

Supporting Information

Status check: Biocatalysis; it's Use With & Without Chemocatalysis.

How does the fine chemicals industry view this area?

Fabrice Gallou,* Harald Gröger,* and Bruce H. Lipshutz*

Fabrice Gallou – Chemical & Analytical Development, Novartis Pharma AG, 4056 Basel, Switzerland; orcid.org/0000-0001-8996-6079; Email: fabrice.gallou@novartis.com

Harald Gröger – Chair of Industrial Organic Chemistry and Biotechnology, Faculty of Chemistry, Bielefeld University, 33615 Bielefeld, Germany; orcid.org/0000-0001-8582-2107; Email: harald.groeger@uni-bielefeld.de

Bruce H. Lipshutz – Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States; orcid.org/0000-0001-9116-7049; Email: lipshutz@chem.ucsb.edu

1. Applied methodology for conducting the survey

A questionnaire composed of three open-ended questions was designed by the authors of this *Viewpoint Article*, following the methodology and process (design, survey, interpretation) described in other life science fields.¹

A very important prerequisite was to collect open and honest, yet confidential feedback. The conversations were designed in such a way that the validity of the claims being made by the interviewees was probed, corroborating each with hard facts and proven track records, typically based on:

(a) publications or patents;

and

(b) public disclosures at referenced conferences, or press releases.

The main source of information used to check validity, to a significant degree, was the published literature, as this constituted a good proxy for the respondents and maturity of the organizations in the various fields of catalysis. Honest, constructive comments were collected that allowed for inclusion of all input. The survey took place in the form of interviews conducted by FG.

The format of the conversation allowed for clarification of all points, and for a genuine open dialogue. There is no relationship or conflict of interest between any of the respondents and any of the authors of this *Viewpoint Article*.

All responses are kept strictly anonymous, being gathered, blinded, and subjected to interpretation only by the authors of this *Viewpoint Article*. Every organization interviewed was first tagged suitably based on its industry, in addition to its business size (small, medium, large).

No analytical data were obtained, so as to not pinpoint any of the organizations surveyed.

Questions were sent to a total of 36 senior scientific thought leaders identified from a diverse range of organizations taken from agrochemicals, pharmaceuticals, and the flavor and fragrance chemical industries. A total of 28 of the contacted peers responded by taking part in the survey.

All these senior professionals have a strategic and scientific role as part of the leadership teams in their companies, but are not necessarily experts in either bio- or chemo-catalysis. All respondents have industrial experience of between 20 to 40 years in the industry, and remain involved at the time of the survey.

The survey was conducted between December 2021 and February 2022.

The first few questions targeted recognition of a company's proven interest and expertise in either bio- or chemo-catalysis, with insight coming from the interviewee as well as from factual information collected from the public domain. This avoided any perception of a "sales" pitch, whether or not intended, from potentially severely altering the value of the responses.

Three distinct questions (Figure S1) were posed to each respondent. Initially, it seemed prudent to assess a company's level of fundamental interest in the biocatalysis area, after

which each was then asked about the area of chemoenzymatic catalysis. The next inquiry focused on the future likelihood of, and value for, potentially merging bio- and chemo-catalysis. Lastly, it was important to assess the hurdles associated with utilizing these types of catalysis, whether real or perceived. The idea, in essence, was to collect a qualitative set of responses, rather than subjecting the acquired data to statistical analysis.

Questions	
1	What is your organization's interest and expertise in biocatalysis? in chemocatalysis? in both combined?
2	What do you foresee as the potential for merged bio- and chemo-catalysis?
3	What do you think are the current challenges and limitations for implementation?

Figure S1. Questions posed by the survey

The following pie chart shows the distribution of the types of companies having participated in this survey (Figure S2). Among them, the majority of companies are from the pharmaceutical, agrochemical, and fragrance industries (in total 15), in addition to fine chemical producers (5) and other types of companies (8).

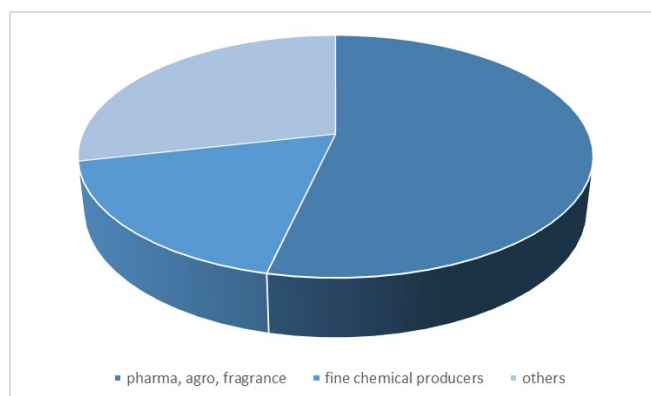


Figure S2. Pie chart showing the types of companies having participated in this survey.

