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Synthesis of fluorinated materials catalyzed by proline or antibody 38C2 in ionic liquid

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Abstract

The utility of reusable ionic liquid–proline (or aldolase antibody 38C2) reaction system, proceeding the aldol reactions, is described. Further, obtained α-chloro-β-hydroxy compounds were transformed to the optically active α,β-epoxy carbonyl compounds. The aldolase antibody 38C2–ionic liquid system was able to reuse in Michael additions and the reaction of fluoromethylated imines.

Keywords: Aldolase antibody; Aldol reaction; Michael addition reaction

1. Introduction

While aldol reactions have been recognized to be useful in organic synthesis, the reactions commonly employ organic solvent and Lewis acid, and in many cases they are removed from the final reaction mixture by water quench which leads to an aqueous waste stream [1]. In synthetic chemistry, replacement of toxic organic solvents and/or development of molecular catalyst systems are one of the most important issues. Their use in organic synthesis inevitably leads to solvent emissions and/or waste. In recent investigations in this field, the research regarding reusable media such as fluorous fluids [2,3] and molten salts (ionic liquids) [4,5] is focused on the reaction media. While carbon–carbon bond forming reactions are carried out in polar organic solvents (such as THF, Et_2O, etc.) [6], synthetic value of ionic liquids still appears to be grossly underestimated. Obviously, asymmetric syntheses in ionic liquids remain a synthetic challenge.

Recently, the development of practical approach for the asymmetric aldol reactions, L-proline–DMSO system including non-metallic and enzyme-like system [7], attracted our attention.

In our continuous research of the fluorinated materials in ionic liquid–catalyst system [4], we examined the aldol reaction of acetone derivatives with aldehydes in the reusable ionic liquid–proline system and the transformation of obtained materials to the optically active fluorinated α,β-epoxy carbonyl compounds. Furthermore, we would like to describe the aldol and the Michael addition reactions based on the utility of aldolase antibody 38C2 (Aldrich) in an ionic liquid.

2. Results and discussion

2.1. Proline promoted aldol reactions

The construction of carbon–carbon bond forming reactions with complete control of the stereochemistry is most important for organic synthesis. In chemical methods, the control of stereochemistry has been accomplished though the use of chiral starting materials, stoichiometric chiral auxiliaries attached to the donor nucleophiles and/or chiral auxiliaries [1].

The reusable of chiral auxiliary in ionic liquids is of considerable interest. Therefore, we examined the L-proline–ionic liquid system as a reusable stereocontrolled reaction for the carbon–carbon bond forming reaction. Initially, we carried out the aldol reactions under the conditions (aldehyde, L- (or D-)proline, and acetone in an ionic liquid ([emim][OTf]) at room temperature). In the reaction of acetone with benzaldehyde, compounds ($PhCH(OH)CH_2COCH_3$: 36%; $PhCH{=}CHCOCH_3$: 47%) were produced. Moreover, in the cases of aliphatic and/or α,β-unsaturated aldehydes, the aldol condensation (Knoevenagel) reaction proceeds to produce unsaturated ketones [8,9] ($C_6H_{13}CH{=}CHCOCH_3$: 42%;

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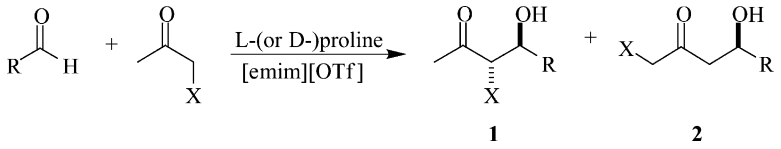


1 **2**

Scheme 1. Aldol reactions in ionic liquid–proline reusable reaction system.

$C_4H_9CH{=}CHCOCH_3$: 40%). In the case of ethyl methyl ketone and/or hydroxyacetone, we have found that it is possible to control the stereochemistry. To make clear the utility of L-proline in this reaction system, we examined the aldol reaction in various molar ratios of L-proline and 4-(trifluoromethyl)benzaldehyde. In the presence of L-proline (50 mol% of aldehyde), successive reuse of the recovered reaction system and in the same reaction yielded amounts and stereoselectivity of product as high as in the first cycle. In the case of D-proline (10 mol%), the reaction proceeded smoothly to give (−)-4-hydroxy-3-methyl-4-{4-(trifluoromethyl)-phenyl}butan-2-one with 83% ee and (−)-5-hydroxy-5-{4-(trifluoromethyl)phenyl}pentan-3-one with 92% ee. In the cases of 4-fluorobenzaldehyde, chiral materials were not obtained, and then aliphatic aldehyde ($C_6H_{13}CHO$) gave unsaturated ketone (23% yield). In the case of fluoroacetone (entry 8), regio- and stereoselectivities are poor. However, the reaction of chloroacetone with aromatic aldehydes proceeded to give the target material with high regioselectivity (>99%). However, in the cases of aliphatic aldehydes (Me_2CHCHO and cyclo-$C_6H_{11}CHO$) as a substrate, the yields were decreased (13 and 23%) (Scheme 1).

In view of 'green chemistry', reuse of the catalyst and solvent are preferable. From the results from the reaction in Table 1 (entries 3, 4 and/or 5, 6), successive reuse of the recovered reaction system is possible to proceed the same reaction.

2.1.1. Epoxidation

Optically active epoxides have much attention during past few years [10–12]. However, the oxidation reaction is particularly troublesome in this respect as traditional methods commonly employ organic solvents and Lewis acid, and in many cases they are removed from the final reaction mixture by a water quench which leads to an aqueous waste stream.

