The Development of Bidentate P,N Ligands for Asymmetric Catalysis

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Received: August 8, 2003; Revised: February 15, 2004; Accepted: February 22, 2004

Abstract: In this review, an attempt is made to systemise the rôle which bidentate phosphinamine (P,N) ligands play in asymmetric catalysis. The ligands will be classified, not by the reaction to which their metal complexes have been applied, but by the nature of their donor atoms. In this manner the development of ligand architectural design can be more easily monitored. The asymmetric transformations to which metal complexes of these ligands have been applied include among others, palladium-catalysed allylic substitutions, copper-catalysed 1,4-additions to enones and rhodium-catalysed hydroboration of vinylarenes. Excellent enantioselectivities, regioselectivities and reactivities have been achieved in each of these processes.

Keywords: allylic substitution; asymmetric catalysis; C-C bond formation; homogeneous catalysis; P,N ligands

1 Introduction

In asymmetric catalysis ligands induce asymmetry in a reaction, not just through steric factors, but also by generating electronic asymmetry on the metal centre through the presence of different donor atoms. The most important and widely used of these heterodentate ligands are those which bear phosphorus and nitrogen as their donor atoms. The π-acceptor character of the phosphorus can stabilise a metal centre in a low oxidation state, while the nitrogen σ-donor ability makes the metal more susceptible to oxidative addition reactions. This combination can help to stabilise intermediate oxidation states or geometries which form during a catalytic cycle.

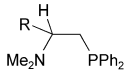
This electronic asymmetry can also be used to optimise a ligand for use in a particular reaction by appropriate choice of the nature of the donor atoms. For instance, bonding the phosphorus directly to a more electronegative atom such as oxygen or nitrogen will lessen its electron-donating ability while also enhancing its π-acceptor capacity. Alternatively, the presence of an imino rather than an amino group will result in a nitrogen donor atom of greater σ-donating capabilities. Overall this will result in a greater electronic disparity between the donor atoms.

In this review which comprehensively covers the literature up to the end of 2002 (with only selected examples from 2003), we attempt to systemise the rôle that bidentate ligands play in asymmetric catalysis. The ligands will be classified, not by the reaction to which their metal complexes have been applied, but by the nature of their donor atoms. In this manner the development of ligand architectural design can be more easily monitored.

2 Amino N Donor, Phosphine P Donor

One of the first applications of centrally chiral P,N ligands in asymmetric catalysis was the report by Hayashi and Kumada on the use of the β-aminoalkylphosphines **1–5**, which are readily prepared from amino acids, in an asymmetric Grignard cross-coupling.[1]

In the nickel-catalysed reaction between 1-phenylethylmagnesium chloride (**6**) and vinyl bromide (**7**) the



1: (*S*)-Alaphos (R = Me)
2 : (*S*)-Phephos (R = CH_2Ph)
3 : (*R*)-PhGlyphos (R = Ph)
4 : (*S*)-Valphos (R = *i*-Pr)
5 : (*R*)-*t*-Leuphos (R = *t*-Bu)

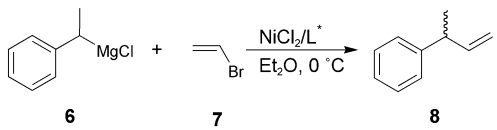
 DOI: 10.1002/adsc.200303138

Pat Guiry was born in County Tipperary, Ireland and graduated with an Honours B.Sc. degree in Chemistry from University College Dublin in 1986. He stayed at University College Dublin for his Ph. D. working under the supervision of Professor Dervilla Donnelly on the application of aryllead triacetates to the synthesis of natural products. During his Ph. D. period 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 Ph. D. degree in 1990 and moved to the group of Dr. John Brown, FRS at the Dyson Perrins Laboratory, Oxford University for post-doctoral studies in the area of asymmetric catalysis. During this three-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 Hughs 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, their application in a broad range of asymmetric catalytic transformations and the total synthesis of biologically important compounds. 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 the lead co-ordinator of the Centre for Synthesis and Chemical Biology, one of the three centres of the Conway Institute of Biomolecular and Biomedical Sciences at University College Dublin. He was the recipient of a President's Research Award in 1996 and a President's Teaching Award in 2000 from University College Dublin. He was promoted to Senior Lecturer in 2002 and to Associate Professor of Synthetic Organic Chemistry in 2003. A keen tennis player, he represented Ireland in 2003 in the Italia Cup (ITF World Team Competition O-35) in Berlin where he was team captain and in the Home Nations Series in Glasgow.

Cormac Saunders was born in Waterford, Ireland in 1976. He studied at University College Dublin receiving his Honours B.Sc. degree in Chemistry in 1997. Working in the group of Professor Pat Guiry he has recently completed his Ph. D. in which he researched the use of chiral P,N ligands in asymmetric metal-catalysed processes. He is currently employed in the pharmaceutical industry with GlaxoSmithKline in Cork, Ireland.

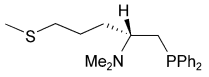
enantioselection observed rose with increasing size of the aminophosphine substituent up to 88% for *tert*-Leuphos (**5**), Scheme 1. The asymmetric induction is thought to result from dissociation of the nitrogen from the metal during the reaction to selectively bind one enantiomer of the racemic Grignard and then direct it onto the metal.

Kellogg has prepared amino acid-derived ligands **9** and **10**, also for use in cross-coupling reactions.[2] The sulfur atom participates in the reductive elimination step and is able to provide an extra element of stereocontrol. Ligand **9**, which has an appropriate length of spacer, also gave an 88% enantiomeric excess for the reaction between 1-phenylethylmagnesium chloride (**6**) and vinyl bromide (**7**), Scheme 1.



6 7 8

Scheme 1.



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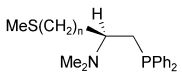
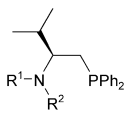


10 : n = 1
11 : n = 2

Faller has applied ligands **9**–**11** in the rhodium-catalysed hydrosilylation of acetophenone obtaining a moderate 62% enantioselection with ligand **10**.[3]



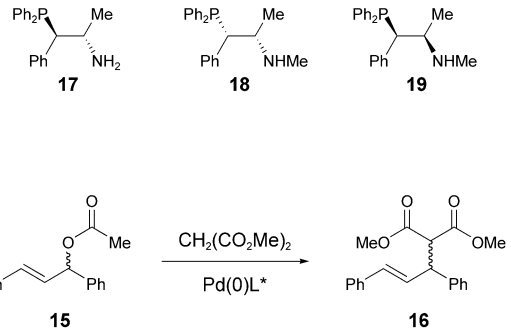
4 : $R^1 = R^2 =$ Me
12 : $R^1 = R^2 =$ Ph
13 : $R^1 =$ Me, $R^2 =$ Ph
14 : $R^1 =$ Me, $R^2 =$ *i*-Pr

More recently, Anderson et al. have applied Valphos (**4**) and the derivatives **12**–**14** in the palladium-catalysed allylic alkylation of (*E*)-1,3-diphenylprop-2-enyl acetate (**15**), Scheme 2.[4] An important feature of **13** and **14** is the potential for the chirality of the backbone to induce a preferential orientation of the amino substituents

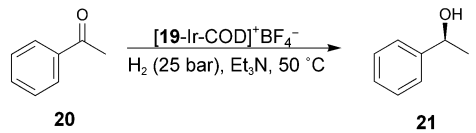
Table 1.

Entry	Ligand	Procedure	Solvent	Time [h]	Yield [%]	ee [%]
1	**4**	BSA	DCM	48	93	60 (*R*)
2	**4**	Sodium ion	THF	96	91	62 (*R*)
3	**12**	BSA	DCM	48	96	80 (*R*)
4	**12**	Sodium ion	THF	72	94	92 (*R*)
5	**13**	BSA	DCM	96	94	83 (*S*)
6	**13**	Sodium ion	THF	96	89	73 (*S*)
7	**14**	BSA	DCM	24	89	56 (*S*)
8	**22**	Malonate/NaH	THF	24	97	50 (*S*)
9	**23**	Malonate/NaH	THF	24	94	68 (*S*)
10	**24**	Malonate/NaH	THF	24	96	63 (*S*)
11	**25**	Malonate/NaH	THF	24	93	69 (*S*)
12	**26**	Malonate/NaH	THF	24	94	62 (*S*)
13	**27**	Malonate/NaH	THF	24	97	75 (*S*)
14	**28**	Malonate/NaH	THF	24	99	57 (*S*)
15	**29**	Malonate/NaH	THF	24	88	48 (*S*)
16	**30**	Malonate/Cs_2CO_3	DCE	24	99	72 (*S*)
17	**31**	Malonate/Cs_2CO_3	DCE	24	67	70 (*S*)
18	**32**	Malonate/Cs_2CO_3	DCM	24	96	62 (*S*)
19	**33**	Malonate/Cs_2CO_3	DCM	24	83	60 (*S*)

upon binding to the metal and hence rendering the nitrogen stereogenic. This effect can be seen in the observation that ligands **4** and **12**, which possess two identical nitrogen substituents, gave the (*R*) product, whereas those with unlike substituents afforded the (*S*) configuration, Table 1, entries 1 and 3 *versus* entries 5 and 7.



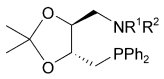
Scheme 2.



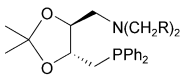
Scheme 3.

Dahlenburg has reported a series of phosphine ligands **17**–**19** whose chirality originates from the amino alcohols norephedrine, pseudoephedrine and ephedrine.[5] As yet only the iridium complex of **19** has been used for the hydrogenation of acetophenone **20** resulting in a 40% enantiomeric excess of (*S*)-1-phenylethanol (**21**), Scheme 3.

Sinou has reported ligands **22**–**29** derived from tartaric acid (P,N analogues of DIOP) which induced enantioselectivities of up to 75% in the allylic alkylation of the diphenylallyl substrate **15**, Scheme 2, Table 1, entries 8–15.[6] These ligands were also tested in the asymmetric hydroformylation of vinylarenes but gave poor enantioselection.[7]

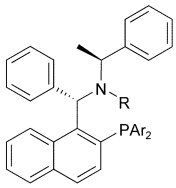


22 : $R^1 = R^2$ = Ph
23 : R^1 = Ph, R^2 = Me
24 : R^1 = *p*-OMe-C_6H_4, R^2 = Me
25 : R^1 = Ph, R^2 = α-Naphthyl



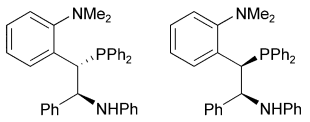
26 : R = Ph
27 : R = Mesityl
28 : R = α-Naphthyl
29 : R = *o*-Biphenyl

Ding used an aminonaphthol, which had previously been successfully used in diethylzinc additions to aromatic aldehydes,[8,9] to provide the basis for the synthesis of a number of related P,N ligands **30**–**33**.[10] Initial testing of these ligands in the allylic alkylation of the diphenylallyl substrate **15** has been performed and ligand **30** affords the best enantioselection under optimised conditions, Table 1, entries 16–19.



	R	Ar
30 :	Me	Ph
31 :	Et	Ph
32 :	Me	*p*-Tolyl
33 :	Et	*p*-Tolyl

Ligands **34** and **35**, developed by Andrieu, bear a further nitrogen group which allows for two possible P-N co-ordination modes.[11] With rhodium, however, only binding through the phosphorus and the secondary amine is observed. No application of these ligands in asymmetric catalysis has yet been reported.



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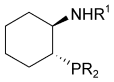
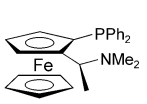
35

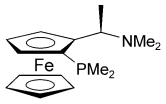


	R^1	R
36 :	H	Ph
37 :	H	Cy
38 :	Pht	Ph

The group of Yudin has recently reported the *trans*-1,2-cyclohexane-based ligands **36**–**38**.[12] These are prepared by an aziridine ring opening reaction which allows the steric and electronic properties of the ligand to be easily varied by appropriate choice of substituents on the aziridine and the phosphorus nucleophile.

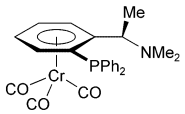


39 : PPFA



40 : MPFA

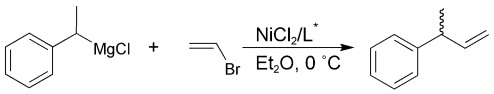
The first report of a planar chiral P,N ligand in asymmetric catalysis was in the work by Kumada and Hayashi who developed the (*S*)-α-[(*R*)-2-diphenylphosphinoferrocenyl]ethyldimethylamine (PPFA) (**39**) and (*R*)-α-[(*S*)-2-dimethylphosphinoferrocenyl]ethyldimethylamine (MPFA) (**40**) ligands and applied them to the catalytic hydrosilylation of ketones.[13] PPFA provided only a 20% enantiomeric excess in that reaction but proved to be more useful in asymmetric cross-coupling of Grignard reagent **6** with vinyl bromide (**7**), Table 2, entries 1 and 2.[14] Many other diphosphine and phosphinamine derivatives of PPFA have since been prepared and applied in various catalytic reactions.[15]



(*R*, S_p)-**41**

By analogy to PPFA, Hayashi also prepared (*R*,S_p)-**41** where the planar chirality is due to a (η^6-arene)chromium moiety rather than a ferrocenyl unit.[16] This ligand was also successful for the coupling of Grignard reagents to vinyl bromides, Table 2, entry 3, and was capable of producing enantiomeric excesses of 92% in the palladium-catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**).[17]

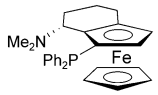
Table 2.



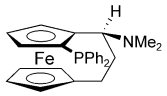
6 **7** **8**

Entry	Ligand	Time [h]	Temp. [°C]	Yield [%]	ee [%]
1	(*S*)-(*R*$_P$)-**39**	24	25	82	61 (*R*)
2[a]	(*R*)-(*S*$_P$)-**39**	24	−20	>95	68 (*S*)
3	(*R*)-(*S*$_P$)-**41**	18	0	67	61 (*S*)
4	(*R*)-(*R*$_P$)-**42**	20	0	95	79 (*R*)
5	(*S*)-(*S*$_P$)-**43**	–	–	–	63

[a] $NiCl_2$ was used in place of palladium

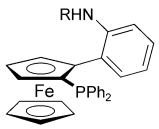


(*R*, R_p)-**42**



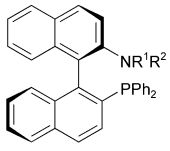
(*S*, S_p)-**43**

Weissensteiner et al. have prepared **42** and **43** where the α-chirality is constrained within a cyclic structure resulting in ligands which are far less flexible than PPFA.[18,19] They have been applied in asymmetric Grignard cross-couplings affording ees of 79% and 63%, respectively, Table 2, entries 4 and 5, and their co-ordination chemistry has also been extensively studied.[20]



(*S*)-**44** : R = H
(*S*)-**45** : R = -C(O)-Pyridyl
(*S*)-**46** : R = -C(O)-*t*-Bu

Johannsen and co-workers have recently reported a modular approach to ligands **44**–**46** and have applied these in copper-catalysed diethylzinc additions.[21] Ligand **46** gave high conversion (95%) and moderate enantioselection (56%) with *trans*-chalcone as the substrate.

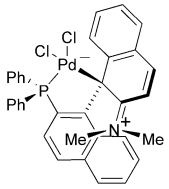


47 : R^1 = R^2 = Me
48 : R^1 = H, R^2 = Me
49 : R^1 = H, R^2 = Et
50 : R^1 = H, R^2 = *i*-Pr
51 : R^1 = H, R^2 = Cy
52 : R^1 = Me, R^2 = *i*-Pr
53 : R^1 = Me, R^2 = Cy
54 : R^1 = R^2 = Cy

In 1998 Kocovsky et al. reported the preparation of a series of axially chiral aminophosphine ligands **47**–**54**, bearing the acronym MAP, which are analogous to Hay-

ashi's MOP by replacing the oxygen atom with a nitrogen.[22] Four members of the series, **47**, **52**, **53** and **54**, were tested for their ability to induce asymmetry in the palladium-catalysed allylic substitution of 1,3-diphenylpropenyl acetate (**15**) with a highest enantiomeric excess of 73% being obtained, Table 3, entries 1–4.

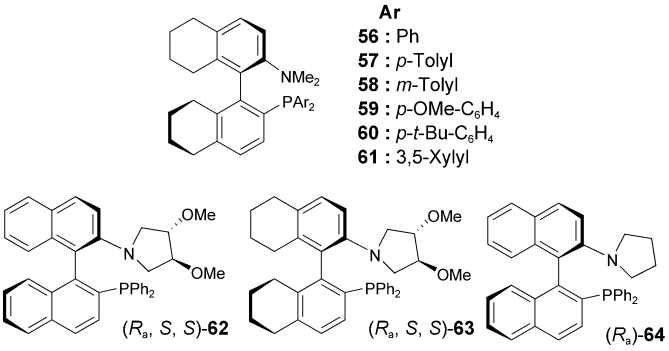
Although these aminophosphine ligands were initially designed to act as P,N chelating species, the palladium dichloride complex of **47** was found by ^{1}H NMR spectroscopy to be an 85:10:5 mixture of three species. As well as the expected P,N chelated complex and the monodentate phosphine complex, the predominant species was found to be **55** which acts as a P-C ligand with an unusual C_σ-Pd bonding mode. The palladium allyl complex exhibited similar behaviour.[23]



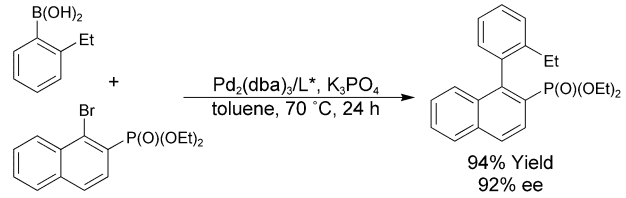
55

In addition, a detailed study by Vyskocil and Lloyd-Jones and co-workers demonstrated that palladium complexes of MAP **47** and MOP were very efficient catalysts for allylic alkylation of racemic cyclopentenyl pivalate with sodium dimethylmalonate. Isotopic desymmetrisation revealed that the reaction occurred with a powerful stereochemical memory effect which was suggested to arise through selective generation of diastereomeric $[Pd\{(P,C)\text{-}L\}(\eta^3\text{-cyclopentenyl})]^+$ ions (L = MAP) and subsequent capture by nucleophile before ion-pair collapse or equilibration occurs.[23b, c]

These ligands were also found to have a strong accelerating effect in both Hartwig–Buchwald aminations and Suzuki cross-couplings.[22b,23a] Buchwald subsequently reported the use of a dicyclohexyl-phosphine version of **47** to prepare axially chiral biaryls in up to 92% enantiomeric excess *via* an asymmetric Suzuki coupling, Scheme 4.[24]

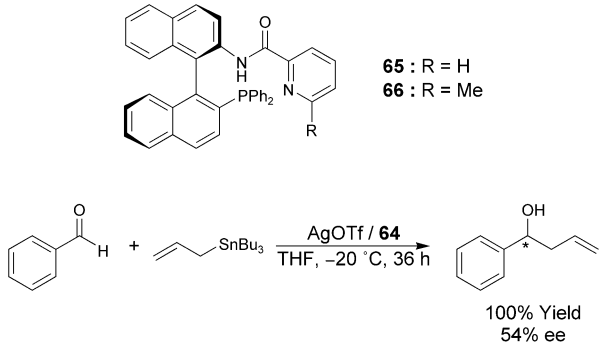


Ar
56 : Ph
57 : *p*-Tolyl
58 : *m*-Tolyl
59 : *p*-OMe-C_6H_4
60 : *p*-*t*-Bu-C_6H_4
61 : 3,5-Xylyl



Scheme 4.

