Chirality Breeding via Asymmetric Phosphination. Palladium-Catalyzed Diastereoselective Synthesis of a P-Stereogenic Phosphine

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Received November 18, 2005

Methylation of the crystallographically characterized primary alkylphosphine-borane $PH_2Men(BH_3)$ (**3**, Men = (−)-menthyl) under phase-transfer conditions, followed by deprotection, gave the secondary phosphine PH(Me)(Men) (**2**). Cross-coupling of **2** with PhI in the presence of $NaOSiMe_3$ selectively gave S_P-PPh(Me)(Men) (**1**, L) with a variety of Pd catalyst precursors, including a complex of diastereopure S_P-**1**, *trans*-$PdL_2(Ph)(I)$ (**6a**). In this reaction, the chiral phosphine L formally acted as a ligand in catalysis of its selective self-reproduction, but **6a** was partially transformed to its diastereomers, *trans*-Pd(S_P-**1**)-(R_P-**1**)(Ph)(I) (**6b**) and *trans*-Pd(R_P-**1**)$_2$(Ph)(I) (**6c**), and several other intermediates were observed during catalysis.

Introduction

Chiral phosphines are valuable ligands in asymmetric catalysis,[1] so new methods for their efficient synthesis are important. Many chiral phosphines are prepared by resolution processes or via asymmetric synthesis using stoichiometric amounts of chiral auxiliaries.[2] Catalytic asymmetric methods would, in principle, be more efficient, and they have been exploited in some cases.[3,4] In a particularly elegant approach, a chiral phosphine is a ligand in a catalytic reaction that selectively forms a chiral precursor to the phosphine. In this way, the ligand "breeds its own chirality", as in the synthesis of Prophos reported by Fryzuk and Bosnich[5] (Scheme 1).[6]

Our recently reported asymmetric synthesis of P-stereogenic phosphines, in which a chiral Pd catalyst mediates enantioselective P−C bond formation,[3c,d,h,i] could enable related chirality breeding, in which a chiral phosphine acts as a ligand in a reaction that selectively reproduces itself *directly* (Scheme 1).[7] We report here attempts to develop this type of catalytic reaction.[8]

Results and Discussion

We chose to prepare PPh(Me)(Men) (**1**, Men = (−)-menthyl),[9] one of the first examples of a chiral phosphine containing both P and C stereocenters, for comparison of the proposed breeding approach to standard methods for synthesis of chiral phosphines. Originally, both diastereomers of **1** were obtained in pure form after tedious fractional recrystallization of the oxide P(O)Ph(Me)(Men).[10] More recently, Vedejs and Donde described an elegant synthesis of the R_P-diastereomer

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(4) For biocatalysis, see: (a) Shioji, K.; Tashiro, A.; Shibata, S.; Okuma, K. *Tetrahedron Lett.* **2003**, *44*, 1103−1105. (b) Kielbasinski, P.; Zurawinski, R.; Albrycht, M.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3379−3384. (c) Kielbasinski, P.; Zurawinski, R.; Pietrusiewicz, K. M.; Zablocka, M.; Mikolajczyk, M. *Tetrahedron Lett.* **1994**, *35*, 7081−7084. (d) Kagan, H. B.; Tahar, M.; Fiaud, J.-C. *Bioorg. Med. Chem.* **1994**, *2*, 15−21. (e) Serreqi, A. N.; Kazlauskas, R. J. *J. Org. Chem.* **1994**, *59*, 7609−7615.

(5) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491−5494. Several conceptually similar asymmetric hydrogenations have been used for the preparation of other chiral phosphines. See for example: Dubrovina, N. V.; Tararov, V. I.; Monsees, A.; Kadyrov, R.; Fisher, C.; Borner, A. *Tetrahedron: Asymmetry* **2003**, *14*, 2739−2745, and references therein.

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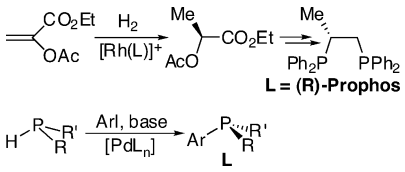
(8) For similar reactions involving reduction of carbonyl groups, see: (a) Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265−7266. (b) Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 982−983. (c) Shibata, T.; Takahashi, T.; Konishi, T.; Soai, K. *Angew. Chem., Int. Ed.* **1997**, *36*, 2458−2460. (d) Soai, K.; Shibata, T.; Sato, I. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1063−1073. (e) Costa, A. M.; García, C.; Carroll, P. J.; Walsh, P. J. *Tetrahedron* **2005**, *61*, 6442−6446.

(9) The (−)-menthyl group is derived from natural (1*R*,2*S*,5*R*)-menthol. For simplicity, the full stereochemical label is not included in the text.

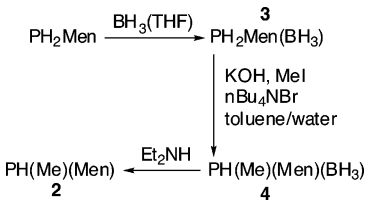
10.1021/om050993f CCC: $33.50
Publication on Web 03/03/2006

Scheme 1. Chirality Breeding via Asymmetric Hydrogenation or Asymmetric Phosphination[a]



[a] [Rh((R)-Prophos)]$^+$-catalyzed asymmetric hydrogenation of an alkene gave an enantioenriched product, which was converted to (*R*)-Prophos after five steps. [PdL$_n$]-catalyzed asymmetric phosphination of an aryl iodide might directly yield the enantioenriched P-stereogenic phosphine L.

Scheme 2



based on crystallization-induced asymmetric transformation in the intermediate PPh(Men)(fluorenyl).[11] This work complements Vedejs' synthesis, since we prepared the S_P-diastereomer selectively (see below).

Direct synthesis of the required secondary phosphine substrate PH(Me)(Men) (**2**) by treatment of $MePCl_2$ with MenMgCl, followed by $LiAlH_4$ reduction, gave impure material (see the Experimental Section for details), so the multistep route shown in Scheme 2 was developed. Treatment of PH_2Men[12] with BH_3-(THF) gave the borane adduct $PH_2Men(BH_3)$ (**3**, Figure 1, Table 1, and Supporting Information). Only a few primary phosphine-boranes have been structurally characterized; the geometry and bond lengths in **3** are similar to those in the methyl- and arylphosphine analogues (Table 2).[13−15]

