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“Organic synthesis—Where now?” is thirty years old. A reflection on the current state of affairs

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This essay is dedicated to Dieter Seebach on the occasion of his 83rd birthday and in recognition of his outstanding contributions to synthesis.

Prologue

“Organic synthesis is a mature science,” say many uninformed scientists.

This essay honors Professor Seebach on the 30th anniversary of his review, “Organic synthesis — Where now?”, published in *Angewandte Chemie*,¹ and provides a summary of the current state of affairs of our guild with highlights of changes over the last three decades. Seebach’s colossal article, which greatly influenced my own writing about organic synthesis, was one of the first that combined praise of the discipline with a critique of approaches and projections for the future. His opinions and predictions have certainly been—and continue to be—validated:

“The primary motivations that once induced chemists to undertake natural product syntheses no longer exist. Instead of target structures themselves, molecular function and activity now occupy center stage. Thus, inhibitors with an affinity for all the important natural enzymes and receptors have moved to the fore as potential synthetic targets.--New synthetic methods are most likely to be encountered in the fields of biological and organometallic chemistry [my emphasis].

Enzymes, whole organisms, and cell cultures for enantioselective synthesis of specific substances have already been incorporated into the synthetic arsenals of both research laboratories and industry. In addition, designing appropriate analogues to transition states and intermediates should soon make it possible, with the aid of the mammalian immune system and gene technology, to prepare catalytically active monoclonal antibodies for almost any reaction; perhaps more important, such processes will increasingly come to be applied on an industrial scale. The discovery of truly new reactions is likely to be limited to the realm of transition-metal

organic chemistry, which will almost certainly provide us with additional “miracle reagents” in the years to come.”

—Dieter Seebach, from the introduction of his 1990 review.¹

This article inspired me to write a review² that guest editor, Paul Wender, placed at the beginning of the 1996 thematic issue of *Chemical Reviews*, which included articles that defined the state of the art of synthesis at the time. I was far more critical of the accomplishments achieved in synthesis than Seebach had been six years earlier, and I have pointed out the many limitations in design that existed at the time. After its publication, Thieme approached me about expanding the article into a book. The result, *The Way of Synthesis*, coauthored by J. W. Reed, was published by Wiley–VCH in 2007,³ and included a compilation of selected syntheses as well as personal recollections and opinions provided by the authors whose work was featured. It offered not only comparative design features for the synthesis of natural products but also provided discussion about the way our entire community operates and evolves, from proposal and manuscript reviews to diminishing integrity of experimental work and the infectious rise of overhyped reporting of results.

Discussion

The last section of *The Way of Synthesis* presented an analysis of various factors that influenced not only organic synthesis but also society and its conduct. Figure 1 shows how the selected factors, primarily new technologies and attitudes, influence organic synthesis. The diagram is discussed in detail in Chapter 6 of *The Way of Synthesis*. Here I briefly discuss any new developments in each of the categories.

