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Synthesis of *N*-Cbz-fluoropyruvaldehyde *N,S*-ketals: construction of highly stereoselective and high yielding synthetic reactions using multivariate modelling and design

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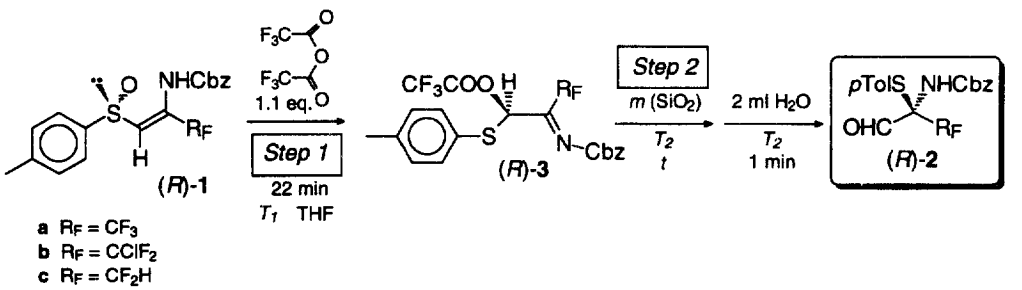
Abstract: The synthesis of (*R*)-fluoropyruvaldehyde-*N,S*-ketals *via* a tandem self-immolative Pummerer-type rearrangement of enantiopure (*R*)-α-fluoroalkyl-β-sulfinylenamines has been studied using statistical experimental design and multivariate modelling. By this study a procedure has been established which simultaneously gives excellent enantioselectivity and synthetically useful yields. The improvement of the ee of the trifluoro derivative was from 69% to 82%. The optimised procedure has been scaled up (10 fold) and extended to the corresponding difluoro and chlorodifluoro derivatives, with similarly good results. The chemometric analysis, along with a crossover experiment, strongly supports the hypothesis of a strictly intramolecular process, according to the previously proposed mechanism. © 1997 Published by Elsevier Science Ltd

We have recently reported a stereospecific synthesis of chiral non-racemic fluoropyruvaldehyde-*N,S*-ketals (*R*)-**2**, through the imine intermediates (*R*)-**3**, by a self-immolative Pummerer-type rearrangement of enantiopure α-fluoroalkyl-β-sulfinylenamines (*R*)-**1** (Scheme 1).[1] Fluoropyruvaldehyde-*N,S*-ketals (*R*)-**2** represent a new class of chiral non-racemic electrophiles, which can be successfully used for the synthesis of biologically interesting organofluoro compounds.[2]



Scheme 1.

For this reason we wanted to improve our existing procedure for preparing the compounds (*R*)-**2**, in particular with respect to the enantioselectivity. Before this study, the best results we were able to obtain for the trifluoro derivative (*R*)-**2a** were 69% ee and 57% yield by using silica gel as promoter of *step 2*, and 67% ee and 85% yield with 5% aqueous $NaHCO_3$.[1b] In order to optimise the performance of the title reaction, we carried out a large number of experiments in a "traditional fashion", namely by performing a series of independent experiments in which a single experimental

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factor was changed within a wide range of values (for example the temperature from rt to −78°C). Disappointingly, the resulting data proved to be difficult to analyse and rationalise, and allowed neither a reliable determination of which experimental factors had an important influence on the reaction, nor the identification of the best conditions for improving the yield and the enantioselectivity. Hence, in order to fulfil the requirement of optimising both yield and enantioselectivity simultaneously, a screening and optimisation study based on statistical experimental design was performed.[3] The method of fractional factorials[3–5] and multivariate modelling/regression[6,7] was used. A statistical experimental design was constructed and applied to the title reaction, using THF as solvent and silica gel for promoting *step 2*, since we considered these conditions to be the most promising, in particular for achieving a high enantioselectivity.

Methods and results

The methodology of statistical experimental design and multivariate regression is well described in the literature,[3–7] and we do not discuss any details of the underlying principle here. Anyway, the basic principle of statistically designed experimental plans is to span the variation of the different experimental variables in such a way that all possible information can be extracted from a pre-defined minimised set of experiments. The "information extraction" from this set of experiments (which constitute the experimental design) is performed by using a multivariate regression method, that is a simultaneous correlation of the single experimental variables and of the two-variable interactions with one or more responses, in this case the yield and the enantiomeric excess.

The experimental design for the title reaction was constructed in order to: (i) determine the importance of the different experimental variables with respect to the yield and (ii) with respect to the stereoselectivity of the reaction (the ee); (iii) determine the experimental settings of the variables which simultaneously give maximum yield with a maximised enantioselectivity.

For the synthetic reaction of *N*-Cbz-trifluoropyruvaldehyde *N,S*-ketal (*R*)-**2a** (Scheme 1), an experimental design for five experimental variables was necessary. A fractional factorial design for five experimental variables at two levels (2^{5-1} and c=3 centre experiments) was thus constructed and performed. This kind of design gives one the possibility to calculate the entire main effects (the regression coefficients for each of the single experimental variables) and all of the two-variable interactions, that are the expression of a synergism or antagonism between the experimental variables. For all of the experiments that were carried out, two responses were measured, the yield (y) and the enantiomeric excess (ee) in term of [α].[8] The experimental design, the selected experimental levels and the corresponding measured responses are given in Table 1, from which the two multivariate models, Eqs 1 and 2 were developed.

