DOI: 10.1002/adsc.201000783

Lewis Acid-Catalyzed [3+4] Annulation of 2-(Heteroaryl)-cyclopropane-1,1-dicarboxylates with Cyclopentadiene

Olga A. Ivanova,[a] Ekaterina M. Budynina,[a,b] Alexey O. Chagarovskiy,[a] Alexey E. Kaplun,[a] Igor V. Trushkov,[a,b] and Mikhail Ya. Melnikov[a,*]

[a] M.V. Lomonosov Moscow State University, Department of Chemistry, Leninskie Gory 1/3, Moscow 119991, Russia
Fax: (+7)-495-939-1814; phone: (+7)-495-939-1316; e-mail: melnikov@excite.chem.msu.ru or melnikov46@mail.ru
[b] Federal Research Center of Pediatric Hematology, Oncology and Immunology, Laboratory of Chemical Synthesis, Leninskii av. 117, Moscow 117997, Russia

Received: October 16, 2010; Revised: January 18, 2011; Published online: May 3, 2011

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000783.

Abstract: A novel Lewis acid-catalyzed [3+4] annulation of 2-(heteroaryl)cyclopropane-1,1-dicarboxylates with cyclopentadiene is reported. This reaction proceeds *via* an electrophilic attack of the Lewis acid-activated donor-acceptor cyclopropane onto cyclopentadiene followed by Friedel–Crafts intramolecular alkylation of the heteroarene substituent. This is the first general example of reactions of donor-acceptor cyclopropanes wherein the donor substituent serves as a nucleophile. The described annulation represents a convenient approach to bicyclo[3.2.1]octa-2,6-dienes with heteroarenes annulated to C(2)-C(3) bond. Its efficiency was demonstrated for a series of furyl, thienyl, pyrrolyl, benzofuryl, benzothienyl, and indolyl substituted cyclopropanes. Additionally, in the case of 2-(5-methyl-2-furyl)cyclopropane-1,1-diester we observed the predominant formation of product of the [3+4] annulation or the tetracyclic 5,8-methanocyclopenta[*a*]azulene derivative, depending on the reaction conditions.

Keywords: annulation; C–C activation; fused-ring systems; heterocycles; small ring systems

Introduction

The interest in cyclopropane derivatives constantly grows owing to the unique and specific reactivity of the cyclopropane framework.[1] Nowadays cyclopropanes are considered to be valuable building blocks for the construction of various ring systems containing small, common, medium and large cycles, as well as complex annulated, bridged, and spiro-condensed architectures, etc.[2] Cyclopropanes with electron-donating and electron-withdrawing groups at the vicinal carbon atoms are referred to as donor-acceptor (DA) cyclopropanes.[3] The presence of both donor and acceptor substituents defines the ambiphilicity of such cyclopropanes and makes them ideal substrates not only for reactions with nucleophiles and/or electrophiles but also for cycloaddition processes. Thus, 2-arylcyclopropane-1,1-dicarboxylates are widely applied for the synthesis of five-membered carbo- and heterocycles *via* Lewis acid-catalyzed [3+2] cycloadditions.[4] In these reactions DA cyclopropanes show 1,3-dipole-like behavior. Moreover, DA cyclopropanes form [3+3] cycloadducts in reactions with some 1,3-dipoles demonstrating dipolarophile-like properties.[5]

Recently we have found that 2-arylcyclopropane-1,1-dicarboxylates in reactions with 1,3-diphenylisobenzofuran and anthracene reveal dienophile-like properties yielding products of [3+4] cycloaddition.[6] This process is a promising route to seven-membered cycles and can be considered a homo-version of the Diels–Alder reaction.

In almost all of the cycloaddition reactions the DA cyclopropanes react with unsaturated compounds as the synthetic equivalent to 1,3-zwitterionic synthons of type **A** (Figure 1). However, there are some rare examples of a different kind of the reactivity of DA cyclopropanes, wherein a nucleophilic center at *ortho*-position of the aromatic ring takes part in the process. In this case the DA cyclopropane enters the annulation reaction as a synthetic equivalent to 1,3-zwitterionic synthon of type **B**. Such a reactivity was observed for cyclopropanes with electron-enriched aromatic substituents.[6b,7,8]

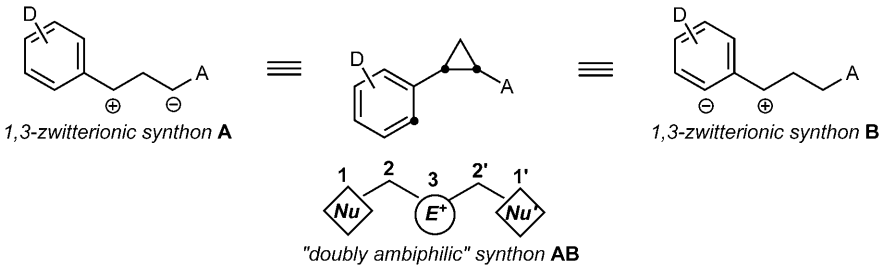
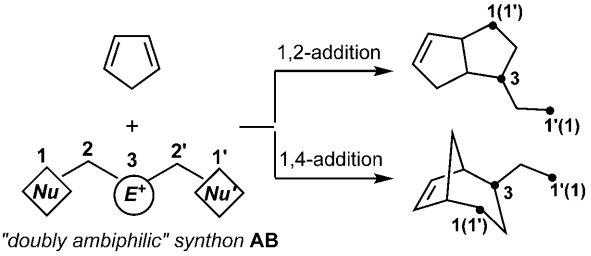


Figure 1. Two possibilities for the ambiphilic reactivity of 2-aryl/heteroaryl-substituted DA cyclopropanes.

Within the framework of our research on the Lewis acid-catalyzed interaction of DA cyclopropanes with 1,3-dienes we have studied the reactivity of cyclopropane-1,1-dicarboxylates, substituted at the C(2) position with electron-enriched five-membered heterocycles, towards cyclopentadiene (**1**). On the one hand, this compound is known to be one of the most reactive 1,3-dienes. On the other hand, unlike 1,3-diphenylisobenzofuran[6a] and anthracene,[6b] it is able to react with the DA cyclopropanes *via* both 1,2- and 1,4-addition reactions resulting in the formation of new five- or seven-membered rings, respectively. In the case of 1,2-addition, a pentalene system should be formed, whereas 1,4-addition should afford the bicyclo[3.2.1]oct-6-ene scaffold (Scheme 1).



Scheme 1. 1,2- and 1,4-additions as two alternative routes in the reaction of cyclopentadiene (**1**) with 2-aryl/heteroarylcyclopropanes.