The target α,β-epoxy carbonyl compounds **3** were obtained via the epoxidation of compound **1** (X = Cl) with triethylamine in ionic liquid [emim][OTf] at room temperature. For example, 3-chloro-4-hydroxy-4-phenylbutan-2-one (diastereomeric ratio 81:19), prepared in L-proline–ionic liquid system, was converted to the corresponding α,β-epoxy carbonyl compound in ionic liquid [emim][OTf]-Et_3N system at room temperature in 69% yield. The product was determined as *trans*-isomer based on the comparison of the reported NMR spectra [11]. Further, the absolute configuration (*trans*-(3*R*, 4*S*)-isomer) was also determined by comparing the measured optical rotation with the reported one [11]. From the above results, the absolute configuration of 3-chloro-4-hydroxy-4-phenylbutan-2-one is *anti*-(3*S*, 4*S*)-isomer with 70% ee. In this epoxidation reaction, the

Table 1
Aldol reactions in ionic liquid–proline system

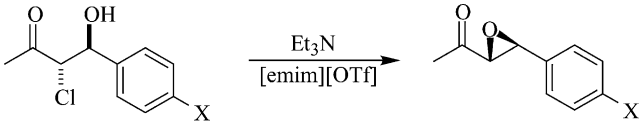
Entry	RCHO	X	Proline (50 mol%)	Yield (%)[a]		d.r.[b] of **1**	% ee[c]	
				1	**2**		**1**	**2**
1	PhCHO	Cl	L	21		81:19		
2		Cl	D	27		79:21		
3[d]	4-$CF_3C_6H_4CHO$	Me	L	68	29	99:1	88	>98
4[e]		Me	L	64	39	99:1	86	88
5[d]		Cl	L	68		83:17		
6[e]		Cl	L	86		85:15		
7		Cl	D	61		85:15		
8		F	L	41	41	78:22		
9		Ome	L	71	20	75:25		
10		OH	L	91		50:50		
11	4-CF_6H_4CHO	Cl	L	45		78:22		
12		Cl	D	22		72:28		

[a] Isolated yield.
[b] The diastereomeric ratio was determined by NMR spectra.
[c] Optical purities were determined by NMR after converting to the corresponding MTPA-ester and/or by HPLC analysis: CHIRALPAK AD; hexane/*i*-PrOH = 98:2; flow rate, 1.25 ml/min. Other optical purities were determined by the comparison of the optical rotation.
[d] First cycle.
[e] Second cycle.

Table 2
Epoxidation

Entry	X	Yield (%)	Optical[a] purity (% ee)	$[\alpha]_D$ (c, $CHCl_3$)
13	H	69	70	−73.4 (1.033)[b]
14		75	66	+67.9 (0.954)
15	F	66	68	−58.4 (1.031)
16		76	65	+52.2 (1.054)
17	CF_3	81	75	−58.2 (1.006)
18		83	69	+52.6 (1.065)

[a] CHIRALPAK AD, hexane/*i*-PrOH = 98:2; flow rate, 1.25 ml/min; $\lambda = 254$ nm.
[b] *trans*-(3*S*, 4*R*)-epoxy-4-phenylbutan-2-one: $[\alpha]_D^{25}$ +96.5 (*c* 1.0, $CHCl_3$), 94% ee [12].



1 (X=Cl) **3**

Scheme 2. Epoxidation in an ionic liquid.

produced epoxides are *trans*-isomer only, and *cis*-isomers are not produced. The optical purities of *trans*-epoxides in Table 2, were determined by HPLC (coloumn: Daicel Chiralpak AD, hexane/*i*-PrOH = 98:2, flow rate 1.25 ml/min, $\lambda = 254$ nm) (Scheme 2).

2.2. Aldolase antibody 38C2 promoted aldol reaction

While the utility of enzyme in an ionic liquid has been reported [13], the enzymatic carbon–carbon bond forming reactions in ionic liquids have not been studied in detail. As it is known that aldol reactions catalyzed by aldolase antibody 38C2 in buffer solution are known to proceed at room temperature [14], we carried out the aldol reaction catalyzed by aldolase antibody 38C2 (Aldrich no. 48157-2) in an ionic liquid. In the present reaction, we carried out the aldol reaction of hydroxyacetone with 4- or 3-(trifluoromethyl)-benzaldehyde (5 mmol) in the antibody aldolase 38C2 (Aldrich no. 48157-2, 10 mg)–ionic liquid ([bmim][PF_6], 3 g). After stirring for 14 days at room temperature, starting materials and products were extracted with diethyl ether (10× 20 ml), and ionic liquid and antibody aldolase 32C2 were recovered. As shown in Table 3, the reaction of hydroxyacetone with 4- or 3-(trifluoromethyl)benzaldehyde in this system proceeded to produce the 3,4-dihydroxy-4-{4- or 3-(trifluoromethyl)phenyl}butan-2-one. However, acetone, methyl ethyl ketone, methoxyacetone, fluoroacetone and chloroacetone did not react in this system. Moreover, in the cases of aliphatic and/or α,β-unsaturated aldehydes, aldol reaction did not proceed. Successive reuse of the recovered Ab32C2–ionic liquid system and in the same reaction yielded amounts of product as higher than the first cycle in the both cases of 3- and 4-(trifluoromethyl)benzaldehyde. In the third and fourth cycles, reuse of this system recovered from the second cycle is possible to produce the same alcohol in the same reaction (Scheme 3).

