On Hype, Malpractice, and Scientific Misconduct in Organic Synthesis

by **Rolf Carlson**[a]) and **Tomas Hudlicky**[b])

[a]) Department of Chemistry, University of Tromsoe, NO-9037 Tromsoe
[b]) Department of Chemistry and Centre for Biotechnology, Brock University, 500 Glenridge Avenue, St. Catharines, ON L2S 3A1, Canada

Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday and in recognition of his many contributions to our discipline

Introduction. – This short essay is written as a tribute to *Dieter* who has had a stellar career in synthesis, and who has motivated countless scores of chemists over the years. Most importantly, *Dieter* has always been an outspoken critic of science and art of synthesis especially when he felt that insufficient detail had been applied to a particular project in favor of rapid publication of results. His *Angewandte Chemie* essay *'Organic Synthesis – Where now?'* [1] was, to our knowledge, the first indication in the literature that something may not quite be right with the way the synthetic community operates. Of course, the essay appeared in 1990 when the conduct of chemists was still considered reasonable and ethical. Those were the days, as one could muse, for today the situation is different, and the day-to-day conduct of organic chemists is out of control. What is worse, the at-times unethical conduct of practitioners is tolerated (and to some degree even elicited) by publishers as well as by funding agencies, and there seems to be no end in sight to reverse the trends in over-hyped science, misconduct, or outright sloppy and wilful reporting of erroneous results. The effects of these trends, should they continue unabated, will have detrimental effect on the training of future generations of chemists.

Since *Dieter*'s essay, many other documents have appeared that are critical of the current state of affairs. Our review in 1996 entitled '*Design constraints in practical syntheses of complex molecules: Current status, case studies with carbohydrates and alkaloids, and future perspectives*' [2] was even more critical of the trends of the time and ultimately led to the publication of a book, '*The Way of Synthesis*' in 2007 [3]. In this book, a detailed analysis of the changes in the conduct of chemists at the onset of the 21st century was presented. Most of these changes were negative and have not contributed to the advancement of our discipline. Since that time, essays have appeared that offered criticism of excess hype [4], and various metrics were invented for judging performance of academics. Be it the 'efficiency' of synthesis, such as the so-called 'atom economy' concept [5], which carries with it no information about the process, or the 'efficiency' of publications, such as the '*h*-index' [6], these 'metrics' do little to advance the integrity of scientific pursuit. Of course, there are scientifically valid metrics developed to evaluate true efficiency of a synthesis, but these are largely ignored by academics[1]). The concern over scientific misconduct [8], fraudulent reporting of

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[1]) For examples of various efficiency metrics, see: *Definition of Evalue/EQvalue:* [7a – 7c]; definition of *Effective Mass Yield* (*EMY*): [7d]; definition of *Reaction Mass Efficiency* (*RME*): [7e].

results, and finally, the alarming rise in retractions of scientific publications [9] is often voiced but very little progress is on the horizon as far as abating these trends.

In this short essay, we attempt to summarize some of these trends and provide suggestions for a reversal and the return to a more honest pursuit of science.

Concerning Current Trends in Hype. – *The Use of Hype in Titles and (Graphical) Abstracts of Publications.* What precisely constitutes hype in organic synthesis, the reader may ask? To answer the question, the reader would have to be older than 50 years so that he or she would be knowledgeable of the manner in which scientific disclosures were made then and now. We may begin with the discussion of titles found in the current literature and compare them to those of the past publications. In the 1970s communications concerning synthesis may have been titled: *'Total Synthesis of Vernolepin'*, for example. Today, one may find catchy descriptors such as: *'Highly Efficient and Remarkably Stereoselective Synthesis of…'*, *'Concise Total Synthesis of…'*, *'Facile Chemoselective Reduction of Highly Functionalized…'*, and much worse. What usually follows, once the reader actually examines the content of the article, is a major disappointment as the contents do not in any way match the advertised merit. Is this hype, false advertising, malpractice, or outright scientific misconduct? In principle, false advertising does not constitute misconduct, especially since it occurs daily in the media: *'Bud, the king of beers'*, is a glaring example of false advertising, as just about any brand of beer is far better than the (American-made) *Budweiser*. In the business-driven society, such blatant and false adverts are accepted by the population at large, and only the more intelligent citizens understand the motives and ignore the message. It would appear that these practices have finally infected the format of scientific disclosures, be it titles or graphical abstracts. Most readers know this trend to be damaging to science but the practice continues because administrators and granting agencies do not evaluate scientists by the content of their articles but rather by the 'perceived' stature (*i.e.*, impact factor) of the journal in which the article is published in. When various 'metrics' such as 'impact factor', or '*h*-index' are used exclusively as means of evaluation of scientific performance, the quality clearly suffers. A very thoughtful commentary by *Richard Ernst*, titled '*The Folies of Citation Indices and Academic Ranking Lists: A Brief Commentary to 'Bibliometrics as Weapons of Mass Citation'* put the inappropriate use of metrics in perspective [10]. The commentary concerns an article on bibliometrics published in *Chimia* by *Molinié* and *Bodenhausen* [11]. *Ernst* concludes the commentary thus:

