Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides

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Received December 14, 2001

The cycloaddition of azides to alkynes is one of the most important synthetic routes to 1*H*-[1,2,3]-triazoles. Here a novel regiospecific copper(I)-catalyzed 1,3-dipolar cycloaddition of terminal alkynes to azides on solid-phase is reported. Primary, secondary, and tertiary alkyl azides, aryl azides, and an azido sugar were used successfully in the copper(I)-catalyzed cycloaddition producing diversely 1,4-substituted [1,2,3]-triazoles in peptide backbones or side chains. The reaction conditions were fully compatible with solid-phase peptide synthesis on polar supports. The copper(I) catalysis is mild and efficient (>95% conversion and purity in most cases) and furthermore, the X-ray structure of 2-azido-2-methylpropanoic acid has been solved, to yield structural information on the 1,3-dipoles entering the reaction. Novel Fmoc-protected amino azides derived from Fmoc-amino alcohols were prepared by the Mitsunobu reaction.

Introduction

N-Heterocyclic compounds are broadly distributed in Nature, including amino acids, purines, pyrimidines, and many other natural products. *N*-Heterocyclic compounds such as [1,2,3]-triazoles may display biological activities and there are numerous examples in the literature including anti-HIV activity,[1,2] antimicrobial activity against Gram positive bacteria,[3] selective β_3 adrenergic receptor agonism,[4] and more. [1,2,3]-Triazoles have also found wide use in industrial applications such as dyes, corrosion inhibition (of copper and copper alloys), photostabilizers, photographic materials, and agrochemicals.[5] Therefore, it is important to develop new and more efficient solid-phase synthetic pathways to a diverse array of [1,2,3]-triazole pharmacophores and screen many analogues against relevant biological targets, possibly while attached to the solid support. The presented method is compatible with solid-phase combinatorial chemistry, so it is possible to make millions of compounds simultaneously using the split and combine method[6] and screen the compounds on the solid phase.[7]

Results and Discussion

Synthesis of [1,2,3]-Triazoles. Several different methods have been described for synthesis of [1,2,3]-triazoles, including the intramolecular cyclization of bishydrazones or mixed hydrazones, miscellaneous oxidations, as well as the 1,3-dipolar cycloaddition of azides to alkynes.[5,8,9] The cycloaddition between azides and alkynes is typically carried out in refluxing toluene, but labile molecules may not survive these conditions. However, by using sodium,[10] lithium,[11] or magnesium[12,13] salts of the alkyne, lower temperatures have been employed but often with limited or no success. L'abbé reported the in situ generation of a propargyl azide by displacement of a sulfonate with lithium azide and copper(I) chloride.[14] Instead of the expected product, an alkyl-substituted [1,2,3]-triazole byproduct was isolated in low yield. This side reaction was not investigated further. One communication with limited scope and experimental details described the solid-phase synthesis of [1,2,3]-triazoles by a diazo transfer reaction with tosyl azide.[15] The present investigations

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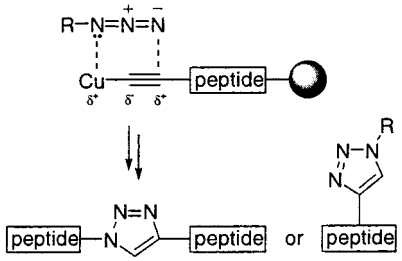
10.1021/jo011148j CCC: $22.00
Published on Web 04/02/2002

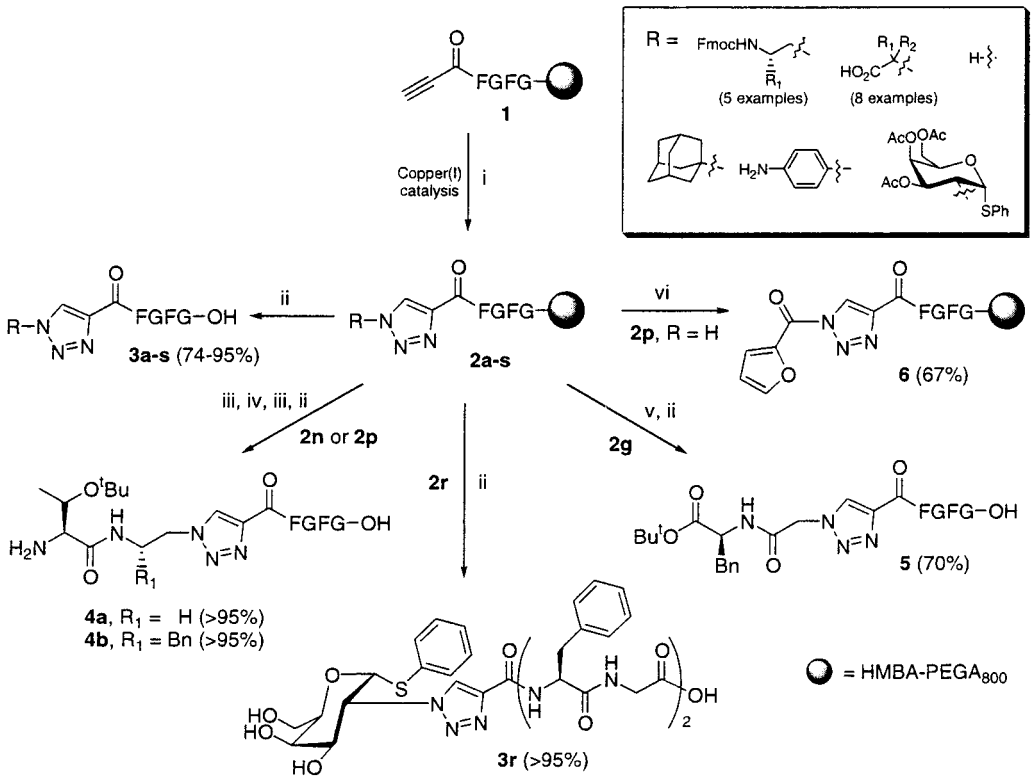
Scheme 1. Copper(I)-Catalyzed 1,3-Dipolar Cycloaddition of Alkynes to Azides Affording Peptidotriazoles or *N*-Substituted Histidine Analogs



into metal-catalyzed reactions on solid supports revealed a mild and efficient method for preparing [1,2,3]-triazoles using copper(I) salts as catalyst for the 1,3-dipolar cycloaddition of terminal alkynes to azides. The resin-bound copper acetylide was reacted with primary, secondary, and tertiary alkyl azides, aryl azides, and an azido sugar at 25 °C, affording diversely 1,4-substituted 1*H*-[1,2,3]-triazoles (Scheme 2) with quantitative conversions and purities ranging from 75% to 99% (Table 1). Full conversion and high purity was observed for the copper(I)-catalyzed 1,3-dipolar cycloaddition in the following tested solvents: acetonitrile, dichloromethane, tetrahydrofuran, toluene, *N*,*N*-dimethylformamide, and neat *N*-ethyldiisopropylamine. In the absence of copper(I) iodide, no reaction took place (entry **3a**, Table 1). Surprisingly, trimethylsilyl azide (entry **8e**, Table 1) did not react with propargylglycine on resin **7**. The very sterically hindered 2-azido-2,2-diphenylacetic acid (entry **3f**, Table 1) did not react even at elevated temperatures and prolonged reaction time. However, it has previously been reported that reactions with this azido group are much more difficult than with most other azido acids, supporting an argument of steric hindrance.[16,17] 1,3-Dipolar cycloadditions with resin **7** (propargylglycine, Scheme 3) showed high conversions (>95%) but slightly lower purities (entry **8a**−**d**, Table 1) than with resin **1** (propargylic acid, entry **3a**−**s**, Table 1). Electron-deficient alkynes are more reactive in cycloaddition reactions,[9] which explains why propargylic acid (resin **1**) displayed slightly higher purities than propargylglycine (resin **7**) did. Furthermore, two peptidotriazoles were prepared in larger amount (26−42 mmol) for full characterization by ^{1}H and ^{13}C NMR as well as HR-MS. Compounds **9** and **10** were isolated in 79% and 87% yield (eight reaction steps; see Scheme 4), respectively. The reaction conditions for the catalyzed cycloaddition, *N*-ethyldiisopropylamine and copper(I) iodide at 25 °C, are mild and fully compatible with Fmoc- and Boc-peptide chemistry. Free amino groups, carboxylic acids, thioglycosides, and Fmoc, *tert*-butyl, trityl, Boc, and Pmc groups were found to be completely stable under the reaction conditions.

