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Multivariate Optimization of a Cyclopropanation, the Key Step in the Synthesis of 3,3,4,4-Tetraethoxybut-1-yne

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Supporting Information

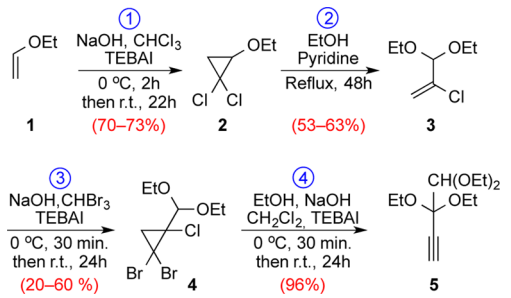
ABSTRACT: 3,3,4,4-Tetraethoxybut-1-yne (TEB) is a versatile synthon that can be produced in a four-step synthesis. The third step of the synthesis is a cycloproanation, which has been thoroughly investigated and optimized by means of statistical experimental design and multivariate modeling. At the outset, an exhaustively pre-experimental design was performed resulting in a copious Ishikawa cause−effect diagram. In total six of the experimental variables were assessed to be of large importance and thus selected for further investigation by fractional factorial design. The results of that screening and first step optimization formed the basis for a response surface modeling (RSM) study. The RSM investigation was completed by using a central composite design from which a response surface was graphically produced as an iso-contour projection. The derived multivariate predictive model in terms the iso-contour projection plots were ultimately utilized to establish experimental conditions that concomitantly provided excellent yield (>99%) and minimized amounts of inputs and thus obtain the desired product at the lowest production cost and minimized side-streams.

INTRODUCTION

A few years ago, a synthesis leading to 3,3,4,4-tetraethoxy-but-1-yne (TEB, **5**) was disclosed by Sydnes and collaborators.[1] TEB possesses a significant potential as a synthon in organic synthesis. The reagent has been utilized to prepare a variety of compounds such as unsaturated alcohols,[2] deoxygenated carbohydrates,[3] furans,[4] and a number of other heterocyclic compounds.[5]

TEB is prepared in a four-step linear synthesis, which encompasses two cyclopropanations steps (1 and 3) and two ring-opening reactions (steps 2 and 4). The synthetic pathway leading to **5** is outlined in Scheme 1.

Scheme 1. Synthesis of 3,3,4,4-tetraethoxybut-1-yne (TEB) 5



During the period since the synthesis of synthon **5** was designed and performed for the first time, the compound has been made a substantial number of times by chemists at various levels of expertise. The overall picture that has emerged is that steps 1, 2, and 4 are reproducible, relatively robust, and provide the expected reaction products (**2**, **3**, and **5**) in high, medium, and excellent yields, respectively. On the other hand, step 3, which is a cyclopropanation that is performed by addition of dibromocarbene to 2-chloro-3,3-diethoxyprop-1-ene **2** to produce 1,1-dibromo-2-chloro-2-diethoxymethyl-cyclopropane **3** under phase-transfer catalytic (PTC) conditions according to Makosza's method,[6] varies significantly and has given yields in the 20−60% range. Attempts to optimize and improve the outcome and the robustness of this synthetic step by evolutionary operations[7] involving simple modifications of the procedure have been implemented over a rather long period of time. Moreover, a considerable surplus of several of the reagents (relative to the amount of the alkene) is used to achieve a tolerable conversion and yield.

METHODS AND RESULTS

On the basis of these facts, we realized the need of a thorough and in-depth investigation of the process step 3 with the goal to develop a robust and high yielding synthetic step 3 that moreover demands minimized quantities of the various inputs.

Pre-experimental Design. Based on the principles and methodology of statistical experimental design[8] and multivariate regression analysis,[9,10] an experimental study was designed and carried through with the goal to solve the challenges that exist in the actual reaction step of the TEB synthesis.

At the outset, we carried through an in-depth analysis of the existing synthetic procedure; the various experimental variables we came across successively were incorporated into an Ishikawa cause−effect (ICE) diagram,[11] see Figure 1.

