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Synthesis and Reactivity of New Chiral Bicyclic Phospholanes as Acyl-Transfer Catalysts

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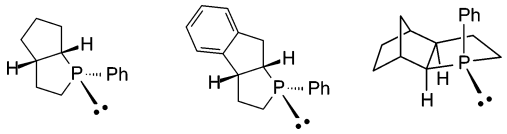
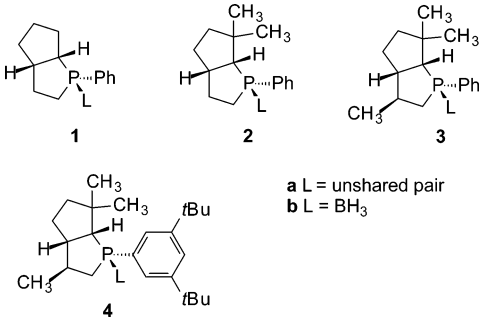


Synthesis of chiral phosphines **1a**, **14a**, and **18a** as nucleophilic catalysts for anhydride activation and kinetic resolution of alcohols is described. Radical cyclization of alkenylphosphines produced the phosphabicyclooctane (PBO) core of catalysts **1a** and **14a**, while **18a** was made by quenching a metallocycle precursor with dichlorophenylphosphine. Catalysts **1a** and **14a** are less reactive, while **18a** is comparable to the most reactive catalysts in the PBO family. The preferred ground-state geometries of phosphine−boranes were identified using computational methods, and were correlated with the catalytic reactivity of the corresponding free phosphines.

Introduction

Recently, we reported that bicyclic phosphabicyclo[3.3.0]-octane (PBO) catalysts **1**−**4** demonstrate impressive reactivity for anhydride activation and good to excellent enantioselectivity in the kinetic resolution of arylalkylcarbinols[1−4] and allylic alcohols.[5] While the PBO catalysts can be very effective in



kinetic resolutions, several issues remain to be addressed. So far, little has been done to evaluate alternative methodology to access the phosphabicyclo[3.3.0]octane subunit[4,6] beyond the nucleophilic phosphide displacement of bismesylates used to prepare **1**−**4**.[2,7] Furthermore, the relationship between catalyst structure and reactivity is not understood sufficiently to identify potentially useful catalysts. In an effort to address both issues, we have targeted ring-fused phospholanes that can be accessed using radical cyclization and carbometalation approaches, as described below.

Results and Discussion

Phosphinyl radical addition to olefins is well-known,[8] and there are several examples of analogous intramolecular additions to make five- and six-membered cyclic phosphines.[9−13] To test

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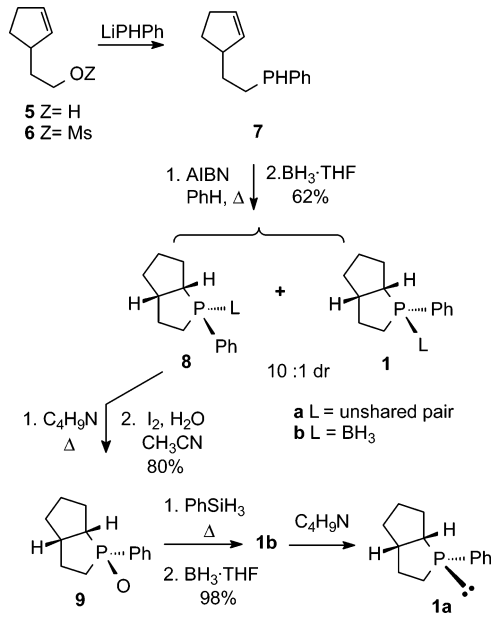
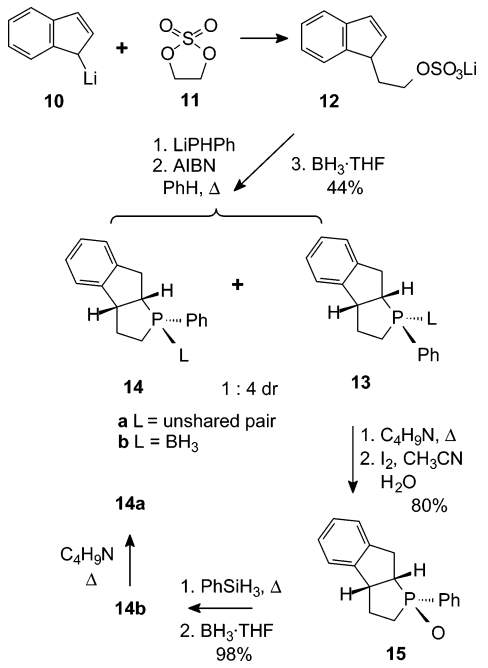
SCHEME 1



the potential of the radical cyclization approach, a synthesis of the known catalyst **1a** was designed from substituted cyclopentene precursors. Previously, the same catalyst had been obtained by a nucleophilic displacement strategy for ring closure, but the earlier route encountered difficult purifications at several stages.[3] The radical cyclization approach has the advantage that the intermediate alcohol **5** is easily prepared and purified.[14] In the key reaction, the known (racemic) mesylate **6** was displaced with lithium phenylphosphide to give **7**, followed by AIBN-induced radical cyclization (Scheme 1). A mixture of *P*-epimers **8a** and **1a** was formed, as evidenced by the isolation of the corresponding borane complexes **8b** and **1b** (10:1 ratio, 62% combined yield) after addition of THF−borane. The major product proved to be the *exo*-phenyl stereoisomer **8a** having the undesired, less reactive phosphorus configuration.[15] The same diastereomers **8b** and **1b** had been obtained earlier from a bismesylate precursor and *P*-lithiophenylphosphine,[3] with **8b** favored by a ratio of 6.7:1.

