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Article

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Evaluation and Development of Methodologies for the Synthesis of Thiophosphinic Acids

Karen R. Winters, and Jean-Luc Montchamp*

Department of Chemistry, Box 298860, Texas Christian University, Fort Worth, Texas 76129 (USA). E-mail: j.montchamp@tcu.edu

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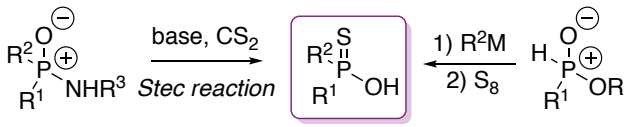


Thiophosphorus Acids

Abstract: Thiophosphorus acids $R^1R^2P(S)OH$ constitute an important class of organophosphorus compounds, in which the phosphorus atom is intrinsically chiral if $R^1 \neq R^2$. In connection with a project aimed at the preparation of chiral thiophosphorus acids, various available literature methods were considered, but few fit the requirement of odorless reagents. Herein, the results of our studies on the synthesis of thiophosphinic acids are reported. Ultimately, two major approaches were selected: 1) the Stec reaction of phosphorus amides with carbon disulfide; and 2) the one-pot synthesis of thiophosphorus acids from *H*-phosphinates, an organometallic nucleophile, and quenching with elemental sulfur. An application to the preparation of a potential chiral phosphorus organocatalyst is also reported.

Introduction

Recently, our laboratory became interested in the preparation of thiophosphorus acids $R^1R^2P(S)OH$ **1**,[1] in connection with a project aimed at developing novel chiral phosphorus acids (CPAs) organocatalysts.[2] Thiophosphorus acids have been known for a long time,[1a] and

resolution to a chiral compound was described as early as 1958.[1b] They exist as a mixture of tautomers: thionic acid **1a** and thiolic acid **1b** (Scheme 1).[1a] The major tautomer depends on the substituents, although it is generally thionic acid **1a**.

Scheme 1. Prototropic Tautomerism in Thiophosphorus acids.

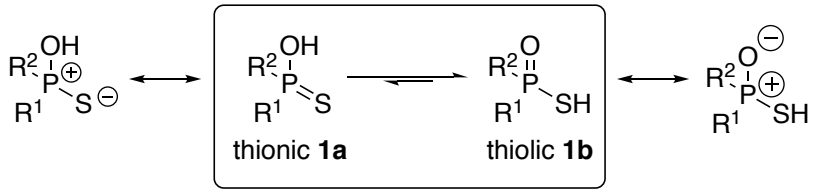
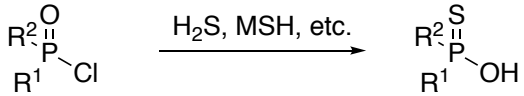
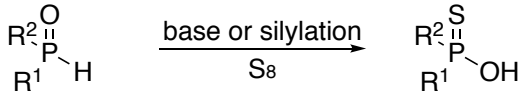
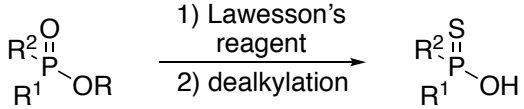
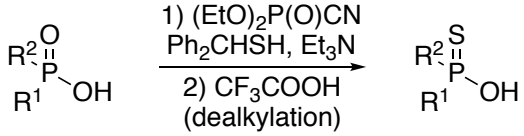
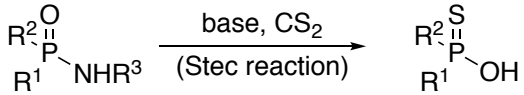
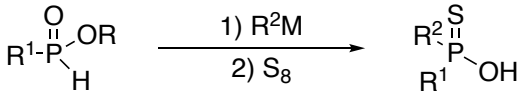


Table 1. Summary of Methodologies for the Preparation of Thiophosphinic Acids and Related Compounds

Entry	Reaction	Comments	Ref.
1		commonly used method stench, toxic	3
2		commonly used method odorless S, Se, BH_3 derivatives	4
3		commonly used method stench often problems during purification	5
4		only one literature report stench	6
5		general reaction, stereospecific odorless	7

6			only one literature example odorless S, Se, BH_3 derivatives	8

When reviewing the literature, we realized that many methods utilized conditions that involved foul-smelling reagents such as Lawesson's reagent,[5,9] phosphorus pentasulfide, thiols, or metal sulfides (Table 1).[3] We desired an approach which would circumvent this drawback.

Whereas Lawesson's reagent[9] has often been used, two issues remain: 1) the foul-smelling characteristic due to hydrolysis of the reagents to form rotten egg-smelling and highly toxic hydrogen sulfide H_2S; and 2) difficulties during isolation and purification of the product associated with byproducts. In our hands, even the reported Lawesson's reagent alternatives[10] to solve problem 2 were not successful. Therefore, we embarked on a study aimed at preparing thiophosphinates (and related compounds) that would solve these problems. We investigated various possibilities (Table 1) for the synthesis of thiophosphorus acids, mainly thiophosphinates (phosphinothioates) and the results are described herein. Ultimately, two methodologies were selected: 1) the Stec reaction (the Wadsworth-Emmons olefination focusing on the phosphorus reactant (Table 1, entry 5), and 2) the displacement of *H*-phosphinates with an organometallic nucleophile followed by *in situ* trapping of the intermediate with elemental sulfur (Table 1, entry 6).

Results and Discussion

Any and all literature methods were considered toward our objective of synthesizing thiophosphorus acids.[1,3-8] Very quickly various issues were identified in some of the methods, and as a result they were deemed unacceptable.

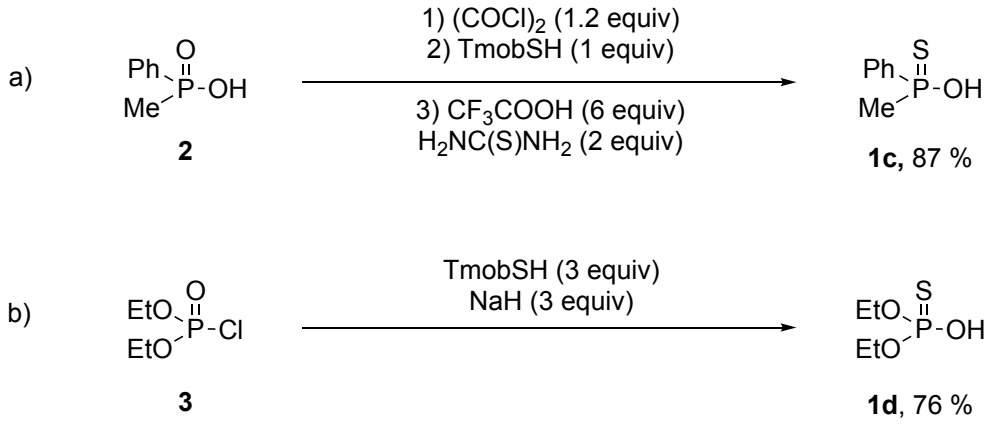
Our investigation initially focused on the reaction of P(O)Cl (Table 1, entry 1), with the direct conversion of P(O)(OR) into P(O)LVG (LVG = leaving group, such as chlorine) as its starting point. Even though the conversion of P(O)(OR) into P(O)Cl is widely reported, the conditions typically employ excess chlorinating agent ($SOCl_2$, $(COCl)_2$, or $POCl_3$) and do not proceed in a one-pot process.[11] Alternatives include the use of triflic anhydride (Tf_2O) even though this approach has its own limitations in terms of scope and expense.[12]

Unlike what is claimed in publications championing triflic anhydride chemistry,[12] the transformation has a broad scope and is generally high-yielding, with CH_2Cl_2, CH_3CN, and DMF the best solvents (~90+% yield for the formation of the acid chloride). Thus, we found that using a small excess (1.2 equiv) of oxalyl chloride produces the acid chloride P(O)Cl cleanly, and in high yield. The next step was to convert this intermediate into the desired thiophosphorus acid (Table 1, entry 1). Reaction with NaSH or Na_2S gave low yields of the desired product because of the salts' lack of solubility in organic solvents, and competing hydrolysis with the formation of acid $R^1R^2P(O)OH$, anhydride $[R^1R^2P(O)(OH)]_2O$, and a trace of mixed anhydride $R^1R^2P(S)OP(O)R^1R^2$. On top of that, the reagents have an awful stench.

The next step was to replace the sulfur nucleophile with organic-soluble, odorless, and inexpensive (6 $/mol) *n*-dodecyl thiol.[13] However, although the formation of the corresponding thioester was successful, cleavage to the desired thioacid was not. Various conditions were attempted, such as S_N2 with various nucleophiles, but all those failed. Cleavage of $PhMeP(O)SC_{12}H_{25}$ **4** via S_N2 with various nucleophiles (DABCO, NaN_3, TFA/thiourea) was unsuccessful (< 20% NMR yield of desired product in the best case). On the other hand, Na_2S (2 equiv)/DMF 100 °C did give a 76% NMR yield (+ 16% unreacted starting material) of desired

salt, but obviously these conditions are far from odorless, the same reason why thiophenol was not tried.

Scheme 2.[a] Synthesis of Thiophosphorus Acids via TmobSH.

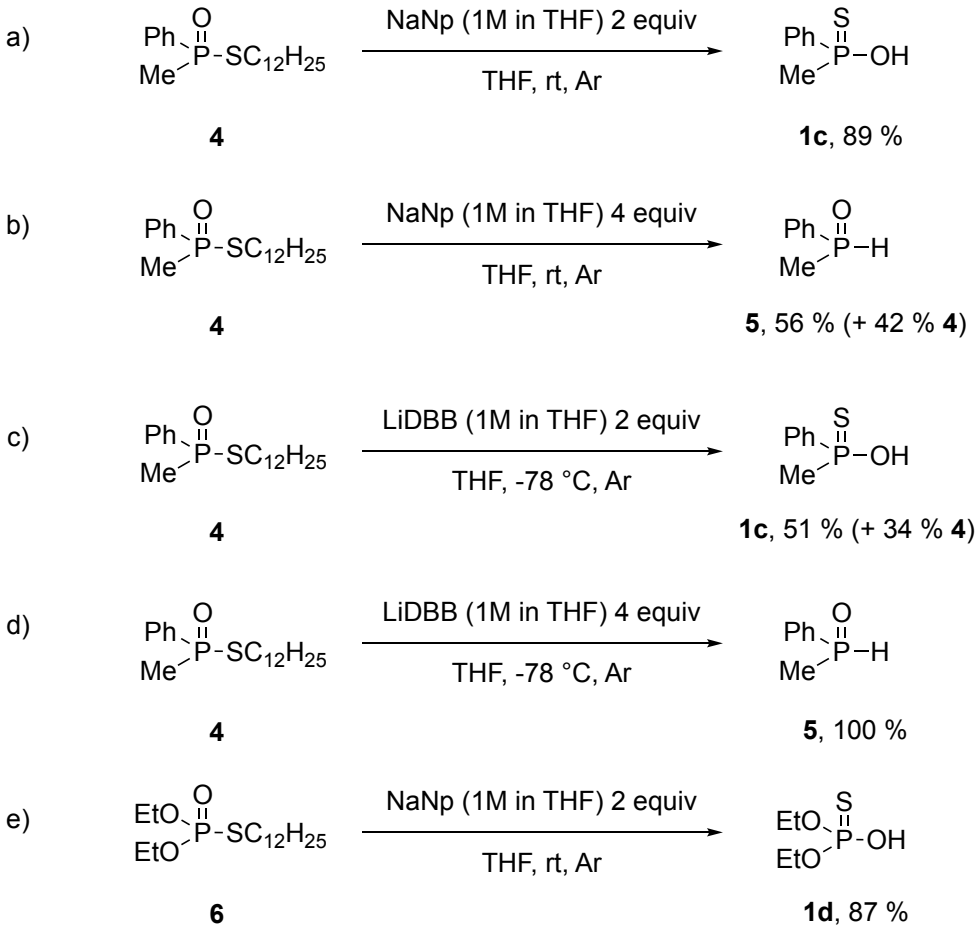


[a] All yields are determined by ^{31}P-NMR.

