LAUDATIO

Rolf Huisgen's Profound Adventures in Chemistry

by **Kendall N. Houk**

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I am honored to be selected to describe the discoveries and accomplishments of *Rolf Huisgen*, who was honored at the Free University of Berlin in 2010 with an honorary degree. Many of the most influential organic chemists of Germany were present. I described Professor *Huisgen*'s achievements as seen by chemists from all over the world. I entitled this Laudatio '*Rolf Huisgen*'s Profound Adventures in Chemistry', taking a suggestion from the title of his autobiography. I speak as a witness to the impact of *Huisgen* (*Fig. 1*) on chemistry and on the chemical community.

My graduate education coincided with an outpouring of discoveries from the Munich laboratories of *Rolf Huisgen* in the 1960s. Consequently, my career has spanned the period in which the *Huisgen* chemistry has reshaped many aspects of organic chemistry. These discoveries include new reactions that we now know have enabled the synthesis of important molecules, especially heterocyclic drugs, and have had a major role in the development of synthetic chemistry. His understanding of mechanisms has

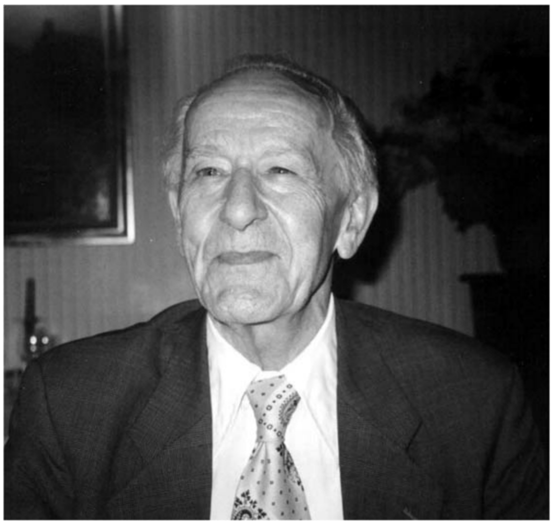

Fig. 1. *Photo of* Rolf Huisgen. Courtesy *Jeffrey I. Seeman.*

helped create the foundations of organic chemistry. His discoveries have impacted materials science and biology as well. I will take this opportunity to note how my research directions have followed in the footsteps of Professor *Huisgen* and his many scientific offspring, many of whom were at the ceremony in Berlin.

I begin with a timeline that chronologizes *Huisgen*'s career in chemistry. In constructing this timeline, I relied on the wonderful record of *Rolf Huisgen*'s life and science in the book, *'The Adventure Playground of Mechanisms and Novel Reactions'* (*Fig. 2*).

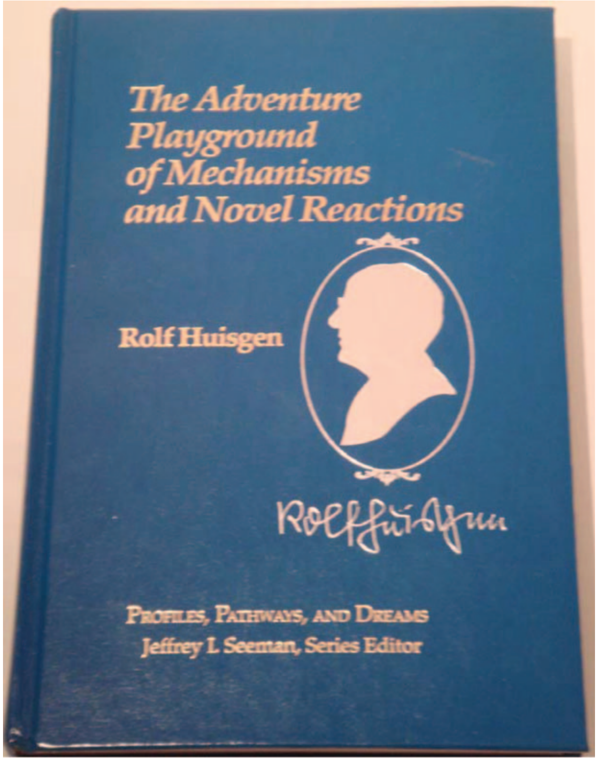

Fig. 2. Huisgen*'s Autobiography* [1]

This autobiography [1], published in 1994, is unusual because, in addition to many personal reflections, it is really a textbook too, full of accounts of chemical discovery. In his typical scholarly way, Professor *Huisgen* places his discoveries in historical context with due credit to precedents and to discoveries by others that came after his work. Now to the timeline (*Fig. 3*).

Huisgen received his Ph.D. in 1943 at age 23 in Munich in the lab of *Heinrich Wieland*, in the midst of World War II. He completed his habilitation there in 1947. Then, he went on to become an Associate Professor in Tübingen in 1949, and then he

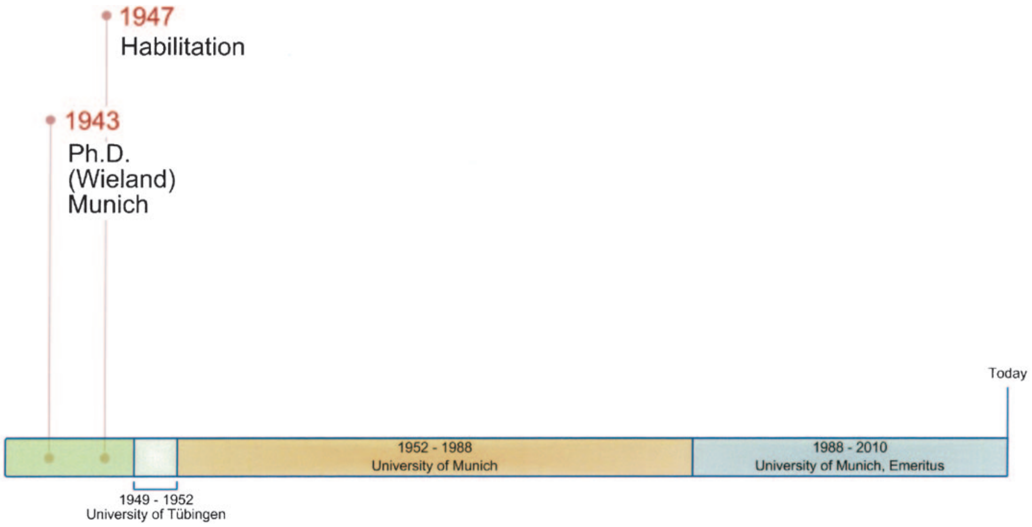

Fig. 3. *Timeline of* Huisgen*'s chemical career*

was called to the Chair at Munich in 1952 at age 32 to build the department back from the ashes, quite literally.

Huisgen did indeed build back to greatness the labs built by *Liebig*, *von Baeyer*, *Willstätter*, and his advisor *Wieland*. At the same time, *Huisgen* built a distinguished career. For 36 years, he discovered many of the most important reactions of organic chemistry. He deduced, from the results of brilliantly designed experiments and keenly analyzed data, the driving forces and mechanisms of these reactions. His influence has spread, because he trained a marvelous group of physical organic chemists who changed the face of organic chemistry in Germany.

Even after becoming Emeritus in 1988, *Huisgen* has continued to publish many important chemical papers.

What chemistry did *Rolf Huisgen* create? After a foray into alkaloid chemistry with *Wieland* during his habilitation and early career, *Huisgen*'s work featured the chemistry of nitroso, azo, and diazonium compounds (*Fig. 4*). This was a time when *Pauling* in the U.S., *Ingold* in England, and *Meerwein* in Germany had strong influence, and physical organic chemistry was just being developed. The basic theoretical underpinnings of organic chemistry were being established, and *Huisgen* soaked up that knowledge and began establishing his own identity and style for discovery.

