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Microwave-Assisted Asymmetric Intermolecular Heck Reaction using Phosphine-Thiazole Ligands

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Dedicated to Professor Jan-E. Bäckvall on his 60th birthday.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

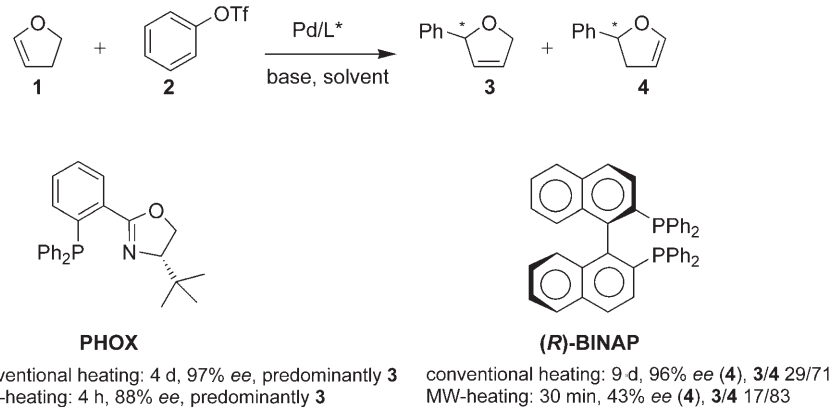
Abstract: A series of new phosphine-thiazole compounds has been synthesized and used as efficient ligands in the palladium-catalyzed asymmetric intermolecular Heck coupling of 2,3-dihydrofuran with aryl triflates and cyclohexenyl triflate. Microwave heating was used to accelerate the reactions and gave complete conversions in as little as one hour. Products were obtained with good to excellent enantioselectivities.

Keywords: asymmetric catalysis; Heck reaction; microwave heating; phosphine-thiazole ligands

Introduction

One of the great challenges in modern synthetic organic chemistry concerns the enantioselective formation of carbon-carbon bonds.[1] One way to achieve this is the asymmetric Pd-catalyzed Heck coupling of aryl and alkenyl halides or triflates to alkenes, a reaction known to be very versatile due to its high tolerance of functional groups.[2a–e] During the last decade chiral bidentate phosphine ligands have successfully been used as ligands in this coupling reaction.[3a–e] Highly enantioselective intramolecular Heck reactions have been reported and this transformation has proven to be a valuable tool in the synthesis of natural products and other complex structures.[4a–d] However, when bidentate phosphine ligands such as BINAP are used in the intermolecular coupling of 2,3-dihydrofuran (**1**) and phenyl triflate (**2**), the compound with the migrated double bond, 2-phenyl-2,3-dihydrofuran (**4**), is obtained as a major product (Scheme 1).[5,6]

The first report on intermolecular Heck coupling of **1** and **2** employing N,P-donor ligands was published by Pfaltz and co-workers, who used their oxazoline-

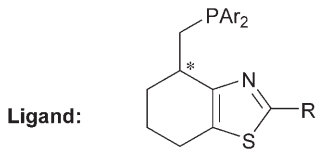


Scheme 1. The asymmetric intermolecular Heck reaction with 2,3-dihydrofuran and phenyl triflate.

based PHOX ligand.[7] After this initial report several N,P-donor ligands have been employed in the asymmetric Heck reaction.[8a–g] Many of these ligands possess an oxazoline functionality but there are reports concerning other N-donor functionalities, such as pyridine and quinoline.[2e,9] Surprisingly when N,P-donor ligands are used, 2-phenyl-2,5-dihydrofuran (**3**) is formed predominantly and highly enantioselectively (Scheme 1). The low tendency of N,P-donor ligated Pd catalysts to promote C–C double bond migration is not yet fully understood.

One of the drawbacks with N,P-donor ligands is the long reaction times required to achieve full conversion. Today it is known that by using controlled microwave dielectric heating, the reaction rates can be accelerated. This is especially important in modern medicinal chemistry where MW-assisted synthesis has aided in high-speed drug development. In a report by Hallberg and co-workers it was demonstrated that the use of MW heating in asymmetric intermolecular Heck reactions greatly shorten the reaction times from several days to some hours and also reduced the need for an inert atmosphere.[10,11] However, the enantioselectivities in their study were lower than those obtained with thermal heating (Scheme 1). Recently Pàmies et al. have reported on the MW-assisted asymmetric intermolecular Heck reaction, using sugar-based phosphite-oxazoline ligands on Pd to achieve complete reactions in 10 min with excellent enantioselectivities.[8a]

We have recently developed a novel class of phosphine thiazole ligands and applied them to the Ir-catalyzed asymmetric hydrogenation of olefins with great success.[12] These structures provide a highly tunable ligand scaffold and the substituents can be varied at both the thiazole and phosphine positions (Figure 1). We reasoned that these compounds might also serve as good ligands in other transition metal-catalyzed reactions. Initial studies using phosphine thiazole ligands in the asymmetric intermolecular Heck coupling reaction of **1** and **2** showed similar selectivities and reaction rates similar to those as in the literature.[13] As it is still important to find catalytic systems that give high enantioselectivies with short reaction times in this coupling reaction, we decided to investigate the use of microwave irradiation as a heating method when using our thiazole based ligands.



