Hexafluoroacetone as Protecting and Activating Reagent: New Routes to Amino, Hydroxy, and Mercapto Acids and Their Application for Peptide and Glyco- and Depsipeptide Modification†

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1. Introduction: Bidentate Protecting/Activating Reagents for α-Functionalized Carboxylic Acids

A considerable number of biologically active naturally occurring products are peptides, depsipeptides, and peptide conjugates. Structure−activity relationship (SAR) studies are

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Jan Spengler was born in Leipzig in 1969. He received his Ph.D. degree from the University of Leipzig (Germany) working with Professor Klaus Burger in the synthesis of amino acid using hexafluoroacetone. From 2000 to 2002 he was a postdoctoral fellow at the Universidad Autònoma de Barcelona (Spain) and developed with Professor Marcial Moreno-Mañas recoverable and reusable Pd catalysts. In 2002 he again joined Professor Burger's group, while a substantial part of his investigation was performed with Professor Fernando Albericio at the Barcelona Science Park. Since 2004 he has been a senior researcher in Professor Albericios group. His research interests include the development of new methodologies for solid-phase peptide synthesis (linkers, coupling reagents) and synthesis of new types of peptidic architectures.

Christoph Böttcher was born in Nordhausen (Germany) in 1976. He studied chemistry at the University of Leipzig and finished his doctoral thesis in 2003 under the supervision of Professor Klaus Burger working on the synthesis of glycosylated α-hydroxy and α-amino acids. He moved to the Leibniz-Institute of Plant Biochemistry in Halle/Saale in 2004, where he is currently working on profiling and structure elucidation of secondary metabolites using high-resolution tandem-mass spectrometry.

relatively easy to perform because peptides have a sequential architecture and can be constructed step by step from monomeric building blocks in solution or on solid phase. Consequently, peptide modification can be performed efficiently by backbone modification and modification of the substituent pattern of the side-chain of the monomers.[1−3]

Direct therapeutic applications of native peptides are limited. However, major drawbacks of peptide drugs, like low selectivity, rapid degradation by proteases, low lipophilicity, and lack of transport systems to direct peptides into cells, can be overcome by incorporation of new types of monomers into strategic positions. This concept is based on an efficient access to monomers with tailor-made side-chains.

An important strategy is the site-selective transformation of readily available α-amino and α-hydroxy acids. For most protocols, protection of the 1-carboxy group and the α-functionality are required. This is achieved by a stepwise

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Klaus Burger, Professor Emeritus at the University of Leipzig, studied chemistry at Technical University Munich (1957–1962), were he earned his Ph.D. degree in Chemistry in 1965 (Professor F. Weygand). He spent a year as a postdoctoral fellow (1967–1968) at UMIST, England (Professor R. N. Haszeldine) with a grant from Stiftung Volkswagenwerk, Hannover. He returned to the Organic Department of TU Munich, where he started his own research. In 1972 he finished his Habilitation Thesis (mentor, Professor I. Ugi). In 1977 he was appointed C-3 professor. From 1988 to 1989 he was Professor at the Maximilian University Munich. He rejoined the Organic Department of TU Munich. Finally, in 1993 he assumed a chair in organic chemistry at the University of Leipzig. His research interests focus on organofluorine, heterocyclic, amino acid chemistry, and peptide modification. He has published over 350 papers, several review articles, and patents.

introduction of protecting groups (Figure 1, i). In this context, bidentate reagents for the protection of α-functionalized carboxylic acids are of interest. They simultaneously protect both the 1-carboxy group and the α-functionality by forma-

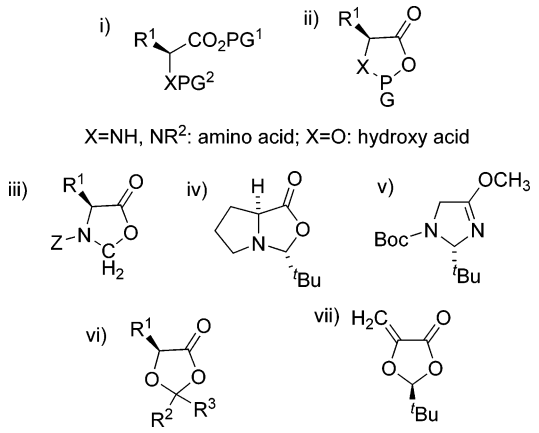


Figure 1.

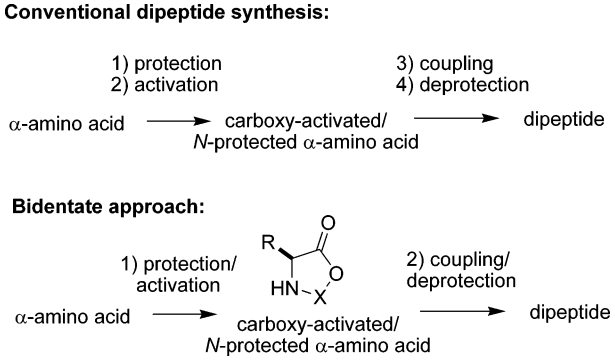
tion of a heterocyclic (mostly five-membered) system (Figure 1, ii). For example, oxazolidinones obtained from *N*-protected amino acids and formaldehyde (Figure 1, iii) are used for site-selective transformations of amino acids, as recently demonstrated for the preparation of N^{δ}-aryl glutamines from Glu[4] and Dap from Asp,[5] or synthesis of *N*-methylamino acids.[6] Pivaldehyde was used as chiral auxiliary for stereoselective synthesis of C^{α}-substituted prolines (Figure 1, iv)[7] and preparation of chiral glycine derivatives for stereoselective amino acid synthesis (Figure 1, v).[8] α-Hydroxy acids react with a variety of ketones and aldehydes to give 1,3-dioxolan-4-ones. Transformation of such compounds into 2-isopropoxy carboxylic acids by ring opening with Lewis acids or ^{t}BuMgCl was described recently (Figure 1, vi).[9] The chiral α,*β*-unsaturated Seebach dioxolanone obtained on treatment of pivaldehyde with lactic acid and successive halogenation/dehydrohalogenation was recently used for the diastereoselective synthesis of α-hydroxy acids by conjugate addition (Figure 1, vii).[10,11]

A synthetically highly attractive extension of the bidentate concept is application of such reagents that protect both the 1-carboxy group and the α-functionality but simultaneously activate the 1-carboxy group toward nucleophiles. One of the great challenges in peptide chemistry is the synthesis of orthogonally protected, selectively activated monomers in a few chemoselective steps. The standard dipeptide synthesis is a four-step procedure. If multifunctional amino acids are involved, additional protection and deprotection steps are usually required.[12−15] A bidentate protecting/activating concept meets this challenge by halving the number of steps if protection of the α-functionality and activation of the adjacent 1-carboxy group as well as subsequent coupling and deprotection of the α-functionality occur simultaneously (Scheme 1).

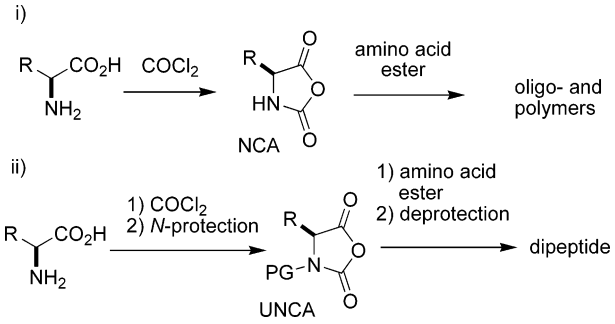
The carboxy anhydride method is a prominent example for the bidentate concept. The 1-carboxy group and α-amino group of α-amino acids react with phosgene to give NCA's. These cyclic anhydrides are highly reactive species, reacting readily with amino acid esters. Dipeptide formation is accompanied by rapid deprotection of the amino group. The deprotected amino group of the dipeptide formed competes with the amino acid ester as acyl acceptor forming oligomers (Scheme 2, i). Additional *N*-protection, producing UNCA's, prevents oligomerization but requires two additional steps (Scheme 2, ii).[16,17]

Recently, dichlorodimethylsilane was used for simultaneous protection and activation of certain α-amino acids without the need of additional *N*-protection. The carboxy-

Scheme 1

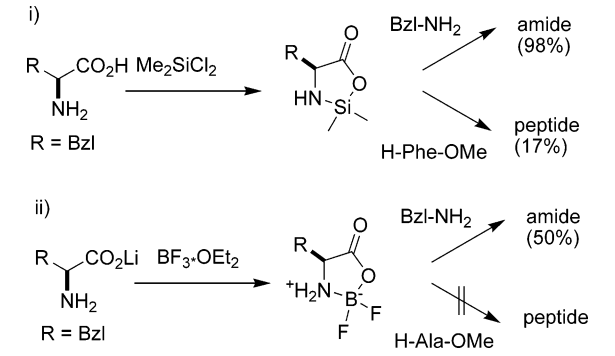


Scheme 2



activated silicon-containing heterocycles react with primary amines to afford amides in very good yields. However, synthesis of dipeptides such as aspartame, gave unsatisfactory yields (Scheme 3, i).[18] Compounds derived from boron

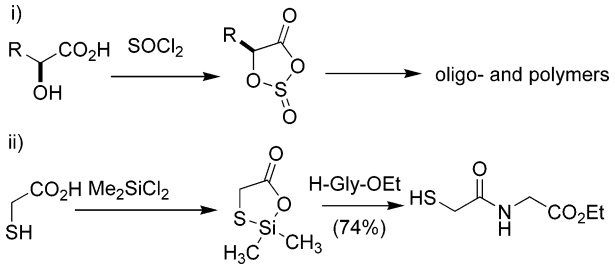
Scheme 3



trifluoride diethyl etherate when used as bidentate protecting/activating reagent exhibit similar limitations (Scheme 3, ii).[19]

Thionyl chloride reacts with α-hydroxy acids to give anhydrosulfites, which tend to polymerize (Scheme 4, i).[20]

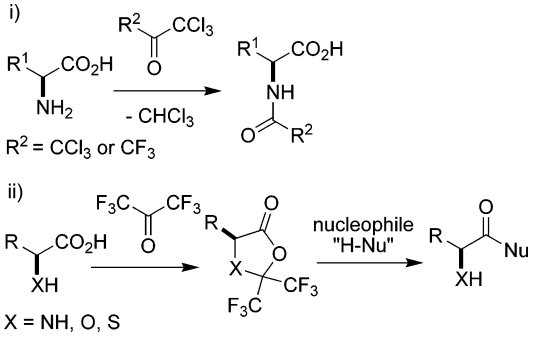
Scheme 4



Dichlorodimethylsilane was used as a bidentate protecting/activating reagent for coupling the α-mercapto acid to amino acid esters (Scheme 4, ii).[21]

Hexachloroacetone and 1,1,1-trichloro-3,3,3-trifluoroacetone react with the α-amino group of amino acids with chloroform elimination to give the corresponding *N*-trichloroacetyl and *N*-trifluoroacetyl amino acids, respectively (Scheme 5, i). In contrast, hexafluoroacetone (HFA) forms

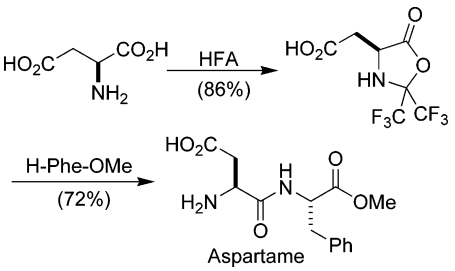
Scheme 5



2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones.[22,23] Remarkably, no additional α-amino protection is required. Furthermore, HFA was also found to react readily with α-hydroxy and α-mercapto acids to give five-membered heterocycles. In a single step the α-placed functionality and α-carboxy group are protected. The lactone ring represents an activated ester and can be cleaved by various *O*- and *N*-nucleophiles in solution and on solid phase to give the corresponding unprotected derivatives in one step (Scheme 5, ii).

HFA protection occurs site selectively even in the presence of unprotected side-chain functionalities, like the *β*-carboxy group of Asp. An impressive application of the HFA concept is the shortest chemical synthesis of the sweetener aspartame. First, Asp is reacted with HFA; second, nucleophilic ring opening of HFA(Asp) with methyl phenylalaninate at room temperature provides aspartame in an overall yield of 62% (Scheme 6).[24] Conventional syntheses of the sweetener

Scheme 6



aspartame are surprisingly laborious procedures, requiring at least four steps.[25] The HFA protocol was also successfully applied to the synthesis of aspartame-related sweeteners such as neotam and alitam.[26,27]

Numerous transformations of functional groups placed in the side chain can be carried out in the presence of HFA protection, providing access to homochiral, nonproteinogenic, and nonnatural α-amino, α-hydroxy, and α-mercapto acids as building blocks of enormous structural diversity. The new products are obtained as carboxy-activated species. *ω*-Acid chlorides and *ω*-isocyanates of HFA-protected α-functionalized carboxylates are double-activated species being susceptible to two consecutive site-selective acylation processes. The new strategy can be used for the construction of tailor-made building blocks for peptide, depsipeptide, and glycopeptide modification in a highly efficient way (see sections 4−7).

