REVIEW

Intermolecular Reactions of γ-Halocarbanions – Stepwise Analogs of 1,3-Dipolar Cycloaddition

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Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

γ-Halocarbanions, short-lived intermediates, add to electron-deficient double bonds of aldehydes, *Michael* acceptors, and imines to form anionic adducts that enter intramolecular 1,5-substitution to form five-membered rings of tetrahydrofurans, cyclopentanes, and pyrrolidines, respectively. Although the γ-halocarbanions can be generated by simple deprotonation of appropriate precursors, a wealth of other methods based on *Lewis* acid-catalyzed opening of cyclopropanes with formation of dipolar species utilizes a similar mechanistic scheme. In our review, we analyze kinetic relations of elementary processes in the multistep transformations, and demonstrate how structural factors influence the mechanisms and selectivity of the reaction.

Introduction. – Halocarbanions contain in a molecule nucleophilic and electrophilic centers, hence they can enter a great variety of reactions. The most interesting are α-halocarbanions in which nucleophilic and potential electrophilic centers are in 1,1 relation. The most characteristic reactions of these species is addition to electron-deficient C=O, C=N, and C=C bonds to produce anionic adducts, in which nucleophilic and electrophilic centers are in 1,3 relation. These anionic adducts undergo subsequently intramolecular 1,3-nucleophilic substitutions to produce three-membered rings. To these category belong the *Darzens* [1] and aza-*Darzens*[1]) reactions leading to oxiranes and aziridines, and synthesis of cyclopropanes *via* reactions of α-halocarbanions with the *Michael* acceptors [3]. Some α-halocarbanions are able to undergo spontaneous C–halogen bond dissociation to produce carbenes that can add to alkenes to give cyclopropanes [4]. Adducts of α-chlorocarbanions to electron-deficient arenes, particularly nitro arenes, can react further along pathway of base-induced β-elimination of HCl in process known as Vicarious Nucleophilic Substitution (VNS) of hydrogen [5].

β-Halocarbanions have not found much application as intermediates in organic synthesis. Attempts to deprotonate β-chloro nitriles, esters, or sulfones, *etc.*, result in β-elimination of HCl according to *E*2 or *E*1*cb* mechanism [6]. β-Halocarbanions are also

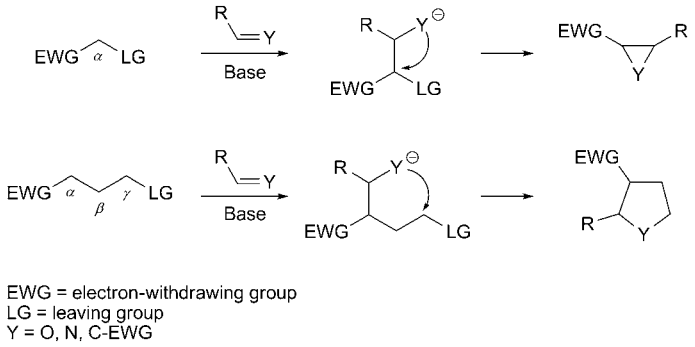
[1]) For stereoselective variants of the aza-*Darzens* reaction, see [2].

produced as short-lived intermediates in vinylic nucleophilic substitution of halogen in β-chlorovinyl ketones and similar compounds [7].

Chemistry of γ-halocarbanions was for a long time limited to intramolecular substitution resulting in formation of cyclopropane derivatives[2]). This reaction was the dominating process independent of way of generation of the carbanions: deprotonation of γ-chlorobutyronitrile and analogs, alkylation of methylenic carbanions with 1,2-dihaloethanes, or addition of α-halocarbanions to the *Michael* acceptors. Due to high rate of intramolecular 1,3-substitution in γ-halocarbanions, this process is often considered γ-elimination. To this category belong also the *Favorsky* rearrangement [9] and the *Ramberg–Bäcklund* reaction [10] that proceed *via* intramolecular 1,3-substitution in α-halo-α'-enolates of α-halo ketones, and α-halo-α'-carbanions of α-halodialkylsulfones.

Comparison of γ-halocarbanions with α-halocarbanions indicates that intermolecular reactions of γ-halocarbanions should offer attractive possibilities for organic synthesis (*Scheme 1*).

Scheme 1. *Reactions of α- and γ-Halocarbanions with Electron-Deficient Double Bonds*



EWG = electron-withdrawing group
LG = leaving group
Y = O, N, C-EWG

Indeed, addition of α-halocarbanions to electron-deficient double bonds changes a mutual relation of nucleophilic and electrophilic centers from 1,1 to 1,3, hence similar addition of γ-halocarbanions should change relation of such centers from 1,3 to 1,5. As a consequence, such reactions should provide possibility of synthesis of five-membered rings of tetrahydrofurans, pyrrolidines, and cyclopentanes. However, due to fast intramolecular 1,3-substitution in γ-halocarbanions, there are only few reports of intermolecular reactions with aldehydes or *Michael* acceptors, when the 1,3-substitution was a slow process or did not proceed due to their structural features.

Tin enolates of 4-chlorobutyrophenones react with aromatic aldehydes to produce 2-aryl-3-benzoyltetrahydrofurans (*Scheme 2*) [11].

Intramolecular 1,3-substitution in γ-halocarbanions is suppressed by exomethylidene group in β-position due to the strain imposed on the transition state of 1,3-intramolecular substitution. Thus γ-bromocarbanion of 3-bromo-2-methylidenepropyl

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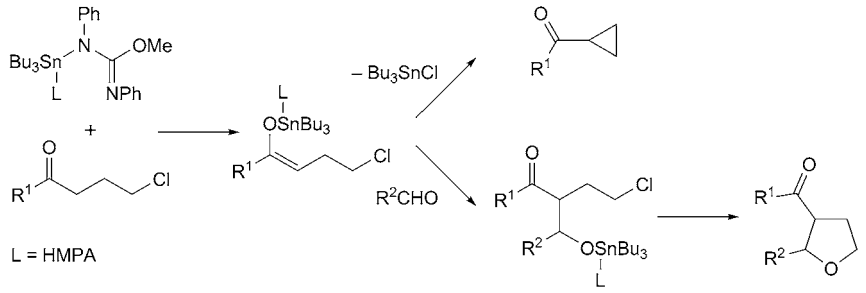
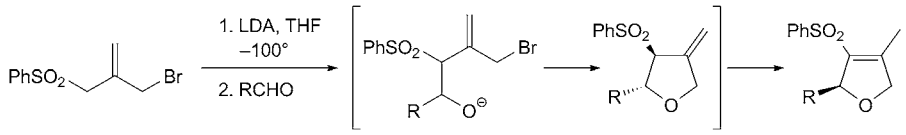
[2]) For an example of generation of (dimethylvinylidene)carbene by deprotonation of 3-chloro-3-methylbut-1-yne applied in synthesis of (dimethylvinylidene)cyclopropanes, see [8].

Scheme 2. *Reactions of Tin Enolates of γ-Chlorobutyrophenones with Aromatic Aldehydes.* HMPA = Hexamethylphosphoric triamide.



