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Domino Reaction for the Chemo- and Stereoselective Synthesis of *trans*-2,3-Dihydrobenzofurans from *N*-Thiophosphinyl Imines and Sulfur Ylides

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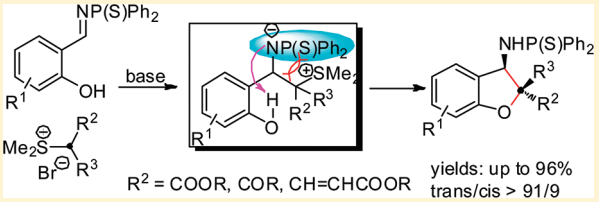
Supporting Information

ABSTRACT: A novel domino annulation between sulfur ylides and salicyl *N*-thiophosphinyl imines was developed. The method allows the synthesis of a highly substituted *trans*-2,3-dihydrobenzofuran skeleton with high yield and excellent chemo- and stereoselectivity.



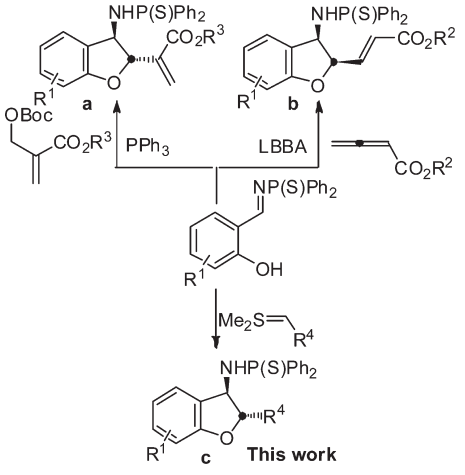
INTRODUCTION

Domino reactions have garnered significant recent attention from the synthetic community as a means to swiftly assemble complex molecules from simple starting materials with minimal time and waste as well as manipulation of reaction intermediates.[1,2f] In particular, these strategies are powerful in the total synthesis of natural products and bioactive molecules.[2] The remarkable significance of the 2,3-dihydrobenzofuran (DHB) ring system in biologically active compounds, synthetic drugs, and natural products has motivated chemists to develop various approaches for the construction of DHBs,[3] such as radical cyclizations, electrocyclizations,[4] anionic cyclizations,[5] biomimetic couplings and cycloadditions,[6] Lewis acid promoted reactions,[7] transition-metal-catalyzed processes,[1a,8] and so on.[9] However, several drawbacks, including unsatisfactory yields, poor chemo- and/or stereoselectivities, tedious processes for purification, and precious reaction conditions, impede their wide application. Hence, simple, convenient, and highly stereoselective methodologies to provide such scaffolds represent an important and attractive objective at the forefront of synthetic chemistry.[2]

Phosphine-catalyzed domino reactions have been extensively employed for a wide range of useful synthetic organic transformation.[10] Intrigued by those elegant studies, we have reported phosphine-catalyzed domino reactions that can construct *cis*-[11] and *trans*-dihydrobenzofuran skeletons with high stereoselectivities.[12] In those reactions allenoates and modified allyic derivatives were first used as 1,1-dipolar synthons.[13] Then, we envisioned that the sulfur ylides, which have been gradually developed as functional units in [2 + 1][14] and [4 + 1] annulation,[15] might also serve as a 1,1-dipolar synthon reacting with salicyl *N*-thiophosphinyl imines[11,12,17] to form *trans*-2,3-dihydrobenzofurans (Scheme 1). However, according to the literature, almost all previous endeavors with unstable or semi-stabilized ylides have suffered from the kinetic preference to form aziridines or cyclopropanes.[15] Recently, electronic and steric effects and high temperature/microwave have been used to alter the kinetic preference.[15,16] On the basis of our previous study on the chemistry of salicyl *N*-thiophosphinyl imines, we speculated that the steric effects on the imine play an important role in the reaction pathway and stereoselectivity.[11,12,17] We envisioned that the steric effects chould be a potential factor to overcome kinetic preference and to form dihydrobenzofurans.

Herein, we report the domino annulation of salicyl *N*-thiophosphinyl imines with sulfur ylides, which allows efficient construction of *trans*-2,3-dihydrobenzofurans with high chemo- and stereoselectivity.

Scheme 1. Stereoselective Construction of *trans*- and *cis*-2,3-Dihydrobenzofuran from Salicyl *N*-Thiophosphinyl Imines and 1,1-Dipolar Synthon[a]



[a] LBBA: 2′-(diethylphosphino)-[1,1′-biphenyl]-2-ol.

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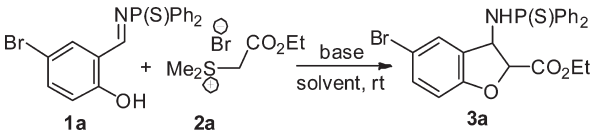
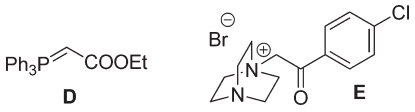
Table 1. Studies on the Reaction of Salicyl *N*-Thiophosphinyl Imines 1a with Sulfonium Salt 2a To Generate 2,3-Dihydrobenzofuran[a]



entry	solvent	base	*t*	yield (%)[b]
1	toluene	DBU	50 min	37
2	toluene	NEt_3	35 h	66
3	toluene	Na_2CO_3	45 h	77
4	toluene	K_2CO_3	6.5 h	76
5	CH_3CN	K_2CO_3	15 min	92
6	THF	K_2CO_3	90 min	64
7	DMF	K_2CO_3	30 min	47
8	CH_3OH	K_2CO_3	30 min	69
9	CH_2Cl_2	K_2CO_3	3.5 h	51
10	CH_3CN	Cs_2CO_3	15 min	67
11[c]	CH_3CN	K_2CO_3	15 min	66
12[d]	CH_3CN	K_2CO_3	30 min	82
13[e]	CH_3CN	K_2CO_3	15 min	82
14[f]	CH_3CN	K_2CO_3	25 min	85
15[g]	CH_3CN		8 h	
16[h]	CH_3CN	K_2CO_3	8 h	

[a] The reaction was carried out in 0.2 mmol scale in solvent (2.0 mL) at rt. The ratio of **1a**/**2a**/base is 1/2.5/2.5. [b] Isolated yields. [c] 1.5 equiv of base was used. [d] **1a**/**2a**/base = 1/1.5/1.5. [e] **1a**/**2a**/base = 1/5/5. [f] **1a**/**2a**/base = 1/1.5/2.5. [g] P-based ylide **D** was used instead of **2a**. [h] N-based ylide **E** was used instead of **2a**.

