

142. An Unexpected Transformation of Benzyl Carbamates into α -Azidobenzeneacetamides

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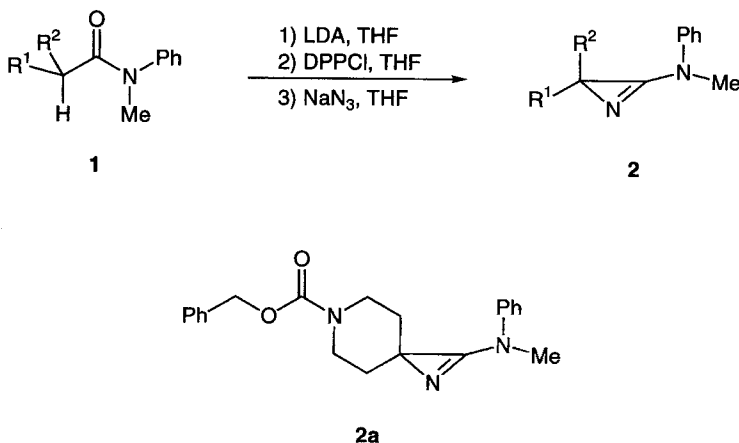
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Successive treatment of benzyl carbamates **5** (Z-protected secondary amines) with lithium diisopropylamide (LDA), diphenyl phosphorochloridate (DPPCl), and NaN_3 yielded the corresponding α -azidobenzeneacetamides **6** in 45–50% yield (*Schemes 2 and 3*). In the case of Z-protected diisopropylamine **5b**, the phosphate **7** was isolated as a minor product. A reaction mechanism for this unexpected transformation is proposed in *Scheme 4*, the key step being the ring closure of a benzylic anion to give an oxirane intermediate **B**. In cursory experiments, it was demonstrated that α -azidobenzeneacetamides **6** can be used as 2-phenylglycine synthons in the formation of dipeptides by using a phosphine-mediated coupling (*Scheme 5*).

Introduction. – Recently, we have described a convenient synthesis of *N*-methyl-*N*-phenyl-2*H*-azirin-3-amines (3-amino-2*H*-azirines) [1–4]. Starting with enolizable *N*-methyl-*N*-phenylamides **1** of carboxylic acids, azirinamines **2** were prepared by consecutive treatment with lithium diisopropylamide (LDA), diphenyl phosphorochloridate (DPPCl), and NaN_3 (*Scheme 1*). In the case of the 2,2-disubstituted azirinamines **2** ($\text{R}^1, \text{R}^2 \neq \text{H}$), diphenyl phosphoroazidate (DPPA) could be used instead of DPPCl/ NaN_3 , whereas in the case of $\text{R}^2 = \text{H}$, reaction of the enolate of **1** and DPPA resulted in an α -amination [5] or a diazo transfer [6].

Scheme 1

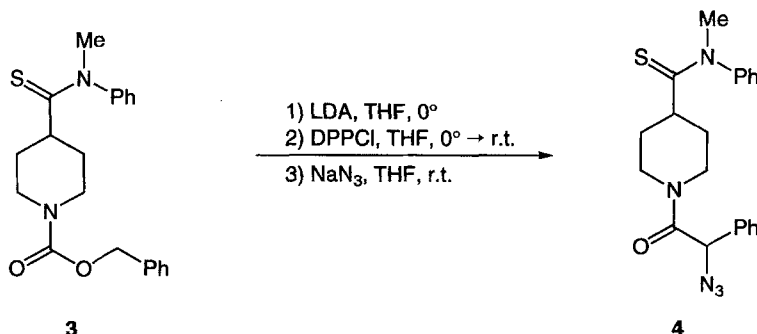


¹⁾ Part of the Ph.D. thesis of C.S., Universität Zürich, 1997.

Within the program of the synthesis of heterospirocyclic azirinamines as synthons for heterocyclic α -amino acids [4], we tried to prepare the *N*-[(benzyloxy)carbonyl]-protected 1,6-diazabicyclo[2.5]oct-1-ene derivative **2a** as a synthon for 4-aminopiperidine-4-carboxylic acid.

Results and Discussion. – Following the protocol of the azirinamine synthesis (*cf.* [4]), a solution of benzyl 4-(*N*-methyl-*N*-phenylthiocarbamoyl)piperidine-1-carboxylate (**3**) in THF was treated with LDA at 0°. Then, DPPCl was added and, after stirring at room temperature for 24 h, the mixture was treated with excess NaN₃. After 3 days, no starting material **3** could be detected, and chromatographical workup gave azido derivative **4** in 47% yield (*Scheme 2*).

