# A modular approach to ligands for asymmetric π-allyl palladium catalysed additions

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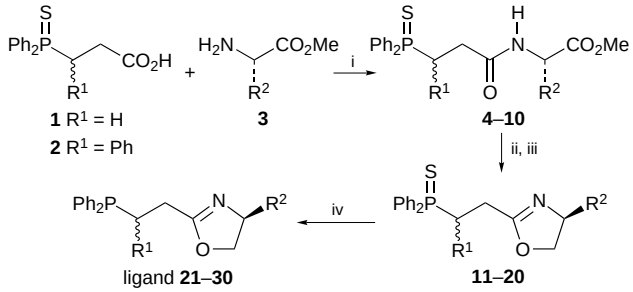
**A route to phosphinodihydrooxazoles is reported, which is used to synthesize ten new ligands whose ability to asymmetrically catalyse the addition of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate is investigated; the best gave a palladium complex which catalyses the addition of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate in 99% yield and 97% ee.**

The pace for the development of new asymmetric ligands is often determined by the availability of new ligand structures. Hence we have been interested in developing a building block based approach to the systematic synthesis of new, structurally varied ligands. Such an approach offers the potential for the discovery of new synthetically useful metal–ligand complexes, as well as the optimization of ligand systems that are known to work to a limited extent. To date, this work has focused on the synthesis and utility of amino acid based phosphine derivatives, for the construction of peptide based ligands.[1–4] We report here that the building blocks used in that approach can also be employed in the synthesis of a variety of phosphinodihydrooxazole ligands. This route allows access to new phosphine ligands without the difficulties often associated with C–P bond formation. We have used this chemistry to synthesize ten new phosphinodihydrooxazole ligands. These ligands have been screened for their ability to control the palladium catalysed asymmetric addition of malonate to 1,3-diphenylprop-2-enyl acetate.[5–7] A number of successful ligands were discovered with the best giving, at room temperature, the addition of malonate with 97% ee. This study also resulted in the observation of an interesting inverse temperature effect, in which the best ligand **28** gives higher ees at room temperature than at −30 °C.

As the starting point for our design we decided to use phosphine dihydrooxazole ligands that were structurally similar to those reported by Pfaltz, Helmchen and Williams.[8–12] This type of ligand has proven useful in asymmetric π-allyl additions[8–12] and asymmetric Heck reactions.[13] To date, the most successful ligands of this type have been six-member chelates with the phosphine attached to the dihydrooxazole through a phenyl ring. To the best of our knowledge only a single system with the phosphine attached to the nitrogen ligand by an alkyl bridge has been reported. That system, which forms a five-member chelate, gave poorer selectivity than the best systems.[10] Our approach makes ligands available that link the phosphine and dihydrooxazole groups with a two-carbon alkyl chain, thus forming a six-member chelate upon metal coordination and allowing a direct comparison to the six-member chelates studied previously by others.[8–12] The use of an alkyl chain to connect the chelating functionality allows the introduction of a second chiral centre, which is next to the phosphine. This results in diastereomeric ligands in which the two chiral centres can, potentially, act in concert or dissonance. Results with both diastereomeric possibilities are reported.




**Scheme 1** *Reagents and conditions:* i, EDC, HOBT, $CH_2Cl_2$, MeCN, room temp.; ii, $LiBH_4$, THF, 0 °C to room temp.; Burgess reagent, THF, reflux; iv, Raney Ni, MeCN, 60–80%

The synthesis of the library of ligands began with modular building blocks **1**, **2** and **3**. We chose to use amino acids **3** and phosphine containing acids (**1** and **2**) as our modules, allowing the synthesis of new ligands by amide bond formation. For the study reported here, we used two phosphine containing acids. One was a diphenylphosphine derivative of acrylate **1**, and the other a derivative of cinnamic acid **2**. The acrylate derivative **1** has been reported earlier as an intermediate in the synthesis of diphenylphosphinoserine.[1,2] The synthesis of the phenyl derivative **2** was performed in the same manner from cinnamic acid.

