Crystallization-Induced Asymmetric Transformation of a Tertiary Phosphine

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An equilibrating diastereomer mixture of the tertiary phosphines **5** and **6** (2.5:1 equilibrium ratio) undergoes crystallization-induced asymmetric transformation upon slow evaporation of solvent from refluxing heptane to give a 20:1 ratio in favor of the more stable crystalline isomer **5**. The process can also be carried out at room temperature by using iodine to catalyze the interconversion of **5** and **6** via a pentavalent intermediate **8**. However, this variation is more sensitive to the purity of the starting phosphine. Crystalline **5** can be converted to the stable borane complex **3**, and reductive cleavage of the fluorenyl group using lithium naphthalenide affords the corresponding lithio derivative **10**. Alkylation with iodomethane or benzyl bromide affords **13** or **17**, respectively, with retention of phosphorus configuration.

We have been involved in studies designed to exploit crystallization-induced asymmetric transformation (abbreviated for convenience as AT) for the preparation of molecules containing stereogenic heteroelements.[1,2] This phenomenon has long been known,[3−6] but it has attracted relatively little attention compared to other methods of asymmetric synthesis. Nevertheless, there are a number of intriguing applications where AT has been used to prepare enantiomerically and diastereomerically homogeneous molecules on a substantial scale by the crystallization of one of two equilibrating diastereomers,[7] as well as related examples where crystallization of an interconverting mixture of positional isomers results in the recovery of one of the components in an amount exceeding that present at equilibrium.[8] Phosphorus examples of AT are also reported, including acylphosphines[1] and secondary phosphines.[9] We now report the first extension of the AT technique to a tertiary phosphine containing three hydrocarbon (alkyl and aryl) substituents at phosphorus.

In contrast to the acylphosphine examples, tertiary phosphines are resistant to pyramidal inversion. Typical inversion barriers exceed 30 kcal/mol,[10] corresponding to equilibration temperatures in excess of 100 °C. For successful AT under thermal equilibration conditions, it would be necessary for one of the phosphine diastereomers to have a melting point that is higher than the equilibration temperature. One way to address this potential limitation would be to use a phosphorus substituent that promotes high crystallinity (efficient packing in the crystal lattice; high mp) and that can be replaced by other groups when desired. Another approach would be to use a catalyst that induces the interconversion of phosphorus epimers at lower temperatures. There are indications in the literature that this should be possible from the reported racemization of methylphenylpropylphosphine by treatment with 10 mol % of iodine in benzene/CH_3CN at 50 °C.[11] If this method can be extended to diastereomer mixtures involving stereogenic phosphorus, then AT might be feasible with a broader range of substrates.

Results and Discussion

Synthesis of Menthyl-Derived Tertiary Phosphines. A straightforward route to diastereomeric tertiary phosphines was evaluated starting from the known **2**, Scheme 1.[12,13] The latter is available from (−)-menthyl chloride **1** via the Grignard reagent and phenyldichlorophosphine[14] as a mixture of diastereomers (2.5:1). Without purification, **2** was treated with organometallic reagents including MeMgBr, *i*-PrMgCl, and 9-fluorenyllithium at 0 °C. The resulting phosphines were evaluated for crystallinity, and promising crystals were obtained in the fluorenyllithium experiment. The crude phosphine mixture was therefore complexed with BH_3-THF to furnish the phosphine boranes **3** and **4** (3:1 ratio), corresponding to the phosphine diastereomers **5** and **6**.

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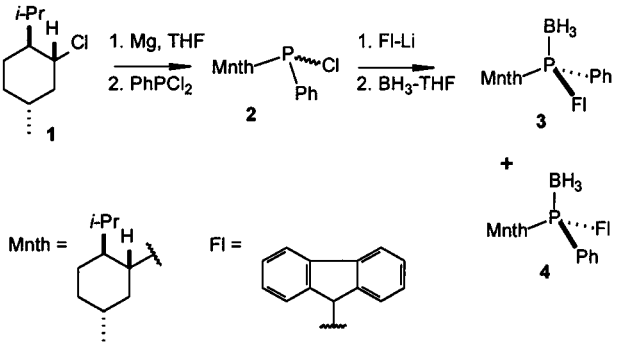
Scheme 1



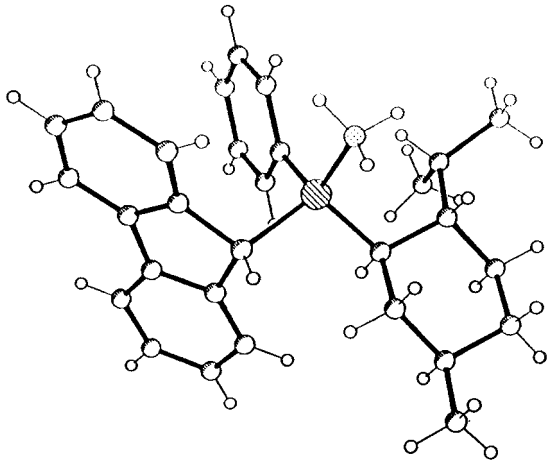


Figure 1. X-ray crystal structure of (R_p)-**4**.

The phosphine boranes were air and moisture stable and could be separated by a combination of crystallization and chromatography. Thus, the major fluorenyl diastereomer **3** was obtained in 32% yield by direct crystallization, while **4** was isolated in 23% yield after careful chromatography and crystallization, procedures that provided an additional 5−10% of impure **3**. Suitable crystals of the minor diastereomer **4** were obtained for an X-ray structure determination to establish relative stereochemistry and the (*R*)-configuration at the phosphorus stereocenter (Figure 1). The major diastereomer **3** must therefore have the (*S*)-configuration as shown.

Conversion of the phosphine boranes to the free phosphines was accomplished by treatment with excess diethylamine (5 h, rt).[15] In the case of the (S_P)-diastereomer **3**, this gave the crystalline S_P-phosphine **5** (mp 140 °C) in 97% yield as a single diastereomer. The diastereomeric (R_P)-phosphine **6** was made in the same way from **4** and was isolated as a viscous oil. An X-ray structure of the crystalline (S_P)-isomer **5** confirmed the expected stereochemistry, corresponding to retention of configuration in the decomplexation step (Figure 2).

