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Synthesis, Application and Kinetic Studies of Chiral Phosphite-Oxazoline Palladium Complexes as Active and Selective Catalysts in Intermolecular Heck Reactions

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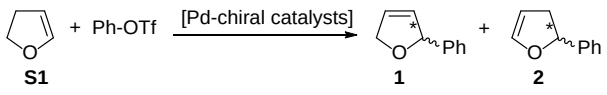
Abstract. This study identifies new phosphite-oxazoline ligands that have been successfully applied in the palladium-catalyzed intermolecular asymmetric Heck reaction. The design of the new phosphite-oxazoline ligands derives from a previous successful generation of phosphine-oxazoline ligands, by replacing the phosphine group with several π-acceptor biaryl phosphite moieties. With these simple modifications, the new phosphite-based ligands, unlike previous phosphine-oxazoline, not only present a modular design with numerous potential phosphite groups available, but they are also air-stable solids, which can be made in the same number of synthetic steps as the phosphine analogues. The substitution of the phosphine by a biaryl phosphite group extended the range of substrates and triflates sources that can be coupled with regio-, enantioselectivities and activities comparable to the few best ones reported. In addition, the ligands that provided the best selectivities contained an isopropyl oxazoline moiety instead of the *tert*-butyl group found in the related phosphine-oxazoline ligands, which is made from a much more expensive precursor. In this paper we have also carried out kinetic studies and a Hammett plot analysis to determine the rate determining step of this system in the regime of interest. We suggest a likely explanation for the fast Heck reaction of the phosphite-oxazoline catalysts.

Keywords: Palladium; Intermolecular Heck reaction; P,N-ligands; asymmetric catalysis; kinetic study

Introduction

The Pd-catalyzed Heck reaction (also known as Mizoroki–Heck reaction), *i.e.*, the coupling of an alkenyl or aryl (pseudo)halide to an alkene, is one of the most powerful C–C bond forming reactions, and Heck´s contribution was recognized with the Nobel Prize in Chemistry in 2010, shared with Negishi and Suzuki.[1] Its applicability to highly functionalized substrates confers the reaction a large substrate scope and it is widely applied in the synthesis of pharmaceuticals, natural products, and fine chemicals.[1] The extensive research dedicated to this process can give the erroneous impression that Heck chemistry is a mature area. Although the Heck reaction has been known since the late 1960s, its asymmetric version was not published until 1980, with most examples dealing with intramolecular reactions, in which the alkene regiochemistry and geometry of the product can be easily controlled.[1] The asymmetric intermolecular Heck reaction was not published until 1991.[2] Although since then many research groups have devoted considerable efforts to the intermolecular version, it is still less developed than the intramolecular version and its synthetic utility remains limited. This is due in part to regioselectivity issues caused by the possible displacement of the carbon-carbon double bond, which leads to mixtures of products. For example, in the Heck coupling of the model substrate 2,3-dihydrofuran (**S1**) with phenyl triflate (Scheme 1), both the 2-phenyl-2,5-dihydrofuran (**1**) and the 2-phenyl-2,3-dihydrofuran (**2**) can be obtained.



Scheme 1. Model Pd-catalyzed Heck reaction of 2,3-dihydrofuran (**S1**) with phenyl triflate

In the beginning, the research in the asymmetric intermolecular reaction focused on the development of diphosphine ligands, BINAP being the central ligand.[1] Although Pd-diphosphine catalysts provided high enantioselectivities, the regioselectivity and activity were less favorable (e.g., BINAP provided enantioselectivities up to 96% but the main product was **2**, in only 71% of regioselectivity, and the reaction time was 9 days)[2]. This moved the research to other types of ligands. A breakthrough was the report by Pfaltz *et al*., who showed that phosphine-oxazoline PHOX ligands (**3**, Figure 1) minimized the double bond isomerization providing high regio- and enantioselectivity to product **1**, although still at low activity with long reaction times (3–7 days to achieve full conversion).[3] Then, the follow up work for the intermolecular Heck reaction focused on Pd-catalysts with modified chiral phosphine-oxazoline ligands.[4,5] Of the many ligands developed, only a few provided high selectivity (Figure 1) and reaction rates and substrate specificity could not be improved significantly either. Although microwave irradiation considerably reduced the reaction times from weeks to days, it affected enantioselectivity − and sometimes regioselectivity − negatively.[6] Additionally, the most successful phosphine-oxazoline ligands contained a ^{t}Bu group in the oxazoline and their synthesis required the use of the expensive amino acid *tert*-leucine. Although alternative phosphine-oxazoline ligands, such as those incorporating geminal substituents at C-4 of ^{i}Pr-PHOX,[4q] were developed to solve this limitation, they had smaller substrate scope and/or their synthesis required more reaction steps. A final limitation of phosphine-oxazoline ligands is that most of them are prone to oxidation. Thus, while the PHOX ligands were found to be extremely successful in many reactions,[7] there remains room for improvement in the intermolecular Heck reactions.

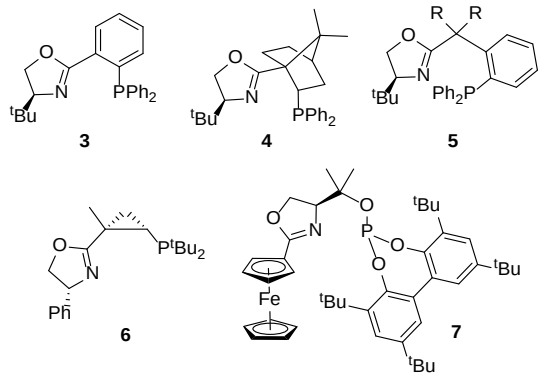


Figure 1. Representative privileged P-oxazoline ligands for Pd-catalyzed asymmetric intermolecular Heck reactions.

The search for efficient ligands prepared in only a few steps from inexpensive raw materials, easy to handle and that induce higher rates and substrate scope has therefore attracted the attention of many researchers. For this purpose two main strategies have been used for ligand design. One, developed recently by the groups of Oestrich and Zhou, illustrates the power of mixed phosphine-phosphine oxides which had been discarded in the Heck reaction for decades. Pd/phosphine-phosphine oxide systems were successfully applied in the intermolecular Heck reaction of several cyclic alkene substrates with various aryl triflates and aryl halides.[8] The second strategy was based on biaryl phosphite-oxazoline ligands. Phosphite-containing ligands are particularly useful for asymmetric catalysis.[9] They are modular, easy to synthesize from available alcohols and more resistant to oxidation than the phosphines. In this respect, an improved generation of air stable phosphite-oxazoline ligand libraries was developed.[10] The application of two of these phosphite-oxazoline libraries in the Heck reaction led to identify a Pd/phosphite-oxazoline **7** catalyst (Figure 1) that provided conversions of 100% at 50 °C in 24 h with excellent regio- and enantioselectivities in the coupling of several cyclic substrates and a variety of aryl triflates.[11] To the best of our knowledge no other phosphite-oxazoline ligands have been applied. Despite the mentioned developments, the use of the phosphite-oxazoline ligands in the intermolecular Heck reaction has several unknowns that must be explored to facilitate/accelerate the search for better catalysts. For example, no mechanistic studies have been made to discern the role of the ligand parameters that explain in a conclusive way the high activity of chiral phosphite-oxazoline ligands compared with their analogues phosphine-N ligands.[12] In contrast to other C–C bond forming reaction such as Pd Tsuji-Trost reactions, most of the mechanistic studies in Heck reaction have focused on achiral systems.[13] In this respect, efficient and accurate kinetic studies have been reported that include the entire catalytic system. However, no kinetic studies have been carried out for the asymmetric version and the few mechanistic studies for specific chiral ligands are mainly computational.[4o,5g,14] Spectroscopic studies by NMR and kinetic studies are hampered by the high reactivity and multifaceted aggregation behaviour of the Pd-precursor that gives unreactive Pd black. The experimental protocol to prevent the formation of Pd black under reaction conditions must still be developed.

To address these points, we report the application of a reduced but structurally valuable library of readily accessible phosphite-oxazoline ligands **L1-L5a-e** (Figure 2). These were obtained by replacing the phosphino group R_2P- in phosphine-oxazoline ligand **5**[4o] by biaryl phosphite moieties $(RO)_2PO$- thus increasing robustness and modularity and allowing a better control of the flexibility of the chiral pocket.[15] In addition, these ligands are solids and stable to air and other oxidizing agents. In a simple two or four step-procedure, which starts from commercially available materials, (Scheme 2) several ligand parameters can be easily tuned to maximize the catalyst performance. With this ligand library we systematically investigated the effect of changing the oxazoline substituents (Ph, ^{i}Pr and ^{t}Bu) and their configuration, the substituents in the benzylic position

(ligands **L1-L3a-e** with hydrogens and ligands **L4a-e** with methyl groups) and the substituents and configuration of the biaryl phosphite moiety (**a-e**). Interestingly, we found that the range of substrates and aryl and alkyl triflates that can be successfully coupled was larger than that for the previous phosphine-oxazoline **5** counterparts, which have emerged as some of the most successful catalysts designed for this process. In addition, the phosphite-oxazoline ligands that provided the best selectivities contained the ^{i}Pr substituent in the oxazoline moiety instead of the costly ^{t}Bu derivative found in the related phosphine-oxazoline **5**. Finally, in this paper we have also carried out kinetics studies and a Hammett plot analysis to determine the rate determining step. For this purpose we have successfully developed experimental conditions that disfavour the formation of Pd black from Pd-intermediate species during the kinetic experiments.