Thus, we turned to Node's odorless 2,4,6-trimethoxybenzyl thiol (TmobSH)[14] in the place of *n*-dodecyl thiol. TmobSH is easily synthesized in three steps from the commercially available aldehyde.[14] In principle, if thiourea were added during the cleavage step, the thiol could be recycled,[14] but this recycling was unsuccessful even though the reaction gave the correct product in an 87% NMR yield (Scheme 2a). This transformation was also tried with an excess of TmobSH in the hope that the excess deprotonated thiol would cleave the benzyl position of the phosphothioester. This proved to be successful in a 76% NMR yield (Scheme 2b). However, despite this sequence of reactions accomplishing the desired transformation, **2** → **1c** and **3** → **1d**, the fact that TmobSH could not be recycled (and took 3 steps to synthesize) seemed wasteful and a significant drawback, thus the approach was set aside.

The reduction of $P(O)SC_{12}H_{25}$ into P(O)H was considered next, since P(O)H is easily converted into P(S)OH with elemental sulfur (Table 1, entry 2), and is also a key intermediate in numerous other transformations. Since the transformation P(O)SR to P(O)H was unknown, this reduction was briefly examined through the use of alkali metals sodium naphthalide (NaNp) and lithium biphenylide (LiDBB), as they have been shown to reduce phosphorus-halogen bonds.[15] (Scheme 3). Interestingly, depending on the stoichiometry of the reducing agent, either the thiophosphorus acid P(S)OH **1c** (Scheme 3a), or the phosphinylidene P(O)H **5** (Scheme 3b) could be obtained. It appears that 2 equivalents give the thiophosphinic acids **1c**, **1d** as the major products (Scheme 3a, 3c, 3e); whereas 4 equivalents produce the more fully reduced phosphinylidene P(O)H **5** (Scheme 3b, 3d), and the nature of the reducing agent is not as important as the stoichiometry.

Scheme 3.[a] Naphthalenide and Biphenylide Reduction of Thioesters.



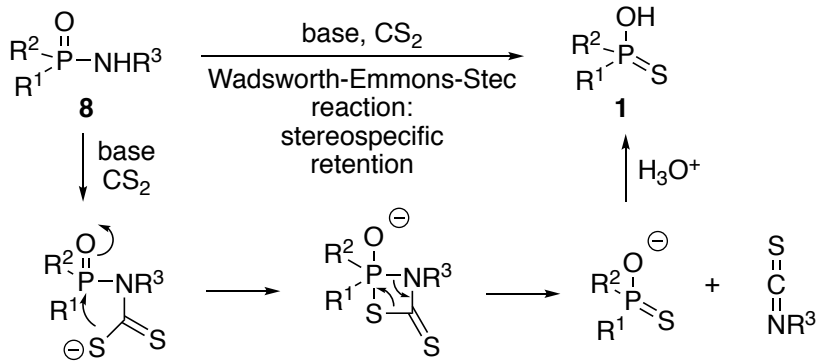
[a] All yields are determined by ^{31}P-NMR.

However, although successful, this transformation was not ideal, because it is lengthy and wasteful. Since the direct conversion of P(O)Cl into P(O)H has been reported a few times,[15] the reduction of P(O)Cl would be a more efficient approach. Our own work to develop this useful transformation will be reported at a later time.

Considered next, was the reaction of ester P(O)(OR) with Lawesson's reagent (and related thionating agent),[9,10] followed by the cleavage of the intermediate thioester P(S)(OR), perhaps the most commonly employed method (Table 1, entry 3).[5] However, Lawesson's reagent and

related thionating agents such as phosphorus pentasulfide, all stench (of toxic hydrogen sulfide). Additionally, the presence of byproducts often impedes purification and lowers the yields of the intermediate P(S)(OR). Finally, when R = Me, Et, the final cleavage is relatively easy, but we could not find conditions for the cleavage of menthyl thioesters P(S)(OMen), which limits applications to *P*-stereogenic products. Because this approach (Table 1, entry 3) did not meet several of our requirements, it was quickly abandoned.

Scheme 4. The Wadsworth-Emmons-Stec Reaction.

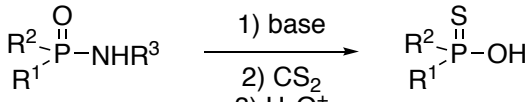


The next iteration focused on the Wadsworth-Emmons-Stec reaction (Table 1, entry 5).[16] The Stec reaction converts a phosphorus amide P(O)NHR **8** using a base and carbon disulfide, into the thiophosphorus acid **1**, stereospecifically,[17] and isothiocyanate (Scheme 4). Wadsworth and Emmons made the initial discovery, but Stec was the first to realize the reaction's usefulness in organophosphorus chemistry.

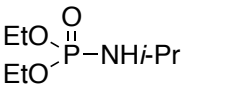
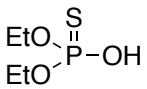
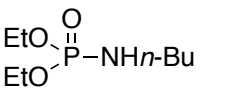
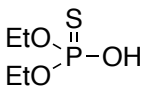
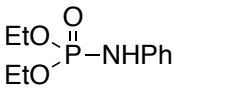
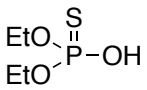
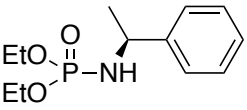
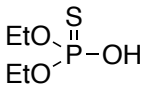
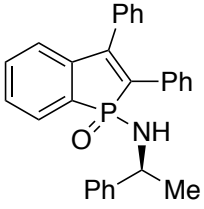
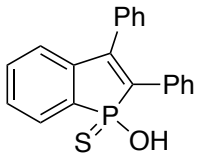
Reaction of the acid chloride P(O)Cl (either from a commercial reagent, or formed *in situ* from the reaction of P(O)(OR) (R = Alk, H)) with a primary amine/aniline unsurprisingly gave good yields of the corresponding amide P(O)NHR **8**. From that point, treatment with a base and CS_2

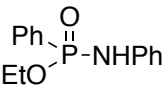
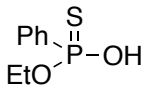
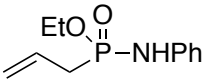
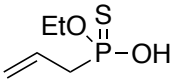
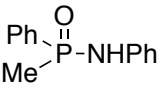
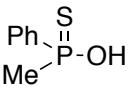
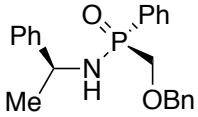
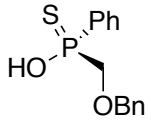
delivered the corresponding thiophosphorus acid **1** uneventfully (Table 2). As expected, various bases were successful in this process. Because the resolutions of various thiophosphorus acid products have been described,[4] this transformation fits all our requirements. It should be noted that a comprehensive study of this transformation has not been reported in the literature, and Stec used it mostly in the area of nucleic acids. An additional advantage is that using inexpensive chiral 1-phenylethylamine (either isomer: 15-20 $/mol) gives an opportunity for resolution, not only by crystallization, but also perhaps standard chromatography.

Table 2. Summary of Methodologies for the Preparation of Thiophosphinic Acids and Related Compounds



8a-i **1c-h**

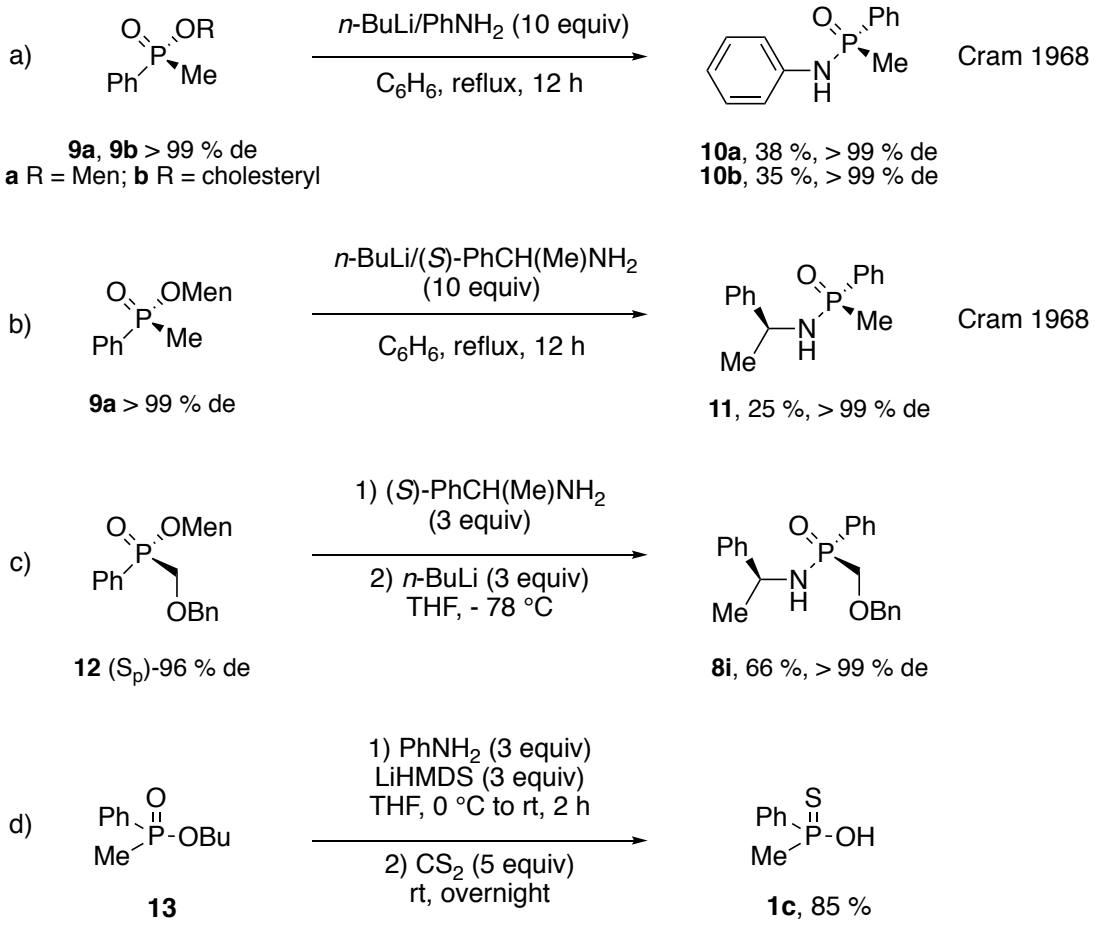
Entry	Substrate		Conditions[a]	Product		Yield (%)[b]
1a		**8a**	A		**1d**	90 (88)
1b			B			88
1c			C			77
2a		**8b**	A		**1d**	91
2b			B			97 (95)
2c			C			91
3a		**8c**	A		**1d**	96
3b			B			100 (99)[c]
3c			C			95[c]
4a		**8d**	A		**1d**	45
4b			B			81 (75)[c]
4c			C			44
5		**8e**	B		**1e**	96 (85)

6		**8f**	B		**1f**	100 (79)
7		**8g**	D		**1g**	90 (76)
8a 8b		**8h**	B D		**1c**	79 94 (85)[c]
9	 > 99 % de	**8i**	E	 > 99 % de	**1h**	88 (72)

[a] Conditions A: NaH (3 equiv), THF, 0 °C to rt, 1 h; then CS_2 (3 equiv), 2 h. Conditions B: *n*-BuLi (2 equiv), THF, -78 °C to rt, 1 h; then CS_2 (3 equiv), 2 h. Conditions C: LiHMDS (1.5 equiv), THF, 0 °C to rt, 1 h; then CS_2 (3 equiv), 2 h. Conditions D: LiHMDS (1.25 equiv), THF, 0 °C to rt, 2 h; then CS_2 (5 equiv), overnight. Conditions E: NaH (2.0 equiv), THF, 0 °C to rt, then CS_2 (5 equiv), overnight. [b] Determined by ^{31}P-NMR. In parentheses: yield of product (> 95% purity) after extractive work-up. [c] The reaction with CS_2 was conducted overnight instead of 2 h.

