The Pivaloylglycol Anchor Group: A New Platform for a Photolabile Linker in Solid-Phase Synthesis

Stefan Peukert and Bernd Giese*

Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

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We have designed a new photolabile linker (**2**) based on 2-pivaloylglycerol for the solid-phase synthesis of acids. The linker was prepared in six steps and anchored to the support via an amide bond. Photocleavage is a two-step process, in which the immobilized acids are released by photolytic generation of a radical center and subsequent spontaneous β-C,O bond scission. The pivaloyl linker (**2**) was found to cleave with high yields and purities the acids in various solvents (THF, CH_2Cl_2, dioxane, DMSO) by irradiation with light above 320 nm. Using this linker, we have demonstrated the solid-phase synthesis of test compounds by peptide synthesis, palladium-catalyzed cross coupling, and epoxidation. The linker proved to be stable toward the treatment with acids and bases. The photolysis rates of our pivaloyl linker (**2**) were compared with the rates of a *o*-nitrobenzyl photolinker (**1**) and proved to be superior.

Introduction

The rapidly growing field of combinatorial chemistry has renewed interest in the use of solid-phase organic synthesis techniques as a convenient means of assembling molecules.[1,2] In addition to synthetic methods amenable to a solid-phase approach, the need for improved and novel linkers anchoring the molecules to the support has greatly expanded. Since their first description, photolabile linkers have received considerable attention during the past 25 years.[3]

It is widely recognized that photolysis offers a mild method of cleavage that takes place under neutral conditions. This detachment is orthogonal to acidic and basic reaction conditions and therefore affords additional flexibility in the synthesis on solid support. The release of the molecules can occur after removal of any protecting groups and washing of the resin, thereby affording the compounds suitable for biological screening without contamination by cleavage reagents.

Photocleavage facilitates a controlled release of molecules with the possibility to control the amount of liberated compound by the exposure time to UV light. Photolabile linkers proved to be valuable for the release of both ligands and tagging molecules.

Several photolabile linkers are currently available. *o*-Nitrobenzyl compounds (**1**) have been widely employed by many researchers for the generation of peptides,[4] oligosaccharides,[5] oligonucleotides,[6] small molecules,[7] and tagging moieties.[8] Less extensively, phenacyl-[9] and benzoin-based[10] linkers have been utilized in solid-phase chemistry in recent years. A new photolinker based on a benzyl thioether that releases molecules without an additional functional group has also been reported. However, its use is restricted to molecules with a biaryl unit.[11]

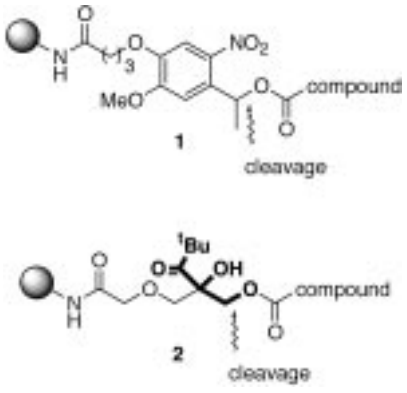

Figure 1.

To provide more options in this area, we wish to report the development of a new photolabile linker (**2**) with a pivaloylglycol moiety (bold type in compound **2**, Figure 1), which is based on radical-induced β-C,O bond cleavage.

Background

Our mechanistic studies on biological processes showed that radical-induced β-C,O bond cleavage plays a pivotal

(1) For reviews on combinatorial chemistry, see: (a) Frobel, K.; Krämer, T. *Chem. Unserer Zeit* **1996**, *30*, 270. (b) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288.

(2) For reviews on solid-phase organic synthesis, see: (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (b) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17.

(3) For a general review of the use of photolabile supports, see: Lloyd-Williams, P.; Albericio, F.; Giralt, E. *Tetrahedron* **1993**, *49*, 11065.

(4) (a) Rich, D. H.; Gurwara S. K. *J. Chem. Soc., Chem. Commun.* **1973**, 610. (b) Lloyd-Williams, P.; Albericio, F.; Giralt, E. *Int. J. Pept. Protein Res.* **1991**, *37*, 58.

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(9) (a) Wang, S.-S. *J. Org. Chem.* **1976**, *41*, 3258. (b) Bellof, D.; Mutter M. *Chimia* **1985**, *39*, 317.

(10) Rock, R. S.; Chan, S. I. *J. Org. Chem.* **1996**, *61*, 1526.

(11) Sucholeiki, I. *Tetrahedron Lett.* **1994**, *35*, 7307.

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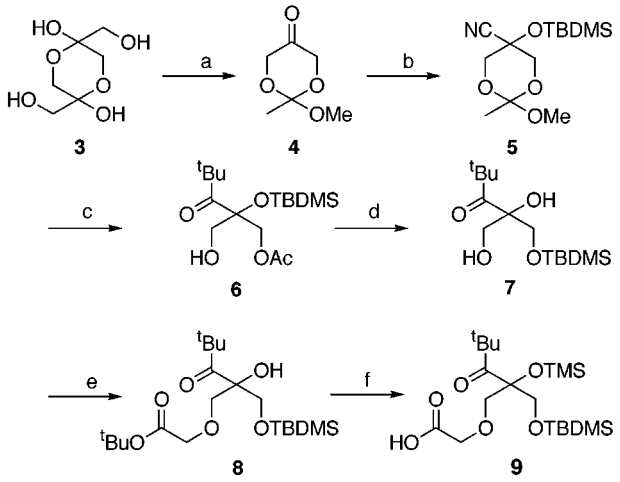
Scheme 1[a]



[a] Reagents: (a) $MeC(OMe)_3$, CSA, dioxane, 81%; (b) TBDMSCN, KCN, 18-crown-6, DMF, 84%: (c) (1) ^{t}BuLi, CuI, Et_2O, (2) AcOH, 84%; (d) K_2CO_3, MeOH, quant; (e) $BrCH_2CO_2{}^t$Bu, Ag_2O, DMF, 72%; (f) TMSOTf, 2,6-lutidine, 96%.

