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Proline-catalyzed direct asymmetric aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with ketones

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Dedicated to Professor Takashi Ishihara on the occasion of his 60th birthday

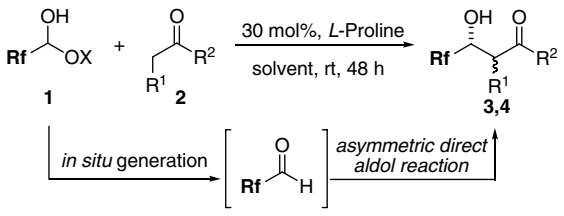
Abstract—L-Proline-catalyzed direct asymmetric aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with unmodified ketones smoothly occurred at ambient temperature to produce β-hydroxy-β-trifluoromethylated ketones with good to excellent diastereo (up to 96% de) and enantioselectivities (up to 91% ee).

Catalytic asymmetric synthesis of trifluoromethylated molecules is one of the most interesting reactions in organofluorine chemistry.[1] Particularly, an atom-economical organocatalytic asymmetric synthesis of fluorine-containing compounds with a simple experimental procedure has been a rapidly growing area.[2]

A variety of methods for the preparation of the trifluoromethylated molecules using trifluoroacetaldehyde (CF_3CHO) or its hemiacetal have been widely developed.[3] However, the method with CF_3CHO has serious drawbacks that it should be prepared from its hemiacetal or hydrate using a large amount of concentrated sulfuric acid under the high reaction temperature just before employment of the aldehyde. Moreover, the generated aldehyde could not be stored because of some notorious properties, such as its gaseous state at room temperature, high hygroscopicity, and high reactivity leading to self-polymerization.[4] A great need for truly practical, convenient, and environmentally friendly methods for the effective generation of CF_3CHO as well as its asymmetric reactions is desired earnestly. During the course of our study on stoichiometric[5,6] and catalytic[7] in situ generation of CF_3CHO from its hemiacetal as well as the successive carbon–carbon bond formation reaction under mild conditions, producing β-hydroxy-β-trifluoromethylated ketone, we report herein, for the first time, the *commercially available* L-proline-catalyzed *direct asymmetric aldol reaction* of CF_3CHO ethyl hemiacetal with unmodified ketones, producing β-hydroxy-β-trifluoromethylated ketones with good to excellent diastereo (up to 96% de) and enantioselectivities (up to 91% ee) (Scheme 1).[8–10]

The present reaction has some advantages, such as the use of *commercially available* L-proline[9] for direct aldol reaction of CF_3CHO ethyl hemiacetal with ketones, not requiring the step for the generation of CF_3CHO, good to excellent diastereo- and enantioselectivities of the products, and complementary diastereoselective synthesis of β-hydroxy-β-trifluoromethyl ketones by just change of the ketones.

The results of the L-proline-catalyzed reaction of CF_3CHO ethyl hemiacetal **1a** with acetone **2a** in various solvents are summarized in Table 1.



Scheme 1.

Keywords: Fluorine and compounds; Aldol reactions; Amino acids and derivatives; Asymmetric reactions.
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Table 1. Screening of reaction conditions for L-proline-catalyzed direct aldol reaction of CF_3CHO ethyl hemiacetal **1a** (Rf = CF_3, X = Et) with acetone **2a** (R^1 = H, R^2 = Me)[a]

Entry	Solvent	Yield[b] (%)	Isomer ratio (*R*:*S*)[c]	ee[c]
1	DMSO	96	50.3:49.7	2.8
2	DMF	94	52.0:48.0	4.0
3	H_2O	0	—	—
4	THF	19	68.7:31.3	37.4
5	Acetone	97 (49)	67.6:32.4	35.2
6	Acetone	96	69.2:30.8[d]	38.4[d]
7[e]	Acetone	18	71.3:28.7	42.6
8	MeCN	64	70.7:29.2	41.5
9	CH_2Cl_2	45	73.9:26.1	47.8
10	$CHCl_3$	31	72.8:27.2	45.6
11	Benzene	32	75.8:24.2	51.6
12	Hexane	19	73.0:27.0	46.0