Next, the direct transamidation of P(O)OR was investigated.[18] In 1968, Cram reported the reactions of chiral menthyl and cholesteryl phosphinate esters **9a** and **9b** with lithium amides derived from aniline and 1-phenylethylamine.[18a] These reactions proceed stereospecifically with formation of **10a**, **10b** and **11**, although the yields were mediocre and the stoichiometry wasteful (Scheme 5a-b). In our case, the reaction of PhP(O)(OMen)CH_2OBn[19] **12** with *S*-1-phenylethylamine/*n*-BuLi also proved to take place stereospecifically and in satisfactory yield to deliver **8i** (Scheme 5c). Unfortunately, a similar one-pot transamidation approach was not successful on phosphonate diesters. In principle, the intermediate phosphorus amide could be deprotonated *in situ* with an excess of base and then reacted with CS_2. This one-pot method was successful in the case of butyl phosphinate **13**, however it failed on menthyl phosphinate **12** which was shown to be successful in a stepwise fashion (Table 2, entry 9).

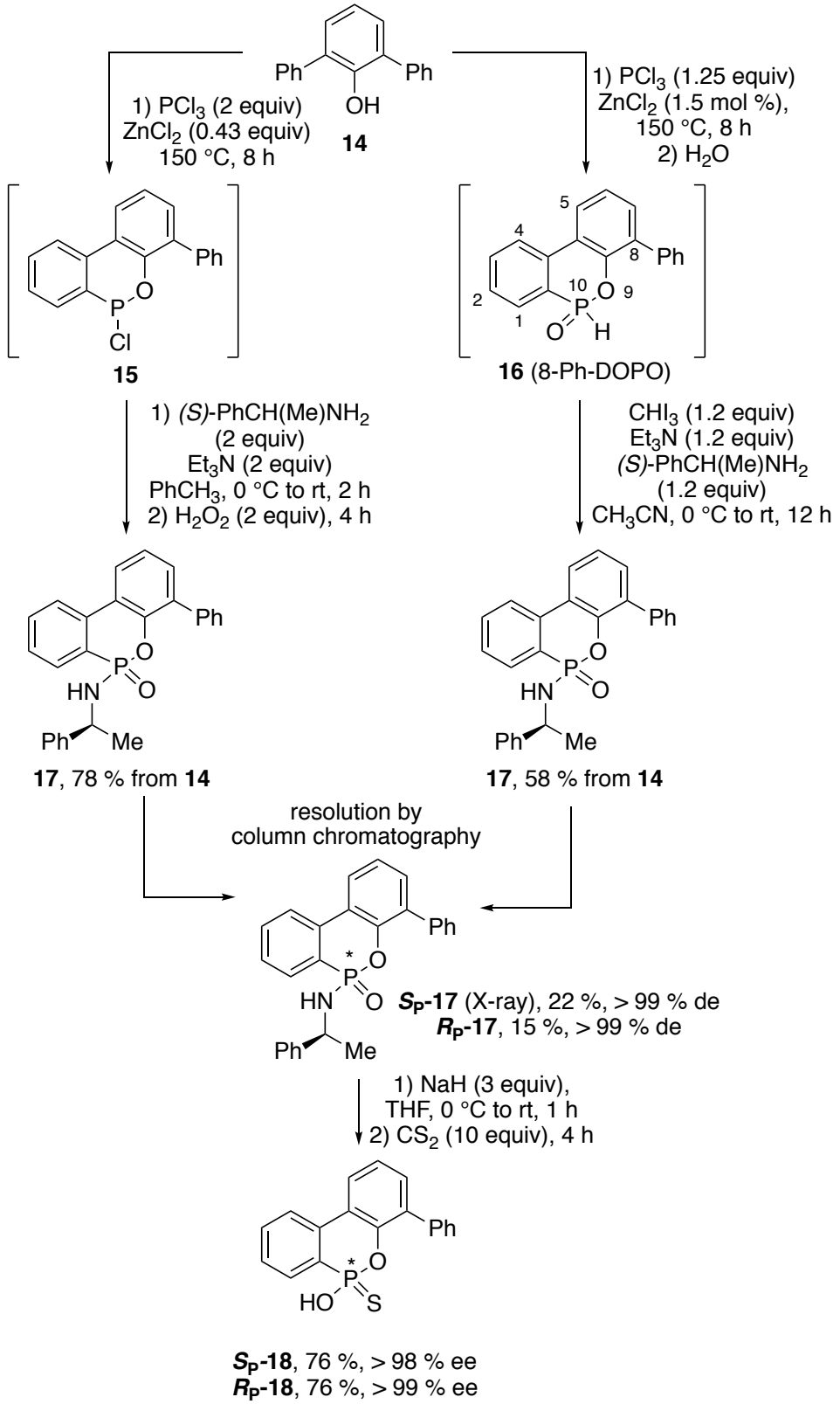
Scheme 5. Transamidation with Lithium Amides.



An application of these investigations is shown on Scheme 6. In order to replace the expensive, high molecular weight, and C_2-symmetrical chiral phosphoric acids based on binaphthol introduced in 2004 by Akiyama[20a] and Terada,[20b] we looked for alternatives. 9,10-Dihydro-9-oxa-10-phosphaphenanthrene-10-oxide (DOPO) is an industrial flame-retardant (> 10,000 tons/year).[21] Terphenol **14** was reacted with phosphorus trichloride and cyclized to the corresponding chloride.[22] At this point the P(III)-Cl intermediate **15** can be reacted with chiral amine $PhCH(Me)NH_2$ followed by oxidation with H_2O_2 to provide amide **17**, or hydrolysis of **15**

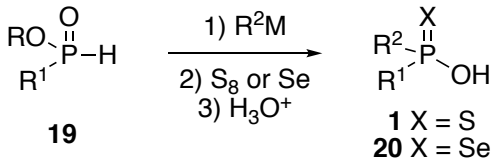
leads to 8-phenyl-DOPO **16**. Atherton-Todd reaction[23] of **16** with *S*-1-phenylethylamine provides the same intermediate **17**. This can be resolved easily by column chromatography, albeit in low yield, into chiral amide S_P-**17** and R_P-**17**. The absolute configuration at phosphorus was determined by X-ray crystallography. Finally, the Stec reaction on S_P-**17** and R_P-**17** (base then CS_2) led to either a racemic ring-opened product[24] or the desired thiophosphorus acid **18**, depending on the nucleophilicity of the base. With sodium hydride, **18** was obtained stereospecifically. The evaluation of Brønsted chiral phosphorus acid (CPA)[2] **18** as a Brønsted organocatalyst will be reported at a later time.

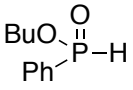
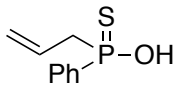
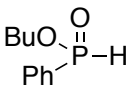
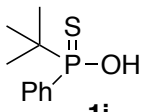
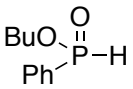
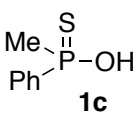
Scheme 6. Synthesis of 8-Phenyl-DOPO Chiral Acid Derivative.

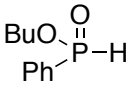
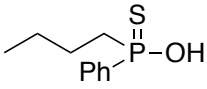
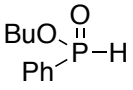
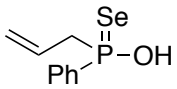
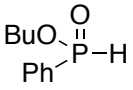
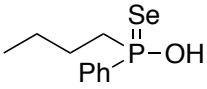
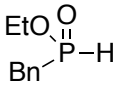
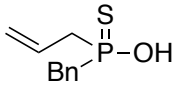


Because our laboratory has been a major contributor in the chemistry of *H*-phosphinates **19**,[25] one last approach (Table 1, entry 6) was examined. The displacement of *H*-phosphinates with organometallics (RLi, RMgX) is well known to deliver the corresponding secondary phosphine oxide.[26] Surprisingly, only one example of functional group interconversion from $R^1P(O)(OR)H$ to $R^1R^2P(S)OH$ could be found in the literature as a two-step process via the isolated secondary phosphine oxide $R^1R^2P(O)H$ intermediate.[8] Because the nucleophilic substitution of a *H*-phosphinate should form R^1R^2POM as the intermediate, quenching with elemental sulfur (or selenium) would deliver the thiophosphorus acid **1** (or selenophosphorus acid **20**) directly, in a one-pot transformation. Indeed, this transformation does occur and the preliminary results are summarized in Table 3.

Table 3. Preparation of Thiophosphinic Acids and Related Compounds via Nucleophilic Substitution of *H*-Phosphinates with Organometallics, Followed by Trapping with Elemental Sulfur or Selenium



Entry	Substrate	Organometallics (equiv)	Trapping (equiv)	Product	Yield (%)[a]
1a	 **19a**	H_2C=$CHCH_2MgBr$ (2.4)	S_8 (3/8)	 **1i**	100 (57)
1b		H_2C=$CHCH_2MgBr$ (3.5)	S_8 (5/8)		83 (67)
1c	 **19a**	*t*-BuMgCl (5)	S_8 (5/8)	 **1j**	37 (-)[b]
1d	 **19a**	MeLi (2.5)	S_8 (3/8)	 **1c**	100 (91)

1e	 **19a**	*n*-BuLi (2.5)	S_8 (3/8)	 **1k**	100 (80)
2a	 **19a**	H_2C=$CHCH_2MgBr$ (3.5)	Se (5)	 **20a**	94 (65)
2b	 **19a**	*n*-BuLi (2.5)	Se (3)	 **20b**	100 (72)
3	 **19b**	H_2C=$CHCH_2MgBr$ (3.5)	S_8 (5/8)	 **1l**	97 (62)

[a] Determined by ^{31}P-NMR. In parentheses: yield of product (> 95% purity) after extractive work-up. [b] Complex mixture of products; not isolated.

In most instances, the product can be obtained in good purity (> 95%) by a simple extractive work-up. However, with *t*-BuMgCl (Table 3, entry 1c) a significant amount of unreacted *H*-phosphinate **19a** is converted into the thiophosphonic acid $R^1P(S)(OR)OH$, which prevents purification. In this case, a two-step process via the secondary phosphine oxide would then be better (Table 1, entry 2). The organolithium organometallics are superior to the Grignard reagents (Table 3, entries 1d-e versus 1a-c). Trapping of the phosphinite anion with elemental selenium was also successful (Table 3, entries 2a-b). Ethyl benzyl-*H*-phosphinate and butyl phenyl-*H*-phosphinate worked equally well (Table 3, entry 3 versus 1b).

Because phosphinates $R^1R^2P(O)(OR)$ are typically derived from *H*-phosphinates $R^1P(O)(OR)H$, this transformation could well be the most efficient approach to thiophosphinic acids $R^1R^2P(S)(OH)$. In terms of fulfilling our requirement for odorless conditions, this one-pot two-step reaction, is much better than the multiple pot four-step reaction via the phosphorus amide ($R^1P(O)(OR)H \rightarrow R^1R^2P(O)(OR)/R^1R^2P(O)(OH) \rightarrow R^1R^2P(O)Cl \rightarrow R^1R^2P(O)NHR \rightarrow$

$R^1R^2P(S)OH$). One drawback (unless the *H*-phosphinate ester is chiral) is that the racemic thiophosphinic acid will need to be resolved via a diastereoisomeric salt. Regardless, we intend to explore more fully the optimization, scope, and limitations of this strategy in a forthcoming study.