The results presented in this article indicate that in reactions with cyclopentadiene (**1**) 2-(heteroaryl)cyclopropane-1,1-dicarboxylates **2** demonstrate the reactivity of a 1,3-zwitterionic synthon **B** yielding heteroarene-annulated bicyclo[3.2.1]octadienes. The bicyclo[3.2.1]octane skeleton is not only a basic framework of numerous biologically active natural compounds but also a powerful building block in organic synthesis. Due to the significant interest in these compounds, multiple approaches to the construction of this scaffold, both saturated and with one or two double bonds, have been proposed.[9] However, no general approach to a preparative synthesis of bicyclo[3.2.1]octadienes with heteroarenes annulated to the C(2)-C(3) bond has been developed as yet.[10] Thus, our method represents the first general convenient route to such compounds.

Results and Discussion

Reaction of Cyclopentadiene (1) with 2-Heteroaryl-Substituted Cyclopropane-1,1-dicarboxylates 2a–j

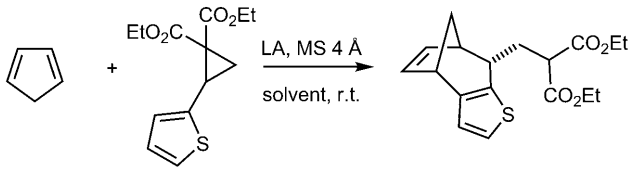
We have chosen thienylcyclopropane **2a** as a model substrate due to its previously reported high reactivity towards unsaturated compounds in [3+2], [3+3] and [3+4] cycloadditions.[6,11] Initially we screened a wide variety of common Lewis acids [$TiCl_4$, $SnCl_4$, TMSOTf, $Sn(OTf)_2$, $Yb(OTf)_3$, etc.] as catalysts in the reaction of **1** with **2a**. The use of highly activating $TiCl_4$, $SnCl_4$, or TMSOTf causes the polymerization of **1**, which proceeds much faster than its interaction with **2a** even at −40 °C. It is consistent with literature data that the DA cyclopropanes can initiate a cationic polymerization of activated alkenes *via* cyclopropane ring opening into a zwitterionic intermediate followed by an attack of its cationic site onto nucleophilic alkene.[12]

The application of moderately activating Lewis acids as catalysts allowed us to avoid the polymerization of the initial substrates in this reaction. Thus, in the presence of the metal triflates, $ZnCl_2$ and MgI_2, the diene **1** was found to react with **2a** yielding product **3a**. The results of catalyst optimization are presented in Table 1. The highest yields of **3a** were obtained when the **1**:**2a** molar ratio was 4:1 and the reaction proceeded at room temperature in the presence of $Yb(OTf)_3$ or $Sn(OTf)_2$ (5 mol%) in CH_2Cl_2 (Table 1, entries 1 and 2). The less activating Lewis acids provided lower conversions of the reagents and yields of **3a** (entries 3–7).

Utilization of di-*tert*-butyl 2-(2-thienyl)cyclopropane-1,1-dicarboxylate instead of diethyl ester **1a** was unsuccessful due to predominant recyclization of the parent cyclopropane into a γ-butyrolactone derivative.[13]

With the optimized reaction conditions in hand, we investigated the reactivity of a series of heteroaryl-

Table 1. The screening of moderately activating Lewis acids as catalyst in the reaction of diene **1** with thienylcyclopropane **2a**.[a]



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

Entry	LA (mol%)	Reaction time [h]	Solvent	Yield of **3a** [%][b] (*endo:exo*)[c]
1	**$Yb(OTf)_3$ (5)**	**26**	**CH_2Cl_2**	**76 (83:17)**
2	**$Sn(OTf)_2$ (5)**	**3.5**	**CH_2Cl_2**	**74 (85:15)**
3	$In(OTf)_3$ (5)	22	$C_2H_4Cl_2$	58 (82:18)
4	$Sc(OTf)_3$ (5)	2.5	CH_2Cl_2	47 (73:27)
5	$Sm(OTf)_3$ (15)	24	CH_2Cl_2	31 (78:22)
6	$ZnCl_2$ (120)	24	CH_2Cl_2	65 (74:26)
7	MgI_2 (5)	3	CH_2Cl_2	25[d]

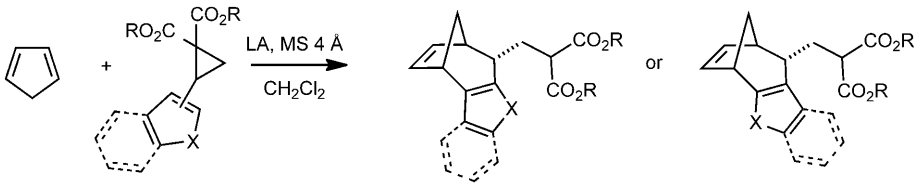
[a] A 0.1 M solution of **2a** in the specified solvent was used.
[b] Isolated yield.
[c] Determined by NMR spectroscopy.
[d] NMR yield.

substituted cyclopropanes **2b–j** towards diene **1** (Table 2).

The reactions between thiophene derivatives **2b**, **c** and diene **1** proceeded efficiently resulting in the corresponding [3+4] annulation products **3b**, **c** in good yields (entries 2 and 3).

A notable decrease in yield was observed for a furan derivative **2d** (Entry 4). We presume that this

Table 2. The reaction of 2-(heteroaryl)cyclopropane-1,1-dicarboxylates **2a–j** with cyclopentadiene (**1**) under optimized conditions.[a]



1 **2a – i** **3a, b, d – h** **3c, i**

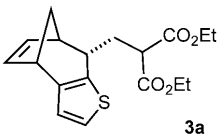
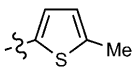
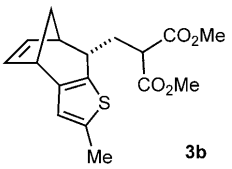
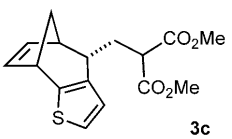
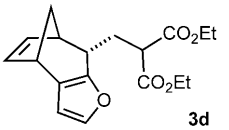
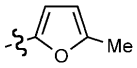
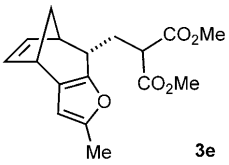
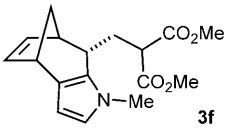
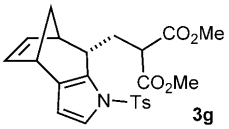
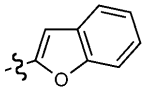
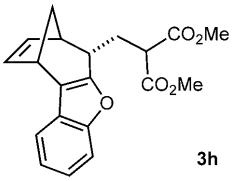
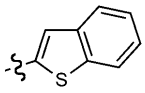
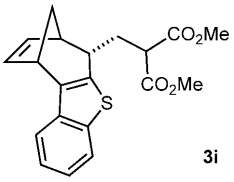
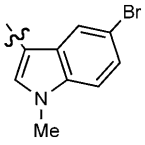
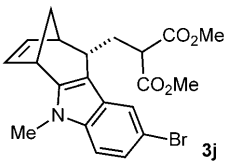
Entry	**2**	R	Ar	LA (mol%)	Reaction time [h]	Product **3**	Yield **3** [%][b] (*dr endo:exo*)[c]
1	**2a**	Et		$Yb(OTf)_3$ (5)	26	 **3a**	76 (83:17)
2	**2b**	Me		$Yb(OTf)_3$ (5)	22	 **3b**	81 (85:15)
3	**2c**	Me		$Sn(OTf)_2$ (5)	24	 **3c**	68 (80:20)

