Organic Process Research & Development **1999**, *3*, 28–37

Investigation of Cocatalysis Conditions Using an Automated Microscale Multireactor Workstation: Synthesis of *meso*-Tetramesitylporphyrin

Richard W. Wagner, Feirong Li, Hai Du, and Jonathan S. Lindsey*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

Abstract:

Prior manual work has shown that the condensation of mesitaldehyde and pyrrole leading to tetramesitylporphyrin depends sensitively on concentration and requires cocatalysis involving BF_3·$O(Et)_2$ and ethanol or other protic species. We have applied an automated microscale chemistry workstation capable of parallel or adaptive experimentation to systematically investigate these cocatalysis conditions. Examination of experimental grids spanning a 1000-fold range of the concentrations of BF_3·$O(Et)_2$ and ethanol identified the best cocatalysis conditions for various mesitaldehyde and pyrrole concentrations. As the reaction concentration increased from 10 to 200 mM, the optimal yields were achieved with a parallel increase in BF_3·$O(Et)_2$ concentration (from 3.3 to 56 mM), but the amount of ethanol remained relatively constant. Catalysis conditions were identified that afforded ~30% yields for reactants in the range of 10−73 mM, thereby enabling the reaction to be performed at increased concentration without loss in yield. Application of a catalyst searching protocol identified ethylene glycol, 2-methoxyethanol, and methanol as effective cocatalysts from a set of 12 candidates. Collectively, these results show the utility of an automated chemistry workstation in acquiring a comprehensive set of data concerning the scope of cocatalysis in the reaction of mesitaldehyde and pyrrole.

Introduction

The search for appropriate conditions for synthetic transformations is often a lengthy process involving investigation of solvents, reagents, catalysts, concentrations of reactants, temperature, and other parameters.[1] The labor-intensive nature of such tasks in synthetic chemistry has prompted the development of a variety of automated chemistry workstations.[2,3] Our efforts in this area have been aimed at developing workstations for systematic investigation of synthetic reactions and optimization of reaction conditions.[4−6] The large numbers of reactions to be performed, and the necessity to investigate reaction parameters in a systematic manner, have dictated the workstation design. In hardware, we have focused on multireactor workstations for performing microscale reactions exclusively involving liquids (Figure 1). The restriction to liquids limits the scope of chemistry but also avoids a host of difficult sample-handling problems. In software, we have focused on the ability to plan and carry out diverse experiments in parallel and to evaluate data automatically in order to focus searches and avoid futile experimentation (Figure 2). Together, these hardware and software features enable the workstation to perform experiments accurately, exhaustively, strategically, and autonomously in selected domains of chemistry in pursuit of the objectives stated by the scientist.

One particularly challenging problem for application on an automated chemistry workstation involves identifying appropriate catalytic conditions for the synthesis of *meso*-tetramesitylporphyrin (TMP). TMP and its derivatives serve as constituents of molecular photonic devices[7] as well as biomimetic oxidation catalysts.[8] TMP was initially prepared using high-temperature (170−220 °C) sealed-bomb reactions.[9] We developed a two-step, one-flask synthesis of porphyrins, in which an acid-catalyzed pyrrole−aldehyde condensation affords the porphyrinogen, which in turn is oxidized to the porphyrin.[10] The reaction is performed at room temperature in CH_2Cl_2 and affords good results with diverse aldehydes, but our initial results with mesitaldehyde and pyrrole afforded no TMP.

In searching for modified conditions for the two-step, one-flask procedure that would be applicable to TMP, we found that the condensation of mesitaldehyde and pyrrole proceeded smoothly at room temperature in the presence of BF_3·$O(Et)_2$ in $CHCl_3$, but not in CH_2Cl_2.[11] We subsequently found that the presence of ethanol as a stabilizer in the commercial source of $CHCl_3$ was the source of the reactivity difference

(1) Lindsey, J. S. In *Combinatorial Chemistry*; Czarnik, A., DeWitt, S. H., Eds.; ACS Publications: Washington, DC, 1997; pp 309−326.
(2) Lindsey, J. S. *Chemom. Intell. Lab. Syst.: Lab. Inf. Manage.* **1992**, *17*, 15−45.
(3) Hardin, J. H.; Smietana, F. R. *Mol. Diversity* **1995**, *1*, 270−274. DeWitt, S. H.; Czarnik, A. W. *Curr. Opin. Biotechnol.* **1995**, *6*, 640−645. Rivero, R. A.; Greco, M. N.; Maryanoff, B. E. In *Combinatorial Chemistry*; Czarnik, A., DeWitt, S. H., Eds.; ACS Publications: Washington, DC, 1997; pp 281−307.
(4) Lindsey, J. S.; Corkan, L. A.; Erb, D.; Powers, G. J. *Rev. Sci. Instrum.* **1988**, *59*, 940−950.
(5) Corkan, L. A.; Lindsey, J. S. *Chemom. Intell. Lab. Syst.: Lab. Inf. Manage.* **1992**, *17*, 47−74.
(6) Plouvier, J.-C.; Corkan, L. A.; Lindsey, J. S. *Chemom. Intell. Lab. Syst.: Lab. Inf. Manage.* **1992**, *17*, 75−94.
(7) Wagner, R. W.; Johnson, T. E.; Lindsey, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 11166−11180.
(8) Meunier, B. In *Metalloporphyrins-Catalyzed Oxidations*; Montanari, F., Casella, L., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1994; pp 1−47.
(9) Badger, G. M.; Jones, R. A.; Laslett, R. L. *Aust. J. Chem.* **1964**, *17*, 1028−1035. Eaton, S. S.; Eaton, G. R. *J. Am. Chem. Soc.* **1975**, *97*, 3660−3666. Bortolini, O.; Meunier, B. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1967−1970. Bortolini, O.; Ricci, M.; Meunier, B.; Friant, P.; Ascone, I.; Goulon, J. *Nouv. J. Chim.* **1986**, *10*, 39−49. Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243−6248.
(10) Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969−4970. Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827−836.
(11) Wagner, R. W.; Lawrence, D. S.; Lindsey, J. S. *Tetrahedron Lett.* **1987**, *28*, 3069−3070.

10.1021/op9800459 CCC: $18.00
Published on Web 11/03/1998

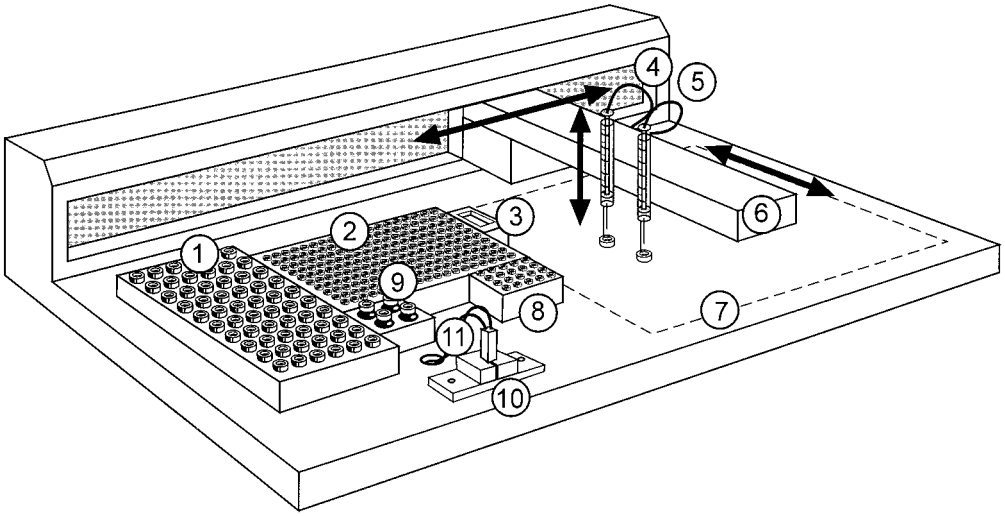


Figure 1. **Automated chemistry workstation. (1) 60-vessel reaction station. Each vessel consists of a 10-mL glass vial fitted with a septum cap and a Teflon-coated magnetic stir bar. The entire station is thermostated, and each vessel is individually stirred. (2) 264-sample-vial rack. (3) Washing station for syringes. (4) Solvent inlet line. Four solvents can be delivered via valving and syringe pumps (not shown). (5) Reagent and sample transfer syringe. The syringe is back-flushed to prevent contamination. (6) Robotic arm with speed of ~1 m/s. (7) Space for location of additional analytical instruments. (8) Reagent rack. (9) Workup reagent rack. (10) UV−visible absorption spectrophotometer equipped with fiber-optic input and output lines (not shown). (11) Solvent inlet and outlet lines to cuvette.**