> ***'… as an ultimate plea, the personal wish of the author remains for sending all bibliometrics and its diligent servants to the darkest omnivoric black hole that is known in the entire universe, in order to liberate academia forever from this pestilence. And there is indeed an alternative: very simply, start reading papers instead of merely ranking them by counting citations! …'***

Hence the clear *'Catch-22'* in dissemination of scientific results and the trends in over-hyped science. As long as the foolish use of various metrics continues there is little hope of return to integrity. Young scientists entering academia and competing for resources and recognition are easily infected with the mantra of importance of publishing in 'high-impact journals' and, therefore, strive to make their work as noticeable as possible by employing excess hype.

It is the reader, not the author, of papers describing synthetic method who should evaluate its merits. Therefore, self-promoting words like *'novel'*, *'new'*, *'efficient'*, *'simple'*, *'high-yielding'*, *'versatile'*, *'optimum'* should not be used in the title of the paper if such qualities are not covered by the actual content of the paper. (For the claims of optimum conditions, see the discussion below.)

Organic synthesis is a challenging field of science that also must be considered as a craft and as an art form. Intuition and creativity are essential components of organic synthesis and more often than not an important discovery can be described as *'a carefully observed accident':*

> *'It is by logic that we prove, but by intuition that we discover. To know how to criticize is good, to know how to create is better'.*
> *Henri Poincaré*, 1854–1912 [12]

However, the final report of any conducted experiment must adhere to precise rules of the scientific method, and must, by definition, be honest and reflect the reality of the experiment. Complex molecules are prepared by joining together smaller, simpler, building blocks by well-defined synthetic reactions to yield the desired target molecule by a selected synthetic route. However, when even one attempted reaction fails, the entire strategy fails. Hence, the development of new synthetic reactions and procedures is vital to the progress of organic synthesis. But the probability of discovery of a brand new method is relatively small:

'… it is not likely that a new synthetic method will be discovered that is based on the chemistry of elements in the first two rows of the periodic table. Almost certainly, any new method will require participation of transition metals'… (*Dieter Seebach*, January 2010 [13])

In this context it is of utmost importance that new synthetic procedures are presented in such a way as to permit a thorough evaluation by future users. Thus, editors and reviewers of submitted manuscripts have a serious task: if a paper claims to present a *new method*, a *new protocol*, or a *new procedure*, then the method *per se* should be evaluated, rather than advertising a single conversion of one compound to another by the reported method.

Inflated Values of Reported Yields. There has been tremendous inflation in the values of the reported yields in the literature in the past 20 or so years. This topic has been addressed on several occasions, most recently in a report that provided experimental proof of the limits in yield values that can be obtained by standard purification methods [14]. This report also provided some insight as to why such yield inflation occurred, and why it continues unabated, despite the fact that most practitioners agree such trend is detrimental to the credibility of results placed in the permanent record.

Yields should always be reported as a range of values obtained in repeated operations of the method. Yields should never be reported as single figures, as this does not provide any information about the reproducibility of the method. Any yield reported in the literature should refer to the isolated yield of the pure compound, and the criteria of purity should always be stated.

All practitioners of organic synthesis understand that a synthetic protocol is composed of several steps: the reaction itself, workup of the crude product, and purification of the crude product. A reported procedure should contain detailed information pertaining to all these steps. That a reaction gives a quantitative *conversion*, as determined by some chromatographic or spectroscopic method, in no way implies that the reaction gives a quantitative *yield*.