Scheme 2



The structure of **4** follows from spectral data and elemental analysis. In the IR spectrum, two strong absorption bands at 2100 and 1650 cm⁻¹ are characteristic for the azido and amide group, respectively. The ESI-MS shows three main peaks at *m/z* 432, 416, and 394 corresponding to $[M + K]^+$, $[M + Na]^+$, and $[M + H]^+$, whereas in the EI-MS, *m/z* 351 ($[M - N_3]^+$) is the base peak. In the NMR spectra, the doubling of signals in (D₆)DMSO at 0° (*e.g.*, 5.52, 5.38 and 62.1, 61.9 ppm (PhCHN₃), 3.60, 3.53 and 45.2, 45.1 ppm (MeN), 206.8, 206.5 ppm (CS), and 166.6, 166.2 ppm (CO)) indicate the presence of two conformers (rotamers); at 100°, the corresponding signals appear at 5.38 and 63.2, 3.60 and 45.3, 208.3, and 166.9 ppm.

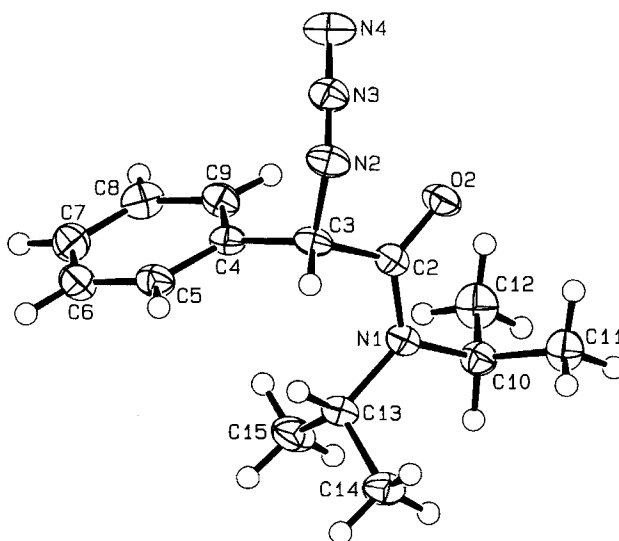
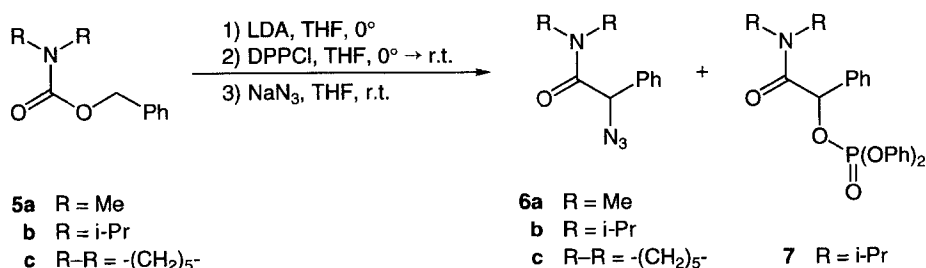
For testing the scope of the unexpected transformation **3** → **4**, we prepared the *Z*-protected secondary amines **5a–c** (*Scheme 3*) by standard methods using benzyl carbonylchloridate (ZCl). Under the above mentioned conditions for the azirinamine synthesis, the α -azidobenzeneacetamides **6a–c** were formed as the main products²⁾. Whereas in the case of **5a**, the starting material was completely consumed, 42 and 28% of **5b** and **5c**, respectively, were recovered. The yields of isolated **6a–c**, calculated with respect to consumed **5**, amounted to 45–50%. In the case of **5b**, phosphate **7** was isolated after chromatography as a by-product in 22% yield.

The structures of the azido-amides **6** were deduced from the spectral data and, in the case of **6b**, it was established by an X-ray crystal-structure determination (*Fig.*).

For the formation of **6** and **7**, we propose the reaction mechanism depicted in *Scheme 4*: Deprotonation at the benzyl position of **5** gives the anion **A** which, in the presence of DPPCl, cyclizes to give the oxiranyl phosphate **B**. This oxirane seems to be

²⁾ Treatment of **5c** with LDA and diphenyl phosphorazidate (DPPA) also yielded **6c** (44%).

