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A Highly Stereoselective Synthesis of Optically Active Trisubstituted 1,2-Ethylenediamines: The First Example of Grignard Addition to *N*-Diphenylphosphinoyl Ketimines Derived from Amino Acids

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The efficient synthesis of optically active trisubstituted 1,2-ethylenediamines is described. Addition of aryl and/or alkyl Grignard reagents to α-amino *N*-diphenylphosphinoyl ketimines derived from α-amino acids was demonstrated to afford the desired trisubstituted 1,2-ethylenediamines in good yields and with high diastereoselectivities. Subsequent removal of the diphenyphosphinoyl group from the adduct was smoothly accomplished in reasonable yield without racemization under newly developed reductive conditions.

Introduction

Optically active multisubstituted 1,2-ethylenediamines are recognized as superb ligands/auxiliaries in asymmetric synthesis.[1] In addition, their derivatives are valuable key intermediates in drug discovery efforts and heavily used for the preparation of pharmacophoric heterocycle substructures.[2] Therefore, much effort has been directed toward an efficient synthesis of these compounds. Application of optically active monosubstituted, vicinal disubstituted, and trisubstituted 1,2-ethylenediamines for asymmetric synthesis has been well documented.[1] Among them, trisubstituted 1,2-ethylenediamines offer an advantage. For example, it is reported that (2*S*)-1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine acts as a more efficient chiral ligand for a ruthenium-catalyzed enantioselective hydrogenation than (*R*,*R*)-*trans*-cyclohexane-1,2-diamine and (*R*,*R*)-1,2-diphenylethylenediamine in terms of both turnover number of the catalyst and enantioselectivity.[3] Syntheses of optically active monosubstituted and vicinal disubstituted 1,2-ethylenediamines have been successfully reported.[1] However, few examples of stereoselective synthesis of trisubstituted 1,2-ethylenediamines have been reported,[4] due to the difficulty in the construction of the quaternary chiral center.[5]

The addition of nucleophiles to ketimines is one of the most direct and promising methods for the preparation of chiral α,α-dibranched amines containing a quaternary carbon.[6,7] Ellman and others have reported the diastereoselective addition of organometallics to a ketimine with chiral auxiliaries (i.e. *tert*-butanesulfinylimine).[6] In general this method provides high diastereoselectivity and allows for the facile removal of the sulfinyl group from the resulting sulfinamides.[6c] We expected that diastereoselective nucleophilic addition to a ketimine would be feasible without chiral auxiliaries on nitrogen if the ketimine has a chiral center at the α-position of the imine. We envisioned that chiral α-aminoketimines, which are readily available from α-amino acids, can undergo diastereoselective nucleophile addition to readily provide the desired chiral trisubstituted 1,2-ethylenediamines.

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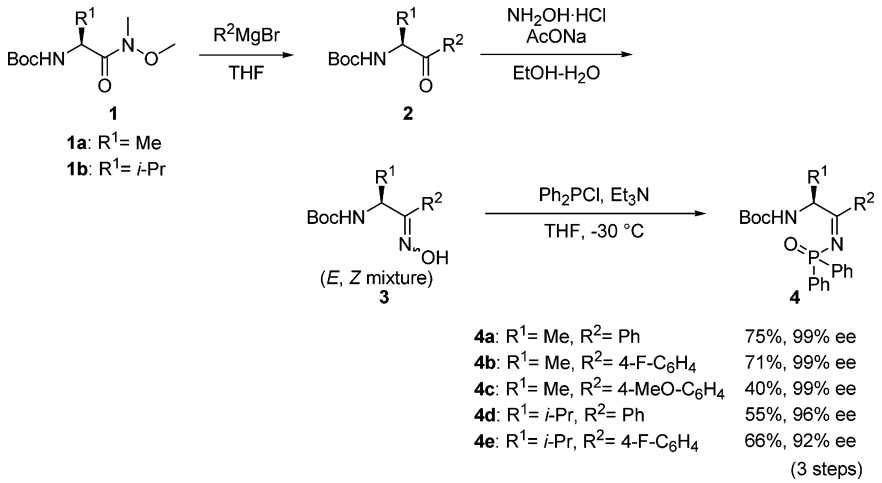
SCHEME 1. Synthesis of *N*-Diphenylphosphinoyl Ketimines 4a−e



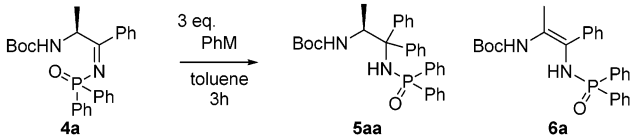
Selection of the proper protecting group for the ketimine is a key issue. Addition of alkyllithiums or Grignard reagents to *N*-*p*-toluenesulfonyl ketimines[8a] and *N*-aryl ketimines[8b] has been reported; however, deprotection of these adducts, in general, requires harsh conditions. Many protecting groups, which are cleaved under mild condition, have been reported for the amino group.[9] Among them, we expected that the *N*-diphenylphosphinoyl protecting group would be one of the most attractive candidates because of its electron-withdrawing ability and its ease of removal under acidic conditions.[9a] Therefore, our research efforts focused on the nucleophilic addition to *N*-diphenylphosphinoyl ketimines.[10] Herein, we wish to report an efficient and stereoselective synthesis of trisubstituted 1,2-ethylenediamines via *N*-diphenylphosphinoyl ketimines.