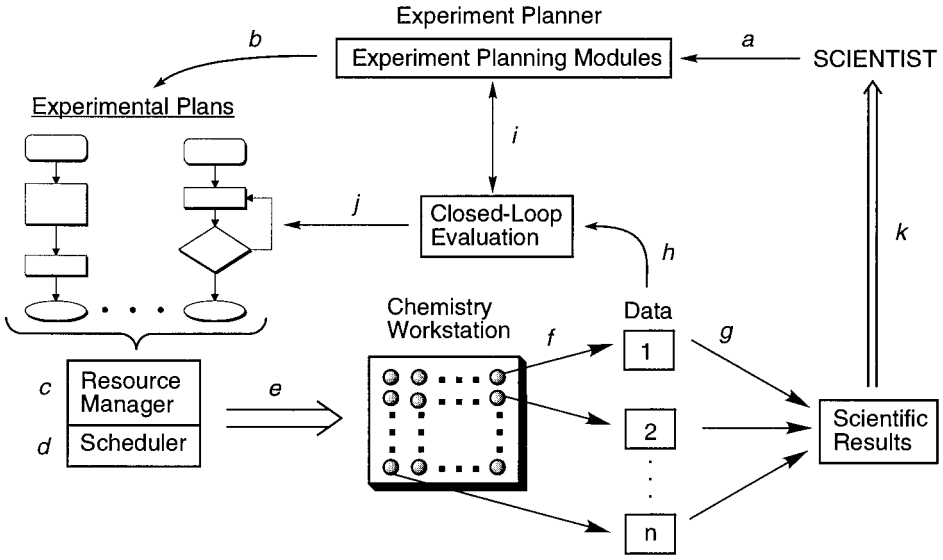


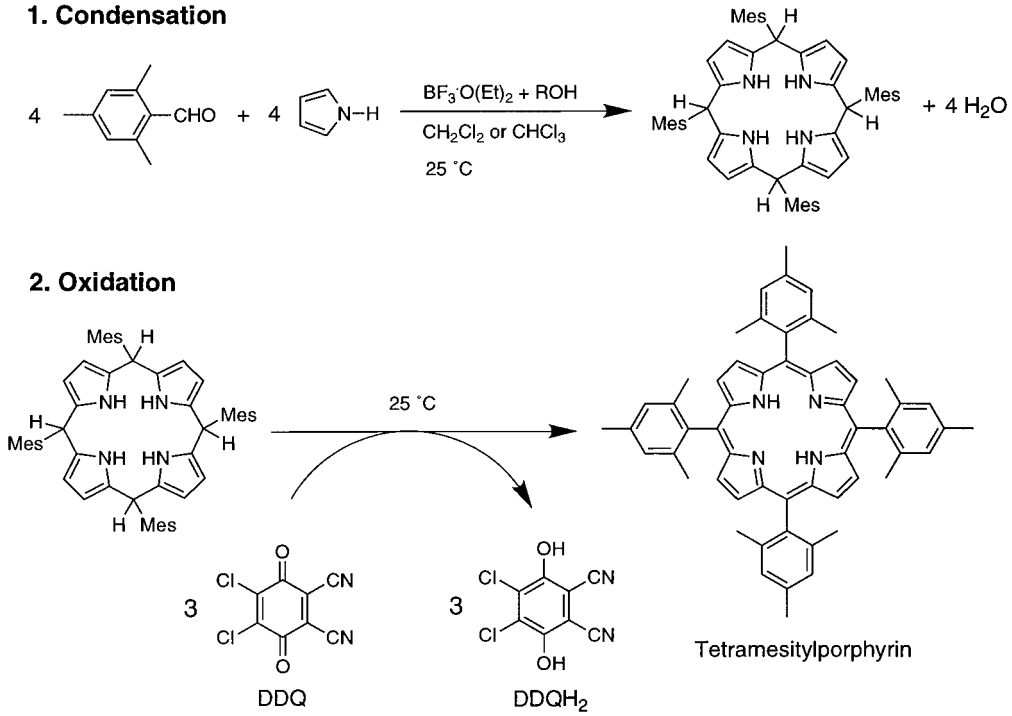
Figure 2. **Flow diagram illustrating the throughput of experiments in an automated chemistry workstation. (a) The scientist works with the experiment planner to compose an experimental plan. (b) Each experimental plan consists of a list of commands, including simple directives or conditionals that depend on experimental data. (c) A resource manager tabulates the total resource demands, including chemicals (reagents, reaction solvents, solvents utilized by instruments) and containers (reaction vessels, sample vials, etc.). The schedule is separated into executable experiments and experiments awaiting resources. Other safeguard features are invoked automatically to prevent overflowing or depleting vessels. As additional resources become available, the experiments in queue can be scheduled. (d) The scheduler renders the experiments in parallel to the extent possible. (e) The executable scheduled experiments are passed to the automated chemistry workstation. (f) Data are generated from the UV−vis instrument. (g) In open-loop experimentation, where no decisions are made automatically about ongoing or planned experiments, the data from common experiments are combined in an output file. (h) In closed-loop experimentation, where decisions are made without user intervention about ongoing or planned experiments, the data are passed to the evaluation unit of the experiment planning module. (i) The data are evaluated in the context of the scientific objective as stated in the experimental plan. (j) Depending on the results of the evaluation, ongoing experiments can be terminated or altered, pending experiments can be expunged from the queue, or new experiments can be spawned. (k) The results from open-loop and closed-loop experiments are available for review by the scientist.**

in the two chlorinated solvents. In the absence of 0.75% ethanol in $CHCl_3$, the reaction essentially failed, while the presence of 0.75% ethanol in $CHCl_3$ or CH_2Cl_2 gave smooth reaction and TMP was obtained in 31% yield. Thus, BF_3−ethanol cocatalysis provides for efficient formation of TMP.[12]

The conditions we identified for the synthesis of TMP involved a 1-h room-temperature condensation of 10 mM mesitaldehyde and pyrrole in $CHCl_3$ (containing 0.75%

(12) Lindsey, J. S.; Wagner, R. W. *J. Org. Chem.* **1989**, *54*, 828−836.

Scheme 1. **Two−step one−flask synthesis of *meso*−tetramesitylporphyrin (TMP)**



ethanol) with 3.3 mM $BF_3{\cdot}O(Et)_2$ (Scheme 1). The yields determined manually were 31% and 13% at 10 and 100 mM reactants, respectively.[12] While these conditions are satisfactory for preparing small quantities of TMP, for preparative purposes we sought higher reaction concentrations. In early studies of the concentration dependence with benzaldehyde and pyrrole, we found that the yield of tetraphenylporphyrin peaks at 10 mM reactants, falling off significantly upon reaching 100 mM reactants.[10] We subsequently found that the decline in yield with higher reactant concentrations could be partially offset with higher acid catalyst concentrations ($BF_3{\cdot}O(Et)_2$ or trifluoroacetic acid).[13] Thus, an exploration of conditions for a high-concentration synthesis must carefully explore the effects of acid catalyst concentration. In the synthesis of TMP, this exploration is complicated because the acid catalysis involves interaction of $BF_3{\cdot}O(Et)_2$ and ethanol in an undefined way.