R = Ph Ar = Ph *R*-(**5**)
R = Ph Ar = *o*-Tol *R*-(**6**)
R = H, Ar = *o*-Tol *S*-(**7**)
R = Ph, Ar = 3,5-Dimethylphenyl *R*-(**8**)
R = 3,5-Dimethylphenyl, Ar = *o*-Tol *S*-(**9**)
R = Mesityl, Ar =Ph *S*-(**10**)

Figure 1. Phosphine-thiazole ligands used in the asymmetric intermolecular Heck reaction.

Herein we report the highly enantio- and regioselective MW-assisted asymmetric Heck coupling of 2,3-dihydrofuran **1** with different triflates (**2**, **23**–**26**) by using thiazole phosphine ligands (**5**–**10**). The choice of the base and solvent and the impact of the ligand structure on the reaction were studied. Both known ligands (**5**–**7**)[12a] and newly prepared ligands (**8**–**10**) were used (Figure 1).

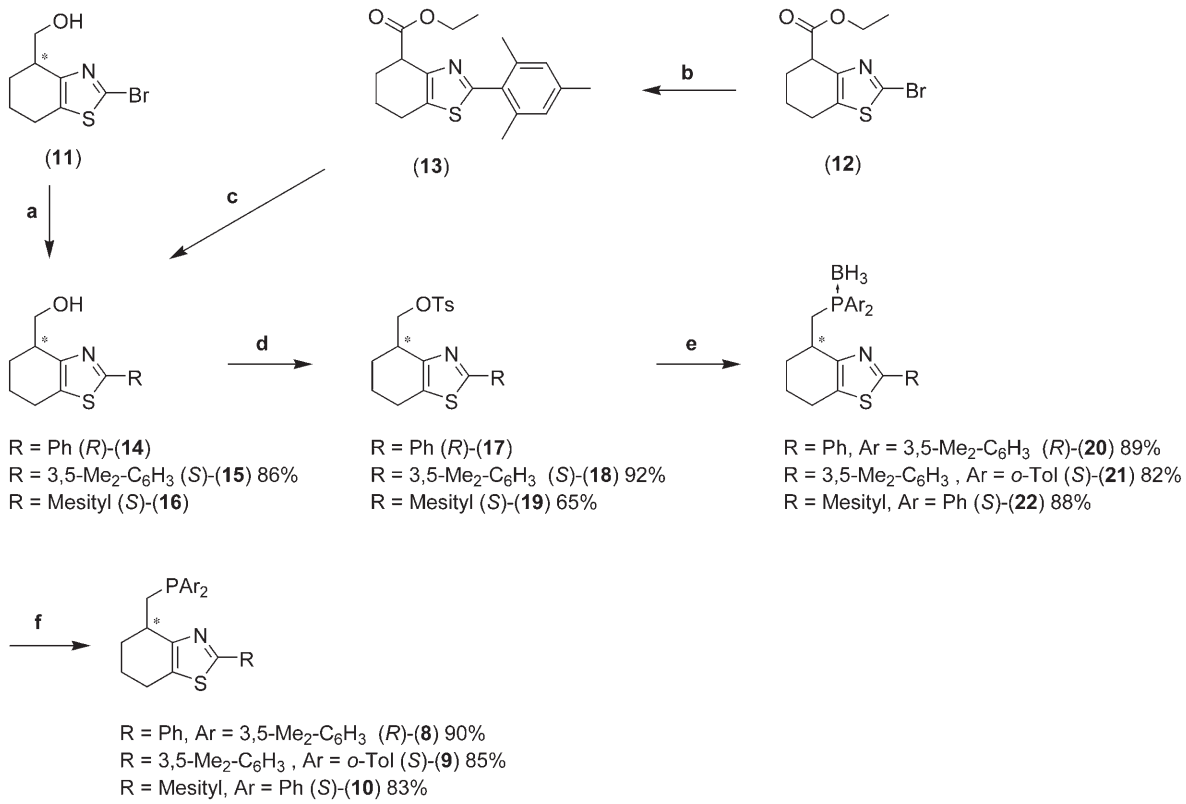
Results and Discussion

Synthesis of the N,P-ligands 8–10

The synthesis of the new ligands started from the known compound **11**[12a] which smoothly underwent Suzuki coupling with 3,5-dimethylphenylboronic acid according to a standard protocol and gave **15** in high yield (Scheme 2).[14] Very large arylboronic acids gave diminished yields and therefore we turned our interest to the catalytic systems developed by Buchwald and co-workers.[15] They have reported highly efficient monophosphines for Suzuki cross-coupling and we chose to use 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine (SPhos), which has given the best results so far and is commercially available, as a ligand.[15] Under Buchwald conditions, alcohol **11** did not give the desired product **16** in the reaction with mesitylboronic acid. However coupling of mesitylboronic acid and ester **12** worked well giving **13** in almost quantitative yield. The ester **13** was reduced to alcohol **16**, which was resolved in to its enantiomers by preparative chiral HPLC (Chiralcel OD). Alcohols **14**–**16**, were converted to the corresponding tosylates **17**–**19** in good yields. Treatment of tosylates **17**–**19** with $Ar_2P(BH_3)Li$ at 0 °C in THF, followed by stirring at room temperature overnight in DMF, yielded the P-borane protected phosphines **20**–**22** in high yields. At this point, the borane adducts were stable to hydrolysis and oxidation. Removal of the borane-protecting group by stirring in neat Et_2NH gave the deprotected phosphines **8**–**10** (Scheme 2).