Results and Discussion

Preparation of optically active α-amino *N*-diphenylphosphinoyl ketimines **4a**−**e** was accomplished from the Weinreb amide of *N*-Boc-protected amino acid **1a** and **1b** in three steps: (i) alkylation of **1**, (ii) formation of oximes from ketones **2**,[11] and (iii) rearrangement of *O*-phosphinooximes generated in situ from oximes **3** and diphenylchlorophosphine (Scheme 1).[12,13] The stereochemistry of the C=N bond of **4a** was confirmed by its X-ray crystallography to be *Z*. The configurations of **4b**, **4c**, **4d**, and **4e** were similarly assigned.

With the desired substrates in hand, we examined the key addition reaction to the ketimine. To simplify the analysis of the products of reaction, we selected phenylmetalated reagents as a model nucleophile and **4a** as a model substrate since the expected products were not diastereomeric (Table 1). Though it is reported that strong bases such as alkyl Grignard reagents are susceptible to enolization of imines to enamines,[6d,14] we expected that the C=N double bond would be activated enough by the electron-withdrawing diphenylphosphinoyl group to promote 1,2-addition while avoiding enolization. Furthermore, *N*-metalation on the α-amino group should reduce the acidity of the α-proton and might offer a positive chelating effect with the imine nitrogen. Thus, metalation would prevent enolization. To explore this possibility, we first examined the reaction using phenyllithium as a nucleophile in noncoordinating toluene as solvent at −78 °C. The desired reaction occurred but the yield of adduct **5aa** was only 18%, and 36% of ketimine **4a** remained unreacted (entry 1). Upon further investigation of the reaction mixture, we found considerable amounts (37%) of enamine **6a**, which was formed via α-proton abstraction of the imine. To address this issue, we proposed the notion that the α-proton abstraction of the imine could be suppressed by reducing the basicity of nucleophile. We next examined the reaction with phenylmagnesium bromide instead of phenyllithium under the same condition; however, **5aa** was not observed with almost complete recovery of **4a** (entry 2). Fortu-

TABLE 1. Nuclephilic Addition of Phenylmetalated Reagents to 4a



			yield (%)[a]		
entry	PhM	temp (°C)	**5aa**	**4a**	**6a**
1	PhLi	−78	18	36	37
2	PhMgBr	−78	0	94	3
3	PhMgBr	−20	61	18	25
4	PhMgBr	0	77	0	22
5	PhMgBr	20	73	0	18
6	PhMgBr	40	31	0	27
7[b]	PhMgBr	0	60	0	27

[a] HPLC assay yield of crude product. [b] The reaction was carried out in THF.

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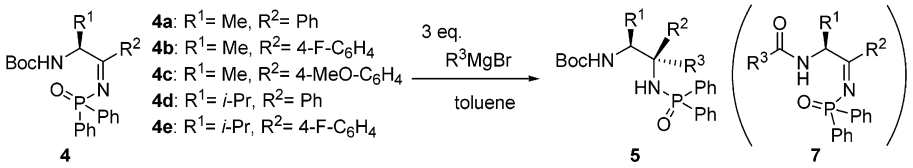
(12) Krzyzanowska, B.; Stec, W. J. *Synthesis* **1978**, 521−524.

(13) It is presumed that slight loss of ee in **4d** and **4e** would take place at the formation of oximes **3**, which required the longer reaction time under reflux condition due to steric bulkiness in **2d** and **2e**.

(14) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178−2180.

TABLE 2. Grignard Addition to *N*-Diphenylphosphinoyl Ketimines 4a−e



5aa: R^1= Me, R^2,R^3= Ph
5ab: R^1= Me, R^2= Ph, R^3= 4-F-C_6H_4
5ac: R^1= Me, R^2= Ph, R^3= 4-MeO-C_6H_4
5ad: R^1,R^3= Me, R^2= Ph
5ba: R^1= Me, R^2= 4-F-C_6H_4, R^3= Ph
5bb: R^1= Me, R^2,R^3= 4-F-C_6H_4
5ca: R^1= Me, R^2= 4-MeO-C_6H_4, R^3= Ph
5da: R^1= *i*-Pr, R^2,R^3= Ph
5db: R^1= *i*-Pr, R^2= Ph, R^3= 4-F-C_6H_4
5ea: R^1= *i*-Pr, R^2= 4-F-C_6H_4, R^3= Ph
7da: R^1= *i*-Pr, R^2,R^3= Ph
7db: R^1= *i*-Pr, R^2= Ph, R^3= 4-F-C_6H_4
7ea: R^1= *i*-Pr, R^2= 4-F-C_6H_4, R^3= Ph

entry	substrate	ee (%)	R^3	temp (°C)	time (h)	adduct	yield (%)[a]	de (%)[b]	ee (%)[c]	Bz-imine	yield (%)[a]	ee (%)[c]
1	**4a**	99	Ph	0	3	**5aa**	66 (77)		98			
2	**4a**	99	4-F-C_6H_4	0	3	**5ab**	75	94	99			
3	**4a**	99	4-MeO-C_6H_4	0	3	**5ac**	(84)	80	99			
4	**4a**	99	Me	0	3	**5ad**	70	>96	99			
5	**4b**	99	Ph	0	3	**5ba**	49	83	98			
6	**4b**	99	4-F-C_6H_4	0	3	**5bb**	74		99			
7	**4c**	99	Ph	0	3	**5ca**	72	96	99			
8	**4d**	96	Ph	25	7	**5da**	(60)		97	**7da**	(40)	96
9	**4d**	96	4-F-C_6H_4	25	7	**5db**	(62)	>96[d]	96	**7db**	(38)	96
10	**4e**	92	Ph	25	5	**5ea**	(58)	>96[d]	92	**7ea**	(39)	92

