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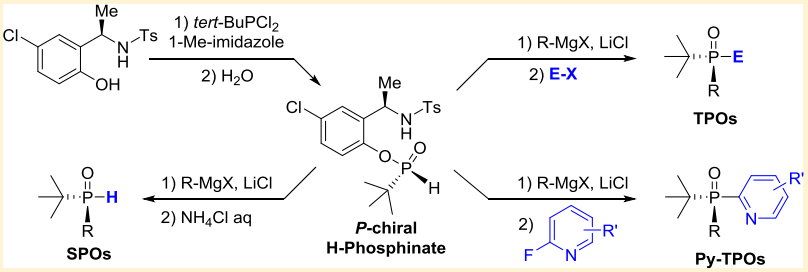
Asymmetric Library Synthesis of P-Chiral *t*-Butyl-Substituted Secondary and Tertiary Phosphine Oxides

Shi-Guang Li,[†,∥] Minglei Yuan,[†,∥] Filip Topic,[†] Zhengxu S. Han,[‡] Chris H. Senanayake,[‡,§] and Youla S. Tsantrizos*[,†]

[†]Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 0B8, Canada
[‡]Chemical Development, Boehringer-Ingelheim Pharmaceuticals Incorporation, 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, United States

Supporting Information



ABSTRACT: An asymmetric synthesis, amenable to library preparation of structurally diverse *P*-chiral *t*-butyl substituted secondary phosphine oxides (SPOs) and tertiary phosphine oxides (TPOs), was developed. A *P*-chiral H-phosphinate building block was prepared via a two-step, one-pot condensation of a chiral auxiliary with *t*-BuPCl$_2$, followed by hydrolysis. Nucleophilic displacement of the chiral auxiliary with Grignard reagents, followed by hydrolysis, provided a library of *P*-chiral SPOs. In situ treatment of the prehydrolysis intermediate with electrophiles also provided a library of *P*-chiral TPOs in high enantiomeric purity.

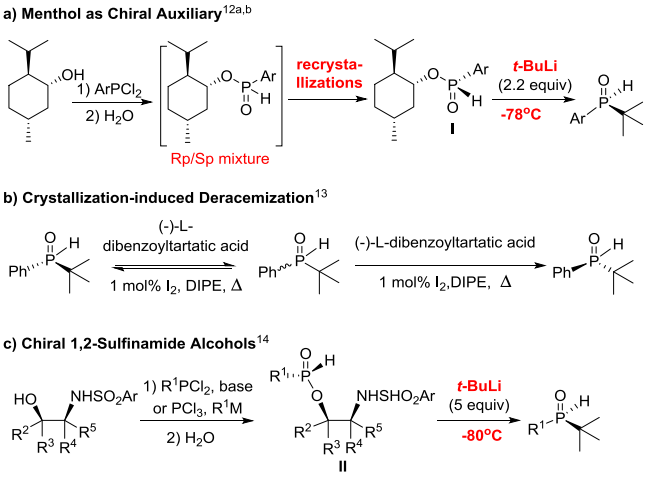
INTRODUCTION

Chiral phosphorus-containing compounds are valuable reagents, metal-coordinating ligands, and organocatalysts for asymmetric synthesis.[1] In particular, organophosphorus compounds with chirality on the phosphorus atom are of considerable interest.[2] Methodologies that allow the preparation of such compounds include the use of chiral auxiliaries followed by separation of diastereomeric mixtures and desymmetrization of symmetrically substituted phosphine oxides. Examples of the latter usually involve metal-mediated transformation of one of the enantiotopic substituents on the phosphorus to a new substituent.[3]

Sterically congested *t*-butyl-substituted *P*-chiral phosphines are of particular interest in catalysis because of their enhanced ability to induce enantioselectivity in various reactions. Such reactions are of enormous value in both research and the large-scale production of various chemicals, including pharmaceuticals.[4] Amongst the best examples are the 3-(*t*-butyl)-2,3-dihydrobenzo[*d*][1,3]oxaphosphole-based ligands, such as BIBOP[5] and its closely related WingPhos,[6] BI-DIME,[7] BoQPhos,[8] HandaPhos,[9] and BABIPhos,[10] which have been used in a wide range of catalytic processes.

Secondary phosphine oxides (SPOs) have been used as ligands in various transformations, including asymmetric hydrogenations.[11] In the past, many studies have been reported for the synthesis of chiral SPOs, including those using menthol (Scheme 1a)[12a,b] or glucosamine-type as chiral auxiliaries.[12c] Crystallization-induced deracemization of *t*-butylphenylphosphine oxide in the presence of iodine and (−)-*O*,*O*′-dibenzoy-

Scheme 1. Examples of Previous Strategies for the Synthesis of Enantiomerically Enriched SPOs



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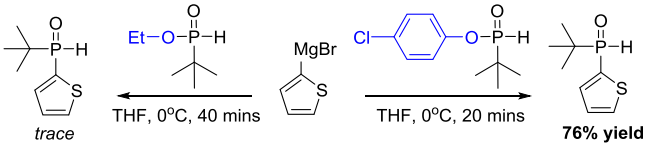
L-tartaric acid has also been reported (Scheme 1b).[13] In many cases, these methods require multiple recrystallizations to achieve high diastereomeric purity and the use of excess amounts of highly pyrophoric *t*-BuLi for the introduction of the *t*-butyl group on the phosphorus (e.g., Scheme 1a).[12,13] More recently, the use of 1,2-amino alcohols as chiral auxiliaries was also reported (Scheme 1c), which allows access to *P*-chiral SPOs with significant structural diversity.[14] However, this method also requires the use of large amounts of *t*-BuLi in order to introduce the *t*-butyl group on the phosphorus. Safety concerns over the handling of *t*-BuLi cannot be underestimated,[15] which led us to explore a safer and more efficient methodology for the preparation of such compounds. Herein, we report a modular asymmetric synthesis of *t*-butyl substituent P-chiral SPOs and tertiary phosphine oxides (TPOs), which avoids the use of *t*-BuLi and provides *P*-chiral SPOs and TPOs with high enantiomeric purity.

RESULTS AND DISCUSSION

We envisioned that a *t*-Bu-substituted starting material could provide a convenient and versatile method for the synthesis of sterically hindered phosphine compounds. As reported previously, methods employing alkyl alcohols as chiral auxiliaries contain strong P−O bonds and consequently require strong nucleophiles to cleave these highly stable P−O bonds (Scheme 1).[12−14] The combination of a bulky *t*-butyl group and an alkoxy substituent on an H-phosphinate intermediate (e.g., **I** or **II**; Scheme 1) was expected to further decrease the reactivity of the P−O bond toward relatively mild nucleophiles. Consequently, we focused our attention on increasing the reactivity of the P−O bond by using a better leaving group, such as a phenol-based chiral auxiliary (Scheme 2). To test this hypothesis, we performed a model reaction

Scheme 2. P−OR Bond Reactivity

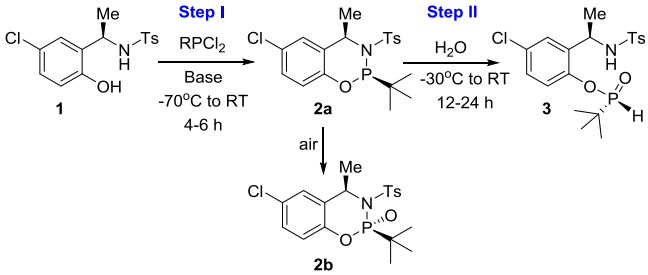


using thiophen-2-ylmagnesium bromide and 4-chlorophenyl *t*-butylphosphinate from which the desired product, *t*-butyl-(thiophen-2-yl)phosphine oxide, was isolated in 76% yield. In contrast, reaction of the same Grignard reagent with the ethyl *t*-butylphosphinate failed to produce any significant amount of the corresponding product.

Subsequently, we selected (*R*)-*N*-(1-(5-chloro-2-hydroxyphenyl)ethyl)-4-methylbenzenesulfonamide (**1**) as the chiral auxiliary (Table 1), which was previously successfully employed in the synthesis of *P*-chiral phosphine oxides.[16] Reaction of *t*-BuPCl$_2$ under basic conditions gave the cyclic oxazaphosphinine intermediate **2a**, which upon quenching with water provided the stable 4-chloro-2-((*R*)-1-((4-methylphenyl)sulfoamido) ethyl)phenyl (*S*)-*t*-butylphosphinate (**3**) in high diastereomeric purity. This one-pot, two-step synthesis is initiated with the slow addition of a base into the mixture *t*-BuPCl$_2$ and the chiral auxiliary **1** at low temperatures (−70 to −40 °C) to induce the nucleophilic attack leading to the displacement of one chloride by the aryloxy moiety. However, nucleophilic attack of the nitrogen was found to be much slower and required higher temperatures in order for the enantioselective cyclization to intermediate **2a** to occur. We presume that the poor dr observed when the temperature of the cyclization step is kept below −30 °C (Table 1, entry 3) is likely due to the incomplete formation of the cyclic intermediate **2a** and the subsequent hydrolysis of the racemic *t*-butylchlorophosphaneyl intermediate. The highest selectivity (98:2 dr) was observed when the chiral chlorophenol **1** was reacted with *t*-BuPCl$_2$ in tetrahydrofuran (THF) in the presence of 1-Me-imidazole at −40 °C for 1 h, followed by slow warming of the reaction mixture to ∼22 °C and stirring at room temperature for an additional 4−5 h, before proceeding to the hydrolysis step at room temperature overnight. Although not essential for small-scale reactions, the addition of a small amount of HCl (e.g., ∼0.5 equiv) was found to increase the reaction rate of the hydrolysis step without adversely affecting the enantiomeric purity of product **3**. After recrystallization, product **3** was isolated in 71% yield and in 99.7:0.3 diastereomeric ratio (Table 1, entry 5). The absolute stereochemistry of S_p-**3** was confirmed by its single-crystal X-ray structure (Figure 1). It is noteworthy that direct assignment of the absolute stereochemistry of **2a** was very challenging, because of its high propensity to form the oxidized product **2b** during isolation. However, the absolute stereochemistry of R_p-**2b** was unambiguously confirmed by crystallography (Figure 1).

Subsequently, intermediate **3** was used as the key building block for the synthesis of a small library of enantiomerically

Table 1. Synthesis of the Enantiomerically Enriched SPO Template



entry	base[a]	step I temp °C	step II temp °C	yield[b] %	3 dr[c]
1	py	−70 to RT	RT	44	75:25
2	py	−40 to RT	RT	28	72:28
3	Im	−70 to −30	RT	nd	53:47
4	Im	−70 to RT	RT	nd	95:5
5	Im	−40 to RT	RT	71	98:2 (99.7:0.3)

[a]Base: pyridine (Py) or 1-methylimidazole (Im). [b]Isolated yield; nd = not determined. [c]Estimated crude dr ratio based on ^{31}P NMR (dr ratio after recrystallization).

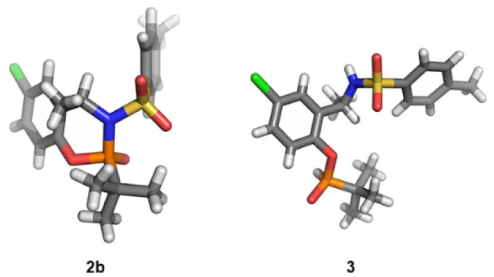


Figure 1. Single-crystal X-ray structures of **2b** and **3**.

