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Regiospecific Organocatalytic Asymmetric Aldol Reaction of Methyl Ketones and α,β-Unsaturated Trifluoromethyl Ketones

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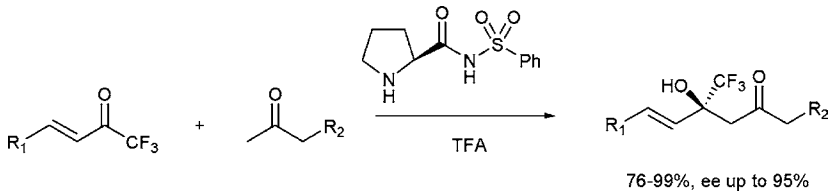
ABSTRACT



The aldol reaction of methyl ketones and α,β-unsaturated trifluoromethyl ketones occurred under mild conditions with the combination of proline-derived *N*-sulfonylamide and trifluoroacetic acid as the catalyst to give the corresponding unsaturated α-trifluoromethyl tertiary alcohols in high yields with good enatioselectivities.

The importance of fluorine-containing compounds in the fields of agricultural, medicinal, and material chemistry is well-known.[1] Among such compounds α-trifluoromethyl tertiary alcohols have attracted much attention because they can serve as liquid crystals[2a] and drugs such as Efavirenz (anti-HIV)[2b,c] and so on. Except for the trifluoromethylation of ketones,[3] most methods for the synthesis of these compounds utilize α-trifluoromethyl ketones as precursors and the aldol reaction of such ketones takes an important place in those synthetic methodologies.[4] However, preformed enol or enolate derivatives are involved in those cases, which is not atom efficient. Recently direct organocatalytic aldol reaction pioneered by List, Barbas, and their co-workers has achieved great success.[5] Proline-catalyzed asymmetric aldol reaction between methyl ketones and aryl trifluoromethyl ketones was realized by Zhang and co-workers, although only moderate enantioselectivities were obtained.[6] Herein we report the first organocatalyzed asymmetric aldol reaction between methyl ketones and α,β-unsaturated trifluoromethyl ketones, which leads to a practical synthesis of unsaturated α-trifluoromethyl tertiary alcohols with good enantioselectivities.

Since there are two reaction sites in the α,β-unsaturated carbonyl functional group, the addition reaction can only be of practical synthetic utility in organic synthesis if one can control the selectivity for the two possible regioisomers.[7] It has been reported that cyclic enamines underwent Michael-aldol reaction with α,β-unsaturated trifluoromethyl ketones

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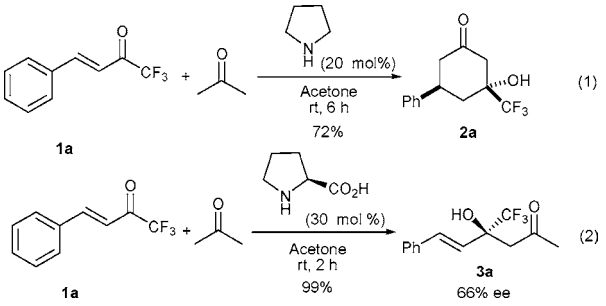
to give bicyclic ketones.[8] We also found that unsaturated ketone **1a** could undergo similar domino Michael-aldol reaction with acetone when pyrrolidine was used as a catalyst (Scheme 1, eq 1).[9] However, the regioselectivity of the

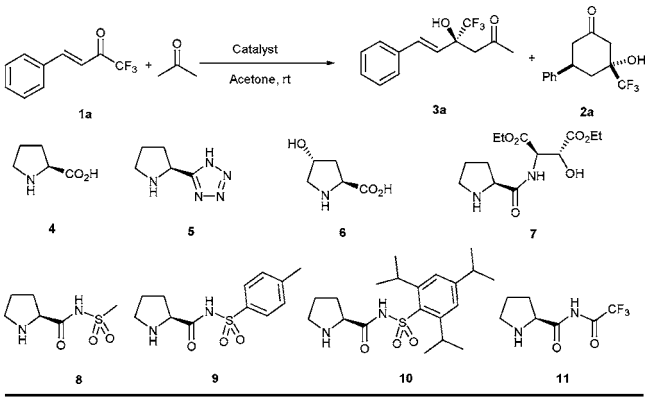
Scheme 1. Regioselective Reaction of **1a** and Acetone



reaction could be changed by using different organocatalyst. In the presence of L-proline the reaction of **1a** and acetone gave the corresponding 1,2-addition product with quantitative yield and moderate enantioselectivity (Scheme 1, eq 2). Notably, it was the first organocatalytic reaction in which unsaturated ketone underwent aldol reaction as acceptor instead of the usual Michael reaction as previously reported.[10]

We began our investigation with the reaction of acetone and unsaturated ketone **1a**. A variety of L-proline derivatives were tested as catalysts to improve the enantioselectivity of the reaction. As shown in Table 1, although tetrazole **5**[11a,b,d] could also catalyze the aldol reaction efficiently, the decrease in enantioselectivity was observed (Table 1, entry 2). Using hydroxy proline **6**[11c] as catalyst gave the desired product in

Table 1. Evaluation of Catalysts for the Aldol Reaction of **1a** and Acetone[a]



entry	catalyst (mol %)	time, h	conversion,[b] %	**3a/2a**[b]	ee,[c] %
1	**4** (30)	2	100	>95:5[d]	67
2	**5** (5)	2	100	>95:5	49
3	**6** (30)	52	22	>95:5	68
4	**7** (5)	52	14	81:19	57
5	**8** (20)	3	100	83:17	59
6	**9** (20)	3	100	86:14	63
7	**10** (20)	1	100	96:4	72
8	**11** (20)	28	50	98:2	14
9	**10** (10)	4	100	>95:5	75[e]
10	**10** (10)	3	100	>95:5	87[f]
11	**10** (10)	6	100	>95:5	92[f,g]
12	**10** (10)	8	48	>95:5	94[f,h]