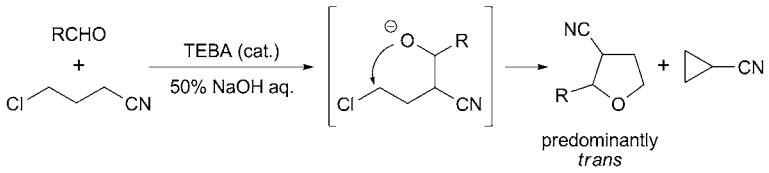
Scheme 3. *Synthesis of Dihydrofurans from β-Methylidene-γ-halocarbanion Precursor and Aldehydes* [12]. LDA = LiN^iPr_2.



phenyl sulfone is a relatively long lived species and can add to aldehydes to give dihydrofurane derivatives (*Scheme 3*) [12a][12b][3]).

A few years ago, we have started systematic studies of intermolecular reactions of γ-halocarbanions generated from the simplest precursors: 3-chloropropyl phenyl sulfone, 4-chlorobutyronitrile, alkyl 4-chlorobutyrates, *etc.* [13][14]. Upon treatment with strong base, these compounds undergo deprotonation and subsequent fast 1,3-intramolecular substitution of the produced carbanions to form substituted cyclopropanes. Nevertheless, when the carbanions are generated in the presence of active electrophiles such as aromatic aldehydes, the intermolecular addition is faster than intramolecular substitution, thus formation of tetrahydrofurans becomes the major process (*Scheme 4*) [13]. The situation is rather complicated, because the addition is a reversible process, so rate of 1,5-intramolecular substitution in the produced aldol-type adducts also affects the outcome of the reaction. Although imines and *Michael* acceptors are usually less active electrophiles than aldehydes, they also can trap some γ-

Scheme 4. *Initial Observation of Synthesis of Substituted Tetrahydrofurans under Phase-Transfer Catalysis* (PTC) *Conditions* [13]. TEBA = Triethyl(benzyl)ammonium chloride.

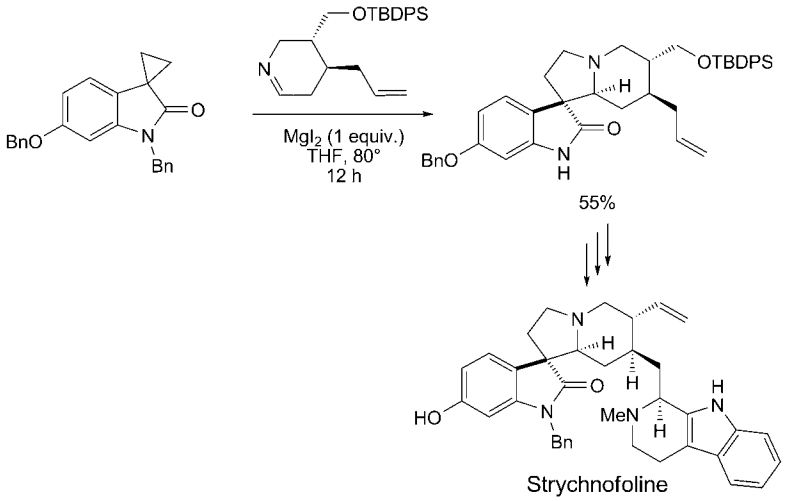


[3]) A similar approach was applied for synthesis of pyrrolidines [12c][12d] and cyclopentanes [12e].

halocarbanions generated *via* deprotonation to produce, as the final products, pyrrolidines [15] and cyclopentanes [16]. The competition between intramolecular formation of cyclopropanes and intermolecular reactions leading to five-membered rings can be affected by a few factors, such as kind of leaving groups and carbanion-stabilizing groups, additional substituents in the carbanion chain, conditions, *etc.* [17].

An interesting and general alternative to synthesis of the five-membered ring systems of tetrahydrofurans, pyrrolidines, and cyclopentanes *via* reactions of γ-halocarbanions are reactions of substituted cyclopropanes with aldehydes, imines, and *Michael* acceptors catalyzed by *Lewis* acids [18][4]). Some of these reactions proceed *via* cyclopropane ring opening resulting in formation of γ-halocarbanions or analogs. Further reactions of these species with imines or aldehydes, followed by 1,5-intramolecular substitution afford pyrrolidines and tetrahydrofurans. Alternatively, the cyclopropyl ring can be directly attacked by a carbonyl or imine group without transient carbanionic intermediate to generate a 1,5-zwitterionic species that undergoes cyclization to a five-membered ring. Taking into account that both paths comprise multiple reversible steps, one can assume, that the whole process is controlled by irreversible formation of five-membered ring (*Scheme 5*) [20].

Scheme 5. *Total Synthesis of (±)-Strychnofoline with Key Step Based on MgI_2-Catalyzed Opening of Cyclopropane Derivative* [20]. TBDPS = ^{t}BuPh$_2$Si.



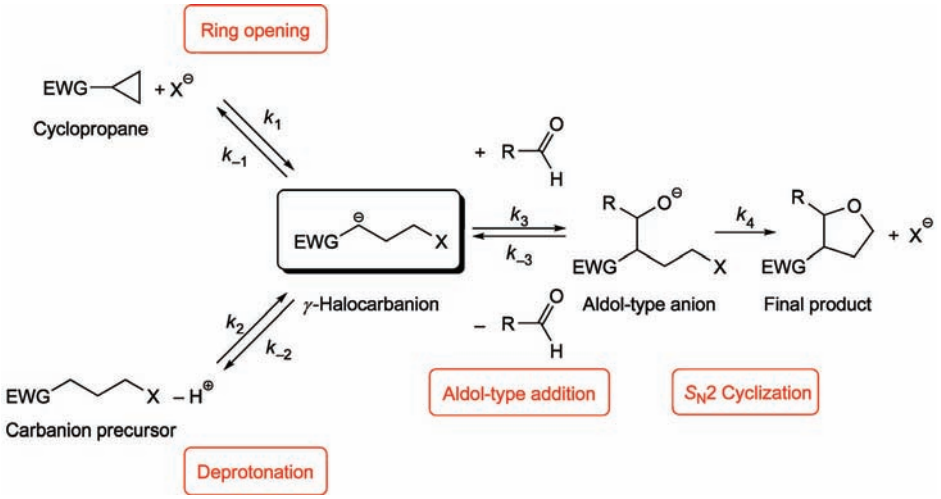
Thus, synthesis of five-membered rings *via* intermolecular reaction of halocarbanions and related species proceeds according to a set of mechanistic variants. Depending on educts and conditions, five-membered rings can be formed stepwise *via* generation of intermediate γ-halocarbanions that add reversibly to aldehydes and subsequent 1,5-intramolecular substitution, or *via* ring opening of activated cyclopropanes, followed by more or less synchronous reactions of generated species with aldehydes. Since our essay is not intended to be a comprehensive review, we will present only examples of stepwise

[4]) For a review of cyclopropane ring-opening methods in synthesis of natural products, see [19].

reactions of separately generated γ-halocarbanions that are less known. Selected, representative examples of formation of five-membered rings *via* ring opening of cyclopropanes are presented in the following sections.

Kinetic Considerations of Generation and Reactions of γ-Halocarbanions and Related Species. – First, we briefly define elementary processes in reactions of γ-halocarbanions with electrophilic multiple bonds (*e.g.*, C=O group of aldehyde). We consider that γ-halocarbanions may be generated by two routes: opening of cyclopropane ring with halide anion (rate constant of the process is k_1) or by deprotonation of a precursor with base (k_2). The intermediate γ-halocarbanion may undergo cyclization (k_{-1}), protonation (k_{-2}) or addition to the C=O group (k_3). Product of the last process, *i.e.*, aldol-type anion, undergoes cyclization to five-membered ring (k_4) or dissociates (k_{-3}), as depicted in *Scheme 6*.

