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The Synthesis of New HetPHOX Ligands and Their Application to the Intermolecular Asymmetric Heck Reaction

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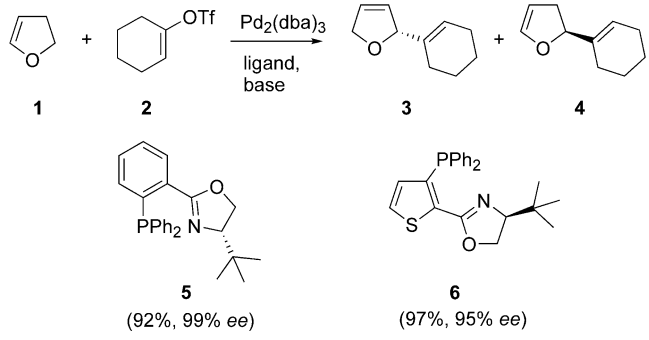
The synthesis of six members of the HetPHOX ligand class and the application of palladium complexes of these ligands to the intermolecular asymmetric Heck reaction is described. The *tert*-leucinol-derived ligands proved the most enantioselective, with palladium complexes of these ligands affording *ee* values of up to 96, 95 and 94 % in the phenylation, cyclohexenylation and naphthylation, respectively, of 2,3-dihydrofuran. As an aid to the explanation of the observed selectivity a palladium complex of the most enantioselective ligand was prepared and an X-ray crystal structure obtained. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2009)

Introduction

The standard Heck reaction is the substitution of a vinylic hydrogen by an alkenyl or aryl group catalysed by Pd^0 complexes. Since its discovery in 1968 by Heck,[1–3] this elaboration of substituted alkenes by direct C–C bond formation at the vinylic carbon centre has evolved into a powerful synthetic transformation. The potential of the intramolecular reaction, and in particular its asymmetric variant, has been exploited in the key steps of many total syntheses.[4,5] The intermolecular variant has not seen wide application to date although Hayashi did employ it in the synthesis of a platelet-activating factor antagonist.[6] Since the first enantioselective intermolecular Heck reactions by Hayashi using the diphosphane ligand BINAP,[7] there has been a recent emphasis on the application of new classes of chiral ligands. The first use of P,N ligands in this reaction was reported by Pfaltz who described the arylation and cyclohexenylation of 2,3-dihydrofuran (**1**).[8] The use of palladium complexes of the *tert*-leucinol-derived "PHOX" ligand **5** in the coupling of 2,3-dihydrofuran (**1**) and cyclohexenyl triflate (**2**) afforded **3** in *ee* values of up to 99%, Scheme 1. Only trace amounts of the thermodynamic product **4** were formed compared to BINAP,[7] thus demonstrating a low amount of double-bond isomerisation after the initial migratory insertion step.

Given the success of this ligand class, much effort was directed toward designing new chiral P,N ligands for this transformation. The groups of Guiry,[9] Gilbertson,[10] Hashimoto,[11] and Hou[12] have all developed highly selective P,N systems with varying chiral scaffolds.[13] Our more recent research has focussed on applying heterocyclic analogues of the PHOX ligands (HetPHOX ligands) to asymmetric catalysis[14] including the phenylation and cyclohexenylation of 2,3-dihydrofuran (**1**).[9a,9b] Palladium complexes of HetPHOX ligand **6** induced high levels of enantioselectivity of up to 95% in the cyclohexenylation of **1**, Scheme 1. In this article, we wish to report the synthesis of a wider range of HetPHOX ligands and the application of their palladium complexes to the phenylation, cyclohexenylation and naphthylation of 2,3-dihydrofuran (**1**). We now report in full on the preparation of four novel HetPHOX ligands **7c**–**f** and their application, along with two existing HetPHOX ligands **7a**–**b**,[14] to the intermolecular asymmetric Heck reaction, Figure 1.



Scheme 1.

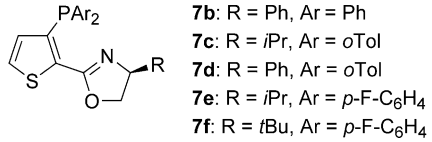


Figure 1. Novel HetPHOX ligands **7c**–**f**.

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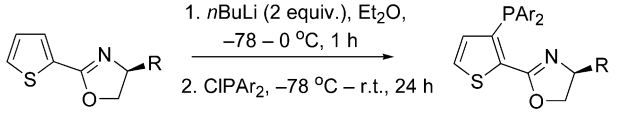
Ligand Synthesis

Two points of possible diversification of the HetPHOX ligands were identified. Firstly, the substituent on the oxazoline ring could be varied to include phenyl as well as isopropyl and *tert*-butyl. The second variation could be achieved at phosphorus with the expectation that introducing *o*-tolyl and *p*-fluorophenyl substituents would vary the sterics and electronics of the donor phosphorus atom and thus the reactivity of the ligand.[14]

The synthesis of diphenylphosphane-derived HetPHOX ligands has been reported previously by directed metalation and quenching with chlorodiphenylphosphane of the corresponding thiophene-oxazoline **8**.[9,16] In order to expand the series we performed a similar directed metalation and quench with the appropriate chlorodiarylphosphane to afford the required ligands **7c**–**f** in moderate yields, Scheme 2.



