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Optimizing Selective Partial Hydrogenations of 4-Nitroacetophenone via Parallel Reaction Screening

Joel M. Hawkins* and Teresa W. Makowski

Pfizer Global Research and Development, Eastern Point Road, Groton, Connecticut 06340, U.S.A.

Abstract:

The hydrogenation of 4-nitroacetophenone was optimized for selective reduction to the corresponding aniline-ketone (97%), aniline-alcohol (95%), and aniline-methylene (99%) as a case study demonstrating the optimization of the selective reduction of a polyfunctional substrate using a parallel pressure reactor. The catalyst, catalyst loading, pressure, temperature, and methanesulfonic acid stoichiometry were varied, first in an initial coarse screen (catalyst and acid stoichiometry), and then in a full factorial screen for selected catalysts. Facile profiling of hydrogen uptake in each reaction aided setting reaction time and parameter ranges for the full factorial analysis, allowed for quickly spotting under- and overreduction, aided predicting robust reaction endpoints, and provided data for analyzing kinetic behavior.

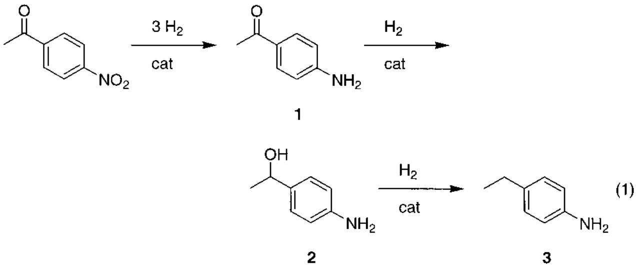
Introduction

Heterogeneous catalytic hydrogenations are ideal reductions in that there are no byproducts and the catalyst can be separated and recovered by simple filtration. Rates and selectivities are exquisitely tunable through the choice of catalyst, solvent, pressure, temperature, and modifiers such as acids, bases, and selective catalyst poisons.[1] These variables are a blessing in that they allow optimization of selectivity and a curse in that optimization relative to multiple variables requires many reactions. While this can be tedious when running reactions one at a time, recently commercially available equipment allows screening multiple hydrogenations in parallel on small scale with individual control of pressure and temperature with good gas–liquid mixing.[2,3] Further, individual monitoring of hydrogen uptake allows profiling rates and modeling kinetics. Here, we describe a case study for optimizing the selective reduction of a polyfunctional substrate using Argonaut's parallel pressure reactor, the Endeavor.[2,4] The hydrogenation of 4-nitroacetophenone was optimized for selective reduction to aniline-ketone **1**, aniline-alcohol **2**, and aniline-methylene **3** by varying the catalyst, catalyst loading, pressure, temperature, and amount of methanesulfonic acid (eq 1).[5] In 44 experiments (six runs of an 8-reactor instrument), reductions to **1**, **2**, and **3** were optimized to give 97, 95, and 99% in situ yield, respectively.

Table 1. **Catalyst screen for the hydrogenation of 4-nitroacetophenone**

catalyst[a]	equiv MsOH	in situ yield[b] 1	2	3
5% Pd/C	0	14	54	21
	1.1	19	21	57
10% Pd/C	0	7	**90**	0
	1.1	0	2	**96**
20% $Pd(OH)_2/C$	0	8	64	16
	1.1	1	1	86
5% $Pd/CaCO_3/Pb$	0	**85**	7	1
	1.1	66	4	26
5% Pt/C	0	66	22	2
	1.1	6	37	53
PtO_2	0	70	20	1
	1.1	4	7	81
5% Rh/C	0	54	39	2
	1.1	25	21	52
5% Rh/Al_2CO_3	0	59	34	2
	1.1	19	31	48

[a] 10% loading, 30 °C, 50 psi, ethanol, 22 h, 500 mg (3.03 mmol) scale. [b] Measured by HPLC using an external standard. This screen showed <1% 4-nitroacetophenone at the end of the reactions.



