Notes

Mild and Selective Palladium(0)-Catalyzed Deallylation of Allylic Amines. Allylamine and Diallylamine as Very Convenient Ammonia Equivalents for the Synthesis of Primary Amines

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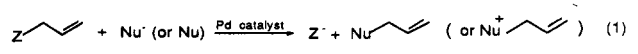
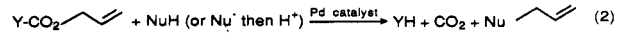
Received March 11, 1993

In addition to being a powerful tool in synthetic organic chemistry, the palladium-catalyzed allylic alkylation reaction (the Tsuji–Trost reaction) has increased the use of allylic groups in protective group chemistry by offering a new general method for deprotection. Of the allylic protecting groups, the allyl group (All) and the allyloxycarbonyl group (Alloc) are the most commonly employed, the former for the protection, *inter alia*, of carboxylic acids, phosphoric acids, or phenols, and the latter for the protection of alcohols and amines. For the palladium-catalyzed removal of these groups (eqs 1 and 2), various



Z = RCO_2, ArO, $(RO)_2P(O)$.

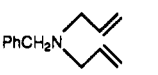
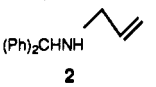
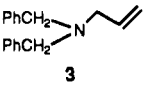
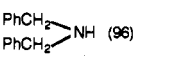
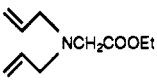
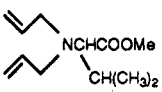
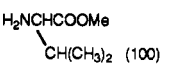
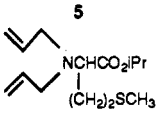
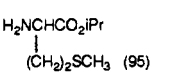


Y = RO, R_2N.

nucleophilic species (Nu^-, NuH) have been used as allyl group scavengers, including oxygen, nitrogen, and carbon nucleophiles, as well as hydride donors[1] (formic acid and tributyltin hydride).

We report herein that *N,N'*-dimethylbarbituric acid (NDMBA, **7**), a carbon nucleophile first proposed by Kunz and März[2] for the deprotection of Alloc derivatives of amines (eq 2), is also a very efficient allyl group scavenger in the palladium-catalyzed deallylation of mono- and diallylamines (eq 1, Z = NR_2). To the best of our knowledge, this deprotection constitutes the first example of a deprotection of allyl derivatives of amines based on π-allyl methodology.[3]

Table I. Deprotection of Allylamines by the Palladium Catalyst/NDMBA System

entry	substrate	temp (°C)	reactn time (h)	product[a] (isolated yield (%))
1	 **1**	30	1.5	$PhCH_2NH_2$ (100)
2	 **2**	30	3	$(Ph)_2CHNH_2$ (91)
3	 **3**	30	1.5	 (96)
4	 **4**	35	2	H_2NCH_2COOEt (92)
5	 **5**	35	2	 (100)
6	 **6**	35	2	 (95)

[a] Isolated as their hydrochloride salts.

We found that *N*-allyl derivatives of primary or secondary amines such as *N,N*-diallylbenzylamine (**1**), *N*-allylbenzhydrylamine (**2**), or *N*-allyldibenzylamine (**3**) were deallylated in 1–3 h by heating them (30 °C) in dichloromethane in the presence of NDMBA (**7**) (1.5 equiv per allyl group) and tetrakis(triphenylphosphine) palladium-(0) (10^{-2} equiv per allyl group). After conventional workup, the deallylated amines could be isolated in virtually quantitative yields as their hydrochloride salts (Table I, entries 1–3). Capillary GC analysis performed on the free bases did not detect any residual allylamines (detection limit <0.5%). Aside from the catalyst, unreacted NDMBA and its 2,2-diallyl derivative **15** were the main side products of the reactions. That the mono-*C*-allyl derivative **8** of NDMBA was detected in small amounts shows that **8**, once formed, acts as a much better allyl scavenger than NDMBA itself.[4]

The palladium-catalyzed deallylation procedure was also successfully tested on *N,N*-diallyl derivatives of α-amino

(1) Merzouk, A.; Guibé, F.; Loffet, A. *Tetrahedron Lett.* **1992**, *33*, 477 and references cited therein.

(2) (a) Kunz, H.; März, J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1375. (b) Braûn, P.; Waldmann, H.; Vogt, W.; Kunz, H. *Synlett* **1990**, 105.

(3) Previously published methods for the deallylation of allylamines involve isomerization to enamines either with potassium *tert*-butoxide (Montgomery, J. A.; Thomas, H. J. *J. Org. Chem.* **1965**, *30*, 3235) or by transition metal (Pd, Rh, Ir) catalysis. The first method involves rather harsh conditions, and, in the second one, careful choice of the catalyst and of the reaction conditions must be exercised to avoid poisoning of the catalyst, competitive reduction of the allyl group to a propyl group, and other side reactions; see for instance: Moreau, B.; Lavielle, S.; Marquet, A. *Tetrahedron Lett.* **1977**, 2591. Sundberg, R. J.; Hamilton, G. S.; Laurino, P. J. *J. Org. Chem.* **1988**, *53*, 976. See also ref 6. The deallylation of allylamines with carbonochloridate reagents (Kapnang, H.; Charles, G. Y. *Tetrahedron Lett.* **1983**, 3233) and, very recently, with a zirconocene species generated *in situ* (Ito, H.; Taguchi, T.; Hanzawa, Y. *J. Org. Chem.* **1993**, *58*, 774) have also been reported.