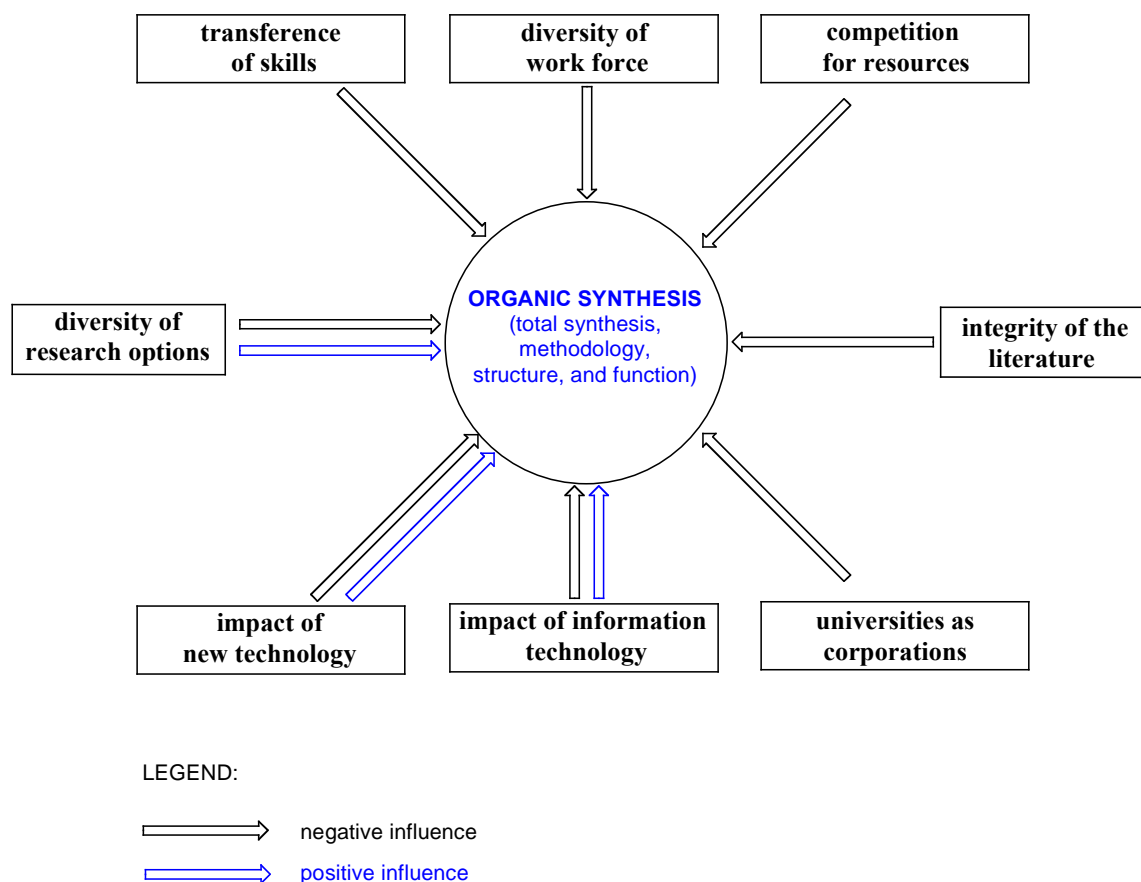


Figure 1. Factors that influence and contribute to further development of organic synthesis.

[Figure 6.1, reprinted with permission from *The Way of Synthesis*, VCH, 2007.]

Impact of new technologies. The older reader can appreciate that, with the introduction of high-field NMR, we were able to move from gram to milligram scale synthesis in fewer than three decades. There is no question that this technology, along with the development of multi-dimensional NMR experiments, had an enormous positive impact on our ability to address the synthesis of complex molecules. The smaller scale of operation, however, obviated proper characterization of compounds by methods such as combustion analysis and melting points, resulting in erroneously calculated yields, and other, less than positive, developments. [Note 1]. In 2010, I proposed a remedy to inaccurate reporting of results in a *Synlett* account and suggested more rigorous demands for proper characterization of compounds.⁴ To my knowledge, the suggestions were ignored by the editorial boards of organic journals, and by most referees. I still believe that a balance can be reached regarding the scale at which we operate so that the proper experimental protocols are undertaken as a matter of course.

Impact of information technology. The emergence of the internet and information-processing technology eventually led to online-only publications and to the rise of overhyped graphical abstracts.⁵ Readers of online literature generally peruse the graphical abstracts and see the entire article only if the abstract captures their attention. They miss much information that might be found by paging through a hard copy, as important items were often located in adjacent articles. There is, however, no question that online data bases such as Scifinder, Reaxys, ISI Web of Knowledge, and others, have had a very positive impact on information gathering. A literature search that once took many hours, or even days, in a library can now be accomplished in minutes. Thirty years ago such advances were still only a distant fantasy. The only drawback of this technology may manifest itself in a decline in focus and attention span as a result of excessive use of online platforms.

Diversity of work force. In the last two decades many groups and/or individuals have been designated with “preferential status”. This in spite of the fact that the percentage of women and minorities in academia and pharmaceutical industry has greatly increased. It follows that, in a social equilibrium, preferential treatment of one group leads to disadvantages for another. New ideologies have appeared and influenced hiring practices, promotion, funding, and recognition of certain groups. Each candidate should have an equal opportunity to secure a position, regardless of personal identification/categorization. The rise and emphasis on hiring practices that suggest or even mandate equality in terms of absolute numbers of people in specific subgroups is counter-productive if it results in discrimination against the most meritorious candidates. Such practice affects the format of interviews and has led to the emergence of mandatory “training workshops” on gender equity, inclusion, diversity, and discrimination [Note 2].

