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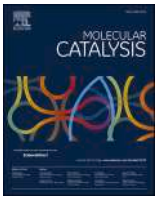

Polydentate P, N-based ligands for palladium-catalyzed cross-coupling reactions

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ABSTRACT

In recent years, Pd-catalyzed cross-coupling reactions have been used widely as expeditious reactions in various fields of chemistry. Traditionally, these cross-coupling reactions have been carried out by using different phosphine ligands. Though the phosphine ligands have been extensively used, they suffer from many limitations like poor air, moisture, and thermal stability. Hence, in recent years phosphine-free ligands such as N-heterocyclic carbenes and amines have attracted countless attention in the field of catalysis. Unfortunately, the ligands having only N as a donor atom can activate aryl iodides and bromides, while aryl chlorides are less reactive. Hence, the P–N ligands containing functional moiety, with donor N or P atom have been prepared and used for different organic transformations. An even more effective mixed donor P, N-ligands have many advantages in asymmetric catalysis because of the distinctly different characteristics like a 'soft' P-ligand as a π-acceptor and a 'hard' N-ligand as a σ-donor. This compressive review highlights the results of the highly active ligands and complexes containing N in combination with P as a donor atom.

1. Introduction

Palladium-catalyzed C-C and C-X coupling reactions [1] have tremendous applications in the field of natural products, pharmaceuticals, agrochemicals, and functional materials [2]. A large number of homogeneous and heterogeneous Pd catalysts have been applied in these coupling reactions [3]. Traditionally, these reactions have been performed using different phosphine ligands. Though the phosphine ligands are extensively used, they suffer from many limitations like poor air, moisture, and thermal stability. Hence, in recent years phosphine-free ligands such as N-heterocyclic carbenes [4] and amines [5] have attracted countless attention in the field of catalysis. Similar to Pd complexes containing N with the C [6], and O [7] as donor atoms, it is possible to develop tunable P–N ligands such as PHOX, Pincers, Atropos, Schiff bases, and Aminophosphines for various cross-coupling reactions.

2. Ligands containing N and P atoms (P, N ligands)

Phosphines (PR_3) are more commonly known as a spectator rather than actor ligands, as electronic and steric properties can be altered systematically and predictably by varying the R groups [8]. Unlike NR_3, they are also π-acids to some extent, which depends on the nature of the R groups. As the R group becomes more electronegative, the σ* orbital of the P−R bond becomes more stable and the P contribution to the σ* orbital increases, so the size of the σ* lobe that points toward the metal increases [9]. The electron-richness and sterically bulky skeletons can facilitate oxidative addition and reductive elimination steps [10]. However, mono phosphine ligands have restricted coordinative flexibility for stabilizing the unstable low-coordinate and low-valent Pd complex. The highly active complexes are converted into inactive Pd black at high temperatures or under prolonged heating, limiting their TON. The use of mixed P–N-type ligands can avoid these limitations. Heterobidentate P and N ligands are interesting ligands as "soft" (P atom), and "hard" (N atom) characters enable fine-tuning in the stabilization of various intermediates in catalytic cycles. Due to the electron disparity between the two P and N distinct coordination sites, and P, N-ligands containing sp^2 hybridized N donors like pyridine, imine, and oxazoline offer unique properties [11]. A large number of ligands containing functional moiety, with donor N or P heteroatoms (P–P and N–N ligands) have been prepared and used for different organic transformations [12]. Because of the distinctly different characteristics of P and N atoms, more effective P–N ligands have many advantages in

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1	•The P-N based ligands can be easily separated from the reaction mixture *via* phase separation under acidic conditions.
2	•The chelate effect of P-N ligand confers stability to the catalyst precursor in the absence of substrates.
3	•The P-N ligands play a dual role, the π-acceptor character of P stabilize a metal center in a low oxidation state and the σ-donor ability of N makes the metal more susceptible to oxidative addition.
4	• In this hard-soft combination, the hard end weakly coordinates to soft metal centers and easily dissociate in solution to afford a vacant site.
5	•This combination also helps to stabilize the intermediate oxidation states during the catalytic cycle.
6	•In addition, it is easy to independent structural alternation for each of the P and N donor sites that makes it convenient to build a set of ligands for special applications in catalysis.
7	•In addition, these ligands can employ a high degree of regiocontrol by '*trans*' effect.

Fig. 1. Advantages of the P-N ligands in transition metal catalysis.

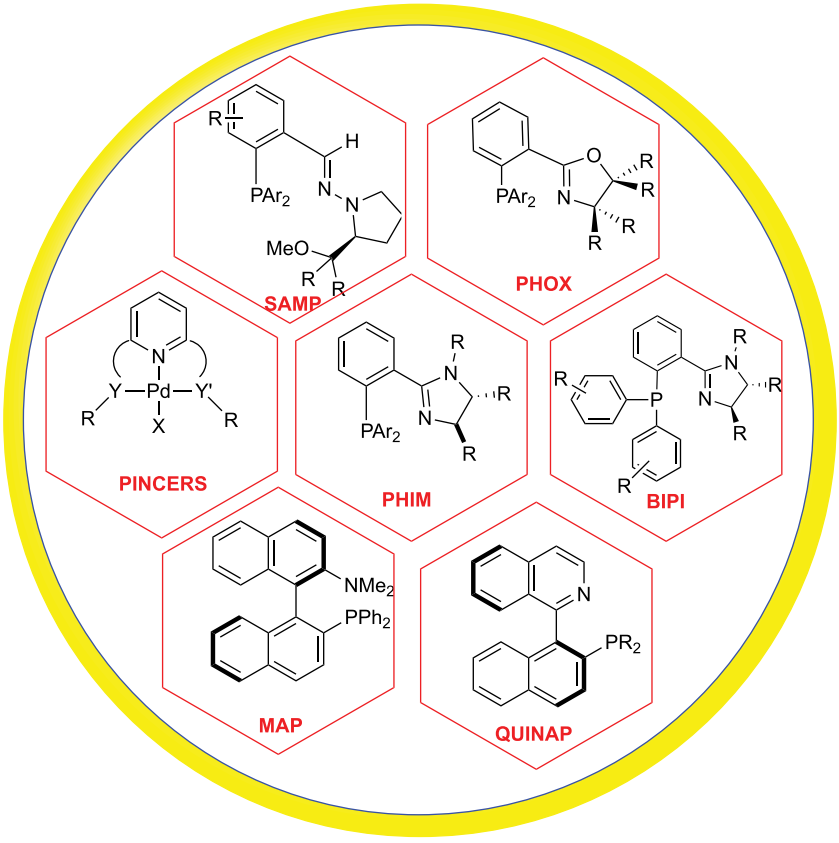


Fig. 2. Privileged P-N ligands used in Pd-catalyzed coupling reactions.

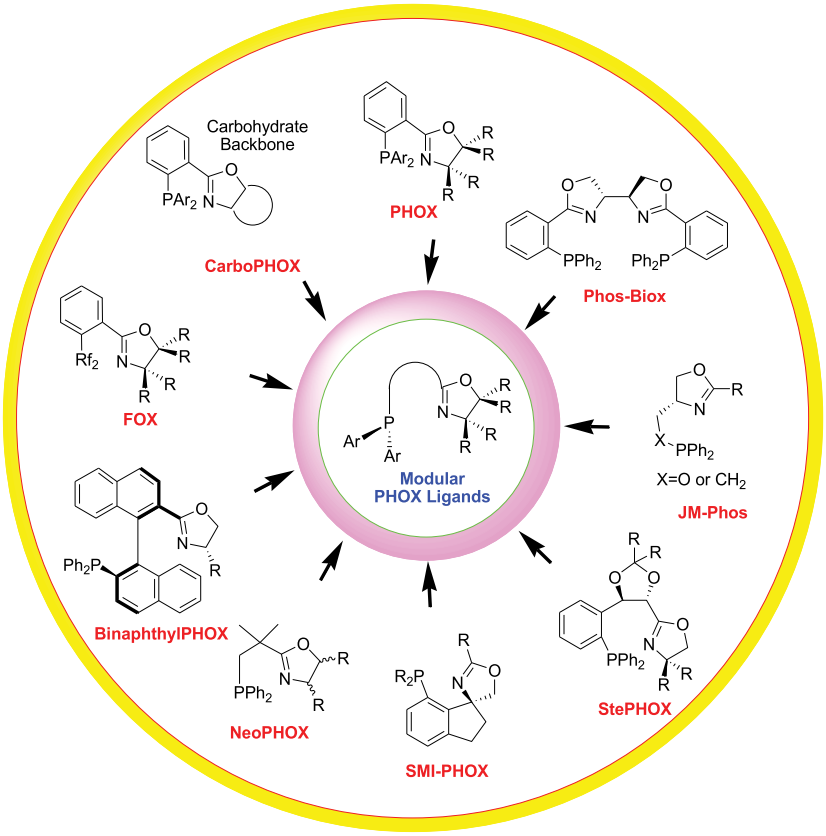


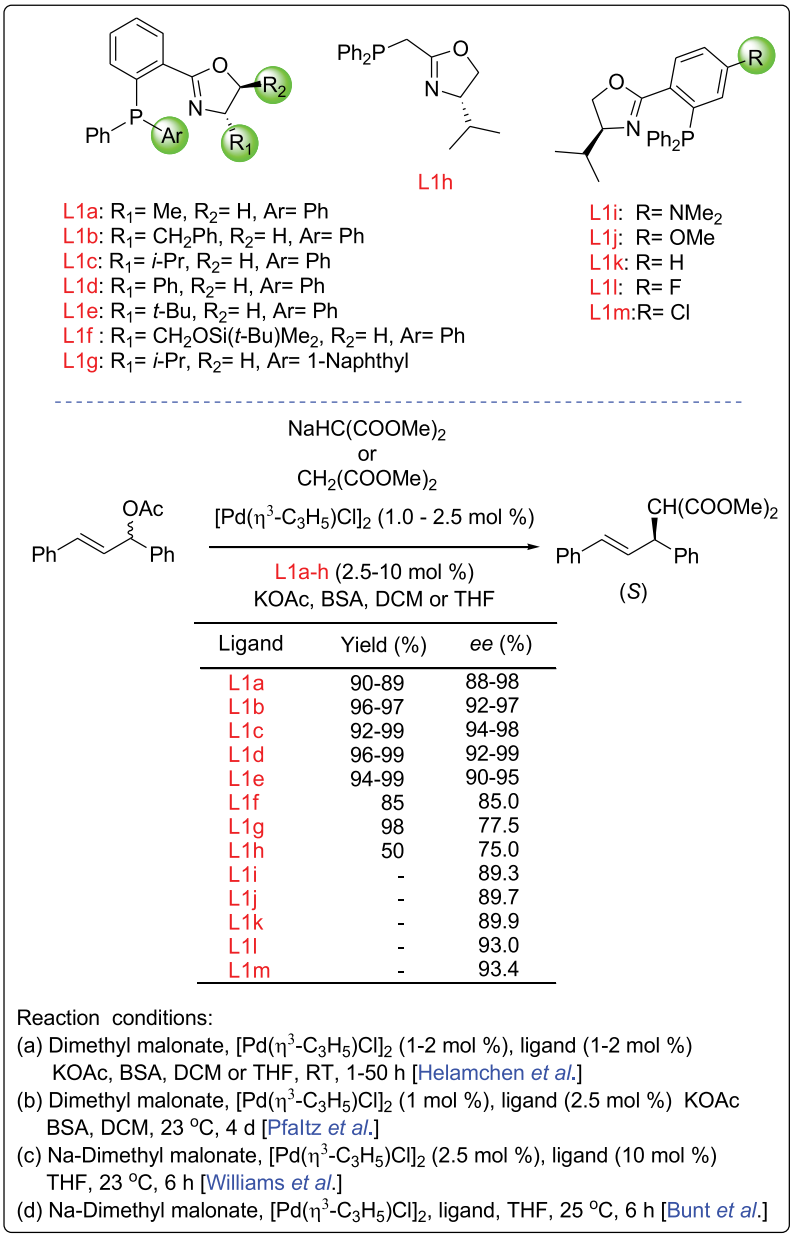
Fig. 3. The scaffolds of PHOX ligands used in Pd-catalyzed coupling reactions.

asymmetric catalysis. These mixed donor ligands are a class of 'hemilabile ligands' that have many applications in asymmetric catalysis [13]. The P–N ligand offers the following advantages (Fig. 1).

In summary, the good π-acceptor character of P and the σ-donor ability of the N atom of P-N ligands created a great interest in the field of asymmetric catalysis [14a]. It was reported that selectivity in asymmetric catalysis depends on the relative energy of the two diastereomeric transition states leading to '*R*' and '*S*' products concerning a common resting state. Many P–N-based ligands provide a unique chiral environment to different intermediates involved in catalytic cycles. Recently, P N-based nonsymmetrical modular ligands have been applied successfully in various metal-catalyzed reactions [14b,c]. In the last decades, mechanistic studies of these reactions were supported by computational studies [15]. In this connection, the present review article covered the reports on different Pd-catalyzed cross-coupling reactions using several P-N ligands such as PHOX, QUNAP, SAMP, MAP, PHIM, BIPI, Aminophosphines, Pincers, and Schiff-bases (Fig. 2).

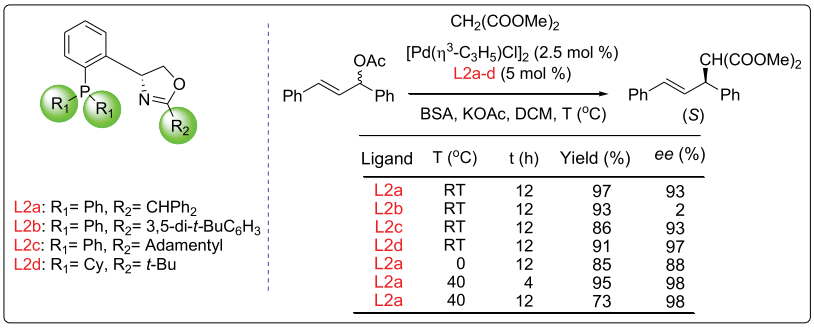
Below are the peculiar distinctive properties of the ligands underlined.

- Due to their ready accessibility and modular construction, PHOX ligands are the most commonly investigated ligands.
- HetPHOX has emerged as a new ligand for asymmetric catalysis, as it easily introduces the required diphenylphosphino groups on the ligand backbone.
- Similar to PHOX ligands, more flexible phosphinoimidazoline-based 'BIPI' ligands containing additional nitrogen were used for the creation of a chiral quaternary center. It allows fine-tuning of the gross electronic properties by varying the substituents. In addition, BIPI ligands could be constructed from chiral diamine in a modular fashion.
- As analogs to that of BIPI-ligands. PHIM ligands have been acting as interesting ligands in asymmetric catalysis, as it is readily available from C_2-symmetric diamine fragments. In addition, these ligands contain a second nitrogen atom that can work as an additional source of molecular diversity, as it allows to adjustment of the electronic properties of the coordinating nitrogen atom. In addition, it is possible to immobilize the ligand on a suitable solid support.
- SAMP and their analogs derived from chiral phosphine hydrazones have also been developed as efficient ligands for many Pd-catalyzed reactions.
- The transition metal ECE and ECE′ type pincer complexes also attracted great interest as a new class of metal complexes for the range of catalytic applications.
- The 'Atropos' ligands like 'QUINAP, PINAP, and QUINAZOLINAP' are a specific type of biaryls, with one component carrying a pendant diaryl substituted phosphine, and the other bears an sp^2 N-atom adjacent to the biaryl link acts as privileged chiral ligands for many asymmetric transformations.



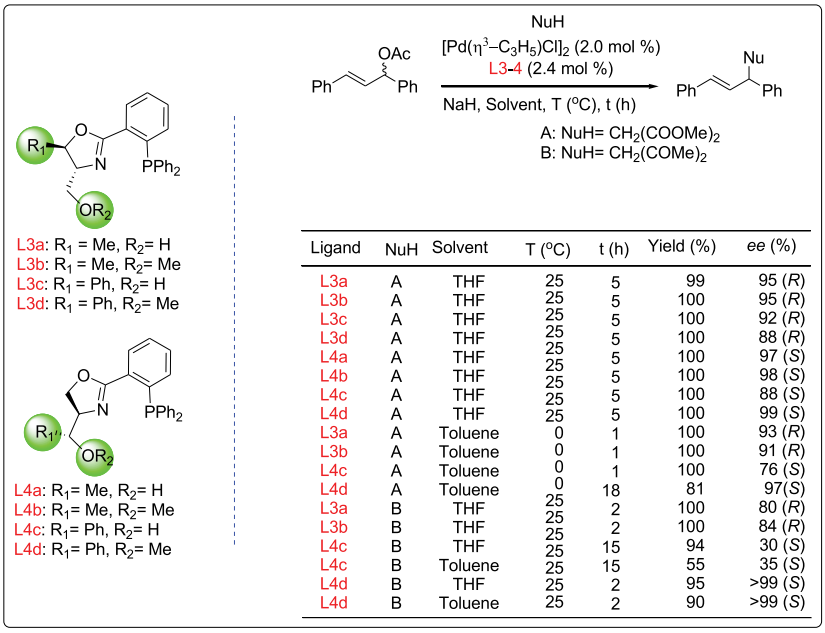
Ligand	Yield (%)	*ee* (%)
L1a	90-89	88-98
L1b	96-97	92-97
L1c	92-99	94-98
L1d	96-99	92-99
L1e	94-99	90-95
L1f	85	85.0
L1g	98	77.5
L1h	50	75.0
L1i	-	89.3
L1j	-	89.7
L1k	-	89.9
L1l	-	93.0
L1m	-	93.4

Scheme 1. C_2 symmetric PHOX ligands used in asymmetric allylic alkylations.



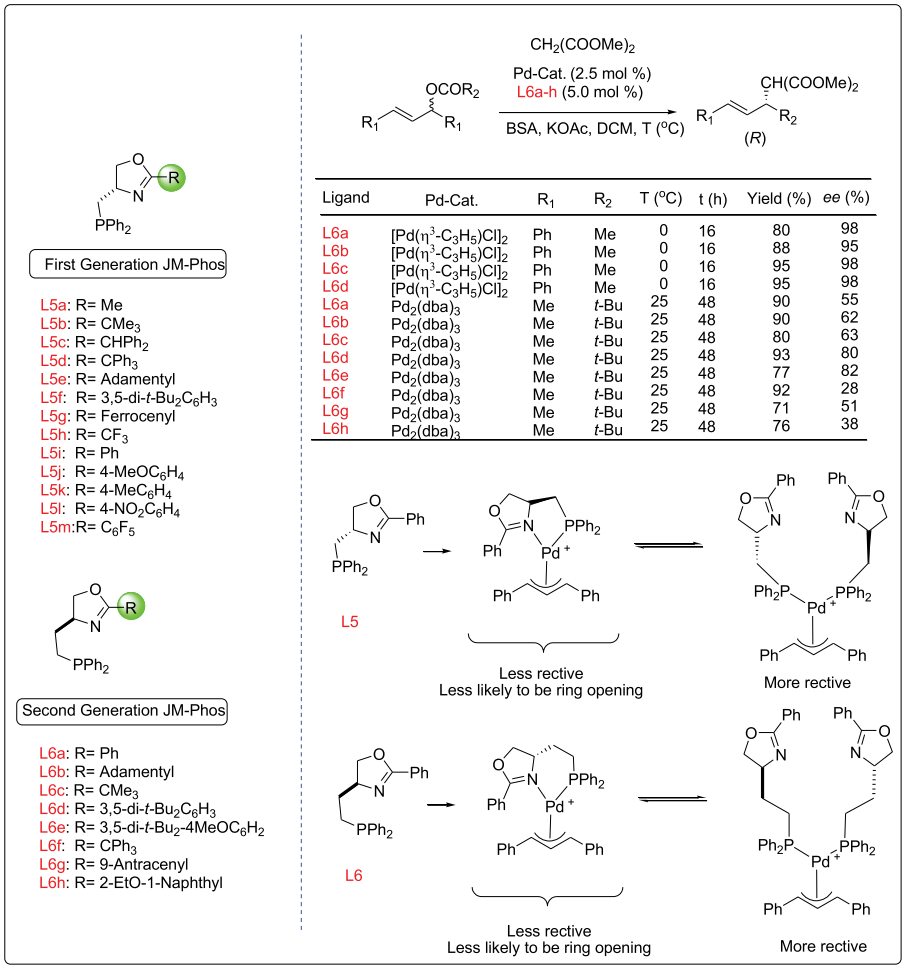
Ligand	T (°C)	t (h)	Yield (%)	*ee* (%)
L2a	RT	12	97	93
L2b	RT	12	93	2
L2c	RT	12	86	93
L2d	RT	12	91	97
L2a	0	12	85	88
L2a	40	4	95	98
L2a	40	12	73	98

Scheme 2. Conformationally rigid PHOX ligands for asymmetric allylic alkylations.



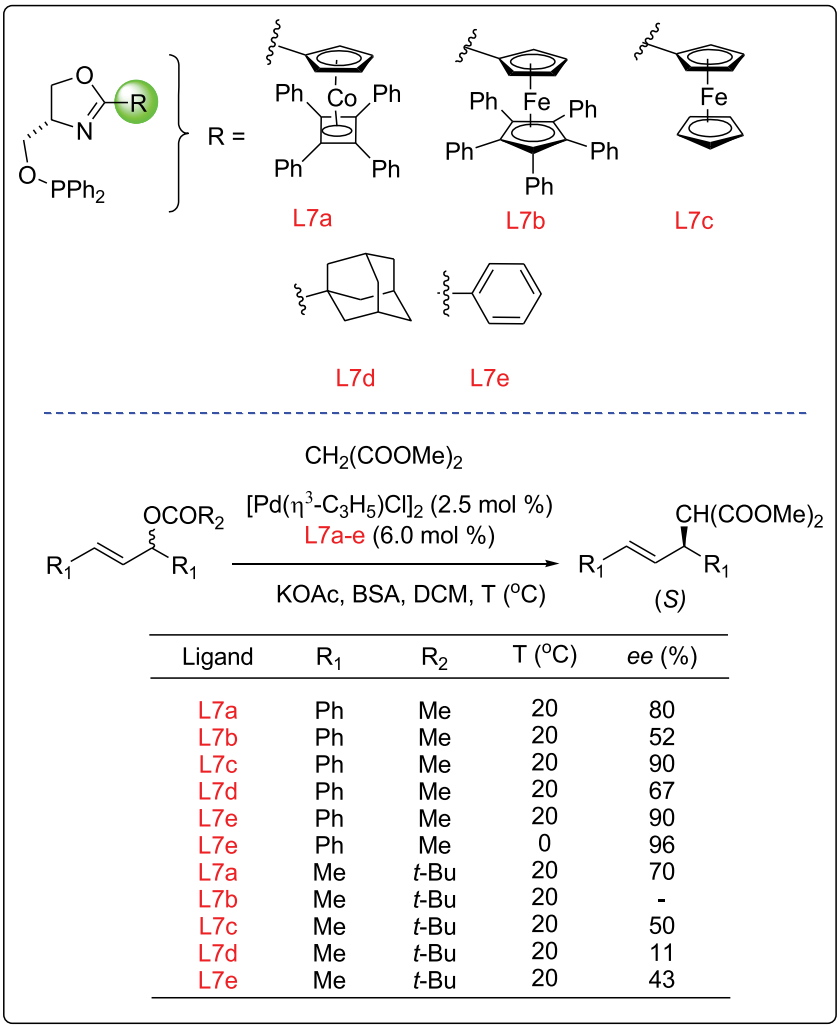
Ligand	NuH	Solvent	T (°C)	t (h)	Yield (%)	*ee* (%)
L3a	A	THF	25	5	99	95 (*R*)
L3b	A	THF	25	5	100	95 (*R*)
L3c	A	THF	25	5	100	92 (*R*)
L3d	A	THF	25	5	100	88 (*R*)
L4a	A	THF	25	5	100	97 (*S*)
L4b	A	THF	25	5	100	98 (*S*)
L4c	A	THF	25	5	100	88 (*S*)
L4d	A	THF	25	5	100	99 (*S*)
L3a	A	Toluene	0	1	100	93 (*R*)
L3b	A	Toluene	0	1	100	91 (*R*)
L4c	A	Toluene	0	1	100	76 (*S*)
L4d	A	Toluene	0	18	81	97(*S*)
L3a	B	THF	25	2	100	80 (*R*)
L3b	B	THF	25	2	100	84 (*R*)
L4c	B	THF	25	15	94	30 (*S*)
L4c	B	Toluene	25	15	55	35 (*S*)
L4d	B	THF	25	2	95	>99 (*S*)
L4d	B	Toluene	25	2	90	>99 (*S*)

Scheme 3. Effect of substituents on the 4-positions of the oxazoline ring on asymmetric allylic alkylations.



Ligand	Pd-Cat.	R_1	R_2	T (°C)	t (h)	Yield (%)	*ee* (%)
L6a	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	Ph	Me	0	16	80	98
L6b	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	Ph	Me	0	16	88	95
L6c	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	Ph	Me	0	16	95	98
L6d	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	Ph	Me	0	16	95	98
L6a	$Pd_2(dba)_3$	Me	*t*-Bu	25	48	90	55
L6b	$Pd_2(dba)_3$	Me	*t*-Bu	25	48	90	62
L6c	$Pd_2(dba)_3$	Me	*t*-Bu	25	48	80	63
L6d	$Pd_2(dba)_3$	Me	*t*-Bu	25	48	93	80
L6e	$Pd_2(dba)_3$	Me	*t*-Bu	25	48	77	82
L6f	$Pd_2(dba)_3$	Me	*t*-Bu	25	48	92	28
L6g	$Pd_2(dba)_3$	Me	*t*-Bu	25	48	71	51
L6h	$Pd_2(dba)_3$	Me	*t*-Bu	25	48	76	38

Scheme 4. Applications of JM-Phos in asymmetric allylic alkylations.



Ligand	R_1	R_2	T (°C)	*ee* (%)
L7a	Ph	Me	20	80
L7b	Ph	Me	20	52
L7c	Ph	Me	20	90
L7d	Ph	Me	20	67
L7e	Ph	Me	20	90
L7e	Ph	Me	0	96
L7a	Me	*t*-Bu	20	70
L7b	Me	*t*-Bu	20	-
L7c	Me	*t*-Bu	20	50
L7d	Me	*t*-Bu	20	11
L7e	Me	*t*-Bu	20	43

Scheme 5. Phosphinite–oxazoline P–N ligands used in asymmetric allylic alkylations.

3. Applications of P–N ligands in Pd-catalyzed reactions

All these modular ligands have been applied successfully in various Pd-catalyzed reactions such as asymmetric Tsuji, Heck, Suzuki, Sonogashira, Buchwald, Stille, and Hiyama coupling reactions under different reaction conditions.

3.1. Tsuji-Trost asymmetric allylic alkylation reactions

The 'Tsuji-Trost reaction' comprehended as 'Trost allylic alkylation' [16] was first introduced by Jirō Tsuji [17] in 1965 and, later in 1973, adapted by Barry Trost [18]. This reaction is expanded now to different nucleophiles, like active methylenes, enolates, amines, and phenols. The chiral phosphine ligands not only lead to improved reactivity but also provided high enantioselectivity and diastereoselectivity under milder reaction conditions. The mild reaction conditions with high selectivity greatly expand the effectiveness of this reaction in both pharmaceuticals as well as natural product synthesis [19]. Today various P–N-based based ligands were applied for this reaction.

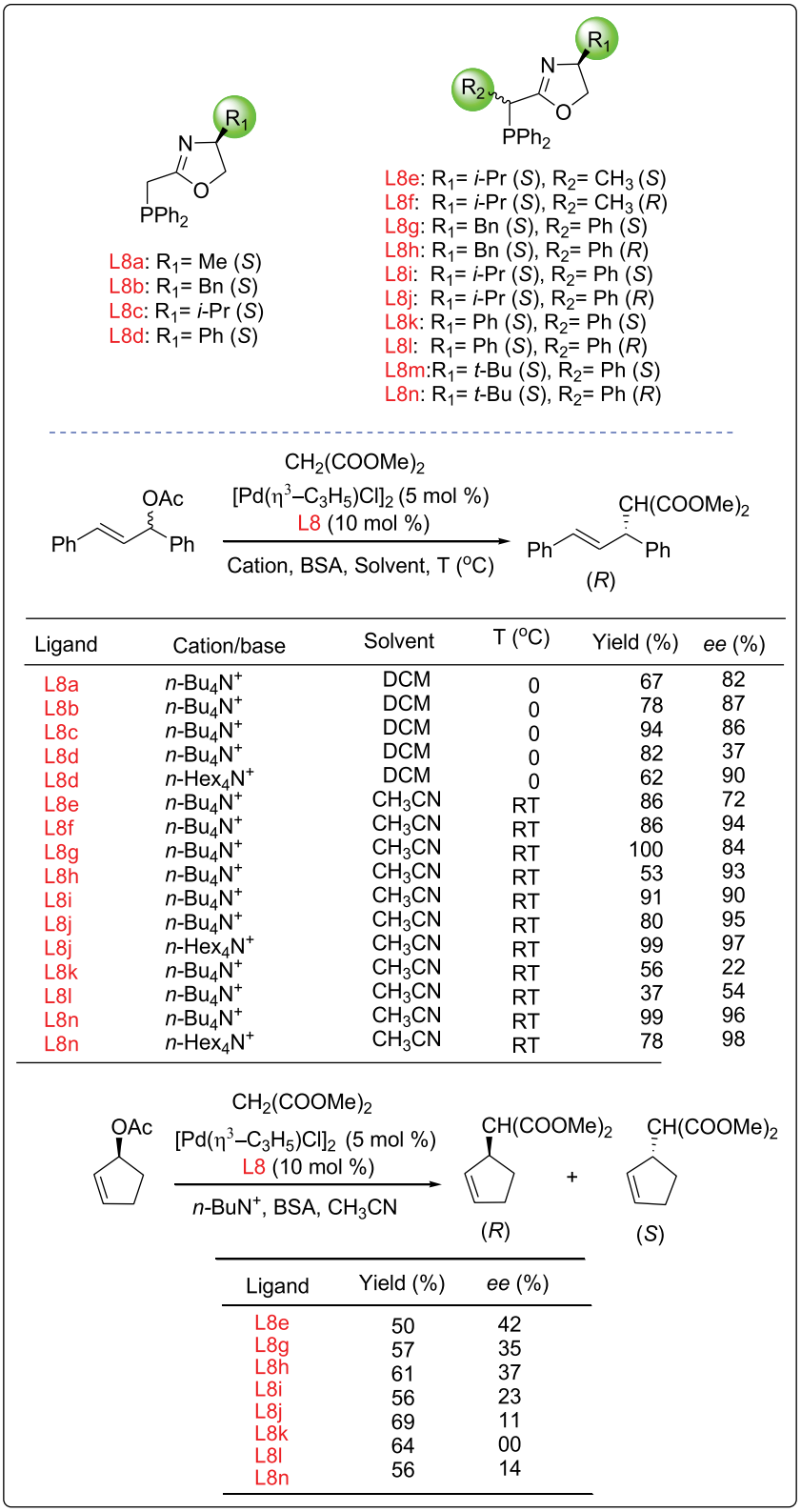
The chiral oxazolines called 'Phosphinooxazoline (PHOX)' ligands have an outstanding ability to differentiate the two allylic termini in Pd-catalyzed allylic alkylation reactions hence these ligands are widely used as 'spectator' ligands [20]. In addition, these tailor-made ligands can be readily accessible from various naturally occurring chiral amino alcohols and achieve a wide range of regio and diastereoselectivities [21].

The following different factors determine regioselectivity and diastereoselectivity in allylic alkylation reactions.

a) Initial conformation of the allylic component.
b) The nature of its leaving group.
c) Conformations of the intermediate allylic Pd complexes.
d) The hardness of the nucleophile.
e) Electronic and steric properties of the ligands bound to the Pd center.

The traditional C_2 symmetric chelate diphosphines such as CHIRAPHOS and BINAPs were not well suited for allylic alkylation reactions. Hence the C_2 symmetric PHOX ligands having a wide bite angle showed good to excellent enantioselectivity. The PHOX ligands with P and N donor atoms have distinctly different π-acceptor strengths. Due to the contrasting 'trans' effects of P and N atoms, a nucleophilic attack on the allyl palladium complexes of PHOX ligands was well controlled. Various derivatives of PHOX can be easily obtained due to the modular nature of the PHOX ligands (Fig. 3). Hence, it is possible to fine-tune to optimize the ligand structures and substrates to give satisfactory results.

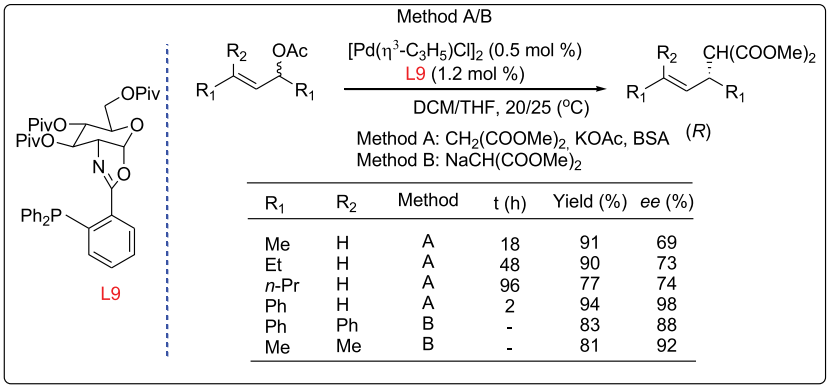
In this regard, the PHOX ligands were first introduced independently by Pfaltz (**L1a-f**), Helmchen (**L1c, L1g**, and **L1h**), and Williams (**L1a-e**) as highly effective C_2 symmetric ligands for asymmetric allylic alkylation reactions [22]. All the ligands showed very high enantioselectivity (up to 99%) for alkylation of racemic 1,3-diphenyl-2-propenyl acetate



Ligand	Cation/base	Solvent	T (°C)	Yield (%)	*ee* (%)
L8a	*n*-Bu_4N^+	DCM	0	67	82
L8b	*n*-Bu_4N^+	DCM	0	78	87
L8c	*n*-Bu_4N^+	DCM	0	94	86
L8d	*n*-Bu_4N^+	DCM	0	82	37
L8d	*n*-Hex_4N^+	DCM	0	62	90
L8e	*n*-Bu_4N^+	CH_3CN	RT	86	72
L8f	*n*-Bu_4N^+	CH_3CN	RT	86	94
L8g	*n*-Bu_4N^+	CH_3CN	RT	100	84
L8h	*n*-Bu_4N^+	CH_3CN	RT	53	93
L8i	*n*-Bu_4N^+	CH_3CN	RT	91	90
L8j	*n*-Bu_4N^+	CH_3CN	RT	80	95
L8j	*n*-Hex_4N^+	CH_3CN	RT	99	97
L8k	*n*-Bu_4N^+	CH_3CN	RT	56	22
L8l	*n*-Bu_4N^+	CH_3CN	RT	37	54
L8n	*n*-Bu_4N^+	CH_3CN	RT	99	96
L8n	*n*-Hex_4N^+	CH_3CN	RT	78	98

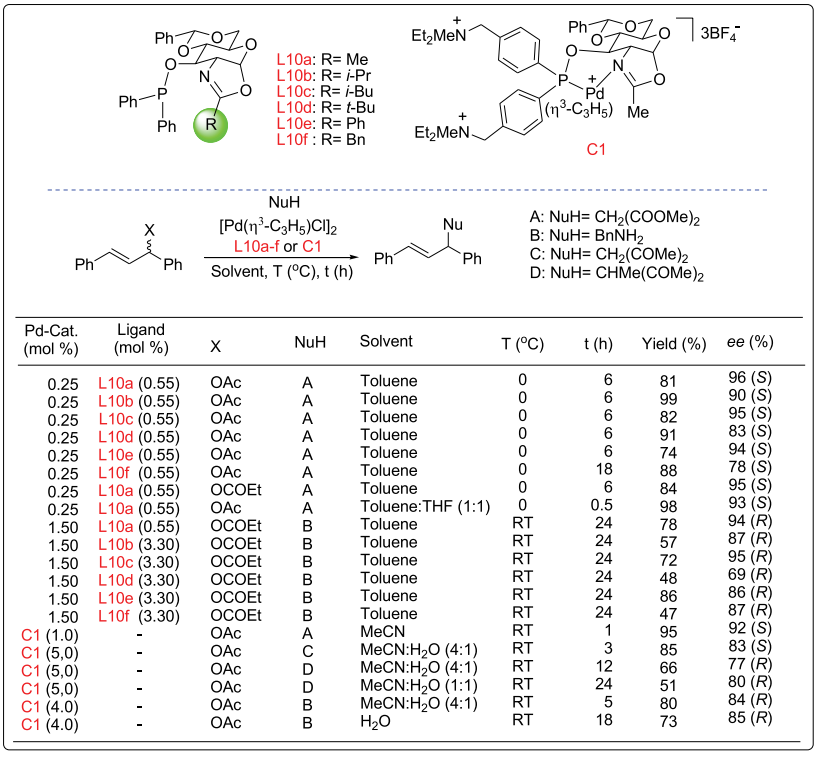
Ligand	Yield (%)	*ee* (%)
L8e	50	42
L8g	57	35
L8h	61	37
L8i	56	23
L8j	69	11
L8k	64	00
L8l	56	14
L8n		

Scheme 6. PHOX ligands containing one and two chiral centers used in asymmetric allylic alkylations.



R_1	R_2	Method	t (h)	Yield (%)	*ee* (%)
Me	H	A	18	91	69
Et	H	A	48	90	73
n-Pr	H	A	96	77	74
Ph	H	A	2	94	98
Ph	Ph	B	-	83	88
Me	Me	B	-	81	92

Scheme 7. Phosphino-α-D-glucopyrano-oxazoline ligand for asymmetric allylic alkylations.



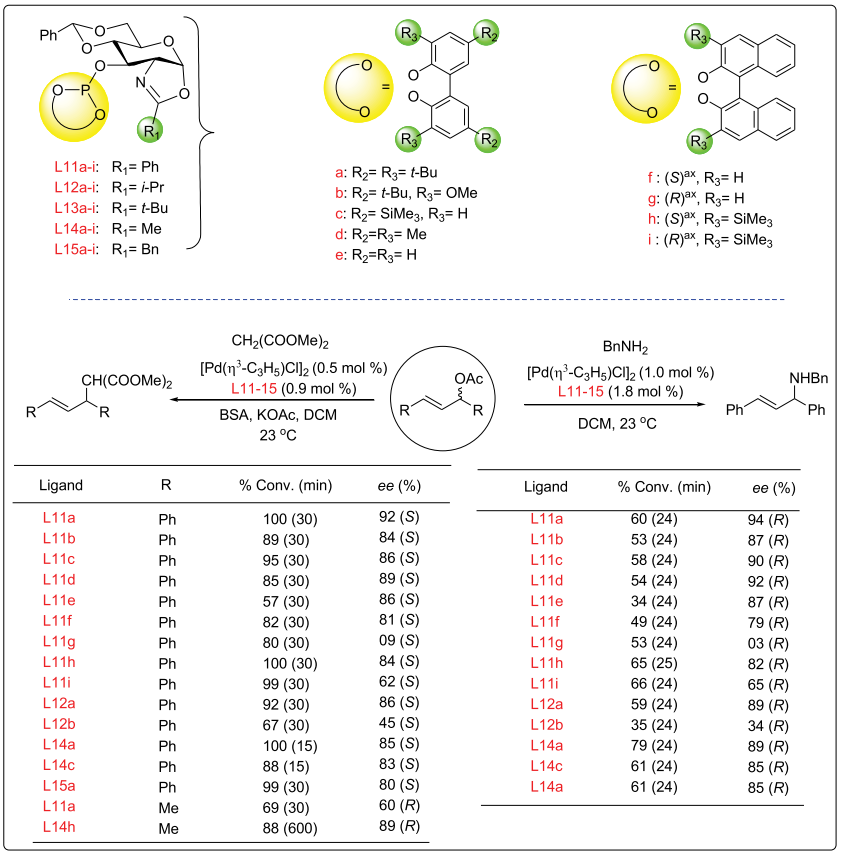
Pd-Cat. (mol %)	Ligand (mol %)	X	NuH	Solvent	T (°C)	t (h)	Yield (%)	*ee* (%)
0.25	L10a (0.55)	OAc	A	Toluene	0	6	81	96 (*S*)
0.25	L10b (0.55)	OAc	A	Toluene	0	6	99	90 (*S*)
0.25	L10c (0.55)	OAc	A	Toluene	0	6	82	95 (*S*)
0.25	L10d (0.55)	OAc	A	Toluene	0	6	91	83 (*S*)
0.25	L10e (0.55)	OAc	A	Toluene	0	6	74	94 (*S*)
0.25	L10f (0.55)	OAc	A	Toluene	0	18	88	78 (*S*)
0.25	L10a (0.55)	OCOEt	A	Toluene	0	6	84	95 (*S*)
0.25	L10a (0.55)	OAc	A	Toluene:THF (1:1)	0	0.5	98	93 (*S*)
1.50	L10a (0.55)	OCOEt	B	Toluene	RT	24	78	94 (*R*)
1.50	L10b (3.30)	OCOEt	B	Toluene	RT	24	57	87 (*R*)
1.50	L10c (3.30)	OCOEt	B	Toluene	RT	24	72	95 (*R*)
1.50	L10d (3.30)	OCOEt	B	Toluene	RT	24	48	69 (*R*)
1.50	L10e (3.30)	OCOEt	B	Toluene	RT	24	86	86 (*R*)
1.50	L10f (3.30)	OCOEt	B	Toluene	RT	24	47	87 (*R*)
C1 (1.0)	-	OAc	A	MeCN	RT	1	95	92 (*S*)
C1 (5,0)	-	OAc	C	MeCN:H_2O (4:1)	RT	3	85	83 (*S*)
C1 (5,0)	-	OAc	D	MeCN:H_2O (4:1)	RT	12	66	77 (*R*)
C1 (5,0)	-	OAc	D	MeCN:H_2O (1:1)	RT	24	51	80 (*R*)
C1 (4.0)	-	OAc	B	MeCN:H_2O (4:1)	RT	5	80	84 (*R*)
C1 (4.0)	-	OAc	B	H_2O	RT	18	73	85 (*R*)

Scheme 8. Chiral PHOX ligands from D-glucosamine for asymmetric allylic alkylations.

with dimethyl malonate or its Na salt in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.0-2.5 mol %) and KOAc-BSA in DCM or THF at room temperature (Scheme 1). The ligands **L1c** and **L1e** were also used for the Pd-catalyzed reaction of allyl acetates and Schiff base derivatives of α-amino phosphonates with good diastereoselectivities (up to 87:13) and enantioselectivities (> 96% *ee*) [23a]. Bunt et al. [23b] carried out the Hammett studies of PHOX ligands **L1i-m** in asymmetric allylic alkylation and amination reactions. It was observed that alkylation with Na salt of dimethylmalonate resulted in only a small difference in the *ee*, nevertheless, amination with benzylamine gave a much wider variation in the *ee*.

Zang et al. [24] synthesized a new class of conformationally rigid PHOX ligands (**L2a-d**) *via* an efficient *ortho*-substitution of phenyl glycinol. All the ligands (5 mol %) except **L2b** showed 86–97% yields with high enantioselectivity (93–97% *ee*) in the asymmetric allylic alkylation reactions of 1,3-diphenyl-2-propenyl acetate with Na salt of dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %), BSA, and KOAc in DCM at room temperature (Scheme 2). It was observed that for ligand **L2a**, lowering the reaction temperature from RT to 0 °C, moderates the product yield from 97% to 85% as well as enantioselectivity from 93% to88 %. On the other hand, an increased temperature to 40 °C increased the yield to 97%, increasing enantioselectivity to 98%. Most interestingly, lowering the Pd loading to 0.1 mol % and 0.2 mol % decreased the yield to 73%, nevertheless, the enantioselectivity remains the same (98% *ee*).

In asymmetric metal catalysis, efficient transfer of chirality and control of the absolute configuration of new stereocenters depends on the ligands' properties. The bisoxazoline ligands containing 4-hydroxy benzyl and 4-methoxybenzyl substituents with the same stereochemistry provided the opposite absolute configuration of the alkylation



Ligand	R	% Conv. (min)	*ee* (%)
L11a	Ph	100 (30)	92 (*S*)
L11b	Ph	89 (30)	84 (*S*)
L11c	Ph	95 (30)	86 (*S*)
L11d	Ph	85 (30)	89 (*S*)
L11e	Ph	57 (30)	86 (*S*)
L11f	Ph	82 (30)	81 (*S*)
L11g	Ph	80 (30)	09 (*S*)
L11h	Ph	100 (30)	84 (*S*)
L11i	Ph	99 (30)	62 (*S*)
L12a	Ph	92 (30)	86 (*S*)
L12b	Ph	67 (30)	45 (*S*)
L14a	Ph	100 (15)	85 (*S*)
L14c	Ph	88 (15)	83 (*S*)
L15a	Ph	99 (30)	80 (*S*)
L11a	Me	69 (30)	60 (*R*)
L14h	Me	88 (600)	89 (*R*)

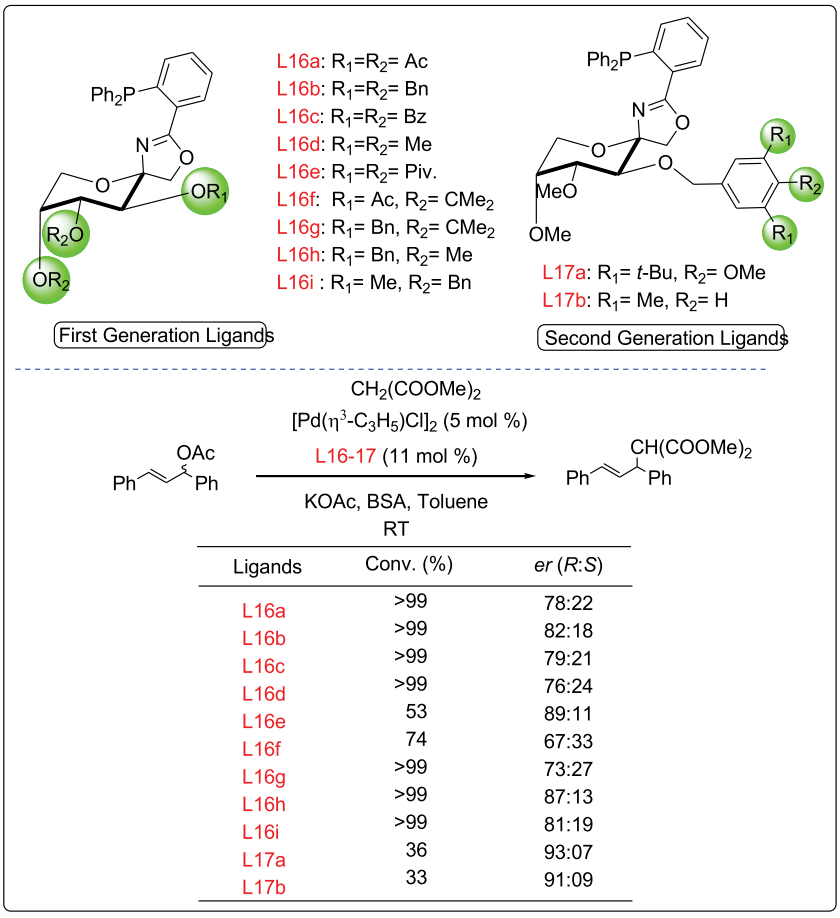
Ligand	% Conv. (min)	*ee* (%)
L11a	60 (24)	94 (*R*)
L11b	53 (24)	87 (*R*)
L11c	58 (24)	90 (*R*)
L11d	54 (24)	92 (*R*)
L11e	34 (24)	87 (*R*)
L11f	49 (24)	79 (*R*)
L11g	53 (24)	03 (*R*)
L11h	65 (25)	82 (*R*)
L11i	66 (24)	65 (*R*)
L12a	59 (24)	89 (*R*)
L12b	35 (24)	34 (*R*)
L14a	79 (24)	89 (*R*)
L14c	61 (24)	85 (*R*)
L14a	61 (24)	85 (*R*)

Scheme 9. A family of carbohydrate-based phosphite-oxazoline ligands for asymmetric allylic alkylations.

products [25]. It is due to the interaction of a hydroxy group of the ligand with the nucleophile *via* hydrogen bonding [26]. Similarly, due to the hydrogen bonding, different enantioselectivities were shown by 2-(1-hydroxyalkyl) and 2-(1-alkoxyalkyl)pyridinooxazolines in allylic alkylation reactions [27]. The effect of hydrogen bonding on selectivity was studied by applying several PHOX ligands containing (1-hydroxy-1-phenyl)methyl (**L3a-d**) and (1-methoxy-1-phenyl)methyl (**L4a-d**) substituents at the 4-positions of the oxazoline ring in allylic alkylations [28]. The conformational preferences and enantiodiscrimination of these ligands were also studied for the reactions of 1,3-diphenyl-2-propenyl acetate and 3-cyclohexenyl with dimethyl malonate and acetylacetone using $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2 mol %) in THF or Toluene at 0 °C (Scheme 3). Both types of ligands showed different enantioselectivities for alkylations of 1,3-diphenyl-2-propenyl acetate with malonate and acetylacetone. This enantiodiscrimination was arising due to the different conformations of the methoxy-containing ligands. The exo-allyl complex containing the methoxy-group resulted in the most stable conformation, leading to products with an *S* configuration, while, the two Pd(0)-olefin complexes originating from exo-allyl and endo-allyl complexes containing a hydroxy group of similar energy, lead to the enantioselectivity. Consequently, the catalysts with the methoxy-containing ligand provided products with high enantioselectivity compared to a hydroxyl-containing ligand. The presence of a hydrogen bond with Pd(0) as the proton acceptor in the hydroxy-containing olefin-Pd(0) complexes induces a conformational change in the ligand leading to different stereoselectivity as analyzed by DFT calculations.

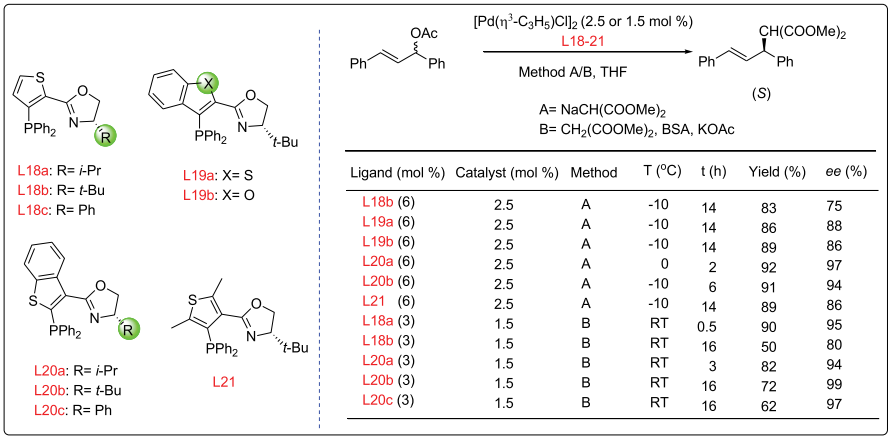
Burgess and coworkers developed a series of PHOX ligands (JM-Phos) (**L5a-m** and **L6a-h**) and successfully used them in Pd-catalyzed allylic alkylation reactions. First-generation ligands **L5a-m** were prepared *via* a divergent synthesis involving the pivotal intermediate and phosphine-substituted amino alcohols (Scheme 4) [29]. The correlation between the nature of substituent (R) of ligand and asymmetric induction in allylation was achieved by using high-throughput screening. Ligands **L5a-m** were screened in the parallel reactor by reacting 1, 3-diphenyl-2-propenyl acetate and dimethyl malonate using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, BSA, and KOAc under different reaction conditions. It showed that DCM was the best solvent as it gave the highest selectivities. However, toluene and THF were better solvents for the pentafluorophenyl ligand (**L5m**). The aryl rings with electron-donating *para* substituents (4-Me and 4-OMe) showed higher enantioselectivities (up to 82% *ee*) than electron-withdrawing substituents (4-NO_2 and C_6F_5). Thus, the high enantiodiscriminations seem to be facilitated by electron-rich oxazoline substituents. It was also observed that the size and shape of the substituent has more significant effects than the electronic features as the pseudo-spherical adamantyl ligand **L5e** was superior (94% *ee*), to the smaller methyl-substituted ligand **L5a** (53% *ee*). The enantiomeric excess was reversed to -6% for the triphenylmethyl-substituted ligand **L5d**. It was revealed that in asymmetric reactions, the substituent topography can be more relevant than size.

They developed the second generation **L6a-d** [30] and **L6e-h** [31] ligands containing fairly conformationally flexible ethylene linkers for Pd-catalyzed allylation reactions using a multiwall reactor. The



Ligands	Conv. (%)	*er* (*R*:*S*)
L16a	>99	78:22
L16b	>99	82:18
L16c	>99	79:21
L16d	>99	76:24
L16e	53	89:11
L16f	74	67:33
L16g	>99	73:27
L16h	>99	87:13
L16i	>99	81:19
L17a	36	93:07
L17b	33	91:09

Scheme 10. Spiro-fused ligands derived from carbohydrates for asymmetric allylic alkylations.