The melting point of (S_P)-**5** was sufficiently high that thermal as well as catalyzed equilibration of phosphorus configuration could be considered for the AT experiments. As expected from precedent with other tertiary phosphines, heating a neat sample of diastereomerically pure **5** to 150 °C for 40 min resulted in a 1.3:1 (S_P/R_P) diastereomeric mixture of **5** and **6**. However, epimerization also occurred upon heating CD_3CN solutions of the

(15) Imamoto, T.; Oshiki,.; Onozawa, T.; Kusumoto,.T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244−52.

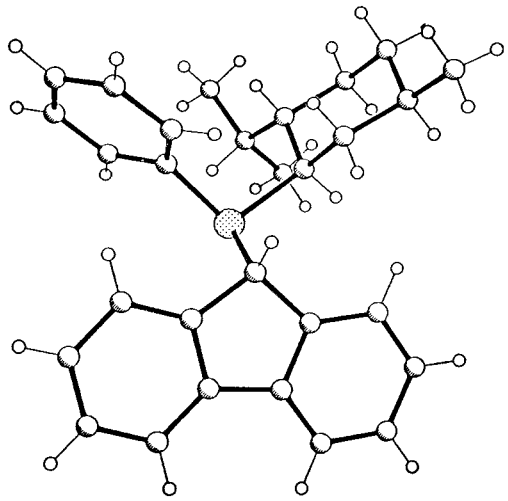


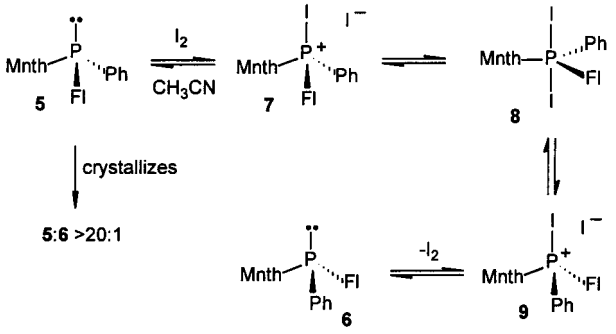
Figure 2. X-ray crystal structure of (S_p)-**5**.

individual diastereomers to 85 °C. NMR analysis after 14 h indicated that equilibrium had been reached (S_P/R_P 2.5:1 from either diastereomer). This temperature is well below the melting point of **5**, but initial attempts to perform the AT experiment encountered considerable difficulty in finding a solvent where interconversion of diastereomers would occur under conditions that allowed crystallization. Attention was therefore focused on the I_2-catalyzed epimerization of purified **5** in the hope that the interconversion with **6** would be feasible at lower temperatures and that this would facilitate the desired crystallization process required for AT. On the basis of earlier work,[11] molecular iodine should add reversibly to the phosphine diastereomers **5** and **6** to generate diastereomeric *P*-iodophosphonium salts **7** and **9**, which should interconvert via the pentavalent phosphorus intermediate **8**. Indeed, treatment of **5** with 10 mol % I_2 in CH_3CN resulted in much faster diastereomer equilibration (10 min vs hours at 80 °C) compared to the uncatalyzed thermal reaction. Subsequent cooling, evaporation of CH_3CN, and complexation with BH_3−THF resulted in a 1.1:1 mixture of diastereomers **3**:**4**. Similar results were obtained using *tert*-butyl methyl ether as the solvent (interconversion of isomers within 10 min, 55 °C), but the corresponding experiment in hexane as solvent (I_2, 20 min, reflux) resulted in formation of a yellow precipitate and very little epimerization. Apparently, the phosphine−iodine adducts are insoluble in hexane, and the catalytic cycle fails.

Initial attempts at iodine-mediated AT with crude mixtures of **5** and **6** gave poor results. Crystals of **5** were sometimes obtained, but the catalytic cycle that could be demonstrated with purified **5** or **6** did not work well when impurities were present. After much effort, it was found that the iodine-catalyzed equilibration could be controlled if the mixture of **3** and **4** obtained from **2** was purified by chromatography and then was decomplexed using diethylamine to give the mixture of relatively pure phosphines **5** and **6**. The AT experiment could then be carried out using a procedure based on previous work in our laboratory with substances containing equilibrating boron diastereomers.[2] In the latter study, a solution of the diastereomeric mixture was heated to a temperature where epimerization was relatively fast and the more stable diastereomer was allowed to crystallize as solvent was slowly evaporated over a time scale of hours. This

procedure allows control over the rate of crystallization by controlling the rate of solvent evaporation, and provides the means to convert the equilibrium mixture almost entirely to the more stable solid (the less soluble diastereomer).

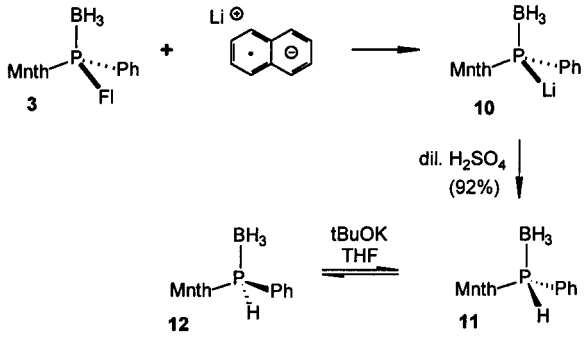
In an early experiment in the phosphorus series, purified, noncrystalline **6** was treated with 10 mol % I_2 in CH_3CN followed by crystallization and slow evaporation of the solvent over 4 h. The crude solid was then