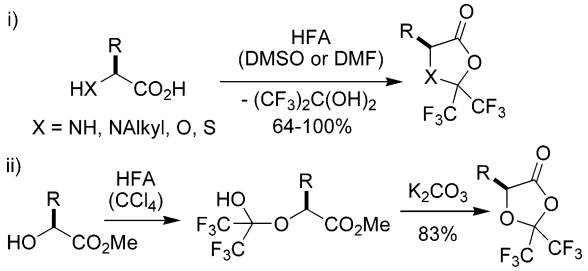
Information on the bidentate concept, especially the HFA strategy, which can be found in recently published monographs on peptide chemistry and protective group strategies, is meager.[12,13] In this context, a critical and comprehensive overview on the synthetic potential of HFA as bidentate reagent for the synthesis of new monomers for peptide, depsipeptide, and glycopeptide modification will be helpful to enlarge the synthetic repertoire. The aim of this review is to draw the attention of synthetic chemists to the potential of this reagent.

2. Reaction of Hexafluoroacetone with α-Functionalized Carboxylic Acids

2.1. Protection/Activation of α-Amino, α-Hydroxy, and α-Mercapto Acids

Gaseous HFA readily reacts with α-amino, α-hydroxy, and α-mercapto acids in DMSO at room temperature to give five-membered lactones (see Abbreviations in section 12). Two equivalents of HFA have to be added; the second equivalent is necessary to trap the water which is eliminated during lactone formation. HFA hydrate is the only byproduct. When the reaction is complete, DMSO and HFA hydrate are removed by extraction with a biphase system (DCM/H_2O). The products are obtained in up to 90% yield. Also, a few other solvents can be used, for example, DMF. For workup DMF can be distilled off under reduced pressure and the HFA hydrate is removed by lyophilization. However, this protocol can only be applied to high-boiling and nonvolatile compounds, but then nearly quantitative yields are obtained (Scheme 7, i).[28] A stepwise protection is described for an

Scheme 7



α-hydroxy acid methyl ester, where the hemiacetal is formed first and subsequent cyclization was achieved by adding K_2CO_3 (Scheme 7, ii).[29]

Lactone formation works especially well with α-amino, α-hydroxy, and α-mercapto acids having aliphatic and aromatic side-chains but also tolerates additional functionalities present in the side-chain. Carboxy groups placed in the side-chain remain unaffected. The reaction proceeds site-selectivity in the case of Asp, malic, and mercaptosuccinic acids and homologues (section 4). ^1H and ^{19}F NMR control of the progress of the reaction revealed that five-membered lactones are formed exclusively. In the case of Ser and Thr, the hydroxy group forms at least partially a hemiacetal with HFA, which can be cleaved by stirring the product in DCM in the presence of silica gel (section 7). HFA protection can also be carried out in the presence of acid-sensitive protecting groups in the side chain, as exemplified by the synthesis of HFA[Cys(Trt)].[30]

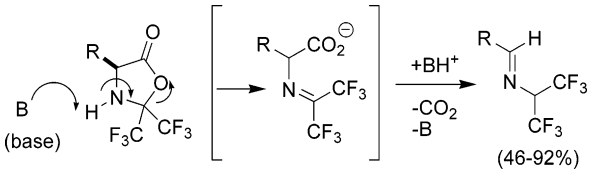
2.2. Some Properties of HFA-Protected Compounds

HFA is commercially available as a gas in lecture bottles or as liquid trihydrate. The gas (bp −28 °C) is obtained on dropwise addition of the trihydrate to concentrated sulfuric acid at 80−100 °C with stirring. Hexafluoroacetone is reported to be highly toxic, corrosive, teratogenic, very harmful on inhalation or ingestion, and a respiratory irritant. For safety reasons all experiments should be carried out in an efficient fume hood.[31]

HFA amino, hydroxy, and mercapto acids are stable liquids or solids that are storable over years on exclusion of moisture. They can be prepared and handled on a multigram scale. They are very soluble in most organic solvents, and some derivatives are distillable under reduced pressure. The progress of reactions of HFA-protected compounds can be monitored conveniently by ^{19}F NMR spectroscopy. Typically, the trifluoromethyl groups of chiral HFA compounds resonate as two quartets in the ^{19}F NMR spectrum.

Chemically, the bis(trifluoromethyl)-substituted lactones exhibit remarkable stability toward water-free acids. During the synthesis of 6-[^{18}F]-fluoro-*meta*-tyrosine, an imaging agent for positron emission tomography (PET), triflate activation had to be carried out; therefore, the Boc/*tert*-butyl protection strategy could not be applied, but HFA protection was employed successfully.[32] However, when HFA amino acids are treated with bases, NH deprotonation starts a fragmentation process (Scheme 8).[33]

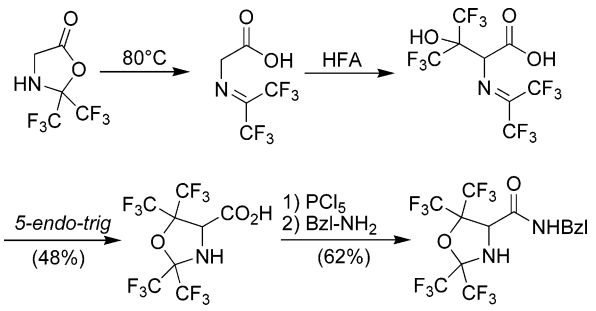
Scheme 8



2.3. Side Reactions: Perfluoromethylated Pseudoproline from Glycine

Side reactions have been observed in the case of amino acids when the reaction was run with a large excess of HFA at elevated temperatures. Reaction of Gly and HFA at elevated temperatures offers a concise access to 2,2,5,5-tetrakis(trifluoromethyl)-1,3-oxazolidine-4-carboxylic acid.[34] A plausible interpretation of this ring transformation is a multistep sequence including aldol addition and intramolecular ring closure of the rare 5-endo-trig type (Scheme 9).[35] This bulky heterocycle represents a perfluoroalkylated pseudoproline. Recently, pseudoprolines found applications as building blocks providing solubility in organic solvents and secondary structure disruptions of peptidomimetics.[36]

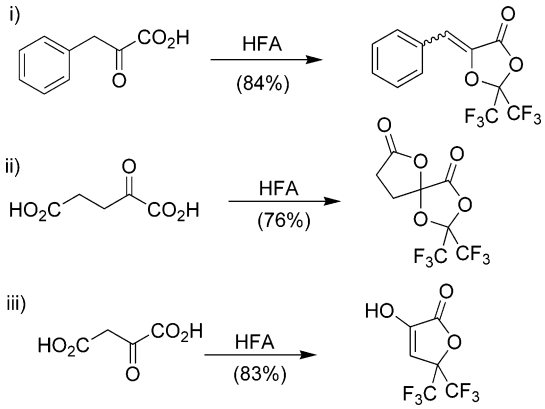
Scheme 9



2.4. Application of HFA in α-Keto Acid Chemistry

α-Keto acids react with HFA to give various types of compounds depending on the substitution pattern. Phenylpyruvic acid gives a HFA-protected enol (Scheme 10, i).

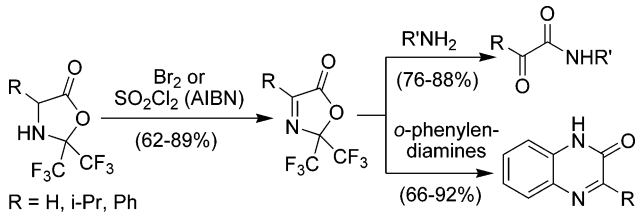
Scheme 10



2-Oxoglutaric acid and HFA give a spiro compound after intramolecular addition of the 5-carboxy group to the enol intermediate (Scheme 10, ii). 2-Oxosuccinic acid provides as main product the butenolide 3-hydroxy-5,5-bis(trifluoromethyl)-2(5*H*)-furanone, via aldol addition, cyclocondensation, and decarboxylation (Scheme 10, iii).[37] These results indicate that the HFA route applied to α-keto acids can be of interest for the synthesis of certain trifluoromethyl-substituted heterocycles, including butenolides, which are naturally occurring compounds with a broad range of biological activities.[38]

α-Keto acid derivatives can be obtained from HFA amino acids (Gly, Val, and Phg) via halogenation/dehydrohalogenation. The oxazolones represent carbonyl-group-protected, carboxy-group-activated, α-keto acid derivatives. Nucleophilic ring opening with various *O*- and *N*-nucleophiles provides access to esters and amides of α-keto acids. With *o*-phenylendiamines, quinoxalines were formed (Scheme 11).[39,40]

Scheme 11

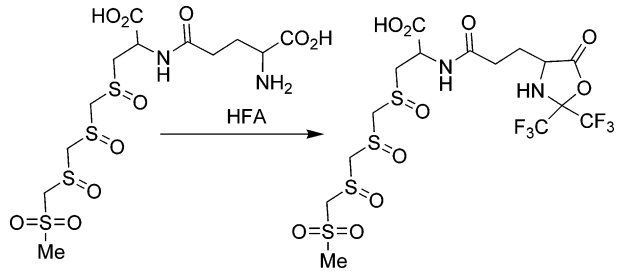


2.5. Reaction of HFA with Peptides

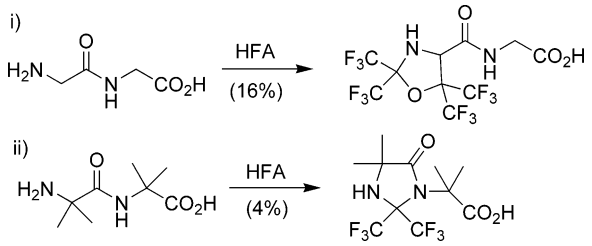
On reaction of HFA with peptides, different types of products, depending on the nature of the peptide, were found. The dipeptide lentinoic acid is a γ-glutamyl-cysteine sulfoxide. HFA reacts site-selectivity with the *C*-terminal glutamyl residue, yielding the corresponding HFA compound, which was used for structural elucidation by NMR (Scheme 12).[41]

On the other hand, the dipeptide H-Gly-Gly-OH adds two equivalents of HFA to the *N*-terminal amino group and the α-CH_2. Via cyclocondensation a tetrakis(trifluoromethyl) oxazolidine is formed (Scheme 13, i). If the C^{α} is dialkylated, as in the case of H-Aib-Aib-OH, only one equivalent of HFA adds to the *N*-terminal amino group. A consecutive intramo-

Scheme 12



Scheme 13



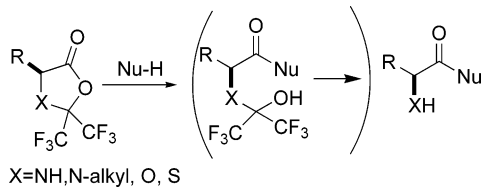
lecular condensation gives a bis(trifluoromethyl)imidazolidin-4-one (Scheme 13, ii),[42] but yields are low.

3. Derivatization/Deprotection of HFA-Amino, HFA-Hydroxy, and HFA-Mercapto Acids

3.1. Derivatization/Deprotection in Solution

HFA-protected/activated α-functionalized carboxylic acids react with *N*- and *O*-nucleophiles to give the corresponding carboxy derivatives; simultaneously, deprotection of the α-functionality takes place (Scheme 14).

Scheme 14



Aminolytic ring opening is fast at room temperature in solvents like ether or 2-propanol. Best yields are obtained when the product crystallizes directly from the reaction mixture. Otherwise, the products have to be separated from the byproduct hexafluoroacetone hydrate by repeated lyophilization, extraction, or chromatographic methods. This has been demonstrated by the preparation of amides, hydrazines, hydroxamates, azapeptides, and peptides in 40−90% yields from HFA(Asp),[43] HFA-hydroxy acids,[44] and HFA-mercapto acids.[45] Derivatives which have been synthesized from the corresponding HFA compounds will be discussed in the following sections.