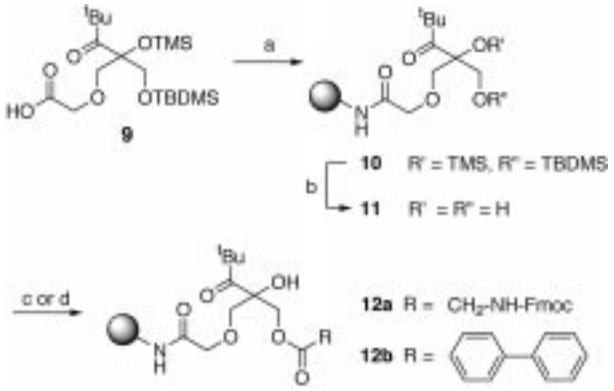
role in several systems. C-4′ DNA radicals can undergo a spontaneous heterolytic β-C,O bond scission, resulting in the cleavage of the DNA strand.[12] Radical-induced cleavage also takes place in the enzymatic deoxygenation of ribonucleotides by ribonucleotide reductase via a C-3 nucleoside radical.[13] A similar mechanism can operate in the β-elimination of phosphocholine from C-2 lysolecithin radicals.[14] Radicals were generated for our mechanistic studies on biological systems by photolysis of suitable radical precursors. The combination of the two reactions, photolytic generation of a radical center and subsequent spontaneous β-C,O bond scission, is utilized in our concept for a new photolabile linker.

Results and Discussion

Synthesis. The linker described below is based on a C-2 pivaloyl-substituted glycerol. *tert*-Butyl ketones are suitable as photolabile radical precursors when exposed to light below 340 nm.[15] The most common method of preparing photolabile supports is to anchor linkers bearing a carboxylic acid tether onto the support as an amide. Combining these facts, a suitable linker may be derived from pivaloyl-substituted glycerol by incorporation of a carboxylic acid moiety on one of the two primary alcohols. The remaining primary alcohol can then be used to immobilize the substrate.

The synthesis of carboxylic acid **9** is outlined in Scheme 1. The dimer of 1,3-dihydroxyacetone **3** was transformed via ortho ester **4**[14] into the silyl-protected cyanohydrin **5**. Copper(I)-catalyzed nucleophilic attack of *tert*-butyllithium and subsequent acidic hydrolysis yielded the *tert*-butyl ketone **6**. Deacetylation occurred with concomitant migration of the silyl group, affording compound **7**. The carboxyl group was introduced by alkylation with *tert*-butyl bromoacetate in the presence of silver(I) oxide to yield **8**. The use of the *tert*-butyl ester was requisite to avoid lactonization by participation of the tertiary hydroxyl group. This was followed by release of the acid and protection of the tertiary alcohol with trimethylsilyl triflate to afford linker **9**. This procedure requires chromatography only after the alkylation step. Intermediates **4** and **5** can be distilled, and intermediates **6** and **7** and the final product are isolated by filtration over silica gel to afford gram quantities of **9** in 40% overall yield.

Scheme 2[a]



[a] Reagents: (a) TentaGel S NH_2, DIC, CH_2Cl_2; (b) $(HF)_3{\cdot}Et_3N$, THF; (c) Fmoc-Gly-anhydride, DMAP; (d) biphenylcarboxylic acid, DIC, DMAP, THF.

Coupling to the Solid Phase and Attachment of Acids. With linker **9** in hand, we set out to explore its photolytic properties and its use in solid-phase chemistry. Coupling of **9** to commercially available amino support (TentaGel S NH_2) was conducted by activation of the silyl-protected linker with diisopropylcarbodiimide (Scheme 2). The anchoring proceeded with complete conversion as judged by the Kaiser test.[16] Desilylation of the two hydroxyl groups was conducted with triethylamine trishydrofluoride on the solid phase to afford the corresponding photolabile support **11**. Experiments in the homogeneous phase showed that this deprotection reaction proceeds with >75% yield.

To study the photolytic properties of the linker, the photolabile support was loaded with Fmoc-glycine (**12a**) and biphenylcarboxylic acid (**12b**). Attachment of amino acids in general was achieved using the symmetrical anhydride approach. The level of first amino acid attachment was estimated by piperidine-mediated cleavage of the Fmoc-protecting group and UV-spectroscopic analysis. Aromatic carboxylic acids were attached using the standard carbodiimide coupling protocol. These reactions were checked qualitatively by gel-phase ^{13}C NMR.[17] In no case was esterification of the tertiary hydroxyl group observed.

Mechanism of Photocleavage. Photocleavage starts with generation of an α-hydroxyalkyl radical (**12b** → **13**) via Norrish I reaction. To gain insight into the photocleavage mechanism not only resin **12b** but also model compound **17** was studied (Scheme 3).

(12) (a) Giese, B.; Beyrich-Graf, X.; Erdmann, P.; Petretta, M.; Schwitter, U. *Chem. Biol.* **1995**, *2*, 367. (b) Von Sonntag, C.; Hagen. U.; Schön-Bopp, A.; Schulte-Frohlinde, D. *Adv. Radical Biol.* **1981**, *9*, 109.

(13) (a) Licht, S.; Gerfer, G. J.; Stubbe, J. *Science* **1996**, *271*, 477. (b) Lenz, R.; Giese, B. *J. Am. Chem. Soc.* **1997**, *119*, 2784.

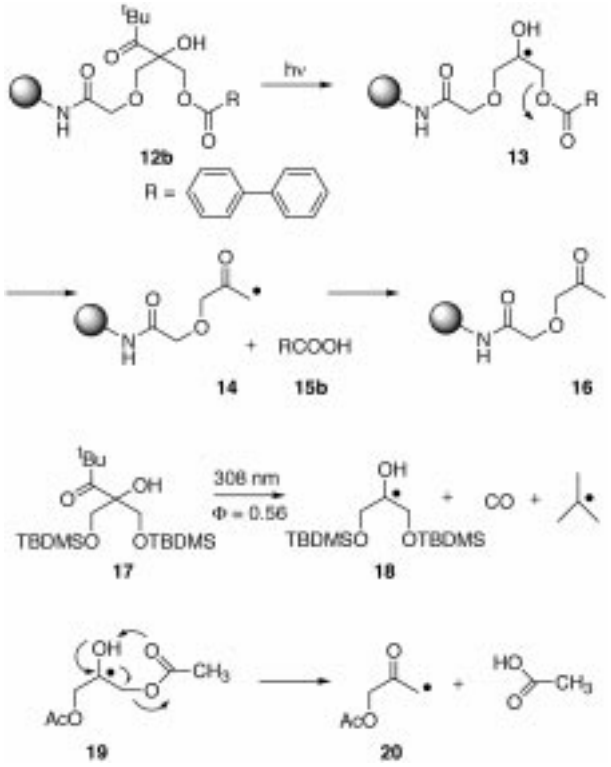
(14) Müller, S. N.; Batra, R.; Senn M.; Giese, B.; Kisel, M.; Shadyro, O. *J. Am. Chem. Soc.* **1997**, *119*, 2795.

