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Cyclic Phosphine Oxides and Phosphinamides from Di-Grignard Reagents and Phosphonic Dichlorides: Modular Access to Annulated Phospholanes

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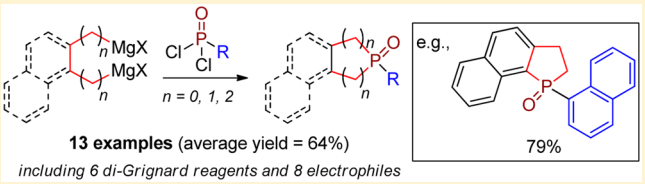
Supporting Information

ABSTRACT: The reaction between 1,4-di-Grignard reagents and phosphonous(III) dichlorides is a classical method for the direct synthesis of phospholanes. Reported here is an extension of this approach to the preparation of value-added, annulated phospholane oxides, achieved through the combination of carbocyclic-fused di-Grignard reagents and readily available phosphonic(V) dichlorides. The procedure is amenable to (benz)annulation at both the 2,3- and 3,4-positions of the phospholane ring, and a variety of aliphatic, cyclic and aryl P-electrophiles are tolerated in reasonable to excellent yields.



The phospholane ring system is a ubiquitous heterocycle in organic synthesis, upon which a plethora of P-ligands[1] and nucleophilic organocatalysts[1c,2] are based. In particular, the privileged BPE and DuPhos families,[3] bearing 2,5-disubstituted phospholanes (**1** and **2**, Figure 1), have seen extensive

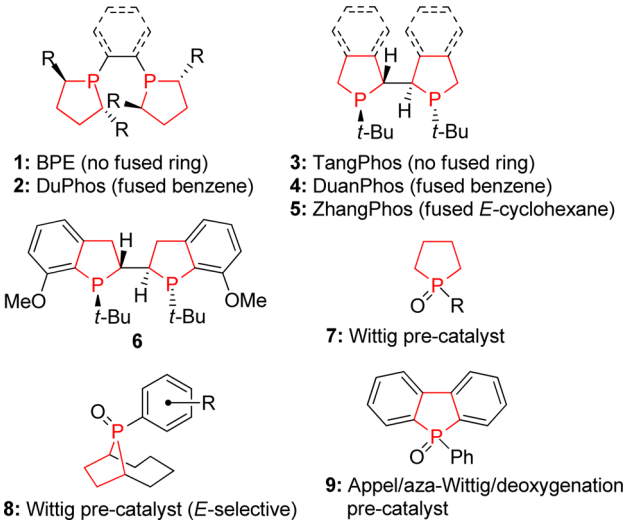


Figure 1. Exemplary P-ligands and organocatalysts containing the phospholane moiety.

application in metal-mediated[4] and metal-free asymmetric catalysis.[2] The P-stereogenic TangPhos/DuanPhos/ZhangPhos series (**3**–**5**),[5] based on 1,1′-di-*tert*-butyl-2,2′-biphospholane and its 3,4-annulated derivatives, is another notable contribution, encompassing some of the most effective ligands ever reported for asymmetric hydrogenation.[6]

Recently, phospholane oxides and their bi- and tricyclic derivatives (fused and bridged) have emerged as effective precatalysts for an expanding new area of organocatalysis involving the P(III): ↔ P(V)═O redox pair (e.g., **7**–**9**, Figure 1).[7] The virtue of these heterocycles to participate in such a catalysis mode stems from their increased rate of reduction compared to that of their larger ring-homologues and acyclic counterparts.[7,8] Current areas of development include catalytic Wittig,[9] aza-Wittig,[10] and Appel reactions[8,11] and, very recently, deoxygenative condensations.[12]

The most common approach to assemble the phospholane system involves the combination of lithiated primary phosphines or phosphine-boranes with 1,4-bis-electrophiles, enabling consecutive inter- and intramolecular P–C bond formations in a single pot. This strategy has furnished a range of valuable phospholanes,[1c] including bicyclic adducts,[5a,b,13] and can be extended to secondary alkyl electrophiles in a stereospecific manner.[3a,14] Despite these favorable aspects, the requirement for the handling and use of pungent, odorous, and potentially pyrophoric primary phosphines remains a significant drawback. Furthermore, this approach is not readily amenable to benzannulation at the phospholane 2,3-position,[15] an emerging structural feature of useful ligands and organocatalysts (e.g., **6** and **9**, Figure 1).[8,12a,15,16]

In our search for an alternate phospholane syntheses that would avoid the use of primary phosphines, while still circumventing acyclic organophosphorus intermediates[17] and backbone redox manipulations,[18] common to most available routes, we turned our attention to the classical umpolung approach, in which a 1,4-diorganometallic reagent is reacted

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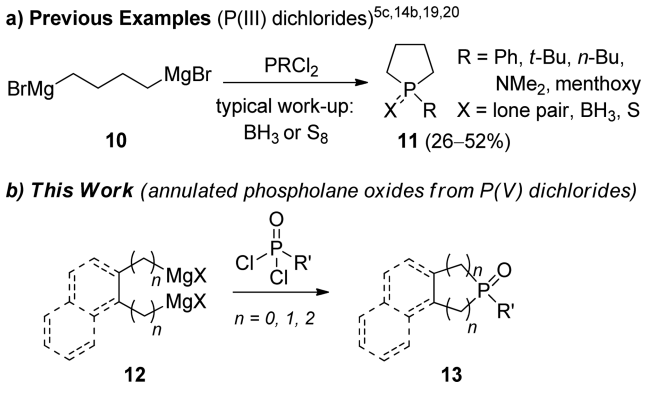
with a P-electrophile. This method was first introduced by Grüttner for the preparation of phenyl phospholane from di-Grignard reagent **10** (Scheme 1a)[19] and has since been applied to a variety of analogues **11** using phosphonous(III) dichlorides[5c,14b,20] or other trivalent P reagents,[21] typically by trapping the products as their stable borane or sulfide adducts.