The primary arylphosphine-boranes $PH_2Ar(BH_3)$ (Ar = Ph or p-$CF_3C_6H_4$) were dimers in the solid state, with close intermolecular P−H···H−B contacts.[14,15] The alkylphosphine-borane **3**, in contrast, formed a one-dimensional chain (Figure 2), in which the closest P−H···H−B distance was 2.60(3) Å, with a P−H···H−B dihedral angle of −120.6°. Such H−H distances tend to be underestimated due to the systematic error in determining hydrogen positions by X-ray crystallography. They may be adjusted using B−H and P−H bond lengths of 1.21 and 1.40 Å, respectively,[14,15] to give a closest H−H contact of 2.497 Å. This is greater than the sum of the van der Waals radii for two hydrogen atoms (2.4 Å) and the adjusted values found in $PH_2Ar(BH_3)$ (Ar = Ph or p-$CF_3C_6H_4$), 2.375 and 2.230 Å, respectively. These observations suggest a weaker P−H···H−B interaction than those observed in the primary *aryl*phosphine-boranes, perhaps because the P−H bond is less polarized in the *alkyl*phosphine-borane **3**.[15]

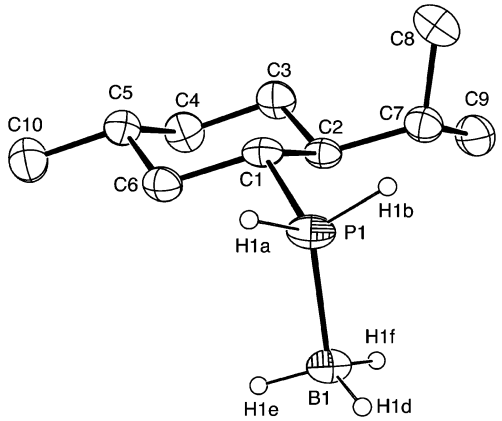


Figure 1. ORTEP diagram of $PH_2Men(BH_3)$ (**3**). Only the hydrogen atoms bound to P and B are shown.

Table 1. Crystallographic Data for 3

empirical formula	$C_{10}H_{24}BP$
fw	186.07
temperature, K	213(2)
space group	*P*2(1)2(1)2(1)
a, Å	8.1069(6)
b, Å	10.5630(8)
c, Å	14.6777(11)
α, deg	90
β, deg	90
γ, deg	90
V, Å^3	1256.90(16)
Z	4
D(calc), g cm^{-3}	0.983
μ(Mo Kα), mm^{-1}	0.174
diffractometer	Bruker CCD
R(*F*), %[a]	4.40
R(*wF*^{2}), %[a]	10.64

[a] Quantity minimized = $R(wF^2) = \sum[w(F_o^2 - F_c^2)^2]/\sum[(wF_o^2)^2]^{1/2}$; $R = \sum\Delta/\Sigma(F_o)$, $\Delta = |(F_o - F_c)|$, $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, $P = [2F_c^2 + \mathrm{Max}(F_o,0)]/3$.

Phosphine-borane **3** was methylated under phase-transfer conditions,[16] then deprotected with Et_2NH to give a 1:1.3 mixture of diastereomers of PH(Me)(Men) (**2**) as an air-sensitive liquid (Scheme 2). Phosphine **2** was obtained in ca. 95% purity, contaminated by two persistent phosphine impurities (see the Experimental Section for details), which were also observed in the synthesis starting from $MePCl_2$ (which gave ca. 88% purity material, with two additional impurities). Protonation of **2** with HBF_4·Me_2O gave the analytically pure phosphonium salt [PH_2-(Me)(Men)][BF_4] (**5**), but deprotonation of this material also failed to provide pure **2**. Although the impurity phosphines could not be separated by chromatography or distillation, or identified, they did not react in the Pd-catalyzed cross-couplings described below and were observed unchanged in reaction mixtures.

Cross-coupling of **2** with PhI using the base $NaOSiMe_3$ and a variety of Pd catalyst precursors was diastereoselective, yielding preferentially (S_P)-P(Me)(Ph)(Men) ((S_P)-**1**, or L; Scheme 3, Table 3), which was isolated in good yield after chromatography under nitrogen.

A Pd((*R*,*R*)-Me-Duphos) catalyst precursor (entry 1) gave good de; high enantioselectivity was also observed for this precursor in cross-coupling of PHMe(Is) (Is = 2,4,6-(*i*-Pr)$_3C_6H_2$) with PhI.[3c] The analogous (R,R)-*i*-Pr-Duphos complex gave higher de (91%, entry 2), while its (*S*,*S*)-enantiomer again yielded S_P-**1** preferentially, but in 58% de (entry 3). Thus, while the chirality of the catalyst precursor was important, diastereo-selectivity in these cases was primarily controlled by the

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(16) Lebel, H.; Morin, S.; Paquet, V. *Org. Lett.* **2003**, *5*, 2347−2349.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for Structurally Characterized Primary Phosphine-Boranes[a]

	$PH_2Men(BH_3)$	$PH_2Me(BH_3)$[13]	$PH_2Ph(BH_3)$[14]	$PH_2(p\text{-}CF_3C_6H_4)(BH_3)$[15]
P−B (Å)	1.911(2)	1.906(6)	1.924(4)	1.900(3)
P−H (av, Å)	1.23(2)	1.404(6)	1.33(4)	1.36(3)
B−H (av, Å)	1.05(3)	1.23(22)	1.11(4)	1.13(4)
H(P)−P−B (av, deg)	115.1(10)	116.3(6)	113.4(18)	112.2(12)
H(B)−B−P (av, deg)	105.6(14)	103(1)	105(2)	105.2(19)

[a] The structure of $PH_2Me(BH_3)$ was determined by microwave spectroscopy; the other structures by X-ray crystallography.

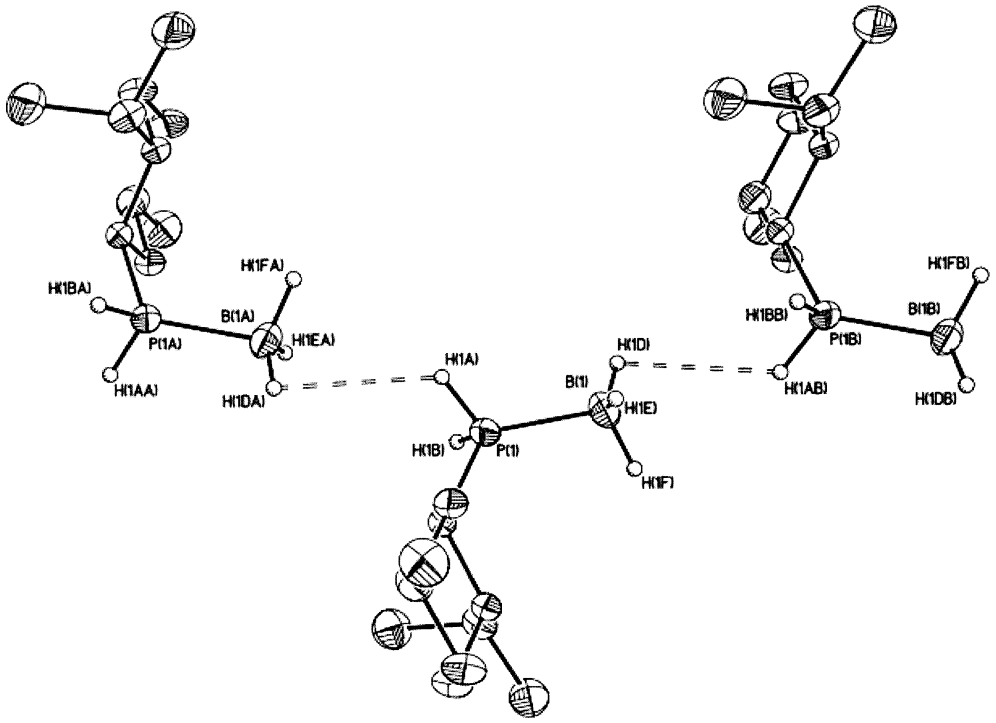
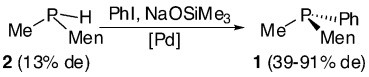