(15) Bamford, C. H.; Norrish, R. G. W. *J. Chem. Soc.* **1935**, 1504.

(16) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.

(17) Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588.

Scheme 3



The UV spectrum of **17** exhibits n−π* carbonyl absorbances between 260 and 340 nm with a maximum at 297 nm ($\epsilon = 32$). The quantum yield for the photolytic radical generation (**17** → **18**) at 308 nm in acetonitrile was determined to be $\Phi = 0.56$. Our proposed mechanism of the subsequent β-C,O bond scission (**13** → **14**) is based on earlier investigations of C-2 glycerol radicals.[14] These experiments suggest a concerted elimination, where the glycerol radical **19** is converted into enolate radical **20** and acetic acid via a seven-membered hydrogen-bridged transition state. The fate of enolate radical **14** was investigated on the solid phase by gel-phase ^{13}C NMR of the cleaved support. Irradiation of resin **12b** in THF resulted in a clean conversion to resin **16**. This can be explained by H atom abstraction of the immobilized enolate radical **14** from the solvent to give resin-bound acetone (**16**).

Photolytic Properties. Cleavage yield, purity, and photolysis rates of the released Fmoc-glycine in various solvents and at different wavelengths were determined by photolyzing the suspended resin beads **12a** in quartz glass cells. The cleavage yield and photolysis rates were measured by UV spectroscopy of the supernatant solution at 290 nm, whereas the purity of the released acid was checked via RP-HPLC analysis. The lamp used was a 500 W Hg high-pressure lamp equipped with cutoff filters, thus affording light above the cutoff wavelengths. The power level of the light beam was adjusted to 1000 mW/cm^2 (measured between 300 and 400 nm).

Six different solvents were chosen for the photolysis study: THF, dioxane, dichloromethane, and acetonitrile represent aprotic organic solvents, 2-propanol represents a protic organic solvent, and DMSO since it is often used as a solvent for drugs in biological assays. Table 1 summarizes the results for the solvents examined.

Acetonitrile turned out to be unsuitable under the conditions of photocleavage; therefore, the yield was not determined here. Apart from this, the cleavage is strikingly solvent independent, affording yields from 78% to 92% and purities of 85% to 92%. THF was used as solvent of choice for all other experiments except for photolysis in open well plates where dioxane was preferred because of its lower volatility.

Table 1. Purity and Yield of Photocleavage in Different Solvents

	solvent					
	THF	CH_2Cl_2[a]	dioxane	DMSO	2-propanol	acetonitrile
purity (%)	90	92	91	91	85	28
yield (%)	92	90	90	87	78	

[a] Contains 0.02% 2-methyl-2-butene.

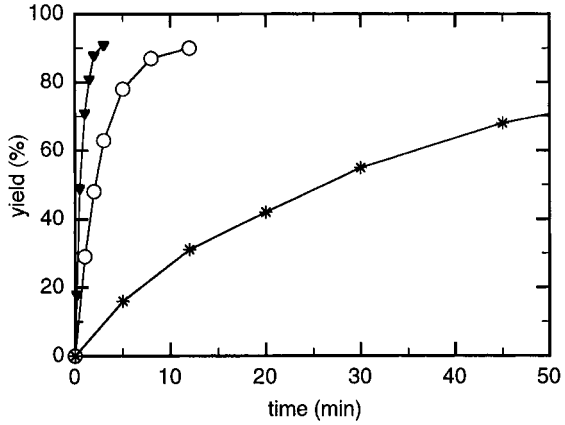


Figure 2. Photolysis rates for the pivaloylglycol linker **12a** at different wavelengths: triangles, $\lambda > 305$ nm; circles, $\lambda > 320$ nm; stars, $\lambda > 335$ nm.

The next step was to investigate the wavelength dependence of photolysis rates (Figure 2). Above 345 nm, no measurable photocleavage took place. Photocleavage started when using the 335 nm cutoff filter (half-life of 25 min). Use of the 320 nm filter greatly increased the photolysis rate (half-life of 2 min), which could be further increased with the 305 nm filter (half-life of 0.5 min).

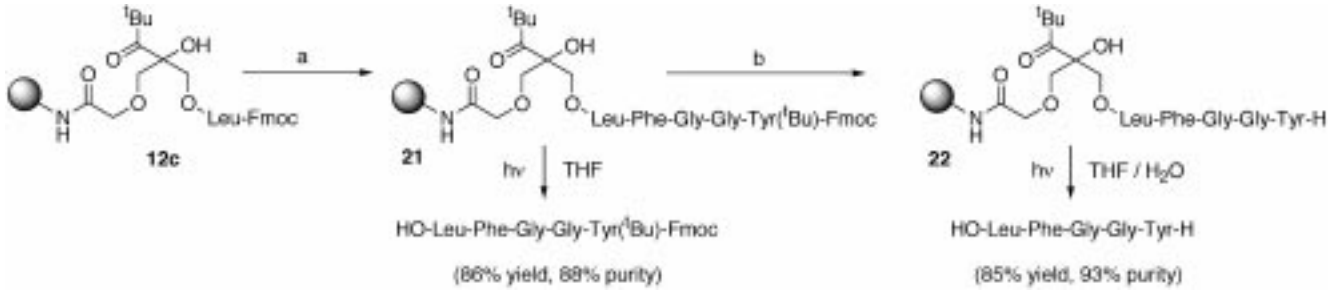
In all cases, photocleavage stopped at roughly 90% conversion even after extended periods of exposure to UV light.

All further irradiations were conducted using the 320 nm cutoff filter. This allowed fast photolytic cleavage (12 min irradiation time for 90% conversion) and minimization of the possible damage by short-wavelength UV light.