Conclusion

The odorless preparation of thiophosphinic acids and derivatives was investigated. The Stec reaction of phosphorus amides P(O)NHR was identified as an odorless solution to foul-smelling conditions (Lawesson's reagent and related). Stec and others have investigated the transformation of phosphorus amides into thiophosphorus acids ($R^1R^2P(O)NHR$ to $R^1R^2P(S)OH$ and this solves a number of issues. In this report, we confirm the superiority of the Stec reaction over Lawesson's reagent and related approaches. The application of compound **18** in asymmetric organocatalysis will be reported in due course. We also provide an alternative based on the displacement of *H*-phosphinate esters with organometallics, followed by trapping of the intermediate with elemental sulfur or selenium. In the final analysis, the latter strategy seems the most efficient. Therefore, this promising method will be explored in more detail at a later time. Notably and in most cases, the two methods (Stec reaction or displacement of *H*-phosphinates) that were utilized during this study deliver products in excellent purity without chromatographic purification, through a straightforward extractive work-up. We expect this work will be useful to others who may be interested in developing alternatives to the currently widely used C2-symmetrical chiral phosphorus acids organocatalysts.

Experimental Section

General Chemistry:

^{1}H NMR spectra were recorded on a 400-MHz Bruker Avance spectrometer. Chemical shifts for ^{1}H NMR spectra (in parts per million) relative to internal tetramethylsilane (Me_4Si, δ = 0.00 ppm) with deuterated chloroform. $^{13}C\{^{1}H\}$ NMR spectra were recorded at 101 MHz. Chemical shifts for $^{13}C\{^{1}H\}$ NMR spectra are reported (in parts per million) relative to $CDCl_3$ (δ = 77.0 ppm). ^{31}P NMR spectra were recorded at 162 MHz, and chemical shifts reported (in parts per million) relative to external 85% phosphoric acid (δ = 0.0 ppm). Flash chromatography experiments were carried out on Silica Gel premium Rf grade (40−75 μm). Ethyl acetate/hexane or ethyl acetate/methanol mixtures were used as the eluent for chromatographic purifications. TLC plates were visualized by UV or immersion in permanganate potassium (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% aq. NaOH and 300 mL of water) followed by heating. Enantiomeric excess was determined by Chiral HPLC analysis on an (S,S)-Whelk-O1 column in comparison to authentic racemates. Chiral HPLC analyses were recorded on the Agilent 1100 Series HPLC system. High resolution mass spectra (HRMS) were obtained by electrospray ionization using a TOF analyzer.

Reagent and solvents:

All starting materials were purchased from commercial sources and used as received, unless otherwise noted. Anhydrous THF and DMF were purchased and used as received. The solvents were distilled under N_2 and dried according to standard procedures (CH_3CN, toluene and dichloromethane from CaH_2).

*Methyl-phenylphosphinic acid **2**.*[27] To a solution of phenyl phosphinic acid (10.0 g, 70.38 mmol, 1.0 equiv) in DCM (140 mL) was added bis(trimethylsilyl)acetamide (37.86 mL, 154.83 mmol, 2.2 equiv) at 0 °C under argon. The reaction mixture stirred for 30 min and iodomethane (5.26 mL, 84.45 mmol, 1.2 equiv) was added at 0 °C and stirred overnight. The reaction mixture was quenched with methanol and concentrated under vacuum. Ethyl acetate was added and washed with a saturated aqueous solution of $NaHCO_3$. The two layers were separated the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford acid as a white solid **2** (7.3 g, 66%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.3 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84 (s, 1H), 7.77 (ddd, *J* = 12.4, 8.3, 1.4 Hz, 2H), 7.51 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.44 (ddd, *J* = 7.6, 3.4, 1.1 Hz, 2H), 1.63 (d, *J* = 14.7 Hz, 3H).

*Methyl-phenylphosphinothioic acid via TmobSH **1c**.* To a solution of **2** (0.1 g, 0.64 mmol, 1.0 equiv) in DCM (2 mL) was added dropwise oxalyl chloride (0.07 mL, 0.77 mmol, 1.2 equiv) at 0 °C under argon. The reaction mixture stirred for 3 h rt, then 2,4,6-trimethoxybenzyl thiol[14a] (0.14 g, 0.64 mmol, 1.0 equiv) dissolved in DCM (2 mL) was added at rt and stirred overnight. The crude mixture was then washed with 1 M HCl. The two layers were separated, the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. This product was used directly in the next step without further purification.

Trifluoroacetic acid (0.3 mL, 3.9 mmol, 6 equiv) was added to a mixture of the phosphothioester (0.22 g, 0.64 mmol, 1 equiv) and thiourea (97 mg, 1.28 mmol, 2 equiv) in toluene (1.5 mL). The mixture stirred for 6 h at rt under argon. The reaction mixture was concentrated under vacuum and the crude was dissolved in ethyl acetate. The organic layer was

washed with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to afford crude **1c** as a colorless oil**.** (NMR Yield: 87%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 77.28 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.90 (ddd, *J* = 13.7, 8.3, 1.4 Hz, 2H), 7.53 – 7.49 (m, 1H), 7.49 – 7.33 (m, 2H), 2.00 (d, *J* = 13.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 135.2 (d, *J* = 104.6 Hz), 132.1 (d, *J* = 3.0 Hz), 130.3 (d, *J* = 11.8 Hz), 128.5 (d, *J* = 13.2 Hz), 25.1 (d, *J* = 78.4 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for C_7H_9OPS 173.0184; Found 173.0185.

*Diethyl-phosphorothioic acid via TmobSH **1d**.*[28] To a solution of 2,4,6-trimethoxybenzyl thiol (1.86 g, 8.7 mmol, 3.0 equiv) in THF (20 mL) was added NaH (60 % dispersion in mineral oil, 0.34 g, 8.7 mmol, 3.0 equiv) at 0 °C, under argon. After 10 min, diethyl chlorophosphate (0.5 g, 2.89 mmol, 1 equiv) was added dropwise and the reaction stirred overnight at rt. Ethyl acetate was then added and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to afford crude **1d** as a light yellow oil. (NMR Yield: 76%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 64.5 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 4.13 (m, *J* = 9.3, 7.0 Hz, 4H), 1.32 (t, *J* = 7.1 Hz, 6H).

*Dodecyl-methylphenylphosphinothioate **4**.* To **2** (3.0 g, 19.2 mmol, 1.0 equiv) in DCM (100 mL) was added dropwise oxalyl chloride (2.0 mL, 23.0 mmol, 1.2 equiv) at 0 °C under argon. The reaction mixture stirred for 3 h rt, then directly added at 0 °C to a solution of 1-

dodecanethiol (9.2 mL, 38.4 mmol, 2.0 equiv) and NaH (60 % dispersion in mineral oil, 1.9 g, 48.0 mmol, 2.5 equiv) that had previously been stirring for 1 h. The reaction mixture stirred overnight at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by column chromatography (hexanes/ethyl acetate 50:50) to afford pure **4** as a white solid (4.8 g, 78%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.4 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.78 (m, 2H), 7.62 – 7.45 (m, 3H), 2.87 – 2.74 (m, 1H), 2.73 – 2.60 (m, 1H), 1.97 (d, J = 13.3 Hz, 3H), 1.65 – 1.50 (m, 2H), 1.36 – 1.13 (m, 18H), 0.89 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 134.4 (d, J = 103.2 Hz), 132.1 (d, J = 3.2 Hz), 130.8 (d, J = 10.4 Hz), 128.7 (d, J = 13.0 Hz), 31.9, 30.6 (d, J = 4.7 Hz), 29.6, 29.5, 29.4, 29.3, 28.9, 28.7 (d, J = 2.6 Hz), 28.5, 22.7, 21.2, 20.5, 14.1; HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{33}SOP$ 341.2062; Found 341.2056.

Dodecyl-diethylphosphorothioate ***6***.[29] To a solution of 1-dodecanethiol (5.5 mL, 23.18 mmol, 1.0 equiv) in THF (100 mL) was added at 0 °C NaH (60 % dispersion in mineral oil, 1.4 g, 34.77 mmol, 1.5 equiv) and stirred under argon for 1 h at rt, then diethyl chlorophosphate (3.36 mL, 23.18 mmol, 1.0 equiv) was added dropwise at rt, and stirred for 1 h. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by column chromatography (hexanes/ethyl acetate 70:30) to afford pure **6** as a colorless oil (5.5 g, 70%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.3 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 – 3.94 (m, 4H), 2.78 (dt, J = 14.4, 7.4 Hz, 2H), 1.64 (p, J = 7.4 Hz, 2H), 1.32 (m, J = 7.1, 0.8 Hz, 8H), 1.21 (m, 16H), 0.93 – 0.76 (t, 3H).

General Procedure for the NaNp and LiDBB Reduction of Thioesters. LiDBB[30] and NaNp[31] were prepared according to the literature. To a solution of the appropriate thioester, **4** or **6**, **(**1 equiv) in THF (0.1 M) was added dropwise to a freshly prepared 1M solution of LiDBB or NaNp in THF (2 – 4 equiv), at -78 °C (LiDBB) or rt (NaNp) under argon. The reaction stirred at rt for the appropriate time (3 – 16 h). Ethyl acetate was added, and the mixture was washed with 3 M HCl. The two layers were separated, and the organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum.

*Methyl-phenylphosphinothioic acid via NaNp **1c**.* Following the general procedure: To a solution of **4** (0.40 g, 1.17 mmol, 1.0 equiv) in THF (10 mL) was added dropwise NaNp (1 M in THF, 2.34 mL, 2.34 mmol, 2.0 equiv) at rt, and stirred for 3 h at rt to afford **1c** as a colorless oil (NMR Yield: 89%). ^{31}P NMR (162 MHz, DMSO-d_6) δ 75.9 (s).

*Methyl-phenylphosphine oxide via NaNp **5**.*[32] Following the general procedure: To a solution of **4** (0.40 g, 1.17 mmol, 1.0 equiv) in THF (10 mL) was added dropwise NaNp (1 M in THF, 4.7 mL, 4.7 mmol, 4.0 equiv) at rt, and stirred for 3 h at rt to afford **5** and **4** as a colorless oil (NMR Yield: 56% and 42% respectively). ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.3 (s), 23.0 (d, J = 485.4 Hz).

*Methyl-phenylphosphinothioic acid via LiDBB **1c**.* Following the general procedure: To a solution of **4** (0.20 g, 0.58 mmol, 1.0 equiv) in THF (10 mL) was added dropwise LiDBB (1 M in THF, 1.16 mL, 1.16 mmol, 4.0 equiv) at -78 °C, and stirred for 16 h at rt to afford **1c** and **4** as

a colorless oil (NMR Yield: 51% and 34% respectively). ^{31}P NMR (162 MHz, $CDCl_3$) δ 77.0 (s), 40.4 (s).

Methyl-phenylphosphine oxide via LiDBB ***5***.[32] Following the general procedure: To a solution of **4** (0.23 g, 0.7 mmol, 1.0 equiv) in THF (10 mL) was added dropwise LiDBB (1 M in THF, 2.8 mL, 2.8 mmol, 4.0 equiv) at -78 °C, and stirred for 16 h at rt to afford **5** as a colorless oil (NMR Yield: 100%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.2 (d, J = 488.1 Hz).

Diethyl-phosphinothioic acid via NaNp ***1d***.[28] Following the general procedure: To a solution of **6** (0.40 g, 1.18 mmol, 1.0 equiv) in THF (10 mL) was added dropwise NaNp (1 M in THF, 2.36 mL, 2.36 mmol, 2.0 equiv) at rt, and stirred for 3 h at rt to afford **1d** as a light yellow oil (NMR Yield: 87%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 65.5 (s).

