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# Facile synthesis of proline based phosphine–oxazoline ligands by formation of a P–N bond

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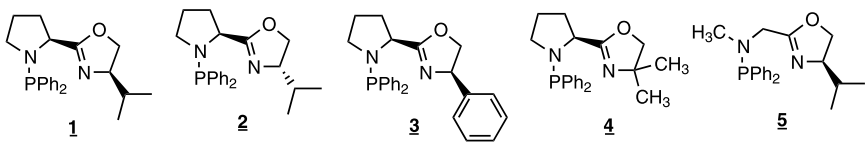
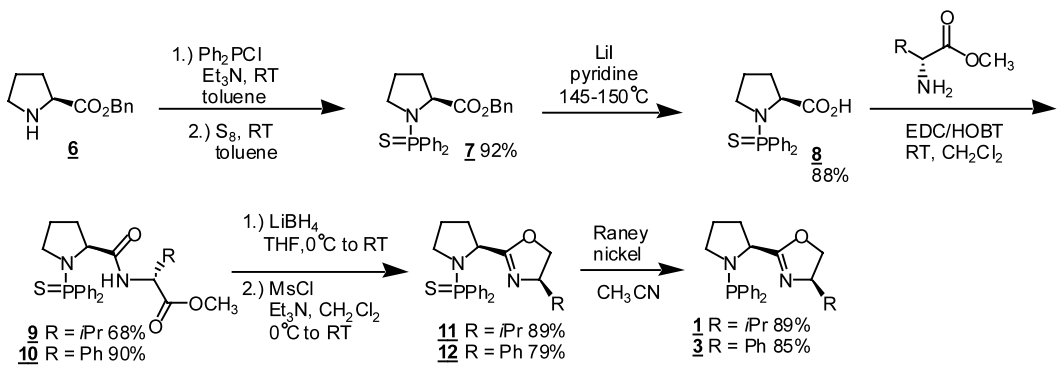
**Abstract**—A series of new P–N ligands in which the phosphorus moiety is introduced by formation of a phosphorus–heteroatom bond are synthesized. These ligands are based on proline with chiral centers from both proline and an oxazoline. The two chiral centers are responsible for the observed stereoselectivity. Palladium complexes of these ligands are shown to be effective in the allylation of dimethyl malonate as well as amination of allyl acetates. 

Phosphine ligands have proven to be one of the most successful types of ligands in asymmetric catalysis. As a measure of this, there have been hundreds of chiral phosphine ligands tested and used in asymmetric catalysis.[1–6] One of the fundamental problems with the use of phosphine ligands has been the relative difficulty with their synthesis. The formation of P–C bonds generally requires reaction conditions that are not suitable to the synthesis of highly funtionalized ligands or the synthesis of multiple ligands in parallel.[7,8] For this reason a number of people have used the formation of a P-hetero-atom bond as the method for the incorporation of phosphorus.[4,9,10] This paper reports the synthesis of a series of ligands (**1**–**5**) of this type, four of which are based on proline. The use of these ligands in palladium-catalyzed allylations, allyl aminations is reported.



The desired ligands are readily available (Scheme 1) by reacting the benzyl ester of proline with diphenylphosphine chloride. Following the formation of the P–N bond, the phosphorus is protected as the phosphine sulfide (**7**) by reaction with elemental sulfur. After this transformation the benzyl ester is removed by treatment with lithium iodide (**8**). Despite the elevated tem-



**Scheme 1.**

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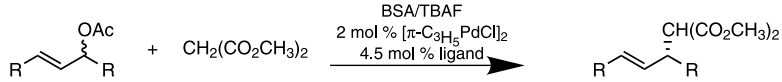
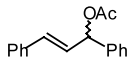
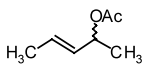
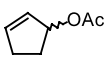
perature there is no racemization of the proline. This is readily apparent when in the next step the amino ester, that will ultimately become the oxazoline, is coupled to the free acid (**8**). Following amide formation the ester is reduced to the alcohol and this molecule is cyclized to the oxazoline (**11** and **12**). Prior to use the phosphine sulfide is reduced to the phosphine with Raney nickel.[†]

