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Stereoselective Synthesis of α-Fluoro-γ-nitro Thioesters under Organocatalytic Conditions

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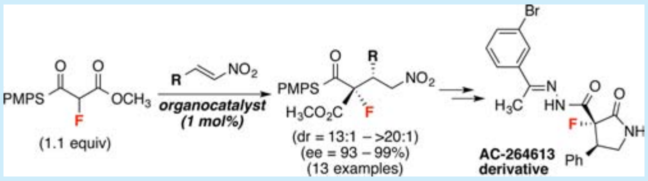
Supporting Information

ABSTRACT: Fluorinated monothiomalonates (F-MTMs) were used as building blocks for the stereoselective synthesis of organofluorine compounds. We present conjugate addition reactions between F-MTMs with nitroolefins that proceed under mild organocatalytic conditions and provide access to α-fluoro-γ-nitro thioesters with adjacent tetrasubstituted and tertiary stereogenic centers. Only 1 mol % of a cinchona alkaloid–urea catalyst is necessary to obtain the addition products in excellent yields and stereoselectivities. The methodology allowed for the straightforward synthesis of a fluorinated analogue of the PAR-2 agonist AC-264613.



Fluorinated nitrogen heterocycles are attracting growing interest in medicinal chemistry due to the unique properties of fluorine.[1] The introduction of fluorine can tune the acidity, lipophilicity, conformation, and metabolic stability of organic molecules.[2] As a result, approximately 20% of all drugs on the market contain at least one fluorine atom.[2,3] In addition, more than half of all FDA-approved small-molecule-based drugs contain nitrogen heterocycles.[4] Several top-selling drugs and drug candidates feature both fluorine and nitrogen heterocycles (Figure 1).[1−5]

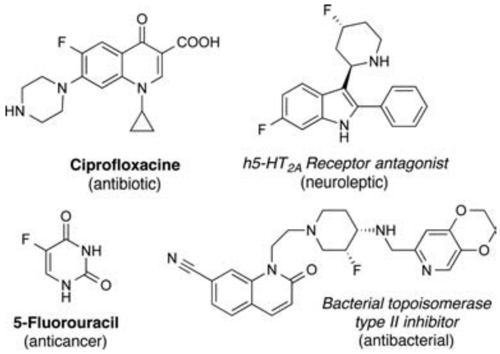


Figure 1. Examples of fluorinated heterocyclic therapeutically active compounds.

However, the selective introduction of fluorine into organic molecules, in particular at sp^3-hybridized carbons, is challenging.[6] The development of effective synthetic methods for the introduction of fluorine into nitrogen-containing compounds is therefore important and needed to further increase the number of fluorinated heterocyclic drug candidates. The use of fluorinated building blocks in combination with asymmetric catalysis is an effective strategy for the stereoselective introduction of fluorine. However, the repertoire of fluorinated building blocks is limited, and control over the stereochemistry of fluorinated centers is nontrivial.[6]

Fluorinated malonates and β-ketoester derivatives have emerged as attractive synthons of fluoro enolates in stereoselective C−C bond formations.[7] Recently, we introduced fluorinated derivatives of malonic acid half thioesters (F-MAHTs) and their protected variants, monothiomalonates (F-MTMs), as synthons of fluorinated thioester enolates.[8,9] Organocatalytic aldol and Mannich-type reactions with F-MAHT and F-MTM, respectively, yielded fluorinated aldol products and β-amino thioesters in high yields and stereoselectivities. Furthermore, the thioester moiety allowed for further functionalization, for example, by Fukuyama reduction followed by a subsequent aldol reaction into polyketide substructures or by coupling-reagent-free peptide synthesis.[8,9] We therefore anticipated that these fluoroacetate analogues would also enable the stereoselective installation of fluorine in other C−C bond-forming reactions under mild reaction conditions and allow for further transformations into versatile synthetic building blocks.

Herein, we disclose organocatalyzed conjugate addition reactions of fluorinated monothiomalonates (F-MTMs) to nitroolefins. The resulting α-fluoro-γ-nitro thioesters were obtained in high yields and stereoselectivities and allowed for straightforward access to fluorinated lactams as showcased by the synthesis of a fluorinated derivative of the PAR-2 agonist AC-264613.

We started by exploring the decarboxylative addition reaction of F-MAHT **1** to β-nitrostyrene. Cinchona alkaloid–urea derivatives were used as catalysts since they had proven optimal for previous reactions with F-MAHTs and unsubstituted MAHTs.[8,10,11] Testing of various solvents showed that F-MAHT **1** reacts with β-nitrostyrene only in ethyl vinyl ether

