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Synthesis of New Bicyclic P–N Ligands and Their Application in Asymmetric Pd-Catalyzed π-Allyl Alkylation and Heck Reaction

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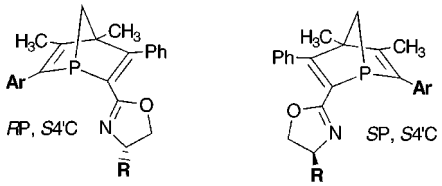
ABSTRACT



The synthesis of phosphine oxazoline ligands based on P-chiral 1-phosphanorbornadienes is reported. The use of these ligands in palladium catalyzed asymmetric allylation and Heck reaction is described.

Optically active C_2-symmetric bisphosphines and nonsymmetric phosphine−oxazoline ligands have been used as chiral ligands in a wide range of metal-catalyzed asymmetric reactions.[1−8] Many of the known phosphine ligands carry the chiral information that is ultimately transferred to a reaction product on their carbon skeleton. Considerably less attention has been paid to ligands with chiral phosphorus donors due to the synthetic difficulties associated with such compounds and their configurational instability particularly at high temperatures.[9−12]

In the past few years, practical routes to *P*-chiral ligands have been developed, and some of these ligands have been successfully used in asymmetric hydrogenations.[13−15] Mathey et al. have developed the synthesis of monodentate *P*-chiral 1-phosphanorbornadienes from phospholes and alkynes.[16−20]

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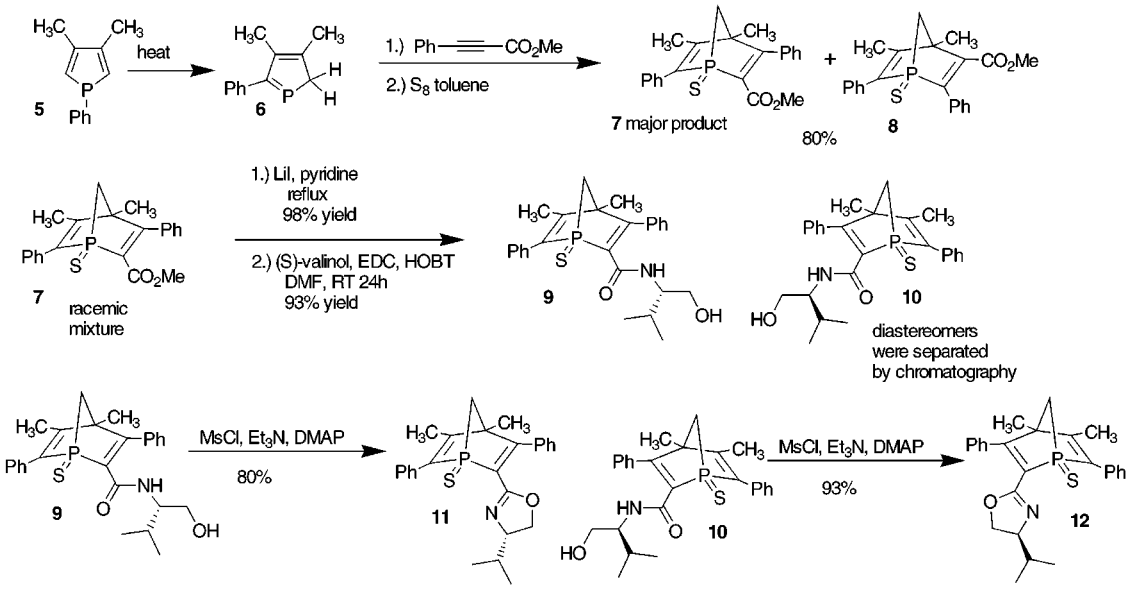
Scheme 1



In these structures, the phosphorus atom, is located in the bridgehead of a rigid bicyclic system, and as a consequence is not subject to racemization. Recently, Mathey prepared a chelating *P*-chiral bisphosphine, BIPNOR, incorporating two phosphanorbornadienyl units.[21] Here we report the synthesis of a new class of P−N phosphine−oxazoline ligands (**1**−**4**), bearing a chiral phosphanorbornadienyl (P-donor) and an oxazoline (N-donor). Additionally, we report their use in both the asymmetric Heck reaction and asymmetric palladium-catalyzed allylations.