Scheme 6. *General Mechanistic Scheme of Generation and Transformations of γ-Halocarbanions.* k_1: *Lewis* acid-catalyzed or thermal ring opening of cyclopropane with halide anions, k_{-1}: cyclization of γ-halocarbanion to cyclopropane, k_2: deprotonation of carbanion precursor, k_{-2}: protonation of γ-halocarbanion, k_3: aldol-type addition of γ-halocarbanion to aldehyde, k_{-3}: dissociation of aldol-type anion to γ-halocarbanion and aldehyde, and k_4: cyclization of aldol-type adduct to tetrahydrofuran.



Generation and Cyclization of γ-Halocarbanions (k_1/k_{-1} and k_2/k_{-2}). Inherent characteristics of intramolecular substitution to three-membered rings and reverse ring opening[5]) to acyclic products require consideration of structure of intermediate γ-halocarbanions. Although the reactions have long history [22], it was not known until 2002 [14] that lifetimes of γ-halocarbanions are very short even at low temperatures due to proximity of the reacting centers [23][24]. Deprotonation (k_2) and reprotonation (k_{-2}) reactions of model substrates and their competition with cyclization to cyclopropane were studied *via* deuterium-exchange experiments [14][24]. It was shown that the halogen atom in γ-position to $ArSO_2$ and CN groups exerts a significant

[5]) For ring opening of non-activated cyclopropanes, see [21].

carbanion-stabilizing effect, enhancing their kinetic acidity by factor of 50–100 as compared with unsubstituted analogs. This offers a reliable explanation why alkylation of methylenic carbanions with 1,2-dihaloethanes cannot be stopped on β-haloethylated products, but proceeds further to cyclopropanes.

Aldol-Type Addition and Dissociation of Aldol-Type Adducts (k_3/k_{-3}). Despite of very short lifetimes of γ-halocarbanions, these reactive species can be trapped with active external electrophiles, such as aldehydes, *etc.* The reaction can be observed provided that the carbanions are generated in the presence of external electrophilic partners, or the carbanion is sufficiently long-living to survive, when deprotonation and addition of electrophile are independent steps.

Intramolecular Nucleophilic 1,5-Substitution (k_4). The process is relatively fast (faster than 1,3-substitution leading to three-membered ring for heteronucleophiles and slower than cyclization to cyclopropanes for carbanions [23]) and takes seconds to minutes at $-50°$ for a S_N2 substitution of chloride [25]. Contrary to cyclopropanes, the formed five-membered rings lack strain energy, and thus the process is considered virtually irreversible.

Generation of γ-halocarbanions can be realized by different methods based on various classes of substrates: *1*) γ-halocarbanion precursors can be deprotonated under basic conditions, *2*) EWG-substituted cyclopropane rings can be opened in catalytic processes to form 1,3-dipolar species of various character, and *3*) α-halocarbanions may undergo conjugate addition to electron-deficient C=C bonds to form anions, which subsequently cyclize in a process of *Michael*-Initiated Ring Closure (MIRC) [26].

In the first approach, γ-halocarbanions are generated by deprotonation and then react along two competitive pathways: intramolecular 1,3-substitution (k_{-1}) and intermolecular aldol-type addition to electrophilic partner (k_3). The competition governs the product distribution (cyclopropane *vs.* five-membered rings), and is related to equilibrium of the aldol addition, $K = k_3/k_{-3}$, reactant concentration (uni- *vs.* bimolecular reaction), temperature (entropic factor), and irreversible formation of five-membered rings (k_4). Thus, under basic conditions acceleration of k_3 and k_4 processes favors formation of product of intermolecular reaction at the expense of side-product, *i.e.*, cyclopropane.

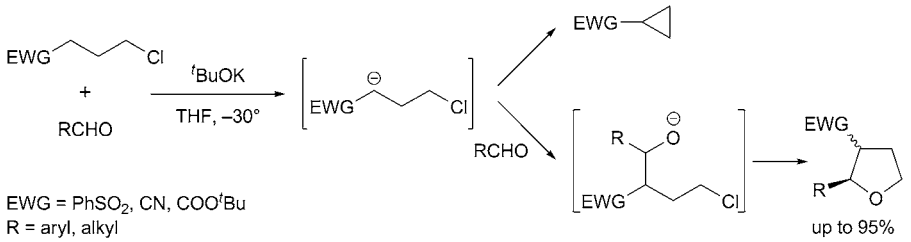
In turn, γ-halocarbanions generated by equilibrium ring opening of cyclopropanes do not suffer from the dead end related to formation of cyclopropane. Both processes assigned as k_1 and k_{-1} proceed at reasonable rates, and the system equilibrates (cyclopropane $\rightleftharpoons$ γ-halocarbanion), until all available cyclopropane substrate is transformed to five-membered ring product *via* addition of electron-deficient double bond and irreversible 1,5-substitution.

Reversibility of the aldol addition is important also for stereochemical consequences of the process. Stereochemical outcome of the reaction may arise from stereoselectivity of the aldol-type addition, which, when followed by fast cyclization (k_4), determines the isomer ratio, or alternatively aldol-type adducts may equilibrate, and then the diastereoisomer ratio depends on relative rates of cyclization of the isomeric aldol-type adducts (*Curtin–Hammett* principle).

Reactions of γ-Halocarbanions Generated by Deprotonation. – *Variations of the Carbanion-Stabilizing Group.* We have shown [14] that, although model γ-halocarban-

ions of 4-chlorobutyronitrile, *tert*-butyl 4-chlorobutanoate, and 3-chloropropyl phenyl sulfone undergo rapid cyclization to substituted cyclopropanes, they can be efficiently trapped with aromatic aldehydes to form aldol-type anions that immediately cyclize to give tetrahydrofurans in excellent yields. Due to high rate of the intramolecular 1,3-substitution, the carbanions must be generated in the presence of aldehydes and in concentrated solution to favor bimolecular addition over unimolecular cyclization to cyclopropanes (*Scheme 7*).

Scheme 7. *Synthesis of 2,3-Disubstituted Tetrahydrofurans under Optimized Basic Conditions*

