Wittig and His Accomplishments: Still Relevant Beyond His 100th Birthday**

Reinhard W. Hoffmann*

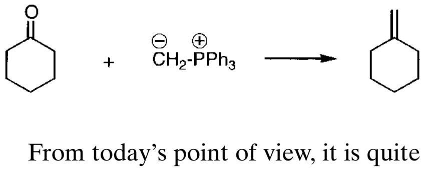
Prof. Georg Wittig

1897	Born in Berlin (Germany)
1916	Enrollment for chemistry at the university of Tübingen
1916 – 1919	Lieutenant and prisoner of war in World War I
1919 – 1923	Studied chemistry in Marburg
1923 – 1926	Habilitation in Marburg
1926 – 1932	Privatdozent in Marburg
1932 – 1937	Junior Professor in Braunschweig
1937 – 1944	Associate Professor in Freiburg
1944 – 1956	Professor in Tübingen
1956 – 1967	Professor in Heidelberg
1979	Award of the Nobel prize for chemistry
1987	Died in Heidelberg

To understand the developments in chemistry at the turn of the 20th into the 21st century, one has to recognize the guidelines laid down at the beginning and in the middle of the last century. Georg Wittig was one of the scientists who, in the middle of the last century, founded such guiding principles. The 100th anniversary of Wittig's birth was in 1997. By virtue of this, Wittig has become a historical person, a subject for the history of chemistry.

Perspectives tend to be shortened when looking at the past, developments are seen in a compression of time and some aspects, which are considered not to be of relevance, are discarded. To evaluate the importance of Wittig's contributions in such a manner one should simply ask which of Wittig's accomplishments are known to the young generation of chemists today. Of course, the Wittig reaction and the Wittig ether rearrangement would be at the top of the list. For many, the name of Wittig is also attached to the chemistry of dehydrobenzene (benzyne). If, however, today's younger chemists do not know more about Wittig's accomplishments, this has to be blamed primarily on those currently in their sixties, for not handing down more information on Wittig to the next generation.

Is the carbonyl olefination of ketones or aldehydes by phosphorous ylids, that is, the Wittig reaction, his most important contribution? The initial investigations by Wittig and Schöllkopf[1] revealed that this reaction allows the conversion of cyclohexanone into methylenecyclohexane [Eq. (1)], a compound with a semicyclic double bond. Structures of this kind could previously only be obtained by circuitous routes and with low selectivity.



(1)

From today's point of view, it is quite normal that this very aspect of Wittig's chemistry found an immediate application

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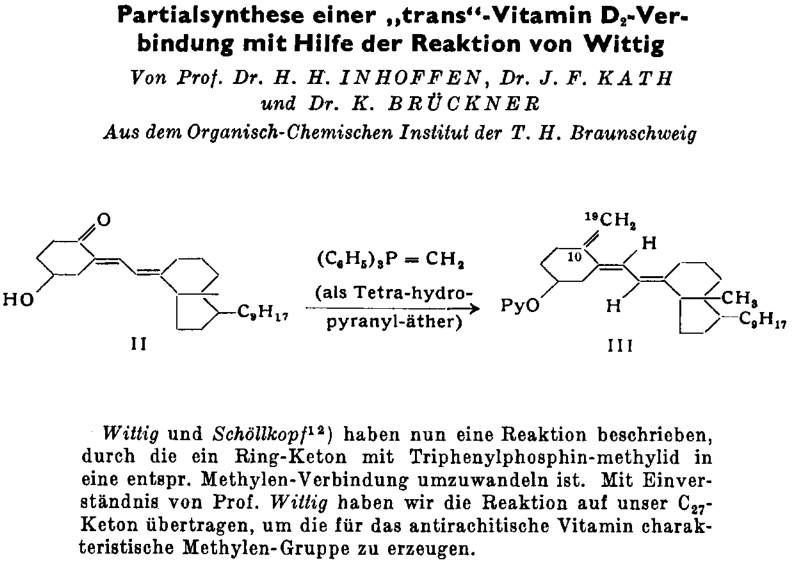
[**] A condensed version of a lecture given on the occasion of the inauguration of the Georg Wittig Lectureship at the Universität Heidelberg (27.10.1999)

in natural product synthesis. As the synthesis of vitamin D required the construction of such a moiety, Inhoffen et al. utilized the Wittig reaction in this context immediately following Wittig and Schöllkopf's first publication on the subject (Figure 1).[2]



