CHEMICAL REVIEWS

Review

The Dehydro-Diels#Alder Reaction

Pablo Wessig, and Gunnar Mu#ller

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The Dehydro-Diels−Alder Reaction

Pablo Wessig* and Gunnar Müller

Institut für Chemie, Humboldt-Universität zu Berlin, Brook-Taylor-Strasse 2, D-12489 Berlin, Germany

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1. Introduction

Cycloaddition reactions occupy an outstanding place among organic reactions, and they have been used in innumerable syntheses for more than a century.[1] One of the most prominent and best-examined cycloaddition reactions is the *Diels−Alder* (DA) reaction, that is the [4 + 2] cycloaddition between a diene and a dienophile (which can be an alkene as well as an alkyne) giving cyclohexene derivatives.[2] Furthermore, numerous heteroanalogous variants have been developed permitting the synthesis of heterocyclic compounds.[3] Two characteristic features are connected with the mechanism of the DA reaction: First, two C−C-σ bonds are formed in the course of the reaction, whereas at the same time two C−C-π-bonds vanish and therefore the reaction is highly exothermic (Scheme 1a). Second, in most cases the DA reaction is according to the *Woodward−Hoffmann* rules a thermally allowed, one-step process, although a two-step mechanism via diradical intermediates was discussed in some special cases.[4] If one or both double bonds in the diene component are replaced by a triple bond, these two statements must be qualified. Due to the neighborhood of the triple bond to the central C−C-single bond of the 4-atom component, the primary products must consequently contain two cumulated double bonds or, with other words, they are cyclic allenes (Scheme 1b−e).[5]

As the consequence of the considerable ring strain of these compounds, the DA reaction is, at least the first step, now endothermic in most cases. Furthermore, the reaction proceeds almost always via multiple steps, and the primarily formed cyclic allenes undergo further transformations (hydrogen migrations in most cases) to reduce the ring strain. The fundamentally different mechanism compared with the DA reaction justifies an independent treatment of the "dehydrogenated" variant of the DA reaction, which is called *Dehydro-Diels−Alder* (DDA) reaction. In this review, we will comprehensively discuss the different types of DDA reactions. The article is subdivided according to the different ways to initiate the DDA reaction (thermally or photochemically). Further subdivision was carried out according to the degree of saturation as depicted in Scheme 1b−e and whether a double bond in the reactants is part of an aromatic ring. Thus, reaction between enynes and alkenes affords isomers of dihydrobenzenes (reaction b), whereas benzene isomers are the products of DDA reaction between enynes and alkynes (reaction c) or between diynes and alkenes (reaction d). It should be noted that for reaction types c and d most examples have been published. The relatively seldom described reaction type e, where a diyne reacts with an alkyne, results in dehydrobenzene derivatives. In section 4 we will summarize the present state of knowledge of the mechanism both of the thermal and photochemical variant of the DDA reaction. Because DDA reactions initiated by bases or catalyzed by transition metals proceed according to a clearly different mechanism, we will discuss these reactions separately in sections 5 and 6, respectively.

2. Thermal Dehydro-Diels−Alder (DDA) Reactions (neutral or acidic conditions)

2.1. Arylacetylenes as Diene Component

2.1.1. Cyclization of 3-Arylpropiolic Acids

The first arylacetylenes, which were employed in DDA reactions were derivatives of 3-phenylpropiolic acid **1**.

More than 120 years ago *Michael* and *Bucher* reported on the dimerization of **1** in the presence of acetic anhydride in a sealed tube to give anhydride **2**.[6] The same product was later obtained in the presence of phosphoryl chloride[7] and from a mixture of 3-phenylpropiolic acid chloride, pyridine, and acetylacetone.[8] But also the ethyl ester **3** undergoes the DDA reaction upon heating, giving the diester **4**.[9] In the following period the reaction was successfully applied for the synthesis of various of substituted naphthalenes from

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* Author to whom correspondence may be addressed. E-mail: pablo.wessig@chemie.hu-berlin.de.

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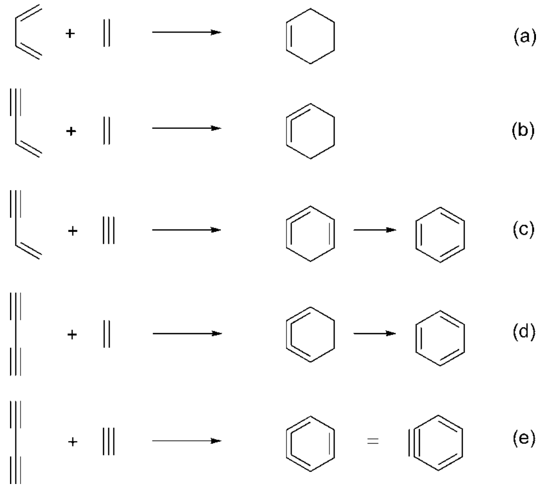
Pablo Wessig, born in Görlitz in 1962, completed his Ph.D. work and Ph.D. graduation at the Humboldt-University of Berlin under the supervision of Prof. H.-G. Henning, 1990. After a Postdoctoral research fellowship (FCI) at the University Basel, Switzerland, in the group of B. Giese (1993) he attended the Habilitation in the group of G. Szeimies at the Humboldt-University (2000). Since 2003 he works as Heisenberg fellow of the DFG at same university. His primary research interests are focused on preparative organic photochemistry, molecular probes, and rigid molecular sticks.

Gunnar Müller was born in 1976 in Salzwedel. He received his diploma from the Humboldt-University Berlin and his Ph.D. from the Humboldt-University Berlin where he worked under the supervision of Dr. P. Wessig to investigate the photochemical variant of the *Dehydro-Diels–Alder reaction*. Currently, he is working as a research fellow in the group of Professor William J. Kerr at the University of Strathclyde.

substituted 3-arylpropiolic acids.[10] As an example, the dimerization of **5** to **6** should be mentioned (Scheme 2).[10b–d] This reaction also elucidates one of the two possible regioselectivity phenomena, which can occur in the DDA reaction. If the aromatic rings are also substituted in the *meta*-position, the *ortho*-positions differ from each other, and two different DDA reaction products may be formed (in the following called "*o*,*o*′-selectivity"). In the case of **5**, only **6** and not **7** is formed, presumably due to the steric hindrance in **7**. Further insight in the DDA of 3-arylpropiolic acid derivatives is thanks to the extensive investigations by *Baddar* and co-workers.[11] They found among other things that in reactions such as **1**→ **2** the anhydride of the acid (phenyl propiolic anhydride) is formed before the DDA reaction takes place.[11b]

The second regioselectivity phenomenon must be considered if the two aromatic rings are differently substituted (in the following called "Ar,Ar′-selectivity"). This was investigated for the first time with unsymmetrical anhydrides prepared from 3-(2-methoxyphenyl)propiolic acid chloride **8** and 3-arylpropiolic acids **9**.[11c] Whereas the reaction between **8** and the 4-unsubstituted acid **9a** afforded preferentially the isomer **10a** (**10a**: **11a** = 3:1), this selectivity completely vanishes if a nitro group is introduced in **9** (Scheme 3).

