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Asymmetric Library Synthesis of P-Chiral \( t \)-Butyl-Substituted Secondary and Tertiary Phosphine Oxides

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Supporting Information Placeholder

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 2-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 pre-hydrolysis 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, due to 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)\(^12,13\) or glucosamine-type as chiral auxiliaries.\(^12c\)
Crystallization-induced deracemization of tert-butylphenylphosphine oxide in the presence of iodine and (-)-
O,O'-dibenzoy-L-tartaric acid has also been reported (Scheme 1b).13 In many cases, these methods require multiple recrystals-
tizzations 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 auxiliarys 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 TPOs, which avoids the use of t-BuLi and pro-
vides P-chiral SPOs and TPOs with high enantiomeric purity.

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

a) Menthol as Chiral Auxiliary12,13

\[
\text{R} \xrightarrow{\text{2) H}_2\text{O}} \xrightarrow{\text{HCl}} \text{R} \text{S} \xrightarrow{\text{2) H}_2\text{O}} \xrightarrow{\text{t-BuLi}} \text{R} \text{S} \text{O} \xrightarrow{\text{2 equiv}} \text{R} \text{S} \xrightarrow{\text{-78°C}} \text{R} \text{S} \text{P} \text{H}
\]

b) Crystallization-induced Deracemization15

\[
\text{Ph} \xrightarrow{\text{1 mol% I}_2, \text{DIEP, Δ}} \xrightarrow{\text{(-)-L-dibenzoyletaric acid}} \text{Ph} \xrightarrow{\text{1 mol% I}_2, \text{DIEP, Δ}} \xrightarrow{\text{R} \text{S} \text{O} \xrightarrow{\text{t-BuLi}} \text{R} \text{S} \text{P} \text{H}}
\]

c) Chiral 1,2-Sulfanilamide Alcohols14

\[
\text{H} \xrightarrow{\text{R}^2 \text{R}^3 \text{R}^4 \text{R}^5 \text{N} \text{H} \text{SO}_3 \text{Ar}^1 \xrightarrow{\text{2) H}_2\text{O}} \text{R}^2 \text{R}^3 \text{R}^4 \text{R}^5 \text{P(O)Cl}_2 \xrightarrow{\text{5 equiv}} \text{t-BuLi}} \text{R}^2 \text{R}^3 \text{R}^4 \text{R}^5 \text{O} \xrightarrow{\text{-40°C}} \text{R}^2 \text{R}^3 \text{R}^4 \text{R}^5 \text{O} \text{P}(\text{OH})\text{H}
\]

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 auxiliarys contain strong P-O bonds and consequently require strong
nucleophiles to cleave these highly stable P-O bonds (Scheme
1).12,13 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 towards 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 per-
formed a model reaction using thiophen-2-ylmagnesium bro-
mide 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.

Scheme 2. P-OR bond reactivity

Subsequently, we selected (R)-N-(1-(5-chloro-2-hydroxy-
phenyl)(ethyl)-4-methylbenzenesulfonamide (I) as the chiral
auxiliary (Table 1), which was previously successfully em-
ploled in the synthesis of P-chiral phosphine oxides.16 Reaction
of t-BuCl2 under basic conditions gave the cyclic oxazaphos-
phinine intermediate 2a, which upon quenching with water pro-
vided the stable 4-chloro-2-((R)-1-((4-methylphenyl)sulfoam-
ido) ethyl)phenyl (S)-t-buty1phosphinate (3) in high diastereo-
omeric purity. This one-pot, two-step synthesis is initiated with the slow addition of a base into the mixture t-BuCl2 and the
chiral auxiliary I at low temperatures (-70°C to -40°C) to induce
the nucleophilic attack leading to displacement of one chloride
by the aryloxy moiety. However, nucleophilic attack of the nitrogen
was found to be much slower and required higher tempera-
tures in order for the enantioselective cyclization to inter-
mediate 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-buty1chlorophosphanenyl intermediate. The high-
est selectivity (98:2 dr) was observed when the chiral chloro-
phenol 1 was reacted with t-BuCl2 in 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, due to 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 enriched SPO compounds; some examples are shown in Table 2. Reagent 3 reacts readily with Grignards to give the corresponding secondary phosphine oxides 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).

Table 1. Synthesis of enantiomerically enriched SPO template

<table>
<thead>
<tr>
<th>entry</th>
<th>Base</th>
<th>Step I Temp/°C</th>
<th>Step I Temp/°C</th>
<th>Yield/%</th>
<th>3 dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>py</td>
<td>-70 to RT</td>
<td>RT</td>
<td>44</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>py</td>
<td>-40 to RT</td>
<td>RT</td>
<td>28</td>
<td>72:28</td>
</tr>
<tr>
<td>3</td>
<td>Im</td>
<td>-70 to -30</td>
<td>RT</td>
<td>d</td>
<td>53:47</td>
</tr>
<tr>
<td>4</td>
<td>Im</td>
<td>-70 to RT</td>
<td>RT</td>
<td>nd</td>
<td>95:5</td>
</tr>
<tr>
<td>5</td>
<td>Im</td>
<td>-40 to RT</td>
<td>RT</td>
<td>71</td>
<td>98:2  (99.7:0.3)</td>
</tr>
</tbody>
</table>

