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# Direct Access to β-Trifluoromethyl-β-hydroxy Thioesters by Biomimetic Organocatalytic Enantioselective Aldol Reaction

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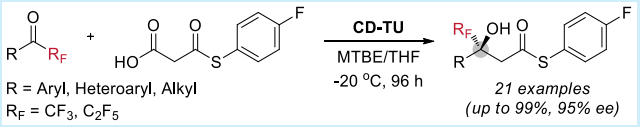
Supporting Information

**ABSTRACT:** A broadly applicable biomimetic enantioselective decarboxylative catalytic aldol reaction of trifluoromethyl ketones with malonic acid half-thioesters (MAHTs) is described. Utilizing cinchona-based thioureas as highly efficient polyketide synthase-mimic catalysts, chiral tertiary aldols, β-trifluoromethyl-β-hydroxy thioesters, were obtained in up to 99% yield and 95% ee. Facile transformation of the thioester moiety of the aldol adducts showcases the synthetic utility of this biomimetic aldol protocol to deliver a range of chiral trifluoromethylated tertiary aldol pharmacophores.




Chiral secondary and tertiary β-hydroxy ester units are encountered in various natural products and biologically and pharmaceutically relevant compounds (Figure 1).[1,2]

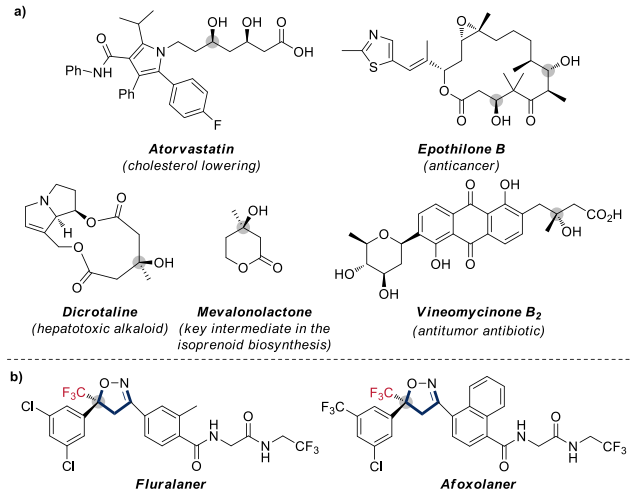



**Figure 1.** (a) Representative examples of acetate aldol containing therapeutic and natural compounds; gray-colored circles represent the positions for the selective incorporation of $CF_3$-group via aldol chemistry. (b) Commercially available antiparasitic isoxazoline drugs bearing synthetic equivalents of chiral β-$CF_3$-β-hydroxy ester.

Currently, the incorporation of fluorine atom(s) into druglike molecules has attracted a great deal of interest in drug discovery, since it can improve the pharmacological properties of a bioactive molecule by altering its lipophilicity, metabolic stability, and bioavailability compared to the nonfluorinated parent compound.[3] In particular, the trifluoromethyl group (−$CF_3$) is frequently used as a bioisostere to improve both pharmacodynamics and pharmacokinetics of the molecule by replacing a chloride or a methyl group.[4]

In this regard, the enantioselective incorporation of $CF_3$ unit into bioactive chiral β-hydroxy ester derivatives would be one outstanding challenge for expansion of the pharmaceutical library with potentially interesting bioactivities (Figure 1a). Some of antiparasitic isoxazoline drugs (e.g., fluralaner and afoxolaner[5]) possessing synthetic equivalents of chiral β-$CF_3$-β-hydroxy esters are already available on the market (Figure 1b).