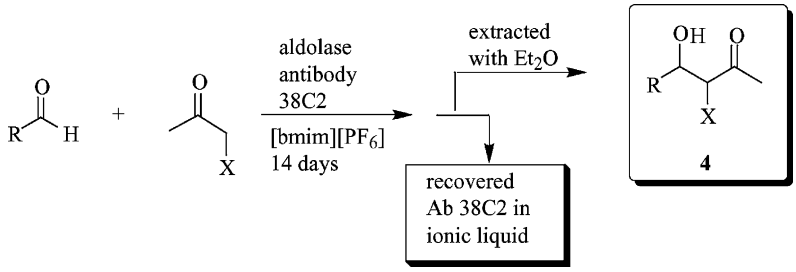
2.3. Antibody aldolase promoted Michael reaction

In the next step, we examined the Michael addition reaction of hydroxyacetone to 2-(phenyl)-ethyl-2-(trifluoromethyl)acrylate in the ionic liquid [emim][OTf]–aldolase antibody 38C2 system. After stirring for 14 days at room

Table 3
Antibody aldolase promoted aldol reaction in the reusable reaction system

Entry	RCHO	X	Ionic liquid	Conversion (%)	d.r.[a]
19	C_6H_5CHO	OH	[bmim][PF_6]	No reaction	
20	4-$CF_3C_6H_4CHO$	OH	[bmim][PF_6]	21 (59)[b]	37:63
21				89[c]	42:58
22				66[d] (75)	36:64
23				46[e] (58)	35:65
24		OH	[emim][Otf]	56	69:31
25		OMe	[bmim][PF_6]	No reaction	
26		H	[bmim][PF_6]	Trace	
27		Cl	[bmim][PF_6]	No reaction	
28		F	[bmim][PF_6]	No reaction	
29	3-$CF_3C_6H_4CHO$	OH	[bmim][PF_6]	17 (33)	42:58
30				45[c] (95)	29:71
31				22[d] (40)	29:71
32	2-$CF_3C_6H_4CHO$	CH_3	[bmim][PF_6]	No reaction	
33	C_6F_5CHO	OH	[bmim][PF_6]	No reaction	

[a] Diastereomeric ratio was determined by NMR.
[b] Conversion yield in parenthesis.
[c] Second cycle.
[d] Third cycle.
[e] Fourth cycle.



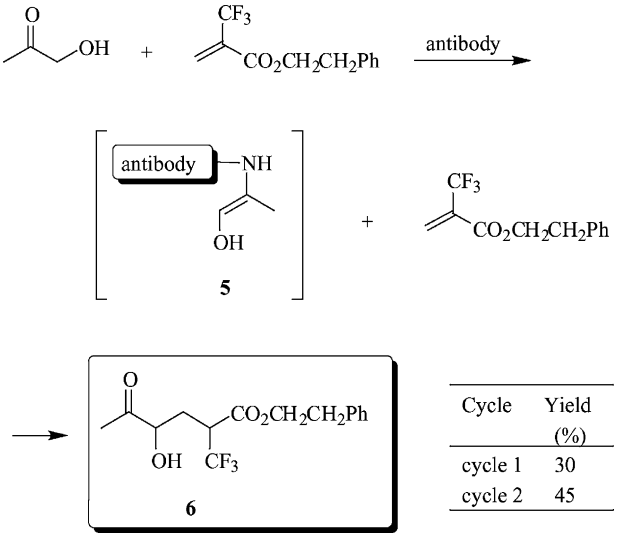
Scheme 3. Antibody 38C2 promoted aldol reaction.

temperature, products were extracted with diethyl ether (10× 20 ml), and ionic liquid and antibody aldolase 32C2 were recovered. On removal of the solvent, the yield of products (diastereomer) was determined by ^{19}F NMR using $C_6H_5CF_3$ as an internal standard.

Products were purified by column chromatography on silica gel using a mixture of hexane–ethyl acetate (3:1) as an eluent. The structure of compound **6** was confirmed by ^{1}H, ^{19}F and ^{13}C NMR spectra. A proposed mechanism for this reaction is shown in Scheme 4. Enamine **5**, generated from the reaction of hydroxyacetone and aldolase antibody 38C2, reacts with the activated methylene group in 2-(phenyl)ethyl-2-(trifluoromethyl)acrylate, resulting the compound **6**.

2.4. The reaction of fluoromethylated imines using antibody aldolase 38C2–ionic liquid system

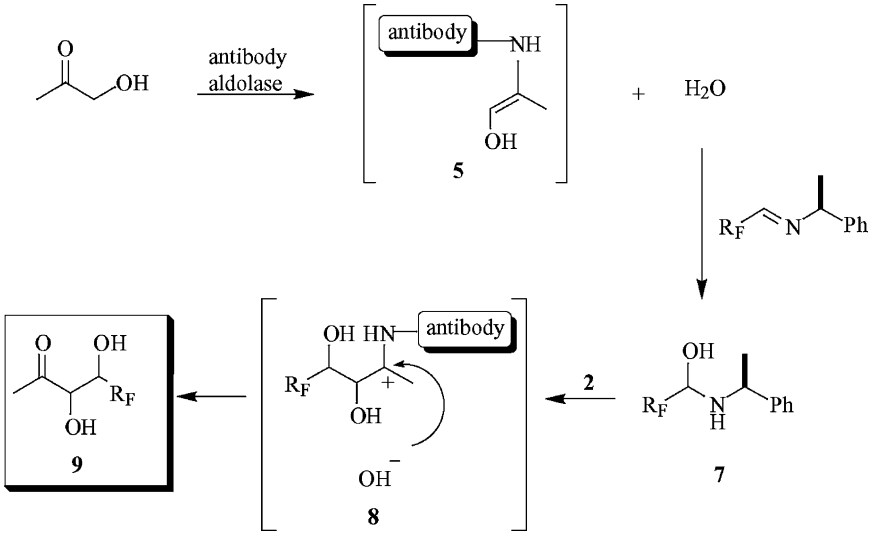
We carried out the reaction of fluoromethylated imines with hydroxyacetone in the antibody aldolase 38C2–ionic liquid system. In this reaction system, the reaction did not proceed in the absence of antibody aldolase 38C2. In the presence of antibody aldolase 38C2, the reaction smoothly proceeded, giving a fluoromethylated carbinol. Proposed reaction mechanism is shown in Scheme 5. At first, reaction



