Asymmetric Organocatalysis

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Stereoselective Organocatalyzed Synthesis of α-Fluorinated β-Amino Thioesters and Their Application in Peptide Synthesis

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Dedicated to Professor Dieter Seebach

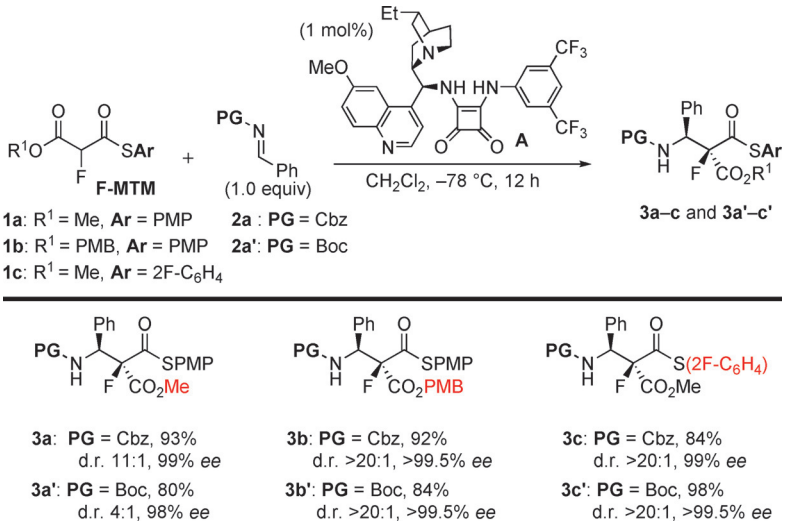
Abstract: *α-Fluorinated β-amino thioesters were obtained in high yields and stereoselectivities by organocatalyzed addition reactions of α-fluorinated monothiomalonates (F-MTMs) to N-Cbz- and N-Boc-protected imines. The transformation requires catalyst loadings of only 1 mol% and proceeds under mild reaction conditions. The obtained addition products were readily used for coupling-reagent-free peptide synthesis in solution and on solid phase. The α-fluoro-β-(carb)-amido moiety showed distinct conformational preferences, as determined by crystal structure and NMR spectroscopic analysis.*

In recent years, peptides have reemerged as highly potent and selective active pharmaceutical ingredients.[1] Fluorination and the use of nonproteinogenic β-amino acids are powerful tools to enhance their proteolytic stability and to control their conformation.[2] α-Fluoro-β-amino acids combine both features and have already proven valuable for directing the conformation of β-peptides.[3–5] Particularly attractive are activated derivatives that can be directly incorporated into peptides without the use of a coupling reagent. However, the stereoselective synthesis of even non-activated α-fluoro-β-amino acids is not straightforward.[3,6–9]

Enantioselective Mannich-type addition reactions of α-fluoroenolates are an attractive option for reaching this goal.[8,9] However, strategies reported so far provided addition products that cannot be readily incorporated into peptides and offer only limited possibilities for orthogonal derivatization.[8,9] Moreover, their scope is typically limited to aromatic imine substrates, and comparatively high catalyst loadings are required.[8,9]

Herein we present highly stereoselective Mannich-type addition reactions of α-fluorinated monothiomalonates (F-MTMs) with imines under mild organocatalytic conditions. Even α-fluorinated β-amino thioesters with aliphatic moieties and functional groups in their side chain formed in excellent yields and stereoselectivities and were readily used in coupling-reagent-free peptide synthesis. Furthermore, we show that the α-fluoro-β-(carb)-amido moiety retains a strong conformational preference after incorporation into α,β-peptides.

We recently developed fluorinated malonic acid half thioesters (F-MAHTs) as activated fluoroacetate enolate equivalents and demonstrated their value for enantioselective organocatalyzed aldol reactions.[10] We now envisioned that F-MAHTs or esterified derivatives thereof (α-fluorinated monothiomalonates, F-MTMs) would also be valuable for Mannich-type reactions and provide direct access to activated α-fluorinated β-amino acids, which could be directly incorporated into peptides (Scheme 1).



Scheme 1. Addition reactions of F-MTMs **1a–c** with imines **2a** and **2a′**. Yields correspond to addition products isolated as a mixture of diastereoisomers. The *ee* value of the major diastereomer was determined by HPLC or supercritical-fluid chromatography (SFC) on a chiral stationary phase. Diastereomeric ratios were determined by ^{1}H or ^{19}F NMR spectroscopy of the crude reaction mixture. When F-MTM **1a** was treated with imine **2a** in the presence of 5 mol% of catalyst **A** at −78 °C, the reaction was complete within 1 h.