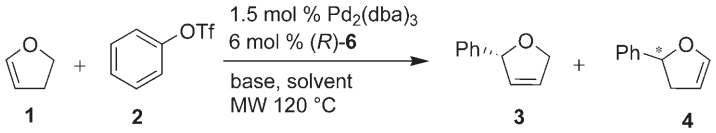
Asymmetric Heck Couplings

The Heck coupling between 2,3-dihydrofuran and phenyl triflate with 3 mol% of catalyst, prepared *in situ* from 1.5 mol% of $[Pd_2(dba)_3]$ and 6 mol% of ligand **6** was chosen as the standard reaction to study the influence of solvent and base (Table 1). The choice of base did not dramatically change the iso-



Scheme 2. Reagents and conditions: a) $ArB(OH)_2$, DPPF·$PdCl_2$ (5 mol%), K_2CO_3 (aqueous), toluene, 80°C; b) SPHOS (8 mol%), $Pd_2(dba)_3$ (4 mol%), mesitylB$(OH)_2$, K_3PO_4, toluene, reflux, overnight, 95%; c) $LiAlH_4$, THF, r.t., overnight, then preparative HPLC, Chiracel OD; d) TsCl, pyridine, 0°C to r.t. overnight; e) $Ar_2P(BH_3)H$, *n*-BuLi, THF, DMF, −78°C to r.t. overnight; f) Et_2NH, r.t., overnight.

Table 1. Optimization of reaction conditions.



Entry	Solvent	Base	Time [h]	Conversion[a] [%]	Ratio[b] **3/4**	*ee*[b] [%]
1	THF	DIPEA	4	>99	98/2	89
2	THF	Et_3N	4	80	96/4	89
3	THF	PS[c]	4	11	97/3	85
4	DMF	DIPEA	4	18	95/5	89
5	THF	DIPEA	12	>99	76/24	89 (76)
6	THF	DIPEA	5	>99	83/17	89 (40)
7	THF	DIPEA	3	90	99/1	89

[a] Determined by ^{1}H NMR.
[b] Determined by GC-MS (CHIRALDEX G-TA). Enantiomeric excess of **3**. Enantiomeric excess of **4** given in parenthesis. Absolute configuration of **4** was not determined.
[c] 1,8-Bis(dimethylamino)naphthalene.

meric ratio of **3/4**, but affected the reaction rates. Employing DIPEA as a base, the reaction proceeded to completion within four hours, whereas using triethylamine and proton sponge as bases gave lower conversions of 80% and 11%, respectively with the same reaction time (Table 1, entries 1–3). When proton sponge was employed as a base lower enantioselectivity (*ee* 85%) was obtained whereas the enantioselectivity was the same when triethylamine and DIPEA were used (*ee* 89%). Even though the ratio of **3/4** was not affected dramatically when different bases were used it should be mentioned that slightly more **4** was formed in the reaction when triethylamine and proton sponge were used when compared to DIPEA. This shows that the choice of base is important for the outcome of the reaction. In our system DIPEA proved superior among the bases employed (Table 1, entry 1).