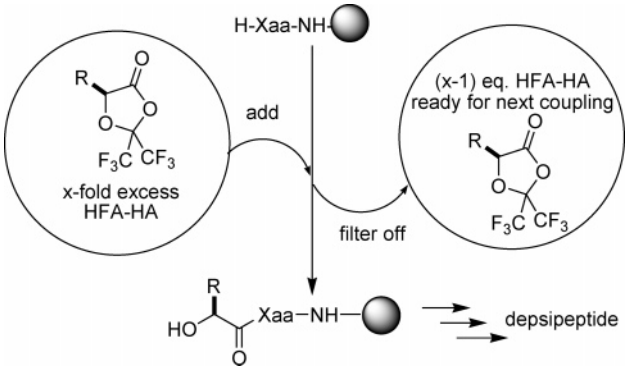
In some cases the deprotection/derivatization step still requires optimization. For example, HFA(Glu) was heated with an excess of amine to yield 52−71% of the amides.[46] Some sterically hindered HFA-prolines (section 8.6) can only be deprotected in boiling concentrated HCl.[47] Weaker nucleophiles such as alcohols and water generally require prolonged reaction times.

Finally, there is the option to exchange the HFA group for another protection scheme. For example, during the preparation of ^{18}F-labeled compounds for PET, an HFA-amino acid was treated with methanol in the presence of acid to give the amino acid methyl ester (section 3.3); then the amino group was Boc-protected and the methyl ester saponified to give the Boc-protected amino acid.[32]

3.2. Derivatization/Deprotection on Solid Phase

In conventional solid-phase peptide synthesis (SPPS), carboxy-activated monomers are coupled to the unprotected *N*-terminus of the resin-bound peptide chain.[48] A 4−10-fold excess of reagents is usually added to the resin in order to drive each reaction to completion. For laboratory-scale runs the excess material is normally nonrecoverable and nonreusable. Therefore, the atom economy of SPPS is low.[49] Carboxy activation is an intrinsic property of HFA monomers, and therefore, no additional activation reagents are required for coupling reactions. The nucleophilic ring opening of HFA-hydroxy acids with solid-phase bound peptide segments was demonstrated to be an elegant and general application of the HFA route for the solid-phase synthesis of depsipeptides. HFA-HAs undergo coupling without racemization in suitable solvents such as THF. The filtrate containing the excess of HFA-hydroxy acid can be evaporated, redissolved, and reused (Scheme 15).[50,51] On the other hand, application of

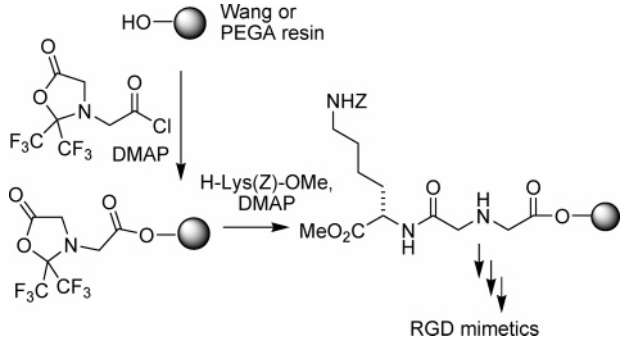
Scheme 15



HFA-amino acids as carboxy-activated species for solid-phase peptide synthesis was found to be limited.[51]

SPPS can also be performed in an inverse mode.[52] HFA-AAs and HFA-HAs can be deprotected/derivatized on solid support if they were anchored before to a solid support via a side-chain functionality (section 4.2). Using this strategy the synthesis of RGD mimetics based on iminodiacetic acid could be improved.[53] HFA(Ida) was anchored to Wang and PEGA resins, respectively. Nucleophilic cleavage of the lactone ring with H-Lys(Z)-OMe provided the solid-phase bound dipeptide (Scheme 16).[54] Concomitantly, the amino group is deprotected and can be directly submitted to further

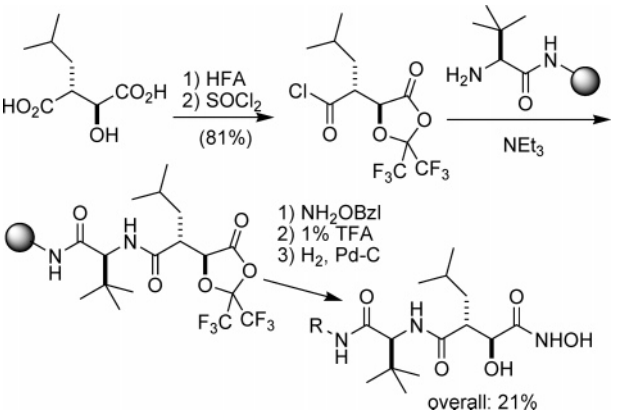
Scheme 16



acyl transfer reactions. This strategy has the advantage that HFA formed as byproduct is transformed into HFA hydrate during workup, which easily can be separated by washing the resin.

HFA-hydroxy acids can also be used in inverse solid-phase peptide synthesis. During a synthesis of conjugates of the hydroxamate-type inhibitor marimastat, (2*S*,3*R*)-HFA-3-isobutylmalate was linked via its side-chain carboxy group to resin-bound *tert*-leucine amide. The HFA-lactone was cleaved with *O*-benzylhydroxylamine. After deprotection and cleavage from the resine, marimastat was obtained HPLC pure.[55]

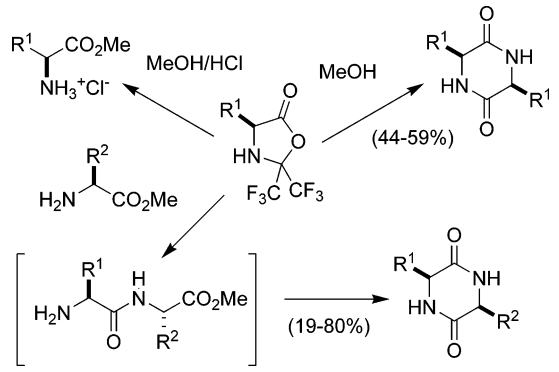
Scheme 17



3.3. Symmetric and Unsymmetric Diketopiperazines

On reaction of HFA-amino acids with an excess of methanol at room temperature, the newly formed amino acid methyl ester attacks a second molecule of HFA(Xaa) to give symmetric diketopiperazines (DKPs). DKP formation can be prevented using methanol saturated with HCl gas, which traps the methyl ester as hydrochloride. The nucleophilic ring opening of HFA-amino acids with amino acid methyl esters provides unsymmetrical DKPs in only one reaction step (Scheme 18).[56] DKPs are abundant peptide derivatives found

Scheme 18



in nature, and many applications in various fields in modern organic chemistry are described.[57−59]

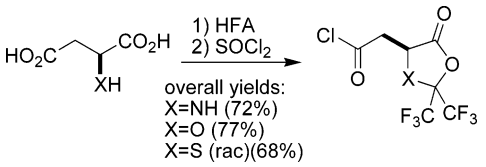
4. Site-Selective Derivatization of α-Functionalized Dicarboxylic Acids

Homochiral HFA(Asp) and HFA(Glu), HFA-malic, and citramalic acid as well as (racemic) HFA-α-mercaptosuccinic acid and achiral HFA(Ida) are α-carboxy-activated species accessible in one step from the corresponding acids and HFA (section 2). Derivatization of the *ω*-carboxy group requires separate activation. On the basis of this simple concept monomers of high structural diversity can be constructed, suitable for peptide, depsipeptide, and glycopeptide modification. All steps proceed stereoconservatively; therefore, both enantiomeric forms are available. Furthermore, the homologues of the HFA-protected monomers are readily accessible via Arndt−Eistert reaction (section 4.5).

4.1. Activation of the *ω*-Carboxy Group

The *ω*-carboxy groups of HFA(Asp), HFA-malic, and HFA-mercaptosuccinic acid can be selectively activated by transformation into acid chlorides on heating with thionyl chloride (Scheme 19). They are easy to handle, synthetically

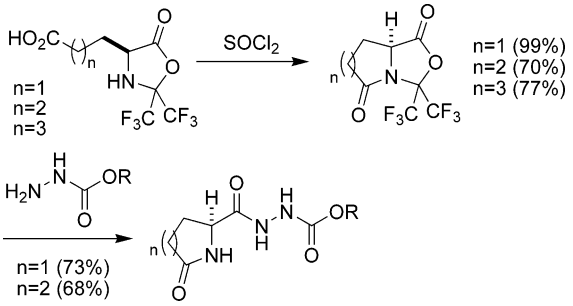
Scheme 19



highly versatile dielectrophiles. The acid chloride is the position of highest electrophilicity. Therefore, under carefully controlled conditions site-selective mono-, di-, and trifunctionalizations of α-functionalized α,*ω*-dicarboxylates are possible in a highly efficient way (sections 4.2−4.5).

However, only certain HFA-protected α-amino acid chlorides are stabile compounds, like HFA[Asp(Cl)] and its higher homologues with chain length > 7, HFA(Glu), HFA-(Aad), and HFA(Api) (chain length 5−7) on treatment with thionyl chloride cyclize spontaneously to give lactams.[28] HFA(pGlu) is a carboxy-activated 2-pyrrolidinone (Scheme 20).[60] 2-Pyrrolidinones exhibit various biological activities

Scheme 20



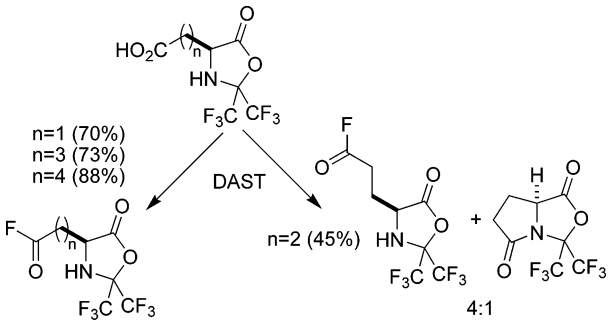
and represent valuable building blocks for heterocyclic chemistry and peptide modification.[61,62]

Fluorides of *N*-protected α-amino acids have been applied in peptide chemistry as acylation agents.[63] HFA[Xaa(F)] have been prepared from the corresponding acids by treatment with DAST and isolated as pure compounds by distillation in vacuo.[28] Lactam formation was observed only in the case of HFA(Glu) {HFA[Glu(F)]:HFA(pGlu) 4:1} (Scheme 21).[54] The acid fluorides have been used for glycosylation reactions (section 4.4). *ω*-Carboxy activation with isobutyl chloroformate or TBTU avoids lactam formation (section 6.3).[64]

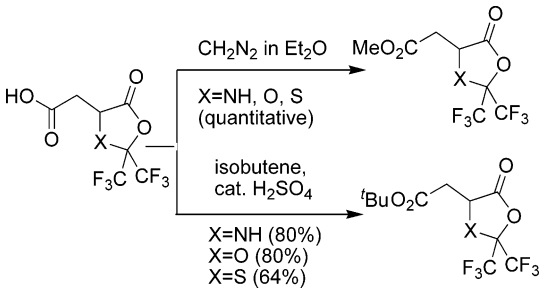
4.2. *ω*-Esters

HFA(Asp), HFA-malic, and HFA-mercaptosuccinic react with diazomethane and isobutene to give the corresponding *ω*-methyl and *ω*-*tert*-butyl esters (Scheme 22).

