Synthetic Methods

Towards Organocatalytic Polyketide Synthases with Diverse Electrophile Scope: Trifluoroethyl Thioesters as Nucleophiles in Organocatalytic Michael Reactions and Beyond**

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Dedicated to Professor Chi-Huey Wong on the occasion of his 60th birthday

Catalytic asymmetric synthesis based on simple ester nucleophiles remains an unmet challenge in organic synthesis. The difficulty with this class of potential nucleophiles lies in the relatively inert nature of the proton at the α -position of a simple carboxylic ester; the pK_a value is approximately 19.^[1] Direct asymmetric transition-metal-based approaches^[2] are well developed for carbonyl compounds bearing activating electron-withdrawing groups at the α -position, and organocatalytic approaches^[3] allow for effective nucleophile generation from simple ketones and aldehydes (via in situ enamine formation). In contrast, effective ester-based approaches are rare. Nature, however, has developed a diverse and elegant solution to this problem in its use of acyl-CoA thioesters and diverse families of polyketide synthase enzymes, which catalyze the reactions of a variety of thioesters like acetyl-CoA, propionyl-CoA, malonyl-CoA, and others en route to the synthesis of medicinally important polyketides and metabolically important fatty acids.^[4] This fact has not escaped the attention of organic chemists, and recently the groups of Shair, Cozzi, Wennemers, and Ricci have reported catalytic enantioselective reactions based on either metal catalysis or organocatalysis.^[5] Significantly, each of these reports utilizes malonic acid half thioesters as enolate precursors, and the decarboxylation of the malonic acid half thioester is used to drive enolate formation. We sought a more atom economical approach that would not require decarboxvlation as a driving force for enolization, and would thus not be constrained by the requirement of an activating carboxylate group at the α -position of the thioester.

Herein we detail the first enantioselective thioester addition reactions of simple trifluoroethyl thioesters. We not only demonstrate the enantioselective organocatalytic

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Michael reactions involving α,β -unsaturated aldehydes, but also the versatility of the trifluoroethyl thioester system in nitroolefin-based Michael, aldol, and amination reactions. We believe that trifluoroethyl thioesters will prove to be important nucleophiles in a wide range of both organocatalytic and metal-based direct catalytic asymmetric reactions.

As noted above, the use of esters in direct catalytic asymmetric synthesis is challenging since the proton at the α -position, which must be removed to generate the nucleophilic enolate, has a relatively high p K_a value. We desired an approach that would not be limited by malonic acid half thioester decarboxylation for enolate generation (Scheme 1).



Scheme 1. a) Decarboxylative approach vs. b) equilibrium approach. E = electrophile.

Rather, we sought to activate α -proton removal by electronic tuning at the thioester such that a wide variety of carboxylic ester derivatives might serve as nucleophiles. Indeed, Nature's access and use of thioester enolates is neither limited to the use of malonic acid half thioesters nor their decarboxylative generation of an active enolate.^[4]

Direct organocatalytic methods based on amine catalysis have a functional pK_a barrier for nucleophile activation that lies between the pK_a values of 16 and 17 (Figure 1). It is known that a malonate diester with a pK_a value of 16.4 can be activated by amine bases to act as a nucleophile in asymmetric



Figure 1. pK_a values of the $\alpha\text{-protons}$ of potential nucleophiles in DMSO. $^{[1]}$

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synthesis,^[6h,i] but ketones with α -proton pK_a values of ca. 18 require amine activation by enamine formation. The relative reactivities of these compounds allowed us to define this functional pK_a barrier.^[1] As illustrated in Figure 1, the change from an oxyphenol ester to a thiophenol ester results in a reduction in the pK_a value of the α -proton of an ester by approximately 2 units, just at the borderline for nucleophile activation using the currently available amine organocatalysts. Thus, we sought appropriate thioesters that might be used to reduce the pK_a value of the α -proton to a suitable range for organocatalysis. In elegant experiments, Um and Drueckhammer studied the kinetic acidities of the α -proton of a series of thioesters.^[7] These studies revealed that trifluoroethyl thioesters have a-proton exchange rates in toluene/triethylamine solutions that are approximately ten times faster than phenyl thioesters, suggesting that the pK_a value of the α -proton of trifluoroethyl thioesters might be close to those of malonate diesters, making them candidate ester nucleophiles in catalytic direct asymmetric synthesis.

