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Onium salt supported peptide synthesis

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ABSTRACT

Task specific ionic liquids and onium salts have been used as soluble supports for peptide synthesis. These new supports combine easy monitoring, high loading capacities, large scale preparation, and homogeneous kinetics characteristics while keeping advantages of solid-phase synthesis including easy purification and workup. Careful structural design of these supports allowed for fine tuning of physical properties leading to better yields, kinetics, and purities.

1. Introduction

Solid-phase peptide synthesis (SPPS) first reported by Merrifield in 1963, spread out rapidly among the scientific community and is now routinely used for peptides synthesis including on industrial scale.[1–3] Mostly related to the heterogeneous nature of the system, advantages of SPPS are numerous and include possible automation and parallel library synthesis. Most importantly, use of excess of reagents accelerating kinetics and improving yields is facilitated by quick and easy purification by filtration and washes. However, some drawbacks remain like low loading capacities of resins, and a difficult access to active sites leading to limitation in kinetics and yields. The latter can be overcome by restoring homogenous conditions. The use of soluble polymers[4,5] and fluorous tagged molecules.[6–9] have been proposed as solutions to these drawbacks. In spite of relative success in using soluble polymers (especially PEG or soluble polystyrene), some specific problems arose hampering the development of this technology, like very low loading capacities and difficult automation. Furthermore, anchoring of peptides with a long peptidic chain alters the solubility properties of the polymer. More recently, based on quasi exclusive affinity of perfluorous alkyl chains for fluorous solvents, some perfluorous alkyl chains tagged supports have been used for peptide synthesis. Albeit efficient, this methodology is limited by Nernst Constant between the fluorous phase and the organic phase, which dramatically decreases when peptidic chain length increases. Indeed, a composition with more than 40% of fluorine is required for exclusive solubility in fluorous solvent. Therefore only small peptide can be obtained using this process.

In this paper we want to report how task specific onium salts (TSOSs) and ionic liquids (TSILs) can be used as soluble supports for peptide synthesis combining advantages of both SPPS and liquid phase reactions.[10,11] The Onium Salt Supported Organic Synthesis (OSSOS) methodology, which we[12,13] and others[14] recently described, relies on using an onium salt on which a specific functionality has been attached. It confers the onium salt specific properties and can be used subsequently as a reagent, a catalyst, or a support. These Task Specific Ionic Liquids (or Onium salts depending on their melting point) can be used either in pure form or as solutions in matrixes, such as ionic liquids or molecular solvents.[13] This matrix prevents from viscosity problems frequently observed when task specific onium salts are used neat, their viscosity and melting point increasing dramatically with functionalization.[14] Since then, these supports have been successfully used for multicomponent reactions,[15–17] radical reactions,[18] biocatalysis,[19–24] transition metal catalyzed reactions, [25,26] oligosaccharides synthesis,[27] and oligonucleotides synthesis.[28] As witnessed by these numerous applications,[29,30,13] OSSOS methodology as a solution phase technology brings advantages as compared to heterogeneous chemistry:

- Reaction conditions are homogeneous leading to kinetics similar to unsupported versions of the reactions.[18]
- No sophisticated analytical methods are required and simple NMR, MS, IR, or HPLC are sufficient for accurate monitoring and characterization.
- Purifications are shrunk to the simplest, filtration and washes remove both excess reagents and eventual non-supported side products.

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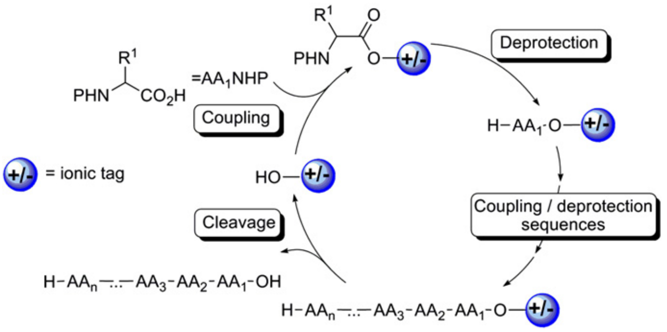
- Due to their low molecular weight, loading capacities of the supports are far higher than classical resin or PEGs.
- Structural flexibility is easily accessible and allows fine tuning of physical properties including solvent miscibility, viscosity. Scale-up is easy and automation conceivable.

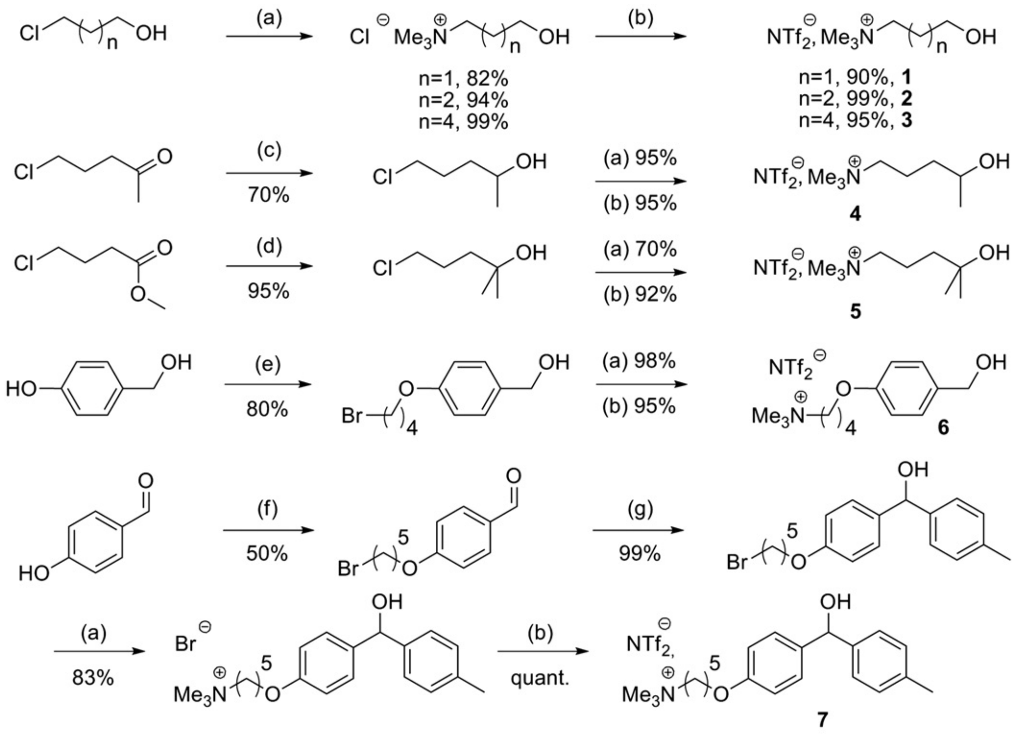
A standard strategy was used for supported synthesis by taking advantages of liquid phase reactions as follows. First a TSOS with a cation bearing a hydroxyl group is synthesized, and by successive coupling/deprotection sequences, a peptidic chain is attached to the support. Cleavage of ester bond would subsequently release the peptide and the support could be reused in another synthesis (Scheme 1). A huge advantage of OSSOS methodology is the structural flexibility allowed by cation and anion in supporting salts. Moreover, task specific onium salts synthesis is extremely simple and products can be synthesized in a couple of steps starting from cheap commercially available products. Such synthesis can be easily carried out in the laboratory on a 500 g scale. For the purpose of supported peptide synthesis, we decided to use the triflimide anion thus conferring a poor aqueous solubility to the corresponding onium salts allowing easy aqueous workups and extraction of excess reagent and side products. Trimethylammonium cation was chosen because it presents several advantages over imidazolium or phosphonium cation, including chemical orthogonality and minimal ^{1}H signals facilitating reaction monitoring. We therefore tackled directly the problem by synthesizing a family of onium salts bearing a hydroxyl group on the cation for amino acids attachment. Primary (**1**–**3**), secondary (**4**), tertiary (**5**) and benzyl alcohol (**6**,**7**) derived onium salts have been prepared following a classical synthetic scheme, i.e., quaternisation of trimethylamine by appropriate alkyl halide, followed by anion metathesis using lithium triflimide or hexafluorophosphoric acid leading to these supports in good overall yields (74–99%). Indeed, with molecular weight in a 260–600 range, these onium salts have a loading capacity between 1.6 and 3.8 mmol g^{-1}. Noticeably in order to work at a traditional 0.1 M concentration, only 26–50 g of support has to be solubilized per liter of solvent as compared to 500 g for classical PEG$_{5000}$.



Scheme 1. Onium Salt Supported Peptide Synthesis (OSSPS) strategy.

2. Synthesis of onium salt supports

Synthesis of hydroxylated onium salts **1**–**7** were performed using standard strategies (Scheme 2). Primary alcohols **1**–**3** were prepared in two steps from corresponding commercially available ω-chloroalcohols. Quaternarisation of trimethylamine in an acetonitrile/water mixture afforded the corresponding ammonium chlorides in 82–99% yields. Triflimide salts were then obtained using a simple anion metathesis with LiNTf$_2$ in a biphasic system CH$_2$Cl$_2$/water in nearly quantitative yields (90–99%). Onium salts **4** and **5** were obtained from the corresponding chloroalcohols resulting from reduction of the 5-chloro-2-pentanone with NaBH$_4$ in EtOH (70% yield) and methyl Grignard addition to the 5-chloro methylbutanoate (95% yield), respectively. Following steps were



(a) NMe$_3$, MeCN/H$_2$O, 70°C (b) LiNTf$_2$, H$_2$O, RT (c) NaBH$_4$, EtOH, RT (d) MeMgI, THF/Et$_2$O, RT then 45°C (e) 1,4-dibromobutane, K$_2$CO$_3$, refluxing acetone (f) 1,5-dibromopentane, K$_2$CO$_3$, refluxing acetone (g) MeC$_6$H$_4$MgBr, Et$_2$O, then MeOH

Scheme 2. Synthesis of hydroxyl derived onium salts developed for peptide synthesis.

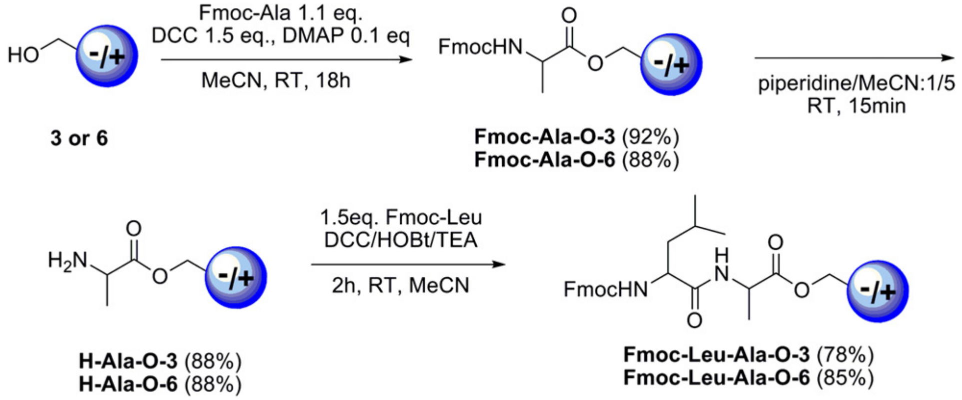
identical to those described before including a trimethylamine quaternarisation (95% and 70% yield, respectively) followed by an anion metathesis with $LiNTf_2$ in a biphasic system CH_2Cl_2/water (95% and 92% yield, respectively). Williamson alkylation in acetone of 4-hydroxybenzylic alcohol, using an excess of 1,4-dibromobutane afforded the corresponding mono substituted product in 80% yield, which could be used for the alkylation of trimethylamine afforded the corresponding trimethylammonium bromide in 98% yield. The triflimide analog **6** was obtained in 95% yield after anion exchange. The benzhydril support was obtained in four steps from 4-hydroxybenzaldehyde. Williamson allylation (50% yield) followed by 4-toluylmagnesium bromide addition to the aldehyde (99%) led to the corresponding diarylmethanol. The same quaternarisation (83%) followed by a quantitative ion metathesis then provides the trimethylammonium salt **7**.

