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Synthesis of 2,3-Dihydro-1-phenylbenzo[*b*]phosphole (1-Phenylphosphindane) and Its Use as a Mechanistic Test in the Asymmetric Appel Reaction: Decisive Evidence against Involvement of Pseudorotation in the Stereoselecting Step

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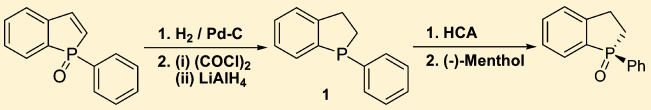
Supporting Information

ABSTRACT: Racemic 2,3-dihydro-1-phenylbenzo[*b*]-phosphole was obtained by reduction of 1-phenylbenzo[*b*]-phosphole-1-oxide, itself derived by ring-closing metathesis of phenylstyrylvinylphosphine oxide. The title compound was then reoxidized under asymmetric Appel conditions. Comparison of the sense and degree of the stereoselectivity to those obtained with an open-chain analogue indicated that the ring system does not affect the selectivity of the process. This in turn strongly suggests that the stereoselection is not related to pseudorotamer preferences in putative phosphorane intermediates.



Pentacoordinate phosphorus intermediates play an important role in synthetically valuable transformations such as the Wittig reaction,[1] the Horner−Wadsworth−Emmons reaction,[2] and reactions promoted by Mitsunobu conditions.[3] Such intermediates can undergo a fast intramolecular ligand exchange process, termed Berry pseudorotation,[4,5] that may have a significant effect on the outcome of the reaction.[6,7] However, in the case of the Appel reaction conditions,[8] while the involvement of chloro- and alkoxyphosphonium species is well-established,[9−11] the extent of participation of pentacoordinate phosphorane intermediates is less clear.[8,9]

Our interest in this question arose through our development[12] of an asymmetric version of the Appel conditions (Scheme 1) wherein racemic arylmethylphenylphosphines are

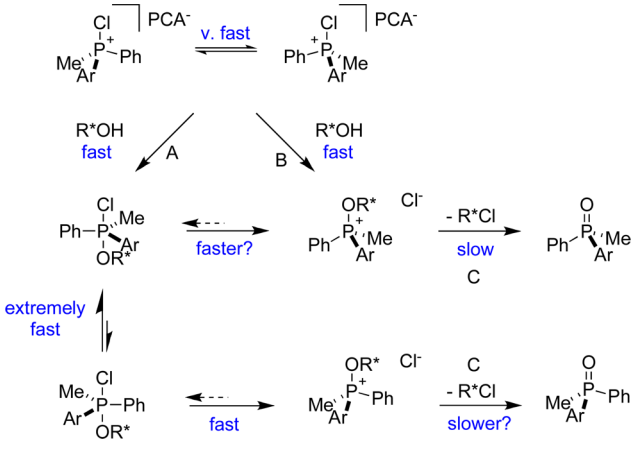
Scheme 1. The Asymmetric Appel Process[a]

[a]HCA, hexachloroacetone; CPS, chlorophosphonium salt; DAPS, diastereomeric alkoxyphosphonium salts; PCA, pentachloroacetonide.

treated with hexachloroacetone (HCA) and a chiral nonracemic alcohol (R*OH) to give high yields of enantioenriched phosphine oxides with enantiomeric excess (ee) up to 82%. This reaction is an effective way to make certain P-stereogenic phosphine oxides and bisphosphine oxides such as DiPAMPO and analogues[12,13] but is clearly limited by the moderate selectivity. As part of our studies to raise the selectivity and expand the substrate scope, we determined that the broad course of the reaction is as shown in Scheme 1 for arylmethylphenylphosphines.[11,14] It involves the transient generation of an intermediate chlorophosphonium salt (CPS) ($\delta_P \approx 70-75$ ppm) and trapping by the alcohol (R*OH) to give unequal amounts of a pair of diastereomeric alkoxyphosphonium salts (DAPS) ($\delta_P \approx 65-70$ ppm), which then undergo slow Arbuzov collapse to form scalemic phosphine oxide.

The likely routes for the source of the stereoselection in the conversion of CPS to DAPS are shown in Scheme 2 along with their required relative rates. Pathway A posits the formation of diastereomeric pentacoordinate alkoxychlorophosphoranes,

Scheme 2. Possible Sources of Stereoselection in the Asymmetric Appel Process



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which would be expected to undergo rapid interconversion via Berry pseudorotation. Selection could then occur as a result of the unequal distribution of pseudorotamers (dynamic thermodynamic resolution) or by their unequal rates of collapse to DAPS (dynamic kinetic resolution) or both. A rather different possibility is shown as pathway B: reaction of the chiral alcohol with rapidly interconverting CPS to generate directly the unequal mixture of diastereomers (also a dynamic kinetic resolution). The selectivity engendered by either pathway A or B might also be either augmented or diminished by unequal rates of the Arbusov collapse to oxides (pathway C) if the DAPS species can interconvert. However, our preliminary studies[11] indicated that their ratios (as measured by ^{31}P NMR spectroscopy) remained relatively unchanged during the course of the reaction and usually corresponded fairly consistently with the ee's in the product oxides.

