CHEMICAL REVIEWS

REVIEW

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Chemistry of Six-Membered Cyclic Oxime Ethers. Application in the Synthesis of Bioactive Compounds

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CONTENTS

1. INTRODUCTION

Interest in the cyclic oxime ethers is due to their high potential for application in the target-oriented synthesis of naturally occurring and biologically active molecules.[1−9] Five-membered cyclic oxime ethers, isoxazoles, and isoxazolines were involved in the practice of organic chemistry as early as the 1960s and nowadays are considered as classic intermediates in the total synthesis of alkaloids, steroids, prostaglandins, and other natural compounds.[4−9] In modern strategies, successive assembling and cleavage of isoxazole or isoxazoline rings is a standard method for the synthesis of β-hydroxy ketones, α,β-unsaturated carbonyl compounds, 1,3-amino alcohols, and 1,3-dicarbonyl compounds.

At the same time, the synthetic potential of six-membered cyclic oxime ethers (SCOE, Scheme 1), viz., 5,6-dihydro-4*H*-1,2-oxazines **1** (further, dihydrooxazines **1**) and 6*H*-1,2-oxazines **2**, remains underestimated in many aspects as compared to their five-membered homologues, though, the first studies on 1,2-oxazines go back to the end of 19th century.[10,11]

For a long time, the absence of convenient methods for the preparation of SCOE made impossible a full-scale study of their synthetic potential. However, a large number of methods for assembling cyclic oxime ethers **1** and **2** have been developed by

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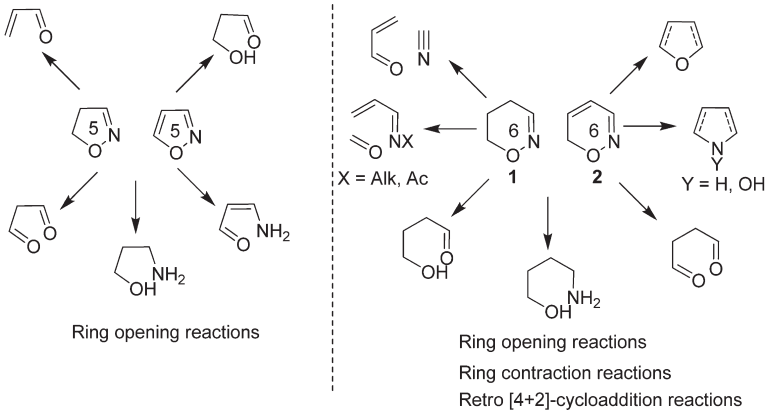
Scheme 1



now, which on the whole open access to SCOE with various character of substitution in the ring.

At the same time, it is obvious that the chemistry of SCOE is more versatile than the chemistry of their five-membered analogs, since, in addition to the ring-opening reactions typical for isoxazoles and isoxazolines, there exist possibilities for ring contraction to five-membered heterocycles, as well as for fragmentation processes by the scheme of retro-[4 + 2]-cycloaddition (see Scheme 1). In addition, due to the rigid six-membered structure of the 1,2-oxazine ring, many reactions of SCOE **1** and **2** proceed with very high stereoselectivity. In the last years, these features of SCOE have found application in many total syntheses of natural products and their analogs.

In contrast to five-membered oxime ethers, to which plenty of monographs are devoted (see, for example, refs 4−8, 12), the chemistry of SCOE has not been earlier considered as a subject of a separate review. Some separate aspects of the chemistry of SCOE along with benzo-1,2-oxazines and 1,2-azapyrylium salts were outlined in reviews by Tsoungas[13] and Reissig and Zimmer,[14] respectively. Therefore, it is reasonable to perform a detailed survey of SCOE covering the very latest progress in their chemistry as well as the early works going back to the beginning of 20th century.

The present review is aimed at stimulating interest in SCOE as valuable intermediates for directed organic synthesis. Here, we systematize the main aspects of the preparation and chemical properties of heterocycles **1** and **2**, as well as consider examples of their application in the synthesis of compounds with known biological activity. 4*H*-1,2-Oxazines isomeric to 6*H*-1,2-oxazines **2** are almost unknown due to their instability and therefore are very briefly discussed in the review.

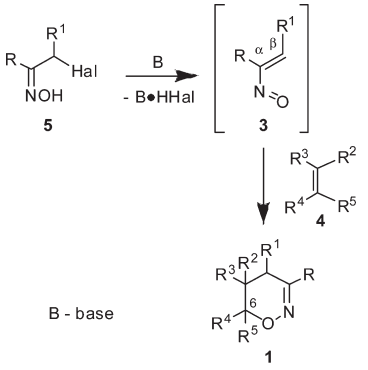
2. SYNTHESIS OF SIX-MEMBERED CYCLIC OXIME ETHERS 1 AND 2

Four general approaches to the synthesis of SCOE are known: (1) [4 + 2]-cycloaddition reactions of heterodienes with the fragment C═C−N═O to olefins, (2) intramolecular cyclization of γ-functionalized oximes, (3) an intramolecular cyclization of functionalized O-substituted hydroxylamines, and (4) transformations of the N−O-containing heterocyclic compounds.

2.1. [4 + 2]-Cycloaddition Reactions

The most common approach to the synthesis of SCOE **1** is the [4 + 2]-cycloaddition of conjugated nitrosoalkenes **3** to olefins **4** (Scheme 2;[15−17] for the properties of heterodienes **3**, see reviews in refs 15, 16). This transformation is a version of the Diels−

Scheme 2



Alder reaction with the inverse electronic demands, where nitrosoalkenes **3** act as an electron-withdrawing 4π-component.[15]

Since most nitrosoalkenes **3** are highly reactive species, they are usually generated in situ from the corresponding α-halooximes **5** upon the action of a base (see Scheme 2, for the synthesis of oximes **5**, see the review in ref 15). Examples of dihydrooxazines **1** syntheses are known, in which intermediates **3** are generated from α-halooxime silyl ethers,[18a] α-halonitroso compounds,[18b] in the course of silylation of some aliphatic nitro compounds,[19] or result from the retro-[4 + 2]-cycloaddition reaction of some 3,6-dihydro-2*H*-[20] and 5,6-dihydro-4*H*-1,2-oxazines.[21]

Table 1 summarizes dienophiles that were successfully involved in the cycloaddition with nitrosoalkenes **3** and the main types of dihydrooxazines (**1a**−**j**) available by the reaction **3** + **4**.

Nitrosoalkenes **3** undergo cycloaddition with different olefins **4** with an electron-enriched double bond: vinyl ethers, trimethylsilyl enolates, enamines, trimethylsilyl ketene acetals, methoxyallene, substituted styrenes, allyltrimethylsilane, conjugated dienes, furans, pyrroles, indoles, as well as dihydroquinolines. The first three types of dienophiles form adducts the most readily and in high yields (dihydrooxazines **1a**−**c** in Table 1). These adducts are widely used in target-oriented synthesis (see section 4).

Nonactivated alkenes (1-octene,[24,46] cyclohexene,[24] and *cis*-cyclooctene[47]) produce the corresponding adducts only with the most electrophilic nitrosoalkenes **3** [R = C(O)CH_3, C(O)H, 4-$NO_2C_6H_4$]. Sterically hindered alkenes (silylenol ethers derived from *tert*-butyl methyl ketone and acetophenone) do not react with nitrosoalkenes **3**.[37] Electron-deficient alkenes such as diethyl

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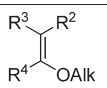
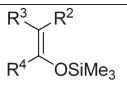
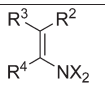
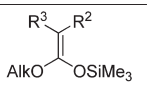
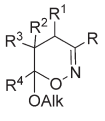
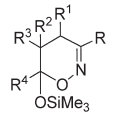
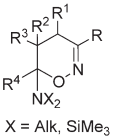
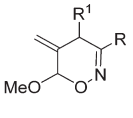
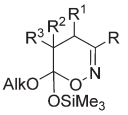
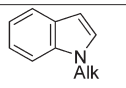
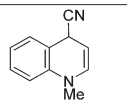
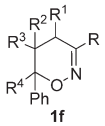
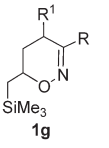
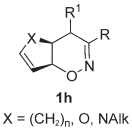
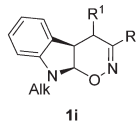
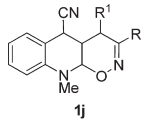
Table 1. Types of Dienophiles 4 Involved in the [4 + 2]-Cycloaddition with Heterodienes 3

Dienophiles **4**					
Adducts **1**	 **1a**	 **1b**	 X = Alk, $SiMe_3$ **1c**	 **1d**	 **1e**
Ref.	18a,19,20,22-31	25,26,31-37	31,38-43a	30,43b,44	45
Dienophiles **4**					
Adducts **1**	 **1f**	 **1g**	 **1h** X = $(CH_2)_n$, O, NAlk n = 1,2	 **1i**	 **1j**
Ref.	18b,24,42,46,47	26,35,33,34,37,48	24,39,42,46-55	21,42,56	57

fumarate,[24] maleic anhydride,[58a] tetracyanoethylene,[58a] and *trans*-1,2-dichloroethylene[24] do not undergo cycloaddition with nitrosoalkenes **3**. However, recently successful cycloadditions of methylacrylate, acrylonitrile, and allyl alcohol to nitrosostyrenes were reported.[18b,58b]

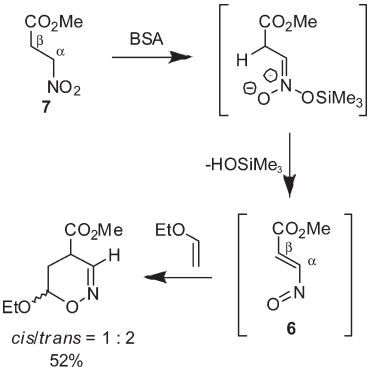
The reactions of **3** + **4** are highly regioselective. When an electron-donating substituent is present in the starting dienophile **4**, it always ends up at the C-6 position of the dihydrooxazine ring (see examples **1a**−**e** in Table 1). In the reactions of nitrosoalkenes **3** with styrenes, the aryl substituent, as a rule, also ends up at the C-6 position (see example **1f** in Table 1).[24,46] *trans*-1-Phenylpropene is an exception and forms a mixture of regioisomeric dihydrooxazines.[46] In the adducts with five-membered aromatic heterocycles (except indoles[21,42,56]), the oxygen atom of the former nitroso group is attached to the β-carbon atom of the former heterocycle (Table 1, products **1h**).

The configuration of the vicinal substituents in olefin **4** is usually retained in the final dihydrooxazine **1**. However, several examples are described when, in the reactions of nitrosoalkenes **3** with individual geometric isomers of 2-substituted enamines[40] and alkoxy-substituted cyclohexadienes,[50] mixtures of dihydrooxazines diastereomeric at positions C-5/C-6 are isolated. The authors[50] suggest that this is due to isomerization of the initial kinetic *cis*-adducts through the reversible oxazine ring-opening via cleavage of the exocyclic C−O bond.

The scope of nitrosoalkenes **3** suitable for cycloaddition is considerably narrower than that of dienophiles **4**. This imposes certain restrictions on the type of substituents at positions C-3 and C-4 of the resulting dihydrooxazines **1**. As a rule, conjugated nitrosoalkenes **3** have an electron-withdrawing or aryl substituent at the α-position [R = CO_2Et, CF_3, $C(O)CH_3$, C(O)H, *trans*-$CH{=}CHCO_2Me$, 4-$NO_2C_6H_4$, Ph, $P(O)(OAlk)_2$ in Scheme 2 and in Table 1]. Among the α-unsubstituted nitrosoalkenes 3 (R = H), only β-nitrosoacrylate **6**, generated by the silylation of methyl β-nitropropionate **7**, undergoes cycloaddition (Scheme 3).[19]

α-Alkyl-substituted nitrosoalkenes **3** (R = Alk), excluding intramolecular [4 + 2]-cycloaddition,[18a] form adducts with alkenes **4** in low yields or do not form them at all.[33,51]

Scheme 3



The β-carbon atom in nitrosoalkenes **3** usually has no substituents (R^1 = H in Scheme 2),[24,46,51] except the aforementioned β-nitrosoacrylate **6** (R^1 = CO_2Me),[19] $MeCH{=}C(Ac)N{=}O$,[24] β-halo-α-nitrosostyrenes (R^1 = Br, Cl),[25,26] and some nitrosoalkenes **3**, in which the C=C double bond conjugated with the nitroso group is a part of a ring system.[34,44a]

Due to the lability of nitrosoalkenes **3** and their tendency toward polymerization,[15] each individual case of the reaction **3** + **4** → **1** requires specific optimization of conditions.[18a] Successful cycloaddition is frequently accomplished only by employing 5−10-fold excess of dienophile **4**, as well as long reaction times and high dilution to maintain low stationary concentration of reacting nitrosoolefin **3**.[24,27] Sometimes, the reaction **3** + **4** is accompanied by the formation of side products, viz., nitrones **8**,[46] vinylhydroxylamines **9**,[59] or enoximes **10**[46] (Figure 1).

Products **8** are formed by the competing [3 + 2]-cycloaddition of nitrosoalkenes **3** to olefins **4**.[15,60] Vinylhydroxylamine **9** was obtained by the silylation of β-nitropropionate **7** (Scheme 3) in the presence of 1-ethoxypropene. Its generation is explained by the ene reaction between $EtOCH{=}CHCH_3$ and the nitroso

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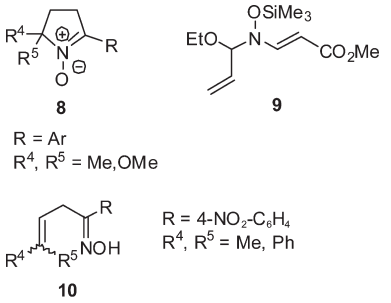
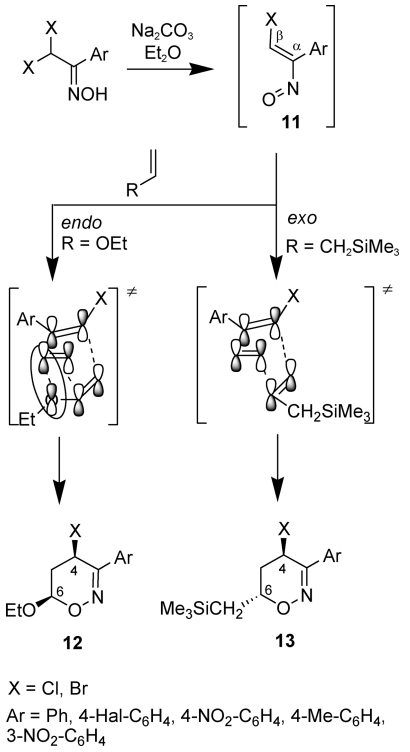


Figure 1

Scheme 4

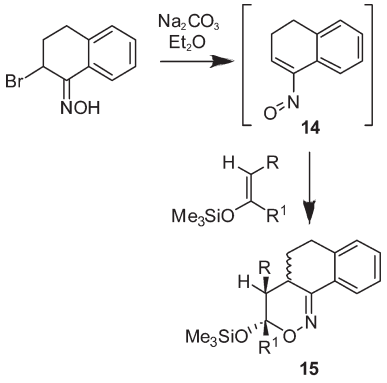


group of β-nitrosoacrylate **6**.[59] The mechanism of enoxime **10** formation is not well understood.[46]

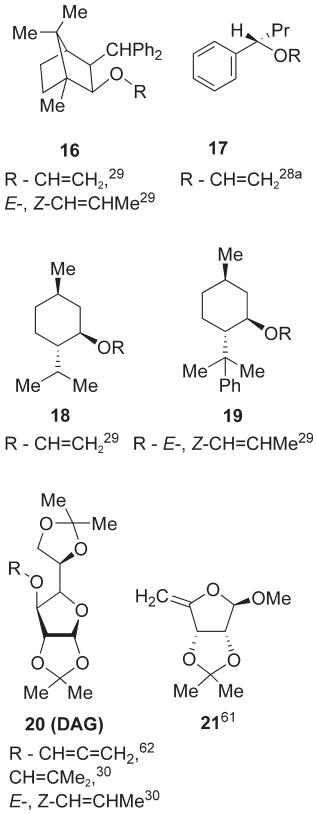
The stereochemistry of resulting dihydrooxazines **1** in the case of β-substituted nitrosoalkenes **3** ($R^1 \neq H$ in Scheme 2) is determined by the ratio of the rates of *endo*- and *exo*-approaches of dienophile **4** to the plane of reacting nitrosoalkene.[18a,34] This ratio significantly depends on the nature of alkene **4**.

The stereochemistry of cycloaddition of ethyl vinyl ether and allyltrimethylsilane to α-aryl-β-halo-α-nitrosoethylenes **11** was studied by Kim[26] (Scheme 4). Ethyl vinyl ether in the reactions with nitrosoalkene **11** exclusively gives 4,6-cis-products **12**, which corresponds to the *endo*-approach of the olefin to the plane of the nitrosoalkene. Such an approach proved favorable due to the presence in the transition state of stabilizing interaction between the π-orbitals of the nitrosoolefin and the p-orbital of one of the lone electron pairs on the oxygen atom of ethyl vinyl ether (Scheme 4). In the case of allylsilane, the absence of such an interaction leads to the realization of a less sterically hindered *exo*-approach of the dienophile, which furnishes 4,6-*trans*-

Scheme 5



Scheme 6



dihydrooxazines **13**.[26] Note that the explanations for the stereochemistry of the formation of products **12** and **13** given by the authors are justified only for the *E*-configuration of nitrosoalkenes **11** suggested by them.

Reissig and co-workers[34] studied the effect of substituents in silyl enol ethers on the stereochemical outcome of the cycloaddition with 3,4-dihydro-1-nitrosonaphthalene **14** (Scheme 5). Unsubstituted trimethylsilyloxyethylene in the reaction with nitrosoalkene **14** produces exclusive *exo*-adduct **15** (R, R^1 = H, Scheme 5). Introduction of substituent R at the *trans*-position to

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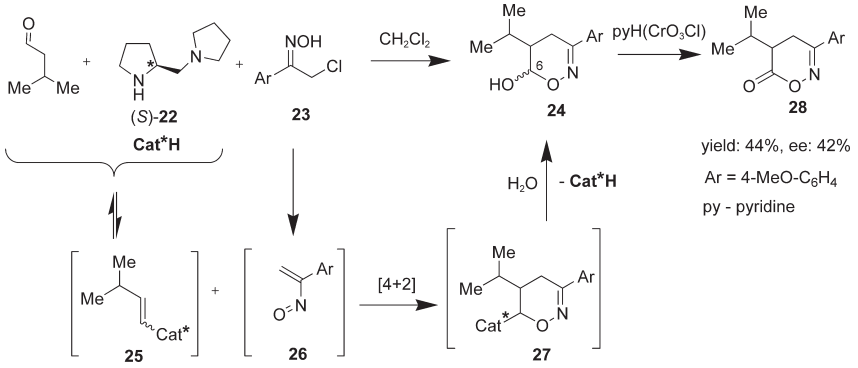
Scheme 7



the trimethylsilyloxy group results in both exo/endo-approaches, whereas introduction of additional substituent R^1 at the carbon atom bound to the trimethylsilyloxy group leads to a predominant formation of the *endo*-adduct.[34]

Cycloaddition reaction of nitrosoalkenes **3** to olefins **4** can be used in asymmetric synthesis[17] if optically pure olefins are employed as dienophiles (for example, olefins **16**−**21** in Scheme 6). In this case, a starting chiral alcohol can be regenerated in the reduction step of the corresponding dihydrooxazine **1** (see sections 3.1.3.1 and 4). Vinyl ethers of natural or synthetic chiral alcohols are commonly used[28−30,61,62] (see examples **16**−**20**). The best results for the diastereoselectivity of cycloaddition were achieved with chiral alkenes **20**[29,30,62] (diacetoneglucose vinyl ether) and **21**,[61] available from natural carbohydrates.

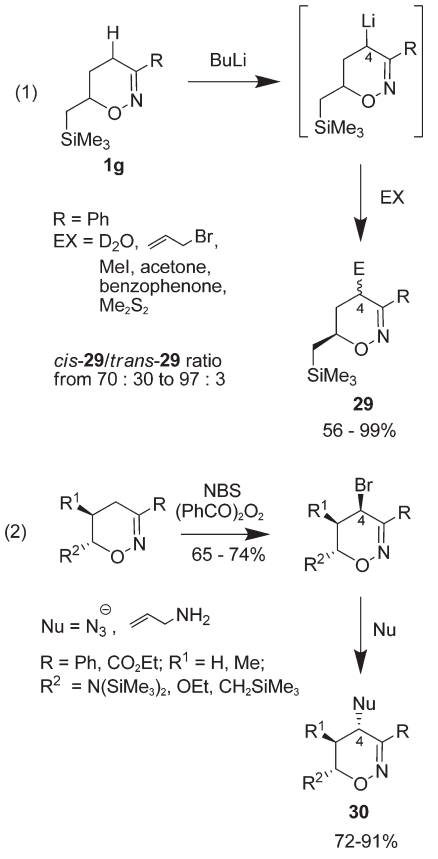
Recently, the first example of asymmetric organocatalysis in the cycloaddition reaction of nitrosoolefins **3** has been reported (Scheme 7).[63] In this reaction, α-chlorooxime **23** react with isobutyric aldehyde in the presence of (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine **22** to yield a mixture of diastereomeric chiral dihydrooxazines **24**. The authors suggest that this transformation proceeds through the generation of chiral enamine **25** from isobutyric aldehyde and pyrrolidine (*S*)-**22**. The [4 + 2]-cycloaddition of **25** to α-nitrosostyrene **26** generated from α-chlorooxime **23** leads to the intermediate dihydrooxazine **27**. Hydrolysis of the latter produces a mixture of isomeric 6-hydroxydihydrooxazines **24**. Oxidation of products **24** with pyridinium chlorochromate affords C-5-substituted oxazinones **28** with moderate enantiomeric enrichment.[63]

As has been already noted, the reaction **3** + **4** → **1** opens the excess predominantly to dihydrooxazines **1** unsubstituted at position C-4 (R^1 = H in Scheme 2). However, lithiation of dihydrooxazines **1g** (R^1 = H) and subsequent treatment of the resulting anionic species with electrophilic reagent led to various 4-substituted dihydrooxazines **29** in good yields and high stereoselectivity (Scheme 8, eq 1).[64−68]

Another method for the modification of position C-4 in dihydrooxazines **1** includes stereoselective bromination of the oxazine ring with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide.[69] Subsequent substitution of the bromine atom by a nucleophile (azide anion or allylamine) provides various 4-substituted dihydrooxazines **30** (Scheme 8, eq 2).

Vinylnitrosonium cations **31**[70,71] (Scheme 9, eq 1) and conjugated nitroalkenes **33**[72−76] (Scheme 9, eq 2) are isoelectronic analogs of nitrosoalkenes **3** in the [4 + 2]-cycloaddition reactions with the inverse electronic demands. In these cases, SCOE derivatives, viz., *N*-alkyldihydrooxazinium salts **32**[70,71]

Scheme 8



and *N*-oxides **34**,[72−78] respectively, are the cycloaddition products.

Cyclic nitronates **34** are very useful intermediates for organic synthesis. First, they can be synthesized from simple and available reactants (aliphatic nitro compounds, aldehydes, and alkenes **4**). Second, the cycloaddition reaction **4** + **33** → **34** is a considerably more general process than the cycloaddition of nitrosoalkenes **3** to **4**. In particular, nonactivated alkenes **4** (R^2−R^5 = H, Alk in Scheme 9) as well as stable α-unsubstituted and α-alkyl-substituted nitro alkenes **33** (R = H, Alk in Scheme 9) can be successfully involved in this process.[72] Third, it is possible to control the exo/endo-selectivity of the cycloaddition reaction and direct it toward preparation of certain stereoisomer of **34** by the variation of the Lewis acid promoter (LA).[72,77a]

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A versatile character of the [4 + 2]-cycloaddition reactions involving nitroalkenes **33** together with their high regio- and stereoselectivity stimulated the study of the synthetic potential of cyclic nitronates **34**.[72] These compounds have found wide application in the enantioselective synthesis of various nitrogen-containing natural compounds, predominantly using the [3 + 2]-cycloaddition reaction of nitronates **34** to different olefins.[72,77,78] A detailed discussion of this aspect of the chemistry and application of cyclic nitronates **34** is beyond the limits of the present review; for reviews on this topic see ref 72.

The availability of nitronates **34** makes them attractive precursors for the synthesis of polysubstituted SCOE **1**. This idea constitutes the basis of the general method recently suggested for the synthesis of oxime ethers **35**, **36**, and **37** with a functionalized alkyl group at C-3 from available aliphatic nitro compounds **38** and other simple molecules (Scheme 10).[79−83]

For instance, silylation of nitronates **34** bearing the methyl substituent at C-3 smoothly leads to 3-haloalkyl-substituted dihydrooxazines **35**.[80,81] The reaction proceeds through the intermediacy of relatively stable cyclic bis(oxy)enamines **39**, which in the reaction with halotrimethylsilane give the corresponding oxazines **35**.[80] In addition, enamines **39**, upon the action of a Lewis acid, undergo an unusual rearrangement, resulting in a 1,3-migration of the exocyclic silyloxy group from the nitrogen atom to the exocyclic carbon atom of the double bond, yielding after hydrolysis oxazines **36**.[82,83]

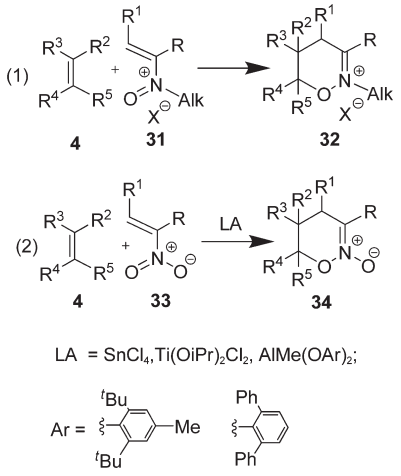
Halides **35** can be easily transformed into a series of dihydrooxazines with various functional groups by catalytic carbonylation[79] (products **37a**) or nucleophilic substitution[81] of halogen atom (for example, with dimethyl malonate anion, products **37b**) (Scheme 10). Note that SCOE with functionalized alkyl substituents at C-3 are virtually unavailable by other methods known by now.

Other applications of nitronates **34** in the synthesis of SCOE are also described. Reduction of the exocyclic N−O bond in nitronate **40** with triethylphosphite upon heating in xylene (see Scheme 11, eq 1) gives the corresponding dihydrooxazine **41**.[84] Addition of allyltrimethylstannane to cyclic nitronate **42** in the presence of $TiCl_4$ leads to 3-allyl-substituted dihydrooxazine **43** (see Scheme 11, eq 2).[85] Most likely, the role of $TiCl_4$ in the latter reaction consists of complexation with the exocyclic oxygen atom of the nitronate group forming a dipolar intermediate, which then reacts with nucleophilic allylstannane.

