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Recent advances in ring-forming reactions of donor-acceptor cyclopropanes

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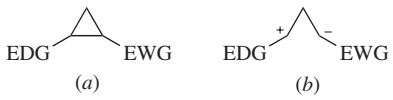
Dedicated to academician O. M. Nefedov in relation to his 80th anniversary

Acceptor and donor together bring
A magic force to three-membered ring.
This ring is inimitable under the sky,
Reacts with radicals, nucleophiles,
Electrophiles, red-ox agents, alkenes,
Imines, aldehydes, conjugated dienes.
It dimerizes, reacts with nitrones,
Nitriles, and alkynes, and so forth, and so on...

Owing to the relative ease of ring-opening under a variety of conditions, donor–acceptor cyclopropanes serve as synthetic building blocks for construction of highly functionalized carbo- and heterocyclic compounds. Recent examples of the ring-forming reactions employing donor–acceptor cyclopropanes are discussed in the present focus article.

An essential element in the quest for the development of efficient, selective and atom-economic chemical reactions is the discovery of processes in which several bonds are formed at once, *i.e.*, cycloadditions, annulations, domino sequences, *etc*. Donor-acceptor (DA) cyclopropanes are powerful reactants, splendidly appropriated for these processes. Specifically, they possess several reaction sites, easily undergo activation under mild conditions and are involved in a large set of ring-forming transformations.[1–7]

The term 'donor–acceptor cyclopropane' was introduced in 1982 by Doyle and van Leusen[8] for designation of cyclopropanes equipped with donor and acceptor groups at vicinal positions [Figure 1(*a*)]. Such arrangement of substituents of an opposite electron effect leads to polarization and elongation of C–C bond between them and, in a limiting case, to its heterolysis with formation of 1,3-zwitterion [Figure 1(*b*)]. 1,3-Relationship of charges allows DA cyclopropanes to be considered as reagents with reactivity *umpolung*.



EDG = electron-donating (cation-stabilizing) group:
OR, NR_2, CH_2SiR_3, Ar, Alk *etc*.

EWG = electron-withdrawing (anion-stabilizing) group:
CO_2R, COR, CN, NO_2 *etc*.

Figure 1

The term 'DA cyclopropane' was initially applied to 2-alkoxycyclopropanecarboxylates as well as their analogues containing amino or alkylthio groups as a donor and carbonyl or nitrile functions as an acceptor.[1,2] Later, silylmethyl group was shown to activate carbonyl-substituted cyclopropanes similarly to an alkoxy group.[4] Currently, 2-alkenyl- and 2-(hetero)arylcyclo-

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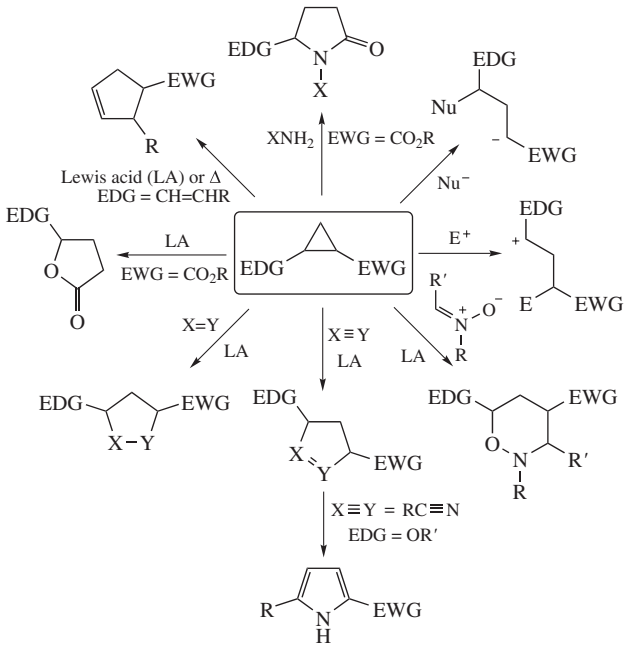
propane-1,1-diesters are the most studied DA cyclopropanes due to their high reactivity, ease of preparation, value products of their transformation.[5–7,9] Alkyl-substituted electrophilic cyclopropanes are also considered as DA cyclopropanes, despite lower cation-stabilizing effect of alkyl group leading to decrease in reactivity of these compounds.

The types of studied reactions of DA cyclopropanes have also altered with time. The early research efforts were predominantly devoted to various electrophilic and nucleophilic cyclopropane ring opening reactions.[1–3] Since the start of the new millennium, priority in DA cyclopropanes investigations has moved to Lewis acid-catalyzed cycloadditions/annulations.† To date, the most studied types of these reactions are (3+2)-cycloaddition and annulation of DA cyclopropanes to aldehydes, imines, nitriles, alkenes, and other compounds containing double or triple bonds.[4–7] In these processes, which provide a powerful approach to highly substituted five-membered carbo- or heterocycles, DA cyclopropanes react as synthetic equivalents of 1,3-dipole. Another facet of DA cyclopropane reactivity was found to be dipolarophile-like properties in (3+3)-cycloaddition with nitrones, affording tetrahydro-1,2-oxazines.[5,6]



Scheme 1

The most important DA cyclopropanes reactions, which have been developed before 2008, are presented in Scheme 1.

The high chemo-, regio- and stereoselectivity of above processes along with elaboration of their asymmetric versions promoted use of DA cyclopropanes in total syntheses of various natural products that was recently reviewed.[6] Among the latest investigations in this area are syntheses of (+)-isatisine A,[10,11] (+)-polyanthellin A,[12,13] (+)-virgatusin,[14] (±)-bruguierol A,[15] platensimycin,[16] (+)-aspidofractinine,[17] (+)-fawcettimine,[18] (±)-actinophyllic acid,[19] *etc*. In these syntheses DA cyclopropanes participated in (3+2)-cycloaddition with carbonyl compounds,[10–16] underwent reductive ring opening[17] or nucleophilic ring opening/ring closure,[18] formed divinylcyclopropane derivative followed by Cope rearrangement.[19] Acid-induced three-membered ring opening was applied for preparation of nemorosone skeleton.[20]

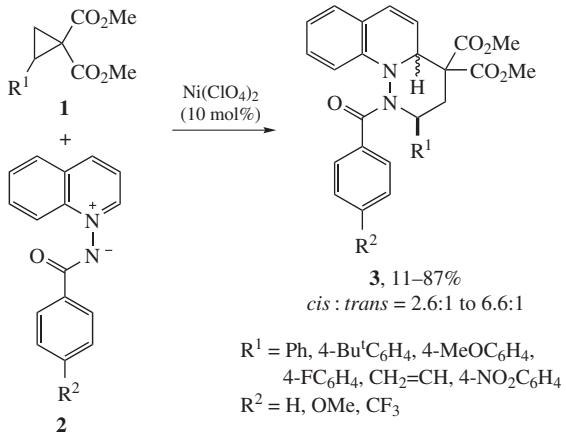
† Hereinafter we use term 'cycloaddition' for DA cyclopropanes addition to unsaturated compounds leading to new ring formation and proceeding without atom (group of atoms) departure or migration. If such addition is accompanied by above secondary processes, we name it 'annulation'.