The complete set of experimental variables that we believed to have influence on the **3** → **4** transformation was divided into two distinct groups, namely, (1) the variables that were related to the performance of the synthetic reaction, and (2) the variables that concern the reaction workup. Herein we focused on the performance of the reaction, so all experimental

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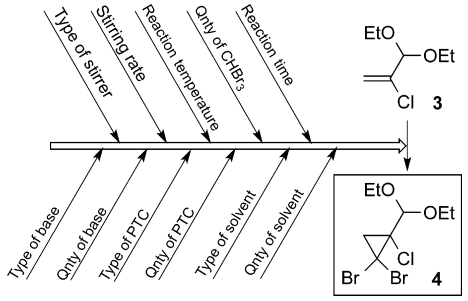

Figure 1. Ishikawa cause–effect (ICE) diagram for the 1,1-dibromo-2-chloro-2-(diethoxymethyl)cyclopropane (**4**). Experimental variables that affect the performance of the reaction.

variables related to the workup were excluded from the final ICE diagram, Figure 1.

This elaborated subset of the experimental variables was further assessed according to priority categories[12] to provide the following list of variables that were forwarded for further investigation in a screening and first step optimization study. This variable subset included x_1, reaction temperature [°C]; x_2, quantity of bromoform [equiv]; x_3, reaction time [h]; x_4, addition time for NaOH [min]; x_5, quantity of NaOH [equiv]; and x_6, amount of phase transfer catalyst (TEBA) [equiv]. Each of the variables x_1, x_2, ..., x_6 were then assessed with respect to ample experimental ranges,; see footnote a of Table 1. The substrate **3** was prepared according to Scheme 1 (**1** → **2** → **3**), the details of which are given in the Experimental Section. The statistical experimental design we selected for this study (Table 1) is a fractional factorial design with a couple of experiments in the center of the experimental domain ($2^{k-r} + c = 2^{6-2} + 2$). The scaled experimental variables x_1, ..., x_6 were used to prepare the confounded two-variable and some of the three-variable interactions; see the model parameters in Table 2.

Table 1. Statistical experimental design for screening of the experimental variables and first step optimization of the reaction using a 2^{6-2} fractional factorial design with one response variable

	experimental variables[a,b]						
entry	x_1	x_2	x_3	x_4	x_5	x_6	y
1	−1	−1	−1	−1	−1	−1	14
2	1	−1	−1	−1	1	−1	63
3	−1	1	−1	−1	1	1	55
4	1	1	−1	−1	−1	1	22
5	−1	−1	1	−1	1	1	42
6	1	−1	1	−1	−1	1	41
7	−1	1	1	−1	−1	−1	4
8	1	1	1	−1	1	−1	98
9	−1	−1	−1	1	−1	1	7
10	1	−1	−1	1	1	1	66
11	−1	1	−1	1	1	−1	75
12	1	1	−1	1	−1	−1	9
13	−1	−1	1	1	1	−1	25
14	1	−1	1	1	−1	−1	18
15	−1	1	1	1	−1	1	9
16	1	1	1	1	1	1	56
17	0	0	0	0	0	0	52
18	0	0	0	0	0	0	51

[a]Experimental variables: x_k (description [unit]) [low level (−1), center level (0), high value (+1)]. x_1 (reaction temperature [°C]) [20, 25, 30]; x_2 (quantity of bromoform [equiv]) [5, 8, 10]; x_3 (reaction time [h]) [12, 24, 36]; x_4 (addition time for NaOH [min]) [5, 10, 15]; x_5 (quantity of NaOH [equiv]) [8, 10, 12]; x_6 (amount of PTC (TEBA) [equiv]) [0.01, 0.015, 0.02]. A fixed quantity of substrate **3** (3.29 g, 20 mmol) was used in all of the experiments 1–18. [b]Generators used in the design: $x_5 = x_1 \times x_2 \times x_3$ and $x_6 = x_2 \times x_3 \times x_4$.