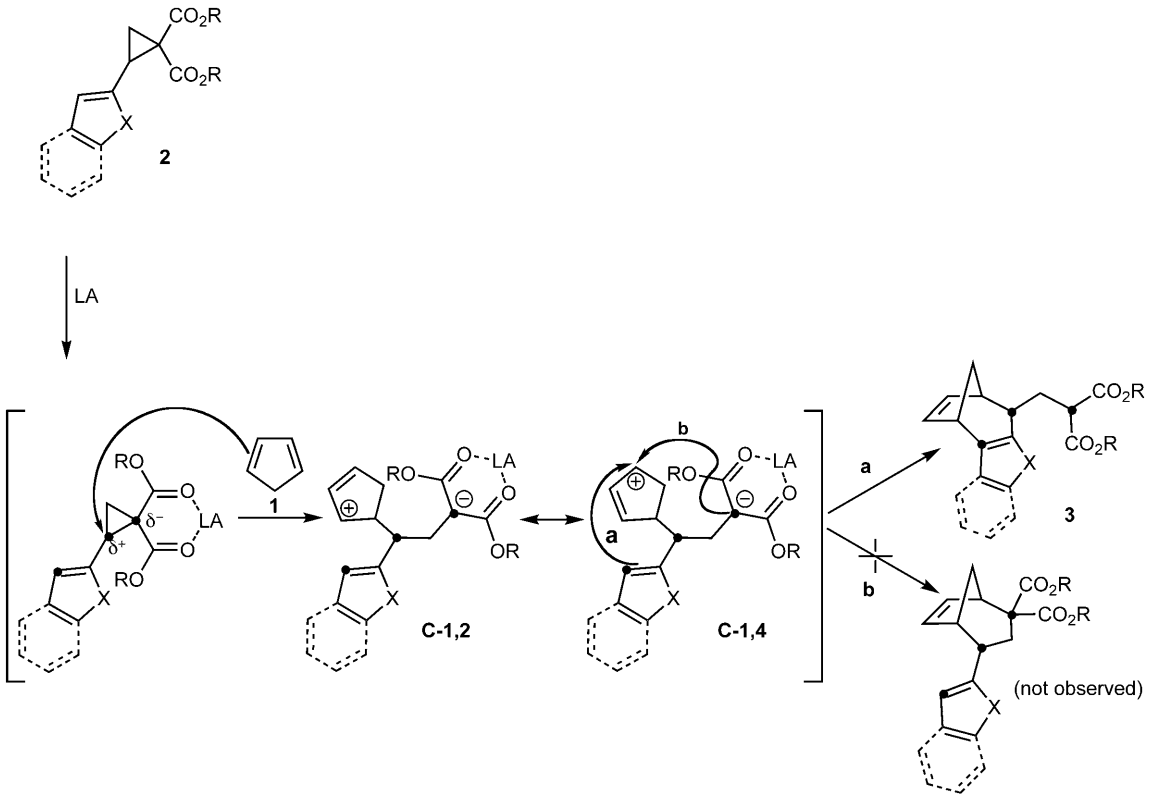
Table 2. (Continued)

Entry	2	R	Ar	LA (mol%)	Reaction time [h]	Product 3	Yield 3 [%][b] (*dr endo:exo*)[c]
4	**2d**	Et		$Yb(OTf)_3$ (5)	23	 **3d**	33 (50:50)
5	**2e**	Me		$Yb(OTf)_3$ (5)	3	 **3e**	53 (77:23)[d]
6	**2f**	Me		$Yb(OTf)_3$ (5) or $Sn(OTf)_2$ (10)	24	 **3f**	traces[e]
7	**2g**	Me		$Sn(OTf)_2$ (10)	2	 **3g**	56 (>95:5)
8	**2h**	Me		$Sn(OTf)_2$ (5)	14	 **3h**	72 (75:25)
9	**2i**	Me		$Sn(OTf)_2$ (10)	24	 **3i**	72 (92:8)
10	**2j**	Me		$Yb(OTf)_3$ (5)	2.5	 **3j**	67 (63:37)

[a] A 0.1 M solution of **2** in CH_2Cl_2 was stirred with the appropriate catalyst and a 4-fold excess of **1** at room temperature, except for **2e**; the reaction with **2e** was performed at −60→0 °C.
[b] Isolated yield.
[c] Determined by NMR spectroscopy.
[d] Compound **3e** (53%) was formed together with **4** (18%) (see text).
[e] Polymeric products are formed predominantly.

33% yield is caused by a low stability of monosubstituted furans in the presence of Brønsted and Lewis acids. 2,5-Disubstituted furans are generally more stable towards electrophiles. So, we examined the reaction of (5-methylfuryl)cyclopropane **2e** with **1** (entry 5). Indeed, the corresponding product **3e** was obtained in 53% yield. In this case the reaction was accompanied by the formation of an unusual by-product **4** as a result of the interaction of **2e** with two cyclopentadiene molecules (see below).

The low stability of *N*-methylpyrrolyl-substituted cyclopropane **2f** prevents its transformation into the corresponding adduct **3f** (entry 6). Fortunately, the more stable related cyclopropane **2g** with *N*-tosylpyrrole as the donor substituent was found to smoothly afford product **3g** in 56% yield (entry 7).



Scheme 2. Proposed mechanism for the interaction between diene **1** and 2-(heteroaryl)cyclopropane-1,1-dicarboxylates **2**.

Finally, [3+4] annulated products **3h–j** were found to be readily formed from the corresponding cyclopropanes **2h–j** containing benzannulated heterocyclic substituents (entries 8–10).

