An Efficient One-Flask Synthesis of N-Confused Tetraphenylporphyrin

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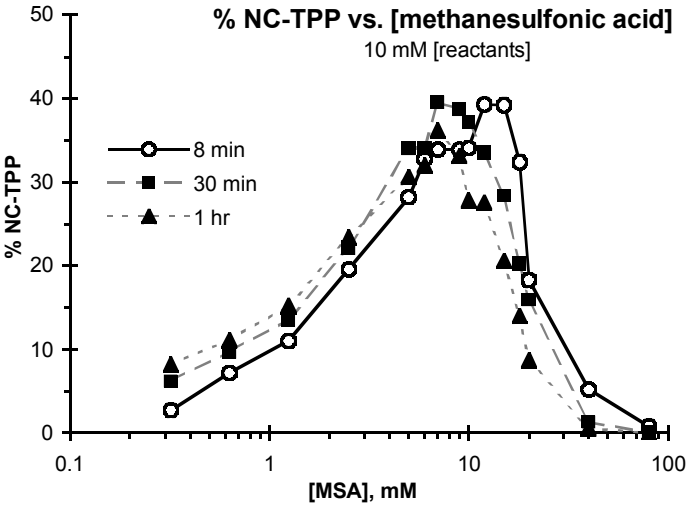
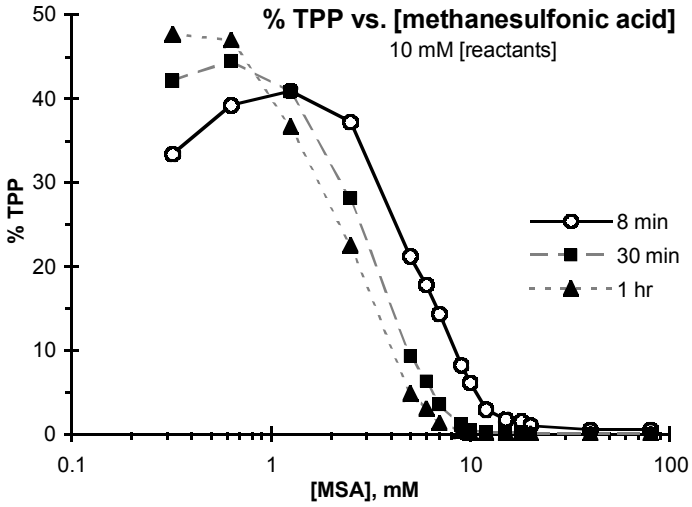
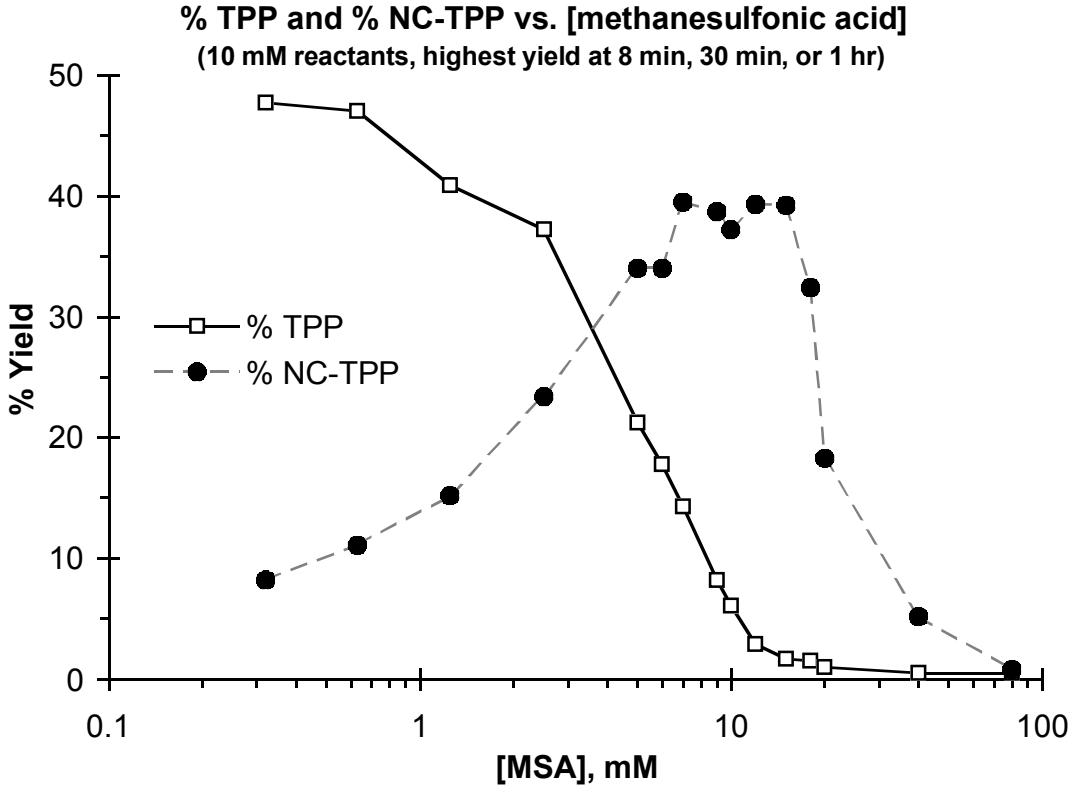
Supporting Information

