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JM-PHOS Ligands: Second-Generation Phosphine Oxazolines for Asymmetric Catalysis

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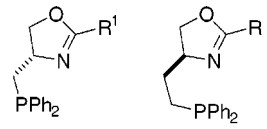
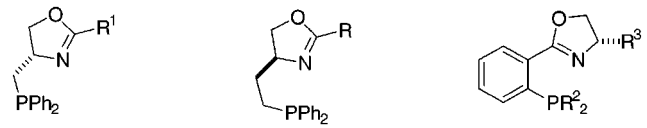
ABSTRACT



1 *first generation* **2** *second generation*

A small library of phosphine oxazoline ligands 2 was prepared and tested in palladium-mediated allylation processes (reactions 1 and 2). They were found to be superior to the first-generation ligands 1 and as effective as the well-known phosphine oxazolines 3.

High throughput screening methods for discovery and optimization of asymmetric reactions may involve large libraries of easily accessible materials or smaller collections focused on lead structures.[1] Our group is particularly interested in the latter approach. Divergent syntheses of small, but carefully designed, ligand sets are critical for that objective. Earlier contributions from these laboratories described syntheses of the phosphine oxazolines **1** and their performance in the asymmetric allylation reaction 1.[2] The best enantiomeric excess obtained in that work was 93%. At that time, we speculated that chelate size was important and that the homologous ligands **2** would give higher enantioselectivities. This Letter describes a synthesis of a small ligand set having the generic structure **2** and tests of our hypothesis.



1 *first generation* **2** *second generation* **3** *Helmchen/Pfaltz Williams Ligand*

a **b** **c** **d**

Ligands **2** and the well-known ligands **3** both form six-membered ring chelates when bound to a metal. Consequently, a goal of this work was to determine if ligands **2** could give enantiomeric excesses that are comparable with those obtained using ligands **3**.[3]

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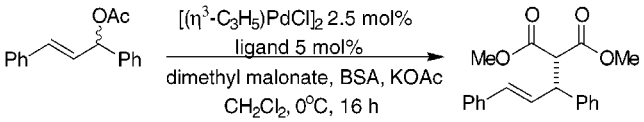
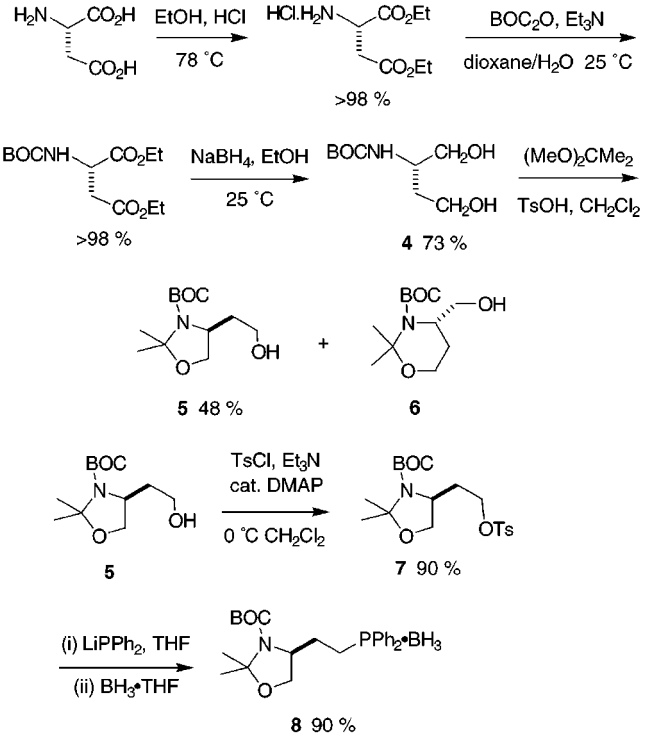