Faced with these multiple possibilities, we sought ways to simplify our analysis. We report here our studies focused on the possible involvement of the pentacoordinate species (pathway A) primarily by the synthesis of a compound designed to reveal its influence.

Rationale for the test compound. Previously we had seen no evidence in the ^{31}P NMR spectra of our reaction mixtures (in toluene solvent) for the intervention of pentacoordinate species, which might be expected in a region of moderately low field shift (δ_P = −30 to −60 ppm)[15] in this solvent, but we were aware that this did not rule it out completely. Therefore, we sought a system that should affect the rate of Berry pseudorotation, in turn imparting a potential difference in stereoselectivity. Inclusion of the phosphorus atom in a ring, especially five-membered, is a well-known stratagem in phosphorus chemistry that has been shown in many instances to impact dramatically the kinetics and mechanism.[7,16] We chose 2,3-dihydro-1-phenylbenzo[*b*]phosphole (1-phenylphosphindane, **1**), a cyclic analogue of methylphenyl(*o*-tolyl)-phosphine (**2**) (Figure 1). The latter had been studied

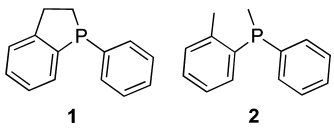


Figure 1. Comparison of phosphines **1** and **2**.

extensively by us in the asymmetric Appel process and had given the previous best enantioselectivity (up to 82% ee).[12,14b] The linking of two of the ligands at phosphorus into a five-membered ring introduces a limit on the number of possible pseudorotamers because the ring can span easily only equatorial and axial positions.[4b] The presence of the ring is also expected to slow the Berry pseudorotation,[4c,16b] so if such pseudorotation is indeed involved in the stereoselection process, we should expect a substantial change in ee relative to **2** under the same conditions. We would also increase our chances of detecting the pentacoordinate species by ^{31}P NMR spectroscopy, since the ring would also be expected to slow its decomposition.[7a,16b]

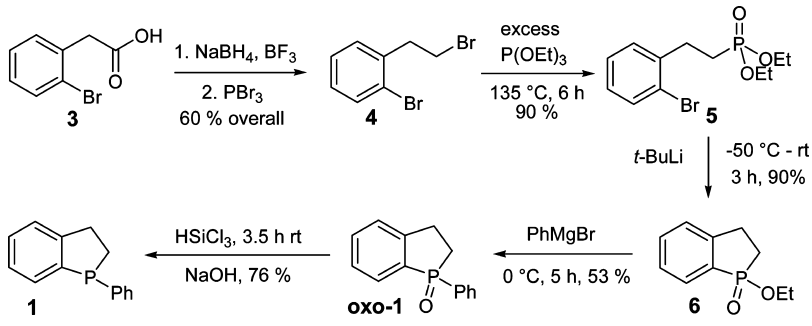
Compounds such as **1** are a valuable synthetic challenge in their own right (e.g., as ligands for catalytic asymmetric hydrogenation[17,18]), but most syntheses of benzophospholanes of type **1** have drawbacks.[19] Herein we report the efficient synthesis of the title compound, its subsequent use in the asymmetric Appel process, the absolute configuration of the resulting oxide, and the implications for the origin of the stereoselectivity of the reaction.

Synthesis of the test compound. Our initial, fairly traditional, synthesis of compound **1** (route A) is outlined in Scheme 3. Reduction[20] and bromination[21] of 2-bromophenylacetic acid (**3**) afforded dibromide **4** in 60% overall yield, which was then subjected to the Arbusov reaction with triethyl phosphite to give a good yield of phosphonate **5**. A notable issue in the latter reaction was the side reaction of ethyl bromide and triethyl phosphite. Consumption of the dibromide required a very substantial excess of triethyl phosphite, resulting in the production of diethyl ethylphosphonate in significant excess over the product **5** (ratio of 4:1), from which **5** had to be purified by careful high-vacuum distillation. Intramolecular cyclization of **5** with *t*-BuLi to give 1-ethoxy-2,3-dihydrophosphole-1-oxide (**6**) proceeded in high yield, but the yield of the subsequent conversion to 2,3-dihydro-1-phenylphosphole-1-oxide (**oxo-1**) with phenylmagnesium bromide could not be raised above 53%, despite extensive attempted optimization. Ironically, this latter problem may be related to the reduced reactivity of the five-membered cyclic pentacoordinated phosphorus intermediate, the stratagem of this research in the first place. Perhaps for similar reasons, the deoxygenation of **oxo-1** with trichlorosilane was also rather unsatisfactory, with difficulties in the isolation of the product and, notably, the persistent presence of **oxo-1** following the reduction.

Although we were able to access our target by route A, the problems encountered prompted us to explore an alternative ring-closing metathesis (RCM) route.[22] In contrast to route A, the phenyl group could be in place prior to the formation of the benzophospholane. The RCM procedure we chose (route B) is given in Scheme 4.

