Synthesis Z. J. Garlets, J. P. Wolfe Special Topic

Asymmetric Synthesis of Six-Membered Cyclic Sulfamides via Palladium-Catalyzed Alkene Carboamination Reactions

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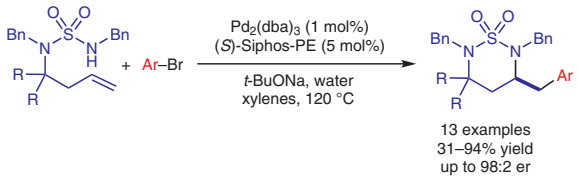

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Abstract The asymmetric synthesis of six-membered cyclic sulfamides via palladium-catalyzed alkene carboamination reactions of *N*-homoallylsulfamides with aryl halides is described. High levels of enantioselectivity were obtained with a catalyst composed of Pd_2dba_3 and (*S*)-Siphos-PE.

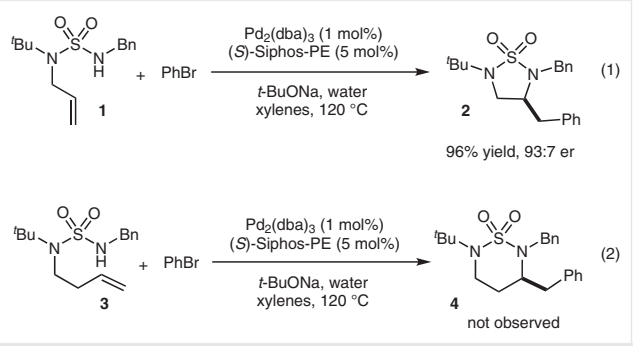
Key words palladium, asymmetric catalysis, alkenes, sulfamides, heterocycles

The development of methods for efficient chemo- and stereoselective construction of new carbon–nitrogen bonds is of significant and longstanding interest to the synthetic community. Specifically, the creation of new methods for accessing cyclic sulfamides is attractive, as these represent important structural motifs present in a number of pharmaceutically relevant compounds.[1] In addition, the SO_2 group can be excised from cyclic sulfamides to provide 1,3-diamines,[2] which are also displayed in a variety of natural products and bioactive compounds.[3] Chiral 1,3-diamines have also been used for the construction of chiral ligands and chiral auxiliaries for asymmetric synthesis.[4]

In recent years, several groups have explored the use of transition-metal catalysis for the synthesis of both five- and six-membered cyclic sulfamides.[5] Although the use of metal catalysis for the synthesis of six-membered sulfamides is less explored than the corresponding five-membered ring compounds, several important developments have been described. Du Bois and co-workers described a C–H functionalization strategy which utilized a Rh-catalyst for the synthesis of six-membered sulfamides.[6] In addition, Zhang and co-workers have elegantly employed metalloradical activation of azides by a cobalt(II) catalyst for a variety of transformations toward the synthesis of different six-membered cyclic sulfamides.[7] Finally, our group has demonstrated the diastereoselective generation of six-membered sulfamides bearing a fused ring through Pd-catalyzed alkene carboamination reactions between aryl triflates and sulfamides derived from 2-allylpyrrolidine or 2-allylpiperidine.[8]

Despite the work devoted to generating cyclic sulfamides, only two methods have been reported that employ transition-metal catalysts for the asymmetric synthesis of cyclic sulfamides, both of which provide five-membered rather than six-membered heterocycles. The Shi group described the asymmetric synthesis of cyclic sulfamides using a chiral Pd-catalyst to effect the diamination of dienes with *N*,*N*′-di-*tert*-butylthiadiaziridine 1,1-dioxide.[5f] Although the transformations proceed with good yields and selectivities, the dithiaziridinone derivative is not commercially available, and the method is limited to conjugated diene substrates; examples with simple alkenes have not been described. In 2016, our group reported an enantioselective synthesis of five-membered cyclic sulfamides via Pd-catalyzed alkene carboamination reactions between aryl bromides and *N*-allylsulfamides **1** bearing a *N*-*t*-Bu protecting group (Scheme 1, eq 1).[9] These transformations provided the desired products **2** in good chemical yields and good enantioselectivities for a variety of different substrate combinations.

Given the scarcity of catalytic asymmetric five-membered cyclic-sulfamide-forming reactions, it is perhaps not surprising that the asymmetric synthesis of six-membered cyclic sulfamides by transition-metal catalysis has yet to be reported. In this communication, we describe the first examples of the catalytic asymmetric synthesis of six-membered cyclic sulfamides through Pd-catalyzed alkene carboamination reactions of acyclic *N*-homoallylsulfamides.

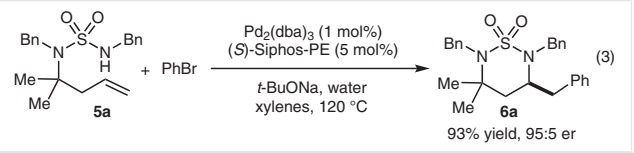


Scheme 1 Synthesis of five- vs six-membered cyclic sulfamides

These transformations effect the enantioselective formation of the ring and one C–N bond, with concomitant generation of a C–C bond external to the ring.

On the surface, the generation of six-membered rings by an extension of our approach to the asymmetric construction of five-membered cyclic sulfamides would appear to be a straightforward process. However, as shown in Scheme 1, although the coupling of *N*-allylsulfamide **1** with bromobenzene provided **2** in excellent yield and 93:7 er (eq 1), attempts to achieve an analogous transformation of *N*-homoallylsulfamide **3** failed to afford the desired product **4**. Instead, decomposition of the substrate to a complex mixture of products was observed.

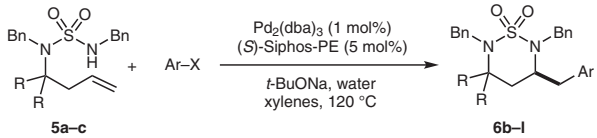
Although the lack of desired reactivity of **3** was disappointing, we felt that a change in the substrate structure may lead to improved results. Our prior studies on the construction of five-membered cyclic sulfamides revealed that the *N*-*tert*-butyl group on the non-cyclizing nitrogen was critical for reactivity, presumably due to a Thorpe–Ingold-type effect[10] that positioned the alkene closer to the cyclizing nitrogen atom. We thought that moving the steric bulk from the non-cyclizing nitrogen in **3** to the carbon adjacent to the nitrogen atom on the homoallyl chain may facilitate reactivity through a similar effect. As such, substrate **5a** was easily prepared in three steps using standard chemistry: (1) conversion of acetone into the corresponding *N*-benzyl imine, (2) addition of allylmagnesium bromide to afford the homoallylic secondary amine, and (3) sulfonylation of the secondary amine to afford **5a**. We were gratified to find that when substrate **5a** was subjected to the standard reaction conditions, the desired cyclization product **6a** was formed with 93% yield and 95:5 er (Scheme 2, eq 3).[11]



Scheme 2 Synthesis of six-membered cyclic sulfamide **6a**

Encouraged by this initial result, we elected to explore the scope of this method with respect to the aryl bromide electrophile (Table 1). The electronic properties of the electrophile had no significant influence on the enantioselectivity; both electron-rich and electron-poor aryl bromides reacted to afford enantioenriched cyclic sulfamides in >95:5 er (entries 1–6). However, the use of 2-bromotoluene as the electrophile led to the formation of **6h** in low yield and moderate enantioselectivity (85:15 er) (entry 7). Efforts to use aryl iodides as electrophiles led to unsatisfactory results; the reaction of 4-iodobiphenyl proceeded in a modest 42% yield and an *average* 82:18 er (entry 8), and enantioselectivities were not reproducible with this substrate, ranging from 82:18 to 91.5:8.5 er. Different substituents on the homoallyl chain [R = Me, Et, and R–R = $-(CH_2)_4-$] were well tolerated (entries 9–12).