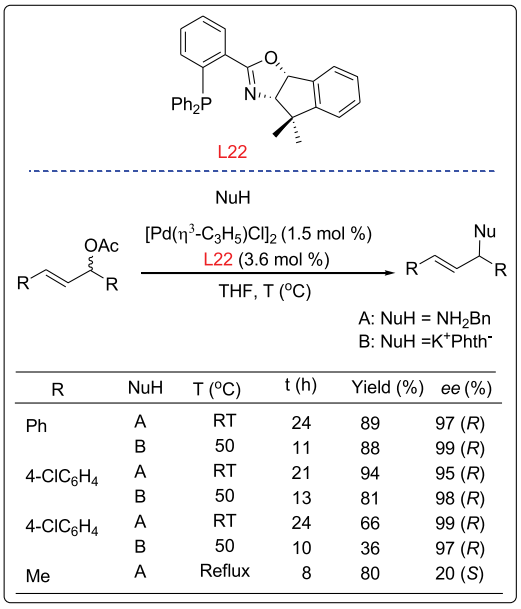


Ligand (mol %)	Catalyst (mol %)	Method	T (°C)	t (h)	Yield (%)	*ee* (%)
L18b (6)	2.5	A	-10	14	83	75
L19a (6)	2.5	A	-10	14	86	88
L19b (6)	2.5	A	-10	14	89	86
L20a (6)	2.5	A	0	2	92	97
L20b (6)	2.5	A	-10	6	91	94
L21 (6)	2.5	A	-10	14	89	86
L18a (3)	1.5	B	RT	0.5	90	95
L18b (3)	1.5	B	RT	16	50	80
L20a (3)	1.5	B	RT	3	82	94
L20b (3)	1.5	B	RT	16	72	99
L20c (3)	1.5	B	RT	16	62	97

Scheme 11. HetPHOX based on thiophene and benzothiophene for asymmetric allylic alkylations.

second-generation ligands were superior to the first-generation ligands. The less likely ring-opening complexes of ligand **L6** hurt the enantioselectivity. The ligands **L6a-d** (2.5 mol %) showed an excellent *ee* (>95%) for the reaction of 1,3-diphenyl-2-propenyl acetate and dimethyl malonate using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, BSA, and KOAc in DCM at 25 °C. While the ligand **L6e** gave a 77% yield with 82% *ee* for the allylation reaction of 1,3-dimethyl-2-propenyl pivalate and dimethyl malonate in the presence of $Pd_2(dba)_3$ under similar reaction conditions. The ligand **L6a** was excellent in terms of the yield and enantioselectivity for the allylation of 1,3-diphenyl-2-propenyl acetate with 3-((*Z*)-1-trimethylsilyloxypro-1-enyl)-2-oxazolidone silyl enolate at 0 °C.

Similarly, Jones and Richards [32] utilized new phosphinite-–oxazoline ligands (**L7a-e**) (6 mol %) in the allylic alkylation reaction of racemic propenyl substrates with dimethyl malonate in the presence of



R	NuH	T (°C)	t (h)	Yield (%)	*ee* (%)
Ph	A	RT	24	89	97 (*R*)
	B	50	11	88	99 (*R*)
4-ClC_6H_4	A	RT	21	94	95 (*R*)
	B	50	13	81	98 (*R*)
4-ClC_6H_4	A	RT	24	66	99 (*R*)
	B	50	10	36	97 (*R*)
Me	A	Reflux	8	80	20 (*S*)

Scheme 12. Indanol-based PHOX ligand for asymmetric allylic alkylations.

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %), BSA, and KOAc in DCM at 20°C (Scheme 5). The ligands were obtained from (*S*)-serine methyl ester and different acid chlorides (RCOCl). The ligands containing relatively small ferrocenyl (**L7c**) or phenyl (**L7e**) groups showed excellent enantioselectivity. The reaction at 0 °C using ligand **L7e** showed slightly increased selectivity (96%). All these results revealed that shifting alkyl diaryl phosphine ligands (**L6**) to structurally similar diarylphosphinite ligands (**L7**) does not change the selectivity or sense of asymmetric induction. However, the conformationally locked nature of phosphinite does not necessarily require for high selectivity.

Gilbertson and Chan [33] developed a modular route for the synthesis of PHOX ligands containing one (**L8a-d**) and two (**L8e-n**) chiral centers from amino acids and phosphino carboxylate building blocks. All these ligands (10 mol %) were tested in the asymmetric alkylation of 1, 3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol %), BSA (Scheme 6).

It was observed that the ligands derived from phenylalanine (**L8b**) and valine (**L8c**) gave the 87% and 86% *ee* in the presence of Bu_4N^+-BSA cation base combination in DCM at 0°C. While the highest enantioselectivity (90% *ee*) was attained using **L8d** in the presence of *n*-Hex_4N^+-BSA. Moreover, except ligands **L8k** and **L8l**, all other ligands containing two chiral centers (**L8e-n**) with an *R, S* configuration were found to be the most selective ligand in acetonitrile. The 42% *ee* was obtained for the ligands **L8e** in allylation of 2-cyclopentenyl acetate with dimethyl malonate in acetonitrile. A chiral center next to the phosphine has little effect on the selectivity of the reaction.

Recently, carbohydrates have evoked much attention as the chiral backbone in many asymmetric transformations [34]. In the Pd-catalyzed asymmetric allylic substitution reactions, the D-Glucosamine-derived chiral PHOX ligands are the best as it provides a chiral environment for catalysts. [35]. In this regard, Kunz et al. [36] synthesized a new enantiomerically pure phosphine-α-D-glucopyrano-oxazoline ligand (**L9**) (Scheme 7). The ligand synthesis involves the N-acylation of glucosamine with 2-fluoro benzoyl chloride, which on O-pivaloylatation gave α-D-glucopyranosyl bromide [37]. These on treatment with Et_4NBr gave 2-(2-fluorophenyl)-oxazoline, which reacts with potassium diphenylphosphine and delivered the desired ligand **L9**. The $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**L9** (0.5:1.2 mol %) catalytic system gave high yields (up to 94%) and enantioselectivity (up to 98% *ee*) for reactions of substituted allyl acetates with dimethyl malonate in presence of BSA and KOAc in THF at 25 °C. The catalytic system also coupled substituted allyl acetates with Na-malonate in DCM at 20 °C with high yields (83%) and enantioselectivity (up to 92% *ee*).

Next, Uemura and coworkers reported the detailed work on novel chiral phosphinite–nitrogen PHOX ligands (**L10a**−**f**) derived from commercially available D-glucosamine hydrochloride [38]. When applied to Pd-catalyzed asymmetric allylic alkylation and amination reactions of 1,3-diphenyl 2-propenyl acetate, a high level of enantioselectivity was obtained in the presence of BSA, KOAc in toluene at 0 °C (Scheme 8).

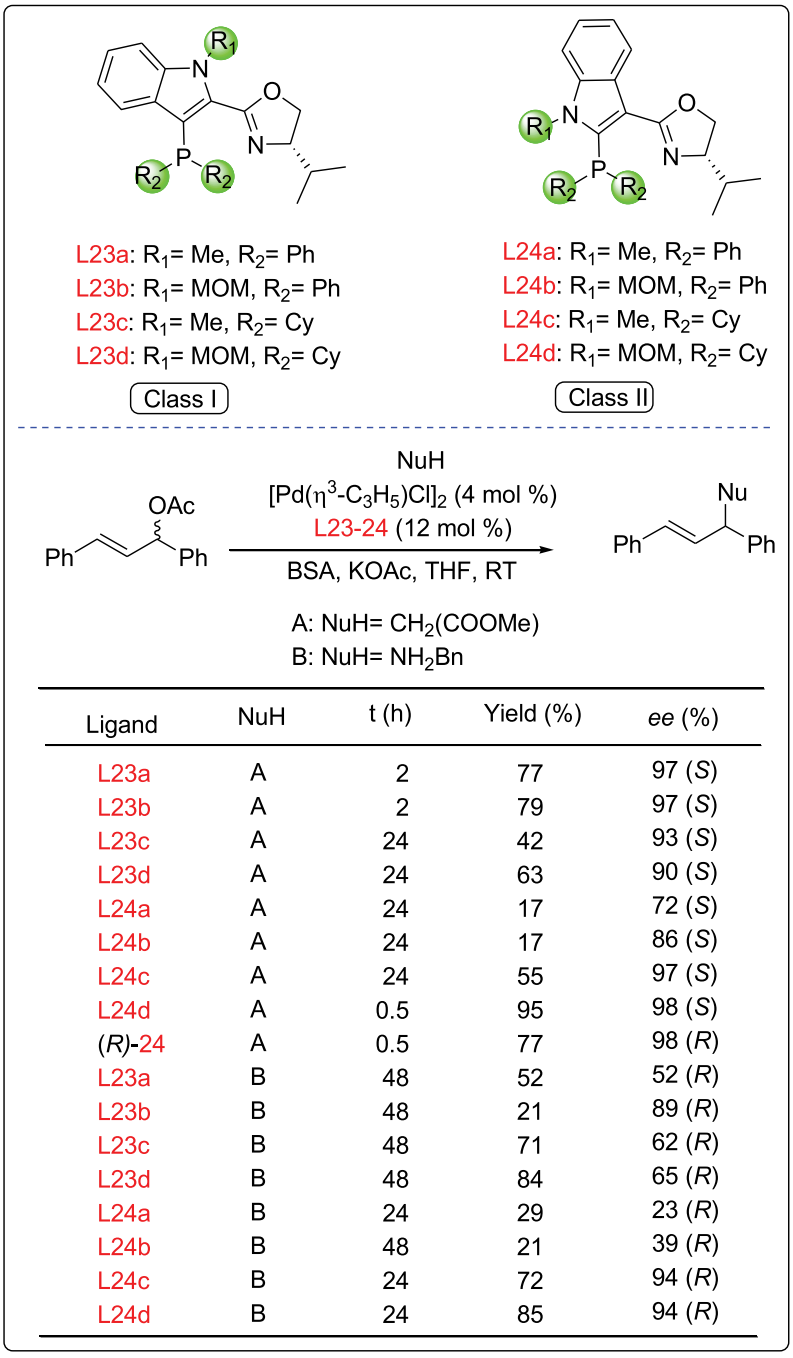
The activity was higher for less sterically demanding substituents present on oxazoline. The activity order was Me>Ph>*i*-Pr>*t*-Bu, and the ligand **L10a** (0.55 mol %) containing the smallest substituent on oxazoline furnished the highest *ee* (96%). Furthermore, the ligand **L10a** was also effective for the amination of ethyl 1,3-diphenylprop-2-enyl carbonate showing 94% *ee*. In the allylic alkylation of 3-acetoxycyclohexene, the $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**L10a** (1.1:0.5 mol %) catalytic system showed the highest enantioselectivity (74% *ee*) with dimethyl malonate in the presence of BSA, KOAc in THF at 0 °C.

The Pd-CarboPHOX (**C1**) containing amphiphilic ligand (**L10a**) having the diethylamino methyl group at the 4-position of the phenyl ring on the phosphorus atom [39] showed up to 92% *ee* in the reaction of 1,3-diphenyl-2-propenyl acetate with dimethylmalonate in acetonitrile, 83% *ee* for acetylacetone in MeCN:H_2O (4:1), and up to 85% *ee* for benzylamine in MeCN:H_2O (4:1) mixture. The catalytic system could be separated easily by simple acid-base extraction and reused at least two times.

Though the ligands **L9** and **L10** are ineffective in allylic substitution of the hindered 1,3-diphenyl-2-propenyl acetate, they showed low enantioselectivity for unhindered cyclic and linear substrates. In this regard, Dieguez and coworkers [40] reported a new family of carbohydrate-based phosphite-oxazoline ligands (**L11-L15**) for allylic substitution reactions. These ligands contain a phosphite group instead of a phosphinite group.

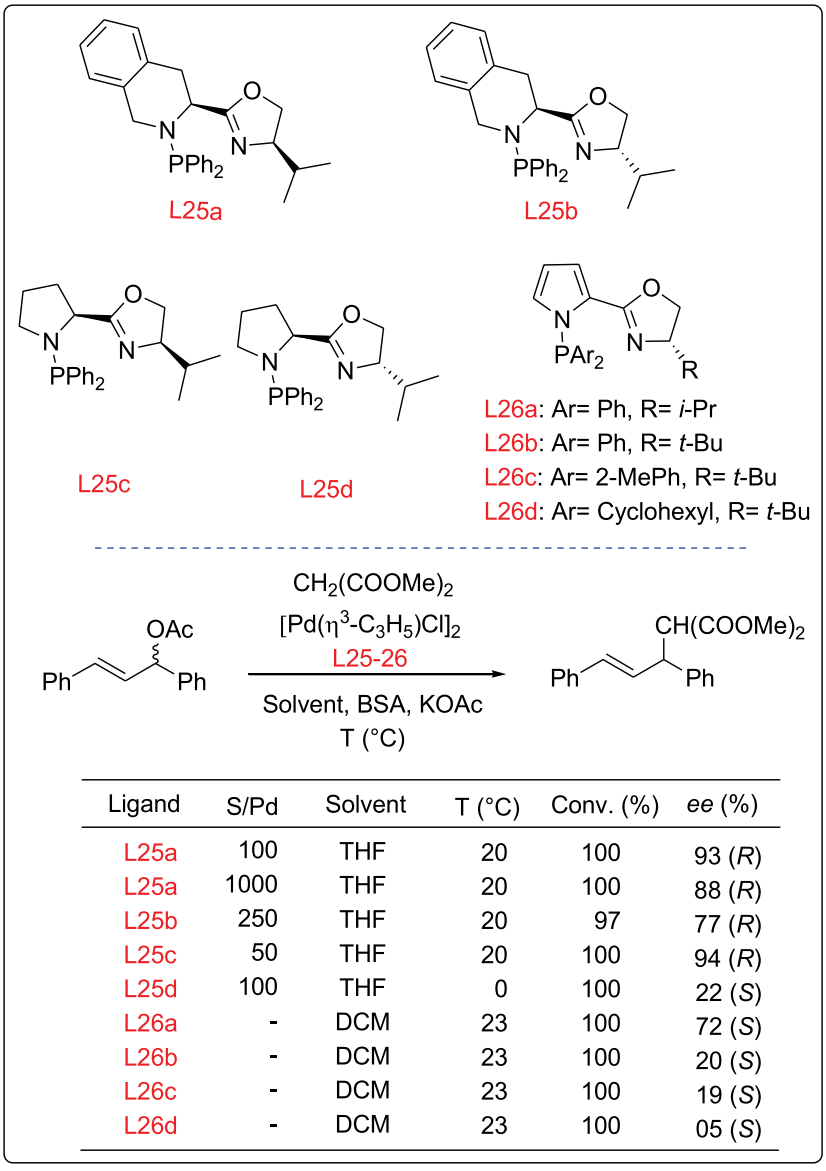
The incorporation of a phosphite moiety into the ligand offers the following advantages. (i) The bulky biphenyl phosphite provides a larger bite angle than phosphinites. (ii) The biphenyl moiety offers more flexibility and can be used to fine-tune the chiral pocket formed upon the complexation of substrates. (iii) Incorporating a phosphite moiety also decreases substrate specificity because the chiral pocket in which the allyl moiety embedded is smaller than for ligands **L9**, but flexible enough to allow the perfect coordination of both hindered and unhindered substrates. (iv) These ligands provide more flexibility that can be finely tuned by phosphite and oxazoline substituents to explore their effect on the catalytic performance. (v) The rate of reaction increases because of the high π-acceptor capacity of the phosphite moiety. (vi) The regioselectivity towards the desired branched isomer in monosubstituted linear substrates increases because the π-acceptor capacity of the phosphite moiety enhances the S_N1 character of the nucleophilic attack.

The ligands were prepared by reacting the corresponding sugar oxazoline-alcohols obtained from D-glucosamine with the corresponding biaryl phosphorochloridite in the presence of pyridine [41]. All the ligands were analyzed by elemental analyses, ^1H, ^{13}C, and ^{31}P NMR spectroscopy. All the ligands (0.9 mol %) were screened for the allylic substitution reactions of 1,3-diphenyl 2-propenyl acetate with dimethyl



Ligand	NuH	t (h)	Yield (%)	*ee* (%)
L23a	A	2	77	97 (*S*)
L23b	A	2	79	97 (*S*)
L23c	A	24	42	93 (*S*)
L23d	A	24	63	90 (*S*)
L24a	A	24	17	72 (*S*)
L24b	A	24	17	86 (*S*)
L24c	A	24	55	97 (*S*)
L24d	A	0.5	95	98 (*S*)
(*R*)-24	A	0.5	77	98 (*R*)
L23a	B	48	52	52 (*R*)
L23b	B	48	21	89 (*R*)
L23c	B	48	71	62 (*R*)
L23d	B	48	84	65 (*R*)
L24a	B	24	29	23 (*R*)
L24b	B	48	21	39 (*R*)
L24c	B	24	72	94 (*R*)
L24d	B	24	85	94 (*R*)

Scheme 13. IndPHOX ligands used in the asymmetric allylic alkylations.



Ligand	S/Pd	Solvent	T (°C)	Conv. (%)	*ee* (%)
L25a	100	THF	20	100	93 (*R*)
L25a	1000	THF	20	100	88 (*R*)
L25b	250	THF	20	97	77 (*R*)
L25c	50	THF	20	100	94 (*R*)
L25d	100	THF	0	100	22 (*S*)
L26a	-	DCM	23	100	72 (*S*)
L26b	-	DCM	23	100	20 (*S*)
L26c	-	DCM	23	100	19 (*S*)
L26d	-	DCM	23	100	05 (*S*)

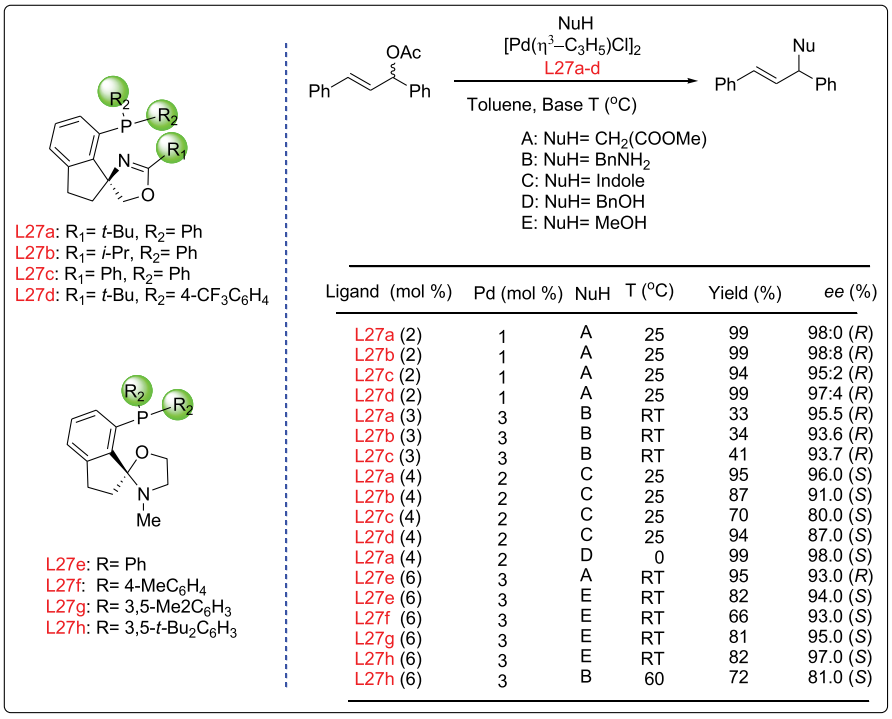
Scheme 14. AminPHOX ligands for asymmetric allylic alkylations.

malonate and benzylamine in the presence $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.5 mol %), BSA, and KOAc as a base in DCM at 23 °C (Scheme 9).

Thus, the ligand **L11a** (0.9 mol %) containing the *t*-butyl group present at both the *ortho* and *para* positions of the biphenyl-phosphite moiety showed the highest activity (100% conversion) as well as enantioselectivity (92% *ee*) for dimethyl malonate in 30 min. The enantioselectivity of **L11a** was further increased by lowering the temperature to 0°C (95%) and changing the solvent from DCM to toluene with increased Pd loading to 2.0 mol % (99%) in 6 h. When the excess of a ligand is present, the phosphite-oxazoline ligand acts as a monodentate ligand. Excellent enantioselectivity was acquired by using the ligand-to-palladium ratio of 0.9. Though, 94% enantioselectivity was observed for benzylamine the activity was lower (60%) than the alkylation reaction of dimethyl malonate in the presence of 1.0 mol % Pd and 1.8 mol % ligands. As compared to other substituents, a phenyl substituent on the oxazoline ring (**L11a**) showed the highest enantioselectivity (99% *ee*). These results are in contrast with the ligand **L10**, in which the oxazoline-containing methyl substituent showed the highest enantioselectivity. The activities of the ligands were affected by substituents at the *ortho* positions of the biphenyl moiety. While enantioselectivities were mainly affected by the substituents at the *para* positions of the biphenyl moiety. Thus, the best result was shown by ligand **L11a**, which contains the optimal combination of ligand parameters. The ligand **L14h** showed the best enantioselectivity (up to 89% *ee*) for less sterically demanding 1,3-dimethyl 2-propenyl acetate using dimethyl malonate as a nucleophile. Thus, ligand **L11a** (1.8 mol %) provided the best enantioselectivity (up to 91% *ee*) for the allylic substitution of unsymmetrical 1,1-diphenyl-1-hepten-3-yl acetate using dimethyl malonate as a nucleophile at 23 °C using 1 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$.

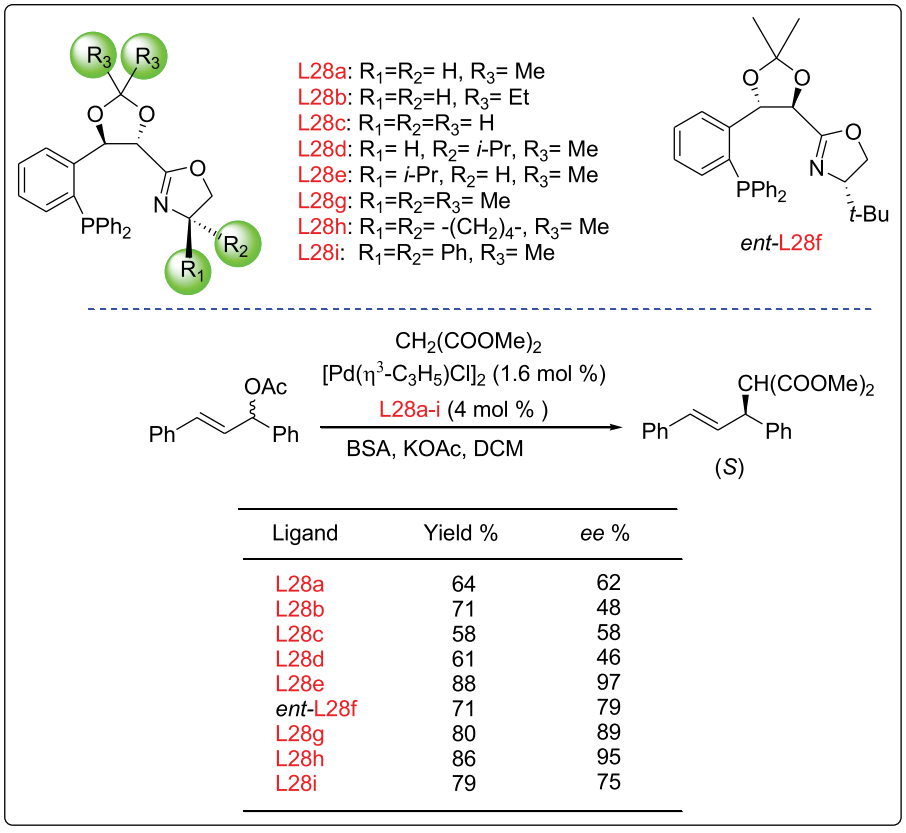
Ziegler and coworkers synthesized spiro-fused ligands containing diphenylphosphino groups (**L16a-i**) from D-fructose [42]. All the ligands showed good to excellent conversion of 1,3-diphenyl 2-propenyl acetate and dimethyl malonate into desired products with an er ranging from 76:24 to 84:16 in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, BSA, and KOAc in various solvents at 0 °C to room temperature (Scheme 10).

It was observed that the bulky substituent at the 3 position and small substituents at the 4 and 5 positions of fructose positively influence the stereoselectivity. The ligand containing pivaloyl groups (**L16e**) provided



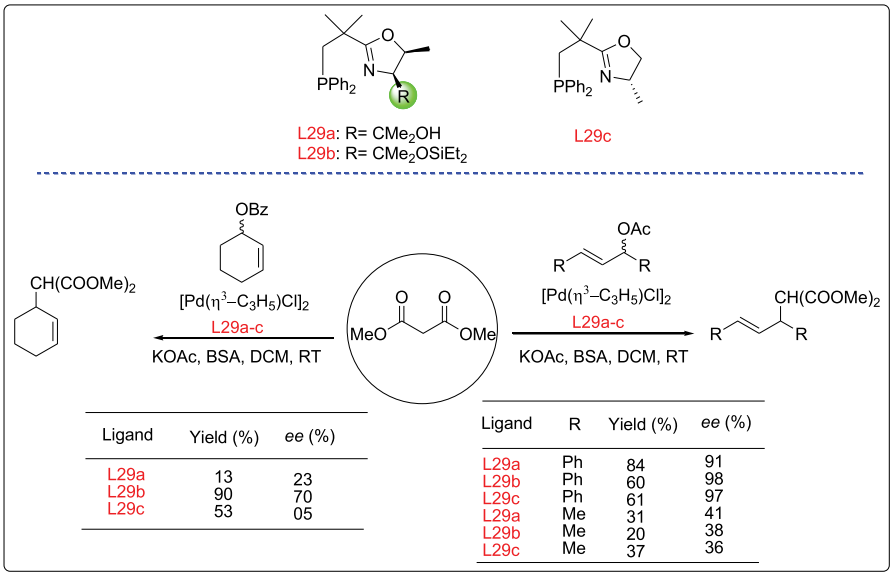
Ligand (mol %)	Pd (mol %)	NuH	T (°C)	Yield (%)	*ee* (%)
L27a (2)	1	A	25	99	98:0 (*R*)
L27b (2)	1	A	25	99	98:8 (*R*)
L27c (2)	1	A	25	94	95:2 (*R*)
L27d (2)	1	A	25	99	97:4 (*R*)
L27a (3)	3	B	RT	33	95.5 (*R*)
L27b (3)	3	B	RT	34	93.6 (*R*)
L27c (3)	3	B	RT	41	93.7 (*R*)
L27a (4)	2	C	25	95	96.0 (*S*)
L27b (4)	2	C	25	87	91.0 (*S*)
L27c (4)	2	C	25	70	80.0 (*S*)
L27d (4)	2	C	25	94	87.0 (*S*)
L27a (4)	2	D	0	99	98.0 (*S*)
L27e (6)	3	A	RT	95	93.0 (*R*)
L27e (6)	3	E	RT	82	94.0 (*S*)
L27f (6)	3	E	RT	66	93.0 (*S*)
L27g (6)	3	E	RT	81	95.0 (*S*)
L27h (6)	3	E	RT	82	97.0 (*S*)
L27h (6)	3	B	60	72	81.0 (*S*)

Scheme 15. SMIPHOX ligands used for asymmetric allylic amination, etherification reactions.



Ligand	Yield %	*ee* %
L28a	64	62
L28b	71	48
L28c	58	58
L28d	61	46
L28e	88	97
ent-L28f	71	79
L28g	80	89
L28h	86	95
L28i	79	75

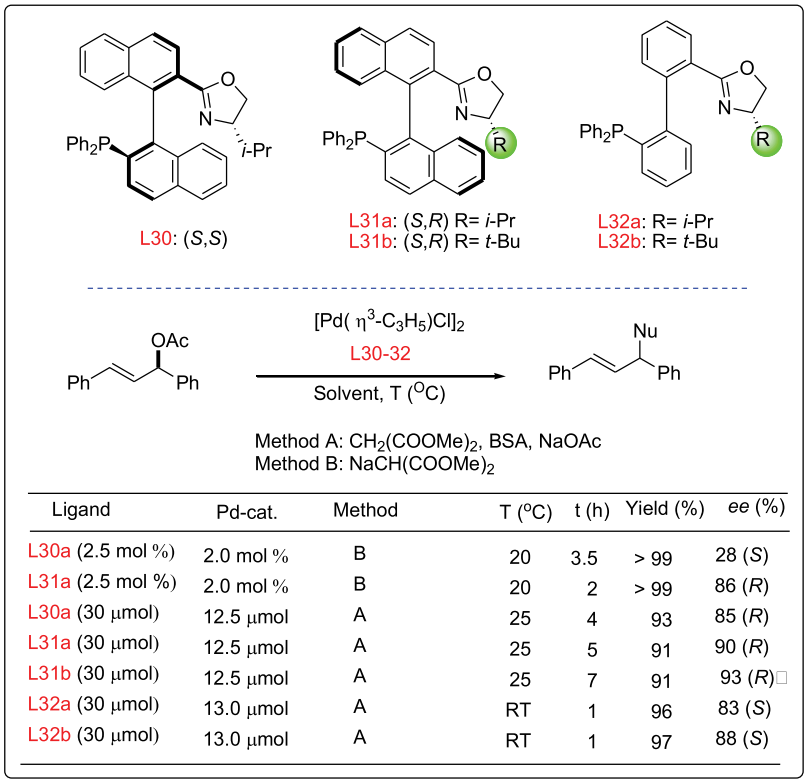
Scheme 16. StePHOX for asymmetric allylic alkylations.



Ligand	Yield (%)	*ee* (%)
L29a	13	23
L29b	90	70
L29c	53	05

Ligand	R	Yield (%)	*ee* (%)
L29a	Ph	84	91
L29b	Ph	60	98
L29c	Ph	61	97
L29a	Me	31	41
L29b	Me	20	38
L29c	Me	37	36

Scheme 17. NeoPHOX ligands for asymmetric allylic alkylations.



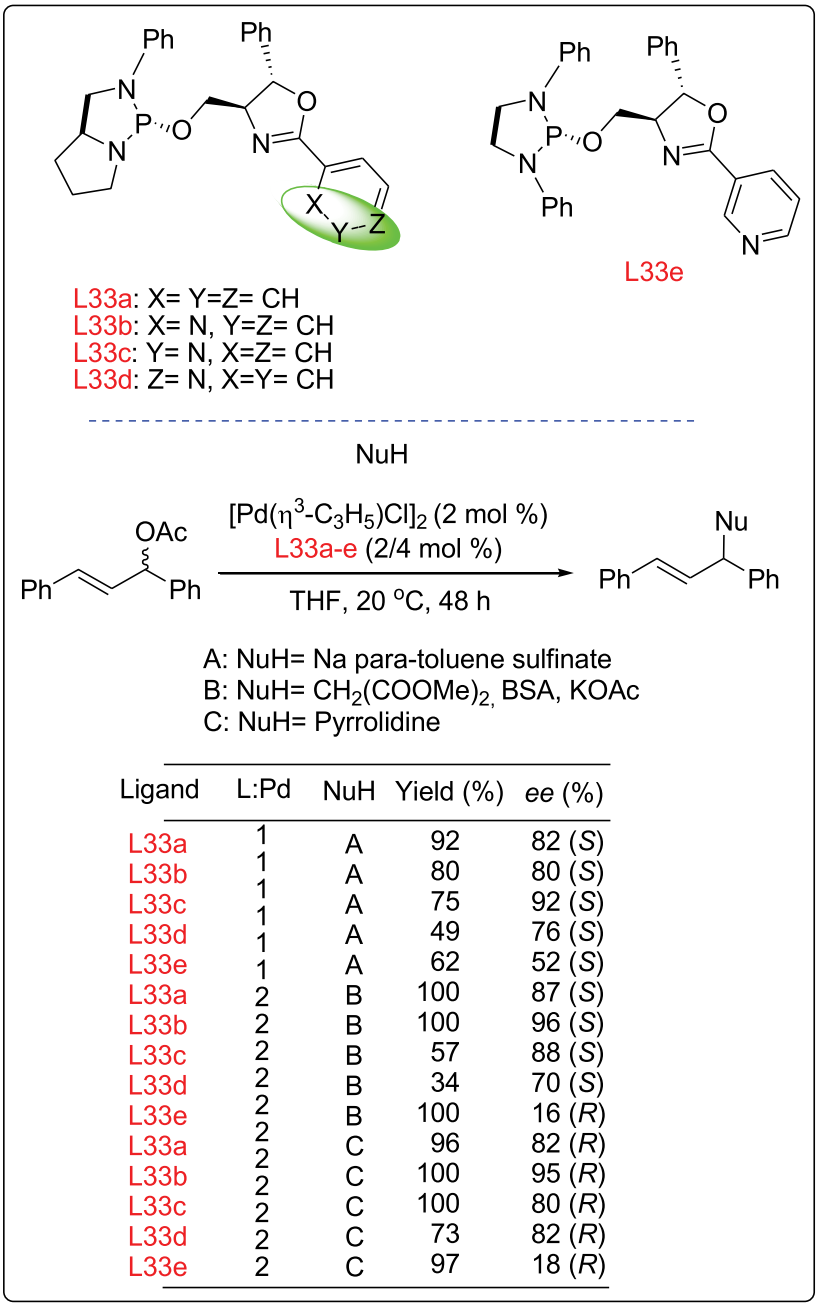
Ligand	Pd-cat.	Method	T (°C)	t (h)	Yield (%)	*ee* (%)
L30a (2.5 mol %)	2.0 mol %	B	20	3.5	> 99	28 (*S*)
L31a (2.5 mol %)	2.0 mol %	B	20	2	> 99	86 (*R*)
L30a (30 μmol)	12.5 μmol	A	25	4	93	85 (*R*)
L31a (30 μmol)	12.5 μmol	A	25	5	91	90 (*R*)
L31b (30 μmol)	12.5 μmol	A	25	7	91	93 (*R*)
L32a (30 μmol)	13.0 μmol	A	RT	1	96	83 (*S*)
L32b (30 μmol)	13.0 μmol	A	RT	1	97	88 (*S*)

Scheme 18. BinaPHOX ligands for asymmetric allylic alkylations.

an *er* ratio of 89:11 in toluene at room temperature. They developed a second-generation D-fructose-based spirofused PHOX ligands (**L17a-b**) having bulky benzyl groups at 3 positions of the fructose moiety. The ligands attained high *er* up to 93:7.

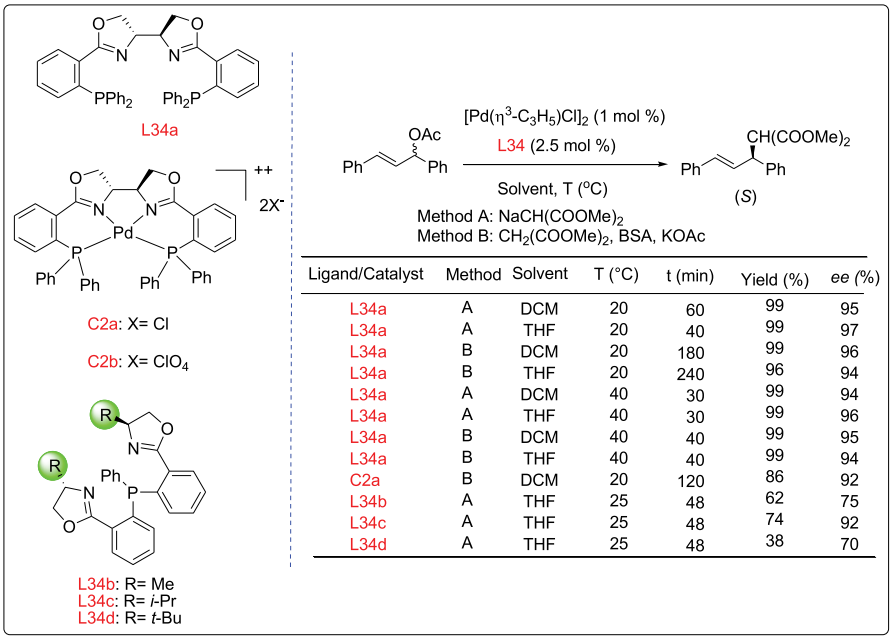
P-N ligands containing heterocycle PHOX (HetPHOX) such as Thio-PHOX, IndanolPHOX, IndPHOX, and AminPHOX have emerged as modular ligands in asymmetric catalysis. HetPHOX allows the easy introduction of the required diphenylphosphino groups on the ligand backbone. A series of HetPHOX based on thiophene and benzothiophene-oxazoline-containing ligands were reported for Pd-catalyzed asymmetric catalysis.

Tietze et al. [43a] and Cozzi et al. [43b] synthesized various chiral thiophene, benzothiophene, and benzofuran-based HetPHOX ligands (**L18-21**). In these ligands, substituents can be introduced at different positions either by direct metallation or by bromination followed by successive halogen metal exchange reactions. All the ligands (6 mol %)



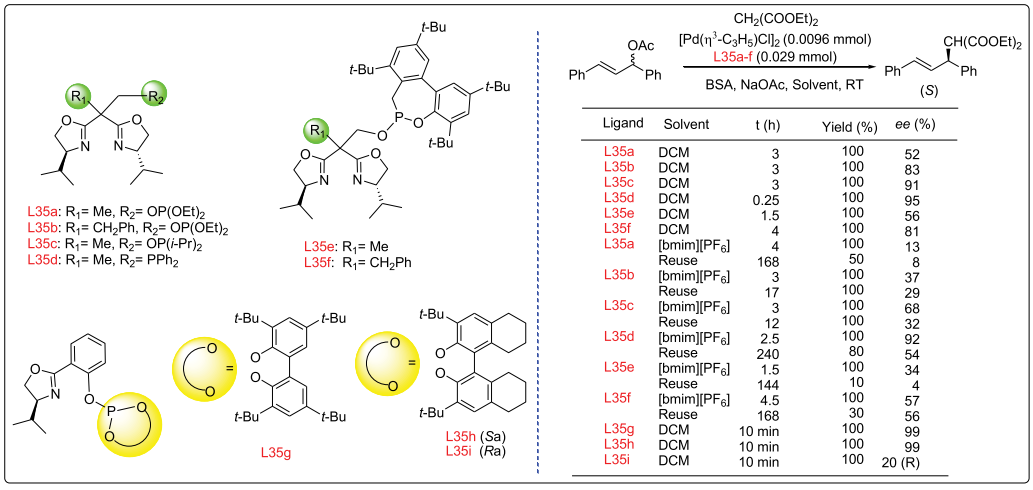
Ligand	L:Pd	NuH	Yield (%)	*ee* (%)
L33a	1	A	92	82 (*S*)
L33b	1	A	80	80 (*S*)
L33c	1	A	75	92 (*S*)
L33d	1	A	49	76 (*S*)
L33e	1	A	62	52 (*S*)
L33a	2	B	100	87 (*S*)
L33b	2	B	100	96 (*S*)
L33c	2	B	57	88 (*S*)
L33d	2	B	34	70 (*S*)
L33e	2	B	100	16 (*R*)
L33a	2	C	96	82 (*R*)
L33b	2	C	100	95 (*R*)
L33c	2	C	100	80 (*R*)
L33d	2	C	73	82 (*R*)
L33e	2	C	97	18 (*R*)

Scheme 19. N, N-diamidophosphite–oxazoline ligands for asymmetric allylic alkylations.



Ligand/Catalyst	Method	Solvent	T (°C)	t (min)	Yield (%)	*ee* (%)
L34a	A	DCM	20	60	99	95
L34a	A	THF	20	40	99	97
L34a	B	DCM	20	180	99	96
L34a	B	THF	20	240	96	94
L34a	A	DCM	40	30	99	94
L34a	A	THF	40	30	99	96
L34a	B	DCM	40	40	99	95
L34a	B	THF	40	40	99	94
C2a	B	DCM	20	120	86	92
L34b	A	THF	25	48	62	75
L34c	A	THF	25	48	74	92
L34d	A	THF	25	48	38	70

Scheme 20. C_2-symmetric Phos-Biox ligand for asymmetric allylic alkylations.



Ligand	Solvent	t (h)	Yield (%)	*ee* (%)
L35a	DCM	3	100	52
L35b	DCM	3	100	83
L35c	DCM	3	100	91
L35d	DCM	0.25	100	95
L35e	DCM	1.5	100	56
L35f	DCM	4	100	81
L35a	[bmim][PF6]	4	100	13
	Reuse	168	50	8
L35b	[bmim][PF6]	3	100	37
	Reuse	17	100	29
L35c	[bmim][PF6]	3	100	68
	Reuse	12	100	32
L35d	[bmim][PF6]	2.5	100	92
	Reuse	240	80	54
L35e	[bmim][PF6]	1.5	100	34
	Reuse	144	10	4
L35f	[bmim][PF6]	4.5	100	57
	Reuse	168	30	56
L35g	DCM	10 min	100	99
L35h	DCM	10 min	100	99
L35i	DCM	10 min	100	20 (R)

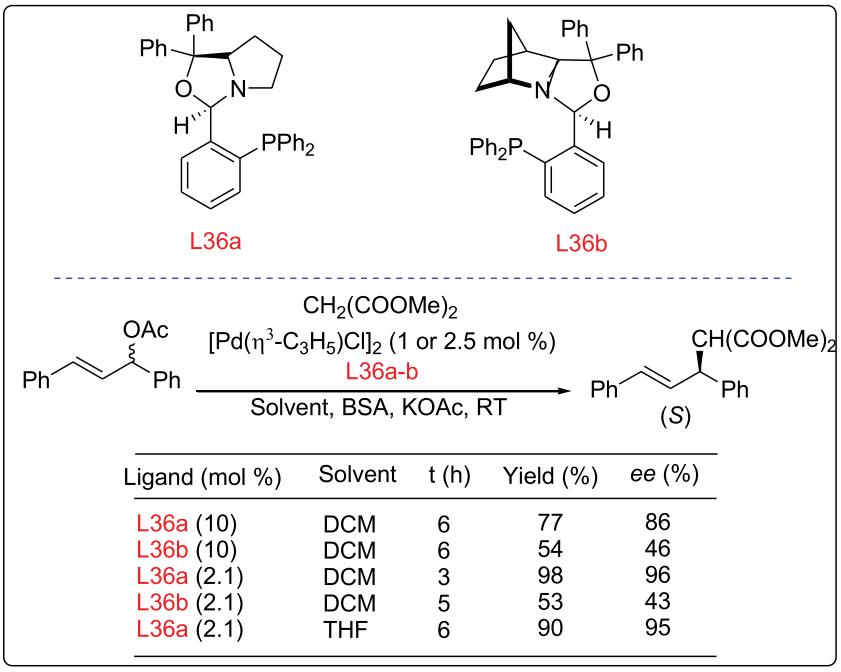
Scheme 21. Bis(oxazolinyl)-type PHOX ligands for asymmetric allylic alkylations.

were applied in the asymmetric allylation of 1,3-diphenyl 2-propenyl acetate with Na-dimethyl malonate or dimethyl malonate using [Pd(η^3-C_3H_5)Cl]$_2$ (2.5 mol %) catalyst in THF. It was observed that the ligand **L20a** with an isopropyl group at the oxazoline moiety gave 92% allylation product with 97% *ee* at 0 °C in 2 h, while the ligand **L20b** containing the *t*-butyl group led to the 91% desired product with 94% *ee* at -10°C (Scheme 11). Similarly, these ligands (3 mol %) also gave up to 90% yield and 99% *ee* for dimethyl malonate in the presence of [Pd(η^3-C_3H_5)Cl]$_2$ (1.5 mol %) in DCM at room temperature.

Saigo and coworkers [44] introduced a bulky indanol-based PHOX ligand (**L22**) derived from non-natural chiral amino alcohol and *cis*-2--amino-3,3-dimethyl-1-indanol. The ligand **L22** (3.6 mol %) was found to be an efficient ligand for enantioselective allylic amination of different 1,3-alkyl/aryl 2-propenyl acetates with benzylamine or potassium phthalimide in presence of $Pd_2(dba)_3$ (1.5 mol %) in THF (Scheme 12). In the amination reaction of 1,3-diphenyl-2-propenyl acetate, the ligand **L22** was more efficient than similar ligands.

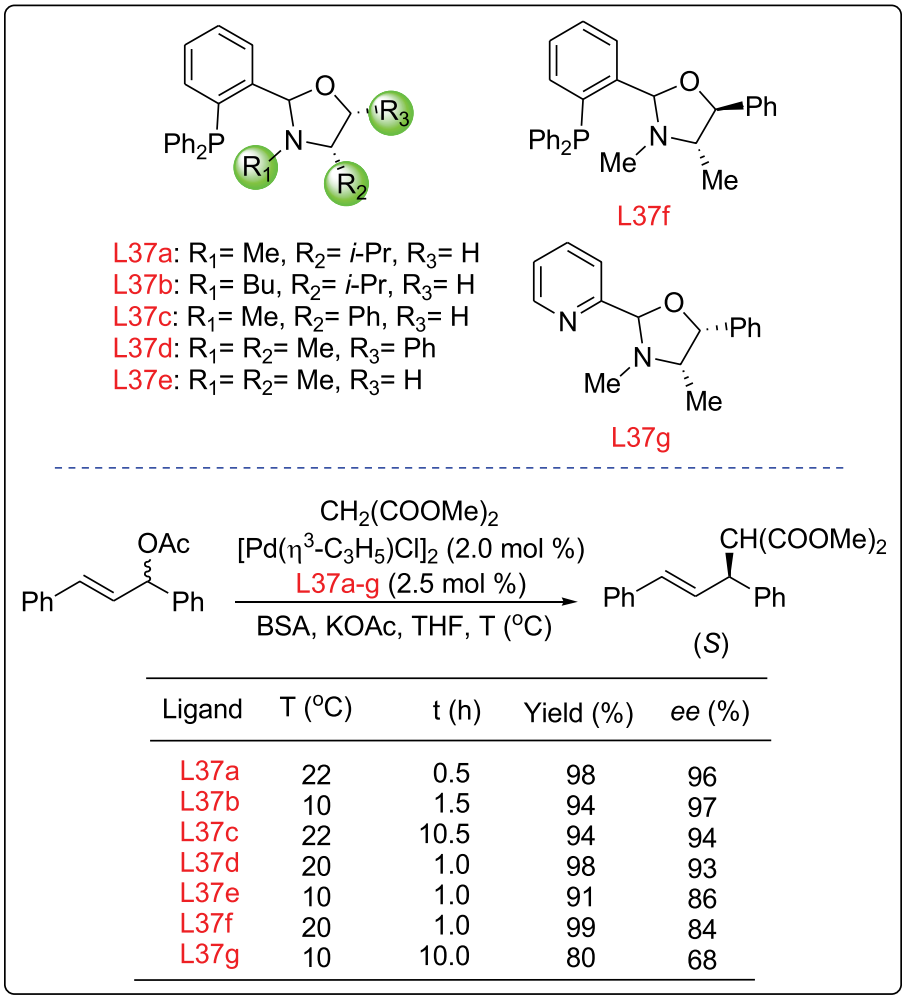
Franzén and coworkers utilized two types of indole-based HetPHOX ligands called 'IndPHOX'. Class I ligands **L23a-d**, and class II ligands **L24a-d** (12 mol %) were applied to the asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate in the presence of [Pd(η^3-C_3H_5)Cl]$_2$ (4 mol %), KOAc, and BSA in THF at room temperature [45]. In amination, the ligands containing diphenylphosphine group at 2-position and oxazoline moiety at 3-position of the indole-moiety **L24a–d** (12 mol %) showed the best results (up to 98% yield and 99% *ee*) [46] (Scheme 13).

Two-fold amino acid-based chiral aminophosphine–oxazoline ligands (AminPHOX) based on tetrahydroisoquinoline carboxylic acid (**L25a-b**) and proline (**L25c-d**) was reported by Niedercorn et al. [47a]. The ligand **L25a** showed 93% *ee* while ligand **L25c** showed 94% *ee* in the allylation of 1,3-diphenyl-2-propenyl acetate using [Pd(η^3-C_3H_5)Cl]$_2$, BSA, and KOAc in THF at 20 °C (Scheme 14). Even improved enantioselectivity was shown in MeCN at 0 °C. Similarly, chiral



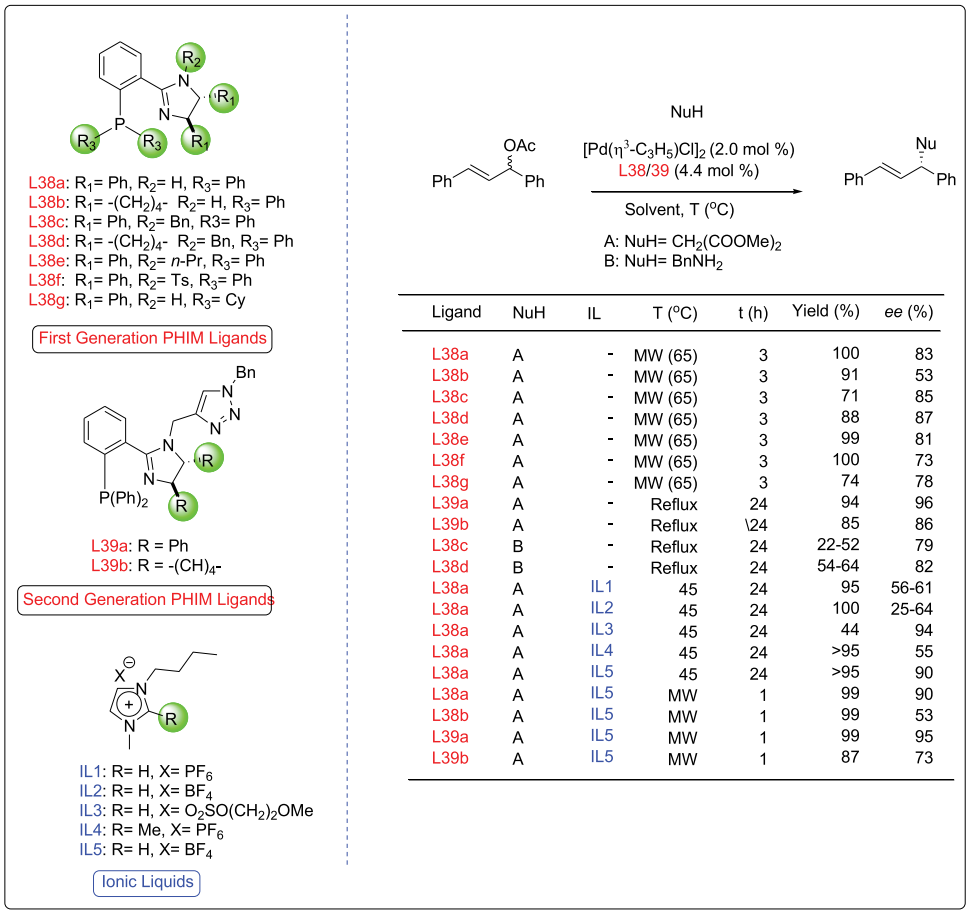
Ligand (mol %)	Solvent	t (h)	Yield (%)	*ee* (%)
L36a (10)	DCM	6	77	86
L36b (10)	DCM	6	54	46
L36a (2.1)	DCM	3	98	96
L36b (2.1)	DCM	5	53	43
L36a (2.1)	THF	6	90	95

Scheme 22. Pyrrolidinyl and 2-azanorbornylphosphinooxazolidine ligands for asymmetric allylic alkylations.



Ligand	T (°C)	t (h)	Yield (%)	*ee* (%)
L37a	22	0.5	98	96
L37b	10	1.5	94	97
L37c	22	10.5	94	94
L37d	20	1.0	98	93
L37e	10	1.0	91	86
L37f	20	1.0	99	84
L37g	10	10.0	80	68

Scheme 23. Ephedrine-derived chiral phosphinooxazolidine and pyridinooxazolidine ligands for asymmetric allylic alkylations.



Ligand	NuH	IL	T (°C)	t (h)	Yield (%)	*ee* (%)
L38a	A	-	MW (65)	3	100	83
L38b	A	-	MW (65)	3	91	53
L38c	A	-	MW (65)	3	71	85
L38d	A	-	MW (65)	3	88	87
L38e	A	-	MW (65)	3	99	81
L38f	A	-	MW (65)	3	100	73
L38g	A	-	MW (65)	3	74	78
L39a	A	-	Reflux	24	94	96
L39b	A	-	Reflux	\24	85	86
L38c	B	-	Reflux	24	22-52	79
L38d	B	-	Reflux	24	54-64	82
L38a	A	IL1	45	24	95	56-61
L38a	A	IL2	45	24	100	25-64
L38a	A	IL3	45	24	44	94
L38a	A	IL4	45	24	>95	55
L38a	A	IL5	45	24	>95	90
L38a	A	IL5	MW	1	99	90
L38b	A	IL5	MW	1	99	53
L39a	A	IL5	MW	1	99	95
L39b	A	IL5	MW	1	87	73

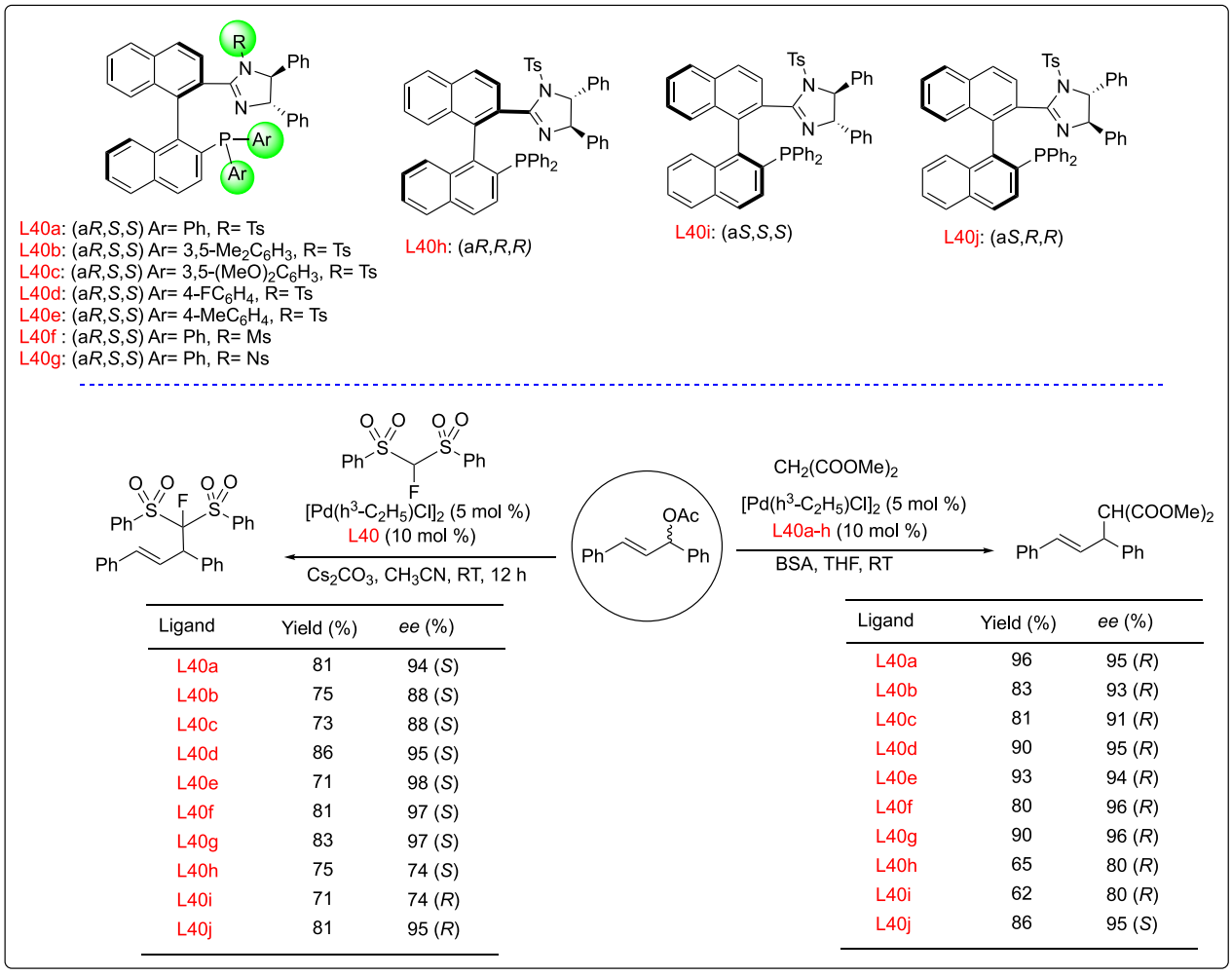
Scheme 24. Phosphine-imidazoline (PHIM) ligands for asymmetric allylic alkylations.

phosphinopyrrolyl-oxazolines (PyroPHOX) ligands (**L26a-d**) (2.4 mol %) [47b] also showed moderate *ee* in the allylation of 1,3-diphenyl-2--propenyl acetate using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol %) in DCM at 23 °C.