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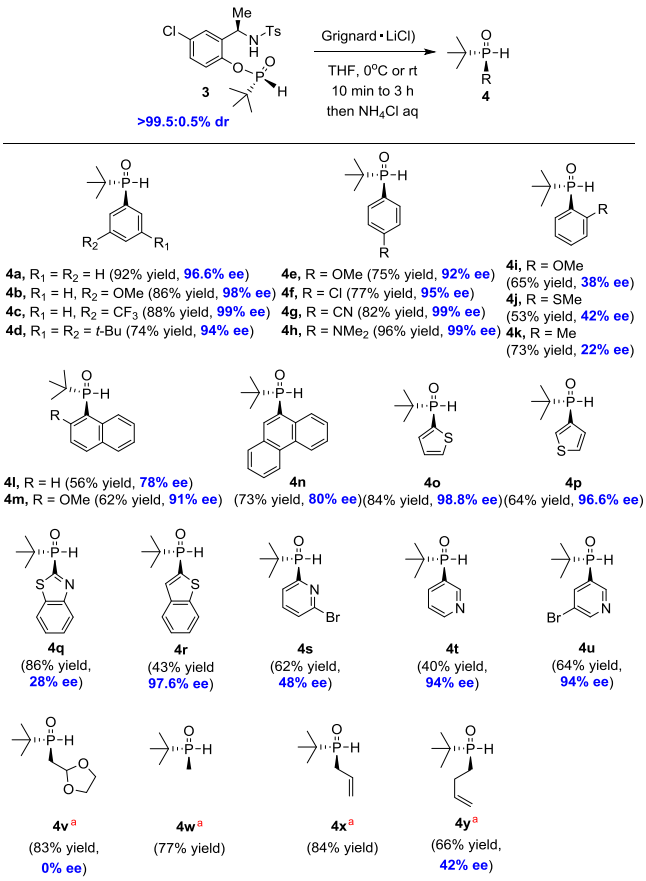
enriched SPO compounds, some examples are shown in Table 2. Reagent **3** reacts readily with Grignards to give the corresponding SPOs **4**. As expected, the steric hindrance of the Grignard nucleophile has an effect on both of the yield and enantioselectivity of the reaction. In general, *meta*- or *para*-substituted aryl magnesium halides gave excellent yields with high enantiomeric purity (e.g., examples **4a–h**), whereas ortho-substituted aryl magnesium halides gave moderate to good yields, with lower enantiomeric purity (e.g., examples **4i–k**). Interestingly, derivatives with an extended aromatic system (**4l–4n**) were obtained in better enantiomeric purity (e.g., **4m** in 91% ee).

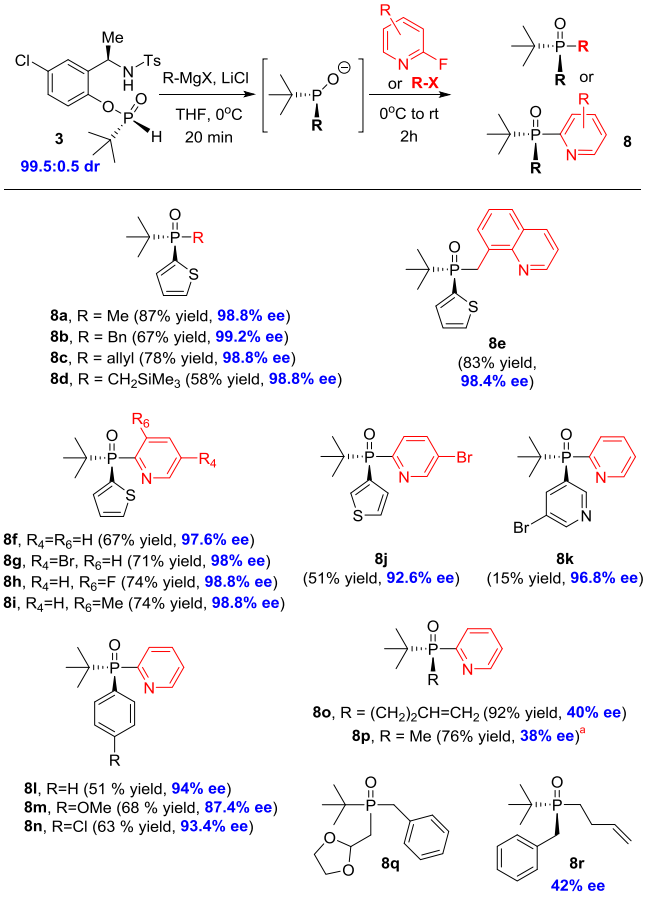
Heteroaryl analogues having the phosphine oxide moiety at the C-2 position of a nitrogen atom, such as the benzothiazole analogue **4q** and pyridine analogue **4s**, formed with lower enantiomeric purity, plausibly because of interfering coordination of the nitrogen with the magnesium metal. For example, the difference in the enantiomeric purity observed between compounds having a *t*-butyl(pyridin-2-yl)phosphine oxide versus a *t*-butyl(pyridin-3-yl)phosphine oxide (i.e., analogue **4s** vs **4t**/**4u**, respectively) is consistent with this hypothesis. Synthesis of the acetal **4v**, methyl and butenyl derivatives **4w–4y** was also achieved in good yields. Lack of UV absorption and the chemical instability of these four analogues prevented direct determination of their enantiomeric purity. However, when the freshly prepared analogues **4v** and **4y** were immediately reacted with benzyl bromide, the expected TPO products **8q** and **8r** (Table 3), respectively, were obtained racemic (**8q**) or in low chiral purity (**8r**).

Table 2. Examples of Enantiomerically Enriched SPOs



[a]Chemically unstable at RT; enantiomeric purity of **4v** and **4y** was estimated from their corresponding TPOs, **8q** and **8r**.

Table 3. Library Synthesis of Enantiomerically Enriched TPOs



[a]Enantiomeric purity when reaction conducted at −65 °C.

In addition to their own value as ligands in catalysis,[11] *P*-chiral SPOs are also valuable precursors of *P*-chiral TPOs.[12−14,17] Recent examples include Pd-catalyzed[18] and Cu-catalyzed[19] cross-coupling reactions of SPOs with sp^2 carbons to give *P*-chiral TPOs. *P*-chiral TPOs could also potentially be important in the synthesis of human therapeutics.[20] In this study, addition of Grignard reagents to intermediate **3**, followed by a nucleophilic substitution on an alkyl, benzyl, or aryl/heteroaryl halide gave a library of the *P*-chiral TPOs in modest to excellent yield and chiral purity (Table 3). Electrophilic reagents such as the corresponding bromides or iodides were used to prepare analogues such as **8a** to **8e**, whereas the pyridine-based TPOs **8f** to **8n** were obtained via the S_NAr reactions with the 2-fluoropyridine-based precursors. High enantiomeric purity was observed for all of these products. The absolute stereochemistry for analogues **8l–8n** was confirmed by comparison of their chiral high-performance liquid chromatography (HPLC) chromatograms with those previously reported under the same conditions.[14]

Although the exact mechanism for the transformation of **3** to **8** remains unclear, we presumed that in the presence of four equivalents of a Grignard, the first two equivalents act as a base, leading to the generation of intermediates **5** and **6a**,

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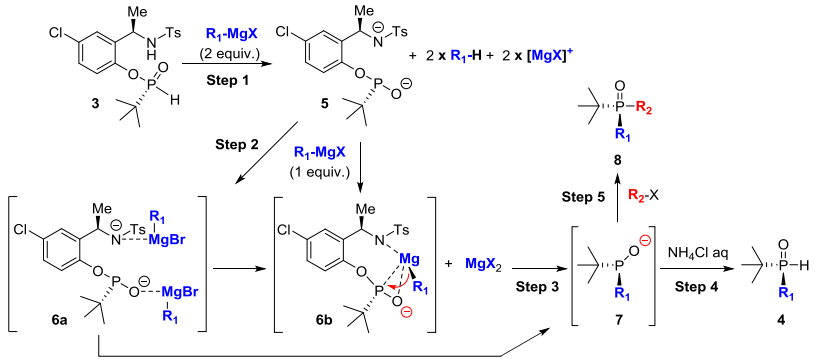
Scheme 3. Proposed Mechanism



whereas the third equivalent could potentially lead to the formation of the cyclic intermediate **6b** (Scheme 3). This plausible bidentate or tridentate coordination of the magnesium cation with the amine anion, the phosphorus atom, and/or the oxygen anion could drive the delivery of the Grignard payload on the opposite side of the *t*-butyl group, via intramolecular attack on the phosphorus, to give the *t*-butyl(alkyl/aryl)phosphinite anion intermediate **7**. However, this coordination of the magnesium cation could be compromised by substituents having a heteroatom, such as nitrogen or oxygen near the $Mg^{\delta+}-C^{\delta-}$ bond (e.g., analogous to the formation of **4i**, **4q**, and **4t**; Table 2) decreasing the enantiomeric purity of the TPO products. Formation of this coordination may also be less favorable when the R_1 group of the Grignard reagent is highly sterically congested, thus favoring the direct conversion of **6a** to **7** via nucleophilic attack on the phosphorus and some loss in enantioselectivity. The exact cause for the low enantioselectivity observed for TPO products made from alkyl/alkenyl Grignards (e.g., analogues **8o** and **8p**) is not very clear. However, it could be (at least in part) due to the inherently higher stereolability for their dialkyl intermediates **7**, as compared to those with two aryl/heteroaryl substituents on the phosphorus atom. Racemization of SPOs with alkyl substituents has been previously observed under a variety of conditions.[12a,19]

CONCLUSIONS

In summary, in this study, we aimed to develop an efficient asymmetric synthesis of *P*-chiral *t*-butyl substituted SPOs and TPOs that is amenable to library synthesis of structurally diverse compounds without the need to use conditions that are tedious or require highly pyrophoric reagents, such as *t*-BuLi. A key building block was prepared via condensation of the chiral auxiliary **1** with *t*-$BuPCl_2$ under basic conditions which upon hydrolysis gives the P−H intermediate **3** in high diastereomeric excess. Treatment of this intermediate with a variety of Grignard reagents, followed by an electrophile in two-step, one-pot reaction, led to the synthesis of a structurally diverse library of *P*-chiral TPOs in good to excellent yield and chiral purity for most analogues. Reduction of TPOs to the trivalent phosphines has been previously achieved without erosion of chirality on the phosphorus.[7,9a,10,18a,21] Analogues with the potential to act as bidentate ligands, such as the corresponding phosphine of analogue **8e**−**8n**, are of particular interest and currently under further investigation.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under anhydrous conditions and an atmosphere of dry argon unless otherwise specified. Completion of all reactions was monitored by thin-layer chromatography (TLC), HPLC, and LCMS. Flash column chromatography was performed on silica gel (SDS, 60 Å C. C. 40−63 mm) as the stationary phase. TLC was performed on alumina plates precoated with silica gel (Merck silica gel, 60 F254), which was visualized by the quenching of UV fluorescence when applicable (λ_{max} = 254 nm and/or 366 nm) and/or by staining with vanillin or anisaldehyde in acidic ethanol and/or $KMnO_4$ in basic water followed by heating. All compounds were fully characterized by ^1H, ^{13}C, ^{31}P NMR, and high-resolution mass spectrometry (HRMS). Chemical shifts (δ) are reported in ppm relative to the internal deuterated solvent. ^1H NMR was recorded at 500 MHz and coupling constants (J) are reported to ±0.5 Hz. $^{13}C\{^1H\}$ NMR was recorded at 125 MHz and $^{31}P\{^1H\}$ NMR was recorded at 202 MHz. Enantiomeric purity of chiral compounds was determined by chiral HPLC using an Agilent 1100 series instrument. The absolute configurations of all new SPO and TOP products were assigned by analogy with the previously reported compounds, the absolute stereochemistry of precursors **2b** and **3**, and the proposed mechanism of the reactions. HRMS were obtained on a TOF instrument by electrospray ionization positive and negative modes (ESI±). The quoted masses are accurate to ±5 ppm. The names of the molecules that appear in the following pages were generated using either Beilstein AutoNom 2000 (CAS) or ChemBioDraw Ultra 12.0.