Results and Discussion

The reduction of 4-nitroacetophenone was first screened versus eight catalysts (10% loading), both with and without methanesulfonic acid (1.1 equiv) in ethanol at 30 °C and 50 psi for 22 h (Table 1). Reductions were run eight at a time on a 500 mg (3.03 mmol) scale in 5 mL of ethanol. The best conditions from this initial screen gave in situ yields of 85% **1**, 90% **2**, and 96% **3** using 5% $Pd/CaCO_3$ (lead

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(1) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985. Augustine, R. L. *Heterogeneous Catalysis for the Synthetic Chemist*; Marcel Dekker: New York, 1995.

(2) Argonaut Technologies, San Carlos, California (www.argotech.com).

(3) For other commercially available parallel pressure reactors with varying configurations and specifications, see products from: Hazard Evaluation Laboratories, Hertfordshire, England, and Chemspeed, Augst, Switzerland.

(4) For other approaches to catalyst screening, see: Simons, K. E. *Top. Catal.* **2000**, *13*, 201. Simms, C.; Singh, J. *Org. Process Res. Dev.* **2000**, *4*, 554. Blackmond, D. G.; Rosner, T.; Pfaltz, A. *Org. Process Res. Dev.* **1999**, *3*, 275. Petra, D. G. I.; Reek, J. N. H.; Kamer, P. C. J.; Schoemaker, H. E.; van Leeuwen, P. W. N. M. *Chem. Commun. (Cambridge)* **2000**, *8*, 683.

(5) We did not attempt to selectively partially hydrogenate the nitro group or to hydrogenate the ketone in the presence of the nitro group. The latter reaction is known for 4-nitroacetophenone with homogeneous catalysts, e.g., Penicaud, V.; Maillet, C.; Janvier, P.; Pipelier, M.; Bujoli, B. *Eur. J. Org. Chem.* **1999**, *7*, 1745 and (enantioselectively) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529.

10.1021/op010016p CCC: $20.00

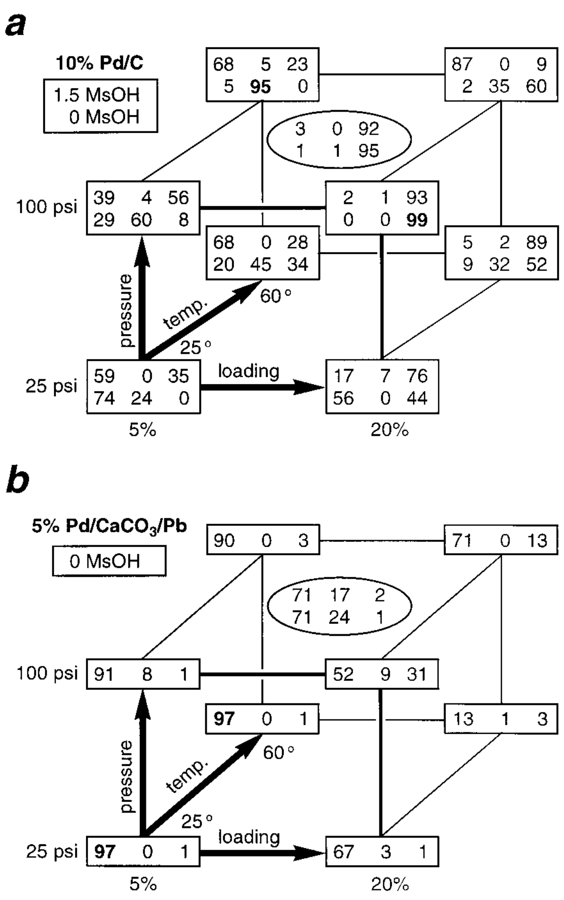

Figure 1. **Full factorial analyses for the reduction of 4-nitroacetophone using 10% Pd/C (*a*) and 5% Pd/CaCO$_3$/Pb (*b*). Percent in situ yields for the reduction products are listed in the boxes positioned at the corresponding catalyst loading, pressure, and temperature in the order: 1, 2, 3.[8] For *a*, the yields listed across the top of each box correspond to 1.5 equiv of MsOH, and the yields listed across the bottom of each box correspond to 0 equiv of MsOH. The data in the ovals correspond to two repeated midpoints for the ranges of loading, pressure, temperature, and MsOH stoichiometry (*a*) and loading, pressure, and temperature (*b*)**

