Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 941

www.rsc.org/obc

PAPER

Phosphite-oxazole/imidazole ligands in asymmetric intermolecular Heck reaction†

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Received 1st September 2010, Accepted 22nd October 2010
DOI: 10.1039/c0ob00656d

We describe the application of a new class of ligands –the phosphite-oxazole/imidazole (**L1–L5a–g**) – in asymmetric intermolecular Pd-catalyzed Heck reactions under thermal and microwave conditions. These ligands combine the advantages of the oxazole/imidazole moiety with those of the phosphite moiety: they are more stable than their oxazoline counterparts, less sensitive to air and other oxidizing agents than phosphines and phosphinites, and easy to synthesize from readily available alcohols. The results indicate that activities, regio- and enantioselectivities, are highly influenced by the type of nitrogen donor group (oxazole or imidazole), the oxazole and biaryl-phosphite substituents and the axial chirality of the biaryl moiety of the ligand. By carefully selecting the ligand components, we achieved high activities, regio- (up to 99%) and enantioselectivities (up to 99%) using several triflate sources. Under microwave-irradiation conditions, reaction times were considerably shorter (from 24 h to 30 min) and regio- and enantioselectivities were still excellent.

Introduction

The Heck reaction is one of the most versatile catalytic methods for C–C bond formation. In this process an aryl or alkenyl halide or triflate is coupled with an alkene.[1] Its applicability to highly functionalized substrates confers upon the reaction a very wide substrate scope, and it has been used in a number of syntheses of complex natural products.[1] During the past decade, research in the Heck reaction has focused on the possibility of controlling its enantioselectivity. The bulk of the reported examples involve intramolecular reactions, which have the advantage that the alkene regiochemistry and product geometry can be easily controlled.[1] Fewer studies, however, have been conducted on the asymmetric intermolecular version. This is mainly because regioselectivity is also often a problem.[1] Although diphosphines (such as BINAP) were used early on this process,[1,2] heterodonor phosphine-oxazolines have recently emerged as more suitable ligands for the intermolecular Heck reaction.[1a–b,3,4] Two drawbacks of these latter ligands are the long reaction times usually required to achieve full conversion and the substrate specificity.

In the last decade, a group of less electron-rich phosphorus compounds – phosphite-containing ligands – have demonstrated their huge potential utility in many transition-metal catalyzed reactions.[5] Their highly modular construction, facile synthesis from readily available chiral alcohols and greater resistance to oxidation than phosphines have proved to be highly advantageous.[6] Despite all these benefits, the use of phosphite-containing ligands for the Pd-catalyzed Heck reaction has not been reported until very recently. In this context, phosphite-oxazolines have emerged as extremely effective ligands for improving the activity and versatility of this process.[7] Despite this success, little attention has been paid to phosphite-containing ligands for this process and their potential as new ligands still needs to be systematically studied.[7]

To further expand the range of ligands and encouraged by the success of biaryl phosphite-oxazoline ligands[7] in this process we report here the first application of a biaryl phosphite-oxazole/imidazole ligand library (**L1–L5a–g**) in the asymmetric intermolecular Pd-catalyzed Heck reaction (Fig. 1). For comparative purposes, we also evaluated phosphinite-oxazole/imidazole analogues (ligands **L6** and **L7**, Fig. 1). Phosphite-oxazoline/imidazole ligands combine *a priori* the above mentioned advantages of introducing a phosphite moiety with those of the oxazole/imidazole moiety. So, ligands **L1–L5a–g** are more stable than their oxazoline counterparts.[8] With this library we fully investigated the effects of either an oxazole or imidazole group in the ligand backbone, the effect of systematically varying the electronic and steric properties of the oxazole substituents (**L1–L4**) and different substituents/configurations in the biaryl phosphite moiety (**a–g**). By carefully selecting these elements,

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† Electronic supplementary information (ESI) available: Profiles of the microwave experiments and ^{1}H and ^{13}C NMR of compounds **L5a–c** and **L7**. See DOI: 10.1039/c0ob00656d