3. Peptide synthesis

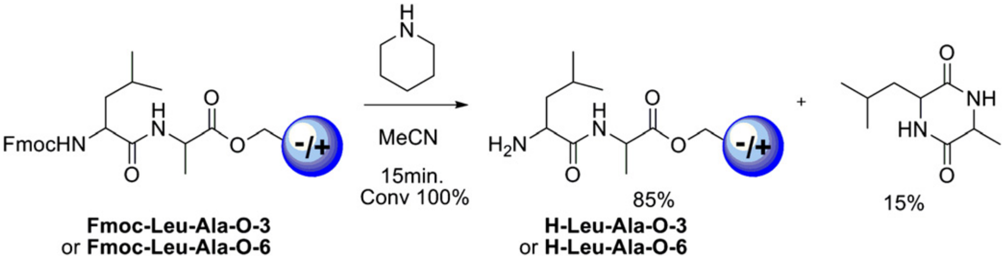
Unfortunately simplest supports **1**–**5** turned out to be problematic. Although usually stable under slightly basic conditions, esters **Fmoc-Ala-O-1** and **Fmoc-Ala-O-2** with the shortest linkers were cleaved when treated with piperidine. Coupling with bulkier alcohol, such as **4** and **5** were not as high yielding (<70%) as with primary alcohol functionalized supports **1**–**2** despite several conditions tested (DCC/DMAP, $Bi(OTf)_3$/DIPC, $Sc(OTf)_3$/DMAP, Al_2O_3/Zn/S) and further studies in this direction were abandoned. To lower the influence of the ammonium cation on the stability of the ester linkage, longer linkers with more carbons between the hydroxyl group and the cationic part of the support were used. Indeed, starting from **3** and **6**, no problems were observed neither during the coupling step with Fmoc-Ala-OH nor in the deprotection step with piperidine in acetonitrile.

Ester formation was carried out under standard conditions using Fmoc-protected alanine in the presence of 1.5 equiv of DCC and 10% of DMAP leading to **Fmoc-Ala-O-3** (92%) and **Fmoc-Ala-O-6** (88%). Conversion for deprotection is quantitative after 15 min of treatment by a 1/5 piperidine/acetonitrile mixture (Scheme 3). Peptide formation was then pursued with the grafting of another amino acid. Under standard peptide coupling conditions using 1.5 equiv of DCC, HOBt, TEA, and Fmoc-leucine, supported protected dipeptides **Fmoc-Leu-Ala-O-3** and **Fmoc-Leu-Ala-O-6** were obtained pure in good yields (78% and 85%, respectively). The following step was the Fmoc deprotection of the supported dipeptides. Conversion was quantitative within 15 min in a 1:5 piperidine: MeCN mixture. However, 15% of the supported peptide was cleaved from its support as a result of diketopiperazine (DKP) formation (Scheme 4). This side reaction has already been observed using Wang resin structurally analogous to our hydroxybenzyl support **6**, especially when a small amino acid is used increasing chain flexibility. Since DKP is not grafted on the onium salt support it was easily removed from the reaction mixture by simple washing with ether leading to the pure supported protected dipeptides **Fmoc-Leu-Ala-O-3** and **Fmoc-Leu-Ala-O-6**. Nevertheless, 15% of DKP side product corresponding to a large loss of the valuable amino acids was unacceptable and strategy using these supports has been discarded. A support analogous to Barlos resin (trityl linker) may avoid this DKP formation. However acidic sensitivity during workup prevented us to develop this strategy. Finally we concentrated our efforts on a benzhydril type support derived from structure **7** (Scheme 2).

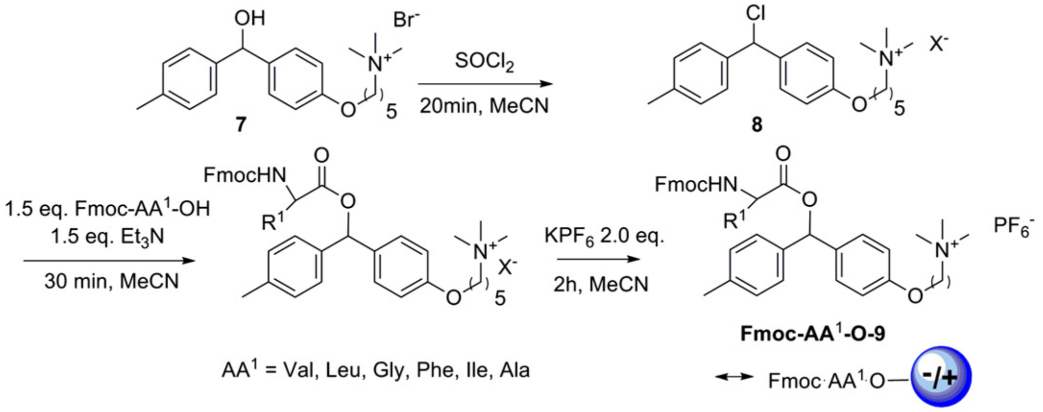
Anchoring strategy for this type of support is slightly different from that previously developed for onium salts **1**–**6**. Indeed, a two steps sequence including chlorination of the **7** onium salt using thionyl chloride followed by esters formation using Fmoc-protected amino acids and triethylamine afforded supported protected amino acids in good yields (Scheme 5). At this point onium salts are obtained as a mixture of chloride and bromide, which confer them a non negligible aqueous solubility incompatible with further aqueous workup. We decided to perform an ion metathesis with potassium hexafluorophosphate to confer hydrophobic properties to our support. This would also allow further washes with an aqueous solution of HPF_6 thus avoiding anion metathesis. Following this procedure, conversions were quasi quantitative and TSOS **AA_1-O-9** derived from α-amino acids, such as Ala, Gly, Ile, Leu, Phe, and Val were obtained in 80–98% yield over four steps from **7**



Scheme 3. Coupling between with Fmoc-Ala-OH and long chain onium salts and deprotection.



Scheme 4. Deprotection of **3** and **6** derived Fmoc-protected dipeptides.



Scheme 5. Benhydril type onium salt supported Fmoc amino acids.

(Table 1). Products were isolated in an excellent state of purity (>98%) reached just by washing with water and ether to remove by-products of the coupling and remaining reagents.

Table 1
Grafting of first amino acid following Scheme 5

Entry	$\mathbf{Fmoc\text{-}AA_1\text{-}O\text{-}9}$	Yield[a] %
1	**Fmoc-Ala-O-9**	95
2	**Fmoc-Gly-O-9**	98
3	**Fmoc-Ile-O-9**	89
4	**Fmoc-Leu-O-9**	89
5	**Fmoc-Phe-O-9**	80
6	**Fmoc-Val-O-9**	80

[a] Over four steps from **Br-7**.

Fmoc deprotection was cleanly achieved using standard piperidine/MeCN (1/5) solution (Scheme 6). Under the same coupling conditions, a second Fmoc-protected α-amino acid (Ala, Gly, Ile, Leu, Val) could be attached to the chain in high yield leading to a series of Fmoc-protected grafted dipeptides (Table 2).

To further validate the technology, supported tripeptides were prepared in good yields (98% over two steps) from $\mathbf{AA_2\text{-}AA_1\text{-}O\text{-}9}$. (Table 3) In that case, Fmoc deprotection with piperidine led to less than 5% of DKP formation, which is suitable for pursuing the synthesis. This side product is easily removed from the reaction mixture by washing with ether since it is not grafted on the task specific onium salt anymore. Alternatively, HBTU turned out to be another good coupling reagent showing that our strategy can be adapted to other methods.

Table 2
Grafting of second amino acid on $\mathbf{H\text{-}AA_1\text{-}8}$ following Scheme 6

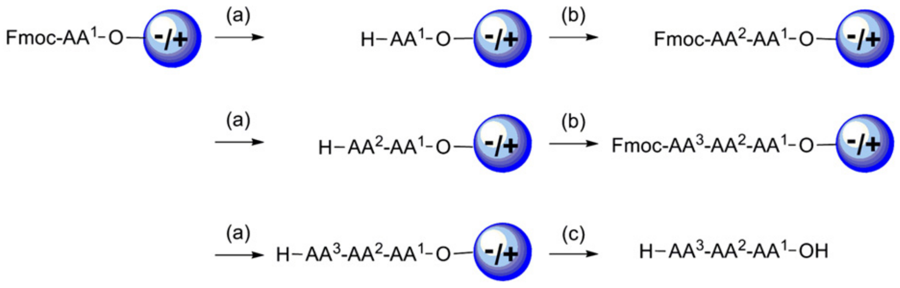
Entry	$\mathbf{Fmoc\text{-}AA_2\text{-}AA_1\text{-}O\text{-}9}$	Yield[a] %
1	**Fmoc-Ala-Ile-O-9**	88
2	**Fmoc-Ala-Phe-O-9**	98
3	**Fmoc-Ala-Val-O-9**	70
4	**Fmoc-Gly-Leu-O-9**	70
5	**Fmoc-Gly-Phe-O-9**	85
6	**Fmoc-Gly-Val-O-9**	95
7	**Fmoc-Ile-Leu-O-9**	78
8	**Fmoc-Leu-Ala-O-9**	94
9	**Fmoc-Val-Ile-O-9**	94

[a] Over two steps from $\mathbf{Fmoc\text{-}AA_1\text{-}O\text{-}9}$.

Table 3
Grafting of third amino acid on $\mathbf{H\text{-}AA_2\text{-}AA_1\text{-}8}$ following Scheme 6

Entry	$\mathbf{Fmoc\text{-}AA_3\text{-}AA_2\text{-}AA_1\text{-}O\text{-}9}$	Yield[a] %
1	**Fmoc-Gly-Ala-Phe-O-9**	98
2	**Fmoc-Leu-Ala-Phe-O-9**	98
3	**Fmoc-Val-Gly-Phe-O-9**	83
9	**Fmoc-Val-Leu-Ala-O-9**	91

[a] Over two steps from $\mathbf{Fmoc\text{-}AA_2\text{-}AA_1\text{-}O\text{-}9}$.



