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An Exceptionally Mild Catalytic Thioester Aldol Reaction Inspired by Polyketide Biosynthesis

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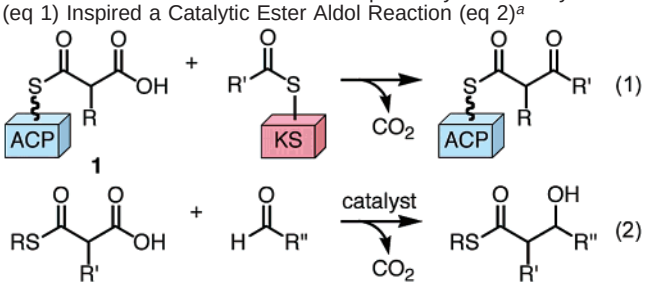
The primary carbon−carbon bond-forming reaction in the biosynthesis of polyketides and fatty acids is a decarboxylative Claisen condensation with malonic acid half thioesters (**1**) (MAHTs) as ester enolate equivalents (Scheme 1, eq 1).[1] Nature uses enzymatic activation of a MAHT to selectively generate a thioester enolate, or its equivalent, in the presence of another thioester, achieving a selective cross-Claisen condensation. The mild and selective activation of MAHTs in nature has inspired us to explore their use in metal-catalyzed decarboxylative aldol reactions (Scheme 1, eq 2).[2] This report details our discovery of a catalytic ester aldol reaction using MAHTs that directly affords β-hydroxythioesters. The reaction does not require in situ aldolate functionalization or excess nucleophile, common strategies in catalytic aldol reactions.[3−5] The reaction is catalyzed by combination of a Cu(II) salt and an amine base, and can be performed under exceptionally mild conditions (23 °C, open to the air, wet solvent[6]).

Scheme 1. Claisen Condensation Step of Polyketide Biosynthesis (eq 1) Inspired a Catalytic Ester Aldol Reaction (eq 2)[a]

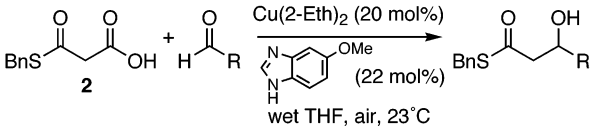


1

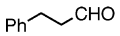
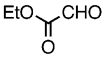
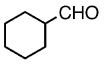
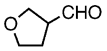
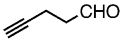
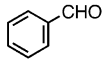
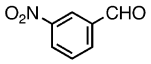
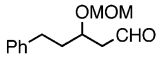
[a] ACP = acyl carrier protein; KS = ketosynthase.

Our first attempts to catalyze a decarboxylative aldol reaction (Scheme 1, eq 2), based on the conditions developed for Claisen condensations using either preformed Mg(II) salts[7] of MAHTs or MAHTs and $Mg(OAc)_2$/imidazole,[8] were unsuccessful. These results prompted us to screen other metal salts including Ni(II), Zn(II), Cu(II), and Cu(I) in combination with amine bases. The first successful decarboxylative aldol reaction, albeit stoichiometric, was observed with a combination of $Cu(OAc)_2$ and imidazole. Catalyst turnover was achieved by replacing imidazole with benzimidazole bases. The best results were obtained using Cu(2-ethylhexanoate)$_2$ as the copper source and 5-methoxybenzimidazole as the amine base. When a 1:1 mixture of **2**[9] and dihydrocinnamaldehyde in wet THF was treated with 20 mol % Cu(2-ethylhexanoate)$_2$ and 22 mol % 5-methoxybenzimidazole, the aldol adduct was obtained in 82% yield (Table 1, entry 1). Catalyst loading can be lowered to 5 mol % Cu(2-ethylhexanoate)$_2$ and 5.5 mol % 5-methoxybenzimidazole affording a 75% yield of the aldol adduct. However, with lower catalyst loadings, 3 equiv of aldehyde must be used to maintain acceptable yields. All other metals tested were significantly less efficient than Cu(II) in catalyzing this reaction.

Table 1. Catalytic Thioester Aldol Reaction



2

Entry[a]	RCHO	Time(h)	Isolated Yield (%)
1		3.5	82
2		3.5	85
3		0.5	97
4		2.5	81
5[b]		2	70[c]
6		2	65
7		24	22
8		8	82
9		24	74[d]

[a] Conditions: **2** (1 equiv), aldehyde (1 equiv), Cu(2-ethylhexanoate)$_2$ (0.2 equiv), 5-methoxybenzimidazole (0.22 equiv), wet THF, 23 °C, open reaction vessel. [b] Aldehyde used as 50% w/w mixture in H_2O. [c] 1:1 ratio of diastereoisomers. [d] From entry 1 aldol product, as a demonstration of two iterations. 1.3:1 ratio of diastereoisomers.