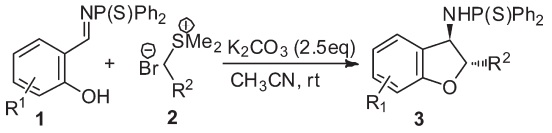


RESULTS AND DISCUSSION

We initiated our investigation by subjecting sulfur ylide **2a** to salicyl *N*-thiophosphinyl imine **1a** in the presence of DBU (2.5 equiv) in toluene at room temperature. To our delight, **3a** was isolated in 37% yield (Table 1, entry 1). Optimization of the reaction conditions revealed that bases and solvents strongly influenced the yield. When K_2CO_3 (2.5 equiv) was used, 76% yield of **3a** could be obtained (entry 4), which is faster than Na_2CO_3 under the same conditions (entry 3). Increasing or decreasing the amount of base resulted in decrease of the efficiency (entries 11 and 13). Of the solvent screened, CH_3CN was found to be the optimal one (entries 4−9). The ratio of **1a**/**2a** also affected the yield and the reaction time; 1/2.5 (**1a**/**2a**) gave the best results (entries 5, 12−14). In addition, P- and N-based ylides were also investigated under the reaction conditions, although the reactions were disordered and no products **3a** were obtained.

The structure and stereochemistry of **3a** were characterized by combination of NMR and HRMS spectra and single-crystal X-ray analysis (see the Supporting Information).

Table 2. Investgating the Scope of Salicyl *N*-Thiophosphinyl Imines 1 and Sulfonium Salt 2 in the Domino Reaction[a]



entry	R^1	R^2	*t*	*trans*/*cis*[b]	yield (%)[c]
1	5-Br	CO_2Et	15 min	96/4	90 (**3a**)
2	5-NO_2	CO_2Et	15 min	95/5	96 (**3b**)
3	H	CO_2Et	25 min	91/9	81 (**3c**)
4	3,5-Bu^t	CO_2Et	20 min	95/5	88 (**3d**)
5	3-Cl	CO_2Et	10 min	94/6	96 (**3e**)
6	3-Ph	CO_2Et	15 min	95/5	92 (**3f**)
7	3-Ph	CO_2Me	15 min	95/5	93 (**3g**)
8	3-Ph	CO_2Bu^t	20 min	94/6	95 (**3h**)
9[d]	5-OMe	COPh	75 min	>99/1	96 (**3i**)
10	5-CH_3	COPh	2.5 h	>99/1	95 (**3j**)
11	5-Bu^t	COPh	2 h	>99/1	91 (**3k**)
12	5-Br	COPh	60 min	>99/1	87 (**3l**)
13[e]	5-Br	COR^3	70 min	>99/1	84 (**3m**)
14[f]	5-Br	COR^4	75 min	>99/1	86 (**3n**)
15[g]	H	COR^5	2 h	94/6	78 (**3o**)
16[h]	H	COR^6	90 min	96/4	95 (**3p**)
17[h]	3-Cl	COR^6	40 min	>99/1	96 (**3q**)
18	3-Cl	COMe	15 min	97/3	86 (**3r**)
19	4-OMe	CO_2Et	50 min	95/5	70 (**3s**)

[a] Unless otherwise noted, the reaction was carried out in 0.2 mmol scale in solvent (2.0 mL), and 0.5 mmol of K_2CO_3 was used. The ratio of **1**/**2** = 1.0/2.5. [b] Determined by ^{31}P NMR of the crude reaction mixture. [c] Isolated yields. [d] Sulfur ylide was directly used without the addition of K_2CO_3. [e] R^3 = *p*-Me(C_6H_4). [f] R^4 = *p*-Cl(C_6H_4). [g] R^5 = furan-2-yl. [h] R^6 = thiophen-2-yl.

A variety of salicyl *N*-thiophosphinyl imines **1** and sulfonium salts **2** were tolerated under the optimized reaction conditions. As summarized in Table 2, the reaction displays a broad scope for the salicyl *N*-thiophosphinyl imines. The electronic property of the aromatic substitute has little effect on the yield and stereoselectivity. Even with a sterically hindered substrate (Table 2, entry 4), the reaction proceeded smoothly to give the desired products in high yields. Additionally, a series of sulfur ylides proved to be suitable for this reaction. Both ester (entries 1−8) and ketone carbonyl (entries 9−14) substituted sulfonium salts **2** were favored to give *trans*-2,3-dihydrobenzofurans **3** in high yields with excellent stereocontrol. Furthermore, the heteroaryl (entries 15−17) and alkenyl (entry 18) substituted sulfonium salts could also be employed in this domino reaction. Trisubstituted *trans*-2,3-dihydrofurans **3** could be achieved by using a disubstituted sulfonium salt **2** as the starting material (Figure 1, **3v**). Preliminary studies about the asymmetric variant of this reaction were conducted with (−)-menthyl ester **2** and **1** as the substrates, although **3w** was obtained in 76% yield with poor diastesoselectivity (Figure 1, **3w**). Importantly, the reaction can be carried out on gram scale without obvious loss in the reaction efficiency (for the details see Experimental Section, **3d**).