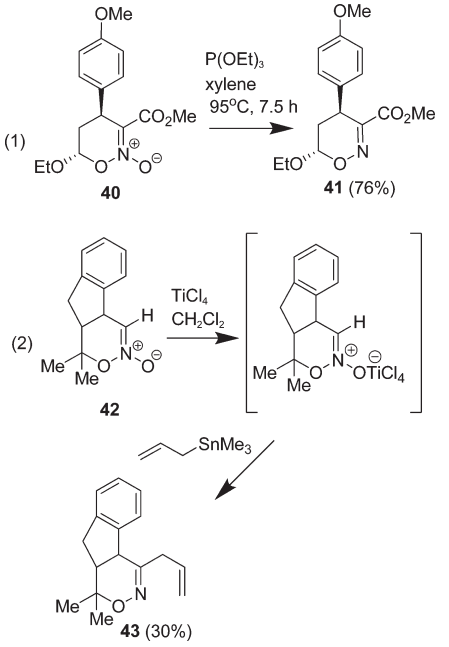
2.2. Intramolecular Cyclization of γ-Functionalized Oximes

A large group of methods for the preparation of SCOE **1** and **2** is based on intramolecular cyclization of oximes bearing an electrophilic center at the γ-position (Scheme 12). Such cyclizations can proceed as nucleophilic substitution or nucleophilic addition

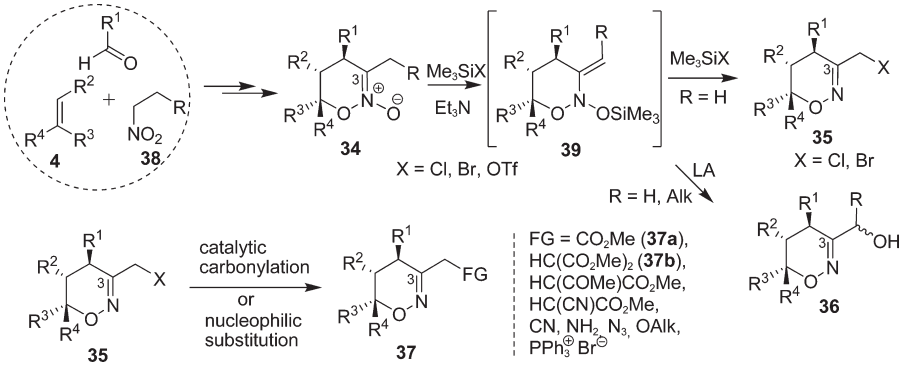
Scheme 9



Scheme 11



Scheme 10



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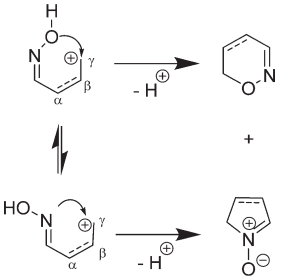
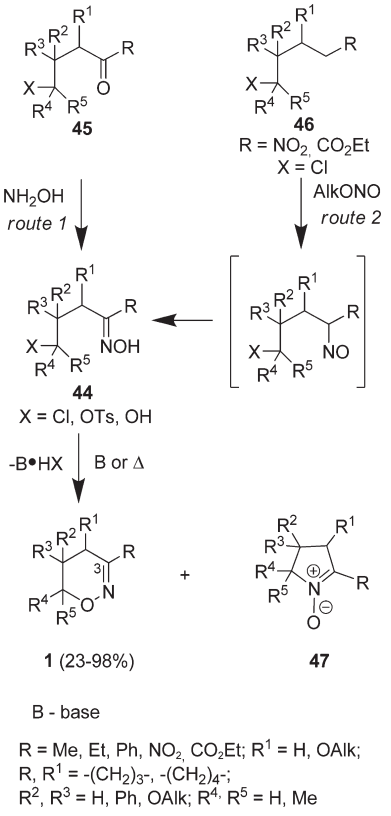
Scheme 12



Scheme 13

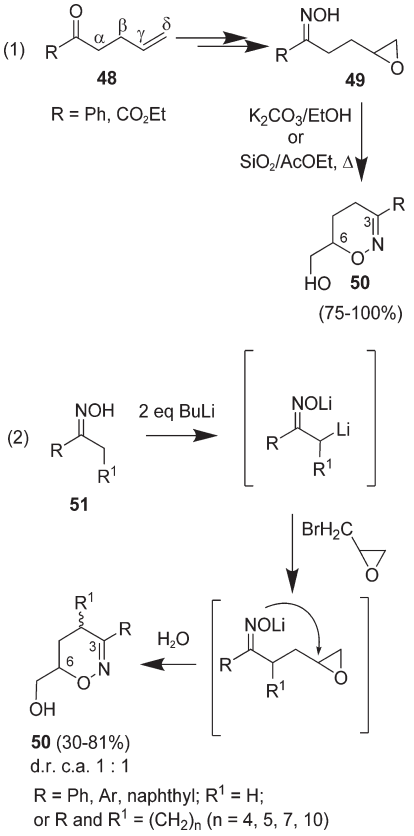


reactions and can lead not only to SCOE but also to five-membered cyclic nitrones, since the oximino group is capable of exhibiting properties of both an O- and N-nucleophile (Scheme 12).

In the most simple version of the approach shown in Scheme 13, oximes **44** with hydroxy, chloro, or tosylate groups at the γ-position are used (X = OH, Cl, OTs). In the case of 4-hydroxyoximes **44** (X = OH), the cyclization requires heating[10] or acid catalysis[86] to take place. When X = Cl or OTs, the cyclization proceeds under mild conditions in the presence of a base (NaOH, K_2CO_3, ammonia, ^{t}BuOK) and furnishes dihydrooxazines **1** in moderate to high yields.[87−91]

The initial functionalized oximes **44** can be obtained from the corresponding ketones **45** and hydroxylamine (route 1, Scheme 13) or by the nitrosation of chlorides **46** containing an activated methylene group (route 2, Scheme 13). In some procedures, the cyclization **44** → **1** occurs simultaneously upon the preparation of the starting oximes.[11,92−96]

Scheme 14



In the cyclization reactions of oximes **44**, in addition to the target oxime ethers **1**, as a rule, nitrones **47** are also obtained.[88,90,92,97] The ratio SCOE/nitrone depends not only on the nature of the starting oxime, but also on the reaction conditions (solvent, temperature, etc.).[90] Brandman and Conley reported the failure to reproduce a procedure suggested earlier for the transformation **44** → **1**, obtaining exclusively nitrone **47**.[90]

The oxygen atom of the oxirane ring can serve as a leaving group in the cyclization of oximes.[98−101] For instance, intramolecular ring-opening of the oxirane ring with the oxime hydroxy group in oximes **49** is a convenient method for the synthesis of dihydrooxazines **50** with a hydroxymethyl group at C-6 (Scheme 14, eq 1).[98] Oximes **49** are available from the corresponding γ,δ-unsaturated ketones **48**.

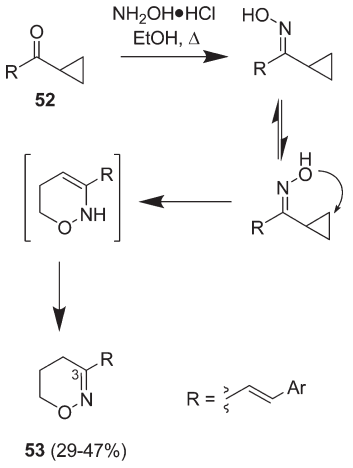
Langer and co-workers[99,100] reported that anions of oximes **49** obtained in situ from the dilithiated derivatives of oximes **51** and epibromohydrine (Scheme 14, eq 2) undergo cyclization with the participation of the epoxide group and the oxygen atom of the oximino group, giving rise to dihydrooxazines **50** in moderate to good yields. If substituent $R^1 \neq H$, the products are obtained as a mixture of diastereomers (dr ~ 1:1).[99]

Other three-membered rings, such as cyclopropanes, can be opened intramolecularly by the oxygen atom of the oximino group as well. This reaction is the basis of an elegant method for the synthesis of 3-vinyl-substituted dihydrooxazines **53** from cyclopropyl vinyl ketones **52** and hydroxylamine (Scheme 15).[102]

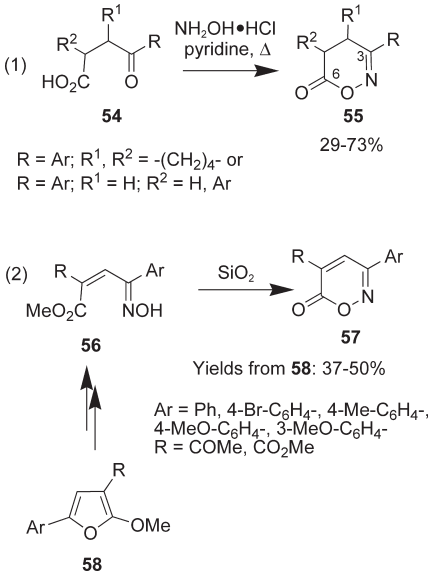
Oximes containing a carbonyl group at the γ-position easily cyclize to dihydrooxazines without the formation of side cyclic nitrones of the type **47** (Scheme 16).[103−118]

Thus, carboxy-substituted oximes generated from the corresponding keto acids **54** and hydroxylamine can dehydrate to

Scheme 15



Scheme 16

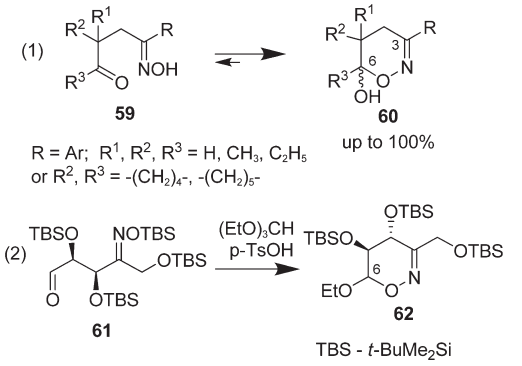


3-aryl-substituted oxazinones **55** directly upon preparation (Scheme 16, eq 1),[103−107] under the action of sulfuric acid in a catalytic amount[108] or upon treatment with dicyclohexylcarbodiimide.[109,110] Methyl esters of unsaturated acids **56** also easily cyclize to 1,2-oxazin-6-ones **57** as well (Scheme 16, eq 2).[111,112] This procedure allows one to synthesize oxazinones **57** from substituted furans **58**.[112]

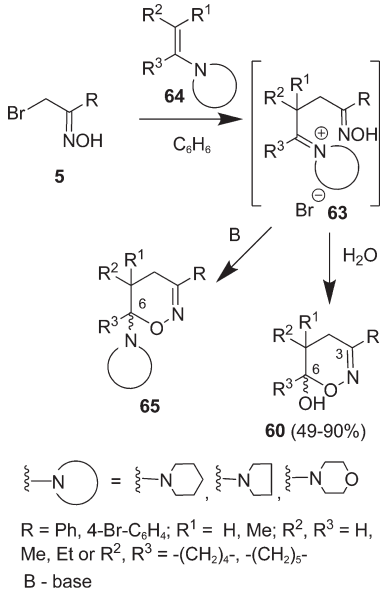
Cyclization of 1,4-dicarbonyl monooximes **59** is reversible; however, the 1,2-oxazine form **60**, as a rule, predominates in the equilibrium mixture (Scheme 17, eq 1).[113−116a] Addition of an alkylating agent to the equilibrium mixture **59** ⇆ **60** allows one to shift the equilibrium to the more stable 6-alkoxydihydrooxazines.[117,118] For instance, selective desilylation of chiral aldoxime derivative **61** in the presence of triethyl orthoformate[118] gave rise to 6-ethoxy-substituted dihydrooxazine **62** (Scheme 17, eq 2).

The initial functionalized monooximes **59** can be obtained by various methods: by alkylation reaction of lithium enolates with α-halooximes,[116] by oximation of γ-hydroxy ketones followed by

Scheme 17



Scheme 18



oxidation of the terminal hydroxy group,[118] or by the reduction of γ-nitro ketone derivatives.[114]

Bravo and co-workers suggested a convenient method for the synthesis of dihydrooxazines **60** with a hydroxy group at C-6 and the aryl group at C-3 via the intermediacy of iminium salts **63** (Scheme 18).[113] In this method, the intermediates **63** are obtained in benzene at room temperature. Subsequent hydrolysis of **63** affords the corresponding 6-hydroxy-substituted dihydrooxazines **60**.

Iminium salts **63** themselves can cyclize to 6-amino-substituted dihydrooxazines **65** upon treatment with a base (Scheme 18).[113,119,120]

Another type of oximes used for the synthesis of dihydrooxazines **1** are γ,δ-unsaturated oximes. Here, the cyclization to oxime ethers is induced by the action of an external electrophile, for example, a proton.[121,122] Tkachev and co-workers[122] described a diastereoselective synthesis of tricyclic chiral dihydrooxazines **67** by cyclization of oximes **66** upon the action of sulfuric acid (Scheme 19). The starting chiral α-aminooximes **66** were obtained by nitrosation of the natural terpene caryophylene with NOCl and subsequent treatment with secondary amine (dimethylamine or morpholine).[122]

Many examples of SCOE synthesis by the cyclization of γ,δ-unsaturated oxime derivatives **68** by selen electrophiles[123−126] or

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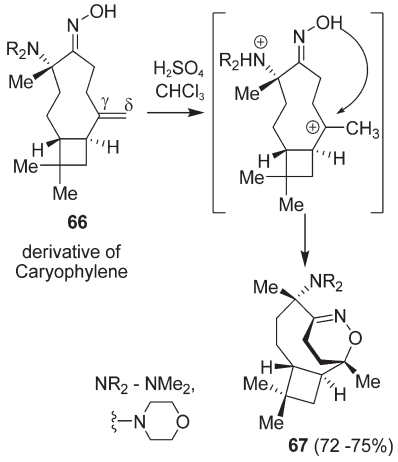
Scheme 19



halogen[127−129] induction are known (Scheme 20). Here, mixtures of dihydrooxazines **69** and cyclic nitrones **70** with the predominance of the latter, as a rule, are the products. The authors note that the ratio of isomers **69**:**70** is determined by many factors, including the ratio of *E*- and *Z*-isomers in the starting oxime **68**, their relative reactivity, the rate of *E*/*Z*-isomerization, and the cyclization conditions.[123,124,127] Only in the case of configurationally stable phenyl-substituted oxime (*E*-**68a**, R = Ph) were dihydrooxazines **69a** (R = Ph) isolated as the only products.[123,126] Treatment of oximes **68** with chiral arylselenyl triflate produces optically pure dihydrooxazines **69** (see Scheme 20).[126]

Other syntheses of SCOE from γ,δ-unsaturated oximes were described: γ-allenyl-substituted oximes cyclize to the corresponding dihydrooxazines upon the action of silver borontetrafluoride,[130] whereas γ,δ-unsaturated oximes containing a phenyl substituent at the C=C bond do so under photochemical activation conditions.[131] In the recent report,[132] the oxidative cyclization involving the oximine group and one of the double bonds of the aromatic ring is used in the synthesis of a zamamistanin (natural 1,2-oxazine) analog. In this reaction, 3-aryl-substituted oxime **71** upon the action of oxidant (2,4,4,6-tetrabromo-2,5-cyclohexadienone) cyclizes to the spiro-fused dihydrooxazine **72** in high yield (Scheme 21).

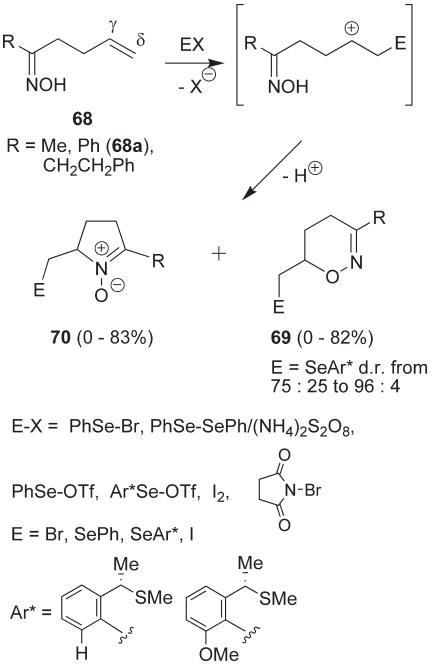
2.3. Intramolecular Cyclization of Functionalized O-Substituted Hydroxylamines

Seemingly obvious intramolecular oximation with participation of the carbonyl and amino groups of O-substituted hydroxylamine is not yet widely used in the synthesis of SCOE. Only several examples of this approach are known.[90,109,133] In particular, treatment of *tert*-butyl-*N*-hydroxycarbamates **73** (γ-keto carboxylic acid derivatives) with trifluoroacetic or *p*-toluenesulfonic acids in CH_2Cl_2 leads to oxazinones **55** in good yields (Scheme 22).[109] In this reaction, the intermediate hydroxamic acids **74** cannot be isolated, since they spontaneously collapse to oxazinones **55**.

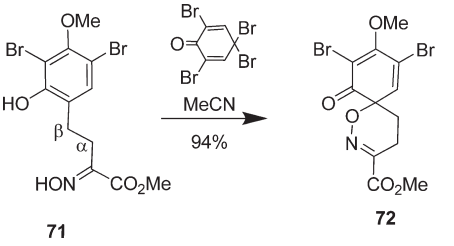
2.4. Synthesis of SCOE from N−O-Containing Heterocyclic Derivatives

2.4.1. Synthesis of SCOE from Other 1,2-Oxazines. 5,6-Dihydro-4*H*-1,2-oxazines **1** can be obtained from tetrahydro-2*H*-1,2-oxazines[95,134−137] (for the synthesis of completely hydrogenated 1,2-oxazines, see reviews in refs 13, 138−140). Tetrahydro-2*H*-1,2-oxazines are dehydrogenated to SCOE **1** upon the action of oxidants such as lead tetraacetate,[135,136] *N*-bromosuccinimide,[134] or

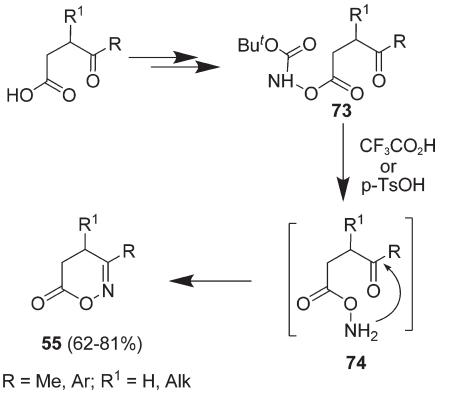
Scheme 20



Scheme 21



Scheme 22



bromine.[136] This approach proved to be very efficient for the synthesis of unsubstituted 5,6-dihydro-4*H*-1,2-oxazine,[136] as well as 3-cyano-5,6-dihydro-4*H*-1,2-oxazine (see Figure 2).[135]

The main methods for the preparation of 6*H*-1,2-oxazines **2** start from the corresponding 5,6-dihydro-4*H*-1,2-oxazines **1**. The first consists of the elimination of HX molecule, where X

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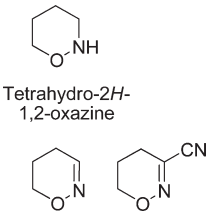
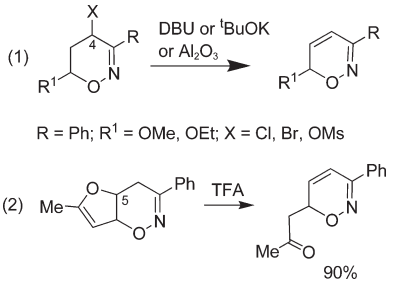
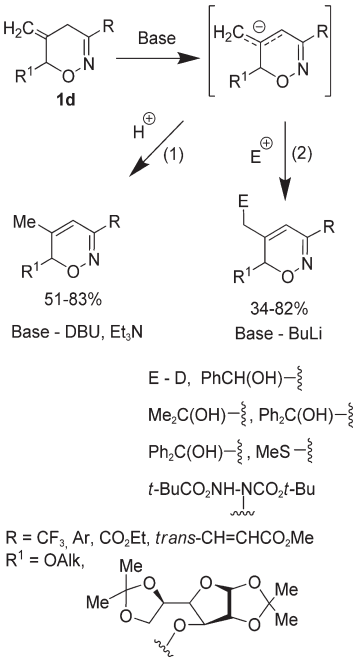


Figure 2

Scheme 23



Scheme 24

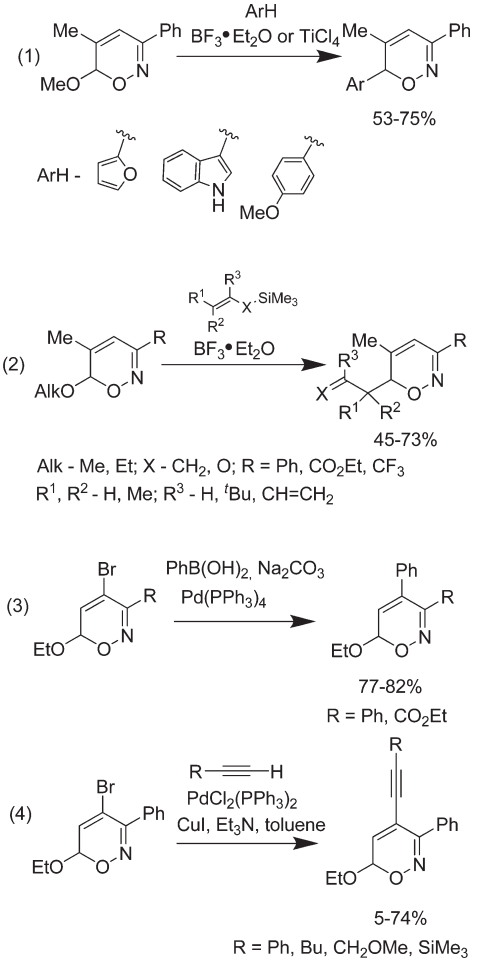


is a good leaving group at position C-4 or C-5 (see Scheme 23, eqs 1 and 2).[25,55,60,69,141]

Another method employs the isomerization of dihydrooxazines **1d** with the exocyclic double bond at atom C-4 upon the action of a nitrogen-containing base (Scheme 24, eq 1; for the synthesis of **1d**, see the data in Table 1).[25,44,62] If BuLi is used as a base, the resulting ambident anion can be further intercepted by an external electrophile E^+ (Scheme 24, eq 2). Addition of the electrophile proceeds regioselectively at the exocyclic carbon atom to form respective 6*H*-1,2-oxazines.[67]

Substitution reactions provide a variety of 6*H*-1,2-oxazines **2**. Thus, the Lewis acid-assisted substitution of the alkoxyl

Scheme 25



group at atom C-6 provides a series of 6-aryl,[44b] 6-hetaryl (see Scheme 25, eq 1),[44b] 6-alkyl,[44c] and allyl-substituted[44b] 6*H*-1,2-oxazines (see Scheme 25, eq 2).[14] Also, 4-bromo-substituted 6*H*-1,2-oxazines can be involved in Suzuki (see Scheme 25, eq 3) and Sonogashira cross-couplings (see Scheme 25, eq 4).[141b]

In turn, 6*H*-1,2-oxazines **2** can be used in the synthesis of 4-substituted and 4,5-disubstituted 5,6-dihydro-4*H*-1,2-oxazines **76**−**78** (see Scheme 26). This method is based on the addition reactions to the endocyclic C(4)═C(5) double bond in oxazines **75**.[25,142−147] Dihydroxylation of oxazines **75** under mild conditions with potassium permanganate or sodium periodate/ruthenium-(III) chloride system provides 4,5-*cis*-dihydroxydihydrooxazines **76** in high yields (Scheme 26, eq 1).[25,143] The reaction is *trans*-selective with respect to substituent R^1.

The [3 + 2]-cycloaddition of nitrile oxides to the C═C double bond of 6*H*-oxazines **75** leads to adducts **77** incorporating annulated five- and six-membered cyclic oxime ethers also with high regio- and stereoselectivity (Scheme 26, eq 2).[144] Other dipoles, such as nitrile imines, nitrile ylides, diazoalkanes, nitrones, and azomethine ylides also can be involved in [3 + 2]-cycloaddition, with 6*H*-oxazines **75** furnishing the corresponding bicyclic products with good to moderate stereoselectivity.[144]

Addition of group R^2 from alkyllithium reagents R^2Li to the conjugated C═C double bond in **75** occurs regioselectively at the position C-5 of the oxazine ring to form *trans*-isomer with respect to substituent R^1. Resulting intermediates **79** can be

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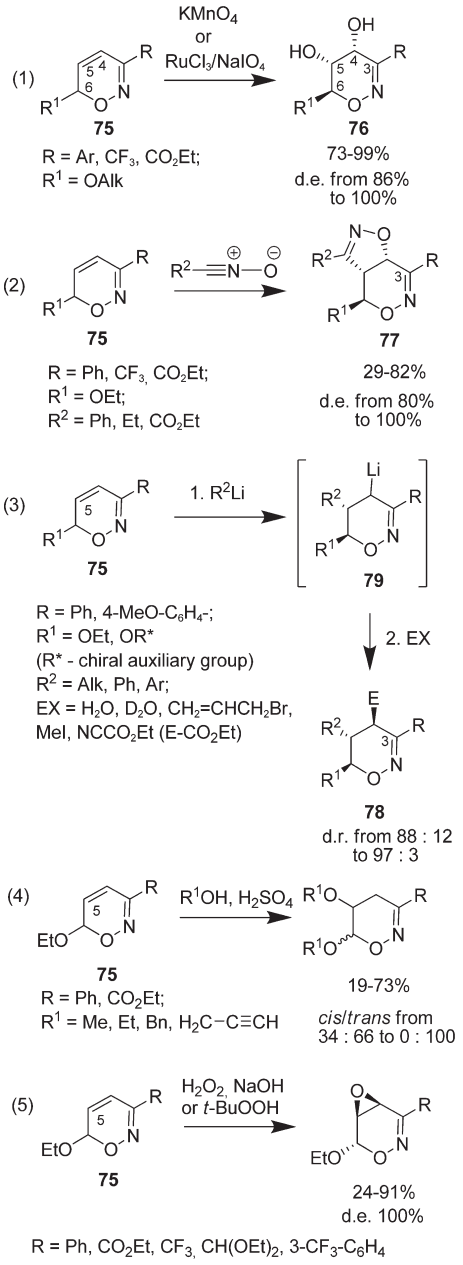
Scheme 26



intercepted using an external electrophile (E−X), producing stereoselectively dihydrooxazines **78** (Scheme 26, eq 3).[145,146a] Alcohols also undergo nucleophilic addition at the C-5 atom of 6*H*-oxazines **75** (Scheme 26, eq 4).[146b] The process is accompanied by a nucleophilic substitution of an alkoxyl group at C-6.

