New potentialities of electrophilic addition in the assembly of polyfunctional compounds from simple precursors

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A novel methodology of the multicomponent coupling based on the controlled sequence of the kinetically independent electrophilic additions is suggested and its promise as an efficient protocol for the short synthesis of the structurally diverse polyfunctional compounds from simple precursors is demonstrated.

Key words: multicomponent coupling, sequence of Ad_E reactions, cationoid intermediates, episulfonium ions, thiophanium ions, dicobalthexacarbonyl complexes of alkynes, Pauson—Khand reaction, aldol cross condensation, diastereoselectivity, vinyl ethers.

1. Introduction

One of the major trends in the strategy of the modern organic synthesis envisages the utilization of the controlled reaction sequences leading to the one-pot formation of several carbon—carbon bonds, which results in a rapid increase in the complexity of the assembled structure and hence to a dramatic shortening of the synthetic schemes. A detailed presentation of the main principles of this methodology and a set of impressive examples showing its efficiency can be found in a number of recent reviews and monographs.[1a—g]

Two limiting types, 1 and 2, of such reaction sequences could be easily identified. In the type 1 all steps are performed as intramolecular transformations of the polyfunctional substrate, while type 2 is based on the consecutive one-pot intermolecular reactions with the sequential introduction of reacting partners into reaction medium.

Quite a number of different reactions can be empolyed as the C—C bond forming elementary steps in the type 1 sequences (often called "domino reactions"). This list may include such reactions as electrophilic, nucleophilic, or radical additions, pericyclic reactions, rearrangements or transition metal catalyzed transformations as well as various combinations of these steps. The efficiences of the use of these types of intramolecular transformations as the key steps in the total synthesis of the polycyclic compounds is well-documented.[1a—e] As an illustration the synthesis of progesterone with the help of intramolecular cationic polyolefin cyclization is shown in Scheme 1.[2] However, it is noteworthy that the synthetical usefulness and scope of the type 1 sequences is limited due to the necessity to synthesise the required polyfunctional precursors, the task which might be rather troublesome. For example, the key step of the above synthesis of progesterone proceeds as a concerted sequence of three intramolecular Ad_E reactions, leading to the formation of three novel C—C bonds in the newly formed tetracyclic system as a result of the single synthetic operation. However, the preparation of the polyenic substrate used as a starting material in the cyclization turned out to be a rather tedious problem and its step-by-step synthesis included about a dozen of separate transformations.

Type 2 sequences (called also "tandem reactions") represent actually the one-pot assembly of the complicated molecular structure from simple precursors. Synthesis of C—D fragment of the steroid framework shown in Scheme 1 is a typical example of this approach.[3a]

Realization of the type 1 transformations does not necessarily imply the formation of stabilized intermediates at each step of the overall sequence.*

On the contrary, the type 2 sequences are feasible only upon the condition that every elementary step of the overall conversion results in the formation of the *kinetically stable discrete intermediate* which serves as the substrate to interact with the next reacting partner added to the reaction mixture.**

* For example, in the afore-mentioned synthesis of progesterone the formation of tetracyclic system occurs in accordance with the mechanism of the concerted process and presentation of the latter as a sequence of the separate steps Ad_E-I—Ad_E-III with the formation of the respective intermediates I_{cat}^{I}—I_{cat}^{III} is a mere convention.

** It is appropriate to comment that in the absence of such stabilization the net result of the series of intermolecular additions across the double bonds of unsaturated substrates would be the formation of the oligomers. This result is well-familiar for a number of reactions initiated by cationic, anionic, or radical reagents.

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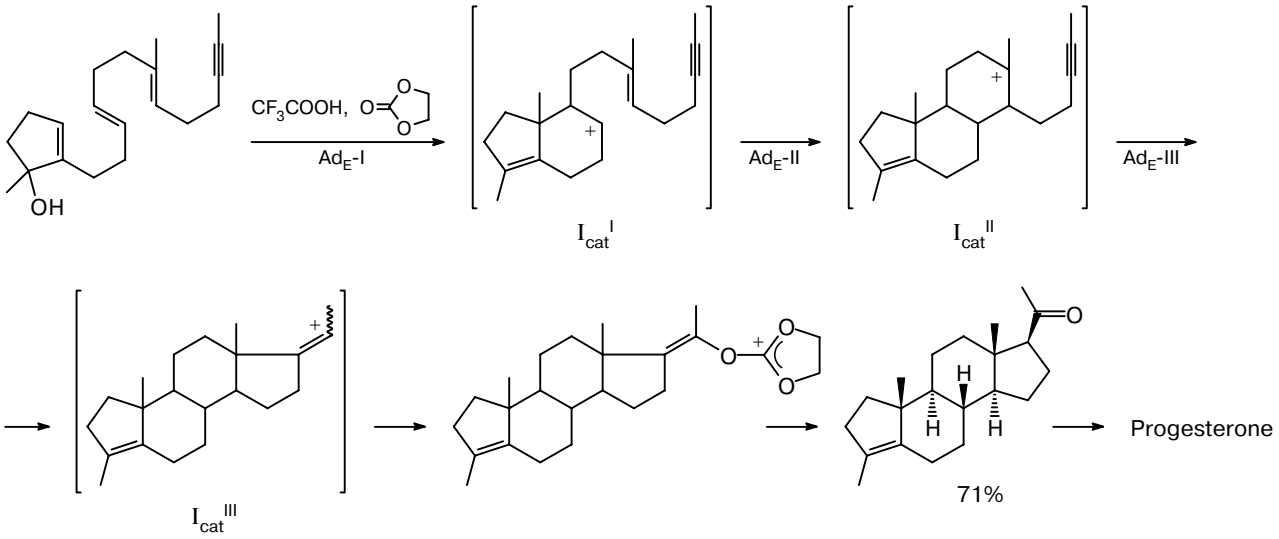
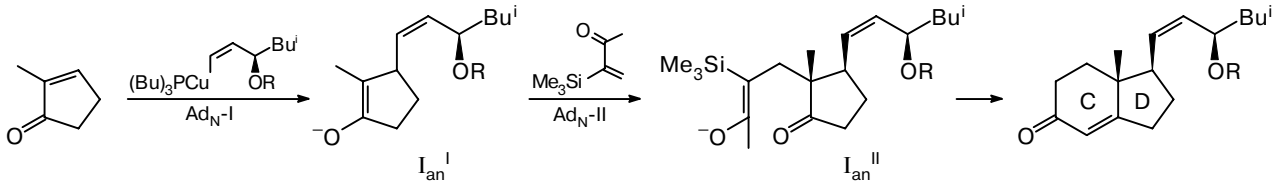
Scheme 1

Type 1: sequence of intramolecular reactions



Type 2: sequence of intermolecular reactions



It is to be emphasized that it is exactly the enhanced stability of the carbanionic-like intermediates of various structure which made it possible to employ widely Ad_N reaction as the key step in the intermolecular sequential transformations as is exemplified in Scheme 1 (*e.g.*, Ad_N-I and Ad_N-II, intermediates I_{an}^{I} and I_{an}^{II} respectively)[1a–c,f,g,3a,b]. In fact, more than a dozen of the compound types could be used as the unsaturated substrates in similar sequences and the nature of both the starting nucleophilic reagent and electrophile used for the quenching of the carbanionic intermediates could be varied independently and within a very broad limits. Basically this is the underlying reason, which explains why the *intermolecular Ad_N reactions* are so widely employed in the convergent schemes of the tandem synthesis[1g,3a,b].

Amazing as it may seem, but in the vast literature dealing with various aspects of the tandem transformations[1a–g] it is hard to find even a hint at the opportunity to elaborate the schemes alternative to the above-mentioned, namely, based upon the utilization of intermolecular Ad_E reactions as the elementary steps in the multicomponent coupling, though the synthetic promise of the latter approach seems to be obvious.*

Below are presented the results of our studies in this field which have been carried out in the groups of W. A. Smit in the Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences and Ron Caple at the University of Minnesota, Duluth within the frame of the cooperative Russian-American joint research program.

2. Two-step mode of electrophilic addition

2.1. General concepts

It was obvious that the utilization of Ad_E reaction as an elementary step in the controlled sequence of intermolecular additions (type 2 sequences) implies that this reaction is carried out as a sequence of kinetically independent steps of addition of electrophile and nucleophile *via* an intermediate formation of the stabilized cationic species. Therefore our initial research efforts were centered at the study of the general problem connected with the separation of the steps of the overall Ad_E reaction.

It is well-known that the classic Ad_E-mechanism envisages that the first step of the reaction involves an interaction of an electrophile with π-electrons of alkene or alkyne molecule, resulting in the formation of the cationic intermediate (I_{cat}) which is capable of reacting further with nucleophilic partner to give the final cova-

* On the contrary, the sequence of the *intramolecular* Ad_E reactions represents a well-established synthetic protocol widely applicable for the preparation of various types of polycyclic compounds (*e.g.*[4a,b] and references cited therein).

lent adduct.[5] This mechanism turned out to be an extremely useful description to account for the observed rate dependences as well as product selectivity, stereoselectivity and regioselectivity patterns of the manifold of various reactions belonging to the type under consideration. Yet it should be emphasized that for the Ad_E reaction carried out under conventional conditions (that is, with the use of the covalent or slightly polarized reagent and in the presence of the active nucleophiles like counterions or solvent molecules), there are no truly compelling reasons to expect the formation of the intermediates of the true cationoid type as kinetically independent species.*

A rather dramatical change of the situation occurred owing to the elaboration of the novel procedure to carry out Ad_E reactions using cationoid-like reagents under non-nucleophilic conditions.**

However, as was amply demonstrated in our initial studies, even under these conditions the stepwise course of the Ad_E reaction with the formation of I_{cat} as kinetically indendent species could be observed only in the cases when additional factors are operating capable of enhancing the stability of these intermediates.***

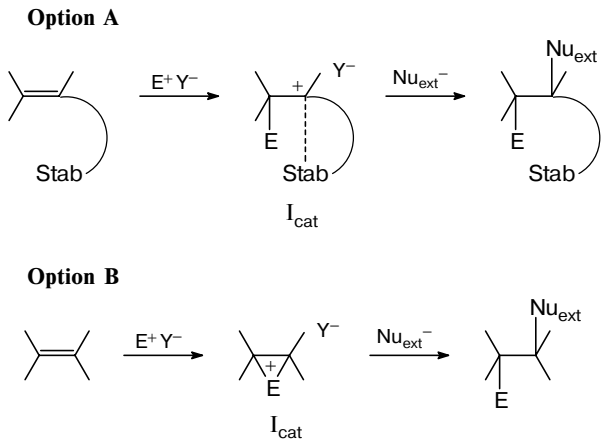
In fact, we have found that under conventional conditions (*i.e.*, not in the superacidic media and at not very low temperature) there are two limiting cases in order to achieve an efficient stabilization of I_{cat}. The first case (option A, Scheme 2) implies the utilization of the substrates bearing the moiety capable of stabilizing the adjacent carbocationic center. An alternative opportunity envisages the use of the electrophilic agents which can stabilize the I_{cat} thanks to the formation of the bridged onium species (option B, Scheme 2).[8a,9]

Below we are going to present the results of our studies aimed at the elaboration of the synthetically useful protocols based on the alternative approaches outlined in Scheme 2.

2.2. Stabilization of the cationoid intermediate owing to the presence of the cation-stabilizing group in the molecule of the starting alkene

The abiltiy of structurally diverse fragments to serve as the efficient stabilizing groups for the adjacent

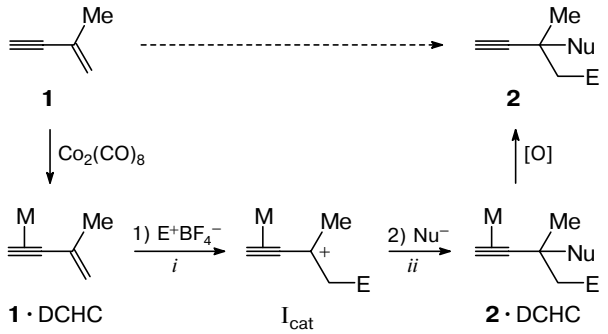
Scheme 2



carbocationic center is well-documented (*e.g.*, data in monograph[7]). Among a number of possible candidates for this role we have chosen μ-alkyne dicobalt hexacarbonyl (DCHC) complexes due to the following reasons: (1) these complexes could be easily prepared from alkynes of any types including conjugated enynes; (2) the formation of DCHC complex is known to be an efficient method to protect the alkyne moiety against the action of various type of the reagents and (3) the DCHC-complexed propargyl cations represent the type of the cationoid species quite stable under ordinary conditions and at the same time sufficiently reactive in the reactions with various nucleophiles (see, for a review Ref. 10).

A viability of the utilization of the conjugated enynes as the substrates in Ad_E reactions with cationoid electrophiles was checked for the reactions of DCHC complex of isopropenylacetylene (**1** · DCHC) taken as a model example (Scheme 3).[11]

Scheme 3



M = $Co_2(CO)_6$; E^+ = $MeCO^+$, *E*-MeCOCH=CHCO$^+$, Me_3C^+, 1-Ad$^+$, ArS^+, NO_2^+; Nu^- = HO^- or MeO^-. Yield **2**: 55—94%.

i. Step 1; *ii.* Step 2.

