

# Organic process research and development by means of statistical experimental design, multivariate modelling, and mechanistic interpretation

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It is shown how the combination of statistical experimental design, multivariate modelling and the interpretation of mechanisms of the involved reactions can be utilised for the development of selective syntheses of industrial interest and low environmental impact. New processes for vanillin, iso-vanillin and heliotropin have been developed from catechol based on this approach, in which the key point were the highly selective oxidation of mandelic acid derivatives by oxygen and  $\text{CuCl}_2$  catalysis and the regio-controlled O-methylation of protocatechualdehyde. A great improvement for the industrial production of vanillin from lignin, where a 75% increase of the relative yield was achieved, is also reported and discussed.

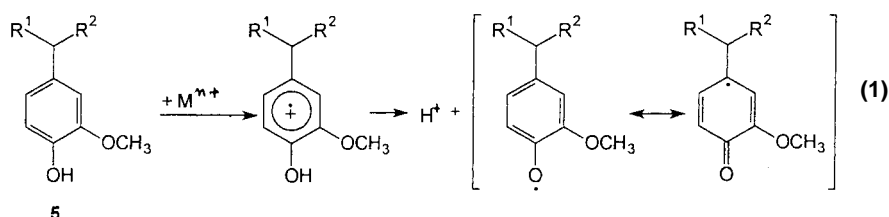
**S**tatistical experimental design [1] and multivariate modelling [2] constitute a powerful tool for the optimisation of chemical reactions. The aim of this paper is to show how the combination of the interpretation of the reaction mechanism and catalysis, statistical experimental design and multivariate modelling can contribute to the development of new industrial processes.

In particular this combination was applied to develop new processes for vanillin **1**, iso-vanillin **2**, heliotropin **3** starting from catechol **4** and the optimisation of the industrial process for the production of vanillin by oxidation of lignosulfonates [3], LS (sulphite spent liquor).

Vanillin **1** is one of the most important flavouring agents in confectionary, beverages, foods and in perfumery; it is also used as an intermediate for pharmaceutical chemicals. For long time it was exclusively produced by oxidation of LS [3, 4]; at present Borregaard (Norway) is the only company, which produces vanillin from LS. The commercial value of vanillin **1** from LS is higher compared to that obtained by synthetic method. The lignin dissolving process is performed by two main pro-

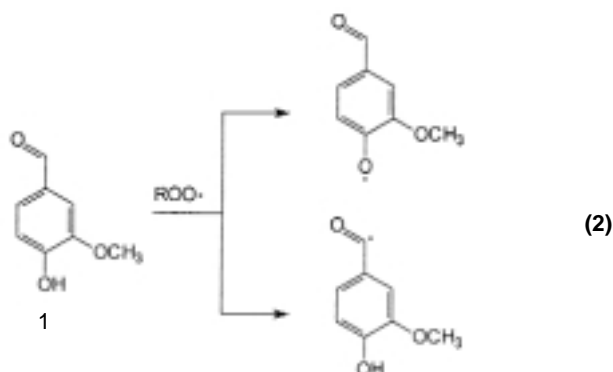
cedures: digestion for 6 hrs at 140-145 °C leads to  $\text{LS}_{750}$  and  $\text{LS}_{850}$ , while digestion at 125-130 °C for 7 hrs gives  $\text{LS}_{1200}$ , or other high viscous cellulose qualities. The qualities of LS are defined by the type of produced cellulose; an important parameter for cellulose is the viscosity and the subscript number in LS indicates the viscosity number measured for the corresponding celluloses.

Lignin is a macromolecule of complex structure [5-8] and precursors of vanillin **1** are structures of the type **5** (lignosulfonate moiety with free hydroxyl group) and **6** (lignosulfonate moiety with ether linkage), which characterise the macromolecule. Combination of basic hydrolysis and oxidation [5] contribute to the formation of vanillin **1**. It is difficult to rationalise the complex mechanism of hydrolysis-oxidation, which is carried out under drastic conditions (170-200 °C in strongly alkaline medium, 10-15 atm of air and metal salt catalysis). However it appears probable that electron-transfer processes by metal salt is involved in the oxidation, shown in Equation 1.



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A radical chain process involving peroxy radicals  $\text{ROO}^\bullet$  appears in fact unlikely considering the high reactivity of vanillin with these radicals (Equation 2).



The presence of an electron withdrawing group as CHO in vanillin **1** reduces the redox potential compared to the lignin fragment structures like **5** and **6** and makes more difficult the oxidation by an electron transfer process. Actually the formation of vanillin **1** occurs in the oxidation by peroxysulphate and nitrobenzene, which can operate by an electron transfer process or by oxygen catalysed by metal salts, such as Cu(II), Ce(IV), Co(III), which are known to act as agents of electron-transfer oxidations [3].

These mechanistic considerations have oriented our general approach in the basic oxidative degradation of lignin LS to vanillin **1**. In order to improve the yields of the current industrial process we have used statistical experimental design and multivariate modelling using multiple linear regression [1, 2, 9-12] and the partial least squares regression [11] to obtain a multivariate relation between the experimental, controllable variables and the response yield of vanillin [3].

