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Introduction to the Chemistry of Donor–Acceptor Cyclopropanes: A Historical and Personal Perspective

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CHAPTER MENU

1.1 Introduction

During the past 15 years, we have seen tremendous progress in new applications of donor–acceptor cyclopropanes (DACs). Between 1980 and 2005, only a handful of papers per year were published mentioning this term; however, starting in 2006, a constant increase of interest could be observed, and recently, 80–100 articles dealing with this type of cyclopropanes as key compounds were released annually (Figure 1.1). This increasing number of contributions and the growing importance of this field are confirmed by the high number of recent review articles and, of course, by the fact that this book will collect articles from many of the key players in this research area. We introduced the term "donor-acceptor-substituted cyclopropane" in 1980 [1] and contributed to this field in its early phase. However, we did not use the term regularly; sometimes, we preferred the more specific name "siloxy-substituted cyclopropanecarboxylate," assuming that it is more precise.

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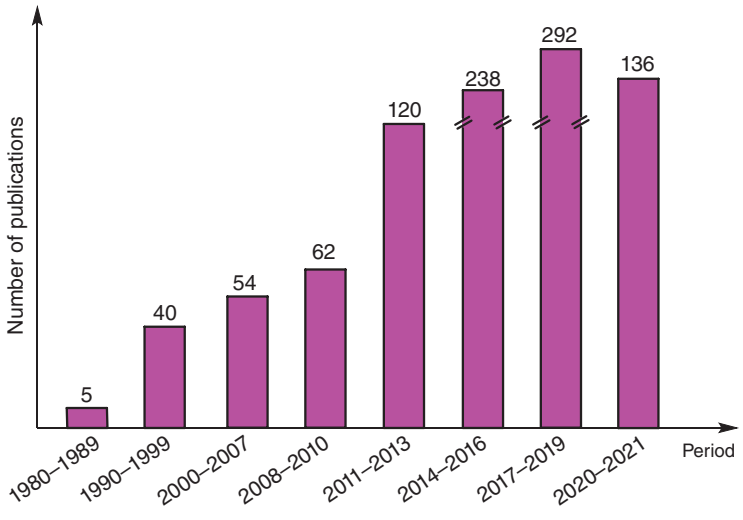


Figure 1.1 Number of publications dealing with the topic "donor–acceptor cyclopropane" or synonyma (according to a search in Web of Knowledge on 26 September 2021).

Also, several of the important contributions of Ernest Wenkert do not name their substrates DACs [2]. Therefore, the statistics in Figure 1.1 are not fully representative of the early period of 1980–2005.

Why did DACs receive this importance in organic synthesis? For a long time, cyclopropanes were regarded as exotic laboratory curiosa. In 1882, August Freund prepared the parent compound in Lemberg [3]; shortly after, in 1884, William Henry Perkin Jr. synthesized the first functionalized cyclopropane (diethyl cyclopropanedicarboxylate) [4] in the Munich laboratory of Adolf von Baeyer, who recognized the special properties of this type of hydrocarbons and formulated his famous concept of ring strain [5]. Over the years and decades, cyclopropane derivatives with different substituents and functional groups were prepared and investigated; however, in general, the reaction mechanisms involved were at the center of interest. The development of efficient methods for their synthesis was essential for this progress, in particular, the use of carbenes and carbenoids allowed simple and selective approaches to various classes of cyclopropanes. It was only in the 1960s and 1970s that it became evident that cyclopropanes can also serve as building blocks in organic synthesis, and very famous chemists were involved in exploring these possibilities. A systematic treatment of "Methods of Reactivity Umpolung" by Dieter Seebach [6] also included certain aspects of cyclopropane chemistry in this seminal review. Here the phrase "cyclopropane trick" was mentioned and connected with reactivity umpolung. A second early key player in this period was Armin de Meijere, who entered the field as a physical organic chemist but subsequently also provided important synthetic contributions in the cyclopropane field [7]. Very important contributors to the use of cyclopropanes in organic synthesis, in particular, in natural product synthesis, were Samuel Danishefsky, Robert V. Stevens, and Ernest Wenkert. Danishesky et al. exploited cyclopropanes activated by two acceptor substituents

