An Unusual Acyliminium Cyclization and Other Drawbacks during an Attempted Synthesis of a Chiral Primary α-Phosphinoalkanamine

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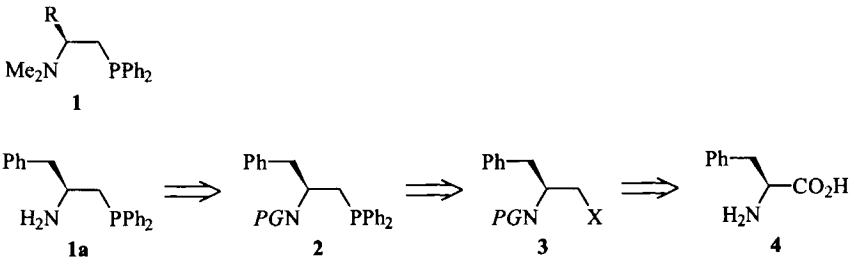
Studies towards the synthesis of a chiral primary α-phosphinoalkanamine **1a** are reported. *O*-Activated, *N*-carbamate-protected phenylalaninol **3a** did not undergo S_N reaction with $KPPh_2$: instead, after *N*-deprotonation, intramolecular substitution led to formation of the aziridine derivative **5a** (*Scheme 2*). *N*-Phthalimido-protected, *O*-activated phenylalaninol **3b** also underwent an intramolecular process on treatment with $KPPh_2$, *i.e.*, an unusual aryl-acyliminium cyclization furnishing the (epoxymethano)isoindolo[1,2-*a*]isoquinolinone **7** (*Scheme 3*). In a reaction with $KPPh_2$, the *N*,*N*-dibenzyl-protected and activated phenylalaninol **3d** finally yielded the intermolecular S_N reaction product **2a** (*Scheme 4*). However, debenzylation by catalytic hydrogenation turned out to be impossible.

Introduction. – Asymmetric C,C-bond-forming reactions are of great significance for the synthesis of optically active compounds, and towards this goal, the application of chiral transition-metal catalysts has become a flourishing field of research. Chelating phosphine ligands are particularly suited for the coordination to late transition metals due to their π-acceptor character, and the preparation of chiral representatives from the readily available starting materials of the chiral pool is an attractive and popular strategy. For example, *Kumada* and coworkers [1] have introduced the *N*,*N*-dimethyl-α-phosphinoalkanamines (= β-(dimethylamino)alkylphosphines) of the general type **1** (*Scheme 1*), which originate from natural α-amino acids, and which have been shown to be highly efficient ligands for catalytic asymmetric *Grignard* cross-coupling reactions applying Ni^{II} or Pd^{II} [2]. In our eyes, the synthesis of analogues like **1a** bearing a primary-amine function seemed to be also an attractive goal. The latter ligands were planned to be applied in our projects on transition-metal-catalyzed *Michael* reactions [3]. Moreover, the presence of the primary amino group should also allow an application as a chiral auxiliary, *e.g.*, after amide or aminocarbene complex [4] formation. A retrosynthetic

Scheme 1. *α-Phosphinoalkanamines: Retrosynthesis*

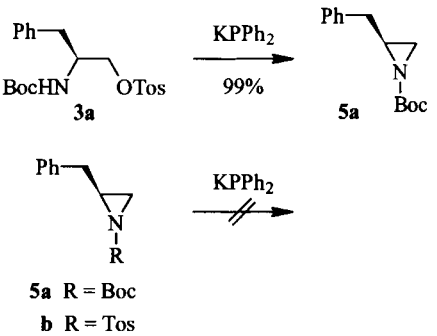


analysis of **1a** seems to be reasonably simple: to introduce the phosphino function by an S_N reaction of **3**, the primary-amine function has to be masked by a protecting group *PG*. The *N*-protected and *O*-activated (X) amino alcohol **3** derives from natural (*S*)-phenylalanine (**4**).

We report on our efforts to prepare **1a**, on the drawbacks which, to date, prevented to finish the synthesis, and, moreover, on an unusual acyliminium cyclization.

Results and Discussion. – *Carbamate as* N-*Protecting Group.* The (*tert*-butoxy)-carbonyl (Boc) group is used extensively in peptide synthesis for amine protection [5]. It is generally understood to be stable to most nucleophiles as well as to basic conditions. However, the *N*-Boc-protected and *O*-activated (by tosylation) (*S*)-phenylalaninol **3a** [6] did not cleanly convert with $KPPh_2$ in THF to an intermolecular S_N reaction product **2**, but instead the *N*-Boc-aziridine **5a** [7] was isolated in quantitative yield (*Scheme 2*). Obviously, under the reaction conditions, **3a** was *N*-deprotonated by $KPPh_2$ followed by intramolecular S_N reaction furnishing the aziridine ring.