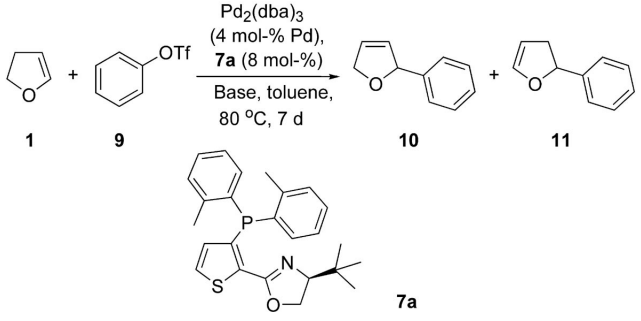
8a: R = *i*Pr
8b: R = *t*Bu
8c: R = Ph

7c: R = *i*Pr, Ar = *o*Tol (42 %)
7d: R = Ph, Ar = *o*Tol (38 %)
7e: R = *i*Pr, Ar = *p*-F-C_6H_4 (37 %)
7f: R = *t*Bu, Ar = *p*-F-C_6H_4 (33 %)

Scheme 2.

Asymmetric Phenylation of 2,3-Dihydrofuran

Following from the work carried out in this research group,[9a,9b] where ligand **6** had proven successful, toluene was chosen as the solvent for these transformations. The initial reactions used palladium complexes of ligand **7a** (4 mol-%) derived in situ from $Pd_2(dba)_3$ (4 mol-% Pd) and a twofold excess of ligand (8-mol-%) at 80 °C for 7 days, Scheme 3.



Scheme 3.

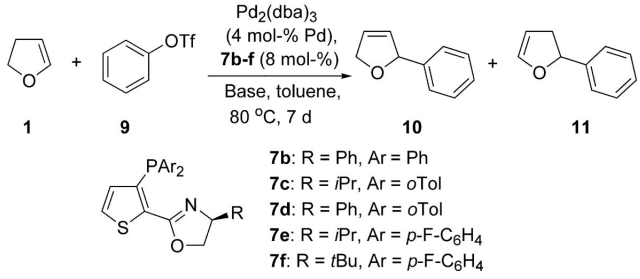
The aim of these initial reactions was to screen a variety of bases: 1,8 bis(dimethylamino)naphthalene (PS), 1,2,2,6,6-pentamethylpiperidine (PMP), dicyclohexylmethylamine, diisopropylethylamine (DIPEA), triethylamine, and tributylamine. The results of the base screen, Table 1, show that good to excellent conversions and excellent enantioselectivities were achieved in all cases for this initial study. As is consistent with many P,N ligands[9–13] low amounts of the thermodynamic product **11** were observed. Using proton sponge as base (Entry 1) provided the best result with complete conversion and 93% *ee* favouring the (*R*)-enantiomer.[17] Relatively moderate conversions were observed using PMP and tributylamine as bases (Entries 2 and 6), although enantioselectivities remained consistently high. Where it was possible to measure the *ee* of the thermodynamic product **8**, results were comparable to those for the kinetic isomer **10**. For example when DIPEA was used as base the *ee* of **11** was found to be 93% (*R*).[17]

Table 1. Asymmetric phenylation of 2,3-dihydrofuran (**1**) using palladium complexes of ligand **7a**.

Entry	Ligand	Base	Conversion[a] (%)	**10**/**11**[b]	*ee* **10** (%)[c] (*R*)
1	**7a**	PS	100	91:9	93
2	**7a**	PMP	51	96:4	95
3	**7a**	Cy_2NMe	100	98:2	92
4	**7a**	DIPEA	100	85:15	94
5	**7a**	Et_3N	83	90:10	96
6	**7a**	Bu_3N	43	89:11	91

[a] Conversions were determined using achiral GC with tri-*n*-decane as internal standard. [b] Product ratios were also determined using achiral GC. [c] Enantiomeric excesses were determined using chiral GC [γ-CD-TFA, 30 m, 80–90 °C, 0.3 °C/min, 90–120 °C, 2 °C/min, 10 min, 15 psi, injection temp. 200 °C, detection temp. 220 °C, t_R (*S*)-**10** = 33.52 min, t_R (*R*)-**10** = 34.78 min].

It was decided to use three bases to test the remaining five ligands in the phenylation of 2,3-dihydrofuran (**1**). PS, Cy_2NMe and DIPEA were chosen as bases as these provided the highest conversions in our initial study. Using the same reaction conditions palladium complexes derived in situ from $Pd_2(dba)_3$ (4 mol-% Pd) and a twofold excess of ligands **7b**–**f** were tested in the phenylation of 2,3-dihydrofuran (**1**), Scheme 4, Table 2.



7b: R = Ph, Ar = Ph
7c: R = *i*Pr, Ar = *o*Tol
7d: R = Ph, Ar = *o*Tol
7e: R = *i*Pr, Ar = *p*-F-C_6H_4
7f: R = *t*Bu, Ar = *p*-F-C_6H_4

Scheme 4.

Ligands **7b**–**f** provided moderate to excellent conversions with good to excellent *ee* values [favouring the (*R*)-product **10**] in the phenylation of 2,3-dihydrofuran (**1**). Again the major product formed was the kinetic isomer **10** although in a few cases there were significant amounts (up to 18%) of thermodynamic product **11** formed (Entries 11 and 12). Palladium complexes of ligand **7c**, which contained an isopropyl-substituted oxazoline, proved the most active and selective catalyst system, giving complete conversion and an enantiomeric excess of 92% when PS was used as base (Entry 4). In this case only 2% of isomer **11** was formed. The two phenylglycinol-derived ligands, **7b** and **7d**, proved only slightly less active and selective producing conversions of 95

Table 2. Asymmetric phenylation of 2,3-dihydrofuran (**1**) using palladium complexes of ligands **7b**–**f**.