(4) *This does not mean that using 0.5 equiv of NDMBA per allyl group is enough to ensure complete deallylation of the starting amine.* If NDMBA is not used in excess in terms of acid–base balance (that is, if at some stage of the reaction, the necessary protonation (see later in the text) of the allylamine is going to depend on a prototropic equilibrium with the acidic form of the deprotected amine), then the deallylation process is considerably slower and hardly goes to completion. A possible explanation is that, in a nonpolar solvent such as dichloromethane, the electrophilicity of the allylammonium species is much reduced through association with unprotonated amines. Another possibility is that the unprotonated amines interfere with the catalytic process through coordination to palladium. We determined that the deallylation processes carried out with 1.5 equiv of NDMBA in the presence of an equimolecular amount (based on NDMBA) of triethylamine are extremly slow, at least under the conditions used in this study. We thank one of the reviewers for raising this question.

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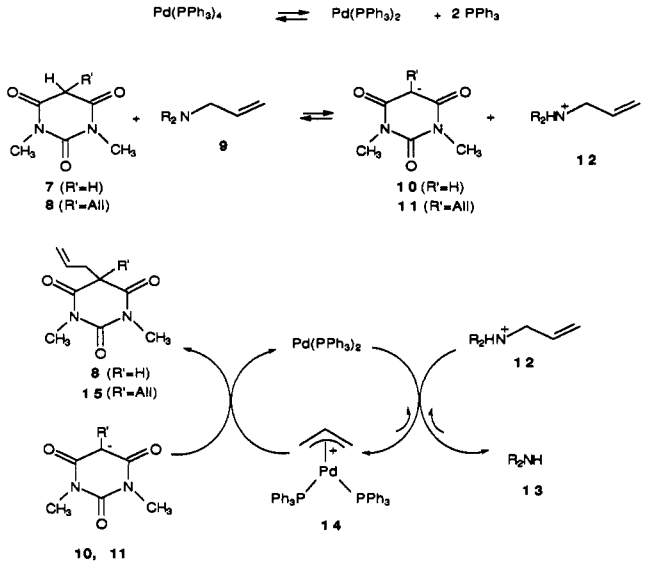
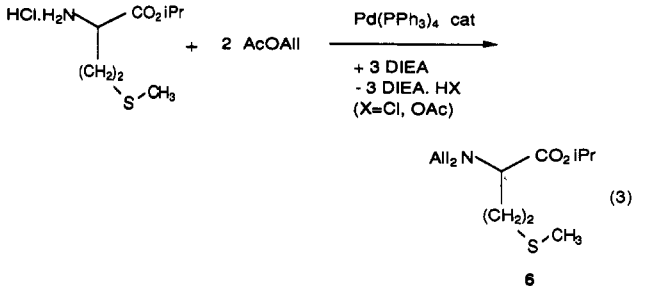
Scheme I



esters (Table I, entries 4–6). Thus, *N,N*-diallylglycine ethyl ester (All_2-Gly-OEt, **4**), *N,N*-diallyl-L-valine methyl ester (All_2-Val-OMe, **5**), and *N,N*-diallyl-L-methionine isopropyl ester (All_2-Met-OiPr, **6**) were selectively deprotected to glycine ethyl ester (Gly-OEt), valine methyl ester (Val-OMe), and methionine isopropyl ester (Met-OiPr), respectively, which were isolated as their hydrochloride salts. After *N*-trifluoroacetylation and analysis on a chiral GC column, the deprotected product from All_2-Met-OiPr was found to consist of 99% of L-Met-OiPr and 1% of D-Met-OiPr. We did not determine whether this small amount of racemization occured during the allylation of L-methionine isopropyl ester or during the deprotection of the *N*-diallyl derivative by the NDMBA/palladium system.

The catalytic cycle most probably involved in the deallylation of allylamines by the palladium/NDMBA system is represented in Scheme I. Allylammonium species **12**, formed together with carbanion **10** or **11** in the prototropic equilibrium between the starting allylamine **9** and NDMBA (**7**) ($pK_a(H_2O) = 4.7$) or its mono-*C*-allyl derivative **8**, reacts, presumably in a reversible manner, with the zerovalent palladium catalyst to give π-allyl palladium(II) complex **14** and deallylated amine **13**;[5] **14** is then trapped irreversibly by carbanion **10** or **11** to give the corresponding C-allylated derivative **8** or **15** with concomitant regeneration of the palladium(0) catalyst.