In order to appraise the existing production process and thus obtain an overview of all of the experimental controllable variables, an Ishikawa cause-effect [12] diagram was produced and more than ten different experimental variables were assumed to have influence on the three responses, the yields of vanillin **1**, vanillic acid **7**, and acetovanillon **8**. However, several of these controllable variables concern the process equipment, that was defined outside the scope of the present process improvement and development study. Even though the vanillin process has been operated for several years, the comprehension of the different variables interactions and influences on the outcome of the process was somewhat faultiness, thus it was decided to perform a screening and first optimisation study in order to strain the important variables from the other less important ones, as well as to determine a proper domain of experimental conditions for further optimisation studies. The experimental variables such as the reaction temperature ( $x_1$ ), the reaction time ( $x_2$ ), the amount of air ( $x_3$ ), the amount of catalyst [ $\text{CuSO}_4$ ] ( $x_4$ ), the amount of base [ $\text{NaOH}$ ] ( $x_5$ ), and the amount of liginosulfonate LS ( $x_6$ ) were all expected to affect the outcome of the process, the yields of vanillin **1**, and were thus investigated by using a statistical experimental design, a  $2^{6-2}$  fractional factorial design with centre experiments (centre points). An empirical model (Equation 3),

$$y_i = \beta_0 + \sum_{k=1}^K \beta_k x_k + \sum_{k=1}^K \sum_{l=1}^K \beta_{kl} x_k x_l + \sum_{k=1}^K \sum_{l=1}^K \sum_{m=1}^K \beta_{klm} x_k x_l x_m + \varepsilon_i \quad (3)$$

including the main effects, the two-factor interactions (the interplay of two variables) and the three-factor interactions (the interplay of three variables), was derived [3]. The regression coefficients were estimated by using the method of partial least squares regression.

Evaluating this model statistically as well as using a prior knowledge concerning the hydrolysis-oxidation reaction, yielded that the experimental variables [3] "the reaction temperature" ( $x_1$ ), "the reaction time" ( $x_2$ ), "the amount of Cu(II)" ( $x_4$ ), and "the amount of NaOH" ( $x_5$ ) were determined to be the most influencing variables.

The variables determined to have significant influence in the screening design were further used in a response surface design, were "the amount of NaOH" is termed  $z_1$ , "the amount of Cu(II)" is termed  $z_2$ , "the reaction temperature" is termed  $z_3$ , and "the reaction time" is termed  $z_4$ . The experimental variables  $z_1$ - $z_3$  were used in a central composite design. For each of these experiments five samplings were performed, at 30, 60, 70, 80 and 100 min and they were all analysed on HPLC. Including the centre experiments, the experimental design becomes  $(2^3 + 2 \times 3 + 3) \times 5^1$  and gives rise to the estimation of a model such as the one shown in Equation 4.

$$y_i = \beta_0 + \sum_{k=1}^K \beta_k x_k + \sum_{k=1}^K \beta_{kk} x_k^2 + \sum_{k \neq l}^K \sum_{l=1}^K \beta_{kl} x_k x_l + \varepsilon_i \quad (4)$$

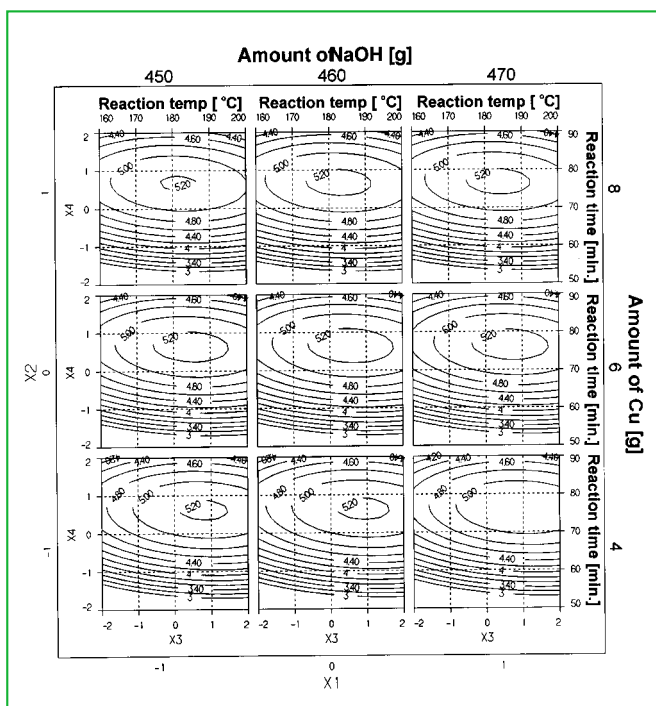


Figure 1 - Response surface projections of a model that include the main, two factor interactions and quadratic terms. The contour lines show the yield of vanillin when the four experimental variables the amount of sodium hydroxide ( $x_1$ ), the amount of Cu(II) ( $x_2$ ), the reaction temperature ( $x_3$ ), and the reaction time ( $x_4$ ) are varied. To read the plot, the large frame shows the variation in the amount of sodium hydroxide ( $x_1$ ) and the amount of Cu(II) ( $x_2$ ). In this frame nine subplot showing the contour lines of the response surface when the experimental variables the reaction temperature ( $x_3$ ) and the reaction time ( $x_4$ ) are varied

The coefficients (the  $\beta$ 's): the main effects, the two-variable cross terms, and the quadratic effects were multivariate correlated by using the partial least-squares method. Statistical analysis of the estimated coefficients of this model shows that the regression coefficients  $\beta_4$ ,  $\beta_3$ ,  $\beta_2$ ,  $\beta_{22}$ ,  $\beta_{33}$ , and  $\beta_{44}$  are the significant ones. The model is graphically represented as a response surface projection plot in Figure 1.

