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Biaryl Phosphite–Oxazoline Ligands from the Chiral Pool: Highly Efficient Modular Ligands for the Asymmetric Pd-Catalyzed Heck Reaction

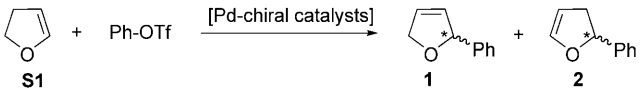
Javier Mazuela, Oscar Pàmies,* and Montserrat Diéguez*[a]

Abstract: A highly modular library of readily available phosphite–oxazoline ligands **L1**–**L21a**–**g** was successfully applied in the asymmetric Pd-catalyzed Heck reactions of several substrates and triflates under thermal and microwave conditions. This ligand library contains three main ligand structures that have been designed by systematic modification of one of the most successful ligand families developed for this process. As well as studying the effect of these three ligand structures on the catalytic performance, we also evaluated the effect of modifying several ligand parameters in these ligand structures. The effectiveness of these ligands at transferring the chiral information into the product can be tuned by correctly choosing the ligand components. Both enantiomers of the Heck coupling products were obtained in excellent activities (conversion: >100% in 10 min), regioselectivities (>99%) and enantioselectivities (>99% *ee*). Under microwave-irradiation conditions, the reaction times were considerably shorter (full conversion was achieved in a few minutes) and the regio- and enantioselectivities were still excellent.

Keywords: asymmetric catalysis · Heck reaction · palladium · oxazolines · phosphites

Introduction

One of the main objectives in modern synthetic organic chemistry is the catalytic enantioselective formation of C–C bonds. One way to achieve this aim is the asymmetric Pd-catalyzed Heck coupling of an aryl or alkenyl halide or triflate to alkenes, a reaction known to be very versatile due to its high tolerance of functional groups.[1] The bulk of the reported examples involve intramolecular reactions, which have the advantage that the alkene regiochemistry and geometry in the product can be easily controlled. In this respect, chiral bidentate phosphanes have turned out to be excellent ligands for this process.[1] Fewer studies, however, have been conducted on the asymmetric intermolecular version, mainly because regioselectivity is often a problem. So, for example, in the intermolecular 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 isomerization process.[1]



S1 **1** **2**

Scheme 1. Model Pd-catalyzed Heck reaction of **S1**. OTf = triflate.

In recent years, heterodonor P–N ligands (mainly phosphane–oxazolines) have emerged as being suitable for the intermolecular Heck reaction (Scheme 2).[1,2,3] Although some of them have provided high regio- and enantioselectivities, there is still a problem of low reaction rates and substrate versatility. Therefore, it is very important to develop ligands that induce higher rates and selectivities (i.e., regio- and enantioselectivities) on a basis of simple starting materials for several substrate types.

In this context, the presence of biaryl–phosphite moieties in ligand design can be highly advantageous.[4] We recently discovered that a pyranoside phosphite–oxazoline ligand library provided excellent activities and regio- and enantioselectivities in the Pd-catalyzed Heck coupling of several substrate types and triflate sources.[4] Despite this success, the use of other phosphite–oxazoline ligands has not yet been reported and a systematic study of the possibilities offered

[a] J. Mazuela, Dr. O. Pàmies, Dr. M. Diéguez
Departament de Química Física i Inorgànica
Universitat Rovira i Virgili, Campus Sescelades
C/Marcel·lí Domingo, s/n 43007 Tarragona (Spain)
E-mail: oscar.pamies@urv.cat
montserrat.dieguez@urv.cat

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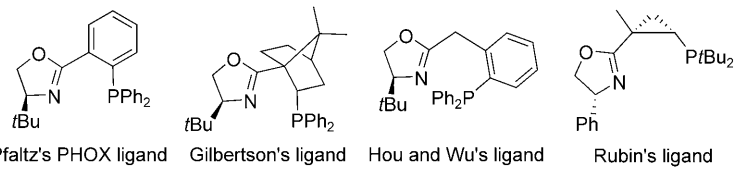


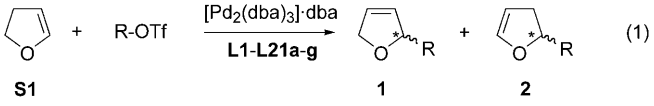
Scheme 2. Privileged phosphane–oxazoline ligands for the Pd-catalyzed intermolecular Heck reaction.