that can be smoothly ring-opened (homo-Michael addition), especially in an intramolecular fashion, to give skeletons suitable for further synthetic elaboration [8]. The known Cloke rearrangement of cyclopropyl imines to dihydropyrrole derivatives was further developed by Stevens and applied to natural product synthesis [9]. On the other hand, Wenkert et al. explored the chemistry of oxycyclopropanes for the synthesis of terpenes and alkaloids. His publications also contained a few examples of alkoxy-substituted cyclopropyl ketones or esters; however, these DACs were semantically not distinguished from the other oxycyclopropanes [2]. Nevertheless, his group should receive the credit for being the first to use DACs in natural product synthesis.

1.2 My Personal Entry to Donor–Acceptor Cyclopropanes

After my doctoral studies with Rolf Huisgen [10] at Ludwig-Maximilians University in Munich, I started a postdoctoral stint in the laboratory of Edward Piers at the University of British Columbia in Vancouver, Canada, in the fall of 1978. In Munich, I worked with diazoalkanes and studied kinetics, as well as the mechanistic aspects of their 1,3-dipolar cycloadditions. In the group of Piers, I was trained as a synthetic chemist, with a research project dealing with cuprate chemistry, the generation of divinylcyclopropanes, and their Cope rearrangements to cycloheptadiene derivatives [11]. My project and the contemporary literature taught me that cyclopropanes are very suitable compounds to achieve synthetic processes, which are not easily possible by alternative methods. Afterward, I had the chance to start my independent academic career as an associate of the group of Siegfried Hünig [12] in Würzburg, and as my first research project, I suggested to use donor-acceptor-substituted cyclopropanes. This idea originated when reading the publications of Danishefsky [8]: instead of an external nucleophile, a directly connected nucleophilic center (donor center) should open the acceptor-activated cyclopropane ring by a strain-driven retro-aldol reaction. For this type of process, only a few related examples could be found in the literature [2]. The original drawing of my grant application to the Fonds der Chemischen Industrie, a very supportive institution in Germany for young scientists, is shown as a copy in Figure 1.2. My proposal was apparently considered to be reasonable, and equipped with a Liebig fellowship, I could start with my project at the end of 1979.

In Vancouver, I had learned that silyl enol ethers are very useful starting materials for many synthetic operations, whereas during my doctoral work in Munich, methyl diazoacetate was one of the key compounds. It was, therefore, a nearby idea to combine this knowledge for the synthesis of siloxy-substituted cyclopropanecarboxylate **2** (Scheme 1.1). They were efficiently available by copper-catalyzed addition of the carbenoid derived from methyl diazoacetate to the silyl enol ethers **1**. As the simplest subsequent reaction, we first studied the ring-opening with fluoride sources to give 1,4-dicarbonyl compounds **3** under very mild conditions. In my very first independent paper published in 1980, we used the term “donor-acceptor-substituted

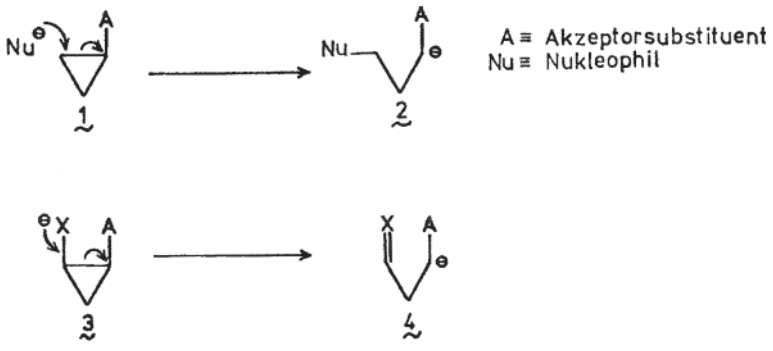
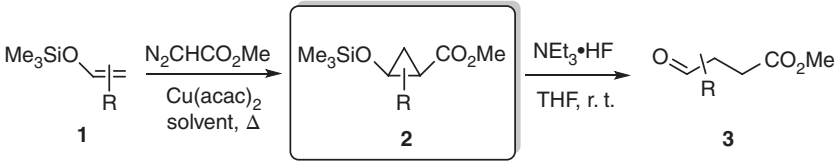