Following a literature precedent for the oxidative inversion of configuration at phosphorus,[4,16] the phosphine **8a** was treated with iodine in aqueous acetonitrile to give the phosphine oxide **9**. Next, **9** was deoxygenated with retention of configuration using phenylsilane.[17] Temporary protection of the resulting phosphine **1a** as the borane adduct afforded **1b**, corresponding to the more reactive phosphorus configuration as established in our prior study using the bismesylate displacement route.[3]

SCHEME 2



By comparison, the new sequence allows easier product isolation and scaleup. Furthermore, the feasibility of radical cyclization for preparation of the phosphabicyclo[3.3.0]octane core is demonstrated.

With the radical cyclization strategy established, a concise synthesis of a benzo-fused analogue, **14a**, was envisioned using a similar approach, as shown in Scheme 2. Indenyllithium (**10**) was generated by lithiation of indene with *n*-butyllithium, followed by the sequential addition of the cyclic sulfate **11**[18] at −78 °C followed by 1.5 equiv of LiPHPh to effect formation of the C−P bond. The resulting secondary phosphine intermediate was not isolated, but was treated with AIBN (benzene, reflux) to induce radical cyclization. Subsequent addition of borane−THF afforded a 4:1 ratio of *P*-epimers **13b** and **14b**, isolated in 44% combined yield after chromatographic separation. The phosphine obtained from the major borane adduct by decomplexation with pyrrolidine did not activate isobutyric anhydride for acyl transfer at room temperature, while the minor phosphine diastereomer was reactive. In all of the other bicyclic phosphines studied to date, the more reactive diastereomer has proven to be the *endo*-phenyl isomer, having the more accessible unshared electron pair at phosphorus as required for nucleophilic catalysis. By that argument, the major radical cyclization product was assigned the stereochemistry as shown in **13a**, while the minor product was identified as the desired phosphine **14a**. This assignment is also consistent with the stereochemical outcome of the radical cyclization from **7** to **8a** described in Scheme 1.

The major phosphine−borane **13b** from radical cyclization was subjected to the same procedure for inversion of phosphorus configuration as used previously. The sequence of decomplexation with pyrrolidine, oxidation of **13a** to **15** with aqueous iodine, and deoxygenation with phenylsilane converted **13b** into **14b** in 78% yield.[4,16,17] Finally, resolution of enantiomers by HPLC was used to obtain enantioenriched **14a** to test enantioselectivity in kinetic resolutions. Considering the one-pot nature

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(15) (a) We have not determined whether **8a** is formed under kinetic or thermodynamic control. Formation of the more stable phosphorus configuration **8a** would be no surprise in a kinetically controlled cyclization. However, reversible phosphinyl radical additions are precedented[15b] and would also be expected to lead to **8a**. (b) Pellon, J. *J. Am. Chem. Soc.* **1961**, *83*, 1915.

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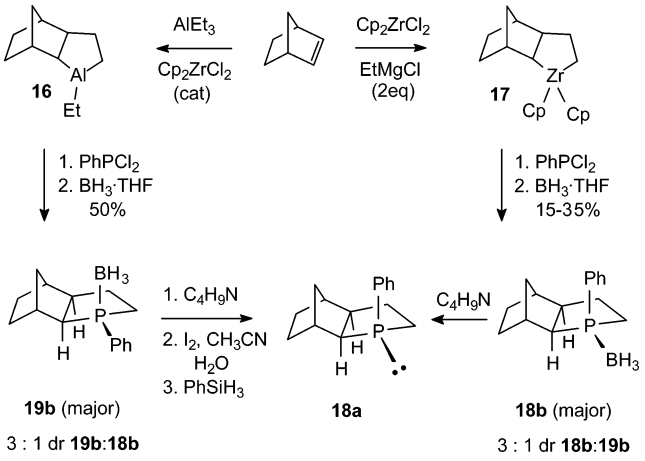
SCHEME 3

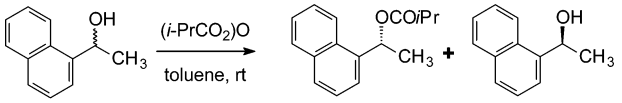


of the conversion from **10** to **13b** + **14b**, this sequence is short and relatively convenient compared to other known synthetic approaches to racemic phosphabicyclo[3.3.0]octanes, despite the need to invert the phosphorus configuration.

