

## Chiral P,N-Ligands Based on Ketopinic Acid in the Asymmetric Heck Reaction

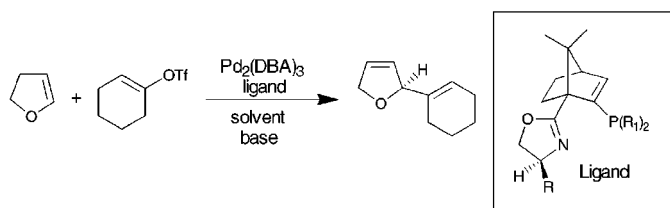
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## ABSTRACT



Novel chiral P,N-ligands were synthesized from (1S)-(+)-ketopinic acid using palladium-catalyzed coupling reaction of a vinyl triflate and either a diarylphosphine or a dialkylphosphine as the key step. Palladium complexes of these ligands are efficient catalysts for asymmetric Heck reaction between aryl or alkenyl triflates and cyclic alkenes. Products were obtained with good to excellent enantioselectivity from arylation and alkenylation of 1,2-dihydrofuran, cyclopentene, and 4,7-dihydro-1,3-dioxepin.

Over the past few years we have been involved in the development of new phosphine ligands for catalysis.<sup>1–9</sup> Recently, we reported that vinyl phosphines are readily accessible from ketones by palladium-catalyzed coupling of the corresponding vinyl triflate with diphenyl phosphine.<sup>2</sup> The development of this transformation has prompted us to use commercially available chiral ketones in the synthesis of novel phosphine ligands. One interesting chiral ketone is (1S)-(+)-ketopinic acid (**1**). A number of chiral auxiliaries and ligands have been developed using this rigid norbornyl backbone.<sup>10–17</sup> However, no phosphine-oxazoline ligands based on this framework have been reported. This paper

reports the synthesis of phosphino-oxazoline ligands **2–7** and their use in the asymmetric palladium-catalyzed intermolecular Heck reaction (Figure 1).

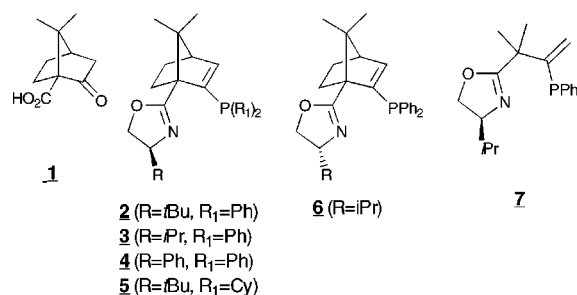


Figure 1. Ketopinic acid based phosphine-oxazolines.

The Heck reaction has been used in organic chemistry since 1968.<sup>18–20</sup> In the original version of this reaction, the

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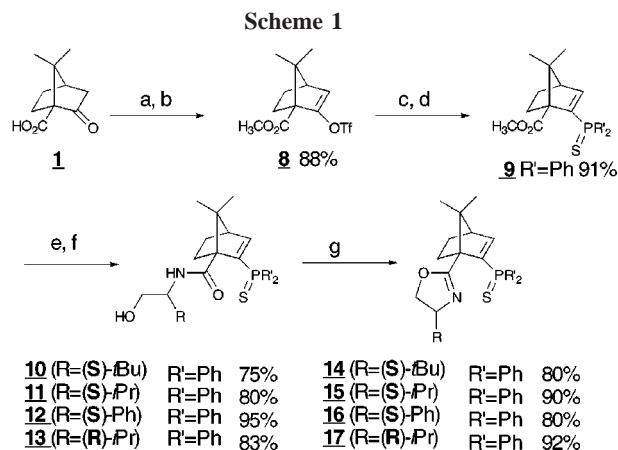
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alkyl palladium intermediates undergo  $\beta$ -hydride elimination toward the vinyl/aryl group that has been added to the double bond. In a number of cases, particularly with cyclic olefins, this is not possible because the only  $\beta$ -hydride *syn* to the metal is away from the newly formed carbon-carbon bond. In these cases this results in the formation of a new chiral carbon. Being able to control this reaction such that one enantiomer is formed selectively would be a significant result. Other than the excellent work of Pfaltz and Hayashi, success with the asymmetric intermolecular version of this reaction has been rather limited.<sup>21–30</sup> Pfaltz has shown that phosphine-oxazoline ligands can be used with palladium to perform asymmetric versions of the Heck reaction on selected substrates. The success of the Pfaltz phosphine-oxazoline system has led us to synthesize and study the system discussed below.