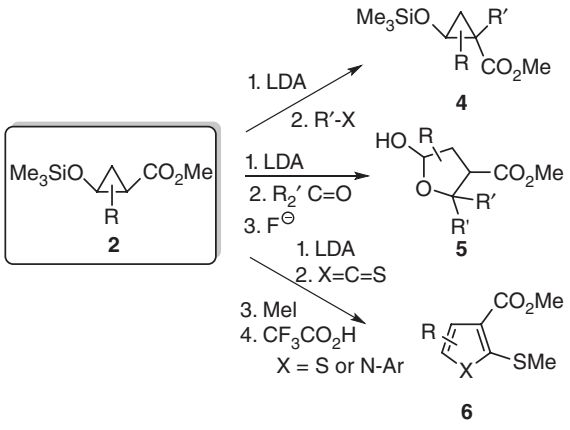
Figure 1.2 Copy of a hand-drawn scheme in a grant proposal submitted by the author to the Fonds der Chemischen Industrie in the summer of 1979.



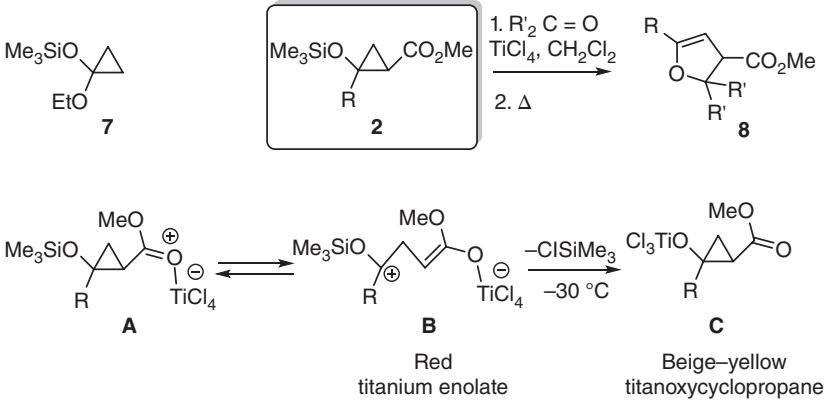
Scheme 1.1 Synthesis and ring-opening of siloxy-substituted cyclopropanecarboxylate **2**, the first cyclopropanes named DACs.

cyclopropanes" for this type of compound [1], which was later shortened to donor–acceptor cyclopropanes (DACs). I am not entirely sure why I had chosen this name, but my thoughts were probably influenced by the review of Seebach, who classified compounds by donor and acceptor centers [6].

One of the initial ideas of this project – the ring-opening with fluoride under aprotic conditions and the trapping of the resulting ester enolate with electrophiles – did not work satisfactorily [13]. However, as an excellent alternative, we found a step-wise method for forming new C—C bonds at the acceptor-substituted cyclopropane carbon atom. Methyl cyclopropanecarboxylate **2** could be smoothly deprotonated with lithium diisopropylamide (LDA) and subsequently trapped with a broad range of electrophiles (Scheme 1.2). This clean deprotonation reaction was not self-evident, since enolates incorporating a cyclopropane ring were essentially unknown around 1980. The reaction with alkyl halides R′-X occurred with surprisingly high stereoselectivity [14], leading to C-1 substituted cyclopropanes **4**, whose ring-opening led to higher substituted 1,4-dicarbonyl compounds. The trapping of the enolates with aldehydes or ketones furnished highly substituted tetrahydrofuran derivatives **5** (synthetically very useful γ-lactols) after treatment with fluoride [15]. The reaction of the enolates with carbon disulfide or aryl isothiocyanates, followed by the addition of methyl iodide, provided a nice route to interestingly functionalized thiophene or pyrrole derivatives **6** [16].