Figure 2. ORTEP diagram of **3** showing intermolecular contacts. Only the P−H and B−H hydrogen atoms are shown.

Scheme 3



substrate.[17] Comparable selectivity was obtained with an *achiral* Pd catalyst precursor (dcpe = $Cy_2PCH_2CH_2PCy_2$, Cy = *cyclo*-C_6H_{11}, entry 4) or even with palladium acetate (entry 5); the latter reaction could be scaled up to produce ~300 mg of **1** without loss of selectivity (entry 6). When the air-stable solid phosphonium salt $[PH_2Me(Men)][BF_4]$ (**5**) was used (with 2 equiv of base) instead of the air-sensitive oil **2**, the results were similar (entry 8).[18]

The commonly employed Pd(0) complexes $Pd(PPh_3)_4$ and $Pd(dba)_2$ also produced active catalysts (entries 9 and 11). The presence of dba and PPh_3 clearly changed the diastereoselectivity in these cases as compared to $Pd(OAc)_2$, and limiting the amount of PPh_3 by using $Pd(PPh_3)_2(Ph)(I)$ (entry 13) also produced an effect. When the product phosphine **1** was added to Pd precursors lacking a bidentate ligand (entries 7, 10, and 12), the results were similar to catalyses without added **1** (entries 5, 9, and 11).

Monitoring the catalytic reactions by ^{31}P NMR spectroscopy showed (as expected in the presence of an excess of the phosphine substrate **2** and product **1**) that the catalyst precursors were modified during the reaction and that several intermediates were present. For example, when $Pd(PPh_3)_2(Ph)(I)$ or $Pd(PPh_3)_4$ was used as a catalyst precursor, free PPh_3 was formed rapidly, and in catalytic reactions with the precursors Pd((*R*,*R*)-Me-Duphos)(*trans*-stilbene) and Pd(dcpe)(Ph)(I) the complexes $Pd(diphos)_2$ were observed before the completion of the reaction.[19] Moreover, in several cases the diastereomer ratio of the secondary phosphine substrate **2** and the product **1** changed over the course of reaction, consistent with the presence of a mixture of catalysts of different activity and selectivity.

To investigate the idealized model of Scheme 1, in which the chiral product **1** could act as a ligand in a Pd complex that catalyzed formation of more **1**, we independently prepared several of the intermediates observed during catalysis (Scheme 4). Treatment of Pd(tmeda)(Ph)(I) with 2 equiv of **1** (25% de) gave a mixture of the expected three diastereomers of *trans*-$PdL_2(Ph)(I)$ (**6**, L = PPh(Me)(Men) (**1**)), which could be distinguished by their ^{31}P NMR spectra in toluene-d_8. The complexes S_P,S_P-**6** ((*S*,*S*)-**6** for short, or **6a**) and (*R*,*R*)-**6** (**6c**) gave rise to singlets at δ 3.3 and 8.2 in C_6D_6, respectively, while the spectrum of (*S*,*R*)-**6** (**6b**) was an AB pattern with the expected large *trans* coupling (δ 4.9, 8.0, J = 419 Hz). The ratio of these diastereomers was 2.1:2.2:1 (**6a**:**6b**:**6c**). Note that since L contains (−)-menthyl, [9] (*R*,*R*)- and (*S*,*S*)-**6** are diastereomers, not enantiomers. When **1** of 80% de was used, pure (*S*,*S*)-**6** (**6a**) was isolated in 31% yield as a single diastereomer after recrystallization from petroleum ether. [20]

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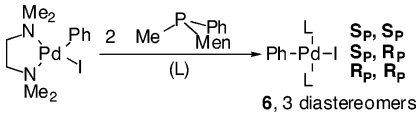
Table 3. Pd-Catalyzed Diastereoselective Synthesis of P(Me)(Ph)(Men) (1) by Cross-Coupling of the Secondary Phosphine PHMe(Men) (2) with PhI[a]

entry	catalyst precursor	time (h)[b]	yield (%)[c]	de (%)[d]
1	Pd((*R*,*R*)-Me-Duphos)(*trans*-stilbene)	48	68	73
2	Pd((*R*,*R*)-*i*-Pr-Duphos)(*trans*-stilbene)	48	72	91
3	Pd((*S*,*S*)-*i*-Pr-Duphos)(*trans*-stilbene)	22	ND[e]	58
4	Pd(dcpe)(Ph)(I)	5	81	80
5[f]	$Pd(OAc)_2$	17	ND[e]	73
6[g]	$Pd(OAc)_2$	168	82	69
7[h]	$Pd(OAc)_2$/2L	17	68	71
8[i]	$Pd(OAc)_2$	24	69	62
9	$Pd(dba)_2$	24	40	56
10[h]	$Pd(dba)_2$/2L	24	66	54
11[j]	$Pd(PPh_3)_4$	12	61	39
12[h]	$Pd(PPh_3)_4$/2L	17	90	42
13	$Pd(PPh_3)_2$(Ph)(I)	24	73	48

[a] Reaction conditions: 5 mol % catalyst precursor, 18−30 mg (0.096−0.16 mmol) of **2**, 1.1 equiv of PhI, 1 equiv of $NaOSiMe_3$ (1.0 M solution in THF), 2 mL of toluene, room temperature. [b] Time for the completion of the reaction. [c] Isolated after column chromatography in the glovebox. [d] By integration of the signals in the ^{31}P NMR spectrum. S_P-**1** was always the favored diastereomer. [e] ND = not determined. [f] After reaction was complete PhI, **2**, and $NaOSiMe_3$ (half of the initial amounts) were added to the mixture. The second round of the reaction was complete in 24 h. The de stayed the same as the final de of the first round of the reaction (73%). [g] Large-scale experiment (259 mg of **2**). The reaction was started with 1% catalyst; after 24 h (72% conversion) loading was increased to 2%. [h] L = P(Me)(Ph)(Men) (**1**), de = 71%, prepared with Pd(dcpe)(Ph)(I) as a catalyst. The final de reflects the de of the phosphine made during the catalysis and the de of the starting phosphine added as a ligand. [i] The substrate was the phosphonium salt $[PH_2Me(Men)][BF_4]$ (**5**) (0.31 mmol); 2 equiv of $NaOSiMe_3$ was used. [j] After reaction was complete PhI, **2**, and $NaOSiMe_3$ (half of the initial amounts) were added to the mixture. The second round of the reaction was complete in 14 h. The de stayed the same as the final de of the first round of the reaction (39%).