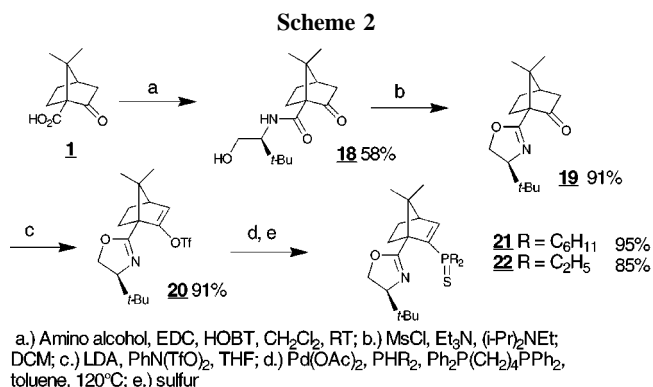
The general route for the synthesis of the desired ligands is illustrated in Scheme 1. Commercially available (*S*)-(+)-



a.) methanol,  $\text{SOCl}_2$ ; b.) LDA,  $\text{PhN}(\text{TfO})_2$ , THF; (c)  $\text{Pd}(\text{OAc})_2$ ,  $\text{PHR}'_2$ ,  $\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2$ , toluene, 70°C; (d)  $\text{S}_8$  toluene room temp. (e) LiI, Pyridine refluxed; (f) Amino alcohol, EDC, HOBT, DMF; (g)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $(i\text{-Pr})_2\text{NEt}$ ; DCM.

diphenylphosphine was followed by protection of the phosphine as its sulfide (**9**). Hydrolysis of the methyl ester proved difficult, ultimately requiring a nonhydrolytic method to obtain the desired acid.<sup>31</sup> This reaction was followed by conversion of the acid to an amide (**10–13**). Mesylation of the alcohols **10–13** followed by sequential cyclization provided the corresponding phosphine-oxazoline sulfides. We have found in previous work that phosphine sulfides are good protecting groups for what are often moderately air sensitive phosphine groups. The free phosphine is readily generated by reaction with Raney nickel prior to use.<sup>32–35</sup>

We also desired this type of ligand with different phosphine groups. The original route to the cyclohexyl derivative of ligands **14–17** was to use the approach described in Scheme 1. However, that route proved problematic in that during the coupling of the amino alcohol the phosphine sulfide was oxidized to the phosphine oxide. After completion of the synthesis, we were not able to reduce the phosphine oxide to the phosphine. Additionally, running the reaction with the careful exclusion of air still resulted in the formation of the phosphine oxide. To circumvent this problem, we decided to synthesize the oxazoline first and then attempt the palladium-catalyzed conversion of the ketone to the vinyl phosphine (Scheme 2). This route



ketopinic acid (**1**) was converted to its methyl ester which was then converted to the corresponding vinyl triflate (**8**). Palladium-catalyzed coupling reaction of triflate **8** and

proceeded smoothly to give the desired dicyclohexylphosphine. We have also used this route to synthesize the

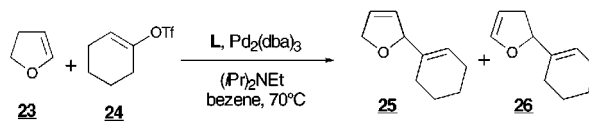
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diethylphosphine derivative. This route allows for the rapid synthesis of a number of different phosphines since the last step in the synthesis is the one that introduces the phosphine functionality. In the case of the dialkylphosphine sulfides, Raney nickel was used to obtain the dialkylphosphine.

Initially ligands **2**–**7** were tested in the Heck reaction of dihydrofuran (**23**) and 1-cyclohexenyl triflate **24** (Table 1).

**Table 1.** Heck Reaction with Dihydrofuran



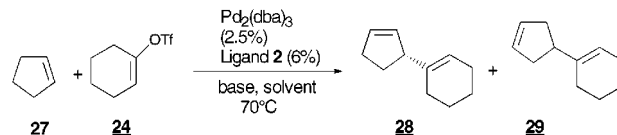
entry	ligand	temp, °C	time, h	convn, %	<b>25</b> , % ee <sup>a</sup>	<b>26</b> , %
1	<b>2</b>	70	22	100	94 <i>R</i>	0
2	<b>3</b>	70	48	91	76 <i>R</i>	1
3	<b>4</b>	70	48	90	56 <i>R</i>	3
4	<b>5</b>	90	24	99	64 <i>R</i>	0
5	<b>6</b>	70	72	45	76 <i>S</i>	2
6	<b>7</b>	70	20	98	6 <i>R</i>	<1

<sup>a</sup> Ratios were determined by GC with CHIRALDEX G-TA 30 M column at 70 °C. The retention times were 24.6 min for the *S* enantiomer, 28.7 for the *R* isomer, and 18.7 min for the isomer (**26**).