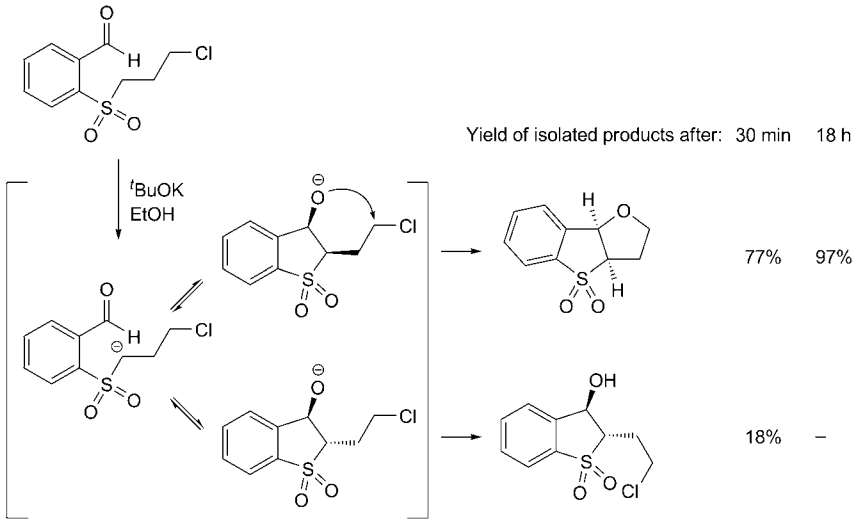


An interesting structural variant, in which both reacting counterparts, γ-halocarbanionic center and electrophilic multiple bond, are in the same molecule, enabled investigation of the competing processes under concentration-independent conditions [27]. For the model carbanion precursor, 3-chloropropyl 2-formylphenyl sulfone was chosen. Since the intramolecular addition of the carbanion to the C=O group is not a stereoselective process, two diastereoisomeric aldol-type adducts are produced, but only that with the anionic O-atom and 2-chloroethyl group in *cis* relation can undergo cyclization. When the reaction is arrested after short time, a substantial quantity of the adduct having OH and CH_2CH_2Cl groups in *trans* relation is isolated. Due to reversibility of the addition, the reaction carried out for a longer time gives tricyclic tetrahydrofuran derivative almost quantitatively. Thanks to location of the C=O group and the carbanionic center in one molecule, intramolecular 1,3-substitution to cyclopropane is not observed, being much slower than 1,5-intramolecular addition of the carbanion to the C=O group (*Scheme 8*).

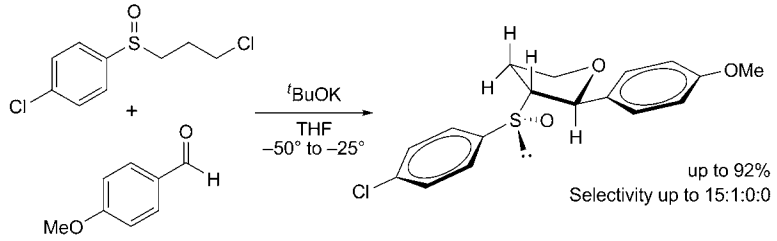
A different approach toward diastereomerically enriched tetrahydrofurans was achieved in reactions of aryl 3-chloropropyl sulfoxides with aldehydes [25]. Contrary to the previous example, in which aldol-type adducts easily equilibrated, and only one of them slowly cyclized to the final product, aldol addition of the sulfoxide-stabilized carbanion was controlled by stereogenic center present on a S-atom and followed by fast cyclization to five-membered ring. Thus, isomer ratio of the produced tetrahydrofurans was controlled by selectivity of the aldol-type addition. From four isomeric tetrahydrofurans possible, main isomer was formed with selectivities up to 15 : 1 : 0 : 0 in very good yields (*Scheme 9*). The preferred isomer most likely arised from a cyclic chair-like transition state of the aldol-type addition, in which substituents occupy preferred equatorial positions.

In contrast to γ-halocarbanions stabilized with electron-withdrawing groups such as COOR, CN, and SO_2Ph, that, in spite of fast intramolecular 1,3-substitution, can be trapped with aldehydes to form tetrahydrofurans, potassium enolates of γ-halobutyr-

Scheme 8. *Intramolecular Variant of γ-Halocarbanions' Reactivity: a One-Pot Synthesis of Tricyclic Tetrahydrofuran Derivative*



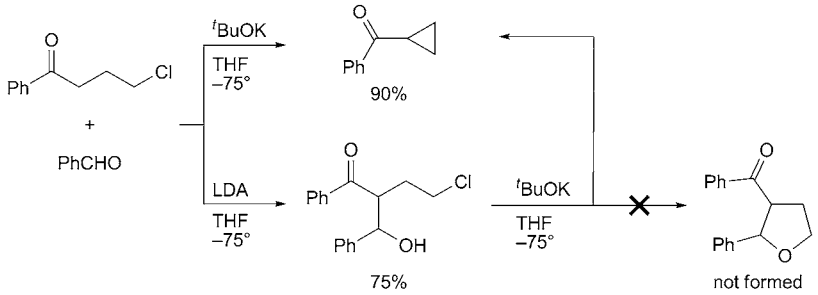
Scheme 9. *Diastereoselective Synthesis of 2,3-Disubstituted Tetrahydrofurans* [28]



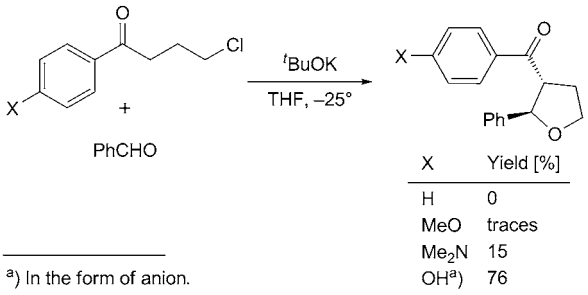
ophenone under similar conditions do not form tetrahydrofurans, but only benzoylcyclopropane. Interestingly, when the reaction of lithium enolate with PhCHO carried out at low temperature was arrested by protonation the aldol-type adduct was isolated as a mixture of diastereoisomers. However, attempts to convert this adduct to tetrahydrofuran by treatment with base failed, and only the cyclopropane was formed (*Scheme 10*) [28].

It seems that dissociation of this adduct was much faster than intramolecular 1,5-substitution, and, due to unfavorable addition equilibrium, only intramolecular 1,3-substitution in the enolate takes place. This rationalization is confirmed by observation that shifting the addition equilibrium towards the aldol-type adduct favors formation of benzoyltetrahydrofuran. This can be achieved in three ways: *a*) increasing the nucleophilicity of the enolate *via* introduction of electron-donating substituents in the aromatic rings (*Scheme 11*) [28]; *b*) using protic solvents that shift equilibrium toward adducts, due to efficient solvation (*Scheme 12*) [28]; and *c*) increasing the electron deficiency of the C=O group (*Scheme 13*) [29].

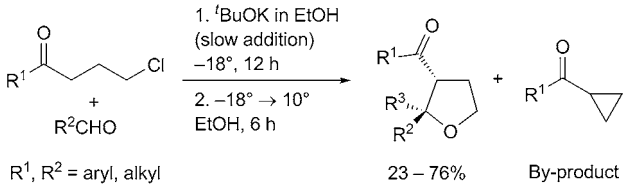
Scheme 10. *Reaction of γ-Chlorobutyrophenone with PhCHO Failed to Give Expected Tetrahydrofuran Derivative* [28]



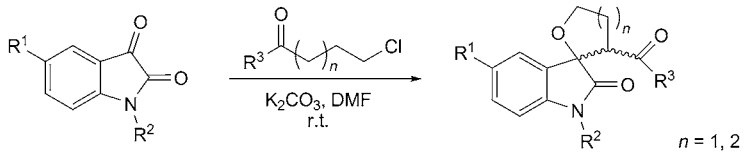
Scheme 11. *Formation of Tetrahydrofuran Derivative from the Reaction of 4-Substituted γ-Chlorobutyrophenones with Benzaldehyde is a Function of Nucleophilicity of the Enolates* [28]



Scheme 12. *Synthesis of 2,3-Substituted Tetrahydrofurans from γ-Chlorobutyrophenone and Aldehydes in a Protic Solvent* [28]