Varying the solvent also had a great impact on the rate of the reaction. When THF was used as a solvent the reaction was complete within 4 h (Table 1, entry 1). When the more polar solvent DMF was used the reaction gave only 18% conversion in four hours (Table 1, entry 4). The enantiomeric excess remained

the same when DMF was used as solvent, but **4** was formed even though the reaction did not proceed to completion.

To our surprise in the commonly used solvent for Heck reactions, benzene, the reaction proceeded slowly when compared to THF and gave various conversions. The regioselectivity and enantioselectivity (76% *ee*) were also lower in benzene.

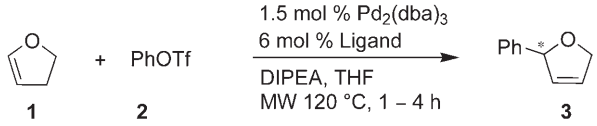
As seen in Table 1, the reaction time was crucial to regioselectivity (Table 1, entries 1 and 5–7). Longer reaction times resulted in lower regioselectivity (entry 5 and 6) whereas the reaction was not complete in 3 h (entry 7). The best results were obtained when the reaction was run for 4 h; this afforded the two regioisomers **3** and **4** in the ratio 98:2 (Table 1, entry 1). The enantiomeric excess of **3** was 89%. Based on the fact that the longer reaction time resulted in more formation of isomer **4**, the isomerization process takes place after the initial formation of **3** in our catalytic system. Lowering the reaction temperature from 120 °C to 100 °C did not enhance the enantioselectivity or regioselectivity, and the reaction proceeded much more slowly.

Effect of Ligand Substituents in the Heck Reaction of 2,3-Dihydrofuran (1) and Phenyl Triflate (2)

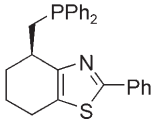
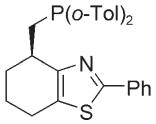
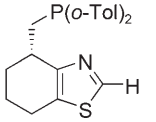
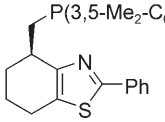
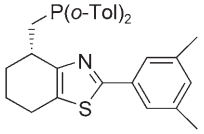
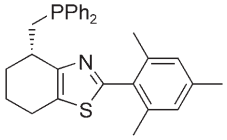
After optimizing the reaction for the formation of **3**, we screened several ligands (**5**–**10**) in order to chart the impact of the ligand structure on the reaction (Table 2). When the substitution pattern on the phosphine was varied with different aromatic substituents that is, phenyl, *o*-tolyl and 3,5-dimethylphenyl, the enantioselectivity varied little, although it can be seen that the *ee* values generally increased with bulkier substituents (Table 2, entries 1, 2 and 4). Different aromatic substituents on the phosphine moiety did not impact on the regioselectivity of the reaction or on the reactivity of the catalyst.

However, varying the substituent at the 2-position of the thiazole from hydrogen to mesityl affected the enantioselectivity of the reaction remarkably. With bulkier substituents, better enantioselectivities were obtained (Table 2, entries 2, 3, 5 and 6). This is in agreement with the findings of Pfaltz and co-workers, who observed that bulkier substituents close to the nitrogen coordinating atom increased the enantioselectivity.[7] When using ligand **7** the enantioselectivity was lower (*ee* 80%) than when using the ligands with aromatic substituents in the 2-position of the thiazole. With ligand **10** the best enantioselectivity was obtained, *ee* 96% (Table 2, entry 6). In our system the reaction rate was enhanced with bulkier substituents in the 2-position of the thiazole; which is in the contrast with the findings from Pàmies et al.[8a,b] The reactions proceeded slowest with ligand **7**, giving 29% conversion in four hours. The reaction was completed in one hour when ligand **10** was employed.

Table 2. Pd-catalyzed phenylation of 2,3-dihydrofuran **1** with ligands **5–10**.



1 2 3

Entry	Ligand	Conversion [%]	*ee* [%]
1	(*R*)-**5** 	98	85 (*R*)
2	(*R*)-**6** 	98	87 (*R*)
3	(*S*)-**7** 	29	80 (*S*)
4	(*R*)-**8** 	98	87 (*R*)
5	(*S*)-**9** 	98	87 (*S*)
6	(*S*)-**10** 	98	96 (*S*)

[a] Reactions were run for 4 h with ligands **5**–**9** and 1 hour with ligand **10**. Conversions to **3** were determined by ^{1}H NMR based on the triflate. Enantiomeric excesses were determined by GC-MS (CHIRALDEX G-TA) and chiral HPLC. The absolute configurations were assigned according to the literature.