An alternative sequence to related structures containing the phosphabicyclo[3.3.0]octane core was considered, following reports by Dzhemilev[19] and Walther[20] detailing the carbometalation of norbornene using zirconocene dichloride together with triethylalane or ethylmagnesium chloride. The triethylalane procedure is catalytic in zirconium and affords the metallacycle **16**, while the EtMgCl method uses a stoichiometric amount of the zirconocene reagent and produces **17**. Quenching either **16** or **17** with phenyldichlorophosphine afforded diastereomeric mixtures of the norbornane-fused phospholanes that were isolated as the corresponding borane complexes **18b** and **19b** (Scheme 3). Interestingly, the diastereomer ratios obtained from **16** and **17** were different and complementary. The zirconacycle **17** gave the desired *endo*-phenyl epimer **18b** as the major product in a 3:1 ratio and in variable yield (15−35% combined for both isomers). On the other hand, the cyclic alane **16** obtained using catalytic Cp_2ZrCl_2 consistently gave ca. 50% of cyclic phosphine products favoring **19b**. In either case, the purified undesired *exo*-phenyl epimer **19b** could be inverted in high yield using the standard sequence of deprotection, oxidative inversion at phosphorus (I_2/H_2O), deoxygenation of P═O with phenylsilane, and reprotection to afford **18b**.[4,16,17] Separation of enantiomers was achieved by HPLC as before, and deprotection of the borane complex by warming with pyrrolidine afforded the free phosphine **18a** as needed for testing enantioselectivity in acyl-transfer reactions.

The new catalysts **14a** and **18a** were compared with the PBO catalyst **2a** in the kinetic resolution of 1-(1-naphthyl)ethanol (**20**), the standard benzylic alcohol test substrate, following procedures developed earlier. Catalyst **14a** proved to have modest reactivity (5−6-fold lower compared to that of **2a**) and poor enantioselectivity in the isobutyroylation of **20** (Table 1, entry 1, $s = 1.5$, vs entry 2). In contrast, the reactivity of catalyst **18a** was comparable to that of **2a** if the relative rates were adjusted for the difference in catalyst loading (entry 2 vs entry 3). However, the enantioselectivity observed with **18a** was somewhat lower, and little improvement in selectivity was observed at lower temperatures (entry 4).

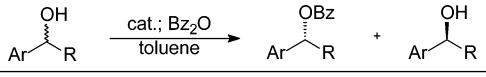
TABLE 1. Isobutyroylation of 20 with Chiral Phosphines 14a, 18a, and 2a



20 (*R*)-**21** (*S*)-**20**

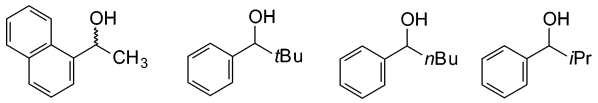
entry	cat. (loading, %)	temp	time (h)	conv (%)	rel rate	*s*
1	**14a** (8)	rt	112	41	1	1.5
2	**2a** (19)	rt	6	44	5.5	9
3	**18a** (2.6)	rt	20.5	29	6.6	5
4	**18a** (2.5)	−25 °C	93	63	1.7	6

TABLE 2. Benzoylations with 18a



entry	alcohol	Ar	R	cat.	temp	*s*
1	**22**	Ph	*t*Bu	**18a**	rt	23
2	**22**	Ph	*t*Bu	**2a**	rt	14[a]
3	**20**	1-naphthyl	Me	**18a**	rt	12
4	**20**	1-naphthyl	Me	**18a**	35 °C	10
5	**20**	1-naphthyl	Me	**2a**	35 °C	10[a]
6	**20**	1-naphthyl	Me	**18a**	−25 °C	19
7	**20**	1-naphthyl	Me	**2a**	−25 °C	28[a]
8	**23**	Ph	*n*Bu	**18a**	rt	10
9	**23**	Ph	*n*Bu	**3a**	rt	11[b]
10	**24**	Ph	*i*Pr	**18a**	rt	10
11	**24**	Ph	*i*Pr	**3a**	rt	15[b]

[a] Ref 3 data. [b] Ref 2 data.



20 **22** **23** **24**

More promising results were obtained when the more reactive catalyst **18a** was used for the activation of benzoic anhydride (Table 2). A ca. 2-fold rate increase was observed in the benzoylation of **22** using **18a** compared to **2a**, and selectivity was improved (entry 1, $s = 23$ for **18a**; entry 2, $s = 14$ for **2a**). With the less hindered alcohol **20**, no significant difference between **18a** and **2a** was observed from room temperature to 35 °C (entries 3−5), although a smaller improvement in enantioselectivity was found at −25 °C for **18a** compared to **2a** (entries 6 and 7). Similar enantioselectivities were also determined when substrates **23** and **24** were benzoylated using catalyst **18a**. Marginally better results had been observed earlier using **3a** as the catalyst (entries 9 and 11 vs entries 8 and 10), but **18a** is a viable catalyst overall in terms of reactivity as well as enantioselectivity.