The above transformations provided a clear cut evidence attesting to the opportunity to carry out Ad_E

* In this connection it is appropriate to quote an old (but probably not totally invalid as yet!) statement of one of the main proponents of the electronic descriptions in organic chemistry, Sir Robert Robinson: "...I have no objections to carbonium ions being written down so long as you know that they do not exist. They are simply a useful summary of the concerted processes." [6]

** General data pertinent to the generation and reactivity pattern of the carbocationic reagents could be found in monograph[7] and references cited therein.

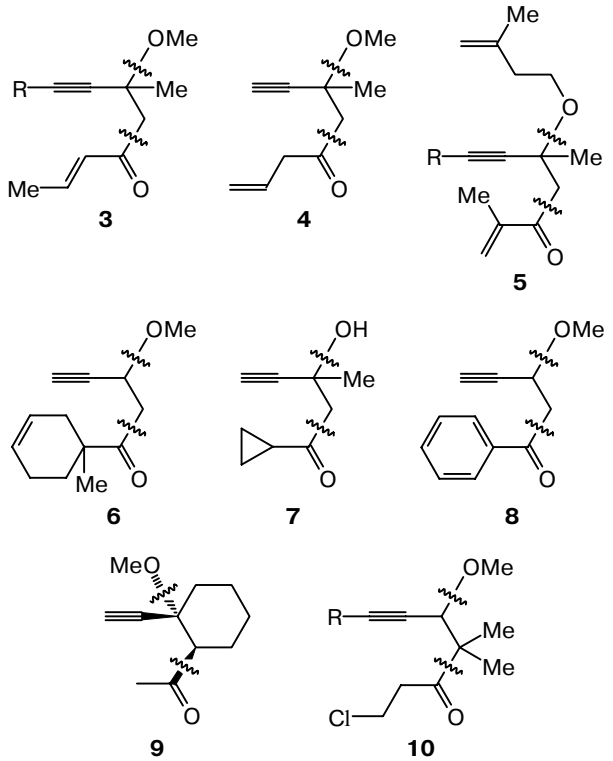
*** The formulation of the concept and analysis of the ample experimental evidence in its support is given in the review.[8a] Problems associated with the formation of 1 : 1 adducts in the reactions of carbocations with alkenes are also considered in Ref. 8b.

reaction with a fairly diverse set of electrophiles across the double bond of the **1** · DCHC complex as a sequence of two independent chemical events, namely electrophile addition leading to the formation of the stable cationoid intermediate I_{cat} followed by the interaction of the latter with the added external nucleophile.[11] The **2** · DCHC complexes thus prepared could undergo further oxidative decomplexation to yield adducts **2**, derived *via* a formal addition of the respective electrophiles and nucleophiles to the double bond of the starting enyne **1**.

It is noteworthy that the reaction shown in Scheme 3 represented actually the first example of the two-step Ad_E reaction mode that secured the possibility of the independent variations of the addends nature. It is also noteworthy that prior to these results it was nearly impossible to carry out the selective 1,2-addition across the double bond of a conjugated enyne, since the Ad_E reactions of the latter generally proceeded non-selectively producing the mixture of 1,2-, 1,4- and 3,4-adducts.[12]

In a similar way other conjugated enynes were shown to undergo the selective 1,2-addition across the double bond. A representative set of the prepared adducts **3—10** given in Scheme 4 may serve also as illustration of some additional opportunities to vary the nature of the electrophiles and nucleophiles which could be involved into this reaction.[13a—c]

Scheme 4



R = Me, TMS

Yields: 63—94%.

Of special interest are the transformations shown in Scheme 5[14a,b]. In fact these reactions were carried out with the use of the stabilized carbocationic reagents such as salts of acyl, *tert*-butyl, 1-adamantyl cations, DCHC-complexed propargylic cations or α-thiostabilized cations as carbon electrophiles (E_C) while silyl enol ethers or allyl silanes were employed as carbon nucleophiles (Nu_C). For this kind of the addend combination the net outcome of the Ad_E reaction with DCHC complexes corresponds to the *1,2-addition of carbon electrophile and carbon nucleophile across the double bond of the conjugated enyne resulting in the formation of two novel C—C bonds* (*e.g.*, structures **11—16**). This outcome which is a rather trivial result for quite a number of Ad_N reactions (see, for examples data in monograph[1g]) had never been observed earlier for the intermolecular Ad_E reactions carried out under classic conditions (*i.e.*, without the separation of the steps)*.

The above results demonstrated the synthetic potential of the stepwise Ad_E reactions with DCHC enyne complexes as a method for *one-pot assembly of the polyfunctional alkyne derivatives from three simple precursors*. The diversity of the functional pattern of the prepared adducts attests to the generality of the scope of the elaborated protocol. Thus, β-ethynylsubstituted ketones formed as a result of acylation (Schemes 3 and 4) can contain fragments bering double bonds at the α,β- (adducts **3** and **5**), β,γ- (adduct **4**) or γ,δ- (adduct **6**) positions as well as the cyclopropane residue (adduct **7**) or aromatic ring (adduct **8**).

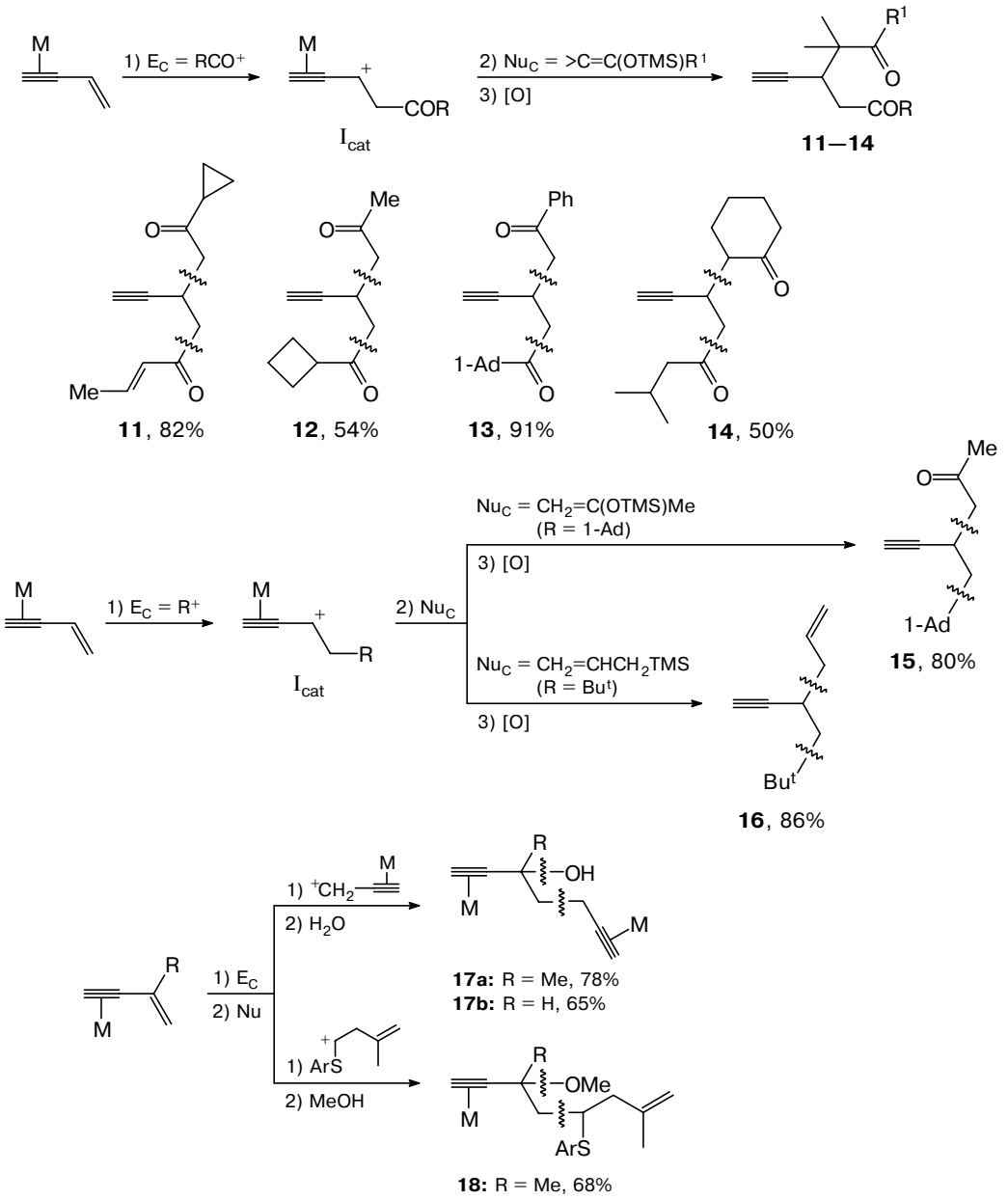
Of special synthetic value is the disclosed opportunity to employ the suggested procedure for the preparation of the unsymmetrically substituted 3-ethynyl-1,5-diketones (adducts **11—14**, Scheme 5) which are difficult to prepare with the help of traditional methods. The preparative promise of the reaction with the use of the stabilized carbenium ion-like reagents is well illustrated by the efficient preparation of the adducts such as ketone **15** or 1,5-enyne **16** or DCHC complexed 1,6-diynes (**17a,b**) or 1,7-enynes (**18**).

The immediate result of the desrcibed three-component coupling is the formation of the DCHC complexed adducts. Hence in the search of the options for their synthetic application it seemed expedient to consider firstly the pathways which envisaged the utilization of this fragment as a reacting functionality. Among a number of the transformations of this type we have chosen alkyne-alkene-carbonyl [2 + 2 +1] cycloaddition (Pauson—Khand reaction, see the review[16]), as the most promising option. Intramolecular version of this reaction shown in Scheme 6 can be carried out easily with the substrates containing 1,6- or 1,7-enyne moiety.

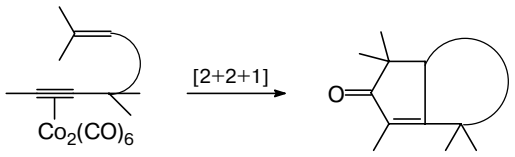
The disclosed opportunity to vary independently the nature of electrophile and nucleophile in the stepwise

* Recently[15] this approach was successfully employed in Ad_E reactions of DCHC enyne complexes, which implied the use of benzhydryl cations as electrophiles and allyl silanes as nucleophiles.

Scheme 5



Scheme 6

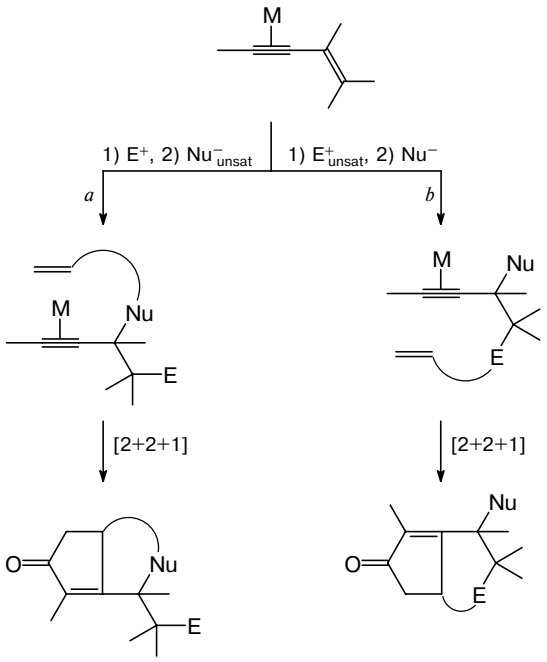


Ad_E reaction of the DCHC complexed conjugated enynes suggested two alternative pathways aimed at the preparation of the compounds amenable to the intramolecular Pauson—Khand cyclization as is shown in Scheme 7.

In the first of this options (route *a*) a fragment containing the requisite double bond is introduced into the assembled structure due to the utilization of the unsaturated nucleophile (Nu_{unsat}) at the second step of Ad_E reaction. In the second option (route *b*) the same goal is achieved thanks to the use of the unsturated electrophile (E_{unsat}) at the first step of the sequence.[17a]

Allylic alcohols as easily available compounds were employed as Nu_{unsat} required for the creation of 1,6-enyne fragment following the route *a*. We have found that the cationoid intermediates formed upon the addition of acyl cations at the double bond of the starting DCHC enyne complexes could be easily

Scheme 7



quenched with allylic alcohols (in the presence of potassium carbonate as a base) to give the respective acylallyloxy adducts and an almost arbitrarily chosen set of all three components could be used in this coupling (see, for example, adducts **19—21**, **25** and **26**, Scheme 8)[13c].

The adducts thus prepared turned out to be very active as the precursors in Pauson—Khand reaction and their cyclization proceeded easily upon a moderate heating of the substrates applied at the surface of silica gel. The expected products, derivatives of 3-oxabicyclo[3.3.0]-octenone such as the adducts **22—24**, **27**, or **28** were prepared in good yields[17a,b].

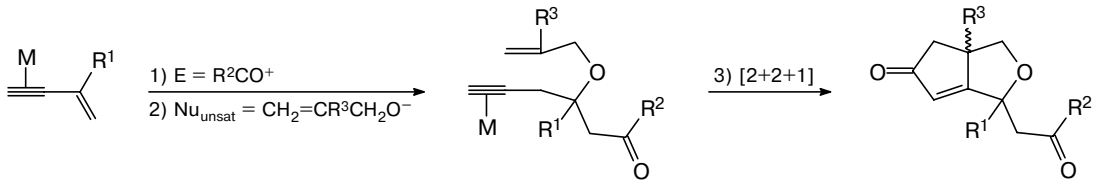
The second of the options presented in Scheme 7 (route *b*) envisaged the utilization of the unsaturated electrophiles as the reagents at the first step of Ad_E reaction. The acyl cations easily generated from the unsaturated acyl halides of fairly diverse structural type were employed for this purpose.