General Procedure for the chlorination of $R^1R^2P(O)OR^3$ and amination of $R^1R^2P(O)Cl$. The appropriate phosphonate or phosphinate (1.0 equiv) in DCM (0.1 - 0.4 M) was added oxalyl chloride (1.2 - 2.0 equiv) and DMF (10 mol %) dropwise under argon. The reaction mixture was brought to reflux and stirred for the appropriate time (24 - 48 h). The crude product was concentrated under vacuum to remove all volatiles and used directly in the next step.

To a solution of DIPEA (1.2 equiv), amine (1.2 equiv) in DCM (0.5 M) was added at 0 °C the appropriate chlorophosphinate or chlorophosphonate (1.0 equiv) dropwise under argon. The reaction mixture was brought to room temperature and stirred overnight. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the

organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to afford the pure product either without further purification or after column chromatography.

Diethyl-N-isopropylphosphoramidate ***8a***.[33] Following the general procedure: $(EtO)_2P(O)Cl$ (1.47 mL, 10.0 mmol, 1.0 equiv) was reacted with isopropylamine (1.03 mL, 12.0 mmol, 1.2 equiv) and DIPEA (2.09 mL, 12.0 mmol, 1.2 equiv) in DCM (20 mL) to afford **8a** as an orange oil (1.6g, 98%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 8.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 – 3.70 (m, 4H), 3.19 (m, *J* = 9.4, 8.0, 6.4 Hz, 1H), 2.84 (t, *J* = 10.1 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 6H), 1.02 (d, *J* = 6.5 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 61.8 (d, *J* = 5.4 Hz), 43.6, 25.1 (d, *J* = 5.7 Hz), 16.1 (d, *J* = 7.3 Hz).

Diethyl-N-butylphosphoramidate ***8b***.[34] Following the general procedure: $(EtO)_2P(O)Cl$ (1.47 mL, 10.0 mmol, 1.0 equiv) was reacted with *n*-butylamine (1.19 mL, 12.0 mmol, 1.2 equiv) and DIPEA (2.09 mL, 12.0 mmol, 1.2 equiv) in DCM (20 mL) to afford **8b** as an orange oil (1.8g, 86%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 9.3 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 – 3.81 (m, 4H), 2.96 – 2.77 (m, 3H), 1.49 – 1.38 (m,2H), 1.33 (d, *J* = 22.5 Hz, 2H), 1.28 (td, *J* = 7.1, 0.8 Hz, 6H), 0.87 (t, *J* = 7.3 Hz, 3H).

Diethyl-N-phenylphosphoramidate ***8c***.[35] Following the general procedure: $(EtO)_2P(O)Cl$ (1.47 mL, 10.0 mmol, 1.0 equiv) was reacted with aniline (1.09 mL, 12.0 mmol, 1.2 equiv) and DIPEA (2.09 mL, 12.0 mmol, 1.2 equiv) in DCM (20 mL) to afford **8c** as an orange oil (1.7g, 74%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 2.5 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.18 (m,

2H), 7.10 – 7.02 (m, 2H), 6.97 (m, *J* = 7.4, 1.1 Hz, 1H), 6.66 (d, *J* = 9.5 Hz, 1H), 4.41 – 3.96 (m, 4H), 1.33 (td, *J* = 7.1, 0.9 Hz, 6H).

Diethyl-N-((S)-1-phenylethyl)phosphoramidate ***8d***.[36] Following the general procedure: $(EtO)_2P(O)Cl$ (1.47 mL, 10.0 mmol, 1.0 equiv) was reacted with *(S)*-1-phenylethylamine (1.55 mL, 12.0 mmol, 1.2 equiv) and DIPEA (2.09 mL, 12.0 mmol, 1.2 equiv) in DCM (20 mL) to afford **8d** as an orange oil (1.7g, 62%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.5 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 2zH), 7.33 – 7.31 (m, 2H), 7.28 – 7.21 (m, 1H), 4.32 (ddd, *J* = 9.2, 8.5, 6.8 Hz, 1H), 4.12 – 4.01 (m, 2H), 3.97 – 3.83 (m, 1H), 3.72 (dt, *J* = 10.0, 7.2 Hz, 1H), 3.34 (t, *J* = 10.1 Hz, 1H), 1.48 (dd, *J* = 6.8, 1.0 Hz, 3H), 1.32 (td, *J* = 7.0, 0.8 Hz, 3H), 1.11 (td, *J* = 7.1, 0.9 Hz, 3H).

1-N-((S)-1-phenylethyl)-2,3-diphenyl-1-phosphindole ***8e***. Following the general procedure: 1-butyl-2,3-diphenyl-1-phosphindole[37] (8.5 g, 22.70 mmol, 1 equiv) in DCM (200 mL) was added oxalyl chloride (3.96 mL, 45.40 mmol, 2.0 equiv) and DMF (0.17 mL, 2.27 mmol, 10 mol %). The mixture was stirred 24 h at reflux. The crude obtained was solubilized in DCM (20 mL) and reacted with DIPEA (4.74 mL, 27.24 mmol, 1.2 equiv), *(S)*-1-phenylethylamine (3.51 mL, 27.24 mmol, 1.2 equiv), DMAP (0.28 g, 2.27 mmol, 10 mol %) in DCM (45 mL) to afford **8e** as an orange oil (6.7g, 71%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.38 (s), 40.34 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (ddd, *J* = 10.2, 6.9, 1.5 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.39 – 7.35 (m, 4H), 7.21 – 7.05 (m, 11H), 7.04 – 6.95 (m, 2H), 4.30 – 4.07 (m, 1H), 3.22 – 3.05 (m, 1H), 1.35 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 148.2 (dd, *J* = 75.7, 25.6 Hz), 144.5 (d, *J* = 3.6 Hz), 144.4 (d, *J* = 2.6 Hz), 142.4 (dd, *J* = 58.0,

31.9 Hz), 134.3 (dd, *J* = 16.9, 5.0 Hz), 133.1 (m), 132.6 (m), 129.1 (m), 128.8 (d, *J* = 12.2 Hz), 128.6, 128.5, 128.4, 128.3, 128.2, 128.1 (d, *J* = 2.6 Hz), 128.1 (d, *J* = 19.7 Hz), 127.6 (d, *J* = 21.9 Hz), 127.0 (d, *J* = 12.1 Hz), 125.8 (d, *J* = 17.7 Hz), 123.5 (dd, *J* = 18.4, 12.5 Hz), 51.0 (d, *J* = 25.2 Hz), 25.6 (d, *J* = 7.2 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{24}NOP$ 422.1668; Found 422.1660.

Ethyl-phenyl-N-phenylphosphoramidate ***8f***.[38] Following the general procedure: diethyl phenylphosphonate (1.91 mL, 10.0 mmol, 1.0 equiv) in DCM (25 mL) was added oxalyl chloride (1.04 mL, 12.0 mmol, 1.2 equiv) and DMF (0.08 mL, 1.0 mmol, 10 mol %). The mixture was stirred 48 h at reflux. After cooling down the reaction to rt, the reaction mixture was added directly at 0 °C to the aniline (9.11 mL, 100 mmol, 10.0 equiv) and was stirred for 5 h at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was crystalized in a mixture of ethyl acetate and hexanes to afford **8f** as a brown solid (1.8 g, 70%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.5 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.81 (m, 2H), 7.50 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.43 (m, *J* = 7.8, 3.8 Hz, 2H), 7.15 (m, *J* = 7.7 Hz, 2H), 7.01 – 6.94 (m, 2H), 6.89 (d, *J* = 7.4 Hz, 1H), 4.41 – 4.29 (m, 1H), 4.26 – 4.09 (m, 1H), 1.41 (t, *J* = 7.1 Hz, 3H).

Allyl-O-ethyl-N-phenylphosphoramidate ***8g.*** Under neat conditions allyl bromide (0.87 mL, 10.0 mmol, 1.0 equiv) and triethyl phosphite (1.71 mL, 10.0 mmol, 1.0 equiv) were brought to reflux for 24 h under argon. After concentration under vacuum, following general procedure, the crude product was solubilized in DCM (25 mL) and oxalyl chloride (1.05 mL, 12.0 mmol,

1.2 equiv) and DMF (0.08 mL, 1.0 mmol, 10 mol %) were added and stirred at reflux for 24 h. After cooling down the reaction to rt, the reaction mixture was added directly at 0 °C to the aniline (9.11 mL, 100 mmol, 10.0 equiv) and was stirred for 5 h at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (ethyl acetate 100%) to afford **8g** as a brown oil (1.6 g, 88%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.9 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 8.5, 7.2 Hz, 2H), 7.09 – 7.02 (m, 3H), 6.98 – 6.86 (m, 1H), 5.91 – 5.69 (m, 1H), 5.19 – 5.00 (m, 2H), 4.23 mt, *J* = 10.2, 7.2 Hz, 1H), 4.06 (m, *J* = 10.2, 7.8, 7.0 Hz, 1H), 2.85 – 2.67 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 140.6, 129.4, 127.1 (d, *J* = 10.4 Hz), 121.2, 120.3 (d, *J* = 14.2 Hz), 117.3 (d, *J* = 6.3 Hz), 60.3 (d, *J* = 7.2 Hz), 31.7 (d, *J* = 127.1 Hz), 16.2 (d, *J* = 6.9 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{16}NO_2P$ 226.0991; Found 226.0991.

Methyl-N,P-diphenylphosphinic amide ***8h***.[39] Following the general procedure: To **2** (7.3 g, 46.75 mmol, 1.0 equiv) in DCM (125 mL) was added dropwise oxalyl chloride (5.4 mL, 62.52 mmol, 1.2 equiv) at 0 °C under argon. The reaction mixture stirred overnight at rt, then was added directly at 0 °C to the aniline (42.6 mL, 467.5 mmol, 10.0 equiv) and was stirred for 5 h at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (ethyl acetate 100%) to afford **8h** as a brown solid (9.2 g, 85%). ^{31}P NMR (162 MHz, DMSO-d_6) δ 23.9 (s); ^1H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, *J* = 11.8 Hz, 1H), 7.79 – 7.71 (m, 2H), 7.49 (m, *J*

= 7.6, 7.2, 3.9 Hz, 3H), 7.08 (dd, *J* = 8.5, 7.3 Hz, 2H), 7.03 – 6.86 (m, 2H), 6.80 – 6.59 (m, 1H), 1.70 (d, *J* = 14.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 142.8, 134.8 (d, *J* = 120.1 Hz), 131.9 (d, *J* = 2.7 Hz), 131.6 (d, *J* = 10.1 Hz), 129.3, 129.0 (d, *J* = 12.3 Hz), 120.6, 117.8 (d, *J* = 6.8 Hz), 17.7 (d, *J* = 91.7 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{14}NOP$ 232.0886; Found 232.0891.