Three optimisation experiments were performed in the pilot plant reactors based on prediction using Figure 1, and the optimized procedure gave a vanillin yield of 5.7% against a yield of 4.1% with the current industrial procedure using lignosulfonate LS<sub>750</sub> as raw material, which correspond to a relative improvement of 37% (Figure 2). The Cu(II) catalyst

**Table 1 - Experimental design with adjacent experimental results.**  
Experiments carried out using LS<sub>750</sub>

<i>Experimental variables<sup>a</sup></i>			<i>Responses<sup>b</sup></i>						
#	<i>x</i> <sub>1</sub>	<i>x</i> <sub>2</sub>	<i>y</i>	<i>Reaction times, t (min)</i>					
				30	40	50	60	70	80
1	-1	-1		2.53	3.70	4.07	4.23	4.38	4.61
2	0	-1		2.95	3.94	4.42	4.77	4.91	4.95
3	+1	-1		3.05	3.97	4.40	4.68	4.83	4.87
4	-1	0		2.93	3.55	3.91	4.06	3.98	4.29
5	0	0		3.05	3.48	4.00	4.21	4.21	4.10
6	+1	0		3.39	3.78	4.10	4.24	4.40	4.40
7	-1	+1		2.45	3.54	3.84	4.59	4.30	4.28
8	0	+1		3.29	4.12	4.77	4.91	5.09	5.42
9	+1	+1		3.71	4.59	5.14	5.44	5.36	5.71

<sup>a</sup> Experimental variables: [-1, +1]  $x_1$  the amount of Cu(II) (2, 4, 6) g,  $x_2$  the amount of NaOH (420, 440, 460) g. 660 g of LS<sub>750</sub> were used in each experiment. <sup>b</sup> Responses measured by HPLC and related to dry substance (LS) of the reaction mixture y (Vanillin/DS)

is used in the vanillin plant as aqueous solution of CuSO<sub>4</sub>. At the end of the extraction processes after the hydrolysis-oxidation process, the catalyst is recovered as sludge of inorganic and organic products, from which Cu(II) is extracted by NH<sub>3</sub> solution and precipitated as CuO. Thus we have considered the possibility to utilise directly CuO as a catalyst in the vanillin plant and we have performed a new experimental design, shown in Table 1, with adjacent experimental results, from which a response surface model as Equation 3 was derived. This model was used to calculate the response surface projections given by Figure 3, with the experimental results of Table 2 and Figure 4. The best yield of vanillin 1 was obtained by using the conditions of entry 4 of Table 2, in which  $y_{exp}=7.2\%$  and the yield predicted by the model is exactly the same,  $y_{pred}=7.2\%$ . This result represents a

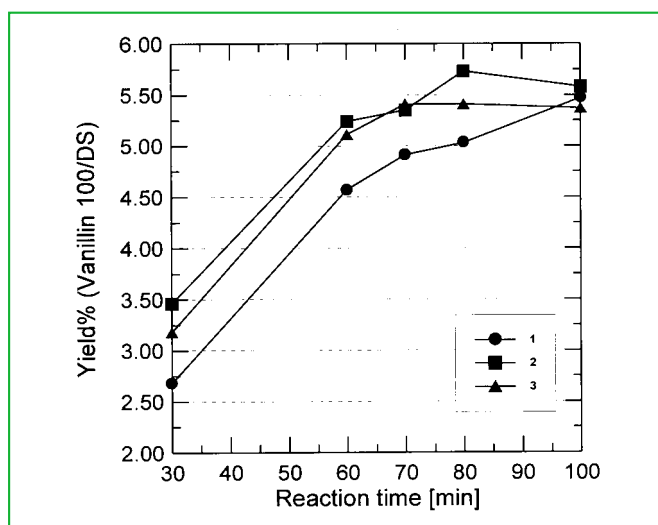


Figure 2 - The course of the optimisation reactions for LS<sub>750</sub> with conditions predicted from the model derived from the experiments in the response surface design. The conditions for the different experiments performed in the pilot plant reactors are for the three experiments: 2630 ml of an approximately 24% lignosulfonate solution (660 g LS) is diluted with 740 ml water, added 465g sodium hydroxide as 50% solution and copper as CuSO<sub>4</sub> solution of approximately 16%. The different amounts of copper were: (●) 5 g Cu, (■) 6 g Cu, and (▲) 7 g Cu. All experiments were performed at a temperature of 182-185 °C

75% relative improvement compared to the standard industrial procedure with LS<sub>750</sub> as raw material (4.1%). Thus the utilized approach has led to two important results:

- great increase of the yield in the hydrolysis-oxidation of LS to vanillin 1;
- easy recover and recycle of the Cu(II) catalyst.

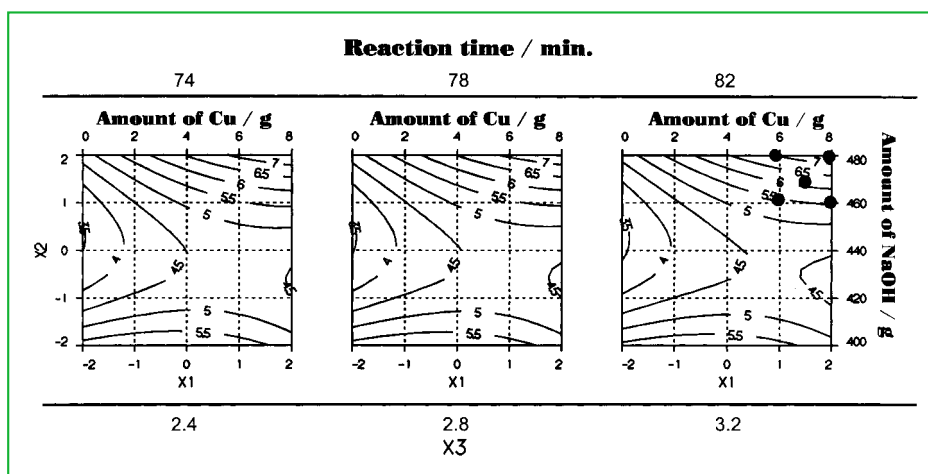


Figure 3 - The contour projections lines show the yield of vanillin when three experimental variables are varied. The contour lines show the yield of vanillin when the experimental variables the amount of Cu ( $x_1$ ), the amount of sodium hydroxide ( $x_2$ ), and the reaction time ( $x_3$ ) are varied. In the present experimental study was recovered and recycled Cu used as catalyst. The copper was charged to the reaction mixture as a "slurry" of CuO. To read the plot, the large frame shows the variation in the reaction time ( $x_3$ ). In this frame three subplot showing the contour lines of the response surface when the experimental variables the amount of Cu(II) ( $x_1$ ) and the amount of sodium hydroxide ( $x_2$ ) are varied. The five points indicated in the subplot given at time 82 min were selected to be carried out as new optimising experiments