4-Chlorophenyl tert-Butylphosphinate. To a solution of 4-chlorophenol (100 mmol, 12.86 g) in 100 mL THF, *tert*-butyldichlorophosphine (120 mL, 1.2 equiv, 1 M solution in ether) was added dropwise at −70 °C, followed by addition of tetraethylammonium (1.2 equiv, 120 mmol, 16.74 mL). The reaction mixture was kept stirring at this temperature for another 75 min to complete the reaction, then water was added and allowed to warmed up to rt and stirring was continued for one more 1 h to complete the reaction. The desired product was obtained (16.28 g) in 70% yield as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 6.8 Hz, 2H), 7.15 (dd, J = 9.0, 1.1 Hz, 2H), 6.94 (d, J = 527.6 Hz, 1H), 1.26 (d, J = 18.4 Hz, 9H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 150.3 (d, J = 10.1 Hz), 130.4 (d, J = 1.3 Hz), 129.9 (d, J = 0.9 Hz), 121.4 (d, J = 4.8 Hz), 31.7 (d, J = 93.4 Hz), 22.7 (d, J = 1.5 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 48.95; HRMS: calcd for $C_{10}H_{15}ClO_2P^+$ [M + H^+], 233.0493; found, 233.0494.

*(2R,4R)-2-(tert-Butyl)-6-chloro-4-methyl-2-(λ⁵-oxidaneyl)-3-tosyl-3,4-dihydro-2H-2λ⁴-benzo[e][1,3,2]oxazaphosphinine (**2b**).* Intermediate **2a** is not air stable; attempts to purify **2a** by flash column chromatography lead to the isolation of the oxidized product **2b** as a white powder in 82% yield (351 mg) and 99.5:0.5 dr ratio (based on ^{31}P NMR). ^1H NMR (500 MHz, $CDCl_3$): δ 8.01−7.96 (m, 2H), 7.23−7.17 (m, 3H), 7.05 (dd, J = 8.6, 1.0 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 4.51−4.42 (m, 1H), 2.38 (s, 3H), 1.60 (d, J = 7.0 Hz, 3H), 1.53 (d, J = 19.2 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ

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145.4 (d, J = 9.8 Hz), 144.7, 134.9, 131.8 (d, J = 7.8 Hz), 130.1, 129.6, 129.5, 128.5, 125.5 (d, J = 1.6 Hz), 121.6 (d, J = 3.6 Hz), 56.4, 34.8 (d, J = 124.6 Hz), 26.3, 24.3, 21.6. $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 37.12. HRMS: calcd for $C_{19}H_{24}ClNO_4PS^+$ [M + H^+], 428.0847; found, 428.0845.

*4-Chloro-2-((R)-1-((4-methylphenyl)sulfonamido)ethyl)phenyl (S)-tert-Butylphosphinate (**3**).* A solution of the chiral template, (*R*)-*N*-(1-(5-chloro-2-hydroxyphenyl)ethyl)-4-methylbenzenesulfonamide (**1**, 16.3 g, 50 mmol) in anhydrous THF (60 mL) at −40 °C (bath of dry ice in CH_3CN) under argon, *tert*-$BuPCl_2$ (55 mmol, 1 M in diethyl ether) was added, followed by 1-Me-imidazole (125 mmol, 9.963 mL) in 60 min while keeping the internal temperature below −30 °C. The mixture was stirred at that temperature for 1 h, then slowly warmed up to rt, and stirred for 4 h to complete the conversion to the cyclic intermediate **2a**. Subsequently, water (50 mL) was added slowly and reaction mixture was stirred vigorously at rt for approximately 12−15 h (large-scale reactions could take longer for complete conversion; the addition of ∼0.5 equiv. HCl increases the rate of the reaction without any adverse consequences to the yield or enantiomeric purity of the product). The reaction mixture was diluted with EtOAc (200 mL). The organic phase was collected and washed once with brine (20 mL), dried over Na_2SO_4, and concentrated to yield a crude product in 98:2 dr. After recrystallization (with EtOAc 100 mL and hexane 100 mL), product **3** was obtained as a white powder in 71% yield (15.3 g) and >99.7:0.3 dr ratio based on ^{31}P NMR. ^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, J = 8.2 Hz, 2H), 7.00 (d, J = 548.1 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.12 (d, J = 8.1 Hz, 2H), 7.06 (dd, J = 2.5, 8.7 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 5.40 (d, J = 6.9 Hz, 1H), 4.85−4.79 (m, 1H), 2.34 (s, 3H), 1.39 (d, J = 7.0 Hz, 3H), 1.29 (d, J = 18.6 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 147.0 (d, J = 9.9 Hz), 143.4, 137.1, 134.5 (d, J = 4.9 Hz), 130.3, 129.4, 128.4, 127.6, 127.0, 120.7 (d, J = 4.5 Hz), 47.7, 31.9 (d, J = 93.6 Hz), 23.0, 22.8 (d, J = 1.1 Hz), 21.4. $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 48.29. HRMS: calcd for $C_{19}H_{26}ClNO_4PS^+$ [M + H^+], 430.1003; found, 430.1005.

General Procedure for Synthesis of SPO Compounds 4. Intermediate compound **3** (1 equiv) was added to a dry three-necked flask under argon, with or without LiCl (1 equiv; as indicated) in anhydrous THF or 2-MeTHF (2−3 mL/mmol) and the mixture was cooled to −10 °C (unless indicated otherwise). A Grignard reagent (4 equiv, commercial available or freshly prepared) was added slowly while monitoring the internal temperature (typically, kept below −5 °C), and then the reaction mixture was allowed to work-up to approximately −5 to 0 °C, unless otherwise indicated. Completion of the reaction was monitored by HPLC (typically 20−120 min). Saturated aqueous NH_4Cl (5 mL) was added slowly to quench the reaction. The organic solvent was collected and the aqueous residue was extracted with DCM (25 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography (deactivated with 10% water) eluted with a solvent gradient of hexane/EtOAc (from 50:50 to 100% EtOAc, unless indicated otherwise) to obtain the desired products **4**.

*(R)-tert-Butyl(phenyl)phosphine Oxide (**4a**).* SPO product **4a** was isolated as a white solid (335 mg) in 92% yield and 96.6% ee. The NMR data shown below are consistent with the literature and the absolute stereochemistry was assigned based on the previously reported chiral HPLC data.[14]

^1H NMR (500 MHz, $CDCl_3$): δ 7.70−7.66 (m, 2H), 7.58 (dt, J = 1.3, 7.1 Hz, 1H), 7.52−7.48 (m, 2H), 7.03 (d, J = 450.0 Hz, 1H), 1.15 (d, J = 16.6 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 132.5 (d, J = 2.8 Hz), 131.0 (d, J = 9.9 Hz), 129.0 (d, J = 89.4 Hz), 128.5 (d, J = 11.7 Hz), 32.0 (d, J = 68.8 Hz), 23.5 (d, J = 2.1 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 47.43. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/isopropanol (90/10), 1.0 mL/min, 220 nm, (S), rt = 12.52 min, (R), rt = 17.54 min.

*(R)-tert-Butyl(3-(trifluoromethyl)phenyl)phosphine Oxide (**4b**).* The crude product was purified by silica gel (deactivated with 10% water) chromatography using a solvent gradient of hexane/EtOAc (50:50 to 0:100) to obtain the desired product as a colorless oil (182 mg) in 86% yield and 97.5% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.53 (dd, J = 14.6, 7.6 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.30−7.23 (m, 2H), 7.21 (d, J = 454.3 Hz, 1H), 2.59 (s, 3H), 1.16 (d, J = 16.5 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 141.9 (d, J = 8.2 Hz), 132.0 (d, J = 14.6 Hz), 132.0, 131.7 (d, J = 10.0 Hz), 127.0 (d, J = 88.2 Hz), 125.4 (d, J = 12.4 Hz), 33.3 (d, J = 68.6 Hz), 23.9 (d, J = 2.3 Hz), 21.0 (d, J = 4.5 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 47.70. HRMS: calcd for $C_{11}H_{18}O_2P^+$ [M + H^+], 213.1039; found, 213.1046.

Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/IPA (85/15), 1.0 mL/min, 220 nm, (S), rt = 11.10 min, (R), rt = 15.04 min.

*(R)-tert-Butyl(3-(trifluoromethyl)phenyl)phosphine Oxide (**4c**).* Compound **4c** was isolated as a white solid (220 mg) in 88% yield and >99% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.98−7.82 (m, 3H), 7.67 (t, J = 7.6 Hz, 1H), 7.12 (dd, J = 458.3, 1.7 Hz, 1H), 1.18 (dd, J = 16.9, 2.1 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 134.2 (d, J = 9.5 Hz), 131.3 (d, J = 11.9 Hz), 131.0 (d, J = 11.9 Hz), 130.5 (d, J = 87.5 Hz), 129.2 (t, J = 3.1 Hz), 129.1, 127.7 (dq, J = 11.1, 3.8 Hz), 32.1 (d, J = 69.4 Hz), 23.3. $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 45.45. HRMS: calcd for $C_{11}H_{15}F_3OP^+$ [M + H^+], 251.0807; found, 251.0816. Chiral HPLC: Chiralpak OJ-H, 4.6 × 250 mm; hexane/IPA (85/15), 1.0 mL/min, 220 nm, (S), rt = 8.67 min, (R), rt = 11.68 min.

*(R)-tert-Butyl(3,5-di-tert-butylphenyl)phosphine Oxide (**4d**).* Freshly prepared 3,5-di-*tert*-butylphenylmagnesium bromide (1 M in THF, 4 mmol, 4 mL) was added slowly to the solution of **3** at 0 °C, while keeping the internal temperature below 5 °C. The crude product was purified by silica gel (deactivated with 10% water) chromatography eluted with a solvent gradient of hexane/EtOAc (from 70:30 to 20:80) to obtain the desired product as a colorless oil (217 mg) in 74% yield and 94% ee.

^1H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, J = 1.5 Hz, 1H), 7.50 (d, J = 1.8 Hz, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.02 (d, J = 446.4 Hz, 1H), 1.34 (s, 18H), 1.14 (d, J = 16.4 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 151.1 (d, J = 11.7 Hz), 127.9 (d, J = 90.9 Hz), 126.5 (d, J = 2.8 Hz), 125.0 (d, J = 10.9 Hz), 35.0 (d, J = 0.7 Hz), 31.9 (d, J = 68.8 Hz), 31.3, 23.6 (d, J = 2.1 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 49.30. HRMS: calcd for $C_{18}H_{32}OP^+$ [M + H^+], 295.2185; found, 295.2187. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/IPA (95/5), 1.0 mL/min, 220 nm, (S), rt = 5.51 min, (R), rt = 11.79 min.

