Synthetic strategies to α-trifluoromethyl and α-difluoromethyl substituted α-amino acids†

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The combination of the unique physical and chemical properties of fluorine with proteinogenic amino acids represents a new approach to the design of biologically active compounds including peptides with improved pharmacological parameters. Therefore, the development of routine synthetic methods which enable the effective and selective introduction of fluorine into the desired amino acids from readily available starting materials is of significant synthetic importance. The scope of this *critical review* is to summarize the most frequently employed strategies for the synthesis of α-difluoromethyl and α-trifluoromethyl substituted α-amino acids (114 references).

1. Introduction

The crucial role of amino acids and peptides in biological functions is well established. While direct applications of modified amino acid derivatives as drugs are known, applications of native peptides as therapeutic agents are limited, mainly because of their proteolytic and conformational instability.[1] An improvement of the therapeutic profile can be achieved by replacement of certain proteinogenic amino acids in strategic positions by tailor-made building blocks,[2,3] for example, by incorporation of fluorinated amino acids.

C^{α}-trifluoromethyl (αTfm) and C^{α}-difluoromethyl (αDfm) amino acids represent a special class of α-amino acids. α,α-Dialkylation leads to the stabilization of certain secondary structure motifs while fluorination brings in its unique properties, such as high electronegativity, high lipophilicity, and a steric demand that non-linearly increases with the number of fluorine atoms. Incorporation of C^{α}-fluoroalkyl amino acids into peptides can retard proteolytic degradation[4,5] and enhance *in vivo* absorption as well as drug permeability through certain body barriers.[6] Stabilization of secondary structure motifs was also observed.[7] A further advantage of fluoromodification is the enhancement of thermal stability of peptides.[8] However, the fluorine effect depends very much on the position of the fluoroalkyl-substituent in a peptide.[9] For example, a trifluoromethyl group bound to aromatic systems undergoes hydrolysis only in strong acid media at elevated temperatures. In contrast,

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Cosimo Damiano Cadicamo was born in Italy in 1974. After receiving a degree in Chimica e Tecnologie Farmaceutiche at the University of Rome "La Sapienza", he moved to St. Andrews in Scotland in 2002 where he obtained a Ph.D. in chemistry under the supervision of Professor David O'Hagan. In 2006 he joined the research group of Professor Beate Koksch at the Free University of Berlin, where he is currently working on the design and synthesis of peptide inhibitors of Candida albicans secreted aspartic proteases.

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 postdoctoral (1967–1968) at UMSIST, England (Professor R. N. Haszeldine). He returned to the Organic Department of TU Munich, where he started his own research. 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.

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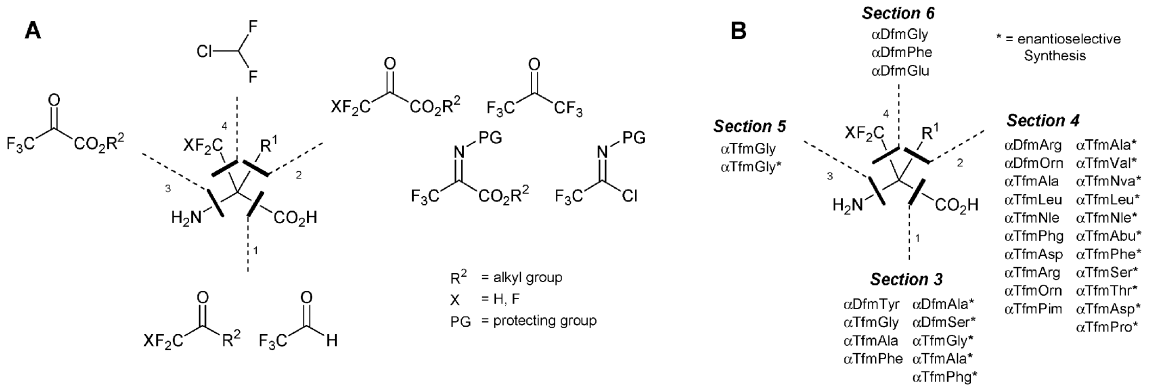


Fig. 1 Retrosynthetic approach to fluorinated amino acids: (A) fluorinated building blocks and (B) examples for αDfm and αTfm amino acids presented in this review.

a trifluoromethyl group attached to carbon atoms possessing acidic hydrogen atoms like 3,3,3-trifluoroalanine is unstable in basic media. Above pH 7.0 the trifluoromethyl group is degraded to give the corresponding carboxylate.[10,11] Incorporation of trifluoromethyl groups generally increases the chemical stability of molecules due to the high bond strength. This phenomenon is unique among halogens.[12] For example, the CC-bond in 1,1,1-trifluoroethane or hexafluoroethane is 59 and 42 kJ more stable than in ethane, respectively.[13,14]

Many important structural questions concerning protein folding[15,16] cannot be addressed using X-ray crystallography and, therefore, have to be solved by NMR spectroscopy. The chemical shifts of the ^{19}F nucleus are extremely sensitive to the environment. The ^{19}F nucleus can be observed with high precision as it is 83% as sensitive as the proton, occurs in 100% abundance, and no background fluorine signals are observed from natural peptides and proteins. Thus, ^{19}F-NMR spectroscopy represents an efficient tool for conformational studies of fluorine-containing peptides as well as for elucidation of metabolic processes.[17–19]

As a result of the exceptionally interesting chemical and biological properties of fluorinated amino acids, much work has been done on their synthesis during the last decades. Several reviews have been published that summarize synthetic methodologies to a broad variety of fluorine containing amino acids.[20–26] The scope of this review is to give an overview on the synthetic repertoire available for the construction of αTfm and αDfm substituted amino acids.

2. Strategies and building blocks for the synthesis of αDfm and αTfm amino acids

There are two fundamentally different strategies to introduce fluoroalkyl groups into organic molecules: (1) direct fluorination and (2) introduction of fluorine *via* fluorine-containing building blocks.[27,28] Although the first approach is more straightforward, provided that suitable fluorinating agents are available, control of regio- and stereoselectivity is often difficult to achieve. Due to the high reactivity of most of the fluorinating agents, many functional groups already present in the molecule may be affected in an undesired way. Therefore, they have to be appropriately protected. Furthermore, many of the reagents currently used for direct introduction of fluorine and perfluoroalkyl groups are expensive, toxic, corrosive, and sometimes explosive. Consequently, the building block strategy represents an attractive alternative concept for the introduction of fluorine and perfluoroalkyl groups into organic molecules.[27]

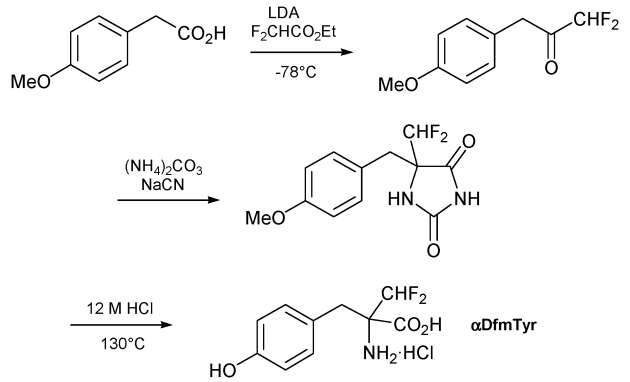
Fig. 1A summarizes the most commonly used, commercially available, fluorinated building blocks that can be applied for the synthesis of α-fluorinated amino acids. Each retrosynthetic disconnection demonstrates the introduction of the missing substituent and is linked to the starting materials that are used for this transformation. The most straightforward approach to αTfm amino acids uses highly functionalized imines of trifluoro pyruvates, delivering structurally diverse target compounds in a few steps. Unfortunately, analogous building blocks are not available for the Dfm series and therefore have to be synthesized from the corresponding difluoromethyl starting materials. Fig. 1B gives an overview about the various αDfm and αTfm amino acids whose synthesis is described in this review. Each route will be discussed in a separate section of this review. For didactic reasons, the introduction of the hydrogen-substituent (R = H) will be presented in sections 3 and 5.

3. αDfm and αTfm amino acids *via* introduction of the carboxylic functionality

3.1 αTfm and αDfm amino acids *via* racemic Strecker-type reactions

The Strecker reaction[29] is one of the most versatile methods for preparing α-amino acids. According to this route, aldehydes and ketones react with cyanide in the presence of an amine hydrochloride to form an α-aminonitrile that is subsequently hydrolyzed to give the desired α-amino acid. The reaction of cyanide with αTfm-ketones, however, generates highly stable trifluoromethyl substituted cyanohydrin intermediates that provide low yields of the expected nitrile derivatives.[30–33] For this reason, the classical Strecker reaction has found limited application for the synthesis of α-fluoroalkyl-α-amino acids.