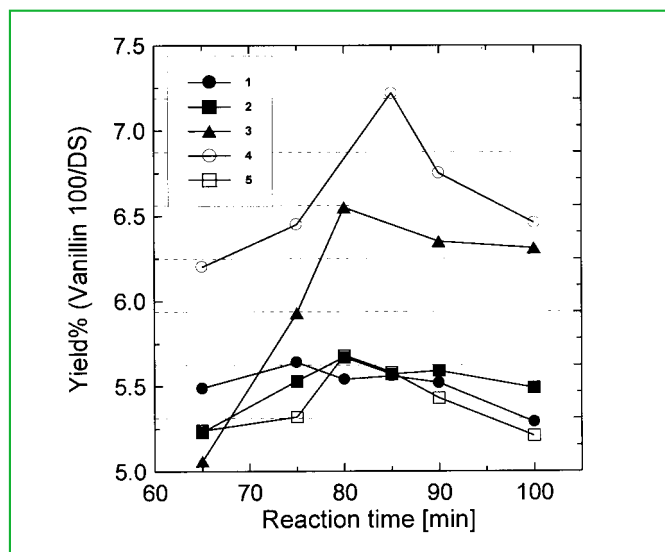


Figure 4 - The figure shows the course of the optimisation reactions with conditions predicted from the model derived from the response surface design. The conditions for the different experiments performed in the pilot plant reactors are for all experiments 2630 ml of an approximately 24% lignosulfonate solution (660 g LS) which is diluted with 740 ml water, added sodium hydroxide as 50% solution and the copper catalyst as recovered copper oxide. The graphs shows: (●) 6 g Cu and 460 g NaOH, (■) 8 g Cu and 460 g NaOH, (▲) 6 g Cu and 480 g NaOH, (○) 8 g Cu and 480 g NaOH, and (□) 7 g Cu and 470 g NaOH. All experiments were performed at 185 °C.

After the development of the industrial process for the production of catechol from phenol and  $H_2O_2$ , vanillin was also produced by the synthetic process according to Scheme 1. Initially, the reaction given in path (a) of Scheme 1, was carried out on industrial scale by Brichima by a catalysed

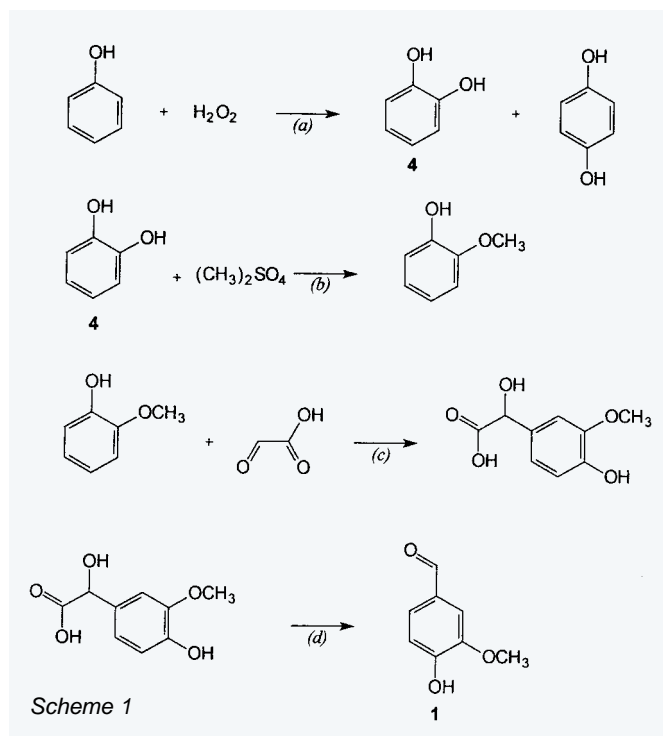


Table 2 - Optimising experiments using LS<sub>750</sub> with conditions and adjacent measured experimental results

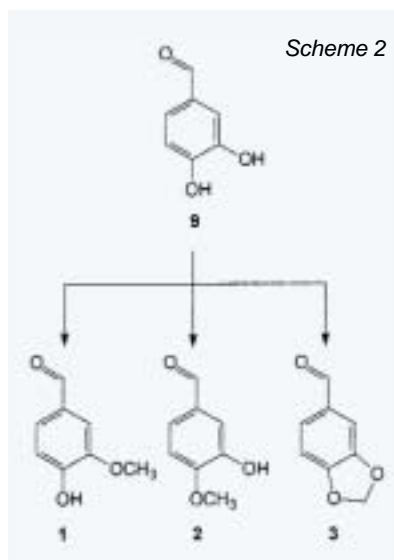
#	Experimental conditions <sup>a</sup> (g)		Response / % Vanillin/LS <sup>b</sup> Reaction times, t (min)					
	Cu	NaOH	65	75	80	85	90	100
1	6	460	5.49	5.64	5.54	5.56	5.52	5.31
2	8	460	5.23	5.53	5.67	5.57	5.59	5.49
3	6	480	5.06	5.93	6.55	5.66	6.35	6.31
4	8	480	6.20	6.45	6.41	7.22	6.75	6.46
5	7	470	5.24	5.32	5.68	5.58	5.43	5.21

<sup>a</sup> The amounts of water, lignosulfonate are given in the experimental description. The hydrolysis-oxidation experiments are performed at 185 °C. <sup>b</sup> The percentage of vanillin is correlated to the amount dry substance found in the sample

free-radical hydroxylation reaction [13]. Afterwards Brichima was purchased by Enichem and the former process was greatly improved by using a very effective catalyst, titanium-silicalite, which combines chemical and shape selectivity and allows much higher conversion without loss of selectivity. Recently the production plants of catechol, guaiacol and guethol in Italy and the vanillin plant in Norway was bought by Borregaard Synthesis, the fine chemical activity of Borregaard Ind. Ltd. (Norway). *iso*-Vanillin and heliotropin (piperonal) are also used in perfumery as flavors and intermediates for fine chemicals.