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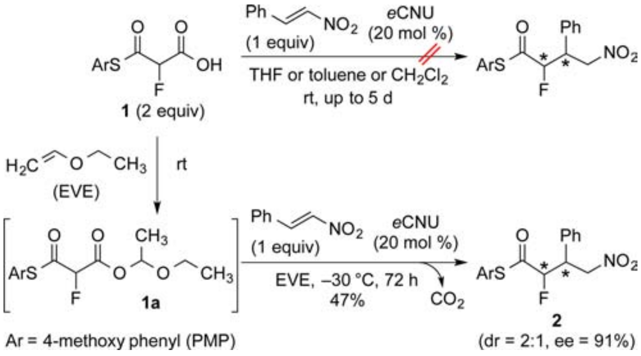
(EVE). In the presence of 20 mol % of *epi*-cinchonine–urea (*e*CNU), γ-nitro thioester **2** was obtained in modest yield (47%) and diastereoselectivity (2:1) but good enantioselectivity (91%, Scheme 1). A closer look at the course of the reaction revealed that F-MAHT initially reacts with EVE in situ to form **1a**,[10] which then further reacts with β-nitrostyrene.

Scheme 1. F-MAHT Addition Reaction to Nitrostyrene

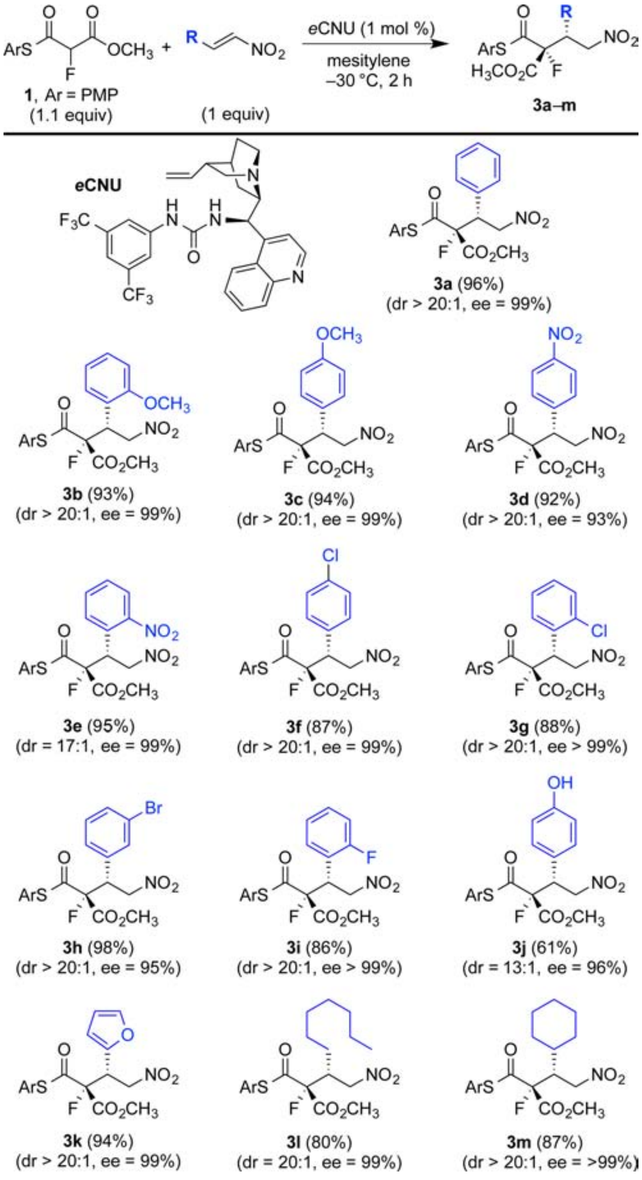


We therefore turned our attention to F-MTMs, the protected variants of F-MAHTs, and probed their reactivity with β-nitrostyrene in the presence of catalytic amounts of cinchona alkaloid–urea derivatives.[12] Reassuringly, the desired α-fluoro-γ-nitro thioester **3a** bearing adjacent tri- and tetrasubstituted stereogenic centers formed readily. Under optimized reaction conditions (see the Supporting Information for details), the conjugate addition product was obtained in 96% yield in the presence of 1 mol % of *e*CNU using close to stoichiometric amounts of the reactants at −30 °C in mesitylene within only 2 h (Scheme 2).

Next, we evaluated the scope of the conjugate addition reaction and reacted a range of aromatic and aliphatic nitroolefins with F-MTM (**1**) in the presence of 1 mol % of catalyst *e*CNU. Electron-poor as well as electron-rich aromatic nitroolefins reacted smoothly with F-MTM (**1**) and provided the addition products **3b–k** in high yields and excellent stereoselectivities (Scheme 2). Even an aromatic nitroolefin bearing a hydroxy group reacted with **1** to afford the corresponding α-fluoro-γ-nitro thioester **3j** in 61% yield with good diastereoselectivity of 13:1 and enantioselectivity of 96%. In addition, the heteroaromatic furanyl α-fluoro-γ-nitro thioester **3k** was obtained in a yield of 94%, with almost perfect stereoselectivity (dr >20:1, 99% ee). Remarkably, even aliphatic nitroolefins, which are known to be particularly challenging substrates, reacted in the presence of 5 mol % of *e*CNU to afford α-fluoro-γ-nitro thioesters **3l** and **3m** in yields greater than 80% and excellent stereoselectivities (dr ≥20:1, ≥ 99% ee).[13]