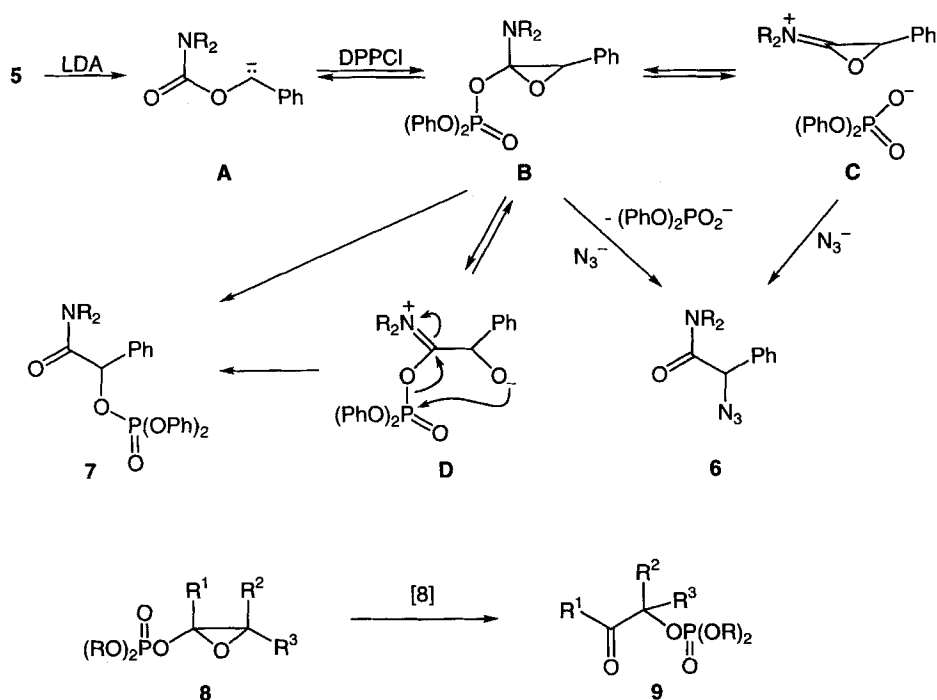
Scheme 3

Figure. ORTEP Plot [7] of the molecular structure of **6b** (with 50% probability ellipsoids)

the crucial intermediate in the formation of the C–C bond between the carbamate C-atom and the benzyl C-atom. Opening of the oxirane ring by nucleophilic attack of N_3^- and elimination of diphenyl phosphate yields azido-amide **6**. A reaction mechanism with initial elimination of diphenyl phosphate from **B** to give the ion pair **C**, followed by ring opening of the oxiraneiminium by N_3^- , is also consistent with the results. Oxiranyl phosphate **B** is also a reasonable intermediate for the formation of **7**. The rearrangement of the phosphate group from C(2) to C(3) and concomitant opening of the three-membered ring leads to **7**. Alternative reaction mechanisms to the concerted rearrangement are the two-step mechanisms *via* the ion pair **C** followed by nucleophilic ring opening by the phosphate anion, and initial ring opening of **B** to give zwitterion **D** which undergoes a 1,4-phosphate shift, respectively. Phosphate **7** could also be a precursor of the azido-amide **6**, the latter being formed *via* a nucleophilic substitution of diphenyl phosphate by the azide ion.

There is a precedent for the rearrangement **B** $\rightarrow$ **7** described by Adam *et al.* [8]. Oxiranyl phosphates of type **8**, prepared by oxidation of enol phosphates with dimethyl-

Scheme 4



dioxirane or with peroxy acids, rearrange smoothly to give the corresponding 2-oxoalkyl phosphates **9** (Scheme 4).

In some preliminary experiments, the azido-amides **6a** and **6c** were tested as 2-phenylglycine (Gly(2Ph)) equivalents for the synthesis of glycyl-2-phenylglycine (Gly-Gly(2Ph)) derivatives. According to Roberts and coworkers [9] (*cf.* also [10] [11]), dipeptide esters are formed from α -azido esters and *N*-protected amino acids by using tertiary phosphines as reducing reagents. The reactive intermediates are iminophosphoranes generated from the azide and the phosphine (*cf.* [12]), and the coupling step most likely proceeds *via* a pentacoordinated P-intermediate [9].

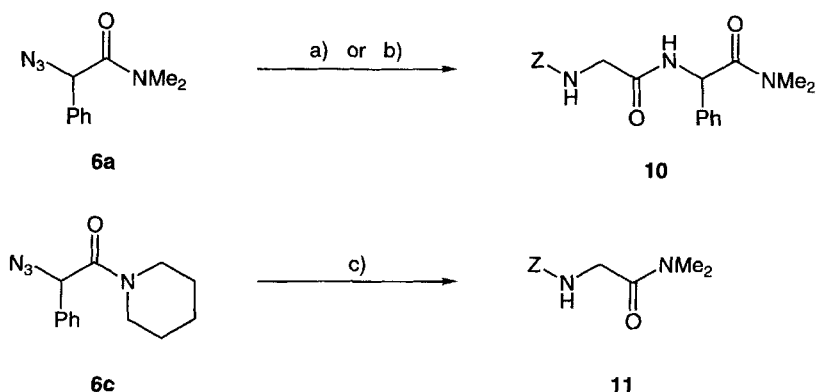
A solution of azido-amide **6a** and an equimolar amount of Bu₃P in toluene was stirred at room temperature for 4 h. After addition of Z-protected glycine (Z-Gly-OH) and heating to 80° for 8 h, the dipeptide derivative Z-Gly-Gly(2Ph)-NMe₂ (**10**, Scheme 5) was obtained in 57% yield³⁾. The same product was prepared in 69% yield *via* catalytic reduction of the azido group of **6a** with H₂ (Pd/C) and coupling of the intermediate α -amino-*N,N*-dimethylbenzeneacetamide (Gly(2Ph)-NMe₂) and Z-Gly-OH using HBPYU⁴⁾ and Et₃N.