(S_p)-N-((S)-1-phenylethyl)(benzoxymethyl)phenylphosphinic amide ***8i***. To a solution of *(S)*-1-phenylethylamine (0.48 mL, 3.74 mmol, 3.0 equiv) in THF (6 mL) at -78 °C was added dropwise *n*-BuLi (2.5 M in Hexanes, 1.30 mL, 3.25 mmol, 2.6 equiv) and stirred for 1 h under argon. *(Sp)*-menthyl(benzoxymethyl)phenylphosphinate[19a] **12** (0.5 g, 1.25 mmol, 1.0 equiv), in THF (4 mL) at -78 °C was added dropwise to the reaction mixture and stirred for 3 h at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (ethyl acetate/methanol 100:0 – 90:10) to afford **8i** as a white solid (300 mg, 66%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.3 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 11.7, 8.2, 1.4 Hz, 2H), 7.57 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.45 – 7.40 (m, 2H), 7.36 – 7.26 (m, 6H), 7.20 – 7.14 (m, 2H), 4.59 (td, *J* = 8.7, 6.7 Hz, 1H), 4.42 (s, 2H), 3.80 – 3.73 (m, 2H), 3.32 (t, *J* = 8.6 Hz, 1H), 1.49 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 145.2 (d, *J* = 4.2 Hz), 137.1, 132.3 (d, *J* = 2.9 Hz), 132.1 (d, *J* = 9.5 Hz), 132.1, 130.9, 128.5 (d, *J* = 12.5 Hz), 128.4 (d, *J* = 12.4 Hz), 127.9, 127.9, 127.2, 126.2, 75.1 (d, *J* = 12.9 Hz), 67.1 (d, *J* = 110.0 Hz), 50.1 (d, *J* = 1.4 Hz), 25.6 (d, *J* = 5.0 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{24}NO_2P$ 366.1617; Found 366.1631.

General Procedure of Stec Reaction with Conditions A. To the appropriate phosphoramidate or phosphinic amide (1 equiv) in THF (0.1 M) was added NaH (60 % dispersion in mineral oil, 3.0 equiv) at 0 °C under argon. The reaction mixture stirred at rt for 1 h. Carbon disulfide (3.0 equiv) was then added dropwise and stirred for 2 h at rt. Ethyl acetate was then added and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to afford the pure product either without further purification.

General Procedure of Stec Reaction with Conditions B. To the appropriate phosphoramidate or phosphinic amide (1 equiv) in THF (0.1 M) was added *n*-BuLi (2.5 M in Hexanes in mineral oil, 2.0 equiv) at -78 °C under argon. The reaction mixture stirred at rt for 1 h. Carbon disulfide (3.0 equiv) was then added dropwise and stirred for 2 h at rt. The workup and purification followed the same procedure as in the general procedure with conditions A.

General Procedure of Stec Reaction with Conditions C. To the appropriate phosphoramidate or phosphinic amide (1 equiv) in THF (0.1 M) was added lithium bis(trimethylsilyl)amide (1.25 M in toluene, 1.5 equiv) at 0 °C under argon. The reaction mixture stirred at rt for 1 h. Carbon disulfide (3.0 equiv) was then added dropwise and stirred for 2 h at rt. The workup and purification followed the same procedure as in the general procedure with conditions A.

General Procedure of Stec Reaction with Conditions D. To the appropriate phosphoramidate or phosphinic amide (1 equiv) in THF (0.1 M) was added lithium bis(trimethylsilyl)amide (1.25 M in toluene, 1.5 equiv) at 0 °C under argon. The reaction mixture stirred at rt for 1 h. Carbon disulfide (5.0 equiv) was then added dropwise and stirred overnight at rt. The workup and purification followed the same procedure as in the general procedure with conditions A.

General Procedure of Stec Reaction with Conditions E. To the appropriate phosphoramidate or phosphinic amide (1 equiv) in THF (0.1 M) was added NaH (60 % dispersion in mineral oil, 2.0 equiv) at 0 °C under argon. The reaction mixture stirred at rt for 1 h. Carbon disulfide (5.0 equiv) was then added dropwise and stirred overnight at rt. The workup and purification followed the same procedure as in the general procedure with conditions A.

*Diethyl-phosphorothioic acid **1d** (Table 2, Entry 1a).*[28] Following general procedure A: **8a** (0.19 g, 1.0 mmol, 1.0 equiv) was reacted with NaH (60 % dispersion in mineral oil, 3.0 mmol, 3.0 equiv) in THF (10 mL). Carbon disulfide (0.18 mL, 3.0 mmol, 3.0 equiv) was added to afford **1d** as a light yellow oil. (0.15 g, 88%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 65.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 4.13 (m, J = 9.3, 7.0 Hz, 4H), 1.32 (t, J = 7.1 Hz, 6H).

*Diethyl-phosphorothioic acid **1d** (Table 2, Entry 2b).*[28] Following general procedure B: **8b** (0.21 g, 1.0 mmol, 1.0 equiv) was reacted with *n*-BuLi (0.8 mL, 2.5 M in Hexanes, 2.0 mmol, 2.0 equiv) in THF (10 mL). Carbon disulfide (0.18 mL, 3.0 mmol, 3.0 equiv) was added to afford **1d** as a light yellow oil (0.16 g, 95%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 65.4 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 4.13 (m, J = 9.3, 7.0 Hz, 4H), 1.32 (t, J = 7.1 Hz, 6H).

*Diethyl-phosphorothioic acid **1d** (Table 2, Entry 3b).*[28] Following general procedure B: **8c** (0.23 g, 1.0 mmol, 1.0 equiv) was reacted with *n*-BuLi (0.8 mL, 2.5 M in Hexanes, 2.0 mmol, 2.0 equiv) in THF (10 mL). Carbon disulfide (0.18 mL, 3.0 mmol, 3.0 equiv) was added and stirred overnight to afford **1d** as a light yellow oil (0.17 g, 99%). ^{31}P NMR (162 MHz, $CDCl_3$) δ

65.4 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 4.13 (m, *J* = 9.3, 7.0 Hz, 4H), 1.32 (t, *J* = 7.1 Hz, 6H).

*Diethyl-phosphorothioic acid **1d** (Table 2, Entry 4b).*[28] Following general procedure B: **8d** (0.26 g, 1.0 mmol, 1.0 equiv) was reacted with *n*-BuLi (0.8 mL, 2.5 M in Hexanes, 2.0 mmol, 2.0 equiv) in THF (10 mL). Carbon disulfide (0.18 mL, 3.0 mmol, 3.0 equiv) was added and stirred overnight to afford **1d** as a light yellow oil (0.13 g, 75%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 65.4 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 4.13 (m, *J* = 9.3, 7.0 Hz, 4H), 1.32 (t, *J* = 7.1 Hz, 6H).

*2,3-diphenyl-1-phosphindole-1-thioic acid **1e** (Table 2, Entry 5).* Following general procedure B: **8e** (0.27 g, 1.0 mmol, 1.0 equiv) was reacted with *n*-BuLi (0.51 mL, 2.5 M in Hexanes, 2.0 mmol, 2.0 equiv) in THF (7 mL). Carbon disulfide (0.12 mL, 3.0 mmol, 3.0 equiv) was added to afford **1e** as a light yellow solid (0.50 g, 85%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 80.8 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 1H), 7.46 (ddt, *J* = 6.5, 3.1, 1.8 Hz, 4H), 7.42 – 7.36 (m, 3H), 7.34 – 7.29 (m, 2H), 7.25 (dq, *J* = 4.9, 1.9, 1.4 Hz, 3H), 7.23 – 7.16 (m, 1H), 6.28 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 147.7 (d, *J* = 25.6 Hz), 141.3 (d, *J* = 31.2 Hz), 133.6 (d, *J* = 17.0 Hz), 133.3 (d, *J* = 6.9 Hz), 132.8 (d, *J* = 1.8 Hz), 132.1 (m), 129.7, 129.6, 129.4 (d, *J* = 11.9 Hz), 129.3, 128.7, 128.7, 128.3, 128.1 (d, *J* = 1.5 Hz), 127.7 (d, *J* = 10.8 Hz), 123.9 (d, *J* = 12.4 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{15}OPS$ 335.0654; Found 335.0648.

*Ethyl-phenylphosphorothioic acid **1f** (Table 2, Entry 6).*[40] Following general procedure B: **8f** (0.39 g, 1.0 mmol, 1.0 equiv) was reacted with *n*-BuLi (1.2mL, 2.5 M in Hexanes, 2.0 mmol, 2.0 equiv) in THF (10 mL). Carbon disulfide (0.27 mL, 3.0 mmol, 3.0 equiv) was added to afford **1f** as a light orange oil (0.24 g, 79%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 79.1 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.06 – 7.84 (m, 2H), 7.53 (m, *J* = 7.2, 1.6 Hz, 1H), 7.45 (m, *J* = 7.0, 2.3 Hz, 2H), 4.19 (m, *J* = 9.5, 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

*Allyl-ethylphosphorothioic acid **1g** (Table 2, Entry 7).* Following general procedure D: **8g** (0.39 g, 1.5 mmol, 1.0 equiv) was reacted with lithium bis(trimethylsilyl)amide (1.87 mL, 1.25 M in toluene, 1.875 mmol, 1.25 equiv) in THF (10 mL). Carbon disulfide (0.45 mL, 7.5 mmol, 5.0 equiv) was added to afford **1g** as a red oil (0.19 g, 76%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 87.0 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 5.81 (m, *J* = 17.0, 8.0 Hz, 1H), 5.28 – 4.99 (m, 2H), 4.16 (m, *J* = 8.0 Hz, 2H), 2.86 (dd, *J* = 19.7, 7.4 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 127.1 (d, *J* = 10.6 Hz), 120.8 (d, *J* = 15.4 Hz), 62.5 (d, *J* = 7.3 Hz), 40.4 (d, *J* = 108.6 Hz), 16.0 (d, *J* = 7.3 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_5H_{11}O_2PS$ 167.0290; Found 167.0290.

*Methyl-phenylphosphinothioic acid **1c** (Table 2, Entry 8b).* Following general procedure D: **8h** (0.35 g, 1.5 mmol, 1.0 equiv) was reacted with lithium bis(trimethylsilyl)amide (1.87 mL, 1.25 M in toluene, 1.875 mmol, 1.25 equiv) in THF (10 mL). Carbon disulfide (0.45 mL, 7.5 mmol, 5.0 equiv) was added and stirred overnight to afford **1c** as a colorless oil (0.22 g, 85%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 81.2 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.94 – 7.83

(m, 2H), 7.53 – 7.48 (m, 1H), 7.47 – 7.40 (m, 2H), 2.00 (d, J = 13.7 Hz, 3H); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for C_7H_9OPS 173.0184; Found 173.0185.

*(S_p)-(benzoxymethyl)phenylphosphinothioic acid **1h** (Table 2, Entry 9).* Following general procedure E: **8i** (0.3 g, 0.82 mmol, 1.0 equiv) was reacted with NaH (65 mg, 60 % dispersion in mineral oil, 1.64 mmol, 2.0 equiv) in THF (5 mL). Carbon disulfide (0.49 mL, 8.2 mmol, 10.0 equiv) was added to afford **1h** as a light yellow oil (0.21 g, 72%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 77.6 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, J = 13.1, 7.6 Hz, 2H), 7.74 – 7.60 (s, 1H), 7.56 (m, J = 7.5 Hz, 1H), 7.47 (m, J = 7.6, 3.8 Hz, 2H), 7.37 – 7.26 (m, 3H), 7.22 – 7.13 (m, 2H), 4.79 – 4.44 (m, 2H), 4.27 – 3.89 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.6, 132.4 (d, J = 2.6 Hz), 131.6 (d, J = 11.2 Hz), 128.5, 128.5, 128.4, 128.1, 128.1, 75.0 (d, J = 9.1 Hz), 72.9 (d, J = 90.5 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{15}O_2PS$ 279.0603; Found 279.0606.

*n-Butyl-methylphenylphosphinate **13**.*[41] To a solution of **2** (2.5 g, 16.01 mmol, 1.0 equiv) in DCM (100 mL) was added dropwise oxalyl chloride (1.68 mL, 19.22 mmol, 1.2 equiv) at 0 °C under argon. The reaction mixture stirred for 3 h rt, then was added directly at 0 °C to a mixture of butanol (1.76 mL, 19.22 mmol, 1.2 equiv) and Et_3N (2.68 mL, 19.22 mmol, 1.2 equiv) and was stirred overnight at rt. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to afford **13** as a colorless oil (2.1 g, 77%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.5 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, J = 12.0, 8.2, 1.5 Hz, 2H), 7.41 (dd, J = 7.4, 1.5 Hz, 1H), 7.38 – 7.32 (m, 2H), 3.87 (dd, J = 10.0, 6.8 Hz, 1H),

3.61 (dd, J = 10.0, 6.9 Hz, 1H), 1.53 (d, J = 14.6 Hz, 3H), 1.50 – 1.41 (m, 2H), 1.33 – 1.16 (m, 2H), 0.75 (t, J = 7.4 Hz, 3H).