Scheme 1.2 Deprotonation of siloxy-substituted cyclopropanecarboxylate **2** with LDA and subsequent reactions with electrophiles leading to products such as **4–6**.



Scheme 1.3 Titanium tetrachloride-promoted ring-opening of siloxy-substituted cyclopropanecarboxylate **2** and reactions with carbonyl compounds leading to dihydrofuran derivatives **8**; titanium intermediates **A**–**C** involved in this process.

An alternative mode of activation and ring-opening of the siloxycyclopropanes **2** employed strong Lewis acids such as titanium tetrachloride (Scheme 1.3). This idea was deduced from the results of Kuwajima and Nakamura published in 1977 [17]. They demonstrated that 1-ethoxy-1-(trimethylsiloxy)cyclopropane **7** (an oxycyclopropane bearing **no** acceptor group) reacts with aldehydes and ketones under $TiCl_4$-promotion in a ring-opening homo-aldol process to yield γ-hydroxy carbonyl compounds. Under similar conditions, siloxy-substituted cyclopropanecarboxylate **2** furnished acyclic products or γ-lactols in good yield. Through elimination, the intermediate γ-lactols could be converted into dihydrofuran derivatives **8** [18]. After these preliminary results, a subsequent mechanistic study revealed an equilibrium

between a $TiCl_4$-complex **A** and a red-colored acyclic titanium enolate **B** at low temperatures [19]. This type of intermediate is likely responsible for the observed *cis-trans*-isomerization of siloxy-substituted cyclopropanecarboxylates at low temperatures [20]. *Today, this type of activation is relevant for most reactions of DACs bearing two alkoxycarbonyl groups as activating substituents*. By warming **A**/**B** to –30 °C, an elimination of chlorotrimethylsilane was observed. This provided a titanoxycyclopropane **C**, which is probably the reacting species with the carbonyl compound to form the new C–C product, again in a homo-aldol type process, but now with the support of the acceptor group.

Although many more studies were subsequently published by our group in the period between 1980 and 1995, I will conclude my personal story concerning DACs with this rather detailed presentation of basic ideas and early results. We used compounds such as **2** as convenient precursors for 1,4-dicarbonyl compounds **3**, which were *in situ* trapped by subsequent reactions; for instance, intramolecular Diels–Alder reactions, and in addition, we also studied Ugi and Gewald multicomponent reactions. The results of the first years were already summarized in a review article published in 1988 [21], and later, Reinhold Zimmer and I wrote a second review published in 2003. It was much more comprehensive, including many contributions from other groups, and so far has been cited almost 1200 times [22]. This second review and an article by Brian Pagenkopf published in 2005 [23] were probably responsible for widely popularizing the term DAC because it was used in the titles of these reviews. These articles drew the attention of many research groups to this type of small-ring compound. Already in 2014, Daniel Werz – one of the current key players in the field – wrote an excellent comprehensive review entitled "A New Golden Age for Donor-Acceptor Cyclopropanes" [24]. Although only selected review articles published afterward can be listed here [25], they all attest to the high importance DACs gained during the last 40 years. It should also be mentioned that a special issue of the *Israel Journal of Chemistry* published in 2016 is also exclusively devoted to the chemistry of DACs and the related donor–acceptor cyclobutanes [26].

