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A Chemometric Approach to Map Reaction Media Chemoselectivity: Example of Selective Debenzylation

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A chemometric process consisting in measuring the reactivity of a set of substrates under standardized and complementary reaction conditions was run to evaluate the possibility of building a coherent database that would give a general overview of the selectivity of a variety of catalysts. This systematic experimental approach was applied to the hydrogenolysis of *O*-benzyl ether compounds. Analysis of collected data revealed reaction conditions with precise chemoselectivity. For instance, Pd/C in EtOH or PdOH in THF enabled the specific cleavage of the benzyl group in the presence of *p*-CF_3Bn groups, and addition of triethylamine in EtOH suppressed the cleavage of the phenoxybenzyl bond. The latter selectivity was exemplified on several polyfunctional substrates.

Introduction

Achieving high levels of chemoselectivity has been the Achilles heel of chemical synthesis.[1] The term "selectivity" refers herein to the discrimination displayed by reagent A when it reacts with two different reactants B and C. To extrapolate possible selectivity from raw bibliographic material it is a basic principle of mechanistic chemistry to transfer structure–reactivity relationships from intermolecular selectivity into intramolecular selectivity. However for a chemist, the intuitive way of selecting appropriate reaction conditions is made uneasy by the poor availability of information about the nontransformation (stability) of functional groups and also by the nonstandardization of reaction media. In this paper we have investigated whether a coherent reaction dataset generated by applying standardized reaction conditions to a collection of simple substrates would provide useful insight into reagent and media selectivity and possibly the uncovering of synthetically useful reagent selectivity.

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Results and Discussion

The reported approach can be seen as orthogonal to the classical high-throughput screening (HTS) methods.[2] Indeed, in HTS strategies, a key substrate or a key reaction is assayed against a large number of catalysts to select the most efficient ones. The reaction analyses usually focus on the measurement of a single product or a single piece of data. Accordingly, the test techniques used, such as IR thermography,[3] capillary electrophoresis,[4] mass spectrometry,[5] sandwich immunoassay[6] and fluorescence screening assays,[7] were optimized to achieve high throughput. On the contrary, our approach is aimed at building a coherent set of chemical data by assaying a set of diverse substrates in a limited but representative number of reaction conditions and collecting exhaustive data on crude mixture compositions.

Because of its ubiquitous use in synthesis, we decided to use the hydrogenation reaction and more particularly the debenzylation reaction as a model system for our study. Indeed, the search for new selectivity in hydrogenation reactions[8] and in debenzylation[9] is a continuous area of interest for organic chemists. Significantly, in the course of our bibliographic search, we noticed that many interesting publications dealing with selective hydrogenation are available only in Japanese or Chinese language, making the use of those results quite difficult.[10]

To implement the envisioned chemometric approach, our first task was to shrink the almost infinite space of reaction conditions to a limited number of standardized conditions. To that end, we performed a large bibliographical analy-

sis[11] of hydrogenation reactions and selected a set of conditions that sample both the most frequently used and the most diverse conditions reported in organic synthesis and medicinal chemistry research. We also selected only commercially available catalysts.

We further restricted the set of catalysts, solvents and conditions to those easily available to any bench chemists. By applying these rules, we ended up with 18 different catalysts and 8 solvents or solvent mixtures (Tables 1 and 2).

Table 1. Most representative solvents in the field of hydrogenation.

Solvents			
S_1	EtOH	S_5	EtOH + 5% TFA
S_2	EtOH + 5% Et_3N	S_6	THF
S_3	EtOH + 5% AcOH	S_7	hexane
S_4	EtOAc	S_8	DMF

Table 2. Most representative catalysts in the field of hydrogenation.