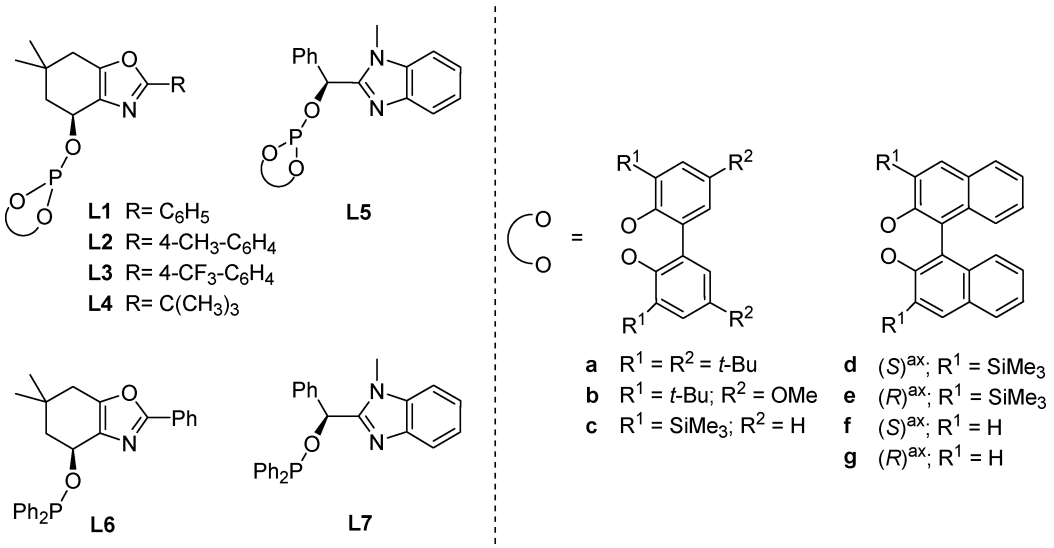


Fig. 1 Phosphite-oxazole/imidazole ligand library **L1–L5a–g** and phosphinite-oxazole/imidazole ligands **L6** and **L7**.

we achieved high selectivities (regio- and enantioselectivities) and activities using several triflate sources.

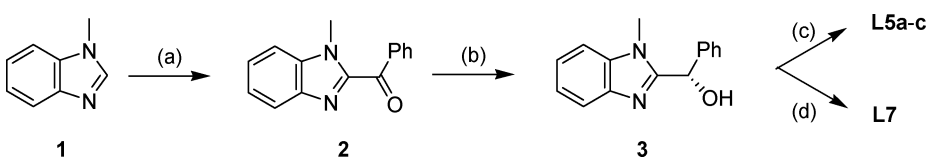
Results and discussion

Synthesis of ligands

Phosphite-oxazole ligands **L1–L4a–g** and phosphinite-oxazoline ligand **L6** have been synthesized from the corresponding easily accessible ketone-oxazole as previously described.[9,10] Scheme 1 illustrates the sequence of synthesis for the new phosphite-imidazole ligands **L5a–c** and phosphinite/imidazole ligand **L7**. They were synthesized very efficiently from the easily accessible hydroxyl-imidazole **3**. This compound was prepared in a few steps from commercially available *N*-methyl benzimidazole **1**. In the first step of the synthesis, **1** was acetylated *via* a two step one pot procedure that involves deprotonation of **1** with LDA followed by reaction with methyl benzoate to produce ketone **2**.[11] Ketone **2** was then reduced by slow addition to a solution of (*R*)-Me-CBS catalyst (10 mol%, (*R*)-Me-CBS = α,α-diphenyl-D-prolinolmethylboronic acid cyclamide ester), employing $BH_3{\cdot}SMe_2$ as stoichiometric reductant in THF.[12] Recrystallization from 95% ethanol of the obtained hydroxyl-imidazole yielded enantiomerically pure **3**. Treating alcohol **3** with 1 equivalent of either the appropriate *in situ* formed phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a–c**) or chlorodiphenylphosphine in the presence of pyridine provided easy access to the desired phosphite-imidazole (**L5a–c**) and phosphinite-imidazole (**L7**) ligands, respectively. All the phosphite-imidazole ligands were stable during purification on neutral alumina under an atmosphere of argon and isolated in moderate-to-good yields as white solids. They were stable at room temperature and very stable to hydrolysis. The elemental analyses were in agreement with the assigned structure. The ^1H, ^{13}C and ^{31}P NMR spectra were as expected for these C_1 ligands. One singlet for each compound was observed in the ^{31}P NMR spectrum. Rapid ring inversions (atropoisomerization) in the biphenyl-phosphorus moieties (**a–c**) occurred on the NMR time scale because the expected diastereoisomers were not detected by low-temperature phosphorus NMR.[13]