by this ligand class for this process is still needed. Herein, we extend our previous study[4b] to other phosphite–oxazoline ligands and other substrate types to fully investigate these possibilities. To do so, we synthesized and screened a library of 147 potential phosphite–oxazoline ligands (Scheme 3), which is based on three main ligand structures: The first **L1**–**L4**[5] is based on the phosphane–oxazoline (PHOX) ligands (Scheme 2), in which the phosphane moiety has been replaced by a biaryl–phosphite group; in the second **L5**, the flat *ortho*-phenylene tether in the previous ligands **L1**–**L4** has been replaced by an alkyl chain; the third **L6**–**L21**[6] is similar to the second but the alkyl chain is at C4 instead of C2 of the oxazoline moiety, thus shifting the chirality from the oxazoline substituent to the alkyl chain. We also evaluated systematic modification of several ligand parameters, which are known to have an important effect on catalytic performance, in these prominent ligand structures. Therefore, we investigated the effect of systematically varying the substituents in the oxazoline ring (R) and the alkyl chain (**L6**–**L12**: Me;**L14**–**L17**: H; **L18** and **L19**: Ph) with this library. We also studied the configuration of the alkyl chain in **L6** and **L13**, the presence of a second stereogenic center in the oxazoline ring and its configuration in **L20** and **L21**, and the substituents and configuration of the biaryl–phosphite moiety in **a**–**g**. By carefully selecting these elements, we achieved excellent activities combined with high regio- and enantioselectivities in several substrate types and triflate sources.

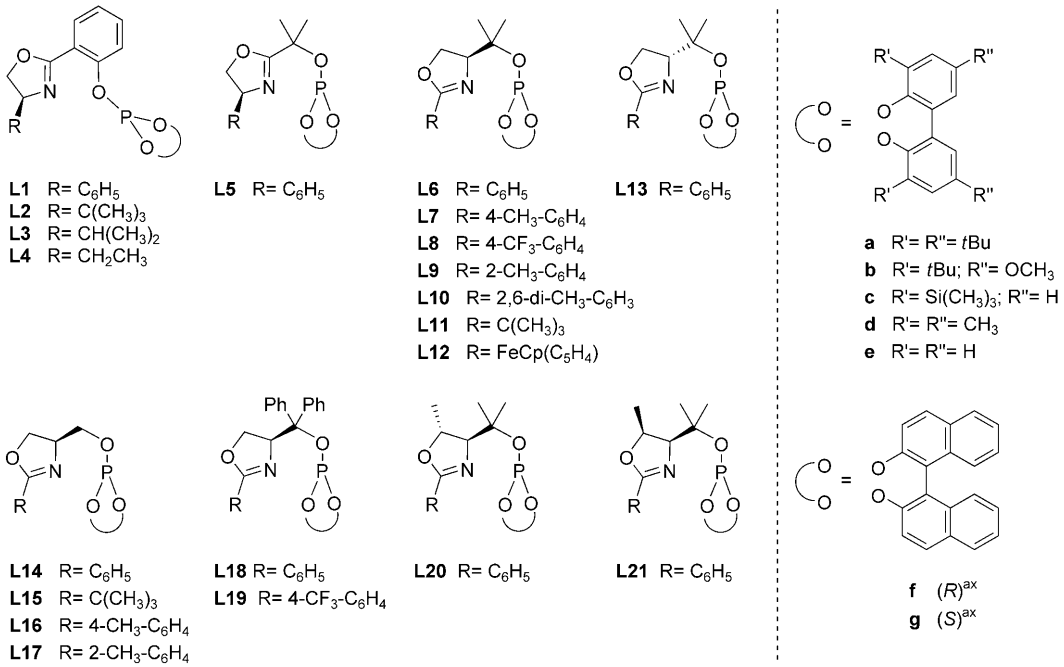
Results and Discussion

Asymmetric Heck reactions under thermal conditions

Asymmetric Heck reaction of 2,3-dihydrofuran (S1) under thermal conditions: We report the use of the chiral phosphite–oxazoline ligand library **L1**–**L21a**–**g** in the Pd-catalyzed asymmetric Heck reaction of **S1** [Eq. (1)] using several triflates with different electronic and steric properties: phenyl triflate, 1-naphthyl triflate, *para*-toluyl triflate, *para*-nitrophenyl triflate, and cyclohexenyl triflate. In all cases, the catalysts were generated in situ by mixing $[Pd_2(dba)_3]\cdot dba$ (dba = dibenzylideneacetone) with the corresponding chiral ligand.



R= C_6H_5, 1-Naphthyl, *p*-CH_3-C_6H_4, *p*-NO_2-C_6H_4, C_6H_9



Scheme 3. Phosphite–oxazoline ligand library **L1**–**L21a**–**g**.