Equation 1 gives the relation between the response y (the yield), the experimental variables x_1, x_2,..., x_5 and the two-variable interactions $x_1 \times x_2$, $x_1 \times x_3$,..., $x_4 \times x_5$, whereas Eq. 2 gives the relation between the response [α], the experimental variables x_1, x_2,..., x_5, and the two-variable interactions $x_1 \times x_2$, $x_1 \times x_3$,..., $x_4 \times x_5$.

$$y = \beta_0 + \sum_{k=1}^{K} \beta_k x_k + \sum_{k<1}^{K} \beta_{kl} x_k x_l \tag{1}$$

$$[\alpha] = \gamma_0 + \sum_{k=1}^{K} \gamma_k x_k + \sum_{k<1}^{K} \gamma_{kl} x_k x_l \tag{2}$$

The model parameters, namely the regression coefficients (the βs and γs of Eqs 1 and 2, respectively) were estimated by using multiple linear regression. The estimated regression coefficients for the models are plotted in Figure 1. This plot shows that the different experimental variables and their two-variable interactions have different importance in the two models.

Table 1. Experimental design with corresponding responses: *yield* and [α][a]

	Experimental variables					Responses	
	C [M]	T_1 [°C]	m [mg]	t [min]	T_2 [°C]	Yield (y)	Enantio selectivity
#	x_1	x_2	x_3	x_4	x_5	% (mg)	[α] (c, $CHCl_3$)
1	−1	−1	−1	−1	+1	64.1 (25)	131.1 (0.726)
2	+1	−1	−1	−1	−1	52.2 (20)	112.2 (0.624)
3	−1	+1	−1	−1	−1	58.9 (23)	131.5 (0.513)
4	+1	+1	−1	−1	+1	56.4 (22)	112.2 (0.676)
5	−1	−1	+1	−1	−1	64.1 (25)	128.6 (0.618)
6	+1	−1	+1	−1	+1	58.9 (23)	110.8 (0.628)
7	−1	+1	+1	−1	+1	64.1 (25)	141.8 (0.719)
8	+1	+1	+1	−1	−1	64.1 (25)	104.2 (0.358)
9	−1	−1	−1	+1	−1	53.8 (21)	118.1 (0.696)
10	+1	−1	−1	+1	+1	69.2 (27)	77.8 (0.857)
11	−1	+1	−1	+1	+1	61.5 (24)	127.3 (0.612)
12	+1	+1	−1	+1	−1	64.1 (25)	115.4 (0.868)
13	−1	−1	+1	+1	+1	58.3 (23)	139.6 (0.810)
14	+1	−1	+1	+1	−1	53.8 (21)	117.4 (0.945)
15	−1	+1	+1	+1	−1	53.8 (21)	142.1 (0.633)
16	+1	+1	+1	+1	+1	53.8 (21)	119.8 (0.901)
17	0	0	0	0	0	58.9 (23)	128.7 (0.729)
18	0	0	0	0	0	53.8 (21)	126.2 (0.804)
19	0	0	0	0	0	53.8 (21)	139.6 (0.627)

Experimental variables: x_k (definition levels) [−1, 0, +1]; C (the concentration of 0.1 mmol of the substrate *(R)*-**1a** in tetrahydrofuran) [0.02 M, 0.11 M, 0.20 M]; T_1 (the reaction temperature of *step 1*) [0 °C, 10 °C, 20 °C]; m (the amount of SiO_2) [20 mg, 50 mg, 80 mg]; t (the reaction time of *step 2*) [1 min., 10 min., 15 min.]; T_2 (the reaction temperature of *step 2*) [0 °C, 10 °C, 20 °C]. The experimental design was constructed using standard order for the variables x_1–x_4. For the variables x_5 the generator $x_5 = x_1 \times x_2 \times x_3 \times x_4$ was used. [a] $[\alpha]^{20}_D$ values are positive (+).

In order to determine the significant model parameters of the two models the cumulative normal probability (CND) plots[9] in Figure 1 (**b**) and (**d**) were used. From the CND plots one can conclude that the coefficients β_5 (the reaction temperature of *step 2*), β_{14} (the substrate *(R)*-**1a** concentration × the reaction time of *step 2*), β_{25} (the reaction temperature of *step 1* × reaction temperature of *step 2*), β_{34} (the amount of SiO_2 × the reaction time of *step 1*), and β_{35} (the amount of SiO_2 × the reaction temperature of *step 2*) have significant influence on the response y (the yield), and that the coefficients γ_1 (concentration of *(R)*-**1a**), γ_2 (reaction temperature of *step 1*), γ_3 (amount of SiO_2), γ_{34} (amount of SiO_2 × reaction time), and γ_{35} (amount of SiO_2 × reaction temperature of *step 2*) have significant influence on the response [α]. The final models for y and [α] are given in Eqs 3 and 4, respectively:

$$y = 58.821 + 1.344x_5 + 2.069(x_1 \times x_4) - 1.981(x_2 \times x_5) - 3.031(x_3 \times x_4) - 1.431(x_3 \times x_5) \quad (3)$$

$$[\alpha] = 122.337 - 11.894x_1 + 3.669x_2 + 4.919x_3 - 3.006(x_1 \times x_5) + 5.119(x_3 \times x_4) + 3.031(x_3 \times x_5) - 2.994(x_4 \times x_5) \quad (4)$$

Interpretation of the models and conditions for the optimised procedure

The models in Eqs 3 and 4 were used to represent graphically the contour projections of the response surfaces for the yield (y) and the enantioselectivity given by [α]. Then, the contour projections given in Figs 2 and 3 were used to identify the conditions for optimising simultaneously yield (y) and enantioselectivity [α]. From their analysis one can conclude that it is beneficial to: (i) perform the reaction at a short reaction time t with a simultaneously large value of the fraction $m(SiO_2)/m$(substrate *(R)*-**1a**); (ii) perform the reaction at 20°C or higher in *step 2*, in order to improve the yield; (iii)

