98	95 (*S*)
9	(*R*)-**196**	BSA	CH_2Cl_2	2	76	94 (*R*)
10	(*S*)-**201**	NaH[e]	THF	24	44	67 (*R*)
11	(*S*)-**201**	NaH[e]	CH_2Cl_2	36	65	87 (*R*)
12	(*S*)-**201**	BSA	CH_2Cl_2	48	90	80 (*R*)
13	(*S*)-**201**	BSA	THF	48	64	68 (*R*)
14	(*S*)-**201**	BSA	Toluene	48	53	73 (*R*)
15	(*R*)-**202**	NaH	THF	48	58	66 (*R*)
16	(*R*)-**202**	NaH	CH_2Cl_2	1	>99	48 (*R*)
17	(*R*)-**202**	BSA	CH_2Cl_2	18	86	20 (*R*)
18	(*R*)-**202**	BSA	DMF	18	>99	36 (*R*)
19	(*R*)-**203**	NaH[e]	DMF	48	67	85 (*R*)
20	(*R*)-**203**	BSA	CH_2Cl_2	6	98	88 (*R*)

[a] Reaction carried out at −20°C.
[b] Reaction carried out at 0°C.
[c] Reaction carried out at −13°C with 15-crown-5.
[d] Reaction carried out at 0°C with 15-crown-5.
[e] Carried out at 25°C with 15-crown-5.

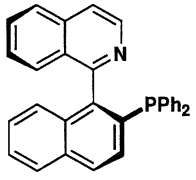
Hayashi (compare entries 1 and 2 with 3). It is interesting to note that (a*S*,*S*)-**185**, which has both (*S*)-axial and (*S*)-central chirality, gave the (*S*)-product in excess, while its diastereomer (a*R*,*S*)-**186**, which has (*R*)-axial chirality and (*S*)-central chirality, furnished the (*R*)-product in excess. In the related diphenylphosphinooxazolines, which contain only (*S*)-central chirality, the (*S*)-enantiomer was formed in excess.[136] This indicates that the axial chirality of the binaphthyl unit has a greater influence than the central chirality of the oxazoline unit in determining the stereochemical outcome of the reaction.

8.5. Isoquinoline-containing ligands

The first axially chiral phosphinamine ligand, 1-(2′-diphenylphosphino-3′,6′-dimethoxyphenyl)isoquinoline **188**, was reported by Brown et al. in 1991.[137] The logic behind its design was to place the nitrogen donor atom in an isoquinoline ring, thus providing a six-membered chelate ring, and to place a suitably bulky arylphosphine at the 1-position. This ligand was, however, found to racemise with an estimated half-life of 1 h at ambient temperature which precluded its application to asymmetric catalysis.[138] From this work, it became clear that further structural alterations were required in order to raise the barrier to rotation about the 1,1′-pivot. This led to the design, preparation and resolution of QUINAP **189**, which was reported in 1993.[139]



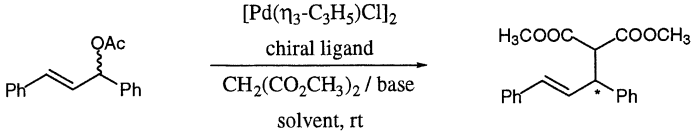
188



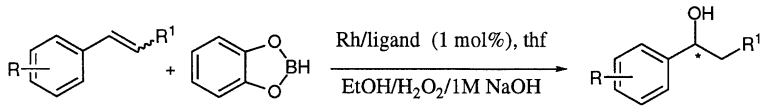
(*S*)-QUINAP **189**

The ligand **189** was successfully employed in enantioselective Pd-catalysed allylic alkylation reactions, achieving enantioselectivities of up to 98% for the reaction of 1,3-diphenyl-2-propenyl acetate and dimethyl malonate ion, when 15-crown-5 was added to complex the sodium cation (Table 12, entry 7, Scheme 71).[140]

The report by Männig and Nöth that Rh-phosphine complexes successfully catalysed the hydroboration of olefins[141] added a new dimension to the hydroboration methodology developed by Brown and co-workers.[142] With catecholborane as the borane source, the catalysed variant offered potential advantages in terms of chemo-, regio- and enantioselectivity.[143] Burgess et al. were the



Scheme 71.



