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Duality of Donor–Acceptor Cyclopropane Reactivity as a Three-Carbon Component in Five-Membered Ring Construction: [3+2] Annulation Versus [3+2] Cycloaddition

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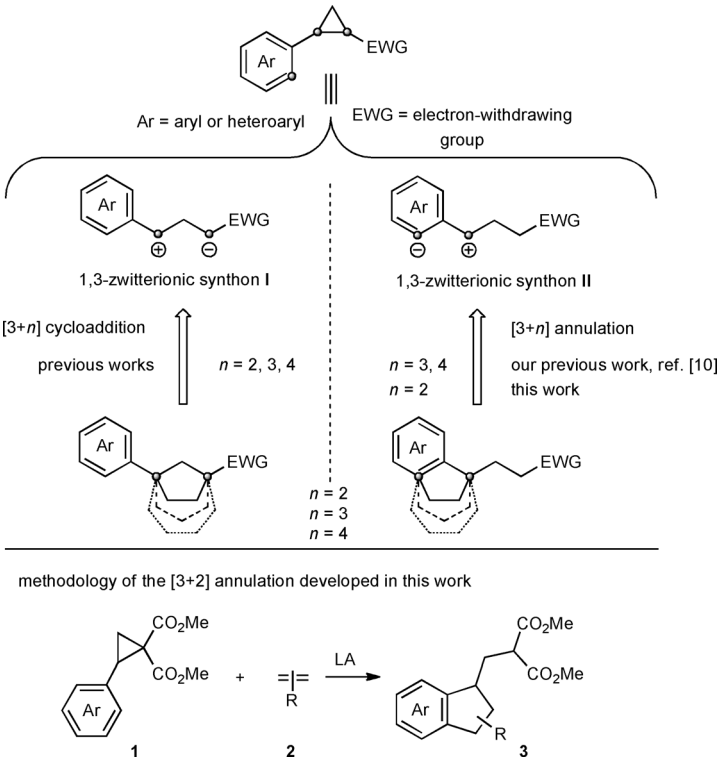
The long-standing and continuous interest in efficient synthetic approaches to cyclopentanoids stems from their value as building blocks in organic chemistry and their ubiquitous occurrence as core scaffolds of numerous bioactive natural and synthetic compounds, including drugs.[1]

One of the most rational and straightforward synthetic routes to cyclopentane-based systems is the [3+2] cycloaddition of three-carbon 1,3-dipoles to C–C double or triple bonds. Therefore, the design of compounds that possess appropriate functionalities to serve as synthetic equivalents of 1,3-carbodipoles still remains a challenging problem in organic synthesis. Among the reported precursors of such dipoles (e.g. conjugated diazoalkenes, allenoates, sources of trimethylenemethanes, and oxyallyl cations), donor–acceptor cyclopropanes play an important role.[2] In recent times, the usefulness of donor–acceptor cyclopropanes is defined by their reactivity in [3+*n*] cycloadditions to various unsaturated compounds. In particular, donor–acceptor cyclopropanes were found to react with various dipolarophiles affording five-membered carbo- and heterocycles through [3+2] cycloaddition,[3,4] as well as undergo [3+3] and [3+4] cycloadditions furnishing six- and seven-membered rings.[5,6] In all these processes, donor–acceptor cyclopropanes exhibit properties of typical umpolung reagents[7] containing a nucleophilic center at the C atom with an acceptor group and electrophilic center at the C atom with a donor substituent (synthon **I** in Scheme 1).



Scheme 1. Two alternative reactivities of (hetero)aryl-derived donor–acceptor cyclopropanes and methodology developed in this work.

Our recent studies of donor–acceptor cyclopropanes, bearing electron-rich aryl or heteroaryl substituents as donor groups, revealed a conceptually new mode of reactivity, in which the electrophilic center of the cyclopropane remains the same but the nucleophilic center is placed in the *ortho*-position of the aromatic substituent (synthon **II** in Scheme 1).[6b,8] In this case, a donor–acceptor cyclopropane serves as a source of a very different three-carbon component that also exhibits reactivity umpolung when participating in transformations that are classified as [3+*n*] annulations.[9]

The discovered reactivity provides wide possibilities for the development of a general strategy for the synthesis of

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diverse (hetero)arene-annulated systems. Recently, this approach was successfully utilized to prepare six- and seven-membered rings fused to (hetero)arenes by [3+3] cyclodimerizations of donor–acceptor cyclopropanes[8b,10] and their [3+4] annulation to conjugated dienes.[6b,8a] These promising results stimulated us to direct our efforts towards the development of a new methodology for the construction of five-membered rings fused to other ring systems by [3+2] annulation of donor–acceptor cyclopropanes to double or triple bonds.