The mechanistic basis of BF_3−ethanol cocatalysis is not known. Several noteworthy observations are as follows. (1) The BF_3−ethanol cocatalysis conditions discovered for mesitaldehyde have proved effective for aryl aldehydes bearing a variety of alkyl or alkoxy substituents at the 2,6-positions.[14] (2) The use of EtOD in the presence of $BF_3{\cdot}O(Et)_2$ causes deuteration of porphyrins at the β-positions under the mild conditions of the pyrrole−aldehyde condensation, suggesting the formation of a new Bronsted acid.[15] Whether such a Bronsted acid is involved in catalyzing the pyrrole−mesitaldehyde condensation is not known. (3) Examination of the reaction of 2,6-dimethyl-4-cyanobenzaldehyde and pyrrole led to the observation that only trace quantities of ethanol were required for effective cocatalysis.[16] The porphyrin yield exhibited a sharply poised requirement for one-tenth the amount of ethanol as used with mesitaldehyde. These observations prompted us to perform a comprehensive exploration of the scope of BF_3−ethanol cocatalysis conditions in the synthesis of TMP. This broad study has been facilitated by use of the automated chemistry workstation.

In this paper, we report application of the automated chemistry workstation to investigate conditions that span a very large range of concentrations of $BF_3{\cdot}O(Et)_2$ and ethanol in the synthesis of TMP. The conditions include those that are useful for preparative applications, especially with increasing concentrations of mesitaldehyde and pyrrole, as well as conditions that are not preparatively useful (i.e., give low yields) but that may help to delineate the scope of cocatalytic effects. The reactions have been monitored over time in order to provide a database about reaction rates with diverse BF_3−ethanol cocatalysis conditions. These studies have been performed by examination of gridded search spaces, which can be examined efficiently using the parallel reaction capabilities of the automated chemistry workstation. The experimental grids are analogous to full factorial designs, but the results are displayed as empirically derived response surfaces without statistical analysis. A strategic searching routine also has been used to screen for other cocatalysts in the TMP reaction. Collectively, these experiments have yielded extensive data concerning the scope of cocatalysis in the synthesis of TMP. The results also illustrate the use of an automated chemistry workstation to address the types

(13) Lindsey, J. S.; MacCrum, K. A.; Tyhonas, J. S.; Chuang, Y. Y. *J. Org. Chem.* **1994**, *59*, 579−587.

(14) Lindsey, J. S. In *Metalloporphyrin-Catalyzed Oxidations*; Montanari, F., Casella, L., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1994; pp 49−86.

(15) Gross, Z.; Kaustov, L. *Tetrahedron Lett.* **1995**, *36*, 3735−3736.

(16) Steiger, B.; Anson, F. C. *J. Heterocycl. Chem.* **1997**, *34*, 269−272.

Table 1. **Experimental plan for a TMP-forming reaction**[a]

operation	start time	finish time	description of the command	duration
1	00:00:00	00:00:53	fill reaction vessel to 10.000 mL with $CHCl_3$[b]	00:53
2	00:00:53	00:01:44	transfer 0.028 mL of pyrrole to reaction vessel to make 10 mM	00:51
3	00:01:44	00:02:35	transfer 0.030 mL of mesitaldehyde to reaction vessel to make 10 mM	00:51
4	00:02:35	00:04:04	transfer 0.405 mL of ethanol to reaction vessel to make 1000 mM	01:29
5	00:04:04	00:04:56	transfer 0.032 mL of $BF_3{\cdot}O(Et)_2$ to reaction vessel to make 3.16 mM	00:52
6	00:04:56	00:06:07	wash transfer needle with DMSO	01:11
7	00:06:07	00:10:22	remove reaction aliquot, oxidize, and collect absorption spectrum	04:15
8	00:10:22	00:14:37	remove reaction aliquot, oxidize, and collect absorption spectrum	04:15
9	00:18:09	00:22:44	remove reaction aliquot, oxidize, and collect absorption spectrum	04:35
10	00:22:44	00:23:55	wash transfer needle with DMSO	01:11
11	00:33:24	00:37:59	remove reaction aliquot, oxidize, and collect absorption spectrum	04:25
12	01:03:09	01:07:44	remove reaction aliquot, oxidize, and collect absorption spectrum	04:35
13	03:03:09	03:07:44	remove reaction aliquot, oxidize, and collect absorption spectrum	04:35
14	03:07:44	03:08:55	wash transfer needle with DMSO	01:11

[a] For a complete experimental plan listing all individual commands, see Supporting Information. [b] The solvent volume actually delivered (assuming additivity of volumes) is such that the final volume after adding all reactants and reagents is 10.000 mL.

of challenging tasks faced on a daily basis by synthetic chemists and process development chemists.

Experimental Section

Materials. Ethanol-free $CHCl_3$ (Aldrich ACS spectrophotometric grade, stabilized with amylenes) was distilled from K_2CO_3. Materials from Aldrich (mesitaldehyde, anhydrous methanol, HPLC grade 2-methoxyethanol, 2,2,2-trifluoroethanol, *N*,*N*-diisopropylamine, anhydrous ethylene glycol, *tert*-butyl alcohol, *N*,*N*-diethylamine, dithiothreitol, $BF_3{\cdot}O(Et)_2$, DDQ), Fisher (THF and toluene, both of HPLC grade), and USP (absolute ethanol) were used as received. Pyrrole (Aldrich) was distilled from CaH_2, and stored samples were used prior to discoloration.

Workstation.[17−20] The automated chemistry workstation builds on the design of our previous workstation[5] as well as computer-aided design simulations for achieving high performance.[21] This workstation has been jointly developed by our group and by Scitec, U.S. (Wilmington, DE). The workstation hardware is outlined in Figure 1, and the software strategy is outlined in Figure 2. The lower limit for handling samples is 10 μL, and the accuracy for sample transfers is -1 μL in the range of 10−50 μL and -0.5 μL in the range of 50−100 μL. The reaction vessels are thermostated and individually stirred. Absorption spectra (Ocean Optics PC1000) were collected in THF. The experiment planner relies on a menu of commands that cause the workstation to dispense, transfer, mix, acquire spectra, and perform other miscellaneous operations. The experiment planner has been described in detail.[17−19]

Workstation Preparation. Mesitaldehyde and pyrrole (the "reactants") were always employed in equimolar amounts. Given a lower limit for handling samples of 10 μL, reactants were used as neat liquids for reactions at $\geq$27 mM, while reactions at 10 mM reactants employed a 3.6 M pyrrole stock solution and a 3.3 M mesitaldehyde stock solution. Similarly, ethanol was used in neat form or as a 1.7 M stock solution in toluene. Stock solutions of $BF_3{\cdot}O(Et)_2$ were prepared by diluting $BF_3{\cdot}O(Et)_2$ (8.1 M) to 0.1 or 4.1 M in toluene or $CHCl_3$. DDQ was used as a 0.05 M solution in THF. Stock solutions were used for two sets of experimental grids and then replaced. For reaction monitoring, samples were removed from the reaction vessels and mixed with excess DDQ (in THF), and then absorption spectra were collected. DDQ rapidly converts the porphyrinogen to the porphyrin (Scheme 1). Measurement of the absorption of the Soret band (λ_{max} = 420 nm, ϵ = 427 000 M^{-1} cm^{-1}) with appropriate baseline correction and knowledge concerning the reactant concentrations and dilution factors enables determination of the yield.[6] The candidate cocatalysts that are solids (phenol, dithiothreitol) were used as 3 M solutions in $CHCl_3$. The candidate cocatalysts that are liquids were used as neat liquids.