Scheme 72.

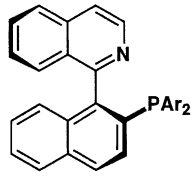
Table 13. Rh-catalysed hydroboration of vinylarenes

Entry	Ligand	Vinylarene	Solvent	Time (h)	Yield (%)	ee (%) Configuration
1	(*S*)-**189**	R=R′=H	THF	1	69	88 (*S*)
2	(*S*)-**189**	R=4-MeO; R′=H	THF	1	57	94 (*S*)
3	(*S*)-**189**	R=4-Cl; R′=H	THF	1	56	78 (*S*)
4	(*S*)-**189**	Indene	THF	1	75	76 (*S*)
5	(*S*)-**189**	Dihydronaphthalene	THF	1	78	96 (*S*)
6	(*S*)-**190**	R=Me; R′=H	THF	2	79	88 (*S*)
7	(*S*)-**190**	R=4-Cl; R′=H	THF	2	72	65 (*S*)
8	(*S*)-**190**	Dihydronaphthalene	THF	2	79	86 (*S*)
9	(*S*)-**191**	R=Me; R′=H	THF	2	77	79 (*S*)
10	(*S*)-**191**	R=4-Cl; R′=H	THF	2	77	54 (*S*)
11	(*S*)-**192**	R=Me; R′=H	THF	2	79	88 (*S*)
12	(*S*)-**192**	R=4-Cl; R′=H	THF	2	78	82 (*S*)
13	(*S*)-**192**	Indene	THF	2	80	78 (*S*)
14	(*S*)-**192**	Dihydronaphthalene	THF	2	81	82 (*S*)
15	(*R*)-**196**	R=R′=H	THF	2	70	67 (*R*)
16	(*R*)-**196**	Indene	THF	2	59	64 (*R*)
17	(*R*)-**196**	Dihydronaphthalene	THF	2	69	84 (*R*)
18	(*R*)-**202**	R=R′=H	THF	2	98	63 (*R*)
19	(*R*)-**202**	R=4-Cl; R′=H	THF	2	95	46 (*R*)
20	(*R*)-**202**	Indene	THF	2	98	84 (*R*)
21	(*R*)-**202**	Dihydronaphthalene	THF	2	>99	89 (*R*)

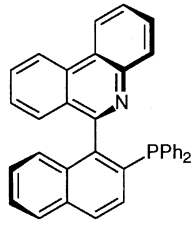
first to report catalytic enantioselective hydroboration[144] and Hayashi et al. subsequently used Rh–BINAP complexes for the hydroboration of styrene, with ees of up to 96%.[33] Brown et al. tested Rh complexes of QUINAP **189** in the enantioselective hydroboration of vinylarenes (Scheme 70) and a selection of the results obtained are presented in Table 13. High selectivities were induced with styrene (88% ee) and 4-methoxystyrene (98% ee) but electron-withdrawing substituents, such as that in 4-chlorostyrene, gave lower ee values (78%).[145] Of importance, however, was the finding that cyclic vinylarenes, such as indene and dihydronaphthalene, gave high ees (76 and 96%, respectively). Such sterically demanding substrates were not as successful when BINAP **1** complexes were used (19% ee for indene and no result for dihydronaphthalene has been reported).[33] This hydroboration/oxidation sequence has subsequently been extended to a synthetically useful hydroboration/amination procedure which produces primary amines from vinylarenes.[146]

The QUINAP ligand is amenable to structural variation at several points including the aryl groups on phosphorus which have been investigated. The analogues **190**–**195** were, therefore, prepared and resolved in a similar manner to QUINAP.[147]

In 1999, Brown reported a study in which comparisons were made between 1,1′-(2-diarylphosphino-1-naphthyl) isoquinolines in Rh-catalysed hydroboration of olefins.[148] A summary of the results found using **190**–**192** is given in



