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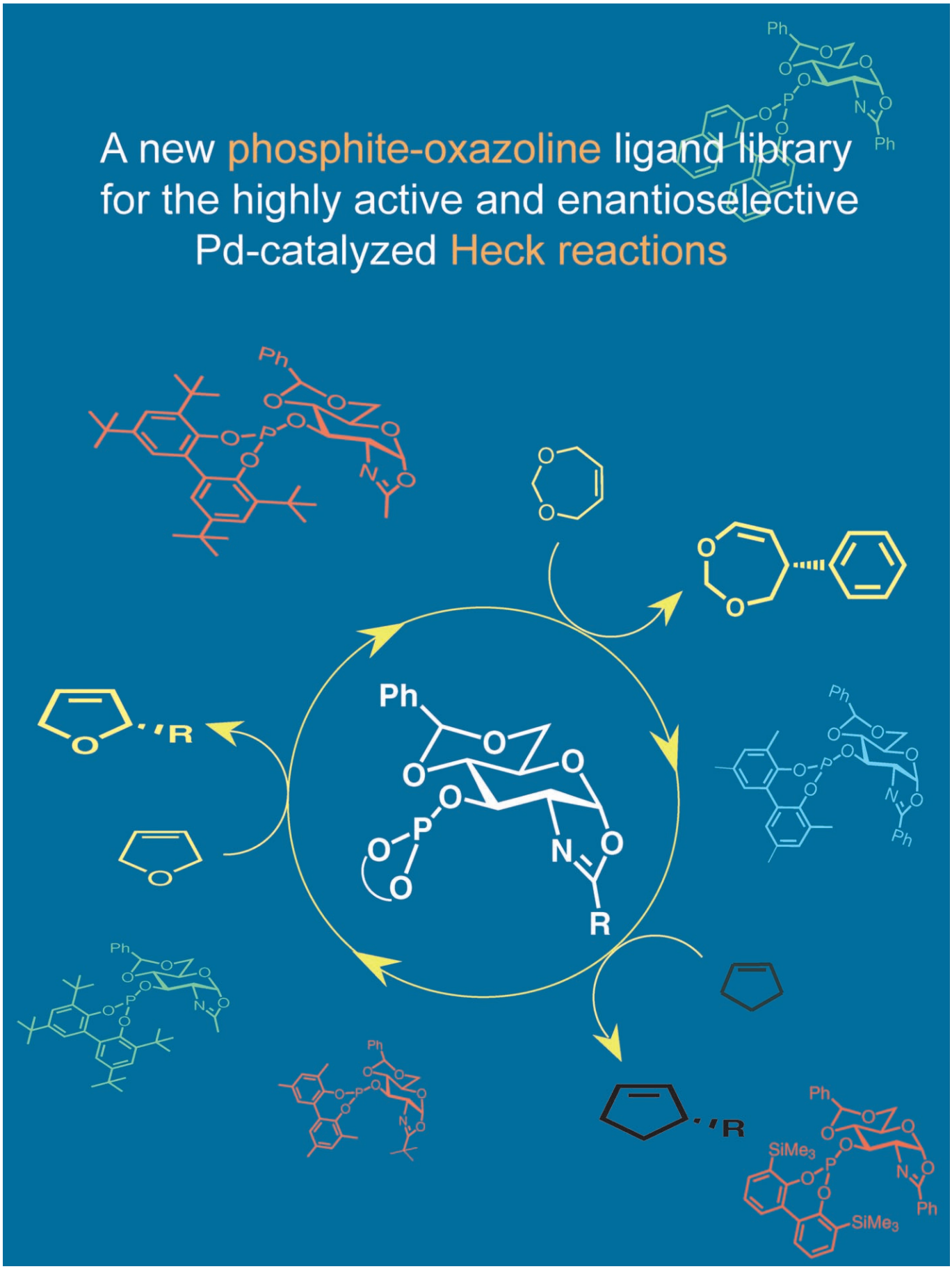
A new phosphite-oxazoline ligand library for the highly active and enantioselective Pd-catalyzed Heck reactions



Screening of a Modular Sugar-Based Phosphite–Oxazoline Ligand Library in Asymmetric Pd-Catalyzed Heck Reactions

Yvette Mata, Oscar Pàmies,* and Montserrat Diéguez*[a]

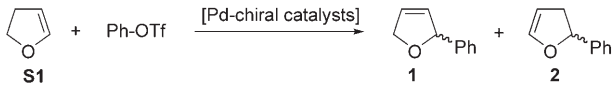
Abstract: We have synthesised a library of phosphite–oxazoline ligands derived from readily available D-glucosamine. These ligands have been successfully screened in the palladium-catalysed Heck reaction of several substrates with high regio- (up to 99%) and enantioselectivities (*ee*'s up to 99%) as well as with improved activities under standard thermal conditions. The results indicate that the catalytic performance is highly affected by the oxazoline and biarylphosphite substituents and the axial chirality of the biaryl moiety of the ligand. The Heck reactions were also performed under microwave irradiation conditions, allowing a considerably shorter reaction time (full conversion in minutes) maintaining the excellent regio- and enantioselectivities.

Keywords: asymmetric catalysis · Heck reaction · P,N ligands · palladium

Introduction

Catalytic asymmetric carbon–carbon bond formation is one of the most actively pursued areas of research in the field of asymmetric catalysis. In this respect, the asymmetric Pd-catalysed Heck reaction, that is, the 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.[1] However, in the intermolecular Heck reaction, regioselectivity is often a problem. So, for example, in the Heck reaction of 2,3-dihydrofuran **S1** with phenyl triflate, a mixture of two products is obtained—the expected product 2-phenyl-2,5-dihydrofuran (**1**) and 2-phenyl-2,3-dihydrofuran (**2**; Scheme 1). The latter is formed due to an isomerisation process.[1]

In the last few years, a class of heterodonor ligands—the phosphanyloxazoline ligands—have emerged as suitable ligands for the intermolecular Heck reaction.[2] Two of the most representative examples of this type of ligands are the phosphanyloxazoline PHOX ligands developed by Pfaltz[2a,b] and co-workers and the phosphanyloxazoline based on ketopinic acid developed by Gilbertson and co-workers.[2e] Despite these successes, ligands that provide good regio- and enantioselectivities usually have two considerable drawbacks: 1) reaction times are usually long and 2) they are prepared from expensive chiral synthons or in tedious synthetic steps (Scheme 2). Therefore, it is very important to develop ligands that induce higher rates and selectivities (regio- and enantioselectivities) based on simple starting materials in this reaction. Carbohydrates are particularly advantageous for this purpose due to their low price and easy modular construction.