Herein, we report the first application of this methodology for the extremely simple and highly efficient synthesis of polyfunctionalized indanes and their heteroanalogues through the [3+2] annulation of donor–acceptor cyclopropanes to alkenes. Using a variety of aryl donor groups in the starting cyclopropanes; namely, alkoxy–phenyl, thienyl, benzothienyl, benzofuryl, indolyl substituents, etc., allows for the preparation of the five-membered-ring fused products that are of a great interest for medicinal chemists, as structural analogues of a large number of bioactive compounds (Figure 1). For instance, polyoxygenated 1-arylindanes are structural subunits of compounds, among which are secaloside A, diisoeugenol, pallidol, and entrasentan, with a broad range of bioactivity, including anticancer.[11] The cyclopenta[*b*]indole ring system occurs in a number of indole alkaloids (i.e. paxilline, paspaline, yuehchukene). Meanwhile, cyclopentannulated benzofurans and benzothiophenes attract interest, in particular, as bioisosters of aforecited cyclopenta[*b*]indoles.

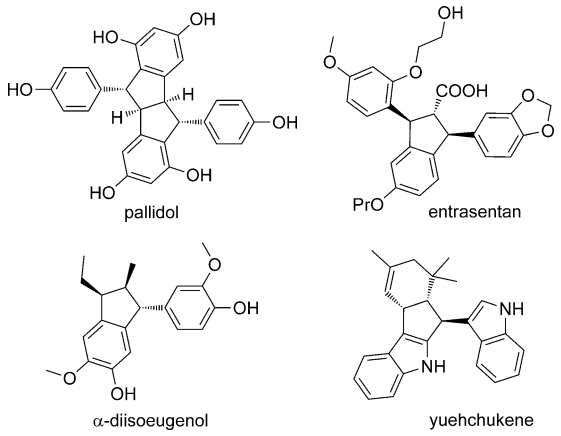
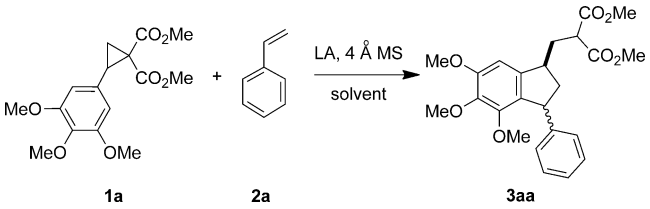


Figure 1. Examples of bioactive compounds with 1-arylindane and cyclopenta[*b*]indole fragments.

We started this work by investigation of the reaction between 2-(3,4,5-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate (**1a**) and styrene (**2a**), which we expected to result in the 1-arylindane skeleton construction (Table 1). The choice of cyclopropane **1a** as a model compound was stipulated by the high chemoselectivity of its [3+3] cyclodimerization and [3+4] annulation in which **1a** reacted exclusively as an equivalent of synthon **II**.[6b,8b] Styrene (**2a**) is well-known as a highly reactive alkene towards electrophiles and provides exclusive control over the regioselectivity.

Table 1. Optimization of reaction conditions for the model [3+2] annulation between cyclopropane **1a** and styrene (**2a**).[a]



1a **2a** **3aa**

Entry	LA (mol%)	Solvent	*T*/*t* [°C/h]	Yield [%][b] (*trans*/*cis*)[c]
1	$Cu(OTf)_2$ (10)	CH_2Cl_2	20/24	–[d]
2	$Sc(OTf)_3$ (10)	CH_2Cl_2	20/24	31 (63:37)
3	$Sn(OTf)_2$ (10)	CH_2Cl_2	20/20	50 (62:38)
4	$Yb(OTf)_3$ (10)	CH_3NO_2	60/4.5	76 (58:42)
5	$ZnCl_2$ (180)	CH_3NO_2	20/75	71 (62:38)
6	$BF_3{\cdot}Et_2O$ (130)	CH_2Cl_2	20/4	78 (53:47)
7	$SnCl_4$ (130)	CH_2Cl_2	20/3	84 (63:37)
8	$GaCl_3$ (30)	CH_2Cl_2	20/1	65 (59:41)

