

# A Case for Mechanisms

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**Abstract:** A case study in the (re)discovery of a non-diazo, catalytic, electrophilic cyclopropanation reaction is presented to illustrate the role of mechanistic concepts in chemical innovation. The specific instance also highlights how specif-

ic personalities interacted in the report, retraction, and re-consideration of a novel methylene transfer reaction. The case study ends with a series of lessons learned, which generalize the findings from the specific case.

**Keywords:** history of science · organometallic chemistry · physical organic chemistry · reaction mechanisms · Wittig reactions

## 1. Introduction

The idea for a *Rosarium philosophorum* on physical organic chemistry originated over dinner in a Druze restaurant in northern Israel at the end of April 2014. It is challenging to write an essay on physical organic chemistry – the state of the field and the prospects for the future – which does not degenerate into generalities or platitudes. Most certainly not appropriate (at least for our contribution) is a list of new fields, for which there are many that can already be found. We find a case study on the role of mechanistic concepts to be perhaps more timely. A specific instance with concrete details from which we abstract more general lessons does correspond better to the way in which one practices organic chemistry. The coalescence of the new subdiscipline within organic chemistry from the various antecedent developments may be dated with the appearance of Louis Hammett's *Physical Organic Chemistry* in 1940. We may find the first paragraphs of the preface to the first edition to be particularly illuminating:

“It is one of the commonest occurrences in the development of science that the necessary subdivision of the subject leads to a temporary neglect of phenomena lying on the borders between the specialized fields. Sooner or later the deficiency becomes too patent to be overlooked, and a new specialty makes its appearance. Something of this sort has been happening in the last two decades on the borderline between physical chemistry and organic chemistry. For a time, it was almost a point of honor with both physical and organic chemists to profess ignorance of the other's field, and it remains a useful defense mechanism, if any is needed, to excuse the fact that specialization entails limitation as well as intensification of knowledge. Meanwhile there has grown up a body of fact, generalization, and theory that may properly be called physical organic chemistry. The name implies the investigation of the phenomena of organic chemistry by quantitative and mathematical methods.

One of the chief directions that the development of the subject has taken has been the study by quantitative methods of the mechanism of reactions and of the related problem of the effect of structure and environment on reactivity. In no other direction have its results been of such immediate practical importance for the basic problem of chemistry, the control of chemical processes. This part of physical organic chemistry forms the subject of the present book.”<sup>[1]</sup>

For this *Rosarium philosophorum*, we would like to explore the question of how physical organic chemistry works for the issues in the Hammett citation above, both with respect to the opportunities, as well as the pitfalls that the particularly mechanistic point-of-view introduces. We choose to relate a narrative on a particular research project in my group, not so much because it will have the impact of transition state theory<sup>[2]</sup> or molecular orbital theory<sup>[3]</sup> in the development of physical organic chemistry, but rather because it casts Hammett's statement that “specialization entails limitation as well as intensification of knowledge” in concrete terms. The limitations posed by specialization make rigor possible, but they also underline the importance that one look for ideas which may be external to a research field. Our modest example serves to show how science is actually done, with all of the very human personalities involved, and it serves to show how ideas set limits, but simultaneously make possible depth, in research. The narrative starts with a chronology and some history, goes to present-day research, and concludes with some lessons which we can take from this particular

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episode in relation to the challenge of new reactivity, which we hope are much more general.

## 2. Chronology

### The Players

In 1960, Georg Wittig (1897–1987) was the head of the Institute of Organic Chemistry at the Ruprecht-Karls-Universität Heidelberg, having been on the faculty in Tübingen (1944–1956), Freiburg (1937–1944), and TU Braunschweig (1932–1937) after university studies and habilitation in Marburg. He had achieved considerable recognition and reputation in the chemistry of carbanions, and more generally as a discoverer of novel reactions, including two transformations, the eponymous olefination and rearrangement, which have been used extensively