Partialsynthese einer „trans"-Vitamin D_2-Verbindung mit Hilfe der Reaktion von Wittig

Von Prof. Dr. H. H. INHOFFEN, Dr. J. F. KATH und Dr. K. BRÜCKNER

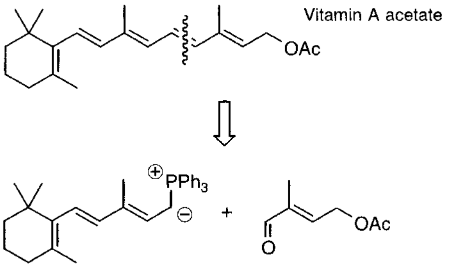
Aus dem Organisch-Chemischen Institut der T. H. Braunschweig

Wittig und *Schöllkopf*12) haben nun eine Reaktion beschrieben, durch die ein Ring-Keton mit Triphenylphosphin-methylid in eine entspr. Methylen-Verbindung umzuwandeln ist. Mit Einverständnis von Prof. *Wittig* haben wir die Reaktion auf unser C_{27}-Keton übertragen, um die für das antirachitische Vitamin charakteristische Methylen-Gruppe zu erzeugen.

Figure 1. Reproduction of the publication by H. H. Inhoffen on the application of the Wittig reaction, *Angew. Chem.* **1955**, *67*, 276 (English translation given in ref. [40]).

This fact, however, is remarkable considering the context of natural product synthesis in those days: in the first half of the twentieth century and even far into the sixties, the onus of natural product synthesis was to provide proof for the proposed structure of a natural product by synthesis.[3] This restricted natural product synthesis to the use of only such reactions, the reliability of which was beyond doubt. It attests to the uniqueness of the Wittig reaction that it was applied in natural product synthesis (Figure 1) within one year of first being reported, despite not being an "established" reaction.

The Wittig reaction was unique in yet another aspect: it was applied just as rapidly in industrial synthesis as in natural product synthesis. Since the fifties vitamin A and other carotenoids had been produced by Hoffmann LaRoche in Basel. Horst Pommer at BASF was studying alternative routes to this class of compounds and he immediately recognized the potential of the Wittig reaction for the synthesis of vitamin A [Eq. (2)].[4]

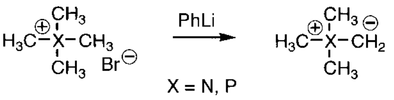


(2)

A collaboration between Wittig and Pommer soon led to a landmark patent.[5] It was an outstanding achievement both scientifically and economically to bring a vitamin A synthesis from the first experiments in the laboratory to large-scale commercial production within five years, an accomplishment, of which BASF can be proud. Ever since, the Wittig reaction has been used like no other as one of the standard reactions to assemble molecules by C=C bond formation.

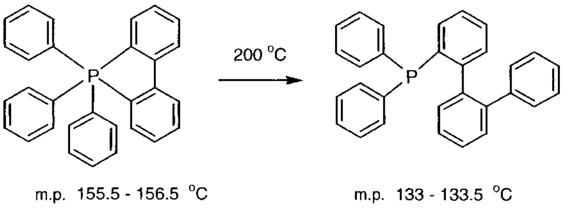
It should be stressed that Wittig did not conceive the Wittig reaction, he discovered it. People today tend to forget that truly innovative research cannot be planned. It is foremost the ability of the scientists to properly comprehend unexpected observations and to recognize their potential. Wittig possessed this ability second to none. In part, this was related to Wittig's tendency to frown upon trendy topics of his time. The choice of his research projects rested completely within his own thinking. For a scientist in an academic institution this is a risky predisposition, that can lead to a loss in standing amongst peers, but this is also a predisposition which is the seedbed of truly novel insights.