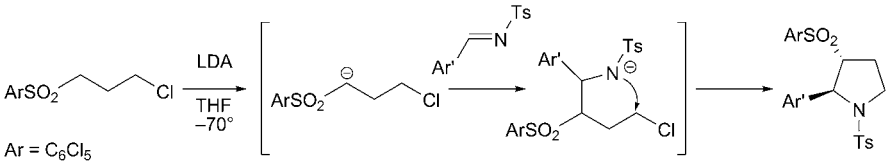
Scheme 13. *Synthesis of Spiro[furan-2,3′-indol]-2′-ones and Spiro[pyran-2,3′-indol]-2′-ones from Electron-Deficient Isatine Derivatives* [29]



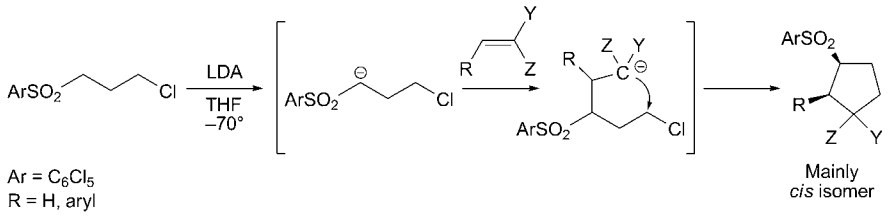
Addition of γ-halocarbanion of 3-chloropropyl phenyl sulfone to the *Michael* acceptors and imines, which are less electrophilic than aldehydes, is slower than 1,3-

intramolecular substitution. It was possible, however, to achieve synthesis of pyrrolidines [15] and cyclopentanes [16], when more acidic 3-chloropropyl pentachlorophenyl sulfone carbanion was used[6]). Due to moderate nucleophilicity of the carbanion, intramolecular 1,3-substitution was slower than addition to activated imines and *Michael* acceptors as shown in *Schemes 14* and *15*, respectively.

Scheme 14. *Synthesis of Pyrrolidines by Reaction of 3-Chloropropyl Pentachlorophenyl Sulfone with Imines* [15]

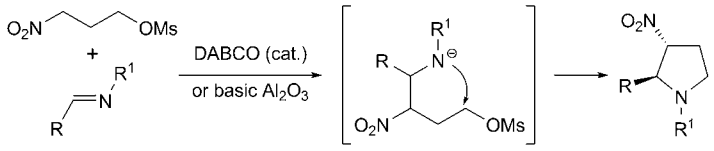


Scheme 15. *Synthesis of Cyclopentanes by Reaction of 3-Chloropropyl Pentachlorophenyl Sulfone with* Michael *Acceptors* [16]



Strong carbanion stabilizing properties of the NO_2 group enabled the one-pot synthesis of 2-substituted-3-nitropyrrolidines. 3-Nitropropan-1-ol methanesulfonate[7]) reacted with non-activated imines (R = aryl, alkyl), prepared *in situ* from aldehydes and aromatic amines, to give substituted pyrrolidines in satisfactory yields (52–90%). The process, consisting of aza-*Henry* reaction, followed by substitution of MsO group by nucleophilic attack of so-formed nitro amine, was catalyzed by DABCO or basic Al_2O_3 and gave products as predominantly *trans*-isomers (*Scheme 16*) [32].

Scheme 16. *Synthesis of Substituted Pyrrolidines from 3-Mesyloxy-1-nitropropane and Imines* [32]. DABCO = 1,4-Diazabicyclo[2.2.2]octane, Ms = methylsulfonyl.

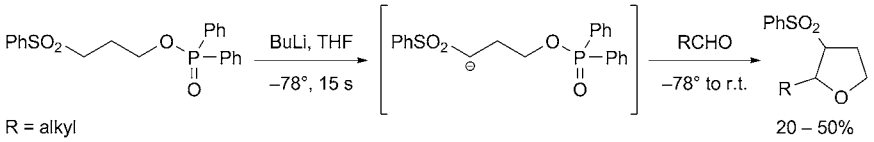


6) For other reactions of 3-chloropropyl pentachlorophenyl sulfone with aldehydes, see [30].

7) For the use of related reagent 1-iodo-3-nitropropane for *in situ* generation of cyclic nitronates and their application as 1,3-dipoles, see [31].

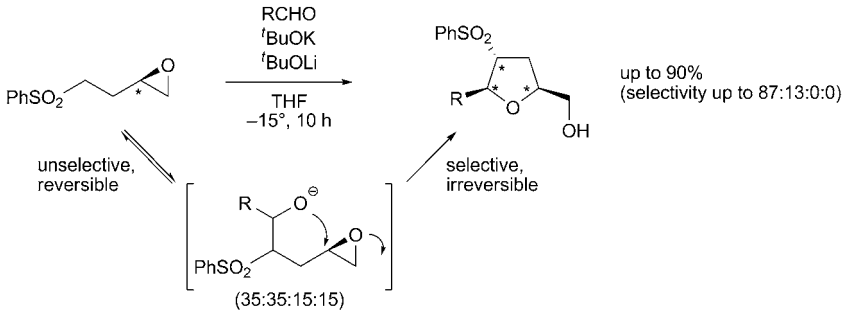
Variations of the Leaving Group. An alternative approach to control rates of intramolecular 1,3-substitution in carbanions bearing leaving group present in a γ-position[8]) was achieved by use of less nucleofugal leaving group [34]. 1,3-Intramolecular substitution in carbanion of 3-(phenylsulfonyl)propyl diphenylphosphinate is slower than in the corresponding chloro carbanion; thus, carbanions can be generated before addition of electrophile. Accordingly, easily enolizable aliphatic aldehydes, which self-condense in the presence of bases, can be engaged to give substituted tetrahydrofurans in reasonable yields 20–50% (*Scheme 17*) [35].

Scheme 17. *Synthesis of 2-Alkyl-3-(phenylsulfonyl)tetrahydrofurans from 3-(Diphenylphosphinoxy)-1-(phenylsulfonyl)propane* [35]



Since ring opening of oxiranes by nucleophiles proceeds as S_N2 reactions, carbanions containing 3,4-epoxyalkyl moieties can be considered as slow-reacting analogs of γ-halocarbanions. Indeed, carbanion of 3,4-epoxybutyl sulfone reacts slowly to form (hydroxymethyl)cyclopropane and, upon addition to aldehydes, affords (hydroxymethyl)tetrahydrofurans. These reactions are catalyzed by *Lewis* acids, such as Li^+ cations. A unique kinetic situation displayed in the system enabled highly diastereoselective formation of 5-(hydroxymethyl)tetrahydrofuran derivatives. Although aldol-type addition was not stereoselective, as was demonstrated by NMR spectra of isolated intermediate adducts, due to fast equilibration of the aldol addition and selective cyclization of one diastereoisomeric intermediate, according to *Curtin–Hammett* principle, the products were formed with high yield and stereoselectivity (*Scheme 18*) [36].

Scheme 18. *Diastereoselective Synthesis of 2,3,5-Substituted Tetrahydrofurans* [36]

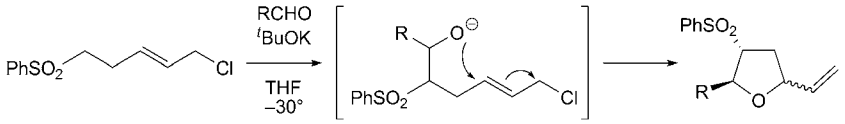


Other Modifications of the γ-Halocarbanion Precursors. Another structural variation that affects competition between inter- and intramolecular reactions was separation of the β- and γ-C-atoms of the γ-halocarbanion precursor by a C=C bond

[8]) For similar processes concerning δ-halocarbanions, see [33].