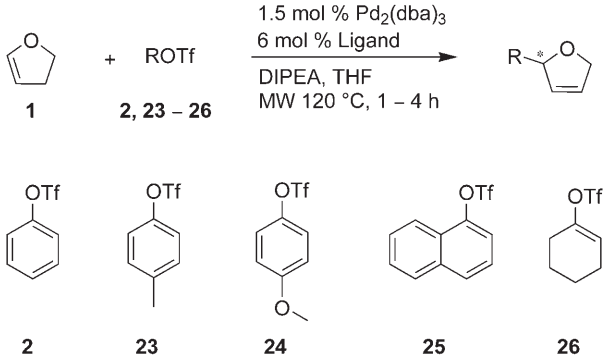
Heck reaction of 2,3-Dihydrofuran (1) with Different Aryl Triflates and Cyclohexenyl Triflate

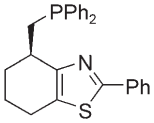
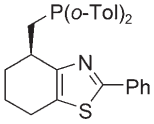
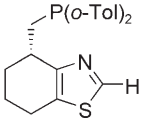
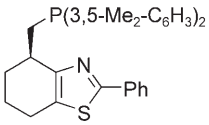
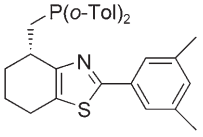
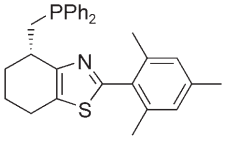
In order to study further the steric and electronic properties of the reaction, we tested the Heck reaction of 2,3-dihydrofuran (**1**)[16] with various aryl triflates (**2, 23**–**25**) and cyclohexenyl triflate (**26**). Aryl triflates were varied from bulky ones (1-naphthyl) to electron-donating ones (*p*-MeOC$_6$H$_4$OTf and *p*-MeC$_6$H$_4$OTf). In our system the best enantioselectivies

were achieved when 1-naphthyl triflate (**25**) was used. Electron-donating substituents (**23** and **24**) on phenyl gave generally higher *ee*s compared to phenyl triflate. Ligand substituent effects on the coupling with different aryl triflates were comparable to those observed in the Heck reaction of 2,3-dihydrofuran and phenyl triflate (Table 2). The ligand with the smallest substituent on the thiazole moiety (**7**) gave the lowest *ee* values varying from 77–80% and the reactions did not go to completion, whereas the ligand with the bulky mesityl substituent gave excellent enantioselectivities (94–98%) with high reactivity.

Surprisingly, when cyclohexenyl triflate (**26**) was employed in the Heck reaction the impact of the ligand structure was not equivalent to what was seen with aryl triflates. Reaction of 2,3-dihydrofuran (**1**) and cyclohexenyl triflate (**26**) gave dramatically increased *ee* values when the aromatic substituent on phosphine was changed from phenyl to the bulkier *o*-tolyl, 50% (Table 3, entry 1) to 80% respectively

Table 3. Evaluation of ligands **5**–**10** with various triflates **2, 23**–**26**.



Entry	Ligand/Triflate	**2** Conv./*ee* [%]	**23** Conv./*ee* [%]	**24** Conv./*ee* [%]	**25** Conv./*ee* [%]	**26**[b] Conv./*ee* [%]
1	(*R*)-**5** 	98/85 (*R*)	98/88 (*R*)	98/88 (*R*)	98/90 (*R*)	98/50 (*R*)
2	(*R*)-**6** 	98/87 (*R*)	98/87 (*R*)	98/86 (*R*)	98/93 (*R*)	98/80 (*R*)
3	(*S*)-**7** 	29/80 (*S*)	28/77 (*S*)	No conv.	30/78 (*S*)	72/79 (*S*)
4	(*R*)-**8** 	98/87 (*R*)	98/92 (*R*)	98/89 (*R*)	98/95 (*R*)	40/28 (*R*)
5	(*S*)-**9** 	98/87 (*S*)	98/89 (*S*)	98/87 (*S*)	98/90 (*S*)	98/86 (*S*)
6	(*S*)-**10** 	98/96 (*S*)	98/97 (*S*)	98/94 (*S*)	98/98 (*S*)	98/68 (*S*)

[a] Reactions were run for 4 h with ligands **5**–**9** and 1 hour with ligand **10**. Conversions to substituted 2,5-dihydrofurans were determined by ^{1}H NMR based on the triflate. Enantiomeric excesses were determined by GC-MS (CHIRALDEX G-TA) and chiral HPLC. The absolute configurations were assigned according to literature.

[b] Reactions were run 6 h with ligands **5**–**9** and 1.5 h with ligand **10**.