Entry	Ligand	Base	Conversion[a] (%)	**10**/**11**[b]	*ee* **10** (%)[c] (*R*)
1	**7b**	PS	58	85:15	67
2	**7b**	Cy_2NMe	95	86:14	88
3	**7b**	DIPEA	53	87:13	76
4	**7c**	PS	100	98:2	92
5	**7c**	Cy_2NMe	100	96:4	92
6	**7c**	DIPEA	68	95:5	91
7	**7d**	PS	78	92:8	78
8	**7d**	Cy_2NMe	92	87:13	69
9	**7d**	DIPEA	81	95:5	70
10	**7e**	PS	34	85:15	78
11	**7e**	Cy_2NMe	36	82:18	81
12	**7e**	DIPEA	46	83:17	82
13	**7f**	PS	28	90:10	68
14	**7f**	Cy_2NMe	32	87:13	71
15	**7f**	DIPEA	38	88:12	70

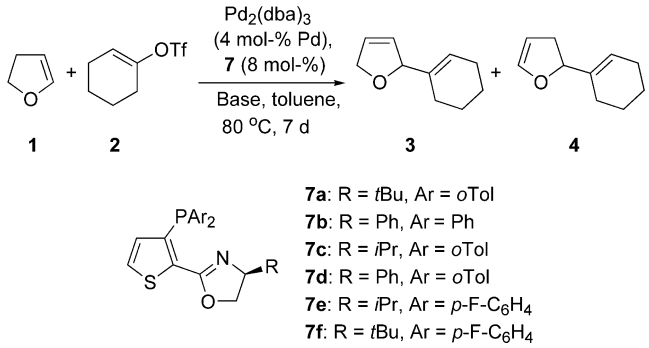
[a] Conversions were determined using achiral GC with tri-*n*-decane as internal standard. [b] Product ratios were also determined using achiral GC. [c] Enantiomeric excesses were determined using chiral GC [γ-CD-TFA, 30 m, 80–90 °C, 0.3 °C/min, 90–120 °C, 2 °C/min, 10 min, 15 psi, injection temp. 200 °C, detection temp. 220 °C, t_R (*S*)-**10** = 33.52 min, t_R (*R*)-**10** = 34.78 min].

and 92% and *ee* values of 88 and 69%, respectively, when dicyclohexylmethylamine was used as base (Entries 2 and 8). However, when the substituent on the phosphorus was changed to *p*-fluorophenyl, ligands **7e**–**f**, the activity of the palladium complexes dropped significantly. Conversions between 28 and 46% were observed although enantioselectivities remained high with ligand **7e** proving the most selective giving an *ee* of 82%.

To conclude, the most active and selective catalyst for the phenylation of 2,3-dihydrofuran was that formed with ligand **7a**. Excellent conversions and enantioselectivities of up to 96% for the predominant kinetic product **10** were observed.

Asymmetric Cyclohexenylation of 2,3-Dihydrofuran

The efficacy of palladium complexes (4 mol-%) derived from $Pd_2(dba)_3$ (4 mol-% Pd) and a twofold excess of ligands **7a**–**f**, once again generated in situ, was tested in the coupling of cyclohexenyl triflate (**2**) and 2,3-dihydrofuran (**1**), Scheme 5, Table 3.



Scheme 5.

Table 3. Asymmetric cyclohexenylation of 2,3-dihydrofuran (**1**) using palladium complexes of ligands **7a**–**f**.

Entry	Ligand	Base	Conversion[a] (%)	**3**/**4**[b]	*ee* **3** (%)[c] (*R*)[17]
1	**7a**	PS	93	98:2	90
2	**7a**	Cy_2NMe	99	94:6	95
3	**7a**	DIPEA	77	90:10	94
4	**7b**	PS	60	96:4	68
5	**7b**	Cy_2NMe	78	92:8	88
6	**7b**	DIPEA	72	91:9	86
7	**7c**	PS	99	91:9	93
8	**7c**	Cy_2NMe	95	93:7	77
9	**7c**	DIPEA	94	97:3	90
10	**7d**	PS	96	93:7	24
11	**7d**	Cy_2NMe	72	99:1	21
12	**7d**	DIPEA	96	94:6	36
13	**7e**	PS	75	85:15	80
14	**7e**	Cy_2NMe	50	80:20	80
15	**7e**	DIPEA	58	75:25	73
16	**7f**	PS	75	87:13	74
17	**7f**	Cy_2NMe	57	70:30	35
18	**7f**	DIPEA	38	65:35	81

[a] Conversions were determined using achiral GC with tri-*n*-decane as internal standard. [b] Product ratios were also determined using achiral GC. [c] Enantiomeric excesses were determined using chiral GC [γ-CD-TFA, 30 m, 80–90 °C, 0.3 °C/min, 90–120 °C, 2 °C/min, 10 min, 15 psi, injection temp. 200 °C, detection temp. 220 °C, t_R (*S*)-**3** = 21.82 min, t_R (*R*)-**3** = 23.36 min].

Excellent enantioselectivities and conversions were observed in many cases for this transformation. Palladium complexes of ligand **7a** proved both the most active and selective with almost complete conversion and 95% *ee* achieved when dicyclohexylmethylamine was used as base (Entry 2). Indeed, varying the base only had a slightly negative effect on the *ee* (Entries 1 and 3). Varying the substituent at the 4-position on the oxazoline from *tert*-butyl to isopropyl had little effect on the activity or selectivity of the catalysts. Palladium complexes of ligand **7c** proved highly reactive providing conversions from 94–96% while the accompanying *ee* values were also high, ranging from 77–93% (Entries 7–9). The two phenylglycinol-derived ligands provided varying results: ligand **7b**, which possesses a diphenylphosphane group, promoted conversion of up to 78% and *ee* of up to 88% (Entry 5). However, the di-*o*-tolylphosphane analogue (ligand **7d**), gave excellent conversions (up to 96%), although the enantioselectivities were poor, with 36% being the best *ee* achieved (Entry 12) and variation of base gave 21–24% *ee* (Entries 10 and 11).