Wittig was impressed by the daring concepts of Meerwein's carbocation chemistry. He was directly exposed to it as a Privatdozent at the Marburg chemical institute (1929–1932) headed by Meerwein. Wittig envisioned carbanion chemistry becoming the counterpart of Meerwein's carbocation chemistry. For this reason, Wittig investigated in breadth reactions that might lead to carbanionic species. This approach led him to ylids such as the simplest nitrogen ylid formed on deprotonation of the tetramethyl ammonium ion [Eq. (3)].



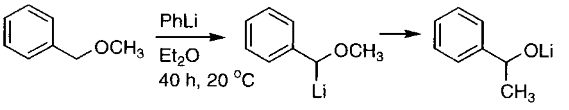
$$\mathrm{H_3C{-}\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{\overset{\oplus}{X}}}{-}CH_3\ \ Br^{\ominus}} \xrightarrow[X\,=\,N,\,P]{PhLi} \mathrm{H_3C{-}\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{\overset{\oplus}{X}}}{-}\overset{\ominus}{C}H_2} \qquad (3)$$

However, in truth, the experiments shown were carried out for a different purpose: Wittig always felt challenged by dogmas. He wanted to prove them wrong or at least define the limits of their validity. One dogma prevalent at Wittig's time was that elements of the first period of the periodic table could only form tetravalent compounds. Pentavalent carbon was considered, if at all, only as a transition state in an S_N2 reaction. Wittig nevertheless wanted to see whether phenyllithium might be added to the tetramethylammonium ion to form a compound with a pentavalent nitrogen atom. He did not succeed, because deprotonation of the ammonium ion led to a nitrogen ylid.[6] As a control, he reacted phenyllithium with the tetramethylphosphonium ion; this constituted the entry to phosphorus ylids and their chemistry.[7] To obtain compounds with pentavalent phosphorous, Wittig turned to phosphonium salts which cannot be deprotonated. Following this line of thought, Wittig generated the first pentarylphosphorane starting from the tetraphenylphosphonium ion.[8] This compound has not reached a similar level of importance as the phosphorus ylids, but these studies exemplify some aspects of Wittig's thinking and work. We tend to forget how important the determination of melting points was to the chemists of the first half of the twentieth century. Melting points provided the only means to prove the identity or nonidentity of two compounds. Accordingly, the process of crystal growing was central to the activities of chemists of those days. In many cases, the "boss" did it himself—at the very least, he reproduced the crystallization process with his own hands. Next, he had to find out whether the "melting point" was a true melting point, or whether it was merely a decomposition point, or caused by a chemical transition or a crystal modification. To clarify those matters, the melt was resolidified in the melting point tube (after taking the melting point) by scratching with a thin wire, and then the melting point was determined a second time. A difference in the melting behavior was a clear indication of an unexpected process. It was this "standard procedure" that brought to light the rearrangement of pentaarylphosphoranes to triarylphosphines [Eq. (4)].[9] I doubt whether present day chemists take advantage of these simple techniques to unveil unprecedented thermal transformations.