Scheme 1



The DDA dimerization of 3-(4-methoxy-3-halophenyl)-propiolic acids **12** is a further interesting example for the subtle substituent effects on *o*,*o*′-selectivity.[11e]

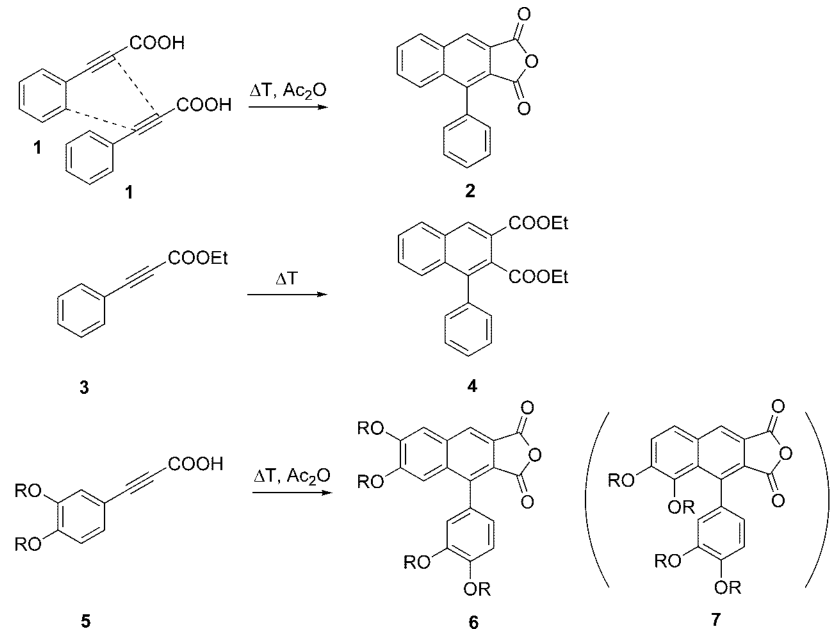
The chloro- and iodo-substituted acids **12a** and **12c** gave naphthalenes **13** with high selectivity, whereas the bromo compound **12b** provided a mixture consisting of **13b** and **14b** in nearly the same amounts. A considerable improvement of the DDA dimerization of 3-arylpropiolic acids was achieved by *Stevenson* by using dicyclohexyl carbodiimide (DCC) as condensing reagent.[12] With DCC the DDA reaction took place under surprisingly mild conditions as shown in Scheme 5 for compound **15**. Admittedly, besides the main product **16**, compounds **17** and **18** were obtained, which resulted from loss (**17**) or migration (**18**) of a bromine atom. This demonstrates the problem that atoms or atom groups, which apparently are blocking an *ortho*-position of an aromatic ring, often do not fulfill this function but are scavenged by the solvent or migrate. The DCC method was also used for the DDA dimerization of heterocyclic 3-arylpropiolic acids such as **19**.[13]

2.1.2. Cyclization of 3-Arylpropiolic Acid Propargyl Esters and Amides As Well As Dipropargyl Ethers

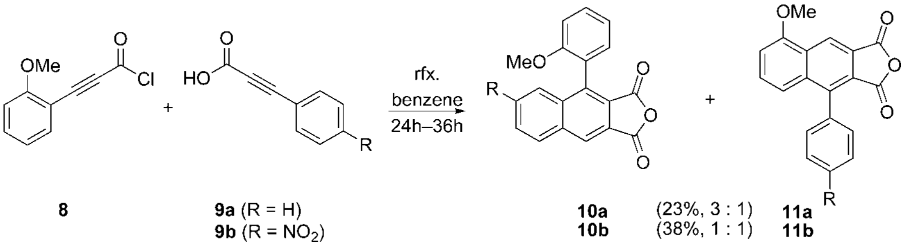
Although it is principally possible to use two different 3-arylpropiolic acids in the DDA reaction (cf. Scheme 3), the scope is clearly expanded if esters, amides, or ethers could be introduced in the linker moiety. The first DDA cyclizations of 3-arylpropiolic acid propargyl esters **21** were reported by *Klemm* who used acetic anhydride as reaction medium.[14] Alternatively, the cyclization takes place also in refluxing xylene (Scheme 6).[15] In most cases a mixture of isomeric lactones **22** and **23** was obtained. It should be noted that both aryl moieties are necessary. Reactants having only one aromatic ring afforded the DDA reaction products only with very low yields.[14c] The structurally analogous amides **24** react in a similar manner to give the lactams **25** and **26**.[14d,16]

In 2001 *Dominguez* and *Saá* reported on the cyclization of amides **27**, in which one of the phenyl rings is replaced by H or TMS and affords predominantly lactams **33** instead of expected compounds **32**. This surprising result was

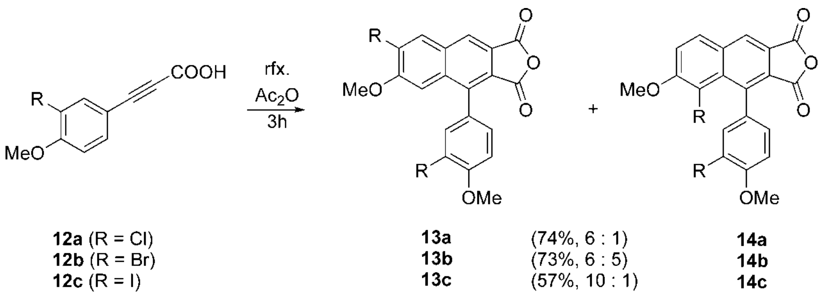
Scheme 2



Scheme 3



Scheme 4



explained by a *retro-Diels−Alder* ring opening of the primarily formed cycloallene **28** to give 1,3,5,7-cyclodecatetraen-9-yne **29**, *E*−*Z*-isomerization to **30**, and *Diels−Alder* ring closure to the allene **31**, followed by hydrogen migration (Scheme 7).[17] This hypothesis is supported by DFT-calculations and deuterium-labeling experiments.

Some years later Saá and co-workers reported on the DDA cyclization of 3-(trimethylsilyl)propiolic amides **34**. Whereas heating in toluene to 160 °C afforded products **35** (analogous to **33**, see Scheme 7), in triethylamine at the same temperature compounds **36** (analogous to **32**) were obtained exclusively. Obviously, the presence of the base triethylamine accelerates the deprotononation−protonation step from the primarily formed cycloallene (cf. **28** → **32**) and suppresses its rearrangement (Scheme 8).[18]

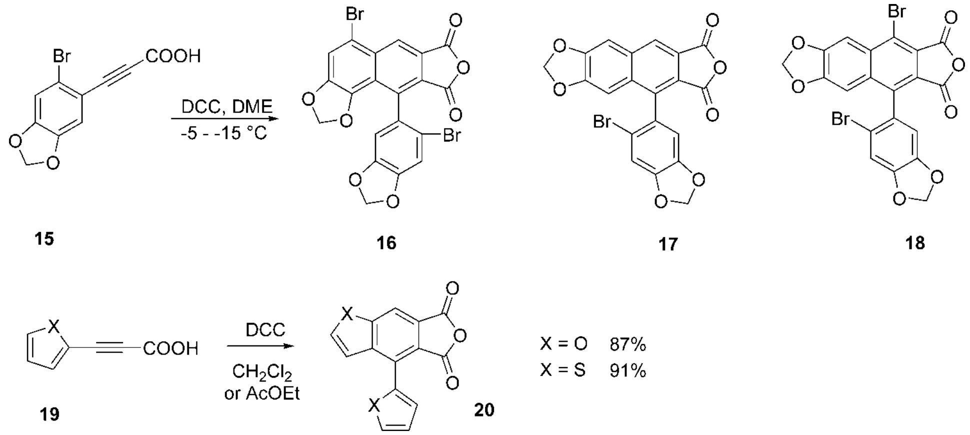
An analogous rearrangement was recently reported by *Shibata* and co-workers upon heating of di-(3-phenylpropargyl)ether, **37**, in xylene.[19] The DDA reaction product **38** and the rearranged compound **39** were formed in a ratio of 3:1. If one of the phenyl groups is replaced by a naphthyl moiety as in **40**, only the DDA reaction products **41** are obtained (Scheme 9). On the other hand, catalysis of these reactions with $AuCl(PPh_3)/AgSbF_6$ causes the exclusive formation of rearrangement products.[19]

A remarkable double DDA cyclization giving the fused perylenes **43** was observed by heating macrocyclic compounds **42**.[20] Finally, the interesting DDA cyclization of the highly substituted bicyclo[3.3.0]octane derivative **44** to **45**, bearing a tricyclo[5.3.0.$0^{4.5}$] decane skeleton, should be mentioned (Scheme 10).[21]