Scheme 4 [a]



[a] The ligand L contains (−)-menthyl[9] and a P stereocenter, so differences in the P stereochemistry result in diastereomers of **6**.

Scheme 5

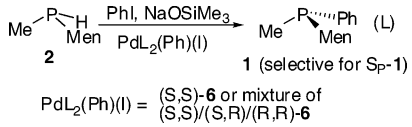


Table 4. Diastereoselective Synthesis of P(Me)(Ph)(Men) (1) by Cross-Coupling of the Secondary Phosphine PHMe(Men) (2) with PhI Using 6 as a Catalyst Precursor[a]

entry	catalyst precursor	time (h) [b]	yield (%)[c]	de (%)[d]
1[e]	(*S*,*S*)-**6**	24	ND[f]	44
		24	ND[f]	46
		24	80	47
2[g]	(*S*,*S*)-**6**	24	77	51
3[h]	(*S*,*S*)-**6**/(*S*,*R*)-**6**/(*R*,*R*)-**6**)	24	82	34

[a] Reaction conditions: 5 mol % catalyst precursor, 1.1 equiv of PhI, 1 equiv of $NaOSiMe_3$ (1.0 M solution in THF), toluene, room temperature. [b] Time for the completion of the reaction. [c] Isolated after column chromatography in the glovebox. [d] By integration of the signals in the ^{31}P NMR spectrum. S_P-**1** was always the favored diastereomer. [e] After the initial reaction was complete, two more batches of product were prepared in the same pot, on the same scale, by adding more PhI, **2**, and $NaOSiMe_3$ to the mixture. [f] ND = not determined. [g] 1% catalyst loading. [h] 5.3:3.6:3.1 initial ratio of diastereomers of **6**.

Comparison of the ^{31}P NMR spectra of complexes **6** with the catalytic reaction mixtures showed that these diastereomers were indeed intermediates observed during catalysis. Moreover, isolated (*S*,*S*)-**6** or mixtures of the three diastereomers generated from Pd(tmeda)(Ph)(I) were active catalyst precursors for diastereoselective synthesis of S_P-**1** (Scheme 5, Table 4).

The data in Table 4 are not directly comparable to those in Table 3, for which **6** was generated during catalysis, and the scale also differed, but the results were similar. The reaction proceeded smoothly at catalyst loading of 5%, and addition of a second and third batch of substrate **2**, PhI, and base to a completed reaction led to further conversion to product with similar diastereoselectivity (entry 1); 1% catalyst loading was also possible (entry 2). Diastereopure (*S*,*S*)-**6** gave somewhat higher diastereoselectivity than the mixture of diastereomers (compare entries 1, 2, and 3), but in all cases a mixture of isomers of **6** was observed at the end of the catalytic reaction.

Scheme 6

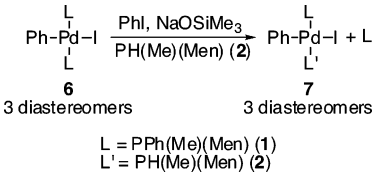


Table 5. ^{31}P NMR Data for Diastereomers of Complex 7[a]

diastereomer	δ (L)	δ (L′)	J_{PP}
7a	9.8	−19.7	434
7b	4.5	−21.9	440
7c	3.9	−29.9	441

[a] Chemical shifts in ppm, external standard 85% H_3PO_4, coupling constants in Hz, solvent = toluene. L = PPh(Me)(Men) (**1**), L′ = PHMe(Men) (**2**).

These experiments formally constitute an example of the desired chirality breeding, since the catalyst ((*S*,*S*)-**6**), which contains diastereopure phosphine **1**, mediates selective formation of more **1**. However, since (*S*,*S*)-**6** is partially transformed into its diastereomers during catalysis, the idealized model of Scheme 1 does not apply. Moreover, during catalysis with (S,S)-**6** or the mixture of diastereomers of **6**, several other intermediates were observed. Three of them were tentatively identified by ^{31}P NMR spectroscopy as diastereomers of the ligand substitution product *trans*-Pd(PPh(Me)(Men))(PHMe(Men))(Ph)(I) (**7**) (Scheme 6, Table 5). The large J_{PP} values, similar to the one observed for (*R*,*S*)-**6**, are consistent with the *trans* geometry, and the chemical shifts assigned to the tertiary phosphine ligand (**1**) are similar to those observed in the diastereomers of **6**. Comparison of these chemical shifts to those in **6** suggests that diastereomers **7b** and **7c** both contain S_P-**1**, while **7a** contains R_P-**1**. The similarity of the chemical shifts assigned to the secondary phosphine in **7a** and **7b** suggests that **2** in these isomers has the same P stereochemistry, which differs from that in **7c**. The anticipated fourth diastereomer was not observed.

As catalysis proceeded and secondary phosphine **2** was converted to product **1**, changes in the speciation of diastereomers **6** and **7** were observed. Once reaction was complete, **7** was consumed and only **6** remained. Besides these intermediates, a broad peak at −22.2 ppm assigned, by analogy with the data for **7**, to coordinated PHMe(Men) (**2**) was also observed; this species may be undergoing exchange with free **2**, whose signals were also somewhat broadened. Thus, although complex **6** acts as a catalyst precursor and is re-formed at the end of the reaction, several intermediates were observed, and it is likely that P−C bond formation occurs by reductive elimination from unobserved Pd-phosphido intermediates.

Conclusions

Pd-catalyzed cross-coupling of the P- and C-stereogenic secondary phosphine PHMe(Men) (**2**) with PhI proceeded with modest to good diastereoselectivity to yield S_P-PPh(Me)(Men) (**1**); this synthesis complements Vedejs' earlier selective synthesis of R_P-**1**. Isolation of a complex of diastereopure **1**, *trans*-Pd(S_P-**1**)$_2$(Ph)(I) (**6a**), and its use as a catalyst precursor to selectively form more S_P-**1** constitute an example of the idealized chirality breeding shown in Scheme 1. However, the conversion of (*S*,*S*)-**6** to its diastereomers during catalysis and the observation of several intermediates showed that the reaction is much more complicated. The lability of **1** suggests that chirality breeding according to Scheme 1 might be more successful using a *bidentate* enantiomerically pure ligand (the results with *i*-Pr-Duphos show that chelate ligands can produce high selectivity), and we are currently investigating this possibility.

