Journal of Organometallic Chemistry, 403 (1991) 159–164
Elsevier Sequoia S.A., Lausanne
JOM 21420

o-Fluorobenzaldehyde-chromium-tricarbonyl: a new chiral complex for highly diastereoselective nucleophilic additions

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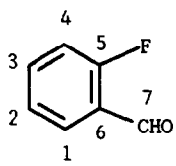
(Received July 30th, 1990)

Abstract

o-Fluorobenzaldehyde-chromium-tricarbonyl complex has been synthesized in 75% overall yields. Its ^{1}H, ^{13}C and ^{19}F NMR spectra have been fully assigned and the tripod conformation estimated. It is shown also that nucleophilic additions to this complex lead to high levels of asymmetric induction (80 to 100%).

Introduction

During work on asymmetric synthesis of bioactive amino-alcohols [1–3] we investigated complex **4** as a route to ephedrine analog **7**.



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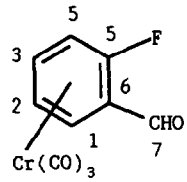
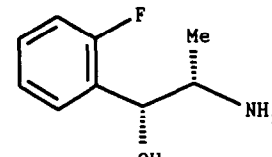


8 **4**



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We describe here the synthesis and spectroscopic properties of complex **4**, along with initial results on the diastereoselectivity observed upon nucleophilic additions to this complex.

Results and discussion

Synthesis

The synthesis was performed in the usual way [4a,b] as depicted in Scheme 1, and the red complex isolated in 75% yield.

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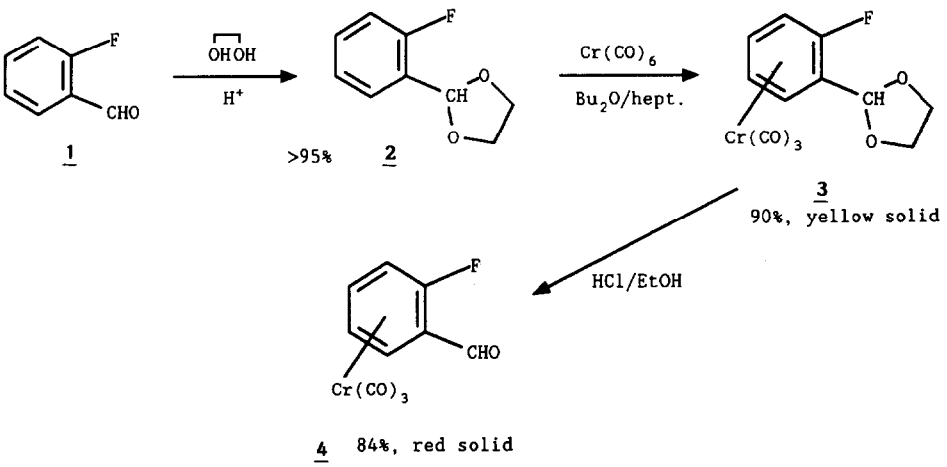


Scheme 1

^1H, ^{13}C and ^{19}F NMR spectroscopy

The ^1H, ^{13}C and ^{19}F NMR of complex **4** and of the starting aldehyde **1** were recorded and the data are given in Tables 1–3.

Assignments of the ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra of compound **1** are based on the pattern of the multiplets and are consistent with the known effects of F and CHO groups in substituted benzenes.

Table 1

200 MHz ^1H NMR of aldehyde **1** and complex **4** ($CDCl_3$/TMS) [a]

		δ	J_{12}	J_{13}	J_{14}	J_{1F}	J_{23}	J_{24}	J_{2F}	J_{34}	J_{3F}	J_{4F}
1	H_1	7.90	7.4	1.9	0	7.4						
	H_3	7.61		1.9			7.4			8.3	5.4	
	H_2	7.27	7.4				7.4	0.9	0			
	H_4	7.16			0			0.9		8.3		10.5
4	H_1	6.15	6.2	1.3	0	3.7						
	H_3	5.77		1.3			6.2			6.2	2.6	
	H_4	5.36			0			0.5		6.2		6.2
	H_2	5.00	6.2				6.2	0.5	2.6			

[a] J in Hz, δ in ppm.