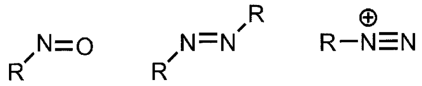

Fig. 4. *Early interests: nitroso, azo, and diazonium compounds*

Beginning in the early 50s, many discoveries were made about benzyne (*Fig. 5*) in the *Huisgen* lab.

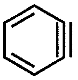

Fig. 5. *The structure of benzyne*

Huisgen investigated the mechanism of formation of benzynes and discovered much about the regioselectivity of unsymmetrical benzyne reactions. In *Fig. 6*, a page from his book [1] is represented. In *Fig. 7*, our quantum-mechanically computed structures of 3-methoxybenzyne and 6,7-indolyne are displayed. This year, we published a direct descendant of *Huisgen*'s work more than 50 years ago – elaborating on the origin of regioselectivity [2]. Methoxybenzyne reactions with nucleophiles occur with high regioselectivity. As shown in this optimized structure, it is not just triple broad polarization, but the consequent distorted geometry that makes attack at the flattened carbon very easy, requiring no distortion. Our work began with a collaboration with our young colleague, *Neil Garg*, on indolynes. The 6,7-indolyne distortion is quite obvious and is due to both ring fusion and electronegativity of the N-atom. Nucleophilic addition occurs only as shown by the arrow.

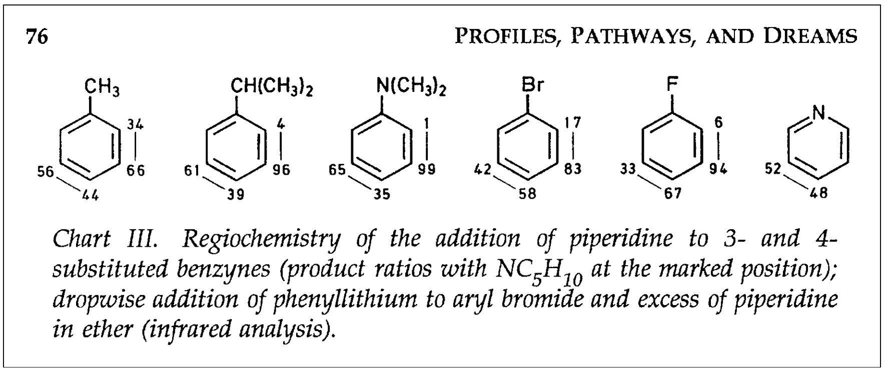

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Chart III. Regiochemistry of the addition of piperidine to 3- and 4-substituted benzynes (product ratios with NC_5H_{10} *at the marked position); dropwise addition of phenyllithium to aryl bromide and excess of piperidine in ether (infrared analysis).*

Fig. 6. *Summary of regioselectivity of nucleophilic additions to arynes* [1]

In the mid-1950s, *Huisgen* worked on physical properties and reactions of medium-ring lactones, and he established in that work a model for the elaboration of structure–reactivity relationships that became the hallmark of physical organic chemistry.

In the late 1950s, *Huisgen* realized that many apparently unrelated reactions could be unified under a single paradigm, that he called the 1,3-dipolar cycloaddition (*Fig. 8*). The first publication came in the famous *Centenary Lecture* that was delivered in London in 1960 [3] (*Fig. 9*). We consider 1960 the public birthdate of the 1,3-dipolar cycloaddition, due to the *Centenary Lecture*, and so this year is the 50th birthday of 1,3-dipolar cycloadditions. The year 1957 is the date of the beginning of the work in the lab, and even in 1955, his review on diazoalkane chemistry included many forerunners to the concepts published in 1961 [4].

In *Fig. 10*, six prominent 1,3-dipoles are described by *Huisgen* according to a unified scheme. This formulation allowed *Huisgen* to predict many others, with O- or S-atoms at the center, and O-atoms at both termini. As I will describe, this concept and the

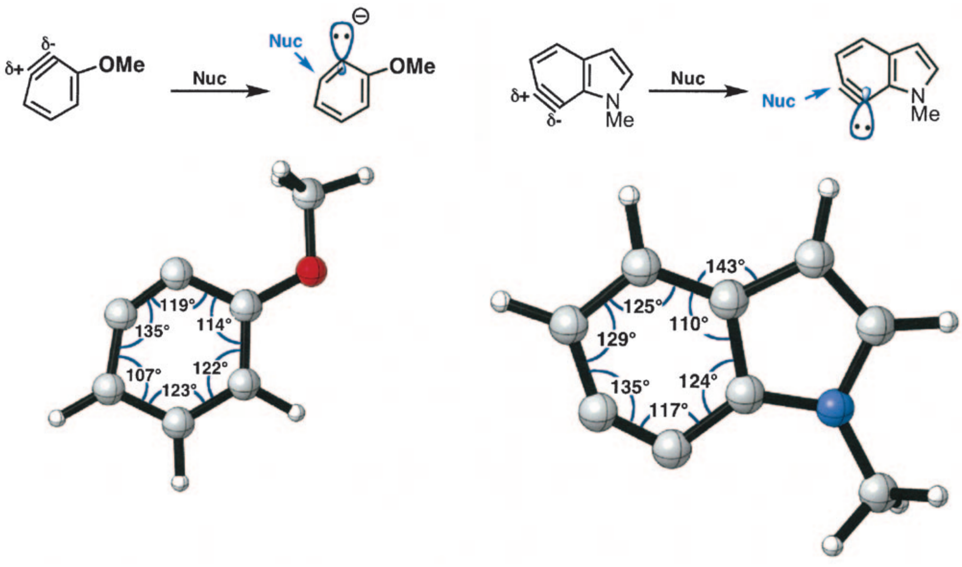


Fig. 7. *Calculated structures of 3-methoxybenzyne and 6,7-indolyne.* Reproduced from [2].

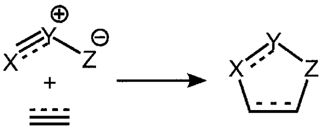
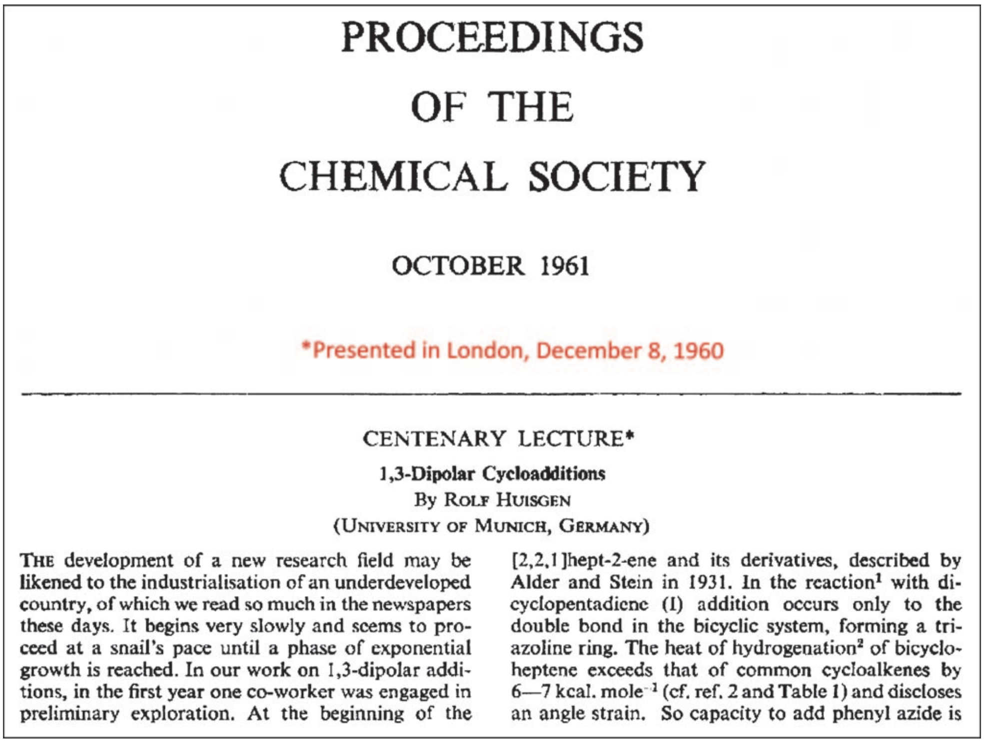


Fig. 8. *1,3-Dipolar Cycloadditions*

reactions discovered in the *Huisgen* labs have had a profound impact on chemistry, biology, and even materials science, and the young field of nanochemistry. *Huisgen*'s 1963 review in *Angewandte Chemie* [5] has been cited nearly 1000 times in the literature and is one of the most influential papers of the 20th century.