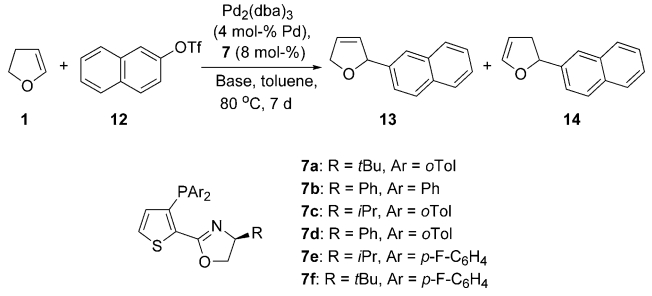
The regioselectivity of the reaction is excellent with the favoured kinetic product **3** formed over the thermodynamic product **4** in ratios of up to 99:1 (Entry 11). However, when palladium complexes of the *p*-fluorophenylphosphane-derived ligands **7e**–**f** were employed, appreciable amounts of the thermodynamic product **4** (up to 35%) were observed (Entry 18). It is also worth noting here that (as was the case in the phenylation) overall conversions with these ligands **7e**–**f** were decreased although the *ee* values remained moderately high (up to 80%, Entry 13).

In summary, similar trends to those observed in the phenylation of 2,3-dihydrofuran (**1**) were observed for this

transformation. Palladium complexes of all ligands produced predominately product **3**. The *t*-leucinol-derived di-*o*-tolylphosphane ligand **7a** proved the most efficacious in inducing excellent levels of enantioselectivity (up to 95%) and conversion (up to 99%) in the cyclohexenylation of 2,3-dihydrofuran (**1**).

Asymmetric Naphthylation of 2,3-Dihydrofuran

The enantiodifferentiating ability of ligands **7a**–**f** in the coupling of 2-naphthyl triflate (**12**) and 2,3-dihydrofuran (**1**) was tested, Scheme 6, Table 4.[18]



Scheme 6.

Table 4. Asymmetric naphthylation of 2,3-dihydrofuran (**1**) using palladium complexes of ligands **7a**–**f**.

Entry	Ligand	Base	Conversion[a] (%)	**13**/**14**[b]	*ee* **13** (%)[c] (*R*)
1	**7a**	PS	84	98:2	92
2	**7a**	Cy_2NMe	99	91:9	94
3	**7a**	DIPEA	94	98:2	94
4	**7b**	PS	100	80:20	54
5	**7b**	Cy_2NMe	100	70:30	66
6	**7b**	DIPEA	100	81:19	66
7	**7c**	PS	88	98:2	82
8	**7c**	Cy_2NMe	99	94:6	88
9	**7c**	DIPEA	95	99:1	88
10	**7d**	PS	100	>99:1	54
11	**7d**	Cy_2NMe	100	99:1	68
12	**7d**	DIPEA	100	98:2	72
13	**7e**	PS	47	80:20	60
14	**7e**	Cy_2NMe	35	79:21	50
15	**7e**	DIPEA	34	85:15	38
16	**7f**	PS	46	80:20	86
17	**7f**	Cy_2NMe	20	70:30	87
18	**7f**	DIPEA	49	81:19	92

[a] Conversions were determined using achiral GC with tri-*n*-decane as internal standard. [b] Product ratios were also determined using achiral GC. [c] Enantiomeric excesses were determined using chiral HPLC (Chiralcel-OD 0.46×25 cm, hexane/IPA, 99:1, 1 mL/min, 25 °C), t_R (*S*)-**13** = 12.65 min, t_R (*R*)-**13** = 16.95 min.

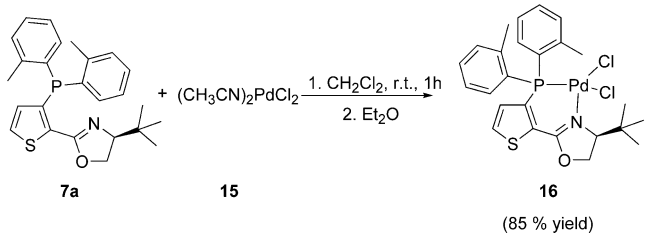
Similar trends to those observed in the phenylation and cyclohexenylation reactions were observed with this transformation. Palladium complexes of ligand **7a** were once again highly successful promoting excellent conversions of up to 99% and *ee* values of up to 94% (Entries 1–3). Variation of the oxazoline 4-substituent from *tert*-butyl to isopropyl had only a slightly deleterious effect on the conversions and *ee* values observed (compare Entries 1–3 and 7–9). When dicyclohexylmethylamine was employed as base the palladium complex of **7c** afforded almost complete conversion and 88% *ee* (Entry 8).

The two phenylglycinol-derived ligands **7b** and **7d** provided quantitative product in all cases. Moderate regioselectivities (from 70:30 to 81:19) were observed with the diphenylphosphane ligand **7b** (entries 4–6) with an optimal *ee* of 66% (Entry 5) whereas the di-*o*-tolylphosphane-containing ligand **7d** gave near perfect regioselectivities of greater than 99:1 (Entries 10–12) and an optimal *ee* of 72% (Entry 12).

The two *p*-fluorophenylphosphane-derived ligands **7e** and **7f** showed similar trends in reactivity and selectivity as observed in our phenylation and cyclohexenylation studies as conversions dropped to between 35 and 49% (Entries 13–18). However, ligand **7f** induced very high enantioselectivities of up to 92% *ee* when DIPEA was used as base (Entry 18).

In all cases, the predominant product formed was the kinetic product **13** with product ratios of greater than 99:1 obtained in some cases. However, in certain cases, particularly with ligands **7e** and **7f**, appreciable amounts of product **14** were formed (Entries 13–18). Where it was possible to analyse the thermodynamic product **14**, *ee* values similar to the kinetic product **13** were observed once again favouring the (*R*)-enantiomer.[19]

We believe that the selectivity model recently proposed for related P,N ligands by Hou[20] is followed in our studies. A palladium dichloride complex of ligand **7a**, the ligand that consistently afforded the highest *ee* values across the range of transformations studied, was prepared and crystals suitable for analysis by X-ray diffraction were grown, Scheme 7, Figure 2 and Table 5.[21] A *syn* conformation



Scheme 7.