The preparation of the *N*-allyl derivatives of amino acids used in this study deserves some comment. In our case, direct allylation of the amino group with allyl bromide in the presence of a base (diisopropylamine (DIEA) in toluene or sodium bicarbonate in aqueous ethanol) as previously reported in the literature for the preparation of *N*-allyl derivatives of tyrosine[6,7] gave satisfactory results only for the preparation of valine derivative All_2-L-Val-OMe; with methionine and glycine esters, yields of *N,N*-diallyl adducts were low because of competitive and extensive formation of *N*-triallylammonium and/or *S*-allylsulfonium derivatives. Since allylammoniums ions are allylating agents under Tsuji–Trost conditions and allylsulfonium species are likely to behave similarly, we relied upon palladium-catalyzed allylic alkylation reactions to obtain selectively the *N,N*-diallyl adducts. *N,N*-Diallyl-L-methionine isopropyl ester **6** was prepared by allowing L-Met-OiPr to react with a *slight*[8] excess of allyl acetate in the presence of the palladium catalyst and DIEA (eq 3).



(3)

All_2-Gly-OEt (**4**) was obtained by palladium-catalyzed redistribution of allyl groups between glycine ethyl ester and its triallylammonium derivative **16** (eq 4) in the presence of DIEA. Small amounts of *N,N*-diallyl-C^{α}-allylglycine ethyl ester were also obtained by this procedure. The C-allylation reaction most probably involves the C^{α}-deprotonated form of the *N,N,N*-triallylammonium species. Since no *N,N,N*-triallylammonium, C^{α}-allyl glycine ethyl ester impurity can be detected by NMR in **16**, the C-allylation reaction must occur during the palladium-catalyzed redistribution process shown in eq 4.

$$HCl\cdot H_2NCH_2CO_2Et + \underset{\mathbf{16}}{2All_3N^+CH_2CO_2Et,Br^-} \xrightarrow[\substack{+3\ DIEA\\ -3DIEA\cdot HX\\ (X = Cl,\ Br)}]{Pd(PPh_3)_4\ cat.} \underset{\mathbf{4}}{3All_2NCH_2CO_2Et} \quad (4)$$

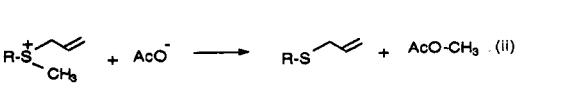
Diallylamine (and monoallylamine as well) are inexpensive and volatile compounds that can be used in large excess without inconvenience. Owing to the ease of deallylation of allylamines by palladium/NDMBA, these allylamines should constitute useful ammonia equivalents for the synthesis of primary amines.[9] To illustrate this possibility, we have devised a new mild procedure for the preparation of (aminomethyl)polystyrene (**19**), a polymeric anchor widely used in solid-phase peptide synthesis

(5) Quaternary allylammonium cations are allylating agents under Tsuji–Trost conditions (Hirao, T.; Yamada, N.; Oshiro, Y.; Agawa, T. *J. Organomet. Chem.* **1982**, *236*, 409), and oxidative addition of protonic allylammonium cations to palladium zero-valent complexes leading to π-allyl complexes is probably involved in the palladium(0)-catalyzed aza-Cope rearrangement of *N*-allylenamines in acidic medium (Murahashi, S. I.; Makabe, Y.; Kunita, K. *J. Org. Chem.* **1988**, *53*, 4489).

(6) Lagazza, B. C.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 1483.

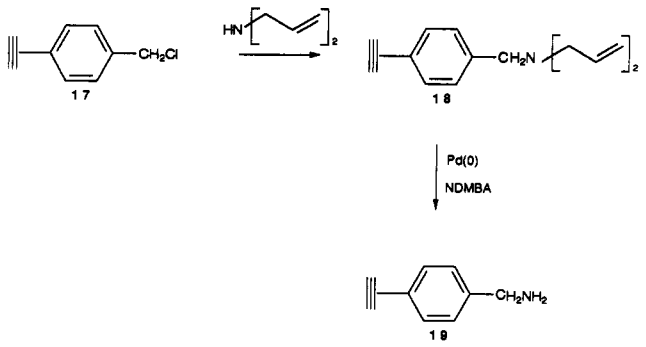
(7) Bardaji, E.; Torres, J. L.; Xaus, N.; Clapès, P.; Jorba, X.; de la Tore, B. G.; Valencia, G. *Synthesis.* **1990**, 531.

(8) If allyl acetate is used in large excess (e.g., 10 or 20 equiv), some *S*-allyl homocysteine is formed as a byproduct. The formation of this byproduct is very likely due to the formation of significant amounts of allylmethylsulfonium ions under these conditions. The sulfonium species could then be demethylated by acetate anions (eqs i and ii).