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

Table 2. Examples of enantiomerically enriched SPOs

| 4a, R₁ = R₂ = H (92% yield, 96.6% ee) | 4e, R = OMe (75% yield, 92% ee) | 4l, R = OMe (65% yield, 38% ee) |
| 4b, R₁ = R₂ = OMe (86% yield, 98% ee) | 4f, R = Cl (77% yield, 95% ee) | 4l, R = OMe (53% yield, 42% ee) |
| 4c, R₁ = H; R₂ = CF₃ (88% yield, 99% ee) | 4g, R = CN (62% yield, 95% ee) | 4x, R = Me (73% yield, 22% ee) |
| 4d, R₁ = R₂ = t-Bu (74% yield, 94% ee) | 4h, R = NMe₂ (90% yield, 99% ee) | 4y, R = CH₂Ph (56% yield, 76% ee) |

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

Heteroaryl analogs having the phosphine oxide moiety at the C-2 position of a nitrogen atom, such as the benzothiazole

Figure 1. Single crystal X-ray structures of 2b and 3
analog 4q and pyridine analog 4s, formed with lower enantiomeric purity, plausibly due to 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 vs a t-butyl(pyridin-3-yl)phosphine oxide (i.e. analog 4s vs 4t/4u, respectively) is consistent with this hypothesis. Synthesis of the acetal 4v, methyl, allyl and butenyl derivatives 4w-4y was also achieved in good yields. Lack of UV absorption and the chemical instability of these four analogs prevented direct determination of their enantiomeric purity. However, when the freshly prepared analogs 4v and 4y were immediately reacted with benzyl bromide with the magnesium metal, the expected TPO products 8q and 8r (Table 3), respectively, were obtained racemic (8q) or in low chiral purity (8r).

**Table 3. Library synthesis of enantiomerically enriched TPOs**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Yields</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>R = Me (87% yield, 98.6% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8b</td>
<td>R = Br (67% yield, 99.2% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8c</td>
<td>R = allyl (78% yield, 98.5% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8d</td>
<td>R = CH$_2$Me (58% yield, 98.6% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8e</td>
<td>(93% yield, 98.4% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8f</td>
<td>R$_1$=R$_2$=H (67% yield, 97.6% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8g</td>
<td>R$_2$=Br, R$_1$=H (71% yield, 98.0% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8h</td>
<td>R$_1$=H, R$_2$=F (74% yield, 98.8% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8i</td>
<td>R$_1$=H, R$_2$=Me (74% yield, 98.8% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8j</td>
<td>(51% yield, 92.6% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8k</td>
<td>(15% yield, 96.8% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8l</td>
<td>R=H (51% yield, 94% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8m</td>
<td>R=OMe (68% yield, 97.4% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8n</td>
<td>R=Cl (63% yield, 93.4% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8o</td>
<td>R = (CH$_2$)$_2$CH=CH$_2$ (92% yield, 90% ee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8p</td>
<td>R = Me (76% yield, 38% ee)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 precursor of P-chiral TPOs.$^{12-14}$

Recent examples include Pd-catalyzed$^{18}$ and Cu-catalyzed$^{19}$ cross-coupling reactions of SPOs with sp$^3$ 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 analogs such as 8a to 8e, whereas the pyridine-based TPOs 8f to 8n were obtained via the SnAr reactions with the 2-fluoropyridine-based precursors. High enantiomeric purity was observed for all of these products. The absolute stereochemistry for analogs 8l-8n was confirmed by comparison of their chiral HPLC chromatograms with those previously reported under the same conditions.$^{14}$

**Scheme 3. Proposed mechanism**

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, 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(alky/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$^{6+}$-C$^+$ 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 coordina-
tion may also be less favorable when the R₁ 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., analogs 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.¹²,¹⁹

CONCLUSION

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-BuPCl₂ 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 analogs. Reduction of TPOs to the trivalent phosphines has been previously achieved without erosion of chirality on the phosphorus.⁷,⁹a,¹⁰,¹⁸a,¹¹ Analogues with the potential to act as bidentate ligands, such as the corresponding phosphine of analog 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 TLC, HPLC and LCMS. Flash column chromatography was performed on silica gel (SDS, 60 Å C. C. 40-63 mm) as the stationary phase. Thin Layer Chromatography (TLC) was performed on alumina plates pre-coated with silica gel (Merck silica gel, 60 F254), which were visualized by the quenching of UV fluorescence when applicable (λmax = 254 nm and/or 366 nm) and/or by staining with vanillin or anisaldehyde in acidic ethanol and/or KMnO₄ in basic water followed by heating. All compounds were fully characterized by ¹H, ¹³C, ³¹P NMR and HRMS. Chemical shifts (δ) are reported in ppm relative to the internal deuterated solvent. ¹H NMR were recorded at 500 MHz and coupling constants (J) are reported to ± 0.5 Hz. ¹³C(¹H) NMR were recorded at 125 MHz and ³¹P(¹H) NMR were recorded at 202 MHz. Enantiomeric purity of chiral compounds was determined by chiral HPLC using an Agilent 1100 series instrument. The absolute configurations 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 with by electrospray ionization positive and negative modes (ESI±). The quoted masses are accurate to ± 0.5 ppm. The names of the molecules that appear in the following pages were generated using either BeilsteinAutoNom 2000 (CAS) or ChemBioDraw Ultra 12.0.