Asymmetric phenylation of 2,3-dihydrofuran (S1) under thermal conditions

In a first set of experiments, we used the Pd-catalyzed phenylation of 2,3-dihydrofuran **S1** to study the potential of ligands **L1–L5a–g** (eqn (1)). **S1** was chosen as the substrate 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] In all cases, the catalysts were generated *in situ* by mixing $[Pd_2(dba)_3]{\cdot}dba$ with the corresponding chiral ligand.[7] The results are summarized in Table 1. We found that the catalytic performance was highly influenced by type of nitrogen donor group (oxazole or imidazole), the substituents at both oxazole and phosphite moieties and by the axial chirality of the biaryl phosphite group. In general, high activity, regio- (up to 97%) and enantioselectivity (up to 98%) were obtained in the phenylation of **S1**.

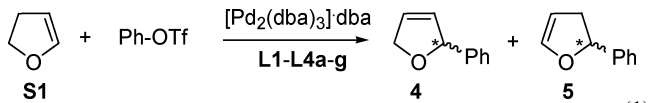


Scheme 1 Synthesis of new phosphite/phosphinite-imidazole ligands **L5a–c** and **L7**. (a) LDA/THF then PhCOOEt (78% yield).[11] (b) (*R*)-Me-CBS/$BH_3{\cdot}SMe_2$/THF (87% yield).[12] (c) $ClP(OR)_2$; $(OR)_2$ = **a–c**/Py/toluene (Yields: 54–71%). (d) $ClPPh_2$/Py/DMAP/THF (68% yield).

Table 1 Selected results for the Pd-catalyzed enantioselective phenylation of 2,3-dihydrofuran **S1** using ligands **L1–L5a–g**[a]

Entry	Ligand	% Conv (**4** : **5**)[b]	% ee **4**[c]
1	**L1a**	77 (97 : 3)[e]	98 (*R*)
2	**L1b**	27 (97 : 3)	97 (*R*)
3	**L1c**	21 (94 : 6)	91 (*R*)
4	**L1d**	17 (96 : 4)	96 (*R*)
5	**L1e**	7 (92 : 8)	89 (*R*)
6	**L1f**	<5	nd[d]
7	**L1g**	<5	nd[d]
8	**L2a**	74 (97 : 3)	98 (*R*)
9	**L3a**	54 (96 : 4)	96 (*R*)
10	**L4a**	<5	nd[d]
11	**L5a**	24 (85 : 15)	75 (*R*)
12	**L5b**	7 (83 : 17)	73 (*R*)
13	**L5c**	8 (84 : 16)	64 (*R*)
14[f]	**L6**	9 (81 : 19)	56 (*R*)
15[f]	**L7**	6 (78 : 22)	21 (*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 percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] Not determined. [e] % isolated yield of **4**. [f] t = 48 h.



(1)

Regarding the effect of the oxazole substituents, we found that these groups affected mainly activities (Table 1, entries 1 and 8–10). Bulky substituents at this position dramatically decreased activities (Table 1, entry 1 *vs.* 10). This contrasts with the oxazoline-substituent effect observed for the vast majority of successful phosphine-oxazoline ligands, for which better results are obtained when bulky *tert*-butyl groups are present.[3] In addition, we also found that the presence of electron-withdrawing substituents also has a negative effect on activity, but almost no effect on the regio- and enantioselectivity of the process (Table 1, entries 1, 8 and 9).