Cycle	Yield (%)
cycle 1	30
cycle 2	45

Scheme 4. Michael addition reaction.

intermediate **5** and H_2O were produced from the reaction of hydroxyacetone and antibody 38C2 and then the produced H_2O attacked on imine to produce the *N*,*O*-acetal **7**. The *N*,*O*-acetal was reacted with reaction intermediate **5**, giving the reaction intermediate **8**. The intermediate **8** was converted to the product **9** with small amount of water containing ionic



Scheme 5. Reaction paths of fluoromethylated imines with hydroxyacetone in antibody aldolase 38C2–ionic liquid.

liquids [15]. To construct the fluorinated materials based on the utility of aldolase antibody, we designed a facile synthetic reaction of *N*,*O*-acetal with CF_3 group. Initially, we carried out the reaction of trifluoroacetaldehyde *N*,*O*-acetal **7** with hydroxyacetone in ionic liquid ([emim][OTf]). After stirring for 14 days at room temperature, the reaction mixture was worked up similarly, giving 2-ethoxy-1,1,1-trifluoro-3-hydroxypentan-4-one in 18% (conversion yield: 57%) yield.

In conclusion, the successful application of this combination of environmentally friendly solvent and antibody catalyst is exciting and is likely to open the door to the development of similar reaction systems for other important organic reactions.

3. Experimental

3.1. General

All commercially available reagents were used without further purification. Chemical shifts of ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in ppm (δ) downfield from the following internal standard (Me_4Si, δ 0.00) in $CDCl_3$. The ^{19}F (282 MHz) NMR spectra were recorded in ppm downfield from internal standard C_6F_6 in $CDCl_3$ using a VXR 300 instrument.

Aldol reaction: Typical procedure is as follows:

3.2. (3S, 4S)-3-Chloro-4-hydroxy-4-phenylbutan-2-one

In the 1-ethyl-3-methyl-1*H*-imidozolium trifluoromethanesulfonate ([emim][OTf], 2 g), benzaldehyde (530 mg, 5 mmol), L-proline (1.0 g) and chloroacetone (0.92 g, 10 mmol) were added, and then the whole was stirred at room temperature. After 48 h of stirring, the product was extracted with diethyl ether (10× 20 ml). The organic layer was dried over anhydrous $MgSO_4$, and then the solvent was removed. Products were purified by column chromatography on silica gel using a mixture of hexane–ethyl acetate (10:1), giving (3*S*, 4*S*)-3-chloro-4-hydroxy-4-phenylbutan-2-one. ^{1}H NMR ($CDCl_3$): δ 2.35 (3H, s), 4.34 (1H, d, $J = 7.97$ Hz), 5.02 (1H, d, $J = 7.97$ Hz), 7.26–7.50 (Ar–H). ^{13}C NMR ($CDCl_3$): δ 27.140, 64.500, 74.599, 126.705, 128.052, 128.245, 138.678, 202.954. IR: 3431 (OH), 1719 (C=O) cm^{-1}. Diastereomer: 2.27 (3H, s), 4.44 (1H, d, $J = 4.67$ Hz), 5.23 (1H, d, $J = 4.67$ Hz), 7.26–7.50 (Ar–H). ^{13}C NMR ($CDCl_3$): δ 28.092, 68.453, 73.309, 126.098, 128.029, 129.668, 133.059, 203.095.

3.3. 4-Hydroxy-3-methyl-4-{4-(trifluoromethyl)-phenyl}butan-2-one and 5-hydroxy-5-{4-(trifluoromethyl)-phenyl}pentan-3-one

In 1-ethyl-3-methylimidazolium trifluoromethanesulfonate [emim][OTf] (2 g), 4-trifluoro-methylbenzaldehyde (880 mg, 5 mmol), L-proline (1 g) and ethyl methyl ketone (1 g) were added, and the mixture was stirred at room temperature. After stirring 48 h of stirring, the product was extracted with diethyl ether (10× 20 ml). The organic layer was dried over anhydrous $MgSO_4$, and then concentrated. Products were purified by column chromatography on silica gel using a mixture of hexane–ethyl acetate (10:1).

4-Hydroxy-3-methyl-4-{4-(trifluoromethyl)phenyl}butan-2-one. ^{1}H NMR ($CDCl_3$): δ 0.98 (3H, d, $J = 7.14$ Hz), 2.22 (3H, s), 2.92 (1H, dq, $J = 7.42$, 7.42 Hz), 3.16 (OH), 4.82 (1H, d, $J = 8.24$ Hz), 7.45–7.64 (Ar–H). ^{19}F NMR ($CDCl_3$): δ 99.15 (s). ^{13}C NMR ($CDCl_3$): δ 13.801, 29.806, 53.407, 75.543, 123.887 (q, $J = 271.7$ Hz), 125.040 (q, $J = 3.72$ Hz), 126.807, 129.475 (q, $J = 32.35$ Hz), 145.901, 212.879. IR: 3429 (OH), 1707 (C=O) cm^{-1}. $[\alpha]_D^{20} + 32.0$ (c 1.009, $CHCl_3$), 83% ee from L-proline. ($[\alpha]_D^{21} - 31.9$ (c 1.069, $CHCl_3$), 83% ee from D-proline.)

