History of Chemistry

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From Discovery to Application: 50 Years of the Vinylcyclopropane–Cyclopentene Rearrangement and Its Impact on the Synthesis of Natural Products

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cycloaddition · history of chemistry ·
natural products synthesis · rearrangement ·
vinylcyclopropanes

1. Introduction

Now the Director of the Office of the Center for Science, Technology and Security Policy at the American Association for the Advancement of Science, Norman P. Neureiter was a young research chemist with Humble Oil and Refining (subsequently Esso, now Exxon) for a few years after having received his PhD degree from Northwestern University in 1957. He left research in 1963 for a distinguished career in public service and as an executive with Texas Instruments, but during those years he spent at the bench, he published 12 articles and 11 patents. Among them was a preparation of 2-chlorocyclopentadiene and 1,1-dichlorocyclopent-3-ene by the pyrolysis of 1,1-dichloro-2-vinylcyclopropane: the first reported vinylcyclopropane–cyclopentene rearrangement.[1] Two patents related to this chemistry followed.[2]

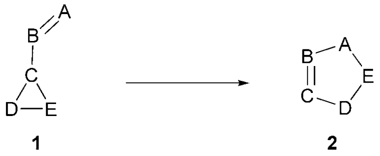
The following year, the conversion of vinylcyclopropane into cyclopentene under thermal conditions was reported independently by Vogel[3] and by Overberger and Borchert.[4] Flowers and Frey[5] as well as Wellington[6] carried out detailed mechanistic studies of this rearrangement in the early 1960s.

The pursuit of applications of this rearrangement to synthesis was no doubt driven by the search for practical methods for the preparation of five-membered rings in approaches to triquinane terpenes in the late 1970s. Unlike six-membered rings, which have perfect "consonant" connectivity with alternating electrostatic charges, cyclopentanes and their derivatives are "dissonant" (according to Evans's nomenclature). As a result, any retrosynthetic analysis invariably leads to connectivity of two fragments with the same latent charge. In the design of heterocyclic analogues, the problem is solved by dipolar cycloaddition reactions, but in carbocyclic synthesis there were no equivalents of the Diels–Alder cycloaddition. Thus, the cyclopropanation of dienes, followed by rearrangement (overall a [4+1] annulation), seemed a viable counterpart to the synthesis of six-membered rings by means of cycloaddition.

This Essay traces the evolution of applications of the vinylcyclopropane–cyclopentene rearrangement and analogous transformations of heteroatom-containing compounds to organic synthesis. Both methodology development and total syntheses of natural products are covered from a historical perspective.

2. Origins

Numerous synthetic applications of the vinylcyclopropane–cyclopentene rearrangement have been implemented since its discovery. The permutations available upon the introduction of heteroatoms into the five-atom system **1** are almost endless and lead to many useful heteroatom variants of **2**, many of which have been exploited in the synthesis of complex molecules. Furthermore, additional permutations of reactivity and product topology are possible if the olefin (A=B) is replaced with an allene or acetylene group, or if the cyclopropane component contains an alkyl substituent. The latter case opens up the possibility of a 1,5-hydrogen-atom shift leading to 1,4-dienes, which are in thermal equilibrium with vinylcyclopropanes.



The all-carbon version of the vinylcyclopropane–cyclopentene rearrangement has been featured in many terpene syntheses, and cyclopropyl ketimines and vinylaziridines have served well in the design of syntheses for many alkaloids. The rearrangements of cyclopropyl ketones and aldehydes or vinyloxiranes have also found use in approaches to targets containing dihydrofurans. Reviews of the parent rearrangement and its heteroatom variants[7] as well as the somewhat

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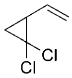
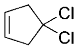
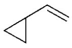
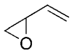
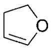
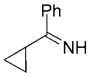
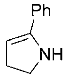
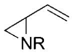
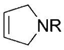
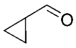
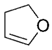
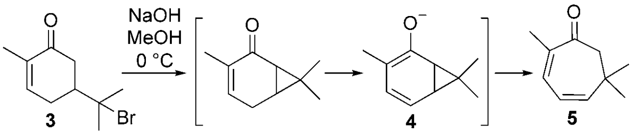
related divinylcyclopropane–cycloheptadiene rearrangement[8] are available. It is curious to note the chronology of the discovery of this rearrangement and its heteroatom variants: the rearrangements of vinylcyclopropanes were last to be observed but first to be studied in detail following the initial reports.

Neureiter reported in 1959 the thermal rearrangement of dichlorovinylcyclopropane to dichlorocyclopentene above 400 °C (Table 1, entry 1).[1] The rearrangement of the parent hydrocarbon to cyclopentene (Table 1, entry 2) was reported a year later,[3,4] although it seems likely that it had occurred unobserved in 1922 during the preparation of vinylcyclopropane by Hofmann elimination at elevated temperatures.[9] The related divinylcyclopropane rearrangement, a pericyclic process, was reported in 1960;[3] however, it was recognized to be involved in the rearrangement of norcaradiene to cycloheptatriene observed by von Doering in 1950.[10] Furthermore, it probably operated in the base-catalyzed preparation of eucarvone (**5**) from carvone hydrobromide (**3**) described by Baeyer in 1894.[11] The base-catalyzed rearrangement of the cyclopropyl-annulated cyclohexenone to the cycloheptadienone almost certainly proceeded by a divinylcyclopropane rearrangement of the enolized system **4**.

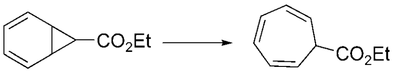
Table 1: Historical milestones in the rearrangement of vinylcyclopropanes and their heteroatom-containing variants.