Experimental Section

General Details. Unless otherwise noted, all reactions and manipulations were performed in dry glassware under a nitrogen atmosphere at 20 °C in a drybox or using standard Schlenk techniques. Petroleum ether (bp 38−53 °C), ether, THF, CH_2Cl_2, and toluene were dried using activated alumina columns.[21] NMR spectra were recorded by using Varian 300 or 500 MHz spectrometers. ^{1}H or ^{13}C NMR chemical shifts are reported versus Me_4Si and were determined by reference to the residual ^{1}H or ^{13}C solvent peaks. ^{31}P NMR chemical shifts are reported versus H_3PO_4 (85%) used as an external reference. Unless otherwise noted, peaks in NMR spectra are singlets and absolute values are reported for coupling constants (in Hz). Elemental analyses were provided by Schwarzkopf Microanalytical Laboratory, and mass spectrometry was performed at the University of Illinois, Urbana−Champaign.

Reagents were from commercial suppliers, except for the following compounds, which were prepared by literature procedures: MenCl,[22] Pd(Me- or *i*-Pr-Duphos)(*trans*-stilbene),[23] Pd(PPh$_3$)$_2$(Ph)(I),[24] PH_2Men,[12] and Pd(tmeda)(Ph)(I).[25] Pd(dcpe)(Ph)(I) was made by treating *trans*-Pd(PPh$_3$)$_2$(Ph)(I) with dcpe.[19]

Synthesis of PH(Me)(Men) (2) from $PMeCl_2$. A 100 mL Schlenk flask was loaded with Mg powder (3.24 g, 0.133 mol, 2.2 equiv) and THF (20 mL) and heated to 50 °C. A small crystal of I_2 was added to the reaction mixture to activate the Mg. MenCl (10.4 g, 0.056 mol, 7.1 mL) was added as a solution in THF (20 mL) via cannula. Upon stirring, the Mg slowly dissolved and the reaction mixture turned gray-brown.[11] It was stirred at 65 °C for 5 h, cooled to room temperature, then added with vigorous stirring to a cooled (−45 °C) solution of $PMeCl_2$ (6.93 g, 0.056 mol) in 20 mL of THF and allowed to warm to room temperature overnight. The solvent was removed in vacuo, and the colorless oily residue was redissolved in ether (20 mL). The resulting solution was added slowly with vigorous stirring to a cooled (0 °C) slurry of $LiAlH_4$ (2.26 g, 0.056 mol) in ether (20 mL). The resulting mixture was stirred for 2 h and quenched cautiously with water (20 mL). The layers were separated via cannula, the water layer was extracted with ether (2 × 20 mL), and the combined organic layers were dried over $MgSO_4$. After removing ether the oily residue was dissolved in benzene and purified by flash chromatography in the glovebox (silica, benzene as an eluent), giving the desired product as a yellowish oil with a yield of 3.747 g (34%) as a 1:1.3 mixture of diastereomers.

PH(Me)(Men) obtained by this method was contaminated with four unidentified impurities (12% total, ^{31}P{^{1}H} NMR (C_6D_6): δ −49.1, −65.3, −88.2, −98.9). All attempts to purify it further by column chromatography and vacuum distillation failed. The multistep method described below gave higher-purity (∼95%) material, which, however, still contained the δ −88.2 and −98.9 impurities.

PH_2Men(BH_3) (3). To a cooled (0 °C) solution of PH_2Men (1.21 g, 7.02 mmol) in THF (10 mL) was added BH_3(THF) (7.7 mL of 1 M solution in THF, 7.7 mmol, 1.1 equiv) via syringe. The cold bath was removed, and the reaction mixture was stirred for 1 h. The solvent was removed in vacuo, and the colorless residue was redissolved in hexanes and filtered. Cooling overnight at −10 °C gave a colorless crystalline solid suitable for X-ray analysis (1.002 g, 77%).

Anal. Calcd for $C_{10}H_{24}PB$: C, 64.55; H, 13.00. Found: C, 64.57; H, 13.94. Calculated HRMS (EI) for $C_{10}H_{21}PB$ $(M - 3H)^+$: *m*/*z* 183.1474. Found: *m*/*z* 183.1753. The parent M^+ cation was not observed. ^{31}P{^{1}H} NMR (C_6D_6): δ −44.8 (br m). ^{1}H NMR (C_6D_6): δ 3.91 (dm, J = 354, 1H, P−H), 3.72 (dm, J = 357, 1H, P-H), 1.74−1.62 (m, 1H), 1.48−1.30 (m, 4H), 1.25−1.15 (m, 2H), 1.00−0.84 (m, 3H), 0.77 (d, J = 6, 3H, Me), 0.69 (d, J = 6, 3H, Me), 0.49 (d, J = 7, 3H, Me). Signals due to the BH_3 protons were not observed. ^{13}C{^{1}H} NMR (C_6D_6): δ 44.0 (d, J = 1, CH), 38.4 (CH_2), 34.4 (d, J = 1, CH_2), 33.1 (d, J = 5, CH), 30.3 (d, J = 34, CH), 28.6 (d, J = 5, CH), 24.4 (d, J = 10, CH_2), 22.1 (Me), 21.1 (Me), 14.9 (Me).

PH(Me)(Men)(BH_3) (4). A Schlenk flask was loaded with KOH (1.41 g, 0.025 mol, 1.55 equiv) and Bu_4NBr (1.06 g, 0.0033 mol, 0.2 equiv) and degassed. Degassed toluene (60 mL) and water (60 mL) were added via cannula. The resulting two-phase mixture was stirred vigorously under N_2. PH_2Men(BH_3) (3.002 g, 0.0161 mol) was added via syringe as a solution in toluene (25 mL) followed by MeI (3.42 g, 0.024 mol, 1.5 mL, 1.5 equiv). The progress of the reaction was monitored by ^{31}P NMR spectroscopy. Along with formation of the desired product, some deprotection of the starting material occurred, yielding PH_2Men (∼20% by integration of the ^{31}P NMR spectrum at the end of the reaction).

The reaction mixture was stirred for 48 h and diluted with ether (100 mL), then worked up in the air. The layers were separated; the water fraction was extracted with ether (100 mL). The combined organic fractions were washed with water (2 × 100 mL) and a saturated solution of NH_4Cl (100 mL), then dried over $MgSO_4$. After solvent was removed, the oily residue was redissolved in hexanes and purified by column chromatography (silica, 10 in. high, 0.75 in. diameter, hexanes/ethyl acetate (95:5)). Removal of solvent

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in vacuo gave the product as a colorless oil that solidified at −10 °C (2.20 g, 68%, 1:1 mixture of diastereomers).