Table 2. Regression coefficients with adjacent estimated numerical values

coefficient and alias	value	coefficient and alias	value
β_0	39.278	β_{13} (+ β_{25})	7.750
β_1 reaction temperature	8.875	β_{14} (+ β_{56})	−4.750
β_2 quantity of bromoform	3.250	β_{15} (+ β_{23} + β_{46})	1.875
β_3 reaction time	−1.125	β_{16} (+ β_{45})	0.125
β_4 addition time, NaOH	−4.625	β_{24} (+ β_{36})	0.875
β_5 quantity of NaOH	22.250	β_{34} (+ β_{26})	−5.000
β_6 amount of TEBA	−0.500	β_{124}	−5.250
β_{12} (+ β_{35})	−3.625	β_{134}	−1.875

Assessment of the Experimental Levels. Prior to the implementation of the whole experimental plan (Table 1), a small subset of experiments were conducted in the laboratory in order to investigate and ensure that the selected experimental levels delivered sufficient variation in the selected response, that is, the yield of cyclopropane **4**. The entries 1, 16, and 17 of Table 1 were thus conducted, which revealed a significant variation and that the selected experimental levels were satisfactory selected. Hence, the rest of the objects of the experimental design (2–15 and 18 that is a replicate of 17) were successively carried out in a random order. The achieved results of all of the experiments are reported in the right-hand columns of Table 1.

Computation: Development of Multivariate Predictive Model. The experimental variables and levels are displayed in Table 1. Each of the variables was scaled according to eq 1 to facilitate the estimation of the regression coefficients, the β's of eq 2. The x_i of the equations is the experimental variable i given in scaled units, z_i is the identical experimental variable i = 1, ..., 6, although expressed in real (noncoded) units, $z_{i,L}$ and $z_{i,H}$ are the selected low (L) and high (H) experimental values in real units, of the experimental variable z_i.[13]

$$x_i = \frac{z_i - \left\{z_{i,\mathrm{L}} + \frac{1}{2}(z_{i,\mathrm{H}} - z_{i,\mathrm{L}})\right\}}{z_{i,\mathrm{H}} - \left\{z_{i,\mathrm{L}} + \frac{1}{2}(z_{i,\mathrm{H}} - z_{i,\mathrm{L}})\right\}}, \qquad i = 1, \ldots, 6 \tag{1}$$

$$y = \beta_0 + \sum_{i=1}^{6} \beta_i \boldsymbol{x}_i + \sum_{i<j}^{6} \sum_{i<j}^{6} \beta_{ij} \boldsymbol{x}_i \boldsymbol{x}_j \tag{2}$$

The model matrix $\boldsymbol{X}$ was created as the following $\boldsymbol{X}$ = [1 $\boldsymbol{D}$ $x_1 \times x_2$ $x_1 \times x_3$ $x_1 \times x_4$ $x_1 \times x_5$ $x_1 \times x_6$ $x_2 \times x_4$ $x_3 \times x_4$ $x_1 \times x_2 \times x_4$ $x_1 \times x_3 \times x_4$], included the design matrix $\boldsymbol{D}$ after a column of ones that was followed by the two-variable interactions ($x_i \times x_j$) for each of the six experimental variables (x_i, i = 1, ..., 6). The final model matrix was used in scaled values [11 lines × 8 columns, eq 2] with their corresponding achieved % yield values of target molecule 1,1-dibromo-2-chloro-2-(diethoxy-methyl)-cyclopropane **4** then submitted to multivariate regression in terms of the multiple linear regression (MLR)[9] and partial

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least-squares regression (PLSR)[10] methods using the SAS[14] and MATLAB[15] computer software packages.

The estimated numerical values and confounding pattern for the various regression coefficients are provided in Table 2. The product statistics[16] show a reasonable good model: R^2 = 0.973, RMSEP = 4.324, and RSD = 4.587.

The cumulative normal probability (CND) plot and the regression coefficient spectrum of the estimated numerical values are displayed in Figure 2, from which it is evident that

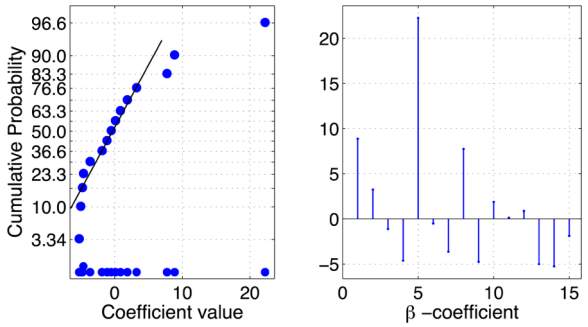

Figure 2. CND plot and β-spectrum (regression coefficients plotted in a bar graph).