Ding prepared the related H_8-MAP ligands **56**–**61** which gave higher enantioselectivities in allylic alkylation, an improvement which was attributed to the larger bite angle of these ligands, Table 3, entries 5–13.[25] Subsequently, these H_8-MAP ligands were shown not to coordinate to palladium in a P,C fashion in sharp contrast to the related ligands **47**.[26] The same group has recently reported ligand **62** and its H_8-MAP analogue **63** which contain both axial and central chirality.[27] These were also applied in allylic alkylation where a strong co-operative effect between the chiral elements was found, Table 3, entries 14–17. These ligands were also tested in the silver(I)-catalysed allylation of benzaldehyde where the unsubstituted pyrrolidine ligand **64** gave the highest enantioselection, Scheme 5.[28]



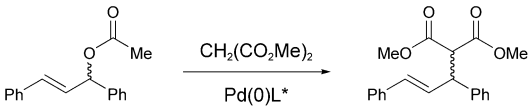
Scheme 5.

Zhang et al. also used the 1-naphthyl-2-naphthylamine framework, in conjunction with a substituted pyridine system, when designing ligands **65** and **66**.[29] These possess relatively large bite angles and are quite conformationally rigid due to the amide linker. They proved to be very useful for the copper-catalysed 1,4-addition of diethylzinc to acyclic enones, Scheme 6, Table 4. Addition to cyclohexenone also proceeded in high enantioselection with 92% ee being obtained under optimum conditions using ligand **66**.

3 Cyclic Amino N Donor, Phosphine P Donor

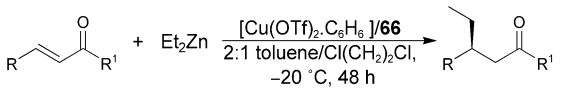
Constraining the nitrogen donor within a ring can be used to orient substituents and give rise to differing steric effects relative to acyclic ligands.

Table 3.

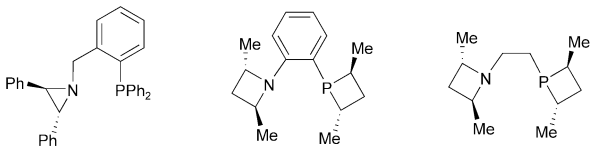


15 **16**

Entry	Ligand	Base	Temp. [°C]	Solvent	Time [h]	Yield [%]	ee [%]
1	**47**	Cs_2CO_3	r.t.	DCM	24	85	71 (*S*)
2	**52**	Cs_2CO_3	r.t.	DCM	24	84	73 (*S*)
3	**53**	Cs_2CO_3	r.t.	DCM	24	80	69 (*S*)
4	**54**	Cs_2CO_3	r.t.	DCM	24	77	68 (*S*)
5	**56**	Cs_2CO_3	20	DCM	12	99	82.5 (*S*)
6	**57**	Cs_2CO_3	20	DCM	12	99	75 (*S*)
7	**58**	Cs_2CO_3	20	DCM	12	99	80 (*S*)
8	**59**	Cs_2CO_3	20	DCM	12	96	79 (*S*)
9	**60**	Cs_2CO_3	20	DCM	12	89	73 (*S*)
10	**61**	Cs_2CO_3	20	DCM	12	98	84 (*S*)
11	**56**	BSA	0	Toluene	36	73	86 (*S*)
12	**61**	BSA	0	Toluene	24	99	87 (*S*)
13	**61**	BSA	−20	Toluene	24	62	91 (*S*)
14	(*S*,*S*,*S*)-**62**	Cs_2CO_3	20	DCM	24	97	83 (*R*)
15	(*R*,*S*,*S*)-**62**	Cs_2CO_3	20	DCM	24	98	27 (*S*)
16	(*S*,*S*,*S*)-**63**	Cs_2CO_3	20	DCM	24	90	50 (*R*)
17	(*R*,*S*,*S*)-**63**	Cs_2CO_3	20	DCM	24	97	31 (*S*)



Scheme 6.



67 **68** **69**

Table 4.

Entry	R	R^1	Yield [%]	ee [%]
1	Ph	Ph	85	96 (*S*)
2	Ph	4-MeO-C_6H_4	69	97 (−)[a]
3	4-MeO-C_6H_4	Ph	97	98 (*S*)
4	4-Cl-C_6H_4	Ph	72	95 (−)[a]
5	Ph	4-Cl-C_6H_4	70	95 (−)[a]
6	*i*-Pr	Me	53	86 (−)[a]

[a] Sign of the optical rotation.

3.1 Aziridine N Donor

Tanner et al. have reported the preparation of the phosphino-aziridine ligand **67** but the results obtained in palladium-catalysed allylic alkylation were poor.[30]

3.2 Azetidine N Donor

Genet has developed ligands **68** and **69** where both the phosphorus and nitrogen are incorporated in four-membered rings which are formed by cyclisation of a 1,3-diol-derived cyclic sulfate around the donor atoms.[31] A wide range of cyclic sulfates is available from 1,3-diketones which allows for facile variation of the ligands. Further accounts detailing the utilisation of these ligands in asymmetric catalysis are expected.

3.3 Pyrrolidine N Donor

Koga reported the pyrrolidinyl ligands **70**–**73** but in the allylic alkylation of 1,3-diphenylprop-2-enyl acetate (**15**) with sodium dimethylmalonate only poor enantioselectivities were obtained, Table 5, entries 1–4.[32] Ligand **73** in which the chirality would seem to be further away from the binding site resulted in the best enantioselectivity (39%).

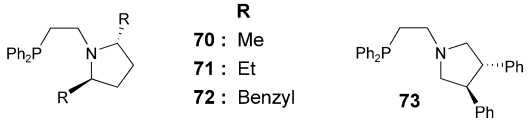
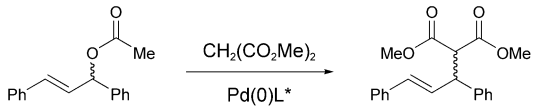


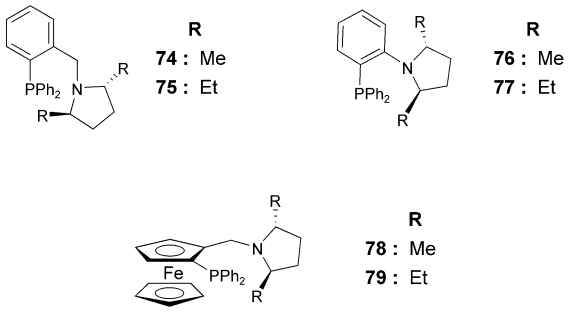
Table 5.



15 **16**

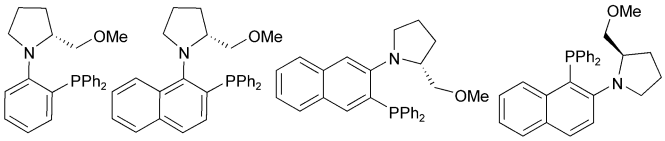
Entry	Ligand	Method	Solvent	Temp. [°C]	Time [h]	Yield [%]	ee [%]
1	**70**	BSA	DCM	r.t.	1.5	94	20 (*S*)
2	**71**	BSA	DCM	r.t.	2.3	96	19 (*S*)
3	**72**	BSA	DCM	r.t.	2.5	95	11 (*R*)
4	**73**	BSA	DCM	r.t.	2.6	93	39 (*R*)
5	**74**	Na Mal	DMF	0	24	62	55 (*R*)
6	**75**	Na Mal	ACN	25	24	89	90 (*R*)
7	**76**	Na Mal	DMF	25	24	63	34 (*R*)
8	**77**	Na Mal	DMF	25	24	62	26 (*R*)
9	(S_p,*R*,*R*)-**78**	Na Mal	DCM	25	24	69	36 (*S*)
10	(*Sp*,*R*,*R*)-**79**	BSA	DCM	25	24	71	20 (*S*)

Guiry and co-workers described the synthesis of ligands **74** and **75** and their application in the asymmetric intermolecular Heck reaction,[33] ees up to 90%, and iridium-catalysed imine reduction,[34] ees up to 91%. In the allylic alkylation of diphenylallyl acetate (**15**) an optimum enantioselectivity of 90% was obtained with **75**, Table 5, entries 5–8.[35] When ligands **76** and **77**, which form smaller five-membered chelates, were used the best enantioselection found was 34%.[36]



In a continuation of this work Guiry recently reported the synthesis of the (2*R*,5*R*)-2,5-dialkyl-1-(ferrocenylmethyl)pyrrolidines **78** and **79** and their application in palladium-catalysed allylic substitution.[37] Unfortunately these ligands gave poor enantioselection, lower than their planar counterparts in all cases. It was found that the sense of enantioselection is reversed upon going from **74**, **75** to **78**, **79** indicating that the planar chirality is the dominant enantiocontrolling feature of these ligands and, moreover, that the low enantioselectivity may be due to the planar and central chiralities acting in a contrary fashion, Table 5, entries 9 and 10.

The group of Mino has developed the methoxymethyl substituted pyrrolidine ligands **80**–**83** and applied them in the allylic alkylation of (*E*)-1,3-diphenylpropenyl acetate (**15**), where ligand **82**, which contains the larger



80 **81** **82** **83**

naphthyl backbone, afforded the highest enantioselectivity of 83%, Table 6, entries 1–6.[38] The ether functionality was expected to interact with the incoming nucleophile to bring about good selectivity and extensions of this ligand class were **84** and **85**,[39] where the chain length of the substituent was increased, and a slight increase in yield and enantioselection was observed with ligand **84**, Table 6, entries 7–9. Ligands **86**–**89**, which were the 6′-substituted analogues of **80**, were also developed and **87** was more successful, giving a 94% enantiomeric excess at −20 °C, although with a decrease in activity, Table 6, entries 10–15.[40] Ligands **90**–**95** which have a hydroxymethyl group on the pyrrolidine unit have also been prepared. These were found to be even more effective in allylic alkylation, Table 6, entries 16 and 17.

Hiroi et al. have used (*S*)-proline as the basis for a similar series of ligands which bear phosphino, organosulfur

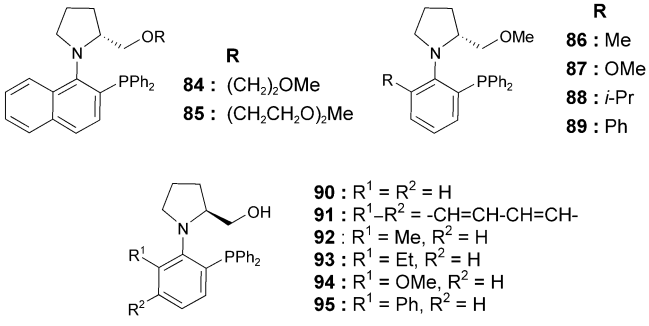
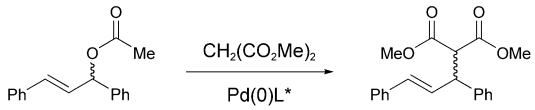


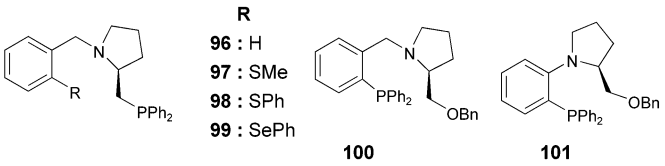
Table 6.



15 **16**

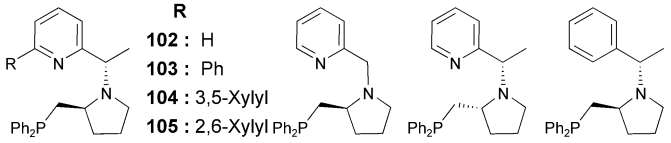
Entry	Ligand	Method	Solvent	Temp. [°C]	Time [h]	Yield [%]	ee [%]
1	(*R*)-**80**	BSA	THF	r.t.	24	93	49 (*R*)
2	(*R*)-**81**	BSA	THF	r.t.	24	79	74 (*R*)
3	(*R*)-**81**	BSA	THF	0	96	99	79 (*R*)
4	(*R*)-**81**	BSA	THF	−20	168	88	83 (*R*)
5	(*R*)-**82**	BSA	THF	r.t.	24	91	24 (*R*)
6	(*R*)-**83**	BSA	THF	r.t.	24	96	35 (*R*)
7	(*S*)-**84**	BSA	THF	r.t.	24	96	79 (*S*)
8	(*S*)-**84**	BSA	THF	−20	168	22	85 (*S*)
9	(*S*)-**85**	BSA	Toluene	r.t.	24	86	76 (*S*)
10	(*R*)-**86**	BSA	Toluene	r.t.	24	96	82 (*R*)
11	(*R*)-**87**	BSA	Toluene	r.t.	24	97	85 (*R*)
12	(*R*)-**87**	BSA	Toluene	0	96	95	88 (*R*)
13	(*R*)-**87**	BSA	Toluene	−20	168	94	94 (*R*)
14	(*R*)-**88**	BSA	Toluene	r.t.	24	95	80 (*R*)
15	(*R*)-**89**	BSA	Toluene	r.t.	24	95	73 (*R*)
16	(*S*)-**92**	BSA	Toluene	r.t.	24	94	92 (*S*)
17	(*S*)-**94**	BSA	Toluene	0	72	94	94 (*S*)
18	(*S*)-**96**	Na Mal	DCM	r.t.	2	73	74 (*R*)
19	(*S*)-**97**	Na Mal	DCM	r.t.	2	73	75 (*R*)
20	(*S*)-**97**	Na Mal	DCM	0	14	75	79 (*R*)
21	(*S*)-**97**	Na Mal	DCM	−20	40	76	82 (*R*)
22	(*S*)-**98**	Na Mal	DCM	r.t.	2	75	81 (*R*)
23	(*S*)-**98**	Na Mal	DCM	0	4	76	84 (*R*)
24	(*S*)-**98**	Na Mal	DCM	−20	40	74	87 (*R*)
25	(*S*)-**99**	Na Mal	DCM	r.t.	60	75	79 (*R*)
26	(*S*)-**99**	Na Mal	DCM	0	90	73	85 (*R*)

or organoselenenyl groups, **96**–**101**, and these ligands were also applied to the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**), Table 6, entries 18–26.[41]



100 **101**

co-ordination to palladium occurs through the pyrrolidine.

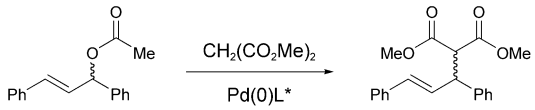


106 **(*R,S*)-102** **107**

Uenishi has reported the P,N ligands **102**–**107** and applied them in the allylic alkylation reaction where the results obtained gave insight into which structural features of the ligands are essential for high enantioselection, Table 7, entries 1–10.[42] Both *ent*-**102** and **106** gave lower enantioselection than **102** indicating, firstly, that there is a co-operative effect between the chiral centres in **102**, and secondly, that it is the pyrrolidine chiral centre which is the major influence on the enantioselection. The high enantioselection which is obtained with **107** show that the pyridyl nitrogen is unnecessary and that

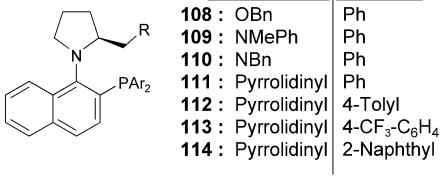
Ligands **108**–**114** and **115**, which are atropoisomeric about the naphthyl-amine bond, have recently been reported by Kondo et al.[43] These ligands can freely rotate in solution but, when bound to a metal one of the two possible diastereomeric rotamers is formed preferentially due to steric interactions. These ligands were evaluated in palladium-catalysed allylic alkylation where the nitrogen atom in the pendant side chain is thought to act similarly to the ether substituent in ligands **80**–**89** and interact with the incoming nucleophile, Table 7, entries 11–17.

Table 7.

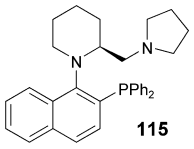


15 **16**

Entry	Ligand	Method	Temp. [°C]	Solvent	Time [h]	Yield [%]	ee [%]
1	(*S*,*S*)-**102**	NaMal	0	THF	3	81	58 (*R*)
2	(*R*,*S*)-**102**	NaMal	0	THF	3	85	26 (*S*)
3	(*S*,*S*)-**103**	NaMal	0	THF	3	68	76 (*R*)
4	(*S*,*S*)-**103**	NaMal	−40	THF	40	79	84 (*R*)
5	(*S*,*S*)-**104**	NaMal	0	THF	3	72	77 (*R*)
6	(*S*,*S*)-**104**	NaMal	−40	THF	40	72	84 (*R*)
7	(*S*,*S*)-**105**	NaMal	0	THF	3	79	75 (*R*)
8	(*S*,*S*)-**105**	NaMal	−40	THF	40	74	86 (*R*)
9	(*S*)-**106**	NaMal	0	THF	3	93	51 (*R*)
10	(*S*,*S*)-**107**	NaMal	0	THF	3	75	73 (*R*)
11	(*S*)-**108**	BSA	−10	DMF	24	68	57 (*S*)
12	(*S*)-**109**	BSA	−10	DMF	24	69	86 (*S*)
13	(*S*)-**110**	BSA	−10	DMF	24	69	83 (*S*)
14	(*S*)-**111**	BSA	−10	DMF	24	81	91 (*S*)
15	(*S*)-**112**	BSA	−10	DMF	24	61	90 (*S*)
16	(*S*)-**113**	BSA	−10	DMF	24	89	90 (*S*)
17	(*S*)-**115**	BSA	−10	Toluene	24	97	98 (*S*)



	R	Ar
108 :	OBn	Ph
109 :	NMePh	Ph
110 :	NBn	Ph
111 :	Pyrrolidinyl	Ph
112 :	Pyrrolidinyl	4-Tolyl
113 :	Pyrrolidinyl	4-CF_3-C_6H_4
114 :	Pyrrolidinyl	2-Naphthyl

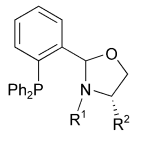


115

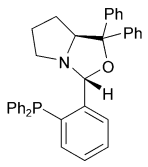
3.4 Oxazolidine N Donor

Oxazolidines **116**–**118** reported by Jin et al. are a different type of cyclic amine donor ligand which are analogous to the very successful diphenylphosphinooxazolines **259**–**263**.[44] Similar ligands **119** and **120** which contain the oxazolidine ring as part of a bi- or tricyclic structure were developed by Nakano.[45]

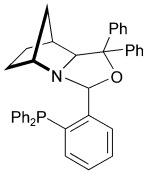
These ligands were tested in the palladium-catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**) where all except ligand **120** afforded the product **16** in excellent yields and enantioselectivities, Table 8, entries 1–5.



	R^1	R^2
116 :	Me	*i*-Pr
117 :	Bu	*i*-Pr
118 :	Me	Ph



119

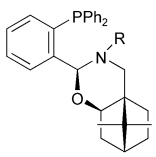


120

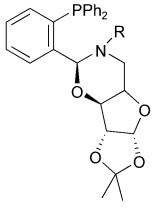
Ligand **119** also gave excellent region- and enantioselection in the asymmetric Diels–Alder reaction between cyclopentadiene and various imide dieneophiles, Scheme 7, Table 9.[46]

3.5 Oxazinane N Donor

Related ligands to **116**–**118** are the oxazinane ligands **121**–**124** and **125**–**128** which contain a six-membered ring.[47,48] Ligands **121**–**124** were also applied in palladium-catalysed allylic alkylation with the standard diphenylallyl substrate **15**, Table 8, entries 6–12, and ligands **125**–**128** were tested in cascade allylic alkylations where ligand **128** afforded a 67% yield and 94% enantiomeric excess of the (*S*)-product **131**, Scheme 8.



	R
121 :	Et
122 :	Pr
123 :	Bu
124 :	Bn

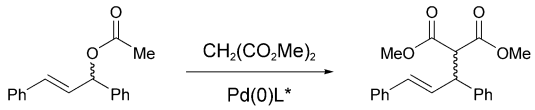


	R
125 :	*i*-Pr
126 :	Bn
127 :	CH_2-$C_{10}H_7$
128 :	(*R*)-CH(CH_3)Ph

3.6 Perimidine N Donor

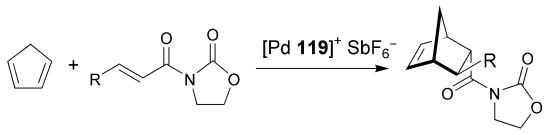
The group of Chung has developed a number of planar chiral arene-chromium tricarbonyl ligands having different types of nitrogen donors, one of which is the

Table 8.