*Methyl-phenylphosphinothioic acid **1c** via one-pot transamidation and CS_2 (Scheme 5, Entry d).* To a solution of aniline (0.27 mL, 3.0 mmol, 3.0 equiv) in THF (10 mL) was added lithium bis(trimethylsilyl)amide (1.25 M in toluene, 3.0 mL, 3.0 mmol, 3.0 equiv) at 0 °C under argon. The reaction stirred at rt for 1 h, then a solution of **13** (0.21 g, 1.0 mmol, 1.0 equiv) in THF (5 mL) was added via cannula at 0 °C and stirred for 2 h at rt. Carbon disulfide (0.30 mL, 5.0 mmol, 5.0 equiv) was then added dropwise at rt and stirred overnight. Ethyl acetate was then added and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to afford **1c** as a colorless oil (0.15 g, 85%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 81.2 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.94 – 7.83 (m, 2H), 7.53 – 7.48 (m, 1H), 7.47 – 7.40 (m, 2H), 2.00 (d, J = 13.7 Hz, 3H); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for C_7H_9OPS 173.0184; Found 173.0185.

*(S_p)/(R_p)-8-phenyl-10-((S)-(1-phenylethyl)amino)dibenzo[c,e][1,2]oxaphosphinine 10-oxide **17** via **16**.* 2,6-Diphenylphenol (2.46 g, 10.0 mmol, 1.0 equiv), zinc chloride (0.0204 g, 0.15 mmol, 1.5 mol %) and phosphorus trichloride (1.1 mL, 12.50 mmol, 1.25 equiv) were added, without a solvent, and brought to 150 °C in an oil bath and stirred for 8 h under argon. After cooling down the reaction to 0 °C, the reaction mixture was quenched with ethyl acetate (20 mL) and H_2O (20 mL) and stirred for 1 h. The mixture was washed with a saturated aqueous

solution of NaHCO3. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to afford **16** as a white solid (2.4 g, 82%). This product was used directly in the next step without further purification.

The crude mixture was dissolved in CH_3CN and added dropwise via addition funnel to a mixture of iodoform (3.89 g, 9.85 mmol, 1.2 equiv), Et_3N (1.37 mL, 9.85 mmol, 1.2 equiv), and *(S)*-1-phenylethylamine (1.27 mL, 9.85 mmol, 1.2 equiv) at 0 °C under argon and stirred overnight at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified and resolved by column chromatography (hexanes/ethyl acetate 45:55) to afford pure **17** as a white solid (2.4 g, 58%. Resolved 22% of S_p and 15% of R_p). Racemic mixture: ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.86 (s), 13.53 (s); (S_p)-**17**: ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.46 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 1H), 7.96 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.74 (d, *J* = 1.2 Hz, 1H), 7.63 – 7.46 (m, 1H), 7.44 – 7.30 (m, 7H), 7.21 (m, 5H), 4.38 – 4.20 (m, 1H), 3.37 (t, *J* = 9.8 Hz, 1H), 1.42 (dd, *J* = 6.8, 0.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.7 (d, *J* = 7.5 Hz), 143.9 (d, *J* = 5.5 Hz), 137.4 (d, *J* = 7.1 Hz), 136.9, 133.7 (d, *J* = 5.8 Hz), 132.7 (d, *J* = 2.5 Hz), 131.7, 130.1 (d, *J* = 9.6 Hz), 129.7, 128.5, 128.1, 127.9 (d, *J* = 14.7 Hz), 127.4, 127.1, 125.7, 125.4, 124.2 (d, *J* = 21.4 Hz), 124.0 (d, *J* = 11.4 Hz), 123.8, 122.8 (d, *J* = 11.6 Hz), 51.2, 25.2 (d, *J* = 4.5 Hz); (R_p)-**17**: ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.8 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 1H), 7.96 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.75 – 7.66 (m, 2H), 7.66 – 7.60 (m, 2H), 7.52 – 7.44 (m, 3H), 7.44 – 7.31 (m, 3H), 7.22 (d, *J* = 2.0 Hz, 3H), 7.16 – 7.09 (m, 2H), 4.44 – 4.18 (m, 1H), 3.34 (t, *J* = 9.4 Hz, 1H), 1.46 (d, *J* = 6.8 Hz, 3H); HRMS (EI+) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{22}NO_2P$ 412.1461; Found 412.1473.

*(S_p)/(R_p)-8-phenyl-10-((S)-(1-phenylethyl)amino)dibenzo[c,e][1,2]oxaphosphinine 10-oxide **17** via **15***. 2,6-Diphenylphenol (2.46 g, 10.0 mmol, 1.0 equiv) and phosphorus trichloride (1.75 mL, 20.0 mmol, 2.0 equiv) were added, without a solvent, and brought to 50 °C in an oil bath and stirred for 3 h under argon. The reaction was cooled down to rt and zinc chloride (0.59 g, 4.3 mmol, 0.43 equiv) was added and brought to 150 °C and stirred for 8 h under argon. After cooling to 0 °C, the crude was solubilized in toluene (20 mL), and Et_3N (2.79 mL, 20.0 mmol, 2.0 equiv) and *(S)*-1-phenylethylamine (2.58 mL, 20.0 mmol, 2.0 equiv) were added and stirred at rt for 2 h under argon. To the reaction mixture H_2O_2 (35 wt. % in H_2O, 1.72 mL, 20.0 mmol, 2.0 equiv) was added at 0 °C and stirred for 4 h at rt. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified and resolved by column chromatography (hexanes/ethyl acetate 45:55) to afford pure **17** as a white solid (3.3 g, 78%. Resolved 22% of S_p and 15% of R_p). Racemic mixture: ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.89 (s), 13.56 (s); (S_p)-**17**: ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.46 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 1H), 7.96 (dd, J = 8.0, 1.7 Hz, 2H), 7.74 (d, J = 1.2 Hz, 1H), 7.63 – 7.46 (m, 1H), 7.44 – 7.30 (m, 7H), 7.21 (m, 5H), 4.38 – 4.20 (m, 1H), 3.37 (t, J = 9.8 Hz, 1H), 1.42 (dd, J = 6.8, 0.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.7 (d, J = 7.5 Hz), 143.9 (d, J = 5.5 Hz), 137.4 (d, J = 7.1 Hz), 136.9, 133.7 (d, J = 5.8 Hz), 132.7 (d, J = 2.5 Hz), 131.7, 130.1 (d, J = 9.6 Hz), 129.7, 128.5, 128.1, 127.9 (d, J = 14.7 Hz), 127.4, 127.1, 125.7, 125.4, 124.2 (d, J = 21.4 Hz), 124.0 (d, J = 11.4 Hz), 123.8, 122.8 (d, J = 11.6 Hz), 51.2, 25.2 (d, J = 4.5 Hz); (R_p)-**17**: ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.8 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 1H), 7.96 (dd, J = 8.1, 1.7 Hz, 1H), 7.75 – 7.66 (m, 2H), 7.66 – 7.60 (m, 2H), 7.52 – 7.44 (m, 3H), 7.44 – 7.31 (m, 3H), 7.22 (d, J = 2.0 Hz, 3H), 7.16 – 7.09 (m, 2H), 4.44 – 4.18 (m,

1H), 3.34 (t, J = 9.4 Hz, 1H), 1.46 (d, J = 6.8 Hz, 3H); HRMS (EI+) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{22}NO_2P$ 412.1461; Found 412.1473.

(S_p)/(R_p)-10-hydroxy-8-phenyldibenzo[c,e][1,2]oxaphosphinine 10-sulfide ***18***. To a solution of (S_p) or (R_p)-**17** (1.0 g, 2.43 mmol, 1.0 equiv) in dry THF (15 mL) was added at 0 °C NaH (60 % dispersion in mineral oil, 0.30 g, 7.30 mmol, 3.0 equiv) under argon. The reaction stirred for 1 h at rt, then carbon disulfide (1.46 mL, 24.30 mmol, 10.0 equiv) was added dropwise and stirred for 4 h at rt. Ethyl acetate and hexanes were added and washed (3x) with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude mixture was solubilized in DCM and the insoluble precipitate filtered out. The filtrate was concentrated under vacuum to afford (S_p) or (R_p)-**18** as an orange oil (0.65 g, 76%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 70.6 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (ddd, J = 16.5, 7.6, 1.5 Hz, 1H), 7.99 – 7.82 (m, 2H), 7.77 – 7.56 (m, 3H), 7.51 (dddd, J = 8.6, 7.5, 3.7, 1.1 Hz, 1H), 7.52 – 7.40 (m, 3H), 7.35 (dddd, J = 8.2, 6.4, 3.2, 1.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 146.6 (d, J = 10.5 Hz), 136.8, 134.8 (d, J = 6.2 Hz), 133.6 (d, J = 5.8 Hz), 132.9 (d, J = 2.6 Hz), 131.8, 130.3 (d, J = 13.7 Hz), 130.2 (d, J = 13.9 Hz), 129.7, 128.5, 128.3, 128.2, 127.6, 124.6, 124.2 (d, J = 11.0 Hz), 123.6 (d, J = 12.2 Hz); HRMS (EI+) *m/z*: Calcd for $C_{18}H_{13}O_2PS$ $[M + H]^+$ 325.0447; Found 325.0439.

The enantiomeric excess of (S_p)-**18**-SMe and (R_p)-**18**-SMe was determined and compared to the scalemic-**18**-SMe (scalemic-**18** after column purification/resolution of **17**). To a solution of (S_p) or (R_p)-**18** (0.10 g, 0.30 mmol, 1.0 equiv) in dry THF (3 mL) was added Et_3N (0.08 mL, 0.62 mmol, 2 equiv) followed by iodomethane (0.04 mL, 0.62 mmol, 2.0 equiv) at 0 °C under

argon. The reaction was brought to rt and stirred for 4 h. The organic layer was washed with a saturated aqueous solution of NH_4Cl. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to afford pure (S_p)-**18-**SMe and (R_p)-**18**-SMe as a white solid (0.10 g, 99%). The enantiomeric excess thus obtained was determined by a chiral HPLC analysis ((S,S)-Whelk-O1; eluent: hexanes/DCM = 50:50 + 0.1% TFA; flow rate: 1 mL/min; λ = 254 nm; t_1 (R_p) = 3.9 min, t_2 (S_p) = 5.0 min; (S_p) enantiopurity: > 98% and (R_p) enantiopurity: > 99%). (S_p)-**18-**SMe: ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.6 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (ddt, *J* = 8.5, 4.9, 2.3 Hz, 2H), 7.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.74 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.56 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.52 – 7.44 (m, 3H), 7.44 – 7.38 (m, 1H), 7.36 (td, *J* = 7.8, 0.7 Hz, 1H), 2.14 (d, *J* = 13.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 146.4 (d, *J* = 9.7 Hz), 136.6 (d, *J* = 7.4 Hz), 136.5, 133.9 (d, *J* = 2.6 Hz), 133.8 (dd, *J* = 6.1, 0.0 Hz), 132.2, 130.4 (d, *J* = 10.9 Hz), 129.5, 128.7 (d, *J* = 14.9 Hz), 128.4, 127.8, 126.2 (d, *J* = 136.0 Hz), 124.9, 124.7 (d, *J* = 1.4 Hz), 124.4 (d, *J* = 11.2 Hz), 123.1 (d, *J* = 11.8 Hz), 11.3 (d, *J* = 3.7 Hz). (R_p)-**18-**SMe: ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.6 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.01 (m, 2H), 7.94 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.84 – 7.69 (m, 1H), 7.67 – 7.55 (m, 3H), 7.49 (ddt, *J* = 7.8, 6.0, 1.5 Hz, 3H), 7.46 – 7.35 (m, 2H), 2.16 (d, *J* = 13.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 146.5, 136.7 (d, *J* = 7.5 Hz), 136.5, 133.9, 132.2, 130.4 (d, *J* = 10.8 Hz), 129.5, 128.7 (d, *J* = 15.0 Hz), 128.3, 127.8, 126.2, 124.9, 124.6, 124.5, 124.3, 123.2 (d, *J* = 12.1 Hz), 11.2 (d, *J* = 3.8 Hz). HRMS (EI+) *m/z*: Calcd for $C_{19}H_{15}O_2PS$ $[M + H]^+$ 339.0603; Found 339.0604.