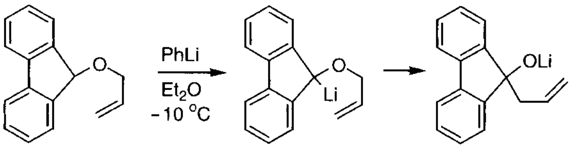
(4)

Another reaction named after Wittig is the anionic ether rearrangement [Eq. (5)]. This reaction was discovered upon



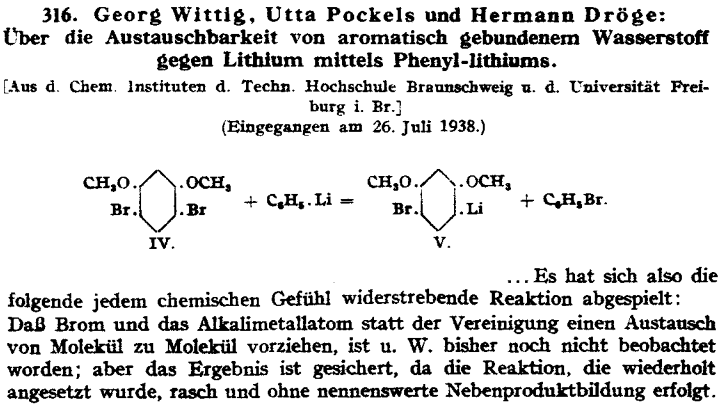
(5)

attempting to generate carbanions by deprotonation of benzyl alkyl ethers.[10] The resulting ether rearrangement forms a new carbon–carbon bond. Such bond-forming reactions are of interest today, as they permit the generation of stereogenic centers in a predefined configuration. Thus, the Wittig rearrangement of benzyl allyl ethers[11] [Eq. (6)] has become an important tool for the stereoselective synthesis of alcohols.[12]



(6)

A reaction of even broader importance is the halogen/metal-exchange reaction, which few chemists today associate with the name of Wittig. The bromine/lithium-exchange reaction was described simultaneously (the manuscripts were received within three months of each other) and independent from one another by Wittig[13] and by Gilman;[14] thus Wittig's contribution is clear! This reaction was so fundamentally novel and paradoxical that Wittig characterized it as shown in Figure 2 (a translation of the original German text is given in ref. [41]). To publish these findings and concepts required courage. If the interpretation had been found to be wrong, the professional career of the young assistant professor at Braunschweig would have been jeopardized. The observations on the halogen/metal-exchange reaction however, turned out to be correct. This reaction has since grown into one of the most widely used procedures for the generation of vinyl- and aryllithium compounds.


316. Georg Wittig, Utta Pockels und Hermann Dröge: Über die Austauschbarkeit von aromatisch gebundenem Wasserstoff gegen Lithium mittels Phenyl-lithiums.

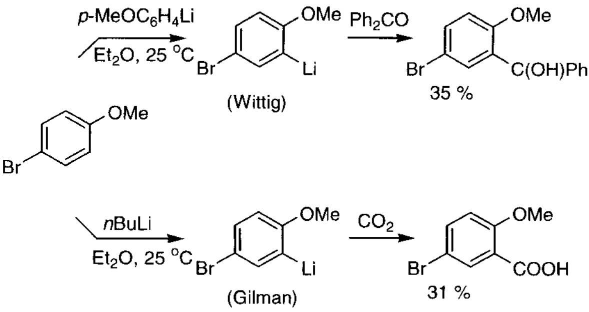
[Aus d. Chem. Instituten d. Techn. Hochschule Braunschweig u. d. Universität Freiburg i. Br.]

(Eingegangen am 26. Juli 1938.)

... Es hat sich also die folgende jedem chemischen Gefühl widerstrebende Reaktion abgespielt: Daß Brom und das Alkalimetallatom statt der Vereinigung einen Austausch von Molekül zu Molekül vorziehen, ist u. W. bisher noch nicht beobachtet worden; aber das Ergebnis ist gesichert, da die Reaktion, die wiederholt angesetzt wurde, rasch und ohne nennenswerte Nebenproduktbildung erfolgt.

Figure 2. Reproduction of the publication by Wittig on the halogen/metal-exchange reaction, *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 1903 (English translation given in ref. [41]).

In this key paper by Wittig,[13] another important observation is documented (again parallel to Gilman's paper[14]), this is the directed metalation of aromatic compounds in the position *ortho* to a methoxy group [Eqs. (7, 8)].