Five Fmoc-protected amino alcohols [Fmoc-Arg(Pmc)-ol, Fmoc-Asp(^{t}Bu)-ol, Fmoc-Gly-ol, Fmoc-Met-ol, and Fmoc-Phe-ol] were subjected to Mitsunobu conditions with HN_3 to convert them into Fmoc-protected amino azides that could be used directly in the cycloaddition reaction. Only the small nucleophile hydrazoic acid[18] successfully converted the Fmoc-amino alcohols into their corresponding azides (48−98% yield), whereas TMS−N_3,

Scheme 2. Copper(I)-Catalyzed [1,2,3]-Triazole Formation from 1 and Further Reactions to Yield Peptidotriazoles[a]



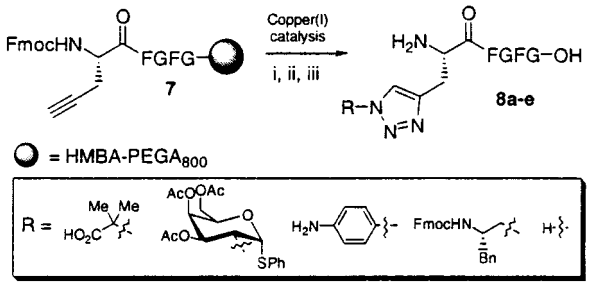
[a] Reported purities (*xx*%) are from analytical HPLC traces (215 nm), and conversions were in all cases quantitative. (i) R−N_3, DIPEA, CuI; (ii) 0.1 M NaOH (aq); (iii) 20% piperidine/DMF; (iv) Fmoc-Thr(^{t}Bu)-OPfp, Dhbt-OH; (v) H−Phe-O^{t}Bu·HCl, PyAOP, HOAt, DIPEA; (vi) 2-furoyl chloride, DIPEA.

Table 1. Purity[a] of the [1,2,3]-Triazoles Formed from Resin 1 and 7 in Schemes 2 and 3

	R	% purity[a]
3a	$C(CH_3)_2CO_2H$ (no CuI)	0
3b	$C(CH_3)_2CO_2H$	>95
3c	$C(CH_3)(C_2H_5)CO_2H$	>95
3d	$C(C_2H_5)_2CO_2H$	>95
3e	$C(n\text{-}C_3H_7)_2CO_2H$	>95
3f	$C(Ph)_2CO_2H$	0
3g	CH_2CO_2H	>95
3h	$CH(n\text{-}C_4H_9)CO_2H$	>95
3i	$CH(n\text{-}C_{14}H_{29})CO_2H$	91
3j	$CH(Ph)CO_2H$	>95
3k	$4\text{-}C_6H_4NH_2$	93
3l	2-amino-5-guanidinopentyl[b,c]	83
3m	$CH_2CH(CH_2CO_2H)NH_2$[b,c]	75
3n	$(CH_2)_2NH_2$[c]	90
3o	$CH_2CH(CH_2CH_2SCH_3)NH_2$[c]	84
3p	$CH_2CH(Ph)NH_2$[c]	>95
3q	1-adamantyl	>95
3r	2-(2-deoxy)-Gal-SPh	>95
3s	H[d]	84
8a	$C(CH_3)_2CO_2H$	75
8b	2-(2-deoxy)-Gal-SPh	78
8c	$4\text{-}C_6H_4NH_2$	90
8d	$CH_2CH(Ph)NH$-Fmoc[b]	79
8e	H[d]	0

[a] Conversion was >95% except for **3a**, **3f**, and **8e**, and the reported purities are from analytical HPLC traces (215 nm). [b] Treatment with TFA/triisopropylsilane/water 95:2.5:2.5 for 2.5 h to remove Pmc and ^{t}Bu groups. [c] The Fmoc group of the primary amine was removed prior to analysis. [d] Trimethylsilyl azide was used.

Scheme 3. Preparation of *N*-Substituted Histidine Analogs from Propargylglycine[a]



[a] (i) R−N_3, DIPEA, CuI; (ii) 20% piperidine/DMF; (iii) 0.1 M NaOH (aq).

diphenylphosphoryl azide,[19] and $Zn(N_3)_2$·2pyridine[20] all failed because of steric hindrance.

Copper(I) Catalysis. The catalytic mechanism has not been investigated, but it is known that copper(I) readily inserts into terminal alkynes in the presence of base, e.g. the Sonogashira coupling.[21] The polarization of the terminal triple bond by the covalently bound copper(I) catalyzes the cycloaddition (Scheme 1), which probably changes from a concerted reaction into a stepwise addition. The present experiments showed that the 1,3-dipolar cycloaddition was catalyzed (0.01 equiv was the lowest stoichiometry tested) by copper(I) chloride, copper(I) bromide−dimethyl sulfide complex, and copper(I) iodide but not by copper(II) salts. The copper(I) catalysis does not work on internal alkynes, as was tested on resin-bound 2-octynoic acid with an azide, giving no trace of the cycloaddition product, and only the starting material was recovered. This suggested a reaction intermediate in which copper(I) was terminally bound to the alkyne, since copper(I) does not catalyze reactions with internal triple bonds. It may therefore be concluded that the 1,3-dipolar cycloaddition of terminal alkynes to azides is catalyzed by copper(I) salts through a preformed copper−acetylide complex followed by a stepwise or concerted addition to an azide.

Regiospecificity. Thermal 1,3-dipolar cycloaddition of alkynes to azides is not a regiospecific reaction.[9] This could be advantageous if both regioisomers were desired but would be considered a disadvantage in preparative work. Fmoc-Phe-ψ[CH_2N_3] (**19**) and resin **1** gave two isomers under thermal conditions (reflux in toluene), **13a** and **13b** in a 2:1 ratio (analytical HPLC and ^{1}H MAS NMR of the two regioisomers from the thermal cycloaddition are presented in Figure 1). The analogous copper(I)-catalyzed reaction gave only one regioisomer, the 1,4-substituted [1,2,3]-triazole (entry **3p**, Table 1). All the other azides, primary, secondary, and tertiary alkyl azides, aryl azides, Fmoc-protected amino azides, and azido sugars proved that the catalysis was generally regiospecific in forming only the 1,4-substituted [1,2,3]-triazole. The triazole proton in **13a** was found at 8.50 ppm, whereas in **13b** it was shifted upfield to 8.23 ppm (Figure 1). In a similar 1,4- and 1,5-substituted [1,2,3]-triazole system, it was concluded that the triazole proton in 1,4-substituted triazoles was always shifted considerably downfield compared to 1,5-substituted triazoles.[22] This supports the evidence that the copper(I)-catalyzed reaction only gives the 1,4-substituted triazole (**13a** in Figure 1) and is in full agreement with HPLC data from coinjection of reaction mixtures from the thermal and the copper(I)-catalyzed 1,3-dipolar cycloaddition. Furthermore, strong NOE effects have been observed between the triazole proton and the *N*-substituted alkyl group in **9** and **10** (Figure 2), suggesting that the triazole proton and *N*-substituent are in close proximity as in the 1,4-substituted triazole.