since. He was one of the discoverers of *o*-benzyne, which came unexpectedly from his studies of ortho-metalation reactions. As noted in a short biography by Hoffmann,<sup>[4]</sup> Wittig was an ardent explorer and discoverer in the chemical realm, and, furthermore, a very careful experimentalist who paid close attention to the details of the work by his students. Hoffmann recounts that Wittig would personally check the raw data of his co-workers. The Wittig olefination of carbonyl compounds with phosphorus ylids is perhaps his most generally known reaction, and it is the entry for most starting chemistry students into the reactions of ylids. Less known, however, is that the initial discovery of ylids, by Wittig and Wetterling in 1947, was not done for phosphorus ylids, but rather nitrogen ylids, produced by a reaction of tetramethylammonium bromide with phenyllithium in ether in an unsuccessful attempt to prepare pentavalent nitrogen.<sup>[5]</sup> The

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Tim den Hartog studied at the University of Amsterdam, NL, and obtained his Ph.D. in 2010 in synthetic organic chemistry (A. J. Minnaard and B. L. Feringa, University of Groningen, NL). From 2010 to 2013 he conducted post-doctoral studies in the Chen group at the ETH Zürich, CH, supported by a Marie Curie IEF personal scholarship. At the ETH Zürich, he pursued the rational development of new methylene methods using alternative methylene analogues. Currently he is a post-doctoral fellow at RWTH Aachen University, DE (J. Klankermayer and W. Leitner) and holds a RWTH Start-Up grant. His research interests include rational method development, elucidation of reaction mechanisms, and sustainable chemistry (cradle-to-cradle design in chemistry).



Juan M. Sarria Toro received his B.S. (2007) and M.S. (2009) degrees in Chemistry at the Universidad Nacional in Bogotá, Colombia. He then moved to Switzerland to earn his Ph.D. (2014) under the supervision of Prof. Peter Chen at the ETH Zurich. His work in the study and development of carbene-mediated reactions was honored with the ETH silver medal. Juan is currently undertaking a postdoctoral stay as an SNF Fellow in the group of Prof. Antonio Echavarren at the Catalan Institute of Chemical Research (ICIQ) in Tarragona.



Prof. Chen, B.S. Chicago 1982, Ph.D. Yale 1987, was Assistant Professor (1988–1991) and Associate Professor (1991–1994) at Harvard University. He was called to the ETH Zürich as Professor of Physical Organic Chemistry in 1994. From September 1, 2007 until September 30, 2009, he was Vice President for Research and Corporate Relations. From 2010 to 2015, he was a member of the Research Council of the Swiss National Science Foundation, from which he was elected to the Executive Board of the Swiss National Science Foundation, serving 2012–2015. His research and teaching centers on reactive intermediates and reaction mechanisms, often using new physical methods. Presently, the chemical focus of the group remains on homogeneous catalysis. In addition to other mandates, he is a Director of Clariant Ltd, a leading specialty chemicals company. Of the numerous honors, Prof. Chen is most proud of the “Golden Owl” in 2005, awarded for the best teaching in each department.



phosphorus ylids were first found by Wittig and Rieber in 1949 in what was supposed to be a control experiment,<sup>[6]</sup> with the olefination reaction following with Wittig and Schollköpf in 1954.<sup>[7]</sup>