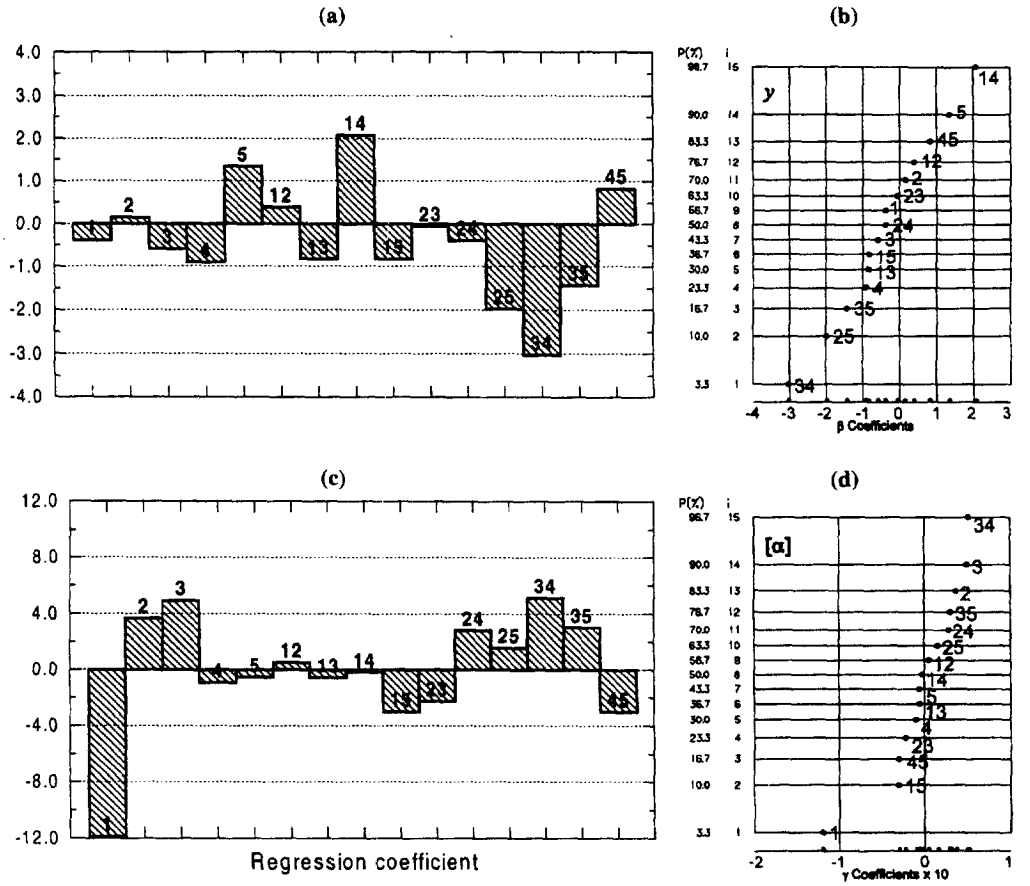


Figure 1. (a) The regression coefficient spectrum for the model which describes the yield (y) of the reaction. (b) The cumulative normal probability plot for the regression coefficients for the model which describes y (the yield). (c) The regression coefficient spectrum for the model which describes the enantiomeric excess (in terms of [α]) for the reaction. (d) The cumulative normal probability plot for the regression coefficients for the model describing [α] (the enantiomeric excess). The bars of Figure 1a and Figure 1c show the "weight" (the regression coefficients) for the experimental variables x_1–x_5 and the two-variables interactions $x_1 \times x_2$, $x_1 \times x_3$,. . ., $x_4 \times x_5$.

Key: x_1=concentration of the substrate (*R*)-**1a**; x_2=temperature of *step 1*; x_3=amount of SiO_2; x_4=reaction time of *step 2*; x_5=temperature of *step 2*.

perform the reaction at 0°C or higher in *step 1* and, most important, (iv) carry out the reaction with a low concentration of the substrate (*R*)-**1a**, in order to obtain a high degree of enantioselectivity.

The graphical presentation of the contour projections given in Figs 2 and 3 was subsequently used to predict the conditions for the optimisation experiments listed in Table 2, that gives the experimental conditions with their corresponding measured and predicted responses. Even if the actual experimental measured values deviate somewhat from the predicted ones, the obtained models (Eqs 3 and 4) show useful predictive ability, giving predictions in the correct "direction" in the experimental domain, improving significantly the synthetic procedure, especially regarding the enantioselectivity. The reason for the observed deviations between the predicted and the measured values is most probably that the actual optimal conditions, both with respect to the improvement of the yield as well as the ee, are not found within the experimental domain, defined in Table 1, but far outside. Such extrapolation may be subject to large deviations with respect to the actual values since the model did not contain any information regarding this area of the experimental space.