S1 1 2

Scheme 1. Model Pd-catalysed Heck reaction of 2,3-dihydrofurane **S1**.

In this context, to further expand the range of ligands and to improve the performance of these asymmetric Pd-catalysed Heck reactions, we designed a library of chiral phosphite–oxazoline ligands **L1–L4a–g**. These ligands are derived from natural D-glucosamine and have the advantages of carbohydrate and phosphite ligands, such as availability at a low price from readily available alcohols and facile modular constructions.[3] Furthermore, they are less sensitive to air than typical phosphanes, which are widely used as li-

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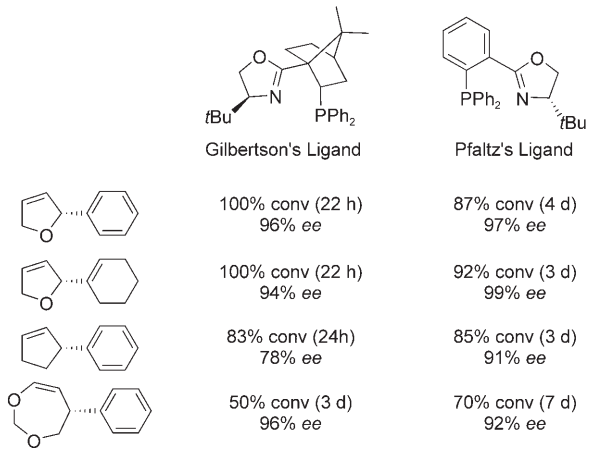
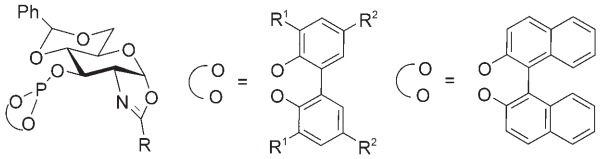
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. It contains the results for the catalytic arylation and cyclohexenylation of **S1** and **S2** and the temperature, power and pressure versus time profiles for the microwave experiments are included.



Scheme 2. Summary of the best results using the most representative ligand families developed for the Pd-catalysed Heck reactions (reactions usually carried out with 3–5 mol% of Pd).

gands in asymmetric catalysis. In addition, the introduction of a phosphite moiety in the ligand design has proved to be highly advantageous in terms of activity because of its greater π-acceptor ability.[4] All these favourable features have enabled us to synthesise and screen a series of chiral ligands in the search for high activity and selectivity. Although carbohydrate-based ligands have been successfully used in other enantioselective reactions,[3] there are only two reports on the enantioselective palladium-catalysed asymmetric Heck reaction using this type of ligand.[5]

In this paper, we report on the design of a library of 28 potential sugar-based chiral phosphite–oxazoline ligands and screen their use in the Pd-catalysed asymmetric Heck reaction of several substrates and triflate sources.[6] The synthesis and screening of the library were performed by using a series of parallel reactors each equipped with 12 different positions. With this library we fully investigated the effects of systematically varying the electronic and steric properties of the oxazoline substituents (**L1–L4**) and different substituents/configurations in the biaryl phosphite moiety (**a**–**g**). By carefully selecting these elements, we achieved high selectivities (regio- and enantioselectivities) and activities in different substrate types and aryl sources.



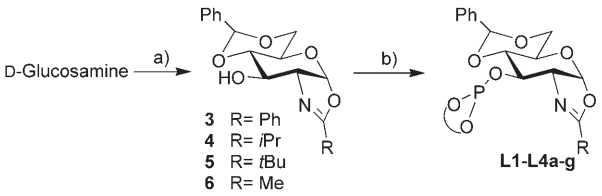
L1 R= Ph
L2 R= *i*Pr
L3 R= *t*Bu
L4 R= Me

a $R^1 = R^2 = t$Bu
b $R^1 = t$Bu; R^2 = OMe
c R^1 =$SiMe_3$; R^2 = H
d $R^1 = R^2$ = Me
e $R^1 = R^2$ = H

f $(S)^{ax}$
g $(R)^{ax}$

Results and Discussion

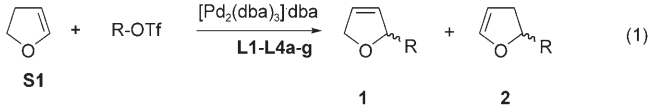
Synthesis of ligands: Ligands **L1**–**L4a**–**g** were efficiently synthesised in one step through the reaction of the corresponding sugar oxazoline alcohols (**3**–**6**) with one equivalent of the corresponding phosphorochloridite (**a**–**g**) in the presence of pyridine (Scheme 3). Oxazoline alcohols **3**–**6** are easily



Scheme 3. Synthesis of phosphite-oxazoline ligand library **L1**– **L4a-g**. a) Ref. 7. b) 1 equiv of $ClP(OR)_2$/Toluene/Py at 80 °C.

prepared on a large scale from D-glucosamine.[7] All the ligands were stable during purification on neutral alumina under an atmosphere of argon and were isolated as white solids. They are stable at room temperature and very stable to hydrolysis. The elemental analyses were in agreement with the assigned structures. The ^{1}H and ^{13}C NMR spectra agree with those expected for these C_1 ligands. One singlet was observed in the ^{31}P NMR spectrum. Rapid ring inversions (atropoisomerisation) in the biphenyl-phosphorus moieties occurred on the NMR timescale, since the expected diastereoisomers were not detected by low-temperature phosphorus NMR spectroscopy.[8]

Asymmetric Heck reactions under thermal conditions—Heck reaction of 2,3-dihydrofuran S1: In this section, we report the use of the chiral phosphite–oxazoline ligand library **L1–L4a–g** in the Pd-catalysed asymmetric Heck reaction of 2,3-dihydrofuran **S1** [Eq. (1)] by using several triflates with different electronic and steric properties: phenyl triflate, 1-naphthyl triflate, toluyl triflate, *para*-nitrophenyl triflate and cyclohexenyl triflate. In all cases, the catalysts were generated in situ by mixing $[Pd_2(dba)_3]$·dba with the corresponding chiral ligand.



(1)

*Heck reaction of 2,3-dihydrofuran **S1** with phenyl triflate [Eq. (1)]*: For an initial evaluation of this new type of ligand in the palladium-catalysed asymmetric Heck reaction, we chose the phenylation of **S1** [Eq (1); R = C_6H_5]. 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.