Recently, the successful epoxidation of the C=C double bond of 6*H*-oxazines **75** was reported (Scheme 26, eq 5).[146b] This reaction also proceeds with very high *trans*-stereoselectivity.

The availability of 6*H*-1,2-oxazines **75** with a chiral alkoxy substituents at C-6[62,147] opens the way to the synthesis of optically pure polysubstituted dihydrooxazines **76**−**78** bearing an electron-withdrawing or aryl substituent at C-3.

2.4.2. Synthesis of SCOE from Isoxazolines and Five-Membered Cyclic Nitronates. SCOE **1** can be obtained by a ring-expansion reaction of some substituted isoxazolines; however, application of such a method is rather restricted.[148−151]

Enantioselective synthesis of 3-aryl-substituted dihydrooxazines **82** and dihydrooxazin-6-ones **55** can be echived by the ring expansion reaction in 5-[hydroxyl(trimethylsilyl)methyl] isoxazolines **81** upon the action of tetrabutylammonium fluoride (Scheme 27).[148,149] The starting substrates **81** are obtained by the [3 + 2]-cycloaddition reaction of aryl-substituted nitrile oxides to enantiomerically enriched 1-(trimethylsilyl)prop-2-en-1-ols **80**.

Apparently, the mechanism of the transformation **81** → **82** includes Si−C bond cleavage in the starting isoxazolines **81** with the fluoride anion to form anions **83**, subsequent isoxazoline ring-opening, and recyclization of arising oxime anions **84**.[148]

Oxidation of the resulting mixture of isomeric 6-hydroxydihydrooxazines **82** with pyridinium chlorochromate leads to chiral dihydrooxazinones **55** in good overall yields.[148,149]

Harada and co-workers described the synthesis of a series of 3-carboxymethyl-substituted 5,6-dihydro-4*H*-oxazines **86a**−**88** by the ring-expansion reactions of 5-methylsulfoxy-substituted isoxazoline *N*-oxides **85** upon the action of titanium tetrahalides (Scheme 28).[150,151] Isoxazoline *N*-oxide **85a** upon the action of titanium(IV) bromide rearranges to 5-hydroxydihydrooxazine **86a** with the reduction of one of the N−O bonds.[150] When $TiCl_4$ is used instead of $TiBr_4$ in the reactions with nitronates **85**, in addition to the ring expansion, the electrophilic substitution of hydrogen in the aromatic ring occurs.[151] Depending on the nature and the position of substituent R in the aromatic ring of the starting substrate **85**, either 3-(*o*-haloaryl)-5,6-dihydro-4*H*-dihydrooxazines **87** or oxazines **88** containing annulated dihydrobenzofuran ring are the products.[151] It is important that, in the course of these rearrangements, the relative configuration of substituents at atoms C-4 and C-5 of the starting isoxazoline *N*-oxides **85** is preserved.

2.5. Other Methods

An interesting approach to assembling the oxazine ring in 6*H*-1,2-oxazines **2** consists of the use of an intramolecular Wittig reaction. For instance, a simple two-component synthesis of substituted 1,2-oxazin-6-ones **89** from oximes of keto acid esters and keteneylidene triphenyl phosphonate was developed (Scheme 29).[152]

In the past few years, new methods for the synthesis of SCOE with specific character of substitution in the ring have been developed.

The reaction of 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid with nitroalkenes **90** in the presence of butyllithium with subsequent heating and acidification furnishes unusual bicyclic 6*H*-1,2-oxazines **91** in moderate yields (Scheme 30).[153] The plausible mechanism of this multistep reaction is shown in Scheme 30. According to the authors' hypothesis, at the first stage the dianion of 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid undergoes Michael addition to a α-nitroalkene **90**. The resulting adduct eliminates pyrrolidine and water to give substituted nitroso diene. The latter undergoes an electrocyclic reaction, furnishing after esterification the final 6*H*-1,2-oxazines **91**.

An approach to the synthesis of SCOE based on the Cope rearrangement of β-alkenyl-substituted nitroso compounds seems promising (see Scheme 31, eqs 1 and 2).[15,154,155] Using this idea, a convenient method for the synthesis of bicyclic dihydrooxazines **93** from bicyclo[2.2.1]-2-heptene or bicycle[2.2.2]-2-octene derivatives **92** (*n* = 1 and 2, respectively, in Scheme 31, eq 1) was suggested.[154] In this method, nitroso compounds **94** are generated by the nitrosation of precursors **92** (silyl enolates (R = H) or silyl ketene acetals (R = OMe) (Scheme 31, eq 1) with a mixture of isopentyl nitrite and titanium(IV) chloride.

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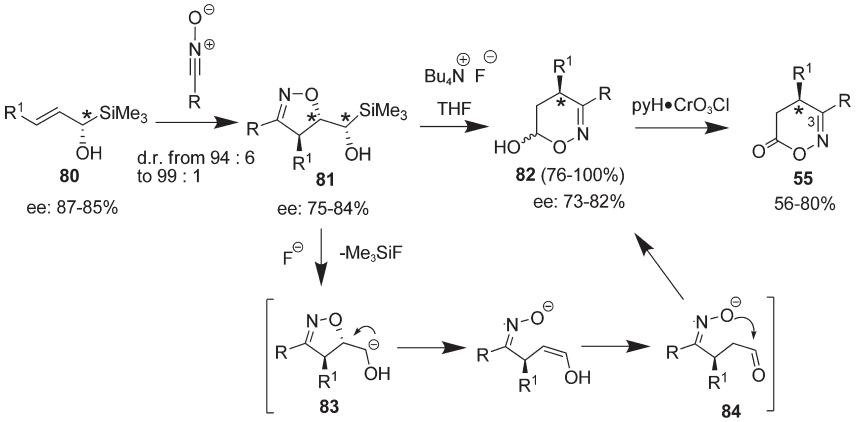
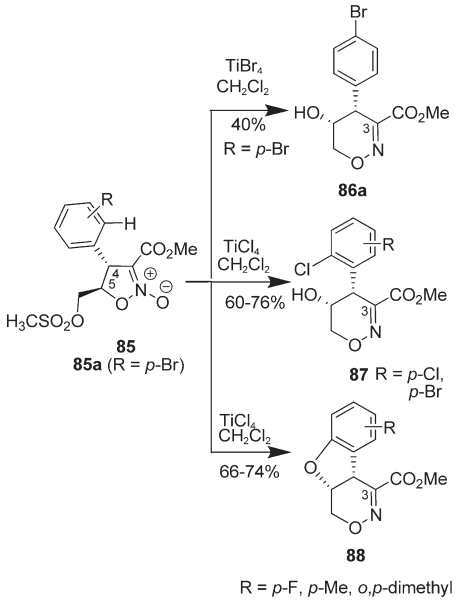
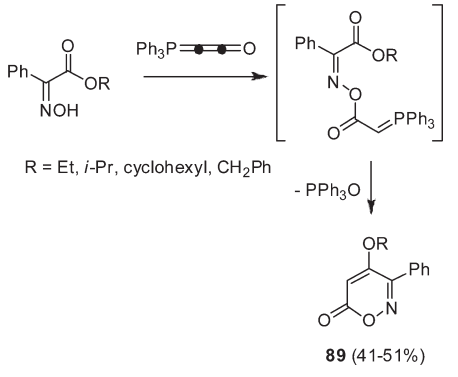
Scheme 27



Scheme 28

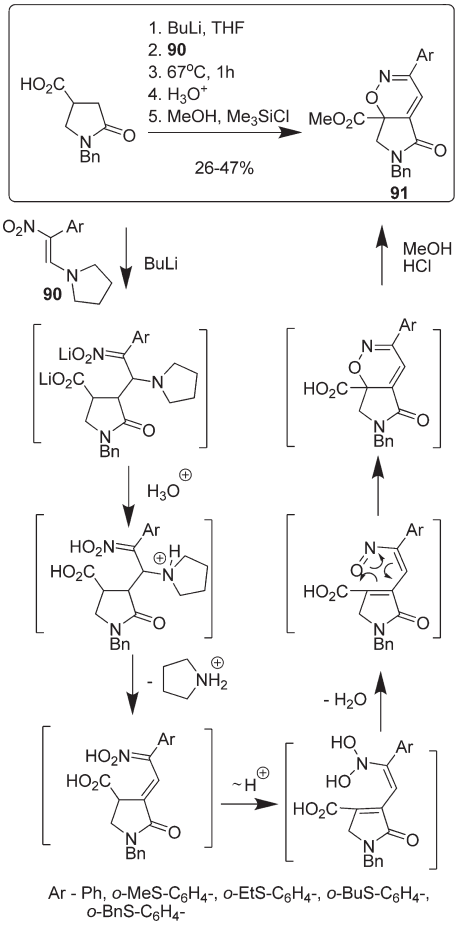


Scheme 29



The *endo*-intermediates **94** undergo the Cope rearrangement directly under nitrosation conditions, giving the target dihydrooxazines **93** stereoselectively and in moderate to good yields.

Scheme 30



In all the cases represented in Scheme 31, the resulting products **93** contain an ester or aldehyde group at C-3.[154]

Baranovsky and co-workers[155] described an unexpected transformation of unsaturated nitro derivative of the steroid series **95** to dihydrooxazine **96** by the reduction of **95** with titanium(III) chloride (Scheme 31, eq 2). Apparently, this reaction also includes 1,2-oxaza-[3,3]-sigmatropic rearrangement of nitroso compound **97**, which is generated by the reduction of the nitro group in the starting steroid **95**.

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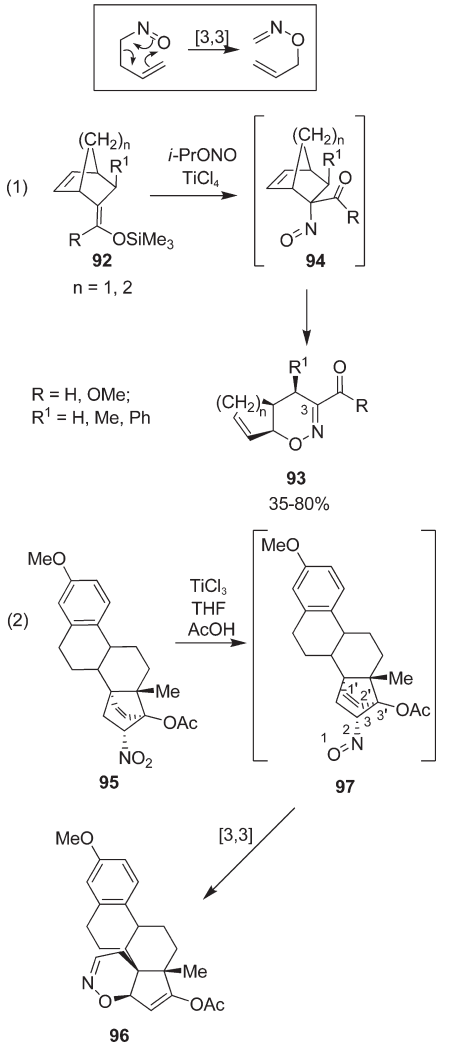
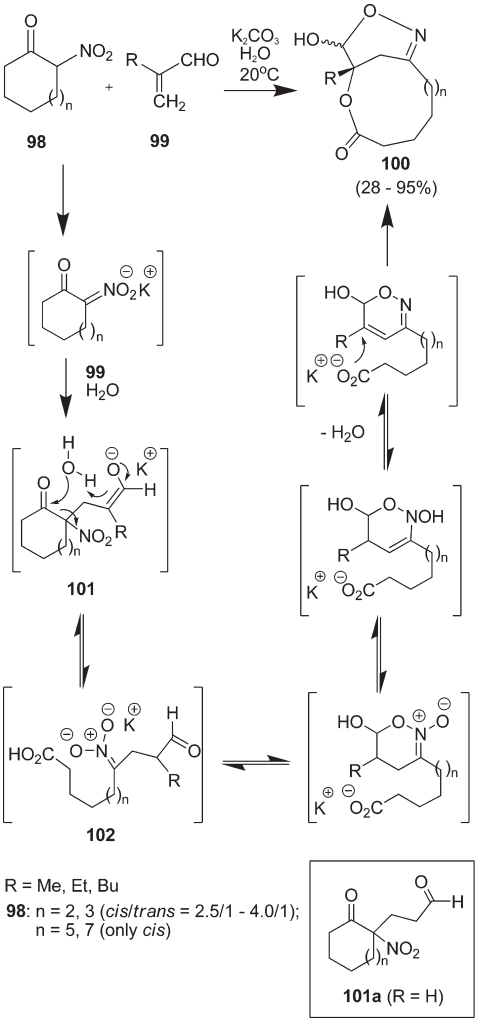
Scheme 31



Scheme 32



Recently, a simple method for the synthesis of unusual SCOE **100** containing a macrocyclic lactone fragment has been suggested involving the reaction of α-nitrocycloalkanones **98** with α-alkyl-substituted acroleines **99** in an aqueous solution of potassium carbonate (Scheme 32).[156] The stereoselectivity of products **100** formation depends on the ring size of the starting α-nitrocycloalkanone **98** (*n* is from 2 to 7). The authors make a reasonable suggestion that the initial adducts of the Michael reaction **101** upon the action of hydroxide anion undergo cleavage at the C−C bond between the carbonyl and nitro groups, whereas acyclic nitronate anions **102** formed successively undergo recyclization with the oxazine ring closure and then the macrocyclic lactone ring closure (Scheme 32). Only α-substituted unsaturated aldehydes **99** (R ≠ H, Scheme 32) undergo this reaction, whereas acroleine yields only the Michael addition product **101a**.[156]

3. CHEMICAL PROPERTIES OF SCOE

SCOE exhibit various reactivity. The presence of the oximino fragment sets up the possibilities of its reduction, nucleophilic addition to a C═N bond, Beckmann rearrangements, and, finally, deoximination. Additionally, the presence of a six-membered heterocycle with the labile N−O bond in SCOE implies the possibility of retro-[4 + 2]-cycloaddition, as well as the heterocycle contraction reactions.

3.1. Reduction of SCOE

Reduction of the oximino group is a key reaction in the known strategies of the SCOE application in directed syntheses, since it allows one to convert the oxazine ring into a heterocyclic or acyclic framework of the target molecules. Therefore, for a successful application of SCOE in total synthesis, it is necessary to know the regio- and stereoregularities of the complex process of their reduction.

Scheme 33 demonstrates a general outline of the reduction of the oximino fragment in 5,6-dihydrooxazines **1** to the amino group. Exhaustive reduction of the oximino fragment in SCOE can be considered as a combination of two separate steps, namely, reductions of the N−O bond and the C═N bond. It can be accomplished in three ways. Pathway (1) suggests initial reduction of the C═N bond and only then the hydrogenolysis of the N−O bond in tetrahydrooxazines **103**. Pathway (2) consists of a reverse sequence of the bond reductions: the N−O bond is reduced first and only then the C═N bond. The intermediates in such a process are highly reactive imines **104**, which can undergo not only reduction, but also other transformations such as heterocyclization and hydrolysis. The third possible approach (3) consists of the initial migration of the double bond from

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Scheme 33

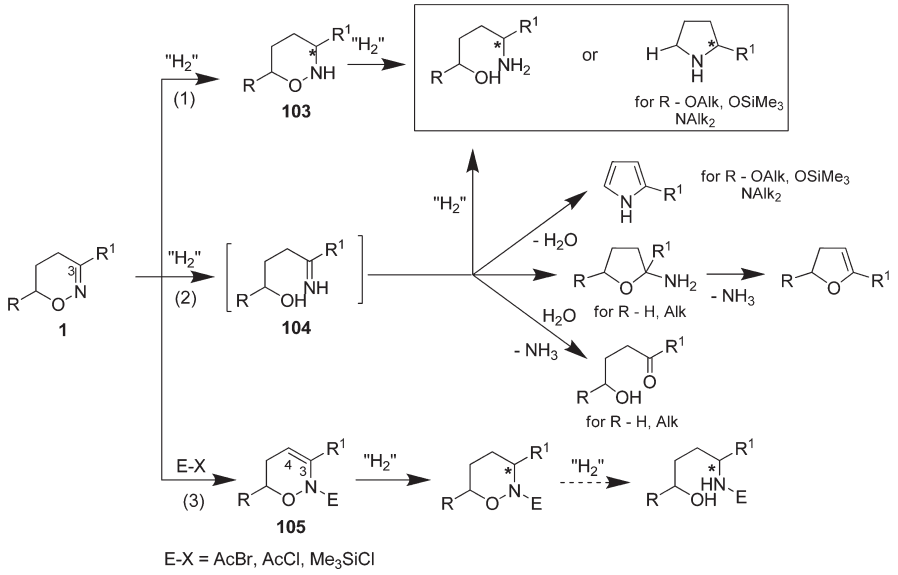

Table 2. Reduction of SCOE

entry	reducing agent	reduction pathway	R	reduction products	ref
1	$NaBH_3CN$/AcOH	1	H, Alk, Ar, OAlk, $OSiMe_3$, $NAlk_2$	tetrahydro-1,2-oxazines	61, 91, 123, 133, 134, 137b, 144, 157−164
2	(1) $NaBH_3CN$/AcOH	1	H, Alk	1,4-amino alcohols	157, 160−164
	(2) H_2/Ra−Ni		OAlk	pyrrolidines	61, 134, 159−164
3	$LiAlH_4$ /Et_2O	1	H, Alk	1,4-amino alcohols	35, 37, 65, 66
4	BH_3−THF/THF	1, major pathway	OAlk	tetrahydro-1,2-oxazines	159
5	(1) BH_3−THF/THF;	1	OAlk	pyrrolidines	159
	(2) H_2/Ra−Ni				
6	Al−Hg	1	H, Alk, Ar	1,4-amino alcohols	23, 42
7	catalytic hydrogenation over Raney nickel or palladium-on-charcoal	2	H, Alk, Ar	1,4-amino alcohols or furan derivatives	164−168
			OAlk, $OSiMe_3$, $NAlk_2$	pyrrolidines or pyrroles	22, 23, 40, 68, 81, 142, 147, 166−170
8	$Mo(CO)_6$/CF_3CO_2H; $Fe_3(CO)_9$/CF_3CO_2H	2	OAlk, $OSiMe_3$, $NAlk_2$	pyrroles	31, 32, 41, 171
9	(1) AcBr or AcCl	3	H, Alk	tetrahydro-1,2-oxazines	95, 172
	(2) H_2/ Pd−C or Rh−C				

position 2,3 to position 3,4, i.e. the formation of 2*H*-1,2-oxazines **105**, with subsequent reduction of the C═C bond and hydrogenation of the N−O bond.

A new stereocenter at the C-3 atom of the starting SCOE emerges in the course of the reduction (the asterisk in Scheme 33), which sets up a problem of stereoselectivity. Depending on the reaction pathway, the new stereocenter is formed in the addition of hydrogen to different intermediates. This can be reflected in the overall stereoselectivity of the reduction, which usually is considerably higher in the reduction of the double bonds in cyclic oxazines **1** or **105** than in the reduction of acyclic imines **104**.

The direction of SCOE reduction depends on the reducing agent used. Table 2 demonstrates how the nature of common reducing agents affects the outcome of the SCOE reduction.

Hydride reducing agents (Table 2, entries 1−5) and aluminum amalgam (Table 2, entry 6) reduce the C═N bond first (Scheme 33, pathway (1)). To make this process proceed more smoothly, an activation of the double C═N bond with a Lewis or Brønsted acid is frequently used. The later coordinates at the nitrogen atom to give more reactive *N*-oxyiminium cations. When $NaBH_3CN$ and BH_3−THF are used, tetrahydrooxazines **103** do not undergo further reduction; however, the N−O bond in them can be easily hydrogenated using Ra−Ni in the framework of a two-step process.

Catalytic hydrogenation of SCOE or treatment with metal carbonyls proceeds as an initial reduction of the N−O bond, leading to the generation of imines **104** (see Scheme 33, pathway (2)). The latter can be hydrogenated at the C═N bond or undergo cyclizations to pyrrole and furan derivatives.

To perform the reduction of SCOE by pathway (3), it is necessary to "shift" irreversibly the double bond, i.e., to convert oxime ethers **1** to 2*H*-1,2-oxazines **105**. This can be achieved

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upon the action of strong electrophiles (acyl halides, chlorotrimethylsilane) on SCOE **1**. The resulting 2*H*-1,2-oxazines are catalytically hydrogenated to tetrahydro-2*H*-1,2-oxazines.

As is seen from Scheme 33 and Table 2, the reduction of SCOE can result in the retention of 1,2-oxazine heterocycle, its opening, or contraction to five-membered heterocycles. Reduction of SCOE to tetrahydrooxazines **103** is little sensitive to the nature of substituents in the ring. However, if the oxazine ring in the course of the reduction is opened, then the nature of the final product depends on the character of substitution in the oxazine ring, and, first of all, on the substituent at the C-6 atom. If atom C-6 is not an acetal or aminal carbon (i.e., R ≠ alkoxy, siloxy, or amino group in Scheme 33), 1,4-amino alcohols are the standard products. Catalytic hydrogenation of SCOE with the same character of substitution can lead to furan derivatives as well. The latter are the products obtained, if the cyclization of imines **104** to aminotetrahydrofurans proceeds faster than their hydrogenation to 1,4-amino alcohols (Scheme 33). If substituent R at C-6 in the starting SCOE is an alkoxy-, siloxy-, or amino group, the final products of the reduction are pyrrolidines or sometimes pyrroles, which are formed through the intermediate imines **104**. In such processes, the oxygen atom of the former oximino fragment is not transferred to the resulting heterocycle and substituent R is exchanged for the hydrogen atom.

Below, the main directions of the SCOE reduction, conditions under which they are accomplished, as well as the stereoselectivity of such processes are considered in detail.

3.1.1. Reduction of SCOE to Tetrahydro-2*H*-1,2-oxazines. Selective reduction of the C═N double bond in dihydrooxazines **1** is accomplished using hydride reducing agents (Table 2). Sodium cyanoborohydride in acetic acid is a common reagent. Under such conditions, various dihydrooxazines **1** are smoothly transformed to the corresponding tetrahydro-2*H*-1,2-oxazines **103** (Scheme 34).[14,61,91,123,133,137b,144,157−164] This reaction usually proceeds with high stereoselectivity and in high yields.[173] Many functional groups in the 1,2-oxazine ring, in particular an ester group, remain intact during the reduction. The latter circumstance is of great importance for the synthesis of amino acids from SCOE (see section 4.1).

In the annulated bicyclic dioxime ether **77**, only the C═N double bond in the six-membered ring is reduced upon the action of 3 equiv of sodium cyanoborohydride (Scheme 35).[144]

Two specific features of the cyanoborohydride method of the SCOE reduction should be mentioned. First, dihydrooxazines bearing a powerful electronegative substituent at the atom C-3, such as a trifluoromethyl group (R = CF_3 in Scheme 34), do not undergo reduction under such conditions.[158,159] Second, during the reduction of dihydrooxazines **1b** with a siloxy group at the C-6 atom (Table 1), replacement of the siloxy group with the hydrogen atom takes place together with the reduction of the endocyclic C═N double bond (Scheme 36).[158]

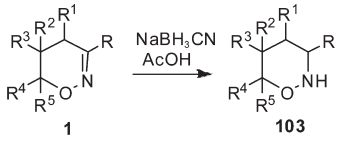
The authors suggest that, in the reaction of **1b** with sodium cyanoborohydride in AcOH, acetolysis of the starting dihydrooxazines and generation of cations **106** initially take place. These cations are reduced to dihydrooxazines **107**, which then upon the action of excess sodium cyanoborohydride give the final tetrahydrooxazines **108**. This mechanism is confirmed by isolation of the intermediate dihydrooxazine **107a** together with tetrahydrooxazine **108a**, as well as by the fact that the stereochemistry of the final products **108** does not depend on the relative configuration of the siloxy group in starting substrates **1b** (Scheme 36).[158]

When reduction of dihydrooxazines **1** is performed with the system $NaBH_3CN$/AcOH, the intermediates are obviously oximinium cations **109**,[162] to which the addition of a hydride ion leads to the final tetrahydro-2*H*-1,2-oxazines **103** (Scheme 37). Thus, the function of acetic acid in the transformation **1** → **103** consists of the electrophilic activation of the C═N double bond in oxime ethers **1**. The absence of the reduction products for 3-trifluoromethyl-substituted dihydrooxazines is explained by difficulties in the generation of the corresponding cations **109** caused by a strong decrease in basicity of the nitrogen atom of the oximino fragment due to the electron-withdrawing effect of the CF_3 group.[158]

Reduction of 5,6-dihydrooxazines with sodium cyanoborohydride, as a rule, is highly stereoselective (see Scheme 38, eqs 1−3).[158,162−164]

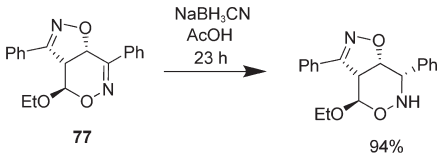
In some cases, it is reasonable in the course of the reduction to protect the arising sp^3 nitrogen atom, for example, by benzoylation with benzoyl chloride, as it is shown in eq 3 in Scheme 38.[162]

Scheme 34

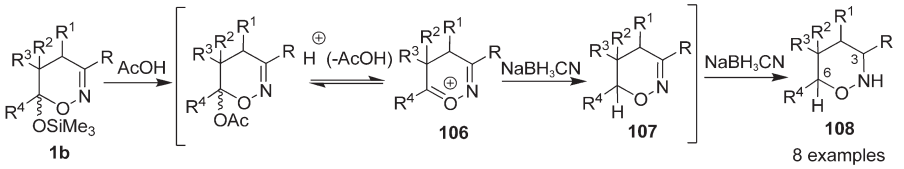


R = H, Me, Ar, CO_2Et, -CH=$CHCO_2Me$; CH_2CO_2Me, $CH_2CH(CO_2Me)_2$, CH_2OH
R^1 = H, Alk, Ar, OAlk, CO_2Me;
R^2, R^3 = H, Me, OAlk;
R^4, R^5 = H, Alk, OAlk, Ph, CH_2SiMe_3, CH_2SePh

Scheme 35



Scheme 36



R = Ph, CO_2Et, *trans*-CH=$CHCO_2Me$; R^1 = H; R^2, R^3 = H, Alk, $OSiMe_3$; R^4 = H, Alk

107a, 108a (R = *trans*-CH=$CHCO_2Me$; R^1, R^2, R^3 = H; R^4 = Me

Yields: 31-80%[158] (ratio 3,6-*cis*/3,6-*trans* from 96 : 6 to 70 : 30)

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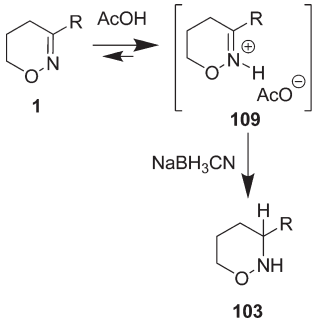
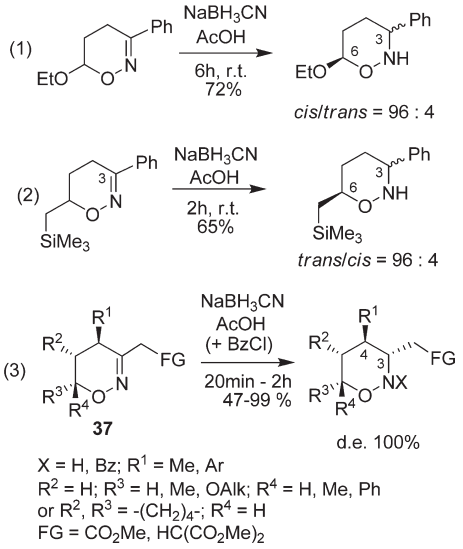
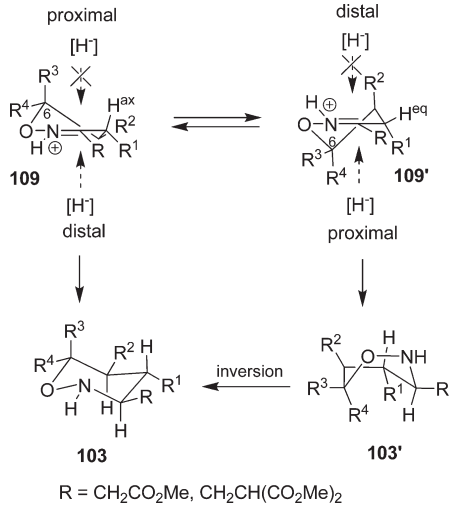
Scheme 37



Scheme 38



Scheme 39



In a recent report,[162] a hypothetic model is suggested, which explains the stereochemical outcome of the reduction of SCOE **37** (Scheme 39). According to this model, the stereochemical result of the reduction process is determined by two factors, e.g., the reactive conformation of cation and the direction of hydride ion approach to it. The preferability of hydride ion attack is

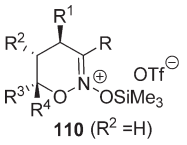
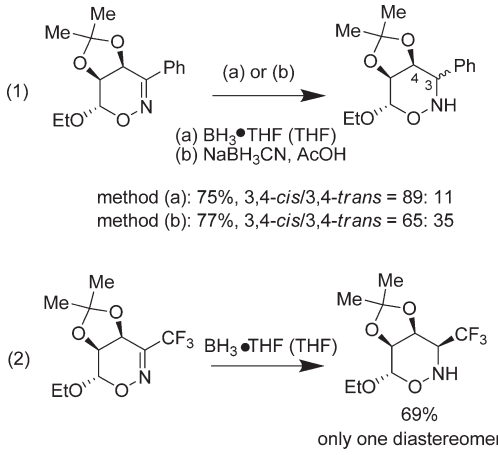


Figure 3

Scheme 40



determined by minimization of sterical interactions in the transition state. In the proximal approach, the sterical hindrance is created by C-6 atom strongly deviated from the plane of the cycle[174] and by its pseudo-axial substituent (e.g., R^3 in **109**, Scheme 39). In the distal approach, the sterical hindrance can be created by a pseudo-axial substituent at C-5 (for example, R^2 in conformation **109′**). As can be seen from Scheme 39, the same stereoconfiguration of target product **103** can be achieved by two different hydride attacks on two possible conformations of the cation (**109** or **109′**, respectively). Thus, for a proper interpretation of the stereochemical result of the process, additional assumptions are required. First, the dominant conformation of cation is assumed to be reactive. Second, the dominant conformation of initial SCOE and its cation are supposed to be identical. The model under consideration seems to be general and can be extended on the coupling of SCOE with other nucleophiles.