A crystal structure of conjugate addition product **3d** confirmed the absolute and relative configuration of the fluorinated γ-nitro thioesters (Figure 2).[14] Moreover, the crystal structure showed an *anti* orientation of the fluorine substituent to the vicinal hydrogen atom, which suggests that the conformation of the addition products is controlled by the fluorine gauche effect.[15] Within the ^{1}H NMR spectra of the addition products **3a–m**, $^{3}J_{\mathrm{HF}}$ coupling constants in the range of 26.5–30.5 Hz showed that this gauche effect is also effective in the solution phase.[9,16]

Scheme 2. Scope of Conjugate Addition Reactions of F-MTMs with Nitroolefins[13]



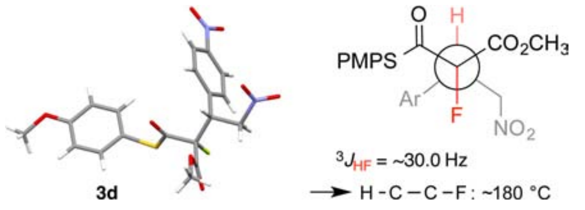
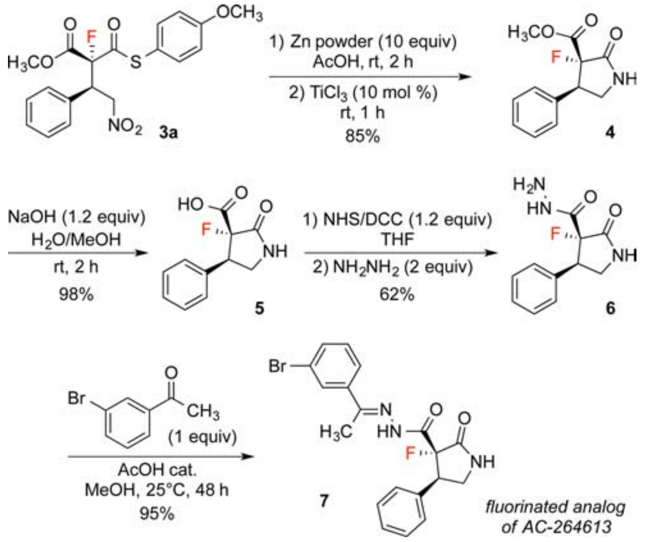


Figure 2. X-ray crystal structure of **3d** and $^{3}J_{\mathrm{HF}}$ coupling constant observed by ^{1}H NMR spectroscopy in solution.

Finally, we explored the value of the α-fluoro-γ-nitro thioesters for accessing fluorinated lactams and chose a fluorinated analogue of the proteinase-activated receptor-2 (PAR-2) agonist AC-264613 as a target compound (Scheme 3).[17] PAR-2 agonists have therapeutic potential as gastroprotective agents as well as against pulmonary inflammation and asthma.[18] AC-264613 was discovered by a high-throughput functional screening.[17] Further modifications hold promise for improving the activity profile. Our methodology allowed for obtaining a fluorinated analogue of AC-264613 starting from α-fluoro-γ-nitro thioester **3a** (Scheme 3). The synthetic route

Scheme 3. Synthesis of a Fluorinated Analogue of AC-264613



involves an initial reductive cyclization of **3a** to afford lactam **4**. Subsequent hydrolysis of the methyl ester yielded carboxylic acid **5**. Activation with *N*-hydroxysuccinimide (NHS) and dicyclohexylcarbodiimide (DCC) followed by reaction with hydrazine afforded hydrazide **6**, which was condensed with 3′-bromoacetophenone to yield the fluorinated analogue **7** of AC-264613 (Scheme 3).

In summary, we have developed an efficient methodology for the synthesis of α-fluoro-γ-nitro thioesters under mild organocatalytic conditions. The products were obtained in excellent yields and stereoselectivities with low catalyst loadings. They can be easily further transformed into, e.g., fluorinated β-lactams as shown by the synthesis of a fluorinated analogue of the PAR-2 agonist AC-264613. These results underline the value of fluorinated monothiomalonates (F-MTMs) as fluoroacetate−enolate equivalents in asymmetric synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02795.

> Experimental details, catalyst and optimization of reaction conditions, as well as X-ray crystal structure data for **3d** (PDF)

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Notes

The authors declare no competing financial interest.

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(13) For the synthesis of conjugate addition products **3d**, **3e**, **3l**, and **3m**, 12 h of reaction time was needed for full conversion. 5 mol % of catalyst was used to obtain compounds **3l** and **3m**.

(14) The stereochemical outcome of the reaction is in agreement with the geometry of the transition state in which F-MTM coordinates to the urea moiety of the catalyst and the aryl thioester of the F-MTM is oriented away from the 3,5-di(trifluoromethyl)phenyl group of the catalyst, see ref 12a for a related model for reactions with alkylated MTMs.

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