[a] Isolated (HPLC assay) yield. Yields were calculated based on the amount of imine **4**. [b] Determined by ^{1}H NMR analysis (500 MHz). [c] Determined by chiral HPLC analysis. [d] Diastereomer was not detected.

nately, the reaction proceeded smoothly when the reaction temperature was warmed to −20 °C to provide the desired product **5aa** as a major product (entry 3). The best result of 77% yield was attained when the reaction was performed at 0 °C (entry 4). Elevated temperatures beyond 0 °C resulted in diminished product yield (entries 5 and 6). The reaction in toluene gave much better results than that in coordinating solvents such as THF (entry 7). Addition of several Lewis acids did not improve the reaction.[15]

With the optimal conditions in hand, the addition of various Grignard reagents to **4** was examined to expand the scope of the reaction. The results are summarized in Table 2. The addition to the imines derived from L-alanine (**4a**, **4b**, and **4c**: R^1 = Me) proceeded smoothly in toluene at 0 °C and the adducts were obtained in moderate to good yields with good to excellent diastereoselectivities (entries 1−7).[16] The reaction with alkyl Grignard reagents such as methylmagnesium bromide afforded the desired product **5ad** in reasonable yield (70%) with >96% de (entry 4). In efforts to improve the diastereoselectivity while suppressing the α-proton abstraction from the imine, we next examined the addition to bulkier imines derived from L-valine (**4d** and **4e**: R^1 = *i*-Pr). Higher temperature and prolonged reaction times were required to complete the reaction. As expected, the reactions proceeded with excellent diastereoselectivity without formation of enamine **6**, although the yields were moderate due to formation of benzoyl imines (Bz-imine: **7da**, **7db**, and **7ea**) caused by nucleophilic attack of Grignard reagents on the Boc group (entries 8−10).[17]

(15) $CeCl_3$, Ti(O*i*-Pr)$_4$, Me_3Al, BF_3·Et_2O, $ZnCl_2$, $MgBr_2$, and LiBr were used.

(16) The main byproduct was corresponding enamide **6**.

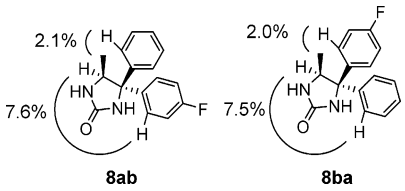


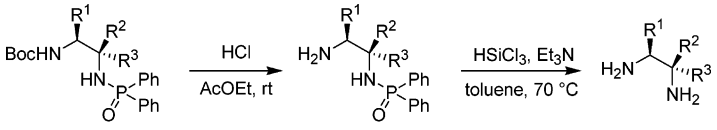
FIGURE 1. Confirmation of absolute configurations of **8ab** and **8ba** by NOE.

Absolute configuration of the newly formed stereogenic center in **5ab** and **5ba** was confirmed by NOE studies of the corresponding imidazolidinones **8ab** and **8ba** as shown in Figure 1.[18] The enantiomeric excesses of **8ab** and **8ba** were the same as those of **5ab** and **5ba**, therefore, no epimerization occurred at C-5. The absolute configuration at C-5 of both imidazolidinones was 5*S* because of its origin from (*S*)-alanine (natural amino acid). For **8ab**, a characteristic NOE was observed between H-5 (imidazolidinone) and the ortho proton of the 4-fluorophenyl group at C-4 (7.6%), and between the methyl proton at C-5 and the ortho proton of the phenyl group at C-4 (2.1%). For **8ba**, a characteristic NOE was observed between H-5 (imidazolidinone) and the ortho proton of the phenyl group at C-4 (7.5%), and between the methyl proton at C-5 and the ortho proton of the 4-fluorophenyl group at C-4 (2.0%). These results supported the absolute configurations of **8ab** and **8ba** as 4*S*,5*S* and 4*R*,5*S*, respectively. The absolute configura-

(17) The enantiomeric excesses of the Bz-imines **7da**, **7db**, and **7ea** were the same as those of the substrate imines **4d** and **4e**. From these results, no enolization occurred because of the bulkiness of the isopropyl group.

(18) **8ab** and **8ba** were prepared by removal of Boc and diphenylphosphinoyl groups from **5ab** and **5ba** consecutive treatment with 1,1′-carbonyldiimidazole, respectively.

TABLE 3. Conversion of the Adducts 5 to Diamines 10



5 9 10

entry	substrate	ee (%)	R^1	R^2	R^3	product	time (h)	yield (%)[a]	product	time (h)	yield (%)[a]	de (%)[b]	ee (%)[c]
1	**5aa**	98	Me	Ph	Ph	**9aa**	4	97	**10aa**	2	64 (89)		99
2	**5ab**	99	Me	Ph	4-F-C_6H_4	**9ab**	1.5	98	**10ab**	4	72	95	98
3	**5ba**	98	Me	4-F-C_6H_4	Ph	**9ba**	1.5	95	**10ba**	4	64	86	98
4	**5bb**	99	Me	4-F-C_6H_4	4-F-C_6H_4	**9bb**	1.5	97	**10bb**	2	73		99

[a] Isolated (HPLC assay) yield. [b] Determined by reversed-phase HPLC analysis. [c] Determined by chiral HPLC analysis.

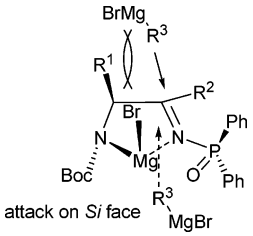


FIGURE 2. Proposed transition state model of the addition.

tions of **5ac**, **5ad**, **5ca**, **5db**, and **5ea** were similarly assigned.