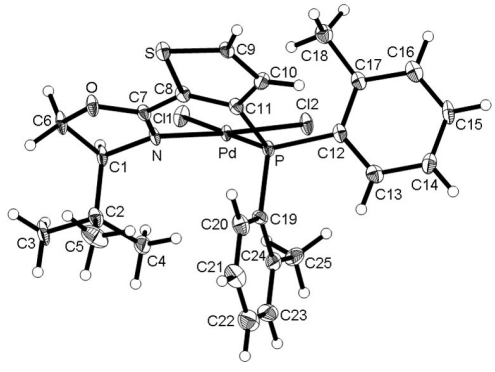


Figure 2. X-ray crystal structure of **16**.

with the (*S*)-*tert*-leucinol-derived ligand is adopted, which as reported by Hou[20] should lead to (*R*)-configured products and this is what is seen experimentally in our studies.

Table 5. Selected bond lengths and angles of **16**.

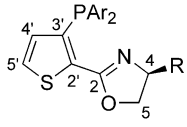
Pd–P bond length [Å]	2.233
Pd–N bond length [Å]	2.052
P–Pd–N bond angle [°]	88.6
Pd–Cl (*trans* to N) [Å]	2.292
Pd–Cl (*trans* to P) [Å]	2.372

Conclusions

Six HetPHOX ligands have been applied to the intermolecular asymmetric Heck coupling of 2,3-dihydrofuran (**1**) with a range of triflates. Excellent selectivity for the (*R*)-enantiomer was observed with *ee* values up to 95%. Palladium complexes of ligand **7a** proved the most successful in all three test reactions. In general, the di-*o*-tolylphosphane-derived ligands proved more active than the *p*-fluorophenylphosphane-derived ligands although enantioselectivities remained consistently high throughout. Results in this study are comparable to results obtained previously in this group with palladium complexes of HetPHOX ligand **6**, where conversions of up to 97% and *ee* values of up to 95% were observed, Scheme 1.[9a,9b]

Experimental Section

General: ^{1}H NMR (300, 400, 500 and 600 MHz) and ^{13}C (75, 100, 125 and 150 MHz) spectra were recorded with Varian VNMRS (Varian NMR System) spectrometers at 400, 500 and 600 MHz and Varian Inova 300 and 500 MHz spectrometers at room temperature in $CDCl_3$ or [D_6]DMSO using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given in parts per million and coupling constants are given in absolute values expressed in Hertz. Please see below for position numbers on the molecular skeletons of compounds **7a**–**f** to aid in the assignment of the NMR peaks obtained.



HRMS was obtained using a Micromass/Waters LCT instrument. Infra-red spectra were recorded with a Varian Infra-red FT spectrometer. Optical rotation values were measured with a Perkin–Elmer 343 polarimeter at room temperature. Melting points were determined in open capillary tubes with a Gallenkamp melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was carried out on plastic sheets pre-coated with silica gel 60 F254 (Merck). Column-chromatography separations were performed using Merck Kieselgel 60 (0.040–0.063 mm). Elemental analyses were performed by Mr. Adam Coburn, School of Chemistry and Chemical Biology, University College Dublin. HPLC analysis was performed using a LC 2010A machine equipped with a UV/Vis detector employing Chiracel® OD and AD columns from Daicel Chemical Industries. GC analysis was performed using a Shimadzu GC-2010 gas chromatograph equipped with a Shimadzu C-R3A chromatopac integrator and a Chiraldex γ-TFA chiral column [30 m, 0.25 mm (diam.) × 0.25 μm] with helium as carrier gas and a flame-ionising detector. All reagents were purchased from Sigma–Aldrich and used as received. Dry solvents were used from a Puresol Grubbs solvent system and degassed by bubbling nitrogen through them. Anhydrous chlorobenzene was purchased from Sigma–Aldrich and used without further purification. Oxygen-free nitrogen was obtained from BOC gases and was used without further drying. Crystal data were collected using a Bruker SMART APEX CCD area detector diffractometer. A full sphere of reciprocal space was scanned by phi-omega scans. Pseudo-empirical absorption correction based on redundant reflections was performed by the program SADABS (X-1). The structures were solved by direct methods using SHELXS-97 (X-2) and refined by full-matrix least-squares on F^2 for all data using SHELXL-97 (X-3). Hydrogen atoms were added at calculated positions and refined using a riding model. Their isotropic temperature factors were fixed to 1.2 times (1.5 times for methyl groups) the equivalent isotropic displacement parameters of the carbon atom the H-atom is attached to. Anisotropic thermal displacement parameters were used for all non-hydrogen atoms. X-1: G.M. Sheldrick, SADABS, Bruker AXS Inc., Madison, WI 53711, 2000.

X-2: G. M. Sheldrick, SHELXS-97, University of Göttingen, 1997. X-3: G. M. Sheldrick, SHELXL-97-2, University of Göttingen, 1997. Racemic samples of 2-phenyl-2,5-dihydrofuran (**10**),[9] 2-cyclohex-1′-en-yl-2,5-dihydrofuran (**3**),[9] and 2-naphthalen-2′-yl-2,5-dihydrofuran (**13**)[18] were prepared and analysed according to literature reports. Conversions for asymmetric reactions were measured using burn ratios with tri-*n*-decane as internal standard.