In 1960, Volker Franzen was a 36 year-old *Privatdozent*<sup>[8]</sup> working at the Max-Planck-Institut für Medizinische Forschung at Heidelberg under the institute director, Richard Kuhn. Since the award of his Ph.D. in Hamburg in 1952,<sup>[9]</sup> Franzen published prolifically, producing original studies, patents, and reviews on reaction mechanisms; SciFinder finds about 100 entries. In particular, he had published a major monograph, titled *Reaktionsmechanismen*, which was undoubtedly one of the first of its kind.<sup>[10]</sup> Starting in 1958, Franzen reported a number of studies on the reactions of ethers and amines with methylene,<sup>[11,12]</sup> as well as some other carbenes,<sup>[13]</sup> produced typically by photolysis of the corresponding diazo compounds. In particular, in his reported reactions of methylene with ethers and amines, he rationalized the end products by postulating an intermediate oxonium or ammonium ylid that subsequently reacted intramolecularly to make the observed products. Franzen further reported<sup>[14,15]</sup> the stoichiometric cyclopropanation of  $\alpha,\beta$ -unsaturated carbonyl compounds with sulfur ylids as a carbene donor contemporaneously with Corey and Chaykovsky.<sup>[16]</sup> Being convinced that methylene and an ether, amine, or sulfide react to form the corresponding O-, N-, or S-ylid, Franzen conjectured that an independently synthesized N-ylid, for example, should dissociate thermally to produce a tertiary amine and free methylene. Amine exchange between trimethylammonium fluorenyl and an external amine was taken as definitive evidence for a reversible,<sup>[13]</sup> thermal generation of a free carbene in solution. One may discuss alternative explanations for the observations, based on what we now know about bond strengths, but the conjecture was quite reasonable, especially for 1960. Wittig and Polster had also reported contemporaneously that the putative N-ylid adduct produced by deprotonation of tetramethylammonium bromide with PhLi gave, among other products, “polymethylene” upon decomposition,<sup>[17]</sup> which was also interpreted at the time as evidence for free methylene.

### The Play

In 1960, Franzen and Wittig<sup>[18]</sup> published a brief report in *Angewandte Chemie* in which it was claimed that the LiBr adduct of trimethylammonium methyllide, an N-ylid produced by deprotonation of tetramethylammonium bromide by a PhLi/PhNa mixture in ether,<sup>[19]</sup> a formulation described as more reactive than the PhLi in the original Wittig and Wetterling recipe,<sup>[5]</sup> could cyclopropanate cyclohexene in 5–18% yield. Accompanying the norcaradiene product was “polymethylene,” which was, as before, taken as evidence supporting the transient intermediacy of free methylene. The experiment had been performed

at the Max-Planck-Institut by Franzen.<sup>[20]</sup> Wittig subsequently gave Dietlinde Krauss, a new student in the group credited by contemporaries in the Wittig laboratory to be an exceptionally careful experimentalist,<sup>[21]</sup> the task to reproduce the cyclopropanation. Given the absence (other than the then-newly-discovered Simmons-Smith reaction)<sup>[22,23]</sup> of a general electrophilic cyclopropanation of unactivated olefins without diazomethane, one may understand the excitement that even the low and variable yield in the 1960 Communication engendered.

### The Sequel

Krauss could not reproduce the 1960 results under any set of conditions. Wittig explicitly retracted the claim in a paper with Krauss published in 1964.<sup>[24]</sup> Krauss' dissertation from the Ruprecht-Karls-Universität Heidelberg documents the systematic and extensive, but nevertheless unsuccessful, attempts to reproduce the methylenation of cyclohexene to norcaradiene.<sup>[25]</sup> According to contemporaries from Heidelberg circa 1960,<sup>[26]</sup> and carbene chemists elsewhere,<sup>[27]</sup> there were rumors and speculations about the original work. In 1962, an American group reported that a separate claim by Franzen in 1960, a trapping of CF<sub>2</sub> by triphenylphosphine to form a P-ylid,<sup>[28]</sup> could not be reproduced,<sup>[29]</sup> worsening the atmosphere. While no formal investigation was initiated, Franzen left Germany and his position at the Max-Planck-Institut, eventually landing at Lonza, a specialty chemical company in Visp, Switzerland, where he rose to become Director of the R&D Division by the time of his retirement in 1989.<sup>[20,30]</sup> Wittig remained at Heidelberg, retiring in 1967. He was awarded the Nobel Prize for Chemistry in 1979, eight years before his death in 1987.<sup>[4]</sup> Dietlinde Krauss remained on staff at the Institute of Organic Chemistry at Heidelberg, heading the institute's analytical services until her retirement in 1994 and death in 2010.<sup>[31]</sup> There have been no further publications following up the 1960 Franzen and Wittig *Angewandte Chemie* Communication after 1964, so definitive was the final judgment by Wittig.