To start our investigations, we chose the addition of α-fluorinated MAHTs and F-MTM **1a** to the Cbz-protected imine **2a** in the presence of bifunctional cinchona alkaloid–(thio)urea catalysts that had proven to be valuable for addition reactions

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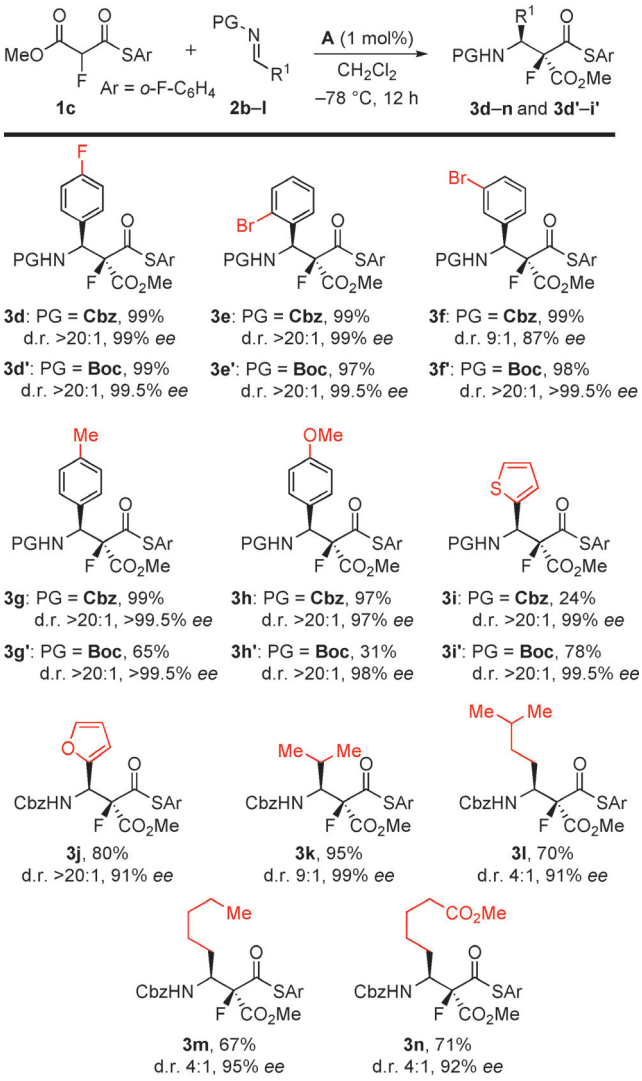
between alkylated MTMs and imines.[11] F-MAHTs did not react with **2a** even in the presence of 20 mol% of the catalysts and with reaction times of several days.[12] Since analogous reactions between unsubstituted or alkylated MAHTs and imines proceed under analogous conditions,[13] this finding shows that the properties of MAHTs are significantly modified by a fluorine substituent in the α-position. Reassuringly, F-MTM **1a** readily reacted with **2a** in the presence of as little as 1 mol% of various cinchona alkaloid-based catalysts.[12] Variations in the catalyst structure showed that, with respect to product yield and stereoselectivity, the *epi*-quinine-derived squaramide **A**[14] was superior to cinchona alkaloid–(thio)urea derivatives previously found to be optimal catalysts for reactions of unsubstituted and alkylated MTMs.[12,15] Further optimization of the reaction parameters enabled the Cbz-protected addition product **3a** to be obtained in high yield (93%) with high stereoselectivity (d.r. 11:1, 99% *ee*) in the presence of only 1 mol% of *epi*-dihydroquinine–squaramide **A** and stoichiometric amounts of the reactants (Scheme 1). Under the same conditions, the corresponding Boc-protected β-amino acid **3a′** also formed in good yield (80%) and enantioselectivity (98% *ee*) but with lower diastereoselectivity (d.r. 4:1).

Having optimized the reaction conditions, we probed the effect of the oxo- and thioester moieties within the F-MTM on the stereoselectivity of the reaction. Pleasingly, when F-MTM **1b** bearing a *p*-methoxybenzyl (PMB) oxoester group was used, the amino thioesters **3b** and **3b′**, bearing a Cbz- and Boc-protecting group, respectively, were obtained with excellent stereoselectivity (d.r. > 20:1, > 99% *ee*; Scheme 1). Similarly high stereoselectivity was observed when F-MTM **1c** bearing an *o*-fluorophenyl (*o*-F-C_6H_4) thioester moiety reacted with the imines (products **3c** and **3c′**, Scheme 1). This more electron deficient thioester moiety was envisioned to be valuable as a better leaving group for peptide coupling (see below).