Recent progress in DA cyclopropane chemistry consists in more detail investigation of above processes, including their mechanistic study and practical applications,[4–7,9,21–25] as well as in development of new transformations of these compounds. Most of these reactions provide new approaches to construction of carbo- and heterocycles. The present focus article reviews the leading examples from the literature and our own laboratory on the latter topic.

(3+3)-Cycloadditions/annulations

a. (3+3)-Cycloaddition with aromatic azomethine imines

Since the discovery of (3+3)-cycloaddition of DA cyclopropanes by Kerr research group,[26] this reaction was shown to proceed with high chemo-, regio- and stereoselectivity, afford six-membered rings in good to excellent yields, and be efficiently applied in the total syntheses of natural compounds.[5–7] A single restriction of this process was a scope of its applicability, as until recently nitrones remained the only type of 1,3-dipoles involved in the reaction. In this aspect the significant contribution to (3+3)-cycloaddition of DA cyclopropanes was made by Charette and co-workers. In 2008 they proposed the use of *N*-(benzoylimino)-quinolinium ylides **2** as 1,3-dipoles in reaction with DA cyclopropanes **1**.[27] This interaction afforded pyridazino[1,6-*a*]quinolines **3** in moderate to good yields (Scheme 2). The diastereoselectivity of this reaction was not very high: *cis*/*trans* ratios varied from 2.6:1 to 6.6:1 depending on donor substituent in the parent cyclopropanes **1**.



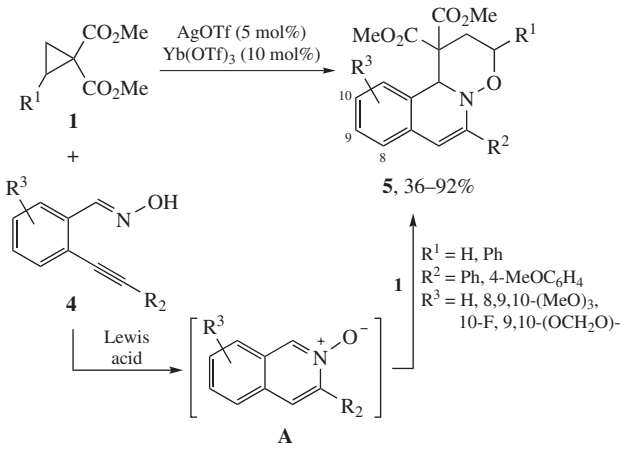
Scheme 2

The stepwise mechanism *via* initial S_N2 attack of anionic center of **2** onto C(2) atom of **1** was deduced from stereochemical studies. Thus, reaction of enantiopure dimethyl (*R*)-2-phenylcyclopropane-1,1-dicarboxylate proceeded with complete inversion at C(2) atom. Meanwhile, the reaction of analogous methyl trideuteriomethyl diester was accompanied by a complete loss of the stereogenic information at C(1) carbon atom.

b. Tandem nitrone formation/(3+3)-cycloaddition

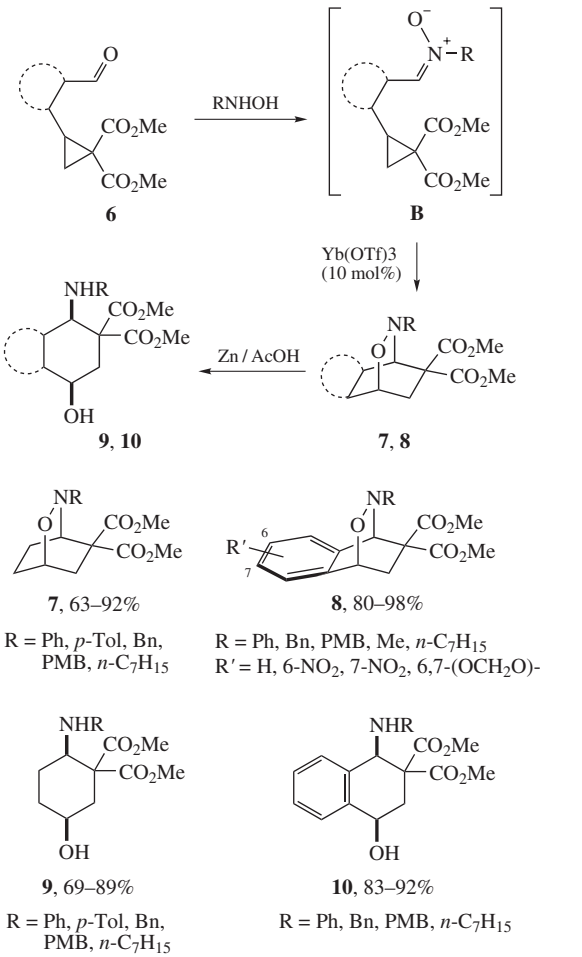
Another way to expand the scope of reaction applicability is a development of new tandem or domino sequences involving this reaction as a key stage. For (3+3)-cycloadditions of DA cyclopropanes with nitrones, this strategy primarily means the elaboration of approaches to *in situ* nitrone generation in the presence of DA cyclopropanes. Thus, Wu and co-workers[28] combined in one-pot process Lewis acid-catalyzed cyclization of 2-alkynylbenzaldoximes **4** into isoquinoline-*N*-oxides **A** and their (3+3)-cycloaddition to cyclopropanes **1** (Scheme 3).The resulted tandem reaction provided [1,2]oxazino[3,2-*a*]isoquinoline derivatives **5** in reasonable yields.

Kerr and Dias employed the same approach to the synthesis of bridged bicyclic tetrahydro-1,2-oxazines.[29] The consecutive



Scheme 3

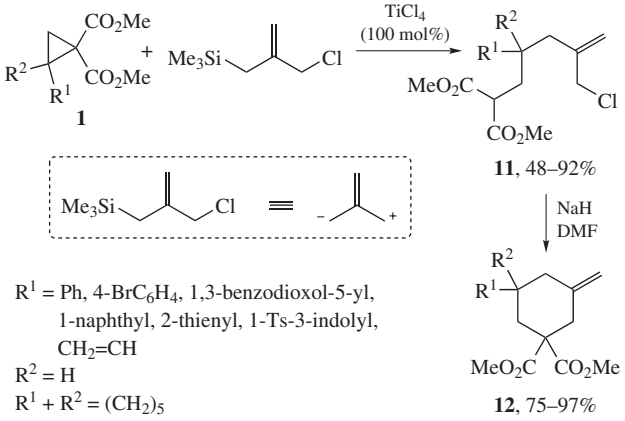
addition of RNHOH and $Yb(OTf)_3$ to DA cyclopropanes **6** with aldehyde group, tethered to small ring *via* alkyl, alkenyl or (hetero)aromatic spacer, led to generation of nitrone functionality in **B** followed by formation of (3+3)-cycloadducts **7**, **8** in high yields (Scheme 4). Reductive N–O bond scission in **7** or **8** afforded **9**, **10** derivatives of *cis*-4-aminocyclohexanol, whose fragment is present in such natural compounds as anti-cancer agent pancratistatin, antibacterial valienamine, or 'zombie powder' tetrodotoxin.