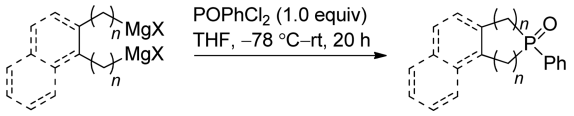
Scheme 1. Proposed Synthesis of Annulated Phospholanes

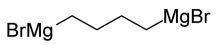
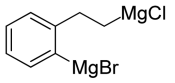
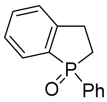
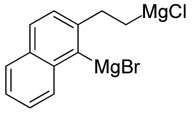
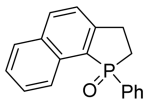
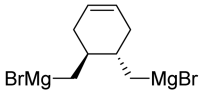
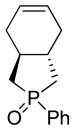
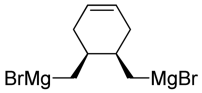
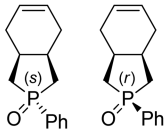
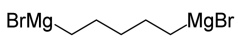


Encouraged by these findings, and considering the fact that extensions of this umpolung synthetic strategy to monoannulated phospholanes (i.e., **13**, Scheme 1b) have been limited,[22] we were inspired to investigate in more detail the application of carbocyclic-fused di-Grignard reagents **12** in this setting.[23] From an additional standpoint, we were drawn to the potential of using higher oxidation level phosphonic(V) dichlorides as electrophiles, which have, surprisingly, remained an essentially unexplored class of reagents for phospholane synthesis,[24] or homologues thereof. Notably, the latter modification would open up a direct entry to phospholane oxides (Scheme 1b). Several practical benefits of their use also could be envisioned, including the stability of P(V) reagents to oxygen, the wide range of commercially available phosphonic dichlorides and their phosphonic acid precursors,[25] and the avoidance of an oxidative workup otherwise required to isolate the desired P-oxide.

Our initial synthetic investigations were based on phenyl phospholane oxide (**19** in Table 1) as a model system through the reaction of di-Grignard reagent **10** and commercially available $POPhCl_2$. A previous study of a related reaction between phosphate ester dichlorides ($PO(OR)Cl_2$) and **10** highlighted the difficulty in achieving cyclization at the P(V) oxidation state due to undesired oligomerizaton.[26] After experiencing similarly low yields of **19** (25–35%) under standard conditions (0 °C to rt),[19,20,26] we progressed to examine the effect of lower temperatures, which, surprisingly, to our knowledge, had never been investigated for the related esters.[26] In the event, by mixing the reactants at −78 °C (1:1 in

Table 1. Di-Grignard Scope[a]



entry	di-Grignard reagent[b]		product		yield (%)[c]	lit. yield (%)[d]
1		**10**		**19**	75	46[e,20b], 56[f,27] (one step)
2		**14**		(±)-**20**	87	80[28a] (three steps)
3		**15**		(±)-**21**	57	36[30] (two steps)
4		(±)-**16**		(±)-**22**	57	-
5		*meso*-**17**		*meso*-(s_P)-**23** *meso*-(r_P)-**23**	43[g] 16[g]	-
6		**18**		**24**	36	75[32] (three steps)

[a]Reactions performed with 0.30–0.58 mmol of $POPhCl_2$ at 0.05–0.10 M. [b]Di-Grignard reagents were prepared in THF with 2.1 equiv of acid-washed Mg flakes and titrated with 1,10-phenanthroline/2-butanol prior to use. [c]Isolated yield after flash chromatography. [d]Highest yield reported among all previous methods. [e]Yield of the corresponding BH_3 adduct obtained from **10** and $PPhCl_2$. [f]Yield of deoxo-**19** obtained from $Li(CH_2)_4Li$ and $PPh(OMe)_2$. [g]Diastereomers separated by flash chromatography.

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THF, 0.1 M), a significant suppression of oligomerization was realized to give **19** in a highly respectable 75% yield (Table 1, entry 1), representing a notable improvement relative to previous syntheses of phenyl phospholane from diorganometallic and P(III) reagents (optimum lit. yields given in Table 1, entry 1).[19,20a,b,27]

With a practical and efficient procedure established, we submitted a series of carbocyclic-fused 1,4-di-Grignard reagents (**14**–**17**) to the reaction with $POPhCl_2$ (Table 1, entries 2–5). The known P-stereogenic benzo- and naphthophospholanes (±)-**20** and (±)-**21** were obtained in 87 and 57% yields, respectively, comparing favorably with previous multistep routes to these compounds (entries 2 and 3).[28−30] Utilizing racemic di-Grignard reagent **16**, the novel bicyclic phospholane oxide (±)-**22** was isolated in a moderate 57% yield (entry 4). The rigid *trans*-cyclohexane-annulated chiral backbone of **22** represents an unsaturated monomeric analogue to the skeleton of ZhangPhos (**5**, Figure 1), which has been previously obtained by the inverse addition of a nucleophilic primary phosphine and the corresponding 1,4-bis-electrophile.[5a] Translation to the homochiral variants of **22** can be readily envisioned, based on the commercial availability of the requisite enantiopure precursors.[31]