Table 2

50 MHz ^{13}C NMR of aldehyde **1** and complex **4** ($CDCl_3$/TMS) [a]

	C1	C2	C3	C4	C5 (J(CF))	C6	C7 (C=O)	C8 (C≡O)
1	128.4 (0)	124.4 (3)	136.1 (9)	116.2 (10)	164.4 (258)	124.1 (5)	186.8 (6)	
4	90.4 (0)	85.3 (0)	93.4 (8)	85.3 (0)	149.4 (273)	84.9 (25)	182.8 (0)	228.7

[a] J in Hz, δ in ppm.

Table 3

376 MHz ^{19}F NMR of aldehyde **1** and complex **4** ($CDCl_3/CFCl_3$) [a]

	δ	aspect	$^3J_{F4}$	$^4J_{F3}$	$^4J_{F1}$	$^5J_{F2}$
1	−122.4	ddd	10.5	5.4	7.4	0
4	−141.5	ddt	6.2	2.6	3.7	2.6

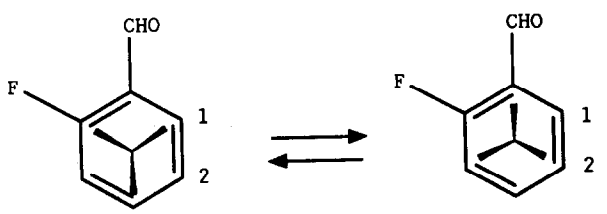
[a] J in Hz, δ in ppm.

The NMR data for the complex **4** are consistent with the general trend observed on $Cr(CO)_3$ complexation of aromatic compounds [5], but it is noteworthy that: (i) ^3J(FH) and ^4J(FH) decrease as expected (−3.8 to −2.8 Hz) but ^5J(FH) increases (+2.6 Hz); (ii) the fluorine signal is shielded by 19 ppm on complexation as already observed for other substituents (H and C); (iii) ^1J(CF) increases (+15 Hz) on complexation; (iv) the non-equivalence between H2 and H4 is inverted in complex **4**. $\Delta\delta(2\text{–}4) = +0.11$ ppm in **1** but −0.36 ppm in **4**.

The population of conformer **Ia** based on the non-equivalence between H1 and H2 and eq. 1 [5,6] is estimated to be 93–96%, which is in accord with the known electron-donor properties of fluorine.

$$\Delta\delta(1\text{–}2) = (2x_a - 1)0.84 + (o\text{–}m)_{CHO}\text{complex} + (m\text{–}p)_F\text{complex} \quad (1)$$

($x_a = 93\%$ if one assumes $(m\text{–}p)_F$complex $= 1/3(m\text{–}p)_F$free ligand $= 0.06$ ppm; $x_a = 96\%$ if one assumes $(m\text{–}p)_F$complex $= 0$ ppm)



Ia (x_a) IIa ($1-x_a$)

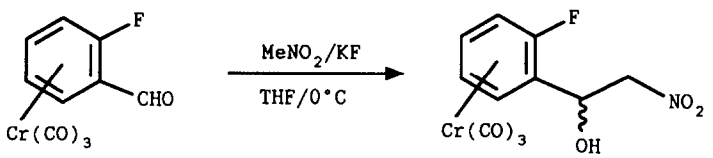
Diastereoselectivity upon nucleophilic additions

Additions of nitromethane and of trimethylsilylcyanide have been studied, and the results are summarised in Table 4.

Table 4

Reagent (equiv.)	Base (equiv.)	Solvent	Temp. (°C)	Time	Yield	diast. ratio
$MeNO_2$ (2)	KF (10)	THF	25	5 d	quant.	75/25
$MeNO_2$ (10)	KF (30)	THF	0	3 d	quant.	93/7
$MeNO_2$ (40)	KF (30)	^{i}PrOH	0	2 h	quant.	91/9
Me_3SiCN	ZnI_2	CH_2Cl_2	25	1 h	quant.	100/0

Addition of nitromethane was carried out with KF as base [1,7]. Under these conditions, protons are always present during the reaction and are readily available to neutralyze the formed alkoxide, so that retro-nitroaldolisation can be avoided.