Experimental Grids. Planning the investigation of the experimental grids was accomplished with an experiment-planning module for factorial design and related combinatorial experiments.[19] An experimental plan is constructed for one experiment as shown in Table 1. In this plan, reaction vessels are charged with solvent, equimolar amounts of reactants (mesitaldehyde and pyrrole), and ethanol. Then $BF_3{\cdot}O(Et)_2$ is added to initiate the reaction. The final total volume of the reaction mixture is 10 mL. Absorption spectral data are obtained at Δt = 3, 7, 15, 30, 60, and 180 min from the start of the reaction (when $BF_3{\cdot}O(Et)_2$ is added). The reaction vessels are thermostated at 25 °C and are individually stirred. This experimental plan is analogous to that used previously.[22] This experimental plan is used repetitively in examining the experimental grid with automatic modification of designated parameters (concentrations of reactants, $BF_3{\cdot}O(Et)_2$, or ethanol). For our applications,

(17) Du, H.; Corkan, L. A.; Yang, K.; Kuo, P. Y.; Lindsey, J. S. *Chemom. Intell. Lab. Syst.*, submitted.
(18) Du, H.; Shen, W.; Kuo, P. Y.; Lindsey, J. S. *Chemom. Intell. Lab. Syst.*, submitted.
(19) Kuo, P. Y.; Du, H.; Corkan, L. A.; Yang, K.; Lindsey, J. S. *Chemom. Intell. Lab. Syst.*, submitted.
(20) Wagner, R. W.; Du, H.; Cork, D. G.; Yang, K.; Corkan, L. A.; Li, F.; Lindsey, J. S. Technical Report TR98-1; Department of Chemistry, North Carolina State University, Raleigh, NC, 1998.
(21) Lindsey, J. S.; Corkan, L. A. *Chemom. Intell. Lab. Syst.: Lab. Inf. Manage.* **1993**, *21*, 139−150.
(22) Corkan, L. A.; Plouvier, J.-C.; Lindsey, J. S. *Chemom. Intell. Lab. Syst.: Lab. Inf. Manage.* **1992**, *17*, 95−105.

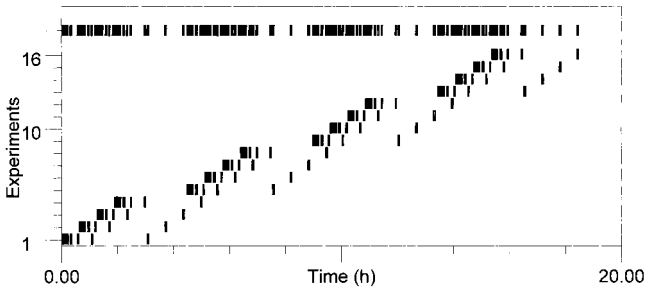


Figure 3. **Gantt chart showing a schedule of 16 experiments. The dark blocks indicate robot activity. The scheduler offsets the start time of experiments, thereby interleaving the individual operations. Note that the first block in each timeline encompasses the commands for additions of solvent and reagents, as well as two analysis procedures. The remaining four blocks are the subsequent analysis procedures. The robotic utilization, shown by the composite schedule at the top, is 51.1%.**

we have generally used 7 × 7, 4 × 4, or 3 × 3 experimental grids (as well as six data points over time for each reaction in the experimental grid). The experiment planner generates the plans for the reactions, and the scheduler interleaves the intact experimental plans in order to maximize parallelism.[17] A typical schedule of 16 reactions is displayed as a Gantt chart (Figure 3). The Gantt chart shows that, at most, four reactions are performed in parallel at any one time, and the duration of the 16 reactions comprising the experimental grid is 18.5 h. The response surfaces and contour plots were generated using Surfer 6.03 (Golden Software, Golden, CO).

Catalyst Screening Protocol. The Catalyst Screening 2.0 protocol was used to screen a set of candidates for catalytic activity.[18] This protocol is tailored for specific applications through a series of dialogue prompts. The screening algorithm is described in the text. Each candidate was used as a neat liquid or as a 3 M solution in $CHCl_3$. Stock solutions were diluted automatically as required to achieve the specified concentrations within the constraints of the liquid-handling system. Data points were collected at $t = 10$, 20, and 30 min following the addition of an aliquot of the candidate cocatalyst. The yield threshold for flagging catalytic activity was set at 5%.

Results and Discussion

1. Investigation of BF_3−Ethanol Cocatalysis. 1.1. Reactions at 10 mM Mesitaldehyde and Pyrrole. Our prior manual work employed mesitaldehyde and pyrrole at 10 mM in $CHCl_3$ (containing 0.75% ethanol, 130 mM) at room temperature. The addition of 3.3 mM $BF_3{\cdot}O(Et)_2$ gives TMP in 31% yield.[12] Other relevant observations include the following. (1) A 3-fold change in $BF_3{\cdot}O(Et)_2$ concentration can significantly alter the course of reaction and the yield of porphyrin.[12] (2) Concentrations of $BF_3{\cdot}O(Et)_2$ ranging from 1 to 316 mM have been examined.[13] To encompass and comprehensively explore these conditions, we sought a 1000-fold concentration range in each of the cocatalysts, with concentration increments of 3.16-fold. These objectives led to 7 × 7 experimental grids with $BF_3{\cdot}O(Et)_2$ ranging from 0.316 to 316 mM and ethanol ranging from 3.16 to 3160 mM.

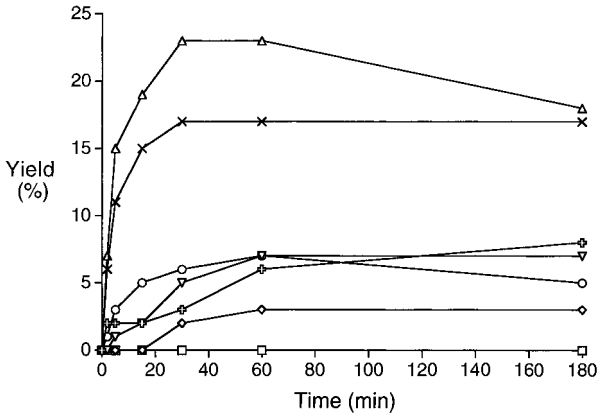


Figure 4. **Time course of TMP formation for seven reactions in $CHCl_3$ at 25 °C with 10 mM reactants, 10 mM $BF_3{\cdot}O(Et)_2$, and various amounts of ethanol. [EtOH]: ✣, 3.16 M; ▽, 1.00 M; ×, 3.16 mM; △, 100 mM; ○, 31.6 mM; ◇, 10.0 mM; □, 3.16 mM.**

The mesitaldehyde−pyrrole reactions were performed in $CHCl_3$ stabilized with amylenes (rather than ethanol). The reactions were automatically initiated and monitored over a 3-h period. In general, reactions using 0.316−10 mM $BF_3{\cdot}O(Et)_2$ gave yields that increased steadily over the 3-h monitoring range, while reactions with 31.6−316 mM $BF_3{\cdot}O(Et)_2$ gave yields that passed through a maximum in 15−30 min and then declined over 3 h. The decrease in yield over time indicates reaction processes that degrade the porphyrinogen.[23] Figure 4 shows the yield versus time plots for the seven reactions performed using 10 mM $BF_3{\cdot}O(Et)_2$ and ethanol ranging from 3.16 to 3160 mM. The highest yield obtained at any time in each of the 49 reactions was used to generate the response surface shown in Figure 5.[24] The response surface reveals that the highest yield obtained is 28% with 3.16 mM $BF_3{\cdot}O(Et)_2$ and 100 mM ethanol. This is generally in accord with our previous findings for the reaction at 10 mM mesitaldehyde and pyrrole, where 3.33 mM $BF_3{\cdot}O(Et)_2$ and 130 mM ethanol afforded a 31% yield of TMP.