Catalysts			
C_1	Pd/C (10%)	C_{10}	Pd $(OH)_2$/C (20%)
C_2	Pt/C (10%)	C_{11}	Pd/$CaCO_3$ (5%) + Pb
C_3	Ru/C (10%)	C_{12}	Pd/Al_2O_3 (5%)
C_4	Pd/$BaSO_4$ (5%)	C_{13}	Pt/C (10%) + H_2O
C_5	Ir/$CaCO_3$ (5%)	C_{14}	Pd(polyethyleneimine) + SiO_2 (1%)
C_6	Rh/C (5%)	C_{15}	Raney Ni
C_7	Ni/SiO_2–Al_2O_3 (66%)	C_{16}	Ir/C (1%) + H_2O
C_8	Pd (8%), Pt (2%)/C + H_2O	C_{17}	Fe/graphite (5%)
C_9	Cu/graphite (5%)	C_{18}	Ru/Al_2O_3

We hypothesized that systematically assaying limited numbers of substrates bearing benzylic bonds with various stereoelectronic environments would result in a data set that would describe the reactivity and the nonreactivity of a wider range of molecules. Our next task was thus to reduce the chemical space by selecting a set of representative substrates. As an illustration of the outcome of this approach, a set of six molecules was chosen (Figure 1). This set of substrates particularly focuses on primary, secondary aromatic *O*-benzyl and *O*-4-trifluoromethyl benzyl ether bonds.

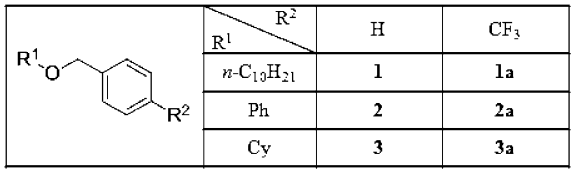


Figure 1. Subset of the *O*-benzyl ethers assayed under selected hydrogenolysis conditions.

All possible combinations of catalysts, solvents and molecules were tested under standardized conditions in a 24-well parallel synthesizer (MiniBlock®). Each set of 144 experiments carried out with substrates **1**–**3** and **1a**–**3a** is presented as a master plate with solvent variation in the rows and catalyst variation in the columns (Figure 2). The compositions of the crude reaction mixture analyzed by gas chromatography are represented by using pie charts. The light-green pies represent debenzylated products, whereas dark-green pies represent the remaining substrates. Blue and red pies correspond to byproducts such as over-reduced compounds. Most importantly, the reliability of the set up was checked by random experiment reproduction.

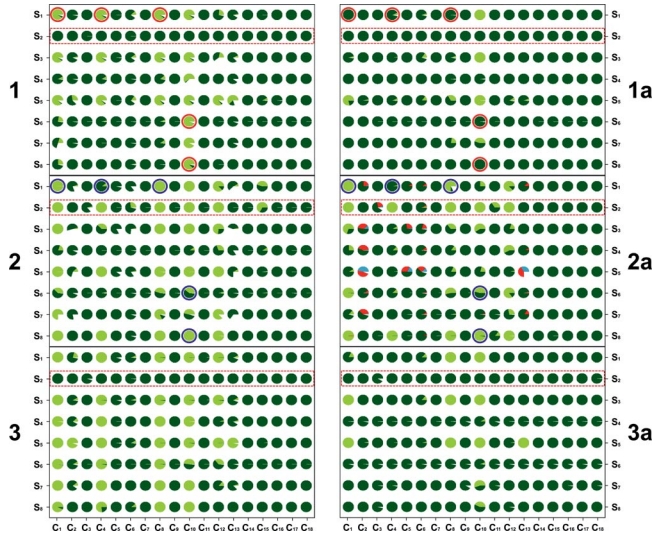
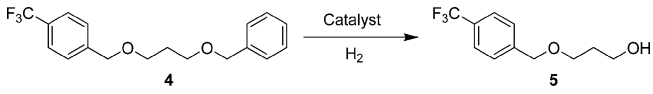


Figure 2. Hydrogenolysis pie charts for molecules **1**, **1a**, **2**, **2a**, **3** and **3a**.