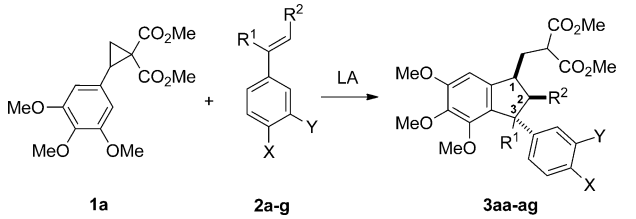
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (4 equiv), solvent (10 mL). [b] Isolated yields. [c] Diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [d] No conversion.

A brief screening of common Lewis acids (LA, Table 1) elucidated that weak Lewis acids, such as $Cu(OTf)_2$, failed to initiate this reaction. Strongly activating $TiCl_4$, TMSOTf, and $EtAlCl_2$ caused a considerable polymerization of starting compounds. Meanwhile, utilization of such Lewis acids as $BF_3{\cdot}Et_2O$, $SnCl_4$, $Sn(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, and $ZnCl_2$ led to the desired [3+2] annulation product **3aa**. Similar to the related cationic cyclizations,[12] **3aa** was formed as a mixture of two diastereomers with a slight predominance of the more stable *trans* isomer.

$SnCl_4$ and $BF_3{\cdot}Et_2O$ provided the highest yields of **3aa** at room temperature for the shortest reaction times and thus were selected to investigate the scope of the [3+2] annulation between **1a** and a broad range of differently substituted alkenes **2a**–**m**. Styrenes **2a**–**g** bearing various substituents in the aryl group and at the double bond (Table 2) exhibited a high conversion to **3** when reacting with **1a**. Some loss in efficiency was observed for **2c**, which contains an electron-donating group due to its significant polymerization under the reaction conditions and in the case of **2d** because of its deactivation by the electron-withdrawing nitro group.

Reaction of **1a** with styrenes **2h**–**j** in which the double bond is enclosed in a cyclic moiety opens a simple route to complex polycyclic products **3ah**–**aj** (Table 3) and, in the near term, to helicene-like systems. The introduction of the second substituent to the β-position of styrene, as observed in **2j**, led to formation of pentacyclic product **3aj** as a single diastereomer. Structures of **3ae**–**ag** and *cis*-**3ah** were unambiguously proved by single-crystal X-ray analysis.[13] To extend the scope of the [3+2] annulation, we introduced less nucleophilic alkyl-substituted alkenes **2l**,**m** into the reaction with **1a** and obtained the corresponding indanes **3al**,**am** in excellent yields (Table 3).

Table 2. [3+2] Annulation of cyclopropane **1a** to styrenes **2a–g**.[a]