Heck reaction of 2,3-dihydrofuran (S1) using phenyl triflate: In the first set of experiments, we used the Pd-catalyzed asymmetric phenylation of **S1** [R = C_6H_5; Eq. (1)] to study the potential of the phosphite–oxazoline ligand library **L1**–**L21a**–**g**. The phenylation of **S1** was chosen because the reaction was performed with a wide range of ligands, which enabled the efficiency of the various ligand systems to be compared directly.[1]

First, we studied the effect of the reaction conditions by conducting a series of experiments with three ligands (i.e., **L1a, L5a**, and **L6a**), different solvents, bases, and temperature. The efficiency of the process was strongly dependent on the nature of the solvent, base, and temperature (see the Supporting Information). The best activity and selectivity (i.e., regio- and enantioselectivities) was achieved with THF as the solvent and either diisopropylamine or a proton sponge as the base at 50 °C. These optimal conditions were used to test the catalytic performance of the complete series of ligands (see Table 1 for the summarized results), from which it was indicated that the catalytic performance (activities and selectivities) is affected by the ligand structure, substituents on the oxazoline ring and the alkyl chain, the presence of a second stereogenic center in the oxazoline ring, and the substituents and configuration of the biaryl–phosphite moiety. In general, the activities, regioselectivities (>99%), and enantioselectivities (>99% *ee*) were high for the phenylation of **S1**.

The effect of the ligand structure was studied with **L1a**, **L5a**, and **L6a**. The regio- and enantioselectivities were highest with **L6**, in which a chiral alkyl chain at C4 of the oxazoline connects the ring to the phosphite moiety (Table 1, entries 6 vs. 1 and 5).

The oxazoline substituents affected both the activities and selectivities (Table 1, entries 1–4, 6, and 13–18). In general, our results showed that the catalytic performance is highly influenced by the steric properties of the substituents in the oxazoline moiety, whereas the electronic properties have little effect. Bulky substituents at this position, therefore, caused a decrease in activity, regioselectivity, and enantioselectivity (i.e., Ph ≈ 4-R-Ph ≈ Et > *i*Pr > *t*Bu). This outcome contrasts with the oxazoline-substituent effect observed for the vast majority of successful phosphane–oxazoline ligands, the enantioselectivities of which are higher when bulky *tert*-butyl groups are present.[2] Interestingly, the introduction of a ferrocenyl substituent has an extremely positive effect on the regio- and enantioselectivities, and (*R*)-**1** is provided almost quantitatively in the enantiomerically pure form (Table 1, entry 18).

We studied the effect of the substituents and configuration of the alkyl chain with **L6a**, **L13a**, **L14a**, and **L18a** (Table 1, entries 6, 19, 20, and 24), thus showing that introducing methyl substituents at this position has an extremely positive effect on activity and enantioselectivity (Table 1, entries 6 vs. 20). However, bulkier substituents, such as the phenyl group, have an extremely negative effect on activity (Table 1, entries 6 vs. 24) and also show that the sense of enantioselectivity is governed by the absolute configuration of the alkyl chain (Table 1, entries 6 vs. 19). Both enantiomers of the phenylation product **1** can, therefore, be accessed in high regio- and enantioselectivity simply by changing the absolute configuration of the alkyl chain.

We tested **L20a** and **L21a** to study how a second stereogenic center in the oxazoline ring and its configuration affects the catalytic performance (Table 1, entries 26 and 27). The results show that the configuration of this second stereocenter and the configuration of the alkyl chain have a cooperative effect on enantioselectivity that results in a matched combination for **L21a**, which has an *S* configuration at both the second stereocenter and the alkyl chain.

Finally, the effects of the biaryl–phosphite moiety were studied with **L6a–g** (Table 1, entries 6–12). These moieties mainly affected activity and regioselectivity, whereas their effect on enantioselectivity was less important. Bulky substituents at the *ortho* positions of the biphenyl moiety, therefore, caused in an increase in the activity and regioselectivity (i.e., *t*Bu ≈ $SiMe_3$ > Me > H; Table 1, entries 6–12).

Table 1. Selected results for the Pd-catalyzed enantioselective phenylation of **S1** with the phosphite–oxazoline ligand library **L1**–**L21a**–**g**.[a]

Entry	Ligand	Conversion [%][b]	(**1**:**2**)	*ee* [%] **1**[c]	Entry	Ligand	Conversion [%][b]	(**1**:**2**)	*ee* [%] **1**[c]
1	**L1a**	100	(91:9)	98 (*R*)	15	**L9a**	75	(92:8)	97 (*R*)
2	**L2a**	21	(72:28)	72 (*R*)	16	**L10a**	100	(95:5)	99 (*R*)
3	**L3a**	36	(79:21)	80 (*R*)	17	**L11a**	13	(95:5)	92 (*R*)
4	**L4a**	100	(89:11)	96 (*R*)	18	**L12a**	99	(>99:1)	>99 (*R*)
5	**L5a**	100	(90:10)	92 (*R*)	19	**L13a**	92	(96:4)	99 (*S*)
6	**L6a**	94	(96:4)	>99 (*R*)	20	**L14a**	61	(94:6)	93 (*R*)
7	**L6b**	93	(97:3)	99 (*R*)	21	**L15a**	6	(64:36)	35 (*R*)
8	**L6c**	80	(96:4)	>99 (*R*)	22	**L16a**	36	(92:8)	96 (*R*)
9	**L6d**	78	(94:6)	99 (*R*)	23	**L17a**	79	(88:12)	90 (*R*)
10	**L6e**	12	(84:16)	98 (*R*)	24	**L18a**	<5		nd[d]
11	**L6f**	6	(83:17)	86 (*R*)	25	**L19a**	<5		nd[d]
12	**L6g**	<5		nd[d]	26	**L20a**	42	(90:10)	86 (*R*)
13	**L7a**	81	(97:3)	99 (*R*)	27	**L21a**	85	(96:4)	96 (*R*)
14	**L8a**	74	(97:3)	98 (*R*)					