The ligands containing the 'spiro' backbone have been recognized as a privileged motif in many catalytic reactions. Such a rigid scaffold of the ligands could reduce the conformational obscurity of the catalyst and create an effective asymmetric environment around the central metal. In this context, a new type of HetPHOX ligands called '**SIPHOX**' (**S**pirobi**I**ndane PHOX), '**SpinPHOX'** (**Spi**ro[4,4]-1,6 **n**onadiene PHOX), and '**HMSI-PHOX**' (**H**exa**M**ethyl-1,10-**S**pirobi**I**ndane PHOX) have been developed for Ir-catalyzed asymmetric hydrogenation reactions and Ni-catalyzed asymmetric arylations [48]. In this connection, Teng and co-workers introduced '**SMIPHOX**' (**S**piro **M**ono-**I**ndane PHOX) ligands (**L27a-d**) for various Pd-catalyzed asymmetric reactions [49]. The ligands were synthesized from commercially available 7-bromo-1-indanone and (*R*)-phenylglycinol and applied in the reaction of 1, 3-diphenyl-2-propenyl acetate and dimethyl malonate in the presence of BSA and KOAc in toluene at different temperatures (−10 to 25 °C) (Scheme 15). The $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**L27a-d** (1:2 mol %) catalytic system afforded the desired product in high yields (94–99%) and enantioselectivities (95.2–98.8 % *ee*). All the ligands showed good yields with excellent *ee* for various substrates. They extended this protocol for enantioselective allylic alkylation of indoles and allylic etherification [50a]. The ligands **L27a-d** (4.0 mol %) showed 87–95% yields and 87–96% enantioselectivity for the reaction of indole with 1, 3-diphenyl-2-propenyl acetate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %) using Cs_2CO_3 as a base in toluene at room temperature. However, yield and enantioselectivity are slightly low for the ligand **L27c**. The ligand **L27a** also worked efficiently in the allylic etherification of primary and secondary alcohols. The desired products formed with excellent enantioselectivity (93–99% *ee*) in the presence of Cs_2CO_3 in DCM at 0 °C. Similar type of amino phosphine ligands (**L27e-h**) bearing Spiro[indane-1,2′-pyrrolidine] backbone synthesized in gram scale [50b]. The ligand **L27h** (6 mol %) gave the highest *ee* of 97% with 82% yield in allylic alkylation of 1,3-diphenyl-2-propenyl acetate with methanol using $[Pd(\eta^3\text{-}C_3H_5)\ Cl]_2$ (3 mol %) and Cs_2CO_3 as the base in toluene at room temperature.

Trudeau and Morken [51] developed a new class of optically active PHOX ligands called 'StePHOX' (**L28a-h**) containing different ligand backbones as well substitution patterns on the oxazoline and dioxolane moiety (Scheme 16). The dioxolane linkage offers additional chirality and tuning element to the PHOX ligands. The ligands **L28a–d** lead to moderate enantioselectivity (46–62% *ee*) in the reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, KOAc, and BSA in DCM. While ligands **L28e** and **L28h** attained excellent enantioselectivity (97 and 95% *ee*).

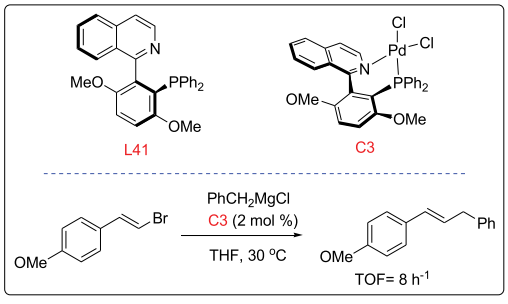
In 2016, Pfaltz and coworkers [52] introduced serine and threonine-derived neopentyl backbone containing ligands (**L29a-c**) called '**NeoPHOX**' for the allylic substitution of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$,



Ligand	Yield (%)	*ee* (%)
L40a	81	94 (*S*)
L40b	75	88 (*S*)
L40c	73	88 (*S*)
L40d	86	95 (*S*)
L40e	71	98 (*S*)
L40f	81	97 (*S*)
L40g	83	97 (*S*)
L40h	75	74 (*S*)
L40i	71	74 (*R*)
L40j	81	95 (*R*)

Ligand	Yield (%)	*ee* (%)
L40a	96	95 (*R*)
L40b	83	93 (*R*)
L40c	81	91 (*R*)
L40d	90	95 (*R*)
L40e	93	94 (*R*)
L40f	80	96 (*R*)
L40g	90	96 (*R*)
L40h	65	80 (*R*)
L40i	62	80 (*R*)
L40j	86	95 (*S*)

Scheme 25. Chiral imidazoline-phosphine ligands for asymmetric allylic alkylations.



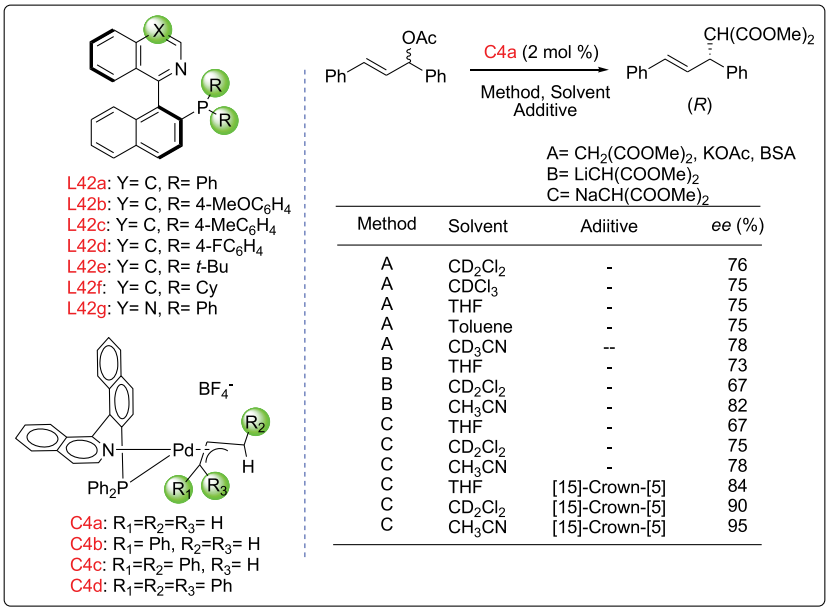
Scheme 26. Pd-QUINAP catalyst used in coupling reaction of vinyl halide with $PhCH_2MgCl$.

KOAc, and BSA in DCM (Scheme 17). The ligands **L29b** and **L29c** with a free hydroxyl group and the trimethylsilyl-protected derivative afforded 98% and 97% *ee*, respectively, while **L29a** provided 91% *ee*. Unfortunately, all the tested ligands were less efficient for 1,3-diphenyl-2-propenyl acetate. On the other hand, ligand **L29b** achieved 70 % *ee* for cyclohex-2-en-1-yl benzoate.

A novel axially chiral PHOX ligands **L30** [53], and **L31a-b** [54] with binaphthyl backbone as well as axis-unfixed biphenyl backbone (**L32a-b**) [55] were applied for Pd catalyzed allylic substitution reactions (Scheme 18). All the ligands gave high chemical yields (up to 99%) and enantioselectivity (up to 93% *ee*) for the reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in different solvents at different temperatures.

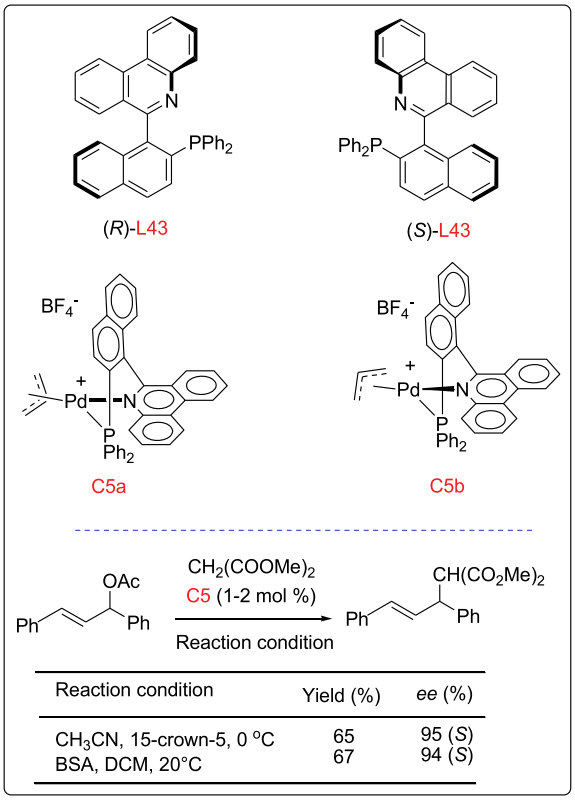
Gavrilov et al. [56] developed a small library of readily available N, N-diamidophosphite–oxazoline ligands (**L33a-e**) containing 1,3,2-diazaphospholidine and a pyridine moiety for Pd-catalyzed asymmetric allylation reactions (Scheme 19). The ligand **L33c** (2 mol %) provided up to 92% *ee* (*S*-product) for allylations of 1,3-diphenyl-2-propenyl acetate with sodium *para*-toluene sulfinate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %) in THF at 20 °C. The ligand **L33b** (4 mol %) provided 96% *ee* for dimethylmalonate in BSA-KOAc and DCM at 20 °C. The 95% *ee* was attained for the amination of 1,3-diphenyl-2-propenyl acetate with pyrrolidine using **L33b** (4 mol %) in THF at 20 °C. The ligands bearing P and C stereocenters in the 1,3,2-diazaphospholidine rings were more efficient. However, the ligands **L33b-c** with pyridin-2-yl or pyridin-3-yl substituents were the most efficient, while the ligand **L33e** containing achiral diamidophosphite showed much lower enantioselectivities.

Lee and coworkers [57a] reported the C_2-symmetric conformationally rigid bisphosphinobioxazoline [(*S, S*)-Phos-Biox] ligand (**L34**). In the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol %), the ligand (2.5 mol %) exhibited very high efficiency (94–97% *ee*) for the reaction of 1,3-diphenyl-2-propenyl acetate and dimethyl malonate or its Na salt with almost quantitative chemical yields of (*S*) product in THF or DCM (Scheme 20).



Method	Solvent	Adiitive	*ee* (%)
A	CD_2Cl_2	-	76
A	$CDCl_3$	-	75
A	THF	-	75
A	Toluene	-	75
A	CD_3CN	--	78
B	THF	-	73
B	CD_2Cl_2	-	67
B	CH_3CN	-	82
C	THF	-	67
C	CD_2Cl_2	-	75
C	CH_3CN	-	78
C	THF	[15]-Crown-[5]	84
C	CD_2Cl_2	[15]-Crown-[5]	90
C	CH_3CN	[15]-Crown-[5]	95

Scheme 27. Applications of QUINAP in asymmetric allylic alkylations.



Reaction condition	Yield (%)	*ee* (%)
CH_3CN, 15-crown-5, 0 °C	65	95 (*S*)
BSA, DCM, 20°C	67	94 (*S*)

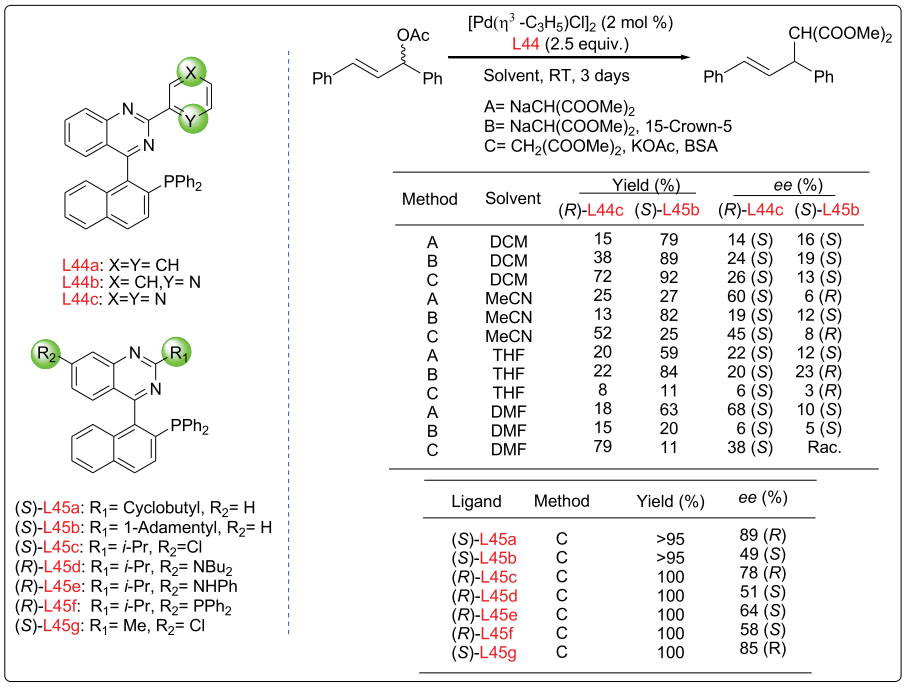
Scheme 28. Applications of PHENAP in asymmetric allylic alkylations.

Moreover, the P, N, N, P-chelated complex (**C2a-b**) obtained from **L34** also exhibited high enantioselectivity (92% *ee*) and good yield (86%) under optimized reaction conditions. The enantio discrimination capacity of **L34** was also examined for meso-dibenzoate of *cis*-2-cyclopenten-1,4-diol with Na salt of dimethyl malonate and N-benzyl-N-methylamine. The catalytic system also carried Pd-catalyzed intramolecular cyclization of biscarbamate of *cis*-2-cyclopenten-1,4-diol with *p*-toluenesulfonyl isocyanate (TsNCO) in THF at 50 °C giving the corresponding biscarbamate mixture (1:3) in 90% yield with 50% *ee*. Similarly, N-P-N type PHOX ligands (**L34c-d**) also showed excellent enantioselectivity in asymmetric allylic substitution reactions [57b]. These ligands coordinated to Pd(II) as bidentate ligands to afford Pd(η^3-C_3H_5)(**L34c-d**)]PF_6 complex. The complex obtained from **L34c** showed high enantioselectivity in the reaction of 1, 3-diphenyl-2-propenyl acetate and Na salt of dimethyl malonate in THF.

Chiral tridentate ligands have a large diversity of binding modes for metals and allow fine-tuning of the catalytic system. In this regard, Castillo and coworkers [58a] introduced tridentate chiral NPN-based PHOX-type ligands (**L35a-f**) for the asymmetric allylic substitution reactions (Scheme 21). The reaction involves the alkylation of 1,3-diphenyl-2-propenyl acetate with diethyl malonate in either DCM or [bmim]PF_6 in the presence of BSA and NaOAc. The phosphorus-based ligands showed increased catalytic activity, leading to total conversions in 4 h. While, analogous bis(oxazoline) and azabis(oxazoline) ligands required 2 to 7 days. Unfortunately, complete recovery of the catalyst and ionic liquid was impossible, and decreased catalytic activity with a drop in enantioselectivity was observed with longer reaction times. A similar type of bidentate PHOX ligands (**L35g-i**) (1.1 mol %) composed of chirally flexible biaryl phosphite showed excellent enantioselectivities in allylic substitutions of a wide range of substrates and nucleophiles in the presence of [Pd(η^3-C_3H_5)Cl]$_2$ (0.5 mol %) in DCM at room temperature [58b]

Hongo and coworkers [59] synthesized pyrrolidinyl and 2-azanorbornyl phosphinooxazolidines (**L36a-b**) from 2-(diphenylphosphino) benzaldehyde and corresponding amines in refluxing toluene. The effectiveness of the ligands was examined in asymmetric allylation of 1, 3-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 22). The ligand **L36a** (2.1 mol %) gave an excellent yield (98%) and *ee* (96%) in the presence of [Pd(η3-C_3H_5)Cl]$_2$ (1 mol %) and BSA-KOAc in DCM at room temperature. Even high enantiomeric excess (95%) was observed in THF. Ligand **L36b** was less effective (53% yield and 43% *ee*) under similar reaction conditions.

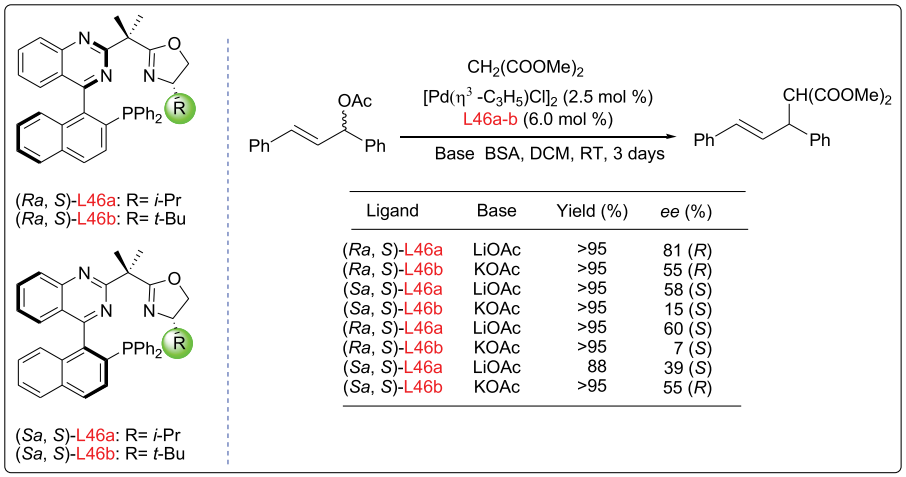
Jin and coworkers [60] developed ephedrine-derived chiral phosphinooxazolidine (**L37a-f**) and pyridinooxazolidine (**L37g**) ligands for the asymmetric allylic substitution reactions of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate, in the presence of [Pd(η^3-C_3H_5)Cl]$_2$ (2.5 mol %) in BSA-KOAc and THF at 0–20 °C (Scheme 23). The ligand



Method	Solvent	Yield (%)		ee (%)	
		(*R*)-L44c	(*S*)-L45b	(*R*)-L44c	(*S*)-L45b
A	DCM	15	79	14 (*S*)	16 (*S*)
B	DCM	38	89	24 (*S*)	19 (*S*)
C	DCM	72	92	26 (*S*)	13 (*S*)
A	MeCN	25	27	60 (*S*)	6 (*R*)
B	MeCN	13	82	19 (*S*)	12 (*S*)
C	MeCN	52	25	45 (*S*)	8 (*R*)
A	THF	20	59	22 (*S*)	12 (*S*)
B	THF	22	84	20 (*S*)	23 (*R*)
C	THF	8	11	6 (*S*)	3 (*R*)
A	DMF	18	63	68 (*S*)	10 (*S*)
B	DMF	15	20	6 (*S*)	5 (*S*)
C	DMF	79	11	38 (*S*)	Rac.

Ligand	Method	Yield (%)	ee (%)
(*S*)-L45a	C	>95	89 (*R*)
(*S*)-L45b	C	>95	49 (*S*)
(*R*)-L45c	C	100	78 (*R*)
(*R*)-L45d	C	100	51 (*S*)
(*R*)-L45e	C	100	64 (*S*)
(*R*)-L45f	C	100	58 (*S*)
(*S*)-L45g	C	100	85 (R)

Scheme 29. Applications of Quinazolinap ligands in asymmetric allylic alkylations.



Ligand	Base	Yield (%)	ee (%)
(*Ra*, *S*)-L46a	LiOAc	>95	81 (*R*)
(*Ra*, *S*)-L46b	KOAc	>95	55 (*R*)
(*Sa*, *S*)-L46a	LiOAc	>95	58 (*S*)
(*Sa*, *S*)-L46b	KOAc	>95	15 (*S*)
(*Ra*, *S*)-L46a	LiOAc	>95	60 (*S*)
(*Ra*, *S*)-L46b	KOAc	>95	7 (*S*)
(*Sa*, *S*)-L46a	LiOAc	88	39 (*S*)
(*Sa*, *S*)-L46b	KOAc	>95	55 (*R*)

Scheme 30. Applications of Quinazox in asymmetric allylic alkylations.

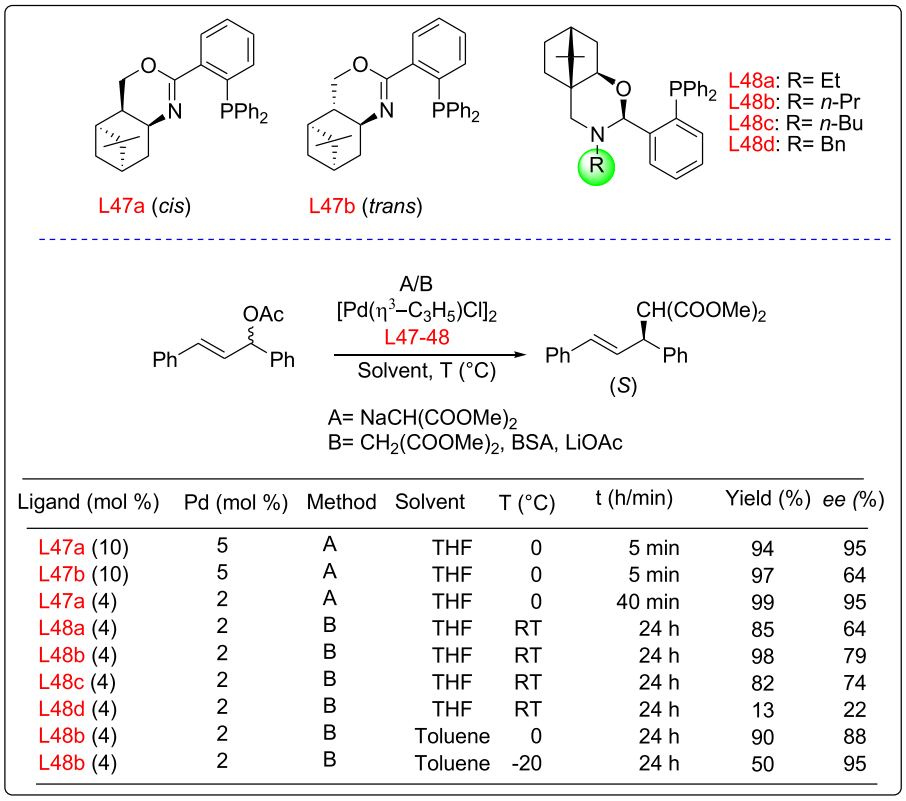
L37e having a methyl group at C4 showed lower enantioselectivity (86% *ee*) than **L37a** and **L37b** containing a bulky *i*-Pr group (98% and 97% *ee*). Compared to ligand **L37e**, the ligand **L37d**, having a phenyl group at C5, enhanced the *ee* up to 93 %, while ligand **L37f** showed lower enantioselectivity (84% *ee*). Even the ligand **L37g** showed low *ee* (68%) in THF. The ligand **L37a** afforded the alkylation product with 98% *ee*, while moderate enantioselectivity (60% *ee*) and yield (51%) were observed in the amination with benzylamine. Predominantly (*S*)-product was formed due to the favorable nucleophilic attack, to a carbon atom of the π-allyl moiety at the trans position to the oxazolidine nitrogen.

Phosphine-imidazoline (PHIM) ligands analogs to that BIPI-ligands have been acting as interesting ligands in asymmetric catalysis [61]. These ligands can be synthesized easily from readily available C_2-symmetric diamine fragments. The ligand contains a second nitrogen atom that can work as an additional source of molecular diversity, as it allows the adjustment of the electronic properties of the coordinating nitrogen atom. Furthermore, it is possible to immobilize it on a suitable solid support.

These ligands are of two types;

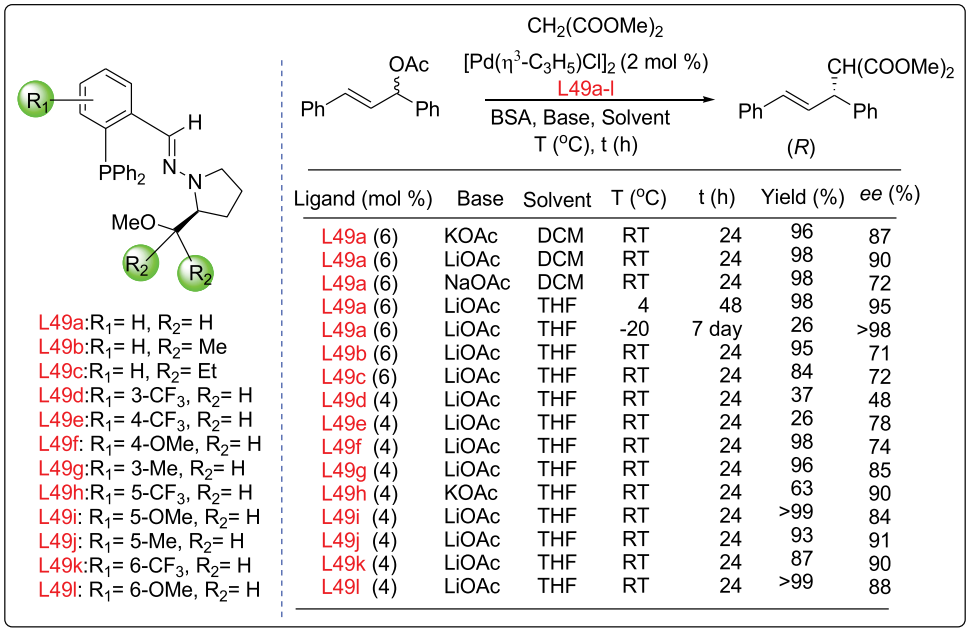
- First-generation PHIM ligands (**L38a-g**): It involves various substituents on the C4 and C5 (R_1) of imidazoline moiety, the non-coordinating nitrogen atom of the imidazoline ring (R_2), and the phosphine moiety (R_3).
- Second generation PHIM ligands (**L39a-b**): These ligands result from the introduction of triazolylmethyl moieties as nitrogen substituents (R_2).

All these ligands were applied for asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate or benzylamine [62] (Scheme 24). The ligands **L38c-d** gave the best enantioselectivity



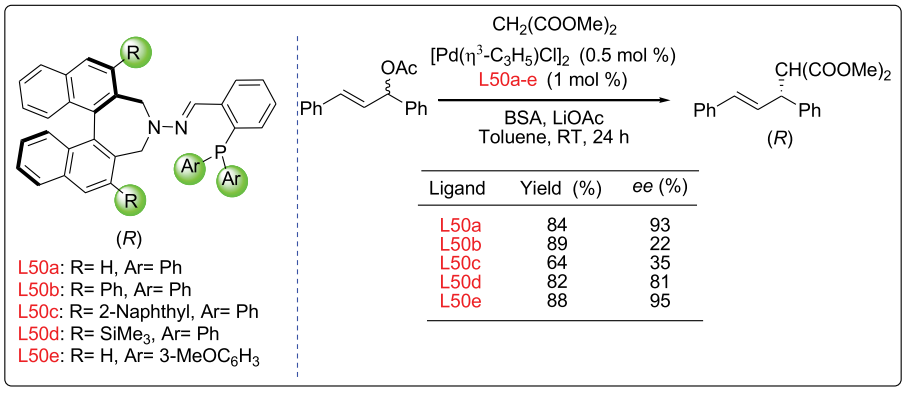
Ligand (mol %)	Pd (mol %)	Method	Solvent	T (°C)	t (h/min)	Yield (%)	*ee* (%)
L47a (10)	5	A	THF	0	5 min	94	95
L47b (10)	5	A	THF	0	5 min	97	64
L47a (4)	2	A	THF	0	40 min	99	95
L48a (4)	2	B	THF	RT	24 h	85	64
L48b (4)	2	B	THF	RT	24 h	98	79
L48c (4)	2	B	THF	RT	24 h	82	74
L48d (4)	2	B	THF	RT	24 h	13	22
L48b (4)	2	B	Toluene	0	24 h	90	88
L48b (4)	2	B	Toluene	-20	24 h	50	95

Scheme 31. Phosphine–oxazinane ligands for asymmetric allylic alkylations.



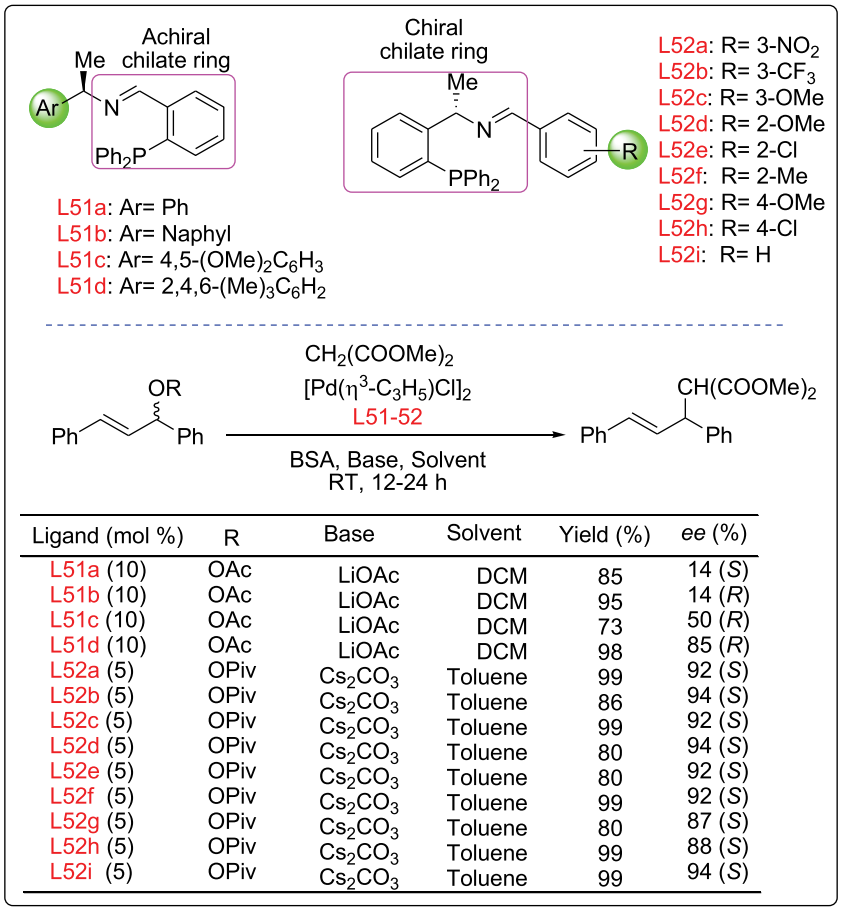
Ligand (mol %)	Base	Solvent	T (°C)	t (h)	Yield (%)	*ee* (%)
L49a (6)	KOAc	DCM	RT	24	96	87
L49a (6)	LiOAc	DCM	RT	24	98	90
L49a (6)	NaOAc	DCM	RT	24	98	72
L49a (6)	LiOAc	THF	4	48	98	95
L49a (6)	LiOAc	THF	-20	7 day	26	>98
L49b (6)	LiOAc	THF	RT	24	95	71
L49c (6)	LiOAc	THF	RT	24	84	72
L49d (4)	LiOAc	THF	RT	24	37	48
L49e (4)	LiOAc	THF	RT	24	26	78
L49f (4)	LiOAc	THF	RT	24	98	74
L49g (4)	LiOAc	THF	RT	24	96	85
L49h (4)	KOAc	THF	RT	24	63	90
L49i (4)	LiOAc	THF	RT	24	>99	84
L49j (4)	LiOAc	THF	RT	24	93	91
L49k (4)	LiOAc	THF	RT	24	87	90
L49l (4)	LiOAc	THF	RT	24	>99	88

Scheme 32. DPPB-SAMP ligands for asymmetric allylic alkylations.



Ligand	Yield (%)	*ee* (%)
L50a	84	93
L50b	89	22
L50c	64	35
L50d	82	81
L50e	88	95

Scheme 33. Phosphino hydrazone with a pendant binaphthyl unit as a chiral modifier used in asymmetric allylic alkylations.



Ligand (mol %)	R	Base	Solvent	Yield (%)	*ee* (%)
L51a (10)	OAc	LiOAc	DCM	85	14 (*S*)
L51b (10)	OAc	LiOAc	DCM	95	14 (*R*)
L51c (10)	OAc	LiOAc	DCM	73	50 (*R*)
L51d (10)	OAc	LiOAc	DCM	98	85 (*R*)
L52a (5)	OPiv	Cs_2CO_3	Toluene	99	92 (*S*)
L52b (5)	OPiv	Cs_2CO_3	Toluene	86	94 (*S*)
L52c (5)	OPiv	Cs_2CO_3	Toluene	99	92 (*S*)
L52d (5)	OPiv	Cs_2CO_3	Toluene	80	94 (*S*)
L52e (5)	OPiv	Cs_2CO_3	Toluene	80	92 (*S*)
L52f (5)	OPiv	Cs_2CO_3	Toluene	99	92 (*S*)
L52g (5)	OPiv	Cs_2CO_3	Toluene	80	87 (*S*)
L52h (5)	OPiv	Cs_2CO_3	Toluene	99	88 (*S*)
L52i (5)	OPiv	Cs_2CO_3	Toluene	99	94 (*S*)

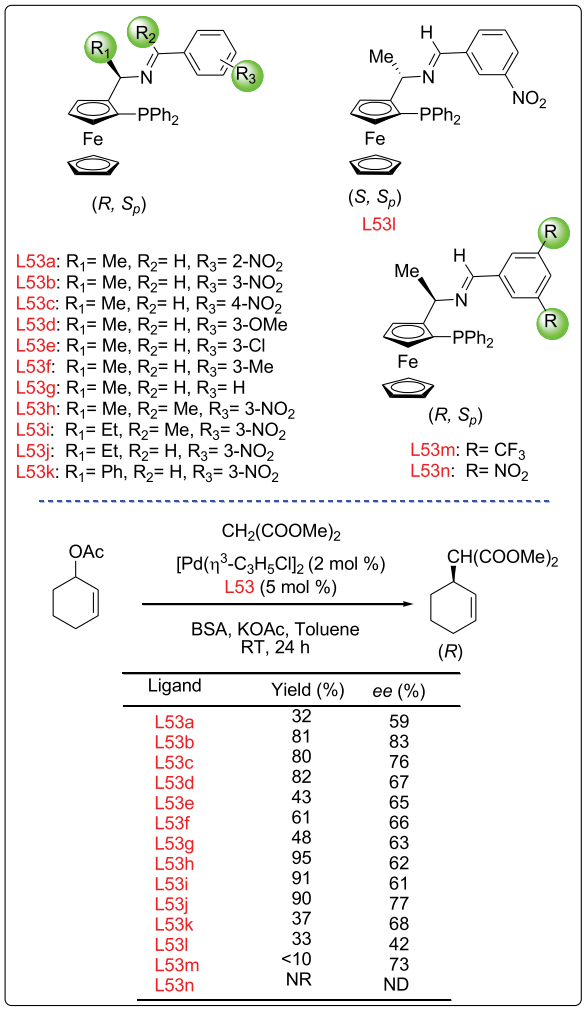
Scheme 34. Phosphine–imine ligands for asymmetric allylic alkylations.

(85% and 87% *ee*, respectively) in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %) and KOAc-BSA in DCM, under MW at 65 °C.

The activity and enantioselectivity of ligands **L38a-b** and **L39a-b** were also studied in different ionic liquids (**IL1-5**) under conventional as well as MW heating. The complete conversion with 90% enantioselectivity was observed in **IL5** using **L38a** (4.4 mol %) at 45 °C. A comparison of ligands showed that ligand **L39a** in **IL5** achieved 95% *ee* under MW irradiation. Moreover, **IL5** and ligand **L38a** or **L39a** could be successfully recycled at least four times under MW irradiation. The conversion and enantioselectivity dramatically decreased after the third run.

Similarly, Shi et al. [63] used chiral imidazoline–phosphine ligands (**L40a-j**) with a 1,1′-binaphthalene framework for allylic alkylation (Scheme 25). For the reaction of 1,3-diaryl-2-propenyl acetate with dimethyl malonate, excellent enantioselectivity (up to 96%) was observed except for **L40h** and **L40i** ligands. In addition, except **L40b-c** and **L40h-i** all the ligands showed up to 98% enantioselectivity in monofluoromethylation of 1,3-diphenyl-2-propenyl acetate with 1-fluorobis(phenylsulfonyl)methane.

The 'Atropos P-N' ligands (APN) are a specific type of biaryls with



Ligand	Yield (%)	*ee* (%)
L53a	32	59
L53b	81	83
L53c	80	76
L53d	82	67
L53e	43	65
L53f	61	66
L53g	48	63
L53h	95	62
L53i	91	61
L53j	90	77
L53k	37	68
L53l	33	42
L53m	<10	73
L53n	NR	ND

Scheme 35. Ferrocene-based phosphine-imine ligands for asymmetric allylic alkylations of cycloalkenyl esters.

one component carrying a pendant diaryl substituted phosphine, and the other bears an sp^2 N-atom adjacent to the biaryl link. The substituents in the biaryl inhibit rotation about the linking bond and form a stable, non-racemizing six-membered chelate ring. In their seminal reports, Guiry et al. [64] and other workers [65] described the evolution of APN type ligands like 'QUINAP, PINAP, and QUINAZOLINAP' as privileged chiral ligands for many asymmetric transformations.

The first new class of hybrid, axially chiral (1-(2′-diphenylphosphino-3′,6′-dimethoxy phenyl)isoquinoline) (**L41**) ligand that creates a six-membered chelate ring was reported by Alcock and coworkers [66a]. The reaction of the **L41** with $(MeCN)_2PdCl_2$ in DCM gave the corresponding racemic chelate Pd-complex (**C3**) having the *cis*-chelate square planar structure as analyzed by X-ray crystallography. The complex **C3** (2 mol %) effectively catalyzed the coupling of vinyl halide with $PhCH_2MgCl$ leading to the formation of stilbene in THF with a TOF= 8 h^{-1} at 30 °C (Scheme 26).

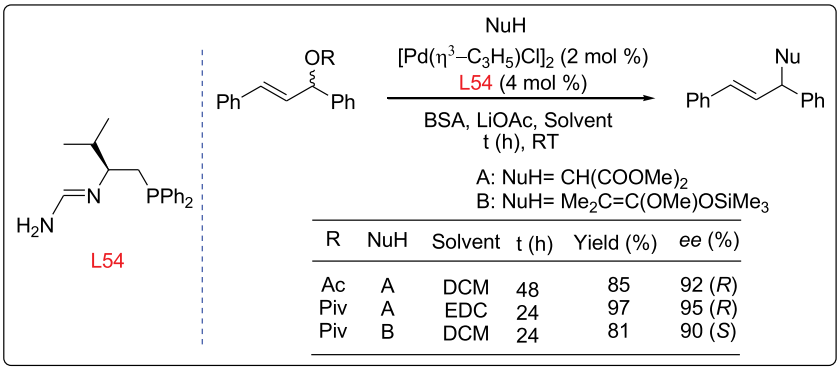
The difference in the electronic nature of N and P atoms would give a potentially more labile intermediate showing different reactivity in asymmetric catalysis. But this ligand racemizes at ambient temperature, which limits its application in asymmetric catalysis. To increase the barrier to rotation around the chiral axis Alcock and coworkers reported 'QUINAP' **L42a** containing a naphthalene-isoquinoline backbone by analogy to 'BINAP' for the asymmetric catalysis (Scheme 27) [66b].

The allylpalladium tetrafluoroborate complexes (**C4a-d**) of Quinap ligand were prepared by reacting $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ with mono, 1,3-di, and 1,1,3-triphenyl analogs [67]. The structures of complexes **C4a-c** were confirmed by electrospray MS. Quinap has continued to be successfully employed in several allylic alkylation reactions. Most of the reactions were carried out by using **C4a** (2 mol %) as well as preparing it *in situ* by reacting **L42a** and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$. Initial screening of **C4a** was carried out with 1,3-diphenyl-2-propenyl acetate and dimethyl malonate in BSA or its Li/Na salts in various solvents. At ambient temperature, asymmetric induction was attained between 67% and 82%. The addition of 15-Crown-5 in DCM significantly enhanced the enantioselectivity to *ee* 90%. Furthermore, *ee* was 95% in acetonitrile at ambient temperature in the presence of 15-Crown-5, which is get enhanced to 97.8% at 0°C, and 98.2% at −13 °C.

Brown et al. [68] synthesized a new (*R*) and (*S*)-6-(2′- diphenylphosphino-l'-naphthyl) phenanthridines called phospinamine (PHENAP) (**L43**). It involves additional fused arene rings. It plays a critical part in defining the coordination sphere through its steric pressure. The ligand was synthesized by starting the Suzuki coupling of 6-chlorophenanthridine with 2-methoxy-l-naphthaleneboronic acid. Excellent enantioselectivity was obtained for allylic alkylation of 1,3-diphenyl-2--propenyl acetate (Scheme 28). The enantioselectivity is similar to the QUINAP ligand. (*R*)-**L43** derived catalyst (**C5a-b**) gives rise to *S*-product.

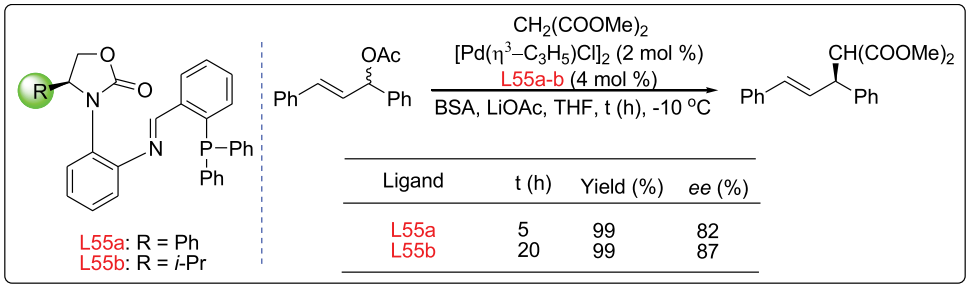
The ^1H NMR spectroscopic studies of Pd-QUINAP complexes showed that in allylic alkylation, the 3-position of the ligand of the isoquinoline unit takes up a position in space. That leads to ligand–reactant steric interactions, which could be important for asymmetric induction. This was the principle behind the design and the preparation of PHENAP (**L43**), which in turn gave high enantioselectivity in Pd-catalyzed allylic substitutions.

In this connection, Guiry and coworkers introduced a new class of axially chiral phosphinamine ligand called 'QUINAZOLINAP' (**L44a**), containing a sterically bulky group at the 2-position of the quinazoline ring [69]. The ligand was synthesized by the Suzuki coupling of 4-chloro-2-phenylquinazoline and 2-methoxy-1-naphthylboronic acid in high



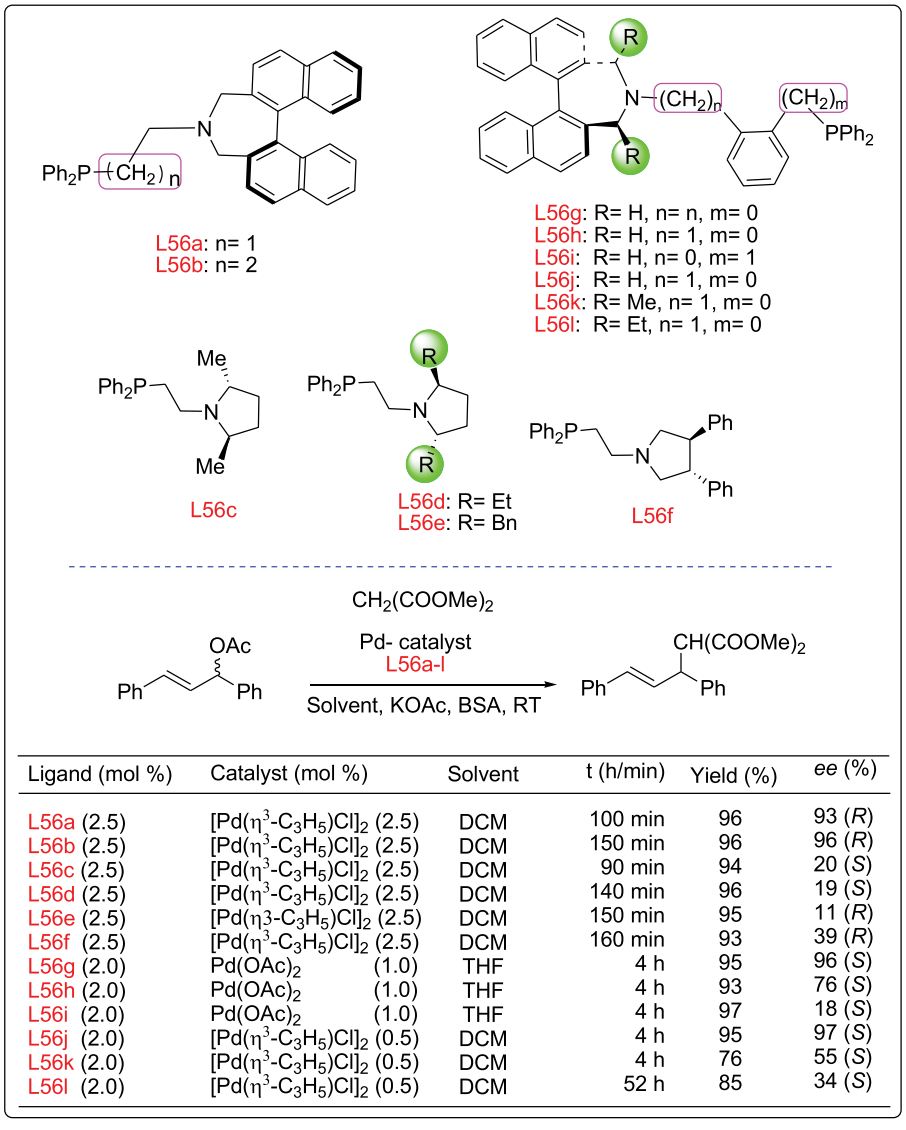
R	NuH	Solvent	t (h)	Yield (%)	*ee* (%)
Ac	A	DCM	48	85	92 (*R*)
Piv	A	EDC	24	97	95 (*R*)
Piv	B	DCM	24	81	90 (*S*)

Scheme 36. Phosphorus-containing chiral amidine ligand in the asymmetric allylic alkylations.



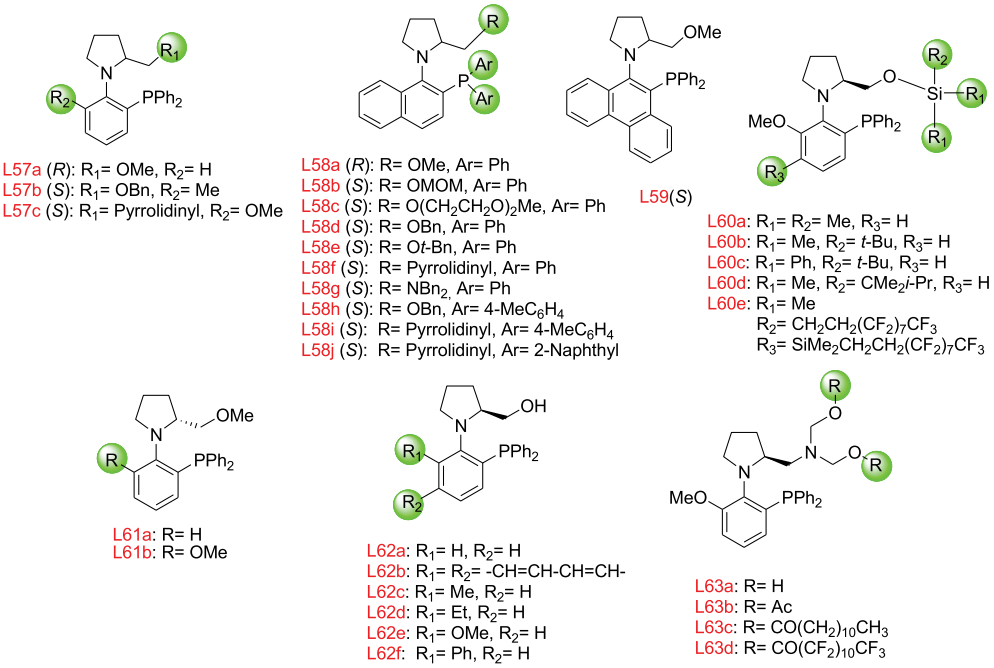
Ligand	t (h)	Yield (%)	*ee* (%)
L55a	5	99	82
L55b	20	99	87

Scheme 37. Evans-type P, N ligands for asymmetric allylic alkylations.



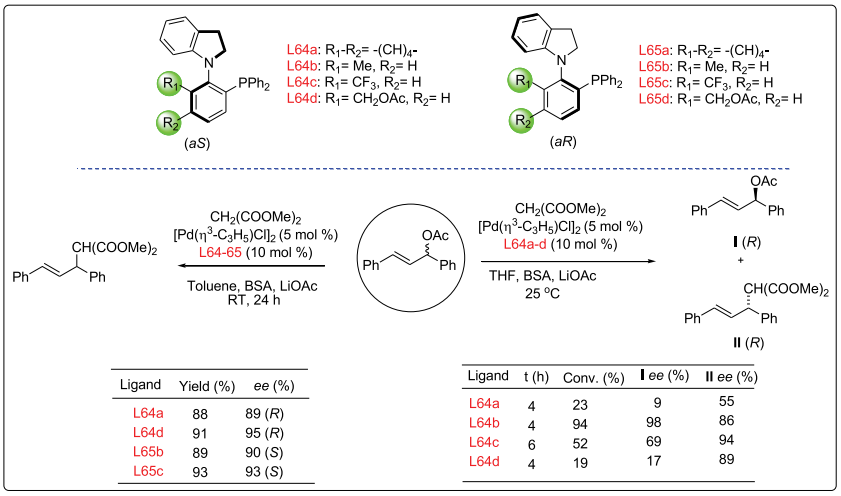
Ligand (mol %)	Catalyst (mol %)	Solvent	t (h/min)	Yield (%)	*ee* (%)
L56a (2.5)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5)	DCM	100 min	96	93 (*R*)
L56b (2.5)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5)	DCM	150 min	96	96 (*R*)
L56c (2.5)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5)	DCM	90 min	94	20 (*S*)
L56d (2.5)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5)	DCM	140 min	96	19 (*S*)
L56e (2.5)	$[Pd(\eta3\text{-}C_3H_5)Cl]_2$ (2.5)	DCM	150 min	95	11 (*R*)
L56f (2.5)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5)	DCM	160 min	93	39 (*R*)
L56g (2.0)	$Pd(OAc)_2$ (1.0)	THF	4 h	95	96 (*S*)
L56h (2.0)	$Pd(OAc)_2$ (1.0)	THF	4 h	93	76 (*S*)
L56i (2.0)	$Pd(OAc)_2$ (1.0)	THF	4 h	97	18 (*S*)
L56j (2.0)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.5)	DCM	4 h	95	97 (*S*)
L56k (2.0)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.5)	DCM	4 h	76	55 (*S*)
L56l (2.0)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.5)	DCM	52 h	85	34 (*S*)

Scheme 38. Asymmetric allylic alkylations using C_2-symmetric aminophosphines.