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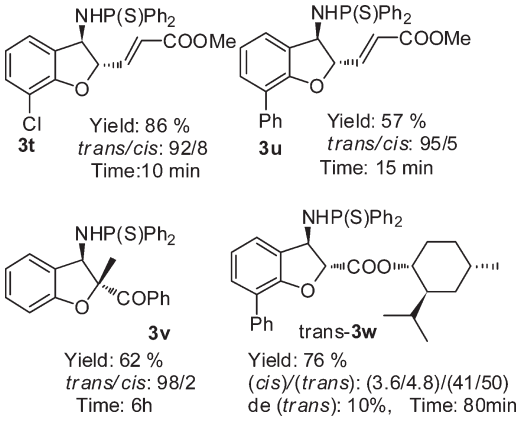
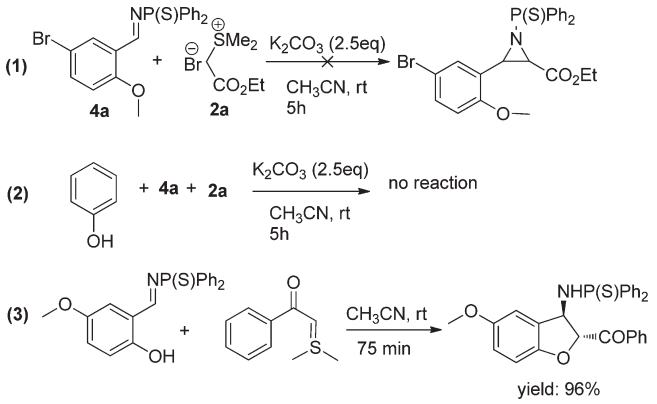
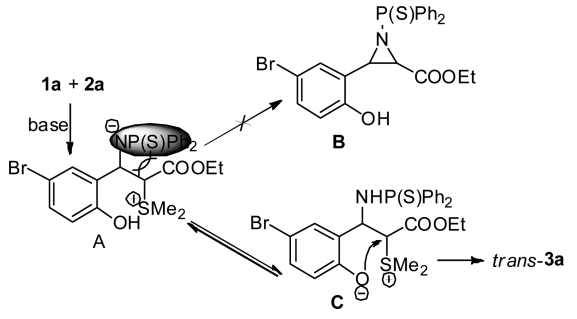


Figure 1. Generality for substituent at the 2,3-dihydrobenzofurans. The reactions were carried out under the previous optimized reaction conditions. The *trans*/*cis* and de value was measured by ^{31}P NMR of the crude reaction mixture.

Scheme 2. Studies of the Mechanism

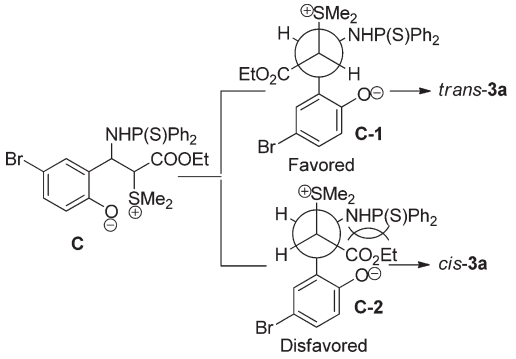


Scheme 3. Possible Mechanism for the Formation of 3a



In order to investigate the mechanism, control experiments were carried out according to Scheme 2. Under the standard reaction, *N*-thiophosphinyl imines of 2-methoxybenzaldehyde **4a**, addition, phenol was used under the above reaction condition, and no C−O bond was formed (Reaction 2). This indicated that the deprotonation of sulfonium salts is faster than C−O bond formation. On the other hand, when the sulfur ylide, instead of sulfonium salts, was directly used without base, product **3** could also be obtained (Reaction 3). The conclusion

Scheme 4. Newman Projections of Intermediate C



could safely be made that C−C bond formation is prior to the C−O bond formation.

According to our experimental results (Scheme 2) and other related studies,[15,16] we proposed a mechanism for this domino reaction as follows (Scheme 3). The reaction might be initiated by the formation of the sulfur ylide *via* the deprotonation of **2a**. Subsequent nucleophilic addition of the sulfur ylide to the electron-dificient imine **1a** yielded the intermediate **A**. The steric hindrance between the COOEt and two phenyl groups on the phosphorus atom alters the kinetic preference to form aziridines **B**. Instead, **A** will transform into intermediate **C** under proton transfer. As shown in Newman projections **C-1** and **C-2**, intermediate **C-1** is the favored one, followed by SN2 substitution to give the 2,3-disubstituted dihydrobenzofuran **3a** with *trans*-enriched configuration (Scheme 4). Moreover, the minor diastereomer *cis*-**3f** was isolated, followed by being resubjected to the reaction conditions. As expected, no *trans*-**3f** was obtained under the conditions for 3 h. This, to some extent, could indicate that the highly diastereoselectivity was determined by the kinetic process not the equilibration. This is further supported by the ^{31}P NMR spectroscopy (Figure 2). For the keto-derived products, which are formed with higher diastereoselectivity than the esters, only one isomer was detected during the reaction process.

■ CONCLUSION

In summary, we have developed a simple, convenient, and highly chemo- and stereoselective domino reaction between salicyl *N*-thiophosphinyl imines and sulfonium salts that provides a new method for the construction of *trans*-2,3-dihydrobenzofurans in excellent yields. Significantly, we not only avert the competitive reaction but also realize the reaction with excellent stereoselectivity. This work could open up new opportunities for selectively constructing other carbon- and heterocycles beyond traditional small rings.

■ EXPERIMENTAL SECTION

General Information. All the solvents were used without further purification. The ^{1}H NMR and spectra was recorded at 300 MHz or 400 MHz, ^{13}C NMR was recorded at 75 MHz or 100 MHz. ^{31}P NMR was recorded at 162 MHz. ^{1}H and ^{13}C NMR Chemical shifts were calibrated to tetramethylsilane as an external reference. Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet: t, triplet; q, quartet; m, multiplet; HRMS were obtained on an IonSpec FT-ICR mass spectrometer with ESI resource. Melting points were measured on a RY-I apparatus and are

