OL Organic Letters

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Decarboxylative Organocatalyzed Addition Reactions of Fluoroacetate Surrogates for the Synthesis of Fluorinated Oxindoles

Dominik Zetschok, Lukas Heieck, and Helma Wennemers*

Cite This: *Org. Lett.* 2021, 23, 1753–1757 Read Online

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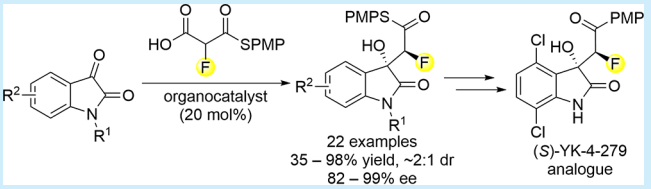
ABSTRACT: Fluorinated malonic acid half thioesters (F-MAHTs) were used as thioester enolate equivalents in organocatalyzed addition reactions to isatins. The products from a range of different *N*-protected and nonprotected isatins were obtained under mild reaction conditions in high yields and enantioselectivities. The unique reactivity of the thioester moiety enabled diverse derivatization and allowed for the straightforward access to a fluorinated analogue of the anticancer agent (*S*)-YK-4-279, a therapeutically active compound against Ewing's sarcoma.



Fluorinated small molecules have found widespread use in medicinal chemistry as the introduction of fluorine can lead to an improved activity, metabolic stability, and lipophilicity of therapeutically active compounds.[1,2] Our group recently introduced fluorinated malonic acid half thioesters (F-MAHTs) as fluoroacetate surrogates for stereoselective organocatalyzed aldol reactions and their protected derivatives, monothiomalonates (F-MTMs), for Mannich and Michael additions.[3−5] These reagents are thioester enolate equivalents (Figure 1A) and allow for the stereoselective introduction of fluorine at sp^3-hybridized carbon centers.[3−5] The decarboxylative aldol addition of F-MAHTs to aldehydes yielded α-fluoro-β-hydroxy thioesters as versatile building blocks for further derivatization, for example, into a fluorinated analog of atorvastatin, a blockbuster antihypercholesterolaemia drug.[3]

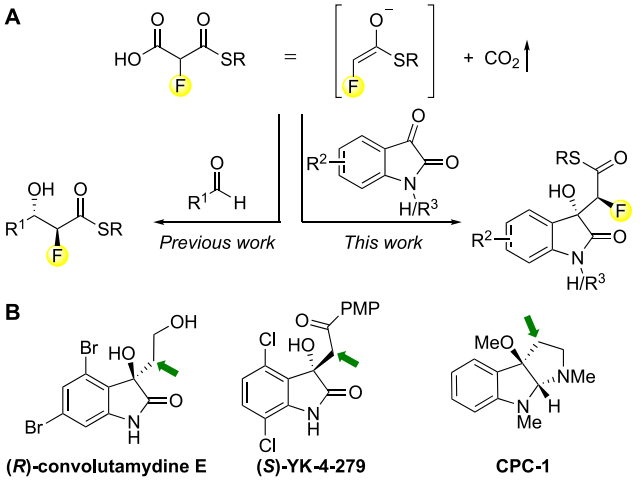


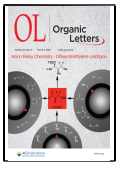
Figure 1. (A) F-MAHTs as fluoroacetate surrogates and the addition reaction to aldehydes and isatins, respectively. (B) Examples of oxindole natural products or pharmaceutically active compounds. The arrows mark positions for selective fluorination via fluoroacetate chemistry.

Oxindoles are widespread among natural products and pharmaceutically active compounds (Figure 1B).[6] Fluorinated derivatives have therefore attracted much attention.[7] Most procedures for the fluorination of oxindoles are, however, limited to the inner oxindole core.[8] Fluorination of the oxindole side chain is desirable as it can lead to metabolically more stable derivatives and more rigid structures due to the fluorine gauche effect (Figure 1B).[1,2] To date, protocols for the preparation of fluorinated 3-hydroxy-3-substituted oxindoles are limited to the installation of a ketone moiety in the side chain.[9−11] There is therefore a need for more versatile methods that allow for the incorporation of fluorine into the side chain of the oxindole scaffold and provide access to different functional moieties.

We anticipated fluorinated thioester−enolate equivalents as effective building blocks for the preparation of fluorinated oxindoles (Figure 1A, right). Further, the thioester should provide a platform for derivatization[12,13] and, thus, be useful for the preparation of, for example, fluorinated oxindoles of therapeutic relevance.