Entry	Vinylcyclopropane or variant	*T* [°C]	Product	Author (year)
1		400–500		Neureiter (1959)
2		325–500		Vogel (1960); Overberger, Borchert (1960)
3		300		Paladini, Chuche (1971)
4		180		Cloke (1929)
5		180		Atkinson, Rees (1967) Lwowski (1968)
6		375–500		Wilson (1947)



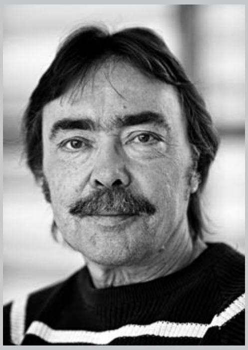
3 **4** **5**

Such a transformation may also constitute the first example of an anion-accelerated pericyclic rearrangement. These rearrangements were reported by Julia and co-workers[12] and by van Tamelen and co-workers[13] in the late 1950s. In a publication by van Tamelen and Hildahl[14] appears the following footnote indicating, almost three years before Vogel reported his vinylcyclopropane–cyclopentene rearrangement, that some awareness already existed of a radical-type reorganization of a constrained divinyl cyclopropane system: "*Contrary to possible expectations norcaradienecarboxylic ester (**6**) is not transformed by alkali in a great measure to a cycloheptatriene but is largely hydrolyzed to the norcaradiene carboxylic acid. … On the other hand the ester ([**6**]) is converted to the ring-enlarged ester ([**7**]) by **heating*** [emphasis by van Tamelen] *at 150–170 °C. The process may be either ionic or, more likely, radical in nature.*"



6 **7**

The corresponding oxygen- and nitrogen-containing analogues of (di)vinylcyclopropanes, the discovery of which preceded the discovery of the parent system(s), also enjoy widespread use in synthesis. In 1971, Paladini and Chuche reported the rearrangement of vinyloxirane to dihydrofuran (Table 1, entry 3).[15] A few years earlier, Vogel and Günther observed 2-vinyldihydrofuran in rearrangements of *trans*-divinyloxirane to oxepine.[16] The cyclopropylimine–pyrroline rearrangement was reported in 1929 by Cloke, who observed the formation of 2-phenylpyrroline hydrochloride during the attempted distillation of phenyl cyclopropyl ketimine hydrochloride under vacuum (Table 1, entry 4).[17] Atkinson and Rees described rearrangements of vinylaziridines to pyrrolines in 1967,[18] and one year later Lwowski and co-workers reported having observed this rearrangement during studies



Born in 1949 in Prague, Czechoslovakia, Tomas Hudlicky emigrated to the USA in 1968. He received his BS in 1973 from Virginia Tech and earned his PhD in 1977 at Rice University under the direction of Ernest Wenkert. After a year at the University of Geneva with Wolfgang Oppolzer, he joined the faculty at the Illinois Institute of Technology in 1978. He returned to Virginia Tech in 1982 and rose to the rank of professor in 1988. In 1995, he moved to the University of Florida in Gainesville. Since 2003 he has been at Brock University, where he currently holds a Canada Research Chair.

A native of North Carolina, Josephine Reed was educated at the University of North Carolina at Greensboro (BA, English), Appalachian State University (BA, biology and chemistry), and Virginia Tech (PhD, chemistry, with David Kingston). She has been working with Tomas Hudlicky and his group as a senior research associate for the last two decades. At the present time she also works at the Office of Research Services at Brock University as a research grants facilitator.

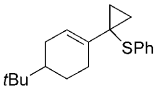
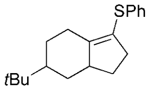
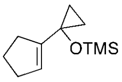
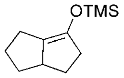
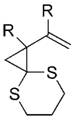
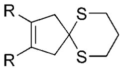
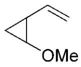
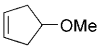
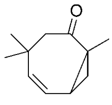
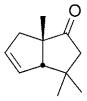
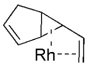
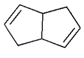
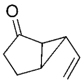
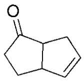
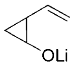
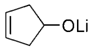
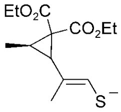
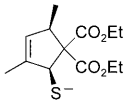
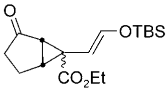
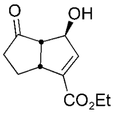
on the addition of singlet and triplet nitrenes to dienes[19] (Table 1, entry 5). Wilson reported the rearrangement of cyclopropylcarbaldehyde to dihydrofuran in 1947 (Table 1, entry 6).[20]

The mechanistic studies that followed in the wake of Neureiter's discovery quickly established the radical nature of the rearrangement (zwitterionic in special cases), although the debate concerning the possibility of a concerted $[2p_s + 2s_s]$ mechanism has not been resolved. A "concerted" rearrangement may well be a possibility in special cases, such as anion-accelerated rearrangements[21] or rearrangements of optically pure vinylcyclopropanes.[22] Such rearrangements proceed with a high degree of stereo- and enantioselectivity with respect to the configuration of atoms bearing substituents at the periphery of the reacting system.

Over the next two decades (1960–1980), thermal, photochemical, and transition-metal-catalyzed rearrangements were reported. Such rearrangements occurred at temperatures ranging from 600 °C to ambient temperature and even to −78 °C. The high temperature required for carbocyclic compounds placed natural limits on the size and functionality of substrates.

Soon several investigators discovered that heteratom substitution (Trost, Miller, Corey, Conia, Paquette) or donor–acceptor functionalities (Wenkert, de Meijere, Reissig) make it possible to carry out the transformation at lower temperatures or even in an ionic medium. As might be expected, the rearrangements of oxa and aza analogues proceed by alternate mechanisms (e.g., zwitterionic) and under more practical conditions and have therefore found many applications. By the mid-1970s, sufficient information had accumulated to enable the widespread application of these reactions in synthetic organic chemistry. The evolution of applications and a detailed description of mechanisms operating on the general structure **1** have been and continue to be adequately described in specialized articles and reviews.[7]

Table 2: Rearrangements of vinylcyclopropanes.[a]