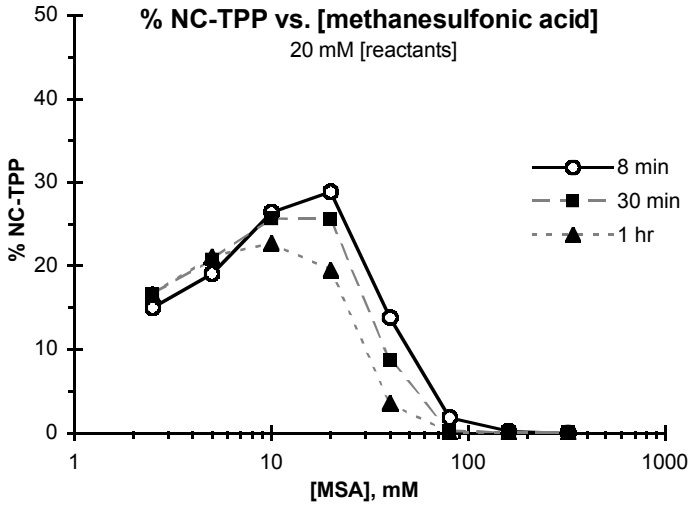
NC-TPP and TPP yields as a Function of MSA Concentration with 10 mM Reactants.