[a] All reactions were carried out with CF_3CHO ethyl hemiacetal **1a** (1 mmol) and L-proline (30 mol %) in the mixed solvent of dry acetone **2a** (2 ml) and solvent (8 ml) or dry acetone (10 ml) for 48 h.
[b] Determined by ^{19}F NMR using benzotrifluoride as an internal standard. Value in parentheses stands for the yield of isolated product.
[c] Determined by HPLC analysis with DAICEL CHIRALCEL OD-H (hexane–*i*-PrOH = 95/5) after *p*-chlorobenzoylation.
[d] Determined by GC with InterCap CHIRAMIX (GL Science).
[e] Carried out with L-proline (100 mol %) at 0 °C for 96 h.

The employment of DMSO or DMF resulted in a significant loss of enantioselectivities (entries 1 and 2). Other solvents, such as acetonitrile, dichloromethane, and chloroform, could be used to produce good yields of the product **3a** with good enantioselectivities (entries 8–10). The reaction in THF or hexane was very sluggish and gave low yields of **3a** (entries 4 and 12). The reaction in water did not proceed at all (entry 3). The reaction in benzene resulted in best enantioselectivity of **3a** but with a decreased yield (entry 11). Importantly, dry acetone **2a** can be used as the solvent as well as a ketone donor with excellent yield in good enantioselectivity (entries 5 and 6).[11] Lowering the reaction temperature (0 °C) resulted in a significant decrease of the product **3a** even in the presence of a stoichiometric amount of L-proline, together with a slight increase of ee (entry 7).

Other CF_3CHO derivatives, such as hydrate **1b** (75 wt %) and 2,2,2-trifluoroethyl hemiacetal **1c** (88 wt %) were also examined, as shown in Table 2.

Table 2. L-Proline-catalyzed direct aldol reaction of CF_3CHO derivatives **1** as well as pentafluoropropionaldehyde hydrate **1d** with acetone **2a** (R^1 = H, R^2 = Me)[a]

Entry	1	Rf	X	Yield[b] (%)	Isomer ratio (*R*:*S*)[c]	ee[c]
1	**1b**[d]	CF_3	H	64	68.9:31.1	37.8
2	**1c**[e]	CF_3	CH_2CF_3	97	70.6:29.4	41.2
3	**1d**	CF_3CF_2	H	69	72.0:28.0	44.0

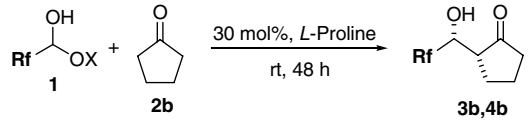
[a] All reactions were carried out with CF_3CHO derivatives **1** (1 mmol) or pentafluoropropionaldehyde hydrate **1d** and L-proline (30 mol %) in dry acetone **2a** (10 ml) for 48 h.
[b] Determined by ^{19}F NMR using benzotrifluoride as an internal standard.
[c] Determined by HPLC analysis with DAICEL CHIRALCEL OD-H (hexane–*i*-PrOH = 95/5) after *p*-chlorobenzoylation.
[d] Hydrate (75 wt %) was used.
[e] Hemiacetal (88 wt %) was used.

Hemiacetals **1a**,**c** are much effective than hydrate **1b** to produce almost quantitative yields of **3a**. There are only slight differences in ee of **3a**. Pentafluoropropionaldehyde hydrate **1d** also reacted with acetone **2a** to give 69% yield of aldol product **6a** with a slightly higher enantioselectivity. The absolute configuration of the major aldol product **3a** generated by the reaction could be determined unambiguously as *R* by the comparison with the reported values of the optical rotation.[12]

The catalytic asymmetric direct aldol reactions of CF_3CHO ethyl hemiacetal and pentafluoropropionaldehyde hydrate **1d** with cyclic ketones **2** are described in Scheme 2.