Table 1 Asymmetric Synthesis of Six-Membered Cyclic Sulfamides[a]



5a: R = Me
5b: R–R = -$(CH_2)_4$-
5c: R = Et

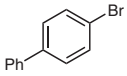
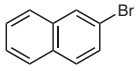
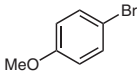
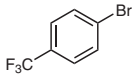
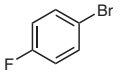
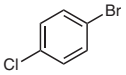
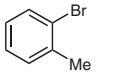
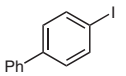
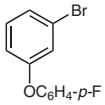
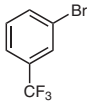
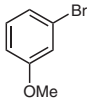
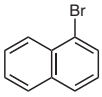
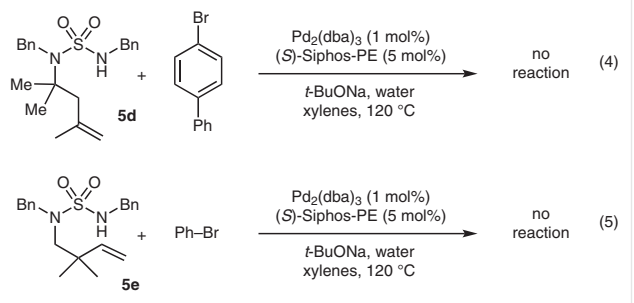
Entry	Substrate	Ar–X	Yield (%)[b]	er[c]
1	**5a**		87 (**6b**) 90[d] (**6b**)	97:3 97:3
2	**5a**		75 (**6c**)	96.5:3.5
3	**5a**		57 (**6d**)	98:2
4	**5a**		75 (**6e**)	96.5:3.5
5	**5a**		94 (**6f**)	96.5:3.5
6	**5a**		65[e] (**6g**)	97:3
7	**5a**		31 (**6h**)	85:15
8	**5a**		42 (**6b**)	82:18[f]

Table 1 (continued)

Entry	Substrate	Ar–X	Yield (%)[b]	er[c]
9	**5b**		92 (**6i**)	95.5:4.5
10	**5b**		92 (**6j**)	96.5:3.5
11	**5b**		90 (**6k**)	97:3
12	**5c**		92 (**6l**)	95:5

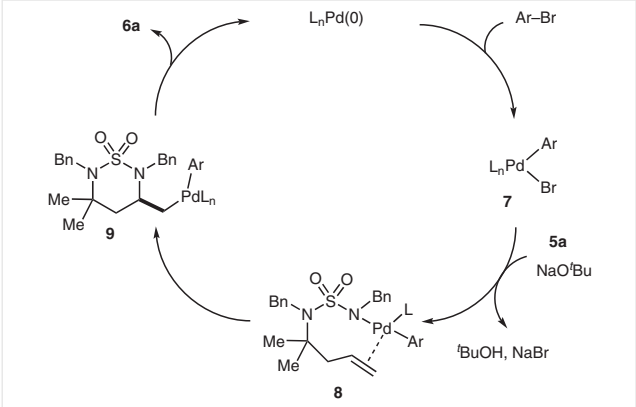
[a] Reaction conditions: substrate **5** (1.0 equiv), R–X (2.0 equiv), *t*-BuONa (2.0 equiv), H_2O (2.0 equiv), [$Pd_2(dba)_3$] (1 mol%), (*S*)-Siphos-PE (5 mol%), xylenes (0.125 M), 120 °C, 18 h. Reactions were conducted on a 0.20 mmol scale.
[b] Yield of isolated product (average of two or more experiments).
[c] Enantiomeric ratios were determined by chiral HPLC analysis.
[d] The reaction was conducted on 1.0 mmol scale.
[e] The product contained ca. 5–10% of an unidentified impurity.
[f] Enantiomeric ratios ranged from 82:18 to 91.5:8.5.

In order to further explore the scope of this method, we also examined the reactivity of sulfamides bearing additional substituents. However, thus far, attempts to accomplish the asymmetric carboamination of **5d** bearing a 1,1-disubstituted alkene have been unsuccessful (Scheme 3, eq 4). In addition, substrate **5e** bearing substitution at the allylic position was unreactive (Scheme 3, eq 5).



Scheme 3 Attempted cyclization of sulfamides bearing additional substituents

Our prior studies on the asymmetric synthesis of five-membered cyclic sulfamides indicated that the reactions proceed via net *syn* addition to the alkene.[9,12] Given the fact that the transformations described in this manuscript employ similar reaction conditions, and for both five- and six-membered ring-forming reactions the use of the (*S*)-Siphos-PE catalyst affords the *S*-enantiomer of the products, we suggest that both transformations proceed through similar mechanisms, which are analogous to the mechanism shown to operate for other alkene carboamination or carboalkoxylation reactions that afford *syn*-addition products.[13] As shown in Scheme 4, the reaction is initiated by oxidative addition of the aryl halide to Pd(0) to afford **7**. Coordination of the sulfamide with concomitant deprotonation forms the Pd-amido complex **8**, which is staged to undergo *syn*-migratory insertion of the alkene into the Pd–N bond to provide **9**.[14] Reductive elimination of **9** yields the heterocycle and also regenerates the Pd catalyst. Alternative mechanistic pathways involving initial carbopalladation of the alkene appear less likely, as we have previously shown that these pathways are not in operation in other related systems.[14a,c]



Scheme 4 Catalytic cycle

In conclusion, we have developed an enantioselective Pd-catalyzed alkene carboamination reaction for the synthesis of six-membered cyclic sulfamides. The starting *N*-homoallylsulfamides are readily prepared in three steps, and the cyclic sulfamides are formed in high enantioselectivity and good to excellent chemical yield. These transformations represent the first examples of asymmetric metal-catalyzed carboamination reactions for the synthesis of six-membered cyclic sulfamides from acyclic precursors. Future work will focus on expanding the scope of this reaction.

Reactions were carried out under nitrogen in flame-dried or oven-dried glassware unless otherwise specified. Tris(dibenzylideneacetone)dipalladium and (*S*)-Siphos-PE were purchased from Strem Chemical Co. and used without further purification. Dichloromethane, diethyl ether, tetrahydrofuran, and toluene were purified using a GlassContour solvent system. Xylenes were purified by distillation over CaH_2 prior to use in reactions. All other solvents and aryl halides were purchased from commercial sources and used as received. Yields refer to isolated compounds that are estimated to be >95% pure as judged by ^1H NMR unless otherwise noted. The yields reported in the

supporting information describe the result of a single experiment, whereas the yields reported in Scheme 2 (eq 3) and Table 1 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those in Scheme 2 (eq 3) and in Table 1. Column chromatography was performed using Silicycle silica gel (mesh size 230-400). Melting points were determined using a Thomas Hoover UNI-Melt capillary melting point apparatus. Optical rotations were recorded using a Jasco P-2000 polarimeter. IR spectra were recorded using a Nicolet iS50 FT-IR spectrophotometer. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded using Varian VNMR spectrometers. HRMS spectra were obtained using a Micromass AutoSpec Ultima Magnetic Sector Mass spectrometer.

α,α-Disubstituted Homoallylic Amines; General Procedure 1

The α,α-disubstituted homoallylic amine substrates were prepared from the corresponding ketones on a 60 mmol scale (unless otherwise noted) by a two-step procedure involving imine formation followed by Grignard addition to the imine.