In contrast, the uncatalyzed thermal reaction of 2-azido-2-methylpropanoic acid (a tertiary alkyl azide) with resin **1** afforded only one regioisomer, the 1,4-substituted triazole, probably due to steric effects. This was substantiated by the X-ray crystal structure of 2-azido-2-methylpropanoic acid (Figure 3), where the two methyl groups and the carboxyl group effectively shield one side of the azido group, thereby blocking the cycloaddition to yield the sterically more crowded 1,5-substituted triazole.

Compatibility. To test the generality of the copper(I)-catalyzed reaction, 13 representative protected tripeptides acylated with propargylic acid at the *N*-terminus were synthesized and subjected to the reaction conditions for the copper(I)-catalyzed 1,3-dipolar cycloaddition with 2-azido-2-methylpropanoic acid (Scheme 5). Alanine, proline, *tert*-butyl-protected threonine/tyrosine/aspartic acid, trityl-protected asparagine/histidine/cysteine, me-

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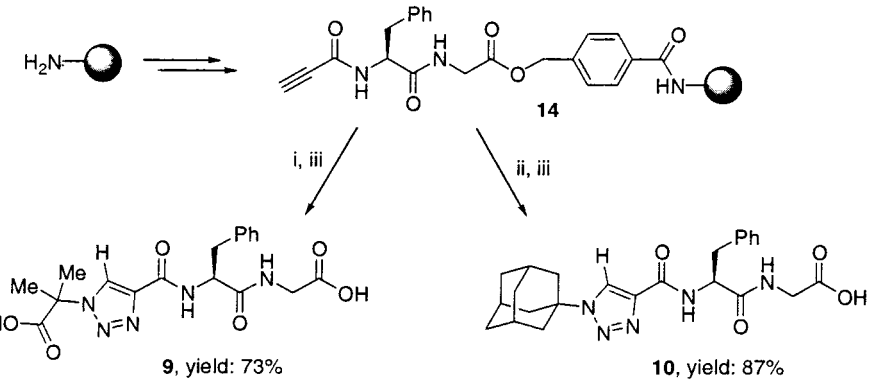
Scheme 4. Synthesis of Peptidotriazoles 9 and 10[a]



[a] (i) 2-Azido-2-methylpropanoic acid, DIPEA, CuI; (ii) 1-azidoadamantane, DIPEA, CuI; (iii) 0.1 M NaOH (aq).

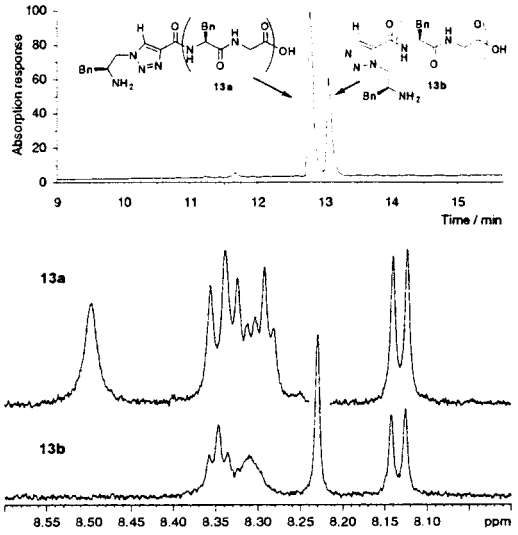


Figure 1. Analytical HPLC profile of 1,4- and 1,5-substituted [1,2,3]-triazole (**13a** and **13b**) and ^{1}H MAS NMR of the two regioisomers' amide protons and triazole protons (singlet signals at 8.50 and 8.23 ppm).

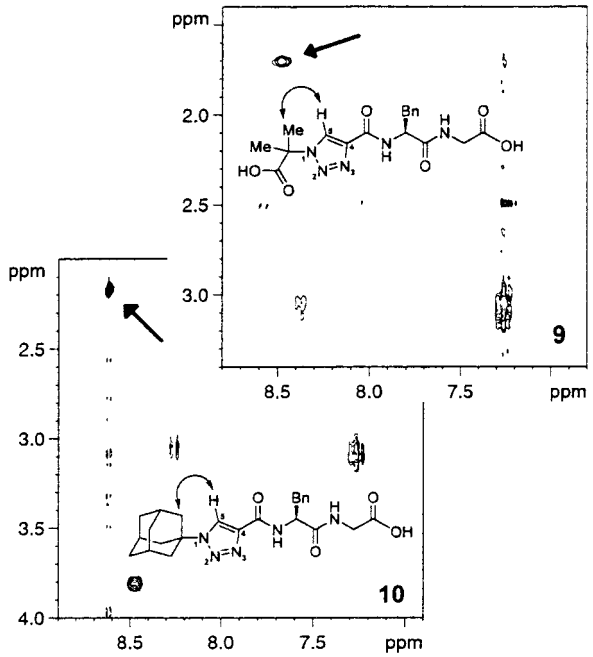


Figure 2. 2D NOESY spectra of **9** and **10**. The NOEs marked with arrows prove the regiospecific 1,4-substitution of the [1,2,3]-triazoles.

thionine, Boc-protected lysine/tryptophan, and Pmc-protected arginine were used and all showed conversions above 95% and 80−95% purity of the resulting peptidotriazoles (**12a**−**l**, Table 2). The following functional groups were included: thioethers; esters; amides; ethers; Fmoc, Boc, *tert*-butyl, trityl, and Pmc groups; and oxidation sensitive residues such as methionine, tryptophan, and cysteine.

Since all peptides gave the expected products without side reactions, the copper(I)-catalyzed 1,3-dipolar cycloaddition was fully compatible with solid-phase peptide synthesis. All reactions have been carried out on $PEGA_{800}$ resin,[23] a hydrophilic tertiary amide−poly(ethylene glycol) based resin, but the reaction conditions were also tested on $SPOCC_{1500}$,[24] a completely inert resin with only primary ether bonds, and it performed equally well (data not shown).

Solid/Solution Phase. Both solution- and solid-phase chemistry have their respective advantages and disadvantages. In the case of the copper(I)-catalyzed 1,3-dipolar cycloaddition, the solution-phase reaction is complicated by cross-coupling products between two terminal alkynes such as the Glaser coupling and Straus coupling.[25] Furthermore, PEGA resin acylated with 2-azido-2-methylpropionic acid was subjected to the reaction conditions with the modification that the reactants were inversely immobilized, i.e., the terminal alkyne in solution and the azide on the resin. Prolonged reaction time, elevated temperature, and a large excess of alkyne gave only starting material because of alkyne cross-coupling. The advantage of solid-phase reactions is the highly solvated state of the PEG-resin-bound intermediates such as the copper acetylide and that cross-couplings do not occur, thereby allowing the copper(I)-catalyzed reaction to proceed smoothly when the alkyne is attached to the resin.

Perspective. The [1,2,3]-triazole can be viewed as a peptide isoster that, when incorporated into a peptide, is displaying hydrogen-bonding capability, aromaticity, and backbone restriction. Compounds **4a** and **4b** (Scheme

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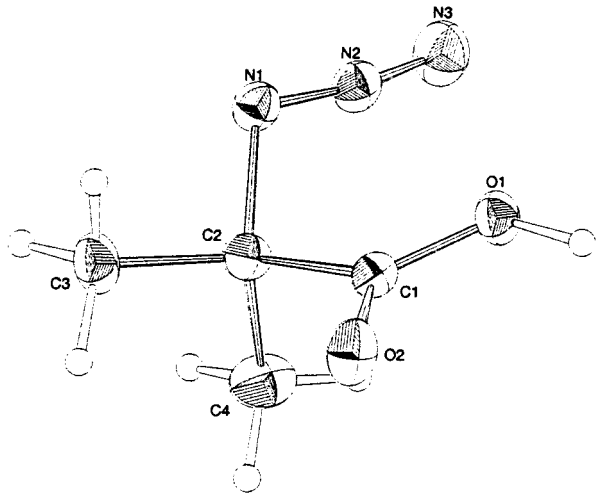
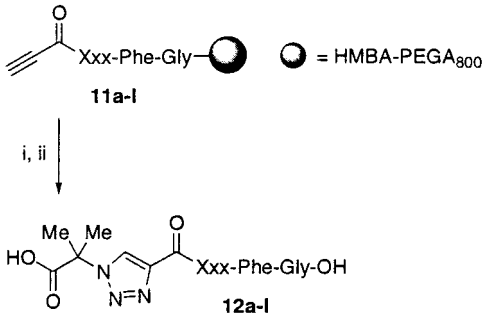


Figure 3. X-ray structure of 2-azido-2-methylpropionic acid: monoclinic; *C*2/*c*; $a \times b \times c$, 10.730 Å × 11.989 Å × 10.811 Å; $\alpha, \beta, \gamma = 90°$, 114.1°, 90°; $R = 0.0441$ and $R_w = 0.426$.