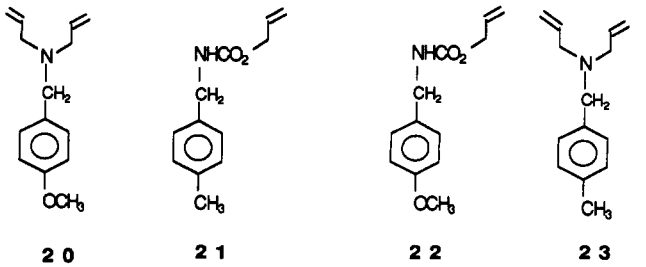
(9) Besides phthalimide (Gabriel reagent), other ammonia equivalents for the synthesis of primary amines include diformylamide, di-*tert*-butyl, and various other dialkyl imidocarbonates, phenacylsulfonylamides, triflamides, phosphoramides, bis(sulfenyl)amides, hydroxylamines, 4,4'-dimethoxybenzhydrylamine, and dibenzylamine. For leading references, see: (a) Yinglen, H.; Hongwen, H. *Synthesis.* **1990**, 122. (b) Grehn, L.; Lurdes, M.; Almeida, S.; Ragnarsson, U. *Synthesis* **1988**, 92. (c) Trost, B. M.; Keinan, E. R. *J. Org. Chem.* **1979**, *44*, 3452. (d) Goal, O. P.; Purchase, C. F. *J. Org. Chem.* **1991**, *56*, 457.

Scheme II



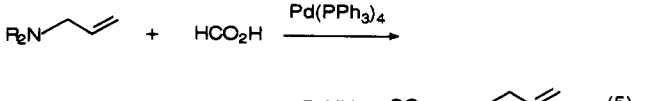
(Scheme II). Heating (chloromethyl)polystyrene (Merrifield resin) **17** at reflux for 24 h in a 28% (v/v) mixture of diallylamine and dichloromethane gave (*N,N*-diallylamino)methyl resin (**18**). No residual chlorine could be detected in **18**, a fact which allowed us to rule out any cross-linking of the polymer through formation of diallyl dibenzyl quaternary ammonium bridges. The IR spectrum of **18** exhibits a characteristic sharp band of medium intensity at 1640 cm^{-1} (C=C stretching vibration). This band is useful for monitoring the deprotection reaction from **18** to **19**, which takes place smoothly in refluxing dichloromethane in the presence of NDMBA and catalytic amounts of tetrakis(triphenylphosphine) palladium(0). To check its efficiency as a polymeric anchor, **19** was coupled with N^{α}-Boc-phenylalanine. Previously published methods for the preparation of **19** from **17** involve intermediate formation of imidomethyl derivatives, i.e., the phtalimidomethyl resin[10] (Gabriel synthesis) or, more recently, the [*N,N*-bis(*tert*-butoxycarbonyl)imido]methyl resin.[11] Direct reaction of ammonia with (chloromethyl)polystyrene has also been described,[12] but undesirable cross-linking of the polymer may occur by this method.[10b]

Finally, the versatility of the palladium-catalyzed removal of allylic groups in general is illustrated by the possibility for selective cleavage of allyl carboxylates in the presence of allylamines. It has already been shown in the literature that selective removal of the carboxylic allyl group of *N,N*-diallyltyrosine allyl ester (protected on the phenolic hydroxyl group) can be achieved[7] with the palladium/morpholine system.[13] We report here that the selective cleavage of allylcarbamates in the presence of allylamines is also possible by means of the ternary system palladium/*N,N*-dimethyl-*N*-(trimethylsilyl)amine/trimethylsilyl acetate.[1,14,15] Indeed, selective deprotection of allyl carbamate **21** in the presence of diallylamine **20** could be achieved under such conditions. Likewise, in a cross experiment, carbamate **22** was selectively deprotected in the presence of diallylamine **23**. In both experiments, careful GC analysis did not show the presence (<0.5%) of



amino compounds other than the starting diallylamine and the free amine from deprotection of the carbamate. Such selectivity in the deprotection of Alloc versus All derivatives of amines should prove useful when difficult problems of differential protection of amino groups are encountered.[16]

To be complete, we want to mention that we also investigated the removal of allyl groups from allylamines with the palladium/formic acid system[1] shown in eq 5. However, this method was found to be much more sluggish and less reliable than that based on NDMBA.



(5)

Experimental Section

General. GLC analyses were performed on a SE 54 coated 15-m glass capillary column and chiral GC analyses on a 50-m fused silica capillary column coated with XE-60-(*S*)-valyl-(*S*)-α-phenylethylamide. GLC/MS analyses were carried out on a CPSILS quartz capillary column; mass spectra were recorded in the electron impact mode, using a potential of 70 eV. With the exception of molecular ion peaks, only peaks with relative intensities of 10% or more are reported. When necessary, unambiguous NMR assignments were obtained by decoupling experiments. Amino acid analyses were carried out on a Beckman 6300 instrument.