*(R)-tert-Butyl(4-methoxyphenyl)phosphine Oxide (**4e**).* Compound **4e** was isolated as a white solid (319 mg) in 75% yield and 91% ee (with 1 equiv of LiCl, the reaction gave 92% ee). The NMR data shown below are consistent with the literature and absolute stereochemistry was assigned based on the previously reported chiral HPLC data.[14] ^1H NMR (500 MHz, $CDCl_3$): δ 7.61 (dd, J = 8.7, 11.7 Hz, 2H), 7.00 (dd, J = 1.9, 8.7 Hz, 2H), 6.99 (d, J = 450.3 Hz, 1H), 1.13 (d, J = 16.6 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 162.9 (d, J = 2.8 Hz), 132.7 (d, J = 11.3 Hz), 120.0 (d, J = 95.9 Hz), 114.1 (d, J = 12.8 Hz), 55.3, 32.1 (d, J = 70.4 Hz), 23.4 (d, J = 2.2 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 46.90. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (S), rt = 8.30 min, (R), rt = 8.99 min.

*(R)-tert-Butyl(4-chlorophenyl)phosphine Oxide (**4f**).* Compound **4f** was obtained as a white solid (335 mg) in 77% yield and 95% ee. The NMR data shown below are consistent with the literature and absolute stereochemistry was assigned based on the previously reported chiral HPLC data.[14] ^1H NMR (500 MHz, $CDCl_3$): δ 7.65−7.61 (m, 2H), 7.51−7.49 (m, 2H), 7.04 (d, J = 453.7 Hz, 1H), 1.15 (d, J = 16.8 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 139.0 (d, J = 3.3 Hz), 132.3 (d, J = 10.7 Hz), 129.0 (d, J = 12.3 Hz), 127.5 (d, J = 90.0 Hz), 32.1 (d, J = 69.7 Hz), 23.4 (d, J = 2.1 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 45.83. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/isopropanol (90/10), 1.0 mL/min, 220 nm, (S), rt = 11.12 min, (R), rt = 12.98 min.

*(R)-tert-Butylhydrophosphoryl Benzonitrile (**4g**).* Compound **4g** was isolated as a yellow oil (170 mg) in 82% yield and 99.2% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.85−7.79 (m, 4H), 7.11 (d, J = 460.1 Hz, 1H), 1.17 (d, J = 17.0 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 M, $CDCl_3$):

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δ 134.5 (d, J = 84.5 Hz), 132.0 (d, J = 11.6 Hz), 131.6 (d, J = 9.9 Hz), 117.7 (d, J = 1.4 Hz), 116.2 (d, J = 2.9 Hz), 32.2 (d, J = 69.0 Hz), 23.3 (d, J = 1.9 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 44.87. HRMS: calcd for $C_{11}H_{15}NOP^+$ [M + H$^+$], 208.0886; found, 208.0894. Chiral HPLC: Chiralpak OJ-H, 4.6 × 250 mm; hexane/IPA (80/20), 1.0 mL/min, 220 nm, (S), rt = 8.12 min, (R), rt = 10.22 min.

*(R)-tert-Butyl(4-(dimethylamino)phenyl)phosphine Oxide (**4h**).* The pure SPO analog **4h** was isolated as a white solid (216 mg) in 96% yield and >99% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.47 (dd, J = 11.8, 8.9 Hz, 2H), 6.91 (d, J = 445.9 Hz, 1H), 6.70 (dd, J = 8.9, 2.1 Hz, 2H), 3.00 (s, 6H), 1.10 (d, J = 16.4 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 M, $CDCl_3$): δ 152.8 (d, J = 2.3 Hz), 132.2 (d, J = 11.2 Hz), 113.4 (d, J = 100.9 Hz), 111.2 (d, J = 12.6 Hz), 40.0, 32.2 (d, J = 70.9 Hz), 23.6 (d, J = 2.0 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 47.82. HRMS: calcd for $C_{12}H_{21}NOP^+$ [M + H$^+$], 226.1355; found, 226.1362. Chiral HPLC: Chiralpak OD, 4.6 × 250 mm; hexane/IPA (85/15), 1.0 mL/min, 220 nm, (S), rt = 10.79 min, (R), rt = 15.43 min.

*(R)-tert-Butyl(2-methoxyphenyl)phosphine Oxide (**4i**).* SPO analogue **4i** was obtained as pale yellow oil (308 mg) in 72% yield but racemic. The addition of 1 equiv of LiCl to the Grignard reagent resulted is a slight improvement in enantioselectivity, giving a 38% ee. The NMR data shown below are consistent with the literature and absolute stereochemistry was assigned based on the previously reported chiral HPLC data.[14] ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, J = 475.8 Hz, 1H), 7.76−7.72 (m, 1H), 7.51 (dt, J = 0.85, 8.2 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.93 (dd, J = 5.2, 8.3 Hz, 1H), 3.84 (s, 3H), 1.16 (d, J = 16.8 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 M, $CDCl_3$): δ 160.6 (d, J = 3.6 Hz), 133.8 (d, J = 2.1 Hz), 133.7 (d, J = 5.8 Hz), 121.0 (d, J = 10.7 Hz), 117.7 (d, J = 88.3 Hz), 110.7 (d, J = 5.8 Hz), 55.3, 32.6 (d, J = 70.8 Hz), 23.8 (d, J = 2.5 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 36.52. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/isopropanol (90/10), 1.0 mL/min, 220 nm, (S), rt = 12.82 min, (R), rt = 22.85 min.

*(R)-tert-Butyl(2-(methylthio)phenyl)phosphine Oxide (**4j**).* The SPO compound **4j** was isolated as colorless oil (232 mg) in 51% yield (containing 10% of an impurity which could not be separated from the product) and 30% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.77 (ddd, J = 11.7, 7.6, 1.2 Hz, 1H), 7.64 (d, J = 471.2 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.38 (dd, J = 7.8, 4.7 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 2.51 (s, 3H), 1.21 (d, J = 16.8 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 142.2 (d, J = 7.4 Hz), 133.1 (d, J = 7.8 Hz), 132.4 (d, J = 2.4 Hz), 128.8 (d, J = 89.9 Hz), 127.9 (d, J = 7.6 Hz), 125.3 (d, J = 10.5 Hz), 33.2 (d, J = 69.7 Hz), 24.0 (d, J = 2.3 Hz), 17.4. $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 37.76. HRMS: calcd for $C_{11}H_{18}OPS^+$ [M + H$^+$], 229.0810; found, 229.0810. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/isopropanol (85/15), 1.0 mL/min, 220 nm, (S), rt = 8.39 min, (R), rt = 16.50 min.

*(R)-tert-Butyl(o-tolyl)phosphine Oxide (**4k**).* A three-necked flask under argon was charged with compound **3** (1 mmol) and LiCl (0.5 M in THF, 2 mL) at rt. *o*-Tolylmagnesium chloride (1 M in THF, 4 mmol, 4 mL) was added slowly while keeping the internal temperature below 30 °C. The reaction mixture was stirred for 10 min for complete conversion. SPO analogue 4k was isolated after purification as a colorless oil (122 mg) in 62% yield and 24% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (dd, J = 7.7, 14.7 Hz, 1H), 7.43 (dt, J = 1.3, 8.9 Hz, 1H), 7.30−7.26 (m, 2H), 7.22 (d, J = 454.0 Hz, 1H), 2.61 (s, 3H), 1.18 (d, J = 16.5 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 141.9 (d, J = 8.1 Hz), 132.1 (d, J = 12.2 Hz), 132.0 (d, J = 2.5 Hz), 131.7 (d, J = 9.9 Hz), 127.1 (d, J = 87.6 Hz), 125.4 (d, J = 12.3 Hz), 33.3 (d, J = 68.3 Hz), 24.0 (d, J = 2.4 Hz), 21.1 (d, J = 4.5 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 47.68. HRMS: calcd for $C_{11}H_{18}OP^+$ [M + H$^+$], 197.1090; found, 197.1089. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/IPA (90/10), 1.0 mL/min, 220 nm, (R), rt = 9.97 min, (S), rt = 17.20 min.

*(R)-tert-Butyl(naphthalen-1-yl)phosphine Oxide (**4l**).* A three-necked flask under argon was charged with compound **3** (1 mmol) and LiCl (0.5 M in THF, 2 mL) at rt. Freshly prepared 1-naphthylmagnesium bromide (1.0 M in THF, 4 mmol, 4 mL) was added slowly while keeping the internal temperature below 30 °C. The reaction mixture was stirred for 10 mins to complete the reaction. The crude product was purified by silica chromatography (loaded on deactivated with 10% water) eluted with a solvent gradient of hexane/EtOAc (from 70:30 to 20:80) to obtained the desired product as a white solid (115 mg) in 50% yield and 78% ee. The NMR data shown below are consistent with the literature and absolute stereochemistry was assigned based on the previously reported chiral HPLC data.[14] ^1H NMR (500 MHz, $CDCl_3$): δ 8.72 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.91 (s, 1H), 7.76 (dd, J = 6.7, 17.8 Hz, 1H), 7.61−7.51 (m, 3H), 7.45 (d, J = 447.5 Hz, 1H), 1.19 (d, J = 16.7 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 134.1 (d, J = 8.0 Hz), 133.8 (d, J = 8.5 Hz), 133.2 (d, J = 2.9 Hz), 131.8 (d, J = 12.8 Hz), 128.8 (d, J = 1.3 Hz), 127.4 (d, J = 0.3 Hz), 126.8 (d, J = 4.7 Hz), 126.7, 125.4 (d, J = 86.4 Hz), 124.2 (d, J = 14.4 Hz), 33.6 (d, J = 68.0 Hz), 24.5 (d, J = 2.4 Hz).

$^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 52.58. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (S), rt = 5.39 min, (R), rt = 6.70 min.

*(R)-tert-Butyl(2-methoxynaphthalen-1-yl)phosphine Oxide (**4m**).* 2-Methoxynaphthalen-1-yl magnesium bromide (1 M in 2-MeTHF, 4 mmol, 4 mL) was added slowly to a solution of **3** in 2-MeTHF at 0 °C, while keeping the internal temperature below 5 °C. SPO analogue **4m** was obtained as a colorless oil (162 mg) in 62% yield and 90% ee. The NMR data shown below are consistent with the literature and absolute stereochemistry was assigned based on the previously reported chiral HPLC data.[14] ^1H NMR (500 MHz, $CDCl_3$): δ 8.95 (d, J = 8.7 Hz, 1H), 8.00−7.97 (m, 1H), 7.90 (d, J = 491.4 Hz, 1H), 7.78−7.73 (m, 1H), 7.54−7.47 (m, 1H), 7.39−7.35 (m, 1H), 7.23 (dd, J = 9.1, 4.8 Hz, 1H), 3.94 (s, 3H), 1.22 (d, J = 16.9 Hz, 9H). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 36.30. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/IPA (85/15), 1.0 mL/min, 220 nm, (S), rt = 7.66 min; (R), rt = 15.92 min.