The corresponding *cis*-di-Grignard reagent **17** reacted similarly with $PPhOCl_2$ to give chromatographically separable *meso*-diastereomers (s_P)-**23** and (r_P)-**23** in a 59% combined yield (Table 1, entry 5), which bear additional P-stereocenters on the molecular symmetry plane. The major isomer was determined by X-ray crystallography to have the (s_P)-configuration at the phosphorus atom, in which the phenyl group lies in an *exo* relationship to the annulated cyclohexene ring (Figure 2). We also established that the method can be

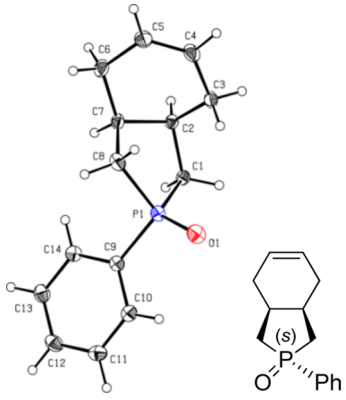
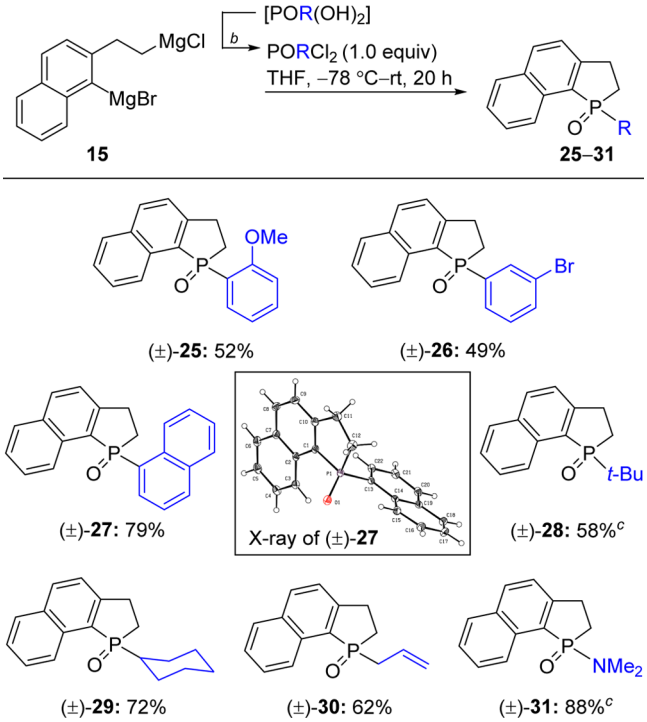


Figure 2. X-ray crystal structure of *meso*-(s_P)-**23** with an ellipsoid contour probability level of 30%.

extended to six-membered homologues using exemplary di-Grignard reagent **18** (entry 6); however, reduced yields should be expected due to a greater degree of oligomerization.[33]

We next turned our attention to the scope of the process with respect to the phosphonic dichloride, targeting a series of novel naphthophospholane derivatives (Table 2). The requisite electrophiles were obtained commercially or by a simple chlorination procedure using oxalyl chloride,[25,34] allowing access to a variety of products (**25**–**31**) in moderate to excellent yields (49–88%). Functionalized 2-methoxy- and 3-bromophenylphosphonic dichlorides provided (±)-**25** and (±)-**26** in yields comparable to that of their unsubstituted analogue (±)-**21** (Table 1, entry 3). The 1-naphthyl substrate

Table 2. Electrophile Scope[a]



[a]Reactions performed with 0.32–0.50 mmol of $PORCl_2$ at 0.08–0.10 M. Yields are of isolated product after flash chromatography. [b]Chlorination conditions: $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt to 40 °C, 1 h.[25] [c]$PORCl_2$ was obtained commercially. The ellipsoid contour probability level of the X-ray structure of **27** is 30%.

performed particularly well, giving (±)-**27** in 79% yield, the structure of which was confirmed by X-ray crystallography (Table 2, inset). Importantly, sterically encumbered aliphatic P-substituents commonly exploited in phosphine ligands were well-tolerated, including *tert*-butyl and cyclohexyl moieties. A phosphoramide dichloride ($PO(NMe_2)Cl_2$) was also accommodated, affording phosphinamide derivative (±)-**31** in high yield (88%).

In addition to having showcased the ability to tune the electronic and steric properties of the naphthophospholane scaffold via this methodology, it is noteworthy that versatile functional handles for further manipulation have been introduced (e.g., allyl, bromo, and methoxy). On the basis of more specific precedents, the methoxy group could offer a potential means of resolving (±)-**25** via the diastereomeric menthyl carbonates,[16] whereas the phosphinamide moiety in **31** should permit a facile entry into the corresponding phosphonic acid,[35] which could, for instance, be reduced to the corresponding secondary phosphine oxide[35b,36] or the secondary phosphine[3a,36] or could be diastereomerically resolved.[35b]

In summary, we have established that annulated phospholane oxides can be obtained in a practical and efficient manner through the combination of phosphonic dichlorides and di-Grignard reagents. The significance of this method has been demonstrated by the synthesis of representative known compounds in yields superior to those obtained with previous methods, its application to backbone-chiral and P-stereogenic phospholanes, and the straightforward electronic and steric modulation of a representative heterocycle through P-substituent variations. The latter is of particular importance in

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the context of analogue throughput in catalyst screening studies, which, as pointed out, could involve applications of the phospholane oxides as new organocatalysts or alternatively, as templates for P-ligand design, based on their well-precedented ability to undergo diastereoselective α-C(sp^3)−H functionalization,[18a,37] including oxidative dimerization to 1,2-bisphosphines.[5b,16]

