Supporting information

Dipole Interaction-Controlled Stereoselectivity in Aldol Reaction of α-CF_3 Enolate with Fluoral

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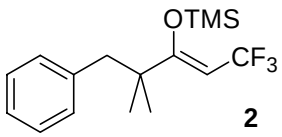
General:

^{1}H NMR and ^{13}C NMR were measured on Varian Gemini 300 (300 MHz) spectrometers and ^{19}F NMR was measured on Varian Gemini 400 (400 MHz) spectrometers. Chemical shift of ^{1}H NMR was expressed in parts per million downfield from tetramethylsilane as an internal standard (δ=0) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard (δ = 77.0) in $CDCl_3$. Chemical shifts of ^{19}F NMR were expressed in parts per million downfield from BTF as an internal standard (δ=-63.24) in $CDCl_3$. Analytical thin layer chromatography (TLC) were performed on a glass plates and /or aluminum sheets pre-coated with silica gel (Merck Kieselgal 60 F_{254}, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid. Column chromatography was performed on Merck Kieselgel 60 and KANTO Silica Gel 60N (spherical, neutral), employing hexane ethyl acetate mixture as an eluent unless otherwise noted. All experiments were carried out under argon atmosphere unless otherwise noted. The calculations were performed with a GAUSSIAN 98 program package using the Hartree-Fock method.

Experimental procedure for the formation of silyl enol ether

To a solution of 1,1,1-trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (**1**)(488 mg, 2.0 mmol) in dichloromethane was added triethylamine (0.92 ml, 6.6 mmol) and trimethylsilyl trifluoromethanesulfonate (1.09 ml, 6.0 mmol) at 0 ºC under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 4 d. To the reaction mixture was added ice water and extracted 3 times with hexane. Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The crude mixture was purified by neutral silica gel column chromatography (hexane only). 489 mg of 3,3-Dimethyl-4-phenyl-1-trifluoromethyl-2-(trimethylsilyloxy)-1-butene was obtained (77%).



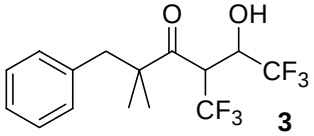
2

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 0.32 (s, 9H), 1.02 (s, 6H), 2.69 (s, 2H), 4.75 (q, *J*=8.4 Hz, 1H), 7.08~7.13 (ddd, *J*=1.8, 2.1, 6.0 Hz, 2H), 7.17~7.30 (m, 3H)
^{13}C NMR ($CDCl_3$, 75 MHz)
δ 0.7, 25.3, 41.4, 45.7, 97.2 (q, *J*=33.0 Hz), 124.1 (q, *J*=269.8 Hz), 126.5, 128.0,
130.6, 138.0, 167.4 (q, *J*=6.1 Hz)
^{19}F NMR ($CDCl_3$, 376 MHz)
δ -56.5 (d, *J*=7.9 Hz)

Experimental procedure for aldol reaction

To a solution of 1,1,1-trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (**1**)(48.9 mg, 0.2 mmol) in dichloromethane (2 ml) was added titanium tetrachloride (26.3 μl, 0.24 mmol) at 0 ºC and stirred for 10 min under argon atmosphere. Then the reaction mixture was cooled to -78 ºC and was added tributylamine (66.7 μl, 0.28 mmol) at the temperature. The reaction mixture was stirred for 15 min and then was added excess amount of freshly distilled fluoral. After stirring for 4 h at -78 ºC, the reaction was quenched by adding phosphorous buffer (pH=7) at the temperature. The mixture was extracted 3 times with ether. Combined organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane:acetone=10:1). 56.7 mg of 5-Hydroxy-2,2-dimethyl-1,5-diphenyl-4-trifluoromethyl-3-pentanone was obtained (**3**)(83%).



