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A New Robust and Versatile Tetradentate Linker for Amides To be Cleaved under Mild Conditions by Unusual Complexation of the Amide Nitrogen to Cu^{++}

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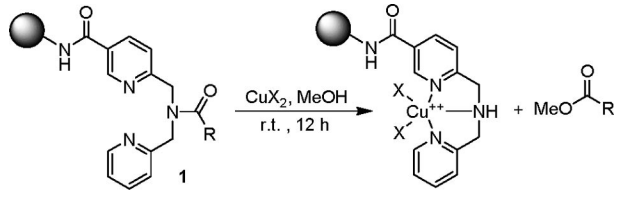
The concept of weakening amide bonds by the rather unusual forced complexation of nitrogen to Cu^{++} is not limited to tridentate ligands and was extended in this work to tetradentate ligands as well. The use of cyclic tetradentate ligands was to no avail, but an open-chain and more-flexible tetradentate ligand allowed mild cleavage by methanolysis after complexation. The principle was applied to the development of a new linker for solid-phase chemistry, which was proven to be extremely robust, yet allowed mild cleavage after activation by Cu^{++} complexation. Its stability and versatility was demonstrated by the successful application to a whole plethora of different types of reactions.

Introduction

Solid-phase organic chemistry has gained increasing interest over the last decades. Originally developed for the synthesis of oligo-2′-deoxynucleotides, RNA fragments, and peptides it is being applied more and more in the realm of synthetic organic chemistry. The main advantage is the possibility to employ excess amounts of reagents, leading to higher yields compared to the same reaction being performed in solution with equivalent amounts of reacting components. Time-consuming purifications can be replaced by simple filtration of the excess amounts of reagents.

In order to widen the scope of solid-phase chemistry there is a constant need for the development of new linker entities connecting the support material with the starting material, intermediates, or the envisaged product. Salient features of such linkers should include robustness towards a wide range of chemical conditions as well as orthogonal deprotection procedures.

Recently, we developed a new amide linker based on bispicolylamide (bpa) cleaved by complexation of Cu^{++} under very mild conditions.[1] The basis of the cleavage is the weakening of the amide bonds in bispicolylamides as a result of the unusual involvement of the amide nitrogen in complexation. Methanolysis leads then directly to the methyl ester (Scheme 1). The linker turned out to be very robust and allowed its application to a wide range of chemical conditions. It turned out to be stable under acidic and basic conditions and we have tested its utility for peptide synthesis, reductive amination, Suzuki–Miyaura coupling, and ring-closing metathesis. Meanwhile, we have extended the range of reactions that are compatible with the linker to Grignard reactions, Horner–Wadsworth–Emmons olefinations, Heck couplings, Mitsunobu reactions, Staudinger reductions, and hydroboration (unpublished results). Salient features of linker **1** are furthermore its straightforward preparation and its recyclability.



Scheme 1. Cu^{++}-assisted methanolysis of bpa linker **1**; X = Cl, OTf.

Results and Discussion

We were wondering whether such a principle could also be realized for a tetradentate ligand and if so, whether the cleavage conditions would be influenced by an additional coordination site.

As reported by Alsfasser, bpa complexes involving an amide bond are moderately stable and tend to dissociate in solution.[2] An additional nitrogen atom for complexation should lead to a more stable complex and as a consequence to a more pronounced weakening of the amide bond allowing, even milder conditions, amide bond cleavage.

Our first focus was on circular ligand **10**, in which a further stabilization was expected due to the macrocyclic effect.[3] A cyclization strategy for peptides with a tetracoor-

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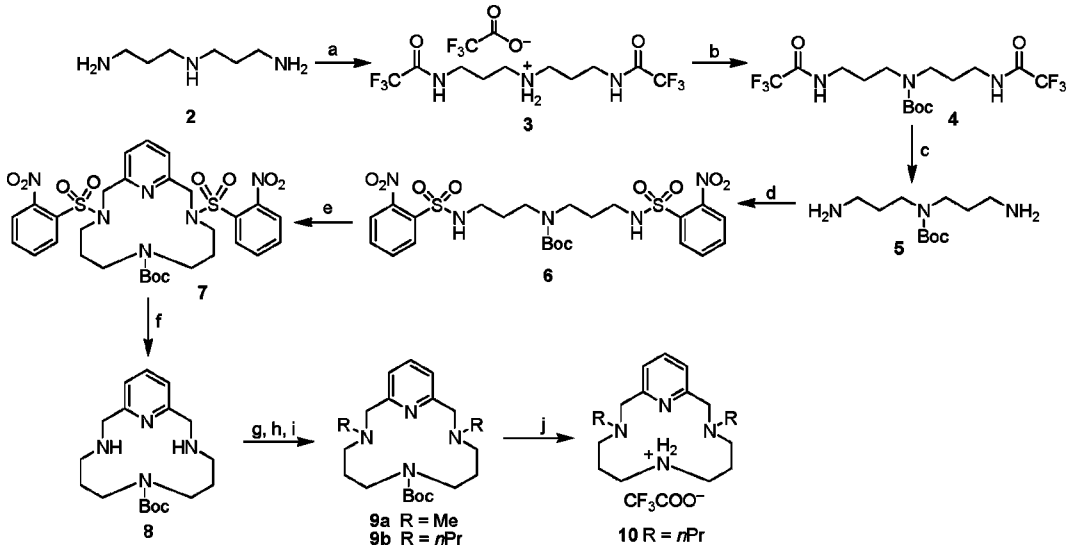


Scheme 2. Synthesis route for cyclic tetradentate ligand **10**. Reagents and conditions: (a) ethyl trifluoroacetate (3.6 equiv.), H_2O (1.2 equiv.), CH_3CN, reflux, 4 h, 97%; (b) Boc_2O (1.1 equiv.), NEt_3 (3.2 equiv.), THF, 0 °C → room temp., overnight, 82%; (c) NaOH (0.2 M in MeOH, 2.8 equiv.), MeOH, 0 °C → room temp., overnight, 73%; (d) 2-nitrobenzenesulfonylchloride (2.0 equiv.), NEt_3 (2.0 equiv.), CH_2Cl_2, overnight, 80%; (e) 2,6-bis(bromomethyl)pyridine (1.3 equiv.), Na_2CO_3 (5.2 equiv.), DMF, room temp., overnight, 87%; (f) thiophenol (3.3 equiv.), Na_2CO_3 (10.2 equiv.), DMF, room temp., overnight, 77%; (g) NaH (2.2 equiv.), MeI (2.4 equiv.), DMF, 0 °C → room temp., overnight, 0%; (h) propionaldehyde (2.0 equiv.), $NaBH(OAc)_3$ (2.8 equiv.), 1,2-DCE, room temp., overnight, 37%; (i) 1-bromopropane (2.2 equiv.), DIEA (3.0 equiv.), CH_3CN, 70 °C, 2 h, 69%; (j) TFA/CH_2Cl_2 (1:1), iPr$_3$SiH (3.1 equiv.), room temp., overnight, quantitative.

dinate Cu^{++} has been reported.[4] The synthetic route for the preparation of cyclic tetradentate ligand **10** is depicted in Scheme 2.

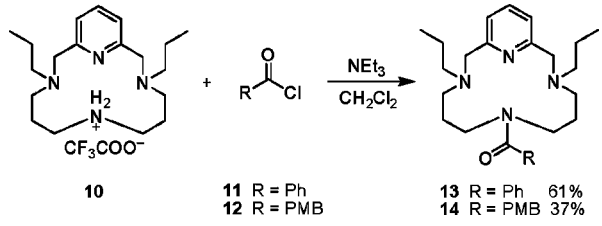
Its synthesis started with the protection of the primary amino groups of **2** with ethyl trifluoroacetate in the presence of water. During this procedure, overreaction was avoided by preferential protonation of the secondary amine,[5] leading to compound **3** in nearly quantitative yield (97%).

The Boc protection of trifluoroacetate (TFA) salt **3** proceeded in a yield of 82%. Afterwards, the trifluoroacetyl groups were removed with a methanolic NaOH solution (73%) and the final nosyl protection leading to **6** proceeded in an isolated yield of 80%.

The key step for the synthesis of **10** was the macrocyclization based on the method of Richman and Atkins.[6] By applying this approach, it was not necessary to work under high dilution. Dropwise addition of a solution of 2,6-bis-(bromomethyl)pyridine in DMF over 5 h to a suspension of **6** and Na_2CO_3 in DMF resulted in protected macrocycle **7** after column chromatography in a yield of 87%. The deprotection of the nosyl protecting group was achieved by thiolysis with thiophenol in a yield of 77%.

Alkylation with methyl iodide and NaH as base to form compound **9a** led to exhaustive alkylation. Such over-alkylations of the secondary amino groups in azamacrocycles are already reported in the literature.[7] A reductive amination with propionaldehyde and sodium triacetoxy borohydride[8] resulted in desired product **9b** although only in a moderate yield of 37%. An alternative alkylation with *n*-propyl bromide in the presence of *N*,*N*-diisopropylethylamine (DIEA) afforded desired product **9b** in a yield of 69%.[9] Final removal of the Boc group by TFA/CH_2Cl_2 (1:1) with triisopropylsilane as scavenger gave **10** as the TFA salt in quantitative yield.

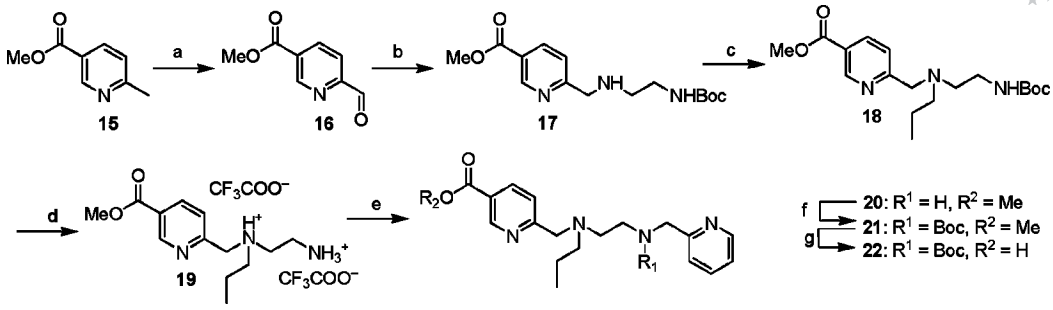
Tetradentate ligand **10** was then transformed into acyl derivatives **13** and **14** by acylation with acyl chlorides **11** and **12** in the presence of NEt_3 as outlined in Scheme 3.