complexed with BH_3−THF at low temperature to give a 3:1 S_P/R_P mixture of phosphine boranes **5** and **6**. Thus, some epimerization had occurred, but the final ratio of diastereomers was not very different from the equilibrium mixture (2.5:1 **5**:**6**). Several possible reasons for the low diastereomer ratio were considered: (1) the hydrolytically unstable phosphine−I_2 adduct decomposes, terminating the catalytic cycle; (2) undesired equilibration of phosphorus configuration occurs when the crystalline phosphine is dissolved prior to complexation with BH_3−THF; and (3) crystallization is too fast relative to equilibration. After further experimentation, it was evident that all three of these factors are important. The hydrolytic instability of the phosphine−I_2 adduct plays a role, as evidenced by improved ratios in the presence of powdered 3 Å molecular sieves to absorb water. Equilibration after the initial crystallization also takes place, apparently due to the presence of residual catalyst in the solid. This problem could be minimized by quenching the phosphine−I_2 adducts derived from the catalyst (presumably, **7**−**9**) with H_2O/K_2CO_3 prior to complexation with BH_3−THF. Finally, monitoring the rate of crystallization as a function of temperature indicated that iodine-catalyzed epimerization is fast enough even at room temperature to give high diastereomer ratios provided that crystallization (i.e., solvent evaporation) is carried out over ca. 30 h. Under the optimized conditions, a 3:1 diastereomer mixture of **5**:**6** was converted to a single diastereomer (>20:1 by ^1H and ^{31}P NMR assay) by crystallization from a CH_3CN solution containing 4 mol % I_2 while evaporating the solvent over 30 h. Pure **5** was obtained after another recrystallization (nonequilibrating conditions; no catalyst, <65 °C) from CH_3CN, giving **5** in 83% yield based on the 3:1 mixture (51% overall from **2**).

The experiments described above were optimized using material that had been prepurified at the stage of **3** + **4**. Application of the optimized conditions to material of lesser purity resulted in little or no enhancement in the final ratios. Presumably, the sensitive nature of the phosphine−I_2 adducts is the cause of these problems. Thus, any nucleophilic impurity that has the potential of intercepting the reactive adducts **7** or **9**, both present

Scheme 2



in catalytic amounts, is capable of shutting down equilibration of diastereomers. This limitation effectively prevented the use of crude **5** + **6**, obtained directly from the reaction of **2** with fluorenyllithium, for the AT experiments. The resulting inefficiency stimulated a reexamination of the thermal (uncatalyzed) AT process where there would be no sensitive *P*-iodophosphonium intermediates.

In principle, the simplest procedure for effecting AT is by crystallization from the melt since this requires no external reagents or solvents. Therefore, this alternative was examined carefully. In the best experiment, a prepurified mixture of **5** and **6** was melted at 150 °C and then allowed to crystallize at 120 °C over several hours. This resulted in an improvement of the diastereomer ratio to 19:1 **5**:**6**. However, the final diastereomer ratio obtained using this method was also highly dependent on the purity of the material. Even the presence of small amounts of impurities resulted in lower ratios (<10:1). The situation was improved by crystallization from solution under AT conditions. High diastereomer ratios (>20:1 **5**:**6** by NMR assay) were obtained by crystallization from refluxing heptane (bp 98 °C) while allowing the solvent to evaporate over a few hours. Other solvents (*n*-butanol, *n*-propanol/H_2O, EtCN, and AcOH) gave inferior results. This procedure was the most tolerant of the purity of the material and even crude material from the reaction of **2** and fluorenyllithium could be used. Under the best conditions, the crude phosphine obtained after simple filtration over silica gel and removal of excess fluorene by sublimation was crystallized from a minimum amount of heptane by allowing the solvent to evaporate over 48 h, resulting in a final ratio of 20:1 **5**:**6**. Recrystallization under nonequilibrating conditions (<65 °C) gave pure **5** in 57% yield based on $PhPCl_2$. This allowed a one pot synthesis of **5** from **2** without the need to prepare and purify the corresponding phosphine boranes **3** and **4**, and **5** could be conveniently made on gram scale.

Attention was turned to reductive removal of the fluorenyl group. This group was originally selected partly because of its reputation for high crystallinity, and also because it is potentially removable under reductive conditions. A key issue was whether reductive cleavage can be accomplished with control of phosphorus configuration. There is precedent for stereospecific reductive transformations of alkoxyphosphine boranes from Imamoto's work.[16] Although the anionic leaving group in the Imamoto experiments is different, the crucial intermediate **10** (Scheme 2) expected from the reductive cleavage

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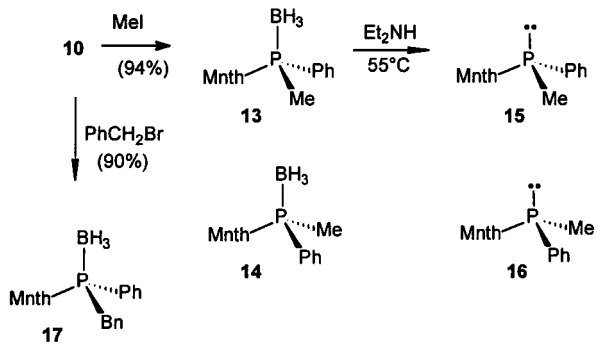
of the borane complex **3** is closely related to the intermediates generated from chiral alkoxyphosphine boranes with one electron reductants such as lithium naphthalenide. Subsequent alkylation or protonation should therefore produce phosphine boranes with high diastereomeric excess if the reduction/alkylation sequence can be performed near −78 °C. Imamoto et al. have shown that significant pyramidal inversion at phosphorus occurs if anionic phosphine boranes similar to **10** are warmed above 0 °C.[16]

Lithium naphthalenide proved highly effective at reducing **3**, and **11** was formed cleanly after protonation of **10** with H_2SO_4/THF at −78 °C. The reaction proceeded with essentially total stereospecificity (>99% de by HPLC assay). Retention of configuration at phosphorus was assigned by analogy to findings from subsequent experiments (see below). Interestingly, phosphorus stereochemistry could be equilibrated in **11** by treatment with *t*-BuOK in THF at room temperature, resulting in a 2:1 diastereomeric mixture after only 20 min. This equilibration probably involves the potassium analogue of **10**.