Entry	Vinylcyclopropane	Conditions	Product	Author (year)
1		350 °C		Trost (1976)
2		350 °C		Trost (1973)
3		200 °C		Corey (1972)
4		220 °C		Simpson, Richey (1973)
5		$h\nu$		Paquette (1969)
6		20–40 °C		Brown (1975)
7		40–80 °C $[(C_2H_4)_2Rh(acac)]$		Hudlicky (1980)
8		25 °C		Danheiser (1980)
9		−78 °C		Larsen (1988)
10		KF, −78 °C		Hudlicky (1990)

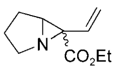
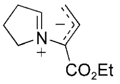
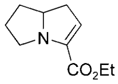
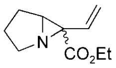
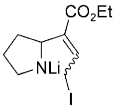
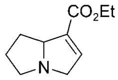
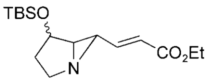
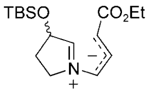
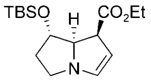
[a] acac = acetylacetonate, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

3. Methodology Development

After the initial mechanistic investigations of this rearrangement, numerous applications to synthesis were reported, including protocols for cyclopentene annulations. In the early 1970s, the most extensively studied protocols were the annulations reported by Trost and co-workers and based on the rearrangements of thiophenyl-[23] or trimethylsiloxy-substituted[24] vinylcyclopropanes (Table 2, entries 1 and 2, respectively). By this time it was known and appreciated that heteroatoms attached to the cyclopropane ring greatly accelerated the rate of the rearrangement and hence enabled the use of lower temperatures, in this case flow pyrolysis. The method was fully developed in the mid-1970s and proved very useful for annulations of cyclopentenes from the site of a carbonyl group and its α carbon atom. Other sulfur- and oxygen-substituted vinylcyclopropanes underwent rearrangement to cyclopentenes in preparatively useful yields, as in the cases reported by Corey and Walinsky[25] and Simpson and Richey[26] (Table 2, entries 3 and 4, respectively). Photochemical (Table 2, entry 5)[27] and transition-metal-mediated rearrangements (Table 2, entries 6 and 7)[28] were also described around this time or soon afterwards. Low-temperature variants were also reported. These last rearrangements, observed by Danheiser et al. (Table 2, entry 8),[29] by Larsen (entry 9),[21] and by us (entry 10),[30] were rationalized by invoking remote charge acceleration, an argument that supports a concerted mechanism and explains the observed stereoselectivity.

The rearrangements of vinyloxiranes and vinylaziridines or cyclopropyl ketiimines, though less common, were also subjected to mechanistic investigations. In the case of these heteroatom variants, dual mechanisms, both biradical and zwitterionic, usually operate. Furthermore, vinylaziridines and vinyloxiranes are subject to rearrangements by nucleophilic opening and subsequent reclosure. The examples listed in Table 3 pertain to the rearrangement of vinylaziridines each obtained from the aziridination of two isomeric dienic acid derivatives. Thermolysis (Table 3, entry 1) generates an azomethine ylide, whose reclosure provides a pyrrolizidine

Table 3: Rearrangements of vinylaziridines.

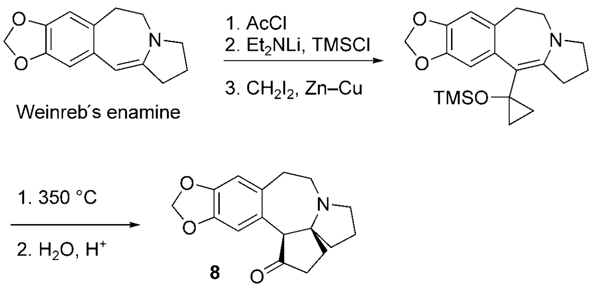
Entry	Vinylaziridine	Conditions	Intermediate	Product	Author (year)
1		480 °C			Hudlicky (1986)
2		LiI (equilibrium)		 (from *E* isomer)	Hudlicky (1987)
3		480 °C		 (single isomer)	Hudlicky (1988)

suitable for elaboration to alkaloids with this substitution pattern found in the animal kingdom (insects).[31] On the other hand, nucleophilic opening and reclosure under mild conditions (Table 3, entry 2) furnishes a pyrrolizidine suited for the synthesis of supinidine[32] and other pyrrolizidines found in the plant kingdom.[33] The thermolysis of a diastereoisomeric mixture of vinylaziridines (Table 3, entry 3) provided, by stereoselective closure of the zwitterion, a single isomer of a pyrrolizidine from which hastanecine and other members of this class may be obtained.[34] Zwitterionic mechanisms operate also in the opening of vinyloxiranes. (For detailed reviews of mechanistic and synthetic studies, consult references [7b,c]).

4. Milestone Events Relevant to Our Research Program

Before my own entry into this area in the late 1970s, several milestone events took place that had a profound influence on my research program. The first was undoubtedly my exposure to Stevens' graduate course on synthesis at Rice University in 1974. Part of this course dealt with the general method of alkaloid synthesis that he had developed based on rearrangements of functionalized cyclopropyl ketimines. (Stevens had been a student of Wenkert, whose research in general methods of synthesis was the hallmark of his career.) He presented to the class a vast array of targets, some already synthesized and some merely proposed. The generality of the method was quite impressive, as was Stevens's drive. (During that period, late at night, Stevens was working long hours on a chapter on this topic for the ApSimon series[35]—drawing structures with stencils and Letraset while drinking Scotch and smoking cigarettes). Meanwhile, in Wenkert's research group, my own project concerned the rearrangement of donor–acceptor-substituted cyclopropanes in the context of indole alkaloid synthesis; however, the idea of using vinylcyclopropanes for annulation did not occur to me until several years later.