Scheme 21

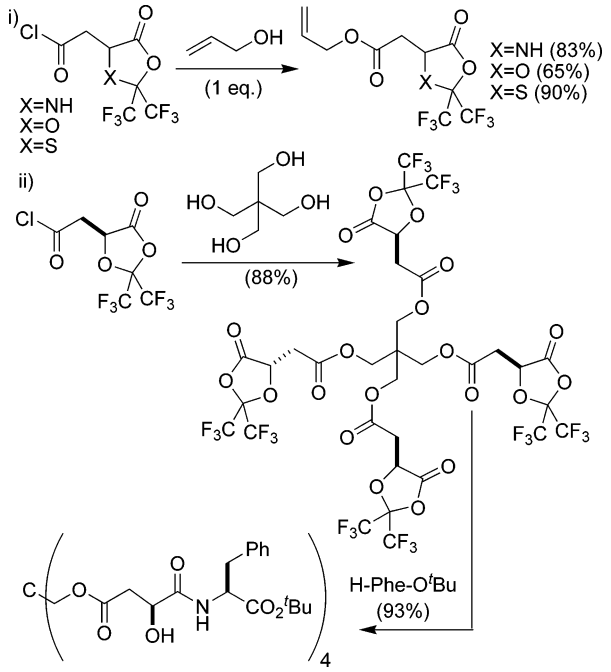


Scheme 22



Allyl protection of the ω-carboxy group can be achieved on heating of the acid chlorides in toluene with equimolar amounts of allyl alcohol (Scheme 23, i). Interestingly,

Scheme 23

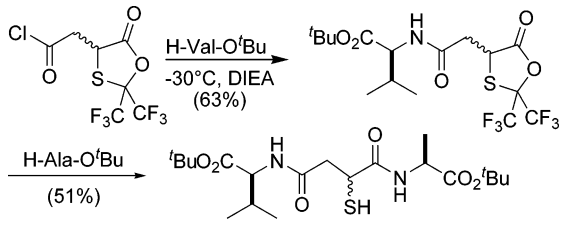


multivalent alcohols such as pentaerythritol can be completely acylated in excellent yields. Subsequent aminolysis of the tetralactone gives rise to branched peptides and depsipeptides in surprisingly high yields (Scheme 23, ii).[65,66] Therefore, this protocol may be useful for the construction of peptide- and depsipeptide-based dendrimers.[67]

4.3. ω-Amides and ω-Peptides

ω-Amides and ω-peptides are accessible by reaction of ω-carboxy-activated HFA-dicarboxylates with equimolar amounts of amines and amino acid esters at low temperatures. By this strategy incorporation of α-functionalized dicarboxylic acids into small peptides can be accomplished site-selectivity as demonstrated for mercaptosuccinic acid. Peptide bond formation via ω-carboxy group was achieved by reaction of the acid chloride with H-Val-O^{t}Bu in a temperature range from -30 to 0 °C. In a second step the lactone is cleaved with H-Ala-O^{t}Bu at room temperature (Scheme 24).[68]

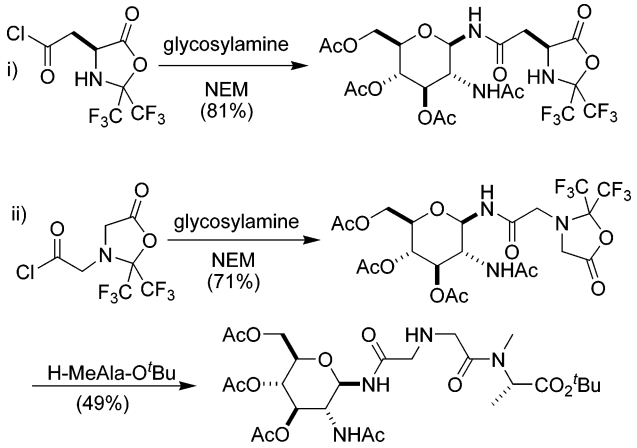
Scheme 24



4.4. Acylation of Glycosylamines

Glycoproteins are ubiquitous in nature, playing a key role in various biological recognition processes both within cells and at cell surfaces. In *N*-glycosides, the carbohydrate moiety is attached to the peptide backbone via the nitrogen atom of the side chain of Asn.[69,70] *N*-Glycosides have been synthesized efficiently by reaction of HFA[Asp(Cl)] with *O*-protected glycosylamines at 0 °C (Scheme 25, i). Analo-

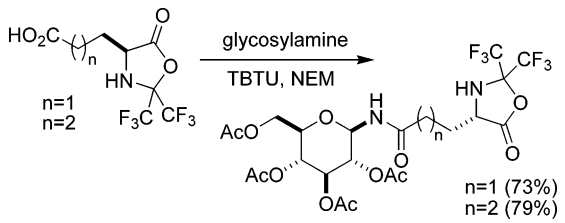
Scheme 25



gously, glycopeptoides[71] are available from HFA[Ida(Cl)] (Scheme 25, ii).[72,73]

For acylation of glycosylamines with HFA(Glu) and HFA(Aad), TBTU activation was used to avoid intramolecular cyclization reactions (Scheme 26, section 4.1).[74]

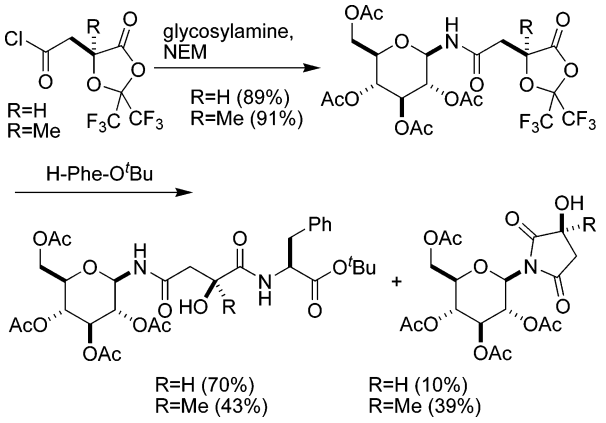
Scheme 26



Likewise, chlorides and fluorides of HFA-malic, -citramalic, and -mercaptosuccinic acid are excellent acylation reagents. The HFA-protected glycoconjugates are carboxy-

activated compounds susceptible for direct application for peptide bond formation. However, a cyclocondensation reaction to give 3-hydroxysuccinimido sugars competes with the peptide coupling process (Scheme 27).[75,76]

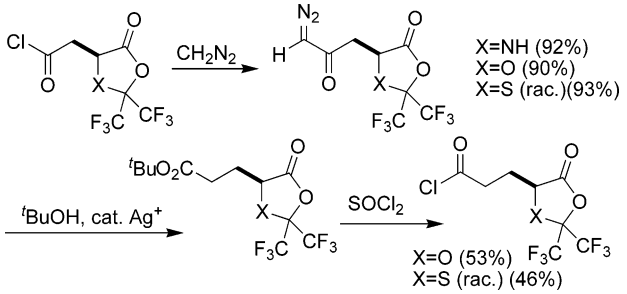
Scheme 27



4.5. Homologation via Arndt–Eistert Reaction of Diazoketones

The Arndt−Eistert reaction, a standard method for homologation of carboxylic acids, proceeds via Wolff rearrangement of diazoketones.[77] Acylation of diazo compounds is the standard route to diazoketones,[78] which can be applied to ω-carboxy-activated HFA-amino, -hydroxy, and -mercapto acids. On reaction of acid chlorides with excess of diazomethane the corresponding diazoketones are obtained in good yields (for further reactions of this compounds, see section 6).[79] When the catalytic decomposition of the diazoketones is carried out in *tert*-butyl alcohol, the *tert*-butyl esters are formed. The ω-carboxy-protected species can be deblocked and activated as ω-carboxylic acid chlorides by heating in the presence of an excess of thionyl chloride in an one-pot procedure (Scheme 28).[80]

Scheme 28

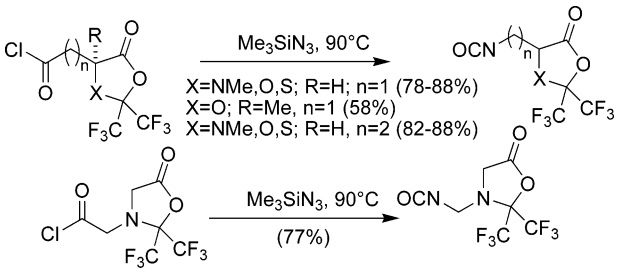


5. ω-Isocyanates from α-Functionalized α,ω-Dicarboxylic Acids

5.1. Synthesis of ω-Isocyanates

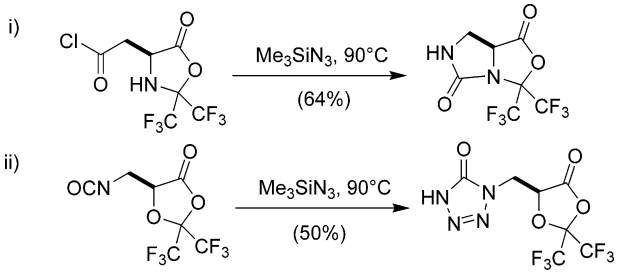
ω-Carboxy-activated HFA(Ida),[66] HFA-N^{α}-methyl amino acids,[81] HFA-hydroxy acids,[82] and HFA-mercapto acids[83] (section 4.1) can be readily transformed into the corresponding ω-isocyanates on heating with one equivalent of trimethylsilyl azide in toluene. The reaction proceeds via Curtius rearrangement[84] of the corresponding ω-azides. The products represent highly versatile ω-amino acid derivatives (sections 5.2 and 5.3).

Scheme 29



However, this protocol cannot be applied to ω-carboxy-activated HFA-amino acids due to intramolecular cyclization reactions with the NH moiety of the oxazolidinone system, yielding bicyclic urea derivatives (Scheme 30, i).[85] With an

Scheme 30



excess of trimethylsilyl azide, tetrazole-5-ones are the result of a [3 + 2] cycloaddition reaction (Scheme 30, ii).[82]

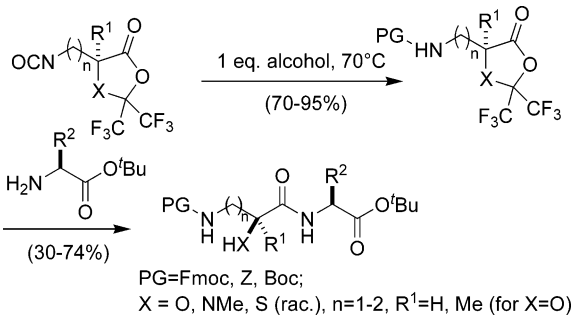
5.2. α-Functionalized ω-Amino Acids: Isoserine, α-Methylisoserine, Isocysteine, N^{α}-Methyl Diamino Propionic Acid, and Homologues

Isoserine is one of the most abundant nonproteinogenic amino acids, found as constituent of biologically and medically important molecules such as taxol.[86] Consequently, isoserine and structurally related compounds have been the target of many synthetic efforts.[87−92]

The HFA route offers a general, concise approach to these compounds from HFA-protected α-functionalized ω-isocyanato carboxylic acids (section 5.1). These compounds are dielectrophiles, where the isocyanato moiety is more electrophilic than the lactone group. Therefore, nucleophilic attack preferentially takes place at the isocyanato group, which represents a hidden amino group. Isocyanates react with alcohols to give urethane-protected α-functionalized ω-amino acids. Starting from malic acid, this protocol provides access to Fmoc-, Z-, and Boc-HFA-isoserine building blocks in four steps.[82] Analogously, HFA-2-methylisoserine was obtained from citramalic acid[93] and HFA-isocysteine from mercaptosuccinic acid.[83] Efficient syntheses (section 4.5) of the homologues HFA-homoisoserine, the nonnatural amino acids HFA-homoisocysteine,[80,94] and HFA-2-methylhomoisoserine are described.[94,95] N^{α}-Methyl-2,3-diaminopropionic acid was found in a variety of natural products, like in the peptide antibiotic *TAN*-1057, which is active against *Staphylococcus aureus*.[96] The HFA route gives rise to derivatives of N^{α}-methyl-2,3-diaminopropionic acid and its homologues.[81] These building blocks are orthogonally protected/activated species ready for peptide synthesis (Scheme 31).

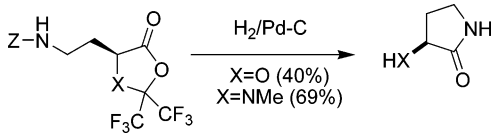
Cleavage of the urethane protecting group of HFA-homoisoserine results in a spontaneously occurring intramolecular cyclization forming the (3*S*)-3-hydroxy-2-pyrrolidi-

Scheme 31



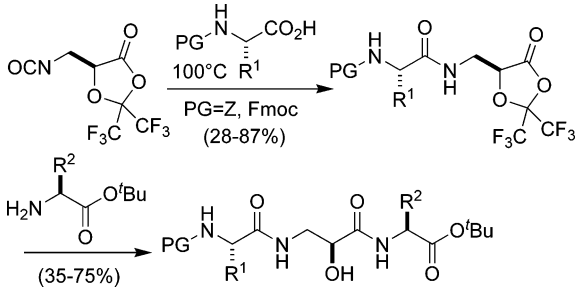
none.[97] (3*S*)-3-Hydroxy-2-pyrrolidinones have been isolated from several natural products representing a lead structure with valuable pharmacological properties and low toxicity.[98,99] Analogously, (3*S*)-3-methylamino-2-pyrrolidinone[81] was obtained from the corresponding HFA-protected building block (X = NMe) (Scheme 32).