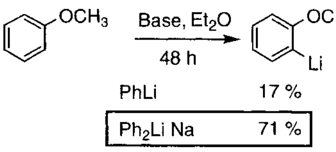


(7)

(8)

Today, it is common knowledge that electronegative substituents which may coordinate a lithium cation can induce a directed *ortho*-metalation by alkyl- or aryllithium reagents.[15] Following the first record of this reaction by Wittig and Gilman, the method has since been developed into a general tool in the chemistry of aromatic compounds.[16] Wittig could not have foreseen that some of today's big-selling drugs such as Losartan[17] or Efavirenz[18] would be produced utilizing a directed *ortho*-metalation. Over the whole breadth of Wittig's research, phenyllithium was the key reagent, he himself described it as his "divining rod". But how did Wittig come to use phenyllithium? The preparation of phenyllithium was pioneered 1930 by Karl Ziegler,[19] a close friend of Wittig's; both started their academic career at Marburg and overlapped there for many years.

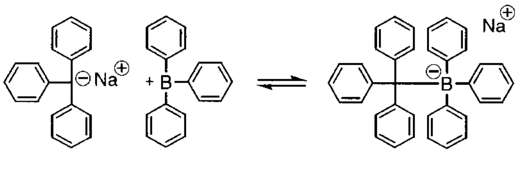
For *ortho*-metalation and complexation assisted metalation Wittig continually tested more and more reactive bases. He was the first to have used complex bases, such as a 1:1 mixture of phenyllithium and phenylsodium. This complex base deprotonated anisole more rapidly than either of its constituents [Eq. (9)].[20]



(9)

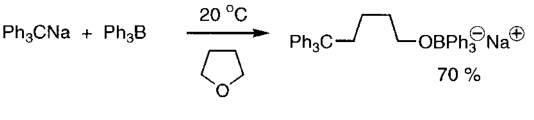
With this finding, Wittig described and studied the forerunner of the complex bases presently in use, such as the Lochmann–Schlosser base (potassium *tert*-butoxide + *n*-butyllithium[21]) or Caubère's system (sodium *tert*-butoxide + sodium amide).[22] The chemistry of these complex bases is still in its infancy.

Another concept of Wittig was quickly accepted by the scientific community: neutral Lewis base plus positively charged electrophile forms an onium-complex. An anionic Lewis base plus a neutral electrophile forms an ate complex, a term coined by Wittig.[23] In studying ate complexes, Wittig hit upon the fascinating combination of triphenylmethylsodium and triphenylboron. In this system the equilibrium for forming an ate complex is not completely on the side of the complex because of steric hindrance in the latter. As a consequence, the Lewis base triphenylmethylsodium and the Lewis acid triphenylboron coexist in substantial concentrations in solution [Eq. (10)].



(10)

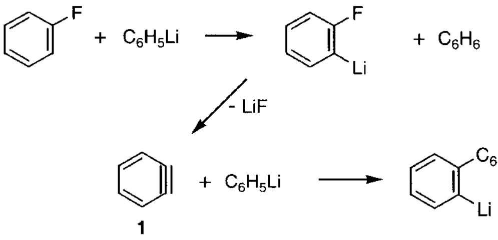
This allowed, for the first time, a Lewis acid catalysis of Lewis base induced reactions,[24] as shown in the following example: triphenylmethylsodium by itself is stable in THF solution, so is triphenylboron. In combination they induce a rapid polymerization of THF [Eq. (11)] the first step being ring opening of the THF.



(11)

Wittig had no doubts about the mechanism of these "triphenylmethylsodium-initiated and triphenylboron-assisted reactions" as he termed them. Subsequent to Wittig's seminal studies, numerous examples of this type of Lewis acid catalyzed reaction of organometallic compounds have been described [25] and the principle rediscovered many times!

The directed *ortho*-metalation was the godfather to another completely unexpected finding by Wittig: 2-biphenyllithium was formed on reaction of fluorobenzene with phenyllithium [Eq. (12)].