Scheme 3. Acylation of cyclic ligand **10** with carbonic acid chlorides **11** and **12**.

Attempts to cleave the amide bonds by $Cu(OTf)_2$ in a 300-fold excess of MeOH at room temperature were to no avail. Higher temperatures and other Cu^{++} sources [$CuCl_2$, $Cu(ClO_4)_2$] resulted in no improvement of the situation.

Alsfasser observed by X-ray analysis, UV spectroscopy, and EPR measurements that during methanolysis the bpa copper complex underwent a change in its coordination sphere from square pyramidal to a distorted octahedral ligand field, of which the latter was then prone to cleavage of the amide bond by MeOH.[2] Hence, we surmised that in the Cu^{II} complexes of **13** and **14** the copper is forced into a square coordination and not flexible enough to adopt the required distorted octahedral shape.

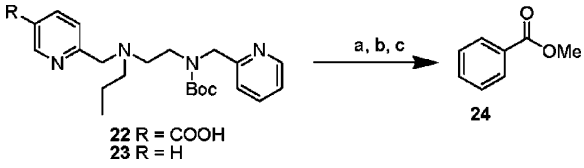


Scheme 4. Synthesis of Boc-protected tetradentate linker **22**. Reagents and conditions: (a) I_2 (1.0 equiv.), *t*BuI (0.4 equiv.), TFA (3.0 equiv.), DMSO, 120 °C, 3 h, 65%; (b) *N*-Boc-ethylenediamine (1.0 equiv.), $NaBH(OAc)_3$ (1.4 equiv.), 1,2-DCE, 1 h, 73%; (c) 1-propylbromide (5.0 equiv.), DIEA (6.0 equiv.), CH_3CN, 70 °C, 15 h, 75%; (d) iPr_3SiH (3.0 equiv.), TFA/CH_2Cl_2 (1:1), 2 h, 100%; (e) pyridine-2-carboxaldehyde (1.0 equiv.), $NaBH(OAc)_3$ (1.4 equiv.), 1,2-DCE, 1 h; (f) Boc_2O (1.3 equiv.), NEt_3 (1.4 equiv.), CH_2Cl_2, 0 °C → room temp., 2 h, 76% over two steps; (g) NaOH (1.1 equiv.), MeOH/H_2O, reflux, 2 h, 90%.

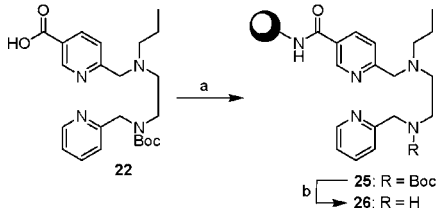
As a consequence, the more flexible linear tetradentate ligand **22** was synthesized (Scheme 4), which after cleavage of the Boc group should allow attachment of carboxylic acids through amide bonds.

Its synthesis started with the oxidation of commercially available methyl 6-methylnicotinate (**15**) to corresponding aldehyde **16**, which proceeded in a yield of 65%.[10] Reductive amination with *N*-Boc-ethylenediamine and sodium triacetoxyborohydride in 1,2-dichloroethane (DCE) gave secondary amine **17** in a yield of 73%.[7] This was transformed into compound **18** in 75% yield by alkylation with 1-bromopropane and DIEA in CH_3CN. Boc deprotection with TFA/CH_2Cl_2 (1:1) to free amine **19** was followed by reductive amination with pyridine-2-carboxaldehyde under the conditions that were applied to the first reductive amination procedure. Resulting secondary amine **20** was directly treated with Boc_2O to yield *N*-Boc-protected methyl ester **21** in 76% yield over the two steps. Saponification with sodium hydroxide in methanol/water resulted then in carboxylic acid **22** in 90% isolated yield.

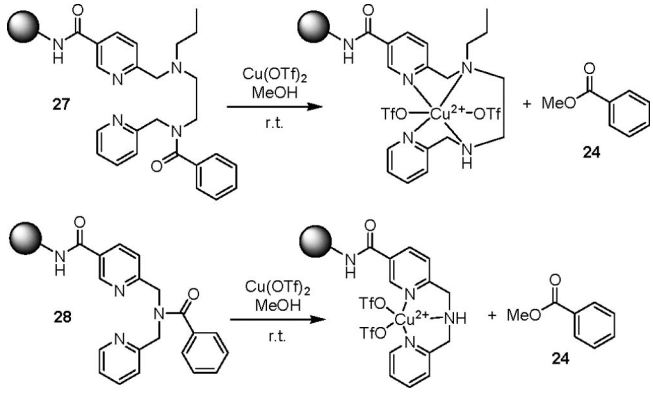
Tetradentate units **22** and **23** (which were synthesized according to Scheme 4, starting with pyridine-2-carboxaldehyde) were then first tested in solution according to



Scheme 5. Boc deprotection, coupling of benzoyl chloride, and subsequent methanolysis of tetradentate ligands **22** and **23**. Reagents and conditions: (a) *i*PrSiH (3.0 equiv.), TFA/CH_2Cl_2 (1:1), 2 h; (b) benzoyl chloride (2.5 equiv.), NEt_3 (2.5 equiv.), CH_2Cl_2, 0 °C → room temp., 15 h; (c) $Cu(OTf)_2$ (1.0 equiv.), MeOH, room temp., 15 h, 55%.



Scheme 6. Coupling of **22** to the solid support and cleavage of the Boc group. Reagents and conditions: (a) HypoGel400-NH_2, DMF, 10 min, then **22** (1.3 equiv.), TBTU (1.3 equiv.), DIEA (8.0 equiv.), DMF, room temp., 8 h; (b) iPr_3SiH (3.0 equiv.), TFA/CH_2Cl_2 (1:1), 2 h.



Scheme 7. Methanolysis reactions of an aromatic amide bond with tetradentate construct **27** and tridentate construct **28**.

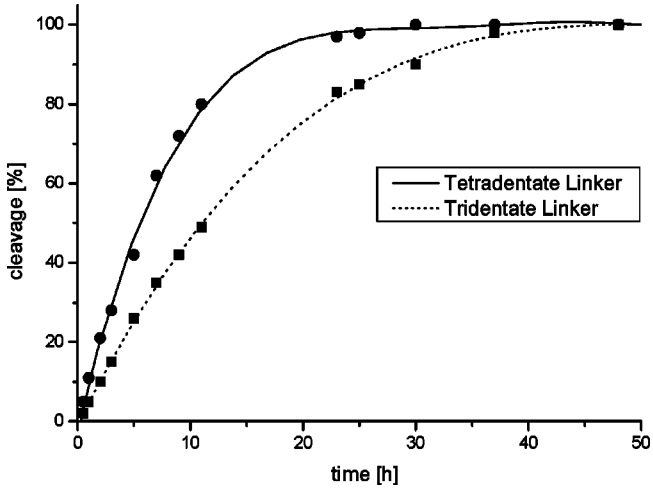
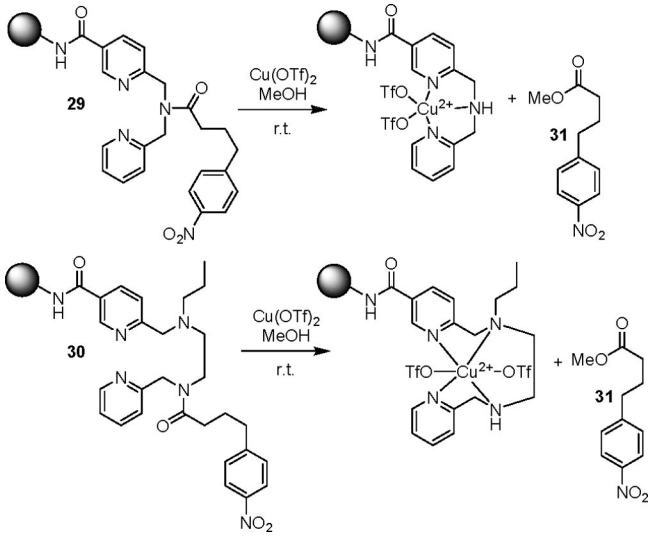


Figure 1. Kinetic data for the methanolysis of an aromatic amide bond with tetradentate construct **27** and tridentate construct **28**.

Scheme 5. After cleavage of the Boc group, benzoyl chloride was coupled to the free amino function. Exposure to $Cu(OTf)_2$ in MeOH for 20 h at room temperature led, to our great satisfaction, to complete cleavage of the amide bond with release of methyl benzoate (**24**). Without Cu^{++} no release was observed. This experiment indicated at the same time that the carboxyl function had no influence on the cleavage conditions.

After this successful preliminary experiment, Boc-protected linker **22** was coupled to the amino-functionalized solid support (HypoGel400-NH_2) by applying a 1.3 molar excess and by using *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) as coupling reagent.[11] A negative Kaiser test[12] indicated completion of the coupling reaction after 8 h. Deprotection of the Boc group from **25** yielded **26** (Scheme 6) ready for the attachment of substrates through the amide bond.

This now gave us the possibility to compare the kinetics of the C–N bond cleavage of the original tridentate bpa linker with that of the new open-chain tetradentate linker. For this reason, benzoyl chloride was coupled to both linkers and resulting constructs **27** and **28** (Scheme 7) were then subjected to $Cu(OTf)_2$ in MeOH with phenol as the internal standard. Aliquots were taken after appropriate time inter-



Scheme 8. Methanolysis reactions of an aliphatic amide bond with tetradentate construct **29** and tridentate construct **30**.