190; Ar = 3-MeC_6H_4
191; Ar = 3,5-di-MeC_6H_3
192; Ar_2 = 2-furyl
193; Ar = biphenylyl
194; Ar = 3-$CF_3C_6H_4$
195; Ar = 3,5-di-$CF_3C_6H_3$



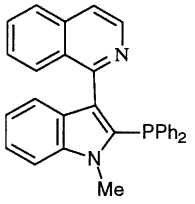
(*R*)-**196** PHENAP

Table 13 in which ees of up to 96% were observed. The key finding from this study was that the parent diphenylphosphino ligand **189** gave superior results for electron-rich vinylarenes, whereas the difurylphosphino ligand **192** gave superior results for electron-poor vinylarenes.

It became apparent during a mechanistic investigation of the allylic alkylation process, both from solution ^{1}H NMR and solid state studies, that the 3-H of the isoquinoline unit takes up a position in space leading to crucial ligand–reactant steric interactions which could be important for asymmetric induction.[140] This observation led to the design principle behind the preparation of the vaulted analogue PHENAP **196**, which was synthesised following the same protocol as QUINAP **189**.[149] PHENAP **196** was also tested in the

asymmetric Pd-catalysed allylic alkylation reaction giving enantioselectivities of up to 95% (Table 12, entries 8 and 9), and mostly slightly lower than those observed with QUINAP **189**. In view of the success of QUINAP **189** in Rh-catalysed hydroboration of vinylarenes, PHENAP **196** was also tested in this transformation (Table 13, entries 15–17).[145b] Impressive enantioselectivities were obtained and again the sterically demanding cyclic vinylarenes were hydroborated in 64–84% ee (Scheme 72).

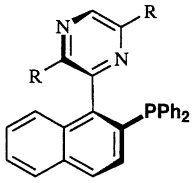
1-Methyl-2-diphenylphosphino-3-(1′-isoquinolyl)indole **197** was also synthesised by Brown and co-workers.[150] The design feature of this ligand maintained the isoquinoline unit and modified the naphthyldiphenylphosphine to a 2-diphenylphosphinoindole in an attempt to determine the effect of a varied bite angle on the reactivity and enantioselectivity. Studies to resolve **197** led to its immediate racemisation and therefore limited its application in enantioselective catalysis. 1,3-Diphenylallyl–Pd complexes of **197** were prepared and its solution structure studied by NMR techniques, from which insights into the mechanistic details of allylic alkylation could be drawn.



197

8.6. Pyrazine-containing ligands

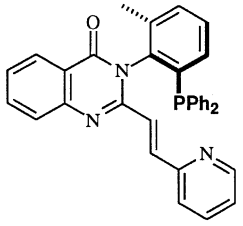
Systematic variation at the 3-position of the isoquinoline is possible but the preparation of 1-chloro-3-substituted isoquinolines is a limiting factor. Chlorinated pyrazines are more accessible and, for this reason, our group has investigated the possibility of preparing axially chiral phosphinamine ligands composed of a naphthyldiphenylphosphine 'half' and a substituted pyrazine 'half', more precisely the 3,6-dimethylpyrazine in 1-(3,6-dimethylpyrazin-2-yl)(2-naphthyl)diphenylphosphine, ligand **198**. The impetus to prepare this ligand was to determine the effect on enantioselection of the 6-methyl group and to investigate the enantiomeric stability given by the interaction of the naphthyl group and the 3-methyl group. In addition, the basicity of the nitrogen donor atom in **198** is considerably different to that of QUINAP **189**. We reported the synthesis and resolution of **198** in 1999.[151] The overall approach chosen for the preparation of **198** was similar to that previously reported for both QUINAP **189** and PHENAP **196**, with the key steps being the metal-catalysed reactions of biaryl coupling and formation of the naphthyl-phosphorous bond. In studies to determine the barrier to racemisation of **198** we found that the half-life of the ligand at 25°C was 24 h. This suggests that the 3-methyl group is insufficiently large to prevent racemisation and future pyrazine-containing ligands should possess a bulkier substituent at this position. In preliminary work, we have prepared and resolved the 1-(3,6-di-*i*-propylpyrazin-2-yl)(2-naphthyl)diphenylphosphine ligand **199** and work is also under way to prepare the 1-(3,6-di-*t*-butylpyrazin-2-yl)(2-naphthyl)diphenylphosphine ligand **200**.[152]