the regression coefficients β_0, β_1, β_5 and the two-factor interaction term β_{13} (+ β_{25}) are significant in the model. The two-variable interactions $x_1 \times x_3$ and $x_2 \times x_5$ are confounded, and it is not straightforward to discern which of the two interactions intervenes in the model. However, from a chemical point of view, it is reasonable to believe that the quantity of bromoform (x_2) and the quantity of sodium hydroxide (x_5) interact (that is, the two factor interaction $x_2 \times x_5$). Thus, the final model includes β_0 (mean yield value) and β_1, β_5, and β_{25}. Moreover, the two coefficients β_{34} (+ β_{26}) and β_{124} are both borderline cases. This means that these can be included in the model (or they may be excluded).

The implementation of the screening revealed the experimental variables with significantly influence and their relative importance (due to the numerical value of each single regressions coefficient). Hence, the experimental variables reaction temperature (x_1), quantity of bromoform (x_2), reaction time (x_3), quantity of NaOH (x_5), and amount of TEBA (x_6) appeared to be essential in the cyclopropanation (step 3) of Scheme 1.

Even though the design and model actually indicated an optimized synthetic protocol (experiment 8 of Table 1), we wanted to further investigate the cyclopropanation step, where we also wanted concomitantly (1) to determine a maximized yield, (2) to design and establish a robust process, and (3) to minimize the inputs and thus the cost of the synthesis, this by means of an detailed iso-contour projection of the response (yield) surface.

Table 3. Statistical experimental design ($2^k + c = 2^3 + 3$) with responses measured by means of a 400 MHz ^{1}H NMR spectrometer

	experimental variables[a]			measured responses[b]				
entry	χ_1	χ_2	χ_3	$y^{(1)}$	$y^{(2)}$	$y^{(3)}$	y [%]	y_{isol} [g][c]
1	−1	−1	−1	89.52	89.41	89.58	89.5	14.58
2	+1	−1	−1	86.48	86.76	86.60	86.6	14.11
3	−1	+1	−1	99.91	99.95	99.93	99.9	16.27
4	+1	+1	−1	99.78	99.69	99.85	99.8	16.26
5	−1	−1	+1	80.24	80.05	80.35	80.2	13.06
6	+1	−1	+1	87.48	87.46	87.60	87.5	14.25
7	−1	+1	+1	93.02	92.88	92.78	92.9	15.13
8	+1	+1	+1	99.97	99.92	99.97	99.9	16.27
9	0	0	0	95.28	95.48	95.32	95.4	15.54
10	0	0	0	96.22	96.67	96.30	96.4	15.70
11	0	0	0	98.76	98.76	98.35	98.6	16.06
12	−1	−1	−1	99.14	99.36	99.02	99.2	*d*
13	−2	0	0	90.96	93.03	92.62	92.2	15.02
14	+2	0	0	93.38	90.98	90.11	91.5	14.91
15	0	−2	0	64.59	64.75	64.86	64.7	10.54
16	0	+2	0	99.94	99.96	99.94	99.9	16.27
17	0	0	−2	94.58	97.43	95.07	96.0	15.64
18	0	0	+2	74.94	75.02	74.87	74.9	12.20
19[e]	−2	−1	−2	76.69	76.56	76.58	76.6	12.48
20[e]	−2	−1	−1	76.02	75.72	75.64	75.8	12.35
21[e]	−1	0	−2	99.97	99.99	99.98	≈100	16.29
22[e]	−1	0	−2.5	99.98	99.97	99.96	≈100	16.29
23[e]	−1	0	−3.0	99.55	99.62	99.56	99.6	16.22

[a]Variable explaination. χ_k: variable name [unit], levels [−2, −1, 0, +1, +2]. χ_1: Q_{PTC} [g], [0.1185 0.158, 0.198, 0.237 0.2765]. χ_2: Q_{NaOH} (as a 50% solution) [g], [22.46 29.95, 37.44, 44.93 52.42]. χ_3: $Q_{bromoform}$ [mL], [31.875 42.50, 53.13, 63.75 74.375]. For each experiment 8.0 g of the substrate 2-chloro-3,3-diethoxyprop-1-ene **3** was used, to which were added the PTC (χ_1), then the bromoform (χ_3), and finally the sodium hydroxide (χ_2) as a 50% aqueous solution over a period of 15−20 min at 0 °C. Then the reaction was stirred at 0 °C for 2 h and then at room temperature for another 22 h. [b]The responses were measured by means of ^{1}H NMR. [c]Isolated yields after workup of the experiment. Total isolated yield achieved during the response surface optimizing study was $\sum y_{isol} \approx 325$ g. [d]Isolated yield not measured for this experiment. [e]Optimization experiments performed in order to test the final model.