The requisite symmetrical ketone (1 equiv), primary amine (1 equiv), 4 Å molecular sieves (200 mg/mmol), and CH_2Cl_2 (2 M) were added to a flame-dried flask (equipped with a stir bar) that had been cooled under a stream of nitrogen. The mixture was vigorously stirred at r.t. until the starting materials had been completely consumed, as determined by TLC analysis. The mixture was then filtered through Celite and the solvent was removed under reduced pressure to afford the corresponding ketimine.

A flame-dried round-bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with allylmagnesium bromide (1 M in Et_2O). This solution was cooled to 0 °C and then a solution of the ketimine (0.4 M in THF) was added dropwise. The reaction was warmed to r.t., and then stirred overnight. The flask was subsequently cooled to 0 °C in an ice bath, and the reaction was slowly quenched with saturated aqueous ammonium chloride (75 mL). The mixture was transferred to a separating funnel, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 200 mL). The organic layers were combined and washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

Homoallylicsulfamides; General Procedure 2

Transformations were carried out on a 20 mmol scale unless otherwise noted. A flame-dried two-neck round-bottom flask equipped with a stir bar, a condenser, and a septum was cooled under a stream of nitrogen. This flask was charged with DMAP (0.20 equiv) and the requisite N-subsituted-2-oxooxazolidin-3-sulfonamide substrate (1.0 equiv). Anhydrous MeCN (100 mL) was added followed by Et_3N (3.0 equiv). This mixture was heated at 80 °C for 15 min with stirring, and then the homoallylic amine was added dropwise. The resulting mixture was stirred at 80 °C for 16–18 h. The reaction mixture was then cooled to r.t., and the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc (50 mL) and washed twice with equal portions of 1 M HCl (50 mL for each wash), and once with brine (50 mL). The organic layer was dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude material was purified by column chromatography using hexanes/EtOAc as the eluent.

N′-Benzyl-*N*-(*tert*-butyl)-*N*-(but-3-en-1-yl)sulfamide (3)

General procedure 2 was employed for the sulfonylation of *N*-(*tert*-butyl)but-3-en-1-amine[15] (1.34 g, 10.5 mmol) with 3-(*N*-benzylsulfonyl)oxazolidin-2-one (2.43 g, 9.5 mmol). This procedure afforded the title compound (670 mg, 24%) as a colorless solid; mp 44–47 °C.

IR (neat): 3322, 1317, 1135, 1088 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 4 H), 7.33–7.29 (m, 1 H), 5.80–5.73 (m, 1 H), 5.09 (dd, *J* = 17.0, 1.5 Hz, 1 H), 5.04 (d, *J* = 10.2 Hz, 1 H), 4.21 (t, *J* = 6.1 Hz, 1 H), 4.16 (d, *J* = 6.1 Hz, 2 H), 3.34–3.30 (m, 2 H), 2.46–2.41 (m, 2 H), 1.46 (s, 9 H).

^{13}C NMR (175 MHz, $CDCl_3$): δ = 136.8, 135.2, 129.0, 128.3, 128.1, 116.9, 58.9, 47.6, 46.6, 36.8, 29.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{25}N_2O_2S$: 297.1631; found: 297.1629.

N-Benzyl-*N*′-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (5a)

General procedure 1 was used for the preparation of *N*-benzyl-2-methylpent-4-en-2-amine from acetone (4.4 mL, 60 mmol), benzylamine (6.6 mL, 60 mmol), 4 Å molecular sieves (12 g), and CH_2Cl_2 (30 mL), with a reaction time of 4 h. This procedure afforded crude *N*-benzylpropan-2-imine, which was then dissolved in THF (150 mL) and treated with allylmagnesium bromide (150 mmol, 1 M solution in Et_2O). Work-up and subsequent purification by column chromatography afforded *N*-benzyl-2-methylpent-4-en-2-amine as a yellow oil (9.9 g, 87% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 4 H), 7.25–7.21 (m, 1 H), 5.93–5.82 (m, 1 H), 5.15–5.08 (m, 2 H), 3.72 (s, 2 H), 2.25 (d, *J* = 7.4 Hz, 2 H), 1.15 (s, 6 H).

General procedure 2 was used to sulfonylate *N*-benzyl-2-methylpent-4-en-2-amine (4.3 g, 22.5 mmol) with 3-(*N*-benzylsulfonyl)oxazolidin-2-one (5.2 g, 20.4 mmol). This procedure afforded the title compound (3.0 g, 41%) as a colorless solid; mp 75–77 °C.

IR (neat): 3330, 1453, 1320, 1132 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.5 Hz, 2 H), 7.36–7.20 (m, 8 H), 5.92–5.80 (m, 1 H), 5.12 (s, 1 H), 5.09 (s, 1 H), 4.58 (s, 2 H), 4.17 (t, *J* = 5.5 Hz, 1 H), 4.13 (d, *J* = 5.4 Hz, 2 H), 2.64 (d, *J* = 7.3 Hz, 2 H), 1.44 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.1, 136.9, 134.5, 128.9, 128.6, 128.2, 128.1, 127.2, 118.7, 62.6, 50.8, 47.7, 46.0, 27.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{27}N_2O_2S$: 359.1788; found: 359.1791.

N-Benzyl-*N*′-benzyl-*N*-(1-allylcyclohexyl)sulfamide (5b)

General procedure 1 was used for the preparation of 1-allyl-*N*-benzylcyclohexan-1-amine from cyclohexanone (2.1 mL, 20 mmol), benzylamine (2.2 mL, 20 mmol), 4 Å molecular sieves (4 g), and CH_2Cl_2 (10 mL), with a reaction time of 4 h. The solution was filtered through Celite, and the solvent was removed under reduced pressure to afford crude *N*-benzylcyclohexanimine, which was dissolved in THF (50 mL) and treated with allylmagnesium bromide (50 mmol, 1 M solution in Et_2O). Work-up and subsequent purification by column chromatography afforded 1-allyl-*N*-benzylcyclohexan-1-amine as a yellow oil (3.1 g, 68% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 6.9 Hz, 2 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.25–7.21 (m, 1 H), 6.02–5.94 (m, 1 H), 5.14–5.07 (m, 2 H), 3.65 (s, 2 H), 2.26 (d, *J* = 7.4 Hz, 2 H), 1.72–1.30 (m, 10 H).

General procedure 2 was used to sulfonylate 1-allyl-*N*-benzylcyclohexan-1-amine (3.1 g, 13.9 mmol) with 3-(*N*-benzylsulfonyl)oxazolidin-2-one (3.2 g, 12.5 mmol) to afford the title compound (1.23 g, 25%) as a colorless solid; mp 77–79 °C.

IR (neat): 3333, 1455, 1414, 1333, 1148 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.4 Hz, 2 H), 7.35–7.22 (m, 6 H), 7.18–7.15 (m, 2 H), 6.03–5.93 (m, 1 H), 5.19–5.11 (m, 1 H), 4.59 (s, 2 H), 4.11 (d, *J* = 5.7 Hz, 2 H), 4.06 (t, *J* = 5.7 Hz, 1 H), 2.79 (d, *J* = 7.2 Hz, 2 H), 2.19 (d, *J* = 12.8 Hz, 2 H), 1.81 (td, *J* = 12.7, 3.7 Hz, 2 H), 1.67–1.53 (m, 3 H), 1.48–1.35 (m, 2 H), 1.27–1.15 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.3, 137.0, 134.6, 128.8, 128.6, 128.2, 128.0, 127.3, 127.2, 118.5, 66.4, 50.2, 47.8, 38.4, 35.3, 25.3, 23.1.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{31}N_2O_2S$: 399.2101; found: 399.2103.