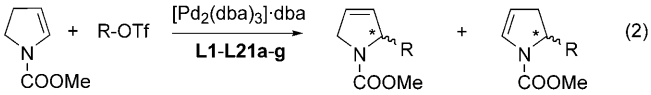
[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), phenyl triflate (0.5 mmol), ligand (2.8×10^{-2} mmol), THF (3 mL), iPr_2NEt (1 mmol), T = 50 °C, t = 24 h. [b] Conversion given in percentage was determined by GC analysis. [c] Enantiomeric excess was measured by GC analysis. [d] Not determined.

In summary, the best results were obtained with **L6a–c**, **L12a–c**, and **L13a–c** (Table 1, entries 6–8, 18 and 19; regioselectivities; >99% and >99% *ee*), which contain the optimal combination of ligand parameters (i.e., ligand structure, substituents at the oxazoline ring and alkyl chain, and substituents in the biaryl–phosphite moiety). Moreover, both enantiomers of phenylation product **1** can be accessed with high activities and high regio- and enantioselectivities simply by changing the absolute configuration of the alkyl chain. These results clearly show the efficiency of using highly modular scaffolds in the ligand design and compete favorably with the best that have been reported previously.[2a,b,e,k,l,4b]

Heck reaction of 2,3-dihydrofuran (S1) with other triflate sources: First, we investigated the effects of the electronic and steric properties of the aryl triflate source on the product outcome. For this purpose, we tested **L1**–**L21a–g** in the Pd-catalyzed 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 2 (entries 1–16). These results followed the same trends as for the phenylation of **S1**. Again, both enantiomers of the arylated products **1** were accessible with high activities, regioselectivities (up to >99%), and enantioselectivities (>99% *ee*). These results indicate that both the steric and electronic parameters of the triflate mainly affected regioselectivity, whereas their effect on enantioselectivity was less important. Thus, the regioselectivities are the highest for the 1-naphthyl and *para*-nitrophenyl triflates. Again, these results compete favorably with the best that have been reported previously.[2f,k,l,4b]

We next evaluated the ligand library in the Heck reaction of **S1** with cyclohexenyl triflate (Table 2, entries 17–21). Again the Pd-catalyst precursors containing **L6a**, **L12a**, and **L13a** provided access to both enantiomers of the alkenylated product **1** with high activity, regioselectivity (>99%), and enantioselectivity (94% *ee*). These results are among the best reported so far.[2a,b,e,k,4b]

Asymmetric Heck reaction of *N*-carbomethoxy-2,3-dihydropyrrole (S2) under thermal conditions: We applied this ligand library in the arylation of **S2** [Eq. (2)]. Although, dihydropyrrole derivatives are suitable substrates and very useful in organic synthesis, the asymmetric Heck reactions of these compounds have hardly been studied.[2b,c,k,7]



R= C_6H_5, *p*-CH_3-C_6H_4

The results with the phosphite–oxazoline ligands **L1**–**L21a–g** are summarized in Table 3 and followed the same trend as for the arylation and alkenylation of **S1**. Again, both enantiomers of product **3** were accessible with high activities, regioselectivities (>99%), and enantioselectivities (99% *ee*) with [Pd/**L6a–c**], [Pd/**L12a–c**], and [Pd/**L13a–c**]. Although, as expected, the activities were lower than in the arylation reaction of **S1**, they were much higher than those obtained with other successful ligands under mild reaction conditions.[2b,c,k,7] Again, these results compete favorably with the best that have been reported previously.[2b,c,k,7]

Table 2. Selected results for Pd-catalyzed enantioselective arylation and cycloalkenylation of **S1** with **L1**–**L21a–g**.[a]