General Procedure for the Preparation of Di-*ortho*-tolylphosphane-Derived Ligands 7c–d: Thiophene-2-oxazoline (2 mmol) **8** was dissolved in diethyl ether (5 mL) and the solution was cooled to –78 °C. A solution of 2.5 M *n*-butyllithium in hexanes (1.6 mL, 4 mmol) was added dropwise. After addition the reaction was kept at –78 °C for a further 30 min, then warmed to 0 °C and stirred at this temperature for 30 min. The reaction was then recooled to –78 °C and chloro-di-*ortho*-tolylphosphane (0.99 g, 4 mmol) was carefully added. The reaction was warmed to room temperature and stirred overnight. It was then quenched with water (5 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (2 × 5 mL). The organic layers were combined, dried with sodium sulfate and concentrated in vacuo. Purification was performed using column chromatography on silica gel with pentane/diethyl ether, 9:1 as the eluent.

(*S*)-2-[3-(Di-*o*-tolylphosphanyl)thiophen-2-yl]-4-isopropyl-4,5-dihydrooxazole (7c): (0.34 g, 42%) was isolated as a white solid; R_f = 0.3 (pentane/diethyl ether); m.p. 90–93 °C. $[\alpha]_D$ = –165 (*c* = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, ^3J = 5.1 Hz, 1 H, H$^{5'}$), 7.27–7.15 (m, 4 H, PAr$_2$), 7.10–7.00 (m, 2 H, PAr$_2$), 6.82–6.75 (m, 2 H, PAr$_2$), 6.35 (dd, ^3J = 5.1, $^3J_{H,P}$ = 0.7 Hz, 1 H, H$^{4'}$), 4.20 (dd, ^3J = 9.38, 7.9 Hz, 1 H, H^{5a}), 4.02–3.95 (m, 1 H, H^{5b}), 3.90 (app. t, ^3J = 7.9 Hz, 1 H, H^4), 2.46 (d, $^3J_{H,P}$ = 1.5 Hz, 3 H, Ar-CH$_3$), 2.42 (d, $^3J_{H,P}$ = 1.5 Hz, 3 H, Ar-CH$_3$), 1.53 [sep., ^3J = 6.8 Hz, 1 H, C*H*(CH$_3$)$_2$], 0.69 [app. t, ^3J = 6.8 Hz, 6 H, (CH$_3$)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4 (d, $^3J_{C,P}$ = 3.5 Hz, C^2), 142.6–142.1 (m, 2 C, Ar*C*-CH$_3$), 140.3 (d, $^2J_{C,P}$ = 26.5 Hz, C$^{2'}$), 136.2 (d, $^1J_{C,P}$ = 10.5 Hz, P*C*-*o*Tol), 135.5 (d, $^1J_{C,P}$ = 10.5 Hz, P*C*-*o*Tol), 133.6 (2 C, *C*-*p*-P), 132.7 (d, $^2J_{C,P}$ = 27 Hz, C$^{4'}$), 132 (d, $^1J_{C,P}$ = 23 Hz, C$^{3'}$), 130.0–129.8 (m, 2 C, *C*-*m*-P), 128.6 (d, $^3J_{C,P}$ = 6.8 Hz, *C*-*m*-P, 2 C), 127.7 (d, $^3J_{C,P}$ = 2 Hz, C$^{5'}$), 126 (d, $^2J_{C,P}$ = 12 Hz, *C*-*o*-P, 2 C), 73.1 (C^4), 70.4 (C^5), 32.8 [*C*H(CH$_3$)$_2$], 21.3 (d,

$^3J_{C,P}$ = 10 Hz, Ar-*C*H$_3$), 21.1 (d, $^3J_{C,P}$ = 10 Hz, Ar-*C*H$_3$), 18.3 (*i*Pr *C*H$_3$), 18.1 (*i*Pr *C*H$_3$) ppm. ^{31}P NMR (162 MHz, CDCl$_3$): δ = –30.2 ppm. IR (KBr disc): $\tilde{\nu}$ = 3056, 2960, 1639 cm^{-1}. HRMS calcd. for $C_{24}H_{26}NOPS$ (M + 1) 408.1551; found 408.1539. $C_{24}H_{26}NOPS$ (407.52): calcd. C 70.74, H 6.43, N 3.44; found C 70.44, H 6.40, N 3.41.

(*S*)-2-[3-(Di-*o*-tolylphosphanyl)thiophen-2-yl]-4-phenyl-4,5-dihydrooxazole 7d (0.36 g, 38%) was isolated as a white solid, R_f = 0.33 (pentane/diethyl ether); m.p. 70–72 °C. $[\alpha]_D$ = –96 (*c* = 1.04, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.34 (d, ^3J = 5.1 Hz, 1 H, H$^{5'}$), 7.30–7.15 (m, 7 H, Ar H's), 7.12–7.06 (m, 2 H, Ar H's), 6.87–6.81 (m, 4 H, Ar H's), 6.41 (d, ^3J = 5.1 Hz, 1 H, H$^{4'}$), 5.33 (dd, ^3J = 9.5, 8.3 Hz, 1 H, H^4), 4.62 (dd, ^3J = 11, 8.3 Hz, 1 H, H^{5a}), 3.98 (t, ^3J = 8.3 Hz, 1 H, H^{5b}), 2.47 (d, $^3J_{C,P}$ = 1.1 Hz, 3 H, Ar-CH^3), 2.39 (d, $^3J_{C,P}$ = 1.1 Hz, 3 H, Ar-CH$_3$) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 160 (d, $^3J_{C,P}$ = 3.6 Hz, C^2), 142.7–142.4 (m, 2 C, Ar*C*-CH$_3$), 142.2 (Ph C), 141.3 (d, $^2J_{C,P}$ = 27 Hz, C$^{2'}$), 136.1–135.5 (m, 2 C, P-C_{oTol}), 133.7 (2 C, *C*-*p*-P), 132.8 (d, $^2J_{C,P}$ = 17 Hz, C$^{4'}$), 131.5 (d, $^1J_{C,P}$ = 23 Hz, C$^{3'}$), 130.1–130.0 (m, 2 C, *C*-*m*-P), 128.7 (m, 2 C, *C*-*o*-P), 128.4 (m, 2 C, *C*-*m*-P), 128.2 (d, $^3J_{C,P}$ = 2 Hz, C$^{5'}$), 127.1 (Ph C), 126.4 (2 C, Ph C), 126.1 (2 C, Ph C), 74.9 (C^4), 70.2 (C^5), 21.3 (d, $^2J_{C,P}$ = 23 Hz, Ar-*C*H$_3$), 21.2 (d, $^2J_{C,P}$ = 23 Hz, Ar-*C*H$_3$) ppm. ^{31}P NMR (121 MHz, CDCl$_3$): δ = –30.4 ppm. IR (KBr disc): $\tilde{\nu}$ = 3057, 2850, 1637 cm^{-1}. HRMS calcd. for $C_{27}H_{24}NOPS$ (M + 1) 442.1394; found 442.1396. $C_{27}H_{24}NOPS$ (441.53) calcd. C 73.45, H 5.48, N 3.17; found C 73.10, H 5.51, N 3.13.