Applications of the Linker in Solid-Phase Synthesis. The use of the photolabile linker was explored by various reactions on the solid phase and subsequent photolytic release. As our first example, we chose a peptide synthesis employing Fmoc chemistry.[18] Leu-enkephalin, chosen as a model peptide, was prepared by stepwise coupling of Fmoc-protected amino acids to resin **12c** (Scheme 4). After four reaction cycles, resin **21** was obtained with 0.147 mmol/g loading of protected Leu-enkephalin. By treatment with piperidine and TFA, Leu-enkephalin was deprotected to yield resin **22** prior to photocleavage. Both peptides (**21** and **22**) could be cleaved photolytically in quartz glass cells after 12 min of irradiation and afforded the desired peptides in high purity and yield. The principal HPLC peak of the photocleavage from resin **22** comigrated with authentic

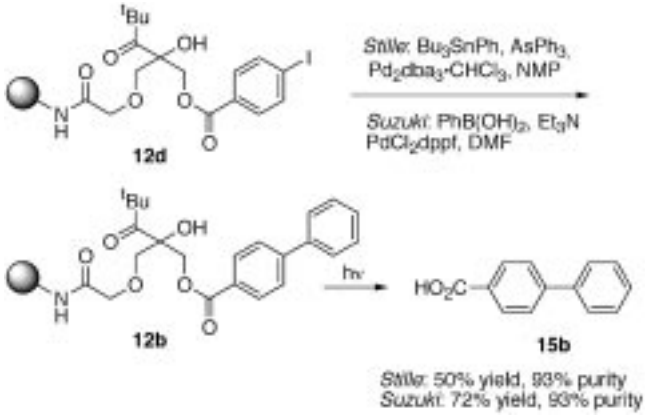
(18) Field, G. B. et al. *Int. J. Peptide Protein Res.* **1990**, *35*, 161.

Scheme 4[a]

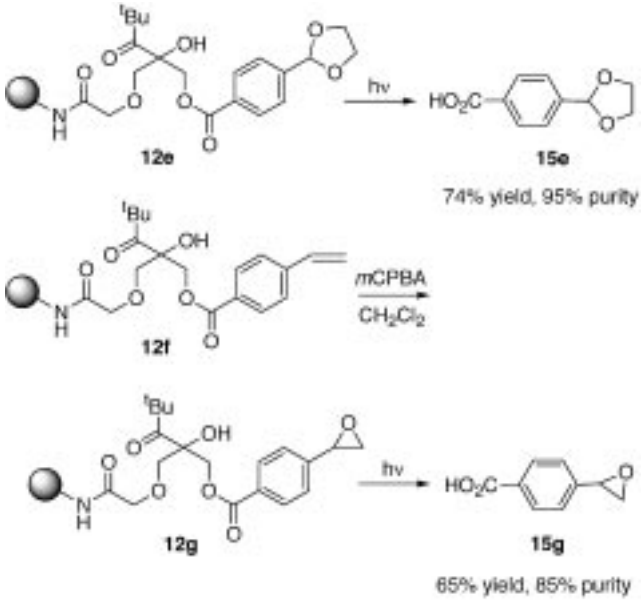


[a] Reagents: (a) (1) piperidine, DMF; (2) Fmoc-amino acid, PyBOP, DIPEA, DMF; (1) + (2): 4×; (b) (1) piperidine, DMF; (2) TFA.

Scheme 5



Scheme 6



Leu-enkephalin, and its identity was confirmed by mass spectrometry.

Additionally, to demonstrate the wide applicability of the photolabile anchor group, palladium-catalyzed cross-couplings were performed with resin-bound iodobenzoic acid **12d** (Scheme 5). Stille[19] and Suzuki[20] coupling with tributylphenyltin and phenylboronic acid, respectively, gave immobilized biphenylcarboxylic acid **12b**.

In the course of the reactions, the beads turned dark. However, the acid **15b** was released in both cases with 93% purity. On the basis of the initial resin loading of 0.29 mmol/g, the amount of cleaved biphenylcarboxylic acid corresponded to an overall yield of 50% (Stille coupling) and 72% (Suzuki coupling), respectively, for five steps.

The detachment of acid-labile substrates from the solid phase is often foiled, as most linkers are cleaved by strong acids. Because of the inherent neutral cleavage conditions, a photolabile support can serve as an alternative for theses substrates, as was demonstrated with the immobilized acetal **12e** and epoxide **12g**. The synthesis of the epoxide was carried out by epoxidation of resin-bound vinylbenzoic acid (**12f**). Photolysis in THF liberated the substrates **15e** and **15g** in good yield and high purity (Scheme 6).

The results demonstrate that the pivaloylglycol linker is compatible with a wide range of reaction conditions (peptide syntheses, Pd-catalyzed cross-couplings, oxidations) and allows for the detachment of acids from the polymeric support under mild and neutral conditions.

(19) Stille coupling on solid phase: Deshpande, M. S. *Tetrahedron Lett.* **1994**, *35*, 5613.
(20) Suzuki coupling on solid phase: Ruhland, B.; Bombrun, A.; Gallop, M. A. *J. Org. Chem.* **1997**, *62*, 7820.

Table 2. Stability of the Linker toward Treatment with Acids and Bases

acid	yield[a] (%)	base	yield[a] (%)
TFA/CH_2Cl_2, rt	93	DIPEA/THF, 60 °C	99
BF_3·Et_2O/CH_2Cl_2, rt	90	2,6-lutidine/THF, 60 °C	92
AcOH/H_2O/THF, 60 °C	89	DBU/toluene, 80 °C	81
HCl_{1M}/THF, rt	100	K($NSiMe_2$)/THF, −78 °C	70
p-TsOH/toluene, 80 °C	99		

[a] Yield of photolysis compared to yield of photolysis of untreated resin.

Stability of the Linker. The stability of the linker toward acids and bases was further examined by incubating resin **12b** with various commonly used acids and bases for 2 h. Then, the resins were washed, dried, and subjected to photolysis. Yields of the photocleavage were compared with results of the photolysis of untreated resin **12b** and are given in Table 2. The linker shows good to excellent stability toward Brønsted and Lewis acids and toward nonnucleophilic bases. Strong nucleophilic reagents such as hydrazine or sodium methanolate, however, result in complete cleavage of the substrates by attacking the ester linkage.

