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Chiral Phosphite-oxazolines: A New Class of Ligands for Asymmetric Heck Reactions

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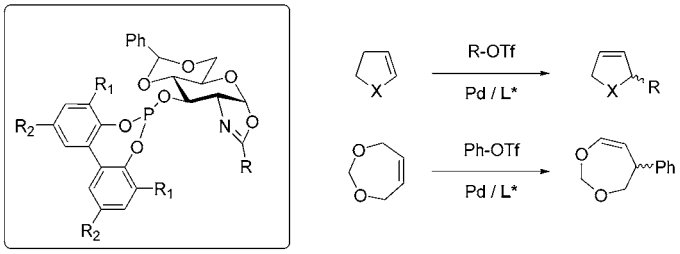
ABSTRACT



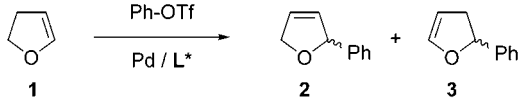
A series of phosphite-oxazoline ligands, derived from readily available D-glucosamine, have been used for the first time in the palladium-catalyzed Heck reaction of several substrates with high regio- and enantioselectivities (ee's up to 99%) and improved activities in standard conditions.

One of the main objectives in modern synthetic organic chemistry is the catalytic enantioselective formation of C−C bonds. In this respect, the asymmetric Pd-catalyzed Heck reaction coupling of an aryl or alkenyl halide or triflate to an alkene is a powerful and highly versatile procedure because it tolerates several functional groups.[1] Chiral bidentate phosphine ligands have played a key role in the success of this process. However, in the intermolecular Heck reaction, the regioselectivity is often a problem. So, for example, in the Heck reaction of 2,3-dihydrofuran **1** with phenyl triflate, a mixture of two products is obtained: the expected product 2-phenyl-2,5-dihydrofuran **2** and 2-phenyl-2,3-dihydrofuran **3** (Scheme 1). The latter is formed by an isomerization process.[1]

In the past few years, a class of heterodonor ligands, the phosphine-oxazolines, have emerged as suitable ligands for the intermolecular Heck reaction.[2] Despite this success, the ligands that provide good regio- and enantioselectivities usually have two important drawbacks: (1) the reaction times are usually long and (2) they are prepared from expensive chiral synthons. Thus, the development of ligands that induce higher rates and enantioselectivitities in this reaction is of great importance.

For this purpose, carbohydrates are particularly advantageous thanks to their low price and easy modular constructions. Although they have been successfully used in other enantioselective reactions,[3] there are only two reports on the highly enantioselective palladium-catalyzed asymmetric Heck reaction using these types of ligands.[4] In recent years,

Scheme 1



(1) For recent reviews, see: (a) Tietze, L. T.; Ila, H.; Bell, H. P. *Chem Rev.* **2004**, *104*, 3453. (b) Dai, L. X.; Tu, T.; You, S. L.; Deng, W. P.; Hou, X. L. *Acc. Chem. Res.* **2003**, *36*, 659. (c) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *44*, 3284. (d) Shibasaki, M.; Vogl E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999. (e) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schemees, N.; Pfaltz, A. *J. Organomet. Chem*. **1999**, ***576***, 16. (f) Beller, M.; Riermeier, T. H.; Stark G. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998.

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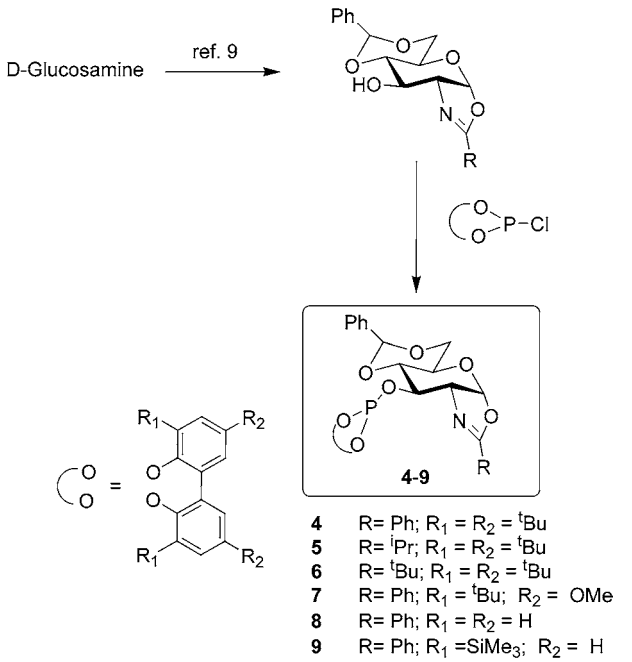
phosphite ligands have emerged as suitable ligands for many metal-catalyzed asymmetric processes.[5] Phosphite ligands are extremely attractive for catalysis because they are easy to prepare from readily available alcohols. The availability of many alcohols makes simple ligand-tuning possible, which allows the synthesis of many series of chiral ligands that can be screened for high activity and selectivity. Taking advantage of this high modularity and following our interest in carbohydrates as highly versatile and cheap raw materials, in this paper we describe a new family of phosphite-oxazoline ligands (Scheme 2) derived from natural D-glucosamine, for

Scheme 2



the highly selective Pd-catalyzed Heck reactions. These ligands provide a highly flexible ligand scaffold because they can be easily tuned in two different regions (phosphite and oxazoline substituents) to explore how they affect the catalytic performance. In addition, the presence of a phosphite moiety is advantageous because the larger π-acceptor ability of the phosphite moiety increases the reaction rates.[6]

To the best of our knowledge, this is the first example of phosphite-oxazoline ligands applied to the Heck reaction.