We now know that 1,3-dipoles are quite ubiquitous. The smog (*Fig. 11*) over my hometown, Los Angeles, is due in part to the 1,3-dipoles, ozone, and nitrous oxide. Ozone is essential in the ozone layer that protects us from the sun's UV, but a pollutant and smog producer near the surface of the earth. N_2O destroys ozone and the ozone layer, so N_2O is not only a smog producer but is damaging to the ozone layer as well.

We have performed molecular-dynamics calculations that let us know 1,3-dipolar cycloadditions happen. In the lecture, I showed a movie of N_2O and acetylene undergoing computed with quantum-mechanical molecular dynamics. These simulation showed reactions, the importance of bending as the molecules achieve geometries where the terminal orbitals of N_2O can overlap with those of acetylene. Another molecular-dynamics simulation of hydrazoic acid, the simplest azide, reacting with ethylene was shown as well.



PROCEEDINGS
OF THE
CHEMICAL SOCIETY

OCTOBER 1961

*Presented in London, December 8, 1960

CENTENARY LECTURE*
1,3-Dipolar Cycloadditions
By ROLF HUISGEN
(UNIVERSITY OF MUNICH, GERMANY)

THE development of a new research field may be likened to the industrialisation of an underdeveloped country, of which we read so much in the newspapers these days. It begins very slowly and seems to proceed at a snail's pace until a phase of exponential growth is reached. In our work on 1,3-dipolar additions, in the first year one co-worker was engaged in preliminary exploration. At the beginning of the

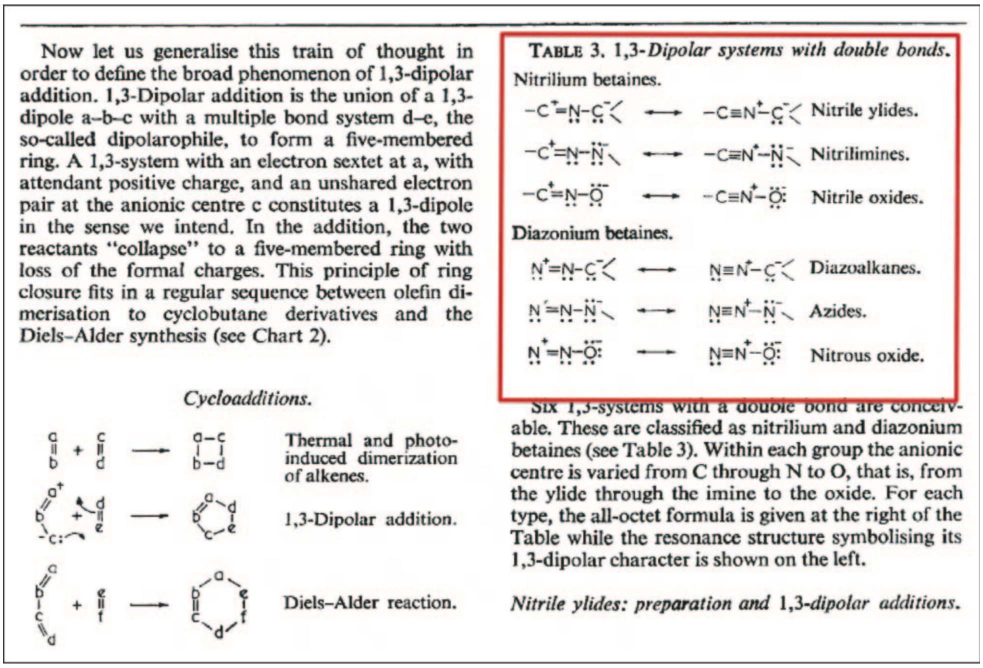
[2,2,1]hept-2-ene and its derivatives, described by Alder and Stein in 1931. In the reaction[1] with dicyclopentadiene (I) addition occurs only to the double bond in the bicyclic system, forming a triazoline ring. The heat of hydrogenation[2] of bicycloheptene exceeds that of common cycloalkenes by 6—7 kcal. mole^{-1} (cf. ref. 2 and Table 1) and discloses an angle strain. So capacity to add phenyl azide is

Fig. 9. *First page of Centenary Lecture* [3]

The two form bonds about exactly the same time, and NNN bending is important in this reaction. While this simulation is the result of developments in quantum mechanics and computers in 2010, Professor *Huisgen* anticipated this in detail 50 years ago: *'However, the rod-like organic azide with its linear three-nitrogen chain must bend in the activation process in order to make contact with the π-bond of the alkene'* [3]. This was in 1960, and the essential features of the mechanism of this reaction were established at that time (*Fig. 12*).

Mechanistic arguments with *Firestone* in the late 1960s showed physical organic chemists how to carry on serious intellectual controversies without anger or personal insults. This contrasted with the rancorous debate in the U.S. about the nonclassical norbornyl cation about the same time. From the experimental point of view, 1977 was the end of the debate about mechanism of the 1,3-dipolar cycloaddition, although our friend, *Ray Firestone*, still carries on until today.

Perhaps the final nail in the coffin of the stepwise mechanism was the careful analysis of this reaction, showing, beyond a shadow of a doubt, that the reaction is stereospecific, without any intermediate that could scramble the stereochemistry. *Hans-Ulrich Reissig* was involved in this [6]. Much later, I collaborated with *Ray Firestone* to show that *cis*- and *trans*-1,2-dideuteroethylene react stereospecifically with nitrile oxide [7].



Now let us generalise this train of thought in order to define the broad phenomenon of 1,3-dipolar addition. 1,3-Dipolar addition is the union of a 1,3-dipole a–b–c with a multiple bond system d–e, the so-called dipolarophile, to form a five-membered ring. A 1,3-system with an electron sextet at a, with attendant positive charge, and an unshared electron pair at the anionic centre c constitutes a 1,3-dipole in the sense we intend. In the addition, the two reactants "collapse" to a five-membered ring with loss of the formal charges. This principle of ring closure fits in a regular sequence between olefin dimerisation to cyclobutane derivatives and the Diels–Alder synthesis (see Chart 2).

Cycloadditions.

Thermal and photo-induced dimerization of alkenes.

1,3-Dipolar addition.

Diels–Alder reaction.

Table 3. 1,3-*Dipolar systems with double bonds.*

Nitrilium betaines.			
$-\overset{+}{C}=N-\overset{-}{C}<$	$\longleftrightarrow$	$-C\equiv\overset{+}{N}-\overset{-}{C}<$	Nitrile ylides.
$-\overset{+}{C}=N-\overset{-}{N}\diagdown$	$\longleftrightarrow$	$-C\equiv\overset{+}{N}-\overset{-}{N}\diagdown$	Nitrilimines.
$-\overset{+}{C}=N-\overset{-}{O}$	$\longleftrightarrow$	$-C\equiv\overset{+}{N}-\ddot{O}:$	Nitrile oxides.
Diazonium betaines.			
$\overset{+}{N}=N-\overset{-}{C}<$	$\longleftrightarrow$	$N\equiv\overset{+}{N}-\overset{-}{C}<$	Diazoalkanes.
$\overset{+}{N}=N-\overset{-}{N}\diagdown$	$\longleftrightarrow$	$N\equiv\overset{+}{N}-\overset{-}{N}\diagdown$	Azides.
$\overset{+}{N}=N-\overset{-}{O}:$	$\longleftrightarrow$	$N\equiv\overset{+}{N}-\overset{-}{O}:$	Nitrous oxide.