Starting from dichlorophenylphosphine, sequential addition of the Grignard reagent derived from 2-bromostyrene at low temperature followed by vinylmagnesium bromide resulted in

Scheme 3. Synthesis of oxo-1 via Route A



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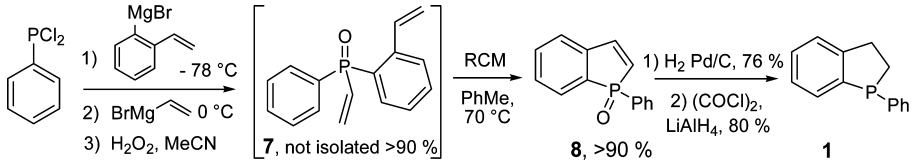
Scheme 4. Synthesis of oxo-1 via Route B Involving RCM Performed with Hoveyda–Grubbs Second-Generation Catalyst



the formation of phenylstyrylvinylphosphine (not isolated), which was immediately oxidized in situ to the corresponding oxide **7**. The latter was unstable, decomposing upon attempted purification, so the crude product was used directly in the next step without purification. For the ring-closing metathesis, the Hoveyda–Grubbs second-generation catalyst was found to be optimal, resulting in the formation of 1-phenylbenzo[*b*]-phosphole-1-oxide (**8**) with >90% conversion as judged by ^{31}P NMR spectroscopy. Compounds of this type are also of interest in their own right;[23] notably, Matano and co-workers recently used **8** in electronic studies of its dimer and related compounds,[24] but again, the syntheses are unsatisfactory. The exocyclic double bond of phosphole oxide **8** was hydrogenated with ease to give **oxo-1** with an overall isolated yield of 80% from dichlorophenylphosphine. For the final deoxygenation of **oxo-1**, we were able to utilize a novel methodology recently reported by our laboratory involving pretreatment with oxalyl chloride (which generates a chlorophosphonium salt) followed by reduction with lithium aluminum hydride.[14,25] This methodology was applied to the direct conversion of **oxo-1** to phosphine **1** in a good yield of 80% isolated with only trace amounts of oxide in the final material.

Testing in the asymmetric Appel process. With the synthesis of compound **1** established, we turned to probing the mechanism of the asymmetric Appel process. Both **1** and **2** were treated with HCA and chiral alcohol at a number of temperatures, and the results are shown in Table 1. Our premise was that if Berry pseudorotation is involved in the stereoselection, then a significantly different selectivity should result upon introduction of the ring. However, the results obtained[26] with (−)-menthol (entries 1–3) showed that across a wide temperature range, the selectivity obtained with phosphine **1** tracked well with that for phosphine **2**. For completeness, we also checked selectivity with a different alcohol, choosing (−)-8-phenylmenthol as it had previously shown a slightly different selectivity profile compared with (−)-menthol.[12] Again, there was no significant difference (entry 4). The reaction of **1** was also followed by ^{31}P NMR spectroscopy, and signals corresponding to DAPS were observed (δ_P = 89.3 and 89.5 ppm). However, at no point during the reaction did we observe a signal for a chloroalkoxyphosphorane. These results provide powerful evidence against the involvement of pentacoordinate intermediates and associated Berry pseudorotation in the stereoselectivity of the asymmetric Appel process.

Table 1. Results of the Asymmetric Appel Process as Applied to Phosphines 1 and 2[a]

			ee (%)[b]	
entry	alcohol	*T* (°C)	oxo-1[c]	oxo-2[c]
1	(−)-menthol	0	50	50
2	(−)-menthol	−44	62	66
3	(−)-menthol	−80	80	76
4	(−)-8-phenylmenthol	−80	82	75

[a]Conditions: HCA (0.11 M), phosphine (0.11 M), alcohol (0.132 M); for the detailed procedure, see the Experimental Section. Yields were >95%, and no other products were visible in the ^{31}P NMR spectra. [b]Measured by CSP-HPLC. [c]The configuration of **oxo-1** was determined to be *R* (see the text); the configuration of **oxo-2** was previously determined to be *R*.[27]

Finally, it remained to check that the absolute configurations of the product oxides were the same. We had previously established that (*R*)-**oxo-2** is the major enantiomer produced with (−)-menthol.[27] Crystallization of scalemic **oxo-1** obtained from the process proved unsuccessful, and we had to resort to preparative CSP-HPLC of the racemic material. Crystals grown of the major enantiomer were reconfirmed as such by analytical CSP-HPLC, and one was analyzed by single-crystal X-ray crystallography (details are provided in the Supporting Information). The absolute configuration was indeed found to be *R*, as expected if phosphines **1** and **2** are comparable within the asymmetric Appel manifold.

In conclusion, we have developed two routes to the phosphindane core structure. Route A provides the possibility for variation of the pendant substituent at phosphorus by the use of alternative nucleophiles with phosphonate **6**. Route B is a short, efficient synthetic route to both 1-phenylbenzo[*b*]-phosphole oxide **8** and 1-phenyl-2,3,dihydrobenzo[*b*]-phosphole **1**, with scope for application toward the synthesis of analogues with a central benzophospholane core. Likewise, variation on the alkyl ring could be achieved by functionalization of the double bond in oxide **8** or having functionality preinstalled before the RCM step. Most importantly, the availability of route B allowed us to study the stereoselection in our asymmetric oxidation of tertiary phosphines, which provided strong evidence against the involvement of Berry pseudorotation in the selecting process.