We have considered the possibility to produce, vanillin **1**, *iso*-vanillin **2**, and heliotropin **3** from the same intermediate protocatechualdehyde **9**, by combining mechanistic interpretation of the designed syntheses, Scheme 2, with statistical experimental design and multivariate modelling [13].

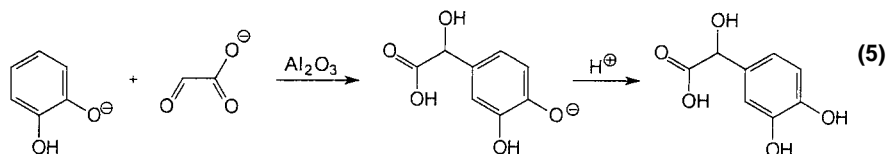
Two processes were reported for the synthesis of *iso*-vanillin **2** (i) regiocontrolled demethylation [14] or, better, dealkylation [15] of respectively 3,4-dimethoxy or 3-alkoxy-4-methoxy benzaldehyde; these syntheses are rather cumbersome because they involve five steps from catechol, while in our process only 3 steps are involved (Equations 17, 7 and 15). Another procedure [16] involves the mono O-methylation of proto-



catechualdehyde **6** with MeI and NaH in DMSO, but it is too expensive for industrial applications. Several syntheses of heliotropin were reported: the chromic oxidation of piperonyl alcohol [17], the condensation of 4-bromo-benzo[1,3]dioxole with *N*-methylformanilide [18], ozonolysis [19] or chromic(VI) oxidation of *iso*-safrole. The key point for the synthesis according to the Scheme 2 is the cheap and simple



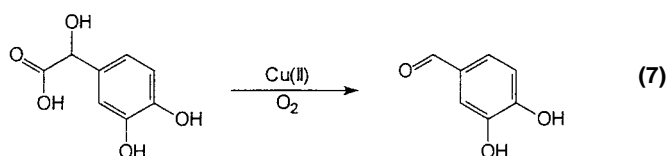
availability of protocatchualdehyde **9**. For the synthesis of protocatchualdehyde **9** we have optimised a process similar to that described in Scheme 1; a literature report [20] indicated that the basic condensation of glyoxylic acid with catechol could be improved by the presence of  $\text{Al}_2\text{O}_3$  (Equation 5). Statistical experimental design and multivariate modeling were utilised for this optimization, exploring only the experimental controllable variables  $x_1$  (amount of glyoxylic acid),  $x_2$  (amount of  $\text{Al}_2\text{O}_3$ )



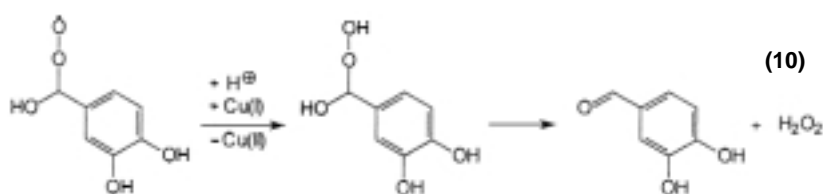
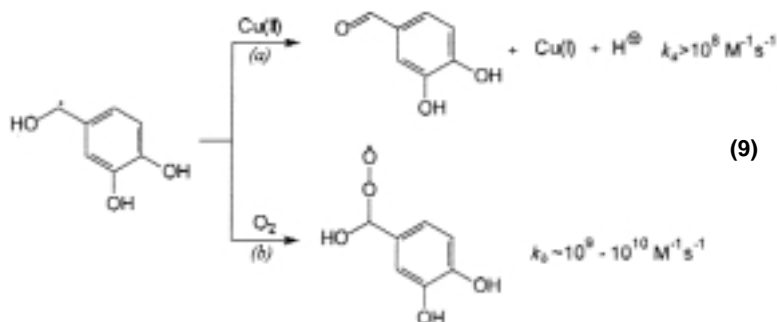
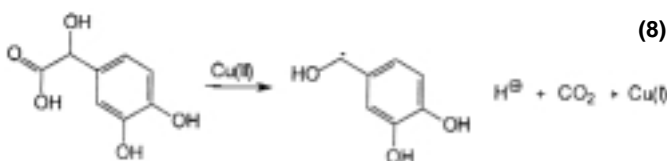
and  $x_3$  (reaction temperature) in a full factorial experimental design with one "center point" ( $2^{3+1} \rightarrow 9$  experiments). The statistical experimental design with the variables  $x_1$ - $x_3$  with their adjacent measured and calculated responses  $\eta=[r, o, s, y]$  are reported in Table 3. The response  $s$ , selectivity %, and the variables  $x_1$ - $x_3$  with their interactions were multivariate correlated using the multiple linear regression method to obtain the regression mode of Equation 6.

$$s = 63.68 + 1.428 \times x_1 - 2.082 \times x_2 - 1.708 \times x_3 + 1.275 \times x_1 \times x_2 + 4.890 \times x_1 \times x_3 - 5.790 \times x_2 \times x_3 + 3.688 \times x_1 \times x_2 \times x_3 \quad (6)$$

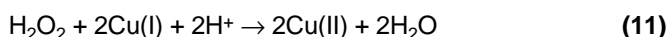
This model was used to represent the response surface projection, from which conditions for an optimisation experiment were predicted. In front of 100% selectivity predicted by the model a selectivity of 90.5% was obtained in the optimization experiment [21]. Attempts to produce protocatchualdehyde **9** from 3,4-dihydroxy mandelic acid according to catalytic oxidation similar to path (d) of Scheme 1 gave poor results (Equation 7).