(a) piperidine/MeCN:1/5, RT, 15min
(b) Fmoc-AA-OH (1.5 eq.) DCC / HOBt / TEA MeCN, 30min, RT
(c) 0.01eq. HPF_6 aq. MeOH, Δ, 1h.
AA^1 = Val, Leu, Gly, Phe, Ile, Ala; AA^2 = Ala, Gly, Ile, Leu, Val ; AA^3 = Gly, Leu, Val

Scheme 6. Onium Salts supported tripeptide synthesis.

Finally, the peptide was cleaved from the TSOS support using a catalytic amount of HPF_6 in refluxing methanol. For purification, peptide was soluble in water, whereas the derivatives from the TSOS were soluble in DCM. The tripeptide **H-Val-Leu-Ala-OH** was isolated in a pure state in 85% yield over the whole coupling sequence (six steps, average yield: 97.3%) Noticeably, ionic liquid [bmim][PF_6] can also be used as solvent in all the N-protecting group cleavage and peptide coupling steps, typically in 0.1–0.3 M concentration range. In that case, all reactions are carried out without purification until the last cleavage step, where the tripeptide is extracted from the ionic matrix with water. After the last step (cleavage using HPF_6), support can be recycled by reaction with thionyl chloride leading to **8**.

Unlike previously described supports, monitoring of the reaction by NMR and/or HPLC without cleavage from the support is easy and could facilitate high throughput and large scale preparation of peptide libraries. Racemisation studies using Marfey's reagent[31] were performed on the Val-Leu-Ala peptide as a model. It appeared that very little racemisation could be observed (below 1% overall). This value is within the precision of the detection method (HPLC-PDA), which indicates that almost no racemisation occurred.

4. Conclusion

In summary, we have demonstrated the possibility to use task specific onium salts as soluble supports for peptide synthesis. Despite its inapplicability to be used as such for long peptides, this methodology highlights the simplicity of using these supports. They are easy to synthesize at a low cost and reactions are driven to completion using standard amount of reagents under mild conditions. These supports properties (solubility and stability) can be modulated by a simple design of structures. Noticeably, no optimization of operating conditions has been made, and direct extrapolation of Solid-Phase methods provided decent results. It is likely that these supports are a valuable addition to the arsenal of tools available for peptide synthesis. This work is also an interesting addition to the possibilities offered by task specific ionic liquids and onium salts as working salts.

5. Experimental section

5.1. General methods

All glassware was oven dried prior to use and reactions were run under an inert atmosphere of argon using standard Schlenk techniques. Yields reported were from isolated products and determined to be pure by GC (DB-5 column) or TLC (pre-coated plates of silica gel 60 F_{254}, stained with an ethanolic phosphomolybdic acid solution), and NMR spectroscopy. Solvents were carefully dried and purified following known procedures[32] prior to use. All other standard chemicals were purchased from ACROS Chemicals, Alfa-Aesar or Aldrich Chemical Co. and used without further purification. Reactions were monitored by gas chromatography (GC–MS) (GC system: HP 6890 series, Mass selective detector HP 5973) using a capillary column DB-5MS. Column chromatography purifications were performed on silica gel Si 60 (40–63 μm, 230–400 mesh, Merck). Melting points were determined on an electrothermal IA9300 digital melting point instrument. NMR spectra were recorded on a Bruker ARX 200 (^{1}H: 200.13 MHz, ^{13}C: 50.32 MHz) or AC 300 P (^{1}H: 300.13 MHz), ^{1}H chemical shifts (δ) are given in parts per million relative to TMS as external standard, J values in hertz, ^{13}C chemical shifts are given relative to the central signal of $CDCl_3$ at 77.0 ppm. IR spectra were obtained on a Bio-Rad FTS 175C FT-IR spectrophotometer. High resolution mass spectra measurements were performed at the Centre Régional de Mesures Physiques de l'Ouest (C.R.M.P.O, University of Rennes 1) using a Varian MAT 311 with BE geometry (reversed NIER-JOHNSON) and EI cathod or Micromass ZABSpec TOF with EBE OA TOF geometry with LSIMS Ionization (Liquid Secondary Ion Mass Spectrometry) at 8 kV with Cs^+ gun in *m*-nitrobenzyl alcohol (mNBA).

5.2. Onium salt supports synthesis

5.2.1. General procedure for quaternisation of trimethylamine (procedure A). To a solution of alkyl halide in acetonitrile (0.1 M) is added 2 equiv of trimethylamine (45% in water). After 18 h at 70 °C, solvents are removed under vacuum and Et2O is added to the residue until complete crystallization. The precipitate is subsequently filtered and washed several times with Et2O (3×10 mL mmol^{-1}).

5.2.2. General procedure for ion metathesis (procedure B). To a saturated aqueous solution of onium halide is added a saturated aqueous solution of $LiNTf_2$ (1.1 equiv). After 1 h at room temperature, an oil corresponding to the triflimide onium salt appears. The mixture is extracted with 3×10 mL mmol^{-1} CH_2Cl_2. If oil appears to be insoluble in CH_2Cl_2, aqueous and organic layers are removed and the residue is dissolved in acetonitrile. Organic fraction containing onium salt (CH_2Cl_2 or acetonitrile) is then dried over Na_2SO_4, filtered and concentrated under reduced pressure.

5.2.3. [HOPrTMA][Cl]. Following general procedure A using 3-chloropropan-1-ol, [HOPrTMA][Cl] is obtained in 82% yield as a white solid. Mp: 158–160 °C ^{1}H NMR (200 MHz, D_2O): δ=1.92 (m, 2H), 3.00 (s, 9H), 3.30 (m, 2H), 3.60 (t, 2H, J=7.1 Hz). ^{13}C (50 MHz, D_2O): δ=64.5, 58.5, 53.3 (t, J_{C-N}=4.1), 25.7. HRMS (FAB): [$2C^+$, A^-] ($C_{12}H_{32}N_2O_2Cl$) calcd 271.2152, found 271.2149.

*5.2.4. [HOPrTMA][NTf$_2$] **1**.* Following general procedure B using [HOPrTMA][Cl], [HOPrTMA][NTF$_2$] is obtained in 90% yield as a colorless oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=2.10 (m, 2H), 3.25 (s, 9H), 3.50–3.80 (m, 4H). ^{13}C (50 MHz, acetone-d_6): δ=121.0 (q, J_{C-F}=321 Hz), 66.1, 60.0, 54.3 (t, J_{C-N}=4.0 Hz), 29.1. HRMS (FAB): [$2C^+$, A^-] ($C_{14}H_{32}N_3O_6F_6S_2$) calcd 516.1636, found 516.1632.

5.2.5. [HOBuTMA][Cl]. Following general procedure A using 4-chlorobutan-1-ol, [HOBuTMA][Cl] is obtained in 94% yield as a white solid. Mp: 118–120 °C ^{1}H NMR (200 MHz, D_2O): δ=1.69 (m, 2H), 1.95 (m, 2H), 3.25 (s, 9H), 3.45 (m, 2H), 3.60 (t, 2H, J=7.2 Hz). ^{13}C (50 MHz, D_2O): δ=66.7, 61.1, 53.2 (t, J=4.1 Hz), 28.4.

*5.2.6. [HOBuTMA][NTf$_2$] **2**.* Following general procedure B using [HOPrTMA][Cl], [HOBuTMA][NTF$_2$] is quantitatively obtained as a colorless oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.63 (m, 2H), 2.04 (m, 2H), 3.38 (s, 9H), 3.57–3.69 (m, 5H). ^{13}C (50 MHz, acetone-d_6): δ=120.3 (q, J_{C-F}=321 Hz), 66.8, 61.4, 53.0 (t, J_{C-N}=3.9 Hz), 29.3, 19.8. ^{19}F (282 MHz, acetone-d_6): δ=−79.9. HRMS (FAB): [$2C^+$, A^-] ($C_{16}H_{36}N_3O_6F_6S_2$) calcd 544.1950, found 544.1928.

5.2.7. [HOHeTMA][Cl]. Following general procedure A using 6-chlorohexan-1-ol, [HOHeTMA][Cl] is quantitatively obtained as a white solid. Mp: 178–180 °C ^{1}H NMR (200 MHz, D_2O): δ=1.27–1.34 (m, 4H), 1.48 (m, 2H), 1.72 (m, 2H), 3.02 (s, 9H), 3.23 (m, 2H), 3.51 (t, 2H, J=6.2 Hz). ^{13}C (75 MHz, D_2O): δ=66.0, 61.5, 53.8 (t, J=3.6 Hz), 31.0, 25.3, 24.6, 22.3. HRMS (FAB): [$2C^+$, A^-] ($C_{18}H_{44}N_2O_2Cl$) calcd 355.3091, found 355.3093.

*5.2.8. [HOHeTMA][NTf$_2$] **3**.* Following general procedure B using [HOHeTMA][Cl], [HOHeTMA][NTf$_2$] is obtained in 95% yield as a colorless oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.36–1.68 (m, 6H), 2.00 (m, 2H), 3.36 (s, 9H), 3.52–3.61 (m, 5H). ^{13}C (75 MHz, acetone-d_6): δ=120.0 (q, J_{C-F}=321 Hz), 66.5, 61.4, 52.5, 32.2, 25.6, 25.0, 22.5. ^{19}F (282 MHz, acetone-d_6): δ=−79.9. HRMS (FAB): [$2C^+$, A^-] ($C_{16}H_{36}N_3O_6F_6S_2$) calcd 544.1950, found 544.1928.

5.2.9. [HOPeTMA][Cl]. Following general procedure A using 5-chloropentan-2-ol, [HOPeTMA][Cl] is obtained in 95% yield as a white solid. ^{1}H NMR (200 MHz, D_2O): δ=1.13 (d, 3H, J=6.2 Hz), 1.46 (m, 2H), 1.78 (m, 2H), 3.05 (s, 9H), 3.27 (m, 2H), 3.81 (q, 1H, J=6.2 Hz).

^{13}C (75 MHz, D_2O): δ=66.9, 66.5, 52.9 (t, J=3.8 Hz), 34.3, 21.9, 18.9. HRMS (FAB): [M$^+$] ($C_8H_{20}NO$) calcd 146.1545, found 146.1547.

5.2.10. [HOPeTMA][NTf$_2$] ***4***. Following general procedure B using [HOPeTMA][Cl], [HOPeTMA][NTf$_2$] is obtained in 95% yield as a colorless oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.18 (d, 3H, J=6.1 Hz), 1.52 (m, 2H), 2.04 (m, 2H), 3.39 (s, 9H), 3.60 (m, 2H), 3.70 (d, 1H, J=4.7 Hz), 3.84 (m, 1H). ^{13}C (75 MHz, acetone-d_6): δ=119.6 (q, J_{C-F}=321 Hz), 66.3, 66.0, 52.3 (t, J_{C-N}=3.8 Hz), 34.7, 22.5, 18.9. HRMS (FAB): [2C$^+$, A$^-$] ($C_{18}H_{40}N_3O_6F_6S_2$) calcd 572.2263, found 572.2266.