The selectivity in a number of solvents was determined using ligand **1** and diphenyl allyl acetate as the model substrate (Table 1, entries 1–6). Acetonitrile was found to be the best solvent, giving the allylation product in 96% yield and 94% ee (Table 1, entry 1). The selectivity appears to be relatively insensitive to solvent effects with a number of solvents giving 90% ee or better. The

**Table 1.** Palladium-catalyzed allylation[a]




| Entry | Substrate | Pd source/Temp. | Ligand | Solvent | Yield (%) | Ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 1 | $CH_3CN$ | 96 | 94 (*R*) |
| |  | | | | | |
| 2 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 1 | THF | 94 | 89 (*R*) |
| 3 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 1 | $CH_2Cl_2$ | 95 | 90 (*R*) |
| 4 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 1 | $Cl(CH_2)_2Cl$ | 94 | 85 (*R*) |
| 5 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 1 | Benzene | 97 | 92 (*R*) |
| 6 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 1 | Toluene | 96 | 90 (*R*) |
| 7 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 2 | $CH_3CN$ | 98 | 25 (*S*) |
| 8 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 3 | $CH_3CN$ | 90 | 56 (*R*) |
| 9 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 4 | $CH_3CN$ | 91 | 65 (*R*) |
| 10 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 5 | $CH_3CN$ | 97 | 41 (*R*) |
| 11 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 1 | Benzene | 93 | 44 (*R*) |
| |  | | | | | |
| 12 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 1 | Toluene | 90 | 40 (*R*) |
| 13 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 1 | $CH_3CN$ | 91 | 35 (*R*) |
| 14 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/$-20$°C | 1 | $CH_3CN$ | 87 | 39 (*R*) |
| 15 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 1 | $CH_3CN$ | 98 | 10 (*R*) |
| |  | | | | | |
| 16 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 2 | $CH_3CN$ | 93 | 10 (*S*) |
| 17 | | $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/rt | 5 | $CH_3CN$ | 94 | 5 (*R*) |

[a] 4.5 mol% ligand, 2 mol% $[Pd(allyl)Cl]_2$, 3 equiv., dimethyl malonate, 3 equiv. BSA, 3 equiv. TBAF, 12 h.

[b] The selectivities for entries 1–10 were determined by HPLC on Chiralpak AD, hexanes/isopropyl alcohol = 9:1, flow rate of 1.0 mL/min. For entries 11–17 selectivities were determined by chiral shift reagent $[Eu(hfc)]_3$.

[†] Representive spectral data:

Amide **9**

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.90–7.83 (m, 4H), 7.49–7.37 (m, 6H), 6.99 (bd, $J$ = 7.8 Hz, 1H), 4.18–4.11 (m, 1H), 3.58–3.54 (m, 2H), 3.18–3.11 (m, 2H), 2.18–2.07 (m, 3H), 1.93–1.76 (m, 3H), 0.87 (d, $J$ = 9.0 Hz, 3H), 0.85 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 174.1, 132.4, 132.2, 132.1, 132.0, 128.9, 128.7, 64.1, 62.4 (d, $J_{p-c}$ = 3.2 Hz), 57.8, 49.3, 31.4 (d, $J_{p-c}$ = 4.3 Hz), 29.4, 25.9 (d, $J_{p-c}$ = 5.4 Hz), 19.6, 19.2; $^{31}$P NMR (125 MHz, $CDCl_3$) $\delta$ 66.3; HRMS (FAB) calcd for $C_{22}H_{29}N_2O_2PSLi^+$ 423.1847 found 423.1866.

