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Asymmetric hydrogenation of aromatic olefins catalyzed by iridium complexes of proline derived phosphine–oxazoline ligands

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Abstract—The synthesis of a series of phosphine–oxazoline ligands is reported. This ligands are synthesized by reaction of a phosphine chloride with the secondary nitrogen of proline. Upon coordination to iridium the resulting complexes can be used in the asymmetric hydrogenation of simple olefins. The effect of different counter ions and substitution at the oxazoline and the phosphine is reported.

Over the past 5 years we have been involved in the development of phosphine–oxazoline ligands for a variety of reactions. One system we have developed uses proline as one of the chiral elements. The initial ligands were based on *trans*-hydroxy proline (**1**) and were synthesized by substitution of the hydroxyl group with phosphine.[1–3] More recently, we have reported proline-based ligands where the phosphorus is attached to the proline through a P–N bond (**2**).[4] Such ligands have an advantage in that the phosphorus group can be readily modified since formation of the P-heteroatom bond is quite facile.[5] We have synthesized a series of iridium complexes with our proline derived ligands and tested these complexes in the asymmetric hydrogenation of simple olefins (Fig. 1).

In the area of asymmetric hydrogenation, the reduction of unfunctionalized olefins has been less developed than the hydrogenation of alkenes containing heteroatoms. Much of the initial success in this area utilized cyclopentadienyl ligands with either titanium or zirconium. The most successful early examples were reported by Buchwald, using Brintzinger type ligands.[6,7] More recently, a number of workers, Pfaltz and Burgess particularly have found that P–N iridium complexes can be highly effective in the asymmetric hydrogenation of styrene derivatives.[5,8–15] In a number of cases these systems provide selectivities as high as 99:1 enantiomeric ratio (er). Additionally these systems proceed with low catalyst loadings.

Reported here is a series of ligands based on proline. These catalysts were varied in three locations: at the oxazoline, the phosphine and by altering the counter ion. Based on our experience, as well as the work of Pfaltz and others, the R group on the oxazoline was chosen to be either *iso*-propyl or *tert*-butyl.[9,12] It should be noted that, since the oxazoline is derived from an

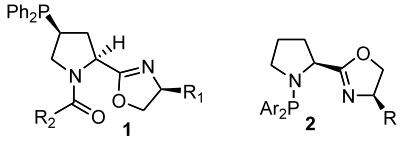
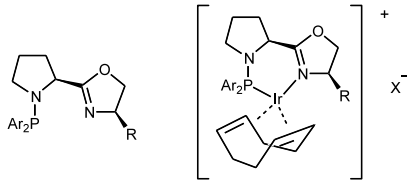


Figure 1. Two proline based ligands.

Table 1. Catalyst systems screened



Cpd #	Ar	R	X
3	Ph	*i*-Pr	PF_6
4	Ph	*i*-Pr	BARF
5	Ph	*t*-Bu	BARF
6	*o*-Tol	*t*-Bu	PF_6
7	*o*-Tol	*t*-Bu	BARF
8	2-Ethylphenyl	*t*-Bu	BARF
9	2,3-Dimethylphenyl	*t*-Bu	BARF
10	2,4-Dimethylphenyl	*t*-Bu	BARF

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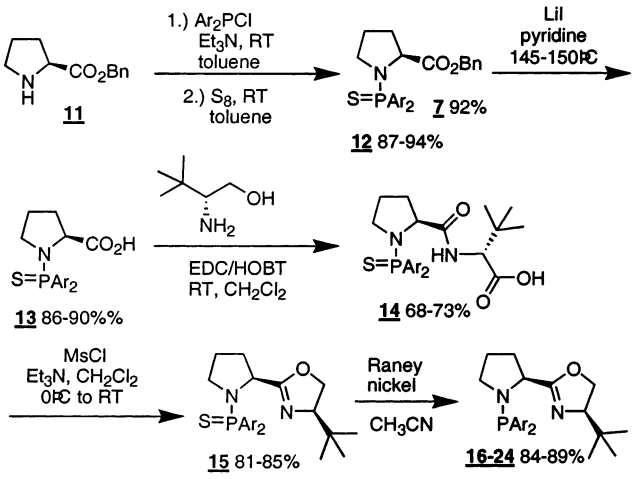
amino acid, there are a wide variety of R groups available for this position. The aromatic group on the phosphine was varied with different substituted benzene derivatives. Sterics were the primary consideration used in making the choices for this position. Additionally, two different counter ions were used, PF_6 and tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate (BARF) (Table 1).

The ligands were readily available by reaction of proline ester with a phosphine chloride followed by protection of the phosphine with sulfur (Scheme 1). Cleavage of the benzyl ester to the acid by reaction with lithium iodide was followed by amide formation with an amino alcohol. Amide formation was then followed by cyclization to the oxazoline. Prior to metalation, the phosphine sulfide was converted to the free phosphine by reaction with Raney nickel.[1,16,17]

In the synthesis of new phosphine ligands, generally the most difficult step is the incorporation of the phosphine by formation of a phosphorus–carbon bond. One of the important features of the chemistry reported here is that the phosphorus is incorporated into the molecule through the formation of a phosphorus–amine bond. The necessary phosphine chlorides are available by reaction of variety of aryl Grignards with PCl_3.[18,19] This allows for the synthesis of a variety of different phosphorus components without the need for the generation of carbanions or phosphide anions.