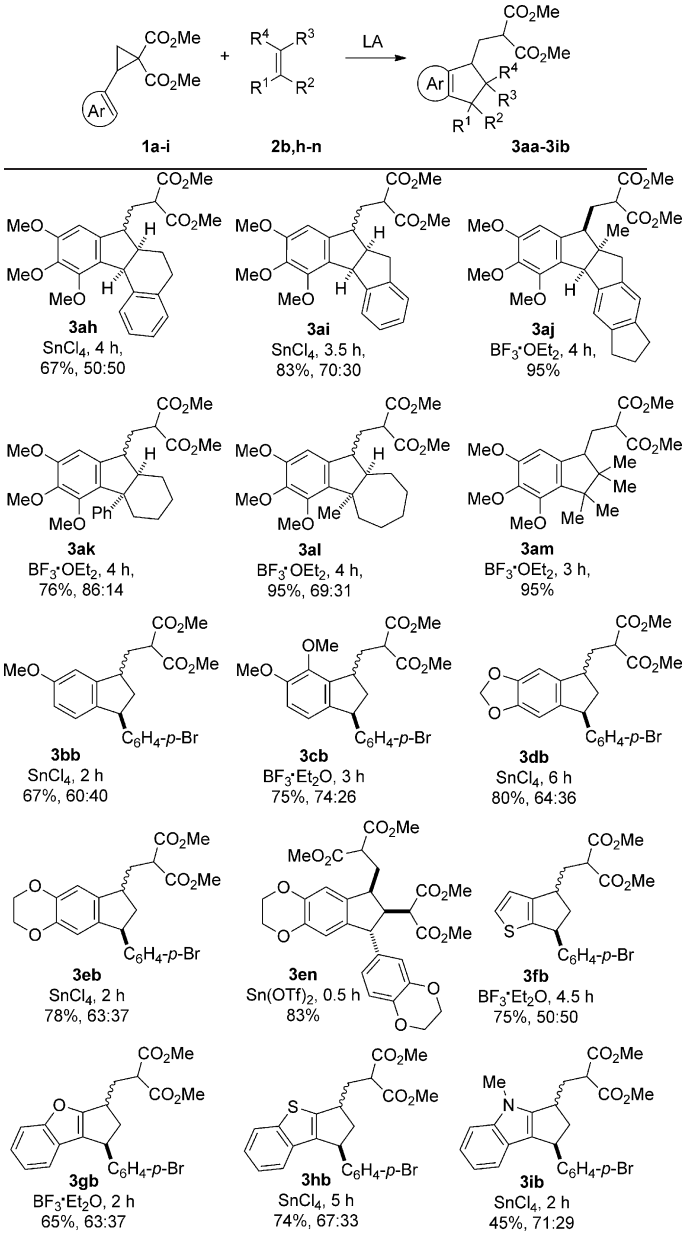


1a 2a-g 3aa-ag

Entry	2	X	Y	R^1	R^2	LA	*t* [h]	3	Yield [%][b] (*trans*/*cis*)[c]
1	**a**	H	H	H	H	$SnCl_4$	3	**aa**	84 (63:37)
2	**b**	Br	H	H	H	$SnCl_4$	3	**ab**	85 (55:45)
3	**c**	AcO	H	H	H	$SnCl_4$	4	**ac**	53 (34:66)
4	**d**	H	NO_2	H	H	$SnCl_4$	4	**ad**	35 (65:35)
5	**e**	H	H	H	Me	$SnCl_4$	4	**ae**	83[d]
6	**f**	H	H	Ph	H	$SnCl_4$	72	**af**	84
7	**f**	H	H	Ph	H	$BF_3{\cdot}Et_2O$	3	**af**	85
8	**g**	H	H	H	Ph	$SnCl_4$	4	**ag**	61 (90:10)

[a] Reaction conditions: **1a** (0.3 mmol), alkene **2** (4 equiv), Lewis acid (1.3 equiv), CH_2Cl_2 (10 mL), 4 Å MS, room temperature. [b] Isolated yields. [c] Diastereomeric ratio (1,3-*trans*/1,3-*cis*) was determined by ^1H NMR spectroscopy. [d] Single diastereomer.

Table 3. Scope of the [3+2] annulation.

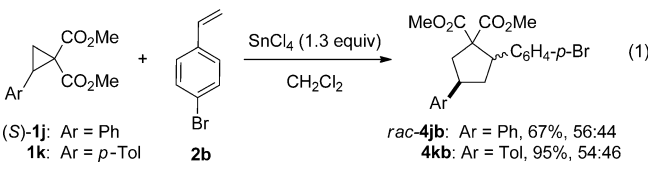


In addition to varying the alkene component, this [3+2] annulation allows for a wide range of aromatic substituents in donor–acceptor cyclopropanes. A representative series of cyclopropanes **1b–i** with electron-rich aryl and heteroaryl substituents were successfully used in the [3+2] annulation with styrene **2b** as a model compound furnishing the corresponding indanes **3bb–eb** and their heteroanalogues **3fb–ib** (Table 3). Despite the possible formation of regioisomers for **1d–f**, their reactions were found to proceed with excellent regioselectivity, affording a single product.