To further investigate the optimal reaction conditions, we examined a fine-grained 3 × 3 grid centered at the apex of the response surface of the 7 × 7 grid shown in Figure 5. The reaction was examined over a 3.16-fold range of $BF_3{\cdot}O(Et)_2$ and ethanol concentrations (with 1.78-fold intervals). The highest yields obtained from each experiment in the 3 × 3 grid are shown superimposed on those from the 7 × 7 grid (Figure 6). The yields match closely. The highest TMP yield (26%) was again observed with 3.16 mM $BF_3{\cdot}O(Et)_2$ and 100 mM ethanol.

1.2. Reactions at Higher Concentrations of Mesitaldehyde and Pyrrole. With mesitaldehyde and pyrrole

(23) Li, F.; Yang, K.; Tyhonas, J. S.; MacCrum, K. A.; Lindsey, J. S. *Tetrahedron* **1997**, *53*, 12339−12360.

(24) The highest yield obtained at any time during the reaction is plotted for two reasons. (1) Some of the reaction yields pass through a maximum and then decline; in these cases, reporting the yield at long times does not accurately reflect the effectiveness of the cocatalysis conditions in giving TMP. In addition, the reactions in different regions of the search space proceed at different rates and plateau or pass through respective maxima at different times. (2) The highest yield is generally of greatest interest from a preparative standpoint. Note that all data are available in tabular form in the Supporting Information and can be used to plot other response surfaces.

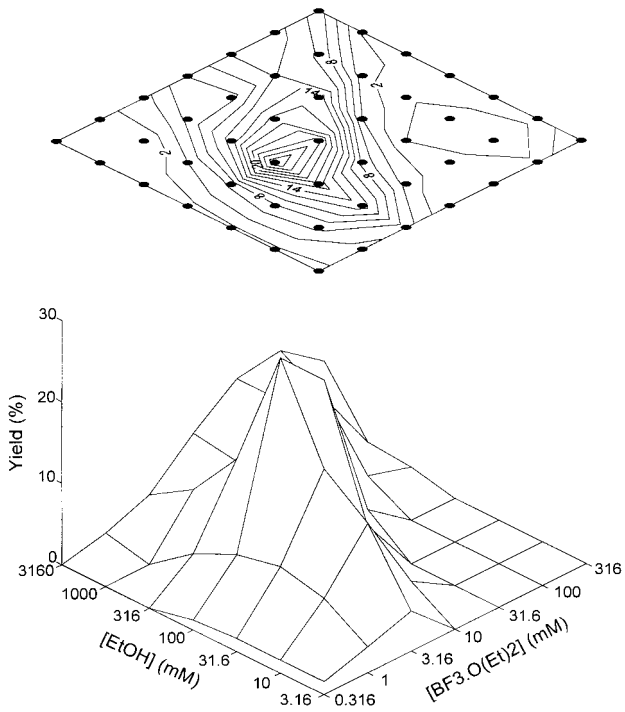


Figure 5. **Response surface from the 7 × 7 experimental grid of the reaction of mesitaldehyde and pyrrole at 10 mM in $CHCl_3$ at 25 °C. The highest yields at any time are shown. The contour plot at the top shows computer-fitted isoyield lines.**

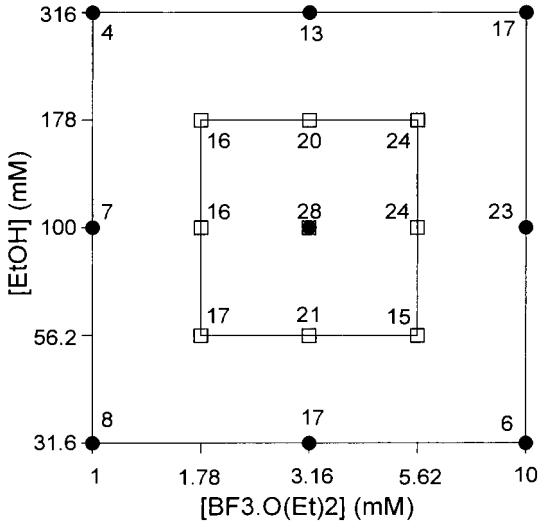


Figure 6. **Superposition of the results from two experimental grids. Open squares are the points from the fine-grained 3 × 3 grid of mesitaldehyde and pyrrole at 10 mM in $CHCl_3$ at 25 °C. Closed circles are the relevant points in the corresponding coarse-grained 7 × 7 grid. The highest yield from each reaction is shown.**

concentrations each at 27, 73, or 200 mM, the reaction was examined over a 1000-fold range of $BF_3{\cdot}O(Et)_2$ and ethanol concentrations (identical search space with the 10 mM reactions). Thus, three 7 × 7 experimental grids were examined using the general experimental plan shown in Table 1, with appropriate changes in reactant concentration. These reactions also afforded yields that decreased after 15−30 min at high $BF_3{\cdot}O(Et)_2$ concentrations (>10 mM $BF_3{\cdot}O(Et)_2$ for 27 mM reactions, >100 mM for 73 and 200 mM reactions). The decline in yield over time indicates the presence of

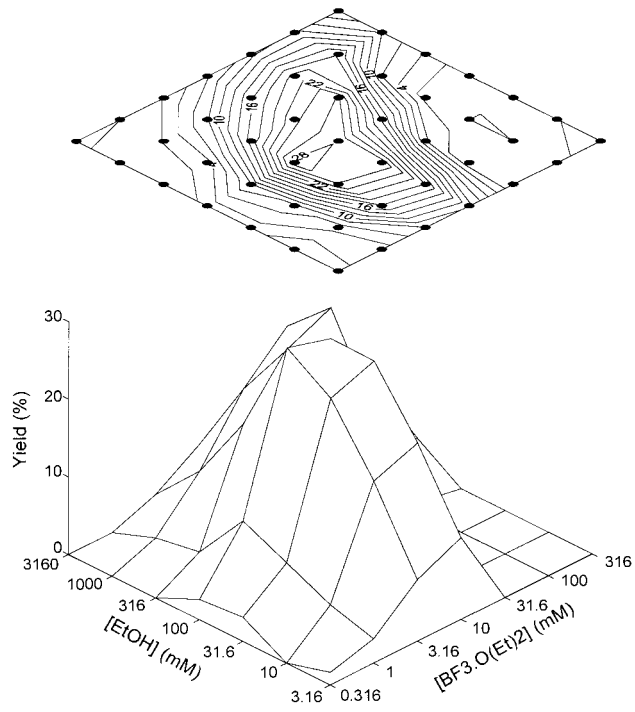


Figure 7. **Response surface from the 7 × 7 experimental grid of the reaction of mesitaldehyde and pyrrole at 27 mM in $CHCl_3$ at 25 °C. The highest yields at any time are shown. The contour plot at the top shows computer-fitted isoyield lines.**

deleterious side reactions in the condensation process. Following each 7 × 7 coarse-grained search, a fine-grained 3 × 3 grid was examined around the apex of the 7 × 7 response surface. The coarse-grained 7 × 7 response surfaces (displaying the highest yields at any time) are shown for the reactions at 27 (Figure 7), 73 (Figure 8), and 200 mM reactants (Figure 9). The results from examining these six experimental grids are listed in Table 2. A significant finding upon comparing these data is that the ethanol:$BF_3{\cdot}O(Et)_2$ ratio affording the highest yield changes from 32 to 1−1.8 as the reactants are increased from 10 to 200 mM (Table 2).