The most relevant catalysts found in the literature for hydrogenolysis are typically formed by palladium, platinum, nickel, iridium, iron and ruthenium metals. According to results shown on the six master plates, palladium is by far the most reactive metal for breaking *O*-benzyl ether, as seen by the light-green colour, which is indicative of the successful splitting of each respective benzyl-protected compound (columns C_1, C_4, C_8, C_{10}, C_{12}, C_{1a}, C_{4a}, C_{8a}, C_{10a} and C_{12a}; Figure 2). A closer look shows interesting selectivity between primary benzyl **1** and primary *p*-trifluoromethylbenzyl ether **1a** in ethanol (S_1) with catalyst C_1, C_4 and C_8 or in THF (S_6) and DMF (S_8) with palladium hydroxide (C_{10}; red circles in Figure 2). Indeed, under these conditions, **1** is split in high yields, whereas **1a** remains mostly without reaction. After a careful search in the literature, it was found that such preferential hydrogenolysis was described sketchily by the group of Spencer[12] with only very few details. We thus set up a short experimental plan to validate whether or not the observed selectivity would translate to information useful with a bifunctional molecule. For that, molecule **4** was synthesized and tested within the five reaction conditions mentioned above (Table 3).

We were pleased to observe the selected reaction conditions turned out to be completely selective. With both a given solvent (row S_1) catalyst-induced and a given catalyst (column C_{10}) solvent-induced, selectivities could be extracted from the specifically designed data set. These first results appeared encouraging to us. By pushing the analysis of the collected data set a bit further, one can observe that with the corresponding secondary benzyl ether **2** and **2a**, the selectivity of reaction media S_1–C_1, S_1–C_4 and S_1–C_8 is totally modified (highlighted by a blue circle in Figure 2). Whereas S_1–C_1 and S_1–C_8 reduce both ether **2** and **2a**, S_1–

Table 3. Hydrogenolysis of bifunctional benzylated compound **4**.



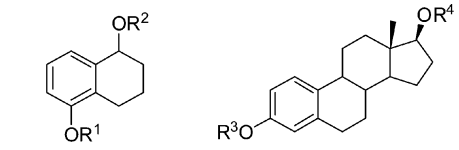
4 **5**

Catalyst	Solvent	Additive	Yield[a] [%]
Pd/C, $\mathbf{C_1}$	EtOH, $\mathbf{S_1}$	–	79
$Pd(OH)_2$, $\mathbf{C_{10}}$	THF, $\mathbf{S_6}$	–	76
$Pd(OH)_2$, $\mathbf{C_{10}}$	DMF, $\mathbf{S_8}$	–	84
$Pd/BaSO_4$, $\mathbf{C_4}$	EtOH, $\mathbf{S_5}$	TFA	99
Pd(8%)/Pt(2%)/C, H_2O, $\mathbf{C_8}$	EtOH, $\mathbf{S_1}$	–	90

[a] Isolated yield, reaction monitored by GC and product identified by ^{1}H NMR spectroscopy.

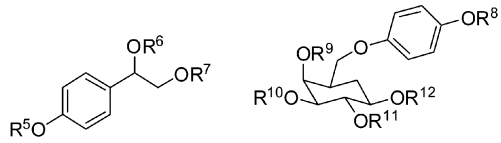
$\mathbf{C_4}$ reduces neither of them.[13] The difficulty to predict the selectivity switch accounts for the difficulty of extracting knowledge from literature sources in which it is unlikely to find a comprehensive set of substrates tested in a given catalytic system and in which conditions that do not transform a substrate are rarely reported. Further analysis revealed clean inhibition of benzyl bond hydrogenolysis by the addition of NEt_3 in the reaction media (highlighted by a red box for rows $\mathbf{S_2}$). Interestingly, this nitrogen-containing base seems to act as a poison for the catalyst for both series **1**, **1a**, **3** and **3a**, whereas phenolic derivatives **2** and **2a** do not seem to be affected. This observation suggests the possible selective removal of the benzyl group from phenolic substrates in the presence of alkoxybenzyls.