All solvents were used dired and freshly distilled under N_2. All reagents used in this study are commercially available. Fresh samples of trimethylsilyl acetate and trimethylsilyldimethylamine were used as such; older samples were distilled over finely powdered CaH_2 before use. Tetrakis(triphenyphosphine)palladium(0) was prepared as previously described.[17] Allylamines **1**, **2**, **3**, **20**, and **23** were prepared by routine alkylation of allyl- or diallylamine with the corresponding benzyl halide in dry acetone or dry acetonitrile. The allylamines were all carefully purified by distillation (purity >99% by GC standard). *N*-(Allyloxycarbonyl) derivatives of *p*-methyl- and *p*-methoxybenzylamine (**21** and **22**, respectively) were prepared by reactions of the amines with allyl chloroformate under Schotten–Bauman conditions:[18] **1**, bp 69–70 °C/1 mmHg; **2**, bp 105–110 °C/0.02 mmHg; **3**, bp 167 °C/10 mmHg; **20**, bp 65 °C/0.1 mmHg; **21**, bp 110–112 °C/0.002 mmHg; mp 47–48 °C; **22**, bp 125 °C/0.002 mmHg; mp 44–45 °C; **23**, bp 77 °C/0.1 mmHg.

All manipulations involving palladium tetrakis(triphenylphosphine) were carried out under an argon atmosphere.

***N,N*-Diallylglycine Ethyl Ester (All$_2$GlyOEt) (4). *N*-(Carbethoxyethyl)-*N,N,N*-triallylammonium Bromide [All$_3$GlyOEt]$^+$Br$^-$ (16).** Allyl bromide (50.76 mL, 0.6 mol, excess) was allowed to react with ethyl glycinate hydrobromide

(10) For leading references, see: (a) Mitchell, A. R.; Kent, S. B. H.; Erickson, B. W.; Merrifield, R. B. *Tetrahedron Lett.* **1976**, 3795. (b) Barany, G.; Merrifield, R. B. Solid-phase peptide synthesis. In Gross, E.; Meienhofer, J. *The Peptides (Special Methods in Peptide Synthesis)*; Academic Press: New York, 1980; Vol. 2, Part A, Chapter 1.

(11) Grehn, L.; Ragnarsson, U. *Synthesis* **1987**, 227.

(12) Rich, D. H.; Gurwara, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 1575.

(13) Kunz, H.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 71.

(14) Trimethylsilyl acetate suppresses the palladium-catalyzed decarboxylative rearrangement of allyl carbamates to allylamines (see ref 1).

(15) However, as expected, the NDMBA/Pd system does not discriminate between allyl groups of allylamines and allyl carboxylates; thus, exposure of *N,N*-diallylmethionine allyl ester to this system results in total deprotection to methionine (observations from this laboratory).

(16) For leading references concerning protection strategies in the synthesis of polyamines, see: (a) Cehen, G. M.; Cullis, P. M.; Hartley, J. A.; Mathen, A.; Symons, M. C. R.; Wheelhouse, R. T. *J. Chem. Soc., Chem. Commun.* **1992**, 298. (b) Jasys, V. J.; Kelbaugh, P. R.; Nason, D. M.; Phillips, D.; Rosnack, K. J.; Forman, J. T.; Saccomano, N. A.; Stroh, J. G.; Volkmann, R. A. *J. Org. Chem.* **1992**, *57*, 1814. (c) Bergeron, R. J.; McManis, J. S. *J. Org. Chem.* **1988**, *53*, 3108.

(17) Four, P.; Guibé, F. *J. Org. Chem.* **1981**, *46*, 4439.

(18) Stevens, C.; Watanabe, R. *J. Am. Chem. Soc.* **1950**, *72*, 725.

(GlyOEt·HBr, 11.05 g, 0.06 mol) and $NaHCO_3$ (50.4 g, 0.6 mol, excess) in 400 mL of absolute ethanol for 6 h at reflux. After the mixture cooled to rt, the insoluble inorganic salts were filtered off, and the filtrate was concentrated under vacuum. The oily residue was taken up in a small volume of aqueous Na_2CO_3 and extracted twice with ether. After evaporation, the ethereal phases were found to contain 0.6 g of *N,N*-diallylglycine ethyl ester. The aqueous phase was acidified with aqueous HBr and extracted four times with $CHCl_3$. The chloroform extracts were combined, dried over $MgSO_4$, and evaporated first on a Rotovap and then under 0.1 mmHg for 1 d to give 14.56 g of crude $[All_3GlyOet]^+Br^-$ as an oily residue, which crystallized on standing at 4 °C. This crude product was used as such in the palladium-catalyzed allyl group redistribution reaction with ethyl glycinate: ^1H NMR ($CDCl_3$) δ 6.19 (m, 3H, internal vinylic H), 5.80 and 5.75 (two broad d (app. t), J = 17 and 11 Hz, *Z* and *E* terminal vinylic H), 4.50 (two overlapping d, 8H, allylic CH_2 and $^{\alpha}CH_2$), 4.25 (q, J = 8 Hz, 2H), 1.3 (t, J = 8 Hz, 3H).