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After the screening study was completed, the developed process (entry 8 of Table 1) was used for a long period (several months) to produce target cyclopropane intermediate **4** and final synthon **5** (see details in the Experimental Section). During this production period, a general evolution of the synthesis process continued. These amendments were mainly related to changes in reaction time, time of addition, and the reaction temperature. As a final task in this exploration and optimization study, we decided to investigate the experimental variables related to reagent quantities, namely, the quantities of phase transfer catalyst (χ_1), sodium hydroxide (χ_2), and bromoform (χ_3), respectively. The three other experimental variables we decided to keep at levels that we had identified to be convenient and comprise an addition time for sodium hydroxide in the range 15−20 min (at 0 °C), then continuously stirring for 2 h at 0 °C, and then at ∼20 °C for a period of 22 h. This information was elaborated and implemented in a central composite design in three variables, where the experimental variables were renamed and renumbered differently from the screening design to provide the design matrix **Δ** provided in Table 3. Based on this, a model matrix ***M*** was created as the following $\boldsymbol{M} = [\mathbf{1}\ \boldsymbol{\Delta}\ \chi_1 \times \chi_2\ \chi_1 \times \chi_3\ \chi_2 \times \chi_3\ \chi_1 \times \chi_1\ \chi_2 \times \chi_2\ \chi_3 \times \chi_3]$. The model matrix ***M*** was multivariate, correlated to the response y_{isol}. The estimated numerical values of the coefficients (α) are provided in Table 4, and presented in a CND and

Table 4. Regression coefficients with adjacent estimated numerical values

coefficient	value	coefficient	value
α_0	98.093	α_{13}	2.981
α_1	0.216	α_{23}	0.996
α_2	7.044	α_{11}	−1.075
α_3	−3.992	α_{22}	−3.451
α_{12}	1.116	α_{33}	−2.665

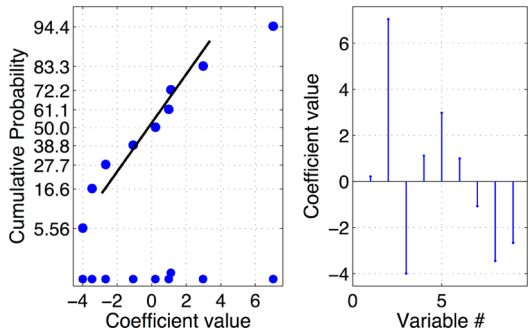

Figure 3. Cumulative normal probability distribution plot (CND) and β-spectrum (all the regression coefficients plotted as a stem graph).

regression coefficient spectrum; see Figure 3. The product statistics for the model shows a reasonable good fit of the data, R^2 = 0.879, RMSEP = 3.289, and RSD = 3.489. The model selection was also supported by using Mallows *Cp* statistics[17] in combination with stepwise regression.[9a] A printout from the regression analyses performed with the SAS program is provided in the Supporting Information.

The CND plot and regression coefficient spectrum shows that in addition to the mean value term α_0, the coefficients α_2, α_3, α_{13}, α_{22}, and α_{33} are significant in contributing in the response surface model.