Unfortunately, the community has chosen and continues to choose the yield values in submitted manuscripts as a measure of overall quality and/or utility of the report. This, of course, encourages the 'adjustment' in the values in order to avoid critique. An additional problem in the reported values is the fact that synthesis is performed on small scales, thanks to advances in NMR and other techniques available for structure determination. On milligram scales it is extremely difficult to accurately determine weight and content of a sample, given the equipment available in typical academic laboratory. Finally, it would appear that the average personnel conducting synthetic organic procedures today is not well trained in techniques and protocols. This last aspect is the result of diminished presence in the laboratory of true 'mentors' or 'masters' to conduct proper training of the 'apprentices'. As long as the professor is busy writing research grants, he or she cannot adequately train the students, and the final consequence of such conduct is the multitude of publications reporting sloppy results and irreproducible science.

Whether the reporting of inflated yield values falls into the category of hype or malpractice is open to discussion; it would seem such action spans both descriptors. There is, however, no question that reporting inflated yield values automatically leads also to inflated descriptors in the tiles of such articles.

Concerning Malpractice. – What constitutes malpractice in medicine or law is usually quite clear to the general public. It can range from incompetence of the professionals involved to wilful misrepresentation of skills or conclusions. It is true also in science but it is important to separate incompetence of the scientist (*i.e.*, malpractice) from wilful falsification of data (*i.e.*, fraud or misconduct):

Mal·prac·tice *n.* 1. Improper or negligent treatment of a patient, as by a physician, resulting in injury, damage, or loss. **2. *Improper or unethical conduct by the holder of a professional or official position.* 3. *The act or an instance of improper practice.* 4. *Immoral, illegal, or unethical professional conduct or neglect of professional duty.* 5. *Any instance of improper professional conduct.***

The points emphasized above certainly apply well to the conduct of scientific research. The fine distinction between malpractice and fraud derives from the definition below which contains the word '*deliberate*'. Thus, malpractice in organic synthesis may be explained (but *NOT* excused) by poor training of the professionals involved. Fraud, on the other hand, clearly occurs with full knowledge and intent of the individual committing it.

Fraud n. 1. *A deception deliberately practiced in order to secure unfair or unlawful gain.* 2. *A piece of trickery; a trick.* 3. *Deliberate deception, trickery, or cheating intended to gain an advantage.* 4. *An act or instance of such deception.*

Further distinctions will be made when we discuss misconduct. Malpractice, as explained above, is usually not deliberate and derives primarily from ignorance or professional incompetence. The most frequent cases involve improper experimental protocols, improper methods used in characterization of compounds, and the lack of correct citations to previous work. It could be stated that the recent rise in retractions of journal articles originates mostly from malpractice and rarely from fraud. However, there have been recent cases of deliberate fraud and fabrication of hundreds of research papers. The story of *Joachim Boldt* [15] or *Yoshitaka Fujii* [16], who have 'faked' many scientific papers, are perhaps the most compelling.

In chemistry, especially in organic synthesis, deliberately fraudulent papers are difficult to prove unless someone repeats the work. Unfortunately, rarely will a 40 + step synthesis be repeated, and thus potential fraud would go undiscovered. When published yield values are found to be irreproducible, the authors are usually not accused of deliberate fraud, as proof of such intent would be difficult.

The Use of Inappropriate Methods and Methodology. The words *optimum*, *optimized*, *optimization* are of Latin origin: '*bonum, melior, optimum*' meaning '*good, better, best*'. Any claims of optimum experimental conditions must be supported by experimental data, showing beyond doubt that there are no other conditions that give even better results.

Often publications contain the following statement: '*the experimental conditions were optimized*'. Such a sentence is totally meaningless unless it is stated explicitly in what respect the conditions were optimized. It could be: the 'maximum yield', the 'maximum selectivity', the 'lowest cost', or any other criterion. Without defining the optimization criteria, the word 'optimum' does not mean anything.

About 30 years ago, one of us (*R. C.*) went through the literature of recent synthetic reactions with a view to testing new methods in an advanced course on synthetic methods. More than 2000 papers that reported new reactions were scrutinized, and 200 were selected for experimental testing. Out of the more than 2000 papers on new procedures, some of them in prestigious journals, only four (4) presented methods that were properly optimized, despite the fact that many of the other papers claimed to present 'versatile', 'efficient', 'convenient', or 'optimum' procedures. A similar survey of the recent literature was repeated 15 years ago with an equally disappointing result. The situation is not much better today.