Ligand	Solvent	T (°C)	Yield (%)	*ee* (%)
L57a	Toluene	RT	97	40 (*R*)
L57c	Diethyl ether	-10	99	95 (*S*)
L58a	Toluene	RT	94	76 (*R*)
L58b	Toluene	RT	93	76 (*R*)
L58c	Toluene	RT	86	76 (*S*)
L59	Toluene	RT	95	57 (*R*)
L60a	Toluene	RT	93	93 (*S*)
L60b	Toluene	RT	90	94 (*S*)
L60c	Toluene	RT	98	78 (*S*)
L60d	Toluene	RT	90	91 (*S*)
L60e	Toluene	20	64	86 (*S*)
L61a	Toluene	RT	97	40 (*R*)
L61b	Toluene	RT	97	85 (*R*)
L62a	Toluene	RT	98	58 (*S*)
L62b	Toluene	RT	86	89 (*S*)
L62c	Toluene	RT	94	92 (*S*)
L62d	Toluene	RT	89	87 (*S*)
L62e	Toluene	RT	91	93 (*S*)
L62f	Toluene	RT	93	83 (*R*)
L63a	Diethyl ether	-10	98	95 (*S*)
L63b	Diethyl ether	0	95	94 (*S*)
L63c	Diethyl ether	0	96	94 (*S*)
L63d	Diethyl ether	0	64	94 (*S*)

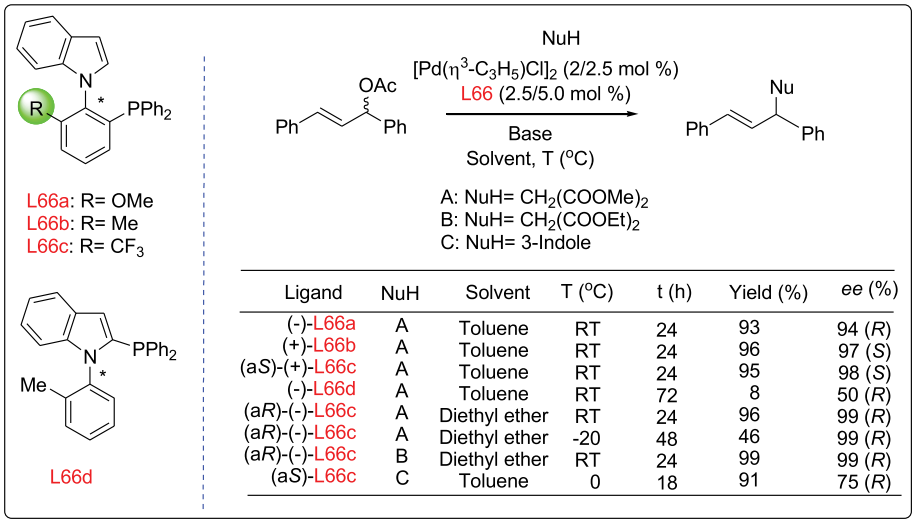
Scheme 39. Asymmetric allylic alkylations using pyrrolidine-derived chiral aminophosphines.



Ligand	Yield (%)	*ee* (%)
L64a	88	89 (*R*)
L64d	91	95 (*R*)
L65b	89	90 (*S*)
L65c	93	93 (*S*)

Ligand	t (h)	Conv. (%)	I *ee* (%)	II *ee* (%)
L64a	4	23	9	55
L64b	4	94	98	86
L64c	6	52	69	94
L64d	4	19	17	89

Scheme 40. Indoline-derived aminophosphines for asymmetric allylic alkylations and kinetic resolution of esters.



Ligand	NuH	Solvent	T (°C)	t (h)	Yield (%)	*ee* (%)
(-)-L66a	A	Toluene	RT	24	93	94 (*R*)
(+)-L66b	A	Toluene	RT	24	96	97 (*S*)
(aS)-(+)-L66c	A	Toluene	RT	24	95	98 (*S*)
(-)-L66d	A	Toluene	RT	72	8	50 (*R*)
(a*R*)-(-)-L66c	A	Diethyl ether	RT	24	96	99 (*R*)
(a*R*)-(-)-L66c	A	Diethyl ether	-20	48	46	99 (*R*)
(a*R*)-(-)-L66c	B	Diethyl ether	RT	24	99	99 (*R*)
(aS)-L66c	C	Toluene	0	18	91	75 (*R*)

Scheme 41. Indole-derived aminophosphines for asymmetric allylic alkylations.

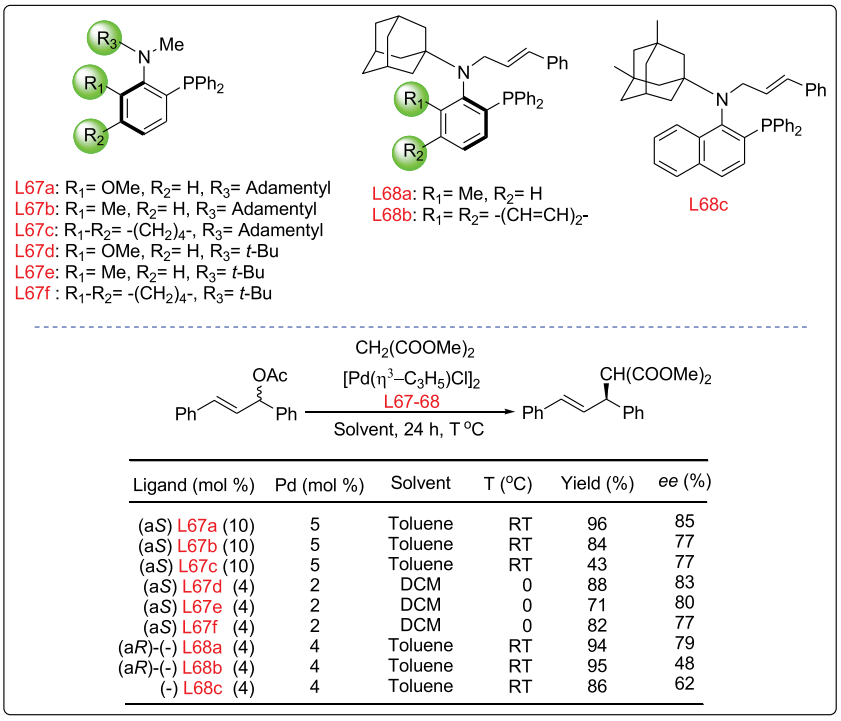
yield (83%) [70]. Similarly, they used two new atropisomer phosphinamine ligands, 2-(2-pyridyl)-Quinazolinap (*S*)-**L44b** and 2-(2-pyrazinyl)-Quinazolinap (*R*)-**L44c** for asymmetric allylic alkylation of 1, 3-diphenyl-2-propenyl acetate with dimethyl malonate under two standard methods (Scheme 29) [71]. In some cases, 15-Crown-5 has been added to aid the dissolution of the preformed sodium malonate. Both the ligands showed low conversions and enantioselectivities, possibly due to the hemilabile nature of the nitrogen atom of the 2-substituent.

Similarly, the Quinazolinap ligands containing a 2-cyclobutyl ring (*S*)-**L45a** and 2-adamantyl ring (*S*)-**L45b** (4.3 mol %) were applied for allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %), BSA and various bases and solvents at room temperature [72]. The ligand (*S*)-**L45a** furnished the alkylated (*R*) product with 95% conversion and 89% *ee* in KOAc and DCM, while (*S*)-**L45b** provided the alkylated (*S*) product with 95% conversion with 49% *ee* in Cs_2CO_3 and DCM. The ligand (*S*)-**L45a** was superior to (*S*)-**L45b** in enantioselectivity. The stereochemical outcome of the reaction depends on the alkali metal salt used. The ligand (*S*)-**L45a** containing the larger counterions (K^+ and Cs^+) provided the product with high optical purity (89% *ee* and 87% *ee*) than smaller counterions Na^+ and Li^+ (82% *ee* and 40% *ee*).

They [73] also developed four new members of the Quinazolinap ligands **L45c-g** for allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. Though all the ligands (6 mol %) showed 100% conversions, ligand (*S*)-**L45g** showed 85% *ee* of (*R*) product in BSA-KOAc and DCM in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) at room temperature.

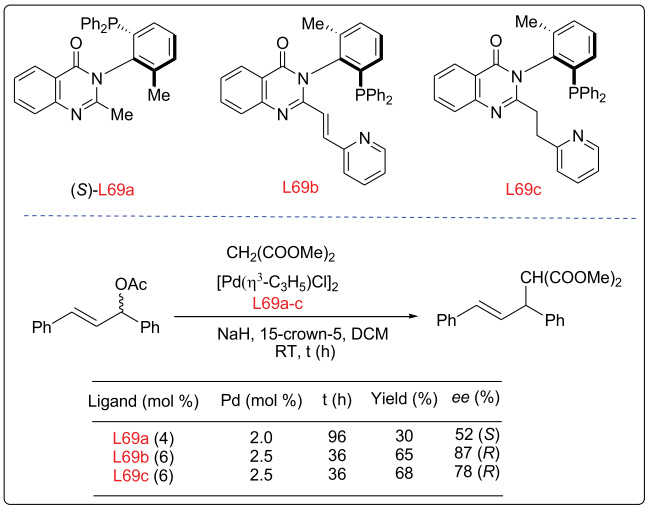
'Quinazox' (**L46a-b**) is an analog of 'Quinazolinap' and contains the oxazoline moiety. The ligands were used in Pd-catalyzed asymmetric allylic alkylation. Though all the ligands (6 mol %) showed > 95% conversions, ligand (*Ra, S*)-**L46a** showed 81% *ee* of (*R*) product in BSA-LiOAc and DCM in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) at room temperature. (Scheme 30) [74].

Evans and Brandt [75] obtained *cis* and *trans*-phosphine-1,3-oxazines (**L47a** and **L47b**) from readily available materials. The preformed catalyst prepared from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and the **L47a-b** (ratio: 1:2) was applied for asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate and Na salt of dimethyl malonate (Scheme 31). The ligand **L47a** (4 mol %) attained 95% *ee* with a 99% yield of the desired product in DCM at 0 °C. Under similar reaction conditions, chiral phosphine–oxazinane ligands (**L48a-d**) are also used in the reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate [76]. The ligand showed 95% *ee* for **L48b**.



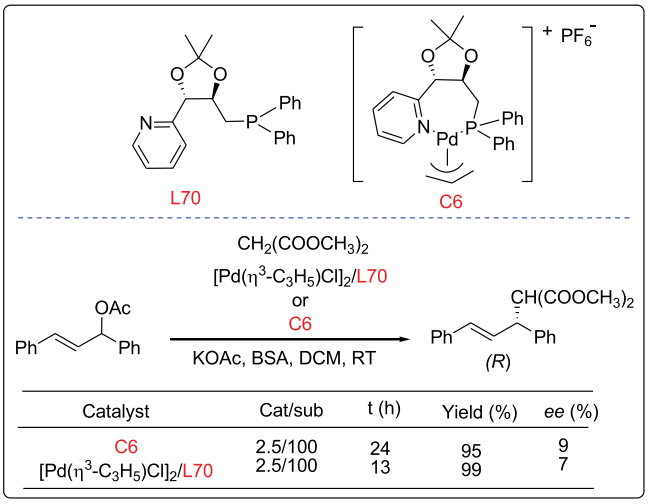
Ligand (mol %)	Pd (mol %)	Solvent	T (°C)	Yield (%)	*ee* (%)
(a*S*) L67a (10)	5	Toluene	RT	96	85
(a*S*) L67b (10)	5	Toluene	RT	84	77
(a*S*) L67c (10)	5	Toluene	RT	43	77
(a*S*) L67d (4)	2	DCM	0	88	83
(a*S*) L67e (4)	2	DCM	0	71	80
(a*S*) L67f (4)	2	DCM	0	82	77
(a*R*)-(-) L68a (4)	4	Toluene	RT	94	79
(a*R*)-(-) L68b (4)	4	Toluene	RT	95	48
(-) L68c (4)	4	Toluene	RT	86	62

Scheme 42. Asymmetric allylic alkylations using aniline-based aminophosphines.



Ligand (mol %)	Pd (mol %)	t (h)	Yield (%)	*ee* (%)
L69a (4)	2.0	96	30	52 (*S*)
L69b (6)	2.5	36	65	87 (*R*)
L69c (6)	2.5	36	68	78 (*R*)

Scheme 43. Atropisomeric monodentate and chelate quinazolinone phosphine ligands for asymmetric allylic alkylations.



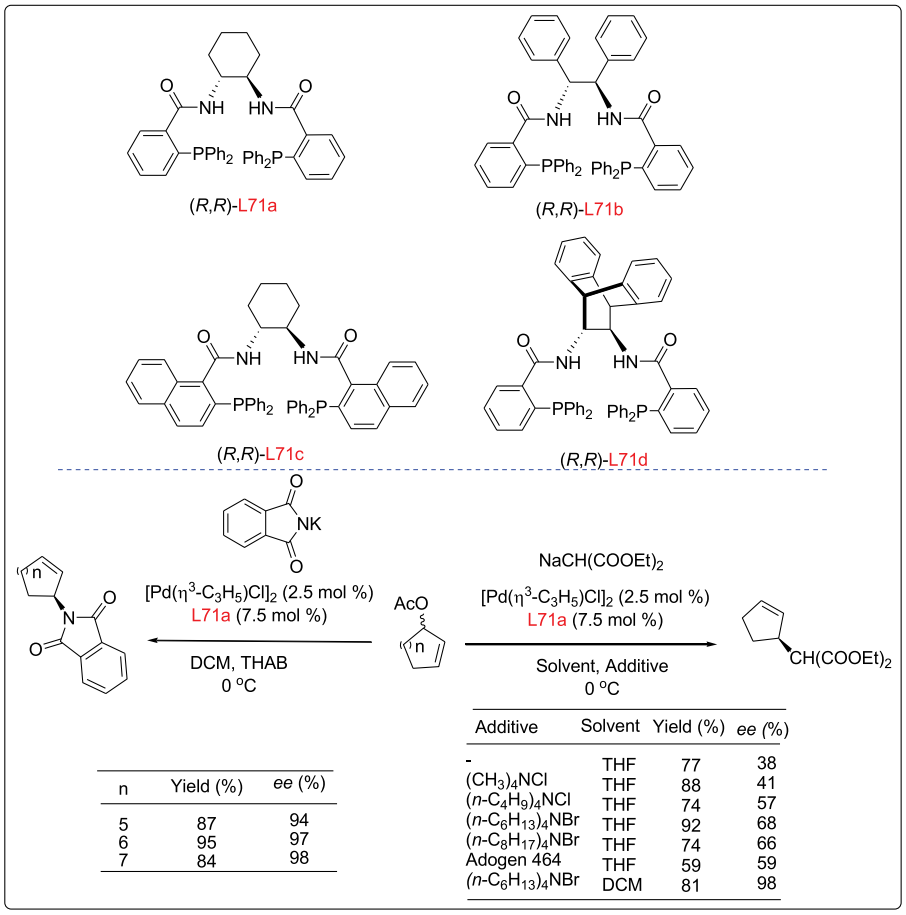
Catalyst	Cat/sub	t (h)	Yield (%)	*ee* (%)
C6	2.5/100	24	95	9
[Pd(η3-C3H5)Cl]2/L70	2.5/100	13	99	7

Scheme 44. Homochiral pyridyl phosphino dioxolane derivatives for asymmetric allylic alkylations.

(*S*)-1-Amino-2-methoxymethyl pyrrolidine (SAMP) and their analogs derived from chiral phosphine hydrazones have been developed as efficient ligands for many Pd-catalyzed reactions [77]. In this regard, extensive work on the Pd-catalyzed asymmetric alkylation reactions using various SAMP hydrazones was reported by Mino and coworkers.

The 2-diphenylphosphinobenzaldehyde-SAMP hydrazone (DPPB-SAMP) ligands were prepared easily from 2-(diphenylphosphino)benzaldehyde and corresponding chiral hydrazines. The ligands **L49a-c** (6 mol %) were applied for asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate, BSA-LiOAc using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %) in different solvents at room temperature (Scheme 32) [78]. The ligand **L49a** gave predominantly, the (*R*)-enantiomer with > 98% enantioselectivity. Though superior enantioselectivity (87% *ee*) was observed in KOAc, the enantioselectivity increased to 90% in LiOAc. However, enantioselectivity decreased to 72% in NaOAc. In addition, the SAMP hydrazone ligands (**L49d-l**) based on ortho fluorobenzaldehyde also showed high enantioselectivity [79]. It was observed that chiral hydrazone ligands **L49j** attained high yields with the highest enantioselectivities (91% *ee*) for the allylic alkylation of 1, 3-diphenyl-2-propenyl acetate with dimethyl malonate in THF at room temperature.

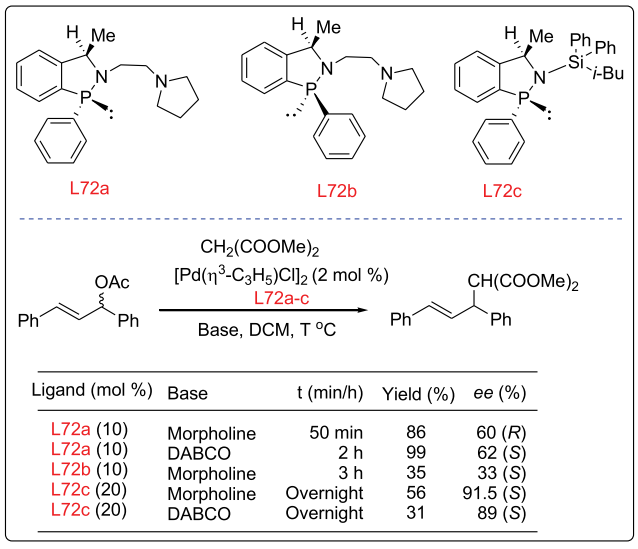
A group of five phosphino hydrazone ligands (**L50a-e**) with a pendant binaphthyl unit as a chiral modifier was synthesized from non-racemic 2,2'-bis(bromomethyl)-1,10-binaphthyl and 3,3'-diiodo-2,20-bis(bromomethyl)-1,10-binaphthyl (Scheme 33) [80]. The $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**L50e** (0.5:1.0 mol %) system showed up to 95% *ee* in allylic



n	Yield (%)	*ee* (%)
5	87	94
6	95	97
7	84	98

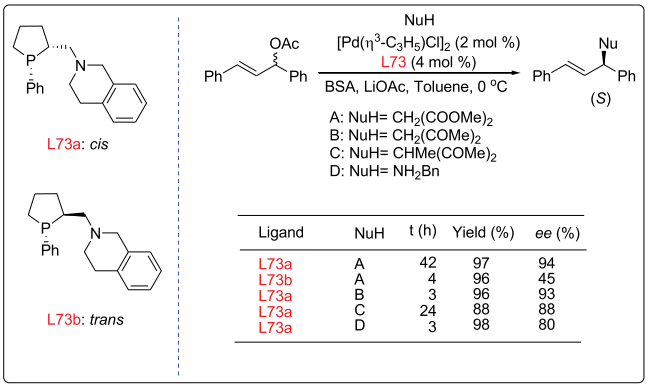
Additive	Solvent	Yield (%)	*ee* (%)
-	THF	77	38
$(CH_3)_4NCl$	THF	88	41
$(n\text{-}C_4H_9)_4NCl$	THF	74	57
$(n\text{-}C_6H_{13})_4NBr$	THF	92	68
$(n\text{-}C_8H_{17})_4NBr$	THF	74	66
Adogen 464	THF	59	59
$(n\text{-}C_6H_{13})_4NBr$	DCM	81	98

Scheme 45. Trost's chiral amino phosphine ligands for asymmetric allylic alkylations.



Ligand (mol %)	Base	t (min/h)	Yield (%)	*ee* (%)
L72a (10)	Morpholine	50 min	86	60 (*R*)
L72a (10)	DABCO	2 h	99	62 (*S*)
L72b (10)	Morpholine	3 h	35	33 (*S*)
L72c (20)	Morpholine	Overnight	56	91.5 (*S*)
L72c (20)	DABCO	Overnight	31	89 (*S*)

Scheme 46. Mono-substituted phosphinous amide ligands for asymmetric allylic alkylations.

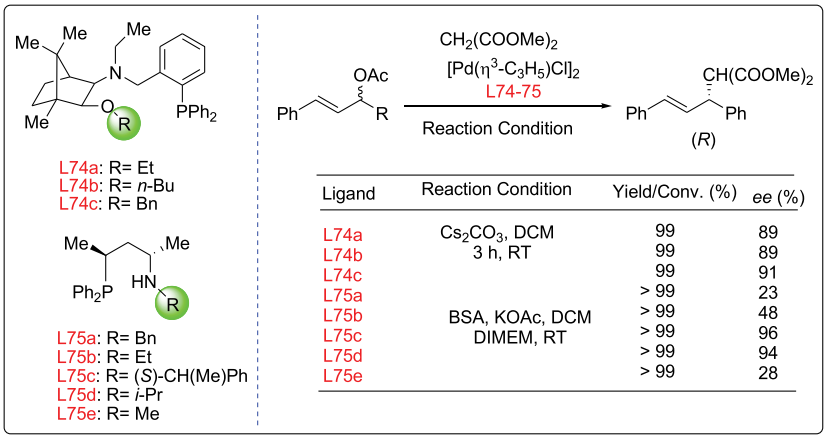


Ligand	NuH	t (h)	Yield (%)	*ee* (%)
L73a	A	42	97	94
L73b	A	4	96	45
L73a	B	3	96	93
L73a	C	24	88	88
L73a	D	3	98	80

Scheme 47. P, N-ligands containing a tetrahydroisoquinoline skeleton for asymmetric allylic alkylations.

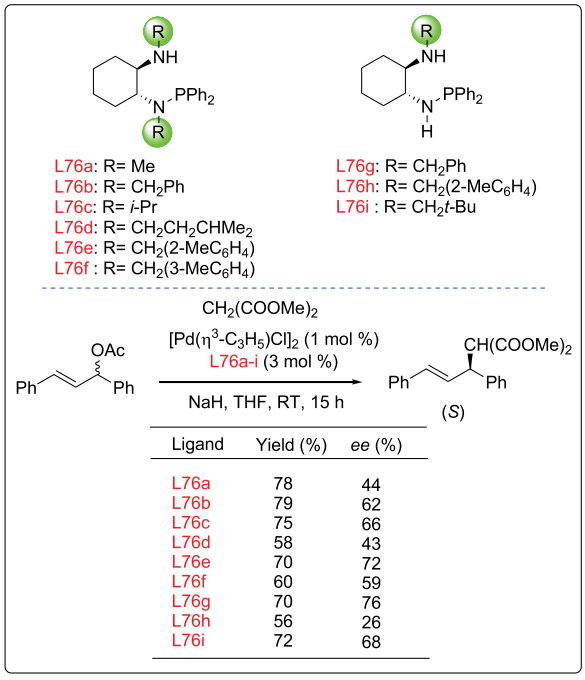
alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate using BSA, LiOAc as a base in toluene at room temperature. The cyclic acetates yielded largely racemic products, and only cycloheptenyl acetate showed good asymmetric induction.

A chiral phosphine–imine ligands derived from 1-mesitylethylamine (**L51a-d**) [81a] and α-phenylethylamine (**L52a-i**) [81b] obtained from phenylethylamine also applied for Pd catalyzed asymmetric allylic alkylation (Scheme 34). The ligand **L51a-b** resulted in only poor enantioselectivity, while **L51c** showed moderate enantioselectivity in the reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) BSA, LiOAc in DCM at room temperature. However, due to the steric effect of the substituents on the aromatic ring, **L51d** showed good enantioselectivity. Similarly, the readily available phosphine-imine ligands (**L52a-i**) from α-phenylethylamine act as highly efficient ligands for alkylation of 1,3-diphenyl-prop-2-en-1-yl pivalate with dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %) BSA, Cs_2CO_3 in toluene at room temperature. All the ligands showed up to 94% *ee* and 99% conversions. It was



Ligand	Reaction Condition	Yield/Conv. (%)	*ee* (%)
L74a	Cs_2CO_3, DCM 3 h, RT	99	89
L74b		99	89
L74c		99	91
L75a	BSA, KOAc, DCM DIMEM, RT	> 99	23
L75b		> 99	48
L75c		> 99	96
L75d		> 99	94
L75e		> 99	28

Scheme 48. Camphene-derived aminophosphines for asymmetric allylic alkylations.



Ligand	Yield (%)	*ee* (%)
L76a	78	44
L76b	79	62
L76c	75	66
L76d	58	43
L76e	70	72
L76f	60	59
L76g	70	76
L76h	56	26
L76i	72	68

Scheme 49. Homochiral amino phosphine ligands for asymmetric allylic alkylations.

observed that the chirality on the chelated ring of ligand **L52** more effectively transfers stereochemical information than ligand **L51**, in which the chirality lay outside the chelate ring.

Zeng et al. [82] used chiral ferrocene-based phosphine-imine ligands (**L53a-n**) for allylic alkylation of cycloalkenyl esters. The ligands substituents of the aryl, ferrocenylmethyl, and benzyliene positions strongly influence the enantioselective induction. Thus the ligand **L53b** (5 mol %) with a nitro group at the *meta* position of the phenyl ring showed the highest enantioselectivity (83% *ee*) in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %), BSA and KOAc in toluene at room temperature for 24 h, which get increased to 91% using LiOAc at 0 °C for 48 h (Scheme 35).

Phosphorus-containing chiral amidine ligand (**L54**) showed excellent yield (up to 99%) and enantioselectivity (up to 95% *ee*) in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate or pivalate with dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.025-0.05 mol %), BSA-LiOAc in various solvents such as THF or DCM or DCE at room temperature (Scheme 36) [83]. In addition, this catalytic system also showed excellent yield (up to 95%) and enantioselectivity (up to 93% *ee*) in the alkylations with ketene silyl acetals [84].

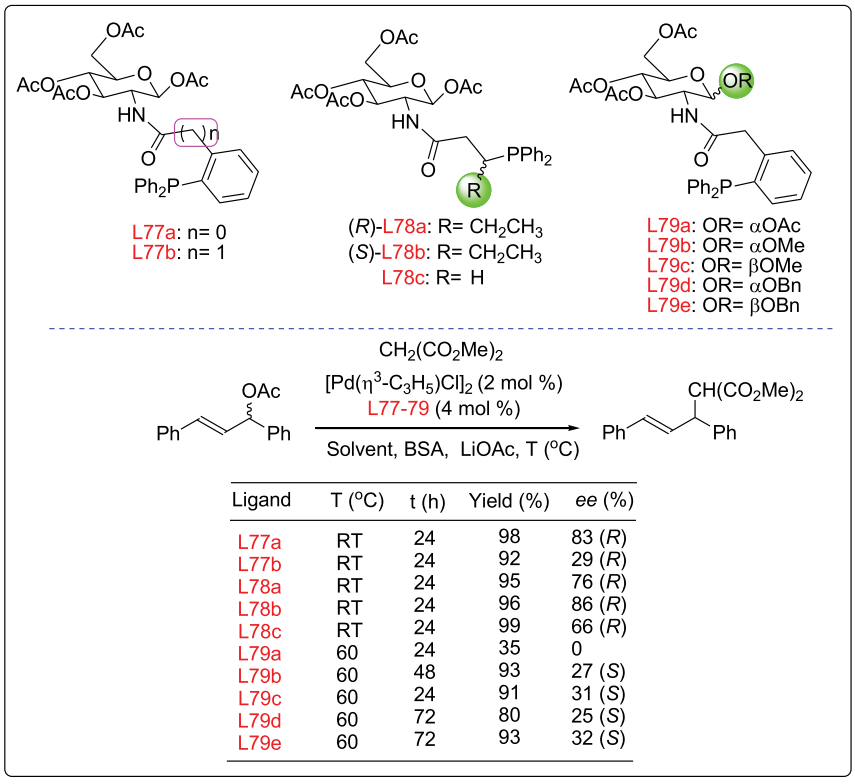
Jiang and coworkers [85] applied Evans-type P, N ligand (**L55a-b**) for the asymmetric allylic alkylation (Scheme 37). These ligands coupled 1,3-diphenyl-2-propenyl acetate and several nucleophiles under optimal reaction conditions. The reactions were smoothly carried out at –10 °C providing the desired product with up to 87% *ee* and excellent yield using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %).

It is shown that the length and rigidity of the P-N bond connecting the carbon backbone determine the "bite-angle" of the ligand, which influences the catalytic activity and stereoselectivity of catalysts. In this regard, aminophosphines are considered versatile ligands in which the N centers can impart additional reactivity features. The first aminophosphine was reported by Michaelis in 1903 [86]. Though aminophosphines are sensitive to air and moisture, research in aminophosphine chemistry is gaining much attention in catalysis, especially in heterocyclic chemistry [87].

The phosphorus-containing C_2-symmetric chiral amine ligand is highly effective for Pd-catalyzed enantioselective allylic substitution reactions. In these connections, Kubota and Koga [88] reported C_2-symmetric chiral ligands (**L56a-f**) for allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %), KOAc-BSA, in DCM at room temperature (Scheme 38). The ligand **L56a** (2.5 mol%) having chiral binaphthyl rings in the axial orientation to the homo piperidine ring would create a better chiral environment as it obtained high *ee* (up to 93%) than the chiral pyrrolidine having a pseudo-equatorial substituent. In addition, the ligand **L56b** having an expanded ring attained up to 96% enantioselectivity as compared to ligand **L56a**.

Widhalm and coworkers [89] reported various chiral aminophosphine ligands for allylic alkylation reactions. Though all the ligands **L56h-i** (2 mol %) gave excellent chemical yield, while, only **L56g** exhibited excellent enantioselectivity (96%) for 1,3-diphenyl-2-propenyl acetate in the presence of $Pd(OAc)_2$ (1 mol %) in THF at room temperature. The ligand **L56j-l** was also used in the allylic substitution of 1,3-substituted propenylacetates with dimethyl malonate [90]. The ligand **L56j** also attained up to 97% *ee* in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.5 mol %), KOAc, BSA, in DCM at room temperature.

Extensive work on the DPPBA-SAMP-derived chiral aminophosphine without hydrazone moiety was reported by Mino and coworkers. Their initial report [91] introduced chiral aminophosphine ligands **L57a, L58a-c**, and **L59** for asymmetric allylic alkylation reaction (Scheme 39). Though all the ligands (4 mol %) showed good to excellent yields, enantioselectivity was moderate (maximum up to 76% *ee*) for the



Ligand	T (°C)	t (h)	Yield (%)	*ee* (%)
L77a	RT	24	98	83 (*R*)
L77b	RT	24	92	29 (*R*)
L78a	RT	24	95	76 (*R*)
L78b	RT	24	96	86 (*R*)
L78c	RT	24	99	66 (*R*)
L79a	60	24	35	0
L79b	60	48	93	27 (*S*)
L79c	60	24	91	31 (*S*)
L79d	60	72	80	25 (*S*)
L79e	60	72	93	32 (*S*)

Scheme 50. D-Glucosamine diphenylphosphino ligands for asymmetric allylic alkylations.

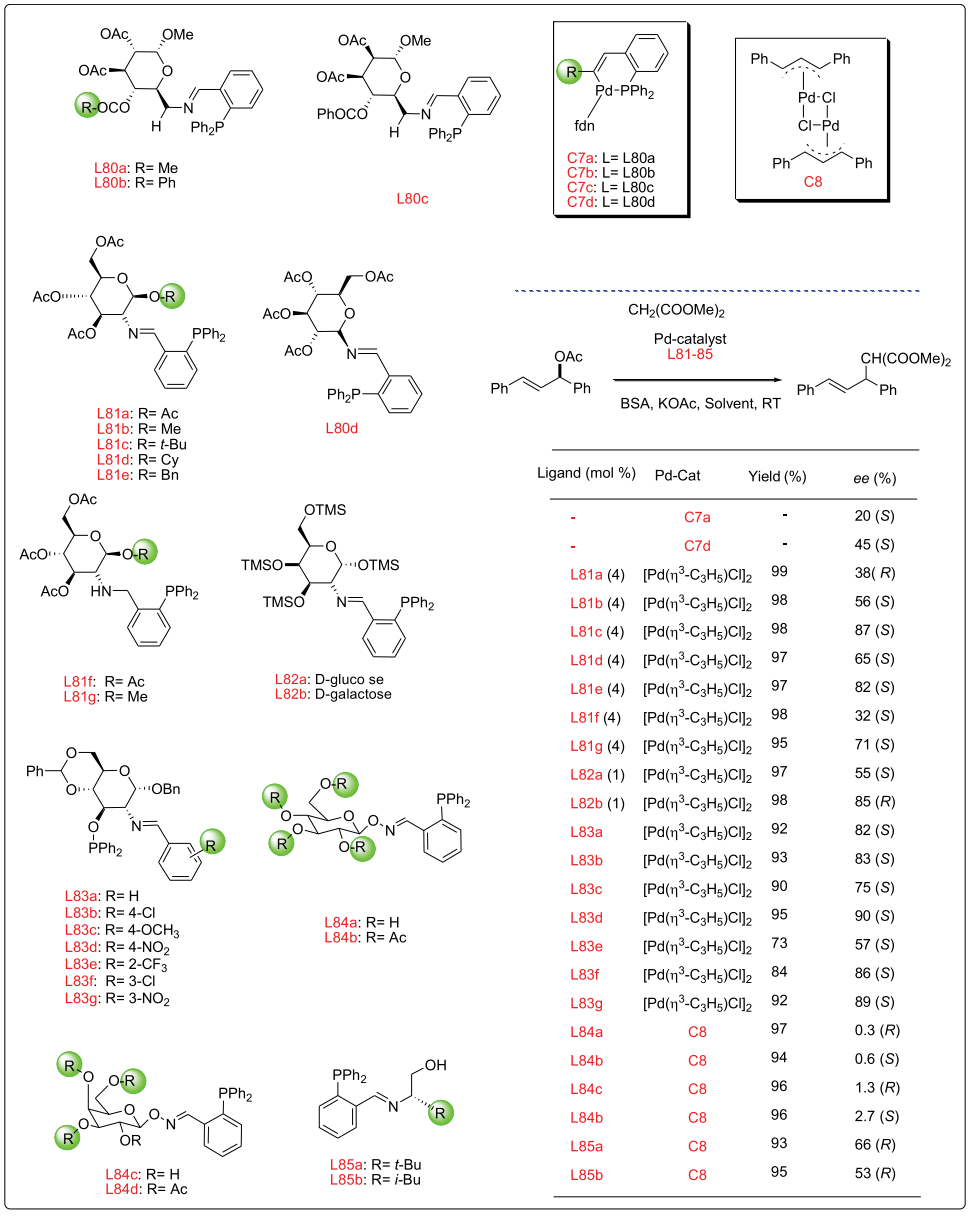
reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %) using BSA-LiOAc system in toluene at room temperature. Compared to **L58a** (94% yield with 76% *ee*), a slight increase in yield and *ee* was observed for **L58b** (96% with 79% *ee*) in THF. This indicated that a methoxy ethoxy methyl group of the pyrrolidine side chain of ligand **L58b** interacts slightly more with the incoming nucleophile.

The reactivity and selectivity of pyrrolidinyl-containing aminophosphines **L60a-d, L61a-b**, and ligands **L62a-f** (4 mol %) were studied for asymmetric allylic alkylation [92]. All other ligands, except **L62a** (58% *ee*), brought high enantioselectivity (83–93% *ee*) for the reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate by using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %), BSA-LiOAc in toluene at room temperature. The enantioselectivity was further improved to 96% by decreasing the reaction temperature to −20 °C. Under the same reaction condition, the more sterically hindered silylated chiral aminophosphine ligands (**L60a-d**) worked efficiently. Except for **L60c** (78% *ee*), all the ligands brought high enantioselectivity (91–94%) at room temperature in toluene. The enantioselectivity was further improved to 97% by decreasing the reaction temperature to −20 °C with only 69%. Under similar reaction conditions, the chiral (*S*)-prolinol-derived aminophosphine ligands **L63a-c** and ligand **L63d** containing two fluorous ponytails showed excellent yield and enantioselectivities (96% yield and 94% *ee* for **L63d**) for alkylation of 1,3-diphenyl-2-propenyl acetate with dialkyl malonate in diethyl ether at various temperatures [93]. The fluorous Pd catalyst (10 mol %) prepared *in situ* from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and **L63d** can be separated easily by simple solid/liquid separation from the reaction mixture and reused up to five times. The catalyst showed consistent four times reusability for the reaction of 1, 3-diphenyl-2-propenyl acetate with dimethyl malonate, while six times reusability for diethyl malonate in diethyl ether at 30 °C.

Mino and coworkers synthesized N-aryl indoline-type aminophosphines by the optical resolution of their diastereomeric Pd complexes. The ligands (**L64a-d** and **L65a-d**) (10 mol %) showed excellent enantioselectivity in the reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol %), BSA-LiOAc in toluene at room temperature (Scheme 40) [94]. The ligand **L64d** attained 95% *ee* with a 91% yield of (*R*) product. The ligands (10 mol %) also carried out the kinetic resolution of starting easters by using Pd-catalyzed asymmetric allylic alkylation of a 1, 3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of LiOAc-BSA and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol %) in various solvents at 25 °C [95]. Ligand **L64c** was an effective ligand for the kinetic resolution with good enantioselectivities (Scheme 40).

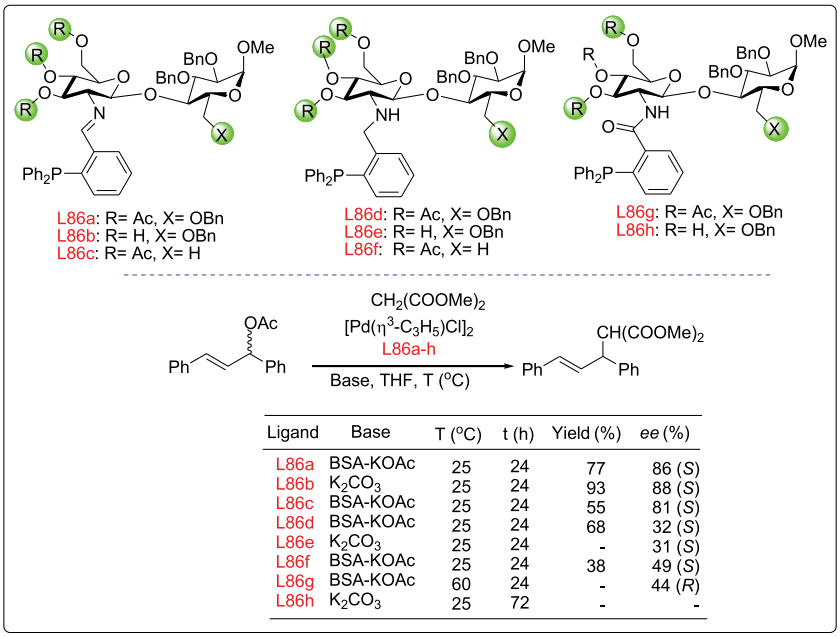
A new N-aryl indole-derived chiral phosphine ligands (**L66a-d**) (4 mol %) were also achieved up to 99% *ee* for asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl with dimethyl malonate under standard reaction conditions (Scheme 41) [96]. Though all the ligands were efficient for the alkylation of indoles with 1,3-diphenyl-2-propenyl acetate [97], the ligand **L66c** (5 mol %) gave the desired products in good to excellent yields with up to 90% *ee* for the reaction of substituted indoles in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %), and K_2CO_3 in toluene at room temperature under argon.

The C(aryl)-N(amine) bond atropisomers of acyclic aminophosphines based on substituted anilines (**L67a-c**) [98], **L67d-f** [99], and **L68a-c** [100] was developed for asymmetric allylic alkylation reactions (Scheme 42). The chiral acyclic amine **L67a** can be resolved by crystallization without any outside chiral source. While ligands **L67d-f**



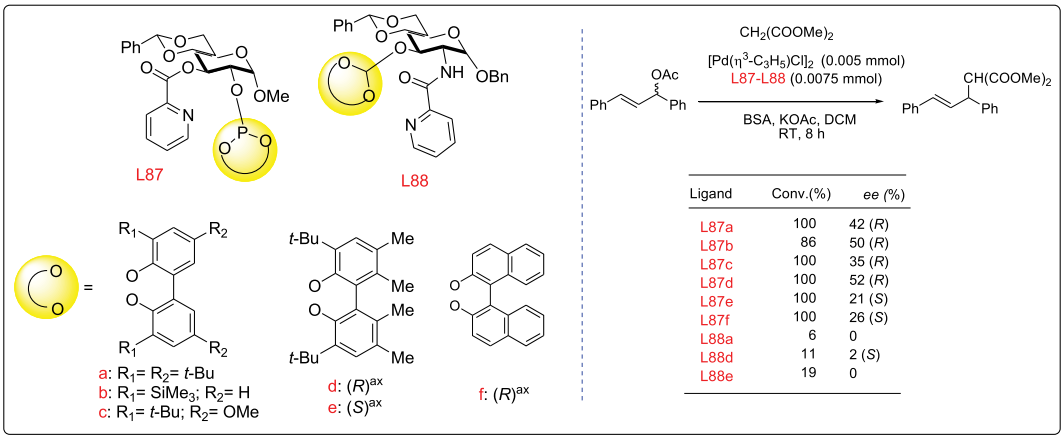
Ligand (mol %)	Pd-Cat	Yield (%)	*ee* (%)
-	C7a	-	20 (*S*)
-	C7d	-	45 (*S*)
L81a (4)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	99	38(*R*)
L81b (4)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	98	56 (*S*)
L81c (4)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	98	87 (*S*)
L81d (4)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	97	65 (*S*)
L81e (4)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	97	82 (*S*)
L81f (4)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	98	32 (*S*)
L81g (4)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	95	71 (*S*)
L82a (1)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	97	55 (*S*)
L82b (1)	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	98	85 (*R*)
L83a	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	92	82 (*S*)
L83b	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	93	83 (*S*)
L83c	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	90	75 (*S*)
L83d	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	95	90 (*S*)
L83e	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	73	57 (*S*)
L83f	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	84	86 (*S*)
L83g	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	92	89 (*S*)
L84a	C8	97	0.3 (*R*)
L84b	C8	94	0.6 (*S*)
L84c	C8	96	1.3 (*R*)
L84b	C8	96	2.7 (*S*)
L85a	C8	93	66 (*R*)
L85b	C8	95	53 (*R*)

Scheme 51. Carbohydrate-based iminophosphinites for asymmetric allylic alkylations.



Ligand	Base	T (°C)	t (h)	Yield (%)	*ee* (%)
L86a	BSA-KOAc	25	24	77	86 (*S*)
L86b	K_2CO_3	25	24	93	88 (*S*)
L86c	BSA-KOAc	25	24	55	81 (*S*)
L86d	BSA-KOAc	25	24	68	32 (*S*)
L86e	K_2CO_3	25	24	-	31 (*S*)
L86f	BSA-KOAc	25	24	38	49 (*S*)
L86g	BSA-KOAc	60	24	-	44 (*R*)
L86h	K_2CO_3	25	72	-	-

Scheme 52. Phosphines-based disaccharides for asymmetric allylic alkylations.



Ligand	Conv.(%)	*ee* (%)
L87a	100	42 (*R*)
L87b	86	50 (*R*)
L87c	100	35 (*R*)
L87d	100	52 (*R*)
L87e	100	21 (*S*)
L87f	100	26 (*S*)
L88a	6	0
L88d	11	2 (*S*)
L88e	19	0

Scheme 53. Pyranoside phosphite-pyridine ligands for asymmetric allylic alkylations.

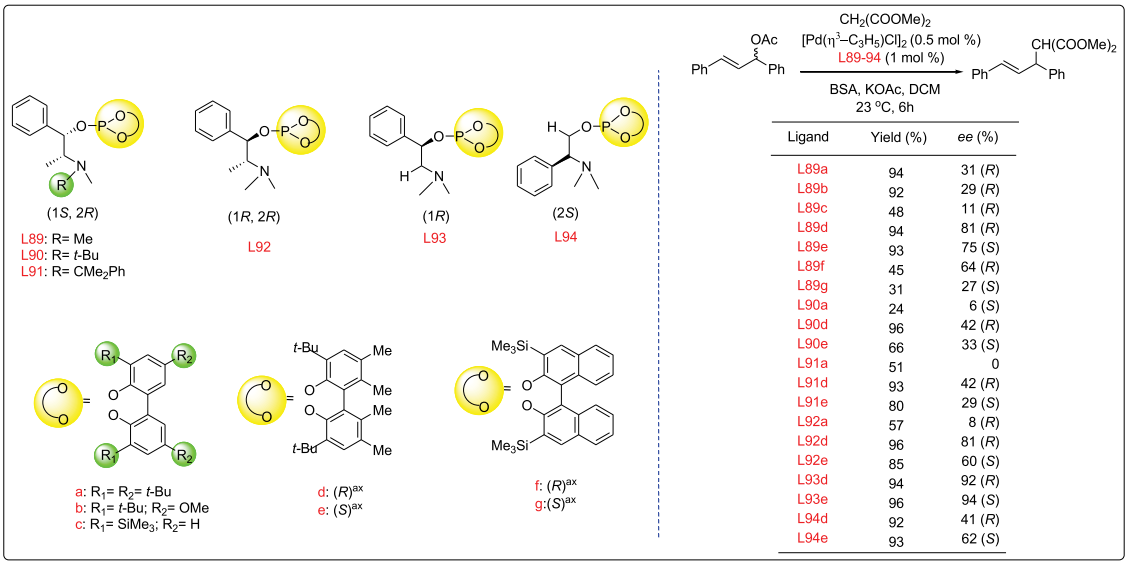
can be resolved by a chiral Pd resolving agent or a chiral HPLC method. The ligand (*aS*)-**L67a** could induce higher enantioselectivity (85% *ee*) than ligand **L67b-c** (up to 77% *ee*) with a 96% yield for the reaction of 1, 3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of BSA and LiOAc in toluene at room temperature. The yield was slightly improved to 98 % with 88% *ee* using MeCN as a solvent at 0 °C. The [Pd(η^3-C_3H_5)Cl]$_2$/**L67d-f** (2:4 mol %) system gave 71–88% yield with 77–83% *ee* for dimethyl malonate in 24 h in DCM at 0 °C. The ligand (*aS*)-**L67d** showed higher enantioselectivity (83% *ee*) than the (*aS*)-**L67e** and (*aS*)-**L67f** in DCM. The enantioselectivity further increased to 90.2% in ether. It was demonstrated that N, N-disubstituted allylic amine type aminophosphines **L68a-c** can also be effective ligands for the allylic alkylation of 1,3-diphenyl-2-propenyl acetate and malonates.

Dai and Virgil [101] achieved asymmetric inductions up to 87% *ee* in the allylic alkylation reactions using a new class of atropisomers monodentate (**L69a)** and its chelate quinazolinone phosphine ligands (**L69b-c**) (Scheme 43).

A homochiral pyridyl, and phosphino derivatives of 2,2-dimethyl-1,3-dioxolane (**L70**) were prepared for allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 44) [102]. The reaction was carried out using either a preformed **C6** complex obtained from pydiphos [Pd(η^3-C_3H_5)Cl]$_2$ with a silver salt or complexes formed *in situ* between precatalyst and ligand **L70**. Though in both cases, quantitative yields were obtained in BSA, and KOAc in DCM enantioselectivity was very low at room temperature.

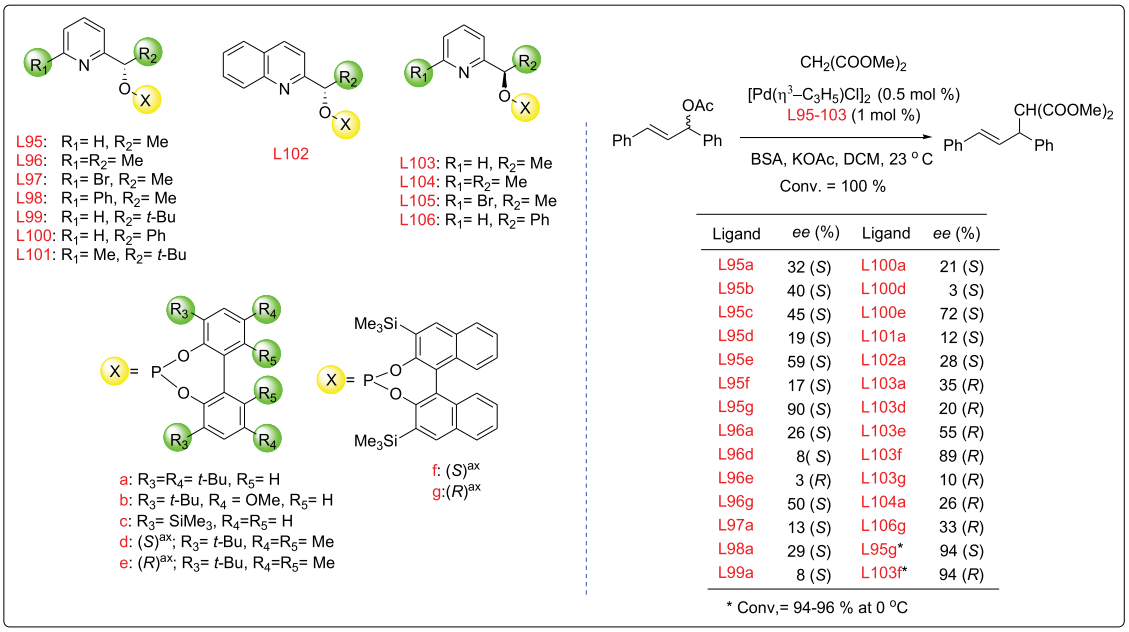
Trost and co-workers introduced four different ligands (**L71a-d**) for Pd-catalyzed asymmetric reactions (Scheme 45). Initially, they studied the role of the nature of the ion pair in the reaction of 3-acetoxycyclopentene with the Na salt of dimethyl malonate. The nature of tetraalkylammonium salts played an important role in asymmetric induction utilizing ligand **L71a** [103]. The limited solubility of the Na salt of dimethyl malonate leads to only 38% *ee*, which was increased to 86% *ee* using THAB, [Pd(η^3-C_3H_5)Cl]$_2$ (2.5 mol %), and **L71a** (7.5 mol %) in THF at 0 °C. As the nature of the ion pair varies with the solvent, the enantioselectivity jumped to 98% in DCM. An excellent result was shown for six and seven-membered ring substrates using a potassium salt of phthalimide under optimized reaction conditions.

Specifically, mono-substituted phosphinous amides (**L72a-c**) (5–20



Ligand	Yield (%)	*ee* (%)
L89a	94	31 (*R*)
L89b	92	29 (*R*)
L89c	48	11 (*R*)
L89d	94	81 (*R*)
L89e	93	75 (*S*)
L89f	45	64 (*R*)
L89g	31	27 (*S*)
L90a	24	6 (*S*)
L90d	96	42 (*R*)
L90e	66	33 (*S*)
L91a	51	0
L91d	93	42 (*R*)
L91e	80	29 (*S*)
L92a	57	8 (*R*)
L92d	96	81 (*R*)
L92e	85	60 (*S*)
L93d	94	92 (*R*)
L93e	96	94 (*S*)
L94d	92	41 (*R*)
L94e	93	62 (*S*)

Scheme 54. Amino phosphite ligands for asymmetric allylic alkylations.



Ligand	*ee* (%)	Ligand	*ee* (%)
L95a	32 (*S*)	L100a	21 (*S*)
L95b	40 (*S*)	L100d	3 (*S*)
L95c	45 (*S*)	L100e	72 (*S*)
L95d	19 (*S*)	L101a	12 (*S*)
L95e	59 (*S*)	L102a	28 (*S*)
L95f	17 (*S*)	L103a	35 (*R*)
L95g	90 (*S*)	L103d	20 (*R*)
L96a	26 (*S*)	L103e	55 (*R*)
L96d	8(*S*)	L103f	89 (*R*)
L96e	3 (*R*)	L103g	10 (*R*)
L96g	50 (*S*)	L104a	26 (*R*)
L97a	13 (*S*)	L106g	33 (*R*)
L98a	29 (*S*)	L95g*	94 (*S*)
L99a	8 (*S*)	L103f*	94 (*R*)

* Conv,= 94-96 % at 0 °C

Scheme 55. Phosphite-pyridine ligands for asymmetric allylic alkylations.

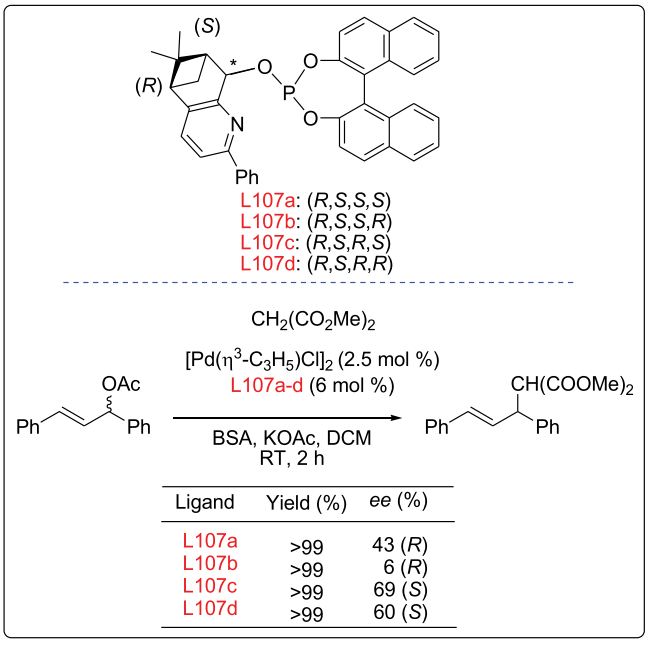
mol %) in which the asymmetric P atom is incorporated in a heterocyclic ring were applied for asymmetric allylic alkylations. The ligand **L72a** showed excellent activity (yield 99%) while ligand **L72a** showed 91.5% *ee* in the alkylation in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %) using morpholine or DABCO as a base in DCM at room temperature (Scheme 46) [104].

P, N-ligands containing a tetrahydroisoquinoline skeleton (**L73a-b**) act as excellent ligands in asymmetric allylic reactions of 1,3-diphenyl-2-propenyl acetate with several nucleophiles in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ [105]. The reaction provided high yields and enantioselectivity. These ligands did not serve as P, N-bidentate but as P-monodentate ligands (Scheme 47).