poisoned) with 0 equiv of MsOH, 10% Pd/C with 0 equiv of MsOH, and 10% Pd/C with 1.1 equiv of MsOH, respectively.[6]

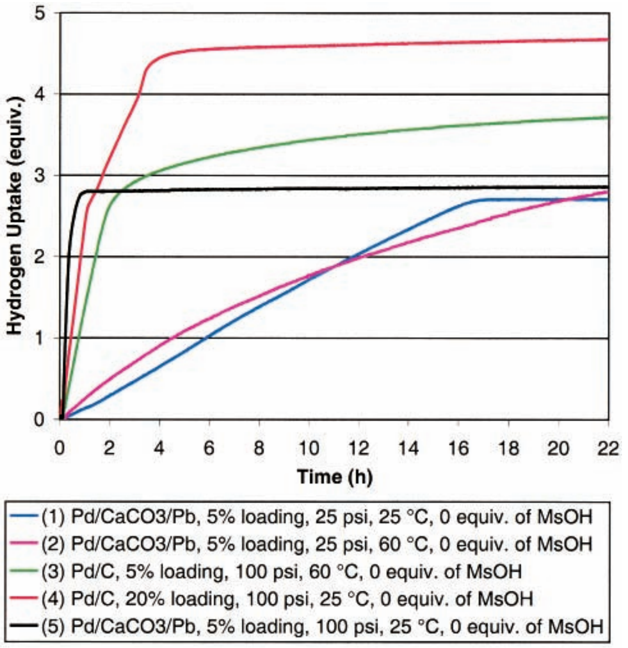

Figure 2. **Hydrogen uptake vs time for the reduction of 4-nitroacetophenone (3.03 mmol) under the indicated conditions. Curves 1, 3, and 4 correspond to the optimized reduction to 1, 2, and 3, respectively.**

These three conditions were then optimized for the two catalysts involved by examining low and high points for catalyst loading (5 and 20%), pressure (25 and 100 psi), temperature (25 and 60 °C), and, for Pd/C, the amount of acid (0 and 1.5 equiv of MsOH). The experiments for these full factorials with three variables correspond to the vertices of cubes,[7] Figure 1a for Pd/C and Figure 1b for Pd/CaCO$_3$/Pb. For Figure 1a, the extra dimension of 1.5 and 0 equiv of MsOH is represented by high and low points per vertex. A pair of midpoints is added to each cube to explore this reaction space and to check for reproducibility. In situ yields of **1**, **2**, and **3** as determined by HPLC[6] are tabulated within the cubes of Figure 1a and b to easily visualize the effect of each variable.[8] The best conditions from this full factorial screen gave in situ yields of 97% **1**, 95% **2**, and 99% **3** using Pd/CaCO$_3$/Pb (0 MsOH, 5% loading, 25 psi, 25 or 60 °C), Pd/C (0 MsOH, 5% loading, 100 psi, 60 °C), and Pd/C (0 MsOH, 20% loading, 100 psi, 25 °C), respectively.[9]