*(R)-tert-Butyl(phenanthren-9-yl)phosphine Oxide (**4n**).* A three-necked flask under argon was charged with **3** (1 mmol) and LiCl (0.5 M in THF, 2 mL) at rt. 9-Phenanthrylmagnesium bromide (0.5 M in THF, 4 mmol, 8 mL) was added slowly while keeping the internal temperature below 30 °C. The crude product was purified by silica gel (deactivated with 10% water) chromatography using a solvent gradient of hexane/EtOAc (from 70:30 to 20:80). SPO analogue **4n** was isolated as a very viscous oil, which solidified to a white foam under vacuum (206 mg) in 73% yield and 80% ee. The NMR data shown below are consistent with the literature and absolute stereochemistry was assigned based on the previously reported chiral HPLC data.[14] ^1H NMR (500 MHz, $CDCl_3$): δ 8.78 (d, J = 8.1 Hz, 1H), 8.74 (d, J = 8.3 Hz, 1H), 8.71 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 19.3 Hz, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.78 (dt, J = 1.1, 8.2 Hz, 1H), 7.72 (dt, J = 1.2, 7.0 Hz, 1H), 7.68−7.65 (m, 2H), 7.53 (d, J = 458.5 Hz, 1H), 1.23 (d, J = 16.8 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 134.6 (d, J = 12.4 Hz), 132.1 (d, J = 2.2 Hz), 131.3 (d, J = 8.2 Hz), 130.6 (d, J = 8.1 Hz), 129.7 (d, J = 14.8 Hz), 129.7, 129.1, 127.8 (d, J = 4.4 Hz), 127.4, 127.3 (d, J = 0.8 Hz), 127.2, 124.5 (d, J = 85.9 Hz), 123.1 (d, J = 1.1 Hz), 122.8 (d, J = 0.8 Hz), 33.7 (d, J = 67.8 Hz), 24.7 (d, J = 2.4 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 53.69. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (S), rt = 6.12 min, (R), rt = 7.25 min.

*(R)-tert-Butyl(thiophen-2-yl)phosphine Oxide (**4o**).* SPO product **4o** was isolated as a white solid (158 mg) in 84% yield and 98.8% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.76−7.75 (m, 1H), 7.63−7.61 (m, 1H), 7.26−7.24 (m, 1H), 7.21 (d, J = 463.9 Hz, 1H), 1.20 (d, J = 17.8 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 135.6 (d, J = 9.4 Hz), 133.2 (d, J = 4.2 Hz), 128.8 (d, J = 94.0 Hz), 128.1 (d, J = 13.2 Hz), 32.2 (d, J = 74.3 Hz), 23.3 (d, J = 2.6 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 36.61. HRMS: calcd for $C_8H_{14}OPS^+$ [M + H$^+$], 189.0497; found, 189.0497. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/IPA (90/10), 1.0 mL/min, 220 nm, (S), rt = 12.26 min, (R), rt = 14.51 min.

*(R)-tert-Butyl(thiophen-3-yl)phosphine Oxide (**4p**).* A three-necked flask under argon was charged starting template-SPO (0.5 mmol) and LiCl (0.5 M in THF, 1 mL) at 0 °C. 3-Thienylmagnesium iodide (0.3 M in THF, 2 mmol, 6.67 mL) was added slowly while keeping the internal temperature below 5 °C. The desired product **4p**

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was isolated as a pale yellow solid (60 mg) in 64% yield and 96.6% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97−7.85 (m, 1H), 7.54−7.44 (m, 1H), 7.35−7.30 (m, 1H), 7.13 (d, J = 456.0 Hz, 1H) 1.17 (d, J = 17.2 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 134.1 (d, J = 13.2 Hz), 130.3 (d, J = 91.9 Hz), 128.3 (d, J = 14.6 Hz), 127.4 (d, J = 14.2 Hz), 32.0 (d, J = 72.3 Hz), 23.4 (d, J = 2.5 Hz). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 37.49. HRMS: calcd for $C_8H_{14}OPS^+$ [M + H$^+$], 189.0497; found, 189.0498. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (S), rt = 5.89 min, (R), rt = 6.35 min.

*(R)-Benzo[d]thiazol-2-yl(tert-butyl)phosphine Oxide (**4q**). Preparation of the Grignard Reagent.* To a solution of benzothiazole (2 mmol) in 1 mL of THF was added 1 M *t*-BuMgCl (2 mmol) while the reaction temperature was maintained between 0 and 5 °C and the solution was allowed to stir for 20 min at this temperature. A three-necked flask under argon was charged with **3** (0.5 mmol) and LiCl (0.5 M in THF, 1 mL) at 0 °C and the freshly prepared Grignard reagent was added slowly while keeping the internal temperature below 5 °C. SPO analogue **4q** was obtained as a slightly pink color solid (103 mg) in 86% yield and 28% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.62−7.58 (m, 1H), 7.55 (dd, J = 11.2, 4.0 Hz, 1H), 7.45 (d, J = 485.0 Hz, 1H), 1.32 (d, J = 17.9 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.0 (d, J = 108.1 Hz), 154.5 (d, J = 21.2 Hz), 136.4, 126.9 (d, J = 0.7 Hz), 126.9, 124.7, 122.1 (d, J = 0.8 Hz), 32.8 (d, J = 69.1 Hz), 23.4 (d, J = 2.1 Hz). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 37.74. HRMS: calcd for $C_{11}H_{15}NOPS^+$ [M + H$^+$], 240.0606; found, 240.0608. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (R), rt = 5.84 min, (S), rt = 7.30 min.

*(R)-Benzo[b]thiophen-2-yl(tert-butyl)phosphine Oxide (**4r**). Preparation of the Grignard Reagent.* Thianaphthene (2 mmol) was dissolved in anhydrous THF (3 mL) in a flame-dried round-bottomed flask, and the solution was cooled to −70 °C. *n*-BuLi (2 mmol, 2.5 M in hexane) was added, and the mixture was stirred for 2 h while warming to 0 °C. The resulting solution was mixed with a slurry of $MgBr_2{\cdot}Et_2O$ (2 mmol) in anhydrous THF (2 mL) at 0 °C and stirred at room temperature for 1 h until all solids were dissolved. A three-necked flask under argon was charged with **3** (0.5 mmol) and LiCl (0.5 M in THF, 1 mL) at 0 °C. Freshly prepared Grignard was added slowly while keeping the internal temperature below 5 °C. The desired SPO product **4r** was obtained as a white solid (51 mg) in 43% yield and 97.6% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97−7.86 (m, 3H), 7.50−7.40 (m, 2H), 7.29 (d, J = 465.9 Hz, 1H), 1.26 (d, J = 17.8 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 143.1 (d, J = 4.8 Hz), 139.0 (d, J = 13.3 Hz), 133.3 (d, J = 8.4 Hz), 129.7 (d, J = 89.1 Hz), 126.5, 125.1 (d, J = 0.9 Hz), 125.0, 122.5 (d, J = 1.6 Hz), 32.4 (d, J = 73.4 Hz), 23.4 (d, J = 2.5 Hz). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 37.43. HRMS: calcd for $C_{12}H_{16}OPS^+$ [M + H$^+$], 239.0654; found, 239.0654. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/isopropanol (80/20), 1.3 mL/min, 220 nm, (S), rt = 6.22 min, (R), rt = 7.19 min.

*(R)-(6-Bromopyridin-2-yl)(tert-butyl)phosphine Oxide (**4s**). Preparation of the Grignard Reagent.* Isopropylmagnesium chloride lithium chloride complex solution (1.3 M, 2 mmol) was added to 2,6-dibromopyridine (2 mmol) in dry THF (1.0 mL) at rt under nitrogen and the mixture was stirred at rt for 2 h. A three-necked flask under argon was charged with **3** (0.5 mmol) in THF (1 mL) and cooled to around 0 °C. Freshly prepared Grignard was added slowly while keeping the internal temperature below 5 °C. The crude product was purified by silica gel chromatography (silica was deactivated with 10% water) eluted with a solvent gradient of hexane/EtOAc/MeOH (50:50:0 to 0:100:0 and then to 0:90:10) to obtain the desired product as a pale yellow solid (81 mg) in 62% yield and 48% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (ddd, J = 7.3, 4.9, 0.9 Hz, 1H), 7.72 (td, J = 7.7, 3.5 Hz, 1H), 7.62 (ddd, J = 8.1, 2.0, 0.9 Hz, 1H), 7.13 (d, J = 477.9 Hz, 1H), 1.22 (d, J = 16.8 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.3 (d, J = 112.5 Hz), 142.4 (d, J = 20.3 Hz), 138.4 (d, J = 8.5 Hz), 130.7 (d, J = 2.5 Hz), 127.4 (d, J = 17.7 Hz), 32.2 (d, J = 66.4 Hz), 23.7 (d, J = 1.7 Hz). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 41.82. HRMS: calcd for $C_9H_{14}BrNOP^+$ [M + H$^+$], 261.9991; found, 261.9991. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (R), rt = 4.30 min, (S), rt = 5.37 min.

*(R)-tert-Butyl(pyridin-3-yl)phosphine Oxide (**4t**). Preparation of the Grignard Reagent.* Isopropylmagnesium chloride lithium chloride complex solution (1.3 M, 2 mmol) was added to 3-bromopyridine (2 mmol) in dry THF (1.0 mL) at rt under nitrogen and the mixture was stirred at rt for 2 h. A three-necked flask under argon was charged with **3** (0.5 mmol) in THF (1 mL) and cooled to 0 °C. Freshly prepared Grignard was added slowly while keeping the internal temperature below 5 °C. After completion of the reaction, the residue was purified by silica gel chromatography (deactivated with 10% water) eluted with a gradient of hexane/EtOAc/MeOH (50:50:0 to 0:100:0 to 0:90:10) to obtain the desired product as a yellow oil (37 mg) in 40% yield and 94% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86 (d, J = 5.5 Hz, 1H), 8.82−8.80 (m, 1H), 8.07−8.02 (m, 1H), 7.48−7.45 (m, 1H), 7.13 (d, J = 458.2 Hz, 1H), 1.19 (d, J = 17.1 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.3 (d, J = 2.2 Hz), 151.4 (d, J = 12.1 Hz), 138.9 (d, J = 7.4 Hz), 125.4 (d, J = 86.0 Hz), 123.6 (d, J = 8.5 Hz), 32.2 (d, J = 70.2 Hz), 23.3 (d, J = 2.2 Hz). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 42.78. HRMS: calcd for $C_9H_{15}NOP^+$ [M + H$^+$], 184.0886; found, 184.0886. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/isopropanol (85/15), 1.0 mL/min, 220 nm, (S), rt = 13.11 min, (R), rt = 14.22 min.

*(R)-(5-Bromopyridin-3-yl)(tert-butyl)phosphine Oxide (**4u**). Preparation of Grignard Reagent.* Isopropylmagnesium chloride lithium chloride complex solution (1.3 M, 2 mmol) was added to 3,5-dibromopyridine (2 mmol) in dry THF (1.0 mL) at rt under nitrogen and the reaction was stirred for 1.5 h.

The crude product was purified using a solvent gradient of hexane/EtOAc/MeOH (from 50:50:0 to 0:100:0 to 0:90:10) to obtain **4u** as a pale yellow solid in 64% yield (84.5 mg) and 96.4% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (t, J = 2.2 Hz, 1H), 8.75 (dd, J = 6.2, 1.6 Hz, 1H), 8.23−8.08 (m, 1H), 7.12 (d, J = 462.3 Hz, 1H), 1.20 (d, J = 17.4 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.5 (d, J = 2.2 Hz), 149.2 (d, J = 11.4 Hz), 141.1 (d, J = 7.8 Hz), 127.3 (d, J = 81.3 Hz), 121.5 (d, J = 9.6 Hz), 32.4 (d, J = 70.1 Hz), 23.3 (d, J = 2.2 Hz). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 40.84. HRMS: calcd for $C_9H_{14}BrNOP^+$ [M + H$^+$], 261.9991; found, 261.9991. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (90/10), 1.0 mL/min, 220 nm, (S), rt = 24.66 min, (R), rt = 25.22 min.