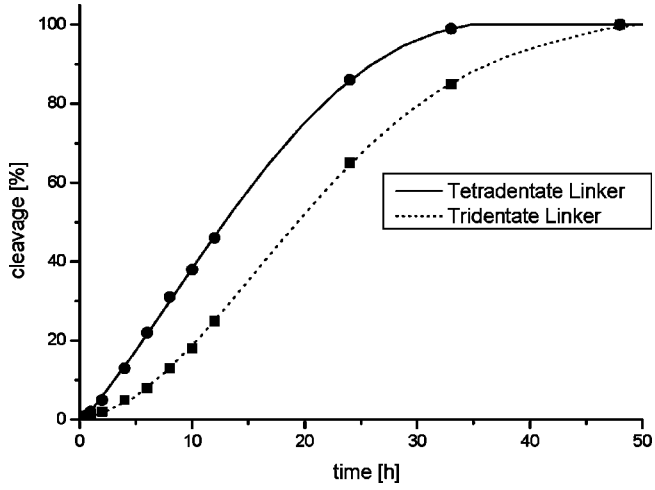
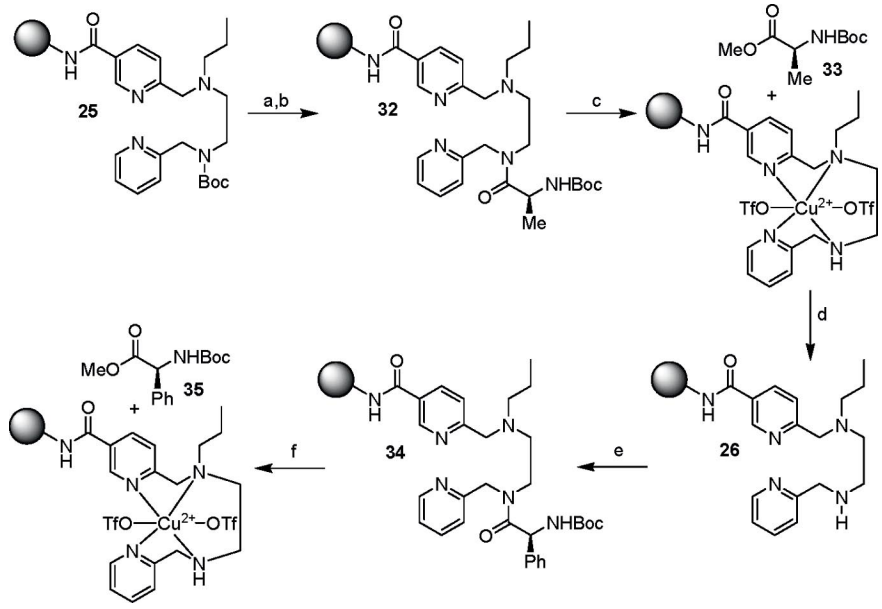


Figure 2. Kinetic data for the methanolysis of an aliphatic amide bond with tetradentate construct **29** and tridentate construct **30**.



Scheme 9. Recycling of the linker. Reagents and conditions: (a) iPr$_3$SiH (3.0 equiv.), TFA/CH_2Cl_2 (1:1), 2 h; (b) Boc-Ala-OH (3.0 equiv.), TBTU (3.0 equiv.), DIEA (8.0 equiv.), DMF, room temp., 12 h; (c) $Cu(OTf)_2$ (1.0 equiv.), MeOH, room temp., 15 h, 60%; (d) KCN (3.0 equiv.), MeOH, room temp., 30 min; (e) Boc-Phe-OH (3.0 equiv.), TBTU, (3.0 equiv.), DIEA (8.0 equiv.), DMF, room temp., 12 h; (f) $Cu(OTf)_2$ (1.0 equiv.), MeOH, room temp., 15 h, 55%.

vals and analyzed by HPLC with respect to formed methylbenzoate (**24**). The kinetic data are depicted in Figure 1.

As can be deduced from these data the cleavage from tetradentate construct **27** occurred to our delight smoothly and the rate of cleavage was higher than the one from tridentate linker construct **28**.

To test whether there is a difference in the cleavage rate of an aromatic amide and an aliphatic amide, the same experiment was repeated after coupling 4-(4-nitrophenyl)-butyric acid to the tridentate and tetradentate linkers (Scheme 8). Here it turned out, that the cleavage rate was slower on both linkers, but proceeded faster on the tetradentate linker system (Figure 2).

Although the new tetradentate linker can be synthesized in a straightforward way, its recyclability is still of concern. For this, the Boc group from **25** was cleaved, which was followed by coupling of Boc-Ala-OH leading to **32** using the standard coupling protocol outlined in Scheme 9. After 12 h a chloranil test indicated complete attachment.[13] Equimolar amounts of $Cu(OTf)_2$ in MeOH led to the release of Boc-Ala methyl ester **33** in an isolated yield of 60% over the three steps. Decomplexation to **26** was achieved by treatment with a methanolic solution of KCN (3 equiv.) over 30 min, whereby the resin lost its green color.

To regenerated linker **26** was coupled Boc-Phe-OH, and the release was again performed with $Cu(OTf)_2$ in MeOH, which resulted in pure Boc-Phe methyl ester **35** in a yield of 55% and without any trace of Boc-Ala methyl ester **33**, indicating that the first release had proceeded quantitatively.

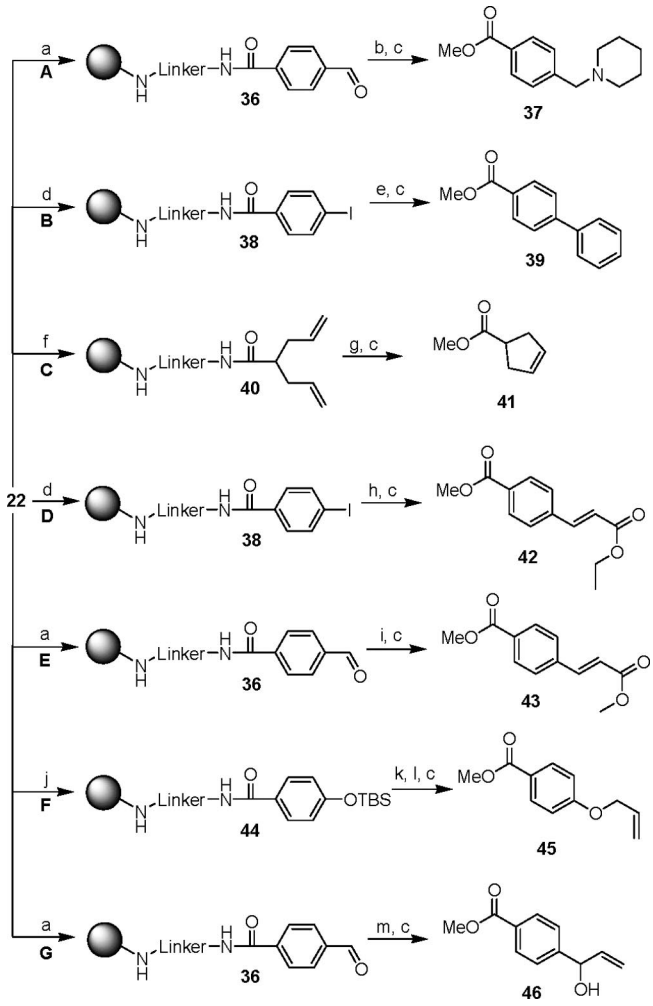
A critical issue for a linker system is its robustness, which is closely related to its compatibility with as many reaction conditions as possible. This will eventually determine its scope of application. Therefore, our next activities were directed towards this topic.

The new linker system turned out to be stable under acidic (50% TFA in DCM) and basic conditions (0.2 M LiOH in water) as well as in the presence of fluoride ions (0.1 M Bu_4NF in THF). To demonstrate the scope of applications of the new linker system the reactions depicted in Scheme 10 (A–G) were carried out.

Reaction A comprises a reductive amination, in which 4-carboxybenzaldehyde was coupled to linker **26** after Boc deprotection from linker **25**, resulting in **36**. This was followed by reductive amination with sodium triacetoxyborohydride in DCE. Methanolysis after complexation with Cu^{++} gave desired methyl ester **37** in a yield of 51% over the four steps (Boc deprotection, attachment of the acid, reductive amination, and release by methanolysis) and based on the original functionalization of the support.

In reaction B 4-iodobenzoic acid was first coupled to linker **26** to yield **38** and then a Suzuki–Miyaura coupling was performed with phenylboronic acid by using $Pd(PPh_3)_4$ as catalyst. Final methyl ester **39** was obtained in a yield of 48%.

In reaction C a ring-closing metathesis (RCM) reaction was carried out by attaching first 2-allyl-4-pentenoic acid to the linker, and resulting **40** was used as a substrate for the RCM by employing 5 mol-% of Grubbs II catalyst in DCM. Methanolysis after Cu^{++} complexation yielded desired methyl ester **41** in a yield of 36%.



Scheme 10. Scope of reactions performed with the new open-chain tetradentate linker. Reagents and conditions: Reductive amination (A): (a) 4-carboxybenzaldehyde (3.0 equiv.), TBTU (3.0 equiv.), DIEA (8.0 equiv.), DMF, room temp., 12 h; (b) piperidine (10 equiv.), $NaBH(OAc)_3$ (10 equiv.), 1,2-DCE, room temp., 12 h; (c) $Cu(OTf)_2$ (1.0 equiv.), MeOH, room temp., 15 h, 51%; Suzuki–Miyaura coupling (B): (d) 4-iodobenzoic acid (3.0 equiv.), TBTU (3.0 equiv.), DIEA (8.0 equiv.), DMF, room temp., 12 h; (e) $PhB(OH)_2$ (5.0 equiv.), K_3PO_4 (10 equiv.), $Pd(PPh_3)_4$ (10 mol-%), DMF, 90 °C, 12 h, 48%; ring-closing metathesis (C): (f) 2-allyl-4-pentenoic acid (3.0 equiv.), TBTU (3.0 equiv.) DIEA (8.0 equiv.), DMF, room temp., 12 h; (g) Grubbs 2nd generation catalyst (5 mol-%), CH_2Cl_2, room temp., 24 h, 36%; Heck reaction (D): (h) acrylic acid ethyl ester (3.0 equiv.), $Pd(OAc)_2$ (10 mol-%), PPh_3 (0.3 equiv.), K_2CO_3 (5.0 equiv.), NBu_4Cl (1.0 equiv.), toluene, 80 °C, 4 d, 55%; Horner–Wadsworth–Emmons reaction (E): (i) diethoxyphosphorylacetic acid methyl ester (3.0 equiv.), *n*BuLi (3.0 equiv.), THF, 0 → –78 °C, 3.5 h, 51%; Mitsunobu reaction (F): (j) 4-(*tert*-butyldimethylsilanyloxy)benzoic acid (3.0 equiv.), TBTU (3.0 equiv.), DIEA (8.0 equiv.), DMF, room temp., 12 h; (k) Cs_2CO_3 (3.0 equiv.), DMF/H_2O (10:1), room temp., 2 h; (l) allyl alcohol (4.5 equiv.), DIAD (4.8 equiv.), PPh_3 (3.6 equiv.), CH_2Cl_2, room temp., 20 h, 72%; Grignard reaction (G): (m) vinylmagnesium chloride (5.0 equiv.), THF, 0 °C → room temp., 15 h, 60%.

Reaction D was a Heck reaction with 4-iodobenzoic acid coupled to linker **38** as a starting point. The reaction was carried out in toluene under an atmosphere of argon by using $Pd(OAc)_2/PPh_3$ as catalyst and an excess amount of ethyl acrylate in the presence of K_2CO_3. Final methyl ester **42** was obtained in a yield of 55%.