Another influence was the appearance of a series of publications by Trost and co-workers[23,24] on cyclopentene annulations of sulfur- and trimethylsilyloxy-substituted vinylcyclopropanes, the latter prepared via his oxaspirocyclopentanes. I incorporated his silyloxyvinylcyclopropane rearrangement into a proposed synthesis of cephalotaxine via the pentacycle **8**, and this transformation formed the basis of my candidacy oral exam in 1976. Although it was never actually implemented, I remain confident that it would work.[36]

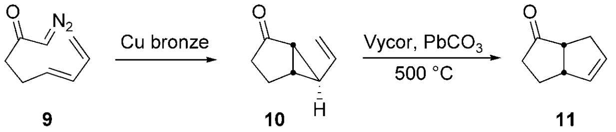


8

Really impressed with Trost's ideas and the superb quality of detail in his publications on this topic,[24] I considered an NIH postdoctoral position with him until Wenkert "suggested" that I join Oppolzer's group in Geneva. Oppolzer had recently left Sandoz, and he had initiated a vigorous academic career in Geneva the very year I was seeking a postdoctoral position. I followed his "advice" and went to Switzerland in the fall of 1977 to work on yet another general method of synthesis: terpene construction by ene reaction methods.

The third influence, and one of far-reaching consequences, was the onset of the "triquinane era" and the great chase by many organic chemists for general methods for making five-membered rings. My project in Oppolzer's research group was the total synthesis of isocomene, which had just been isolated by Zalkow et al.[37] It was during this time that I formulated the idea for a five-membered-ring equivalent to the Diels–Alder reaction, namely, the [4+1] cyclopentene annulation, which was to become the mainstay of our program for almost two decades. The first model study I undertook upon arrival at Illinois Institute of Technology in September 1978 was the cyclization of the diazo compound **9**. When we got to the stage of pyrolysis, we were using "standard" conditions, that is, a glass tube, glass helices, 400–500 °C; the yields of the rearranged products were not high, as dienes were formed preferentially by fragmentation.

The fourth influence, reading a report by Corey and Wollenberg in 1975 on cyclopentene annulation in Corey's



approach to prostanoids,[38] led to great improvements in these thermolyses. They described the conversion of **10** into **11** in the following way: "*Thermolysis of [**10**] by evaporation at 0.2 mm pressure through a 33 cm column heated to 600 °C (packed with chips of leaded potash glass) afforded ketone [**11**] …*" Because they provided this important information describing the hardware used in the pyrolysis, we set out to find "lead–potash glass". It was no longer available, no doubt as a result of the drive by the Environmental Protection Agency to eliminate all leaded products from our society. The best approximation we could come up with was to condition a Vycor column with an aqueous slurry of lead carbonate, dry it under high vacuum, and then distill the vinylcyclopropane through the hot zone. The method produced superior results and greatly reduced the formation of by-products of the rearrangement.

From the viewpoint of experimental execution, the description provided by Corey and Wollenberg had far-reaching consequences with regard to our ability to carry out the rearrangements: had this seemingly trivial detail not been mentioned, we may not have been as successful as we were in the many subsequent applications of this rearrangement to the total synthesis of triquinanes.

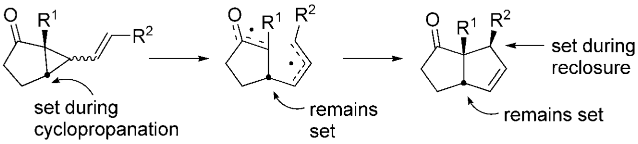
The [4+1] methodology developed exclusively for triquinane synthesis evolved into a more efficient [3+2] protocol that we used in syntheses of pentalenic[39] and retigeranic acids.[40] By analogy, both [4+1] and [3+2] annulations were developed into general methods for the synthesis of pyrrolizidine alkaloids[41] and tetrahydrofuran-containing terpenes, such as ipomeamarone.[42]

Between 1978 and 1989 we developed a fully general methodology for the synthesis of linear and nonlinear triquinanes, pyrrolizidine alkaloids, and dihydrofuran-containing natural products.[43] In all of these and subsequent syntheses (see Tables 4 and 5 for examples), the rearrangements of vinylcyclopropanes, vinylaziridines, or vinyloxiranes constituted the key steps.

By the early 1990s we were able to design a fully general and exhaustive method of synthesis for natural products containing five-membered rings. During the process we also developed protocols to avoid the high temperatures required in the early versions of the annulations. Thus, we were able to obtain cyclopentenes at room temperature, or even at −78 °C, by means of the anion acceleration effect operating in some of the [3+2] annulations, such as that used in the synthesis of specionin.

In the domain of the pyrrolizidine alkaloids, the nucleophilic opening of vinylaziridines with trimethylsilyl iodide (TMSI) was performed at −50 °C. Following these developments, few challenges remained in the discipline. The vinylcyclopropane–cyclopentene rearrangement of racemic substrates led to stereoselective ring closure with well-defined peripheral substitution preferentially on the *exo* face of the product. When the cyclopentene is substituted with carboxylate groups, both *exo* and *endo* isomers become available through hydrogenation (which leads to the *endo* isomer) and equilibration (which provides the *exo* isomer).

The main remaining challenge was to perform these rearrangements in an asymmetric mode; however, close examination of the reactive system reveals that, of the three stereogenic centers in the cyclopropane, only one remains unperturbed during the reorganization. Because the resulting cyclopentene will be *cis*-fused, and because the peripheral substitution favors the *exo* configuration, it is only necessary to introduce asymmetry in the cyclopropanation step, as the configuration of the single cyclopropane carbon atom controls the configurations of the remaining centers formed during the rearrangement.



Asymmetric cyclopropanation was solved adequately by the chiral catalysis developed by the Doyle research group, the Davies research group, and others.[44] We may therefore conclude that the only remaining challenges in the use of this rearrangement will be more complex applications in synthesis, in cascade sequences and higher-order cycloaddition reactions, and possibly also new developments in, for example, transition-metal catalysis of the rearrangement. Indications that this hypothesis is correct are evident in more recent applications, such as the [5+2] annulations developed by the Wender research group and described in Section 6.