*(S)-((1,3-Dioxolan-2-yl)methyl)(tert-butyl)phosphine Oxide (**4v**).* SPO compound **4v** was isolated as yellow oil in 83% yield (159 mg), however, it was found to be chemically unstable. However, when **4v** was immediately reacted with BnBr under basic conditions, the TPO product (see Supporting Information, compound **8q**) obtained was racemic. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78 (*d*, J = 522.1 Hz, 1H), 6.48 (dd, J = 14.3, 6.8 Hz, 1H), 4.34−4.25 (m, 2H), 4.22 (dd, J = 14.3, 2.3 Hz, 1H), 4.06 (dd, J = 6.8, 2.3 Hz, 1H), 3.97−3.88 (m, 2H), 1.14 (d, J = 17.8 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 151.4, 87.3, 67.2 (d, J = 5.2 Hz), 64.2 (d, J = 7.7 Hz), 31.2 (d, J = 94.7 Hz), 22.6 (d, J = 1.6 Hz). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 51.16. HRMS: calcd for $C_8H_{18}O_3P^+$ [M + H$^+$], 193.0988; found, 193.0988.

*(S)-tert-Butyl(methyl)phosphine Oxide (**4w**).* SPO analogue **4w** was isolated as colorless oil in 77% yield 186 mg. The product was chemically unstable, even when stored in a refrigerator at 4 °C overnight. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60 (dd, J = 445.3, 3.8 Hz, 1H), 1.49 (dd, J = 12.8, 3.8 Hz, 3H), 1.18 (d, J = 16.7 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 30.8 (d, J = 69.5 Hz), 23.3 (d, J = 2.3 Hz), 9.7 (d, J = 61.2 Hz). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 45.43.

*(S)-Allyl(tert-butyl)phosphine Oxide (**4x**).* SPO product **4x** was obtained as colorless oil in 84% yield (247 mg), however, it was found to be chemically unstable. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.43 (ddd, J = 446.4, 5.0, 1.9 Hz, 1H), 5.98−5.89 (m, 1H), 5.32−5.22 (m, 2H), 2.85−2.45 (m, 2H), 1.20 (d, J = 16.4 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 127.9 (d, J = 9.2 Hz), 120.4 (d, J = 11.3 Hz), 31.7

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(d, J = 65.6 Hz), 30.6 (d, J = 57.5 Hz), 23.8 (d, J = 1.8 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 50.96.

*(S)-But-3-en-1-yl(tert-butyl)phosphine Oxide (**4y**).* The SPO compound **4y** was isolated as colorless oil in 66% yield (212 mg), however, it was found to be chemically unstable. ^1H NMR (500 MHz, $CDCl_3$): δ 6.47 (dd, J = 439.4, 7.1 Hz, 1H), 5.95−5.82 (m, 1H), 5.10 (ddd, J = 13.6, 11.2, 1.2 Hz, 2H), 2.65−2.35 (m, 2H), 1.93−1.65 (m, 2H), 1.19 (d, J = 16.2 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 136.9 (d, J = 12.5 Hz), 115.9, 31.0 (d, J = 67.5 Hz), 26.5 (d, J = 4.1 Hz), 23.7 (d, J = 1.9 Hz), 23.2 (d, J = 60.3 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 50.25. It is noteworthy that when the freshly prepared SPO **4y** was reacted with benzyl bromide the expected TOP product was isolated in low but in low yield and only 42% ee (see Supporting Information; compound **8r**).

General Procedure for the Synthesis of TPO Compounds 8. Intermediate compound **3** (1 equiv) was added in a dry three-necked flask under argon, with LiCl (1 equiv) in anhydrous THF at 0 °C. A Grignard reagent (4 equiv, commercial available or freshly prepared) was added slowly while keeping the internal temperature below 5 °C. The reaction mixture was stirred at 0 °C for 20 min, before an electrophile was added dropwise and the mixture was slowly warmed-up to rt and stirring was continued for approximately 2 h; completion of the reaction was monitors by HPLC. Saturated aqueous NH_4Cl solution (5 mL) was added slowly to quench the reaction. The organic solvent was collected and the aqueous residue was extracted with DCM (25 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography eluted with a solvent gradient of hexane/EtOAc/MeOH (as indicated for each example) to obtain the desired TPO product **8**.

*(R)-tert-Butyl(methyl)(thiophen-2-yl)phosphine Oxide (**8a**).* The electrophile used was MeI and the crude product was purified by silica gel chromatography using a solvent gradient of hexane/EtOAc/MeOH (from 50:50:0 to 0:100:0 to 0:90:10) to obtain **8a** as a colorless viscous oil in 87% yield (35.1 mg) and 98.8% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.73−7.68 (m, 1H), 7.56 (ddd, J = 6.1, 3.6, 0.9 Hz, 1H), 7.22 (ddd, J = 5.0, 3.6, 1.7 Hz, 1H), 1.74 (d, J = 12.3 Hz, 3H), 1.19 (d, J = 15.6 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 135.6 (d, J = 7.8 Hz), 132.6 (d, J = 3.8 Hz), 132.0 (d, J = 93.9 Hz), 128.1 (d, J = 12.4 Hz), 32.8 (d, J = 75.4 Hz), 24.2 (d, J = 1.1 Hz), 12.6 (d, J = 68.3 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 44.95. HRMS: calcd for $C_9H_{16}OPS^+$ [M + H^+], 203.0654; found, 203.0654. Chiral HPLC: Chiralpak OD-H, 4.6 × 250 mm; hexane/isopropanol (90/10), 1.0 mL/min, 220 nm, (R), rt = 9.84 min, (S), rt = 14.10 min.

*(R)-Benzyl(tert-butyl)(thiophen-2-yl)phosphine Oxide (**8b**).* The electrophile used was BnBr and the crude product was purified by silica gel chromatography using a solvent gradient of hexane/EtOAc (50:50 to 0:100) to obtain **8b** as a white solid in 67% yield (37.5 mg) in 99.2% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.68−7.65 (m, 1H), 7.51 (ddd, J = 5.9, 3.6, 1.0 Hz, 1H), 7.29−7.13 (m, 6H), 3.59−3.15 (m, 2H), 1.21 (d, J = 15.4 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 136.6 (d, J = 7.1 Hz), 132.7 (d, J = 3.5 Hz), 131.7 (d, J = 8.2 Hz), 130.2 (d, J = 91.3 Hz), 130.1 (d, J = 5.2 Hz), 128.4 (d, J = 2.2 Hz), 128.0 (d, J = 12.3 Hz), 126.7 (d, J = 2.6 Hz), 34.2 (d, J = 61.4 Hz), 33.6 (d, J = 72.0 Hz), 24.6 (d, J = 0.5 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 44.34. HRMS: calcd for $C_{15}H_{20}OPS^+$ [M + H^+], 279.0967; found, 279.0967. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (R), rt = 3.81 min, (S), rt = 4.35 min.

*(R)-Allyl(tert-butyl)(thiophen-2-yl)phosphine Oxide (**8c**).* Allyl bromide was used as the electrophile and the product was purified by silica gel chromatography eluting with a solvent gradient of hexane/EtOAc (from 50:50 to 0:100) to give **8c** as a white solid in 78% yield (35.9 mg) and 98.8% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 7.72 (t, J = 4.2 Hz, 1H), 7.57 (dd, J = 5.1, 3.7 Hz, 1H), 7.24−7.19 (m, 1H), 5.98−5.72 (m, 1H), 5.23−5.13 (m, 2H), 3.03−2.69 (m, 2H), 1.21 (d, J = 15.4 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 136.3 (d, J = 7.2 Hz), 132.8 (d, J = 3.5 Hz), 130.2 (d, J = 91.4 Hz), 128.1 (d, J = 12.3 Hz), 127.5 (d, J = 9.5 Hz), 120.6 (d, J = 11.0 Hz), 33.4 (d, J = 72.2 Hz), 32.4 (d, J = 63.5 Hz), 24.5 (d, J = 0.6 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 45.16. HRMS: calcd for $C_{11}H_{18}OPS^+$ [M + H^+], 229.0810; found, 229.0810. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/isopropanol (95/5), 1.0 mL/min, 220 nm, (R), rt = 17.37 min, (S), rt = 18.27 min.

*(S)-tert-Butyl(thiophen-2-yl)((trimethylsilyl)methyl)phosphine Oxide (**8d**).* Iodomethyltrimethylsilane was used as the electrophile and the product was purified by silica chromatography (solvent gradient: hexane/EtOAc from 50:50 to 0:100) to obtain **8d** as a white solid in 58% yield (32 mg) and 98.8% ee.

^1H NMR (500 MHz, $CDCl_3$): δ 7.65 (ddd, J = 4.7, 3.6, 1.0 Hz, 1H), 7.49 (ddd, J = 6.0, 3.5, 1.0 Hz, 1H), 7.17 (ddd, J = 5.0, 3.6, 1.6 Hz, 1H), 1.30 (ddd, J = 23.3, 15.5, 11.6 Hz, 2H), 1.13 (d, J = 15.5 Hz, 9H), 0.00 (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 135.5 (d, J = 7.5 Hz), 133.7 (d, J = 90.7 Hz), 132.2 (d, J = 3.5 Hz), 127.8 (d, J = 12.1 Hz), 33.7 (d, J = 74.4 Hz), 24.1 (d, J = 1.1 Hz), 14.3 (d, J = 59.4 Hz), 0.0 (d, J = 2.6 Hz).

$^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 46.38. HRMS: calcd for $C_{12}H_{24}OPSSi^+$ [M + H^+], 275.1049; found, 275.1048. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH(95/5), 1.3 mL/min, 220 nm, (R), rt = 6.60 min, (S), rt = 6.99 min.

*(R)-tert-Butyl(quinolin-8-ylmethyl)(thiophen-2-yl)phosphine Oxide (**8e**).* 8-(Bromomethyl)quinoline was used as the electrophile and the product was purified by silica chromatography (solvent gradient: hexane/EtOAc from 50:50 to 0:100) to obtain **8e** as a white solid in 61% yield (40 mg) and 98.4% ee.

^1H NMR (500 MHz, $CDCl_3$): δ 8.92 (dd, J = 4.1, 1.7 Hz, 1H), 8.09 (dt, J = 7.5, 3.8 Hz, 2H), 7.66 (d, J = 8.2 Hz, 1H), 7.58−7.50 (m, 2H), 7.46 (t, J = 7.7 Hz, 1H), 7.38 (dd, J = 8.2, 4.2 Hz, 1H), 7.01 (ddd, J = 5.2, 3.6, 1.8 Hz, 1H), 4.64−4.15 (m, 2H), 1.20 (d, J = 15.4 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 149.2 (d, J = 0.7 Hz), 146.4 (d, J = 5.5 Hz), 136.4, 135.7 (d, J = 7.9 Hz), 132.5 (d, J = 3.7 Hz), 131.2 (d, J = 91.9 Hz), 131.2 (d, J = 7.6 Hz), 131.2 (d, J = 5.1 Hz), 128.4 (d, J = 1.6 Hz), 127.5 (d, J = 12.4 Hz), 126.6 (d, J = 2.6 Hz), 126.5 (d, J = 2.8 Hz), 120.9, 33.9 (d, J = 72.3 Hz), 26.4 (d, J = 62.5 Hz), 24.6 (d, J = 0.7 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 46.65. HRMS: calcd for $C_{18}H_{21}NOPS^+$ [M + H^+], 330.1076; found, 330.1076. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (R), rt = 4.98 min, (S), rt = 5.58 min.