A typical set of the adduct structures **29—32** prepared along this route is shown in Scheme 9. However the direct utilization of these products as the substrates for Pauson—Khand reaction turned out to be impossible due to the reduced donor ability of the conjugated double bond as a reaction partner. Therefore, we had to add an additional step, namely Grignard reaction or hydride reduction of the carbonyl group in order to restore the ability of the double bond to participate in Pauson—Khand cyclization. The products formed as a result of this auxiliary operation underwent [2 + 2 + 1] cycloaddition smoothly to give the expected derivatives of biyclo[3.3.0]octenone in good to excellent yields (adducts **33—36**, Scheme 9)[18a,b].

The bicyclic products of the type shown in Scheme 9 are of obvious preparative interest as the advanced intermediates in the synthesis of various polyquinanes. For example, the adduct **36**, prepared in six step from isobutyric aldehyde in 40% overall yield, contains the A/B ring system with gem-dimethyl fragment, the common structural element of a number of the linearly fused triquinanes (hirsutane derivatives) plus a set of the functional groups useful for the further chemical transformations leading to the formation of the missing ring C.

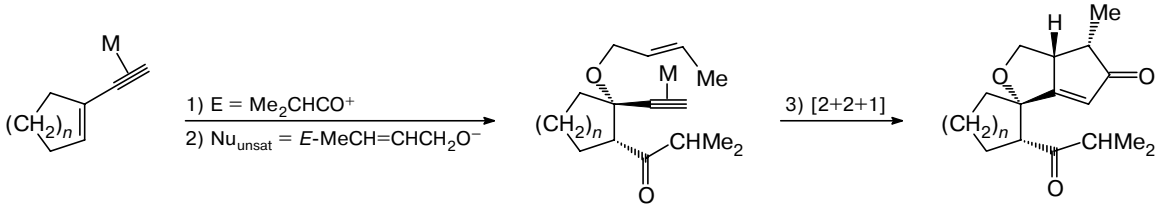
Scheme 8

Route *a*



19—21, 50—72% **22—24**, 43—61%

19, 22: R^1 = Me, R^2 = CH=CH_2, R^3 = H; **20, 23:** R^1 = H, R^2 = R^3 = Me; **21, 24:** R^1 = R^2 = R^3 = Me



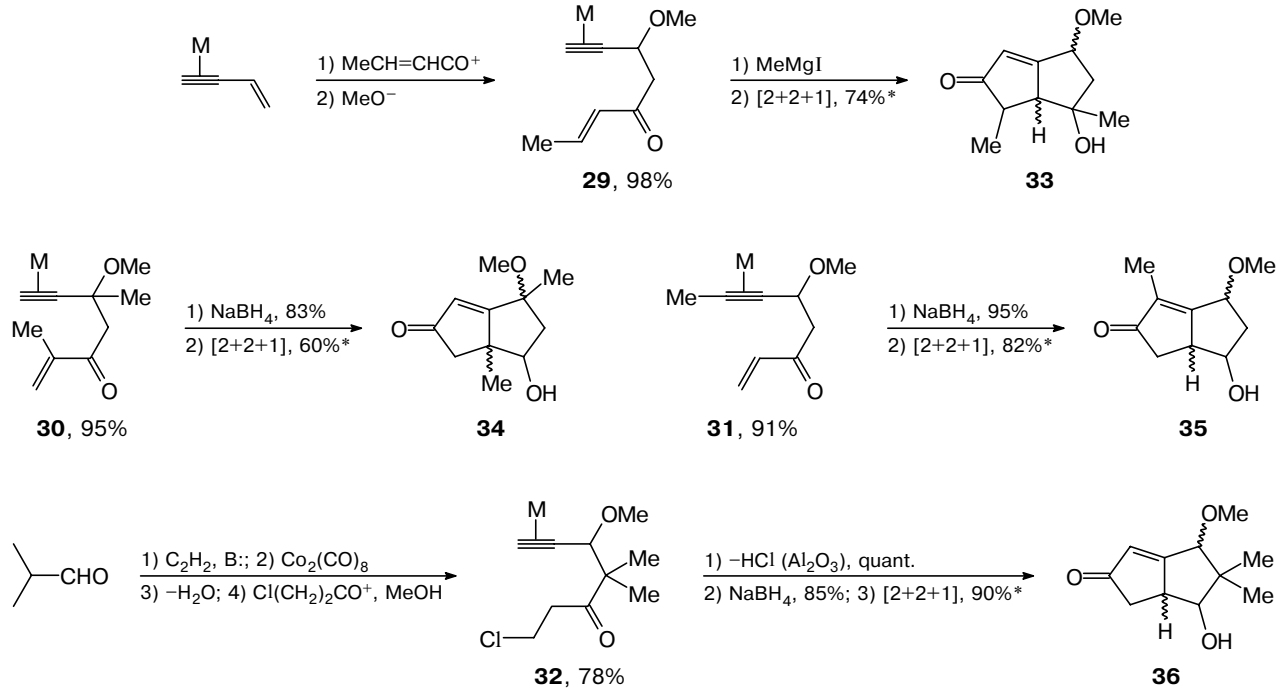
25, *n* = 1, 54%
26, *n* = 2, 64%

27, *n* = 1, 68%
28, *n* = 2, 48%

Note. Nu_{unsat} is alkenyloxy group, E are acyl cations.

Scheme 9

Route *b*



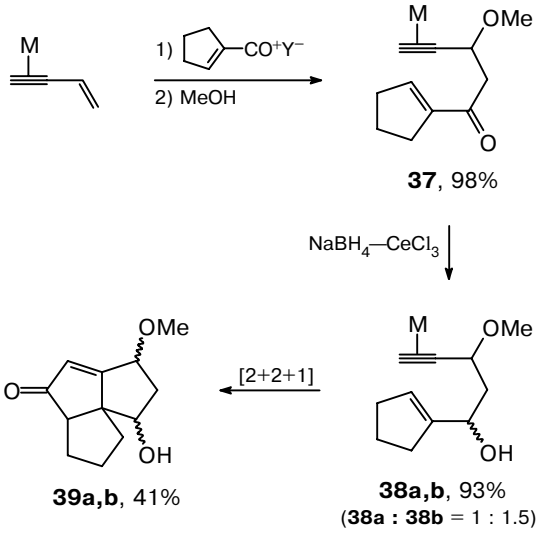
Note. E_{unsat} are α,β-unsaturated acyl cations (or their equivalents), Nu is methoxy group.

* The yields are given for the reaction of the main isomer isolated from the mixture of diastereomers formed at the carbonyl group transformation step.

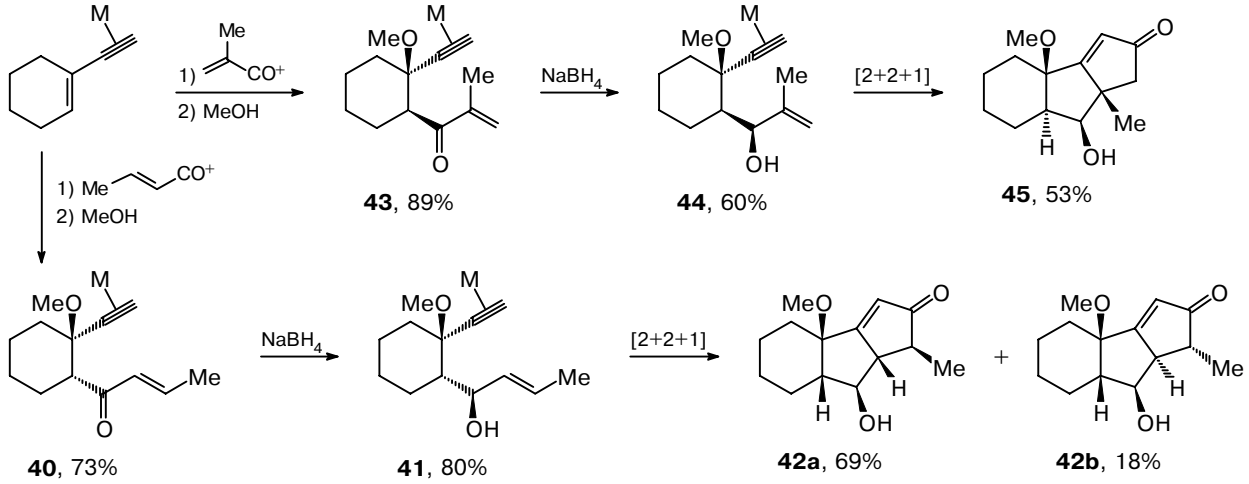
It is appropriate to comment that the reaction sequences shown in Schemes 8 and 9 are based upon the exhaustive utilization of the chemical potential of dicobalthexacarbonyl group. In fact, this fragment plays initially a role of the protecting group for the triple bond of the starting enyne, next it serves as the group stabilizing the intermediately formed complexed propargylic cation and finally, it participates as the reacting species at the cyclization step.

An opportunity to employ a number of the structurlly diverse addends in the described coupling enabled us to apply an approach represented as route *b* in general Scheme 7 for the synthesis of more complex compounds. For example, methoxyacylation of DCHC complex of vinylacetylene using acylium ion derived from cyclopenten-1-carboxylic acid led to a nearly quantitative preparation of the adduct **37** (Scheme 10). Hydride reduction of the latter proceeded non-stereoselectively to give the mixture of diastereomers **38a,b**. Both isomers turned out to be suitable substrates for [2 + 2 + 1] cycloaddition which resulted in the formation of the respective angularly fused tricyclic compounds **39a,b**[19a,b] (this transformation is shown only for one of the diastereomers, *viz.*, **38a**→**39a,b**), strucutrally similar to the natural triquinanes (see for examples, reviews[20]). In fact synthesis of the related structure had been already performed previously using Pauson—Khand cyclization as the key step, but the procedure for the preparation of the required substrates was rather tedious and involved several steps.[21] The synthesis of **38a,b** shown in Scheme 10 was accomplished in two steps from the readily available precursors.

Scheme 10



Scheme 11

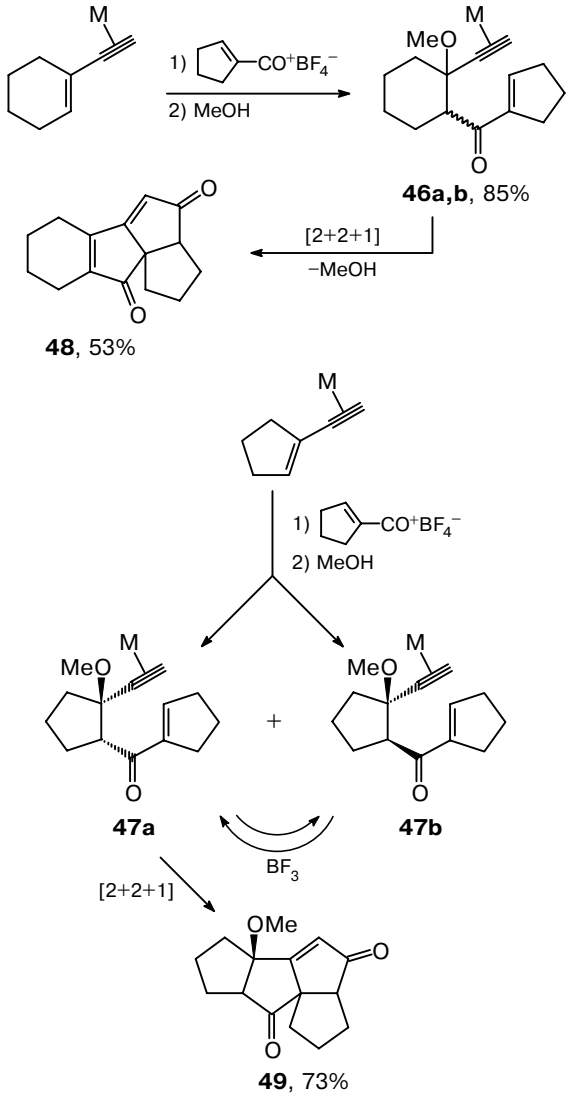


An alternative approach aimed at the synthesis of linearly fused triquinanes took an advantage of the use of readily available 1-ethynylcycloalkenes as the alkene substrates. Thus methoxyacylation of DCHC-complex of 1-ethynylcyclohexene with crotonoyl tetrafluoroborate furnished the adduct **40** which was further converted by a diastereoselective reduction into the hydroxyderivative **41**. Cyclization of the latter proceeded with a good overall yield to give the tricyclic adduct **42a,b** with a significant predominance of the major diastereomer **42a** (Scheme 11). For the adduct **43** prepared from the same enyne but using methacryloyl tetraluoroborates, all steps shown in Scheme 11 proceeded with a nearly complete diastereoselectivity. In fact the intermediate products **43** and **44** as well as the final tricyclic product **45** had been obtained as single diastereomers[19a,b].