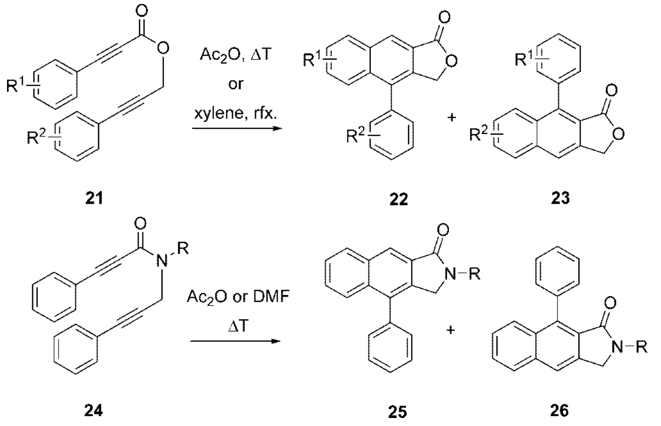
2.1.3. Linker Bearing an Aromatic Ring

In this section, DDA reactions of compounds will be discussed where one or several C−C bonds of the linker unit are part of an aromatic ring. This approach provides a

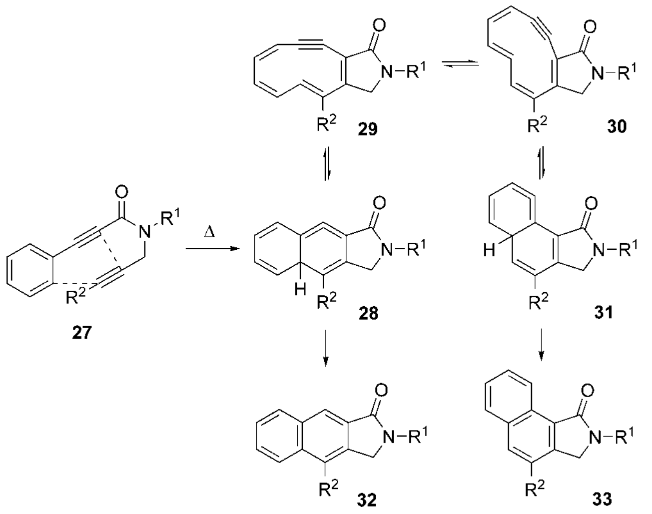
Scheme 5



Scheme 6



Scheme 7



straightforward access to complex polycyclic molecules and was therefore intensively investigated. The first type of such reactants is described by formula **46** where either R^1 or R^2 must be an aromatic ring but not necessarily both residues. Depending on which case is present (**46a** or **46b**) products **47a** and **47b** result (or a mixture of both if R^1 and R^2 are aryl residues, Scheme 11).

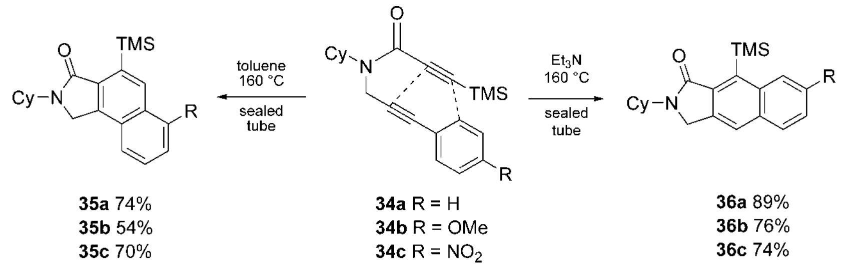
In Scheme 12 a variety of reactants are collected which correspond to this concept. The linking group X may be represented by a sp^3-carbon atom (**48**,[22,23] **49**,[23,24a] **50**[25]), a carbonyl group (**51**,[26] **52**[24,26b]), a nitrogen atom bearing an electron-withdrawing group (**53**[27]), an amide moiety (**54**[28]) or an OCH$_2$-group (**55**[28]). In some of these cases products arising from a rearrangement of the intermediate cyclic allene (cf. Scheme 7) were observed in addition to the DDA reaction products. For details we refer the reader to the cited literature.

The characteristic feature of the second type is that the entire linker is represented by an aromatic skeleton. In the simplest case **56**, where the linker consists of an *o*-substituted benzene ring, no DDA reaction but only dimerization and *Bergmann*-cyclization is observed.[29] On the other hand, a smooth DDA reaction occurs from o,o'-disubstituted diphenyl **57** and 1,8-disubstituted naphthalene **59** giving benzo[b]triphenylene **58** and benzo[k]fluoranthene **60a** respectively.[30] The latter system was investigated in detail and expanded to substituted and heterocyclic compounds for which the reaction behavior of **61** should be depicted as an example.[31] The cyclization of **59** in the presence of pentachloroethane or sulfur is instructive from mechanistic point of view. In these cases the cyclic allenes formed as reactive intermediates (see section 6) are obviously intercepted by the reagents and the chlorine (**60b**[32]) or sulfur (**60c**[33]) substituted products are obtained (Scheme 13).

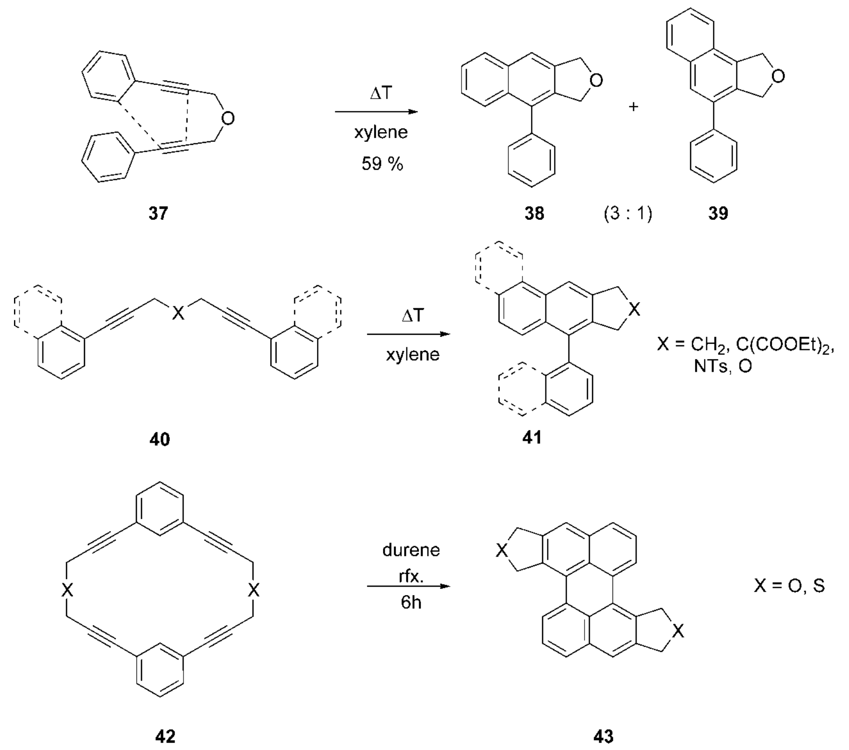
2.2. Enynes and Diynes as Diene Component

The main difference between the DDA reaction of arylacetylenes discussed in the previous section and the analogous reaction of enynes and diynes is that in the latter case no aromaticity must be temporarily revoked. Furthermore, the primarily formed cyclic allenes are often more stable and have longer lifetimes and, consequently, intermolecular following reactions may take place, which are not observed with arylacetylenes. The simplest DDA reaction of an enyne is the dimerization of vinylacetylene to styrol catalyzed by acids, which was already described in 1934.[34] Some years later *Butz* and co-workers reported on the reaction of various dienynes **65** with electron-poor alkenes (maleic anhydride, fumarates, *p*-benzoquinone). The primarily formed cycloallenes **66** undergo a second *Diels*–*Alder* reaction providing compounds **67** as final products.[35]Nearly at the same time *Dane* and co-workers described DDA reactions of 4-ethynyl-1,2-dihydronaphthalene **68** with maleic anhydride to the anhydride **69b** and with propiolates to dihydrophenanthrenes **70a** and **70b**.[36] A careful reexamination of the former reaction in 1994 revealed that the product has instead the isomeric structure **69a**. Additionally, evidence was supplied that the cycloaddition takes place