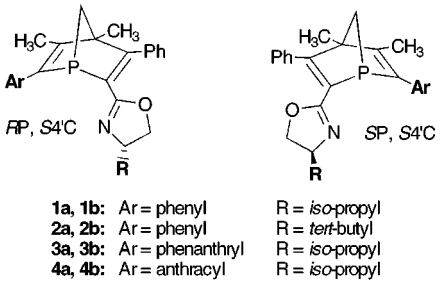


Figure 1. Phosphanorbornadienyl-based ligands.

The desired ligand is readily available through the Scheme 1, shown below. The phosphanorbornadienyl unit is prepared by the [4 + 2]-cycloaddition of 1-arylphospholes and alkynes, as described by Mathey.[16−20] Cycloaddition of phenylpropiolate gives a 2:1 mixture of regioisomers with the desired isomer (**7**) as the major product. After the cycloaddition reaction the phosphine functionality was protected as the phosphine sulfide. Conversion of the ester to the acid[22] and coupling of an amino alcohol, *S*-valinol, gives two diastereomeric products, **9** and **10**, which are easily separated.[23] Each diastereomer was carried forward since it was not known which combination of chiral centers would prove most effective. The separation was followed by reaction with methansulfonyl chloride and triethylamine to give the desired set of oxazolines (**11**, **12**). The identity of the two diastereomeric phosphine oxazolines was determined by X-ray crystal structure of ligand **12**.

While 1-phenyl-3,4-dimethylphosphole (**5**) is readily available,[24] there are few examples of phospholes where the aryl group is something other than phenyl.[25−27] To readily synthesize the desired ligands with a variety of aryl groups on the bicyclic system it was necessary to develop a route to phospholes with a variety of aromatic substituents. We have found that such phospholes (**15**−**18**) can be prepared by palladium-catalyzed phosphine coupling of Stille, using the conditions developed by Liebeskind.[28]

We found this method to be effective in the synthesis of a number of phosphole derivatives. The coupling was successfully carried out with 1-iodonaphthalene (26%), 9-iodophenanthrene (26%), 9-iodoanthracene (30%), and

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(23) The separation of the diastereomers was carried out by column chromatography using mixture of 60%EtOAc and 40% hexane as eluent to give **9** (0.20 g) and **10** (0.26 g) as white solids (combined yield 93%).
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(25) Some phospholes bearing heteroaromatic substituents at phosphorus have been prepared. Lithium phospholide reacts with 2-bromopyridine or 2-bromophosphinine generally in the presence of Pd(0) or Ni(0) catalysts to give the corresponding 1-pyridinylphosphole and 1-phosphininylphosphole. The reaction takes place also without a catalyst.
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1-iodo-2,6-dimethoxybenzene (7%). The less hindered proceeded in 12−15 h, while the more hindered example, 1-iodo-2,6-dimethoxybenzene, required higher catalyst concentrations and 14 days to completely react. Ligands **1**−**4** were examined in the asymmetric Pd-catalyzed π-allyl addition of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate (**19**) (Table 1). It was found that the palladium complex of **1a** catalyzed the addition of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate in 94% ee, giving the *S*-enantiomer in essentially 100% yield with benzene as solvent, at room temperature (Table 1). When the other diastereomer (**1b**) was used as ligand in this reaction, the *R*-enantiomer was the major product, again with good enantioselectivity (81% ee). The change in sense of chirality obtained illustrates that ligands **1**−**4** behave differently from the phosphine−oxazoline ligands reported previously. In the systems reported by Pfaltz, Helmchen, and Williams,[4−6] the chiral group that directs the sense of the asymmetric induction is next to the nitrogen atom of the oxazoline ring. In the reaction of 1,3-diphenylprop-2-enyl acetate Helmchen reports that the configuration of the soft ligand (the phosphine) is unimportant.[29] The above results indicate that the significant chirality in this system is the phosphorus atom since in both diastereomers the oxazoline moiety is the same, but the two diastereomeric ligands **1a** and **1b** give the opposite enantiomers as the major product.