■ EXPERIMENTAL SECTION

General Experimental. All reagents were purchased from commercial sources and unless noted otherwise were used as received without further purification. All dry solvents were processed through a Grubbs-type solvent purification system and stored over molecular sieves (4 Å). All molecular sieves were flame-dried in a flask and heated to ∼200 °C with a heat gun under vacuum prior to use. Flash chromatography was performed on silica having a particle size of 0.04–0.06 mm. NMR spectra were recorded at 25 °C on 300–600 MHz spectrometers. Chemical shifts (δ) are reported in parts per million relative to internal Me_4Si. ^{13}C NMR spectra were assigned with the aid of two-dimensional cross-coupling experiments. All NMR samples of air- or moisture-sensitive compounds were made up under nitrogen in dry $CDCl_3$ in a Schlenk tube designed specifically for NMR preparation that could be dried and backfilled via standard Schlenk techniques. $CDCl_3$ was dried over activated molecular sieves (4 Å) under an atmosphere of nitrogen and stored in a Schlenk flask over sieves. High-resolution mass spectrometry was carried out on a electrospray ionization mass spectrometer with a TOF analyzer. IR spectra were obtained on an FTIR spectrometer and are reported here in units of cm^{-1}. Samples were prepared as thin films between NaCl plates. Phenyl(methyl)(*o*-tolyl)phosphine and its corresponding oxide were synthesized as per previous reports by our group.[10]

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2-(2-Bromophen-1-yl)ethanol.[20] To a solution of 2-bromophenylacetic acid (10 g, 46.5 mmol, 1 equiv) in dry THF (20 mL) cooled in an ice water bath were added $NaBH_4$ pellets (2.28 g, 60.4 mmol, 5.2 eq. of hydride) under a flow of nitrogen in lots over 15 min. To the resulting mixture was added $BF_3{\cdot}Et_2O$ (8.6 mL, 70 mmol, 1.5 equiv) dropwise by syringe over 15 min. A white precipitate was noted. The mixture was allowed to stir at room temperature for 24 h and was monitored by ^1H NMR spectroscopy by sampling the mixture and carrying out a workup as below. Upon completion, the THF was removed under reduced pressure, and the mixture was quenched by addition of HCl (100 mL, 1 M). To this was added ethyl acetate (50 mL), and the mixture was washed with sat. $NaHCO_3$ (50 mL × 2) followed by a final wash with brine (50 mL × 2). The organic layer was further dried over Na_2SO_4 and concentrated under reduced pressure to yield a pale-yellow oil (7.40 g, 70%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.54−7.52 (m, 1H, ArH), 7.29−7.19 (m, 2H, ArH), 7.10−7.03 (m, 1H, ArH) 3.84 (t, J = 7.5 Hz, 2H, HO−C**H**$_2$) 3.00 (t, J = 7.5 Hz, 2H, Ar−C**H**$_2$). In accordance with the literature, used without further purification.

2-(2-Bromophen-1-yl)ethyl Bromide (4).[21] The oil from the previous procedure was added to a nitrogen-flushed two-neck round-bottom flask equipped with a condenser. To this neat PBr_3 (3.8 mL, 40 mmol, 1.2 equiv) was added slowly via syringe dropwise over 30 min at room temperature. The mixture was heated to 80 °C and stirred at this temperature for 2 h. The solution was then cooled to 0 °C, diluted with DCM (100 mL), quenched with sat. $NaHCO_3$ (2 × 50 mL), and finally washed with distilled H_2O (2 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to an oil. This was purified using flash chromatography on silica (80:20 cyclohexane/ethyl acetate) to afford a clear oil (7.57 g, 85%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.5 (d, J = 8.4 Hz, 1H, Ar**H**), 7.27−7.24 (m, 2H, Ar**H**), 7.14−7.08 (m, 1H, Ar**H**), 3.58 (t, J = 7.5 Hz, 2H, Br−C**H**$_2$), 3.28 (t, J = 7.6 Hz, 2H, Ar−C**H**$_2$). In accordance with the literature, used without further purification.