Scheme 5. [1,2,3]-Triazole Formation from 12 Protected Tripeptides To Assess Side-Chain Stability[a]



Xxx = Ala, Pro, Thr(tBu), Tyr(tBu), Asp(tBu), Asn(Trt), His(Trt), Cys(Trt), Met, Lys(Boc), Trp(Boc), Arg(Pmc)

[a] (i) 2-Azido-2-methylpropionic acid, DIPEA, CuI; (ii) 0.1 M NaOH (aq).

Table 2. Purity[a] of Peptidotriazoles with Protected Amino Acids from Scheme 5

	Xxx	% purity[a]		Xxx	% purity[a]
12a	Ala	>95	**12g**	His(Trt)	80
12b	Pro	>95	**12h**	Cys(Trt)	81
12c	Thr(tBu)	>95	**12i**	Met	85
12d	Tyr(tBu)	>95	**12j**	Lys(Boc)	>95
12e	Asp(tBu)	>95	**12k**	Trp(Boc)	>95
12f	Asn(Trt)	90	**12l**	Arg(Pmc)	88

[a] Conversion was >95% in all cases, and the reported purities are from analytical HPLC traces (215 nm).

3) are examples where peptide synthesis has been continued in the normal direction (C- to N-direction) with high conversions and purities (>95%). In compound **5**, the direction of the peptide has been reversed after the [1,2,3]-triazole (N- to C-direction), showing the versatility of the construct depending on which azide is used in the cycloaddition. Millions of peptidotriazoles are currently being synthesized in a split and combine library based on the construct similar to **4a**, as will be reported elsewhere. Compounds **8a**−**d** (Scheme 4) are also interesting as side chain analogues of *N*-substituted histidines that, due to the efficiency of the reaction, also can be incorporated into a library format.

Conclusion. The described copper(I)-catalyzed 1,3-dipolar cycloaddition of terminal alkynes to azides gave access to one specific regioisomer, the 1,4-substituted [1,2,3]-triazole, worked excellently on solid support (>95% conversion and purity at 25 °C in most cases), and was fully compatible with solid-phase peptide synthesis, all the amino acids, and their protecting groups. Cross-coupling reactions in solution were not a problem on solid support, because of the highly solvated PEG-resin-bound copper acetylide. A diverse set of 1,4-substituted [1,2,3]-triazoles have been prepared, and synthesis of large libraries is in progress. The X-ray structure of 2-azido-2-methylpropanoic acid has been solved and illustrates the steric environment in α,α-disubstituted azido acids.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX250 (250 MHz) and MAS NMR spectra on a Varian Unity Inova 500 MHz spectrometer equipped with a 4 mm ^{1}H-observe Nano NMR-probe. Electrospray mass spectrometry was performed in the positive mode on a Fisons VG Quattro instrument. Analytical and preparative reverse-phase HPLC separations were performed on a Waters HPLC system using analytical Zorbax 300SB-C_{18} (4.5 × 50 mm) and Delta PAK (47 × 300 mm) C_{18} columns with a flow rate of 1 and 20 cm^3 min^{-1}, respectively. Detection was at 215 nm on a multiwavelength detector (Waters 490E) for analytical purposes, and a photodiode array detector (Waters M991) was used for preparative separations. A solvent system consisting of (A) 0.1% TFA in water and (B) 0.1% TFA in 90% acetonitrile−10% water was used. IR spectra were recorded on a Perkin-Elmer 1600 FTIR instrument as neat liquids or as KBr pellets. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 25 °C. Melting points were determined with a Büchi B-540 apparatus and were uncorrected.

General Procedures. Coupling of Fmoc-amino acid-OPfp-esters to amino groups was performed with 3 equiv Fmoc-AA-OPfp and 1 equiv Dhbt-OH in DMF. Fmoc deprotection was effected with 20% piperidine in DMF for 2 + 18 min followed by washing of the resin six times with DMF. The resin was washed six times with the appropriate solvent between each reaction step. Amino acid couplings were followed by the Kaiser test.[26] Two equivalents of copper(I) iodide was used for practical reasons because of the small-scale reactions (ca. 5 mg of resin), but lower stoichiometry can be used (0.01 equiv dissolved in pyridine).

Analysis. Cleavage of the peptide for analytical purposes was effected with 0.1 M NaOH (aq) for 2 h in a small Eppendorf tube followed by neutralization with 0.1 M HCl (aq) and centrifugation. The supernatant was analyzed by analytical HPLC and collected fractions by ESI-MS.

Preparation of the α-azido acids used in the experimental work has been described previously.[27] Fmoc-Gly-ol and phenyl-3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-α-D-galactopyranoside were kindly provided by Dr. Jürgen Beyer and Dr. Shiro Komba, respectively. All amino acids were L-amino acids. The following commercially available chemicals were used as purchased without further purification: 1-azidoadamantane, 4-azidoaniline hydrochloride, CuBr·Me_2S, CuCl, CuI, Dhbt-OH, DIAD, DIPEA, EEDQ, Fmoc-L-propargylglycine, Fmoc-Aa-OH/Fmoc-Aa-OPfp, 2-furoyl chloride, HATU, HMBA, HOAt, MSNT, *N*-ethylmorpholine, *N*-methylimidazole, H-Phe-O^{t}Bu·HCl, $(PhO)_2P(O)N_3$, piperidine, propargylic acid, PyAOP, TBTU, trimethylsilyl azide, and triphenylphosphine.

Abbreviations: Dhbt-OH, 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine; DIAD, diisopropyl azodicarboxylate; DIPEA, *N*,*N*-diisopropylethylamine; EEDQ, 2-ethoxy-1-ethoxy-

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(27) Tornøe, C. W.; Davis, P.; Porreca, F.; Meldal, M. *J. Pept. Sci.* **2000**, *6*, 594−602.

carbonyl-1,2-dihydroquinoline; FGFG, Phe-Gly-Phe-Gly; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; HMBA, 4-hydroxymethylbenzoic acid; HOAt, 7-aza-1-hydroxybenzotriazole; MSNT, mesitylenesulfon-1-yl-3-nitro-1,2,4-triazole; NEM, *N*-ethylmorpholine; TBTU, *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide; PyAOP, 7-azabenzotriazol-1-yl-*N*-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate. One- and three-letter codes are used for the amino acids according to IUPAC rules.

Propynoyl-Phe-Gly-Phe-Gly-HMBA-PEGA$_{800}$ (1). PEGA$_{800}$ resin (2.5 g, 0.41 mmol/g, 10 mmol) was treated with a solution of 4-hydroxymethylbenzoic acid (HMBA, 3 equiv), TBTU (2.9 equiv), and NEM (4 equiv) in DMF after 5 min of preactivation. After the resin was washed with DMF, it was treated with a solution of Fmoc-Gly-OH (3 equiv), MSNT (3 equiv), and MeIm (6 equiv) for 1 h. The MSNT coupling was repeated. The Fmoc group was removed as described in the general procedures. The unprotected amine was acylated with 3 equiv of Fmoc-Phe-OPfp using Dhbt-OH (1 equiv) as catalyst in DMF. The acylation was followed by Fmoc deprotection and similar acylation with Fmoc-Gly-OPfp and Fmoc-Phe-OPfp as described above. The resin was washed with CH_2Cl_2 after Fmoc deprotection. Propargylic acid (3 equiv) and EEDQ (3.1 equiv) were mixed in CH_2Cl_2 and transferred to the resin (reaction for 16 h). The resin was washed, a small sample was cleaved, and the product was analyzed by HPLC and MS. HPLC: t_R = 12.1 min. ESI-MS: calcd ($MH^+ = C_{25}H_{27}N_4O_6^+$), 479.2 Da; found ($MH^+$), *m*/*z* 479.3.