5. Applications in Total Synthesis

Building on the foundation provided by Stevens, Trost, Corey, and others in the methodology of these rearrangements, applications to total synthesis followed. Tables 4 and 5 present a sampling of these applications. Not included are the triquinane syntheses developed by the Wender research group based on *meta* photocycloaddition of arenes; although some of these syntheses, such as that of cedrene,[45] do involve endocyclic vinylcyclopropanes, strictly speaking they do not involve rearrangements to cyclopentenes. The complete listing of targets obtained by the rearrangements can be found in specific reviews.[46]

The targets shown in Table 4 were attained mostly by rearrangements performed at high temperature. Because most are carbocycles with limited functionality, either flow pyrolysis or flash vacuum pyrolysis could be successfully applied. The only other limiting feature is volatility; compounds such as the vinylcyclopropanes leading to aphidicolin, antheridiogen-An, and retigeranic acid are probably at the limit of molecular weight.

Table 4: Vinylcyclopropane–cyclopentene rearrangement in total synthesis.

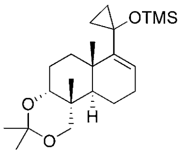
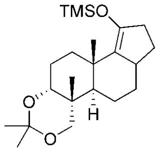
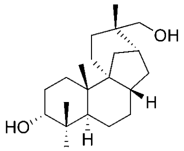
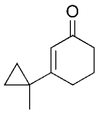
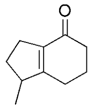
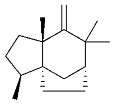
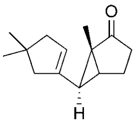
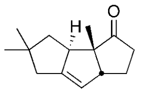
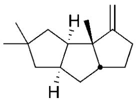
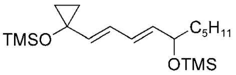
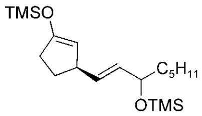
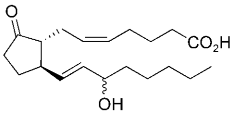
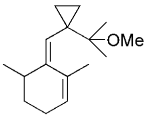
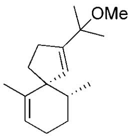
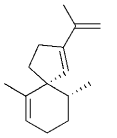
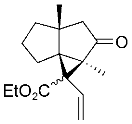
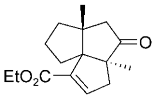
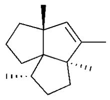
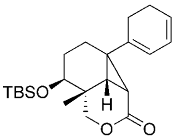
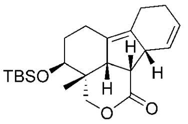
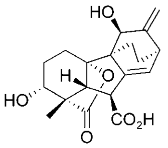
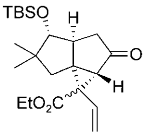
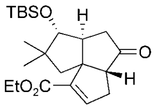
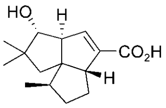
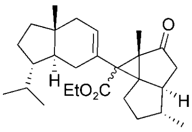
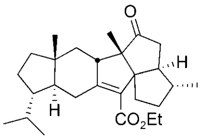
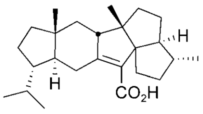
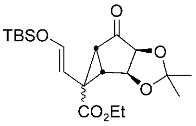
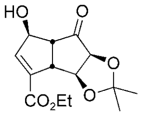
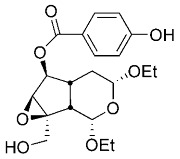
Vinylcyclopropane	Cyclopentene	Target	Author (year)[63]
		 aphidicolin	Trost (1979)
		 zizaene	Piers (1979)
		 hirsutene	Hudlicky (1980)
		 11-deoxyprostaglandin E_2	Salaün (1981)
		 α-vetispirene	Paquette (1982)
		 isocomene	Hudlicky (1984)
		 antheridiogen-An	Corey (1985)
		 pentalenic acid	Hudlicky (1987)
		 retigeranic acid	Hudlicky (1988)
		 specionin	Hudlicky (1992)

Table 5: Rearrangements of heteroatom-containing analogues of vinylcyclopropanes in total synthesis.[a]

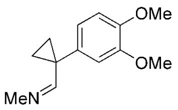
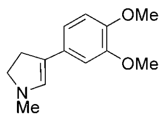
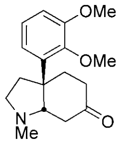
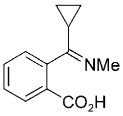
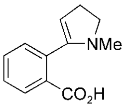
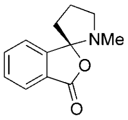
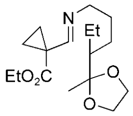
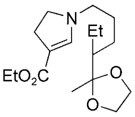
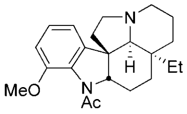
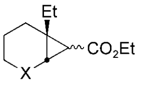
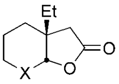
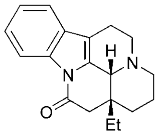
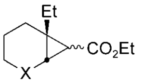
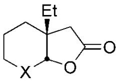
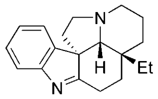
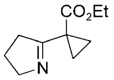
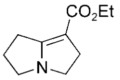
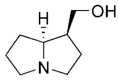
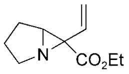
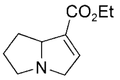
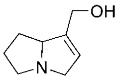
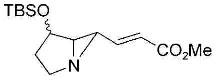
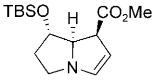
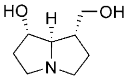
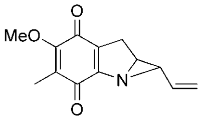
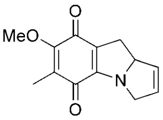
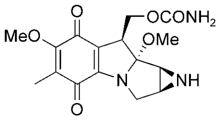
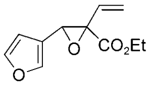
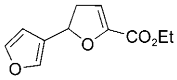
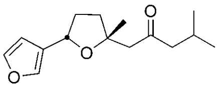
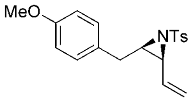
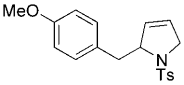
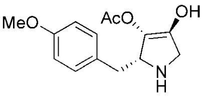
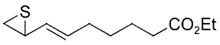
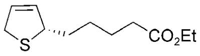
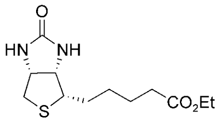
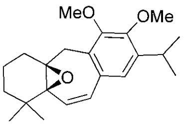
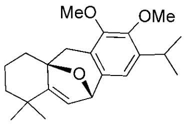
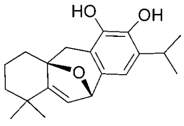
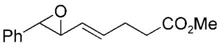
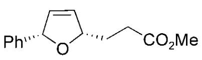
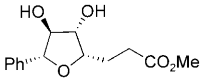
Starting material	Product	Target	Author (year)[64]
		 mesembrine	Stevens (1968)
		 shihunine	Breuer (1969)
		 aspidospermine	Stevens (1971)
 X = O, NCO_2Me		 eburnamonine	Wenkert (1978)
 X = O, NCO_2Me		 dehydroaspidospermidine	Wenkert (1978) (published 1988)
		 isoretronecanol	Pinnick (1979)
		 supinidine	Hudlicky (1985)
		 hastanecine	Hudlicky (1986)
		 mitomycin A	Maruyama (1987)
		 ipomeamarone	Hudlicky (1990)
		 anisomycin	Somfai (2005)