In a first set of experiments, we determined the optimal reaction conditions by conducting a series of experiments in which we varied the solvent, temperature and base. In all cases, the formation of the desired product 2-phenyl-2,5-dihydrofuran **1** was favoured over the formation of 2-phenyl-2,3-dihydrofuran **2**.

We first studied the effect of the solvent. Four solvents (tetrahydrofuran (THF), benzene, toluene and dimethylformamide (DMF)) and four ligands (**L1a**, **L2a**, **L3a** and **L4a**) were tested. The results show that the efficiency of the process strongly depended on the nature of the solvent (Figure 1). The best activity and selectivity (regio- and enantioselectivity) was achieved with tetrahydrofurane as the solvent.

We next studied the effect of varying the temperature. The conversion and selectivity when THF was used as a solvent and ligands **L1a** and **L4a** are shown in Table 1 (similar tendencies were observed with other solvents and ligands). We observed that this parameter affected both activity and selectivity. Increasing the temperature from 50 °C to 75 °C had a negative effect on regio- and enantioselectivity (entries 1 and 4 versus 2 and 5). Lowering the temperature to 25 °C hardly affected regio- and enantioselectivity, but activities dropped considerably (entry 1 and 3 versus 4 and 6). The best trade-off between activity and selectivity was therefore achieved at 50 °C.

We then studied the effect of several bases. The conversion and selectivity when THF was used as a solvent with ligands **L1a** and **L4a** are shown in Table 2 (similar trends were observed for the other solvents and ligands). Although the activities and regioselectivities obtained with proton sponge (PS) and diisopropylethylamine are comparable, the use of the latter base provides slightly better enantioselectivities (entries 1 and 9 versus 2 and 10). On the other hand, sodium acetate yielded the highest regioselectivity, but its activities and enantioselectivities are lower than those of diisopropylethylamine (entries 1 and 9 versus 3 and 11). The remainder of the bases tested provided lower activities and selectivities than those obtained with diisopropylamine (entries 1 and 9 versus 4–8, 12 and 13). In conclusion we chose diisopropylethylamine as our base.

In the end we found that, the optimum trade-off between selectivities and reaction rates was achieved with tetrahydrofuran, a temperature of 50 °C and diisopropylethylamine as a base. These optimal conditions were then used to test the catalytic performance of the complete series of ligands. The results, which are summarised in Table 3, indicate that the catalytic performance (activity and selectivity) is highly affected by the substituents at both oxazoline and phosphite moiety and by the axial chirality of the biaryl phosphite moiety. In general, high activities, regio- (up to 98 %) and enantioselectivities (*ee*'s up to 99 %) were obtained in the phenylation of **S1**.

The effect of the oxazoline substituent was studied with ligands **L1a, L2a, L3a, L4a** (Table 3, entries 1, 8–10). We found that these substituents affected both activities and selectivities. Therefore, we observed that when the size of the group on the oxazoline decreased, the regio- and enantioselectivity of the catalyst increased (i.e., Me > Ph > *i*Pr > *t*Bu). This contrasts with the oxazoline-substituent effect observed for phosphanyloxazoline PHOX ligands, the enantioselectivites of which are higher when bulky *tert*-butyl groups are present.[2a,b] In terms of activity, this is mainly affected by the bulkiness of the oxazoline group. Therefore, activity decreases when bulky substituents are present (Table 3, en-

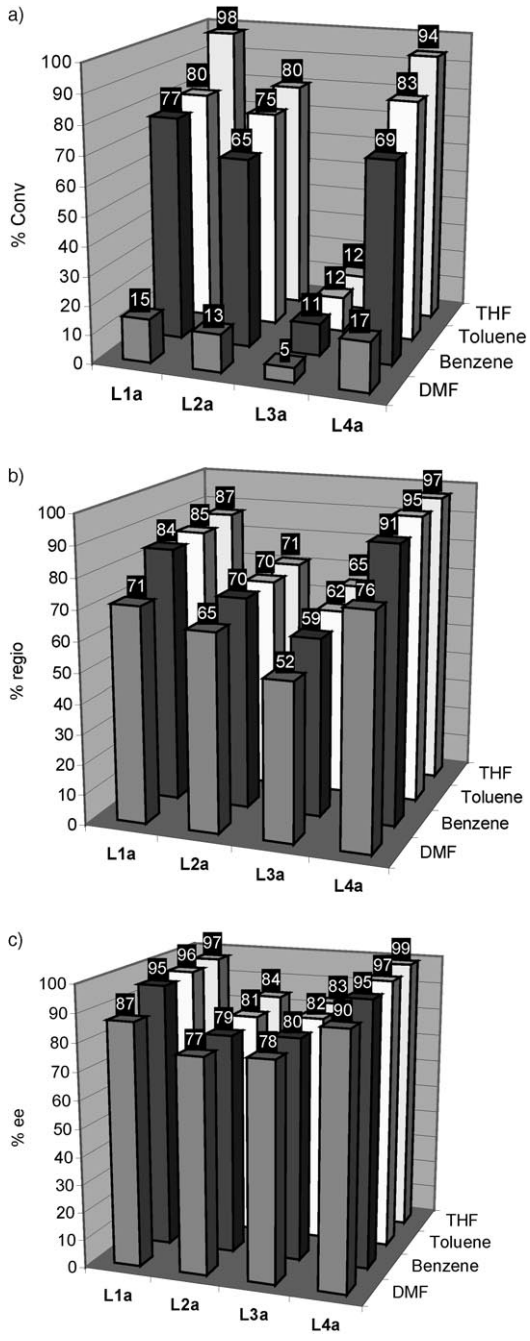


Figure 1. Results of the catalytic phenylation of **S1** by using ligands **L1a**, **L2a**, **L3a** and **L4a** in four solvents at 50 °C and using $i\mathrm{Pr}_2\mathrm{NEt}$ as base. a) Conversions after 24 h. b) Regioselectivities in product **1**. c) Enantioselectivities of product **1**. Positive numbers refer to the formation of the *R*-isomer in excess.