5.2.11. [HOMPeTMA][Cl]. Following general procedure A using 5-chloro-2-methylpentan-2-ol[33] [HOMPeTMA][Cl] is obtained in 70% yield as a white solid. Mp: 132–134 °C ^{1}H NMR (200 MHz, D_2O): δ=1.16 (s, 6H), 1.43 (m, 2H), 1.77 (m, 2H), 3.04 (s, 9H), 3.25 (m, 2H). ^{13}C (75 MHz, D_2O): δ=71.0, 66.6, 52.9 (t, J=3.9 Hz), 38.7, 27.8, 17.9. LRMS (LSIMS) de ($C_{18}H_{44}N_2O_2Cl$): [2C$^+$, Cl$^-$] m/z=355.3.

5.2.12. [HOMPeTMA][NTf$_2$] ***5***. Following general procedure B using [HOPeTMA][Cl], [HOMPeTMA][NTf$_2$] is obtained in 92% yield as a colorless oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.23 (s, 6H), 1.53 (t, 2H, J=7.8 Hz), 2.06 (m, 2H), 3.39 (s, 9H), 3.45 (s, 1H), 3.58 (m, 2H). ^{13}C (75 MHz, acetone-d_6): δ=119.6 (q, J_{C-F}=320 Hz), 71.3, 67.0, 51.1, (t, J_{C-N}=4.0 Hz), 39.0, 27.9, 18.1. ^{19}F (282 MHz, acetone-d_6): δ=−79.9. HRMS (FAB): [2C$^+$, A$^-$] ($C_{20}H_{44}N_3O_6F_6S_2$) calcd 600.2576, found 600.2583.

5.2.13. 4-(4-Bromobutoxy)benzyl alcohol. To a solution of 4-hydroxybenzyl alcohol (10.0 g, 80.6 mmol) in acetone (125 mL) were added 1,4-dibromobutane (19.2 mL, 161 mmol) and K_2CO_3 (11.1 g, 80.6 mmol). After 18 h under refluxing conditions, the reaction mixture is filtered. Upon cooling, a solid forms in the filtrate and eliminated by filtration. The filtrate is concentrated under reduced pressure and crystallized by a slow addition of pentane. The residue is filtered, washed with 3×20 mL of pentane and dried under reduced pressure. 16.9 g of a white solid are obtained and used in the next steps without further purification (Yield: 80%). Mp <45 °C ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.65 (s, 1H), 1.91–2.21 (m, 4H), 3.50 (t, 2H, J=6.5 Hz), 4.04 (t, 2H, J=5.7 Hz), 6.92 (d, 2H, J=8.6 Hz), 7.33 (d, 2H, J=8.9 Hz). ^{13}C (50 MHz, $CDCl_3$): δ=158.5, 133.2, 128.7, 114.5, 66.9, 65.0, 33.5, 29.5, 27.9. HRMS (FAB): [M$^{+\bullet}$] ($C_{11}H_{15}O_2Br$) calcd 258.0255, found 258.0266.

5.2.14. [HOMPhBTMA][Br]. Following general procedure A using 4-(4-Bromobutoxy)benzyl alcohol, [HOMPhBTMA][Br] is obtained in 98% yield as a white solid. Mp: 144–146 °C ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.74–1.99 (m, 4H), 3.04 (s, 9H), 3.32 (m, 2H), 4.06 (t, 2H, J=5.1 Hz), 4.50 (s, 2H), 6.95 (d, 2H, J=8.6 Hz), 7.29 (d, 2H, J=8.6 Hz). ^{13}C (50 MHz, $CDCl_3$): δ=157.6, 133.1, 129.3, 114.9, 67.4, 66.1 (J_{C-N}=3.0 Hz), 63.4, 52.8 (J_{C-N}=3.8 Hz), 25.2, 19.3 HRMS (FAB): [M$^{+\bullet}$] ($C_{14}H_{24}NO_2$) calcd 238.1807, found 238.1811.

5.2.15. [HOMPhBTMA][NTf$_2$] ***6***. Following general procedure B using [HOMPhBTMA][Br], [HOMPhBTMA][NTf$_2$] is obtained in 95% yield as a yellowish oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.91 (m, 2H), 2.17 (m, 2H), 3.40 (s, 9H), 3.70 (m, 2H), 4.03–4.11 (m, 3H), 4.56 (d, 2H, J=5.5 Hz), 6.89 (d, 2H, J=8.6 Hz), 7.28 (d, 2H, J=8.5 Hz). ^{13}C (75 MHz, acetone-d_6): δ=158.2, 134.1, 128.6, 120.0 (q, J=321 Hz), 114.4, 66.8, 66.2, 63.6, 52.6, 25.7, 19.6. ^{19}F (282 MHz, acetone-d_6): δ=−79.9. HRMS (FAB): [2C$^+$, A$^-$] ($C_{30}H_{48}N_3O_8F_6S_2$) calcd 756.2787, found 756.2785.

5.2.16. 4-(4-Bromopentoxy)benzaldehyde. To a solution of 4-hydroxybenzaldehyde (8.9 g, 73 mmol) in acetone (115 mL) were added 1,5-dibromopentane (20 mL, 146 mmol) and K_2CO_3 (10 g, 73 mmol). After 18 h under refluxing conditions, the reaction mixture is filtered. Upon cooling, a solid forms in the filtrate and eliminated by filtration. The filtrate is concentrated under reduced pressure and the residue is distilled affording 9.7 g of a yellow oil (yield: 50%). Bp 125 °C (P=0.05 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.69 (m, 2H), 1.78–2.06 (m, 4H), 3.47 (t, 2H, J=6.6 Hz), 4.08 (t, 2H, J=6.3 Hz), 7.01 (d, 2H, J=8.8 Hz), 7.86 (d, 2H, J=8.8 Hz), 9.90 (s, 1H). ^{13}C (50 MHz, $CDCl_3$): δ=190.5, 163.9, 131.8, 129.7, 114.7, 67.9, 33.7, 33.3, 28.1, 24.6. HRMS (FAB): [M$^{+\bullet}$] ($C_{11}H_{15}O_2Br$) calcd 258.0255, found 258.0266.

5.2.17. 1-[4-(5-Bromopentyloxy)phenyl]-1-(4-methylphenyl)methanol. To a solution of 4-methylphenylmagnesium bromide (1 M in Et_2O, 57.8 mmol) is added dropwise at 0 °C a solution of 4-(4-bromopentoxy)benzaldehyde (7.5 g, 27.5 mmol) in 50 mL of Et_2O. After addition, the reaction mixture is allowed to warm up to room temperature and stir for another hour. After careful methanol addition (30 mL), the mixture is concentrated under reduced pressure. The residue is extracted with 3×50 mL of Et_2O, organic layers were combined and concentrated under vacuum to afford 10.0 g of a yellow oil used without further purification. (yield 99%) ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.65 (m, 2H), 1.76–2.08 (m, 4H), 2.25 (d, 1H, J=3.4 Hz), 2.38 (s, 3H), 3.48 (t, 2H, J=6.7 Hz), 4.00 (t, 2H, J=6.3 Hz), 5.82 (d, 1H, J=3.4 Hz), 6.91 (d, 2H, J=9.5 Hz), 7.17–7.34 (m, 6H). ^{13}C (50 MHz, $CDCl_3$): δ=158.8, 141.9, 137.4, 137.0, 129.6, 128.4, 127.0, 114.9, 76.0, 68.1, 34.4, 33.1, 29.0, 25.4, 21.8. HRMS (FAB): [M$^{+\bullet}$] ($C_{11}H_{15}O_2Br$) calcd 258.0255, found 258.0266.

5.2.18. [HOMPPTMA][Br] ***7***. Following general procedure A using 1-[4-(5-bromopentyloxy)phenyl]-1-(4-methylphenyl)methanol, [HOMPPTMA][Br] is obtained in 83% yield as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.51 (m, 2H), 1.69–1.94 (m, 4H), 2.03–2.34 (m, 4H), 3.42 (s, 9H), 3.72 (m, 2H), 4.01 (t, 2H, J=6.2 Hz), 5.73 (s, 1H), 6.89 (d, 2H, J=8.8 Hz), 7.08–7.38 (m, 6H). ^{13}C (50 MHz, $CDCl_3$): δ=157.9, 143.0, 138.1, 136.3, 128.8, 127.8, 126.6, 114.3, 74.0, 67.5, 66.0, 52.7, 28.4, 22.6, 22.4, 20.4. HRMS (FAB): [M$^{+\bullet}$] ($C_{22}H_{32}NO_2$) calcd 342.2433, found 342.2435.

5.2.19. [HOMPPTMA][NTf$_2$]. Following general procedure B using [HOMPPTMA][Br], [HOMPPTMA][NTf$_2$] is obtained in 90% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=1.61 (m, 2H), 1.87 (m, 2H), 2.08 (m, 2H), 2.29 (s, 3H), 2.83 (s, 1H), 3.38 (s, 9H), 3.62 (m, 2H), 4.01 (t, 2H, J=6.2 Hz), 5.74 (s, 1H), 6.84 (d, 2 h, J=8.7 Hz), 7.07–7.33 (m, 6H). ^{13}C (75 MHz, acetone-d_6): δ=158.1, 142.8, 137.8, 136.2, 128.8, 127.7, 126.4, 120.1 (q, J=321 Hz), 114.1, 74.8, 67.2, 66.5, 52.7 (q, J=3.8 Hz), 28.5, 22.7, 22.4, 20.3. ^{19}F (282 MHz, acetone-d_6): δ=−79.9. LRMS (IE): 342 (2C$^+$).

5.3. Supported peptides synthesis

5.3.1. General procedure for coupling (procedure C). To a solution of onium salt in acetonitrile (0.1 M) is added 1.5 equiv of DCC, 1.5 equiv of Fmoc-protected amino acid and 0.1 equiv of DMAP. After 18 h at room temperature, the reaction mixture is filtered and concentrated under reduced pressure. The residue is washed with Et_2O then dissolved in CH_2Cl_2 (10 mL mmol^{-1}). The organic layer is washed with twice 1 mL mmol^{-1} of aqueous 1 M HCl, dried over sodium sulfate, filtered, and concentrated under reduced pressure.

5.3.2. General procedure for Fmoc deprotection (procedure D). To a solution in acetonitrile (0.1 M) of onium salt bearing a Fmoc-protected α-amino acid residue is added piperidine (20% in acetonitrile, 10 equiv). After 15 min at room temperature, solvent is removed under vacuum and the residue is washed with 3×1 mL mmol^{-1} Et_2O.

5.3.3. General procedure for coupling of second amino acid with triflimide salts (procedure E). To a solution of onium salt in acetonitrile (0.1 M) were added 1.5 equiv of DCC, 1.5 equiv of HOBt, 1.5 equiv of TEA, and 1.5 equiv of Fmoc-protected amino acid. After

2 h at room temperature, the reaction mixture is filtered and concentrated under reduced pressure. The residue is washed with Et_2O then dissolved in CH_2Cl_2 (10 mL mmol^{-1}). The organic layer is washed with twice 1 mL mmol^{-1} of aqueous 1 M HCl, dried over sodium sulfate, filtered, and concentrated under reduced pressure.