15 **16**

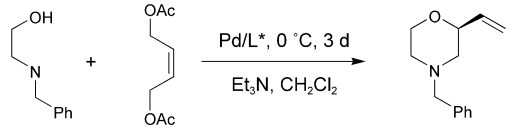
Entry	Ligand	Solvent	Temp. [°C]	Time [h]	Yield [%]	ee [%]
1	**116**	THF	10	0.5	98	98 (*S*)
2	**117**	THF	10	1.5	94	97 (*S*)
3	**118**	THF	r.t.	1.5	94	94 (*S*)
4	**119**	DCM	r.t.	3	98	96 (*S*)
5	**120**	DCM	r.t.	5	53	43 (*S*)
6	**121**	THF	r.t.	24	85	64 (*R*)
7	**122**	THF	r.t.	24	98	79 (*R*)
8	**123**	THF	r.t.	24	82	74 (*R*)
9	**124**	THF	r.t.	24	13	22 (*R*)
10	**122**	Toluene	r.t.	24	81	85 (*R*)
11	**122**	Toluene	0	100	90	88 (*R*)
12	**122**	Toluene	−20	100	50	95 (*R*)



Scheme 7.

Table 9.

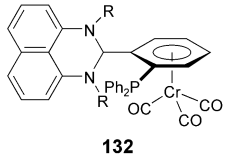
Entry	R	Temp. [°C]	Time [h]	*endo*/*exo*	Yield [%]	ee [%]
1	H	−45	24	97:3	96	98 (*R*)
2	Me	−35	36	96:4	73	98 (*R*)
3	CO_2Et	−45	24	94:6	95	98 (*S*)



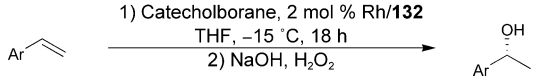
129 **130** **131**

Scheme 8.

N,*N*-acetal compound **132**.[49] This ligand gave moderate to good enantioselectivities in the asymmetric hydroboration of styrenes, Scheme 9, Table 10.



132



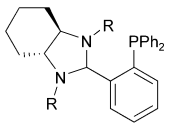
Scheme 9.

Table 10.

Entry	Substrate	Yield [%]	ee [%]
1	Styrene	95	53 (*R*)
2	4-Methoxystyrene	87	62 (*R*)
3	4-Bromostyrene	80	19 (*R*)
4	3,4-Dimethoxystyrene	65	75 (*R*)
5	2,4-Dimethylstyrene	94	81 (*R*)

3.7 Imidazolidine N Donor

The chiral imidazolidine ligands **133**–**135** have recently been prepared by Kim et al.[50] They were very effective in the allylic alkylation of (*E*)-1,3-diphenylpropenyl acetate (**15**) with the less sterically hindered **133** giving the best results with 99% yield and 97% enantioselectivity.

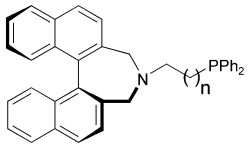


133 : R = Me
134 : R = Et
135 : R = Bn

3.8 Azepine N Donor

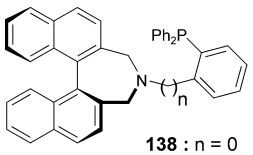
In 1994, Koga and Kubota, along with synthesising the 2,5-disubstituted pyrrolidinyl ligands **70**–**73**, also describ-

ed the axially chiral ligands **136** and **137** in which the key chiral inducing group is the 3,5-dihydro-4*H*-dinaphthazepine unit.[31] These worked well in the allylic alkylation of 1,3-diphenylpropenyl acetate (**15**) giving enantiomeric excesses of 93% and 96%, respectively, Table 11, entries 1 and 2.

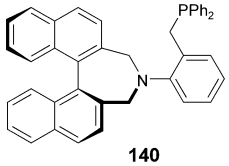


136 : n = 0
137 : n = 1

Widhalm later reported the similar phosphinamine ligands **138**–**140** which possess a less flexible carbon backbone connecting the phosphorus and nitrogen atoms and so will have different bite angle characteristics than **136** and **137**.[51] Ligands **138**–**140** were also tested in enantioselective palladium-catalysed allylic alkylations where **138** gave 96% ee and **139** afforded up to 97%, Table 11, entries 3–5. A much lower value of 18% was obtained with **140** which the authors suggested might result from the ligand becoming monodentate during the reaction. Other metal-catalysed transformations to which these ligands were applied included the nickel-catalysed cross-coupling of phenylethylmagnesium chloride with vinyl bromide, which gave poor results, and the asymmetric hydrogenation of unsaturated mono- and dicarbonic acids where optimum enantioselectivities of 77% were obtained.

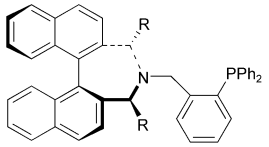


138 : n = 0
139 : n = 1



140

In an attempt to improve these results Widhalm and Bourghida proceeded to modify this class of ligands by introducing steric bulk in closer proximity to the nitrogen co-ordination site.[52] Ligands **141** and **142** showed significantly lower reactivities and enantioselectivities in the allylic substitution of 1,3-diphenylpropenyl acetate (**15**) however, Table 11, entries 6 and 7, in the case of the smaller 3-penten-2-yl acetate substrate (**147**) enantioselection increased to 68% (from 5% with **139**) showing that the increased bulk around the nitrogen donor atom facilitated larger enantiomeric excesses for smaller substrates.

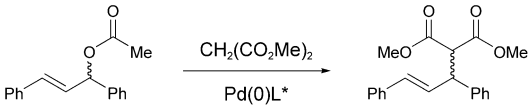


141 : R = Me
142 : R = Et

In a further extension of this work Widhalm et al. prepared the ligands **143** and **144** which incorporate both axial and planar chiral elements.[53] These ligands not only have different bite angles relative to **138** but are also capable of steric interactions above or below the ligand-metal substrate plane, due to the ferrocenyl unit. Because of these interactions the enantioselectivities obtained in the allylic alkylation of 2-cyclopenten-1-yl acetate (**147**) rose from 15% with **138** to 71% with the new ligand **143**, Table 12, entries 1–8.

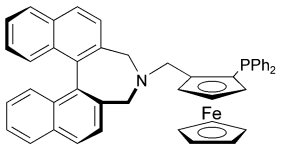
A problem with **143** was that the biaryl angle was small meaning that the chiral information was too remote from the metal centre to provide a strong interaction with the substrate. For this reason a series of ligands such as **145** and **146** was recently synthesised in which the biaryl unit is replaced by a biferrocenyl moiety.[54]

Table 11.

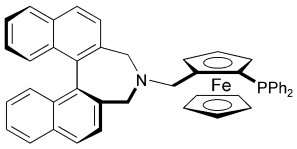


15 **16**

Entry	Ligand	Base	Temp. [°C]	Solvent	Time [h]	Yield [%]	ee [%]
1	(*R*)-**136**	BSA	r.t.	DCM	1.6	96	93 (*R*)
2	(*R*)-**137**	BSA	r.t.	DCM	2	96	96 (*R*)
3	(*S*)-**138**	NaH	r.t.	THF	4	95	96 (*S*)
4	(*S*)-**139**	NaH	r.t.	THF	4	93	79 (*S*)
5	(*S*)-**140**	NaH	r.t.	THF	4	97	18 (*S*)
6	(*S*)-**141**	BSA	r.t.	DCM	4	76	55 (*S*)
7	(*S*)-**142**	BSA	r.t.	DCM	52	85	34 (*S*)
8	(*S*,*S*)-**150**	BSA	r.t.	DCM	6	100	98 (*S*)
9	(*R*,*S*)-**151**	BSA	r.t.	DCM	8	100	59 (*S*)

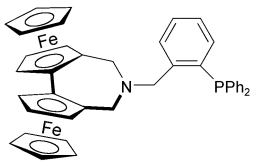


(S_a,S_P)-**143**

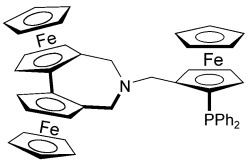


(S_a,R_P)-**144**

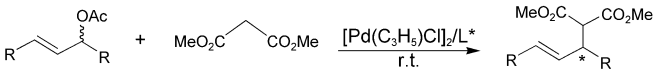
It was thought that these ligands would afford larger steric interactions close to the metal centre but it was found that the conformation adopted by the azepine ring in **145** is different to that adopted by the biaryl ligand **143**. Interestingly for **146** the enantioselection obtained with acyclic substrates is controlled by the biferrocenyl unit while that of cyclic substrates is determined primarily by the configuration of the ferrocene which links the two donor atoms, Table 12, entries 9–16.



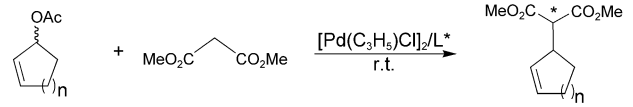
(R_p,R_p)-**145**



(R_p,R_p,S_p)-**146**



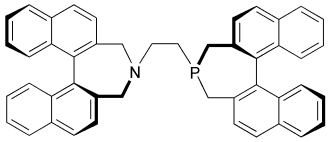
R = Me **147**
R = Ph **15**



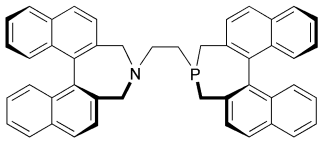
n = 1 **148**
n = 2 **149**

n = 1, 2

Recently Moberg and co-workers have also described ligands containing the 3,5-dihydro-4*H*-naphthazepine unit.[55] Compounds **150** and **151** are diastereomeric and possess *pseudo*-C_2 and *pseudo*-meso symmetry, respectively. Their palladium complexes were applied in allylic alkylation where **150** exhibited higher reactivity and enantioselectivity, Table 11, entries 8 and 9.



150

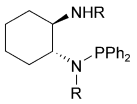


151

4 Amino N Donor, Heteroatom Bound P Donor

Ligands **152**–**159** have been reported by Spilling and were prepared by the monophosphinylation of enantiopure *trans*-cyclohexanediamines.[56] Testing in the palladium-catalysed allylic alkylation of **15** showed enantioselection generally increasing with substituent size to a maximum of 72% for ligand **157**.

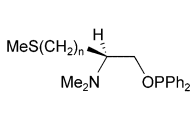
Faller has applied ligands **160** and **161**, which are related to the aminophosphine ligands **9**–**11**, in the rhodium-catalysed hydrosilylation of acetophenone but very poor enantioselection (maximum 9%) was obtained.[3]



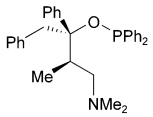
R	R
152 : H	**156** : $(CH_2)_2$-*i*-Pr
153 : Me	**157** : CH_2(*o*-Tolyl)
154 : Bn	**158** : CH_2(*m*-Tolyl)
155 : *i*-Pr	**159** : CH_2-*t*-Bu

Table 12.

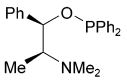
Entry	Ligand	Acetate	Method	Solvent	Yield [%]	ee [%]
1	(*S*,*S*)-**143**	R = Me	BSA	CH_2Cl_2	73	37 (*R*)
2	(*S*,*S*)-**143**	R = Ph	BSA	CH_2Cl_2	79	44 (*S*)
3	(*S*,*S*)-**143**	Cyclopentenyl	BSA	CH_2Cl_2	64	71 (*R*)
4	(*S*,*S*)-**143**	Cyclohexenyl	BSA	CH_2Cl_2	23	36 (*R*)
5	(*S*,*R*)-**144**	R = Me	BSA	CH_2Cl_2	–	33 (*R*)
6	(*S*,*R*)-**144**	R = Ph	BSA	CH_2Cl_2	–	54 (*S*)
7	(*S*,*R*)-**144**	Cyclopentenyl	BSA	CH_2Cl_2	–	37 (*S*)
8	(*S*,*R*)-**144**	Cyclohexenyl	BSA	CH_2Cl_2	–	49 (*S*)
9	(*R*,*R*)-**145**	R = Me	BSA	CH_2Cl_2	–	15 (*S*)
10	(*R*,*R*)-**145**	R = Ph	BSA	CH_2Cl_2	–	87 (*R*)
11	(*R*,*R*)-**145**	Cyclopentenyl	BSA	CH_2Cl_2	–	33 (*S*)
12	(*R*,*R*)-**145**	Cyclohexenyl	BSA	CH_2Cl_2	–	50 (*S*)
13	(*R*,*R*,*S*)-**146**	R = Me	BSA	CH_2Cl_2	–	46 (*S*)
14	(*R*,*R*,*S*)-**146**	R = Ph	BSA	CH_2Cl_2	–	69 (*R*)
15	(*R*,*R*,*S*)-**146**	Cyclopentenyl	BSA	CH_2Cl_2	–	59 (*R*)
16	(*R*,*R*,*S*)-**146**	Cyclohexenyl	BSA	CH_2Cl_2	–	65 (*R*)



160 : n = 1
161 : n = 2



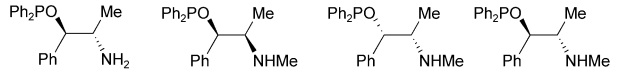
162



163

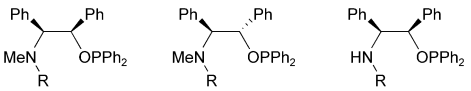
Faraone has described the synthesis of the amino alcohol-derived phosphinite ligands **162** and **163** and their application in the asymmetric Grignard cross-coupling, Scheme 1.[57] Although conversions were good the enantioselectivity was less than 10% in each case which may be due to the large chelate size. Also the π-acidity of the phosphinite may have an adverse effect, as ligands which have an alkyl group bonded to phosphorus have been found to give higher ees.

Dahlenburg prepared the β-aminophosphinite ligands **164**–**167** but has not applied them towards enantioselective catalysis.[5]



164 **165** **166** **167**

Chan et al. have also employed amino alcohols as starting materials for their synthesis of the phosphinite ligands **168**–**175**, in this case using (1*R*,2*S*) and (1*S*,2*S*)-1,2-diphenyl-2-aminoethanol.[58] In the allylic alkylation of the standard diphenyl-substituted allyl substrate **15** the enantioselectivity decreased on going from **168** to **169** and the configuration was inverted with **170** and **171**, Table 13, entries 1–4. The use of ligands **173**–**175** gave a dramatic improvement whereby enantiomeric excesses of up to 95% were obtained. This enhancement may be due to an interaction between the amine proton and the nucleophile which would not be available to the dialkyl-substituted ligands.



R
168 : Me
169 : Et
170 : *i*-Pr
171 : Benzyl

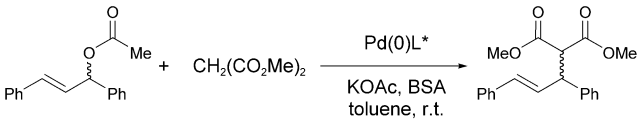
R
172 : Benzyl

R
173 : Benzyl
174 : Bu
175 : *i*-Pr

Sugars provide a readily available, inexpensive source of chirality and have easily modified structures which has led Claver et al. to prepare the amino-phosphite ligands **176**–**178** using D-xylose as a starter.[59]

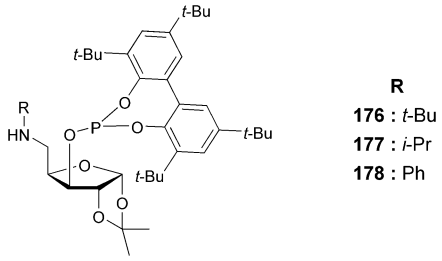
These ligands were tested in the copper-catalysed 1,4 addition of diethylzinc to 2-cyclohexenone (**179**) where the enantioselection was found to depend strongly on the aminoalkyl substituent, Scheme 10. Ligand **176** gave the (*R*) product while **177** and **178** gave (*S*)-**180**, the highest enantioselectivity of 63% being obtained with **178**.

Table 13.

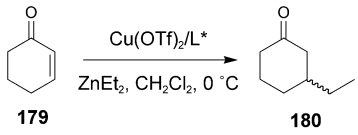


15

Entry	Ligand	Temp. [°C]	Time [h]	Yield [%]	ee [%]
1	**168**	25	6	95	46 (*R*)
2	**169**	25	10	98	40 (*R*)
3	**170**	25	10	98	8 (*S*)
4	**171**	25	10	98	22 (*S*)
5	**172**	30	5	90	28 (*S*)
6	**173**	20	12	88	87 (*R*)
7	**174**	30	6	98	73 (*R*)
8	**174**	0	24	96	75 (*R*)
9	**174**	−20	36	90	84 (*R*)
10	**174**	−78	72	84	95 (*R*)
11	**175**	0	36	88	93 (*R*)
12	**175**	−20	48	75	95 (*R*)



R
176 : *t*-Bu
177 : *i*-Pr
178 : Ph

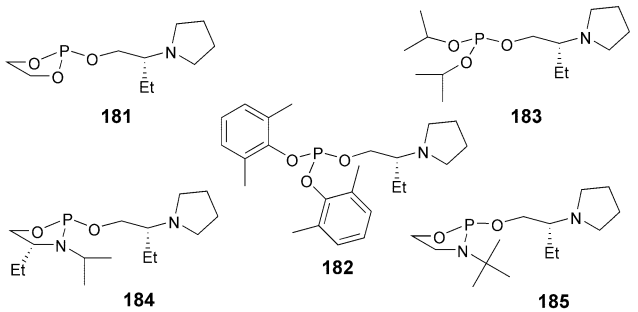


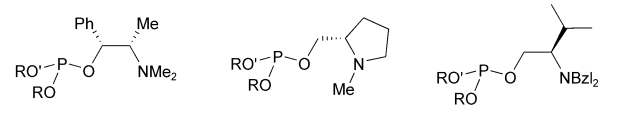
179 **180**

Scheme 10.

Gavrilov et al. have described the preparation of a series of pyrrolidino-phosphites **181**–**185** derived from (2*R*)-2-pyrrolidin-1-ylbutan-1-ol. Preliminary experiments in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**) gave a moderate ee of 61% with **183**.[60]

More recently the same group has reported aminophosphite ligands, some of which are shown: **186**–**191**, which have both cyclic and acyclic phosphite donors. Ligands **187** and **188** were tested in the allylic substitution of methyl 3-penten-2-yl carbonate (**147**) but very low enantioselection (< 20%) was observed in each case.

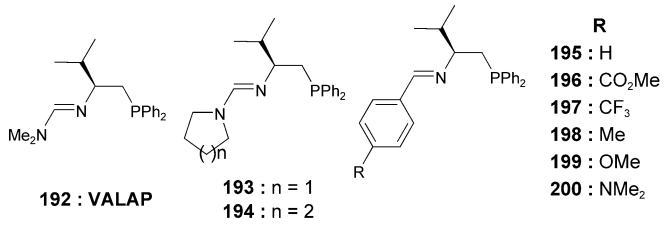




5 Imine N Donor, Phosphine P Donor

As mentioned in the introduction, sp^2-hybridized nitrogen atoms are more electron-rich than their amino counterparts and should therefore be capable of forming stronger bonds to a metal.

Saitoh et al. have developed the chiral amidine ligands **192**–**200**, based on the amino acid valine, and applied them in the allylic alkylation of (*E*)-1,3-diphenylprop-2-enyl pivalate (**201**). Variation of the phenyl substituent allowed for the evaluation of electronic effects upon the reaction, Table 14, and the use of ketene silyl acetals as harder nucleophiles was also investigated.[61,62]



Subsequent testing of VALAP (**192**) in the conjugate addition of diethylzinc to 2-cyclohexenone gave no enantiodiscrimination. However, the preparation of derivatives with a pyridyl side-arm which allowed the ligand to act in a tridentate fashion enabled enantioselectivities of up to 91% to be obtained.[63]

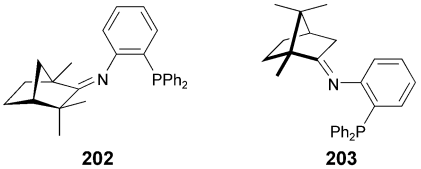
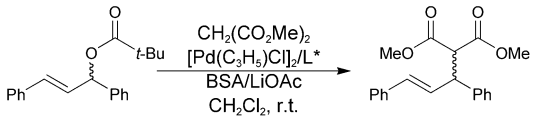
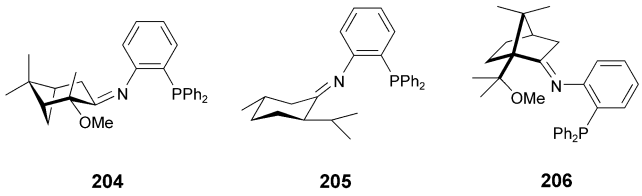


Table 14.