Table 1. Selected results for the Pd-catalysed enantioselective phenylation of **S1** using ligands **L1a** and **L4a**. Effect of temperature.[a]

	Ligand	T [°C]	conv [%] (**1**:**2**)[b]	*ee* [%] **1**[c]	*ee* [%] **2**[c]
1	**L1a**	50	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1a**	75	100 (80:20)	93 (*R*)	87 (*R*)
3	**L1a**	25	28 (88:12)	98 (*R*)	88 (*R*)
4	**L4a**	50	94 (97:3)	99 (*R*)	nd[d]
5	**L4a**	75	100 (91:9)	94 (*R*)	91 (*R*)
6	**L4a**	25	29 (97:3)	99 (*R*)	nd[d]

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), iPr$_2$NEt (1 mmol), $t=24$ h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] Not determined.

Table 2. Selected results for the Pd-catalysed enantioselective phenylation of 2,3-dihydrofuran **S1** using ligands **L1a** and **L4a**. Effect of the base.[a]

	Ligand	Base	conv [%] (**1**:**2**)[b]	*ee* [%] **1**[c]	*ee* [%] **2**[c]
1	**L1a**	iPr$_2$NEt	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1a**	PS	99 (87:13)	95 (*R*)	87 (*R*)
3	**L1a**	NaOAc	91 (91:9)	91 (*R*)	56 (*R*)
4	**L1a**	NEt_3	97 (82:18)	87 (*R*)	84 (*R*)
5	**L1a**	KOAc	53 (82:18)	43 (*R*)	47 (*R*)
6	**L1a**	K_2CO_3	89 (86:14)	88 (*R*)	27 (*R*)
7	**L1a**	Li_2CO_3	92 (68:32)	95 (*R*)	92 (*R*)
8	**L1a**	DBU	6 (72:28)	65 (*R*)	43 (*R*)
9	**L4a**	iPr$_2$NEt	94 (97:3)	99 (*R*)	nd[d]
10	**L4a**	PS	94 (96:4)	98 (*R*)	nd[d]
11	**L4a**	NaOAc	89 (98:2)	92 (*R*)	nd[d]
12	**L4a**	NEt_3	93 (88:12)	95 (*R*)	89 (*R*)
13	**L4a**	KOAc	62 (84:16)	57 (*R*)	38 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), base (1 mmol), $T=50$ °C, $t=24$ h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] Not determined.

Table 3. Selected results for the Pd-catalysed enantioselective phenylation of 2,3-dihydrofuran **S1** by using phosphite–oxazoline ligand library **L1–L4a–g**.[a]

	Ligand	conv [%] (**1**:**2**)[b]	*ee* [%] **1**[c]	*ee* [%] **2**[c]
1	**L1a**	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1b**	86 (85:15)	97 (*R*)	89 (*R*)
3[d]	**L1c**	100 (97:3)	99 (*R*)	nd[e]
4	**L1d**	42 (72:28)	25 (*R*)	16 (*R*)
5	**L1e**	45 (60:40)	80 (*R*)	69 (*R*)
6	**L1f**	32 (58:42)	6 (*R*)	19 (*R*)
7	**L1g**	28 (55:45)	73 (*R*)	48 (*R*)
8	**L2a**	80 (71:29)	84 (*R*)	90 (*R*)
9	**L3a**	12 (65:35)	83 (*R*)	23 (*R*)
10	**L4a**	94 (97:3)	99 (*R*)	nd[e]
11	**L4c**	100 (98:2)	99 (*R*)	nd[e]

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), solvent (3 mL), iPr$_2$NEt (1 mmol), T = 50 °C, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] $t=15$ h. [e] Not determined.

tries 8 and 9 versus 1 and 10). However, the electronic properties of the oxazoline substituent have a slight, but important effect on activity. Activities are therefore highest when a phenyl oxazoline moiety is present (Table 3, entries 1 versus 10).

The effects of phosphite moieties were studied using ligands **L1a–g** (Table 3, entries 1–7). We found that this moiety affected both activity and selectivity. Bulky substituents in the *ortho* positions of the biphenyl moiety are needed for high activities as well as high regio- and enantioselectivities. Thus, ligands **L1a–c** with bulky substituents at the *ortho* positions of the biphenyl moiety provided higher activities and selectivities than ligands **L1d** and **L1e** with small substituents in these positions (Table 3, entries 1–3 versus 4–5). However, substituents in the *para* positions also play a small but crucial role. Therefore, the best activities and selectivities were obtained by using ligand **L1c**, which contains bulky trimethylsilyl groups at the *ortho* positions and a hydrogen atom at the *para* positions of the biphenyl moiety. To further investigate how enantioselectivity was influenced by the groups attached to the biaryl moiety, ligands **L1f** and **L1g** containing different enantiomerically pure binaphthyl moieties were also tested (Table 3, entries 6 and 7). The results indicate that there is a cooperative effect between the configuration of the biaryl moiety and the configurations of the ligand backbone on enantioselectivity that results in a matched combination for ligand **L1g**, which contains an (*R*)-binaphthyl moiety.

To sum up, the best result was obtained with ligand **L4c**, which contains the optimal combination of substituents in the oxazoline and in the biaryl phosphite moieties (entry 11). These results clearly show the efficiency of using highly modular scaffolds in the ligand design. In addition, comparing these excellent results with the activities obtained with Pfaltz's and Gilberston's ligand Pd-systems (Scheme 2) in the phenylation of **S1** we can conclude that the presence of a phosphite moiety in ligands **L1–L4a-g** has been highly advantageous. These results are among the best reported so far.[2a,b,e]

*Heck reaction of 2,3-dihydrofuran **S1** with other aryl triflate [Eq. (1)]*: To further study the effects of electronic and steric properties of the aryl triflate source on the product outcome, we tested these new ligands in the Pd-catalysed Heck reaction of **S1** with several aryl triflates, in which these properties were systematically varied [Eq. (1), R = 1-naphthyl, p-CH_3-C_6H_4, p-NO_2-C_6H_4]. The most noteworthy results are shown in Table 4. They followed the same trend in terms of the effect of the oxazoline and phosphite moieties as the phenylation of **S1** (see Supporting Information). In general, high activities, regio- (up to 99%) and enantioselectivities (*ee*'s up to 99%) were also obtained in the arylation of **S1**. The results indicate that both steric and electronic parameters on the triflate affected catalytic performance. Thus, enantioselectivities are best for 1-naphthyl- and phenyltriflate (Table 4, entries 1, 2, 5, 6, 9 and 10). On the other hand regioselectivities are better when electron-withdrawing aryl triflates are used (Table 4, entries 4, 8, 12).