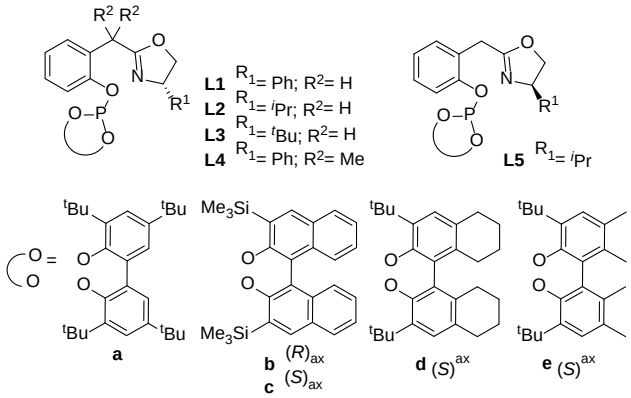


Figure 2. Phosphite-oxazoline ligand library **L1-L5a-e**.

Results and Discussion

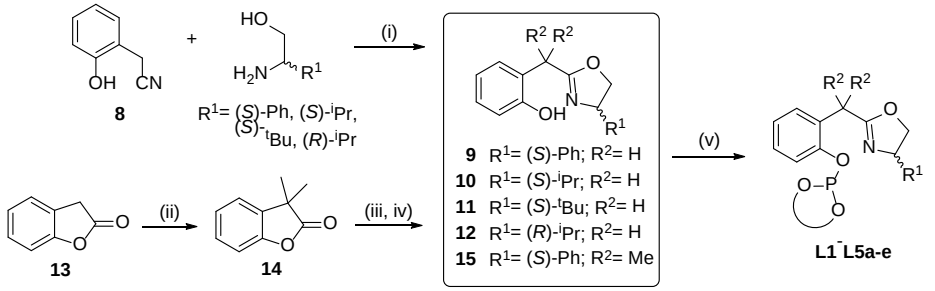
Synthesis of ligands

The sequence of the ligand synthesis is illustrated in Scheme 2. Phosphite-oxazoline ligands **L1-L3a-e** and **L5c** were synthesized very efficiently in a two-step procedure as previously reported by our group from readily available starting materials.[15] Therefore, coupling of hydroxyl-cyanide **8** with the appropriate amino alcohol yielded the hydroxyl-oxazolines **9-12** with diverse oxazoline substituents (Scheme 2, step i).[16] Then, compounds **9-12** readily react with the corresponding phosphorochloridites ($ClP(OR)_2$ $(OR)_2$ = **a-e**) to yield the desired phosphite-oxazoline ligands **L1-L3a-e** and **L5a**. For the synthesis of new phosphite-oxazoline ligands **L4**, which differs from **L1-L3** in the presence of methyl groups on the benzylic position, the commercially available 2(3*H*)-benzofuranone **13** was converted into the corresponding benzofuranone **14** by treatment with methyl iodide and sodium hydride (step ii).[17] Subsequent reaction of **14** with 3-amino-3-phenylpropan-1-ol (amino alcohol) followed by cyclization with *p*-TsCl afforded the desired hydroxyl-oxazoline **15** (steps iii and iv). Finally, condensation of the desired *in situ* formed phosphorochloridites ($ClP(OR)_2$ $(OR)_2$ = **a-c**) with hydroxyl-oxazoline **15** yielded phosphite-oxazoline ligands **L4a-c**, with different biaryl phosphite groups.

All ligands were isolated as white solids in good-to-high yields. As mentioned earlier, they can be manipulated and stored in air. Ligands were characterized by $^{31}P\{^{1}H\}$, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra and mass spectrometry. All data were in agreement with assigned structures (see experimental and supporting information sections for details). The ^{1}H, ^{13}C, and ^{31}P NMR spectra showed the expected pattern for these C_1-ligands. The VT-NMR spectra in CD_2Cl_2 (+35 to -85 °C) for ligands **L1-L4a** showed only one isomer in solution.

Asymmetric Heck reaction of 2,3-dihydrofuran (S1)

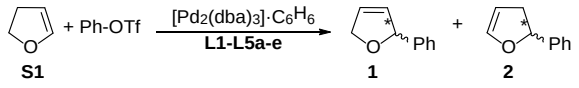
We first applied the ligands **L1-L5a-e** to the Pd-catalyzed phenylation of 2,3-dihydrofuran **S1**. For comparison, ligands were evaluated using the optimal reaction conditions reported in our previous studies with other phosphite-oxazoline ligands.[11] Reactions were thus performed in tetrahydrofuran, at 50 °C, using 2.5 mol% of *in-situ* generated catalyst, by mixing the $[Pd_2(dba)_3].C_6H_6$[18] with the corresponding chiral ligand, and $^{i}Pr_2NEt$ as base. The results are collected in Table 1. The catalytic performance was



Scheme 2. Synthetic route for the synthesis of phosphite-oxazoline ligands **L1-L5a-e**. (i) amino alcohol, $ZnCl_2$, C_6H_5Cl, reflux, 16 h (yields 68-78%);[16] (ii) NaH, MeI, THF, -78 °C to rt (43% yield);[17] (iii) Aminoalcohol, NaH, MeOH, THF, 0 °C to rt, 4 h, (75% yield). (iv) *p*-TsCl, NEt_3, DMAP, CH_2Cl_2, 0 °C to rt, overnight (89% yield). (v) $ClP(OR)_2$ ($(OR)_2$ = **a-e**), Py, toluene at rt for 18 h (40-78% yields).

found to depend on the ligand structure, i.e., the substituents on the oxazoline ring and on the benzylic position and the substituents/configuration of the biaryl phosphite moiety.

Table 1. Pd-catalyzed enantioselective phenylation of 2,3-dihydrofuran **S1** using ligands **L1**-**L5a-e**.[a]



Entry	Ligand	%Conv (**1**:**2**)[b]	%ee **1**[c]
1	**L1a**	94 (98:2)	67 (*R*)
2	**L1b**	50 (52:48)	81 (*R*)
3	**L1c**	92 (99:1)	75 (*R*)
4	**L2a**	100 (97:3)[d]	90 (*R*)
5	**L2b**	42 (58:42)	47 (*S*)
6	**L2c**	97 (96:4)	71(*R*)
7	**L2d**	99 (98:2)[e]	92 (*R*)
8	**L2e**	88 (97:3)[f]	92 (*R*)
9	**L3a**	20 (44:56)	85 (*R*)
10	**L3b**	47 (43:54)	10 (*S*)
11	**L3c**	85 (96:4)	81 (*R*)
12	**L4a**	48 (20:80)	4 (*R*)
13	**L4b**	5(45:55)	15 (*R*)
14	**L4c**	13 (43:57)	20 (*R*)
15	**L5a**	100 (96:4)[g]	90 (*S*)
16[h]	**L2a**	6 (89:11)	78 (*R*)
17[i]	**L2a**	100 (97:3)	85 (*R*)
18[j]	**L2a**	64 (87:13)	71 (*R*)

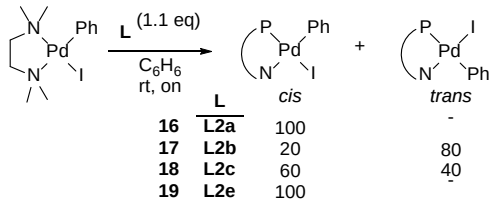
[a] $[Pd_2(dba)_3]$.benzene ($1.25\cdot10^{-2}$ mmol), **S1** (2.0 mmol), phenyl triflate (0.5 mmol), ligand ($2.8\cdot10^{-2}$ mmol), THF (3 ml), $^{i}Pr_2NEt$ (1 mmol), 50 °C, 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] 89% isolated yield. [e] 86% isolated yield. [f] 71% isolated yield. [g] 87% isolated yield. [h] Reaction carried out at 23 °C. [i] Reaction carried out at 70 °C. [j] Reaction carried out in benzene.

The reactions that proceeded with the highest activities, regio- and enantioselectivities (e.g. entries 4-6 vs 1-3 and 9-11) all have ligands containing the ^{i}Pr oxazoline group (ligands **L2**). This contrasts with the oxazoline-substituent effect observed in the vast majority of successful phosphine-oxazoline ligands (such as the $^{t}BuPHOX$ **3** and the Gilberston phosphine-oxazoline ligand based on ketopinic acid **4**; see Figure 1) the enantioselectivities of which are higher when *tert*-butyl groups are present. Interestingly, by comparing the results with those from the analogous Pd-phosphine-oxazoline systems **5**[4o] (Figure 1, R=H) it was found that the simple substitution of the phosphine by biaryl phosphite groups is advantageous since the ligands that provided the best selectivities contained the ^{i}Pr substituent in the oxazoline moiety instead of the costly ^{t}Bu derivative. As expected, the sense of enantioselectivity is governed by the absolute configuration of the oxazoline substituent (entry 4 ligand **L2a** vs entry 15 ligand **L5a**). Both enantiomers of the phenylation product **1** can therefore be accessed by simply changing the absolute configuration of the oxazoline group.