Anal. Calcd for $C_{11}H_{26}PB$: C, 66.02; H, 13.10. Found: C, 66.24; H, 13.70. Calculated HRMS (EI) for $C_{11}H_{26}PB$ $(M - 3H)^+$: *m*/*z* 197.1630. Found: *m*/*z* 197.1634. The parent M^+ cation was not observed. $^{31}P\{^1H\}$ NMR (C_6D_6): δ −15.0 (br m), −17.3 (br m). ^1H NMR (C_6D_6): δ 4.32 (dm, J = 360, 1H, P-H), 4.25 (dm, J = 357, 1H, P-H overlapped with previous signal), 2.00−1.88 (m, 1H), 1.88−1.76 (m, 1H), 1.72−1.60 (m, 1H), 1.54−1.20 (m, 11H), 1.12−0.94 (m, 5H), 0.85 (d, J = 7, 3H, Me), 0.80−0.66 (m, 16H), 0.59 (d, J = 7, 3H, Me), 0.49 (d, J = 7, 3H, Me). Signals due to the BH_3 protons were not observed. $^{13}C\{^1H\}$ NMR (C_6D_6): δ 43.3 (d, J = 3, CH), 43.2 (CH), 36.1 (CH_2), 34.4 (d, J = 1, CH_2), 34.4 (CH_2), 34.3 (d, J = 1, CH_2), 34.2 (CH), 33.8 (d, J = 7, CH), 33.2 (d, J = 14, CH), 33.1 (d, J = 25, CH), 28.0 (d, J = 3, CH), 27.8 (d, J = 5, CH), 24.5 (d, J = 9, CH_2), 24.4 (d, J = 10, CH_2), 22.3 (Me), 22.2 (Me), 21.2 (Me), 15.0 (Me), 14.9 (Me), 3.3 (d, J = 37, P-Me), 3.0 (d, J = 34, P-Me).

PH(Me)(Men) (2). A Schlenk flask was loaded with PH(Me)(Men)(BH_3) (1.404 g, 7.016 mmol) and degassed. Et_2NH (10 mL, freshly distilled from KOH) was added via cannula. The reaction mixture was heated at 50 °C overnight. Solvent was removed in vacuo, and the oily residue was purified by column chromatography in a glovebox (silica, 5 in. high, 0.5 in. diameter, petroleum ether/THF (95:5)). Removing solvent in vacuo gave a colorless oil as a 1:1.3 mixture of two diastereomers in 68% yield (0.885 g).

The product PH(Me)(Men) always contained two impurities with ^{31}P NMR chemical shifts in C_6D_6 δ −88.2 (2% by integration) and −98.9 (2.6%), which we were unable to separate from PH(Me)(Men) or identify. These impurities did not participate in the catalytic phosphination reaction and were observed in all spectra of **2** and the product, **1**, in the same relative amounts.

Anal. Calcd for $C_{11}H_{23}P$: C, 70.93; H, 12.45. Found: C, 70.93; H, 16.63. Calculated HRMS (EI) for $C_{11}H_{23}P$ (M^+): *m*/*z* 186.1537. Found: 186.1533. $^{31}P\{^1H\}$ NMR (C_6D_6): δ −69.6 (minor), −75.6 (major). ^1H NMR (C_6D_6): δ 3.24 (dm, J = 198, 1H, P-H), 2.99 (dm, J = 196, 1H, P-H), 2.37−2.27 (m, 1H), 2.17−2.06 (m, 1H), 1.92−1.85 (m, 1H), 1.66−1.53 (m, 6H), 1.34−0.92 (m, 7H), 0.92−0.73 (m, 25H), 0.71 (d, J = 2.5, 3H, Me). $^{13}C\{^1H\}$ NMR (C_6D_6): δ 47.1 (d, J = 11, CH), 45.9 (d, J = 10, CH), 42.5 (d, J = 3, CH_2), 40.7 (d, J = 6, CH_2), 36.6 (d, J = 11, CH), 35.34 (CH_2), 35.30 (CH_2), 35.1 (d, J = 10, CH), 34.0 (d, J = 6, CH), 33.6 (d, J = 6, CH), 28.7 (d, J = 12, CH), 28.6 (d, J = 12, CH), 25.3 (d, J = 7, CH_2), 25.1 (d, J = 7, CH_2), 22.7 (Me), 22.6 (Me), 21.8 (Me), 21.6 (Me), 15.3 (Me), 15.2 (Me), 2.4 (d, J = 15, Me-P), 0.6 (d, J = 15, Me-P).

$[PH_2(Me)(Men)][BF_4]$ (5). We could not obtain satisfactory elemental analyses for the air-sensitive liquid phosphine PH(Me)(Men), but it was conveniently protonated to give the air-stable white solid **5** in analytically pure form. To a stirred solution of $HBF_4{\cdot}Me_2O$ (101.3 mg, 0.757 mmol, 1.03 equiv) in ether (∼0.5 mL) was added PH(Me)(Men) (137.2 mg, 0.737 mmol) dropwise as a solution in 3 mL of ether; a white precipitate formed. The reaction mixture was stirred for 10 min and allowed to settle. The solvent was pipetted off, and the white precipitate was washed with 2 mL of ether and dried in vacuo, giving 169.7 mg (84%) of the salt. Recrystallization from acetonitrile/ether gave analytically pure material.

Anal. Calcd for $C_{11}H_{24}PBF_4$: C, 48.20; H, 8.83. Found: C, 48.18; H, 9.08. $^{31}P\{^1H\}$ NMR (acetonitrile-d_3): δ −25.7 (br s). ^1H NMR (acetonitrile-d_3): δ 6.00 (br d, J = 480, 2H), 2.65−2.49 (m, 1H), 2.02−1.90 (m, 2H), 1.90−1.72 (m, 2H), 1.82 (d, J = 16, 3H, P-Me, overlapped with previous signal), 1.64−1.44 (m, 2H), 1.34−1.10 (m, 2H), 1.00 (d, J = 7, 3H, Me), 0.95 (d, J = 7, 3H, Me), 0.86 (d, J = 7, 3H, Me). $^{13}C\{^1H\}$ NMR (acetonitrile-d_3): δ 44.0 (d, J = 3, CH_2), 36.6 (d, J = 3, CH), 34.8 (d, J = 2, CH_2), 33.9 (d, J = 16, CH), 31.4 (d, J = 46, CH), 30.5 (d, J = 6, CH), 25.2 (d, J = 13, CH_2), 22.6 (Me), 21.7 (Me), 15.6 (Me), −3.1 (d, J = 50, P-Me). $^{19}F\{^1H\}$ NMR (acetonitrile-d_3): −152.0.