Given that the chirality at the phosphine portion of the ligand seems to be important, we felt that increasing the size of the aromatic group on the bicyclic phosphine should result in increased selectivity. Unfortunately, this did not prove to be the case. Examination of three ligands with the group on the oxazoline held constant, entries 1, 7, and 9, resulted in a decrease in selectivity as the size of the aromatic groups was increased. It is interesting to note that the ligand with the largest aryl group anthracene gives the opposite selectivity from the ligands with phenyl or phenanthrene. In the case of **1b** and **4b**, this effect resulted in a complete reversal of the catalysts selectivity, 81% ee for the *R* enantiomer with **1b** and 83% ee of the *S* enantiomer with **4b**.

Examples of intermolecular asymmetric Heck reactions are rather limited. Recently, Pfaltz et al. reported that phosphine-oxazolines are efficient ligands in the Heck reaction between alkenyl triflates and cyclic alkenes.[30,31] The reaction between 2,3-dihydrofuran and cyclohex-1-en-1-yl trifluoromethane sulfonate with the Pfaltz system produced **23** in high enantiomeric excesses. The author also reported that the reaction is very slow and after 3 days at 50 °C only the ligand with R = *t*-Bu gives 95% conversion. With ligands bearing smaller alkyl groups the conversion is below 30% under the same conditions. Ligands **1**−**4** were screened in this reaction. Their palladium complexes catalyze the reaction to completion at room temperature (Table 2). In the case of

Scheme 2

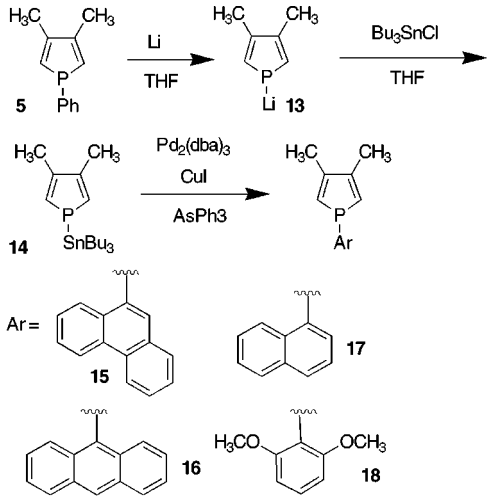
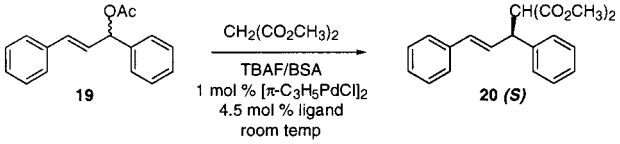


Table 1. Enantioselective Allylic Alkylation



entry	ligand[a]	solvent	*T* (°C)	yield[b] *(%)*	ee[c] (%)
1	**1a**	C_6H_6	rt	100	94 (*S*)
2	**1a**	$C_6H_5CH_3$	−10	100	94 (*S*)
3	**1a**	CH_2Cl_2	0	100	61 (*S*)
4	**1b**	C_6H_6	rt	100	81 (*R*)
5	**2a**	C_6H_6	rt	100	93 (*S*)
6	**2b**	C_6H_6	rt	100	68 (*R*)
7	**3a**	C_6H_6	rt	100	39 (*S*)
8	**3b**	C_6H_6	rt	100	44 (*S*)
9	**4a**	C_6H_6	rt	85	25 (*R*)
10	**4b**	C_6H_6	rt	100	83 (*S*)

[a] The ligands were stored as their phosphine sulfides and were converted to the phosphine just before use. The phosphines were reduced by the following procedure; Raney nickel (∼25 equiv) in a Schlenk tube was washed three times with CH_3OH, three times with Et_2O, and three times with degassed CH_3CN. A solution of phosphine sulfide in CH_3CN was added, and the mixture was freeze−pump−thaw-degassed for three cycles. The suspension was stirred until the reduction was complete (^{31}P NMR, usually 1−1.5 h). Thus obtained phosphines (**1**, **2**, **3**, or **4**) were used directly in a catalyst preparation. [b] The yields are of the isolated product after column chromatography. [c] The enantiomeric excesses are determined by ^1H NMR ($CDCl_3$) using eu(hfc)$_3$ shift reagent. The reactions were carried out with 1 mol % [Pd(allyl)Cl]$_2$, 4,5 mol % ligand, and 3 equiv of each of dimethyl malonate, BSA, and TBAF (1 M in THF). The reactions were complete in 30 min.