***N,N*-Diallylglycine Ethyl Ester (4).** Ethyl glycinate hydrochloride (1.52 g, 1.09×10^{-2} mol) was mixed with 6.97 g of $[All_3GlyOEt]^+Br^-$ (6.97 g, 2.29×10^{-2} mol, 2.1 equiv), diisopropylethylamine (5.86 mL, 3.43×10^{-2} mol, 3.1 equiv), and tetrakis(triphenylphosphine)palladium (200 mg, 1.7×10^{-4} mol, 1.6 10^{-2} equiv) in 30 mL of degassed THF. The heterogeneous mixture was heated overnight at 60 °C with vigorous magnetic stirring. After that period, the lower oily phase observed at the beginning of the reaction had been replaced by a white solid precipitate of diisopropylethylamine hydrohalide. The reaction mixture was cooled to rt, and the precipitate was filtered off and washed with two portions of ether. The organic filtrate was evaporated, and 25 mL of ether and a few mL of saturated aqueous Na_2CO_3 were added to the residue. The precipitated yellow palladium catalyst was filtered off. The aqueous layer was decanted and reextracted twice with small portions of ether. The ethereal fractions were combined, dried over $MgSO_4$, and evaporated. The crude residue was purified by distillation under reduced pressure to give 3.51 g (58% yield) of *N,N*-diallylglycine ethyl ester ($All_2GlyOEt$, 4) (bp 58–60 °C/0.7 mmHg) contaminated by small amounts of *N*-monoallylglycine ethyl ester and of *N,N*-diallyl-C^{α}-allylglycine ethyl ester (3% and 2%, respectively, by GC). A higher boiling fraction (0.5 g) contained 75% of $All_2GlyOEt$ and 25% of *N,N*-diallyl,C^{α}-allylglycine ethyl ester. 4: ^1H NMR ($CDCl_3$) δ 5.85 (m, 2H, internal vinylic H), 5.30 and 5.25 (two overlapping broad d (app t), J = 17 and 11 Hz, *Z* and *E* terminal vinylic H), 4.15 (q, J = 7.5 Hz, 2H), 3.30 (s, 2H), 3.25 (d, J = 7 Hz, 4H, allylic H), 1.25 (t, J = 7.5 HZ, 3H); ^{13}C NMR ($CDCl_3$) δ 14.1, 53.7, 57.0, 60.1, 117.9, 135.1, 171.1; GC/MS *m/z* 183 (0.35, M^+), 142 (10, $M^+ - 41$(allyl)), 110 (100, $M^+ - 73$ (carboethoxy)), 41 (21). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.55; H, 9.34; N, 7.64; O, 17.47. Found: C, 65.08; H, 9.17; N, 8.03; O, 17.72. $All_2Gly(C^{\alpha}$-allyl)OEt: ^1H NMR ($CDCl_3$, spectrum determined on the mixture of 75% of All_2Gly OEt and 25% of $All_2Gly(C^{\alpha}$-allyl)OEt; only the peaks corresponding to the C^{α}-allyl group and the C^{α} proton are reported here) δ 5.70 (m), 5.08 and 5.02 (two overlapping d), 3.5 (t, J = 8 Hz, $C^{\alpha}H$), 3.1 (m, allylic H); GC/MS *m/e* 182 (62, $M^+ - 41$(allyl)), 151 (12), 150 (100, $M^+ - 73$ (carboethoxy)), 81 (12.5), 68 (11), 41 (46).

***N,N*-Diallyl-L-valine Ethyl Ester (5).** *N,N*-Diallyl-L-valine methyl ester 5 was prepared by a procedure very similar to the one described[6] for *N,N*-diallyl-*O*-methyl tyrosine methyl ester. L-Valine methyl ester hydrochloride (0.02 mol), allyl bromide (10 equiv, large excess) and diisopropylethylamine (3.5 equiv) in toluene (50 mL) under dry atmosphere were heated first at 60 °C for 6 h and then at 100 °C for 8 h. After conventional workup, the product was purified by distillation, yield 2.15 g (51%). 5: bp 49–51 °C/0.25 mmHg; $[\alpha]^{20}_D$ –93.4° (*c* 2.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.76 (m, 2H, internal vinylic H), 5.20 (dt, ^3J_d = 18 Hz, ^4J_t = 0.5 Hz, 2H, *Z* terminal vinylic H) and 5.10 (d overlapping with the preceding peak, ^3J_d = 12 Hz, 2H, *E* terminal vinylic H), 3.7 (s, 3H), 3.42 (ddt, 2H), and 2.84 (dd, 2H, nonequivalent allylic H, ABXYY′ system, $^2J_{AB}$ = 15.5 Hz, low field H: ^3J_d = 5 Hz, ^4J_t = 0.5–1 Hz, high field H: ^3J_d = 9 Hz), 2.98 (d, J = 11.5 Hz, 1H, $C^{\alpha}H$), 2.03 (dsept, J_d = 11.5 Hz, J_{sept} = 7 Hz, 1H), 0.97 (d, J = 7 Hz, 3H), 0.85 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) 19.4, 19.8, 50.4, 53.8, 68.7, 116.7, 136.5; GC/MS *m/e* 211 (3.2, M^+), 170 (14, $M^+ - 41$ (allyl)), 169 (19), 168 (62, $M^+ - 43$ (isopropyl)), 153 (40), 152 (68, $M^+ - 59$ (carbomethoxy), 81 (26), 68 (38), 55 (41), 41 (100, allyl$^+$). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63; O, 15.14. Found: C, 68.50; H, 9.98; N, 6.75; O, 14.77.