Amide **10**

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.03–7.96 (m, 2H), 7.89–7.85 (m, 2H), 7.65 (bd, $J$ = 7.2 Hz, 1H), 7.55–7.22 (m, 11 H), 5.39 (d, $J$ = 7.2 Hz, 1H), 4.13–4.06 (m, 1H), 3.74 (s, 3H), 3.36–3.22 (m, 2H), 2.22–2.10 (m, 2H), 1.99–1.91 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 172.2, 171.5, 136.4, 132.5, 132.4, 132.3, 132.1, 129.2, 129.0, 128.9, 128.9, 128.7, 128.6, 127.5, 62.5, 56.5, 53.1, 48.9, 31.7, 25.5 (d, $J_{p-c}$ = 4.6 Hz); $^{31}$P NMR (125 MHz, $CDCl_3$) $\delta$ 69.5; HRMS (FAB) calcd for $C_{26}H_{27}Li^+N_2O_3PS$ 485.1640, found 485.1642.

Oxazoline phosphine sulfide **11**

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.20–8.03 (m, 4H), 7.50–7.27 (m, 6H), 4.30–4.21 (m, 1H), 4.10–4.04 (t, $J$ = 8.4 Hz, 1H), 3.85–3.79 (t, $J$ = 8.4 Hz, 1H), 3.77–3.69 (m, 1H), 3.36–3.16 (m, 2H), 2.22–2.10 (m, 1H), 2.02–1.88 (m, 2H), 1.65–1.52 (m, 1H), 0.88 (d, $J$ = 6.9 Hz, 3H), 0.82 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.3, 132.8, 132.7, 132.6, 132.6, 131.8, 131.8, 128.6, 128.5, 128.3, 128.1, 72.4, 70.5, 56.2 (d, $J_{p-c}$ = 4.0 Hz), 48.6 (d, $J_{p-c}$ = 2.0 Hz), 32.8, 31.7, 25.8 (d, $J_{p-c}$ = 4.8 Hz), 19.3, 18.5; $^{31}$P NMR (125 MHz, $CDCl_3$) $\delta$ 68.0; HRMS (FAB) calcd for $C_{22}H_{27}Li^+N_2OPS$ 405.1742 found 405.1761.

Oxazoline phosphine sulfide **12**

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.19–8.06 (m, 4H), 7.44–7.26 (m, 11H), 4.52 (dd, $J$ = 9.3, 8.4 Hz, 1H), 4.43 (dd, $J$ = 9.3, 8.4 Hz, 1H), 4.01–3.88 (m, 2H), 3.30–3.18 (m, 2H), 2.25–1.95 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.3, 142.3, 132.8, 132.7, 132.6, 132.6, 132.5, 132.5, 131.9, 129.0, 128.9, 128.7, 128.6, 128.4, 128.9, 128.8; 75.0, 69.7, 56.3, 48.8 (d, $J_{p-c}$ = 6.5 Hz), 33.2, 29.9, 25.8 (d, $J_{p-c}$ = 4.9 Hz); $^{31}$P NMR (125 MHz, $CDCl_3$) $\delta$ 68.5; HRMS (FAB) calcd for $C_{25}H_{25}Li^+N_2OPS$ 439.1585 found 439.1579.

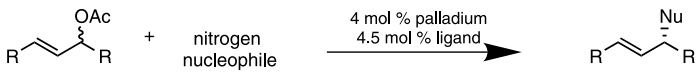
type of base used to generate the malonate anion was also examined. The BSA/TBAF system (94% ee) developed in our laboratory[11] appears to be superior to BSA/KOAc (84% ee) or BSA/NaOAc (63% ee). Ligands **2**–**5** were also examined. These ligands provided significantly lower selectivity. Ligand **1**, with an isopropyl on the oxazoline, proved to be the best ligand. The chiral center on the oxazoline of ligand **2** appears to be no longer complementary to the chirality of the proline. It is also observed that the phenyl ring on ligand **3** and the geminal dimethyl groups on ligand **4** do not offer the same steric hindrance as an isopropyl group on ligand **1**. In other proline based ligands we have found oxazolines such as ligand **4** to be effective at inducing asymmetric induction.[11–14]

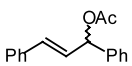
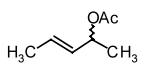
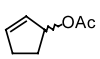
Additionally a number of substrates were examined. As is often the case, substrates other than diphenyl allyl acetate resulted in moderate to low selectivities. Aliphatic acyclic allyl acetates (Table 1, entries 11–14) proceeded with selectivities up to 44% ee while the difficult substrate cyclopentenyl acetate gave the desired product in only 10% ee (Table 1, entries 15–17).