Finally a similar approach was found to be applicable for the preparation of tetracyclic derivatives, provided the acylation of DCHC complexes of 1-ethynylcycloalkene is carried out with the use of the derivatives of cycloalkene-1-carboxylic derivatives. It was found that acylmethoxyadducts **46** or **47** thus formed are capable of directly undergoing the Pauson—Khand cyclization despite the deactivating effects of the conjugated carbonyl function (Scheme 12)*.

As is shown in the Scheme 12, the preparation of the tetracyclic products **48** and **49**, containing a system of the anglularly and linearly fused cycles required only two steps starting from rather simple precursors[19b,22]. It is worthwhile to mention that the adduct **48** contains the same A—B—C—D ring system as is found in the natural tetraquinane crinimpellin[23], while the ring system of the adduct **49** is similar to the B—C—D—E ring system of the pentacyclic tetraterpene retigeranic acid[24].

Scheme 12



* In case of the adducts **47a,b** only the former (*cis*-isomer) was amenable to the cyclization but the adduct **47b** could be recovered from the reacion mixture and isomerized into **47a** by the treatment with a Lewis acid.

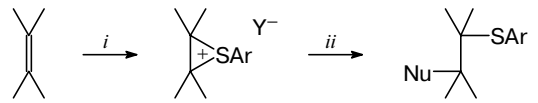
The afore-mentioned results provided a convincing evidence attesting to the synthetic promise of the two-step Ad_E reaction with DCHC-complexed conjugated enynes as a promising and fairly general method for the ready preparation of various types of functionalized alkyne derivatives. This method in conjunction with the subsequent cycloaddition of the prepared adducts may serve as an efficient protocol for the convergent synthesis of polycyc compounds of various structural types.

The second approach to the solution of the problem of step separation in Ad_E-like processes envisaged the utilization of the cationoid electrophiles capable of stabilizing the arising cationoid intermediates (I_{cat}) due to the formation of cyclic (bridged) onium ions (see Scheme 2, option B). Results of our studies aimed at the elucidation of the opportunity to employ the sulfur containing electrophiles in this role will be considered in the next section.

2.3. Stabilization of I_{cat} due to the formation of the bridged ions with a participation of sulfur atoms of the electrophilic reagent

Traditionally the mechanistic descriptions of the Ad_E reactions with the reagents like arylsulfenyl halides was based on the concept of the formation of the bridged intermediates of episulfoniumion (ESI) type[5]. However, the study of the reaction course under conditions of the increased polarity as well as the direct comparison of the reactivity patterns of the addition of the conventional covalent reagents, ArSHal and their cationoid counterparts such as ArS^+Y^- (where Y^- is non-nucleophilic counter-ion) clearly demonstrated that only in the latter case the concept of the intermediate formation of ESI could be considered as a truly adequate representation of the sequence of the elementary reaction steps[25]. For a number of the model reactions the formation of ESI-like intermediates had been proven by their isolation as the stable salts and/or NMR studies of their structure. From a synthetic viewpoint the most important peculiarity of these intermediates is their ability to serve as a rather active electrophiles toward a number of nucleophiles, both heteroatomic (Nu_{het})[25] and carbon (Nu_C) including several types of π-donors[26a—h] (Scheme 13).

Scheme 13



I_{cat} = ESI

Reagents and conditions: *i*. 1) ArSCl, 2) Lewis acid; *ii*. Nu_{het} or Nu_C.

ArS^+Y^- (ArSCl + AgY); Y = BF_4, SbF_6 *etc.*;
Nu_{het} = H_2O, ROH, RCOOH, HNR_2, RSH *etc.*;
Nu_C = TMS vinyl ethers, TMS ketene acetals, allylsilane, Ar^1H.

Generation of ESI intermediates can be carried out either by the interaction of the starting alkene with the cationoid reagent ArS^+Y^- or *via* the intermediate formation of the conventional 1,2-ArSHal-alkene adducts followed by the treatment of the latter with Lewis acid. For a number of cases the latter procedure was found to be preferable.

The sequence of the independent steps of ArS addition and interaction of the arising ESI intermediate with an almost arbitrarily chosen nucleophile represented in Scheme 13 was shown to be fairly general and some options available for the reactant variations are given in Scheme 14[26a—h].

The transformations shown above most usually proceed with a nearly exclusive formation of the trans-adducts (see for example, adducts **50a, b**) and a highly predominant Markovnikov-like selectivity (see adducts, **51—54**, Scheme 14). Alkoxyalkenes were found to be the especially suitable substrates for these reactions and their usage enabled us to develop a novel option for the aldol cross condensation in accordance with a general scheme:

$$ArS^+ + C{=}C{-}OR + C{=}C{-}OTMS \rightarrow \text{adduct}^{27}$$

This route was found to be applicable for a wide range of the substrates of this type. Typical examples of the adducts of the general type of γ-arylthio-β-alkoxycarbonyl derivatives are shown in Scheme 15 (adducts **55** and **56**).

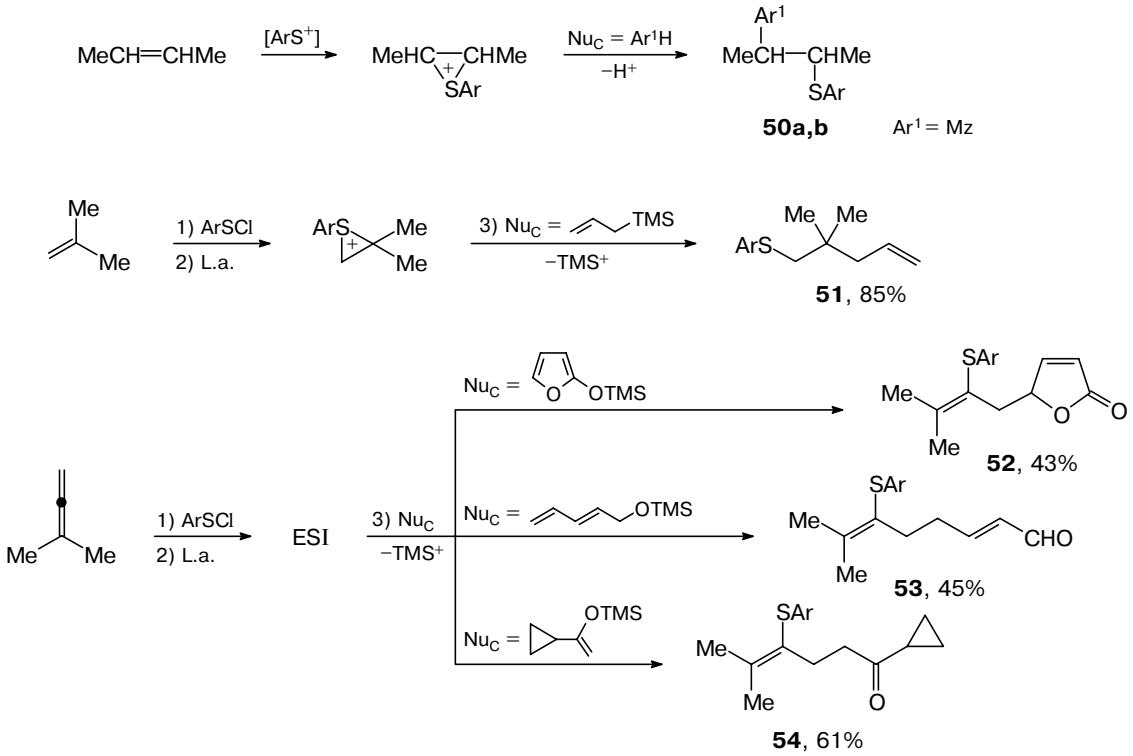
The application of this approach for the case of cyclic vinyl ethers, namely glycals, opened an entry toward elaboration of a novel approach for the synthesis of C-glycosides, analogs of the natural carbohydrates stable under the conditions of the enzymatic glycolyisis (see review[28]). General reaction scheme for tri-*O*-benzyl-D-glucal (**57**) and the representative set of examples of adducts **58—64** which were prepared using this approach[29a,c] are given in Scheme 16.

In the transformations shown in Schemes 14—16 reactions of ESI intermediates with Nu_C proceeded as an initial attack of the electrophilic species at the double bond of π-donor, concomitant with the elimination of proton (formation of the product **50**, Scheme 14) or Me_3Si^+ cation (in all other cases).

In this respect alkyl vinyl ethers seemed to be rather unsuitable candidates to be used as Nu_C since there is no good cationoid leaving group in their structure. Therefore it was really surprising to find out that in fact various alkyl vinyl ethers could be also employed as Nu_C in a similar coupling[30a—d]. Typical examples of this reaction type are given in Scheme 17.

As could be easily seen adducts **65—68**, like previously mentioned adducts **55** and **56**, belong also to the category of the aldol cross condensation products with the only difference that in the latter cases both aldol fragments originate from vinyl ether units (VE-I and VE-II) possessing no good leaving group such as TMS. It is noteworthy that the the transformations shown in Scheme 17 are not accompanied by the formation of the

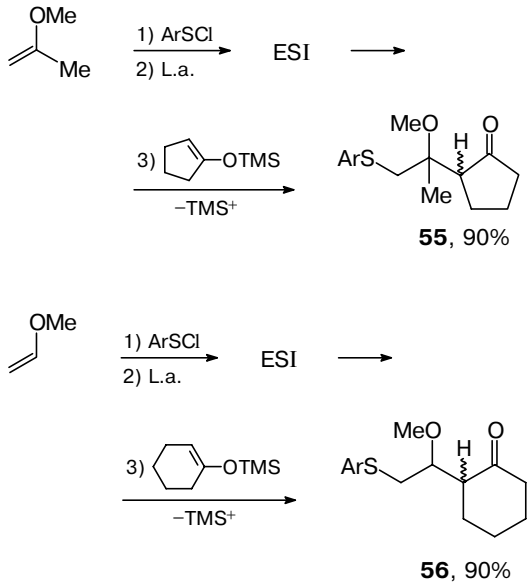
Scheme 14



Note. *treo*-Isomer **50a** is formed from *cis*-butene (>95%); *erythro*-isomer **50b** is fromed from *trans*-butene. L.a. is Lewis acid.

oligomeric products which are typically formed as a result of various reactions of vinyl ethers with carbocationic reagents (see, for example, data in the review[31]). Hence it seemed reasonable to suggest that an immediate result of the interaction of ESI intermediate with the molecule of the second vinyl ether (VE-II) component is the formation of the next cationoid intermediate, tentatively assigned to the structure of the five-membered thiophanium ion (TPI) salt. This suggestion was supported by a series of the experiments, which demonstrated that the described coupling of the VE-components might lead not only to the formation of carbonyl compounds, but to other type of the adducts, their structure being determined by the nature of final nucleophile used for the quenching of the reaction mixture[32a] (Scheme 18).

Scheme 15

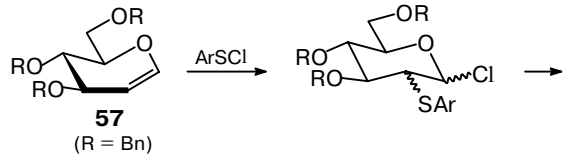


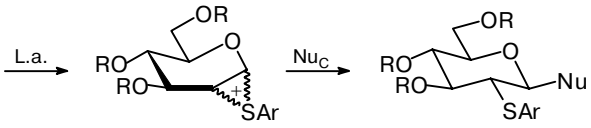
L.a. is Lewis acid.

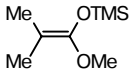
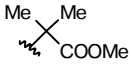
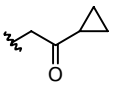
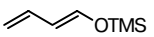
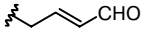
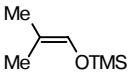
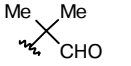
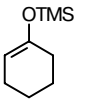
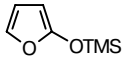
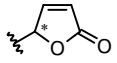
Among the reactions shown in Scheme 18 the most interesting are the transformations which involved the utilization of Grignard reagent as the final Nu_C. The net outcome of these couplings is the preparation of some polyfunctional compounds (*e.g.*, adducts **72—74**) *via* one-pot sequence of reactions with the formation of two novel C—C bonds[32a]. The generality of this protocol was established for quite a number of the couplings, which were carried out with a fairly wide set of the compounds used as VE-I and VE-II components[32a—c].

However, even more interesting ramifications of the above finding were disclosed as a result of the studies of the electrophilic activity of the presumed TPI intermediates toward π-donors. The first example which turned out to be indicative of the promise of these studies is given in Scheme 19.[33a]

Scheme 16





Nu$_C$	Adduct, Nu	Compound	Yield (%)
		**58**	87
		**59**	48
		**60**	78
		**61**	31
		**62**	73
		**63**	75
		**64**	40

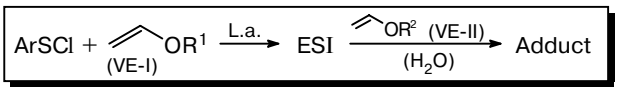
Note. L.a. is Lewis acid

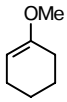
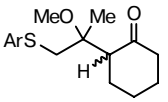
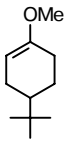
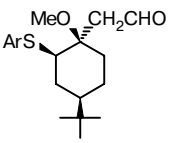
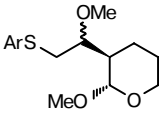
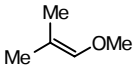
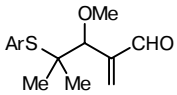
* Only the structure of the main isomer is shown; a mixture of the reaction products may also contain 3—10% of α-manno-isomer.