Entry	Ligand	R	Conversion [%][b]	(**1**:**2**)	*ee* [%] **1**[c]
1	**L1a**	C_6H_5	100	(91:9)	98 (*R*)
2	**L1a**	4-$NO_2C_6H_4$	100	(99:1)	99 (*R*)
3	**L1a**	1-naphthyl	100	(93:7)	98 (*R*)
4	**L5a**	C_6H_5	100	(90:10)	92 (*R*)
5	**L5a**	4-$NO_2C_6H_4$	100	(94:6)	99 (*R*)
6	**L6a**	C_6H_5	94	(96:4)	>99 (*R*)
7	**L6a**	4-$CH_3C_6H_4$	80	(92:8)	99 (*R*)
8	**L6a**	4-$NO_2C_6H_4$	86	(98:2)	99 (*R*)
9	**L6a**	1-naphthyl	98	(99:1)	99 (*R*)
10	**L12a**	C_6H_5	99	(>99:1)	>99 (*R*)
11	**L12a**	4-$CH_3C_6H_4$	93	(97:3)	99 (*R*)
12	**L12a**	4-$NO_2C_6H_4$	100	(>99:1)	>99 (*R*)
13	**L12a**	1-naphthyl	100	(>99:1)	>99 (*R*)
14	**L13a**	C_6H_5	92	(96:4)	99 (*S*)
15	**L13a**	4-$CH_3C_6H_4$	85	(93:7)	99 (*S*)
16	**L13a**	4-$NO_2C_6H_4$	90	(98:2)	99 (*S*)
17	**L1a**	C_6H_9	100	(92:8)	90 (*R*)
18	**L5a**	C_6H_9	100	(89:11)	89 (*R*)
19	**L6a**	C_6H_9	100	(>99:1)	94 (*R*)
20	**L12a**	C_6H_9	100	(>99:1)	94 (*R*)
21	**L13a**	C_6H_9	100	(99:1)	94 (*S*)

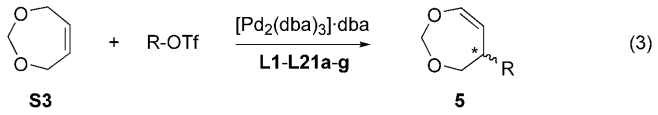
[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), triflate (0.5 mmol), ligand (2.8×10^{-2} mmol), THF (3 mL), *i*Pr_2NEt (1 mmol), $T = 50\,^{\circ}C$, $t =$ 24 h. [b] Conversion given in percentage was determined by GC or ^{1}H NMR spectroscopic analysis. [c] Enantiomeric excess was measured by GC or HPLC analysis.

Table 3. Selected results for the Pd-catalyzed enantioselective arylation of **S2** with the phosphite–oxazoline ligand library **L1**–**L21a–g**.[a]

Entry	Ligand	R	Conversion [%][b]	(**3**:**4**)	*ee* [%] **3**[c]
1	**L1a**	C_6H_5	99	(>99:1)	93 (*R*)
2	**L5a**	C_6H_5	95	(>99:1)	88 (*R*)
3	**L6a**	C_6H_5	99	(>99:1)	99 (*R*)
4	**L6b**	C_6H_5	99	(99: 1)	99 (*R*)
5	**L6c**	C_6H_5	100	(99: 1)	98 (*R*)
6	**L6e**	C_6H_5	11	(76:24)	96 (*R*)
7	**L7a**	C_6H_5	88	(>99:1)	92 (*R*)
8	**L8a**	C_6H_5	92	(>99:1)	88 (*R*)
9	**L12a**	C_6H_5	99	(>99:1)	99 (*R*)
10	**L13a**	C_6H_5	97	(99:1)	99 (*S*)
11	**L14a**	C_6H_5	69	(>99:1)	73 (*R*)
12	**L6a**	4-$CH_3C_6H_4$	99	(>99:1)	99 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.5×10^{-2} mmol), **S2** (2.0 mmol), aryl triflate (0.5 mmol), ligand (3.5×10^{-2} mmol), THF (3 mL), *i*Pr_2NEt (1 mmol), $T =$ 67 °C, $t = 72$ h. [b] Conversion given in percentage was determined by GC analysis. [c] Enantiomeric excess was measured by HPLC analysis.

Asymmetric Heck reaction of 4,7-dihydro-1,3-dioxepin (S3) under thermal conditions: To study the potential of these readily available ligands further, we also examined **L1**–**L21a**–**g** in the arylation of **S3** [Eq. (3)].



R= C_6H_5, *p*-CH_3-C_6H_4

This substrate is of great importance because the resulting enol ethers **5** are easily converted into chiral β-aryl-γ-butyrolactones, which are useful synthetic intermediates.[8] Despite this interesting characteristic, there are only a few reports that provided good enantioselectivities for this substrate and only with low reaction rates (i.e., typically 5–7 days).[2a,b,e,h,4b] The most noteworthy results are shown in Table 4.