5-Hydroxy-5-{4-(trifluoromethyl)phenyl}pentan-3-one. ^{1}H NMR ($CDCl_3$): δ 1.21 (3H, t, $J = 6.86$ Hz), 2.82 (2H, d, 6.04 Hz), 3.48 (2H, q, $J = 6.87$ Hz), 5.23 (1H, t, $J = 6.04$ Hz), 7.45–7.64 (Ar–H). ^{19}F NMR ($CDCl_3$): δ 99.17 (s). ^{13}C NMR ($CDCl_3$): δ 7.519, 36.844, 50.448, 69.280, 125.300 (q, $J = 3.72$ Hz), 125.756 (q, $J = 271.4$ Hz), 125.768, 129.804 (q, $J = 66.42$ Hz), 146.664, 211.335. IR: 3446 (OH), 1712 (C=O) cm^{-1}. $[\alpha]_D^{21}$ +38.4 (c = 0.580, $CHCl_3$), >98% ee from L-proline. ($[\alpha]_D^{20}$ −33.6 (c 1.875, $CHCl_3$), 92% ee from D-proline.)

3.4. 3-Chloro-4-hydroxy-4-{4-(trifluoromethyl)phenyl}butan-2-one

In the above reaction, chloroacetone (1 g), 4-(trifluoromethyl)benzaldehyde (880 mg, 5 mmol), L-proline (1 g) and 1-ethyl-3-methylimidazolium trifluoromethanesulfonate [emim][OTf] (2 g) were used, and then worked up similarly. ^{1}H NMR ($CDCl_3$): δ 2.39 (3H, s), 3.25 (OH), 4.29 (1H, d, $J = 7.96$ Hz), 5.09 (1H, d, $J = 7.96$ Hz), 7.50–7.66 (Ar–H).^{19}F NMR ($CDCl_3$): δ 99.04 (s).^{13}C NMR ($CDCl_3$): δ 27.496, 63.923, 74.075, 123.755 (q, $J = 271.4$ Hz), 125.065 (q, $J = 3.72$ Hz), 126.580, 127.327, 130.091 ($q = 32.35$ Hz), 203.008. IR: 3447 (OH), 1718 (C=O) cm^{-1}. Diastereomer: ^{1}H NMR ($CDCl_3$): δ 2.36 (3H, s), 3.09 (OH), 4.43 (1H, d, $J = 3.84$ Hz), 5.36 (1H, d, $J = 3.82$ Hz), 7.50–7.66 (Ar–H). ^{19}F NMR ($CDCl_3$): δ 99.07 (s). ^{13}C NMR ($CDCl_3$): δ 28.179, 67.986, 72.463, 23.755 (q, $J = 271.4$ Hz), 125.065 (q, $J = 3.72$ Hz), 126.580, 127.327, 130.091 ($q = 32.35$ Hz), 203.429.

3.5. 3-Fluoro-4-hydroxy-4-{4-(trifluoromethyl)-phenyl}butan-2-one and 1-fluoro-4-hydroxy-4-{4-(trifluoromethyl)phenyl}butan-2-one

In the above reaction, fluoroacetone (1 g), 4-(trifluoromethyl)benzaldehyde (880 mg, 5 mmol), L-proline (1 g) and 1-ethyl-3-methylimidazolium trifluoromethanesulfonate [emim][OTf] (2 g) were used, and then worked up similarly.

3-Fluoro-4-hydroxy-4-{4-(trifluoromethyl)phenyl}butan-2-one. ^{1}H NMR ($CDCl_3$): δ 2.12 (3H, d, $J = 5.22$ Hz), 4.83 (1H, dd, $J = 48.9$, 5.22 Hz), 5.12 (1H, dd, $J = 15.1$, 5.22 Hz), 5.24 (1H, dd, $J = 25.8$, 2.47 Hz), 7.18–7.70 (Ar–H). Diastereomer: 2.32 (3H, d, $J = 4.94$ Hz), 4.85 (1H, dd $J = 48.1$, 3.02 Hz). ^{13}C NMR ($CDCl_3$): δ 27.185, 73.089, 96.377 (d, $J = 192.1$ Hz), 125.182 (q, $J = 3.72$ Hz), 125.316 (q, $J = 270.9$ Hz), 127.168, 130.436 (q, $J = 32.35$ Hz), 141.553, 206.887 (d, $J = 25.48$ Hz), 27.439, 72.804, 96.743 (d, $J = 195.3$ Hz), 123.811 (q, $J = 271.4$ Hz), 125.227 (q, $J = 3.44$ Hz), 126.595, 130.233 (q, $J = 32.64$ Hz), 142.711, 207.481 (d, $J = 29.92$ Hz). ^{19}F NMR ($CDCl_3$): δ −33.92 (ddq, $J = 44.25$, 15.26, 4.57 Hz), 99.28 (s) ppm from ext. C_6F_6.

Fluoro-4-hydroxy-4-{4-(trifluoromethyl)phenyl}butan-2-one. ^{1}H NMR ($CDCl_3$): δ 2.90 (1H, dm, J =17.6 Hz), 3.03 (1H, ddd, $J = 17.6$, 8.79, 2.19 Hz), 4.85 (1H, dd, $J = 48.1$, 0.55 Hz), 5.12 (1H, dd, $J = 15.4$, 5.49 Hz), 5.31 (1H, dd, $J = 8.79$, 3.57 Hz), 7.45–7.70 (Ar–H). ^{13}C NMR ($CDCl_3$): δ 46.939, 68.662 (d, $J = 1.72$ Hz), 84.952 (d, $J = 184.9$ Hz), 129.845 (q, $J = 32.35$ Hz), 129.975, 146.364, 205.886 (d, $J = 19.18$ Hz). ^{19}F NMR ($CDCl_3$): δ 99.14 (s), −46.61 (td, $J = 52.8$, 3.16 Hz) ppm from ext. C_6F_6.