4-Chlorophenyl tert-butylphosphinite. To a solution of 4-chlorophenol (100 mmol, 12.86 g) in 100 mL THF, tert-butylchlorophosphinite (120 mL, 1.2 equiv, 1 M solution in ether) was added dropwise at -70°C, followed by addition of TEA (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 warm 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 (500MHz, CDCl₃): δ 7.30 (d, J = 6.8 Hz, 2 H), 7.15 (dd, J = 9.0, 1.1 Hz, 2 H), 6.94 (d, J = 527.6 Hz, 1 H), 1.26 (d, J = 18.4 Hz, 9 H). ¹³C(¹H) NMR (125MHz, CDCl₃): 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). ³¹P(¹H) NMR (202 MHz, CDCl₃): δ 48.95; HRMS: Calculated for C₁₉H₁₂ClO₃P [M+H⁺]: 323.0493; Found: 323.0494. (2R,4R)-2-(tert-Butyl)-6-chloro-4-methyl-2-(α₁-oxidaneyl)-3-tosyl-3,4-dihydro-2H-2′-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 ³¹P NMR). ¹H NMR (500 MHz,
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 CH₂CN) under argon, tert-ButylPCl₃ (55 mmol, 1 M in diethyl ether) was added, followed by 1-Meimidazole (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 Na₂SO₄ 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 ³¹P NMR. ¹H NMR (500MHz, CDCl₃): δ 7.56 (d, J = 8.2 Hz, 2 H), 7.00 (d, J = 548.1 Hz, 1 H), 7.19 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 8.1 Hz, 2 H), 7.06 (dd, J = 2.5, 8.7 Hz, 1 H), 7.01 (d, J = 2.4 Hz, 1 H), 5.40 (d, J = 6.9 Hz, 1 H), 4.85-4.79 (m, 1 H), 2.34 (s, 3 H), 1.39 (d, J = 7.0 Hz, 3 H), 1.29 (d, J = 18.6 Hz, 9 H). ¹³C[¹H] NMR (125MHz, CDCl₃): 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. ³¹P[¹H] NMR (202 MHz, CDCl₃): δ 48.29. HRMS: Calculated for C₂₀H₂₇ClNO₅PS³⁺ [M+³⁺]: 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°C to 0°C, unless otherwise indicated. Completion of the reaction was monitored by HPLC (typically 20-120 min). Saturated aqueous NH₄Cl (5 mL) was added slowly to quench the reaction. The organic solvent was collected and the aqueous residue was extracted with DCM (25 mL x3). The combined organic extracts were dried over anhydrous Na₂SO₄ 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 obtained 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 is consistent with the literature and the absolute stereochemistry was assigned based on the previously reported chiral HPLC data.¹⁴

¹H NMR (500MHz, CDCl₃): δ 7.70-7.66 (m, 2 H), 7.58 (dt, J = 1.3, 7.1 Hz, 1 H), 7.52-7.48 (m, 2H), 7.03 (d, J = 450.0 Hz, 1 H), 1.15 (d, J = 16.6 Hz, 9 H). ¹³C[¹H] NMR (125MHz, CDCl₃): 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). ³¹P[¹H] NMR (202 MHz, CDCl₃): δ 47.43. Chiral HPLC: Chiralpack AD-H, 4.6 x 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 chromatography using a solvent gradient of hexane/EtOAc (50:50 to 100%) to obtained the desired product as a colorless oil (182 mg) in 86% yield and 97.5% ee. ¹H NMR (500MHz, CDCl₃): 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). ¹³C[¹H] NMR (125MHz, CDCl₃): δ 141.9 (d, J = 8.2 Hz, 9H), 132.0 (d, J = 14.6...
The NMR data shown below is consistent with the literature and the absolute stereochemistry was assigned base on the previously reported chiral HPLC data.\textsuperscript{14} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 7.61 (dd, \(J = 8.7, 11.7\) Hz, 2 H), 7.00 (dd, \(J = 1.9, 8.7\) Hz, 2 H), 6.99 (d, \(J = 450.3\) Hz, 1 H), 1.13 (d, \(J = 16.6\) Hz, 9 H). \textsuperscript{13}C\textsuperscript{1}H NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 162.9 (d, \(J = 2.8\) Hz), 132.7 (d, \(J = 11.3\) Hz), 120.0 (d, \(J = 9.5\) Hz), 114.1 (d, \(J = 12.8\) Hz), 55.3, 32.1 (d, \(J = 70.4\) Hz), 23.4 (d, \(J = 2.2\) Hz). \textsuperscript{31}P\textsuperscript{1}H NMR (202 MHz, CDCl\textsubscript{3}): \(\delta\) 46.90. Chiral HPLC: Chiralpack IC-3, 4.6 x 250 mm; Hexane/Event (80/20), 1.3 mL/min, 220 nm, \(R\), \(\tau\) = 8.30 min, \(R\), \(\tau\) = 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 is consistent with the literature and the absolute stereochemistry was assigned base on the previously reported chiral HPLC data.\textsuperscript{14} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 7.65-7.61 (m, 2 H), 7.51-7.49 (m, 2 H), 7.04 (d, \(J = 453.7\) Hz, 1 H), 1.15 (d, \(J = 16.8\) Hz, 9 H). \textsuperscript{13}C\textsuperscript{1}H NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 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). \textsuperscript{31}P\textsuperscript{1}H NMR (202 MHz, CDCl\textsubscript{3}): \(\delta\) 45.83. Chiral HPLC: Chiralpack AD-H, 4.6 x 250 mm; Hexane/Isopropanol (90/10), 1.0 mL/min, 220 nm, \(S\), \(R\), \(\tau\) = 11.12 min, \(R\), \(\tau\) = 12.98 min.