Although moderate yields were attained in the present system, the addition of a strongly basic Grignard reagent such as phenylmagnesium bromide or methylmagnesium bromide to an enolizable imine has generally resulted in lower yields because of their propensity to act as a base. Nitrogen−magnesium bond formation on the α-amino group would reduce the acidity of the α-proton of the imines. Moreover, excellent diastereoselectivities were also obtained. These results could be rationalized by invoking a chelation mechanism through a five-membered transition structure by coordination of magnesium ion on nitrogen atom to ketimine nitrogen as shown in Figure 2.[19] Magnesium ion activates unreactive ketimine and Grignard reagent approaches the less-hindered *Si* face of the C=N bond. This proposal is supported by the results obtained from reactions performed in the coordinating THF solvent: decreased adduct formation and increased enamine formation (Table 1, entry 7).

It is well-known that the diphenylphosphinoyl group can be removed under acidic conditions.[9] Accordingly, we expected that diphenylphosphinoyl and Boc groups in the adducts would be simultaneously removed under acidic conditions.[20] However, the diphenylphosphinoyl group was not removed by the usual acidic conditions, although the Boc group was easily removed by treatment with HCl in ethyl acetate to give monoamide **9** quantitatively. Regardless of further trials under many acidic conditions, removal of the diphenylphosphinoyl group from **9** to the desired diamine **10** did not occur.[21] We thought this difficulty of removal could be due to steric hindrance around the diphenylphosphinoyl group. To overcome this difficulty, an alternative approach was required. In efforts to decrease the bulkiness of the protecting group, removal of the oxygen atom from the diphenylphosphinoyl group was investigated. Furthermore, it has been reported that aminophosphines readily react with an alcohol to afford an alkyl phosphinate under milder reaction conditions than that for the corresponding phosphorus(V) adduct.[22] One can envision that reduction to the aminophosphine would allow it to react smoothly with water to liberate diphenylphosphinic acid. On the basis of this idea, reduction conditions were extensively studied with use of trichlorosilane,[23a] triethoxysilane,[23b] and lithium aluminum hydride.[23c] We found that reduction with trichlorosilane in the presence of triethylamine in toluene at 70 °C efficiently cleaves the diphenylphosphinoyl group even from a bulky α,α-dibranched amine as shown in Table 3.[24] Adduct **5** was typically transformed to the desired diamine **10** via cleavage of the Boc group as depicted in Table 3. Under these conditions, no racemization was observed; **10aa**, **10ab**, **10ba**, and **10bb** were obtained in 98−99% ee, and **10ab** and **10ba** were obtained in 95% de and 86% de, respectively.

Conclusion

We have demonstrated the first example of a diastereoselective addition of aryl and alkyl Grignard reagents to *N*-diphenylphosphinoyl ketimines derived from amino acids. The reaction proceeds in moderate to good yield (up to 75%) and good to excellent diastereoselectivity (up to >96% de). In addition, cleavage of the resulting phosphinoyl amide to the desired amine was efficiently achieved via a trichlorosilane/triethylamine protocol. This methodology provides a novel process for the preparation of trisubstituted 1,2-ethylenediamines. Asymmetric reactions with these chiral diamines are currently under investigation.

Experimental Section

General Procedure for Synthesis of *N*-Diphenylphosphinoyl Ketimines (4). A typical experimental procedure was exemplified by the synthesis of **4a** (Scheme 1): Phenylmagnesium bromide (1.03 M, THF solution, 52 mL, 53.8 mmol) was dropwise added to a stirred suspension of **1a** (5.00 g, 21.5 mmol) in THF (50 mL) at 0 °C, and the mixture was stirred for 13.5 h at 25 °C. After the mixture was cooled to 0 °C, aqueous $KHSO_4$ solution (8.79 g, 64.6 mmol in 75 mL of water) was added. The reaction mixture was stirred at ambient temperature for 30 min and extracted with *tert*-butyl methyl

(19) We consider that *Z*-ketimines converted to *E*-isomers in the reaction system and *E*-ketimines constructed a five-membered transition structure by coordination of magnesium ion on nitrogen atom to ketimine nitrogen. It is reported that *N*-diphenylphosphinoyl ketimines exist in a very fast equilibrium between *E*- and *Z*-isomers, see: Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634−5635.

ether (50 mL × 2). The organic layer was washed with water (50 mL) and brine (25 mL), dried over Na_2SO_4, and concentrated in vacuo. Crude ketone **2a** (5.85 g) was obtained as a colorless solid. Crude **2a** (5.85 g, 21.5 mmol) was dissolved in ethanol (107 mL). To it was added hydroxylamine hydrochloride (3.74 g, 53.8 mmol), sodium acetate (4.41 g, 53.8 mmol), and water (21 mL). The mixture was stirred for 1.5 h under reflux, cooled to room temperature, neutralized with saturated aqueous $NaHCO_3$ (27 mL), and concentrated under reduced pressure to remove ethanol. The residual solution was extracted with ethyl acetate (27 mL × 3). The organic layer was dried over Na_2SO_4, and concentrated in vacuo. The residue was passed through a pad of silica gel (heptane/ethyl acetate = 20/1 to 4/1). Crude oxime **3a** (5.82 g) was obtained as a colorless solid. Crude **3a** (5.82 g, 21.5 mmol) was dissolved in THF (57 mL), followed by the addition of triethylamine (3.6 mL, 25.8 mmol), and the mixture was cooled to −30 °C. Chlorodiphenylphosphine (4.1 mL, 22.6 mmol) was added dropwise at −30 °C, and the mixture was stirred for 3 h at the same temperature. It was then warmed to room temperature over 30 min. Water (57 mL) was added and the organic layer was separated. The aqueous layer was extracted with *tert*-butyl methyl ether (57 mL × 2). The combined organic layer was washed with brine (13 mL), dried over Na_2SO_4, and concentrated in vacuo. The orange oily residue was chromatographed on silica gel (heptane/*tert*-butyl methyl ether = 4/1 to 2/1) to give **4a** as a colorless solid (7.21 g, 75%).