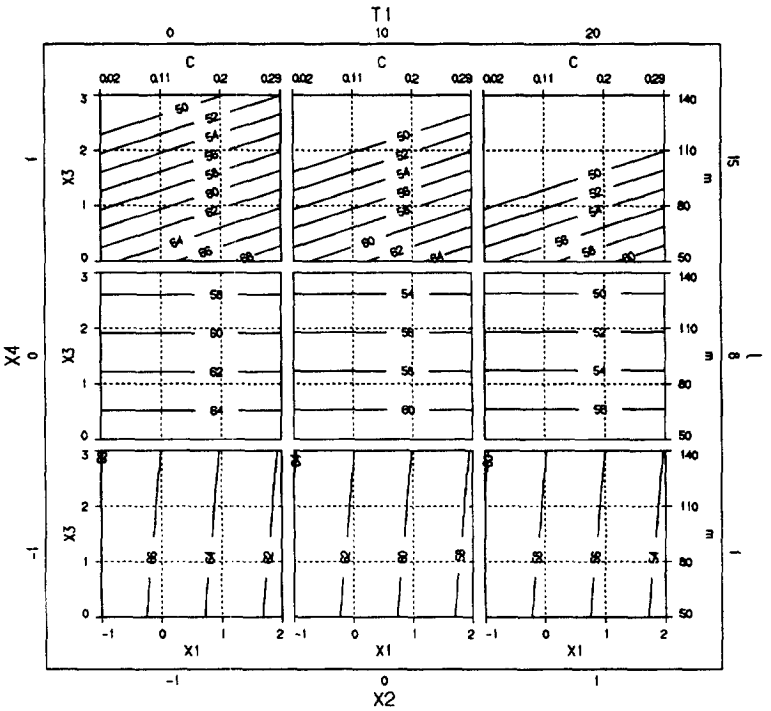


Figure 2. Contour projections of the response surfaces showing the yield. The plots show the variations of the response *y* (the yield) when four experimental variables are varied. To read the plot, the large frame shows the variation in the reaction temperature for *step 1* (T_1) and the reaction time *t*. In this frame, nine subplots showing the contour projections of the response surface when the substrate concentration in THF (*C*) and the amount of SiO_2 (*m*) are varied. The settings for variable x_5 (that is the reaction temperature of *step 2*, T_2) was set to x_5=+2 (T_2=30°C). As an example, the variation in response for the settings x_2=−1 (T_1=0°C) and x_4=+1 (*t*=15 min.) and the varying of x_1 (*C*) and x_3 (*m*) is shown in the subplot in the upper left corner of the figure. Other settings are evaluated analogously. The plot actually describes a variation in five dimensions, namely four experimental variables (x_1–x_4) and one response (*y*).

The optimised procedure of entry 2 (Table 2) was tested also for other, but similar substrates, namely the chlorodifluoro (*R*)-**1b**→ (*R*)-**2b** and the difluoro derivative (*R*)-**1c**→ (*R*)-**2c** (Scheme 1). The results were also remarkable: [α]=+183.1 (c 0.74, $CHCl_3$), ee 79%, *y*=68% for (*R*)-**2b**, and [α]=+326.6 (c 1.08, $CHCl_3$), ee 72%, *y*=83.3% for (*R*)-**2c**. Next, the optimised procedure was scaled up to 1.0 mmol of (*R*)-**1a** and (*R*)-**1c**, providing almost identical results.

Discussion

We have recently shown that *cis* geometry of the β-sulfinylenamines (*R*)-**1a–c** (Scheme 1) is strictly necessary for achieving high enantioselectivity in the rearrangement,[1b] because the NHCbz group prevents the TFAA-promoted racemization of the sulfinyl stereocenter, occurring at a fast rate on *trans* β-sulfinylenamines, which produce a nearly racemic product, and on *N,N*-disubstituted β-sulfinylenamines, which do not give rise to the rearrangement. NMR experiments showed that the corresponding imines (*R*)-**3a–c** (Scheme 1) are moderately stable reaction intermediates, produced in the Pummerer rearrangement (*step 1*), which can be transformed in the final fluoropyruvaldehyde-*N,S*-ketals (*R*)-**2a–c** *via* 1,2-migration of the *p*-tolylthio group, triggered by cleavage of the trifluoroacetyl group (*step 2*). On these bases the mechanism depicted in Scheme 2 was proposed.

In *step 1* the trifluoroacetoxysulfonium salt **I**, formed by action of TFAA on (*R*)-**1**, should produce the cyclic four-membered chiral sulfurane **II**, which stereoselectively affords the intermediate imine (*R*)-**3** through migration of the trifluoroacetoxy group from the sulphur to the α-carbon. In *step 2*,