Thus we have investigated the mechanism of this reaction in order to understand the differences between the path (d) of Scheme 1 and Equation 7. We recognized that two mechanisms lead to the formation of the aldehyde **9** in the presence of oxygen. The first step in any case is the inner-sphere electron transfer oxidation of the mandelic acid derivative by the  $\text{Cu}(\text{II})$  salt (Equation 8). The hydroxybenzyl radical reacts very fast either with  $\text{Cu}(\text{II})$  or with  $\text{O}_2$ , Equation 9 path (a) and (b).



The peroxy radical is reduced by  $\text{Cu}(\text{I})$  leading to protocatchualdehyde **9**, Equations 10 and 11, path (a) and (b).

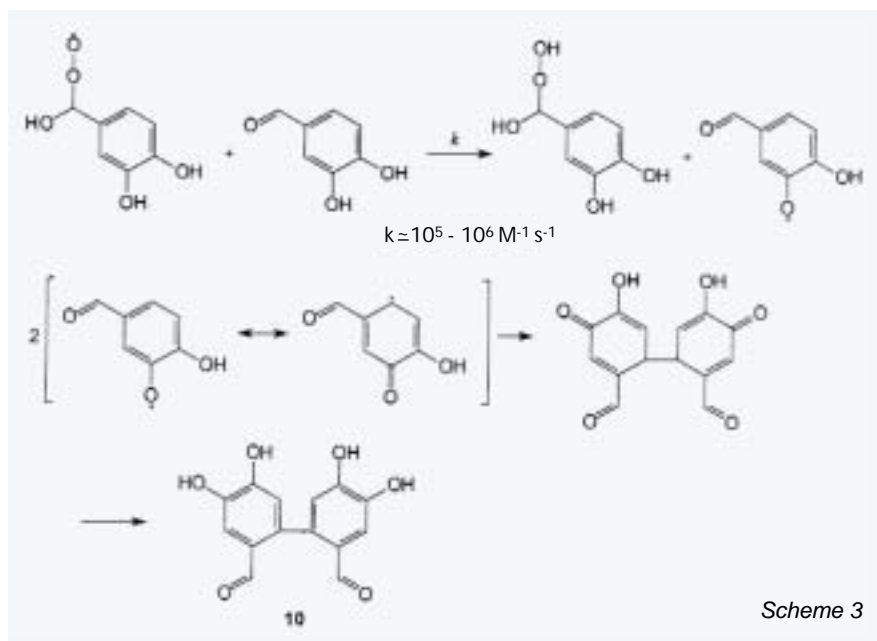


We soon realized that path (a) of Equation 9 gives high selectivities of protocatchualdehyde **9**, while path (b) gives poor results. We have carefully analysed the products of the catalytic oxidation in the presence of oxygen and recog-

**Table 3 - Experimental conditions with corresponding measured and calculated responses for the screening and introductory optimisation study of the reaction between catechol and glyoxylic acid to 3,4-dihydroxy mandelic acid**

Experimental variables <sup>a</sup>				Responses <sup>b</sup>			
#	$x_1$	$x_2$	$x_3$	$r$	$o$	$s$	$y$
1	-1	-1	-1	10.34	24.78	70.66	54.57
2	+1	-1	-1	11.00	18.53	53.81	40.81
3	-1	+1	-1	15.08	20.67	68.15	45.52
4	+1	+1	-1	9.22	25.75	71.15	56.71
5	-1	-1	+1	12.80	20.11	61.67	44.29
6	+1	-1	+1	10.04	27.99	79.13	61.64
7	-1	+1	+1	12.15	16.88	50.75	37.17
8	+1	+1	+1	6.87	22.57	58.56	49.70
9	0	0	0	12.09	19.76	59.30	43.51

<sup>a</sup> In each experiment: 45.41 mmol of catechol, 80.37 mmol of  $\text{NaOH}$ , 55 ml of water and a reaction time of 24h were used. The other experimental variables were varied:  $x_1$ : amount of glyoxylic acid / [mmol] [34.96, 45.41],  $x_2$ : amount of aluminiumoxide / [mmol] [22.70, 31.79],  $x_3$ : reaction temperature / [°C] [25, 50]. <sup>b</sup>  $r$ =mmol recovered catechol,  $o$ =mmol of 3,4-dihydroxy mandelic acid,  $s$ =per cent selectivity to 3,4-dihydroxy mandelic acid, and  $y$ =yield per cent of 3,4-dihydroxy mandelic acid calculated from catechol



Scheme 3

The selectivity for the formation of **9** in this way is particularly high (>95%) with complete conversion and the process is catalytic in Cu(II) because the aqueous solution can be recycled without limitations [21]. The methylation of protocatechualdehyde **9** by dimethylsulphate in basic medium can lead to three different products (Equation 13).