Nevertheless, modifications of this methodology constitute preparatively valuable approaches for the synthesis of the aforementioned compounds. The Bucherer–Bergs



Scheme 1 Synthesis of αDfmTyr using the Bucherer–Bergs modification.

modification, using potassium or sodium cyanide and ammonium carbonate, generates fluoroalkyl substituted hydantoins, which deliver the corresponding α-fluoroalkyl-α-amino acids after hydrolysis. Some examples are the synthesis of αDfmTyr (Scheme 1), αTfmAla and αTfmPhe.[34–36]

The amines and imines derived from fluoral[37] or fluoroalkyl ketones, shown in Fig. 2, are valuable synthons for Strecker-type additions. The addition of cyanide nucleophiles to compounds **2–4** is normally carried out under Lewis acid activation. An iminium intermediate is formed by the action of the promoter that then reacts with the cyanide to give the corresponding nitrile derivative.[38–40] The CN double bond of imines **1** is activated for nucleophilic addition by the electron-withdrawing CF_2X-group. Therefore, the cyanation reaction occurs typically without the need of additives, especially when the imines **1** bear *N*-activating groups.

Weygand and Steglich reported the first synthesis of an αTfm substituted amino acid, 3,3,3-trifluoroalanine (αTfmGly).[41–43] Highly electrophilic *N*-acyl trifluoroacetaldimines obtained from trifluoroacetaldehyde and carboxamides upon elimination of water react *via* hydrocyanation to form αTfmGly hydrochloride after hydrolysis (Scheme 2).[44]

N-Acylimines of fluoral exhibit a pronounced tendency to polymerize, especially at elevated temperatures, while *N*-acyl-1-chloro-2,2,2-trifluoromethyl amines are relatively stable crystalline compounds. Therefore, the use of the *in situ* technique for the generation of fluoral *N*-acylimines is an advantageous approach.[45]

3.2 αTfm and αDfm amino acids *via* asymmetric reactions

Stereoselective construction of the stereogenic quaternary center of fluorinated amino acids is a challenge in organo-

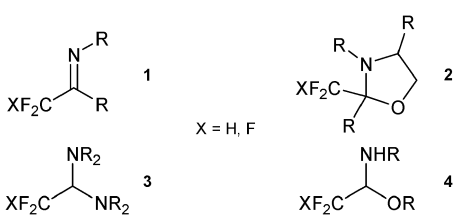
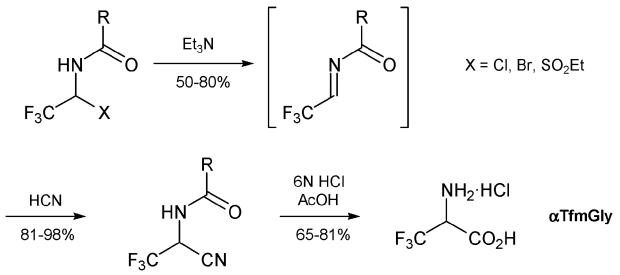


Fig. 2 Synthons used to generate αTfm and αDfm amino acids *via* Strecker-type reactions: imines **1**, oxazolidines **2**, aminals **3**, *N*,*O*-acetals **4**.

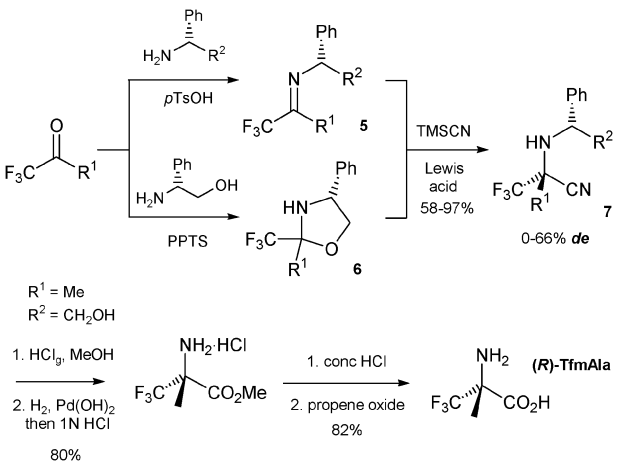


Scheme 2 Synthesis of αTfmGly *via* *N*-acyl trifluoroacetaldimines.

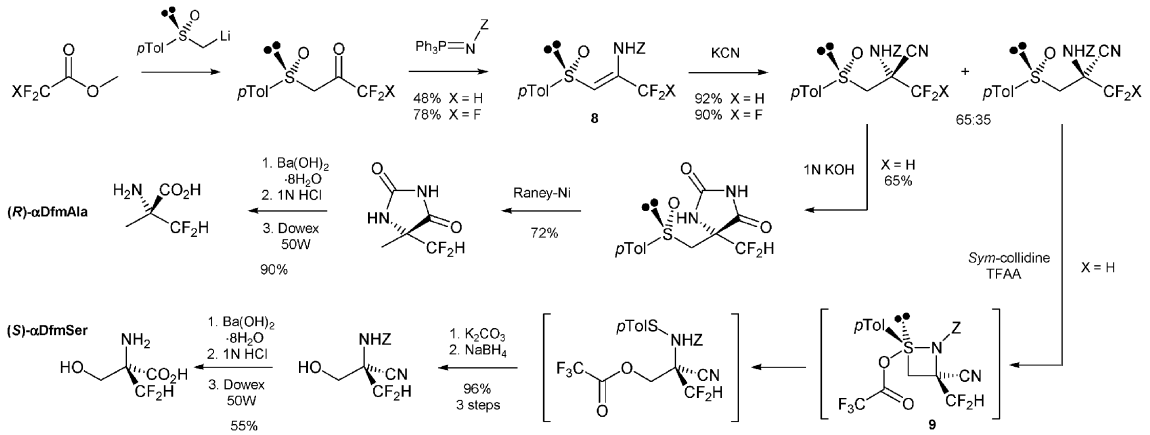
fluorine chemistry. The existing synthetic approaches for an enantioselective introduction of the carboxylic function use chiral auxiliaries or optically active starting materials. The stereoselective version of the Strecker reaction has been widely employed for the preparation of enantiomerically enriched α-amino acids.[46–49] However, this reaction has been scarcely applied to fluorinated amino acids.

Brigaud and co-workers investigated the asymmetric Strecker-type reaction of chiral imines **5** and oxazolidines **6** with trimethylsilyl (TMS) cyanide and a series of Lewis acids (Scheme 3).[40,50] These intermediates were prepared from fluoral hemiacetal or αTfm ketones and (*S*)-α-methylbenzylamine or (*R*)-phenylglycinol and derivatives. The chiral auxiliaries are readily available and easily removable to give the free fluoroalkyl amino acids. The synthons afforded the desired amino nitriles **7** generally in high yield, although the diastereoselection proved to be low to moderate. An enhanced diastereoselectivity was observed for the conversion of oxazolidines **6**. In this case, best results were obtained in the presence of catalytic amounts of TMSOTf or 1.5 equivalents of $BF_3{\cdot}OEt_2$. The products derived from this Strecker-type reaction were easily separated by flash chromatography. Afterwards, the major diastereoisomer was conveniently converted into the corresponding αTfm amino acid. This methodology proved to be effective for the enantioselective synthesis of αTfmGly[40] and αTfmAla.[50]

Chiral sulfoxides are also suitable auxiliaries that can be used for the preparation of optically pure α-fluoroalkyl-α-amino acids. Zanda and co-workers reported that



Scheme 3 Synthesis of αTfmAla using (*R*)-phenylglycinol as a chiral auxiliary.

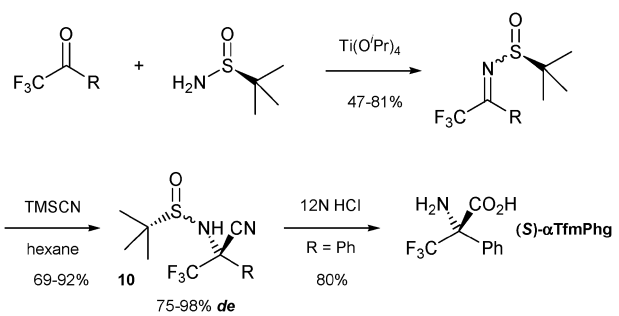


Scheme 4 Enantioselective synthesis of αDfm amino acids using chiral sulfoxides.