Six 1,3-systems with a double bond are conceivable. These are classified as nitrilium and diazonium betaines (see Table 3). Within each group the anionic centre is varied from C through N to O, that is, from the ylide through the imine to the oxide. For each type, the all-octet formula is given at the right of the Table while the resonance structure symbolising its 1,3-dipolar character is shown on the left.

Nitrile ylides: preparation and 1,3-*dipolar additions.*

Fig. 10. *1,3-Dipoles in Centenary Lecture* [3]

Reiner Sustmann made a major breakthrough in understanding 1,3-dipolar reactivity, and I had the pleasure and opportunity to also contribute by showing how the concerted reaction could nevertheless be regioselective, not always in the same directions as predicted by the stepwise mechanism.

In 1976, I had one of the best experiences of my scientific life. I was a young professor at Louisiana State University, and had the opportunity to visit Munich. Flying from Baton Rouge to New York to Munich, I arrived about 8 a.m., and Professor *Huisgen* met me at the airport. We went immediately to his laboratory and began to discuss 1,3-dipolar cycloadditions. Professor *Huisgen* had read my papers on the theory of 1,3-dipolar cycloadditions very carefully, and he had many insightful questions. May I say that he grilled me about every aspect of my work, and challenged me with a cornucopia of exciting experimental results to explain from the *Huisgen* labs. This serious and exhausting discussion went on through luncheon, which was brought into his office, and then on well into the afternoon. After a welcome nap with visions of 1,3-dipoles dancing in my head, I was invited to a concert with Professor *Huisgen* and Frau *Trudl Huisgen*, and I must admit to dozing off a bit after such an intellectually challenging and exhilarating day. Some questions he asked then, 36 years ago, are ones I still seek to answer in current research.

Back to the 1,3-dipolar cycloaddition timeline, in the 1980s until now, the applications of 1,3-dipolar cycloadditions to synthesis have been numerous. Not just

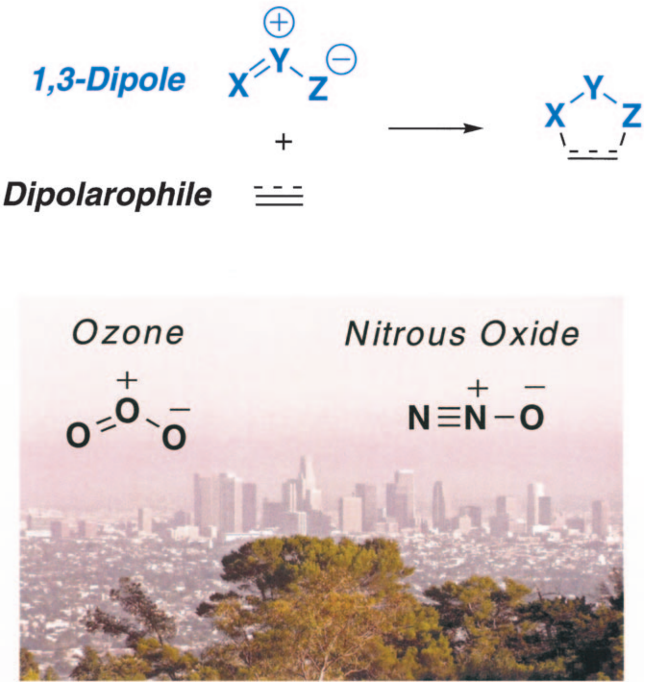


Fig. 11. *The reaction and 1,3-dipolar components of smog*

the obvious heterocycle synthesis, but a variety of applications. There have been a great many, let me tell you of a few.

The great synthetic chemist *Gilbert Stork* with his young students *Danishefsky* and *McMurry* made progesterone, using a nitrile oxide 1,3-dipolar cycloaddition as a key step [8] (*Fig. 13*).

Last year, *Erick Carreira* synthesized erythronolide A, and two Mg-directed nitrile oxide cycloadditions were used [9] (*Fig. 14*). It brought back memories to me of the last time I heard *R. B. Woodward* speak in 1979, the year he died. At the Morgantown, West Virginia, Organic Symposium, he described at that time his attempts to make erythromycin with nitrile oxide cycloadditions.

A further application of *Huisgen*'s cycloadditions began with *Barry Sharpless*'s concept of *'Click Chemistry'* in 2000 (*Fig. 15*). The reaction is a Cu-catalyzed azide cycloaddition to terminal alkynes. *'Click'* because you just mix them and *'click!'*: one product, high yield, no by-products. Here he used it to synthesize an acetylcholinesterase inhibitor [10]. Libraries of azides and alkynes are mixed with the protein, and only those that bind 'click' together – an fm inhibitor is formed. *Bertozzi* has developed azide cycloadditions to cycloalkynes – and a prototype for bio-orthogonal chemistry – *i.e.*, reactions that can be controlled and have no interference from reactions with natural biological molecules [11] (*Fig. 16*).

Sugars labeled with azides are incorporated into cells, and the azides are expressed on cell surfaces. Reactions with cycloalkynes tagged with fluorescent dyes give cells

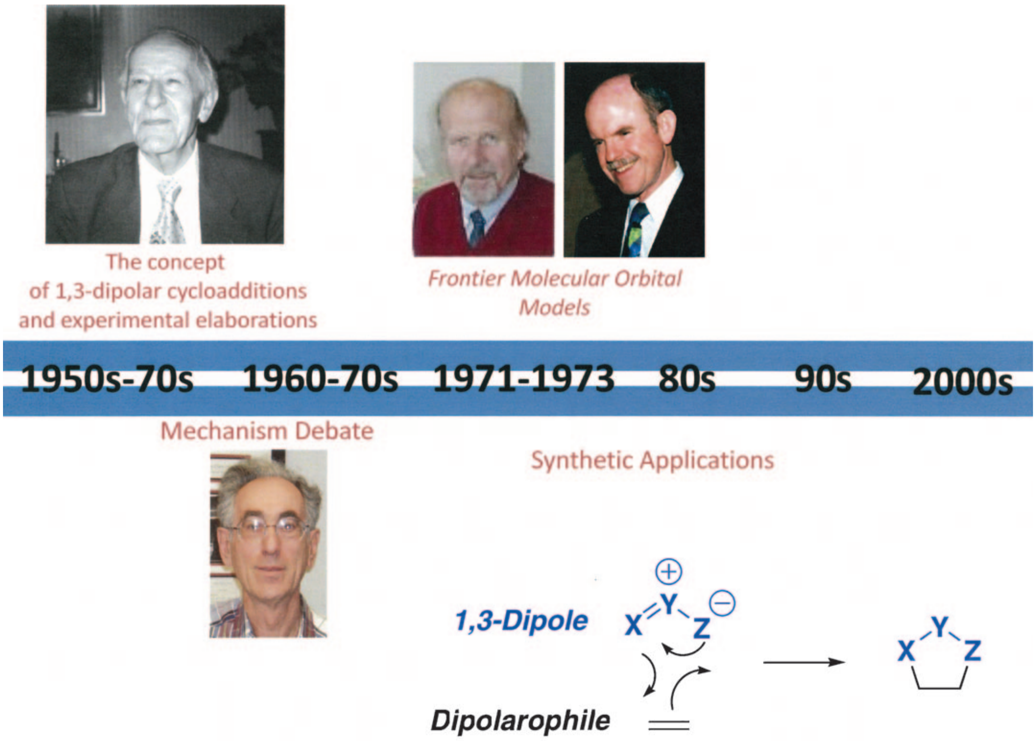


Fig. 12. *Mechanistic timeline*

that can be imaged. Another example gives biotin labels to be detected by binding to streptavidin.