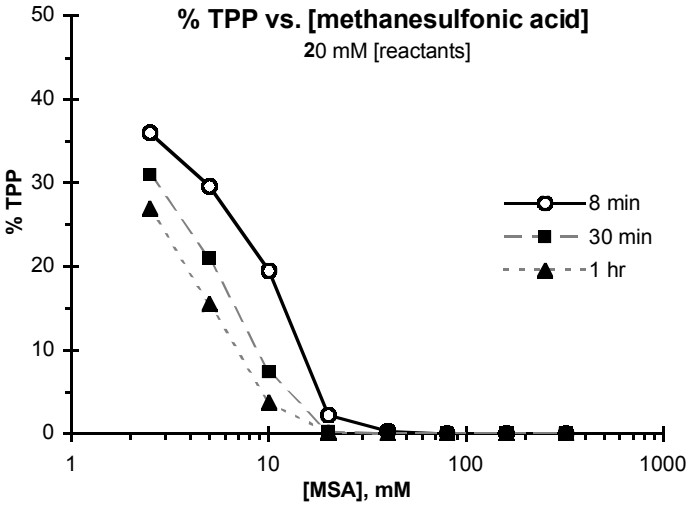


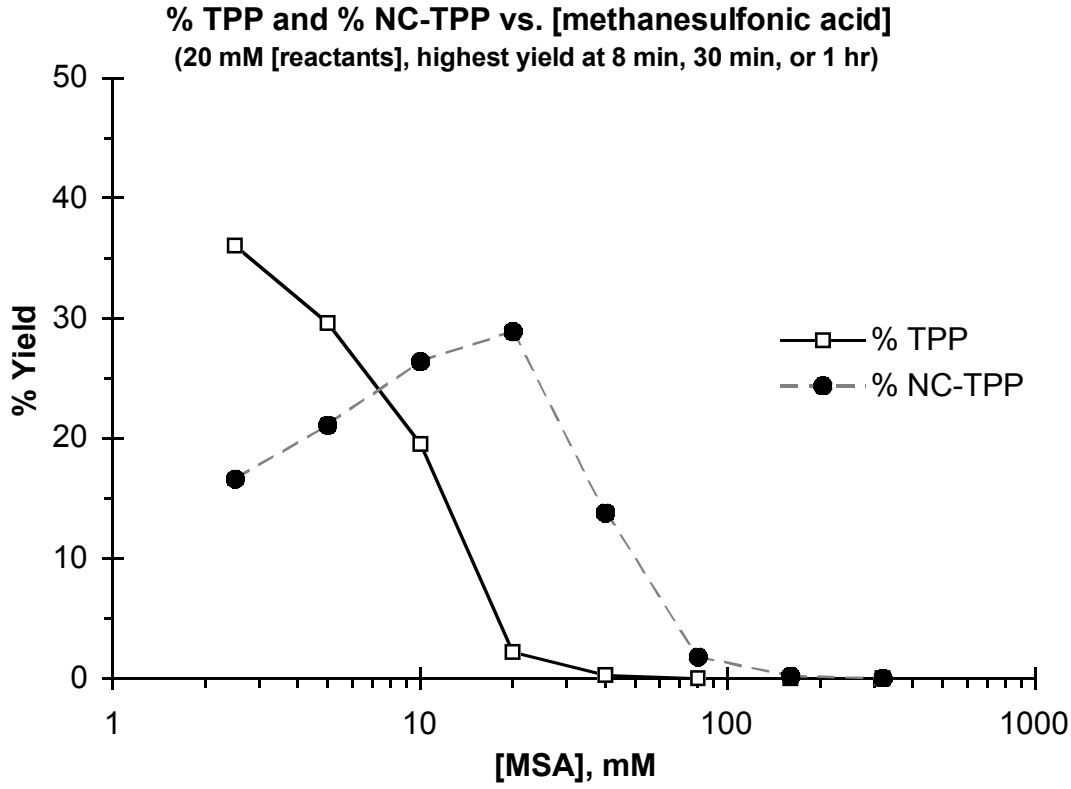




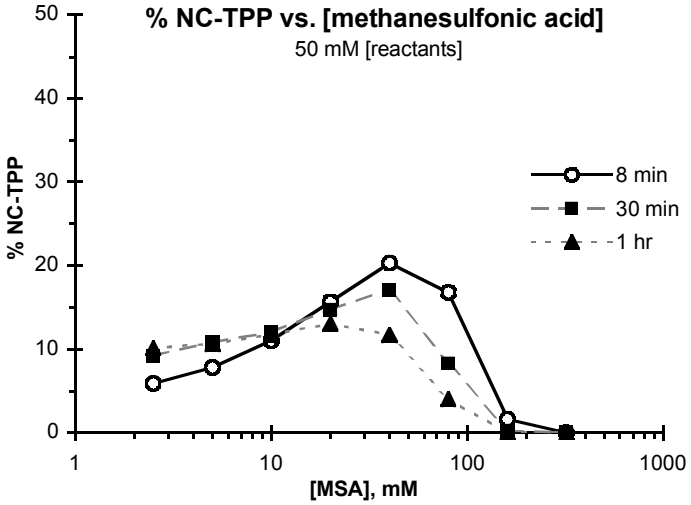
NC-TPP and TPP yields as a Function of MSA Concentration with 20 mM Reactants.