α-(fluoroalkyl)-β-sulfinylenamines **8**, readily prepared from α-fluorinated-α′-sulfinyl ketones[51] *via* Staudinger (aza-Wittig) reaction with triphenyliminophosphoranes, are valuable templates for the asymmetric Strecker reaction.[52,53] The simultaneous presence of the α-fluoroalkyl substituent and the β-sulfinyl group render the carbon C-2 highly reactive towards nucleophiles. The hydrocyanation of such sulfinylenamines can be achieved in high yields, affording the *syn*-product as the major diastereoisomer (Scheme 4). Although diastereoselectivity was rather low, pure amino nitriles were obtained after chromatographic separation, and subsequently used as precursors for the synthesis of enantiopure α-fluoroalkyl-α-amino acids.

The removal of the chiral auxiliary sulfinyl group was achieved by reductive desulfurization, as reported for the preparation of αDfmAla. Alternatively, this group could be replaced by an oxygen atom under Pummerer rearrangement conditions, which afforded eventually αDfmSer. Interestingly, the latter process occurred *via* an unusual nonoxidative Pummerer rearrangement, probably involving the formation of the four membered ring σ-sulforane **9**.[54]

An example of an asymmetric Strecker reaction involving chiral sulfinimines derived from α-trifluoromethyl ketones and (*R*)-*tert*-butylsulfinamide was recently reported by Lu *et al.*[55] These authors investigated the reaction of αTfm-sulfinimines with TMS cyanide, in the absence of catalysts (Scheme 5). The diastereoselection and the yield of this reaction were extremely dependent on the solvent used. Best results were obtained in hexane, furnishing stereoisomer **10** in 98% de. Polar solvents generally resulted in a decrease of the major diastereomer **10**.



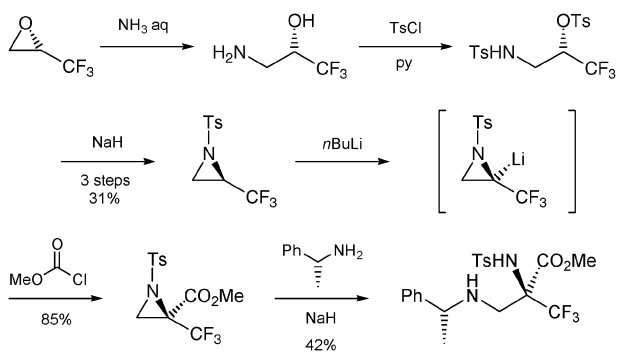
Scheme 5 Synthesis of αTfmPhg *via* chiral sulfinimines.

Interestingly, the diastereoselective outcome using DMF as the solvent was opposite to that encountered in hexane. The generated sulfinamides can be hydrolyzed with HCl to afford optically active αTfm-α-amino acids as demonstrated for the synthesis of αTfm-phenylglycine (αTfmPhg).

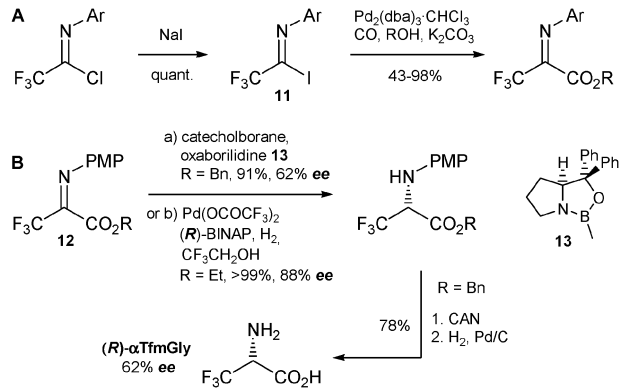
3.3 αTfm and αDfm amino acids *via* alkoxycarbonylation reactions

The alkoxycarbonylation of an opportune enantiomerically pure fluorinated synthon represents another valuable method for introducing the carboxyl functionality in a stereoselective manner. In this context, Uneyama reported a new approach to enantiopure αTfm-α-amino acids, which involves the use of optically pure α-trifluoromethylated aziridines as intermediates.[56,57] These compounds can be prepared starting from optically pure 2,3-epoxy-1,1,1-trifluoropropane. Regioselective deprotonation at the chiral carbon of the *N*-protected aziridines generates a racemization-stable aziridinyl anion. Therefore, these anions can be trapped with ethyl chloroformate or other electrophiles to afford enantiomerically pure alkoxycarbonylation products. The strained addition products exhibit a high reactivity towards ring-opening reactions with nucleophiles and can be used for the preparation of quaternary chiral α-trifluoromethylated amino acid derivatives (Scheme 6).

Another straightforward method to introduce the carbonyl functionality into fluorinated amino acid precursors was published by the same group.[58] A series of *N*-aryl substituted



Scheme 6 Stereoselective synthesis of αTfm amino acid derivatives *via* aziridines.



Scheme 7 **A** Alkoxycarbonylation and **B** stereoselective reduction to αTfmGly.

trifluoroacetoimidoyl iodides were synthesized and used as templates for a palladium-catalyzed alkoxycarbonylation reaction (Scheme 7A). After palladation of the carbon–iodide bond, the formed intermediate was trapped by an alcohol to generate an α-imino trifluoropyruvate derivative.

The rate and the yield of the reaction were affected by the nature of the *N*-aryl group and the alcohol. *N*-Electron-donating substituents such as *p*-methoxyphenyl (PMP) and the use of primary alcohols proved to promote the conversion. Tertiary and secondary alcohols are not good trapping reagents due to their steric hindrance. In a modification of this transformation,[59] the use of DMF or 1,3-dimethyl-2-imidazolidinone as an additive remarkably promoted the *tert*-butoxycarbonylation of **11**, which is of clear advantage due to the mild way this group can be removed in comparison with other alkyl esters.

The α-imino esters derived from this reaction were stereoselectively reduced with chiral agents to afford enantiomerically enriched αTfmGly after removal of the protecting groups (Scheme 7B).[60,61] Best results in terms of yield and enantioselectivity were achieved when an oxaborolidine–catecholborane system was used as the reducing agent. More recently, Uneyama and Amii reported the transition-metal-catalyzed asymmetric hydrogenation of **12**.[62] The combination of palladium(II) trifluoroacetate and BINAP, and the use of a fluorinated alcohol as the solvent resulted in an improvement of the chemical yields with ee's up to 88%. The reduction was also carried out using a Dfm-derivative of **12**, furnishing the corresponding product in 30% ee.

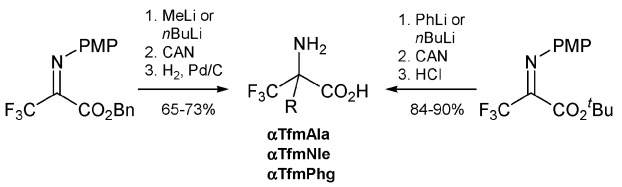
N-Substituted imines of trifluoropyruvates can also be used as precursors of $C^{\alpha,\alpha}$-disubstituted fluorinated amino acids by addition of nucleophiles. This approach will be discussed in detail in the next section.

4. αTfm and αDfm amino acids *via* introduction of the alkyl substituent

The most general approach to $C^{\alpha,\alpha}$-disubstituted fluorinated amino acids is based on the addition of carbon nucleophiles to the CN double bond of *N*-substituted imines of alkyl trifluoro- and difluoropyruvate.[63–66] Grignard reagents are the nucleophiles of choice because they tolerate certain functional groups, including CC double, CC triple bonds, and metall-organic moieties like organosilicon, organotin, and organocobalt substructures,[67,68] which can be reacted further to give multifunctional αTfm and αDfm amino acids.[69,70] Moreover, this strategy allows the incorporation of the Boc- and Z-group for orthogonal protection.