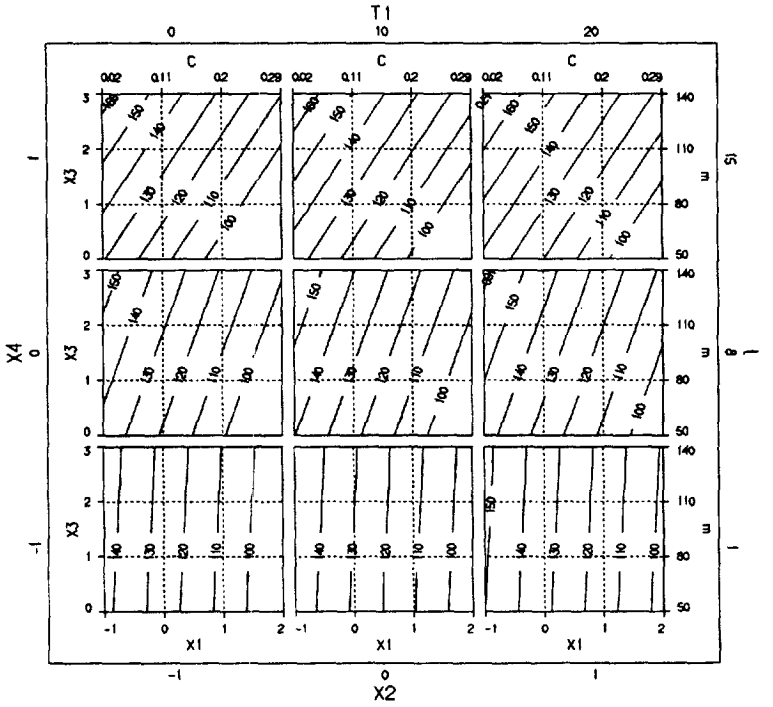
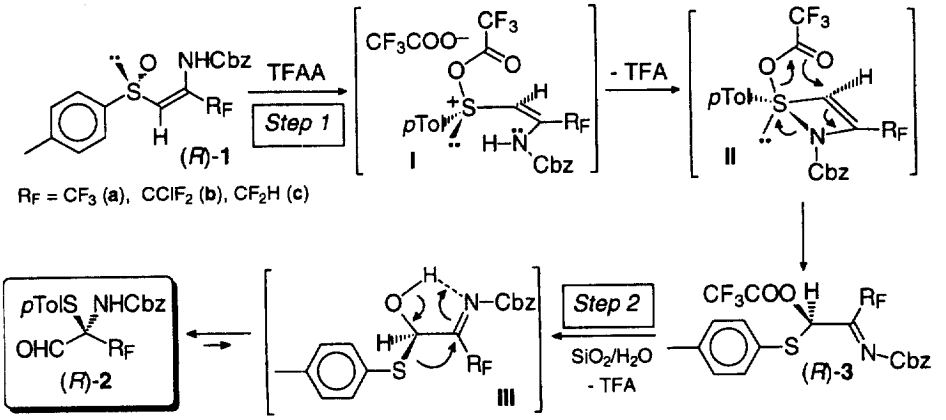


Figure 3. Contour projections of the response surfaces showing the ee in terms of [α]. The plots show the variations of the response [α] when four experimental variables are varied. To read the plot, the large frame shows the variation in the reaction temperature for *step 1* (T_1) and the reaction time t. In this frame, nine subplots showing the contour projections of the response surface when the substrate concentration in THF (C) and the amount of SiO_2 (m) are varied. The settings for variable x_5 (that is the reaction temperature of *step 2*, T_2) was set to x_5=+2 (T_2=30°C). As an example, the variation in response for the settings x_2=−1 (T_1=0°C) and x_4=+1 (t=15 min.) and the varying of x_1 (C) and x_3 (m) is shown in the subplot in the upper left corner of the figure. Other settings are evaluated analogously. The plot actually describes variation in five dimensions, namely four experimental variables (x_1–x_4) and one response ([α]).

Table 2. Conditions and results for optimisation experiments when using predicted experimental conditions

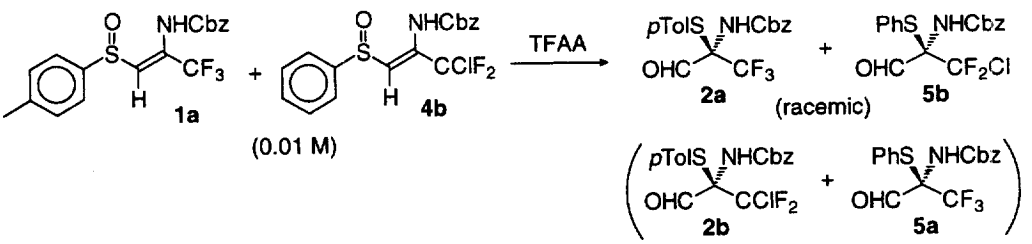
	Experimental variables					Responses Measured		Predicted	
	C [mol ml^{-1}]	T_1 [°C]	m [mg]	t [min.]	T_2 [°C]	Yield		Yield (y)	
#	x_1	x_2	x_3	x_4	x_5	% (mg)	[α] (c, $CHCl_3$)	%	[α]
1	0.0100	20	110	1	30	59.0 (23)	+ 161.4 (0.45)	60	+ 164
2	0.0100	20	125	1	30	61.5 (24)	+ 166.1 (0.61)	60	+ 167
3	0.0140	20	100	15	20	56.4 (22)	+ 152.0 (0.49)	49	+ 161
4	0.0060	20	200	1	30	46.1 (18)	+ 167.5 (0.42)	61	+ 182
5	0.0060	20	200	1	40	48.7 (19)	+ 167.3 (0.35)	53	+ 204
6	0.0125	20	250	1	30	53.8 (21)	+ 156.7 (0.62)	61	+ 190
7	0.0100	20	140	1	30	61.5 (24)	+ 152.2 (0.60)	60	+ 169
8	0.0100	0	140	1	30	64.1 (25)	+ 153.7 (0.81)	68	+ 162



Scheme 2.

the wet SiO_2 cleaves the trifluoroacetyl group of (*R*)-**3**, producing the transient α-hydroxy-imine **III**, which undergoes a suprafacial 1,2-migration of the *p*-tolylthio group through the five membered cyclic conformation having a hydrogen bond between the hydroxy and the imino functions.