(R)-tert-Butyl(4-chlorophenyl)phosphine oxide (4f). Compound 4g was isolated as a yellow oil (170 mg) in 82% yield and 99.2% ee. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 7.85-7.79 (m, 4H), 7.11 (d, \(J = 460.1\) Hz, 1 H), 1.17 (d, \(J = 17.0\) Hz, 9H). \textsuperscript{13}C\textsuperscript{1}H NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 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). \textsuperscript{31}P\textsuperscript{1}H NMR (202 MHz, CDCl\textsubscript{3}): \(\delta\) 44.87. HRMS: Calculated for C\textsubscript{13}H\textsubscript{12}N\textsubscript{2}O\textsubscript{2}: 208.0886; Found: 208.0894. Chiral HPLC: Chiralpack OJ-H, 4.6 x 250 mm; Hexane/IPA (80/20), 1.0 mL/min, 220 nm, \(S\), \(R\), \(\tau\) = 8.12 min, \(R\), \(\tau\) = 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. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 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). \textsuperscript{13}C\textsuperscript{1}H NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 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). \textsuperscript{31}P\textsuperscript{1}H NMR
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-naphthylimagnesium 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 is consistent with the literature and the absolute stereochemistry was assigned based on the previously reported chiral HPLC data.14 1H NMR (500 MHz, CDCl3): δ 7.87 (d, J = 8.3 Hz, 1 H), 8.04 (d, J = 8.2 Hz, 1 H), 7.91 (s, 1 H), 7.76 (dd, J = 6.7, 17.8 Hz, 1 H), 7.61-7.51 (m, 3 H), 7.45 (d, J = 447.5 Hz, 1 H), 1.19 (d, J = 16.7 Hz, 9 H). 13C[1H] NMR (125MHz, CDCl3): 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). 31P[1H] NMR (202 MHz, CDCl3): δ 52.58. Chiral HPLC: Chiralpack IC-3, 4.6 x 150 mm; Hexane/EOF (80:20), 1.3 mL/min, 220 nm, (S), tR = 5.39 min, (R), tR = 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 analog 4m was obtained as a colorless oil (162 mg) in 62% yield and 90% ee. The NMR data shown below is...
conscient with the literature and the absolute stereochemistry
was assigned base on the previously reported chiral HPLC
31P{1H} NMR (202 MHz, CDCl3): δ 36.30. Chiral HPLC: Chiralpack
AD-H, 4.6 x 250 mm; Hexane/IPA (100/10), 1.0 mL/min, 220
nm, (S), rt = 12.6 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-Thienyl-
magnesium 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 was isolated as a pale yellow solid (60 mg)
in 64% yield and 96.6% ee. 1H NMR (500MHz, CDCl3): δ 7.97-
7.85 (m, 1 H), 7.54-7.44 (m, 1 H), 7.35-7.30 (m, 1 H), 7.13 (d,
J = 456.0 Hz, 1 H) 1.17 (d, J = 17.2 Hz, 9 H). 13C{1H} NMR
(125MHz, CDCl3): δ 131.3 (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). 31P{1H} NMR (202 MHz,
CDCl3): δ 37.49. HRMS: Calculated for C18H18OPS: [M+H+]
: 189.0497; Found: 189.0497. Chiral HPLC: Chiralpack IC-3, 4.6
x 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 Grignard reagent: To a solution of benzothiazole
(2 mmol) in 1 mL of THF was added 1 M r-BuMgCl (2 mmol)
while the reaction temperature was maintained between 0°C
and 5 °C and the solution was allowed to stir for 20 min at that
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 freshly
prepared Grignard reagent was added was added slowly while
keeping the internal temperature below 5 °C. SPO analog 4q
was obtained as a slightly pink color solid (103 mg) in 86% yield
and 28% ee. 1H NMR (500MHz, CDCl3): δ 8.21 (d, J =
8.0 Hz, 1 H), 8.05 (d, J = 8.1 Hz, 1 H), 7.62 – 7.58 (m, 1 H), 7.55
(dd, J = 11.2, 4.0 Hz, 1 H), 7.45 (d, J = 485.0 Hz, 1 H), 1.32
(d, J = 17.9 Hz, 9 H). 13C{1H} NMR (125MHz, CDCl3): 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). 31P{1H} NMR (202 MHz,
CDCl3): δ 37.74. HRMS: Calculated for C18H18OPS: [M+H+]
: 240.0606; Found: 240.0608. Chiral HPLC: Chiralpack IC-3, 4.6
x 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 Grignard reagent: Thiophenethione (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, 2.5M 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 MgBr₂·Et₂O (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. ¹H NMR (500MHz, CDCl₃): δ 7.97–7.86 (m, 3 H), 7.50–7.40 (m, 2 H), 7.29 (d, J = 465.9 Hz, 1 H), 1.26 (d, J = 17.8 Hz, 9 H). ¹³C[¹H] NMR (125MHz, CDCl₃): 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). ³¹P[¹H] NMR (202 MHz, CDCl₃): δ 37.43. HRMS: Calculated for C₁₂H₁₆OPS⁺ [M+H⁺]: 239.0654; Found: 239.0654. Chiral HPLC: Chiralpack IC-3, 4.6 x 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 (1.3M, 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 gel deactivated with 10% water) eluted with a gradient of hexane/EtOAc/MeOH (50:50:0 to 0:100:0 to 0:90:10) to obtained the desired product as a yellow oil (37 mg) in 40% yield and 94% ee. ¹H NMR (500MHz, CDCl₃): δ 8.86 (d, J = 5.5 Hz, 1 H), 8.82–8.80 (m, 1 H), 8.07–8.02 (m, 1 H), 7.48–7.45 (m, 1 H), 7.13 (d, J = 458.2 Hz, 1 H), 1.19 (d, J = 17.1 Hz, 9 H). ¹³C[¹H] NMR (125MHz, CDCl₃): 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). ³¹P[¹H] NMR (202 MHz, CDCl₃): δ 42.78. HRMS: Calculated for C₉H₁₅NOP⁺ [M+H⁺]: 184.0886; Found: 184.0886. Chiral HPLC: Chiralpack AD-H, 4.6 x 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 (1.3M, 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 and then to 0:90:10) to obtained 4u as a pale yellow solid in 64% yield (84.5 mg) and 96.4% ee. ¹H NMR (500MHz, CDCl₃): δ 8.87 (t, J = 2.2 Hz, 1 H), 8.75 (dd, J = 6.2, 1.6 Hz, 1 H), 8.23–8.08 (m, 1 H), 7.12 (d, J = 462.3 Hz, 1 H), 1.20 (d, J = 17.4 Hz, 9 H). ¹³C[¹H] NMR (125MHz, CDCl₃): 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). ³¹P[¹H] NMR (202 MHz, CDCl₃): δ 40.84. HRMS: Calculated for
C₇H₁₄BrNOP⁺ [M+H⁺]: 261.9991; Found: 261.9991. Chiral HPLC: Chiralpak IC-3, 4.6 x 150 mm; Hexane/EtOH (90/10), 1.0 mL/min, 220 nm, (S), rt = 24.66 min, (R), rt = 25.22 min.