Diethyl 2-(2-Bromophen-1-yl)ethylphosphonate (5). In a dry nitrogen-flushed flask, a neat mixture of **4** (5.6 g, 21.3 mmol, 1 equiv) and triethyl phosphite (16 mL, 96 mmol, 4.5 equiv) was stirred at 135 °C. When the reaction was complete (6 h, as determined by ^{31}P NMR), the side product, diethyl ethylphosphite, was removed by high-vacuum distillation, leaving behind the required product as a colorless liquid (6.48 g, 94%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 7.6 Hz, 1H, Ar**H**), 7.24−7.26 (m, 2H, Ar**H**), 7.06−7.11 (m, 1H, Ar**H**), 4.06−4.16 (m, 4H, O−C**H**$_2$), 2.98−3.07 (m, 2H, P−C**H**$_2$), 2.03−2.13 (m, 2H, Ar−C**H**$_2$), 1.33 (t, J = 7.1 Hz, 6H, C**H**$_3$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.2, 132.9, 130.2, 128.1, 127.6, 124.0, 61.6 (d, $^2J_{PC}$ = 6.5 Hz, O−**C**H$_2$), 29.4 (d, $^2J_{PC}$ = 3.9 Hz, Ar−**C**H$_2$), 25.8 (d, $^1J_{PC}$ = 139.3 Hz, P−**C**H$_2$), 16.4 (d, $^3J_{PC}$ = 6.1 Hz, **C**H$_3$). ^{31}P NMR (121 MHz, $CDCl_3$): δ 30. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{19}BrO_3PH$ 321.0255, found 321.0267. IR: 3054, 2985, 1265 (P═O) cm^{-1}. Used without further purification.

1-Ethoxy-2,3-dihydrobenzo[*b*]phosphole-1-oxide (6). To a dry nitrogen-flushed flask was added a solution of **5** (3.0 g, 9.3 mmol, 1 equiv) in dry THF (30 mL), and the flask was cooled under nitrogen in a dry ice−acetone bath. *t*-BuLi (1.7 M in pentane, 11.0 mL, 18.7 mmol, 2.1 equiv) was added dropwise via syringe over 30 min. After the mixture was stirred for 1 h at −78 °C, the solution was allowed to warm to room temperature, where the mixture turned pale-yellow and was stirred for a further 30 min. The mixture was then cooled to −50 °C, quenched by the addition of water (25 mL) dropwise via syringe, and diluted subsequently with ethyl acetate (100 mL). This mixture was allowed to warm to room temperature, and the separated organic layer was washed with brine (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield a pale-yellow oil. The crude product was purified by flash chromatography on silica (90:10 cyclohexane/ethyl acetate) to yield the desired product as a colorless oil (1.63 g, 90.5% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (apparent t, J = 8.4 Hz, 1H, Ar**H**$_{peri}$), 7.44−7.53 (m, 1H, Ar**H**), 7.28−7.38 (m, 2H, Ar**H**), 4.00−4.26 (dq, J = 7 Hz, 2H, O−C**H**$_2$), 3.04−3.19 (m, 2H, P−**C**H$_2$), 2.08−2.24 (m, 2H, Ar−**C**H$_2$), 1.32 (t, J = 7.0 Hz, 3H, C**H**$_3$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.2 (d, J_{PC} = 37.5 Hz, Ar), 132.6 (d, $^4J_{PC}$ = 2.5 Hz, Ar), 130.3 (d, $^1J_{PC}$ = 130.8 Hz, Ar), 127.6 (d, J_{PC} = 9.0 Hz, Ar), 127.3 (d, $^3J_{PC}$ = 10.8 Hz, Ar), 126.9 (d, $^3J_{PC}$ = 12.9 Hz, Ar), 61.1 (d, $^2J_{PC}$ = 6.5 Hz, O−**C**H$_2$), 26.0 (d, $^3J_{PC}$ = 6.5 Hz, Ar−**C**H$_2$), 23.7 (d, $^1J_{PC}$ = 96.5 Hz), 16.5 (d, $^3J_{PC}$ = 6.1 Hz, **C**H$_3$). ^{31}P NMR (121 MHz, $CDCl_3$): δ 65.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_{13}O_2PH$ 197.0731, found 197.0727. IR: 2983, 2936, 1598, 1211 (P═O) cm^{-1}.

1-Phenyl-2,3-dihydrobenzo[*b*]phosphole-1-oxide (oxo-1) by Route A. A dry nitrogen-flushed flask was charged with a solution of **6** (0.75 g, 3.82 mmol 1 equiv) in dry THF (50 mL) and cooled in an ice−water bath. Phenylmagnesium chloride (2.0 M in THF, 2.66 mL, 5.34 mmol, 2.5 equiv) was added dropwise via syringe over 30 min, and the mixture was stirred for 15 min at 0 °C. This mixture was slowly heated to reflux for 6 h, and a dark-brown color was noted. The mixture was cooled to −10 °C, and the THF was removed under reduced pressure. To this was added ethyl acetate (100 mL), and the mixture was quenched with aq. HCl (1.0 M) at −10 °C until a neutral pH was obtained. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to yield a dark oil. This was purified by flash chromatography on silica (70:30 ethyl acetate/cyclohexane) to yield the desired product as a pale-yellow solid. Subsequent recrystallization from hot ethyl acetate and cyclohexane afforded pale-yellow crystals (0.35 g, 53.5%, mp 73−77 °C). See below for characterization.