Many industrial processes rely on *Huisgen* chemistry. In *Fig. 17*, a photo from the BASF website of a new industrial plant to make cyclopentanone and cyclododecanone is displayed [12]. It is green chemistry using an industrial by-product, the smog producing N_2O, which undergoes *Huisgen*'s 1,3-dipolar cycloaddition and then loses N_2 with an H-shift. A small amount of the by-product, the unsaturated aldehyde, is formed by a *retro*-1,3-dipolar cycloaddition and loss of N_2.

Returning to the full timeline – *Huisgen*'s group developed many classes of 1,3-dipoles, including the corresponding dipole with a double bond, and cyclic azomethine ylides known as *Münchnones* (*Fig. 18*). Previously, in Sydney, Australia, the corresponding compounds with an additional N-atom in the ring were found and studied by *Ollis*. Those were named *Sydnones*, and *Huisgen* discovered much of the cycloaddition chemistry of these substances. My group helped name a third *'metropolitan 1,3-dipole'*, the *Montrealones* [13].

While at UCLA, *Rebek* used this novel münchnone for the synthesis of this mitosene [14] (*Fig. 19*).

The *Huisgen* lab was the principal place where knowledge about electrocyclic reactions was created (*Fig. 20*). Here is a sequence of conrotatory and disrotatory

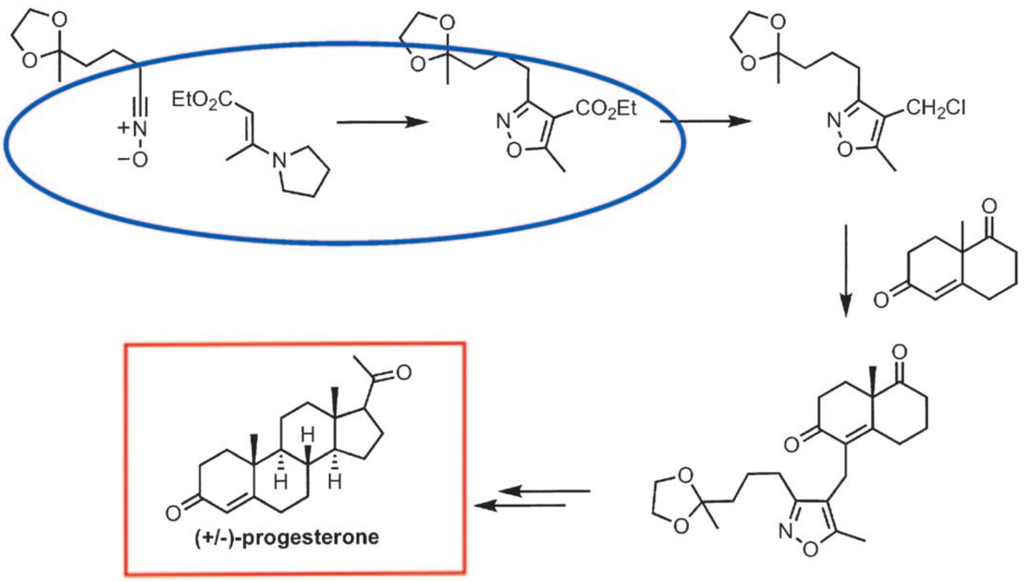


Fig. 13. Stork*'s synthesis of progesterone* [8]

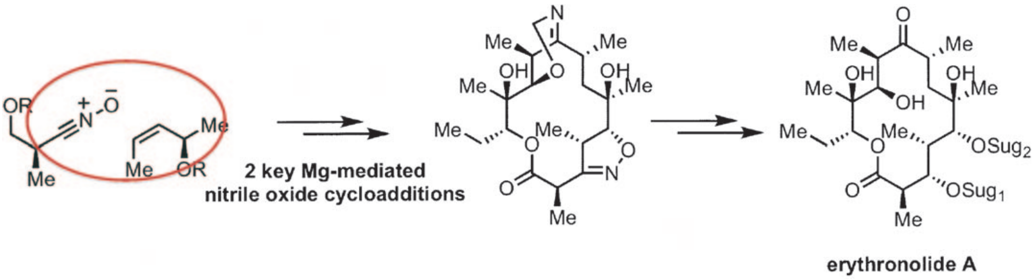


Fig. 14. Carreira*'s synthesis of erythronolide A* [9]

processes, and discoveries about this had much to do with this creation and verification of the *Woodward–Hoffmann* Rules.

Huisgen established much of what we know about ketene cycloadditions (*Fig. 21*). About this time, *Woodward* proposed that the reactions are forbidden [2 + 2] processes, and the must, therefore, be stepwise. However, *Huisgen* informed *Woodward* that *Herbert Mayr*, also a speaker in Berlin, had established that these reactions are stereospecific and, therefore, concerted.

I remember well the *Woodward* group meeting at Harvard at that time trying to figure out how this could be. Remember, it was *Woodward* who would say: *'Violations? There are none'* [15], and in successive weeks, he came up with the $_{\pi}2_a + _{\pi}2_s$ mechanisms and, finally, the [2 + 2 + 2] mechanism that eliminated the apparent violation. In any case, it was the work in the *Huisgen* laboratory that led to this insight.

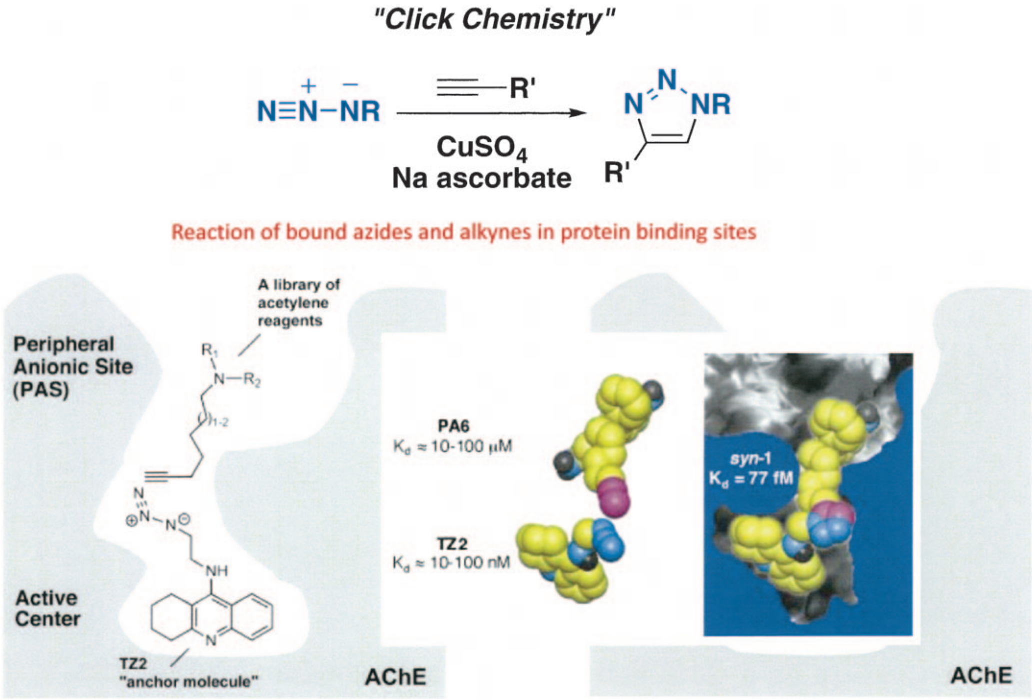


Fig. 15. *2001 Extension of* Huisgen*'s 1,3-dipolar cycloadditions into biology* [10]. *Top:* Azide cycloaddition in 'click chemistry'. *Bottom:* Reaction of bound azides and alkynes in protein binding sites.

Later, there was work on azides, and I have already described *Sharpless*'s 'Click' reactions, a direct outgrowth of this work on azide cycloadditions in Munich. *Huisgen* also described 1,4-dipolar cycloadditions. This unique reaction involves zwitterionic intermediates generated from reactions of unsaturated nucleophiles and electrophiles.