EXPERIMENTAL SECTION

General Methods and Materials. All reactions were carried out in standard laboratory glassware with magnetic stirring. Thin-layer chromatography (TLC) was performed on aluminum-backed 0.20 mm silica gel plates. Visualization was accomplished with UV light. Flash chromatography was performed under positive air pressure using Silica Gel 60 of 230−400 mesh (40−63 μm). Melting points (mp) are uncorrected. Proton and carbon magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on a 300 or 500 MHz spectrometer, as specified. Spectra were aquired in $CDCl_3$ and are reported relative to tetramethylsilane (^{1}H: δ = 0.00 ppm) and solvent resonance (^{13}C: δ = 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (abbreviations: d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, td = triplet of doublets, m = multiplet), coupling constant (Hz), and integration. Coupling constants listed in the ^{13}C NMR spectral data refer to coupling between carbon and phosphorus nuclei. High-resolution mass spectrometry (HRMS) was performed on a QTOF ESI spectrometer.

Anhydrous tetrahydrofuran was obtained commercially. Di-Grignard reagents were prepared from Mg flakes that were freshly washed with 1 M HCl, followed sequentially by washing with water, EtOH, THF, and Et_2O before being dried for 20 min under high vacuum. 1-Bromo-2-(2-chloroethyl)benzene,[38] 1-bromo-2-(2-chloroethyl)naphthalene,[31] (±)-*trans*-4,5-bis(bromomethyl)cyclohex-1-ene,[31] and *cis*-4,5-bis(bromomethyl)cyclohex-1-ene[39] were prepared according to literature procedures. Phenylphosphonic dichloride ($POPhCl_2$), *tert*-butylphosphonic dichloride ($PO(t\text{-}Bu)Cl_2$), and *N*,*N*-dimethylphosphoramide dichloride ($PO(NMe_2)Cl_2$) were obtained commercially. The remaining phosphonic dichlorides utilized in Table 2 were prepared from their corresponding known phosphonic acids via chlorination with oxalyl chloride.[25,34] All other reagents and solvents were obtained reagent grade from commercial sources and used as received.

General Procedure A for the Preparation of Di-Grignard Reagents. A dry round-bottomed flask was charged with the appropriate neat dihalo compound (0.24−0.58 mmol, 1.0 equiv) and Mg (2.1 equiv).[40] The flask was evacuated and refilled with N_2 (single cycle); then, THF was added (0.50 M in dihalo compound), and the suspension was stirred rapidly for 2 h at a temperature dependent on the substrate. Aliphatic di-Grignard reagents (**10**, (±)-**16**, *meso*-**17**, and **18**) were prepared at rt, whereas mixed aliphatic/aromatic substrates (**14** and **15**) were prepared by gradually heating from rt to 65 °C over 30 min, maintaining this temperature for 1 h, and then returning to rt over 30 min (for these reactions, the flask was equipped with a condenser). In each case, titration of the resultant supernatant was carried out with a 1.00 M solution of 2-butanol in toluene using 1,10-phenanthroline as indicator[41] to determine the total concentration of organomagnesium species, which was halved to obtain the di-Grignard reagent concentration quoted in the experimental descriptions below.

General Procedure B for the Synthesis of Cyclic Phosphine Oxides from Di-Grignard Reagents. To a solution of a phosphonic dichloride (0.30−0.58 mmol) in the specified volume of THF at −78 °C (liquid N_2/EtOAc slush bath) under N_2 was added dropwise over 2 min a solution of a freshly titrated di-Grignard reagent (1.0 equiv) in THF. The resulting solution (generally 0.10 M in both reactants) was allowed to warm to rt with stirring over 20 h. The reaction was quenched with water (5 mL); then, saturated NH_4Cl (5 mL) was added, followed by EtOAc (20 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography with the specified eluent provided the desired cyclic phosphine oxide.

*1-Phenylphospholane-1-oxide (**19**).* This was prepared according to General Procedure B using a solution of $POPhCl_2$ (97.5 mg, 0.50 mmol) in THF (3.31 mL) and a solution of di-Grignard reagent **10** (0.295 M in THF, 1.69 mL, 0.50 mmol). Flash chromatography (100% EtOAc to 2% NEt_3/EtOAc) gave the known phospholane **19** (67.6 mg, 75%) as a yellow oil. NMR data was in good agreement with that previously reported.[8] TLC (2% NEt_3/EtOAc) R_f = 0.20; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, J = 11.4, 7.3 Hz, 2H), 7.56−7.46 (m, 3H), 2.27−1.88 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9 (d, J = 90.1 Hz), 131.4 (d, J = 2.9 Hz), 129.6 (d, J = 9.6 Hz), 128.4 (d, J = 11.6 Hz), 29.4 (d, J = 67.6 Hz), 25.0 (d, J = 8.1 Hz).