***N,N*-Diallyl-L-methionine Isopropyl Ester (6).** A solution of L-methionine isopropyl ester hydrochloride (3.61 g, 1.6×10^{-2} mol), diisopropylamine (8.35 mL, 4.8×10^{-2} mol, 3 equiv), tetrakis(triphenylphosphine) palladium (1.85 g, 0.16×10^{-2} mol, 0.1 equiv), and allyl acetate (4.31 mL, 4×10^{-2} mol, 2.5 equiv) in 80 mL of degassed dioxane was stirred under argon in an oil bath at 80 °C for 24 h. The reaction mixture was cooled to rt, and the dioxane was evaporated on a Rotovap. The residue was partitioned between either and a small volume of 10% aqueous HCl. The precipitated yellow palladium catalyst was filtered off. The aqueous phase was decanted, and the ethereal fraction was reextracted with two small portions of 10% aqueous HCl. The combined aqueous layers were basified (pH > 10) by the addition, with cooling, of solid Na_2CO_3 decahydrate. The basic aqueous phase was extracted three times with ether; the combined ethereal extracts were dried over $MgSO_4$ and concentrated under vacuum. Distillation of the residue under vacuum gave 3.56 g (82%) of $All_2MetOiPr$ (bp 100 °C/0.005 mmHg) contaminated by 1.5% of monoallyl derivative as revealed by GC/MS. 6: $[\alpha]^{20}_D$ –60.5° (*c* 2.3 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.76 (m, 2H, internal vinylic H), 5.20 and 5.10 (two d (apparent t), ^3J = 18 and 13 Hz, 2H + 2H, *Z* and *E* terminal vinylic H), 5.05 (sept, partially overlapping with the preceding peaks, J = 6.5 Hz, 1H, isopropyl CH), 3.56 (d, ^3J = 11 Hz, 1H, C^{α}-H), 3.36 (ddt, 2H) and 3.08 (dd, 2H, nonequivalent allylic H, ABXYY′ system, $^2J_{AB}$ = 14.5 Hz, low field H: ^3J_d = 5 Hz, ^4J_t = 0.5–1 Hz, high field H: ^3J_d = 8 Hz), 2.55 (m, 2H, C^{γ}-H_2), 2.1 (s, 3H), 1.95 (m, 2H, $^{\beta}CH_2$), 1.27 and 1.24 (two d, J = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 22.0, 22.1, 29.2, 30.9, 53.5, 60.6, 67.7, 116.9, 136.6, 172.3; GC/MS *m/e* 271 (0.15, M^+), 230 (13, $M^+ - 41$ (allyl)), 184 (100, $M^+ - 87$(carboisopropoxy), 136 (21), 96(16), 41 (66). Anal. Calcd for $C_{14}H_{25}NO_2S$: C, 61.95; H, 9.28; N, 5.16. Found: C, 61.99; H, 9.21; N, 5.33.

General Procedure for Palladium-Catalyzed Deprotection of Allylamines with *N,N′*-Dimethylbarbituric Acid. A solution of the allylamine in dry degassed CH_2Cl_2 (2.5 mL per mmol of amine) was added with a syringe through a rubber septum cap in a Schlenk tube containing the catalyst (tetrakis(triphenylphosphine)palladium (10^{-2} molar equiv per allyl group to be removed)) and N,N′-dimethylbarbituric acid (3 equiv per allyl group) under argon. The usually homogenous mixture was stirred at 35 °C for a few hours (see Table I). With some substrates, precipitation of the NDMBA salt of the deallylated amine could be observed during the reaction. After cooling, the CH_2Cl_2 was removed under vacuum and replaced by ether. The ethereal mixture was extracted twice with small volumes of saturated aqueous Na_2CO_3 to remove the unreacted NDMBA and its mono-*C*-allyl derivative. If this extraction with alkaline water is omitted, difficulties may be encountered later on because of contamination of the hydrochloride salt of the deprotected amine with NDMBA. The amine contained in the ether solution was then converted to the hydrochloride salt by the addition of 4 N HCl until an acidic pH (<2) was reached. If some solid amine hydrochloride separated at this point, it was collected by filtration and washed with ethyl acetate to remove any palladium compounds. The ethyl acetate washings were then reextracted with a small volume of 4 N HCl. The aqueous acidic phases were combined and washed again with ethyl acetate. The aqueous layer was decanted, and the water was removed by azeotropic evaporation (ethanol–benzene) on a Rotovap. If no amine salt precipitated, the aqueous acidic phase was directly treated as described. The hydrochloride salts were dried under vacuum (0.1 mmHg) in the presence of P_2O_5.

