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DIASTEREOSELECTIVITY IN THE DIRECTED ALDOL REACTIONS OF 1-FLUORO-3,3-DIMETHYL-BUTANONE ENOLATES AND ENOL SILYL ETHERS.

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Abstract: High diastereoselectivity was observed in the directed aldol reaction of lithium enolates of 1-fluoro-3,3-dimethylbutanone while an apparent reversal of diastereoselection was found in Lewis acid mediated reactions of corresponding enol silyl ethers.

Application of the directed aldol reaction[1] to α-fluorinated enolates would provide a convenient route to the stereoselective synthesis of a variety of specifically fluorinated molecules. Halogenated enolates[2] and fluorinated enolates[3] have been reported, but, with few exceptions[4], there has been little or no discussion of the stereoselectivity of enolate fmation or the diastereoselectivity of aldol product formation. Other than isotopic substitution, fluorine is the smallest substituent (Van der Waals radius 1.35 A, C-F bond length 1.39 A) that can be employed to study the steric demands on diastereoselectivity. With its high relative electronegativity, it is an electronically demanding substituent as well.

Recently, we reported a high yield method for the directed aldol reaction of ethyl fluoroacetate.[5] As is often the case with ester enolates,[6] the lithium enolate of ethyl fluoroacetate was generally not diastereoselective. In sharp contrast the directed aldol reaction of the lithium enolate of 1-fluoro-3,3-dimethylbutanone has shown excellent diastereoselectivity. (See Table 1). The required fluoroketone is readily prepared by treatment of the bromoketone with potassium fluoride in anhydrous ethylene glycol.

$$BrCH_2COC(CH_3)_3 + KF \longrightarrow FCH_2COC(CH_3)_3 \quad (1)$$

$$FCH_2COC(CH_3)_3 + LiHMDS \longrightarrow LiCHFCOC(CH_3)_3 \quad (2)$$

$$LiCHFCOC(CH_3)_3 + RCHO \longrightarrow RCH(OH)CHFCOC(CH_3)_3 \quad (3)$$

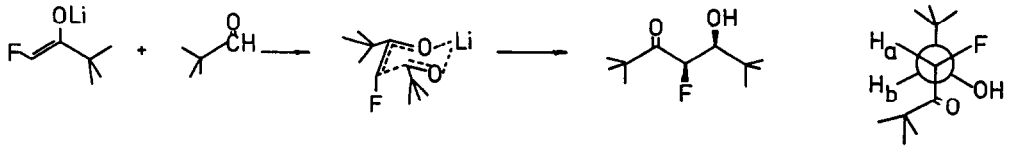
The lithium enolate was generated by the addition of the fluoroketone to a solution of lithium hexamethyldisilazide (LiHMDS) in THF containing one equivalent of hexamethylphosphoramide (HMPA) at -78 [C. Analogously to the enolate of ethyl t-butyl ketone, the enolate most likely exists in the Z configuration. Trapping experiments with

Table 1. Directed Aldol Reaction of Lithium Enolate of 1-Fluoro-3,3-dimethylbutanone.[a]

Entry	RCHO	Yield[b] %	Diastereoselectivity[c]
1.	CH_3CH_2	63	16:1
2.	$CH_3CH_2CH_2$	74	19:1
3.	$(CH_3)_2CH$	50	24:1
4.	$(CH_3)_3C$	62	49:1
5.	C_6H_5	70	7:1
6.	3,3-dimethyl-2,4-dioxal-1-yl	90	32:1

[a] To a solution of 0.01 mol LiHMDS and 0.01 mol of HMPA dissolved in 50 mL of anhydrous THF at -78 °C was added 0.5 g (0.004 mol) of 1-fluoro-3,3-dimethylbutanone in THF over 1 min. To the solution of the enolate was then rapidly added 0.003 mol of the aldehyde in THF. After stirring an additional 2 min, the reaction was quenched by rapid addition of a saturated ammonium chloride solution. Extractive workup with hexanes yielded on evaporation the product as a clear colorless oil. [b] Isolated yield.[7] [c] Diastereoselectivity was determined by ^{13}C NMR spectroscopy and by gas chromatographic analysis (50 m x 0.025 mm OV-101 open tubular column).

chlorotrimethylsilane clearly indicate that one enolate is formed predominantly (>95%).[8] If the Zimmerman chair configuration model for the transition state[9] is assumed, then the major product probably has the syn configuration. Examination of a space-filling model of the syn product of the condensation with pivalaldehyde clearly illustrates that the antiperiplanar conformation should be favored. In such a gauche relationship, the value of $J_{Ha,Hb}$ is predicted to be less than 5 Hz, in good agreement with observed value $J_{Ha,Hb}$ of 1.5 Hz.