The reductive cleavage activation procedure allowed access to other chiral phosphines in excellent yield. Thus, treatment of **3** with lithium naphthalenide and subsequent alkylation with MeI (THF −78 °C) gave the methyl substituted derivative (**13**) in 90% yield. None of the diastereomer **14** could be detected by NMR methods. Furthermore, deprotection with diethylamine afforded a single diastereomer of the known phosphine **15**[17,18] without contamination by **16** (assay by NMR in deuteriobenzene). Likewise, a similar sequence from **2** using benzyl bromide as the alkylating agent furnished the corresponding benzyl-substituted phosphine **17** in 94% yield (single diastereomer, >20:1, ^{1}H NMR assay).



Comparison with the published ^{1}H NMR data ($CDCl_3$) for the diastereomers **15** and **16** allowed correlation of the relative configuration at phosphorus and demonstrated that the original fluorenyl cleavage from **3** proceeds with retention of configuration. By analogy, overall retention of configuration was also assigned for **11** and **17**. Similar findings were reported by Imamoto et al. starting from chiral alkoxyphosphines.[16]

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(18) In the course of the correlation experiments, it was observed that diastereomerically pure **15** equilibrates with **16** in $CDCl_3$ (deoxygenated and filtered through K_2CO_3), resulting in a 1.2: 1 diastereomer mixture after 2.5 h at room temperature. The configurational instability of electron rich P-chiral phosphines in $CDCl_3$ has been recently noted[19] and may be related mechanistically to the iodine-mediated equilibration discussed earlier if $CDCl_3$ acts as a positive chlorine source.

Summary

These studies demonstrate the feasibility of crystallization-induced asymmetric transformation approaches for the control of phosphorus configuration in tertiary phosphines. The *P*-fluorenyl substituent functions as a crystallization promoter that is compatible with the conditions required for AT. After the crystallization event, the *P*-fluorenyl subunit can be replaced stereospecifically by other alkyl groups using a sequence of reductive cleavage and alkylation. The thermal AT experiment with phosphine **5** is the most efficient, but other applications of this approach would be limited to tertiary phosphines with melting points >100 °C. The low-temperature iodine-catalyzed alternative is also demonstrated. This procedure is complicated by the sensitive nature of the *P*-iodophosphonium intermediates and by the need to purify the mixture of phosphine diastereomers. Further studies will be needed to extend the AT approach to lower-melting tertiary phosphines.

Experimental Section

General Methods. Flash column chromatography was performed using silica gel 60 (230−400 mesh). Solvents were purified as follows: tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone ketyl under N_2. CH_3CN was distilled from P_2O_5, then from anhydrous K_2CO_3, and stored over 3 Å molecular sieves. Reagents were used as received or purified as noted. All air- and/or moisture-sensitive reactions were run under an atmosphere of N_2 in flame- or oven-dried glassware.

(−)-Menthyl Chloride (1). The published procedure was followed.[13a] Thus, (−)-menthol (37.9 g, 0.24 mol, Aldrich), $ZnCl_2$ (110.1 g, 0.81 mol, Mallinckrodt), and HCl (75.0 mL, 37%, 0.90 mol, Fisher) gave (−)-menthyl chloride (37.9 g, 0.22 mmol, 92%, bp 81.0−83.0 °C/5 Torr; lit.[13a] 100−101.5 °C/21 Torr) as a colorless liquid. The NMR spectrum agreed with the published spectrum.[13b]

Menthylmagnesium Chloride. The published procedure was followed with modification:[14] To a suspension of Mg turnings (1.684 g, 69.3 mmol, Fisher) in THF (10 mL) was added dibromoethane (0.10 mL, 0.53 mmol). After the reaction had started, the flask was placed in a 50 °C oil bath, and a solution of (−)-menthyl chloride (6.0 mL, 32.1 mmmol) in THF (10 mL) was added over 20 min. The oil bath was then warmed to 60−70 °C, and the reaction mixture was stirred for 5 h. The solids were allowed to settle, and the clear, brown solution of menthylmagnesium chloride was removed by cannula, titrated, and used immediately.

Menthyl(1-naphthyl)phenylphosphine Borane. A solution of menthylmagnesium chloride (12.8 mL, 0.59 M in THF, 7.5 mmol) was added dropwise, over 1.5 h, to a cooled (bath temperature = −45 °C) solution of $PhPCl_2$ (1.0 mL, 7.4 mmol, distilled, Aldrich) in THF (10 mL). The resulting cloudy mixture was allowed to warm to room temperature and stirred for 22 h.

To another flask, containing a solution of 1-naphthyl bromide (1.1 mL, 7.9 mmol, Aldrich) in THF (10 mL), was added *t*-BuLi (8.8 mL, 1.8 M/pentane, 15.8 mmol) at −78 °C, and the yellow suspension was stirred for 20 min. At this time, the chlorophosphine solution was diluted with 9 mL of THF to dissolve solids and was added to the 1-naphthyllithium mixture by cannula over 15 min. The original flask was rinsed with THF (4 mL), and the yellow reaction mixture was allowed to warm to room temperature.

After 18 h at room temperature, the clear yellow solution was cooled to 0 °C, and BH_3−THF (11.0 mL, 1 M/THF, 11.0 mmol, Aldrich) was added. The solution was stirred for 3 h, and the reaction was quenched with 10 mL 1 M HCl. The mixture was extracted with ether, and the combined ether extracts were dried ($MgSO_4$), filtered, and evaporated (aspira-

tor) to leave an oil. The crude oil was purified by flash chromatography on silica gel (12 × 5 cm) 1:9 acetone/hexane eluent to give menthyl(1-naphthyl)phenylphosphine borane (1.36 g, 48% yield) as a 1:1 mixture of diastereomers. A pure diastereomer was obtained by crystallization of the foam from cold hexane (−20 °C) and further recrystallization of the resulting solid from hot benzene/hexane to give colorless crystals: mp 147.0 °C, dec; analytical TLC on silica gel, 1:9 acetone/hexane, $R_f = 0.50$; no parent ion for $C_{26}H_{34}BP$; M - 14 (BH_3), 374.2160, error = 1 ppm; IR ($CDCl_3$, cm^{-1}) 2394 (BH); 500 MHz NMR (C_6D_6, ppm) δ 8.7−8.6 (2H, m), 8.06−8.01 (2H, m), 7.47−6.89 (8H, overlapping m), 3.10−3.02 (1H, m), 2.5−1.7 (3H, broad m), 2.2−2.1 (2H, m), 1.68−1.51 (3H, overlapping m), 1.41−1.33 (1H, m), 1.19−1.13 (1H, broad m), 1.1−1.0 (1H, m), 0.92 (3H, d, $J = 6.7$ Hz), 0.8−0.7 (1H, m), 0.69 (3H, d, $J = 6.4$ Hz), 0.46 (3H, d, $J = 6.3$ Hz).