Table 5: (Continued)

Starting material	Product	Target	Author (year)[64]
		 biotin	Njardarson (2007)
		 salviasperanol	Majetich (2008)
		 goniothalesdiol	Njardarson (2008)

[a] Ts = *p*-toluenesulfonyl.

The trimethylsilyloxyvinylcyclopropane used in the specionin synthesis was subjected to rearrangement at low temperature in an anion-accelerated process, as the intermediate species contained an enolate anion. The vinylcyclopropane leading to the linear triquinane intermediate for hirsutene also underwent rearrangement under rhodium catalysis at lower temperatures.

Table 5 shows examples of rearrangements involving heteroatom-containing analogues of vinylcyclopropanes. These processes proceed at far lower temperatures than the corresponding rearrangements of vinylcyclopropanes. Most are promoted by either nucleophilic or acid catalysis. The cyclopropylketimine rearrangement has been applied successfully to several alkaloid targets without resorting to pyrolytic conditions. Rearrangements of vinylaziridines to pyrrolines in syntheses of pyrrolizidine alkaloids were also performed at lower temperatures under conditions of nucleophilic opening and reclosure. The tosyl vinylaziridine used in the synthesis of anisomycin was subjected to rearrangement with LiI under microwave irradiation.

Similar processes may operate in the rearrangements of vinyloxiranes. Acid catalysis at 0 °C was employed in the vinyloxirane rearrangement leading to salviasperanol. Recently, copper-catalyzed rearrangements of vinyloxiranes, vinylthiiranes, and vinylaziridines at temperatures in the range of 120–150 °C were reported and used in the synthesis of biotin and goniothalesdiol.[47]

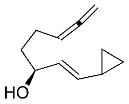
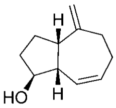
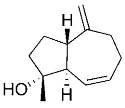
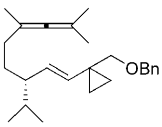
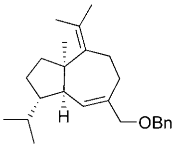
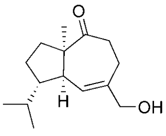
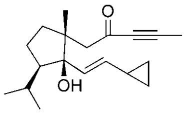
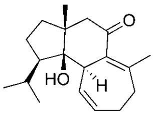
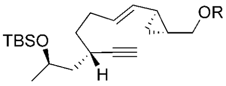
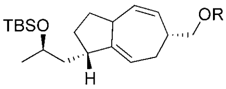
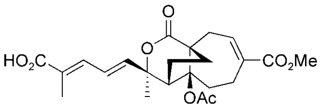
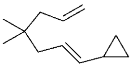
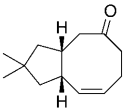
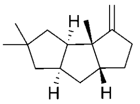
6. Current Status and Perspectives

The triquinane era has receded into the past, and the quest for pyrroline and pyrrolizidine alkaloids is no longer a priority of synthetic chemists, yet there is no shortage of new developments in the application of vinylcyclopropanes in synthetic design, nor has the development of new cyclopentane annulations ceased. At the end of 1990s and in the early 2000s, Wender and co-workers reported a rhodium-promoted addition of vinylcyclopropanes to allenes[48] and acetylenes.[49] This [5+2] annulation protocol was efficiently applied to several total syntheses, including the synthesis of terpenes containing the hydroazulene skeleton. Dictammol, aphanamol, pseudolaric acid, and the allocyanthin core were attained by either rhodium- or ruthenium-catalyzed [5+2] cycloaddition reactions (Table 6).

Vinylcyclopropanes are still often used in synthesis (Table 7). For example, de Meijere and co-workers, who continue to make contributions to the chemistry of cyclopropanes in general, reported cyclopentene annulations by flash vacuum pyrolysis in 1985, 1998, and 2001 (Table 7, entry 1).[50] Their synthesis of tetrahydropentalenes also involved flash vacuum pyrolysis of vinylcyclopropanes.[50b] Pattenden and co-workers used a radical cyclization cascade initiated by a cyclopropylcarbinyl rearrangement in an elegant approach to steroids (Table 7, entry 2).[51] Alper and co-workers reported a palladium-catalyzed thiocarbonylation of vinylcyclopropanes to give olefinic thioesters (Table 7, entry 3).[52] A nickel(0)-catalyzed vinylcyclopropane–cyclopentene rearrangement was reported to proceed at room temperature under catalysis by N-heterocyclic carbenes (NHCs; Table 7, entry 4).[53] The process was later subjected to detailed computational analysis.[54] Copper catalysis reported recently by Njardarson and co-workers allows for milder conditions in the rearrangement of vinyloxiranes to dihydrofurans (Table 7, entry 5),[55] of vinylthiiranes to dihydrothiophenes (entry 6),[56] and of vinylaziridines to pyrrolines (entry 7).[57] Several reviews dealing with the chemistry of vinylcyclopropanes have appeared during the last decade.[7g–j]