To validate the synthetic opportunity of these observations we first submitted equimolar mixtures of compounds **1**, **2** and **3** to the five better catalysts. As expected, only phenolic substrate **2** was hydrogenolyzed. After that, a set of four compounds with different molecular weights, geometries and numbers of primary, secondary alcohol and/or phenolic functions were perbenzylated and tested with our five most efficient catalysts (Table 4).



6 : $R^1 = R^2 = Bn$
6a : $R^1 = H$; $R^2 = Bn$

7 : $R^3 = R^4 = Bn$
7a : $R^3 = H$; $R^4 = Bn$



8 : $R^5 = R^6 = R^7 = Bn$
8a : $R^5 = H$; $R^6 = R^7 = Bn$

9 : $R^8 = R^9 = R^{10} = R^{11} = R^{12} = Bn$
9a : $R^8 = H$; $R^9 = R^{10} = R^{11} = R^{12} = Bn$

In all cases, only the expected product was formed in the reaction media. However, in some reactions, the kinetics of the reactions were found to be slower. That observation was expected, as diffusion at the interface is greatly influenced by the size and structure of the substrate. We circumvented the problem by letting the reaction run for a longer length of time. We also decided to run an experiment on a 1-g scale in a round-bottomed flask to investigate possible upscale difficulties. Satisfactorily, the reaction gave a similar yield with, however, a longer reaction time (24 h) probably due to poor gas–liquid exchange. It thus appears that when a catalytic system shows high chemoselectivity, transposition on complex substrates is quite straightforward. Neither the reaction time nor the concentration seems to drastically modify the outcome of the reaction.

Table 4. Hydrogenolysis of various benzylated compounds by the Et_3N-promoted chemoselective conditions.

Entry	Catalyst	Product	Time [h]	Yield[a] [%]
1	P/C	**6a**	5	87
		7a	5	90
		8a	5	90
		9a	15	79
2	Pd(8%)/Pt(2%)/C	**6a**	5	95
		7a	5	86
		8a	5	95
		9a	15	82
3	$Pd(OH)_2/C$	**6a**	5	95
		7a	5	91
		8a	5	94
		9a	15	76
4	Pd/Al_2O_3	**6a**	15	83
		7a	5	60
		8a	15	63
		9a	15	42
5	$Pd/BaSO_4$	**6a**	15	79
		7a	5	72
		8a	15	72
		9a	15	39

[a] Isolated yield, products identified by ^{1}H NMR spectroscopy.

Conclusions

To conclude, we have showed that a data set that encompasses reactions of simple but complementary substrates under standardized conditions easily reveals useful chemoselectivity. For instance, the simple observation of specific conditions that transformed a given substrate but did not transform others led to the identification of robust reaction media for selective debenzylation. Using automated platforms, extension of such data collection strategies to key organic transformations such as reduction, oxidation, C–C coupling and protecting group chemistry would shed light on the selectivity space that is poorly covered by existing reagents and thus highly desirable to reach.

Supporting Information (see footnote on the first page of this article): Experimental procedure for data collection, reproducibility of hydrogenolysis platform, procedures for the synthesis of substrates and analytical data of new compounds; additional references.

Acknowledgments

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[13] An equimolar mixture of substrates **2** and **2a** was reacted under the selected conditions. The results were in line with expectations according to the analysis in Figure 1. $\mathbf{S_1}$–$\mathbf{C_1}$, $\mathbf{S_1}$–$\mathbf{C_8}$ and $\mathbf{S_8}$–$\mathbf{C_{10}}$ gave mostly complete reduction of both substrates. $\mathbf{S_1}$–$\mathbf{C_4}$ gave less than 10% reduction and $\mathbf{S_6}$–$\mathbf{C_{10}}$ resulted in a mixture of starting materials and reduced compounds.

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