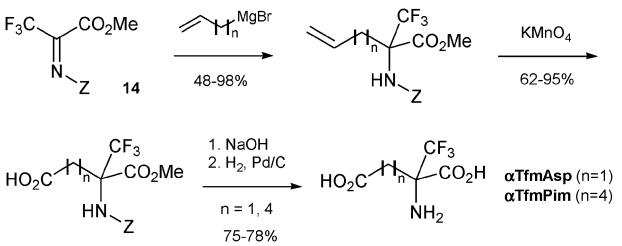
4.1 Racemic αTfm and αDfm amino acids generated from additions to fluorinated pyruvate derivatives

N-Protected imines of fluorinated pyruvates have been successfully submitted to alkylation procedures to give αDfm and αTfm amino acids of high structural diversity. The addition of saturated alkyl chains to these imines was used as an easier and more straightforward method for the preparation of αTfmAla, αTfmPhg and αTfm-norleucine (αTfmNle) (Scheme 8).[58,59] In this case, the target amino acids were obtained easily by removal of the protecting groups after the alkylation reaction.



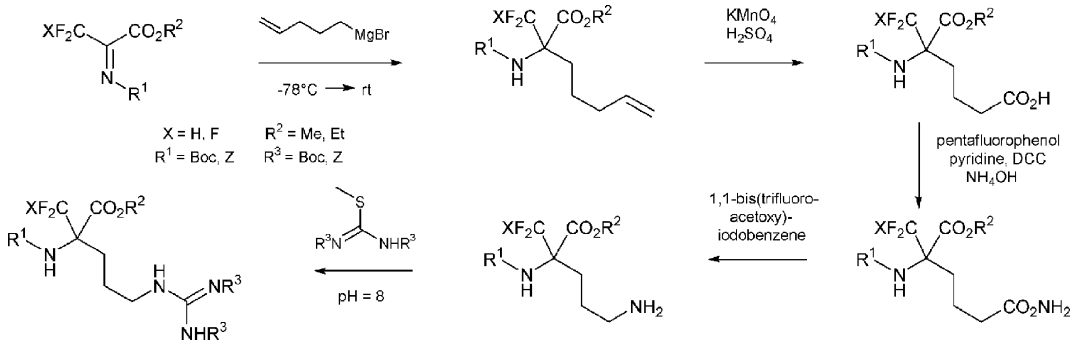
Scheme 8 Synthesis of αTfm amino acids *via* alkylation of pyruvate derivatives.

The introduction of unsaturated alkyl chains into **14** proved to be a valuable method for more complex and functionalized $C^{\alpha,\alpha}$-disubstituted fluorinated amino acids. This strategy has been used successfully to prepare αTfmAsp and αTfm-2-aminoheptanedioic acid (αTfmPim).[69] After addition of the alkene side chain *via* Grignard reaction, the CC double bond was oxidized to yield the desired compounds after deprotection (Scheme 9).



Scheme 9 Synthesis of αTfm amino acids *via* addition of unsaturated Grignard reagents to **14**.

The same approach was used for the synthesis of αTfm- and αDfm-arginines (Scheme 10).[71] Acylimines of trifluoro- and difluoropyruvates were reacted with 4-penten-1-yl magnesium bromide, oxidized with $KMnO_4$ and subsequently transformed to 2,5-diamino pentanoates. In the final step, the amine was subjected to a guanidinylation reaction. Alternatively, the side chain was introduced by adding a *N*-protected lithiated propargyl amine. In this case, it is advantageous to perform the guanidinylation step before hydrogenating the CC triple bond. Orthogonally protected αTfm- and αDfm-arginines could be made available in large quantities by this preparatively simple route.

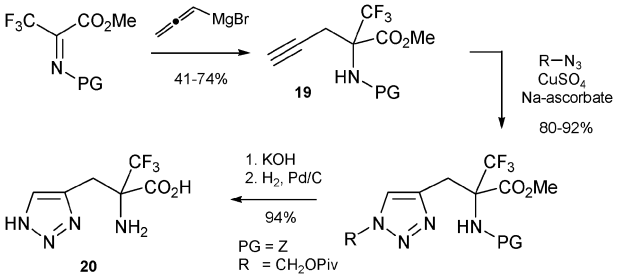


Scheme 10 Synthesis of αDfm and αTfm arginine derivatives.

A new approach to αTfm and αDfm ornithine (Orn) is based on the addition of an organo-lithiated nucleophile to alkoxycarbonyl imines of trifluoro- and difluoropyruvate.[72] The adducts **16**, generated by reaction of **15** with lithiated *N*,*N*-bis(trimethylsilyl)aminomethyl acetylide, were cyclized to 2-piperidone derivatives **17** *via* hydrogenation of the triple bond (Scheme 11). Simultaneous cleavage of the Boc group and ring opening on treatment with HCl afforded αTfm- and αDfmOrn hydrochlorides in excellent yields. In addition, the lactam intermediates **17** were used as precursors for the synthesis of αTfm and αDfm thalidomide **18**.[73] After cleavage of the Boc group, the amino group was diacylated with *o*-phthaloyl dichloride. The following oxidation with sodium metaperiodate/RuO_2 delivered the fluorinated thalidomides in moderate yields.

The addition of side chains containing a terminal triple bond to *N*-substituted imines of trifluoropyruvate also represents a useful strategy for the generation of a variety of fluorinated amino acids. In this context, Osipov recently reported an approach to αTfm-azahistidine analogues **20** based on the "click chemistry" concept introduced by Sharpless and co-workers.[74] α-Progargyl-αTfm-α-amino esters **19**, derived from addition of allenylmagnesiumbromide to highly electrophilic imines of Tfm pyruvate, were subjected to a 1,3-dipolar Huisgen cycloaddition with a variety of organic azides (Scheme 12).

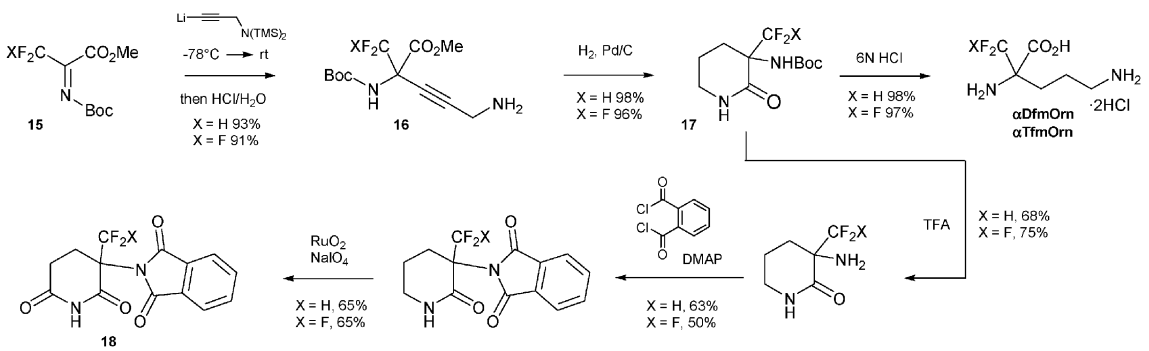
The alkyne–azide coupling occurred regioselectively in the presence of catalytic amounts of Cu(I) salts and a base to yield protected azahistidine derivatives. An *in situ* generation of Cu(I) from $CuSO_4$ proved to be superior to the application of Cu(I) salts due to an easier purification procedure of the



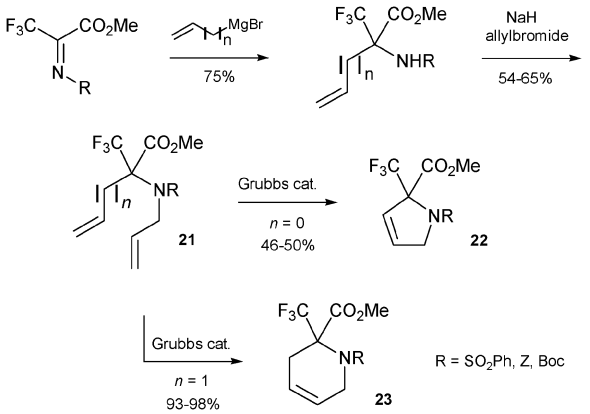
Scheme 12 Synthesis of αTfm azahistidine using "click chemistry".

products. The target compound **20** was obtained after stepwise removal of the protecting groups.

The twofold addition of unsaturated side chains to *N*-substituted imines of trifluoropyruvate and subsequent intramolecular ring-closing metathesis (RCM) can be used as a general approach for the preparation of cyclic fluorinated amino acid derivatives. An elegant application of this strategy for the synthesis of αTfm dehydroprolinate **22** and dehydropipecolate **23** was described by Osipov and Dixneuf (Scheme 13).[75] The preparation of the key compounds **21** decorated with two alkene chains was achieved in two steps: (1) introduction of the vinyl (or allyl) side chain *via* Grignard addition and (2) *N*-allylation with allyl bromide in the presence of NaH. Subsequent RCM employing Grubbs catalyst delivered racemic 5- or 6-membered cyclic αTfm amino acid derivatives. Moreover, vinyl-substituted dehydroprolinates were synthesized by this stategy.[76] A similar methodolgy that involves a ruthenium-catalysed tandem alkenylation/cyclopropanation procedure has been employed to access bicyclo[4.1.0]heptane amino acid derivatives.[77]



Scheme 11 Synthesis of αTfm- and αDfm-Orn and thalidomide *via* piperidin-2-ones **17**.