The response surfaces at t = 3, 7, 30, and 180 min from the reactions with 73 mM mesitaldehyde and pyrrole and various amounts of $BF_3{\cdot}O(Et)_2$ and ethanol are shown in Figure 10. Three key features emerge upon examining these kinetic data. (1) The isoyield lines generally exhibit a concentric pattern with low yields toward the corners of the search space, indicating again that both $BF_3{\cdot}O(Et)_2$ and ethanol are required for catalysis. (2) The reaction is quite fast, with yields >15% achieved in 3 min. The yields steadily increased over 180 min for all regions of the contour surface except the corner having the highest concentrations of both $BF_3{\cdot}O(Et)_2$ and ethanol, where the yields passed through a maximum and then declined. (3) As time progresses, the peak in the response surface shifts toward lower total amounts of $BF_3{\cdot}O(Et)_2$ and ethanol. However, the ratio of ethanol:$BF_3{\cdot}O(Et)_2$ that affords the highest yield at any time remains constant at 5.6-fold. The shift of the peak in the response surface is a consequence of a slower reaction with lesser amounts of $BF_3{\cdot}O(Et)_2$ and ethanol, as well as a leveling off of the reaction after 30 min with the

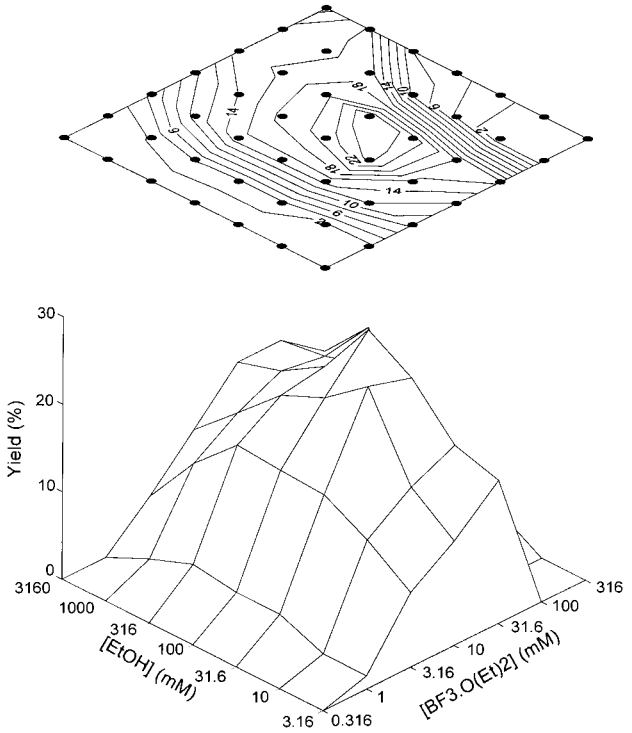


Figure 8. **Response surface from the 7 × 7 experimental grid of the reaction of mesitaldehyde and pyrrole at 73 mM in $CHCl_3$ at 25 °C. The highest yields at any time are shown. The contour plot at the top shows computer-fitted isoyield lines.**

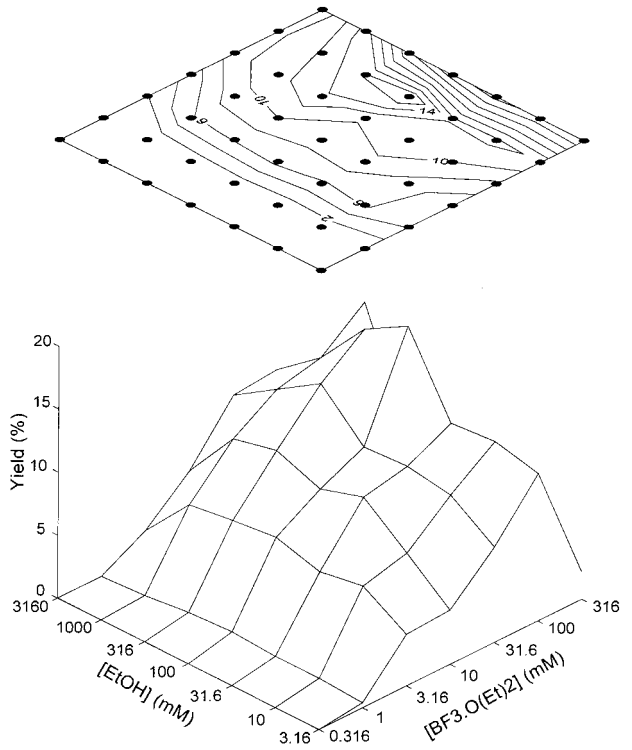


Figure 9. **Response surface from the 7 × 7 experimental grid of the reaction of mesitaldehyde and pyrrole at 200 mM in $CHCl_3$ at 25 °C. The highest yields at any time are shown. The contour plot at the top shows computer-fitted isoyield lines.**

higher amounts of $BF_3{\cdot}O(Et)_2$ and ethanol. The kinetic trends observed for the reaction at 73 mM mesitaldehyde and pyrrole were generally also observed for the other mesitaldehyde and pyrrole concentrations.

Table 2. **Concentrations of $BF_3{\cdot}O(Et)_2$ and ethanol affording the highest yields of TMP[a]**

[reactants][c] (mM)	optimal concentrations (mM)[b]		[EtOH]/	TMP yield	time
	$BF_3{\cdot}O(Et)_2$	EtOH	$[BF_3{\cdot}O(Et)_2]$	(%)	(min)[d]
10[e]	3.3	130	40	25	60
10	3.16	100	32	26	180
27	5.62	56.2	10	34	180
73	17.8	100	5.6	28	180
200	56.2	56.2, 100	1, 1.8	20	30−60

[a] Each reaction was performed in 10 mL of $CHCl_3$ stabilized with amylenes at 25 °C. Data points were collected at Δt = 3, 7, 15, 30, 60, and 180 min after the addition of the $BF_3{\cdot}O(Et)_2$. [b] Concentration affording the highest yield in the search. [c] The concentration of mesitaldehyde and pyrrole. [d] The time at which the maximum yield was obtained. [e] Performed manually in CH_2Cl_2.

The results from the various experimental grids are best compared in Figure 11, which shows the concentrations of $BF_3{\cdot}O(Et)_2$ and ethanol that gave yields within three-fourths of the highest yield for a given mesitaldehyde and pyrrole concentration. This graph illustrates two important observations. (1) Each of these 75% cutset scatter plots includes at least six data points covering a significant portion of the search space, illustrating the robustness of the pyrrole−mesitaldehyde condensation conditions toward slight changes in $BF_3{\cdot}O(Et)_2$ and ethanol concentrations. Specifically, the ethanol and $BF_3{\cdot}O(Et)_2$ concentrations can each be varied from 1.78- to 10-fold and still obtain TMP in a yield within three-fourths that of the highest yield observed for a given concentration of mesitaldehyde and pyrrole. (2) As the reaction concentration increases, the highest yield of TMP is obtained by a significant increase in the concentration of $BF_3{\cdot}O(Et)_2$ but with no increase in the ethanol concentration. The ethanol:$BF_3{\cdot}O(Et)_2$ ratio declines from 32 to less than 2 on going from reactants at 10−200 mM, as listed in Table 2.