General Procedure to 1-Alkyl/Aryl-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3a−s). DIPEA (50 equiv), CuI (2 equiv), and R−N_3 (2 equiv) were added to resin **1** (5 mg of resin, ca. 2 μmol swollen in 200 μL of THF) and reacted for 16 h at 25 °C, unless stated otherwise. The resin samples (**2a**−**s**) were washed with THF, water, and THF. A sample of each resin was cleaved and the product analyzed by HPLC and MS. Conversions were above 95% (except for **3a** and **3f**) with 75%−99% purity (Table 1).

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe Gly-OH (3a). R−N_3: 2-azido-2-methylpropionic acid. No CuI was added, giving 0% conversion.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3b). R−N_3: 2-azido-2-methylpropionic acid. HPLC: t_R = 13.1 min. ESI-MS: calcd ($MH^+ = C_{29}H_{34}N_7O_8^+$), 608.2 Da; found ($MH^+$), *m*/*z* 608.1.

1-(1-Carboxy-1-methylpropyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3c). R−N_3: 2-azido-2-methylbutanoic acid. HPLC: t_R = 13.6 min. ESI-MS: calcd ($MH^+ = C_{30}H_{36}N_7O_8^+$), 622.3 Da; found ($MH^+$), *m*/*z* 622.1.

1-(1-Carboxy-1-ethylpropyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3d). R−N_3: 2-azido-2-ethylbutanoic acid. HPLC: t_R = 14.2 min. ESI-MS: calcd ($MH^+ = C_{31}H_{38}N_7O_8^+$), 636.3 Da; found ($MH^+$), *m*/*z* 636.1.

1-(1-Carboxy-1-propylbutyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3e). R−N_3: 2-azido-2-propylpentanoic acid. HPLC: t_R = 15.7 min. ESI-MS: calcd ($MH^+ = C_{32}H_{42}N_7O_8^+$), 664.3 Da; found ($MH^+$), *m*/*z* 664.2.

1-(1-Carboxydiphenylmethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3f). R−N_3: 2-azido-2,2-diphenylacetic acid. 0% conversion after 48 h at 50 °C.

1-(1-Carboxymethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3g). R−N_3: 2-azidoacetic acid. HPLC: t_R = 12.1 min. ESI-MS: calcd ($MH^+ = C_{27}H_{30}N_7O_8^+$), 580.2 Da; found ($MH^+$), *m*/*z* 580.0.

1-(1-Carboxy-pentyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3h). R−N_3: (±)-2-azidohexanoic acid. HPLC: t_R = 14.6 and 14.8 min (the starting material was racemic). ESI-MS: calcd ($MH^+ = C_{31}H_{38}N_7O_8^+$), 636.3 Da; found ($MH^+$), *m*/*z* 636.2 for both peaks.

1-(1-Carboxypentadecyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3i). R−N_3: (±)-2-azidohexadecanoic acid. HPLC: t_R = 23.1 and 23.4 min (the starting material was racemic). ESI-MS: calcd ($MH^+ = C_{41}H_{58}N_7O_8^+$), 776.4 Da; found ($MH^+$), *m*/*z* 776.1 for both peaks.

1-(1-Carboxyphenylmethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3j). R−N_3: (±)-2-azido-2-phenylacetic acid. HPLC: t_R = 14.1 and 14.3 min (the starting material was racemic). ESI-MS: calcd ($MH^+ = C_{33}H_{34}N_7O_8^+$), 656.2 Da; found ($MH^+$), *m*/*z* 656.3 for both peaks.

1-(4-Aminophenyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3k). R−N_3: 4-azidoaniline hydrochloride. HPLC: t_R = 12.6 min. ESI-MS: calcd ($MH^+ = C_{31}H_{33}N_8O_6^+$), 613.2 Da; found ($MH^+$), *m*/*z* 613.2.

1-[(*S*)-2-Amino-5-guanidinopentyl]-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3l). R−N_3: **15**. The Pmc group was removed with TFA/triisopropylsilane/water 95:2.5:2.5 for 2.5 h and then the Fmoc group was removed prior to analysis. HPLC: t_R = 11.1 min. ESI-MS: calcd ($MH^+ = C_{31}H_{42}N_{11}O_6^+$), 664.33 Da; found ($MH^+$), *m*/*z* 664.30.

1-[(*S*)-2-Amino-3-carboxy-propyl]-1*H*-[1,2,3]-triazol-4-yl-carbonyl-Phe-Gly-Phe-Gly-OH (3m). R−N_3: **16**. The *tert*-butyl group was removed with TFA/triisopropylsilane/water 95:2.5:2.5 for 2.5 h and then the Fmoc group was removed prior to analysis. HPLC: t_R = 10.8 min. ESI-MS: calcd ($MH^+ = C_{29}H_{35}N_8O_8^+$), 623.26 Da; found ($MH^+$), *m*/*z* 623.31.

1-(2-Amino-ethyl)-1*H*-[1,2,3]-triazol-4-yl-carbonyl-Phe-Gly-Phe-Gly-OH (3n). R−N_3: **17**. The Fmoc group was removed prior to analysis. HPLC: t_R = 11.0 min. ESI-MS: calcd ($MH^+ = C_{27}H_{33}N_8O_6^+$), 565.2 Da; found ($MH^+$), *m*/*z* 565.1.

1-[(*S*)-2-Amino-4-methylsulfanylbutyl]-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3o). R−N_3: **18**. The Fmoc group was removed prior to analysis. HPLC: t_R = 12.0 min. ESI-MS: calcd ($MH^+ = C_{30}H_{39}N_8O_6S^+$), 639.27 Da; found ($MH^+$), *m*/*z* 639.16.

1-[(*S*)-2-Amino-3-phenylpropyl]-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3p). R−N_3: **19**. The Fmoc group was removed prior to analysis. HPLC: t_R = 12.7 min. ESI-MS: calcd ($MH^+ = C_{34}H_{39}N_8O_6^+$), 655.3 Da; found ($MH^+$), *m*/*z* 655.2.

1-(1-Adamantyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3q). R−N_3: 1-Azidoadamantane. HPLC: t_R = 17.2 min. ESI-MS: calcd ($MH^+ = C_{35}H_{42}N_7O_6^+$), 656.3 Da; found ($MH^+$), *m*/*z* 656.3.

1-(2-Deoxy-1-phenyl-1-thio-α-D-galactopyranos-2-yl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3r). R−N_3: phenyl-3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-α-D-galactopyranoside. HPLC: t_R = 13.9 min. ESI-MS: calcd ($MH^+ = C_{37}H_{42}N_7O_{10}S^+$), 776.3 Da; found ($MH^+$), *m*/*z* 776.8.

1*H*-[1,2,3]-Triazol-4-ylcarbonyl-Phe-Gly-Phe-Gly-OH (3s). R−N_3: trimethylsilyl azide. Reaction was at 50 °C without DIPEA. HPLC: t_R = 12.3 min. ESI-MS: calcd ($MH^+ = C_{25}H_{28}N_7O_6^+$), 522.2 Da; found ($MH^+$), *m*/*z* 522.3.