This hypothesis is in good agreement with the data on a similar process, viz., the C,C-coupling of π-nucleophiles with bis(oxy)iminium cations **110** (R^2 = H, Figure 3) generated by silylation of six-membered cyclic nitronates **34** (see Scheme 10).[175,176] The authors showed[175,176] that addition of a nucleophile to these cations occurs stereoselectively through the distal (with respect to atom C-6) approach of the nucleophile to a predominant conformation of cation **110**. The conformation of the cation was shown to be the same as the conformation of the starting nitronate **34**.

Sodium cyanoborohydride is not the only reagent suitable for the selective reduction of the C═N bond in SCOE. Reissig and coworkers demonstrated on several examples that borane−tetrahydrofuran complex also reduces SCOE to tetrahydro-2*H*-1,2-oxazines, with the stereoselectivity of the reaction possibly being even higher than with sodium cyanoborohydride (Scheme 40, eq 1).[159] An important advantage of the BH_3−THF complex as compared to sodium cyanoborohydride is its ability to reduce 3-trifluoromethyl-substituted dihydrooxazines (Scheme 40, eq 2).[159]

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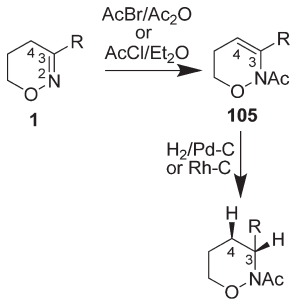
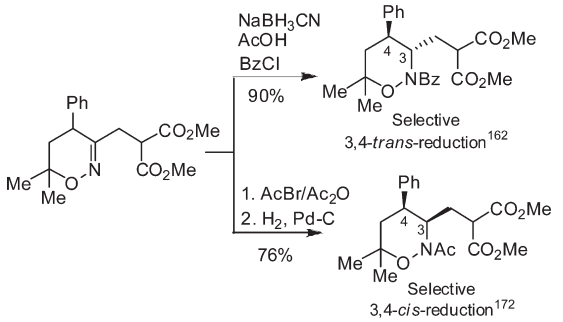
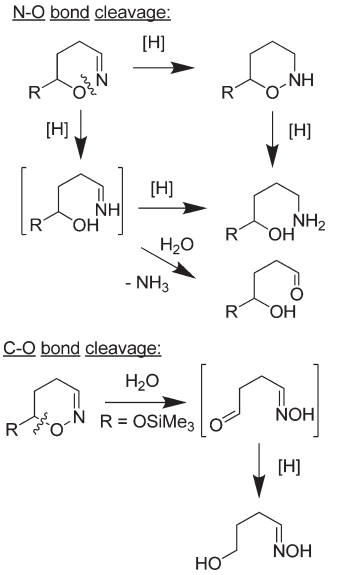
Scheme 41



Scheme 42



Scheme 43



The synthesis of tetrahydrooxazines from SCOE can be also accomplished by a two-step scheme, where initial migration of the double bond from position 2,3 to position 3,4 takes place followed by its reduction (see pathway 3 in Scheme 33 and Scheme 41).[95,172] The first step is accomplished upon the action of acetylating agent and the second by catalytic hydrogenation of the intermediate **105** on palladium[172] or rhodium catalyst.[95]

At present, possibilities of this approach for the reduction of SCOE are not sufficiently studied; however, it is known that it can give products with relative configurations of stereocenters opposite to the configurations obtained after the reduction of SCOE with sodium cyanoborohydride (see the representative example in Scheme 42).

3.1.2. Reduction of SCOE with 1,2-Oxazine Ring-Opening. 1,2-Oxazine ring-opening during the reduction of SCOE can occur either by cleavage of the N−O bond or the C−O bond. In the first case, 1,4-amino alcohols or carbonyl compounds are the final products, whereas in the second case, hydroxy oximes are obtained (Scheme 43).

3.1.2.1. Reduction of SCOE to 1,4-Amino Alcohols. Transformation of SCOE to 1,4-amino alcohols can be accomplished by two principally different methods (see pathways 1 and 2 in Scheme 33); i.e., it is possible to initially reduce the N−O bond or one can start from the reduction of the C═N bond. The first process is performed under catalytic hydrogenation conditions, whereas the second used a combination of hydride reduction of SCOE and subsequent catalytic hydrogenation of tetrahydrooxazines **103** (see Scheme 33).

Recently,[164,166] transformation of a representative series of dihydrooxazinyl acetates **37a** to the corresponding 1,4-amino alcohols **111** was accomplished by catalytic hydrogenation (Scheme 44). The authors demonstrated that the formation of products **111** independently on the catalyst used (palladium-on-charcoal or Raney Ni) proceeds through the initial cleavage of the N−O bond, leading to imines **104**.[166] The latter can be isolated in the form of more stable tautomers **112** and **113**, if the hydrogenolysis is carried out under milder conditions.[166]

Catalytic hydrogenation of 6*H*-1,2-oxazines **2** containing no alkoxy substituent at C-6 also leads to 1,4-amino alcohols (see Scheme 45).[167] In this case, in addition to exhaustive reduction of the oximino fragment, the endocyclic C═C double bond also undergoes hydrogenation (Scheme 45).

Reduction of dihydrooxazines **1** with aluminum amalgam similarly to catalytic hydrogenation leads to 1,4-amino alcohols as mixtures of diastereomers (Scheme 46).[23,42]

The major disadvantage of the approach to the synthesis of 1,4-amino alcohols under consideration (see Schemes 44−46) consists of the low stereoselectivity of the new stereocenter formed at atom C-3. It is obvious that the generation of a new stereocenter takes place here in low stereodifferentiating reactions of hydrogen addition to acyclic imines of the type **104** (Scheme 44).[164,166,167] Apparently, the stereoselectivity of the reduction to 1,4-amino alcohols can be increased, if the order of the bond reductions in the oximino fragment is changed, i.e., to initially reduce the C═N bond and only then the N−O bond, since, as was shown above, the hydride reduction of the C═N bond in SCOE usually proceeds stereoselectively.

1,4-Amino alcohols **114** can be obtained with high stereoselectivity from the corresponding dihydrooxazines **1g** by reduction with lithium aluminum hydride in diethyl ether (Scheme 47).[35,66] The isolation of stable tetrahydrooxazine **115** when the "aged" $LiAlH_4$ was used directly indicates the sequence of the reduction of the bonds in the oximino fragment.[35]

Lithium aluminum hydride is, of course, incompatible with a whole number of common functional groups, and this decreases the scope of its application. However, this disadvantage can be overcome by the successive use of sodium cyanoborohydride (for the reduction of the C═N bond, see section 3.1.1), followed by catalytic hydrogenation (for the reduction of the N−O bond (Scheme 48, eq 1).[160−164] Such a method for the reduction of the dihydrooxazine ring is the most preferable from the point of view of chemo- and stereoselectivity for the generation of a representative series of the target 1,4-amino alcohols **116**. (For the stereoselectivity of hydride reduction of the C═N bond, see

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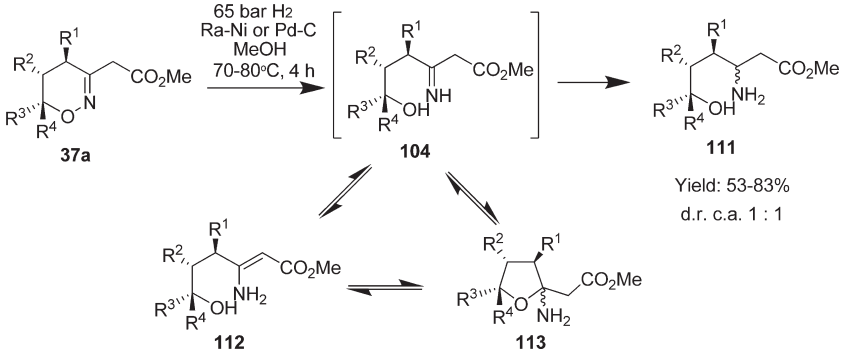
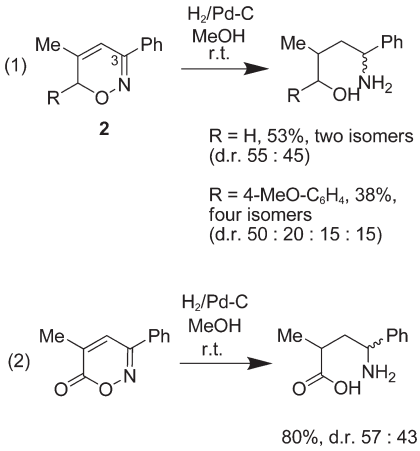
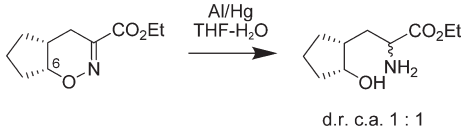
Scheme 44



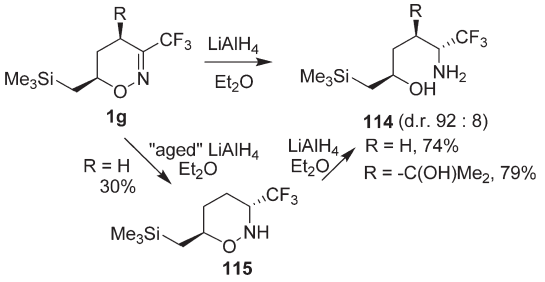
Scheme 45



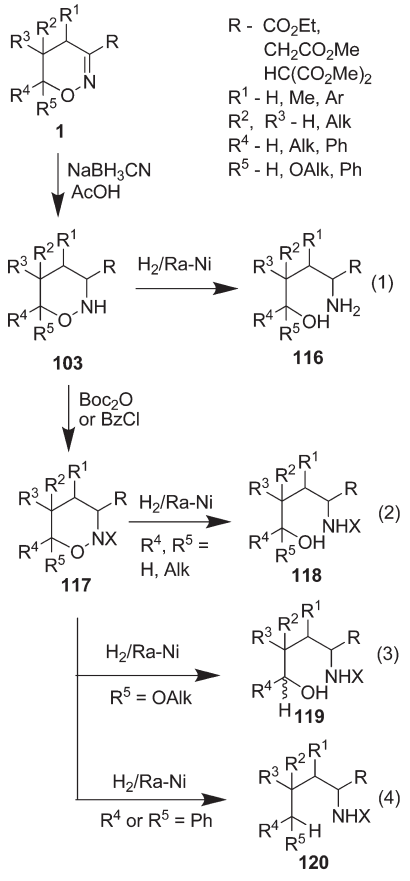
Scheme 46



Scheme 47



Scheme 48

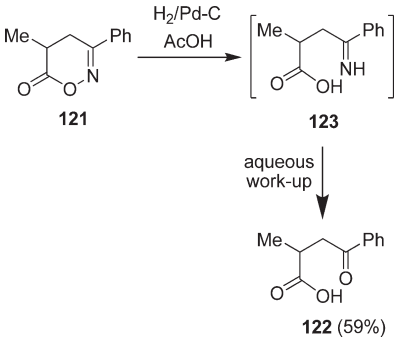


the discussion in section 3.1.1.) Sometimes, prior the hydrogenation it is reasonable to protect the nitrogen atom in tetrahydrooxazines **103** (Scheme 48, eq 2, products **117**).[160−162] In this case, 1,4-amino alcohols **118** protected at the nitrogen atom are the final hydrogenation products. If 1,2-oxazines **117** have an alkoxy substituent at position C-6 (R^5 = OAlk), it is replaced with the hydrogen atom in the final 1,4-amino alcohols **119** (Scheme 48, eq 3).[160,161] If $R^4 \neq H$, this process, as a rule, is not stereoselective. The presence of a phenyl substituent at the C-6 of tetrahydrooxazines **117** leads to the reduction of the hydroxy group in products **118** to yield amines **120** (Scheme 48, eq 4).[162]

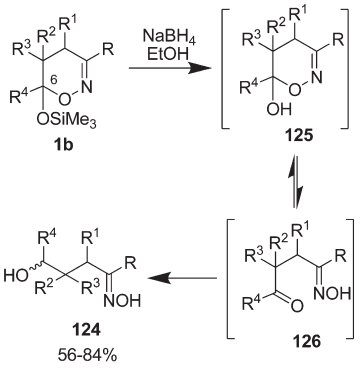
3.1.2.2. Reduction of SCOE to Carbonyl Compounds. Some SCOE can undergo deoximation with the reductive cleavage of the endocyclic N−O bond and transformation of the imino group to a carbonyl. For example, hydrogenation of dihydrooxazin-6-one **121** on palladium catalyst in acetic acid afforded keto acid **122**

dx.doi.org/10.1021/cr100292w |*Chem. Rev.* 2011, 111, 5004–5041

Scheme 49



Scheme 50



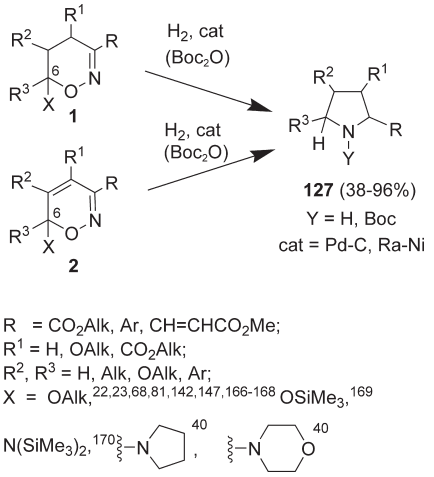
(Scheme 49).[167] A mechanism suggested for this transformation includes reduction of the N−O bond with the formation of imine **123**, which upon aqueous workup is hydrolyzed to the corresponding ketone.[167]

3.1.2.3. Reduction of SCOE to γ-Hydroxyoximes. 6-Siloxy-substituted dihydrooxazines **1b** upon the action of sodium borohydride undergo the oxazine ring-opening by cleavage of the C−O bond to form γ-hydroxyoximes **124** (Scheme 50). This transformation includes reduction of the acetal center at the atom C-6, rather than the oximino group (cf. with Scheme 36).[169] In the reaction, desilylation of the starting SCOE **1b** occurs first to give 6-hydroxy-substituted dihydrooxazines **125**. The latter are in equilibrium with the corresponding acyclic keto forms **126**, which are reduced by sodium borohydride.[169] Note that if $R^1 \neq H$, the hydride addition to the carbonyl group (the atom C-6 in initial SCOE) is not stereoselective.

3.1.3. Reduction Reactions of SCOE with 1,2-Oxazine Ring Contraction. Reduction of SCOE can lead to the 1,2-oxazine ring contraction in such a way that only one out of two heteroatoms (nitrogen or oxygen) remains in the final heterocyclic system, i.e., pyrrole or furan derivatives. Such processes proceed through the initial oxazine ring-opening (usually by cleavage of the N−O bond) and subsequent recyclization. In this case, the nature of the final heterocycle is primarily determined by the character of substitution at the C-6 atom in the starting SCOE.

3.1.3.1. Reduction of SCOE to Pyrrolidines. Reduction of SCOE bearing an alkoxy, siloxy, or amino group at the C-6 atom

Scheme 51



usually leads to pyrrolidines. This reaction seems to be the most important in the chemistry of SCOE and is widely used in the synthesis of natural products containing a pyrrolidine ring (alkaloids, substituted prolines, etc.; see section 4).

Like the reduction to 1,4-amino alcohols, the synthesis of pyrrolidines can be accomplished by catalytic hydrogenation or the two-step protocol "hydride reduction catalytic hydrogenation" (see Scheme 33 and Table 2).

Scheme 51 +demonstrates the catalytic hydrogenation of SCOE **1** and **2** to pyrrolidines **127**.[14,22,23,40,68,81,142,147,166−170] In the course of SCOE hydrogenolysis, the oximino fragment is reduced to the amino group and a new C−N bond is formed between the former carbon atom C-6 and nitrogen atom of the amino group. In this case, the X group is not retained in the final products **127**.

Hydrogenation of SCOE **1** and **2** usually is carried out in alcohols at atmospheric, less often at elevated, pressure of hydrogen using Raney nickel (Ra−Ni) or palladium-on-charcoal (Pd−C) as catalyst. A trapping reagent, di-*tert*-butyl carbonate (Boc_2O), is frequently added to transform pyrrolidines (**127**, Y = H, Scheme 51) into stable carbamates (**127**, Y = Boc, Scheme 51).[68,147,170]

Introduction of a protecting group at the nitrogen atom of pyrrolidines allows one to significantly simplify the procedure of their isolation, and in addition, it is quite necessary in those cases when free pyrrolidines **127** (X = H) are unstable under catalytic hydrogenation conditions.[147,169,170] For example, during the hydrogenation of 3-aryl-substituted dihydrooxazines **128**, the corresponding pyrrolidines **129** cannot be isolated, since they are easily hydrogenated at the C(2)−N bond to form 2-substituted 4-arylbutylamines **130** (Scheme 52).[146b,169,170] However, when Boc_2O is added to the reaction mixture, pyrrolidines **129** are successfully trapped as the corresponding stable *N*-Boc-pyrrolidines **131**.[147]

Pyrroles **132** are the major side products in the hydrogenation of SCOE to pyrrolidines.[14,23,68,142,147,168] Their amount depends on the structure of initial SCOE and catalytic hydrogenation conditions (pressure, temperature, and the nature of the catalyst). Sometimes, pyrroles are the major products of the SCOE hydrogenation.[68,142,168] In the report,[147] it is noted that for the prevention of pyrrole formation and an increase in the yields of the target pyrrolidines **127**, more extreme hydrogenation conditions are required (high temperatures

and hydrogen pressure), as well as increase in the amount of catalyst.

The mechanism of pyrrolidine formation by the hydrogenation of SCOE **1** and **2** is complicated and so far is not studied in detail. The most probable pathway for this process is shown in Scheme 53.[166,168] If 6*H*-1,2-oxazines **2** are involved in hydrogenation, the endocyclic C=C double bond is reduced first.[142,167] Hydrogenation of the N−O bond of the oxime ether **1** produces imines **104** (step (1)). Then elimination of the HX molecule takes place to generate imines **133** (step (2)). Intramolecular cyclization of the latter gives 2-hydroxydihydropyrroles **134**, which either undergo further hydrogenation to pyrrolidines **127** (steps 4−6, through pyrrolines **135**) or eliminate water, giving rise to pyrroles **132**. Thus, the proportion pyrrolidine/pyrrole in the final products is determined by the relative rates of steps 4 and 7.[168]

Such a +scheme of the SCOE hydrogenolysis is confirmed by the isolation of some intermediates[167] or their stable tautomeric forms.[166] It cannot be excluded that the sequence of steps in Scheme 53 may be different; however, it is reliably established that the first step of the process is the reduction of the N−O bond, not the C=N double bond.[164,166,168]

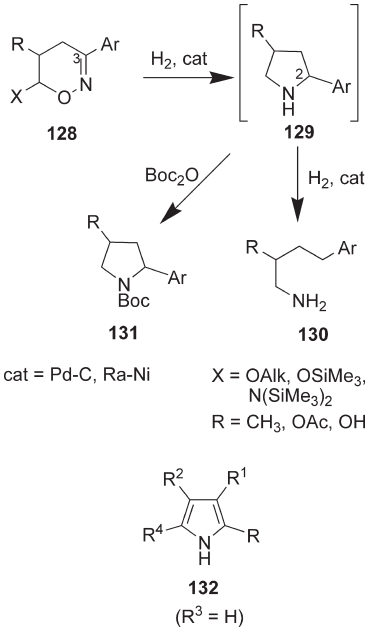
Direct synthesis of pyrrolidines from SCOE can be accomplished not only using catalytic hydrogenation but also with the use of some other reducing agents, in particular, aluminum amalgam.[23]

Transformation of SCOE to pyrrolidines can be performed stepwise with the reverse order of reduction of the bonds in the oximino group, i.e. reducing first the C=N bond with sodium cyanoborohydride or borane−tetrahydrofuran complex and hydrogenating the N−O bond in the resulting tetrahydrooxazine **103** (see Scheme 34).[157,159−164] In this case, the formation of pyrroles as side products is not possible. In addition, such a procedure is more preferable for the stereoselective formation of a new stereocenter at C-2 of the pyrrolidine ring. A characteristic example[164] illustrating this statement is shown in Scheme 54.

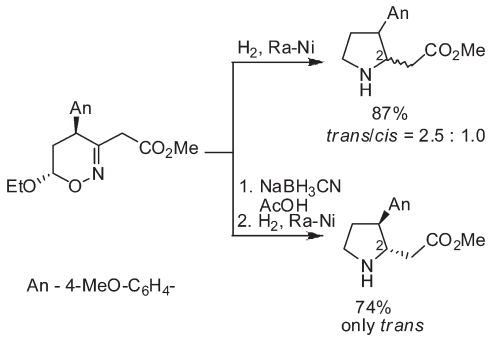
On the other hand, the formation of a stereocenter at C-5 in the two-step process can be less stereoselective than in the one-step procedure[164,166] (Scheme 55).

3.1.3.2. Reduction of SCOE to N-Hydroxypyrrolidines. The reduction of SCOE possessing a trimethylsiloxy at the C-6 atom

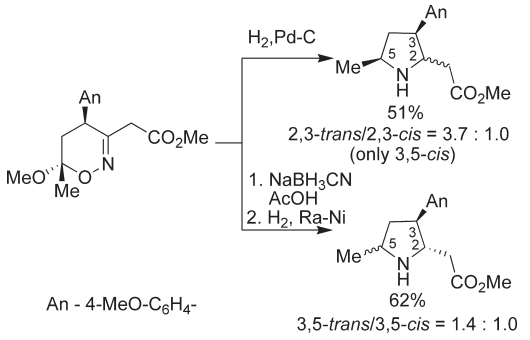
Scheme 52



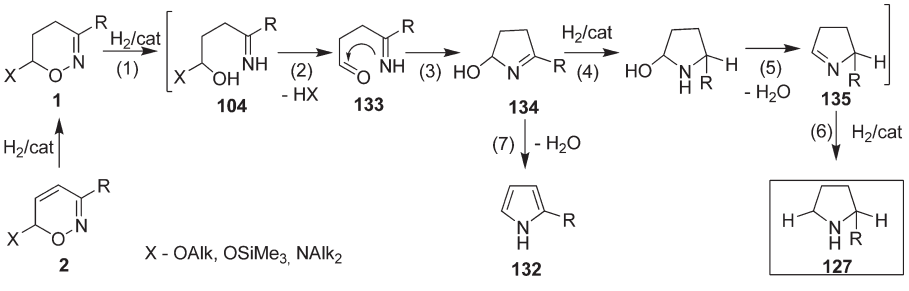
Scheme 54



Scheme 55



Scheme 53



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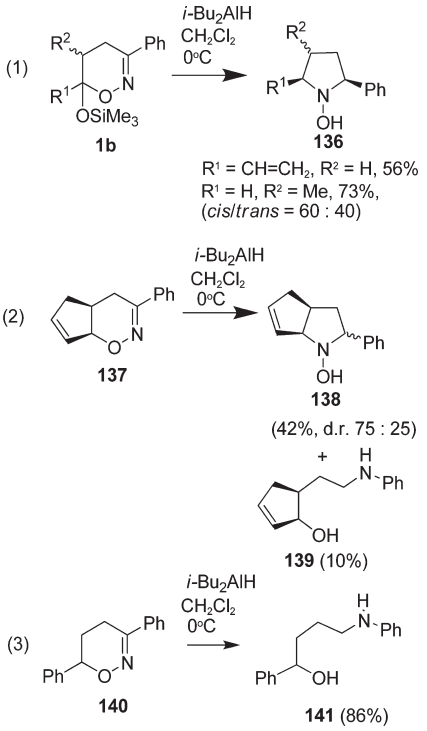
with diisobutylaluminum hydride (*i*-Bu_2AlH) can lead to *N*-hydroxypyrrolidines **136** in moderate to good yields (Scheme 56, eq 1).[169] Under analogous conditions, bicyclic oxazine **137** yields *N*-hydroxypyrrolidine **138** as the major product and 1,4-amino alcohol **139** as the minor component. Note that in the course of the transformation **137** → **139**, the phenyl substituent from the C-3 atom in **137** migrates to the nitrogen atom (Scheme 56, eq 2).[169] On the other hand, 6-phenyl-substituted SCOE **140** in the reduction with *i*-Bu_2AlH gives exclusively the amino alcohol **141** (Scheme 56, eq 3).[169]

The observed differences in behavior of oxazines **1b**, **137**, and **140** observed are interpreted by the authors[169] from the point of view of the following mechanistic scheme (Scheme 57). In the first step, *i*-Bu_2AlH is coordinated at the endocyclic oxygen atom, giving rise to complexes **142**. Their further behavior depends on the nature of substituent R. If this substituent is able to efficiently stabilize a positive charge on atom C-6 (R is a siloxy group or vinyl), complexes **142** undergo the oxazine ring-opening by cleavage of the endocyclic C−O bond to give zwitterionic intermediates **143**. Recyclization and subsequent reduction of intermediates **143** lead to the resulting *N*-hydroxypyrrolidines **136** and **138**.