Herein, we report the enantioselective, organocatalyzed addition of F-MAHTs to isatins. We show that the obtained fluorinated oxindole-thioesters can be converted into multiple different derivatives in good yields. The methodology also provided access to a fluorinated analogue of (*S*)-YK-4-279, a

Received: January 18, 2021
Published: February 16, 2021



https://dx.doi.org/10.1021/acs.orglett.1c00172
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therapeutically active compound against the rare bone cancer Ewing's sarcoma.[14]

We started our investigations by allowing F-MAHT **1** and F-MTM **2** to react with *N*-methylisatin in THF in the presence of an *epi*-quinidine–urea organocatalyst (Cat **A**) that had been optimal for related reactions (Table 1, top).[3] The reaction with F-MTM did not yield the desired product **3**, and only starting material was recovered. Here, the reactants are most likely in equilibrium with the addition product **3**, but the equilibrium lies on the side of the starting materials. In contrast, the addition of F-MAHT **1** to isatin proceeded well and afforded the product **4a** with 91% yield and an encouraging 64% ee. These results show that the decarboxylation of F-MAHT over the course of the addition provides a strong driving force and is key for the reaction to proceed.[4,15−17]

Variations of the hydrogen-bonding motif within the cinchona alkaloid catalyst with urea, thiourea, squareamide and sulfonamide moieties showed that sulfonamide **D** catalyzes the addition reaction of **1** to *N*-methyl isatin with the highest conversion (quant.) and enantioselectivity (82% ee, Table 1, entry 4). Subsequently we tested modifications of catalyst **D** and performed a screening of the reaction parameters, including the solvent, stoichiometry, additives, and temperature.[18] These studies revealed that *epi*-cinchonidine–sulfonamide catalyst **E**[19,20] is optimal for catalyzing the addition of F-MAHT to *N*-methylisatin. In acetone at 10 °C, **4a** was obtained in 98% yield, 1.5:1 dr, and 92% ee (Table 1 entry 8).

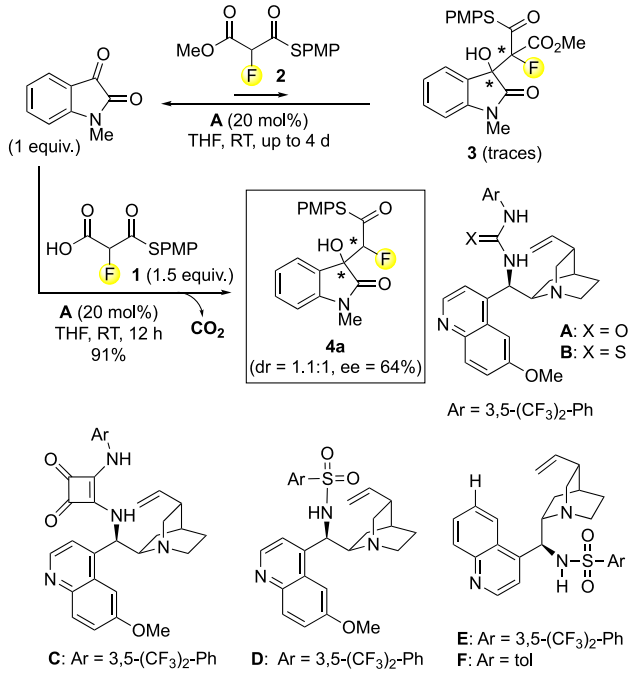
Regardless of the conditions, the diastereoselectivity of the addition remained poor. This finding is likely due to decarboxylation of the F-MAHT after C–C bond formation[15−17] without substrate or catalyst control. Neither basic or acidic additives nor catalyst optimization improved the diastereoselectivity of the reaction.[18] However, the obtained diastereoisomers could be separated by column chromatography, thus enabling the isolation of both diastereoisomers.

