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Enantioselective Organocatalytic Michael Addition of Aldehydes to Trifluoroethylidene Malonates

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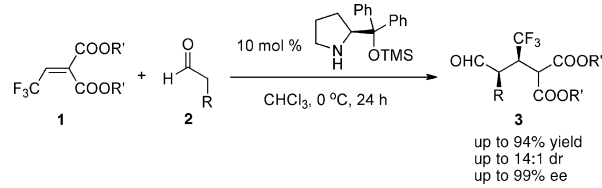
ABSTRACT



An efficient, highly enantioselective, organocatalytic Michael addition reaction of aldehydes with trifluoroethylidene malonates is described. The asymmetric reaction provided highly optically pure *β*-trifluoromethyl aldehydes which can be conveniently transformed into 4,4,4-trifluoromethyl butyric acid and trifluoromethyl substituted *δ*-lactones without loss in enantioselectivity.

Over the past 10 years, asymmetric organocatalytic Michael addition has emerged as a powerful and environmentally friendly tool for the production of enantiomerically pure organic compounds.[1] Among these transformations, direct Michael addition of carbonyl donors by chiral secondary amines via enamine activation represents a particularly attractive route, affording versatile functionalized adducts in an atom-economical manner.[2] A variety of Michael acceptors such as nitroolefins,[3] vinyl ketones,[4,5] alkylidene malonates,[6] vinyl sulfones,[7,8] vinyl phosphonates,[8,9] γ-keto-α, β-unsaturated esters,[10] and α,β-unsaturated thiol esters[11] have been shown to be efficient in these reactions. In contrast, Michael additions of aldehydes to electron-deficient alkenes bearing a trifluoromethyl group such as a Michael acceptor have rarely been reported.[12] Due to the unique physical properties of organofluorine compounds, broad research efforts have been focused on the strategic introduction of fluorine substitution into druglike molecules in medicinal and agricultural chemistry.[13] More specifically, catalytic enantioselective construction of trifluoromethyl-containing stereogenicity has become a current challenge in organofluorine chemistry.[14] Herein, we report a prolinol silyl ether catalyzed highly enantioselective Michael addition

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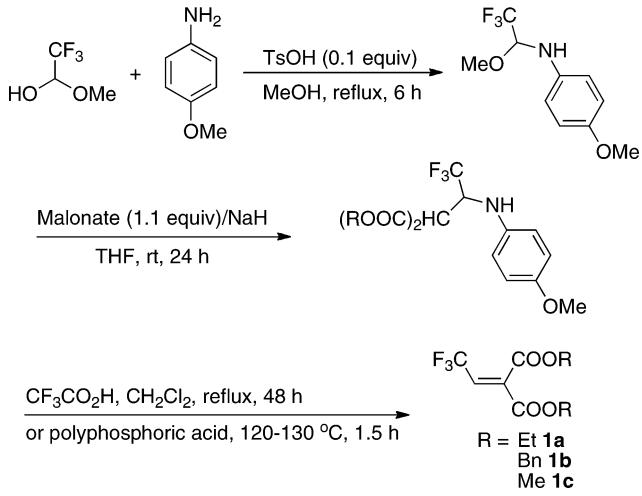
Scheme 1. Synthesis of 2,2,2-Trifluoroethylidene Malonates

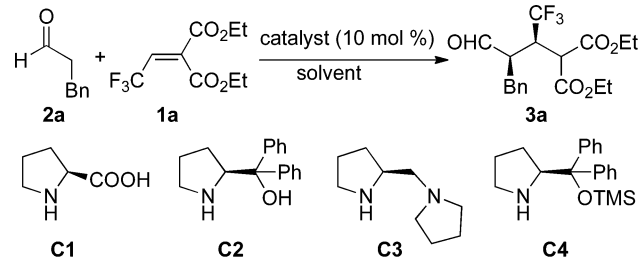


of aldehydes to 2,2,2-trifluoroethylidene malonates (Scheme 1).

2,2,2-Trifluoroethylidene malonates **1a**−**c** were prepared according to a modified procedure reported in the literature.[15] Condensation of trifluoroacetaldehyde methyl hemiacetal and 4-methoxyaniline under acidic conditions gave *N*,*O*-disubstituted aminal intermediate. Reaction of the aminal intermediate with dialkyl malonate and sodium hydride in dry THF proceeded smoothly, producing 2-substituted malonic acid dialkyl ester in high yield. Treatment of 2-substituted malonic acid dialkyl ester under acidic conditions gave the corresponding deamination products **1a**−**c** in moderate to good yields.