N-Benzyl-*N*′-benzyl-*N*-(3-ethylhex-5-en-3-yl)sulfamide (5c)

General procedure 1 was used for the preparation of *N*-benzyl-3-ethylhex-5-en-3-amine from 3-pentanone (3.2 mL, 30 mmol), benzylamine (3.3 mL, 30 mmol), 4 Å molecular sieves (6 g), and CH_2Cl_2 (15 mL), with a reaction time of 24 h. The solution was filtered through Celite, and the solvent was removed under reduced pressure to afford crude *N*-benzylpentan-3-imine, which was then dissolved in THF (75 mL) and treated with allylmagnesium bromide (75 mmol, 1 M solution in Et_2O). Work-up and subsequent purification by column chromatography afforded *N*-benzyl-3-ethylhex-5-en-3-amine as a yellow oil (2.6 g, 40% over two steps).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 6.9 Hz, 2 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.25–7.21 (m, 1 H), 5.89–5.79 (m, 1 H), 5.17–5.05 (m, 2 H), 3.61 (s, 2 H), 2.17 (dt, *J* = 7.4, 1.3 Hz, 2 H), 1.42 (qd, *J* = 7.4, 2.2 Hz, 4 H), 0.86 (t, *J* = 7.4 Hz, 6 H).

General procedure 2 was used to sulfonylate *N*-benzyl-3-ethylhex-5-en-3-amine (2.64 g, 12.2 mmol) with 3-(*N*-benzylsulfonyl)oxazolidin-2-one (2.83 g, 11 mmol) to afford the title compound (450 mg, 11%) as a colorless oil.

IR (neat): 3296, 1318, 1144 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 7.5 Hz, 2 H), 7.34–7.31 (m, 2 H), 7.30–7.24 (m, 4 H), 7.18–7.15 (m, 2 H), 5.90 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1 H), 5.14–5.12 (m, 1 H), 5.12–5.10 (m, 1 H), 4.59 (s, 2 H), 4.14 (d, *J* = 6.1 Hz, 2 H), 4.08 (t, *J* = 6.1 Hz, 1 H), 2.64 (d, *J* = 7.3 Hz, 2 H), 1.89–1.78 (m, 4 H), 0.94 (t, *J* = 7.4 Hz, 6 H).

^{13}C NMR (175 MHz, $CDCl_3$): δ = 140.3, 137.1, 134.5, 128.8, 128.6, 128.2, 128.0, 127.6, 127.2, 118.5, 69.9, 50.8, 48.0, 39.7, 28.4, 8.9.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{31}N_2O_2S$: 387.2101; found: 387.2106.

N-Benzyl-*N*′-benzyl-*N*-(2,4-dimethylpent-4-en-2-yl)sulfamide (5d)

General procedure 1 was used for the preparation of *N*-benzyl-2,4-dimethylpent-4-en-2-amine from acetone (4.4 mL, 60 mmol), benzylamine (6.6 mL, 60 mmol), 4 Å molecular sieves (12 g) and CH_2Cl_2 (30 mL), with a reaction time of 4 h. The solution was filtered through Celite, and the solvent was removed under reduced pressure to afford crude *N*-benzylpropan-2-imine which was dissolved in THF (150 mL) and treated with allylmagnesium chloride (150 mmol, 1 M solution in Et_2O). Work-up and subsequent purification by column chromatography afforded *N*-benzyl-2,4-dimethylpent-4-en-2-amine as a yellow oil (3.05 g, 25% over two steps).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 6.7 Hz, 2 H), 7.31 (t, *J* = 7.5 Hz, 2 H), 7.23 (t, *J* = 7.1 Hz, 1 H), 4.91 (s, 1 H), 4.73 (s, 1 H), 3.76 (s, 2 H), 2.24 (s, 2 H), 1.85 (s, 3 H), 1.18 (s, 6 H).

General procedure 2 was used to sulfonylate *N*-benzyl-2,4-dimethylpent-4-en-2-amine (2.4 g, 12 mmol) with 3-(*N*-benzylsulfonyl)oxazolidin-2-one (2.56 g, 10.0 mmol) to afford the title compound (1.4 g, 37%) as a viscous oil.

IR (neat): 3300, 1317, 1134 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.4 Hz, 2 H), 7.35–7.21 (m, 8 H), 4.93–4.91 (m, 1 H), 4.79 (s, 1 H), 4.60 (s, 2 H), 4.23 (t, *J* = 6.1 Hz, 1 H), 4.12 (d, *J* = 6.1 Hz, 2 H), 2.64 (s, 2 H), 1.81 (s, 3 H), 1.50 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.2, 140.1, 137.0, 128.9, 128.6, 128.2, 128.0, 127.3, 127.2, 116.2, 63.3, 50.8, 48.3, 47.7, 28.3, 25.3.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{29}N_2O_2S$: 373.1944; found: 373.1948.

N-Benzyl-*N*′-benzyl-*N*-(2,2-dimethylbut-3-en-1-yl)sulfamide (5e)

2,2-Dimethylbut-3-enoic acid[16] (1.1 g, 10 mmol) was suspended in CH_2Cl_2 (30 mL) and trimethylamine (2.8 mL, 20 mmol) was added. The mixture was cooled to 0 °C, and then ethyl chloroformate (0.96 mL, 10 mmol) was added dropwise. The solution was stirred at 0 °C for 30 min, and then benzylamine (1.3 mL, 12 mmol) was added dropwise. The reaction was warmed to r.t., and then stirred at r.t. overnight. The reaction was then quenched with saturated sodium bicarbonate (30 mL). The mixture was transferred to a separating funnel, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined and washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford *N*-benzyl-2,2-dimethylbut-3-enamide as a yellow oil (1.3 g, 65%).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 2 H), 7.30–7.27 (m, 1 H), 7.25–7.21 (m, 3 H), 6.02 (dd, *J* = 17.4, 10.6 Hz, 1 H), 5.23 (d, *J* = 17.5 Hz, 1 H), 5.19 (d, *J* = 10.6 Hz, 1 H), 4.41 (d, *J* = 5.7 Hz, 2 H), 1.33 (s, 6 H).

N-Benzyl-2,2-dimethylbut-3-enamide was added to a flame-dried three-necked round-bottom flask equipped with a reflux condenser. Anhydrous Et_2O (13 mL) was added, and then the solution was cooled to 0 °C. Lithium aluminum hydride (20 mL, 1 M solution in Et_2O, 20 mmol) was added dropwise, and then the mixture was heated to reflux with stirring overnight. The reaction mixture was quenched using the Fieser work-up. First, the mixture was diluted with Et_2O (10 mL) and then cooled to 0 °C. Then, H_2O (750 μL) was added dropwise, followed by the dropwise addition of 15% aqueous sodium hydroxide (750 μL). H_2O (2.2 mL) was added and the mixture was allowed to warm to r.t. and then stirred for 15 min. The mixture was dried over magnesium sulfate, filtered through a plug of Celite, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford *N*-benzyl-2,2-dimethylbut-3-en-1-amine as a yellow oil (1.0 g, 82%).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.29 (m, 4 H), 7.26–7.21 (m, 1 H), 5.78 (dd, *J* = 17.2, 11.1 Hz, 1 H), 5.02–4.95 (m, 2 H), 3.79 (s, 2 H), 2.43 (s, 2 H), 1.03 (s, 6 H).