Concerning the effect of the phosphite moiety on the catalytic performance, we found that bulky *tert*-butyl substituents at both the *ortho* and *para* positions are necessary for high activity and regio- and enantioselectivity (Table 1, entry 1 *vs.* 2 and 3). To further investigate how enantioselectivity was influenced by the axial chirality of the biaryl moiety, ligands **L1d** and **L1e**, containing different enantiomerically pure trimethylsilyl-substituted binaphthyl moieties, were also tested (Table 1, entries 4 and 5). The results indicate that there is a cooperative effect between the configuration of the biaryl moiety and the configuration of the ligand backbone on enantioselectivity that results in a matched combination for ligand **L1d**, which contains an *S*-binaphthyl moiety (Table 1, entry 4). In addition, by comparing the results obtained using ligand **L1c** with those of the related binaphthyl ligands **L1d** and **L1e** (Table 2, entries 3–5), we can conclude that: a) atropoisomerization in the biphenyl moiety can be controlled if substituents at the *para* position are present, and b) the biphenyl phosphite moieties in ligands **L1a** and **L1b** adopt *S*-configurations upon complexation to palladium.[14]

Finally, after comparing these results with those from phosphite-imidazole ligands **L5**, we found that the presence of an imidazole donor group has a negative effect on activity, regio- and enantioselectivity (Table 1, entries 11–13 *vs.* 1–3).

Table 2 Selected results for Pd-catalysed enantioselective arylation of 2,3-dihydrofuran **S1** using ligands **L1–L5a–g**[a]

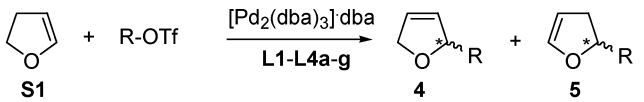
Entry	L	R	% Conv (**4** : **5**)[b]	% Yield **4**	% ee **4**[c]
1	**L1a**	4-CH_3-C_6H_4	69 (92 : 8)	60	99 (*R*)
2	**L1b**	4-CH_3-C_6H_4	23 (92 : 8)	18	99 (*R*)
3	**L1c**	4-CH_3-C_6H_4	24 (90 : 10)	17	92 (*R*)
4	**L1d**	4-CH_3-C_6H_4	23 (92 : 8)	16	98 (*R*)
5	**L1e**	4-CH_3-C_6H_4	19 (89 : 11)	15	87 (*R*)
6	**L4a**	4-CH_3-C_6H_4	<5	nd[d]	nd[d]
7	**L5a**	4-CH_3-C_6H_4	21 (84 : 16)	15	73 (*R*)
8	**L1a**	4-NO_2-C_6H_4	99 (>99:<1)	97	99 (*R*)
9	**L1b**	4-NO_2-C_6H_4	37 (99 : 1)	34	99 (*R*)
10	**L1c**	4-NO_2-C_6H_4	31 (96 : 4)	28	97 (*R*)
11	**L4a**	4-NO_2-C_6H_4	<5	nd[d]	nd[d]
12	**L5a**	4-NO_2-C_6H_4	26 (88 : 12)	21	72 (*R*)
13	**L1a**	1-Naphthyl	98 (95 : 5)	93	>99 (*R*)
14	**L1a**	1-Cyclohexenyl	92 (99 : 1)	90	69 (*R*)
15	**L4a**	1-Cyclohexenyl	<5	nd[d]	nd[d]
16	**L5a**	1-Cyclohexenyl	15 (80 : 20)	9	54 (*R*)

[a] $[Pd_2(dba)_3]$·dba (2.5×10^{-2} mmol), **S1** (4.0 mmol), triflate (1 mmol), Ligand (5.6×10^{-2} mmol), THF (6 mL), $^iPr_2NEt$ (2 mmol), T = 50 °C, t = 24 h. [b] Conversion percentages determined by GC or ^{1}H-NMR (see Experimental section). [c] Enantiomeric excesses measured by GC or HPLC (see Experimental section). [d] Not determined.

To sum up, the best activities, regio- (up to 97%) and enantioselectivities (up to 98%) were obtained with ligand **L1a**, which contains the optimal combination of substituents in the oxazole and in the biaryl phosphite moiety. Interestingly, when this latter result is compared with the enantioselectivities obtained with their corresponding Pd-phosphinite-oxazole/imidazole (Pd-**L6**/**L7**) catalytic systems (Table 1, entries 14 and 15), we can conclude that introducing a phosphite moiety into the ligand design is advantageous. These results also clearly show the efficiency of using highly modular scaffolds in the ligand design and are among the best that have been reported in the literature.[3a,b,e,k,l,7b,c]

Asymmetric Heck reaction of 2,3-dihydrofuran (S1) using other triflate sources under thermal conditions

To further study the potential of these readily available ligands, we also examined **L1–L5a–g** in the Pd-catalyzed Heck reaction of **S1** with several aryl triflates. Therefore the effects of the electronic and steric properties of the aryl triflate source on the product outcome were systematically evaluated (eqn (2), R = *p*-CH_3-C_6H_4, *p*-NO_2-C_6H_4, 1-naphthyl).