198; R = Me
199; R = *i*-Pr
200; R = *t*-Bu

8.7. Quinazolinone-containing ligands

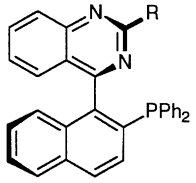
In 1999, the group of Virgil et al. reported a novel class of quinazolinone-containing ligands and one of which, the ligand **201**, was a chelate phosphinamine in which the axial chirality arises from restricted rotation about the amide nitrogen to arylphosphine bond.[153] As with previous examples of phosphinamine ligands, Pd complexes of (*S*)-**201** were tested in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Table 12, entries 10–14). The enantioselectivities obtained ranged from 67–87%, in which the favoured product was the (*R*)-enantiomer.



201

8.8. Quinazoline-containing ligands

In 1996, we initiated a research project to incorporate the quinazoline unit into a range of axially chiral phosphinamine ligands. The initial target ligand was diphenyl[1-(2-phenylquinazolin-4-yl)(2-naphthyl)] phosphine **202** (2-phenyl-Quinazolinap). The 2-phenylquinazoline unit in particular was chosen as we expected that the naphthalene-quinazoline pivot would be essentially inert to racemisation and, once resolved, we could investigate the effect on enantioselection relative to QUINAP **189** and PHENAP **196** of the increased steric bulk at the 2-position. In addition, the donor nitrogen atom is predicted to be substantially less basic as the pK_a values of simpler heteroaromatics related to **189** and **202** is 5.1 and 3.3, respectively.[154] We reported the synthesis and resolution of the first quinazoline-containing atropisomeric phosphinamine ligand **202** for asymmetric catalysis in 1999.[155] The synthetic approach chosen for its preparation was similar to that previously reported for ligands (**188**, **196** and **198**) in which the two key steps were the metal-catalysed naphthalene–quinazoline coupling and naphthyl-phosphorus bond forming reactions. The ligand was successfully resolved using standard fractional crystallisations of diastereomeric palladacycles.[156]



202; R = Ph
203; R = Me
204; R = H

The results of our preliminary investigations using (*R*)-**202** in Pd-catalysed allylic substitutions are summarised in Table 12 (entries 15–18). The principal observations are

that the conversions are good (up to 99% yield) but the enantioselectivities are moderate (optimised to 66%) and show the *opposite* sense of asymmetric induction compared to QUINAP **189** and PHENAP **196**, i.e. (*R*)-**189** and (*R*)-**196** afford an excess of the (*S*)-enantiomer whereas (*R*)-**202** gives the (*R*)-enantiomeric product in excess.[157] As the major structural difference between **189**, **196**, and **202** is the presence of the 2-phenyl substituent on the quinazoline, this substituent must cause steric interactions which lead to lowered and opposite asymmetric induction.

We have also tested cationic Rh complexes of (*R*)-**202** and the results are summarised in Table 13 (entries 18–21).[158] These results demonstrate an extremely enantioselective catalyst system which affords high enantioselectivities for substituted styrenes and the cyclic vinylarenes, indene (84% ee) and dihydronaphthalene (89% ee). We explain these results by inferring that the increased steric demand of the olefin is more easily accommodated by our less sterically demanding ligand **202**.

In the light of our observations with the ligand **202**, we wished to determine the influence of a smaller substituent than a phenyl group at the 2-position. We, therefore, recently reported the synthesis and resolution of 2-methyl-Quinazolinap **203**, the second member of this class of quinazoline-containing atropisomeric phosphinamine ligands.[159] Our preliminary applications of this ligand in Pd-catalysed allylic substitutions are shown in Table 12 (entries 19 and 20) and it is clear that the enantioselectivities have been improved with the smaller 2-substituent on the ligand.