[a] Experimental conditions: **1a** (0.2 mmol) was added to a solution of catalyst in acetone (1 mL) at room temperature. [b] Determined by ^{19}F NMR analysis of crude reaction mixture. [c] Determined by HPLC. [d] Only aldol product **3a** was observed. [e] 10 mol % acetic acid was added. [f] 10 mol % TFA was added. [g] Reaction performed at 0 °C. [h] Reaction performed at −20 °C.

low conversion and similar ee as using L-proline (Table 1, entry 3). A dramatic decrease in both yield and selectivity was obtained when amide **7** was tested (Table 1, entry 4). Further evaluation of several proline-derived *N*-sulfonylamides[11d,e] showed compound **10** to be optimal, giving the highest enantioselectivity and good regioselectivity (Table 1, entries 5−7). Addition of acids along with catalyst **10**

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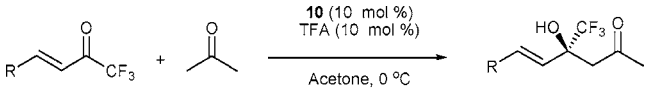
could improve the selectivity significantly, and strong acid provided higher enantioselectivity than weak acid (Table 1, entries 9 and 10). The best result with respect to both yield and selectivity was achieved by carrying out the reaction with catalyst **10** and trifluoroacetic acid additive at 0 °C (Table 1, entry 11).

Experiments that probed the scope of α,β-unsaturated trifluoromethyl ketone component are summarized in Table 2. With use of the optimized conditions, the corresponding

Table 2. Aldol Reaction of α,β-Unsaturated Trifluoromethyl Ketones and Acetone[a]



1 3

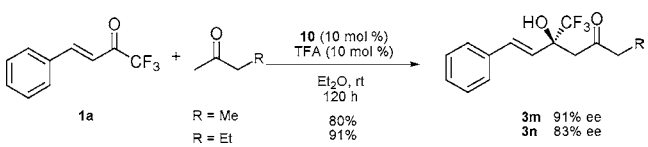
entry	1	R	time, h	3[b]	yield,[c] %	ee,[d] %
1	**1a**	Ph	6	**3a**	93	92
2	**1b**	4-Cl-Ph	10	**3b**	92	94
3	**1c**	4-Br-Ph	14	**3c**	98	95[e]
4	**1d**	4-MeO-Ph	24	**3d**	94	94
5	**1e**	4-Me−Ph	20	**3e**	99	89
6	**1f**	1-naphthyl	22	**3f**	85	92
7	**1g**	2-furyl	12	**3g**	87	86
8	**1h**	Ph-C≡C	22	**3h**	99	81
9	**1i**	Ph-CH=CH	31	**3i**	76	87
10	**1j**	$Ph(CH_2)_3$	28	**3j**	86	88

[a] Experimental conditions: unsaturated ketone **1** (0.4 mmol) was added to a solution of catalyst **10** (10 mol %) and TFA (10 mol %) in acetone (2 mL) at 0 °C, and the reaction mixture was stirred for the time indicated in the table. [b] **3** was the only product as determined by ^{19}F NMR analysis of crude reaction mixture. [c] Yields of isolated products. [d] Determined by HPLC. [e] Reaction performed at −20 °C.

α-trifluoromethyl tertiary alcohols were obtained in excellent yields with high enantioselectivities in all cases. As shown in Table 2 entries 2−5, the reaction tolerated both electron-rich and electron-deficient phenyl-substituted unsaturated ketones. Similar results were obtained in the cases of ketones with heteroaromatic and naphthyl groups (Table 2, entries 6 and 7). Furthermore, unsaturated ketones carrying alkynyl, alkenyl, or alkyl substituents at the β position were also good substrates for the reaction (Table 2, entries 8−10). The assignment of the absolute stereochemistry of the resulting β-hydroxyl-β-trifluoromethyl ketones was based on X-ray crystallographic studies of product **3c**.

Except for acetone, other ketones were also investigated. Butanone and 2-pentanone gave similar results (Scheme 2).

Scheme 2. Aldol Reaction of **1a** with Butanone and 2-pentanone



However, cyclic ketones such as cyclohexanone failed to yield the desired product.

The stereochemistry of the reaction may be rationalized by the transition state shown in Figure 1, which is based on

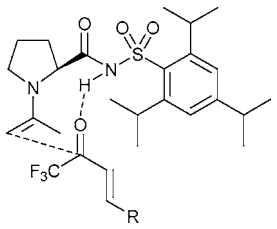


Figure 1. Proposed transition state of the aldol reaction.

a previous model for proline supported by both experiments and DFT calculations.[12] In the transition state the bulky trifluoromethyl group adopts a pseudoequatorial position to avoid the nonbonding interactions with the sulfonylamide moiety.[13] The role of TFA additive is still unknown.[14] It might not only favor the formation of the enamine intermediate in Figure 1, but also serve to decrease the electron density of the carbonyl group of unsaturated ketones through the hydrogen bonding interaction and make it more active toward nucleophilic attack.[14i]

In summary, organocatalyzed asymmetric aldol reaction of methyl ketones and α,β-unsaturated trifluoromethyl ketones was achieved for the first time. By using the combination of proline-derived *N*-sulfonylamide **10** and trifluoroacetic acid as catalyst, the reaction occurred under mild conditions to give the corresponding unsaturated α-trifluoromethyl tertiary alcohols in high yields with good enatioselectivities.

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Supporting Information Available: Experimental procedures, structural proofs, NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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