The synthesis of the ligands began with the coupling of phosphine acids **1** or **2** to a given amino acid yielding the phosphine sulfide amides **4–10** (Scheme 1). The desired ligands were then obtained by a simple three step procedure. Reduction of the methyl ester with $LiBH_4$ followed by cyclization with Burgess reagent[14] [$MeO_2CNSO_2NEt_3$] gave the dihydrooxazole phosphine sulfides **11–20**. Reaction with Raney nickel then removed the sulfur and gave the free phosphines. Reaction of **2** with an amino acid gave two diastereomeric products. These diastereomers were readily separated by chromatography, after $LiBH_4$ reduction, yielding both the (*SS*) and (*RS*) pair of diastereomers. The ligands are fully characterized as the phosphine sulfides. After reduction of the phosphine sulfides to the free phosphines the ligands were treated with palladium and used in catalysis without purification.†

The ligands were investigated in two groups; ligands with one chiral centre (Table 2) and ligands with two chiral centres (Table 3). Of the ligands with one chiral centre, the ligands derived from phenylalanine ($R^2$ = Bn) **22** and valine ($R^2$ = $Pr^i$) **23** gave the highest ees (87 and 86%) (Table 2, entries 2 and 3).

**Table 1** Synthesis of phospine dihydrooxazole ligands

| $R^1$ | $R^2$ | Compound | Yield (%) | Compound | Yield (%) | Ligand |
|---|---|---|---|---|---|---|
| H | Me (*S*) | **4** | 33 | **11** | 62 | **21** |
| H | Bn (*S*) | **5** | 31 | **12** | 66 | **22** |
| H | $Pr^i$ (*S*) | **6** | 64 | **13** | 72 | **23** |
| H | Ph (*S*) | **7** | 56 | **14** | 84 | **24** |
| Ph (*S*) | Bn (*S*) | **8** | 69[a] | **15** | 71 | **25** |
| Ph (*R*) | Bn (*S*) | **8** | 69[a] | **16** | 85 | **26** |
| Ph (*S*) | $Pr^i$ (*S*) | **9** | 62[a] | **17** | 45 | **27** |
| Ph (*R*) | $Pr^i$ (*S*) | **9** | 62[a] | **18** | 91 | **28** |
| Ph (*S*) | Ph (*S*) | **10** | 47[a] | **19** | 48 | **29** |
| Ph (*R*) | Ph (*S*) | **10** | 47[a] | **20** | 90 | **30** |

[a] Yields reported for **8**–**10** are for the mixture of the two diastereomers.

The effect of solvent on the reaction was probed using ligand **23** and the $Bu_4N^+$/BSA cation base combination (entries 3, 8, 9 and 10).[15] Of the solvents tested, $CH_2Cl_2$ was found to be the best solvent for this ligand (entry 3). The counter ion and base associated with the malonate anion have been shown to be important in these additions and so their effect was also investigated (entries 3, 5, 6 and 7). The optimal system for this class of ligand was found to be $(C_6H_{13})_4N^+$/BSA, as the counter ion and base, and $CH_2Cl_2$ as the solvent (entry 6), giving an ee of 90%.

Of the ligands with two chiral centres, the ligands derived from valine were again found to perform the best. Both combinations of the two chiral centres were looked at. It is interesting to note that the chirality at the carbon next to the phosphine had little effect on the selectivity of the catalysis, 90 *vs*. 93% ee for the (*SS*) *vs*. (*RS*) pair (Table 3, entries 3 and 4). Ligand **28** with a (*RS*) configuration, was found to be the most selective ligand (entry 4). The optimal reaction conditions for this ligand were then determined. The best solvent system for this ligand was found to be MeCN, and the best counter ion system was $(C_6H_{13})_4N^+$/BSA (entry 14).