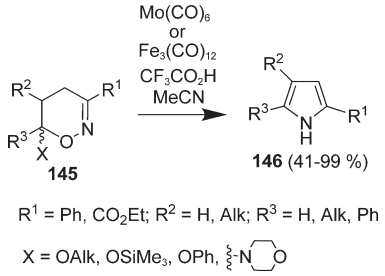
If substituent R is a phenyl group, generation of the zwitterionic intermediate of the type **143** becomes unfavorable and complex **142** undergoes the Beckmann rearrangement, leading to the intermediate **144**. Its further reduction with an excess of *i*-Bu_2AlH gives the final 1,4-amino alcohol **141**.

3.1.3.3. Reduction of SCOE to Pyrroles. Pyrroles can be synthesized from dihydrooxazines **145** containing a heteroatomic substituent at C-6, for example, when X is an alkoxy, siloxy, or amino group (Scheme 58). Nakanishi[31,41] and Reissig[32,171] showed that dihydrooxazines **145** are smoothly transformed into pyrroles **146** upon the action of metal carbonyls [$Mo(CO)_6$,

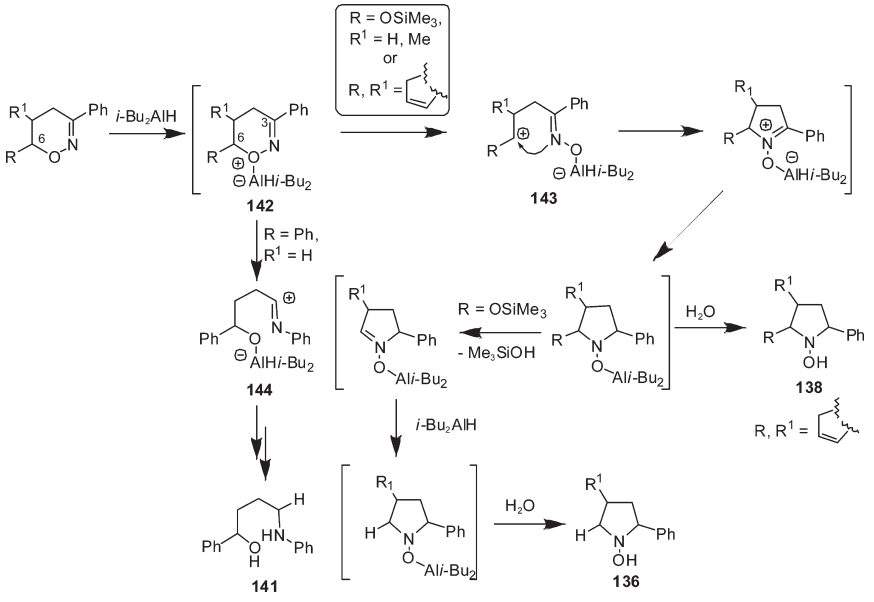
Scheme 56



Scheme 58



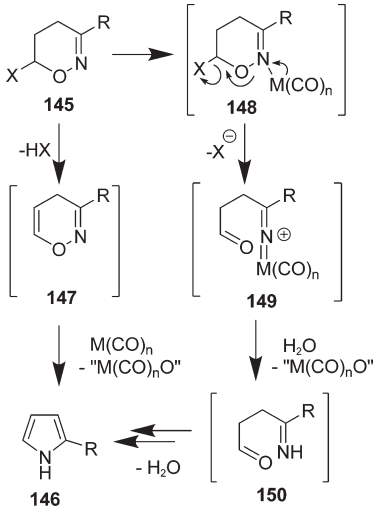
Scheme 57



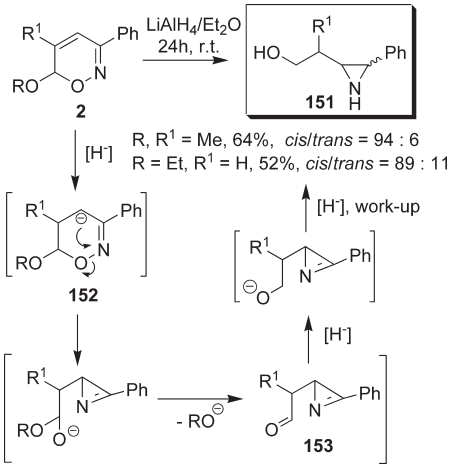
dx.doi.org/10.1021/cr100292w |*Chem. Rev.* 2011, 111, 5004–5041

$Fe(CO)_5$, $Fe_2(CO)_9$, and $Fe_3(CO)_{12}$] (Scheme 58). The best yields are obtained when $Mo(CO)_6$ or $Fe_3(CO)_{12}$ in the presence of trifluoroacetic acid is employed.

Scheme 59



Scheme 60



Two possible mechanisms were suggested for the transformation **145** → **146** (see Scheme 59). According to the first one,[31,41] the reaction proceeds via the deoxygenation of unstable 4*H*-1,2-oxazine **147** upon the action of metal carbonyl $M(CO)_n$. The intermediate **147** is suggested to result from the elimination of HX molecule from the starting dihydrooxazine **145**. The second variant[171] postulates the initial cleavage of the weak N−O bond in oxazine **145** with carbonyl $M(CO)_n$ to form complex **149**. The latter decomposes upon the action of acid HX, giving aldimine **150**, which further is cyclized to the final pyrrole **146**.

3.1.3.4. Reduction of SCOE to Aziridines. Reissig and co-authors discovered that 6*H*-1,2-oxazines **2** containing an alkoxy substituent at C-6 atom are transformed to *cis*-2,3-disubstituted aziridines **151** with high stereoselectivity by reduction with lithium aluminum hydride (Scheme 60).[177]

Probably, the transformation **2** → **151** includes addition of hydride anion at the endocyclic C═C double bond of oxazine **2** with the formation of anion **152**, its subsequent Neber rearrangement leading to the oxazine ring-opening and formation of 2*H*-azirine **153**. Its exhaustive reduction leads to the final aziridine **151**.[177]

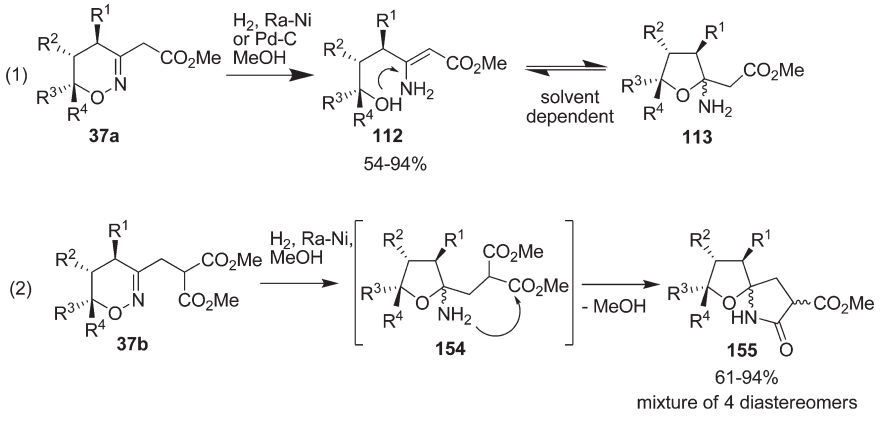
3.1.3.5. Reduction of SCOE to Furan Derivatives. In the examples considered above, only the nitrogen atom was transferred into the final heterocycle in the course of SCOE reduction, whereas the oxygen atom was "pushed out" of the resulting heterocycle. However, another pathway is also possible if only oxygen atom is transferred into the final heterocycle, i.e., the reduction leads to the furan derivatives. This process usually takes place when SCOE containing alkyl substituents and/or hydrogen at atom C-6 are hydrogenated and competes with the reduction to 1,4-amino alcohols (see section 3.1.2).

It was already mentioned[166] that mild catalytic hydrogenation of substituted dihydrooxazinyl acetates **37a** produces 2-amino-tetrahydrofurans **113**, which are in tautomeric equilibrium with acyclic isomers **112** (Scheme 61, eq 1).[166]

If an ester group is placed in the γ-position to the amino group in 2-aminofurans (intermediate **154**, Scheme 61, eq 2), a ring closure to a five-membered lactam takes place in the course of hydrogenation of **37b** to give oxaazaspirononanones **155** as the major hydrogenolysis products. The latter are formed as chromatographically separable mixtures of diastereomers.[168]

Other examples of the reduction of SCOE leading to the furan derivatives were also reported (Scheme 62).[137b,155,159,178] Thus,

Scheme 61



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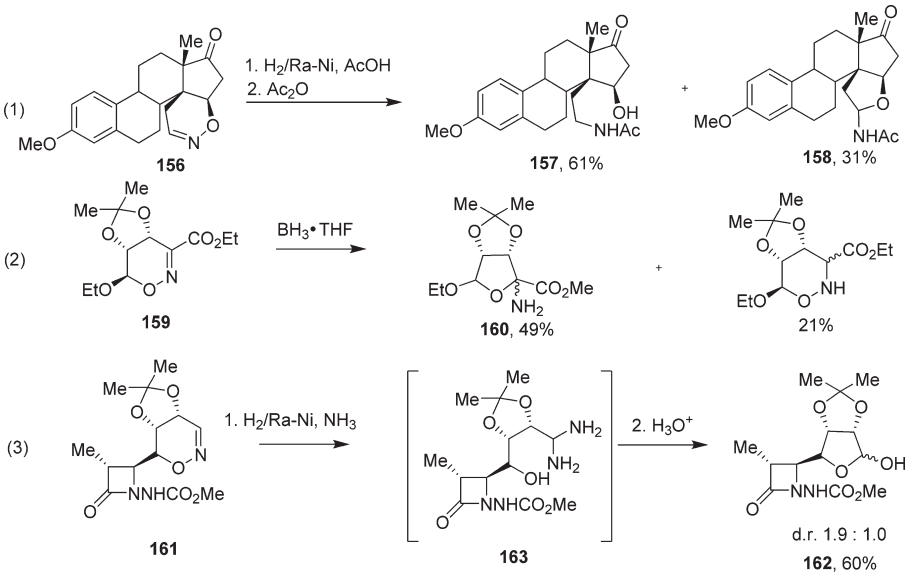
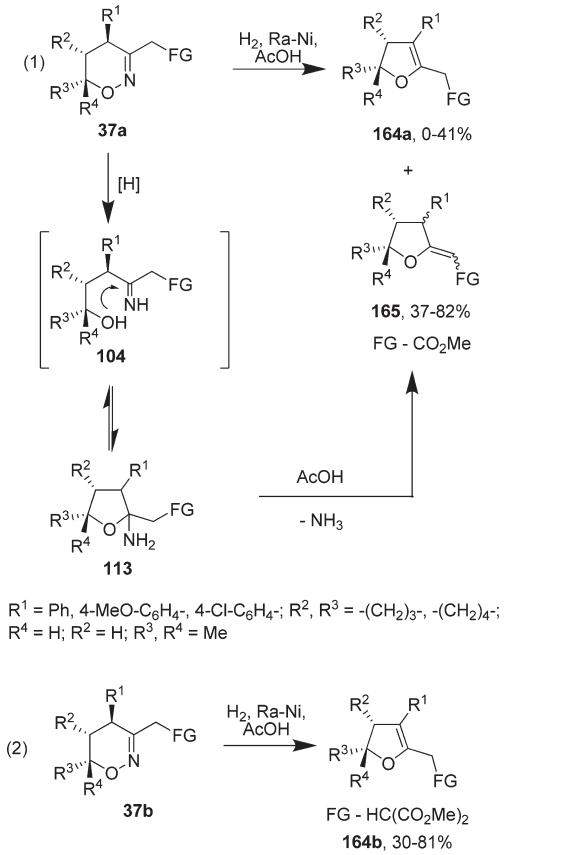
Scheme 62



Scheme 63



after hydrogenolysis of dihydrooxazine **156** and subsequent acylation of the resulting products, 2-(acetylamino)tetrahydrofuran **158** was isolated as a side product in addition to amino alcohol derivative **157** (Scheme 62, eq 1).[155] 2-Aminotetrahydrofuran **160** was obtained as the major product in the reduction of dihydrooxazine **159** with BH_3−THF complex (Scheme 62, eq 2).[159] Chiral 2-hydroxytetrahydrofuran **162** was obtained by hydrogenation of SCOE **161** on Raney nickel in the presence of ammonia, followed by hydrolysis of the intermediate **163** (Scheme 62, eq 3).[178]

Recently, it was found that SCOE can be precursors of not only tetrahydro- but also dihydrofurans. For instance, SCOE **37a**, **b**, containing a functionalized substituent at C-3 and an aryl substituent at C-4, are transformed to dihydrofurans **164a**,**b** or isomeric 2-alkylidenetetrahydrofurans **165** by hydrogenolysis on Raney nickel in acetic acid.[165,166] The yields of the target products are in the range from moderate to good (Scheme 63).

It was shown in control experiments[166] that transformation of SCOE **37** to the furan derivatives **164** and **165** includes initial reduction of the N−O bond with the formation of imines **104**, their cyclization to aminofurans **113** (FG is CO_2Me) or **154** [FG is $HC(CO_2Me)_2$], and final elimination of ammonia from these intermediates upon the action of acetic acid.

The application scope of the approach represented in Scheme 63 for SCOE with various types of substitution is not yet studied. On the whole, it should be concluded that the possibility of the synthesis of furan derivatives from SCOE is not yet studied sufficiently.

3.2. Addition Reactions to the C=N Double Bond of SCOE

Reduction with hydride anion is the most known reaction of nucleophilic addition to the C=N bond of SCOE. This reaction has been already considered in this review (see section 3.1.1). Just a few examples of the addition of other nucleophiles to SCOE are published. Note that the activation of the C=N−O bond fragment with Lewis acids is necessary for the successful coupling with a nucleophiles.

Addition of C-nucleophile (5-methylthiophen-2-yllithium) to unsubstituted 5,6-dihydro-4*H*-1,2-oxazine with the formation of tetrahydro-2*H*-1,2-oxazine **166** in moderate yield is described (Scheme 64, eq 1).[179] Analogous addition of trimethylsilyl cyanide to the same dihydrooxazine gives 3-cyanotetrahydro-2*H*-1,2-oxazine (Scheme 64, eq 2).[135] Both reactions are carried out in the presence of a Lewis acid.

Oxazinium salts **32** (for their synthesis, see refs 92, 180−182 and section 2.1) readily react with nucleophiles. Examples of successful

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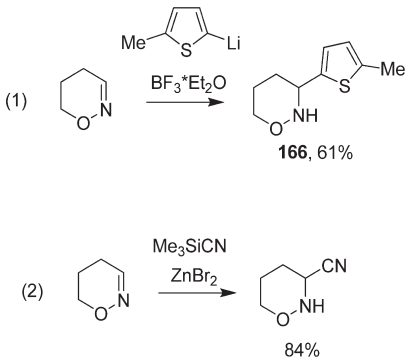
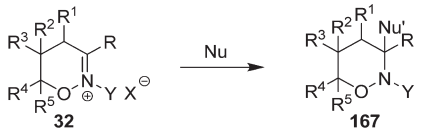
Scheme 64



Scheme 65



Nu (Nu') = NaCN (CN), BuLi (Bu), $NaBH_4$ (H), H_2O (OH), $PH(O)(OPh_2)$ $(P(O)(OPh_2)_2)$

Y = *n*-Bu, Bn, *t*-Bu, cyclohexyl; X = Br, I, BF_4

R = H, Me; R^1, R^2, R^3 = H, Alk; R^4, R^5 = H, Alk, OAc

coupling of **32** with cyanide anion[125,183,184] and *n*-butyllithium,[183] their reduction with sodium borohydride,[125] as well as addition of water[183] and $PH(O)(OPh)_2$[181] are known (Scheme 65).

Similarly to the reduction of SCOE with sodium cyanoborohydride, the reaction **32** + Nu → **167** proceeds with high levels of stereoselectivity. For example, in the reactions of salt **168** with cyanide anion and water, only 3,6-*cis*-substituted tetrahydrooxazines **169** are generated (Scheme 66).[125]

The C═N double bond of the dihydrooxazine ring can act as a dipolarophile in the [3 + 2]-reactions with nitrosostyrenes **26**; however, the yields of the corresponding nitrones are not very high (Scheme 67).[60,185]

3.3. 1,2-Oxazine Ring-Opening in SCOE

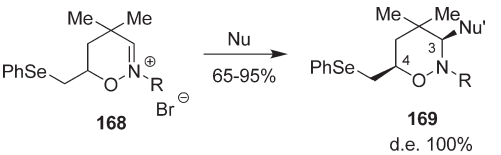
Treatment of SCOE **1** with acids can lead to the oxazine ring-opening by cleavage of the C(6)−O bond with the retention of the oximino group. For instance, dihydrooxazines **1g** with CH_2SiMe_3 substituent at C-6 are converted to ene oximes **68** upon treatment with aqueous $HClO_4$ (Scheme 68).[35,65] TBAF also induces ring-opening in SCOE **1g** via desilylation accompanied by a E_2 type elimination.[65]

SCOE with an acetal center at C(6) are cleaved at the endocyclic C−O bond giving rise to 3-oximino-substituted carbonyl compounds (Scheme 69, eq 1).[186] Dihydrooxazines **1e** are cleaved similarly (Scheme 69, eq 2),[45] furnishing mixtures of ethyl γ-ketocarboxylate oximes **170** and oxazin-6-ones **55**.[45]

Dihydrooxazines **171** annulated with dihydrothiophene,[187] dihydrobenzothiophene,[187] or dihydrofuran[35,188] fragments in the reaction with strong acids (e.g., trifluoroacetic acid) are smoothly converted to the corresponding heterocyclic oximes **172** in the same manner (Scheme 70).

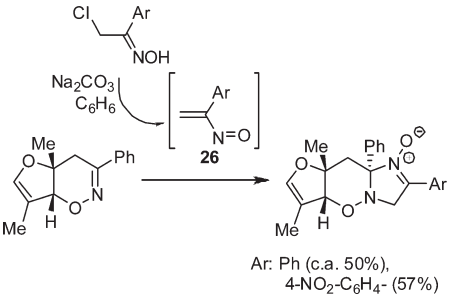
An example of the photochemical ring-opening in SCOE is also described. Oxime ether **173** upon irradiation produces alkenyl-substituted oxime **174** as a mixture of *E,Z*-isomers (Scheme 71).[89]

Scheme 66



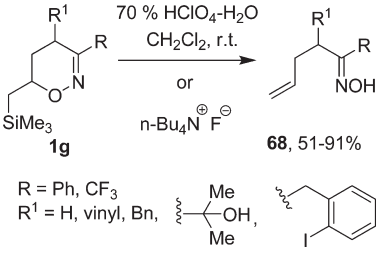
R = *n*-Bu, Bn; Nu (Nu') = NaCN (CN), H_2O (OH)

Scheme 67



Ar: Ph (c.a. 50%), 4-NO_2-C_6H_4- (57%)

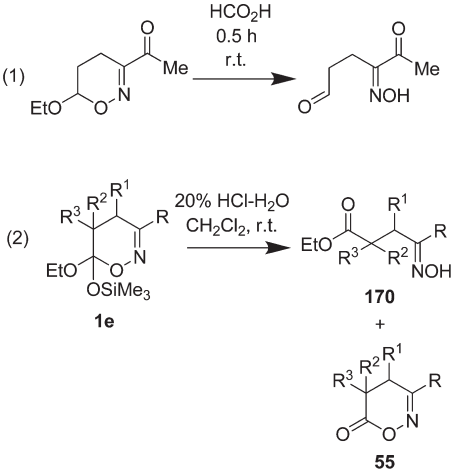
Scheme 68



R = Ph, CF_3

R^1 = H, vinyl, Bn,

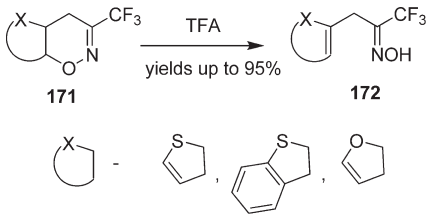
Scheme 69



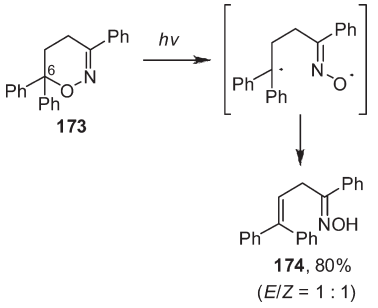
R	R^1	R^2	R^3	Yield, %	
				170	**55**
Ph	Et	Et	Et	35	42
Ph	H	Et	Et	49	-
Ph	H	Bu	Et	67	-
Ph	Me	Me	Et	-	98
4-Cl-C_6H_4-	Me	Me	Et	-	90
4-Cl-C_6H_4-	Et	Et	Et	35	53

dx.doi.org/10.1021/cr100292w |*Chem. Rev.* 2011, 111, 5004–5041

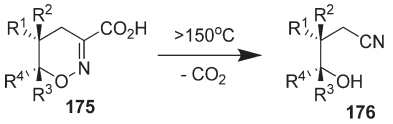
Scheme 70



Scheme 71



Scheme 72



R^1	R^2	R^3	R^4	Yield of **176**, %
H	H	Me	Ph	99
H	-CH_2CH=CH-		H	73
H	-CH_2-*o*-C_6H_4-		H	83
H	-$(CH_2)_6$-		H	91

The oxazine ring-opening can be accompanied by the transformation of the oximino group to a cyano group. Such a process, a thermal decarboxylation/fragmentation of 5,6-dihydro-4*H*-1,2-oxazine-3-carboxylic acid **175** to γ-hydroxybutanonitriles **176**, was described by Gilchrist (Scheme 72).[47]

3.4. Deoximation of SCOE

SCOE give the corresponding carbonyl compounds after oxazine ring-opening under hydrolysis conditions.

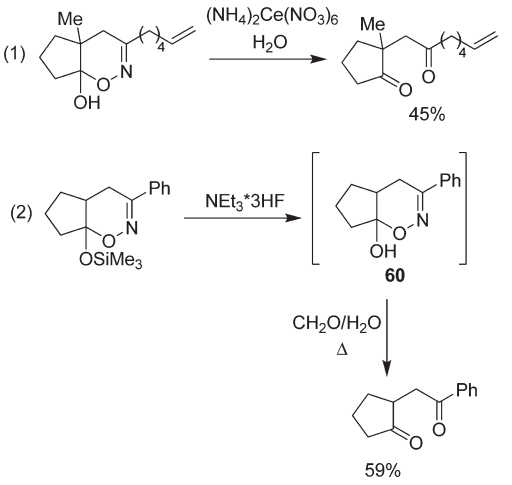
In particular, deoximation of 6-hydroxy-substituted SCOE of type **60** can be considered as an interesting pathway for the synthesis of 1,4-dicarbonyl compounds. The deoximation of SCOE is carried out upon the action of cerium ammonium nitrate[116a] (Scheme 73, eq 1) or upon heating in aqueous formaldehyde (Scheme 73, eq 2).[171] In the case of 6-siloxy-substituted SCOE, preliminary removal of the silyl group is performed.

The authors[48] showed that SCOE **177** upon the action of $HClO_4$ is smoothly converted to alkenyl-substituted ketones **178** (Scheme 74, cf. with Scheme 68). This transformation includes deoximation and subsequent Peterson elimination.

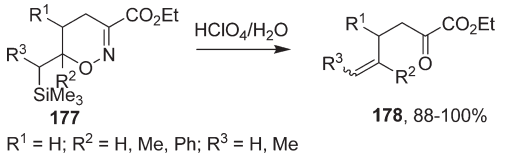
3.5. 1,2-Oxazine Ring Rearrangements in SCOE

A large group of SCOE reactions include transformation of a 1,2-oxazine ring into another heterocycle. Some such

Scheme 73



Scheme 74



R^1 = H; R^2 = H, Me, Ph; R^3 = H, Me

Scheme 75

R = Me, 44%
R = Ph, 44%
R = OEt, 56%

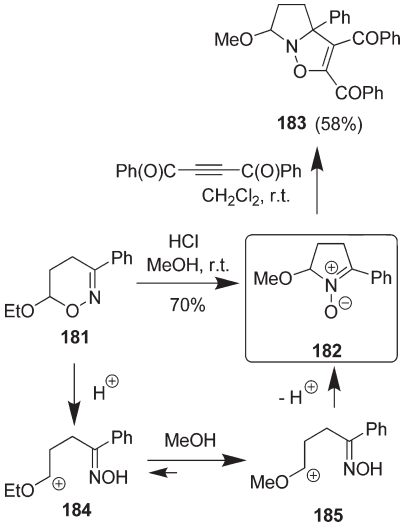
transformations occurring upon the action of reducing agents have been considered above. Here, rearrangements of oxazine ring proceeding without the assistance of reducing agents are discussed.

Dihydrooxazines **179** upon reflux in xylene undergo rearrangement to five-membered cyclic nitrones **180** in moderate yields (Scheme 75).[187] The mechanism of this transformation has not been studied, but the authors suggest a homolytic cleavage/recombination pathway or a concerted [1,2]-sigmatropic shift.[189] Also the transformation **179** → **180** may proceed via a mechanism involving retro-oxa-Michael reaction followed by a N-Michael addition.