The origins of reactivity and selectivity for PBO catalysts are not well understood, but a possible correlation between catalyst reactivity and ground-state conformational preferences has been noted.[3] Simple *P*-phenylphospholanes are relatively unreactive, apparently because they prefer a geometry having the lone pair (lp) eclipsed by the *P*-Ph group (Figure 1, **26**; dihedral angle θ near 0°) over alternatives such as structure **25** where *P*-Ph eclipses one of the ring CH_2 groups (θ near 60°). The latter geometry has the less hindered unshared electron pair required for effective nucleophilic catalysis, but the increased

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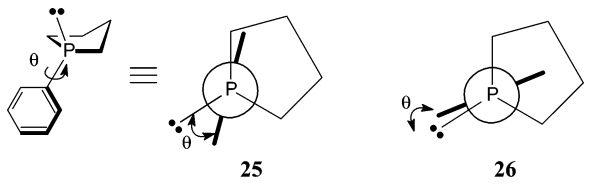

FIGURE 1. $CH_2\cdots$*P*-Ph eclipsed (**25**) and lp$\cdots$*P*-Ph eclipsed (**26**) conformers of 1-phenylphospholane.

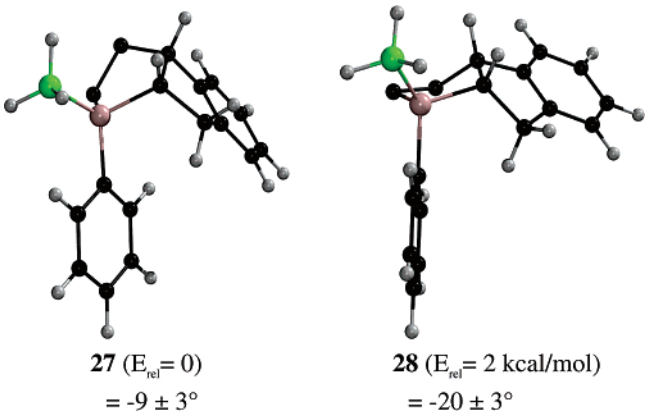

FIGURE 2. Energy minima (**27**, **28**) for **14b** (3-21G*; selected H atoms erased for clarity).

Ph$\cdots CH_2$ interaction destabilizes the transition state for acyl transfer. However, geometries intermediate between the limiting cases **25** and **26** should have improved reactivity and fewer steric repulsions. This conformational argument was supported by computational modeling (HF/3-21G*) of ground-state geometries for monocyclic and bicyclic phosphines.[3] Borane complexes of the catalytically active phosphines were also modeled, and were used as deliberately oversimplified surrogates for the transition states corresponding to acyl transfer. Of course, the phosphine−boranes were not expected to closely mimic the transition states for acyl transfer, but they did provide an opportunity to develop a confidence level in the HF/3-21G* geometries by comparison with three solid-state conformers observed in the X-ray crystal structure of the borane complex **2b**, and could be modeled without encountering unknowns that arise in any detailed description of the acyl-transfer process. Using this indirect approach to probe conformational preferences, a tentative correlation was made between the high reactivity of catalyst **2a** and access to low-energy conformers having substantial *P*-phenyl dihedral angles θ relative to the unshared electron pair at phosphorus in **2a**, or the BH_3 group in **2b**.

The same computational approach (HF/3-21G* level) and search for local energy minima in 3° increments[3] was used to evaluate conformational preferences for borane complexes **14b** and **18b** corresponding to the new catalysts **14a** and **18a**. In the case of the ineffective benzo-fused catalyst **14a**, two energy minima were obtained (Figure 2). The more stable conformer **27** has a relatively small dihedral angle, $\theta = -9 \pm 3°$, between the *P*-Ph group and the P−B bond, a result that correlates with lower reactivity due to increased steric hindrance near the unshared electron pair of the catalyst **14a**. The less stable (by 2 kcal/mol) conformer **28** has a larger dihedral angle, $\theta = -20 \pm 3°$. If the dihedral angle/reactivity correlation holds, then the conformer of **14a** that resembles **28** would be more reactive than a geometry similar to **27**. However, the less reactive phosphine geometry resembling **27** would be dominant at equilibrium because it is more stable.

Computational modeling of **18a** by the same approach revealed two local minima, **29** and **30** (Figure 3). Conformer **30** has the lower calculated energy by 1 kcal/mol and the larger dihedral angle ($\theta = -40 \pm 3°$), consistent with high catalytic reactivity for the corresponding conformer of catalyst **18a**. The phospholane ring geometry of **30** is virtually identical to that found in one of the energy minima for **2a**/**2b** (conformer **31**; $\theta = -42 \pm 3°$) consistent with the proposition that the high reactivity of **2a** as well as **18a** may be due to access to similar transition-state geometries for acyl transfer. Because of the fused norbornane subunit, structure **18a** is far more rigid than is **2a** and has relatively few conformational options. Therefore, the similar reactivities and good enantioselectivities of **18a** and **2a** can be taken as evidence that the preferred transition-state geometries for acyl transfer resemble conformers **30** and **31**, respectively. According to this analysis, reactive catalysts should have low-energy conformers with θ in the range of 35−45° to provide a less hindered environment near the unshared electron pair at phosphorus. This conclusion may be helpful in the design of new conformationally constrained catalyst families containing the phosphole ring and having high nucleophilic reactivity.