(S_P)/(R_P)-(9-Fluorenyl)menthylphenylphosphine Borane (3, 4). A solution of menthylmagnesium chloride (35.5 mL, 1.03 M/THF, 36.6 mmol) was added dropwise to a cooled (bath temperature −49 °C) solution of $PhPCl_2$ (5.0 mL, 36.8 mmol, distilled) in THF (50 mL) over 1.25 h. The cloudy mixture was brought to room temperature and allowed to stir for 17 h.

In another flask, 9-fluorenyllithium was prepared by addition of *n*-BuLi (23.3 mL, 1.59 M/hexanes, 37.0 mmol) to an ice-cold solution of fluorene (6.166 g, 37.0 mmol, recrystallized from hexanes) in 40 mL of THF over 15 min. THF, 15 mL, was added to dissolve some solids and the resulting orange solution stirred for 20 min at 0 °C.

At this time, the fluorenyllithium solution was added by cannula to an ice-cold solution of the chlorophosphine over 30 min (rinsing with 10 mL THF). The clear orange solution was stirred for 23 h at room temperature and then heated (bath temp 55−60 °C) for 2.5 h. The reaction was cooled in an ice bath and treated with BH_3−THF (50.0 mL, 1 M/THF, 50.0 mmol, Aldrich) and the solution stirred for 1 h at 0 °C and 0.5 h at room temperature.

The reaction was quenched by cautious addition of 100 mL of 1 M HCl and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered, and evaporated (aspirator) to leave a thick, cloudy yellow oil. The oil was filtered through silica gel (10 × 4 cm) eluting with CH_2Cl_2 to leave a yellow foam after solvent removal (aspirator). Proton NMR analysis (comparing the fluorenyl doublets: δ 4.73 ppm for (S_P)-**3** and 4.58 ppm for (R_P)-**4**) showed S_P/R_P 3:1.

The crude product was triturated with hexanes (30 mL), and a white solid slowly formed. The solid (6.88 g) was collected by vacuum filtration and washed with hexanes. Recrystallization from acetonitrile (ca. 55 mL) gave two crops of white crystals. Crop 1 (4.961 g, 11.6 mmol, 32%) was pure (S_P)-(9-fluorenyl)menthylphenylphosphine borane (**3**) by NMR, while crop 2 (0.723 g, 1.7 mmol, 5%) was a 10:1 S_P/R_P mixture. Characterization data for the pure diastereomer: mp 162.0 °C, dec; analytical TLC on silica gel, 1:1 dichloromethane/hexane, $R_f = 0.40$; M − 14 (BH_3), 412.2310, error = 3 ppm; base peak 165 amu; IR ($CDCl_3$, cm^{-1}) 2391 (BH), 1067; 200 MHz NMR (C_6D_6, ppm) δ 8.01 (1H, d, $J = 6.9$ Hz), 7.44−6.74 (12H, m), 4.73 (1H, d, $J = 11.8$ Hz), 2.84−2.59 (2H, m), 1.90−0.62 (11H, overlapping m), 0.96 (3H, d, $J = 6.9$ Hz), 0.93 (3H, d, $J = 6.9$ Hz), 0.70 (3H, d, $J = 5.6$ Hz).

The supernatant from the hexane trituration and the mother liquor from the recrystallization were combined and purified by flash chromatography on silica gel (15 × 9 cm; 50 mL fractions; gradient elution of hexanes, 1:4 CH_2Cl_2/hexanes, 1:1 CH_2Cl_2/hexane) to give 3.67 g (8.6 mmol, 23%) of (R_P)-(9-fluorenyl)menthylphenylphosphine borane (**4**) and impure (S_P)-**3** (0.923 g, 2.2 mmol, 6%, after further purification by recrystallization from CH_3CN). X-ray quality crystals of (R_P)-**4** were obtained by recrystallization from acetonitrile, confirming the relative stereochemistry at the phosphorus center as (*R*): mp 168.0 °C, dec; analytical TLC on silica gel 1:1 dichloromethane/hexane, $R_f = 0.50$; HRMS, M − 14 (BH_3), 412.2269, base peak = 165 amu; IR ($CDCl_3$, cm^{-1}) 2387 (BH), 1067; 270 MHz NMR (C_6D_6, ppm) δ 8.41 (1H, d, $J = 7.7$ Hz), 7.61−7.56 (1H, m), 7.34−6.49 (11H, m), 4.58 (1H, d, $J = 10.3$ Hz), 2.67−1.43 (11H, overlapping m), 1.02−0.68 (2H, overlapping m), 1.00 (3H, d, $J = 6.9$ Hz), 0.73 (3H, d, $J = 6.9$ Hz), 0.10 (3H, d, 6.7 Hz).