R= *p*-CH_3-C_6H_4, *p*-NO_2-C_6H_4, 1-Naphthyl, 1-Cyclohexenyl

(2)

The most noteworthy results are shown in Table 2 (entries 1–13). They followed the same trends as for the phenylation of **S1**. Again, the arylated products **4** were accessible in high activities, and high regio- (up to >99%) and enantioselectivities (ee's up to >99%) with Pd/**L1a** catalytic system. The results indicate that both the steric and electronic parameters of the triflate affected mainly regioselectivity, whereas their effect on enantioselectivity was less

Table 3 Selected results for the microwave-assisted Pd-catalyzed enantioselective Heck reaction of 2,3-dihydrofuran **S1** using ligands **L1–L5c–g**[a]

Entry	L	R	T/°C	t/min	% Conv (**4** : **5**)[b]	% ee **4**[c]
1	**L1a**	C_6H_5	50	30	<5	nd[d]
2	**L1a**	C_6H_5	70	10	48 (98 : 2)	99 (*R*)
3	**L1a**	C_6H_5	70	30	100 (98 : 2)	99 (*R*)
4	**L1c**	C_6H_5	70	30	32 (94 : 6)	92 (*R*)
5	**L2a**	C_6H_5	70	30	96 (98 : 2)	98 (*R*)
6	**L3a**	C_6H_5	70	30	85 (96 : 4)	96 (*R*)
7	**L4a**	C_6H_5	70	30	<5	nd[d]
8	**L5a**	C_6H_5	70	30	69 (89 : 11)	76 (*R*)
9	**L1a**	4-CH_3-C_6H_4	70	30	92 (99 : 1)	99 (*R*)
10	**L1a**	4-NO_2-C_6H_4	70	30	96 (98 : 2)	98 (*R*)
11	**L1a**	1-Naphthyl	70	30	92 (97 : 3)	99 (*R*)
12	**L1a**	1-Cyclohexenyl	80	360	89 (92 : 8)	89 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), triflate (0.5 mmol), ligand (2.8×10^{-2} mmol), THF (3 mL), $^iPr_2NEt$ (1 mmol). [b] Conversion percentages determined by GC or ^{1}H-NMR (see Experimental section). [c] Enantiomeric excesses measured by GC or HPLC (see Experimental section). [d] Not determined.

important (Table 2, entries 1, 8 and 13). Thus, regioselectivities are best with the electron-deficient *para*-nitrophenyl triflate. Again, these results are among the best that have been reported in the literature.[3f,k,l,7b]

We next evaluated the ligand library in the Heck reaction of **S1** with cyclohexenyl triflate (eqn (2), R = 1-cyclohexenyl; Table 2, entries 14–16). Although the Pd-catalyst precursors containing ligand **L1a** again provided the alkenylated product **4** in high activity and regioselectivity (up to 99%), enantioselectivity was only moderate (up to 69% ee).

Microwave-assisted asymmetric Heck reactions

The benefits of microwave irradiation, including reduction of reaction times and electricity costs, have already been reported in several C–C coupling reactions.[15] In this context we have recently shown that, when microwaves are used as the source of heat, the reaction proceeds much faster and retains excellent enantioselectivity, allowing for a highly selective intermolecular Heck reaction.[7b,16] Therefore, we decided to use ligands **L1–L5a–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** using phenyl triflate with ligand **L1a** (Table 3). We found that the optimal temperature was 70 °C. At a lower temperature, activities decreased considerably (Table 3, entries 1 *vs.* 2 and 3). Under these optimized conditions, we evaluated the complete series of ligands. The most noteworthy results are shown in Table 3 (entries 3–8). Catalytic performance in the Pd-catalyzed phenylation of **S1** under microwave conditions followed the same trend as for the phenylation under thermal conditions. As expected, however, using controlled microwave dielectric heating considerably improved activities (from 24 h to 30 min), while maintaining the excellent regio- (up to 98%) and enantioselectivities (up to 99% ee). These observations are also true for other aryl triflate sources, so activities, and regio- (up to 99%) and enantioselectivities (up to 99% ee) are excellent (Table 3, entries 9–11).