Based on the above surveys, several inappropriate uses of the word 'optimum' have been noted:

1. A footnote '*yields are not optimized*' is added to the experimental section. This is, at least, honest, but is not appropriate if the paper claims to present a '*new*', '*versatile*', '*efficient*' method.
2. The best result obtained is reported as the 'optimum' result without giving any experimental details to support the conclusions as to the 'optimality' of the method.
3. The experimental conditions have been explored by investigating one-variable-at-a-time. That such an approach is inappropriate when there are interaction effects between the variables was clearly demonstrated in 1935 [17], and in synthesis optimization more than 60 years ago [18]. Interaction effects occur

when the influence of a variable is affected by the setting of other variables. It may well be that the variables can be *adjusted* independently, but when they act upon the reaction, they may have a joint influence. By investigation of one-variable-at-a-time there is no way to have any information, whatsoever, on the interaction effect, and, hence, any conclusions as to the optimum conditions from such studies can be completely misleading.

4. A more sophisticated, but equally misleading, method is to *derive* the optimum conditions from physical-chemical models. Such models are generally one-variable models, and as such they do not account for interaction effects.

For optimization of the experimental condition against any criterion of optimality, it is necessary to use an experimental design that can jointly handle all the variables considered. *i.e.*, a multivariate statistical design [19]. It is, therefore, astonishing and disappointing that statistically designed experiments are so seldom used in academic reports on new synthetic methods. An often heard argument against such methods is that they are too mathematical. This is *not* a valid argument, since the same persons who forward such criticism gladly use *ab initio* or *DFT* methods to support their chemical reasoning, and they as well use *fast* Fourier *transfom spectroscopy*. Such methods involve quite advanced mathematics. Maybe we will see a change in the future, since *Design of Experiments* (DoE) and *Quality by Design* (QbD) are now necessary in process development for pharmaceutical production.

Standardized Experimental Conditions. Should we have written a book on bread-making in which we claimed that all kinds of bread (sponge cakes, ginger biscuits, peanut cookies…) should be baked for exactly the same time in the oven and at the same temperature, we doubt that anyone would have taken such a book seriously. Every baker and every housewife know that it is necessary to adjust the baking condition to fit the bread being made. However, this common knowledge seems to stop at the doorstep of the synthesis laboratory. The dough is defined by its constituents (flour, salt, water/milk, fat, yeast/baking soda, spices, *etc.*) and their relative proportions. It is then subjected to thermal treatment in the oven. Bread-making is not very different from organic synthesis. A reaction mixture is defined by its constituents (nature of substrate, nature of reagents and co-reagents, catalyst, solvent, *etc.*) and their relative proportions. The constituents are then subjected to further treatment such as heating or cooling, stirring, and other experimental conditions.

The *reaction space* can be defined as the combination of all possible substrates, reagents, catalysts, and solvents. A specific reaction system is defined by one selection of these possible combinations. The example shown below is a clear-cut illustration of an improper methodology when the objective is to determine the scope of new reagents.

The following is a quotation from a review paper by *H. C. Brown* and *S. Krishnamurthy* titled '*Forty years of hydride reductions*' [20]:

> **'Methodology for the exploration of general characteristic of new reagents Objectives.** *For defining the reducing characteristics of each new reagent, its reactivity was determined towards a group of 56 representative organic compounds (in recent years the group has been expanded to over 70 compounds) containing the*

> *more common functional groups of interest in reductions.* ***The reactions were carried out under standard conditions (usually tetrahydrofuran solvent, 0°). Normally, four equivalents of hydride per mole of the functional group were employed.*** (Emphasis by the present authors.) *The solutions were permitted to stand for varying intervals of time, and the aliquots were analyzed for residual hydride. In this way we were able to define the approximate rate and the stoichiometry of the reaction. In this review we shall attempt to define the characteristics in terms of its behaviour towards twelve representative organic functional groups: aldehyde, ketone, acid chloride, lactone, epoxide, ester, carboxylic acid, carboxylic acid salt,* tert-*amide, nitrile, aromatic nitro compound, and olefin.* ***Such an explorative study carried out under standard condition gave us insight into the possible areas of application for the new reagent.*** (Emphasis by the present authors)'