Scheme 13 Synthesis of αTfm dehydroprolinate and dehydropipecolate *via* RCM.

4.2 αTfm and αDfm amino acids *via* asymmetric additions to fluorinated pyruvate derivatives

Racemic α-fluorinated amino acids are less important for the pharmaceutical industry, despite the large number of structurally diverse substances that can be prepared from additions to imines of trifluoro- and difluoro-pyruvate. Considering the divergent biological activities of the enantiomers of C^{α}-fluoroalkyl substituted amino acids and their diasteromeric peptide derivatives, the availability of these compounds in their enantiomerically pure form is highly desirable. This section summarizes the approaches to αTfm and αDfm amino acids *via* asymmetric additions to fluorinated pyruvate derivatives. All of the presented methodologies use chiral auxiliaries to produce a diastereomeric mixture. Although the formation of these stereoisomers often occurs with low diastereomeric control, both forms can be used to provide an access to each enantiomer of α-fluorinated amino acids.

An elegant application of a chiral auxiliary for the preparation of optically pure (*S*)-αTfmPro has been reported recently from Brigaud.[78] The key step of this strategy involves the Lewis acid promoted diastereoselective allylation of chiral αTfm imines or oxazolidines (Scheme 14). These synthons can be prepared from trifluoropyruvate by reaction with commercially available (*R*)-phenylglycinol or a protected derivative thereof.

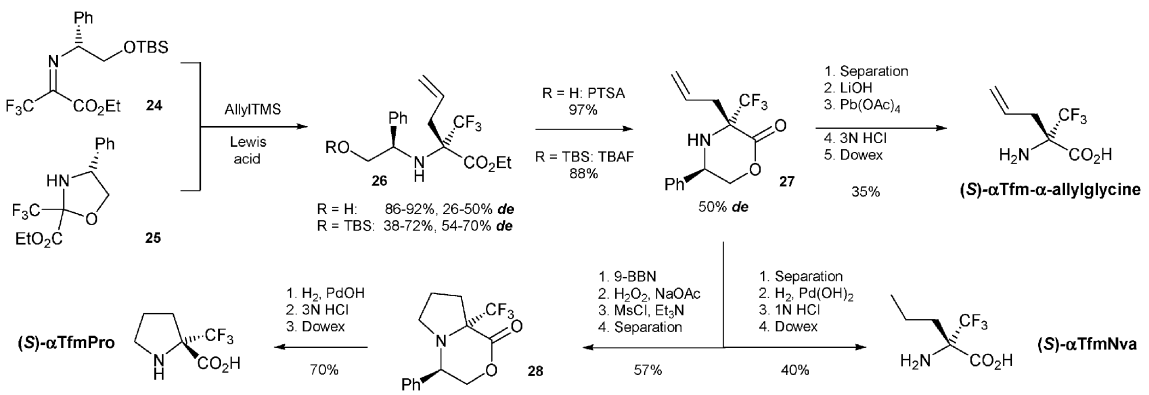
The allylation of synthon **25** gave altogether better yields compared to the reaction of synthon **24**, although a slightly lower diastereoselection was encountered. After cyclization of the allylated intermediates **26** to morpholinones **27**, the diastereomers could be separated by flash chromatography. The diastereomerically pure morpholinone **27** could be converted to (*S*)-αTfm-allylglycine and (*S*)-αTfm-norvaline (αTfmNva), whereas the diastereomeric mixture was used for the synthesis of (*S*)-αTfmPro.

The pyrrolidine ring was constructed *via* hydroboration of the double bond and subsequent ring closure, which afforded the diastereomerically pure bicyclic compound **28** after chromatographic separation. The chiral auxiliary of each diastereomer was removed delivering enantiomerically pure (*S*)- and (*R*)-αTfmPro. This methodology shows the high versatility of phenylglycinol as a chiral auxiliary for the preparation of fluorinated amino acids.

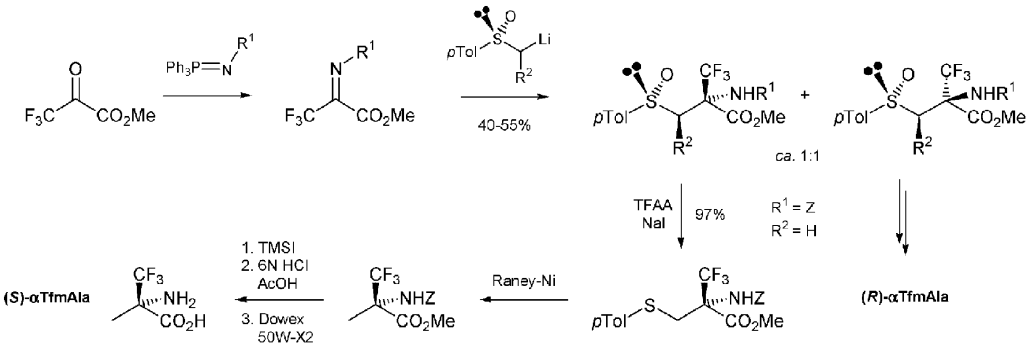
Alternatively, optically pure αTfm amino acids can be prepared by reacting the *N*-alkoxycarbonyl imines of alkyl trifluoropyruvates with a chiral lithiated sulfoxide.[79] Although the addition of the lithiated sulfoxide proceeded without stereopreference, the obtained diastereomers could be isolated in their enantiomerically pure forms. After stepwise cleavage of the chiral auxiliary and deprotection, optically pure (*S*)- and (*R*)-αTfmAla were released (Scheme 15).

Furthermore, this methodology proved to be successful for the synthesis of both enantiomeric forms of αTfm-threonine[54] and αTfmSer derivatives.[80] The fact that more complex or functionalized αTfm amino acids cannot be prepared *via* this route constitutes a limitation of this strategy.

Zanda and co-workers investigated a more sophisticated approach to prepare αTfm amino acids that is based on the use of highly electrophilic sulfinimines.[81,82] These compounds can be prepared by the Aza-Wittig reaction of the chiral Staudinger reagent **30**, synthesized from the Davis sulfinamide **29**, with ethyl trifluoropyruvate. The sulfinimines obtained are much more stable towards hydrolysis compared to the corresponding *N*-acyl and *N*-alkoxycarbonyl derivatives. Moreover, the chiral auxiliary can be easily recovered as menthyl sulfinate allowing the cost-effective preparation of non-racemic αTfm amino acids on a multi-gram scale. The sulfinimines **31** were reacted with a wide range of Grignard reagents to produce a library of non racemic αTfm amino acid derivatives. The diastereoselective outcomes depend on the nature of the Grignard reagent. Normally, sterically hindered nucleophiles gave the best results providing de's up to 76%. The



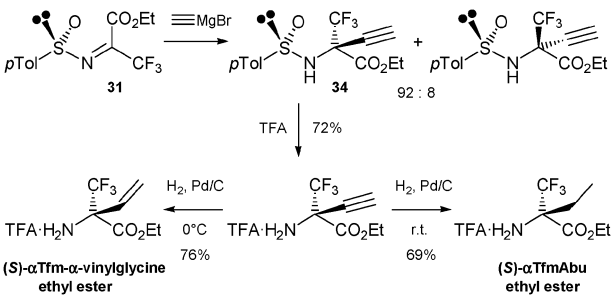
Scheme 14 Enantioselective synthesis of αTfm amino acids using (*R*)-phenylglycinol as a chiral auxiliary.



Scheme 15 Synthesis of (*R*)- and (*S*)-αTfmAla *via* chiral sulfoxides.

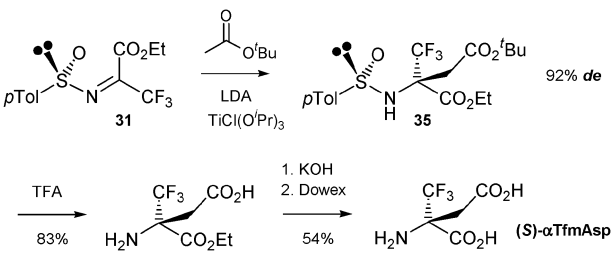
diastereomeric sulfinamides **32** and **33** derived from this reaction were purified by flash chromatography and were easily converted to the corresponding αTfm amino acids (Scheme 16).