[3+2] Annulation of cyclopropanes **1** to styrenes, containing hydroxy or alkoxy groups in the aromatic ring, represents a promising access to polyoxygenated 1-arylindanes, similar to the bioactive compounds in Figure 1. However, the low stability of such styrenes under acidic conditions makes carrying out this reaction a challenging problem. We overcame this by using a styrene **2n**, stabilized with a β-bis-(methoxycarbonyl)methyl substituent and, thus, synthesized **3en** (Table 3), a structural analogue of α-diisoeugenol (Figure 1). Styrene **2n** and similar alkenes can be easily prepared by isomerization of donor–acceptor cyclopropanes **1**.[14]

Introduction of a substituent at the β-position of styrenes not only provides a solution to their stability problem but also improves the reaction diastereoselectivity. Thus, indanes **3ag** and **3ak** were obtained with reasonable diastereoselectivity; indanes **3ae** and **3en** were formed as single diastereomers. Similarly, introduction of a methyl group at the β-position of cyclic styrene analogues (**2j** in comparison with **2h** and **2i**) was accompanied by a drastic increase in reaction stereoselectivity.

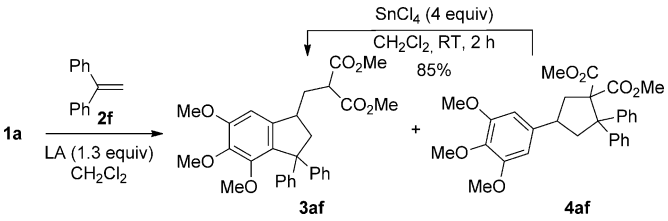
All above reactions afford products of [3+2] annulation **3** with excellent chemoselectivity, that is, formation of [3+2] cycloadducts did not occur at all. On the contrary, cyclopropanes **1j**,**k** bearing a less nucleophilic aryl group, namely phenyl or tolyl, failed to give [3+2] annulation products in reactions induced by $SnCl_4$ or $BF_3{\cdot}Et_2O$ but yielded the corresponding cyclopentanes by [3+2] cycloaddition [Eq. (1)]. This reaction proceeds through a cyclopropane ring opening into the 1,3-zwitterion that was proved by formation of racemic **3jb** in the reaction of optically active (*S*)-**1j**.



(1)

Therefore, the chemoselectivity of the reaction between donor–acceptor cyclopropanes **1** and alkenes **2** depends crucially on the nucleophilicity of the donor (hetero)aryl substituent in **1**. However, it is not a single factor influencing this dichotomy. We have found that the chemoselectivity in some cases can be efficiently controlled by the reaction conditions. More dramatically this effect was observed in the reaction of cyclopropane **1a** with 1,1-diphenylethylene (**2f**). Thus, this reaction when carried out at room temperature and quenched in 3 h exhibited low chemoselectivity and afforded a mixture of products of [3+2] annulation **3af** and [3+2] cycloaddition **4af** in a 3:2 ratio (Table 4). Meanwhile,

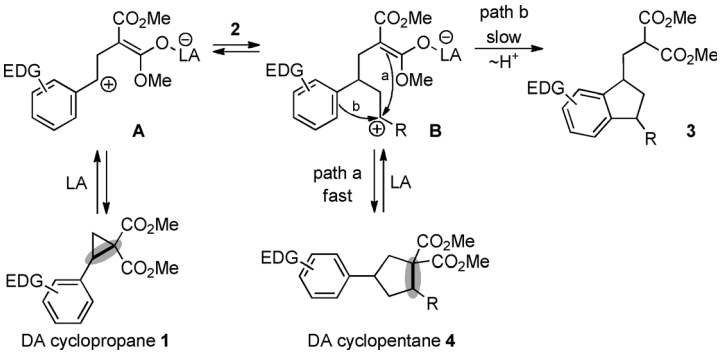
Table 4. [3+2] Annulation versus [3+2] cycloaddition in the reaction of **1a** with **2f**.