General Procedure for the Nucleophilic Substitution of *H*-Phosphinates with Organometallics; Followed by Trapping with Elemental Sulfur or Selenium. *Butyl-phenyl-*

H-phosphinate **19a**[42] and *ethyl-benzyl-H-phosphinate* **19b**[43] were prepared according to the literature. To a solution of RM (2.5 – 3.5 equiv, M = Li or MgX) in THF or Et_2O (0.25 M) was added dropwise a solution of the appropriate *H*-phosphinate (1.0 equiv) in THF or Et_2O (0.6 M) at -78 °C or 0 °C, over 30 min under argon. The reaction was stirred for an additional 3 h at rt and was then quenched with elemental sulfur or selenium (3 – 5 equiv) and let stir overnight at rt under argon. Ethyl acetate was added to the reaction mixture and washed (3x) with a saturated aqueous solution of $NaHCO_3$. The two layers were separated, the aqueous layer was acidified with 3 M HCl until pH = 1 and extracted with ethyl acetate (3x). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to afford the pure product without further purification.

Allyl-phenylphosphinothioic acid ***1i*** *(Table 3, Entry 1a).* Following the general procedure: allylmagnesium bromide (1.0 M in diethyl ether, 6.05 mL, 6.05 mmol, 2.4 equiv) in THF (10 mL) at 0 °C was reacted with a solution of **19a** (0.50 g, 2.52 mmol, 1.0 equiv) in THF (4 mL). Elemental sulfur (0.24 g, 7.57 mmol, 3.0 equiv) was added to afford crude **1i** as a light yellow oil (0.35 g, 57%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 82.0 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.85 (ddd, *J* = 13.1, 8.3, 1.4 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.49 – 7.40 (m, 2H), 5.85 – 5.42 (m, 1H), 5.25 – 4.86 (m, 2H), 3.12 – 2.63 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 133.8 (d, *J* = 103.5 Hz), 132.2 (d, *J* = 3.0 Hz), 131.0 (d, *J* = 11.2 Hz), 128.4 (d, *J* = 13.1 Hz), 127.1 (d, *J* = 9.4 Hz), 121.1 (d, *J* = 14.1 Hz), 43.3 (d, *J* = 72.5 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_9H_{11}OPS$ 199.0341; Found 199.0349.

*Allyl-phenylphosphinothioic acid **1i** (Table 3, Entry 1b).* Following the general procedure: allylmagnesium bromide (1.0 M in diethyl ether, 8.75 mL, 8.75 mmol, 3.5 equiv) in THF (10 mL) at 0 °C was reacted with a solution of **19a** (0.50 g, 2.50 mmol, 1.0 equiv) in THF (4 mL). Elemental sulfur (0.40 g, 12.5 mmol, 5.0 equiv) was then added to afford pure **1i** as a light yellow oil (0.4 g, 67%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 82.0 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.85 (ddd, *J* = 13.1, 8.3, 1.4 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.49 – 7.40 (m, 2H), 5.85 – 5.42 (m, 1H), 5.25 – 4.86 (m, 2H), 3.12 – 2.63 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 133.8 (d, *J* = 103.5 Hz), 132.2 (d, *J* = 3.0 Hz), 131.0 (d, *J* = 11.2 Hz), 128.4 (d, *J* = 13.1 Hz), 127.1 (d, *J* = 9.4 Hz), 121.1 (d, *J* = 14.1 Hz), 43.3 (d, *J* = 72.5 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_9H_{11}OPS$ 199.0341; Found 199.0349.

*Phenyl-tert-butylphosphinothioic acid **1j** (Table 3, Entry 1c).* Following the general procedure: *tert*-butylmagnesium chloride (1.0 M in THF, 12.5 mL, 12.5 mmol, 5.0 equiv) in THF (10 mL) at 0 °C was reacted with a solution of **19a** (0.50 g, 2.50 mmol, 1.0 equiv) in THF (4 mL). Elemental sulfur (0.4 g, 12.5 mmol, 5.0 equiv) was then added to afford crude **1j** as a brown oil (NMR Yield: 37 %). ^{31}P NMR (162 MHz, $CDCl_3$) δ 71.3 (s).

*Methyl-phenylphosphinothioic acid **1c** (Table 3, Entry 1d).* Following the general procedure: methyllithium (1.6 M in diethyl ether, 3.91 mL, 6.25 mmol, 2.5 equiv) in diethyl ether (10 mL) at -78 °C was reacted with a solution of **19a** (0.50 g, 2.50 mmol, 1.0 equiv) in THF (4 mL). Elemental sulfur (0.24 g, 7.5 mmol, 3.0 equiv) was then added to afford pure **1c** as a colorless oil (0.40 g, 91%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 81.1 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.90 (ddd, *J* = 13.7, 8.3, 1.4 Hz, 2H), 7.53 – 7.49 (m, 1H), 7.49 – 7.33 (m,

2H), 2.00 (d, J = 13.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 135.2 (d, J = 104.6 Hz), 132.1 (d, J = 3.0 Hz), 130.3 (d, J = 11.8 Hz), 128.5 (d, J = 13.2 Hz), 25.1 (d, J = 78.4 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for C_7H_9OPS 173.0184; Found 173.0185.

n-Butyl-phenylphosphinothioic acid ***1k*** *(Table 3, Entry 1e).* Following the general procedure: *n*-butyllithium (2.5 M in hexanes, 2.5 mL, 6.25 mmol, 2.5 equiv) in diethyl ether (10 mL) at -78 °C was reacted with a solution of **19a** (0.50 g, 2.50 mmol, 1.0 equiv) in THF (4 mL). Elemental sulfur (0.24 g, 7.5 mmol, 3.0 equiv) was then added to afford pure **1k** as a light yellow oil (0.43 g, 80%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 86.6 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.97 – 7.75 (m, 2H), 7.56 – 7.49 (m, 1H), 7.47 – 7.35 (m, 2H), 2.24 – 1.97 (m, 2H), 1.62 – 1.43 (m, 2H), 1.40 – 1.23 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 134.2 (d, J = 101.2 Hz), 131.9 (d, J = 3.0 Hz), 130.7 (d, J = 11.3 Hz), 128.4 (d, J = 12.9 Hz), 36.9 (d, J = 75.2 Hz), 24.5 (d, J = 3.4 Hz), 23.4 (d, J = 18.1 Hz), 13.6; HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{15}OPS$ 215.0654, Found 215.0659.

Allyl-phenylphosphinoselenoic acid ***20a*** *(Table 3, Entry 2a).* Following the general procedure: allylmagnesium bromide (1.0 M in diethyl ether, 8.75 mL, 8.75 mmol, 3.5 equiv) in THF (10 mL) at 0 °C was reacted with a solution of **19a** (0.50 g, 2.50 mmol, 1.0 equiv) in THF (4 mL). Elemental selenium (1.0 g, 12.5 mmol, 5.0 equiv) was then added to afford pure **20a** as an orange oil (0.50 g, 65%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 78.6 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.87 (m, J = 13.3, 8.3, 1.5 Hz, 2H), 7.50 (dd, J = 7.3, 2.0 Hz, 1H), 7.44 (m, J = 6.9, 5.5, 2.6 Hz, 2H), 5.69 (ddd, J = 16.7, 9.8, 6.5 Hz, 1H), 5.16 (m, J = 10.2, 5.0, 1.4 Hz, 1H), 5.04 (m, J = 17.0, 6.0, 1.5 Hz, 1H), 3.11 (ddd, J = 17.1, 7.5, 2.0 Hz, 2H); $^{13}C\{^{1}H\}$ NMR

(101 MHz, $CDCl_3$) δ 133.7 (d, *J* = 91.3 Hz), 132.2 (d, *J* = 3.1 Hz), 131.0 (d, *J* = 11.4 Hz), 128.3 (d, *J* = 13.1 Hz), 127.3 (d, *J* = 9.4 Hz), 121.1 (d, *J* = 14.1 Hz), 45.0 (d, *J* = 62.9 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_9H_{11}OPSe$ 246.9785; Found 246.9785.

*n-Butyl-phenylphosphinoselenoic acid **20b** (Table 3, Entry 2b).* Following the general procedure: *n*-butyllithium (2.5 M in hexanes, 2.5 mL, 6.25 mmol, 2.5 equiv) in diethyl ether (10 mL) at -78 °C was reacted with a solution of **19a** (0.50 g, 2.50 mmol, 1.0 equiv) in THF (4 mL). Elemental selenium (0.6 g, 7.5 mmol, 3.0 equiv) was then added to afford pure **20b** as an orange oil (0.45 g, 72%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 83.8 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, *J* = 13.3, 8.2, 1.5 Hz, 2H), 7.55 – 7.49 (m, 1H), 7.49 – 7.42 (m, 2H), 7.26 – 7.22 (m, 1H), 2.45 – 2.12 (m, 2H), 1.68 – 1.44 (m, 2H), 1.46 – 1.17 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 134.4 (d, *J* = 89.7 Hz), 132.0 (d, *J* = 3.0 Hz), 130.7 (d, *J* = 11.6 Hz), 128.4 (d, *J* = 12.9 Hz), 38.6 (d, *J* = 65.1 Hz), 24.9 (d, *J* = 3.2 Hz), 23.3 (d, *J* = 18.1 Hz), 13.6; HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{15}OPSe$ 257.0158, Found 257.0161.

*Allyl-benzylphosphinothioic acid **1l** (Table 3, Entry 3).* Following the general procedure: allylmagnesium bromide (1.0 M in diethyl ether, 8.75 mL, 8.75 mmol, 3.5 equiv) in THF (10 mL) at 0 °C was reacted with a solution of **19b** (0.46 g, 2.50 mmol, 1.0 equiv) in THF (4 mL). Elemental sulfur (0.4 g, 12.5 mmol, 5.0 equiv) was then added to afford pure **1l** as a light yellow oil (0.33 g, 62%). ^{31}P NMR (162 MHz, $CDCl_3$) δ 88.6 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.46 (m, 1H), 7.32 m, *J* = 11.2, 8.8, 5.0, 2.9 Hz, 5H), 6.03 – 5.73 (m, 1H), 5.35 – 5.04 (m, 2H), 3.42 (d, *J* = 14.9 Hz, 2H), 2.96 – 2.62 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 131.1 (d, *J* = 8.4 Hz), 130.3 (d, *J* = 5.8 Hz), 128.6 (d, *J* = 3.2 Hz), 127.5 (d, *J* = 9.1 Hz), 127.3 (d, *J* = 3.7 Hz),

121.2 (d, J = 13.7 Hz), 42.2 (d, J = 64.5 Hz), 39.8 (d, J = 68.3 Hz); HRMS (EI+) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{13}OPS$ 213.0497; Found 213.0497.

Supporting Information

Copies of HPLC spectral data and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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