*(racemic)-2,3-Dihydro-1-phenyl-1H-phosphindole-1-oxide (**20**).* This was prepared according to General Procedure B using a solution of $POPhCl_2$ (97.5 mg, 0.50 mmol) in THF (3.61 mL) and a solution of di-Grignard reagent **14** (0.36 M in THF, 1.39 mL, 0.50 mmol). Flash chromatography (100% EtOAc to 2% NEt_3/EtOAc) gave the known benzophospholane **20** (99.8 mg, 87%) as a white solid. NMR data was in good agreement with that previously reported.[28a] mp 86−88 °C (lit.[28c] mp 97−101 °C); TLC (2% NEt_3/EtOAc) R_f = 0.29; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (t, J = 8.2 Hz, 1H), 7.62−7.48 (m, 4H), 7.47−7.34 (m, 4H), 3.49−3.37 (m, 1H), 3.25−3.14 (m, 1H), 2.54−2.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3 (d, J = 30.7 Hz), 133.1 (d, J = 97.7 Hz), 132.5 (d, J = 103.1 Hz), 132.4 (d, J = 2.5 Hz), 131.5 (d, J = 2.9 Hz), 130.2 (d, J = 10.5 Hz), 128.6 (d, J = 9.3 Hz), 128.3 (d, J = 12.0 Hz), 127.5 (d, J = 10.4 Hz), 126.1 (d, J = 11.4 Hz), 27.9 (d, J = 3.9 Hz), 27.8 (d, J = 71.0 Hz); IR (neat) ν 3442, 1593, 1434, 1195, 1136, 1115, 777, 765, 742 cm^{-1}; HRMS (ESI) [M + H]$^+$ calcd for $C_{14}H_{14}OP$, 229.0782; found, 229.0790.

*(racemic)-1-Phenyl-2,3-dihydro-1H-benzo[g]phosphindole-1-oxide (**21**).* This was prepared according to General Procedure B using a solution of $POPhCl_2$ (113.0 mg, 0.58 mmol) in THF (3.80 mL) and a solution of di-Grignard reagent **15** (0.29 M in THF, 2.00 mL, 0.58 mmol). Flash chromatography (100% EtOAc to 2% NEt_3/EtOAc) gave the known compound **21** (91.4 mg, 57%) as a white solid. Previously, no ^{1}H NMR data and only partial ^{13}C NMR data have been reported for **21**. Our ^{13}C NMR data was in good agreement with the available information.[30] mp 177−178 °C (lit.[30] mp 200−202 °C); TLC (2% NEt_3/EtOAc) R_f = 0.37; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13−8.05 (m, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.86−7.78 (m, 1H), 7.63 (dd, J = 12.3, 7.3 Hz, 2H), 7.46−7.31 (m, 6H), 3.57−3.38 (m, 1H), 3.37−3.20 (m, 1H), 2.67−2.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9 (d, J = 31.1 Hz), 133.8 (d, J = 96.7 Hz), 133.7 (d, J = 2.7 Hz), 132.5 (d, J = 8.0 Hz), 131.7 (d, J = 9.1 Hz), 131.5 (d, J = 3.0 Hz), 130.1 (d, J = 10.4 Hz), 128.4 (d, J = 12.0 Hz), 128.2 (d, J = 1.6 Hz), 128.0 (d, J = 101.5 Hz), 127.6, 126.1, 125.1 (d, J = 4.8 Hz), 123.8 (d, J = 12.7 Hz), 28.6 (d, J = 4.6 Hz), 27.9 (d, J = 71.4 Hz); IR (neat) ν 2360, 1201, 1186, 1111, 818, 784, 740, 691 cm^{-1}; HRMS (ESI) [M + H]$^+$ calcd for $C_{18}H_{16}OP$, 279.0939; found, 279.0931.

*(racemic)-trans-2-Phenyl-2,3,3a,4,7,7a-hexahydro-1H-isophosphindole 2-Oxide (**22**).* This was prepared according to General Procedure B using a solution of $POPhCl_2$ (97.5 mg, 0.50 mmol) in THF (3.20 mL) and a solution of di-Grignard reagent **16** (0.13 M in THF, 3.85 mL, 0.50 mmol). Flash chromatography (100% EtOAc to 2% NEt_3/EtOAc) gave **22** (66.4 mg, 57%) as a white solid. mp 88−92 °C; TLC (2% NEt_3/EtOAc) R_f = 0.38; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81−7.71 (m, 2H), 7.59−7.45 (m, 3H), 5.72 (s, 2H), 2.56−2.35 (m, 4H), 2.30−2.19 (m, 1H), 2.09−1.98 (m, 1H), 1.98−1.77 (m, 3H), 1.62 (ddd, J = 15.0, 12.5, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.4 (d, J = 90.1 Hz), 131.6 (d, J = 2.9 Hz), 129.8 (d, J = 9.9 Hz), 128.6 (d, J = 11.6 Hz), 126.2 (d, J = 1.9 Hz), 126.1 (d, J = 1.9 Hz), 40.4 (d, J = 8.2 Hz), 38.9 (d, J = 7.7 Hz), 37.6 (d, J = 66.4 Hz), 36.9 (d, J = 67.6 Hz), 33.2 (d, J = 9.3 Hz), 33.0 (d, J = 9.8 Hz); IR (neat) ν 3408, 2887, 1437, 1223, 1187, 927, 852, 786, 726, 692, 655 cm^{-1}; HRMS (ESI) [M + H]$^+$ calcd for $C_{14}H_{18}OP$, 233.1095; found, 233.1087.