Scheme 2. *Carbamate as* N-*Protecting Group, Aziridine Ring-Opening Strategy*



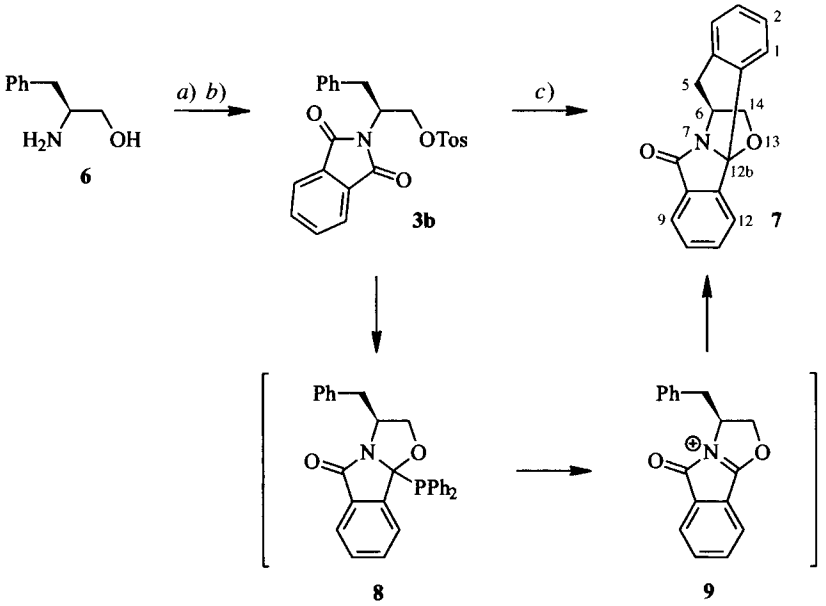
Inspired by this result, we thought a *N*-acceptor-substituted aziridine **5** might serve as an electrophilic synthon for a conversion with $KPPh_2$. But conversion of neither *N*-Boc-aziridine **5a** nor the more electron-withdrawing *N*-Tos-aziridine **5b** [8] led to a ring-opening product **2**, not even with *Lewis*-acid ($ZnCl_2$) assistance. Instead, either no conversion of the aziridine or unspecified decomposition was observed in both cases.

Phthalimide as N-*Protecting Group.* To prevent intramolecular S_N reaction as ascertained in the *N*-Boc case, the *N*-phthalimide moiety was chosen for *N*-protection. This protecting group is more electron-withdrawing, and thus the nucleophilicity at the N-atom is reduced as compared to a carbamate. Moreover, no acidic proton is present thanks to disubstitution at the N-atom. In other words, an intermolecular substitution seemed to be more likely than another intramolecular process.

However, the *O*-activated *N*-phthalimide-protected (*S*)-phenylalaninol **3b**, which was readily accessible by standard procedures [9][10], did not furnish a phosphino derivative **2** upon reaction with $KPPh_2$ in THF. Instead, one single unique product was isolated after workup and chromatography, and, to our surprise, it was elucidated to be the (epoxymethano)-bridged tetracyclic lactam **7** (*Scheme 3*). A mechanistic rationale postulates again an intramolecular S_N reaction; however, in this case, a carbonyl O-atom

replaces the OTos leaving group. The electron density at the nucleophilic O-atom is probably increased by intermediate and reversible addition of $KPPh_2$ to a carbonyl C-atom. The first postulated intermediate is compound **8**, for which actually precedence exists in the literature. *Neidlein* and coworkers [11] were able to isolate a number of phosphinate adducts to a *N*-phthalimido moiety of amino alcohols, which are analogous to **8**. However, they did never observe subsequent elimination of a R_2P anion to give a resonance-stabilized acyliminium ion such as **9**, which we propose as a second intermediate. Cation **9** might undergo an aryl-acyliminium cyclization yielding the bridged tetracyclic skeleton of **7**. Acyliminium cyclizations are well-precedented reactions in organic synthesis [12].

Scheme 3. *Phthalimide as* N-*Protecting Group*



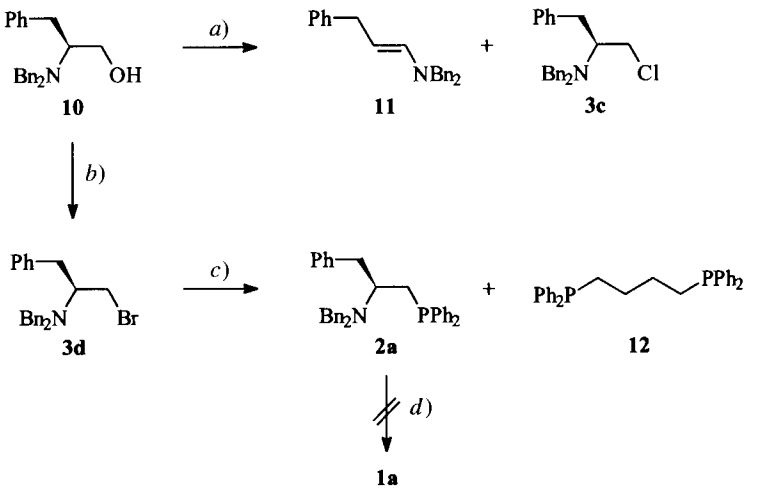
a) Phthalic anhydride, xylene, reflux; 87%, *b*) Pyridine, TosCl; 92%. *c*) $KPPh_2$, THF; 72%.