Nitrogen based nucleophiles where also examined with this ligand system.[15–23] When 1,3-diphenylprop-2-enyl acetate was used both benzyl amine and phthalimide potassium salt were found to be effective nucleophiles. Benzyl amine added up to 93% ee (Table 2, entry 1) while phthalimide added with good selectivity (91% ee) but low yield (29%) (Table 2, entry 4). In the case of benzyl amine addition, changing the palladium source to $[Pd(allyl)Cl]_2$ or changing the temperature (Table 2, entries 2 and 3) resulted in a decrease in selectivity. The addition to dimethyl 2-acetoxy-3-pentene and cyclopentenyl acetate proceeded with moderate selectivity, 56% and 48% ee, respectively.

Ligand **5** was synthesized to determine the influence of the proline chirality. This ligand has the same type and number of atoms between the oxazoline nitrogen and the phosphorus as ligands **1**–**4**. However, it lacks the chiral rigid structure of the proline five member ring as well as the proline chiral center. As can be seen the selectivity for both the reaction with malonate and the nitrogen nucleophiles is generally lower than the ligands containing proline.

**Table 2.** Addition of nitrogen nucleophiles




| Entry | Substrate | Nucleophile | Ligand | Solvent | Yield (%) | Ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 |  | $BnNH_2$ | 1 | THF | 97 | 93 (*S*)[a] |
| 2 | | $BnNH_2$ | 1 | THF | 95 | 88 (*S*)[c] |
| 3 | | $BnNH_2$ | 1 | THF | 70 | 89 (*S*)[a,d] |
| 4 | | Phthalimide | 1 | THF | 29 | 91 (*S*)[a,e] |
| 5 | | $BnNH_2$ | 2 | THF | 97 | 81 (*R*)[a] |
| 6 | | Phthalimide | 2 | THF | 72 | 89 (*R*)[a,f] |
| 7 | | $BnNH_2$ | 3 | THF | 93 | 14 (*S*)[a] |
| 8 | | $BnNH_2$ | 4 | THF | 97 | 54 (*S*)[a] |
| 9 | | Phthalimide | 4 | THF | 36 | 25 (*S*)[a,e] |
| 10 | | $BnNH_2$ | 5 | THF | 95 | 78 (*S*)[a] |
| 11 | | Phthalimide | 5 | THF | 33 | 90 (*S*)[a,e] |
| 12 |  | $BnNH_2$ | 1 | THF | 79 | 56[a] |
| 13 | | $BnNH_2$ | 1 | THF | 89 | 48[a] |
| 14 |  | Phthalimide | 5 | THF | 76 | 9[a,f] |

[a] 4.5 mol % ligand, 2 mol % $Pd_2(dba)_2$ 3 equiv., nucleophile, reaction time 12 h at room temperature.
[b] ee was determined by HPLC on Daicel Chiralcel OD column, hexanes/isopropyl alcohol = 100:1, flow rate of 0.5 mL/min.
[c] $[Pd(allyl)Cl]_2$ was the palladium source.
[d] Reaction temperature 0°C.
[e] Reaction temperature 0°C.
[f] Reaction temperature reflux.

A proline-based P–N ligand system has been developed. The system has proven to be effective as a catalyst for the palladium-catalyzed addition to diphenyl allyl acetate. The selectivities obtained with other substrates were lower, however comparable to a number of others systems that have been investigated. One of the key features of this system is the ease with which the desired ligands were synthesized. Clearly formation of a P–N bond is easier then a P–C bond. It is becoming clear that discreet complexes where the phosphorus is linked through a heteroatom are viable ligands for asymmetric catalysis.

## Acknowledgements

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