The synthesis of ligands **4**−**6** is straightforward (Scheme 2).[7] They are easily prepared by attaching several phosphorochloridites[8] to the hydroxy-oxazoline scaffolds.[9] The highly modular construction of these ligands enables us to easily study the effects of both the phosphite and the oxazoline moieties on catalytic activity and selectivity. By carefully selecting these elements we achieved high regio- and enantioselectivities and improved activities for several substrates.

For an initial evaluation of this new type of ligand for the palladium-catalyzed asymmetric Heck reaction, we chose the phenylation of 2,3-dihydrofuran **1** (Scheme 1). As this reaction has been carried out with a variety of ligands carrying different donor groups, it is possible to directly compare the efficacy of different ligand systems. The reactions were carried out with the palladium complex generated in situ by mixing the corresponding chiral ligand and $[Pd_2(dba)_3]\cdot dba$.[10]

In a first set of experiments, we used ligand **4** to investigate how the solvent and temperature affected the activity and selectivity of the catalyst (Table 1, entries 1−6). In all cases,

Table 1. Pd-Catalyzed Enantioselective Phenylation of 2,3-Dihydrofuran **1** Using Phosphite-oxazoline Ligands **4**−**9**[a]

entry	ligand	solvent	% conv (**2**:**3**)[b]	% ee **2**[c]	% ee **3**[c]
1	**4**	toluene	80 (85:15)	96 (*R*)	70 (*R*)
2	**4**	benzene	77 (84:16)	95 (*R*)	60 (*R*)
3	**4**	DMF	15 (71:29)	87 (*R*)	nd
4	**4**	THF	98 (87:13)	97 (*R*)	88 (*R*)
5[d]	**4**	THF	100 (80:20)	93 (*R*)	87 (*R*)
6[e]	**4**	THF	28 (88:12)	98 (*R*)	88 (*R*)
7	**5**	THF	80 (71:29)	84 (*R*)	90 (*R*)
8	**6**	THF	12 (65:35)	83 (*R*)	23 (*R*)
9	**7**	THF	86 (85:15)	97 (*R*)	89 (*R*)
10	**8**	THF	45 (60:40)	80 (*R*)	69 (*R*)
11[f,g]	**9**	THF	100 (97:3)	99 (*R*)	nd

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25×10^{-2} mmol), **1** (2.0 mmol), phenyl triflate (0.5 mmol), ligand (2.8×10^{-2} mmol), solvent (3 mL), $^{i}Pr_2NEt$ (1 mmol), T = 50 °C, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] T = 75 °C. [e] T = 25 °C, t = 67 h. [f] t = 15 h. [g] Isolated yield of **2** was 86%.

the formation of the expected product 2-phenyl-2,5-dihydrofuran **2** was favored toward the formation of 2-phenyl-2,3-dihydrofuran **3**.

Our results indicated that the solvent and the temperature each affect both the activity and selectivity of the process. The optimum tradeoff between activities and selectivities was obtained using THF as solvent and a temperature of 50 °C.

(2) See for instance: (a) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200. (b) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338. (c) Tu, T.; Hou, X. L.; Dai, L. X. *Org. Lett.* **2003**, **5**, 3651. (d) Gilbertson, S. R.; Xie, D.; Fu, Z. *J. Org. Chem.* **2001**, *66*, 7240. (e) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161.

(3) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189. (b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165. (c) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957. (d) Pàmies, O.; Diéguez, M.; Ruiz, A.; Claver, C. *Chem. Today* **2004**, 12.

(4) (a) Yonehara, K.; Mori, K.; Hashizume, T.; Chung, K. G.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **2000**, *603*, 40. (b) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184.

(5) See for instance: (a) Diéguez, M.; Pàmies O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113. (b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. In *Methodologies in Asymmetric Catalysis*; American Chemical Society: Washington, DC, 2004; Chapter 11 and references therein.

(6) van Strijdonck, G. P. F.; Boele, M. D. K.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1999**, 1073.

(7) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* In press.

(8) Phosphorochloridites are easily prepared in one step from the corresponding bisphenol as described in Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625.

(9) Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 9374.

The other ligands were compared under standard conditions (THF, 24 h, and $T = 50$ °C).