*(meso)-(2s,3aR,7aS)-2-Phenyl-2,3,3a,4,7,7a-hexahydro-1H-isophosphindole 2-Oxide ((s$_P$)-**23**) and (meso)-(2r,3aR,7aS)-2-Phenyl-2,3,3a,4,7,7a-hexahydro-1H-isophosphindole 2-Oxide ((r$_P$)-**23**).* The

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title compounds were prepared according to General Procedure B using a solution of $POPhCl_2$ (58.0 mg, 0.30 mmol) in THF (3.00 mL) and a solution of di-Grignard reagent **17** (0.06 M in THF, 4.00 mL, 0.24 mmol). Flash chromatography (100% EtOAc to 5% NEt_3/EtOAc) gave (s_P)-**23** (24.0 mg, 43% based on **17**) as a white solid. mp 76−79 °C; TLC (5% NEt_3/EtOAc) R_f = 0.55; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81−7.74 (m, 2H), 7.55−7.46 (m, 3H), 5.69 (s, 2H), 2.50−2.32 (m, 4H), 2.31−2.20 (m, 2H), 2.17−2.09 (m, 2H), 2.09−1.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.9 (d, J = 89.6 Hz), 131.2 (d, J = 2.9 Hz), 129.5 (d, J = 9.6 Hz), 128.3 (d, J = 11.5 Hz), 123.9, 35.1 (d, J = 7.3 Hz), 34.9 (d, J = 66.4 Hz), 27.3 (d, J = 7.7 Hz); IR (neat) ν 3400, 2904, 1653, 1436, 1407, 1180, 911, 845, 792, 744, 717, 696, 661 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{14}H_{18}OP$, 233.1095; found, 233.1085. Further elution (10% NEt_3/EtOAc) gave (r_P)-**23** (9.0 mg, 16% based on **17**) as an amorphous solid. TLC (5% NEt_3/EtOAc) R_f = 0.18; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83−7.75 (m, 2H), 7.57−7.47 (m, 3H), 5.64 (s, 2H), 2.78−2.66 (m, 2H), 2.37−2.27 (m, 2H), 2.24−2.12 (m, 2H), 2.11−2.02 (m, 2H), 1.94−1.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.6 (d, J = 90.0 Hz), 131.6 (d, J = 2.8 Hz), 130.0 (d, J = 9.7 Hz), 128.7 (d, J = 11.8 Hz), 124.4, 34.2 (d, J = 67.0 Hz), 34.1 (d, J = 7.2 Hz), 27.5 (d, J = 7.9 Hz); IR (neat) ν 3407, 2910, 1647, 1436, 1405, 1178, 934, 846, 797, 737, 728, 694, 661 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{14}H_{18}OP$, 233.1095; found, 233.1095.

*1-Phenylphosphinane Oxide (**24**).* This was prepared according to General Procedure B using a solution of $POPhCl_2$ (97.5 mg, 0.50 mmol) in THF (8.68 mL) and a solution of di-Grignard reagent **18** (0.38 M in THF, 1.32 mL, 0.50 mmol). Flash chromatography (100% EtOAc to 10% NEt_3/EtOAc) gave **24** (34.6 mg, 36%) as a white solid. NMR data was in good agreement with that previously reported.[42] mp 114−117 °C (lit.[17a] mp 125−127 °C); TLC (2% NEt_3/EtOAc) R_f = 0.15; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82−7.70 (m, 2H), 7.57−7.43 (m, 3H), 2.25−1.70 (m, 9H), 1.59−1.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.2 (d, J = 94.4 Hz), 131.6 (d, J = 2.5 Hz), 129.9 (d, J = 9.2 Hz), 128.6 (d, J = 11.5 Hz), 28.2 (d, J = 65.2 Hz), 26.6 (d, J = 6.8 Hz), 22.0 (d, J = 5.6 Hz); HRMS (ESI) $[M + H]^+$ calcd for $C_{11}H_{16}OP$, 195.0939; found, 195.0946.

*(racemic)-1-(2-Methoxyphenyl)-2,3-dihydro-1H-benzo[g]-phosphindole-1-oxide (**25**).* This was prepared according to General Procedure B using a solution of $PO(2\text{-}OMePh)Cl_2$ (71.9 mg, 0.32 mmol) in THF (2.13 mL) and a solution of di-Grignard reagent **15** (0.30 M in THF, 1.07 mL, 0.32 mmol). Flash chromatography (100% EtOAc to 2% NEt_3/EtOAc) gave **25** (51.2 mg, 52%) as an off-white solid. mp 168−169 °C; TLC (2% NEt_3/EtOAc) R_f = 0.27; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, J = 13.2, 7.7 Hz, 1H), 8.10 (dd, J = 6.2, 3.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.85−7.79 (m, 1H), 7.47−7.37 (m, 4H), 7.12 (t, J = 7.5 Hz, 1H), 6.75 (dd, J = 8.3, 5.5 Hz, 1H), 3.55−3.43 (m, 4H), 3.39−3.29 (m, 1H), 2.74−2.64 (m, 1H), 2.50−2.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4 (d, J = 4.5 Hz), 148.0 (d, J = 33.5 Hz), 134.1 (d, J = 6.2 Hz), 133.7 (d, J = 2.0 Hz), 133.1 (d, J = 2.7 Hz), 132.5 (d, J = 8.1 Hz), 132.0 (d, J = 9.1 Hz), 128.7 (d, J = 104.4 Hz), 128.2 (d, J = 1.4 Hz), 127.5, 125.9, 125.3 (d, J = 4.7 Hz), 123.9 (d, J = 13.3 Hz), 121.4 (d, J = 95.6 Hz), 120.9 (d, J = 11.1 Hz), 110.9 (d, J = 6.3 Hz), 55.3, 29.2 (d, J = 5.1 Hz), 26.7 (d, J = 73.6 Hz); IR (neat) ν 2914, 1589, 1507, 1477, 1273, 1241, 1200, 1148, 1017, 816, 803, 783, 750, 740 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{19}H_{17}NaO_2P$, 331.0864; found, 331.0876.