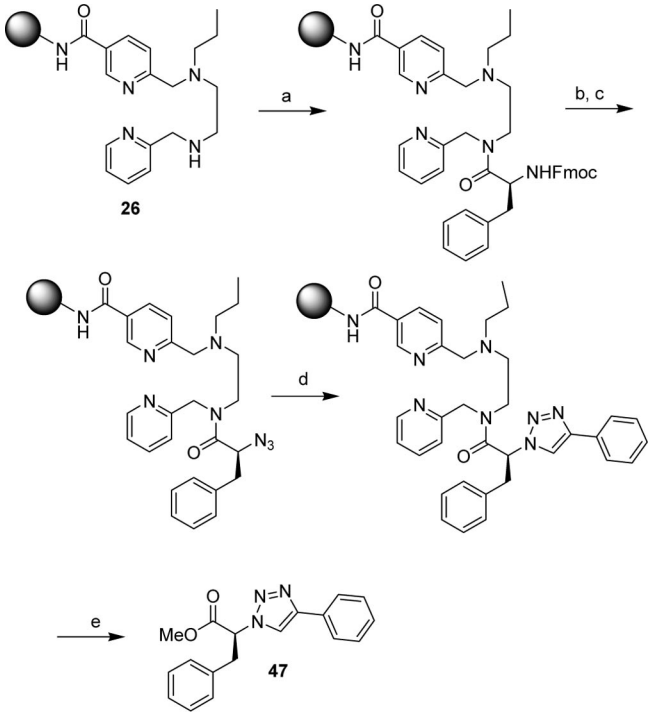
For the Horner–Wadsworth–Emmons reaction (reaction E), **36** was treated with a solution of *n*BuLi and diethoxyphosphorylacetic acid methyl ester in THF at –78 °C. After Cu^{++} complexation and methanolysis, methyl ester **43** could be isolated in a yield of 51%.

For the envisaged Mitsunobu reaction (reaction F) TBS-protected *p*-hydroxybenzoic acid was first coupled to **26**, yielding intermediate **44**. After deprotection of the TBS group with Cs_2CO_3 in DMF/H_2O (10:1) at room temperature for 2 h the Mitsunobu condensation was carried out with allyl alcohol in the presence of DIAD and PPh_3 in DCM. Methanolysis after Cu^{++} complexation led to the desired product in a yield of 72% over the five steps (Boc deprotection, attachment of the acid, TMS deprotection, Mitsunobu condensation, methanolysis).

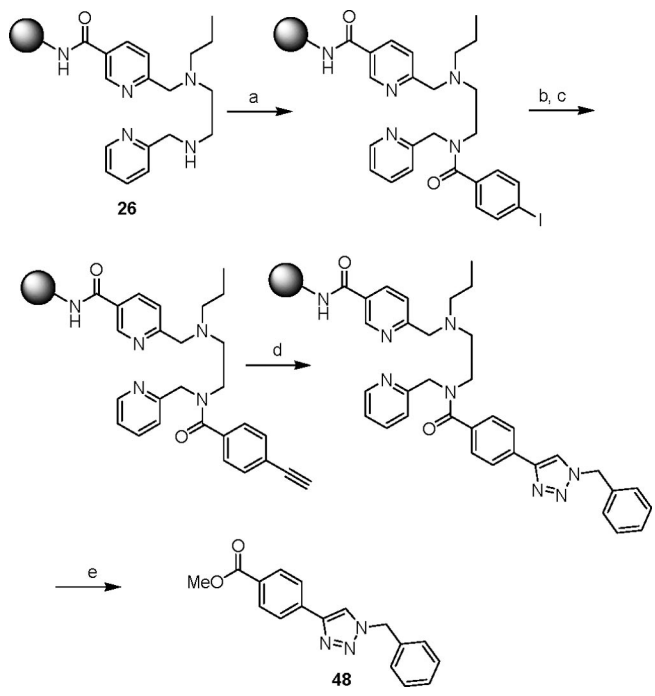
Finally, a Grignard reaction (reaction G) was performed starting from **36** by adding vinylmagnesium chloride in THF dropwise at 0 °C. Desired methyl ester **46** was obtained in a yield of 60%.

In addition to the examples illustrated in Scheme 10 two reaction sequences on the linker system were performed involving click chemistry, which is so rampant these days. In the first reaction sequence (Scheme 11), Fmoc-Phe-OH was coupled to linker **26**, which in turn had been obtained after cleavage of the Boc group from **25**. This was followed by cleavage of the Fmoc group with 20% piperidine in DMF. A diazo transfer with the use of triflic azide[14] and a catalytic amount of $CuSO_4 \cdot 5H_2O$ led to quantitative azide formation, which was proven by a negative Kaiser test. For this diazo transfer a small amount of MeOH was added to the reaction mixture to enhance the solubility of $CuSO_4$, although this might have caused a minute amount of premature cleavage by methanolysis. To the azide was added an excess amount of phenylacetylene and catalytic amounts of L-(+)-ascorbic acid and $CuSO_4 \cdot 5H_2O$ in DMF. After agitation for 20 h at room temperature and several washing steps, subsequent methanolysis after Cu^{++} complexation yielded methyl ester **47** in an overall yield of 53% as a single product in pure form (determined by HPLC analysis). This high yield over seven steps (starting from Hypogel400-NH_2) implies an individual yield per step of over 90%, which indicates that, if at all, only a small amount was cleaved prematurely during the diazo transfer reaction.

In the alternative sequence, *p*-iodobenzoic acid was first attached to support **26**. This was followed by a Sonogashira reaction employing ethinyltrimethylsilane and catalytic



Scheme 11. Diazo transfer and click reaction. Reagents and conditions: (a) Fmoc-Phe-OH (3.0 equiv.), TBTU (3.0 equiv.), DIEA (8.0 equiv.) room temp., 12 h; (b) piperidine/DMF (2:8, 2 × 4 mL, 5 min); (c) triflic azide solution in pyridine (18 equiv.), $CuSO_4 \cdot 5H_2O$ (10 mol-%), MeOH (10% v/v), room temp., 20 h; (d) phenylacetylene (2.0 equiv.), L-(+)-ascorbic acid (0.1 equiv.), $CuSO_4 \cdot 5H_2O$ (2 mol-%), DMF, room temp., 24 h; (e) $Cu(OTf)_2$ (1.0 equiv.), MeOH, room temp., 15 h, 53% over seven steps.



Scheme 12. Sonogashira reaction, TMS deprotection, and click reaction. Reagents and conditions: (a) *p*-iodobenzoic acid (3.0 equiv.), TBTU (3.0 equiv.), DIEA (8.0 equiv.), DMF, room temp., 12 h; (b) ethinyltrimethylsilane (2.0 equiv.), $PdCl_2(PPh_3)_2$ (5 mol-%), CuI (10 mol-%), PPh_3 (0.2 equiv.), DMF/NEt_3 (2:1), 80 °C, 24 h; (c) TBAF·$3H_2O$ (1.2 equiv.), THF, room temp., 24 h; (d) benzyl azide (2.0 equiv.), L-(+)-ascorbic acid (0.1 equiv.), $CuSO_4 \cdot 5H_2O$ (2 mol-%), DMF, room temp., 24 h; (e) $Cu(OTf)_2$ (1.0 equiv.), MeOH, room temp., 15 h, 41% over seven steps.

amounts of $PdCl_2(PPh_3)_2$, CuI, and PPh_3 in DMF/NEt_3 (2:1) at 80 °C (Scheme 12). The TMS protecting group was cleaved with TBAF in THF, and the resulting alkyne was converted into the triazole through a click reaction with an excess amount of benzyl azide and catalytic amounts of L-(+)-ascorbic acid and $CuSO_4 \cdot 5H_2O$ in DMF. Methanolysis after Cu^{++} complexation gave methyl ester **48** in an overall yield of 41% yield as determined by HPLC.

Conclusions

We have demonstrated that the concept of weakening amide bonds by forced complexation of the nitrogen to Cu^{++} is not limited to tridentate ligands but can be extended to tetradentate ligands. A prerequisite is obviously a certain flexible arrangement of the coordination sites, which cannot be achieved by cyclic tetradentate ligands. An open-chain tetradentate ligand allowed mild cleavage of amides by methanolysis after complexation. The principle was used for the development of a new linker for solid-phase chemistry, and comparison with our previously published tridentate ligand revealed that cleavage of amides was faster by applying the new system.

The linker was synthesized in a straightforward manner and we also demonstrated its recyclability. Besides that, the linker turned out to be very robust. It is stable towards basic and acidic conditions and its versatility was demonstrated by its compatibility with a whole myriad of different types of reactions. The demonstrated examples are by no means exhausted and we are confident that the generality of the concept will stimulate further applications.

Experimental Section

General: All reactions with air- and moisture-sensitive compounds were carried out under an argon atmosphere. All solvents were analytical grade or better. Dry CH_2Cl_2 was distilled from CaH_2. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker AM 400 spectrometer with Me_4Si as internal reference. Mass spectrometry was carried out with a Finnigan MAT312 spectrometer by using chemical ionization (CI) method and a Finnigan MAT8200 spectrometer by using electrospray ionization (ESI) method. Elemental analyses were measured with an Elementar Vario EL (Elementar Analysesysteme GmbH). For column chromatography, Merck silica gel 60 (40–63 μm) was used. The progress of the reactions was checked on TLC plates (silica gel 60, F-254, Merck). HPLC analysis was performed with an Agilent 1100 Series HPLC system. An Agilent Zorbax Eclipse 4.6 × 150 mm XDB-C8 column was used with a flow rate of 1 mL min^{-1} and a H_2O/CH_3CN gradient (70:30 → 30:70).

General Procedure for Coupling of Carboxylic Acids to Linker 26: The solid phase carrying linker **25** (300 mg, 0.163 mmol) was suspended in DMF (2 mL). After 10 min, a solution of the corresponding acid (3.0 equiv.), TBTU (157.0 mg, 0.489 mmol 3.0 equiv.) and DIEA (0.223 mL, 1.30 mmol, 8.0 equiv.) in DMF (3 mL) was added. The mixture was agitated at room temperature for 12 h. The solid support was filtered and washed alternately with DMF/*i*PrOH (5 × 3 mL) and subsequently with CH_2Cl_2 (3 mL) and Et_2O (3 mL).