1.3 A Few Principles of the Chemistry of Donor–Acceptor Cyclopropanes

We must start with an unanswerable question: What is a donor, and what is an acceptor substituent? When the author of this chapter introduced the term DAC in 1980, his intention was to apply this name to cyclopropane derivatives bearing relatively strong electron-donating substituents such as alkoxy, siloxy, amido, or amino groups, in combination with a vicinally positioned electron-withdrawing substituent, and in most cases this substituent was a carbonyl or a cyano group. Later, the term DAC was less strictly employed, and cyclopropanes with substituents that are able to stabilize a positive or a negative charge can now be generally regarded.

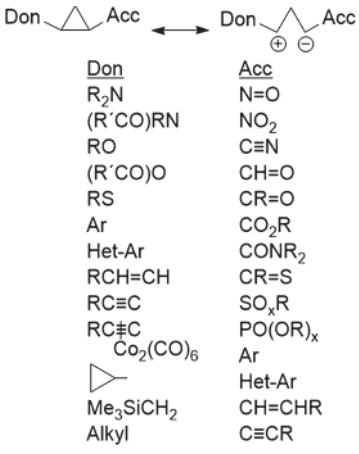
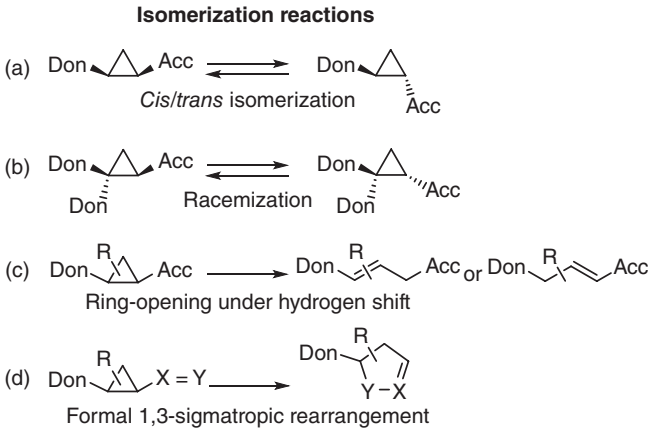


Figure 1.3 DACs polarized by different donor and acceptor substituents, respectively, and the respective zwitterionic mesomeric formula.

These substituents polarize the bond between the carbon atoms bearing the activating groups, a situation that can be characterized by a *zwitterionic mesomeric formula*, as depicted in a simplified manner in Figure 1.3. Many substituents can now be included in this (incomplete) list.

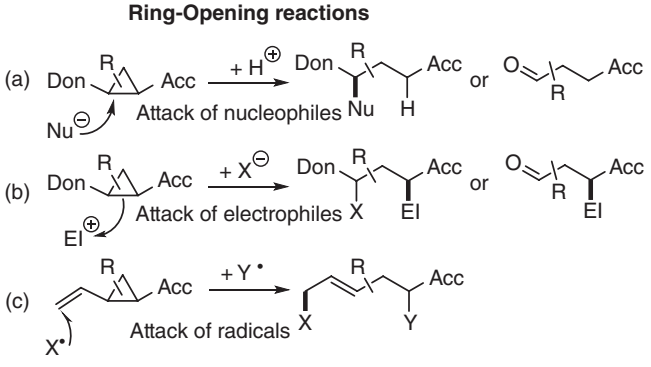
On the donor side, many more substituents can be considered, in particular, aryl, hetaryl, or alkenyl groups. Even alkyl groups are able to stabilize a positive charge better than a hydrogen atom. The acceptor substituents are generally X=Y double bond or X≡Y triple bond systems containing one or two heteroatoms. However, aryl, hetaryl, alkenyl, and alkynyl groups are also able to stabilize a negative charge and should be added as acceptor substituents in a systematic survey. It is obvious that two donor or two acceptor substituents should have a stronger influence on the reactivity of the cyclopropane than just one of these substituents. A very useful scale of the activating property of many of these substituents has been provided by Werz et al. who performed DFT calculations of the rearrangement of DACs to the corresponding five-membered ring systems [27]. The effect of substituents on the reactivity of DACs in the presence of Lewis acids was also studied by Werz et al. [28], whereas Ofial et al. examined the reactivity of several acceptor-substituted cyclopropanes, including a few DACs, in nucleophilic ring-opening reactions by thiols in the absence of Lewis acids [29].