1-Phenyl-2,3,dihydrobenzo[*b*]phosphole (1) via Silane Reduction. To a solution of **oxo-1** (0.5 g, 2.14 mmol) in toluene (10 mL) was added trichlorosilane (3.0 mL, 21.4 mmol). The reaction mixture was stirred at room temperature for 3.5 h. After hydrolysis with excess 30% NaOH (10 mL), the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 25 mL). The combined extracts were washed with water (2 × 10 mL), dried over Na_2SO_4, filtered, and concentrated, yielding **1** (0.35 g, 76%) as a pale-yellow oil. See below for characterization.

Phenyl(*o*-vinylphenyl)(vinyl)phosphine Oxide (7). To a dry nitrogen-flushed two-neck flask charged with magnesium turnings (0.28 g, 11.5 mmol, 1 equiv), 1 mL of a solution of 2-bromostyrene (2.6 g, 14 mmol, 1.2 equiv) in dry THF (5 mL) was added dropwise via syringe at room temperature, and initiation was noted. The remaining 2-bromostyrene solution (4 mL) was added dropwise via syringe over 10 min, followed by dry THF (10 mL). The mixture was heated to reflux and stirred for 3 h until the magnesium was consumed. In a dry nitrogen-flushed two-neck flask, a solution of dichlorophenylphosphine (2.1 g, 11.5 mmol, 1 equiv) in dry THF (100 mL) was prepared. This was cooled to −78 °C using a dry ice−acetone bath. To this the above prepared Grignard solution was added dropwise via syringe over 20 min, and a yellow color was noted upon addition. The mixture was allowed to warm to room temperature. Formation of solely the monoaddition product was confirmed by ^{31}P NMR analysis following removal of a sample via syringe and workup by filtration after dissolution in $CDCl_3$. Following this, the solution was cooled using in an ice−water bath, and vinylmagnesium bromide solution (14 mL, 14 mmol, 1 M, 1.2 equiv) in THF was added via a dropping funnel over 20 min. The resulting mixture was allowed to warm to room temperature and stirred overnight. The mixture was concentrated under reduced pressure to a slurry. To this degassed DCM (100 mL) was added, and the reaction was quenched using degassed sat. NH_4Cl solution (100 mL). The mixture was concentrated to give a yellow oil. Acetonitrile (50 mL) was added, and the mixture was cooled in an ice−water bath. To the mixture was added H_2O_2 (3 equiv, 30% w/v) dropwise via syringe over 10 min, and the solution was stirred for 1 h. To this was added H_2O (20 mL), and acetonitrile was removed under reduced pressure, leaving a cloudy aqueous solution. **Caution:** do not evaporate to dryness. This was extracted with DCM (100 mL), and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield a yellow solid (crude yield 2.38 g, >90%). ^1H NMR ($CDCl_3$, 600 MHz): δ 7.67−7.62 (m, 4H, Ar**H**), 7.54−7.49 (m, 2H, Ar**H**), 7.47−7.42 (m, 2H, Ar**H**), 7.36−7.32 (m, 1H, Ar**H**), 7.24 (dd, J_{trans} = 17.2 Hz, J_{cis} = 10.9 Hz, 1H, Ar−C**H**), 6.71 (m, 1H, P−C**H**), 6.37−6.25 (m, 2H, P−CH−C**H**$_2$), 5.60 (dd, J_{trans} = 17.2 Hz, J_{gem} = 1 Hz, 1H, Ar−CH−C**H**$_a$),

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5.20 (dd, J_{cis} = 10.9 Hz, J_{gem} = 1 Hz, 1H, Ar−CH−C**H**$_b$). ^{13}C NMR (151 MHz, $CDCl_3$): δ 142.2 (d, $^2J_{PC}$ = 7.5 Hz, Ar**C**$_{ortho}$), 135.3 (d, $^3J_{PC}$ = 5.8 Hz, Ar−**C**H−CH$_2$), 134.8 (P−CH−**C**H$_2$), 133.1 (d, $^1J_{PC}$ = 103 Hz, Ph**C**$_{ipso}$) 132.9 (d, J_{PC} = 11.5 Hz, PhC$_{para}$), 131.9 (d, $^2J_{PC}$ = 3 Hz, ArCH$_{ortho}$), 132.4 (d, $^3J_{PC}$ = 3 Hz, ArCH$_{meta}$), 131.3 (Ph**C**$_{meta}$), 131.5 (d, $^1J_{PC}$ = 99 Hz, P−**C**H−CH$_2$), 129.5 (d, $^1J_{PC}$ = 99 Hz, Ar**C**$_{ipso}$) 128.6 (d, $^2J_{PC}$ = 12.2 Hz, Ph**C**$_{ortho}$), 127.3 (d, $^4J_{PC}$ = 12.3 Hz, Ar**C**H$_{para}$), 127 (d, $^3J_{PC}$ = 10.1 Hz, Ar**C**H$_{meta}$), 117.2 (Ar−CH−**C**H$_2$). ^{31}P NMR ($CDCl_3$ 121 MHz): δ 25.0. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{16}H_{15}OPNa$ 277.0753, found 277.0761. IR: 3081, 3058, 1656, 1261 (P═O) cm^{-1}. Used in the next step without further purification.