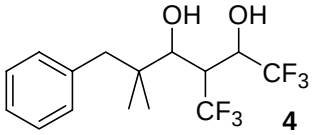
3

^{1}H NMR ($CDCl_3$, 300 MHz)
δ 1.15 (s, 3H), 1.17 (s, 3H), 2.77 (d, *J*=13.2 Hz, 1H), 2.90 (d, *J*=13.5, 1H), 4.19 (dq, *J*=2.8, 7.7 Hz, 1H), 4.44~4.58 (m, 2H), 7.10~7.16 (m, 2H), 7.21~7.33 (m, 3H)
^{13}C NMR ($CDCl_3$, 75 MHz)
δ 23.3, 23.7, 43.8, 45.9 (q, J=26.9 Hz), 50.1, 69.6 (qq, J=33.0, 3.7 Hz), 122.9 (q, J=283.2 Hz), 123.8 (q, J=284.5 Hz), 126.9, 128.2, 131.2, 136.5, 211.8
^{19}F NMR ($CDCl_3$, 376 MHz)
δ -77.7 (dd, *J*=2.3, 3.4 Hz, 3F), -63.0 (dd, *J*=2.6, 7.9 Hz, 3F) (-77.3 (dd, *J*=2.3, 6.8 Hz, 3F), -60.6 (dd, *J*=2.3, 7.9 Hz, 3F) for minor isomer)

Experimental procedure for hydroboration of the aldol product

To a solution of 5-hydroxy-2,2-dimethyl-1-phenyl-4,5-bis(trifluoromethyl)-3-pentanone (**3**) (20.1 mg, 0.059

mmol) in THF was added borane-methyl sulfide complex (25.5 μl, 0.352 mmol) under argon atmosphere. The reaction mixture was refluxed for 1 h and then quenched with 1N HCl. The mixture was extracted 3 times with ether, washed with saturated aqueous solution of sodium bicarbonate, washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude mixture (mixture of two diastereomer) was purified by silica gel column chromatography (hexane:ethylacetate=5:1). 3-Hydoroxy-4,4-dimethyl-5-phenyl -1,2-bis(trifluoromethyl)-1-pentanol (**4**) (as a single isomer) was obtained in 38% yield.



4

^{1}H NMR ($CDCl_3$, 400 MHz)

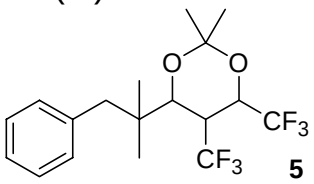
δ 0.85 (s, 3H), 0.95 (s, 3H), 2.15 (d, *J*=6.4 Hz, 1H), 2.56 (d, *J*=13.2, 1H), 2.74 (d, *J*=13.2 Hz, 1H), 2.82 (dq, *J*=1.2, 9.6 Hz, 1H), 3.54 (d, *J*=6.0 Hz, 1H), 4.12 (d, *J*=6.0 Hz, 1H), 4.47 (quint, *J*=7.2 Hz, 1H), 7.11~7.16 (m, 2H), 7.17~7.30 (m, 3H)

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -77.0 (d, *J*=7.9 Hz, 3F), -61.5 (d, *J*=9.4 Hz, 3F)

Experimental procedure for acetonide protection of 1,3-diol

To a solution of 3-hydoroxy-4,4-dimethyl-5-phenyl -1,2-bis(trifluoromethyl)-1-pentanol (**4**)(14.5 mg, 0.042 mmol) in acetone (0.5 ml) was added $AlCl_3$ dissolved in ether (1 ml) at 0 °C under argon atmosphere. The reaction mixture stirred for 2 h at room temperature and 1.5 h at 40 °C. The reaction was quenched with saturated aqueous solution of sodium bicarbonate and extracted 3 times with ether. Combined organic layer was washed with brine, filtered through filt paper and evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane:ethylacetate=100:0 to 30:1) to afford 9.3 mg (58 %) of 4-(1,1-dimethyl-2-phenyl-ethyl)-2,2-dimethyl-5,6-bis(triflu oromethyl)-[1,3]dioxane (**5**).



