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Synthesis of Chiral Aminophosphines from Chiral Aminoalcohols via Cyclic Sulfamidates

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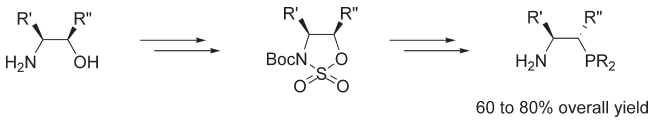

Protic aminophosphines with multiple chiral centers were synthesized in good yields and high purity by the nucleophilic ring-opening of N-protected cyclic sulfamidates with metal phosphides, followed by hydrolysis and deprotection. This synthetic approach is clean, scalable, and high yielding. The method provides an efficient alternative route for the synthesis of chiral aminophosphines.

The asymmetric hydrogenation of C=C, C=O, and C=N double bonds catalyzed by rhodium,[1−3] ruthenium,[4,5] or iridium[6,7] complexes is an efficient and attractive approach to desired single enantiomer products. Combinations of these transition metals and a variety of chiral ligands provide a wide range of catalysts for asymmetric hydrogenation. The highly modular nature of chiral aminophosphine ligands and their derivatives play a very important role in such reactions.[8,9] These single enantiomer chiral compound incorporating phosphorus and nitrogen donor atoms is of increasing interest for applications in enantioselective catalysis. Chelating aminophosphines have a combination of hard Lewis base (nitrogen) and soft Lewis base (phosphorus) centers which make these ligands particularly useful in a variety of catalytic reactions.[10,11] In the 1990s, Noyori and co-workers first developed the efficient $RuCl_2$(diphosphine)-(diamine) catalytic system for the hydrogenation of simple ketones.[12] This was also shown to be useful for the hydrogenation of imines.[13] Subsequently, researchers have shown that $RuCl_2$(diphosphine)(aminophosphine) and $RuCl_2$(aminophosphine)$_2$ complexes are very efficient catalysts for the hydrogenation of simple ketones and imines as well.[14,15] Nevertheless, the available methods for the preparation of chiral aminophosphines remain limited. This has restricted the development and application of $RuCl_2$(diphosphine)-(aminophosphine) or $RuCl_2$(aminophosphine)$_2$ catalyst systems in asymmetric hydrogenation and other catalytic applications. The most established protocol for the preparation of aminophosphines involves nucleophilic phosphide

(1) (a) Kagan, H. B.; Dang, T. P. *J. Chem. Soc. D* **1971**, *10*, 481. (b) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429. (c) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *127*, 11934. (d) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799. (e) Jiang, Q.; Xiao, D.; Zhang, Z.; Chao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 516. (f) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934.

(2) (a) Chan, A. S. C.; Hu, W.; Pai, C. C.; Lau, C. P.; Jiang, Y.; Mi, A.; Yan, M.; Sun, J.; Lou, R.; Deng, J. *J. Am. Chem. Soc.* **1997**, *119*, 9570. (b) Chan, A. S. C.; Zhang, F. Y.; Yip, C. W. *J. Am. Chem. Soc.* **1997**, *119*, 4080. (c) Clyne, D. S.; Mermet-Bouvier, Y. C.; Nomura, N.; RajanBabu, T. V. *J. Org. Chem.* **1999**, *64*, 7601.

(3) (a) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889. (b) van den Berg, M.; Minnaars, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539. (c) Hu, A. G.; Fu, Y.; Xie, J. H.; Zhou, H.; Wang, L. X.; Zhou, Q. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348.

(4) (a) Pai, C. C.; Lin, C. W.; Lin, C. C.; Chen, C. C.; Chan, A. S. C. *J. Am. Chem. Soc.* **2001**, *123*, 3186. (b) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264. (c) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207. (d) Xie, J. H.; Wang, L. X.; Fu, Y.; Zhu, S. F.; Fan, B. M.; Duan, H. F.; Zhou, Q. L. *J. Am. Chem. Soc.* **2003**, *125*, 4404.