The model matrix ***M*** was pruned (that is, removal of the nonsignificant variables), and a new final multivariate regression model with a product statistics of R^2 = 0.853, RMSEP = 3.638, and RSD = 3.859 was established. The final variable-pruned empirical model is provided in eq 3. The model, eq 3, was subsequently utilized for the production of the iso-contour projections of the multidimensional response surface, that is spanned by the three experimental variables χ_1, ..., χ_3 and the response *y*. The two most influencing variables, χ_2 and χ_3, were investigated continuously over the whole range [−2, +2] of the experimental space, as defined in the experimental design. The third of the experimental variables was investigated at five discrete values, namely, at the five set values [−2, −1, 0, +1, +2] as used in the experimental design. From the iso-contour map, Figure 4, it is evident how the effect of the variation of the variables influences the outcome of the process.

$$\begin{aligned} y &= f(\chi_1, \chi_2, \chi_3) \\ &= \alpha_0 + \alpha_2\chi_2 + \alpha_3\chi_3 + \alpha_{13}\chi_1\chi_3 + \alpha_{22}\chi_2^2 + \alpha_{33}\chi_3^2 \\ &= 96.35 + 6.959\chi_2 - 4.077\chi_3 + 3.152\chi_1\chi_3 - 3.022\chi_2^2 \\ &\quad - 2.236\chi_3^2 \end{aligned} \tag{3}$$

CONCLUSION

Step 3 of Scheme 1 was investigated and successfully optimized by means of multivariate modeling to provide an excellent yield (>99%) of 1,1-dibromo-2-chloro-2-(diethoxy-methyl)-cyclopropane **4**. The optimized process was *not saddled* with production of any impurities or such impurities were only formed in quantities that could be removed via the normal workup procedure. Furthermore, these models operated as (1) tools for the purpose of optimizing the yield of the process, (2) a means to insight into how the various experimental variables influence the performance of the process, thus mading it possible to establish a high-yielding and robust process, and (3) an instrument to concomitantly minimize the inputs, i.e., the consumption of bromoform as an crucial reagent, which is beneficial for the process economy and environmental aspects. During the response surface modelling, 325 g of intermediate **4** was successfully produced, which subsequently was converted to TEB. Thus, this optimization study operated also as a reagent supply source for several TEB reagent reliant projects in progress. For the sake of completeness a complete experimental procedure for the steps for the total synthesis (1−4) of Scheme 1 is included.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were obtained using a NMR spectrometer operating at 400 MHz. Chemical shifts are given relative to internal TMS. 2-Chloro-3,3-diethoxyprop-1-ene **3** was synthesized as described in the literature,[1a] and reagents were purchased commercially and used without further purification.

Procedure for the Synthesis of 1,1-Dichloro-2-ethoxycyclopropane 2 from Ethoxyethene 1. A three-necked round-bottom flask was charged with ethoxyethene (0.8 mol, 57.688 g), chloroform (3.2 mol, 381.952 g), and TBAI (3.0 mmol, 1.124 g) and placed in a water−ice bath under vigorously stirring. To this mixture was added dropwise a

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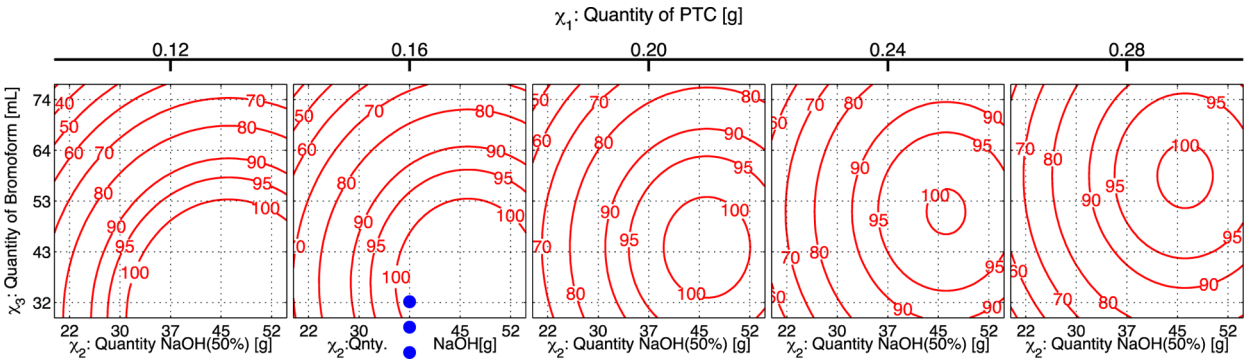