Scheme 32



Reaction of isocyanates with carboxylic acids and *N*-protected amino acids (Goldschmidt reaction)[100] offers direct access to β-acylated HFA-isoserines and β-peptides, respectively. Subsequent aminolytic cleavage of the lactone moiety with amino acid esters provides tripeptide fragments with isoserine in the middle position (Scheme 33).[82]

Scheme 33

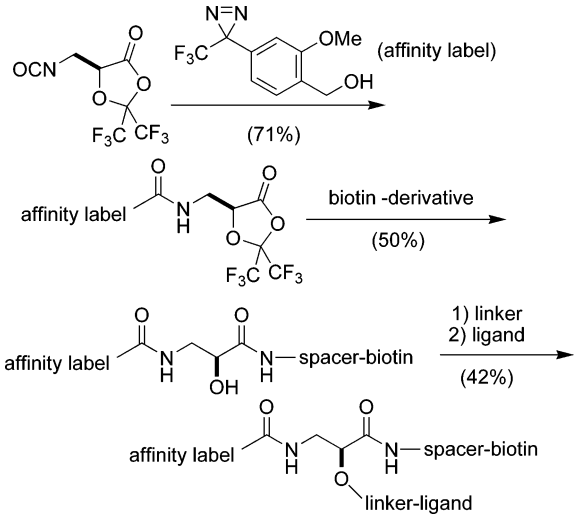


5.3. α-Functionalized ω-Amino Acids as Multifunctional Scaffolds and Urea-Linked Glycoconjugates

As shown above (section 5.2), HFA-protected α-functionalized ω-isocyanato carboxylic acids are well suited for di- and trifunctionalization with a minimum of steps. Recently, isoserine was accommodated with three different functionalities using this route for an improved reagent for photoaffinity labeling. An aryl trifluoromethyl diazirine unit (Hatanaka's affinity label) was linked to the isocyanate group. The α-carboxy derivatization was accomplished by nucleophilic ring opening with a biotin derivative. Finally, the deprotected α-OH group of the isoserine core was coupled via linker (4-isocyanato benzoyl chloride) to the ligand (moenomycine) (Scheme 34).[101,102]

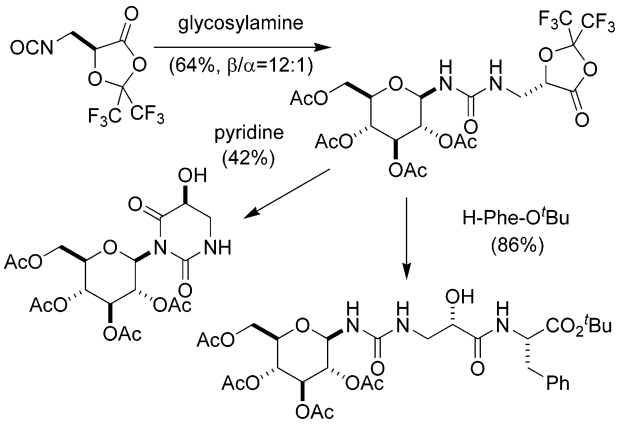
Recently, a new approach to glycopeptide mimetics was disclosed, where *O*- and *N*-glycosidic linkages are replaced by urea glycosyl bonds. The urea glycosyl bond was constructed by coupling glycosyl isocyanates and amino acid

Scheme 34



derivatives.[71] The isocyanate readily obtainable from HFA-protected malic acid reacts with *O*-protected β-D-glycosylamine at 0 °C to give the HFA-activated urea-linked glycoconjugate. On treatment of the β-anomer with acids, formation of the α-anomer was observed. On treatment with bases, the urea NH is capable of intramolecular nucleophilic lactone cleavage providing glycosylated dihydropyrimidindiones (see also section 4.4). Nucleophilic cleavage of the lactone ring with amino acid esters or allyl alcohol yields glycosylated depsipeptides or esters, respectively (Scheme 35).[103,104]

Scheme 35



6. ω-Diazoketones from α-Functionalized Dicarboxylic Acids

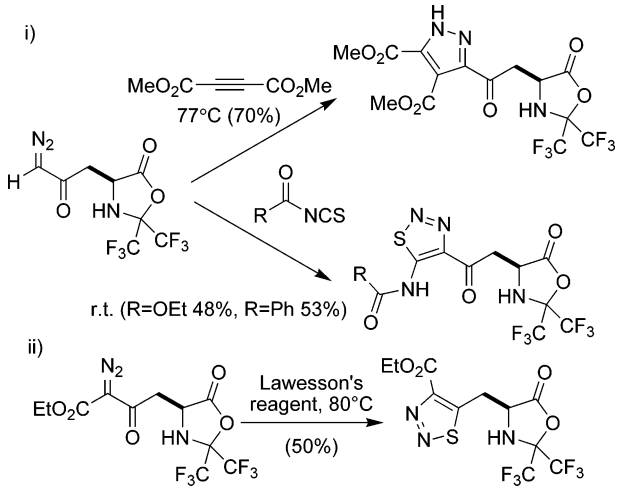
Application of diazoketones of HFA-amino, -hydroxy, and -mercapto acids for homologation reactions has been already mentioned (section 4.5). Diazoketones represent versatile precursors for the synthesis of nonnatural α-functionalized carboxy acids. A selection of preparatively interesting transformations of diazoketones will be discussed.

6.1. Heterocyclic Amino Acids via Cycloadditions

Recently, the synthesis of nonnatural amino acids bearing heterocycles in the side-chain received a lot of attention due to their interesting properties associated with DNA binding.[105−108] The substructure $-CH{=}N_2$ represents a 1,3-dipolar species capable of [3 + 2] cycloaddition reactions.

Diazo compounds derived from HFA-Asp add dipolarophiles decorated with electron-withdrawing substituents such as acetylene dicarboxylates to give pyrazoles. With acylisothiocyanates, 1,2,3-thiadiazoles are formed (Scheme 36, i). The

Scheme 36

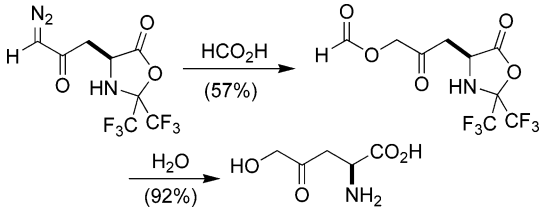


2-diazo-1,3-diketones, obtained from HFA[Asp(Cl)] and diazoethyl acetate (section 6.3), react with Lawesson's reagent to give β-(1,2,3-thiadiazol-5-yl)alaninates (Scheme 36, ii).[79] Diazoketones of HFA(Ida) react similarly.[66]

6.2. Acid-Catalyzed Decomposition of the Diazo Compounds: HON, 4-Oxoornithine, Hantzsch Reaction

Due to the remarkable stability of the 2,2-bis(trifluoromethyl)-substituted lactone ring (section 2.2) toward dry acids, decomposition of diazo compounds on treatment with acids is a preparatively valuable process. Depending on the structure of the acid, haloketones and hydroxyketones have been obtained.[79] Interestingly, reaction of the diazo compounds derived from HFA(Asp) with formic acid provides an *O*-formyl-protected hydroxyketone. Deprotection of three functional groups has been achieved in a one-pot reaction at room temperature in 2-PrOH/H_2O to provide the antibiotic 5-hydroxy-4-oxonorvaline (HON) in acceptable yields (Scheme 37).[109,110]

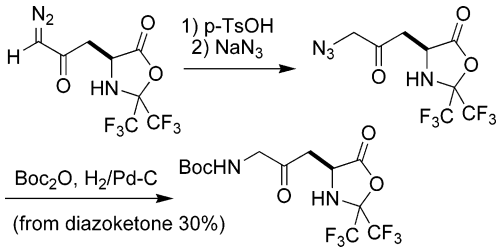
Scheme 37



Construction of (2*S*)-4-oxoornithine can be achieved by replacing the diazo group by a tosylate moiety as leaving group to introduce the azide group. Hydrogenation of the azide moiety in the presence of Boc_2O gave the N^{ω}-Boc-protected HFA-(2*S*)-4-oxoornithine (Scheme 38).[111]

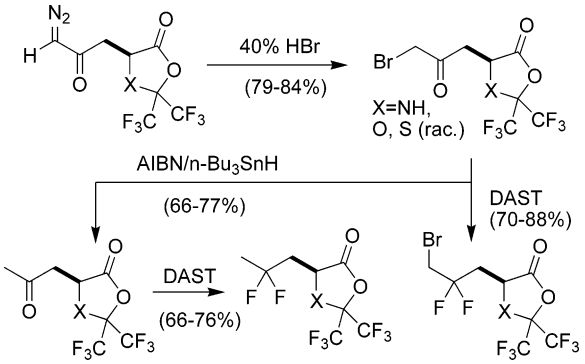
On decomposition of the diazoketones with HBr at 0 °C bromoketones are formed. These bromoketones can be dehalogenated to give the corresponding methyl ketones, providing HFA-protected oxonorvaline and its α-hydroxy and α-mercapto analogues. Fluorodeoxygenation with DAST provides α-amino, α-hydroxy, and α-mercapto-γ,γ-difluo-

Scheme 38



ropentanoic acid derivatives. Interestingly, this protocol works also with the bromomethyl ketones and gives rise to so far unknown 2-functionalized 5-bromo-4,4-difluoropentanoic acid derivatives (Scheme 39). From 1-carboxy-

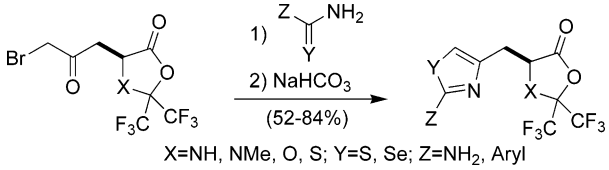
Scheme 39



activated species the unprotected acids and peptides have been prepared.[112]

On application of the Hantzsch protocol, 3-(thiazol-4-yl)-2-aminopropionic,[113] -2-N^{α}-methylaminopropionic,[114] -2-hydroxypropionic,[44] and -2-mercaptopropionic acids[45] become available from the bromoketones and the corresponding thioamides and thioureas, respectively. Likewise, 3-(selenazol-4-yl)-2-aminopropionic acid derivatives have been prepared by this route (Scheme 40).[113] 3-(Thiazol-4-yl)-2-

Scheme 40

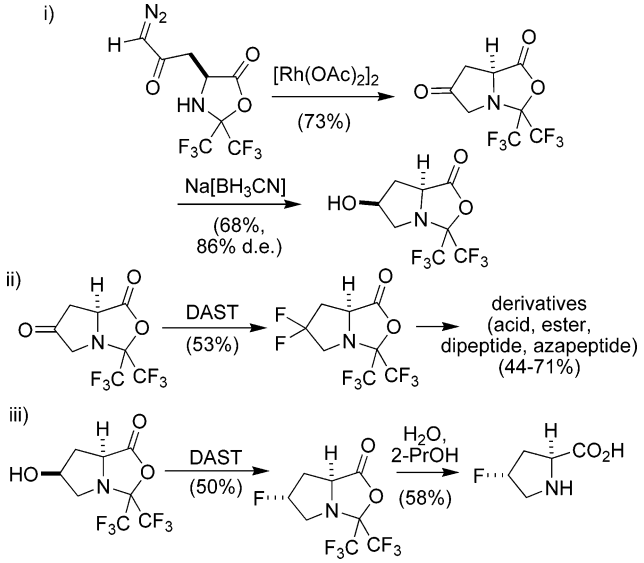


aminopropionic[115] and -2-hydroxypropionic acids[116] are pharmacologically relevant heteroarylalanines.[117]

6.3. Intramolecular Rhodium-Catalyzed NH Insertion: New Routes to Prolines, Pipecolic Acids, and Bulgecinine

Transition-metal-catalyzed decomposition of α-diazocarbonyl compounds proceeds via electrophilic Fischer-type carbene complexes suppressing the Wolff rearrangement completely. Now NH insertion becomes the dominating process.[118] In the presence of catalytic amounts of dirhodium tetraacetate the carbenoids formed from the diazoketone of HFA-Asp undergo an intramolecular NH insertion to give the HFA-protected 4-oxoproline. Reduction of the 4-oxo group gives HFA-(2*S*,4*S*)-hydroxyproline with 86% de because of the concave shape of the bicyclic system (Scheme 41, i and Scheme 43). Fluorodeoxygenation with DAST