In 1968, a general review of cycloadditions presented a general classification and definition that is now used universally [16]. In contrast to the *Woodward–Hoffmann* classification, the *Huisgen* approach is based upon the overall reaction, not on presumption of mechanism.

Why are the cycloadditions that *Huisgen* developed so important? Synthesis is about enabling and controlling bond formation, and *Diels–Alder* and *Huisgen* cycloadditions, and the others classified in *Huisgen*'s review are among the very best ways to make C,C and C,X bonds, and rings at the same time, from which many molecular skeletons can be made. Such reactions have become among the most important synthetic tools.

Huisgen was not adverse to stepwise cycloadditions when they occur, and his group established the mechanisms of many 2+2 cycloadditions involving zwitterionic intermediates (*Fig. 22*). The solvent polarity dependence and trappability of intermediates stand in stark contrast to 1,3-dipolar cycloadditions.

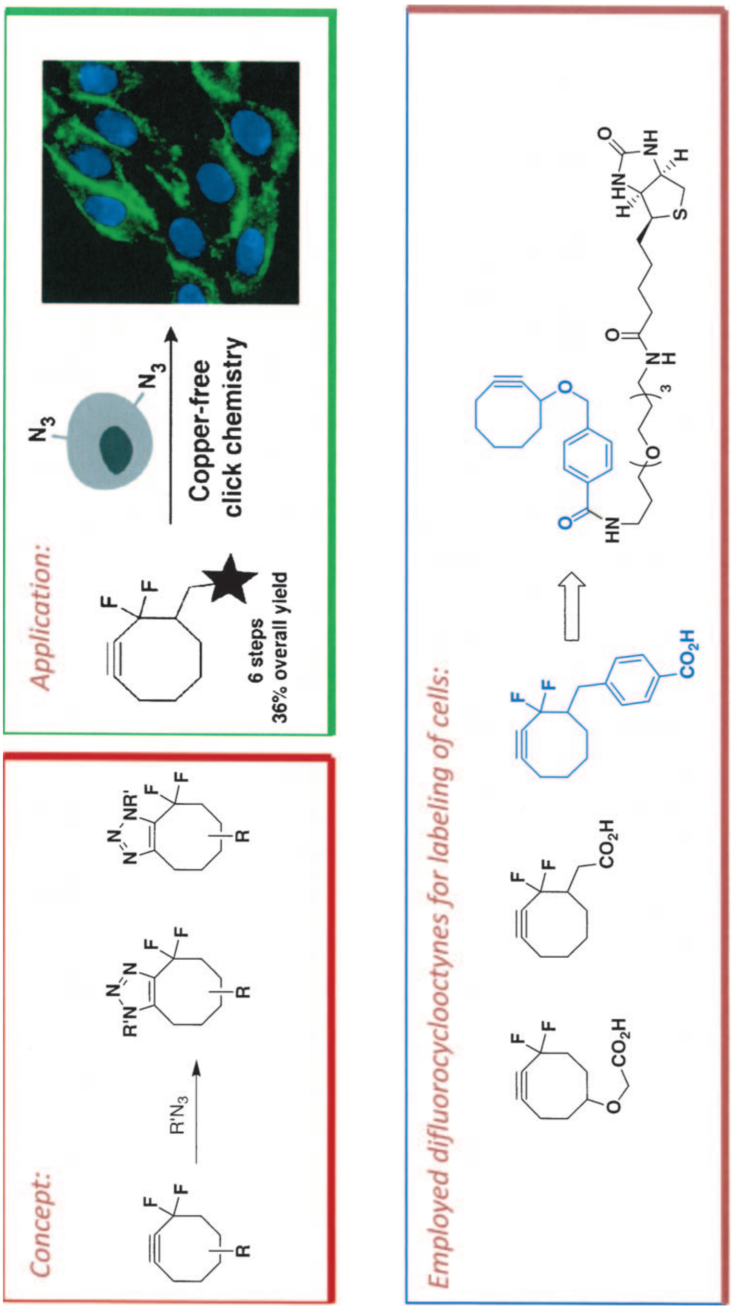


Fig. 16. Bertozzi's *Cu-free click chemistry* [11] – *Cell labeling with 1,3-dipolar cycloadditions: Bio-orthogonal chemical reactions*

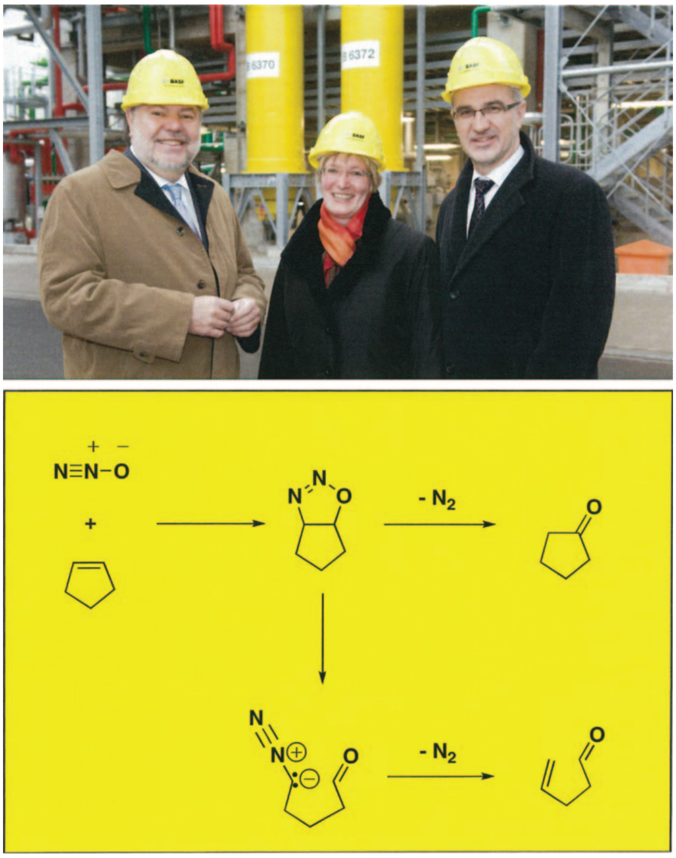


Fig. 17. Huisgen*'s 1,3-dipolar cycloadditions in industrial processes. Top:* CDon PlantBASF started up a new plant complex for the production of cyclopentanone (CPon) and cyclododecanone (CDon) at its Ludwigshafen Verbund site on November 30, 2009. *Kurt Beck* (*left*), prime minister of Rhineland-Palatinate, Dr. *Beate Ehrle* (*middle*), President of BASF's Intermediates division, and Dr. *Harald Schwager* (*right*), member of BASF's Board of Executive Directors in front of the new plant (Photo: BASF – The Chemical Company, 2009). *Bottom:* BASF's processes based on N_2O cycloadditions.

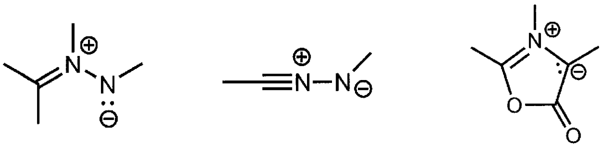


Fig. 18. *Azomethine imines, nitrile imines, and Münchnones*

The 1970s and 1980s involved many studies of formation and reactions of carbonyl ylides (*Fig. 23*) – a prominent type of 1,3-dipole with a central O-atom.

In 1980, a review brought together many reactions that can be considered to be 1,5-electrocyclizations [16] (*Fig. 24*).