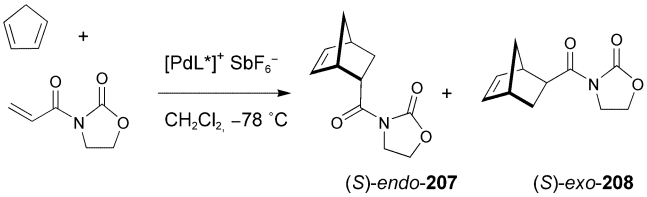


Entry	Ligand	Yield [%]	ee [%]
1	**192**	98	95 (*R*)
2	**193**	94	91 (*R*)
3	**194**	92	92 (*R*)
4	**195**	57	52 (*R*)
5	**196**	42	19 (*R*)
6	**197**	46	38 (*R*)
7	**198**	76	74 (*R*)
8	**199**	88	85 (*R*)
9	**200**	99	92 (*R*)

Hiroi has reported iminophosphines **202**, **203** derived from the terpenes fenchone and camphor.[64] In the allylic alkylation of the diphenylallyl substrate **15**, ligand **202** gave the (*S*) product in good to excellent enantioselectivities (up to 90%) while **203** afforded the (*R*) product in lower selectivity (maximum 51%).



These results prompted the preparation of other terpene-derived iminophosphines **204**–**206** and all the ligands were applied to the palladium-catalysed Diels–Alder reaction, Scheme 11.[65] Ligand **203** favoured the *endo* product **207** in a 93:7 ratio and in 84% enantiomeric excess, Table 15.

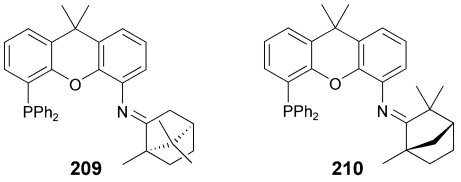


Scheme 11.

Table 15.

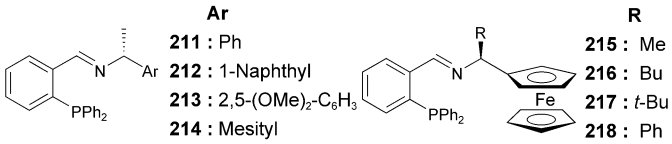
Entry	Ligand	Time [h]	Yield [%]	*endo*/*exo*	ee [%]
1	**202**	8	89	95/5	72 (*S*)
2	**203**	8	99	93/7	84 (*S*)
3	**204**	16	74	85/15	44 (*R*)
4	**205**	8	94	87/13	48 (*S*)
5	**206**	36	81	83/17	75 (*S*)

Barloy has described the synthesis of the xanthene-derived iminophosphines **209** and **210**,[66] analogues of the diphosphine xanthphos ligands, which also use (1*S*)-fenchone and (1*R*)-camphor as the sources of chiral information.[67] They gave poor ees for the allylic substitution of diphenylallyl acetate (**15**) (0 and 17%, respectively) but gave slightly better results for the more problematic dimethylallyl substrate **147** (20 and 36%).

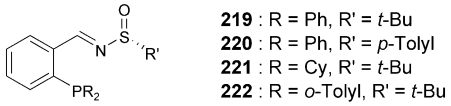


Hashimoto prepared the iminophosphines **211**–**214** by reacting the appropriate chiral amine with *o*-(diphenylphosphino)benzaldehyde.[68] Ligand **214** which carries the most steric bulk was by far the most effective ligand in the allylic alkylation of 1,3-diphenylallyl acetate (**15**), Table 16, entries 1–5, and also gave good results with the dimethylallyl substrate **147**.

This work provided the impetus for Iwao to develop the structurally similar ligands **215**–**218** which possess the very bulky ferrocenyl group.[69] Testing of these ligands in the allylic alkylation gave further improvements in enantioselection, Table 16, entries 6–10.

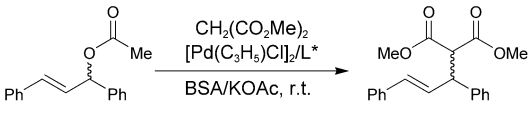


Ellman et al. have prepared **219**–**222** which are chiral due to the presence of a stereogenic sulfur centre.[70] The ligands are easily prepared by condensation of the appropriate aldehyde with the commercially available *tert*-butanesulfinamide. These ligands were also applied in allylic alkylation where **222** gave excellent results, Table 16, entry 11.



Recent work by Hoveyda has involved the use of peptide-based catalysts such as **223** and their application in copper-catalysed alkylzinc additions to both cyclic and acyclic enones, Scheme 12.[71] Excellent enantioselectivities were obtained with cyclopentenone and aliphatic substrates which had previously been problem substrates for this reaction.

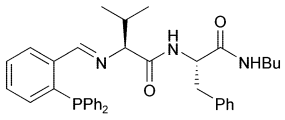
Table 16.



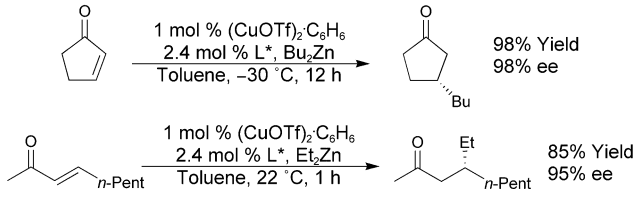
15 16

Entry	Ligand	Solvent	Time [h]	Yield [%]	ee [%]
1[a]	(*R*)-**211**	DCM	12	85	14 (*S*)
2[a]	(*R*)-**212**	DCM	12	95	14 (*R*)
3[a]	(*R*)-**213**	DCM	12	73	50 (*R*)
4[a]	(*R*)-**214**	DCM	12	98	85 (*R*)
5[a, d]	(*R*)-**214**	DCE	24	98	94 (*R*)
6[b]	(*S*)-**215**	Et_2O	2	98	74 (*S*)
7[b]	(*S*)-**216**	Et_2O	2	97	84 (*S*)
8[b]	(*S*)-**217**	DCM	2	17	78 (*S*)
9[b]	(*S*)-**218**	Et_2O	2	97	94 (*S*)
10[b, e]	(*S*)-**218**	Et_2O	2	98	97 (*S*)
11[c]	**222**	DCM	1	100	96 (*S*)

[a] 5 mol % L*, 2.5 mol % $[Pd(C_3H_5)Cl]_2$.
[b] 2.5 mol % L*, 1 mol % $[Pd(C_3H_5)Cl]_2$.
[c] 5 mol % L*, 5 mol % $[Pd(C_3H_5)Cl]_2$.
[d] At 0 °C.
[e] Lithium acetate used.



223

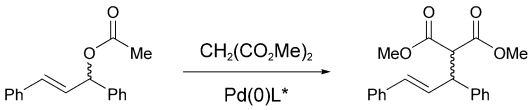


Scheme 12.

The group of Mino have described the use of the chiral hydrazone ligands **224**–**226**, which were easily synthesised from 2-diphenylphosphinobenzaldehyde and the well known SAMP-type chiral auxiliaries, in allylic alkylation and obtained enantioselectivities of up to 98%, Table 17, entries 1–5.[72] A crystal structure showed that **224** binds through the imino rather than the pyrrolidinyl nitrogen.[73]

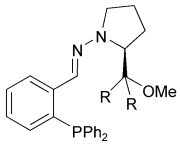
Although Enders[74] had previously described the use of hydrazones for the *ortho*-functionalisation of ferro-

Table 17.

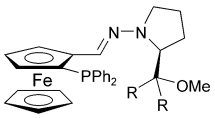


15 **16**

Entry	Ligand	Solvent	Temp. [°C]	Time [h]	Yield [%]	ee [%]
1	(*S*)-**224**	THF	r.t.	24	96	92 (*R*)
2	(*S*)-**224**	THF	4	48	98	95 (*R*)
3	(*S*)-**224**	THF	-20	168	26	98 (*R*)
4	(*S*)-**225**	THF	r.t.	24	95	71 (*R*)
5	(*S*)-**226**	THF	r.t.	24	84	72 (*R*)
6	(*S*,*S*)-**227**	toluene	r.t.	20	93	96 (*R*)
7	(*S*,*R*)-**227**	toluene	r.t.	20	94	46 (*S*)
8	(*S*,*S*)-**228**	toluene	r.t.	20	90	90 (*R*)
9	(*S*,*S*)-**229**	toluene	r.t.	20	88	74 (*R*)



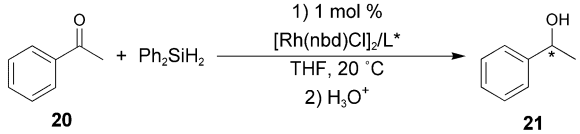
R
224 : H
225 : Me
226 : Et



R
227 : H
228 : Me
229 : Et

cenes, Mino was the first to apply ferrocenylphosphine hydrazones **227**–**229** towards asymmetric catalysis.[75] These ligands were also examined in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**), Table 17, entries 6–9. Enantioselectivities were uniformly high (74–96%) and in this case the central chirality was found to be the dominant enantiocontrolling element.

Hayashi has described the use of the iminophosphine ligands **230**–**233** in the asymmetric hydrosilylation of acetophenone, where all catalysts afforded 1-phenylethanol (**21**) in good yields and enantioselectivities while those which bore electron-withdrawing groups on the phosphorus displayed higher catalytic activity, Scheme 13, Table 18.[76]

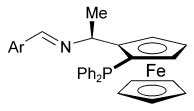


20 **21**

Scheme 13.

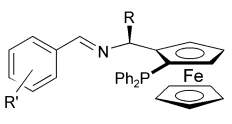
Table 18.

Entry	Ligand	Time	Yield [%]	ee [%]
1	**230**	< 1 h	90	87 (*S*)
2	**231**	< 10 min	90	90 (*S*)
3	**232**	< 10 min	94	89 (*S*)
4	**233**	< 10 min	86	89 (*S*)

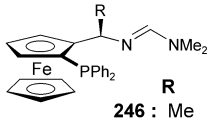


Ar
230 : Ph
231 : *m*-CF_3-C_6H_4
232 : *p*-CF_3-C_6H_4
233 : C_6F_5

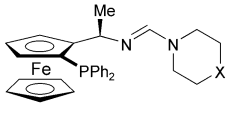
Zheng has recently modified Hayashi's ligand to prepare ligands **234**–**245** which have been applied in palladium-catalysed allylic alkylation.[77] The substituents on the phenyl ring allowed variation of the steric and electronic properties of the ligands. Those which bore electron-withdrawing chloro or nitro groups gave higher catalytic activities and enantioselectivities, Table 19, entries 1–4. The *meta*-nitro substituted ligand gave the best enantioselection with both acetate and pivalate leaving groups, Table 19, entries 4–6. Increasing the size of the ferrocenylmethyl substituent to an ethyl group resulted in a slight increase in enantioselection but a phenyl group in this position proved to be detrimental, Table 19, entries 7 and 8.



	R	R'		R	R'
234 :	Me	H	**240 :**	Me	*p*-NMe_2
235 :	Me	*p*-Me	**241 :**	Me	*p*-NO_2
236 :	Me	*p*-OMe	**242 :**	Me	*o*-NO_2
237 :	Me	*m*-OMe	**243 :**	Me	*m*-NO_2
238 :	Me	*m*-Cl	**244 :**	Et	*m*-NO_2
239 :	Me	*p*-Cl	**245 :**	Ph	*m*-NO_2

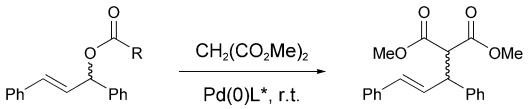


R
246 : Me
247 : Et
248 : Ph



249 : X = CH_2
250 : X = O

Table 19.



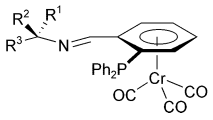
15 : R = Me
201 : R = *t*-Bu

16

Entry	Ligand	Procedure	Substrate	Solvent	Time [h]	Yield [%]	ee [%]
1	**235**	BSA	**15**	Toluene	24	59	83 (*S*)
2	**236**	BSA	**15**	Toluene	24	53	83 (*S*)
3	**238**	BSA	**15**	Toluene	24	96	90 (*S*)
4	**243**	BSA	**15**	Toluene	24	99	93 (*S*)
5	**243**	BSA	**201**	Toluene	24	99	94 (*S*)
6[a]	**243**	BSA	**201**	Toluene	24	91	96 (*S*)
7	**244**	BSA	**201**	Toluene	24	99	96 (*S*)
8	**245**	BSA	**201**	Toluene	24	89	83 (*S*)
9	**246**	BSA	**201**	Toluene	48	96	92 (*S*)
10	**247**	BSA	**201**	Toluene	48	98	94 (*S*)
11	**248**	BSA	**201**	Toluene	48	61	37 (*S*)
12	**249**	BSA	**201**	Toluene	48	91	81 (*S*)
13	**250**	BSA	**201**	Toluene	48	90	65 (*S*)
14	**251**	NaMal	**15**	DMSO	5	68	82 (*S*)
15	**252**	NaMal	**15**	DMSO	6	74	85 (*S*)
16	**253**	NaMal	**15**	DMSO	7	71	79 (*S*)
17	**254**	NaMal	**15**	DMSO	6	82	91 (*S*)
18	**255**	NaMal	**15**	DMSO	6	93	98 (*S*)
19	*ent*-**255**	NaMal	**15**	DMSO	6	85	95 (*R*)

[a] Temperature = 10 °C.

A further development of this ligand structure are the ferrocenylphosphine-amidine ligands **246**–**250**.[78] Again the ligand bearing an ethyl group, **247**, gave the best results. Both the yield and enantioselection were decreased significantly when the dimethylamino group was replaced by either a piperidine or a morpholine unit, Table 19, entries 9–13.



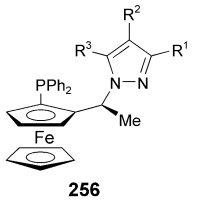
251 : R^1 = Ph; R^2 = Me; R^3 = H
252 : R^1 = Me; R^2 = Ph; R^3 = H
253 : R^1 = Me; R^2 = Me; R^3 = Me
254 : R^1 = Ph; R^2 = H; R^3 = H
255 : R^1 = Ph; R^2 = Ph; R^3 = H

Furthering their work on arene-chromium tricarbonyl ligands the group of Chung has developed the iminophosphine ligands **251**–**255** which were applied in palladium-catalysed allylic alkylation.[79] The asymmetric induction was found to be due solely to the planar chirality, with the nature of the stereogenic centre having no effect, although an increase in enantiomeric excesses was noted when bulky groups were present, Table 19, entries 14–19.

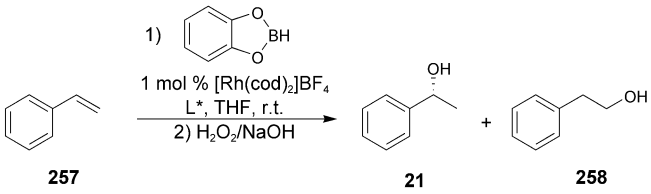
6 Cyclic Imino N Donor, Phosphine P Donor

6.1 Pyrazole N Donor

Togni has developed the pyrazole-containing ligands **256** in which the substituents, both on the phosphorus and on the pyrazole ring, are easily varied allowing for the optimisation of both steric and electronic factors for any particular reaction.[80] They have been applied in a number of asymmetric metal-catalysed reactions, for instance, norbornene was hydrosilylated in greater than 99% enantiomeric excess.[81] They were capable of high enantioselectivities in the rhodium-catalysed hydroboration of styrene although the regioselectivity obtained was only moderate, Scheme 14, Table 20.[82] In the allylic amination of 1,3-diphenyl-2-propenyl acetate (**15**), where the addition of small potentially coordinating anions, such as fluoride or borohydride, was found to enhance the selectivity of the system and enantiomeric excesses of 99.5% were obtained.[83] The general ligand structure has also been used in the preparation of bi-metallic and dendrimer type catalysts for asymmetric synthesis.[84]



256



257 21 258

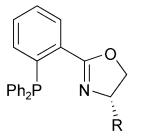
Scheme 14.

Table 20.

Entry	Ligand				**21/258**	Yield [%]	ee [%]
	R^1	R^2	R^3	Ar			
1	Me	H	Me	Ph	66:34	91	95 (*R*)
2	Me	Me	Me	Ph	79:21	90	96 (*R*)
3	Me	Br	Me	Ph	65:35	80	96 (*R*)
4	Ph	H	Me	Ph	47:53	92	80 (*R*)
5	Me	H	Me	4-CF_3-C_6H_4	60:40	68	98 (*R*)
6	Me	H	Me	4-MeO-C_6H_4	61:39	61	90 (*R*)

6.2 Oxazoline N Donor

One of the most successful ligand classes are the diphenylphosphinoaryloxazolines **259**–**263** which were reported independently by the groups of Pfaltz,[85] Helmchen[86] and Williams.[87] These highly modular ligands are readily synthesised from commercially available amino acids[88] and have proved to be excellent ligands for the palladium-catalysed allylic substitution of 1,3-diphenyl-2-propenyl acetate (**15**) with a number of different nucleophiles, Table 21.

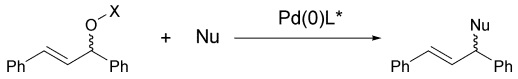


R
259 : Me
260 : *i*-Pr
261 : *t*-Bu
262 : Ph
263 : Bn

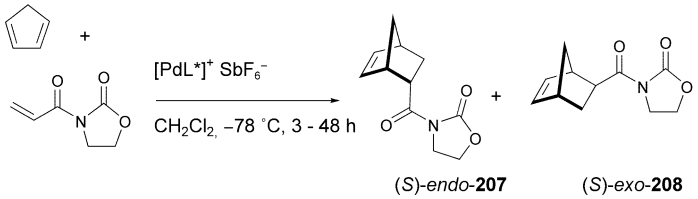
They have also been successfully applied in many other asymmetric reactions with the best results coming in enantioselective Diels–Alder reactions (Scheme 15, Table 22), asymmetric intermolecular Heck reactions (Scheme 16, Table 23) and the iridium-catalysed hydrogenation of alkenes (Scheme 17, Table 24).[89]

In contrast to the regioisomer problem associated with Pd{BINAP} catalysts, the phenylation of 2,3-dihydrofuran produced only the (*R*)-2-phenyl-2,5-dihydrofuran and in an impressive 97% ee (entry 1) and in a

Table 21.



Entry	Ligand	X	Nucleophile	Yield [%]	ee [%]
1	**260**	Ac	Dimethyl malonate/BSA	99	98
2	**262**	Ac	Acetylacetone/BSA	97	98
3	**261**	Ac	$TsNH^-Na^+$	96	97
4	**261**	CO_2Me	$PhCH_2NH_2$	98	94
5	**262**	Ac	*t*-$BuSO_2^-Li^+$	69	93

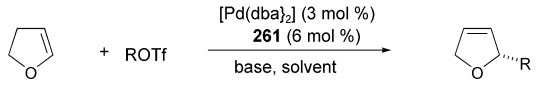


(*S*)-*endo*-**207** (*S*)-*exo*-**208**

Scheme 15.

Table 22.