The introduction of methyl groups at the benzylic position had a negative effect on both activity and selectivity (Table 1, entries 12-14 vs 1-3). This contrasts with the results reported for related phosphine-oxazoline **5**[4o] where the introduction of Me substituents at the benzylic position provided the reverse enantiomer although with somewhat lower enantioselectivity (from 93 % (*R*) with a H substituent to 81 % (*S*) with a Me substituent) and regioselectivity.

Finally, concerning the effect of the biaryl phosphite group, we found that its configuration affected activity and selectivity. In general, ligands with an *S*-configuration of the biaryl phosphite moiety provided higher conversion, regio- and enantioselectivities than ligands with an *R*-configuration (Table 1, entries 6-8 vs 5) although ligand **L2a** with the aquiral biaryl phosphite group also provided high activities and selectivities (Table 1, entry 4). This ligand maintains the economic benefits of using an ^{i}Pr oxazoline substituent and has the added advantage that an achiral inexpensive biaryl phosphite moiety **a** is used. By comparing the results of **L2a** with those of the related enantiopure biaryl ligands **L2b** and **L2c**, (entry 4 vs 5 and 6), it can be concluded that the tropoisomeric biphenyl moiety in **L2a** adopts an *S*-configuration. The results also show that the substituent of the biaryl phosphite moiety has an important effect on selectivity since ligands **L2d-e** provided higher selectivity than **L2c** (entries 7-8 vs 6).

In an attempt to prove that the tropoisomerism of the achiral biphenyl phosphite can be controlled by the ligand backbone upon coordination to Pd and also to rationalize the lower enantioselectivities with ligands **L2b** and **L2c** than those obtained with ligands **L2a**,**d-e**, we investigated the coordination ability of ligands **L2a-c**,**e**. For that purpose, the corresponding [Pd(I)(Ph)(**L**)] (**L**=**L2a-c**,**e**) neutral complexes **16-19** were prepared. These complexes were prepared by reaction of [Pd(I)(Ph)(TMEDA)] (TMEDA= N,N,N,N-tetramethylethlendiamine) with one equivalent of the corresponding ligands (Scheme 3).



Scheme 3. Preparation of [Pd(I)(Ph)(**L**)] (**L**=**L2a-c**,**e**) neutral complexes. The ratio of each isomer measured by ^{31}P-NMR spectroscopy is also shown.

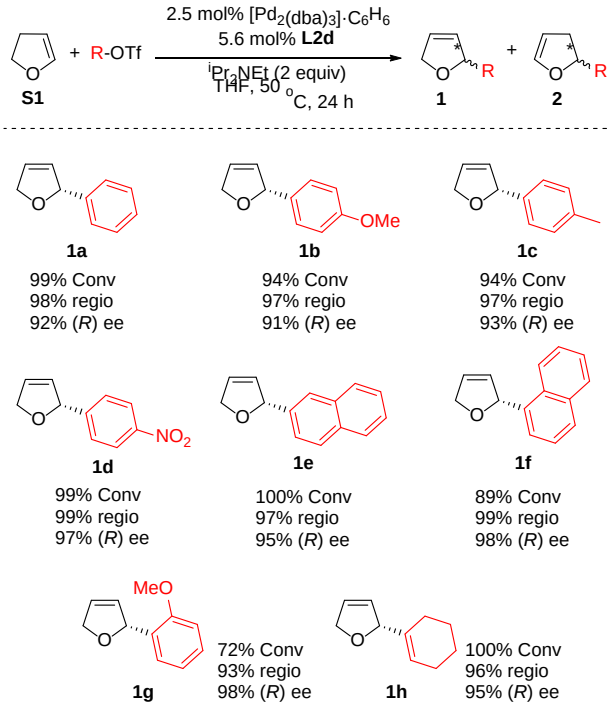
For complex **16**, containing tropoisomeric ligand **L2a**, only one isomer was detected by VT-NMR (30 ºC to –80 ºC) which has been assigned to the *cis* isomer (Scheme 3). In contrast, for complexes containing ligands **L2b** and **L2c** (compounds **17** and **18**) the two isomers *cis* and *trans* were observed (Scheme 3). The minor isomer of [Pd(I)(Ph)(**L2b**)] and the major isomer of [Pd(I)(Ph)(**L2c**)] were assigned to the *cis*

isomers. Finally, coordination of ligand **L2e**, led to the formation of *cis*-[Pd(I)(Ph)(**L2e**)] (**19**) exclusively, as in the case of tropoisomerically labile ligand **L2a**. All these results, therefore, support the conclusion that the flexible biphenyl phosphite moiety in ligand **L2a** adopts an *S*-configuration upon coordination to Pd. In addition, the presence of a mixture of isomers upon coordination of ligands **L2b** and **L2c** (with trimethylsilyl groups at the *ortho* positions of the binaphthyl phosphite moiety), may explain the lower enantioselectivities achieved using Pd/**L2b-c**, in the phenylation of **S1**, than those with ligands **L2a**,**d-e** (containing *tert*-butyl groups, see Table 1, entries 4, 7 and 8 vs 5 and 6).

All complexes were characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and HR-mass spectrometry. The spectral assignments were confirmed using ^{1}H-^{1}H, ^{31}P-^{1}H, ^{13}C-^{1}H, ^{1}H-^{1}H NOESY and ^{31}P DOSY experiments. Therefore, the ^{31}P DOSY spectra for both isomers of complexes with ligands **L2b** and **L2c**, show the same diffusion coefficients. Both isomers also show the same HR-mass spectra. All this agrees with the presence of the two possible isomers, *cis* and *trans*. The *cis* disposition of complexes with ligands **L2a**, **L2d** and the minor isomer of [Ph(I)(Ph)(**L2b**)] and major isomer of [Pd(I)(Ph)(**L2c**)] has been clearly established by the small carbon-phosphorus coupling constant observed for the C_{ipso} of the phenyl ligand ($J_{C\text{-}P}$ < 20 Hz). For the *trans* isomers the NOESY shows NOE interactions between the isopropyl substituent of the oxazoline group and some of the aromatic protons of the phenyl ligand.

In summary, the highest regio- (up to 98%) and enantioselectivities (up to 92%) were achieved with phosphite-oxazoline ligands **L2a**,**d-e** and **L5a**. We next studied the effect of the temperature with one of the best ligands (entries 16, 17). Lowering the temperature to 23 ºC has a negative effect on both selectivity and activity (only 6% of conversion after two days). High temperature (70 ºC) has also a negative effect on enantioselectivity whereas the good selectivity in favour of compound **1** is maintained. Finally, we studied the effect of changing the solvent to benzene. Most of the successful ligands reported in the literature gave better catalytic performance using benzene instead of THF.[3] This was not the case; activities and selectivities were lower in benzene (entry 18).

Other aryl and alkyl triflates. We next studied other aryl and alkyl triflates. The results follow the same trend, in terms of the effect of the ligand parameters, as the phenylation of **S1**. Again, the best results were obtained with **L2a**,**d**,**e** and **L5a**. As an example, Scheme 4 shows the results using ligand **L2d** which had provided one of the best results in the phenylation of **S1** (the full results are shown in the Supporting Information). Both enantiomers of the coupling products **1a-h** were accessible with high activity, regio- (up to 99%) and enantioselectivity (up to 98%). Improving results reported in the literature, it was found that the catalytic performance was hardly affected by the steric and electronic properties of the aryl groups. Therefore, a variety of triflates with different electronic and steric properties (1- and 2-naphthyl, *p*-CH_3-C_6H_4, *p*-NO_2-C_6H_4, *p*-OMe-C_6H_4 and *o*-OMe-C_6H_4) reacted with **S1** in regio- and enantioselectivities as high as or higher than those obtained with phenyl triflate. Even the sterically demanding 1-naphthyl and *o*-methoxyphenyl triflates were cross-coupled efficiently (products **1f** and **1g**). Finally, it is also worth mentioning that the addition of cyclohexenyl triflate that usually reacted with less regio- and enantioselectively than the coupling of phenyl triflate proceeded with comparable high regio- and enantioselectivity. All these results are among the best that have been reported in the literature[1c,n] and surpass the range of aryl and alkyl triflates that could be coupled with the phosphine-oxazoline analogues **5**[4o].



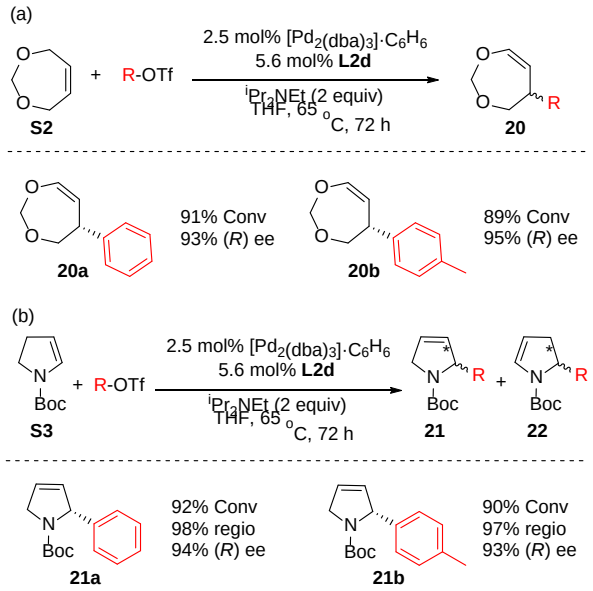
Scheme 4. Asymmetric Heck reaction of 2,3-dihydrofuran **S1**.