Scheme 4

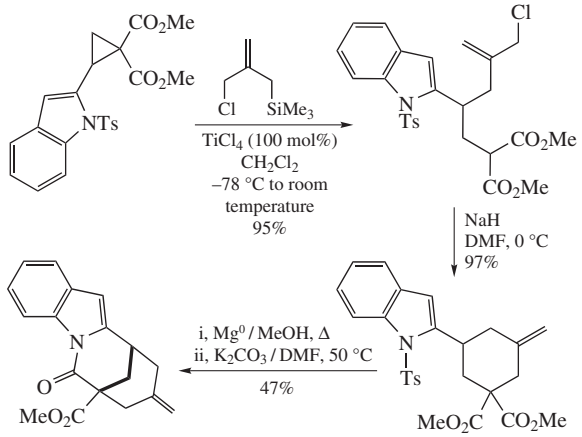
c. New three-atom components in (3+3)-annulation with DA cyclopropanes

Lewis acid-promoted sequences of ring opening/cyclization reactions of DA cyclopropanes originate from earlier investigations by Reissig.[1] Recently Kerr and co-workers developed similar synthetic strategy to six-membered rings construction. Thus, [2-(chloromethyl)allyl]trimethylsilane, which was previously utilized as synthetic equivalent of zwitterionic trimethylenemethane in various (3+2)- and (3+3)-annulations with unsaturated compounds, was successfully involved into $TiCl_4$-catalyzed allylation of DA cyclopropanes **1**.[30] Following base treatment of allylation products **11** induced intramolecular nucleophilic substitution affording methylidenecyclohexanes **12** in high yields (Scheme 5). Authors referred this process in whole to stepwise formal (3+3)-annulation.



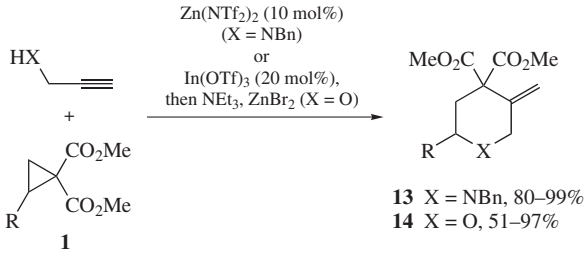
Scheme 5

This nucleophilic ring opening/cyclization sequence was successfully applied, in particular, to preparation of a pyrido[1,2-*a*]indole skeleton which is present in tronocarpine and some other *Iboga* alkaloids (Scheme 6).



Scheme 6

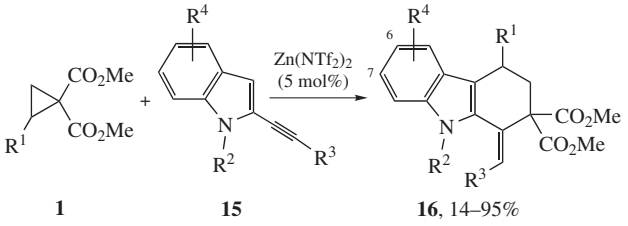
As an extension of approach to six-membered rings, Kerr *et al*. developed tandem ring opening/Conia-ene reactions of DA cyclopropanes with propargylamines[31] and propargylic alcohols[32]



Scheme 7

leading to piperidines **13** and tetrahydropyrans **14**, respectively (Scheme 7). The reaction, performing with enantiomerically pure cyclopropanes **1**, proceeded with complete inversion at the cyclopropane stereogenic center.

Very recently this approach was expanded to (3+3)-annulation of DA cyclopropanes to 2-alkynylindoles **15** providing carbazole derivatives **16** (Scheme 8).[33] Generally, substituent in the 2-alkynyl moiety, except an acceptor group, prevented cyclization, while methyl 3-(1-methylindol-2-yl)propynoate gave the corresponding carbazole in 95% yield.



1 **15** **16**, 14–95%

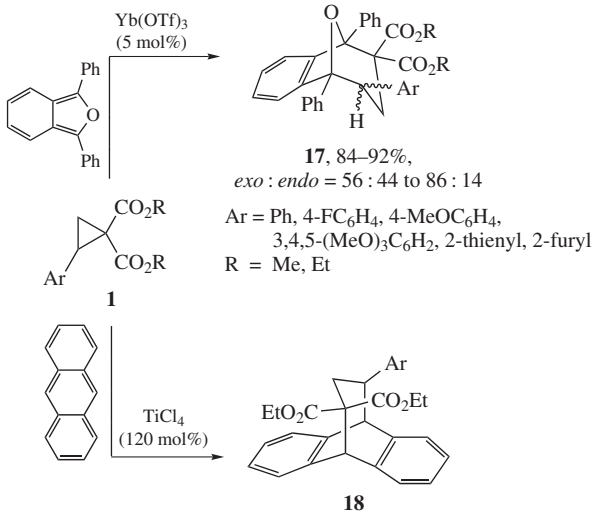
R^1 = Ph, 1,3-benzodioxol-5-yl, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$MeO_2CC_6H_4$, 4-NCC_6H_4, 2-furyl, 2-thienyl, 1-Ts-3-indolyl, PhCH=CH, CH_2=CH, H
R^2 = H, Me, Bn; R^3 = H, CO_2Me; R^4 = H, 7-CF_3, 7-CO_2Me, 6-Me

Scheme 8

(3+4)-Cycloaddition/annulation

a. Reactions with active 1,3-dienes

Based on the well-known analogy between reactivity of alkenes and cyclopropanes, our research group undertook an investigation of the Diels–Alder-like reaction between 1,3-dienes and DA cyclopropanes as dienophiles. 2-Arylcyclopropane-1,1-dicarboxylates **1** in $Yb(OTf)_3$-catalyzed reaction with 1,3-diphenylisobenzofuran were found to give (3+4)-cycloadducts **17** with the predominant formation of the less stable *exo*-isomers (Scheme 9).[34] Similar reaction occurred between anthracene and phenyl- or *para*-fluorophenyl-substituted cyclopropanes **1** which formed products of (3+4)-cycloaddition **18**.[35] Due to less reactivity of anthracene in comparison with 1,3-diphenylisobenzofuran, reaction with the former diene demanded utilization of more activating Lewis acid, such as $TiCl_4$ or $SnCl_4$.



17, 84–92%,
exo : *endo* = 56 : 44 to 86 : 14

Ar = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 2-thienyl, 2-furyl
R = Me, Et

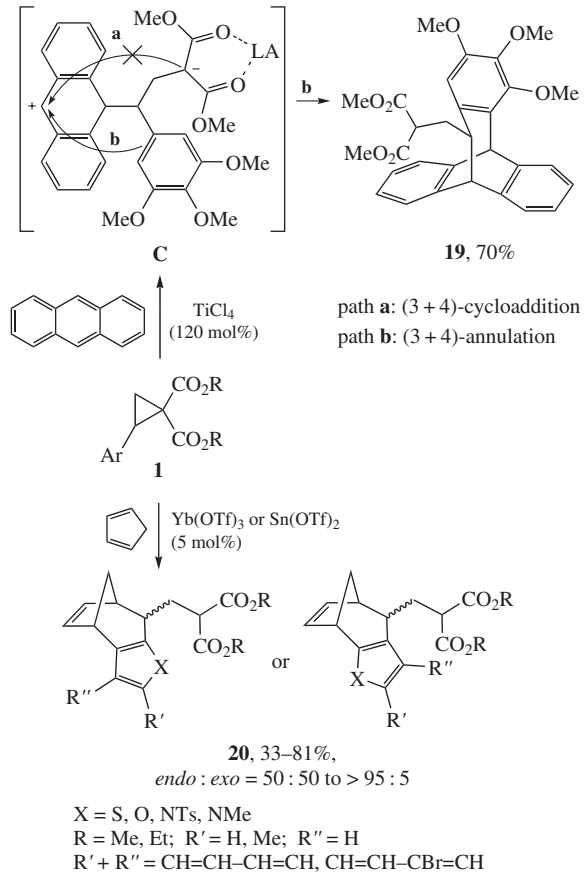
1

18

Ar = Ph (85%), 4-FC_6H_4 (72%)