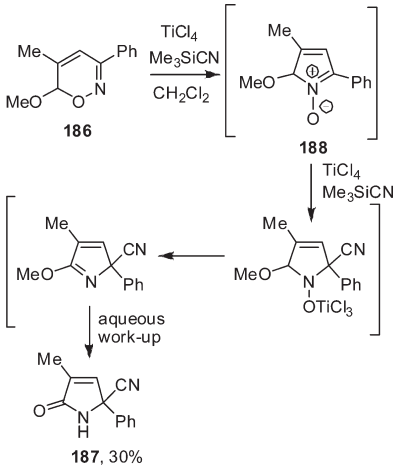
6-Alkoxy[27] and 6-siloxy[171] substituted dihydrooxazines **1** also can undergo rearrangement to five-membered cyclic nitrones upon the action of acids, as is shown in Scheme 76. 6-Ethoxydihydrooxazine **181** upon treatment with hydrochloric acid in methanol gives nitrone **182** in good yield. The structure of the latter was confirmed by the transformation to a stable [3 + 2]-adduct with dibenzoylacetylene **183**.[27] In this case, the dihydrooxazine ring contraction can proceed through the protonation of oxazine **181** and generation of stabilized cation **184**. Its reaction with methanol and subsequent elimination of the ethoxy group upon the action of acid give cation **185**, the cyclization of

dx.doi.org/10.1021/cr100292w |*Chem. Rev.* 2011, 111, 5004–5041

Scheme 76



Scheme 77



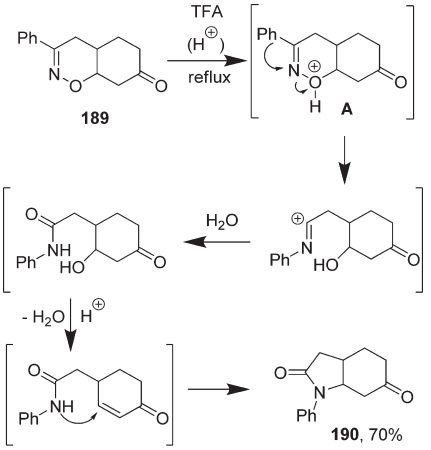
which, with elimination of the proton, leads to the final nitrone **182**.[27]

Similar transformations were also observed for 6*H*-1,2-oxazines **2**.[190] For example, SCOE **186** upon the action of trimethylsilyl cyanide in the presence of titanium tetrachloride gives α-pyrrolidone **187**. The authors suggest that the reaction proceeds through the initial rearrangement to nitrone **188** (Scheme 77). Addition of trimethylsilyl cyanide to this intermediate and subsequent hydrolysis affords the final five-membered heterocyclic product **187**.[190]

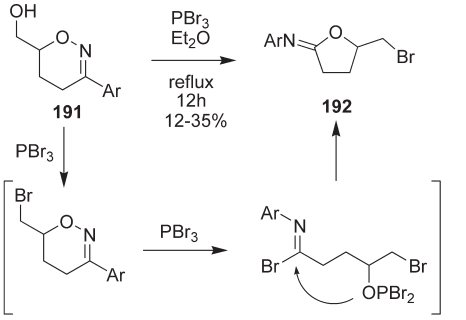
Another group of acid-induced transformations of dihydrooxazines includes the Beckmann rearrangement. Iscanderl[50] showed that SCOE **189** upon reflux in trifluoroacetic acid gives bicyclic pyrrolidone **190**, resulting from the Beckmann rearrangement of the sextet cationic intermediate **A**, addition of water to the rearranged product, and subsequent cyclization (Scheme 78).

Similar rearrangement has been recently described by the Langer group in a series of 3-aryl-6-(hydroxymethyl)-substituted SCOE **191** (Scheme 79).[100] These oxime ethers upon the action of phosphorus tribromide are converted to tetrahydrofurans **192** in poor yields. In this reaction, the hydroxy group is initially

Scheme 78

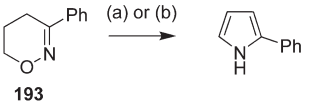


Scheme 79



Ar - 3-Me-C_6H_4-, 4-MeO-C_6H_4-, 3-Me-C_6H_4-, 2-naphthyl

Scheme 80



(a) KOH, DMSO, 100°C, yield: 44%
(b) *hv*, 254 nm, CH_3CN, yield: 100%

substituted with bromine followed by Beckmann rearrangement of the arising intermediate, as is shown in Scheme 79.[100]

Formation of pyrroles is another version of the 1,2-oxazine ring contraction. For instance, 3-phenyl-substituted dihydrooxazine **193** is converted to 2-phenylpyrrole upon treatment with potassium hydroxide in dimethyl sulfoxide[88] or upon photochemical activation[89] (Scheme 80).

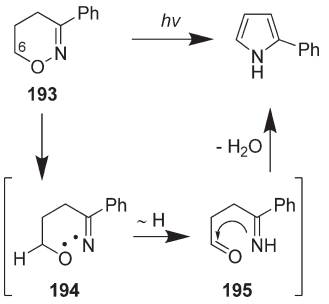
The mechanism of the first process is not exactly known.[88] The photochemical transformation[89] includes homolytic cleavage of the N—O bond, rearrangement of biradical **194** with the migration of one hydrogen atom from atom C-6 to the nitrogen, and subsequent cyclization of imine intermediate **195** (Scheme 81).

Rearrangement to pyridines is a separate group of reactions in the chemistry of functionalized SCOE.[27,44b,55]

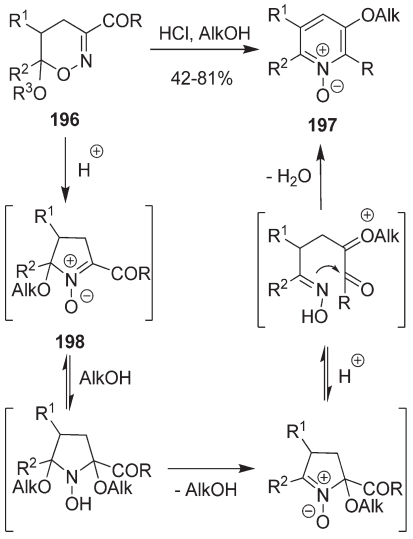
Gilchrist and coauthors[27] demonstrated that dihydrooxazines **196** containing an alkoxy substituent at atom C-6 and a fragment —C(O)R at atom C-3 are converted to pyridine *N*-oxides **197** upon

dx.doi.org/10.1021/cr100292w |*Chem. Rev.* 2011, 111, 5004–5041

Scheme 81



Scheme 82



R = Me, Ph; R^1 = H, Me; R^2 = H, Me; R^3 = Me, Et
Alk = Me, Et

treatment with hydrochloric acid in ethanol (Scheme 82). The yields of final pyridine *N*-oxides varied from good to moderate.

The authors[27] reasonably suggest a well-known acid-assisted generation of five-membered nitrones **198** as the intermediates in the first step. Further cascade of transformations involves addition of the alcohol molecule to nitrones **198**, five-membered ring-opening, recyclization, and elimination of water.

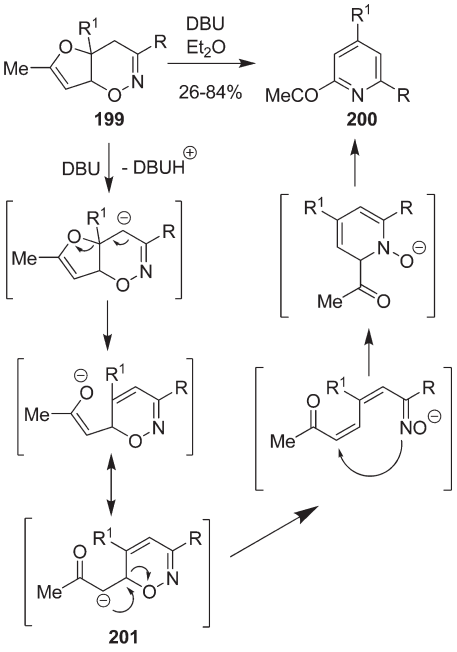
In other report,[55] the rearrangement of annulated furooxazines **199** upon the action of DBU is suggested as a new method for the synthesis of acetyl-substituted pyridines **200** (Scheme 83). The mechanism of this rearrangement includes initial cleavage of the furan ring with the formation of 6*H*-1,2-oxazines **201**. The latter were isolated from the reaction mixtures in some cases. The oxazine ring-opening in the intermediate **201**, subsequent recyclization, and aromatization afford the final pyridines **200** (Scheme 83).[55]

3.6. 1,2-Oxazine Ring Fragmentation Reactions in SCOE

It is known that the fragmentation of the 1,2-oxazine ring in SCOE with the cleavage of the endocyclic C−C bonds can proceed via several routes. First, separate examples of retro-[4 + 2]-cycloaddition of 5,6-dihydro-4*H*-1,2-oxazines with the formation of α-nitrosoalkenes and olefins are known[21] (see the example in Scheme 84).

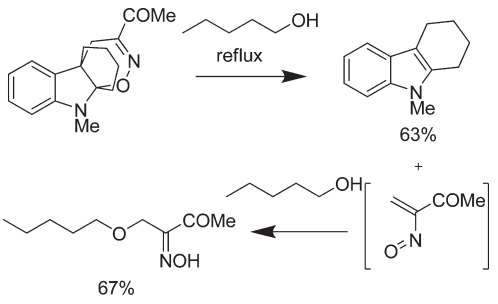
The second type of the oxazine ring fragmentation is illustrated in Scheme 85. In this process, 5,6-dihydro-4*H*-1,2-

Scheme 83

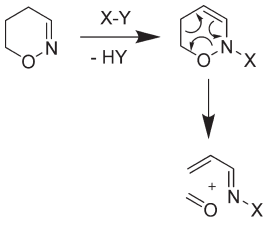


R = CO_2Alk, C(O)Et, C(O)Ph, Ph; R^1 = H, Me

Scheme 84



Scheme 85

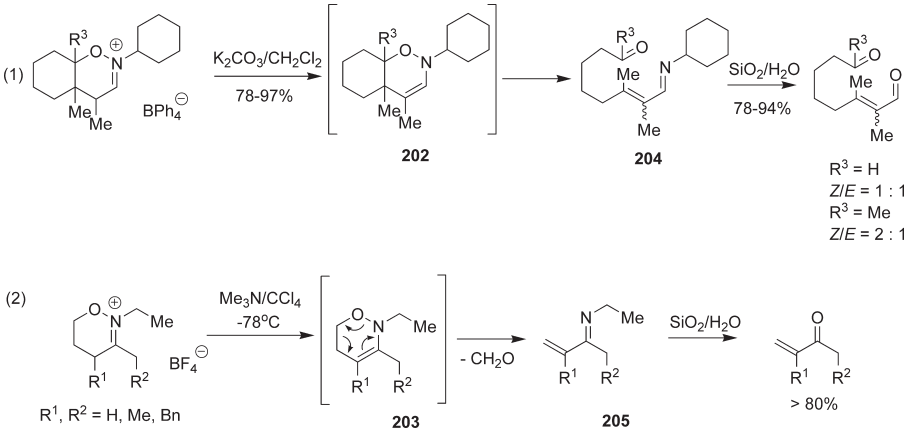


oxazines are initially converted to 5,6-dihydro-2*H*-1,2-oxazines, which then smoothly undergo retro-[4 + 2]-cycloaddition with the cleavage of the labile N−O bond leading to carbonyl compounds and α,β-unsaturated imines.[19,92,93,172,182,191,192]

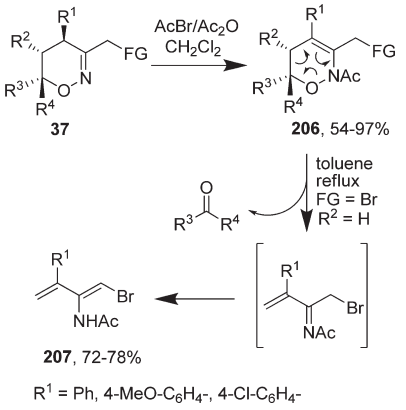
Such a process was observed by Eschenmoser[191] and Shatzmiller[92,93,182,192] in the fragmentation of *N*-alkyldihydrooxazine salts (see Scheme 86, eqs 1 and 2). The latter react with a base to give unstable 5,6-dihydro-2*H*-1,2-oxazines **202** or **203**, which undergo a rapid fragmentation to give products **204** or **205**, respectively. These intermediates are hydrolyzed to the

dx.doi.org/10.1021/cr100292w |*Chem. Rev.* 2011, 111, 5004–5041

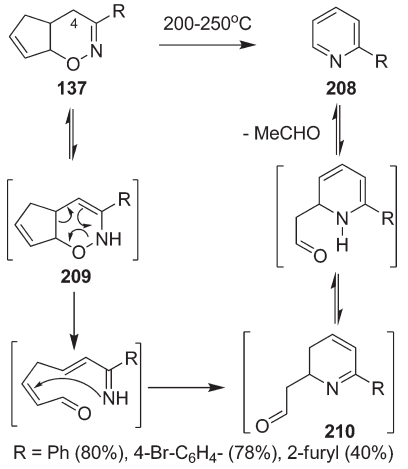
Scheme 86



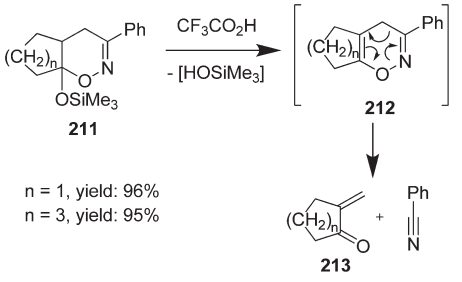
Scheme 87



Scheme 88



Scheme 89



corresponding carbonyl compounds on wet silica gel.[182,191] Such an approach was suggested as a convenient method for the synthesis of substituted α,β-unsaturated carbonyl compounds.

The approach given in Scheme 85 can be accomplished by acylation of SCOE as well (Scheme 87).[172] Acetylation of SCOE **37** with the system AcBr/Ac_2O in dichloromethane smoothly produces *N*-acetyl-dihydro-2*H*-1,2-oxazines **206**.[172] In contrast to *N*-alkyl-substituted analogs, these derivatives are quite stable at room temperature and undergo fragmentation only upon refluxing in toluene. The resulting dienes **207** are obtained in good yields.[172]

In some fundamental transformations of SCOE, the fragmentation given in Scheme 85 is suggested as one of the steps. Thus, Gilchrist and co-workers[188] discovered an unusual transformation of bicyclic SCOE **137** to 2-substituted pyridines **208** during their thermolysis (Scheme 88). The process presumably proceeds through the reversible migration of the proton from C-4 to the nitrogen, electrocyclic ring-opening of 2*H*-1,2-oxazine **209**, cyclization of the emerging intermediate to dihydropyridine **210**, its isomerization, and elimination of the acetaldehyde molecule.[188]

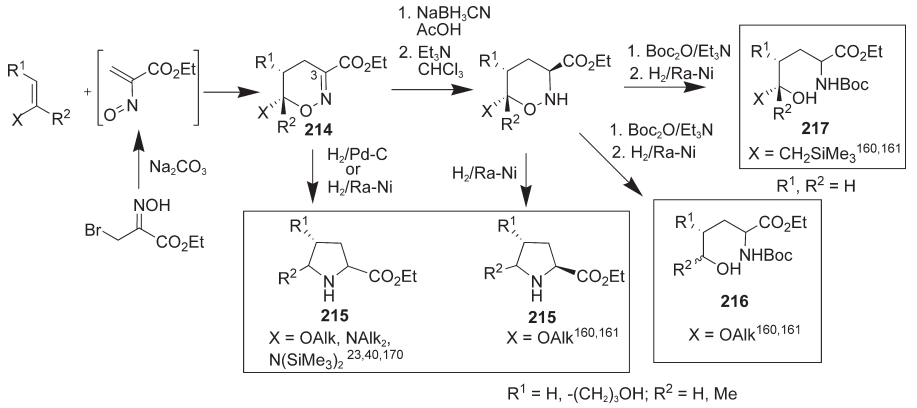
Another pathway for the fragmentation of SCOE is also possible, that is, the cleavage of the N−O and C(3)−C(4) bonds in the unstable intermediate 4*H*-1,2-oxazines **212** (Scheme 89).[113,116b,171,172] In particular, this occurs when bicyclic dihydrooxazines **211** are treated with TFA and leads to high yields of unsaturated ketones **213** and benzonitrile. Obviously, a retro-[4 + 2]-cycloaddition of unstable 4*H*-1,2-oxazines **212** takes place, which emerge after elimination of trimethylsilanol from the starting SCOE **211** upon the action of CF_3CO_2H.

4. SCOE IN THE SYNTHESIS OF NATURAL PRODUCTS AND BIOLOGICALLY ACTIVE COMPOUNDS

SCOE are considered as promising intermediates for total synthesis. First, they are synthetic equivalents of pyrrolidines, 1,4-amino alcohols, pyrroles, and functionalized carbonyl compounds, which are known building blocks for the construction of

dx.doi.org/10.1021/cr100292w |*Chem. Rev.* 2011, 111, 5004–5041

Scheme 90



many natural and medically relevant substances. Second, many reactions of SCOE exhibit high stereoselectivity. Third, effecient pathways for the synthesis of chiral SCOE are known, and therefore, new promising strategies for asymmetric synthesis can be developed.

Numerous examples of the application of SCOE in the synthesis of unnatural amino acids, amino sugars, and pheromones, as well as perspective pharmaceutical drugs are known from the literature.

4.1. Synthesis of Amino Acids

SCOE containing ester or carboxy groups are considered as convenient precursors of various natural and unnatural amino acids, which are of interest for the synthesis of modified peptides and as pharmaceutical drugs with a wide range of biological activity.[23,40,68,157,160−162,164,170]

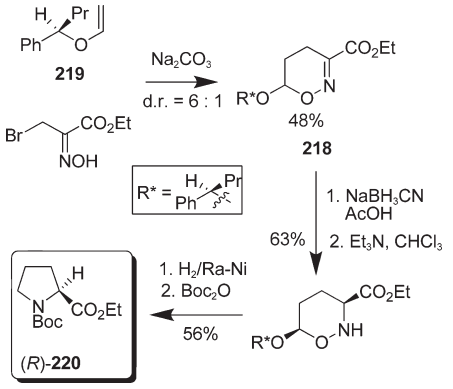
Several reports[23,40,160,161] suggested a general approach to the synthesis of diastereomerically pure derivatives of various α-amino acids, substituted proline esters **215**, and *N*-Boc-protected *δ*-hydroxy-α-amino acids **216** and **217** from very simple precursors via the intermediacy of 3-carboxyethyl-substituted SCOE **214** (Scheme 90). The intermediate dihydrooxazines **214** are obtained by the [4 + 2]-cycloaddition of ethyl α-nitrosoacrylate to vinylic ethers (X = OAlk), enamines (X = $NAlk_2$), or allyltrimethylsilane (see section 2.1). Selective reduction of the dihydrooxazine ring in products **214** is accomplished by the direct catalytic hydrogenation on Pd−C[23] or Ra−Ni[40] or the two-step protocol[160,161] including reduction of the C═N double bond with sodium cyanoborohydride in the first step and catalytic hydrogenation of the N−O bond in the second.

The synthesis of proline esters of the type **215** shown in Scheme 90 can be accomplished in an asymmetric version as well.[160] For instance, the reduction of chiral oxazine **218** synthesized from (*R*)-1-phenylbutyl vinyl ether **219** and ethyl 3-bromo-2-oxopropionate oxime affords the *N*-Boc derivative of (*R*)-proline ethyl ester **220** (Scheme 91).[160]

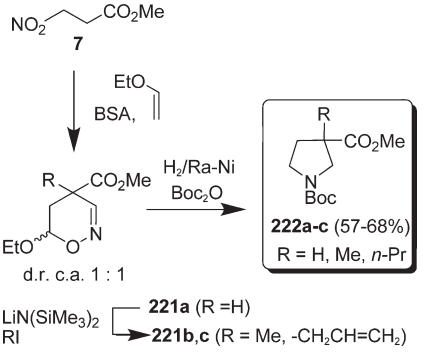
Recently, it has been shown that in the strategies for the synthesis of *β*- and *γ*-amino acids employing SCOE as intermediates, aliphatic nitro compounds can serve as convenient starting reagents. Thus, 4-methoxycarbonyl-substituted SCOE **221a**−**c** were synthesized from *β*-nitropropionate **7** (see also section 2.1, Scheme 3). Their reduction leads to methyl esters of substituted *β*-prolines **222a**−**c** (Scheme 92).[68]

Another example of the application of SCOE **221a** in the preparation of amino acids is the synthesis of the *N*-Boc

Scheme 91



Scheme 92

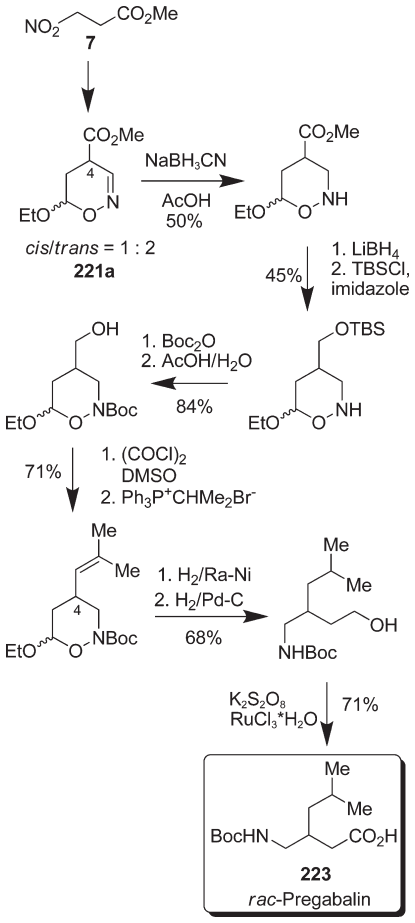


derivative of racemic *γ*-amino acid pregabalin **223** (an anticonvulsant drug marketed by Pfizer), which has been accomplished recently by Gallos group (Scheme 93).[157] It includes selective reduction of the C═N double bond in dihydrooxazine **221a** with sodium cyanoborohydride, introduction of the Boc-protection at the nitrogen atom, transformation of the ester group at C-4 atom to 2,2-dimethylvinyl unit, successive catalytic hydrogenation of the N−O and C═C bonds, and final oxidation of the hydroxyl group to the carboxylic group.

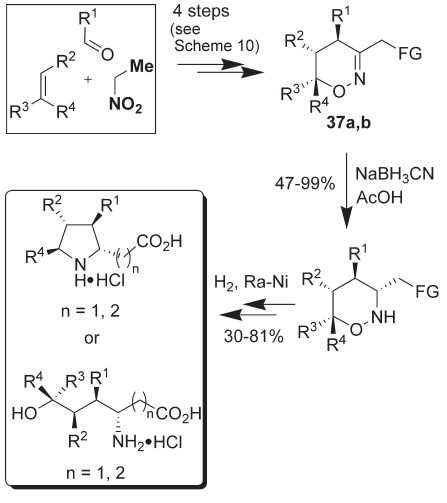
Recently, another aliphatic nitro compound, viz., nitroethane, was suggested as an initial reagent for the synthesis of four types

dx.doi.org/10.1021/cr100292w |*Chem. Rev.* 2011, 111, 5004–5041

Scheme 93



Scheme 94



R1 = Me, Ar; R2 = H, Alk; R3 = H, Alk, OAlk; R4 = H, Alk
FG = CO_2Me, $HC(CO_2Me)_2$

of diastereomerically pure unnatural β- and γ-amino acids (Scheme 94).[162,164,193] The key step of these syntheses is the diastereoselective reduction of C-3 functionalized dihydrooxazines **37a,b** with sodium cyanoborohydride (see also section 3.1.1).

4.2. Synthesis of Polyhydroxylated Pyrrolidines

Reduction of SCOE is a convenient approach to substituted pyrrolidines, which are subunits of many alkaloids (pyrrolidine, pyrrolizidine, and indolizidine types) and amino sugars. This approach is especially promising for the synthesis of polyhydroxylated pyrrolidines, since convenient methods for the preparation of their precursors, polyhydroxy-substituted dihydrooxazines, exist (see, for example, section 2.4).

The synthesis of racemic pyrrolidine **226**, which is the known precursor[194] of the natural alkaloid swainsonine (a mannosidase inhibitor and anticancer drug candidate), can be accomplished from readily available SCOE **160** (Scheme 95).[22] This synthesis employs the catalytic hydrogenation of SCOE **160** on Pd−C as a key stage. A significant disadvantage here is the poor stereoselectivity of the hydrogenation, leading to a virtually equimolar mixture of diastereomeric pyrrolidines **224** and **225**, which were separated by column chromatography.[22]

Also pyrrolidines **224** and **225** can be easily transformed into the salts of *cis*-hydroxylated prolinols **227** and **228**, respectively, which are known galactosidase inhibitors.[22]

Dihydrooxazines bearing chiral OR or NR_2 groups at the atom C-6 are convenient precursors of enantiomerically pure pyrrolidines. In the asymmetric synthesis of the unnatural amino sugar **234** (a highly active glucosidase inhibitor), the intermediate optically pure tetrahydro-1,2-oxazine **231** is generated as a single stereoisomer by the [4 + 2]-cycloaddition reaction of chiral diene **229** with benzyl nitrosocarbamate and subsequent bishydroxylation of the adduct **230** (Scheme 96).[134] However, the product **231** isolated had an unsuitable 3,4-trans-configuration. The inversion of configuration of the stereocenter at C-3 was achieved by the oxidation of product **231** to SCOE **232** with *N*-bromosuccinimide and subsequent stereoselective reduction of the C=N double bond in **232** with sodium cyanoborohydride. Catalytic hydrogenation of tetrahydrooxazine **233** and deprotection of the arising dioxolane led to the target amino sugar as a hydrochloric salt **234**.[134]

Turner and co-workers[118] accomplished the synthesis of unusual chiral amino sugar **236** bearing a hydroxyl group at the nitrogen atom N-1 from SCOE **62** (Scheme 97). The key step here is the reduction of protected SCOE **62** to *N*-hydroxypyrrolidine **235** upon the action of sodium cyanoborohydride in acetic acid. Removal of the protecting groups gives the final *N*-hydroxyamino sugar **236**.[118] Interestingly the transformation **62** → **235** is the only example when reduction of SCOE with sodium cyanoborohydride leads not to the corresponding tetrahydro-2*H*-1,2-oxazine but to *N*-hydroxypyrrolidine (cf. with the data in section 3.1.1). The authors[118] do not give any explanation for this anomaly.