General Procedure for the Preparation of Di-*p*-fluorophenylphosphane-Derived Ligands 7e–f: Thiophene-2-oxazoline **8** (2 mmol) was dissolved in diethyl ether (5 mL) and the solution was cooled to –78 °C. A solution of 2.5 M *n*-butyllithium in hexanes (1.6 mL, 4 mmol) was added dropwise. After addition the reaction was kept at –78 °C for a further 30 min, then warmed to 0 °C and stirred at this temperature for 30 min. The reaction was then recooled to –78 °C and chloro-di-*p*-fluorophenylphosphane (0.88 mL, 4 mmol) was carefully added. The reaction was warmed to room temperature and stirred overnight. It was then quenched with water (5 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (2 × 5 mL). The organic layers were combined, dried with sodium sulfate and concentrated in vacuo. Purification was performed using column chromatography on silica gel with pentane/diethyl ether, 9:1 as the eluent.

(*S*)-2-{3-[Bis(4-fluorophenyl)phosphanyl]thiophen-2-yl}-4-isopropyl-4,5-dihydrooxazole (7e): (0.31 g, 37%) was isolated as a sticky oil. R_F = 0.28 (pentane/diethyl ether, 9:1). $[\alpha]_D$ = –118.8 (*c* = 2.0, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.34–7.22 (m, 5 H, 4 PAr$_2$H's, H$^{5'}$), 7.05–6.98 (m, 4 H, PAr$_2$ CH's), 6.35 (dd, ^3J = 5.1, $^3J_{H,P}$ = 1.0 Hz, 1 H, H$^{4'}$), 4.23 (dd, ^3J = 9.1, 7.7 Hz, 1 H, H^{5a}), 4.02–3.90 (m, 2 H, H^{4,5b}), 1.61–1.54 [m, 1 H, C*H*(CH$_3$)$_2$], 0.74 (d, ^3J = 6.7 Hz, 3 H, CH$_3$), 0.70 (d, ^3J = 6.7 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$: δ = 164.5 (d, $^1J_{C,F}$ = 12 Hz, F-C_{Ar}), 162.0 (d, $^1J_{C,F}$ = 12 Hz, F-C_{Ar}), 155.6 (d, $^3J_{C,P}$ = 4 Hz, C^2), 141.0 (d, $^2J_{C,P}$ = 26 Hz, C$^{2'}$), 135.9–135.5 (m, 2 C, *C*-*o*-F), 135.3–134.9 (m, 2 C, *C*-*o*-F), 133.7–133.5 (m, P-C_{Ar}), 133.0 (C$^{4'}$), 133.0–132.8 (m, P-C_{Ar}), 131.9 (d, $^1J_{C,P}$ = 22 Hz, C$^{3'}$), 127.8 (C$^{5'}$), 115.8–115.4 (m, 4 C, *C*-*o*-P), 73.2 (C^4), 70.5 (C^5), 32.8 [*C*H(CH$_3$)$_2$], 18.4 (*i*Pr *C*H$_3$), 18.1 (*i*Pr *C*H$_3$). ^{31}P NMR (162 MHz, CDCl$_3$): δ = –17 (app. t, *J* = 4.3 Hz) ppm. ^{19}F NMR (376 MHz, CDCl$_3$) δ = –112.8–112.7 (m), –112.3–112.2 (m) ppm. IR (KBr disc): $\tilde{\nu}$ = 2960, 2873, 2349 cm^{-1}. HRMS calcd. for $C_{22}H_{20}F_2NOPS$ (M + 1) 416.1050; found 416.1056.