(1S,3S,5R)-1,3-Dioxolan-2-yl)methyl(tert-butyl)phosphine oxide (4r). SPO compound 4r was isolated as yellow oil in 83% yield (159 mg), however, it was found to be chemically unstable.

However, when 4r was immediately reacted with BnBr under basic condition the TPO product (see Supporting Information, compound 8q) obtained was racemic. ¹H NMR (500MHz, CDCl₃): δ 6.78 (dd, J = 522.1 Hz, 1 H), 6.48 (dd, J = 14.3, 6.8 Hz, 1 H), 4.34–4.25 (m, 2 H), 4.22 (dd, J = 14.3, 2.3 Hz, 1 H), 4.06 (dd, J = 6.8, 2.3 Hz, 1 H), 3.97–3.88 (m, 2 H), 1.14 (d, J = 17.8 Hz, 9 H). ¹³C[¹H] NMR (125MHz, CDCl₃): δ 151.4, 87.3, 67.2 (d, J = 5.2 Hz), 64.2 (d, J = 7.7 Hz), 31.7 (d, J = 94.7 Hz), 22.6 (d, J = 1.6 Hz). ³¹P[¹H] NMR (202 MHz, CDCl₃): δ 51.16.

HRMS: Calculated for C₇H₁₄O₃P⁺ [M+H⁺]: 193.0988; Found: 193.0988.