Of the six ligands, ligand **2** bearing the bulky *tert*-butyl group on the oxazoline ring gave product **25** with the highest enantioselectivity (entry 1) without formation of regioisomer **26**. Reactions using ligands **3** and **4** with smaller isopropyl and phenyl groups on the oxazoline ring were slower and resulted in moderate enantioselectivity. When the chirality of the carbon center on the oxazoline ring was changed, the selectivity of the reaction also changed. The reaction using ligand **6** gave (*S*)-**25** (entry 5), the enantiomer of the product obtained from the reaction using ligand **3** (entry 2). This result indicates that the enantioselectivity of this system is controlled by the chirality of the chiral carbon of the oxazoline ring, rather than the chirality of the norbornyl ring system. The reaction using the dialkylphosphine oxazoline ligand **5** did not improve the selectivity of the reaction, resulting in (*R*)-**25** in 64% ee.

Reaction of cyclopentene and cyclohexenyl triflate using ligand **2** in benzene at 70 °C was slower than that of 2,3-dihydrofuran and cyclohexenyl triflate (Table 2, entry 1). Only 78% conversion of the reaction was observed at 70 °C after 2 days. The major product was observed with 94% ee, together with 30% of the isomer. To improve the selectivity of the reaction, a study of various solvents and bases was undertaken (Table 2). When THF was employed as the solvent in the presence of diisopropylethylamine, significantly lower amounts of the minor isomer **29** resulted (4%, Table 2, entry 2); however, the major isomer (*R*)-**28** was observed with 69% ee (entry 2). Using Proton Sponge as base, the enantioselectivity of the reaction increased slightly

**Table 2.** Solvent and Base Effects on the Heck Reaction



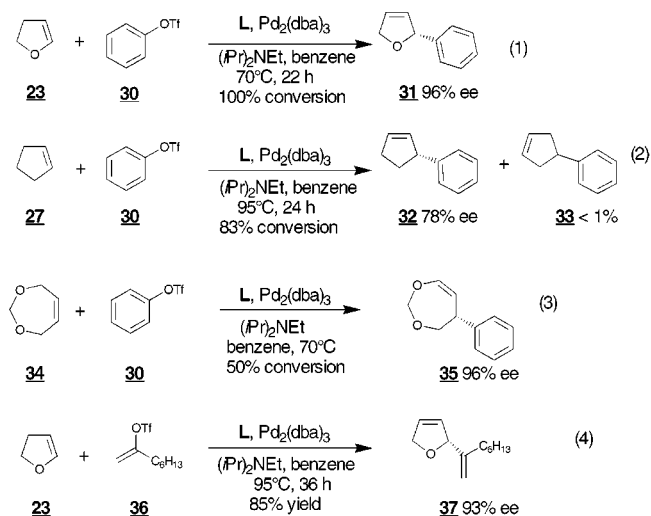
entry	solvent	base	time, h	convn, %	<b>28</b> ee, %	<b>29</b> , %
1	benzene	<i>i</i> Pr <sub>2</sub> EtN	48	78	94	30
2	THF	<i>i</i> Pr <sub>2</sub> EtN	22	100	69	4
3	THF	Proton Sponge	24	93	76	33
4	benzene/THF	<i>i</i> Pr <sub>2</sub> EtN	48	100	90	32
5	CH <sub>2</sub> Cl <sub>2</sub>	<i>i</i> Pr <sub>2</sub> EtN	48	76	47	6
6	dioxane	<i>i</i> Pr <sub>2</sub> EtN	24	100	85	28
7	dioxane	Bu <sub>4</sub> NOAc	24	100	75	45
8	DMF	<i>i</i> Pr <sub>2</sub> EtN	24	100	59	41
9	NMP	<i>i</i> Pr <sub>2</sub> EtN	24	100	40	31

<sup>a</sup> Ratios were determined by GC with CHIRALDEX G-TA 30 M column at 50 °C. The retention times were 24.6 min for the *S* enantiomer, 28.7 for the *R* isomer, and 18.7 min for isomer (**29**).