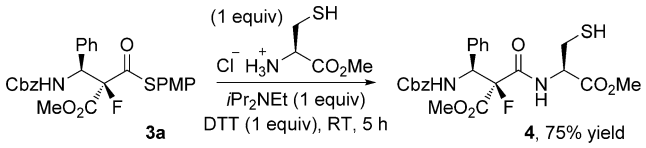
Next, we evaluated the scope of the addition reaction and treated a range of *N*-Cbz- and *N*-Boc-protected imines with F-MTM **1c** in the presence of catalyst **A** (1 mol%). Electron-poor as well as electron-rich aromatic imines reacted smoothly with F-MTM **1c** and provided the addition products **3d**–**h** and **3d′**–**h′** in high yields with excellent stereoselectivity (Scheme 2). Notably, the Cbz- and the Boc-protected imines reacted in most cases equally well under the reaction conditions. Heteroaromatic imines were also tolerated and yielded the addition products **3i**, **3j**, and **3i′** with very good stereoselectivity (d.r. > 20:1, 91–≥ 99% *ee*). Even aliphatic *N*-Cbz-protected imines and an imine bearing an ester moiety afforded upon reaction with F-MTM **1c** the α-fluorinated β-amino thioesters **3k**–**n** in moderate to good yields (67–95%) and diastereoselectivity (d.r. ≥ 4:1) as well as excellent enantioselectivity (91–99% *ee*).[16] These findings are remarkable, since aliphatic imines are known to be particularly challenging substrates,[8,9] and imines with functional groups are unexplored substrates in organocatalytic Mannich-type addition reactions. Yet, β-amino acid derivatives with aliphatic and functional groups in their side chains are highly valuable for mimicking the functional moieties of proteinogenic amino acids. The broad generality of the reaction evidences the robustness of the methodology.



Scheme 2. Addition reactions of F-MTM **1c** with imines **2b**–**l**. Reactions were performed on a 0.1 mmol scale. Yields correspond to addition products isolated as a mixture of diastereoisomers over two reaction steps, including the in situ generation of the imines from the respective α-amido sulfones. The ee value of the major diastereomer was determined by HPLC or SFC on a chiral stationary phase. Diastereomeric ratios were determined by ^{1}H or ^{19}F NMR of the crude reaction mixture.

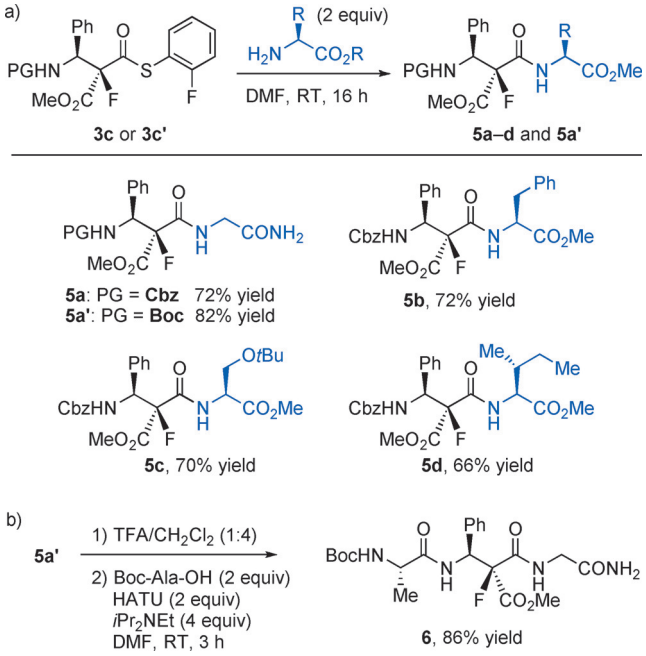
Next, we explored the synthetic versatility of the α-fluoro-β-amino thioesters for peptide synthesis. The use of coupling reagents, which are required in excess in particular for the coupling of β-amino acids, is a wasteful approach but common practice in peptide synthesis.[17] We envisioned that the thioester moiety within addition products **3** would enable direct, coupling-reagent-free peptide synthesis. Previous studies with nonfluorinated analogues of **3** bearing *p*-methoxyphenyl (PMP) thioesters had shown that reactions with amines were slow and required forcing conditions (e.g., microwave irradiation) to proceed.[11] Also attempts to react the PMP α-fluoro-β-amino thioester **3a** with amino esters such as H-Phe-OMe, H-Gly-OMe, H-β-Ala-OMe, and H-