With respect to configuration, we assume that no epimerization at C(2) of **3b** (amino-acid numbering) takes place during the reaction. Moreover, the cyclization step has to be stereospecific for steric reasons: the epoxymethano bridge has to be attached in *cis*-configuration to the fused isoindolo[1,2-*a*]isoquinoline ring structure. Compound **7** was obtained as a single diastereoisomer. Although the formation of **7** was a drawback in our attempts to synthesize compound **1a**, it seems nevertheless promising to us with respect to novel pathways of amino-alcohol functionalization. Hydrolysis of the lactam as well as the hemi-aminal moiety of **7** would lead to a product which is an *ortho*-aryl-carbonyl derivative of phenylalaninol. The scope of this reaction is presently under investigation in our laboratory.

N,N-*Dibenzyl Protection.* (Dibenzylamino) alcohols derived from α-amino acids were introduced by *Reetz* and coworkers [13], and the corresponding aldehydes have found

manifold applications in stereoselective C,C-bond-forming reactions. We were able to prepare the *N,N*-dibenzylphenylalaninol (**10**) [14] by an improved protocol. The OTos derivative of **10** is not a stable species. At room temperature, it underwent intramolecular substitution to give the corresponding aziridinium tosylate as an intermediate, which further yielded a mixture of the enamine **11** and the chloro derivative **3c** [15] (*Scheme 4*). We thought that a variation of the leaving group might improve the stability of a *N,N*-dibenzyl compound **3**, and thus prepared the bromo derivative **3d**. The latter successfully reacted with $KPPh_2$ in THF to give the *N,N*-dibenzyl-α-phosphinoalkanamine **2a**; however, a significant amount of the bisphosphine **12** [16] (dppb) was also generated, presumably by reductive degradation of the solvent THF (*Scheme 4*). By-product **12** was removed by crystallization followed by chromatography.

Scheme 4. N,N-*Dibenzyl Protection*

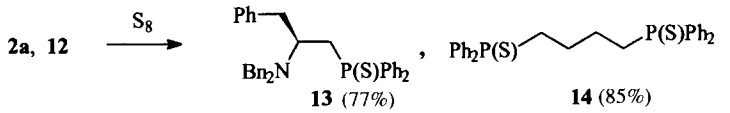


a) Et_3N, TosCl; **11** 52%; **3c** 15%. *b*) $SOBr_2$, THF; 75%. *c*) $KPPh_2$, THF; **2a**, 64%; **12**, 30%. *d*) Pd (up to 10 mol-%), H_2 (up to 4.7 bar), temp. up to 75°; no conversion.

Both compounds **2a** and **12** are air-sensitive due to their tendency to be oxidized to the respective phosphine oxides. Thus, the purification procedure for **2a** had to be accomplished under exclusion of O_2. Moreover, the air sensitivity made a proper analytical characterization impossible in our hands. Therefore, we oxidized an amount of **2a** as well as of **12** with sulfur to the phosphine sulfides **13** and **14** [17], respectively, which were air-stable and crystalline and provided satisfying analytical data (*Scheme 5*).

To date, we were not able to deprotect **2a** by hydrogenolysis. Even applying up to 10 mol-% Pd/C, temperatures up to 75°, and pressures up to 4.7 bar H_2 did not yield any

Scheme 5. *Oxidation of Phosphines with Sulfur*



debenzylated product **1a**. In all cases, **2a** was recovered. Choice of Pt as the catalyst led to arene hydrogenation. We do not know so far whether the lack of reactivity is caused by the steric congestion generated by the Ph_2P group, or whether the phosphino group poisoned the catalyst by irreversible coordination. Experiments on *Lewis*-acid-assisted debenzylation [18] are subject of current efforts in our laboratory.

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Experimental Part

General. All reagents used were commercially available. Compounds **3a** [6], **5b** [8], and **6** [19] were prepared according to the literature. The synthetic protocols for **10** [13][14] and **3d** [15] represent significantly improved procedures. All operations involving $SOBr_2$, $KPPh_2$, and alkyldiarylphosphines were carried out in flame-dried glassware under Ar. Anaerobic conditions are particularly required for the workup including chromatography of alkyldiarylphosphines. Solvents and reagents were dried according to standard procedures and Ar-saturated. Column chromatography was accomplished with *Merck* silica gel (type *60*, 0.063–0.200 mm) using *t*-butyl methyl ether (*t*-BuOMe). Optical rotations: *Perkin Elmer Polarimeter 341*. IR: *Nicolet Magna IR 750*; in cm^{-1}. ^{1}H-NMR: *Bruker AM 400* (400 MHz) and *AC 200* (200 MHz). ^{13}C-NMR: *Bruker AM 400* (100 MHz) and *AC 200* (50 MHz); assignments by DEPT experiments. ^{31}P-NMR: *Bruker ACX 300* (121.5 MHz) and *AC 200* (81 MHz), external standard PPh_3 (= – 6.0 ppm). GC and GC/MS: *HP 5890 II* with FID or *HP MSD 5971A*. MS: Varian *MAT 711* and *MAT 955Q* (high resolution); *m/z* (rel. %). Elemental analysis: *Analytik Jena Vario EL*.