(Table 3, entry 2). However when the bulky substituent 3,5-dimethylphenyl on the phosphine was used in the coupling of **1** and **26**, the reaction proceeded in low *ee* (28%) and low conversion (Table 3, entry 4). With cyclohexenyl triflate (**26**), the substitution pattern at the 2-position of the thiazole did not play as crucial role as with aryl triflates.

Conclusions

In conclusion, we have shown that the phosphine-thiazole ligands developed in our group for the Ir-catalyzed hydrogenation of olefins also perform extremely well in the asymmetric Pd-catalyzed Heck coupling between 2,3-dihydrofuran and various triflates, giving enantioselectivities among the best reported so far. We have also shown that, when using microwaves as the source of heat, the reaction proceeds much faster and retains excellent enantioselectivity, allowing for a highly selective, fast screening of the asymmetric Heck coupling.

Experimental Section

All reactions were conducted under nitrogen using dried glassware and magnetic stirring. THF was freshly distilled from sodium-benzophenone ketyl under N_2 prior to use. CH_2Cl_2 was freshly distilled from powdered CaH_2 under N_2 prior to use. Benzene was freshly distilled from sodium under N_2 prior to use. Anhydrous dimethylformamide was purchased from Sigma–Aldrich. Triflates **2**, **23** and **25** were purchased from Sigma–Aldrich and triflates **24** and **26** were synthezised according to the literature procedures. 2,3-Dihydrofuran was purchased from Sigma–Aldrich. Diisopropylethylamine (DIPEA) was distilled from ninhydrin and then from potassium hydroxide. Flash chromatography was performed using silica gel 60 Å (37–70 μm). Analytical TLC was carried out utilizing 0.25 mm precoated plates, silica gel 60 UV_{254} and spots were visualized by the use of UV light. NMR samples were dissolved in $CDCl_3$ or benzene-d_6 and run at room temperature; ^1H (500 MHz), ^{13}C (126 MHz) NMR spectra were recorded on a 500 MHz spectrometer whereas ^{31}P (121 MHz) NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts for protons are reported using the residual $CHCl_3$ as internal reference ($\delta =$ 7.26). Carbon spectra were referenced to the shift of the ^{13}C signal of $CDCl_3$ ($\delta = 77.0$). Microwave heating was carried out using automatic single-mode synthesizer from Biotage, which produces a radiation frequency of 2.45 GHz. Temperature in the microwave oven was measured by an IR sensor sitting in the reaction cavity. Melting points are reported as their uncorrected values.

Ethyl 2-(2,4,6-Trimethylphenyl)-4,5,6,7-tetrahydrobenzo[*d*]thiazol-4-carboxylate (13)

An oven-dried, round-bottomed flask was charged with $Pd_2(dba)_3$ (0.126 g, 0.138 mmol), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl [S-PHOS] (0.226 g, 0.552 mmol), **7** (2.0 g, 6.9 mmol), 2,4,6-trimethylphenylboronic acid (2.26 g, 13.8 mmol) and powdered, anhydrous K_3PO_4 (5.86 g, 27.6 mmol). The flask was capped with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). Dry toluene (15 mL) was added and the septum was replaced by a condenser. The reaction mixture was heated to reflux and the mixture was stirred for 16 h under nitrogen. The reaction mixture was then allowed to cool down to room temperature, diluted with diethyl ether and filtered through Celite. The filtrate was concentrated under vacuum giving the crude product. The crude product was purified by flash chromatography (toluene:EtOAc, 90:10) giving product **8** as an oil; yield: 2.16 g (95%). $R_f = 0.35$ (toluene:EtOAc, 90:10); IR (KBr): $\nu_{max} = 2937$, 2864, 1731, 1462, 1218, 1177, 1158, 909 cm^{-1}; ^1H NMR: $\delta = 1.23$ (t, $J = 7.2$ Hz, 3H, CH_2CH_3), 1.88–1.95 (m, 1H, CH_2), 1.99–2.07 (m, 1H, CH_2), 2.10–2.17 (m, s overlapping, 1H, CH_2), 2.14 (s, m overlapping, 6H, $2CH_3$), 2.21–2.27 (m, 1H, CH_2), 2.30 (s, 3H, CH_3), 2.91 (dddd, $J = 1.6$, 5.7, 6.9, 13.6 Hz, 1H, CH_2), 3.93–3.96 (m, 1H, CH), 4.12–4.22 (m, 2H, CH_2CH_3), 6.89–6.90 (m, 2H, ArH); ^{13}C NMR: $\delta = 14.2$, 20.2, 21.1, 21.2, 23.4, 26.9, 43.0, 60.8, 128.2, 131.0, 132.4, 137.6, 138.8, 146.7, 163.5, 173.6; MS (EI): *m/z* (rel. intensity) = 331.06 (MH^+, 26%), 329.46 (M^+, 100%), 256.54 (44%), 255.16 (80%), 253.17 (22%); anal. calcd. (%) for $C_{19}H_{23}NO_2S$ (329.1): C 69.27, H 7.04, N 4.25; found: C 69.25, H 7.28, N 4.37.