5.3.4. General procedure for first amino acid attachment on [HOMPhBTMA] (procedure F). At 0 °C under inert atmosphere, was added dropwise 1.5 equiv of thionyl chloride in a solution in acetonitrile of [HOMPTTMA][Br]. After 20 min at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in acetonitrile and 1.5 equiv of Fmoc-protected amino acid and 1.5 equiv of triethylamine were successively added. After 30 min at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was washed with 3×1 mL mmol^{-1} of Et_2O and dissolved in acetonitrile. KPF6 (3.0 equiv) was added to the solution. After 3 h at room temperature, the reaction mixture was concentrated under reduced pressure and the residue dissolved in CH_2Cl_2. The solution was washed with water, dried over anhydrous Na_2SO_4, and concentrated under vacuum. A piperidine solution (10 equiv, 20% in acetonitrile) was added and allows to react for 15 min at room temperature. The reaction mixture was concentrated, washed with Et_2O, dissolved in CH_2Cl_2, and washed with water. After drying over Na_2SO_4, concentration under reduced pressure afford the expected product with over 95% purity.

5.3.5. General procedure for coupling of second amino acid with hexafluorophosphate salts (procedure G). To a solution of onium salt in acetonitrile (0.1 M) is added 1.5 equiv of DCC, 1.5 equiv of HOBt, 1.5 equiv of TEA, and 1.5 equiv of Fmoc-protected amino acid. After 2 h at room temperature, the reaction mixture is filtered and concentrated under reduced pressure. The residue is washed with Et_2O then dissolved in CH_2Cl_2 (10 mL mmol^{-1}). The organic layer is washed with 3×1 mL mmol^{-1} of water followed by 3×aqueous 1% HPF_6, dried over sodium sulfate, filtered, and concentrated under reduced pressure.

5.3.6. General procedure for deprotection of dipeptides and coupling of third amino acid (procedure H). To a solution in acetonitrile (0.1 M) of onium salt bearing a Fmoc-protected amino acid residue is added piperidine (20% in acetonitrile, 10 equiv). After 15 min at room temperature, solvent are removed under vacuum and the residue is washed with 3×1 mL mmol^{-1} Et_2O. The residue is dissolved in CH_2Cl_2 and washed with 3×aqueous 1% HPF_6, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue is dissolved in acetonitrile (0.1 M) before adding 1.5 equiv of DCC, 1.5 equiv of HOBt, 1.5 equiv of TEA, and 1.5 equiv of Fmoc-protected amino acid. After 2 h at room temperature, the reaction mixture is filtered and concentrated under reduced pressure. The residue is washed with Et_2O then dissolved in CH_2Cl_2 (10 mL mmol^{-1}). The organic layer is washed with 3×1 mL mmol^{-1} of water followed by 3×aqueous 1% HPF_6, dried over sodium sulfate, filtered, and concentrated under reduced pressure.

5.3.7. [Fmoc-Ala-O-PrTMA][NTf$_2$]. Following general procedure C using [HOPrTMA][NTf$_2$] and Fmoc-Ala-OH, [Fmoc-Ala-Pr-O-TMA][NTf$_2$] is obtained in 80% yield as a yellow oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.45 (d, 3H, J=7.3 Hz), 2.37 (m, 2H), 3.38 (s, 9H), 3.71 (m, 2H), 4.21–4.41 (m, 6H), 7.07 (m, 1H), 7.33–7.50 (m, 4H), 7.73 (d, 2H, J=7.2 Hz), 7.91 (d, 2H, J=7.5 Hz). ^{13}C (50 MHz, acetone-d_6): δ=174.1, 157.5, 145.4, 142.5, 129.1, 128.4, 126.5, 121.4 (q, J_{C-F}=321 Hz), 121.3, 67.6, 65.1, 62.5, 54.1 (t, J_{N-C}=4.0 Hz), 51.2, 48.3, 24.0, 17.9.

5.3.8. [H-Ala-Pr-O-TMA][NTf$_2$]. Following general procedure D using [Fmoc-Ala-Pr-O-TMA][NTf$_2$], [H-Ala-O-PrTMA][NTf$_2$] is obtained in 97% yield as a yellow oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.43 (d, 3H, J=7.3 Hz), 1.80 (m, 2H), 2.05 (m, 2H), 3.34 (s, 9H), 3.72 (m, 2H), 4.28 (t, 2H, J=6.1 Hz), 4.37 (q, 1H, J=6.7 Hz). ^{13}C (75 MHz, acetone-d_6): δ=178.8, 120.01 (q, J_{C-F}=321 Hz), 63.9, 61.2, 57.9, 52.8, 26.0, 20.7. HRMS (LSIMS): [M$^{+\bullet}$] ($C_9H_{21}N_2O_2$) calcd 189.1603, found 189.1610.

5.3.9. [Fmoc-Ala-O-BuTMA][NTf$_2$]. Following general procedure C using [HOBuTMA][NTf$_2$] and Fmoc-Ala-OH, [Fmoc-Ala-O-BuTMA][NTf$_2$] is obtained in 71% yield as a yellow oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.45 (d, 3H, J=7.3 Hz), 2.37 (m, 2H), 3.38 (s, 9H), 3.61 (m, 2H), 4.12–4.42 (m, 6H), 7.03 (m, 1H), 7.33–7.47 (m, 4H), 7.71 (d, 2H, J=7.42 Hz), 7.89 (d, 2H, J=6.9 Hz). ^{13}C (50 MHz, acetone-d_6): δ=172.9, 156.1, 144.1, 141.2, 127.8, 127.1, 125.3, 120.1 (q, J_{C-F}=321 Hz), 118.0, 66.3, 66.0, 63.5, 52.7 (t, J_{N-C}=4.0 Hz), 49.9, 47.1, 25.3, 19.4, 16.7. HRMS (LSIMS): [M$^{+\bullet}$] ($C_{25}H_{33}N_2O_4$) calcd 425.2440, found 425.2437.

5.3.10. [H-Ala-Bu-O-TMA][NTf$_2$]. Following general procedure D using [Fmoc-Ala-O-BuTMA][NTf$_2$], [H-Ala-O-BuTMA][NTf$_2$] is obtained in 87% yield as a yellow oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.30 (d, 3H, J=6.7 Hz), 1.80 (m, 2H), 2.06 (m, 2H), 2.86 (m, 2H), 3.41 (s, 9H), 3.66 (m, 2H), 4.15–4.28 (m, 3H). ^{13}C (75 MHz, acetone-d_6): δ=172.9, 120.0 (q, J_{C-F}=321 Hz), 66.6, 63.2, 58.2, 52.7, 25.2, 19.5, 18.0.

5.3.11. [Fmoc-Ala-O-HeTMA][NTf$_2$] Fmoc-Ala-O-3. Following general procedure C using [HOHeTMA][NTf$_2$] and Fmoc-Ala-OH, [Fmoc-Ala-O-HeTMA][NTf$_2$] is obtained in 92% yield as a yellow oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.40 (d, 3H, J=7.6 Hz), 1.50–2.03 (m, 8H), 3.35 (s, 9H), 3.37 (m, 2H), 4.15 (t, 2H, J=6.2 Hz), 4.23–4.40 (m, 4H), 6.95 (m, 1H), 7.33–7.50 (m, 4H), 7.71 (d, 2H, J=7.4 Hz), 7.92 (d, 2H, J=7.1 Hz). ^{13}C (75 MHz, acetone-d_6): δ=172.9, 156.0, 144.1, 141.2, 127.8, 127.1, 125.3, 120.1 (q, J_{C-F}=321 Hz), 120.0, 66.5, 66.4, 64.4, 52.7 (t, J_{N-C}=4 Hz), 49.8, 47.1, 28.1, 25.5, 25.0, 22.4, 17.0 HRMS (LSIMS): [C$^+$] ($C_{27}H_{37}N_2O_4$) calcd 453.2753, found 453.2753.

5.3.12. [H-Ala-O-HeTMA][NTf$_2$] H-Ala-O-3. Following general procedure D using [Fmoc-Ala-O-HeTMA][NTf$_2$], [H-Ala-O-HeTMA][NTf$_2$] is obtained in 90% yield as a yellow oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.27 (d, 3H, J=6.6 Hz), 1.42–1.53 (m, 4H), 1.68 (m, 2H), 1.98 (m, 2H), 2.78 (m, 2H), 3.38 (s, 9H), 3.59 (m, 2H), 4.06 (t, 2H, J=6.6 Hz), 4.20 (q, 1H, J=6.7 Hz). ^{13}C (75 MHz, acetone-d_6): δ=177.1, 120.0 (q, J_{C-F}=321 Hz), 66.5, 64.2, 52.6, 50.3, 28.1, 25.5, 25.1, 22.5, 21.0.

5.3.13. [Fmoc-Ala-O-MPhBTMA][NTf$_2$] Fmoc-Ala-O-6. Following general procedure C using [HOMPhBTMA][NTf$_2$] and Fmoc-Ala-OH, [Fmoc-Ala-O-MPhBTMA][NTf$_2$] is obtained in 88% yield as a yellow oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.42 (d, 3H, J=7.3 Hz), 1.90 (m, 2H), 2.16 (m, 2H), 3.40 (s, 9H), 3.69 (m, 2H), 4.06 (t, 2H, J=5.9 Hz), 4.14–4.42 (m, 4H), 5.11 (s, 2H), 6.80–6.91 (m, 3H), 7.28–7.37 (m, 4H), 7.43 (m, 2H), 7.71 (d, 2H, J=7.4 Hz), 7.88 (d, 2H, J=7.5 Hz). ^{13}C (75 MHz, acetone-d_6): δ=172.9, 158.9, 156.1, 144.2, 141.2, 129.9, 128.3, 127.2, 126.5, 125.3, 120.1 (q, J_{C-F}=321 Hz), 120.0, 114.4, 66.8, 66.4, 66.3, 66.2, 52.8 (t, J_{N-C}=4.1 Hz), 50.0, 47.0, 25.7, 19.7, 17.0. HRMS (ESI): [C$^+$] ($C_{32}H_{39}N_2O_5$) calcd 531.2859, found 531.2859.

5.3.14. [H-Ala-O-MPhBTMA][NTf$_2$] H-Ala-O-6. Following general procedure D using [Fmoc-Ala-O-MPhBTMA][NTf$_2$], [H-Ala-O-MPhBTMA][NTf$_2$] is obtained in 88% yield as a yellow oil. ^{1}H NMR (200 MHz, acetone-d_6): δ=1.28 (d, 3H, J=6.6 Hz), 1.93 (m, 2H), 2.18 (m, 2H), 2.94 (m, 2H), 3.40 (s, 9H), 3.70 (m, 2H), 4.11 (t, 2H, J=6.0 Hz), 4.24 (q, 1H, J=6.7 Hz), 5.06 (s, 2H), 6.93 (d, 2H, J=8.6 Hz), 7.32 (d, 2H, J=8.6 Hz). ^{13}C (75 MHz, acetone-d_6): δ=176.9, 158.9, 129.9, 128.5, 120.0 (q, J_{C-F}=321 Hz), 114.5, 66.8, 66.3, 65.9, 52.7 (t, J_{N-C}=3.9 Hz), 50.4, 25.8, 21.0, 19.7.