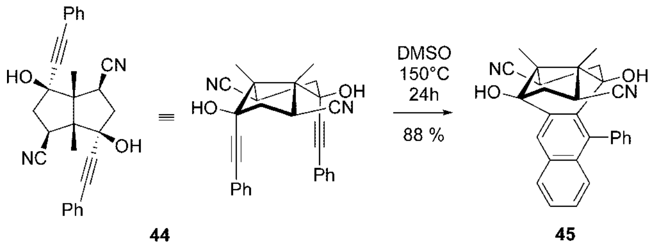
Scheme 8



Scheme 9



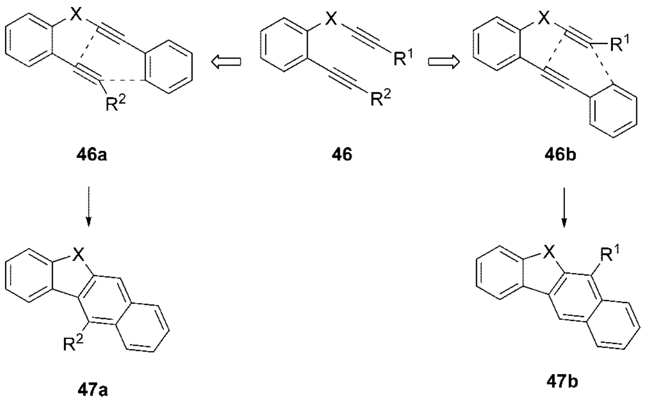
Scheme 10



by acid catalysis via a DA reaction of a halodiene formed by addition of hydrogen halides on the triple bond (Scheme 14).[37]

Furthermore, a series of DDA reactions is known where the aryl moiety of the arylacetylene is replaced by a (substituted) vinyl group.[17,27,28,38] This should be exemplified by the cyclization of ynamides **71** (cf. compound **53** in the preceding section) to carbazole derivatives **72**. As mentioned above the activation barrier of the initial step of the DDA reaction of enynes is considerably lower than that of arylacetylenes and therefore it is not surprising that in some cases the reaction takes place with an enyne reactant but not with the analogous arylacetylene. Whereas the enyne **71c** reacts smoothly to the carbazole **72c**, the analogous reaction with **73** failed (Scheme 15).[27]

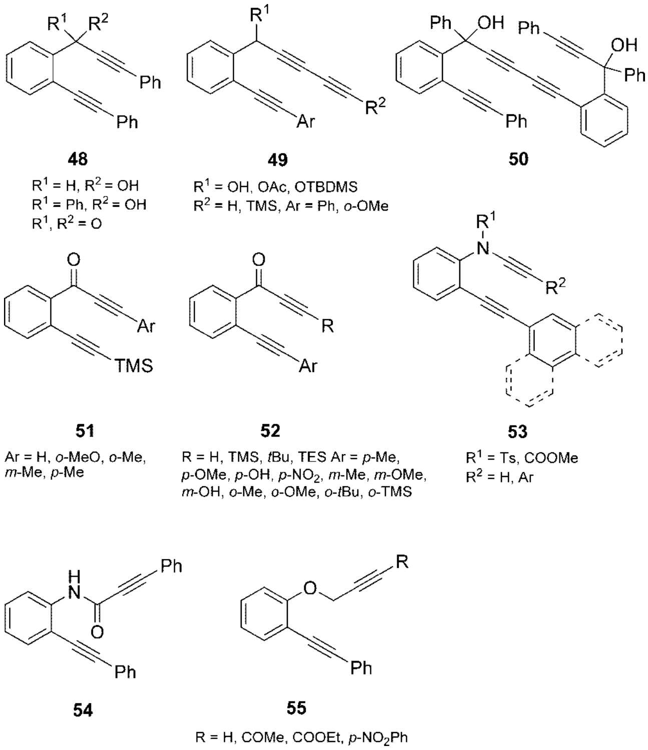
Scheme 11



An interesting application on the synthesis of tricyclic compounds has been presented by *Hoffmann* in 1993. Thus, the acetal **74** could be cyclized to **75** under very mild conditions upon catalysis with ZnCl$_2$ (Scheme 16).[39] This result is all the more remarkable as **75** has a considerable ring strain due to the bridgehead position of one of the double bonds. The reaction was also catalyzed by *Brønstedt* acids.

The DDA cyclization of compounds of type **76** where an enyne moiety was connected with acetylene by various linkers X was extensively investigated by *Danheiser*. The

Scheme 12



reactions were performed under *Lewis* or *Brønstedt* acidic conditions and, furthermore, it was found that compounds where R is an electron withdrawing substituent are particularly reactive.[40] An elegant approach to fluoranthene derivatives **79** was developed by *Echavarren* starting from 1,8-disubstituted naphthalenes **78** (Scheme 17, for Pd catalyzed DDA reactions see section 6).[41]

Only few DDA reactions of diynes are known. A very early example goes back to *Berthelot* who reported the trimerization of acetylene in 1866 (Scheme 18).[42] A century later it was shown that this reaction proceeds by an oxidative dimerization of acetylene to butadiyne followed by a DDA reaction with another acetylene molecule.[43] Another example is the cyclization of the tetraacetylene **80** to the fluorene derivative **81** (Scheme 18). The primary formation of benzynes (cf. Scheme 1e) was proven by detection of their DA adducts.[44]

3. Photochemically Initiated DDA Reactions

As every chemistry student learned already, the (concerted) *Diels–Alder* reaction is a thermally allowed but photochemically forbidden process, according to the *Woodward–Hoffmann* rules that are based on orbital symmetry considerations.[45] Admittedly, this statement is no longer applicable if the underlying reaction mechanism is a multistage process and the first step is the formation of only one chemical bond. As already mentioned in the preceding sections, the latter almost always applies to the DDA reaction. Hence, it is something surprising that so little was known about the *Photochemical Dehydro Diels–Alder* (PDDA) reaction until our own systematic investigations.[49]

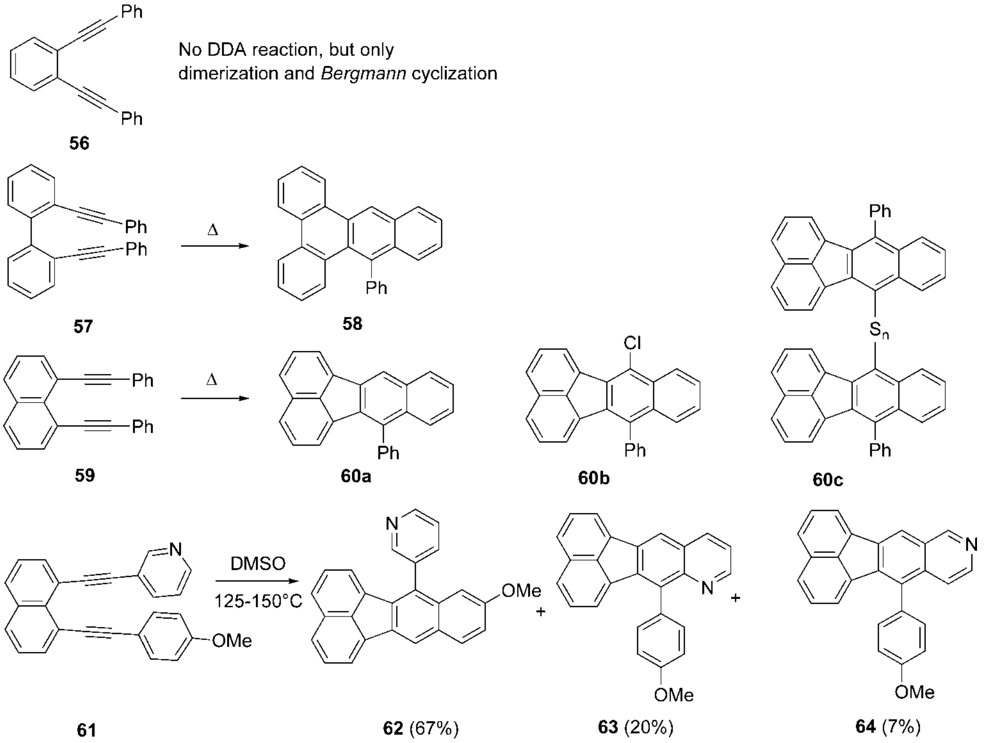
Already in 1948 Baddar[11b] wrote "Phenylpropiolic anhydride, . . ., dimerised readily when heated on the water-bath, exposed to sun-light, or even kept at room temperature, . . ." (cf. Scheme 2). In fact, a PDDA reaction was also observed with other conformationally restricted compounds mentioned in previous sections of this article (e.g., **57** and **59**[30]). In our experience, nearly every known DDA reaction should also be initiated photochemically (although often other byproduct and selectivities were observed), but it is difficult to prove that these are really photochemical reactions (i.e., excited states are involved at least in the first step of the reaction) and not proceed via "hot" ground states. On the other hand, many compounds are known, which undergo only a PDDA and not a thermal DDA reaction. This section mainly deals with these cases.