Entry	LA	T [°C]	t	Yield **3af** [%]	Yield **4af** [%]
1	$SnCl_4$	−30	45 min	–	76
2	$SnCl_4$	20	3 h	52	33
3	$SnCl_4$	20	72 h	84	–
4	$SnCl_4$	42	3 h	80	–
6	$BF_3{\cdot}Et_2O$	20	3 h	85	–

an increase in either the duration or the temperature of the reaction leads to formation of product **3af** exclusively, which was also formed as a single product in high yield when the harder Lewis acid, $BF_3{\cdot}Et_2O$, was utilized as a catalyst. Conversely, a decrease in reaction temperature led to the selective formation of [3+2] cycloadduct **4af**. These results point to the kinetic control of the cycloaddition reaction, leading to **4af**, while the annulation product **3af** is likely to be formed under thermodynamic control. An additional evidence for this hypothesis comes from the fact that a kinetic product **4af** undergoes complete isomerization to a more stable product **3af** after stirring for 2 h at room temperature in the presence of excess $SnCl_4$.

Based on these results, we proposed the following mechanism for these transformations (Scheme 2). Lewis acid induces cyclopropane ring opening into a zwitterionic species **A** followed by its electrophilic attack onto alkene **2** resulting in a new zwitterion **B** in accordance with Markovnikov's rule. Zwitterion **B** can undergo 1,5-cyclization of two types. If the electrophilic center in **B** is trapped by a malonate anion (path a) cyclopentane **4** is formed as a kinetic product, whereas Friedel–Crafts electrophilic substitution (path b) yields (hetero)arene-annulated cyclopentane **3** as a thermodynamic product. Due to reversibility of the formation of **4**, the product **3** can arise directly from the starting compounds **1** and **2** as well as from **4** through C–C σ-bond cleavage be-



Scheme 2. Possible mechanism of reaction between cyclopropanes **1** and alkenes **2**.

tween the donor and acceptor groups in the five-membered ring.[15] Therefore, analogously to donor–acceptor cyclopropanes, compounds of type **4** can be classified as "push–pull" donor–acceptor cyclopentanes.

We investigated the cytotoxicity of a series of indanes **3**. All of the compounds studied were found to be nontoxic towards rat fibroblasts, while demonstrating low-to-moderate cytotoxicity against breast cancer MCF-7 cells. Indane **3en** bearing an oxygenated aryl substituent in the α-position was found to be more cytotoxic against HEK-293 cells (IC_{50} = 8.7 μM) than against SiHa cells (IC_{50} = 110 μM).

In conclusion, we have disclosed a brand new facet of hetero(aryl)-derived donor–acceptor cyclopropane reactivity towards alkenes that significantly extends the range of the valuable transformations of these alicycles. The [3+2] annulation, described here, allowed us to develop a conceptually new simple synthetic approach to cyclopentannulated (hetero)arenes. Further expansion of this methodology to other compounds with double or triple bonds as well as bioactivity of the reaction products is currently under investigation.

Experimental Section

General procedure: A solution of a Lewis acid (1.3 equiv) in CH_2Cl_2 (1 mL) was added in one portion to a vigorously stirred solution of cyclopropane **1** (1 equiv, 0.03 M) and alkene **2** (4 equiv) in CH_2Cl_2 under an argon atmosphere at the specified temperature. The resulting mixture was stirred for the specified time. The reaction progress was monitored by TLC analysis and ^1H NMR spectroscopy. The reaction mixture was then poured into a saturated aqueous solution of $NaHCO_3$ (1:1 by volume). After extraction with CH_2Cl_2 (3×5 mL), the combined organic fractions were washed with an aqueous solution of Trilon B (1×5 mL). The organic layer was dried with Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography (SiO_2).

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Keywords: annulation · cycloaddition · cyclopropanes · fused-ring systems · Lewis acids

[1] Examples of drugs containing cyclopentane fragments are alprostadil, bimatoprost, carboprost, cycrimine, donepezil, latanoprost, peramivir, prednisone, rifapentine, ticagrelor, zafirlukast, etc.

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[9] To differentiate two processes, in which donor–acceptor cyclopropanes exhibit alternative reactivities as synthetic equivalents of synthons **I** and **II**, we used two different terms: cycloaddition and annulation, respectively. Term cycloaddition (IUPAC Gold Book: "a reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity") was used when a new ring is formed by a combination of the reaction partners without any secondary migration or elimination processes. Term annulation (id.: "a transformation involving fusion of a new ring to a molecule by two new bonds") was used if a new ring formation is accompanied by atoms elimination or migration.

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