General Procedure for Cu^{++}-Assisted Cleavage of the Linker Systems: The corresponding solid support was suspended in MeOH (3 mL). After 10 min, a solution of $Cu(OTf)_2$ (1.0 equiv.) in MeOH (2 mL) was added. The mixture was agitated for 15 h at room temperature. The solid support was filtered off, and the methanolic solution was evaporated. The residue was taken up in CH_2Cl_2 (5 mL) and extracted with aqueous EDTA solution (0.5 M, 2 × 10 mL) and H_2O (10 mL). The organic layer was dried with Na_2SO_4 and evaporated to yield the corresponding methyl ester.

General Procedure for Copper Decomplexation of the Tri- and Tetradentate Linker: The corresponding solid support was suspended in MeOH (3 mL). After 10 min, a solution of KCN (3.0 equiv.) in MeOH (2 mL) was added. The mixture was agitated at room temperature for 30 min. The solid support was filtered and washed with H_2O (3 × 5 mL), DMF (3 × 5 mL), MeOH (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), and Et_2O (3 × 5 mL).

Bis[3-(2,2,2-trifluoroacetamido)propyl]ammonium 2,2,2-Trifluoroacetate (3): A solution of *N*,*N*-bis(3-aminopropyl)amine (**2**; 3.0 mL, 21 mmol) and ethyl trifluoroacetate (9.0 mL, 76 mmol, 3.6 equiv.) in CH_3CN (60 mL) and H_2O (0.5 mL) was heated at reflux for 4 h. After cooling to room temperature the product precipitated as a white solid (7.9 g, 18 mmol, 85%). From the mother liquor additional product **3** could be obtained by partial evaporation (1.1 g, 2.5 mmol, 12%). Overall yield: 9.0 g (20.5 mmol, 97%; ref.[15] 97%). M.p. 173–174 °C (ref.[15] 120–121 °C). ^1H NMR (400 MHz, [D$_6$]acetone): δ = 2.12 (tt, J = 9.6, 9.4 Hz, 4 H, 2 × NH_2-CH_2-CH_2-), 3.26 (t, J = 9.6 Hz, 4 H, 2 × NH-CH_2-), 3.49 (m_c, 4 H, 2 × NH_2-CH_2-), 8.95 (br. s, 2 H, -NH_2^+-), 9.32 (br. s, 2 H, 2 × N*H*-) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 26.2, 37.3, 46.1, 117.0 (q, $J_{C,F}$ = 287 Hz), 118.0 (q, $J_{C,F}$ = 294 Hz), 158.0 (q, $J_{C,F}$ = 37 Hz), 161.9 (q, $J_{C,F}$ = 34 Hz) ppm. MS (CI, NH_3): *m*/*z* (%) = 325.1 (13) [M + 1]$^+$, 324.1 (100) [M]$^+$, 183.0 (11).

***tert*-Butyl Bis[3-(2,2,2-trifluoroacetamido)propyl]carbamate (4):** To a suspension of TFA salt **3** (4.0 g, 9.1 mmol, 1.0 equiv.) in NEt_3 (4.0 mL, 29 mmol, 3.2 equiv.) was added a solution of Boc_2O (2.4 mL, 10 mmol, 1.1 equiv.) in THF (10 mL) dropwise at 0 °C. The solution was stirred at room temperature overnight, and the reaction was terminated by the addition of H_2O (100 mL). The aqueous phase was extracted with ethyl acetate (EE) (3 × 100 mL), the combined organic layer was dried with Na_2SO_4, and the solvents were evaporated. Recrystallization from Et_2O/*n*-hexane gave product **4** as a white solid (3.1 g, 7.4 mmol, 82%; ref.[15] 90%). The spectroscopic data are in accordance to those reported in literature.[16]

***tert*-Butyl Bis(3-aminopropyl)carbamate (5):** To a solution of protected triamine **4** (1.95 g, 4.69 mmol, 1.0 equiv.) in MeOH (60 mL) was added a solution of NaOH (0.2 M in MeOH, 65 mL, 13 mmol, 2.8 equiv.) was added dropwise at 0 °C. The solution was stirred at room temperature overnight, and the solvent was removed under reduced pressure. The residue was dissolved in H_2O (20 mL) and extracted with MeOH/$CHCl_3$ (9:1, 3 × 30 mL). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure to yield **5** (790 mg, 3.42 mmol, 73%; ref.[15] 97%). as a colorless oil. The spectroscopic data are in accordance to those reported in literature.[16]

***tert*-Butyl Bis[3-(2-nitrophenylsulfonamido)propyl]carbamate (6):** To a solution of mono Boc-protected triamine **5** (59 mg, 0.26 mmol, 1.0 equiv.) and NEt_3 (72 μL, 0.51 mmol, 2.0 equiv.) in CH_2Cl_2 (2 mL) was added dropwise at room temperature a solution of 2-nitrobenzoylsulfonyl chloride (113 mg, 0.51 mmol, 2.0 equiv.) in CH_2Cl_2 (2 mL). The solution was stirred overnight, and the reaction was terminated by the addition of H_2O (10 mL). The aqueous

phase was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layer was dried with Na_2SO_4, and the solvents were evaporated. Column chromatography (CH_2Cl_2/MeOH, 98:2) gave title compound **6** as a white foam (126 mg, 0.21 mmol, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, -O*t*Bu), 1.70 (dd, J = 6.6, 6.3 Hz, 4 H, 2 × NHBoc-CH_2-CH_2-), 3.08 (m_c, 4 H, 2 × NHBoc-CH_2-), 3.22 (t, J = 6.6 Hz, 4 H, 2 × NHBoc-CH_2-CH_2-CH_2-), 7.70–7.78 (m, 4 H, $H_{arom.}$), 7.80–7.88 (m, 2 H, $H_{arom.}$), 8.08–8.16 (m, 2 H, $H_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.4, 28.3, 41.1, 46.1, 80.5, 125.3, 130.9, 132.7, 133.6 (2 overlayed signals), 148.0, 156.1 ppm. MS (CI, NH_3): m/z (%) = 502.2 (100) $[M + 1 - Boc]^+$.

3,11-Bis(2-nitrobenzenesulfonyl)-7-*tert*-butyloxycarbonyl-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(16),13(17),14-triene (7): A suspension of protected triamine **6** (3.24 g, 5.38 mmol, 1.0 equiv.) and Na_2CO_3 (2.97 g, 28.0 mmol, 5.2 equiv.) in DMF (140 mL) was stirred at room temperature for 1.5 h, followed by the addition of a solution of 2,6-bis(bromomethyl)pyridine (1.85 g, 6.99 mmol, 1.3 equiv.) in DMF (140 mL) over a period of 5 h. The resulting solution was stirred at room temperature overnight, DMF was removed by recondensation, and the residue was redissolved in CH_2Cl_2 (250 mL). The organic phase was washed with NaOH (0.1 M, 2 × 100 mL), dried with Na_2SO_4, and evaporated under reduced pressure. Column chromatography [cyclohexane (CH)/EE, 60:40 → 0:100] gave title compound **7** as a white foam (3.30 g, 4.68 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, -O*t*Bu), 1.61 (m_c, 4 H, 2 × NHBoc-CH_2-CH_2-) 3.07 (t, J = 6.2 Hz, 4 H, 2 × NHBoc-CH_2-), 3.26 (t, J = 7.5 Hz, 4 H, 2 × NHBoc-CH_2-CH_2-CH_2-), 7.56 (br. d, J = 7.5 Hz, 2 H, $H_{arom.}$), 7.64–7.82 (m, 7 H, $H_{arom.}$), 8.03–8.08 (m, 2 H, $H_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 28.7, 46.8, 47.5, 54.1, 79.8, 123.8, 124.3 (2 overlayed signals), 130.7, 131.0, 131.8, 132.8, 133.7, 148.2, 155.5 ppm. MS (ESI+): m/z (%) = 727.2 (100) $[M + Na]^+$, 704.9 (12) $[M]^+$, 648.9 (17), 627.2 (21), 606.2 (12), 605.2 (43). $C_{30}H_{36}N_6O_{10}S_2$ (704.77): calcd. C 51.51, H 5.41, N 11.28, S 8.70; found C 51.13, H 5.15, N 11.92, S 9.10.

7-*tert*-Butyloxycarbonyl-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(16),13(17),14-triene (8): To a suspension of ternary protected tetraazamacrocycle **7** (3.30 g, 4.70 mmol, 1.0 equiv.) and Na_2CO_3 (5.10 g, 48.0 mmol, 10.2 equiv.) in DMF (200 mL) was added dropwise thiophenol (1.70 g, 15.5 mmol, 3.3 equiv.). The solution was stirred at room temperature overnight. DMF was removed by recondensation, and the residue was redissolved in CH_2Cl_2 (250 mL). The organic phase was washed with H_2O (2 × 100 mL), and the combined aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). To obtain a clear solution, MeOH (10 mL) was added to the combined organic layer before they were dried with Na_2SO_4 and evaporated under reduced pressure. Column chromatography (CH_2Cl_2 → MeOH → MeOH/25% aq. NH_3 95:5) and lyophilization of the product fractions after evaporation of H_2O (10 mL) gave title compound **8** as a yellow resin-like solid (1.21 g, 3.60 mmol, 77%). ^{1}H NMR (400 MHz, MeOD): δ = 1.23 (s, 9 H, -O*t*Bu), 1.85 (m_c, 4 H, 2 × NHBoc-CH_2-CH_2-), 2.50 (m_c, 4 H, 2 × NHBoc-CH_2-CH_2-CH_2-), 3.33 (m_c, 4 H, 2 × NHBoc-CH_2-), 4.04 (s, 4 H, 2 × py-CH_2-), 7.24 [d, J = 7.7 Hz, 2 H, C(3,5) of pyridine], 7.73 [t, J = 7.7 Hz, 1 H, C(4) of pyridine] ppm. ^{13}C NMR (100 MHz, MeOD): δ = 28.5, 31.6, 46.2, 48.0, 53.5, 80.9, 122.9, 138.8, 157.6, 158.4 ppm.