(12)

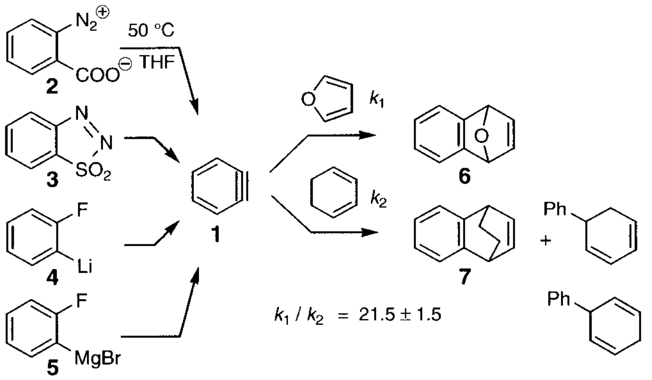
Wittig's interpretation of this transformation envisioned an *ortho*-lithiation of fluorobenzene as the first step. The resulting *ortho*-fluorophenyllithium was then postulated to loose lithium fluoride forming dehydrobenzene (benzyne; **1**) as a reactive intermediate which was then trapped by phenyllithium forming the 2-biphenyllithium end product.[26]

This may seem reasonable for a chemist of today but, to a chemist before 1950, this was a dare-devil proposition. We should recognize that during the forties there was no perception of reactive intermediates in the mind of most German chemists. The only thing that mattered in a reaction was the starting material and the product. In line with this, the carbocation concept of Meerwein had not yet found general acceptance. To postulate such a novel reactive intermediate back in those days could easily have put an academic career at risk. This may explain why Wittig hesitated for years before publishing his hypothesis. He always was (and remained) skeptical about hypotheses, especially his own. Hence, he referred for decades to "dehydrobenzene" as being a "chemistry as if".[27] To Wittig, all the results obtained were consistent with the dehydrobenzene hypothesis, nevertheless they failed to prove the existence and structure of this reactive intermediate. This skepticism remained even after J. D. Roberts proved the symmetrical nature of this intermediate by brilliant isotope labeling experiments,[28] and after Wittig himself provided the most convincing evidence in trapping dehydrobenzene in Diels–Alder reactions.[29]

It was finally in 1964 that Wittig accepted dehydrobenzene as a reality, after Huisgen showed through his elegant determination of competition constants[30] (cf. Scheme 1) that a common intermediate is generated from the different precursors **2**–**5**, an intermediate that selects between furan and cyclohexadiene in an identical manner.

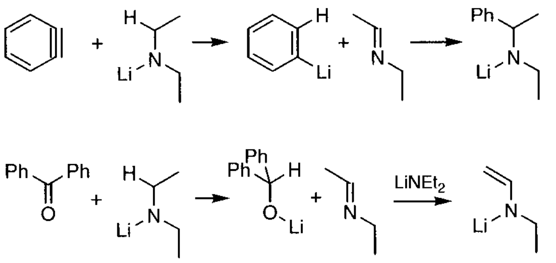
It follows that the same intermediate is generated in all these reactions. Simple comparison of the structures of the precursor compounds on the one side and of the trapping products **6** and **7** on the other leaves no doubt that the reactive intermediate has to be dehydrobenzene **1** with the shown connectivity of atoms.

Wittig was the first to note that lithium dialkylamides may transfer hydride to acceptor molecules, a reaction which Wittig had neither planned nor sought. It was again seren-



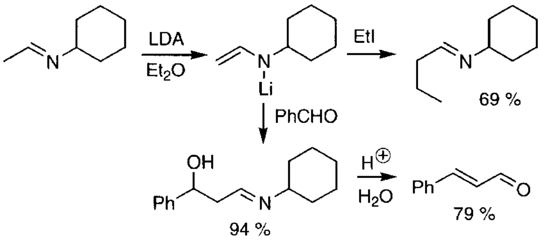
Scheme 1. Huisgen's confirmation, by using various precursors, of the identity of the intermediate dehydrobenzene.

dipity, but Wittig recognized right away the importance of this finding. The plan had been to generate dehydrobenzene from fluorobenzene using lithium diethylamide as base. Wittig noted that the dehydrorobenzene generated was transformed under these conditions into phenyllithium in a process in which lithium diethylamide served as a hydride source (Scheme 2),[31] much akin to the Meerwein–Verley–Ponndorf reduction.