The camphene-derived aminophosphine ligands (**L74a-c**) also showed excellent enantioselectivity (up to 91%) for allylic alkylation of 1,3-diphenyl-2-propenyl acetate (Scheme 48) [106]. Similarly, Bakos and coworkers [107] reported the pentane-2,4-diyl-based P, N-ligands (**L75a-e**) for asymmetric allylic alkylation reactions. The substituent on N directs the substrate coordination which, influences the reactivity of the catalytically active species. Hence, ligands **L75c-d** provided high enantioselectivity (up to 96%) (Scheme 48)

A series of homochiral amino phosphine ligands (**L76a-f**) showed up to 76% *ee* in allylic alkylation of 1,3-diphenyl-2-propenyl acetate with Na salt of dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as the pre-catalyst using NaH in THF at room temperature (Scheme 49) [108]. The enantioselectivity was affected mostly by the nature of the substituent on nitrogen.

Framery *et al.* [109] reported various carbohydrate-based aminophosphine ligands for Pd-catalyzed allylic alkylation reactions (Scheme



Scheme 56. Pyridine-phosphite ligands for asymmetric allylic alkylations.

50). The flexible **L77b** and **L78a-c** ligands [110] gave the desired alkylation product with the (*R*)-configuration. The ligand **L77b** (4 mol %) gave the lowest enantioselectivity (29%), while ligand **L78b** gave 86% *ee* in the reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in THF. The ligands **L78a–b** bearing a stereogenic center on the spacer showed similar or lower enantioselectivity than **L77a** (83% *ee*). The ligand **L77a** (4 mol %) showed up to 97% enantioselectivity for the alkylation of 1,3-diphenyl-2-propenyl acetate with various carbon and aminonucleophiles in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %) and BSA, LiOAc in THF. In this continuation, they [111] studied the influence of the enantioselectivity modifying the configuration and the nature of the substituent at the anomeric position of the phosphine-amide ligands (**L79a-e**). It is necessary to have an acetoxy group at the anomeric center in *β*-position to obtain enantioselectivity, while the size of the alkyl groups (methyl or benzyl) has not influenced the enantioselectivity.

The P, N-ligands (**L80a-d**) derived from D-glucose and D-mannose on treatment with $[Pd_3(dba)_2]$ and Fumarodinitrile (a prochiral olefin) in dry toluene gave corresponding [Pd(**L80a-d**)(fumarodinitrile)] Pd(0) complexes (**C7a-d**) [112]. Complex **C7a** showed only 20% enantioselectivity with (*S*) enantiomer in allylic alkylation of 1,3-diphenyl-2-propenyl acetate and sodium dimethyl malonate in dry THF. Better enantioselectivity (45% *ee*) could be attained by using complex **C7d** (Scheme 51).

Similarly, the monosaccharides imino and amino phosphine ligands (**L81a-g**) (4 mol %) based on alkyl *β*-D-glucopyranose also exhibited good to excellent activity and enantioselectivities (up to 87% *ee*) in the reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4 mol %) and BSA-KOAc in THF at 25 or 60 °C [113]. Under similar reaction conditions, phosphine–imine ligands derived from D-glucose- and D-galactosamine ligands (**L82a-b**) (1 mol %) achieved a high level of enantioselectivity (up to 85% at 25 °C and 99% at 0 °C) [114].

A series of novel carbohydrate-based iminophosphinite ligands (**L83a-g**) was successfully applied in asymmetric allylic alkylation, and 90% *ee* was achieved by *p*-nitro-substituted ligand **L83d** at 25 °C [115].

A hydrolytically stable oxime (**L84a-d**) based on O-*β*-D-glucopyranosyl was applied for the Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 51) [116]. Though all ligands exhibited good catalytic activity, the enantioselectivity was very poor under standard reaction conditions in DCM at room temperature. However, the ligands **L85a** and **L85b** induced significant stereoselectivity.

It was observed that the disaccharide aminophosphines (**L86a-h**) proved to be superior to the corresponding monosaccharide phosphine-amides in terms of enantiomeric excesses in the reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in THF using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %). The ligand **L86b** (4 mol %) containing free hydroxyl groups on the D-glucosamine framework resulted in high reactivity (93% yield) and enantioselectivity (88% *ee*) (Scheme 52) [117].

Phosphite ligands are extremely attractive and widely used for transition metal catalysis. They are easy to prepare from readily available alcohol [118]. Also, they are less sensitive to air and other oxidizing agents than phosphines.

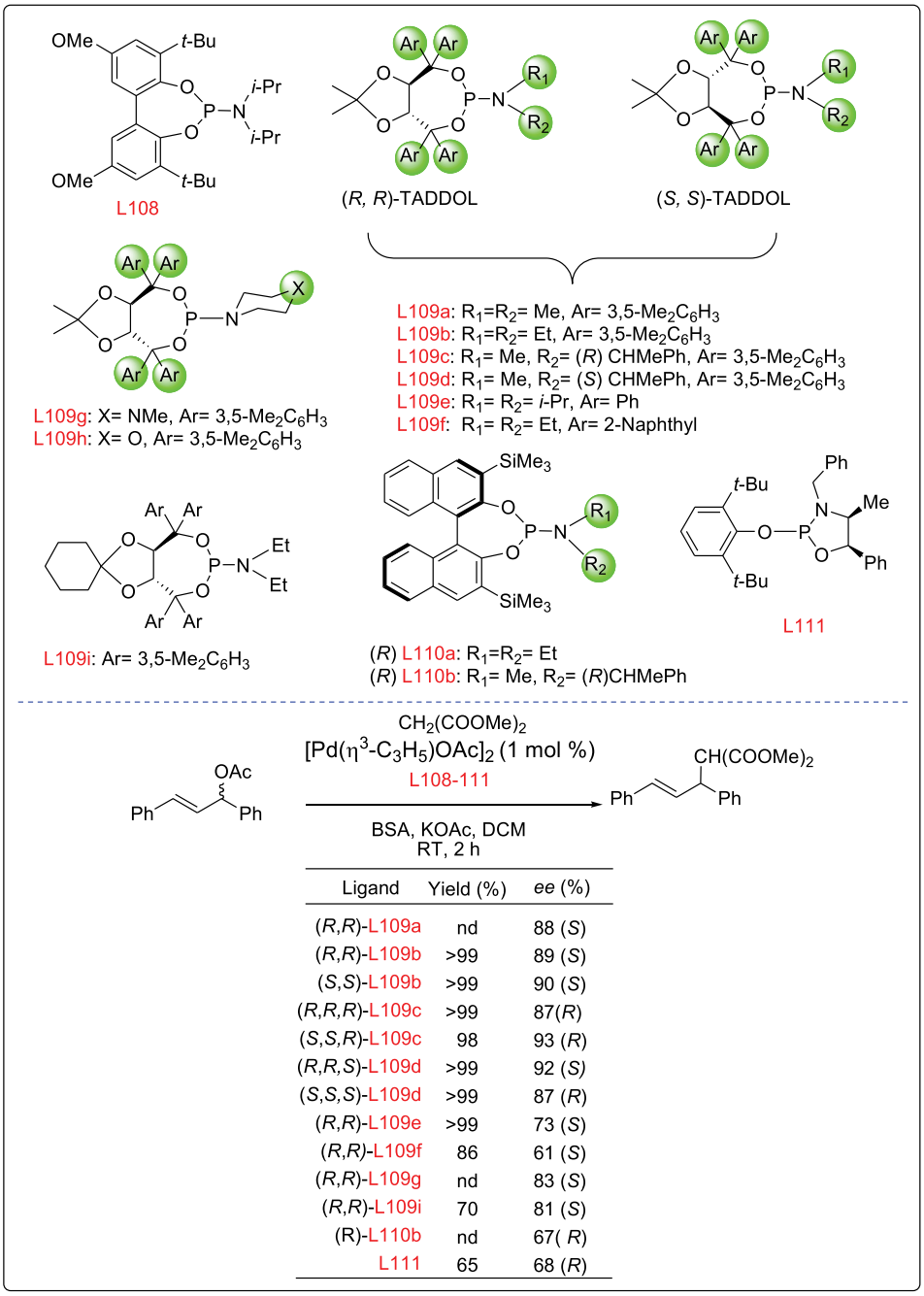
The pyranoside phosphite-pyridine ligands were developed for enantioselective allylic substitution of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of the $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (Scheme 53) [119]. Two libraries of ligands were developed by the immediate functionalization of D-glucose and D-glucosamine. The ligands involve systematic variations of the positions of the phosphite group at both C-2 (**L87**) and C-3 (**L88**) positions of the pyranoside backbone. The ligands also consist of different substituents and configurations in the biaryl phosphite moiety which maximize the catalyst performance. It was indicated that enantioselectivity depends on the position of the phosphite moiety at C-2 or C-3 of the pyranoside backbone as well as the substituents and configuration of the biaryl phosphite moiety. The ligand **L88** with the phosphite group attached to the C-3 of the pyranoside backbone showed lower activity and enantioselectivity than ligand **L87**.

Similarly, a library of amino phosphite ligands (**L89-94**) obtained from enantiopure amino alcohols was applied for asymmetric allylic reactions (Scheme 54) [120]. Various factors, like substituents (**L89, L91**, and **L92**), configuration (**L89** and **L90**) at the ligand backbone, the amine substituents (**L89**), the substituents, and configuration of the biaryl phosphite moiety (**L92a–g**) affects on the activity of the ligands. The presence of trimethylsilyl groups at the ortho positions of the biaryl phosphite moiety negatively affects both the activity and the enantioselectivity.

The best enantioselectivity was obtained for the ligands **L92d** and **L93e** containing enantiopure biaryl phosphite moiety containing the *t*-butyl group at the *ortho* positions. The effect of the amine substituents on **L89a-c** indicated that ligand **L89a** containing dimethylamine group showed better enantioselectivity than the **L89b-c**. The effect of the configuration of the ephedrine backbone was studied by comparing **L89a** and **L90**. Evaluation of **L93** and **L94** showed that the ligands, which do not have the methyl substituent at the stereogenic C-2 position of the ephedrine backbone provided the highest enantioselectivities (92% *ee* and 94% *ee* for **L93d** and **L93e**), while ligand **L94e** leads to similar enantioselectivity as that of **L92e**.

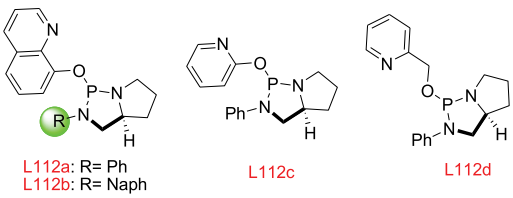
Similarly, a library of phosphite-pyridine ligands **L95-L106** synthesized from the corresponding easily accessible racemic hydroxyl-pyridine compounds were also applied for the allylic substitution reactions of various di- and trisubstituted substrates with C, N, and O nucleophiles (Scheme 55) [121]. High activity and enantioselectivity (up to 94%) were obtained for both **L95g** and **L103f** ligands in the reaction of 1,3-diphenyl-2-propenyl acetate in presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.5 mol %) in DCM at 23 °C. The effect of the substituents at the ligand backbone (R_1 and R_2) showed that for **L95–L102a**, enantioselectivity decreases with steric hindrance at both positions. The best enantioselectivity was observed for **L95** containing hydrogen and a methyl substituent at R_1 and R_2 positions with the formation of (*S*) product, predominantly.

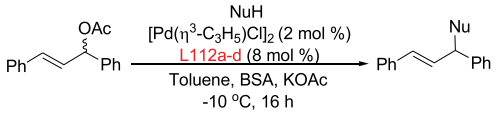
Meng et al. [122] synthesized a series of pyridine-phosphite ligands (**L107a-d**) from PCl_3, chiral BINOL, and 4H-quinolyl alcohols and applied them to asymmetric allylic substitution reactions (Scheme 56).



Ligand	Yield (%)	*ee* (%)
(*R*,*R*)-L109a	nd	88 (*S*)
(*R*,*R*)-L109b	>99	89 (*S*)
(*S*,*S*)-L109b	>99	90 (*S*)
(*R*,*R*,*R*)-L109c	>99	87(*R*)
(*S*,*S*,*R*)-L109c	98	93 (*R*)
(*R*,*R*,*S*)-L109d	>99	92 (*S*)
(*S*,*S*,*S*)-L109d	>99	87 (*R*)
(*R*,*R*)-L109e	>99	73 (*S*)
(*R*,*R*)-L109f	86	61 (*S*)
(*R*,*R*)-L109g	nd	83 (*S*)
(*R*,*R*)-L109i	70	81 (*S*)
(R)-L110b	nd	67(*R*)
L111	65	68 (*R*)

Scheme 57. TADDOL-derived phosphoramidite for asymmetric allylic alkylations.





A: NuH= $CH_2(COOMe)_2$
B: NuH= $NaCH(COOMe)_2$
C: NuH= NH_2CH_2Ph

Ligand	Nu	Conv. (%)	*ee* (%)
L112a	A	100	85 (*R*)
L112c	A	100	87 (*R*)
L112d	A	85	76 (*R*)
L112a	B	100	71 (*R*)
L112a	C	95	93 (*S*)
L112b	C	36	78 (*S*)
L112c	C	70	92 (*S*)
L112d	C	95	93 (*S*)

Scheme 58. C_2-symmetric and non-symmetric chiral ligands for asymmetric allylic alkylations.

All the ligands (6 mol %) showed excellent yield (> 99%) with moderate enantioselectivity for the reaction of 1,3-diphenyl-2-propenyl acetate and dimethyl malonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %), BSA, KOAc in DCM at room temperature. The ligands **L107a** and **L107b** gave a product with (*R*) configuration while **L107c** and **L107d** gave products with (*S*) configuration. Under optimized reaction conditions, moderate enantioselectivity was observed by the ligand **L107c** in the asymmetric allylic aminations with *p*-anisidine.

A series of bulky monodentate phosphoramidite ligands (**L108-L111**) based on TADDOL backbones was employed in the allylic alkylations of both symmetric and nonsymmetric substrates (Scheme 57) [123]. Thus, (*R,R*)-**L109b** showed 89% *ee*, with (*S*) configuration for the alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate using $[Pd(\eta^3\text{-}C_3H_5)(OAc)]_2$ (1 mol %), BSA, KOAc at room temperature. It was observed that changing the ligand stereochemistry in the TADDOL backbone (*S,S*)-**L109b** resulted in the same enantioselectivity, with the formation of an opposite enantiomer (*R*). Ligands (*S,S,R*)-**L109c** and (*R, R,S*)-**L109d** also showed excellent enantioselectivity.

In most of the C_2-symmetric and non-symmetric chiral ligands, the phosphorus atom is not stereogenic, while chirality is mainly induced by a chiral N atom. In contrast to this, Buono and coworkers introduced quiniline and pyridine-phosphines (**L112a-d**) as new nonsymmetric chiral ligands bearing the chiral phosphorus atom for Pd-catalyzed asymmetric alkylation reactions (Scheme 58). The ligands were synthesized from tris(dimethylamino)phosphine and (*S*)-(+)-2-anilinomethylpyrrolidine and pyridine. The ligand **L112c** (8 mol %) achieved up to 87% *ee* in the allylic substitution of 1,3-diphenyl-2-propenyl acetate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol %) and BSA-KOAc in toluene at −10 °C [124]. The ligand also attained up to 94% *ee* in the allylic amination of 1,3-diphenyl-2-propenyl acetate or1, 3-diphenyl-2-propenyl carbonate with primary or secondary amines such as benzylamine, veratrylamine, or morpholine [125].

Bravo and coworkers [126] reported a library of bis(diamidophosphite) ligands (**L113-122**) for asymmetric allylic substitution reactions (Scheme 59). Enantiopure bis(diamidophosphite) ligands (**L113-L115**) with a heterocyclic terminal fragment were derived from (*R*)- and (*S*)-N,N′-dimethyl-1,1′-binaphthyldiamine. The bridging fragments were derived from (*S,S*)-2,3-butanediol, (*4R,5R*)-4,5-di(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane, and (*R*)-and (*S*)-1, 1′-bi-2-naphthol. These ligands create a well-defined chiral pocket as analyzed by NMR spectra. The cationic allylic complexes **C9-C12** of general formula $[Pd(\eta^3\text{-}2\text{-}CH_3\text{-}C_3H_4)(P\text{-}P)][PF_6]$ were obtained by reaction of the organometallic precursor $[Pd(\eta^3\text{-}2\text{-}CH_3\text{-}C_3H_4)(\mu\text{-}Cl)]_2$ with the stoichiometric amount of the appropriate ligands at low temperature in the presence of $NaPF_6$.

The effect of the nature and absolute configuration of both the terminal and bridging fragments of the ligands were studied for the asymmetric allylic alkylation and amination reactions. All the catalysts were tested for reactions of 1,3-diphenyl-2-propenyl acetate with Na dimethyl malonate or benzylamine as a nucleophile in DCM at 25°C. The catalyst **C11a** derived from ligand **L115a** was best in terms of enantioselectivity (*ee* up to 85%) in both alkylation and amination reactions DCM at 25 °C. In addition, a decrease in the enantioselectivity was observed for the "*in situ*" generated catalysts by mixing $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and the appropriate amount of the corresponding ligand. All the complexes were also applied for the allylic amination of 1,3-diphenyl-2-propenyl acetate by benzylamine. The ligand **L115a** was best in terms of enantioselectivity (*ee* up to 89%) and conversion (100%) with the formation of (*S*) product.

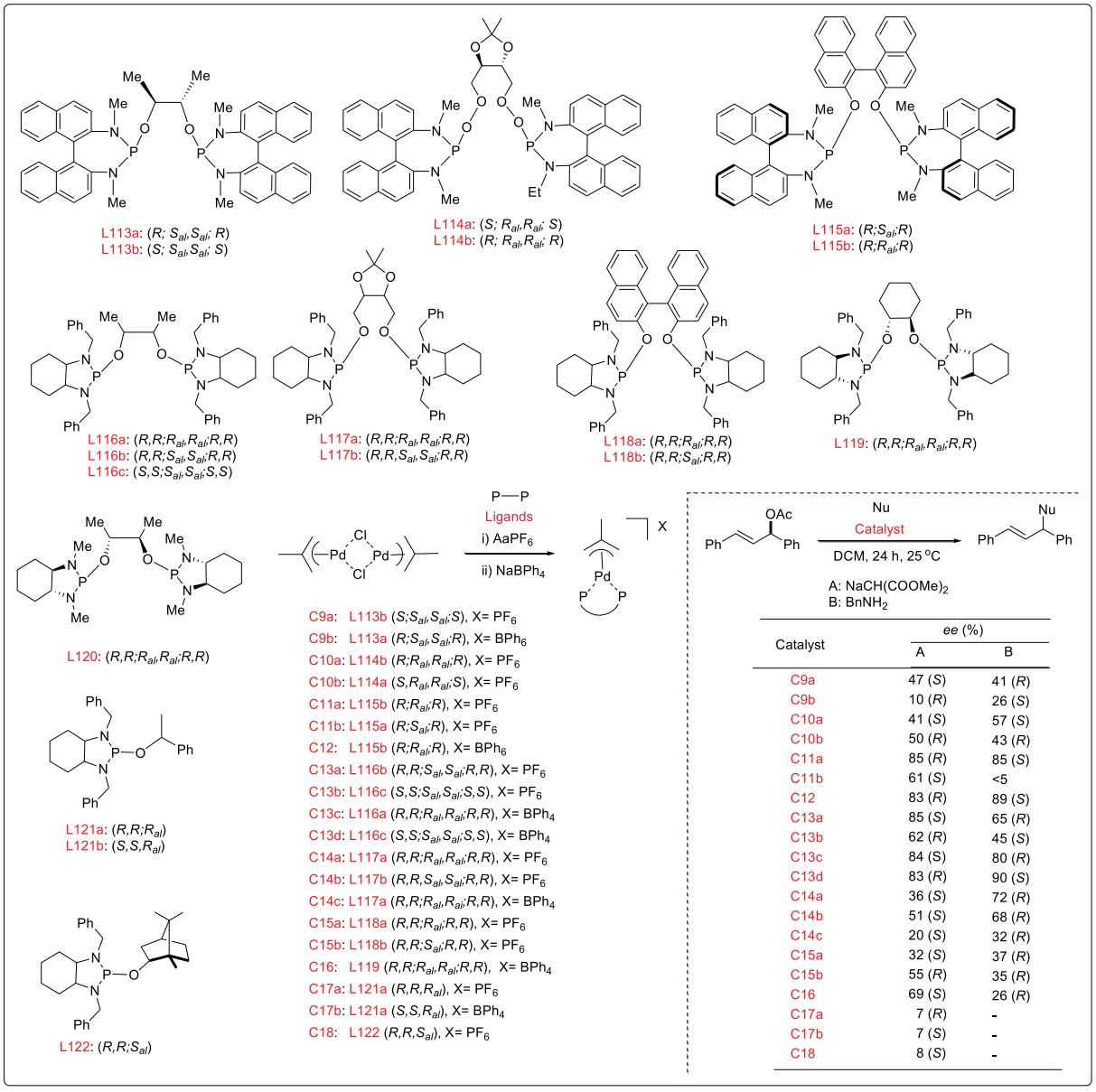
As an extension, they reported enantiopure bis(diamidophosphite) ligands (**L116-122**) bearing a cyclohexane-1,2-diamine skeleton in the allylic substitution reactions [127]. The cationic allyl Pd complexes **C13-18** obtained from the $[PdCl_2(COD)]$ and corresponding ligands were also tested for allylic alkylations. The catalyst **C13c** showed 100% conversion with good *ee* for alkylation (84%) and amination (80%) reactions.

Extensive work on a recyclable amphiphilic resin-supported P, N chelating Pd complexes was carried out by Uozumi and coworkers. They prepared novel P, N-chelate chiral ligands having pyrrolo[1,2-*c*]imidazolone skeleton as a basic chiral unit immobilized on the PS-PEG resin. All the ligands (**L123a-c** and **L124**) and catalysts (**C19a-c**) were applied for different coupling reactions under mild reaction conditions in an aqueous medium. The catalyst **C19a** achieved up to 90% *ee* in the asymmetric allylic substitutions of cyclic substrates in the presence of Li_2CO_3 in water at 40 °C [128]. The catalyst was recovered by simple filtration and reused without any loss of activity and stereoselectivity (Scheme 60).

The **C19a** also showed excellent yield and enantioselectivity (90–98% *ee*) for asymmetric allylic amination of cycloalkenyl carbonates and gave the corresponding cycloalkenylamines [129]. The recycling experiments showed that the catalyst **C19a** exhibited good catalytic activity and stereoselectivity for at least three runs in the amination reaction of cycloheptenyl ester with dibenzyl amine. Furthermore, the homogeneous catalytic system using **L124**, which lacks PS-PEG supports, gave only 6% of the desired product in DCM. The catalytic asymmetric etherification of cycloalkenyl esters with phenolic nucleophiles was also carried out using **C19a** (2 mol %). The reaction gave optically active aryl ethers (cycloalkenyl) with up to 94% *ee* in water [130].

Pd-catalyzed allylic substitutions of monosubstituted allylic compounds such as cinnamyl acetates and chlorides are very interesting reactions because these substrates are readily accessible. In addition, the obtained branched products can be transformed into different useful chiral intermediates. In this regard, various P–N ligands were used for the allylic substitutions of cinnamyl acetates and chlorides.

It was also known that strongly π-accepting phosphine ligands significantly reduce the electron density at the transition metal center, which makes it more reactive. It also imparts the Lewis acidic character to the catalyst, which can be advantageous for asymmetric catalysis. Due to the strong π-accepting properties of the perfluorinated alkyl phosphines [131], Shen et al. [132] reported a range of new (perfluoroalkyl) phosphinooxazoline (FOX) ligands (**L125a-h** and **L126a-h**) containing the CF_3 and C_2F_6 groups for asymmetric catalysis (Scheme 61). The CF_3 group on phosphorus makes the ligand a much stronger π-acceptor. It



Catalyst	ee (%) A	ee (%) B
C9a	47 (*S*)	41 (*R*)
C9b	10 (*R*)	26 (*S*)
C10a	41 (*S*)	57 (*S*)
C10b	50 (*R*)	43 (*R*)
C11a	85 (*R*)	85 (*S*)
C11b	61 (*S*)	<5
C12	83 (*R*)	89 (*S*)
C13a	85 (*S*)	65 (*R*)
C13b	62 (*R*)	45 (*S*)
C13c	84 (*S*)	80 (*R*)
C13d	83 (*R*)	90 (*S*)
C14a	36 (*S*)	72 (*R*)
C14b	51 (*S*)	68 (*R*)
C14c	20 (*S*)	32 (*R*)
C15a	32 (*S*)	37 (*R*)
C15b	55 (*R*)	35 (*R*)
C16	69 (*S*)	26 (*R*)
C17a	7 (*R*)	-
C17b	7 (*S*)	-
C18	8 (*S*)	-

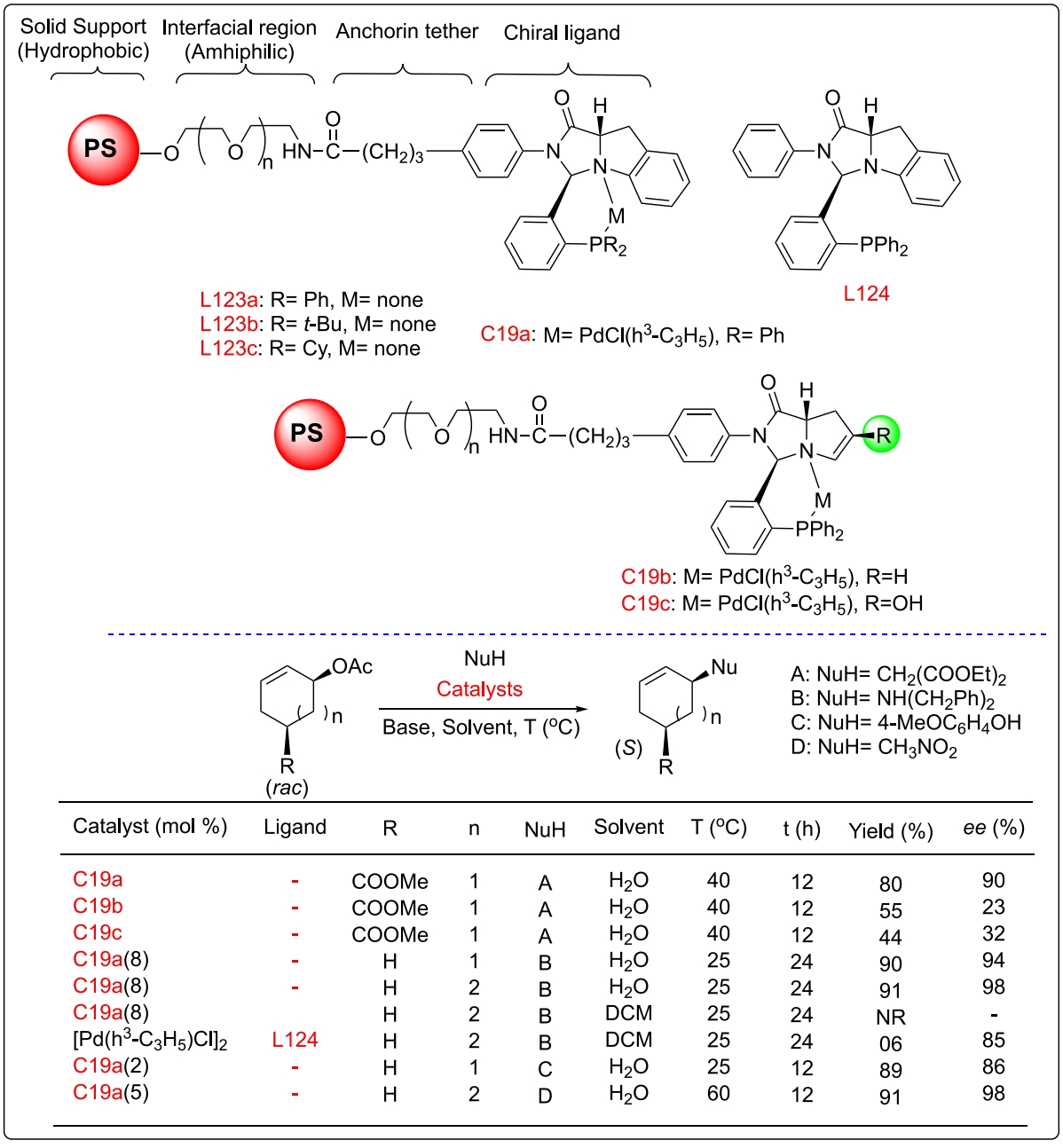
Scheme 59. Bis(diamidophosphite) ligands for asymmetric allylic alkylations.

enables the introduction of asymmetry in monosubstituted allyl substrates with enhanced regio and enantioselectivity.

The ligand **L125d** (4 mol %) and $Pd(dba)_2$ (4 mol %) showed full conversion of (*E*)-cinnamyl acetate and dimethyl malonate with 11.5:1 regioselectivity and 94% *ee* using BSA, LiOAc in DCM at room temperature. When **L125h** was applied, the enantioselectivity improved to 97%, with slightly lowered regioselectivity (9:1). A series of monosubstituted cinnamyl acetates or carbonates were fully converted into the desired product in excellent regio, and enantioselectivity using **L125d** or **L125h** within 8 h. The high regio and enantioselectivity of the Pd-Fox system were supported by the solid structure of the [Pd(**L125d**)(η^3-cinnamyl)]SbF_6 intermediate.

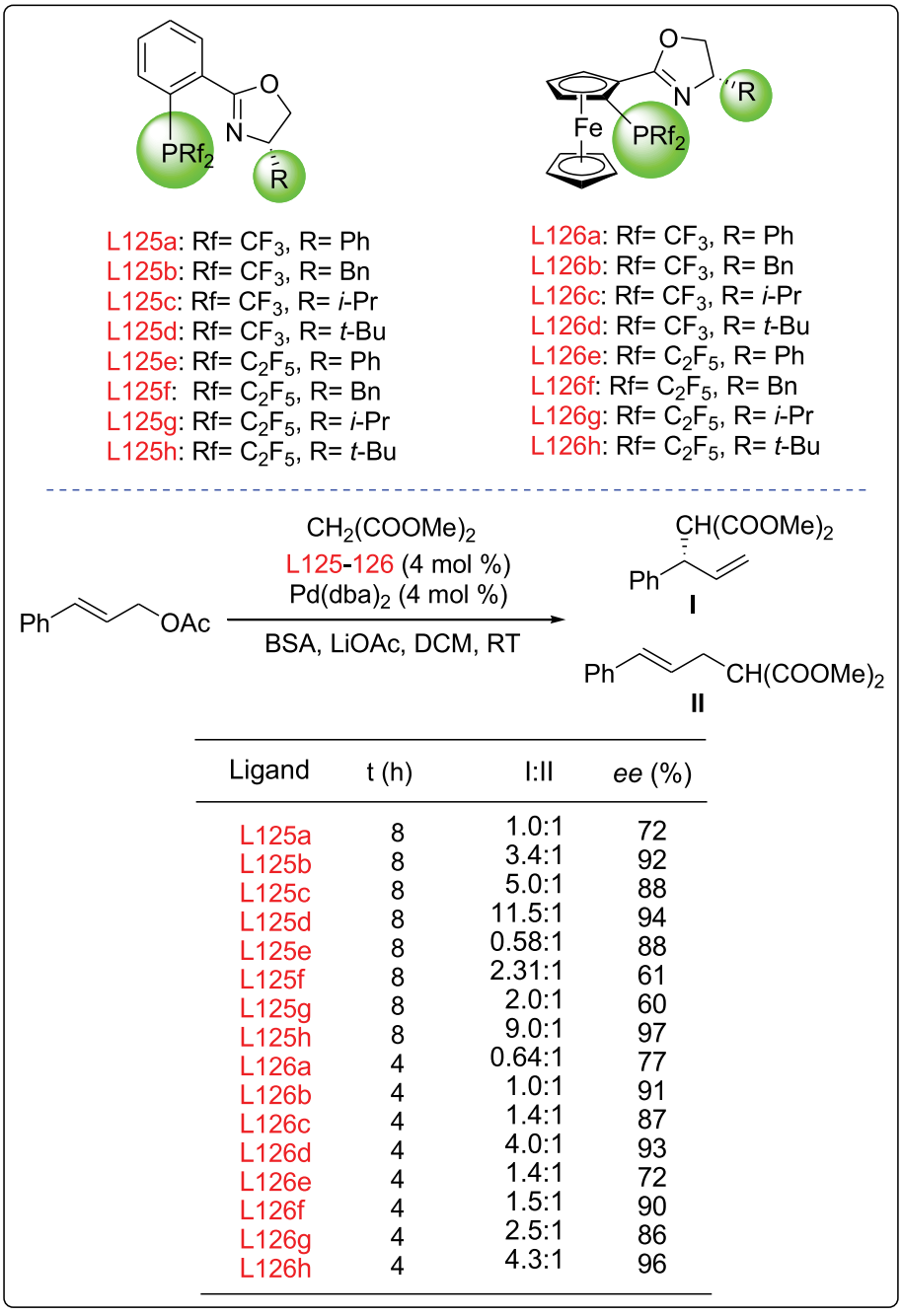
Pfaltz and co-workers showed that replacing phenyl substituent of PHOX (**L1e**) by electron-withdrawing pentafluorophenyl groups (C_6F_5) group (**L127a**) shifts the regioselectivity from 4:96 to 47:53 for enantioselective allylic alkylation of 3-phenyl-2-propenyl acetate by dimethyl malonate in the presence of [Pd(η^3-C_3H_5)Cl]$_2$ (1 mol %), and BSA-KOAc in DCM at 23 °C (Scheme 62). Consequently, replacing the phenyl substituent of PHOX (**6**) with the biphenylphosphite group (**L127b**: 2.5 mol %) further shifts the regioselectivity to 63:37 [133]. The introduction of a second stereogenic unit derived from binaphthol (**L128a**) further improved the regioselectivity to 76:24 and enantioselectivity to 90% *ee*. Furthermore, the introduction of two ortho-methyl groups in the binaphthol (**L128d**) improved the enantioselectivity to 91% with decreased regioselectivity (39:61). On the other hand, a comparison of results of **L128** with **L129** indicated that the enantioselectivity is determined largely by the chiral dihydro oxazole ring, while the binaphthol unit has a minor, but the still significant effect as **L129** showed 92% enantioselectivity with decreased regioselectivity (55:45). Of various substrates used, 1-naphthyl-substituted allylic acetates showed the best regioselectivity (95:5) with excellent enantioselectivity (94%) for ligand **L128a**.

As promising results were shown by **L128** and **L129**, the chiral bis(N-tosylamino)phosphines (**L130a-d**) and TADDOL-phosphite oxazoline ligands (**L130e**) were acts as an efficient ligands for allylic alkylation of various substrates (Scheme 62) [134]. The [Pd(η^3-C_3H_5)Cl]$_2$/**L130a**



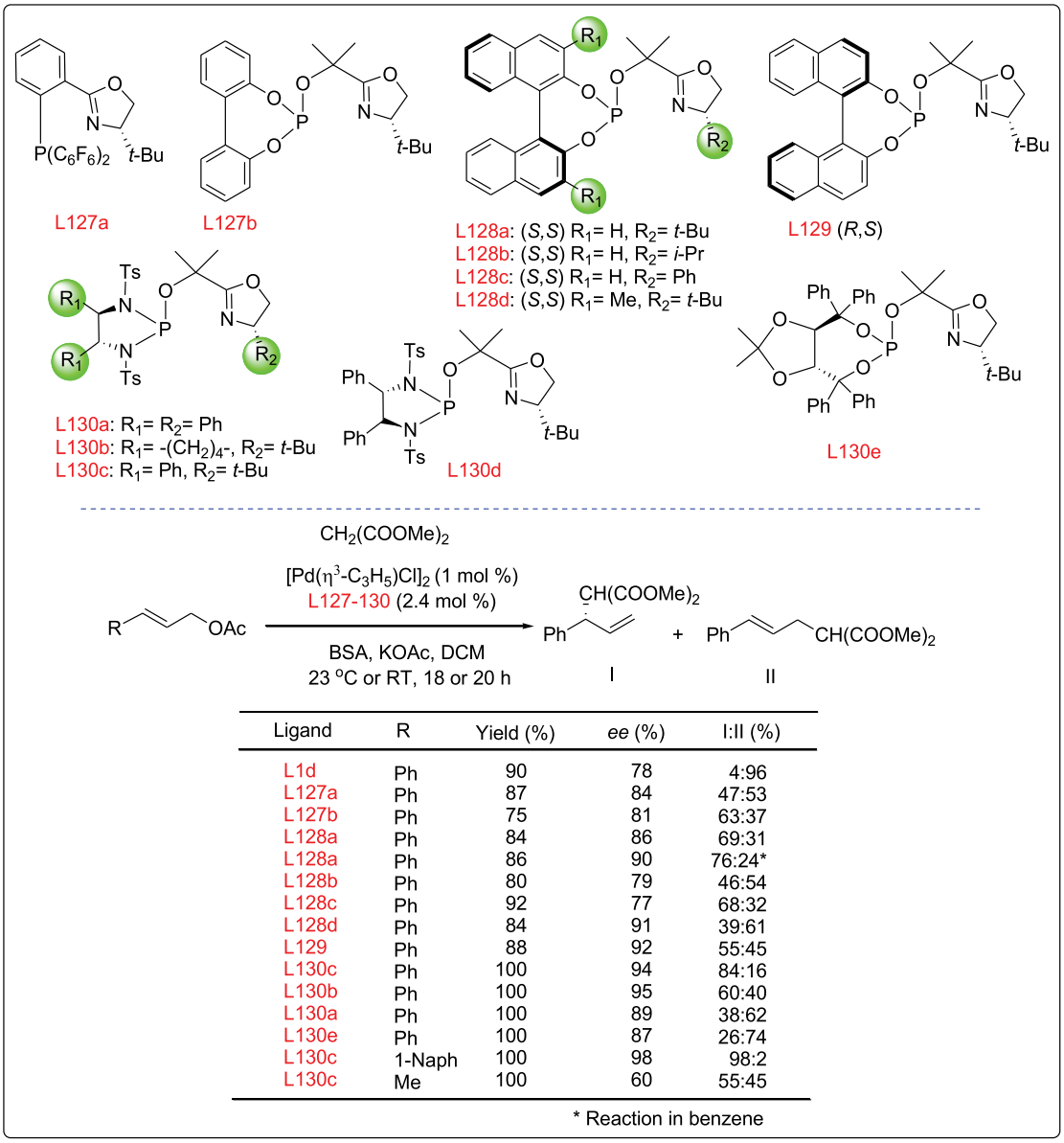
Catalyst (mol %)	Ligand	R	n	NuH	Solvent	T (°C)	t (h)	Yield (%)	*ee* (%)
C19a	-	COOMe	1	A	H_2O	40	12	80	90
C19b	-	COOMe	1	A	H_2O	40	12	55	23
C19c	-	COOMe	1	A	H_2O	40	12	44	32
C19a(8)	-	H	1	B	H_2O	25	24	90	94
C19a(8)	-	H	2	B	H_2O	25	24	91	98
C19a(8)		H	2	B	DCM	25	24	NR	-
$[Pd(h^3\text{-}C_3H_5)Cl]_2$	L124	H	2	B	DCM	25	24	06	85
C19a(2)	-	H	1	C	H_2O	25	12	89	86
C19a(5)	-	H	2	D	H_2O	60	12	91	98

Scheme 60. Recyclable amphiphilic resin-supported P, N-chelating Pd complexes for coupling reactions.



Ligand	t (h)	I:II	*ee* (%)
L125a	8	1.0:1	72
L125b	8	3.4:1	92
L125c	8	5.0:1	88
L125d	8	11.5:1	94
L125e	8	0.58:1	88
L125f	8	2.31:1	61
L125g	8	2.0:1	60
L125h	8	9.0:1	97
L126a	4	0.64:1	77
L126b	4	1.0:1	91
L126c	4	1.4:1	87
L126d	4	4.0:1	93
L126e	4	1.4:1	72
L126f	4	1.5:1	90
L126g	4	2.5:1	86
L126h	4	4.3:1	96

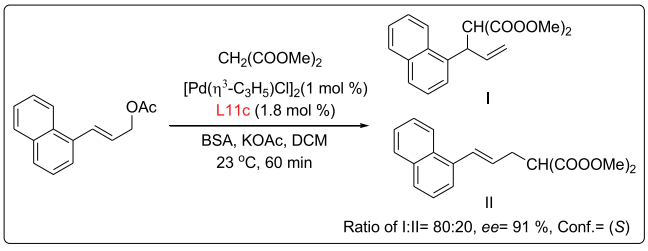
Scheme 61. Bis(perfluoroalkyl) phosphine-oxazolines for asymmetric allylic alkylations.



Ligand	R	Yield (%)	*ee* (%)	I:II (%)
L1d	Ph	90	78	4:96
L127a	Ph	87	84	47:53
L127b	Ph	75	81	63:37
L128a	Ph	84	86	69:31
L128a	Ph	86	90	76:24*
L128b	Ph	80	79	46:54
L128c	Ph	92	77	68:32
L128d	Ph	84	91	39:61
L129	Ph	88	92	55:45
L130c	Ph	100	94	84:16
L130b	Ph	100	95	60:40
L130a	Ph	100	89	38:62
L130e	Ph	100	87	26:74
L130c	1-Naph	100	98	98:2
L130c	Me	100	60	55:45

* Reaction in benzene

Scheme 62. Biphenylphosphites and TADDOL-phosphite oxazolines for asymmetric allylic alkylations.

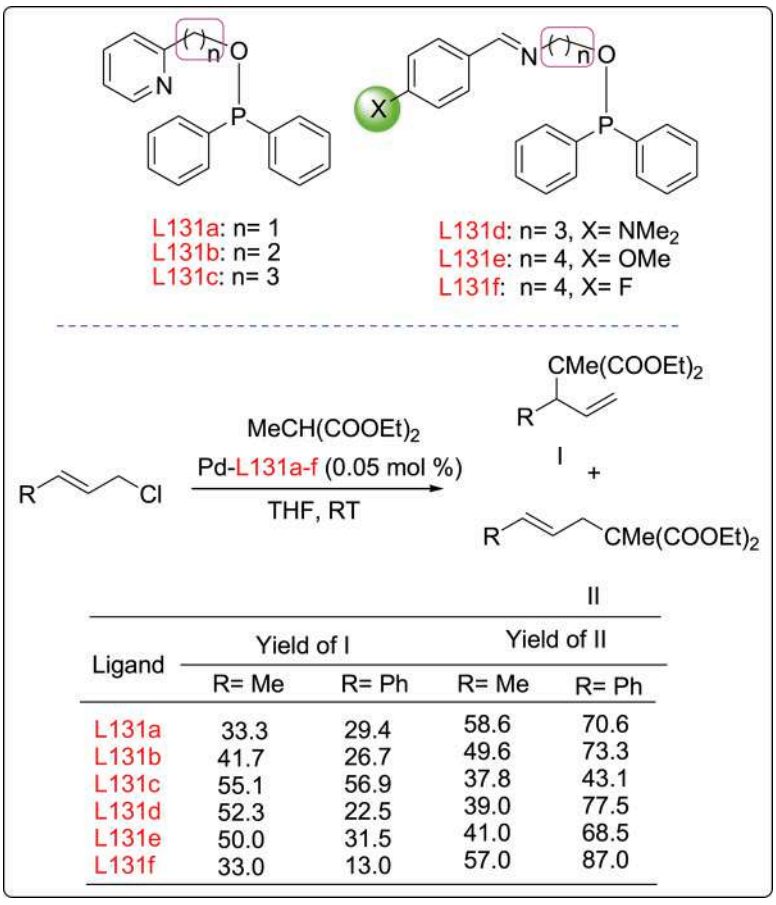


Scheme 63. Carbo-PHOX for asymmetric allylic alkylations.

(1:2.5 mol %) was very effective in reactions of 3-aryl-2-propenyl acetates as well as for 1-naphthyl-2-propenyl acetates in the presence of BSA, KOAc in DCM at 23°C. Moreover, ligand **L130a** also proved to be superior for cyclohexenyl acetate under similar reaction conditions.

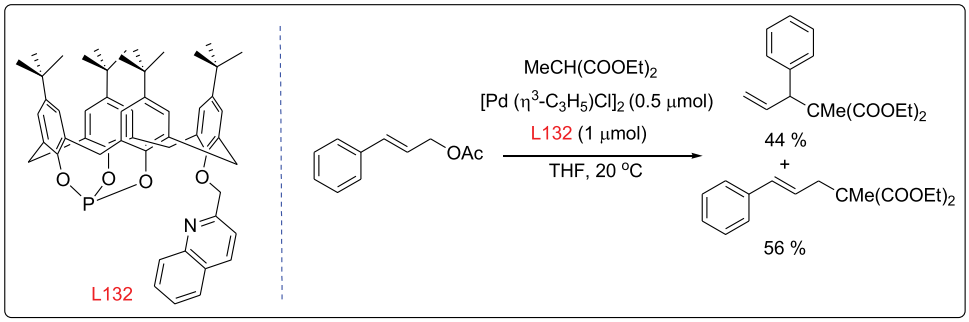
The ligands **L11c** (1.8 mol %) produced the desired branched isomer **I** as the major product with 88 % enantioselectivity and 80:20 regioselectivity in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol %) and BSA-KOAc in DCM at 23 °C. [40b] (Scheme 63).

Leeuwen and coworkers [135] studied the influence of the relative donor-acceptor strength of N and P atoms, steric hindrance in the transition state, and the bite angle of the ligand on the regioselective formation of branched products (Scheme 64). For this study, they synthesized two sets of ligands **L131a-c** and **L131d-f** based on a mixture of P and N donor atoms. The first set consists of a Ph_2PO unit connected ortho to pyridine *via* different alkyl chain lengths, while the second set consists of Ph_2PO units of varying chain lengths linked to an imine moiety. The reaction of the appropriate ligand with the $[(C_4H_7$ or $C_9H_9)PdCl]_2$ dimers, followed by chloride abstraction with silver triflate, gives the cationic crotyl and cinnamyl palladium complexes. The stoichiometric and catalytic allylation reactions of crotyl chloride (*trans*-but-2-enyl chloride) and cinnamyl chlorides (*trans*-3-phenylprop-2-enyl chloride) with Na salt of diethyl-2-methyl malonate showed that ligands with larger bite angles lead to higher regioselectivity in THF at room temperature. Stoichiometric alkylation using $[Pd(C_4H_7)\{\mathbf{L131e}\}][O_3SCF_3]$ proceeds with 88% regioselectivity to the branched product.



Ligand	Yield of I		Yield of II	
	R= Me	R= Ph	R= Me	R= Ph
L131a	33.3	29.4	58.6	70.6
L131b	41.7	26.7	49.6	73.3
L131c	55.1	56.9	37.8	43.1
L131d	52.3	22.5	39.0	77.5
L131e	50.0	31.5	41.0	68.5
L131f	33.0	13.0	57.0	87.0

Scheme 64. P–N ligands for asymmetric allylic alkylations of crotyl and cinnamyl chlorides.

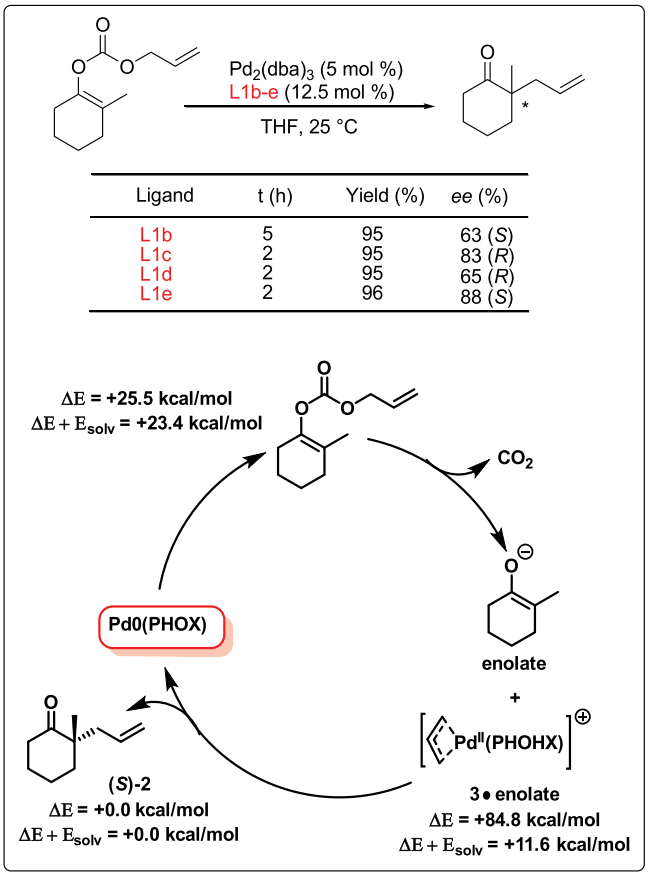


Scheme 65. Calix[4],quinoline-based P, N-ligand for asymmetric allylic alkylations of cinnamyl acetate.

Similarly, the calix[4],quinoline-based P, N-ligand **L132** was applied to Pd-catalyzed allylic alkylation of cinnamyl acetate with sodium diethyl 2-methylmalonate (Scheme 65) [136]. The ligand involves quinoline-containing moiety at the lower rim of the cavity. The calix [4]-cavity adopts a cone confirmation with an *exo* orientation of the phosphorus lone pair enabling chelation. The character of the P has been increased by using a μ^3-bridging phosphite unit linked to three proximal phenolic oxygen atoms at the lower rim of a calix[4]arene cavity that displays the unique air-robustness and stability. The ligand **L132** was obtained from *t*-butylcalix[4]arene through a two-step synthesis. The catalysts were prepared *in situ* by mixing $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ with two equivalents of **L132** in THF solution. The catalyst (0.1 mol %) showed quantitative conversion in 20 h providing only the 56% linear *trans* and the 44% branched products, while no linear *cis* product was observed at 20 °C.

Tsuji allylation reaction [137] is an ideal reaction for the preparation of asymmetric *α*-quaternary cycloalkanones. The reaction involves the selective formation of the enol carbonate moiety and provides position control to the enolate.

In this regard, Stoltz and coworkers [138] reported the use of PHOX ligands (**L1b-e**) for an enantioselective Tsuji allylation of allyl enol carbonates (Scheme 66). Using these reactions, they prepared various 2-alkyl-2-allyl cyclohexanone derivatives. The ligands **L1b-e** (12.5 mol %) were effective in terms of yield and enantioselectivity in the presence



Scheme 66. Enantioselective Tsuji allylation reactions using PHOX ligands.

of $Pd_2(dba)_3$ (5 mol %) in THF at 25 °C. Though all the ligands showed a high degree of enantioselectivity and reactivity, the ligand **L1e** was more active in terms of yield (96%) and *ee* (88%). Various allyl enol carbonates of substituted cyclic ketones were converted easily into their corresponding products with 81-96% yields and 79–92% *ee* in the presence of $Pd_2(dba)_3$/**L1e** (2.5:6.25 mol %) system in 1-9 h. The different tetra-substituted trimethylsilyl enol ethers also showed smooth α-allylation by commercially available diallyl carbonates using the same catalytic system in the presence of a sub-stoichiometric amount of $Bu_4NPh_3SiF_2$ (TBAT). The yield of the reactions was 79–99% with 79–92% *ee* at 25 °C. Using quantum chemistry calculations, they suggested the formation of a likely intermediate in the reaction and there involvement in the inner-sphere process (Scheme 66) [139].

They also reported a practical method for the deracemization of quaternary carbon stereocenters using a $Pd_2(dba)_3$/**L1e** catalytic system (2.5:6.25 mol %) [140]. The method involves enantioconvergent decarboxylative allylation of β-substituted 2-carboxy allyl cyclohexanones and β-ketoesters. The catalyst was well involved in stereoablative (C-C bond breaking) and stereoselective (C-C bond-forming) reactions. The ligand also showed 80-99% yields with 81-91% *ee* in the decarboxylative allylations of various α-substituted 2-carboxy allyl cyclohexanones in THF or Et_2O at 25-30 °C (Scheme 67). Moreover, the various substituted cyclic quaternary β-ketoesters were converted into the corresponding products in high yields (77–97%) and enantioselectivities (85–92% *ee*) under similar reaction conditions. The ligand also afforded cascade product by double allylation of a corresponding substrate. It involves the conversion of reactive enol carbonate and a β-ketoester moiety into a mixture of C_2/Meso diastereomers (4:1) with a 76% yield. The major (-) diastereoisomer was obtained with 92% *ee*.