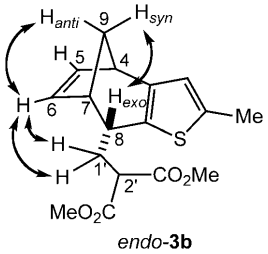
Reaction of **1** with **2b**, **d**, **e**, **j** is efficiently catalyzed with $Yb(OTf)_3$. Conversely, for cyclopropanes **2c**, **g, h**, **i**, the application of $Yb(OTf)_3$ in this reaction results in low (*ca.* 30%) conversion. A moderate heating and use of higher catalyst/substrate ratio does not increase the yield of **3** but initiates the polymerization process. The full conversion of reagents and good yields of **3c**, **g**, **h**, **i** were achieved only when cyclopropanes **2c**, **g**, **h**, **i** reacted in the presence of the more activating $Sn(OTf)_2$.

The interaction of **1** with **2** proceeds chemoselectively *via* 1,4-addition of **1** to the DA cyclopropane as synthon **B** and yields polycyclic compounds **3** as mixtures of two diastereomers (Table 2). Generally, the diastereoselectivity of the reaction correlates well with the electron-donating ability of heteroaromatic substituent in the starting DA cyclopropanes **2**, i.e., the cyclopropanes with more electron-donating hetarenes demonstrate lower stereoselectivity in this annulation. The possible mechanism for the formation of products **3** is shown in Scheme 2. The coordination of the Lewis acid to the acceptor group(s) of **2** leads to polarization and lengthening of the C(1)–C(2) bond. The resulting electrophilic center at C(2) atom attacks the diene **1** affording intermediate **C**. This intermediate has at least two nucleophilic sites, namely, malonyl anion and *ortho*-position of the heterocycle. However, only the aromatic nucleophilic site takes part in the reaction, since the formation of [3+4] cycloadducts was not observed in these cases at all. Therefore, an electrophilic attack of allylic cation in **C-1,4** onto the *ortho*-position of heterocycle accomplishes the process and gives rise to the formation of the bicyclo-[3.2.1]octadiene scaffold of **3**.

NMR Spectral Studies and Configurational Assignments

To elucidate the structure of products **3**, the careful analysis of ^1H and ^{13}C NMR spectra and their comparison with the described spectral data of related systems was carried out. Herein we present a summary of the structural characterization of **3**.

The ^1H and ^{13}C NMR spectra of **3** were assigned using 2D COSY, HETCORR, HMBC and NOESY NMR techniques. The NMR data revealed the formation of a bridged framework, containing two CH–CH_2–CH systems in **3** that unambiguously proves that: a) the DA cyclopropanes **2** react as synthon **B** but not **A** (Figure 1) and b) the conjugated diene **1** reacts as a 4π-component (Scheme 1).



endo-**3b**

Figure 2. Representative NOE responses for the *endo*-isomer of **3b**.

The bridged CH–CH_2–CH fragment was characterized by the following patterns. The characteristic value of the ^2J coupling constant for the protons of bridged CH_2 group is *ca.* 10 Hz. The signal of H-9_{syn} (enumeration is given according to Figure 2) appeared as a doublet with notable line broadening, i.e., $^3J \leq 1$ Hz, whereas for the H-9_{anti} proton the values of $^3J_{9anti,4}$ and $^3J_{9anti,7}$ are higher (4.3–4.9 Hz). Moreover, intensive cross-peaks are observed for the correlations between H-9_{anti} and H-4, H-9_{anti} and H-7 in the COSY NMR spectra. The low-field aliphatic resonances at $\delta_C = 38$–44 ppm were assigned to the carbon atom of this bridged CH_2 group. These results are in full accordance with the literature data for the similar compounds containing the bicyclo[3.2.1]octadiene scaffold.[14]

The second CH–CH_2–CH fragment consists of a C(8)H methine group and a side-chain attached to it. The ^{1}H NMR spectra reveal the full coupling patterns for the CH–CH_2 fragment protons, namely ^2J of *ca.* 14 Hz and ^3J of *ca.* 5–7 and 8–11 Hz, which are typical for an aliphatic chain.

Our assignment of structure **3** is also supported by the fact that a new signal of a quaternary carbon atom is observed in the aromatic region of the ^{13}C NMR spectra instead of the carbon atom resonance of a methine group.

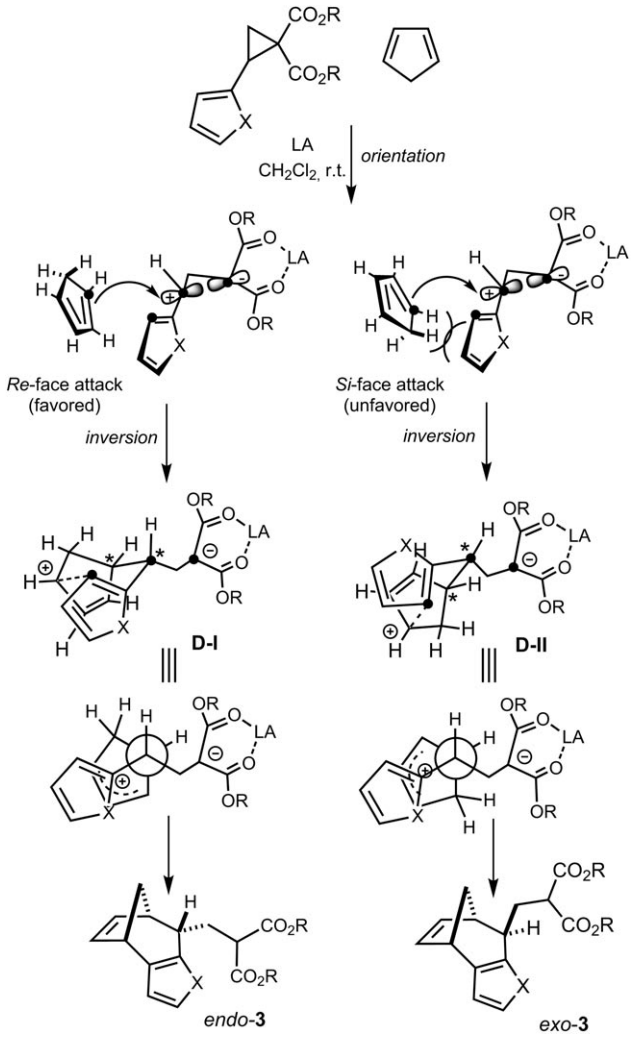
To determine the relative configuration of the major and minor isomers of **3**, we estimated the vicinal coupling constants for the protons of the bicyclo-[3.2.1]octadiene fragment. The coupling patterns that are important for the stereochemical characterization of diastereomers of **3** are $^3J_{7,8exo}$ and $^3J_{7,8endo}$. According to literature data for bicyclo[3.2.1]octadienes, the dihedral angle between protons H-7 and H-8_{exo} approximately equals 40°, whereas the dihedral angle between protons H-7 and H-8_{endo} is *ca.* 60°. Thus, in accordance with the Karplus rule, the larger coupling constant $^3J_{7,8}$ of *ca.* 5.0–5.5 Hz was observed for the *endo*-orientation of substituent (*exo*-proton) and $^3J_{7,8}$ was 0–2 Hz for the *exo*-isomer (*endo*-proton).[14] We have also performed *ab initio* geometry optimization of **3b** using the MP2/6-311G method.[13] According to our calculations, the H–C(7)–C(8)–H dihedral angles for the *endo*- and *exo*-isomers are 45° and 78°, respectively, that correspond to the expected $^3J_{7,8}$ values of 5.1 and 0.9 Hz.