The most important for the development of our project was the finding that the formation of the adducts **75—78** was achieved as a result of the unprecedented sequence of three kinetically independent intermolecular Ad_E reactions which proceeded with a consecutive formation of two sulfur-stabilized cationoid intermediates, ESI and TPI and is terminated by the removal of good cationoid leaving group, Me_3Si^+. This one-pot four-component coupling is carried out following a very simple experimental procedure, namely by the sequential addition of the required reactants to the pre-cooled solution of methyl vinyl ether in CH_2Cl_2 at −70—−20 °C with a careful TLC control of the completeness of the transformation at every step.

In order to outline the scope of the preparative usefulness of the described transformation we checked

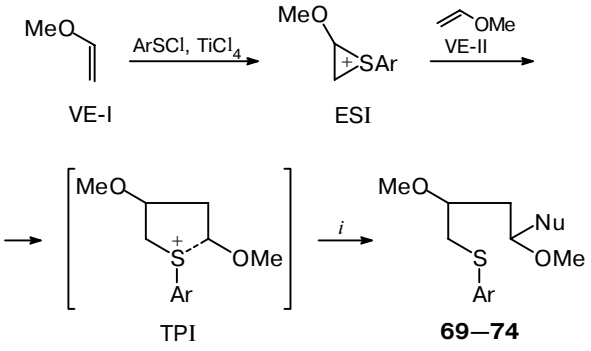
Scheme 17



VE-I	VE-II	Adduct
		 **65**, 76%
		 **66**, 62%
		 **67**, 90%
		 **68**, 76%

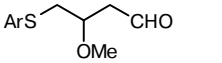
L.a. is Lewis acid.

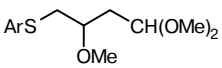
Scheme 18

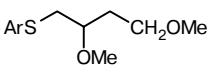


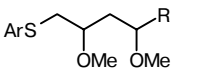
i. Nu$_{het}$ or Nu$_C$

Adducts (Nu$_{het}$ or Nu$_C$):

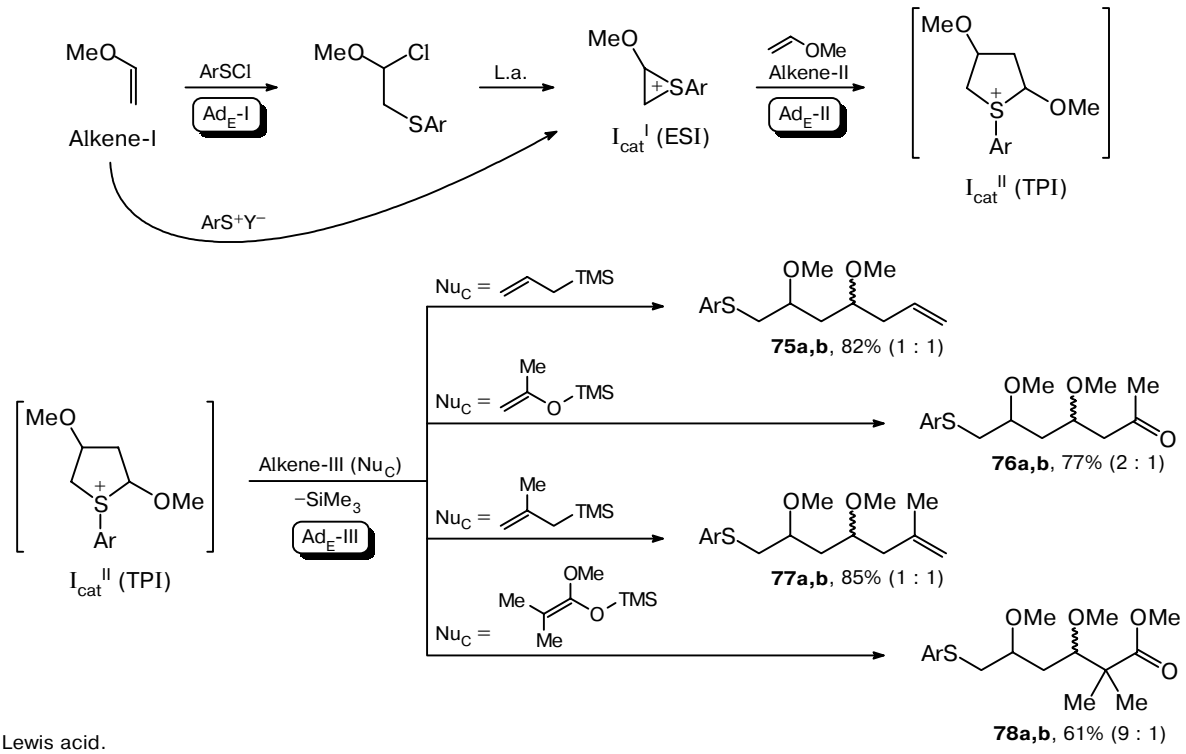
 (H$_2$O) **69**, 89%

 (MeOH) **70**, 95%

 (Bu$_4$NBH$_4$) **71**, 60%

 (PhMgCl) **72**, 60%
(PhCH$_2$MgCl) **73**, 68%
(CH$_2$=CHCH$_2$MgCl) **74**, 69%

Scheme 19



L.a. is Lewis acid.

its applicability for a number of variable combinations of the all components involved. A set of the representative examples given in Scheme 20 (alkene-I and alkene-II are acyclic vinyl ethers) and Scheme 21 (alkene-I or alkene-II are cyclic vinyl ethers) shows clearly that the structurally diverse vinyl ethers may serve as the first two alkene components in an almost arbitrarily chosen combinations. Even more diversity is allowable for the Nu_C (alkene-III component). In fact, various silyl vinyl ethers, derived from aldehyde or ketones and containing acyclic or cyclic, aromatic or alkene fragments, or acyclic or cyclic silylketene acetals as well as typical allyltin or silicon derivatives were shown to be rather effective to be used in this role.

One may also add, that methyl vinyl ether as VE-I and/or VE-II component can be substituted by *tert*-butyl vinyl ether. Instead of *p*-tolylsulfenyl chloride shown in Schemes 20 and 21, other arylsulfenyl halides such as *p*-chlorobenzenesulfenyl chloride or mesitylsulfenyl chloride could be employed as the starting electrophiles. The reaction can be carried out with a number of various Lewis acid such as $TiCl_4$, $SnCl_4$, TMSOTf, Et_2AlCl, $LiClO_4$, $AgSbF_6$, *etc.* Yields given in the Schemes 20 and 21 refer to the isolated and purified products; no attempts were made to optimize the procedures.

The variability of the starting components nature and the diversity of the structure of the prepared products **79—92** warrants the conclusion that the elaborated protocol of one-pot sequence of three intermolecular Ad_E reactions could be considered as a fairly general method for the assembly of polyfunctional compounds from four simple precursors with the formation of three novel bonds (one C—S and two C—C).[33a—c] It is noteworthy that the nature of all partners of this coupling could be varied independently and within rather broad limits.

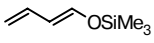
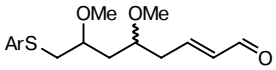
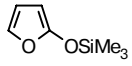
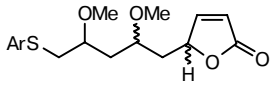
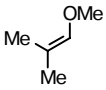
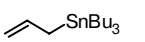
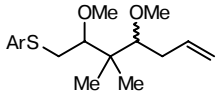
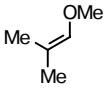
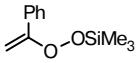
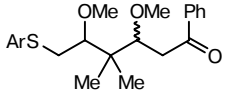
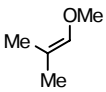
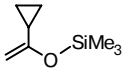
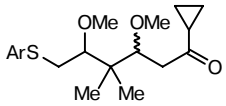
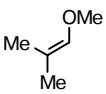
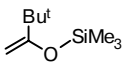
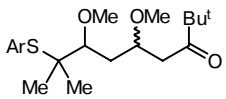
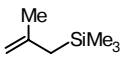
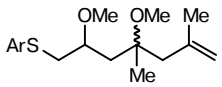
The course and the outcome of the described coupling could be considered as a particular case of the general sequence shown in Scheme 22, where E^+ stands for ArS^+, and I_{cat}^{I} and I_{cat}^{II} are stabilized sulfonium ion intermediates (ESI and TPI respectively). At the final step of this sequence (Ad_E-III) the electrophilic attack at the double bond of alkene-III component is accompanied by the removal of the cationoid leaving group MR_3^+ (the termination step of the whole sequence).

It is to be emphasized that while the usefulness of the intramolecular Ad_E reactions as an efficient and reliable synthetic tool is well-documented by the numerous studies (see, for example, progesterone synthesis in Scheme 1 and the data in Refs. 1a—e) prior to our studies no general method was described which could be useful in order to perform a controlled sequence of the intermolecular Ad_E sequences (for a general discussion of this problem see Ref. 8a).

2.4. Structure of intermediates, mechanism, and stereochemistry

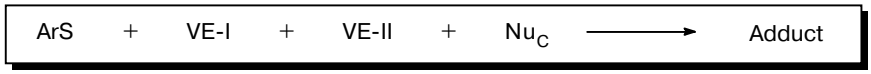
The above-mentioned structure of thiophanium ion-like cationoid intermediate formed at the Ad_E-II stage

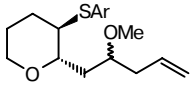
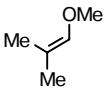
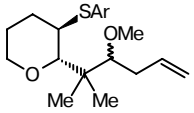
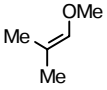
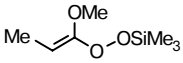
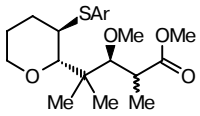
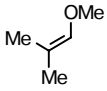
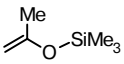
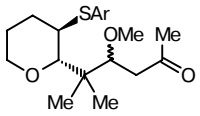
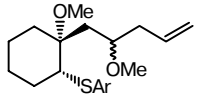
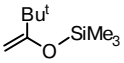
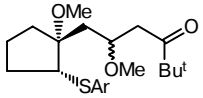
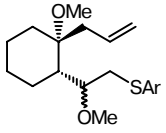
Scheme 20

ArS	VE-I	VE-II	Nu$_C$	Adduct	Yield (%)	Ratio of stereoisomers
p-TolS				 **79**	40	1 : 1
p-TolS				 **80**	73	1 : 1 : 1 : 1
p-TolS				 **81**	90	1.5 : 1
p-TolS				 **82**	60	1 : 1
p-TolS				 **83**	93	1 : 1
p-TolS				 **84**	68	1.3 : 1
p-TolS				 **85**	80	1 : 1

might have been considered as a plausible suggestion to account for the observed results. However, the credibility of this suggestion could be questioned in view of the plethora of literature data on the reactivity of the stable thiophanim salts. In fact, it is well known that these species exhibit a rather low electrophilic activity toward nucleophiles of various types[34a,b]. For example, 1-aryl-2,4-diarylthiophanium salts do not react at ambient temperature with such nucleophiles as water and they undergo acetolysis with the ring opening only upon a prolonged heating with AcOH—AcONa[34a] (see also data in review[34b]). Furthermore, it is a common knowledge that reactions which proceed *via* the formation of the bridged cationoid intermediates most typically result in a highly selective formation of the diastereomer arising from the S_N2-like opening of the bridge with the inversion of the configuration at the reaction center. At the same time our data on the diastereomeric composition of the adducts formed in the described ArS-mediated coupling clearly demonstrated that the overall stereochemistry of the reaction may vary from a nearly complete non-selectivity (see Scheme 20) to a significant or even very high diastereoselectivity (see Scheme 21). Obviously no consistent explanation of such an ambiguity could be advanced in the absence of data on the structure of key intermediates of this transformation. Below will be presented the results of our studies aimed at the solution of this problem.

Scheme 21

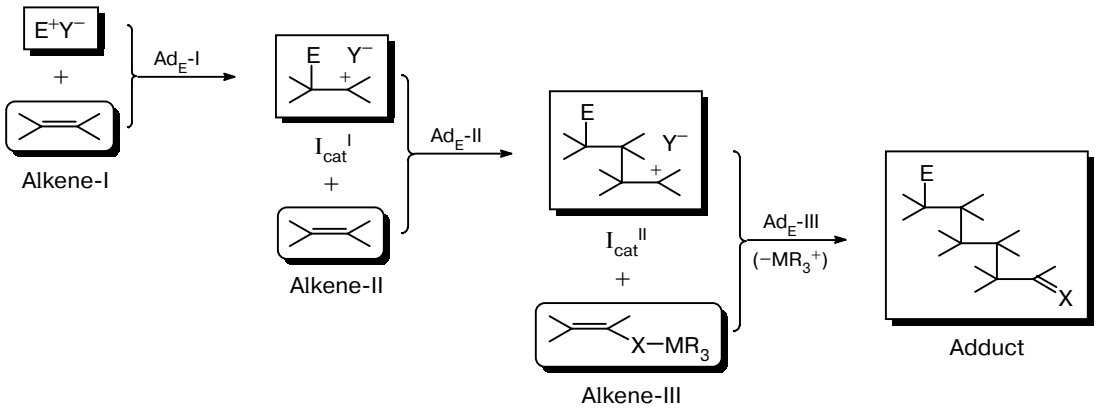


ArS	VE-I	VE-II	Nu$_C$	Adduct	Yield (%)	Ratio of stereoisomers
p-TolS				 **86**	82	1 : 1.5
p-TolS				 **87**	61	4 : 1
p-TolS				 **88**	81	7 : 1
p-TolS				 **89**	75	10 : 1
p-TolS				 **90**	73	>15 : 1
p-TolS				 **91**	76	>15 : 1
p-TolS				 **92**	53	2 : 1

As for the structure of the first cationoid intermediate (I_{cat}^{I}), episulfonium ion (ESI, see Schemes 18 and 19), the results of the previous studies perfomed in our group[25—27] and elsewhere (see for the pertinent data review[25]) provided an ample evidence showing that the ring opening of these intermediates proceeds practically in all cases as a stereospecific process to give the products of the trans-addition of reactant across the double bond of the starting alkene. Hence there were a rather solid reasons to assume that the overall steric course of our reaction shoud be primarily dependent on the stereochemistry of the formation and/or ring opening of the second cationoid intermediate (I_{cat}^{II}), tentatively identified as thiophanium ion (TPI).