In principle, chiral β-trifluoromethyl β-hydroxy esters can be directly accessed by a catalytic asymmetric aldol reaction of trifluoromethyl ketones as aldol acceptors with ester enolate derivatives as aldol donors. Surprisingly, the direct catalytic enantioselective aldol reaction engaging trifluoromethyl ketones with simple ester enolate equivalents is little explored since simple esters without electron-withdrawing α-substituents are regarded as challenging aldol donor precursors in terms of reluctant enolization.[6] To the best of our knowledge, the direct aldol reaction of trifluoromethyl ketones with enolates possessing the oxidation state of carboxylic acid derivatives have so far not been realized.[7]

By contrast, Nature freely uses the enzymatic decarboxylative activation of malonic acid half-thioesters (MAHTs) to generate simple ester enolates or their equivalents in the biosynthesis of polyketides and fatty acids.[8] Inspired by Nature, recently, we successfully utilized MAHTs as ester enolate equivalents in the organocatalytic decarboxylative aldol reactions of MAHTs with aldehydes to obtain enantioenriched β-hydroxy thioesters.[9] Thus, we presumed that interconnecting MAHTs and trifluoromethyl ketones via biomimetic aldol reactions would allow for facile access to a tertiary β-hydroxy ester units with $CF_3$-group. Systematic and cooperative hydrogen-bonding catalysis mimicking the action of polyketide synthases might be crucial for the deprotonation/stabilization of MAHTs and orientation of trifluoromethyl ketones for high facial selectivity (Figure 2).

Herein we report a broadly applicable organocatalytic enantioselective decarboxylative aldol reaction of MAHTs

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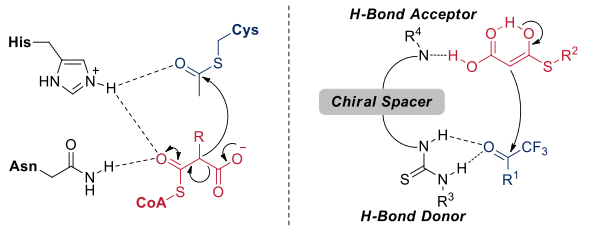
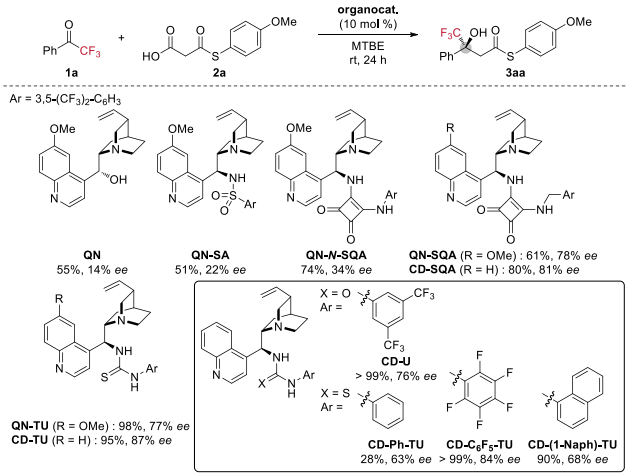



**Figure 2.** Reaction mechanism of the polyketide synthase catalyzed malonyl-CoA addition to a thioester (left) and a plausible working model of an organocatalyzed aldol reaction of MAHT and trifluoromethyl ketones (right).

with a variety of trifluoromethyl ketones using cinchona-based thioureas as highly efficient polyketide synthase-mimic catalysts. The resulting enantio-enriched trifluoromethyl-substituted $\beta$-hydroxy thioesters were easily converted into a range of chiral trifluoromethylated tertiary aldol pharmacophores, highlighting the synthetic utility of the present biomimetic aldol protocol.

For our initial studies, the addition of MAHT (**2a**) and 2,2,2-trifluoroacetophenone (**1a**) in methyl *tert*-butyl ether (MTBE) at room temperature was chosen as a model reaction (Scheme 1). Acid−base bifunctional cinchona alkaloid

**Scheme 1. Catalyst Screening**[abc]




[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv, 0.3 mmol), catalyst (10 mol %, 0.02 mmol), MTBE (anhydrous, 0.1 M, 2.0 mL), rt, 24 h. [b]The conversion was determined by $^{19}$F NMR integration. [c]The % ee values were determined by HPLC analysis using a chiral stationary phase.