According to the experimental design described above, a series of test substrates is studied with *one* reagent in *one* solvent. This corresponds to a one-dimensional excursion through the reaction space. The other dimensions are not explored at all, which leaves a large part of the possible reaction space unexplored. In addition, the reactions are studied under *'standard conditions'*. The sad fact is that such designs will reveal the scope of a new reaction *only, and only if* each of the studied reactions gives an excellent result. If some of the substrates should give inferior results, it is not a valid conclusion that the reagent is unsuited for these substrates. It might well be that the *experimental conditions* should have been adjusted to fit these substrates, or that the reaction should have been run in another solvent. Unfortunately, results obtained by procedures like the one above are legion and enter into review articles, books as new knowledge on synthetic reactions. To make fair comparisons, the experimental conditions should be taken into account, and adjusted towards an acceptable outcome of the reaction, not necessarily the optimum conditions even if this would be highly desirable. The danger of using 'standardized conditions' has been emphasized in [19c].

Improper Methods of Characterization. There is no question that the use of high-field NMR methods greatly accelerated progress in organic synthesis and made it possible to lower the scale at which reactions are performed. On the other hand, the dependence of practitioners on (primarily) *ONE* method of determination of structure has led to numerous errors in structure assignments, as evidenced by a recent compilation of such errors by *Nicolaou* and *Snyder* [21]. Because of lower scales of operation, many methods of characterization, once taken for granted, are not being performed. It is very unfortunate that most organic journals do not require combustion analysis as a criterion of purity and accept high-resolution mass-spectral data and NMR spectra for such purpose. It is also unfortunate that a large majority of students and postdocs do not understand the concepts such as constant values of melting points, boiling points, or optical rotations. Thus, the current literature contains melting point values (without solvent data!) that were determined on material that solidified after column chromatography and was not further crystallized. Such information in the permanent record is absolutely meaningless. The cause for such conduct, clearly labelled as malpractice, is certainly a lack of emphasis on proper training that was once conducted by professors, not fellow graduate students. Until the practicing chemists and journal editors return to proper practices of integrity in synthesis, the data deposited into the permanent record may not have any lasting value for future generations. Or, as the Research Manager at *Cambrex Karlskoga AB*, *Lars Eklund*, said with frustration: *'The yields reported in* Justus Liebigs Annalen der Chemie *from the 19th century are more trustworthy than the yields reported in* JACS *today for milligram-scale synthesis'.*

Concerning Scientific Misconduct. – In this last section, we address briefly scientific misconduct as it relates to organic synthesis. The desire of scientists to be recognized provides many opportunities for dishonest conduct and such trait is likely as old as humanity. Nevertheless, there has been a sharp rise in occurrence of misconduct and the issue is a frequent topic of discussion [22]. As pointed out above, such misconduct is difficult to prove. One of us (*T. H.*) once had an agreement with a senior organic chemist in the US about publishing our total syntheses back-to-back. This agreement was made when the senior chemist was behind in delivery of his results. Once caught up, not only did he not honor the agreement but he published data that we shared with him under his name only. Later, he submitted parts of another chemist's grant application as his own to a funding agency. Other than some mild form of censure, no real punishment befell this investigator.

Plagiarized copies of books sold in China²) constitute another form of misconduct and indicate low level of respect for intellectual property. There is little legal recourse available to stop or even reduce scientific misconduct. The competition for resources in the pursuit of science in the 21st century has driven many people to desperate measures. The quantity of research papers is growing exponentially (as evidenced by the tremendous increase in the annual pages of journals) while quality clearly sufferes. Until the scientific community 'equilibrates' and returns to high-integrity practice, malpractice, fraud, and misconduct will continue. The last 20 years have witnessed many essays on these topic as well as analysis as to the reasons for occurrence. *Gottfried Schatz*'s essay entitled *'Letter to a young scientist'* outlines the challenges facing the New Professor [24]:

> '*Half of what we taught you is probably wrong, but unfortunately we do not know which half*'.