(S_P)-(9-Fluorenyl)menthylphosphine (5). The phosphine borane (S_P)-**3** (0.152 g, 3.6 mmol) was dissolved in deoxygenated Et_2NH (5 mL, distilled, Aldrich), and the clear, colorless solution was stirred for 16 h at room temperature. The Et_2-NH was removed under an N_2 stream, and the residue was taken up in deoxygenated benzene and filtered through a pad of silica gel under N_2. The benzene was removed under vacuum to give (S_P)-(9-fluorenyl)menthylphenylphosphine **(5)** as a white crystalline solid (0.145 g, 3.5 mmol, 97%). Pure material was obtained by recrystallization from deoxygenated acetonitrile, mp 140.2−142.0 °C (sealed capillary), colorless prisms. X-ray analysis confirmed the stereochemistry as S_P: analytical TLC on silica gel, 1:9 EtOAc/hexane, $R_f = 0.36$; molecular ion calcd for $C_{29}H_{33}P$ 412.23206, found $m/e = 412.2337$, error = 4 ppm; base peak = 165 amu; 270 MHz NMR (C_6D_6, ppm) δ 7.7−7.6 (5H, m), 7.3−7.1 (6H, overlapping m), 6.92−6.85 (2H, m), 4.82 (1H, s), 2.84−2.78 (1H, m), 2.35 (1H, d, $J = 12.2$ Hz), 2.19−2.16 (1H, m), 1.6−1.4 (3H, m), 1.2−0.5 (4H, overlapping m), 0.95 (3H, d, $J = 6.6$ Hz), 0.77 (3H, d, $J = 6.9$ Hz), 0.63 (3H, d, $J = 6.6$ Hz); ^{31}P NMR (202 MHz, {^1H}, C_6D_6, ppm) δ −0.4.

(R_P)-(9-fluorenyl)menthylphenylphosphine (6). Obtained as a viscous oil in >98% yield using the same procedure: ^1H NMR 200 MHz (C_6D_6, ppm) δ 7.84 (1H, d, $J = 7.2$ Hz), 7.68 (1H, d, 6.9 Hz), 7.4−6.6 (11H, m), 4.62 (1H, d, $J = 3.6$ Hz), 2.43−2.34 (2H, m), 1.9−0.8 (11H, overlapping m), 0.95 (3H, d, $J = 6.4$ Hz), 0.73 (3H, d, $J = 6.7$ Hz), 0.36 (3H, d, $J = 6.7$ Hz); ^{31}P NMR (121 MHz, {^1H}, C_6D_6, ppm) δ 13.2.

Optimized I_2-Mediated AT for 5. To a three-neck round-bottom flask, equipped with magnetic stirring and a coarse fritted funnel, was added powdered 3 Å molecular sieves (0.54 g), and the apparatus was flame dried under N_2. The phosphine (0.436 g, 1.06 mmol, S_P/R_P 3:1) was added, and then a solution of I_2 (9.7 mg, 0.04 mmol, Mallinckrodt) in deoxygenated CH_3CN (3.5 mL) was added by cannula. The resulting yellow mixture was heated in an oil bath (bath temperature 55 °C) for 10 min, at which time all but a few crystals had dissolved. The mixture was allowed to cool to room temperature, crystallization began, and the solvent was removed over 30 h with a gentle N_2 stream to leave a solid mass.

To the solid mass was added K_2CO_3 (16 mg, 0.11 mmol) in deoxygenated H_2O (0.5 mL). The mixture was too thick, so more H_2O was added until the mass could be stirred and broken up (a total of 0.75 mL was added). Deoxygenated CH_3-CN (0.25 mL) was added, and the creamy tan mixture was stirred further. At this time, the mixture was taken into deoxygenated THF, dried ($MgSO_4$), and filtered through the glass frit under N_2. Evaporation of the solvent and ^1H NMR analysis indicated $S_P/R_P > 20:1$. The crude solid was recrystallized from hot deoxygenated CH_3CN under N_2 to give pure (S_P)-**5** (0.364 g, 0.88 mmol, 83%).

(S_P)-5 by Thermal AT (One-Pot Procedure from $PhPCl_2$). Menthylmagnesium chloride (4.0 mL, 4.0 mmol, 1.0 M/THF) was diluted with 6.8 mL of THF and added to a solution of $PhPCl_2$ (0.51 mL, 3.76 mmol, Aldrich, distilled) in THF (6.4 mL), cooled to −48 °C, over 40 min by cannula with magnetic stirring. The Grignard flask was rinsed with THF (1 mL) and the resulting off-white suspension allowed to warm to room temperature. The clear, slightly yellow solution was stirred for 17 h at room temperature and then cooled to −75 °C.

In another flask, an ice-cold solution of fluorene (0.656 g, 3.95 mmol, Aldrich, recrystallized from hexanes) in 20 mL of THF was treated with *n*-BuLi (2.5 mL, 1.6 M/hexanes) with magnetic stirring. The clear, orange solution was stirred for 30 min and then cooled to −48 °C.

At this time, the fluorenyllithium solution was added to the cold chlorophosphine solution over 55 min by cannula. The orange mixture was stirred for 1 h and then allowed to warm to room temperature. After 3 h at room temperature, the clear, yellow solution was quenched by addition of CF_3CO_2H (0.20 mL, 2.6 mmol, distilled from P_2O_5). After 20 min, Et_3N (0.60 mL, 4.3 mmol, distilled from CaH_2) was added and a white

precipitate formed. After 10 min, the volatiles were removed in vacuo. The crude foam was taken into deoxygenated benzene and filtered through a pad of silica gel under N_2. The excess fluorene was removed by sublimation at 65−70 °C/0.08−0.04 Torr for 19 h with occasional agitation to leave a slightly yellow solid (1.26 g). The original ratio of 5:1 had increased to 8.5:1 during this process, presumably by AT. The crude product was transferred to a one-piece 25 mL flask-condenser apparatus. Deoxygenated heptane (0.8 mL, Fisher) was added and the mixture placed in an 85 °C oil bath (some solid still remained). A gentle N_2 stream was applied to slowly evaporate the heptane. After 24 h, the mixture appeared as a thick oil, the N_2 stream was increased, and this was accompanied by more crystallization. After another 24 h, the solid was allowed to cool to room temperature. NMR (^{1}H,^{31}P) analysis indicated S_P/R_P 20:1. Recrystallization from deoxygenated CH_3CN (+65 to −20 °C) gave S_P-**5** (0.890 g, 2.16 mmol, 57% based on $PhPCl_2$) as colorless prisms.