(S)-tert-Butyl(methyl)phosphine oxide (4w). SPO analog 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. ¹H NMR (500MHz, CDCl₃): δ 6.60 (dd, J = 445.3, 3.8 Hz, 1 H), 1.49 (dd, J = 12.8, 3.8 Hz, 3 H), 1.18 (d, J = 16.7 Hz, 9 H). ¹³C[¹H] NMR (125MHz, CDCl₃): δ 30.8 (d, J = 69.5 Hz), 23.3 (d, J = 2.3 Hz), 9.7 (d, J = 61.2 Hz). ³¹P[¹H] NMR (202 MHz, CDCl₃): 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. ¹H NMR (500MHz, CDCl₃): δ 6.43 (ddd, J = 446.4, 5.0, 1.9 Hz, 1 H), 5.98 – 5.89 (m, 1 H), 5.32–5.22 (m, 2 H), 2.85 – 2.45 (m, 2 H), 1.20 (d, J = 16.4 Hz, 9 H). ¹³C[¹H] NMR (125MHz, CDCl₃): δ 127.9 (d, J = 9.2 Hz), 120.4 (d, J = 11.3 Hz), 31.7 (d, J = 65.6 Hz), 30.6 (d, J = 57.5 Hz), 23.8 (d, J = 1.8 Hz). ³¹P[¹H] NMR (202 MHz, CDCl₃): 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 (500MHz, CDCl₃): δ 6.67 (dd, J = 439.4, 7.1 Hz, 1 H), 5.95 – 5.82 (m, 1 H), 5.10 (ddd, J = 13.6, 11.2, 1.2 Hz, 2 H), 2.65 – 2.35 (m, 2 H), 1.93 - 1.65 (m, 2 H), 1.19 (d, J = 16.2 Hz, 9 H).

¹³C[¹H] NMR (125MHz, CDCl₃): 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). ³¹P[¹H] NMR (202 MHz, CDCl₃): 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 warm-up to rt and stirring was continued for approximately 2 h; completion of the reaction was monitors by HPLC. Saturated aqueous NH₄Cl 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 x3). The combined extracts were dried over anhydrous Na₂SO₄ 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 obtained 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 obtained 8a as a colorless viscous oil in 87% yield (35.1 mg) and 98.8% ee. ¹H NMR (500MHz, CDCl₃): δ 7.73 – 7.68 (m, 1 H), 7.56 (ddd, J = 6.1, 3.6, 0.9 Hz, 1 H), 7.22 (ddd, J = 5.0, 3.6, 1.7 Hz, 1 H), 1.74 (d, J = 12.3 Hz, 3 H), 1.19 (d, J = 15.6 Hz, 9 H).

¹³C[¹H] NMR (125MHz, CDCl₃): 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). ³¹P[¹H] NMR (202 MHz, CDCl₃): δ 44.95. HRMS: Calculated for C₁₉H₁₄OPS⁺ [M+H⁺]: 261.0654; Found: 261.0654. Chiral HPLC: Chiralpak OD-H, 4.6 x 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 obtained 8b as a white solid 67%
yield (37.5 mg) in 99.2% ee. $^1$H NMR (500 MHz, CDCl$_3$): 87.68 – 7.65 (m, 1 H), 7.51 (ddd, $J = 5.9, 3.6, 1.0$ Hz, 1 H), 7.29 – 7.13 (m, 6 H), 3.59 – 3.15 (m, 2 H), 1.21 (d, $J = 15.4$ Hz, 9 H).

$^{13}$C($^1$H) NMR (125 MHz, CDCl$_3$): $\delta$ 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($^1$H) NMR (202 MHz, CDCl$_3$): $\delta$ 44.34. HRMS: Calculated for C$_3$H$_3$_2OPSSi: [M+H$^+$]: 275.1049; Found: 275.1048.