Conclusions. – Organic synthesis is a discipline that demands total devotion and a life-long dedication from its practitioners. We (the authors) would hope that we fall into such a category. We have published many papers, not for the sake of augmenting our lists of publications or for improving our CVs, but because we are proud and happy to share our accomplishments with the chemical community. We do not see too many examples of such conduct in the current community, as today things are certainly different from the *'Golden Days of Synthesis'*, *i.e.*, 1960–1990, or so.

When the writing of the book *'The Way of Synthesis'* was finally coming to an end, the last part of the book, called *'Outlook'* [25], offered a variety of reasons why the field of organic synthesis is in a state of crisis. Many articles and reflections have been written

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²) The book cited in [23a] is an unauthorized Chinese translation of [23b]. Even the figures and illustrations have been taken form the original published by *Elsevier*.

on the topics of fast and sloppy science, whether deliberate or not. The primary cause for all the misplaced agendas that we are the victims of today is the single paradigm shift in university life in the last three or four decades: the universities are now run and managed as corporations by people who are not academics but rather businessmen, interested in profit. All problems mentioned in this and other essays derive from this single and most unfortunate evolution ever to occur in academia. This is why the book mentioned above ended with the following quote, one of my favourite ones:

'Things don't have to be the way they are. Despite all the evidence to the contrary, I remain optimistic' [26].

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Personal Recollections:

Rolf Carlson. My first recollection of you was from a paper from you on the metalation of the methyl group of thioanisole with BuLi and TMEDA as reagents. This paper was the starting point of my involvement in synthetic chemistry. I was with *Salo Gronowitz* at that time, and he wanted me to investigate possible lateral metalation in methyl-substituted five-membered heterocyles such as thiophene, pyrrol, and furan. It was my diploma work for B.Sc. Then, *Salo* kicked me out (we did not like each other), and I continued at the University of Umeå with Prof. *Christoffer Rappe*.

I first met you personally at the very first ESOC meeting in Köln in 1979. You left the lecture hall and went to your car to load some boxes of German wine into your car. I approched you with the intention of introducing myself and share with you my ideas for an experimental program that I was about to start. I wanted to focus on the experimental approach whereby an idea for a synthetic reaction could be elaborated into a reliable method. This involves statistically designed experiments. This was then an almost virgin area of synthetic chemistry domain. You listened to what I had to say, but I could see that you were a little reluctant to my ideas.

Nevertheless, I continued down my own trail, and when I had the opportunity to invite you to the Norwegian Winter Organic meeting in 2010 I was very happy that you accepted my invitation. I wanted to show you what happened with my wild ideas put forward in 1979. I have now written two books on Design and Optimization in Organic Synthesis, and I was happy to show them to you.

Best wishes and happy Birthday!

Tomas Hudlicky. My own recollection of meeting you, *Dieter*, dates back to September 1982. I had just arrived at Virginia Tech and I was 'selected' to pick you up at the Roanoke airport; you were visiting us as the first Atlantic Coast Lecturer that year, the inaugural year of this program. You told me later that you would never forget how we met at the airport and I threw your luggage in the back of my *F-150* pickup truck (the 'official' vehicle of the American South, complete with a gun rack) for the ride to Blacksburg. You also recalled that, during the ride over, I told you stories from my previous place of employment, Illinois Institute of Technology on Chicago's South

Side, where it was customary to travel around the neighborhood with at least a knife in one's boot, if not something more effective than that in one's pocket. Your lecture *'Organometallic Reagents in Synthesis – from Lithium to Titanium and Zirconium'* was fantastic. I also enjoyed a nice dinner with you and colleagues before you went off to the other five universities that participated in the Atlantic Coast Lectureship program.

As I wrote the chapter for *Paul Wender*'s topical issue of *Chemical Reviews* in 1996, I was inspired by your *Angewandte* essay *'Organic Synthesis – Where now?'* (and I still am). After all, my chapter as well as the book *'The Way of Synthesis'* that evolved from it, begin with a reference to your essay. I am reminded almost daily of the fact that you were a co-author on the seminal paper *J. Org. Chem.* 1975 on the use of dithianes in synthesis (likely one of the very few full papers that *Corey* ever published!). And I was very happy to see you again in *Fefor* in 2010, in full force, and very critical of the young charlatans working in (but not understanding the details of) organocatalysis in another one of your inspiring lectures. Let's keep after all the various frauds and impostors that abound in our community!

It has been a real pleasure to know you, and I wish you the very best on your birthday.

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