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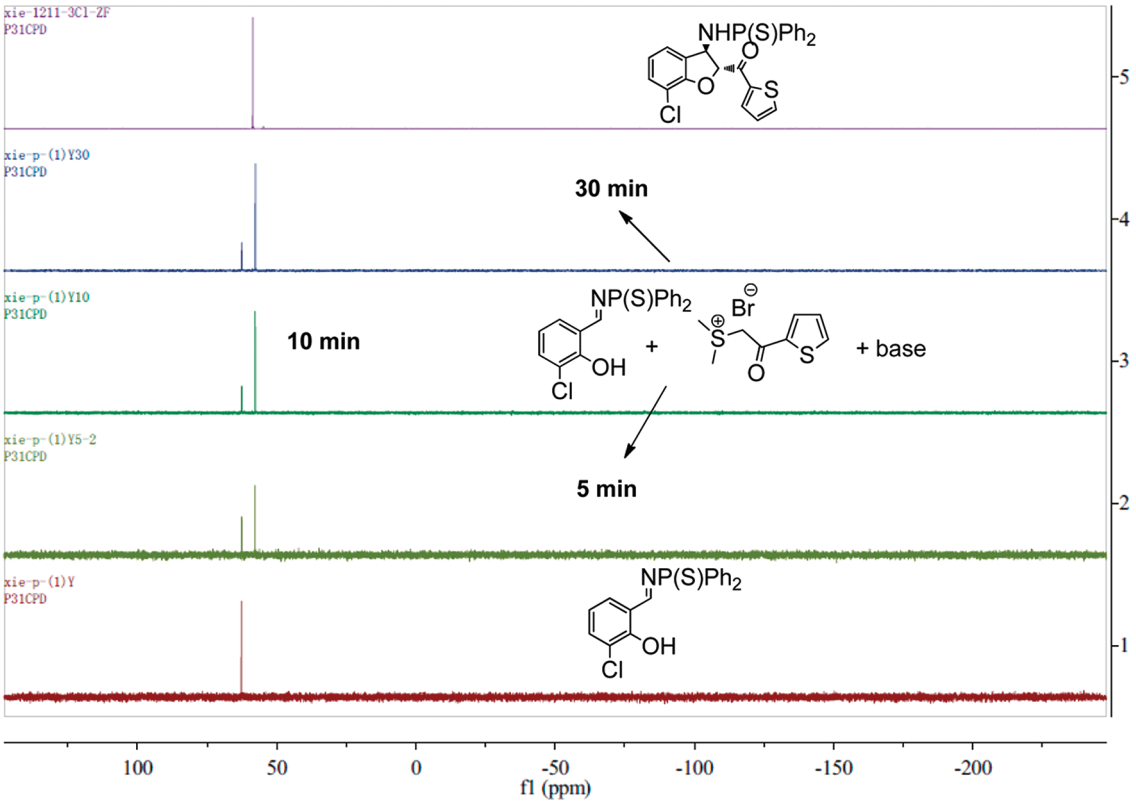

Figure 2. ^{31}P NMR experiments.

reported uncorrected. Salicyl N-thiophosphinyl imines[11,12,17] and sulfonium salt[15] compound were prepared according to the known methods.

Method for the Synthesis of 4a. To a mixture **1a** (414 mg, 1.0 mmol) and K_2CO_3 (280 mg, 2.0 mmol) in acetone (5 mL), was added MeI (282 mg, 2.0 mmol), and the mixture was refluxed for 5 h, After being cooled to room temperature, the mixture was filtered though Celite, and concentrated in vacuo and the residue was purified via column chromatography (Petroleum ether (60−90)/ethyl acetate =10:1) to give **4a** 426 mg (yield 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.78 (d, J = 39.5, 1H), 8.30 (d, J = 2.6, 1H), 8.06−7.96 (m, 4H), 7.57 (dd, J = 8.9, 2.6, 1H), 7.51−7.39 (m, 6H), 6.85 (d, J = 8.9, 1H), 3.89 (s, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 61.74. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.3, 170.3, 160.8, 138.4, 136.1, 135.0, 132.3, 132.3, 132.1, 132.1, 132.1, 132.0, 132.0, 131.8, 129.2, 129.1, 126.4, 126.1, 114.2, 114.1, 56.7. HRMS (ESI/[M + Na]$^+$) calcd for $C_{20}H_{17}BrNOPSNa$ 451.9844, found 451.9840.

Large Scale for the Construction of 3d. Imine **1d** 2.24 g (5.0 mmol) and sulfonium salt **2a** 2.85 g (12.5 mmol) were dissolved in dry CH_3CN (50 mL), and then, K_2CO_3 1.72 g (12.5 mmol) was added to this solution. The reaction was stirred at room temperature overnight. After completion of the reaction (The reaction was monitored by TLC), all volatiles were removed in vacuo and the residue was dissolved in CH_2Cl_2 and filtered through silica and solvent was evaporated to afford the crude 3d 2.50 g (93%, trans/cis: 94/6). Further purification by recrystallization afford pure 3d.

General Procedure for the Synthesis of *trans*-2,3-Diyhdrobenzofurans. Imine **1**(1.00 equiv) and sulfonium salt **2** (2.5 equiv) were dissolved in dry CH_3CN (2.0 mL), and then, K_2CO_3 (2.50 equiv) was added to this solution. The reaction was stirred at room temperature. As indicated by TLC, after completion of the reaction (The reaction was monitored by TLC), all volatiles were removed in vacuo and the residue was purified via column chromatography (Petroleum ether (60−90)/ethyl acetate =10:1).

Ethyl-5-bromo-3-(diphenylphosphorothioylamino)-*trans*-2,3-dihydrobenzofuran-2-carboxylate (*trans*-3a). Mp: 142−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07−7.95 (m, 4H), 7.57 (d, J = 1.5, 1H), 7.55−7.44 (m, 6H), 7.32 (dd, J = 8.6, 1.9, 1H), 6.78 (d, J = 8.6, 1H), 5.24 (dd, J = 10.6, 3.3, 1H), 5.19 (d, J = 3.3, 1H), 4.06 (q, J = 7.1, 2H), 3.14 (dd, J = 10.6, 5.8, 1H), 1.13 (t, J = 7.1, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 59.35. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.7, 158.3, 134.1, 133.9, 133.4, 133.1, 132.9, 132.2, 132.2, 132.1, 132.0, 132.0, 131.9, 131.7, 131.6, 129.2, 128.9, 128.9, 128.8, 128.7, 128.5, 113.7, 112.2, 87.0 (d, J = 5.0 Hz), 61.9, 57.4, 14.0. HRMS (ESI/[M + Na]$^+$) calcd for $C_{23}H_{21}BrNO_3PSNa$ 524.0047, found 524.0055.

Ethyl-3-(diphenylphosphorothioylamino)-5-nitro-*trans*-2,3-dihydrobenzofuran-2-carboxylate (*trans*-3b). Mp: 142−143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.34 (d, J = 2.0, 1H), 8.17 (dd, J = 8.9, 2.3, 1H), 8.09−7.96 (m, 4H), 7.60−7.44 (m, 6H), 6.97 (d, J = 8.9, 1H), 5.37 (d, J = 3.8, 1H), 5.31 (td, J = 10.7, 3.7, 1H), 4.12 (q, J = 7.1, 2H), 3.25 (dd, J = 10.6, 5.7, 1H), 1.17 (t, J = 7.1, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 59.67. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.1, 164.0, 143.0, 133.9, 133.7, 132.9, 132.6, 132.4, 132.3, 132.2, 132.2, 131.9, 131.8, 131.7, 131.6, 128.9, 128.7, 128.6, 128.3, 128.2, 127.4, 122.9, 110.7, 88.1 (d, J = 5.0 Hz), 62.2, 56.8, 14.0. HRMS (ESI/[M + Na]$^+$) calcd for $C_{23}H_{21}N_2O_5PSNa$ 491.0800, found 491.0801.