## 3. Chemical Solution to the Mystery

### Our Starting Point

Our starting point in this story is the mechanism-based design of catalytic, electrophilic cyclopropanation reactions that do not need diazo compounds. Electron-poor olefins, e.g., enones, may be cyclopropanated by lithium carbenoids,<sup>[32,33]</sup> or sulfur ylids using the Corey-Chaykovsky reaction,<sup>[16]</sup> in both of which the to-be-transferred (nascent) methylene group reacts as a nucleophile. Aside from the aforementioned Simmons-Smith reaction,<sup>[22,23]</sup> however, there are few electrophilic, non-diazo, cyclopropanations, i.e., reactions where the to-be-transferred methylene reacts as an electrophile,<sup>[34–39]</sup> despite scattered

reports pointing to the possibility of a catalyzed reaction.<sup>[40]</sup> Having spent somewhat more than a decade on mechanistic studies of ruthenium and rhenium carbene complexes for olefin metathesis,<sup>[41]</sup> we believed that we had the expertise and experience to design a new reaction *de novo*. We tried the reaction of sulfur ylids with the Fp cation, as its triflate salt,  $(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2\text{OTf}$ , which would be effectively an umpolung of the  $\text{CH}_2$  on the sulfur ylid. We saw cyclopropanation, but only stoichiometrically, as perhaps one should have expected.<sup>[42]</sup> Irreversible deactivation of the electrophilic metal center by the freed sulfide prevented catalytic turnover. Switching from the very electrophilic Fe center in the Fp cation to the much less sensitive Au(I) complexes, and use of phosphorus ylids, instead of sulfur ylids, opened up the way for an extensive series of mechanistic studies on cationic Au carbene complexes,<sup>[43]</sup> or perhaps more properly termed, Au-stabilized carbocations,<sup>[44]</sup> but these systems also showed no evidence of catalytic turnover in solution, the deactivation of the electrophilic metal by freed phosphine still being unsurmountable.<sup>[45]</sup> We sought a leaving group that would coordinate less strongly to an electrophilic metal, and preferentially also remove itself from the reaction medium. One route led to our published work with imidazolium sulfones as carbene donors.<sup>[46]</sup> Our original idea, however, revolved around trimethylamine and the corresponding N-ylid. Trimethylamine, as a leaving group, met the requirements, being a poor ligand for softer electrophiles, and boiling at only  $3^\circ\text{C}$ , which would mean that it could escape from the reaction as does dimethylsulfide in a Swern oxidation.<sup>[47]</sup> Feeling self-satisfied with a clever idea, we were very disappointed to find that Franzen and Wittig had reported cyclopropanation with trimethylammonium methylide, the N-ylid, and that it had been done five decades previously.<sup>[18]</sup> The retraction was sobering and unambiguous,<sup>[24]</sup> but it left open questions. The 1960 Communication reported identification of the norcarane by distillation of the product out of the reaction and verification against an authentic sample. Even with the low yield, this would mean that norcarane had been isolated in macroscopic amounts. A macroscopic amount of an isolated product is much more difficult to misinterpret than a peak in an NMR or mass spectrum, or a TLC plate spot. Either Franzen misrepresented his results, which made no sense (at least to these authors), or the reaction had worked at least once, even if it could not be reproduced reliably later. Having started looking for a transition metal-catalyzed reaction, we considered the working hypothesis that the presence (or absence) of an adventitious metal cation could have been responsible for the lack of reproducibility of the 1960 report.