The photochemical dimerization of phenylacetylenes **82** is known for a long time but it has limited preparative value because the yields of the PDDA products **83** were very low and often the azulenes **84** were formed as main products.[46] In 1995 *Fleming* reported on the PDDA cyclization of the silyl bis(phenylpropargyl) ether **85** to the naphthalene **86** and subsequent deprotection to the diol **87**.[47] The interesting PDDA reaction of various 2-ethynyl cyclohexenones **88** with 2-methyl-1-buten-3-yne **89** to partly saturated naphthalenes **90**, reported recently by *Margaretha* and co-workers[48] demonstrates that the PDDA reaction is not limited to arylacetylenes as diene component, although the reaction is almost always accompanied by the formation of [2 + 2] cycloaddition products (Scheme 19).

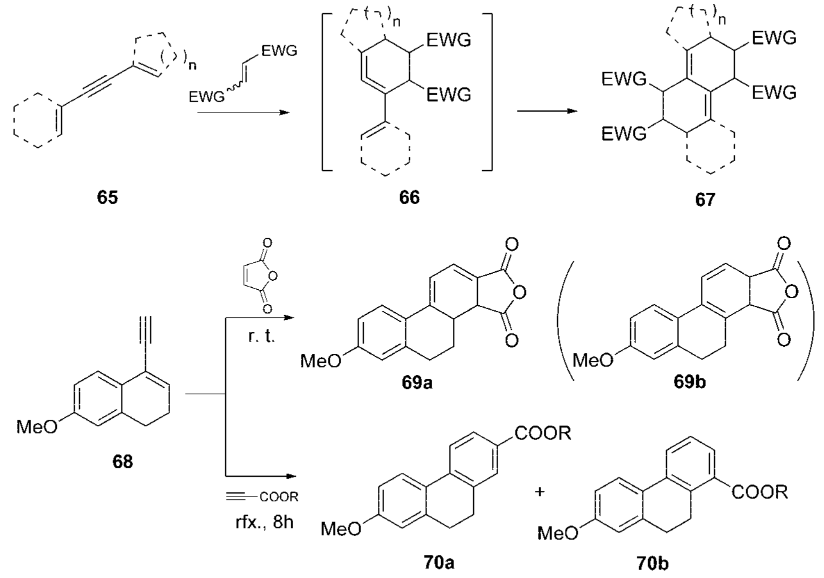
Phenylacetylenes and their derivatives (such as **85**) show negligible absorption above 300 nm in their UV–vis spectra, and hence the irradiation requires UV-B and UV-C light sources and quartz glass equipment. A considerable improvement was achieved with 3-arylynones as photoactive components which absorb well above 300 nm, thus allowing the utilization of UV-A light sources and reactors consisting of normal laboratory glass. Simple 3-phenylynones **91** undergo smooth PDDA dimerization to diacylnaphthalenes **92**, albeit only with moderate yields.[49a]The same reaction applied to esters **93** provided the remarkable complex arylnaphthalenes **94**. It should be noted that compounds **94** are axially chiral and the enantiomers could be separated by HPLC using a chiral stationary phase. [49b] The scope of these intermolecular PDDA reactions is extended if ynones **91** are irradiated in the presence of another arylacetylene (**95**). In this case the heteromolecular PDDA reaction is predominately observed, and only traces of the dimerization products **92** were formed. Furthermore, the reaction is remarkably regioselective, and 4-substituted 2-acetylnaphthalenes **96** are the main products besides minor amounts of isomers **97**. The selectivity could be explained by steric hindrance in 1,2,6-substituted naphthalenes **97** (Scheme 20).[49b]

The often relatively low yields of *intermolecular* PDDA reactions shown in Schemes 18 and 19 could be at least partly explained by the limited lifetimes of the excited states, within which they must meet the other reactant. Consequently, this situation should be improved if the reactants are joined together with a linker. Following this approach we developed a series of PDDA reactant systems **98** with different linkers, X. With the exception of symmetric diketones **98a**, always two modes **A** and **B** of the PDDA reaction are possible, and therefore two different naphthalenes, **99** and **100**, can be formed. All compounds of the first generation (**98a**–**e**) were ketones or diketones, and the linker unit consisted of simple alkyl chains (**98a-c**) or contained ether (**98d**) or substituted amine moieties (**98e**). The second generation is constituted by esters (**98f**,**g**) and amides (**98h**) and is especially characterized by a considerably simplified synthetic accessibility. This can be illustrated by the straightforward

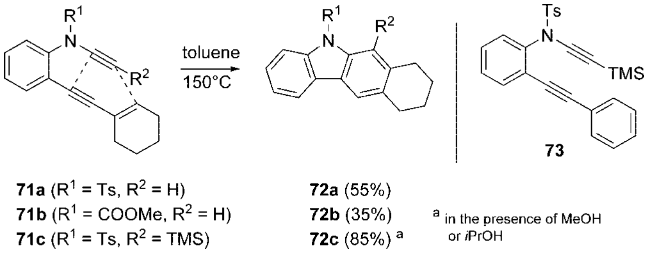
Scheme 13



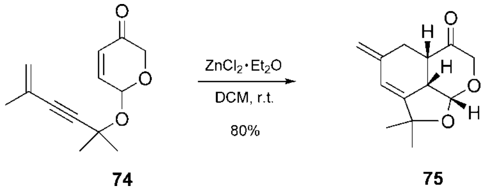
Scheme 14



Scheme 15



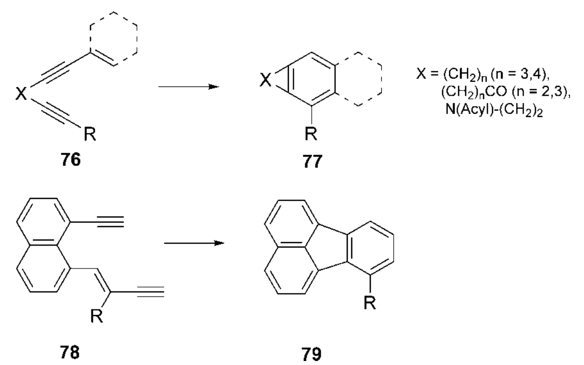
Scheme 16



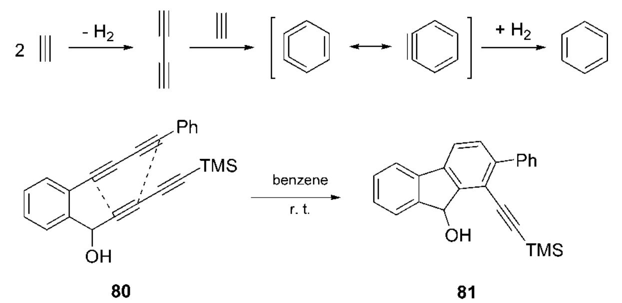
synthesis of binaphthyls **102** by PDDA cyclization of esters **101** (Scheme 21).[49d]

In contrast to ketones, the PDDA reaction of esters and amides requires acetone as solvent, which acts as triplet sensitizer.[49d] The reaction to compounds **102** demonstrates at the same time a possibility to avoid the formation of a mixture of **99** and **100**. The aryl moiety, which should not be attacked in the course of the PDDA reaction, must be blocked in both *ortho* positions. This purpose can be fulfilled by functional groups with a low tendency to form radicals (e.g., OMe in **101**), whereas alkyl groups are less suited owing to their proneness to migrate or be scavenged by the

Scheme 17



Scheme 18



solvent.[49a] It is also possible to control the ratio of **99** to **100** by the electronic influence of appropriately chosen substituents in *meta-* or *para*-position of the aromatic rings, but as a rule it is not possible to completely suppress the formation of isomers **99/100**.[49b]