Ethyl-3-(diphenylphosphorothioylamino)-*trans*-2,3-dihydrobenzofuran-2-carboxylate (*trans*-3c). Mp: 131−133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08−7.96 (m, 4H), 7.55−7.42 (m, 7H), 7.23 (t, J = 7.7, 1H), 6.95 (t, J = 7.4, 1H), 6.90 (d, J = 8.1, 1H), 5.25 (td, J = 10.8, 3.4, 1H), 5.16 (d, J = 3.5, 1H), 4.06 (q, J = 7.1, 2H), 3.12 (dd, J = 10.1, 6.0, 1H), 1.12 (t, J = 7.1, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 59.08. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.2, 159.1, 134.3, 133.3, 132.1, 132.0, 131.9, 131.6, 131.5, 130.5, 128.7, 128.6, 128.5, 126.6, 126.6, 126.2, 122.0, 110.5, 86.6 (d, J = 5.0 Hz), 61.7, 57.7, 14.0. HRMS

(ESI/[M + Na]$^+$) calcd for $C_{23}H_{22}NO_3PSNa$ 446.0950, found 446.0953.

Ethyl-5,7-di-*tert*-butyl-3-(diphenylphosphorothioylamino)-*trans*-2,3-dihydrobenzofuran-2-carboxylate (*trans*-3d). Mp: 141−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08−7.97 (m, 4H), 7.54−7.42 (m, 6H), 7.36 (d, J = 1.6, 1H), 7.20 (d, J = 1.8, 1H), 5.27−5.09 (m, 2H), 4.11−3.96 (m, 2H), 3.11 (dd, J = 9.9, 6.0, 1H), 1.38 (s, 9H), 1.28 (s, 9H), 1.12 (t, J = 7.1, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.80. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.7, 155.1, 144.7, 134.6, 134.6, 133.6, 133.5, 133.0, 132.1, 131.9, 131.9, 131.9, 131.9, 131.7, 131.6, 128.6, 128.6, 128.5, 128.5, 126.3, 126.3, 124.2, 120.4, 86.3 (d, J = 5.0 Hz), 61.4, 57.8, 34.7, 34.4, 31.8, 29.4, 14.0. HRMS (ESI/[M + Na]$^+$) calcd for $C_{31}H_{38}NO_3PSNa$ 558.2202, found 558.2203.

Ethyl-7-chloro-3-(diphenylphosphorothioylamino)-*trans*-2,3-dihydrobenzofuran-2-carboxylate (*trans*-3e). Mp: 177−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09−7.93 (m, 4H), 7.57−7.41 (m, 7H), 7.28−7.19 (m, 1H), 6.89 (t, J = 7.8, 1H), 5.30 (td, J = 11.0, 3.6, 1H), 5.19 (d, J = 3.7, 1H), 4.07 (q, J = 7.1, 2H), 3.17 (dd, J = 10.5, 5.9, 1H), 1.13 (t, J = 7.1, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 59.48. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.4, 155.1, 134.2, 134.1, 133.2, 133.0, 132.1, 132.1, 132.1, 132.0, 131.9, 131.6, 131.5, 130.6, 128.7, 128.7, 128.6, 128.5, 124.7, 123.0, 115.9, 87.0 (d, J = 5.0 Hz), 61.8, 58.2, 14.0. HRMS (ESI/[M + Na]$^+$) calcd for $C_{23}H_{21}ClNO_3PSNa$ 480.0561, found 480.0567.

Ethyl-3-(diphenylphosphorothioylamino)-7-phenyl-*trans*-2,3-dihydrobenzofuran-2-carboxylate (*trans*-3f). Mp: 140−141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10−7.95 (m, 4H), 7.72 (d, J = 7.6, 2H), 7.57−7.35 (m, 10H), 7.31 (t, J = 7.3, 1H), 7.04 (t, J = 7.6, 1H), 5.27 (td, J = 10.7, 2.9, 1H), 5.19 (d, J = 3.0, 1H), 4.06 (q, J = 7.1, 2H), 3.12 (dd, J = 10.2, 5.9, 1H), 1.13 (t, J = 7.1, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 59.04. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.2, 156.4, 136.4, 134.3, 133.3, 132.1, 132.0, 132.0, 131.7, 131.5, 130.3, 128.7, 128.6, 128.6, 128.5, 127.5, 127.4, 125.3, 124.7, 122.6, 86.4, 61.6, 57.7, 14.0. HRMS (ESI/[M + Na]+) calcd for $C_{29}H_{26}NO_3PSNa$ 522.1263, found 522.1269.

Ethyl-3-(diphenylphosphorothioylamino)-7-phenyl-*trans*-2,3-dihydrobenzofuran-2-carboxylate (*cis*-3f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−7.90 (m, 4H), 7.70 (d, J = 7.2 Hz, 2H), 7.60−7.31 (m, 11H), 7.01 (t, J = 7.6 Hz, 1H), 5.59 (td, J = 11.8, 8.8 Hz, 1H), 5.20 (d, J = 8.5 Hz, 1H), 4.63−4.61 (m, 1H), 4.22 (ddq, J = 76.2 $_{(P-H)}$, 10.8, 7.2 Hz, 2H), 3.40 (dd, J = 11.0, 6.6 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 59.63. ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.53, 155.96, 136.40, 135.24, 134.64, 134.24, 133.60, 131.94, 131.68, 131.64, 131.57, 131.53, 130.01, 128.64, 128.62, 128.51, 128.49, 128.43, 127.83, 127.41, 125.29, 124.44, 83.28, 83.22, 61.65, 55.42, 14.13. HRMS (ESI/[M + Na]$^+$) calcd for $C_{29}H_{26}NO_3PSNa$ 522.1263, found 522.1269.