The reactions of DACs can be roughly classified into the categories of isomerization reactions, ring-opening reactions, and cycloadditions. In Scheme 1.4, isomerizations are subdivided into reactions under the maintenance of the cyclopropane ring [case a)] *cis*/*trans*-isomerizations and [case b)] racemizations), reactions under ring-opening [case c)], and rearrangements under ring-enlargement [case d)]. The latter case can be regarded as a (formal) 1,3-sigmatropic rearrangement; the 3,3-sigmatropic Cope-rearrangements of cyclopropane derivatives bearing two alkenyl groups or their heteroanalogs, which lead to seven-membered carbo- or heterocycles, are not listed here.



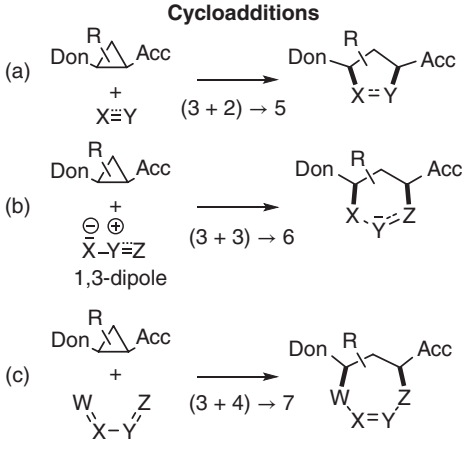
Scheme 1.4 Isomerization reactions of DACs (presentation in part under disregard of configurational aspects).

Ring-opening reactions under the incorporation of reagents (Scheme 1.5) can occur through a primary nucleophilic attack at the donor-substituted carbon [case a)], an electrophilic attack at the acceptor-substituted carbon [case b)], or the attack of a radical, often observed as the addition of the radical to an alkenyl group as donor substituent [case c)]. Donors such as siloxy groups allow a reaction with fluoride as a nucleophile at the silicon center, delivering a cyclopropoxy anion whose ring opening directly generates a carbonyl group in a retro-aldol process [case a), also see Scheme 1.1]. Similarly, the reactions of electrophiles can also lead to the formation of a carbonyl group if their counter ion X^- reacts with the siloxy group [case b), also see Scheme 1.3]. The ring-opening of acceptor-substituted vinylcyclopropanes by palladium or other metal complexes, which affords π-allyl complexes ready for further reactions with external or internal nucleophiles, is not presented here.



Scheme 1.5 Ring-opening reactions of DACs.

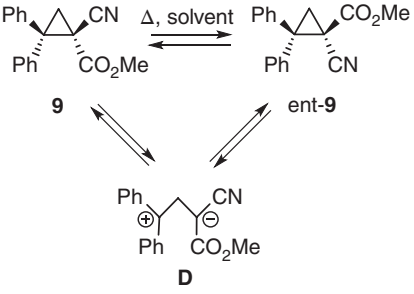
Cycloadditions constitute a particularly important class of reactions of DACs. Only a few can occur without external promoters; however, Lewis acids are generally employed in stoichiometric or catalytic amounts in order to activate the cyclopropanes. Most frequently, the combination of two alkoxycarbonyl groups on the acceptor side and an (electron-rich) aryl group on the donor side was used. In the simplified Scheme 1.6, only the overall processes are illustrated, showing that (3+2)-cycloadditions give rise to five-membered ring systems [case a)], and that several 1,3-dipoles have been used in (3+3)-cycloadditions, which furnish six-membered heterocycles [case b)]. A few examples of dimerizations of DACs have been reported, which also belong to the category of (3+3)-cycloadditions. To complete the picture, (3+4)-cycloadditions of DACs with 1,3-(hetero)dienes are listed here [case c)], although this process is relatively rare. Higher-order cycloadditions and reactions where a rearrangement of the DAC occurs before a cycloaddition proceeds have also been studied.