5.3.15. [Fmoc-Leu-Ala-O-HeTMA][NTf$_2$] Fmoc-Leu-Ala-O-3. Following general procedure E using [H-Ala-O-HeTMA][NTf$_2$] and Fmoc-Leu-OH, [Fmoc-Leu-Ala-O-HeTMA][NTf$_2$] is obtained in 78% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.93 (d, 3H, J=6.6 Hz), 0.95 (d, 3H, J=6.6 Hz), 1.36 (d, 3H, J=7.3 Hz), 1.40–1.53 (m, 4H), 1.59–1.70 (m, 4H), 1.78 (sept, 1H), 1.97 (m, 2H), 3.37 (s, 9H), 3.58 (m, 2H), 4.10 (t, 2H, J=6.4 Hz), 4.19–4.46 (m, 5H), 6.62 (m, 1H), 7.32–7.46 (m, 4H), 7.59 (m, 1H), 7.71 (d, 2H, J=7.4 Hz), 7.89 (d, 2H, J=7.5 Hz). ^{13}C (75 MHz, acetone-d_6): δ=172.6, 172.4, 156.3, 144.2, 141.2, 127.8, 127.1, 125.3, 120.0, 120.0 (q, J_{C-F}=321 Hz), 66.4, 66.4, 64.5, 53.4, 52.7 (t, J_{N-C}=4.0 Hz), 48.2, 47.1, 41.4, 28.1, 25.4, 25.0, 24.5, 22.4, 21.2, 16.9. HRMS (ESI): [C$^+$] ($C_{33}H_{48}N_3O_5$) calcd 566.3594, found 566.3603.

5.3.16. [Fmoc-Leu-Ala-O-MPhBTMA][NTf$_2$] Fmoc-Leu-Ala-O-6. Following general procedure E using [H-Ala-O-MPhBTMA][NTf$_2$] and Fmoc-Leu-OH, [Fmoc-Leu-Ala-O-MPhBTMA][NTf$_2$] is obtained in 85% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.91 (d, 3H, J=6.9 Hz), 0.93 (d, 3H, J=7.0 Hz),1.36 (d, 3H, J=7.3 Hz), 1.60 (m, 2H), 1.76 (m, 1H), 1.91 (m, 2H), 2.16 (m, 2H), 3.40 (s, 9H), 3.69 (m, 2H), 4.09 (t, 2H, J=5.9 Hz), 4.17–4.39 (m, 4H), 4.47 (m, 1H), 5.08 (s, 2H), 6.92 (d, 2H, J=8.5 Hz), 6.62 (m, 1H), 7.28–7.37 (m, 4H), 7.43 (m, 2H), 7.61 (m, 1H), 7.72 (m, 2H), 7.88 (d, 2H, J=7.5 Hz). ^{13}C (75 MHz, acetone-d_6): δ=173.6, 173.6, 160.2, 157.4, 145.5, 142.5, 131.20, 129.7, 129.0, 128.3, 126.6, 121.4 (q, J_{C-F}=321 Hz), 121.2, 115.6, 68.1, 67.6, 67.5, 67.3, 54.6, 54.1, 49.3, 48.4, 42.7, 27.1, 25.9, 23.9, 22.3, 21.1, 18.1. HRMS (ESI): [C$^+$] ($C_{38}H_{50}N_3O_6$) calcd 644.3700, found 644.3699.

5.3.17. [H-Ala-O-MPPTMA][PF$_6$] H-Ala-O-9. Following general procedure F using [HOMPPTMA][Br] and Fmoc-Ala-OH, [H-Ala-O-MPPTMA][PF$_6$] is obtained in 95% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=1.33 (d, 3H, J=6.6 Hz), 1.60 (m, 2H), 1.87 (m, 2H), 2.02 (m, 2H), 2.29 (m, 2H), 2.31 (s, 3H), 3.36 (s, 9H), 3.50–3.63 (m, 3H), 4.03 (t, 2H, J=6.2 Hz), 6.78 (s, 1H), 6.90 (d, 2H, J=8.5 Hz), 7.11–7.39 (m, 6H). ^{13}C (75 MHz, acetone-d_6): δ=171.5, 158.7, 138.2, 137.2, 133.0, 129.0, 128.3, 126.6, 114.3, 76.5, 67.2, 66.4, 58.5, 52.7, 28.4, 22.3, 20.2, 20.1, 18.0. HRMS (ESI): [C$^+$] ($C_{25}H_{37}N_2O_3$) calcd 413.2804, found 413.2789.

5.3.18. [H-Gly-O-MPPTMA][PF$_6$] H-Gly-O-9. Following general procedure F using [HOMPPTMA][Br] and Fmoc-Gly-OH, [H-Gly-O-MPPTMA][PF$_6$] is obtained in 98% yield as a brownish oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=1.59 (m, 2H), 1.88 (m, 2H), 2.05 (m, 2H), 2.31 (s, 3H), 3.33 (s, 9H), 3.53–3.62 (m, 3H), 4.03 (t, 2H, J=6.2 Hz), 6.83 (s, 1H), 6.91 (d, 2H, J=8.7 Hz), 7.18 (d, 2H, J=8.0 Hz), 7.29–7.38 (m, 4H). ^{13}C (75 MHz, acetone-d_6): δ=171.2, 158.8, 138.1, 137.4, 132.9, 129.2, 128.5, 126.7, 114.5, 76.8, 67.4, 66.3, 53.3, 52.6, 28.4, 22.6, 22.3, 20.4. HRMS (ESI): [C$^+$] ($C_{24}H_{35}N_2O_3$) calcd 399.2648, found 399.2649.

5.3.19. [H-Ile-O-MPPTMA][PF$_6$] H-Ile-O-9. Following general procedure F using [HOMPPTMA][Br] and Fmoc-Ile-OH, [H-Ile-O-MPPTMA][PF$_6$] is obtained in 89% yield as a brownish oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.80–0.96 (m, 6H), 1.17 (m, 1H), 1.49 (m, 1H).1.59 (m, 2H), 1.79–1.97 (m, 3H), 2.05 (m, 2H), 2.31 (s, 3H), 3.33 (s, 9H), 3.48–3.60 (m, 3H), 4.03 (t, 2H, J=6.2 Hz), 6.80 (s, 1H), 6.91 (d, 2H, J=8. 6 Hz), 7.18 (d, 2H, J=10.3 Hz), 7.19–7.32 (m, 4H). ^{13}C (75 MHz, acetone-d_6): δ=170.6, 158.8, 138.1, 137.3, 132.9, 129.1, 128.6, 126.7, 114.4, 76.5, 69.0, 67.3, 66.4, 52.6, 38.2, 28.5, 24.9, 22.7, 22.3, 20.4, 15.3, 10.9. HRMS (ESI): [C$^+$] ($C_{28}H_{43}N_2O_3$) calcd 455.3274, found 455.3286.

5.3.20. [H-Leu-O-MPPTMA][PF$_6$] H-Leu-O-9. Following general procedure F using [HOMPPTMA][Br] and Fmoc-Leu-OH, [H-Leu-O-MPPTMA][PF$_6$] is obtained in 89% yield as a brownish oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.84 (d, 3H, J=6.5 Hz), 0.91 (d, J=6.5, 1H), 1.50–1.97 (m, 7H), 2.05 (m, 2H), 2.31 (s, 3H), 3.36 (s, 9H), 3.53–3.67 (m, 3H), 4.03 (t, 2H, J=6.2 Hz), 6.78 (s, 1H), 6.91 (m, 2H), 7.09–7.34 (m, 6H). ^{13}C (75 MHz, acetone-d_6): δ=171.3, 158.7, 138.2, 137.3, 132.9, 129.1, 128.4, 126.7, 114.4, 76.6, 67.3, 66.3, 62.0, 52.6, 42.2, 28.5, 24.6, 22.7, 22.3, 21.7, 20.4. HRMS (ESI): [C$^+$] ($C_{28}H_{43}N_2O_3$) calcd 455.3274, found 455.3272.

5.3.21. [H-Phe-O-MPPTMA][PF$_6$] H-Phe-O-9. Following general procedure F using [HOMPPTMA][Br] and Fmoc-Phe-OH, [H-Phe-O-MPPTMA][PF$_6$] is obtained in 80% yield as a brownish oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=1.60 (m, 2H), 1.93 (m, 2H), 2.05 (m, 2H), 2.31 (s, 3H), 2.87–3.06 (m, 2H), 3.33 (s, 9H), 3.50–3.61 (m, 3H), 4.03 (t, J=6.1, 2H), 6.77 (s, 1H), 6.88 (m, 2H), 7.09–7.33 (m, 11H). ^{13}C (75 MHz, acetone-d_6): δ=170.7, 158.7, 138.3, 138.0, 137.3, 132.7, 129.6, 129.1, 128.5, 128.3, 126.7, 126.4, 114.4, 76.8, 67.3, 66.4, 65.4, 52.6, 39.3, 28.5, 22.7, 22.3, 20.4. HRMS (ESI): [C$^+$] ($C_{31}H_{41}N_2O_3$) calcd 489.3117, found 489.3121.

5.3.22. [H-Val-O-MPPTMA][PF$_6$] H-Val-O-9. Following general procedure F using [HOMPPTMA][Br] and Fmoc-Val-OH, [H-Val-O-MPPTMA][PF$_6$] is obtained in 80% yield as a brownish oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.80–1.00 (m, 6H), 1.60 (m, 2H), 1.87 (m, 2H), 2.05 (m, 2H), 2.23–2.39 (m, 4H), 3.34 (s, 9H), 3.50–3.61 (m, 3H), 4.03 (t, 2H, J=6.1 Hz), 6.79 (s, 1H), 6.90 (d, 2H, J=8.7 Hz), 7.12–7.36 (m, 6H). ^{13}C (75 MHz, acetone-d_6): δ=170.6, 158.8, 138.1, 137.3, 132.9, 129.1, 128.3, 126.7, 114.4, 76.5, 69.8, 67.3, 66.4, 52.6, 31.7, 28.5, 22.7, 22.3, 20.4, 18.9, 18.0. HRMS (ESI): [C$^+$] ($C_{27}H_{41}N_2O_{33}$) calcd 441.3117, found 441.3120.