Methyl-3-(diphenylphosphorothioylamino)-7-phenyl-*trans*-2,3-dihydrobenzofuran-2-carboxylate (*trans*-3g). Mp: 138−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12−8.01 (m, 4H), 7.76 (d, J = 7.3, 2H), 7.60−7.40 (m, 10H), 7.35 (t, J = 7.4, 1H), 7.08 (t, J = 7.6, 1H), 5.30 (td, J = 10.4, 3.2, 1H), 5.25 (d, J = 3.3, 1H), 3.63 (s, 3H), 3.24−3.12 (m, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 59.11. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.7, 156.4, 136.4, 134.2, 133.2, 132.1, 132.0, 131.9, 131.7, 131.6, 130.3, 128.7, 128.6, 128.6, 128.6, 128.5, 128.5, 127.5, 127.4, 127.4, 125.3, 124.7, 122.7, 86.3 (d, J = 5.0 Hz), 57.8, 52.5. HRMS (ESI/[M + Na]$^+$) calcd for $C_{28}H_{24}NO_3PSNa$ 508.1103, found 508.1095.

***tert*-Butyl-3-(diphenylphosphorothioylamino)-7-phenyl-*trans*-2,3-dihydrobenzofuran-2-carboxylate (*trans*-3h).** Mp: 145−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11−7.97 (m, 4H), 7.80 (d, J = 7.4, 2H), 7.58−7.40 (m, 10H), 7.35 (t, J = 7.4, 1H), 7.07 (t, J = 7.6, 1H), 5.37 (td, J = 10.7, 2.4, 1H), 5.13 (d, J = 2.6, 1H), 3.15 (dd, J = 10.1, 6.5, 1H), 1.39 (s, 9H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.68. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.0, 157.4, 137.2, 135.4, 135.4, 134.4, 132.7, 132.6, 132.5, 132.3, 132.2, 130.9, 129.4, 129.4, 129.3, 129.2, 129.2, 129.1, 128.4, 128.3, 128.1, 125.9, 125.3, 123.2, 87.4 (d, J = 1.0 Hz), 83.3, 58.3, 28.7. HRMS (ESI/[M + Na]$^+$) calcd for $C_{31}H_{30}NO_3PSNa$ 550.1576, found 550.1580.

***N*-(2-Benzoyl-5-methoxy-*trans*-2,3-dihydrobenzofuran-3-yl)-*P*,*P*-diphenylphosphinothioic Amide (*trans*-3i).** Mp: 137−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (dd, J = 23.8, 8.6, 6H), 7.59 (t, J = 7.3, 1H), 7.54−7.35 (m, 8H), 7.06 (s, 1H), 6.77 (s, 2H), 5.99 (d, J = 2.5, 1H), 5.51 (t, J = 10.2, 1H), 3.74 (s, 3H), 3.36 (s, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.20. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 192.5, 153.9, 151.8, 133.5, 133.3, 132.6, 132.3, 130.9, 130.8, 130.7, 130.6, 130.5, 128.3, 127.6, 127.6, 127.5, 127.4, 126.8, 126.7, 115.3, 110.1, 109.6, 88.0 (d, J = 2.0 Hz), 55.1, 55.0. HRMS (ESI/[M + Na]$^+$) calcd for $C_{28}H_{24}NO_3PSNa$ 508.1103, found 508.1098.

***N*-(2-Benzoyl-5-methyl-*trans*-2,3-dihydrobenzofuran-3-yl)-*P*,*P*-diphenylphosphinothioic Amide (*trans*-3j).** Mp: 152−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08−7.96 (m, 4H), 7.91 (d, J = 7.9, 2H), 7.59−7.42 (m, 7H), 7.35−7.23 (m, 3H), 6.75 (d, J = 8.5, 1H), 6.10 (d, J = 3.0, 1H), 5.48 (t, J = 9.1, 1H), 3.22 (dd, J = 10.9, 5.5, 1H), 2.45 (s, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.29. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 192.4, 158.1, 144.9, 134.3, 133.6, 133.2, 132.6, 132.2, 132.2, 132.1, 132.0, 131.9, 131.8, 131.6, 131.5, 129.5, 129.4, 129.0, 128.8, 128.7, 128.7, 128.6, 113.5, 112.1, 88.9 (d, J = 4.0 Hz), 55.5, 21.8. HRMS (ESI/[M + Na]$^+$) calcd for $C_{28}H_{24}NO_2PSNa$ 492.1157, found 492.1155.

***N*-(2-Benzoyl-5-*tert*-butyl-*trans*-2,3-dihydrobenzofuran-3-yl)-*P*,*P*-diphenylphosphinothioic Amide (*trans*-3k).** Mp: 153−155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04−7.92 (m, 6H), 7.55 (t, J = 7.4, 1H), 7.49−7.36 (m, 9H), 7.26−7.20 (m, 1H), 6.76 (d, J = 8.5, 1H), 5.95 (d, J = 3.3, 1H), 5.52 (td, J = 10.5, 2.8, 1H), 3.27 (dd, J = 10.3, 6.3, 1H), 1.27 (s, 9H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.21. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 193.6, 156.7, 145.1, 134.6, 134.4, 133.7, 133.6, 133.4, 132.0, 131.9, 131.8, 131.7, 131.6, 129.4, 128.7, 128.7, 128.6, 127.5, 126.7, 126.6, 122.9, 109.7, 89.3 (d, J = 4.0 Hz), 56.1, 34.5, 31.7. HRMS (ESI/[M + Na]$^+$) calcd for $C_{31}H_{30}NO_2PSNa$ 534.1627, found 534.1625.

***N*-(2-Benzoyl-5-bromo-*trans*-2,3-dihydrobenzofuran-3-yl)-*P*,*P*-diphenylphosphinothioic Amide (*trans*-3l).** Mp: 80−81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06−7.91 (m, 6H), 7.58 (t, J = 7.3, 1H), 7.54−7.37 (m, 10H), 7.29 (d, J = 8.0, 1H), 6.71 (d, J = 8.5, 1H), 6.10 (d, J = 3.0, 1H), 5.46 (t, J = 8.9, 1H), 3.26 (dd, J = 10.5, 5.2, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.33. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 192.8, 158.0, 134.4, 134.2, 133.9, 133.5, 133.2, 132.5, 132.2, 132.2, 132.0, 131.9, 131.6, 131.5, 129.5, 129.4, 129.0, 128.8, 128.7, 128.7, 128.6, 113.5, 112.1, 88.9 (d, J = 3.0 Hz), 55.5. HRMS (ESI/[M + Na]$^+$) calcd for $C_{27}H_{21}BrNO_2PSNa$ 556.0106, found 556.0100.