derivatives are known to promote addition reactions of MAHTs,[9,10] and we therefore examined their catalytic performance in this model reaction. As shown in Scheme 1, the catalyst screening revealed thiourea-type catalysts (QN-TU and CD-TU) and showed promising catalytic results, whereas all the others (QN, QN-SA, QN-*N*-SQA, QN-SQA, and CD-SQA) gave inferior catalytic results (see the Supporting Information for further catalyst screening results). Notably, the absence of a methoxy group at the 6′-position of the quinoline moiety in the thiourea catalysts provoked a dramatic change in enantioselectivity (77% ee using QN-TU vs 87% ee using CD-TU). These results prompted us to further investigate cinchonidine thiourea type catalysts in detail, to improve activity and enantioselectivity. However, a modification of aromatic moiety in cinchonidine-based catalysts did not improve the catalytic outcomes. The incorporation of an urea moiety instead of a thiourea was also not beneficial in terms of enantioselectivity and reactivity (87% ee using CD-TU vs 76% ee using CD-U). Thus, further optimization studies were conducted with CD-TU as the optimal catalyst. Lowering reaction temperatures resulted in increased enantioselectivity (87% ee at rt; 90% ee at 0 °C, entry 1; 92% ee at −20 °C, entry 3). The enantioselectivity could be further increased (91% ee at 0 °C, entry 2; 95% ee at −20 °C, entry 4) by employing the *para*-fluorophenyl substituted MAHT (**2b**) (see the Supporting Information for further MAHT screening results). However, only 50% conversion after 96 h was observed at −20 °C (entry 4). Even with higher catalyst loading (30 mol %), the reaction proceeded very slowly (entry 5). To our delight, however, a significant increase in yield without any erosion of the enantioselectivity was achieved simply by adding THF as a cosolvent (entry 6 and 7). Further solvent screening did not improve the catalytic outcome (see the Supporting Information for further solvent screening results). Thus, the reaction condition of entry 7 (using **2b**, MTBE/THF (1:1 v/v)) proved to be optimal in terms of both chemical yield and enantioselectivity.

Under the optimized reaction conditions (entry 7 of Table 1), a variety of trifluoromethyl ketones **1a**−**1u** were subjected to this protocol. As shown from the results summarized in Scheme 2, most of the trifluoromethylated tertiary aldols (**3**) were obtained in high yields and enantioselectivity. Regardless of the electronic and steric nature of the aromatic substituent, high enantioselectivity (up to 95% ee) was achieved. In addition to aryl trifluoromethyl ketones **1a**−**1q**, heteroaromatic trifluoromethyl ketones were also smoothly converted into the desired products **3r**−**3s** with good enantioselectivity. Aliphatic trifluoromethyl ketone **1t** was tolerated and yielded the desired aldol products **3t**, however, only with moderate enantioselectivity. Notably, the reaction also worked well with ketone with $CF_2CF_3$ group to give the corresponding tertiary aldol **3u** in good enantioselectivity. In addition, the absolute configuration of **3a** and **3d** was determined to be (*S*) by comparison with the sign of optical rotation of the transesterification products **4a** and **4d** reported in the literature (Scheme 3).[11]

Thioesters are ubiquitous not only in many biosynthetic reactions (e.g., in the biosynthesis of fatty acids, polyketides and nonribosomal peptides)[12] but also in many functional group manipulations and C−C bond forming reactions, since they are more reactive toward nucleophiles than analogous oxyesters due to smaller orbital overlap between the sulfur as well as the higher acidity of $\alpha$-proton.[13,14a] Thus, to illustrate the synthetic utility of our aldol protocol, diverse transformation of the thioester moiety of enantio-enriched $CF_3$-containing tertiary aldols **3** were performed. Products (**4a** and **4d**) of direct transesterification were successfully obtained without any erosion of ee values.[11] The $\beta$-hydroxy amides, **5a**, **5j**, and **5r**, key building blocks in the synthesis of trifluoromethylated analogues of antidepressant drugs, such as (*R*)-fluoxetine, (*R*)-tomoxetine, and (*R*)-duloxetine, were also accessed by direct amidation.[9,14] The $CF_3$-analogue **6i** of antidepressant drug fenpentadiol[15] was also simply obtained from **3i**, using Grignard reaction. Furthermore, the ketones **7j** and **7o**, key intermediates in the synthesis of the antiparasitic isoxazoline drugs such as fluralaner and afoxolaner,[5b] respectively, were accessed from **3j** and **3o**, using Liebe-