Both the choice of catalyst and the reaction parameters have a significant affect on the selectivity of the reduction. The reaction time was not explicitly pursued as a variable, but the extent of reaction versus time is evident from the hydrogen uptake graphs generated in real time by the instrument, for example, Figures 2 and 3.[10] These graphs allow determining the best reaction time for a reduction screen, 22 h in this case, and looking for reactions which end with close to zero hydrogen uptake (flat regions of the graph), suggesting robust reaction end points for scale up. For example, aniline-ketone **1** can be obtained in 97% in situ yield at either 25 or 60 °C, but the hydrogen uptake graph at 25 °C shows a more pronounced stoppage of hydrogen uptake than that at 60 °C, suggesting a more robust reaction end point at 25 °C (Figure 2, curves 1 and 2, respectively). Optimum individual reaction times are also evident from these graphs; many of the reactions are complete in less than 22 h. Figure 2, curves 3 and 4, correspond to the optimized reduction to aniline-alcohol **2** and aniline-methylene **3**, respectively. While low or high hydrogen uptake can flag under- or overreduction, flat endpoints in the hydrogen uptake graphs do not necessarily

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(6) In situ yields were determined at the end of the reactions by HPLC using an external standard as described in the Experimental Section.

(7) Havilcek, L. L.; Crain, R. D. *Practical Statistics for the Physical Sciences*; American Chemical Society: Washington, DC, 1988; Chapter 13.

(8) Unreacted 4-nitroacetophenone was also measured by HPLC but is not listed in Figure 1 for clarity. The mass balance for 4-nitroacetophenone + **1** + **2** + **3** averaged 96%.

(9) The HPLC selectivity data from the full factorial screen with midpoints can be further analyzed using Design of Experiment software. In this particular case, the predicted optimum conditions were very close to the listed conditions.

(10) Eight curves are generated at a time when using each of the reaction vessels on the Endeavor. Selected curves are shown in Figures 2 and 3 with the vertical axis converted from mmol to equiv of hydrogen for clarity.

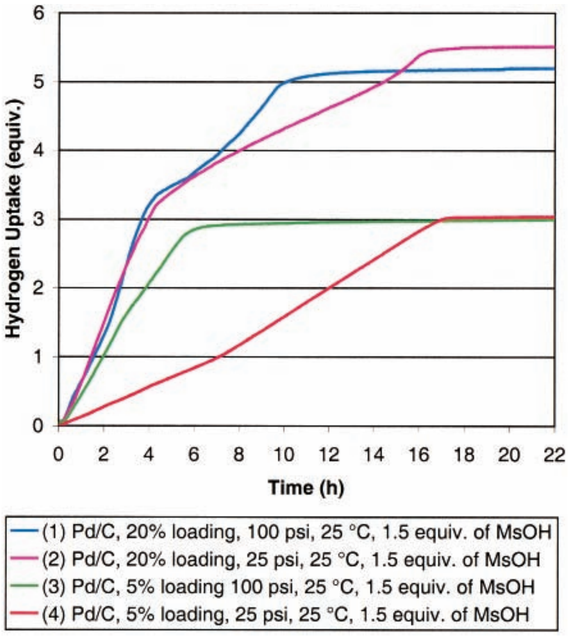

Figure 3. **Hydrogen uptake vs time for the reduction of 4-nitroacetophenone (3.03 mmol) under the indicated conditions demonstrating various kinetic behaviors. This "quartet" of curves shows the effect of catalyst loading and pressure for constant catalyst, temperature, and modifier stoichiometry.**

correspond to selective reactions in this case study. For example, Figure 3, curves 3 and 4, both have crisp end points for hydrogen uptake, yet they both have <60% selectivity. Comparison of the observed hydrogen uptake at the end of the reactions with the calculated hydrogen uptake (based on the in situ yields of **1**, **2**, and **3**) showed that the observed values are typically ±20% of theory.[8]