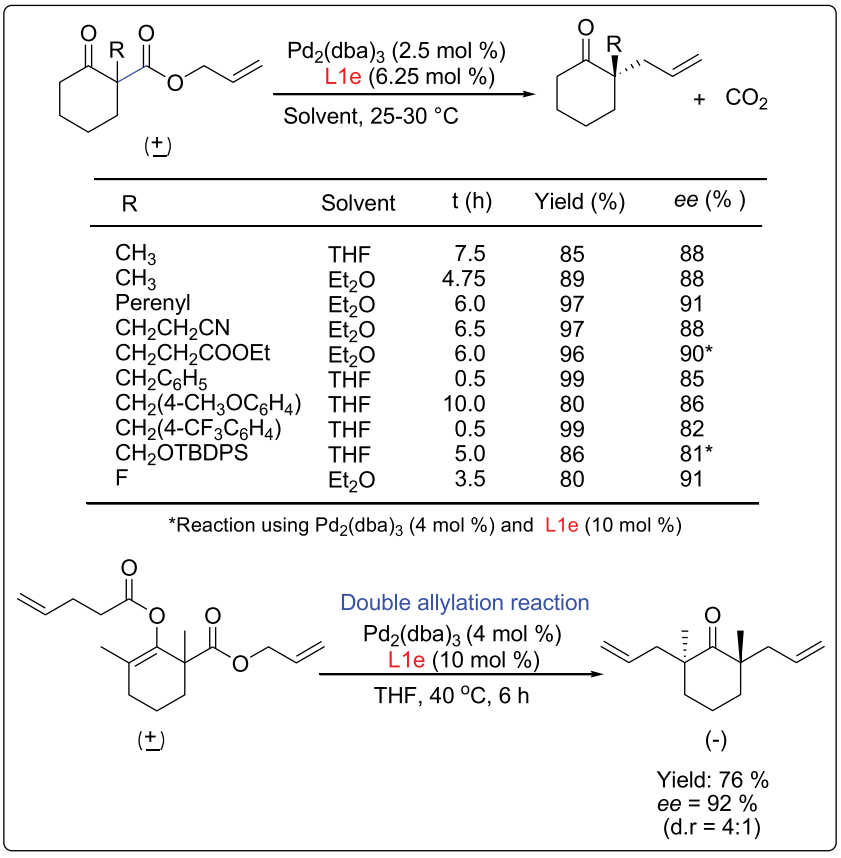
As an extension, they [141] synthesized cyclopentanoid, cyclohexanoid, and cycloheptanoid cores and used them in the total synthesis of natural products. All these compounds were easily prepared by enantioselective decarboxylative allylation of seven-membered methyl-substituted β-ketoesters using **L1e, L133a**, and **L133b** ligands. The catalytic system **L1e**/$Pd_2(pmdba)_3$ (2.5:6.25 mol %) gave vinylogous esters with 94% yield and 84% *ee* in THF at 30 °C (Scheme 68). As compared to other ligands, the electron-deficient **L133a** ligand (12.5 mol %) displayed improved enantioselectivity (90%) at the cost of higher $Pd_2(pmdba)_3$ loading (5 mol % Pd) and lower yield (57%). Similarly, structurally modified **L133b** ligand proved to be less effective with reduced yield (77%) and *ee* (72%). The **L1e**/$Pd_2(pmdba)_3$ system (2.5:6.25 mol %) well alkylated several aromatic and heteroaromatic α-substituted β-ketoesters with 75–99% yield and 58–92% *ee* in toluene at 30 °C.

In 2012, Paquin et al. [142] applied various PHOX ligands (**L134a-j**) for three types of Pd-catalyzed enantioselective transformations. The first transformation is an enantioselective Tsuji−Trost allylation reaction of fluorinated silyl enol ether using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.25 mol %), and **L134a-g** (3.1 mol %) in the presence of TBAB (35 mol %) in toluene at 40 °C (Scheme 69). The valine-based ligands (**L134a-d**) showed good performance (87–93% yields with 95:5 *er*) as compared to ligand **L1e** (91% yield with 96:4% *er*). The ligands derived from leucine (**L134e** and **L134f**) and isoleucine (**L134g**) gave 89–92% yields with low enantioselectivity (94.5:5.5 *er*). They also carried out the allylation reaction of fluorinated enol carbonates in the presence of $Pd_2(dba)_3$ (2.5 mol %) and **L134a-g** (1.25 mol %) in toluene at 40 °C. Except for ligand **L134b** (79% yield with 93.5:6.5 *er*), the ligands derived from valine (**L134a, L134c**, and **L134d**) gave fluoroketone with 83–93% yields and the same enantioselectivity (95:5 *er*). In terms of product yields, the ligand derived from leucine (**L134e**) performed well (73%) but gave lower enantioselectivities (93:7 *er*). While isoleucine-based ligand **L134g** showed comparable results (80% yield with 95:5% *er*) to the valine-based ligands.

The 'StePHOX' [51] ligands (**L28a-h**) (8 mol %) also showed excellent activity and enantioselectivity for the asymmetric Tsuji allylation in THF in the presence of $Pd_2(dba)_3$ (2.5 mol %) (Scheme 70).

In 2005, all the (*R, R*)-**L71a-d** ligands [143] were applied for the asymmetric allylation of simple ketones to generate both quaternary and tertiary centers from allyl enol carbonate using $Pd_2(dba)_3CHCl_3$ (2.5 mol %) in toluene at 23 °C (Scheme 71). Among all, ligand (*R, R*)-**L71d** (5.5 mol %) gave the best *ee* (85%) and yield (88%), hence used in allylation of a range of five, six, and seven-membered ketones. It gave 78–99% yield with 78–99% *ee* of monoalkylated products. This protocol was also advanced for the preparation of many α-tertiary ketones that showed 98% *ee* through asymmetric α-allyl alkylation of acyclic ketones in dioxane at 23 °C [144]. Similarly, the catalytic system $Pd_2(dba)_3$/(*R, R*)-**L71d** also showed an excellent yield and *ee* in the asymmetric allylic alkylation of vinylogous thioesters under neutral conditions [145].

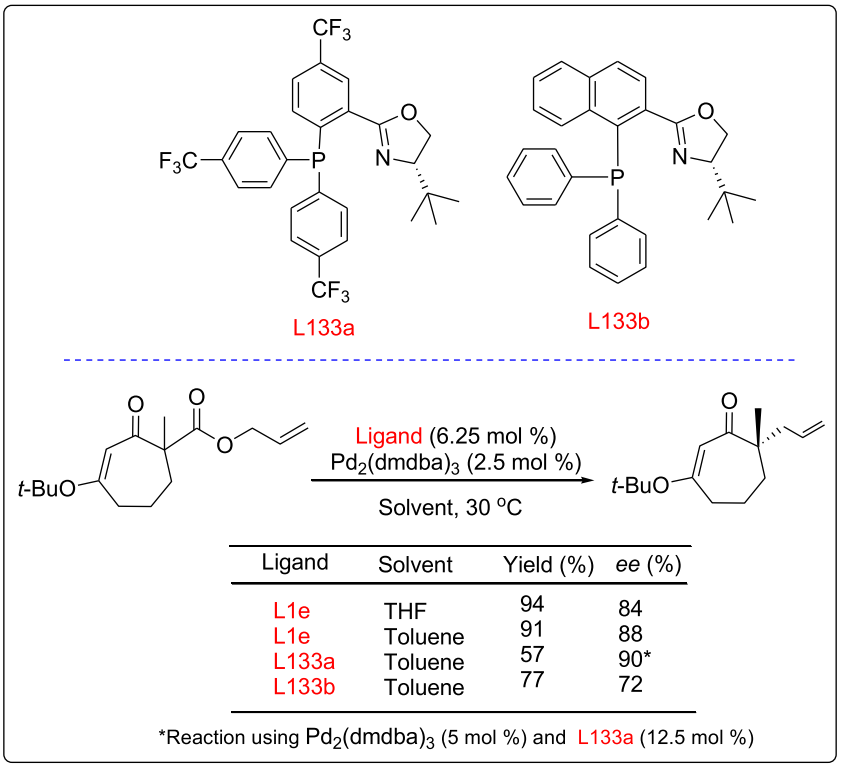
The (*S,S*)-**L71b** ligand was also successfully used in the asymmetric allylic alkylation of six-membered non-stabilized ketone enolates (Scheme 72) [146]. The ligand (5 mol %) with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) gave an excellent yield (99%) and enantioselectivity (88% *ee*) in the presence of LDA and $(CH_3)_3SnCl$ in DME in 30 min. Under optimized conditions, a range of tetralone, benzylidene, and thioacetal derivatives are well alkylated with various alkylating agents. Linearly substituted allyl systems (either *E/Z* isomers) gave products of only *E* isomers with



R	Solvent	t (h)	Yield (%)	*ee* (%)
CH_3	THF	7.5	85	88
CH_3	Et_2O	4.75	89	88
Perenyl	Et_2O	6.0	97	91
CH_2CH_2CN	Et_2O	6.5	97	88
CH_2CH_2COOEt	Et_2O	6.0	96	90*
$CH_2C_6H_5$	THF	0.5	99	85
$CH_2(4\text{-}CH_3OC_6H_4)$	THF	10.0	80	86
$CH_2(4\text{-}CF_3C_6H_4)$	THF	0.5	99	82
$CH_2OTBDPS$	THF	5.0	86	81*
F	Et_2O	3.5	80	91

*Reaction using $Pd_2(dba)_3$ (4 mol %) and L1e (10 mol %)

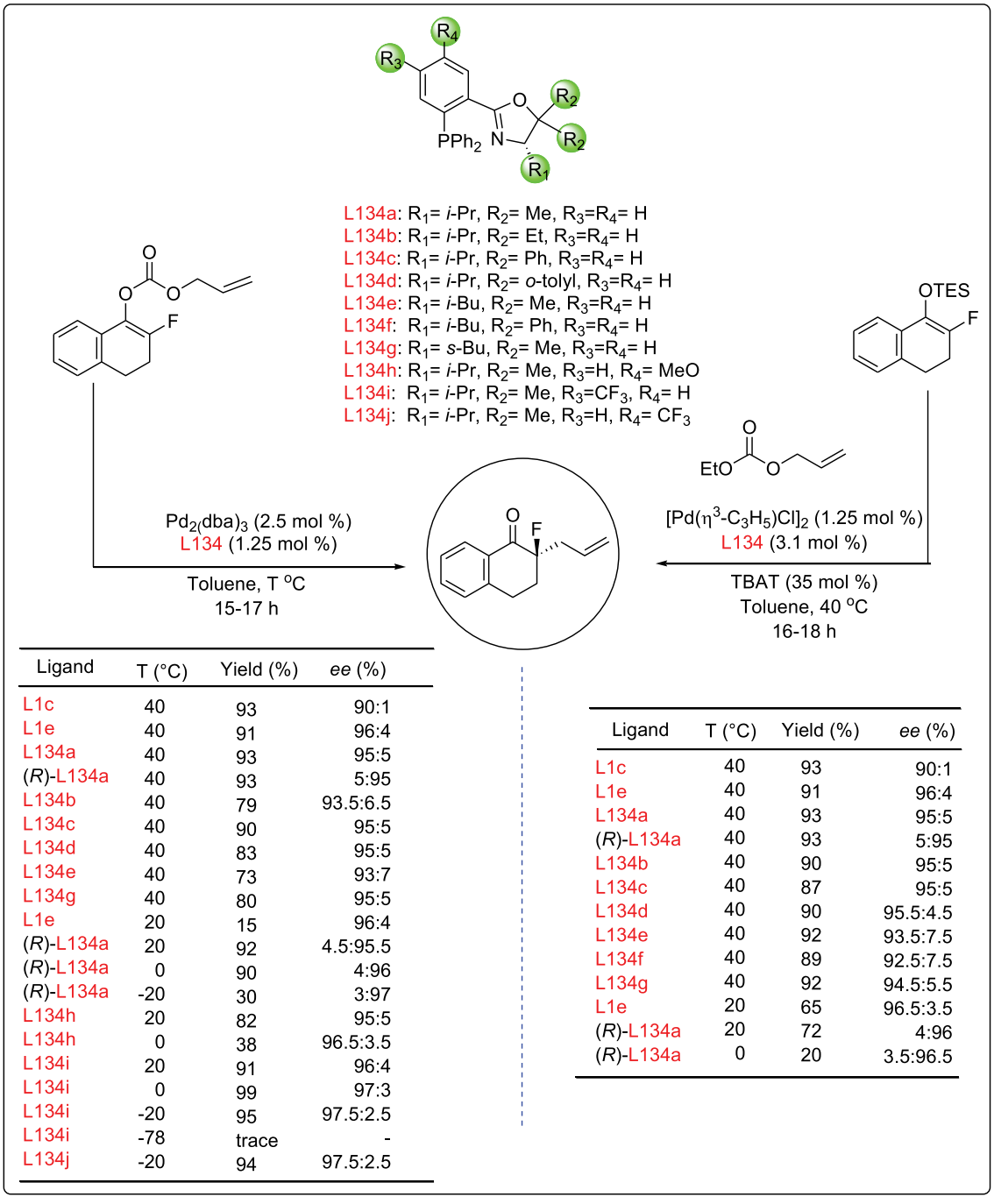
Scheme 67. Deracemization of quaternary carbon stereocenters and cascade enantioselective allylations using (*S*)-*t*-Bu-PHOX ligand.



Ligand	Solvent	Yield (%)	*ee* (%)
L1e	THF	94	84
L1e	Toluene	91	88
L133a	Toluene	57	90*
L133b	Toluene	77	72

*Reaction using $Pd_2(dmdba)_3$ (5 mol %) and L133a (12.5 mol %)

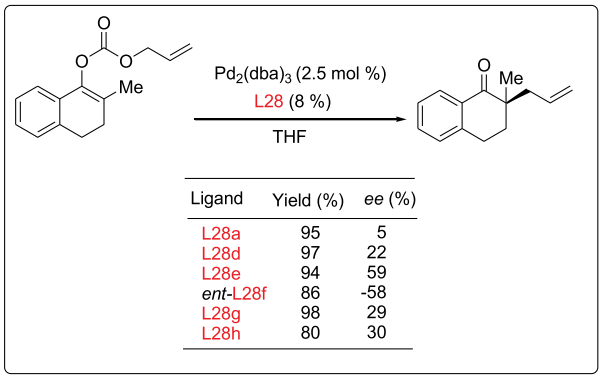
Scheme 68. Asymmetric alkylation of seven-membered methyl-substituted *β*-ketoesters using PHOX ligands.



Ligand	T (°C)	Yield (%)	*ee* (%)
L1c	40	93	90:1
L1e	40	91	96:4
L134a	40	93	95:5
(*R*)-L134a	40	93	5:95
L134b	40	79	93.5:6.5
L134c	40	90	95:5
L134d	40	83	95:5
L134e	40	73	93:7
L134g	40	80	95:5
L1e	20	15	96:4
(*R*)-L134a	20	92	4.5:95.5
(*R*)-L134a	0	90	4:96
(*R*)-L134a	-20	30	3:97
L134h	20	82	95:5
L134h	0	38	96.5:3.5
L134i	20	91	96:4
L134i	0	99	97:3
L134i	-20	95	97.5:2.5
L134i	-78	trace	-
L134j	-20	94	97.5:2.5

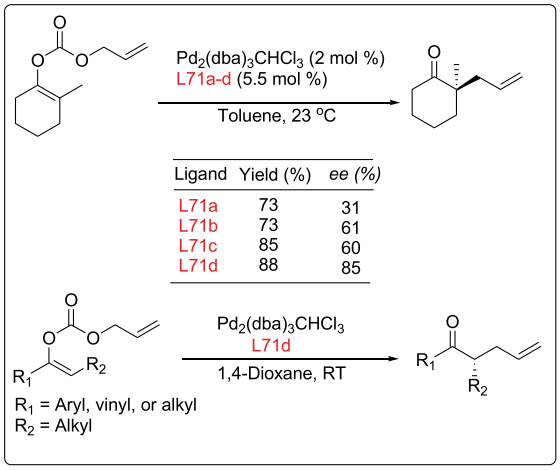
Ligand	T (°C)	Yield (%)	*ee* (%)
L1c	40	93	90:1
L1e	40	91	96:4
L134a	40	93	95:5
(*R*)-L134a	40	93	5:95
L134b	40	90	95:5
L134c	40	87	95:5
L134d	40	90	95.5:4.5
L134e	40	92	93.5:7.5
L134f	40	89	92.5:7.5
L134g	40	92	94.5:5.5
L1e	20	65	96.5:3.5
(*R*)-L134a	20	72	4:96
(*R*)-L134a	0	20	3.5:96.5

Scheme 69. Asymmetric allylic alkylations of fluorinated enol carbonates using PHOX ligands.



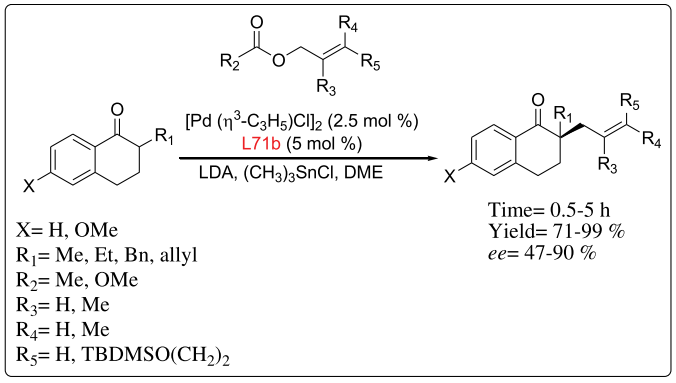
Ligand	Yield (%)	*ee* (%)
L28a	95	5
L28d	97	22
L28e	94	59
ent-L28f	86	-58
L28g	98	29
L28h	80	30

Scheme 70. StePHOX ligands for asymmetric allylic alkylations.



Ligand	Yield (%)	*ee (%)*
L71a	73	31
L71b	73	61
L71c	85	60
L71d	88	85

Scheme 71. Asymmetric allylic alkylations of simple ketones and vinylogous thioesters.



Scheme 72. Asymmetric allylic alkylations of non-stabilized ketone enolates of six-membered rings.

good *ee*, while a branched system gave lower *ee*. The activity, as well as enantioselectivity, was highly influenced by ring size and reaction temperature. Changing the ring size to either indanone or benzosuberone led to low *ee*. The benzylidene also gave the alkylated product with 98% yield and 82% *ee*. Moreover, in the case of the furanylidene derivative, the product yield was 89% with 79% *ee* at room temperature. The enantioselectivity increased to 92% at 0 °C. Similarly, at room temperature, the ketene thioacetal gave 70% *ee*, which was increased to 82% *ee* at −10 °C.

3.2. Heck coupling reactions

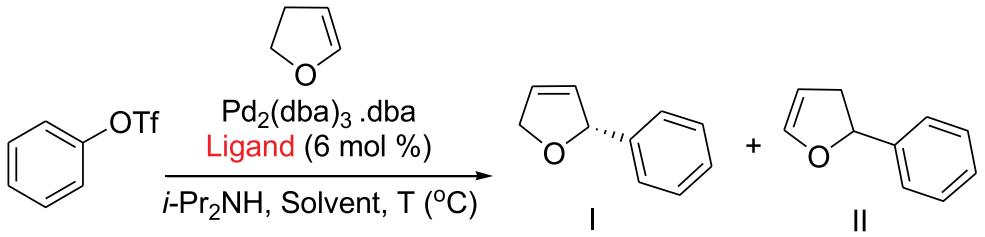
Due to their wide applications in organic transformations [147], the Heck coupling reaction [148] has been found to be most widely studied Pd-catalysed reaction as that other coupling reactions. Enantioselective intermolecular and intramolecular Heck coupling reactions [149] have been widely used extensively for the synthesis of many important compounds. This synthesis has been carried out using various P-N ligands.

The various PHOX ligands such as **L1c, L1e, L2a-d,** and **L134a-g** were applied for enantioselective Heck coupling reaction of 2,3-dihydrofuran and phenyl triflate (Scheme 73). The oxazoline ring containing a bulky R_2 substituent was beneficial for both reactivity and enantioselectivity. Thus, ligands **L2a** and **L2d** (6.0 mol %) provided desired products with 97% and 91% yield with 93% and 97% *ee* in the presence of $Pd_2(dba)_3$.dba (6 mol %) using *i*-Pr_2NEt as a base in benzene or THF at 78 °C [24]. Similarly, the ligands derived from leucine (**L134e-f**) and isoleucine (**L134g**) worked well as compared to the valine-based ligands (**L134a-d**) in the presence of $Pd_2(dba)_3$ (1.5 mol %), in THF at 100 °C under MW [142].

The carbohydrate-derived PHOX ligands (**L10a−f**) [150a] and **L11-14** [150b,c] also gave high yields and enantioselectivity in the asymmetric Heck coupling reactions of 2,3-dihydrofuran and phenyl triflate in the presence of *i*-Pr_2NEt in THF (Scheme 74). The **L10a-f** (5.6 mol %) gave 2-aryl-2,5-dihydrofuran with up to 96% *ee* in presence of Pd $(dba)_2$ (5 mol %) at 65 °C. The **L11-14** (5.6 mol %) gave 2-aryl-2,5-dihydrofuran with up to 99% *ee* in presence of $[Pd_2(dba)_3]$·dba (5 mol %) at 55 °C. Ligands **L12a** and **L13a** showed lower activity as well as regio and enantioselectivities than ligands **L11a**. The activity as well as regio and enantioselectivity of the catalyst decreases (i.e., Ph > *i*-Pr > *t*-Bu) with an increase in the size of the group present on the oxazoline ring. The activity, regioselectivity, and enantiomeric excesses depend strongly on both the phosphite and oxazoline substituents, as ligand **L11c** and **L14c** containing $SiMe_3$ group at the *ortho* position of the biphenyl moiety showed excellent regio and enantioselectivity. In the presence of ligand **L11a**, the reaction of dihydrofuran and 1-cyclohexenyl triflate gave the coupling product with high enantioselectivity (98% *ee*) and regioselectivity (98%) with 100% conversion in 18 h. However, the reaction of cyclopentene and phenyl triflate gave the coupling product with 94% *ee* and 100% conversion, but there is the formation of a small amount of achiral 4-phenylcyclopentene at 70 °C. In addition, the reaction of phenyl triflate and 4,7-dihydro-1,3-dioxepin also proceeded with 92% *ee*. These ligands were also screened successfully in the Heck coupling reactions of several substrates under thermal as well as microwave conditions and showed high regio (up to 99%) and enantioselectivities (*ee* up to 99%).

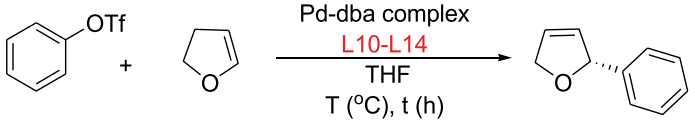
The Heck coupling reactions of 2,3-dihydrofurans and 2,2-dialkyldihydro furans were carried out successfully by using the thiophene-based HetPHOX ligands (**L18a-b**, and **L20a-c**). The ligand showed excellent enantioselectivity (up to 95% *ee*) and yields (up to 97%). The ligand **L18b** containing the *t*-butyl group was the most active and enantioselective ligand [151].

The Indanol PHOX ligand **L22** (15 mol %) with $[Pd_2(dba)_3$.dba] also worked efficiently for the Heck coupling reaction of 2,3-dihydrofuran and phenyl triflate using *i*-Pr_2EtN as a base with high enantioselectivities (up to 96%) and yields (81%) in benzene at 70 °C [44]. Various gem-disubstituted and electronically varied thiophene-oxazoline (HetPHOX: **L135a-f**) and ferrocene-oxazoline (FcPHOX: **L135g**) ligands were used in asymmetric intermolecular Heck arylation of 2, 3–dihydrofuran under microwave irradiation (100 °C, 150 W) (Scheme 75) [152a]. The ligand **L135c** (6 mol %) gave 95% *ee* using $Pd_2(dba)_3$ (6 mol %) in the presence of *i*-Pr_2NH as a base under MW in 18 h. The enantioselectivity increased to 97% in THF under conventional heating at 70 °C for 40 h. A dramatic switch of enantioselectivity was observed by a PHOX ligands (6 mol %) with and without substituents at the benzylic position in asymmetric Heck coupling of dihydrofuran and



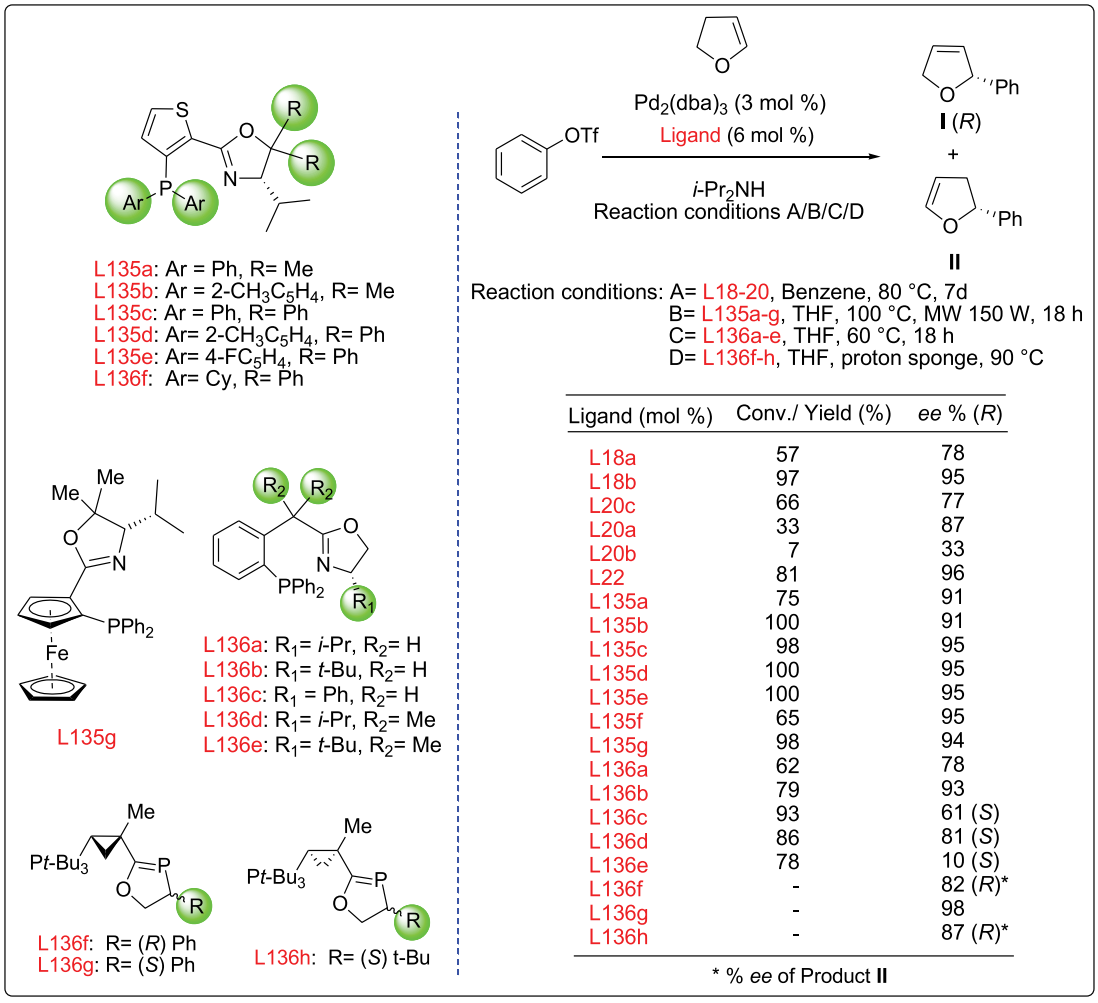
Ligand (mol %)		Solvent	T (°C)	t (h)	Yield (%)	*er/ee* (%)
L1c	(1.5	THF	100	18	45	93:7
L1e	(1.5)	THF	100	18	81	98:2
(*S*) L134a	(1.5)	THF	100	18	76	95.5:4.5
(*R*) L134a	(1.5)	THF	100	18	73	4:96
(*S*) L134b	(1.5)	THF	100	18	17	94:6
(*S*) L134c	(1.5)	THF	100	18	81	97.5:2.5
(*S*) L134d	(1.5)	THF	100	18	48	97:3
(*S*) L134e	(1.5)	THF	100	18	50	95:5
(*S*) L134g	(1.5)	THF	100	18	70	95.5:4.5
L2a	(6.0)	Benzene	70	3 d	87	91
L2b	(6.0)	Benzene	70	3 d	32	88
L2c	(6.0)	Benzene	70	3 d	45	78
L2d	(6.0)	Benzene	70	3 d	91	90

Scheme 73. Enantioselective Heck coupling reactions using PHOX ligands.



Ligand	T (°C)	t (h)	Yield/Conv. (%)	*ee* (%)
L10a	65	4 d	88	91
L10b	65	3 d	84	88
L10c	65	3 d	100	93
L10d	65	3 d	24	92
L10e	65	2 d	96	85
L10f	65	1 d	100	96
L11a	50	24	98	97
L11b	50	24	86	97
L11c	50	24	100	99
L11d	50	24	42	25
L11e	50	24	45	80
L11f	50	24	32	06
L11g	50	24	28	73
L12a	50	24	80	84
L13a	50	24	12	83
L14a	50	24	94	99
L14c	50	24	100	99

Scheme 74. Asymmetric Heck coupling reactions using Carbo-PHOX ligands.



Ligand (mol %)	Conv./ Yield (%)	*ee* % (*R*)
L18a	57	78
L18b	97	95
L20c	66	77
L20a	33	87
L20b	7	33
L22	81	96
L135a	75	91
L135b	100	91
L135c	98	95
L135d	100	95
L135e	100	95
L135f	65	95
L135g	98	94
L136a	62	78
L136b	79	93
L136c	93	61 (*S*)
L136d	86	81 (*S*)
L136e	78	10 (*S*)
L136f	-	82 (*R*)*
L136g	-	98
L136h	-	87 (*R*)*

* % *ee* of Product **II**

Scheme 75. PHOX and HetPHOX-based ligands for asymmetric Heck coupling reactions.

phenyl triflates [152b]. The ligands **L136a-c** offer products with (*R*)-configuration while ligands **L136d-e** resulted in products with (*S*)-configuration.

Similarly, dramatic stereo- and enantioselectivity were observed in the asymmetric Heck reaction using cyclopropane-based PHOX ligands (**L136f-h**) (6 mol %) using $Pd(OAc)_2$ (6 mol %) in the presence of proton sponge in THF at 60 °C [152c].

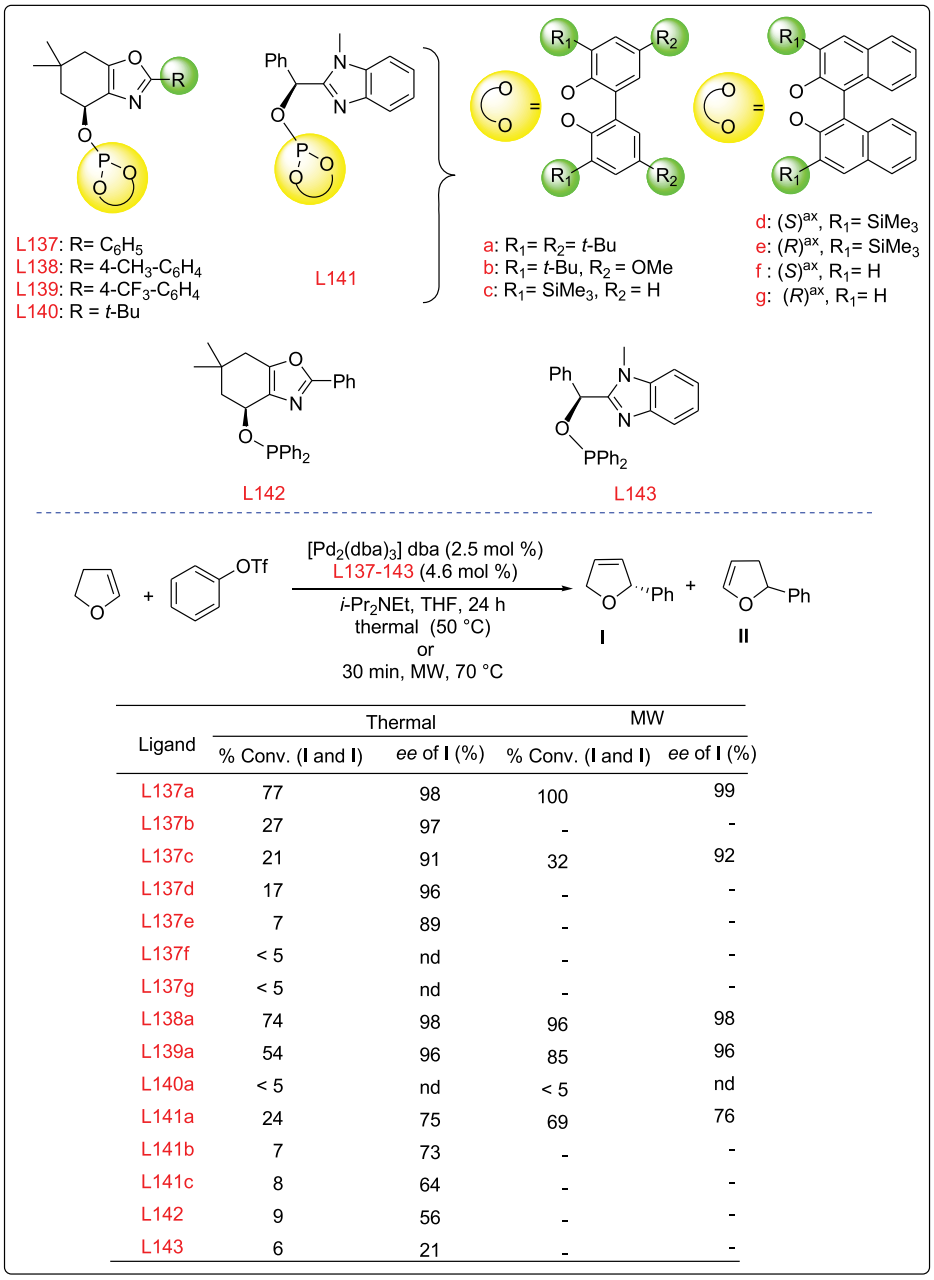
Due to their ease of preparation from readily available alcohols, phosphite ligands are extremely attractive and widely used for transition metal catalysis [153]. They are less sensitive to air and other oxidizing agents than phosphines and are applied for parallel synthesis.

In this connection, Dieguez *et al.* [154] reported an air-stable phosphite oxazole/imidazoline **L137-L143** ligands for intermolecular asymmetric Heck coupling reactions under thermal and MW conditions (Scheme 76). The activity, regioselectivity, and enantioselectivity of ligands depend on the type of nitrogen donor group (oxazole or imidazole), the nature of oxazole, and biaryl-phosphite substituents, as well as the chirality of the biaryl moiety of the ligand. It was observed that MW is beneficial in terms of yield and time as an excellent activity (up to 100% conversion in 30 min), regioselectivity (up to > 99%), and enantioselectivity (up to 99% *ee*) were obtained using several triflates.

Busacca and coworkers developed a family of novel and flexible phosphinoimidazoline ligands similar to PHOX, having additional nitrogen-containing different R_3 substituents called 'BIPI' (Boehringer-Ingelheim Phosphino Imidazoline) ligands (**L144-149**) for intramolecular asymmetric Heck coupling reactions [155]. All these ligands were applied for the creation of a chiral quaternary center. Its enantioselectivity depends linearly on phosphine electron density. The BIPI ligands were designed such that gross electronic tuning could be achieved by varying the substituents at R_2 or R_3. These groups are mostly alkyl and acyl groups. The alkyl groups R_2 and R_3 lead to strongly basic systems, while acyl and sulfonyl R_3 groups lead to more neutral ligands. The ligands were constructed in a modular fashion, in which *o*-haloimidate reacts with a chiral diamine and furnishes the haloimidazolines (Scheme 77). The S_NAr reaction of phosphite nucleophiles with haloimidazolines gave phosphinoimidazolines which could be converted into desired ligands in two different methods [156].

All the ligands (**L144-149**) were screened for intramolecular asymmetric Heck coupling reactions of triflates (**I-III**) in the presence of $Pd_2(dba)_3$, PMP (1,2,2,6,6-pentamethyl-piperidine), Ph_2O at 95 °C (Scheme 78). Initial screening was carried out for triflate **I** by varying the phosphine substituent R_1 holding R_2/R_3 as phenyl and R_4 as a 2-naphthoyl (**L144a-h**). The phosphine substituted with 3,5-difluorophenyl (**L144h**) gave oxindole with 78% *ee*, which was significantly higher than both (*R*)-BINAP and **L144e** under similar reaction conditions.

The screening of C_2-symmetric ligands **L145a-g** (R_2=R_3) and non-C_2-symmetric ligands **L145h-m** ($R_2 \neq R_3$) was carried out by varying R_2 and R_3 substituents by keeping the phosphine substituent R_1 as phenyl and R_4 as a 2-naphthoyl. The results showed that compared to neutral ligands electron-rich and electron-poor ligands gave increased enantioselectivity. In addition, all the ligands having different R_2 and R_3 substituents gave lower enantioselectivity. Thus, in terms of



Ligand	Thermal		MW	
	% Conv. (I and I)	*ee* of I (%)	% Conv. (I and I)	*ee* of I (%)
L137a	77	98	100	99
L137b	27	97	-	-
L137c	21	91	32	92
L137d	17	96	-	-
L137e	7	89	-	-
L137f	< 5	nd	-	-
L137g	< 5	nd	-	-
L138a	74	98	96	98
L139a	54	96	85	96
L140a	< 5	nd	< 5	nd
L141a	24	75	69	76
L141b	7	73	-	-
L141c	8	64	-	-
L142	9	56	-	-
L143	6	21	-	-

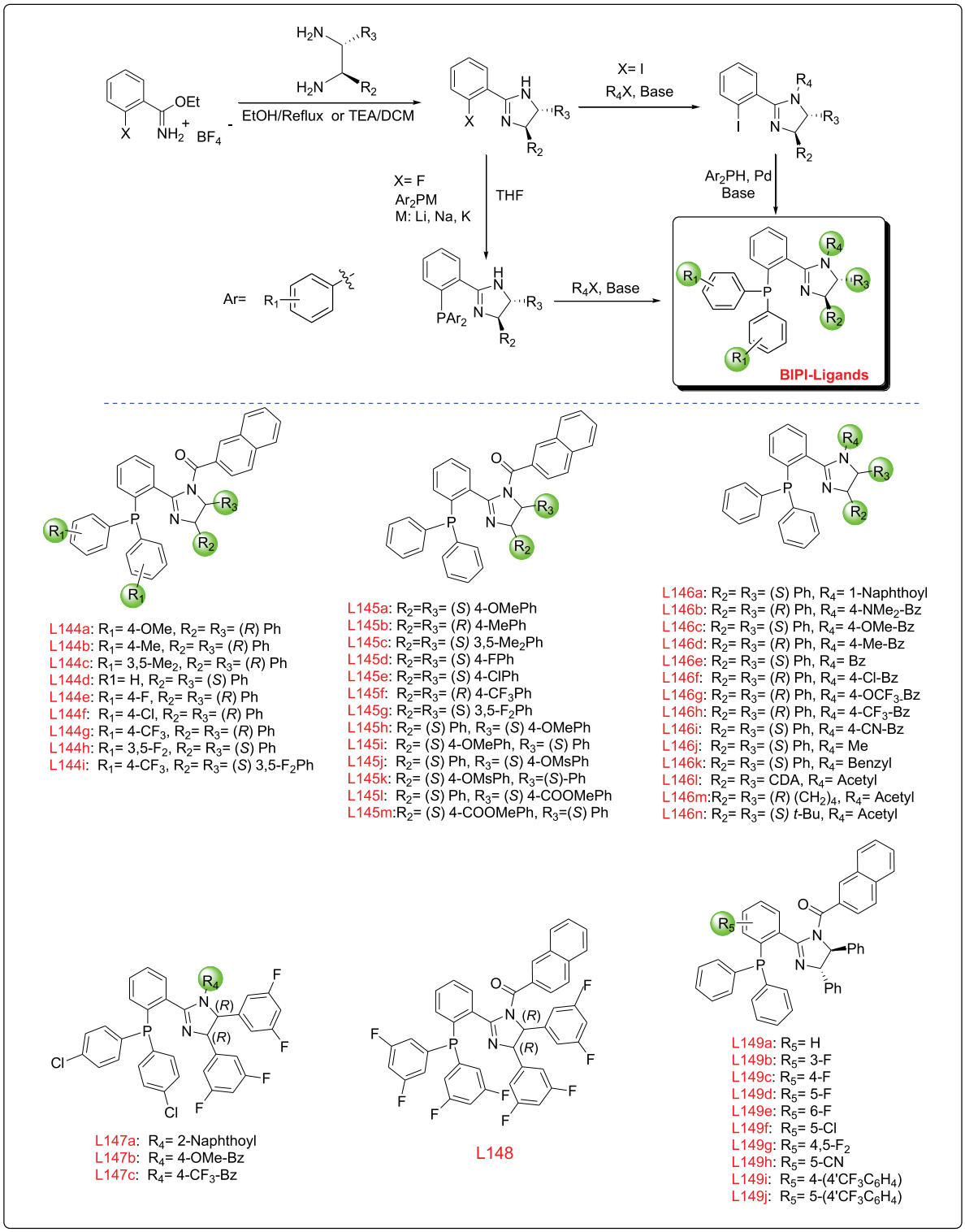
Scheme 76. Phosphite oxazole-imidazoline ligands for asymmetric Heck coupling reactions.

enantioselectivity (62.7% *ee*) and yield (93%), the best results were shown by the **L145g** containing a 3,5-difluoro system.

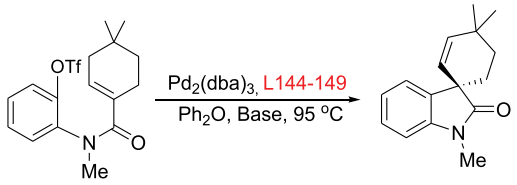
An examination of R_4 substituted ligands (**L146a-n**) doesn't have so much effect on enantioselectivity. Compared to ligands derived from aryl diamines or ligands with electron-withdrawing substituents on N, the ligands **L146a-n** gave the opposite enantiomer. Moreover, out of **L147a-c**, ligand **L147a** gave excellent enantioselectivity (80.6% *ee*). Thus, the ligands **L147a** having chlorophosphine with 2-naphthoyl as the optimum R_4 group showed 75.9–80.6% *ee* using different bases. However, the ligand **L148** containing R_2 and R_3 as difluorophenyl with 2-naphthoyl R_4 gave the highest enantioselectivity of 87.6%. They also briefly examined the effect of substituents R_5 on the central benzene ring (**L149a-j**) by keeping the standard phenyl substituent at R_1, R_2, and R_3 and holding R_4 as 2-naphthoyl. It was observed that **L149f** gave the best results.

The screening of ligands for triflate (**II**) showed that the highest enantioselectivity (77.5% *ee*) was obtained for ligand **L148**. For triflate (**III**), ligand **L148** was excellent in terms of *ee* (82.8%), while ligand **L144h** was excellent in terms of yield (99%) as well as *ee* (69.9%). The p-trifluoromethyl ligand (**L144g**) was practically good in terms of yield and *ee* for an asymmetric Heck coupling reaction of triflate **IV** bearing the protected tetrahydropyridine functionality.

Guary and coworkers [157] synthesized indanol-derived ligand **L150** by direct metalation followed by a reaction with chlorodiphenylphosphine of oxazoline obtained from thiophene-2-carbonitrile (Scheme 79). The ligand was applied for intramolecular Heck coupling reactions of aryl iodides and aryl triflates in toluene at 80°C in the presence of PMP as a base. The ligand (10 mol %) proved to be less successful both in terms of conversion (13%) and enantioselectivity (22% *ee*). The ee was increased up to 76% with the tert-butyl-substituted HetPHOX ligand **L18b** [43] in the presence of a proton sponge [1,8-bis(dimethylamino)naphthalene].

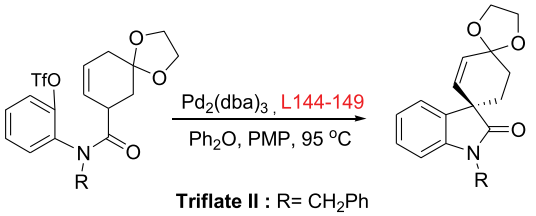


Scheme 77. Synthesis of various BIPI ligands.



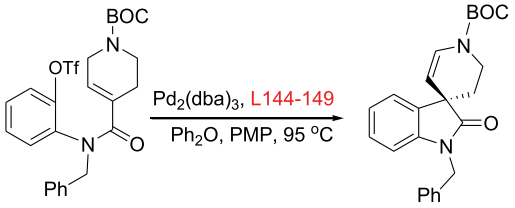
Triflate I

Ligand	Base	Yield (%)	*ee* (%)
L144a	PMP	15	39.9 (-)
L144b	PMP	15	54.5 (-)
L144c	PMP	82	49.9 (-)
L144d	PMP	68	44.6 (+)
L144e	PMP	68	53.3 (-)
L144f	PMP	30	66.1 (-)
L144g	PMP	25	72.9 (-)
L144h	PMP	39	78.1 (+)
L145a	PMP	13	51.6 (+)
L145b	PMP	25	45.2 (-)
L145c	PMP	85	46.7 (+)
L145d	PMP	61	48.3 (+)
L145e	PMP	17	61.5 (+)
L145f	PMP	12	64.6 (-)
L145g	PMP	93	62.7 (+)
L145h	PMP	75	41.4 (+)
L145i	PMP	73	40.8 (+)
L145j	PMP	70	58.2 (+)
L145k	PMP	86	47.8 (+)
L145l	PMP	65	40.9 (+)
L144m	PMP	57	42.6 (+)
L146a	PMP	85	40.6 (+)
L146b	PMP	25	37.0 (-)
L146c	PMP	27	47.6 (+)
L146d	PMP	81	32.7 (-)
L146e	PMP	76	42.2 (+)
L146f	PMP	71	40.1 (-)
L146g	PMP	88	33.7 (-)
L146h	PMP	90	41.9 (-)
L146i	PMP	83	36.6 (+)
L146j	PMP	17	20.5 (-)b
L146k	PMP	16	11.9 (-)b
L146l	PMP	18	36.7 (-)
L146m	PMP	21	29.2 (+)
L146n	PMP	88	29.1 (-)
L147a	PMP	25	80.6 (-)
L147b	PMP	28	78.2 (-)
L147c	PMP	26	74.9 (-)
L147a	(R)CEP	51	79.3 (-)
L147a	(S)CEP	48	78.8 (-)
L147a	(R,S)-Pin	51	76.4 (-)
L147a	(R,S)-Pin	45	79.0 (-)
L147a	PS	NR	NA
L147a	Quin	NR	NA
L148	PMP	38	87.6 (-)
L148	(S)-CEP	50	86.8 (-)
L149a	PMP	68	44.6 (+)
L149b	PMP	15	27.3 (+)
L149c	PMP	15	52.8 (+)
L149d	PMP	46	52.8 (+)
L149e	PMP	73	26.3 (+)
L149f	PMP	50	55.6 (+)
L149g	PMP	NR	NA
L149h	PMP	NR	NA
L149i	PMP	13	44.0 (+)
L149j	PMP	14	34.0 (+)



Triflate II : R= CH_2Ph
Triflate III: R= Me

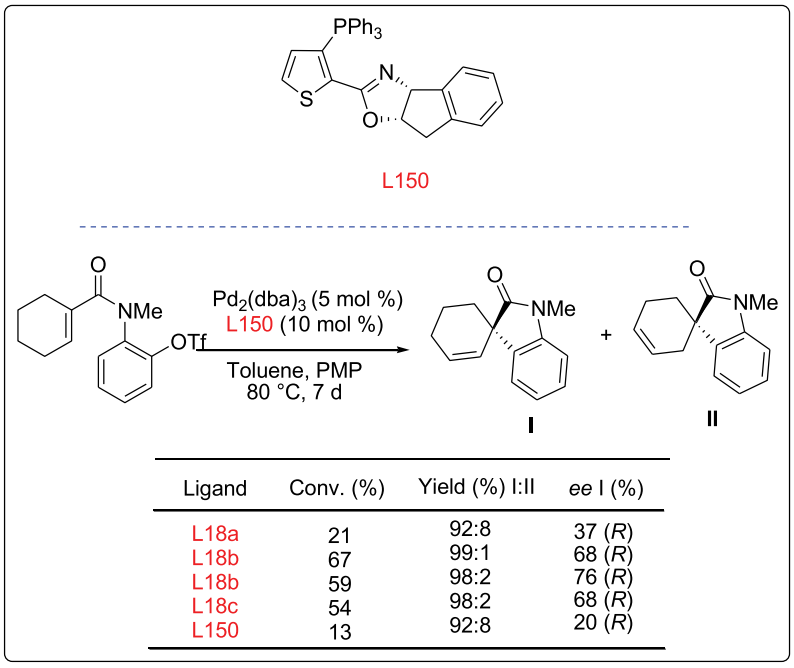
Ligand	R	Yield (%)	*ee* (%)
L144a	CH_2Ph	65	2.3 (*R*)
L144b	CH_2Ph	60	10.9 (*R*)
L144c	CH_2Ph	71	16.2 (*R*)
L144e	CH_2Ph	98	6.6 (*S*)
L144f	CH_2Ph	89	17.7 (*R*)
L144g	CH_2Ph	97	17.7(*R*)
L144h	CH_2Ph	89	31.1 (*S*)
L145a	CH_2Ph	46	13.0 (*S*)
L145b	CH_2Ph	87	0.6 (*R*)
L145c	CH_2Ph	86	4.5 (*S*)
L145e	CH_2Ph	81	25.9 (*S*)
L145f	CH_2Ph	79	32.6 (*R*)
L145g	CH_2Ph	95	31.4 (*S*)
L145h	CH_2Ph	85	5.4 (*S*)
L145i	CH_2Ph	46	7.8 (*S*)
L145j	CH_2Ph	64	23.8 (*S*)
L145k	CH_2Ph	57	8.4 (*S*)
L145l	CH_2Ph	84	13.9 (*S*)
L145m	CH_2Ph	86	13.0 (*S*)
L146n	CH_2Ph	82	50.9 (*R*)
L147c	CH_2Ph	81	55.9 (*R*)
L148	CH_2Ph	67	77.5 (*R*)
L144f	Me	80	62.7 (*S*)
L144h	Me	99	69.9 (*R*)
L145e	Me	68	52.1 (*R*)
L148	Me	53	82.8 (*S*)



Triflate IV

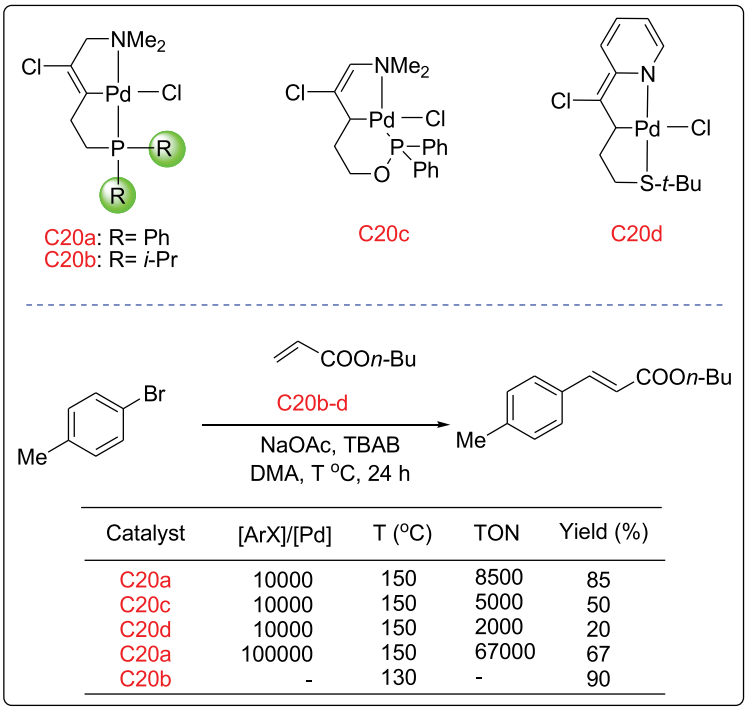
Ligand	Yield (%)	*ee* (%)
L144a	70	11.4 (+)
L144d	83	21.4 (-)
L144f	85	39.4 (+)
L144g	71	46.9 (+)
L144h	88	29.8 (-)
L144i	11	50.1 (-)
L145a	44	15.7 (-)
L145b	83	23.6 (+)
L145d	51	32.0 (-)
L145e	58	34.1 (-)
L145g	68	35.0 (-)
L147a	25	41.5 (+)
L148	62	35.6 (+)

Scheme 78. BIPI-PHOX for the synthesis of oxindole by intramolecular asymmetric Heck coupling reactions.



Ligand	Conv. (%)	Yield (%) I:II	*ee* I (%)
L18a	21	92:8	37 (*R*)
L18b	67	99:1	68 (*R*)
L18b	59	98:2	76 (*R*)
L18c	54	98:2	68 (*R*)
L150	13	92:8	20 (*R*)

Scheme 79. Indanol-derived PHOX ligand for intramolecular asymmetric Heck coupling reactions.



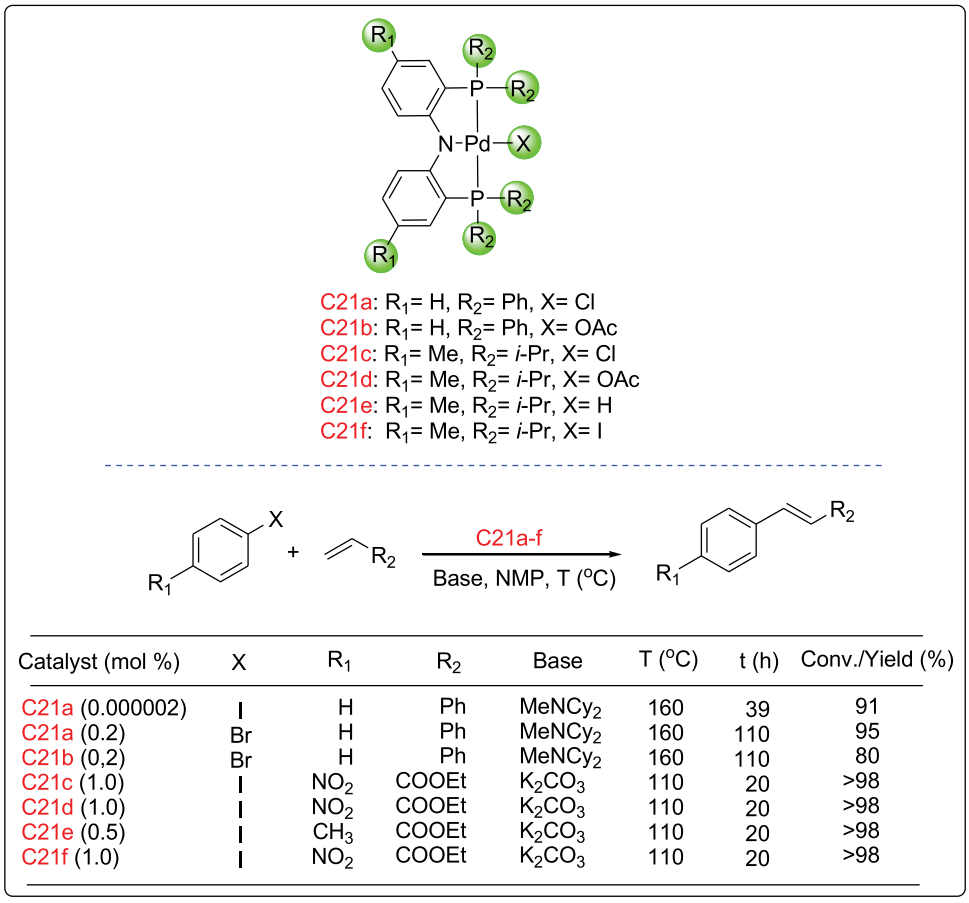
Catalyst	[ArX]/[Pd]	T (°C)	TON	Yield (%)
C20a	10000	150	8500	85
C20c	10000	150	5000	50
C20d	10000	150	2000	20
C20a	100000	150	67000	67
C20b	-	130	-	90

Scheme 80. Pd(II)-NCP pincers for the Heck coupling reactions.