*(S)-tert-Butyl(pyridin-2-yl)(thiophen-2-yl)phosphine Oxide (**8f**).* 2-Fluoropyridine was used as the electrophile and the product was obtained as a white solid in 67% yield (35.8 mg) and 97.6% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 8.80 (d, J = 4.4 Hz, 1H), 8.24−8.16 (m, 1H), 7.91 (ddd, J = 6.1, 3.6, 1.0 Hz, 1H), 7.83 (tdd, J = 7.7, 3.6, 1.7 Hz, 1H), 7.75−7.70 (m, 1H), 7.43−7.35 (m, 1H), 7.19 (ddd, J = 4.8, 3.6, 2.1 Hz, 1H), 1.23 (d, J = 15.8 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 155.8 (d, J = 123.9 Hz), 149.4 (d, J = 18.6 Hz), 137.3 (d, J = 7.4 Hz), 135.9 (d, J = 8.7 Hz), 133.8 (d, J = 3.3 Hz), 129.2 (d, J = 97.1 Hz), 128.7 (d, J = 18.3 Hz), 127.5 (d, J = 13.1 Hz), 125.2 (d, J = 3.2 Hz), 33.9 (d, J = 73.6 Hz), 24.4 (d, J = 0.6 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 34.36. HRMS: calcd for $C_{13}H_{17}NOPS^+$ [M + H^+], 266.0763; found, 266.0764. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/isopropanol (80/20), 1.3 mL/min, 220 nm, (R), rt = 3.87 min, (S), rt = 4.37 min.

*(S)-(5-Bromopyridin-2-yl)(tert-butyl)(thiophen-2-yl)phosphine Oxide (**8g**).* 5-Bromo-2-fluoropyridine was used as the electrophile and the product was purified by silica chromatography (solvent gradient: hexane/EtOAc from 50:50 to 0:100) to obtain **8g** as a pale yellow solid (48.7 mg) in 71% yield and 98% ee. ^1H NMR (500 MHz, $CDCl_3$): δ 8.87 (d, J = 2.2 Hz, 1H), 8.10 (dd, J = 7.8, 4.8 Hz, 1H), 8.00−7.95 (m, 1H), 7.88 (ddd, J = 6.1, 3.6, 1.0 Hz, 1H), 7.76−7.70 (m, 1H), 7.20 (ddd, J = 4.8, 3.6, 2.1 Hz, 1H), 1.22 (d, J = 16.0 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 154.1 (d, J = 122.6 Hz), 150.7 (d, J = 19.0 Hz), 138.6 (d, J = 9.3 Hz), 137.4 (d, J = 7.5 Hz), 134.0 (d, J = 3.4 Hz), 129.8 (d, J = 19.0 Hz), 128.6 (d, J = 98.3 Hz), 127.7 (d, J = 13.2 Hz), 123.6 (d, J = 3.2 Hz), 34.0 (d, J = 74.0 Hz), 24.3 (d, J = 0.5 Hz). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 34.56. HRMS: calcd for $C_{13}H_{16}BrNOPS^+$ [M + H^+], 343.9868; found, 343.9870. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/

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isopropanol (80/20), 1.3 mL/min, 220 nm, (R), rt = 3.99 min, (S), rt = 4.39 min.

*(S)-tert-Butyl(3-fluoropyridin-2-yl)(thiophen-2-yl)phosphine Oxide (**8h**).* 2,3-Difluoropyridine was used as the electrophile and the product was purified by silica gel chromatography (solvent gradient: hexane/EtOAc/MeOH from 50:50 to 0:100 to 0:90:10) to obtain **8h** as a white solid (42 mg) in 74% yield and 99.2% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, J = 3.9 Hz, 1H), 7.92 (dd, J = 5.8, 4.0 Hz, 1H), 7.76 (t, J = 4.1 Hz, 1H), 7.54−7.39 (m, 2H), 7.25−7.17 (m, 1H), 1.26 (d, J = 16.2 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.5 (dd, J = 267.3, 11.8 Hz), 144.9 (dd, J = 17.0, 4.8 Hz), 142.6 (dd, J = 121.2, 14.3 Hz), 138.1 (d, J = 7.8 Hz), 134.5 (d, J = 3.2 Hz), 128.9 (d, J = 101.9 Hz), 127.4 (d, J = 13.7 Hz), 127.0 (dd, J = 4.8, 3.1 Hz), 124.5 (dd, J = 20.2, 4.9 Hz), 34.9 (d, J = 75.2 Hz), 24.3. ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 36.88 (d, J = 11.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ −113.02 (d, J = 11.4 Hz).

HRMS: calcd for $C_{13}H_{16}FNOPS^+$ [M + H^+], 284.0669; found, 284.0669. Chiral HPLC: Chiralpak OD-H, 4.6 × 150 mm; hexane/isopropanol (95/5), 1.0 mL/min, 220 nm, (R), rt = 28.40 min, (S), rt = 32.91 min.

*(S)-tert-Butyl(3-methylpyridin-2-yl)(thiophen-2-yl)phosphine Oxide (**8i**).* 3-Methyl-2-fluoropyridine was used as the electrophile and the product was purified by silica gel chromatography (solvent gradient: hexane/EtOAc/MeOH from 50:50:0 to 0:100:0 to 0:90:10) to obtain **8i** as a white solid in 78% yield (43.4 mg) and 98.8% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (d, J = 4.3 Hz, 1H), 7.88 (dd, J = 5.6, 3.7 Hz, 1H), 7.71 (t, J = 4.1 Hz, 1H), 7.55−7.49 (m, 1H), 7.29−7.25 (m, 1H), 7.18 (t, J = 5.2 Hz, 1H), 2.77 (s, 3H), 1.21 (d, J = 15.5 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 152.0 (d, J = 126.2 Hz), 145.6 (d, J = 19.3 Hz), 140.9 (d, J = 19.9 Hz), 139.2 (d, J = 8.7 Hz), 137.8 (d, J = 7.7 Hz), 134.5 (d, J = 2.4 Hz), 130.3 (d, J = 98.4 Hz), 127.2 (d, J = 13.5 Hz), 124.8 (d, J = 3.2 Hz), 35.1 (d, J = 73.2 Hz), 24.6, 18.7. ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 39.60. HRMS: calcd for $C_{14}H_{19}NOPS^+$ [M + H^+], 280.0919; found, 280.0920. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (R), rt = 3.18 min, (S), rt = 3.49 min.

*(R)-(5-Bromopyridin-2-yl)(tert-butyl)(thiophen-3-yl)phosphine Oxide (**8j**).* 5-Bromo-2-fluoropyridine was used as the electrophile and the product was purified by silica chromatography (solvent gradient: hexane/EtOAc from 50:50 to 0:100) to obtain **8j** as a yellow oil in 51% yield (35.2 mg) and 92.6% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86 (d, J = 2.1 Hz, 1H), 8.23 (dd, J = 6.0, 2.4 Hz, 1H), 8.11 (dd, J = 8.2, 4.9 Hz, 1H), 7.97 (dt, J = 8.2, 2.4 Hz, 1H), 7.70 (dd, J = 5.0, 1.1 Hz, 1H), 7.42 (dt, J = 5.1, 2.6 Hz, 1H), 1.19 (d, J = 15.6 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.8 (d, J = 118.8 Hz), 150.7 (d, J = 18.4 Hz), 138.6 (d, J = 9.1 Hz), 135.6 (d, J = 10.8 Hz), 130.5 (d, J = 12.4 Hz), 130.3 (d, J = 95.4 Hz), 130.1 (d, J = 18.2 Hz), 126.1 (d, J = 13.5 Hz), 123.5 (d, J = 3.2 Hz), 33.8 (d, J = 72.3 Hz), 24.3. ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 32.86. HRMS: calcd for $C_{13}H_{16}BrNOPS^+$ [M + H^+], 343.9868; found, 343.9869. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/isopropanol (85/15), 1.0 mL/min, 220 nm, (R), rt = 10.41 min, (S), rt = 20.68 min.

*(R)-(5-Bromopyridin-3-yl)(tert-butyl)(pyridin-2-yl)phosphine Oxide (**8k**).* A three-necked flask under argon charged with **3** (0.2 mmol) was cooled to 0 °C. Freshly prepared Turbo Grignard (4 equiv) was added slowly while keeping the internal temperature below 5 °C. The mixture was stirred for 20 min to complete the reaction and then 10 equiv of 2-fluoropyridine was added dropwise at 0 °C, the mixture was slowly warmed up to rt and allowed to stir overnight to complete the reaction. Saturated and degassed NH_4Cl aqueous solution (10 mL) was added slowly to quench the reaction. The organic solvent was collected and the aqueous residue was extracted with DCM (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography eluted with hexane/EtOA (50:50 to 0:100) to obtain TPO **8k** as a yellow solid in 15% yield (10.5 mg) and 96.8% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (dd, J = 4.0, 1.4 Hz, 1H), 8.83 (d, J = 4.7 Hz, 1H), 8.78 (t, J = 2.0 Hz, 1H), 8.70 (dt, J = 9.8, 1.9 Hz, 1H), 8.28−8.17 (m, 1H), 7.86 (tdd, J = 7.7, 3.6, 1.7 Hz, 1H), 7.48−7.41 (m, 1H), 1.23 (d, J = 15.7 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.2 (d, J = 120.6 Hz), 153.2 (d, J = 1.9 Hz), 151.4 (d, J = 8.0 Hz), 149.8 (d, J = 18.4 Hz), 142.7 (d, J = 6.1 Hz), 136.3 (d, J = 8.8 Hz), 129.3 (d, J = 17.7 Hz), 128.6 (d, J = 81.0 Hz), 125.6 (d, J = 3.2 Hz), 120.7 (d, J = 9.0 Hz), 34.2 (d, J = 69.9 Hz), 24.4. ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 30.28. HRMS: calcd for $C_{14}H_{17}BrN_2OP^+$ [M + H^+], 339.0256; found, 339.0257. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (S), rt = 6.06 min, (R), rt = 7.94 min.

*(R)-tert-Butyl(phenyl)(pyridin-2-yl)phosphine Oxide (**8l**).* In the synthesis of **8l**, in addition to the Grignard, LiCl (0.5 M in THF, 0.4 mL) was added in the first step, 2-fluoropyridine was added next as the electrophile and the product was purified by silica gel chromatography (solvent gradient: hexane/EtOAc from 50:50 to 0:100) to obtain **8l** as a white solid in 77% yield (40 mg) and 94% ee. The NMR data shown below are consistent with the literature and absolute stereochemistry was assigned based on the previously reported chiral HPLC data.[14] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.28−8.19 (m, 3H), 7.81 (tdd, J = 7.7, 3.3, 1.7 Hz, 1H), 7.53−7.47 (m, 1H), 7.44 (tdd, J = 8.4, 2.9, 1.3 Hz, 2H), 7.38 (dddd, J = 8.0, 4.8, 2.1, 1.3 Hz, 1H), 1.23 (d, J = 15.1 Hz, 9H). ^{13}C{^{1}H} NMR (125 M, $CDCl_3$): δ 156.9 (d, J = 117.2 Hz), 149.3 (d, J = 17.6 Hz), 135.9 (d, J = 8.5 Hz), 132.8 (d, J = 7.6 Hz), 131.4 (d, J = 2.8 Hz), 130.1 (d, J = 89.7 Hz), 129.2 (d, J = 17.0 Hz), 127.8 (d, J = 10.9 Hz), 125.0 (d, J = 3.1 Hz), 33.9 (d, J = 69.6 Hz), 24.6. ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 32.52. Chiral HPLC: Chiralpak AD-H, 4.6 × 250 mm; hexane/isopropanol (90/10), 1.0 mL/min, 220 nm, (S), rt = 12.07 min, (R), rt = 13.06 min.