Asymmetric Heck reaction of other substrates

The potential of **L1**-**L5a-e** ligands was further studied by using them in the Pd-catalyzed Heck reaction of other challenging substrates. Initially the arylation of 4,7-dihydro-1,3-dioxepin **S2** with phenyl- and *p*-tolyl triflates was studied (Scheme 5a). The enol ethers **20** resulting from these substrate are easily converted into chiral β-aryl-γ-butyrolactones, which are useful synthetic intermediates.[19] Despite its relevance, successful examples in literature are scarce and most of them require long reaction times for full conversion.[20] The results are summarized in Scheme 5a and followed the same trends as for the arylation of **S1**. Again, catalysts Pd/**L2a**,**d-e** and Pd/**L5a** provided

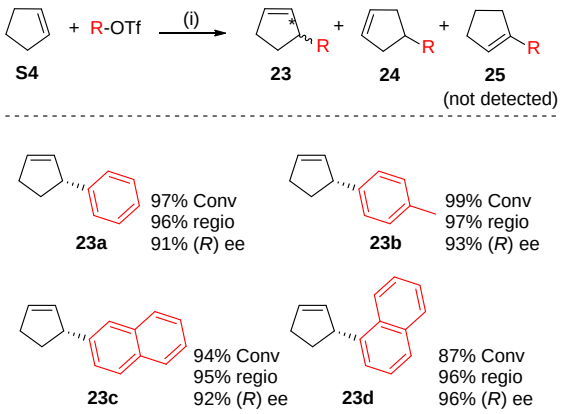
both enantiomers of the arylation products **20a** and **20b** in high enantioselectivities (up to 95%) comparable to the best reported so far (see Supporting Information for complete set of results).

Dihydropyrroles are another important set of substrates which are widely present in biological compounds and have versatile synthetic applications.[21] Therefore, the asymmetric Heck reaction of *N*-Boc-2,3-dihydropyrrole **S3** with phenyl and *p*-tolyl triflates was investigated (Scheme 5b). So far, only a few examples have been reported.[1] Again, ligands **L2a**,**d**,**e** and **L5a** that contain the ^{i}Pr substituent in the oxazoline moiety (see the complete results in the Supporting Information) provided the best results with activities, regio- (up to 98%) and enantioselectivities (up to 94%) comparable to the best ones reported in the literature.[1]



Scheme 5. Asymmetric Heck reaction of (a) 4,7-dihydro-1,3-dioxepin **S2** and (b) *N*-Boc-2,3-dihydropyrrole **S3**.

Finally the attention was turned to the asymmetric alkenylation of cyclopentene **S4** (Scheme 6). Due to extensive double-bond displacement, the selectivity is more difficult to control in this substrate than in functionalized alkenes, such as **S1** and **S3**.[1] Most of the catalysts fail to control the regioselectivivity and, in addition to the desired product **23**, the corresponding achiral regioisomers **24** and **25** can be obtained.[1] Catalytic systems Pd/**L2a**,**d-e** and Pd/**L5a** turned out to be efficient in the alkenylation of **S4** using four aryl triflates with different electronic and steric proprieties (Scheme 5 and Supporting Information for full set of results). In all cases high activities, regio- and enantioselectivities in both enantiomers of the arylation products **23a-d** were achieved without the formation of the undesired achiral product **25**.

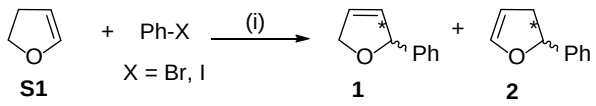


Scheme 6. Asymmetric Heck reaction of cyclopentene **S4**. (i) 2.5 mol% $[Pd_2(dba)_3]\cdot C_6H_6$, 5.6 mol% **L2d**, $^{i}Pr_2NEt$ (2 equiv), THF, 50 °C, 48 h.

In summary, the replacement of the phosphine by a phosphite group in the phosphine-oxazoline ligands **5** provided air stable ligands which in addition extended the range of substrates and aryl and alkyl triflates that could be successfully coupled with regio-, enantioselectivities and activities that were among the few best reported so far.[1] In addition, the ligands that provided the best enantioselectivities contained the ^{i}Pr substituent in the oxazoline moiety instead of the ^{t}Bu substituent leading to a cost reduction.

Asymmetric Heck reaction of 2,3-dihydrofuran with aryl halides

Carbon electrophiles in the asymmetric intermolecular Heck reaction have been mostly restricted to aryl or vinyl triflates. To date, only a few successful examples using aryldiazonium salts,[5h,22] arylboronic acids[23] and benzylic electrophiles[24] and one using aryl halides[8d] have been reported. With aryl halides, mixed phosphine-phosphine oxide ligands were found to be the best choice whilst BINAP and ^{t}Bu-PHOX provided very low activities (< 10%) and BINAP also extremely low enantioselectivity (<5% ee).[8d] The success of this transformation also required the addition of 1 equiv. of additive (mainly *p*-NO_2PhCO_2H although silver salts such as AgOTf were also used) and ethylene glycol or methanol as solvents (the more common toluene, ether and 1,4 dioxane led to poor results). In addition, most of the electrophiles were aryl bromides and only a few were ArCl. Aryl iodides gave not only lower enantioselectivity but also a shift to the preferential formation of regiosomer **2** (i.e., the phenylation of **S1** afforded **1** and **2** at a 1:2 ratio).[8d] Under these reaction conditions, we tested whether ligands **L1**-**L5a**-**e** could do the desired coupling (Scheme 7). The reaction of **S1** with phenyl bromide provided the desired regioisomer **1** as a major product in high enantioselectivity (87% ee), albeit with low conversion. The use of phenyl iodide led to similar levels of enantioselectivities although the formation of isomer **2** is favored.



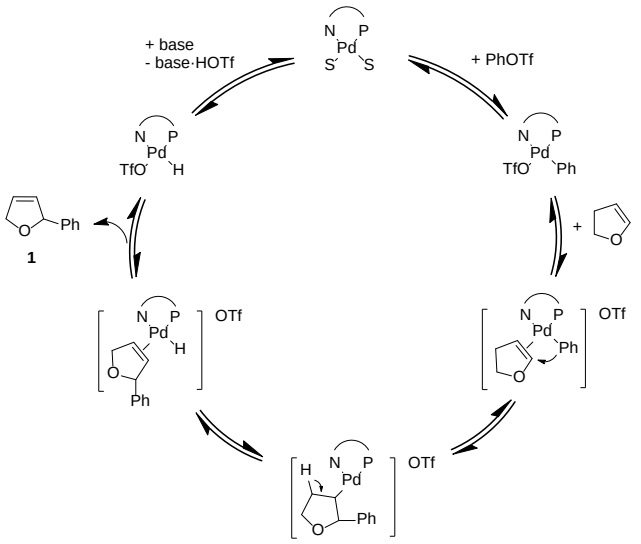
X	% Conv	% Regio (**1**:**2**)	% ee **1**
Br	19	80:20	87 (*R*)
I	48	40:60	83 (*R*)

Scheme 7. Asymmetric Heck reaction of **S1** with aryl halides. (i) 2.5 mol% $[Pd_2(dba)_3]\cdot C_6H_6$, 3 mol% **L2a**, $^{i}Pr_2NEt$ (3 equiv), AgOTf (1.5 equiv), ethylene glycol, 80 °C, 24 h.

Kinetic studies and Hammett plot analysis

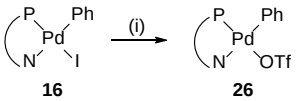
There are no mechanistic studies that give a conclusive reason why the chiral phosphite-oxazoline ligands give a higher activity than most of the phosphine-oxazolines.[11] Old studies (<2000) on achiral systems mostly containing an excess of PPh_3 or dba reported evidence for the oxidative addition as the rate-limiting step in this chemistry, which in the present case would have led to a faster reaction of the phosphine analogues.[25] Since then kinetic studies using achiral monophosphite ligands[13a,e] and studies using metallocyclic phosphine and imine precursors[13b,c] showed that the rate determining step in those systems is the alkene coordination or the migratory insertion of the alkene, the migratory insertion being the most plausible choice as tentatively suggested by further electronic alkene effects.[13a,e]

We decided to perform a brief kinetic study under practical conditions to determine the rate determining step in the reactions of the Pd/phosphite-oxazoline catalysts reported in this manuscript. To achieve this goal first a viable catalyst precursor was synthesized and new reactions conditions were developed to prevent the formation of Pd black. Scheme 8 presents the generally accepted mechanism for the Heck coupling reaction that served as the basis for the kinetic study (all steps shown as reversible). The catalytic cycle is initiated by the oxidative addition of phenyl triflate to the Pd(0)-PN* complex resulting in the four coordinate aryl-Pd(II) complex which then reacts with the olefin to form the π-complex. Insertion of the olefin into the Pd-Ph bond leads to a Pd-alkyl species which undergoes β-hydride elimination, followed by dissociation to the product and a Pd-hydride complex. The catalytic cycle is completed by base-assisted reductive elimination of HOTf regenerating the catalytically active Pd(0)complex.