5.3.23. [Fmoc-Ala-Ile-O-MPPTMA][PF$_6$] Fmoc-Ala-Ile-O-9. Following general procedure G using [Ile-MPPTMA][PF$_6$] and Fmoc-Ala-OH, [Fmoc-Ala-Ile-MPPTMA][PF$_6$] is obtained in 88% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.78–0.90 (m, 6H), 1.03–1.28 (m, 2H), 1.35 (d, 3H, J=7.0 Hz), 1.59 (m, 2H), 1.86 (m, 2H), 1.97–2.09 (m, 3H), 2.23–2.33 (m, 3H), 3.37 (s, 9H), 3.60 (m, 2H), 4.00 (m, 2H), 4.21–4.40 (m, 4H),4.53 (m, 1H), 6.68–6.94 (m, 4H), 7.03–7.50 (m, 11H), 7.71 (m, 2H), 7.88 (d, J=7.5, 2H). ^{13}C (75 MHz, acetone-d_6): δ=173.8, 171.4, 159.7, 157.0, 145.0, 142.1, 138.6, 138.2, 133.4, 130.0, 129.6, 128.7, 128.1, 127.5, 126.2, 120.9, 115.2, 78.1, 68.2, 67.4, 67.3, 57.8, 53.6, 51.3, 38.2, 48.0, 29.6, 25.7, 23.6, 23.3, 21.3, 18.8, 16.1, 11.9. HRMS (ESI): [C$^+$] ($C_{46}H_{58}N_3O_6$) calcd 748.4325, found 748.4319.

5.3.24. [Fmoc-Ala-Phe-O-MPPTMA][PF$_6$] Fmoc-Ala-Phe-O-9. Following general procedure G using [H-Phe-O-MPPTMA][PF$_6$] and Fmoc-Ala-OH, [Fmoc-Ala-Phe-O-MPPTMA][PF$_6$] is obtained in 98% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=1.30 (d, 3H, J=7.1 Hz), 1.61 (m, 2H), 1.83 (m, 2H), 2.04 (m, 2H), 2.30 (d, 3H, J=10.0 Hz), 2.92–3.25 (m, 2H), 3.36 (s, 9H), 3.59 (m, 2H), 4.01 (m, 2H), 4.12–4.36 (m, 4H), 4.86 (m, 1H), 6.70 (m, 1H), 6.79 (s, 1H), 6.88 (m, 2H), 7.05–7.48 (m, 15H), 7.51 (m, 1H), 7.71 (m, 2H), 7.88 (d, J=7.4, 2H). ^{13}C (75 MHz, acetone-d_6): δ=173.5, 171.2, 159.7, 157.0, 145.0, 142.1, 138.5, 138.2, 137.6, 133.4, 130.3, 130.1, 129.6, 129.3, 127.9, 127.7, 127.6, 127.5, 126.3, 121.0, 115.3, 78.5, 68.2, 67.3, 66.5, 54.8, 53.5, 51.4, 48.0, 38.1, 29.7, 23.6, 22.3, 21.3, 18.8. HRMS (ESI): [C$^+$] ($C_{49}H_{56}N_3O_6$) calcd 782.4169, found 782.4175.

5.3.25. [Fmoc-Ala-Val-O-MPPTMA][PF$_6$] Fmoc-Ala-Val-O-9. Following general procedure G using [H-Val-O-MPPTMA][PF$_6$] and Fmoc-Ala-OH, [Fmoc-Ala-Val-O-MPPTMA][PF$_6$] is obtained in 70% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.86 (d, 3H, J=6.9 Hz), 0.90 (d, 3H, J=6.8 Hz), 1.35 (d, 3H, J=7.1 Hz), 1.57 (m, 2H), 1.83 (m, 2H), 2.04 (m, 2H), 2.22 (m, 1H), 2.30 (d, 3H, J=4.7 Hz), 3.36 (s, 9H), 3.59 (m, 2H), 4.00 (m, 2H), 4.16–4.40 (m, 4H), 4.52 (m, 1H), 6.72 (m, 1H), 6.82 (s, 1H), 6.88 (m, 2H), 7.06–7.49 (m, 11H), 7.71 (m, 2H), 7.88 (d, J=7.4, 2H). ^{13}C (75 MHz, acetone-d_6): δ=173.7, 171.4, 159.7, 157.0, 145.0, 142.1, 138.6, 138.2, 133.4, 130.0, 129.5, 128.7, 128.1, 127.8, 126.2, 120.9, 115.2, 78.1, 68.2, 67.3, 67.3, 58.5, 53.5, 51.3, 48.0, 31.6, 29.6, 23.6, 23.3, 21.3, 19.7, 18.8, 18.3. HRMS (ESI): [C$^+$] ($C_{45}H_{56}N_3O_6$) calcd 734.4169, found 734.4173.

5.3.26. [Fmoc-Gly-Leu-O-MPPTMA][PF$_6$] Fmoc-Gly-Leu-O-9. Following general procedure G using [H-Leu-MPPTMA][PF$_6$] and Fmoc-Gly-OH, [Fmoc-Gly-Leu-O-MPPTMA][PF$_6$] is obtained in 70% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.88 (d, 6H, J=4.0 Hz), 1.48–1.75 (m, 5H), 1.85 (m, 2H), 2.05 (m, 2H), 2.29 (m, 3H), 3.35 (s, 9H), 3.59 (m, 2H), 3.81–4.08 (m, 4H), 4.20–4.42 (m, 3H), 4.62 (m, 1H), 6.78 (s, 1H),6.80–6.95 (m, 3H), 7.01–7.57 (m, 11H), 7.73 (m, 2H), 7.88 (d, 2H, J=7.5 Hz). ^{13}C (75 MHz, acetone-d_6): δ=172.3, 170.5, 159.7, 157.7, 145.0, 142.1, 138.7, 138.2, 133.5, 130.0, 129.3, 128.7, 128.1, 127.6, 126.2, 121.0, 115.3, 78.1, 68.2, 67.6, 67.3, 53.5, 51.9, 48.0, 44.7, 41.2, 29.6, 25.5, 23.6, 23.3, 22.1, 21.3. HRMS (ESI): [C^+] ($C_{45}H_{56}N_3O_6$) calcd 734.4169, found 734.4170.

5.3.27. [Fmoc-Gly-Phe-O-MPPTMA][PF$_6$] Fmoc-Gly-Phe-O-9. Following general procedure G using [H-Phe-O-MPPTMA][PF$_6$] and Fmoc-Gly-OH, [Fmoc-Gly-Phe-O-MPPTMA][PF$_6$] is obtained in 85% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=1.61 (m, 2H), 1.85 (m, 2H), 2.04 (m, 2H), 2.30 (d, 3H, J=4.4 Hz), 2.96–3.24 (m, 2H), 3.36 (s, 9H), 3.59 (m, 2H), 3.86 (m, 2H), 4.02 (m, 2H), 4.17–4.40 (m, 3H), 4.86 (m, 1H), 6.78 (s, 1H), 6.88 (m, 2H), 7.05–7.45 (m, 16H), 7.54 (m, 1H), 7.73 (d, 2H, J=7.2 Hz), 7.88 (d, 2H, J=7.4 Hz). ^{13}C (75 MHz, acetone-d_6): δ=171.2, 170.1, 159.7, 157.6, 145.0, 142.1, 138.8, 138.2, 137.5, 133.4, 130.0, 129.8, 129.3, 129.2, 128.7, 128.1, 127.8, 127.6, 126.2, 120.9, 115.2, 78.3, 68.1, 67.5, 67.3, 54.7, 53.5, 48.0, 44.7, 38.1, 29.4, 23.6, 23.2, 21.2. HRMS (ESI): [C^+] ($C_{48}H_{54}N_3O_6$) calcd 768.4012, found 768.4012.

5.3.28. [Fmoc-Gly-Val-O-MPPTMA][PF$_6$] Fmoc-Gly-Val-O-9. Following general procedure G using [H-Val-O-MPPTMA][PF$_6$] and Fmoc-Gly-OH, [Fmoc-Gly-Val-O-MPPTMA][PF$_6$] is obtained in 95% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.86 (d, 3H, J=7.0 Hz), 0.90 (d, 3H, J=6.8 Hz), 1.58 (m, 2H), 1.85 (m, 2H), 2.04 (m, 2H), 2.22 (m, 1H), 2.30 (s, 3H), 3.35 (s, 9H), 3.58 (m, 2H), 3.88–4.08 (m, 4H), 4.20–4.40 (m, 3H), 4.56 (m, 1H), 6.82 (s, 1H), 6.84–6.98 (m, 3H), 7.09–7.51 (m, 11H), 7.73 (m, 2H), 7.88 (d, 2H, J=7.5 Hz). ^{13}C (75 MHz, acetone-d_6): δ=171.5, 170.6, 159.7, 157.7, 145.0, 142.1, 138.5, 138.3, 133.4, 130.0, 129.5, 128.7, 128.1, 127.6, 126.2, 121.0, 115.3, 78.2, 68.2, 67.6, 67.3, 58.6, 53.5, 48.0, 44.8, 31.6, 29.7, 23.6, 23.3, 21.3, 19.7, 18.3. HRMS (ESI): [C^+] ($C_{44}H_{54}N_3O_6$) calcd 720.4013, found 720.4015.

5.3.29. [Fmoc-Ile-Leu-O-MPPTMA][PF$_6$] Fmoc-Ile-Leu-O-9. Following general procedure G using [H-Leu-O-MPPTMA][PF$_6$] and Fmoc-Ile-OH, [Fmoc-Ile-Leu-O-MPPTMA][PF$_6$] is obtained in 78% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.73–0.98 (m, 12H), 1.17 (m, 1H), 1.45–1.75 (m, 6H), 1.86 (m, 2H), 1.94–2.12 (m, 3H), 2.31 (m, 3H), 3.37 (s, 9H), 3.58 (m, 2H), 3.94–4.17 (m, 3H), 4.19–4.40 (m, 3H), 4.65 (m, 1H), 6.55 (m, 1H), 6.80 (s, 1H), 6.91 (m, 2H), 7.03–7.50 (m, 10H), 7.48 (m, 1H), 7.72 (m, 2H), 7.88 (d, 2H, J=7.6 Hz). ^{13}C (75 MHz, acetone-d_6): δ=172.6, 172.4, 159.7, 157.2, 145.1, 142.1, 138.7, 138.2, 133.5, 130.0, 129.5, 128.7, 128.1, 127.8, 126.2, 121.0, 115.3, 78.2, 68.2, 67.3, 67.3, 60.5, 53.5, 51.9, 48.1, 41.3, 38.1, 29.7, 25.6, 25.5, 23.3, 23.3, 22.1, 21.4, 16.2, 11.7. HRMS (ESI): [C^+] ($C_{49}H_{64}N_3O_6$) calcd 790.4795, found 790.4798.