The hydrogen uptake graphs also give qualitative and quantitative kinetic information. The steepest initial hydrogen uptake curves define the limits of mass transfer of hydrogen between gas and liquid, for example, Figure 2, curve 5.[11] Many curves showed zero-order behavior (linear hydrogen uptake) well away from the mass-transfer limit consistent with saturation kinetics (high initial substrate concentration and/or strong substrate-catalyst binding). Figure 3, curve 4, shows zero-order reaction for the first equiv of hydrogen followed by zero-order reaction at a *higher rate*, consistent with the nitroarene starting material inhibiting subsequent reduction of the nitroso intermediate. Several curves showed *rate increases just before the reaction stopped* (e.g., Figure 3, curves 1 and 2). This negative order behavior is consistent with Horiuti−Polanyi kinetics where one of the intermediates binds strongly to the catalyst, for example, amino-alcohol **2** in the case of curve 2.[12] These and other interesting kinetic phenomena will be further explored with compositional data versus time.

Conclusions

We optimized eq 1 in two steps: (1) an initial screen crossing a discontinuous variable (the choice of catalyst) with a continuous variable (modifier stoichiometry), and (2) optimization for selected catalysts by a full factorial analysis of four continuous variables (catalyst loading, pressure, temperature, and modifier stoichiometry). This combination allowed the rapid optimization of the selective hydrogenation of 4-nitroacetophenone to three different reduction endpoints, **1**, **2**, and **3**. Charting in situ yields measured by HPLC on cube graphs of the full factorial variables allowed easy visualization of the selectivity data.

The Argonaut Endeavor facilitated running reactions eight at a time under well-defined and -controlled hydrogenation conditions in a small footprint. The measurement of hydrogen uptake aided setting reaction time and parameter ranges for the full factorial analysis, allowed for quickly spotting under- and overreduction, aided predicting robust reaction endpoints, and provided data for analyzing kinetic behavior. These techniques can be applied to the rapid optimization of reactivity and selectivity for the hydrogenation of a variety of polyfunctional molecules.

Experimental Section

Hydrogenations were run eight at a time in a parallel pressure reactor (the Endeavor manufactured by Argonaut Technologies[2]). The glass liners of the reaction vessels were loaded with 500 mg (3.03 mmol) of 4-nitroacetophenone followed by the catalyst (catalyst and catalyst loadings listed in Table 1 and Figure 1), 4.7−5.0 mL of absolute ethanol (to give a total volume with the methanesulfonic acid of 5.0 mL), and methanesulfonic acid if used (151 μL = 0.75 equiv, 221 μL = 1.1 equiv, or 301 μL = 1.5 equiv as indicated in Table 1 and Figure 1). The glass tubes were loaded into the stainless steel pressure reactors, sealed with the reactor head, and stirred at 390 rpms.[11] The instrument was programmed to purge the reactors with nitrogen 10 times, pressurize with hydrogen and maintain the set pressures and temperatures for each reactor for 22 h, and then cool and purge the reactors with nitrogen. Hydrogen-uptake data (mmol), pressure, and temperature are displayed in real time for each of the eight reaction vessels. At the end of the reactions, the reaction mixtures were filtered through Celite with the aid of acetonitrile and diluted to a total volume of 100 mL with acetonitrile. Aliquots (100 μL) of these solutions were further diluted with 1 mL of acetonitrile and injected onto an HPLC (Zorbax SB CN column, 0.5 mL/min, gradient of 20−60% acetonitrile/0.2% H_3PO_4 aqueous buffer over 15 min, gradient hold for 5 min, UV detection at 210 nm). In situ yields of 4-nitroacetophenone, **1**, **2**, and **3** were determined using external standards prepared from commercial samples (1 mg/mL in acetonitrile). Hydrogen-uptake data can be exported to Excel for further analysis.

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(11) These hydrogenation screens were preformed using the anchor-shaped stirrers originally supplied by Argonaut. We now generally use the oar-shaped stirrers currently supplied by Argonaut.

(12) Satterfield, C. N. *Heterogeneous Catalysis in Industrial Practice*, 2nd ed.; McGraw-Hill: New York, 1991; Chapter 3.