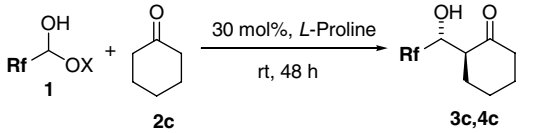
Interestingly, cyclopentanone **2b** also nicely underwent the L-proline-catalyzed direct aldol reaction with CF_3CHO ethyl hemiacetal **1a** as well as pentafluoropropionaldehyde hydrate **1d** to give the corresponding aldol product **3b**,**4b** in 77–96% yields with excellent *syn*-diastereoselectivities (dr = 94–98:2–6) as well as high enantioselectivities (er = 88.6–88.8:11.2–11.4). The reason for this *syn*-selective outcome is not clear at present. Cyclohexanone **2c** reacted smoothly, via the proposed transition state by List and Houk,[13] with the CF_3CHO ethyl hemiacetal **1a** as well as pentafluoropropionaldehyde hydrate **1d** in the presence of 30 mol % of L-proline to produce **3c**,**4c** in 68–71% yields with high *anti*-selectivities (dr = 96–99:4–1) as well as excellent enantioselectivities (er = 95.5–96.7:3.3–4.5).

The relative configurations of the product **3b**,[9] **c**[14] could be determined as *syn*-isomer for **3b** and *anti*-isomer for



1a : Rf = CF_3, X = Et Yield : 96%[a] (77%)[b], *Syn* : *Anti* = 98 : 2[c]
R : *S* = 88.8 : 11.2[d], 77.6% *ee*[d]

1d : Rf = CF_3CF_2, X = H Yield : 77%[a] (72%)[b], *Syn* : *Anti* = 94 : 6[c]
R : *S* = 88.6 : 11.4[d], 77.2% *ee*[d]



1a : Rf = CF_3, X = Et Yield : 68%[a] (41%)[b], *Syn* : *Anti* = 4 : 96[c]
R : *S* = 95.5 : 4.5[c], 91.0% *ee*[c]

1d : Rf = CF_3CF_2, X = H Yield : 71%[a] (64%)[b], *Syn* : *Anti* = 1 : 99[c]
R : *S* = 96.7 : 3.3[e], 93.4% *ee*[e]

[a] Determined by ^{19}F NMR using benzotrifluoride as an internal standard.
[b] Yields of isolated products.
[c] Determined by ^{19}F NMR before isolation.
[d] Determined by GC with InterCap CHIRAMIX (GL Science).
[e] Determined by GC with Chiralsil-Dex CB (Chrompack).

Scheme 2. L-Proline-catalyzed direct asymmetric aldol reaction of polyfluoroalkylaldehyde hemiacetal or hydrate with cyclopentanone or cyclohexanone.

3c. The absolute configuration of the unpredicted *syn*-aldol product **3b** could be determined unambiguously as *R* by the comparison with the reported values of the optical rotation.[9] Unfortunately, the reaction of diethyl ketone **2d** as a linear α,α′-disubstituted ketone with hemiacetal **1a** did not proceed at all.

In summary, we have elaborated that the first *commercially available* L-proline-catalyzed asymmetric direct aldol reaction of CF_3CHO ethyl hemiacetal with unmodified ketones occurred under extremely mild conditions to produce the corresponding β-hydroxy-β-trifluoromethylated ketones with good to excellent diastereo- (up to 96% de) and enantioselectivities (up to 91% ee).