With the aim to increase the yields by using more nucleophilic phosphines, we treated azido-amide **6c** with hexamethylphosphorous triamide under the conditions described

³⁾ No reaction was observed when Ph₃P was used instead of the more nucleophilic Bu₃P.

⁴⁾ *O*-(1*H*-Benzotriazol-1-yl)-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate.

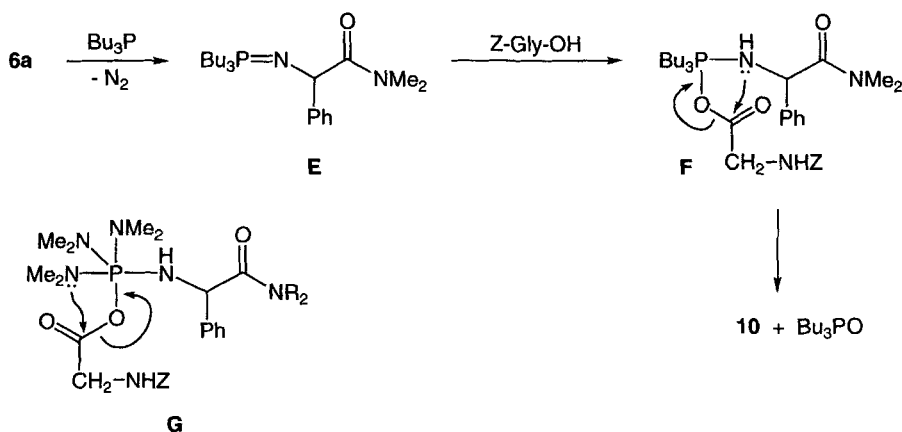
Scheme 5



- a) 1. Bu_3P , toluene, r.t., 4h; 2. Z-Gly-OH, toluene, 80° , 8h.
 b) 1. H_2 , Pd/C, MeOH, r.t., 1h; 2. Z-Gly-OH, HBPYU, Et_3N , CH_2Cl_2 , r.t., 16h.
 c) 1. $(\text{Me}_2\text{N})_3\text{P}$, toluene, r.t., 1h; 2. Z-Gly-OH, toluene, 80° , 8h.

above. Very surprisingly, we isolated the *N,N*-dimethylamide **11** of Z-protected glycine (Z-Gly-NMe₂) as the sole product of the reaction. This result, as well as the peptide coupling, can be rationalized by the same reaction mechanism (Scheme 6).

Scheme 6



As described in [9], the first intermediate is an iminophosphorane, *e.g.*, **E**, which reacts with the carboxylic acid to give the pentacoordinated P-compound **F**. The new peptide bond is then formed *via* an intramolecular acyl transfer in **F** and expulsion of tributylphosphine oxide. Using hexamethylphosphorous triamide, the pentacoordinated P-intermediate corresponding to **F** should be **G**, in which the acyl transfer to a dimethylamino group seems to be preferred.

We thank the analytical sections of our institute for spectra and elemental analyses and Dr. A. Linden for performing the X-ray crystal-structure determination. Financial support by the Swiss National Science Foundation and F. Hoffmann-La Roche AG, Basel, is gratefully acknowledged.

Experimental Part

General. See [4]. If not otherwise stated, IR spectra in CHCl_3 , NMR spectra in CDCl_3 (^1H : 300 MHz; ^{13}C : 75.4 MHz), CI-MS with NH_3 .