Figure 4. Response surface iso-contour projection produced by using the multivariate empirical model eq 3. The iso-contour lines (red lines) shows the predicted %- yield of target intermediate 1,1-dibromo-2-chloro-2-(diethoxymethyl)cyclopropane (**4**). To read the plot: the outer frame, that is, the horizontal row composed of the five subplots, shows the variation in the quantity of the phase transfer catalyst (x_1) at five discrete experimental levels. Each of the five subplots displays the iso-contour lines of the response surface when the two experimental variables quantity of sodium hydroxide (x_2) and the quantity of bromoform (x_3) are continuously varied within the limits of the abscissa and ordinate axes. The second subplot from left, when $x_1 = 0.16$ was used to predict of the setting values of the variables x_2 and x_3 with the goal to approach an optimized procedure. The blue bullet points shown in the subplot predicted for phase transfer catalyst (PTC) quantity of 0.16 g show the optimization experiments 21−23 of Table 3, experiments that confirm the excellent predictive ability of the model eq 3 as all three experiments provided practically quantitative yields.

50% fresh aqueous solution of sodium hydroxide (192.01 g) using a dropping funnel. The temperature was controlled at 0 °C. The reaction mixture was left vigorously stirring at 0 °C for 2 h, and then at room temperature for 22 h. The reaction mixture was quenched by adding 240 mL of 6 M hydrochloric acid. Then water (420 mL) was added, and the aqueous phase was extracted with dichloromethane (5 times 200 mL). The combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford an almost colorless residue (the raw product), which was distilled under reduced pressure to give 106.4 g (86%) of the title intermediate 1,1-dichloro-2-ethoxycyclopropane **2**.

Procedure for the Synthesis of 3 from 2. A single-necked flask is charged with absolute ethanol (250 mL), pyridine (0.45 mol, 35 g), and 1,1-dichloro-2-ethoxycyclopropane (0.35 mol, 54.250 g). The resulting mixture was refluxed for 48 h and then was cooled to room temperature before was concentrated under reduced pressure until the volume was around 100 mL. After the residue was transferred to a separatory funnel, water was added, and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with a 0.7 M aqueous solution of copper sulfate, dried over magnesium sulfate, filtered through a plug of aluminum oxide, concentrated, and distilled to give 37.767 g (66%) of 2-chloro- 3,3-diethoxyprop-1-ene.

Procedure for the Synthesis of 1,1-Dibromo-2-chloro-2-(diethoxymethyl-cyclopropane 4 Used in the Experimental Design. Aqueous sodium hydroxide (50%, 29.95 or 44.93 g) was added dropwise using a syringe to a gently stirred mixture of 2-chloro-3,3-diethoxyprop-1-ene **3** (8.00 g, 24 mmol), bromoform (122.8 g, 42.50 mL or 184.2 g, 63.75 mL), and tetrabutylammonium (TBAI) (0.158 g or 0.237g). The resulting mixture was stirred vigorously at ∼0 °C for 2 h and then at room temperature for another 22 h. The experiments were performed in random order from which three samples were withdrawn and analyzed by ^{1}H NMR to determine the quantity of **4**. The mean value of the three samples was used as the response value for the actual experiment of the statistical experimental design.

Workup. Water (comparable in volume to the organic phase) was then added. The aqueous phase was extracted with dichloromethane (3 × 1/3 the volume of the aqueous phase) after the phases were separated. The dichloromethane layers was combined and dried with magnesium sulfate ($MgSO_4 \cdot xH_2O$) overnight, filtered, and concentrated under reduced pressure on a rotary evaporator. Distillation of the crude residue gave the title product **4**.

Optimized Procedure Leading to 1,1-Dibromo-2-chloro-2-(diethoxymethyl)-cyclopropane 4. Aqueous sodium hydroxide (50%, 37.44 g) was added dropwise using a syringe to a gently stirred mixture of 2-chloro-3,3-diethoxyprop-1-ene **3** (8.00 g, 24 mmol), bromoform (31.875 g), and tetrabutylammonium (TBAI) (0.158 g). The resulting mixture was stirred vigorously at ∼0 °C for 2 h and then at room temperature for another 22 h. After that, three samples were withdrawn and analyzed by ^{1}H NMR to determine the quantity of **4**. The mean value of the three samples demonstrated a quantitative conversion to target molecule **4**.