Scheme 9

The increase in nucleophilicity of aromatic substituent, as it is in 3,4,5-trimethoxyphenyl group, directed the reaction of DA cyclopropanes with anthracene along (3+4)-annulation pathway providing product **19** (Scheme 10). This process occurs *via* two consecutive Friedel–Crafts reactions: 1) intermolecular alkylation of anthracene by the Lewis acid-activated DA cyclopropane yielding intermediate formation of **C** and 2) intramolecular alkylation of nucleophilic aromatic ring by cationic center in **C**. In case of diethyl 2-(2-thienyl)cyclopropane-1,1-dicarboxylate products of both (3+4)-cycloaddition and annulation were formed in 1:5 ratio.



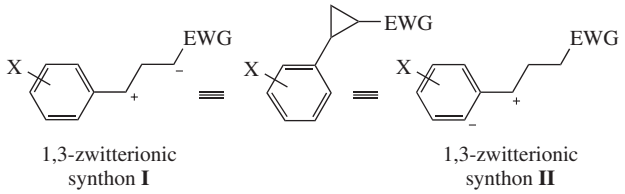
20, 33–81%,
endo : *exo* = 50 : 50 to > 95 : 5

X = S, O, NTs, NMe
R = Me, Et; R′ = H, Me; R″ = H
R′ + R″ = CH=CH–CH=CH, CH=CH–CBr=CH

Scheme 10

Analogous (3+4)-annulation was observed when 2-(2/3-heteroaryl)cyclopropane-1,1-dicarboxylates **1** reacted with cyclopentadiene furnishing products of **20** type (Scheme 10).[36] The strongly activating Lewis acids, such as $TiCl_4$ and $SnCl_4$, caused fast polymerization of cyclopentadiene even at low temperatures, while $Yb(OTf)_3$ and $Sn(OTf)_2$ were found to be efficient catalysts of this annulation. Reaction proceeded with excellent chemoselectivity and variable diastereoselectivity affording predominantly *endo*-isomers. Cyclopropanes, containing low-nucleophilic aromatic substituents, did not undergo this transformation. (3+4)-Annulation of DA cyclopropanes to cyclopentadiene provides convenient and efficient preparation of heteroarene-fused bicyclo[3.2.1]octadienes.

In above (3+*n*)-cycloadditions DA cyclopropanes react as synthetic equivalents of typical 1,3-zwitterionic synthon **I** (Figure 2). Oppositely, in (3+4)-annulations cyclopropanes demonstrate the principally different type of reactivity acting as synthetic equivalents of unusual 1,3-zwitterionic synthon **II**. To the best of our



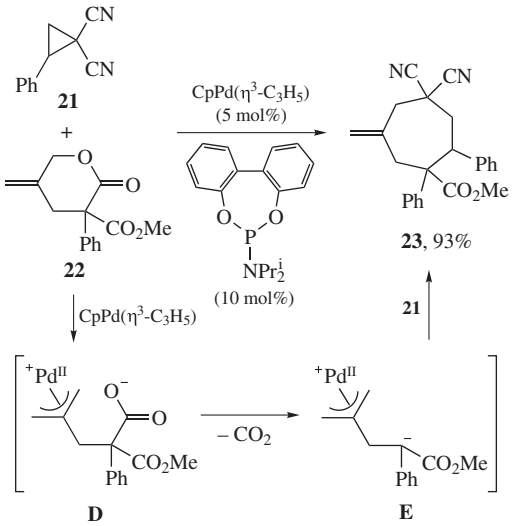
1,3-zwitterionic synthon **I** 1,3-zwitterionic synthon **II**

Figure 2 Two possibilities for ambiphilic reactivity of 2-aryl-substituted DA cyclopropanes.

knowledge, such untypical behavior has been previously found in two recyclization processes only.[37,38]

b. Decarboxylative (3 + 4)-annulation

Shintani and co-workers described palladium-catalyzed decarboxylative (3+4)-annulation between 2-phenylcyclopropane-1,1-dinitrile **21** and 5-methylidene-3-methoxycarbonyl-3-phenyltetrahydropyran-2-one **22** (Scheme 11).[39] This reaction proceeded *via* intermediate formation of allylpalladium complex **D** that was accompanied by decarboxylation. The resulting 1,4-zwitterionic species **E** interacted with **21** affording cycloheptane **23**. The replacement of phenyl group in **22** with less anion-stabilizing alkyl substituents prevented decarboxylation of **D** and led to formation of (6+3)-cycloadducts.

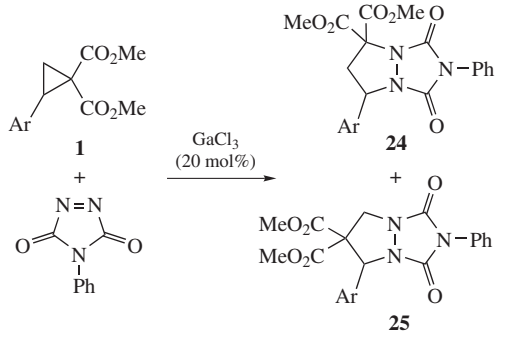


Scheme 11

Anomalous (3+2)-reactions with diazenes

a. Anomalous regiochemistry in reaction with N*-aryltriazolinedione*

Currently, N=N double bond is the only type of heteroatom–heteroatom bond successfully involved in (3+2)-cycloaddition with DA cyclopropanes. Thus, de Meijere and co-workers demonstrated that Lewis acid-induced reaction of various 2-arylcyclopropane-1,1-diesters **1** with *N*,*N*′-azodicarboxylates, phenyldiazenecarboxylate and azobenzene smoothly and regioselectively produced pyrazolidines.[40] An exception case was $GaCl_3$-catalyzed reaction between **1** and *N*-aryltriazolinedione affording the mixtures of 'normal' (3+2)-cycloadducts **24** and their regioisomers **25**. No interconversion of **24** and **25** was observed, that allowed authors to proposed formation of **24** and **25** along independent pathways. Additional experiments with enantiomerically pure cyclopropanes **1** allowed for supposition the following pathways. Namely, **24** was formed *via* initial interaction of *N*-aryltriazolinedione as a nucleophile with electrophilic center of ring-opened 1,3-zwitterionic form [Figure 1(*b*)] of parent cyclopropane **1** followed by 1,5-cyclization. This stage sequence is typical of most DA cyclopropane cycloadditions. In case of **25** formation, cyclopropane **1** was hypothesized to turn the table on diazene. Here, cyclopropane reacted as a nucleophile against electron-deficient N=N bond of diazene, which was added to the less sterically hindered methylene group of **1**. Following coupling of nucleophilic nitrogen and benzylic cation resulted in **25**. The anomalous cyclopropane ring opening, leading to **25**, is the only example of such reactivity of 2-arylcyclopropane-1,1-diesters hitherto.