We initially examined L-proline and three substituted pyrrolidines (10 mol % each) as potential catalysts for the reaction of diethyl 2,2,2-trifluoroethylidene malonate **1a** with phenylpropyl aldehyde **2a** (Table 1). When L-proline was used as the catalyst, the reaction occurred to 66% conversion

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	time (h)	convn[b] (%)	dr[b]	ee[c] (%)
1	**C1**	DMSO	rt	17	66	5.0:1	13
2	**C2**	CH_3CN	rt	24	trace	-	-
3	**C3**	$CHCl_3$	rt	48	27	2.6:1	-
4	**C4**	CH_3CN	rt	48	84	4.0:1	95
5	**C4**	CH_3OH	rt	24	48	5.2:1	96
6	**C4**	DMF	rt	24	trace	-	-
7	**C4**	Dioxane	rt	24	35	5.7:1	-
8	**C4**	Toluene	rt	24	93	3.7:1	97
9	**C4**	$CHCl_3$	rt	24	95	4.2:1	97
10	**C4**	$CHCl_3$	0	24	91	5.2:1	99
11	**C4**	$CHCl_3$	−15	24	69	5.5:1	99

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), and catalyst (10 mol %) in solvent (0.5 mL) at the indicated temperature. [b] The conversion and dr (syn/anti) of adducts were determined by ^{19}F NMR analysis of the crude reaction mixture. [c] The ee value was determined by chiral-phase HPLC analysis.

after 17 h at room temperature, affording **3a** in low yield and 13% ee (Table 1, entry 1). Reactions in the presence of substituted pyrrolidines **C2** or **C3** were even slower (Table 1, entries 2 and 3). When prolinol silyl ether **C4** was used as the catalyst,[4] to our delight, good diastereoselectivity and excellent enantioselectivity were observed (Table 1, entry 4). Different solvents were then examined to improve the yield and diastereoselectivity. It was found that reactions in toluene or chloroform occurred to full conversion after 24 h at room temperature to give the desired product **3a** in excellent enantioselectivity, while reactions in methanol or dioxane occurred much more slowly (Table 1, entries 5−9). Furthermore, the diastereoselectivity and enantioselectivity of the reaction in chloroform was further improved from 4.2: 1 dr and 97% ee to 5.2: 1 dr and 99% ee, respectively, by lowering the temperature to 0 °C (Table 1, entry 10).

On the basis of the results summarized in Table 1, the reaction conditions of entry 10 in Table 1 were chosen to study the scope of the Michael reactions using a series of aldehydes and 2,2,2-trifluoroethylidene malonates, and the results are summarized in Table 2. In most cases, the adducts were obtained in excellent yields, excellent enantioselectivities (up to 99% ee), and moderate diastereoselectivities (up to 14: 1 dr). Generally, the nature of the substituents on 2,2,2-trifluoroethylidene malonates slightly influences the yields and enantioselectivities. The reactions of methyl, ethyl, or benzyl 2,2,2-trifluoroethylidene malonates proceeded smoothly to afford Michael adducts in excellent enantioselectivities (96−99% ee) and good diastereoselectivities (syn/anti up to

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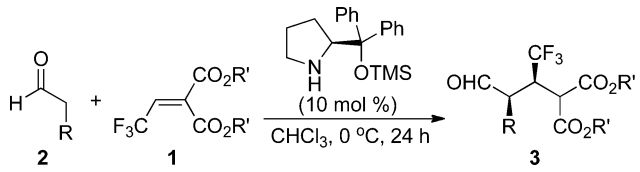
Table 2. Enantioselective Michael Addition of Aldehydes to 2,2,2-Trifluoroethylidene Malonates[a]