Scheme 1.6 Schematic presentation of (3+*n*)-cycloaddition reactions of DACs (simplified presentation without Lewis acids frequently required in these processes).

All these basic reactions have been described in detail in the published reviews, and certainly, they will be discussed again in the following chapters. Here, I just want to draw attention to the very interesting early studies reported by Cram and coworkers, starting in 1970. As physical–organic chemists, they carefully studied the isomerizations of specifically substituted cyclopropanes, which are clearly DACs according to our current definition [30]. Scheme 1.7 shows a typical example: the thermal racemization of compound **9** involves zwitterionic intermediate **D** as a crucial species. Cram et al. called these systems "carbanion-carbonium ion intermediates," discussed the character of the intermediates (1,3-zwitterion vs. singlet 1,3-diradical), and determined the activation parameters. As expected, the rate of racemization is dependent on the polarity of the solvent, with a relative rate of 1 in benzene and 75 in dimethylformamide in the presence of lithium bromide. The lithium cation acts as a Lewis acid in these reactions, which are more complex due

to subsequent ring-opening and ring-enlargement steps. In the case depicted in Scheme 1.7, the zwitterion **D** is a real existing intermediate with a certain lifetime, which is formed by the ring-opening of **9** or *ent*-**9**. It should not be mixed up with the zwitterionic mesomeric formula presented in Figure 1.3, which expresses the charge distribution of DACs.



Scheme 1.7 Racemization of DAC **9** via zwitterionic intermediate **D** as studied by Cram et al.

This almost forgotten study by Cram et al., published 50 years ago, is presented to emphasize that DAC chemistry is not entirely new and that a lot of information and inspiration can be gained by reading these detailed reports.

1.4 Remarks Regarding the Terminology Applied to the Use of Donor–Acceptor Cyclopropanes

The correct use of unambiguous nomenclature and terminology is inevitable to avoid confusion. It facilitates smooth communication between scientists and is particularly important in teaching. Reactions of DACs are often described by applying incorrect or ambiguous terms, and therefore a few of these issues are discussed here.

(a) The term "1,3-dipole" or "1,3-dipolar synthon" for DACs is misleading and incorrect. Huisgen clearly defined 1,3-dipoles [31] as conjugated 4π-system as depicted in Figure 1.4. These species always contain sp^2- or sp-hybridized heteroatoms Y in their center, which can bear a positive charge in an electron octet formula.

The bonding situation of cyclopropanes can be described by the MO-model by Walsh, which suggests that the C—C "single" bonds have considerable π-character (below, σ/π is used to describe this type of bonding). The interaction of cyclopropane bonds with adjacent substituents is therefore stronger than expected [7a, 27]. The zwitterionic mesomeric formula of DACs reflects the polarization of the bond between donor- and acceptor-substituted carbons and the dominating interaction with the substituents, but it has no common feature with 1,3-dipoles. The central atom is – by definition – a carbon atom and therefore not in strong interaction with the two adjacent carbons.

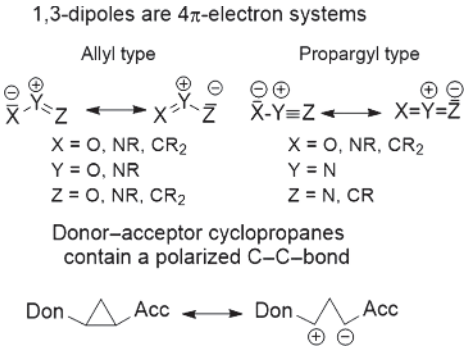


Figure 1.4 1,3-Dipoles according to Huisgen's systematic classification and polarization of DACs.