*Heck reaction of 2,3-dihydrofuran **S1** with cyclohexenyl triflate [Eq. (1)]*: We also evaluated the ligand library in the Heck reaction of **S1** with cyclohexenyl triflate. The prelimi-

Table 4. Selected results for Pd-catalysed enantioselective arylation of 2,3-dihydrofuran **S1** using ligands **L1a**, **L1c** and **L4a**.[a]

	Ligand	R	conv [%] (**1**:**2**)[b]	*ee* [%] **1**[c]	*ee* [%] **2**[c]
1	**L1a**	C_6H_5	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1a**	1-naphthyl	88 (86:14)	97 (*R*)	89 (*R*)
3	**L1a**	*p*-CH_3-C_6H_4	99 (82:18)	94 (*R*)	91 (*R*)
4	**L1a**	*p*-NO_2-C_6H_4	94 (95:5)	88 (*R*)	nd[f]
5[e]	**L1c**	C_6H_5	100 (97:3)	99 (R)	nd[f]
6[e]	**L1c**	1-naphthyl	89 (95:5)	99 (*R*)[d]	93 (*R*)
7[e]	**L1c**	*p*-CH_3-C_6H_4	94 (85:15)	96 (*R*)	93 (*R*)
8[e]	**L1c**	*p*-NO_2-C_6H_4	89 (>99:1)	90 (*R*)	nd[f]
9	**L4a**	C_6H_5	94 (97:3)	99 (*R*)	nd[f]
10	**L4a**	1-naphthyl	85 (95:5)	99 (*R*)	nd[f]
11	**L4a**	*p*-CH_3-C_6H_4	95 (87:13)	96 (*R*)	89 (*R*)
12	**L4a**	*p*-NO_2-C_6H_4	87 (>99:1)	91 (*R*)	nd[f]

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), aryl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), iPr$_2$NEt (1 mmol), T = 50 °C, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] Enantiomeric excesses measured by HPLC. [e] t = 15 h. [f] Not determined.

nary investigations performed on the solvent and base effect revealed a different trend regarding the base effect than those with the previously tested aryl triflates. Therefore, the best selectivities (regio- and enantioselectivities) and reaction rates were obtained when THF and proton sponge were used as a solvent and base, respectively (see Supporting Information).

The results of using ligands **L1–L4a--g** under the optimised conditions are shown in Table 5. In general, high activities, regio- (up to 98%) and enantioselectivities (*ee*'s up to 98%) were also obtained in this case. Again enantioselectivity was affected by the substituents at both oxazoline and phosphite moiety and the cooperative effect between stereocenters. However, the effect of these parameters was different from those observed in the arylation of **S1**. Thus, regio- and enantioselectivities were best with ligand **L1a** (regioselectivity up to 98%, *ee*'s up to 98%). These results clearly show the importance of using modular scaffolds in the ligand design.

Regarding the effect of the oxazoline substituents, again the presence of bulky substituents in this position considerably decreased activities and selectivities (Table 5, entries 1, 8–10). However, in contrast to the arylation of **S1**, the electronic effect was more important. Therefore, selectivities are higher when a phenyl substituent is present (Table 5, entry 1 versus 10).

Concerning the effect of the phosphite moiety on catalytic performance, again the presence of bulky substituents in the *ortho* positions of the biphenyl moiety was necessary for high selectivities. However, the effect of the type of substituents at the *para* positions in selectivity is more pronounced than for the arylation of **S1**. Thus, whereas good selectivities are obtained with ligands **L1a** and **L1c**, regioselectivity dropped considerably for ligand **L1b**, which contains methoxy groups at the *para* positions (Table 5, entries 1 and 3 versus 2).

Finally, the effect of the configuration of the biaryl phosphite moiety follows a similar trend as those with the previous arylation of **S1** (Table 5, entries 6 and 7).

Asymmetric Heck reactions under thermal conditions—Heck reaction of cyclopentene S2 [Eq. (2)]: We also screened the phosphite–oxazoline ligand library in the phenylation and alkenylation of cyclopentene **S2** [Eq. (2)]. Selectivity for **S2** is more difficult to control than for functionalised alkenes such as **S1**, due to extensive double-bond migration.[1] Moreover, in addition to the desired product **7**, regioisomer **8** and the achiral product **9** can also be obtained. Therefore, to date only high regio- (regioselectivity up to 96% in product **7**) and enantioselectivities (*ee*'s up to 91%) have been obtained with the phosphanyloxazoline PHOX ligands developed by Pfaltz and co-workers.[2a,b]

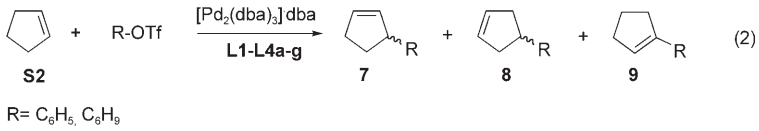


Table 5. Selected results for the Pd-catalysed enantioselective cyclohexenylation of 2,3-dihydrofuran **S1** using ligands **L1–L4a–g**.[a]

	Ligand	conv [%] (**1**:**2**)[b]	*ee* [%] **1**[c]	*ee* [%] **2**[c]
1	**L1a**	100 (98:2)	98 (*R*)	nd[d]
2	**L1b**	88 (80:20)	96 (*R*)	36 (*R*)
3	**L1c**	100 (92:8)	97 (*R*)	52 (*R*)
4	**L1d**	99 (74:26)	82 (*R*)	76 (*R*)
5	**L1e**	57 (58:42)	45 (*R*)	32 (*R*)
6	**L1f**	42 (55:45)	12 (*R*)	9 (*R*)
7	**L1g**	38 (53:47)	38 (*R*)	9 (*R*)
8	**L2a**	94 (84:16)	98 (*R*)	45 (*R*)
9	**L3a**	44 (51:49)	77 (*R*)	5 (*R*)
10	**L4a**	100 (88:12)	95 (*R*)	56 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), cyclohexyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), proton sponge (1 mmol), T = 50 °C, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] Not measured.

In this section, we report that the chiral phosphite–oxazoline ligands **L1–L4a–g** applied in the previous section to the Pd-catalysed arylation and alkenylation of substrate **S1**, can also be used for unfunctionalised alkene substrate **S2**. In this case, two triflate sources were used [Eq. (2)]: phenyl triflate and cyclohexenyl triflate. In general, high activities and selectivities (regioselectivity up to 94% and *ee*'s up to 96%) were obtained in the phenylation and cyclohexenylation of **S2**. Interestingly, the formation of achiral product **9** did not take place. These results compete favourably with the best reported in the literature.[2a,b]

Preliminary investigations into the solvent and base effects revealed the same trends as those with the previously tested substrate **S1** with aryltriflate. The trade-off between selectivities and reaction rates was optimum with THF as

solvent and diisopropylthylamine as base (see Supporting Information).