Scheme 3

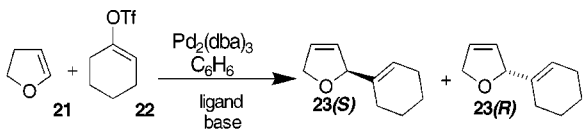


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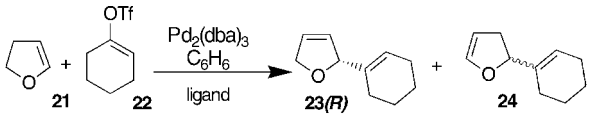
Table 2. Enantioselective Heck Reaction[a]



entry	ligand[a]	solvent	*T* (°C)	time (h)	yield[b] of **23** (%)	ee (%)
1	**1a**	C_6H_6	rt	120	92	76 (*R*)
2	**1a**	THF	70	72	76	76 (*R*)
3	**1a**[b]	THF	55	96	73	78 (*R*)
4	**1b**	THF	55	24	90	48 (*R*)
5	**2a**	C_6H_6	rt	120	85	90 (*R*)
6	**2a**[c]	THF	rt	80	91	93 (*R*)
7	**2b**	C_6H_6	rt	60	94	80 (*R*)
8	**3a**	C_6H_6	rt	120	81	69 (*R*)
9	**4a**	C_6H_6	rt	20	94	56 (*R*)
10	**4b**	C_6H_6	rt	8	98	18 (*R*)

[a] The ligands were stored as their phosphine sulfides and were converted to the phosphine just before use. See Table 1 for sample precedure. [b] The yields and the enantiomeric excesses were determined by GC (Chiraldex γ-CD-TFA; 30 m). The reactions were carried out with 3 mol % $Pd_2(dba)_3$, 8.5 mol % ligand, 5 equiv of 2,3-dihydrofuran, and 3 equiv of *i*-Pr_2NEt. [c] In these cases Proton Sponge was used as base.

the Heck reaction, the larger the aromatic group the faster the reaction proceeds. The palladium complex of **4a** catalyzes the complete conversion of starting materials **21** and **22** in less than 20 h at room temperature. The Pd-complex of **1a** requires 120 h at room temperature to go to completion.

It is interesting that in the case of the Heck reaction the important chirality appears to be the chiral center next to the oxazoline nitrogen, with all ligands giving predominantly the *R*-enantiomer. While increasing the size of the substitutent on bicyclic phosphine portion of the molecule increases the rate of the reaction it has a deleterious effect on the selectivity. Complex **4a** provides the fastest catalysis but gives the product in 56% ee. This is in contrast to **1a** which requires 120 h but gives the product in significantly higher selectivity (entries 1 versus 9).

Just as in the case of the Pfaltz system, when the size of the group on the oxazoline is increased from isopropyl to *tert*-butyl, the selectivity of the catalyst is increased, ultimately giving the product in 93% ee. With ligands **1**−**4** the formation of product **24** is observed in 10% or less. It has been reported that this is the major product obtained in the Pd−BINAP-catalyzed reaction.[32]

In summary, we have prepared a new class of *P*-chiral phosphine−oxazoline ligands containing a nonracemizable chiral P-donor. The synthetic methodology provides both diastereomers in good yield from the easily available 3,4-dimethyl-1-phenylphosphole and chiral amino alcohols. The Pd-complexes of **1**−**4** are efficient catalysts in the enantioselective π-allyl alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl tetrabutylammoniummalonate and the Heck reaction between 2,3-dihydrofuran and cyclohex-1-en-1-yl trifluoromethane sulfonate. Further studies on the application of these ligands in asymmetric catalysis are in progress.

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Supporting Information Available: Experimental and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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