tert-*Butyl (S)-2-Phenylaziridine-1-carboxylate* (**5a**). At –78°, a soln. of 0.5M $KPPh_2$ in THF (5.00 ml, 2.50 mmol) was added to a solution of *N*-Boc-*O*-Tos-phenylalaninol (**3a**; 1.01 g, 2.50 mmol) in THF (5 ml). After warming up to r.t., the mixture was stirred overnight and then partitioned between H_2O (20 ml) and CH_2Cl_2 (3 × 10 ml). After drying of the combined org. layers ($MgSO_4$) and evaporation, chromatography (SiO_2, *t*-BuOMe; R_f 0.11) yielded **5a** (580 mg, 99%). Colorless solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.43 (*s*, 9 H); 2.01–2.04 (*m*, 1 H); 2.28–2.32 (*m*, 1 H); 2.56–2.72 (*m*, 2 H); 2.89–3.03 (*m*, 1 H); 7.27–7.33 (*m*, 5 H). ^{13}C{^{1}H}-NMR ($CDCl_3$, 50 MHz): 27.62 (Me); 31.05 (CH_2); 38.01 (CH); 38.13 (CH_2); 80.66 (C); 126.24 (CH); 128.13 (CH); 128.50 (CH); 137.74 (C); 162.06 (C=O). GC/MS: 233 ($C_{14}H_{19}NO_2^+$, M^+; calc. 233.31).

*(–)-(S)-1-{{[4-(Methylphenyl)sulfonyl]oxy}methyl}-2-phenylethyl}-1*H*-isoindol-1,3(2*H*)-dione* (**3b**). A mixture of phthalic anhydride (2.96 g, 20.0 mmol), L-phenylalaninol (**6**) (3.03 g, 20.0 mmol), and xylene (50 ml) was heated in a *Dean-Stark* trap for 3 h. Hexane (150 ml) was added to the hot mixture, and part of the product crystallized at 0° overnight. The supernatant was evaporated and the residue recrystallized from toluene/hexane 1:3 (100 ml) to give a total amount (4.86 g, 87%) of *(–)-(S)-2-[1-(hydroxymethyl)-2-phenylethyl]-1*H*-isoindole-1,3(2*H*)-dione*. Colorless crystals. M.p. 98.5°. $[\alpha]_D^{r.t.} = -130$ (*c* = 5.7 g/l, $CHCl_3$). IR (ATR): 3460*m*, 3028*w*, 2842*w*, 1772*m*, 1705*vs*, 1468*m*, 1395*s*, 1370*s*, 1117*m*, 1033*m*, 874*m*, 720*s*, 701*m*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.75 (br. *s*, OH); 3.20 (*d*, *J* = 8.1, PhCH_2); 3.93 (*dd*, *J* = 11.9, 3.5, 1 H, CH_2O); 4.07 (*dd*, *J* = 11.9, 7.1, 1 H, CH_2O); 4.64 (*tdd*, *J* = 8.0, 7.3, 3.4, CHN); 7.14–7.18 (*m*, 1 H); 7.20–7.23 (*m*, 4 H); 7.68–7.71 (*m*, 2 H); 7.76–7.79 (*m*, 2 H). ^{13}C{^{1}H}-NMR ($CDCl_3$, 50 MHz): 34.57 (CH_2); 55.09 (CH); 62.41 (CH_2); 123.06 (CH); 126.44 (CH); 128.33 (CH); 128.82 (CH); 131.40 (C); 133.84 (CH); 137.31 (C). EI-MS (70 eV): 281 (14, M^+), 250 (30, $[M - CH_2OH]^+$), 190 (100, $[M - C_7H_7]^+$), 172 (42, $[M - C_7H_7 - H_2O]^+$), 134 (48, $C_7H_7CH{=}CHOH^+$). HR-MS: 281.1052 (calc. 281.1052). Anal. calc. for $C_{17}H_{15}NO_3$ (281.31): C 72.58, H 5.37, N 4.98; found: C 72.58, H 5.37, N 5.00.

An amount of the above isoindoledione (1.55 g, 5.51 mmol) was added to a suspension of TosCl (1.05 g, 5.51 mmol) in pyridine (1 ml) and CH_2Cl_2 (1 ml). After stirring overnight at r.t., 1M HCl (50 ml) was added, and the mixture extracted with CH_2Cl_2 (3 × 10 ml). The combined org. layer was washed with Na_2CO_3 soln., dried (Na_2SO_4), and evaporated. Chromatography (SiO_2, hexane/*t*-BuOMe 1:5; R_f 0.48) yielded **3b** (2.21 g, 92%). Colorless crystals. M.p. 55°. $[\alpha]_D^{r.t.} = -70$ (*c* = 9.7 g/l, $CDCl_3$). IR (ATR): 3064*m*, 3030*m*, 2958*m*, 2926*m*, 1775*s*, 1711*vs*, 1598*m*, 1468*m*, 1456*m*, 1385*s*, 1362*vs*, 1190*s*, 1177*vs*, 1096*m*, 1003*s*, 981*s*, 874*m*, 832*s*, 815*m*, 789*m*, 752*m*, 721*s*, 702*m*, 666*s*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.35 (*s*, Me); 3.08 (*dd*, *J* = 13.9, 6.4, 1 H, PhCH_2); 3.19 (*dd*, *J* = 13.8, 9.0, 1 H, PhCH_2); 4.27–4.30 (*m*, CHN); 4.67–4.78 (*m*, CH_2O); 7.08–7.23 (*m*, 7 H); 7.64–7.73 (*m*, 6 H). ^{13}C{^{1}H}-NMR ($CDCl_3$, 50 MHz): 21.30 (Me); 34.14 (CH_2); 51.23 (CH); 68.07 (CH_2); 122.85 (CH); 126.65 (CH); 127.41 (CH); 128.33 (CH); 128.47 (CH); 129.52 (CH); 131.00 (C); 132.34 (C); 133.72 (CH); 135.90