(5) (a) Takaya, H.; Ohta, T.; Mashima, K. *Yukagaku* **1990**, *39*, 866. (b) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (c) Gao, J. X.; Ikariya, T.; Noyori, R. *Organometallics* **1996**, *15*, 1087. (d) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (e) Guo, R.; Elpelt, C.; Chen, X.; Song, D.; Morris, R. H. *Chem. Commun.* **2005**, *24*, 3050. (f) Guo, R.; Chen, X.; Elpelt, C.; Song, D.; Morris, R. H. *Org. Lett.* **2005**, *7*, 1757.

(6) (a) Zhu, S. F.; Xie, J. B.; Zhang, Y. Z.; Li, S.; Zhou, Q. L. *J. Am. Chem. Soc.* **2006**, *128*, 12886. (b) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425. (c) Lam., K. H.; Xu, L.; Feng, L.; Fan, Q. H.; Lam, F. L.; Lo, W. H.; Chan, A. S. C. *Adv. Synth. Catal* **2005**, *347*, 1755.

(7) (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (b) Wu, J.; Wang, F.; Ma, Y.; Cui, X.; Cun, L.; Zhu, J.; Deng, J.; Yu, B. *Chem. Commun.* **2006**, *16*, 1766. (c) Ohkuma, T.; Noyori, R. *Compr. Asymmetric Catal., Suppl.* **2004**, *1*, 43–53.

(8) (a) Amoroso, D.; Graham, T.; Guo, R.; Tsang, C. W.; Abdur-Rashid, K. *Aldrichim. Acta* **2008**, *41*, 15. (b) Fang, Y. Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660. (c) Zeng, W.; Chen, G. Y.; Zhou, Y. G.; Li, Y. X. *J. Am. Chem. Soc.* **2007**, *129*, 750. (d) Kawamura, K.; Fukuzawa, H.; Hayashi, M. *Org. Lett.* **2008**, *10*, 3509.

(9) (a) Li, X.; Jia, X.; Xu, L.; Kok, S. H. L.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2005**, *347*, 1904. (b) Deng, J.; Duan, Z. C.; Huang, J. D.; Hu, X. P.; Wang, D. Y.; Yu, S. B.; Xu, X. F.; Zheng, Z. *Org. Lett.* **2007**, *9*, 4825. (c) Boaz, N. W.; Mackenzie, E. B.; Debenham, S. D.; Large, S. E.; Ponasik, J. A. Jr. *J. Org. Chem.* **2005**, *70*, 1872. (d) Boaz, N. W.; Large, S. E.; Ponasik, J. A.; Moore, M. K.; Barnette, T.; Nottingham, W. D. *Org. Process Res. Dev.* **2005**, *9*, 472.

(10) (a) Coutelier, O.; Nowogrocki, G.; Paul, J. F.; Mortreux, A. *Adv. Synth. Catal.* **2007**, *349*, 2259. (b) Bonnaventure, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6330.

(11) (a) Guo, R.; Morris, R. H.; Song, D. *J. Am. Chem. Soc.* **2005**, *127*, 516. (b) Kuriyama, M.; Nagai, K.; Yamada, K.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* **2002**, *124*, 8932.

(12) (a) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703. (b) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem, Soc.* **1998**, *120*, 13529.

(13) (a) Abdur-Rashid, K.; Lough, A. J.; Morris, R. H. *Organometallics* **2001**, *20*, 1047–1049. (b) Abdur-Rashid, K.; Lough, A. J.; Morris, R. H. *Organometallics* **2000**, *19*, 2655–2657. (c) Cobley, C. J.; Henschke, J. P.; Ramsden, J. A. *PCT Int. Appl.* WO 2002008169 A1, 2003. (d) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195.

(14) Guo, R.; Lough, A. J.; Morris, R. H.; Song, D. *Organometallics* **2004**, *23*, 5524.

(15) (a) Abdur-Rashid, K.; Morris, R. H. *PCT Int. Appl.* WO 2003097571 A1, 2003. (b) Abdur-Rashid, K. *PCT Int. Appl.* WO 2005056513 A1, 2005.