The integrity of literature. The content of the literature has changed drastically over the last three decades, as evidenced by the increase in pagination of journals [Note 3]. The quality of experimental sections has diminished. The appearance of incorrect and incomplete data has led to frequent retractions. As well, potential fraud became quite common, for example as in the case of P.Chiranjeevi.⁶ As of this writing there have only been seven recently documented cases of fraud in chemistry,⁶ but it appears to be more prevalent (or more detectable because of more frequent repetitions of experiments) in the biomedical sciences. Over the last two decades, these trends have been noticed by numerous chemists, whose critical articles warn of consequences of inaccurate or fraudulent data reporting that was rare in the 20th century.⁷

A qualitative survey of chemistry publications over time shows that the dominant force in chemistry publications in the 19th century was Germany, in the 20th the US, the UK, Japan, and the Soviet Union. In the 21st century, more publications on organic synthesis originate in China than from any other country [Note 4]. The pressure on Chinese academics to publish in “western” journals is immense and it is therefore not surprising that fraud and improper publication protocols are common. A 2013 essay in *Science* brought to light some of the publication practices used in China, including commercial concerns that guarantee a publication in a high-impact journal for a fee [Note 5].⁸ Another editorial, written by Wei Yang, addressed the unethical publication practices in the context of competition for resources and the emergence of and the emphasis on various evaluation metrics.⁹ A recent set of disclosures of involvement of US scientists with the Thousand Talents program has brought up misuse of funding issues.¹⁰ My own criticism of the current state of affairs was best summarized in the 2010 *Synlett* article.⁴ We demonstrated experimentally the impossibility of obtaining yields greater than 96% from reactions performed on small scales. Although the paper has been well cited, reporting of ~99% isolated yields in current literature has not abated though it is less likely due to deliberate fraud¹¹ than the absence of rational data analysis and high-integrity experimental techniques no longer taught to students of synthesis.

Transference of skills. The training and mentoring of new generations of professionals must be attended to by proper relationships of “masters and apprentices” without dilution of standards. Polanyi¹² stated two conditions under which the successful transfer of skills can occur: first, if the skill is not transferred within three generations, it is lost forever, and second, there must be “an unconditional submission of the apprentice to his/her master.” This applies not only in the sciences but also in art, music, and martial arts.

Skills already lost in organic synthesis are many: acid-base extraction, crystallization and distillation on small scales, the use of refractive index, analysis of UV and IR spectra (viz Bohlman-Wenkert rules,¹³ as an example of assignment of stereochemistry by the use of IR), to list just a few. Of course, the advent of NMR, mass spectrometry, and computational methods has allowed accurate and rapid analysis and even predictions of the outcomes of synthetic experiments. However, we should continue to teach classical tried-and-true methods.

Submission to one’s mentor is rarely attainable today, especially in a university setting. Many students are unwilling to submit to any level of hard work demanded by professors. The

university does not support professors in this endeavor as it views students as financial assets and hence protects them from any undue hardships that may be demanded by the “masters.” This situation, coupled with the fact that professors have less and less time to mentor students in the laboratory, cannot provide for a productive transfer of skills, especially the maintenance of standards and integrity of research [Note 6].

Universities as corporations. Universities have become focused on revenue rather than education and research. This was made possible by hiring upper-level administrators from the business sector rather than from academic ranks. The drive for (overhead-bearing) grants and recruitment of international students who pay higher tuition has resulted in diminishment of standards, lack of emphasis on graduate research, focus on metrics to evaluate faculty, and a lack of transparency in important decisions. The new system could be labeled as “academic feudalism” in which the working class (faculty) has little influence on the governance of the system, entirely controlled by the administrative “elite”. Finally, the drive to replace retiring full-time, tenured faculty with contract instructors (who have no job security or benefits) has led to higher profits for the Universities [Note 7].

Competition for resources. The competition for resources has increased to the point where faculty actually have little time to engage in research and education. The cut-off rates at most major funding agencies in the US have become so low that professors spend most of their time submitting grant applications rather than focusing on actual research and mentoring. In Canada, NSERC provides basic levels of funding at very reasonable rates of success. Paradoxically, as the number of research-active faculty decreases because of increasing numbers of contract instructors, this situation may actually improve; however, as fewer professors train more students homogeneity of thinking will result.