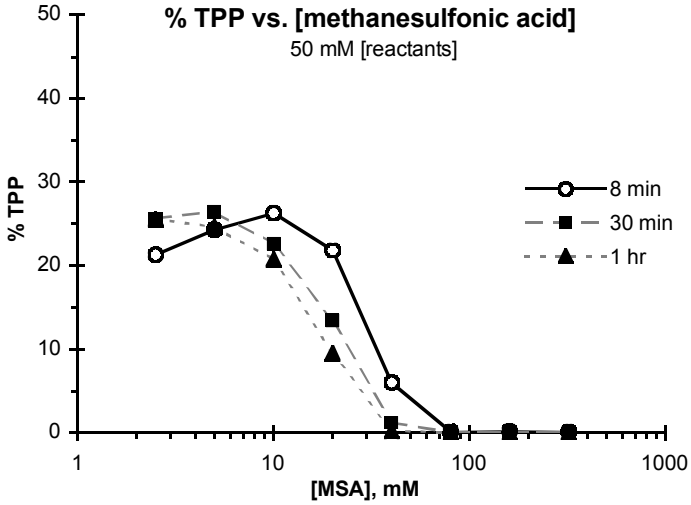


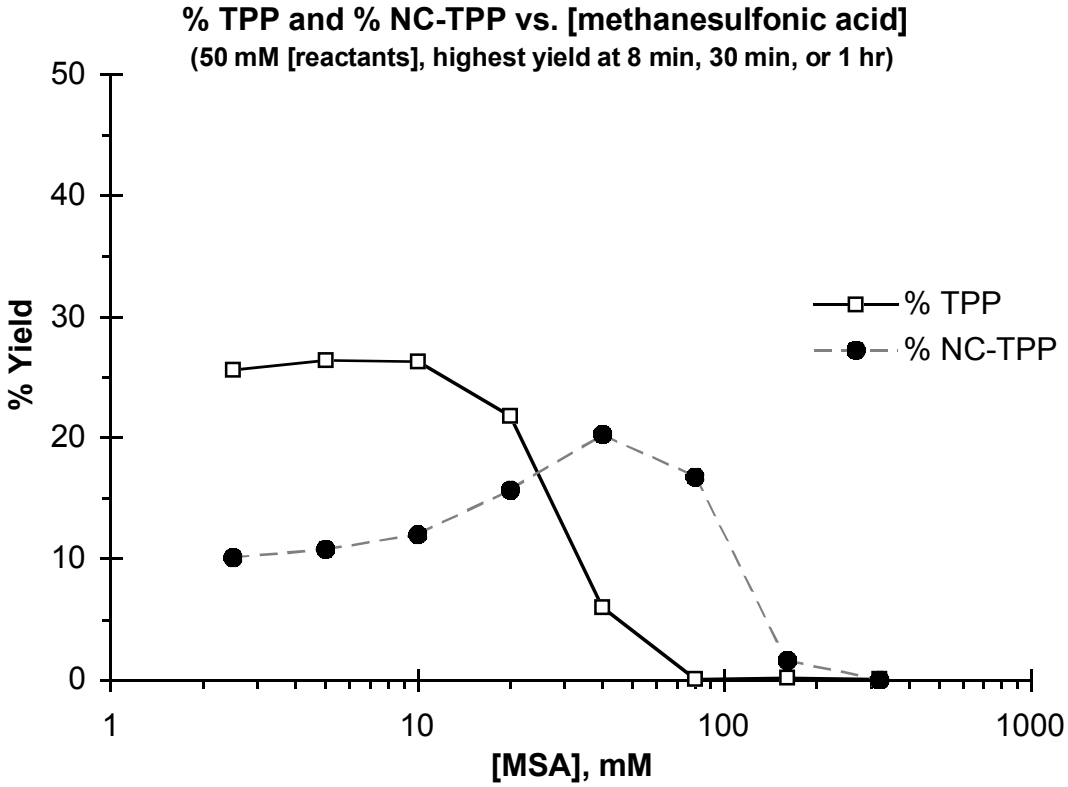




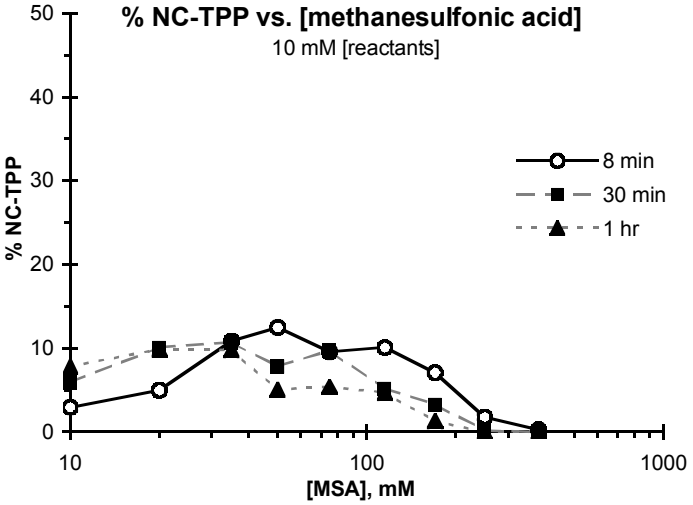
NC-TPP and TPP yields as a Function of MSA Concentration with 50 mM Reactants.