Next, we evaluated the scope of the F-MAHT addition to isatins (Scheme 1). At first, we examined differently substituted *N*-methylisatins and observed that both electron-rich and electron-poor isatins reacted efficiently to yield 3-hydroxyoxindoles in good to excellent yields (78–98%) and enantioselectivities (87–93% ee, **4c**, **4d**, **4f–h**). Whereas previous synthetic protocols for the synthesis of monofluorinated 3-hydroxyoxindoles[10] did not tolerate substituents at C4, F-MAHT **1** reacted readily with 4-substituted isatins in good yields and excellent enantioselectivities (**4i**, **4j**, **4l–n**). Even the isatin with a sterically demanding bromine substituent reacted, and addition product **4l** was isolated in 79% yield and 96% ee. The poorest reactivity was observed for the bulky biphenyl derivative **4m** that was still isolated in 35% yield and 99% ee. In addition, 3-hydroxyoxindoles with substituents at each of the other positions and/or more than one substituent were readily obtained (**4n**, **4q–v**). We also probed derivatives with different substituents at the isatin N and found that methyl and benzyl protection afforded products with high yields and stereoselectivities (**4n** and **4p**). Boc-protected isatins did not yield the desired product, which was probably due to competitive hydrogen bonding with the catalyst and/or the increased steric hindrance. Remarkably, reactions with unprotected isatin derivatives provided the addition products (**4b**, **4e**, **4k**, **4o**) in comparable yields and enantioselectivity as observed for the *N*-alkylated analogues (**4a**, **4d**, **4j**, **4n**). These findings show that isatins with a broad range of substituents and substitution patterns and even unprotected isatins react readily to enantioenriched fluorinated 3-hydroxyoxindoles under the optimized reaction conditions.

Single crystals of **4p** revealed the absolute and relative configuration of the fluorinated 3-hydroxyoxindole (Scheme 1).[21] Within the crystal structure, the relative orientation of the vicinal F and OH groups is gauche and that of the F and thioester groups is anti. This finding suggests that the conformation of the 3-hydroxyoxindoles is controlled by a gauche effect.

Next, we explored the synthetic versatility of the thioester moiety. The transformation of **4a** into oxoester **5** and amide **6** by the addition of an alcohol or amine, respectively, afforded the desired products in quantitative yields (Scheme 2, top). Furthermore, we were able to obtain the corresponding alcohol **7** by reduction with sodium borohydride and ketone **8** under Liebeskind–Srogl conditions[22] in good yields (Scheme 2, bottom).

Table 1. Addition of a F-MAHT and a F-MTM to *N*-Methylisatin



entry	cat.	solvent[a]	additive[b]	conv[c]	dr[d]	ee[e]
1	**A**	THF		91	1.1:1	−64
2	**B**	THF		>98	1.3:1	−30
3	**C**	THF		>98	1.2:1	14
4	**D**	THF		>98	1.5:1	−82
5	**D**	CH_2Cl_2		12	1.1:1	−82
6	**D**	toluene		8	1.4:1	−82
7	**D**	acetone		>98	1.4:1	−90
8	**E**	**acetone**		**>98**	**1.5:1**	**92**
9	**F**	acetone		>98	1.6:1	73
10	**E**	acetone	DMAP	83	1.8:1	31
11	**E**	acetone	$PhCO_2H$	75	1.5:1	89
12	**E**	acetone	Et_3N	>98	1.3:1	57

[a]*N*-Methylisatin 25 mM, F-MAHT 37.5 mM. [b]0.5 equiv. [c]Conversion as estimated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [d]dr as determined by ^{1}H NMR spectroscopy. [e]ee as determined by chiral stationary-phase HPLC and/or SFC.