Summary

As the first member of a new family of chiral phosphabicyclooctanes, **18a** is noteworthy because it has good reactivity

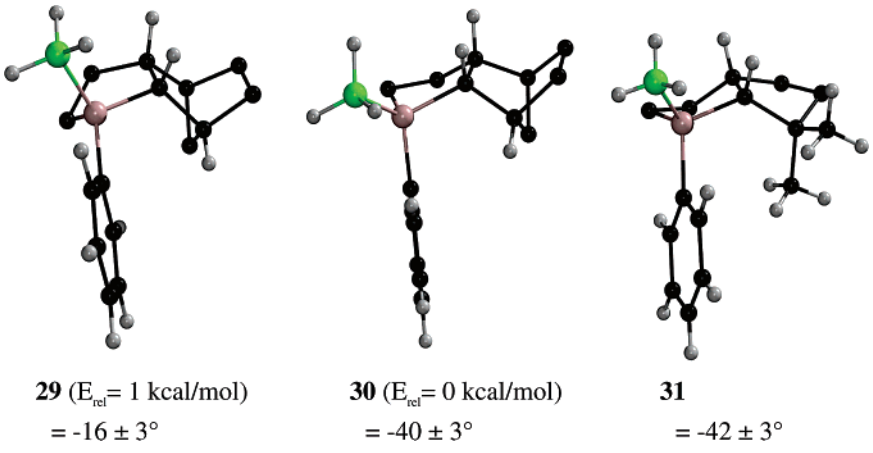

FIGURE 3. Geometries of energy minima (3-21G*) for **18b** (**29**, **30**) and **2b** (**31**).

as well as enantioselectivity in the kinetic resolution of alcohols by benzoylation.[21] The synthesis of **18a** via the metallacycle **16** is short compared to the nucleophilic displacement or radical cyclization routes used to prepare **1a**. The radical cyclization approach to **14a** is also short, but **14a** has poor enantioselectivity and reactivity. Conformational modeling studies support the correlation between catalyst reactivity and *P*-phenyl dihedral angle preferences. Future efforts to develop chiral phospholane acylation catalysts will need to keep these geometrical preferences in mind.

Experimental Section

***exo*-2-(Phenylphospha)bicyclo[3.3.0]octane−Borane Complex (8b) and e*ndo*-2-(Phenylphospha)bicyclo[3.3.0.]octane−Borane Complex (1b)**. To a flame-dried, N_2-purged flask were added phenylphosphine (0.42 mL, 4.18 mmol; *caution! stench!*) and toluene (16 mL). The solution was cooled to 0 °C, and *n*BuLi (2.8 mL of a 1.54 M solution in hexanes, 4.3 mmol) was added dropwise. A solution of mesylate **6**[14] in toluene (16 mL) was added, and the solution was warmed to room temperature and stirred for 1 h. Assay by ^{31}P NMR (unlocked, crude reaction mixture) showed the presence of a secondary phosphine ($\delta_P = -51$ ppm). A reflux condenser was attached, and the crude solution was heated to 85 °C with the slow addition of AIBN (161 mg, 0.98 mmol) in toluene (10 mL) via syringe pump over 4 h. Stirring was continued for 8 h. Assay by ^{31}P NMR (unlocked, crude reaction mixture) showed the presence of two tertiary phosphines in a 10:1 ratio ($\delta_P = 6.9$ and −1.5 ppm). After the addition of borane−THF complex (4.6 mL of a 1 M solution in THF), the colorless solution was stirred for 1 h, the solvent was evaporated (N_2 stream), and HCl (25 mL, 10% solution in water) was added. Next, the white residue was extracted with CH_2Cl_2 (3 × 30 mL), dried ($MgSO_4$), and evaporated (aspirator), and the residue was purified by flash chromatography on silica gel (16 × 4 cm), 4:1 hexanes/toluene → 1:1 hexanes/toluene eluent.

Fractions containing **8b** (*exo*-isomer) were combined to give 452 mg (53%) of a thick oil which solidified on standing. All physical properties were identical to previously reported data for this compound.[5] Analytical TLC, 1:1 hexanes: $R_f = 0.19$. MS: no parent ion for $C_{13}H_{20}BP$; M − BH_3, $m/z = 204.1060$, error 4 ppm, base peak 204 amu. IR (neat, cm^{-1}): 2373, B−H. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.75−7.65 (2 H, m), 7.49−7.40 (3 H, m), 2.98−2.82 (1 H, m), 2.74−2.61 (1 H, m), 2.21−1.73 (8 H, m), 1.69−1.54 (1 H, m), 1.50−1.36 (1 H, m), 1.32−0.16 (3 H, br m). ^{31}P NMR (21.4 MHz {H}, $CDCl_3$, ppm): δ 25.7−23.6 (br m).