Scheme 8. Accepted mechanism for the asymmetric Pd-catalyzed Heck reaction of **S1**.

[Pd(Ph)(OTf)(**L2a**)] **26** was used as a viable catalyst precursor for the kinetic study. The use of $Pd_2(dba)_3$/**L2a** or its [Pd(dba)(**L2a**)] analogues was discarded because the active species form too slowly under the employed conditions.[26] Complex **26** was synthesized from the corresponding compound [Pd(I)(Ph) **L2a**)] (**16**) by iodine abstraction with AgOTf (Scheme 9). Complex **26** was characterized by ^{31}P, ^{1}H and ^{13}C NMR spectroscopy. The VT-NMR experiments (–78 to 30 °C) indicated the formation of a single stereoisomer. This is in agreement with the atropoisomerism of the biphenyl phosphite moiety being controlled by the ligand backbone upon coordination to the Pd-centre observed in Table 1 (*vide supra*).[27] The NMR data also indicated that, as previously observed for other P,N-containing complexes, the phenyl ligand is located *cis* to the phosphite moiety.[5a] To prove the viability of **26** as a catalyst precursor, we first performed the stoichiometric reaction by adding 2 equivalents of **S1** and an excess of base. The regio- and enantioselectivity achieved were similar to those achieved using the catalytic conditions (95% regioselectivity and 88% ee), which clearly indicated that [Pd(Ph)(OTf)(**L2a**)] is a viable intermediate.



Scheme 9. Preparation of [Pd(Ph)(OTf)(**L2a**)] (**26**). (i) AgOTf, THF (90% yield).

Prior to the kinetic studies we performed a control experiment to study the stability of compound **26** under catalytic conditions monitoring the reaction during 24 h. Unfortunately, deactivation of the molecular system was observed after 10–15 minutes,

due to the formation of an inactive black precipitate. This contrasts with the stability observed in the catalytic runs using [$Pd_2(dba)_3$]/**L1**–**L5a**–**e** catalytic precursors (see vide supra) and this suggests that the presence of dba (although it does not participate in the catalytic cycle) and/or the excess of ligand are necessary to stabilize the molecular Pd(0) species thus preventing the formation of the inactive Pd precipitate. It was found that the addition of 12 mol% of excess of ligand prevents the deactivation of the molecular system. Thus, the precipitation of Pd was not observed during the first 12 hours.

With the appropriate reaction conditions in hand the kinetic studies were performed using a simple approach[28], in which the concentration of each of the reagents involved was varied and the reaction rate measured after 1 h (TOF_{ini}).[29] Rates were plotted versus the concentrations (Figure 3). The rate of the reaction between **S1** and phenyl triflate catalyzed by Pd-complex **26** was independent of the concentration of N,N-diisopropylethylamine (0.16–2.7 M; Figure 3a) and phenyl triflate (0.16–2 M; Figure 3b). The zero order dependence in phenyl triflate agrees with a rapid oxidative addition. The independence of the reaction rate on the concentration of N,N-diisopropylethylamine agrees with the fact that the elimination/reduction steps, that are base-assisted, are also fast. The effect of the Pd loading (2–16 mM) on the activity (Figure 3c) indicates a first order-dependency, because the rate of product formation is proportional to the Pd concentration. This is in contrast with the involvement of dimeric species reported for monodentate ligands (including phosphites).[13a-e] Finally, the kinetic study shows a linear dependence of the initial turn-over frequency (TOF_{ini}) on alkene concentration (Figure 3d). The first-order rate dependence on the alkene concentration clearly shows that the substrate is involved in the turn-over limiting step, either directly or in a pre-equilibrium. According to Scheme 8 this implies that either the alkene coordination to Pd or the subsequent insertion into the Pd–Ph bond must be the turn-over limiting step. These two steps cannot be distinguished from the kinetic results described so far. To analyse this in more detail, we next determined the initial reaction rates with several *para*-substituted phenyl triflates (*p*-R-C_6H_4OTf; R= OMe, Me, H, NO_2) using Pd-complex **26** under the same reaction conditions. The Hammett plot (Figure 4) shows a linear correlation between the Hammett σ value and the relative reaction rates,[30] with a negative ρ value (ρ = –0.89). Thus, the use of electron-withdrawing aryl triflates led to lower reaction rates, exhibiting the order *p*-NO_2<*p*-H<*p*-Me<*p*-OMe. Both rate and equilibrium constant of the alkene coordination are only slightly affected by the electron donicity of the aryl group as it is in a *cis* position; besides the reverse order would have been expected. Thus the Hammett plot is not in line with a rate-limiting alkene coordination step. Migration of the aryl group, however, is known to be enhanced by increasing electron density on the migrating group,[31] which is in agreement with the observed Hammett relation. Thus, we conclude that the migratory insertion is the rate-limiting step.

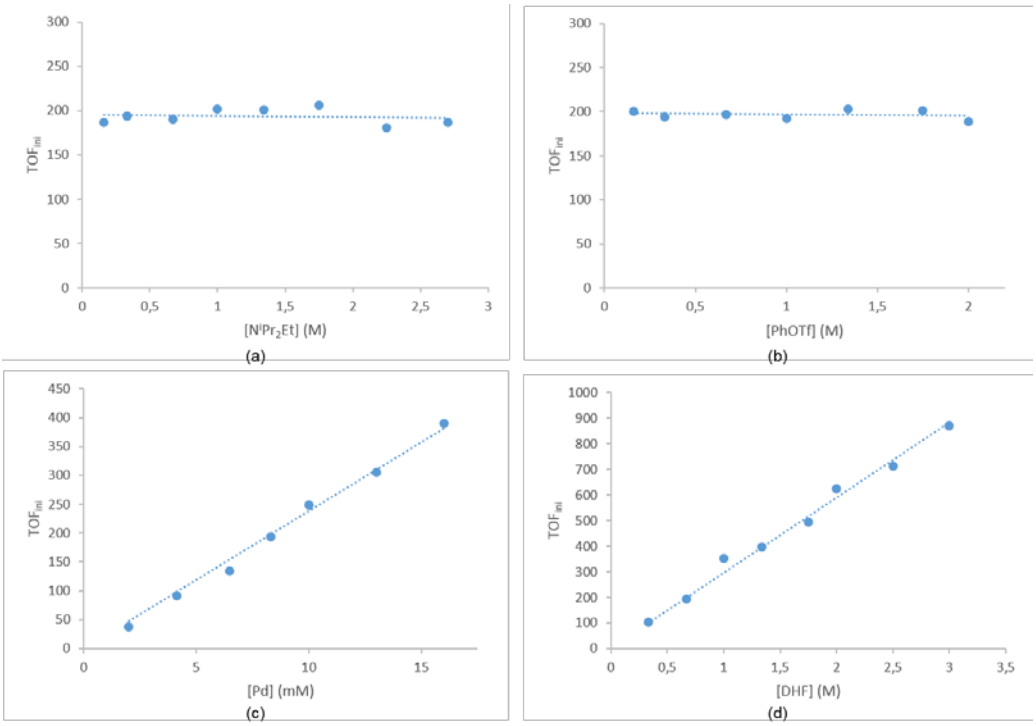


Figure 3. Kinetic measurements. Plots of TOF_{ini} versus (a) [N^iPr_2Et], (b) [PhOTf], (c) [Pd] and (d) [**S1**] for the reaction of **S1** with PhOTf in THF at 50 °C catalyzed by complex [Pd(Ph)(OTf)(**L2a**)]. TOF_{ini} measured after 1 h (conversions typically of 5-10%).

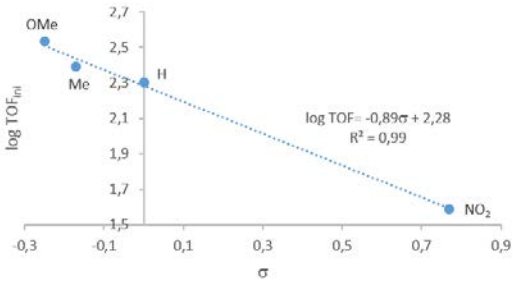
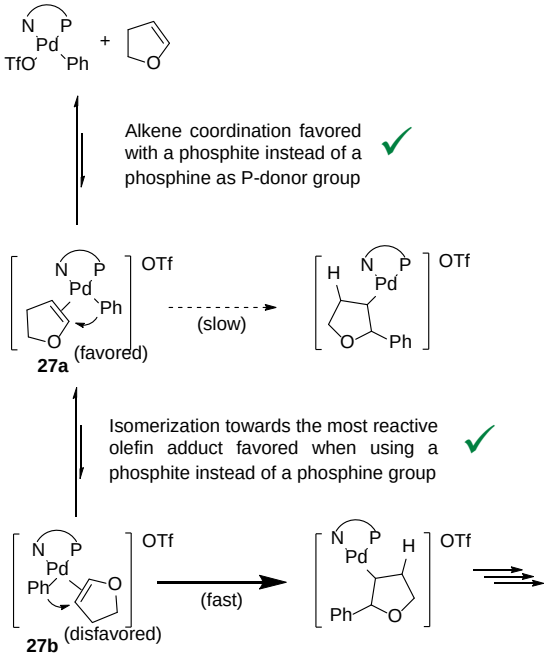


Figure 4. Hammet plot showing the effect of substituents on the Heck reaction using catalytic system Pd/**L2a**.