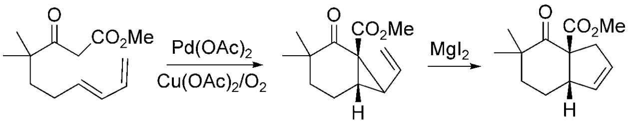
Extrapolation to the cycloaddition of allenes[58] and cyclopropyl ketimines (Table 7, entry 8),[59] extended the generality of this method for the synthesis of compounds with seven-membered rings. Analogous ruthenium-catalyzed annulations of acetylenes and vinylcyclopropanes were reported by Trost and co-workers[60] and recently an iron(0)-catalyzed [5+2] cycloaddition leading to functionalized bicyclo[5.3.0]decanes was described by Fürstner et al. (Table 7, entry 9).[61]

Table 6: Application of [5+2] annulations in total synthesis.[a]

Vinylcyclopropane	Cycloheptene	Target	Author (year)[65]
		 dictammol	Wender (1999)
		 aphanamol	Wender (2000)
	 core of allocyathin B_2	(–)	Wender (2001)
 R = TBDPS		 (–)-pseudolaric acid B	Trost (2007)
		 hirsutene	Yu (2009)

[a] Bn = benzyl, TBDPS = *tert*-butyldiphenylsilyl.

At the time of this writing, the most recent report on cyclopentene annulation was that of Coscia and Lambert, who in 2009 described the palladium-catalyzed cyclopropanation of dienic ketoesters in the presence of the cooxidant $Cu(OAc)_2/O_2$.[62] The resulting activated vinylcyclopropanes underwent rearrangement by nucleophilic ring opening and reclosure in direct analogy to processes already used in pyrroline annulations.



From this vantage, it is important to acknowledge the significance of the disclosure of this rearrangement by Neureiter. Hundreds of projects have been conceived on the basis of this report, and the ensuing accumulation of mechanistic details permitted the evolution of applications to synthesis. Furthermore, the seemingly random event described by Cloke in 1929 and retrieved from the literature by Stevens in the 1960s provided the foundation for many applications in alkaloid synthesis. The current generation of chemists wishing to pursue new and more complex applications should be aware of and give proper credit to all those who, for the last 50 years, preceded them in designing imaginative projects based on a simple five-atom unit.

Personal Recollection of Norman P. Neureiter

It was a wonderful nostalgic moment to receive the e-mail from Tomas Hudlicky inviting me to comment on my "discovery" of the thermal rearrangement of vinyldichlorocyclopropane to chlorocyclopentene. I am pleased to comment on my "discovery" of the thermal rearrangement of vinyldichlorocyclopropane to chlorocyclopentene. Having finished my PhD degree at Northwestern in mid-1957, I moved in August for my first job as a chemist to Baytown, Texas, and the Humble Oil and Refining Co. In the small but well equipped research center, under the leadership of Joe Franklin (a pioneer in ion molecule chemistry and later to become a distinguished professor of chemistry at Rice University), a strong basic research tradition had been developed and some highly talented PhD chemists were mixed in with the engineers whose job it was to keep the world's largest oil refinery continuing to produce petrochemical feedstocks. After thinking back through events in my life in 1959, and after some consultation with Bob Perry, one of my close colleagues, on our work at Humble, here is my best recollection of how I came to this interesting rearrangement reaction.

Table 7: Other applications of the vinylcyclopropane and related rearrangements in the last decade.[a]

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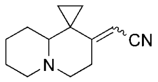
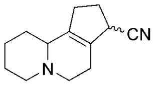
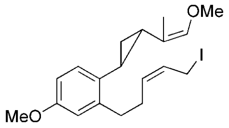
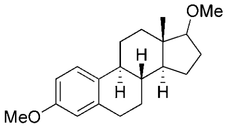
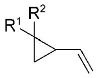
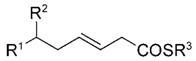
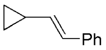
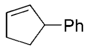
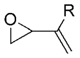
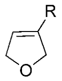
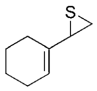
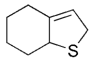
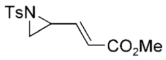
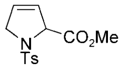
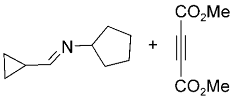
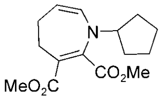
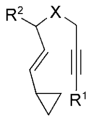
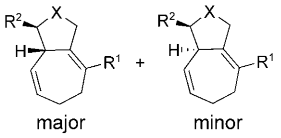
1		550 °C		de Meijere (2001)
2		Bu_3SnH, AIBN		Pattenden (2009)
3		R_3SH, CO, $Pd(OAc)_2$		Alper (2009)
4		$[Ni(cod)_2]$, NHC ligand, 100 °C		Zuo, Louie (2004)
5		$[Cu(hfacac)_2]$, neat, 150 °C		Njardarson (2006)
6		$[Cu(hfacac)_2]$, 100 °C		Njardarson (2008)
7		$[Cu(hfacac)_2]$, toluene, 150 °C		Njardarson (2008)
8		$[\{Rh(CO)_2Cl\}_2]$, 60 °C, DCE		Wender (2002)
9		$[Fe^0Cp(C_2H_2)_2]$, TMEDA		Fürstner (2008)

[a] AIBN = azobisisobutyronitrile, cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethene, hfacac = hexafluoroacetylacetonate, NHC = N-heterocyclic carbene, TMEDA = *N,N,N′,N′*-tetramethylethylenediamine.