Encouraged by these excellent results, we also studied the cyclohexenylation of **S1**, which provided moderate enantioselectivity under thermal conditions (Table 2, entry 12). After the reaction parameters had been optimized, we found that the optimal temperature was 80 °C. By using microwave irradiation, enantioselectivity increased up to 89% with a regioselectivity of 92% (Table 3, entry 12).

Conclusions

We have described the first application of phosphite-oxazole/imidazole ligands in asymmetric intermolecular Pd-catalyzed Heck reactions under thermal and microwave conditions. These ligands are more stable than their oxazoline counterparts, less sensitive to air and other oxidizing agents than phosphines and phosphinites, and easy to synthesize from readily available alcohols. In addition, they can be easily tuned in the oxazole and biaryl phosphite moieties, so that their effect on catalytic performance can be explored. We found that regio- and enantioselectivities and activities are highly influenced by the ligand components. By carefully selecting them, excellent activities (up to 100% conversion in 30 min) and regio- (up to >99%) and enantioselectivities (up to 99% ee) were obtained using several triflate sources. The use of microwave irradiation conditions allowed considerably shorter reaction times maintaining excellent regio- and enantioselectivities. In addition, the efficiency of this ligand design is also corroborated by the fact that these Pd-phosphite-oxazole/imidazole catalysts provided higher enantioselectivity than their phosphinite analogues. These results open up a new class of robust phosphite-oxazole ligands for the highly active and enantioselective Pd-catalyzed Heck reaction, which will be of great practical interest.

Experimental section

General considerations

All syntheses were performed with standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Ligands **L1–L4a–g** and **L6** were synthesized as previously described.[9,10] All other reagents were used as commercially available. ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR spectra were recorded on a 400 MHz spectrometer. The chemical shifts are referenced to tetramethylsilane (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. The ^{1}H and ^{13}C NMR spectral assignments were determined by ^{1}H-^{1}H and ^{1}H-^{13}C correlation spectra. Microwave experiments were carried out using a CEM Explorer, in which the temperature is controlled by a non-contact infrared sensor that is located beneath the cavity floor and "looks" up to the bottom of the vessel.

General procedure for the preparation of ligands L5a–c

The corresponding phosphorochloridite (1.5 mmol) produced *in situ* was dissolved in toluene (6 mL) and pyridine (0.57 mL, 12 mmol) was added. Hydroxyl-imidazole **3**[12] (333.6 mg, 1.4 mmol) was azeotropically dried with toluene (3 × 2 mL) and then dissolved in toluene (6 mL) to which pyridine (0.57 mL, 12 mmol) was added. The imidazole 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 in alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as a white solid.

L5a. Yield: 0.67 g, 71%. ^{31}P NMR (400 MHz, C_6D_6), δ: 143.0 (s). ^{1}H NMR (400 MHz, C_6D_6), δ: 1.25 (br, 36H, CH_3, ^{t}Bu), 2.97 (s, 3H, CH_3-N), 6.86 (d, 1H, CH-O, J = 9.2 Hz), 6.76–7.92 (m, 13H, CH═). ^{13}C NMR (400 MHz, C_6D_6), δ: 30.7 (CH_3-N), 31.8 (CH_3, ^{t}Bu), 32.5 (CH_3, ^{t}Bu), 35.6 (C, ^{t}Bu), 36.3 (C, ^{t}Bu), 75.3 (d, C-O, J_{C-P} = 8.4 Hz), 110–155 (aromatic carbons). Anal. Calc (%) for $C_{43}H_{53}N_2O_3P$: C 76.30, H 7.89, N 4.14; found C 76.35, H 7.92, N 4.11.