With the enol silyl ether, 1-fluoro-2-trimethylsiloxy-3,3-dimethylbut-1-ene, in hand, boron trifuoride-etherate mediated condensation reactions with aldehydes were studied. In previous studies, this reaction demonstrated poor simple diastereoselectivity,[10] except in the case reported by Reetz,[11] but good diastereofacial selectivity.[12]

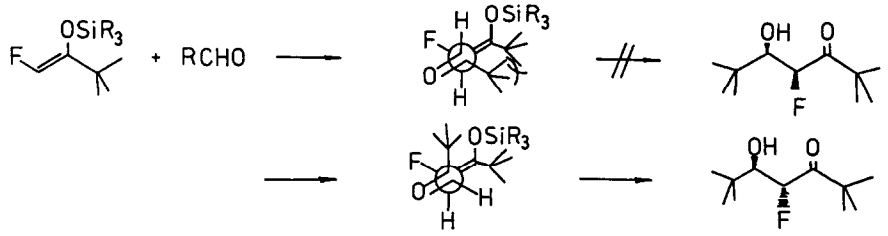
$$CHF{=}C(OSi(CH_3)_3)C(CH_3)_3 + RCHO \longrightarrow RCH(OH)CHFCOC(CH_3)_3 \qquad (4)$$

Table 2. Lewis Acid Mediated Addition of 1-Fluoro-2-trimethylsiloxy-3,3-dimethylbut-1-ene to Aldehydes.[a]

Entry	RCHO	Yield[b] %	Diastereoselectivity[c]
1.	CH_3CH_2	79	1:1.6
2.	$CH_3CH_2CH_2$	74	1:1.5
3.	$(CH_3)_2CH$	81	1:1.4
4.	$(CH_3)_3C$	32	1:1.9
5.	C_6H_5	88	1:1.8

[a] To 0.01 mol of enol silyl ether, prepared by trapping of the enolate anion with chloro trimethylsilane, in 20 mL of CH_2Cl_2 was added 0.01 mol of boron trifluoride etherate and 0.01 mol of the aldehyde dissolved in an additional 20 mL of CH_2Cl_2. After stirring at ambient temperature for 3 h, the solution was diluted with 50 mL of CH_2Cl_2, was washed with water, dried and the solvent was evaporated. [b] Isolated yield. [c] Diastereoselectivity was determined by ^{13}C NMR spectroscopy and by gas chromatographic analysis (50 m x 0.025 mm OV-101 open tubular column).

In contrast to the known Lewis-acid mediated condensations, the fluoroenol silyl ethers are unreactive at -78 °C; at least ambient temperature is required for reactfor reaction when boror trifluoride etherate is used as the Lewis acid. Significantly although the relative diastereoselectivity is poor, the selectivity is reversed from that which is found with the lithium enolates. This suggests either that the enol silyl ethers are somehow equilibrating under the reaction conditions[13], or that the reactions do not have a common six-membered chair transition state. If an open transition state[14] is employed, steric interactions would favor formation of the presumed anti product as is found.



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7. All new compounds exhibited satisfactory microanalytical and/or spectroscopic properties.

8. ^{13}C NMR chemical shifts in $CDCl_3$ solution in ppm from TMS; δ 132.6 $J_{C,F}$=238 Hz, δ 191.7 $J_{C,F}$=63 Hz, δ 64.6 $J_{C,F}$=25 Hz, δ 27.4, δ 2.53. ^1H NMR chemical shifts in $CDCl_3$ solution in ppm from TMS; δ 5.95 d ($J_{H,F}$=80 Hz) 1H, δ 0.97 s 9Hs, δ 0.23 s 9Hs.

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