(C); 144.51 (C); 167.36 (C=O). EI-MS (70 eV): 436 (4, $[M + H]^+$), 264 (86, $[M - C_7H_7SO_3]^+$), 117 (64, $C_7H_7CH{=}CH^+$), 91 (100, $C_7H_7^+$). HR-MS: 436.1221 ($[M + H]^+$, calc. 436.1219). Anal. calc. for $C_{24}H_{21}NO_5S$ (435.49): C 66.19, H 4.86, N 3.22; found: C 66.28, H 4.91, N 3.24.

(+)-(6S,12bS)-5,6-Dihydro-12b,6-(epoxymethano)-8H-isoindolo[1,2-a]isoquinolin-8-one (**7**). A mixture of **3b** (618 mg, 1.42 mmol) and 0.5M $KPPh_2$ in THF (4.25 ml, 2.13 mmol) was stirred at 65–70° overnight in a sealed flask. The resulting mixture was partitioned between H_2O (5 ml) and CH_2Cl_2 (3 × 5 ml). The combined org. layer was washed with brine (2 ml), dried (Na_2SO_4), and evaporated, and the residue chromatographed (SiO_2, hexane/*t*-BuOMe 1:5; R_f 0.50): **7** (268 mg, 72%). Colorless crystals. M.p. 305°. $[\alpha]_D^{r.t.} = +48$ ($c = 1.5$ g/l, $CHCl_3$). IR (ATR): 3026*m*, 2926*m*, 2895*m*, 1718*vs*, 1610*m*, 1465*m*, 1340*s*, 1301*s*, 1184*m*, 1102*m*, 1021*m*, 1003*m*, 749*s*, 728*m*, 702*s*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 3.44 (*dd*, $J = 13.4, 9.1$, 1 H, CH_2O); 3.69 (*dd*, $J = 13.6, 6.9$, 1 H, CH_2O); 4.47 (*d*, $J = 6.5$, $CH_2(5)$); 4.76 (*ddt*, $J = 9.1, 6.8, 6.6$, H–C(6)); 7.22–7.45 (*m*, 7 H); 7.56–7.58 (*m*, 1 H). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 50 MHz): 40.36 (CH_2); 57.88 (CH); 76.61 (CH_2); 103.73 (C); 123.79 (CH); 123.82 (CH); 126.73 (CH); 128.62 (CH); 129.35 (CH); 130.33 (CH); 132.46 (C); 132.93 (CH); 137.89 (C); 144.35 (C); 174.85 (C=O). EI-MS (70 eV): 263 (64, M^+), 116 (68, $C_9H_8^+$), 69 (100, $O{=}C{=}N{-}CH{=}CH_2^+$). HR-MS: 263.0941 ($C_{17}H_{13}NO_2^+$, M^+; calc. 263.0946).

(S)-β-[Bis(phenylmethyl)amino]benzenepropanol (**10**). To a suspension of L-phenylalanine (**4**; 67.9 g, 0.411 mol) in H_2O/EtOH 10:1 (300 ml), NaOH (33.0 g, 0.825 mol) and K_2CO_3 (130 g, 0.940 mol) were added. After 2 h stirring at r.t. (→ homogeneous soln.), the mixture was heated to reflux and benzyl bromide (147 ml, 211 g, 1.23 mol) added dropwise over 30 min. After refluxing for another hour and cooling to r.t., the aq. layer was extracted with Et_2O (3 × 100 ml) and the combined org. layer washed with brine, dried ($MgSO_4$), and evaporated: crude N,N-*dibenzylphenylalanine benzyl ester* (178.2 g, 99%) as a colorless solid which was submitted to reduction without further purification. An anal. pure sample was obtained by crystallization from hexane/EtOH 20:1. Colorless crystals. M.p. 71°. IR (KBr): 3060*s*, 3026*s*, 2964*m*, 2855*m*, 2717*w*, 1956*m*, 1879*w*, 1815*w*, 1724*vs*, 1603*m*, 1585*w*, 1550*w*, 1497*s*, 1454*s*, 1372*s*, 1325*s*, 1159*s*, 1124*s*, 752*vs*, 697*vs*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 3.06 (*A* of *ABX*, $J = 14$, 8.1, 1 H, $CH_2(3)$), 3.16 (*B* of *ABX*, $J = 13.9$, 7.4, 1 H, $CH_2(3)$); 3.58 (*d*, $J = 14.0$, 2 H, $PhCH_2N$); 3.74 (*X* of *ABX*, $J = 7.6$, 7.8, H–C(2)); 3.97 (*d*, $J = 13.9$, 2 H, $PhCH_2N$); 5.16 (*A* of *AB*, $J = 12.1$, 1 H, $CH_2(1)$); 5.27 (*B* of *AB*, $J = 12.3$, 1 H, $CH_2(1)$); 7.04–7.06 (*m*, 2 H); 7.17–7.19 (*m*, 4 H); 7.21–7.29 (*m*, 10 H); 7.38–7.42 (*m*, 4 H). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 100 MHz): 35.41 (CH_2); 54.21 (CH_2); 62.16 (CH), 65.77 (CH_2); 126.06; 126.74; 127.97; 128.04; 128.25; 128.32; 128.50; 129.26; 135.83; 137.85; 139.04; 171.77 (C=O). EI-MS (70 eV): 344 (33, $[M - C_7H_7]^+$), 300 (20, $[M - PhCH_2CO_2]^+$), 91 (100, $C_7H_7^+$). Anal. calc. for $C_{30}H_{29}NO_2$ (435.54): C 82.73, H 6.71, N 3.22; found: C 82.66, H 6.81, N 3.13. HR-MS: 435.2209 (M^+; calc. 435.2198).