Diversity of research options. Seebach pointed out that it is likely that major advances in synthesis will come either from transition-metal catalysis or from the union of synthetic and biological methods. Already the field of catalysis has produced some remarkable advances such as cross-coupling and metathesis of olefins and alkynes. Four Nobel Prizes in chemistry in the last 50 years were awarded for invention of catalytic pathways, three since Seebach’s review: Fischer-Wilkinson (1973), Knowles-Noyori-Sharpless (2001), Chauvin-Grubbs-Schrock (2005), Heck-Negishi-Suzuki (2010). The literature in this field, however, is currently saturated by a plethora of reports of transformations that are made to appear more complex and are usually

more expensive than the protocols from which they were derived. Organometallic chemists should work on important and yet unsolved transformations known in Nature but not having synthetic equivalents, e.g., enantioselective dihydroxylations of arenes or fully site-selective functionalization of alkanes.

In the union of biology and chemistry, the potential is seemingly limitless. The reason enzymes are highly selective is because they control the *environment* in which the reaction is taking place. The chemist's approach, however, has been and continues to be focused on controlling the *reaction*, not the environment, although it is clear which approach leads to higher selectivity and efficiency. Advances in chemical biology, though, are making it possible to create task-oriented strains of microorganisms for production of specific compounds. Molecular biology has experienced a greater evolution in methods compared to organic synthesis [Note 8].

Gibson's synthesis of indigo,¹⁴ a beautiful example of strain engineering [Note 9], was later adopted by Genencor to produce indigo solely by fermentation on large scales by use of plasmid engineering.¹⁵ For further such achievements to be possible, chemists and biologists must work together in multidisciplinary collaborations with an open mind and mutual respect. To accomplish this the perception of and attitude toward the use of biological methods in synthesis must be more supportive, especially by funding agencies [Note 10].

The future manufacturing of important compounds will be accomplished by biological, not chemical methods, precisely as Seebach stated 30 years ago and as understood today by anyone involved in either biocatalysis or chemical biology. A case in point is that for decades, Abbott has been manufacturing erythromycin analogues by semisynthesis from an intermediate made by fermentation. What would such drugs cost if they were made from scratch (and on ton scale) by total synthesis?

Epilogue

The foregoing discussion focused primarily on various recent developments in organic synthesis and I attempted to describe both positive and negative attributes that have emerged in our field in the last three decades, especially in the last 15 years. To return our guild to the level of integrity that existed in the past the *modus operandi* with regard to data reporting needs to change. The authors, referees, funding agencies, and, especially editors of journals must declare common interest and work together to increase integrity and diminish excess hype, inaccurate reporting, or fraudulent publications. The guidelines on how to accomplish this were provided in our 2010

Synlett account⁴ but have yet to be implemented. Reduction of journal pagination by an increased rejection rate would also contribute to the quality of published work. I do, on the other hand, believe that ALL results, including negative ones, should be published so they are available in the permanent record, which creates a contradiction. I do not see a viable solution to this obvious paradox.

As for the future of our profession, the one major positive factor is that we will never run out of new ideas, especially if we avail ourselves of the interest in and the incorporation of biological methods. Seebach pointed this out 30 years ago and I fully endorse the thought. New ideas, an open mind, and attention to detail will see us through to greater inventions and a return to high integrity.

Notes

1. The younger generation no longer performs combustion analysis or proper melting points. A few years ago a young chemist and I argued about the lack of integrity of published experimentals. When I mentioned that people no longer reported melting points correctly (i.e., with solvent of crystallization and an annotation “crystallized to a constant value”, he commented: “There is no value in a melting point.”

Another chemist, sometime later, when questioned about the lack of combustion analysis said it is not useful because “the samples after chromatography have solvents and would not pass.” How then, I asked, would the yields be calculated, I asked? He had no response.

It should be the responsibility of editorial boards to demand a return to proper experimental integrity.

2. An example of focusing on “underrepresented minorities” can be seen in the recently established “Power Hour” at Gordon Research Conferences. While this effort is commendable in order to increase the participation of women in science it diminishes the contributions by men (or any other group). Universities have established various centers for “Equity, Diversity and Inclusion”, complete with mandatory seminars and training. These issues have influenced hiring practices to the point where the candidate’s inclusion in one of the preferred social groups may override his or her qualifications.

3. The increase in pagination of most journals has been exponential. *Angew. Chem. Int. Ed.*, for example, has seen a 24-fold increase since its inception in 1962:

Year	1962	1970	1980	1990	2000	2010	2018
Pages	693	988	1050	1522	4617	10,229	17,264

Has the quality of publications increased at a similar rate?