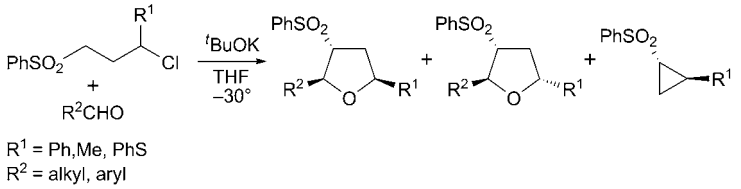
according to the vinylogy concept[9]). In this case, the leaving group (the Cl-atom) was present in an allylic position and was replaced by S_N2' mechanism to give vinyl-substituted products. The variant was realized in reactions of (*E*)- and (*Z*)-isomer of 1-chloro-5-(phenylsulfonyl)pent-2-ene with aldehydes. Although attempts of intramolecular reactions of these carbanions were unsuccessful giving mixtures of cyclopropane, cyclopentane, and butadiene derivatives, their intermolecular reactions with aldehydes proceeded well. Under standard reaction conditions (*t*-BuOK, THF, $-78°$), 2-substituted 3-(phenylsulfonyl)-5-vinyltetrahydrofurans were formed in moderate-to-good yields: 49–90% (*Scheme 19*) [38].

Scheme 19. *Synthesis of 2,3-Disubstituted 5-Vinyltetrahydrofurans* [38]



Additional substituents in γ-position of 3-chloropropyl phenyl sulfone decelerated cyclization of the carbanion to cyclopropane, as well as intramolecular 1,5-substitution of the aldol-type adducts. However by using toluene, in which ion pairs of O-anions of intermediate aldol-type adducts with K^+ cations are expectedly more tight, 2,3,5-trisubstituted tetrahydrofurans were obtained in good yields as mixtures of diastereoisomers (*Scheme 20*) [39].

Scheme 20. *Reactions of γ-Substituted γ-Halocarbanion Precursors with Aldehydes* [39]



Modifications of the γ-Halocarbanion Precursor by Heteroatoms. Although our essay is devoted to reactions of carbanions containing leaving group in γ-position, an interesting variation of the mechanistic scheme is displayed by systems bearing heteroatoms in the carbanion chain. When the heteroatom forms the anionic center (α-position), simple precursor of the anion is 2-chloroethanol and its derivatives. It is known that cyclization of 2-haloalkoxides (*e.g.*, potassium 2-chloroethoxide) is slower than cyclization of 4-haloalkoxides, contrary to relative rates of cyclization of γ- and ε-halocarbanions, for which formation of three-membered rings is faster [23]. Indeed, we observed that aromatic aldehydes can be easily transformed by reaction of 2-chloroethanol and 3-chloropropan-1-ol to the cyclic acetals (dioxolanes and dioxanes, resp.) under basic conditions (*Scheme 21*). From kinetic perspective, main drawback of the process is unfavorable equilibrium of the addition of moderately nucleophilic O-anions of halo alcohols to the C=O group because of competitive intramolecular

[9]) For a vinylogy concept, see [37a]; for a γ-halocarbanion precursor, in which the double bond is a part of alkyl chain, see [37b].

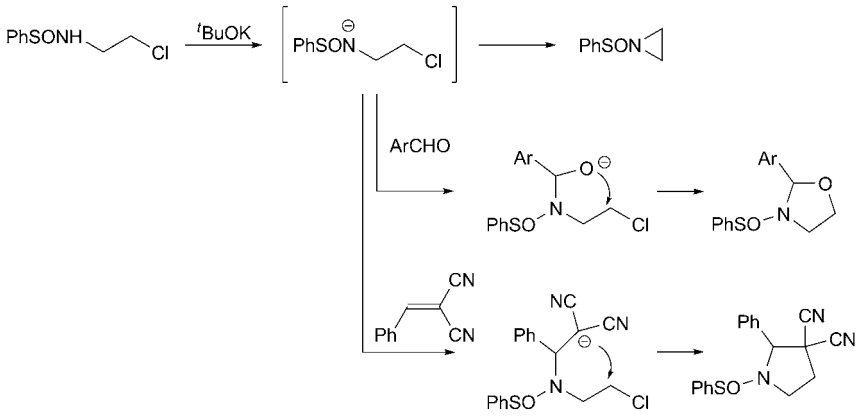
cyclization of the alkoxides to oxiranes. Thus, more electrophilic substrates reacted easily, while aldehydes and ketones bearing electron-donating substituents gave only poor yields of acetals. It is worth to stress that the limitations are opposite to those displayed under common acid-catalyzed acetalization with diols, and the products under basic conditions are stable toward isomerization. Synthesis of enantiomerically enriched products was achieved, when one enantiomer of 1-chloropropane-2,3-diol was used as a substrate [40].

Scheme 21. *Synthesis of Cyclic Acetals under Unusual Basic Conditions* [40]

Thus, anions of chlorohydrines that behave as hetero-analogs of γ-halocarbanions undergo fast 1,3-intermolecular substitutions, but also add to active C=O group of aldehydes to form anionic adducts that *via* intramolecular 1,5-substitution form cyclic acetals.

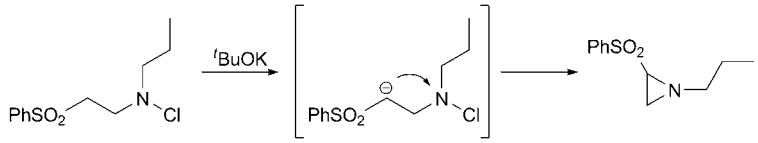
N-Anion of *N*-(chloroethyl)benzenesulfinamide behaves also as hetero-analog of γ-chlorocarbanion. It undergoes intramolecular 1,3-substitution to form 1-(phenylsulfinyl)aziridine, but also adds to aldehydes and the *Michael* acceptors to form five-membered rings of oxazolidines and pyrrolidines, respectively (*Scheme 22*) [41].

Scheme 22. *Intra- and Intermolecular Reactions of* N-*(Chloroethyl)benzenesulfinamide under Basic Conditions* [41]



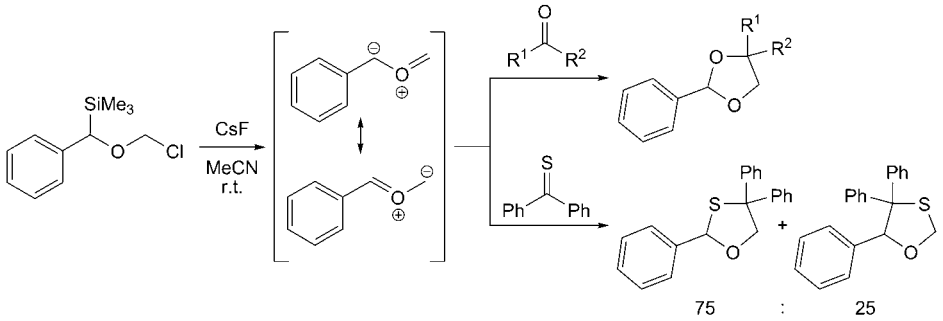
Deprotonation of *N*-chloro amines containing carbanion-stabilizing groups in β-position generates carbanions that can be considered as analogs of γ-halocarbanion, in which halogen is attached to the N-atom. Such carbanions undergo fast intramolecular 1,3-substitution to form aziridines; however, intermolecular addition of these carbanions to aldehydes and *Michael* acceptors was not observed (*Scheme 23*) [42].