4.3. Synthesis of Pyrrolizidine and Indolizidine Alkaloids and Their Analogs

Functionalized SCOE **1** and 6*H*-1,2-oxazines **2** proved to be convenient reagents for the preparation of products with two annulated nitrogen-containing rings, pyrrolizidine and indolizidine alkaloid frameworks.[61,142,163,195] For instance, stereoselective catalytic hydrogenation of racemic oxazines **237** with the MeO_2C group in the side chain of the substituent at atom C-3 and the alkoxy group at atom C-6 induces successive closure of five-membered rings A and B and leads to bicyclic pyrrolizidinones **238**.[142] Further reduction of the amide group in products **238** with borane−dimethyl sulfide complex gives target pyrrolizidines **239** in satisfactory overall yield (Scheme 98).

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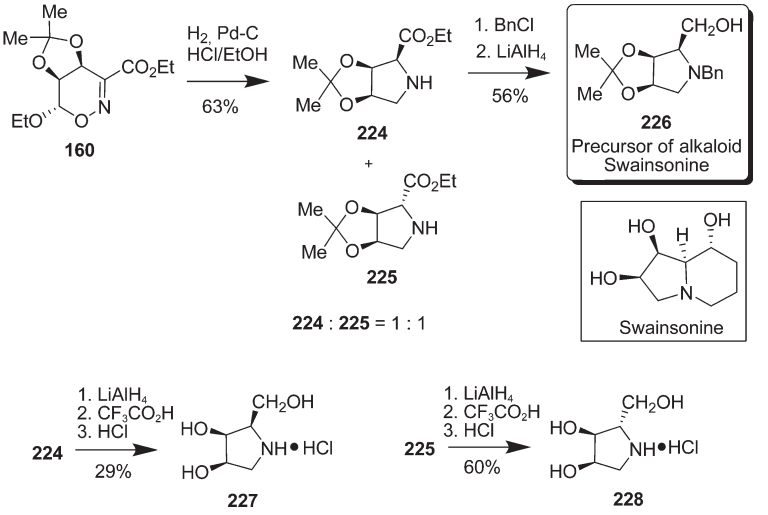
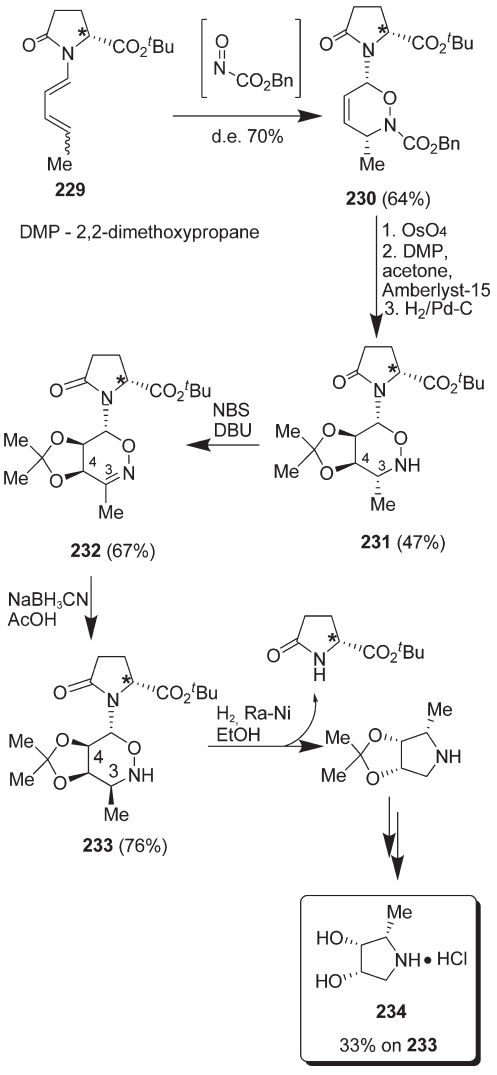
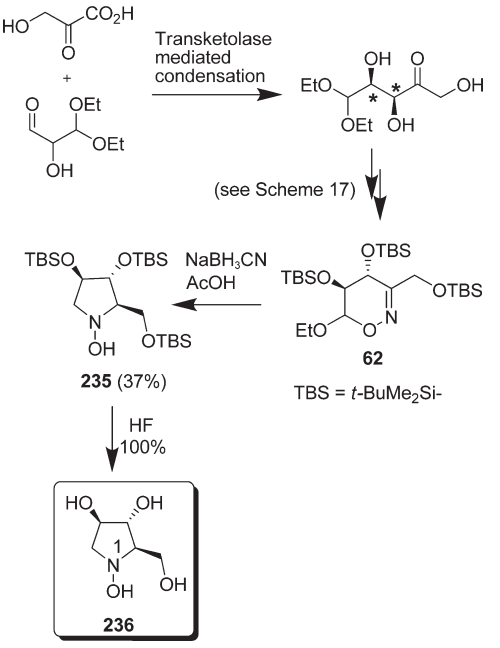
Scheme 95



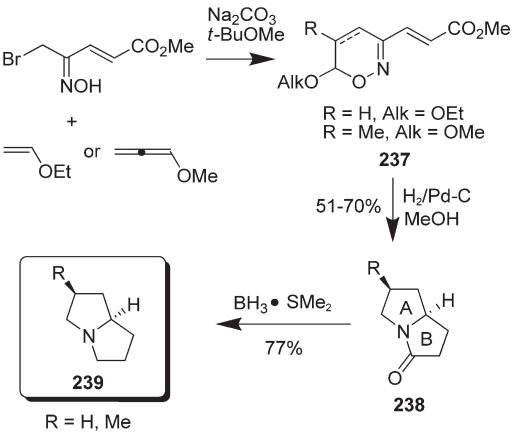
Scheme 96



Scheme 97

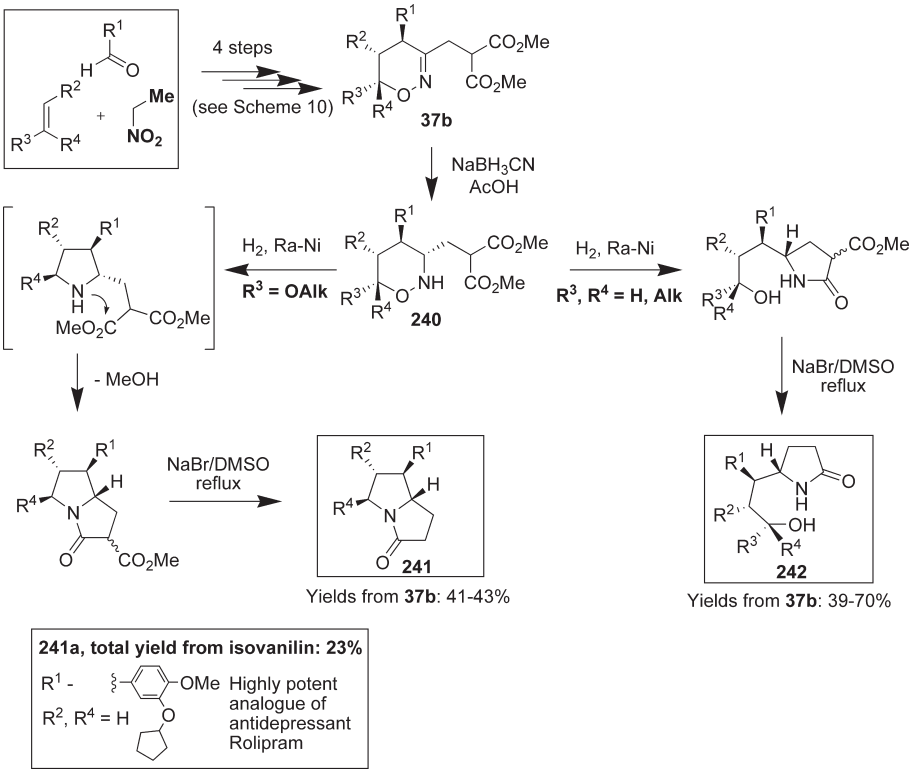


Scheme 98



dx.doi.org/10.1021/cr100292w |Chem. Rev. 2011, 111, 5004–5041

Scheme 99



The authors[163] suggest a convenient scheme for the synthesis of diastereomerically pure substituted pyrrolizidinones **241** from SCOE **37b**, available from nitroethane, aldehydes, and olefins (Scheme 99). Their stereoselective reduction with $NaBH_3CN$/AcOH system usually produces 3,4-*trans*-tetrahydro-2*H*-1,2-oxazines **240**. Hydrogenation of oxazines **240** proceeds via initial ring-opening and successive pyrrolidine (if R^3 is OAlk) and pyrrolidone ring closures, which yields the formation of the pyrrolizidine framework. Final decarboxylation furnishes target heterocycles **241** in satisfactory overall yields. Hydrogenation of tetrahydrooxazines **240** without an alkoxyl substituent at C-6 (Scheme 99) leads to the α-pyrrolidone ring closure only.[163] A standard decarboxylation of the resulting products gives 5-(3-hydroxypropyl)-2-pyrrolidones **242**, which are utilized in the synthesis of highly selective EP4 antagonists suggested by Pfizer.

The concept represented in Scheme 99 was successfully applied for the stereoselective synthesis of pyrrolizidinone **241a**, a highly active analog of the antidepressant rolipram introduced by GlaxoSmithKline, from nitroethane and isovaniline.[163,196]

An innovative synthesis of optically pure 5-hydroxymethyl-1,2-dihydroxypyrrolizidine **246**, an analog of pyrrolizidine alkaloids of the alexine family, via the generation of dihydro-1,2-oxazines was suggested recently (Scheme 100).[61,195] The synthesis starts from the enantiopure vinyl ether **21** available from D-ribose. Its [4 + 2]-cycloaddition with ethyl 2-nitrosoacrylate generated from ethyl 3-bromo-2-oxopropionate oxime produces a single stereoisomer of the chiral dihydrooxazine **243**. In the following step, adduct **243** is reduced to diastereomerically and enantiomerically pure tetrahydrooxazine **244** with sodium cyanoborohydride. Its catalytic hydrogenation finally leads to pyrrolizidine **245** (Scheme 100). Further standard transformations of product **245** gave the final hydroxypyrrolizidine **246** as a hydrochloric salt.[61,195]

Dihydrooxazine **221a** already discussed above (see section 4.1) was used in the preparation of indolizidine **248a** and quinolizidine **248b** derivatives, potential precursors of some alkaloids (Scheme 101).[68] To accomplish this strategy, the starting oxazine **221a** was acylated with unsaturated acyl chlorides to form 2*H*-1,2-oxazines **247a**−**c**. The latter upon heating underwent retro-[4 + 2]-cycloaddition with the formation of highly reactive 1-aza-1,3-butadienes **249**. For n = 1,2 an intramolecular trapping of these intermediates by [4 + 2]-cycloaddition leads to the target products **248a,b**. Such a scheme is suitable for the preparation of only 6,5- and 6,6-fused heterocycles **248a** and **248b**. In the corresponding reaction of oxazine **248c**, only a mixture of its destruction products was obtained.[68]

4.4. Synthesis of Biologically Active 2-Aryl-Substituted Pyrrolidines and Amines

SCOE bearing aryl substituents on the ring are promising intermediates for the preparation of chiral aryl-substituted amines and pyrrolidines well-known for their high biological activity, in particular, their neurotropic action.[62,147,197]

Reissig and coauthors suggested a convenient method for the synthesis of chiral 2-*R*-4-phenyl-*n*-butylamines **130** by catalytic hydrogenation of enantiomerically pure 3-phenyl-substituted SCOE **250** containing auxiliary R*O at the C-6 atom (Scheme 102).[62,197] Here, the initial SCOE **252** were generated by the addition of lithium reagent RLi to the optically pure 6*H*-1,2-oxazine **251**. The latter was obtained from the racemic oxazine **250** by its treatment with boron trifluoride diethyl

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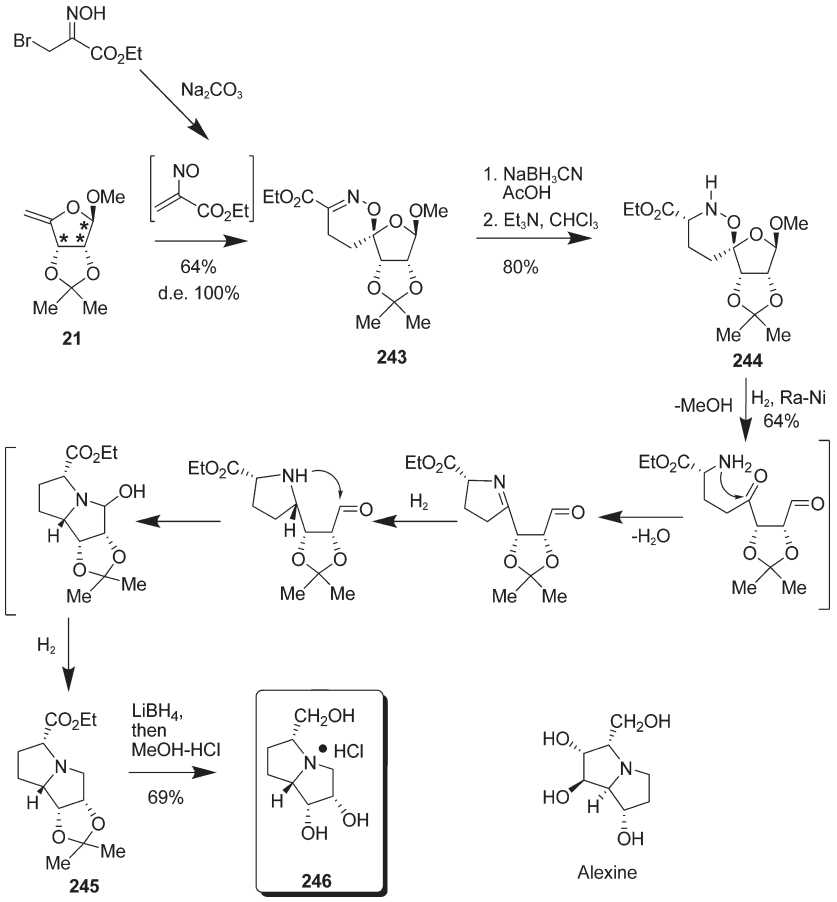
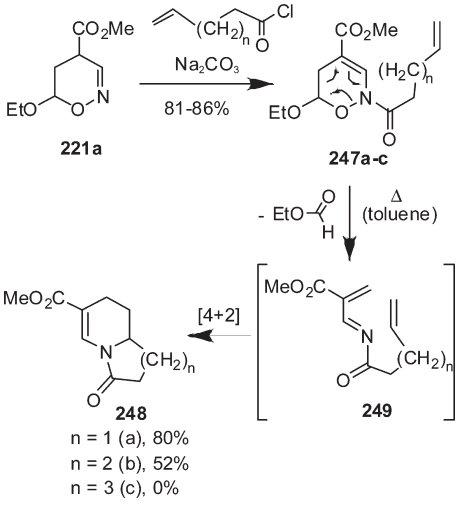
Scheme 100



Scheme 101



etherate and (−)-menthol with subsequent chromatographic separation of diastereomers.[197]

An analogous strategy was used in the asymmetric synthesis of pyrrolidine **254**, a precursor of the highly efficient endotheline receptors antagonist ABT-637 (atrasentan) introduced by Abbott Laboratories (Scheme 103).[147] A key step in this synthesis is the catalytic hydrogenation of chiral SCOE **253** containing the OR* group at atom C-6 [R* is (+)-menthyl]. To successfully accomplish the transformation **253** → **254**, quite harsh conditions are required: high hydrogen pressure, a large excess of the catalyst, and the addition of a trapping reagent (Boc_2O) to the reaction mixture. However, the ratio of diastereomers **254**/**255** in the hydrogenation process was only about 2:1 in favor of the desired stereoisomer **254** with *cis*-disposition of the aryl substituents.[147]

4.5. Synthesis of Other Natural Compounds

Reissig and coauthors introduced a simple synthesis of substituted pyrrole **257**, pheromone of the ant *Atta texana*, using methyl 3-bromo-2-oxopropionate oxime and silyl enol ether derived from propanal (Scheme 104).[32] A smooth transformation of the intermediate SCOE **256** to pyrrole **257** was accomplished with the assistance of molybdenium hexacarbonyl in the presence of trifluoroacetic acid.[32]

In this report,[32] the synthesis of cyclopentenone **260**, a precursor of the terpenoid *cis*-jasmone (a natural component of perfumes and cosmetics),[199] from SCOE **258** was accomplished as well (Scheme 105). In this synthesis, the step of reducing deoximation of oxime ether **258** was performed by catalytic hydrogenation in the presence Ra−Ni in an aqueous methanol solution of hydrochloric acid. The process involved reduction of the N−O bond of the oxazine ring and hydrolysis of the resulting imine to 1,4-diketone **259**. Here, the C═C double bond underwent hydrogenation as well.[32] Intramolecular aldol−

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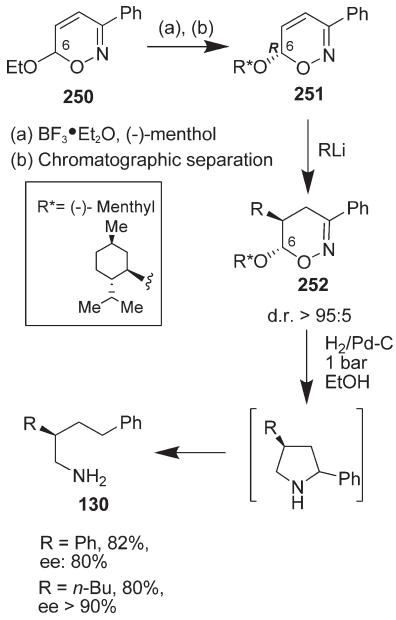
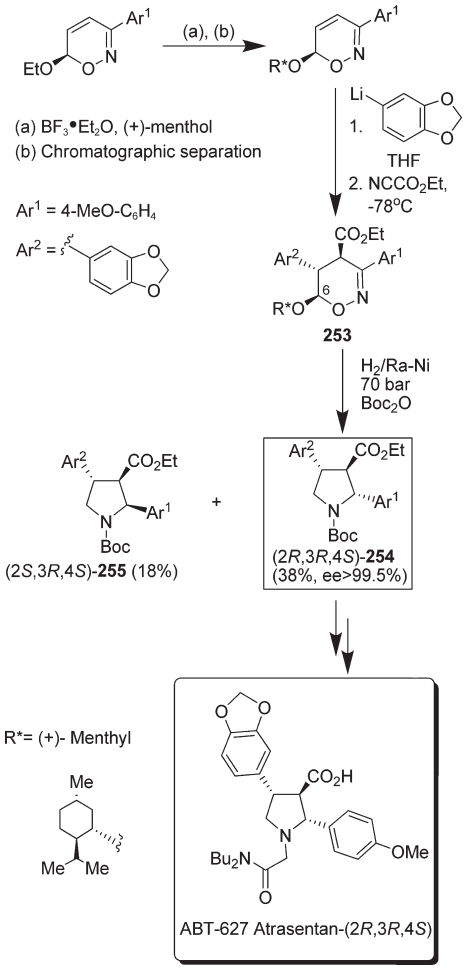
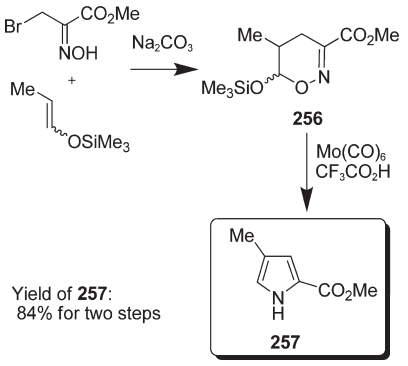
Scheme 102



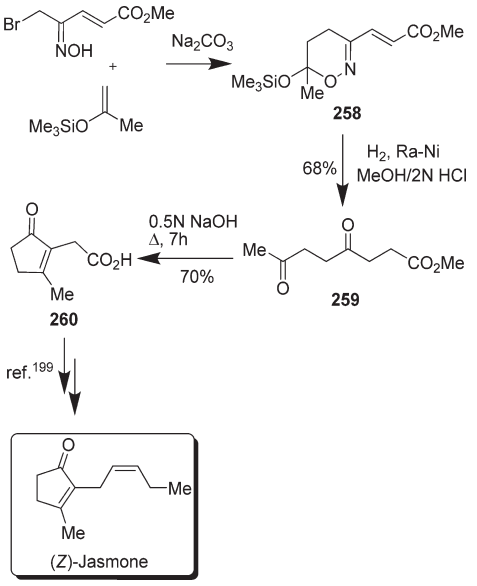
Scheme 103



Scheme 104



Scheme 105



crotonic condensation of diketone **259** gave the target cyclopentenone **260** in good yield.

5. CONCLUSION

Thus, the material summarized in this review clearly demonstrates the synthetic potential of SCOE for organic synthesis. The large number of methods for the synthesis of SCOE **1** and **2** in combination with their various reactivities, as well as the high stereoselectivity of many of their transformations, makes them very promising reagents for assembling stereochemically complex structures. There is no doubt that the application of heterocycles **1** and **2** in the total synthesis of natural compounds and in medicinal chemistry will increase in the future.

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BIOGRAPHIES

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Sema L. Ioffe was born in Moscow, in 1938. He graduated from the Moscow D. I. Mendeleev Institute of Chemical Technology in 1960. From 1960 to 1963, he was a graduate student at the N. D. Zelinsky Institute of Organic Chemistry. He then worked as Junior Researcher (1963−1967), Senior Researcher (1967−1985), and, since 1985, as Principal Researcher at the N. D. Zelinsky Institute of Organic Chemistry. He received his Ph.D. in 1964 and his Doctor of Science in 1980. He has been a Professor since 1993. His scientific interests include different topics of the chemistry of aliphatic nitro and polynitrogen compounds. His additional interest is connected with the advanced chemical education of gifted youth at Moscow Chemical Lyceum and Russian Academy of Sciences.

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REFERENCES

(1) Ioffe, S. L. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis. Novel Strategies in Synthesis*, 2nd ed.; Feuer, H., Ed.; Wiley: Hoboken, 2008; pp 83, 516.
(2) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 1st ed.; VCH Publishers, Inc.: New York, 1988.
(3) Reissig, H.-U.; Zimmer, R. *Science of Synthesis*; Molander, G. A., Ed.; Thieme: Stuttgart, 2006; Vol. 33, p 371.
(4) Jager, F.; Collinas, P. A. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; John Wiley & Sons: New York, 2002; p 361.
(5) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, *10*, 857.
(6) (a) Jager, V.; Grund, H.; Buss, V.; Schwab, W.; Muller, I.; Schohe, R.; Franz, R.; Ehrler, R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1039. (b) Huisgen, R. *Bull. Soc. Chim. Fr.* **1965**, *12*, 3431.
(7) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.
(8) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.
(9) For recent examples, see:Yokoshima, S.; Uedo, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.
(10) Marshal, T. R.; Perkin, W. H. *J. Chem. Soc.* **1891**, *59*, 853.
(11) Wohlgemuth, H. *Ann. Chim. (Paris)* **1914**, *2*, 403. (*Chem. Abstr.* **1915**, *10*, 1602.)
(12) Kochetkov, N. K.; Sokolov, S. D. *Adv. Heterocycl. Chem.* **1963**, *2*, 365.
(13) (a) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 915. (b) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 1149.
(14) Zimmer, R.; Reissig, H.-U.; Homann, K. *J. Prakt. Chem.* **1995**, *337*, 521.
(15) Lyapkalo, I. M.; Ioffe, S. L. *Russ. Chem. Rev.* **1998**, *67*, 467.
(16) Gilchrist, T. L. *Chem. Soc. Rev.* **1983**, *12*, 53.
(17) Gilchrist, T. L.; Wood, J. E. In *Comprehensive Heterocyclic Chemistry II*; Boulton, A. J., Ed.; Pergamon Press: Oxford, 1996; Vol. 6, p 279.
(18) (a) Denmark, S. E.; Dappen, M. S.; Sternberg, J. A. *J. Org. Chem.* **1984**, *49*, 4741. (b) Gaonkar, S. L.; Rai, K. M. L. *J. Heterocycl. Chem.* **2005**, *42*, 877.
(19) Ioffe, S. L.; Lyapkalo, I. M.; Tishkov, A. A.; Danilenko, V. M.; Strelenko, Y. A.; Tartakovsky, V. A. *Tetrahedron* **1997**, *53*, 13085.
(20) Tishkov, A. A.; Lyapkalo, I. M.; Ioffe, S. L.; Strelenko, Y. A.; Tartakovsky, V. A. *Org. Lett.* **2000**, *9*, 1323.
(21) Davies, D. E.; Gilchrist, T. L. *J. Chem. Soc. Perkin Trans. 1* **1983**, *7*, 1479.
(22) Angermann, J.; Homann, K.; Reissig, H.-U.; Zimmer, R. *Synlett* **1995**, *10*, 1014.
(23) (a) Chrystal, E. J. T.; Gilchrist, T. L.; Stretch, W. *J. Chem. Res. (M)* **1987**, 1563. (b) Chrystal, E. J. T.; Gilchrist, T. L.; Stretch, W. *J. Chem. Res. (S)* **1987**, *6*, 180.
(24) Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc. Perkin Trans. 1* **1983**, *6*, 1283.
(25) Zimmer, R.; Angermann, J.; Hain, U.; Hiller, F.; Reissig, H.-U. *Synthesis* **1997**, *12*, 1467.
(26) Yoon, S. C.; Kim, K.; Park, Y. J. *J. Org. Chem.* **2001**, *66*, 7334.
(27) Gilchrist, T. L.; Iscander, G. M.; Yagoub, A. K. *J. Chem. Soc. Perkin Trans. 1* **1985**, *12*, 2769.