Compounds 4a and 4b. Resins **2n** and **2p** (2.5 mg of resin, ca. 1 μmol swollen in DMF) were Fmoc-deprotected, washed, and acylated with Fmoc-Thr(^{t}Bu)-OPfp (3 equiv) and Dhbt-OH (1 equiv) in DMF for 8 h. After washing with DMF, water, and THF, a sample of each resin was cleaved and the product analyzed by HPLC and MS (both **4a** and **4b** showed conversion and purity above 95%). **(4a)** HPLC: t_R = 12.6 min. ESI-MS: calcd ($MH^+ = C_{35}H_{48}N_9O_8^+$), 722.4 Da; found ($MH^+$), *m*/*z* 722.2. **(4b)** HPLC: t_R = 14.3 min. ESI-MS: calcd ($MH^+ = C_{42}H_{54}N_9O_8^+$), 812.4 Da; found ($MH^+$), *m*/*z* 812.4.

Compound 5. DIPEA (6 equiv), HOAt (1 equiv), PyAOP (3 equiv), and H−Phe-O^{t}Bu·HCl (3 equiv) were added to resin **2g** (2.5 mg of resin, ca. 1 μmol swollen in DMF) under argon. After 16 h of reaction, it was washed, cleaved, and analyzed by HPLC and MS (70% conversion to **5**). HPLC: t_R = 17.0 min. ESI-MS: calcd ($MH^+ = C_{40}H_{47}N_8O_9^+$), 783.3 Da; found ($MH^+$), *m*/*z* 783.2.

Compound 6. 2-Furoyl chloride (5 equiv) and DIPEA (10 equiv) were added to resin **2s** (2.5 mg resin, ca. 1 μmol swollen in dry dichloromethane) under argon. After 2 h it was washed and analyzed by HPLC and MS (>90% conversion and 67% purity). HPLC: t_R = 16.0 min. ESI-MS: calcd ($M + K^+ = C_{30}H_{29}N_7O_8K^+$), 654.2 Da; found ($M + K^+$), *m*/*z* 654.0.

Fmoc-L-propargylglycyl-Phe-Gly-Phe-Gly-HMBA-PEGA$_{800}$ (7). Resin **7** was prepared in a manner similar to that of resin **1** but instead of propargylic acid and EEDQ in CH_2Cl_2, Fmoc-L-propargylglycine (3 equiv), TBTU (2.9 equiv),

and NEM (4 equiv) were added to the resin after 5 min of preactivation in DMF. The resin was washed with DMF and lyophilized. A sample of the resin was Fmoc-deprotected, cleaved, and analyzed by HPLC and MS. HPLC: t_R = 11.0 min, ESI-MS: calcd ($MH^+ = C_{27}H_{32}N_5O_6^+$), 522.2 Da; found ($MH^+$), *m*/*z* 522.4.

General Procedure to *N*-Substituted Histidine Analogues (8a−e). DIPEA (50 equiv), CuI (2 equiv), and R−N_3 (2 equiv) were added to resin **7** (0.41 mmol/g, 5 mg of resin, ca. 2 μmol swollen in 200 μL of THF). Each reaction was left for 16 h and then washed with THF, water, and DMF. Fmoc deprotection was effected, a sample of each resin was cleaved, and the product was analyzed by HPLC and MS.

(*S*)-2-Amino-3-[1-(1-carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-yl]propionyl-Phe-Gly-Phe-Gly-OH (8a). R−N_3: 2-azido-2-methylpropionic acid. HPLC: t_R = 11.3 min. ESI-MS: calcd ($MH^+ = C_{31}H_{39}N_8O_8^+$), 651.3 Da; found ($MH^+$), *m*/*z* 651.5.

(*S*)-2-Amino-3-[1-((*S*)-2-amino-3-phenylpropyl)-1*H*-[1,2,3]-triazol-4-yl]propionyl-Phe-Gly-Phe-Gly-OH (8b). R−N_3: **19**. HPLC: t_R = 11.8 min. ESI-MS: calcd ($MH^+ = C_{36}H_{44}N_9O_6^+$), 698.3 Da; found ($MH^+$), *m*/*z* 698.3.

(*S*)-2-Amino-3-[1-(2-deoxy-1-phenyl-1-thio-α-D-galactopyranos-2-yl)-1*H*-[1,2,3]-triazol-4-yl]propionyl-Phe-Gly-Phe-Gly-OH (8c). R−N_3: phenyl-3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-α-D-galactopyranoside. HPLC: t_R = 12.3 min. ESI-MS: calcd ($MH^+ = C_{39}H_{47}N_8O_{10}S^+$), 819.3 Da; found ($MH^+$), *m*/*z* 819.3.

(*S*)-2-Amino-3-[1-(4-aminophenyl)-1*H*-[1,2,3]-triazol-4-yl]propionyl-Phe-Gly-Phe-Gly-OH (8d). R−N_3: 4-azidoaniline hydrochloride. HPLC: t_R = 11.4 min. ESI-MS: calcd ($MH^+ = C_{33}H_{38}N_9O_6^+$), 656.3 Da; found ($MH^+$), *m*/*z* 656.2.

(*S*)-2-Amino-3-[1*H*-[1,2,3]-triazol-4-yl]propionyl-Phe-Gly-Phe-Gly-OH (8e). R−N_3: trimethylsilyl azide. Reaction at 50 °C without DIPEA. 0% conversion.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazole-4-carbonyl-Phe-Gly-OH (9). DIPEA (50 equiv), CuI (2 equiv), and 2-azido-2-methylpropionic acid (2 equiv) were added to resin **14** (72 mg, 26 mmol, swollen in THF) and reacted for 16 h. After washing with THF, water, and THF, the product was cleaved from the resin with 0.1 M NaOH (aq), neutralized with 0.1 M HCl (aq), and purified by preparative RP-HPLC, affording 8 mg of **9** (73% yield). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.74 (s, 6 H, Aib-β-CH_3), 3.1 (m, 2 H, Phe-H^β), 3.76 (d, 2 H, *J* = 5 Hz, Gly-H^α), 4.8 (m, 1 H, Phe-H^α), 7.1−7.3 (m, 5 H, Phe aromatic protons), 8.26 (d, 1 H, *J* = 8 Hz, Phe-N*H*), 8.36 (t, 1 H, *J* = 5 Hz, Gly-N*H*), 8.50 (s, 1 H, triazole-H^5). ^{13}C NMR (62.9 MHz, MeCN-d_3/D_2O): δ = 24.4 (CH_3^β, Aib), 36.9 (CH_2^β, Phe), 40.5 (CH_2^α, Gly), 53.8 (CH^α, Phe), 65.0 (C^α, Aib), 125.4 (triazole-C^5), 126.5, 128.2, 128.9, 136.5 (Phe aromatic carbons), 141.0 (triazole-C^4), 160.3 (triazole-*C*O), 171.6, 172.0, 173.1 (Phe-*C*O, Gly-*C*O, Aib-*C*O). HR-MS: calcd ($M + H^+ = C_{18}H_{22}N_5O_6^+$), 404.1565 Da; found ($M + H^+$), *m*/*z* 404.1573.

1-(Adamantan-1-yl)-1*H*-[1,2,3]-triazole-4-carbonyl-Phe-Gly-OH (10). DIPEA (50 equiv), CuI (2 equiv), and 1-azidoadamantane (2 equiv) were added to resin **14** (118 mg, 42 mmol, swollen in THF) and reacted for 16 h. After washing with THF, water, and THF, the product was cleaved from the resin with 0.1 M NaOH (aq), neutralized with 0.1 M HCl (aq), and purified by preparative RP-HPLC, affording 17 mg of **10** (87% yield). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.73 (s, 6 H, Adamantyl-CH_2), 2.18 (br s, 9 H, Adamantyl-C*H*, −CH_2), 3.1 (m, 2 H, Phe-H^β), 3.81 (d, 2 H, *J* = 6 Hz, Gly-H^α), 4.8 (m, 1 H, Phe-H^α), 7.1−7.3 (m, 5 H, Phe aromatic protons), 8.25 (d, 1 H, *J* = 9 Hz, Phe-N*H*), 8.47 (t, 1 H, *J* = 6 Hz, Gly-N*H*), 8.62 (s, 1 H, triazole-H^5). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 29.2 (*C*H, adamantyl), 35.5, 42.4 (CH_2, adamantyl), 37.8 (CH_2^β, Phe), 40.5 (CH_2^α, Gly), 53.8 (CH^α, Phe), 60.1 (C_q, adamantyl), 123.7 (triazole-C^5), 126.6, 128.4, 129.5, 138.1 (Phe aromatic carbons), 142.1 (triazole-C^4), 159.8 (triazole-*C*O), 171.4, 171.6 (Phe-*C*O, Gly-*C*O). HR-MS: calcd ($M + Na^+ = C_{24}H_{29}N_5O_4Na^+$), 474.2112 Da; found ($M + Na^+$), *m*/*z* 474.2090.