General procedure 2 was used to sulfonylate *N*-benzyl-2,2-dimethylbut-3-en-1-amine (1.0 g, 5.3 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (1.24 g, 4.85 mmol) to afford the title compound (1.61 g, 93%) as a colorless solid; mp 69–71 °C.

IR (neat): 3310, 2965, 1320, 1131 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 7.4 Hz, 2 H), 7.37–7.27 (m, 6 H), 7.22–7.18 (m, 2 H), 5.93 (dd, *J* = 17.5, 10.7 Hz, 1 H), 5.06 (d, *J* = 17.5 Hz, 1 H), 5.02 (d, *J* = 10.6 Hz, 1 H), 4.50 (s, 2 H), 4.10 (d, *J* = 6.0 Hz, 2 H), 4.07–4.01 (t, *J* = 6.1 Hz, 1 H), 3.21 (s, 2 H), 1.09 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.3, 136.9, 136.6, 128.87, 128.86, 128.84, 128.10, 128.05, 112.4, 58.2, 53.5, 47.7, 39.5, 25.5; one signal is missing due to incidental equivalence.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{26}N_2O_2S$: 359.1793; found: 359.1788.

Asymmetric Pd-Catalyzed Carboaminations; General Procedure 3

Transformations were carried out on 0.2 mmol scale unless otherwise noted. An oven-dried test tube equipped with a stir bar and a rubber septum was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol%), (*S*)-Siphos-PE (5 mol%), the sulfamide substrate (1.0 equiv), and *t*-BuONa (2.0 equiv). The flask was purged with N_2, and then the aryl or alkenyl halide (1.40–2.0 equiv), H_2O (0 or 2.0 equiv), and xylenes (0.125 M) were added. The resulting mixture was heated to 120 °C with stirring for 18 h. The reaction mixture was then cooled to r.t., and saturated aqueous ammonium chloride (1 mL) was added. The mixture was extracted with EtOAc (3 × 2 mL) and then the combined organic layers were dried over anhydrous Na_2SO_4, filtered through a plug of Celite, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent.

(*S*)-(–)-2,5,6-Tribenzyl-3,3-dimethyl-1,2,6-thiadiazinane 1,1-Dioxide (6a)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (**5a**) (72.0 mg, 0.20 mmol) and bromobenzene (42 µL, 0.4 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (80 mg, 92%) as a colorless solid; mp 149–153 °C; $[\alpha]_D^{23}$ –65 (*c* 1.6, CH_2Cl_2).

IR (neat): 1495, 1452, 1330, 1151, 1136 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.9 Hz, 4 H), 7.32 (td, *J* = 7.5, 2.6 Hz, 4 H), 7.28–7.21 (m, 4 H), 7.21–7.17 (m, 1 H), 7.06 (d, *J* = 7.0 Hz, 2 H), 4.71 (d, *J* = 15.8 Hz, 1 H), 4.64 (d, *J* = 16.8 Hz, 1 H), 4.41 (dddd, *J* = 12.7, 10.1, 4.8, 2.9 Hz, 1 H), 4.30 (d, *J* = 15.8 Hz, 1 H), 4.14 (d, *J* = 16.8 Hz, 1 H), 2.89 (dd, *J* = 13.6, 4.8 Hz, 1 H), 2.58 (dd, *J* = 13.6, 10.2 Hz, 1 H), 2.03 (dd, *J* = 14.3, 12.2 Hz, 1 H), 1.39 (dd, *J* = 14.3, 2.9 Hz, 1 H), 1.28 (s, 3 H), 1.12 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.4, 138.4, 137.4, 129.2, 128.8, 128.6, 128.5, 128.1, 127.5, 127.4, 127.2, 126.9, 60.4, 57.3, 50.1, 45.8, 40.9, 38.7, 31.0, 22.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{31}N_2O_2S$: 435.2101; found: 435.2106.

The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (Chiralcel ODH, 15 cm × 4.6 mm, 3% *i*-PrOH/hexanes, 0.8 mL/min, λ = 210 nm, t_R = 16.7 and 22.3 min).

(*S*)-(–)-5-([1,1′-Biphenyl]-4-ylmethyl)-2,6-dibenzyl-3,3-dimethyl-1,2,6-thiadiazinane 1,1-Dioxide (6b)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (**5a**) (72.0 mg, 0.20 mmol) and 4-bromobiphenyl (104 µL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (80 mg, 78%) as a white solid; mp 174–178 °C; $[\alpha]_D^{23}$ –154.5 (*c* 1.98, CH_2Cl_2).

IR (neat): 1488, 1452, 1332, 1153, 1137 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.3 Hz, 2 H), 7.46 (d, *J* = 8.1 Hz, 2 H), 7.43 (t, *J* = 7.2 Hz, 6 H), 7.36–7.29 (m, 5 H), 7.27–7.22 (m, 2 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 4.72 (d, *J* = 15.8 Hz, 1 H), 4.64 (d, *J* = 16.8 Hz, 1 H), 4.49–4.41 (m, 1 H), 4.32 (d, *J* = 15.8 Hz, 1 H), 4.15 (d, *J* = 16.8 Hz, 1 H), 2.92 (dd, *J* = 13.7, 5.0 Hz, 1 H), 2.64 (dd, *J* = 13.6, 10.0 Hz, 1 H), 2.07 (t, *J* = 13.3 Hz, 1 H), 1.46 (dd, *J* = 14.3, 2.6 Hz, 1 H), 1.32 (s, 3 H), 1.14 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.9, 140.4, 139.7, 138.3, 136.4, 129.6, 129.0, 128.61, 128.55, 128.1, 127.52, 127.45, 127.43, 127.2, 127.1, 60.5, 57.2, 50.1, 45.8, 40.5, 38.9, 31.0, 23.0; 1 carbon signal is missing due to incidental equivalence.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{35}N_2O_2S$: 511.2414; found: 511.2413.

The enantiopurity was determined to be 97:3 er by chiral HPLC analysis when 4-bromobiphenyl served as the electrophile (Chiralcel ODH, 15 cm × 4.6 mm, 7% *i*-PrOH/hexanes, 1.00 mL/min, λ = 254 nm, t_R = 16.5 and 29.7 min).

When 4-iodobiphenyl was used as the electrophile, the enantioselectivity was less reproducible providing enantiomeric ratios that ranged from 82:18 to 91.5:8.5.

This reaction was also conducted on 1 mmol scale using 4-bromobiphenyl as the electrophile. General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (**5a**) (358.50 mg, 1.0 mmol) and 4-bromobiphenyl (466 mg, 2.0 mmol) using a catalyst composed of $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol) and (*S*)-Siphos-PE (25.3 mg, 0.05 mmol), *t*-BuONa (192 mg, 2.0 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (8.0 mL) and H_2O (36 µL). The reaction was conducted in a 25 mL round-bottom flask rather than in a test tube. This procedure afforded the title compound (458 mg, 90%) as a white solid. The enantioselectivity was determined to be 97:3 er.

(*S*)-(–)-2,6-Dibenzyl-3,3-dimethyl-5-(naphthalen-2-ylmethyl)-1,2,6-thiadiazinane 1,1-Dioxide (6c)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (**5a**) (72.0 mg, 0.20 mmol) and 2-bromonaphthalene (83 mg, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (72 mg, 74%) as a colorless solid; mp 168–172 °C; $[\alpha]_D^{23}$ –43 (*c* 1.7, CH_2Cl_2).