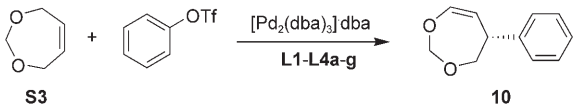
The results of using the phosphite–oxazoline ligand library under the optimised conditions are shown in Table 6. In general, they follow the same trends as for the alkenylation of **S1**. Although, as expected, the activities were lower than in the alkenylation of **S1**, they were much higher than those obtained with the most successful ligand system.[2a,b] Again, the presence of a phosphite moiety in the ligand design has been highly advantageous in terms of activity and enantioselectivity.

Table 6. Selected results for Pd-catalysed enantioselective phenylation and cycloalkenylation of cyclopentene **S2** using ligands **L1–L4a-g**.[a]

	Ligand	R	conv [%] (**7**:**8**)[b]	*ee* [%] **7**[c]	*ee* [%] **8**[c]
1	**L1a**	C_6H_5	100 (94:6)	95 (*R*)	nd[d]
2	**L1b**	C_6H_5	98 (85:15)	94 (*R*)	66 (*R*)
3	**L1c**	C_6H_5	100 (92:8)	95 (*R*)	82 (*R*)
4	**L1d**	C_6H_5	93 (79:21)	75 (*R*)	57 (*R*)
5	**L1e**	C_6H_5	47 (51:49)	44 (*R*)	34 (*R*)
6	**L1f**	C_6H_5	42 (45:55)	12 (*R*)	9 (*R*)
7	**L1g**	C_6H_5	44 (52:48)	45 (*R*)	42 (*R*)
8	**L2a**	C_6H_5	94 (86:14)	87 (*R*)	68 (*R*)
9	**L3a**	C_6H_5	34 (49:51)	59 (*R*)	11 (*R*)
10	**L4a**	C_6H_5	100 (93:7)	94 (*R*)	86 (*R*)
11	**L1a**	C_6H_9	100 (95:5)	96 (*R*)	nd[d]
12	**L1b**	C_6H_9	94 (83:17)	95 (*R*)	67 (*R*)
13	**L1c**	C_6H_9	100 (93:7)	96 (*R*)	78 (*R*)
14	**L1d**	C_6H_9	100 (78:22)	82 (*R*)	79 (*R*)
15	**L1e**	C_6H_9	45 (54:46)	51 (*R*)	60 (*R*)
16	**L1f**	C_6H_9	41 (52:48)	11 (*R*)	5 (*R*)
17	**L1g**	C_6H_9	47 (53:47)	49 (*R*)	16 (*R*)
18	**L2a**	C_6H_9	98 (85:15)	93 (*R*)	89 (*R*)
19	**L3a**	C_6H_9	56 (63:37)	61 (*R*)	18 (*R*)
20	**L4a**	C_6H_9	100 (92:8)	94 (*R*)	89 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S2** (2.0 mmol), triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), iPr$_2$NEt (1 mmol), $T=70$ °C, $t=48$ h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] Not determined.

Asymmetric Heck reactions under thermal conditions—Heck reaction of 4,7-dihydro-1,3-dioxepin S3 [Eq. (3)]: Encouraged by the excellent results obtained for the arylation and alkenylation of 2,3-dihydrofuran **S1** and cyclopentene **S2**, we also examined the phenylation of 4,7-dihydro-1,3-dioxepin **S3** [Eq. (3)]. This substrate is of great importance, since the resulting enol ethers **10** are easily converted to chiral β-aryl-γ-butyrolactones, which are useful synthetic intermediates.[9] Despite this interesting characteristic, there are only few reports that study this substrate.[2a,b,e,h] An important drawback for this substrate is that the catalysts developed to date proceed at low reaction rates (i.e., the reaction takes typically 5 to 7 days for full conversion).[2a,b,e,h]



S3 10 (3)

Interestingly, under non-optimised conditions, our new ligands also proved to be highly efficient in terms of activity and enantioselectivity in the phenylation of **S3** (Table 7).

Table 7. Selected results for the Pd-catalysed enantioselective phenylation of **S3** using ligands **L1–L4a–g**.[a]

	Ligand	conv [%][b]	% *ee* [%] **10**[c]
1	**L1a**	100	92 (*R*)
2	**L1b**	98	88 (*R*)
3[d]	**L1c**	100	92 (*R*)
4	**L2a**	95	75 (*R*)
5	**L3a**	54	61 (*R*)
6	**L4a**	100	90 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S3** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), iPr$_2$NEt (1 mmol), $T=70$ °C, $t=2.5$ days. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] $t=2$ days.

The results indicated that enantioselectivities and activities are mainly affected by the steric properties of the oxazoline substituents. We found that when the size of the group on the oxazoline increased, activity and enantioselectivity of the catalyst decreased (entries 1 versus 4 and 5). The highest enantioselectivities (*ee*'s up to 92%) and activities were obtained using ligands **L1a** and **L1c**. In addition, comparing these excellent results with the activities obtained with Pfaltz's and Gilbertson's ligand Pd-systems (Scheme 2) in the phenylation of **S3**, we can conclude that the presence of a phosphite moiety has been highly advantageous. These results are among the best reported so far.[2a,b,e]

Microwave-assisted asymmetric Heck reactions: The benefits of microwave irradiation, including reduction of reaction rates and electricity costs, have already been reported in several C–C coupling reactions.[10] Therefore, we decided to use the advantages of microwave irradiation in the asymmetric Pd-catalysed Heck reactions using the ligand library **L1–L4a–g**. To the best of our knowledge there is only one report on the use of microwave irradiation for the enantioselective Heck reactions by using Pfaltz's PHOX and BINAP ligands. Under optimal reaction conditions they considerably shortened reaction times (from 4 days to 1 hour) but enantioselectivities were lower compared to those obtained under thermal conditions.[11]

As an initial evaluation we studied the Pd-catalysed asymmetric Heck reaction of substrate **S1** using two different triflate sources (phenyl triflate and cyclohexenyl triflate) with ligands **L1a** and **L1c** (Table 8). After studying three different temperatures, we found that the optimal temperature was 70 °C. At lower temperatures, activities and selectivities decreased (entries 3 and 6 versus 1, 2, 4 and 5).