We return to the question why phosphite-oxazolines give faster catalysts than phosphine-oxazolines. Assuming that in the two related ligand groups the mechanism remains the same, the electron-withdrawing phosphites will raise the alkene-Pd adduct concentration (**27a** in Scheme 10 and species 4-o´clock in Scheme 8) and thus this will increase the rate of reaction, other things being equal. However, migratory insertion in palladium complexes containing non-symmetric bidentates is a complicated process.[32] As shown in Scheme 10 a slow migratory insertion may take place in the alkene adduct **27a** (Schemes 8 and 10) or this intermediate may first isomerize to the more reactive isomer **27b**, as found before for a small number of examples[33]. In the absence of more data we refrain from speculations on these details and propose that the higher rate for phosphite catalysts is caused by the higher population of alkene adducts **27a**–**b** as stated above and depictured in Scheme 10.



Scheme 10. Olefin coordination and migratory insertion pathways leading to the products.

Conclusion

A new series of robust phosphite-oxazoline ligands has been successfully applied in the Pd-catalyzed enantioselective intermolecular Heck reaction. These ligands are based on one of the most successful phosphine-oxazoline ligand family **5** for this process, in which the phosphine moiety has been replaced by several biaryl phosphite groups. With these simple modifications, the phosphite-based ligands not only present, unlike **5**, a modular design with numerous potential phosphite groups available, but they are also air-stable solids made in the same number of synthetic steps as the phosphine analogs. With a careful selection of the ligand components, (oxazoline substituent and its configuration, the substituents in the benzylic position and the substituents and configurations of the biaryl phosphite moiety) the new ligands were superior to the privileged phosphine-oxazolines **5**, extending the range of substrates and triflates sources than can be coupled with high regio-, enantioselectivities and activities. In addition, the phosphite-oxazoline ligands that provided the best selectivities contained the ^{i}Pr substituent in the oxazoline moiety instead of the expensive ^{t}Bu substituent found in the related phosphine-oxazoline **5**. Interestingly, ligand **L2a** with the achiral biphenyl phosphite group provided activities and selectivities as high as those achieved using ligands containing chiral biaryl phosphite moieties. Studies of the coordination chemistry of the Pd-aryl intermediates have shown that the chirality of the oxazoline ligand backbone is able to control the tropoisomerism of the achiral biphenyl phosphite moiety in **L2a**, thus making the use of chiral phosphites superfluous. Preliminary kinetic studies in a practical regime indicated that migratory insertion of the alkene is rate-limiting and that most likely the more favourable formation of alkene adducts makes the phosphite based catalysts more active than the phosphine based ones.

Experimental Section

General information

All syntheses were performed with standard Schlenk techniques under argon atmosphere. The kinetic studies were performed using a glove box. Solvents were purified by standard procedures. All reagents were used as commercially available. Compounds **9-12**,[16] **14**,[17] phosphochloridites,[34] ligands **L1-L3a-e**[15] and [Pd(Ph)(I)(TMEDA)][35] were prepared as previously reported. ^{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{^{1}H} NMR spectral assignments were determined by ^{1}H-^{1}H and ^{1}H-^{13}C correlation spectra.

General procedure for the preparation of phosphite-oxazoline ligands

To a solution of in situ generated phosphochloridite (1.1 mmol) in dry toluene (6 mL), pyridine (0.16 mL, 2.0 mmol) was added. Then, this solution was placed in a -78 ºC bath.

After 2 min at that temperature, a solution of the corresponding alcohol-oxazoline (1.0 mmol) and pyridine (0.16 mL, 2.0 mmol) in toluene (6 mL) was added drop wise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral alumina and dry toluene as eluent system) to afford the corresponding phosphite-oxazoline as white solids.

(*S*)-4-Phenyl-2-(2-(2-((2,4,8,10-tetra-*tert*-butyldibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)oxy)phenyl)propan-2-yl)-4,5-dihydrooxazole (L4a): Yield: 261.5 mg (40%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 137.0 ppm (s). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.22 (s, 9H, CH_3, ^{t}Bu), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.78 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 3.71 (m, 1H, CH_2-O), 3.98 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ = 10.0 Hz, $^3J_{H\text{-}H}$ = 7.6 Hz), 4.92 (dd, 1H, CH-N, $^3J_{H\text{-}H}$ = 9.6 Hz, $^3J_{H\text{-}H}$ = 7.6 Hz), 6.83 (m, 1H, CH=), 6.90 (m, 1H, CH=), 7.01 (m, 2H, CH=), 7.09 (m, 3H, CH=), 7.21 (s, 1H, CH=), 7.23 (s, 1H, CH=), 7.03 (d, 1H, $^3J_{H\text{-}H}$ = 2.0 Hz), 7.35 (d, 1H, $^3J_{H\text{-}H}$ = 2.4 Hz), 7.54 (m, 2H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 27.0 (CH_3), 27.9 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 39.7 (C, CMe_2), 69.6 (CH-N), 74.5 (CH_2-O), 120.6-150.3 (aromatic carbons), 173.1 (C=N).

(4*S*)-2-(2-(2-(((11b*R*)-2,6-Bis(trimethylsilyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)oxy)phenyl)propan-2-yl)-4-phenyl-4,5-dihydrooxazole (L4b). Yield: 261.5 mg (40%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 142.1 ppm (s). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.37 (s, 9H, CH_3-Si), 0.41 (s, 9H, CH_3-Si), 1.61 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 3.51 (t, 1H, CH2-O, $^3J_{H\text{-}H}$ = $^2J_{H\text{-}H}$ = 10.0 Hz), 3.86 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ = 10.0 Hz, $^3J_{H\text{-}H}$ = 8.0 Hz), 4.60 (dd, 1H, CH-N, $^3J_{H\text{-}H}$ = 10.0 Hz, $^3J_{H\text{-}H}$ = 8.0 Hz), 6.79 (m, 4H, CH=), 6.96 (m, 2H, CH=), 7.07 (m, 4H, CH=), 7.24 (m, 4H, CH=), 7.65 (m, 3H, CH=), 8.07 (s, 1H, CH=), 8.14 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.2 (d, CH_3-Si, $J_{C\text{-}P}$= 4.5 Hz), 0.0 (CH_3-Si), 27.0 (CH_3), 27.9 (CH_3), 40.0 (C, CMe_2), 69.0 (CH-N), 74.1 (CH_2-O), 119.6-152.4 (aromatic carbons), 172.8 (C=N).

(4*S*)-2-(2-(2-(((11b*S*)-2,6-Bis(trimethylsilyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)oxy)phenyl)propan-2-yl)-4-phenyl-4,5-dihydrooxazole (L4c). Yield: 261.5 mg (40%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 142.3 ppm (s). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.38 (s, 9H, CH_3-Si), 0.40 (s, 9H, CH_3-Si), 1.62 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 3.48 (m, 1H, CH_2-O), 3.68 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ = 10.4 Hz, $^3J_{H\text{-}H}$ = 8.0 Hz), 4.25 (dd, 1H, CH-N, $^3J_{H\text{-}H}$ = 10.0 Hz, $^3J_{H\text{-}H}$ = 8.0 Hz), 6.80 (m, 5H, CH=), 6.88 (m, 1H, CH=), 6.9-7.1 (m, 5H, CH=), 7.23 (m, 4H, CH=), 7.63 (m, 1H, CH=), 7.66 (m, 1H, CH=), 8.08 (s, 1H, CH=), 8.09 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.2 (d, CH_3-Si, $J_{C\text{-}P}$= 4.5 Hz), 0.0 (CH_3-Si), 26.8 (CH_3), 28.4 (CH_3), 39.7 (C, CMe_2), 69.0 (CH-N), 74.4 (CH_2-O), 119.9-152.3 (aromatic carbons), 172.5 (C=N).

Synthesis of (S)-2-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)propan-2-yl)phenol (15)

MeOH (7.21 ml, 0.29 mmol) was added to a solution of NaH (60% in mineral oil, 244.16 mg, 6.10 mmol) in THF (5.1 ml) at 0°C under argon and string for 1 h. The solution of 3,3-dimethylbenzofuran-2(3*H*)-one **14** (700 mg, 5.55 mmol) in THF (5.1 ml) was added at 0 °C. The resultant mixture was warmed to room temperature during 1 h. A solution of (*S*)-(+)-2-phenylglycinol (837.34 mg, 6.10 mmol) in THF (5.1 ml) was added dropwise. The mixture was stirred for 2 h. The mixture was suspended in CH_2Cl_2 (30 mL) and washed with NaOH solution (2 × 50 mL), then with 2 M HCl solution to reach to pH = 2. After drying over $MgSO_4$, solvent was evaporated to obtain intermediate (*S*)-N-(2-hydroxy-1-phenylethyl)-2-(2-hydroxyphenyl)-2-methylpropanamide as a white solid. Yield: 1.17 g (75%). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.59 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 3.72 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ = 11.4 Hz, $^3J_{H\text{-}H}$ = 7.2 Hz), 3.90 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$ = 11.4 Hz, $^3J_{H\text{-}H}$ = 4.0 Hz), 5.11 (m, 1H, CH), 6.12 (d, 1H, NH, $^3J_{H\text{-}H}$ = 7.6 Hz), 6.92 (m, 2H, CH=), 7.18 (m, 3H, CH=), 7.29 (m, 4H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= 25.2 (CH_3), 25.9 (CH_3), 45.3 (C, CMe_2), 55.6 (CH-N), 66.05 (CH_2-O), 117-155 (aromatic carbons).