(1R,3R)-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 obtained 8e as a white solid in 61% yield (40 mg) and 98.4% ee. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.92 (d, $J = 4.1, 1.7$ Hz, 1 H), 8.09 (dt, $J = 7.5, 3.8$ Hz, 2 H), 7.66 (d, $J = 8.2$ Hz, 1 H), 7.58 – 7.50 (m, 2 H), 7.46 (t, $J = 7.7$ Hz, 1 H), 7.38 (dd, $J = 8.2, 4.2$ Hz, 1 H), 7.01 (ddd, $J = 5.2, 3.6, 1.8$ Hz, 1 H), 4.64 – 4.15 (m, 2 H), 1.20 (d, $J = 15.4$ Hz, 9 H). $^{13}$C($^1$H) NMR (125 MHz, CDCl$_3$): $\delta$ 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($^1$H) NMR (202 MHz, CDCl$_3$): $\delta$ 46.65. HRMS: Calculated for C$_3$H$_3$_2NOPS: [M+H$^+$]: 330.1076; Found: 330.1076. Chiral HPLC: Chiralpack IC-3, 4.6 x 150 mm; Hexane/EtOH (80/20), 1.3 mL/min, 220 nm, (R), rt = 3.81 min, (S), rt = 4.35 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. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.80 (d, $J = 4.4$ Hz, 1 H), 8.24 – 8.16 (m, 1 H), 7.91 (ddd, $J = 6.1, 3.6, 1.0$ Hz, 1 H), 7.83 (ddd, $J = 7.7, 3.6, 1.7$ Hz, 1 H), 7.75 – 7.70 (m, 1 H), 7.43 – 7.35 (m, 1 H), 7.19 (ddd, $J = 4.8, 3.6, 2.1$ Hz, 1 H), 1.23 (d, $J = 15.8$ Hz, 9 H). $^{13}$C($^1$H) NMR (125 MHz, CDCl$_3$): $\delta$ 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($^1$H) NMR (202 MHz, CDCl$_3$): $\delta$ 34.36. HRMS: Calculated for C$_3$H$_3$_2NOPS: [M+H$^+$]: 266.0763; Found: 266.0764. Chiral HPLC: Chiralpack IC-3, 4.6 x 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 (500MHz, CDCl3): δ 8.87 (d, J = 2.2 Hz, 1 H), 8.10 (dd, J = 7.8, 4.8 Hz, 1 H), 8.00 – 7.95 (m, 1 H), 7.88 (ddd, J = 6.1, 3.6, 1.0 Hz, 1 H), 7.76 – 7.70 (m, 1 H), 7.20 (ddd, J = 4.8, 3.6, 2.1 Hz, 1 H), 1.22 (d, J = 16.0 Hz, 9 H). 13C{1H} NMR (125MHz, CDCl3): 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). 31P{1H} NMR (202 MHz, CDCl3): δ 34.56. HRMS: Calculated for C13H16BrNOPS* [M+H]+: 343.9868; Found: 343.9870. Chiral HPLC: Chiralpack IC-3, 4.6 x 150 mm; Hexane/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-3-yl)phosphine oxide (8h). 2,3-Difluoropyridine was used as the electrophile and the product was purified by silica 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. 1H NMR (500MHz, CDCl3): δ 8.61 (d, J = 3.9 Hz, 1 H), 7.92 (dd, J = 5.8, 4.0 Hz, 1 H), 7.76 (t, J = 4.1 Hz, 1 H), 7.54 – 7.39 (m, 2 H), 7.25 – 7.17 (m, 1 H), 1.26 (d, J = 16.2 Hz, 9 H). 13C{1H} NMR (125MHz, CDCl3): 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. 31P{1H} NMR (202 MHz, CDCl3): δ 36.88 (d, J = 11.5 Hz). 19F NMR (471 MHz, CDCl3): δ -113.02 (d, J = 11.4 Hz). HRMS: Calculated for C13H16F2NOPS* [M+H]+: 284.0669; Found: 284.0669. Chiral HPLC: Chiralpack OD-H, 4.6 x 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-3-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. 1H NMR (500MHz, CDCl3): δ 8.60 (d, J = 4.3 Hz, 1 H), 7.88 (dd, J = 5.6, 3.7 Hz, 1 H), 7.71 (t, J = 4.1 Hz, 1 H), 7.55 – 7.49 (m, 1 H), 7.29 – 7.25 (m, 1 H), 7.18 (t, J = 5.2 Hz, 1 H), 2.77 (s, 3 H), 1.21 (d, J = 15.5 Hz, 9 H). 13C{1H} NMR (125MHz, CDCl3): 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. 31P{1H} NMR (202 MHz, CDCl3): δ 39.60. HRMS: Calculated for C13H16BrNOPS* [M+H]+: 343.9868; Found: 343.9869. Chiral HPLC: Chiralpack IC-3, 4.6 x 150 mm; Hexane/Isopropanol (80/20), 1.3 mL/min, 220 nm, (R), rt = 3.18 min, (S), rt = 3.49 min.