Interestingly, the reaction of **31** with vinyl and phenylmagnesium halides resulted in the complete addition of the Grignard reagent to the sulfur atom. Nevertheless, αTfm-α-vinylglycine could be synthesized by an indirect approach *via* addition of ethynylmagnesium bromide to sulfinimines **31** and subsequent chemoselective reduction of the triple bond.[83] The addition of the ethynyl Grignard to **31** occurred with surprisingly high diastereocontrol (84% de, Scheme 17). Afterwards, cleavage of the chiral auxiliary and hydrogenation of the major diastereomer **34** provided access to ethyl esters of (*S*)-αTfm-α-vinylglycine and (*S*)-αTfm-α-aminobutyric acid (αTfmAbu).



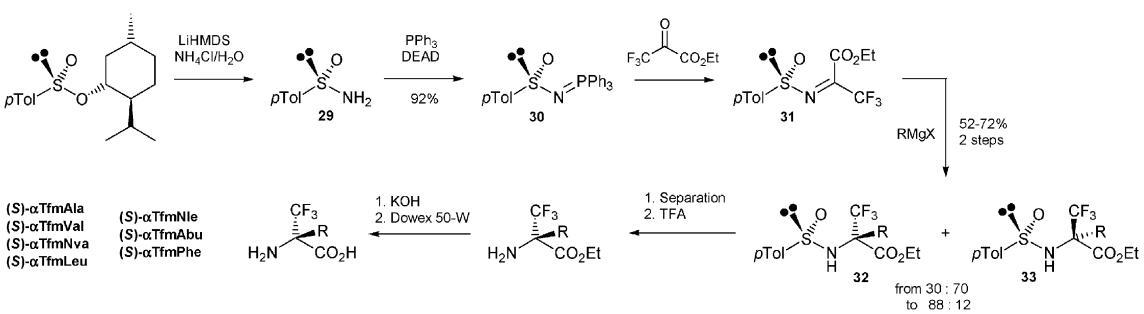
Scheme 17 Asymmetric synthesis of ethyl esters of (*S*)-αTfm-α-vinylglycine and (*S*)-αTfmAbu.

Chiral sulfinimines **31** were also used as templates to prepare αTfmAsp *via* a diastereoselective Mannich-type addition.[84] Different reagents were screened for the generation of the metal enolate of *tert*-butyl acetate to carry out the addition step. The use of LDA for the lithiation and $TiCl(O\text{-}^{i}Pr)_3$ to perform a subsequent transmetallation succeeded the best, and furnished diastereomer **35** in 92% de. The de could even be raised to 97% by crystallization. Finally, (*S*)-αTfmAsp was released by a deprotection sequence (Scheme 18). It was also possible to perform the addition step with further methylene active nucleophiles even though a decrease of selectivity was noticed.[85]

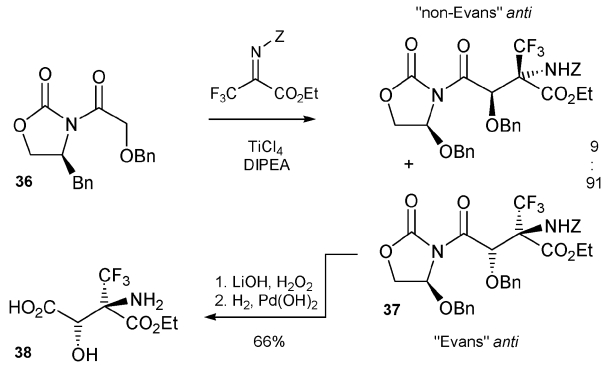


Scheme 18 Enantioselective synthesis of (*S*)-αTfmAsp.

Another example of a stereoselective Mannich-type reaction to approach an aspartate derivative was published by the same group (Scheme 19).[86] Here, an optically active enolate was used for the addition to an achiral trifluoropyruvate derivative. Thus, the reaction of different metal enolates of commercially available (*S*)-(α-benzyloxy)acetyl 2-oxazolidinone **36** was investigated. Best results were achieved by applying the chlorotitanium enolate of the chiral oxazolidinone, delivering only two of the four possible stereoisomers. The "non-Evans" and the "Evans" *anti* adducts were formed exclusively in a 9 : 91 ratio. Consecutive removal of the chiral auxiliary and the protecting groups from the major diastereoisomer **37** gave rise to the D-*erythro*-αTfm-β-hydroxy aspartate **38**.



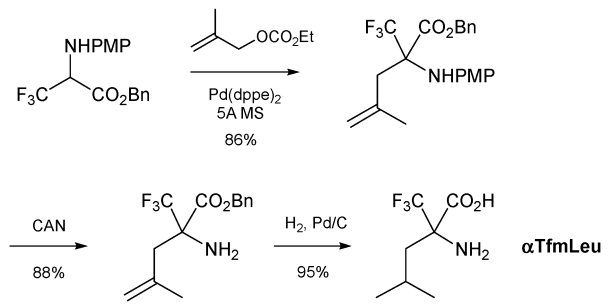
Scheme 16 Synthesis of enantiomerically pure αTfm amino acids *via* sulfinimines.



Scheme 19 Stereoselective Mannich-type reaction using oxazolidinone **36**.

4.3 αTfm amino acids from αTfmGly *via* palladium-catalyzed allylation reaction

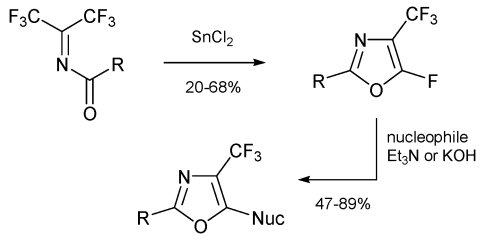
Konno *et al*. disclosed a new methodology to prepare $C^{\alpha,\alpha}$-disubstituted fluorinated amino acids.[87] This route is based on the palladium-catalyzed allylation of αTfmGly derivatives with allyl carbonates. The reaction most likely involves the formation of a π-allylpalladium complex that reacts with an αTfm enolate to give the corresponding α-allylated αTfm amino acid. When the conversion was carried out with *N*-Z-protected αTfmGly as the starting compound, not only the desired *C*-monoallylated products, but also the *C*,*N*-diallylated and *N*-monoallylated derivatives were obtained. Exchange of the protecting group from Z to PMP led to a reduced acidity of the amino group and, consequently, to the exclusive formation of the *C*-monoallylated compound (Scheme 20). Attempts to conduct the reaction in a stereogenic environment using chiral ligands resulted in a poor enantioselection (ee's up to 9%). This new methodology provides a very smooth way for the introduction of allylic side chains to αTfmGly, as demonstrated for the synthesis of racemic αTfmLeu.



Scheme 20 Palladium-catalyzed allylation reaction of protected αTfmGly.

4.4 Hexafluoroacetone as building block for the synthesis of αTfm amino acids

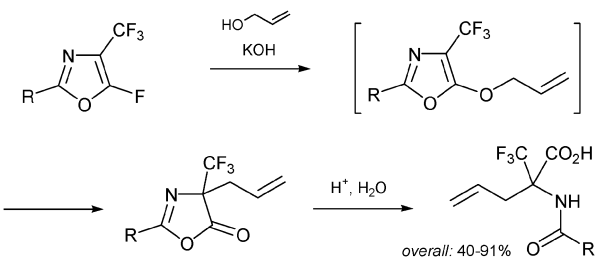
N-Acylimines of hexafluoroacetone can be transformed into 5-fluoro-4-trifluoromethyl-oxazoles in a one-pot procedure with tin(II) chloride[88–90] or with zinc on sonication.[91] The first mentioned reaction sequence starts with a [4 + 1] cycloaddition of tin(II) chloride to the heterodiene to give a five-membered heterocycle (Scheme 21). The cycloaddition reaction can be interpreted



Scheme 21 One-pot procedure to trifluoromethyl-substituted oxazoles and fluorine displacement.