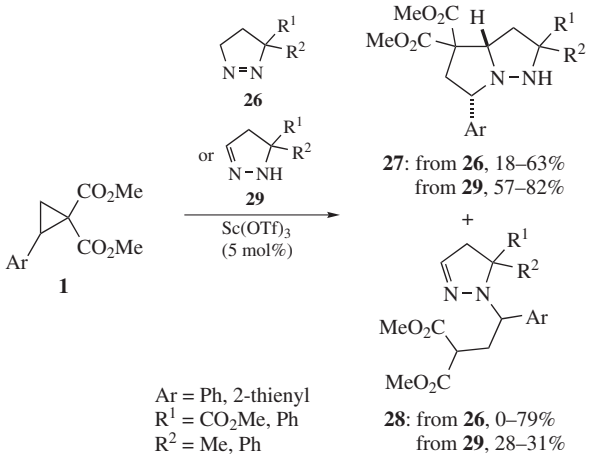
Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4

Yields of **24** + **25**, 55–67%
24 : **25** ratios of 1 : 1.5 to 1 : 3

Scheme 12

b. Unusual reactivity of Δ^1*-pyrazolines*

Another example of abnormal reactivity of diazenes towards DA cyclopropanes was reported recently by Tomilov and co-workers.[41] Mostly depending on the Lewis acid applied, reaction of **1** with Δ^1-pyrazolines **26** led to two types of products: perhydropyrrolo-[1,2-*b*]pyrazoles **27** and products of N-alkylation **28** (Scheme 13). Actually, compounds **27** were (3+2)-cycloadducts of interaction between cyclopropanes **1** and Δ^2-pyrazolines **29**, which were formed as a result of considerable tautomerization of **26** in the presence of Lewis acid. The direct reaction of **29** with **1** produced **27** in even higher yields.



Ar = Ph, 2-thienyl
R^1 = CO_2Me, Ph
R^2 = Me, Ph

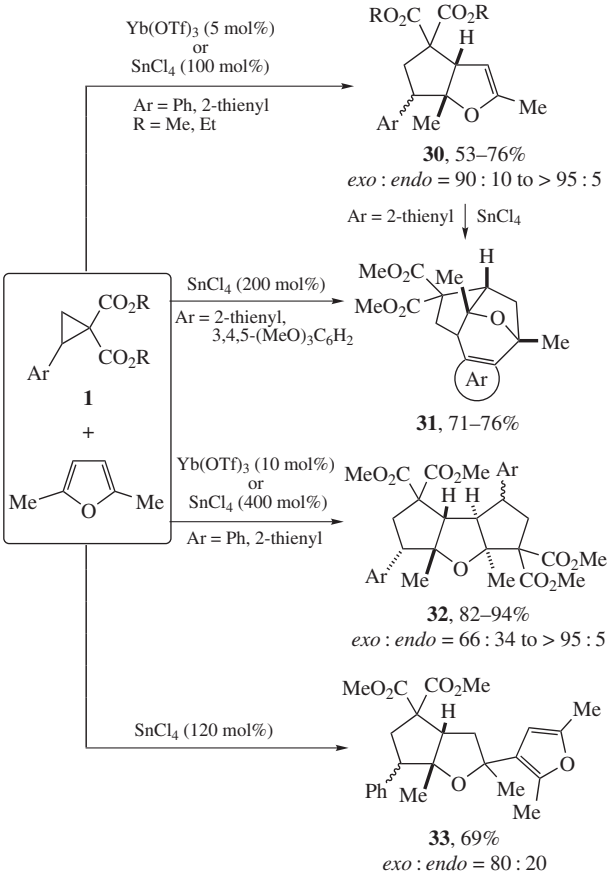
Scheme 13

(3+2)-Cycloaddition/annulation to aromatic heterocycles

To date, cycloaddition/annulation reactions between DA cyclopropanes and (hetero)aromatic compounds has been only scarcely studied, except ring-forming reactions with indole derivatives.[5,42]

a. Reactions with furans

Being aromatic compounds, furan and its derivatives meanwhile demonstrate diene-like behavior as 2π- or 4π-component in reactions with dipoles. As have been mentioned above, 1,3-diphenylisobenzofuran gave (3+4)-cycloadducts **17** in reaction with DA cyclopropanes **1** (Scheme 9). Oppositely, $Yb(OTf)_3$ or $SnCl_4$ initiated reaction of 2,5-dimethylfuran with DA cyclopropanes **1** yielding products of (3+2)-cycloaddition **30** (Scheme 14).[43] The presence of reactive enol ether fragment in **30** provided secondary processes under appropriate conditions. Utilization of more activating $SnCl_4$ for cyclopropanes, containing highly nucleophilic 2-thienyl and 3,4,5-trimethoxyphenyl substituents, induced intramolecular Friedel–Crafts alkylation within **30** leading to the non-trivial cage compounds **31**. When excess of **1** was used, products of double (3+2)-cycloaddition **32** were obtained; while with excess of 2,5-dimethylfuran, the initially formed **30** attacked the second furan molecule yielding product of Friedel–Crafts alkylation **33**.

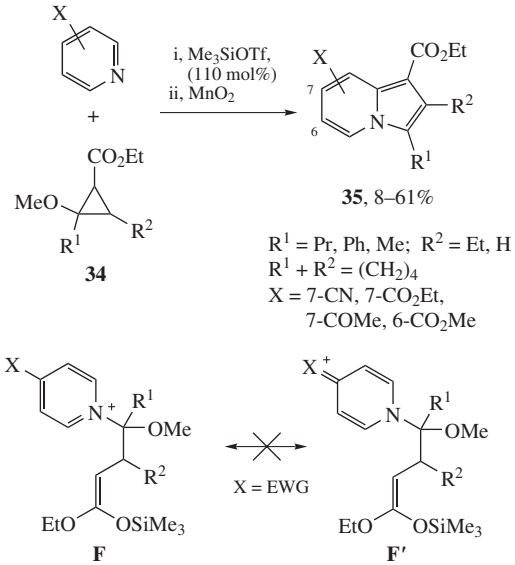


Scheme 14

Reactions of **1** with 2,5-dimethylfuran proceeded in high chemo- and regioselective manner. Adducts **30** were formed through attack of C(2) cyclopropane carbon atom onto α-position of furan ring and C(1) atom onto β-position. The opposite regiochemistry was observed for addition of the second cyclopropane molecule to **30** leading to tricyclic compounds **32**. This result is in a good accordance with well-known fact, that electrophiles selectively attack α-position of furan and β-position of enol ethers.

b. (3 + 2)-Annulation with pyridines

Recently Pagenkopf and co-workers described an interesting example of (3 + 2)-annulation of 2-alkoxycyclopropanecarboxylates **34** to C(1)–C(2) bond of pyridines producing indolizines **35**

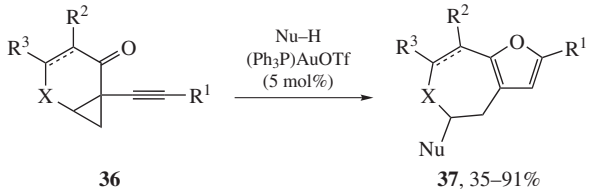


Scheme 15

(Scheme 15).[44] The same interaction of quinolines with **34** led to benzoindolizine derivatives. The particularity of this process was necessity to employ acceptor-substituted pyridines and quinolines acting as nucleophiles. Authors explained this seeming contradiction by the following mechanistic speculations. Despite acceptor group makes unfavorable a nucleophilic attack of pyridine leading to intermediate **F** at the first stage, this group accelerates the second stage which is crucial for the process in whole.