Adventitious traces of a transition metal had already played positive and negative roles in several discoveries. Perhaps the most prominent is the nickel effect in the discovery of the Ziegler catalysts. While Ziegler catalysts for

polyolefins are usually described as formulations based on Ti, Zr, or Hf, the original discovery was with Ni, as described in the 1955 retrospective review by Ziegler and coworkers.<sup>[48]</sup> Traces of virtually insoluble nickel phosphate, produced accidentally by an oxidizing acid wash followed by a cleaning with a phosphate-containing solution of an autoclave previously used for catalytic hydrogenation, were lodged in microscopic cracks in that particular autoclave. The nickel salts were inadvertently activated by alkyl aluminum reagents during an investigation of the *Wachstumreaktion* of the alkyl aluminums themselves, producing first dimers, and later polymers, of ethylene. Recognition of the catalysis by a transition metal motivated screening beyond Ni, leading to the optimization of the early transition metal catalysts involved now in the production of polyolefins on the order of 100 Mio tons annually. A more recent, but equally instructive, case has been summarized by Nicholas Leadbeater, who had claimed in 2003 to have discovered a Pd-free Suzuki coupling after extensive controls to exclude transition metals,<sup>[49]</sup> only to find subsequently that Pd contamination, even at a level of 50 ppb(!), of the stoichiometric base,  $\text{Na}_2\text{CO}_3$ , was responsible for the reaction.<sup>[50]</sup> Lastly, recently reported Fe-catalyzed cross-couplings have been found to be due to trace amounts of Cu present in the reagents.<sup>[51]</sup> In the extreme limit, a catalyst need only be present in virtually homeopathic concentrations; the best catalysts showing  $>10^6$  turnovers need, by definition, only sub-ppm concentrations. We considered it therefore plausible that such a transition metal catalyst could have played a role in Heidelberg.

It was possible in principle; could it have happened in fact? Could there have been transition metal impurities in the reaction in 1960? The PhLi and PhLi/PhNa in Heidelberg in 1960 were prepared in the laboratory from PhLi (synthesized from metallic Li),<sup>[52]</sup> organomercurials, and Na wire,<sup>[53]</sup> and then used as prepared with no further purification.<sup>[18,25]</sup> One may speculate that transition metal impurities could have found their way into some of the preparations, especially given that the elemental analyses were by far insufficient to detect traces below the percent level, and the reagents were prepared *in situ*. Moreover, in our own work, we have found Fe, Ni, Cu, and Zn traces ranging up to hundreds of ppm,<sup>[54]</sup> determined by quantitative ICP-MS analysis, even in tetramethylammonium triflate, clean according to ordinary analyses after ordinary recrystallizations. We presume the metals entered via some past contact of an acid with a metal vessel, and were carried along in each subsequent, preparative step. Treatment of the ammonium salt with a strong chelation agent, followed by repeated (3 $\times$ ) recrystallizations from high-purity isopropanol, reduced the transition metal traces by about fifty-fold, but levels in the low single-digit ppm range remained stubbornly detectable. In other words, it is certainly plausible that small, but variable, amounts of potentially catalytic transi-



tion metals in the different stoichiometric reagents could provide sufficient concentrations of a catalyst to induce a reaction.

### Unusual Features of the Reaction

In a recent Communication in *Angewandte Chemie*, we report the Ni-catalyzed cyclopropanation of unactivated olefins, ranging from norbornene to  $\alpha$ -olefins to cyclooctene and cyclohexene, with lithiomethyl trimethylammonium triflate in THF.<sup>[55]</sup> The methylene donor reagent is comparable to the LiBr adduct of trimethylammonium methyllide used by Franzen and Wittig,<sup>[18]</sup> albeit with a different counterion and THF instead of diethyl ether as solvent. The differences produced a soluble and fast reacting “N-ylid” which stands in contrast to the barely soluble and almost wholly uncharacterizable formulation first reported in 1947. We had fully characterized the soluble “N-ylid,” which is more properly to be regarded as a trimethylammonium-substituted alkylolithium.<sup>[56]</sup> The reagent performs methylenations of carbonyl compounds and imines to epoxides and aziridines, and it cyclopropanates styrenes and stilbenes efficiently,<sup>[57]</sup> by way of a carbolithiation/intramolecular ring-closure mechanism, much in analogy to lithium carbenoid reactions,<sup>[32,33]</sup> as well as the Corey-Chaykovsky reaction.<sup>[16]</sup> With unactivated olefins, however, lithiomethyl trimethylammonium triflate displays no reactivity whatsoever, especially when care is taken to exclude transition metals. The cyclopropanation of cyclooctene was chosen as the principal representative for which the analytical aspects of the experiment were optimal, and because the moderate yield meant that there was room up and down for the yield to move as we explored conditions. We found that cyclopropanation of an unactivated olefin does indeed proceed, however, only with transition metal catalysis, which may be regarded as the sought-after umpolung of the to-be-transferred CH<sub>2</sub> moiety.<sup>[55]</sup> The reaction, however, does display a number of odd features which help explain why it was so difficult to find.