4. I am grateful for the data below, kindly provided by Dr. Susanne Haak, Managing Editor, Chemistry Journals, Georg Thieme Verlag KG]. It shows clearly that the majority of papers in these two journals is from China:

Synthesis

Year	China	Germany	USA	India	Russia	UK
2018	21%	10%	8%	7%	6%	4%
2017	19%	14%	5%	7%	6%	4%
2016	18%	10%	6%	9%	3%	2%
2015	23%	10%	7%	15%	3%	3%
2014	22%	14%	8%	14%	2%	2%
2008	12%	17%	10%	10%	2%	3%

Synlett

Year	China	Germany	USA	India	Russia	UK
2018	31%	5%	10%	10%	3%	3%
2017	27%	7%	12%	8%	2%	4%
2016	20%	7%	9%	9%	2%	10%
2015	22%	9%	7%	9%	1%	5%
2014	20%	6%	8%	13%	1%	4%
2008	13%	10%	5%	10%	1%	8%

5. An editorial titled “China’s publication bazaar”⁸ provided evidence of “purchasing” research data or publishing fraudulent results for a fee of ~\$14,000, payable on publication. With the ever-increasing volume of publications it is rare that a repetition of published work would uncover either sloppy science or fraud. We recently had the opportunity to repeat published (and later retracted) work from China. In that particular case it became clear that had the authors run a single IR spectrum they would not have published their work.¹⁶

6. Fifty years ago professors took an active part in all laboratory instructions and they taught advanced techniques to research undergraduates, graduate students, and even postdocs. During

my postdoctoral stay in Geneva Professor Oppolzer personally showed me how to distill 3 mg of an oil after I commented that it could not be done. Such practices are all but absent at present. Students are not taught by professors, most of whom have not been at the bench for decades, but by more senior personnel in the research laboratory. At the undergraduate level, I have noticed that some of the TAs in the 2nd year organic teaching laboratories might very likely fail the laboratory course had they been enrolled as students. This situation seems to be the result of the pressure put on faculty to raise research funding in preference to instructional activities. Professors simply do not have the time for hands-on instruction as their tenure and promotion depends on fund raising. The lack of transfer of advanced skills then contributes to lower levels of experimental integrity in the current literature.

7. The trend of replacing full-time faculty with contract instructors is alarming and may eventually lead to abolishing of tenure and the concomitant end of academic freedom of expression. In Canada, the contract instructors make up >50% of university faculty. In the sciences, they account for 34% of the work force.¹⁷

8. Professor Marc Tius's quote, which we used in a recent review on the synthesis of morphine alkaloids, puts the difference in evolution of biological versus chemical methods in perspective:¹⁸

Consider that if you could resurrect an organic chemist from 100 years ago, he would recognize most of the glassware in the lab, and once he spent a month reading about transition metal reagents and a few other novelties from the past 50 years he could understand pretty much everything we are doing, because the goals of organic synthesis have scarcely changed in a century. Now think about performing the same thought experiment with a biologist. The biologist of 100 years ago would be completely mystified by today's biology. Organic synthesis either finds its mojo again or this branch of chemistry as we know it and practice it will be extinct.

—Marc Tius, October 2014

9. Gibson was able to produce indigo by dihydroxylation of indole by a strain of *E.coli* expressing naphthalene dioxygenase. This discovery led to a large-scale synthesis of indigo at Genencor by employing a fermentation process. This stands out as a great example of the use of plasmid engineering for the preparation of compounds of interest. The EPA program titled Green Chemistry Challenge recognized several companies for producing chemicals or polymers via

biotechnology.¹⁹ A recent feature in *Chem. Eng. News* provides an update on making a “greener” indigo dyeing process.²⁰

Advances in Chemical Biology in recent years has allowed publication of unprecedented accomplishments that would not be possible through traditional synthesis. One of the outstanding examples of enzyme engineering is Bachmann’s synthesis of antiretroviral nucleoside analog didanosine (2’,3’-dideoxyinosine)²¹ and the synthesis of islatravir by Merck.²² These bode well for the future of biocatalysis.

10. In the US the reception of biocatalysis by the academic community and by NIH study sections has not been overly positive. Many highly creative chemists have been driven out of business once they switched from “pure” synthesis to enzymatic methods. In the future the funding agencies need to take a more positive view of biological methods applied to synthesis.

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