Alkynylcyclopropyl ketones in highly substituted furan synthesis

Transition-metal catalyzed cyclization of 3-alkyn-1-ones and related compounds into furan derivatives is known for at least 20 years.[45,46] However, in 2006 J. Zhang and H.-G. Schmalz demonstrated that combination of these functionalities and cyclopropane ring opens broad possibilities for synthesis of new cyclic compounds.[47] Thus, reaction of 1-alkynylbicyclo[n.1.0]alkan-2-ones **36** with various nucleophiles allowed for the synthesis of condensed ring systems **37** through Au-catalyzed ring expansion (Scheme 16).



R^1 = Ph, 1-cyclohexenyl, cyclopropyl, Bu, H, TMS
$R^2 = R^3$ = H; $R^2 + R^3$ = CH=CH–CH=CH
X = CH_2, $(CH_2)_2$, O
Nu = MeO, Pr^iO, Bu^iO, $PhC{\equiv}CCH_2O$, 4-$MeOC_6H_4O$, AcO, 3-indolyl

Scheme 16

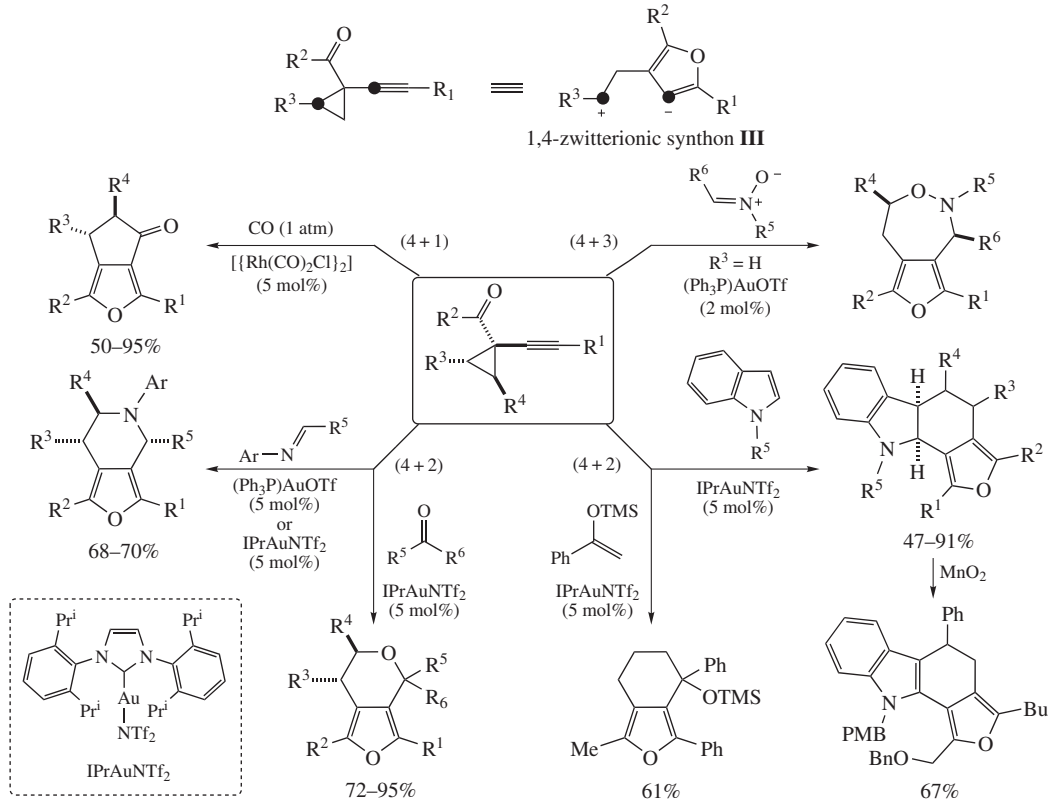
Retrosynthetic analysis of structures **37** elucidates that in this process compounds **36** behave as synthetic equivalents of 1,4-dipolar synthon of **III** type (Scheme 17). The same reactivity of alkynylcyclopropyl ketones was revealed during their further investigation. Thus, J. Zhang group performed (4 + 1)-annulation of such cyclopropanes with CO,[48] (4+2)-annulation with imines,[49] (4+3)-annulation with nitrones[50] (Scheme 17). Independently, L. Zhang and co-workers demonstrated possibility to involve indoles, carbonyl compounds and silyl enol ethers in the same (4+2)-annulation.[51]

Cyclodimerization of DA cyclopropanes

Cyclodimerizations are interesting transformations in organic chemistry as they allow for significant increase of structure complexity starting from one simpler compound. Cyclodimerizations of the three-membered carbocycles are almost unknown despite their high potential for preparation of various cyclic molecules. The presence of both nucleophilic and electrophilic centers in DA cyclopropane molecules implies the possibility of their self-condensation, such as dimerization, oligo- and polymerization. However, the results of systematic study of DA cyclopropanes dimerization did not appear in literature until this year.

a. (3 + 3)-Cyclodimerization

During the course of our study concerning DA cyclopropane reactivity, cyclopropane-1,1-diesters **1**, substituted with highly nucleophilic (hetero)aromatic groups, were found to undergo (3+3)-cyclodimerization reaction yielding various six-membered ring systems (Scheme 18).[52] Depending on the reaction conditions and substituents in the parent cyclopropane, this cyclodimerization proceeds *via* three different routes, that provides new straightforward one-step accesses to highly substituted derivatives of *cis*-1,4-diarylcyclohexanes **38**, 1-aryl-1,2,3,4-tetrahydronaphthalenes **39** or 9,10-dihydroanthracenes **40**.