Ligands **5** and **6**, whose substituents in the oxazoline moiety are different from that of ligand **4**, showed lower activities and lower regio- and enantioselectivities than ligand **4** (Table 1, entries 7 and 8 vs 4). We thus observed that when the size of the group on the oxazoline increases, the activity, regio- and enantioselectivity of the catalyst decreases (i.e., Ph > ^{i}Pr > ^{t}Bu). This contrasts with the oxazoline-substituent effect observed for phosphine-oxazoline PHOX ligands, whose enantioselectivites are higher when bulky *tert*-butyl groups are present.[2a,b]

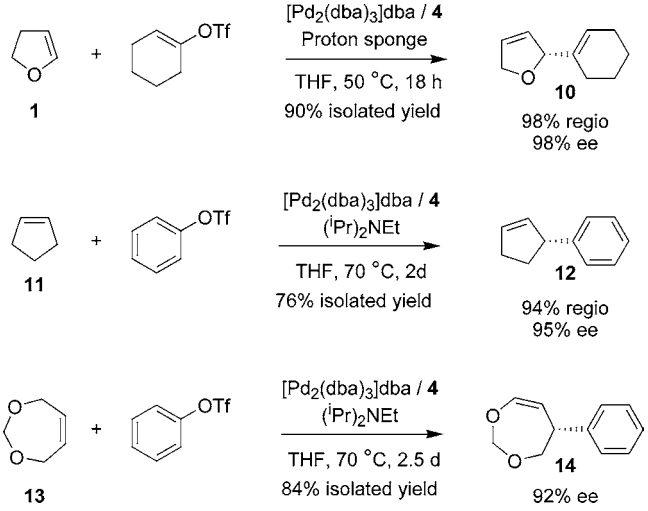
The use of ligands **4** and **7**−**9** showed that the phosphite moiety had an important effect on the activities and selectivities of the process. Ligand **7**, with methoxy groups instead of the *tert*-butyl groups in the *para* positions of the biphenyl moieties, produced slightly lower regioselectivity and lower activities than the catalytic system Pd/**4** (Table 1, entry 9 vs 4). Ligand **8**, with a unsubstituted biphenyl moiety, provided much lower activity and selectivity (regio- and enantioselectivity) (Table 1, entry 10). The use of ligand **9**, with $SiMe_3$ groups in the *ortho* position of the biphenyl moiety, showed excellent regio- and enantioselectivities combined with high activity (Table 1, entry 11).

Our results clearly show that activities, regioselectivities, and enantiomeric excesses depended strongly on both the phosphite and oxazoline substituents. Therefore, the best regio- and enantioselectivities were obtained using ligand **9**, containing trimethylsilyl groups at the *ortho* positions of the biphenyl phosphite moiety and a phenyl substituent in the oxazoline. This result is among the best reported for this type of substrate.[1]

To further study the potential of these modular and readily available ligands, we subsequently applied them in the Pd-catalyzed Heck reaction of other substrates and another triflate (Scheme 3). The best results were obtained with ligand **4**, which contains bulky substituents at the *ortho* and *para* positions of the biphenyl phosphite moiety and a phenyl substituent in the oxazoline.

Reaction of dihydrofuran **1** and 1-cyclohexenyl triflate gave an excellent result, with the coupling product **10** observed with 98% ee in high regioselectivity (98%) and activity (100% conversion in 18 h). Reaction of cyclopentene **11** and phenyl triflate at 70 °C gave the coupling product **12** with 94% ee in 100% conversion, together with small amounts of achiral 4-phenylcyclopentene. Reaction of phenyl triflate and 4,7-dihydro-1,3-dioxepin **13** also proceeded with high enantioselectivity (92%) and good activity. These results compete favorably with the best ligands developed for these substrates.[1]

Scheme 3



In summary, we have described the first application of phosphite-oxazoline ligands in asymmetric Heck reactions. These ligands can be prepared in a few steps from commercial D-glucosamine as an inexpensive natural chiral source. We found that the degree of isomerization and the effectiveness in transferring the chiral information in the product and the activity can be tuned by suitable choice of the ligand components (phosphite and oxazoline substituents). These ligands compete favorably with the most successful ligands developed for this reaction.[1] Note also that these ligands provided higher activities than those for other successful ligands. These facts together with the low cost of the ligands make these catalyst systems highly attractive for further research. These results open up a new class of ligands for the enantioselective Pd-catalyzed Heck reaction, which will be of great practical interest. For example, phosphites are less sensitive to oxidation than phosphines. Moreover, because of the modular construction of phosphite-oxazoline ligands, structural diversity is easy to achieve, so activities and regio- and enantioselectivity can be maximized for each new substrate as required.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and elemental analysis for compounds **4**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **Typical Procedure.** A mixture of $[Pd_2(dba)_3]dba$ (1.25×10^{-2} mmol) and the chiral ligand (2.8×10^{-2} mmol) in dry degassed solvent (3.0 mL) was stirred under argon at room temperature for 15 min. The corresponding triflate (0.50 mmol), base (1.0 mmol), and olefin (2.0 mmol) were added to the catalyst solution. The solution was stirred at the desired temperature under argon. After the desired reaction time, the mixture was diluted with additional diethyl ether and washed with water, dried over $MgSO_4$, and evaporated. Conversion and enantiomeric excesses were determined by gas chromatography with a Chiraldex G-TA column following ref 2e.