The catalytic cyclopropanation of unactivated olefins with lithiomethyl trimethylammonium triflate appears to work exclusively with Ni.<sup>[55]</sup> All indications point to Ni(0), but virtually all Ni complexes appear to work to some extent, with Ni(II) complexes likely reduced to Ni(0) under the reaction conditions of large molar excesses of organolithium reagents over Ni. Fe, Co, Rh, Pd, Pt, Cu, Zn, and Au complexes do not produce cyclopropanation. This stands in contrast to the behavior of diazomethane, for example, which cyclopropanates olefins, with greater or lesser efficiency, with a very broad range of transition metal catalysts.<sup>[58]</sup> The other transition metals appear to catalyze the decomposition of lithiomethyl trimethylammonium triflate into trimethylamine and polyethylene, presumably via ethylene, the latter being observed in some cases.<sup>[57]</sup>

In contrast to many catalytic processes, the yield of product displays a strongly non-monotonic dependence on the catalyst load.<sup>[55]</sup> More specifically, zero catalyst gives zero cyclopropanation; 5 mol% catalyst also gives zero cyclopropanation. The maximum yield of cyclopropanation appears for catalyst loading between 0.1 and 1 mol%. It is important to recognize that the maximum catalytic activity occurs at roughly the part-per-thousand level of the Ni complex relative to the N-ylid, which means part-per-million levels in the solution.

The ordinary Ni-catalyzed cyclopropanation of cyclooctene with lithiomethyl trimethylammonium triflate requires a closed reaction vessel when the Ni catalyst is phosphine-free,<sup>[55]</sup> which we discovered serendipitously because we performed some NMR experiments in tubes closed with Teflon Young valves. Two identical Schlenk tubes, charged from the same stock solutions, differ only in that one is sealed after the introduction of all reagents, while the other remains open, under slight positive pressure on an Ar line. Cyclopropanation occurs in the first Schlenk tube, albeit with variable yield, but not at all in the second. Moreover, a phosphine-containing ligand on the Ni catalyst, or the addition of a phosphine to the reaction when the Ni catalyst has no phosphine ligand otherwise, raises the yield of cyclopropanation and erases the difference between open and closed reactors.

Our (speculative, but largely consistent) mechanistic hypothesis rationalizes the open/closed dichotomy, the phosphine effect, and the non-monotonic dependence of yield on catalyst loading by postulating a *reversible* trapping of the reactive nickel carbene species by a nucleophile,<sup>[59,60]</sup> which reduces the steady-state concentration of that carbene species by a pre-equilibrium, thereby selectively disfavoring homocoupling to ethylene,<sup>[61]</sup> which is second-order kinetically in carbene, relative to cyclopropanation, which is kinetically first-order, all in analogy to the persistent radical effect.<sup>[62,63]</sup> The mechanistic hypothesis is speculative because the detailed work to identify the intermediates, determine their structure, thermochemistry, and kinetics, and then engineer improvements into the catalytic cycle, is only now beginning.