(76% ee) but amount of the isomer **29** increased to 33%. Reaction in a more polar solvent such as DMF or NMP resulted in lower selectivity and significant amounts of the isomer **29** being formed (entries 8 and 9). Other solvent/base combinations did not result in a significant improvement in the selectivity of this system.

The Heck reaction of other substrates using ligand **2** was also investigated. Reaction of dihydrofuran **23** and phenyl triflate **30** gave an excellent result, with the coupling product (*R*)-**31** observed with 96% ee in quantitative conversion (Scheme 3, eq 1). Reaction of cyclopentene **27** and aryl

**Scheme 3**

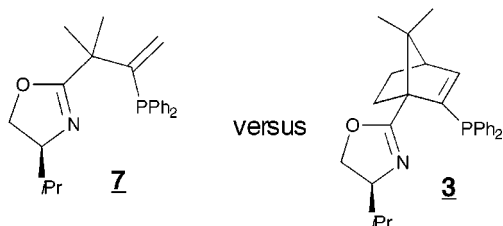


triflate **30** at 95 °C gave the coupling product **32** with 78% ee in 83% conversion, together with trace amounts of isomer

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**33** (eq 2). The reaction of triflate **30** and alkene **34** was very slow, with only a 50% conversion observed for the reaction at 70 °C over 3 days. Product **35** was observed with 96% ee. Interestingly, reaction of dihydrofuran **23** and acyclic enol triflate **36** at 95 °C resulted in the product **37** with 93% ee in 85% yield.

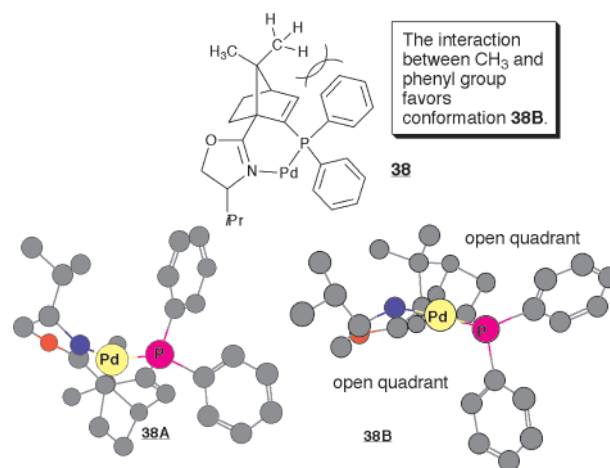
Since the selectivity appears to be determined primarily by the chirality of the oxazoline, a ligand was synthesized that positioned the functionality found in ligand **3** in the same locations but not in a 2.2.1 bicyclic system (Figure 2). Ligand



**Figure 2.** Minimal model of ketopinic acid based ligand.

**7** consists of a vinyl phosphine attached to a tertiary carbon which also has the oxazoline moiety attached. Ligand **7** performs the Heck reaction between dihydrofuran and cyclohexenyl triflate in high conversion but only 6% ee.

Models of these two complexes were examined to attempt to determine the key interaction in the bicyclic system that is not present in the acyclic case. It appears that an important interaction in the bicyclic system that is not present in the acyclic case is between one of the geminal dimethyl groups on the one-carbon bridge and one of the phenyl groups on the phosphine (Figure 3). This interaction causes one of the number of potential conformations to be favored (**38B**). In this conformation the top phenyl group is in a pseudoequatorial position while the bottom phenyl group is in a pseudoaxial orientation. Having one preferred conformation rather than a number of conformations may be responsible for the significantly better selectivity that is observed with this ligand compared to its acyclic analogue. There also appears to be one preferred conformation in systems such as Pfaltz's, where the oxazoline and the phosphine are attached though only  $sp^2$  hybridized carbons.



**Figure 3.** Two possible conformations of complex **38**.

In summary, we have successfully synthesized a number of phosphine-oxazoline ligands from (1*S*)-(+)-ketopinic acid (**1**). These ligands, especially the ligand with the *tert*-butyl group (**2**), were effective in the Heck reaction of cyclic and acyclic triflates with cyclic alkenes in excellent selectivity. Currently experiments are underway to determine whether the difference in the selectivity between the cyclic and acyclic ligand is as stated in the paper. Ligands that will extenuate these effects are being synthesized. Additionally the best ligands in this paper are being tested with other metals and in other reactions.

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**Supporting Information Available:** Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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