3.6. 4-Hydroxy-3-methoxy-4-{4-(trifluoromethyl)-phenyl}butan-2-one and 4-hydroxy-1-methoxy-4-{4-(trifluoromethyl)phenyl}butan-2-one

In the above reaction, methoxyacetone (1 g), 4-(trifluoromethyl)benzaldehyde (880 mg, 5 mmol), L-proline (1 g) and 1-ethyl-3-methylimidazolium trifluoro-methanesulfonate [emim][OTf] (2 g) were used, and then worked up similarly.

4-Hydroxy-3-methoxy-4-{4-(trifluoromethyl)phenyl}butan-2-one. ^{1}H NMR ($CDCl_3$): δ 2.12, 3.32, 3.72 (d, $J = 6.04$ Hz), 4.96 (d, $J = 6.32$ Hz), 7.45–7.55; diastereomer: 2.16, 3.36, 3.77 (d, $J = 4.20$ Hz), 4.99 (d, $J = 5.49$ Hz), 7.45–7.55. ^{13}C NMR ($CDCl_3$): δ 26.646, 58.460, 73.058, 89.853, 123.742 (q, $J = 271.4$ Hz), 124.565 (m), 126.773, 129.393 (q, $J = 32.35$ Hz), 144.088, 209.650; diastereomer: 27.048, 59.048, 73.165, 90.050, 124.615, 126.299, 129.322 (q, $J = 32.07$ Hz), 209.977. ^{19}F NMR ($CDCl_3$): δ 99.2 ppm from ext. C_6F_6.

4-Hydroxy-1-methoxy-4-{4-(trifluoromethyl)phenyl}butan-2-one. ^{1}H NMR ($CDCl_3$): δ 2.86–2.91 (2H, m), 3.42, 4.03, 4.99 (OH, br), 5.27 (dd, $J = 7.70$, 4.67 Hz), 7.45–7.55. ^{13}C NMR ($CDCl_3$): 47.383, 58.912, 68.756, 77.580, 123.806 (q, $J = 271.69$ Hz), 124.841 (q, $J = 3.72$ Hz), 125.038 (q, $J = 3.72$ Hz), 146.963, 207.423. ^{19}F NMR ($CDCl_3$): δ 99.2 ppm from ext. C_6F_6.

3.7. 3-Chloro-4-hydroxy-4-{4-(fluoro)phenyl}butan-2-one

In the above reaction, chloroacetone (1 g), 4-fluorobenzaldehyde (630 mg, 5 mmol), L-proline (1 g) and 1-ethyl-3-methylimidazolium trifluoromethanesulfonate [emim][OTf] (2 g) were used, and then worked up similarly. ^{1}H NMR ($CDCl_3$): δ 2.37 (3H, s), 3.11 (OH), 4.28 (1H, d, $J = 8.24$ Hz), 5.02 (1H, d, $J = 8.24$ Hz), 7.07–7.38 (Ar–H). ^{13}C NMR ($CDCl_3$): δ 27.583, 64.344, 74.052, 115.171 (d, $J = 21.47$ Hz), 128.596 (d, $J = 21.47$ Hz), 134.577 (d, $J = 3.44$ Hz), 162.419 (d, $J = 246.78$ Hz), 203.121. ^{19}F NMR ($CDCl_3$): δ 48.67 (m) from ext. C_6F_6. IR: 3446 (OH), 1720 (C=O) cm^{-1}. Diastereomer; ^{1}H NMR ($CDCl_3$): δ 2.29 (3H, s), 2.97 (OH), 4.39 (1H, d, $J = 4.67$ Hz), 5.22 (1H, d, $J = 4.67$ Hz), 7.07–7.38 (Ar–H). ^{13}C NMR ($CDCl_3$): δ 28.331, 68.164, 72.706, 115.224 (d, $J = 21.47$ Hz), 128.038 (d, $J = 8.30$ Hz), 134.420 (d, $J = 3.15$ Hz), 162.273 (d, $J = 246.49$ Hz), 203.150. ^{19}F NMR ($CDCl_3$): δ 48.43 (m) from ext. C_6F_6.

3.8. trans-(3R, 4S)-Epoxy-4-phenylbutan-2-one [11]

A mixture of 3-chloro-4-hydroxy-4-phenylbutan-2-one (186 mg, 0.94 mmol) derived from L-proline system and triethylamine (1.22 g, 1.22 mmol) in ionic liquid [emim][OTf] (2 g) was stirred for 48 h at room temperature. The reaction mixture was diluted with diethyl ether (20 ml), and then the whole was washed with 1N HCl and water. On removal of the solvent, the crude material was purified by flash column on silica gel, giving the target material in 69% yield. ^{1}H NMR ($CDCl_3$): δ 2.20 (3H, s), 3.50 (1H, d, $J = 1.92$ Hz), 4.01 (1H, d, $J = 1.92$ Hz), 7.26–7.39 (Ar–H). ^{13}C ($CDCl_3$): δ 24.813, 57.676, 63.386, 125.467, 128.490, 128.821, 134.740, 203.923. IR: 1711 (C=O) cm^{-1}. $[\alpha]_D^{27}$ −73.4 (c 1.033, $CHCl_3$).