In several cases the measuring of coupling constants for major isomers of **3** was hindered by a notable overlapping of the resonances corresponding to the H-7 and H-8 atoms. Fortunately, the signals of the H-7 and H-8 atoms for major isomers of **3b**, **c**, **j** are clearly observed. The values of $^3J_{7,8}$ for these compounds were determined to be 4.7–5.3 Hz which is in accordance with an *exo*-configuration of H-8 and an *endo*-configuration of the side-chain. For minor isomers in most cases the problem of overlapping does not emerge and signals and coupling constants can be identified. For minor isomer of **3a** $^3J_{7,8}$ is not observable, i.e., ≤ 1 Hz. However, in the cases of **3b**, **e**, **h** the corresponding $^3J_{7,8}$ values were measured and amounted to 1.0–1.1 Hz. Therefore, the major diastereomers of **3** were assigned to *endo*-isomers, while the minor diastereomers were assigned to *exo*-isomers.

Our conclusions were confirmed with the NOESY spectrum of **3b**. The strong NOE between H-9_{syn} and H-8 in the major isomer is in accordance with the predominant formation of the *endo*-product. The representative NOE responses for *endo*-**3b** are summarized in Figure 2.

The Origin of Chemo- and Stereoselectivity

The high chemoselectivity and predominant *endo*-selectivity could be explained in terms of charge transfer precomplex formation. We believe the reaction is initiated by a coordination of Lewis acid to the acceptor group(s) of **2**, as in the absence of catalyst the reaction does not proceed at all. The coordination of Lewis acid causes a significant increase of the cyclopropane C(1)–C(2) bond polarization that might result in a configurationally stable intimate ion pair formation. The electron-enriched heterocyclic substituent provides stabilization of an electrophilic site at C(2) that leads to delocalization of developing positive charge to heterocycle, i.e., to its electron deficiency. Diene **1** approaches the electrophilic site at C(2) in such a way as to be in parallel with the heteroarene ring as this orientation provides interaction of the electron-enriched conjugated π-system of **1** with the electron-depleted heterocyclic substituent resulting in a π-π* donor-acceptor complex. Then the diene **1** as a nucleophile attacks the C(2) atom of **2** that leads to the formation of new zwitterions **D** with inversion at C(2) position.[4g,5b,d,11d,15] During this step two stereogenic centers are formed which determine unambiguously the stereochemistry of the final product **3**. A *Re*-face nucleophilic attack leading to *endo*-**3** minimizes the steric interaction, while in the case of an *Si*-face attack leading to *exo*-**3** steric repulsions arise between the heteroaryl substituent and one of

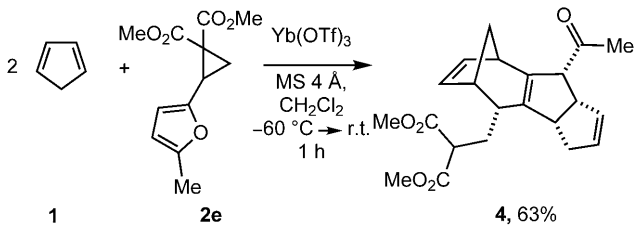


Scheme 3. A model for the observed chemo- and stereoselectivity in the formation of **3**.

H-5 atoms of diene **1**. The formation of the bicyclo-[3.2.1]octane skeleton is ruled by orbital interactions between the allylic cation system and the heteroarene ring in intermediates **D-I** and **D-II**. Whereupon the exceptional chemoselectivity can be explained by the close proximity of two reaction centers in **D-I** (or **D-II**), i.e., allylic cation and nucleophilic *ortho*-position of heterocycle. Despite the higher nucleophilicity of the malonyl anion,[16] its attack in this case is not competitive (Scheme 3).

Reaction of Cyclopentadiene (1) with (5-Methyl-2-furyl)cyclopropane (2e)

We pointed out above that in the reaction between **2e** and **1** a tricyclic adduct **3e** was obtained as major product together with minor tetracycle **4**, which was formed *via* interaction of **2e** with two equivalents of **1**. The yields of **3e** and **4** depend significantly on the



Scheme 4. Reaction of diene **1** with (5-methyl-2-furyl)cyclopropane **2e**.

reaction conditions and **1**:**2e** molar ratio. The best yields of **3e** were obtained when an equivalent of **2e** was added to four equivalents of **1** in CH_2Cl_2 at −60 °C in the presence of 5 mol% of the catalyst followed by slow warming of resulting solution up to 0 °C for 3 h. These conditions provide a 53% yield of **3e** and an 18% yield of **4** (Table 2). Whereas, a five-fold excess of **1** and rapid warming up to room temperature for 1 h affords **4** in 63% yield (Scheme 4). The addition order does not influence the yields of **3e** and **4**.

The reaction of **2e** with two molecules of **1** proceeds in high chemo-, regio- and stereoselective manner and affords **4** as a single diastereomer containing six stereogenic centers. The composition and structure of **4** were unambiguously proved by an elemental analysis and 1D and 2D NMR spectroscopy. ^{1}H and ^{13}C NMR data clearly revealed the presence of the bicyclo[3.2.1]octadiene framework in **4**, which is similar to the analogous motif in **3e**. A careful analysis of the aromatic region disclosed that upfield resonances corresponding to the furan moiety are absent. Instead, a low-field resonance at $\delta_C = 210.2$ ppm is observed in the ^{13}C NMR spectrum, which was assigned to a carbon atom of the arising C=O group. NMR data also indicate that the tetracyclic skeleton of **4** is formed as a result of annulation of the second molecule of **1** *via* the C(1)−C(2) bond. Among these evidences are: 1) the absence of characteristic patterns for the second bridged motif; 2) the $^2J_{3,3}$ value of 16.9 Hz that dramatically differs from $^2J = ca.$ 10 Hz for H atoms of bridged CH_2 group; 3) intensive cross-peaks for correlations between H atoms of C(1)H=C(2)H fragment and methylene C(3)H_2 and methine C(9a)H groups in the COSY NMR spectrum. The stereochemical assignment for **4** was made using 2D NOESY ^{1}H NMR spectroscopy. All representative NOE responses are shown in Figure 3.