An Et_2O soln. (150 ml) of *N,N*-dibenzylphenylalanine benzyl ester (154 g, 0.354 mol) was added dropwise to a suspension of $LiAlH_4$ (16.4 g, 0.432 mol) in abs. Et_2O (250 ml) at 0°. The mixture was stirred overnight at r.t., then excessive hydride was carefully hydrolyzed by dropwise addition of H_2O (water-ice cooling bath). Finally, a 5% aq. NaOH soln. (200 ml) was added, the org. layer separated, and the aq. suspension extracted with Et_2O (4 × 300 ml). The combined Et_2O extract was washed with brine, dried ($MgSO_4$), and evaporated, and the colorless crude recrystallized from hexane/AcOEt 2:1 (100 ml): **10** (95.7 g, 82%). Colorless crystals. M.p. 97–98°. $[\alpha]_D^{r.t.} = +42$ ($c = 5.5$ g/l, $CDCl_3$). IR (KBr): 3462*vs*, 3085*m*, 3065*m*, 3031*s*, 2925*s*, 2846*vs*, 1604*s*, 1495*vs*, 1454*vs*, 1403*s*, 1116*s*, 1077*s*, 1033*vs*, 796*s*, 756*vs*, 731*vs*, 791*vs*, 561*s*, 473*s*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.47 (*dd*, $J = 12.9$, 9.4, 1 H, $CH_2(1)$); 3.05 (br. *s*, OH); 3.08–3.17 (*m*, $CH_2(3)$); 3.34–3.41 (*m*, H–C(2)); 3.52 (*d*, $J = 13.2$, 2 H, $PhCH_2N$); 3.54 (*t*, $J = 10.4$, 1 H, $CH_2(1)$); 3.96 (*d*, $J = 13.3$, 2 H, $PhCH_2N$); 7.12–7.14 (*m*, 2 H); 7.20–7.38 (*m*, 13 H). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 100 MHz): 31.68 (CH_2); 53.15 (CH_2); 60.29 (CH); 60.77 (CH_2); 126.15 (CH); 126.53 (CH); 128.45 (CH); 128.91 (CH); 139.01 (C); 139.10 (C). EI-MS (70 eV): 300 (17, $[M - CH_2OH]^+$), 240 (39, $[M - C_7H_7]^+$), 91 (100, $C_7H_7^+$). Anal. calc. for $C_{23}H_{25}NO$ (331.44): C 83.35, H 7.60, N 4.23; found: C 83.30, H 7.70, N 4.21. HR-MS: 331.1853 (M^+, calc. 331.1858).

(–)-(S)-α-(Bromomethyl)-N,N-bis(phenylmethyl)benzeneethanamine (**3d**). $SOBr_2$ (2.00 ml, 5.28 g, 25.4 mmol) was added dropwise to a soln. of **10** (5.61 g, 16.9 mmol) in THF (5 ml). The mixture was stirred 3 h at 50°, then poured into 10% aq. KOH soln. (50 ml) which was, after 10 min stirring, extracted with *t*-BuOMe (3 × 20 ml). The combined ether extracts were dried ($MgSO_4$), evaporated, and chromatographed (SiO_2, hexane/*t*-BuOMe 50:1; R_f 0.20); **3d** (5.01 g, 75%). Viscous oil. $[\alpha]_D^{r.t.} = -6.6$ ($c = 5.4$ g/l, $CDCl_3$). IR (neat): 3060*m*, 3028*s*, 2927*m*, 2802*m*, 1603*m*, 1494*s*, 1453*s*, 1366*m*, 1119*m*, 1072*m*, 1031*m*, 745*s*, 697*vs*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.63 (*dd*, $J = 14.7, 9.4$, 1 H, $CH_2(1)$); 2.81 (*A* of *ABX*, $J = 13.5, 8.2$, 1 H, $CH_2(3)$); 2.88 (*B* of *ABX*, $J = 13.5, 6.3$, 1 H, $CH_2(3)$); 3.38 (*dd*, $J = 14.7, 4.3$, 1 H, $CH_2(1)$); 3.52 (*A* of *AB*, $J = 13.5$, 2 H, $PhCH_2N$); 3.63 (*B* of *AB*, $J = 13.5$, 1 H, $PhCH_2N$); 4.01 (*dddd*, $J = 9.4, 8.2, 6.3, 4.3$, H–C(2)); 6.97–7.01 (*m*, 2 H); 7.12–7.32 (*m*, 13 H). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 50 MHz): 42.56 (CH_2); 53.38 (CH_2); 59.23 (CH_2); 61.23 (CH); 126.19 (CH);

126.46 (CH); 128.18 (CH); 128.26 (CH); 128.94 (CH); 128.99 (CH); 138.71 (C); 138.84 (C). EI-MS (70 eV): 395 (17, M^+), 314 (21, $[M - Br]^+$), 222 (21, $Bn_2NCCH_2^+$), 210 (100, $Bn_2NCH_2^+$), 117 (23, $[M - NBn_2 - HBr]^+$), 91 (74, $C_7H_7^+$). HR-MS: 395.1071 (M^+, $C_{23}H_{24}BrN^+$; calc. 395.1072).