(*S*)-4-*tert*-Butyl-2-{3-[bis(4-fluorophenyl)phosphanyl]thiophen-2-yl}-4,5-dihydrooxazole (7f): (0.28 g, 33%) was isolated as a sticky white solid, R_f = 0.25 (pentane/diethyl ether, 9:1). $[\alpha]_D$ = –156.7 (*c* = 0.52, CHCl$_3$). ^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.31 (d, ^3J = 5.0 Hz, 1 H, H$^{5'}$), 7.30–7.22 (m, 4 H, PAr$_2$H's), 7.04–6.99 (m, 4 H, PAr$_2$H's), 6.34 (dd, ^3J = 5.0, $^3J_{H,P}$ = 0.8 Hz, 1 H, H$^{4'}$), 4.17 (dd, ^3J = 9.9, 8.1 Hz, 1 H, H^{5a}), 4.04 (app. t., ^3J = 8.1 Hz, 1 H, H^{5b}), 3.96 (dd, *J* = 9.9, 8.1 Hz, 1 H, H^4), 0.68 (s, 9 H, 3CH$_3$) ppm. ^{13}C NMR (150 MHz, CDCl$_3$): δ = 164.2 (d, $^1J_{C,F}$ = 12 Hz, F-C_{Ar}), 162.5 (d, $^1J_{C,F}$ = 12 Hz, F-C_{Ar}), 157.9 (d, $^3J_{C,P}$ = 4 Hz, C^1), 141 (d, $^2J_{C,P}$ = 26 Hz, C$^{2'}$), 135.9–135.7 (m, 2 C, *C*-*o*-F), 135.2–134.9 (m, 2 C, *C*-*o*-F), 133.9–133.7 (m, P-C_{Ar}), 133.1 (C$^{4'}$), 133.1–133.0 (m, P-C_{Ar}), 131.9 (d, $^1J_{C,P}$ = 22 Hz, C$^{3'}$), 127.7 (C$^{5'}$), 115.8–115.5 (m, 4 C, *C*-*o*-P), 77.0 (C^4), 68.9 (C^5), 33.8 (*C*CH$_3$), 25.6 [3 C, (CH$_3$)$_3$] ppm. ^{31}P NMR (162 MHz, CDCl$_3$): δ = –17 (app t, *J* = 4.3 Hz) ppm. ^{19}F NMR (376 MHz, CDCl$_3$): δ = –112.8–112.7 (m), –112.3–112.2 (m) ppm. IR (KBr disc): $\tilde{\nu}$ = 2957, 2917, 2349 cm^{-1}. HRMS calcd. for $C_{23}H_{22}F_2NOPS$ (M + 1) 430.1206, found 430.1219. $C_{23}H_{22}F_2NOPS$ (429.47): calcd. C 64.32, H 5.16, N 3.26; found C 64.14, H 5.17, N 3.16.

General Procedure for Asymmetric Heck Reactions: A solution of $Pd_2(dba)_3$ (2.3 mg, 0.002 mmol) and ligand (0.008 mmol) in toluene (0.5 mL) was stirred at room temperature under nitrogen until it was evident by the appearance of a transparent solution that the complex had formed (ca. 1 h). A solution of the required triflate **16**, **19** or **22** (0.13 mmol) and tri-*n*-decane (13 μL, 0.11 mmol) in toluene (0.5 mL) was added. This was followed by the addition of **15** (50 μL, 0.65 mmol) and the relevant base (0.78 mmol). The reaction vessel was sealed and heated to 80 °C for 7 d with precipitation of Base.HOTF proving the reaction was proceeding. The reaction was cooled to room temperature and pentane (10 mL) was added. The resulting suspension was filtered through 2 cm of silica with further elution using diethyl ether (10 mL). This solution was the concentrated and the yield calculated using GC (Se-30, 11 psi, 50 °C, 4 min, 15 °C/min, 170 °C, 10 min) by the internal standard method. The determination of the *ee* values was carried out as described above. Absolute configuration was assigned by comparison with literature values.[2,14]

Preparation of the Palladium Dichloride Complex 16 of Ligand 7a: Ligand **7a** (6.6 mg, 0.016 mmol) and bis(acetonitrile)dichloropalladium(II) (3.76 mg, 0.015 mmol) were stirred in CH_2Cl_2 (1 mL) in a Schlenk tube for 1 h at room temperature. Diethyl ether (1 mL) was than added slowly down the side of the Schlenk tube and two layers were formed. The mixture was then left for crystals to form. The palladium dichloride complex **16** (7.6 mg, 85%) was isolated as a yellow solid. $[\alpha]_D$ = +202 (*c* = 0.2, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.70 (d, ^3J = 4.9 Hz, 1 H, H$^{5'}$), 7.53–7.44 (m, 3 H, PAr$_2$H's), 7.33 (app dd., ^3J = 6.6, 6.3 Hz, 1 H, PAr$_2$ CH), 7.15–7.05 (m, 2 H, PAr$_2$H's), 6.86 (ddd, ^3J = 14.0, 7.8, $^3J_{H,P}$ = 0.8 Hz, 1 H, PAr$_2$H), 6.60 (app dd., ^3J = 3.9, 3.4 Hz, 1 H, H$^{4'}$), 6.36–6.28 (m, 1 H, Ar H), 5.42 (dd, ^3J = 8.9, 4.3 Hz, 1 H, H^{5a}), 4.57–4.59 (m, 2 H, H^{4,5b}), 3.05 (s, 3 H, Ar-CH$_3$), 2.76 (s, 3 H, Ar-CH$_3$), 0.71 [s, 9 H, (CCH$_3$)$_3$] ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 159.2 (C^2), 145.2 (Ar-*C*-CH$_3$), 143.4 (Ar-*C*-CH$_3$), 134.2 (C$^{5'}$), 133.8 (C$^{2'}$), 133.0–132.1 (7 C, C$^{2'}$, C$^{4'}$, C$^{5'}$, 4 × PAr$_2$ C), 131.5 (PAr$_2$ C), 126.5 (PAr$_2$ C), 125.9 (PAr$_2$ C), 122.6–122.0 (2 C, 2 × C-*i*-P), 73.4 (C^4), 72.0 (C^5), 34.4 [*C*(CH$_3$)$_3$], 25.5 [(CH$_3$)$_3$], 24.4 (Ar-CH$_3$), 24.2 (Ar-CH$_3$) ppm. ^{31}P NMR (162 MHz, CDCl$_3$): δ = 3.9 ppm. IR (KBr disc): δ = 2912, 1701, 1622 cm^{-1}. ESI-HRMS calcd. for $C_{25}H_{28}Cl_2NOPPdS$ (M + 1 – HCl) 562.0353; found 562.0369.

Supporting Information (see footnote on the first page of this article): Relevant ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra and GC and HPLC traces are included.

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[21] CCDC-697071 (for **16**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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