Since our 2000 report,^[3c] a variety of pyrrolidine-based iminium catalysts of Michael additions have broadened the scope and efficiency of the iminium-based Michael reaction.^[3,6] As illustrated in Scheme 2, we screened a number of these organocatalysts together with benzoic acid co-catalyst, for catalysis of the Michael addition of thioester **1a** to cinnamaldehyde **2a**. A number of the pyrrolidine-based catalysts were effective. In particular, the trialkylsilyl-protected diarylprolinols (**4–6**) pioneered by Hayashi and coworkers and Jørgensen and co-workers provided the product



Scheme 2. Evaluation of organocatalysts together with a benzoic acid co-catalyst, for catalysis of the Michael addition of thioester 1a to cinnamaldehyde 2a. The yields of 3a are shown below the respective catalysts. [a] Reaction was performed in a 1.0 M solution in the presence of 15 mol% of 7 and benzoic acid.

in excellent chemical yield and with high enantioselectivity.^[6] With respect to our hypothesis concerning the pK_a window accessible for catalysis with these catalysts, the analogous phenylthioester of **1a** was unreactive, whereas the trifluoro-ethyl thioester was reactive.

Catalyst **4** was the most promising of those evaluated with respect to chemical yield and *ee* values; we therefore set out to optimize this reaction. A variety of solvents and co-catalysts were evaluated (see Table 1S in the Supporting Information). Nonpolar solvents were ineffective in the absence of a co-catalyst (Table 1S, entries 2–4); however, the polar protic solvents, such as methanol and ethanol, were highly effective and provided the desired product in 95% and 83% yield, respectively, on the basis of conversion after 48 hours at room temperature (Table 1S, entries 9 and 10). Surprisingly, isopropanol provided less than 5% conversion. We next studied a variety of acid co-catalysts in methanol. We found that the co-catalysts benzoic acid, 5-methyl-1*H*-tetrazole, or water were equally effective, whereas trifluoroacetic acid poisoned the reaction (Table 1S, entries 12–15).

To determine the scope of this reaction we synthesized a variety trifluoroethyl thioesters derived from arylacetic acids, and analyzed the products and the yields of the addition reactions to α , β -unsaturated aldehydes (Table 1). We noted significant electronic effects: faster reactions were observed with thioesters derived from arylacetic acids having electronwithdrawing groups, whereas reaction of thioesters derived from arylacetic acids with electron-donating groups were significantly slower (compare Table 1, entries 4 and 8). With cinnamaldehyde as the Michael acceptor substrate, the yields of the isolated products ranged from 46 to 88% and the enantioselectivities were up to 98%. Although most of these reactions were performed at room temperature, we were able to demonstrate in the *p*-nitrophenylacetic acid ester case that the ee value of the product could be improved from 66 to 91 % by simply performing the reaction at 0°C (compare Table 1, entries 4 and 6). With the highly reactive *p*-nitrophenylacetic acid ester substrate, we observed that the reaction was reversible during extended reaction times, ultimately eroding the ee value of the product (compare Table 1, entries 4 and 5). Other less active thioesters such as *p*-methoxyphenylacetic acid and napthylacetic acid esters (Table 1, entries 8 and 9) were studied by monitoring the reaction under extended reaction times or with excess catalyst, and no erosion of the ee values was noted. The trifluoroethyl thioester of propionic acid was not reactive under these conditions, suggesting that an aromatic functionality was required to bring the pK_a value of the α -proton down to a functional range.

Modification of the Michael acceptor substrate was also possible and the *o*-methoxycinnamaldehyde acceptor provided product with 96% *ee* (Table 1, entry 12). Crotonaldehyde was significantly less effective, and Michael product **3k** was obtained with only 54% *ee*. It is known that catalyst **4** may be a poor catalyst for crotonaldehyde-based Michael reactions.^[6h] The overall diastereoselectivity of these reactions was modest and the relative configurations of the products were assigned after conversion of the phenylacetic acid product (Table 1, entry 7) into a known product (see the

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Table 1: Thioester addition reactions to α,β -unsaturated aldehydes.^[a]

		$F_{3}C \frown S \bigcap_{R^{1}}^{O} + R^{2} \frown CHO \xrightarrow{4 (10 \text{ mol}\%)}{PhCO_{2}H (10 \text{ mol}\%)} F_{3}C \frown S \bigcap_{R^{1}}^{R^{2}} CHO$ $1 \qquad 2 \qquad MeOH (0.5 \text{ M}), \text{ RT} \qquad 3$					
Entry	Thioester (R ¹)	Aldehyde (R ²)	Product	<i>t</i> [h]	Yield [%] ^[b]	anti:syn ^[c]	ee [%] ^[d]
1	1 a (4-ClC ₆ H ₄)	2a (Ph)	3 a	17	70	65:35	90 ^[e]
2	1b $(2-C C_6H_4)$	2 a (Ph)	3 b	19	75	65:35	89
3	1c (4-CF ₃ C ₆ H ₄)	2 a (Ph)	3 c	18	74	74:26	93
4	1d (4-NO ₂ C ₆ H ₄)	2 a (Ph)	3 d	1	88	57:43	66 ^[e,f]
5	$1d(4-NO_2C_6H_4)$	2 a (Ph)	3 d	16	45	60:40	33 ^[e,f]
6 ^[g]	$1d(4-NO_2C_6H_4)$	2a (Ph)	3 d	2	84	61:39	91 ^[e,f]
7 ^[h]	1e (Ph)	2 a (Ph)	3 e	16	71	67:33	82 ^[e]
8 ^[h,i]	$1 f (4-MeOC_6H_4)$	2 a (Ph)	3 f	48	46 (44)	64:36	84
9 ^[h,i]	1g (1-naphthyl)	2 a (Ph)	3g	48	66 (28)	63:37	67 ^[e]
10	1 h (2-thienyl)	2 a (Ph)	3 ĥ	24	57	81:19	84
11 ^[h]	1i (PhCH=CH)	2 a (Ph)	3 i	24	70	78:22	98 ^[e]
12 ^[h]	$1a(4-C C_6H_4)$	2b (2-MeOC ₆ H ₄)	3 j	72	63	71:29	96
13 ^[h,j]	$1a(4-C C_6H_4)$	2c (Me)	3 k	36	51	63:37	54 ^[e]