General Procedure to Propynoyl-Xxx-Phe-Gly-OH (11a−l). Resins **11a−l** were prepared in a manner similar to that of resin **1** until H-Phe-Gly-HMBA-PEG$_{800}$ was obtained and it was acylated with 12 different Fmoc-amino acid-OPfp esters [Ala, Pro, Thr(^{t}Bu), Tyr(^{t}Bu), Asp(^{t}Bu), Asn(Trt), His(Trt), Cys(Trt), Met, Lys(Boc), Trp(Boc) and Arg(Pmc)], Fmoc-deprotected, and acylated with propargylic acid as with resin **14**, affording resins **11a−l**.

General Procedure to 1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Xxx-Phe-Gly-OH (12a−l). DIPEA (50 equiv), CuI (2 equiv), and 2-azido-2-methylpropionic acid (2 equiv) were added to resin samples **11a−l** (0.41 mmol/g, 5 mg of resin, ca. 2 μmol swollen in 200 μL of THF). Each reaction was left for 16 h and then washed with THF, water, and THF. A sample of each resin was cleaved and the product analyzed by HPLC and MS (conversions were >95% and purities ranging from 80% to 99%, Table 2).

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Ala-Phe-Gly-OH (12a) HPLC: t_R = 10.5 min. ESI-MS: calcd ($M + Na^+ = C_{21}H_{26}N_6O_7Na^+$), 497.2 Da; found ($M + Na^+$), *m*/*z* 497.2.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Pro-Phe-Gly-OH (12b) HPLC: t_R = 11.3 min. ESI-MS: calcd ($M + Na^+ = C_{23}H_{28}N_6O_7Na^+$), 523.2 Da; found ($M + Na^+$), *m*/*z* 523.2.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Thr(^{t}Bu)-Phe-Gly-OH (12c) HPLC: t_R = 14.2 min. ESI-MS: calcd ($M + Na^+ = C_{26}H_{36}N_6O_8Na^+$), 583.3 Da; found ($M + Na^+$), *m*/*z* 583.0.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Tyr(^{t}Bu)-Phe-Gly-OH (12d) HPLC: t_R = 14.9 min. ESI-MS: calcd ($M + Na^+ = C_{31}H_{38}N_6O_8Na^+$), 645.3 Da; found ($M + Na^+$), *m*/*z* 645.1.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Asp(^{t}Bu)-Phe-Gly-OH (12e) HPLC: t_R = 13.3 min. ESI-MS: calcd ($M + Na^+ = C_{26}H_{34}N_6O_9Na^+$), 597.2 Da; found ($M + Na^+$), *m*/*z* 597.1.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Asn(Trt)-Phe-Gly-OH (12f) HPLC: t_R = 16.7 min. ESI-MS: calcd ($M + Na^+ = C_{41}H_{41}N_7O_8Na^+$), 782.3 Da; found ($M + Na^+$), *m*/*z* 782.4.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-His(Trt)-Phe-Gly-OH (12g). HPLC: t_R = 15.7 min. ESI-MS: calcd ($MH^+ = C_{43}H_{43}N_8O_7^+$), 783.3 Da; found ($MH^+$), *m*/*z* 783.4.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Cys(Trt)-Phe-Gly-OH (12h) HPLC: t_R = 18.4 min. ESI-MS: calcd ($M + Na^+ = C_{40}H_{40}N_6O_7SNa^+$), 771.3 Da; found ($M + Na^+$), *m*/*z* 772.0.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Met-Phe-Gly-OH (12i) HPLC: t_R = 12.0 min. ESI-MS: calcd ($M + Na^+ = C_{23}H_{30}N_6O_7SNa^+$), 557.2 Da; found ($M + Na^+$), *m*/*z* 557.6.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Lys(Boc)-Phe-Gly-OH (12j) HPLC: t_R = 13.7 min. ESI-MS: calcd ($M + Na^+ = C_{29}H_{41}N_7O_9Na^+$), 654.3 Da; found ($M + Na^+$), *m*/*z* 654.1.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Trp(Boc)-Phe-Gly-OH (12k) HPLC: t_R = 16.8 min. ESI-MS: calcd ($M + Na^+ = C_{34}H_{39}N_7O_9Na^+$), 712.3 Da; found ($M + Na^+$), *m*/*z* 712.0.

1-(1-Carboxy-1-methylethyl)-1*H*-[1,2,3]-triazol-4-ylcarbonyl-Arg(Pmc)-Phe-Gly-OH (12l) HPLC: t_R = 16.2 min. ESI-MS: calcd ($M + Na^+ = C_{38}H_{51}N_9O_{10}SNa^+$), 848.4 Da; found ($M + Na^+$), *m*/*z* 848.2.

Compounds 13a and 13b. Compound **19** (10 equiv) was added to resin **1** (ca. 10 μmol swollen in toluene) under argon and heated to 110 °C for 16 h. The Fmoc group was removed after washing with toluene and DMF, then a sample was cleaved, and the product was analyzed by HPLC, MS, and ^{1}H MAS NMR (>95% conversion and purity for the two regioisomers, **13a** and **13b**). **13a**: HPLC: t_R = 12.7 min. ESI-MS: calcd ($MH^+ = C_{34}H_{39}N_8O_6^+$), 655.3 Da; found ($MH^+$), *m*/*z* 655.2. ^{1}H MAS NMR of amide region (500 MHz, DMSO-d_6): δ = 8.13 (d, 1 H, *J* = 8.6 Hz, Phe-N*H*), 8.34 (t, 1 H, *J* = 8.5 Hz, Gly-N*H*), 8.29 (t, 1 H, *J* = 5.5 Hz, Gly′-N*H*), 8.50 (s, 1 H, triazole-H^5). **13b**: HPLC: t_R = 13.1 min. ESI-MS: calcd ($M = C_{34}H_{39}N_8O_6^+$), 655.3 Da; found (MH^+), *m*/*z* 655.2. ^{1}H MAS NMR

of amide region (500 MHz, DMSO-d_6): δ = 8.13 (d, 1 H, J = 8.4 Hz, Phe-N*H*), 8.23 (s, 1 H, triazole-H^4), 8.31 (m, 1 H, Gly-N*H*), 8.35 (t, 1 H, J = 5.4 Hz, Gly′-N*H*).

Propynoyl-Phe-Gly-HMBA-PEGA$_{800}$ (14). Resin **14** was prepared in a manner similar to that of resin **1** until H-Phe-Gly-HMBA-PEGA$_{800}$ was obtained, and it was then washed with CH_2Cl_2. Propargylic acid (3 equiv) and EEDQ (3.1 equiv) were mixed in CH_2Cl_2, transferred to the resin, and reacted for 16 h. The resin was washed with CH_2Cl_2, cleaved, and analyzed by HPLC and MS. HPLC: t_R = 8.9 min. ESI-MS: calcd (M + Na$^+$ = $C_{14}H_{14}N_2O_4Na^+$), 297.1 Da; found (M + Na$^+$), m/z 297.0.