Since 1970 [158], the transition metal ECE and ECE′ type pincer complexes attracting great interest as a new class of metal complexes. These complexes have a diverse range of applications in catalysis [159].

In 2004, Dupont and co-workers prepared [160] mixed NCP pincer catalysts **C20a** and **C20c-d** for the Heck coupling reactions. The phosphine-containing palladacycle **C20a**was relatively more active than the phosphinite analog **C20c**. Even under a very low catalyst loading, **C20a** was more active in coupling 4-bromotoluene and 4-bromoanisole with *n*-butyl acrylate using NaOAc as the base in DMA and the presence of TBAB at 150 °C (Scheme 80). The complex **C20b** (0.5 mol %) also works efficiently in the Heck coupling of 4-bromotoluene with olefins in the presence of Na_2CO_3, in TBAB and DMF at 130 °C [161]. The protocol was extended for the synthesis of 5,8-π-extended quinoxaline and 2,1, 3-benzothio derivatives which act as good chromophores for photo-luminescence applications [162].

Huang and Liang [163] developed two PNP pincer complexes



Catalyst (mol %)	X	R_1	R_2	Base	T (°C)	t (h)	Conv./Yield (%)
C21a (0.000002)	I	H	Ph	$MeNCy_2$	160	39	91
C21a (0.2)	Br	H	Ph	$MeNCy_2$	160	110	95
C21b (0,2)	Br	H	Ph	$MeNCy_2$	160	110	80
C21c (1.0)	I	NO_2	COOEt	K_2CO_3	110	20	>98
C21d (1.0)	I	NO_2	COOEt	K_2CO_3	110	20	>98
C21e (0.5)	I	CH_3	COOEt	K_2CO_3	110	20	>98
C21f (1.0)	I	NO_2	COOEt	K_2CO_3	110	20	>98

Scheme 81. P-N-P pincer-type complexes for the Heck coupling reactions.

(**C21a-b**) containing o-phenylene-derived amido diphosphine ligands. The complexes were obtained as brick red solids by the metathetical reaction of [PNP]Li(THF)$_2$ with $PdCl_2(PhCN)_2$ or $Pd(OAc)_2$ in THF at −35 °C. The utility of the complexes was investigated for the Heck coupling of a variety of aryl halides and styrene using Cy_2NMe as a base in NMP at 160 °C. The catalysts showed TON up to 4.5×10^7 and TOF up to $1.1 \times 10^6\ h^{-1}$ (Scheme 81). Similarly, Ozerov et al. [164] reported the synthesis of PNP-Pd pincer complexes (**C21c-f**) wherein *o*-arylene units link the amido and phosphine sites that offer increased rigidity, devoid of *β*-hydrogens and moisture-sensitive functionalities. All the complexes (**C21c-f**) were used as pre-catalysts for the Heck coupling of aryl halides with ethyl acrylate in NMP and K_2CO_3 at 110 °C.

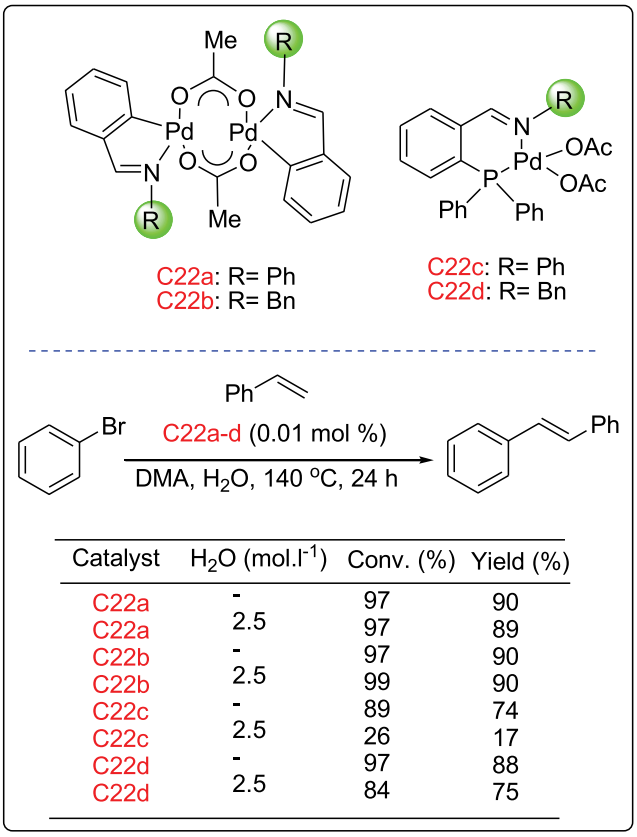
A Pd coordinated with Schiff bases ligands (iminophosphine) was found to be a remarkably active catalyst for many coupling reactions [165]. In this regard, Pfaltz et al. [166] applied an air and moisture-stable dimeric, acetate-bridged phosphine-free Pd (II) Schiff base complexes (**C22a-b**), as well as monomeric, air and moisture-stable phosphine-containing Schiff base complexes (**C22c-d**) for the Heck coupling reactions of bromobenzene with styrene. In the presence of NaOAc in DMA at 140 °C, essentially high yields of *trans*-stilbene were obtained with 0.01 mol % of the **C22a-b**, while complexes **C22b-d** gave slightly lower yields (Scheme 82). Moreover, catalysts **C22a-b** are more sensitive as compared to complexes **C22c-d**.

Singh et al. [167] used Pd(0) complexes of P-N ligands anchored on silica gel (**C23a-c**) for the Heck coupling reactions between aryl bromides and iodides with acrylic acid or styrene in *p*-xylene and TEA at 110–140 °C (Scheme 83). There was a selective formation of *trans* products in good yields (92%). The catalysts showed 15–16 times reusability without significant loss of activity. Recently, magnetically separable iminophosphine Pd–Fe_3O_4–PEG catalyst was also applied for the Suzuki coupling reactions in pure water [168].

Yilmaz et al. [169] used new hemilabile ligand systems for the green synthesis of substituted olefins *via* Heck coupling reactions in supercritical CO_2 (Scheme 84). They designed Pd(II) complexes (**C24a-f**) bearing hetero donor phosphine-imine ligands for the reactions of aryl halides in DIPEA at 120 °C, in CO_2 (15 MPa) in the presence of Bu_4NBr. The catalytic system (0.5 mol %) leads to slower reaction times, good conversions, and selectivity, than the previously reported mono or bisphosphine Pd precatalysts.

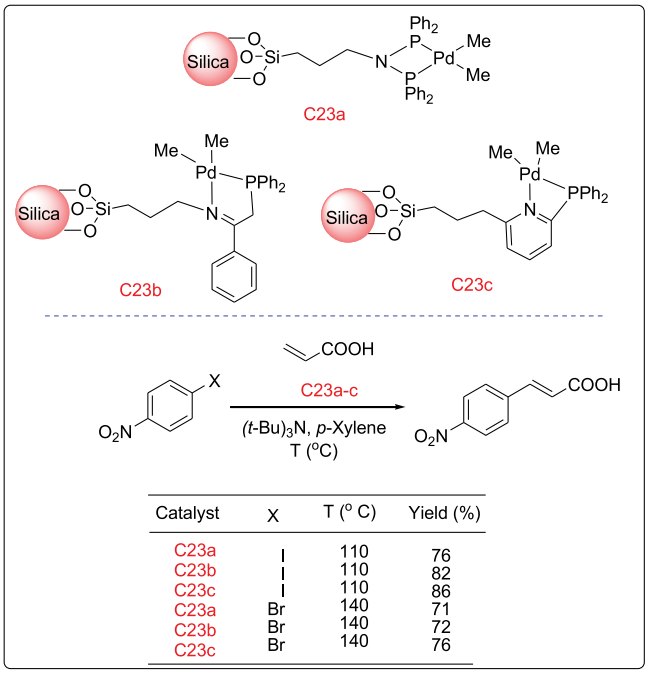
Verkade et al. [170] reported [$Pd_2(dba)_3$/**L151** (2:4 mol %) catalytic system for the one-pot synthesis of a variety of symmetrically and unsymmetrically substituted *trans*-4-N,N-diaryl aminostilbenes and N, N-diarylaminostyrenes (Scheme 85). This catalytic system was also used for both amination and intermolecular Heck coupling reactions. The 5, 6-dihydro-7H-dibenz[b,d]azepine was also synthesized in moderate yield in a one-pot amination/Suzuki coupling reaction using a Pd $(OAc)_2$/**L151** (4:8 mol %) catalytic system.

Iranpoor et al. [171] used 1,3,2,4-diazadiphosphetidine-based phosphazanes as a new generation of heterogeneous bidentate ligands (**L152a-d**) for the Heck coupling reactions (Scheme 86). The reactions of aryl halides with different olefins were carried out under base-free conditions in the presence of $PdCl_2$ (2.5 mol %) in water at reflux. The ligand **L152a** was found to be highly efficient and can be reused at least 10 successive runs for the reaction of bromobenzene and styrene. The use of this ligand provides the possibility of performing the reaction in water under heterogeneous reaction conditions.



Catalyst	H_2O (mol.l^{-1})	Conv. (%)	Yield (%)
C22a	-	97	90
C22a	2.5	97	89
C22b	-	97	90
C22b	2.5	99	90
C22c	-	89	74
C22c	2.5	26	17
C22d	-	97	88
C22d	2.5	84	75

Scheme 82. Pd(II)-Schiff base complexes for the Heck coupling reactions.

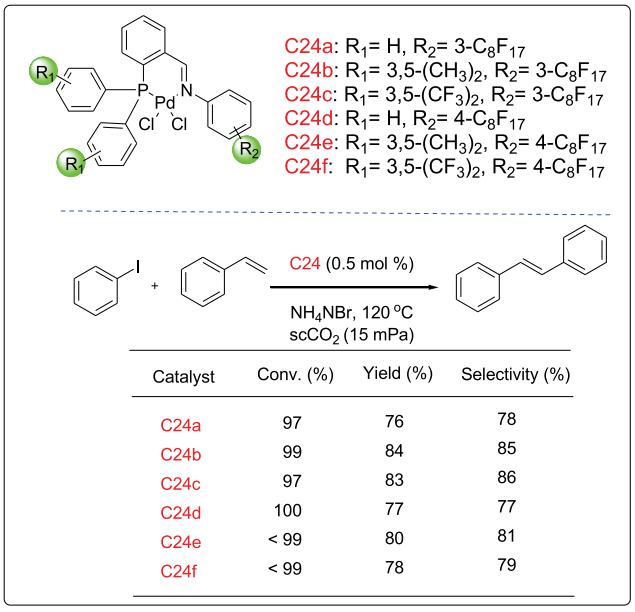


Catalyst	X	T (° C)	Yield (%)
C23a	I	110	76
C23b	I	110	82
C23c	I	110	86
C23a	Br	140	71
C23b	Br	140	72
C23c	Br	140	76

Scheme 83. Pd(0) complexes of P-N ligands anchored on silica gel for the Heck coupling reactions.

3.3. Suzuki coupling reactions

It has been known that asymmetric Suzuki coupling reactions have been widely used for the synthesis of many important compounds [172].

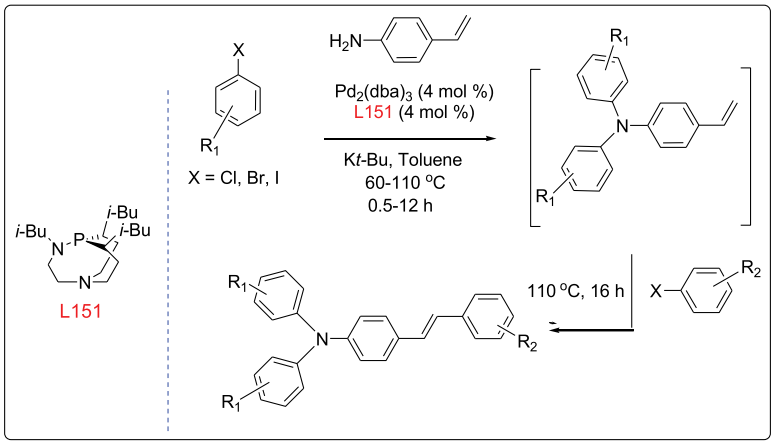


Catalyst	Conv. (%)	Yield (%)	Selectivity (%)
C24a	97	76	78
C24b	99	84	85
C24c	97	83	86
C24d	100	77	77
C24e	< 99	80	81
C24f	< 99	78	79

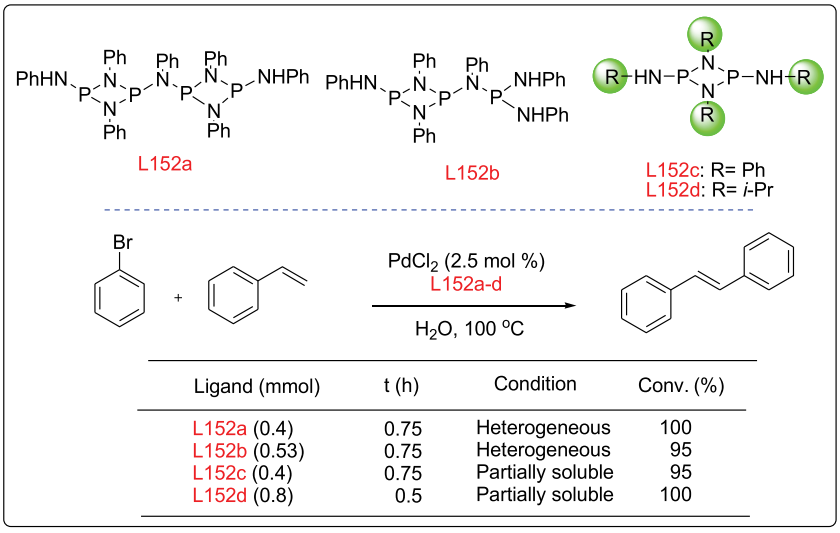
Scheme 84. Heck coupling reactions in supercritical CO_2 using phosphine-imine ligands.

In this connection, unsymmetrical chiral PCN pincer Pd(II) complexes **C25a-h** based on (imidazolinyl)aryl phosphinite were synthesized by one-pot phosphorylation/palladation reaction *via* C-H bond activation [173]. All the complexes were characterized by XRD and adopted a typical distorted-square-planar geometry. The complexes showed moderate enantioselectivities in the asymmetric Suzuki coupling reactions (Scheme 87). It was found that except for **C25b**, with an *i*-Pr_2PO group, the other Pd complexes were effective catalysts in the coupling reaction of 1-iodo-2-methoxynaphthalene with 1-naphthylboronic acid. Thus, **C25a** was the most active catalyst, giving a 92% yield of the product but with less enantioselectivity (up to 26% *ee*). They proposed the cleavage of the Pd-C bond in the complexes to form the Pd(0) species that take part in the reaction.

Extensive work on a chiral phosphine hydrazone ligand was reported by Lassaletta and coworkers [174]. The bidentate **L153a-c** ligands were synthesized from commercially available 2-(diphenylphosphino)benzaldehyde and C_2-symmetric hydrazines. The ligands **L153d—h** with different PAr_2 groups were synthesized by reaction of the corresponding diarylphosphinobenzaldehydes with (*2S, 5S*)-1-amino-2,5-diphenylpyrrolidine. The ligand **L153i** was obtained by condensation of corresponding phosphine oxide with diphenyl-substituted pyrrolidine followed by reductive deoxygenation using $HSiCl_3$ in Et_3N and toluene at reflux (Scheme 88). The phosphine hydrazones **L153a-c** react with $[PdCl_2(CH_3CN)_2]$ and afforded **C27a-c** a neutral Pd(II)complexes. The $PdCl_2(CH_3CN)_2$/**L153a-i** (5:5 mol %) were tested in the asymmetric Suzuki coupling reaction of 1-bromo-2-methoxynaphthalene and 1-naphthyl boronic acid for the synthesis of axially chiral biaryls in the presence of Cs_2CO_3 in toluene at room temperature. The pyrrolidine-based phosphine hydrazones (**L153a** and **L153c**) provided a better chiral environment than the piperidine-based analog (**L153b**). This result was attributed to the higher conformational rigidity associated with the stronger n-π conjugation. Though the enantioselectivity (*er*= 95:5) was observed previously for bis-hydrazone ligands, the ligands **L153a** and **L153c** were promising alternatives in terms of catalytic activity. The ligands **L153i** showed poor catalytic activity and afforded the racemic mixture of the desired product. The reactions carried out using preformed complexes **C27a** and **C27c** afforded improved results. The scope of the protocol was explored in the



Scheme 85. $[Pd_2(dba)_3/P(i\text{-}BuNCH_2CH_2)_3N$ for the one-pot synthesis of a diaryl amino stilbenes and N, N-diaryl amino styrenes.



Ligand (mmol)	t (h)	Condition	Conv. (%)
L152a (0.4)	0.75	Heterogeneous	100
L152b (0.53)	0.75	Heterogeneous	95
L152c (0.4)	0.75	Partially soluble	95
L152d (0.8)	0.5	Partially soluble	100

Scheme 86. Diazadiphosphetidine-based phosphazanes as a heterogeneous bidentate ligand for the Heck coupling reactions.

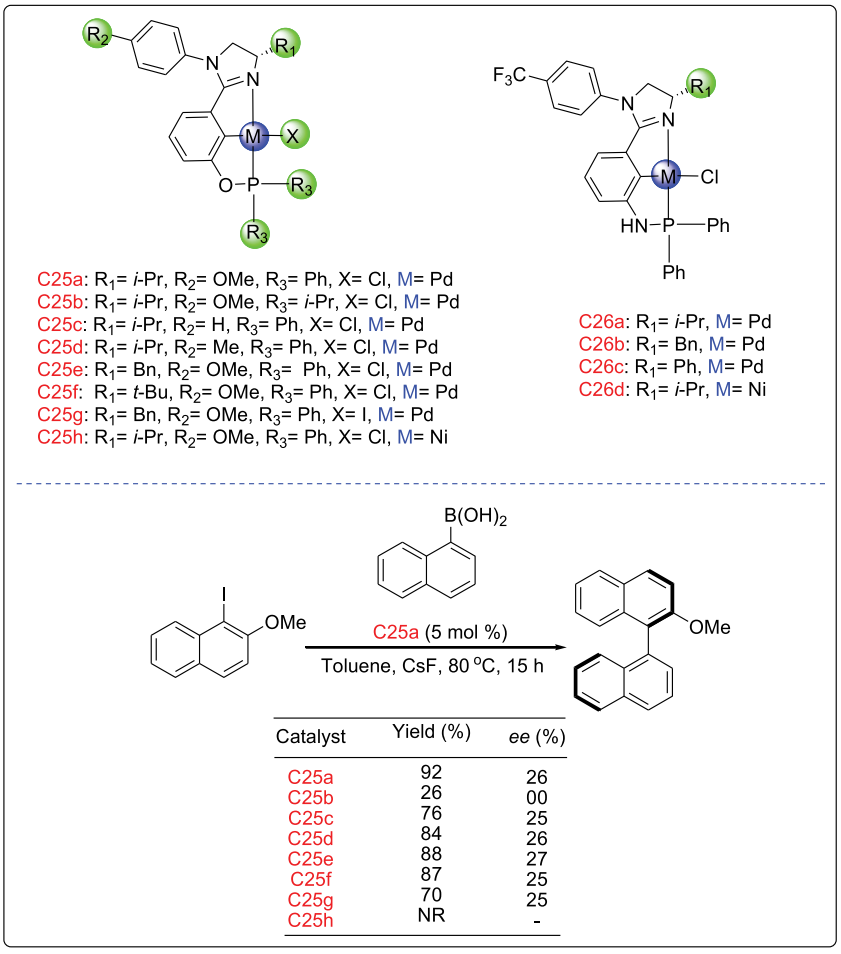
asymmetric Suzuki coupling of a variety of aryl bromides and triflates with aryl boronic acids. The functionalized biaryls afforded good yields and enantioselectivities.

Recently, the dynamic kinetic asymmetric transformation (DYKAT) technique was used for the synthesis of 2′-substituted 2-aryl pyridines/isoquinolines and related heterobiaryls [175]. Such compounds were obtained by the Pd-catalyzed coupling of racemic 2-triflates with aryl boroxines using a monodentate TADDOL-derived phosphoramidite. The ligand **L154** gives good to excellent enantioselectivities. The catalytic system $[Pd_2(dba)_3]$/**L154** (10:10 mol %) showed complete conversion of *p*-anisyl boroxine with 1-(isoquinolin-1-yl)naphthalene-2-yl triflate into expected coupling product with 91% yield and 34% *ee* in the presence of Cs_2CO_3 as a base in THF at 55 °C (Scheme 89). Alternatively, $Pd(dba)_2$/**L154** (5:5 mol %) led to 76% yield and 84% *ee* in dioxane. Moreover, several combinations of heterobiaryl triflates with arylboroxines afforded desired products in good to excellent yields and high *ee* in the presence of Cs_2CO_3 as a base in dioxane at 25–55 °C.

A chiral imidazoindole phosphines supported on amphiphilic polystyrene-poly(ethylene glycol) resin (**L123a-c**) (10 mol %) was successfully carried out asymmetric Suzuki coupling of 2-substituted 1-iodonaphthalenes and 2-substituted naphthalene-1-ylboronic acid into (*S*)-2,2′-disubstituted 1,1′-binaphthyl in the presence of $Pd(OAc)_2$ (10 mol %) with 94% *ee* in water (Scheme 90) [176]. XRD analysis of the complex **L123a**-$PdCl_2$ showed that the ligand coordinates to Pd(II) in a P, N-chelating fashion. The catalytic system could be recycled at least 4 times with consistent activity and selectivity.

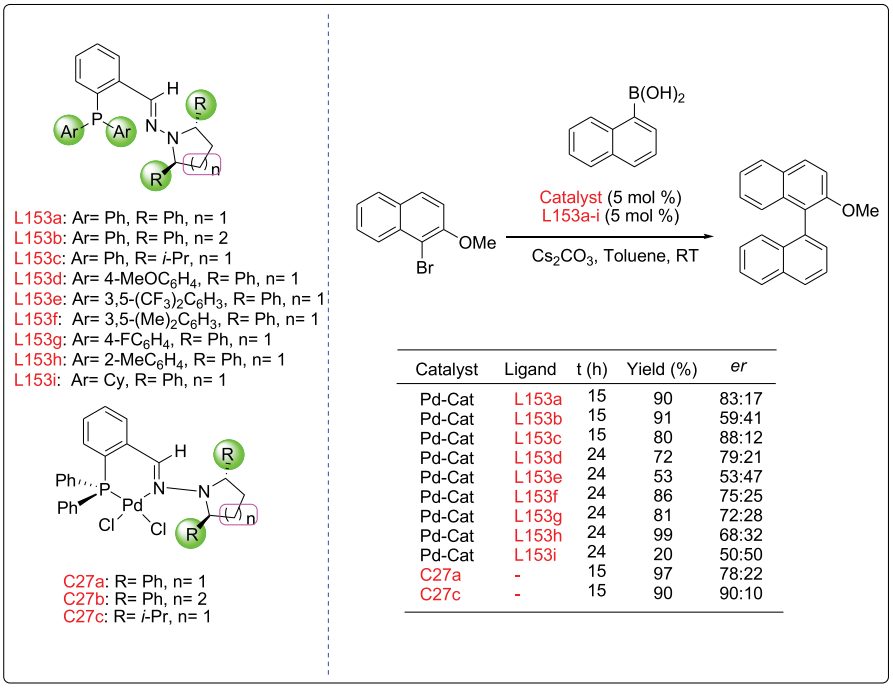
Dupont and co-workers [177] reported the air and water stable, non-symmetrical NCP type pincer complex **C20c** for the Suzuki coupling of arylboronic acids with electron-rich and electron-poor aryl chlorides. The catalyst furnished the corresponding coupling products with excellent yields (70–98%) in the presence of CsF as a base in dioxane at 130 °C. The complex **C20c** (0.5 mol %) was also active in coupling sterically hindered bromomesitylene with a 2-methyl phenylboronic acid in CsF, TBAB, and dioxane at 130 °C. A series of aryl bromides and iodides undergo easy coupling with various aryl boronic acids in the presence of complex **C20c** (0.2 mol %) in K_3PO_4 and dioxane at 100 °C and 130 °C (Scheme 91).

The catalysts **C21a** and **C21c** were applied for the Suzuki coupling reactions [178]. Several electronically activated, unactivated, and deactivated (hetero)aryl bromides and iodides were coupled with aryl boronic acids using $K_3PO_4.H_2O/K_3PO_4$ as a base in 1,4-dioxane/toluene at 110–80 °C under aerobic conditions.



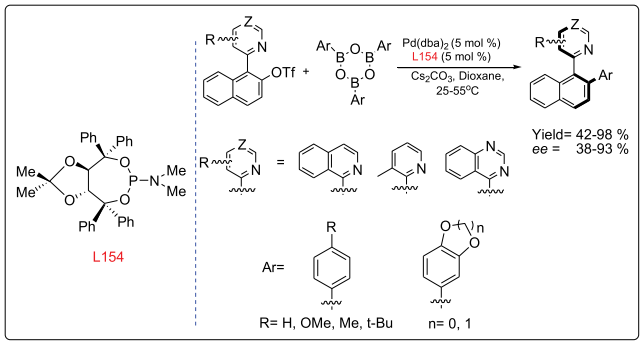
Catalyst	Yield (%)	*ee* (%)
C25a	92	26
C25b	26	00
C25c	76	25
C25d	84	26
C25e	88	27
C25f	87	25
C25g	70	25
C25h	NR	-

Scheme 87. Chiral Pd(II)-PCN pincer complexes for asymmetric Suzuki coupling reactions.

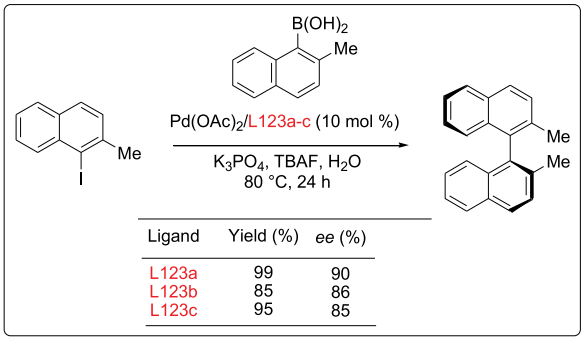


Catalyst	Ligand	t (h)	Yield (%)	*er*
Pd-Cat	L153a	15	90	83:17
Pd-Cat	L153b	15	91	59:41
Pd-Cat	L153c	15	80	88:12
Pd-Cat	L153d	24	72	79:21
Pd-Cat	L153e	24	53	53:47
Pd-Cat	L153f	24	86	75:25
Pd-Cat	L153g	24	81	72:28
Pd-Cat	L153h	24	99	68:32
Pd-Cat	L153i	24	20	50:50
C27a	-	15	97	78:22
C27c	-	15	90	90:10

Scheme 88. Phosphino hydrazones for asymmetric Suzuki coupling reactions.



Scheme 89. TADDOL-derived phosphoramidite for coupling of racemic 2-triflates with aryl boroxines.



Ligand	Yield (%)	*ee* (%)
L123a	99	90
L123b	85	86
L123c	95	85

Scheme 90. Recyclable amphiphilic resin-supported P-N chelating Pd complexes for asymmetric Suzuki coupling reactions.

Arriortua et al. [179] prepared PCN Pd pincer complex (**C28**) containing a phosphinoamino group. The complex was readily obtained from available 1-(3-nitrophenyl)pyrazole and $Pd(COD)Cl_2$ in toluene. The structure of the complex was confirmed by ^1H NMR, DEPT, HSQC, and X-ray diffractometry analysis. The complex was tested in the Suzuki coupling reactions in aqueous media. Various biaryls were obtained in excellent yields in the presence of **C28** (0.01 mol %), and K_2CO_3 in H_2O at 100 °C for 2 h (Scheme 92).

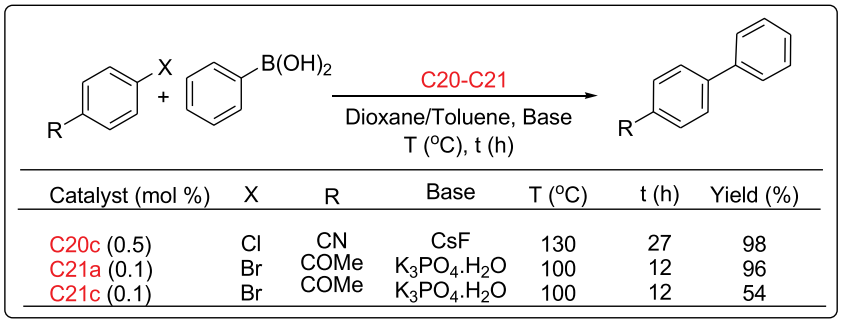
Song et al. [180] reported the facile synthesis of achiral and chiral PCN pincer Pd(II) complexes (**C29a–e**) in two steps from commercially available 3-hydroxybenzaldehyde and amines (Scheme 93). The structure of **C29a** and **C29b** were determined by single-crystal X-ray analysis. After optimization of all the catalysts, complex **C29a** (0.1–1.0 mol %) was found to be an effective catalyst for the Suzuki coupling reactions of various aryl bromides with phenylboronic acids in $K_3PO_4.7H_2O$, EtOH at 50 °C, under air.

Similarly, Xia et al. [181] synthesized iminophosphinite pincer Pd complexes **C29f–j** and evaluated catalytic potential (0.010 mmol) in the Suzuki coupling reactions of various aryl bromides and chlorides with phenylboronic acid in the presence of Cs_2CO_3 in dioxane at 100 °C. The catalyst preparation involves the complexation of imines with $Pd_2(dba)_3$ to give the Pd iminophosphinite pincer complexes **C29f–i**. The reaction of **C29g** with AgTFA in THF at room temperature afforded the Pd iminophosphinite trifluoroacetate complex (**C29j**).

Cyclopalladated azido complexes (**C30a-h**) containing ligands with C and N-donor atoms were studied for the Suzuki coupling reactions (Scheme 94) [182]. The activity of complexes (1 mol %) was evaluated in the coupling of 4-acetylbromobenzene with phenylboronic acid in the presence of K_2CO_3 in toluene at 80 °C. All the catalysts exhibited high activity. However, the reactions involving aryl chloride showed poor reactivity. The catalysts **C30h** also exhibited excellent activity in ethanol.

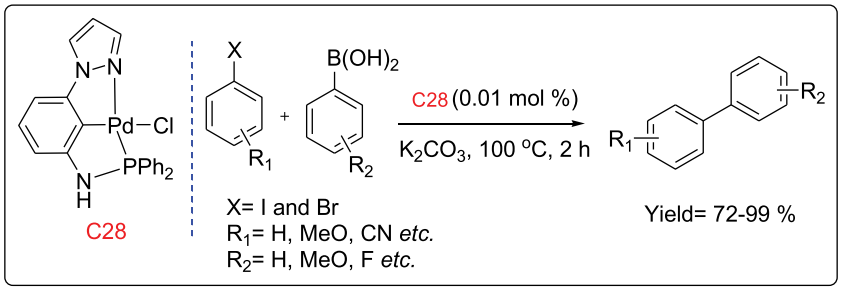
Recently, Kapdi et al. [183] used triple Suzuki coupling reactions for the synthesis of anthracene-based OLED emitters using K_2CO_3 as a base in aqueous THF (Scheme 95). The synthesis involves the use of palladacyclic complexes (**C31a-b**) containing imidate ligands. All the synthesized molecules were studied by UV–vis spectroscopy and TG-DSC analysis. The DFT studies of the different properties showed that all the derivatives possess a more significant hole mobility character than electron transfer capability.

Scrivanti et al. studied the role of olefin in catalyst stabilization by using η^2-(olefin)Pd(0) complexes containing iminophosphine ligands

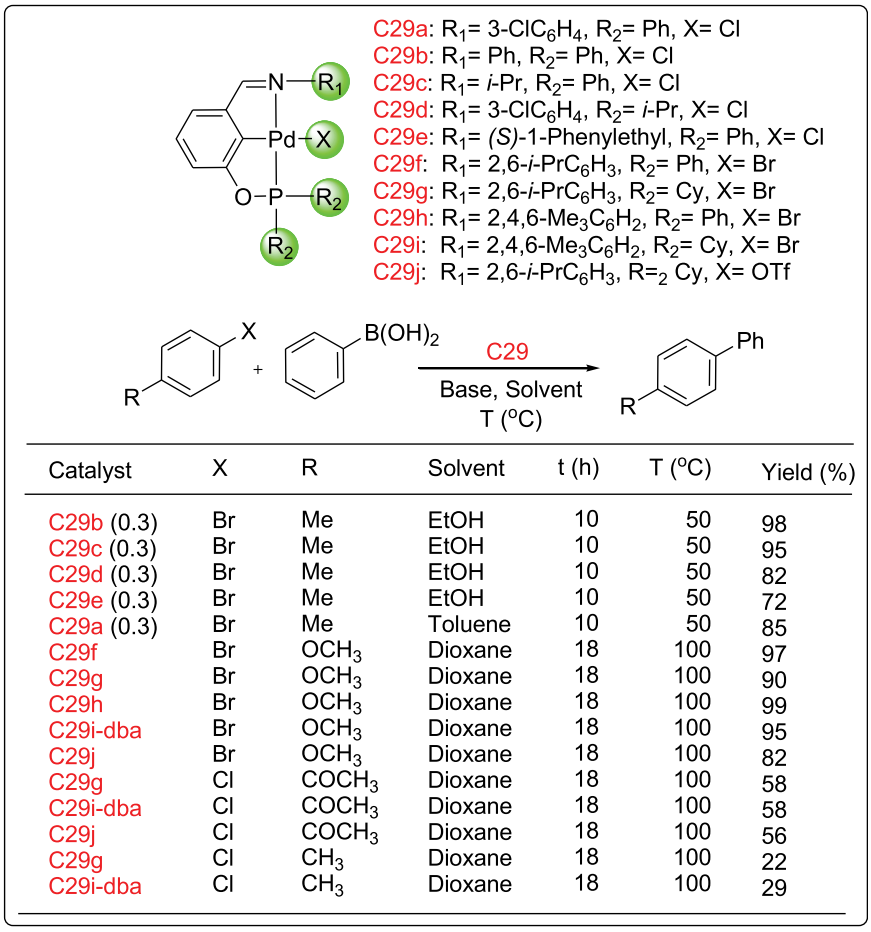


Catalyst (mol %)	X	R	Base	T (°C)	t (h)	Yield (%)
C20c (0.5)	Cl	CN	CsF	130	27	98
C21a (0.1)	Br	COMe	$K_3PO_4.H_2O$	100	12	96
C21c (0.1)	Br	COMe	$K_3PO_4.H_2O$	100	12	54

Scheme 91. Pd(II)-NCP pincers for the Suzuki coupling reactions.

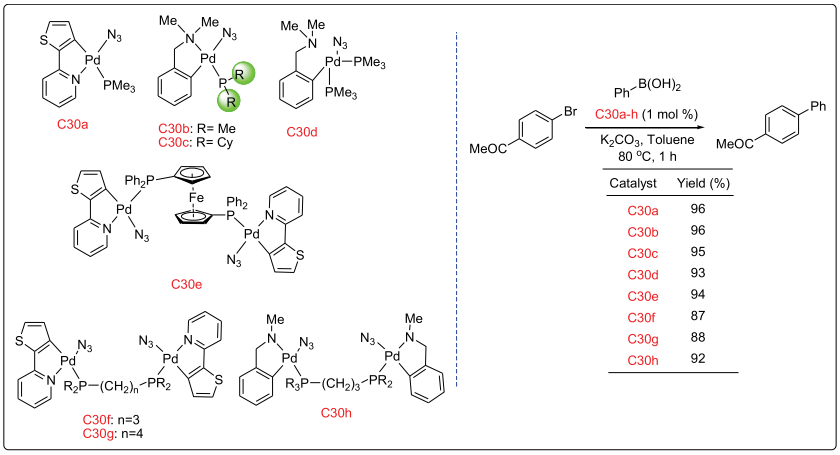


Scheme 92. Pd(II)-NCP pincers for the Suzuki coupling reactions.



Catalyst	X	R	Solvent	t (h)	T (°C)	Yield (%)
C29b (0.3)	Br	Me	EtOH	10	50	98
C29c (0.3)	Br	Me	EtOH	10	50	95
C29d (0.3)	Br	Me	EtOH	10	50	82
C29e (0.3)	Br	Me	EtOH	10	50	72
C29a (0.3)	Br	Me	Toluene	10	50	85
C29f	Br	OCH_3	Dioxane	18	100	97
C29g	Br	OCH_3	Dioxane	18	100	90
C29h	Br	OCH_3	Dioxane	18	100	99
C29i-dba	Br	OCH_3	Dioxane	18	100	95
C29j	Br	OCH_3	Dioxane	18	100	82
C29g	Cl	$COCH_3$	Dioxane	18	100	58
C29i-dba	Cl	$COCH_3$	Dioxane	18	100	58
C29j	Cl	$COCH_3$	Dioxane	18	100	56
C29g	Cl	CH_3	Dioxane	18	100	22
C29i-dba	Cl	CH_3	Dioxane	18	100	29

Scheme 93. Iminophosphinite Pd pincers for the Suzuki coupling reactions.



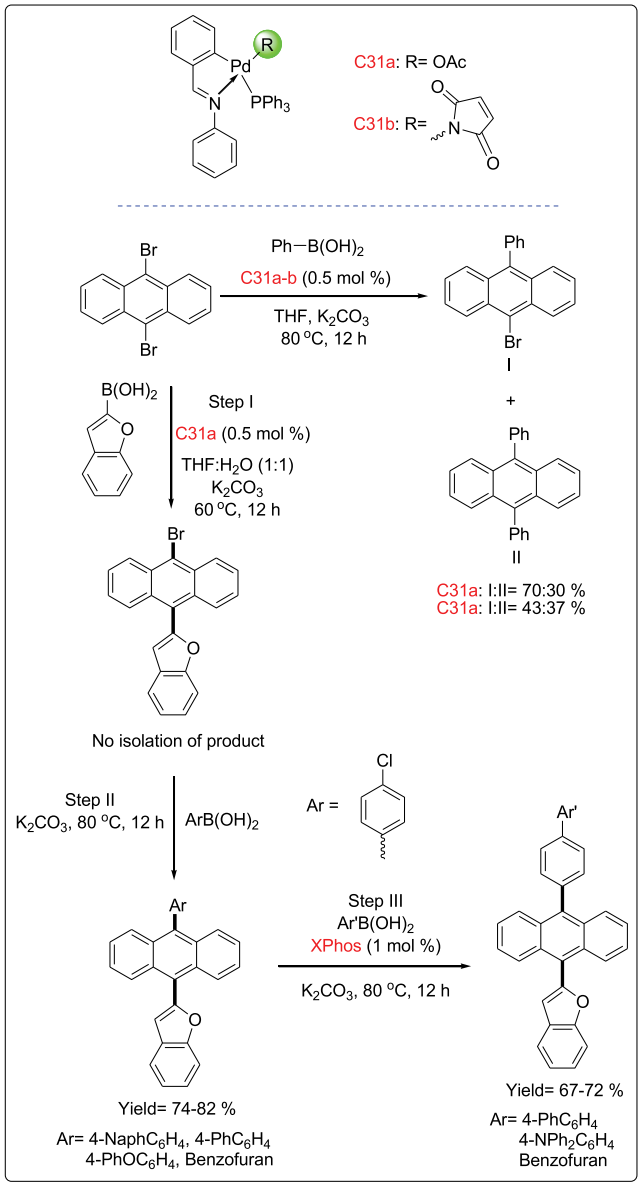
Catalyst	Yield (%)
C30a	96
C30b	96
C30c	95
C30d	93
C30e	94
C30f	87
C30g	88
C30h	92

Scheme 94. Cyclopalladated azido complexes for the Suzuki coupling reactions.

(**C32a-e** and **C32h**) in the Suzuki coupling reactions [184]. The coupling of 4-bromoacetophenone with phenylboronic acid showed that **C32c** was the best catalyst in toluene in the presence of K_2CO_3 at 110 °C. The catalyst obtained high efficiency with TON up to 10^5 h^{-1}. The system is also applied for the synthesis of undecaaryl substituted corroles (Scheme 96).

Buono and coworkers [185] synthesized a tunable P-stereogenic P, N-phosphine ligands (**L155**), and their Pd complex (**C33**). Both were fully characterized by spectroscopic and crystallographic studies. The new ligand and catalyst were tested in the Suzuki coupling reaction with 92% yields, and the intramolecular α-arylation of ketones (Scheme 97).

Kwong and coworkers explored and developed a new class of indolylphosphine ligands for the Suzuki coupling reactions. They applied Pd $(OAc)_2$/(**L156a-h**) system for aryl chlorides [186]. The ligands **L157a-c** and **L158a-e** also used in the Suzuki coupling reactions of aryl tosylates [187] under different reaction conditions (Scheme 98). Dramatic reactivity differences were observed when the position of the phosphino group interchanged (**L157b** and **L158d**). It may be the phosphino group



Scheme 95. Triple Suzuki coupling reactions for the synthesis of OLED emitters.

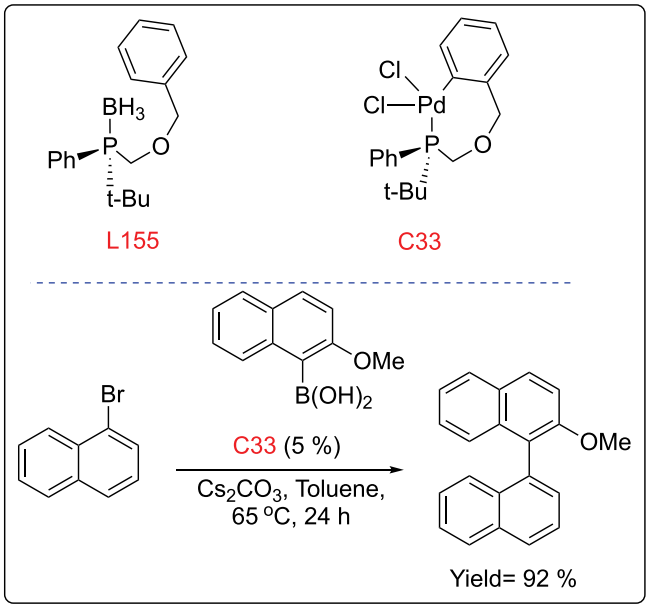
on the aryl ring instead of on the heterocyclic ring provides better geometry of chelation to the Pd and facilitates the oxidative addition of the Ar-OTs. Similarly, a new P, N-type "PhMezole-phos" ligands (**L159a-c**) acts as an efficient ligand for the Suzuki coupling reactions of sterically hindered aryl chlorides in presence of $K_3PO_4.H_2O$ in dioxane:mesitylene (1:2) mixture at 135 °C [188]. The catalyst loading could be reduced to 0.001 mol % Pd with 80000 TON.

Sarkar *et al.* [189] synthesized pyrazole-derived (**L160a–f**) and pyrrole (**L160g-j**) bidentate ligands for the Suzuki coupling reactions of the aryl bromides and chlorides. The ligand **L160b** gave an excellent yield of the coupling products in presence of $Pd_2(dba)_3$ and CsF in toluene at 65–85 °C (Scheme 99). An enhanced catalytic activity due to steric crowding in the Pd complex suggested the participation of a chelated structure in the intermediate catalytic steps.

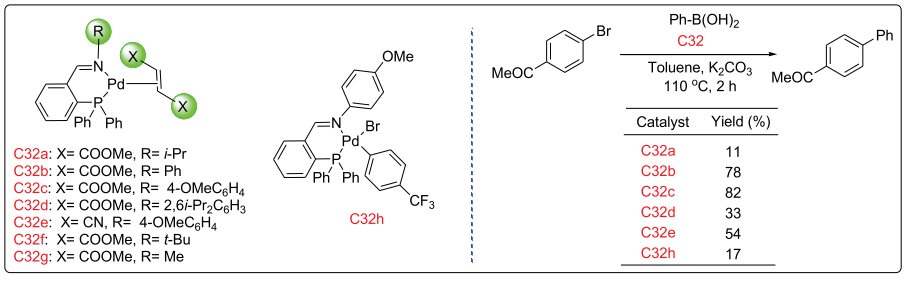
It was known that strongly basic and sterically demanding ligands activate the less reactive aryl chlorides. In this regard, Scrivanti *et al.* [190] reported [$PdCl_2$(P–N)] complexes (**C34a-b**) containing the basic and sterically demanding 8-(di-*t*-butylphosphinooxy)-quinoline (P–N) ligand. The complex **C34a** showed good to excellent activity for the Suzuki coupling reactions of the aryl bromides and chlorides with phenylboronic acid using K_2CO_3 as a base in toluene at 110 °C (Scheme 100). The catalytic activity of **C34b** was almost identical to that of **C34a**.

Frost et al. [191] synthesized water-soluble Pd complexes of trisubstituted PTA derivatives called PTA_{R3} (**L161**) and their precatalysts (**C35**). The **L161c** with $Pd(OAc)_2$ or $PdCl_2$ was found to be the most active catalytic system for the Suzuki coupling of aryl bromides and phenylboronic acid in water: acetonitrile (1:1) mixture at 80 °C. The Pd $(OAc)_2$/**L161c** system showed good yields with comparable activity to TPPMS and TPPTS. While less active than water-soluble diamines and phosphines like TXPTS (Scheme 101).

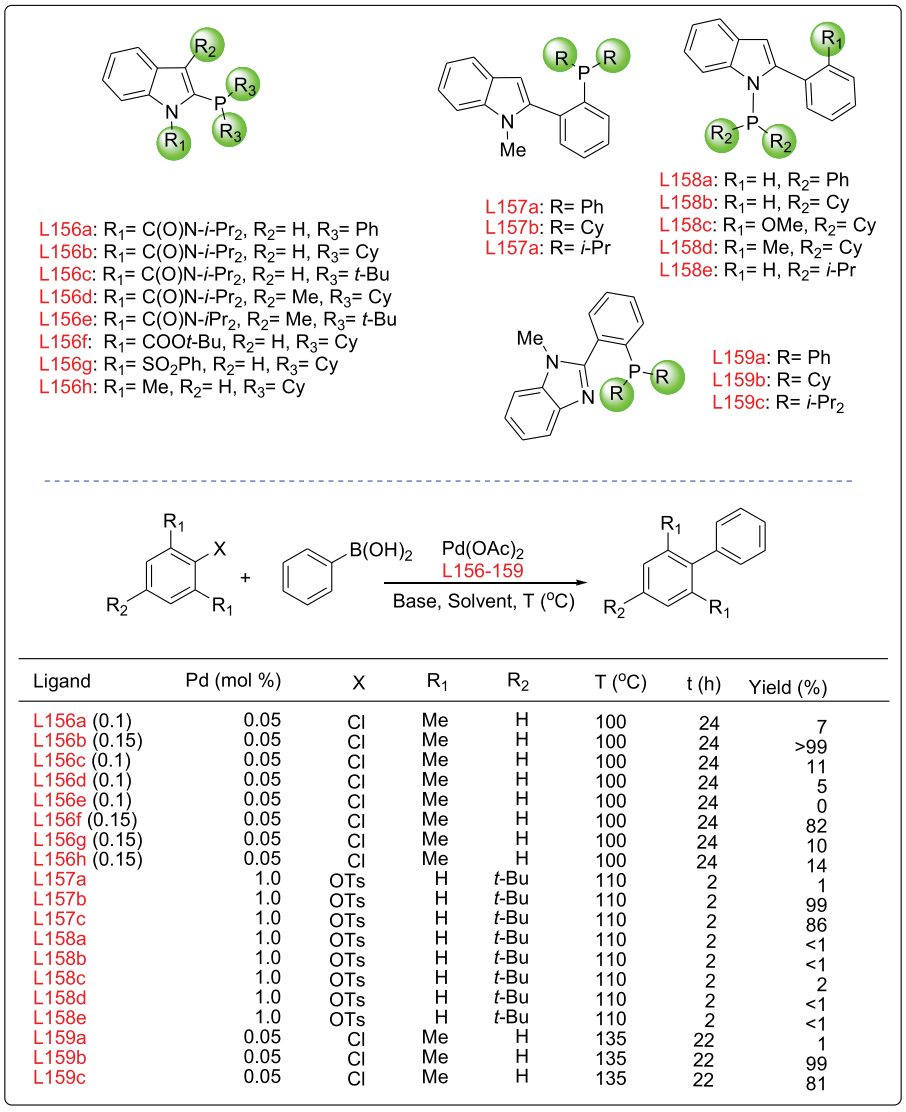
Floch et al. [192] synthesized Ni (**C36a**) and Pd (**C36b**) complexes



Scheme 97. Tunable P-stereogenic P–N phosphine ligands for the Suzuki coupling reactions.



Scheme 96. Pd(0)-Schiff base complexes based on P–N ligands for the Suzuki coupling reactions.



Ligand	Pd (mol %)	X	R_1	R_2	T (°C)	t (h)	Yield (%)
L156a (0.1)	0.05	Cl	Me	H	100	24	7
L156b (0.15)	0.05	Cl	Me	H	100	24	>99
L156c (0.1)	0.05	Cl	Me	H	100	24	11
L156d (0.1)	0.05	Cl	Me	H	100	24	5
L156e (0.1)	0.05	Cl	Me	H	100	24	0
L156f (0.15)	0.05	Cl	Me	H	100	24	82
L156g (0.15)	0.05	Cl	Me	H	100	24	10
L156h (0.15)	0.05	Cl	Me	H	100	24	14
L157a	1.0	OTs	H	*t*-Bu	110	2	1
L157b	1.0	OTs	H	*t*-Bu	110	2	99
L157c	1.0	OTs	H	*t*-Bu	110	2	86
L158a	1.0	OTs	H	*t*-Bu	110	2	<1
L158b	1.0	OTs	H	*t*-Bu	110	2	<1
L158c	1.0	OTs	H	*t*-Bu	110	2	2
L158d	1.0	OTs	H	*t*-Bu	110	2	<1
L158e	1.0	OTs	H	*t*-Bu	110	2	<1
L159a	0.05	Cl	Me	H	135	22	1
L159b	0.05	Cl	Me	H	135	22	99
L159c	0.05	Cl	Me	H	135	22	81

Scheme 98. Indol-derived aminophosphines for the Suzuki coupling reactions.

containing PNNP tetradentate ligand. The ligands were obtained from commercially available bis(diphenylphosphino)methane and ethylenediamine (Scheme 102). The activity of complexes was examined in the Suzuki coupling reactions of bromobenzene with phenylboronic acid. The reaction was carried out in toluene, water, and toluene: water mixture (1:1) in the presence of a $TBABF_4$ at 60 °C. The Pd complex **C36b** was more efficient than their corresponding nickel complex (**C36a**). Though the complex **C36b** (1 mol %) was couped activated aryl chlorides successfully, the yields were lower (34–44%). While chlorobenzene was almost unreactive. The aqueous phase containing catalyst **C36b** can be separable easily from the organic phase and reused at least four times without any noticeable loss in activity.

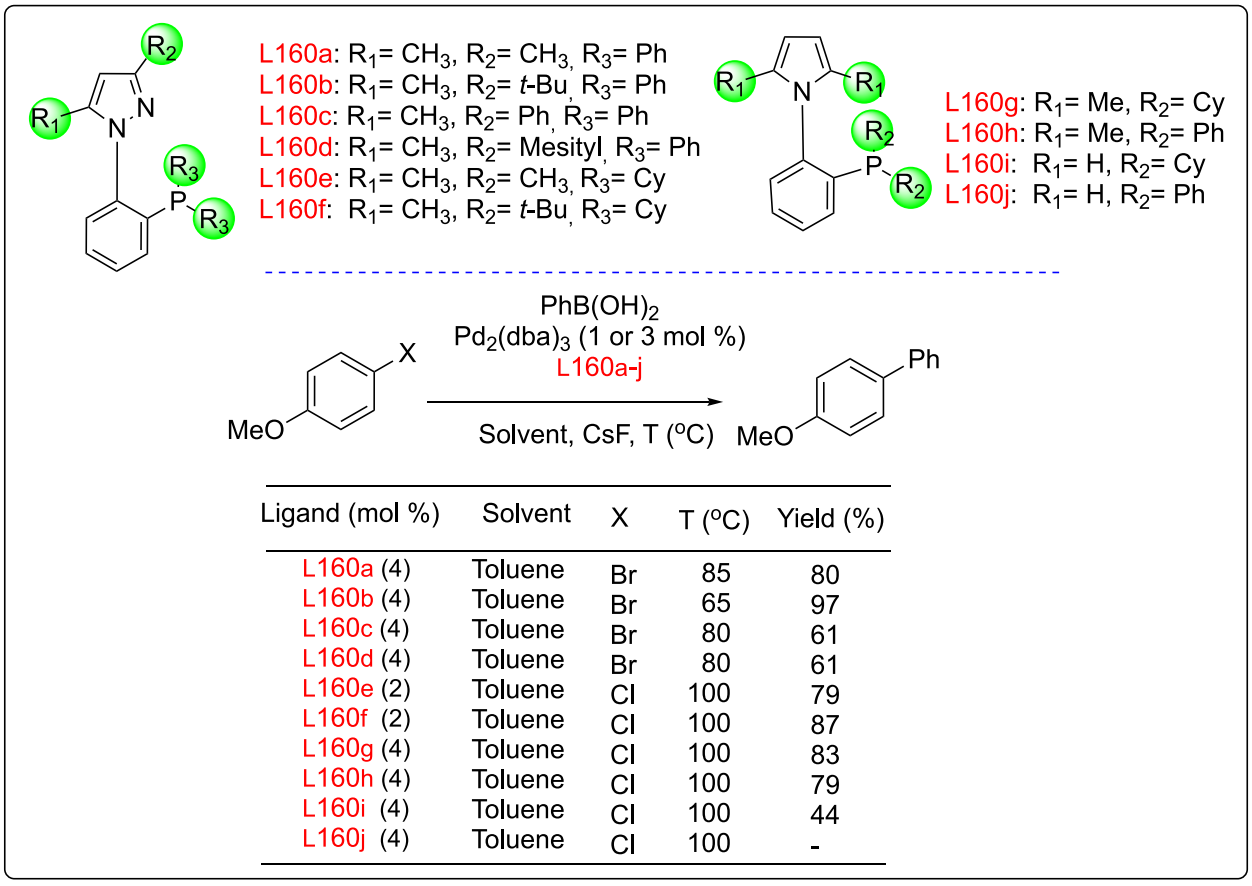
Various P-imidate Pd complexes **C37a-d** were used for the Suzuki coupling reactions [193]. A variety of aryl halides were coupled with aryl boronic acids. The corresponding cross-coupled products were obtained in good to excellent yields using **C37a** and **C37b** (1 mol %) in a THF at 60 °C (Scheme 103).