(28) (a) Boa, A. N.; Dawkins, D. A.; Hergueta, A. R.; Jenkins, P. R. *J. Chem. Soc. Perkin Trans. 1* **1994**, *8*, 953. (b) Guimaraes, E.; Lemos, A.; Lopes, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 2149.
(29) Arnold, T.; Reissig, H.-U. *Synlett* **1990**, *9*, 514.
(30) Arnold, T.; Orschel, B.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1033.
(31) Nakanishi, S.; Otsuji, Y.; Itoh, K.; Hayashi, N. *Bull. Chem. Soc. Jpn.* **1995**, *63*, 3595.
(32) Zimmer, R.; Collas, M.; Roth, M.; Reissig, H.-U. *Liebigs Ann. Chem.* **1992**, *7*, 709.
(33) Hippeli, C.; Reissig, H.-U. *Liebigs Ann. Chem.* **1990**, *3*, 217.
(34) Reissig, H.-U.; Hippeli, C.; Arnold, T. *Chem. Ber.* **1990**, *123*, 2403.
(35) Zimmer, R.; Reissig, H.-U. *J. Org. Chem.* **1992**, *57*, 339.
(36) Hofmann, B.; Reissig, H.-U. *Chem. Ber.* **1994**, *127*, 2337.
(37) Hippeli, C.; Reissig, H.-U. *Synthesis* **1987**, *1*, 77.
(38) Maccioni, A.; Marongiu, E.; Bianchetti, G. *Gazz. Chim. Ital.* **1970**, *100*, 288. (*Chem. Abstr.* **1970**, *73*, 120574*u*).
(39) (a) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Chem. Commun.* **1976**, *15*, 581.
(40) Henning, R.; Lerch, U.; Urbach, H. *Synthesis* **1989**, *4*, 265.
(41) Nakanishi, S.; Shirai, Y.; Takahashi, K.; Otsuji, Y. *Chem. Lett.* **1981**, *10*, 869.
(42) Gilchrist, T. L.; Lingham, D. A.; Roberts, T. G. *J. Chem. Soc., Chem. Commun.* **1979**, *23*, 1089.
(43) (a) Paulini, K.; Reissig, H.-U.; Rademacher, P. *J. Prakt. Chem.* **1995**, *337*, 209. (b) Zimmer, R.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1518.
(44) (a) Zimmer, R.; Reissig, H.-U. *Liebigs Ann. Chem.* **1991**, *6*, 553. (b) Zimmer, R.; Reissig, H.-U. *Synthesis* **1989**, *12*, 908. (c) Homann, K.; Zimmer, R.; Reissig, H.-U. *Heterocycles* **1995**, *40*, 531.
(45) Tanimoto, S.; Matsumoto, H.; Hojo, M.; Toshimitsu, A. *J. Chem. Soc. Perkin Trans. 1* **1991**, *12*, 3153.
(46) Davies, D. E.; Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc. Perkin Trans. 1* **1983**, *6*, 1275.
(47) Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Chem. Commun.* **1979**, *23*, 1090.
(48) Nakanishi, S.; Higuchi, M.; Flood, T. C. *J. Chem. Soc., Chem. Commun.* **1986**, *1*, 30.
(49) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc. Perkin Trans. 1* **1979**, *1*, 249.
(50) Iskanderl, G.; Gulta, V. S. *J. Chem. Soc. Perkin Trans. 1* **1982**, *8*, 1891.
(51) Francotte, E.; Merenyi, R.; Vandenbulcke-Coyette, B.; Viehe, H.-G. *Helv. Chim. Acta* **1981**, *64*, 1208.
(52) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Chem. Commun.* **1977**, *8*, 252.
(53) Gilchrist, T. L.; Lemos, A. *J. Chem. Soc. Perkin Trans. 1* **1993**, *13*, 1391.
(54) Gilchrist, T. L.; Stretch, W. *J. Chem. Soc. Perkin Trans. 1* **1987**, *10*, 2235.
(55) Gilchrist, T. L.; Hughes, D.; Stretch, W. *J. Chem. Soc. Perkin Trans. 1* **1987**, *11*, 2505.
(56) Plate, R.; Theunisse, A. W. G.; Ottenheijm, H. C. J. *J. Org. Chem.* **1987**, *52*, 370.
(57) Tahdi, A.; Titouani, S. L.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 65.
(58) (a) Just, G.; Zehetner, W. *J. Chem. Soc., Chem. Commun.* **1971**, *2*, 81. (b) Manjula, M. K.; Rai, K. M. L.; Gaonkar, S. L.; Raveesha, K. A.; Satish, S. *Eur. J. Med. Chem.* **2009**, *44*, 280.
(59) Tishkov, A. A. . Ph.D. thesis; N. D. Zelinsky Institute of Organic Chemistry RAS, Moscow, 2002; p 111.
(60) Lai, E. C. K.; Mackay, D.; Taylor, N. J.; Watson, K. N. *J. Chem. Soc. Perkin Trans. 1* **1990**, *6*, 1497.
(61) Gallos, J. K.; Sarli, V. C.; Stathakis, C. I.; Koftis, T. V.; Nachmia, V. R.; Coutouli-Argyropoulou, E. *Tetrahedron* **2002**, *58*, 9351.
(62) Zimmer, R.; Orschel, B.; Scherer, S.; Reissig, H.-U. *Synthesis* **2002**, *11*, 1553.
(63) Wabnitz, T. C.; Saaby, S.; Jorgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 828.
(64) Hippeli, C.; Reissig, H.-U. *J. Org. Chem.* **1988**, *53*, 3884.
(65) Reissig, H.-U.; Hippeli, C. *Chem. Ber.* **1991**, *124*, 115.
(66) Zimmer, R.; Reissig, H.-U. *J. Fluorine Chem.* **1996**, *80*, 21.
(67) Unger, C.; Zimmer, R.; Reissig, H.-U.; Wurthwein, E.-U. *Chem. Ber.* **1991**, *124*, 2279.
(68) Tishkov, A. A.; Reissig, H.-U.; Ioffe, S. L. *Synlett* **2002**, *6*, 863.
(69) Paulini, K.; Reissig, H.-U. *Chem. Ber.* **1994**, *127*, 685.
(70) Kempe, U. M.; Das Gupta, T. K.; Blatt, K.; Gygax, P.; Felix, D.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 2187.
(71) Riediker, M.; Graf, W. *Helv. Chim. Acta* **1979**, *62*, 205.
(72) (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.(b) Denmark, S. E.; Cottel, J. J. In *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, Padwa, A.; Pearson, W. H., Eds.; Wiley-Interscience: New York, 2002; p 83. (c) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W.; Moon, Y.-C.; Middleton, D. S. In *Proceedings of the 5th International Kyoto Conference on New Aspects of Organic Chemistry*; Yoshida, Z.-I., Ed.; VCH: New York, 1992; p 215. (d) Ioffe, S. L. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis. Novel Strategies in Synthesis*, 2nd ed.; Feuer, H., Ed.; Wiley: Hoboken, NJ, 2008; p 591.
(73) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, 3221.
(74) (a) Risaliti, A.; Forchiassin, M.; Valentin, E. *Tetrahedron* **1968**, *24*, 1889. (b) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2001**, *3*, 229. (c) Amantini, D.; Fringuelli, F.; Pizzo, F. *J. Org. Chem.* **2002**, *67*, 7238.
(75) (a) Bradamante, P.; Pitacco, G.; Risaliti, A.; Valentin, E. *Tetrahedron Lett.* **1982**, *23*, 2683.
(76) Seebach, D.; Brook, M. A. *Helv. Chim. Acta* **1985**, *68*, 319.
(77) (a) Denmark, S. E.; Schnute, M. E.; C. Senanayake, B. W. *J. Org. Chem.* **1993**, *58*, 1859. (b) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046. (c) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125. (d) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668.
(78) For recent examples see:(a) Denmark, S. E.; Montgomery, J. I. *Angew. Chem., Int. Ed.* **2005**, *44*, 3732. (b) Denmark, S. E.; Nguen, S. T.; Biazitov, R. Y. *Heterocycles* **2008**, *76*, 143. (c) Denmark, S. E.; Kramps, L. A.; Montgomery, J. I. *Angew. Chem., Int. Ed.* **2002**, *41*, 4122.
(79) Eliseev, O. L.; Ivashkin, P. E.; Ostapenko, A. G.; Lesiv, A. V.; Khomutova, Yu. A.; Ioffe, S. L.; Lapidus, A. L. *Synlett* **2006**, *14*, 2239.
(80) Klenov, M. S.; Lesiv, A. V.; Khomutova, Yu. A.; Nesterov, I. D.; Ioffe, S. L. *Synthesis* **2004**, *8*, 1159.
(81) Sukhorukov, A. Yu.; Klenov, M. S.; Ivashkin, P. E.; Lesiv, A. V.; Khomutova, Y. A.; Ioffe, S. L. *Synthesis* **2007**, *1*, 97.
(82) Tabolin, A. A.; Lesiv, A. V.; Khomutova, Yu. A.; Nelyubina, Yu. V.; Ioffe, S. L. *Tetrahedron* **2009**, *65*, 4578.
(83) Tabolin, A. A.; Lesiv, A. V.; Ioffe, S. L. *Synthesis* **2009**, *18*, 3099.
(84) Tohda, Y.; Yamawaki, N.; Matsui, H.; Kawashima, T.; Ariga, M.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 461.
(85) Uno, H.; Goto, K.; Watanabe, N.; Suzuki, H. *J. Chem. Soc. Perkin Trans. 1* **1989**, *2*, 289.
(86) Wolff, M. E.; Morioka, T. *J. Org. Chem.* **1965**, *30*, 2553.
(87) Stevens, C. L.; Traynelis, V. J. *J. Org. Chem.* **1954**, *19*, 533.
(88) Ellames, G. J.; Hewkin, C. T.; Jackson, R. F. W.; Smith, D. I.; Standen, S. P. *Tetrahedron Lett.* **1989**, *30*, 3471.
(89) Saiki, H.; Mukai, T. *Chem. Lett.* **1982**, *11*, 1561.
(90) Brandman, H. A.; Conley, R. T. *J. Org. Chem.* **1973**, *38*, 2236.
(91) Kaiser, A.; Mayer, K.; Sellmer, A.; Wiegrebe, W. *Monatsh. Chem.* **2003**, *134*, 343.
(92) Shatzmiller, S.; Shalom, E. *Liebigs Ann. Chem.* **1983**, *6*, 897.
(93) Goldberg, I.; Saad, D.; Shalom, E.; Shatzmiller, S. *J. Org. Chem.* **1982**, *47*, 2192.
(94) Wade, P. *J. Org. Chem.* **1978**, *43*, 2020.
(95) Lee, V. J.; Woodward, R. B. *J. Org. Chem.* **1979**, *44*, 2487.
(96) Yusubov, N. N.; Radvan, S.; Ismailov, V. M.; Dzshanibekov, N. F. *Bull. Russ. Acad. Sci., Div. Chem. Sci.* **1992**, *41*, 1310. (*Chem. Abstr.* **1993**, *118*, 80834*t*).
(97) Chevrier, C.; LeNouen, D.; Neuburger, M.; Defoin, A.; Turner, C. *Tetrahedron Lett.* **2004**, *45*, 5363.

(98) Donald, J. R.; Edwards, M. G.; Taylor, R. J. K. *Tetrahedron Lett.* **2007**, *48*, 5201.
(99) Albrecht, U.; Gerwien, K.; Langer, P. *Tetrahedron Lett.* **2005**, *46*, 1017.
(100) Dang, T. T.; Albrecht, U.; Gerwien, K.; Siebert, M.; Langer, P. *J. Org. Chem.* **2006**, *71*, 2293.
(101) Al-Qawasmeh, R. A.; Al-Tel, T. H.; Abdel-Jalil, R. J.; Voelter, W. *Chem. Lett.* **1999**, *28*, 541.
(102) Rentzea, C. N. *Angew. Chem.* **1980**, *92*, 195.
(103) Clarke, R. W. L.; Lapworth, A. *J. Chem. Soc.* **1906**, *89*, 1869.
(104) Sammour, A.; Elhashash, M. *J. Prakt. Chem.* **1972**, *314*, 906.
(105) (a) Hishmat, O. H.; Atta, S. M. Sh.; Atalla, M. M.; Abd El Rahman, A. H. *Pharmazie* **1985**, *40*, 460. (b) El-Mobayed, M. M.; Hussein, A. M.; Mohlhel, W. M. *J. Heterocycl. Chem.* **2010**, *47*, 534.
(106) Birkofer, L.; Feldmann, H. *Liebigs Ann. Chem.* **1964**, *677*, 150.
(107) Khachatryan, R. A.; Khachikyan, R. D.; Karamyan, N. V.; Panosyan, G. A.; Indzhikyan, M. G. *Chem. Heterocycl. Compds. Engl. Transl.* **2004**, *4*, 541.
(108) Stajer, G.; Csende, F.; Bernath, G.; Sohar, P.; Szunyog, J. *Monatsh. Chem.* **1994**, *125*, 933.
(109) Hardegger, B.; Shatzmiller, S. *Helv. Chim. Acta* **1976**, *59*, 2499.
(110) Crow, W. D.; McNab, H.; Philip, J. M. *Aust. J. Chem.* **1976**, *29*, 2299.
(111) Widtsoe, J. A. *Am. Chem. J.* **1897**, *19*, 631.
(112) Iesce, M. R.; Cermola, F.; Guitto, A. *Synlett* **1999**, *4*, 417.
(113) Bravo, P.; Gaudiano, G.; Ponti, P. P.; Umani-Ronchi, A. *Tetrahedron* **1970**, *26*, 1315.
(114) Miyashita, M.; Awen, B. Z. E.; Yoshikoshi, A. *Tetrahedron* **1990**, *46*, 7569.
(115) Lusinchi, X. *Tetrahedron Lett.* **1967**, *8*, 177.
(116) (a) Oppolzer, W.; Battig, K.; Hudlicky, T. *Tetrahedron* **1981**, *37*, 4359. (b) Li, P.; Majireck, M. M.; Witek, J. A.; Weinreb, S. M. *Tetrahedron Lett.* **2010**, *51*, 2032. (c) Boberg, F.; Ruhr, M.; Garburg, K.-H.; Garming, A. *J. Heterocycl. Chem.* **1986**, *23*, 759.
(117) Kohler, E. P. *J. Am. Chem. Soc.* **1926**, *48*, 754.
(118) Humphrey, A. J.; Parsons, S. F.; Smith, M. E. B.; Turner, N. J. *Tetrahedron Lett.* **2000**, *41*, 4481.
(119) Moldvai, I.; Szantay, C., Jr.; Szantay, C. *Heterocycles* **2001**, *55*, 2147.
(120) Nemes, A.; Kreidl, J.; Czibula, L.; Nograni, K.; Farkas, M.; Szantay, J. C.; Tarkanyi, G.; Balogh, G.; Juhasz, I.; Kalman, A.; Parkanyi, L. *Heterocycles* **2000**, *53*, 1697.
(121) Bishop, R.; Hawkins, S. C.; Quibuen, T. A. O.; Brooks, P. R. *Tetraherdon Lett.* **1988**, *29*, 6805.
(122) Tkachev, A. V.; Agafontsev, A. M.; Rybalova, T. V.; Gatilov, Y. V. *Mendeleev Commun.* **2000**, *10*, 211.
(123) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Marini, F. *J. Chem. Soc. Perkin Trans. 1* **1993**, *17*, 1989.
(124) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markundu, J. *J. Chem. Soc. Chem. Commun.* **1992**, *20*, 1537.
(125) Tiecco, M.; Testaferri, L.; Bagnoli, L. *Tetrahedron* **1996**, *52*, 6811.
(126) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Purgatorio, V.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2001**, *12*, 3297.
(127) Dondas, A.; Grigg, R.; Hadjisoteriou, M.; Markundu, J.; Thornton-Pett, M. *Tetrahedron* **2001**, *57*, 1119.
(128) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markundu, J.; Thornton-Pett, M. *J. Chem. Soc. Chem. Commun.* **1993**, *17*, 1340.
(129) Bowman, W. R.; Davies, R. V.; Slawin, A. M. Z.; Sohal, G. S.; Titman, R. B.; Wilkins, D. J. *J. Chem. Soc. Perkin Trans. 1* **1997**, *2*, 155.
(130) Lathbury, D.; Gallagher, T. *J. Chem. Soc. Chem. Commun.* **1986**, *13*, 1017.
(131) Armesto, D.; Austin, M. A.; Griffiths, O. J.; Horspool, W. M.; Carpintero, M. *J. Chem. Soc., Chem. Commun.* **1996**, *24*, 2715.
(132) Hayakawa, I.; Teruya, T.; Kigoshi, H. *Tetrahedron Lett.* **2006**, *47*, 155.
(133) Best, W. N.; Macdonald, J. M.; Skelton, B. W.; Stick, R. V.; Matthew, D.; Tilbrook, G.; White, A. H. *Can. J. Chem.* **2002**, *80*, 857.
(134) Joubert, M.; Defoin, A.; Tarnus, C.; Streith, J. *Synlett* **2000**, *9*, 1366.
(135) Motorina, I. A.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1997**, *62*, 2098.
(136) Norman, R. O. C.; Purchase, R.; Thomas, C. B. *J. Chem. Soc. Perkin Trans. 1* **1972**, *13*, 1701.
(137) (a) Fritz, H.; Henlin, J.-M.; Reisen, A.; Tschamber, T.; Zehnder, M.; Streith, J. *Helv. Chim. Acta* **1988**, *71*, 822. (b) Pfrengle, F.; Al-Harrasi, A.; Brüdgam, I.; Reissig, H.-U. *Eur. J. Org. Chem.* **2009**, *2*, 282.
(138) Streith, J.; Defoin, A. *Synthesis* **1994**, *11*, 1107.
(139) Streith, J.; Defoin, A. *Synlett* **1996**, *3*, 189.
(140) Kresze, G. *1,4-Cycloaddition Reactions*; Hamer, J., Ed.; Academic Press: New York, 1967; p 453.
(141) (a) Forester, A. R.; Thomson, R. H.; Woo, S. O. *J. Chem. Soc. Perkin Trans. 1* **1978**, *7*, 755. (b) Zimmer, R.; Schmidt, E.; Andrä, M.; Duhs, M.-A.; Linder, I.; Reissig, H.-U. *Beilstein J. Org. Chem.* **2009**, *5*, 44. (c) Homann, K.; Angermann, J.; Collas, M.; Zimmer, R.; Reissig, H.-U. *J. Prakt. Chem.* **1998**, *340*, 649.
(142) Zimmer, R.; Collas, M.; Czerwonka, R.; Hain, U.; Reissig, H.-U. *Synthesis* **2008**, *2*, 237.
(143) Zimmer, R.; Homann, K.; Angermann, J.; Reissig, H.-U. *Synthesis* **1999**, *7*, 1223.
(144) Schmidt, E.; Reissig, H.-U.; Zimmer, R. *Synthesis* **2006**, *12*, 2074.
(145) Zimmer, R.; Hiller, F.; Reissig, H.-U. *Heterocycles* **1999**, *50*, 393.
(146) (a) Buchholz, M.; Reissig, H.-U. *Synthesis* **2002**, *10*, 1412. (b) Zimmer, R.; Buchholz, M.; Collas, M.; Angermann, J.; Homann, K.; Reissig, H.-U. *Eur. J. Org. Chem.* **2010**, *21*, 4111.
(147) Buchholz, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2003**, *18*, 3524.
(148) Kamimura, A.; Kaneko, Y.; Ohta, A.; Kakehi, A.; Matsuda, H.; Kanemasa, S. *Tetrahedron Lett.* **1999**, *40*, 4349.
(149) Kamimura, A.; Kaneko, Y.; Ohta, A.; Matsuura, K.; Fujimoto, Y.; Kakehi, A.; Kanemasa, S. *Tetrahedron* **2002**, *58*, 9613.
(150) Harada, K.; Shimozono, Y.; Kaji, E.; Takayanagi, H.; Ogura, H.; Zen, S. *Chem. Pharm. Bull.* **1992**, *40*, 1921.
(151) Harada, K.; Shimozono, Y.; Kaji, E.; Zen, S. *Heterocycles* **1993**, *36*, 2497.
(152) Loffler, J.; Schobert, R. *Synthesis* **1997**, *3*, 283.
(153) Felluga, F.; Gombac, V.; Pitacco, G.; Valentin, E.; Zangrando, E.; Morganti, S.; Rizzato, E.; Spinelli, D.; Petrillo, G. *Tetrahedron* **2006**, *62*, 8787.
(154) Zakarian, A.; Lu, C.-D. *J. Am. Chem. Soc.* **2006**, *128*, 5356.
(155) Baranovsky, A. V.; Bolibrukh, D. A.; Bull, J. R. *Eur. J. Org. Chem.* **2007**, *3*, 445.
(156) Giorgi, G.; Miranda, S.; Lopez-Alvarado, P.; Avendano, C.; Rodriguez, J.; Menendez, J. C. *Org. Lett.* **2005**, *7*, 2197.
(157) Gallos, J. K.; Alexandraki, E. S.; Stathakis, C. I. *Heterocycles* **2007**, *71*, 1127.
(158) Zimmer, R.; Arnold, T.; Homann, K.; Reissig, H.-U. *Synthesis* **1994**, *10*, 1050.
(159) Reissig, H.-U.; Homann, K.; Hiller, F.; Zimmer, R. *Synthesis* **2007**, *17*, 2681.
(160) Gallos, J. K.; Sarli, V. C.; Massen, Z. S.; Varvogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N. G. *Tetrahedron* **2005**, *61*, 565.
(161) Gallos, J. K.; Sarli, V. C.; Varvogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N. G. *Tetrahedron Lett.* **2003**, *44*, 3905.
(162) Sukhorukov, A. Yu.; Lesiv, A. V.; Khomutova, Yu. A.; Ioffe, S. L. *Synthesis* **2009**, *5*, 741.
(163) Sukhorukov, A. Yu.; Lesiv, A. V.; Khomutova, Yu. A.; Ioffe, S. L.; Tartakovsky, V. A. *Synthesis* **2009**, *12*, 1999.
(164) Sukhorukov, A. Yu.; Lesiv, A. V.; Eliseev, O. L.; Khomutova, Yu. A.; Ioffe, S. L. *Synthesis* **2009**, *15*, 2570.
(165) Sukhorukov, A. Yu.; Lesiv, A. V.; Eliseev, O. L.; Homutova, Yu. A.; Bondarenko, T. N.; Lapidus, A. L.; Ioffe, S. L. *Mendeleev Commun.* **2007**, *17*, 122.
(166) Sukhorukov, A. Yu.; Lesiv, A. V.; Eliseev, O. L.; Khomutova, Yu. A.; Ioffe, S. L.; Borissova, A. O. *Eur. J. Org. Chem.* **2008**, *23*, 4025.

(167) Zimmer, R.; Hoffmann, M.; Reissig, H.-U. *Chem. Ber.* **1992**, *125*, 2243.
(168) Sukhorukov, A. Yu.; Lesiv, A. V.; Khomutova, Yu. A.; Ioffe, S. L.; Nelyubina, Yu. V. *Synthesis* **2008**, *7*, 1205.
(169) Hippeli, C.; Reissig, H.-U. *Liebigs Ann. Chem.* **1990**, *5*, 475.
(170) Paulini, K.; Gerold, A.; Reissig, H.-U. *Liebigs Ann. Chem.* **1995**, *4*, 667.
(171) Hippeli, C.; Zimmer, R.; Reissig, H.-U. *Liebigs Ann. Chem.* **1990**, *5*, 469.
(172) Ivashkin, P. E.; Sukhorukov, A. Yu.; Eliseev, O. L.; Lesiv, A. V.; Khomutova, Yu. A.; Ioffe, S. L. *Synthesis* **2007**, *22*, 3461.
(173) Only one example where the 1,2-oxazine ring is not preserved in the course of SCOE reduction with $NaBH_3CN$ is known.[118] Here an *N*-hydroxypyrrolidine is the major product (see Scheme 97).
(174) Nesterov, I. D.; Lesiv, A. V.; Ioffe, S. L.; Antpin, M. Yu. *Mendeleev Commun.* **2004**, *14*, 280.
(175) Smirnov, V. O.; Ioffe, S .L.; Tishkov, A. A.; Khomutova, Yu. A.; Nesterov, I. D.; Antpin, M. Yu.; Smit, W. A.; Tartakovsky, V. A. *J. Org. Chem.* **2004**, *69*, 8485.
(176) Khomutova, Yu. A.; Smirnov, V. O.; Mayr, H.; Ioffe, S. L. *J. Org. Chem.* **2007**, *72*, 9134.
(177) Zimmer, R.; Homann, K.; Reissig, H.-U. *Liebigs Ann. Chem.* **1993**, *10*, 1155.
(178) Tschamber, T.; Craig, C. J.; Muller, M.; Streith, J. *Tetrahedron* **1996**, *52*, 6201.
(179) Rodriques, K. E.; Basha, A.; Summers, J. B.; Brooks, D. W. *Tetrahedron Lett.* **1988**, *29*, 3455.
(180) Denmark, S. E.; Cramer, C. J.; Dappen, M. S. *J. Org. Chem.* **1997**, *62*, 2098.
(181) Shatzmiller, S.; Dolitzky, B.-Z.; Meirovich, R.; Neidlein, R.; Weik, C. *Liebigs Ann. Chem.* **1991**, *2*, 161.
(182) Lidor, R.; Shatzmiller, S. *J. Am. Chem. Soc.* **1981**, *103*, 5916.
(183) Hardegger, B.; Shatzmiller, S. *Helv. Chim. Acta* **1976**, *59*, 2765.
(184) Shatzmiller, S. *Liebigs Ann. Chem.* **1982**, *11*, 1933.
(185) Mackay, D.; Watson, K. N. *J. Chem. Soc., Chem. Commun.* **1982**, *14*, 775.
(186) (a) Gilchrist, T. L.; Moxey, J. R.; Yagoub, A. K. *J. Chem. Res. (M)* **1987**, 3030. (b) Gilchrist, T. L.; Moxey, J. R.; Yagoub, A. K. *J. Chem. Res. (S)* **1987**, *11*, 357.
(187) Grunewald, G. L.; Seim, M. R.; Bhat, S. R.; Wilson, M. E.; Criscione, K. R. *Bioorg. Med. Chem.* **2008**, *16*, 542.
(188) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc. Perkin. Trans. 1* **1979**, *1*, 258.
(189) Deshayes, C.; Gelin, S. *Tetrahedron Lett.* **1981**, *22*, 2557.
(190) Zimmer, R.; Reissig, H.-U.; Lindner, H. J. *Liebigs Ann. Chem.* **1992**, *6*, 621.
(191) Gygax, P.; Das Gupta, T. K.; Eshenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 2205.
(192) Shalom, E.; Zenou, J.-L.; Shatzmiller, S. *J. Org. Chem.* **1977**, *42*, 4213.
(193) Sukhorukov, A. Yu. . Ph.D. thesis; N. D. Zelinsky Institute of Organic Chemistry RAS, Moscow, 2009; p 104.
(194) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull.* **1990**, *38*, 2712.
(195) Gallos, J. K.; Sarli, V. C.; Koftis, T. V.; Coutouli-Argyropoulou, E. *Tetrahedron Lett.* **2000**, *41*, 4819.
(196) Ioffe, S. L. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis. Novel Strategies in Synthesis*, 2nd ed.; Feuer, H., Ed.; Wiley: Hoboken, NJ, 2008; p 726.
(197) Buchholz, M.; Hiller, F.; Reissig, H.-U. *Eur. J. Org. Chem.* **2002**, *16*, 2838.
(198) Winn, M.; von Geldern, T. W.; Opgenorth, T. J.; Jae, H.; Tasker, A. S.; Boyd, S. A.; Kester, J. A.; Mantei, R. A.; Bal, R.; Sorensen, B. K.; Wu-Wong, J. R.; Chiou, W. J.; Dixon, D. B.; Novosad, E. I.; Hernandez, L.; Marsh, K. C. *J. Med. Chem.* **1996**, *39*, 1039.
(199) Birch, A. J.; Keogh, K. S.; Mamdapur, V. R. *Aust. J. Chem.* **1973**, *26*, 2671.