Remarkably, the metal-catalyzed aldol reaction is performed open to the air, at 23 °C, with reagents added in any order, and in wet THF.[10,11] Furthermore, the reaction can be run in an open vial, using acetone or EtOAc from a laboratory wash bottle as solvent. The mildness of the reaction is demonstrated by the use of aliphatic, enolizable aldehydes (Table 1, entries 1, 6, and 9) which are typically poor substrates in catalytic aldol reactions that do not use pre-enolized nucleophiles (enolsilanes).[12] The products of aldehyde self-condensation have not been observed in any of the reactions, demonstrating the mildness and selectivity of MAHTs activation under the Cu(II)/benzimidazole conditions. The reaction can even be performed with tetrahydrofuran-3-carboxaldehyde (entry 5) that is supplied as a 50% w/w solution in water. While only a modest yield of aldol product was obtained with benzaldehyde (entry 7), activated 3-nitrobenzaldehyde afforded the aldol adduct in 82% yield (entry 8). More reactive aldehydes, such as ethyl glyoxylate, performed well, yielding the aldol product in 97% yield (entry 3). Malonic acid half oxyesters, when used instead of MAHTs, do not participate in the catalytic aldol reaction.

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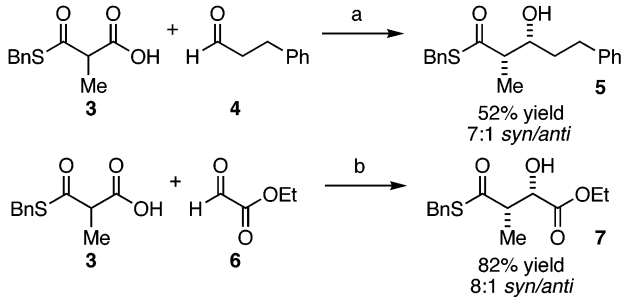
Scheme 2 [a]



[a] Conditions: (a) **3** (1 equiv), **4** (2 equiv), Cu(2-ethylhexanoate)$_2$ (0.2 equiv), 5-methoxybenzimidazole (0.2 equiv), wet THF, 23 °C, open reaction vessel. (b) **3** (1.5 equiv), **6** (1 equiv), Cu(2-ethylhexanoate)$_2$ (0.2 equiv), 5-methoxybenzimidazole (0.2 equiv), wet THF, 23 °C, open reaction vessel.

To evaluate the diastereoselectivity of this reaction, methylmalonic acid half thioester (**3**) and dihydrocinnamaldehyde (**4**) were treated with our standard catalyst combination at 23 °C, in wet THF, and open to the air. Aldol product **5** was isolated in 52% yield and as a 7:1 *syn/anti* mixture of diastereoisomers (Scheme 2). The same thioester in a reaction with ethyl glyoxylate (**6**) afforded aldol **7** in 82% yield and as a 8:1 *syn/anti* mixture of diastereoisomers. A 3:1 *anti/syn* ratio of propionate aldol diastereoisomers was not altered upon exposure to the reaction conditions, indicating that the selectivity for the *syn* product is not the result of equilibration of the aldol adducts.

Preliminary experiments have been performed to elucidate the mechanism of this reaction. If all reagents are mixed together with the exception of an aldehyde, decarboxylation[13,14] is not observed, suggesting that a Cu(II) thioacetate enolate is not generated. In addition, *gem*-dimethylmalonic acid half thioesters do not participate in the catalytic aldol reaction. Although by no means conclusive, this result suggests that enolization of the MAHT may be required for the reaction to proceed. Exposure of aldol product (Table 1, entry 1) to Cu(2-ethylhexanoate)$_2$, 5-methoxybenzimidazole, and cyclohexane carboxaldehyde did not afford any detectable crossover product, indicating that under the reaction conditions a retro-aldol reaction is not operative.[15]

The use of substrates, such as ATP, that are thermodynamically unstable (relatively high $\Delta G_f°$) *and* kinetically stable (relatively high $\Delta G°^{‡}$) is often encountered in biochemistry.[16] Another example is MAHTs, used in the Claisen condensation step of polyketide biosynthesis. The energy released upon loss of CO_2, in part responsible for the thermodynamic instability of MAHTs, provides a driving force for the Claisen condensation. Their kinetic stability makes enzymatic activation a necessity. In borrowing MAHTs from nature for our Cu(II)/amine-catalyzed aldol reaction, we are inheriting thermodynamic and kinetic properties that are useful in laboratory reactions. The kinetic stability of MAHTs[17] allows these ester enolate equivalents to be compatible with water and air. Their thermodynamic instability renders this reaction energetically favorable, obviating the need for aldolate functionalization or excess reagent to drive the reaction to completion.

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Supporting Information Available: Experimental procedures and product characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Wet solvent refers to solvent that was handled without protection from the air. In some examples, up to 20:1 THF/H_2O is tolerated.
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