Scheme 17

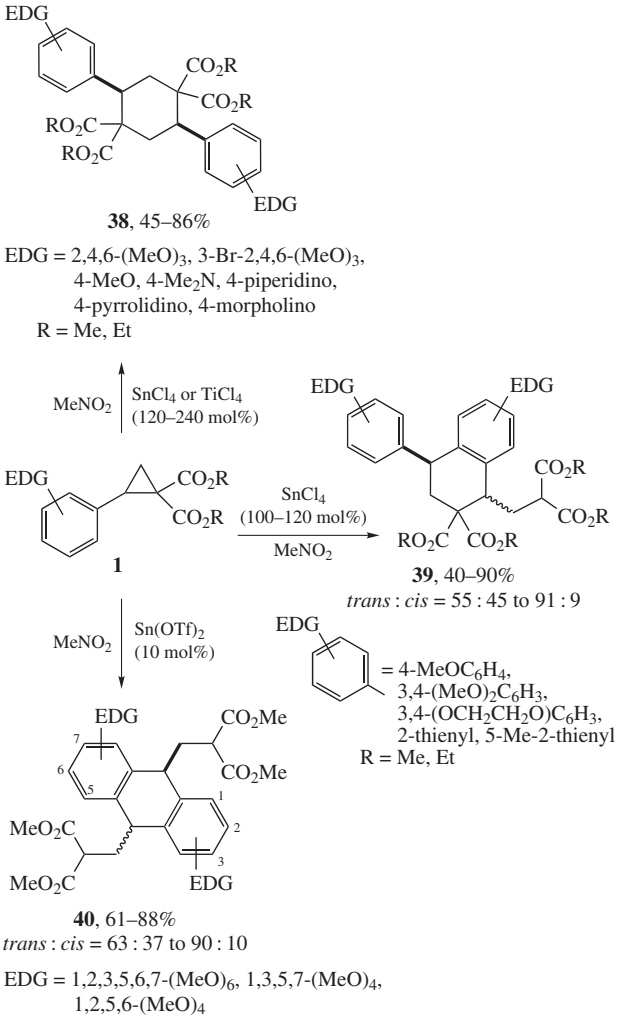
Thus, the treatment of 4-(dialkylamino)phenyl- or 2,4,6-trimethoxyphenyl-substituted cyclopropanes **1** with strongly activating $SnCl_4$ or $TiCl_4$ in polar nitromethane afforded cyclohexane derivatives **38** through cyclopropane ring opening into 1,3-zwitterion **G** followed by crosswise coupling of cation and anion centers of two species **G** (paths **a**, **b** in Scheme 19). In this process both DA cyclopropane molecules reacted as synthetic equivalents of synthon **I** (Figure 2). Stepwise mechanism *via* intermediate formation of zwitterion **H** was supported by isolation of acyclic dimeric alkenes under non-optimized reaction conditions.

Cyclodimers **39** were obtained from DA cyclopropanes **1**, containing thienyl, 4-methoxy and 3,4-dialkoxyphenyl groups as donor substituents (Scheme 18). Formation of **39** was proposed to proceed *via* the same zwitterion **H** which underwent intramolecular Friedel–Crafts alkylation. The efficiency of the latter process is enhanced with increase in nucleophilicity of aromatic substituent (paths **a**, **c** in Scheme 19). In this (3 + 3)-cyclodimerization DA cyclopropanes demonstrate dual behavior as synthetic equivalent of synthons of both **I** and **II** types (Figure 2).

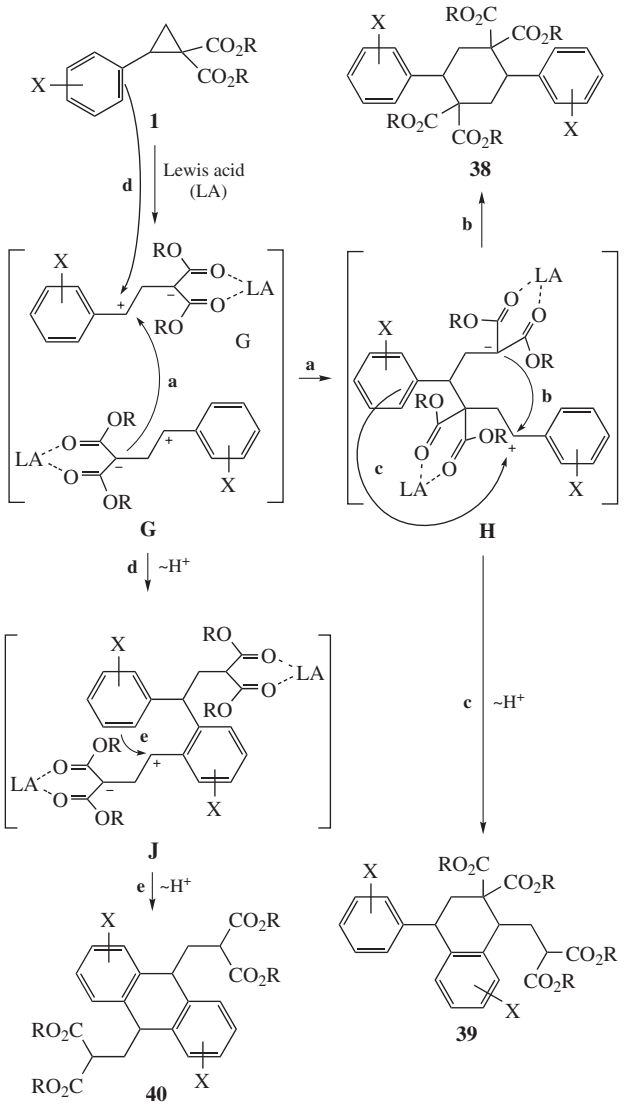
The further increase in nucleophilicity of aromatic substituent, as it is in 2,3- or 3,5-dimethoxy- or 3,4,5-trimethoxyphenyl groups, leads to new alteration of chemoselectivity of (3+3)-cyclodimerization towards 9,10-dihydroanthracenes **40** formation. Strongly activating $SnCl_4$ as well as moderately activating $Sn(OTf)_2$ was found to be well-proven promoters. This process proceeds through the attack of electrophilic center of zwitterion **G** onto *ortho*-position of aromatic ring in the second molecule of **1** followed by the second three-membered ring opening with formation of zwitterion **J** (path **d**, Scheme 19). The cyclodimerization is completed by intramolecular Friedel–Crafts alkylation leading to **40** (path **e**). Therefore, in this reaction DA cyclopropanes participate as synthetic equivalents of synthon **II** (Figure 2).

b. Domino-cyclodimerization of indole-derived cyclopropane-1,1-diesters

On the contrary to other nucleophilic arenes, 3-substituted indoles are prone to electrophilic attack at *ipso*- but not *ortho*-position.