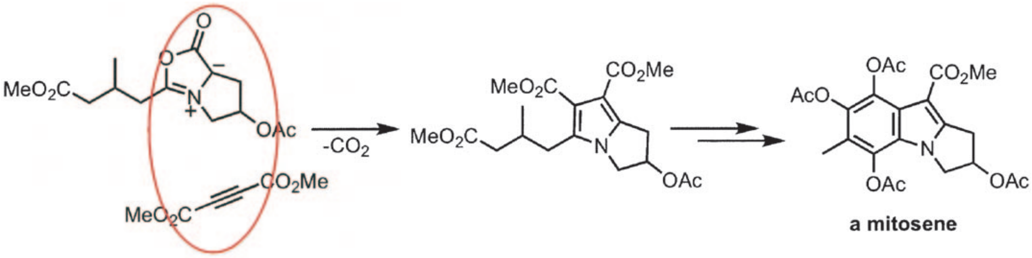


Fig. 19. Rebek*'s mitosene synthesis* [14]

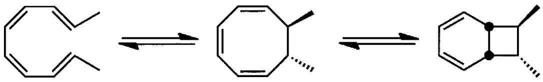


Fig. 20. *Electrocyclic reaction cascade*

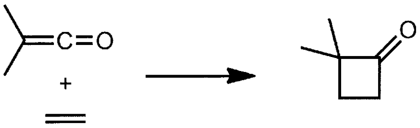


Fig. 21. *Ketene cycloaddition*

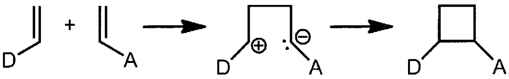


Fig. 22. *Zwitterionic [2+2] cycloaddition*

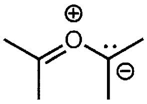


Fig. 23. *A carbonyl ylide*

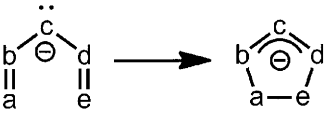


Fig. 24. *1,5-Electrocyclic reaction*

In *Fig. 25* are listed some, but not all, of *Huisgen*'s areas of discovery. The publications, over 580 so far, have paralleled the work but are still coming, describing some of the brilliant experimental discoveries from the Munich labs in the latter part of the 20th century.