4. Mechanism of the DDA Reaction

4.1. Mechanism of the Thermal DDA Reaction

As mentioned above, the concerted [4 + 2] cycloaddition is, based on orbital symmetry considerations, an allowed process, and indeed it is accepted that the DDA reaction of simple enynes proceeds in one step to cyclic allenes according to the eqs b−e in Scheme 1.[50a]

Considering, on the other hand, reactant systems such as **103/104** where one or both triple bonds are in conjugation with an aromatic ring, it is assumed that for the moment only one C−C bond is formed, giving the butadienediyl diradicals **105** due to the benzylic stabilization of the radical centers.[50b] In the second step one of these radical centers attacks an *ortho* position of the opposite aromatic ring to provide the cyclic allene **106**. It is obvious that the double bond between atoms 4 and 4a in **106** is not a "true" double bond because the involved p-orbitals stand nearly perpendicular to each other. Thus, the electronic structure of **103** is actually better represented by the diradical formula **106-B**, but also by the zwitterionic notation **106-C**.[51] In the last step a hydrogen migration from C-8a to C-4 must take place which can proceed by three different ways. From extensive quantum chemical calculations it was concluded that the *intramolecular* H-migration consists of two consecutive [1,2]-H shifts rather than one [1,5]-H shift.[17,26b,50a,c] The first [1,2]-H shift to the cyclic carbene **108** requires an activation barrier of 25−30 kcal/mol, the second [1,2]-H shift proceeds nearly barrierless to **109**.[50a]This mechanism seems to be the dominant one in the absence of any proton source, e.g. in the gas phase or in hydrocarbons as solvents. It should be noticed here that cycloallenes **106** are also prone to an above (Scheme 7)-mentioned ring opening to dehydro[10]annulenes and a subsequent new ring-closure. This process often takes place faster than the [1,2]-H shift. If, however, protons are present (e.g., in alcohols as solvents or cosolvents, or in the presence of phenol), **106** is first protonated at C-4 (from **106-C**) followed by deprotonation at C-8a which was unambiguously proven by isotope-labeling experiments (Scheme 22).[50b] The protic pathway also completely suppresses the rearrangement via the dehydro[10]annulenes.

4.2. Mechanism of the PDDA reaction

The present knowledge of the mechanism of the PDDA reaction is mainly the result of extensive quantum chemical calculations as well as photophysical investigations.[49a,c] The most important results are summarized in Scheme 23. After photochemical excitation to the **S_1** state, which has (at least in the case of ynones) n−π character, an intersystem crossing (**ISC**) takes place giving the $\pi-\pi^*$ triplet state **T_1** of the reactants. Now, the diradicals **DR** are formed in a strongly exothermic process and with a relatively low activation barrier ($E_1 \approx 3-6$ kcal/mol, depending on X) via **TS$_1$**. At the stage of diradicals **DR** triplet and singlet state are nearly degenerate, facilitating the second **ISC** back to the singlet potential energy surface. This assumption is supported by the fact that the activation barrier of the next step, the attack of one radical center on the opposite aromatic ring (**TS$_2$**), is much higher in the triplet than in the singlet state ($E_2 \approx 7-8$ kcal/mol, $E_3 \approx 20$ kcal/mol). The result of this step is the formation of cycloallenes **CA**. To these species apply the same statements as made in the preceding section for cycloallenes **106** in the thermal DDA reaction. Because PDDA reactions are normally performed at room temperature, the barrier of the initial [1,2]-H shift is too high, and consequently, the conversion of **CA** into the final products should almost always take place by a protonation−deprotonation sequence as discussed in the preceding section (**106-C** → **107** → **109**). This explains the common use of alcohols as solvents of choice in PDDA reactions (Scheme 23).

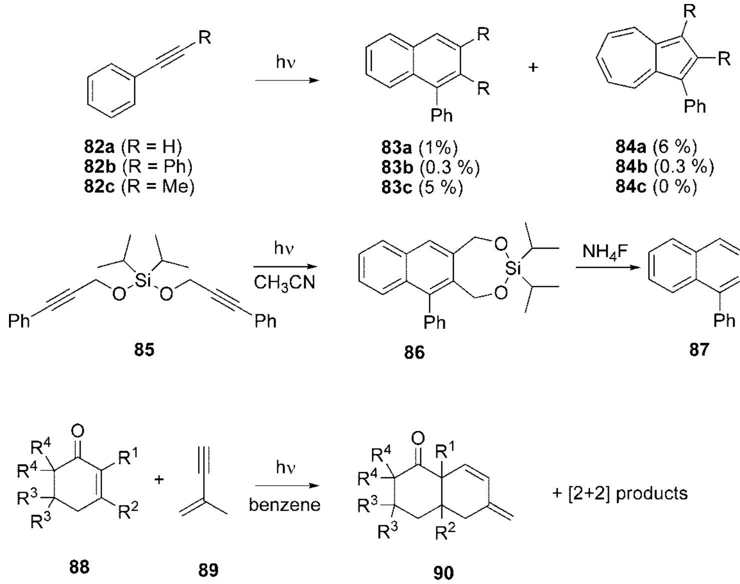
5. DDA Reactions Catalyzed by Bases

In this section reactions between enyne or arylacetylene moieties and another multiple bond within the same molecule will be discussed that are catalyzed by strong bases and formally look like DDA reactions. As it will be shown in the following, the underlying mechanism of these reactions completely differs from that outlined in the preceding sections for the DDA reaction. In fact, the [4 + 2] cycloaddition step is, in these cases, rather an ordinary (but nonconcerted) *Diels−Alder* reaction surrounded by isomerization processes than a true DDA reaction, thus justifying covering them in a separate section.

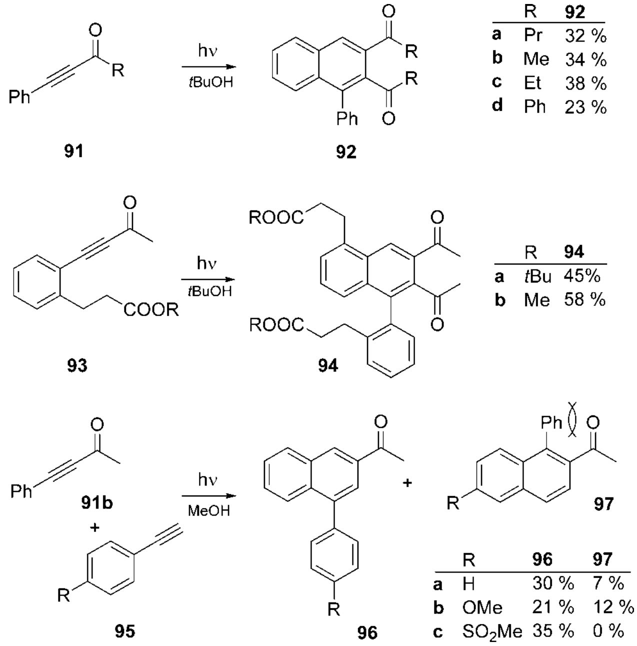
It has been well-known for a long time that propargyl ethers **110a**, amines **110b**, or thioethers **110c** undergo an isomerization to allenes **111** and acetylenes **112** upon treatment with strong bases (Scheme 24).[52]

If two propargyl groups are present in the same molecule as in compounds of type **113**, products **119** were isolated after treatment with bases, which could be explained by an "ordinary" DDA reaction. Indeed, such a mechanism was postulated in the first report on this topic by *Iwai* and coworkers in 1963.[53a] From a good correlation of the reaction

Scheme 19



Scheme 20



	R	92
a	Pr	32 %
b	Me	34 %
c	Et	38 %
d	Ph	23 %

	R	94
a	tBu	45%
b	Me	58 %

	R	96	97
a	H	30 %	7 %
b	OMe	21 %	12 %
c	SO_2Me	35 %	0 %

times and the yields with the electronegativity of atom X the same authors concluded one year later that a DA reaction occurs with monoallenes **114** instead of a DDA reaction with **113**.[53b] Later *Garratt* and co-workers questioned this presumption and suggested the presently accepted mechanism summarized in Scheme 25.[54] The key step of this mechanism is the cyclization of bis-allenes **115** to the diradicals **116**. Further evidence for these diradicals was produced by interception with oxygen, giving compounds **121** after rearrangement of the primarily formed endoperoxides **120** (Scheme 25).[55]