3,11-Bispropyl-7-*tert*-butyloxycarbonyl-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(16),13(17),14-triene (9b): A solution of Boc-protected tetraazamacrocycle **8** (97 mg, 0.029 mmol, 1.0 equiv.), 1-brompropane (59 μL, 0.64 mmol, 2.2 equiv.), and DIEA (0.15 mL, 0.87 mmol, 3.0 equiv.) in CH_3CN (4 mL) was heated to 70 °C for 2 h. The solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (10 mL), the organic phase was washed with H_2O (10 mL), and the aqueous phase was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layer was dried with Na_2SO_4, and the solvents were evaporated. Column chromatography (CH_2Cl_2/MeOH, 90:10) gave title compound **9b** as a yellow resin (85 mg, 0.20 mmol, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.3 Hz, 2 × -$CH_2CH_2CH_3$), 1.32 (s, 9 H, -O*t*Bu), 1.52–1.76 (m, 8 H, 2 × -$CH_2CH_2CH_3$, 2 × NHBoc-CH_2-CH_2-), 2.52 (t, J = 7.0 Hz, 4 H, 2 × NHBoc-CH_2-CH_2-CH_2-), 2.61 (t, J = 7.5 Hz, 4 H, 2 × NHBoc CH_2-), 3.10 (t, J = 6.3 Hz, 4 H, 2 × -$CH_2CH_2CH_3$), 3.79 (s, 4 H, 2 × py-CH_2-), 7.22 [d, J = 7.6 Hz, 2 H, C(3,5) of pyridine], 7.58 [t, J = 7.6 Hz, C(4) of pyridine] ppm. MS (EI): m/z (%) = 419.2 (8) $[M + 1]^+$, 418.1 (31) $[M]^+$, 322.1 (11), 321.1 (58), 221.1 (11), 163.1 (15), 159.0 (11), 148.0 (21), 133.0 (10), 127.1 (14), 107.0 (100), 106.0 (42), 98.0 (70), 86.0 (16), 70.0 (11), 57.0 (23), 41.0 (16).

3,11-Bispropyl-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(16),13(17),14-triene 2,2,2-Trifluoroacetate (10): A solution of Boc-protected tetraazamacrocycle **9b** (60 mg, 0.14 mmol, 1.0 equiv.) and *i*Pr_3SiH (88 μL, 0.43 mmol, 3.1 equiv.) in CH_2Cl_2/TFA (1:1, 3 mL) was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (CH_2Cl_2/MeOH, 90:10 → 85:15) to give title compound **10** as a yellow oil (61 mg, 0.14 mmol, 100%). ^{1}H NMR (400 MHz, MeOD): δ = 0.92 (t, J = 7.4 Hz, 6 H, 2 × -$CH_2CH_2CH_3$), 1.70 (qt, J = 7.8, 7.4 Hz, 4 H, 2 × -$CH_2CH_2CH_3$), 2.24 (tt, J = 5.3, 2.7 Hz, 4 H, 2 × NHBoc-CH_2-CH_2-), 2.81 (m_c, 4 H), 3.24–3.31 (m, 8 H), 4.26 (s, 4 H, 2 × py-CH_2-), 7.52 [d, J = 7.7 Hz, 2 H, C(3,5) of pyridine], 7.91 [t, J = 7.7 Hz, 1 H, C(4) of pyridine] ppm. ^{13}C NMR (100 MHz, MeOD): δ = 11.5, 19.4, 22.0, 49.3, 52.1, 56.6, 57.5, 118.2 (q, $J_{C,F}$ = 293 Hz), 126.5, 140.2, 155.0, 163.0 (q, $J_{C,F}$ = 34 Hz) ppm. MS (ESI+): m/z (%) = 319.2 (100) $[M + 1]^+$, 234.2 (6), 114.7 (8).

3,11-Bispropyl-7-benzoyl-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(16),13(17),14-triene (13): To a solution of benzoyl chloride (**11**; 23 μL, 0.19 mmol, 2.5 equiv.) in CH_2Cl_2 (1 mL) was added at 0 °C a solution of tetraazamacrocycle **10** (33 mg, 0.076 mmol, 1.0 equiv.) and NEt_3 (28 μL, 0.19 mmol, 2.5 equiv.) in CH_2Cl_2 (1.5 mL). The solution was stirred at room temperature overnight. The organic phase was washed with H_2O (2 × 3 mL), dried with Na_2SO_4, and the solvents were evaporated. Column chromatography (CH_2Cl_2/MeOH, 95:5 → 90:10) gave title compound **13** as a yellow resin (17 mg, 0.046 mmol, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.2 Hz, 6 H, 2 × -$CH_2CH_2CH_3$), 1.43–2.10 (m, 8 H), 2.34–2.91 (m, 8 H), 3.14–3.59 (m, 4 H), 3.73–4.04 (m, 4 H), 7.24–7.32 (m, 7 H), 7.67 [t, J = 7.6 Hz, 1 H, C(4) of pyridine] ppm. MS (EI): m/z (%) = 423.4 (9) $[M + 1]^+$, 422.4 (32) $[M]^+$, 326.3 (20), 325.5 (100), 259.3 (10), 250.3 (10), 219.2 (16), 164.2 (10), 163.2 (17), 162.1 (30), 107.1 (48), 106.1 (30), 105.1 (63), 98.1 (63), 77.1 (18), 36.0 (11).

3,11-Bispropyl-7-(4-methoxyphenyl)acetyl-3,7,11,17-tetraazabicyclo-[11.3.1]heptadeca-1(16),13(17),14-triene (14): To a solution of 4-methoxyphenylacetyl chloride (**12**; 95 μL, 0.61 mmol, 2.5 equiv.) in CH_2Cl_2 (3 mL) was added at 0 °C a solution of tetraazamacrocycle **10** (106 mg, 0.245 mmol, 1.0 equiv.) and NEt_3 (87 μL, 0.61 mmol, 2.5 equiv.) in CH_2Cl_2 (1.5 mL). It was stirred at room temperature overnight. The organic layer was washed with H_2O (2 × 3 mL), dried with Na_2SO_4, and the solvents were evaporated. Column chromatography (CH_2Cl_2/MeOH, 95:5 → 90:10) gave title compound **14** as a yellow resin (43 mg, 0.091 mmol, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.3 Hz, 6 H, 2 × -$CH_2CH_2CH_3$), 1.49–1.80 (m, 8 H, 2 × -$CH_2CH_2CH_3$, 2 × NHCO-

CH_2-CH_2-), 2.44–2.67 (m, 8 H, 2 × -$CH_2$$CH_2$$CH_3$, 2 × NHCO-$CH_2$-$CH_2$-C$H_2$-), 3.19–3.35 (m, 4 H, 2 × NHCO-CH_2-), 3.54 (s, 4 H, 2 × py-CH_2-), 3.72 (s, 2 H, Ar-CH_2-CO-), 3.80 (s, 3 H, -OMe), 6.81 (m_c, 2 H, $H_{arom.}$), 7.09 (m_c, 2 H, $H_{arom.}$), 7.15–7.30 (m, 2 H, $H_{arom.}$), 7.59 [t, J = 7.6 Hz, 1 H, C(4) of pyridine] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 20.0 (2 overlayed signals), 39.6, 44.4, 46.8, 51.5, 55.2, 59.6, 114.0, 123.0, 123.2, 127.5, 129.6, 136.8, 158.3, 171.1 ppm. MS (EI): *m*/*z* (%) = 467.4 (100) $[M + 1]^+$, 262.3 (15).

Methyl 6-Formylnicotinate (16): To a solution of methyl 6-methylnicotinate (**15**; 2.00 g, 13.2 mmol, 1.0 equiv.) in DMSO (50 mL) was added iodine (3.35 g, 13.2 mmol, 1.0 equiv.), TFA (3.05 mL, 39.6 mmol, 3.0 equiv.), and *t*BuI (0.62 mmol, 5.2 mmol, 0.4 equiv.). The mixture was heated to 120 °C for 3 h. After cooling to room temperature an aqueous solution of $Na_2S_2O_3$ (0.1 M, 100 mL) and a solution of $NaHCO_3$ (10%, 120 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL), the organic layer was dried with Na_2SO_4, and the solvents were evaporated. Column chromatography (CH_2Cl_2/MeOH, 98:2) gave title compound **21** as a brown oil (1.43 g, 8.7 mmol, 65%). The spectroscopic data were in accordance with those reported in literature.[10]

Methyl 6-{[2-(*tert*-Butoxycarbonylamino)ethylamino]methyl}-nicotinate (17): To a solution of **16** (1.27 g, 7.69 mmol, 1.0 equiv.) and *N*-Boc-ethylenediamine (1.21 mL, 7.69 mmol, 1.0 equiv.) in 1,2-DCE (30 mL) was added $NaBH(OAc)_3$ (2.28 g, 10.8 mmol, 1.4 equiv.). The mixture was stirred at room temperature for 1.5 h. An aqueous solution of $NaHCO_3$ (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), the organic layer was dried with Na_2SO_4, and the solvents were evaporated. Column chromatography (CH_2Cl_2/MeOH, 98:2 → 95:5) gave title compound **17** as a brown oil (1.74 g, 5.61 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, -O*t*Bu), 2.77 (t, J = 5.8 Hz, 2 H, -CH_2-NH-CH_2-), 3.24 (td, J = 5.8, 5.7 Hz, 2 H, -CH_2-NH-Boc), 3.91 (s, 3 H, -CO_2*Me*), 3.96 (s, 2 H, py-CH_2-), 5.05 (br. s, 1 H, -N*H*-), 7.37 (d, J = 8.1 Hz, 1 H, $H_{arom.}$), 8.22 (dd, J = 8.0, 2.1 Hz, 1 H, $H_{arom.}$), 9.13 (br. dd, J = 2.1, 0.6 Hz, 1 H, $H_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5, 48.9, 52.4, 54.6, 121.8, 124.5, 137.6, 150.6, 156.2, 164.3, 165.8 ppm. MS (ESI+): *m*/*z* (%) = 310.1 (100) $[M + 1]^+$, 210.1 (56) $[M + 1 – Boc]^+$. $C_{15}H_{23}N_3O_4$ (309.36): calcd. C 58.24, H 7.49, N 13.58; found C 57.95, H 7.57, N 13.39.

Methyl 6-{[2-(*tert*-Butoxycarbonylamino)ethyl](propyl)amino}methyl-nicotinate (18): To a solution of methyl ester **17** (1.60 g, 5.17 mmol, 1.0 equiv.) in CH_3CN (40 mL) was added DIEA (5.31 mL, 31.02 mmol, 6.0 equiv.) and propyl bromide (2.35 mL, 25.9 mmol, 5.0 equiv.), and the mixture was stirred under reflux for 15 h. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (100 mL). The organic layer was washed with H_2O (2 × 100 mL), dried with Na_2SO_4, and the solvents were evaporated. Column chromatography (CH_2Cl_2/MeOH, 98:2 → 95:5) gave title compound **18** as a brown oil (1.36 g, 3.88 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.4 Hz, 3 H, -CH_2-CH_3), 1.42 (s, 9 H, -O*t*Bu), 1.45–1.51 (m, 2 H, -CH_2-CH_3), 2.47 (t, J = 7.4 Hz, 2 H, -CH_2-CH_2-CH_3); 2.60 [t, J = 6.1 Hz, 2 H, -CH_2-N(propyl)-CH_2-], 3.17 (td, J = 6.0, 5.7 Hz, 2 H, -CH_2-NHBoc), 3.79, (s, 2 H, py-CH_2-), 3.93 (s, 3 H, -CO_2*Me*), 5.15 (br. s, 1 H, -N*H*-), 7.50 (d, J = 8.2 Hz, 1 H, $H_{arom.}$), 8.24 (dd, J = 8.1, 2.2 Hz, 1 H, $H_{arom.}$), 9.11 (dd, J = 2.2, 0.8 Hz, 1 H, $H_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 20.3, 28.5, 38.5, 52.3, 53.9, 56.7, 60.5, 122.4, 124.5, 137.5, 150.4, 156.1, 165.0, 165.9 ppm. MS (APCI+): *m*/*z* (%) = 352.0 (100) $[M + 1]^+$. $C_{18}H_{29}N_3O_4$ (351.44): calcd. C 61.52, H 8.32, N 11.96; found C 61.35, H 8.45, N 11.79.