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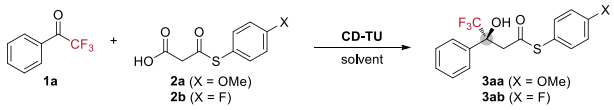
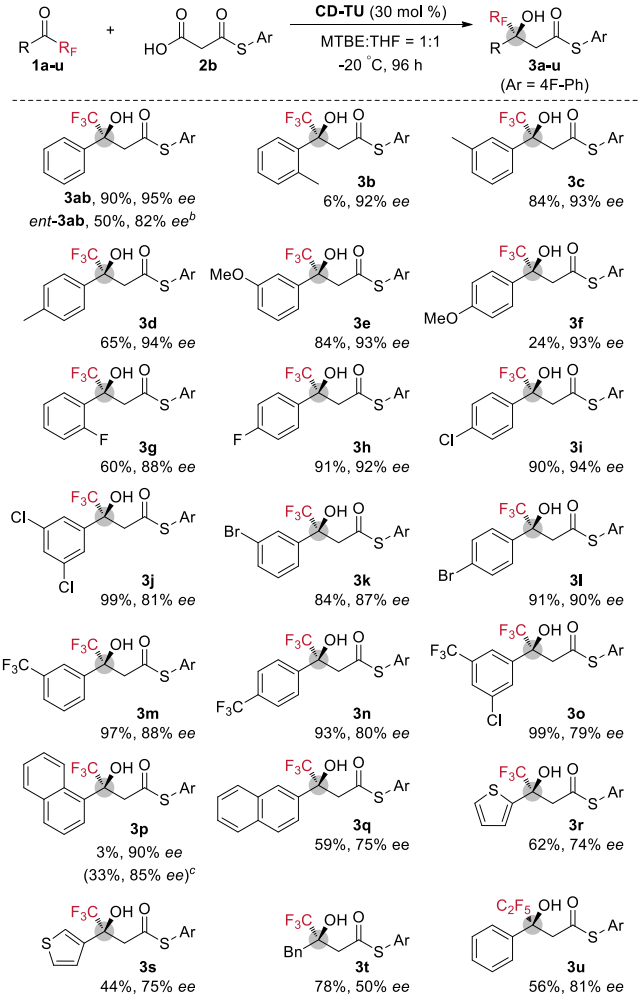
**Table 1. Reaction Condition Optimization**[a]




| entry | cat (mol %) | MAHT | solvent | temp (°C) | time (h) | conv (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | 10 | **2a** | MTBE | 0 | 48 | 95 | 90 |
| 2 | 10 | **2b** | MTBE | 0 | 48 | 50 | 91 |
| 3 | 20 | **2a** | MTBE | −20 | 96 | 74 | 92 |
| 4 | 20 | **2b** | MTBE | −20 | 96 | 50 | 95 |
| 5 | 30 | **2b** | MTBE | −20 | 205 | 82 | 95 |
| 6 | 30 | **2b** | MTBE/THF 9:1 | −20 | 96 | 82 | 95 |
| 7 | 30 | **2b** | MTBE/THF 5:5 | −20 | 96 | 87 | 95 |