[a] See the Experimental Section for reaction conditions. [b] Yield of products that were isolated as a mixture of *anti:syn* isomers. Yields of recovered **1** is shown in parentheses. [c] Determined by ¹H NMR analysis of the crude reaction mixture. [d] Enantiomeric excess for the *anti* product was determined by chiral phase HPLC analysis. [e] Determined by chiral phase HPLC analysis after NaBH₄ reduction. [f] NaBH₄ was added directly to the Michael reaction mixture. [g] Reaction performed at 4°C. [h] Reaction performed in 1.0 μ solution. [j] Used 20 mol% of **4**. [j] DMF was used as the solvent.

Supporting Information). The relative configurations of the other products were assigned by analogy.

To study the role of the α -proton acidity of our esters and its influence on reactivity and enantioselectivity in the Michael reaction, we performed deuterium exchange experiments under conditions similar to those established by Um and Drueckhammer^[7] (Figure 2). There was a good correlation between the exchange rate and the Michael reaction times noted in Table 1. No significant correlation of the electronic effect with the *ee* value was noted. The trifluoroethyl thioester of propionic acid did not undergo α -proton exchange under these conditions and was not active in the Michael reaction, indicating that the pK_a value of the α proton was outside of the range of these organocatalytic conditions.





Figure 2. Time course for α -proton exchange for thioesters 1 as monitored by ¹H NMR analysis. The $t_{1/2}$ was < 5 min for 1d (\blacksquare), 45 min for 1a (\Box), 120 min for 1e (\triangle), 230 min for 1f (\blacktriangle), >5000 min for S-trifluoroethyl thiopropionate (\bullet).



Scheme 3. Other reactions using thioester 1a. Conditions: a) 4-NO₂PhCHO, DBU (10 mol%), toluene, 4°C, 3 h; b) (NCO₂Bn)₂, DLproline (20 mol%), DMF, 4°C, 72 h; c) (E)-PhCHCHNO₂, quinuclidine (20 mol%), DMF, 4°C, 1 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

the development of novel direct asymmetric aldol reactions of esters and in the synthesis of α - and γ -amino acids and derivatives. These studies suggest that a wide range of electrophiles will be reactive with these thioesters, thus, the use of trifluoroethyl thioesters will likely be applicable to the development of a wide-range of novel direct catalytic ester reactions.

In summary, we have developed the first direct catalytic asymmetric reactions of trifluoroethyl thioesters, thereby establishing a new class of nucleophiles for direct catalytic reactions. Given the synthetic versatility of thioesters,^[8] thioester-based reactions promise access not only to the products that Nature has targeted in its use of thioesters, but to a much wider array of compounds. The development of direct asymmetric aldol, amination, Mannich, and cascade reactions based on trifluoroethyl thioesters is under investigation and will be reported in due course.

Experimental Section

Typical procedure for Michael addition of thioesters to α,β -unsaturated aldehydes (Table 1, entry 1): 2a (1.3 equiv, 0.26 mmol, 32.5 µL) was added to a solution of catalyst 4 (10 mol%, 12.0 mg, 0.02 mmol) and benzoic acid (10 mol%, 2.4 mg, 0.02 mmol) in MeOH (0.2 mL). After stirring the resulting mixture at room temperature for 15 min, a previously prepared (2-3 minutes before addition) MeOH (0.2 mL) solution of 1a (53.3 mg, 0.2 mmol) was added dropwise, after which the reaction mixture was stirred for 17 h. MeOH was then evaporated and the diastereomeric ratio was determined by ¹H NMR analysis of the crude product mixture. The crude product mixture was purified by flash chromatography (hexane/EtOAc=20:1) to afford 3a as a mixture of diastereomers in a total yield of 70%. The major diastereomer (anti product) could be obtained in pure form by flash chromatography. The ee value was determined by chiral-phase HPLC analysis of the corresponding alcohol, which was obtained after reaction with NaBH₄ in MeOH at 0°C.

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