Comparison of Pivaloyl and *o*-Nitrobenzyl Linkers. Among the known photolabile linkers, the veratryl-based *o*-nitrobenzyl linkers developed by Affymax are commercially available and most frequently used.[7c,21] Photolabile support **1** (compound = biphenylcarboxylic

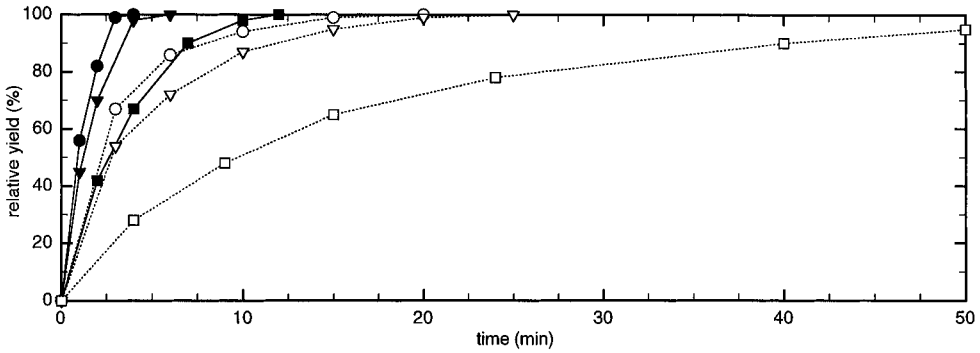


Figure 3. Photolysis rates in dependency of the power level for pivaloylglycol linker **12b** (bold lines) and *o*-nitrobenzyl linker **1** (dotted lines): circles, 500 mW/cm^2; triangles, 200 mW/cm^2; squares, 50 mW/cm^2.

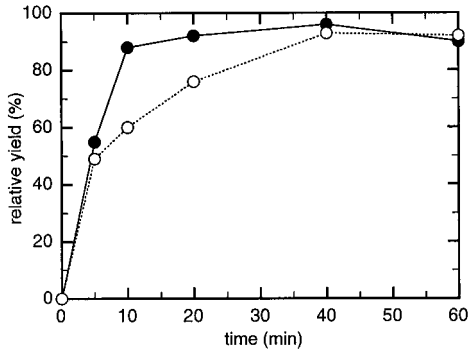


Figure 4. Photolysis rates in 96-well microtiter plates: bold line, pivaloylglycol linker **12b**; dotted line, *o*-nitrobenzyl linker **1**.

acid) was therefore chosen as a reference for the evaluation of the rates of photochemical cleavage in comparison to our photolabile support **12b**. To establish the cleavable loading of acid on the resins, photolyses were performed in quartz glass cells until no further conversion was observed. The purity of the liberated biphenylcarboxylic acid was >95% with both linkers. In all subsequent time- and power-dependent irradiations, the yields are expressed relative to the cleavable loading determined as described above. The results of photocleavage in quartz glass cells are shown in Figure 3.

Photolysis of pivaloyl resin **12b** is roughly three to four times faster than that of *o*-nitrobenzyl resin **1** at the same power level. Strikingly, the photocleavage from resin **1** became significantly slower with increasing conversion. This effect is presumably due to the formation of support-bound nitroso ketone, which may act as an internal light filter. With the pivaloyl-based linker that generates only CO, isobutene, and resin-bound acetone upon photocleavage this effect is not observed as the photoproducts are transparent above 300 nm. With both linkers, the support-bound photolysis becomes faster with increasing power level of the UV light, albeit no linearity was observed. This is probably due to light scattering, shielding, or shadowing effects of the resin beads, which causes a large proportion of the light to remain unused. Therefore, a power level of 50−100 mW/cm^2 seems to be sufficient for irradiation of photolabile supports.

The kinetics of the photolytic cleavage of the two linkers were also examined in 96-well microtiter plates. In each well was placed a few milligrams of resin, and the resin was covered with dioxane, which is reported to be the best solvent for *o*-nitrobenzyl linkers.[7a] With a 500 W Hg lamp equipped with a 280−400 nm dichroic mirror and 320 nm cutoff filter (power level 100 mW/cm^2), the samples were irradiated from above. The results confirmed the findings of the photolyses in quartz glass cells. The 10 min irradiation time for 90% conversion for the pivaloyl linker **12b** compared to 40 min for **1** underscored the advantage of our pivaloyl linker (Figure 4).

Conclusion

The new photolabile linker based on 2-pivaloylglycerol represents an excellent alternative for the cleavage of carboxylic acids. Photolytic cleavage is rapid and produces high yields of released acids with very high purity. The linker may be photolyzed by 320−340 nm light, which allows easy handling in the laboratory without precautions. The photobyproducts are either volatile (CO and isobutene/isobutane) or inert (resin-bound acetone) and are transparent above 320 nm to prevent inner filter effects from interfering with the course of the photolysis. Finally, the linker is compatible with many reagents and reactions, which allows broad applicability in combinatorial chemistry. Further investigations in the utility of photolabile supports based on this concept for the detachment of compounds other than acids are underway and will be reported in due course.

Experimental Section

General Methods. All quoted temperatures are uncorrected. Materials and reagents were of the highest grade available commercially and used without further purification. Commercial resin (TentaGel S NH_2) was obtained from Rapp Polymere, Tübingen, Germany. THF was distilled from potassium/benzophenone before use. The level of attachment of amino acids was estimated according to the protocol in the Novabiochem handbook.[21] ^{1}H and ^{13}C NMR data were measured in the indicated solvent with tetramethylsilane as internal standard. The gel phase marks data that are taken from resin swollen in $CDCl_3$. Fast atom bombardment (FAB) mass spectra were obtained with *m*-nitrobenzyl alcohol as matrix. Combustion analyses were performed by the Mikroanalytisches Labor, University of Basel. Quantum yield was determined at 308 nm and di-*tert*-butyl ketone as reference compound.[22] Analytical HPLC was performed on (a) Kontron Instruments and (b) Waters Alliance 2690 using columns as follows: (a) Merck Lichrospher 100, RP 18 (5 μm), 250 mm ×

(21) Novabiochem AG, Läufelfingen, Switzerland, Catalog & Peptide Synthesis Handbook, 1997/1998.