as a redox reaction. The tin(II) species is oxidized to give a tin(IV) moiety. Consequently, two electrons are transferred from the tin(II) moiety to the heterodiene skeleton. Upon heating, the metallacycle undergoes a heterolytic ring cleavage. After fluoride elimination an electrocyclization occurs. During the last step of this cascade reaction, a heteroaromatization accompanied by HF-elimination takes place.[92] In the second case, the two electron transfer occurs directly from zinc to the heterodiene. The single fluorine atom placed at C-(5) is activated for nucleophilic displacement reactions by the adjacent trifluoromethyl group.[93–95]

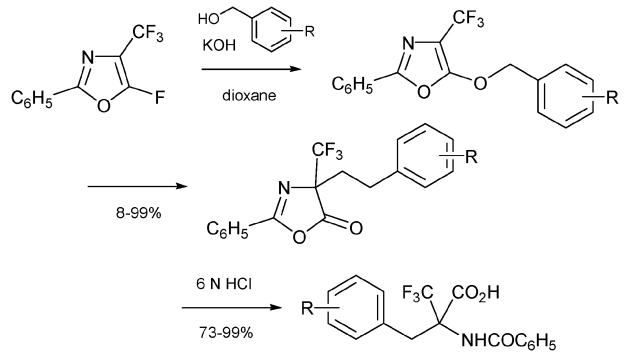
5-Fluoro-4-trifluoromethyloxazoles possess the complete backbone of *N*-protected 3,3,3-trifluoroalanine and therefore can be used as αTfmGly synthon. Allyl alcohols react readily in the presence of KOH to give a substitution product with a 1,5-diene subunit, which is susceptible to undergo a low temperature Claisen rearrangement (Scheme 22).[96] The 4-allyl, 4-allenyl, and 4-heteroallyl substituted 4-trifluoromethyl-5(4H)-oxazol-5-ones formed represent carboxy-activated αTfm amino acid derivatives, which can be readily transformed into *N*-benzoyl αTfm amino acids. Cleavage of the *N*-benzoyl group can be achieved in boiling conc. HCl.[96]



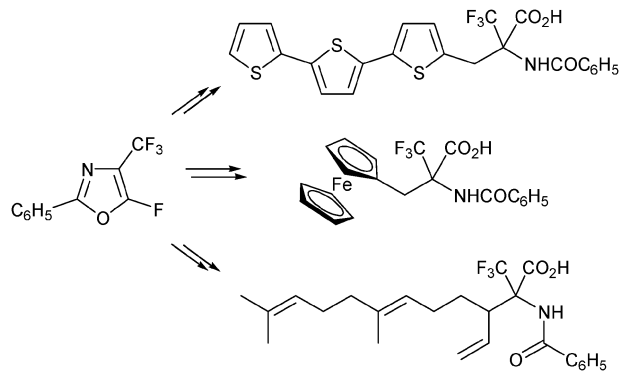
Scheme 22 Tandem fluorine substitution and Claisen rearrangement.

5-Fluoro-4-trifluoromethyloxazoles and benzylalcohols (the allyl system is now part of the aromatic system) react to give 4-trifluoromethyl-5(4H)-oxazolones (Scheme 23).[97] The domino reaction consists of a nucleophilic displacement followed by a 1,3-benzyl shift from oxygen to carbon. Interrelated experiments revealed that the reaction is a non-concerted process, most likely a radical pair mechanism. αTfmPhe and αTfmTyr derivatives could be synthesized after hydrolysis with hydrogen chloride.[97]

The examples reported show the utility of 5-fluoro-4-trifluoromethyl-oxazoles as valuable synthons for the generation of αTfm amino acids with unsaturated side chains. Furthermore, these building blocks could be used to introduce heteroaromatic, metallorganic and terpene moieties into the side chain (Scheme 24).[96]



Scheme 23 Reaction of 5-fluoro-4-trifluoromethyloxazoles with benzylalcohols.



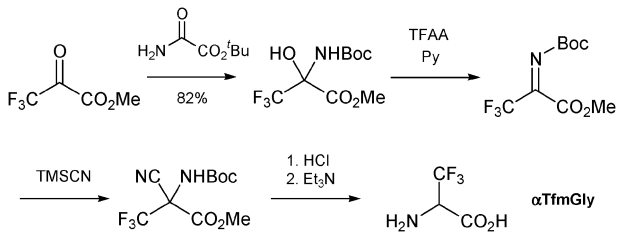
Scheme 24 High versatility of the 5-fluoro-4-trifluoromethyloxazole building block in the synthesis of αTfm amino acids.

5. αTfm amino acids *via* carbon–nitrogen bond formation

The construction of the carbon–nitrogen bond *via* amination reactions of fluorinated pyruvates, ketones, and derivatives thereof constitutes a valuable approach for the preparation of αTfm amino acid precursors. In most cases, the carbonyl double bond is condensed with an appropriate amine to furnish the corresponding imine that can be reduced and further elaborated to generate αTfmGly. The use of chiral substrates or reducing reagents provides access to enantiomerically enriched or pure αTfmGly. The alkylation of these imines delivers $C^{\alpha,\alpha}$-disubstituted amino acids as described in section 4. Alternative approaches to αTfm-α-alkyl amino acid derivatives by carbon–nitrogen bond formation proceed *via* reduction of γ-hydroxy-α-fluoro-αTfm carboxyamides[98] or Rh(II)-catalyzed carbene transfer with 2-diazo-3,3,3-trifluoropropionate.[99] The carbene transfer strategy can be used for the *C*-terminal incorporation of αTfmGly into peptides.[100]

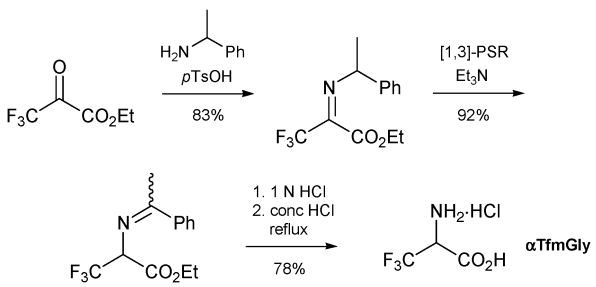
5.1 Amination reactions of trifluoropyruvates

A direct condensation of trifluoropyruvates and amines to afford *N*-alkyl imines is often complicated due to the exceptionally high stability of the intermediate hemiaminals towards dehydration.[101] Consequently, stepwise procedures are frequently used.[102] The conversion of trifluoropyruvate with carbamic acid *tert*-butyl ester delivers a hemiaminal, which is subsequently treated with trifluoroacetic anhydride to produce the desired imine (Scheme 25).[94] After Strecker-type reaction of the imine, the resulting amino nitrile is decarboxylated and deprotected by the action of hydrogen chloride to give αTfmGly.



Scheme 25 Synthesis of αTfmGly *via* aminoalkylation of methyl trifluoropyruvate.

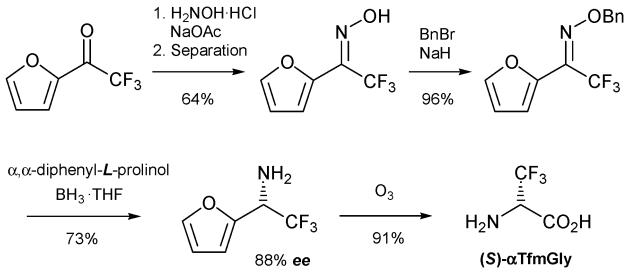
An improvement of this methodology was published by Soloshonok *et al.*[103] The use of 1-phenyl-ethylamine enabled a direct transamination of the α-keto trifluorocarboxylic esters to give the corresponding Schiff base. Subsequent base-catalyzed [1,3]-proton shift reaction (PSR) under mild reaction conditions yielded an isomeric ketimine that can be hydrolyzed to afford αTfmGly (Scheme 26). This biomimetic PSR occurs without the presence of a reducing agent and was used for a large-scale preparation of αTfmGly. Attempts to carry out a stereoselective transamination reaction using the imine of (*R*)-1-phenyl-ethylamine failed. A similar approach proceeds *via* conversion of α-trifluoromethyl acid fluorides with sodium azide or trimethylsilyl azides to isocyanates, from which αTfmGly esters can be liberated by treatment with hydrogen fluoride.[104]



Scheme 26 Biomimetic transamination of ethyl trifluoropyruvate.