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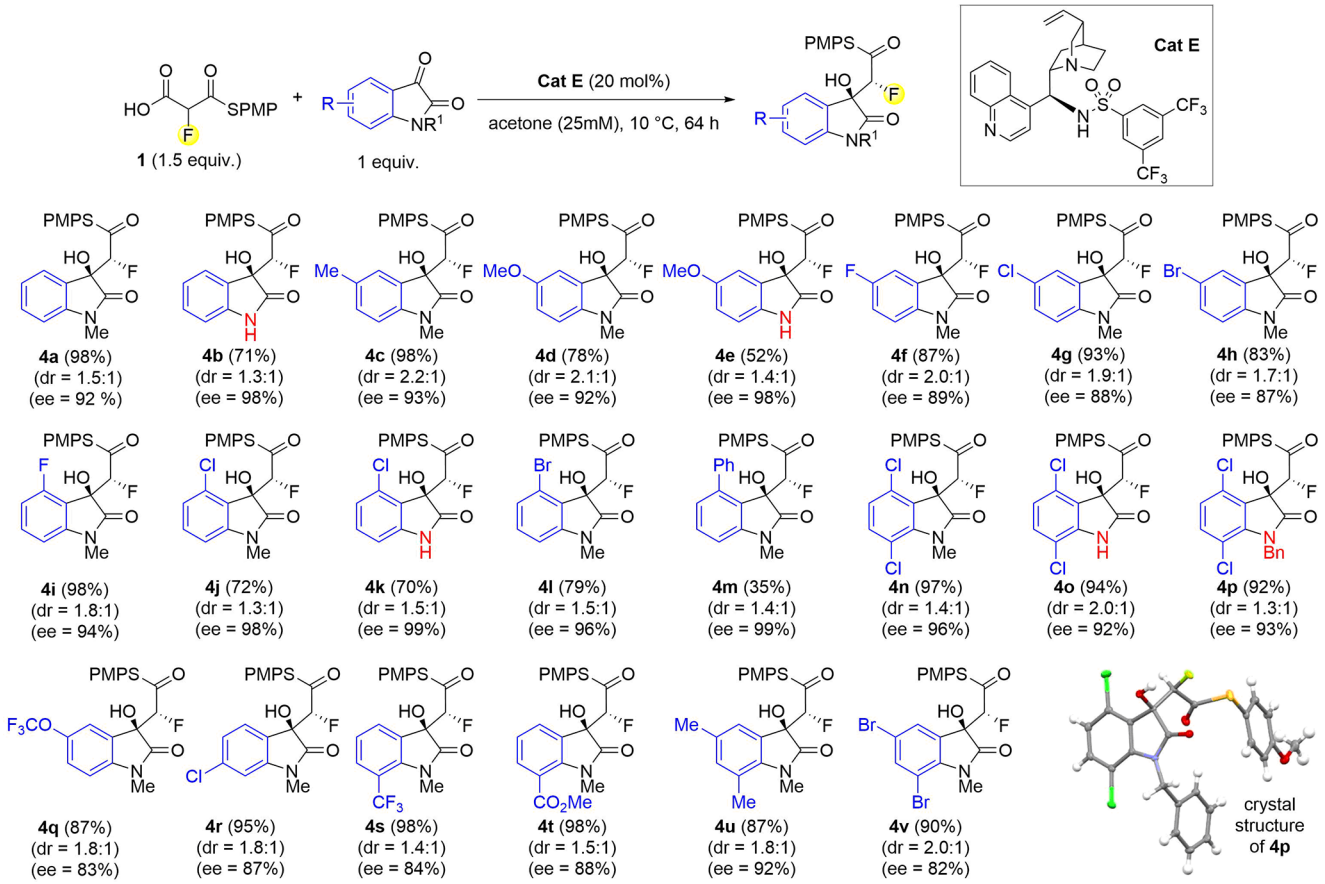
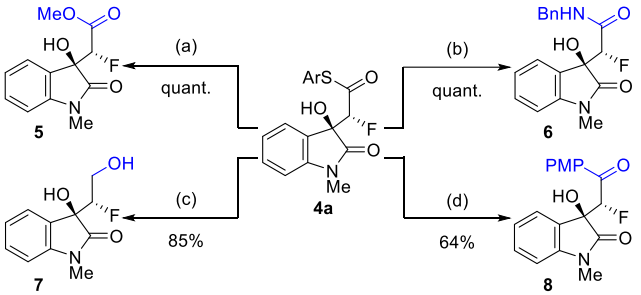
Scheme 1. Scope of the F-MAHT Addition to Isatins



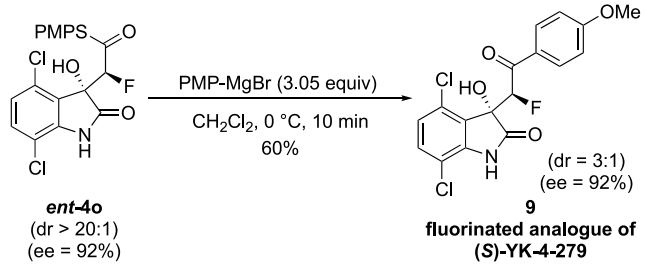
Scheme 2. Derivatization of the Thioester Moiety[a]



[a]Conditions: (a) K_2CO_3 (3.0 equiv), MeOH, rt, 2 h; (b) $BnNH_2$ (3.0 equiv), CH_2Cl_2, rt, 5 h; (c) $NaBH_4$ (5.0 equiv), THF, 0 °C, 1 h; (d) CuTC (1.6 equiv), $PMPB(OH)_2$ (1.2 equiv), Pd_2dba_3 (5 mol %), $(furyl)_3P$ (15 mol %), THF, 50 °C, 20 h.