IR (neat): 1495, 1452, 1331, 1151, 1136 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81–7.77 (m, 1 H), 7.75–7.70 (m, 2 H), 7.48–7.41 (m, 7 H), 7.35–7.28 (m, 4 H), 7.26–7.19 (m, 3 H), 4.75 (d, *J* = 15.8 Hz, 1 H), 4.64 (d, *J* = 16.8 Hz, 1 H), 4.51 (dddd, *J* = 12.6, 10.0, 4.8, 2.8 Hz, 1 H), 4.35 (d, *J* = 15.8 Hz, 1 H), 4.14 (d, *J* = 16.8 Hz, 1 H), 3.05 (dd, *J* = 13.5, 4.8 Hz, 1 H), 2.73 (dd, *J* = 13.6, 10.2 Hz, 1 H), 2.08 (dd, *J* = 14.3, 12.2 Hz, 1 H), 1.41 (dd, *J* = 14.4, 2.9 Hz, 1 H), 1.26 (s, 3 H), 1.11 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.4, 138.4, 134.9, 133.6, 132.5, 128.63, 128.55, 128.52, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.24, 127.18, 126.3, 125.8, 60.5, 57.4, 50.2, 45.8, 41.1, 38.8, 31.0, 22.9.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{33}N_2O_2S$: 485.2257; found: 485.2260.

The enantiopurity was determined to be 96.5:3.5 er by chiral HPLC analysis (Chiralcel ADH, 25 cm × 4.6 mm, 4% *i*-PrOH/hexanes, 1.0 mL/min, λ = 254 nm, t_R = 30.4 and 33.5 min).

(*S*)-(–)-2,6-Dibenzyl-5-(4-methoxybenzyl)-3,3-dimethyl-1,2,6-thiadiazinane 1,1-Dioxide (6d)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (**5a**) (72.0 mg, 0.20 mmol) and 4-bromoanisole (50 µL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (55 mg, 59%) as a colorless solid; mp 135–138 °C; $[\alpha]_D^{23}$ –78 (*c* 1.2, CH_2Cl_2).

IR (neat): 1604, 1512, 1494, 1454, 1329, 1152, 1136 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.6 Hz, 4 H), 7.32 (td, *J* = 7.5, 1.4 Hz, 4 H), 7.27–7.21 (m, 2 H), 6.97 (d, *J* = 8.6 Hz, 2 H), 6.77 (d, *J* = 8.5 Hz, 2 H), 4.70 (d, *J* = 15.9 Hz, 1 H), 4.63 (d, *J* = 16.8 Hz, 1 H), 4.35 (dddd, *J* = 12.5, 10.1, 4.8, 2.8 Hz, 1 H), 4.28 (d, *J* = 15.8 Hz, 1 H), 4.13 (d, *J* = 16.8 Hz, 1 H), 3.77 (s, 3 H), 2.82 (dd, *J* = 13.7, 4.8 Hz, 1 H), 2.52 (dd, *J* = 13.7, 10.2 Hz, 1 H), 2.00 (dd, *J* = 14.3, 12.3 Hz, 1 H), 1.39 (dd, *J* = 14.3, 2.8 Hz, 1 H), 1.28 (s, 3 H), 1.11 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5, 140.4, 138.4, 130.1, 129.3, 128.6, 128.5, 128.1, 127.5, 127.4, 127.2, 114.2, 60.4, 57.5, 55.4, 50.0, 45.7, 40.0, 38.7, 31.0, 22.8.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{33}N_2O_3S$: 465.2206; found: 465.2204.

The enantiopurity was determined to be 98:2 er by chiral HPLC analysis (Chiralcel ADH, 25 cm × 4.6 mm, 4% *i*-PrOH/hexanes, 1.00 mL/min, λ = 205 nm, t_R = 32.9 and 38.9 min).

(*S*)-(–)-2,6-Dibenzyl-3,3-dimethyl-5-[4-(trifluoromethyl)benzyl]-1,2,6-thiadiazinane 1,1-Dioxide (6e)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (**5a**) (72.0 mg, 0.20 mmol) and 4-bromobenzotrifluoride (56 µL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.001 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (74 mg, 73%) as a colorless solid; mp 159–161 °C; $[\alpha]_D^{23}$ –77 (*c* 1.5, CH_2Cl_2).

IR (neat): 1495, 1452, 1328, 1154, 1136 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (dd, *J* = 11.0, 7.8 Hz, 4 H), 7.36–7.20 (m, 8 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 4.64 (t, *J* = 16.3 Hz, 2 H), 4.42 (dddd, *J* = 12.0, 9.1, 6.1, 3.1 Hz, 1 H), 4.31 (d, *J* = 15.8 Hz, 1 H), 4.18 (d, *J* = 16.8 Hz, 1 H), 2.92 (dd, *J* = 14.0, 6.1 Hz, 1 H), 2.68 (dd, *J* = 14.0, 9.0 Hz, 1 H), 2.09 (dd, *J* = 14.3, 11.9 Hz, 1 H), 1.41 (dd, *J* = 14.3, 3.1 Hz, 1 H), 1.32 (s, 3 H), 1.16 (s, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 141.4, 140.2, 137.8, 129.4, 129.1 (q, J_{C-F} = 31.7 Hz), 128.61, 128.58, 128.1, 127.6, 127.4, 127.2, 125.6 (q, J_{C-F} = 3.5 Hz), 124.3 (q, J_{C-F} = 272.8 Hz), 60.4, 56.9, 50.4, 45.8, 40.5, 39.0, 30.7, 23.4.

^{19}F NMR (377 MHz, $CDCl_3$): δ = –62.54.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{30}F_3N_2O_2S$: 503.1975; found: 503.1977.

The enantiopurity was determined to be 96.5:3.5 er by chiral HPLC analysis (Chiralcel ODH, 15 cm × 4.6 mm, 4% *i*-PrOH/hexanes, 0.50 mL/min, λ = 210 nm, t_R = 15.6 and 17.9 min).

(*S*)-(–)-2,6-Dibenzyl-5-(4-fluorobenzyl)-3,3-dimethyl-1,2,6-thiadiazinane 1,1-Dioxide (6f)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (**5a**) (72.0 mg, 0.20 mmol) and 1-bromo-4-fluorobenzene (44 µL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.001 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (82 mg, 91%) as a colorless solid; mp 132–133 °C; $[\alpha]_D^{23}$ –68 (*c* 1.7, CH_2Cl_2).

IR (neat): 1495, 1452, 1330, 1153, 1137 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.2 Hz, 2 H), 7.39 (d, *J* = 7.1 Hz, 2 H), 7.35–7.28 (m, 4 H), 7.27–7.22 (m, 2 H), 7.02–6.96 (m, 2 H), 6.91 (t, *J* = 8.6 Hz, 2 H), 4.69 (d, *J* = 15.8 Hz, 1 H), 4.63 (d, *J* = 16.8 Hz, 1 H), 4.36 (dddd, *J* = 12.3, 8.8, 5.3, 2.9 Hz, 1 H), 4.28 (d, *J* = 15.8 Hz, 1 H), 4.15 (d, *J* = 16.8 Hz, 1 H), 2.84 (dd, *J* = 13.8, 5.4 Hz, 1 H), 2.56 (dd, *J* = 13.9, 9.6 Hz, 1 H), 2.04 (dd, *J* = 14.3, 12.1 Hz, 1 H), 1.39 (dd, *J* = 14.3, 2.9 Hz, 1 H), 1.30 (s, 3 H), 1.14 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8 (d, J_{C-F} = 243.8 Hz), 140.30, 138.16, 133.0 (d, J_{C-F} = 3.8 Hz), 130.5 (d, J_{C-F} = 7.5 Hz), 128.60, 128.55, 128.1, 127.6, 127.4, 127.2, 115.6 (d, J_{C-F} = 21.2 Hz), 60.4, 57.3, 50.2, 45.8, 39.9, 38.8, 30.9, 23.1.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –116.35 to –116.21 (m).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}FN_2O_2S$: 453.2012; found: 453.2007.