1-Phenylbenzo[*b*]phosphole-1-oxide (8). To a dry flask charged with nitrogen was added the solid from the previous procedure (2.38 g, 10 mmol, 1 equiv) followed by dry toluene (150 mL). This was heated to 60 °C, and Hoveyda−Grubbs second-generation catalyst (0.15 g, 2.5 mol %) was added as a solid. The mixture was stirred at 60 °C under nitrogen and monitored by ^{31}P NMR by removal of 1 mL portions, which were filtered through a pad of Celite and concentrated. Once the starting material had been consumed after 24 h, the mixture was concentrated under reduced pressure to yield a green solid (>90%, 2.85 g). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73−7.69 (m, 2H, Ar**H**), 7.62−7.59 (m, 1H, Ar**H**), 7.34−7.53 (m, 6H, Ar**H**; 1H, Ar−C**H**), 6.45 (dd, $^2J_{PH}$ = 25 Hz, J_{HH} = 8 Hz, 1H, P−C**H**). ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.34 (d, $^2J_{PC}$ = 13 Hz), 141 (d, J_{PC} = 30 Hz), 132 (d, $^1J_{PC}$ = 2.0), 131.3 (d, $^1J_{PC}$ = 3), 129.7, 129.8, 128.6 (d, J_{PC} = 10.4), 127.9 (d J_{PC} = 10 Hz) 127.8, 128.94, 126.8 (d, $^1J_{PC}$ = 99 Hz, P−C**H**), 124.9 (d, $^3J_{PC}$ = 13 Hz). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 41.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{11}OPH$ 227.0626, found 227.0622. IR: 3056, 2963, 1630, 1262 (P═O) cm^{-1}. Used in the next step without further purification.

1-Phenyl-2,3-dihydrobenzo[*b*]phosphole-1-oxide (oxo-1) by Route B. The green solid from the previous procedure (2.20 g, 11 mmol, 1 equiv) was added to a round-bottom flask, followed by MeOH (150 mL). To this was added 5 mol % Pd/C (10% w/w). The flask was degassed by brief application of a vacuum and then was charged with hydrogen via a balloon, and the mixture was stirred vigorously for 48 h. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to give a dark solid (2.3 g, quantitative). To this was added DCM (100 mL), and the solution was washed with 2 N nitric acid (50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield a pale-brown oil (1.9 g). Recrystallization from hot cyclohexane and acetone afforded pale-brown crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61−7.67 (m, 9H, Ar**H**), 3.36−3.50 (m, 1H, C**H**$_b$), 3.12−3.25 (m, 1H, P−C**H**$_a$), 2.33−2.53 (m, 2H, Ar−C**H**$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.7 (d, J_{PC} = 31 Hz, ArC$_{ortho}$), 132.9 (d, $^1J_{PC}$ = 98 Hz, ArC$_{ipso}$), 132.9 (d, $^3J_{PC}$ = 3 Hz, ArC$_{para}$), 132.4 (d, $^1J_{PC}$ = 103 Hz, PhC$_{ipso}$), 131.8 (d, $^3J_{PC}$ = 3 Hz, Ar$_{meta}$), 130.7 (d, $^3J_{PC}$ = 10.4 Hz, Ar$_{meta}$), 129.2 (d, $^2J_{PC}$ = 9.5 Hz, ArC$_{peri}$), 128.7 (d, $^2J_{PC}$ = 12 Hz, Ph$_{ortho}$), 128 (d, $^3J_{PC}$ = 10 Hz, Ph$_{para}$), 126.6 (d, $^3J_{PC}$ = 11.3 Hz, Ph**C**$_{meta}$), 28.4 (d, $^2J_{PC}$ = 4 Hz, Ar−**C**H$_2$), 28.2 (d, $^1J_{PC}$ = 70 Hz, P−**C**H$_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 53.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{13}OPH$ 229.0782, found 229.0779.