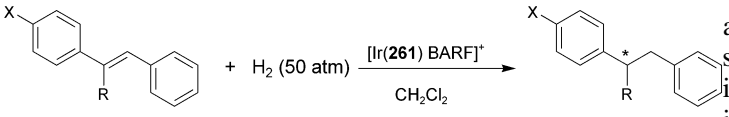
Entry	Ligand	Time [h]	Temp. [°C]	Yield [%]	*endo*/*exo*	ee [%]
1	**260**	3.5	−78	88	92/8	82 (*S*)
2	**261**	3.5	−78	93	93/7	92 (*S*)
3	**261**	48	16	76	97/3	99 (*S*)



Scheme 16.

Table 23.

Entry	R in ROTf	Base	Temp. [°C]	Solvent	Yield [%]	ee [%]
1	Ph	DIPEA	70	THF	87	97
2	1-Cyclohexenyl	DIPEA	30	Benzene	92	>99
3	1-Cyclohexenyl	Proton sponge	30	Benzene	95	98
4	1-Cyclohexenyl	Et_3N	30	Benzene	78	>99
5	1-Cyclopentenyl	Proton sponge	50	Benzene	95	88



Scheme 17.

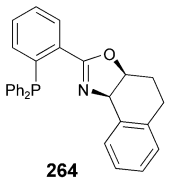
Table 24.

X	R	ee [%]
H	Me	97 (−)
Cl	Me	95 (−)
MeO	Me	98 (*R*)
MeO	Et	95 (−)

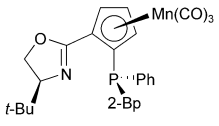
shorter reaction time (4 rather than 9 days). Alkenylations employing cyclohexenyl triflate or cyclopentenyl triflate similarly afforded only the kinetic regioisomer.

Although the basic phosphinooxazolines were very successful, there were a number of areas where the activity or enantiodiscrimination could be improved upon and this led to the design and synthesis of new ligands.

The phosphinooxazolines mainly provide steric interactions at their wings so while 1,3-diphenyl-2-propenyl acetate (**15**) was an excellent substrate the enantioselection provided with the smaller dimethyl- and cyclohexenylallyl acetate substrates, **147**, **149**, was poor (56% and 0%, respectively).



264

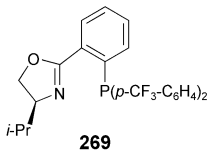


265

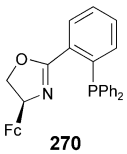
The enantioselectivity of palladium-catalysed allylic alkylation depends on a number of factors, one of which is the ratio of the diastereomeric ligand-Pd-allyl species. The ligands **264**[90] and **265**[91] were developed for the acyclic and cyclic substrates, respectively, and work by selectively destablising one of the possible allyl species in favour of the other. Ligand **264** gave enantioselectivities of up to 90% with pent-3-enyl 2-acetate (**147**). The planar chiral ligand **265**, which is able to provide steric interactions above the ligand-metal co-ordination plane, similar to ligands **143** and **144**, gave enantiomeric excesses of above 90% with cyclopentenyl, cyclohexenyl and cycloheptenyl substrates. Helmchen has employed ligand **265** to make intermediates in a number of natural product syntheses.[92]

For the allylic alkylation of monosubstituted allyl systems the use of palladium complexes of the phosphinooxazolines **259**–**263** led almost exclusively to the achiral linear product, Table 25, entry 1. Although this could be overcome by employing tungsten as the metal, the low reactivity of the resultant complexes necessitated the use of the more reactive diethyl phosphate as leaving group and thus limited the reaction to a narrow range of substrates, Table 25, entries 2 and 3.[93]

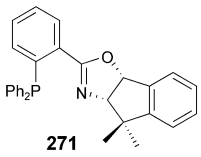
Helmchen found that iridium complexes of phosphinooxazolines which had electron-withdrawing groups present on the phosphorus (i.e., **269**) afforded high regio- and enantioselectivity, Table 25, entries 4–6.[94]



269

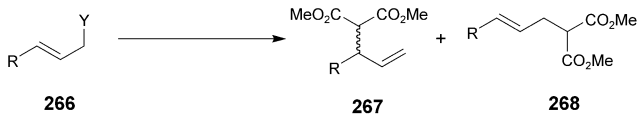


270



271

The success of the original phosphinooxazolines also prompted other groups to develop oxazoline-containing ligands. A ferrocenyl-substituted variant **270** has been reported independently by Patti and Moyano.[95,96] This ligand was successfully applied in the allylic alkylation of 1,3-diphenyl-prop-2-enyl acetate (**15**) giving the (*R*)-product **16** in 63% yield and 99% enantiomeric excess under optimal conditions.



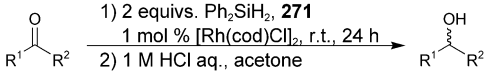
266 267 268

Scheme 18.

Table 25.

Entry	Ligand	R	Y	Temp. [°C]	**267: 268**	Yield [%]	ee [%]
1	**261**	Ph	OAc	50	4:96	90	78 (*S*)
2	**260**	Ph	$OPO(OEt)_2$	−10	75:25	95	96 (*R*)
3	**260**	1-Naphthyl	$OPO(OEt)_2$	24	96:4	95	88 (*R*)
4	**269**	Ph	OAc	65	95:5	99	91 (*R*)
5	**269**	4-(MeO)-C_6H_4	OAc	65	99:1	98	95 (*R*)
6	**269**	CH_2CH_2Ph	OAc	65	62:38	93	78 (*R*)

Saigo used *cis*-2-amino-3,3-dimethyl-1-indanol, which is readily available in both enantiomeric forms, to prepare the ligand **271**.[97] Testing of **271** in allylic amination gave superior results to the phosphinooxazoline ligands (>99% ee for a range of substrates), while in the asymmetric Heck reaction comparable enantioselectivities were obtained but conversions were lower.[98] Ligand **271** was also an efficient ligand for the rhodium-catalysed hydrosilylation of ketones, Scheme 19, Table 26.[99]

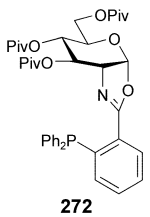


Scheme 19.

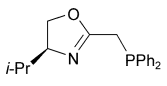
Table 26.

Entry	Ketone	Yield [%]	ee [%]
1	Acetophenone	84	94 (*R*)
2	Propiophenone	91	91 (*R*)
3	1-Acetylnaphthone	90	92 (*R*)
4	α-Tetralone	89	89 (*R*)
5	Cyclohexyl methyl ketone	85	87 (*R*)

Kunz has developed the oxazoline **272** which is based upon a carbohydrate backbone. This was successful in the palladium-catalysed allylic substitution of a range of substrates affording a best asymmetric induction of 98% for 1,3-diphenyl-2-propenyl acetate (**15**).[100]

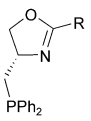


272



273

In his original publication on the phosphinooxazolines Helmchen also described the use of the related ligand **273** in the palladium-catalysed allylic alkylation, however, it gave poorer enantioselectivities.[80] Braunstein has recently reported the use of **273** in the transfer hydrogenation of acetophenone obtaining a maximum enantioselectivity of 74%.[101]

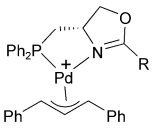


R
274 : Me
275 : *t*-Bu
276 : $CH(Ph)_2$
277 : $C(Ph)_3$
278 : Adamantyl
279 : 3,5-di-*t*-Bu-C_6H_3

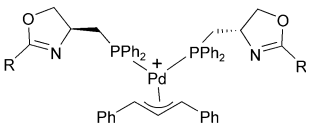
R
280 : Ferrocenyl
281 : CF_3
282 : Ph
283 : *p*-OMe-C_6H_4
284 : *p*-tolyl
285 : *p*-NO_2-C_6H_4
286 : C_6F_5

The group of Burgess developed a method for the optimisation of the ligands **274**–**286** in palladium-catalysed allylic alkylation *via* a high throughput screening technique.[102] These ligands differ in that the phosphine is connected to the oxazoline at the 4 position while the alkyl/aryl group is located at the 2 position. This leads to two advantages, firstly the R group originates from carboxylic acids and so a much wider range is available than can be derived from amino acids as in the phosphinooxazoline ligands and secondly, the electronic nature of the nitrogen donor atom can be varied by conjugation of the R group through the imine bond. The best enantioselectivity (94%), which was obtained with the large adamantyl substituent (i.e., **278**), was lower than that obtained with the phosphinooxazolines. A strong dependence of enantioselectivity upon catalyst concentration and ligand to metal ratio was noted with these ligands, with improved enantioselectivities being observed at lower ligand to metal ratio. This was rationalised by suggesting that the palladium chelate **287** is favoured at low ligand to metal ratios whereas the unselective diphosphine complex **288** is formed at high ligand to metal ratios.

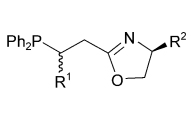
These observations led to the development of the second generation oxazolines **289**–**292** which will form a



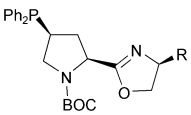
287



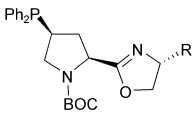
288



293



294 : *i*-Pr
295 : Ph
296: *t*-Bu



297 : *i*-Pr
298 : Ph

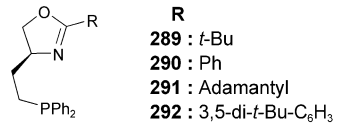
six-membered chelate.[103] These gave improved results in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**), Table 27,[104] and have also been used in iridium-catalysed hydrogenations.[105]

The group of Gilbertson has prepared a number of oxazoline-containing ligands **293**–**298**.

Ligands **293** possess an extra chiral centre and this would potentially allow for co-operative effects although testing in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**) showed that the chiral centre next to phosphorus had very little effect, Table 28.[106] It was found that the enantioselectivity was increased when a tetraalkylammonium fluoride additive was used in conjunction with BSA.

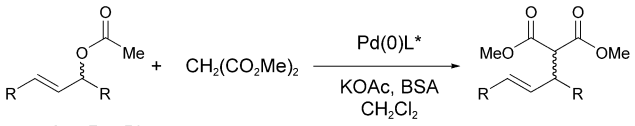
The ligands **294**–**298**, which are based on proline were also applied in the allylic alkylation reaction where ligand **294** gave excellent results with a number of cyclic substrates, Scheme 20, Table 29.[107] It is unusual in that the enantioselection is determined by the configuration at the pyrrolidine ring rather than at the oxazoline.

Ligand **294** was also useful in the asymmetric Heck reaction, Scheme 21, Table 30.[108]



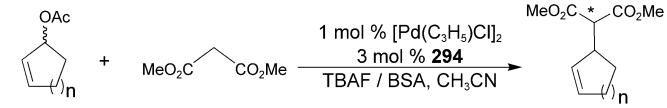
R
289 : *t*-Bu
290 : Ph
291 : Adamantyl
292 : 3,5-di-*t*-Bu-C_6H_3

Table 27.



15 : R = Ph
147 : R = Me

Entry	Ligand	Substrate	Time [h]	Temp. [°C]	Yield [%]	ee [%]
1	**289**	**15**	16	0	80	98 (*R*)
2	**291**	**15**	16	0	95	98 (*R*)
3	**292**	**15**	16	0	95	98 (*R*)
4	**291**	**147**	48	25	93	80 (*R*)
5	**292**	**147**	48	25	80	63 (*R*)



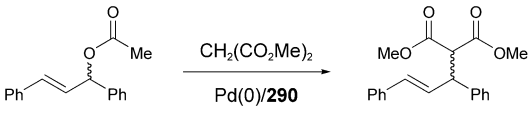
148 : n = 1
149 : n = 2
299 : n = 3

Scheme 20.

Table 29.

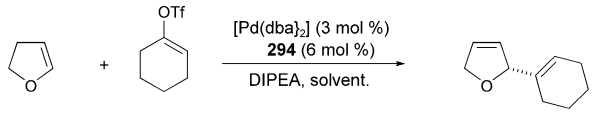
Entry	Substrate	Temp [°C]	Time [h]	Yield [%]	ee [%]
1	**148**	0	1	94	90 (*S*)
2	**148**	−20	6	99	94 (*S*)
3	**148**	−35	20	79	96 (*S*)
4	**149**	25	5	93	80 (*S*)
5	**299**	0	3	96	80 (*S*)

Table 28.



15 **16**

Entry	Ligand	Cation/Base	Solvent	Temp. [°C]	Yield [%]	ee [%]
1	R^1=Me (*S*), R^2=*i*-Pr (*S*)	Bu_4N^+/BSA	CH_3CN	r.t.	86	72 (*S*)
2	R^1=Me (*R*), R^2=*i*-Pr (*S*)	Bu_4N^+/BSA	CH_3CN	r.t.	86	94 (*S*)
3	R^1=Ph (*S*), R^2=*i*-Pr (*S*)	Bu_4N^+/BSA	CH_3CN	r.t.	91	90 (*S*)
4	R^1=Ph (*R*), R^2=*i*-Pr (*S*)	Bu_4N^+/BSA	CH_3CN	r.t.	80	95 (*S*)
5	R^1=H, R^2=*i*-Pr (*S*)	Bu_4N^+/BSA	DCM	0	94	86 (*S*)
6	R^1=H, R^2=*i*-Pr (*S*)	K_+/BSA	DCM	0	87	66 (*S*)
7	R^1=Ph (*R*), R^2=*i*-Pr (*S*)	Hex_4N^+/BSA	CH_3CN	r.t.	99	97 (*S*)



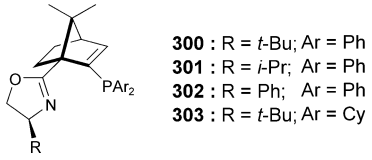
Scheme 21.

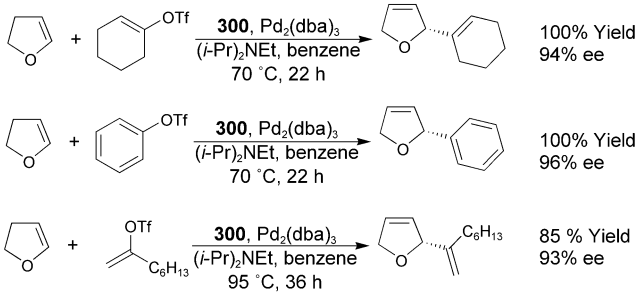
Table 30.

Entry	Solvent	Time [h]	Yield [%]	ee [%]
1	Benzene	24	98	80
2	Toluene	48	84	50
3	Dioxane	36	99	80
4	DMF	48	80	28
5	DMSO	72	99	68

Another ligand class developed by this group are the bicyclic ligands **300**–**303** which are based on ketopinic acid. These have been applied in the intermolecular Heck reaction where **300** gave excellent enantioselection with a number of substrates, Scheme 22.[109]

This selectivity for the kinetic regiosomer, in which the double bond stays where it was originally formed, without subsequent isomerisation, was previously noted for the phosphinooxazolines **259**–**263**.

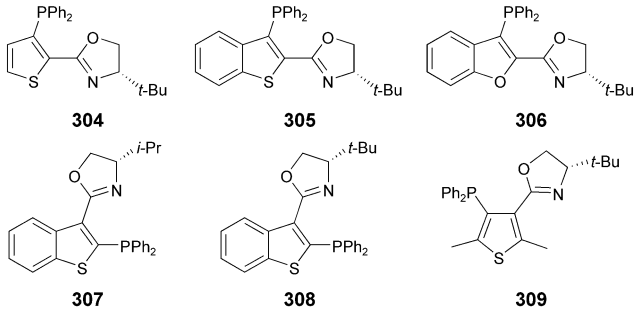




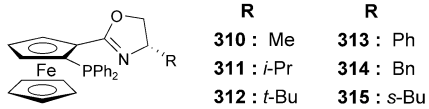
Scheme 22.

The phosphinooxazoline ligands **304**–**309**, which have thiophene, benzothiophene or benzofuran backbones, have recently been reported by Tietze.[110] In initial testing of the ligands in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**) using the malonate ion method, ligand **307** gave the best results, affording **16** in 92% yield and 97% enantiomeric excess.

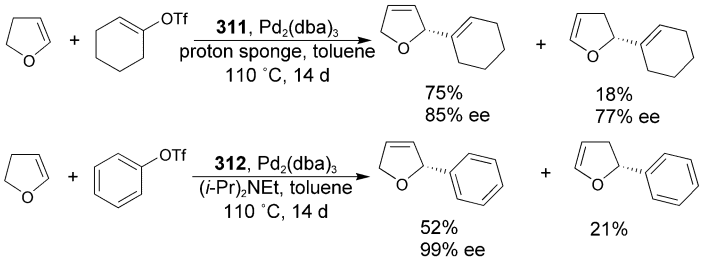
Following the success of the phosphinooxazolines and with the known ability of ferrocenyl units to efficiently induce asymmetry in a range of reactions, an obvious



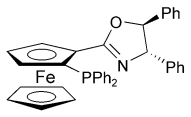
evolution in ligand design was the combination of the two. The first reports on the *ortho*-lithiation of ferrocenyloxazolines appeared in 1995[111] and diastereoselectivities of greater than 500:1 were soon available.[112] Quenching of these lithiations with chlorodiphenylphosphine has provided an array of ligands **310**–**315**. Their diastereomers are available through the appropriate protection-phosphinylation-deprotection sequence.



Ligands of this type have been employed by many groups, including our own, in numerous metal-catalysed transformations[113] giving excellent results in palladium-catalysed allylic substitution,[114] the asymmetric Heck reaction (Scheme 23)[115] and the transfer hydrogenation of ketones,[116] Scheme 24, Table 31.

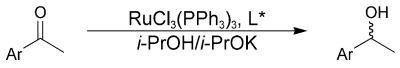


Scheme 23.



316

Uemura et al. initially tested **311** and **313** in the rhodium-catalysed hydrosilylation of acetophenone but a maximum enantiomeric excess of 60% was obtained. A significant improvement in selectivity was obtained



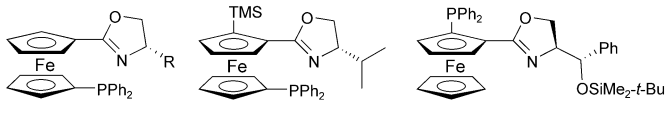
Scheme 24.

Table 31.

Entry	Ligand	Ar	Time [h]	Temp. [°C]	Conv. [%]	ee [%]
1	**310**	Ph	8	r.t.	92	92 (*R*)
2	**311**	Ph	3	r.t.	93	92 (*R*)
3	**312**	Ph	6	r.t.	51	94 (*R*)
4	**313**	Ph	6	r.t.	93	94 (*R*)
5	**314**	Ph	6	r.t.	93	90 (*R*)
6	**313**	1-Naphthyl	3	50	92	91 (*R*)
7	**313**	2-Naphthyl	7	28	82	95 (*R*)
8	**313**	*o*-Tolyl	1	50	83	93 (*R*)
9	**313**	4-Cl-C_6H_4	6	28	83	93 (*R*)
10	**313**	4-MeO-C_6H_4	2	50	75	84 (*R*)
11	**313**	Mesityl	1	80	81	95 (*R*

through the introduction of an additional substituent on the oxazoline to give **316**.[117] The reduction of acetophenone afforded 1-phenylethanol (**21**) in 91% ee and similar selectivities were observed for other aryl methyl ketones (88–90% ee) and bulky alkyl methyl ketones (87–89% ee). When iridium was used in place of rhodium the absolute configuration of the product changed and generally higher enantioselectivities were obtained.[118] Subsequently, iridium and ruthenium complexes of the parent ligands **310**–**315** were found to be effective catalysts for the reduction of a range of both ketone and imine substrates.[119]

Other derivatives such as **317**–**319**,[120] **320**[121] and **321**[122] have been prepared and tested in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**), Table 32. It should be noted that ligands **317**–**319** do not possess planar chirality but, similar to ligands **108**–**114**, form an axially chiral system when complexed to a metal.

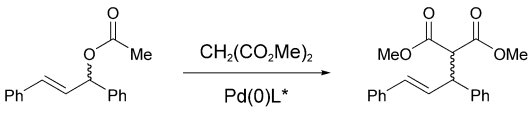


R
317 : Ph
318 : *i*-Pr
319 : *t*-Bu

320 **321**

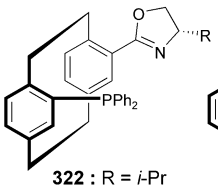
Ligand **320** which does possess planar chirality has also been shown to be effective in the Heck reaction between phenyl triflate and 2,3-dihydrofuran affording a 92% enantiomeric excess.[123]

Table 32.