(S_P)-(L-Menthyl)phenylphosphine Borane (11). Lithium naphthalenide was prepared according to the procedure of Rieke:[20] To a 50 mL round-bottom flask were added naphthalene (0.493 g, 3.8 mmol, crystallized from ether), lithium (50 mg, 7.2 mmol, Aldrich), and THF (12 mL) under N_2. After being stirred for 3 h, the black solution was cannula transferred to another 50 mL round-bottom flask, rinsed with THF (2 × 1 mL), and cooled to −78 °C.

The lithium naphthalenide solution was cooled to −78 °C, and a precooled (−78 °C) solution of (S_P)-(9-fluorenyl)menthylphenylphosphine borane **5** (0.418 g, 0.98 mmol) in THF (6 mL) was added by cannula over 11 min. After 30 min, a precooled (−78 °C) solution of H_2SO_4 (0.50 mL, 9.0 mmol, EM, 95−98%) in THF (5 mL) was added by cannula over 5 min. The resulting colorless solution was allowed to warm to room temperature by removing the bath. After 1 h, the cloudy, white mixture was evaporated and partitioned between 10 mL of H_2O and 20 mL of CH_2Cl_2. An emulsion formed, so 10 mL of saturated NH_4Cl solution was added. The aqueous layer was extracted further with CH_2Cl_2, and the combined CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and evaporated (aspirator) to leave a white solid. The crude product was filtered through a plug of silica gel (2.5 × 2.5 cm; CH_2Cl_2 eluent).

The diastereomeric purity of **11** was assayed by HPLC (Gilson silica gel column, 0.46 × 25 cm, hexanes eluent, UV detection at 240 nm). A sample containing both diastereomers (S_P/R_P 1.9:1 by ^{1}H NMR) was prepared starting from S_P-**11** by treatment with *t*-BuOK (0.3 equiv in THF, rt 20 min). The HPLC trace of this mixture gave two peaks at 14.6 and 16.7 min in a ratio of 1.0:1.1. The HPLC trace of the crude reaction mixture gave the same two peaks in a ratio of 104:1, indicating that the peak at 14.6 min is due to (S)$_P$-**11**, the peak at 16.7 is due to (R_P)-**12**, and the response factor is 2.1. Thus, these results indicate a diastereomer ratio of S_P/R_P 218:1 in the present reaction. The product was purified by flash chromatography on silica gel (10 × 3 cm), 20% CH_2Cl_2/hexanes eluent, taking 5−10 mL fractions, to give a white crystalline solid (0.235 g, 0.90 mmol, 92%). Analytical TLC on silica gel, 1:1 dichloromethane/hexane, R_f = 0.49. Pure material was obtained by crystallization from hexane (−20 °C): mp 97.3−99.0 °C, fine, white needles; HRMS, M − 14 (BH_3), 248.1675, error = 8 ppm; IR (KBr, cm^{-1}) 2384, BH; 300 MHz NMR (C_6D_6, ppm) δ 7.6−7.5 (2H, m), 7.1−7.0 (3H, m), 5.36 (1H, dqd, J = 365.0, 7.0, 2.7 Hz), 2.1−1.0 (9H, overlapping m), 0.9−0.6 (13H, overlapping m); the methyl doublets of the menthyl group could not be integrated accurately because of overlapping peaks but appear at 0.90 (J = 7.0 Hz) 0.73 (J = 6.6 Hz), and 0.58 (J = 6.6 Hz); ^{31}P NMR (202 MHz, {^{1}H}, C_6D_6, ppm) δ −3.7 to −4.2 (broad m). Anal. Calcd: C, 73.28; H, 10.78. Found: C, 73.21; H, 10.52.

(R_P)-(L-Menthyl)methylphenylphosphine Borane (13). Lithium naphthalenide was prepared according to the procedure of Rieke:[20] To a 25 mL round-bottom flask were added naphthalene (0.427 g, 3.3 mmol, crystallized from ether) and lithium (47 mg, 7.2 mmol, Aldrich). The dry mixture was stirred under N_2 for 20 min, THF (10 mL) was added, and the dark solution was stirred further for 3 h. The black solution was then cannula transferred to a 50 mL round-bottom flask (rinsing with THF, 2 × 1 mL) and cooled to −78 °C.

To the cold lithium naphthalenide solution was added a precooled (−78 °C) solution of (S_P)-(9-fluorenyl)menthylphenylphosphine borane **3** (0.359 g, 0.84 mmol) in THF (8 mL) by cannula over 5 min (rinsing with cold THF, 2 × 1 mL). After 45 min, a precooled (−78 °C) solution of CH_3I (0.52 mL, 8.35 mmol, Aldrich, filtered through basic alumina) in THF (4 mL) was added by cannula over 5 min. The resulting orange solution was stirred for 30 min and then allowed to warm to room temperature. After another 30 min, 20 mL of H_2O was added. The mixture was extracted with ether, and the combined ether extracts were dried ($MgSO_4$), filtered, and evaporated (aspirator) to leave an oily yellow solid. ^{1}H NMR analysis indicated a single diastereomer (>20:1). The product was purified by flash chromatography on silica gel (5 × 2.5 cm) using a gradient from hexane to 1:1 hexane/CH_2Cl_2 to give a white crystalline solid (0.209 g, 0.76 mmol, 90%); analytical TLC on silica gel, 1:1 dichloromethane/hexane, R_f = 0.40. Pure material was obtained by crystallization from hexane (−20 °C): mp 85.5−86.3 °C, colorless crystals; HRMS, M − 14 (BH_3), 262.1814; base peak = 262 amu; IR (KBr, cm^{-1}) 2386, BH; 300 MHz ^{1}H NMR (C_6D_6, ppm) δ 7.64−7.57 (2H, m), 7.10−7.07 (3H, m), 2.3−2.2 (1H, m), 2.2−1.2 (11H, overlapping m), 1.0−0.6 (13H, overlapping); the P-methyl doublet and the doublets of the menthyl group could not be integrated accurately but appear at 1.28 (J = 9.3 Hz), 0.88 (J = 7.0 Hz), 0.69 (J = 7.0 Hz), 0.63 (J = 5.8 Hz), respectively; ^{31}P NMR (202 MHz,{^{1}H}, C_6D_6, ppm) δ 17.2−15.6 (broad m). Anal. Calcd: C, 73.91; H, 10.97. Found: C, 73.31; H, 10.44.