2-Outcome and analysis

2.1-Potential for merging bio- and chemo-catalysis

In terms of recognized potential for merging bio- and chemo-catalysis, concrete examples reported using physical or chemical compartmentalization were offered to the interviewees with some of the seminal work described in the literature.² Interestingly, a clear split in the nature of the responses followed immediately. The more mature organizations in both fields quickly picked up on the opportunities, although with rapid movement towards identifying limitations (6.7% of respondents, see graph below), while the less mature companies struggled to formulate potential near-term opportunities (30 + 13.3%). The relatively recent literature on the topic^{3,4} can make the field of chemoenzymatic catalysis difficult to grasp for non-experts and non-practitioners. Nonetheless, the perception was that it is no longer considered low hanging-fruit to just improve sustainability performance by recognizing an obvious need for improvement in this area, and then to rapidly design a suitable strategy to generate those improvements. Rather, this area of sustainable production of industrial chemicals has become highly sophisticated, relying on a wealth of literature and technology scouting that embeds otherwise very complex science.⁵ One, therefore, needs to dig into operational details, such

as the bill of materials or a detailed analysis of environmental metrics to gauge the impact on sustainability, something that non-experts rarely, if ever, do. The more enthusiastic respondents, however, generally provided comments that were both immediate and excitingly positive. Thus, two different tunes could be heard, essentially reflecting the practice within their respective organizations. The enthusiasts within organizations were receptive to merged catalyses, while those within more dogmatic organizations were slightly more frustrated, not as open to these new developments, and relied exclusively on one type of catalysis (16.6 + 3.3% of respondents). An interesting population (26.7 + 3.3%) was found to be made up of experts in one area of catalysis, while also engaged in the other (shown diagrammatically in Figure S3).

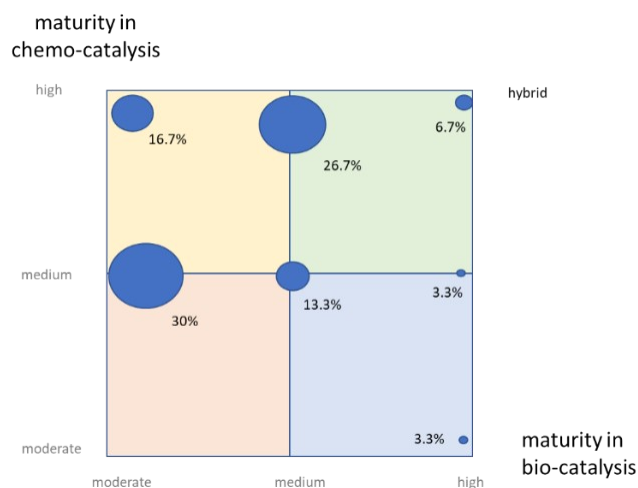


Figure S3. Maturity of the organizations interviewed in bio-, chemo- and mixed bio- and chemo-catalyses

In general, the scientific challenge of combining these two “different worlds of catalysis”, namely bio- and chemo-catalysis, towards one-pot processes in water is noted in several responses received, as represented by the following:

“To me the biggest challenge is culture (in academia and industry) since biocatalysis is not part of the educational curriculum at most universities (hence chemists are later reluctant to even consider biocatalysis). ...”

Analyzed through a different lens, and gauging the levels of excitement and action, almost all respondents have started the journey towards merged catalyses (16.7 + 26.7 + 23.3%), embracing the opportunities it will provide (Figure S4). On the other hand, (23.3 + 3.3 + 6.7)% witness limited or no action, mainly for business reasons, thus leading to severe levels of frustration in the most extreme cases.

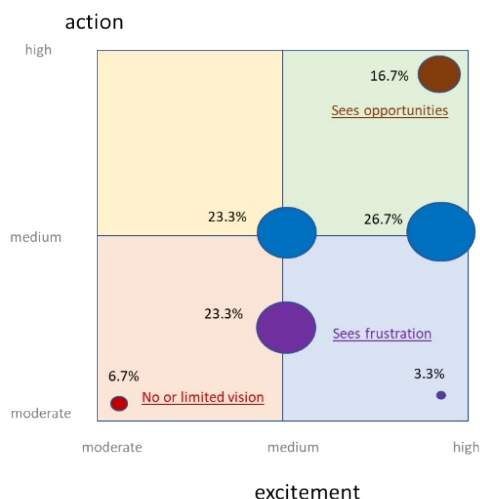


Figure S4. Levels of excitement by the organizations interviewed in bio-, chemo-, and mixed bio- and chemo-catalyses

One major reason for the limited use of biocatalysis in industry, however, can be traced back to the manner in which chemists have been trained; that is, to a stage prior to entering industry. Their typical lack of experience in biocatalysis, therefore, makes the choice of this technology as a means of solving synthetic problems using enzymes less likely. This limited background, where biocatalysis is viewed as a “routine working tool” in standard industrial laboratories is widely recognized, as succinctly highlighted by the following statement of one respondent:

“... the two approaches on paper are considered still by many to be incompatible with enzymes operating in aqueous media while chemocatalysis is still primarily in the realm of organic solvents.”

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