Encouraged by these results, we explored the synthesis of a fluorinated analogue of (*S*)-YK-4-279, a biologically active compound against the rare bone cancer Ewing's sarcoma.[14] We envisioned a concise access to the fluorinated target ketone **9** by addition of F-MAHT **1** to 4,7-dichloroisatin in the presence of the pseudoenantiomer of catalyst **E**[23] as the key step. Indeed, the mirror-image addition product *ent*-**4o** was obtained with the same high enantioselectivity (92% ee), and the diastereoisomers (dr 1.8:1) were separated by column chromatography.[24] Somewhat surprisingly, Fukuyama coupling[13] with (4-methoxyphenyl)zinc bromide under different conditions did not yield ketone **9**, and only starting material remained. In addition, Liebeskind–Srogl conditions with the corresponding boronic acid did not enable the conversion of thioester *ent*-**4o**. This significantly lower reactivity of *ent*-**4o** compared to **4a** is most likely due to the greater steric congestion caused by the chlorine substituent, thereby hindering the oxidative addition onto the palladium catalyst. Reassuringly, careful addition of the corresponding Grignard reagent to thioester *ent*-**4o** allowed for the preparation of ketone **9** in 60% yield, albeit with an erosion of the diasteroselectivity under the basic reaction conditions (Scheme 3). No evidence of overaddition of the Grignard reagent to the formed ketone was observed.

Scheme 3. Synthesis of Fluorinated (*S*)-YK-4-279



In summary, we have developed an efficient organocatalytic method for the synthesis of fluorinated 3-hydroxyoxindoles with excellent yields and enantioselectivities. The methodology puts forth the first addition of F-MAHTs to ketones and tolerates both protected and unprotected isatins with a diverse set of substituents and substitution patterns. The thioester

https://dx.doi.org/10.1021/acs.orglett.1c00172
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moiety provides a platform for fruitful follow up chemistry and allowed the concise synthesis of a fluorinated analogue of (*S*)-YK-4-279. The results highlight the versatility and utility of F-MAHTs as fluoroacetate surrogates in decarboxylative addition reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00172.

Experimental details, optimization of reaction conditions and catalyst, as well as analytical data including NMR spectra, HPLC chromatograms, and X-ray crystal structure of **4m** and **4p** (PDF)

Accession Codes

CCDC 2049349 and 2056442 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Helma Wennemers − *Laboratory of Organic Chemistry, D-CHAB, ETH Zurich, CH-8093 Zurich, Switzerland;* orcid.org/0000-0002-3075-5741; Email: helma.wennemers@org.chem.ethz.ch

Authors

Dominik Zetschok − *Laboratory of Organic Chemistry, D-CHAB, ETH Zurich, CH-8093 Zurich, Switzerland*

Lukas Heieck − *Laboratory of Organic Chemistry, D-CHAB, ETH Zurich, CH-8093 Zurich, Switzerland*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00172

Author Contributions

D.Z. and L.H. conducted the experiments. D.Z. and H.W. conceived and designed the project, analyzed the data, and prepared this manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Swiss National Science Foundation (grant 200020_169423). We thank Dr. Nils Trapp and Michael Solar from the Small Molecule Crystallography Center (SMoCC) of ETH Zurich for recording the X-ray crystal structures.

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(21) The stereochemical outcome of the addition reaction is in agreement with a transition-state geometry in which the F-MAHT coordinates to the sulfonamide and the phenyl thioester moiety of the F-MAHT is oriented away from the 3,5-di(trifluoromethyl)phenyl group of the catalyst. For a depiction of a plausible transition-state model, see, for example: (a) Bahlinger, A.; Fritz, S. P.; Wennemers, H. Stereoselective Organocatalyzed Synthesis of a-Fluorinated β-Amino Thioesters and Their Application in Peptide Synthesis. *Angew. Chem., Int. Ed.* **2014**, *53*, 8779−8783. (b) Arakawa, Y.; Fritz, S. P.; Wennemers, H. Organocatalytic Stereoselective Synthesis of Acyclic γ-Nitrothioesters with All-Carbon Quaternary Stereogenic Centers. *J. Org. Chem.* **2014**, *79*, 3937−3945.
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(24) Note that the separation of the diastereoisomers by column chromatography was tested with selected examples and was feasible for all of these spot checks.

https://dx.doi.org/10.1021/acs.orglett.1c00172
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