***tert*-Butyl (*Z*)-*N*-{(2*S*)-1-[(diphenylphosphinoyl)imino]-1-phenyl-2-propyl}carbamate (4a):** A colorless solid. Mp: 149−151 °C. $[\alpha]^{26}_D$ −20.6 (*c* 1.02, $CHCl_3$, 99% ee). HPLC: DAICEL CHIRALPAK AD (hexane/2-propanol = 9/1, flow 0.5 mL/min) t_R 22.0 min (minor) and 27.9 min (major). ^{1}H NMR: δ 8.10−8.03 (m, 4H), 7.90 (m, 2H), 7.69 (d, J = 9.5 Hz, 1H), 7.56 (dd, J = 7.5, 7.3 Hz, 1H), 7.51−7.43 (m, 6H), 7.39 (m, 2H), 5.43 (dq, J = 9.5, 7.2 Hz, 1H), 1.48 (d, J = 7.2 Hz, 3H), 1.22 (s, 9H). ^{13}C NMR: δ 186.9 (d, J = 9 Hz), 159.7, 155.6, 138.2 (d, J = 22 Hz), 134.2, (d, J = 141 Hz), 133.9 (d, J = 129 Hz), 132.5, 132.0 (d, J = 9 Hz), 131.5 (d, J = 3 Hz), 131.4, 128.7 (d, J = 15 Hz), 128.5 (d, J = 13 Hz), 128.4 (d, J = 13 Hz), 79.0, 49.9 (d, J = 11 Hz), 28.2, 19.4. IR (KBr): ν 3238, 3057, 2975, 1707, 1637, 1534, 1440, 1365, 1274, 1231, 1182, 1122, 1098, 1024, 856, 725, 698, 552, 525 cm^{-1}. HRFABMS *m*/*z* calcd for $C_{26}H_{29}N_2O_3PH$ (MH^+) 449.1994, found 449.1990.

***tert*-Butyl (*Z*)-*N*-{(2*S*)-1-[(diphenylphosphinoyl)imino]-3-methyl-1-phenyl-2-butyl}carbamate (4d):** A colorless solid. Mp: 49−54 °C. $[\alpha]^{27}_D$ −22.6 (*c* 1.04, $CHCl_3$, 96% ee). HPLC: DAICEL CHIRALPAK AD (hexane/2-propanol = 9/1, flow 0.5 mL/min) t_R 12.6 min (minor) and 19.2 min (major). ^{1}H NMR: δ 8.10 (d, J = 7.5 Hz, 2H), 8.04 (m, 2H), 7.90 (dd, J = 12.0, 7.2 Hz, 2H), 7.61−7.37 (m, 10H), 5.03 (dd, J = 9.5, 9.4 Hz, 1H), 2.34 (m, 1H), 1.27 (s, 9H), 1.02 (d, J = 6.6 Hz, 3H), 0.67 (d, J = 6.8 Hz, 3H). ^{13}C NMR: δ 186.9, 156.1, 140.2 (d, J = 22 Hz), 134.1 (d, J = 133 Hz), 134.0 (d, J = 138 Hz), 132.3, 131.8 (d, J = 9 Hz), 131.6 (d, J = 9 Hz), 131.6 (d, J = 3 Hz), 131.5 (d, J = 3 Hz), 128.8 (d, J = 10 Hz), 128.6 (d, J = 13 Hz), 128.4 (d, J = 13 Hz), 78.9, 60.0 (d, J = 10 Hz), 32.7, 28.2, 20.1, 19.8. IR (KBr): ν 3448, 3276, 3059, 2972, 2930, 2871, 1706, 1639, 1508, 1439, 1366, 1288, 1235, 1181, 1121, 1106, 1004, 726, 695, 550, 526 cm^{-1}. HRFABMS *m*/*z*.calcd for $C_{28}H_{33}N_2O_3PH$ (MH^+) 477.2307, found 477.2325.

4b, **4c**, and **4e** were prepared analogously. Their analytical and spectroscopic data are compiled in the Supporting Information.

General Procedure for Grignard Addition to *N*-Diphenylphosphinoyl Ketimines (4). Typical experimental procedure was exemplified by the addition of 4-fluorophenylmagnesium bromide to **4a** in toluene at 0 °C (entry 2 in Table 2): To a stirred solution of **4a** (500 mg, 1.11 mmol) in toluene (10 mL) at 0 °C was added 4-fluorophenylmagnesium bromide (1.0 M, THF solution, 3.3 mL, 3.33 mmol). After the mixture was stirred at 0 °C for 3 h, to it was added aqueous $KHSO_4$ (0.446 M, 10 mL, 4.46 mmol). After stirred for 30 min, the reaction mixture was extracted with ethyl acetate (10 mL × 3). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The colorless solid residue was chromatograped on silica gel (heptane/ethyl acetate = 7/3) to give **5ab** as a colorless solid (454 mg, 75%).