reaction 1

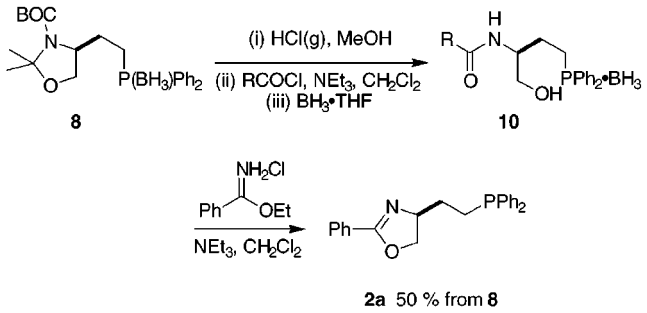
Aspartic acid was the starting material used for synthesis of ligands **2a**−**d** (Scheme 1). This amino acid was esterified, BOC-protected, and then reduced via literature procedures[4] that can be performed on a large scale without resorting to chromatographic separations. Conversion of diol **4** to the desired oxazolidine **5** is also a known procedure.[4] Product **5** was contaminated with the undesired oxazine **6**, but the oxazolidine could be isolated by fractional crystallization from heptane or via flash chromatography. Incorporation of the phosphine moiety was achieved via tosylate **7**, nucleophilic displacement, and protection in situ by formation of phosphine borane **8**.[2] Compound **8** is the hub of our divergent ligand synthesis.

Scheme 1. Synthesis of the Key Intermediate **8**



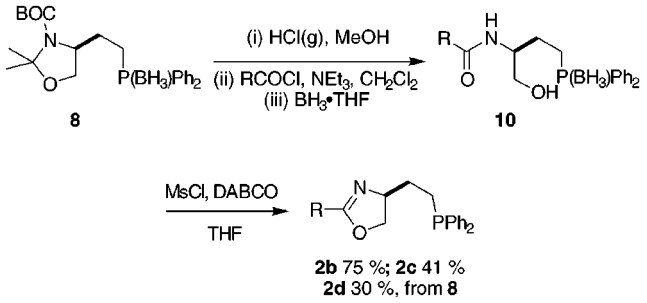
Different methods were used for conversion of oxazolidine **8** into the required ligands. Phenyl-substituted oxazoline **2a** was prepared by condensation of an imidate with amino alcohol **9** (Scheme 2).

Scheme 2. One-Step Route to Oxazolines **2**



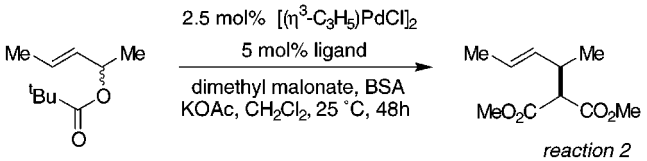
Ligands **2b**−**d** (and several others, data not shown) were readily obtained via acylation/mesylation (Scheme 3). The procedures outlined in Schemes 1−3 facilitate preparations of ligands **2** in gram quantities.

Scheme 3. Two-Step Route to Oxazolines **2**



Ligands **2** (called JM-PHOS ligands after the major sponsor for this research) were tested in the allylation reaction 1 using a multiwell reactor as described previously.[2] In three of the four experiments the enantiomeric excess of the allylation product was greater than 98%, as determined by HPLC analysis on a Chiralcel OD column (Figure 1a).

Reaction 2 provides a stringent test of ligand performance. In one isolated example, an enantiomeric excess of 92% was reported for this reaction,[5] but values of less than 74% are the norm under these conditions.[6] The best ee obtained in this reaction for the first-generation ligands **1** was 75%. Data collected for the JM-PHOS series (Figure 1b) gave an optimum (80% ee) that compares favorably with those in the previous studies.



reaction 2

Ligands **2** give more enantioselective catalysts (Figure 1) than our first design **1**. This supports our previous assertion that equilibria of the type shown in Figure 2 are more