***N*-[(5-Methoxycarbonyl)pyridine-2-yl]methyl-*N*-propylethane-1,2-diaminium 2,2,2-trifluoroacetate (19):** To a solution of methyl ester **18** (0.97 g, 2.8 mmol, 1.0 equiv.) in TFA/CH_2Cl_2 (1:1, 10 mL) was added *i*Pr_3SiH (1.7 mL, 8.3 mmol, 3.0 equiv.). The mixture was stirred at room temperature for 2 h, followed by removal of the solvent under reduced pressure. Column chromatography (CH_2Cl_2/MeOH, 98:2 → 90:10) gave title compound **19** as a brown oil (1.32 g, 2.75 mmol, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.3 Hz, 3 H, -CH_2-CH_3), 1.57–1.82 (m, 2 H, -CH_2-CH_3), 2.99 (m_c, 2 H, -CH_2-CH_2-CH_3), 3.44 [m_c, 4 H, -CH_2-N(propyl)-CH_2-,-CH_2-NH_3^+], 3.93 (s, 3 H, -CO_2*Me*), 4.33 (s, 2 H, py-CH_2-), 7.48 (d, J = 8.2 Hz, 1 H, $H_{arom.}$), 8.33 (dd, J = 8.1, 2.1 Hz, 1 H, $H_{arom.}$), 9.15 (d, J = 2.0 Hz, 1 H, $H_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.9, 18.2, 35.9, 51.7, 52.6, 56.8, 57.1, 116.4, 123.8, 126.2, 138.8, 150.5, 157.0, 165.1 ppm. ^{19}F NMR: δ = –75.81 ppm. MS (ESI+): *m*/*z* (%) = 252.1 (100) $[M – 2CF_3COO^– H]^+$.

Methyl 6-({2-[*tert*-Butoxycarbonyl(pyridine-2-ylmethyl)amino]ethyl-(propyl)amino}methyl)nicotinate (21): To a solution of methyl ester **19** (1.29 g, 2.69 mmol, 1.0 equiv.) and pyridine-2-carboxaldehyde (0.256 mL, 2.69 mmol, 1.0 equiv.) in 1,2-DCE (12 mL) was added $NaBH(OAc)_3$ (0.78 g, 3.77 mmol, 1.4 equiv.). The mixture was stirred at room temperature for 1.5 h, followed by the addition of an aqueous solution of $NaHCO_3$ (12 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), the organic layer was dried with Na_2SO_4, and the solvents were evaporated to give crude secondary amine **20** as a brown oil (0.85 g, 2.48 mmol, 92%). To a solution of crude **20** (0.85 g, 2.48 mmol, 1.0 equiv.) and NEt_3 (0.49 mL, 3.52 mmol, 1.4 equiv.) in CH_2Cl_2 (20 mL) was added slowly Boc_2O (0.70 mL, 3.27 mmol, 1.3 equiv.) at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature for 2 h. After addition of H_2O (30 mL) the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried with Na_2SO_4 and the solvents were evaporated. Column chromatography (CH_2Cl_2/MeOH, 97:3) gave title compound **21** as a brown oil (0.84 g, 1.9 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, J = 7.3 Hz, 3 H, -CH_2-CH_3), 1.38 (s, 9 H, O*t*Bu), 1.42–1.48 (m, 2 H, -CH_2-CH_3), 2.42 (m_c, 2 H, -CH_2-CH_2-CH_3), 2.64 [m_c, 2 H, -CH_2-N(propyl)-CH_2], 3.38 (m_c, 2 H, -CH_2-NBoc-), 3.78 [s, 2 H, py-CH_2-N(propyl)-], 4.52 (d, J = 14.8 Hz, 2 H, py-CH_2-NBoc-) 3.93 (s, 3 H, -CO_2*Me*), 7.11–7.24 (m, 2 H, $H_{arom.}$), 7.51–7.65 (m, 2 H, $H_{arom.}$), 8.21 (d, J = 8.2 Hz, 1 H, $H_{arom.}$), 8.49 (s, 1 H, $H_{arom.}$), 9.07 (dd, J = 2.1, 0.6 Hz, 1 H, $H_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 20.5, 28.5, 45.7, 52.3, 52.7, 53.0, 53.5, 56.8, 60.9, 120.7, 121.7, 122.0, 122.1, 124.4, 136.7, 137.5, 149.2, 150.2, 155.8, 159.0, 166.0 ppm. MS (ESI+): *m*/*z* (%) = 443.2 (100) $[M + 1]^+$, 343.2 (42) $[M – Boc + 1]^+$. $C_{24}H_{34}N_4O_4$ (442.55): calcd. C 65.14, H 7.74, N 12.66; found C 64.97, H 7.91, N 12.47.

6-({2-[*tert*-Butoxycarbonyl(pyridine-2-ylmethyl)amino]ethyl(propyl)-amino}methyl)nicotinic Acid (22): To a solution of methyl ester **21** (0.82 g, 1.85 mmol, 1.0 equiv.) in MeOH (15 mL) was added an aqueous solution of NaOH (2 M, 1.02 mL, 2.04 mmol, 1.1 equiv.), and the mixture was heated to reflux for 1.5 h. The solvents were removed, and the residue was dissolved in H_2O (20 mL) and acidified with 2 M HCl (pH 6). The aqueous phase was extracted with CH_2Cl_2 (7 × 20 mL). The combined organic layer was dried with Na_2SO_4, and the solvents were evaporated to yield title compound **22** as a white solid (0.71 g, 1.66 mmol, 90%). ^{1}H NMR (400 MHz, CD_3OD): δ = 0.94 (t, J = 7.3 Hz, 3 H, -CH_2-CH_3), 1.14 (s, 9 H, O*t*Bu), 1.28–1.39 (m, 2 H, -CH_2-CH_3), 1.61–1.85 (m, 2 H, -CH_2-CH_2-CH_3), 3.53 [t, J = 5.4 Hz, 2 H, -CH_2-N(propyl)-CH_2], 3.91 (t, J = 5.5 Hz, 2 H, -CH_2-NBoc-), 4.55 [s, 2 H, py-CH_2-N(propyl)], 4.63 (s, 2 H, py-CH_2-NBoc-), 7.31–7.42 (m, 2 H, $H_{arom.}$), 7.53 (d, J = 8.1 Hz, 1 H, $H_{arom.}$), 7.85 (dd, J = 7.8, 7.8 Hz, 1 H, $H_{arom.}$),

8.31 (dd, J = 8.0, 2.1 Hz, 1 H, $H_{arom.}$), 8.49–8.64 (m, 1 H, $H_{arom.}$), 9.02 (s, 1 H, $H_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3, 18.2, 28.3, 28.5, 44.7, 53.2, 53.4, 56.6, 56.91, 82.2, 123.8, 124.1, 124.3, 133.2, 139.2, 139.4, 149.8, 151.6, 154.9, 157.1, 159.9, 171.0 ppm. MS (CI, NH_3): m/z (%) = 429.2 (100) $[M + 1]^+$. $C_{23}H_{32}N_4O_4$ (428.52): calcd. C 64.46, H 7.53, N 13.07; found C 64.26, H 7.72, N 12.89.

Coupling of Tetradentate Linker 22 to the Solid Support and Subsequent Boc Deprotection to Yield Resin 26 Ready for the Attachment of Carboxylic Acids: Hypogel400-NH_2 (1.50 g, 1.04 mmol, 1.0 equiv.) was suspended in DMF (10 mL). After 10 min a solution of carboxylic acid **22** (604 mg, 1.41 mmol, 1.3 equiv.), TBTU (453 mg, 1.41 mmol, 1.3 equiv.), and DIEA (1.11 mL, 6.48 mmol, 6.0 equiv.) in DMF (5 mL), which was preactivated for 5 min, was added to the suspended resin. The solid support was agitated for 8 h. A negative Kaiser test showed complete coupling of carboxylic acid **22**. The solid support was filtered and washed alternately with DMF/*i*PrOH (5 × 5 mL), CH_2Cl_2 (5 mL), and Et_2O (5 mL). The resin was suspended in CH_2Cl_2 (15 mL) and after 10 min TFA (15 mL) and iPr$_3$SiH were added. The resin was agitated for 2 h and was then washed again with DMF and *i*PrOH (5 × 5 mL), CH_2Cl_2 (5 mL), and Et_2O (5 mL). After drying under high vacuum modified resin **26** (1.91 g) was obtained.