It is very likely on the other hand that monoallenes such as **123**, formed from quaternary allyl propargyl ammonium salts **122** cyclize upon treatment with bases in a concerted [4 + 2] process to compounds **124** which are subject to a [1,5]-hydrogen shift, giving dehydronaphthalenes **125** (Scheme 26).[56,57]

6. Transition Metal-Catalyzed DDA reactions

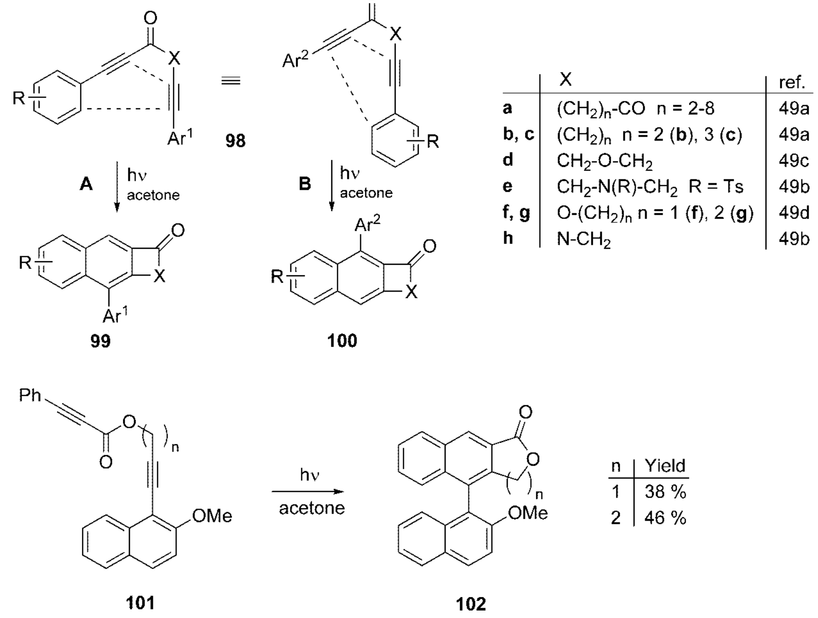
6.1. Rhodium and Platinum

At first it is worth mentioning that the term "*Dehydro-Diels–Alder* reaction" was never used in the original work underlying this section, but the reaction was called [4 + 2] benzannulation in some cases. The first example of a DDA reaction involving a transition metal was reported by Müller in the 1970s. Thus, rhodium complex **127**, obtained from diyne **126** upon treatment with the Wilkinson catalyst $Rh(PPh_3)_3Cl$, undergoes a reaction to naphthacene **128** under harsh conditions and with low yields (Scheme 27).[58] Naturally, this is not a catalyzed reaction particularly as the direct thermal cyclization from **126** to **128** takes place under milder conditions.[59] The first really transition metal-catalyzed DDA reactions were reported nearly 20 years later. As catalysts served mixtures of $RhCl_3$ or $PtCl_4$ with a phase transfer catalyst (Aliquat 336 = methyltrioctylammonium chloride). In the presence of the former catalyst the diyne **129** underwent a smooth cyclization to compound **130** (Scheme 27).[60b] This result is remarkable insofar as it was known from previous reports of the same group that the $RhCl_3$/Aliquat 336-catalyst rather furnishes cyclotrimerization products and actually suppresses the formation of DDA products in some cases.[60a,b] The surprisingly selective formation of **130** was explained by the larger number of atoms between the triple bonds (5 atoms) compared with compound **57** (4 atoms) which gave under the same conditions only a product (9,10-dibenzoylphenanthrene) resulting from oxidation of the primarily formed metallacyclic compound.[60b] Besides this isolated example Rh- and Pt-complexes seem to be rather less suited to catalyze the DDA reaction.

6.2. Palladium

Not surprisingly, palladium is the second metal which plays a role in transition metal-catalyzed DDA reactions. This field of research is relatively new, and the first report was published as recently as 1996.[61] It described the regioselective cyclodimerization of 2-substituted enynes **131** to 1,4-disubstituted benzenes **132** in the presence of tetrakis(triph-

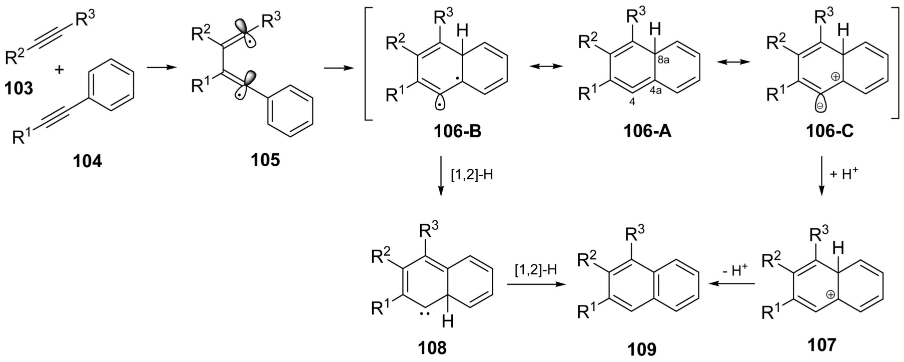
Scheme 21



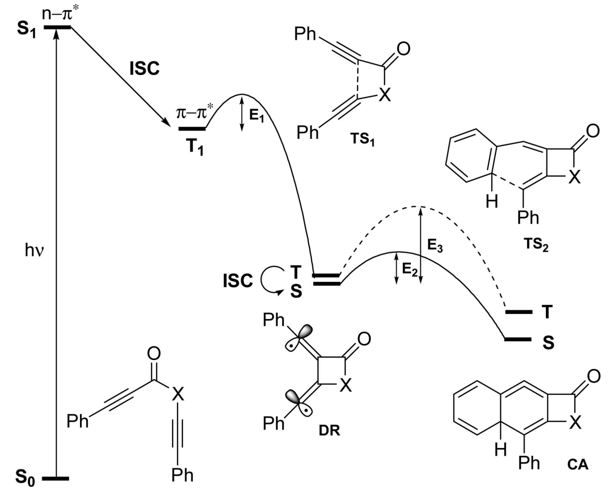
	X	ref.
a	$(CH_2)_n$-CO n = 2-8	49a
b, c	$(CH_2)_n$ n = 2 (**b**), 3 (**c**)	49a
d	CH_2-O-CH_2	49c
e	CH_2-N(R)-CH_2 R = Ts	49b
f, g	O-$(CH_2)_n$ n = 1 (**f**), 2 (**g**)	49d
h	N-CH_2	49b

n	Yield
1	38 %
2	46 %

Scheme 22

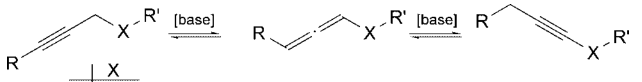


Scheme 23



enylphosphane)palladium(0). The other conceivable isomer **133** could not be detected in the crude reaction mixture. The reaction also succeeded with the bridged bis(enyne) **134**, giving the *para*-cyclophane **135** with a conspicuous high yield (Scheme 28). In the sequel this reaction was intensively investigated, and the results were summarized in several excellent reviews[62] which should not be duplicated here, but the most important results should be briefly outlined.

