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Proline derived phosphine–oxazoline ligands in the asymmetric Heck reaction

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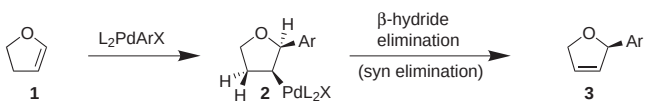
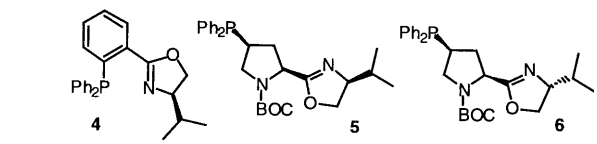
Abstract—A phosphine–oxazoline ligand system based on hydroxyproline is used as an asymmetric ligand for palladium. Complexes of this type are reported as catalysts for the asymmetric Heck reaction. © 2001 Published by Elsevier Science Ltd.

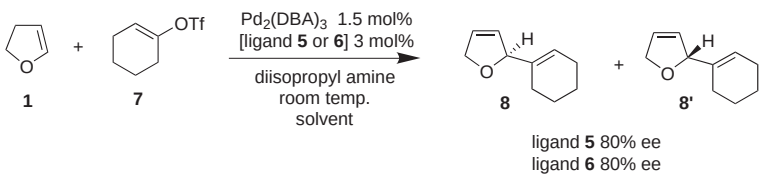
The Heck reaction has been used in organic chemistry for many years.[1–4] This reaction is generally thought of as the formation of a bond between two sp^2 hybridized carbons, one from an olefin and the other from a vinyl or aryl triflate. In this reaction the *syn* addition of the vinyl/aryl palladium species is followed by a β-hydride elimination. In the case of acyclic olefins, this generally results in the formation of a new double bond between the carbon bearing the palladium and the carbon to which the vinyl/aryl group added. With cyclic olefins the β-hydride elimination must occur in the other direction, since the only β-hydride on the same face of the ring as the metal is the hydrogen away from the newly formed carbon–carbon bond. This combination of events leads to the formation of a new stereogenic center (Scheme 1).



Scheme 1.



The intramolecular Heck reaction has been used by a number of workers, in particular Overman, for the synthesis of organic molecules.[5–10] In a practical sense, much less has been accomplished with the intermolecular Heck reaction. Pfaltz and Hayashi have been two of the pioneers in the development of this reaction for the formation of new asymmetric centers.[11–16] One of the ligand systems that has been relatively successful is the phosphine–oxazoline moiety (**4**).[14,15,17,18] With the success of phosphine–oxazoline ligands in this and a number of other reactions as incentive,[19–27] we have recently reported the synthesis of a new phosphine oxazoline ligand based on proline.[28] We have been investigating the use of this type of ligand in a variety of asymmetric transformations and this paper reports the use of palladium complexes of this ligand in an asymmetric variant of the Heck reaction.



Scheme 2.

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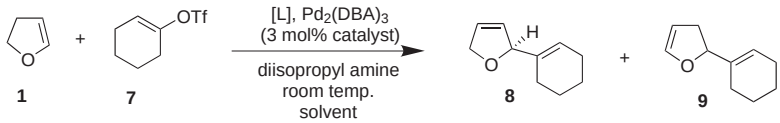
Table 1. Heck reaction in various solvents with palladium complex of ligand **5**



Entry #	Solvent	Time	% Conversion	% *ee* **8**[a]	% Isomer **9**
1	Benzene	24 h	98	80	<2
2	Toluene	2 days	84	50	4
3	Benzene/hexane	5 days	99	58	<2
4	Dioxane	36 h	99	80	<2
5	Dichloroethane	3 days	46	80	40
6	THF	3 days	88	70	5
7	Dichloromethane	6 days	52	74	24
8	Acetonitrile	3 days	52	12	33
9	NMP	20 h	99	67	5
10	DMF	2 days	80	28	4
11	DMSO	3 days	99	68	9

[a] Ratios were determined by GC with CHIRALDEX G-TA 30M 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 isomer (**9**).

Table 2. Effect of base on Heck reaction with palladium complex of ligand **5**[a]

Entry #	Base	Time	% Conversion	% *ee* **8**[b]	% Isomer (**9**)
1	$(i\text{Pr})_2\text{NEt}$	36 h	98	80[c]	<2
2	Et_3N	36 h	99	86[c]	7
3	K_2CO_3	6 days	84	60[c]	5
4	Proton sponge	6 days	69	72[c]	11
5	NaOAc	5 days	39	22[d]	2
6	*t*BuONa	4 days	66	10[c]	32
7	Bu_4NOAc	20 h	98	10[d]	<2
8	DBU	3 days	7	0	<2
9	$Me_4NOH{\cdot}5H_2O$	5 days	28	16[c]	40
10	Et_3N/Bu_4NF (1:1)	3 days	56	0	18

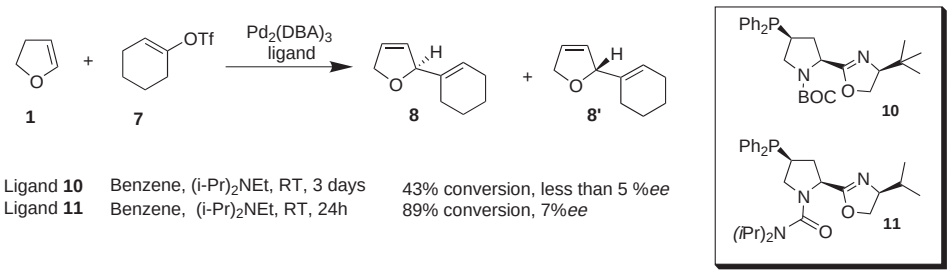
[a] All the reactions in this table were run at room temperature in benzene following the sample procedure give below.
[b] Ratios were determined by GC with CHIRALDEX G-TA 30M column at 70°C. The retention times were 24.6 min for the *S* enantiomer, 28.7 for the *R* isomer and 18.7 min for isomer (**9**).
[c] In this case major product was the *S* enantiomer.
[d] In this case the major product was the *R* enantiomer.