To a cold (0 °C) solution of (*S*)-*N*-(2-hydroxy-1-phenylethyl)-2-(2-hydroxyphenyl)-2-methylpropanamide (1.25 g, 4.18 mmol) in CH_2Cl_2 (10 mL) was sequentially added triethylamine (2.91 mL, 20.88 mmol), DMAP (76 mg, 0.63 mmol) and methanesulfonyl chloride (0.36 mL, 4.59 mmol). The resultant mixture was warmed to room temperature and stirred overnight. The excess methanesulfonyl chloride was hydrolyzed by adding water (10 mL) and heating to reflux for 30 min. Another portion of water (25 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. After filtration and removal of the solvent under vacuum, the product was purified by flash chromatography, 5 % methanol in dichloromethane. Yield: 705 mg (60%). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.69 (b, 6H, CH_3), 4.08 (b, 1H, CH_2), 4.63 (b, 1H, CH), 4.5.17 (b, 1H, CH_2), 6.8-7.4 (m, 9H, CH=). MS HR-ESI [found 281.1416, $C_{18}H_{19}NO_2$ requires 281.1417].

General procedure for the synthesis of [Pd(I)(Ph)(L)] complexes 16-19

A solution of [Ph(I)(Ph)(TMEDA)] (25 mg, 0.058 mmol) and the corresponding ligand (0.058 mmol) in dry degassed benzene (3 ml) was stirred under Ar atmosphere at r.t. for 48 h. The reaction was monitored by ^{31}P{^{1}H} NMR during this time. The organic solvent was removed under reduced pressure. Purification by column chromatography (neutral Al_2O_3; toluene/CH_2Cl_2 gradient 1:0 to 0:1) yielded the desired products as pale-yellow solids.

(Iodo)[(*S*)-4-isopropyl-2-(2-((2,4,8,10-tetra-*tert*-butyldibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)oxy)benzyl)-4,5-dihydrooxazole](phenyl)palladium [Pd(I)(Ph)(L2a)] (16). Yield: 37 mg (66 %). MS HR-ESI [found 840.3371, $C_{47}H_{61}NO_4PPd^+$ requires 840.3368]. ^{31}P NMR (162 MHz, CD_2Cl_2) δ 96.7. ^{1}H NMR (400 MHz, C_6D_6), δ: 7.56 (d, 2H, *J* = 2.3 Hz, CH=), 7.46 (d, 1H, *J* = 2.3 Hz, CH=), 7.13 (d, 1H, $^3J_{H\text{-}H}$ = 7.5 Hz, CH=), 7.02 (d, 1H, $^3J_{H\text{-}H}$ = 6.9 Hz, CH=), 6.85-6.80 (m, 4H, CH=), 6.77 – 6.68 (m, 2H, CH=), 6.63 – 6.54 (m, 2H, CH=), 5.94 (d, 1H, $^3J_{H\text{-}H}$ = 7.3 Hz, CH-N), 4.67 (d, 1H, $^2J_{H\text{-}H}$ = 14.5 Hz, CH_2), 3.72 – 3.60 (m, 2H, CH-O), 3.10 (d, 1H, $^2J_{H\text{-}H}$ = 14.6 Hz, CH_2), 2.94 (m, 1H, CH, ^{i}Pr), 1.58 (s, 18 H, CH_3, ^{t}Bu), 1.19 (s, 9 H, CH_3, ^{t}Bu), 1.13 (s, 9 H, CH_3, ^{t}Bu), 0.97 (d, 3H, $^3J_{H\text{-}H}$ = 6.8 Hz, CH_3, ^{i}Pr), 0.87 (d, 3H, $^3J_{H\text{-}H}$ = 6.9 Hz, CH_3, ^{i}Pr). ^{13}C NMR (100 MHz, C_6D_6), δ: 166.3 (C=N), 152.7 (d, C_{ipso}, $J_{C\text{-}P}$= 15.8 Hz), 148.4 (d, C-O, $J_{C\text{-}P}$= 16.1 Hz), 147.3 (d, C-O, $J_{C\text{-}P}$= 6.2 Hz), 148.445.6 (d, C-O, $J_{C\text{-}P}$= 11.2 Hz),138.7-121.3 (aromatic carbons), 72.3 (CH-O), 69.8 (CH-N), 36.2 (CH_2), 34.6 (C), 31.7 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.0 (C, ^{i}Pr), 19.3 (CH_3, ^{i}Pr), 16.2 (CH_3, ^{i}Pr).

(Iodo)(phenyl)[(4*S*)-2-(2-(((11b*R*)-2,6-bis(trimethylsilyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)oxy)benzyl)-4-isopropyl-4,5-dihydrooxazole]palladium [Pd(I)(Ph)(L2b)] (17). Yield: 6 mg (12%). MS HR-ESI [found 860.1959, $C_{45}H_{49}NO_4PPdSi_2^+$ requires 860.1967]. Major isomer: ^{31}P NMR (162 MHz, CD_2Cl_2) δ 112.3 (b, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2), δ: 0.62 (s, 18H, $SiMe_3$), 0.96 (d, 6H, $^3J_{H\text{-}H}$= 5.6 Hz, CH_3, ^{i}Pr), 2.61 (m, 1H, CH, ^{i}Pr), 4.27 (m, 1H, CH_2), 4.30 (m, 2H, CH_2-O), 4.40 (m, 1H, CH_2), 4.70 (m, 1H, CH-N), 6.10 (m, 1H, CH=), 6.7-7.9 (m, 17H, CH=), 8.20 (s, 1H, CH=). Minor isomer: ^{31}P NMR (162 MHz, CD_2Cl_2) δ 104.6 (b, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2), δ: 0.45 (s, 18H, $SiMe_3$), 0.91 (d, 3H, $^3J_{H\text{-}H}$= 5.6 Hz, CH_3, ^{i}Pr), 0.93 (d, 3H,

$^3J_{H-H}$= 5.6 Hz, CH_3, ^{i}Pr), 2.61 (m, 1H, CH, ^{i}Pr), 4.24 (m, 1H, CH_2), 4.31 (m, 2H, CH_2-O), 4.40 (m, 1H, CH_2), 4.73 (m, 1H, CH-N), 5.94 (m, 1H, CH=), 6.7-7.9 (m, 17H, CH=), 8.25 (s, 1H, CH=).

(Iodo)(phenyl)[(4*S*)-2-(2-(((11b*S*)-2,6-bis(trimethylsilyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)oxy)benzyl)-4-isopropyl-4,5-dihydrooxazole]palladium [Pd(I)(Ph)(L2c)] (18). Yield: 36 mg (73%). MS HR-ESI [found 860.1961, $C_{45}H_{49}NO_4PPdSi_2^+$ requires 860.1967]. Major isomer: ^{31}P NMR (162 MHz, CD_2Cl_2) δ 101.2. ^{1}H NMR (400 MHz, CD_2Cl_2), δ: 0.62 (s, 9H, $SiMe_3$), 0.65 (s, 9H, $SiMe_3$), 1.02 (d, 3H, $^3J_{H-H}$= 5.8 Hz, CH_3, ^{i}Pr), 1.10 (d, 3H, $^3J_{H-H}$= 5.6 Hz, CH_3, ^{i}Pr), 2.74 (m, 1H, CH, ^{i}Pr), 3.57 (d, 1H, $^2J_{H-H}$= 11.0 Hz, CH_2), 4.27 (m, 1H, CH_2-O), 4.41 (dd, 1H, $^2J_{H-H}$= 8.4 Hz, $^3J_{H-H}$= 7.2 Hz, CH_2-O), 4.60 (d, 1H, $^2J_{H-H}$= 11.0 Hz, CH_2), 5.15 (m, 1H, CH-N), 5.84 (d, 1H, $^3J_{H-H}$= 6.6 Hz, CH=), 5.97 (m, 1H, CH=), 6.26 (m, 1H, CH=), 6.71 (m, 2H, CH=), 6.84 (m, 1H, CH=), 7.03 (m, 1H, CH=), 7.12 (m, 3H, CH=), 7.26 (m, 1H, CH=), 7.44 (m, 3H, CH=), 7.95 (m, 3H, CH=), 8.14 (s, 1H, CH=), 8.25 (s, 1H, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2), δ: 0.3 (CH_3-Si), 0.46 (CH_3-Si), 16.1 (CH_3, ^{i}Pr), 19.6 (CH_3, ^{i}Pr), 30.6 (CH, ^{i}Pr), 34.7 (CH_2), 70.0 (CH_2-O), 71.9 (CH-N), 113.7-138.2 (aromatic carbons), 150.3 (d, C-O, J_{C-P}= 11 Hz), 151.5 (d, C-O, J_{C-P}= 6.4 Hz), 151.6 (d, C_{ipso}, J_{C-P}= 18.6 Hz), 151.7 (d, C-O, J_{C-P}= 3.2 Hz), 166.5 (d, C=N, J_{C-P}= 3.0 Hz). Minor isomer: ^{31}P NMR (162 MHz, CD_2Cl_2) δ 110.8. ^{1}H NMR (400 MHz, CD_2Cl_2), δ: 0.63 (s, 9H, $SiMe_3$), 0.66 (s, 9H, $SiMe_3$), 1.02 (d, 3H, $^3J_{H-H}$= 5.8 Hz, CH_3, ^{i}Pr), 1.09 (d, 3H, $^3J_{H-H}$= 5.6 Hz, CH_3, ^{i}Pr), 2.74 (m, 1H, CH, ^{i}Pr), 3.59 (d, 1H, $^2J_{H-H}$= 11.0 Hz, CH_2), 4.27 (m, 1H, CH_2-O), 4.46 (dd, 1H, $^2J_{H-H}$= 8.2 Hz, $^3J_{H-H}$= 7.2 Hz, CH_2-O), 4.61 (d, 1H, $^2J_{H-H}$= 11.4 Hz, CH_2), 4.95 (m, 1H, CH-N), 5.80 (d, 1H, $^3J_{H-H}$= 6.6 Hz, CH=), 6.13 (m, 1H, CH=), 6.71 (m, 2H, CH=), 6.84 (m, 1H, CH=), 6.90 (m, 1H, CH=), 7.03 (m, 1H, CH=), 7.12 (m, 3H, CH=), 7.26 (m, 1H, CH=), 7.44 (m, 3H, CH=), 7.95 (m, 3H, CH=), 8.11 (s, 1H, CH=), 8.26 (s, 1H, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2), δ: 0.2 (CH_3-Si), 0.3 (CH_3-Si), 16.1 (CH_3, ^{i}Pr), 19.5 (CH_3, ^{i}Pr), 30.7 (CH, ^{i}Pr), 34.7 (CH_2), 69.4 (CH-N), 69.9 (CH_2-O), 113.7-138.2 (aromatic carbons), 150.4 (d, C-O, J_{C-P}= 10 Hz), 151.4 (d, C-O, J_{C-P}= 6.4 Hz), 151.7 (d, C-O, J_{C-P}= 3.0 Hz), 166.4 (d, C=N, J_{C-P}= 2.6 Hz).