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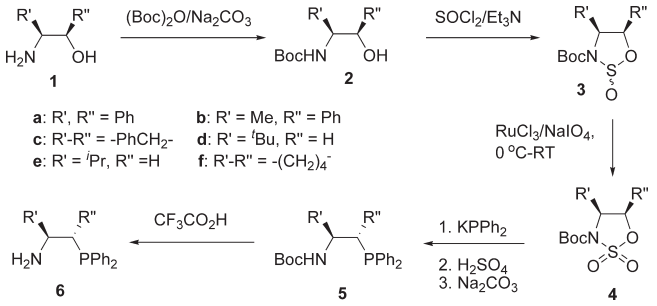
SCHEME 1. Preparation of Aminophosphines with Multiple Chiral Centers



substitution of tosylates or mesylates derived from aminoalcohols, which are in turn derived from natural or unnatural chiral aminoacids and their derivatives.[16] Another method is the ring-opening of aziridines with diaryl- or dialkylphosphines catalyzed with Lewis acids.[17] The drawback of the tosylate (or mesylate) route is the formation of significant amounts of byproduct during the reaction. The aziridine route gives a racemic product when the aziridine ring is symmetrically substituted.

In this report, we introduce an alternative route for the synthesis of protic aminophosphines containing multiple chiral centers in high yields and purity. The S_N2 ring-opening of cyclic N-protected sulfamidates with a metal phosphide followed by hydrolysis and N-deprotection provides new aminophosphines potentially useful for the development of new catalytic systems for applications in asymmetric catalysis (Scheme 1). The advantages of this approach are the following: (a) the reaction is relatively fast and clean, yielding little or no byproduct; (b) the possibility for racemization is effectively eliminated; and (c) multiple chiral centers are readily incorporated into the aminophosphines.[18]

Initial efforts to synthesize (1*S*,2*S*)-2-(diphenylphosphino)-1,2-diphenylethanamine **6a** (Figure 1) via the tosylate route failed. Starting with (1*R*,2*S*)-1,2-diphenyl-2-aminoethanol **1a** as precursor, reaction with $(Boc)_2O$ gave the N-Boc product **2a** in high yield. Reaction of **2a** with tosyl chloride gave 1,3-oxazolidin-2-one **7** as the only isolated product (Scheme 2).

Oxazolidinone **7** does not react with nucleophilic metal phosphides. Due to the low reactivity of oxazolidinones toward nucleophiles, the ring-opening with phosphines needs harsh reaction conditions and must be catalyzed by strong acids.[18b] Recently Jiang and Tewson reported the synthesis of N-substituted cyclic sulfamidates and their reactions with nucleophiles.[19,20] We postulated that reactions of

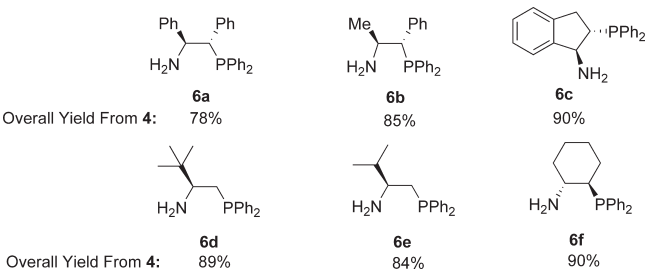
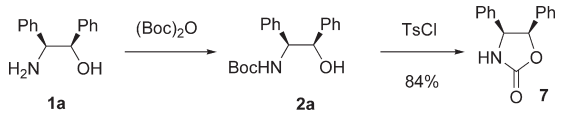
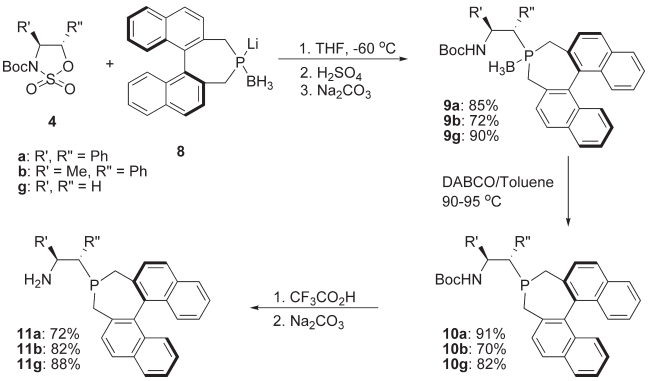


FIGURE 1. Representative examples of chiral aminophosphines derived from cyclic sulfamidates.