***N*-(5-Bromo-2-(4-methylbenzoyl)-*trans*-2,3-dihydrobenzofuran-3-yl)-*P*,*P*-diphenylphosphinothioic Amide (*trans*-3m).** Mp: 152−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08−7.97 (m, 4H), 7.91 (d, J = 7.9, 2H), 7.59−7.43 (m, 7H), 7.32 (d, J = 8.6, 1H), 7.26 (d, J = 7.9, 2H), 6.75 (d, J = 8.5, 1H), 6.10 (d, J = 3.0, 1H), 5.48 (t, J = 9.1, 1H), 3.22 (dd, J = 10.9, 5.5, 1H), 2.45 (s, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.29. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 192.4, 158.1, 144.9, 134.3, 133.6, 133.2, 132.6, 132.2, 132.2, 132.1, 132.0, 131.9, 131.8, 131.6, 131.5, 129.5, 129.4, 129.0, 128.8, 128.7, 128.7, 128.6, 113.5, 112.1, 89.0 (d, J = 3.0 Hz), 55.5, 21.8. HRMS (ESI/[M + Na]$^+$) calcd for $C_{28}H_{23}BrNO_2PSNa$ 570.0263, found 570.0265.

***N*-(5-Bromo-2-(4-chlorobenzoyl)-*trans*-2,3-dihydrobenzofuran-3-yl)-*P*,*P*-diphenylphosphinothioic Amide (*trans*-3n).** Mp: 138−141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10−7.92 (m, 6H), 7.60−7.40 (m, 9H), 7.33 (d, J = 8.6, 1H), 6.75 (d, J = 8.6, 1H), 6.11 (d, J = 3.1, 1H), 5.47 (t, J = 9.0, 1H), 3.23 (dd, J = 11.0, 5.5, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.32. ^{13}C NMR (101 MHz, $CDCl_3$) δ =

191.8, 157.9, 140.4, 134.2, 133.3, 133.1, 132.8, 132.3, 132.3, 132.2, 132.2, 132.0, 131.9, 131.5, 131.4, 130.8, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.6, 113.6, 112.2, 88.8, 55.4. HRMS (ESI/[M + Na]$^+$) calcd for $C_{27}H_{20}BrClNO_2PSNa$ 589.9716, found 589.9710.

***N*-(2-(Furan-2-carbonyl)-*trans*-2,3-dihydrobenzofuran-3-yl)-*P*,*P*-diphenylphosphinothioic Amide (*trans*-3o).** Mp: 110−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10−7.98 (m, 4H), 7.58−7.40 (m, 8H), 7.37 (s, 1H), 7.24 (t, J = 7.7, 1H), 6.98 (t, J = 7.4, 1H), 6.89 (d, J = 8.1, 1H), 6.53 (s, 1H), 5.80 (d, J = 2.5, 1H), 5.44 (t, J = 9.1, 1H), 3.27 (d, J = 5.0, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.50. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 181.7, 157.9, 149.5, 146.5, 133.3, 133.1, 132.3, 132.1, 130.9, 130.9, 130.9, 130.9, 130.7, 130.7, 130.6, 130.6, 129.3, 127.7, 127.6, 127.5, 127.4, 126.0, 125.9, 125.2, 120.9, 119.2, 111.5, 109.3, 88.0 (d, J = 3.0 Hz), 55.3. HRMS (ESI/[M + Na]$^+$) calcd for $C_{25}H_{20}NO_3PSNa$ 468.0794, found 468.0790.

***P*,*P*-Diphenyl-*N*-(2-(thiophene-2-carbonyl)-*trans*-2,3-dihydrobenzofuran-3-yl)phosphinothioic Amide (*trans*-3p).** Mp: 121−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13−7.99 (m, 4H), 7.93 (d, J = 2.9, 1H), 7.69 (d, J = 4.3, 1H), 7.58−7.42 (m, 7H), 7.30−7.22 (m, 1H), 7.12 (s, 1H), 6.99 (t, J = 7.4, 1H), 6.91 (d, J = 8.0, 1H), 5.85 (d, J = 2.5, 1H), 5.45 (t, J = 8.9, 1H), 3.23 (s, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.24. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 186.2, 157.8, 140.0, 134.1, 133.4, 133.1, 132.8, 132.1, 131.8, 131.0, 130.9, 130.8, 130.7, 130.6, 129.3, 127.7, 127.6, 127.6, 127.5, 127.3, 126.0, 125.9, 125.2, 121.0, 109.4, 88.9 (d, J = 4.0 Hz), 55.6. HRMS (ESI/[M + Na]$^+$) calcd for $C_{25}H_{20}NO_2PS_2Na$ 484.0565, found 484.0560.

***N*-(7-Chloro-2-(thiophene-2-carbonyl)-*trans*-2,3-dihydrobenzofuran-3-yl)-*P*,*P*-diphenylphosphinothioic Amide (*trans*-3q).** Mp: 163−165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14−7.93 (m, 6H), 7.71 (d, J = 4.8, 1H), 7.62−7.41 (m, 8H), 7.33−7.20 (m, 1H), 7.14 (t, J = 4.1, 1H), 6.93 (t, J = 7.7, 1H), 5.90 (d, J = 3.0, 1H), 5.51 (t, J = 8.9, 1H), 3.26 (dd, J = 9.6, 5.3, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.59. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 185.7, 153.8, 139.9, 134.5, 133.7, 132.9, 132.7, 131.9, 131.7, 131.1, 131.0, 130.8, 130.7, 130.64, 129.5, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 123.6, 122.0, 114.8, 89. Four (d, J = 5.0 Hz), 56.3. HRMS (ESI/[M + Na]$^+$) calcd for $C_{25}H_{19}ClNO_2PS_2$-Na 518.0175, found 518.0170.

***N*-(2-Acetyl-7-chloro-*trans*-2,3-dihydrobenzofuran-3-yl)-*P*,*P*-diphenylphosphinothioic Amide (*trans*-3r).** Mp: 168−169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09−7.95 (m, 4H), 7.58−7.44 (m, 6H), 7.40 (d, J = 7.3, 1H), 7.24 (d, J = 8.2, 1H), 6.90 (t, J = 7.6, 1H), 5.26 (d, J = 2.3, 1H), 5.17 (t, J = 10.3, 1H), 3.13 (dd, J = 10.0, 5.5, 1H), 2.18 (s, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.77. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 203.7, 155.0, 133.9, 133.8, 132.9, 132.8, 132.2, 131.9, 131.8, 131.7, 130.6, 128.8, 128.7, 128.6, 128.5, 124.8, 123.1, 115.9, 92.6 (d, J = 5.0 Hz), 56.7, 26.6. HRMS (ESI/[M + Na]$^+$) calcd for $C_{22}H_{19}ClNO_2PSNa$ 450.0455, found 450.0450.