*(racemic)-1-(3-Bromophenyl)-2,3-dihydro-1H-benzo[g]-phosphindole-1-oxide (**26**).* This was prepared according to General Procedure B using a solution of $PO(3\text{-}BrPh)Cl_2$ (136.9 mg, 0.50 mmol) in THF (3.21 mL) and a solution of di-Grignard reagent **15** (0.28 M in THF, 1.79 mL, 0.50 mmol). Flash chromatography (100% EtOAc to 2% NEt_3/EtOAc) gave **26** (88.3 mg, 49%) as a white solid. mp 114−116 °C; TLC (2% NEt_3/EtOAc) R_f = 0.45; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09−8.03 (m, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.89−7.80 (m, 2H), 7.57 (d, J = 8.1 Hz, 1H), 7.52−7.40 (m, 4H), 7.27−7.21 (m, 1H), 3.58−3.46 (m, 1H), 3.39−3.26 (m, 1H), 2.65−2.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2 (d, J = 31.7 Hz), 136.7 (d, J = 93.4 Hz), 134.7 (d, J = 2.6 Hz), 134.2 (d, J = 2.6 Hz), 133.0 (d, J = 11.1 Hz), 132.7 (d, J = 7.8 Hz), 131.7 (d, J = 9.0 Hz), 130.2 (d, J = 12.6 Hz), 128.7 (d, J = 10.2 Hz), 128.4 (d, J = 1.4 Hz), 128.0, 127.5 (d, J = 102.6 Hz), 126.4, 125.1 (d, J = 4.7 Hz), 123.9 (d, J = 12.9 Hz), 123.2 (d, J = 15.2 Hz), 28.7 (d, J = 4.8 Hz), 27.9 (d, J = 71.8 Hz); IR (neat) ν 2975, 2350, 1559, 1507, 1395, 1185, 1123, 1066, 824, 777, 681, 664 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{18}H_{14}(^{79}Br)NaOP$, 378.9863; found, 378.9868.

*(racemic)-1-(1-Naphthyl)-2,3-dihydro-1H-benzo[g]-phosphindole-1-oxide (**27**).* This was prepared according to General Procedure B using a solution of PO(1-naphthyl)Cl_2 (122.5 mg, 0.50 mmol) in THF (3.33 mL) and a solution of di-Grignard reagent **15** (0.30 M in THF, 1.67 mL, 0.50 mmol). Flash chromatography (100% EtOAc to 1% NEt_3/EtOAc) gave **27** (129.8 mg, 79%) as a white solid. mp 208−210 °C; TLC (2% NEt_3/EtOAc) R_f = 0.77; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 8.3 Hz, 1H), 8.31 (d, J = 7.5 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.95−7.80 (m, 3H), 7.60−7.30 (m, 6H), 7.24 (t, J = 7.7 Hz, 1H), 3.55−3.35 (m, 1H), 3.22−3.04 (m, 1H), 2.74−2.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9 (d, J = 31.1 Hz), 133.8 (d, J = 2.5 Hz), 133.7 (d, J = 8.7 Hz), 132.8 (d, J = 9.1 Hz), 132.6 (d, J = 2.7 Hz), 132.5, 132.4, 131.5 (d, J = 11.2 Hz), 129.5 (d, J = 93.7 Hz), 128.9, 128.4 (d, J = 1.5 Hz), 127.83, 127.82 (d, J = 103.5 Hz), 127.3, 126.3, 126.2, 125.9 (d, J = 5.4 Hz), 125.6 (d, J = 4.6 Hz), 124.4 (d, J = 13.8 Hz), 124.1 (d, J = 12.7 Hz), 28.7 (d, J = 4.9 Hz), 28.4 (d, J = 70.6 Hz); IR (neat) ν 2990, 1507, 1199, 1187, 1160, 1058, 872, 836, 801, 775, 732, 702, 672 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{22}H_{17}NaOP$, 351.0915; found, 351.0904.

*(racemic)-1-tert-Butyl-2,3-dihydro-1H-benzo[g]phosphindole-1-oxide (**28**).* This was prepared according to General Procedure B using a solution of PO(*t*-Bu)Cl_2 (87.5 mg, 0.50 mmol) in THF (3.21 mL) and a solution of di-Grignard reagent **15** (0.28 M in THF, 1.79 mL, 0.50 mmol). Flash chromatography (2% NEt_3/EtOAc) gave **28** (74.7 mg, 58%) as an off-white solid. mp 138−140 °C; TLC (2% NEt_3/EtOAc) R_f = 0.44; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.61−7.45 (m, 2H), 7.33 (dd, J = 8.4, 2.3 Hz, 1H), 3.40−3.20 (m, 1H), 3.16−3.01 (m, 1H), 2.62−2.48 (m, 1H), 2.36−2.14 (m, 1H), 1.20 (d, J = 15.0 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4 (d, J = 28.3 Hz), 133.4 (d, J = 2.8 Hz), 133.2 (d, J = 8.6 Hz), 132.7 (d, J = 7.6 Hz), 128.2, 127.3, 126.6 (d, J = 2.9 Hz), 126.1, 125.3, 123.9 (d, J = 11.7 Hz), 34.9 (d, J = 67.9 Hz), 29.2 (d, J = 4.5 Hz), 24.7 (d, J = 1.4 Hz), 23.4 (d, J = 62.7 Hz); IR (neat) ν 2954, 1511, 1464, 1179, 1148, 873, 832, 815, 779, 735, 667, 640 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{16}H_{19}NaOP$, 281.1071; found, 281.1077.