Recycling of Linker 26: The amino acid Boc-Ala-OH was coupled to solid support **26** by applying the general procedure. After methanolysis by the general procedure Boc-Ala-OMe was obtained as a white solid (19.9 mg, 0.098 mmol, 60%). The spectroscopic data were in accordance to those reported in the literature.[17] After decomplexation by the general procedure Boc-Phe-OH was coupled to the solid support by applying the general procedure. Subsequent methanolysis gave Boc-Phe-OMe as a white solid (23.9 mg, 0.090 mmol, 55%). The spectroscopic data are in accordance to those reported in literature.[18]

Reactions with Tetradentate Linker 26

A) Reductive Amination

Methyl 4-(Piperidin-1-ylmethyl)benzoate (37): 4-Carboxybenzaldehyde (73.4 mg, 0.489 mmol, 3.0 equiv.) was coupled to solid support **26** by the general procedure. After the washing steps solid support **36** was suspended in DMF (5 mL) for 10 min before piperidine (161 μL, 1.63 mmol, 10 equiv.) and $NaBH(OAc)_3$ (345 mg, 1.63 mmol, 10 equiv.) were added. The solid support was agitated for 12 h. After methanolysis of the solid support by the general procedure, methyl ester **37** was obtained as an orange oil (19.4 mg, 83 μmol, 51%). The spectroscopic data were in accordance to those reported in the literature.[19]

B) Suzuki–Miyaura Coupling

Methyl Biphenyl-4-carboxylate (39): *p*-Iodobenzoic acid (121.3 mg, 0.489 mmol, 3.0 equiv.) was coupled to solid support **26**. After the washing steps solid support **38** was suspended in DMF (5 mL). After 10 min phenyl boronic acid (99.4 mg, 0.815 mmol, 5.0 equiv.), K_3PO_4 (173 mg, 0.815 mmol, 5.0 equiv.), and $Pd(PPh_3)_4$ (18.5 mg, 0.016 mmol, 10 mol-%) were added. The solid support was agitated at 90 °C for 12 h. After methanolysis of the solid support by the general procedure, methyl ester **39** was obtained as a white solid (16.6 mg, 78 μmol, 48%). The spectroscopic data were in accordance to those reported in the literature.[20]

C) Ring-Closing Metathesis

Methyl Cyclopent-3-enecarboxylate (41): 2-Allyl-4-pentenoic acid (68.5 mg, 0.489 mmol, 3.0 equiv.), which had been synthesized according to a literature procedure,[21] was coupled to solid support **26**. After the washing steps solid support **40** was suspended in CH_2Cl_2 (3 mL). After 10 min a solution of Grubbs 2nd generation catalyst (6.8 mg, 0.008 mmol, 5 mol-%) in CH_2Cl_2 (2 mL) was added. The solid support was agitated at room temperature for 24 h. After methanolysis of the solid support, methyl ester **41** was obtained as a colorless liquid (7.4 mg, 59 μmol, 36%). The spectroscopic data were in accordance to those reported in the literature.[22]

D) Heck Reaction

(*E*)-Methyl 4-(3-Ethoxy-3-oxoprop-1-enyl)benzoate (42): *p*-Iodobenzoic acid (121.3 mg, 0.489 mmol, 3.0 equiv.) was coupled to solid support **26**. After the washing steps solid support **38** was suspended in toluene. After 10 min $Pd(OAc)_2$ (3.7 mg, 0.017 mmol, 10 mol-%), PPh_3 (12.8 mg, 0.0490 mmol, 30 mol-%), K_2CO_3 (112.8 mg, 0.816 mmol, 5.0 equiv.), NBu_4Cl (45.4 mg, 0.163 mmol, 1.0 equiv.), and ethyl acrylate (53.0 μL, 0.489 mmol, 3.0 equiv.) were added. The solid support was heated to reflux for 4 d. After methanolysis of the solid support, methyl ester **42** was obtained as a brown solid (21 mg, 90 μmol, 55%). The spectroscopic data were in accordance to those reported in the literature.[23]

E) Horner–Wadsworth–Emmons Reaction

(*E*)-Methyl 4-(3-Methoxy-3-oxoprop-1-enyl)benzoate (43): After coupling of 4-carboxybenzaldehyde (73.4 mg, 0.489 mmol, 3.0 equiv.) to solid support **26** and after subsequent washing steps solid support **36** was suspended in THF (1.5 mL) and cooled to –78 °C. To a solution of diethoxyphosphorylacetic acid methyl ester (89.5 μL, 0.490 mmol, 3.0 equiv.) in THF (3 mL) was added dropwise at 0 °C *n*BuLi (1.5 M, 350 μL, 0.490 mmol, 3.0 equiv.). The resulting solution was cooled to –78 °C and added dropwise to solid support **36**. The resin was shaken at –78 °C for 3.5 h before it was quenched by the addition of H_2O/MeOH (1:1, 0.7 mL). After the methanolysis, methyl ester **43** was obtained as a brown solid (18.3 mg, 83 μmol, 51%). The spectroscopic data were in accordance to those reported in the literature.[24]

F) Mitsunobu Reaction

Methyl 4-(Allyloxy)benzoate (45): After coupling of 4-(*tert*-butyldimethylsilanyloxy)benzoic acid (176.0 mg, 0.489 mmol, 3.0 equiv.) to solid support **26** and subsequent washing steps solid support **44** was suspended in DMF (4 mL). After 10 min a solution of Cs_2CO_3 (159.5 mg, 0.4896 mmol, 3.0 equiv.) in H_2O (0.4 mL) was added. The resin was agitated for 2 h, before it was washed alternately with DMF/*i*PrOH (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL). After the deprotection, the resin was suspended under an atmosphere of argon in CH_2Cl_2 (2 mL) for 10 min before a solution of allyl alcohol (50.1 μL, 0.734 mmol, 4.5 equiv.), DIAD (151.2 μL, 0.7834 mmol, 4.8 equiv.), and PPh_3 (154.1 mg, 0.5875, 3.6 equiv.) in CH_2Cl_2 (1 mL) was added. The resin was agitated at room temperature for 20 h. After methanolysis of the solid support, methyl ester **45** was obtained as a yellow oil (22.6 mg, 0.117 mmol, 72%). The spectroscopic data were in accordance to those reported in the literature.[25]

G) Grignard Reaction

Methyl 4-(1-Hydroxyallyl)benzoate (46): After coupling of 4-carboxybenzaldehyde (73.4 mg, 0.489 mmol, 3.0 equiv.) to solid support **26** and after subsequent washing steps solid support **36** was suspended under an atmosphere of argon in THF (5.0 mL). After 10 min vinylmagnesium chloride (1.5 M in hexane, 532 μL, 0.816 mmol, 5.0 equiv.) was added dropwise at 0 °C. The resin was agitated at room temperature for 15 h. After the methanolysis of the solid support, methyl ester **46** was obtained as a brown oil

(17.4 mg, 0.0978 mmol, 60%). The spectroscopic data were in accordance to those reported in the literature.[26]

Reaction Sequences with Tetradentate Linker 26

A) Diazo Transfer and Click Reaction

(*S*)-Methyl 3-Phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoate (47): After coupling of Fmoc-Phe-OH (189.3 mg, 0.489 mmol, 3.0 equiv.) to solid support **26** and after subsequent washing steps, solid support **34** was suspended in DMF/piperidine (8:2, 2 × 4 mL, 5 min) to yield the Fmoc-deprotected solid support. For the following diazo transfer, a freshly prepared solution of triflic azide[14] in pyridine (0.7 M, 4.2 mL, 2.94 mmol, 18 equiv.), $CuSO_4 \cdot 5H_2O$ (4.2 mg, 17 μmol, 10 mol-%), and MeOH (0.5 mL) were added to the solid support. The solid support was agitated at room temperature for 20 h, before it was washed with DMF (3 × 5 mL), DMF/DIEA (99.5:0.5, 3 × 5 mL, 2 min), diethyldithiocarbamate sodium salt in DMF (0.05 M, 3 × 5 mL, 10 min), DMF (5 × 3 mL, 5 min), and CH_2Cl_2 (3 × 5 mL, 3 min). The solid support was suspended in DMF (3 mL). After 10 min phenylacetylene (37.6 μL, 0.342 mmol, 2.1 equiv.), L-(+)-ascorbic acid (3.0 mg, 17 μmol, 10 mol-% equiv.), and $CuSO_4 \cdot 5H_2O$ (0.9 mg. 3.6 μmol, 2 mol-%) were added. The solid support was agitated at room temperature for 20 h. After methanolysis of the solid support, methyl ester **47** was obtained as a white solid (26.6 mg, 86 μmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.54 (m, 2 H, Ph-CH_2-), 3.77 (s, 3 H, -CO_2Me), 5.63 (t, J = 7.5 Hz, 1 H, MeO_2C-CH-), 7.05–7.10 (m, 2 H, $H_{arom.}$), 7.22–7.27 (m, 4 H, -CH=C-, $H_{arom.}$), 7.32–7.36 (m, 1 H, $H_{arom.}$), 7.42 (m_c, 1 H, $H_{arom.}$), 7.78–7.83 (m, 3 H, $H_{arom.}$) ppm. MS (CI, NH_3): *m*/*z* (%) = 308.1 (100) $[M + 1]^+$. HPLC: t_R = 12.36 min.

B) Sonogashira Reaction, TMS Deprotection, and Click Reaction

Methyl 4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)benzoate (48): After coupling of *p*-iodobenzoic acid (121.3 mg, 0.489 mmol, 3.0 equiv.) to solid support **26** and subsequent washing steps, solid support **38** was suspended under an atmosphere of argon in degassed DMF/NEt_3 (2:1, 4.5 mL). After 10 min ethinyltrimethylsilane (45.2 μL, 0.326 mmol, 2.0 equiv.), $PdCl_2(PPh_3)_2$ (5.8 mg, 8.2 μmol, 5 mol-%), PPh_3 (8.6 mg, 32.6 mmol, 20 mol-%), and CuI (3.1 mg, 16 μmol 10 mol-%) were added to the solid support. The solid support was heated to 80 °C for 24 h. After subsequent washing steps with DMF, *i*PrOH, and CH_2Cl_2 the solid support was suspended in THF (4 mL). After 10 min TBAF·$3H_2O$ (61.8 mg, 0.196 mmol, 1.2 equiv.) was added. The solid support was agitated at room temperature for 24 h and again washed with DMF, *i*PrOH, and CH_2Cl_2. The resulting solid support was suspended in DMF (3 mL). After 10 min benzyl azide (43.5 mg, 0.326 mmol, 2.0 equiv.), L-(+)-ascorbic acid (3.0 mg, 17 μmol, 10 mol-%), and $CuSO_4 \cdot 5H_2O$ (0.9 mg, 3.6 μmol, 2 mol-%) were added. The solid support was agitated at room temperature for 24 h. After subsequent washing steps with DMF (3 × 3 mL), *i*PrOH (3 × 3 mL), and CH_2Cl_2 (3 × 3 mL) and the following methanolysis of the solid support, methyl ester **48** was obtained as a yellow solid (19.6 mg, 66.8 μmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, -CO_2Me), 5.51 (s, 2 H, Ph-CH_2-), 7.22–7.27, (m, 1 H, $H_{arom.}$), 7.29–7.34 (m, 2 H, $H_{arom.}$), 7.48–7.56 (m, 1 H, $H_{arom.}$), 7.66 (s, 1 H, -C=CH-), 7.80 (m_c, 2 H, $H_{arom.}$), 7.99 (m_c, 3 H, $H_{arom.}$) ppm. MS (CI, NH_3): *m*/*z* (%) = 294.1 (100) $[M + 1]^+$. HPLC: t_R = 11.31 min.

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