*(R)-tert-Butyl(4-methoxyphenyl)(pyridin-2-yl)phosphine Oxide (**8m**).* In the synthesis of **8m**, in addition to the Grignard, LiCl (0.5 M in THF, 0.4 mL) was added in the first step, 2-fluoropyridine was used as the electrophile and the product was purified by silica chromatography (solvent gradient: hexane/EtOAc from 50:50 to 0:100) to obtain **8m** as a pale yellow oil in 68% yield (39.1 mg) and 87.4% ee. The NMR data shown below are consistent with the literature and absolute stereochemistry was assigned based on the previously reported chiral HPLC data.[14] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.79 (d, J = 4.7 Hz, 1H), 8.27−8.21 (m, 1H), 8.16 (t, J = 9.2 Hz, 2H), 7.80 (tdd, J = 7.7, 3.2, 1.8 Hz, 1H), 7.41−7.33 (m, 1H), 6.96 (dd, J = 8.9, 2.3 Hz, 2H), 3.83 (s, 3H), 1.21 (d, J = 15.1 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.2 (d, J = 2.9 Hz), 157.2 (d, J = 116.7 Hz), 149.2 (d, J = 17.5 Hz), 135.9 (d, J = 8.4 Hz), 134.6 (d, J = 8.7 Hz), 129.0 (d, J = 16.9 Hz), 124.8 (d, J = 3.1 Hz), 121.0 (d, J = 96.0 Hz), 113.5 (d, J = 11.8 Hz), 55.2, 33.9 (d, J = 70.5 Hz), 24.6. ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 32.84. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/isopropanol (80/20), 1.3 mL/min, 220 nm, (S), rt = 3.68 min; (R), rt = 4.16 min.

*(R)-tert-Butyl(4-chlorophenyl)(pyridin-2-yl)phosphine Oxide (**8n**).* In the synthesis of **8n**, in addition to the Grignard, LiCl (0.5 M in THF, 0.4 mL) was added in the first step, 2-fluoropyridine was added next as the electrophile and the product was purified by silica gel chromatography (solvent gradient: hexane/EtOAc from 50:50 to 0:100) to obtain **8n** as a colorless oil in 63% yield (37 mg) and 93.4% ee. The NMR data shown below are consistent with the literature and absolute stereochemistry was assigned based on the previously reported chiral HPLC data.[14] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80 (d, J = 4.2 Hz, 1H), 8.28−8.14 (m, 3H), 7.83 (tdd, J = 7.8, 3.4, 1.8 Hz, 1H), 7.47−7.36 (m, 3H), 1.21 (d, J = 15.3 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.4 (d, J = 118.3 Hz), 149.4 (d, J = 17.8 Hz), 138.2, 136.0 (d, J = 8.6 Hz), 134.3 (d, J = 8.2 Hz), 129.2 (d, J = 17.1 Hz), 128.6 (d, J = 90.2 Hz), 128.2 (d, J = 11.4 Hz), 125.1 (d, J = 3.1 Hz), 33.9 (d, J = 69.9 Hz), 24.5. ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 32.04. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (90/10), 1.3 mL/min, 220 nm, (S), rt = 5.59 min, (R), rt = 5.95 min.

*(S)-But-3-en-1-yl(tert-butyl)(pyridin-2-yl)phosphine Oxide (**8o**).* In the synthesis of **8o**, in addition to the Grignard, LiCl (0.5 M in THF, 0.4 mL) was added in the first step, 2-fluoropyridine was added next as the electrophile and the product was purified by silica gel chromatography (solvent gradient: hexane/EtOAc/MeOH from 50:50:0 to 0:100 then to 0:90:10) to obtain **8o** as a colorless oil in

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92% yield (43.7 mg) and 40% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (d, J = 4.6 Hz, 1H), 8.13 (dd, J = 6.9, 5.4 Hz, 1H), 7.82 (t, J = 7.7 Hz, 1H), 7.38 (dd, J = 8.1, 4.3 Hz, 1H), 5.92−5.74 (m, 1H), 4.97 (dd, J = 39.7, 13.6 Hz, 2H), 2.59−2.34 (m, 2H), 2.16−1.93 (m, 2H), 1.18 (d, J = 14.4 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.5 (d, J = 112.2 Hz), 149.5 (d, J = 17.5 Hz), 137.9 (d, J = 14.6 Hz), 135.7 (d, J = 8.1 Hz), 129.3 (d, J = 16.4 Hz), 125.0 (d, J = 3.0 Hz), 114.9, 32.7 (d, J = 66.6 Hz), 25.6 (d, J = 4.1 Hz), 24.6, 21.9 (d, J = 64.2 Hz). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 49.38. HRMS: calcd for $C_{13}H_{21}NOP^+$ [M + H$^+$], 238.1355; found, 238.1354. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (90/10), 1.3 mL/min, 220 nm, (R), rt = 6.07 min, (S), rt = 6.40 min.

*(S)-tert-Butyl(methyl)(pyridin-2-yl)phosphine Oxide (**8p**).* In the synthesis of **8p**, in addition to the Grignard, LiCl (0.5 M in THF, 0.4 mL) was added in the first step, 2-fluoropyridine was added next as the electrophile and the product was purified by silica gel chromatography (solvent gradient: hexane/EtOAc/MeOH from 50:50:0 to 0:90:10) to obtained **8p** as a colorless oil (30 mg) in 76% yield; however, the product is racemic if the reaction is carried out at 0 °C and enantiomerically enriched to 38% ee, if the reaction is carried out at −65 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (d, J = 4.6 Hz, 1H), 8.19−8.07 (m, 1H), 7.82 (t, J = 6.9 Hz, 1H), 7.44−7.33 (m, 1H), 1.79 (d, J = 12.9 Hz, 3H), 1.17 (d, J = 14.7 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 156.4 (d, J = 115.6 Hz), 149.5 (d, J = 17.8 Hz), 135.7 (d, J = 8.3 Hz), 128.5 (d, J = 17.2 Hz), 125.1 (d, J = 3.0 Hz), 32.6 (d, J = 68.5 Hz), 24.4, 9.7 (d, J = 67.6 Hz). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 48.09. HRMS: calcd for $C_{10}H_{17}NOP^+$ [M + H$^+$], 198.1042; found, 198.1043. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (R), rt = 4.48 min, (S), rt = 4.81 min.

*((1,3-Dioxolan-2-yl)methyl)(benzyl)(tert-butyl)phosphine Oxide (**8q**).* To a stirring degassed THF solution of freshly prepared SPO **4v** (0.2 mmol, 38.5 mg) was added sodium bis(trimethylsilyl)amide (1.1 equiv, 1 M in THF) dropwise at rt and allowed to stir for 15 min. The solution became turbid as the phosphinite anion was formed, a degassed solution of benzyl bromide (1.2 equiv) was added dropwise to the mixture, and reaction mixture was stirred at rt for 2 h. To quench the mixture, the equivalent volume of H_2O was added and the mixture was extracted five times with equal volumes of DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under vacuum to yield the crude TPO product. After flash column chromatography, the desired product was obtained as pale yellow oil in 60% yield (34 mg) but found to be completely racemic. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/ethanol (95/5), 1.0 mL/min, 220 nm, (R), rt = 8.45 min, (S), rt = 8.97 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46−7.07 (m, 5H), 6.41 (dd, J = 14.3, 6.8 Hz, 1H), 4.11 (dd, J = 14.3, 2.2 Hz, 1H), 4.04−3.93 (m, 2H), 3.88−3.75 (m, 1H), 3.70−3.48 (m, 2H), 3.27−2.98 (m, 2H), 1.18 (d, J = 15.5 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 151.5, 131.7 (d, J = 9.2 Hz), 130.2 (d, J = 5.1 Hz), 128.5 (d, J = 2.5 Hz), 126.7 (d, J = 2.8 Hz), 86.9, 67.6 (d, J = 4.8 Hz), 63.2 (d, J = 7.1 Hz), 33.6 (d, J = 91.6 Hz), 32.1 (d, J = 77.5 Hz), 24.4. ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 59.20. HRMS: calcd for $C_{15}H_{24}O_3P^+$ [M + H$^+$], 283.1458; found, 283.1459.

*(R)-Benzyl(but-3-en-1-yl)(tert-butyl)phosphine Oxide (**8r**).* To a stirring degassed THF solution of freshly prepared SPO **4y** (0.1 mmol, 16 mg), was added sodium bis(trimethylsilyl)amide (1 equiv, 1 M in THF) dropwise at room temperature and allowed to stir for 15 min. The solution became turbid as the phosphinite anion formed, a degassed solution of benzyl bromide (1 equiv) was added dropwise (a white precipitate formed), and the reaction mixture was stirred at rt for 2 h. To quench the mixture, an equivalent volume of H_2O was added and the mixture was extracted 5× with equal volumes of DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under vacuum to yield the crude TPO product **8r**. After flash column chromatography on silica gel, the desired product was obtained as white solid in 37% yield (9.3 mg) and 42% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47−7.12 (m, 5H), 5.81−5.60 (m, 1H), 4.90 (dd, J = 13.5, 2.2 Hz, 2H), 3.31−2.87 (m, 2H), 2.23 (d, J = 6.5 Hz, 1H), 1.97−1.53 (m, 4H), 1.19 (d, J = 14.1 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 138.1 (d, J = 13.8 Hz), 132.8 (d, J = 7.5 Hz), 129.9 (d, J = 4.8 Hz), 128.7 (d, J = 2.1 Hz), 126.8 (d, J = 2.5 Hz), 114.8, 33.0 (d, J = 55.8 Hz), 33.0 (d, J = 65.3 Hz), 26.0 (d, J = 4.1 Hz), 24.7, 23.2 (d, J = 60.8 Hz). ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ 52.41.

HRMS: calcd for $C_{15}H_{24}OP^+$ [M + H$^+$], 251.1559; found, 251.1559. Chiral HPLC: Chiralpak IC-3, 4.6 × 150 mm; hexane/ethanol (90/10), 1.3 mL/min, 220 nm, (R), rt = 6.87 min, (S), rt = 7.92 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00945.

^{1}H, ^{13}C, and ^{31}P NMR spectra, and chiral HPLC chromatograms (CIF)

X-ray data collection and structure refinement for **2b** and **3** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Youla.tsantrizos@mcgill.ca.

ORCID

Filip Topic: 0000-0003-3811-6036

Zhengxu S. Han: 0000-0001-8386-1356

Youla S. Tsantrizos: 0000-0002-6231-7498

Present Address

§AstaTech(Chengdu) BioPharmaceutical Corporation, 488 Kelin West Road, Wenjiang, Chengdu, Sichuan 611130, P.R. China.

Author Contributions

‖S.-G.L. and M.Y. Contributed equally.

Notes

The authors declare no competing financial interest.

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