The multivariate regression analysis evidences that the impact of the concentration of (*R*)-**1a** (x_1) on the enantioselectivity of the process is impressive and much more important than any other variable. This strongly favourable "dilution effect" supports the hypothesis that both *step 1* (the Pummerer rearrangement) and *step 2* (the 1,2-migration of the *p*-tolylthio group) are strictly intramolecular processes, according to the mechanism proposed in Scheme 2. In order to clarify definitively this point we carried out a "crossover" experiment (Scheme 3). An artificial 1:1 mixture of trifluoro (*p*-tolylsulfinyl)enamine **1a** and chlorodifluoro β-(phenylsulfinyl)enamine **4b** was submitted to reaction, following the conditions of entry 2 in Table 2 (0.01 M solution of **1a**+**4b**). The raw reaction mixture was analysed by 400 MHz NMR spectroscopy, allowing us to detect only the signals of the two fluoropyruvaldehydes **2a** and **5b**, which are produced *via* intramolecular migration of the corresponding arylthio residues. The absence of the "crossover" products **2b** and **5a** was confirmed by adding to the reaction mixture an equimolar amount of **2b**, whose signals were easily distinguished from those of **2a** and **5b**.



Scheme 3.

Interestingly, both the yield and the enantioselectivity of the tandem process are strongly affected by interaction variables, which reflect an antagonism or synergism between two experimental variables. From Figure 1a and Figure 1c it can be seen that the most important one is the interaction between "the amount of SiO_2 × the reaction time of *step 2*" (represented by the regression coefficient β_{34}). Probably the cleavage of the CF_3CO moiety of the intermediate imines (*R*)-**3** (Scheme 2), which triggers the 1,2-migration of the arylthio group, occurs on the surface of the wet SiO_2, which also catalyses the migration. Therefore, it can be argued that the amount of SiO_2 must be high enough to allow a fast

cleavage of the CF_3CO moiety and to avoid undesired side-reactions. On the other hand SiO_2 was also shown to catalyse the racemization and the partial decomposition of the fluoropyruvaldehydes (*R*)-**2**,[1b] probably through the equilibrium with the intermediate hydroxy-imine **III** (Scheme 2). For this reason, a prolonged time of exposure of the final products (*R*)-**2** to SiO_2 should be responsible for the lowering of the ee as well as of the yield.

In summary, the present study has shown that it is possible to improve the stereoselectivity of a synthetic procedure by controlling accurately the experimental variables, using statistical experimental design and multivariate modelling. Through the training set of experiments (Table 1) the final models, Eqs 3 and 4 were developed and used successfully to predict the conditions for a simultaneously high yielding and highly stereoselective synthetic procedure. The improvement of the enantiomeric excess of the product (*R*)-**2a** was from 69% ee ([α]=+141.8) to 82% ee ([α]=+167.5), while the yield was kept at an acceptable level (61.5%). Even if the prediction shows some deviation from the subsequently measured values, the two developed models, Eqs 3 and 4, show a good accordance with the experimental results. The multivariate regression analysis provided further evidence regarding the mechanism of the title reaction, which supports the previously proposed intramolecular tandem outcome.

Experimental

General procedure

^1H, ^{19}F and ^{13}C nuclear magnetic resonance samples were prepared as dilute solutions in $CDCl_3$. Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Me_4Si was used as internal standard (δ_H and δ_C=0.00) for ^1H and ^{13}C nuclei, while C_6F_6 was used as external standard (δ_F=−162.90) for ^{19}F nuclei. Enantiomeric excesses have been determined by ^1H and ^{19}F NMR analysis of pure samples of fluoropyruvaldehydes (*R*)-**2**, by using the chiral shift reagent (+)-[Eu(hfc)$_3$] in $CDCl_3$ solution. Anhydrous THF was distilled from sodium and benzophenone. In all other cases commercially available reagent-grade solvents were employed without purification. Reactions performed in dry solvents were carried out under a nitrogen atmosphere. Melting points are uncorrected and were obtained on a capillary apparatus. Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F_{254} of 0.25 mm thickness were used. Merck silica gel 60 (230–400 ASTM mesh) was employed as a reagent (*step 2*) and for flash column chromatography (FC). Combustion microanalyses were performed by Redox SNC, Cologno M. (Milano). Synthesis of compounds (*R*)-**1a–c**, has been already described.[10]

Computing

In-house developed software routines written in Zortech C/C++ V3.0 were used for plotting the cumulative normal probability graphs, and for representing the estimated models as contour projections of the response surfaces. MATLAB was used to estimate the regression coefficients by using the MLR method. All computations were performed on a IBM ThinkPad 755Cs microcomputer under PC DOS ver. 7.00 Rev. 0 and Windows 3.11 or on a IBM ThinkPad 760 ED microcomputer under Windows 95. 4.00.950a.

Synthetic procedure

In the present procedure, the parameters C, T_1, T_2, m, and t are used to indicate: the concentration of 0.1 mmol of (*R*)-**2a** in dry THF, the reaction temperatures of *step 1* and *step 2*, the quantity of SiO_2 and the reaction time of *step 2*, respectively. These experimental variables have been varied, and their numerical values are given in Tables 1 and 2.

A C molar solution of compound (*R*)-**1a** (39 mg, 0.1 mmol) in dry THF at temperature T_1 °C was treated with 1.1 equiv. of neat TFAA (added in one portion *via* syringe). Two minutes after the addition of TFAA the reaction temperature was changed to T_2 °C with a cryogenic apparatus. After a reaction time of 24 min (time after the addition of TFAA), m mg of SiO_2 were added in one portion. The

reaction mixture was then left under stirring for *t* min. at the temperature T_2°C. Water (2.0 ml) was then added and vigorously stirred for 1 min (still at temperature T_2°C). The stirring was stopped and the phases were separated, and the aqueous layers were extracted with ethyl acetate. The collected organic phases were dried on Na_2SO_4, filtered and the solvent removed at reduced pressure. The product was purified by flash chromatography, using a glass column of 1 cm diameter filled with 12 cm of SiO_2. The eluent was an *n*-hexane/ethyl acetate mixture (85:15).