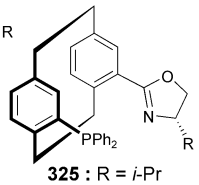


15 **16**

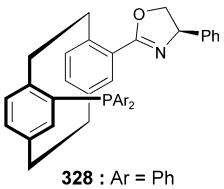
Entry	Ligand	Procedure	Temp. [°C]	Solvent	Time [h]	Yield [%]	ee [%]
1	**317**	BSA	25	DCM	20 min	96	93 (*S*)
2	**318**	NaMal	20	THF	6	>90	93 (*S*)
3	**318**	BSA	25	DCM	10 min	96	99 (*S*)
4	**319**	BSA	25	DCM	30 min	99	99 (*S*)
5	**320**	BSA	r.t.	DCM	–	99	98.6 (*S*)
6	**321**	BSA	36	DCM	24	98	95 (*R*)
7	**322**	BSA	25	Toluene	1.5	98	62 (*S*)
8	**323**	BSA	25	Toluene	1	98	42 (*S*)
9	**326**	BSA	25	Toluene	1.5	98	41 (*S*)
10	**327**	BSA	25	Toluene	1	98	73 (*R*)
11	**328**	BSA	25	Toluene	20 min	98	90 (*R*)



322 : R = *i*-Pr
323 : R = *t*-Bu
324 : R = Bn

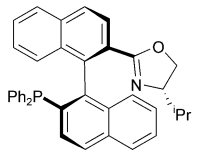


325 : R = *i*-Pr
326 : R = *t*-Bu
327 : R = Bn

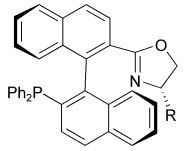


328 : Ar = Ph
329 : Ar = *o*-Tol
330 : Ar = *p*-Tol
331 : Ar = *p*-$OMeC_6H_4$

Hou and co-workers have prepared planar chiral phosphinooxazolines based on the [2.2]paracyclophane skeleton.[124] All the ligands were highly active in the allylic alkylation of 1,3-diphenylpropenyl acetate with the phenyl-substituted **328** giving the highest enantioselection (90%). Further increases in enantioselectivity could be achieved by variation of the phosphine substituents. For this ligand the enantioselectivity is determined by the central rather than the planar chirality, Table 32, entry 8 *versus* entry 9.



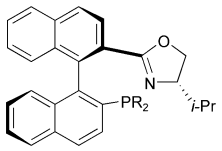
(*S*,*S*)-**332**



(*S*,*R*)-**333 :** R = *i*-Pr
(*S*,*R*)-**334 :** R = *t*-Bu

In 1998 the groups of Hayashi and Ikeda independently reported the synthesis of the diastereomers (*S*,*S*)-**332** and (*S*,*R*)-**333** and the *tert*-butyl analogue (*S*,*R*)-**334** and their application in the palladium-catalysed allylic alkylation of 1,3-diphenylprop-2-enyl acetate (**15**), Table 33, entries 1–4.[125,126] The enantioselectivities observed ranged from 28–96% with Ikeda's bulkier *t*-butyl substituted (*S*,R_a)-**334** giving the best result of 96% ee and 90% yield. The BSA method employed by Ikeda worked better than the malonate ion procedure used by Hayashi and the stereochemical outcome of the reaction was found to be determined by the axial chirality of the binaphthyl unit.

Pregosin and co-workers subsequently achieved enantioselectivities up to 99% in the allylic amination



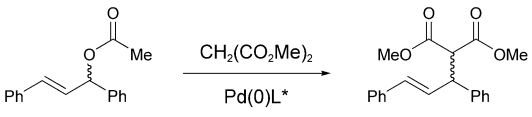
(*S*,*R*)-**335** : R = 3,5-Xylyl
(*S*,*R*)-**336** : R = 3,5-*t*-$Bu_2C_6H_3$

reaction using ligand (*S*,*R*)-**333**.[127] They also prepared ligand (*S*,*R*)-**335** and (*S*,*R*)-**336** which bore 3,5-dialkyl-substituted phenyl groups on the phosphorus.[128] Due to a combination of steric and electronic effects these ligands have a more rigid chiral pocket which led to an increase in enantiodiscrimination in the allylic alkylation of 1,3-diphenylpropenyl acetate (**15**) Table 33, entry 5. In the Heck reaction between 2,3-dihydrofuran and phenyl triflate an improvement of enantioselectivity was observed from 74% with (*S*,*R*)-**333** to 86% and 98% with (*S*,*R*)-**335** and (*S*,*R*)-**336**, respectively.

6.3 Oxazine N Donor

Ligands related to the oxazolines are the six-membered ring oxazines. A two-dimensional schematic of these ligands, **338**, suggests that the substituent at the stereogenic centre should be closer to the metal than in the corresponding oxazolines **337** and as such should exert a larger steric influence over the reaction. However, while the oxazoline ring is quite flat, oxazine rings can exist in chair- and boat-like conformations which may hinder the efficient transfer of chirality. One method to reduce the number of possible conformations is to fuse the oxazine onto another ring, an approach which has been employed by Kündig and co-workers who used an aro-

Table 33.

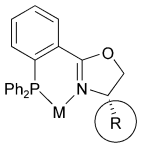


15 **16**

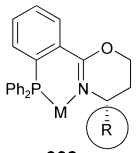
Entry	Ligand	Method	Temp. [°C]	Solvent	Time [h]	Yield [%]	ee [%]
1	(*S*,*S*)-**332**	NaMal	20	THF	3.5	99	28 (*S*)
2	(*S*,*R*)-**333**	NaMal	−20	THF	48	99	91 (*R*)
3	(*S*,*S*)-**332**	BSA	25	THF	4	93	85 (*S*)
4	(*S*,*R*)-**333**	BSA	25	THF	5	91	90 (*R*)
5	(*R*,*S*)-**334**	BSA	0	THF	20	90	96 (*R*)
6	(*S*,*R*)-**335**	BSA	r.t.	DCM	2	99	97 (*R*)

matic ring to render the heterocyclic system rigid, i.e., **339** and **340**.[129]

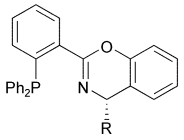
These ligands were applied in a wide range of reactions, one of which was allylic alkylation, under conditions which allowed direct comparison to the phosphinooxazolines and the yields and enantioselection obtained were generally comparable, Table 34, entries 1–3.



337

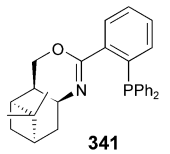


338

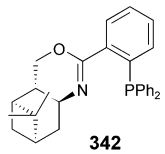


R
339 : *t*-Bu
340 : *i*-Pr

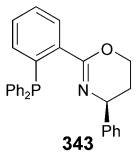
Evans chose fusion to a β-pinene ring for his ligand system, **341** and **342**.[130] Application in the allylic substitution of 1,3-diphenyl-2-propenyl acetate (**15**) showed ligand **341** to give high yields and enantioselectivities over a wide range of conditions, Table 34, entries 4 and 5. Interestingly, under analogous reaction conditions the oxazine ligand **341** had a superior turnover rate to the phosphinooxazolines.



341



342

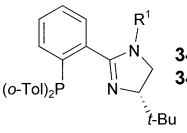


343

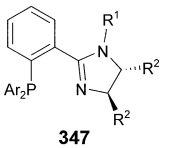
An unfused oxazine ligand **343** was prepared by Zehnder and gave excellent enantioselection in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**), Scheme 25, Table 34, entries 6 and 7.[131]

6.4 Imidazoline N Donor

Several groups have recently reported the synthesis of phosphinoimidazoline ligands. These ligands possess a chelate structure analogous to the phosphinooxazolines **259**–**263** but the additional nitrogen atom provides a further point for electronic tuning of the ligand. The group of Pfaltz has applied a number of these ligands in the iridium-catalysed enantioselective hydrogenation of various alkene substrates.[132] Ligands **345** and **346** gave the best results, surpassing those achieved with the oxazoline ligands in some cases. Busacca et al. tested ligands such as **347** in the asymmetric intermolecular Heck reaction and discovered several interesting electronic effects, Scheme 26.[133] Basic ligands (R^1 = Me, Bn) gave the opposite enantiomer to non-basic ligands (*N*-acylated). Also, ligands with alkyl substituents on the imidazoline ring gave the enantiomer opposite to that obtained with aryl-substituted ligands. A direct correlation between phosphine electron density and enantioselectivity was also found.

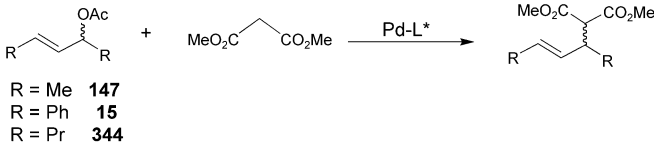


345 : R^1 = Ph
346 : R^1 = Bn



347

R^1 = 2-naphthyl
R^2 = (*R*,*R*)-3,5-$F_2C_6H_3$
Ar = 3,5-$F_2C_6H_3$



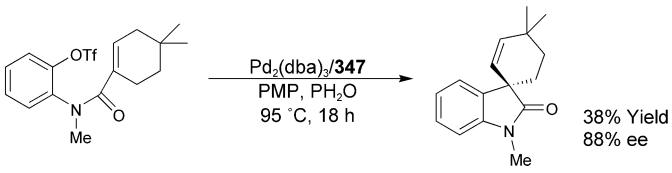
R = Me **147**
R = Ph **15**
R = Pr **344**

Scheme 25.

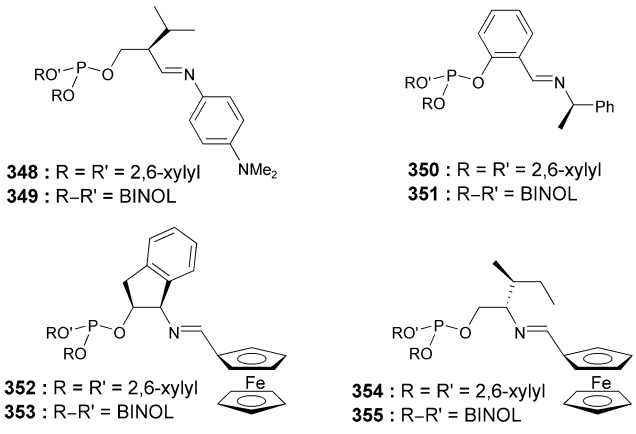
Table 34.

Entry	Ligand	Substrate	Procedure	Temp. [°C]	Time [h]	Yield [%]	ee [%]
1	**339**	**15**	BSA	23	2	>90	94 (*S*)
2	**339**	**147**	BSA	23	2	>90	82 (*S*)
3	**339**	**341**	BSA	23	2	>90	74 (*S*)
4	**341**	**15**	Na ion	0	40 min	94	95 (*S*)
5[a]	**341**	**15**	Na ion	0	5 min	94	95 (*S*)
6	**343**	**15**	BSA	r.t.	48	80	99 (*R*)
7	**343**	**147**	BSA	r.t.	168	58	54 (*R*)

[a] THF as solvent.



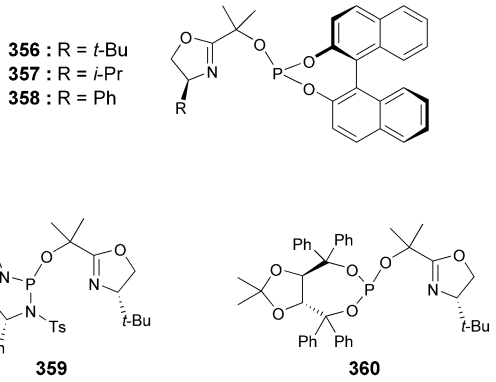
Scheme 26.

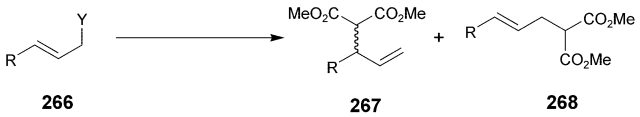


7 Imino N Donor, Heteroatom Bound P Donor

Gavrilov et al. have prepared a wide range of iminophosphite ligands some of which are shown: **348**–**355**.[134] Due to the nature of the donor atoms, metals which complex to these ligands should experience a highly electronically dissymmetric environment. These ligands were capable of good results in allylic alkylation reactions with both ligands **354** and **355** providing an 82% enantiomeric excess with the dimethylallyl substrate **147**.[135–137] They were also applied in the hydrosilylation of acetophenone where the ferrocene-substituted ligand **354** again gave the best results (80% ee).

Oxazolinophosphite ligands have been reported by a number of groups. The first, ligands **356**–**358**, were designed by the group of Pfaltz to afford high regio- and enantioselectivity in the allylic alkylation of monosubstituted allyl substrates based upon two factors.[138] Firstly, the large steric bulk around the phosphorus should force the substrate into an orientation with the more substituted carbon *trans* to phosphorus and then the large electronic disparity between the donor atoms will strongly favour nucleophilic attack at this position. This combination of steric and electronic effects provided the branched product **267** in good enantiomeric excess, Scheme 27, Table 35, entries 1–5. The success of these ligands led to the development of the bis(*N*-tosylamino)phosphine- and TADDOL-phosphite-oxazolines **359** and **360**, the first of which gave even better results, Table 35, entries 6–11.[139]



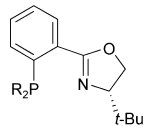


Scheme 27.

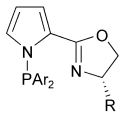
Table 35.

Entry	Ligand	R	Y	Temp. [°C]	**267 : 268**	Yield [%]	ee [%]
1	**356**	Ph	OAc	50	69 : 31	84	86 (*S*)
2	**356**	4-MeO-C_6H_4	OAc	50	76 : 24	–	–
3	**356**	4-(NC)-C_6H_4	OAc	50	13 : 87	–	–
4	**356**	1-Naphthyl	OAc	25	90 : 10	93	95 (*S*)
5	**356**	Me	OAc	50	30 : 70	75	41 (*S*)
6	**359**	Ph	OAc	r.t.	84 : 16	90	94 (*S*)
7	**359**	1-Naphthyl	OAc	r.t.	98 : 2	90	98 (*S*)
8	**359**	Me	OAc	r.t.	55 : 45	90	60 (*S*)
9	**360**	Ph	OAc	r.t.	26 : 74	90	87 (*S*)
10	**360**	1-Naphthyl	OAc	r.t.	66 : 34	90	94 (*S*)
11	**360**	Me	OAc	r.t.	38 : 62	90	23 (*S*)

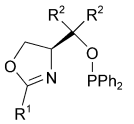
The TADDOL-derived oxazoline **360** was successfully used for the hydrosilylation of ketones affording enantioselectivities of 88% for acetophenone and 94% for pinacolone.[140] Both ligands were also applied in the iridium-catalysed hydrogenation of olefins and high enantioselectivities were observed, Table 36.[141]



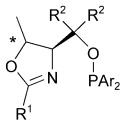
361 : R = Cy
362 : R = *o*-Tolyl



	R	Ar
363 :	*i*-Pr	Ph
364 :	*t*-Bu	Ph
365 :	*t*-Bu	*o*-Tolyl
366 :	*t*-Bu	Cy

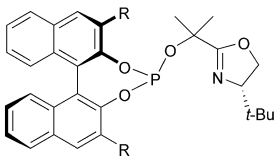


367 : R^1 = Fc, R^2 = *i*-Pr
368 : R^1 = biphenyl-4-yl, R^2 = *i*-Bu
369 : R^1 = naphthyl, R^2 = *i*-Bu
370 : R^1 = 3,5-*t*-Bu$_2$C$_6$H$_3$, R^2 = *i*-Bu
371 : R^1 = 3,5-*t*-Bu$_2$C$_6$H$_3$, R^2 = Bn
372 : R^1 = Fc, R^2 = Bn
373 : R^1 = Fc, R^2 = *i*-Bu
374 : R^1 = Ph, R^2 = *i*-Pr
375 : R^1 = Ph, R^2 = Bn
376 : R^1 = *t*-Bu, R^2 = Bn



377 :	R^1 = Ph;	R^2 = Bn;	Ar = Ph;	4*S*,5*S*
378 :	R^1 = Ph;	R^2 = Bn;	Ar = Ph;	4*S*,5*R*
379 :	R^1 = Ph;	R^2 = Bn;	Ar = *o*-Tolyl;	4*S*,5*S*
380 :	R^1 = Ph;	R^2 = Me;	Ar = Ph;	4*S*,5*S*
381 :	R^1 = 3,5-Xylyl;	R^2 = Bn;	Ar = Ph;	4*S*,5*S*
382 :	R^1 = 3,5-*t*-Bu$_2$C$_6$H$_3$;	R^2 = Bn;	Ar = Ph;	4*S*,5*S*

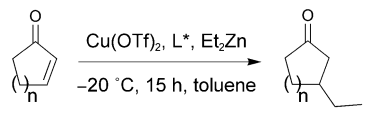
The same rationale of electronic asymmetry was also behind the development of the PyrPHOX ligands **363**–**366** and the phosphinite ligands **367** and **376** as well as **377**–**382**.[142,143] All these ligands proved to be excellent catalysts for the iridium-catalysed hydrogenation of ketones.[144] With **363**–**366** enantiomeric excesses obtained surpassed those previously obtained with the phosphinooxazolines, while the phosphinite ligands, in particular the threonine-derived **377**–**382**, were capable of excellent enantioselection over a much wider range of substrates than previous P,N ligands, Table 36.



R
383 : Me
384 : Ph
385 : Biphenyl
386 : Mesityl
387 : 3,5-di-*t*-Bu-C$_6$H$_3$

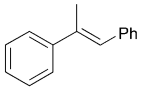
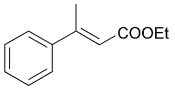
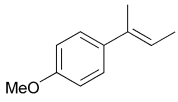
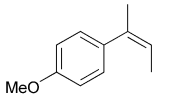
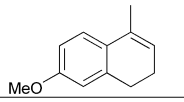
Ligands such as **383**–**387**, which are analogues of the BINOL-phosphito-oxazoline **353**–**355**, were found to be effective for the conjugate addition of alkylzinc reagents to various cyclic enones, Scheme 28.[145]

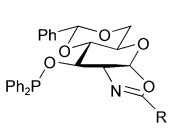
Uemura has reported the phosphitooxazolines **388**–**393** which are derived from D-glucosamine. All were



Scheme 28.

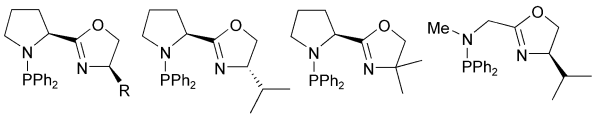
Table 36.