The enantiopurity was determined to be 96.5:3.5 er by chiral HPLC analysis (Chiralcel ODH, 15 cm × 4.6 mm, 4% *i*-PrOH/hexanes, 0.50 mL/min, λ = 210 nm, t_R = 16.1 and 17.7 min).

(*S*)-(–)-2,6-Dibenzyl-5-(4-chlorobenzyl)-3,3-dimethyl-1,2,6-thiadiazinane 1,1-Dioxide (6g)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (**5a**) (72.0 mg, 0.20 mmol) and 1-bromo-4-chlorobenzene (77 mg, 0.4 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (72 mg, 77%) as a colorless solid; mp 145–148 °C; $[\alpha]_D^{23}$ –80 (*c* 1.5, CH_2Cl_2). This material contained ca. 5–10% of an inseparable impurity. Data are for the title compound.

IR (neat): 1493, 1452, 1320, 1136 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 2 H), 7.38 (d, *J* = 7.0 Hz, 2 H), 7.31 (ddd, *J* = 9.8, 8.4, 6.7 Hz, 4 H), 7.27–7.22 (m, 2 H), 7.20–7.16 (m, 2 H), 6.98–6.94 (m, 2 H), 4.69 (d, *J* = 15.8 Hz, 1 H), 4.63 (d, *J* = 16.8 Hz, 1 H), 4.36 (dddd, *J* = 12.3, 8.8, 5.4, 2.9 Hz, 1 H), 4.28 (d, *J* = 15.8 Hz, 1 H), 4.15 (d, *J* = 16.8 Hz, 1 H), 2.84 (dd, *J* = 13.8, 5.4 Hz, 1 H), 2.56 (dd, *J* = 13.9, 9.5 Hz, 1 H), 2.04 (dd, *J* = 14.3, 12.1 Hz, 1 H), 1.38 (dd, *J* = 14.3, 3.0 Hz, 1 H), 1.30 (s, 3 H), 1.14 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.3, 138.1, 135.8, 132.6, 130.4, 128.9, 128.6, 128.6, 128.0, 127.6, 127.4, 127.2, 60.4, 57.1, 50.2, 45.7, 40.1, 38.7, 30.9, 23.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}ClN_2O_2S$: 469.1711; found: 469.1710.

The enantiopurity was determined to be 97:3 er by chiral HPLC analysis (Chiralcel ADH, 15 cm × 4.6 mm, 4% *i*-PrOH/hexanes, 1.0 mL/min, λ = 210 nm, t_R = 26.2 and 28.6 min).

(*S*)-(–)-2,6-Dibenzyl-3,3-dimethyl-5-(2-methylbenzyl)-1,2,6-thiadiazinane 1,1-Dioxide (6h)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (**5a**) (72.0 mg, 0.20 mmol) and 1-bromo-2-methylbenzene (48 µL, 0.4 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (26 mg, 29%) as a colorless solid; mp 118–124 °C; $[\alpha]_D^{23}$ –44.2 (*c* 2.0, CH_2Cl_2).

IR (neat): 1604, 1494, 1452, 1320, 1138 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.41 (m, 4 H), 7.32 (q, *J* = 7.5 Hz, 4 H), 7.28–7.22 (m, 2 H), 7.13–7.02 (m, 4 H), 4.74 (d, *J* = 15.9 Hz, 1 H), 4.65 (d, *J* = 16.8 Hz, 1 H), 4.42 (tdd, *J* = 9.9, 4.7, 2.3 Hz, 1 H), 4.30 (d, *J* = 15.9 Hz, 1 H), 4.14 (d, *J* = 16.8 Hz, 1 H), 2.85 (dd, *J* = 13.9, 4.6 Hz, 1 H), 2.62 (dd, *J* = 13.9, 10.0 Hz, 1 H), 2.19 (s, 3 H), 2.09 (t, *J* = 14.3 Hz, 1 H), 1.40 (dd, *J* = 14.3, 2.9 Hz, 1 H), 1.27 (s, 3 H), 1.13 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.4, 138.5, 136.5, 135.7, 130.7, 129.7, 128.6, 128.5, 128.0, 127.5, 127.4, 127.2, 126.9, 126.2, 60.4, 56.2, 50.1, 45.8, 38.83, 37.99, 31.0, 22.8, 19.7.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{33}N_2O_2S$: 449.2257; found: 449.2258.

The enantiopurity was determined to be 85:15 er by chiral HPLC analysis (Chiralcel ADH, 25 cm × 4.6 mm, 4% *i*-PrOH/hexanes, 1.0 mL/min, λ = 210 nm, t_R = 13.9 and 23.3 min).

(*S*)-(–)-1,3-Dibenzyl-4-[3-(4-fluorophenoxy)benzyl]-2-thia-1,3-diazaspiro[5.5]undecane 2,2-Dioxide (6i)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(1-allylcyclohexyl)sulfamide (**5b**) (80.0 mg, 0.20 mmol) and 1-bromo-3-(4-fluorophenoxy)benzene (107 mg, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (98 mg, 84%) as a colorless solid; mp 122–125 °C; $[\alpha]_D^{23}$ –65 (*c* 1.6, CH_2Cl_2).

IR (neat): 1497, 1441, 1330, 1198, 1157, 1110 cm^{-1}.

^1H NMR (700 MHz, $CDCl_3$): δ = 7.43–7.38 (m, 4 H), 7.34–7.28 (m, 4 H), 7.26–7.20 (m, 3 H), 7.04–6.99 (m, 2 H), 6.92–6.88 (m, 2 H), 6.85–6.81 (m, 2 H), 6.67 (t, *J* = 2.0 Hz, 1 H), 4.67 (dd, *J* = 16.5, 11.7 Hz, 2 H), 4.31 (d, *J* = 15.7 Hz, 1 H), 4.28–4.21 (m, 2 H), 2.86 (dd, *J* = 13.6, 4.9 Hz, 1 H), 2.57 (dd, *J* = 13.6, 10.0 Hz, 1 H), 2.20–2.14 (m, 1 H), 2.07 (dd, *J* = 14.6, 2.9 Hz, 1 H), 1.74 (t, *J* = 14.1 Hz, 1 H), 1.63–1.47 (m, 5 H), 1.41 (d, *J* = 13.1 Hz, 1 H), 1.17 (qt, *J* = 13.4, 3.7 Hz, 1 H), 1.02 (qt, *J* = 13.8, 4.0 Hz, 1 H), 0.84 (qt, *J* = 13.4, 4.6 Hz, 1 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 158.9 (d, J_{C-F} = 242.9 Hz), 157.9, 153.1 (d, J_{C-F} = 3.5 Hz), 140.6, 139.6, 138.2, 130.1, 128.6, 128.5, 128.1, 127.5, 127.1, 127.0, 124.0, 120.5 (d, J_{C-F} = 8.8 Hz), 119.1, 117.0, 116.5 (d, J_{C-F} = 22.9 Hz), 63.8, 56.8, 50.4, 44.9, 40.7, 38.2, 31.0, 29.5, 25.3, 23.0, 22.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –120.00 to –120.07 (m).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{38}FN_2O_3S$: 585.2582; found: 585.2582.