SCHEME 2. Reaction of 2a with Tosyl Chloride



SCHEME 3. Preparation of Chiral Aminophosphepine Ligands via Cyclic Sulfamidates



N-protected cyclic sulfamidates with phosphides followed by N-deprotection should yield aminophosphines with primary amine groups. We successfully synthesized **4a** by reacting **2a** with thionyl chloride to give the sulfamidite, which was oxidized with $RuCl_3/NaIO_4$ to give the desired cyclic sulfamidate in high yield. Ring-opening of **4a** with potassium diphenylphosphide followed by hydrolysis and deprotection with trifluoroacetic acid gave **6a** in high yield and purity. Five other aminophosphines **6b**−**f** (Figure 1) were also successfully synthesized from the precursors **1b**−**f** following this route. The known ligands **6b**, **6d**, **6e**, and **6f** were obtained in high yields and purity by using this approach as well.

Introduction of another chiral center into the aminophosphine backbone is facile by ring-opening of **4** with the chiral phosphide **8** derived from the reaction of butyllithium and the respective phosphepine−borane, followed by hydrolysis and N-deprotection.

In this approach, the products **9a**−**g** (Scheme 3) resulting from the ring-opening of **4** are air-stable crystalline solids which are easily purified. Removal of borane with DABCO in toluene at 90 °C gave the Boc-protected phosphepine intermediates **10a**−**g** which were deprotected with trifluoroacetic acid to give the novel aminophosphepines **11a**−**g** in good overall yields (Figure 2).

In summary, we have developed an alternative route for the synthesis of aminophosphines with multiple chiral

(16) (a) Saitoh, A.; Uda, T.; Morimoto, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4501. (b) Anderson, J. C.; Cubbon, R. J.; Harling, J. D. *Tetrahedron: Asymmetry* **2001**, *12*, 923. (c) Quirmbach, M.; Holz, J.; Tararov, V. I.; Borner, A. *Tetrahedron* **2000**, *56*, 775. (d) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Giuliani, A.; Marcantoni, E.; Mecozzi, T.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2002**, *67*, 9111.

(17) (a) Dahlenburg, L.; Gotz, R. J. *Organometallics* **2001**, *619*, 88. (b) Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 2597.

(18) (a) Ronnholm, P.; Sodergren, M.; Hilmersson, G. *Org. Lett.* **2007**, *9*, 3781. (b) Ito, M.; Osaku, A.; Kobayashi, C.; Shiibashi, A.; Ikariya, T. *Organometallics* **2009**, *28*, 390.

(19) Qin, Y.; Wang, C.; Huang, Z.; Xiao, X.; Jiang, Y. *J. Org. Chem.* **2004**, *69*, 8533.

(20) (a) Posakony, J. J.; Tewson, T. J. *Synthesis* **2002**, 766. (b) Posakony, J. J.; Grierson, J. R.; Tewson, T. J. *J. Org. Chem.* **2002**, *67*, 5164. (c) Ghosh, A.; Sieser, J. E.; Caron, S.; Watson, T. N. J. *Chem. Commun.* **2002**, *15*, 1644.