The indicated relative stereochemistry of **4** allowed us to propose the following mechanism for its formation (Scheme 5). The interaction of cyclopropane **2e** with the first molecule of diene **1** leads to zwitterion **E** with an *endo*-orientation of substituent. Such a stereochemical result is in accordance with the predominant formation of *endo*-**3e** (Table 2), since **E** is a direct precursor of **3e**. The second molecule of **1** at-

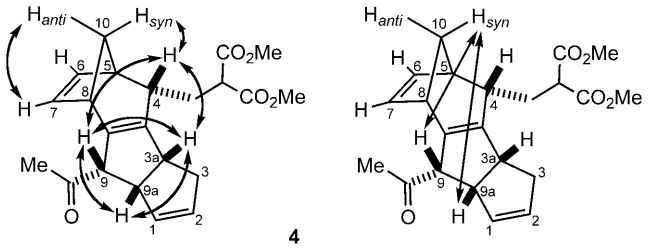


Figure 3. Representative NOE responses for adduct **4**.

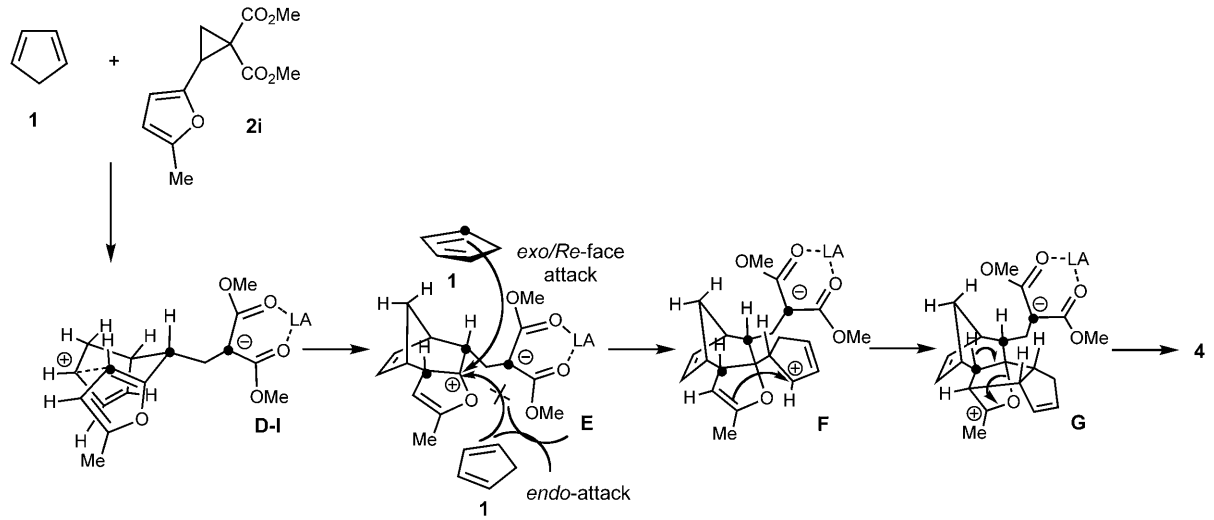
tacks the cationic center in **E** followed by a new cyclopentane ring closure and furan ring opening to afford **4**. Similar recyclizations are quite typical for 2,5-disubstituted furans[17] whereas they are much less efficient for other heterocycles tested here. The relative configuration of stereogenic centers in the final product **4** indicates that diene **1** approaches **E** from the *exo*-surface, probably, due to the lower steric repulsion caused by the bridged CH_2 group in comparison to those from the bulky $CH_2CH(CO_2Me)_2$ substituent. Then attack of the cationic center in **E** onto the *Re*-face of **1** occurs, while the alternative *Si*-face approach is shielded by *exo*- and bridged H atoms in **E**. It is noteworthy that diene **1** reacts with **E** as a 2π- but not as a 4π-component. The possible reason is a higher thermodynamic stability of **4** in comparison to the isomeric doubly bridged products. Indeed, our *ab initio* calculations show that **4** is 25–26 kJ mol^{-1} more stable than the corresponding isomers formed *via* 1,4-addition of the second cyclopentadiene molecule.[13]

Therefore, the formation of **4** is an unusual electrophilic cascade resulting in the formation of four new C–C bonds and three new cycles. This reaction proceeds with an exceptional stereoselectivity: despite the formation of six stereocenters during this transformation, compound **4** was obtained as a single diastereomer.

Conclusions

In summary, we have developed a powerful general approach to heteroarene-fused bicyclo[3.2.1]octadienes *via* a novel Lewis acid-catalyzed [3+4] annulation of 2-(heteroaryl)cyclopropane-1,1-diesters to cyclopentadiene. In this process DA cyclopropanes can be viewed as the synthetic equivalent to an unusual ambiphilic synthon containing an electrophilic site at the C(2) atom of the small ring and a nucleophilic site at the *ortho*-position of the heterocycle, whereas cyclopentadiene reacts as a 4π-component. In general, the reaction can be represented as a sequence of electrophilic processes: an interaction of the cyclopropane electrophilic center with cyclopentadiene followed by an intramolecular Friedel–Crafts alkylation at the *ortho*-position of the heteroarene substituent. The high chemoselectivity and predominant *endo*-stereoselectivity of the reaction might be reasoned by the initial formation of a π-π* complex between cyclopentadiene and the electron-depleted heteroarene moiety in the Lewis acid-activated DA cyclopropane.

The proposed procedure provides a more convenient and efficient preparation of heteroarene-fused bicyclo[3.2.1]octadienes in comparison with the photochemical approach to these systems.[10e] Additionally, the simple access to the numerous parent 2-(heteroaryl)cyclopropane-1,1-diesters *via* standard Knoevenagel/Corey–Chaykovsky reactions allows for an easy extension of the diversity of the desired products. These compounds can be applied as useful building blocks in various transformations due to the presence of an easily modified double bond, a heteroaromatic fragment and a malonyl moiety. The cage structure of these molecules provides high stereoselectivity for the further transformations. Thus, the proposed strategy for the construction of heteroarene-fused bicyclo-



Scheme 5. Proposed mechanism for the reaction of diene **1** with (5-methyl-2-furyl)cyclopropane **2e**.

[3.2.1]octadiene skeleton can be a useful tool in target-oriented synthesis.