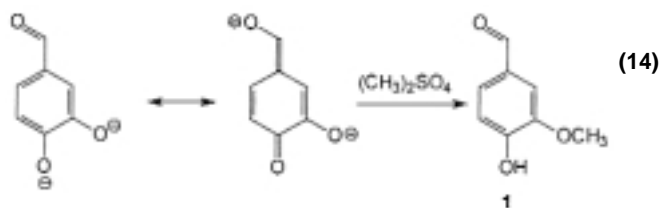
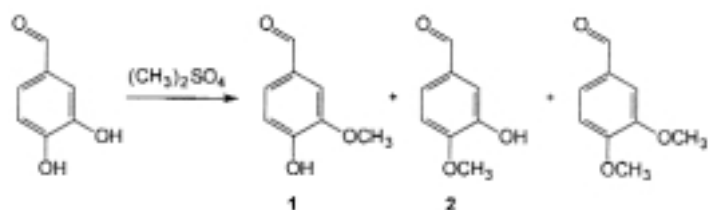
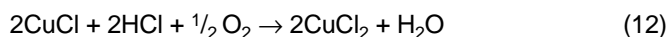
Also in this case the combination of mechanistic interpretation and statistical experimental design associated with the multivariate modelling has allowed us to develop regio-controlled methylations leading with good selectivity to *iso*-vanillin and vanillin.

The use of an excess of dimethylsulphate and sodium hydroxide, leads to veratraldehyde (dimethylation); thus partial conversion can be performed by using one or less mole of dimethylsulphate for mole of protocatechualdehyde **9** in

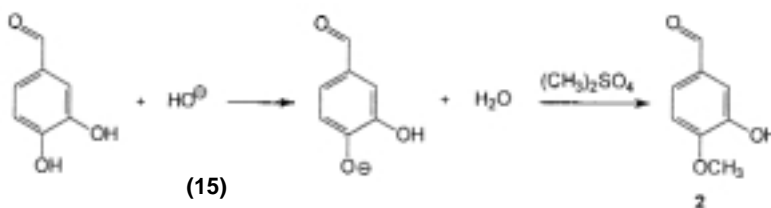
nized that the main by-product arises from the oxidative dimerisation of protocatechualdehyde **9** with formation of the dimer **10**. Since **10** is not found in the absence of  $\text{O}_2$  the only reasonable explanation for its formation is the reaction of the peroxy radical of Equation 9, path (a), with **9** in competition with path (a) [21] (Scheme 3).

The relevant mechanistic aspect of this interpretation is that the hydroxyl group in position 3 of compound **9** is much more reactive towards the peroxy radical than the hydroxyl group in position 4; we explain this behaviour by the higher acidity of this last hydroxyl ( $pK_{a(4\text{-OH})} \approx 7.5$ ;  $pK_{a(3\text{-OH})} \approx 11.6$ ), due to the influence of the carbonyl group in *para* position [21]. This interpretation also explains why a dimer like **10** is not found in the synthesis of vanillin by catalytic oxidation of 3-methoxy-4-hydroxy mandelic acid [Scheme 1 (d)]; in vanillin only the hydroxyl group in position 4 is available. The understanding of the reaction mechanism has allowed us to develop a simple oxidation process of industrial interest, based on the two steps and a two phase reaction system (water: ethyl acetate) [21].

In the first step the oxidation is carried out with stoichiometric amount of  $\text{CuCl}_2$  under nitrogen atmosphere; only the path (a) of Equation 9 takes places, the oxidation occurs in the aqueous phase and the formed aldehyde **9** is continuously extracted by ethyl acetate. The  $\text{CuCl}_2$  aqueous solution separated from the organic phase is simply regenerated by bubbling air and recycled (Equation 12).



order to obtain high selectivity in monomethylation and to minimise the formation of veratraldehyde. Mechanistic considerations suggested that in the presence of an excess of NaOH the phenoxide ion in position 3 is more nucleophilic than the ion in position 4, which is conjugated with the carbonyl group (Equation 14). Under these conditions monomethylation should preferentially take place in the position 3 leading to vanillin **1**.



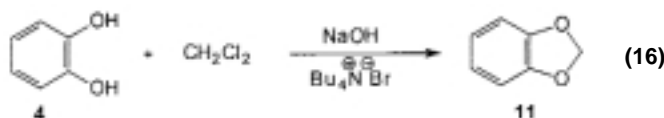
On the other hand by using one mole or less of NaOH for mole of protocatechualdehyde **9**, the more acidic OH groups should be salified and the methylation should occur at this position (Equation 15) leading to *iso*-vanillin.

Based on these mechanistic considerations we have carried out some preliminary experiments and recognized that the ratios among the products **1**, **2** and veratraldehyde in Equation 14 are influenced by the following variables: the addition time of reagents ( $x_1$ ), the reaction time ( $x_2$ ), the additional amount of sodium hydroxide during the reaction ( $x_3$ ), the initial amount of sodium hydroxide ( $x_4$ ), the reaction temperature ( $x_5$ ), the amount of dimethylsulphate ( $x_6$ ), and the volumes of dichloromethane

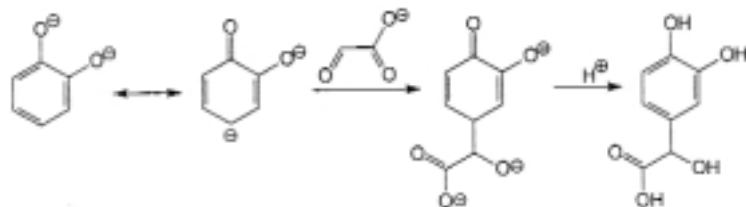
( $x_7$ ) and water ( $x_8$ ). A fractional factorial design of the type  $2^{8-4}$  was used. The final models for vanillin and *iso*-vanillin were used to produce the response surfaces in Figure 5 and Figure 6, respectively.

Experiments with optimised conditions based on the models for vanillin and *iso*-vanillin (graphically represented in Figures 5 and 6) were performed and a 94.6% selectivity with 42.5% of conversion of protocatechualdehyde **9** and a 86.8% selectivity with 44.6 % of conversion of protocatechualdehyde **9** were obtained respectively for *iso*-vanillin and vanillin [21]. The separation and the recycle of unreacted **9** is easy and unexpensive; it is based on the higher acidity of **9** compared to **1** and **2**.