3.9. trans-3,4-Epoxy-4-{4-(trifluoromethyl)phenyl}butan-2-one

In the above reaction, 3-chloro-4-hydroxy-4-{4-(trifluoromethyl)phenyl}butan-2-one derived from L-proline system and triethylamine in ionic liquid [emim][OTf] were used, and then worked up similarly. ^{1}H NMR ($CDCl_3$): δ 2.21 (3H, s), 3.47 (1H, d, $J = 1.65$ Hz), 4.08 (1H, d, $J = 1.65$ Hz), 7.40–7.65 (Ar–H). ^{19}F ($CDCl_3$): δ 99.03 (s) ppm from int. C_6F_6. ^{13}C ($CDCl_3$): δ 24.802 (d, $J = 1.14$ Hz), 56.845, 63.280, 123.679 (q, $J = 271.7$ Hz), 125.479 (q, $J = 4.0$ Hz), 125.494, 130.832 (q, $J = 32.64$ Hz), 138.991 (q, $J = 0.86$ Hz), 203.270. $[\alpha]_D^{27}$ −58.2 (c 1.006, $CHCl_3$). Anal. calc. for $C_{11}H_9F_3O_2$: C, 57.40; H, 3.94. Found. C, 57.15; H, 4.08.

3.10. trans-3,4-Epoxy-4-{4-(fluoro)phenyl}butan-2-one

In the above reaction, 3-chloro-4-hydroxy-4-{4-(fluoro)-phenyl}butan-2-one derived from L-proline system and triethylamine in ionic liquid [emim][OTf] were used, and then worked up similarly. ^{1}H NMR ($CDCl_3$): δ 2.20 (3H, s), 3.46 (1H, d, $J = 1.64$ Hz), 4.00 (1H, d, $J = 1.64$ Hz), 7.06–7.25 (Ar–H). ^{19}F ($CDCl_3$): δ 49.48 (m) ppm from int. C_6F_6. ^{13}C ($CDCl_3$): δ 24.786, 57.077, 63.306, 115.554 (q, $J = 21.8$ Hz), 127.296 (d, $J = 8.6$ Hz), 130.616 (d, $J =$

2.87 Hz), 132.027 (d, $J = 9.73$ Hz), 203.737. $[\alpha]_D^{27}$ −58.4 (*c* 1.031, $CHCl_3$). IR: 1712 (C=O) cm^{-1}. Anal. calc. for $C_{10}H_9FO_2$: C, 66.66; H, 5.03. Found. C, 66.35; H, 5.29.

3.11. 3,4-Dihydroxy-4-{4-(trifluoromethyl)phenyl}butan-2-one

(A) *First cycle*: A mixture of 4-(trifluoromethyl)benzaldehyde (870 mg, 5 mmol), hydroxyacetone (1 g) and antibody aldolase 38C2 (Aldrich no. 48157-2, 10 mg) in 1-butyl-3-methyl-1*H*-imidozolium hexafluorophosphate ([bmim][PF_6], 3 g) was stirred at room temperature. After stirring of 14 days at that temperature, organic materials were extracted with diethyl ether (10× 10 ml), and ionic liquid containing antibody was recovered. The organic layer was dried over anhydrous $MgSO_4$, and then the solvent was removed. 3,4-Dihydroxy-4-{4-(trifluoromethyl)-phenyl}butan-2-one was obtained by silica gel chromatography using a mixture of hexane and ethyl acetate (10:1).

(B) *Second cycle*: Into the recovered ionic liquid–aldolae antibody medium ftom the above reaction, 4-(trifluoromethyl)benzaldehyde (870 mg, 5 mmol) and hydroxyacetone (1 g) were added, and then the mixture was stirred at room temperature. After 14 days of stirring, organic materials were extracted with diethyl ether (10× 10 ml), and ionic liquid containing antibody was recovered. The organic layer was dried over anhydrous $MgSO_4$, and then the solvent was removed. 3,4-Dihydroxy-4-{4-(trifluoromethyl)phenyl}butan-2-one was obtained by silica gel chromatography using a mixture of hexane and ethyl acetate (10:1). The recovered ionic liquid–aldolae antibody medium was used in the third cycle—mixture of diastereomer.

(C) *Third and fourth cycles*: In the third and/or fourth cycles, the same manner using the recovered ionic liquid–aldolase antibody medium was carried out.

^{1}H NMR (CD_3COCD_3): δ 2.32, 4.39 (1H), 4.46 (1H, d, $J = 4.40$ Hz), 5.05 (1H, d, $J = 4.12$ Hz), 5.14 (1H), 7.53–7.66 (Ar–H). ^{13}C NMR (CD_3COCD_3): δ 24.939, 26.032, 72.106, 73.438, 79.682, 79.788, 123.317 (q, $J = 270.82$ Hz), 123.354 (q, $J = 270.83$ Hz), 123.510 (m), 123.527 (m), 125.108, 125.145, 125.961, 126.454, 144.744, 145.301, 204.866, 207.127, 207.608. ^{19}F NMR (CD_3COCD_3): δ 99.23, 99.21 ppm from ext. C_6F_6. Anal. calc. for $C_{11}H_{11}F_3O_3$: C 53.23; H, 4.47. Found: C. 52.51; H, 4.39.

3.12. 3,4-Dihydroxy-4-{3-(trifluoromethyl)phenyl}butan-2-one

In the above reaction, 3-(trifluoromethyl)benzaldehyde (870 mg, 5 mmol), hydroxyacetone (1 g) and antibody aldolase 38C2 (Aldrich no. 48157-2, 10 mg) in 1-butyl-3-methyl-1*H*-imidozolium hexafluorophosphate ([bmim][PF_6], 3 g) were used, and then worked up similarly.