(*S*)-[2-(3,5-Dimethylphenyl)-4,5,6,7-tetrahydrobenzo-[*d*]thiazol-4-yl]methanol (15)

To a solution of **11** (0.1 g, 0.4 mmol) in toluene (1.5 mL) was added Na_2CO_3 (0.085 g, 0.8 mmol) followed by H_2O (0.35 mL), 3,5-dimethylphenylB$(OH)_2$ (0.089 g, 0.6 mmol) and $PdCl_2$·dppf·$CHCl_3$ (0.025 g, 0.030 mmol) and the resulting mixture was degassed and vigorously stirred at 80 °C under nitrogen until TLC indicated complete disappearance of **11**. H_2O (5 mL) and toluene (5 mL) were added followed by 1M NaOH (5 mL). After separation, the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL) and the combined organic extracts were washed with H_2O (10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated to dryness. Purification by flash chromatography (toluene:EtOAc, 90:10) gave **15** as a white solid; yield: 0.094 g (86%); mp 98.5–100.5; $R_f = 0.46$ (toluene:EtOAc 80:20); $[\alpha]_D^{25}$: +84.9° (*c* 1.1, $CHCl_3$); IR (KBr): $\nu_{max} = 3338$, 3063, 2941, 2856, 1531, 1499, 1456, 1428, 1310, 1228, 1036, 763, 732, 691 cm^{-1}; ^1H NMR: $\delta = 1.34$–1.46 (m, 1H, CH_2), 2.78–1.89 (m, 1H, CH_2), 1.95–2.10 (m, 2H, CH_2), 2.36 (s, 6H), 2.69–2.90 (m, 2H), 3.03–3.09 (m, 1H), 3.68 (dd, $J = 4.8$, 10.6 Hz, 1H, CH), 3.82 (dd, $J = 9.7$, 10.6 Hz, 1H, CH_2OH), 4.77 (brs, 1H, OH), 7.03 (m, 1H, ArH), 7.49 (m, 1H, ArH); ^{13}C NMR: $\delta =$ 21.2, 22.4, 23.6, 25.5, 39.4, 67.3, 124.0, 129.5, 131.6, 133.2, 138.5, 153.3, 165.7; MS (EI): *m/z* (rel. intensity) = 274.1 (MH^+, 41%), 243.2, (100%), 242.2 (62%) 200.1 (11%), 249.9 (18%), 132.2 (17%), 111.1 (22%); anal. calcd. (%) for $C_{16}H_{19}NOS$ (273.1): C 70.29, H 7.00, N 5.12; found: C 70.15, H 7.06, N 5.03.

(*S*)-[2-(2,4,6-Trimethylphenyl)-4,5,6,7-tetrahydrobenzo[*d*]thiazol-4-yl]methanol (16)

Compound **13** (2.15 g, 6.53 mmol) was dissolved in dry THF (25 mL) and added to a slurry of $LiAlH_4$ (0.50 g,

13.07 mmol) in THF (15 mL) at 0 °C. The temperature was allowed to rise to room temperature and the mixture was stirred overnight. The reaction mixture was recooled to 0 °C and the reaction was quenched by slow addition of water (0.5 mL), followed by 2 M NaOH (1.0 mL) and additional water (0.5 mL). The resulting mixture was stirred for 3 h at room tempertaure. Filtration on Celite, followed by washing of the filter cake with THF (2×15 mL) and evaporation of the filtrate gave the crude product; yield: 1.65 g (90 %).