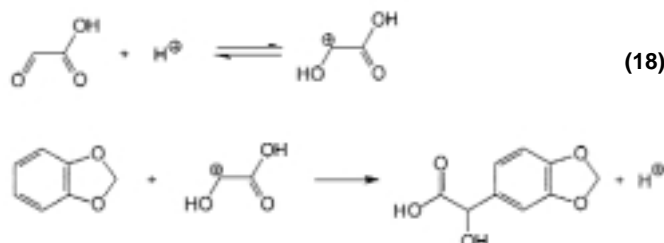
Attempts to prepare piperonal according to the Scheme 2 gave only moderate yields probably for the instability of **9** under the basic experimental conditions. Thus we have considered the possibility to reverse the sequence of the step starting from catechol which is known can be transformed in benzo[1,3]dioxole, **11**, with high yields, (Equation 16).



The condensation of **11** with glyoxylic acid cannot be catalysed by a basic medium as with guaiacol [Scheme 1, route (c)] or catechol (Equation 5), which involves the nucleophilic addition of the phenoxide ion to the carbonyl group (Equation 17).



We have developed a catalysis by sulphuric acid which has led with high selectivity (>90%) to the mandelic acid derivative (Equation 18).



The oxidative decarbonylation of the mandelic acid derivatives to heliotropin was carried out by high yield (>90%) by oxygen catalysed by  $\text{CuCl}_2$  [21]. The absence of hydroxyl groups prevents the further oxidation of heliotropin, as described in Scheme 3.

This oxidation, as well as that described in equation 9 (path a), is characterised by a very low environmental impact, because the processes are carried out in a two phase system (aqueous:organic) and the aqueous phase containing the catalyst is continuously recycled.

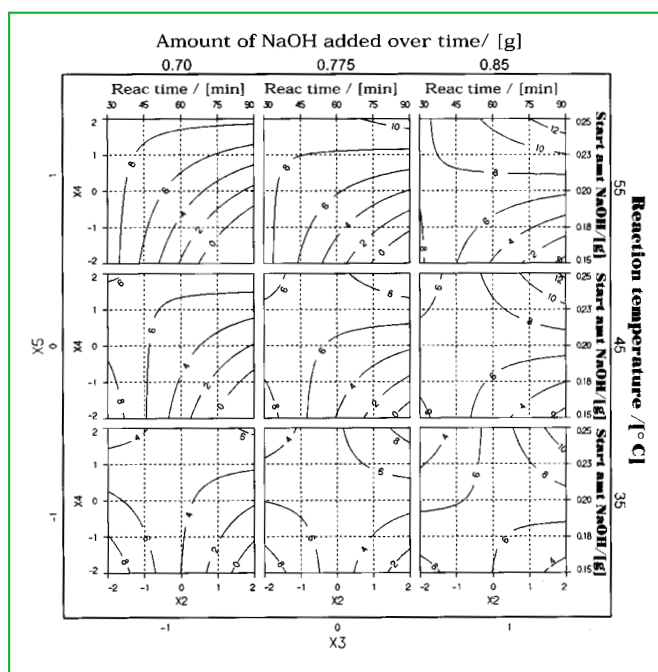


Figure 5 - The contour projections lines show the yield of vanillin

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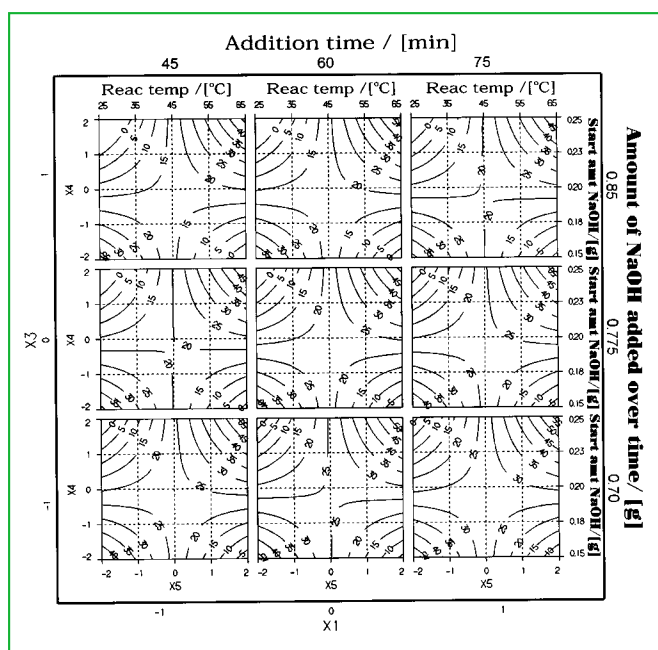


Figure 6 - The contour projections lines show the yield of *iso*-vanillin

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## Ricerca e sviluppo di processi organici attraverso progetti sperimentali statistici, modelli multivariati e interpretazioni meccanicistiche

Si mostra come la combinazione di metodologie chemio-metriche e lo studio dei meccanismi delle reazioni coinvolte possa essere utilizzata per lo sviluppo di sintesi selettive di interesse industriale e basso impatto ambientale. Nuovi processi per la produzione di vaniglina, isovaniglina ed eliotropina da pirocatechina sono stati sviluppati sulla base di questa combinazione, in cui i punti cruciali sono stati l'ossidazione catalitica ( $\text{CuCl}_2$ ) con ossigeno altamente selettiva di derivati mandelici e la monometilazione regio-selettiva dell'aldeide protocatechica. Sempre sulla base di questo approccio viene riportato e discusso un rilevante miglioramento (aumento del 75% della resa relativa) nella produzione industriale di vaniglina per ossidazione catalitica della lignina con ossigeno.