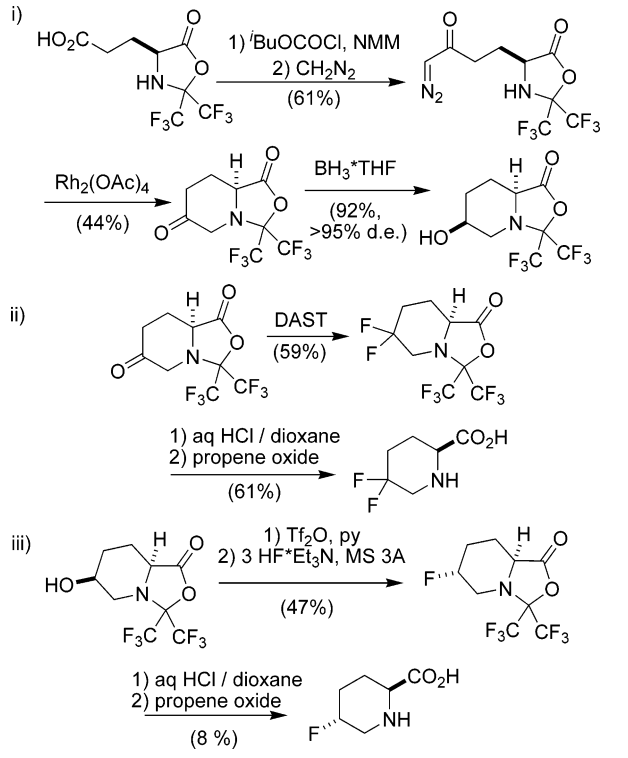
Scheme 41



provides after deprotection (*S*)-4,4-difluoroproline (Scheme 41, ii) and fluorodehydroxylation of 4-hydroxyproline (2*S*,4*R*)-4-fluoroproline (Scheme 41, iii).[119]

By the same strategy, (2*S*)-5-oxopipecolic and (2*S*,5*S*)-5-hydroxy pipecolic acid as well as their 5-fluoro analogues are available starting from HFA(Glu). The diazoketone was obtained from HFA(Glu) by ω-carboxy activation as mixed anhydride (section 4.1) and reaction with an excess of diazomethane. Intramolecular NH insertion is catalyzed by dirhodium tetraacetate. Reduction of the 5-oxo group with BH_3·THF proceeds stereoselectively (de = 95%) to give HFA-(2*S*,5*S*)-5-hydroxy pipecolic acid (Scheme 42, i, and

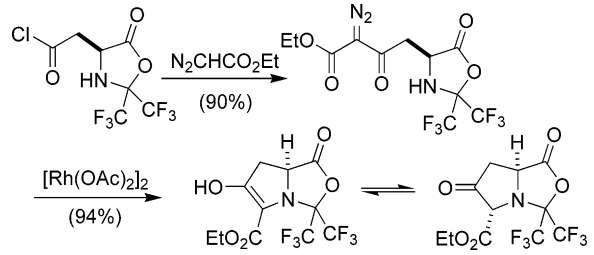
Scheme 42



Scheme 43). Fluorodeoxygenation with DAST provides HFA-(2*S*)-5,5-difluoropipecolic acid (Scheme 42, ii). For HFA-(2*S*,5*R*)-5-fluoropipecolic acid a detour was necessary. Substitution of the triflate-activated hydroxy group by 3HF·NEt_3 gave better yields than the direct fluorination with DAST, but hydrolysis of the HFA group gave the unprotected acid (Scheme 42, iii) in poor yields.[64]

The diazoketone derived from HFA[Asp(Cl)] and ethyl diazoacetate when treated with dirhodium tetraacetate forms a cyclic enol, which tautomerizes during purification to give the ketone. The trans-stereoisomer is formed exclusively.[120,121] The stereoselectivity can be explained by the concave shape of the bicyclic HFA-prolines. Thus, substituents such as the ethyl carboxylate prefer the exo position to avoid steric strain, giving the *trans*-dicarboxylate (Scheme 43). Further ex-

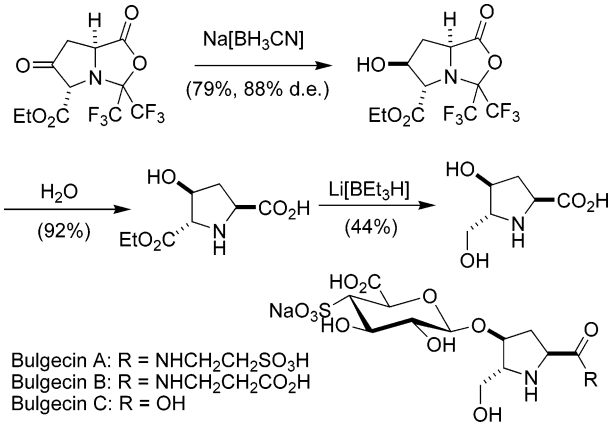
Scheme 43



amples of this kind of stereocontrol are given in sections 7.3, 8.6, and 8.7. This phenomenon has its pendant in Seebach's concept of self-reproduction of chirality.[7]

Reduction of the 4-oxo group with Na[BH_3CN] proceeds stereoselectively because the hydride transfer occurs preferentially from the Re face (de = 88%). Subsequent cleavage of the lactone and reduction of the ethyl carboxylate in the 5-position provides efficient access to bulgecinine [(2*S*,4*S*,5*R*)-4-hydroxy-5-hydroxymethylproline] (Scheme 44).[120,121] Bulge-

Scheme 44



cinine is the aglycone of bulgecines, a class of glycopeptide antibiotics attracting growing interest due to their synergistic effect on the antibacterial activities of β-lactams.[122−124]

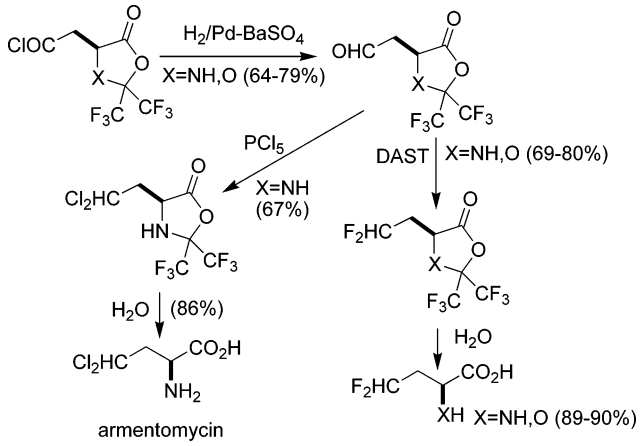
7. Further Site-Selective Transformations of Side-Chain Carboxy Groups

7.1. Rosenmund Reduction: Armentomycin and Fluoro Analogues

Several synthetic routes to the antibiotic (*S*)-armentomycin[125] proceed via aspartic acid β-semialdehyde as key intermediate. The semialdehydes of Asp and Glu are available by site-selective reduction of the corresponding ω-methyl esters with DIBAL[126] or from the ω-acid chloride via

Rosenmund reduction.[127] In both cases protection of the α-amino and the adjacent carboxy group is required. Application of the Rosenmund protocol (H_2, Pd−$BaSO_4$) to HFA[Asp(Cl)] furnishes the corresponding aldehyde. Halogenation of the aldehyde group has been achieved with phosphorus pentachloride to give HFA-armentomycin; on treatment with DAST its difluoroanalogue is formed. Both (*S*) and (*R*) enantiomers have been prepared. Subsequent hydrolysis gave the unprotected amino acids in 26−33% overall yield starting from L- or D-Asp.[128] This protocol was recently applied to construct peptidomimetic inhibitors of the hepatitis C virus.[129] Analogously, HFA-malic acid gives rise to γ,γ-difluoro-α-hydroxybutanoic acid (Scheme 45).[130]

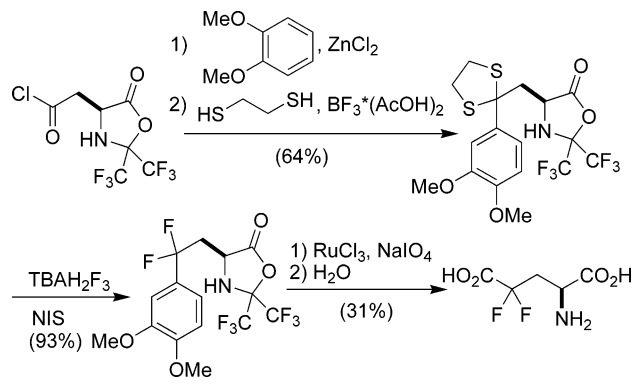
Scheme 45



7.2. Friedel–Crafts Acylation: Aroylalanines, 4,4-Difluoroglutamic Acid

Aroylalanines[131−133] become readily available by Friedel−Crafts reaction of HFA[Asp(Cl)] with aromatic and heteroaromatic compounds in the presence of Lewis acids, such as $ZnCl_2$ and $FeCl_3$ or in special cases $AlCl_3$. This protocol prefers to work with aromatic compounds bearing electron-donor substituents. Heteroaromatics such as furan and thiophene react to give the 2-substituted derivatives. Standard protocols can be applied for derivatization reactions and deprotection.[134] Recently, it was demonstrated that fluorodesoxygenation of carbonyl groups which are part of an aroyl subunit can be achieved under milder conditions with improved yields when the carbonyl group is transformed into a dithioketal before being treated with DAST. By this strategy 4,4-difluoroglutamic acid was synthesized from Friedel−Crafts adducts (Scheme 46).[135]

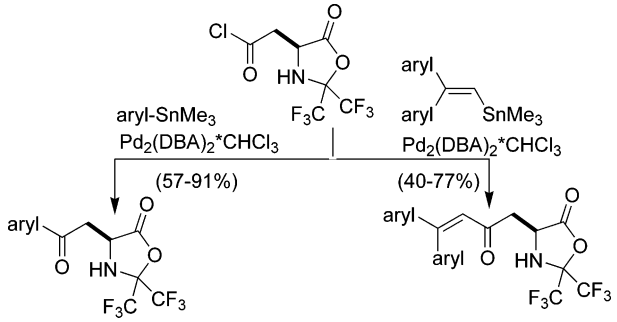
Scheme 46



7.3. Stille Reaction: Aroylalanines and Pipecolic Acids

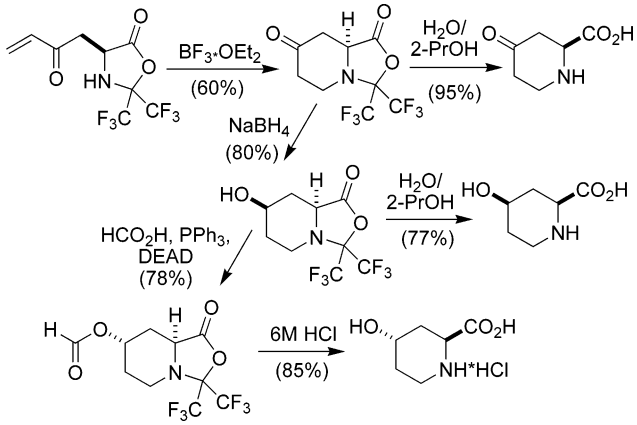
The Stille cross-coupling[136] of HFA[Asp(Cl)] with tributyl tin compounds in the presence of Pd(0) is a preparatively simple alternative approach to γ-oxo-α-amino acids. Furthermore, with tributylstannyl olefines, γ-oxo-α-amino acids with additional CC double bonds in the side chain are accessible (Scheme 47).