Trifluoropyruvaldehyde N,S-*ketal (*R*)-**2a**

Yellowish oil; $[\alpha]_D^{20}$ +167.5 (c 0.42, $CHCl_3$), ee 82%; R_f 0.45 (85:15 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 9.37 (1H, q, J_{FH}=1.7 Hz), 7.43–7.32 (5H, m), 7.20 (2H, d, *J*=8 Hz), 7.01 (2H, d, *J*=8 Hz), 5.53 (1H, br s), 5.20 (1H, d, 2H, *J*=12 Hz), 5.07 (1H, d, 2H, *J*=12 Hz), 2.32 (3H, s); ^{19}F NMR ($CDCl_3$) δ −70.45 (q, J_{HF}=1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 183.0 (q, J_{CF}=1.8 Hz), 153.3, 141.7, 138.1, 135.3, 130.3, 128.8, 128.7, 122.7 (q, J_{CF}=287 Hz), 120.7, 72.8 (q, J_{CF}=28.9 Hz), 67.9, 21.4; MS (EI, 70 eV) m/Z (%) 383 (M^+, 8), 124 (35), 91 (100). Anal. Calcd for $C_{18}H_{16}NO_3F_3S$: C, 56.39; H, 4.21; N, 3.65. Found: C, 56.49; H, 4.30; N, 3.50.

Chlorodifluoropyruvaldehyde N,S-*ketal (*R*)-**2b**

(*R*)-**2b** was obtained in 68% yield, following the general procedure, according to the conditions of entry 2, Table 2; $[\alpha]_D^{20}$ +183.1 (c 0.74, $CHCl_3$), ee 79%; solid; R_f 0.46 (80:20 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 9.40 (1H, s), 7.44–7.32 (5H, m), 7.22 (2H, d, *J*=8 Hz), 7.01 (2H, d, *J*=8 Hz), 5.65 (1H, br s), 5.22 (1H, d, *J*=12 Hz), 5.08 (1H, d, *J*=12 Hz), 2.32 (3H, s); ^{19}F NMR ($CDCl_3$) δ −54.6 (1F, d, J_{FF}=168 Hz), −58.2 (1F, d, J_{FF}=168 Hz); ^{13}C NMR ($CDCl_3$) δ 183.1, 153.3, 141.6, 138.2, 135.5, 130.3, 128.8, 128.7, 128.6, 127.9, (dd, J_{CF}=299 and 306 Hz), 121.7, 68.1, 21.3; MS (EI, 70 eV) m/Z (%) 399 (M^+, 4), 371 (4), 262 (12), 244 (18), 124 (100), 91 (100); FTIR (cm^{-1}) 3372 (br), 1721, 1494, 1245. Anal. Calcd for $C_{18}H_{16}NO_3F_2ClS$: C, 54.07; H, 4.03; N, 3.50. Found: C, 54.15; H, 4.05; N, 3.47.

Difluoropyruvaldehyde N,S-*ketal (*R*)-**2c**

(*R*)-**2c** was obtained in 83.3% yield, following the general procedure, according to the conditions of entry 2, Table 2; $[\alpha]_D^{20}$ +326.6 (c 1.08, $CHCl_3$), ee 72%; white solid, the racemate could be crystallized from diisopropyl ether: mp 81–82°C; R_f 0.67 (80:20 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 9.49 (1H, s), 7.48–7.32 (5H, m), 7.07 (2H, d, *J*=8 Hz), 6.95 (2H, d, *J*=8 Hz), 6.90 (1H, t, J_{HF}=55 Hz), 5.64 (1H, br s), 5.22 (1H, d, *J*=12 Hz), 4.98 (1H, d, *J*=12 Hz), 2.30 (3H, s); ^{19}F NMR ($CDCl_3$) δ −132.6 (1F, dd, J_{HF}=55 Hz and J_{FF}=290 Hz), −122.1 (1F, dd, J_{HF}=56 Hz and J_{FF}=290 Hz); ^{13}C NMR ($CDCl_3$) δ 183.2 (t, J_{CF}=4 Hz), 153.7, 141.3, 137.9, 135.5, 130.2, 128.9, 121.2, 113.4 (dd, J_{CF}=247.6 Hz and 252.4 Hz), 73.2 (t, J_{CF}=23 Hz), 67.6, 21.4; MS (EI, 70 eV) m/Z (%) 365 (M^+, 4), 124 (35), 91 (100); FTIR (cm^{-1}) 3372 (br), 1721 (br), 1494, 1245. Anal. Calcd for $C_{18}H_{17}NO_3F_2S$: C, 59.17; H, 4.69; N, 3.83. Found: C, 59.48; H, 4.85; N, 3.58.

Synthesis of 3-chloro-3,3-difluoro-2-oxopropyl phenyl sulfoxide

A solution of phenyl methyl sulfoxide (7.13 mmol) in dry THF (15 ml) was added dropwise to a stirred solution of LDA (8.6 mmol), prepared from diisopropylamine (1.21 ml) and a 2.5 M solution of butyllithium in hexane (3.44 ml), maintaining the temperature at −75°C, and under nitrogen. After five minutes a solution of methyl chlorodifluoro acetate (8.6 mmol) in THF (25 ml) was added at the same temperature and stirring was continued for 10 min. The reaction was then quenched with a saturated aqueous solution of ammonium chloride (35 ml) at −75°C. The pH was neutralized with 1 N hydrochloric acid, the layers were separated and the aqueous phase was extracted with ethyl acetate (3×50 ml). The collected organic layers were dried with anhydrous sodium sulfate. Purification of the residue by crystallization from ethyl acetate gave 1.6 g (83% yield) of pure product, obtained as 2,2-*gem*-diol. R_f (1:1 *n*-hexane:ethyl acetate) 0.52; mp (ethyl acetate) 107–110°C; ^{1}H NMR (acetone d_6) δ 7.86–7.81 (m, 2H), 7.7–7.6 (m, 3H), 6.98 (d, *J*=2.45 Hz, 1H), 6.97 (br s, 1H), 3.44 (d, *J*=13.2 Hz,