***tert*-Butyl *N*-{(1*S*,2*S*)-1-[(diphenylphosphinoyl)amino]-1-(4-fluorophenyl)-1-phenyl-2-propyl}carbamate (5ab):** A colorless solid. $[\alpha]^{26}_D$ −66.0 (*c* 1.02, $CHCl_3$, 99% ee, 94% de). HPLC: DAICEL CHIRALPAK AD (hexane/2-propanol = 4/1, flow 0.5 mL/min) t_R 18.4 min (minor) and 45.5 min (major). ^{1}H NMR: δ 7.76 (m, 2H), 7.64 (m, 2H), 7.41−7.19 (m, 14H), 6.49 (dd, J = 8.7, 8.7 Hz, 2H), 4.98 (dq, J = 9.6, 6.8 Hz, 1H), 4.56 (br, 1H), 1.46 (s, 9H), 1.02 (d, J = 6.6 Hz, 3H). ^{13}C NMR: δ 161.7 (d, J = 247 Hz), 156.5, 142.0, 134.4 (d, J = 127 Hz), 134.2 (d, J = 131 Hz), 132.5 (d, J = 6 Hz), 131.7 (d, J = 10 Hz), 131.3, 131.2, 130.8, 128.3 (d, J = 12 Hz), 127.9 (d, J = 13 Hz), 127.7, 127.4, 127.2, 113.9 (d, J = 21 Hz), 80.0, 68.5, 53.7, 28.4, 17.8. IR (KBr): ν 3431, 3239, 3057, 2978, 2931, 1701, 1605, 1511, 1439, 1366, 1161, 1121, 1053, 860, 754, 720, 698, 540 cm^{-1}. HRFABMS *m*/*z* calcd for $C_{32}H_{34}FN_2O_3PH$ (MH^+) 545.2369, found 545.2364.

***tert*-Butyl *N*-{(1*S*,2*S*)-1-[(Diphenylphosphinoyl)amino]-1-(4-fluorophenyl)-3-methyl-1-phenyl-2-butyl}carbamate (5db).** Yields were determined by HPLC assay with the following conditions: Column, YMC AQ-303 (0.1% aqueous phosphoric acid/acetonitrile = 50/50 to 5/95 in 30 min, flow 1.0 mL/min) t_R 13.1 min (**7db**), 19.7 min (**4d**), and 21.5 min (**5db**). After workup, this product was obtained as a mixture of **5db** and **7db**. Authentic samples were prepared as follows: A mixture of **5db** and **7db** (551 mg) was treated with HCl (4 N, ethyl acetate solution, 2.8 mL) and stirred for 2 h at room temperature. Aqueous NaOH (5 N, 2.3 mL) was added and stirred for 30 min at room temperature. The mixture was extracted with ethyl acetate (2.8 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The pale yellow oily residue was chromatographed on silica gel (heptane/ethyl acetate = 1/1 to $CHCl_3$/methanol = 9/1) to afford des-Boc **5db** as a colorless solid (235 mg) and **7db** as a colorless solid (204 mg). To a stirred solution of des-Boc **5da** (25.9 mg, 0.0548 mmol) in dioxane (0.52 mL) was added aqueous NaOH (1 N, 0.055 mL, 0.0548 mmol) and di-*tert*-butyl dicarbonate (14.3 mg, 0.0655 mmol). After being stirred for 9 h at 40 °C, the mixture was directly subjected to column chromatography (heptane/ethyl acetate = 7/3) to afford **5db** as a colorless solid (24.0 mg, 76%). $[\alpha]^{26}_D$ −31.1 (*c* 1.00, $CHCl_3$, 96% ee, >96% de). HPLC: DAICEL CHIRALPAK AD (hexane/2-propanol = 9/1, flow 0.5 mL/min) t_R 19.9 min (minor) and 33.4 min (major). ^{1}H NMR: δ 7.74 (m, 2H), 7.64 (m, 2H), 7.37−7.26 (m, 13H), 6.51 (dd, J = 8.6, 8.5 Hz, 2H), 5.28 (br, 1H), 4.79 (d, J = 10.4 Hz, 1H), 4.49 (d, J = 7.5 Hz, 1H), 1.86 (m, 1H), 1.48 (s, 9H), 0.95 (d, J = 6.6 Hz, 3H), 0.26 (d, J = 6.2 Hz, 3H). ^{13}C NMR: δ 161.8 (d, J = 247 Hz), 157.3, 142.6, 134.9, 134.6 (d, J = 128 Hz), 134.0 (d, J = 131 Hz), 132.4 (d, J = 8 Hz), 131.8 (d, J = 10 Hz), 131.2 (d, J = 3 Hz), 131.1 (d, J = 3 Hz), 130.8, 128.4, 128.2 (d, J = 3 Hz), 127.9, 127.8, 127.3, 113.9 (d, J = 21 Hz), 79.9, 68.6, 68.4, 28.4, 28.3, 23.7, 17.3. IR (KBr): ν 3441, 3222, 3058, 2964, 2930, 2873, 1703, 1605, 1511, 1439, 1391, 1366, 1232, 1166, 1121, 884, 833, 753, 720, 699, 539 cm^{-1}. HRFABMS *m*/*z* calcd for $C_{34}H_{38}FN_2O_3PH$ (MH^+) 573.2682, found 573.2682.