Mixture of diastereomer—^{1}H NMR ($CDCl_3$): δ 2.39, 4.41 (1H, d, $J = 2.47$ Hz), 4.46 (1H, d, $J = 4.67$ Hz), 5.04 (1H, d, $J = 4.67$ Hz), 5.17 (1H, d,$J = 2.75$ Hz), 7.7–8.15 (Ar–H). ^{13}C NMR ($CDCl_3$): δ 27.519, 72.967, 74.250, 122.919 (m), 124.470 (m), 128.632, 129.584, 123.812 ($J = 271.69$ Hz), 140.294, 141.117, 208.304. ^{19}F NMR ($CDCl_3$): δ 99.13, and 99.18 ppm from ext. C_6F_6. Anal. calc. for $C_{11}H_{11}F_3O_3$: C, 53.23; H, 4.47. Found: C, 53.56; H, 4.21.

3.13. 2-(Phenyl)ethyl 4-hydroxy-5-oxo-2-(trifluoromethyl)hexanate

(A) *First cycle*: In the above reaction, 2-(phenyl)ethyl-2-(trifluoromethyl)acrylate (1.22 g, 5 mmol) and hydroxyacetone (1 g) were used, and then worked up similarly, giving 2-(phenyl)ethyl-4-hydroxy-5-oxo-2-(trifluoromethyl)hexanate. Mixture of diastereomer—^{1}H NMR ($CDCl_3$): δ 2.10, 2.38 (2H, m), 2.18, 2.23 (3H, s), 2.97 (2H, m), 3.50 (2H, m), 3.90, 4.22 (1H, m), 4.35, 4.47 (2H, m), 7.20–7.35 (Ar–H). ^{13}C NMR ($CDCl_3$): δ 24.968, 25.109, 29.481 (q, $J = 2.0$ Hz), 29.791 (q, $J = 2.29$ Hz), 34.620, 34.742, 46.368 (q, $J = 27.8$ Hz), 46.552 (q, $J = 27.8$ Hz), 66.334, 33.357, 73.243, 74.024, 124.324 (q, $J_{C-F} = 279.7$ Hz), 124.458 (q, $J_{C-F} = 279.8$ Hz), 126.488, 126.541, 128.316, 128.343, 128.362, 128.684, 136.967, 136.993, 166.954 (q, $J = 3.43$ Hz), 166.598 (q, $J = 2.86$ Hz), 207.740, 207.759. ^{19}F NMR ($CDCl_3$): δ 93.46 (d, $J_{F-H} = 8.62$ Hz), 93.83 (d, $J_{F-H} = 7.75$ Hz) ppm from ext. C_6F_6. Anal. calc. for $C_{15}H_{17}F_3O_4$: C 56.60; H, 5.38. Found: C, 56.31; H, 5.50.

(B) *Second cycle*: Into the recovered ionic liquid–aldolae antibody medium from the above reaction, 2-(phenyl)ethyl-2-(trifluoromethyl)acrylate (1.22 g, 5 mmol) and hydroxyacetone (1 g) were used, and then worked up similarly.

3.14. 1,1,1-Trifluoro-2,3-dihydroxypentan-4-one [14]

In the above reaction, imine (RF = CF_3, 5 mmol), hydroxyacetone (1 g) and antibody aldolase 38C2 (Aldrich no. 48157-2, 10 mg) in 1-methyl-3-ethyl-1*H*-imidozolium trifluoromethansulfonate ([emim][OTf], 3 g) were used, and then worked up similarly, giving 1,1,1-trifluoro-2,3-dihydroxypentan-4-one.^{1}H NMR ($CDCl_3$): δ 2.35 (3H, s), 4.35 (1H, qd, $J = 6.84$, 1.23 Hz), 4.43 (1H, d, $J = 1.23$ Hz). ^{19}F NMR ($CDCl_3$): δ 84.9 (d, $J = 6.10$ Hz). ^{13}C NMR ($CDCl_3$): δ 25.068, 69.273 (q, $J = 31.5$ Hz), 74.423 (q, $J = 1.43$ Hz), 123.788 (q, $J = 282.9$ Hz), 205.075. IR: 3418 (OH), 1719 (C=O) cm^{-1}.

3.15. 1,1-Difluoro-2,3-dihydroxypentan-4-one [14]

In the above reaction, imine (RF = CHF_2, 5 mmol) and hydroxyacetone (1 g) were used, and then worked up similarly, giving 1,1-difluoro-2,3-dihydroxypentan-4-one. Main—^{1}H NMR ($CDCl_3$): δ 2.38 (3H, s), 4.18 (1H, m), 4.40 (1H, d,), 5.85 (1H, td, $J = 56.3$, 6.04 Hz). ^{19}F NMR ($CDCl_3$): δ 30.85 (ddd, $J = 292.1$, 57.7, 10.3 Hz), 33.59 (ddd, $J = 292.1$, 55.2, 10.3 Hz). ^{13}C NMR ($CDCl_3$): δ 25.220, 70.747 (dd, $J = 27.49$, 23.19 Hz), 75.532,

114.724 (t, $J = 243.3$ Hz), 207.000. Minor—^{1}H NMR ($CDCl_3$): δ 2.39 (3H, s), 4.18 (1H, m), 4.38 (1H, d,), 5.90 (1H, td, $J = 55.8$, 4.39 Hz). ^{19}F NMR ($CDCl_3$): δ 33.53 (ddd, $J = 291.3$, 54.3, 5.17 Hz), 28.23 (ddd, $J = 291.3$, 56.0, 14.7 Hz). ^{13}C NMR ($CDCl_3$): δ 26.620, 71.317 (dd, $J = 25.19$, 22.62 Hz), 75.612, 114.450 (t, $J = 243.3$ Hz), 207.100.

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