5.2 Amination reactions of trifluoropyruvates followed by stereoselective reductions

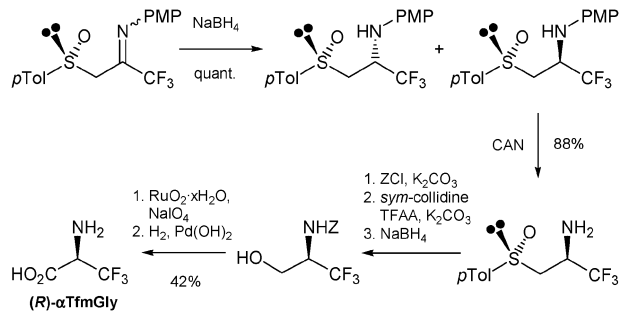
An enantioselective synthesis of αTfmGly was reported by Demir *et al.*[105] Furyl trifluoromethyl ketones were reacted with hydroxylamine to give isomeric oximes (Scheme 27). After chromatographic separation of the isomers, the sole *E* or *Z*-oximes were protected as *O*-benzyl ethers and stereoselectively reduced using oxazaborolidine complexes that were prepared from borane and three different amino alcohols. *In situ* reduction of the pure *Z*-oxime gave the (*S*)-configurated amine. The best result was achieved with the oxazaborolidine derived from α,α-diphenyl-L-prolinol, furnishing the desired product in 88% ee. The stereocontrol of the reduction step is provided by the oxime configuration. Conversion of the



Scheme 27 Stereoselective synthesis of αTfmGly using chiral oxazaborolidine complexes.

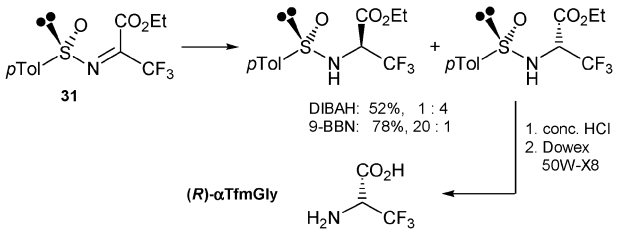
E-oxime with the same reductant delivered the (*R*)-amine in 86% ee. (*S*)- and (*R*)-αTfmGly were finally released by ozonolysis of the furan ring. One disadvantage of this procedure is that a small excess of oxazaborolidine complex (1.25 equivalents) is required as the use of a catalytic amount of the reductant system results in a dramatic drop of enantioselectivity. Nevertheless, the amino alcohols used for the preparation of the oxazaborolidine-complex can be recovered as hydrochloride salts in nearly quantitative yields after work-up.

A different approach to enantiomerically enriched αTfmGly is based on the use of a chiral auxiliary instead of chiral reducing agents. Aza-Wittig reaction between *N*-aryl iminophosphoranes and γ-trifluoro-β-ketosulfoxides[51] gives rise to enantiomerically pure trifluoromethyl (arylsulfinyl)methyl imines in good yields.[106] The electron withdrawing fluorine substituents accelerate this reaction. Subsequent reduction employing sodium borohydride furnishes the corresponding amine in 66% de in favor of the newly generated (*R*)-stereocenter (Scheme 28). After separation of the diastereomers, the (*S*)-configured amine was transformed to enantiomerically pure (*R*)-αTfmGly. This strategy enables the synthesis of optically pure αTfmGly, although only one enantiomer can be prepared in good overall yield. Furthermore, an access to enantiopure αDfmGly should be made available by applying this methodology.



Scheme 28 Stereospecific synthesis of αTfmGly using chiral sulfoxides.

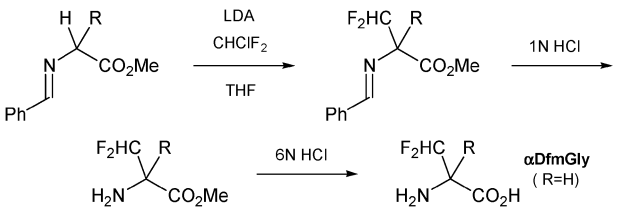
The aza-Wittig reaction was also performed with an inverse arrangement of coupling functionalities to provide the highly electrophilic sulfinimine **31** (see section 4.2).[107] The latter was reacted with a variety of reducing agents to deliver diastereomerically enriched sulfinamines (Scheme 29). Treatment with 9-BBN gave the best stereoselectivities, supplying the newly formed (*S*)-stereocenter in 90% de. This result can be rationalized by a coordination of the sulfinimine *via* a six-membered chair-like transition state. An opposite selectivity was observed when the substrate was reduced with DIBAH or DIBAH/$ZnBr_2$. The former gave a 4 : 1 diastereomeric mixture in favor of the carbon (*R*)-stereocenter. Eventually, the DIBAH reduction product was transformed into the free amino acid. Simultaneous saponification of the ester and cleavage of the chiral auxiliary afforded (*R*)-αTfmGly with an ee value higher than 70%.



Scheme 29 Stereoselective synthesis of αTfmGly *via* chiral sulfinimines.

6. αDfm amino acids *via* introduction of the fluoroalkyl substituent

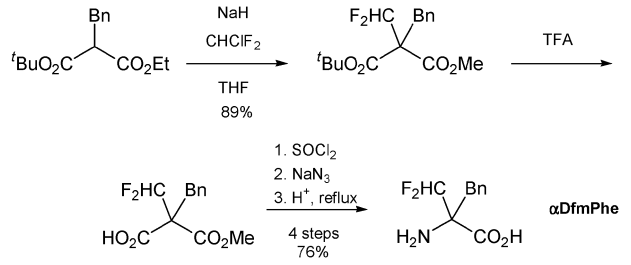
The preparation of α-fluorinated amino acids *via* a fluorohalomethylation strategy is limited to the synthesis of racemic α-monofluoromethyl (αMfm) and αDfm derivatives. Usually, amino acid imines are deprotonated with strong bases like LDA or NaH and the formed anions are alkylated with chlorodifluoromethane (Scheme 30). This approach was used for the synthesis of αDfmGly[108–111] and αDfmGlu diester.[111]



Scheme 30 Alkylation of Schiff bases with chlorodifluoromethane.

Application of the difluoromethylation protocol to iminomalonates gives the corresponding difluoromethylated products that can be hydrolyzed and decarboxylated under acidic conditions.[112] An extension of this method to aminomalonates is possible by using strongly basic tris(diethylamino)-*N*-methylphosphazene for the deprotonation step.[113] Hence, αDfmGly can be prepared in a better yield under mild reaction conditions. The fluoro-halomethylation is also useful for the synthesis of αDfm amino acids from ethyl *tert*-butyl malonates (Scheme 31).[114] Cleavage of the *tert*-butyl ester with trifluoroacetic acid and transformation of the carboxy group into an amino function *via* Curtius rearrangement provides access to αDfmPhe.

So far, the synthesis of only racemic αDfm amino acids constitutes a major limitation of the halomethylation approach. Enantioselective strategies need to be developed in the future to make this strategy more attractive for a broad application.



Scheme 31 Synthesis of αDfm-substituted amino acids *via* alkylation of malonates and Curtius rearrangement.

Conclusions

The incorporation of one or more fluorine substituents into amino acids and peptides is an attractive approach to generate desired physical, chemical, and structural properties of peptide based drugs or proteins. Modern fluorine-organic chemistry has dramatically widened the synthetic repertoire for the specific introduction of fluorine into organic molecules. In particular, efficient methods have been developed for the synthesis of a variety of αTfm and αDfm substituted amino acids and derivatives. Considering the great importance of enantiomerically pure αTfm and αDfm amino acids, much work has been done to develop their asymmetric syntheses.

Fig. 1 summarizes the different strategies that can be applied for the introduction of these substituents *via* fluorinated building blocks and gives some examples. The most general procedure is the amidoalkylation of carbon nucleophiles with alkyl-2-(alkoxy-carbonylimino)-3,3,3-trifluoropropionates (disconnection 2) leading to multifunctional C^{α}-fluorinated components. The big advantage of this methodology is that it gives access to a great variety of structurally diverse αDfm and αTfm amino acids that can be synthesized from the same building block by the incorporation of different alkyl groups. Further $C^{\alpha,\alpha}$-disubstituted amino acids can be efficiently made available from fluorinated precursors by introduction of the carboxy function (disconnection 1). The construction of C^{α}-multifluorinated amino acids *via* carbon–nitrogen bond formation (disconnection 3) is limited to the synthesis of αTfm dervatives, whereas only αDfm amino acids can be made available by introduction of the fluoroalkyl substituent (disconnection 4).

With constantly increasing knowledge about the impact that fluorine has on peptide and protein structure and properties, fluorinated amino acids develop more and more into highly desired building blocks for a rational drug design.

Acknowledgements

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