(R)-5-Bromopyridin-3-yl(tert-butyl)(pyridin-2-yl)phosphine oxide (8j). A three-necked flask under argon charged with 3 (0.2 mmol) was cooled to 0 °C. Freshly prepared Turbo Grignon (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 NH4Cl 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 x 3). The combined organic extracts were dried over anhydrous Na2SO4 and concentrated. The residue was purified by silica gel chromatography eluted with hexane/EtOA (50:50 to 0:100) to
obtained TPO 8k as a yellow solid in 15% yield (10.5 mg) and 96.8% ee. 1H NMR (500MHz, CDCl3): δ 9.36 (dd, J = 4.0, 1.4 Hz, 1 H), 8.83 (d, J = 4.7 Hz, 1 H), 8.78 (t, J = 2.0 Hz, 1 H), 8.70 (dt, J = 9.8, 1.9 Hz, 1 H), 8.28 – 8.17 (m, 1 H), 7.86 (td, J = 7.7, 3.6, 1.7 Hz, 1 H), 7.48 – 7.41 (m, 1 H), 1.23 (d, J = 15.7 Hz, 9 H). 13C{1H} NMR (125MHz, CDCl3): 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. 31P{1H} NMR (202 MHz, CDCl3): δ 30.28. HRMS: Calculated for C13H18BrN2OP+ [M+H]+: 339.0256; Found: 339.0257. Chiral HPLC: Chiralpack IC-3, 4.6 x 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 (0.5M in THF, 0.4ml) 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 is consistent with the literature and the absolute stereochemistry was assigned by comparison to the previously reported chiral HPLC data. 1H NMR (500MHz, CDCl3): δ 8.81 (ddd, J = 4.8, 1.7, 0.9 Hz, 1 H), 8.28 – 8.19 (m, 3 H), 7.81 (td, J = 7.7, 3.3, 1.7 Hz, 1 H), 7.53 – 7.47 (m, 1 H), 7.44 (td, J = 8.4, 2.9, 1.3 Hz, 2 H), 7.38 (dddd, J = 8.0, 4.8, 2.1, 1.3 Hz, 1 H), 1.23 (d, J = 15.1 Hz, 9 H). 13C{1H} NMR (125MHz, CDCl3): 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. 31P{1H} NMR (202 MHz, CDCl3): δ 32.52. Chiral HPLC: Chiralpack AD-H, 4.6 x 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 (0.5M in THF, 0.4ml) 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 is consistent with the literature and the absolute stereochemistry was assigned by comparison to the previously reported chiral HPLC data. 1H NMR (500MHz, CDCl3): δ 8.79 (d, J = 4.7 Hz, 1 H), 8.27 – 8.21 (m, 1 H), 8.16 (t, J = 9.2 Hz, 2 H), 7.80 (tdd, J = 7.7, 3.2, 1.8 Hz, 1 H), 7.41 – 7.33 (m, 1 H), 6.96 (dd, J = 8.9, 2.3 Hz, 2 H), 3.83 (s, 3 H), 1.21 (d, J = 15.1 Hz, 9 H). 13C{1H} NMR (125MHz, CDCl3): 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. 31P{1H} NMR (202 MHz, CDCl3): δ 32.84. Chiral HPLC: Chiralpack IC-3, 4.6 x 150 mm; Hexane/Isopropanol (80/20), 1.3 mL/min, 220 nm, (S), rt = 3.68 min, (R), rt = 4.16 min.
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: Chiralpack IC-3, 4.6 x 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 (500MHz, CDCl\(_3\)): \(\delta\) 7.46 – 7.07 (m, 5 H), 6.41 (dd, \(J = 14.3\), 6.8 Hz, 1 H), 4.11 (dd, \(J = 14.3\), 2.2 Hz, 1 H), 4.04 – 3.93 (m, 2 H), 3.88 – 3.75 (m, 1 H), 3.70 – 3.48 (m, 2 H), 3.27 – 2.98 (m, 2 H), 1.18 (d, \(J = 15.5\) Hz, 9 H). \(^3\)C[\(^1\)H] NMR (125MHz, CDCl\(_3\)): \(\delta\) 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. \(^3\)P[\(^1\)H] NMR (202 MHz, CDCl\(_3\)): \(\delta\) 59.20. HRMS: Calculated for C\(_{15}\)H\(_2\)O\(_2\)P\(_3\) [M+H\(^+\)]: 283.1458; Found: 283.1459. 

(S)-tert-butyl(methyl)(pyridin-2-yl)phosphine oxide (8p). In the synthesis of 8p, in addition to the Grignard, LiCl (0.5M in THF, 0.4ml) 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 (500MHz, CDCl\(_3\)): \(\delta\) 8.72 (d, \(J = 4.6\) Hz, 1 H), 8.19 – 8.07 (m, 1 H), 7.82 (t, \(J = 6.9\) Hz, 1 H), 7.44 – 7.33 (m, 1 H), 1.79 (d, \(J = 12.9\) Hz, 3 H), 1.17 (d, \(J = 14.7\) Hz, 9 H). \(^1\)C[\(^1\)H] NMR (125MHz, CDCl\(_3\)): \(\delta\) 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). \(^3\)P[\(^1\)H] NMR (202 MHz, CDCl\(_3\)): \(\delta\) 48.09. HRMS: Calculated for C\(_{16}\)H\(_3\)N\(_2\)OP\(_3\) [M+H\(^+\)]: 198.1042; Found: 198.1043. Chiral HPLC: Chiralpack IC-3, 4.6 x 150 mm; Hexane/EthOH (80/20), 1.3 mL/min, 220 nm, (R), rt = 6.07 min, (S), rt = 6.40 min.

(R)-Benzyl(but-3-en-1-yl)(tert-buty1)phosphine oxide (8r). To a stirring degassed THF solution of freshly prepared SPO 4v (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 benzylic 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\(_2\)O was added and the mixture was extracted 5x with equal volumes of DCM. The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), 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 (500MHz, CDCl\(_3\)): \(\delta\) 7.47 – 7.12 (m, 5 H), 5.81 – 5.60 (m, 1 H), 4.90 (dd, \(J = 13.5\), 2.2 Hz, 2 H), 3.31 – 2.87 (m, 2 H), 2.23 (d, \(J = 6.5\) Hz, 1 H), 1.97 – 1.53 (m, 4 H), 1.19 (d, \(J = 14.1\) Hz, 9 H). \(^1\)C[\(^1\)H] NMR (125MHz, CDCl\(_3\)): \(\delta\) 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). \(^3\)P[\(^1\)H] NMR (202 MHz, CDCl\(_3\)): \(\delta\) 52.41.

HRMS: Calculated for C\(_{15}\)H\(_3\)N\(_2\)OP\(_3\) [M+H\(^+\)]: 251.1559; Found: 251.1559. Chiral HPLC: Chiralpack IC-3, 4.6 x 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.

References
1H, 13C, 31P NMR spectra and chiral HPLC chromatograms.
X-ray data collection and structure refinement for 2b and 3.

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