***N*-{(2*S*)-1-[(Diphenylphosphinoyl)imino]-3-methyl-1-phenyl-2-butyl}-4-fluorobenzamide (7db):** A colorless solid. $[\alpha]^{27}_D$ −199.4 (*c* 0.76, $CHCl_3$, 96% ee). HPLC: DAICEL CHIRALPAK AD (hexane/2-propanol = 4/1, flow 0.5 mL/min) t_R 16.0 min (major) and 41.3 min (minor). ^{1}H NMR: δ 7.94 (dd, J = 13.5, 7.1 Hz, 2H), 7.69 (m, 2H), 7.59 (dd, J = 7.6, 6.4 Hz, 1H), 7.52 (ddd, J = 7.6, 7.3, 3.4 Hz, 2H), 7.42 (m, 2H), 7.33 (dd, J = 7.6, 7.3 Hz, 1H), 7.30−7.28 (m, 3H), 7.14 (ddd, J = 7.8, 7.6, 3.7 Hz, 2H), 7.04 (m, 2H), 6.87 (dd, J = 8.9, 8.5 Hz, 2H), 5.10 (s, 1H), 4.12 (d, J = 1.8 Hz, 1H), 1.39 (m, 1H), 0.78 (d, J = 7.1 Hz, 3H), 0.74 (d, J = 6.4 Hz, 3H). ^{13}C NMR: δ 162.3 (d, J = 248 Hz), 160.9 (d, J = 7 Hz), 142.0 (d, J = 3 Hz),

138.3, 133.1 (d, J = 130 Hz), 132.3 (d, J = 11 Hz), 132.0 (d, J = 3 Hz), 131.9 (d, J = 11 Hz), 131.8 (d, J = 8 Hz), 131.5 (d, J = 3 Hz), 131.4, 129.6, 128.3 (d, J = 14 Hz), 127.3, 127.2, 126.9, 114.1 (d, J = 21 Hz), 75.9, 69.8 (d, J = 6 Hz), 30.0, 21.5, 15.1. IR (KBr): ν 3432, 3221, 3061, 2962, 2933, 2875, 1707, 1602, 1509, 1438, 1385, 1315, 1226, 1121, 1105, 1061, 1016, 843, 806, 752, 727, 699, 591, 529 cm^{-1}. HRFABMS m/z calcd for $C_{30}H_{28}FN_2O_2PH$ (MH^+) 499.1951, found 499.1942.

5aa, **5ac**, **5ad**, **5ba**, **5bb**, **5ca**, **5da**, **5ea**, **7da**, and **7ea** were prepared analogously. Their analytical and spectroscopic data are compiled in the Supporting Information.

(*Z*)-*tert*-Butyl *N*-{α-[(Diphenylphosphinoyl)amino]-β-methylstyryl} carbamate (6a).[25] An authentic sample was prepared according to the following procedure: To a solution of **4a** (100 mg, 0.22 mmol) in THF (2 mL) was added lithium diisopropylamide (2.0 M, 0.33 mL, 0.67 mmol) at −78 °C and the reaction mixture was stirred for 2 h. To it was added water (2 mL) and then the mixture was allowed to warm to room temperature and extracted with ethyl acetate (2 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The pale yellow oily residue was chromatographed on silica gel (heptane/ethyl acetate = 3/2) to afford **6a** as a colorless solid (90 mg, 90%). ^{1}H NMR: δ 7.73 (d, J = 7.7 Hz, 2H), 7.72 (dd, J = 12.4 1.1 Hz, 2H), 7.42 (m, 2H), 7.33−7.30 (m, 5H), 7.11−7.07 (m, 3H), 7.01 (m, 2H), 5.41 (d, J = 6.4 Hz, 1H), 1.86 (d, J = 1.8 Hz, 3H), 1.47 (s, 9H). ^{13}C NMR: δ 153.8, 137.6, 132.2 (d, J = 129 Hz), 131.9 (d, J = 10 Hz), 131.7 (d, J = 3 Hz), 130.2, 128.2 (d, J = 13 Hz), 127.6, 127.2, 125.3, 123.4, 80.1, 28.4, 17.8. IR (KBr): ν 3239, 3058, 2977, 2928, 2871, 1717, 1484, 1440, 1366, 1318, 1247, 1169, 1123, 1069, 895, 780, 752, 729, 696, 540, 513 cm^{-1}. HRFABMS m/z calcd for $C_{26}H_{29}N_2O_3PH$ (MH^+) 449.1994, found 449.2014.

General Procedure for Deprotection of the *N*-*tert*-Butoxycarbonyl Group from 5. A typical experimental procedure was exemplified by the deprotection of the *N*-*tert*-butoxycarbonyl group from **5ab** (entry 2 in Table 3): **5ab** (200 mg, 0.367 mmol) was treated with HCl (4 N, ethyl acetate solution, 1.0 mL) and stirred for 1.5 h at room temperature. Aqueous NaOH (5 N, 0.8 mL) was added with stirring over 30 min. The mixture was extracted with ethyl acetate (1.0 mL × 3). The organic layer was dried over Na_2SO_4, and concentrated in vacuo. **9ab** was obtained as a colorless solid (159 mg, 98%).

(1*S*,2*S*)-1-[(Diphenylphosphinoyl)amino]-1-(4-fluorophenyl)-1-phenyl-2-propylamine (9ab): A colorless solid. $[\alpha]^{26}_D$ −7.8 (*c* 1.05, $CHCl_3$, 99% ee, 94% de). ^{1}H NMR: δ 7.75 (m, 2H), 7.54 (m, 2H), 7.39−7.28 (m, 9H), 7.22−7.15 (m, 4H), 6.53 (dd, J = 8.7, 8.6 Hz, 2H), 5.80 (br, 1H), 4.14 (q, J = 6.4 Hz, 1H), 1.55 (br, 2H), 1.06 (d, J = 6.5 Hz, 3H). ^{13}C NMR: δ 161.8 (d, J = 247 Hz), 141.2 (d, J = 6 Hz), 135.0 (d, J = 129 Hz), 134.9, 133.9 (d, J = 131 Hz), 133.0 (d, J = 8 Hz), 131.6 (d, J = 9 Hz), 131.3 (d, J = 9 Hz), 131.0 (d, J = 3 Hz), 130.7 (d, J = 3 Hz), 129.3, 128.2 (d, J = 13 Hz), 127.8 (d, J = 13 Hz), 127.1, 127.1, 113.6 (d, J = 21 Hz), 68.5, 53.5 (d, J = 3 Hz), 21.4. IR (KBr): ν 3390, 3315, 3210, 3057, 2971, 2932, 2875, 1605, 1511, 1439, 1377, 1236, 1200, 1119, 1071, 1032, 870, 831, 756, 719, 698, 628, 540 cm^{-1}. HRFABMS m/z calcd for $C_{27}H_{26}FN_2OPH$ (MH^+) 445.1845, found 445.1841.