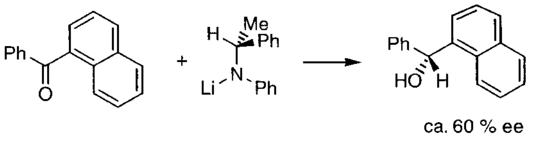
Scheme 2. Lithium diethylamide as a hydride donor.

As a corollary lithium diethylamide was also dehydrogenated by benzophenone to a Schiff base which underwent deprotonation to furnish an azaenolate. This very experiment provided the first access route to azaenolates, which are now standard reagents in organic synthesis. Wittig himself demonstrated the potential of azaenolates to effect directed aldol additions [Eq. (13)].[32]



(13)

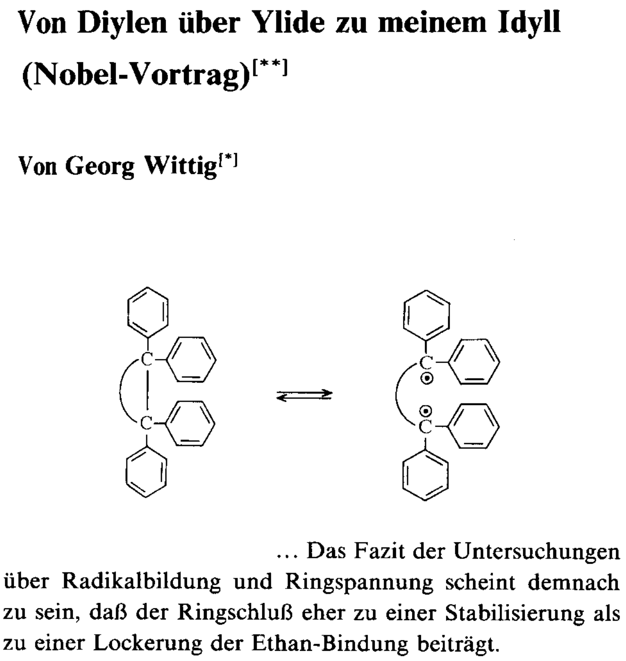
However, let us rather focus on the first step of the above reaction sequence of Equation (13) the ability of lithium diethylamide to serve as a hydride donor. Wittig demonstrated the possibility to reduce non-enolizeable ketones by lithium diethylamide (see Scheme 2). Thus, it should be possible to reduce prochiral ketones by application of a chiral "lithium diethylamide". This can indeed be accomplished as Wittig showed in 1969 [Eq. (14)].[33]



(14)

Wittig reached an asymmetric induction of 60 % *ee*, a value, which was surely a highlight at the end of the sixties. With more elaborate chiral derivatives of lithium diethylamide, enantioselectivities of >95 % *ee* were recorded in 1999.[34] Wittig was therefore one of the forerunners in the development of chiral reducing agents for prochiral ketones.