Experimental Section

Synthesis of Dimethyl [(7,10-Dihydro-6*H*-7,10-methanobenzo[*b*]cyclohepta[*d*]furan-6-yl)methyl]-malonate (3h); Typical Procedure

The solution of cyclopropane **2h** (356 mg, 1.3 mmol), cyclopentadiene (**1**) (340 mg, 0.43 mL, 5.2 mmol), and $Sn(OTf)_2$ (27 mg, 0.065 mmol) in CH_2Cl_2 (10 mL) was stirred under an argon atmosphere in the presence of 4 Å molecular sieves for 14 h. The reaction progress was monitored by TLC and ^{1}H NMR. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane:$CHCl_3$, 1:1, as eluent) to afford **3h** as a yellow oil; yield: 318 mg (72%); R_f = 0.63 (ethyl acetate:petroleum ether; 1:3); *endo:exo* 75:25. IR (nujol): ν = 2965, 2930, 2875, 1735, 1606, 1465, 1380, 1140, 1120, 980, 900, 845, 820, 730 cm^{-1}; The enumeration in NMR assignments does not correspond to IUPAC name. It is given according to Figure 2 for simple comparison with data for other adducts **3**. ^{1}H NMR ($CDCl_3$, 600 MHz for *endo*-isomer): δ = 1.92 (d, $^2J_{9,9}$ = 9.9 Hz, 1 H, H_{syn}-9), 2.10 (ddd, $^2J_{1',1'}$ = 14.0 Hz, $^3J_{1'a,2'}$ = 7.0 Hz, $^3J_{1'a,8}$ = 8.3 Hz, 1 H, H_a-1′), 2.29–2.35 (m, 2 H, H_b-1′, H_{anti}-9), 3.16–3.21 (m, 2 H, H-7, H-8), 3.56 (dd, $^3J_{4,5}$ = 2.9 Hz, $^3J_{4,9anti}$ = 4.3 Hz, 1 H, H-4), 3.79 (s, 3 H, CH_3O), 3.82 (s, 3 H, CH_3O), 4.02 (dd, $^3J_{2',1'a}$ = 7.0 Hz, $^3J_{2',1'b}$ = 8.1 Hz, 1 H, H-2′), 5.77 (dd, $^3J_{6,7}$ = 2.8 Hz, $^3J_{6,5}$ = 5.7 Hz, 1 H, H-6), 6.60 (dd, $^3J_{5,4}$ = 2.9 Hz, $^3J_{5,6}$ = 5.7 Hz, 1 H, H-5), 7.16–7.20 (m, 2 H), 7.39–7.42 (m, 1 H), 7.48–7.50 (m, 1 H); ^{1}H NMR ($CDCl_3$, 600 MHz for *exo*-isomer): δ = 1.95 (d, $^2J_{9,9}$ = 10.1 Hz, 1 H, H_{syn}-9), 2.06 (ddd, $^2J_{9,9}$ = 10.1 Hz, $^3J_{9,4}$ = 4.3 Hz, $^3J_{9,7}$ = 4.6 Hz, 1 H, H_{anti}-9), 2.29–3.35 (m, 1 H, H^a-1′), 2.50 (ddd, $^2J_{1',1'}$ = 14.0 Hz, $^3J_{1'b,8}$ = 6.4 Hz, $^3J_{1'b,2'}$ = 8.7 Hz, 1 H, H_b-1′), 2.72 (ddd, $^3J_{8,7}$ = 1.1 Hz, $^3J_{8,1'b}$ = 6.4 Hz, $^3J_{8,1'a}$ = 8.0 Hz, 1 H, H-8), 2.90 (ddd, $^3J_{7,8}$ = 1.1 Hz, $^3J_{7,6}$ = 3.1 Hz, $^3J_{7,9anti}$ = 4.6 Hz, 1 H, H-7), 3.62 (dd, $^3J_{4,5}$ = 2.8 Hz, $^3J_{4,9anti}$ = 4.3 Hz, 1 H, H-4), 3.76 (s, 3 H, CH_3O), 3.83 (s, 3 H, CH_3O), 4.05 (dd, $^3J_{2',1'a}$ = 6.4 Hz, $^3J_{2',1'b}$ = 8.7 Hz, 1 H, H-2′), 5.83 (dd, $^3J_{6,7}$ = 3.1 Hz, $^3J_{6,5}$ = 5.5 Hz, 1 H, H-6), 6.44 (dd, $^3J_{5,4}$ = 2.8 Hz, $^3J_{5,6}$ = 5.5 Hz, 1 H, H-5), 7.16–7.20 (m, 2 H), 7.39–7.42 (m, 1 H), 7.48–7.50 (m, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz for *endo*-isomer): δ = 28.82 [C(1′)H_2], 35.83 [C(4)H], 37.81 [C(8)H], 43.50 [C(7)H], 44.38 [C(9)H_2], 49.91 [C(2′)H], 52.68 (2 × CH_3O), 111.18 (CH), 118.19 (CH), 120.34 (C), 122.31 (CH), 122.79 (CH), 126.60 (C), 128.45 [C(6)H=], 144.31 [C(5)H=], 152.98 (C), 153.27 (C), 168.69 (CO_2Me), 169.93 (CO_2Me); ^{13}C NMR ($CDCl_3$, 150 MHz for *exo*-isomer): δ = 33.60 [C(1′)H_2], 35.87 [C(4)H], 36.73 [C(8)H], 38.86 [C(9)H_2], 44.35 [C(7)H], 50.04 [C(2′)H], 52.68 (2 × CH_3O), 111.18 (CH), 118.28 (CH), 120.20 (C), 122.29 (CH), 122.92 (CH), 126.58 (C), 130.17 [C(6)H=], 141.78 [C(5)H=], 153.27 (C), 153.38 (C), 169.74 (CO_2Me), 169.91 (CO_2Me); GC-MS: *m*/*z* (%) = 340 (5) $[M]^+$, 209 (14), 208 (100), 207 (39), 181 (11), 169 (7), 168 (16), 165 (10), 152 (9), 115 (5), 59 (17); anal. calcd. for $C_{20}H_{20}O_5$: C 70.57, H 5.92; found: C 70.82, H 5.93.

Acknowledgements

We thank the Russian Foundation of Basic Research (Project 09-03-00244-a) for financial support of this work.

References

[1] a) *The Chemistry of the cyclopropyl group*, Vol. 1, (Ed.: Z. Rappoport), John Wiley & Sons, Chichester, **1987**, 1739; b) *The Chemistry of the cyclopropyl group*, Vol. 2, (Ed: Z. Rappoport), John Wiley & Sons, Chichester, **1995**, 962 pp; c) *Houben-Weyl, Methods of Organic Chemistry*, Vol. E17c, (Ed: A. de Meijere), Thieme, Stuttgart, **1997**, 2694 pp.

[2] a) J. R. Y. Salaün, *Top. Curr. Chem.* **1988**, *144*, 1–71; b) A. de Meijere, S. I. Kozhushkov, *Chem. Rev.* **2000**, *100*, 93–142; c) N. Iwasawa, K. Narasaka, *Top. Curr. Chem.* **2000**, *207*, 69–88; d) A. de Meijere, S. I. Kozhushkov, A. F. Khlebnikov, *Top. Curr. Chem.* **2000**, *207*, 89–147; e) A. de Meijere, S. I. Kozhushkov, H. Schill, *Chem. Rev.* **2006**, *106*, 4926–4996.