*(racemic)-1-Cyclohexyl-2,3-dihydro-1H-benzo[g]phosphindole-1-oxide (**29**).* This was prepared according to General Procedure B using a solution of $POCyCl_2$ (77.6 mg, 0.39 mmol) in THF (2.61 mL) and a solution of di-Grignard reagent **15** (0.31 M in THF, 1.25 mL, 0.39 mmol). Flash chromatography (100% EtOAc to 2% NEt_3/EtOAc) gave **29** (78.9 mg, 72%) as an off-white solid. mp 133−134 °C; TLC (2% NEt_3/EtOAc) R_f = 0.15; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 3.32 (td, J = 17.0, 10.0 Hz, 1H), 3.15−3.02 (m, 1H), 2.55−2.44 (m, 1H), 2.29−2.08 (m, 3H), 1.87−1.76 (m, 1H), 1.76−1.58 (m, 3H), 1.45−1.31 (m, 1H), 1.31−1.10 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7 (d, J = 28.6 Hz), 133.1 (d, J = 2.8 Hz), 132.7 (d, J = 8.7 Hz), 132.4 (d, J = 7.7 Hz), 128.3 (d, J = 1.0 Hz), 127.5, 127.0 (d, J = 93.5 Hz), 126.1, 125.5 (d, J = 3.6 Hz), 123.9 (d, J = 11.9 Hz), 39.9 (d, J = 68.0 Hz), 28.5 (d, J = 4.6 Hz), 26.1 (d, J = 5.5 Hz), 26.0 (d, J = 6.2 Hz), 25.8 (d, J = 1.6 Hz), 25.6 (d, J = 1.7 Hz), 25.4 (d, J = 2.8 Hz), 23.1 (d, J = 65.0 Hz); IR (neat) ν 2923, 2845, 1507, 1198, 1175, 828, 809, 779, 740 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{18}H_{22}OP$, 285.1408; found, 285.1404.

*(racemic)-1-Allyl-2,3-dihydro-1H-benzo[g]phosphindole-1-oxide (**30**).* This was prepared according to General Procedure B using a solution of PO(allyl)Cl_2 (79.5 mg, 0.50 mmol) in THF (4.95 mL) and a solution of di-Grignard reagent **15** (0.29 M in THF, 1.72 mL, 0.50 mmol). Flash chromatography (100% EtOAc to 5% NEt_3/EtOAc) gave **30** (75.3 mg, 62%) as a pale yellow gum. TLC (2% NEt_3/EtOAc) R_f = 0.10; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.61 (t, J = 7.6 Hz,

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1H), 7.53 (t, J = 7.8 Hz, 1H), 7.33 (dd, J = 8.5, 2.3 Hz, 1H), 5.60−5.50 (m, 1H), 5.12−5.03 (m, 2H), 3.36 (td, J = 16.7, 10.0 Hz, 1H), 3.15−2.96 (m, 3H), 2.53−2.45 (m, 1H), 2.36−2.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5 (d, J = 30.3 Hz), 133.3, 132.4 (d, J = 7.7 Hz), 132.1 (d, J = 9.1 Hz), 128.4, 127.7, 127.6 (d, J = 104.6 Hz), 127.3 (d, J = 7.9 Hz), 126.2, 124.9 (d, J = 4.1 Hz), 123.8 (d, J = 12.4 Hz), 119.9 (d, J = 11.8 Hz), 37.0 (d, J = 62.4 Hz), 28.4 (d, J = 4.6 Hz), 24.2 (d, J = 68.9 Hz); IR (neat) ν 3410, 2927, 1510, 1204, 1176, 1150, 1116, 1010, 924, 818, 749 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{15}H_{15}NaOP$, 265.0758; found, 265.0759.

*(racemic)-1-Dimethylamino-2,3-dihydro-1H-benzo[g]-phosphindole-1-oxide (**31**).* This was prepared according to General Procedure B using a solution of $PO(NMe_2)Cl_2$ (81.0 mg, 0.50 mmol) in THF (3.33 mL) and a solution of di-Grignard reagent **15** (0.30 M in THF, 1.67 mL, 0.50 mmol). In this case, due to the potential susceptibility of the NMe_2 group to hydrolysis, the reaction was quenched by the addition of crushed ice (5 g) instead of water. Otherwise, workup was performed as described. Flash chromatography (2% NEt_3/EtOAc) gave **31** (107.9 mg, 88%) as an off-white solid. mp 123−125 °C; TLC (2% NEt_3/EtOAc) R_f = 0.17; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 3.32−3.20 (m, 1H), 3.20−3.08 (m, 1H), 2.61 (d, J = 10.4 Hz, 6H), 2.26−2.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4 (d, J = 35.3 Hz), 133.1 (d, J = 2.8 Hz), 132.3 (d, J = 7.6 Hz), 131.5 (d, J = 8.4 Hz), 128.1 (d, J = 1.2 Hz), 127.4, 126.4 (d, J = 117.9 Hz), 126.0, 124.9 (d, J = 4.5 Hz), 124.1 (d, J = 13.8 Hz), 35.2 (d, J = 4.1 Hz), 26.9 (d, J = 6.8 Hz), 22.1 (d, J = 85.8 Hz); IR (neat) ν 2910, 1507, 1455, 1282, 1199, 974, 824, 752, 601, 647 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{14}H_{16}NNaOP$, 268.0867; found, 268.0862.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01476.

^{1}H and ^{13}C NMR spectra for all compounds, selected gCOSY and gHSQC NMR spectra, and X-ray crystallographic information for compounds (s_P)-**23** and **27** (PDF, CIF, CIF).

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Notes

The authors declare no competing financial interest.

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