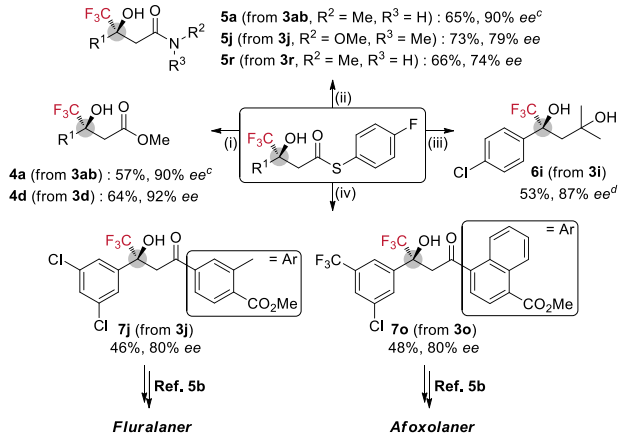
[a]Reaction conditions: **1a** (0.1 mmol), **2** (3 equiv, 0.3 mmol), CD-TU, solvent (anhydrous, 0.1 M, 1.0 mL). [b]The conversion was determined by $^{19}F$ NMR integration. [c]The % ee values were determined by HPLC analysis using a chiral stationary phase.

**Scheme 2. Substrate Scope**[a]




[a]Reaction conditions: **1a−u** (0.3 mmol), **2b** (3.0 equiv, 0.9 mmol), CD-TU (30 mol %, 0.09 mmol), MTBE/THF = 1:1 (anhydrous, 0.1 M, 3.0 mL), −20 °C, 96 h. [b]Cinchonine thiourea (CN-TU) was used. [c]Reaction was performed at rt.

**Scheme 3. Synthetic Utility of the Aldol Products**[ab]




[a]Reaction conditions: (i) Mg, MeOH, rt, 2 h. (ii) $RNH_2$, MeOH, rt, 12 h or MeNH(OMe)·HCl, $AgOCOCF_3$, $Et_3N$, DCM, rt, 72 h. (iii) (a) TMSOTf, 2,6-Lutidine, DCM, rt, 18 h. (b) MeMgBr, DCM, rt, 18 h. (c) TBAF, THF, rt, 24 h. (iv) (a) TMSOTf, 2,6-Lutidine, DCM, rt, 18 h. (b) $ArB(OH)_2$, CuTC, TFP, $Pd_2(dba)_3$, THF, reflux, 18 h. (c) TetraEG, KF, rt, 6 h. [b]Abbreviations: TMSOTf = trimethylsilyl trifluoromethanesulfonate, TBAF = *n*-tetrabutylammonium fluoride, CuTC = copper thiophene-2-carboxylate, TFP = tri(2-furyl)-phosphine, $Pd_2(dba)_3$ = tris(dibenzylideneacetone) dipalladium, TetraEG = tetraethylene glycol. [c]**3ab** (90% ee) was used. [d]**3i** (87% ee) was used.

skind-Srogl coupling.[16] Notably, a recent report suggests that fluralaner and afoxolaner can be utilized in the control of vector-borne human diseases including malaria, zika fever, and leishmaniasis.[17]

Finally, on the basis of in situ electrospray ionization mass spectroscopy (ESI-MS) analysis of the reaction mixture (see Supporting Information for details), it is proposed that nucleophilic addition of MAHTs to trifluoromethyl ketones precedes decarboxylation to complete the catalytic cycle by releasing the desired aldol products. Other types of catalytic aldol reactions using MAHTs have also been proposed to occur via a similar reaction sequence.[8b,9]

In conclusion, we have developed a broadly applicable enantioselective biomimetic aldol reaction of malonic acid half thioesters as acetate enolate precursors with a variety of trifluoromethyl ketones. Utilizing chiral cinchona-based thioureas as efficient polyketide synthase-mimic catalysts, a range of aromatic and nonaromatic trifluoromethyl ketones were converted into the corresponding *β*-hydroxy esters in good to excellent yields and enantioselectivities. The resulting enantio-enriched trifluoromethyl-substituted *β*-hydroxy thioesters were easily converted into a range of chiral



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trifluoromethylated tertiary aldol pharmacophores, facilitated by the synthetic flexibility of the sulfur atom. Thus, the current methodology will lead to various applications in the field of the development of new pharmaceutical compounds with improved therapeutic properties.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01469.

Experimental details and analytical data (PDF)

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### Notes

The authors declare no competing financial interest.

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