1. Azido Derivatives 4 and 6. **1-(2-Azido-2-phenylacetyl)-N-methyl-N-phenylpiperidine-4-carbothioamide (4).** To a soln. of benzyl 4-(N-methyl-N-phenylthiocarbamoyl)piperidine-1-carboxylate (**3**; 1.820 g, 4.939 mmol) in THF (20 ml) at 0° , 2M lithium diisopropylamide (LDA) in THF (3.0 ml, 6.0 mmol) was added, and the mixture was stirred for 1 h. Then, diphenyl phosphorochloridate (DPPCl; 1.49 ml, 5.56 mmol) was added at 0° , the mixture stirred for 1 h at r.t., and NaN_3 (963 mg, 14.81 mmol) added. After stirring at r.t. for 4 h, the precipitate was removed by filtration. Evaporation and CC (SiO_2 , hexane/AcOEt 2:1) of the residue yielded 887 mg (45.7%) of **4**. Pale yellow crystals. M.p. $110\text{--}112^\circ$. IR: 3060w, 3020m (sh), 3000m, 2960m (sh), 2920w, 2860w, 2100s, 1650s, 1595w, 1495s, 1470m, 1450s, 1390m, 1370w, 1355m, 1310w, 1270m, 1220m, 1190m, 1170m, 1120m, 1090m, 1040w, 1025w, 1000w, 990w, 960m, 930w, 910w, 880w, 700s, 660m, 630m. ^1H -NMR (300 MHz, $(\text{D}_6)\text{DMSO}$, 373 K): 7.5–7.3, 7.25–7.2 (2m, 10 arom. H); 5.38 (s, PhCHN_3); 4.1–3.95 (t-like, br., 2 H_{ax} of CH_2NCH_2); 3.60 (s, MeN); 2.75–2.65, 2.55–2.3 (2m, 2 H_{eq} of CH_2NCH_2 , H–C(4)); 1.9–1.75, 1.55–1.45 (2m, CH_2CHCH_2). ^1H -NMR (600 MHz, $(\text{D}_6)\text{DMSO}$, 273 K; 2 conformers): 7.5–7.3 (m, 10 arom. H); 5.52, 5.38 (2s, PhCHN_3); 4.4–4.35, 3.65–3.55 (2m, 2 H_{ax} of CH_2NCH_2); 3.60, 3.53 (2s, MeN); 2.6–2.55, 2.3–2.15, 1.95–1.5, 1.2–1.15, 0.9–0.85 (5m, 2 H_{eq} of CH_2NCH_2 , H–C(4), CH_2CHCH_2). ^{13}C -NMR (75.4 MHz, $(\text{D}_6)\text{DMSO}$, 373 K): 208.3 (s, C=S); 166.9 (s, C=O); 145.8, 135.2 (2s, 2 arom. C); 130.2, 129.2, 129.0, 128.7, 128.1, 126.0 (6d, 10 arom. CH); 63.2 (d, PhCHN_3); 46.4 (d, C(4)); 45.3 (q, MeN); 43.3 (t, CH_2NCH_2); 32.3, 32.0 (2t, CH_2CHCH_2). ^{13}C -NMR (150.9 MHz, $(\text{D}_6)\text{DMSO}$, 273 K; 2 conformers): 206.8, 206.5 (2s, C=S); 166.6, 166.2 (2s, C=O); 144.9, 134.3 (2s, 2 arom. C); 130.0, 129.2, 129.1, 129.0, 128.8, 128.6, 127.8, 127.7, 125.6, 125.5 (10d, 10 arom. CH); 62.1, 61.9 (2d, PhCHN_3); 46.0, 45.9 (2d, C(4)); 45.2, 45.1 (2q, MeN); 44.2, 44.1, 41.3, 41.2 (4t, CH_2NCH_2); 32.4, 31.7, 31.4, 31.2 (4t, CH_2CHCH_2). ESI-MS: 432 (12, $[\text{M} + \text{K}]^+$), 416 (100, $[\text{M} + \text{Na}]^+$), 394 (14, $[\text{M} + 1]^+$). EI-MS: 351 (100, $[\text{M} - \text{N}_3]^+$), 261 (28, $[\text{M} - \text{PhCHN}_3]^+$), 178 (45), 82 (49), 77 (49). Anal. calc. for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{OS}$ (393.51): C 64.10, H 5.89, N 17.80; found: C 63.81, H 5.92, N 17.30.

α -Azido-N,N-dimethylbenzeneacetamide (6a). In analogy to the previous experiment, benzyl N,N-dimethylcarbamate (**5a**; 1.388 g, 7.745 mmol) was treated successively with LDA (4.7 ml, 9.4 mmol), DPPCl (2.289 mg, 8.521 mmol), and NaN_3 (1.523 g, 23.43 mmol). The crude product was bulb-to-bulb distilled at $130^\circ/8 \cdot 10^{-2}$ mbar: 708 mg (45%) of **6a**. Colourless oil. IR (neat): 3060w, 3030w, 2930m, 2140m, 2100s, 1660s, 1600w, 1580w, 1495m, 1455m, 1420m (sh), 1400m, 1300w, 1250m, 1235m, 1180w, 1140m, 1080w, 1060w, 1000w, 970w, 910w, 875m, 840w, 775w, 760w, 720m, 710m, 625m, 610m. ^1H -NMR: 7.45–7.4 (m, 5 arom. H); 4.96 (s, PhCHN_3); 3.00, 2.81 (2s, Me₂N). ^{13}C -NMR: 168.8 (s, C=O); 133.8 (s, 1 arom. C); 129.4, 129.2, 128.0 (3d, 5 arom. CH); 63.7 (d, PhCHN_3); 36.8, 36.1 (2q, Me₂N). CI-MS: 205 (100, $[\text{M} + 1]^+$), 177 (41).