9aa, **9ba**, and **9bb** were prepared analogously. Their analytical and spectroscopic data are compiled in the Supporting Information.

General Procedure for Preparation of Trisubstituted Diamine 10. A typical experimental procedure was exemplified by the preparation of **10ab** (entry 2 in Table 3): To a mixture of **9ab** (100 mg, 0.225 mmol) and triethylamine (0.63 mL, 4.50 mmol) in toluene (3 mL) was added trichlorosilane (0.23 mL, 2.25 mmol) at 0 °C. The reaction mixture was warmed to 70 °C, stirred for 4 h, and cooled to 0 °C. Aqueous NaOH (5 N, 3.0 mL) was carefully added followed by stirring for 10 min at 70 °C and cooled to room temperature. After phase cut, the aqueous layer was extracted with ethyl acetate (3 mL × 3). The combined organic layers were washed with water (3 mL × 2) and extracted with aqueous HCl (1 N, 3 mL × 3). The aqueous layer was washed with ethyl acetate (3 mL × 2), basified by aqueous NaOH (5 N, 1.5 mL), and extracted with ethyl acetate (3 mL × 3). The organic layer was washed with brine (3 mL), dried over Na_2SO_4, and concentrated in vacuo. Crude **10ab** was obtained as a colorless oil. Column chromatography on NH-silica gel (heptane/ethyl acetate = 4/1 to 7/3) afforded pure **10ab** as a colorless solid (39.8 mg, 72%).

Enantiomeric excess of **10ab** was determined by analysis of corresponding imidazolidinone. Diasteromeric excess of **10ab** was determined by reversed-phase HPLC: YMC AQ-303 (0.1% aqueous phosphoric acid/acetonitrile = 95/5 to 90/10 in 20 min, to 80/20 in 10 min, flow 1.0 mL/min) t_R 17.5 min (**10ab**) and 18.2 min (**10ba**).

(1*S*,2*S*)-1-(4-Fluorophenyl)-1-phenyl-1,2-propanediamine (10ab): A colorless solid. $[\alpha]^{27}_D$ +17.6 (*c* 0.82, $CHCl_3$, 98% ee, 95% de). HPLC: DAICEL CHIRALPAK AD (hexane/2-propanol = 4/1, flow 0.5 mL/min) t_R 14.0 min (minor) and 20.6 min (major). ^{1}H NMR: δ 7.51 (dd, J = 8.7, 5.4 Hz, 2H), 7.45 (d, J = 7.5 Hz, 2H), 7.29 (dd, J = 7.9, 7.5 Hz, 2H), 7.19 (dd, J = 7.1, 6.9 Hz, 1H), 6.97 (dd, J = 8.7, 8.6 Hz, 2H), 4.03 (q, J = 6.3 Hz, 1H), 1.54 (br, 4H), 1.00 (d, J = 6.3 Hz, 3H). ^{13}C NMR: δ 160.1 (d, J = 246 Hz), 146.3, 142.8 (d, J = 3 Hz), 128.3 (d, J = 8 Hz), 128.2, 126.5, 126.4, 115.0 (d, J = 21 Hz), 64.0, 52.1, 17.9. IR (KBr): ν 3371, 3288, 3067, 3037, 3000, 2980, 2938, 2875, 1600, 1504, 1446, 1377, 1223, 1154, 1107, 1038, 932, 867, 829, 809, 765, 723, 705, 634, 579, 542 cm^{-1}. HRFABMS m/z calcd for $C_{15}H_{17}FN_2H$ (MH^+) 245.1454, found 245.1459.

10aa, **10ba**, and **10bb** were prepared analogously. Their analytical and spectroscopic data are compiled in the Supporting Information.

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Supporting Information Available: Spectroscopic and analytical data for **4b**, **4c**, **4e**, **5aa**, **5ac**, **5ad**, **5ba**, **5bb**, **5ca**, **5da**, **5ea**, **7da**, **7ea**, **9aa**, **9ba**, **9bb**, **10aa**, **10ba**, **10bb**, **8ab**, and **8ba**; ^{1}H and ^{13}C NMR spectra of **4a**−**e**, **5aa**−**5ad**, **5ba**, **5bb**, **5ca**, **5da**, **5db**, **5ea**, **6a**, **7da**, **7db**, **7ea**, **9aa**, **9ab**, **9ba**, **9bb**, **10aa**, **10ab**, **10ba**, **10bb**, **8ab**, and **8ba**; X-ray crystallographic data for **4a**, and CIF file of **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The diphenylphosphinoyl group is slightly less stable to acid than the Boc group, see ref 9a.

(21) We examined HCl, trifluoroacetic acid, methanesulfonic acid, BF_3·Et_2O, $ZnCl_2$, trimethylsilyl chloride, $AlCl_3$, and $TiCl_4$.

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(24) The assay yield of the desired product in the crude reaction mixture by HPLC did not concur with the isolated yield since isolation of diamines is difficult because of their polar and protic nature (Table 3, entry 1).

(25) Stereochemistry was assigned by consideration of the reaction mechanism.