(22) Adam, W.; Fragale, G.; Klapstein, D.; Nau, W. M.; Wirz, J. *J. Am. Chem. Soc.* **1995**, *117*, 12578.

4 mm and (b) Rainin Microsorb, Type C18 (3 μm), 50 mm × 4.6 mm. Gradients used for elution were as follows: (a) 0−30 min, 30−100% B in A with A = 0.1% TFA in water and B = acetonitrile; (b) 0−1 min, 100% A; 1−13 min, 0−100% B in A; 13−15 min, 100% B with A = 0.1% TFA in water and B = 0.1% TFA in water/acetonitrile (1:9).

5-[(*tert*-Butyldimethylsilyl)oxy]-5-cyano-2-methoxy-2-methyl-1,3-dioxane (5). To a stirred solution of ketone **4**[14] (1.75 g, 12.0 mmol) in DMF (13 mL) were added a few crystals of potassium cyanide and 18-crown-6, and the mixture was cooled to 0 °C under argon. *tert*-Butyldimethylsilyl cyanide (1.95 g, 13.8 mmol) in DMF (3 mL) was added slowly. After 30 min, the mixture was diluted with ether (200 mL) and washed with water (2 × 200 mL) and brine (100 mL), the organic solvent was removed, and the residue was distilled in a Kugelrohr oven (at 150 °C at 0.08 mbar). A diastereomeric mixture of **5a** and **5b** (2.90 g, 84% yield) in a ratio of 8:1 was obtained as a clear oil. Data for **5a**: ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 4H), 3.30 (s, 3H), 1.50 (s, 3H), 0.87 (s, 9H), 0.24 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 120.2, 111.5, 66.2, 63.6, 51.0, 25.4, 21.2, 17.9, −3.5. Data for **5b**: ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 4H), 3.31 (s, 3H), 1.46 (s, 3H), 0.90 (s, 9H), 0.24 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 118.8, 111.5, 66.2, 63.6, 50.8, 25.7, 20.9, 17.9, −3.8; IR (film) 2237, 1263, 1152 cm^{-1}; MS (CI) *m*/*z* 288 $(MH)^+$. Anal. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found: C, 54.68; H, 8.57; N, 4.83.

1-Acetoxy-2-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-2-pivaloylpropane (6). Cyanohydrin **5a**,**b** (2.60 g, 9.0 mmol), CuI (17.5 mg, 0.09 mmol), and dry diethyl ether (150 mL) were stirred and cooled to −78 °C under argon. *tert*-Butyllithium (22.6 mL, 36 mmol, 1.6 M in pentane) was added in 10 min, upon which the reaction mixture turned dark green. After 3.5 h at −78 °C, acetic acid (30 mL, 50% in water) was rapidly added. The reaction mixture was allowed to warm to room temperature, additional acetic acid (100 mL, 30% in water) was added, and the mixture was vigorously stirred overnight. The phases were separated, the aqueous phase was extracted with diethyl ether (2 × 50 mL), and the combined organic phases were dried over magnesium sulfate and concentrated in vacuo. Acetic acid was removed by coevaporation with toluene and the residue filtered over silica gel to give ketone **6** (2.45 g, 84% yield) as a white solid: mp 61−62 °C; ^{1}H NMR ($CDCl_3$) δ 4.37 (d, 1H, J = 11.7 Hz), 4.22 (d, 1H, J = 11.7 Hz), 3.83 (dd, 1H, J = 9.2, 11.2 Hz), 3.65 (dd, 1H, J = 3.6, 11.2 Hz), 2.21 (dd, 1H, J = 3.6, 9.2 Hz), 2.05 (s, 3H), 1.30 (s, 9H), 0.98 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 217.5, 170.3, 86.9, 68.2, 66.9, 45.1, 26.3, 26.0, 20.8, 18.7, −2.2, −2.4; IR (film) 3518, 1748, 1698, 1254 cm^{-1}; MS (FAB) *m*/*z* 333 $(MH)^+$. Anal. Calcd for $C_{16}H_{32}O_5Si$: C, 57.79; H, 9.70. Found: C, 57.77; H, 9.77.

1-[(*tert*-Butyldimethylsilyl)oxy]-2,3-dihydroxy-2-pivaloylpropane (7). To a solution of acetate **6** (3.90 g, 11.7 mmol) in methanol (25 mL, 95% in water) was added potassium carbonate (0.25 g), and the mixture was stirred for 5 h at room temperature. The reaction mixture was filtered over silica gel and the solvent removed to yield silyl ether **7** (3.40 g, quantitative) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 3.86 (d, 1H, J = 9.8 Hz), 3.74 (d, 1H, J = 9.8 Hz), 3.69 (dd, 1H, J = 8.0, 11.3 Hz), 3.65 (s, 1H), 3.59 (dd, 1H, J = 5.3, 11.3 Hz), 2.39 (dd, 1H, J = 5.3, 8.0 Hz), 1.26 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 217.4, 84.2, 66.5, 65.8, 44.8, 26.4, 25.8, 18.2, −5.5, −5.6; IR (film) 3482, 1693, 1256 cm^{-1}; MS (FAB) *m*/*z* 291 $(MH)^+$. Anal. Calcd for $C_{14}H_{30}O_4Si$: C, 57.89; H, 10.41. Found: C, 57.70; H, 10.23.

6-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-3-oxa-5-pivaloylhexanoic Acid *tert*-Butyl Ester (8). To a solution of alcohol **7** (2.80 g, 9.66 mmol) in DMF (20 mL) were added at 0 °C silver(I) oxide (3.35 g, 14.5 mmol) and *tert*-butyl bromoacetate (4.25 mL, 29 mmol). The suspension was allowed to warm to room temperature and stirred in the dark for 18 h. The reaction mixture was diluted with ether (200 mL) and washed with water (3 × 50 mL), and the organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (hexanes/EtOAc 9:1) yielded ester **8** (2.80 g, 72% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.08 (s, 1H), 4.03 (d, 1H, J = 16.7 Hz), 3.93 (d, 1H, J = 16.7 Hz), 3.87 (d, 1H, J = 9.6 Hz), 3.85 (d, 1H, J = 10.0 Hz), 3.63 (d, 1H, J = 10.0 Hz), 3.53 (d, 1H, J = 9.6 Hz), 1.48 (s, 9H), 1.27 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 216.9, 170.0, 85.2, 82.1, 75.4, 69.2, 66.9, 44.9, 28.1, 26.6, 25.9, 18.3, −5.4, −5.5; IR (film) 3440, 1732, 1694, 1253 cm^{-1}; MS (FAB) 405 $(MH)^+$. Anal. Calcd for $C_{20}H_{40}O_6Si$: C, 59.37; H, 9.96. Found: C, 59.21; H, 9.98.