Met-OMe under various conditions afforded none or only trace amounts of the desired dipeptides.[12] However, the treatment of **3a** with cysteine under conditions resembling those of native chemical ligation[18] provided the dipeptide **4** in good yield with stoichiometric amounts of the reactants (Scheme 3).



Scheme 3. "Native chemical ligation" of the *p*-methoxyphenyl α-fluoro-β-amino thioester **3a**. DTT = 1,4-dithiothreitol.

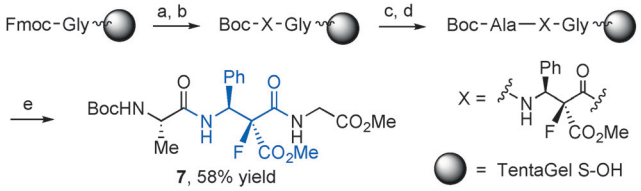
We then evaluated amino acid coupling with α-fluorinated β-amino thioesters bearing the more electron withdrawing *o*-fluorophenyl thioester moiety.[19] Pleasingly, **3c** and **3c′** reacted smoothly with various amino esters and amides at room temperature. Despite the presence of a fully substituted carbon center adjacent to the thioester, the corresponding dipeptides **5a–d** and **5a′** were obtained in good yields (Scheme 4). Tripeptide **6** was also formed in good yield



Scheme 4. a) Coupling-reagent-free peptide-bond formation with *o*-fluorophenyl α-fluoro-β-amino thioesters **3c** and **3c′**. b) N-terminal extension to tripeptide **6**. DMF = *N*,*N*-dimethylformamide, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, TFA = trifluoroacetic acid.

after *N*-Boc deprotection of **5a′**, followed by coupling with Boc-Ala-OH. This synthesis demonstrated that the α-fluorinated β-amino thioester building blocks can be readily extended at both the N and C termini (Scheme 4).

The coupling-reagent-free peptide-bond-formation reactions also proceeded on solid phase, with microwave irradiation to ensure complete coupling.[20] For example, the *N*-Boc-protected α-fluoro-β-amino thioester **3c′** was readily incorporated into α,β-peptide **7**, which was isolated in 58% overall yield (Scheme 5).



Scheme 5. Solid-phase peptide synthesis with *o*-fluorophenyl α-fluoro-β-amino thioesters. a) 20% piperidine/DMF; b) Boc-α-F-α-CO_2Me-β-Phe-S(2F-C_6H_4) (**3c′**), DMF, microwave irradiation, 75 °C, 1 h, then room temperature, 16 h; c) 50% TFA/CH_2Cl_2; d) Boc-Ala-OH, HCTU, iPr_2NEt, DMF; e) 10% NEt_3/MeOH. Fmoc = fluorenylmethoxycarbonyl, HCTU = *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(6-chloro-1*H*-benzotriazol-1-yl)-uronium hexafluorophosphate.

Finally, we analyzed the conformational properties of the α-fluoro-β-(carb)amido moiety within the thioesters and the α,β-peptides. Previous studies on small molecules and β-peptides had shown that α-fluoro amides have a strong preference for an antiperiplanar (*ap*) orientation of the O=C–C–F moiety.[5,21] Such an *ap* conformation was also observed in a crystal structure obtained for the α,β-peptide **5a** and corroborated by $^4J_{HN-F}$ coupling constants of 3.5–3.9 Hz observed between the N–H and F atoms within the α-fluoro amide moiety in the ^{1}H NMR spectra of the α,β-di- and tripeptides **5**–**7**.[5b] The α-fluoro-β-amino thioesters **3a′**, **3b**, **3c′**, **3h**, and **3i′** crystallized with an *ap* orientation of the C–F bond and the C=O bond of the thioester.[22] These crystal structures also enabled the unambiguous assignment of the absolute and relative configuration of the addition products.[23] Furthermore, all of the thioesters and peptide **5a** crystallized with an *anti* orientation between the vicinal C–F and C–H bonds. ^{1}H and ^{19}F NMR spectra corroborated this gauche effect between the electron-withdrawing fluorine atom and the carbamate/amide substituents with $^3J_{HF}$ coupling constants of 29.0–32.0 Hz (Figure 1).[24] Thus, the