Scheme 23. *Reaction of 2-[Chloro(propyl)amino]-1-(phenylsulfonyl)ethane under Basic Conditions* [42]



A quite disparate reactivity is displayed by γ-halocarbanion precursors, in which the heteroatom is in a β-position. When the related precursor bearing TMS group was treated with CsF to generate carbanion, fast γ-elimination process took place. However the γ-elimination product was not a cyclopropane, but a 1,3-dipole[10]), which undergoes cycloaddition to C=O and C=S groups to form dioxolanes and thiodioxolanes (*Scheme 24*) [45]. Thus, the reaction proceeding through electrocyclic transition state gave two isomeric products in contrast to reactivity expected for simple anionic species[11]).

Scheme 24. *γ-Halocarbanion Precursor with Heteroatom Substituent in β-Position Forms Dipoles, Which React along Electrocyclic Pathway* [45].



The different reactivity displayed by precursor with O-atom in a β-position of the alkyl chain is likely due to its ability to form dipolar species, where lone pair of the heteroatom facilitates elimination of the leaving group and stabilizes the positive charge of the dipole.

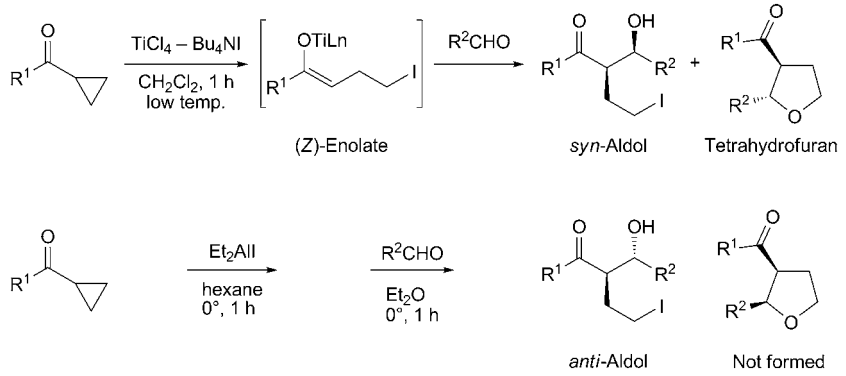
Reactions of Intermediates Generated by Cyclopropane Ring Opening. – An alternative method of generation of γ-halocarbanions and their analogs is based on *Lewis* acid-catalyzed ring opening of cyclopropane derivatives containing electron-withdrawing groups. This methodology was used for selective generation of (*Z*)- and (*E*)-enolates of γ-iodobutyrophenone and 5-iodopentan-2-one (*Scheme 25*) [47]. The authors observed that, by variation of *Lewis* acid, 3-iodopropylenolates can be generated as pure (*Z*)- and (*E*)-isomers. In the next step, the intermediates added to aldehydes to afford *syn*- and *anti*-adducts as single isomers. The isomeric adducts

[10]) Derivatives of bromoacetone also spontaneously form dipoles, and the dipolar species exist in equilibrium with cyclopropanones, see [43] (see also [44]).

[11]) For a proposal of a stepwise mechanism, see [46].

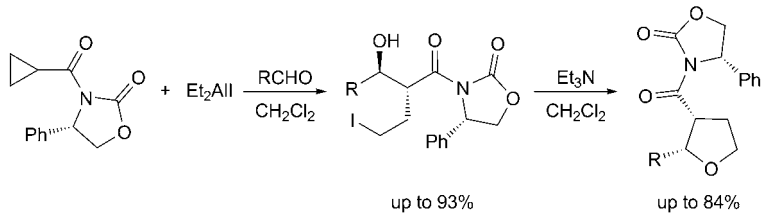
displayed different reactivities, *i.e.*, only *syn*-aldol adducts cyclized to *trans*-2,3-disubstituted tetrahydrofurans, while the *anti*-adducts were stable under the reaction conditions. Full conversion of the starting materials to tetrahydrofurans was observed, when the reaction was promoted by alumina. Equilibration of intermediate aldols, followed by 1,5-nucleophilic substitution, gave tetrahydrofurans as the only products (60–94%; *Scheme 25*).

Scheme 25. *Generation of Titanium γ-Iodoenolates from Cyclopropyl Ketones and Their Reaction with Aldehydes to Give 2,3-Substituted Tetrahydrofurans* [47]



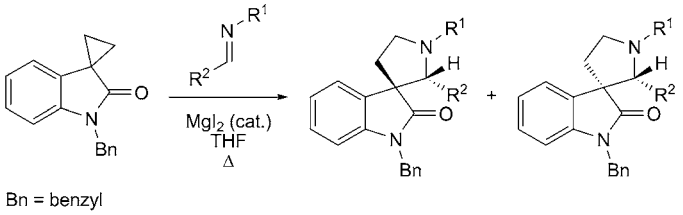
Addition of aluminum γ-iodoenolates generated *via* cyclopropyl ring opening of chiral 3-(cyclopropylcarbonyl)-4-phenyloxazolidin-2-one to aldehydes proceeds with high stereoselectivity when carried out in CH_2Cl_2. The adducts obtained undergo selective cyclization in the presence of Et_3N to give tetrahydrofurans as single diastereoisomers in very good yields: 82–93% (*Scheme 26*) [48].

Scheme 26. *Asymmetric Version of Haloaldol Reaction of Enolates Generated by Cyclopropane Ring Scission* [48]



Although, in both of the presented examples (*Schemes 25* and *26*), γ-haloenolates are generated by opening of substituted cyclopropane ring, the approach is similar to reactions of γ-halocarbanions generated *via* deprotonation of appropriate precursors. Particularly, in the latter case, the product is formed under kinetic control, and formation of cyclopropane is an irreversible undesired side-process. A very different approach performed as a one-pot procedure under equilibrium conditions, was developed by *Carreira* and co-workers for the synthesis of spiro[pyrrolidin-3,3′-indole] ring system (*Scheme 27*) [49]. Ring expansion of spiro[cyclopropan-1,3′-oxindole] with imines was catalyzed by MgI_2, in which the *Lewis* acidity of the metal center (Mg^{2+})

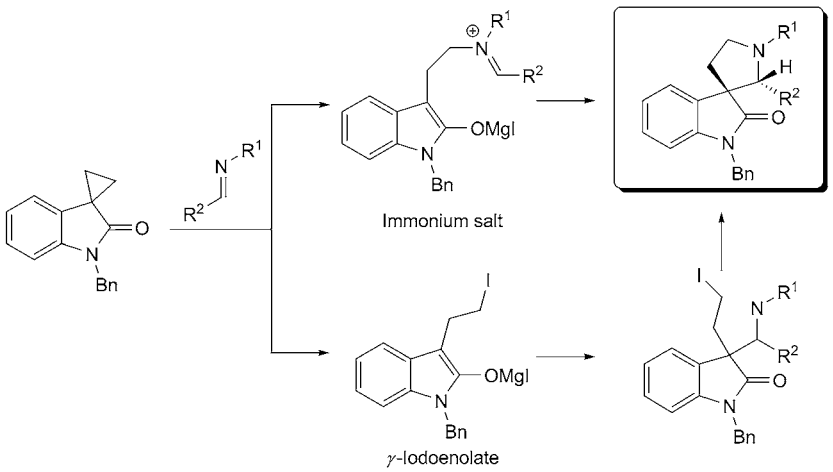
Scheme 27. *Synthesis of Spiro[indole-pyrrolidine] Derivatives Described by* Carreira *and co-workers* [49]



and nucleophilicity of the counterion (I^-) cooperate. The reaction gave good yields and diastereoselectivities of pyrrolidine derivatives.