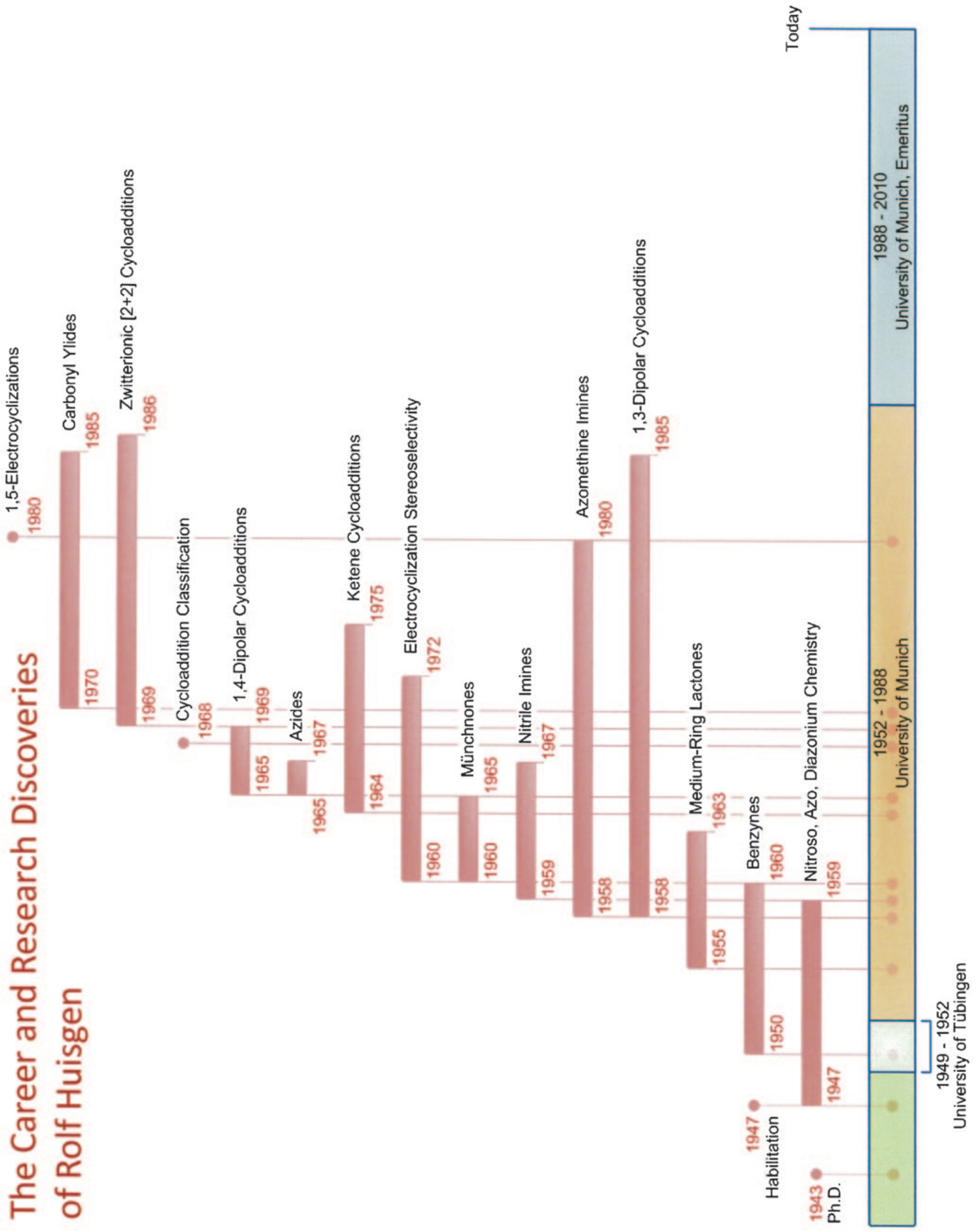


Fig. 25. *Summary of* Huisgen*'s discoveries on the timeline*

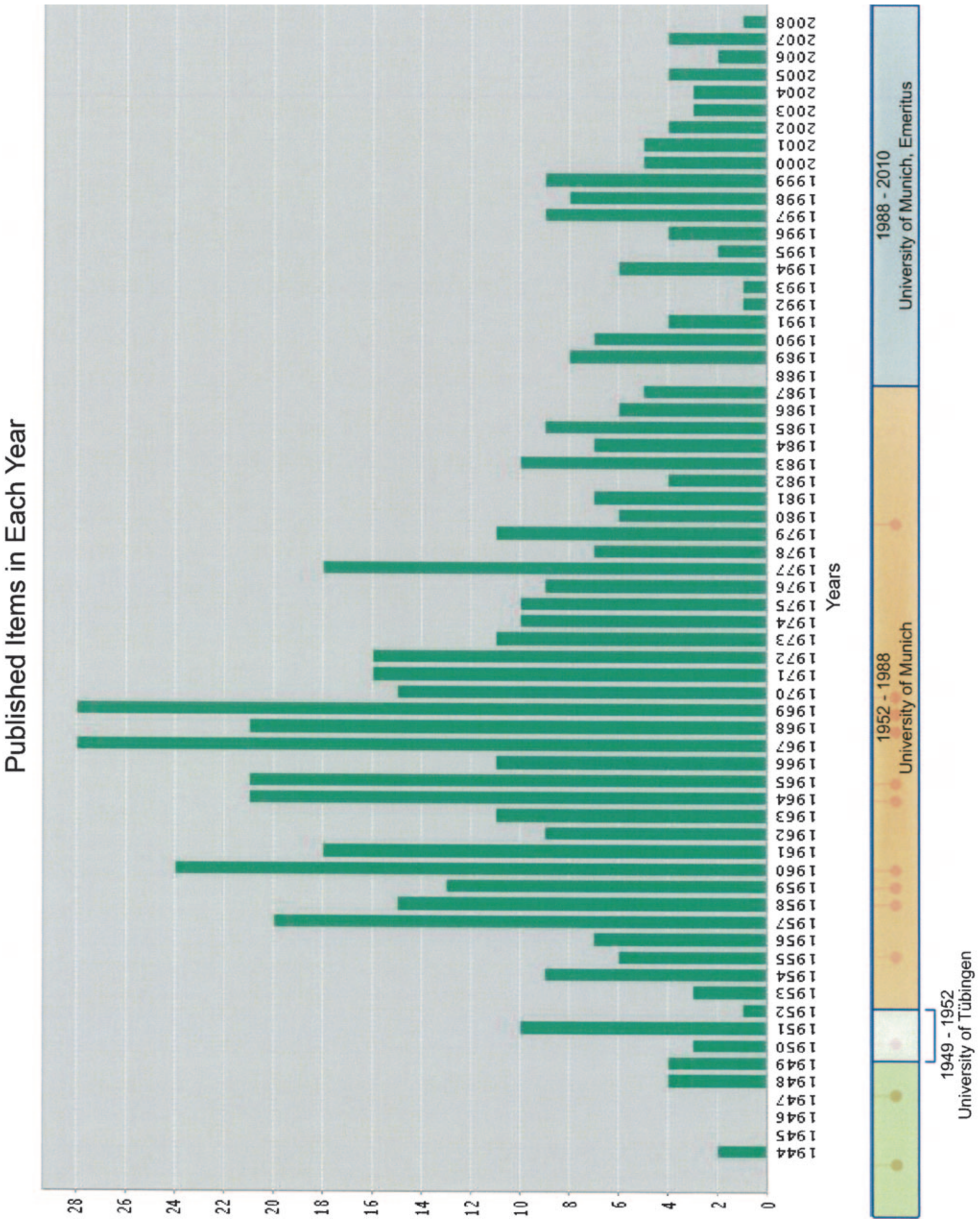


Fig. 26. *Graph of* Huisgen*'s publications*

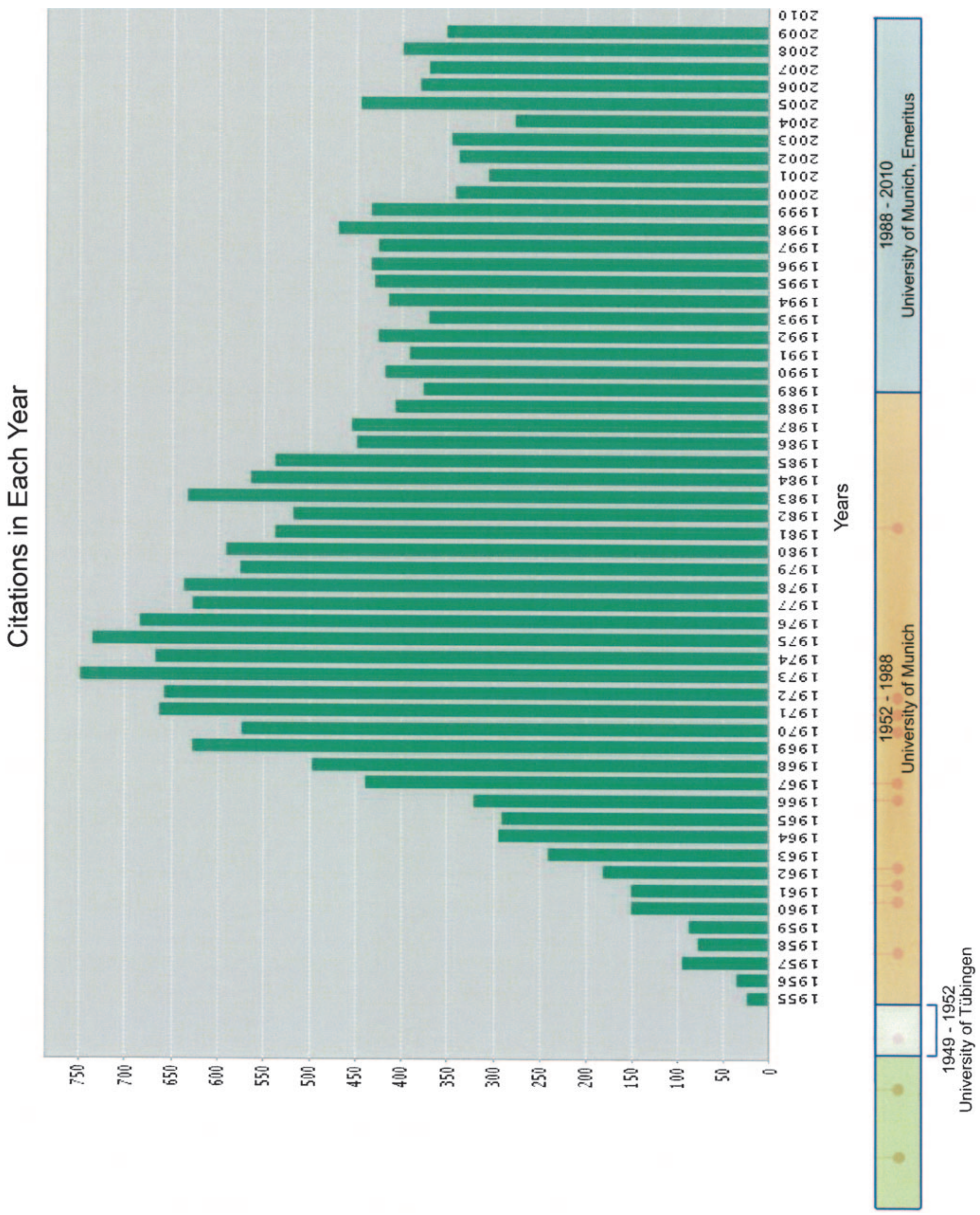


Fig. 27. *Citations to* Huisgen*'s papers*

Fig. 26 shows a graph, from *ISI* of these publications, reaching nearly 30 a year in the late 1970s but continuing even until now [17]. The influence of these papers has grown over time.

Fig. 27 shows a graph of citations of *Huisgen*'s work. *Huisgen* is the most cited German organic chemist, and for those who keep track of these things, his *h*-index is 76, meaning 76 of his papers have received 76 or more citations. There are more than 300 citations per year to his work during his career, and from 300–750 citations each year since the early 1960s [17].

Huisgen's chemical legacy has influenced chemistry the world over. Perhaps even more importantly, he trained many of the leading European organic chemistry faculty while stimulating and inspiring others all over the world. He has given honored lectureships, more than two dozen, at the major universities of the world. He has received not only the top honors of Germany but of many countries including the U.S., where he is an elected member of the American Academy of Arts and Sciences and the National Academy of Sciences.

Fig. 28. Rolf *and* Trudl Huisgen. Courtesy *Jeffrey I. Seeman*.

Fig. 29. *The author in his office with the poster of the* 'Elan Vital' *exhibition*

Rolf Huisgen is one of the top organic chemists of the 20th century, but he had other loves and active interests besides chemistry. *Fig. 28* shows *Rolf* with his wife, *Trudl*, who was with him through all the years of chemical discovery, until her passing five years ago.

And he loves art, especially German expressionism. As many of us have witnessed, *Rolf Huisgen* has great admiration for art, especially German Expressionist art. Going with *Rolf* to one of the museums in Munich is a unique cultural and moving experience. In his autobiography, he says, *'I regard theatre, music, and art as a world complimentary to science, with exposure to one acting as a stimulus for the other'* [1]. In my office at UCLA, there is a poster to remind me of wonderful tours of museums that *Rolf* gave me and my wife, too. This is a poster from the Haus der Kunst in Munich (*Fig. 29*), acquired during a visit there with *Rolf*.

'Elan Vital' was a famous exhibit of paintings at the time in Munich. The words mean vital force, and they seem appropriate today. To me and to chemists all over the world, *Rolf Huisgen* has been the vital force of organic chemistry for 60 years.

I am indebted to my student *Peng Li* for assistance preparing the illustrations.

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