5

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 0.92 (s, 3H), 0.93 (s, 3H), 1.41 (s, 3H), 1.47 (s, 3H), 2.61 (d, J=13.2 Hz, 1H), 2.75 (d, *J*=13.2 Hz, 1H), 2.86 (m, 1H), 3.82 (bq, J=1.8 Hz, 1H), 4.38 (quint., J=5.7 Hz, 1H), 7.12~7.17 (m, 2H), 7.19~7.32 (m, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 21.9, 22.6, 23.0, 25.7, 37.0, 41.8 (q, *J*=25.4 Hz), 44.0, 67.3 (qq, *J*=3.6, 31.6 Hz), 74.7, 102.4, 124.0 (q, *J*=279.1 Hz), 126.2 (q, *J*=280.3 Hz), 126.3, 127.9, 131.1, 138.1

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -79.4 (quint., *J*=5.7 Hz, 3F), -62.1 (m, 3F)

Ab initio calculations

Reaction of Li-(*Z*)-enolate of α-CF_3-acetone and fluoral

TS1

E(MP2/6-31G*//HF/6-31G*) = -1295.1698504228 hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.850078	1.543546	0.915354
2	6	0	0.267045	2.014923	0.658814
3	6	0	1.462277	1.271024	0.689500
4	6	0	0.980650	0.429364	-1.465003
5	8	0	-0.120399	-0.079586	-1.411967
6	6	0	2.203130	-0.466412	-1.627132
7	6	0	1.565453	0.137247	1.641603
8	1	0	1.144827	1.426256	-1.854716
9	1	0	2.384580	1.818765	0.617516
10	6	0	0.319055	3.450407	0.179903
11	9	0	3.332226	0.151252	-1.352776
12	9	0	2.249530	-0.806625	-2.912444
13	9	0	2.131120	-1.569608	-0.925143
14	9	0	1.387592	0.486150	2.919675
15	9	0	2.768555	-0.425090	1.586426
16	9	0	0.678345	-0.839901	1.424805
17	3	0	-1.496387	-0.000022	-0.009085
18	8	0	-1.965807	-1.860955	0.598352
19	6	0	-1.216911	-2.977809	0.184506
20	6	0	-2.470568	-1.969312	1.904291
21	8	0	-3.328617	0.551953	-0.674789
22	6	0	-4.003954	-0.214649	-1.634065
23	6	0	-3.742763	1.892681	-0.619803
24	1	0	-0.825799	-2.760234	-0.796619
25	1	0	-1.852776	-3.857330	0.141017
26	1	0	-0.392913	-3.159870	0.863125
27	1	0	-3.121237	-2.834616	1.989689
28	1	0	-3.039836	-1.074505	2.109827
29	1	0	-1.661265	-2.052607	2.620820
30	1	0	-5.072019	-0.219101	-1.436722
31	1	0	-3.625915	-1.223108	-1.570609
32	1	0	-3.828583	0.176171	-2.631975
33	1	0	-3.150385	2.379517	0.136855
34	1	0	-4.796376	1.952168	-0.362573
35	1	0	-3.584685	2.380756	-1.577512
36	1	0	0.015562	4.094095	0.999473
37	1	0	-0.395627	3.589928	-0.624602
38	1	0	1.304013	3.753721	-0.151911

TS2

E(MP2/6-31G*//HF/6-31G*) = -1295.1735818670 hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.450817	0.170198	1.660910
2	6	0	-0.789737	0.181880	1.695917
3	6	0	-1.596668	0.921737	0.811656
4	6	0	-1.167483	-0.407968	-1.124314
5	8	0	-0.018239	-0.785168	-1.056529
6	3	0	1.454142	-0.202812	0.105204
7	1	0	-1.469439	0.471478	-1.674822
8	6	0	-1.104614	2.207377	0.265446
9	6	0	-2.281997	-1.428124	-0.934929
10	1	0	-2.649345	0.964474	1.025003
11	6	0	-1.462461	-0.709728	2.716569
12	9	0	-0.907448	3.160668	1.177603
13	9	0	-1.981759	2.715500	-0.604306
14	9	0	0.055514	2.118776	-0.399825
15	9	0	-2.065952	-2.235267	0.079907
16	9	0	-2.334256	-2.168909	-2.034990
17	9	0	-3.464440	-0.867772	-0.787686
18	8	0	2.808256	1.000087	-0.762082
19	6	0	2.652737	1.476988	-2.073640
20	6	0	3.434629	1.912213	0.104616
21	8	0	2.615309	-1.807853	0.508469
22	6	0	3.211596	-2.490757	-0.560283
23	6	0	2.245809	-2.638909	1.579418
24	1	0	4.104457	-3.012743	-0.228892
25	1	0	3.485376	-1.757158	-1.303302
26	1	0	2.519807	-3.205747	-0.994891
27	1	0	1.800401	-2.010230	2.332633
28	1	0	3.119423	-3.140766	1.985027
29	1	0	1.525030	-3.383385	1.254765
30	1	0	2.121335	0.721628	-2.632897
31	1	0	3.623472	1.649690	-2.528967
32	1	0	2.081108	2.397382	-2.083775
33	1	0	4.429044	2.155986	-0.256949
34	1	0	3.511825	1.441210	1.073221
35	1	0	2.847186	2.819020	0.192973
36	1	0	-1.286683	-0.282343	3.699363
37	1	0	-1.010934	-1.693973	2.697688
38	1	0	-2.529439	-0.799410	2.562987