Two different mechanisms for this process were considered: nucleophilic opening of the cyclopropane ring by aldimine with formation of immonium salt, or nucleophilic attack of I^- anion with formation of magnesium γ-iodoenolate (*Scheme 28*). Although both pathways were possible, the latter was considered more plausible. When instead of MgI_2, magnesium trifluoromethanesulfonate ($Mg(OTf)_2$)-containing non-nucleophilic anion was used, the reaction was suppressed. Since both *N*-alkyl and *N*-arylsulfonyl aldimines undergo the reaction indicates that nucleophilic attack of N-atom is less probable. Presumably, the cyclopropane undergoes numerous ring-opening/ring-closure reactions, addition of transient magnesium γ-iodoenolate to imine, followed by irreversible intramolecular 1,5-substitution in the adduct, shifts the process until five-membered ring product is formed in high yield (*Scheme 28*) [49].

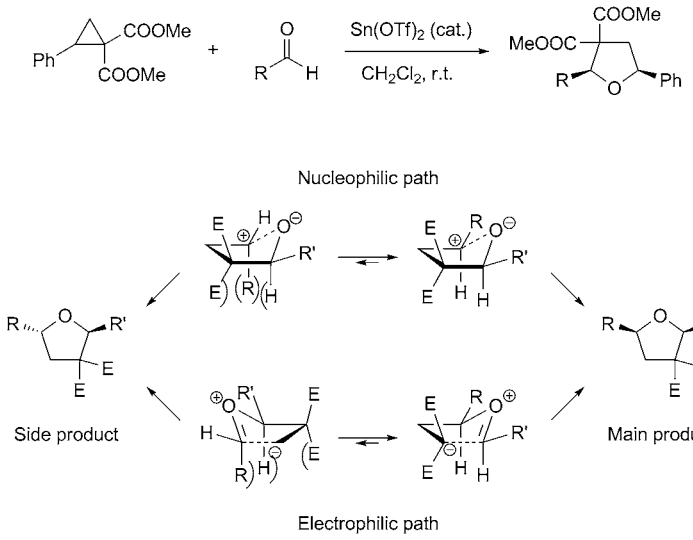
Scheme 28. *Mechanistic Considerations on Synthesis of Spiro[indole-pyrrolidine] Derivatives* [49]



This methodology was successfully applied in numerous total syntheses of natural products such as, *e.g.*, (±)-strychnofoline (*Scheme 5*) [20], (−)-α-kainic acid [50], and others [19].

The *Lewis* acid-catalyzed reactions of trisubstituted cyclopropanes bearing two electron-withdrawing groups with aldehydes provide tetrasubstituted tetrahydrofurans (*Scheme 29*) [51]. In contrast to conditions described by *Carreira* and co-workers (*Scheme 27*) [49], the reaction is catalyzed by *Lewis* acid $Sn(OTf)_2$ associated with non-nucleophilic counterion, thus ring opening of cyclopropane with formation of a kind of γ-halocarbanionic species is less plausible in this case. More probably, cyclopropane ring is directly attacked by the C=O group of the aldehyde, and underwent *Lewis* acid-assisted opening, followed by recombination of resulted 1,5-zwitterionic species. Two mechanisms of the process along nucleophilic and electrophilic paths were postulated, and in both cases high diastereoselectivity was explained by favorable orientation of substituents in transition state of the reaction[12]).

Scheme 29. *Highly Diastereoselective Synthesis of Tetrahydrofurans Described by* Pohlhans *and* Johnson [51]



1,3-Dipolar species generated *via Lewis* acid-catalyzed cyclopropane ring opening can also react with monosubstituted acetylenes to give substituted cyclopentenes (*Scheme 30*) [53]. Mechanism of the reaction consisted of $TiCl_4$-catalyzed opening of the cyclopropanes with formation of dipolar species stabilized with silyl and C=O groups. Nucleophilic attack of the terminal acetylenic C-atom on positive end of the dipol, and interception of enolate intermediate by the resulting vinyl cation, gave cyclopentene derivatives. The mechanism was supported by the fact that acetylenic reagents require presence of aryl group, which possibly stabilize the intermediate vinyl cation, while alkyl acetylenes do not undergo this reaction.

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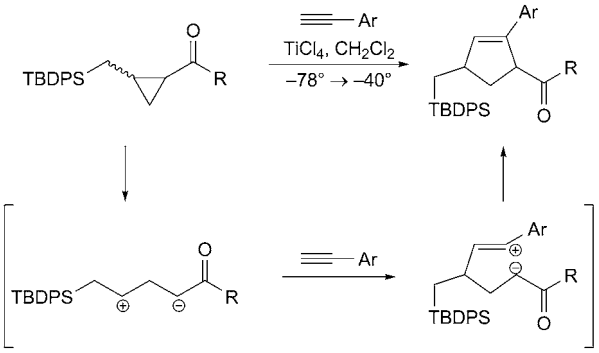
[12]) Similar reactions with nitrones were discussed with alternative stepwise and concerted reaction pathways in [52].

Scheme 30. *Synthesis of Substituted Cyclopentenes from (Cyclopropylmethyl)silanes* [53]



With a palette[13]) of the reaction mechanisms ranging from stepwise annulations with short-living carbanions to concerted processes of dipolar species[14]) generated under equilibrium conditions, formation of five-membered ring products is a valuable synthetic method for construction of carbo- and heterocyclic ring systems.

Conclusions. – The major way of synthesis of five-membered carbo- and heterocyclic systems are reactions between C=O, C=N, and C=C bonds and 1,3-dipolar species. These reactions cover full range of mechanistic pathways and timings of bond-forming processes from clear-cut stepwise formation of 1,3-dipolar reagent, its addition to a polar double bond, followed by five-membered ring closure, to concerted 1,3-dipolar cycloaddition. In this essay, we focused on discussion of the former processes, *i.e.*, stepwise reactions of γ-halocarbanions and analogs generated by deprotonation of the appropriate precursors that can be trapped by active electrophilic double bonds, followed by five-membered-ring closure. These reactions are complementary to much better known generation of γ-halocarbanions and 1,3-dipolar species *via* ring opening of cyclopropanes. Nevertheless, the former processes, which should be carried out at low temperatures, are kinetically controlled, whereas the latter, which require elevated temperatures for the cyclopropane opening, are thermodynamically controlled.

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13) For other examples of stepwise reactivity of 1,3-donor/acceptor species described in literature, see, *e.g.*, [54].

14) In exceptional cases, for the same substrates the process can be switched between synchronous and nonsynchronous depending on conditions and nature of dipolar species; see [55].

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