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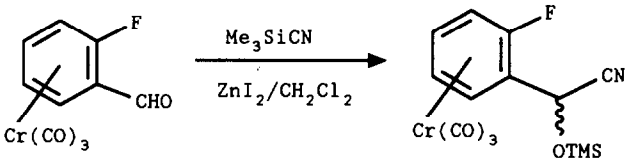
Provided a large excess of KF (10 to 30 equiv.) and an excess of CH_3NO_2 (2 to 10 equiv.) are used, the addition proceeds even in THF, in accord with our previous results [8], but it is much faster in isopropanol. The asymmetric inductions obtained are high, and slightly better in THF (93/7) than ^{i}PrOH (91/9).

ZnI_2-induced addition of Me_3SiCN [2,9] proceeds rapidly and the asymmetric induction even higher: > 98/< 2 (the other diastereomer was not detected).



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It thus appears that, as previously observed [1,2], the later reaction is the more efficient. Therefore, although fluorine is a "small" substituent, isogeometric with hydrogen (van der Waals radii: F, 1.35; H, 1.2 Å) the presence of a fluorine atom in the ortho position leads to more than 96% of asymmetric induction, probably because of a larger bond length (C_{sp^3}–F, 1.38; C_{sp^3}–H, 1.02 Å) and electronic effects.

Complex **4** thus appears to have potential as a starting material for the synthesis of optically pure amino-alcohols, and this aspect is under investigation.

Experimental

All starting materials were commercially available research grade chemicals and used without further purification. All reactions were carried out under argon. Solvents were dried before use: THF was refluxed over $LiAlH_4$ and ^{i}PrOH was refluxed over CaO then distilled and stored over molecular sieve 4A. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 and ^{19}F NMR on a Bruker AM 400 spectrometer. IR spectra were recorded on a Perkin–Elmer 1310 spectrometer. Melting points were taken on a Reichert microscope (and uncorrected).

Protection of the aldehyde 1

A mixture of *o*-fluorobenzaldehyde **1** (13.5 g, 127 mmoles), ethylene glycol (75 ml), and *p*-toluenesulfonic acid (0.5 g) in 150 ml of benzene was refluxed in a

Dean–Stark apparatus overnight. The benzene was evaporated under vacuum, 150 ml of a saturated NaCl solution was added, and the aqueous phase extracted with ether (5 × 20 ml). The combined organic phases were dried over Na_2SO_4 and the solvent removed under vacuum. 20 g of protected aldehyde **2** (95% yield) was obtained by vacuum distillation (85–90 °C, 1.5 mmHg).

Complexation

2.42 g (10 mmoles) of $Cr(CO)_6$, 1.6 g (9.5 mmoles) of protected aldehyde **2**, 24 ml of heptane, and 36 ml of dibutyl ether (distilled over LAH) were placed under argon in a Strohmeier apparatus and the mixture was refluxed at 160 °C for 4 days. After cooling the solution was filtered through Celite. Half of the solvent was removed under vacuum and the remaining solution kept overnight at 0–5 °C to 2.6 g yields of yellow crystals of complex **3** (90% yield).

Deprotection

Complex **3** (750 mg, 2.48 mmoles) was dissolved in 15 ml of EtOH and 15 ml of concentrated hydrochloric acid was added with stirring. Stirring was maintained for 15 min at room temperature, during which the color changes from yellow to red. 50 ml of ether and 250 ml of cold water were added, and the organic layer was separated, the aquous layer extracted twice with 20 ml of ether, and the organic layers are combined and washed twice with 30 ml of a saturated solution of $NaHCO_3$. The extract was then dried over Na_2SO_4 and the solvent removed to give 544 mg of complex **4** (84%) as a dark red solid.

Addition of nitromethane

A mixture of complex **4** (130 mg, 0.5 mmoles), nitromethane (4 to 40 equiv., 0.1 to 1 ml) and 10 to 30 equiv. of KF in 10 ml of the chosen solvent (THF or ^iPrOH) was stirred at the appropriate temperature until no starting material remained, as shown by TLC. The mixture was then added to 100 ml of cold water. After extraction with ether (3 × 10 ml) the combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. The products (about 160 mg) were analysed by ^1H NMR (200 MHz) before and after purification; see Table 4.