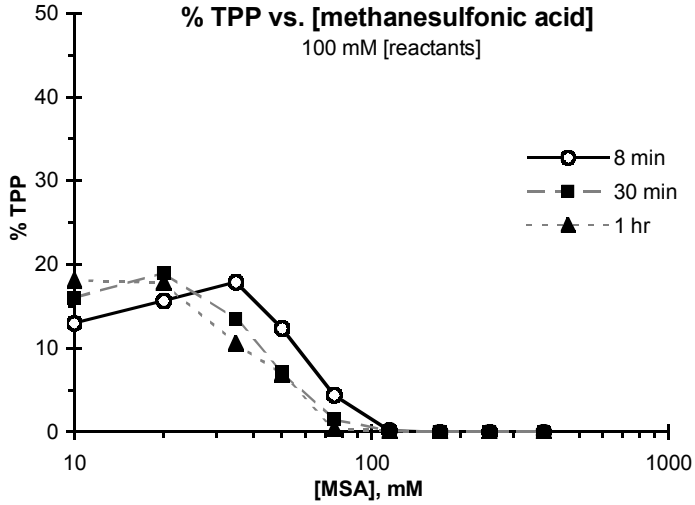


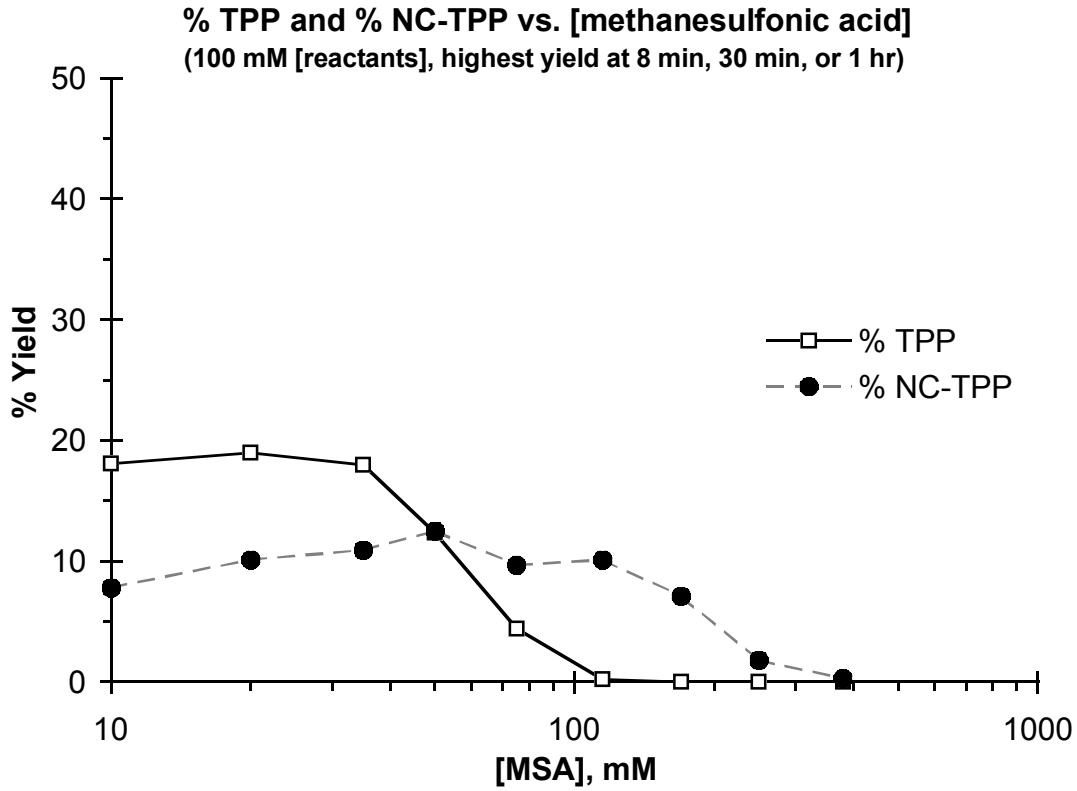




NC-TPP and TPP yields as a Function of MSA Concentration with 100 mM Reactants.







Treatment of a Single Reactant with MSA Prior to Addition of the Second Reactant. Experiments were performed probing the effect of MSA reaction with a single reactant (pyrrole or benzaldehyde) prior to addition of the second reactant on TPP and NC-TPP yields. The first reactant was added followed by MSA. After some reaction time (T_1) the second reactant was added and in some cases an additional aliquot of MSA also was added. The reaction was then monitored (T_2). The experiments were performed at 10 mM reactants.

First reactant	[MSA], mM	T_1, min	Additional [MSA], mM	T_2, min	% NC-TPP	% TPP
pyrrole	7	0	0	8	33	13
pyrrole	7	0	0	30	38	3
pyrrole	7	0	0	60	34	1
pyrrole	7	5	0	8	13	12
pyrrole	7	5	0	30	11	5
pyrrole	7	5	0	60	12	3
pyrrole	7	15	0	8	5	11
pyrrole	7	15	0	30	3	7
pyrrole	7	15	0	60	2	4
pyrrole	7	30	0	8	3	9
pyrrole	7	30	0	30	1	4
pyrrole	7	30	0	60	0.5	2
pyrrole	1.25	5	5.75	8	34	10
pyrrole	1.25	5	5.75	30	34	2
pyrrole	1.25	5	5.75	60	26	1
pyrrole	1.25	15	5.75	8	30	10
pyrrole	1.25	15	5.75	30	30	3
pyrrole	1.25	15	5.75	60	23	1
pyrrole	1.25	30	5.75	8	29	11
pyrrole	1.25	30	5.75	30	25	3
pyrrole	1.25	30	5.75	60	23	1
pyrrole	1.25	0	0	8	11	41
pyrrole	1.25	0	0	30	14	41
pyrrole	1.25	0	0	60	15	37
pyrrole	1.25	5	0	8	12	40