Table 4. Selected results for the Pd-catalyzed enantioselective arylation of **S3** with the phosphite–oxazoline ligand library **L1**–**L21a**–**g**.[a]

Entry	Ligand	R	Conversion [%][b]	*ee* [%] **5**[c]
1	**L1a**	C_6H_5	100	95 (*R*)
2	**L5a**	C_6H_5	98	91 (*R*)
3	**L6a**	C_6H_5	99	98 (*R*)
4	**L6b**	C_6H_5	100	98 (*R*)
5	**L6c**	C_6H_5	97	97 (*R*)
6	**L6e**	C_6H_5	<5	nd[d]
7	**L7a**	C_6H_5	92	95 (*R*)
8	**L8a**	C_6H_5	89	92 (*R*)
9	**L12a**	C_6H_5	99	98 (*R*)
10	**L13a**	C_6H_5	96	98 (*S*)
11	**L14a**	C_6H_5	72	82 (*R*)
12	**L6a**	4-$CH_3C_6H_4$	94	98 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.5×10^{-2} mmol), **S3** (2.0 mmol), aryl triflate (0.5 mmol), ligand (3.5×10^{-2} mmol), THF (3 mL), *i*Pr_2NEt (1 mmol), $T=67$ °C, $t=72$ h. [b] Conversion given in percentage was determined by GC analysis. [c] Enantiomeric excess was measured by GC analysis. [d] Not determined.

In general, the effect of the ligand parameters on activity and regio- and enantioselectivity followed the same trends as for the arylation of **S1** and **S2**. Again, the catalyst precursors containing phosphite–oxazoline ligands **L6a–c**, **L12a–c**, and **L13a–c** provided both enantiomers of the arylated products **5** in high enantioselectivities (>98% *ee*). Again, these results compete favorably with the best that have been reported previously.[2a,b,e,h,4b]

Asymmetric Heck reaction of cyclopentene (S4) under thermal conditions: Encouraged by the excellent results obtained, we decided to go one step further and study the arylation of **S4** [Eq. (4)]. The selectivity for **S4** is more difficult to control than for functionalized alkenes, such as **S1** and **S2**, due to extensive double-bond migration.[1] Moreover, in addition to the desired product **6**, achiral regioisomers **7** and **8** can also be obtained. There are, therefore, fewer successful catalyst systems for the Pd-catalyzed arylation of this substrate than for the arylation of functionalized alkenes, such as **S1**.[2a,b,4b]

In this section, we report that the chiral phosphite–oxazoline ligands **L1**–**L21a**–**g** applied previously to the Pd-catalyzed arylation and alkenylation of substrates **S1**–**S3** can also be used for unfunctionalized alkene substrate **S4**. The

same trend as for the alkenylation of **S1**–**S3** was seen (the results are summarized in Table 5). Both enantiomers of the phenylated product **6** were obtained with high activities, regioselectivities (>94%), and enantioselectivities (99% *ee*). Although, as expected, the activities were lower than in the alkenylation of **S1**, they were much higher than those obtained with the most successful phosphane–oxazoline ligands.[2a,b] Interestingly, the formation of achiral product **8** did not take place. Again, these results compete favorably with the best that have been reported previously.[2a,b,4b]

Table 5. Selected results for the Pd-catalyzed enantioselective phenylation of **S4** with the phosphite–oxazoline ligand library **L1**–**L21a**–**g**.[a]

Entry	Ligand	Conversion [%][b]	(**6**:**7**)	*ee* [%] **6**[c]
1	**L1a**	100	(84:16)	94 (*R*)
2	**L5a**	100	(82:18)	90 (*R*)
3	**L6a**	100	(90:10)	99 (*R*)
4	**L6b**	100	(89:11)	99 (*R*)
5	**L6e**	9	(86:14)	95 (*R*)
6	**L7a**	99	(89:11)	98 (*R*)
7	**L11a**	15	(88:12)	87 (*R*)
8	**L12a**	100	(94:6)	99 (*R*)
9	**L13a**	100	(89:11)	99 (*S*)
10	**L14a**	73	(87:13)	91 (*R*)
11	**L18a**	<5		nd[d]

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S4** (2.0 mmol), phenyl triflate (0.5 mmol), ligand (2.8×10^{-2} mmol), THF (3 mL), *i*Pr_2NEt (1 mmol), $T=50$ °C, $t=48$ h. [b] Conversion given in percentage was determined by GC analysis. [c] Enantiomeric excess was measured by GC analysis. [d] Not determined.