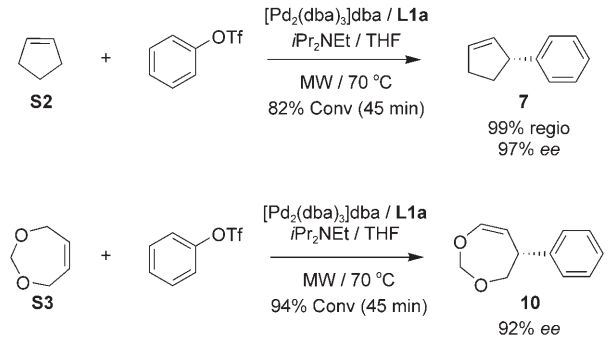
It is interesting to note that under microwave irradiation, reaction times have been dramatically improved (from 15 h to 10 minutes) while maintaining the excellent regio- (up to 98%) and enantioselectivities (*ee*'s up to 99%) obtained under thermal conditions.

Table 8. Microwave-assisted Pd-catalysed enantioselective arylation and alkenylation of 2,3-dihydrofuran **S1** using ligands **L1a** and **L1c**.[a]

	Ligand	R	T [°C]	t [min]	conv [%] (**1**:**2**)[b]	*ee* [%] **1**[c]
1	**L1a**	C_6H_5	50	15	81 (96:4)	93 (*R*)
2	**L1a**	C_6H_5	40	15	12 (94:6)	91 (*R*)
3	**L1a**	C_6H_5	70	10	99 (96:4)	96 (*R*)
4	**L1c**	C_6H_5	70	10	100 (98:2)	99 (*R*)
5	**L1a**	C_6H_9	50	15	82 (93:7)	89 (*R*)
6	**L1a**	C_6H_9	70	10	100 (95:5)	93 (*R*)
7	**L1c**	C_6H_9	70	10	100 (93:7)	97 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), iPr$_2$NEt (1 mmol). [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC.

Encouraged by these excellent results, we also studied the phenylation of cyclopentene **S2** and 4,7-dihydro-1,3-dioxepin **S3**, which required longer reaction times under thermal conditions than substrate **S1** (Scheme 4). Again, the use of microwaves was highly advantageous, providing excellent regio- and enantioselectivities with much lower reaction times (from 2 days to 45 minutes). It should be noted that for substrate **S2**, the use of microwave irradiation also improved regio- and enantioselectivity. Therefore, the reaction of cyclopentene **S2** and phenyltriflate at 70 °C gave the coupling product **7** with 97 % *ee* in 99 % regioselectivity.



Scheme 4. Pd-catalysed Heck reactions of **S2** and **S3** using ligand **L1a** under microwave irradiation.

Conclusion

A library of readily available phosphite–oxazoline ligands has been synthesised and applied in Pd-catalysed asymmetric Heck reactions of several substrates and triflates under thermal and microwave conditions. These ligands have the advantage that they are easily prepared in a few steps from commercial D-glucosamine as an inexpensive natural chiral source. In addition, they can be easily tuned in the oxazoline and biarylphosphite moieties, so that their effect on catalytic performance can be explored. We found that the degree of isomerisation and the effectiveness in transferring the chiral information in the product and the activity can be tuned by correctly choosing ligand components (phosphite and oxazoline substituents). Excellent activities (up to 100 % conversion in 10 minutes), and regio- (up to >99 %) and enantioselectivities (*ee*'s up to 99 %) were obtained in a wide range of substrates and triflate sources. These results compete favourably with the most successful ligands developed for this reaction.[1] Note also that these ligands provided higher activities than those for other successful ligands. The use of microwave irradiation conditions allowed a considerably shorter reaction times (full conversion in few minutes) maintaining excellent regio- and enantioselectivities. These results open up a new class of ligands for the highly active and enantioselective Pd-catalysed Heck reaction, which will be of great practical interest.

Experimental Section

General considerations: All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Compounds **3**–**6** were prepared by previously described methods.[7] Phosphorochloridites were prepared as previously described.[12] Ligands **L1a**–**c**, **L1e**, **L2a**, **L3a**, **L4a** have been previously synthesised.[13] All other reagents were used as commercially available. ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. The chemical shifts are referenced to tetramethylsilane (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. The ^{1}H and ^{13}C NMR spectral assignments were determined by ^{1}H-^{1}H and ^{1}H-^{13}C correlation spectra. Microwave experiments were carried out by using a CEM Explorer, in which the temperature is controlled by a non-contact infrared sensor that is located beneath the cavity floor and "looks" up at the bottom of the vessel.

General procedure for the preparation of ligands L1–L4: The corresponding phosphorochloridite (3.0 mmol), produced in situ, was dissolved in toluene (12.5 mL); pyridine (1.14 mL, 14 mmol) was added. Hydroxyoxazoline (2.8 mmol) was azeotropically dried with toluene (3×2 mL) and then dissolved in toluene (12.5 mL) to which pyridine (1.14 mL, 14 mmol) was added. The oxazoline solution was transferred slowly at 0 °C to the solution of phosphorochloridite. The reaction mixture was stirred overnight at 80 °C, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography (toluene/NEt_3 = 100:1) to produce the corresponding ligand as a white solid.

Ligand L1d: Yield: 0.17 g, 28 %; ^{31}P NMR (400 MHz, C_6D_6, 25 °C, H_3PO_4): δ = 150.3 ppm (s); ^{1}H NMR (400 MHz, C_6D_6, 25 °C, TMS): δ = 2.27 (s, 3H; CH_3), 2.30 (s, 3H; CH_3), 2.31 (s, 3H; CH_3), 2.42 (s, 3H; CH_3), 3.50 (m, 1H; H-6′), 3.67 (m, 2H; H-4, H-5), 4.20 (m, 1H; H-6), 4.31 (m, 1H; H-2), 4.81 (m, 1H; H-3), 5.47 (s, 1H; H-7), 5.70 (d, $^2J(H_1,H_2)$ = 7.5 Hz, 1H; H-1), 7.0–8.3 ppm (m, 14H; CH=); ^{13}C NMR (400 MHz, C_6D_6, 25 °C, TMS): δ = 17.2 (CH_3), 17.4 (CH_3), 21.1 (CH_3), 63.9 (C-5), 68.9 (C-6), 69.5 (C-2), 78.6 (d, ^2J(C,P) = 20 Hz, C-3), 79.0 (C-4), 102.2 (C-7), 103.5 (C-1), 126.0 (CH=), 127.2 (CH=), 129.0 (CH=), 129.3 (CH=), 129.4 (CH=), 129.6 (CH=), 131.0 (C), 131.6 (CH=), 131.7 (CH=), 132.3 (CH=), 134.3 (CH=), 138.2 (C), 138.31 (C), 139.3 (C), 146.9 (C), 164.1 ppm (C); elemental analysis calcd (%) for $C_{36}H_{34}NO_7P$: C 69.33, H 5.50, N 2.25; found: C 69.39, H 5.52, N 2.23.