Ethyl-3-((diphenylphosphorothioyl)amino)-6-methoxy-2,3-dihydrobenzofuran-2-carboxylate (*trans*-3s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−7.94 (m, 4H), 7.55−7.38 (m, 7H), 6.54−6.45 (m, 2H), 5.20 (d, J = 3.0 Hz, 1H), 5.18−5.10 (m, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.76 (s, 1H), 3.05 (dd, J = 10.1, 5.7 Hz, 1H), 1.11 (t, J = 7.1 Hz, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 58.72. ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.20, 162.11, 160.68, 134.32, 133.30, 132.06, 131.95, 131.89, 131.63, 131.52, 131.23, 131.12, 128.69, 128.58, 128.56, 128.45, 128.40, 126.52, 118.51, 108.55, 96.26, 87.43, 87.38, 61.65, 57.38, 55.57, 13.99. HRMS (ESI/[M + Na]$^+$) calcd for $C_{24}H_{24}NO_3PSNa$ 476.1056, found 476.1062.

(*E*)-Methyl-3-(7-chloro-3-(diphenylphosphorothioylamino)-*trans*-2,3-dihydrobenzofuran-2-yl)acrylate (*trans*-3t). Mp: 104−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11−7.95 (m, 4H), 7.59−7.44 (m, 6H), 7.37 (d, J = 7.5, 1H), 7.26 (d, J = 8.0, 1H), 6.91 (t, J = 7.7, 1H), 6.83 (dd, J = 15.6, 4.8, 1H), 6.01 (d, J = 15.6, 1H), 5.49 (s, 1H), 4.88 (td, J = 10.5, 3.3, 1H), 3.70 (s, 3H), 3.24 (s, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.95. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.1, 155.1, 142.7, 133.2, 132.2, 131.8, 131.7, 131.6, 130.6, 128.8, 128.7, 128.6, 128.3, 124.7, 122.8, 121.8, 116.0, 89.0 (d, J = 3.0 Hz), 59.4, 51.7. HRMS (ESI/[M + Na]$^+$) calcd for $C_{24}H_{21}ClNO_3PSNa$ 492.0560, found 492.0568.

(*E*)-Methyl-3-(3-(diphenylphosphorothioylamino)-7-phenyl-*trans*-2,3-dihydrobenzofuran-2-yl)acrylate (*trans*-3u). Mp: 69−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13−7.92 (m, 4H), 7.68 (d, J = 7.4, 2H), 7.57−7.36 (m, 11H), 7.32 (t, J = 7.3, 1H), 7.04 (t, J = 7.6, 1H), 6.85 (dd, J = 15.7, 5.0, 1H), 5.95 (dd, J = 15.7, 1.4, 1H), 5.50−5.40 (m, 1H), 4.85 (td, J = 10.3, 3.3, 1H), 3.66 (s, 3H), 3.17 (dd, J = 10.0, 6.3, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 58.62. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.2, 156.3, 143.7, 136.3, 134.4, 134.2, 133.4, 133.1, 132.2, 132.1, 131.9, 131.8, 131.7, 131.6, 130.2, 128.8, 128.7, 128.7, 128.6, 128.5, 128.4, 127.5, 127.4, 125.3, 124.6, 122.4, 121.6, 88.4 (d, J = 3.0 Hz), 58.96, 51.7. HRMS (ESI/[M + Na]$^+$) calcd for $C_{30}H_{26}NO_3PSNa$ 534.1263, found 534.1260.

***N*-(2-Benzoyl-2-methyl-*trans*-2,3-dihydrobenzofuran-3-yl)-*P*,*P*-diphenylphosphinothioic Amide (*trans*-3v).** Mp: 121−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (dd, J = 13.8, 7.9, 2H), 7.81 (dd, J = 13.7, 8.1, 2H), 7.57−7.38 (m, 12H), 7.18 (t, J = 7.7, 1H), 7.00−6.85 (m, 2H), 5.50−5.35 (m, 1H), 3.61 (td, J = 10.7, 2.9, 1H), 1.06 (s, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 59.47. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.2, 136.6, 136.5, 135.6, 135.5, 134.0, 131.7, 131.6, 131.5, 131.4, 131.2, 131.1, 130.3, 129.3, 129.0, 128.7, 128.6, 128.6, 128.5, 128.3, 127.4, 122.7, 121.8, 121.8, 117.0, 90.0, 67.7 (d, J = 3.0 Hz), 50.3, 17.0. HRMS ESI/[M + Na]$^+$) calcd for $C_{28}H_{24}NO_2PSNa$ 492.1157, found 492.1150.

2-Isopropyl-4-methylcyclohexyl-3-((diphenylphosphorothioyl)amino)-7-phenyl-2,3-dihydrobenzofuran-2-carboxylate (*trans*-3w). Value of dr for the two stereomers was determined by ^{31}P NMR of the crude product. The absolute configuration was not determined. Mp: 69−71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10−7.94 (m, 4H), 7.73 (d, J = 7.7, 2H), 7.55−7.35 (m, 10H), 7.35−7.27 (m, 1H), 7.04 (t, J = 7.6, 1H), 5.35−5.13 (m, 2H), 4.68−4.54 (m, 1H), 3.09 (s, 1H), 1.68−1.55 (m, 3H), 1.44−1.33 (m, 1H), 1.30−1.24 (m, 1H), 0.89−0.76 (m, 10H), 0.61 (dd, J = 15.4, 6.8, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 59.08, 58.62. 13C NMR (101 MHz, $CDCl_3$) δ = 168.9 168.8, 156.5, 156.4, 136.5 136.4, 134.4, 134.3 133.4, 133.3 132.1, 132.0, 132.0, 131.9, 131.7, 131.6, 131.5, 130.3, 130.2, 128.7, 128.6, 128.5, 127.6, 127.4, 125.3, 124.7, 122.57, 86.5 (d, J = 4.0 Hz),, 75.8, 57.6, 46.6, 40.3, 34.1, 31.4, 25.90, 22.9, 22.0, 20.9, 15.9. HRMS ESI/[M + Na]$^+$) calcd for $C_{37}H_{40}NO_3PSNa$ 632.2359, found 632.2356.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. ^{1}H and ^{13}C NMR spectra of **3** and **4** and CIF files for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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