Problem of the structure of the latter was first addressed for the coupling carried out with the acyclic vinyl ethers used as both alkene-I and alkene-II components which most typically proceeded with a rather low diastereoselectivity (see Scheme 19 and 20, adducts **75—77** and **79—85**)[33a—c]. For the model reaction shown

Scheme 22



X = O, CH_2; M = Si, Sn

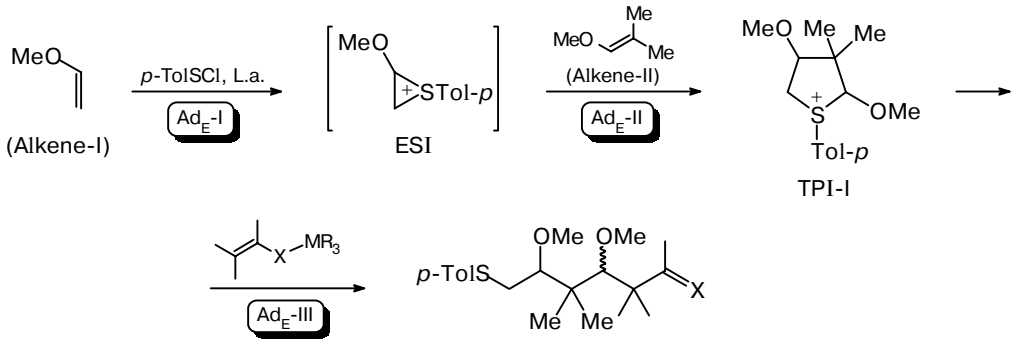
in Scheme 23, carried out under a slightly modified conditions, we succeeded in isolating the presumed intermediate TPI-I in a free state as the stable hexaflouroantimonate salt **93**.[35a]

Structure of salt **93** as shown in Scheme 23 was unambigiously established by a single crystal X-ray determination. Detailed analysis of ^1H and ^{13}C NMR spectral parameters revealed that it has the same structure in the solution. It was also established that the interaction of the isolated salt **93** with trimethylallyl silane (alkene-III, Ad_E-III step) furnished the same adduct **81** as was obtained as a result of the non-interrupted one-pot sequence of three consecutive Ad_E reactions. Hence there are solid reasons to assume that the structure of the salt **93** represents the structure of a true intermediate formed *in situ* at the Ad_E-II step of the overall sequence.

The established fact of the formation of TPI-I intermediate as a single diastereomer led to the mandatory conclusion that the observed non-diastereoselectivity of the formation of adducts such as **75—77** or **79—85** in the couplings involving acyclic vinyl ethers used as

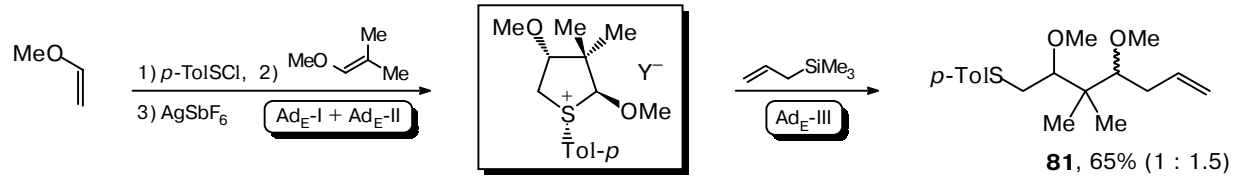
Scheme 23

Generation of TPI-I *in situ:*



81—83, 60—94% (1 : 1.1—1.5)

Isolation of TPI-I (**93**) salt in the free state:

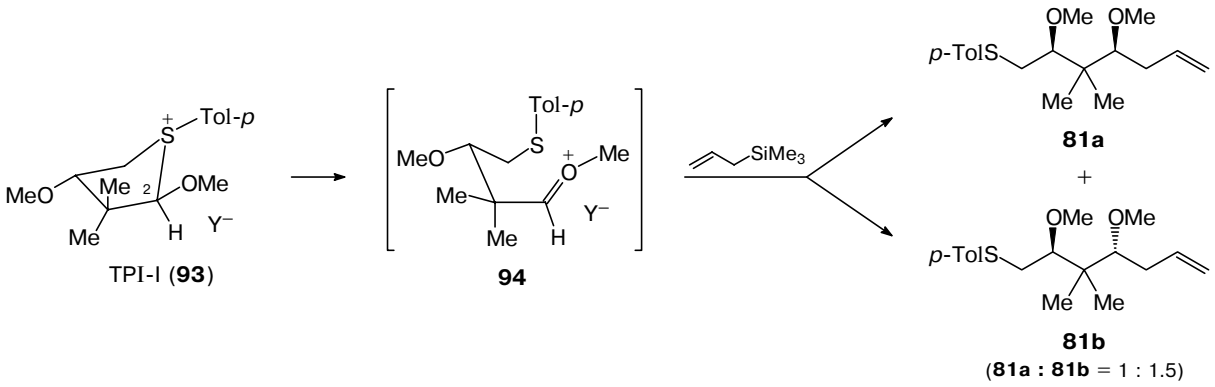


TPI-I, **93**, 66%

81, 65% (1 : 1.5)

L.a. = $TiCl_4$, $SnCl_4$, $LiClO_4$ *etc.*; X = CH_2, O; M = Si, Sn; Y = SbF_6.

Scheme 24



alkene-I and alkene-II components (Schemes 19 and 20) is determined by a non-selectivity of the ring opening of this intermediate at Ad-III step. Hence this step cannot proceed as a direct attack of Nu_C at C(2) center of intermediate **93** (S_N2-like process). It is much more likely that an alternative mechanism is operative in this reaction, which involves an initial ring opening of TPI-I resulting in the formation of acyclic oxocarbenium cation **94** (see Scheme 24, S_N1 mechanism).[35a] Obviously, the interaction of the latter with Nu_C should proceed non-diastereoselectively, at least in the absence of additional factors which might effectively block the reagent approach from one of the alternative sites*.

It is also noteworthy that above-mentioned unprecedented reactivity of the thiophanium salts like **93** as the electrophiles could be actually ascribed to the effect of the presence of methoxy-group in α-position to the sulfonium center, as the factor, which facilitates the opening of onium ring and the formation of an active electrophile, oxocarbenium ion intermediate **94**.

The same approach was applied for the analysis of the mechanism of the reactions which exhibited a rather noticeable diastereoselectivity. As a model example, a highly diastereoselective coupling leading to the formation of the predominant diastereomer **87a** is shown in Scheme 25. In this case we have also succeded in isolation of the presumed intermediate TPI-II in a free state as the hexafluoroantimonate salt **95**.[35b,c]

Structure of the salt **95** was firmly established by the X-ray analysis (for crystal) and by NMR studies (for the solution). Interaction of the isolated salt **95** with allyl stannane or 2-siloxypropene (Ad_E-III step, alkene-III component) led to the formation of the adducts **87** and **89** respectively with satisfactory (for **87**) or good (for 89) diastereoselectivity (Scheme 26). This result might have suggested the S_N2 mechanism of the nucleophilic ring opening of TPI-II intermediate in these reactions. Such a representation implied that the ring opening of TPI-II should proceed as a direct attack of Nu_C at C(2) carbon and hence with an inversion of the configuration at this center. However, much to our surprise the X-ray data for the major diastereomer **87a** (for the sulfone prepared from the latter) revealed that the configuration at C(4) in this product is identical to that at C(2) center of TPI-II. Hence the formation of this diastereomer proceeded with a retention of configuration at the reacting center of the cationoid intermediate **95**.

This result clearly indicated that the product **87a** could not have been formed *via* a direct ring opening of the bridged intermediate TPI-II **95** (S_N2 mechanism). Hence it seemed logical to conclude that the reaction of **95** with Nu_C (Ad_E-III step) also proceeds as S_N1 reaction which involved an initial formation of the oxocarbenium ion intermediate **96** as the active electrophile in the reaction with alkene-III component[35c,36] (see Scheme 26). Much more complicated is the problem of the nature of the factors which may determine the observed site selectivity of the nucleophile approach at sp^2-center of the intermediate **96**. It seemed reasonable to assume that the observed stereoselectivity pattern might be accounted for if one assumes that two alternative reaction routes involve the formation of the respective quasi-bicyclic transition states **97a** and **97b**. Consideration of the molecular models revealed that the former is definitely less-hindered sterically and hence the formation of diastereomer **87a** should be the preferable outcome of the overall coupling.

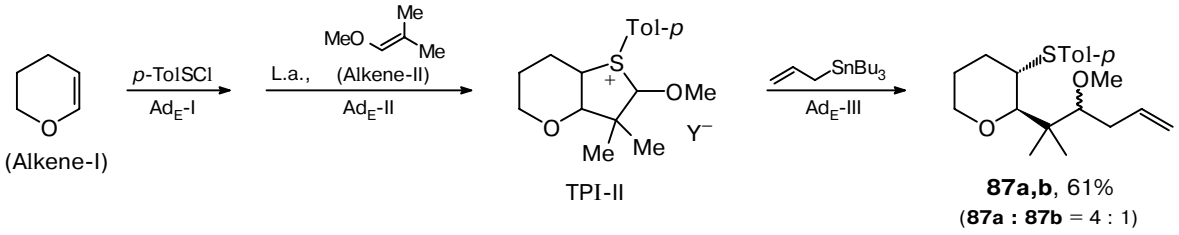
Needless to say that the suggested mechanism is nothing more than a working hypothesis and further studies are needed in order to accumulate additional experimental data on the dependence of the stereochemistry of the coupling on the variations of such factors as the nature of ArS-group or Nu_C.

The same reasoning seems to be applicable for the more complicated cases, namely formation of the ad-

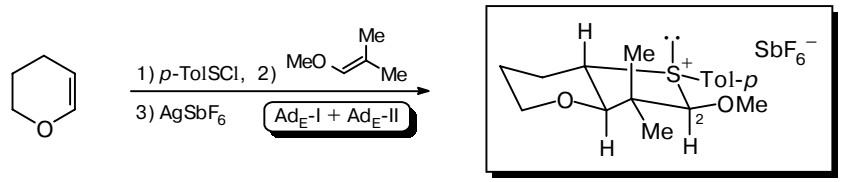
* Similar reasoning had been applied earlier to the analysis of the data on the course and stereochemistry of the related reaction, namely Lewis acid initiated reaction of acetals with allylsilanes. It was concluded that the direct substitution of alkoxy group (S_N2 mechanism) is an unlikely mechanistic options for this reaction and for the majority of the studied cases a consistent explanation of the experimental data can be given only in the terms of S_N1 mechanism, which suggests the formation of oxocarbenium ion intermediate.[36a,b]

Scheme 25

Generation of TPI-II *in situ:*

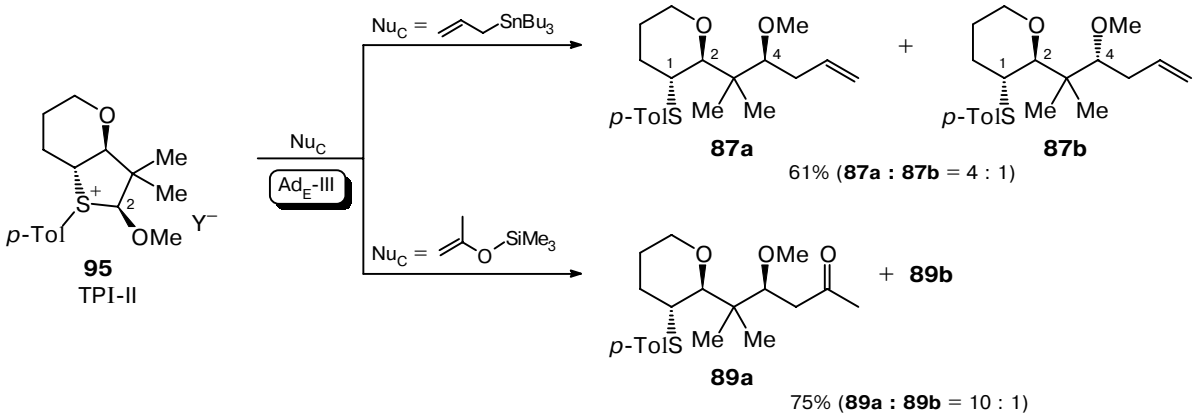


Isolation of TPI-II salt in the free state:

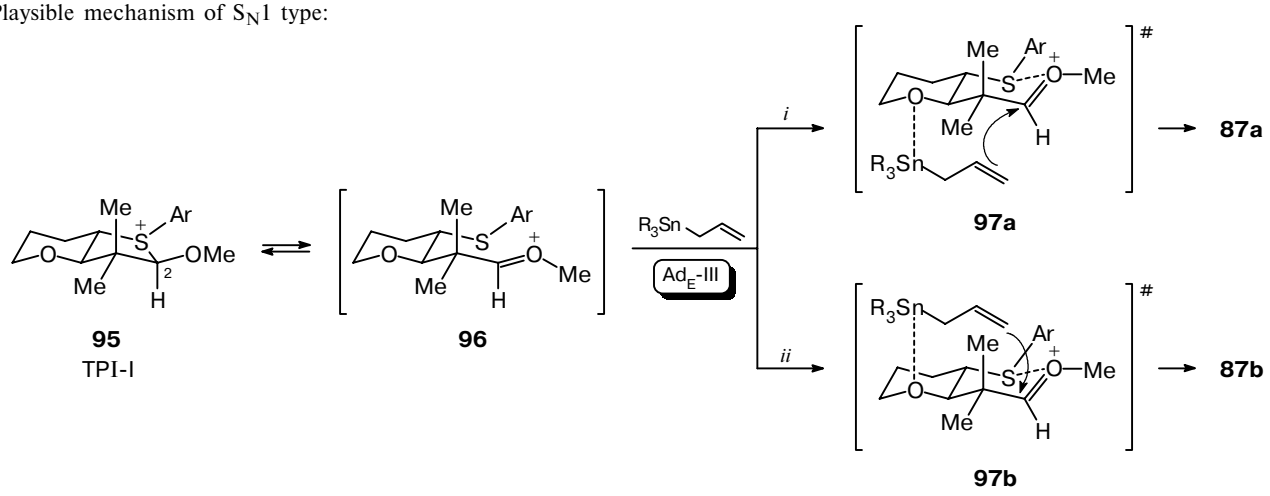


Scheme 26

Diastereoselective formation of three chiral centers (at C(1), C(2), and C(4)) in the prepared adducts:



Playsible mechanism of S_N1 type:



Note. i, *re*-attack; *ii*, S_i attack; **97a** is major isomer; **97b** is minor isomer.

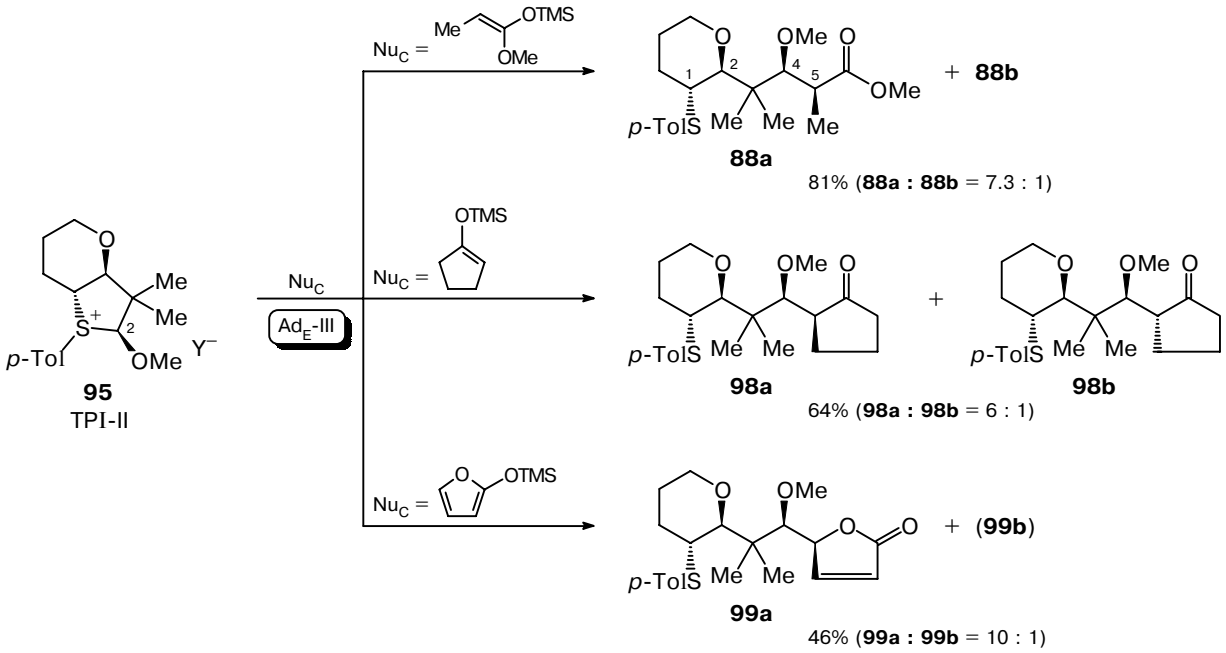
ducts **88**, **98**, and **99** (Scheme 27). Preparation of these adducts involves the assembly of the polyfunctional compounds bearing four newly-formed chiral centers from the achiral building blocks and hence could have resulted in the fomation of eight diastereomers. An already established fact of the diastereselective formation of the key intermediate **95** reduces to four the number of the expected diastereomers. In fact, it was experimentally found that only two diastereomers are formed with one of them being highly preponderant.[35b,c]

For adduct **98** the structure of both diastereomers **98a** and **98b** has been unequivocally established by a single crystal X-ray analysis. It turned out that these products differ only by the configuration at α-carbon of cyclopentanone fragment while their configuration at three other chiral centers is identical to the one established earlier for the adduct **87a**.

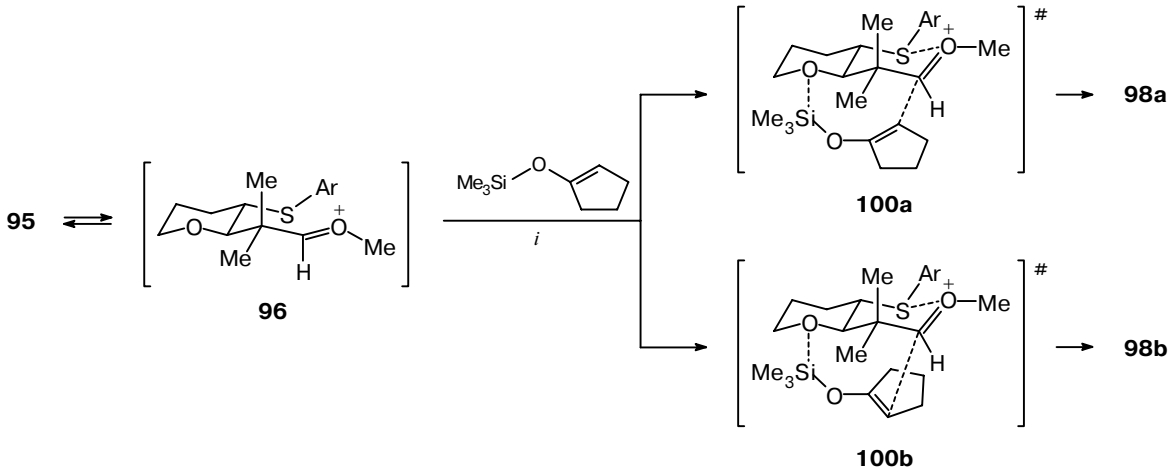
Hence the formation of these adducts occurs also as a result of exclusive re-attack of the nucleophile at the oxocarbenium ion center of the intermediate **96**. However, thanks to the prochirality of the final Nu_C, 1-siloxycyclopentene, this attack may proceed *via* the formation of two alternative transition states **100a** and **100b**, corresponding to the two alternative orientations of the ap-

Scheme 27

Diastereoformation of four chiral centers (at C(1), C(2), C(4), and C(5)) in the prepared adducts:



Plausible mechanism of S_N1 type:

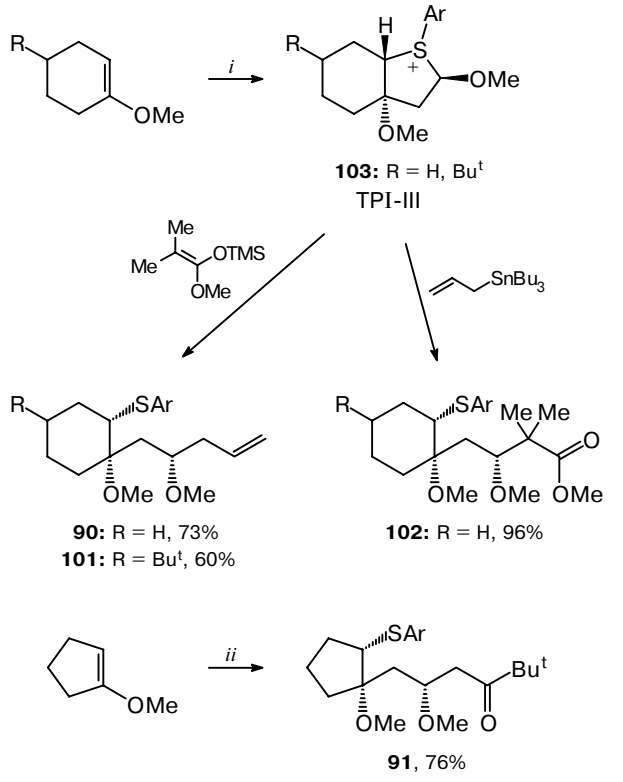


Note. *i*, *re*-attack; **100a** is major isomer; **100b** is minor isomer.

proaching reagent. Molecular modelling analysis revealed that the former is less sterically encumbered and thus the approach leading to the formation of adduct **98a** seems to be the preferable pathway. It is likely that similar mechanistic description could be also used to account for the observed stereoselectivity of the formation of adducts **88** and **99** (see Scheme 27).

A nearly complete diastereoselectivity at three newly formed chiral centers seems to be a common pattern of the couplings which involve the utilization of 1-alkoxyalkene as alkene-I component (Scheme 28). In fact the ^{1}H NMR spectra for the adducts **90**, **91**, **101** and **102** do not reveal the presence of the diastereomers other than those shown in Scheme 28.[35b] The attempts to isolate in a free state the thiophanium ion intermediates presumably formed in these transformations failed but for the reaction with 1-methoxycyclohexene the respective intermediate TPI-III was prepared as the perchlorate salt **103a** stable in a solution. Structure of this salt was firmly established by the analysis of its ^{1}H NMR spectral parameters. Comparison of the stereochemisty of **103a** and that of the adduct **90** prepared thereof (X-ray data) revealed that the formation of the latter proceeded also with a retention of the configuration at the reacting center of the intermediate **103a**. Hence one may safely assume that the above suggestions about the mechanism of Ad_E-III step are equally applicable for the conversion **103a** → **90** and formation of the latter also involves the intermediacy of the oxocarbenium ion **104** and transition state **105** (Scheme 29).

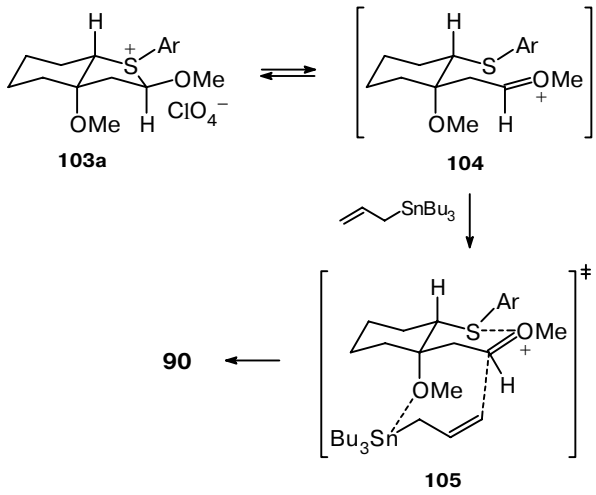
Scheme 28



Reagents and conditions: *i.* 1) *p*-TolSCl, 2) $TiCl_4$, 3) ⟩OMe; *ii.* 1) *p*-TolSCl, 2) $TiCl_4$, 3) ⟩OMe, 4) ⟩(OTMS)(OBu^t).

Scheme 29

Plausible mechanism of S_N1 type for salt TPI-III:



Obviously, the reservations about the validity of a similar mechanism presented in Scheme 26 refer also to the mechanistic descriptions presented in Schemes 27 and 29. Yet it is noteworthy, that while S_N1 mechanism is used widely in numerous studies which dealt with the stereoselectivity of the related reactions of acetals with various Nu_C, the relaive importance of reaction conditions and substate structure as the factors determining the steric outcome of these transformations is still a matter of discussion (see, for example, data in Refs. 36 and 37).

3. General conclusions

Below are summarized some main results of our studies.

The validity of a general concept of the stepwise Ad_E reaction which proceeds *via* the formation of a stabilized cationoid intermediate was established and its potential as the basis for the elaboration of a new methogology of the multicomponent coupling was demonstrated. Two general approaches to achieve this goal have been investigated. The first approach suggested the utilization of such compounds as μ-DCHC complexes of the conjugated enynes as the alkene substrates in Ad_E reactions (route A), while the second takes the advantage of the utilization of sulfur-containing reagents as the electrophiles in these reactions (route B).

It was found that the route A is widely applicable for the transformations which involve the utilization of vari-

ous cationoid electrophiles at the first step of Ad_E reaction with DCHC complexed conjugated enynes and a fairly diverse set of nucleophiles at the second step of this process. This sequence was employed as a novel approach for the preparation of various series of the functionalized alkyne derivatives, including those which can be directly used as the substrates for the intramolecular [2 + 2 + 1] cycloaddition. The efficiency of this methodology as a short route (2—3 steps) preparation of a number of polycyclic compounds from simple precursors was demonstrated.