### Comparison to What Happened in Heidelberg

Laboratory records from Franzen's group in Heidelberg a half-century ago are no longer available. The very brief description from the 1960 Communication states only that the reaction was performed by addition of ethereal PhLi/PhNa to a *stark turbinierten*, cooled suspension of tetramethylammonium bromide in cyclohexene.<sup>[18]</sup> The original report of the N-ylid by Wittig and Wetterling in 1947 specified that the reaction of tetramethylammonium bromide with PhLi in ether was conducted in a shaker over several days,<sup>[5]</sup> which would necessarily be a closed vessel. The more reactive PhLi/PhNa formulation, prepared *in situ*, deprotonated the ammonium salt in two

hours, again as a suspension in a shaker, rather than 40–90 hours, according to Wittig's report from 1956.<sup>[17]</sup> The 1960 Communication from Franzen and Wittig appears to use a similar formulation,<sup>[18]</sup> but the text does not specify if the vessel was open or closed, nor is there a detailed experimental describing the preparation of the reagent. When asked, Franzen indicated that he recalled, but not with great certainty, that the vessel was closed.<sup>[20]</sup>

The work reported in the 1964 retraction by Wittig and Krauss<sup>[24]</sup> is much better documented in the dissertation by Dietlinde Krauss.<sup>[25]</sup> A reading of the different parts of the experimental section of the dissertation finds that Krauss specified when particular reactions were done in a sealed vessel. These were done in instances where the reaction needed vigorous shaking. In the great majority of cases, however, the reactions were performed in a three-necked flask open to a nitrogen line.<sup>[64]</sup>

Although strictly speaking not related to the N-ylid story itself, the 1962 claim by Speziale and Ratts,<sup>[29]</sup> in which it was reported that Franzen's 1960 trapping of CF<sub>2</sub> by triphenylphosphine<sup>[28]</sup> could not be reproduced, did not bolster the credibility of the 1960 Communication on cyclopropanation at the time.<sup>[18]</sup> One should note, however, that the formation of a phosphonium ylid from CF<sub>2</sub> and triphenylphosphine has been recently confirmed by three separate groups.<sup>[65–67]</sup>

### Lessons

Although reconstruction of historical events is always fraught with assumptions, and a historical event cannot be truly reproduced in the sense that experimental science demands, one can consider arguments on the plausibility of a given hypothesis. Even in the best cases, a historical hypothesis will necessarily remain speculative, but it may still provide a guide to experimentation. In the present instance, our recent report indicates that it is plausible that the Franzen and Wittig cyclopropanation of cyclohexene with an N-ylid, or its equivalent, could have happened as described, albeit with the intervention of an unsuspected Ni catalyst. Krauss' unsuccessful attempts to reproduce the work can also be explained by the odd features we found for the reaction. While in her survey of reaction conditions, she did execute some reactions in closed vessels, and she did add on one occasion (a large amount of) triphenylphosphine, presumably in an attempt to trap CH<sub>2</sub> stoichiometrically, she never looked for transition metal catalysis. There is no blame to be assigned for not trying something which lay outside the scope of the known or imagined experimental parameters, and the highly specific nature of the catalyst, only Ni, the peculiar requirement of a closed vessel, and the narrow range of catalyst loading that proves effective, means that the sheer size of the parameter space that would have had to have been searched makes it highly improbable that she could have chanced upon the specific combination of con-

ditions that we postulate Franzen found inadvertently. Even modern high-throughput experimentation would have found the problem extremely challenging without the prior mechanistic hypothesis of transition metal catalysis.<sup>[68,69]</sup> This particular narrative, for all of its particularity to one reaction and a few, very specific personalities, contains several general lessons.

The first lesson is the easiest: read the old literature. There is an unfortunate tendency to dismiss old literature as, well, old, and therefore no longer relevant. Even when older work is deemed relevant, it is usually seen only through reviews and textbooks. The actual experimental observations get lost, and one sees only the conclusion filtered through the eyes of someone else. There are jewels buried in the literature, and it takes reading of the original, primary publications to dig them out.