L5b. Yield: 0.47 g, 54%. ^{31}P NMR (400 MHz, C_6D_6), δ: 143.1 (s). ^{1}H NMR (400 MHz, C_6D_6), δ: 1.23 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 9H, CH_3, ^{t}Bu), 3.09 (s, 3H, CH_3-N), 3.32 (s, 3H, CH_3-O), 3.34 (s, 3H, CH_3-O), 6.80 (d, 1H, CH-O, J = 7.2 Hz), 6.72–7.98 (m, 13H, CH═). ^{13}C NMR (400 MHz, C_6D_6), δ: 30.3 (CH_3-N), 31.1 (CH_3, ^{t}Bu), 35.7 (C, ^{t}Bu), 55.5 (CH_3-O), 74.9 (d, C-O, J_{C-P} = 13 Hz), 110–155 (aromatic carbons). Anal. Calc (%) for $C_{37}H_{41}N_2O_5P$: C 71.14, H 6.62, N 4.48; found C 71.21, H 6.68, N 4.43.

L5c. Yield: 0.53 g, 63%. ^{31}P NMR (400 MHz, C_6D_6), δ: 143.7 (s). ^{1}H NMR (400 MHz, C_6D_6), δ: 0.16 (s, 9H, CH_3-Si), 0.19 (s, 9H, CH_3-Si), 3.00 (s, 3H, CH_3-N), 6.89 (d, 1H, CH-O, J = 9.2 Hz), 6.84–8.00 (m, 15H, CH═). ^{13}C NMR (400 MHz, C_6D_6), δ: 0.0 (CH_3-Si), 0.1 (CH_3-Si), 30.1 (CH_3-N), 74.2 (d, C-O, J_{C-P} = 3.8 Hz), 110–155 (aromatic carbons). Anal. Calc (%) for $C_{33}H_{37}N_2O_3PSi_2$: C 66.41, H 6.25, N 4.69; found C 66.38, H 6.21, N 4.71.

Procedure for the preparation of ligand L7

A solution of chlorodiphenylphosphine (0.14 mL, 0.77 mmol) in THF (3 mL) was slowly added at 0 °C to a solution of **3** (166.8 mg, 0.7 mmol) and 18.3 mg (0.15 mmol) of DMAP in pyridine (1 mL). The reaction mixture was stirred overnight at room temperature. Diethyl ether was then added and the pyridine salts were removed by filtration. The residue was purified by flash chromatography (eluent: toluene/NEt_3 100/1, R_f 0.9) to produce 0.10 g (34%) of a colorless oil. ^{31}P-NMR (400 MHz, C_6D_6), δ: 99.8 (s). ^{1}H-NMR (400 MHz, C_6D_6), δ: 2.94 (s, 3H, CH_3-N), 6.43 (m, 1H, CH-O), 6.7–8.0 (m, 19H, CH═). ^{13}C NMR (400 MHz, C_6D_6), δ: 30.3 (CH_3-N), 69.8 (b, CH-O), 110–155 (aromatic carbons). Anal. Calc (%) for $C_{27}H_{23}N_2OP$: C 76.76, H 5.49, N 6.63; found C 76.75, H 5.51, N 6.61.

General procedure for Pd-catalyzed enantioselective Heck reactions

A mixture of $[Pd_2(dba)_3]$dba (12 mg, 1.25×10^{-2} mmol) and the appropriate chiral ligand (2.8×10^{-2} mmol) in dry degassed THF (3.0 mL) was stirred under argon at room temperature for 15 min. The olefin (2.0 mmol), triflate (0.50 mmol) and base (1.0 mmol) were added to the catalyst solution. The solution was stirred at the desired temperature under argon. After the desired reaction time, the mixture was diluted with additional diethyl ether and washed with water, dried over $MgSO_4$, and evaporated. For compounds 2-(1-naphthyl)-2,5-dihydrofuran and 2-(4-nitrophenyl)-2,5-dihydrofuran, conversion and regioselectivity were measured by ^{1}H-NMR and enantioselectivity was measured by HPLC.[3b] For the rest of the compounds, conversion and selectivity were determined by GC.[3e]

Acknowledgements

We thank the Spanish Government (Consolider-Ingenio CSD2006-0003, CTQ2010-15835/BQU, 2008PGIR/07 to O. Pàmies and 2008PGIR/08 to M. Diéguez and ICREA Academia award to M. Diéguez) and the Catalan Government (2009SGR116), COST D40, Vetenskapsrådet (VR), and Astra Zeneca for support. Knut and Alice Wallenbergs Stiftelse are also gratefully acknowledged for generous financial support.

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