Scheme 47



The HFA-γ-oxo amino acids with *CC* double bonds in the side chain in the presence of BF_3·OEt_2 undergo intramolecular Michael addition in refluxing benzene to give the HFA-protected 4-oxo-(*S*)-pipecolic acid. Reduction of the 4-oxo group with $NaBH_4$ in the presence of C_6F_5OH at −30 °C proceeds stereoselectively due to the concave shape of the bicyclic system (section 6.3) to give HFA-*cis*-4-hydroxy-(*S*)-pipecolic acid via exo attack of the hydride. Inversion of the stereochemistry has been achieved via Mitsunobu reaction[137,138] to give the HFA-*trans*-4-hydroxy-(*S*)-pipecolic acid derivative (Scheme 48).[139]

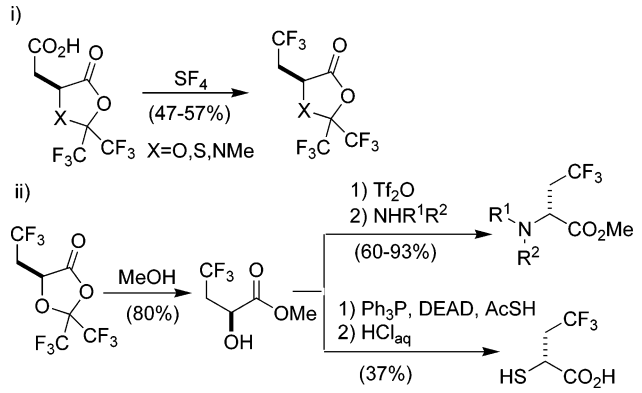
Scheme 48



7.4. ω-Trifluoromethyl-Substituted Compounds via SF_4 Fluorination

Fluorine is a unique tool for modifying profiles of bioactive compounds.[140−143] Transformation of HFA(MeAsp), HFA-malic, and HFA-mercaptosuccinic acids into the corresponding ω,ω,ω-trifluoro compounds can be readily accomplished by treatment with sulfur tetrafluoride in an autoclave (Scheme 49, i). However, when HFA(Asp) and HFA(Glu) were subjected to SF_4 fluorination, yields were low because of intramolecular side reactions (section 4.1). ω,ω,ω-Trifluoro-substituted α-amino and N^{α}-methyl amino acids have been obtained from the ω,ω,ω-trifluoro-α-hydroxy acid ester via its triflate on nucleophilic substitution

Scheme 49

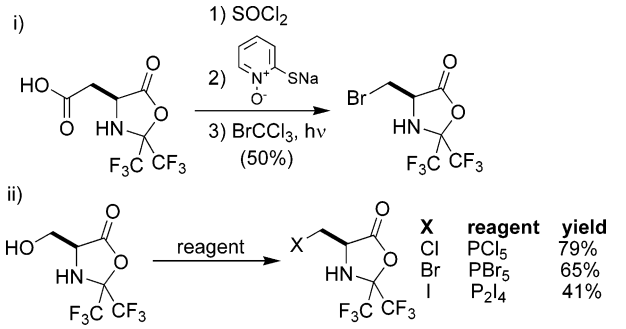


with benzylamine and benzylmethylamine and consecutive hydrogenolytic debenzylation.[144] Alternatively, homochiral 4,4,4-trifluoro-2-mercaptobutanoate was obtained from the corresponding hydroxy acid via Mitsunobu reaction (Scheme 49, ii).[145]

7.5. Miscellaneous: Bromoalanine Analogues, (*S*)-γ-Oxoornithine, Dihydroorotic Acid

Hunsdiecker reaction was employed for the transformation of HFA(Asp) into a HFA bromoalanine derivative.[146] It represents an alanine equivalent capable for radical reactions (Scheme 50, i, and section 9.2). Alternatively, this compound

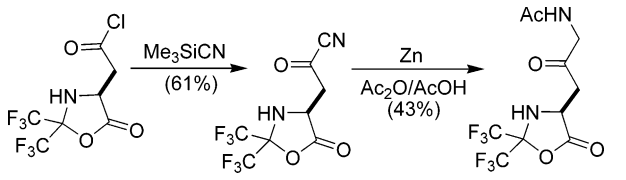
Scheme 50



can be obtained from HFA-Ser by treatment with PBr_5.[147] The chloro derivative was obtained with PCl_5[148] and the iodo compound with P_2I_4[147] (Scheme 50, ii).

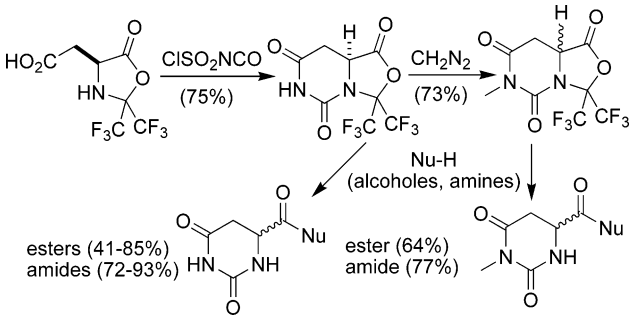
Reaction of HFA[Asp(Cl)] with trimethylsilylcyanide and subsequent reduction of the cyano group with zinc in a [1:1] mixture of acetic acid/acetic anhydride provides the HFA-protected 5-acetylamino-4-oxonorvaline derivative (Scheme 51).[139]

Scheme 51



Dihydroorotic acid plays an important role in the biosynthesis of pyrimidines. Certain small peptides having dihydroorotic acid in the *N*-terminal position are CNS active.[149] Using HFA as protecting and activating reagent, carboxy-activated dihydroorotic acid was obtained in a preparatively simple procedure by heating HFA(Asp) with an excess of chlorosulfonyl isocyanate in toluene. *N*-Methylation can be achieved on treatment with diazomethane, but racemization was observed during *N*-methylation. Several esters and amides of dihydroorotic acid have been prepared (Scheme 52).[150]

Scheme 52



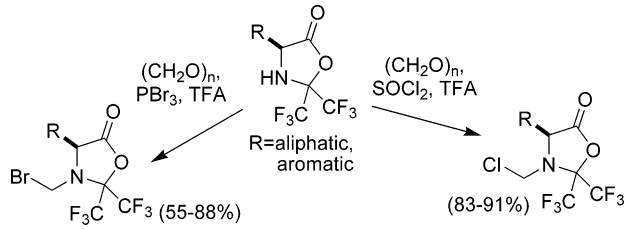
8. Transformations of HFA-Amino Acids Including the NH Function

Bis(trifluoromethyl)-substituted oxazolidinones are sensitive toward bases because deprotonation of the NH function initiates a fragmentation process (Scheme 8). Therefore, base-catalyzed substitution reactions involving a NH deprotonation step are ruled out. However, the NH function of HFA-protected amino acids reacts readily with various electrophiles. Intramolecular ring closures with Fischer's carbene complexes (NH insertion) (section 6.3), intramolecular Michael additions (section 7.3), as well as pyrimidine syntheses on addition of sulfonyl isocyanate have been described (section 7.5). Formaldehyde as a strong electrophile is capable of reacting with the NH function of HFA-amino acids in acidic media. Synthetic applications of this reaction are described in the following section.

8.1. *N*-Halomethylation of HFA-Protected Amino Acids

HFA-amino acids, paraformaldehyde, and thionyl chloride undergo a three-component reaction to give *N*-chloromethyl HFA-amino acids.[151] When phosphorus tribromide is used instead of thionyl chloride, the corresponding *N*-bromomethyl compounds are obtained.[152] The *N*-halomethyl-HFA-amino acid derivatives (Scheme 53) represent versatile educts for

Scheme 53



the synthesis of various types of N^{α}-substituted amino acids (section 8.2−8.7). In the literature very few *N*-halomethyl compounds, like *N*-chloromethylglycine[153] and *N*-chloromethyl pyroglutamic acid esters,[154] are described.

8.2. One-Pot Synthesis of N^{α}-Methyl Amino Acids

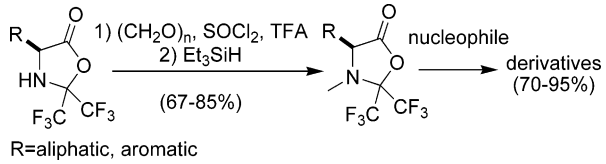
Many cyclic peptides[1] and depsipeptides[2] with highly interesting therapeutic profiles comprise N^{α}-methylamino acids. Consequently, a number of synthetic routes to homo-

chiral N^{α}-methylamino acids have been developed.[155] The HFA route offers a new preparatively simple approach to N^{α}-methylamino acids and their derivatives. The *N*-halomethylation (vide supra) can be combined with a consecutive reductive dehalogenation step with triethylsilane/TFA, resulting in an elegant one-pot *N*-methylation procedure. Via this route, HFA-N^{α}-methylamino acids with simple aliphatic and aromatic side chains and their derivatives are accessible in high yields.[151]

8.3. ω-Carboxy-N^{α}-Methylamino Acids

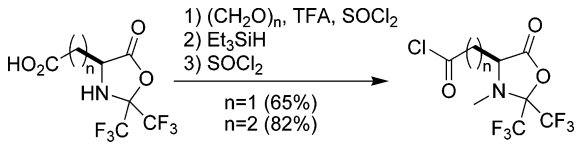
Most *N*-methylation protocols are not suitable for the synthesis *N*-MeAsp and homologues.[155] Recently, a general *N*-methylation protocol via cyclization of *N*-Z amino acids with formaldehyde to give oxazolidinones and subsequent reduction has been described. However, protection of side-chain functionalities is required.[156]

Scheme 54



The new HFA-based *N*-methylation strategy (section 8.2) can also be applied to ω-carboxy-α-amino acids. HFA(Asp), HFA(Glu), and HFA(Aad) react with paraformaldehyde and thionyl chloride in the presence of TFA to give the *N*-chloromethyl derivatives, which were converted into the *N*-methylamino acid derivatives on treatment with triethylsilane/TFA. TFA prevents lactam formation in the case of Glu (section 4.1). Alternatively, dry HCl gas can be used.[157] Subsequent reduction with triethylsilane/TFA and treatment with thionyl chloride yields HFA[MeAsp(Cl)] and HFA-[MeGlu(Cl)], which can be purified by distillation (Scheme 55).[114] Homologation of HFA[MeGlu(Cl)] provides HFA-

Scheme 55



(MeAad) (section 4.5; for further reactions, see sections 5.2 and 6.2).

8.4. N^{α}-Ethylamino Acids

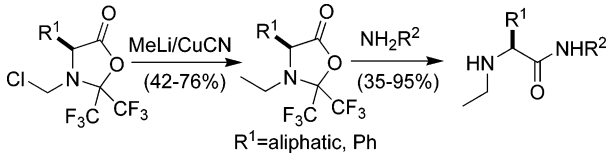
In comparison to *N*-methyl amino acids, less information exists about *N*-ethyl amino acids.[158] Substitution of *N*-methyl leucine of cyclosporin A by various *N*-ethyl amino acids was performed with the aim of blocking the main metabolic degradation pathway.[159]

Systematic investigations on the applicability of *N*-chloromethyl HFA-amino acids for nucleophilic displacement reactions with hetero and carbon nucleophiles revealed that *N*-ethylation can be achieved smoothly by reaction with a cuprate prepared from copper(I) cyanide and one equivalent of methyllithium.[160] A series of *N*-ethylamino acid amides and hydroxamates has been synthesized by nucleophilic ring opening (Scheme 56).

8.5. *N*-Phosphinoylmethylamino Acids

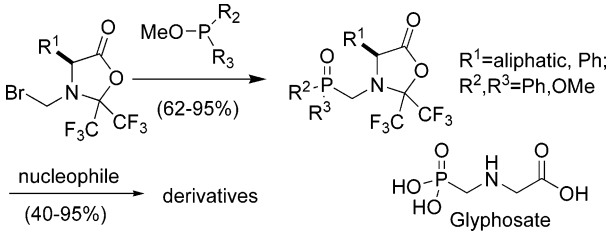
N-Phosphorylated peptides are naturally occurring species. However, the biological half-life is short because of the

Scheme 56



lability of the phosphorus−nitrogen bond. A methylene spacer between phosphorus and nitrogen was introduced to overcome this drawback.[161] *N*-Phosphonomethyl glycine (glyphosate) belongs to the most widely used herbicides today.[162] The *N*-halomethyl compounds (section 8.1) offer simple access to related compounds via Michaelis−Arbusov reaction with P(III) species. While *N*-bromomethyl and *N*-iodomethyl derivatives react exothermally within minutes, the *N*-chloromethyl compounds needed several days at room temperature until the reaction was complete. The resulting HFA-*N*-phosphonomethyl amino acids can be directly derivatized to give *N*-phosphono methyl amino acid amides, peptides, depsipeptides, and azapeptides (Scheme 57).[152,163]

Scheme 57

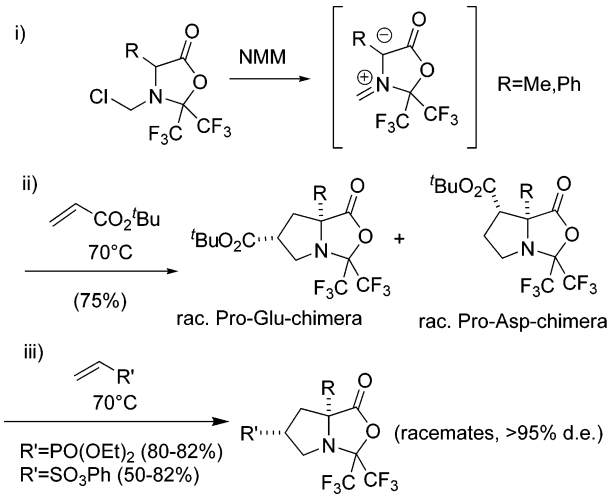


8.6. Conformationally Restricted Chimeric Amino Acids

Conformationally restricted α-amino acids have gained significant attention during recent years because they are valuable tools for studying the spatial requirements for receptor affinity and biological activity of natural amino acids. In this context, proline analogues possessing the characteristics of other amino acids (chimeras) are of current interest. Replacement of natural amino acids in bioactive peptides by proline amino acid chimeras has led, at least in some cases, to better understanding of their bioactive conformation.[164,165] Among the many routes developed for the synthesis of prolines and its derivatives, the [3 + 2] cycloaddition concept is the most flexible one.[166]