*(S)-α-[(Diphenylphosphino)methyl]-*N,N*-bis(phenylmethyl)benzeneethanamine* (**2a**). A soln. of **3d** (12.8 g, 32.5 mmol) in THF (50 ml) was added at −78° within 1 h to a soln. of 0.5M $KPPh_2$ in THF (57.6 ml, 28.8 mmol). After stirring at −78 to −40° overnight, H_2O (50 ml) was added, the aq. layer extracted with CH_2Cl_2 (3 × 50 ml), the combined org. layer filtered through Na_2SO_4 (5 cm) and then evaporated, and the residue dissolved in toluene/hexane 1:1 (40 ml) and filtered hot. Overnight, **12** (1.81 g, 30% reg. $KPPh_2$) crystallized from the filtrate at −30° (see below). The supernatant was evaporated and the residue chromatographed (SiO_2, hexane/CH_2Cl_2 1:1; R_f 0.50): **2a** (9.21 g, 64% reg. $KPPh_2$). Colorless oil. IR (neat): 3061*s*, 3028*s*, 2928*s*, 2801*s*, 1601*m*, 1495*s*, 1452*s*, 1435*s*, 1265*s*, 1117*m*, 1069*m*, 1028*m*, 739vs, 698vs. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.49–2.55 (*m*, 1 H); 2.58–2.66 (*m*, 1 H); 2.71–2.86 (*m*, 2 H); 2.88–2.94 (*m*, 1 H); 3.44 (*A* of *AB*, J = 13.5, 2 H); 3.56 (*B* of *AB*, J = 13.5, 2 H); 7.05–7.07 (*m*, 2 H); 7.22–7.43 (*m*, 21 H); 7.52–7.56 (*m*, 2 H). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 100 MHz): 35.72 (*d*, J = 9.7, CH_2); 36.27 (*d*, J = 15.3, CH_2); 55.72 (*d*, J = 15.3, CH); 58.88 (*s*, CH_2); 125.84 (*s*); 126.95 (*s*); 128.15 (*d*, J = 2.8); 128.22 (*s*); 128.27 (*s*); 128.34 (*s*); 128.44 (*s*); 129.32 (*d*, J = 2.8); 133.51 (*d*, J = 19.4); 133.97 (*d*, J = 19.4); 136.20 (*d*, J = 16.5); 137.08 (*d*, J = 16.6); 137.00 (*s*); 139.31 (*s*); 140.94 (*s*); 140.98 (*s*). $^{31}P\{^1H\}$-NMR (hexane, 121.5 MHz): −7.82. EI-MS (70 eV): 499 (1, M^+), 424 (15, $[M - Ph + 2H]^+$), 408 (100, $[M - C_7H_7]^+$), 314 (10, $[M - PPh_2]^+$), 222 (16, $[M - HPPh_2 - C_7H_7]^+$), 210 (96, $Bn_2N{=}CH_2^+$), 185 (67, PPh_2^+), 91 (92, $C_7H_7^+$). HR-MS: 499.2422 (M^+, $C_{35}H_{34}NP^+$; calc. 499.2429).

Butane-1,4-diylbis[diphenylphosphine] (**12**): Colorless solid. M.p. 195°. R_f (SiO_2, hexane/CH_2Cl_2 1:1) 0.40. IR (ATR): 3066*m*, 3051*m*, 3020*w*, 2933*m*, 2883*w*, 1480*m*, 1431*s*, 1194*m*, 1187*m*, 1120*m*, 1099*m*, 1027*m*, 744*s*, 741*s*, 721*s*, 695vs. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.57–1.59 (*m*, 4 H); 2.02–2.06 (*m*, 4 H); 7.32–7.42 (*m*, 20 H). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 100 MHz): 27.46 (*d*, J = 13.9; CH_2); 27.66 (*dd*, J = 12.5, 8.3, CH_2); 128.34 (*d*, J = 6.9, CH); 128.44 (*s*, CH); 132.66 (*d*, J = 19.4, CH); 138.76 (*d*, J = 12.5, C). $^{31}P\{^1H\}$-NMR ($CDCl_3$, 121.5 MHz): −16.41 (*s*). EI-MS (70 eV): 426 (38, M^+), 349 (100, $[M^+ - Ph]^+$), 241 (100, $Ph_2PCH_2CH_2CH_2CH_2^+$), 213 (11, $Ph_2PCH_2CH_2^+$), 199 (10, $Ph_2PCH_2^+$), 185 (54, Ph_2P^+), 108 (61, PhP^+), 77 (23, Ph^+). HR-MS: 426.1671 (M^+, $C_{28}H_{28}P_2^+$; calc. 426.1666).