More polar fractions containing **1b** (*endo*-isomer) were evaporated to give 79 mg (9%) of an oil. All physical properties were identical to previously reported data for this compound.[5] Analytical TLC, 1:1 hexanes/toluene: $R_f = 0.09$. Separation into enantiomers was effected using a CHIRALCELL OJ analytical HPLC column (11% ethanol/hexanes, 1 mL/min), retention times of enantiomers, 9.3 min, 11.2 min. MS: no parent ion for $C_{13}H_{20}BP$; M − BH_3, $m/z = 204.1061$, error 4 ppm, base peak 204 amu. IR (neat, cm^{-1}): 2369, B−H. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.70−7.60 (2 H, m), 7.52−7.41 (3 H, m), 2.95−2.79 (1 H, m), 2.64 (1 H, dq, J = 9.1, 3.7 Hz), 2.46−2.21 (2 H, m), 2.13−2.00 (1 H, m), 1.92−1.44 (5 H, m), 1.43−1.29 (1 H, m), 1.4−0.2 (3 H, br m), 1.21−1.03 (1 H, m). ^{31}P NMR (121.4 MHz {H}, $CDCl_3$, ppm): δ 41.2−38.9 (br m).

***exo*-1-Phenyl-1,2,3,3a,8,8a-hexahydro-1-phosphacyclopenta-[*a*]indene−Borane Complex (13b) and *endo*-1-Phenyl-1,2,3,3a,8,-8a-hexahydro-1-phosphacyclopenta[*a*]indene−Borane Complex (14b)**. To a flame-dried, N_2-purged flask were added indene (0.59 mL, 5 mmol; freshly distilled) and THF (5 mL). The solution was cooled to −78 °C, and *n*BuLi (3.8 mL of a 1.44 M solution in hexanes, 5.5 mmol) was added dropwise. After the resulting solution was stirred at −78 °C for 5 min, the cooling bath was removed and the reaction was allowed to stir at room temperature for 20 min. The resulting solution was added to a solution of 1,3,2-dioxathiolane 2,2-dioxide (**11**) (620 mg, 5.0 mmol) in THF (8 mL) at −78 °C via cannula. Stirring was continued for 2 h before the solution was warmed to room temperature. In a separate flask, lithiophenylphosphide was prepared by addition of *n*BuLi (5.6 mL of a 1.44 M solution in hexanes, 8.0 mmol) to phenylphosphine (0.75 mL, 7.5 mmol) in toluene (30 mL) at 0 °C followed by stirring for 30 min. The reaction mixture was recooled to −78 °C, and to it was added the lithiophosphide via cannula. After the addition, the mixture was stirred at −78 °C for 3 h and then warmed to room temperature. Benzene (50 mL, degassed) was added, a short path condenser was attached, and THF was removed by distillation until the temperature of the distillate reached 80 °C. Assay by ^{31}P NMR (unlocked, crude reaction mixture) showed the presence of a secondary phosphine ($\delta_P = -51$ ppm). A reflux condenser was attached, and the crude solution was heated to reflux with the slow addition of AIBN (200 mg, 0.24 mmol) in benzene (40 mL) via a syringe pump over 6 h. Stirring continued for 8 h. Assay by ^{31}P NMR (unlocked, crude reaction mixture) showed the presence of a 4:1 ratio of two tertiary phosphines ($\delta_P = 13.2$ and −4.7 ppm). After the addition of borane−THF complex (9.0 mL of a 1 M solution in THF), the colorless solution was stirred for 1 h, the solvent was evaporated (N_2 stream), and HCl (25 mL, 10% solution in water) was added. Next, the white residue was extracted with CH_2Cl_2 (3 × 30 mL), dried ($MgSO_4$), and evaporated (aspirator), and the residue was purified by flash chromatography on silica gel (16 × 4 cm), 2:1 hexanes/toluene eluent. The first 400 mL was blank, then the next 550 mL contained impurities, and the next 50 mL contained the minor diastereomer **14b**. The eluent was switched to 1:1 hexanes/toluene, and the elution was continued, collecting a mixture of the two *P*-epimers in the next 100 mL, followed by pure **13b**, the major diastereomer, in the next 575 mL.

Fractions containing pure **14b** (*endo*-isomer) were evaporated to give 68 mg (5%) of colorless crystals. Analytical TLC, 1:1 hexanes/toluene, $R_f = 0.25$. Pure material was obtained by crystallization from ethanol, mp 75−76 °C. Separation into enantiomers was effected using a CHIRALCELL OJ analytical HPLC column (10% ethanol/hexanes, 1 mL/min), retention times of enantiomers, 8.9 min, 14.0 min. ESMS: $C_{17}H_{20}BP$ (M − 1), m/z = 265.1311, base peak 252.1 amu. IR (neat, cm^{-1}): 2370, B−H; 2335, B−H. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.43 (1 H, dddd, J = 7.8, 7.5, 3.0, 1.6 Hz), 7.31−7.26 (4 H, m), 7.20−7.16 (3 H, m), 6.91 (1 H, d, J = 7.6 Hz), 4.11 (1 H, ddd, J = 20.0, 6.6, 6.6 Hz), 3.18−3.09 (1 H, m), 3.03 (1 H, t, J = 8.1 Hz), 2.68−2.58 (1 H, m), 2.48−2.34 (2 H, m), 2.12 (1 H, dd, J = 13.7, 5.9 Hz), 1.93−1.83 (1 H, m), 1.2−0.4 (3 H, br m). ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm): δ 143.2, 143.1, 133.1 (d, J = 9.2 Hz), 131.5, 131.5, 128.3 (d, J = 9.9 Hz), 127.4 (d, J = 28.2 Hz), 125.9 (d, J = 45.8 Hz), 124.6, 123.2, 52.0 (d, J = 4.6 Hz), 41.4 (d, 33.6 Hz), 34.1 (d, J = 4.6 Hz), 29.2 (d, J = 6.1 Hz), 23.4 (d, J = 36.6 Hz). ^{31}P NMR (161.9 MHz {H},$CDCl_3$, ppm): δ 38.6 (br m).