pyrrole	1.25	5	0	30	13	37
pyrrole	1.25	5	0	60	12	34
pyrrole	1.25	15	0	8	10	37
pyrrole	1.25	15	0	30	11	37
pyrrole	1.25	15	0	60	11	33
pyrrole	1.25	30	0	8	8	37
pyrrole	1.25	30	0	30	7	35
pyrrole	1.25	30	0	60	9	34
benzald.	7	0	0	8	33	13
benzald.	7	0	0	30	38	3
benzald.	7	0	0	60	34	1
benzald.	7	5	0	8	32	14
benzald.	7	5	0	30	36	4
benzald.	7	5	0	60	26	2
benzald.	7	15	0	8	32	14
benzald.	7	15	0	30	34	4
benzald.	7	15	0	60	31	2
benzald.	7	30	0	8	35	13
benzald.	7	30	0	30	34	4
benzald.	7	30	0	60	28	2

Addition of MSA to a solution containing only pyrrole, followed by addition of benzaldehyde, provided a decreased yield of NC-TPP. The higher the concentration of MSA initially added, the greater the decrease. The longer the time period between addition of MSA and benzaldehyde the greater the decrease. For example, in as little as 5 min of pre-benzaldehyde addition the yield of NC-TPP declined from ~35% to 13%. The yield of TPP was little affected by the reaction of pyrrole and MSA prior to addition of benzaldehyde indicating the decline in NC-TPP formation was not simply due to destruction of free pyrrole. Furthermore, the pyrrole + MSA solutions were colorless indicating that the putative polymer "pyrrole red" was not formed under these conditions. When benzaldehyde was added first, followed by MSA addition prior to addition of pyrrole, little to no change was observed on either the NC-TPP or TPP yield.