When Wittig received the Nobel price in 1979, he was at an age which permitted only a retrospective. In his Nobel lecture "From diyls to ylides to my idyll", he reviewed the leading themes of his oeuvre (Figure 3).[35] The chemistry of free radicals marked the outset. He tried to generate kinetically persistent diradicals = diyls; he modeled his target compounds on the persistent triphenylmethyl radical of M. Gomberg.[36]



Von Diylen über Ylide zu meinem Idyll (Nobel-Vortrag)[**]

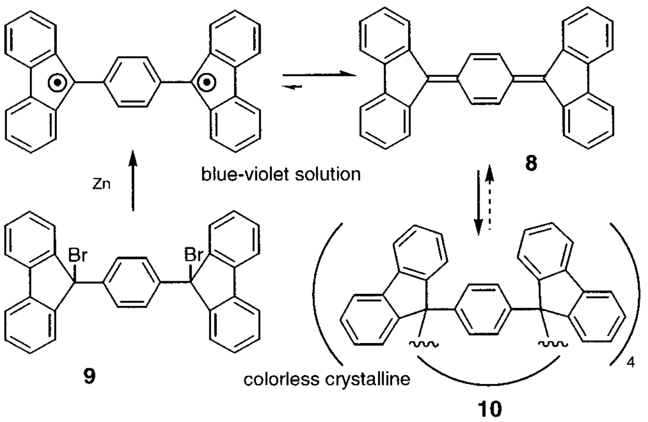
Von Georg Wittig[*]

... Das Fazit der Untersuchungen über Radikalbildung und Ringspannung scheint demnach zu sein, daß der Ringschluß eher zu einer Stabilisierung als zu einer Lockerung der Ethan-Bindung beiträgt.

Figure 3. Reproduction of Wittig's retrospective on the chemistry of diyls (Nobel Lecture), *Angew. Chem.* **1980**, *92*, 671 (English translation given in ref. [42]).

Wittig hoped to arrive at persistent diradicals by stabilization of the radical centers by π delocalization and by destabilization of the dimerization products by ring strain. Out of this context the experiment shown in Scheme 3 was performed.

The reduction of the dibromo compound **9** furnished a $C_{32}H_{20}$ hydrocarbon, a stable diradical? Careful determination of the molecular weight indicated the hydrocarbon **10** to be a "tetramer" $C_{128}H_{80}$;[37] its constitution was revealed years



Scheme 3. Tetramerization of a stabilized diyl to the hydrocarbon $(C_{32}H_{40})_4$.

later by X-ray crystal structure analysis.[38] This compound held an additional fascination for Wittig, it was piezochromic and thermochromic. We should remember that Wittig is a representative of a generation of chemists, for whom the elucidation of the relationship between color and constitution was a life task. Every graduate student in Wittig's group knew how much Wittig insisted on finding explanations for each color phenomenon observed. As we know today, the color generated on heating **10** is caused by the appearance of the desired diradical in conjunction with the dissociation of the "tetramer" into the monomer **8**.

These studies rested unnoticed for decades. Today, they have become important in quite a different context: on tetramerization of the diradical **8**, four readily accessible building blocks are joined in a single operation to give a spherical molecular object. Thus, in 1999 a 32-armed dendrimer with a compact core was assembled in one stroke based on Wittig's studies.[39]

The many examples provided in this essay show that Wittig's accomplishments become and remain important to chemists in changing contexts far beyond his hundredth birthday. The next generation of chemists has only to realize that Wittig's oeuvre is still a gold mine of facts and concepts to be exploited.

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[40] Title: "Partial Synthesis of a "*trans*" Vitamin D_2 Compound by means of the Wittig Reaction", Wittig and Schöllkopf have described a reaction in which a ring ketone is converted into the corresponding methylene compound with triphenylphosphine-methylid. With the consent of Professor Wittig we have transferred this reaction to our C_{27} ketone to generate the methylene group characteristic of the antirachitic vitamin.

[41] Title: "On the Exchange of Aromatic-Bound Hydrogen for Lithium by Phenyllithium". The following reaction that runs contrary to all chemical intuition has been observed: that bromine and alkali metal atoms exchange between molecules rather than unite was not been observed before; however, the result is fully secured, the reaction has been tested repeatedly and occurs rapidly and without the formation of any significant by-products.

[42] …The conclusion of the investigations of radical formation and ring strain seems to be that the ring closure tends to cause a stabilization, rather than a weakening of the ethane bond.