More polar fractions containing pure **13b** (*exo*-isomer) were combined to yield 520 mg of a colorless solid (39%). Analytical TLC, 1:1 hexanes/toluene: $R_f = 0.20$. Pure material was obtained by crystallization from ethanol, mp 96.0−96.8 °C. ESMS: $C_{17}H_{20}$-BP (M − 2), m/z = 264.1246, base peak 252.1 amu. IR (neat, cm^{-1}): 2374, B−H; 2339, B−H. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.77−7.72 (2 H, m), 7.52−7.46 (3 H, m), 7.28−7.17 (4 H, m), 4.17 (1 H, dddd, J = 7.6, 7.6, 3.8, 3.8 Hz), 3.67 (1 H, ddd, J = 17.6, 17.6, 3.3 Hz), 3.37−3.28 (1 H, m), 3.20 (1 H, dddd, J = 8.1, 8.1, 8.1, 3.3 Hz), 2.49−2.40 (1 H, m), 2.38−2.28 (1 H, m), 2.20−2.14 (1 H, m), 1.84−1.76 (1 H, m), 1.1−0.2 (3 H, br m). ^{13}C NMR (100.57 MHz, $CDCl_3$, ppm): δ 143.2 (d, J = 29.0 Hz),

(21) For recent reviews on the kinetic resolution of alcohols using chiral nucleophilic catalysts, see: (a) Fu, G. C. *Acc. Chem Res.* **2000**, *33*, 412. (b) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (c) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.

131.5, 131.5 (d, J = 47.3 Hz), 131.4, 131.2, 129.2 (d, J = 10.7 Hz), 127.1, 127.8, 125.0, 53.0, 41.3 (d, J = 33.6 Hz), 34.1 (d, J = 4.6 Hz), 31.9, 26.6. ^{31}P NMR (161.9 MHz {H}, $CDCl_3$, ppm): δ 43.6 (br m).

***exo*-3-Phenyl-3-phosphatricyclo[5.2.1.0^{2,6}]decane−Borane Complex (19b) and *endo*-3-Phenyl-3-phosphatricyclo[5.2.1.0^{2,6}]-decane−Borane Complex (18b)**. The cyclic alane intermediate **16** was prepared according to a literature procedure.[19] To a flame-dried, Ar-flushed round-bottom flask were added Cp_2ZrCl_2 (50 mg, 0.17 mmol), norbornylene (250 mg, 2.66 mmol; sublimed), and a magnetic stir bar. A glass stopcock was attached and wrapped with Teflon tape, and the flask was flushed with argon for 5 min (note: norbornylene is volatile, and flushing with argon for too long will evaporate the reagent). The flask was cooled to 0 °C, and neat triethylaluminum (0.39 mL, 2.8 mmol; *caution! highly pyrophoric!*) was added via syringe. The flask was flushed briefly with argon, and the stopcock was closed. The reaction was stirred for 11 h, during which the cooling bath warmed to room temperature. Benzene (2 mL) was added via syringe to the yellow mixture, and the reaction was recooled to 0 °C. Dichlorophenylphosphine (0.79 mL, 5.85 mmol; freshly distilled) was then added dropwise over ca. 8 min via syringe. The cooling bath was removed, and the mixture was allowed to stir for 24 h. The mixture was cooled to 0 °C, and borane−THF (7 mL, 1 M solution in THF, 7 mmol) was added via syringe to quench the reaction. The mixture was stirred for 5 h at room temperature, the solvent was evaporated (N_2 stream), and HCl (10 mL of a 5% solution in water; *caution! foaming!*) and Et_2O (20 mL) were added, followed by stirring for 15 min. The mixture was extracted with Et_2O (3 × 20 mL). The extracts were combined and dried ($MgSO_4$). After removal of the solvent (aspirator), the residue was adsorbed on silica and purified by flash chromatography (15 × 5 cm), eluting with 600 mL of 3:1 hexanes/toluene and then switching to 2:1 hexanes/toluene. The first 1350 mL was discarded followed by 500 mL of eluent containing the major diastereomer **19b**, 500 mL containing a ca. 1:1 mixture of diastereomers, and then 1 L containing the minor diastereomer **18b**. The mixed fractions were resubmitted to flash chromatography.