Microwave-assisted asymmetric Heck reactions

It is known that by using controlled microwave dielectric heating, several C–C coupling reactions can be accelerated.[9] In 2002, Hallberg and co-workers demonstrated that the use of microwave irradiation for the enantioselective Heck reactions using the Pfaltz PHOX and 2,2'-bis(diphe-

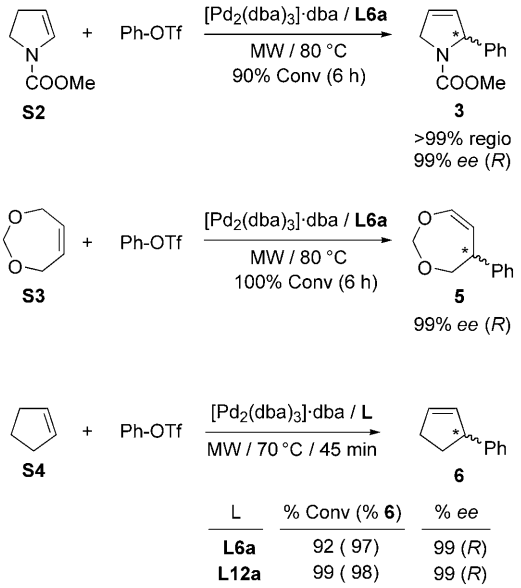
nylphosphino)-1,1'-binaphthyl (BINAP) ligands considerably shortened reaction times (from 4 days to 1 h), but enantioselectivities were lower than those obtained under thermal conditions.[10] Recently, we and others[4b,11] have also shown that the reaction proceeds much faster and retains excellent enantioselectivity when microwaves are used as the source of heat, thus allowing for a highly selective intermolecular Heck reaction. Therefore, we decided to use ligand library **L1**–**L21a**–**g** to take advantage of microwave irradiation in asymmetric Pd-catalyzed Heck reactions.

We first studied how temperature affected the Pd-catalyzed asymmetric Heck reaction of substrate **S1** by using phenyl triflate with **L1a** and **L6a** (Table 6). The optimal temperature was 70 °C, and the activities and enantioselectivities decreased at lower temperatures (Table 6, entries 1 and 3 vs. 2 and 4). Under these optimized conditions, we evaluated the complete ligand library. The most noteworthy results are shown in Table 6. It is interesting to note that under microwave-irradiation conditions, the reaction times improve dramatically (from 24 h to 10 min) and the excellent regioselectivities (>99 %) and enantioselectivities (99 % *ee*) obtained under thermal conditions are maintained (Table 6, entries 2 and 4–7). These observations are also true for other triflate sources (i.e., aryl or cyclohexenyl triflates); therefore, the activities (full conversion in 10 min), regioselectivities (>99 %), and enantioselectivities (>99 % *ee*) are excellent (Table 6, entries 8–11).

Table 6. Selected results of the microwave-assisted Pd-catalyzed enantioselective arylation and alkenylation of **S1** with **L1a**, **L5a**, **L6a**, **L12a**, and **L13a**.

Entry	L	R	*T* [°C]	*t* [min]	Conversion [%][b]	(1:2)	*ee* [%] **1**[c]
1	**L1a**	C_6H_5	50	20	98	(92:8)	96 (*R*)
2	**L1a**	C_6H_5	70	10	100	(93:7)	98 (*R*)
3	**L6a**	C_6H_5	50	15	96	(98:2)	95 (*R*)
4	**L6a**	C_6H_5	70	10	100	(97:3)	98 (*R*)
5	**L5a**	C_6H_5	70	10	100	(92:8)	92 (*R*)
6	**L12a**	C_6H_5	70	10	100	(99:1)	99 (*R*)
7	**L13a**	C_6H_5	70	10	100	(97:3)	98 (*S*)
8	**L6a**	4-$NO_2C_6H_4$	70	10	100	(94:6)	98 (*R*)
9	**L6a**	4-$CH_3C_6H_4$	70	10	100	(98:2)	99 (*R*)
10	**L6a**	1-naphthyl	70	10	100	(>99:1)	99 (*R*)
11	**L6a**	C_6H_9	70	10	100	(99:1)	94 (*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), *i*Pr_2NEt (1 mmol). [b] Conversion given in percentage was determined by GC or ^{1}H NMR spectroscopic analysis. [c] Enantiomeric excess was measured by GC or HPLC.



Scheme 4. Selected results for the Pd-catalyzed enantioselective arylation of **S2**–**S4** under microwave-irradiation conditions.

Encouraged by these excellent results, we also studied the arylation of **S2**–**S4**, which required longer reaction times under thermal conditions than substrate **S1** (Scheme 4). After the reaction parameters had been optimized, the optimal temperature was 80 °C for substrates **S2** and **S3** and 70 °C for substrate **S4**. Again, the use of microwave irradiation was highly advantageous: the regio- and enantioselectivities were excellent and the reaction times much shorter (**S2** and **S3**: 6 h versus 3 days; **S4**: 45 min versus 2 days). It should be noted that the use of microwave irradiation also improved the regioselectivity for **S4**. Therefore, the reaction of **S4** and phenyl triflate at 70 °C gave the coupling product **6** with a regioselectivity of 98 % and enantioselectivity of 99 % *ee*.