5.3.30. [Fmoc-Leu-Ala-O-MPPTMA][PF$_6$] Fmoc-Leu-Ala-O-9. Following general procedure G using [H-Ala-O-MPPTMA][PF$_6$] and Fmoc-Ile-OH, [Fmoc-Leu-Ala-O-MPPTMA][PF$_6$] is obtained in 94% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.90 (d, 3H, J=5.8 Hz), 0.92 (d, 3H, J=6.1 Hz), 1.40 (dd, 3H, J_1=7.2 Hz, J_2=3.2 Hz), 1.50–1.67 (m, 6H), 1.74 (m, 1H), 1.85 (m, 2H), 2.30 (d, 3H, J=4.5 Hz), 3.32 (s, 9H), 3.56 (m, 2H), 4.00 (m, 2H), 4.18–4.43 (m, 4H), 4.59 (m, 1H), 6.65 (m, 1H), 6.78 (s, 1H), 6.89 (dd, 2H, J_1=8.5 Hz, J_2=3.4 Hz), 7.11–7.50 (m, 10H), 7.63–7.74 (m, 3H), 7.86 (d, 2H, J=8.0). ^{13}C (75 MHz, acetone-d_6): δ=171.4, 171.3, 158.7, 156.2, 144.2, 141.2, 137.9, 137.2, 132.7, 129.0, 128.3, 127.7, 127.1, 126.7, 125.3, 120.0, 114.3, 77.1, 67.2, 66.4, 66.3, 53.3, 52.7 (t, J_{C-N}=4.0 Hz), 48.2, 47.2, 41.5, 28.4, 24.5, 22.7, 22.4, 21.0, 20.2, 16.8. HRMS (ESI): [C^+] ($C_{46}H_{58}N_3O_6$) calcd 748.4325, found 748.4321.

5.3.31. [Fmoc-Val-Ile-O-MPPTMA][PF$_6$] Fmoc-Ile-Val-O-9. Following general procedure G using [H-Ile-O-MPPTMA][PF$_6$] and Fmoc-Val-OH, [Fmoc-Val-Ile-O-MPPTMA][PF$_6$] is obtained in 94% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.77–0.97 (m, 12H), 1.19 (m, 1H), 1.37 (m, 1H), 1.58 (m, 2H), 1.86 (m, 2H), 1.90–2.09 (m, 4H), 2.30 (d, 3H, J=5.1 Hz), 3.37 (s, 9H), 3.61 (m, 2H), 4.02 (m, 2H), 4.08–4.37 (m, 4H), 4.58 (m, 1H), 6.54 (m, 1H), 6.76–6.94 (m, 3H), 7.02–7.52 (m, 11H), 7.72 (m, 2H), 7.88 (d, 2H, J=7.5 Hz). ^{13}C (75 MHz, acetone-d_6): δ=172.6, 171.5, 157.3, 159.8, 145.1, 142.1, 138.7, 138.2, 133.4, 130.0, 129.7, 128.7, 128.1, 127.5, 126.2, 120.9, 115.2, 78.2, 68.2, 67.3, 67.3, 61.2, 57.8, 53.5, 48.0, 38.2, 31.9, 29.6, 25.7, 23.6, 23.3, 21.3, 20.0, 18.5, 16.1, 11.9. HRMS (ESI): [C^+] ($C_{48}H_{62}N_3O_6$) calcd 776.4638, found 776.4633.

5.3.32. [Fmoc-Gly-Ala-Phe-O-MPPTMA][PF$_6$] Fmoc-Gly-Ala-Phe-O-9. Following general procedure H using [Fmoc-Ala-Phe-O-MPPTMA][PF$_6$] and Fmoc-Gly-OH, [Fmoc-Gly-Ala-Phe-O-MPPTMA][PF$_6$] is obtained in 98% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=1.24 (d, 3H, J=6.9 Hz), 1.58 (m, 2H), 1.86 (m, 2H), 2.07 (m, 2H), 2.29 (m, 3H), 2.90–3.25 (m, 2H), 3.34 (s, 9H), 3.56 (m, 2H), 3.80–4.07 (m, 4H), 4.16–4.40 (m, 3H), 4.48 (m, 1H), 4.81 (m, 1H), 6.77 (s, 1H), 6.80–6.95 (m, 3H), 7.05–7.54 (m, 17H), 7.69 (m, 2H), 7.87 (d, 2H, J=7.4 Hz). ^{13}C (75 MHz, acetone-d_6): δ=172.3, 170.3, 169.3, 158.8, 157.0, 144.2, 141.2, 137.7, 137.3, 136.7, 132.5, 129.3, 129.1, 128.7, 128.6, 128.2, 127.2, 126.9, 126.7, 125.3, 120.0, 114.3, 77.5, 67.3, 66.7, 66.4, 54.1, 52.7, 48.7, 47.0, 44.3, 37.1, 28.4, 22.7, 22.3, 20.3, 17.6. HRMS (ESI): [C^+] ($C_{51}H_{59}N_4O_7$) calcd 839.4383, found 839.4378.

5.3.33. [Fmoc-Leu-Ala-Phe-O-MPPTMA][PF$_6$] Fmoc-Leu-Ala-Phe-O-9. Following general procedure H using [Fmoc-Ala-Phe-O-MPPTMA][PF$_6$] and Fmoc-Leu-OH, [Fmoc-Leu-Ala-Phe-O-MPPTMA][PF$_6$] is obtained in 98% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.92 (d, 3H, J=6.3 Hz), 0.94 (d, 3H, J=6.4 Hz), 1.25 (d, J=7.0, 3H), 1.50–2.08 (m, 9H), 2.30 (m, 3H), 2.90–3.23 (m, 2H), 3.34 (s, 9H), 3.58 (m, 2H), 4.01 (m, 2H), 4.12–4.50 (m, 5H), 4.81 (m, 1H), 6.67–6.77 (m, 2H), 6.88 (m, 2H), 7.02–7.60 (m, 17H), 7.70 (m, 2H), 7.87 (d, 2H, J=7.4 Hz). ^{13}C (75 MHz, acetone-d_6): δ=172.3, 172.1, 170.2, 158.8, 156.5, 144.2, 141.2, 137.2, 137.9, 136.7, 132.5, 129.3, 129.0, 128.4, 128.2, 127.7, 126.9, 126.7, 126.3, 126.2, 120.0, 114.3, 77.4, 67.3, 66.4, 66.4, 53.9, 53.7, 52.7 (t, J_{C-N}=3.7 Hz), 48.7, 47.1, 41.1, 37.3, 28.5, 24.6, 22.7, 22.4, 21.1, 20.3, 17.7. HRMS (ESI): [C^+] ($C_{55}H_{67}N_4O_7$) calcd 895.5009, found 895.5006.

5.3.34. [Fmoc-Val-Gly-Phe-O-MPPTMA][PF$_6$] Fmoc-Val-Gly-Phe-O-9. Following general procedure H using [Fmoc-Gly-Phe-O-MPPTMA][PF$_6$] and Fmoc-Val-OH, [Fmoc-Val-Gly-Phe-O-MPPTMA][PF$_6$] is obtained in 83% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.99 (d, 6H, J=6.7 Hz), 1.58 (m, 2H), 1.86 (m, 2H), 2.07 (m, 3H), 2.29 (m, 3H), 2.95–3.20 (m, 2H), 3.34 (s, 9H), 3.56 (m, 2H), 3.70–4.05 (m, 4H), 4.18–4.55 (m, 4H), 4.80 (m, 1H), 6.71–6.82 (m, 2H), 6.86 (m, 2H), 7.05–7.54 (m, 16H), 7.53–7.73 (m, 3H), 7.86 (d, J=7.5, 2H). ^{13}C (75 MHz, acetone-d_6): δ=171.9, 170.3, 168.9, 158.8, 158.1, 144.1, 141.2, 137.7, 137.2, 136.7, 132.5, 129.3, 129.0, 128.6, 128.4, 127.8, 127.2, 126.9, 126.7, 125.3, 120.0, 114.3, 77.4, 67.2, 66.6, 66.4, 61.1, 54.1, 52.6, 47.1, 42.4, 37.4, 30.5, 28.5, 22.7, 22.4, 20.3, 18.9, 17.8. HRMS (ESI): [C^+] ($C_{53}H_{63}N_4O_7$) calcd 867.4696, found 867.4693.

*5.3.35. [Fmoc-Val-Leu-Ala-O-MPPTMA][PF$_6$] Fmoc-Val-Leu-Ala-O-**9**.* Following general procedure H using [Fmoc-Leu-Ala-O-MPPTMA][PF$_6$] and Fmoc-Val-OH, [Fmoc-Val-Leu-Ala-O-MPPTMA][PF$_6$] is obtained in 91% yield as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6): δ=0.85 (d, 3H, J=6.3 Hz), 0.86 (d, 3H, J=6.4 Hz), 0.96 (d, 3H, J=6.6 Hz), 0.99 (d, 3H, J=5.5 Hz), 1.37 (dd, 3H, J_1=7.1 Hz, J_2=2.9 Hz), 1.52–1.67 (m, 6H), 1.70 (m, 1H), 1.86 (m, 2H), 2.30 (d, 3H, J=2.9 Hz), 3.34 (s, 9H), 3.57 (m, 2H), 4.00 (m, 2H), 4.09–4.44 (m, 5H), 4.50–4.61 (m, 2H), 6.77 (s, 1H), 6.72 (m, 1H), 6.88 (dd, 2H, J_1=8.8 Hz, J_2=2.8 Hz), 7.11–7.49 (m, 10H), 7.57 (m, 1H), 7.66–7.78 (m, 3H), 7.87 (d, J=7.5, 2H). ^{13}C (75 MHz, acetone-d_6): δ=171.8, 171.4, 171.4, 158.7, 156.6, 144.2, 141.2, 137.9, 137.2, 132.8, 129.0, 128.3, 128.3, 126.7, 126.7, 126.3, 119.9, 114.3, 77.0, 67.2, 66.5, 66.5, 60.6, 52.7 (t, J_{C-N}=3.7 Hz), 51.2, 48.2, 47.1, 41.1, 30.9, 28.5, 24.4, 22.6, 22.4, 21.2, 20.2, 18.9, 17.6, 16.8, HRMS (ESI): [C^+] ($C_{51}H_{67}N_4O_7$) calcd 847.5010, found 847.5024.

5.3.36. H-Val-Leu-Ala-OH[34] *[57791-45-4].* To a solution in acetonitrile (10 mL) of [Fmoc-Val-Leu-Ala-O-MPPTMA][PF_6] (1 mmol) is added piperidine (20% in acetonitrile, 10 mmol). After 15 min at room temperature, solvent are removed under vacuum and the residue is washed with 3×10 mL Et_2O. The residue is dissolved in 50 mL CH_2Cl_2 and washed with 3×aqueous 1% HPF_6, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is dissolved in methanol (10 mL) and 100 μL of 60% aqueous HPF6 is added dropwise. After 1 h under refluxing conditions, solvents are removed under vacuum. 10 mL of water and 10 mL of CH_2Cl_2 are added, solvent removal affords [HTMPPTMA][PF_6] in 87% yield from the organic phase and H-Val-Leu-Ala-OH in 85% yield as a colorless oil from the aqueous layer. ^{1}H NMR (300 MHz, D_2O): δ=0.82 (dd, 6H, J_1=6.3 Hz, J_2=6.0 Hz), 0.92 (t, J=6.5, 6H), 1.23 (d, 3H, J=7.2 Hz), 1.46–1.54 (m, 3H), 2.11 (m, 1H), 3.72 (d, 1H, J=5.8 Hz), 4.03 (q, 1H, J=7.2 Hz), 4.33 (t, 1H, J=7.3 Hz).

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.07.016.

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