Fractions containing the major diastereomer (*exo*-isomer) were combined to give 246 mg (37%) of **19b**. Pure material was obtained by crystallization from hexane, mp 62.0−62.8 °C. Analytical TLC, 1:1 ether/toluene: R_f = 0.24; HRMS: $C_{14}H_{22}BP$ (M − BH_3 + H), m/z = 231.1309, base peak 231 amu. IR (neat, cm^{-1}): 2370, B−H; 2359, B−H; 2327, B−H. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.74−7.69 (2 H, m), 7.50−7.42 (3 H, m), 2.68−2.64 (1 H, m), 2.44−2.36 (1 H, m), 2.35−2.22 (1 H, m), 2.19−2.12 (2 H, m), 2.10−2.03 (1 H, m), 2.01−1.90 (1 H, m), 1.82−1.72 (1 H, m), 1.71−1.67 (1 H, m), 1.63−1.52 (2 H, m), 1.24−1.10 (3 H, m), 1.1−0.4 (3 H, br m). ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm): δ 131.7 (d, J = 47.6 Hz), 131.5 (d, J = 8.7 Hz), 130.9 (d, J = 2.3 Hz), 128.7 (d, J = 9.6 Hz), 51.1 (d, J = 1.4 Hz), 47.2 (d, J = 53 Hz), 41.7, 38.0 (d, J = 5.0 Hz), 35.3, 31.1 (d, J = 6.9 Hz), 30.2 (d, J = 12.4 Hz), 28.5, 27.4 (d, J = 36.6 Hz). ^{31}P NMR (161.9 MHz {H}, $CDCl_3$, ppm): δ 39.8 (m).

More polar fractions containing **18b** (*endo*-isomer) were combined to give 87 mg (13%) of product. Pure material was obtained by crystallization from hexane, mp 79−81 °C. Analytical TLC, 1:1 ether/toluene: R_f = 0.17. Separation into enantiomers was effected using a CHIRALPAK AS semiprep HPLC column (3% ethanol/hexanes, 4 mL/min), retention times of enantiomers (not baseline separation), 13.2 min, 13.9 min. Analytical HPLC, CHIRALCEL OJ (10% 2-propanol/hexanes, 1 mL/min): retention times of enantiomers, 9.5 min, 11.4 min. HRMS: $C_{14}H_{22}BP$ (M − BH_3), m/z = 230.1221, base peak 230 amu. IR (neat, cm^{-1}): 2374, B−H; 2351, B−H; 2328, B−H. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.65−7.59 (2 H, m), 7.52−7.42 (3 H, m), 2.52−2.31 (3 H, m), 2.24−2.16 (1 H, m), 2.11−2.03 (1 H, br s), 1.94−1.83 (1 H, m), 1.69−1.58 (1 H, m), 1.55−1.40 (2 H, m), 1.3−0.4 (3 H, br m), 1.24−1.13 (2 H, m), 0.76−0.67 (2 H, m). ^{13}C NMR (100.6 MHz {H}, $CDCl_3$, ppm): δ 131.7 (d, J = 8.4 Hz), 130.8 (d, J = 2.3 Hz), 128.6 (d, J = 9.9 Hz), 127.1 (d, J = 43.5 Hz), 51.0, 47.2 (d, J = 31.3 Hz), 40.9, 37.9 (d, J = 3.8 Hz), 34.0, 32.2, 30.2 (d, J = 11.4 Hz), 28.2, 23.9 (d, J = 37.4 Hz). ^{31}P NMR (161.9 MHz {H}, $CDCl_3$, ppm): δ 45.6 (br m).

An alternative preparation of **18b** and **19b** was a modification of a literature procedure:[20] To a flame-dried, Ar-flushed round-bottom flask was added Cp_2ZrCl_2 (250 mg, 0.86 mmol). A glass stopcock was attached and wrapped with Teflon tape, and the flask was flushed with Ar for 5 min. Next, THF (2 mL) was added, and the suspension was cooled to −78 °C. Ethylmagnesium chloride (0.84 mL, 2.0 M in THF, 1.67 mmol) was added dropwise via syringe, and the mixture was stirred for 1 h, during which the solution turned pale yellow. Norbornylene (81 mg, 0.855 mmol; sublimed) was added as a solution in 0.5 mL of THF. The mixture was warmed to room temperature and stirred for 13 h, during which the solution turned red. The solution was cooled to −78 °C, and dichlorophenylphosphine (0.23 mL, 1.71 mmol; freshly distilled) was added over 5 min via syringe. The reaction was stirred for 11 h, during which the cooling bath warmed to room temperature. Borane−THF (3 mL, 1 M solution in THF, 3 mmol) was added via syringe, the pale yellow mixture was stirred for 5 h at room temperature, and then the solvent was removed (N_2 stream). Careful addition of water (5 mL) quenched the excess BH_3, and the mixture was extracted with Et_2O (3 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated (aspirator). Assay of the crude mixture by ^{31}P NMR showed a ratio of ca. 3:1 **18b**:**19b**. The residue was adsorbed on silica and purified as above to afford ca. 50 mg of **18b** (24%) and 25−30 mg of impure material containing **19b**. All spectroscopic properties were identical to those reported in the previous synthesis of **18b** and **19b**.

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Supporting Information Available: General procedures for catalyst manipulations, acylations, and assay and spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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