Addition of trimethylsilyl cyanide

To a stirred solution of complex **4** (260 mg, 1 mmole) in 3 ml of CH_2Cl_2 was added ZnI_2 (50 mg) and then, dropwise, 1.1 equiv. of Me_3SiCN at room temperature. The reaction was monitored by TLC, and when no starting material remained the solvent was evaporated off under vacuum, 30 ml of diethyl ether were added and the organic phase was washed twice with 1 ml of water, then dried over Na_2SO_4 and concentrated under vacuum. The product (370 mg) was analysed before and after purification.

Complex **3**. Yellow crystals, m.p. = 105 °C. Anal. Found: C, 47.44; H, 3.08. $C_{12}H_9FO_5Cr$ calc.: C, 47.38; H, 2.98%. ^1H NMR (200 MHz, $CDCl_3$/TMS) δ ppm: 4.15 (m, 4H, O–CH_2–CH_2–O); 4.84 (tdd, 1H, H2, $J_{21} = J_{23} = 6.2$ Hz, $J_{24} = 0.8$ Hz, $J_{2F} = 2$ Hz); 5.30 (td, 1H, H4, $J_{43} = J_{4F} = 6.2$ Hz, $J_{42} = 0.8$ Hz); 5.51 (tdd, 1H, H3, $J_{32} = J_{34} = 6.2$ Hz, $J_{31} = 1.2$ Hz, $J_{3F} = 2.7$ Hz); 5.80 (ddd, 1H, H1, $J_{12} = 6.2$ Hz, $J_{13} = 1.2$ Hz, $J_{1F} = 3.9$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$/TMS) δ ppm: 228.2 (C≡O); 145.8 (d, $^1J(CF) = 267$ Hz, C5); 97.8 (O–CH–O); 94 (d, $^2J(CF) = 15$ Hz,

C6); 93.1 (d, ^2J(CF) = 10 Hz, C4); 91.2, 84.6, 77.9 (C1, C2, C3); 65.8 (O–CH_2–CH_2–O).

Complex **4**. Red crystals, m.p. = 90 °C. Anal. Found: C, 46.33; H, 2.1. $C_{10}H_5FO_4Cr$ calc.: C, 46.17; H, 1.94%. ^{1}H, ^{13}C and ^{19}F NMR: see above Table 1–3.

Complex **5**. Mixture of diastereomers. ^{1}H NMR (200 MHz, $CDCl_3$/TMS): I/II = 75/25. δ ppm: 4.6 (2H, AB part of an ABX, I + II); 4.85 (td, 1H, H2 dia II(minor); 4.95 (td, 1H, H2 dia I (major); 5.33 (t, 1H, H4 dia II); 5.37 (t, 1H, H4 dia I); 5.5 (broad, 2H, H3 and X part of the ABX, dia I + II); 5.85 (t, 1H, H1, dia I); 5.96 (t, 1H, H1, dia II).

Complex **6**. Yellow solid, m.p. 94–95 °C. R_f = 0.75 (Ethyl ether/hexane, 1/1). ^{1}H NMR (200 MHz, $CDCl_3$/TMS) only one diastereomer: δ ppm: 0.4 (S, 9H, $SiMe_3$); 4.9 (tdd, 1H, H2, $J_{21} = J_{23}$ = 6 Hz, J_{24} = 0.8 Hz, J_{2F} = 2 Hz); 5.33 (td, 1H, H4, J_{42} = 0.8 Hz, $J_{43} = J_{4F}$ = 6 Hz); 5.4 (S, 1H, CH(CN)OTMS); 5.6 (tdd, 1H, H3, $J_{34} = J_{32}$ = 6 Hz, J_{31} = 1.5 Hz, J_{3F} = 2.5 Hz); 5.9 (ddd, 1H, H1, J_{12} = 6 Hz, J_{13} = 1.5 Hz, J_{1F} = 4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$/TMS) δ ppm: 230 (C≡O); 145.7 (d, ^1J(CF) = 266 Hz, C5); 118.1 (C≡N); 94.2 (d, ^2J(CF) = 15 Hz, C6); 94.0 (d, ^2J(CF) = 10 Hz, C4); 91.2, 85.2, 77.4 (C1, C2, C3); 57.3 (*C*H(CN)OTMS); 0.1 (Me).

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