Experimental Section

Materials. Pyrrole (Acros) was distilled from calcium hydride and stored at -15°C until use. The distilled pyrrole was used prior to any discoloration. CH_2Cl_2 (Fisher, ACS grade) used for analytical scale experiments was distilled from potassium carbonate and stored over 4-Å Linde molecular sieves. CH_2Cl_2 (Fisher, ACS grade) for preparative scale experiments was used as received. Benzaldehyde (Aldrich, 99.5%), methanesulfonic acid (Aldrich, 99%), and DDQ (Aldrich) were used as received. Column chromatography was done using activity III basic alumina obtained by adding 6% water to activity I Brockman basic alumina, 60-325 mesh (Fisher). Pre-HPLC sample clean-up was done using activity II basic alumina obtained by adding 3% water to activity I Brockman basic alumina, 60-325 mesh (Fisher). All other materials and solvents were used as received.

General Analytical Scale Reaction Conditions. CH_2Cl_2, pyrrole, and benzaldehyde were dispensed into 20-mL vials containing a micro stir bar. The volume of CH_2Cl_2 was selected so that the final volume of the reaction mixture would be 10 mL, assuming additivity of volumes. Benzaldehyde and pyrrole were dispensed as neat reagent, or as 1 M stock solutions in CH_2Cl_2 depending on the desired final concentration. The reactions were initiated by addition of methanesulfonic acid (MSA) (neat acid or 1 M stock solutions in CH_2Cl_2). The reaction mixtures were stirred and tightly capped. The reactions were monitored by transfer of an aliquot to a 1 dram vial containing pre-weighed, neat DDQ. The acid was quenched by the addition of 4-8 molar equivalents of triethylamine (TEA) relative to the acid.

Specific Procedure for 10 mM Reactants, 7 mM MSA Analytical Scale Experiment. To a 20 mL vial containing a micro stir bar, 9.8 mL CH_2Cl_2 and 100 μL of 1 M stock solutions of pyrrole and benzaldehyde were added. The reaction was initiated by addition of 70 μL of a 1 M stock solution of MSA. The reaction was monitored at 8 min, 30 min, and 1 h by removal of 2 mL of the crude reaction mixture which was immediately transferred to a 1 dram vial containing 6 mg (26 μmol) of DDQ. To the oxidized reaction mixture, 15 μL (0.11 mmol) of TEA was added.

Analysis of TPP and NC-TPP Yields for Analytical Scale Experiments. Analyses were performed as described in an earlier publication.[1] Key details are repeated here. Prior to HPLC analysis, an aliquot of the crude, oxidized reaction mixture (1.5 mL for 10 mM reactions

(1) Geier, G. R., III; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1596-1603.

and 0.5 mL for 100 mM reactions) was passed through a pipet column containing 1.4 g of activity II basic alumina. The sample was eluted with three 1-mL portions of CH_2Cl_2 and 1-2 drops of TEA (to ensure all NC-TPP passes through the column). The solvent was driven off the column by application of mild pressure using a handheld pipet tool. The eluant was transferred immediately to an autosampler vial and capped. HPLC analysis was performed using a Hewlett-Packard 1100 series HPLC with a quaternary pump, an autosampler, thermostated column compartment at 25ºC, and a diode array UV-vis detector. A silica gel analytical column was used (Alltech, Altima, 4.6 mm by 250 mm) with an isocratic solvent mixture of 92.5% hexanes and 7.5% acetone. The hexanes was 50% water saturated by mixing equal volumes of dry hexanes and hexanes stored over water. The solvent flow rate was controlled as follows: T= 0 to 5 min, 1 mL/min; T = 5 to 7 min, linear increase to 2.5 mL/min; T = 7 to 10.5 min, 2.5 mL/min; T = 10.5 to 11.5 min, linear decrease to 1 mL/min; and T = 11.5 to 13 min, 1 mL/min. The solvent front occurred at 2.5 min, TPP eluted at 5.0 min and NC-TPP eluted at 9.9 min. Detection was performed at the following wavelengths: TPP, 417 nm and 590 nm; and NC-TPP, 438 nm. The yield of TPP was also determined spectrophotometrically as described previously.[2]