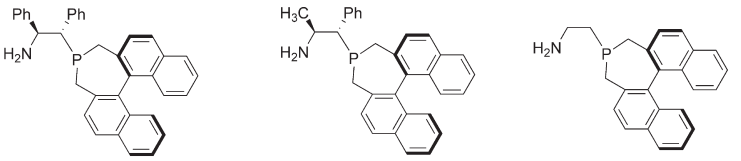


FIGURE 2. Representative examples of chiral aminophosphepines.

centers, which have potential applications in asymmetric catalysis. This method broadens the scope of the use of chiral aminoalcohols as precursors for the synthesis of aminophosphines. We are currently exploring the applications of these new compounds in a variety of catalytic processes, including asymmetric hydrogenations. Our progress will be reported in due course.

Experimental Section

Compounds **2a**−**f** were prepared according to literature procedures.[19]

General Procedure for Preparation of Cyclic Sulfamidates 4a−f. Method 1: A solution of $SOCl_2$ (20 g, 168 mmol) in CH_2Cl_2 (100 mL) was added to a solution of **2** (142 mmol) and triethylamine (43 g, 425 mmol) in CH_2Cl_2 (1300 mL) at −40 °C. The mixture was stirred for 1.5 h. Water (100 mL) was added to quench the reaction and the mixture was allowed to warm to rt, then water (500 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (300 mL). The combined organic layer was washed with brine (20%, 800 mL) and dried over $MgSO_4$. The solvent was removed to give the crude cyclic sulfamidite **3**, which was used directly for the next step without purification. A weighed amount of **3** (prepared above) was dissolved in CH_2Cl_2 (300 mL) and CH_3CN (500 mL), then water (600 mL) was added. $RuCl_3 \cdot nH_2O$ (300 mg) was added to the suspension and solid $NaIO_4$ (45 g, 210 mmol) was added in portions at 0 °C. The color of the mixture changed to yellow. The mixture was stirred at 0 °C for 1 h, then at rt for 1 h. The aqueous layer was extracted with ether (2 × 200 mL) and the combined organic layer was washed with brine (2 × 500 mL) and dried over $MgSO_4$. The filtrate was concentrated to almost dryness. To the residue was added CH_2Cl_2 (50 mL) and then hexane (400 mL) was added to crystallize the product. The resulting suspension was stirred for 4 h, then filtered and dried to give **4** as a colorless crystalline solid (60−88% overall yield for two steps).

Example: Preparation of 4a. A 44.5 g sample of **2a** (142 mmol) was used to prepare 50 g of **3a** (139 mmol) that was directly used without purification to synthesize 46 g of **4a** (86%). ^{1}H NMR (CD_2Cl_2) δ 7.24−7.14 (m, 6H), 7.10−7.06 (m, 2H), 7.00−6.95 (m, 2H), 6.20 (d, J = 5.6 Hz, 1H), 5.45 (br, J = 5.6 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 148.4 (s), 133.7 (s), 130.7 (s), 129.5 (s), 128.7 (s), 128.5 (s), 128.4 (s), 127.4 (s), 126.47 (s), 85.8 (s), 83.5 (s), 66.8 (s), 28.1 (s). Anal. Calcd for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73; S, 8.54. Found: C, 61.10; H, 5.25; N, 3.95; S, 8.28. Mp 152.5−153.4 °C.

Method 2: To a solution of $SOCl_2$ (30 mL) in CH_3CN (300 mL) was added **2** (200 mmol) in CH_3CN (150 mL) at 0 °C, then pyridine (81 mL) was added. The resulting mixture was warmed to rt and then stirred for 2 h. The solvent was removed, and ethyl acetate (1400 mL) and water (400 mL) were added to the residues. The solution was then stirred at rt for 20 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The combined organic layer was washed with brine (3 × 400 mL). The solvent was removed and crude **3** was redissolved in CH_3CN (400 mL). $RuCl_3 \cdot 3H_2O$ (96 mg) was added, then $NaIO_4$ (85 g, 397 mmol) was added in portions at 0 °C. The mixture was stirred at rt for 2 h and the color of the mixture changed from black to orange. Ether (500 mL) was added, the organic layer was separated, and the aqueous layer was extracted with ether (2 × 300 mL). The combined organic layer was washed with brine (3 × 400 mL) and dried over $MgSO_4$ for 2 h. The solution was then filtered through a silica gel pad, the solvent was removed, and the residue was dissolved in a small amount of CH_2Cl_2 (30 mL), then hexane (300 mL) was added slowly to precipitate the product. The solution was filtered and the solid was washed with hexane (80 mL) and dried to give **4** as a colorless crystalline solid (85−95% overall yield for two steps).