1-Phenyl-2,3,dihydrobenzo[*b*]phosphole (1) via Oxalyl Chloride/Hydride Reduction. In a dry nitrogen-flushed flask, a solution of **oxo-1** (0.60 g, 2.6 mmol, 1 equiv) in dry DCM (10 mL) was prepared under nitrogen and cooled in an ice−water bath, and oxalyl chloride (0.27 mL, 3.2 mmol, 1.25 equiv) was added dropwise via syringe over 5 min. Bubbling was noted, and the mixture turned a light orange and was allowed to warm to room temperature. A sample was taken via syringe and added to a dry nitrogen-flushed flask; the solvent was removed under reduced pressure, and the resulting solid was dissolved in dry $CDCl_3$. The sample was prepared under nitrogen for NMR analysis, and the complete formation of the chlorophosphonium salt was confirmed by ^{31}P NMR (δ 89.8). The mixture was cooled in an ice−water bath, and to this $LiAlH_4$ (1.3 mL, 4 M in diethyl ether, 4 hydride equiv) was added dropwise via syringe over 15 min. A suspension was noted. Following this, the mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed under reduced pressure, and the mixture was quenched by addition of 20 mL of degassed ethyl acetate followed by slow addition of aq. HCl (1M) via syringe over 5 min. The aqueous layer was further extracted with degassed ethyl acetate (20 mL), and the combined organic layers were dried over $MgSO_4$, passed through a short silica plug, and concentrated under reduced pressure to yield a yellow oil (0.45 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (apparent t, J_{HH} = 8.5 Hz, 1H, Ar−**H**$_{peri}$) 7.61−7.35 (m, 8H, Ar), 3.22−3.07 (m, 2H, Ar−C**H**$_2$), 2.36−2.26 (m, 1H, P−C**H**), 2.02−2.12 (m, 1H, P−C**H**). ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.5 (d, $^2J_{PC}$ = 3 Hz, Ar**C2**$_{ortho}$), 139.9 (d, $^1J_{PC}$ = 44 Hz, Ar**C**$_{ipso}$), 139.8 (d, $^1J_{PC}$ = 60 Hz, Ph**C**$_{ipso}$), 131.48 (d, $^2J_{PC}$ = 17 Hz, PhC$_{ortho}$), 131.46 (d, $^2J_{PC}$ = 25 Hz, Ar**CH**$_{peri}$), 129.1 (s, Ar**C4**$_{meta}$), 128.3 (d, $^4J_{PC}$ = 6.3 Hz, Ph**C**$_{para}$), 128.1 (s, PhC$_{meta}$), 126.8 (d, $^4J_{PC}$ = 8.3 Hz, ArC$_{para}$), 125 (d, $^3J_{PC}$ = 3 Hz, Ar**C2**$_{meta}$), 27.7 (d, $^1J_{PC}$ = 9 Hz, P-**C**H$_2$), 34.4 (d, $^3J_{PC}$ = 6 Hz, Ar-**C**H$_2$). ^{31}P NMR (121 MHz, $CDCl_3$): δ −2.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{13}PH$ 213.0833, found 213.0825.

Preparation of Stock Solutions. Molecular sieves (~25, 4 Å) were added to a dry 100 mL nitrogen-flushed flask, flame-dried, and placed under reduced pressure and left to cool. Following this, the flask was heated for 2 min, concentrating on the sieves, and then allowed to cool before being backfilled with nitrogen three times via standard Schlenk techniques. In a separate flask under a flow of nitrogen, the reagent (menthol or HCA or phosphine) and dry toluene were added to prepare the desired solution. This was then transferred via cannula under a flow of nitrogen directly into flask containing the sieves and left for 24 h prior to use.

Procedure for Asymmetric Appel Reaction. A 50 mL Schlenk flask equipped with molecular sieves (~1 g, 4 Å) and a magnetic stirrer was flame-dried and placed under reduced pressure and left to cool. Following this, the flask was heated for 2 min, concentrating on the sieves, and then allowed to cool before being backfilled with nitrogen three times via standard Schlenk techniques. Dry toluene (3 mL), a solution of menthol in dry toluene (3 mL, 0.396 mmol, 0.132 M, 1.2 equiv), and a solution of HCA in dry toluene (3 mL, 0.330 mmol, 0.11 M, 1 equiv) were added and left over sieves for 1 h. The mixture was cooled to the desired temperature (dry ice−acetone, dry ice−acetonitrile, or ice−water bath). Following this, a solution of phosphine in dry toluene (3 mL, 0.330 mmol, 0.11 M, 1 equiv) was added dropwise over 10 min. The temperature was maintained, and the mixture was allowed to stir for 1 h. Following this, the mixture was allowed to warm to room temperature overnight and then heated to 50 °C and stirred for 2 h. On cooling, the mixture was filtered and concentrated under reduced pressure to give an oil, which was dissolved in HPLC eluent to give a homogeneous solution. The solution was filtered through an PTFE membrane (0.2 μm) syringe filter directly into a vial, and analysis was carried out by HPLC.

HPLC Conditions. *1-Phenyl-2,3-dihydrobenzo[b]phosphole-1-oxide (**oxo-1**).* CHIRALPAC IA column, 90:10 heptane/ethanol, flow rate 1 mL/min. Retention times: 20.5 min for (*R*)-**oxo-1** and 22.2 min for (*S*)-**oxo-1**.

*Phenyl(methyl)(o-tolyl)phosphine oxide (**oxo-2**).* CHIRALPAC IA column, 80:10 heptane/ethanol, flow rate 1 mL/min. Retention times: 8.9 min for (*S*)-**oxo-2** and 9.8 min for (*R*)-**oxo-2**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C, and ^{31}P NMR spectra; HPLC analysis for the Appel reaction procedure; and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(26) Molecular sieves in the reaction mixture are necessary to keep it dry during the reaction. As discussed previously (ref 12a), water has a strong detrimental effect by hydrolysis of reactive intermediates, which results in racemic phosphine oxide formation. For the cyclic case reported here (**1**), a control was also carried out with no molecular sieves, which showed a detrimental effect on the ee, lowering it by 16% (the HPLC trace is included in the Supporting Information). This reduction is consistent with that obtained previously (ref 12a) for the acyclic system (**2**).

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