α -Azido-N,N-diisopropylbenzeneacetamide (6b). As in the previous experiment, benzyl N,N-diisopropylcarbamate (**5b**, 1.473 g, 6.259 mmol) was treated with LDA (3.75 ml, 7.5 mmol), DPPCl (1.860 g, 6.924 mmol) and NaN_3 (1.230 g, 18.92 mmol). CC (SiO_2 , hexane/Et₂O 1:3) yielded 474 mg (29%) of **6b**, 615 mg (42%) of **5b**, and 374 mg (13%) of [(diisopropylcarbamoyl)(phenyl)methyl]diphenyl phosphate (**7**).

6b: Colourless crystals. M.p. $104\text{--}105^\circ$. IR: 3060w, 3020m (sh), 3000s, 2970s, 2960m, 2870w, 2440w, 2400w, 2100s, 1650s, 1585w, 1495w, 1470m, 1445s, 1380m, 1370m, 1340m, 1220m, 1180w, 1155m, 1145m, 1075w, 1040m, 1000w, 960w, 915w, 890w, 870w, 710m, 700m, 660w. ^1H -NMR: 7.45–7.25 (m, 5 arom. H); 4.87 (s, PhCHN_3); 3.71 (sept., $J = 6.6$, Me₂CHN); 3.36 (sept., $J = 6.8$, Me₂CHN); 1.48, 1.44 (2d, $J = 6.8$, Me₂CHN); 1.10, 0.65 (2d, $J = 6.6$, Me₂CHN). ^{13}C -NMR: 167.2 (s, C=O); 134.6 (s, 1 arom. C); 129.3, 129.0, 127.8 (3d, 5 arom. CH); 65.0 (d, PhCHN_3); 48.7, 46.5 (2d, (Me₂CH)₂N); 20.6, 19.8, 19.5 (3q, (Me₂CH)₂N). CI-MS: 261 (100, $[\text{M} + 1]^+$). Anal. calc. for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}$ (260.34): C 64.59, H 7.74, N 21.52; found: C 64.43, H 7.86, N 21.69.

7: Colourless oil. IR: 3460w, 3010w, 2970m, 2930m, 2870w, 1720w, 1660s, 1590m, 1490s, 1450m, 1370s, 1345m, 1280s, 1180m, 1160s, 1140w, 1050m, 1025s, 1010m, 950s, 905w, 690m, 605w. ^1H -NMR: 7.4–7.0 (m, 15 arom. H); 6.14 (d, $J = 8.0$, $\text{PhCHOP}(\text{O})(\text{OPh})_2$); 3.85 (sept., $J = 6.6$, Me₂CHN); 3.31 (sept., $J = 6.8$, Me₂CHN); 1.43, 1.36 (2d, $J = 6.8$, Me₂CHN); 1.00, 0.70 (2d, $J = 6.6$, Me₂CHN). ^{13}C -NMR: 165.3 (s, C=O); 150.5, 150.3, 135.1 (3s, 3 arom. C); 129.7, 129.6, 129.1, 128.9, 127.5, 125.3, 125.2, 120.5, 120.2 (9d, 15 arom. CH); 79.1 (d, $\text{PhCHOP}(\text{O})(\text{OPh})_2$); 48.2, 46.4 (2d, (Me₂CH)₂N); 20.5, 19.7, 19.5 (3q, (Me₂CH)₂N). CI-MS: 469 (26), 468 (100, $[\text{M} + 1]^+$), 218 (42, $[\text{M} - \text{OP}(\text{O})(\text{OPh})_2]^+$).