Example: Preparation of 4c. A 50.0 g sample of **2c** (200 mmol) was used to synthesize 53.4 g of **4c** (85%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.49 (d, 1H), 7.28−7.25 (m. 3H), 5.64 (d, J = 5.4 Hz, 1H), 5.44 (m, 1H), 3.30 (br, 2H), 1.53 (s, 9H). ^{13}C NMR (CD_2Cl_2) δ 149.95 (s), 138.93 (s), 138.31 (s), 130.13 (s), 126.11 (s), 125.51 (s), 85.89 (s), 82.89 (s), 65.40 (s), 36.62 (s), 27.98 (s). Anal. Calcd for $C_{14}H_{17}NO_5S$: C, 54.01; H, 5.50; N, 4.50; S, 10.30. Found: C, 54.29; H, 5.59; N, 4.76; S, 10.56. Mp 139.0−140.2 °C.

General Procedure for Preparation of Aminophosphines 6a−f. A solution of $KPPh_2$ (70 mL, 0.5 M in THF, 35 mmol) was added dropwise to a solution of **4** (32 mmol) in THF (150 mL) cooled in an acetone/dry ice bath. The mixture was stirred at −60 °C for 0.5 h, then slowly warmed to rt and stirred overnight. H_2SO_4 (10 mL, 2 N) and brine (20%, 100 mL) were added to the mixture, which was stirred at rt for 1 h. Saturated sodium carbonate (30 mL) was added to neutralize the mixture and make the solution basic. The aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layer was washed with brine (2 × 100 mL) and dried over $MgSO_4$ for 2 h. The mixture was then filtered and the filtrate was concentrated to almost dryness to give crude **5**, which was redissolved in CH_2Cl_2 (100 mL). An aliquot of CF_3CO_2H (30 mL) was added to it at 0 °C and the mixture was stirred for 1 h, then allowed to warm to rt and stirred for 4 h. All the volatiles were removed under vacuum. CH_2Cl_2 (100 mL) was added to dissolve the residues, then Na_2CO_3 (saturated, 100 mL) was added to neutralize the mixture and make the solution basic. The aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layer was washed with brine (20%, 100 mL) and dried over $MgSO_4$. The solution was then filtered and the solvent was removed to give the crude product **6**, which was purified with silica gel chromatography. The mixture was first eluted with CH_2Cl_2/hexane (1:1, 300 mL) to remove impurities, then CH_2Cl_2/THF (9/1, 250 mL) to wash out the product. The solvent was removed under vacuum to give pure **6** (85−90% yield over two steps).

Example: Preparation of 6a. A 12.0 g sample of **4a** (32 mmol) was used to prepare 13.0 g of **5a** (27 mmol) that were used to synthesize 9.4 g of **6a** (78%). ^{1}H NMR (CD_2Cl_2) δ 7.88−7.81 (m, 2H), 7.50−7.42 (m, 3H), 7.22−6.88 (m, 15H), 4.43 (dd, 1H), 4.05 (dd, 1H), 1.60 (br, 2H). ^{31}P NMR (CD_2Cl_2) δ −7.15 ppm. ^{13}C NMR (CD_2Cl_2) δ 144.3 (s), 138.6 (s), 138.4 (s), 134.0−127.7 (m), 59.5 (d). HRMS (ESI) $[M + H]^+$ calcd for $C_{26}H_{25}NP$ 382.1719, found 382.1718. Mp 294.0−295.0 °C.