The enantiopurity was determined to be 95.5:4.5 er by chiral HPLC analysis (Chiralcel ADH, 25 cm × 4.6 mm, 6% *i*-PrOH/hexanes, 1.0 mL/min, λ = 210 nm, t_R = 24.6 and 33.5 min).

(*S*)-(–)-1,3-Dibenzyl-4-[3-(trifluoromethyl)benzyl]-2-thia-1,3-diazaspiro[5.5]undecane 2,2-Dioxide (6j)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(1-allylcyclohexyl)sulfamide (**5b**) (80.0 mg, 0.20 mmol) and 3-bromobenzotrifluoride (56 µL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (98 mg, 90%) as a colorless solid; mp 119–121 °C; $[\alpha]_D^{23}$ –70 (*c* 1.6, CH_2Cl_2).

IR (neat): 1495, 1453, 1327, 1154, 1116, 1074 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.39 (m, 3 H), 7.38–7.20 (m, 11 H), 4.68 (d, *J* = 2.5 Hz, 1 H), 4.65 (d, *J* = 4.7 Hz, 1 H), 4.37–4.25 (m, 3 H), 2.95 (dd, *J* = 14.0, 5.7 Hz, 1 H), 2.69 (dd, *J* = 14.0, 9.2 Hz, 1 H), 2.17 (d, *J* = 11.7 Hz, 1 H), 2.06 (dd, *J* = 14.6, 3.0 Hz, 1 H), 1.83 (t, *J* = 13.2 Hz, 1 H), 1.65–1.42 (m, 6 H), 1.18 (q, *J* = 13.0 Hz, 1 H), 1.00 (q, *J* = 13.0 Hz, 1 H), 0.83 (q, *J* = 12.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.5, 138.5, 137.8, 132.3, 131.0 (q, J_{C-F} = 32.5 Hz), 129.2, 128.6, 128.5, 128.1, 127.7, 127.1, 125.8 (q, J_{C-F} = 3.75 Hz), 124.1 (q, J_{C-F} = 270 Hz), 123.7 (q, J_{C-F} = 3.75 Hz), 63.9, 56.6, 50.7, 44.9, 40.5, 38.1, 31.1, 29.8, 25.3, 22.9, 22.6; 1 carbon signal is missing.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –62.65 (s).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{34}F_3N_2O_2S$: 543.2288; found: 543.2292.

The enantiopurity was determined to be 96.5:3.5 er by chiral HPLC analysis (Chiralcel ADH, 25 cm × 4.6 mm, 6% *i*-PrOH/hexanes, 1.0 mL/min, λ = 210 nm, t_R = 15.4 and 18.9 min).

(*S*)-(–)-1,3-Dibenzyl-4-(3-methoxybenzyl)-2-thia-1,3-diazaspiro[5.5]undecane 2,2-Dioxide (6k)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(1-allylcyclohexyl)sulfamide (**5b**) (80.0 mg, 0.20 mmol) and 3-bromoanisole (51 µL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (89 mg, 88%) as a colorless solid; mp 141–144 °C; $[\alpha]_D^{23}$ –52 (*c* 1.9, CH_2Cl_2).

IR (neat): 1584, 1496, 1452, 1327, 1150, 1111 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.5 Hz, 4 H), 7.32 (t, *J* = 7.6 Hz, 4 H), 7.24 (q, *J* = 7.1 Hz, 2 H), 7.17 (t, *J* = 7.9 Hz, 1 H), 6.74 (dd, *J* = 8.2, 2.5 Hz, 1 H), 6.70–6.66 (m, 1 H), 6.60 (t, *J* = 2.0 Hz, 1 H), 4.68 (dd, *J* = 16.4, 13.1 Hz, 2 H), 4.29 (dd, *J* = 30.4, 16.6 Hz, 3 H), 3.76 (s, 3 H), 2.89 (dd, *J* = 13.5, 4.6 Hz, 1 H), 2.58 (dd, *J* = 13.5, 10.3 Hz, 1 H), 2.18 (d, *J* = 12.2 Hz, 1 H), 2.09 (dd, *J* = 14.6, 2.6 Hz, 1 H), 1.74 (t, *J* = 12.0 Hz 1 H), 1.65–1.36 (m, 6 H), 1.24–1.08 (m, 1 H), 1.07–0.91 (m, 1 H), 0.90–0.73 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 140.7, 139.1, 138.4, 129.7, 128.6, 128.5, 128.1, 127.5, 127.1, 127.0, 121.4, 114.6, 112.5, 63.9, 56.9, 55.4, 50.4, 44.9, 41.0, 38.2, 31.1, 29.5, 25.3, 22.9, 22.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{37}N_2O_3S$: 505.2519; found: 505.2523.

The enantiopurity was determined to be 97:3 er by chiral HPLC analysis (Chiralcel ADH, 25 cm × 4.6 mm, 6% *i*-PrOH/hexanes, 1.0 mL/min, λ = 210 nm, t_R = 32.5 and 35.2 min).

(*S*)-(–)-2,6-Dibenzyl-3,3-diethyl-5-(naphthalen-1-ylmethyl)-1,2,6-thiadiazinane 1,1-Dioxide (6l)

General procedure 3 was employed for the coupling of *N*-benzyl-*N*′-benzyl-*N*-(3-ethylhex-5-en-3-yl)sulfamide (**5c**) (77.0 mg, 0.20 mmol) and 1-bromonaphthalene (56 µL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-Siphos-PE (5.1 mg, 0.010 mmol), *t*-BuONa (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in xylenes (1.6 mL) and H_2O (7 µL). This procedure afforded the title compound (89 mg, 86%) as a colorless solid; mp 58–62 °C; $[\alpha]_D^{23}$ –59 (*c* 2.2, CH_2Cl_2).

IR (neat): 1495, 1454, 1331, 1153 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.82–7.78 (m, 1 H), 7.70 (d, *J* = 8.2 Hz, 1 H), 7.61–7.57 (m, 2 H), 7.51 (d, *J* = 7.4 Hz, 2 H), 7.48–7.40 (m, 4 H), 7.40–7.35 (m, 2 H), 7.34–7.28 (m, 3 H), 7.27–7.22 (m, 2 H), 4.59 (d, *J* = 15.1 Hz, 1 H), 4.51 (d, *J* = 15.1 Hz, 1 H), 4.47 (d, *J* = 16.6 Hz, 1 H), 4.36 (d, *J* = 16.6 Hz, 1 H), 4.15 (ddt, *J* = 14.4, 9.4, 4.3 Hz, 1 H), 3.34 (dd, *J* = 13.7, 4.6 Hz, 1 H), 3.08 (dd, *J* = 13.7, 10.0 Hz, 1 H), 2.35 (dd, *J* = 14.9, 12.1 Hz, 1 H), 1.67 (dq, *J* = 15.1, 7.6 Hz, 1 H), 1.60–1.37 (m, 3 H), 1.31 (dd, *J* = 15.0, 4.1 Hz, 1 H), 0.70 (t, *J* = 7.3 Hz, 3 H), 0.35 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.1, 137.8, 134.0, 133.7, 131.9, 129.0, 128.78, 128.75, 128.5, 128.1, 127.9, 127.64, 127.58, 127.2, 126.3, 125.8, 125.5, 123.6, 66.0, 56.3, 52.8, 46.2, 39.2, 30.5, 29.4, 29.0, 9.2, 7.9.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{37}N_2O_2S$: 513.2570; found: 513.2572.

The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (Chiralcel ODH, 15 cm × 4.6 mm, 2% *i*-PrOH/hexanes, 0.75 mL/min, λ = 210 nm, t_R = 17.1 and 20.2 min).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591574.

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