6-[(*tert*-Butyldimethylsilyl)oxy]-3-oxa-5-pivaloyl-5-[(trimethylsilyl)oxy]hexanoic Acid (9). To a solution of ester **8** (2.30 g, 5.68 mmol) in dry THF (20 mL) were added at 0 °C 2,6-lutidine (1.98 mL, 17 mmol) and trifluoromethanesulfonic acid trimethylsilyl ester (TMSOTf, 2.57 mL, 11.4 mmol). The solution was allowed to warm to room temperature and heated to 40 °C after 1 h. After an additional 2 h, 2,6-lutidine (1.32 mL, 11.4 mmol) and TMSOTf (1.54 mL, 8.5 mmol) were added. The reaction was quenched by addition of acetic acid (20 mL, 30% in water) and extracted with ether (200 mL). The organic phase was washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. Filtration over silica gel gave acid **9** (2.29 g, 96% yield) as off-white crystals: mp 84−86 °C; ^{1}H NMR ($CDCl_3$) δ 4.06 (s, 2H), 3.89 (d, 1H, J = 9.3 Hz), 3.79 (d, 1H, J = 10.4 Hz), 3.73 (d, 1H, J = 10.4 Hz), 3.61 (d, 1H, J = 9.3 Hz), 1.25 (s, 9H), 0.89 (s, 9H), 0.24 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 216.7, 172.2, 88.6, 75.6, 68.4, 67.4, 45.1, 26.7, 25.9, 18.5, 2.1, −5.5; IR (film) 3100, 1732, 1698, 1250 cm^{-1}; MS (FAB) *m*/*z* 421 $(MH)^+$. Anal. Calcd for $C_{19}H_{40}O_6Si_2$: C, 54.25; H, 9.58. Found: 54.42; H, 9.57.

1,3-Bis[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-2-pivaloylpropane (17). To a solution of monosilyl ether **7** (200 mg, 0.69 mmol) in DMF (0.7 mL) were added *tert*-butyldimethylsilyl chloride (167 mg, 1.1 mmol) and imidazole (150 mg, 3.2 mmol) and the mixture stirred for 18 h. The mixture was diluted with ether (10 mL) and washed with water (3 × 10 mL), and the organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (hexanes/EtOAc 30:1) afforded the bissilyl ether **17** (251 mg, 90% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.82 (d, 2H, J = 9.9 Hz), 3.58 (d, 2H, J = 9.9 Hz) 3.38 (s, 1H), 1.25 (s, 9H), 0.88 (s, 18H), 0.05 (s, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 216.8, 85.2, 66.7, 44.7, 26.6, 25.8, 18.3, −5.4, −5.5; IR (film) 3541, 1698, 1258 cm^{-1}; MS (FAB) 405 $(MH)^+$; UV (MeCN) 297 (ϵ = 32). Anal. Calcd for $C_{20}H_{44}O_4Si_2$: C, 59.35; H, 10.96. Found: C, 59.24; H, 10.80.

Photolinker−TentaGel (11). TentaGel S NH_2 (1.0 g, 0.28/0.29 mmol/g loading) was suspended in dry CH_2Cl_2 (5 mL), and photolinker **9** (183 mg, 0.435 mmol), DMAP (9 mg, 0.07 mmol), and diisopropylcarbodiimide (DIC, 112 μL, 0.73 mmol) were added. The resin was shaken for 18 h at room temperature and washed with CH_2Cl_2, DMF, and CH_2Cl_2. Kaiser test revealed complete reaction. The resin was then suspended in THF (4 mL) and $(HF)_3{\cdot}Et_3N$ (1 mL) was added. After 24 h the resin was washed with THF, CH_2Cl_2 and dried to yield the photolabile support **11** (1.01 g); gel phase ^{13}C NMR ($CDCl_3$) δ 216.5, 170.1, 84.8, 76.1, 69.8, 65.7, 45.0, 38.8, 25.6.

General Procedure for Attachment of the First Amino Acid. Photolinker−TentaGel (**11**, 100 mg, 29 μmol) was washed with DMF, a 0.5 M solution of symmetrical anhydride (prepared from 10 equiv of Fmoc amino acid and 5 equiv of DIC in 5 mL of CH_2Cl_2 at 0 °C) in DMF was added and the amino acid coupled to the resin for 1 h by the addition of DMAP (1 equiv). The resin was washed successively with CH_2Cl_2, DMF, and CH_2Cl_2 and dried. Fmoc-Gly photolinker−TentaGel (**12a**): 0.183 mmol/g. Fmoc-Leu−photolinker−TentaGel (**12c**): 0.191 mmol/g.

General Procedure for Attachment of Aromatic Carboxylic Acids. To a suspension of photolinker resin **11** (200 mg, 58 μmol) in THF (2 mL) were added the aromatic carboxylic acid (2 equiv), DMAP (0.2 equiv), and DIC (1.2 equiv), and the mixture was shaken for 18 h at room temperature. Washing (THF and CH_2Cl_2) and drying afforded the acid−photolinker resins **12b**,**d**,**e**,**f**. Gel phase ^{13}C NMR ($CDCl_3$) data: **12b** δ 215.1, 169.7, 166.4, 146.0, 139.8, 130.3, 129.1, 128.4, 127.3, 127.2, 83.6, 75.6, 69.7, 68.0, 45.3, 38.9, 26.8; **12d** δ 215.1, 169.7, 165.9, 137.8, 131.2, 129.2, 101.2, 83.4, 75.5, 69.7,

68.1, 45.3, 38.9, 26.7; **12e** δ 215.0, 169.7, 166.2, 143.4, 130.2, 129.8, 126.6, 102.9, 83.6, 75.6, 69.7, 68.1, 65.4, 45.3, 38.9, 26.8; **12f** δ 215.1, 169.7, 166.2, 142.4, 136.0, 130.1, 126.3, 126.2, 117.0, 83.9, 75.6, 69.8, 68.0, 45.3, 38.9, 26.8.