Entry	Ligand	Substrate	Yield [%]	ee [%]
1	**361**		100	99 (*R*)
2	**357**		100	75 (*R*)
3	**365**		100	99 (*R*)
4	**367**		100	97 (*R*)
5	**371**		100	98 (*R*)
6	**377**		100	99 (*R*)
7	**362**		86	84 (*R*)
8	**357**		100	75 (*R*)
9	**365**		99	92 (*R*)
10	**373**		100	90 (*R*)
11	**371**		100	62 (*R*)
12	**381**		100	94 (*R*)
13	**362**		100	61 (*R*)
14	**357**		100	76 (*R*)
15	**366**		100	75 (*R*)
16	**367**		100	93 (*R*)
17	**371**		100	95 (*R*)
18	**377**		100	99 (*R*)
19	**362**		97	42 (*S*)
20	**357**		100	90 (*S*)
21	**366**		100	70 (*S*)
22	**367**		100	85 (*S*)
23	**371**		100	77 (*S*)
24	**381**		100	92 (*S*)
25	**365**		100	92 (*S*)
26	**367**		100	85 (*S*)
27	**371**		100	81 (*S*)
28	**378**		100	85 (*S*)



R
388 : Me
389 : *i*-Pr
390 : *t*-Bu
391 : Ph
392 : Bn
393 : *i*-Bu

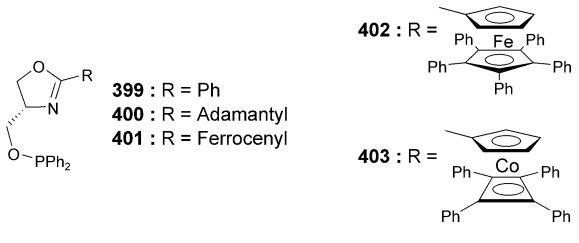
successful in palladium-catalysed allylic substitution of 1,3-diphenyl-2-propenyl acetate (**15**) with **388** affording the best asymmetric induction of 96%.[146] Ligand **393** was also employed in the Heck reaction giving up to 93% enantiomeric excess for the addition of phenyl triflate to 2,3-dihydrofuran.[147]

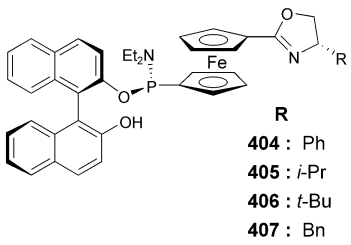


394 : (R = Ph)
395 : (R = *i*-Pr)
396
397
398

The ligands **394**–**398**, which have been reported recently by Gilbertson, are analogous to the PyrPhox **363**–**366** ligands described earlier.[148] They have been applied in allylic substitution reactions but only give good enantioselectivities with diphenylallyl substrates (up to 94% with ligand **395**).

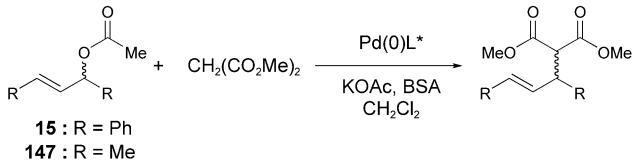
Richards and co-workers have prepared phosphinite ligands **399**–**403** using very bulky R groups which are analogues of the JMPhos ligands of Burgess, **286**–





289.[149] Initial results in the palladium-catalysed allylic alkylation were good with 96% and 70% enantioselectivity obtained respectively for the diphenyl- and dimethylallyl substrates, Table 37.

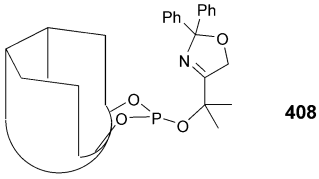
Table 37.



Entry	Ligand	Substrate	Time [h]	Temp. [°C]	Yield [%]	ee [%]
1	**399**	**15**	24	20	>95	90 (*S*)
2	**399**	**15**	24	0	>95	96 (*S*)
3	**401**	**15**	24	20	>95	90 (*S*)
4	**403**	**15**	24	20	>95	80 (*S*)
5	**401**	**147**	48	20	>95	50 (*S*)
6	**403**	**147**	48	20	>95	70 (*S*)

Dai, in an attempted synthesis of cyclic phosphonites, accidentally prepared a series of BINOL-containing ligands **404**–**407** which gave excellent results in the palladium-catalysed allylic alkylation of monosubstituted allyl substrates, Scheme 29, Table 38.[150]

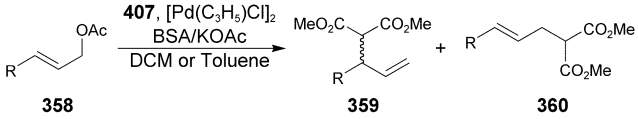
An interesting recent publication was the coupling of an oxazoline with a cavitand, **408**, in an effort to couple molecular recognition with catalysis; however, this system has not yet been applied to the generation of chiral products.[151]



8 Pyridine Type N Donor, Phosphine P Donor

Chelucci has developed the PYDIPHOS ligand **409** whose chirality originates from tartaric acid. These ligands were tested in a number of catalytic reactions such as allylic alkylation, diethylzinc additions to benzaldehyde and hydroformylation of styrene and while catalytic activity was generally good the asymmetric induction provided was poor in all cases.[152]

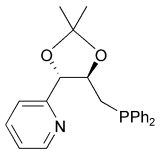
Ito and Katsuki reported the pyridylphosphines **410**–**415** which form the same chelate size as the phosphinooxazolines. Assessment of these ligands in the allylic alkylation showed **411** to be the ligand of choice as it is one of few ligands capable of high enantiodiscrimination



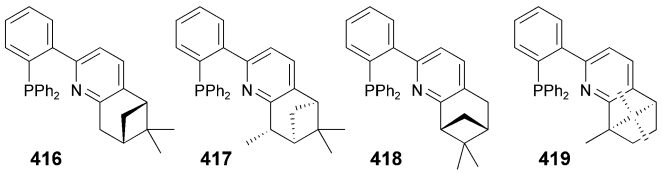
Scheme 29.

Table 38.

Entry	Substrate (R)	Temp. [°C]	Time [h]	**359/360**	Yield [%]	ee [%]
1	Ph	0	2	95:5	98	95
2	1-Naphthyl	0	1	99:1	95	93
3	1-Naphthyl	−43	7	99:1	97	97
4	4-MeO-C_6H_4	−20	2	93:7	97	97
5	4-Cl-Ph	0	1	94:6	97	94
6	4-(NC)-C_6H_4	0	1	90:10	96	95
7	Me	0	2	97:3	95	94



409

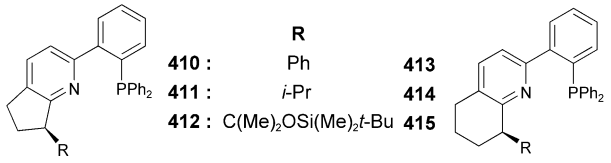


416 **417** **418** **419**

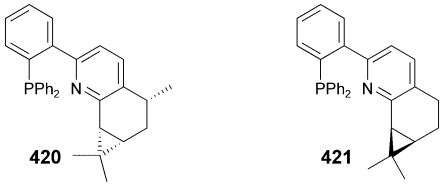
with both cyclic, Table 39, and acyclic substrates, Scheme 30, Table 40.[153]

Similar ligands were described by Chelucci and coworkers who used terpene backbones to provide the chirality, i.e., **416**–**419**; however, only moderate enantiomeric excess while (−)-**417** produced the opposite enantiomer with 88% enantioselectivity.

Knochel has recently described the preparation of a number of ferrocenyl-phosphinamine ligands **422**–**430**.[156] These were successfully applied in the rhodium-catalysed hydroboration of styrene with a 92% enantiomeric excess being achieved with **428** although the regioselectivity was poor. Good results were also obtained in the allylic alkylation of 1,3-diphenylallyl where all except **426** gave enantiomeric excesses above 80%.



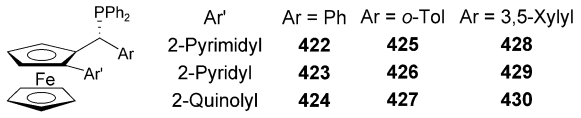
R		
410 :	Ph	**413**
411 :	*i*-Pr	**414**
412 :	$C(Me)_2OSi(Me)_2t$-Bu	**415**



420 **421**

Table 39.

Entry	Substrate	Temp. [°C]	Time [h]	Yield [%]	ee [%]
1	n = 1	−20	25	98	87 (*S*)
2	n = 2	−20	1	86	78 (*S*)
4	n = 2	−20	12	92	91 (*S*)
5	n = 3	−40	72	98	94 (*S*)

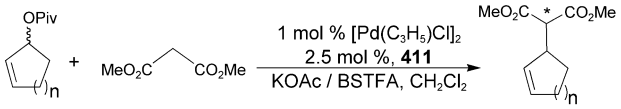


Ar'	Ar = Ph	Ar = *o*-Tol	Ar = 3,5-Xylyl
2-Pyrimidyl	**422**	**425**	**428**
2-Pyridyl	**423**	**426**	**429**
2-Quinolyl	**424**	**427**	**430**

selection (maximum 71%) was found in the allylic alkylation of 1,3-diphenylprop-2-enyl acetate (**15**).[154]

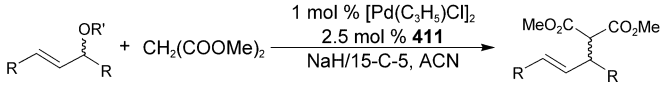
In an earlier publication by the group of Kocovsky the ligands **416**–**418** along with **420** and **421** were prepared and successfully applied in the asymmetric Heck reaction between phenyl triflate and dihydrofuran.[155] Ligand (+)-**420** afforded the (*S*) product in 70% enantio-

A new type of ferrocenylphosphine **431** has recently been reported by Fu and this ligand gave excellent results in the hydrosilylation of a number of ketones.[157] Acetophenone, propiophenone and α-tetralone were



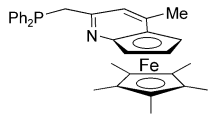
Scheme 30.

Table 40.



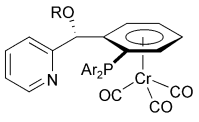
Entry	Substrate	Temp. [°C]	Time [h]	Yield [%]	ee [%]
1	R = Ph, R′ = Ac	0	1	100	98 (*S*)
2	R = Ph, R′ = Ac	0	1	44	86 (*S*)
4	R = Ph, R′ = CO_2Ph	0	2.5	70	88 (*S*)
5	R = Ph, R′ = CO_2Ph	−25	48	85	93 (*S*)

reduced in 98% enantiomeric excess and in excellent yield when the bulky mesitylphenylsilane was used as the silane source. For dialkyl ketones di-*o*-tolylsilane proved to give the best results, reducing cyclohexyl methyl ketone and 2-octanone in 94% and 72% enantiomeric excess, respectively, values which are competitive with the best that can be obtained through hydrogenation.



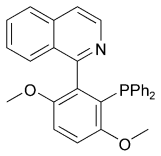
431

The group of Chung has developed a series of planar chiral pyridylphosphine ligands **432**–**439**. These were applied to the asymmetric hydroboration of styrenes where **434** gave good enantioselectivity (>80%) for a range of substrates.[158] In the palladium-catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**) those ligands with electron-withdrawing groups on the phosphorus were found to give the best enantioselection, Table 41.[159]

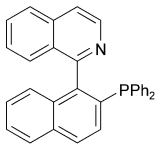


	R	Ar
432 :	H;	Ph
433 :	Me;	Ph
434 :	Bn;	Ph
435 :	4-MeOC$_6$H$_4$;	Ph
436 :	H;	4-CF$_3$C$_6$H$_4$
437 :	H;	3,5-di-CF$_3$C$_6$H$_3$
438 :	Me;	4-CF$_3$C$_6$H$_4$
439 :	Me;	3,5-di-CF$_3$C$_6$H$_3$

The first ever axially chiral phosphinamine ligand, 1-(2′-diphenylphosphino-3′,6′-dimethoxyphenyl)isoquinoline (**440**), was reported by Brown and Woodward in 1992.[160] However the methoxy group in the 5′-position was not sufficiently bulky to prevent rotation about the biaryl bond and this ligand was found to racemise, with an estimated half life of 1 h at ambient temperature. This led to the development of the QUINAP ligand **441** which has a more hindered binaphthyl type backbone.[161] Ligand **441** was successfully employed in enantioselective palladium-catalysed allylic alkylation and enantiomeric excesses of up to 98% were obtained for the 1,3-diphenylallyl substrate **15** with sodiodimethyl malonate provided 15-crown-5 was added to complex the sodium cation, Table 43, entry 1.[162] Rhodium complexes of QUINAP were tested for the hydroboration of vinylarenes where high asymmetric induction was found for styrene and 4-methoxystyrene but electron-withdrawing substituents resulted in lower ee values, Scheme 31, Table 42, entries 1–5.[163] It should be noted that the cyclic vinyl arenes indene and dihydronaphthalene also gave high asymmetric induction.



440



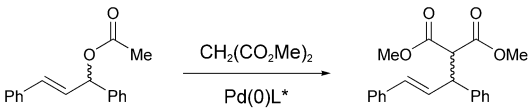
441

The hydroboration/oxidation sequence has since been extended to a synthetically useful hydroboration/amination procedure[164] and to the kinetic resolution of 1,2-dihydronaphthalenes.[165]

The QUINAP ligand is amenable to structural variation at some points and a series of ligands **442**–**447** was prepared with differing aryl substituents on the phosphorus.[166] These ligands were also applied in rhodium-catalysed hydroborations where it was found that while the parent QUINAP ligand **441** was best for electron-rich substrates, the difurylphosphino ligand **444** gave superior results for electron-deficient vinylarenes, Table 42, entries 6–14.[167]

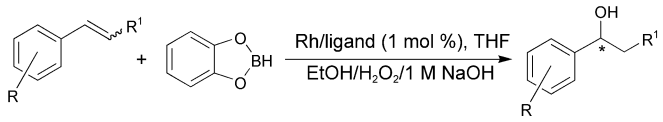
During a mechanistic investigation of QUINAP (**441**) in palladium-catalysed allylic alkylation it was discovered that the 3-H proton of the isoquinoline ring occu-

Table 41.



15 **16**

Entry	Ligand	Procedure	Temp. [°C]	Solvent	Time [h]	Yield [%]	ee [%]
1	**432**	BSA	0	DCM	3	87	77 (*R*)
2	**433**	BSA	0	DCM	7	90	63 (*R*)
3	**436**	BSA	0	DCM	6	91	90 (*R*)
4	**437**	BSA	0	DCM	6	92	84 (*R*)
5	**438**	BSA	0	DCM	5	98	86 (*R*)
6	**439**	BSA	0	DCM	8	95	89 (*R*)



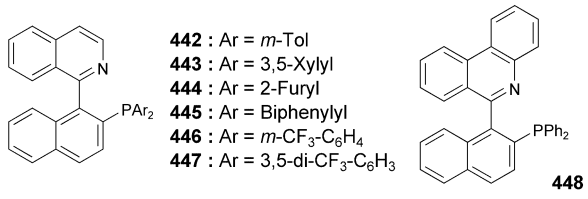
Scheme 31.

Table 42.

Entry	Ligand	Vinylarene	Time [h]	Yield [%]	ee [%]
1	(*S*)-**441**	R = R^1 = H	1	69	88 (*S*)
2	(*S*)-**441**	R = 4-MeO; R^1 = H	1	57	94 (*S*)
3	(*S*)-**441**	R = 4-Cl; R^1 = H	1	56	78 (*S*)
4	(*S*)-**441**	Indene	1	75	76 (*S*)
5	(*S*)-**441**	Dihydronaphthalene	1	78	96 (*S*)
6	(*S*)-**442**	R = Me; R^1 = H	2	79	88 (*S*)
7	(*S*)-**442**	R = 4-Cl; R^1 = H	2	72	65 (*S*)
8	(*S*)-**442**	Dihydronaphthalene	2	79	86 (*S*)
9	(*S*)-**443**	R = Me; R^1 = H	2	77	79 (*S*)
10	(*S*)-**443**	R = 4-Cl; R^1 = H	2	77	54 (*S*)
11	(*S*)-**444**	R = Me; R^1 = H	2	79	88 (*S*)
12	(*S*)-**444**	R = 4-Cl; R^1 = H	2	78	82 (*S*)
13	(*S*)-**444**	Indene	2	80	78 (*S*)
14	(*S*)-**444**	Dihydronaphthalene	2	81	82 (*S*)
15	(*R*)-**448**	R = R^1 = H	2	70	67 (*R*)
16	(*R*)-**448**	Indene	2	59	64 (*R*)
17	(*R*)-**448**	Dihydronaphthalene	2	69	84 (*R*)
18[a]	(*R*)-**450**	R = R^1 = H	18	72	90 (*R*)
19[a]	(*R*)-**450**	R = 4-MeO; R^1 = H	–	–	94 (*R*)
20[a]	(*R*)-**450**	R = 4-Cl; R^1 = H	–	–	79 (*R*)

[a] At 0 °C.

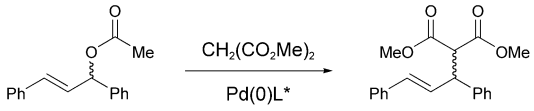
pies a region in space near the metal, leading to crucial ligand-reactant steric interactions which may play an important role in the asymmetric outcome of the reaction. This observation led to the design and synthesis of PHENAP (**448**), the phenanthridine analogue of QUINAP (**441**).[168] Ligand **448** was also tested in both palladium-catalysed allylic alkylation, giving slightly lower enantioselectivities than QUINAP, and the rhodium-catalysed hydroborations, Table 43, entries 2 and 3, and Table 42, entries 16 and 17.[169]



448

Another isoquinoline type ligand, the 1-methyl-2-diphenylphosphino-3-(1′-isoquinolyl)indole (**449**) was

Table 43.

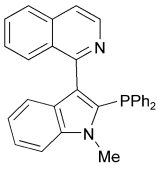


15 **16**

Entry	Ligand	Method	Temp. [°C]	Solvent	Time [h]	Yield [%]	ee [%]
1[a]	(*S*)-**441**	NaMal	0	CH_3CN	1	95	98 (*R*)
2[a]	(*R*)-**448**	NaMal	0	CH_3CN	1	98	95 (*S*)
3	(*R*)-**448**	BSA	r.t.	DCM	2	76	94 (*R*)
4[a]	**460**	NaH	r.t.	DCM	36	65	87 (*R*)
5[a]	**461**	NaH	r.t.	DCM	36	68	78 (*R*)

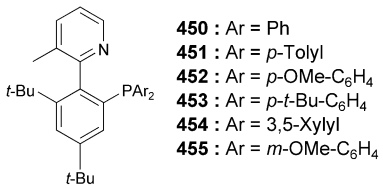
[a] 15-crown-5 added.

also synthesised by Brown et al. in an attempt to determine the effect of a variation in bite angle upon reactivity and enantioselectivity.[170] Unfortunately **449** was found to be prone to rapid racemisation and so could not be utilised in asymmetric catalysis although its 1,3-diphenylallyl-palladium complexes were studied by NMR techniques to gain insights into the mechanism of allylic alkylations.

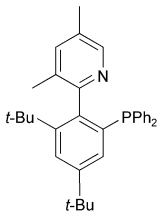


449

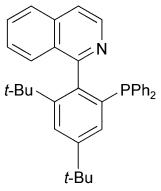
Chan and co-workers have developed a new method for the phosphinylation of aryl triflates which employs inexpensive air stable triarylphosphines as reagents.[171] Using this method they have successfully synthesised a series of axially chiral ligands, **450**–**459**.[172] To date only ligand **450** has been applied in asymmetric catalysis, Table 42, entries 18–20.[173] As with QUINAP a strong dependence of enantioselectivity upon the electronic characteristics of the substrate was found. Interestingly the pyridyl unit of the ligand makes it possible to recycle **450** by a simple acidic extraction/neutralisation/organic extraction procedure.



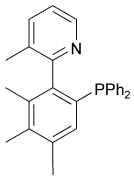
450 : Ar = Ph
451 : Ar = *p*-Tolyl
452 : Ar = *p*-OMe-C_6H_4
453 : Ar = *p*-*t*-Bu-C_6H_4
454 : Ar = 3,5-Xylyl
455 : Ar = *m*-OMe-C_6H_4



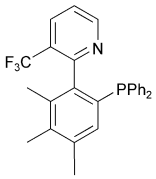
456



457

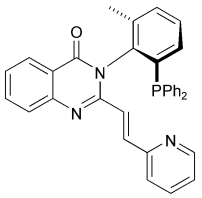


458

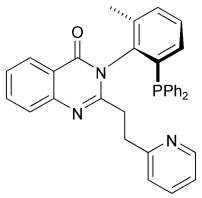


459

In 1999 Virgil and Dai reported the synthesis of a new class of mono- and bidentate quinazolinone-containing ligands which have axial chirality as a result of restricted rotation about the amide nitrogen to arylphosphine bond.[174] These ligands were tested in the palladium-catalysed allylic alkylation reaction and the enantiomeric excesses obtained ranged from 67–87%, Table 43, entries 4 and 5. Ligand **460**, which should form a more rigid palladacycle, gave slightly higher enantioselection.