Pd-Catalyzed Synthesis of P(Ph)(Me)(Men) (1). Method I. To a solution of Pd-catalyst (5 mol %, 0.008 mmol) in 1 mL of toluene was added PhI (18 μL, 33 mg, 0.16 mmol) via syringe, followed by PH(Me)(Men) (32 μL, 29 mg, 0.16 mmol) and $NaOSiMe_3$ (160 μL, 1.0 M solution in THF, 0.16 mmol). The reaction mixture was transferred to an NMR tube. The vial was rinsed with 0.5 mL of toluene that was combined with the rest of the reaction mixture. The progress of the reaction was monitored by $^{31}P\{^1H\}$ NMR spectroscopy. Once the reaction was complete, toluene was removed in vacuo. The residue was slurried in petroleum ether (10 mL), and the product phosphine was isolated by column chromatography (20:1 petroleum ether/THF eluent, 1 in. column, 0.5 cm diameter) as a colorless oil.

Method II (with added 1). To a solution of Pd-catalyst (5 mol %, 0.008 mmol) was added P(Ph)(Me)(Men) (4.3 mg, 0.016 mmol, 10 mol %, 71% de, see Table 3), prepared as a stock solution in toluene. After stirring for 2 min, PhI (18 μL, 33 mg, 0.16 mmol) was added via syringe, followed by PH(Me)(Men) (32 μL, 29 mg, 0.16 mmol) and $NaOSiMe_3$ (160 μL, 1.0 M solution in THF, 0.16 mmol). The reaction mixture was transferred to an NMR tube, and the vial was rinsed with 0.5 mL of toluene that was combined with the rest of the reaction mixture. The progress of the reaction was monitored by $^{31}P\{^1H\}$ NMR spectroscopy. Once the reaction was complete, toluene was removed in vacuo. The residue was slurried in petroleum ether (10 mL), and the product phosphine was isolated by column chromatography (20:1 petroleum ether/THF eluent, 1 in. column, 0.5 cm diameter) as a colorless oil.

The de of **1** was measured by integration of the ^{31}P NMR spectrum. The ^{31}P NMR chemical shifts of **1** were previously reported in Et_2NH, $CDCl_3$, and C_6D_6;[10,11] data for toluene is included in Table 6 below so that the de of the crude reaction mixtures could be measured during catalysis. Samples of phosphine **1** isolated from catalytic reactions were dissolved in $CDCl_3$, and the ^{31}P and ^1H NMR spectra were compared to the literature report (characteristic signals for S_P-**1**: δ 2.60−2.53 (m, 1H, CH), 1.21 (d, J = 3.7, 3H, P-Me); for R_P-**1**: δ 2.85−2.77 (m, 1H, CH), 1.34 (d, J = 4.8, 3H, P-Me))[11] to confirm that the catalytic reactions yielded S_P-**1** preferentially.

Table 6. ^{31}P NMR Chemical Shifts of S_P-1 and R_P-1 in Different Solvents[10,11]

	δ ^{31}P NMR, ppm			
diastereomer	Et_2NH	$CDCl_3$	C_6D_6	toluene
S_P-**1**	−31.3	−30.3	−32.0	−30.1
R_P-**1**	−34.3	−33.1	−34.9	−33.1

Synthesis of P(Me)(Men)(Ph) (1) from $[PH_2(Me)(Men)][BF_4]$ (5). To a solution of $Pd(OAc)_2$ (3 mg, 0.016 mmol, 5 mol %) in toluene (1 mL) was added PhI (63.4 mg, 0.312 mmol) followed by $[PH_2(Me)(Men)][BF_4]$ (85 mg, 0.312 mmol) as a slurry in 1 mL of toluene. Upon addition, the reaction mixture changed color from light yellow to orange. $NaOSiMe_3$ (630 μL of 1.0 M solution in THF, 0.630 mmol, 2 equiv) was added to the reaction mixture dropwise. Upon addition of the base, a white fluffy precipitate formed. After 1 h of the reaction the de was 62%, according to the ^{31}P NMR spectrum; this did not change at the completion of the reaction (24 h). The product phosphine was isolated by column chromatography as a reddish oil (yield 56.7 mg, 69%).

***trans*-Pd(S_P-1)$_2$(Ph)(I) (6a).** P(Ph)(Me)(Men) (93 mg, 0.35 mmol, 2 equiv, 10.4:1 S_P:R_P) was dissolved in THF (2 mL) and added to a stirring solution of Pd(tmeda)(Ph)(I) (75.5 mg, 0.177 mmol) in THF (5 mL). The mixture was stirred for 4 h. The $^{31}P\{^1H\}$ NMR spectrum (THF) showed a 6.6:1 mixture of complexes **6a** (Pd(S_P-**1**)$_2$(Ph)(I)) and **6b** (Pd(R_P-**1**)(S_P-**1**)(Ph)(I)), as well as some remaining phosphine. The solvent was removed in vacuo.

The residue was dissolved in petroleum ether (3 mL), and the solution was cooled to −30 °C overnight. The supernatant was removed via a pipet, and the off-white solid was dried in vacuo to give the desired product as a single diastereomer **6a** in 31% yield (49.6 mg).

Anal. Calcd for $C_{40}H_{59}P_2PdI$: C, 57.53; H, 7.12. Found: C, 57.60; H, 7.17. $^{31}P\{^1H\}$ NMR (C_6D_6): δ 3.3. ^1H NMR (C_6D_6): δ 8.18−8.10 (m, 4H, Ar), 7.22−7.15 (m, 4H, Ar), 7.15−7.04 (m, 4H, Ar), 7.00−6.94 (m, 2H, Ar), 6.94−6.89 (m, 2H, Ar), 4.02−3.93 (m, 2H, CH), 3.12−3.01 (m, 2H, CH), 1.56−1.49 (m, 2H), 1.46 (br d, J = 11, 4H), 1.28 (d, J = 7, 6H, Me), 1.25−1.13 (m, 4H), 0.99−0.91 (m, 2H), 0.89 (d, J = 7, 6H, Me), 0.68−0.63 (m, 6H, Me), 0.57−0.54 (m, 2H), 0.50 (d, J = 6.5, 6H, Me), 0.47−0.35 (m, 2H). $^{13}C\{^1H\}$ NMR (C_6D_6): δ 159.2 (t, J = 4, Pd-Ph), 135.4 (t, J = 5, Ar), 134.3 (t, J = 5, Ar), 131.9 (t, J = 18, Ar), 129.5 (Ar), 128.3 (Ar), 128.1 (Ar), 123.4 (Ar), 45.8 (CH), 40.7 (t, J = 13, CH_2), 37.7 (CH), 34.9 (CH_2), 32.9 (t, J = 5, CH), 28.2 (t, J = 6, CH), 26.1 (t, J = 5, CH_2), 22.6 (Me), 22.5 (Me), 19.1 (Me), 3.7 (t, J = 15, Me-P).