Leu-Enkephalin (Fmoc,^{t}Bu)−Photolinker−TentaGel (21) and Leu-Enkephalin−Photolinker−TentaGel (22). The peptide resins were prepared on Leu−photolinker−resin **12c** (200 mg, 0.191 mmol/g) according to the synthesis cycle described below. All amino acids were *N*-Fmoc protected. The side chain functionality of Tyr was protected as the *tert*-butyl ether.

Coupling. To the resin were added a 0.1 M solution of amino acid (2.5 equiv) in DMF, a 0.5 M solution of PyBOP (2.5 equiv) in DMF, and DIPEA (5 equiv). The suspension was mixed at room temperature for 30 min, the supernatant was sucked off, and the resin washed successively with DMF, CH_2Cl_2, and DMF. The Kaiser test was negative in all cases.

Amine Deprotection. Piperidine (20%) in DMF (2 mL) was added, and the suspension was mixed for 7 min at room temperature. The supernatant was sucked off, and the resin was washed with DMF.

Following Fmoc removal from the final tyrosine residue, side-chain protection was removed by treating the resin with TFA/water/triethylsilane (95:2.5:2.5, 2 mL) and allowing the suspension to stand 1 h at room temperature. Leu-Enkephalin (Fmoc,^{t}Bu)−photolinker−TentaGel (**21**): 0.147 mmol/g.

Epoxidation: 4-Oxiranylbenzoic Acid−Photolinker−TentaGel (12g). Resin-bound vinyl benzoic acid (**12f**, 100 mg, 29 μmol) was suspended in CH_2Cl_2 (1 mL), *m*-CPBA (55%, 31 mg, 0.1 mmol) was added, and the suspension was shaken for 24 h. The resin was washed successively with CH_2Cl_2, THF, and CH_2Cl_2 and dried: gel phase ^{13}C NMR ($CDCl_3$) δ 215.0, 169.7, 166.1, 143.6, 130.0, 129.4, 125.6, 83.6, 75.6, 69.8, 68.0, 51.8, 51.5, 45.2, 38.9, 26.8.

Stille Reaction with Resin 12d. To a degassed suspension of polymer-bound iodobenzoic acid (**12d**, 100 mg, 28 μmol) in anhydrous NMP (1 mL) were added Pd_2dba_3·$CHCl_3$ (3.1 mg, 3 μmol) and $AsPh_3$ (3.7 mg, 12 μmol). After 5 min, Bu_3SnPh (20 μL, 58 μmol) was added and the reaction allowed to stand at 50 °C. After 6 h, again Pd_2dba_3·$CHCl_3$ (1.5 mg, 1.5 μmol), $AsPh_3$ (1.8 mg, 6 μmol), and Bu_3SnPh (10 μL, 29 μmol) were added. The reaction mixture was maintained at 50 °C for 36 h, washed with NMP, THF, and CH_2Cl_2, and dried to afford dark-brown resin **12b**.

Suzuki Reaction with Resin 12d. To a degassed suspension of polymer-bound iodobenzoic acid (**12d**, 100 mg, 28 μmol) in DMF (1 mL) were added $PhB(OH)_2$ (14 mg, 112 μmol), $PdCl_2$(dppf) (4 mg, 6 μmol), and Et_3N (39 μL, 0.28 mmol). After 18 h at 65 °C, the reaction mixture was washed with DMF and CH_2Cl_2 and dried to afford a brown resin **12b**.

Resin-Bound Acetone (16). Biphenyl carboxylic acid−photolinker−TentaGel (**12b**, 100 mg, 29 μmol) was suspended in four portions of THF (3 mL, quartz glass cells) and irradiated according to the general photolysis conditions (see below), followed by washing with THF and CH_2Cl_2 to yield resin **17** (93 mg) and biphenyl carboxylic acid (4.0 mg, 68% yield): gel phase ^{13}C NMR ($CDCl_3$) δ 204.9, 169.0, 76.4, 69.6, 38.7, 26.2.

General Photolysis Conditions. Photolyses in quartz glass cells (1 cm path length, equipped with stir bar) were conducted with 2−8 mg of resin suspended in 3 mL of solvent in the beam of a 500 W Hg high-pressure lamp fitted with a water filter and various cutoff filters. The power level (measured between 300 and 400 nm) at the cell was adjusted by a collimating lens between 50 and 1000 mW/cm^2. The cells were maintained at 20 °C and irradiated horizontally with gentle mixing of the beads by means of a magnetic stirrer. After photolysis, the supernatant was analyzed by UV spectroscopy and reversed-phase HPLC.

Photolyses in 96-well microtiter plates were conducted with 2−7 mg of resin and 0.2 mL of dioxane. Photolyses were performed by irradiating the samples with a 500 W Hg high-pressure lamp fitted with a 280−400 nm dichroitic mirror and a 320 nm cutoff filter from above. The power level was adjusted to 100 mW/cm^2. After photolysis, a defined amount of benzoic acid was added as internal standard. After mixing, an aliquot was removed and analyzed by reversed-phase HPLC with detection at 214 nm.

Stability toward Acids and Bases. Biphenylcarboxylic acid−photolinker−TentaGel (**12b**, 0.204 mmol/g, 3−6 mg each) was incubated for 2 h with 2 mL of (a) TFA (50% in CH_2Cl_2), rt; (b) BF_3·Et_2O (5% in CH_2Cl_2), rt; (c) 1 M HCl (20% in THF), rt; (d) AcOH/H_2O/THF (3:1:1), 60 °C; (e) *p*-TsOH (1% in toluene), 80 °C; (f) DIPEA (10% in THF), 60 °C; (g) 2,6-lutidine (10% in THF), 60 °C; (h) DBU (5% in toluene), 80 °C; and (i) K($NSiMe_2$) (5 equiv in THF), −78 °C; washed (THF and CH_2Cl_2, in case of basic reagents first with 5% HOAc in CH_2Cl_2) and dried, followed by photolysis. Yields were compared with the photolysis yield of untreated resin **12b**.

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