2. Catalyst Screening Experiments. Prior manual work showed that cocatalysis in the mesitaldehyde−pyrrole condensations is not limited to ethanol but can encompass other proton donors such as acetic acid,[12] *tert*-butyl alcohol,[12] or methanol[25] (though acetic acid and *tert*-butyl alcohol gave quite low yields). To screen for cocatalysts that are effective with $BF_3{\cdot}O(Et)_2$ in catalyzing the formation of TMP, we developed catalyst searching protocols.[18,22] The catalyst searching protocols make use of the adaptive features of the workstation, where data from an ongoing experiment are used to alter the experiment in progress as well as to plan new experiments. In the protocol used herein (Catalyst Screening 2.0),[18] reactants and $BF_3{\cdot}O(Et)_2$ are added to CH_2Cl_2 in a reaction vessel, and then an aliquot of the test cocatalyst is added. If the yield is below a preset threshold at the end of an appropriate wait period, an additional aliquot of the test cocatalyst is added to the reaction vessel, and monitoring is continued for an additional wait period. This process is repeated until the entire concentration range of the cocatalyst has been stepped through or the yield has reached the threshold. Then the next candidate cocatalyst is tested in a new reaction vessel, and this screening process is continued

(25) Kihn-Botulinski, M.; Meunier, B. *Inorg. Chem.* **1988**, *27*, 209−210.

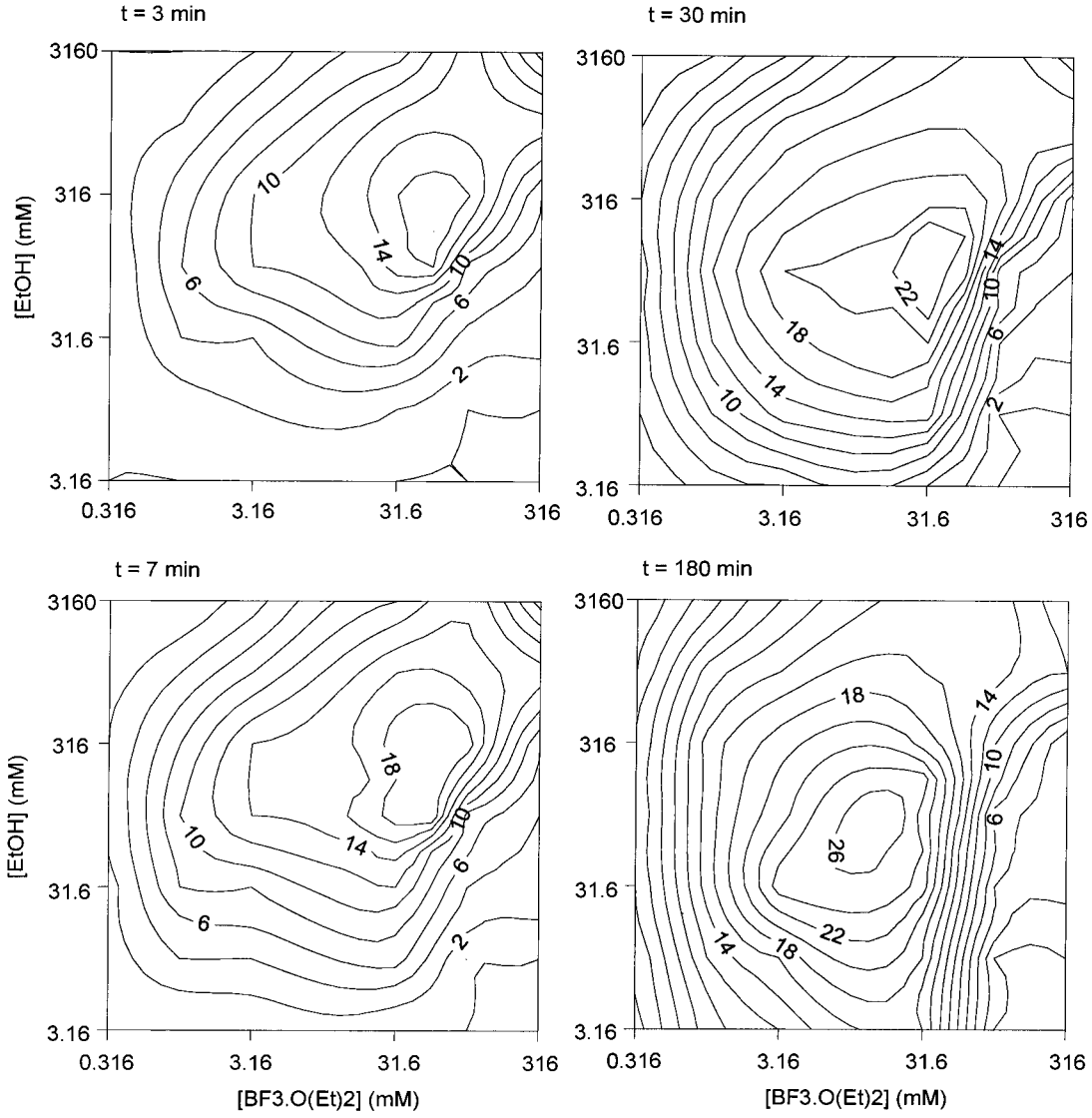


Figure 10. **Response surfaces obtained at selected times from the reactions with 73 mM mesitaldehyde and pyrrole and various amount of $BF_3{\cdot}O(Et)_2$ and ethanol at 25 °C in $CHCl_3$. The contour plots show computer-fitted isoyield lines. Note the yields of ~16% at $t = 3$ min, and the shift of the peak in the response surface along the diagonal at $t = 30$ min.**

until all candidates are examined. Those candidates that reach the threshold are flagged as effective cocatalysts, the concentration at which the threshold is reached is noted, monitoring is discontinued, and the next candidate is examined.

The catalyst screening protocol has been used to screen 12 candidate cocatalysts in conjunction with $BF_3{\cdot}O(Et)_2$ in the TMP-forming reaction (Table 3). The candidate cocatalysts were screened over a range of 3.16−1000 mM, with mesitaldehyde and pyrrole concentrations of 10 mM, and $BF_3{\cdot}O(Et)_2$ at 3.16 mM in $CHCl_3$. Data points were collected at $t = 10$, 20, and 30 min following the addition of an aliquot of the candidate cocatalyst. The threshold for catalytic activity was set equal to a 5% yield of TMP. The candidates identified with catalytic activity (methanol, pK_a 15.5; 2-methoxyethanol, pK_a 14.8; ethylene glycol, pK_a 14.2) have pK_a values resembling that of ethanol (15.9).[26] Those that failed to meet the 5% threshold can be categorized as more acidic than ethanol (trifluoroacetic acid, acetic acid, 2,2,2-trifluoroethanol, phenol), more hindered than ethanol (2-propanol, *tert*-butyl alcohol), or containing thiol or amino functional groups. Though the catalyst screening protocol is an inherently serial algorithm, each candidate cocatalyst was screened for activity across a reasonable concentration range in less than 3 h, and the survey required 36 h in total.

Prompted by the positive response of the catalyst searching experiments for methanol, ethylene glycol, and 2-methoxyethanol, we investigated experimental grids involving these three alcohols. Each experimental grid was selected on the basis of the concentration at which activity was observed in the catalyst screening protocol. In so doing, an anomaly was noted for ethylene glycol.[27] The results are shown in Table 4. 2-Methoxyethanol (26%) and ethylene glycol (24%) gave yields comparable to those with ethanol (25%), while methanol was less active (19%). The time evolution of TMP formation and the response surfaces due

(26) Riddick, J. A.; Bunger, W. A. *Organic Solvents*, 3rd ed.; Wiley-Interscience: NY, 1970.