Analytical Scale Kinetic Experiment. The experiment was performed at 10 mM reactants and 7 mM MSA as described above except the reaction volume was increased to 40 mL. The reaction was monitored at 15 sec, 30 sec, 1 min, 2 min, 4 min, 8 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, and 24 h.

Single Reactant + MSA Experiments. Reactions were performed at 10 mM reactants with 1.25 or 7 mM MSA. To a 20 mL vial, 9.8 mL CH_2Cl_2 and 100 μL of a 1 M stock solution of pyrrole were added. MSA was then added (either 70 or 12.5 μL of a 1 M stock solution). The solution was then stirred for 5, 15, or 30 min prior to addition of 100 μL of a 1 M stock solution of benzaldehyde. For the reactions containing 1.25 mM MSA, at the time of benzaldehyde addition either no fresh MSA or 57.5 μL of a 1 M stock solution of MSA was added (to bring the MSA concentration to 7 mM). The reactions were monitored at 8, 30, and 60 min after addition of benzaldehyde. Order of reagent addition experiments were also performed with benzaldehyde and MSA added first, followed by pyrrole (only using 7 mM MSA).

Preparative Scale Synthesis of NC-TPP. To a 2 L flask, CH_2Cl_2 (1.5 L), pyrrole (1.04 mL, 15.0 mmol), and benzaldehyde (1.52 mL, 15.0 mmol) were added. The reaction was initiated by addition of MSA (0.681 mL, 10.5 mmol). The reaction mixture turned dark brown and was stirred at room temperature for 30 min. DDQ (3.00 g, 13.2 mmol) was added and the mixture was allowed to stir for 1 min and then the acid was quenched by addition of TEA (5.8 mL, 42 mmol). A 1.5 mL aliquot was prepared for HPLC analysis. HPLC analysis as described above provided yields of 37% NC-TPP and 5% TPP. Without evaporation of solvent, the crude reaction mixture was passed through a 500 mL separatory funnel containing 300 g activity III basic alumina (prepared by mixing 300 g activity I grade with 19 g of water). After the 1.5 L of reaction solvent had eluted, the alumina was rinsed with 1 L of CH_2Cl_2 containing ~1% TEA. All eluant was collected as a single fraction. After elution the top of the alumina was black and the bottom was pale tan. The crude TPP and NC-TPP solution was evaporated to near dryness and then adsorbed onto 15 g of activity III basic alumina. The adsorbed sample was added to the top of a column containing 300 g activity III basic alumina in 3:1 hexanes/CH_2Cl_2. The polarity of the eluant was increased from 3:1 to 1:1 to 1:2 hexanes/CH_2Cl_2 to 100% CH_2Cl_2, with about

(2) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827-836.

400-500 mL of each eluant mixture being used. Fractions of ~50 mL were collected. The TPP was largely eluted with the 3:1 hexanes/CH_2Cl_2 and was completely removed by the 1:1 mixture. The NC-TPP began to slowly elute at 1:2 hexanes/CH_2Cl_2 and was completely removed by 100% CH_2Cl_2. The fractions were analyzed by TLC (alumina, 1:1 hexanes/CH_2Cl_2) and pooled. The combined fractions were evaporated to dryness and placed under vacuum providing 800 mg (35%) NC-TPP and 140 mg (6%) TPP. Both isolated compounds were identical to authentic samples and published analytical data (UV-vis, ^{1}H-NMR, LD-MS).[1,2]