2-Azido-2-phenyl-1-(piperidin-1-yl)ethanone (= 1-[Azido(phenyl)acetyl]piperidine; 6c). a) As in the previous experiment, benzyl piperidine-1-carboxylate (**5c**; 1.606 g, 7.324 mmol) was treated with LDA (4.0 ml, 8.0 mmol), DPPCl (1.65 ml, 8.0 mmol), and NaN_3 (1.428 g, 21.96 mmol). CC (SiO_2 , hexane/AcOEt 2:1) yielded 603 mg (34%) of **6c** and 457 mg (28%) of **5c**. **6c:** Pale yellow oil. B.p. $170^\circ/8 \cdot 10^{-2}$ mbar. IR (neat): 3080w, 3020w, 3000w,

2940m, 2860m, 2100s, 1650s, 1600w, 1585w, 1490m, 1455s (sh), 1445s, 1370w, 1350w, 1300w, 1280m, 1270m, 1245m, 1220s, 1180w, 1160w, 1140m, 1125w, 1080w, 1020m, 960m, 915m, 870m, 850m, 810w, 770w, 760w, 715m, 700m, 670w. ¹H-NMR: 7.45–7.35 (*m*, 5 arom. H); 4.99 (*s*, PhCHN₃); 3.8–3.7, 3.5–3.4, 3.2–3.15 (*3m*, CH₂NCH₂); 1.6–1.45, 1.35–1.2, 1.0–0.95 (*3m*, 3 CH₂). ¹³C-NMR: 166.7 (*s*, C=O); 134.2 (*s*, 1 arom. C); 129.2, 129.0, 127.7 (*3d*, 5 arom. CH); 63.9 (*d*, PhCHN₃); 46.4, 43.4 (*2t*, C(2), C(6) of piperidine); 25.5, 25.3, 24.1 (*3t*, C(3), C(4), C(5) of piperidine). CI-MS: 245 (100, [*M* + 1]⁺), 219 (24), 217 (77), 85 (24), 71 (31), 69 (34).

b) To a soln. of **5c** (1.609 g, 7.338 mmol) in THF (20 ml) at 0°, 2*M* LDA in THF (4.0 ml, 8.0 mmol) was added slowly. After stirring for 2 h at 0°, diphenyl phosphorazidate (DPPA; 1.75 ml, 8.1 mmol) was added and the mixture stirred for 3 days at r.t. The precipitate was removed by filtration and the solvent evaporated. The residue was dissolved in CH₂Cl₂ and washed with 5% NaHCO₃ soln. The combined aq. phase was extracted with CH₂Cl₂ and the org. phase dried (MgSO₄) and evaporated. CC (SiO₂, hexane/Et₂O 2:1) gave 600 mg (33%) of **6c** and 376 mg (23%) of **5c**.

2. *Dipeptides from Azido-amides 6*. α-{2-[(Benzyloxy)carbonyl]amino}ethanoyl]-N,N-dimethylbenzeneacetamide (**10**). a) A soln. of **6a** (37 mg, 0.181 mmol) and Bu₃P (techn. 85%; 55 μl, 0.19 mmol) in dry toluene (1 ml) was stirred at r.t. (slow N₂ evolution). After 4 h, Z-Gly-OH (38 mg, 1.182 mmol) was added and the mixture heated to 80° for 8 h. Then, CH₂Cl₂ was added, the soln. washed with 10% NaHCO₃ soln., brine, and 1*N* HCl, and the aq. layers were extracted with CH₂Cl₂. The combined CH₂Cl₂ phase was dried (MgSO₄) and evaporated and the residue recrystallized from AcOEt: 38 mg (57%) of **10**. Colourless crystals. M.p. 162–163°. IR: 3400w (br.), 3030w (sh), 3000m, 2840w, 1730m, 1690m (sh), 1680m, 1660m (sh), 1650s, 1495s, 1470m (sh), 1455m, 1415m, 1405m, 1335w, 1250m, 1150m, 1090w, 1050w, 920w. ¹H-NMR: 7.51 (br. *d*, *J* = 6.9, 1 NH); 7.4–7.25 (*m*, 10 arom. H); 5.83 (*d*, *J* = 7.3, PhCH); 5.55–5.45 (br. *m*, 1 NH); 5.09 (*s*, PhCH₂O); 3.95–3.8 (*m*, NHCH₂CO); 2.97, 2.88 (*2s*, Me₂N). ¹³C-NMR: 169.3, 167.7 (*2s*, 2 C=O); 156.3 (*s*, OCONH); 136.8, 136.2 (*2s*, 2 arom. C); 129.0, 128.4, 128.3, 128.0, 127.9, 127.8 (*6d*, 10 arom. CH); 67.0 (*t*, PhCH₂O); 53.9 (*d*, PhCH); 44.2 (*t*, NHCH₂CO); 36.8, 35.9 (*2q*, Me₂N). CI-MS: 371 (19), 370 (91, [*M* + 1]⁺), 262 (100, [*M* – PhCH₂O]⁺). Anal. calc. for C₂₀H₂₃N₃O₄ (369.42): C 65.02, H 6.27, N 11.37; found: C 64.86, H 6.28, N 11.36.

b) A suspension of **6a** (35 mg, 0.171 mmol) and 5% Pd/C (5 mg) in abs. MeOH (1 ml) was stirred for 1 h under H₂. Then, the catalyst was removed by filtration through a *Celite* pad and the solvent evaporated. The residue was dissolved in CH₂Cl₂, and Z-Gly-OH (45 mg, 0.215 mmol), *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate (HBPfU; 91 mg, 0.221 mmol), and Et₃N (30 μl, 0.215 mmol) were added. After stirring the soln. for 16 h at r.t., it was washed twice with 1*N* HCl, and the aq. layers were extracted with CH₂Cl₂. The org. phase was dried (MgSO₄) and evaporated. FC (SiO₂, AcOEt/hexane 7:1) and crystallization from AcOEt yielded 44 mg (69%) of **10**. Colourless crystals.