Conclusions

A highly modular library of readily available phosphite–oxazoline ligands has been applied in the Pd-catalyzed asymmetric Heck reactions of several substrates and triflates under thermal and microwave conditions. This ligand library contains three main ligand structures that have been designed by systematic modification of one of the most successful ligand families developed for this process. As well as studying the effect of these three ligand structures on catalytic performance, we also evaluated the effect of modifying several ligand parameters (i.e., substituents in the oxazoline ring and alkyl chain, the configuration of the alkyl chain, the presence of a second stereogenic center in the oxazoline ring and its configuration, and the substituents and configuration of the biaryl–phosphite moiety). The activities, regioselectivities, and enantioselectivities were highly affected by the ligand components. We highlight the excellent activities (up to 100 % conversion in 10 min), regioselectivities (>99 %), and enantioselectivities (>99 % *ee*) obtained in both enantiomers of the Heck coupling products for a wide range of substrates and triflate sources with ligands **L6a–c**, **L12a–c**, and **L13a–c**. These results compete favorably with the most successful ligands that have been developed for this reaction. Interestingly, the results were better than those obtained with pyranoside phosphite–oxazoline ligands,[4b] which have recently emerged as a privileged ligand class for this process.[15]

Experimental Section

General: All the syntheses were performed by using standard Schlenk techniques in an argon atmosphere. The solvents were purified by using standard procedures. Ligands **L1–L4a–c**[5] and **L6–L21a–g**[6a,c] were synthesized previously. Substrate **S2** was synthesized as previously reported and azeotropically dried with toluene prior to use.[12] All the 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 (TMS; ^{1}H and ^{13}C) as an internal standard or H_3PO_4 (^{31}P) as an 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. The microwave experiments were carried out with a CEM Explorer, in which the temperature is controlled by a noncontact IR sensor that is located beneath the cavity floor and "looks" up to the bottom of the vessel.

Preparation of ligand L5a: Pyridine (1.14 mL, 14 mmol) was added to (3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)phosphorochloridite (3.0 mmol) that had been produced in situ[13] dissolved in toluene (12.5 mL). Pyridine (1.14 mL, 14 mmol) was added to (*S*)-2-(1-hydroxy-1-methylethyl)-4-phenyl-1,3-oxazoline[14] (2.8 mmol) that had been azeotropically dried with toluene (3×2 mL) and dissolved in toluene (12.5 mL). 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 (0.63 g, 35 %). ^{31}P NMR (400 MHz, C_6D_6): $\delta = 148.3$ ppm (s); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 0.97$ (s, 18H, CH_3, *t*Bu), 1.36 (s, 9H, CH_3, *t*Bu), 1.38 (s, 9H, CH_3, *t*Bu), 1.42 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.54 (t, 1H, CH_2, $J = 8.0$ Hz), 3.87 (dd, 1H, CH_2, $J = 10.0$, $J = 8.0$ Hz), 4.66 (dd, 1H, CH, $J = 10.0$, $J = 8.0$ Hz), 6.7–7.4 ppm (m, 9H, CH=); ^{13}C NMR (400 MHz, C_6D_6): $\delta = 28.7$ (d, CH_3, $J_{C-P} = 5.4$ Hz), 28.8 (d, CH_3, $J_{C-P} = 5.4$ Hz), 31.9 (b, CH_3, *t*Bu), 34.9 (b, C, *t*Bu), 35.9 (C, *t*Bu), 36.0 (C, *t*Bu), 70.4 (CH), 75.6 (CH_2), 76.5 (d, C, $J_{C-P} = 10.9$ Hz), 124–151 (Ar C), 169.8 ppm (C=N); elemental analysis (%) calcd for $C_{40}H_{54}NO_4P$: C 74.62, H 8.45, N 2.18; found C 74.59, H 8.39, N 2.16.

General procedure for Pd-catalyzed enantioselective Heck reactions: A mixture of $[Pd_2(dba)_3]$·dba (12 mg, 1.25×10^{-2} mmol for substrates **S1** and **S4**; and 15 mg, 1.5×10^{-2} mmol for substrates **S2** and **S3**) and the corresponding chiral ligand (2.3 equiv) 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, washed with water, dried over $MgSO_4$, and evaporated. For compounds 2-(1-naphthyl)-2,5-dihydrofuran, 2-(4-nitrophenyl)-2,5-dihydrofuran, and 1-(methoxycarbony)-5-toluyl-3-pyrroline, the conversion was measured by ^{1}H NMR spectroscopic analysis and selectivity was measured by HPLC analysis.[2b] For the rest of the compounds, the conversion and selectivity were determined by GC analysis.[2e]

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[15] Optimization of the reaction conditions, the results of the catalytic arylation of **S1**, and examples of the temperature, power, and pressure versus time profiles for the microwave-irradiation experiments are given in the Supporting Information.

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