Deprotection reactions were generally run on a 2 mmol scale. After conversion to the free base and GC analysis, all deprotected amines were found to contain less than 0.5% of residual mono- or diallylamines. In the case of *N,N*-diallyl-L-methionine isopropyl ester, N-trifluoroacetylation of the deallylated product and analysis by chiral GC were performed as described.[19]

(*N,N*-Diallylamino)methyl Resin (18). Chloromethyl resin (17) (5 g, Nova-biochem, 1% DVB, 200–400 mesh, 0.78 mmol of

(19) Dangles, O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4985.

Cl per g of resin) was suspended in a mixture of 20 mL of anhydrous diallylamine and 50 mL of CH_2Cl_2. The mixture was refluxed under a dry atmosphere in an oil bath at 80 °C for 24 h. The resin beads were then collected on a sintered glass funnel and washed according to the following scheme: (1) CH_2Cl_2 wash (3×); (2) 1:9 (v/v) triethylamine/CH_2Cl_2 wash (3×); (3) methanol wash (2×); water wash (2×); methanol wash (6×). The resin was finally dried first in a stream of air and then under 0.1 mmHg of pressure. The absence of chloride in the new resin was checked by the copper wire (Beilstein) test: IR (KBr) 1640 cm^{-1}, m, sh.($\nu_{C=C}$). Anal. Calcd for N (0.75 mmol per g): N, 1.05. Found: N, 1.15.

Aminomethyl Resin (19). (Diallylamino)methyl resin (18) (4 g, approximately 3.28 mmol of diallylamino groups) was refluxed for 6 h in a solution of *N,N'*-dimethylbarbituric acid (3.03 g, 19.45 mmol, 6 equiv) and tetrakis(triphenylphosphine)-palladium (0.15 g, 0.13 mmol, 4×10^{-2} molar equiv) in 40 mL of dried degassed CH_2Cl_2 under argon. The resin was then collected by filtration and washed according to the following scheme: (1) CH_2Cl_2 wash (2×); (2) 1/9 (v/v) trifluoroacetic acid/CH_2Cl_2 (2×); (3) CH_2Cl_2 wash (4×); (4) 1/9 (v/v) triethylamine/CH_2Cl_2 wash (2×); (5) CH_2Cl_2 wash (2×); (6) methanol wash (2×); water wash (2×); (8) methanol wash (4×). Finally, the resin was dried as described above for (diallylamino)methyl resin. Anal. Calcd for N (0.79 mmol per g): N, 1.11. Found: N, 1.14.

Attachment of Boc-L-phenylalanine to the Aminomethyl Resin. Boc-Phe-OH (0.159 g, 0.6 mmol, 3 equiv) in solution in 1 mL of CH_2Cl_2 and 0.6 mL of a 1 M solution of dicyclohexylcarbodiimide in CH_2Cl_2 were added to a suspension of aminomethyl resin (19) (0.227 g, approximately 0.2 mequiv of amino group) in 10 mL of CH_2Cl_2. The reaction mixture was allowed to stand at rt for 1 h with occasional shaking. The resin was collected by filtration and treated as follows: (1) CH_2Cl_2 wash, 0.5 min (2×); (2) DMF wash 0.5 min (4×); CH_2Cl_2 wash 0.5 min (4×). In order to obtain a thoroughly negative Kaiser test, the coupling procedure had to be repeated once. Anal. Calcd (theoretical value based on total substitution of chlorines of the initial Merrifield resin by Boc-Phe-O residues): N, 1.85. Found: N, 1.91. Amino acid analysis gave a slightly lower value for incorporation of Boc-L-phenylalanine: 0.57 mmol per g (83% of the theoretical 0.66 mmol per g value.)

Selective Deprotection of Allyl Carbamates in the Presence of Allylamines. A CH_2Cl_2 solution (1 mL) containing *N*-(allyloxycarbonyl)-*p*-methoxybenzylamine (22) (0.221 g, 1 mmol) and *N,N*-diallyl-*p*-methylbenzylamine (23) (0.201g, 1 mmol) was added to 5 mL of a solution of (trimethylsilyl)dimethylamine (0.48 mL, 3 mmol), trimethylsilyl acetate (0.45 mL, 3 mmol), and palladium tetrakis(triphenylphosphine) (0.057 g, 0.05 mmol) in CH_2Cl_2. The reaction mixture was heated in an oil bath at 40 °C for 15 min. The reaction mixture was then cooled in an ice bath and basified with 1 mL of aqueous saturated Na_2CO_3. The organic phase was decanted, dried over $MgSO_4$, concentrated under vacuum, and directly analyzed. Only *p*-methoxybenzylamine and *N,N*-diallyl-*p*-methylbenzylamine were detected by GC (detection limit <0.5%). The molar ratio of *N,N*-diallyl-*p*-methylbenzylamine and *p*-methoxybenzylamine was found to be one by NMR.

Acknowledgment. We thank the Glaxo Co. for the award of a doctoral scholarship (to F.G.-H). We thank Pr. E. Giralt for allowing us to perform the amino acid analyses in his laboratory.