The second lesson is more subtle. Consider what it means to get negative results. Evidence that something *does not work* is no proof that it *cannot work*. Positive results are, by their very nature, existence proofs, even if the yield is low or the conditions peculiar. With even a small, positive result, one can begin the iterative process of optimization and improvement. Negative results, on the other hand, have a much higher burden-of-proof. Even completely negative experiments need careful controls and documentation, but, done properly, they can be immensely informative. At a recent lecture, a prominent academic answered a question concerning things which did not work, saying, that in his group, it is customary not to consider negative results at all. Our present system of publication also mitigates against reporting negative results. This is a problematic attitude.

The third lesson pertains directly to the theme of this *Rosarium philosophorum* on physical organic chemistry. Consider the role of mechanistic hypotheses, in particular, or physical organic chemistry, in general, in the discovery of new reactivity. We all agree that discovery of something new rates among the highest goals to which we aspire. Does the idea precede the discovery, or does discovery precede the idea? Whereas most practitioners of chemical research would underline the importance of working in both directions, there being both rational design and serendipitous observations, mechanistic hypotheses play an increasingly important role in the practice of chemistry, both because of the growing complexity of the questions being asked, and because observations are hardly ever "raw data" anymore. For the latter claim about raw data, consider, for example, what an x-ray structure really means,<sup>[70,71]</sup> especially given how seductively quantitative, and "elementary," the bond lengths and bond angles seem to be. How "raw" are the data actually, or, put in another way, how model-dependent is the bond length that one takes as an experimental "fact?" Among other things, our group builds instruments and develops methods to reduce energy-resolved collision-induced dissociation cross-sections (an experimental

result) to a bond energy (a physical value) in an organometallic catalyst.<sup>[72]</sup> The results are *a priori* model-dependent, and one works with best effort to make sure that the model is physically realistic enough to represent the phenomena adequately. Nevertheless, one inevitably sees data filtered through an interpretive framework from the very onset of the experiment. On the one hand, a mechanistic model constrains the space in which one must work, and by drawing a fence around a particular problem, facilitates the in-depth and rigorous treatment of that problem. It defines what questions are legitimate, and what constitutes a *sufficient and proper* answer to the question. By defining what constitutes a legitimate experiment and what constitutes a proper answer, the mechanistic model necessarily excludes approaches or ideas which could, in fact, be relevant. Here we return to the Hammett quote in the Introduction. While one could take this exclusion as an essential blindness in physical organic chemistry, we would rather see the other side of the coin and suggest that it is *the construction and elaboration of interpretive frameworks*, of which mechanistic models are for us the most immediately visible instance, that constitute the most creative, and the most challenging part of the design and execution of a research project. Construction and elaboration of mechanistic models lie at the heart of physical organic chemistry. At least in the opinion of these authors, physical organic chemistry has fallen too much in love with technological advances, be they spectroscopic/instrumental or computational, much to the detriment of defining new problems and new fields in which the mechanistic outlook inherent to physical organic chemistry may facilitate discoveries that would not have been evident otherwise. New technology is good, because technology helps us solve the problems, but new ideas are better because they define and delimit the problems that may be solved.

The last lesson is perhaps obvious from this essay. Critically question what your professors say. The education of a scientist is successful when he or she exercises reason and creativity to form an opinion despite what authority says must be true. Science is ultimately self-correcting.

#### 4. Conclusion

As Hammett noted 75 years ago, physical organic chemistry originated in the confluence of organic chemistry with concepts and methods from physical chemistry. It is often interpreted as the application of new physical methods, meaning techniques, to organic problems, which is undoubtedly fruitful and has produced significant results. Nevertheless, there is a more important challenge. From the interfaces around organic and organometallic chemistry, we need to harvest ideas, not just techniques. The ideas are more difficult because they give us the chance to see things, even in old results, which we could not see

before. The narrative here is a limited, and very specific, instance, but it teaches the lesson all the same. At the interfaces, we harvest the ideas to learn to see that to which we would be otherwise blind, even in the decidedly classical problem identified by Hammett in his preface: “the control of chemical processes.” The story here is just one example, and perhaps a modest one, but it represents the potential achieved when one changes the question that one asks.

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