N²-[(Benzyloxy)carbonyl]-N¹,N¹-dimethylglycinamide (Z-Gly-NMe₂; **11**). To an ice-cooled soln. of **6c** (35 mg, 0.143 mmol) in toluene (1 ml), hexamethylphosphorous triamide (26 μl, 0.160 mmol) was added and the mixture stirred for 1 h at r.t. Then, Z-Gly-OH (34 mg, 0.162 mmol) was added and the mixture heated to 80°. After 8 h, CH₂Cl₂ was added, the soln. washed with 10% NaHCO₃ soln., brine, and 1*N* HCl, and the H₂O layers were extracted with CH₂Cl₂. The org. phase was dried (MgSO₄) and evaporated and the residue purified by FC (AcOEt/hexane 7:1): 20 mg (59%) of **11**. Colourless solid. ¹H-NMR: 7.3–7.2 (*m*, 5 arom. H); 5.74 (br. *s*, 1 NH); 5.05 (*s*, PhCH₂O); 3.93 (*d*, *J* = 4.2, CH₂ of Gly); 2.91, 2.89 (*2s*, Me₂N). ¹³C-NMR: 167.8 (*s*, C=O); 156.1 (*s*, OCONH); 136.4 (*s*, arom. C); 128.4, 128.0, 127.9 (*3d*, 5 arom. CH); 66.7 (*t*, PhCH₂O); 42.6 (*t*, CH₂ of Gly); 35.7, 35.5 (*2q*, Me₂N). ESI-MS: 275 (14, [*M* + K]⁺), 260 (13), 259 (100, [*M* + Na]⁺), 237 (29, [*M* + 1]⁺).

Crystal Structure Determination of 6b (see Table and Fig.)⁵⁾. The intensities were collected on a Rigaku-AFC5R diffractometer using graphite-monochromated MoK_α radiation (λ 0.71069 Å) and a 12-kW rotating anode generator. The intensities were corrected for Lorentz and polarization effects, but not for absorption. Data collection and refinement parameters are listed in the Table, and a view of the molecule is shown in the Figure. The structure was solved by direct methods using SHELXS86 [13], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were located in a difference electron density map, and their positions were allowed to refine together with individual isotropic displacement parameters. All refinements were carried out on *F* using full-matrix least-squares procedures. A correction for secondary

⁵⁾ Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-10/57. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44-091223-336033; or email: teched@-ccdc.cam.ac.uk).

Table. Crystallographic Data of Compound 6b

Crystallized from	CHCl ₃ /hexane	D_x [g cm ⁻³]	1.206
Empirical formula	C ₁₄ H ₂₀ N ₄ O	μ (MoK α) [mm ⁻¹]	0.0793
Formula weight	260.34	Scan type	$\omega/2\theta$
Crystal colour, habit	colourless, prism	$2\theta_{(max)}$ [°]	55
Crystal dimensions [mm]	0.30 × 0.33 × 0.50	Total reflections measured	3660
Temperature [K]	173(1)	Symmetry-independent reflections	3287
Crystal system	monoclinic	Reflections used [$I > 2\sigma(I)$]	2459
Space group	$P2_1/n$	Parameters refined	253
Z	4	Final R	0.0508
Reflections for cell determination	25	wR ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$)	0.0457
2θ range for cell determination [°]	37–40	Goodness of fit	2.097
Unit cell parameters	a [Å]	Secondary extinction coefficient	$9.0 \cdot 10^{-7}$
	b [Å]	Final Δ_{max}/σ	0.0004
	c [Å]	$\Delta\rho$ (max; min) [e Å ⁻³]	0.28; -0.23
	β [°]	Range of $\sigma(d(C-C))$ [Å]	0.002–0.003
	V [Å ³]		
	1433.8(6)		

extinction was applied. Neutral-atom scattering factors for non-H-atoms were taken from [14a] and the scattering factors for H-atoms from [15]. Anomalous dispersion effects were included in F_{calc} [16]; the values for f' and f'' were those of [14b]. All calculations were performed using the TEXSAN crystallographic software package [17].

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