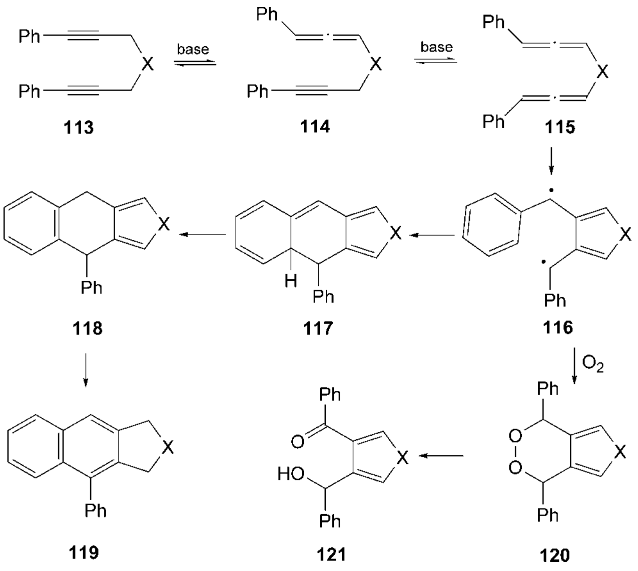
Scheme 24



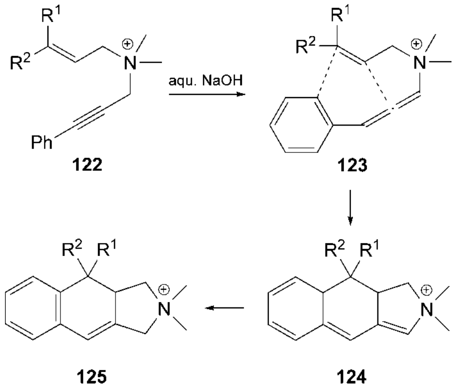
	X
a	O
b	NR
c	S

Besides 2-substituted enynes **131**, 4-substituted enynes **136** are also suitable reactants for the Pd(0)-catalyzed dimerization. The 2,6-disubstituted styrenes **137** are formed in good to excellent yields, again without formation of the other possible isomer (**138**, Scheme 28). Enynes bearing more than one substituent show hardly any dimerization reactivity but react smoothly with diynes and triynes, which considerably extends the scope of the reaction. Once again, the reaction between enynes **139** and diynes **140** proceeds highly regioselectively, giving benzenes **141** where R^1 is arranged in *ortho* position relative to $R^4{-}C{\equiv}C$. Furthermore, only *Z*-configured enynes **139** undergo this reaction. The mechanism of the Pd(0)-catalyzed DDA reaction of enynes with themselves or with diynes and triynes is still not fully elucidated, but the formation of the metallacyclic species **142** in the first step was suggested (Scheme 29).[62e]

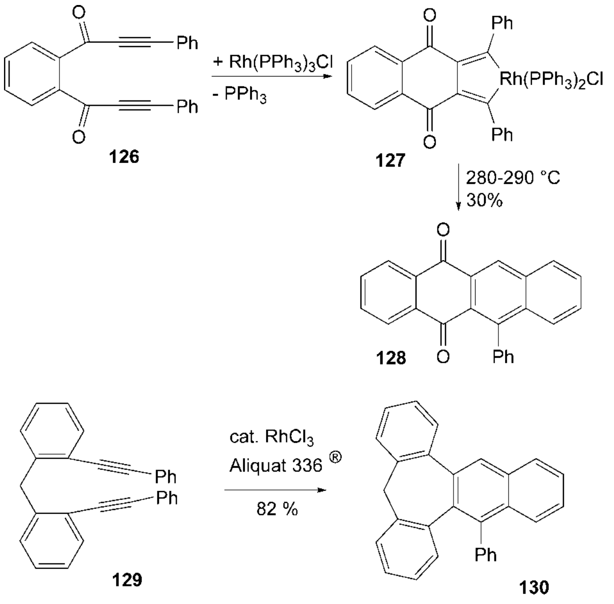
Scheme 25



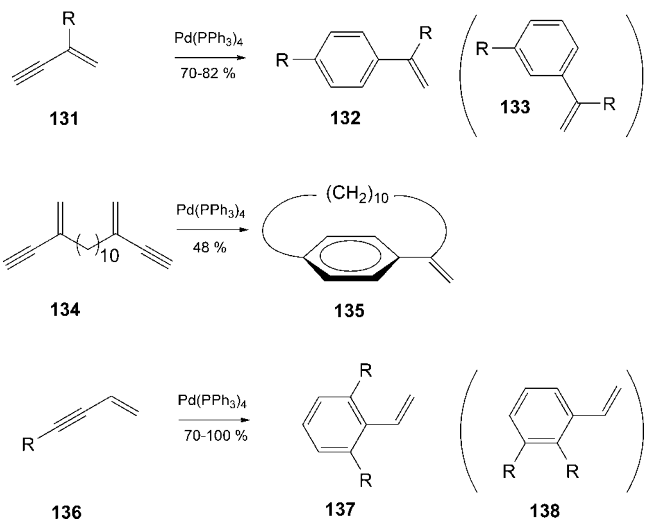
Scheme 26



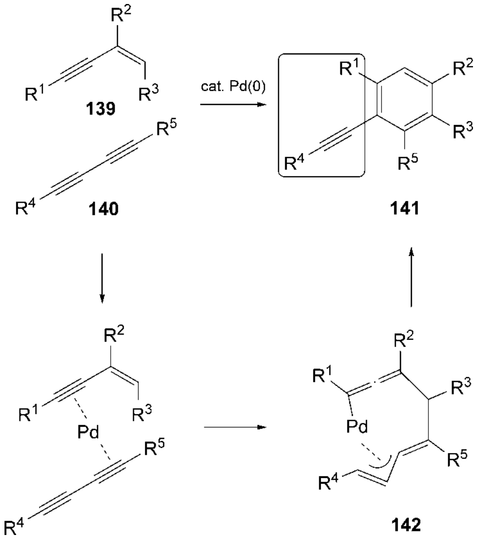
Scheme 27



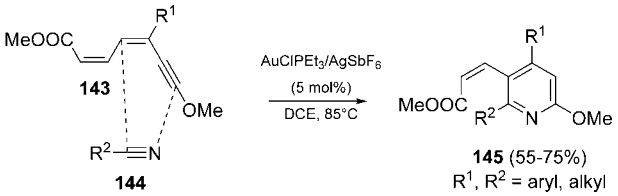
Scheme 28



Scheme 29



Scheme 30



6.3. Gold

In contrast to the transition metals discussed in the preceding sections, the usefulness and versatility of gold in catalyzed organic transformations was realized only in the past few years.[63] The vast majority of these gold-catalyzed reactions are based on activation of alkyne moieties. Very recently *Barluenga*, *Aguilar*, and co-workers[64] reported on the first gold-catalyzed DDA reaction. Thus, the treatment of dienynes **143** with various aliphatic and aromatic nitriles **144** in the presence of catalytic amounts of gold(I) complex afforded smoothly the pyridines **145** with satisfactory yields. Furthermore, this is the first example of *hetero*-DDA reaction (Scheme 30).

7. Conclusions

In this review both the history and current trends of the *Dehydro-Diels−Alder* (DDA) reaction have been presented in detail. The term "DDA reaction" should be defined as a [4 + 2] cycloaddition whereby at least one of the multiple bonds of the 4-atom component is a triple bond, independent from the mechanism underlying the reaction. In contrast to the *Diels−Alder* reaction itself, DDA reactions can be actuated by varying manners, and the review is structured according to these conditions.

The simplest way to perform a DDA reaction is to heat the reactants, but the required temperatures vary over a broad area including often rather harsh conditions. On the other hand, DDA reactions are known that take place at room temperature and below. The *photochemically* initiated DDA reaction (PDDA reaction) presents new capabilities with reactants inaccessible to the thermal DDA reaction, and a remarkable structural diversity has been developed by now. The treatment of DDA reactants with strong bases may cause an isomerization of alkynes to allenes, mostly driven by acquisition of conjugation energy. These allenes can now undergo "normal" *Diels−Alder* reactions followed by hydrogen migrations. Catalysis with transition metals is the fourth option to initiate DDA reactions, but there are very few examples for Rh- and Pt-catalyzed DDA reactions, and the intensively investigated Pd(0)-catalyzed DDA reactions are, unfortunately, limited to enynes as 4-atom components. Very recently published DDA reactions catalyzed by gold appear promisingly.

The hitherto known DDA reactions provided regularly diaryls as products which may be axially chiral if the rotation around the central aryl−aryl single bond is hindered by steric reasons. Owing to the great interest in such enantiomerically pure diaryls, there is an ongoing need for powerful asymmetric synthetic methods for diaryls, and it therefore represents a very worthwhile research objective to develop asymmetric DDA (ADDA) reactions, unknown at the present time.

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