1H), 3.12 (dd, J=12.94 and 1.2 Hz, 1H); ^{19}F NMR (acetone d_6) δ −66.1 (d, J=162.8 Hz, 1F), −67.4 (d, J=162.8 Hz, 1F); ^{13}C NMR (acetone d_6) δ 144.8, 133.2, 131.1, 129.8 (t, J=300.4 Hz), 125.6, 97.6 (t, J=28.6 Hz), 59.5.

Synthesis of N-*Cbz* α-*chlorodifluoro-*β-*phenylsulfinyl enamine* ***4b***

To a stirred solution of 3-chloro-3,3-difluoro-2-oxopropyl phenyl sulfoxide (200 mg, 0.74 mmol) in dry benzene (4 ml) was added solid *N*-CBz-imino-triphenylphosphorane (for the synthesis of this compound see Arnone *et al.*[10]) (334 mg, 0.81 mmol). The mixture was refluxed for 18 h and then the solvent was removed under reduced pressure. The crude was purified by flash-chromatography (*n*-hexane/ethyl acetate from 7/3 to 3/2), giving 200 mg of product **4b** (70% yield) along with 20 mg (10%) of unreacted starting material. Mp 107–109°C (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.87–7.83 (m, 2H), 7.54–7.51 (m, 3H), 7.39–7.34 (m, 5H), 7.03 (br s, 1H), 6.56 (s, 1H), 5.28 (d, J=12.2 Hz, 1H), 5.23 (d, J=12.2 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ −59.44 (d, J=166.7 Hz, 1F), −60.35 (d, J=166.7 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ 153.9, 142.2, 135.0, 133.6 (t, J=29.6 Hz), 131.6, 129.7, 129.5, 128.7, 128.3, 125.2, 122.3 (t, J=292.5 Hz), 68.7.

Chlorodifluoropyruvaldehyde N,S *ketal* ***5b***

The general procedure of the Pummerer-type rearrangement was applied. The pure racemic product was obtained by flash chromatography (eluent mixture *n*-hexane/ethyl acetate from 87/13 to 4/1) on a short silica gel column in 80% yield, as a yellowish oil, from the corresponding enamine **4b**. ^{1}H NMR ($CDCl_3$) δ 9.39 (s, 1H), 7.41–7.31 (m, 8H), 7.22–7.16 (m, 2H), 5.66 (br s, 1H), 5.18 (d, J=12.05 Hz, 1H), 5.06 (d, J=12.05 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ −54.68 (d, J=167.7 Hz, 1F), −58.18 (d, J=167.7 Hz, 1F); ^{13}C NMR (acetone d_6) δ 187, 156.03, 140, 137.57, 132.33, 130.8, 130.01, 129.8, 128.87 (dd, J=302.22 and 299.45 Hz), 127.6, 78.23 (dd, J=25.88 and 22.18 Hz), 68.87.

References

1. (a) Bravo, P.; Crucianelli, M.; Fronza, G.; Zanda, M. *Synlett* **1996**, 249–251. (b) Volonterio, A.; Zanda, M.; Bravo, P.; Fronza, G.; Cavicchio, G.; Crucianelli, M. submitted for publication.
2. Volonterio, A.; Bravo, P.; Capelli, S.; Meille, S. V.; Zanda, M. *Tetrahedron Lett.* **1997**, *38*, 1847–1850.
3. Box, G. E. P.; Hunter, J. S. *Technometrics* **1961**, *3*, 311–351.
4. Box, G. E. P.; Hunter, J. S. *Technometrics* **1961**, *3*, 449–458.
5. Box, G. E. P.; Hunter, W. G.; Hunter, J. S. *Statistics for Experimenters, an Introduction to Design, Data Analysis, and Model Building*, Wiley, New York, 1978, pp. 306–351, pp. 374–418.
6. Montgomery, D. C.; Peck, E. A. *Introduction to Linear Regression Analysis.* Wiley, New York, 1982, pp. 1–504.
7. Draper, N. R.; Smith, H. *Applied Regression Analysis, 2nd Ed.* Wiley, New York, 1981, pp. 1–709.
8. Several pure samples of fluoropyruvaldehyde-*N*,*S*-ketals (*R*)-**2a–c** were submitted to polarimetric analysis at comparable concentrations and to determination of the ee by means of the chiral shift reagent (+)-[Eu(hfc)$_3$]. The results showed an almost linear correlation between the $[\alpha]_D^{20}$ and the corresponding ee values, suggesting that the latter can be reliably determined by polarimetric analysis. It can be calculated that a sample of enantiomerically pure trifluoro derivative (*R*)-**2a** should have $[\alpha]_D^{20}$ +204 (c 0.5–0.8, $CHCl_3$).
9. Daniel, C. *Technometrics* **1959**, *1*, 311–341.
10. Arnone, A.; Bravo, P.; Capelli, S.; Fronza, G.; Meille, S. V.; Zanda, M.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1996**, *61*, 3375–3387. Corrigenda: *J. Org. Chem.* **1996**, *61*, 9635.

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