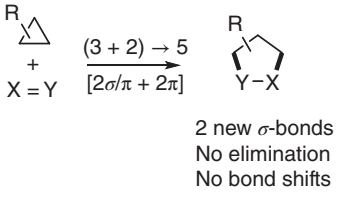
(b) Very often, DACs are named "1,3-dipolar synthons," which is wrong in two aspects. For the use of "1,3-dipole," see the the previous discussion under (a). The term "synthon" was initially introduced by Corey to characterize a hypothetical (charged) unit within a target molecule that represents a potential precursor reagent [32]. However, Corey noted in 1988 that "synthon" has now come to be used to mean "synthetic building block" rather than a retrosynthetic fragment. Since the original meaning of "synthon" is still useful in retrosynthetic analysis, I suggest calling DACs "1,3-zwitterionic building blocks" (or synthetic equivalents of a "1,3-zwitterionic synthon").

(c) Surprisingly, the term "(3+n)-cycloaddition" is inconsistently used when the reactions of DACs are discussed. It should be recalled first that parentheses, for instance, in (3+2)-cycloaddition, should be used to define the number of centers involved in a cycloaddition, whereas brackets, for instance, in [4+2]-cycloaddition, denote the number of (π)-electrons involved in a cycloaddition. For reactions of DACs, several authors prefer the more general term "(3+n)-annulation" or the even less specific "(3+n)-cyclizations".

Indeed, the definition of cycloaddition reactions is ambiguous if cyclopropanes are involved. According to the criteria, as collected long ago by Huisgen [33], cycloadditions are ring-forming reactions with an increase in the number of σ bonds. They are not associated with the elimination of small compounds or with the shift of atoms – at least in the ring-forming step. The reaction mechanism involved (thermally or photochemically, concerted as pericyclic reactions or stepwise via intermediates, uncatalyzed or catalyzed) is irrelevant. Later, IUPAC recommends similar criteria but notes that two or more unsaturated molecules should participate in the formation of a cyclic adduct in which a net reduction of bond multiplicity can be observed [34]. Cyclopropanes are usually not regarded as unsaturated molecules, but their partial π-character (see the previous discussion under (b)) justifies treating them as ethene homologs and calling the reactions summarized in Scheme 1.6 "real" cycloadditions if all other criteria are met. The prototype

of a (3+2)-cycloaddition of a cyclopropane to a five-membered ring (Scheme 1.8) is electronically characterized as a [2σ/π+2π]-process, in analogy to a (2+2)-cycloaddition of two alkenes, which is a [2π+2π]-process. I strongly recommend to act pragmatic and stay with the well-established and frequently used term "(3+*n*)"-cycloadditions for cyclopropanes if the above-mentioned criteria are met.

Scheme 1.8 (3+2)-Cycloadditions of cyclopropanes to a double bond system X = Y.



1.5 Conclusions

This introductory chapter should illustrate how the author was guided to introduce the term DACs and which types of reactions are possible with DACs. Studies conducted in the 1980s already revealed some of the important features of reactivity, for instance, the activation of DACs by Lewis acids. Later, the definition of DACs was expanded to include many new cyclopropane derivatives, particularly compounds with aryl groups as donor substituents. A tremendous development could be observed with many synthetically very useful transformations employing DACs as crucial C3-building blocks. Impressive examples already exist on catalytic enantioselective processes [25h, 25i], and it can be expected that these will be further advanced. The currently observed increase in electron-transfer-promoted reactions may also influence the chemistry of DACs. Recent examples employing electrochemical methods can already be found in the literature [35]. Some functionalized bicyclo[1.1.0]butanes can also be classified as DACs, and a few ring-opening reactions of these very strained compounds were reported [36]. This compound class is not particularly difficult to access, and therefore, more applications can be expected in the future. Finally, and most importantly, surprising and entirely new reactions of DACs are certainly still possible. The golden age of DACs is not finished.

Abbreviations

Acc	acceptor substituent
DAC	donor–acceptor cyclopropane
Don	donor substituent
LDA	lithium diisopropylamide

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