The utilization of sulfur containing electrophiles of the arylsulfenyl halide type as implied in the route B opened an entry toward elaboration of the sequences of two or even three kinetically independent Ad_E reactions with the use of the structurally diverse unsaturated compounds as the susbstrates. This approach was shown to represent an efficient protocol to achieve a ready assembly of the polyfunctional substrates from three or four simple precursors the structure of the latter being variable independently and within a rather broad limits.

The structure of the intermediates arising at the key step of the route B coupling has been firmly established and factual data about the steric course of the product determining step have been accumulated. The results of these studies attested to the promise of the utilization of multicomponent coupling carried out with the help of the sulfur containing electrophile as a prospective protocol of diastereoslective synthesis.

Summing up, the main result of the reviewed studies consists in the demonstration of the possibilities and the synthetic potential of the use of electrophilic addition as the basic step in the controlled sequences of intermolecular transformations. In essence the elaborated novel approach could be considered as the "reversed polarity" protocol which complements the well-known method based upon Ad_N reactions, and as the latter it might find an extensive use in organic synthesis.

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References

1. (a) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; L. F. Tietze and U. Beifuss, *Angew. Chem.*, *Int. Ed. Engl.*, 1993, **32**, 131; (b) T. Hudlicky, *Chem. Rev.*, 1996, **96**, 3; (c) P. I. Parsons, C. S. Penkett, and A. J. Shell, *Chem. Rev.*, 1996, **96**, 195; (d) G. H. Posner, *Chem. Rev.*, 1986, **86**, 831; (e) T.-L. Ho, *Tandem Reactions in Organic Synthesis*, Wiley-Interscience, New York, 1992, 537 pp.; (f) P. A. Wender and B. P. Miller, in *Organic Synthesis: Theory and Applications*, Ed. T. Hudlicky, JAP Press, Greenwich, CT, 1993, Vol. **2**, p. 27; (g) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Series, Pergamon, Oxford, 1992, 373 pp.
2. W. S. Johnson, *Angew. Chem.*, *Int. Ed. Engl.*, 1976, **15**, 9.
3. (a) T. Takahashi, H. Okumoto, and T. Tsuji, *Tetrahedron Lett.*, 1984, **25**, 1925; T. Takahashi, Y. Naito, and T. Tsuji, *J. Am. Chem. Soc.*, 1981, **103**, 5261; (b) G. Posner, *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, New York, 1980, 139 pp.
4. P. V. Fish and W. S. Johnson, *J. Org. Chem.*, 1994, **59**, 2324; C. H. Heathcock, *Angew. Chem.*, *Int. Ed. Engl.*, 1992, **31**, 665.
5. P. B. D. De la Mare and R. Bolton, *Electrophilic Additions to Unsaturated Systems*, Elsevier, Amsterdam, 1982, 645 pp.
6. R. Robinson, in *CIBA Foundation Symposium on the Biosynthesis of Terpenes and Sterols*, Eds. G. E. Wolstenholme, M. J. O´Connor, and A. Churchil, LTD, London, 1959, p. 16.
7. P. Vogel, *Carbocation Chemistry*, in *Studies in Organic Chemistry*, Vol. **21**, Elsevier, Amsterdam, 1985, p. 426.
8. (a) W. A. Smit, I. P. Smolyakova, and R. Caple, *Chem. Rev.*, 1994, **94**, 2359; (b) H. Mayr, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1371; H. Mayr, *Control of Electrophilicity in Aliphatic Friedel Crafts Reactions*, in *Selectivities in Lewis Acid Promoted Reactions*, Ed. D. Schinzer, Kluwer Academic Publishers, Dodrecht, 1989, p. 21.
9. R. Caple, *Utilization of Stepwise Ad_E reactions in Designing Organic Synthesis*, in *Organic Synthesis: Modern Trends*, Ed. O. V. Chizhov, Blackwell Scientific Publications, London, 1987, p. 119.
10. K. M. Nicholas, *Acc. Chem. Res.*, 1987, **20**, 207.
11. A. A. Schegolev, W. A. Smit, Y. B. Kalyan, M. Z. Krimer, and R. Caple, *Tetrahedron Lett.*, 1982, **23**, 4419.
12. H. Neunhoeffer and W. K. Franke, *Konjugierte en-yne*, in *Houben-Weil, Methoden der Organischen Chemie*, Bd. V/1d, 1972.
13. (a) A. A. Shchegolev, W. A. Smit, G. S. Mikaelyan, A. S. Gybin, Yu. B. Kal´yan, M. Z. Krimer, R. Caple, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 2571 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 2355 (Engl. Transl.)]; (b) G. S. Mikaelyan, W. A. Smit, A. S. Batsanov, and Yu. T. Struchkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 2105 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 1922 (Engl. Transl.)]; (c) W. A. Smit, A. A. Schegolev, A. S. Gybin, G. S. Mikaelian, and R. Caple, *Synthesis*, 1984, 887.
14. (a) G. S. Mikaelian, A. S. Gybin, W. A. Smit, and R. Caple, *Tetrahedron Lett.*, 1985, **26**, 1269; (b) G. S. Mikaelyan, A. S. Gybin, and W. A. Smit, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 2277 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1985, **34**, 2106 (Engl. Transl.)].
15. H. Mayr, O. Kuhn, C. Schlief, and A. R. Ofial, *Tetrahedron*, 2000, **56**, 4219.
16. N. E. Schore, *The Pauson-Khand Cycloaddition Reaction for Synthesis of Cyclopentenones*, in *Organic Reactions*, Vol. **40**, Ed. L. A. Paquette, Wiley, New York, 1991, Ch. 1.
17. (a) W. A. Smit, A. S. Gybin, A. S. Shashkov, Y. T. Struchkov, L. G. Kuz´mina, G. S. Mikaelian, R. Caple, and E. D. Swanson, *Tetrahedron Lett.*, 1986, **27**, 1241; (b) W. A. Smit, S. O. Simonyan, G. S. Mikaelyan, S. S. Mamyan, A. S. Gybin, A. S. Shashkov, and R. Caple, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 334 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 285 (Engl. Transl.)];
18. (a) A. S. Gybin, W. A. Smit, A. L. Veretenov, S. O. Simonyan, A. S. Shashkov, Yu. T. Struchkov, L. G.

Kuz′mina, and R. Caple, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 2756 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, (Engl. Transl.)]; (b) A. L. Veretenov, A. S. Gybin, W. A. Smit, V. A. Chertkov, and A. S. Shashkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 1879 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 1725 (Engl. Transl.)].

19. (a) W. A. Smit, A. S. Gybin, S. O. Simonyan, A. L. Veretenov, and A. S. Shashkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 232 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 225 (Engl. Transl.)]; (b) A. S. Gybin, W. A. Smit, R. Caple, A. L. Veretenov, A. S. Shashkov, L. G. Vorontsova, M. G. Kurella, V. S. Chertkov, A. A. Carapetyan, A. Y. Kosnikov, M. S. Alexanyan, S. V. Lindeman, V. N. Panov, A. V. Maleev, Y. T. Struchkov, and S. M. Sharpe, *J. Am. Chem. Soc.*, 1992, **114**, 5555.
20. L. A. Paquette, *Top. Curr. Chem.*, 1979, **79**, 41; 1984, **119**, 1.
21. N. E. Schore and M. J. Knudsen, *J. Org. Chem.*, 1987, **52**, 569.
22. A. L. Veretenov, W. A. Smit, L. G. Vorontsova, M. G. Kurella, R. Caple, and A. S. Gybin, *Tetrahedron Lett.*, 1991, **32**, 2109.
23. G. Mehta, K. S. Rao, and M. S. Reddy, *J. Chem. Soc., Perkin Trans. 2*, 1991, 693.
24. E. J. Corey, M. C. Desai, and T. A. Engler, *J. Am. Chem. Soc.*, 1985, **107**, 4339.
25. W. A. Smit, N. S. Zefirov, I. V. Bodrikov, and M. Z. Krimer, *Acc. Chem. Res.*, 1979, **12**, 282.
26. (a) M. A. Ibragimov, O. V. Lyubinskaya, and W. A. Smit, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1983, 1204 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1983, **32**, 1088 (Engl. Transl.)]; (b) M. A. Ibragimov and W. A. Smit, *Tetrahedron Lett.*, 1983, **24**, 961; (s) M. A. Ibragimov, O. V. Lyubinskaya, and W. A. Smit, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1983, 1839 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1983, **32**, 1665 (Engl. Transl.)]; (d) M. A. Ibragimov, W. A. Smit, and M. I. Lazareva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 392 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1985, **34**, 359 (Engl. Transl.)]; (e) S. K. Patel and I. Paterson, *Tetrahedron Lett.*, 1983, **24**, 1315; (f) R. P. Alexander and I. Paterson, *Tetrahedron Lett.*, 1983, **24**, 5911; (g) I. P. Smolyakova and W. A. Smit, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 485 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1985, **34**, 443 (Engl. Transl.)]; (h) I. P. Smolyakova and W. A. Smit, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 198 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1988, **37**, 183 (Engl. Transl.)].
27. M. A. Ibragimov, M. I. Lazareva, and W. A. Smit, *Synthesis*, 1985, 880.
28. M. H. D. Postema, *Tetrahedron*, 1992, **48**, 8545.
29. (a) I. P. Smoliakova, W. A. Smit, E. A. Zal′chenko, O. S. Chizhov, A. S. Shashkov, R. Caple, S. Sharpe, and C. Kuehl, *Tetrahedron Lett.*, 1993, **34**, 3047; (b) I. P. Smoliakova, W. A. Smit, J. Gong, A. S. Shashkov, and R. Caple, *J. Org. Chem.*, 1995, **60**, 1221; (c) I. P. Smolyakova, Y. H. Kim, M. J. Barnes, R. Caple, W. A. Smit, and A. S. Shashkov, *Mendeleev Commun.*, 1995, 15.
30. (a) I. P. Smolyakova, W. A. Smit, and A. I. Lutsenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 119 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 104 (Engl. Transl.)]; (b) I. P. Smolyakova, W. A. Smit, A. I. Lutsenko, and E. D. Daeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 114 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 101 (Engl. Transl.)]; (s) I. P. Smolyakova and W. A. Smit, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 279 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1988, **37** (Engl. Transl.)]; (d) I. P. Smolyakova and W. A. Smit, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 2036 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 1850 (Engl. Transl.)].
31. P. Fisher, in *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulfur Analogs*, Ed. S. Patai, Wiley, New York, 1980, Supplement E, Ch. 17.
32. (a) I. P. Smolyakova, W. A. Smit, and B. Ohinov, *Tetrahedron Lett.*, 1991, **32**, 2601; (b) I. P. Smolyakova, W. A. Smit, Yu. N. Bubnov, and A. S. Shashkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 1100 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 981 (Engl. Transl.)]; (c) I. P. Smolyakova, R. Caple, V. R. Magnuson, V. R. Polyakov, W. A. Smit, A. S. Shashkov, and B. Ohinov, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1065.
33. (a) A. Heyford, M. Lovdahl, M. I. Lazareva, Y. K. Krishenko, T. Johnson, A. D. Dilman, W. A. Smit, R. Caple, and I. P. Smolyakova, *Mendeleev Commun.*, 1997, 48; (b) M. I. Lazareva, Y. K. Krischenko, A. Heyford, M. Lovdahl, R. Caple, and W. A. Smit, *Tetrahedron Lett.*, 1998, **39**, 1083; (c) M. I. Lazareva, Yu. K. Kryshchenko, A. Heyford, M. Lovdahl, R. Caple, W. A. Smit, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1998, 924 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1998, **47**, 895 (Engl. Transl.)].
34. (a) I. V. Bodrikov, L. V. Chumakov, A. N. Pryadilova, G. A. Nisnevich, Yu. V. Gatilov, I. Yu. Bagryanskaya, V. I. Mamatyuk, G. N. Dolenko, and V. A. Barkhash, *Zh. Org. Khim.*, 1984, **20**, 2257 [*J. Org. Chem. USSR*, 1984, **20** (Engl. Transl.)]; (b) D. Dittmer and B. H. Patwardhan, in *The Chemistry of Sulfonium Group*, Eds. C. J. M. Stirling and S. Patai, Wiley, New York, 1981, Ch. 13.
35. (a) M. I. Lazareva, Y. K. Krischenko, R. Caple, D. Wakefield, A. Heyford, W. A. Smit, and A. S. Shashkov, *Tetrahedron Lett.*, 1998, **39**, 8789; (b) M. I. Lazareva, Y. K. Krischenko, R. Caple, V. G. Young, Jr., and W. A. Smit, *Mendeleev Commun.*, 1999, 24; (c) M. I. Lazareva, Yu. K. Kryshchenko, R. Caple, W. A. Smit, K. A. Lysenko, and A. S. Shashkov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 82 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 85].
36. T. Sammakia and R. S. Smith, *J. Am. Chem. Soc.*, 1994, **116**, 7915; S. E. Denmark and N. G. Almstead, *J. Am. Chem. Soc.*, 1991, **113**, 8089.
37. C. Genari, *Selectivities in Lewis Acid Promoted Reactions*, Ed. D. Schinzer, Kluwer Academic Publishers, Dordrecht, 1989; M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 566.

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