We have also recently prepared and resolved the C_2-unsubstituted analogue, Quinazolinap **204**, which allows a direct comparison with QUINAP **189** from which we could infer the importance of the change in electronics at the chelating nitrogen.[160] We have not yet applied this ligand in asymmetric catalysis and are currently investigating different 2-substituted analogues including structural variation of the diarylphosphine grouping.[161]

9. Conclusions

Since the initial report of BINAP, a large and diverse range of homobidentate and heterobidentate axially chiral ligands have been designed and prepared for use in asymmetric catalysis. Their metal complexes have been applied in a variety of important asymmetric transformations and excellent enantioselectivities, regioselectivities and reactivities have been achieved in each of these processes. Even a brief glance at the results obtained, however, underlines how the electronic and steric properties of each ligand must be finely tuned for individual substrates and applications. To date, a ligand, which provides the maximum reactivity and selectivity across a wide range of substrates and applications, remains elusive. Nevertheless, the future for this class of chiral ligand in asymmetric catalysis seems assured due to the high reactivity exhibited by their metal complexes and because of the impressive enantioselectivities thus far obtained. It will be of interest to see how quickly examples of this technology will be transferred to industrial applications.[162]

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Biographical sketch

Mary McCarthy, born in Dublin, graduated with an Honours BSc degree in Chemistry from University College Dublin in 1995. She received her PhD in chemistry (1999) from the same institution where she investigated the synthesis of new chiral ligands and their application in asymmetric catalysis under the supervision of Dr Patrick Guiry. She then began postdoctoral research on palladium-catalysed amidocarbonylation under the guidance of Professor Dr Piet W. N. M. van Leeuwen at the Institute for Molecular Chemistry, University of Amsterdam. In February 2001, she will commence a fellowship at the Max-Planck-Institut für Kohlenforschung, Mülheim at the laboratory of Dr Walter Leitner, where her research will involve the further development of the use of supercritical carbon dioxide in catalysis.

Patrick Guiry, born on December 1964 in Clonmel, County Tipperary (Ireland), graduated with an Honours BSc degree in Chemistry from University College Dublin in 1986. He stayed at University College Dublin for his PhD working under the supervision of Professor Dervilla Donnelly on the application of aryllead triacetates to the synthesis of natural products. During his PhD he also worked in Marseille in 1988 under the supervision of Dr Jean-Pierre Finet (Cu-catalysed N-arylation) and at Texas A & M in 1989 with Professor Sir Derek Barton (mechanistic studies of arylation/phenol arylation). He received his PhD degree in 1990 and moved to the group of Dr John Brown at the Dyson Perrins Laboratory, Oxford University for postdoctoral studies in the area of asymmetric catalysis. During this 3-year stay he was appointed in 1991 as a Tutorial Fellow at Wadham College, Oxford and in 1992 as College Lecturer/Director of Studies at St Hugh's College, Oxford. He returned to University College Dublin as a College Lecturer in 1993 where he started his independent research. His research interests are the design and preparation of chiral ligands and their application in a broad range of asymmetric catalytic transformations. Palladium catalysis is of special interest and new and useful substrates for the Heck reaction have recently been studied. Mechanistic studies in asymmetric catalysis are also investigated and approaches include the use of X-ray crystallography and multinuclear NMR techniques and this is supplemented by computational studies in collaboration with Professor Per-Ola Norrby at the Technical University of Denmark. He was a visiting researcher in the group of Professor Andreas Pfaltz at the Max Planck Institut für Kohlenforschung at Mülheim an der Ruhr (Germany) in 1996. He is a core investigator of the Conway Institute of Biomolecular and Biomedical Sciences at University College Dublin and has two collaborative research projects on the physiology and pharmacology of Ecstasy, amphetamine and related phenylethylamines. He was the recipient of a President's Research Award in 1996 and a President's Teaching Award in 2000 from University College Dublin. His research group currently consists of 10 PhD students and one postdoctoral fellow and he has also supervised two postdoctoral researchers, four visiting Erasmus students and graduated seven PhD students to date. A keen tennis player, he has represented his province Munster at all levels, was awarded his Colours from University College Dublin and represented Ireland in the Italia Cup (ITF World Team Competition) in Germany in 1999, the Home Nations Series in 2000 and again in the Italia Cup 2000 in Argentina where he was team captain.