[(4*S*)-2-(2-(((11a*S*)-4,8-di-*tert*-butyl-1,2,10,11-tetramethyldibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)oxy)benzyl)-4-isopropyl-4,5-dihydrooxazole](iodo)(phenyl)palladium [Pd(I)(Ph)(L2e)] (19). Yield: 32 mg (71%). MS HR-ESI [found 784.2739, $C_{43}H_{53}NO_4PPd^+$ requires 784.2742]. ^{31}P NMR (162 MHz, CD_2Cl_2) δ 91.3 (s). ^{1}H NMR (400 MHz, CD_2Cl_2), δ: 0.99 (s, 6H, CH_3, ^{i}Pr), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 2.20 (s, 3H, CH_3), 2.23 (s, 6H, CH_3) 2.30 (s, 3H, CH_3), 2.73 (m, 1H, CH, ^{i}Pr), 3.53 (d, 1H, $^2J_{H-H}$= 14.0 Hz, CH_2), 4.22 (m, 1H, CH_2-O), 4.34 (m, 1H, CH_2-O), 4.56 (d, 1H, $^2J_{H-H}$= 14.0 Hz, CH_2), 5.05 (m, 1H, CH-N), 5.84 (d, 1H, $^3J_{H-H}$= 7.6 Hz, CH=), 6.51 (m, 2H, CH=), 6.7-7.3 (m, 7H, CH=), 7.35 (s, 1H, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2), δ: 15.6 (CH_3, ^{i}Pr), 15.7 (CH_3, ^{i}Pr), 19.1 (CH_3), 19.7 (CH_3), 20.0 (CH_3), 30.8 (CH, ^{i}Pr), 31.1 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 34.1 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.7 (CH_2), 69.7 (CH_2-O), 71.9 (CH-N), 121.0-143.7 (aromatic carbons), 145.3 (d, C_{ipso}, J_{C-P}= 16.4 Hz), 166.5 (C=N).

Synthesis of (iodo)[(S)-4-isopropyl-2-(2-((2,4,8,10-tetra-tert-butyldibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)oxy)benzyl)-4,5-dihydrooxazole](trifluoromethanesulphonate)palladium [Pd(Ph)(OTf)(L2a)] (26)

Silver triflate (16 mg, 0.062 mmol) was added to a vigorously stirred solution of the complex [Pd(I)(Ph)(**L2a**)] (30 mg, 0.031 mmol) in dry degassed THF (4 ml) under Ar atmosphere at r.t.. Stirring was continued for 1h, during which period a pale grey precipitate was formed. The reaction mixture then filtered over celite, and all volatiles were removed under reduced pressure to yield the final product as a pale brown solid (55 mg, 90 %). ^{31}P NMR (162 MHz, CD_2Cl_2), δ: 96.99. ^{1}H NMR (401 MHz, CD_2Cl_2), δ: 7.59 (d, 1H, $^3J_{H-H}$ = 2.3 Hz, CH=), 7.47 (d, 1H, $^3J_{H-H}$ = 2.1 Hz, CH=), 7.34 – 7.27 (m, 3H, CH=), 7.09 (t, 1H, $^3J_{H-H}$ = 7.5 Hz, CH=), 7.01 (dd, 1H, $^3J_{H-H}$ = 7.9, 1.3 Hz, CH=), 6.99 – 6.88 (m, 5H, CH=), 5.84 (d, 1H, $^3J_{H-H}$ = 8.1 Hz, CH=), 4.57 (d, 1H, $^2J_{H-H}$ = 14.6 Hz, CH_2), 4.48 (d, 1H, $^3J_{H-H}$ = 8.3 Hz, CH_2-O), 4.38 (m, 1H, CH-N), 4.29 (m, 1H, CH_2-O), 3.71 (d, 1H, $^2J_{H-H}$ = 14.5 Hz, CH_2), 2.52 (m, 1H, CH, ^{i}Pr), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.07 (d, 3H, ^{i}Pr, $^3J_{H-H}$ = 6.9 Hz), 1.03 (d, 3H, ^{i}Pr, $^3J_{H-H}$ = 6.7 Hz).^{13}C NMR (101 MHz, CD_2Cl_2), δ: 169.2 (C=N), 151.7-121.3 (aromatic carbons), 70.9 (CH-O), 69.8 (CH-N), 34.5 (CH_2), 34.1 (C), 33.9 (C), 31.9 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 30.0 (C, ^{i}Pr), 19.1 (CH_3, ^{i}Pr), 16.4 (CH_3, ^{i}Pr). ^{19}F NMR (377 MHz, CD_2Cl_2), δ: -78.01. MS HR-ESI [found 840.3372, $C_{47}H_{61}NO_4PPd^+$ requires 840.3368].

General procedure for Pd-catalyzed enantioselective Heck reactions with several triflates

A mixture of $[Pd_2(dba)_3]\cdot C_6H_6$ (12 mg, 1.25×10^{-2} mmol) and the corresponding chiral ligand (2.3 equiv) in dry degassed solvent (3.0 mL) was stirred at room temperature for 20 min. The corresponding olefin (2.0 mmol), triflate (0.50 mmol) and *N*-diisopropylethylamine (1.0 mmol) were added to the catalyst solution. The vial was sealed and brought out and the solution was vigorously stirred at the desired temperature. After the desired reaction time, the reaction mixture was cooled to ambient temperature and internal standard (undecane, 0.5 mmol) was added. The mixture was diluted with additional diethyl ether and after agitation, the mixture was filtered through a short silica gel plug and analyzed by ^{1}H-NMR or GC to determine the conversion and regioselectivity. The crude was subjected to flash chromatography (pentane/Et_2O) to give the purified product. Enantioselectivities were determined using chiral HPLC or GC (see Supporting Information for details).

Pd-catalyzed enantioselective Heck reactions of 2,3-dihydrofuran with aryl halides

$[Pd(dba)_2]\cdot C_6H_6$ (8.5 mg, 0.013 mmol) and ligand (0.015 mmol) in degassed ethylene glycol (1.0 mL) were stirred at room temperature for 20 min. Aryl halide (0.50 mmol), *N*-diisopropylethylamine (255 μL, 1.5 mmol, 3 equiv), silver triflate (192.7 mg, 0.75 mmol, 1.5 equiv) and 2,3-dihydrofuran (75 μL, 1.0 mmol, 2 equiv) were added to the catalyst solution. The vial was sealed and brought out and the mixture was vigorously stirred in an oil bath at 80 oC, for 24h. The reaction mixture was cooled to ambient temperature and internal standard (undecane, 0.5 mmol) was added. The mixture was diluted with additional diethyl ether and after agitation, the mixture was filtered through a short silica gel plug and analyzed by ^{1}H-NMR or GC to determine the conversion and regioselectivity. The crude was subjected to flash chromatography (pentane/Et_2O) to give the purified product. Enantioselectivities were determined using chiral HPLC or GC (see Supporting Information for details).

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