*(S)-α-[(Diphenylphosphinothioyl)methyl]-*N,N*-bis(phenylmethyl)benzeneethanamine* (**13**). Phosphinoamine **2a** (510 mg, 1.00 mmol) was mixed with 0.5M sulfur in toluene (20 ml) and heated to reflux for 5 min. At −30°, the sulfur excess partly crystallized overnight. The supernatant was evaporated and the residue recrystallized from hexane/CH_2Cl_2 1:1 (20 ml): **13** (420 mg, 77%). Colorless crystals. M.p. 38°. $[\alpha]_D^{r.t.} = -1.33$ (c = 15.8 g/l, $CHCl_3$). IR (KBr): 3059*m*, 3026*m*, 2926*m*, 2853*m*, 2822*m*, 2808*m*, 1601*m*, 1495*s*, 1435*s*, 1097*s*, 1072*s*, 752vs, 740vs, 492*s*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.84–2.81 (*m*, 1 H); 2.84–2.96 (*m*, 1 H); 3.01–2.12 (*m*, 1 H); 3.17–3.22 (*m*, 1 H); 3.24 (*d*, J = 13.70, 2 H, $PhCH_2N$); 3.58 (*d*, J = 13.69, 2 H, $PhCH_2N$); 6.91–6.93 (*m*, 2 H); 7.03–7.09 (*m*, 7 H); 7.16–7.28 (*m*, 9 H); 7.42–7.50 (*m*, 3 H); 7.68–7.74 (*m*, 2 H); 7.93–7.97 (*m*, 2 H). $^{13}C\{^1H\}$-NMR: 33.61 (CH_2); 38.73 (*d*, J = 52.7, CH); 54.61 (*d*, J = 5.6, CH_2); 58.54 (CH_2); 126.23 (*d*, J = 115.2); 127.88 (*s*); 127.92 (*s*); 128.00 (*s*); 128.14 (*s*); 128.28 (*s*); 128.38 (*d*, J = 115.2); 128.92 (*s*); 130.68 (*d*, J = 2.8); 130.99 (*d*, J = 2.8); 131.00 (*d*, J = 9.7); 131.17 (*d*, J = 9.7); 131.27 (*d*, J = 77.7); 132.15 (*d*, J = 77.7); 138.34 (*s*); 139.99 (*s*); $^{31}P\{^1H\}$-NMR ($CDCl_3$, 121.5 MHz): 49.18 (*s*). EI-MS (70 eV): 532 (1, $[M + H]^+$), 531 (0.4, M^+), 530 (1, $[M - H]^+$), 440 (33, $[M - C_7H_7]^+$), 408 (14, $[M - C_7H_7 - S]^+$), 313 (83, $[M - Ph_2PS - H]^+$), 222 (76, $[M - Ph_2PS - C_7H_7 - H]^+$), 217 (7, Ph_2PS^+), 210 (30, $Bn_2N{=}CH_2^+$), 185 (12, PPh_2^+), 117 (24, $BnNC^+$), 106 (9, $BnNH^+$), 91 (100, $C_7H_7^+$). Anal. calc. for $C_{35}H_{34}NPS$ (531.70): C 79.06, H 6.45, N 2.63; found: C 78.76, H 6.45, N 2.71. HR-MS: 531.2133 (M^+; calc. 531.2149).

Butane-1,4-diylbis[diphenylphosphine Sulfide] (**14**). Bisphosphine **12** (850 mg, 1.99 mmol) was mixed with 0.5M sulfur in toluene (10 ml) and heated to reflux for 5 min. At −30°, **14** (830 mg, 85%) crystallized overnight. Colorless crystals. M.p. 225°. IR (KBr): 3049*m*, 930*m*, 2905*w*, 2868*w*, 1632*m*, 1479*m*, 1435*s*, 1178*m*, 1103*s*, 841*s*, 770*s*, 721*s*, 691*s*, 610*s*, 523*s*, 492*s*, 415*m*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.69–1.71 (*m*, 4 H); 2.38–2.44 (*m*, 4 H); 7.40–7.49 (*m*, 12 H); 7.73–7.79 (*m*, 8 H). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 100 MHz): 23.32 (*dd*, J = 17.3, 2.1, CH_2); 32.27 (*d*, J = 56.9, CH_2); 128.65 (*d*, J = 11.1, CH); 130.94 (*d*, J = 10.1, CH), 131.26 (*d*, J = 3.0, CH); 132.54 (*d*, J = 80.5, C). $^{31}P\{^1H\}$-NMR (CH_2Cl_2, 121.5 MHz): 40.93 (*s*). EI-MS (70 eV): 490 (4, M^+), 458 (4, $[M - S]^+$), 426 (1, $[M - 2S]^+$), 273 (100, $[M - SPPh_2]^+$), 241 (36, $[M - SPPh_2 - S]^+$), 217 (49, $SPPh_2^+$), 185 (18, PPh_2^+), 140 (9, $SPPh^+$), 108 (7, PPh^+). Anal. calc. for $C_{28}H_{28}P_2S_2$ (490.61): C 68.55, H 5.75; found: C 68.89, H 5.84. HR-MS: 490.1122 (M^+; calc. 490.1107).

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