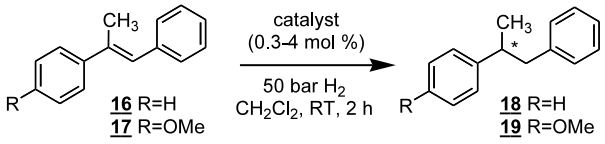
The initial substrate that was examined, *trans*-α-methylstilbene (**16**), has been examined by a number of groups. It was observed in this system that the selectivity was dependent on all three possible variables (Table 2). The best counter ion in terms of selectivity and lowest catalyst loading is BARF. When BARF was used as the counter ion a catalyst loading of 0.3 mol% was generally used. The need to use BARF as a counter ion has also been observed by Pfaltz and Burgess.[9–11] Complexes with PF_6 as the counter ion result in slow reaction with catalyst loading as high as 10 mol%. In a number of cases no reaction was observed with PF_6 complexes. NMR studies in the literature indicate that when PF_6 is the counter ion the catalytically inactive bridging iridium hydride is more readily formed than with the sterically larger BARF counter ion.[20]

As is generally true for oxazoline-based ligands, the group on the oxazoline has the most significant impact on the selectivity of the ligand. In this case *tert*-butyl gave better selectivity than the ligands with *iso*-propyl on the oxazoline. It was determined early in this study that the optimal oxazoline stereochemistry was the (*R*) configuration. The diastereoisomer of ligand **5** with the oxazoline in the (*S*) configuration and BARF as the counter ion give an 17:83 (*R*:*S*) enantiomer ratio. Substitution on the phosphine also influences the selectivity of the catalyst. The ligand with ethyl in the *ortho* position (**8**) gave higher selectivity than the simple benzene case (**5**). This ligand was also more selective than the ligands with methyl at the *ortho* position (**7**, **9**, and **10**). Ligand **8** proved to be the ligand that provided



Scheme 1. Synthesis of proline based ligands.

Table 2. Hydrogenation of methylstilbene analogs



Entry	R	Catalyst (mol%)	Conversion (%)	er[a] *R*:*S*
1	H	**3** (4.0)	99	73:17
2	H	**4** (0.3)	99	85:15
3	H	**5** (0.3)	99	93:7
4	H	**6** (4.0)	50	92:8
5	H	**7** (0.3)	99	95:5
6	H	**8** (0.3)	99	96:4
7	H	**9** (0.3)	99	95:5
8	H	**10** (0.3)	99	93:7
9	MeO	**5** (0.3)	99	94:6
10	MeO	**7** (0.3)	99	96:4
11	MeO	**8** (0.3)	99	96:4
12[b]	MeO	**8** (0.2)	99	97:3
13	MeO	**9** (0.3)	99	95:5
14	MeO	**10** (0.3)	99	95:5

[a] The enantiomeric ratios were determined by HPLC on Chiralcel OJ column, entries 1–8, Hex/*i*PrOH = 99:1; entries 9–14, Hex/*i*PrOH, 95:5, flow rate = 0.5 mL/min, 20°C.
[b] 20 bar H_2 at 0°C.

the highest selectivity with all of the substrates tested, giving a selectivity of 97:3 enantiomeric ratio with *para*-methoxymethylstilbene (**17**) and 96:4 er with *trans*-α-methylstilbene (**16**) (Fig. 2).

Catalyst from ligand **8** was examined with a number of styrene derivatives. In general trisubstituted double bonds proceed with fair to good selectivity. When the double bond is in a ring (**20** and **21**) a ratio of enantiomers as high as 84 to 16 was obtained. The reaction proceeds with low selectivity as well as slow rate with tetrasubstituted olefins (**22**). Additionally, terminal double bonds give low selectivity (**25**). Reaction with the trisubstituted allyl alcohol (**27**) proceeded with good selectivity, giving a 97 to 3 ratio of enantiomers.

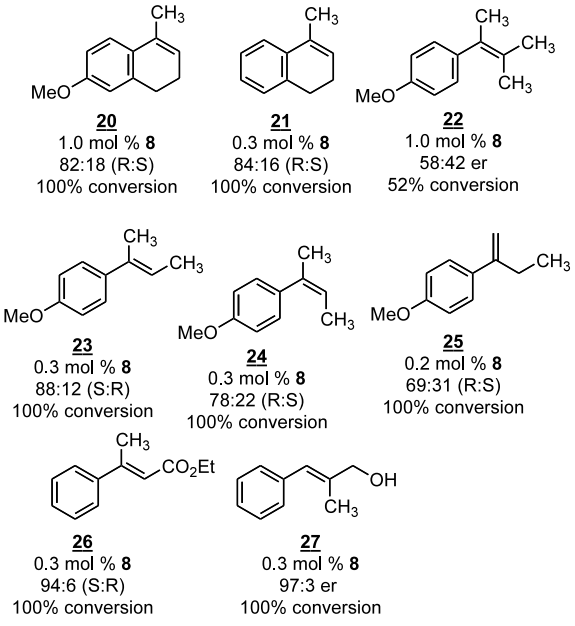


Figure 2.

In previous papers we have reported the use of other proline based phosphine–oxazoline ligands.[1–3] When the ligand system based on hydroxyproline (**1**) was tested low reactivity and selectivity were obtained. We had found that this ligand system provided excellent selectivity in the alkylation of cyclic allyl acetates and in the Heck reaction.[1–3] This result illustrates the need to have a variety of methods for the synthesis of different ligands. Since a ligand that provides excellent selectivity in one reaction, in many cases provides poor selectivity in a different reaction.

In this paper we report the synthesis of a new proline-derived ligand that when coordinated to iridium, provides a catalyst that gives good selectivity in the hydrogenation of simple unfunctionalized olefins. We are currently working on methods to synthesize this system with more hindered phosphines. Additionally a number of other reactions are being examined.

Acknowledgements

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