The reaction that was chosen to study with this ligand was the Heck reaction between dihydrofuran (**1**) and the 1-cyclohexenyl triflate (**7**) (Scheme 2). The two ligands that were initially used were our proline based phosphine oxazoline **5** and its diastereomer **6**. Comparison of these two ligands revealed that, unlike many of the phosphine–oxazoline systems reported previously, the stereochemistry of the oxazoline portion of the molecule is relatively unimportant. The reaction catalyzed by ligand **5** gave an 80% *ee*. While the reaction with ligand **6**, a diastereomer of **5**, gave the same selectivity. The proline-based system possesses three chiral centers and it appears that in the case of this ligand the orientation of the two chiral centers derived from hydroxy proline dominate the selectivity that is obtained.

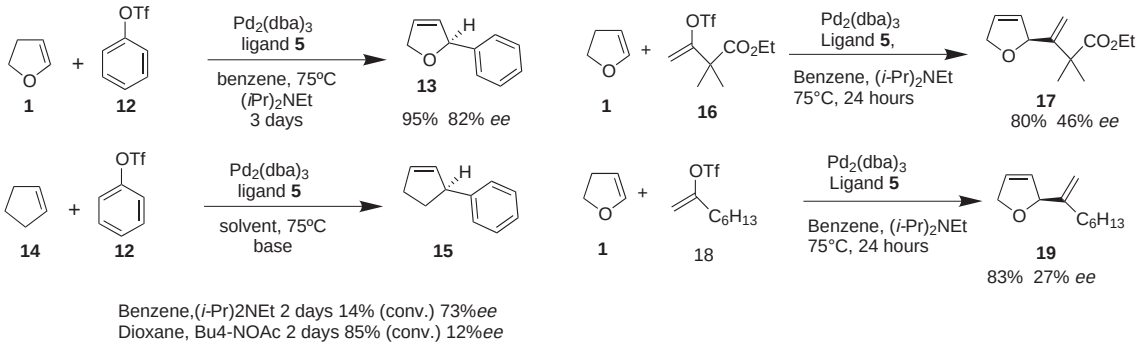
One of the fundamental problems with the intermolecular Heck reaction is the low reactivity of the known catalyst systems. In an attempt to increase both the rate of the reaction and the selectivity we embarked on a study of the effect of different solvents and different bases on this reaction. A number of solvents were examined at in an attempt to optimize the conditions for this ligand system. Table 1 illustrates that, when using diisopropylamine as the base, the best solvent appears to be either benzene or dioxane.

Table 2 illustrates that the choice of base can have a large effect on the selectivity of the reaction; with triethylamine or diisopropylethylamine being the best base in terms of selectivity of the reaction. The base Bu_4NOAc seems to increase the rate of the reaction but gives the product with little selectivity.

In addition, ligand **10** with a *t*-butyl group on the oxazoline was tested (Scheme 3). Interestingly, that ligand gave significantly lower conversion as well as lower selectivity than the ligands **5** or **6**. In the case of the ligands developed by Pfaltz the catalyst with *t*-butyl on the oxazoline gave the best selectivity and reactivity. In other reports it appears that greater steric bulk



Scheme 3.



Scheme 4.

around the metal increases the rate of the Heck reaction. With this in mind a ligand where the carbamate-protecting group on the proline nitrogen was replaced with a urea was also tested (**11**). That ligand provided a catalyst with good activity but unfortunately low selectivity.

Additional substrates were examined to determine if this ligand system is reasonably general. Reaction of aryl triflate **12** with dihydrofuran gives good selectivity and high conversion at 75°C (Scheme 4). The reaction of cyclopentene with phenyl triflate gave fair selectivity in benzene but with low conversion, while in dioxane the conversion was higher but the selectivity was low. Two acyclic triflates were also tested. Both of these molecules proceeded with good rate but gave the product in only moderate selectivity.[29]

The asymmetric Heck reaction is a transformation that has considerable promise. Once catalyst systems can be found that, perform the reaction with good selectivity, under mild conditions, and on a variety of substrates this reaction will be a valuable tool for synthetic organic chemists. This paper illustrates that this proline based system has some application in this reaction. Also the study of the reaction in different solvents and with a variety of bases should serve as a guide for others working in this area. Obtaining high selectivity in this reaction is complicated by the problem of isomerization of the double bond of the product. We have observed that the amount of isomerization can be controlled by both the solvent and the base used in this reaction.

General procedure: A mixture of triflate, alkene (5 mol equiv.), base (3 equiv.), $Pd_2(dba)_3$ (1.5 mol%) and ligand (3 mol%) in degassed solvent was stirred at the reaction temperature. The progress of the reaction was monitored by GC and TLC. Upon completion, the mixture was diluted with additional diethyl ether and washed with water and brine, dried and evaporated.

Acknowledgements

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29. The absolute stereochemistry of these two products has yet to be determined.