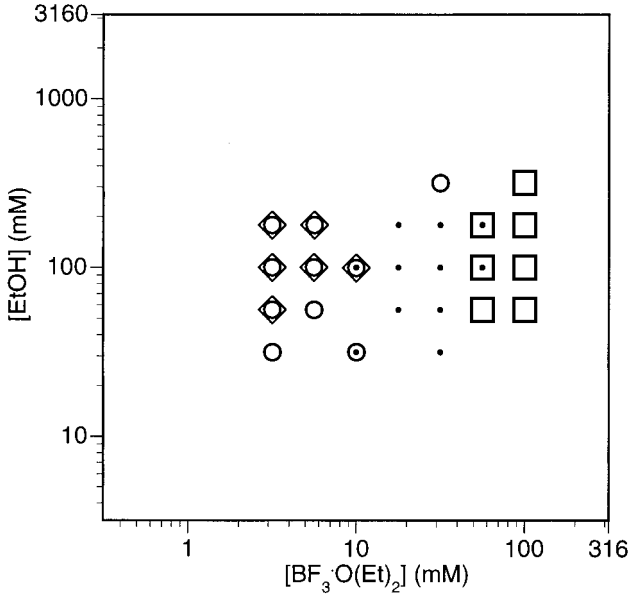


Figure 11. **Comparison of the 75% cutset data for reactions of mesitaldehyde and pyrrole at different concentrations (abstracted from the response surfaces in Figures 5, 7−9). As the concentration of reactants increases, the highest yields are obtained with increasing amounts of BF_3·O(Et)$_2$ while the concentration of ethanol remains relatively constant. The entire region examined in the experimental grids is displayed. Legend: 10 (◇); 27 (○), 73 (●), and 200 mM (□).**

to cocatalysis with methoxyethanol resemble those with ethanol. These data show that BF_3−ROH cocatalysis of the mesitaldehyde−pyrrole condensation is not restricted to ethanol but can be achieved with several alcohols of related structure and acidity.

Conclusions

Through the use of an automated chemistry workstation, we have now performed a comprehensive study of the reaction conditions for forming TMP with mesitaldehyde and pyrrole concentrations ranging from 10 to 200 mM. Altogether, 11 experimental grids comprising 284 reactions were examined over a 10-week period, yielding 1704 data points. Where comparisons can be made, the yield data are nearly identical in the automated and manual studies. While no yield improvement has been achieved, several new insights have been obtained. (1) As the reactant concentration increases, the amount of BF_3·O(Et)$_2$ required for reaction increases steadily, while the amount of ethanol remains essentially constant. In particular, the ethanol:BF_3·O(Et)$_2$ ratio affording the highest yield changes from 32 to 1−1.8 as the reactants are increased in concentration from 10 to 200 mM. By using the optimal amounts of BF_3·O(Et)$_2$ and ethanol, a relatively constant 25% to ∼30% yield of TMP can be obtained as the reactant concentrations are increased from 10 to 73 mM. (2) As time progresses, the peak in the response surface shifts toward lower total amounts of BF_3·O(Et)$_2$ and ethanol, but the ratio of BF_3·O(Et)$_2$ and ethanol that affords the highest yield at any time remains constant for a given concentration of reactants. (3) The reaction at 73 mM reactants is quite fast, with yields >15% achieved in 3 min, but 28% attained only after 180 min. (4) The response surface for BF_3·O(Et)$_2$−ethanol cocatalysis is somewhat broad for the mesitaldehyde and pyrrole concentrations examined. For example, at 73 mM, the ethanol and BF_3·O(Et)$_2$ concentrations can each be varied by 5.6-fold and still give TMP in 21−28% yield, which is within three-fourths that of the highest yield (28%) observed. Thus, unlike the results with 2,6-dimethyl-4-cyanobenzaldehyde and pyrrole,[16] the reaction of mesitaldehyde and pyrrole does not require sharply poised concentrations of BF_3·O(Et)$_2$ and ethanol. The comprehensive set of data accumulated herein establishes the scope of BF_3−ethanol cocatalysis in the synthesis of TMP and should be useful for planning syntheses

Table 3. **Cocatalyst screening results[a]**

	total concentration of cocatalyst (mM)					
candidate cocatalyst	3.16	10	31.6	100	316	1000
trifluoroacetic acid	−	−	−	−	−	−
acetic acid	−	−	−	−	−	−
phenol	−	−	−	−	−	−
2,2,2-trifluoroethanol	−	−	−	−	−	−
methanol	−	+				
ethanol	−	+				
2-methoxyethanol	−	−	+			
ethylene glycol	+[b]					
2-propanol	−	−	−	−	−	−
tert-butyl alcohol	−	−	−	−	−	−
dithiothreitol	−	−	−	−	−	−
N,*N*-diethylamine	−	−	−	−	−	−
N,*N*-diisopropylamine	−	−	−	−	−	–

[a] Each reaction was performed in 10 mL $CHCl_3$ at 25 °C. The − symbols indicate yields below threshold; the + symbols indicate the concentration of the cocatalyst at which the 5% TMP yield threshold was reached. Monitoring was discontinued when the threshold was reached. [b] The activity observed with ethylene glycol is anomalously high.[27]

Table 4. **Concentrations of BF_3·O(Et)$_2$ and ROH affording the highest yields of TMP[a]**

	optimal concentrations (mM)			TMP	
ROH	BF_3·O(Et)$_2$	ROH	[ROH]/[BF_3·O(Et)$_2$]	yield (%)	time (min)[b]
methanol[c]	10	316	32	19	60
2-methoxyethanol[d]	10	316	32	26	60
ethylene glycol[e]	10	31.6	3.2	24	180
ethanol[f]	3.16	100	32	25	60

[a] Each reaction was performed with 10 mM mesitaldehyde and pyrrole in 10 mL of $CHCl_3$ at 25 °C. Data points were collected at Δt = 3, 7, 15, 30, 60, and 180 min after the addition of BF_3·O(Et)$_2$. [b] Time at which the maximum yield was obtained. [c] A 4 × 5 grid with the [BF_3·O(Et)$_2$] spanning 3.16−100 mM and the [ROH] spanning 10−1000 mM. [d] A 4 × 4 grid with the [BF_3·O(Et)$_2$] spanning 3.16−100 mM and the [ROH] spanning 31.6−1000 mM. [e] A 4 × 4 grid with the [BF_3·O(Et)$_2$] spanning 3.16−100 mM and the [ROH] spanning 3.16−100 mM. [f] From Table 2.

(27) An anomaly with ethylene glycol became apparent during the course of this work. The catalyst screening protocol identified ethylene glycol as an active cocatalyst at 3.16 mM. During manual preparation of the stock solutions for the experimental grids, we noted that ethylene glycol was not soluble in $CHCl_3$, and we elected to use acetonitrile as the stock solution solvent. The resulting experimental grids showed that ethylene glycol had little activity at 3.16 mM (but was active at 31.6 mM). Thus, the activity observed at 3.16 mM in the catalyst screening program is a false positive, originating with the automated dilution procedures in the catalyst screening program (which prepared diluted stock solutions of candidates as needed in $CHCl_3$). The resulting stock solution of ethylene glycol was undoubtedly biphasic, leading to delivery of an amount of ethylene glycol in excess of the required 3.16 mM target solution. This anomaly highlights a pitfall of automation that at present can only be overcome through user vigilance.

as well as in studies aimed at elucidating the mechanism(s) of catalysis.

Acknowledgment

This work was supported by Takeda Chemical Industries, Ltd. (Osaka, Japan) and the NIH (GM36238).

Supporting Information Available

A complete experimental plan for investigating one of the reactions in the experimental grids, a complete table of data for each of the 11 experimental grids, and response surfaces for the experimental grids with the cocatalysts methanol, 2-methoxyethanol, and ethylene glycol (23 pages). See any current masthead page for ordering and Internet access instructions.

Received for review May 26, 1998. Accepted October 2, 1998.

OP9800459