An early assignment to me at Humble by my boss Henry Schutze was to try to find new uses for butadiene of which there seemed to be a surplus coming out of the refinery processes. William von Eggers Doering was a consultant for Humble at the time and during his visits always spent time with us "organikers", invariably richly informative and highly entertaining. On one of his visits, Doering introduced us to the exciting area of carbene chemistry, and I tried it with butadiene using the procedure reported by Woodworth and Skell. Why I then went on to pyrolysis of the product is now not clear to me—perhaps because of the remarkable stability of the dichloro compound reported by Woodworth and Skell. Unfortunately, without my notebooks from those days, I do not remember my observations with the dibromo analog, though it appears from the footnote in the article to have been much less stable than the dichloro compound.

A careful look at the paper makes it apparent that most of the analytical conclusions were drawn from a combination of chromatographic separation, mass spectrometry, infrared spectra, and nuclear magnetic resonance spectra of the various fractions in the pyrolysis mixtures, in addition to Diels–Alder and hydrogenation reactions and analysis of those products. We were very fortunate at Humble to have very high competence in the areas of mass spectrometry (thanks to Joe Franklin) and excellent work in nuclear magnetic resonance carried out by Nugent F. Chamberlain and his associates. I am deeply grateful to them for giving me sufficient confidence in the analytical results to publish this paper. Nugent was truly a pioneer in the application of NMR in organic analysis and has left a very distinguished set of publications in the field. The special thanks extended to him and his group at the end of the paper were richly deserved.

The dates of receipt (June 26, 1959) and publication (December 1959) of this Note on the rearrangement in the *Journal of Organic Chemistry* are particularly interesting. In early June of 1959, I began a four-month leave from Humble and was married, followed by a trip to Washington to meet, along with 74 other young Russian-speaking Americans, President Eisenhower and to be officially dispatched to our new jobs as Guides at the American National Exhibition in Moscow. This was a 40-day long, fair-like event displaying and explaining to some 50000 Russians a day every conceivable aspect of American daily life—from a kitchen (the famous Nixon–Khruschev kitchen debate took place there) to fashion, books, color TV, IBM computers, and on and on. My exhibit was an operating plastic molding machine, turning out hundreds of little polyethylene cups a day, which were snatched up as souvenirs as fast as they were made.

Following my return from Moscow I qualified as a State Department escort interpreter, which over the next two years, with leave again granted by Humble, provided two important opportunities for additional contributions to the U.S.–Soviet relationship. One was to serve as one of the interpreters for the first Soviet petroleum delegation to travel throughout the U.S. This had great implications at the time for possible entry of the Soviets into the global oil market. The second was to be interpreter for a Soviet organic chemist in his extended trip around the U.S., ostensibly to lecture on chemistry. However, the more important purpose of the trip, in his dual roles as a Vice President of the Soviet Academy of Sciences and a key Soviet delegate to the Pugwash conferences on arms control, was to carry on semi-official discussions with academic advisors to the Kennedy Administration on the issue of limiting the testing of nuclear weapons.

After my return to Humble (which was some 87 % owned by Exxon at the time), the company soon became very involved in developing an industrial scale process for commercial production of polypropylene, based on a license purchased by Exxon in Europe. Soon much of my work at Humble was devoted to stabilizer systems for polypropylene and a study of the mechanism of the inhibiting action against oxidation of the polymer by addition of small amounts of mixtures of hindered phenols and organic sulfide compounds.

After almost six years at Humble, however, I still found the excitement and unique value of international science diplomacy tugging at me and actively looked for a job that would combine my science background with international diplomacy. In 1963, I moved to the National Science Foundation's international office and became director of the U.S.–Japan Cooperative Science Program created by President Kennedy. In 1965 I joined the Department of State as a science attaché. Today I am still actively working in science diplomacy, presently as Senior Advisor at the American Association for the Advancement of Science.

It is indeed a great pleasure to learn that my modest paper about this reaction in the *Journal of Organic Chemistry* in 1959 has played at least some role in the rich chemistry that has followed its disclosure 50 years ago.

Personal recollection of Robert H. Perry

I joined Humble Oil and Refining Company (now Exxon) in Baytown, Texas, in 1952 during what was later perceived as being a golden era of industrial chemical research. The company had hired a number of us PhDs not knowing exactly what we should do other than something relevant, so we originated projects on our own. I was in an exploratory chemical research section and elected to determine what potentially useful and value-added chemical products could be produced from some of the myriad of petroleum derivatives that otherwise were going into motor gasoline.

Wm. von E. Doering, then a professor at Yale, was a consultant to Humble, and we "organikers" enjoyed bouncing our ideas off of him and hearing of his research activities that might have some relevance to our company business. In one of his visits to Baytown (circa mid-to-late 1950's), he described to me some of his discoveries in late-breaking research having to do with a new chemical entity, carbenes. These were the metastable intermediates formed under certain conditions by the dehydrochlorination of halomethanes using potassium *tert*-butoxide. Typically, dichlorocarbene was formed in this manner from chloroform, and it could be "trapped", as it were, by reaction with a suitable substrate such as an olefin. Thus, dichlorocyclopropane derivatives could be prepared from olefins, and a whole new field of chemistry opened up.

Starting with some simple monoolefins, I prepared several dichlorocyclopropane derivatives with the goal of determining what useful properties they might have in various applications per se and, to a lesser extent, as potentially useful chemical intermediates. I don't recall to what other applications groups in our Jersey organization (Standard Oil) these compounds were submitted for evaluation, but the tests were not extensive and included uses in several areas, such as pesticides, solvents, plasticizers and other prosaic applications. No properties were found that showed any of them to be any better than existing chemical products in those areas costing much less. Hence, not much more work was done, as "pure research" was not in the province of that group's activities or charter.

The authors are most grateful to the co-workers who participated in the various methodology and total-synthesis projects connected with this topic between 1978 and 1992. During that period, 16 graduate students, 57 undergraduates, and 38 postdoctoral fellows contributed to our research; their names appear in the cited references. The funding for most of our work at that time was provided by the following agencies and institutions: NIH, NSF, Jeffress Trust Fund, ACS-PRF, Research Corporation, Illinois Institute of Technology, Virginia Tech, TDC Research, Inc., and TDC Research Foundation.

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