Acknowledgements

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9. During our work, an example dealing with the catalytic generation of CF_3CHO as well as only one proline-derived tetrazole catalyzed direct aldol reaction with cyclopentanone has been reported, see: Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1893–1986, However, this catalyst is not commercially available. So it has to be prepared by five steps from commercially available L-proline.
10. For a recent book of organocatalytic asymmetric synthesis, see: *Asymmetric Organocatalyst*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH Verlag GmbH and Co. KGaA: Weinheim, 2005.
11. *A typical procedure:* To a suspension of a catalytic amount of L-proline (0.035 g, 0.3 mmol) in dry acetone (10 ml) was added CF_3CHO ethyl hemiacetal (0.148 g, 1.03 mmol) at room temperature under an inert atmosphere. After being stirred at room temperature for 48 h, the reaction mixture was quenched with saturated brine (40 ml), followed by extraction with Et_2O (30 ml × 3). The organic layer was dried over Na_2SO_4 and the solvent was removed by distillation under reduced pressure with cold ice bath. After the measurement of the residue by ^{19}F NMR using benzotrifluoride, purification by flash chromatography on silica gel (hexane–Et_2O, 3:1) gave (*R*)-**3a** (0.073 g, 49%). Compound (*R*)-**3a**: $[\alpha]_D^{26}$ +10.7 (*c* 1.07, $CHCl_3$, 36.2% ee); IR (KBr) 3411.2 (OH), 1716.9 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.24 (3H, s, CH_3), 2.78 (1H, dd, $J = 17.83$, 3.01 Hz, CH_ACH_B), 2.84 (1H, dd, $J = 17.83$, 8.88 Hz, CH_ACH_B), 3.41 (1H, br s, OH), 4.44–4.51 (1H, m, CF_3CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.60, 42.83, 66.33 (q, $J = 32.17$ Hz), 124.64 (q, $J = 280.64$ Hz), 206.39; ^{19}F NMR (471 MHz, $CDCl_3$, TFA): δ −1.76 (d, $J = 6.86$ Hz); HRMS (CI) Found: *m*/*z* 157.0479. Calcd for $C_5H_8O_2F_3$: M+H, 157.0476. Compound *syn*-(2*R*,1′*R*)-**3b**: Chiral GC InterCap CHIRAMIX (GL Science), 30 m × 0.25 mm, I.D. = 0.25 μm, 80–120 °C (2 °C/min), 120 °C (20 min), then 120–130 °C (2 °C/min), $t_R = 51.79$ min for minor isomer, 53.30 for major isomer; $[\alpha]_D^{24}$ +102.0 (*c* 1.00, $CHCl_3$, 77.6% ee); IR (KBr) 1713.0 (C=O), 3458.8 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.72–1.89 (m, 1H), 2.06–2.23 (m, 4H), 2.34–2.51 (m, 2H), 3.17–3.27 (br s, 1H, OH), 4.58 (br s, 1H, CF_3CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.46 (s), 22.27 (s), 37.95 (s), 49.24 (s), 67.65 (q, $J = 31.70$ Hz), 125.03 (q, $J = 282.02$ Hz), 218.61 (s); ^{19}F NMR (376 MHz, $CDCl_3$): δ −0.3 (d, $J = 7.45$ Hz); HRMS (EI) Found: *m*/*z* 182.0555. Calcd for $C_7H_9F_3O_2$: M, 182.0555. Compound *anti*-(2*S*,1′*R*)-**3c**: Chiral GC InterCap CHIRAMIX (GL Science), 30 m × 0.25 mm, I.D. = 0.25 μm, 80–140 °C (2 °C/min), $t_R = 32.51$ min for major isomer, 33.20 for minor isomer; $[\alpha]_D^{24}$ −23.1 (*c* 1.02, $CHCl_3$, 93.4% ee); IR (KBr)

1792.1 (C=O), 3447.2 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.64–1.81 (m, 3H), 1.93–1.98 (m, 1H), 2.14–2.24 (m, 2H), 2.37–2.49 (m, 2H), 2.74–2.80 (m, 1H) 4.00–4.09 (m, 1H, CF_3CH), 4.38 (d, $J = 5.85$ Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.89 (s), 28.07 (s), 31.59 (s), 42.95 (s), 50.29 (s), 71.77 (q, $J = 31.43$ Hz), 124.74 (q, $J = 282.85$ Hz), 213.67 (s); ^{19}F NMR (376 MHz, $CDCl_3$, TFA): δ 2.04 (d, $J = 7.63$ Hz); HRMS (EI) Found: m/z 196.0711. Calcd for $C_8H_{11}F_3O_2$: M, 196.0711.

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