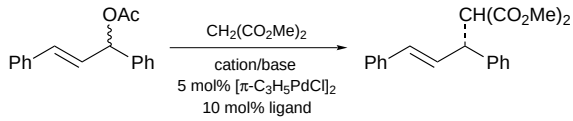



**Table 2** Results with ligand containing single chiral centre

| Entry | Ligand (config.) | Cation/base | Yield (%) | ee (%)[a] | Solvent |
|---|---|---|---|---|---|
| 1 | **21** (*S*) | $Bu_4N^+$/BSA | 67 | 82 | $CH_2Cl_2$ |
| 2 | **22** (*S*) | $Bu_4N^+$/BSA | 78 | 87 | $CH_2Cl_2$ |
| 3 | **23** (*S*) | $Bu_4N^+$/BSA | 94 | 86 | $CH_2Cl_2$ |
| 4 | **24** (*S*) | $Bu_4N^+$/BSA | 82 | 37 | $CH_2Cl_2$ |
| 5 | **23** (*S*) | $K^+$/BSA | 87 | 66 | $CH_2Cl_2$ |
| 6 | **23** (*S*) | $(C_6H_{13})_4N^+$/BSA | 62 | 90 | $CH_2Cl_2$ |
| 7 | **23** (*S*) | $(C_6H_{13})_4NBr$/Me/NaH | 22 | 81 | THF |
| 8 | **23** (*S*) | $Bu_4N^+$/BSA | 93 | 11 | CN |
| 9 | **23** (*S*) | $Bu_4N^+$/BSA | 14 | 64 | THF |
| 10 | **23** (*S*) | $Bu_4N^+$/BSA | 25 | 78 | $C_6H_6$ |

[a] The enantiomeric excesses were determined by chiral shift reagent [Eu(hfbc)$_3$] (ref. 11). BSA = bis(trimethylsilyl)acetamide.

**Table 3** Results with ligands containing two chiral centres[a]

| Entry | Ligand (config.) | Cation/base | Yield (%) | ee (%) | Solvent |
|---|---|---|---|---|---|
| 1 | **25** (*S*,*S*) | $Bu_4N^+$/BSA | 100 | 84 | MeCN |
| 2 | **26** (*R*,*S*) | $Bu_4N^+$/BSA | 53 | 93 | MeCN |
| 3 | **27** (*S*,*S*) | $Bu_4N^+$/BSA | 91 | 90 | MeCN |
| 4 | **28** (*R*,*S*) | $Bu_4N^+$/BSA | 80 | 93 | MeCN |
| 5 | **29** (*S*,*S*) | $Bu_4N^+$/BSA | 56 | 22 | MeCN |
| 6 | **30** (*R*,*S*) | $Bu_4N^+$/BSA | 37 | 54 | MeCN |
| 7 | **27** (*S*,*S*) | $Bu_4N^+$/BSA | 91 | 90 | MeCN |
| 8 | **27** (*S*,*S*) | $Bu_4N^+$/BSA | 43 | 65 | $CH_2Cl_2$ |
| 9 | **28** (*R*,*S*) | $Bu_4N^+$/BSA | 80 | 93 | MeCN |
| 10 | **28** (*R*,*S*) | $Bu_4N^+$/BSA | 33 | 85 | $CH_2Cl_2$ |
| 11 | **28** (*R*,*S*) | $Bu_4N^+$/BSA | 48 | 88 | THF |
| 12 | **28** (*R*,*S*) | $Bu_4N^+$/BSA | 49 | 79 | $C_6H_6$ |
| 13 | **28** (*R*,*S*) | TBAOAc/BSA | 93 | 82 | MeCN |
| 14 | **28** (*R*,*S*) | $(C_6H_{13})_4N^+$/BSA | 99 | 97 | MeCN |

[a] General procedure given in the footnote†.

In the case of the ligands reported by Pfaltz, where the phosphine is attached to the dihydrooxazole through a phenyl ring, a phenyl substituent next to the nitrogen gave the highest selectivities, with isopropyl only slightly poorer.[9] In the system reported here, the best substituent, in the position next to nitrogen, was isopropyl while phenyl was found to be the poorest (ligand **28** *vs*. **30**). The source of the difference between the two systems is unknown, but probably has its origins in different conformational preferences for the two complexes. The positioning of an $sp^3$ hybridized carbon, with a phenyl ring attached, changes the canting of the phenyl rings on the phosphine. This effect may be responsible for the difference between these two ligands.

Through the use of modular building blocks we have developed a new ligand for palladium catalysed π-allyl additions. We are currently studying the use of these ligands in other metal catalysed reactions. We are also using the phosphine acid building blocks discussed here in the synthesis of other collections of ligands for a variety of transition metal catalysed reactions.

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## Footnotes

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† *General procedure* for π-allyl addition: The phosphinooxazoline ligand was mixed with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in degassed MeCN. After 30 min, 1,3-diphenylprop-2-enyl acetate (10 equiv.) in MeCN was added. To this solution at the desired reaction temperature, a solution of dimethyl malonate (30 equiv.), $Bu_4NF$ (30 equiv.) and BSA (30 equiv.) in MeCN was added over 1 h. After complete reaction, as judged by TLC, the reaction mixture was worked up extractively.

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