Generation of a Mixture of *trans*-Pd(S_P-1)$_2$(Ph)(I) (6a), *trans*-Pd(S_P-1)(R_P-1)(Ph)(I) (6b), and *trans*-Pd(R_P-1)$_2$(Ph)(I) (6c). To a slurry of Pd(tmeda)(Ph)(I) (28.5 mg, 0.067 mmol) in toluene (2 mL) was added P(Ph)(Me)(Men) (**1**, 35 mg, 0.13 mmol, 2 equiv, 25% de) as a solution in 1 mL of toluene. After 30 min of stirring at room temperature the precipitate dissolved completely and the solution became slightly yellow. After stirring for 2 h the reaction mixture was transferred to an NMR tube. $^{31}P\{^1H\}$ NMR spectroscopy (toluene) showed the presence of complexes **6a**, **6b**, and **6c** in the ratio 2.1:2.2:1. The NMR tube was placed in an oil bath (70 °C) and heated for 5 days. The diastereomeric ratio became 2.3:2.1:1. Some dark precipitate, presumably Pd metal, was observed also. $^{31}P\{^1H\}$ NMR (toluene-d_8): δ 3.5 (**6a**); 4.9, 8.0, J_{AB} = 419 Hz (AB pattern, **6b**), 8.2 (**6c**).

Synthesis of P(Me)(Men)(Ph) with Pd(S_P-1)$_2$(Ph)(I) (6a) as a Catalyst Precursor. To a solution of Pd(S_P-**1**)$_2$(Ph)(I) (**6a**, 11.8 mg, 0.014 mmol, 5%) in toluene (2 mL) was added PhI (63.8 mg, 0.312 mmol, 1.1 equiv) followed by PH(Me)(Men) (51.2 mg, 0.275 mmol) as a solution in toluene (0.5 mL) and $NaOSiMe_3$ (275 μL, 0.275 mmol, 1.0 M solution in THF). The reaction mixture changed color from light yellow to deep yellow, and a white precipitate started to form after 15 min. A ^{31}P NMR spectrum recorded after 1 h showed 58% conversion and product de = 53%. After the reaction was complete (24 h, final de = 44%), a second portion of reagents (PhI, PH(Me)(Men), and base, same amounts as above) was added to the reaction mixture. The second round of the reaction was done in 24 h with final product de of 46%. A third round (same conditions as above) was also complete in 24 h, with final product de = 47%. The product phosphine was isolated by column chromatography (column: 10 cm × 1 cm, silica, petroleum ether as an eluent) as a yellowish oil (172.7 mg, 80%).

Synthesis of P(Me)(Men)(Ph) with Pd(S_P-1)$_2$(Ph)(I) (6a) as a Catalyst Precursor (1% loading). To a solution of Pd(S_P-**1**)$_2$(Ph)(I) (**6a**, 10 mg, 0.012 mmol, 1%) in toluene (1 mL) was added PhI (273.5 mg, 1.34 mmol, 1.1 equiv), followed by PH(Me)(Men) (223 mg, 1.20 mmol) as a solution in toluene (1 mL) and $NaOSiMe_3$ (1.2 mL, 1.2 mmol, 1.0 M solution in THF). The reaction mixture changed color from light yellow to deep yellow, and a white precipitate appeared after 15 min. The product de decreased slightly from 56% at 67% conversion to 51% at completion. After completion (24 h) a mixture of the three diastereomers **6a**, **6b**, and **6c** was observed by ^{31}P NMR spectroscopy in the reaction mixture. The product phosphine was isolated by column chromatography (column: 10 cm × 1 cm, silica, petroleum ether as an eluent) as a yellowish oil (242 mg, 77%).

Synthesis of P(Me)(Men)(Ph) with a Mixture of 6a, 6b, and 6c as a Catalyst Precursor. To solid Pd(tmeda)(Ph)(I) (140.4 mg, 0.329 mmol) was added P(Me)(Men)(Ph) (173 mg, 0.658 mmol, initial de = 46%) as a solution in 1.0 mL of THF. After 24 h, all the solid had dissolved, and the ratio of Pd(S_P-**1**)$_2$(Ph)(I), Pd(R_P-**1**)$_2$(Ph)(I), and Pd(S_P-**1**)(R_P-**1**)(Ph)(I) observed by ^{31}P NMR spectroscopy was 5.3:1:3.6. The mixture was used as a catalyst precursor without further purification.

To toluene (0.5 mL) was added a sample of the mixture of diastereomers of **6**, generated as described above (36 μL, 0.012 mmol, 5%). PhI (54.7 mg, 0.268 mmol, 1.1 equiv) was added to the reaction mixture via syringe, followed by PH(Me)(Men) (45.2 mg, 0.24 mmol) as a solution in toluene (1 mL) and $NaOSiMe_3$ (240 μL of a 1.0 M solution in THF, 0.24 mmol). The reaction mixture changed color from light yellow to deep yellow, and a white precipitate appeared after 15 min. Over the course of the reaction the product de decreased from 42% at 65% conversion to 34% at completion. After the reaction was complete (24 h) the catalyst precursors were observed as a 1.9:1:3.9 mixture of the (*S*,*S*), (*R*,*R*), and (*S*,*R*) diastereomers. The product phosphine was isolated via column chromatography as a yellowish oil (51.8 mg, 82%).

Observation of Intermediates in the Synthesis of P(Me)(Men)(Ph) with Pd(S_P-1)$_2$(Ph)(I) as a Catalyst Precursor. To a solution of Pd(S_P-**1**)$_2$(Ph)(I) (**6a**, 10 mg, 0.012 mmol, 5%) in toluene (1 mL) was added PhI (54.7 mg, 0.268 mmol, 1.1 equiv) followed by PH(Me)(Men) (45.2 mg, 0.240 mmol) as a solution in toluene (0.5 mL) and $NaOSiMe_3$ (240 μL, 0.240 mmol, 1.0 M solution in THF). The reaction mixture changed color from light yellow to deep yellow. The progress of the reaction was monitored by ^{31}P NMR spectroscopy. Similar experiments were carried out using a mixture of the diastereomers **6a**−**c**, generated from **1** and Pd(tmeda)(Ph)(I) as described above, and with **6a** in the presence of tmeda.

Acknowledgment. We thank the NSF for support, and Dartmouth College for a Presidential Scholarship for K.C.M.

Supporting Information Available: Details of the X-ray crystallographic study. This material (including a CIF document) is available free of charge via the Internet at http://pubs.acs.org.

OM050993F