[3] a) H.-U. Reissig, *Top. Curr. Chem.* **1988**, *144*, 73–135; b) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151–1196; c) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321–347; d) D. Agrawal, V. K. Yadav, *Chem. Commun.* **2008**, 6471–6488; e) F. De Simone, J. Waser, *Synthesis* **2009**, 3353–3374; f) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051–3060; g) T. P. Lebold, M. A. Kerr, *Pure Appl. Chem.* **2010**, *82*, 1797–1812.

[4] Recent publications: a) A. Karadeolian, M. A. Kerr, *Angew. Chem.* **2010**, *122*, 1151–1153; *Angew. Chem. Int. Ed.* **2010**, *49*, 1133–1135; b) J. Campbell, J. S. Johnson, *Synthesis* **2010**, 2841–2852; c) S. Xing, W. Pan, C. Liu, J. Ren, Z. Wang, *Angew. Chem.* **2010**, *122*, 3283–3286; *Angew. Chem. Int. Ed.* **2010**, *49*, 3215–3218; d) M. M. Abd Rabo Moustafa, B. L. Pagenkopf, *Org. Lett.* **2010**, *12*, 3168–3171; e) B. Hu, S. Xing, J. Ren, Z. Wang, *Tetrahedron* **2010**, *66*, 5671–5674; f) A. T. Parsons, A. G. Smith, A. J. Neel, J. S. Johnson, *J. Am. Chem. Soc.* **2010**, *132*, 9688–9692; g) M. J. Campbell, J. S. Johnson, A. T. Parsons, P. D. Pohlhaus, S. D. Sanders, *J. Org. Chem.* **2010**, *75*, 6317–6325; h) G. Yang, Y. Shen, K. Li, Y. Sun, Y. Hua, *J. Org. Chem.* **2011**, *76*, 229–233.

[5] a) K. Sapeta, M. A. Kerr, *J. Org. Chem.* **2007**, *72*, 8597–8599; b) A. Karadeolian, M. A. Kerr, *J. Org. Chem.* **2007**, *72*, 10251–10253; c) C. A. Carson, I. S. Young, M. A. Kerr, *Synthesis* **2008**, 485–489; d) C. Perreault, S. R. Goudreau, L. E. Zimmer, A. B. Charette, *Org. Lett.* **2008**, *10*, 689–692; e) Q. Ding, Z. Wang, J. Wu, *Tetrahedron Lett.* **2009**, *50*, 198–200; f) Y. Zhang, F. Liu, J. Zhang, *Chem. Eur. J.* **2010**, *16*, 6146–6150.

[6] a) O. A. Ivanova, E. M. Budynina, Yu. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Angew. Chem.* **2008**, *120*, 1123–1126; *Angew. Chem. Int. Ed.* **2008**, *47*, 1107–1110; b) O. A. Ivanova, E. M. Budynina, Yu. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Eur. J. Org. Chem.* **2008**, 5329–5335.

[7] C. Venkatesh, H. Ila, H. Junjappa, S. Mathur, V. Hush, *J. Org. Chem.* **2002**, *67*, 9477–9480.

[8] The similar DA cyclopropane reactivity was earlier found in reaction of 2-(1-siloxyvinyl)cyclopropane-1,1-dicarboxylate with cyclopentadiene wherein β-carbon atom of C=C bond worked as nucleophile: M. Ohno, K. Mori, T. Hattori, S. Eguchi, *J. Org. Chem.* **1990**, *55*, 6086–6091.
[9] M.-H. Filippini, J. Rodriguez, *Chem. Rev.* **1999**, *99*, 27–76.
[10] a) M. K. Eberle, G. G. Kahle, *Tetrahedron* **1973**, *29*, 4049–4052; b) D. L. Boger, J. Schumacher, M. D. Mullican, M. Patel, J. S. Panek, *J. Org. Chem.* **1982**, *47*, 2673–2675; c) B. Abarca, R. Ballesteros, C. Soriano, *Tetrahedron* **1987**, *43*, 991–998; d) J. P. Olson, H. M. L. Davies, *Org. Lett.* **2008**, *10*, 573–576; e) D. Vidakovic, I. Skoric, M. Horvat, Z. Marinic, M. Sindler-Kulyk, *Tetrahedron* **2008**, *64*, 3928–3934, and references cited therein; f) M. F. Ali, R. Caliskan, E. Sahin, M. Balci, *Tetrahedron* **2009**, *65*, 1430–1437.
[11] a) I. S. Young, M. A. Kerr, *Org. Lett.* **2004**, *6*, 139–141; b) M. D. Ganton, M. A. Kerr, *J. Org. Chem.* **2004**, *69*, 8554–8557; c) P. D. Pohlhaus, J. S. Johnson, *J. Org. Chem.* **2005**, *70*, 1057–1059; d) C. A. Carson, M. A. Kerr, *J. Org. Chem.* **2005**, *70*, 8242–8244; e) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650; f) A. O. Chagarovskiy, E. M. Budynina, O. A. Ivanova, Yu. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Tetrahedron* **2009**, *65*, 5385–5392.
[12] a) J.-Y. Lee, S.-O. Cho, A. B. Padias, H. K. Hall, *Bull. Korean Chem. Soc.* **1991**, *12*, 271–273; b) T. Li, A. B. Padias, H. K. Hall, *Macromolecules* **1992**, *25*, 1387–1390.
[13] See the Supporting Information.
[14] a) L. A. Paquette, W. E. Volz, *J. Am. Chem. Soc.* **1976**, *98*, 2910–2917; b) H. M. L. Davies, B. Hu, E. Saikali, P. R. Bruzinski, *J. Org. Chem.* **1994**, *59*, 4535–4541; c) S. Taskesenlioglu, A. Dastan, E. Dalkilic, M. Güney, R. Abbasoglu, *New J. Chem.* **2010**, *34*, 141–150 and references cited therein.
[15] a) D. Wanapun, K. A. Van Gorp, N. J. Mosey, M. A. Kerr, T. K. Woo, *Can. J. Chem.* **2005**, *83*, 1752–1767; b) P. D. Pohlhaus, J. S. Johnson, *J. Am. Chem. Soc.* **2005**, *127*, 16014–16015; c) J. Zhang, W. Shen, M. Li, *Eur. J. Org. Chem.* **2007**, 4855–4866.
[16] H. Mayr, A. R. Ofial, *J. Phys. Org. Chem.* **2008**, *21*, 584–595.
[17] A. S. Dmitriev, V. T. Abaev, W. Bender, A. V. Butin, *Tetrahedron* **2007**, *63*, 9437–9447.