(R_P)-Benzyl(L-menthyl)phenylphosphine Borane (17). Lithium naphthalenide was prepared according to the procedure of Rieke:[20] To a 50 mL round-bottom flask were added naphthalene (0.491 g, 3.8 mmol, crystallized from ether), lithium (39.7 mg, 5.7 mmol, Aldrich), and THF (6 mL) under N_2. The lithium was cut under the solvent, and the resulting dark green solution was magnetically stirred for 3.5 h. The lithium naphthalenide solution was cannula transferred to a 100 mL round-bottom flask, rinsing with THF (2 × 2 mL) and cooled to −78 °C.

To the cold lithium naphthalenide solution was added a precooled (−78 °C) solution of (S_P)-(9-fluorenyl)menthylphenylphosphine borane **3** (0.410 g, 0.96 mmol) in THF (6 mL) by cannula over 12 min. The phosphine borane flask was rinsed with THF (2 × 2 mL), and the rinses were added to the reaction mixture. After 30 min, a precooled (−78 °C) solution of benzyl bromide (1.2 mL, 10.1 mmol, Aldrich, filtered through basic alumina) in THF (5 mL) was added by cannula over 5 min. The resulting orange solution was stirred for 15 min at −78 °C and then allowed to warm to room temperature by removal of the bath. After 1.5 h, the colorless reaction mixture was quenched by addition of 1 M HCl (15 mL).

The mixture was extracted with ethyl acetate (1 × 25 mL, 2 × 15 mL), and the combined extracts were dried ($MgSO_4$), filtered, and evaporated (aspirator). The residue was purified by radial chromatography on silica gel PF254 (4 mm) in two passes, 1:4 dichloromethane/hexane eluent to give **17** (0.315 g, 0.90 mmol, 94%); analytical TLC on silica gel, 1:1 dichloromethane/hexane, R_f = 0.43. Pure material was obtained by crystallization from hexane: mp 149 °C, dec, fine white needles; molecular ion calcd for $C_{23}H_{34}BP$ 352.24914, found m/e = 352.2496, error = 1 ppm; IR (KBr, cm^{-1}) 2393, BH; 300 MHz NMR (C_6D_6, ppm) δ 7.54−7.47 (2H, m), 7.01−6.85 (8H, m), 3.41 (1H, dd, J = 13.8, 6.8 Hz), 3.11 (1H, dd, J = 13.8, 13.8 Hz), 2.59−2.55 (1H, m), 2.05−0.60 (21H, m); the methyl doublets of the menthyl group could not be integrated accurately due to overlapping peaks but appear at 0.98 (J = 7.0 Hz), 0.83 (J = 6.6 Hz), 0.61 (J = 6.2 Hz); ^{31}P NMR (202 MHz, C_6D_6, {^{1}H}, ppm) δ 28.5−26.4 (broad m). Anal. Calcd: C, 78.40; H, 9.75. Found: C, 78.49; H, 9.43.

(R_P)-(L-Menthyl)methylphenylphosphine (15). Phosphine borane **13** (0.056 g, 0.20 mmol) was dissolved in Et_2NH (1 mL, distilled from NaOH) and the solution brought to reflux

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under N_2 (bath temperature 60−65 °C). After 4 h, the solution was allowed to cool to room temperature and directly analyzed by ^{31}P NMR, which showed a single peak at −34.4 ppm. The NMR sample was rinsed back into the flask with deoxygenated (N_2 purge) benzene, and the volatiles were evaporated (N_2 stream). The residue was filtered through a plug of silica gel (3 × 1 cm) eluting with deoxygenated (N_2 purge) benzene and the benzene evaporated (N_2 stream, vacuum pump) to leave a colorless oil (0.053 g, 0.20 mmol, 100%). The oil was dissolved in deoxygenated $CDCl_3$ (N_2 purge; filtered through K_2CO_3), and the ^1H and ^{31}P NMR spectra were recorded. The diastereomeric purity was 1:15 S_P/R_P, which decayed to 1:1.2 after 2.5 h: ^1H NMR for the (R_P) diastereomer (300 MHz, $CDCl_3$, ppm) δ 7.4−7.3 (5H, m), 2.85−2.77 (1H, m), 1.7−0.6 (20H, overlapping m), 0.4−0.25 (1H, m). The P-Me doublet could not be integrated accurately but appeared at 1.34 ppm (J = 4.8 Hz). Key signals for the (S_P) diastereomer: 2.60−2.53 (1H, m) and the P-Me at 1.21 (J = 3.7 Hz). These signals were used to compare with those reported in the literature[17a] for both diastereomers and allowed for assignment of **12** as the (R_P) diastereomer: ^{31}P NMR (not reported in ref 17a) (121 MHz, $CDCl_3$, ppm) (R_P)-**15** δ −33.1; (S_P)-**16** −30.3; in Et_2NH: δ −31.3 ppm (S_P), −34.3 ppm (R_P).

Following the same procedure on 10 mg of **13** resulted in 67% yield of the free phosphine. ^1H NMR analysis indicated a single diastereomer (>20:1) based on only one set of signals: (300 MHz, C_6D_6, ppm) δ 7.45−7.35 (2H, m), 7.2−7.05 (3H, m), 3.15−3.0 (1H, m), 1.7−0.7 (19H, overlapping m), 0.65−0.45 (2H, m). The characteristic P-Me doublet was observed at δ 1.18 (J = 5.5 Hz).

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Supporting Information Available: NMR spectra of new substances; X-ray data tables for the more stable phosphine **5** and for the borane complex **4**, corresponding to the less stable phosphine diastereomer. This material is available free of charge via the Internet at http://pubs.acs.org.

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