The crude product was pure enough for the chiral separation. The two enantiomers were separated by semipreparative HPLC [Chiracel OD column (20×250 mm), hexane:*i*-PrOH = 95:5, 5 mL min^{-1}, 30 mg loading, t_R 21.08 (*S*) and 24.83 (*R*) (chirality decided assuming the same optical rotation as for **14**[12]] to afford a white solid; mp 149.6–150.4; R_f = 0.30 (toluene:EtOAc, 80:20); $[\alpha]_D^{25.3}$: +52° (*S*) (*c* 0.9, $CHCl_3$); IR (KBr): ν_{max} = 3402, 2927, 2860, 2246, 1447, 1041, 978. 908 cm^{-1}; ^{1}H NMR: δ = 1.39–1.47 (m, 1H CH_2), 1.81–1.89 (m, 1H, CH_2), 1.97–2.02 (m, 1H, CH_2), 2.05–2.11 (m, 1H, CH_2), 2.15 (s, 6H, CH_3), 2.32 (s, 3H, CH_3), 2.75–2.82 (m, 1H, CH_2), 2.86–2.91 (m, 1H, CH_2), 3.06–3.13 (m, 1H, CH), 3.66 (ddd, *J* = 1.6 Hz, 9.4 Hz, 10.5 Hz, 1H, CH_2OH), 3.81 (ddd, *J* = 4.2 Hz, 10.5 Hz, 1H, CH_2OH), 4.55 (dd, *J* = 1.6 Hz, 10.5 Hz, 1H, OH), 6.93 (m, 2H, ArH); ^{13}C NMR: δ = 20.31, 21.13, 22.42, 23.52, 25.56, 39.44, 67.43, 128.36, 130.71, 130.83, 137.54, 139.01, 152.53, 163.83; MS (EI): *m/z* (rel. intensity) = 288.14 (MH^+, 100 %), 257.52 (32 %), 255.84 (18 %); anal. calcd. (%) for $C_{17}H_{21}NOS$ (287.1): C 71.04, H 7.36, N 4.87; found: C 70.83, H 7.21, N 4.73.

Compounds **17**–**22** and **8**–**10** were synthesized according to the reported procedures.[12]

General Procedure for MW-Assisted Asymmetric Intermolecular Heck Reaction (Table 1)

(*R*)-**6** (3.2 mg, 6 mol %) and $Pd_2(dba)_3$ (1,7 mg, 3 mol % Pd) were weighed into an MW-vial and dry solvent (0.5 mL) was added. The vial was sealed and the mixture was gently heated with a heat gun until the colour remained the same in the mixture (usually the colour changed from purple to yellow-green). The reaction mixture was then allowed to cool down to room temperature before addition of phenyl triflate (20 μL, 0.13 mmol, 1 equiv.), 2,3-dihydrofuran (48 μL, 0.63 mmol, 5 equivs.) and base (0.38 mol, 3 equivs.). The mixture was microwave-heated for the chosen time and temperature. After cooling, the mixture was diluted in diethyl ether and filtered through a short column of silica. The filtrate was analyzed by the method reported in the literature and identified as 2-phenyl-2,5-dihydrofuran.[8e]

General Procedure for MW-Assisted Asymmetric Intermolecular Heck Reaction (Table 2 and Table 3)

Ligand (6 mol %) and $Pd_2(dba)_3$ (1,7 mg, 3 mol % Pd) were weighed into an MW-vial and dry THF (0.5 mL) was added. The vial was sealed and the mixture was gently heated with a heat gun until the colour remained the same in the mixture (usually the colour changed from purple to yellow-green). The reaction mixture was then allowed to cool down to room temperature before addition of triflate (0.13 mmol, 1 equiv.), 2,3-dihydrofuran (48 μL, 0.63 mmol, 5 equivs.) and DIPEA (65 μL, 0.38 mol, 3 equivs.). The mixture was microwave-heated at 120 °C for the given time. After cooling, the mixture was diluted with diethyl ether and filtered through a short column of silica. The filtrate was concentrated and the residue was analyzed by ^{1}H NMR and the enantioselectivity was determined by the method reported in the literature or by the given method. The products were 2-phenyl-2,5-dihydrofuran,[8e] 2-*p*-methoxyphenyl-2,5-dihydrofuran,[10] and 2-(cyclohex-1′-en-1′-yl)-2,5-dihydrofuran.[8e]

2-*p*-Tolyl-2,5-dihydrofuran:[17] The same method as was used for 2-phenyl-2,5-dihydrofuran; GC-MS (G-TA, 80 °C, 0.3 °C/min, 90 °C, 5 °C/min, 125 °C, 15 psi): T_{R1} = 32.7 min (*S*), T_{R2} = 34.3 min (*R*). The absolute configuration assumes the same sense of asymmetric induction as with 2-phenyl-2,5-dihydrofuran.

2-(1-Naphthyl)-2,5-dihydrofuran:[8e] GC-MS (G-TA 120 °C, 1 °C/min, 170 °C, 12 psi): T_{R1} = 34.8 min (−), T_{R2} = 35.5 min (+). According to the literature (+) gives (*R*).[18]

Supporting Information

The characterization data of the compounds **17**–**22** and **8**–**10** are available in the Supporting Information.

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