The water-soluble Pd-imidate complexes (**C38a-d**) were developed as highly efficient catalysts for the synthesis of C5-arylated pyrimidine nucleosides (Scheme 104) [194]. The complexes were prepared by the direct reactions of *trans*-$[Pd(imidate)_2(SMe_2)_2]$ and 1,3,5-triaza-7-phospha adamantane (PTA). Moreover, the catalyst **C38d** (1 mol %) was found to be a more efficient catalyst for the synthesis of 5-arylated deoxyuridine analogs using 5-iodo-2′-deoxyuridine and various phenylboronic acids in the presence of TEA in water at room temperature or 80 °C. After completion of the reaction, the product was isolated by extracting the aqueous layer with ethyl acetate and then recharging the aqueous phase with fresh substrates and bases. It was found that the catalyst was active for five consecutive runs without significant loss of activity.

3.4. *Sonogashira coupling reactions*

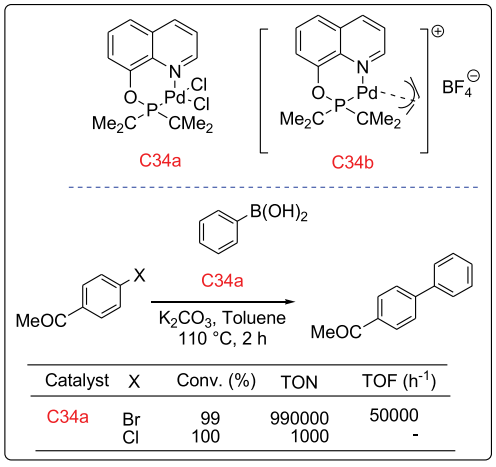
The Pd-catalyzed Sonogashira cross-coupling reactions between aryl halides and acetylenes are an important reaction for the synthesis of acetylene derivatives [195].

The firstly prepared Pd-PNF pincer-type complex (**C39**) bearing a halogen (fluorine) arm facilitated the Sonogashira coupling reactions [196] (Scheme 105). This 8-fluoroquinoline-based chelated Pd(II) complex was prepared *via* the base-assisted dearomatization of a phosphine-quinoline (P-N) ligand. This dearomatization is reversible and facilitates catalytic coupling. The catalyst (1 mol %) showed moderate to excellent catalytic activity for the Sonogashira coupling of various aryl iodides and bromides in NaO*t*-Bu and benzene at 55 °C.



Ligand (mol %)	Solvent	X	T (°C)	Yield (%)
L160a (4)	Toluene	Br	85	80
L160b (4)	Toluene	Br	65	97
L160c (4)	Toluene	Br	80	61
L160d (4)	Toluene	Br	80	61
L160e (2)	Toluene	Cl	100	79
L160f (2)	Toluene	Cl	100	87
L160g (4)	Toluene	Cl	100	83
L160h (4)	Toluene	Cl	100	79
L160i (4)	Toluene	Cl	100	44
L160j (4)	Toluene	Cl	100	-

Scheme 99. Pyrazole-tethered aryl phosphine ligands for the Suzuki coupling reactions.



Catalyst	X	Conv. (%)	TON	TOF (h^{-1})
C34a	Br	99	990000	50000
	Cl	100	1000	-

Scheme 100. Quinoline-based P–N ligands for the Suzuki coupling reactions.

The PCN-Pd pincer complex **C28** was also tested for the copper-free Sonogashira coupling reactions in aqueous media [179]. The complex was also applied to the arylation of phenylacetylene with a series of aryl iodides, providing moderate to good yields under three reaction conditions (Method A: Et_3N, CH_3CN, room temperature, 12 h; Method B: pyrrolidine, H_2O, 50 °C, 24 h; Method C: 100 °C, 6 h). The catalyst was highly active for various aryl iodides with phenylacetylene (Scheme 106). In addition, the complex **C29a** (1 mol %) was also applied to copper-free Sonogashira coupling reactions of halobenzene, and acetylenes in Cs_2CO_3 and MeOH under air at room temperature [180].

Wendt and coworkers [197] reported aromatic PCN-Pd pincer complexes (**C40a-c**) for the decarboxylative cross-coupling reactions of phenyl propiolic acid and iodobenzene (Scheme 107). The best result (54% yield) was shown by the **C40a** using a catalytic amount of CuI in the presence of K_2CO_3 as a base in MeCN at 135 °C for 48 h.

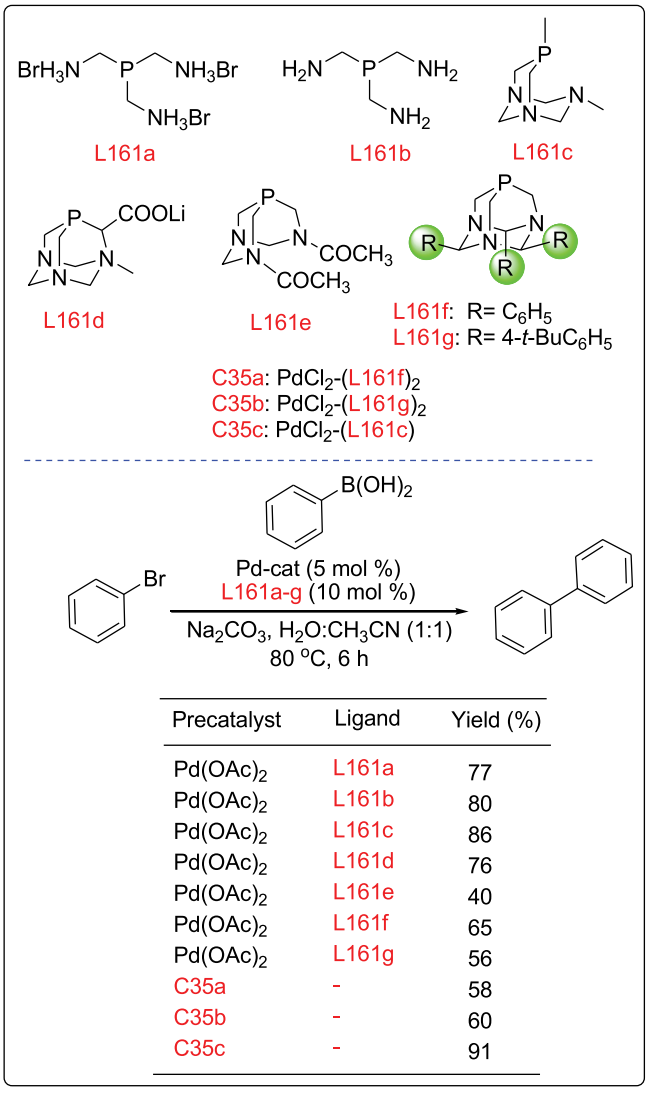
3.5. Stille coupling reactions

The Stille coupling reactions are powerful organic transformations, used for the synthesis of important biological compounds [198].

In this regard, Koprowski *et al.* [199] applied Pd complexes (**C41a-d**) of a variety of *β* and *γ*-iminophosphines as well as Schiff base ligands (**L162a-d**) to Stille coupling reactions (Scheme 108). The Pd complexes of the *β*-iminophosphine **L162d** and its corresponding metallic dendrimer **C41d** are better catalysts than the other complexes. In addition, catalyst **C41d** can be easily recycled at least three times with a slight decrease in yields.

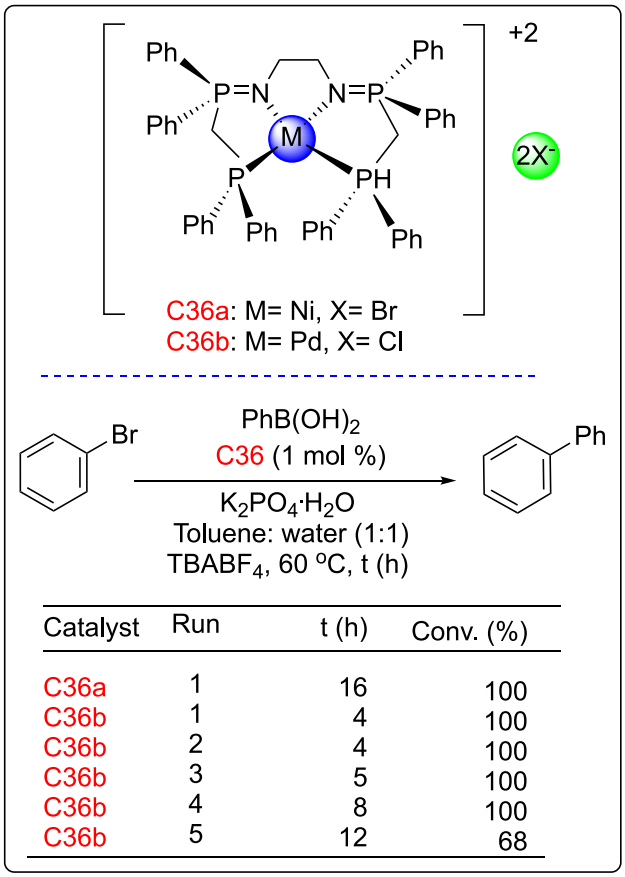
An air and moisture-stable monodentate **C37c-d** and **C42a-c** and bidentate **C42d-f** Pd(II) phosphine complexes were applied for the Stille coupling of benzyl bromide and *Z*-organostannane in toluene at 60 °C (Scheme 109) [200]. The complex **C37c** exhibited the best result with 99% formation of the desired product in 1.5 h. Thus, **C37c** was shown to be an efficient catalyst for the Stille coupling reactions of a range of allylic and benzylic halides with different vinylstannanes.

Scrivanti et al. [201] studied the role of olefin in catalyst stabilization by using [η^2-(olefin)Pd(0)] complexes containing iminophosphine ligands (**C32b**, and **C32e-g**) in the Stille coupling reactions. The catalytic efficiency depends on the nature of the complex ([Pd(η^2-dmfu)



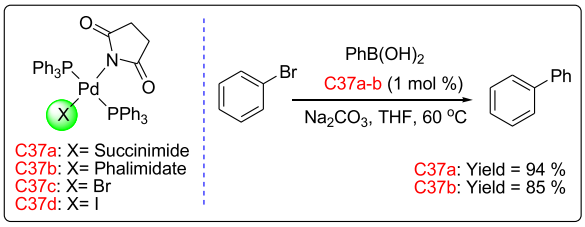
Precatalyst	Ligand	Yield (%)
$Pd(OAc)_2$	L161a	77
$Pd(OAc)_2$	L161b	80
$Pd(OAc)_2$	L161c	86
$Pd(OAc)_2$	L161d	76
$Pd(OAc)_2$	L161e	40
$Pd(OAc)_2$	L161f	65
$Pd(OAc)_2$	L161g	56
C35a	-	58
C35b	-	60
C35c	-	91

Scheme 101. Pd complexes of trisubstituted PTA derivatives for the Suzuki coupling reactions.



Catalyst	Run	t (h)	Conv. (%)
C36a	1	16	100
C36b	1	4	100
C36b	2	4	100
C36b	3	5	100
C36b	4	8	100
C36b	5	12	68

Scheme 102. Biphasic Suzuki coupling reactions using iminophosphorane ligands.



Scheme 103. Pd-imidate complexes for the Suzuki coupling reactions.

$(P–N)_2]$ >[Pd(η^2-dmfu)(P–N)]), and substituent. The genuine active catalyst was Pd(0) complex (Scheme 110). The screening of catalysts and their corresponding ligands was carried out by coupling iodobenzene with tributylphenylethynyl stannane in THF at 50 °C. The highest reaction rates were achieved by using aryl-substituted iminophosphines **C32b** and **C32e**.

3.6. C–H arylation

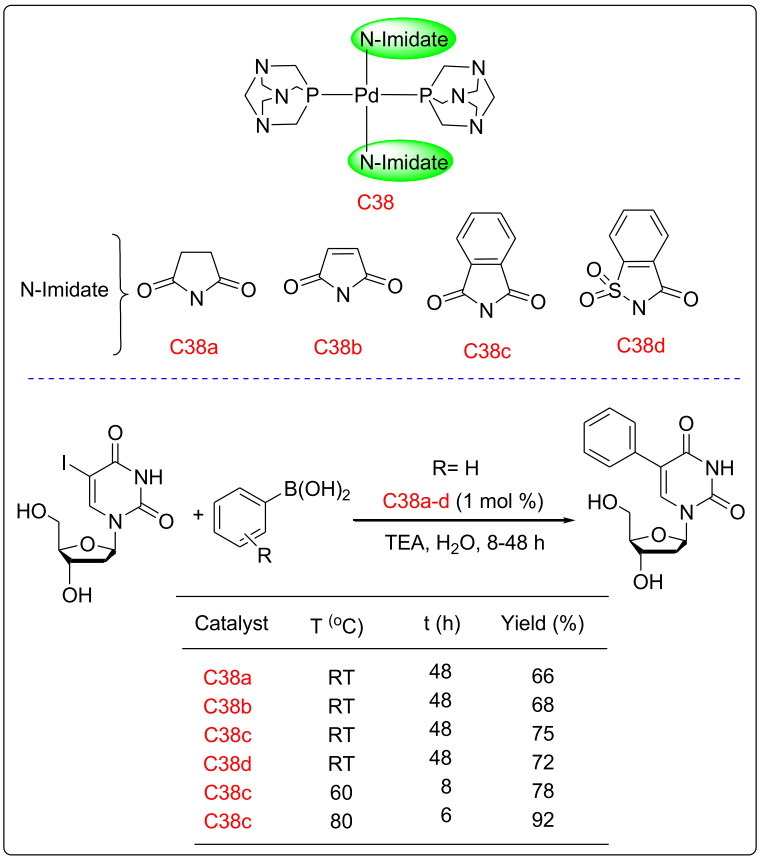
Asymmetric C–H functionalization is one of the most significant and challenging bond-forming reactions. It is used for the synthesis of a variety of functionalized molecules [202].

In this regard, the Pd-phosphine imine derived from various amino acids (**L163a-l**) showed excellent activity (up to 99% yield) and enantioselectivity (up to 98% *ee*) in the asymmetric arylation of cyclic N-sulfonyl imines. The reaction forms cyclic N-sulfonyl aldimines and ketimines with five and six-membered ring structures (Scheme 111) [203]. The ligand **L163l** (5.5 mol %) was found to be highly effective both in terms of yield and *ee* in the presence of $PdCl_2(PhCN)_2$ (5 mol %), $AgBF_4$ (5 mol %) in dichloroethane at 65 °C.

Similarly, 'SMIPHOX' ligands **L27a-d** (7.5 mol %) were applied for Pd-catalyzed asymmetric arylation of cyclic N-sulfonyl imines. All the ligands were highly efficient in terms of yields (up to 99%) and enantioselectivities (up to 99% *ee*) for the reaction of cyclic N-sulfonyl aldimines and phenylboronic acid in the presence of $Pd(TFA)_2$ (5 mol %) in TFE at 40 °C [204].

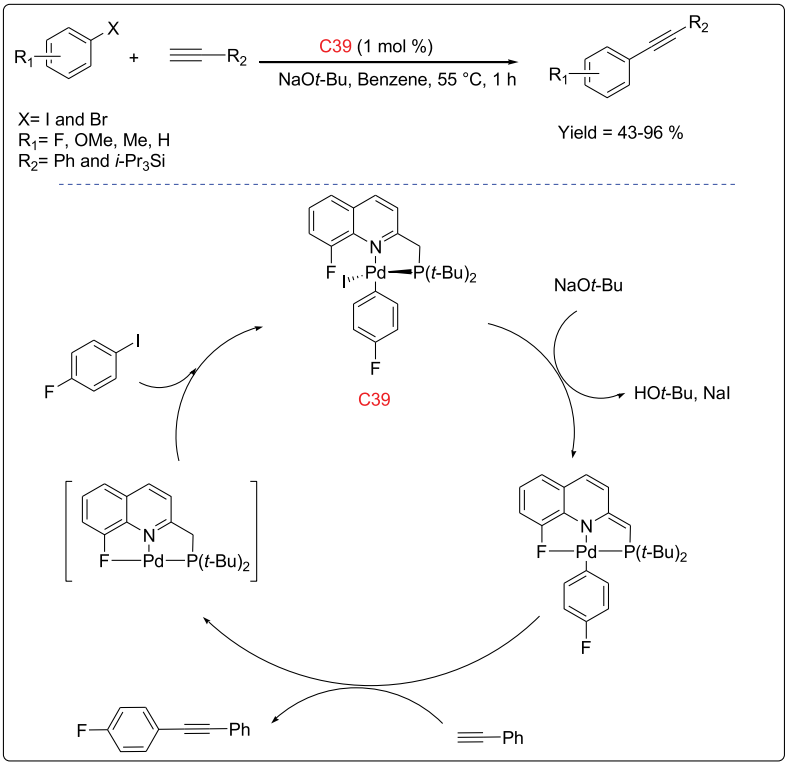
Punji and coworkers reported an extensive mechanistic investigation of PCN pincers like **C43** and **C44** for C–H arylation [205]. This investigation was based on a study of the activity of pincer-based-[PdCl(*i*-Pr_2POCNEt_2)] complex (**C43a**) along with CuI catalyzed direct arylation of azoles involving a Pd(II)–Pd(IV)–Pd(II) redox catalytic pathway (Scheme 111). They also reported the synthesis, characterization, and applications of phosphinito aryl benzimidazole PCN pincer Pd(II) complexes (**C44a-c**) in C–H arylation of azoles with aryl iodides [206].

Unsymmetrical pincer Pd(II)-NHC-N-P chelated complexes **C45a** and **C45b** were synthesized and applied for C(sp2)-H arylation of benzoxazoles (Scheme 112) [207]. The catalytic system offers the direct arylation of aryl bromides with a catalyst loading as low as 0.25 mol %. The

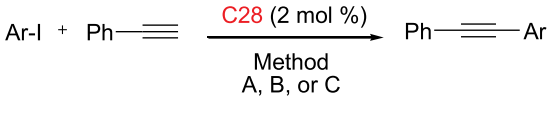


Catalyst	T (°C)	t (h)	Yield (%)
C38a	RT	48	66
C38b	RT	48	68
C38c	RT	48	75
C38d	RT	48	72
C38c	60	8	78
C38c	80	6	92

Scheme 104. Pd-imidate complexes for the synthesis of C5-arylated pyrimidine nucleosides using Suzuki coupling reactions.



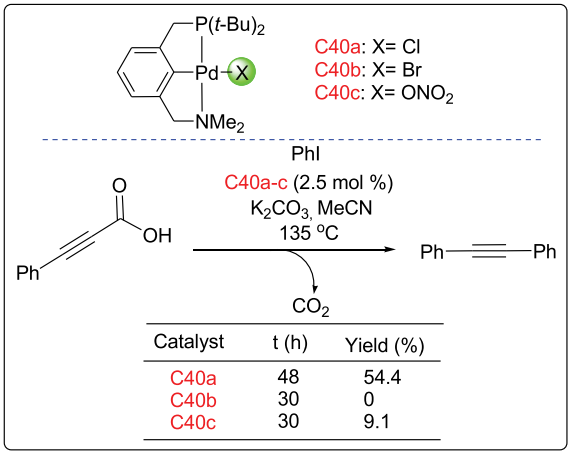
Scheme 105. Pd-PNF pincer-type complex for the Sonogashira-type coupling reactions.



Method A: C28 (2 mol %), Et_3N, CH_3CN, RT, 12 h
Method B: C28 (2 mol %), pyrrolidine, H_2O, 50 °C, 24 h
Method C: C28 (2 mol %), pyrrolidine, 100 °C, 6 h

Ar	Method A (%)	Method B (%)	Method C (%)
Ph	84	83	>99
1-Naph	77	44	93
4-$MeOC_6H_4$	52	50	89
2-MeC_6H_4	33	62	84
3-MeC_6H_4	71	73	<5
4-$NH_2C_6H_4$	36	16	75
4-$NO_2C_6H_4$	97	60	60
4-ClC_6H_4	<5	<5	>99

Scheme 106. PCN-Pd pincer for the copper-free Sonogashira coupling reactions.



Catalyst	t (h)	Yield (%)
C40a	48	54.4
C40b	30	0
C40c	30	9.1

Scheme 107. Pd-PCN pincers for the decarboxylative coupling reactions.

complex **C45a** (0.5 mol %) give up to 97% arylation products for aryl bromides.

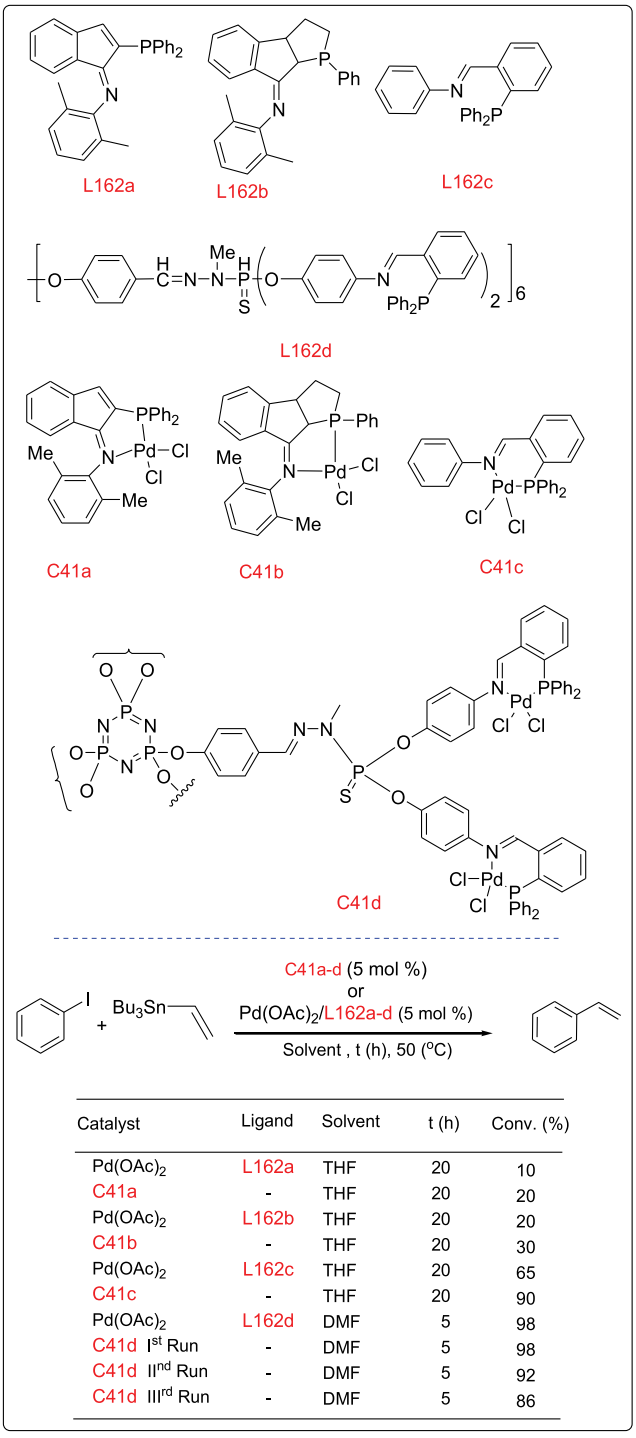
3.7. Kumada coupling reactions

Kumada coupling reaction is very important in organic synthesis [208]. In this regard, Aoyama et al. [209] studied the activity of ligands **L57b-c, L58b, L58d-j**, and **L164a-c** in the asymmetric Kumada-Corriu cross-coupling reaction (Scheme 113). Optimization of various reaction conditions for the reaction of 1-phenyl ethyl magnesium chloride with *β*-bromostyrene showed that the piperidine-based ligand **L164c** possessing the pendant piperidinyl group gave better results (58% yield, 66% *ee*) in the presence of $PdCl_2(MeCN)_2$ (5 mol %) in $CF_3C_6H_5$ at 0 °C.

3.8. Hiyama coupling reactions

Since the last decade, Hiyama cross-coupling reactions have attracted much more attention in metal catalysis [210].

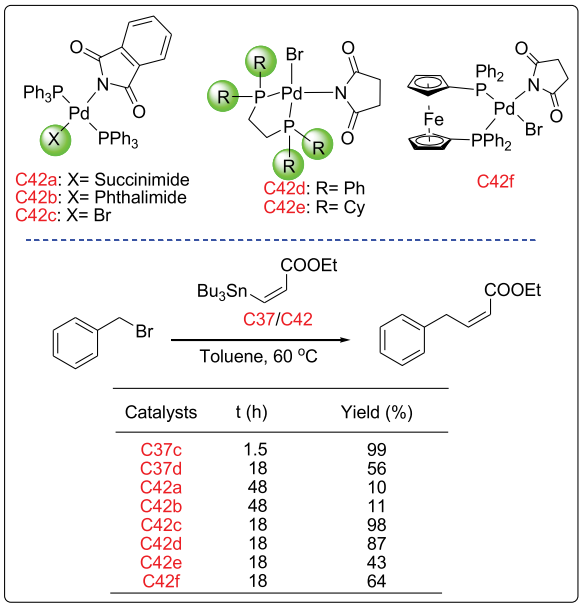
In this regard, the PCN-Pd pincer complex (**C28**) was tested for the Hiyama coupling reactions in aqueous media [179]. The complex was



Catalyst	Ligand	Solvent	t (h)	Conv. (%)
$Pd(OAc)_2$	L162a	THF	20	10
C41a	-	THF	20	20
$Pd(OAc)_2$	L162b	THF	20	20
C41b	-	THF	20	30
$Pd(OAc)_2$	L162c	THF	20	65
C41c	-	THF	20	90
$Pd(OAc)_2$	L162d	DMF	5	98
C41d I^{st} Run	-	DMF	5	98
C41d II^{nd} Run	-	DMF	5	92
C41d III^{rd} Run	-	DMF	5	86

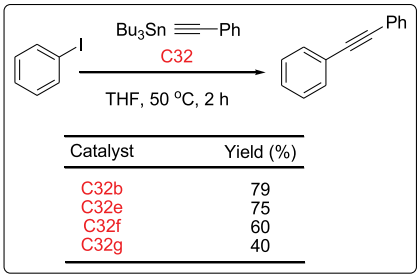
Scheme 108. Pd complexes of β and γ-iminophosphines for the Stille coupling reactions.

less active in the Hiyama coupling reaction of (trimethoxysilyl)benzene and different aryl bromides under different conditions (Method A: **C28** (2 mol %) NaOH, H_2O, 140 °C, 3 h; Method B: **C28** (4 mol %) TBAF, *o*-xylene, 80 °C, 4 h. Similarly, the $Pd(OAc)_2$/**L157** (2:8 mol %) was also efficient for Hiyama coupling aryl and heteroaryl mesylates in the presence of TBAF in *t*-BuOH at 90 °C [211]. Sarkar et al. [189] applied pyrazole-derived bidentate ligands to the Hiyama coupling reactions of the aryl bromides and chlorides. The pyrrole (**L160g-j**) derived ligands containing aryldicyclohexylphosphino or aryldiphenylphosphino donor



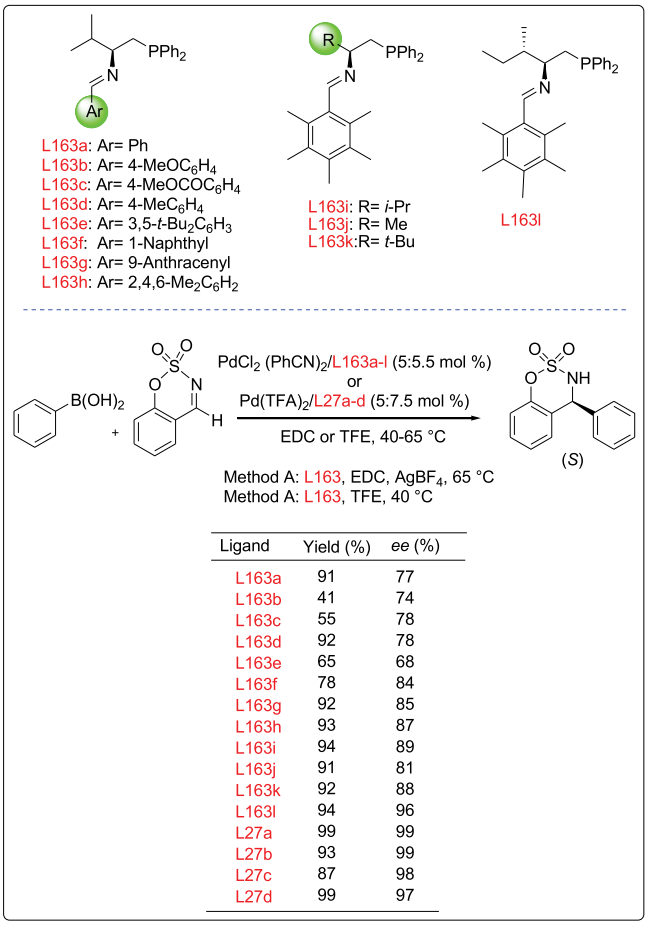
Catalysts	t (h)	Yield (%)
C37c	1.5	99
C37d	18	56
C42a	48	10
C42b	48	11
C42c	18	98
C42d	18	87
C42e	18	43
C42f	18	64

Scheme 109. Pd-imidate complexes for the Stille coupling reactions.



Catalyst	Yield (%)
C32b	79
C32e	75
C32f	60
C32g	40

Scheme 110. The iminophosphine ligands for the Stille coupling reactions.



Ligand	Yield (%)	*ee* (%)
L163a	91	77
L163b	41	74
L163c	55	78
L163d	92	78
L163e	65	68
L163f	78	84
L163g	92	85
L163h	93	87
L163i	94	89
L163j	91	81
L163k	92	88
L163l	94	96
L27a	99	99
L27b	93	99
L27c	87	98
L27d	99	97

Scheme 111. P–N ligands used for asymmetric arylation of cyclic N-sulfonyl imines.

group showed moderate activity in Hiyama coupling reactions (Scheme 114).

The ligand (**L158a-b**) (0.1 mol %) was first time applied for Pd-catalyzed titanium-mediated cross-coupling of aryl halides (Br and Cl) in the presence of $Pd(OAc)_2$ (0.05 mol %) in toluene at 90-110°C [212].

3.9. Buchwald–Hartwig amination reactions

The Pd-catalyzed amination reaction of aryl halides by using various ligands has attracted much attention for the synthesis of substituted amines [213].

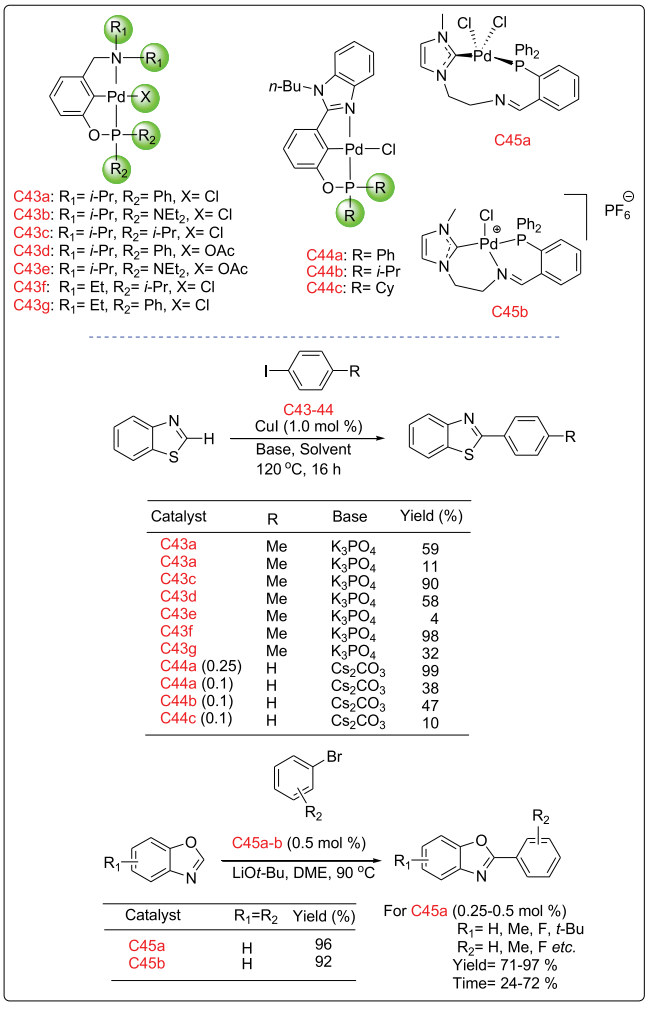
In this regard, Lassaletta et al. [214] applied various Quinap ligands (**L42a-g**) in the Pd-catalyzed dynamic kinetic asymmetric Buchwald–Hartwig amination reaction (Scheme 115). The catalytic system $Pd_2(dba)_3$/**L42a** (10:12 mol %) showed a high level of enantioselectivity (87–92% *ee*) with a 99% yield for different substrates in toluene at 50 or 60 °C. Other ligands **L42b-g** containing modified diaryl and dialkyl phosphine groups led to no improved enantioselectivities. In addition, they [215] applied a similar type of catalytic system for dynamic kinetic Pd-catalyzed alkynylation of racemic heterobiaryl nonaflates with excellent enantioselectivity. The $Pd(OAc)_2$/**L42a** and **L42d** (5:6 mol %) precatalysts provided products in excellent yields (> 99%) and enantioselectivity (93–97%) using TEA as a base in DMSO at 40 °C.

Kocovsky and coworkers reported Pd(II) complexes of 2-dimethylamino-2′-diphenylphosphino-1,1′-binaphthyl (MAP) (*R*) **L165** in allylic substitution, Buchwald amination, and Suzuki coupling reactions (Scheme 116). The ligand exhibited a dramatic accelerating effect in the amination reaction of amino alcohol and diamine with bromobenzene in toluene at 60 °C [216]. These ligands were assumed to coordinate Pd *via* P, N-chelation however, it was evidenced that (*S*) **L165** acts as a P, C ligand with an unusual Cσ-Pd bonding mode [217]. Moreover, a substantial rate acceleration was observed for the m $(PhCN)_2PdCl_2$/(*S*) **L165** (3 mol %) in the coupling reaction of 4-*t*-BuC_6H_4Br with *n*-Bu_2NH at 50 °C. The phenylation of 4-Cl-C_6H_4CHO with phenyl boronic acid also occurred in < 20 h at room temperature in the presence of Pd $(OAc)_2$/(*S*) **L165** (3:4.5 mol %) in CsF or Cs_2CO_3.

P-N phosphinobenzimidazole ligands (**L166a-d**) were used in Pd-catalyzed C-N coupling reactions (Scheme 117) [218]. The ligand contains a sterically large and exceptionally powerful P(*t*-Bu)$_2$ as a donor group attached at the 2-position of a benzimidazole backbone, which interacts dynamically with the Pd center under conditions of catalysis. A precatalytic system was designed from $[Pd(cinnamyl)Cl]_2$ and **L166a** (1:2 mol %) and proved to be effective for the reaction of aryl bromides with aryl amines using KO*t*-Bu as a base in toluene at 80 °C.

Hong et al. [219] carried out C–N and C–C coupling reactions using the alkyne bridged dicobalt phosphine ligands (**L167**) and their Pd complexes (**C46**) (Scheme 118). The complex **C46c** was characterized by spectroscopic as well as single-crystal X-ray diffraction techniques. The catalyst **C46b** lead to excellent results for the reaction of bromobenzene with morpholine in the presence of NaO*t*-B in toluene at 80 °C.

Hii et al. [220] reported that the incorporation of a hemilabile amino group containing a bulky, and electron-rich di-*t*-butyl phosphine aminophosphine ligand (**L168**) reversed the order of amination reactivity of



Catalyst	R	Base	Yield (%)
C43a	Me	K_3PO_4	59
C43a	Me	K_3PO_4	11
C43c	Me	K_3PO_4	90
C43d	Me	K_3PO_4	58
C43e	Me	K_3PO_4	4
C43f	Me	K_3PO_4	98
C43g	Me	K_3PO_4	32
C44a (0.25)	H	Cs_2CO_3	99
C44a (0.1)	H	Cs_2CO_3	38
C44b (0.1)	H	Cs_2CO_3	47
C44c (0.1)	H	Cs_2CO_3	10

Catalyst	R_1=R_2	Yield (%)
C45a	H	96
C45b	H	92

Scheme 112. Pd(II)-NHC-N-P chelated complexes for C(sp2)-H arylation of benzoxazoles.

aryl bromides (Scheme 119). Compared with **L168**, the dppf ligand was highly ineffective under the optimized reaction conditions.

3.10. Asymmetric addition reactions

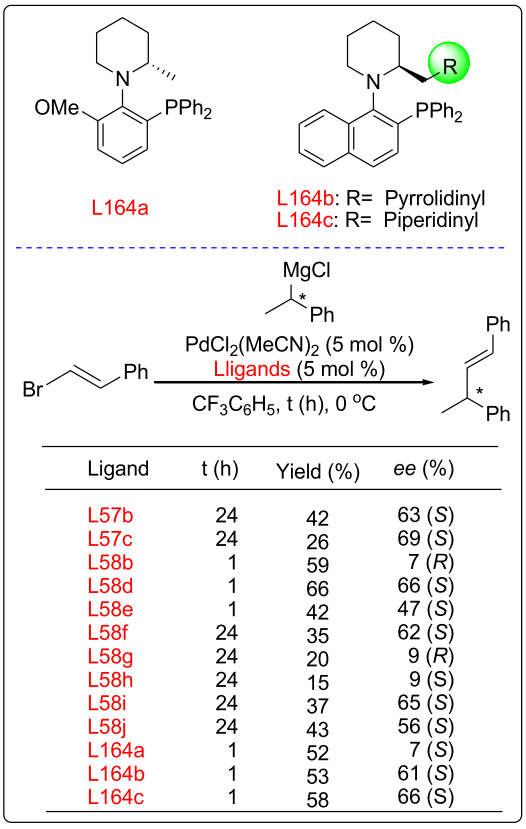
The unsymmetrical chiral PCN pincer Pd (II) complexes (**C26a-e**) with aryl-based aminophosphineImidazoline ligands were applied for asymmetric addition of diaryl phosphines to *β*-aryl enones, (Scheme 120) [221]. The products were obtained in high yields (up to 99%) and enantioselectivities (94% *ee*).

Shi et al. [222] reported diethylzinc-mediated asymmetric umpolung allylation of aldehydes to homoallylic alcohols using chiral phosphine-Schiff base type ligands (**L169a-f**) (0.02 mmol) in the presence of $Pd(OAc)_2$ (0.01 mmol), and Et_2Zn in THF at room temperature (Scheme 121). Moderate enantioselectivities and high syn diastereoselectivities were achieved using ligand **L169c** under mild conditions.

The enantiopure tetra-*ortho*-substituted biphenyl phosphinoimine ligands (*Ra,S*)-3 and (*Sa,S*)-3 (**L170a-d**) ligands (10 mol %) provided 3-aryl-3-hydroxyoxindoles with moderate yields and enantioselectivity *via* Pd-catalyzed asymmetric addition of aryl boronic acids to N-benzylisatin in the presence of $Pd(OAc)_2$ (5 mol %) and $BF_3.Et_2O$ in THF at room temperature (Scheme 122) [223].

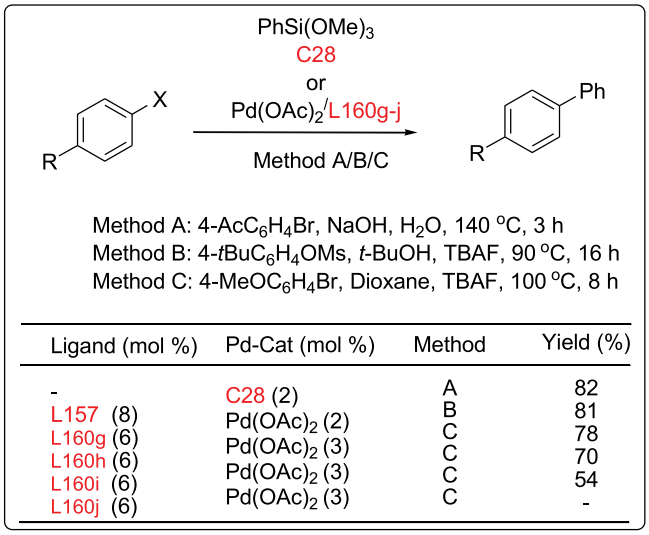
4. Conclusion

The present part of the review offers a critical overview of the utility



Ligand	t (h)	Yield (%)	*ee* (%)
L57b	24	42	63 (*S*)
L57c	24	26	69 (*S*)
L58b	1	59	7 (*R*)
L58d	1	66	66 (*S*)
L58e	1	42	47 (*S*)
L58f	24	35	62 (*S*)
L58g	24	20	9 (*R*)
L58h	24	15	9 (S)
L58i	24	37	65 (*S*)
L58j	24	43	56 (*S*)
L164a	1	52	7 (*S*)
L164b	1	53	61 (*S*)
L164c	1	58	66 (S)

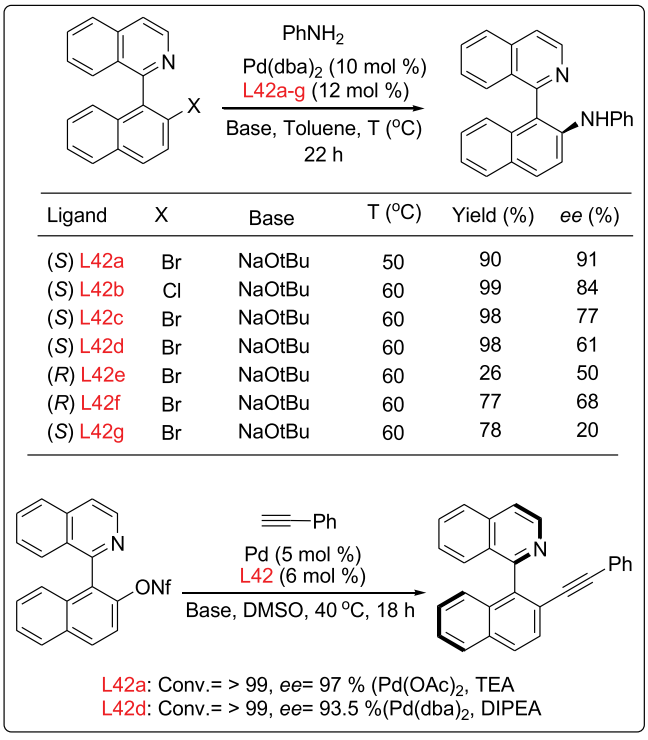
Scheme 113. Asymmetric Kumada coupling reactions using piperidine-based ligands.



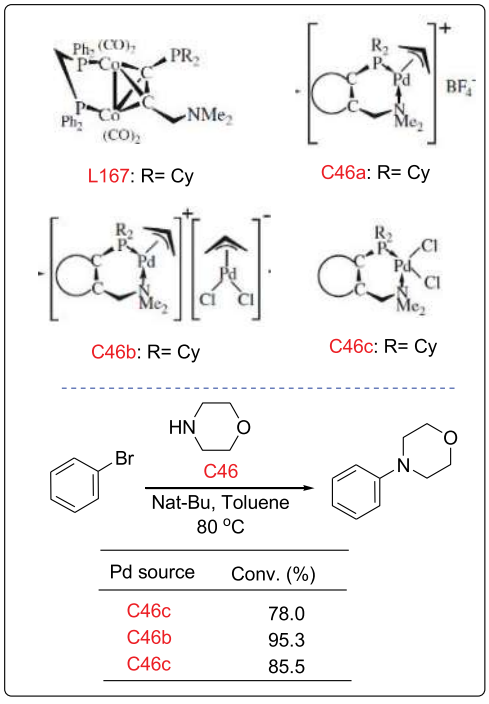
Ligand (mol %)	Pd-Cat (mol %)	Method	Yield (%)
-	C28 (2)	A	82
L157 (8)	$Pd(OAc)_2$ (2)	B	81
L160g (6)	$Pd(OAc)_2$ (3)	C	78
L160h (6)	$Pd(OAc)_2$ (3)	C	70
L160i (6)	$Pd(OAc)_2$ (3)	C	54
L160j (6)	$Pd(OAc)_2$ (3)	C	-

Scheme 114. P–N ligands for the Hiyama coupling reactions.

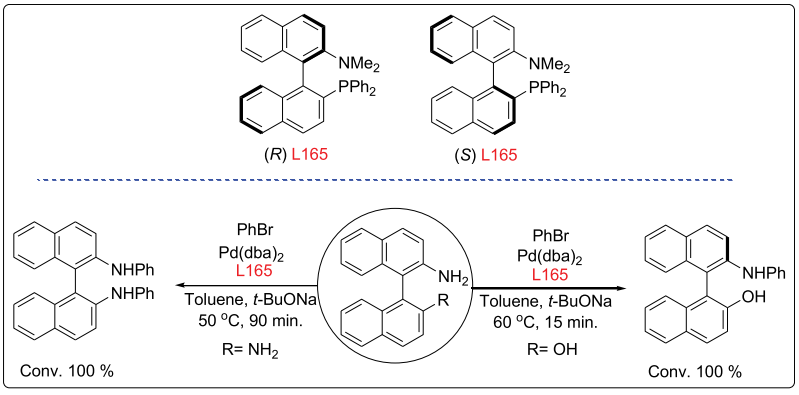
of the various strategies used in the activation and stabilization of Pd by the different P-N-based ligands. Most of the ligands are chiral scaffolds and have wide applications in Pd-catalyzed asymmetric alkylation reactions. Furthermore, distinctly different characteristics like a 'soft' P-ligand as a π-acceptor and a 'hard' N-ligand as a σ-donor provides extraordinary opportunities for cross-coupling strategies, especially in asymmetric catalysis. Most significantly, P–N ligands permit to carry out the reactions under mild reaction conditions. These ligands and catalytic systems showed broad substrate scope, supreme catalytic efficiency, and



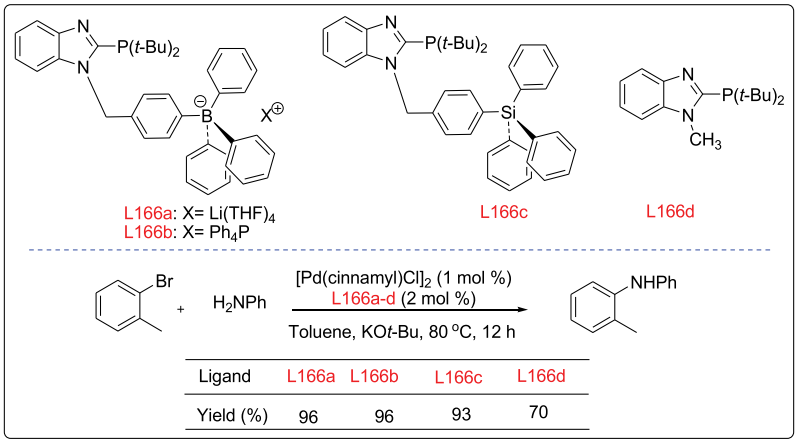
Scheme 115. Dynamic kinetic asymmetric Buchwald-Hartwig amination and alkynylation reactions using QUINAP ligands.



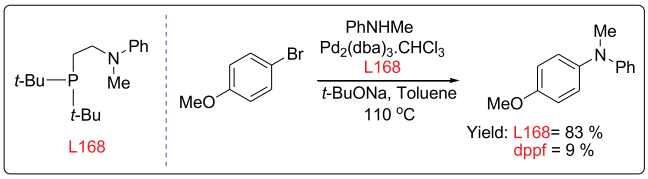
Scheme 118. Alkyne bridged dicobalt phosphine ligands for amination reactions.



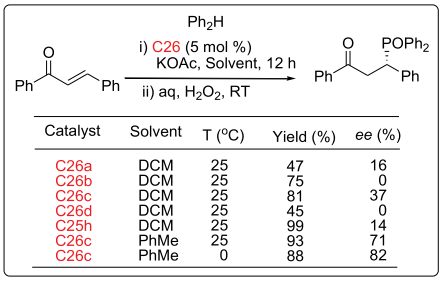
Scheme 116. MAP ligands for the Buchwald amination reactions.



Scheme 117. P-N phosphinobenzimidazole ligands in C–N coupling reactions.

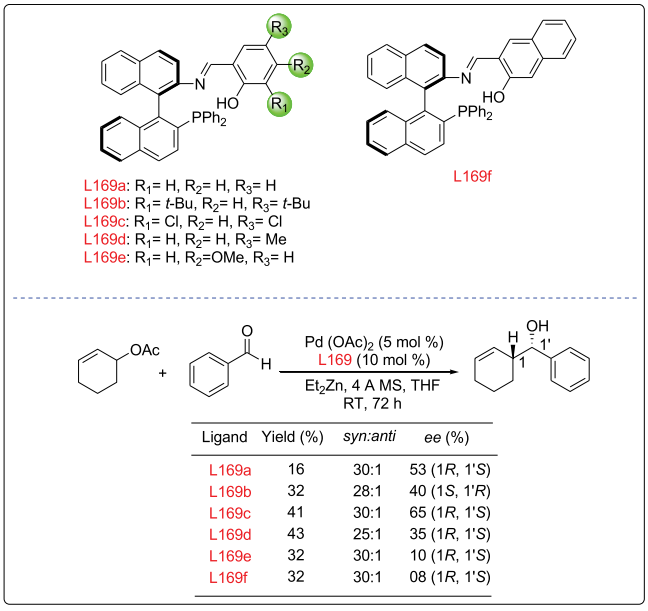


Scheme 119. Hemilabile amino group-containing bulky, electron-rich phosphorus ligand for amination reactions.



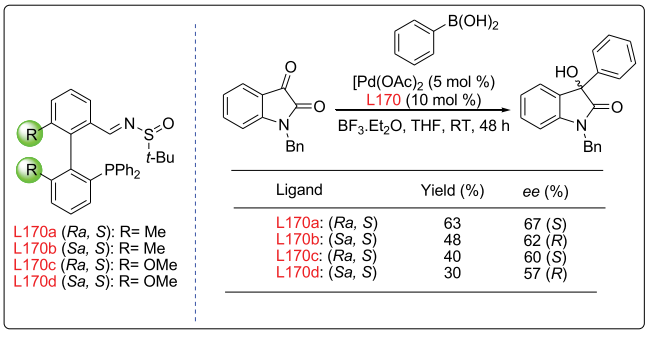
Catalyst	Solvent	T (°C)	Yield (%)	*ee* (%)
C26a	DCM	25	47	16
C26b	DCM	25	75	0
C26c	DCM	25	81	37
C26d	DCM	25	45	0
C25h	DCM	25	99	14
C26c	PhMe	25	93	71
C26c	PhMe	0	88	82

Scheme 120. Chiral Pd(II)-PCN pincer complexes for asymmetric addition of diaryl phosphines to enones.



Ligand	Yield (%)	*syn:anti*	*ee* (%)
L169a	16	30:1	53 (1*R*, 1'*S*)
L169b	32	28:1	40 (1*S*, 1'*R*)
L169c	41	30:1	65 (1*R*, 1'*S*)
L169d	43	25:1	35 (1*R*, 1'*S*)
L169e	32	30:1	10 (1*R*, 1'*S*)
L169f	32	30:1	08 (1*R*, 1'*S*)

Scheme 121. Asymmetric umpolung allylation of aldehydes using chiral phosphine-Schiff base ligands.



Ligand	Yield (%)	*ee* (%)
L170a: (*Ra, S*)	63	67 (*S*)
L170b: (*Sa, S*)	48	62 (*R*)
L170c: (*Ra, S*)	40	60 (*S*)
L170d: (*Sa, S*)	30	57 (*R*)

Scheme 122. Enantiopure tetra-ortho-substituted biphenyl phosphinoimines for asymmetric addition of aryl boronic acids to N-benzylisatin.

excellent enantioselectivities. In addition, commercially available natural amino acids have been utilized for the synthesis of most of these ligands. The P-N-based ligand systems have been continuously employed in industrial processes also. Indeed, most catalysts showed excellent catalytic activities and stereoselectivities with easy recovery and good recyclability. The design and development of new P–N ligands are likely to facilitate further progress in the field, and there is broad scope in these fields. A new design of these ligands for the range of substrates is to be studied. In forthcoming years, this area of catalysis will lead to the synthesis of many important biomolecules having wide applications in the field of theoretical and pharmaceutical chemistry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

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