(5) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520.
(6) (a) Matt, P. V.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (b) Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1179.
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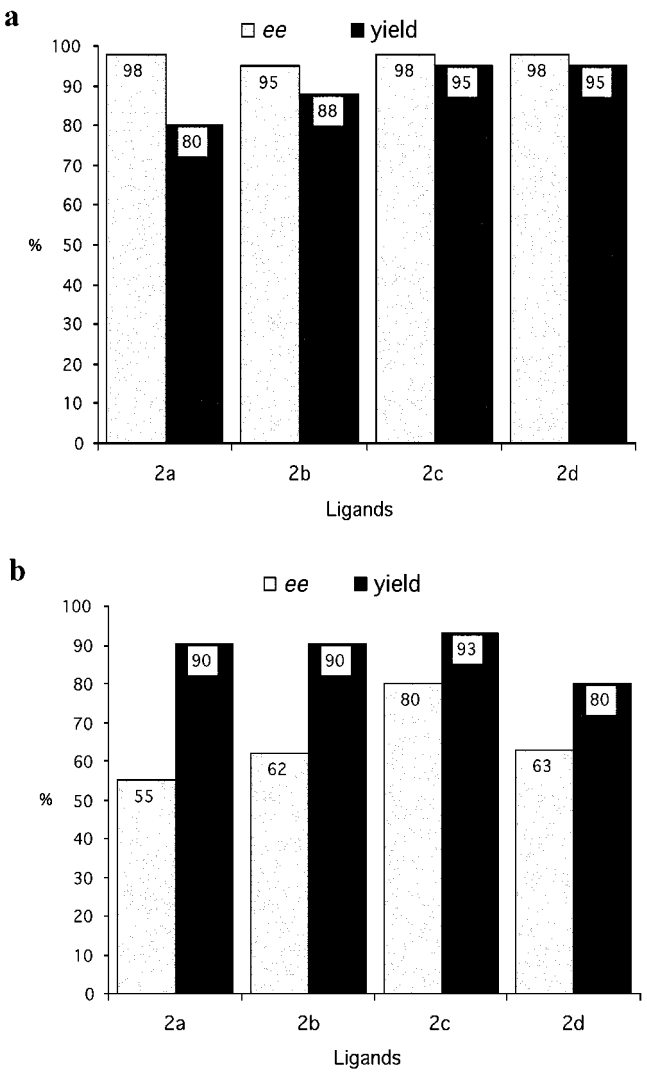

Figure 1. Chemical and optical yield data for (a) reaction 1 and (b) reaction 2. Chemical yields were determined by adding an internal standard. Enantioselectivity data shown in Figure 1b were determined via GC. In both reactions 1 and 2, the experiments were repeated at least two times, and good reproducibility was observed.

significant for ligands **1**. Indeed, a crystallographic analysis of complex **11** (PF_6 salt) that shows the P−Pd−N angle is 90.5 °, close to the ideal for a square planar complex, and implying a lack of ring strain in the chelate of ligand **2**. Details of this crystallographic analysis will be reported elsewhere. The implication of this observation is that complexes of ligand **2** are less likely to ring-open, giving diphosphine complexes. Small amounts of the diphosphine

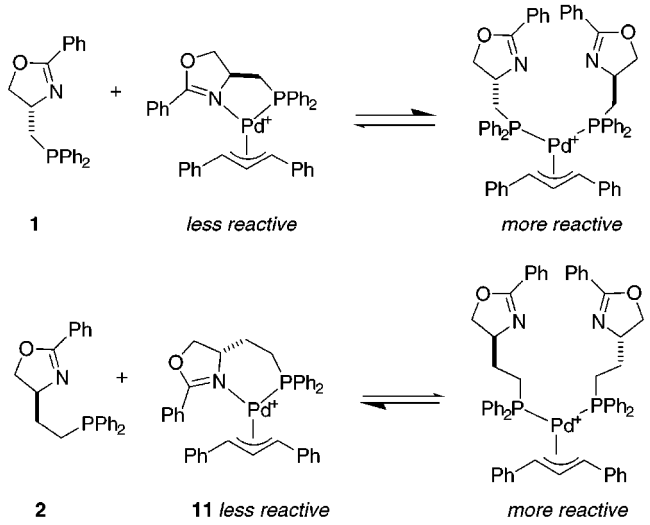

Figure 2. Postulate to explain why superior enantioselectivities were observed using ligand **2** compared with **1**. The presumed positions of the equilibria are accentuated to highlight the postulated differences.

complexes could adversely affect the enantiomeric excesses obtained. We postulate that these diphosphine complexes are more prevalent for ligands **1** than for **2**; hence the latter give more enantioselective catalysts. Unfortunately, however, we were unable to measure equilibrium constants for these situations because the diphosphine complexes could not be isolated or observed under nonequilibrating conditions.

Factors other than the one outlined in Figure 2 must also have an impact on asymmetric allylations involving ligands **1** and **2**. ^{31}P NMR studies of [(η^3-PhCHCHCHPh)Pd(ligand)]$^+$ complexes revealed *syn:anti* ratios in $CDCl_3$ at 25 °C of approximately 3:1 for ligand **1** and 4:1 for **2**, whereas that reported for **3** was 9:1.[8] These data provide insights into stereoelectronic properties of the ligand metal complexes. Implications of these observations and some further applications of the JM-PHOS ligands will be reported in the full account of this work.

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Supporting Information Available: Experimental procedures for preparation of compounds **2**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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