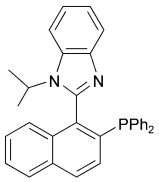


460



461

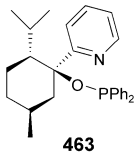
Very recently, Figge et al. have reported the synthesis and resolution of a new type of axially chiral phosphinamine ligand BIMNAP **462**.[175] The *iso*-propyl group on the imidazole ring provides sufficient steric interaction to prevent racemisation. As yet, no examples of its application in asymmetric catalysis have been described.



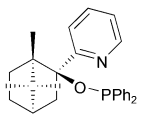
462

9 Pyridine N Donor, Heteroatom Bound P Donor

The structurally similar ligands **463** and **464** which are derived from menthol and (+)-camphor were reported by Faraone and Chelucci, respectively.[176,177] Both were applied to the rhodium-catalysed hydroformylation of olefins where **463** proved to be the superior ligand, Scheme 32, Table 44.



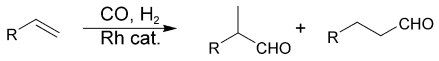
463



464

Following the work of Pfaltz on the phosphite oxazolines **353**–**355**, a number of other BINOL-derived P,N ligands were prepared such as the quinoline-containing ligands **465** and **466** which have been reported by Arena.[178,179] Application of these ligands in the copper-catalysed conjugate addition of diethylzinc to cyclohexenone resulted in a best enantioselection of 51% with **466**.

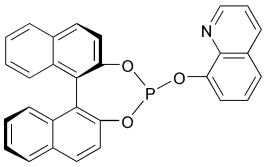
Arena subsequently prepared the related pyridine-phosphonite ligands **467** and **468**.[180] These were tested in the asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**) where they afforded only racemic products, Table 45, entries 1 and 2. This was thought to result from the lack of steric hindrance around the pyridyl donor relative to a diphenylphosphine moiety.



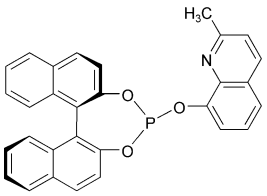
Scheme 32.

Table 44.

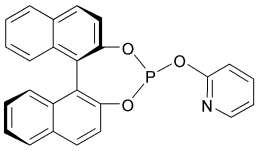
Entry	Ligand	R	Pressure [atm]	Temp. [°C]	Time [h]	Conv. [%]	B/L	ee [%]
1	**463**	Ph	50	70	4	100	88:12	6 (*R*)
2	**463**	2-Naphthyl	80	100	16	100	100	78 (*R*)
3	**463**	CO_2Me	60	60	16	95	97:3	92 (*R*)
4	**464**	Ph	n/a	80	24	95	80:20	9 (*S*)
5	**464**	2-Naphthyl	n/a	80	24	98	72:28	45 (*S*)



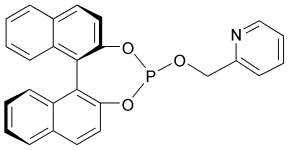
(*R*)-**465**



(*R*)-**466**



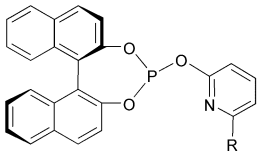
(*R*)-**467**



(*R*)-**468**

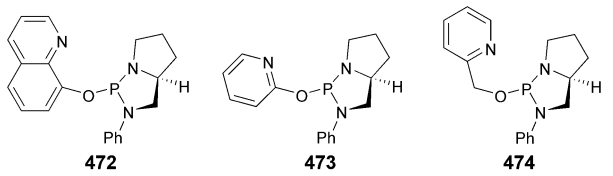
To investigate if this was in fact the case the substituted pyridine analogues **469**–**471** were prepared and applied under the same conditions; however, the substituents were not sterically demanding enough to provide acceptable enantioselection, Table 45, entries 3–5.[181]

Buono et al. have developed pyridylphosphonite ligands **472**–**474** which are chiral at phosphorus, and successfully applied them in allylic substitution reactions with various nucleophiles. The use of β-ketoesters as nucleophiles allowed the production of chiral quaternary carbon centres, Scheme 33.

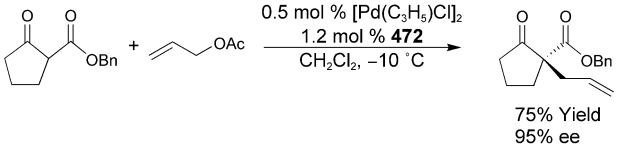


469 : R = Me
470 : R = Br
471 : R = Ph

Ligand **472** was found to be an especially favoured ligand as it was stable to air and moisture and amenable to large-scale preparation. It was also used in copper-catalysed Diels–Alder reactions and diethylzinc conjugate additions and gave good results in each case.[182]

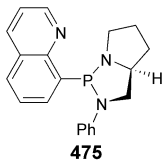


472 **473** **474**



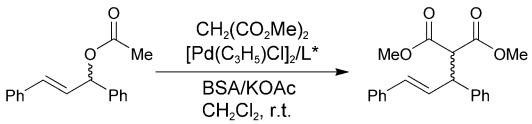
Scheme 33.

Most recently Buono has reported the synthesis of the diazaphospholidine derivative **475** which will allow for evaluation of the electronic and chelate size effects of these ligands, however no catalytic results have been disclosed to this time.[183]



475

Table 45.



15 **16**

Entry	Ligand	Time [h]	Yield [%]	ee [%]
1	**467**	16	94	0
2	**468**	16	95	0
3	**469**	16	91	11 (*S*)
4	**470**	4	94	7 (*S*)
5	**471**	16	95	7 (*S*)

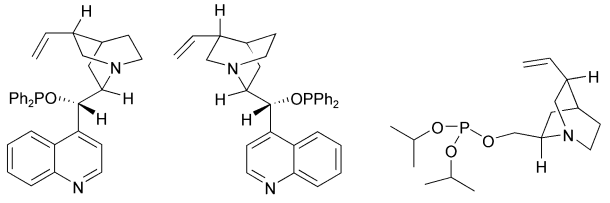
10 Ligands with Chiral Donor Atoms

Efforts have been made to develop ligands which bear chiral nitrogen or phosphorus atoms as their metal complexes will have the chiral information very close to the metal centre.

10.1 Chiral N Donor

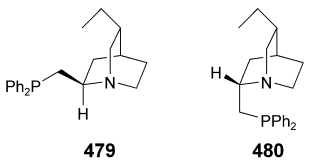
There are a number of ligand systems where the nitrogen donor atom becomes stereogenic upon coordination to a metal, for example, ligands **13** and **14**);[4] however, the preparation of ligands that contain a stable stereogenic nitrogen is hampered by the rapid inversion of amines. The bridgehead nitrogen atoms of alkaloids such as quinine are incapable of inversion and so provide a good starting point for the construction of chiral-at-nitrogen ligands.

This approach was first taken by Buono et al. for the development of the phosphinite ligands **476** and **477** which gave poor to moderate ees in the hydrosilylation of acetophenone.[184] Gavrilov has reported phosphite ligands such as **478** but only their complexation behaviour with rhodium and palladium has been described.[185]



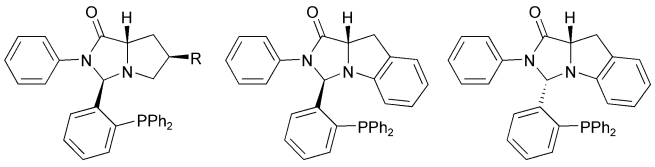
476 **477** **478**

More recently Lemaire has disclosed the synthesis of the quincorine and quincoridine-derived phosphines **479** and **480**. These ligands proved to be inefficient in the hydroformylation of styrene and the hydrosilylation of acetophenone but were useful in the nickel-catalysed reaction of 1-phenylethylmagnesium chloride (**6**) and vinyl bromide (**7**) affording the alkene product **8** in an 85% enantiomeric excess with ligand **480**, Scheme 1.[186]



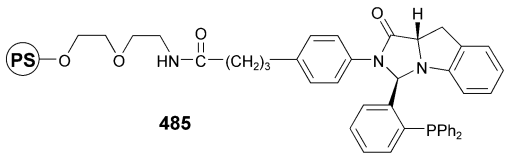
479 **480**

Uozumi has developed a number of chiral-at-nitrogen ligands **481**–**484** which contain a hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one backbone.[187] Ligand **483** gave the best results in allylic alkylation providing enantiomeric excesses of above 80% with a range of cyclic substrates. Interestingly, when **483** was bound to an amphiphilic polystyrene poly(ethyleneglycol) co-polymer **485**, asymmetric allylic alkylations could be carried out in aqueous solution.[188] The system was useful for both cyclic and acyclic substrates and could be recycled without any loss in enantioselection, Scheme 34, Table 46. The enantioselectivities obtained were higher than those observed with the free ligand in organic solution although the yields were lower.

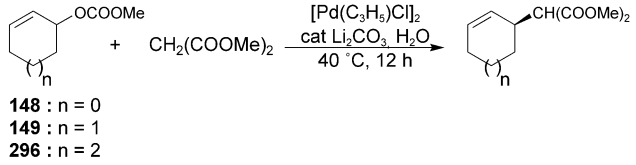


481 : R = H
482 : R = OH

483 **484**



485



148 : n = 0
149 : n = 1
296 : n = 2

Scheme 34.

Table 46.

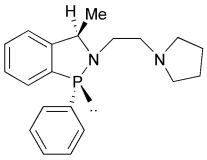
Entry	Substrate	Yield [%]	ee [%]
1	**148**	68	92 (*S*)
2	**149**	71	89 (*S*)
3	**296**	84	97 (*S*)
4	**15**	86	91 (*S*)

10.2 Chiral Phosphorus Donor

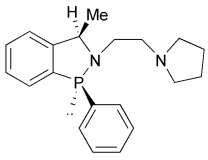
Ligands such as **486** and **487** which bear a stereogenic phosphorus atom have been reported and were tested in allylic alkylations giving up to 60% enantioselectivity, Table 42, entries 1 and 2.[189] Observations made during the course of these reactions led to the development of the monodentate phosphine ligand **488** which was capable of much higher enantioselections (92%).

Brandi has described the pyrrolidine-phospholane ligand **489** but it was not applied in catalysis.[190]

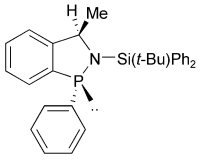
Recent examples from Gilbertson are the ligands **490**–**497** which, similar to the alkaloid systems, owe



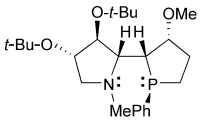
486



487

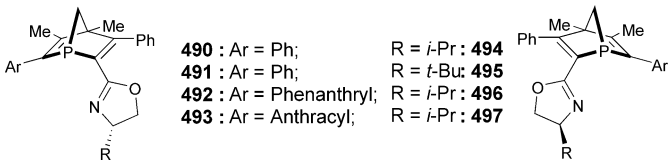


488



489

their stability to the donor atom, in this case phosphorus, being located at the bridgehead position of a rigid bicyclic system.[191]

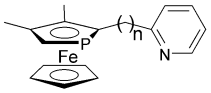


490 : Ar = Ph; R = *i*-Pr : **494**
491 : Ar = Ph; R = *t*-Bu: **495**
492 : Ar = Phenanthryl; R = *i*-Pr : **496**
493 : Ar = Anthracyl; R = *i*-Pr : **497**

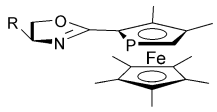
These ligands were applied in the palladium-catalysed allylic alkylation with the diphenylallyl substrate **15**, Table 47, entries 3–10. Ligands **490** and **491** gave high enantioselection but as the aromatic substituent became larger the opposite enantiomer was formed in a lower enantiomeric excess. In the Heck reaction between 2,3-dihydrofuran and cyclohexenyl triflate **491** proved to be the better ligand giving a 93% enantiomeric excess of the (*R*) product.

Phosphaferrocenes, in which the phosphorus donor atom is contained within a π-complexed heterocyclic ring are well known in coordination chemistry.[192] In these ligands the phosphorus has the electronic characteristics of an sp^2 centre and is strongly π accepting.

Ganter has developed ligands **498** and **499** which are able to coordinate to a metal through both the phosphorus and the nitrogen on the substituent. Once complexed the metal is positioned near to the element of planar chirality and it was hoped that this would allow for efficient transfer of chirality in asymmetric reactions. However, initial testing in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**15**) gave disappointing results, Table 47, entries 11 and 12.[193] Better enantioselection was obtained with the phosphaferrocenyl oxazoline ligands **500** and **501** which have been reported by Fu et al., Table 47, entries 13 and 14.[194] Fu has recently developed other phosphaferrocenyl oxazoline ligands and has successfully applied them to the copper-catalysed asymmetric conjugate addition of diethylzinc to a range of acyclic enones with generally high enantioselectivity (61–91%).[195]

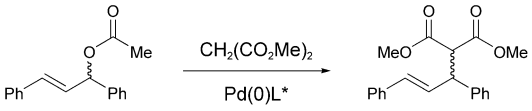


498 : n = 1
499 : n = 2



500 : *i*-Pr
501 : *t*-Bu

Table 47.



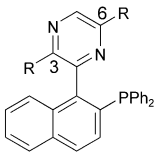
15 **16**

Entry	Ligand	Procedure	Time [h]	Temp. [°C]	Yield [%]	ee [%]
1	**497**	BSA		r.t.	86	60 (*R*)
2	**497**	BSA	3	r.t.	35	33 (*S*)
3	**490**	BSA	1	r.t.	100	94 (*S*)
4	**494**	BSA	1	r.t.	100	81 (*R*)
5	**491**	BSA	1	r.t.	100	93 (*S*)
6	**495**	BSA	1	r.t.	100	68 (*R*)
7	**492**	BSA	1	r.t.	100	39 (*S*)
8	**496**	BSA	1	r.t.	100	44 (*S*)
9	**493**	BSA	1	r.t.	85	25 (*R*)
10	**497**	BSA	1	r.t.	100	83 (*S*)
11	**498**	NaMal	3	r.t.	65	19 (*R*)
12	**499**	NaMal	3	r.t.	80	11 (*R*)
13	**500**	BSA	4.5	r.t.	94	79 (*S*)
14	**501**	BSA	4.5	r.t.	92	82 (*S*)

11 Development of Axially Chiral Ligands within our Group

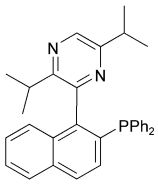
Our interest in axially chiral phosphinamine ligands also started with the observation that the position of the 3-H proton of QUINAP was important in asymmetric reactions. The isoquinoline unit of QUINAP (**441**) was replaced with a 3,6-dialkyl-substituted pyrazine moiety. This would allow the evaluation of the effect upon enantioselection of different substituents at the 6-position. It was also of interest to investigate the enantiomeric stability provided by the steric interactions of the substituent in the 3-position of the pyrazine ring. Firstly, we reported the synthesis of the 3,6-dimethyl-substituted ligand **502**.[196] Unfortunately this was found to racemise easily indicating that the methyl group in the 3-position is insufficiently large to prevent rotation about the biaryl pivot. In an effort to increase the barrier to this rotation the synthesis of the bulkier *tert*-butyl analogue **503** was attempted.[197] However the *tert*-butyl group proved to be too large to allow the key cross-coupling step to proceed.

Both of these observations prompted the synthesis of the diisopropyl pyrazinap ligand **504** which was found to be configurationally stable and has been applied in

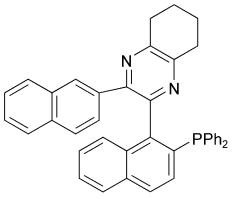


502 : R = Me
503 : R = *t*-Bu

asymmetric catalysis. A related ligand which has also been prepared is the naphthyl-cyclohexyl pyrazine ligand **505** whose cyclohexenyl group should be of similar size to the fused phenyl ring in PHENAP allowing for the comparison of these ligands.[198]

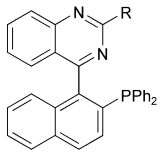


504



505

A second type of ligand architecture has also been developed within our laboratories which bears a quinazoline unit as one half of the biaryl structure. The possibility for variation of the substituent at the 2′-position will allow the investigation of various steric effects upon asymmetric reactions. In addition, the donor nitrogen of the quinazolines is considerably less basic than that of QUINAP (**441**) (e.g., the pK_a of **441** is 5.1 while the pK_a of **506** is 3.3). The first of this class of ligands to be synthesised was 2-phenyl-Quinazolinap (**506**).[199] Investigations using **506** in palladium-catalysed allylic alkylation showed good reactivity but only moderate enantioselectivity, Table 48. Interestingly (*R*)-**506** gave the opposite sense of asymmetric induction to QUINAP and PHENAP, i.e., (*R*)-**441** and (*R*)-**448** afford an excess of (*S*)-product whereas (*R*)-**506** gives the (*R*) enantiomer preferentially. As the major structural difference between QUINAP and **506** is the presence of the 2-phenyl substituent on the quinazoline, this substituent must cause steric interactions which lead to the lowered and opposite asymmetric induction. This observation led to the development of the 2-methyl-substituted quinazoline **507** which gave improved enantioselectivities in allylic alkylation.[200]

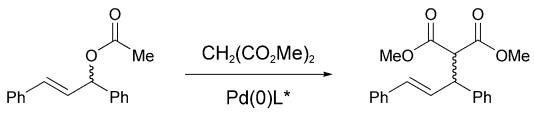


506 : R = Ph
507 : R = Me
508 : R = *i*-Pr
509 : R = *t*-Bu
510 : R = Bn
511 : R = 2-Pyridyl

12 Conclusion

We hope that, as a result of the many examples of bidentate P,N ligands detailed in this review, readers will be more informed as to the current success of such ligand systems in catalysis. The asymmetric transformations to which their metal complexes have been applied include among others, palladium-catalysed allylic substitutions, copper-catalysed 1,4-additions to enones and rhodium-catalysed hydroboration of vinylarenes. Excellent enantioselectivities, regioselectivities and reactivities have been achieved in each of these processes. How-

Table 48.



15 **16**

Entry	Ligand	Procedure	Temp. [°C]	Solvent	Time [h]	Yield [%]	ee [%]
1	(*R*)-**506**	NaMal	r.t.	THF	48	58	66 (*R*)
2	(*R*)-**506**	BSA	r.t.	DMF	48	99	36 (*R*)
3	(*S*)-**507**	NaMal	r.t.	DMF	48	67	85 (*R*)
4	(*S*)-**507**	BSA	r.t.	DCM	6	98	88 (*R*)
5	(*S*)-**508**	BSA	0	ACN	18	68	90 (*R*)
6	(*S*)-**508**	BSA	0	DCM	18	85	91 (*R*)
7	(*S*)-**504**	NaMal	r.t.	DMF	48	13	91 (*R*)
8	(*S*)-**504**	NaMal	r.t.	DCM	48	100	83 (*R*)
9[a]	(*S*)-**504**	NaMal	r.t.	DCM	72	52	92 (*R*)
10	(*S*)-**504**	BSA	r.t.	ACN	28	91	86 (*R*)
11[b]	(−)-**505**	NaMal	r.t.	DCM	7.5	50	78 (*R*)
12[b]	(−)-**505**	BSA	r.t.	DCM	19	99	76 (*R*)

[a] 15-Crown-5 added.
[b] Sign of optical rotation.

ever, even a brief glance at the results obtained also underlines how the electronic and steric properties of each ligand must be finely tuned for individual substrates and applications. To date, a ligand that provides the maximum reactivity and selectivity across a wide range of substrates and applications remains elusive. Nevertheless, the diphenylphosphinooxazoline ligand class does stand out in terms of accessibility, modularity, stereoinduction and application range. The future for this class of heterobidentate ligands in asymmetric catalysis seems assured due to the high reactivity their metal complexes exhibit compared to diphosphines and diamines and also because of the impressive enantioselectivities obtained thus far. It will be of interest to see how successful they become in the future.

Acknowledgements

CPS acknowledges financial support from Enterprise Ireland Research Scholarship (BR/97/047).

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