Ligand L1f: Yield: 0.1 g, 16 %; ^{31}P NMR (400 MHz, C_6D_6, 25 °C, H_3PO_4): δ = 154.7 ppm (s); ^{1}H NMR (400 MHz, C_6D_6, 25 °C, TMS): δ = 3.40 (m, 1H; H-6′), 3.53 (m, 2H; H-4, H-5), 4.06 (m, 2H; H-2, H-6), 4.66 (m, 1H; H-3), 5.44 (d, $^2J(H_1,H_2)$ = 7.8 Hz, 1H; H-1), 5.51 (s, 1H; H-7), 6.90–8.15 ppm (m, 22H; CH=); ^{13}C NMR (400 MHz, C_6D_6, 25 °C, TMS): δ = 63.7 (C-5), 68.8 (C-6), 69.3 (C-2), 78.7 (d, ^2J(C,P) = 13.7 Hz, C-3), 78.8 (C-4), 101.9 (C-7), 103.5 (C-1), 122.6 (CH=), 123.0 (CH=), 125.5 (CH=), 126.9 (CH=), 127.0 (CH=), 127.8 (CH=), 127.9 (CH=), 128.9 (CH=),

129.0 (CH=), 129.1 (CH=), 129.6 (CH=), 130.2 (CH=), 131.1 (CH=), 132.0 (C), 132.3 (CH=), 132.4 (C), 133.7 (C), 133.9 (C), 138.3 (C), 148.7 (C), 148.8 (C), 164.1 ppm (C); elemental analysis calcd (%) for $C_{40}H_{30}NO_7P$: C 71.96, H 4.53, N 2.10; found: C 71.59, H 4.59, N 2.07.

Ligand L^{1}g: Yield: 0.08 g, 12%; ^{31}P NMR (400 MHz, C_6D_6, 25°C, H_3PO_4): $\delta = 154.2$ ppm (s); ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): $\delta = 3.27$ (m, 1H; H-6′), 3.45 (m, 2H; H-4, H-5), 4.02 (m, 1H; H-6), 4.14 (dd, $^2J(H_1,H_2) = 7.6$ Hz, $^2J(H_2,H_3) = 5.2$ Hz, 1H; H-2), 4.62 (m, 1H; H-3), 5.29 (s, 1H; H-7), 5.55 (d, $^2J(H_1,H_2) = 7.6$ Hz, 1H; H-1), 6.90–8.15 ppm (m, 22H; CH=); ^{13}C NMR (400 MHz, C_6D_6, 25°C, TMS): $\delta = 63.1$ (C-5), 68.7 (C-6), 69.2 (C-2), 78.3 (d, $^2J(C,P) = 19.0$ Hz, C-3), 78.7 (C-4), 101.7 (C-7), 103.5 (C-1), 122.5 (CH=), 123.5 (CH=), 125.5 (CH=), 125.6 (CH=), 126.9 (CH=), 127.0 (CH=), 127.1 (CH=), 127.8 (CH=), 127.9 (CH=), 128.8 (C), 128.9 (CH=), 129.0 (CH=), 129.1 (CH=), 129.5 (CH=), 129.8 (C), 130.4 (CH=), 131.1 (CH=), 132.1 (C), 132.4 (CH=), 133.6 (C), 133.8 (CH=), 138.5 (CH=), 147.8 (C), 147.9 (C), 164.2 ppm (C); elemental analysis calcd (%) for $C_{40}H_{30}NO_7P$: C 71.96, H 4.53, N 2.10; found: C 71.74, H 4.56, N 2.12.

Ligand L4c: Yield: 0.22 g, 30%; ^{31}P NMR (400 MHz, C_6D_6, 25°C, H_3PO_4): $\delta = 150.2$ ppm (s); ^{1}H NMR (400 MHz, C_6D_6, 25°C, TMS): $\delta = 0.42$ (s, 9H; CH_3-Si), 0.50 (s, 9H; CH_3-Si), 1.55 (d, 3H, J(H,P) = 1.6 Hz; CH_3), 3.37 (m, 1H; H-6′), 3.52 (m, 1H; H-5), 3.84 (dd, $^3J(H_4,H_3) = 10$ Hz, $^3J(H_4,H_5) = 7.6$ Hz, 1H; H-4), 4.05 (m, 1H; H-2), 4.10 (m, 1H; H-6), 4.91 (m, 1H; H-3), 5.37 (d, 1H, $^2J(H_1,H_2) = 7.6$ Hz; H-1), 5.40 (s, 1H; H-7), 7.0–7.6 ppm (m, 11H; CH=); ^{13}C NMR (400 MHz, C_6D_6, 25°C, TMS): $\delta = 0.8$ (CH_3-Si), 14.2 (CH_3), 63.4 (C-5), 69.4 (C-6), 70.2 (C-2), 72.2 (d, $^2J(C,P) = 13.7$ Hz, C-3), 80.9 (C-4), 101.9 (C-1), 102.4 (C-7), 125.6 (CH=), 125.8 (CH=), 127.4 (CH=), 128.9 (CH=), 129.6 (CH=), 129.9 (C), 132.3 (C), 132.4 (C), 133.3 (CH=), 134.4 (C), 136.0 (CH=), 136.1 (CH=), 137.9 (C), 138.2 (C), 153.8 (C), 155.1 (C), 164.0 ppm (C); elemental analysis calcd (%) for $C_{43}H_{56}NO_7P$: C 70.76, H 7.73, N 1.92; found: C 70.79, H 7.74, N 1.95.

General procedure for the Pd-catalysed enantioselective Heck reactions: A mixture of $[Pd_2(dba)_3]$·dba (12 mg, 1.25×10–2 mmol) and the corresponding 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 olefin (2.0 mmol), triflate (0.50 mmol) and base (1.0 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. For compounds 2-(1-naphthyl)-2,5-dihydrofuran and 2-(4-nitrophenyl)-2,5-dihydrofuran conversion was measured by ^{1}H NMR spectroscopy and selectivity was measured by HPLC.[2b] For the rest of compounds, conversion and selectivity were determined by GC.[2e]

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