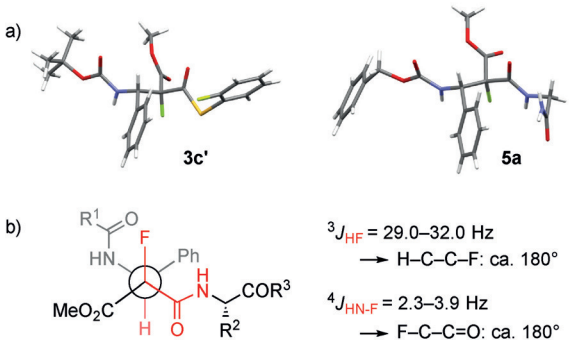


Figure 1. a) X-ray crystal structures of α-fluoro-β-amino thioester **3c′** and dipeptide **5a**. b) Preferred conformation of α,β-peptides in CD_2Cl_2 or CD_3OH on the basis of ^{1}H and ^{19}F NMR spectroscopy.[12]

dihedral angles of the α-fluoro-β-amino moiety are controlled within the thioesters and the α,β-peptides by a combination of the fluorine gauche effect and the *ap* preference of C–F and C=O bonds.

In summary, we have developed a straightforward method that provides acyclic α-fluoro-β-amino thioesters with adjacent fully substituted and tertiary stereogenic centers in high yields with excellent stereoselectivity. The Mannich-type reactions proceed under mild organocatalytic conditions with catalyst loadings as low as 1 mol%. The methodology is so robust that fluorinated β-amino acid derivatives bearing a wide variety of functional groups, including aliphatic and ester moieties, in their side chains were accessed. Optimization of the stereoelectronic properties of the thioester moiety allowed us to tune the reactivity of the α-fluoro-β-amino thioesters and enabled their coupling-reagent-free incorporation into peptides. Furthermore, spectroscopic and crystallographic analysis showed that the conformation of the obtained α-fluoro-β-(carb)amido thioesters and peptides was controlled by a gauche effect in combination with a preferred *ap* orientation of vicinal C–F and C=O bonds.

Experimental Section

Synthesis of **3a–n** and **3a′–i′**: A 1.4 M aqueous solution of K_2CO_3 (0.05 M) was added to a suspension of the α-amido sulfone (0.1 mmol) in CH_2Cl_2 (0.05 M), and the mixture was stirred vigorously for 3–4 h at room temperature. The phases were separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with brine and then dried over Na_2SO_4. All volatiles were removed under reduced pressure, and the residue was dried in vacuo to afford the corresponding imine. The freshly prepared imine was used without further purification in the organocatalyzed Mannich-type addition reactions. The catalyst (1 mol%, 0.01 equiv) was added (0.02 mL of a solution in CH_2Cl_2, 0.25 M) to a solution of the imine (0.1 mmol) and the F-MTM (0.1 mmol) in CH_2Cl_2 (0.5 mL, 0.2 M) at −78 °C. The reaction mixture was stirred for the indicated amount of time and then quenched by immediate filtration through a short pad of silica (eluent: EtOAc) to remove the catalyst. The crude product was purified by flash chromatography on silica (eluent: EtOAc/*n*-hexane).

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Keywords: cinchona alkaloids · fluorine · organocatalysis · thioesters · β-amino acids

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[20] The reaction was carried out with 5 equivalents of Boc-α-F-α-CO_2Me-βPhe-S(2F-C_6H_4) (**3c′**) to ensure complete coupling. The excess fluorinated amino acid was recovered by filtration and chromatography on a short silica-gel column.

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[22] This conformation might be driven by packing effects within the solid state. It is nevertheless noteworthy, since the *ap* conformation of O=C–C–F moieties has been attributed to the minimum interaction energy between local electric dipole moments of C–F and C=O moieties (Ref. [19]), which would imply an *ap* conformation between the C–F bond and the C=O group of the oxoester.

[23] The stereochemical outcome of the addition reaction is in agreement with a transition-state geometry in which the F-MTM coordinates to the squaramide, and the phenyl thioester moiety of the F-MTM is oriented away from the 3,5-di(trifluoromethyl)phenyl group of the catalyst. See Refs. [11] and [15a] for a related model for reactions with alkylated MTMs.

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