On treatment with bases, like *tert*-amines, HFA-*N*-chloromethyl amino acids are transformed into azomethine ylides (Scheme 58, i), which can be trapped in situ by a variety of dipolarophiles to give proline derivatives. This strategy can be used for generation of prolines with highly variable substituent patterns. The reaction proceeds via a concave transition state. Sterically demanding groups preferentially occupy exo positions; therefore, the relative stereochemistry can be controlled (section 6.3). However, the products obtained are racemates. This protocol was applied for the synthesis of conformationally restricted glutamic acid as well as the phosphorus and sulfur analogues. Reaction with *tert*-butyl acrylate yields two regioisomers in a 2:1 ratio. The cycloadducts represent Pro-Glu and Pro-Asp chimeras, respectively (Scheme 58, ii). In contrast, diethyl vinylphosphonate and phenyl vinylsulfonate on reaction with azomethine ylides provide the [3 + 2] cycloadducts regio- and stereospecifically. The sulfur-containing proline derivative mimics a conformationally rigid taurine (Scheme 58, iii).[47]

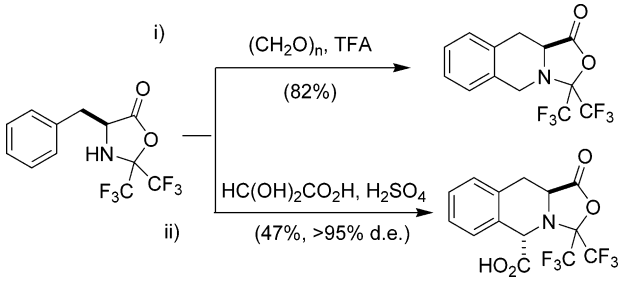
Scheme 58



8.7. Asymmetric Pictet–Spengler Reaction: Tic Chimeras

1,2,3,4-Tetrahydroisoquinoline-3-carboxylate (Tic-3) has been applied in many instances as a replacement for phenylalanine for the design of topographically constrained peptides to study effector/receptor interactions.[167] HFA-Phe and paraformaldehyde undergo a Pictet−Spengler reaction in TFA/$CHCl_3$ to give HFA-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (HFA-Tic-3, Scheme 59, i). The scope of the

Scheme 59



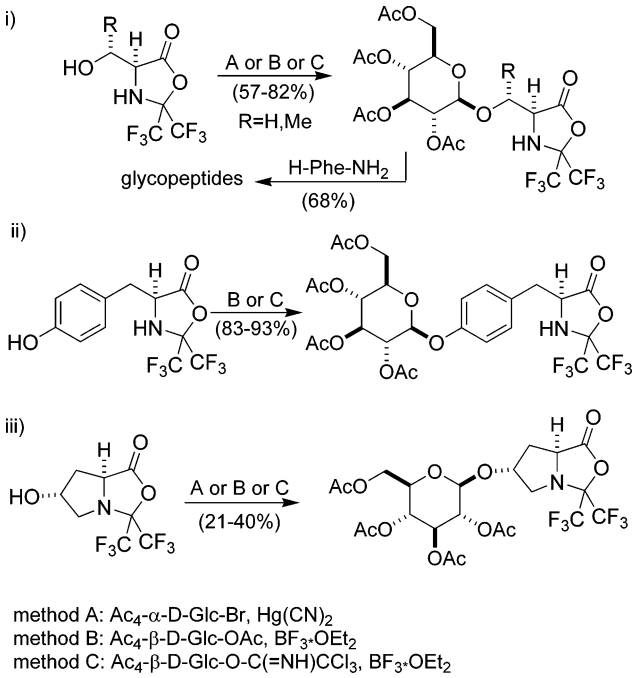
Pictet−Spengler reaction using HFA-Phe was found to be limited, but interestingly, glyoxylic acid hydrate in the presence of concentrated sulfuric acid provides enantiomerically pure (1*S*,3*S*)-1,2,3,4-tetrahydroisoquinoline-1,3-dicarboxylate (Tic-1,3). The relative configuration was determined by X-ray structure analysis. Both carboxy groups are placed trans with respect to the bicyclic system. On the basis of the known configuration of *C*-3, the (*S*)-configuration was assigned to the newly formed stereocenter at *C*-1 (Scheme 59, ii).[168]

9. Further Site-Selective Transformations

9.1. *O*-Glycosylation of HFA-Protected Ser, Thr, Tyr, and 4-OH–Pro

O-Glycosylation of Ser and Thr besides *N*-glycosylation of Asn provide the most common connecting motifs for amino acids and carbohydrates found in nature.[169] HFA(Ser), HFA(Thr), HFA(Tyr), and HFA(4-HO−Pro) (section 2.1) can be efficiently *O*-glycosylated with β-D-glycopyranosyl trichloroacetimidates.[170] The yields are good (Scheme 60, i,ii), except for HFA-hydroxyproline (section 6.3, Scheme

Scheme 60

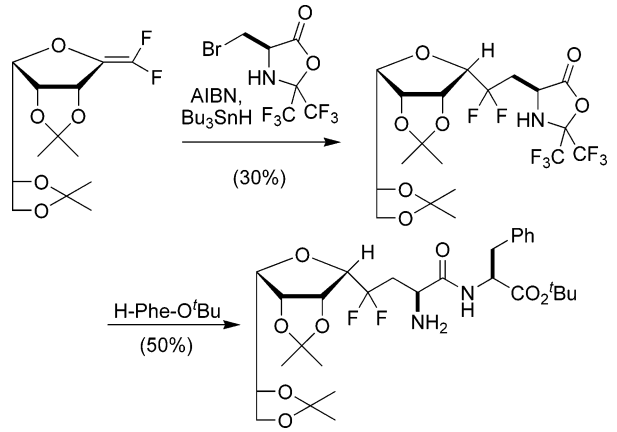


60, iii). The *O*-glycosylated HFA building blocks have been used as activated esters for glycopeptide synthesis (Scheme 60, i).[171,172]

9.2. *C*-Glycosylated Amino Acids

With the aim of overcoming enzymatic deglycosylation of glycoconjugates, the exocyclic anomeric oxygen atom in serine-based glycopeptides was replaced by a difluoromethylene group. The *gem* difluoro enol ether was linked to HFA-protected bromo alanine (section 7.5) by a radical reaction under tributyl stannane-mediated conditions to give the *C*-glycosylated HFA-amino acid, already activated for incorporation into peptides (Scheme 61). The HFA route gave better yields than the standard Boc protocol.[146]

Scheme 61

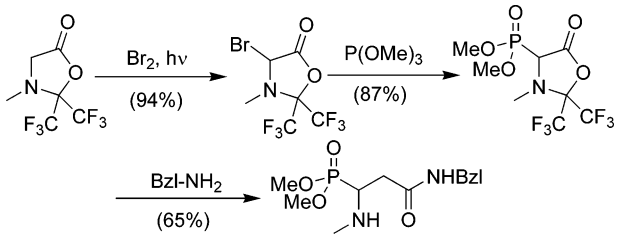


9.3. Phosphonyl Sarcosine Derivatives

HFA-*N*-methyl glycine (HFA-sarcosine) is prone to radical substitution reactions at C-4 because this carbon atom is flanked by capto-dative substituents.[173] Photochemical bromination in the presence of one equivalent bromine using a mercury high-pressure lamp results in formation of a mixture of the monobrominated, dibrominated, and *N*-bromomethyl

compounds. However, with a "Schwarzlichtlampe", the 4-bromo compound was formed exclusively in excellent yield. The C(4)−Br reacts with various P(III) species and offers preparatively simple access to phosphono, phosphino, and phosphinyl sarcosine derivatives, which as carboxy-activated species are suitable for various derivatization reactions (Scheme 62).[174] Many natural and synthetic ami-

Scheme 62

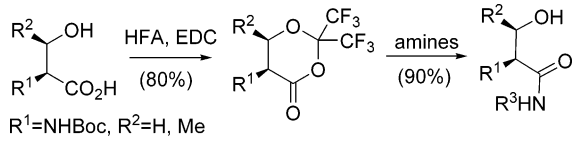


nophosphonic acids exhibit antibacterial, anticancer, and antiviral properties as well as pesticidal, insecticidal, and herbicidal activities.[175,176] However, in comparison to α-alkylamino phosphonic and α-aminophosphinic acid, the chemistry of the *N*-methyl analogues is far less investigated.[177]

10. Outlook

Application of HFA as a bidentate protecting and activating reagent to compounds such as Asp, malic, citramalic, and thiomalic acids and homologues as well as iminodiacetic acid allows efficient site-selective mono-, di-, and trifunctionalization, saving steps compared to conventional methodologies. However, we are convinced that a good part of the potential of this reagent still remains to be discovered. For example, during the preparation of this manuscript we found an extension of the hexafluoroacetone strategy to *β*-hydroxy acids. By reaction of *β*-hydroxy acids with HFA in the presence of carbodiimides, six-membered lactones [2,2-bis(trifluoromethyl)-1,3-dioxan-4-ones] are obtained in good yields. For the Ser and Thr derivatives it was demonstrated that reaction with amines at room temperature gives the corresponding amides (Scheme 63). Investigations

Scheme 63



on further applications of this new protocol are in progress.[178]

11. Abbreviations

General: Proteinogenic amino acids are abbreviated with the three-letter codes (Xaa), and for their derivatives, common presentation like H-Phe-OMe for methyl phenylalaninate is used. Abbreviations used for nonproteinogenic amino acids are listed alphabetically below. Hexafluoroacetone is abbreviated with HFA. HFA-amino acids are 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones, HFA-hydroxy acids are 2,2-bis(trifluoromethyl)-1,3-dioxolan-4-ones, HFA-mercapto acid are 2,2-bis(trifluoromethyl)-1,3-oxathiolan-4-ones. Within this review, abbreviations combining HFA and the three-letter coded amino acids are used. HFA(Xaa) means a HFA-α-amino-protected/1-carboxy-activated amino acid Xaa. The use of parentheses is logical because HFA is bound to the *N*- as well to the *C*-terminus of an amino acid. Thus, HFA(Asp) means HFA-α-amino-protected/1-carboxy-activated aspartic acid with unprotected side-chain carboxy group. Consequently, HFA[Asp(Cl)] means HFA-α-amino-protected/1-carboxy-activated aspartic acid with side-chain carboxy chloride and HFA[Cys(Trt)] means HFA-α-amino-protected/1-carboxy-activated cysteine with side-chain SH protected with the trityl group.

Abbreviations

Aad	2-aminoadipic acid
Ac	acetyl
Aib	α-aminoisobutyric acid
AIBN	azobisisobutyronitrile
Api	2-aminopimelinic acid
Boc	*tert*-butyloxycarbonyl
^{t}Bu	*tert*-butyl
Bzl	benzyl
cat.	catalytic
CNS	central nervous system
Dap	2,3-diamino propionic acid
DAST	diethylamino sulfurtrifluoride
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIBAL	diisobutyl aluminum hydride
DIEA	diisopropyl ethylamine
DKP	diketopiperazine
DMAP	4-(dimethylamino)pyridine
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
DNA	desoxyribonucleic acid
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
gem	geminal
HON	5-hydroxy-4-oxo-L-norvaline
HPLC	high-performance liquid chromatography
Ida	iminodiacetic acid
Me	methyl
NEM	*N*-ethyl morpholine
NCA	*N*-carboxyanhydrides
NIS	*N*-iodosuccinimide
NMM	*N*-methyl morpholine
NMR	nuclear magnetic resonance
4-OH-Pro	4-hydroxy proline
PEGA	poly(ethylene glycol)-dimethylacrylamide copolymer
PET	positron emission tomography
pGlu	pyroglutamic acid
PG	protecting group
Ph	phenyl
Phg	phenylglycine
Pr	propyl
rac	racemic
RGD	amino acid sequence Arg-Gly-Asp
SPPS	solid-phase peptide synthesis
TBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
Tf_2O	trifluoromethane sulfonic acid anhydride
THF	tetrahydrofuran
Tic	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
Trt	tripenylmethyl (trityl)
UNCA	*N*-urethane-protected *N*-carboxyanhydrides
Z	benzyloxycarbonyl

12. Acknowledgments

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University Munich. Their names can be taken from relevant references. For financial support we thank the Deutsche Forschungsgemeinschaft, Stiftung Volkswagenwerk, Herrmann-Schlosser Stiftung, and European Union. Special thanks to Prof. Dr. G. Siegemund, Hoechst AG, Frankfurt, who supported us with hexafluoroacetone.

13. References

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