General Procedure for Conversion of Fmoc-Amino Alcohols to Fmoc-Amino Azides (15−19). The Fmoc-amino alcohol (1 equiv, 1 mmol), Ph_3P (1.5 equiv), and HN_3 in toluene (5 equiv, 1.5 M) were dissolved in dry THF (12 mL) under argon and cooled to 0 °C. Diisopropyl azodicarboxylate (1.6 equiv) was added dropwise, and the reaction was stirred at 25 °C for 1.5 h. Everything was concentrated in vacuo and purified by flash chromatography.

(4-[(Amino-(2,2,5,6,8-pentamethylchroman-7-sulfonylimino)methyl)amino]-(*S*)-1-azidomethylbutyl)carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester, Fmoc-Arg(Pmc)-ψ[CH$_2$N$_3$] (15). Fmoc-Arg(Pmc)-ol (0.717 mmol) afforded **15** (350 mg, 72%) after flash chromatography (PE/EA 2:5). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30 (s, 6H, $C_q(CH_3)_2$), 1.50 (m, 4H, CH_2^{β} and CH_2^{γ}), 1.78 (m, 2H, Ar−CH_2CH_2), 2.12 and 2.62 (s, 9H, Ar−CH_3), 2.59 (m, 2H, Ar−CH_2), 3.21 (m, 2H, CH_2^{δ}), 3.29 (m, 2H, CH_2N_3), 3.72(m, 1H, CH^{α}), 4.16 (m, 1H, $CHCH_2O$), 4.38 (m, 2H, $CHCH_2O$), 5.42 (d, J = 8 Hz, 1H, NH^{α}), 6.36 (br s, 3H, NH and NH_2 of guanidino group), 7.28−7.78 (8H, Fmoc-aromatic protons). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.4, 15.5 and 18.8 (3·Ar-CH_3), 19.9 (Ar-CH_2), 27.0 (CH_2^{γ}), 28.0 ($C_q(CH_3)_2$), 30.6 (CH_2^{β}), 34.0 (Ar−CH_2CH_2), 42.0 (CH_2^{δ}), 48.5 ($CHCH_2O$), 52.1 (CH^{α}), 56.1 (CH_2N_3), 68.1 ($CHCH_2O$), 74.9 Ar-OC_q), 119.3−145.1 (aromatic carbons), 154.9 (C=NH), 157.6 (Fmoc-*C*O). Mp: 80−82 °C. IR: 1719, 2101 cm^{-1}. $[\alpha]^{25}_D$ = −5° (c = 2.0, $CHCl_3$).

4-Azido-(*S*)-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-butyric Acid tert-Butyl Ester, Fmoc-Asp(tBu)-ψ[CH$_2$N$_3$] (16). Fmoc-Asp(^{t}Bu)-ol (2.68 mmol) afforded **16** as a syrup (1.11 g, 98%) after flash chromatography (PE/EA 5:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.46 (s, 9H, *tert*-butyl), 2.53 (d, 2H, J = 5 Hz, CH_2CO), 3.51 (m, 2H, CH_2N_3), 4.15 (m, 1H, CH^{α}), 4.22 (t, J = 7 Hz, 1H, $CHCH_2O$), 4.42 (d, J = 7 Hz, 2H, $CHCH_2O$), 5.43 (d, J = 8 Hz, 1H, N*H*), 7.28−7.78 (8H, Fmoc aromatic protons). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 28.4 (CH_3), 37.7 (CH_2CO), 47.6 ($CHCH_2O$), 48.3 (CH^{α}), 54.1 (CH_2N_3), 67.3 ($CHCH_2O$), 82.1 (C_qCH_3), 120.4−144.2 (aromatic carbons), 156.0 (Fmoc-*C*O), 170.5 (Asp-*C*O). IR: 1732, 2103 cm^{-1}. $[\alpha]^{25}_D$ = −3° (c = 1.0, $CHCl_3$).

(1-Azidoethyl)carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester, Fmoc-Gly-ψ[CH$_2$N$_3$] (17). Fmoc-Gly-ol (2.02 mmol) afforded **17** (530 mg, 85%) after flash chromatography (PE/EA 5:2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.38 (m, 2H, $CH_{2\alpha}$), 3.43 (m, 2H, CH_2N_3), 4.23 (t, J = 7 Hz, 1H, $CHCH_2O$), 4.44 (d, J = 7 Hz, 2H, $CHCH_2O$), 5.09 (m, 1H, N*H*), 7.29−7.79 (8H, Fmoc aromatic protons). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 40.0 (CH^{α}), 46.7 ($CHCH_2O$), 50.6 (CH_2N_3), 66.4 ($CHCH_2O$), 119.5−143.3 (aromatic carbons), 155.8 (Fmoc-*C*O). Mp: 87−89 °C. IR: 1721, 2105 cm^{-1}. HR-MS: calcd (M + Na$^+$ = $C_{27}H_{31}N_5O_6Na^+$), 331.1165 Da; found (M + Na$^+$), m/z 331.1170.

(*S*)-(1-Azidomethyl-3-methylsulfanylpropyl)carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester, Fmoc-Met-ψ[CH$_2$N$_3$] (18). Fmoc-Met-ol (1.41 mmol) afforded **18** (261 mg, 48%) after flash chromatography (PE/EA 4:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.80 (m, 2H, CH_2^{β}), 2.09 (s, 3H, SCH_3), 2.50 (t, J = 7 Hz, 2H, CH_2^{γ}), 3.44 (m, 2H, CH_2N_3), 3.91 (m, 1H, CH^{α}), 4.21 (t, J = 7 Hz, 1H, $CHCH_2O$), 4.45 (d, J = 7 Hz, 2H, $CHCH_2O$), 4.95 (m, 1H, N*H*), 7.28−7.78 (8H, Fmoc aromatic protons). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 15.9 (SCH_3), 30.9 (CH_2^{γ}), 31.9 (CH_2^{β}), 47.7 ($CHCH_2O$), 50.6 (CH^{α}), 54.9 (CH_2N_3), 67.1 ($CHCH_2O$), 120.4−144.2 (aromatic carbons), 156.2 (Fmoc-*C*O). Mp: 92.6−93.5 °C. IR: 1793, 2103 cm^{-1}. $[\alpha]^{25}_D$ = −11° (c = 1.0, $CHCl_3$).

(1-Azidomethyl-(*S*)-2-phenylethyl)carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester, Fmoc-Phe-ψ[CH$_2$N$_3$] (19). Fmoc-Phe-ol (2.09 mmol) afforded **19** (698 mg, 84%) after flash chromatography (PE/EA 5:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.86 (m, 2 H, CH_2N_3), 3.40 (m, 2H, CH_2^{β}, Phe), 4.04 (m, 1 H, CH^{α}, Phe), 4.20 (t, 1 H, J = 6 Hz, Fmoc-$CHCH_2$), 4.40 (d, 2 H, J = 6 Hz, Fmoc-CH_2), 4.84 (m, 1 H, Phe-N*H*), 7.18−7.78 (13 H, fluorenyl and Phe aromatic protons). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 38.5 (Phe-CH_2–N_3), 47.7 (Fmoc-$CHCH_2$), 52.3 (CH^{α}, Phe), 53.6 (CH_2^{β}, Phe), 67.1 (Fmoc-CH_2), 120.4−144.2 (fluorenyl and Phe aromatic carbons), 156.0 (*C*=O). Mp: 76.2−77.6 °C. $[\alpha]^{25}_D$ = −14° (c = 1.0, $CHCl_3$). IR: 1715 and 2103 cm^{-1}. The data were in agreement with literature[29] values except for the higher melting point observed.

Acknowledgment. This work was supported by the Danish National Research Foundation. The assistance of Flemming Hansen and Henning O. Sørensen with the X-ray structure is greatly appreciated.

Supporting Information Available: The crystallographic information file (CIF) for 2-azido-2-methylpropanoic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

JO011148J

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