Reaction of Li-(*Z*)-enolate of α-CH_3-acetone and acetaldehyde

TS1'

E(MP2/6-31G*//HF/6-31G*) = -701.01118380521 hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	8	0	0.417037	-0.812402	-1.320658
2	6	0	1.619451	-1.010888	-1.033610
3	6	0	2.511271	-0.001622	-0.669326
4	6	0	1.759727	-0.020291	1.421458
5	8	0	0.575453	0.355171	1.376557
6	6	0	2.806421	0.889455	2.017261
7	6	0	2.245607	1.423143	-1.098001
8	1	0	1.971137	-1.077880	1.551038
9	1	0	3.548135	-0.290370	-0.602667
10	6	0	2.071391	-2.457060	-0.978062
11	1	0	3.812298	0.534458	1.833432
12	1	0	2.638402	0.913449	3.093140
13	1	0	2.695753	1.898187	1.642887
14	1	0	2.120899	1.512119	-2.176115
15	1	0	3.070621	2.070385	-0.814745
16	1	0	1.344936	1.818871	-0.639569
17	3	0	-0.673265	-0.015134	0.001352
18	8	0	-1.722231	1.677743	-0.353844
19	6	0	-1.371157	2.892674	0.254393
20	6	0	-2.341147	1.817311	-1.603282
21	8	0	-2.207246	-1.294325	0.363238
22	6	0	-2.994638	-1.132736	1.509292
23	6	0	-2.128809	-2.615909	-0.102080
24	1	0	-0.839993	2.655194	1.162023
25	1	0	-2.261583	3.471855	0.483530
26	1	0	-0.726682	3.475742	-0.396146
27	1	0	-3.261405	2.387911	-1.512973
28	1	0	-2.568112	0.826618	-1.967268
29	1	0	-1.679850	2.313516	-2.306544
30	1	0	-4.016096	-1.451741	1.321051
31	1	0	-2.989473	-0.083424	1.762746
32	1	0	-2.590719	-1.704613	2.339478
33	1	0	-1.472118	-2.613558	-0.956453
34	1	0	-3.113323	-2.975972	-0.388027
35	1	0	-1.723457	-3.268951	0.666034
36	1	0	1.956398	-2.896673	-1.964137
37	1	0	1.429273	-3.013898	-0.301230
38	1	0	3.101936	-2.569769	-0.664134

TS2′

E(MP2/6-31G*//HF/6-31G*) = -701.01103328957 hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.607672	0.248750	-1.399467
2	6	0	-1.824637	0.178841	-1.115577
3	6	0	-2.415802	-0.907017	-0.467273
4	6	0	-1.673827	-0.373177	1.552029
5	8	0	-0.445783	-0.202039	1.474762
6	3	0	0.664602	0.060137	-0.024875
7	1	0	-2.044860	-1.353518	1.833709
8	6	0	-1.799381	-2.284213	-0.574473