General Procedure for Preparation of Aminophosphepines 11a, 11b, and 11g. A solution *n*-butyllithium (12 mL, 2.5 M in hexane, 30 mmol) was slowly added to a solution of (11b*S*)-4,5-dihydro-3*H*-dinaphtho[2,1-C:1′,2′-*e*]-phosphepine−borane (9.4 g, 28.8 mmol) in THF (100 mL) at −60 °C. The mixture was stirred for 1 h, then added to a suspension of **4** (26.6 mmol) in THF (200 mL) cooled in a dry ice/acetone bath. The mixture was stirred for 1 h, then slowly warmed to rt and stirred for an additional 24 h. H_2SO_4 (20 mL, 2 N) was added to the mixture, which was then stirred for 1 h. Na_2CO_3 (saturated, 50 mL) and brine (20%, 100 mL) were added to neutralize the mixture and make the solution basic. The aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layer was washed with brine (2 × 100 mL) and dried over $MgSO_4$ for 2 h. This solution was then filtered and the filtrate was concentrated to almost dryness to give the crude product as a pale-yellow solid that was dissolved in CH_2Cl_2 (100 mL). Hexane (400 mL) was added slowly to precipitate the product. The resulting slurry was stirred at rt for 4 h. The solid was filtered and washed with hexane (50 mL) and dried under vacuum to give **9** as a colorless crystalline solid. DABCO (3.1 g, 27.6 mmol) was added to a suspension of **9** (22 mmol) in toluene (150 mL). The mixture was stirred at 90−95 °C under argon overnight. All the volatiles were removed under vacuum. To the residue was added CH_3CN/MeOH (1:1, 80 mL) and the mixture was stirred for 6 h to remove impurities. The mixture was then filtered and the solid was washed with CH_3CN/MeOH (1:1, 30 mL) to give pure **10** as a white solid (91%). Trifluoroacetic acid (30 mL) was added to a solution of **10** (19.7 mmol) in CH_2Cl_2 (100 mL) at 0 °C and the mixture was stirred at rt overnight. The volatiles were removed under vacuum and the residue was dissolved in CH_2Cl_2 (150 mL). The solution was neutralized with Na_2CO_3 (saturated, 50 mL) in brine (20%, 100 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layer was washed with brine (20%) and dried over $MgSO_4$ for 3 h. The solvent was removed to give crude **11** as a white solid, which was purified by recrystallization in CH_3CN/MeOH (1:1, 80 mL) and water (100 mL). The mixture was then filtered and dried to give **11** as a white solid (65−75% yield).

Example: Preparation of 11a. A 10.0 g sample of **4a** (26.6 mmol) was used to prepare 14.0 g of **9a** (85%). A 13.5 g sample of **9a** (22 mmol) was used to synthesize 12.0 g (19.7 mmol) of **10a** (91%) that was directly used to synthesize 7.2 g of **11a** (72%). ^{1}H NMR (CD_2Cl_2) δ 8.05 (dd, J_1 = 8.3 Hz, J_2 = 22.2 Hz, 2H), 7.88 (dd, J_1 = 7.2 Hz, J_2 = 15.5 HZ, 2H), 7.63 (d, J = 7.2 Hz, 1H), 7.47−6.73 (m, 17H), 4.47 (dd, J_1 = 5.1 Hz, J_2 = 9.2 Hz, 1H), 3.31 (dd, J_1 = 5.0 Hz, J_2 = 14.0 Hz, 1H), 3.06 (dd, J_1 = 6.6 Hz, J_2 = 9.3 Hz, 1H), 2.61 (dd, J_1 = 11.4 Hz, J_2 = 14.3 Hz, 1H), 1.89 (m, 4H). ^{31}P NMR (CD_2Cl_2) δ 14.9 ppm. ^{13}C NMR (CD_2Cl_2) δ 145.6 (s), 135.5−132.2 (m), 129.4−125.0 (m), 61.7 (d), 52.7 (d), 45.6, 44.9, 31.1−30.8 (m). HRMS (ESI) $[M + H]^+$ calcd for $C_{36}H_{31}NP$ 508.2188, found 508.2173. Mp 150.1−152.0 °C.

Supporting Information Available: Details of the preparations and the NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.