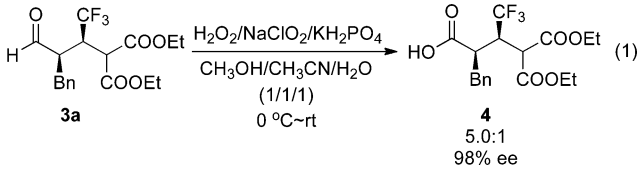


entry	R	R′	product	yield[a] (%)	dr[b]	ee[c] (%)
1	Bn	Et	**3a**	91	5.2:1	99
2	Bn	Me	**3b**	94	5.7:1	98[d]
3	Bn	Bn	**3c**	90	5.1:1	96
4	Me	Bn	**3d**	94	6.5:1	91[d]
5[e]	Et	Bn	**3e**	84	6.1:1	97
6[e]	^{n}Pr	Bn	**3f**	91	5.9:1	98
7	^{i}Pr	Bn	**3g**	91	14:1	96
8	Allyl	Bn	**3h**	93	6.9:1	97
9[f]	Allyl	Bn	**3h**	93[g]	5.3:1	97

[a] Isolated yield. [b] Determined by ^{19}F NMR of the crude adducts. [c] The ee value was determined by chiral-phase HPLC analysis. [d] The ee value was determined by chiral-phase HPLC analysis after conversion to the corresponding lactone. [e] The reaction was stirred for 48 h. [f] 5 mol % catalyst loading. The reaction was stirred for 36 h. [g] The conversion was determined by ^{19}F NMR analysis of the crude adducts.

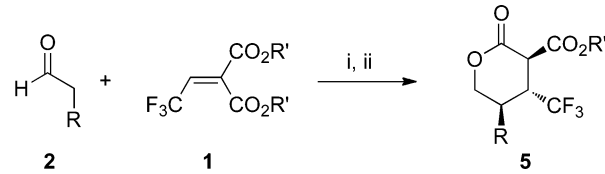
5.7:1) (Table 2, entries 1−3). While the length of the linear chain aldehydes slightly influenced the yields, enantioselectivities, or diastereoselectivities (Table 2, entries 4−6), the steric bulk of the substituents on the aldehydes significantly affected the diastereoselectivity of the Michael adducts. Upon changing the substituent on the aldehyde from *n*-propyl to isopropyl, the diastereoselectivity of the Michael additions increased from 5.9:1 to 14:1 (Table 2, entries 6 and 7). In addition, lowering the catalyst loading to 5 mol % led to a slight decrease in diastereoselectivity but without loss in enantioselectivity (Table 2, entries 8 and 9).

The relative configuration of the Michael adduct **3d** was determined by NOE and COSY experiments of its derivative **5a** (see the Supporting Information). Compound **5a** was obtained in high yield by reduction of **3d** with $NaBH_3CN$, followed by intramolecular lactonization (Table 3, entry 1). The relative stereochemical results can be explained by related transition-state models previously discussed for (*S*)-diphenylprolinol silyl ether catalyzed Michael reactions.[16]



To demonstrate the utility of the reaction, Michael adduct **3a** was converted to multifunctionalized and highly optically

Table 3. Synthesis of δ-Lactones **5a**−**c**[a]



entry	R	R′	product	yield[b] (%)	dr[c]	ee[d] (%)
1	Me	Bn	**5a**	95	13.7:1	91
2	Bn	Et	**5b**	88	15:1	97
3	Bn	Me	**5c**	91	4.7:1	98

[a] Reaction conditions: (i) **1** (0.1 mmol), **2** (0.2 mmol), and catalyst (10 mol %) in chloroform (0.5 mL) at 0 °C for 24 h; (ii) 1.5 equiv of $NaBH_3CN$ in HOAc/THF at rt for 24 h. [b] Isolated yield. [c] Determined by ^{19}F NMR. [d] Determined by chiral-phase HPLC analysis.

pure 4,4,4-trifluoromethylbutyric acid **4** under mild oxidation conditions (eq 1).[17] Alternately, Michael adducts **3a** and **3b** were converted into δ-lactones **5b**,**c** with three consecutive asymmetric centers in excellent yields under similar conditions, as in the case of **3d** (Table 3, entries 1−3).

In conclusion, we have developed a new protocol for the asymmetric Michael addition of aldehydes to trifluoroethylidene malonates in good yields and with good diastereoselectivities and excellent enantioselectivities. The Michael adducts could be readily transformed into polyfunctionalized, optically pure 4,4,4-trifluoromethyl butyric acid **4** and δ-lactones **5a**−**c** in high yields without loss in enantioselectivities. Mechanistic studies, synthetic applications of these transformations as well as development of other organocatalytic enantioselective conjugate addition reactions are ongoing in our laboratory.

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Supporting Information Available: All experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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