9	6	0	-2.565862	0.769697	1.972862
10	1	0	-3.493299	-0.890152	-0.408352
11	6	0	-2.660557	1.402752	-1.433627
12	1	0	-1.886557	-2.699740	-1.577826
13	1	0	-2.289614	-2.980820	0.102258
14	1	0	-0.745680	-2.270753	-0.323114
15	1	0	-2.293170	1.682470	1.459313
16	1	0	-2.408748	0.930647	3.038423
17	1	0	-3.613802	0.552841	1.809194
18	8	0	2.076674	-1.391005	-0.060452
19	6	0	2.057384	-2.454478	0.854340
20	6	0	2.700345	-1.689174	-1.279425
21	8	0	1.859361	1.701449	-0.052177
22	6	0	2.657397	1.975120	1.065145
23	6	0	1.386729	2.844633	-0.715334
24	1	0	3.534161	2.549301	0.778431
25	1	0	2.970771	1.029294	1.480675
26	1	0	2.097954	2.528253	1.813569
27	1	0	0.761682	2.506967	-1.525572
28	1	0	2.217635	3.428420	-1.101902
29	1	0	0.802206	3.464279	-0.040883
30	1	0	1.494705	-2.127108	1.713918
31	1	0	3.069209	-2.718236	1.149980
32	1	0	1.576412	-3.325997	0.421010
33	1	0	3.738348	-1.967991	-1.120343
34	1	0	2.657386	-0.802048	-1.893051
35	1	0	2.185956	-2.499631	-1.786211
36	1	0	-2.706458	1.514890	-2.513144
37	1	0	-2.178209	2.291671	-1.038990
38	1	0	-3.671202	1.341400	-1.049782

Reaction of $TiCl_3$-(*Z*)-enolate of α-CF_3-acetaldehyde and fluoral

TS1

E(B3LYP/LANL2DZ for Ti, 6-31G* for others) = -2380.68778800 hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.449520	0.241556	-1.520970
2	6	0	0.769757	0.554992	-1.776088
3	6	0	1.601297	1.264968	-0.931772
4	6	0	1.484309	-0.608028	0.547018
5	8	0	0.348997	-1.083640	0.350064
6	22	0	-1.546836	-0.361266	-0.043377
7	1	0	1.679557	0.128623	1.331255
8	6	0	1.114632	2.268221	0.068109
9	6	0	2.696895	-1.418220	0.079710
10	1	0	2.621819	1.437679	-1.256965
11	1	0	1.190684	0.110959	-2.682662
12	9	0	0.880454	3.464073	-0.495751
13	9	0	2.027780	2.454946	1.046884
14	9	0	-0.044154	1.886036	0.682548
15	9	0	2.498471	-1.941274	-1.136707

16	9	0	2.908593	-2.418227	0.951088
17	9	0	3.796932	-0.645986	0.050482
18	17	0	-2.425975	-2.236131	-0.708103
19	17	0	-1.845497	-0.331830	2.152931
20	17	0	-3.097439	1.123230	-0.555348

TS2

E(B3LYP/LANL2DZ for Ti, 6-31G* for others) = -2380.67759909 hartree

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.770139	0.859083	-1.455940
2	6	0	0.388641	1.064453	-1.965886
3	6	0	1.550535	1.218055	-1.233107
4	6	0	1.287922	-1.153838	-0.927498
5	8	0	0.119769	-1.244309	-0.503255
6	6	0	2.476494	-1.381424	0.022061
7	6	0	1.530591	1.795840	0.153506
8	1	0	1.527004	-1.401915	-1.970029
9	1	0	2.478493	1.383278	-1.769506
10	1	0	0.446742	0.997220	-3.057778
11	9	0	3.590997	-0.784211	-0.432672
12	9	0	2.695233	-2.713516	0.018981
13	9	0	2.230371	-0.990741	1.267888
14	9	0	1.258588	3.115657	0.120320
15	9	0	2.714721	1.645640	0.766272
16	9	0	0.578679	1.226523	0.951555
17	22	0	-1.604562	-0.183402	-0.045289
18	17	0	-3.009851	-1.460936	-1.114610
19	17	0	-1.492095	-1.072503	1.972755
20	17	0	-2.849308	1.556107	0.491366