Scheme 18



Scheme 19

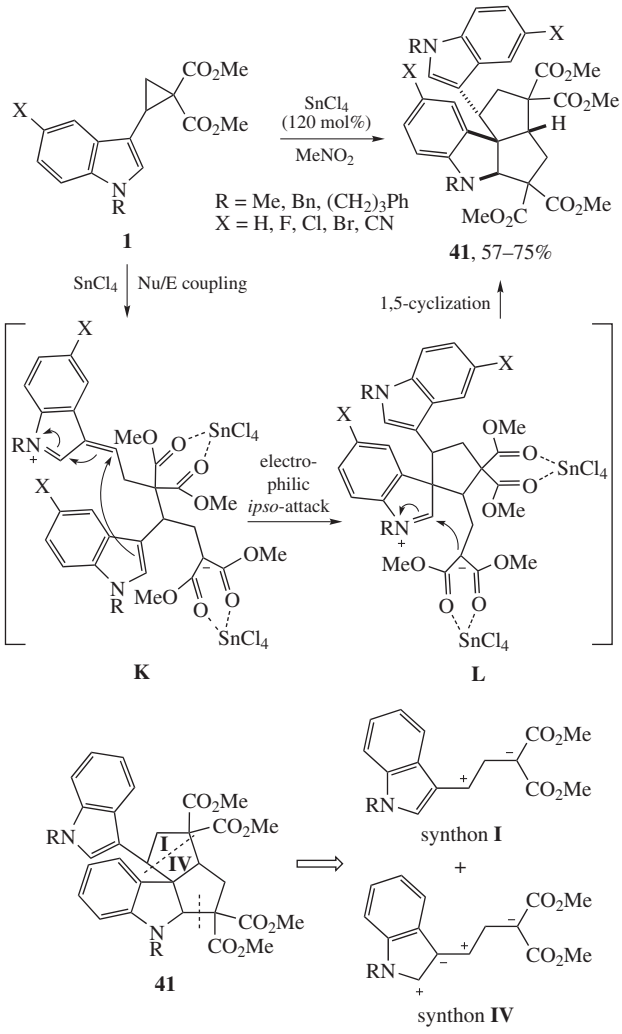
Such particularity provides new direction of cyclodimerization for 3-indole-derived DA cyclopropanes. Thus, 2-(1-alkylindol-3-yl)cyclopropane-1,1-dicarboxylates were recently found to undergo $SnCl_4$-induced cyclodimerization affording polycyclic compounds **41** with unprecedented pentaleno[1,6a-*b*]indole scaffold (Scheme 20).[53] The first stage of the reaction, generating dimeric zwitterion **K**, is analogous to path **a** in Scheme 19, whereas following electrophilic attack within **K** is directed towards *ipso*-position of indole substituent, in contrast to above *ortho*-attack in **H** and **J**, furnishing naphthalenes **39** and anthracenes **40**, respectively. Construction of pentaleno[1,6a-*b*]indole skeleton of **41** is completed by 1,5-cyclization in **L**. During this cyclodimerization, the formation of two rings, three C–C σ-bonds and four stereogenic centers occurs with exceptionally high chemo-, regio- and stereoselectivity. In this reaction the DA cyclopropanes demonstrate a conceptually new type of reactivity (synthon **IV**) with participation of four reaction sites: two nucleophilic [C(1) atom of cyclopropane and C(3) atom of indole] and two electrophilic [C(2) atom of cyclopropane and C(2) atom of indole] centers.

c. (3 + 2)-Cyclodimerization

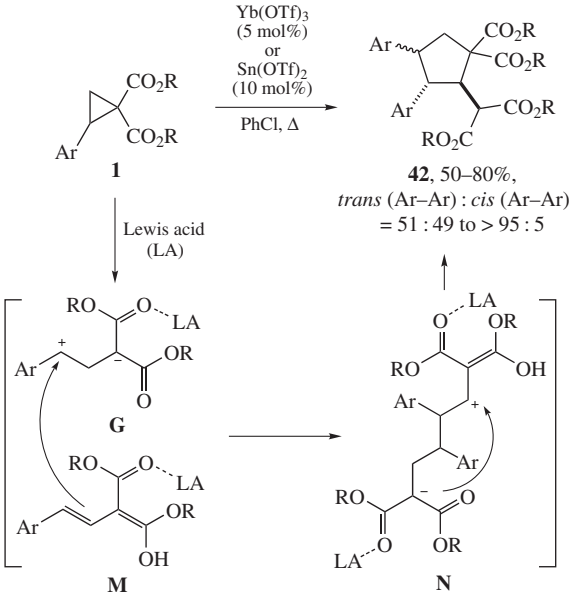
As contrasted to above (3+3)-cyclodimerizations, unusual (3+2)-cyclodimerization of DA cyclopropane **1** represents a general convenient approach to highly functionalized cyclopentanes **42**. The formation of cyclodimers **42** proceeds for DA cyclopropanes, containing aromatic substituents with wide spread in donating ability, under catalysis with moderately or weakly activating Lewis acids in low polar chlorobenzene under reflux.[54] The possible mechanism includes Lewis acid-induced cyclopropane ring opening with formation of 1,3-zwitterion **G** and its transformation into dienol **M**. The interaction of **M** with electrophilic center of another intermediate **G** yields new zwitterionic species **N** which undergoes 1,5-cyclizations into cyclopentanes **42** (Scheme 21). In this reaction DA cyclopropanes demonstrate both typical reactivity umpolung acting as synthetic equivalents of 1,3-zwitterionic synthon **I**, and unusual for cyclopropanes, 'normal' reactivity, working as synthetic equivalents of synthons **V** and providing only two-carbon unit for the newly formed ring.

Independently, Tomilov and co-workers reported the same (3+2)-cyclodimerization of **1** into **42** proceeding at room temperature when 1.2 equiv. of $GaCl_3$ was applied for reaction initiation.[55] The replacement of $GaCl_3$ by less activating complexes $GaCl_3$·THF (1 equiv.) or $SnCl_4$·THF (2 equiv.) induced (3+3)-cyclodimerization of **1** into tetraline of **39** type or its oligomeric analogues (Scheme 22).

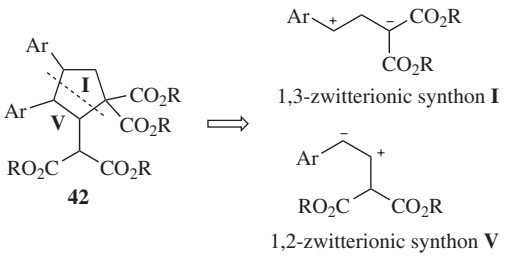
To conclude, the synergism of three-membered ring and functional groups of an opposite electronic effect, joint in a DA cyclopropane molecule, significantly expands the reactivity of these compounds. Along with 'classical' reactions with electrophiles, nucleophiles, radicals, oxidizing and reducing agents, these substrates participate efficiently in (3+2)- and (3+3)-cycloaddition/annulation reactions. Moreover, a large number of new transformations of DA cyclopropanes were disclosed during the last few years, most of them being ring expansion processes, such as new types of (3+*n*)-cycloaddition/annulations, various types of



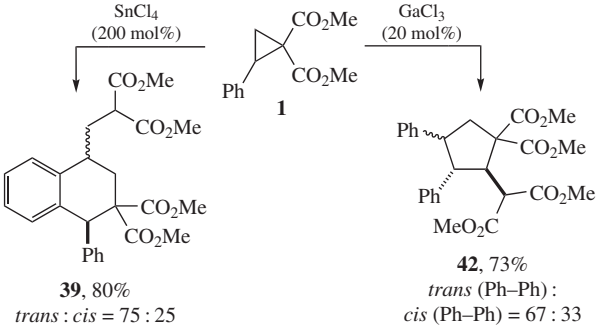
Scheme 20



Ar = Ph, 2-thienyl, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2,4,6-$(MeO)_3C_6H_2$, 4-$Me_2NC_6H_4$, 4-pyrrolidinophenyl, 4-morpholinophenyl
R = Me, Et



Scheme 21



Scheme 22

dimerizations and domino reactions. Among these reactions, there are processes wherein DA cyclopropanes demonstrate conceptually new types of reactivity. The discovery of these untypical reactions enlarged significantly the scope of DA cyclopropanes transformations that allows one to expect a splash of interest in chemistry of these compounds in the nearest future. Due to their multifacet reactivity, high efficiency of the most of their reactions, excellent chemo- and regioselectivity, high stereoselectivity, DA cyclopropanes provide, similarly to magic wand in hands of synthetic chemists, simple and efficient approaches to complex organic molecules.

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