Workup. Water (comparable in volume to the organic phase) was then added. The aqueous phase was extracted with dichloromethane (3 × 1/3 the volume of the aqueous phase) after the phases were separated. The dichloromethane layers was combined and dried with magnesium sulfate ($MgSO_4 \cdot xH_2O$) overnight, filtered, and concentrated under reduced pressure by on a rotary evaporator. Distillation of the crude residue gave the title product **4**.

Procedure for the Synthesis of 5 from 4. To a stirred mixture of 1,1-dibrom-2-chloro-2-diethoxymethylcyclopropane (168.00 g, 0.50 mol), ethanol (138.00 g, 3.00 mol), TBAI (1.6 g), and dichloromethane (700 mL) kept in an water−ice bath was added dropwise fresh 50% aqueous sodium hydroxide (160.00 g). The mixture above was stirred vigorously at bath temperature for 24 h, before water was added. The aqueous phase was extracted with dichloromethane. Then combined organic extracts were dried over magnesium sulfate, filtered, concentrated, and distilled to give TEB (110.8 g, 96%) as a clear liquid.

Chemical Analysis by Means of ^{1}H NMR. When the reaction was complete, the reaction mixture was left in the flask for precipitation of the solids. An aliquot of the mixture was stored in refrigerator, and after ∼15 min three samples were withdrawn for recording of the ^{1}H NMR spectra.

Each of the three samples that were withdrawn from each single experiment (from statistical experimental design and the

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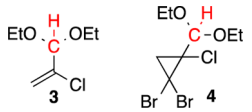
follow-up experiments) was analyzed on a ^{1}H NMR spectrometer in order to determine the quantity of target intermediate **4**. Relative quantification was used to calculate the yield of each sample, using the molar ratio between the target intermediate **4** and the unconverted substrate **3**.

The unreacted substrate **3** and target intermediate **4** both have a single proton at a tertiary carbon (red methine hydrogen in Chart 1). Both protons appears as a singlet with chemical shifts 4.86 and 4.57 ppm, respectively.

Chart 1



*2-Chloro-3,3-diethoxyprop-1-ene (**3**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.23−1.27 (t, 6H), 3.50−3.69 (m, 4H), 4.86 (s, 1H), 5.48 (d, J = 0.76, 1H), 5.68 (t, J = 1.1, 1H).

*1,1-Dibromo-2-chloro-2-diethoxymethylcyclopropane (**4**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25−1.34 (m, 6H), 2.02 (d, J = 9.4, 1H), 2.12 (d, J = 9.4, 1H), 3.59−3.84 (m, 4H), 4.57 (s, 1H).

■ ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) Categories used in the context of the Ishikawa diagram and statistical experimental design that also can be mentioned as pre-experimental design or prelude to experimental design are (A) experimental variables known to influence the performance of the reaction, (B) experimental variables suspected to influence the performance of the reaction, (C) experimental variables suspected not to influence the performance of the reaction, and (D) experimental variables known not to influence the performance of the reaction.

(13) When scaling is performed according to eq 1 the scaled low value is set at −1, and the scaled high value becomes set at +1.

(14) The SAS program system was used for the regression analysis; see: *SAS/STAT 9.1 User's Guide*; SAS Institute Inc.: Cary, NC, 2004.

(15) The MATLAB program was utilized for the graphical representation of the results and models; see: (a) *Using MATLAB Version 6*; The MathWorks, Inc., Natick, MA, 2000. (b) *Using MATLAB Graphics Version 6*; The MathWorks, Inc., Natick, MA, 2000.

(16) Product statistics are calculated according to the following equation: R2 = 1 − SSresidual/(SSmodel + SSresidual)], R2Adj is an R2 adjusted for the number of parameters in the model relative to the number of experiments in the experimental design. The R2Adj provides a measure of the amount of variation about the mean explained by the model. R2Pred = 1 − (PRESS/ SStotal). PRESS = Predicted Residual Sum of Squares for the model. PRESS provides a measure of how well a model fits each of the experiments of the design. The first step is to calculate the coefficients, the β's, for the model without including the first experiment in the modelling. This model is then used to predict the value of the omitted experiment, and the residual for this point is then calculated. This procedure is performed for each of the experiments of the design. Finally the squared residuals are summed.

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