Alkoxyallenes as building blocks for organic synthesis†

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Alkoxyallenes are unusually versatile C3 building blocks in organic synthesis. Hence this tutorial review summarizes the most important transformations, including subsequent reactions and their applications in the synthesis of relevant compounds, e.g. natural products. The reactivity patterns involved and the synthons derived from alkoxyallenes are presented. Often alkoxyallenes can serve as substitutes of acrolein or acrolein acetals, utilisation of which has already led to interesting products. Most important is the use of lithiated alkoxyallenes which smoothly react with a variety of electrophiles and lead to products with unique substitution patterns. The heterocycles or carbocycles formed are intermediates for the stereoselective synthesis of natural products or for the preparation of other structurally relevant compounds. The different synthons being put into practice by the use of lithiated alkoxyallenes in these variations will be discussed.

Key learning points
(1) This review highlights the synthetic versatility of alkoxyallenes for the synthesis of carbocycles and heterocycles.
(2) Isomerisation of propargylic ethers to alkoxyallenes.
(3) Alkoxyallenes as tamed equivalents of acrolein.
(4) Deprotonation of alkoxyallenes affords reactive nucleophiles that add to electrophiles such as carbonyl compounds or nitriles.
(5) Cyclisation of primary adducts provides heterocycles that are precursors of natural products or other important compounds.

Introduction

The fascinating and versatile chemistry of allenes has been summarized in numerous reviews.¹,² Due to the specific bond properties of allenes with a sp-hybridised carbon in the centre of the cumulene they display higher reactivity compared to otherwise similar alkenes, a feature that has been exploited in many useful transformations. As to be expected, functional groups at one or at both double bonds of the allene moiety strongly influence the reactivity of the compounds (Scheme 1).

Whereas alkyl and aryl groups modify the reactivity of allenes only moderately, strongly electron-withdrawing substituents such as carbonyl or sulfonyl groups lead to preferred reactions with nucleophiles or to cycloaddition. Compounds from these two major classes of allenes have frequently been used as components in transition metal-catalyzed transformations.²

The influence of electron-donating substituents such as alkoxy groups seems to be simple, because the double bond bearing this substituent preferentially reacts with electrophiles as to be expected. However many contributions in the literature show that alkoxyallenes display chameleon type reactivity.

They may also react with nucleophiles at the two terminal carbons and most importantly, they allow a smooth metatation at the carbon next to the oxygen substituent. The combination of these properties makes alkoxyallenes extremely versatile C3 building blocks for the synthesis of acyclic, carbocyclic and heterocyclic compounds, in part with high complexity.³,⁴ As a consequence they have also been employed as crucial precursors for the preparation of a variety of natural products or their analogues. In this tutorial review we try to systematically describe the reactivity patterns of alkoxyallenes and their typical applications in organic synthesis.
1. Synthesis of alkoxyallenes

The importance of alkoxyallenes for organic synthesis is also due to the straightforward access to this product class. Alkoxyallenes are most frequently generated from propargylic ethers such as 2 by base-promoted isomerisation. The precursor propargylic derivatives are easily accessible by a Williamson ether synthesis of the adequate reaction partners, hence propargylic alcohol can smoothly be O-alkylated by an appropriate SN2-active alkyl halide (Scheme 2, pathway a). Alternatively, a propargylic halide is treated with the corresponding alkyl alcohol or phenol derivative (Scheme 2, pathway b). The second approach has also been employed to prepare alkoxyallenes with enantiopure auxiliaries at the oxygen such as diacetone glucose (Scheme 2, pathway c).

Alternative methods for the synthesis of alkoxyallenes have no general importance. However, C-3 substituted alkoxyallenes are simply accessible starting from unsubstituted alkoxyallenes 2 (Scheme 3). Deprotonation at C-1 (see Section 2.4) followed by C-silylation introduced a protective group that allowed a deprotonation at C-3. The generated lithiated species regioselectively reacts with alkyl halides to give trisubstituted allenes being converted into the desired C-3 substituted alkoxyallenes 9 by subsequent desilylation with fluoride. This approach should also allow the preparation of C-3 disubstituted alkoxyallenes.

This approach is usually more efficient than the isomerisation of C-3 substituted propargylic ethers, however, for C-3 aryl-substituted alkoxyallenes 11, compounds 10 easily available by Sonogashira reactions of simple propargylic ethers, can be converted into their allene isomers by treatment with n-butyllithium and subsequent quenching with proton sources or other electrophiles (Scheme 4). Alkoxyallenes of type 11 are more sensitive to hydrolysis and are often used in situ for further functionalisations. 1,3-Disubstituted allenes such as 9 and 11 are axially chiral compounds and produced in racemic form using the procedures described here. They will give rise to the formation of diastereomers when added to prochiral electrophiles. The generation of axially chiral alkoxyallenes and their use in synthesis are with the exception of Nazarov cyclisations (see Section 2.4.5 and Scheme 53) so far not very broadly investigated.

2. Reactions of alkoxyallenes

2.1 General reactivity pattern

At first glance alkoxyallenes are special enol ethers which imply that electrophiles add to the central carbon of the allene react with the nucleophile to give the desired product.
moiety. Obviously, this centre is electron-rich due to the electron-donating effect of the alkoxy group. As a consequence nucleophiles can add either to carbon C-1 or at the terminal allene carbon C-3 (Scheme 5). The additions of nucleophiles are often catalysed by Brønsted or Lewis acids. This polarisation of alkoxyallenes resembles that of \( \alpha, \beta \)-unsaturated carbonyl compounds and it is also responsible for the regioselectivity of cycloadditions to alkoxyallenes.

A dramatic change in the reactivity of alkoxyallenes \( 3 \) is achieved by the selective deprotonation at C-1.\(^9\) This process generates a fairly strong nucleophile being suitable to react with a variety of electrophiles. In general, lithiated alkoxyallenes \( 12 \) add electrophiles to C-1 and hence they can be regarded as an \( \alpha, \beta \)-unsaturated acyl anion synthon \( 13 \) (Scheme 6). This kind of umpolung reactivity is synthetically extremely useful and hence lithiated alkoxyallenes \( 12 \) have found numerous applications in the synthesis of compounds with unique patterns of functional groups. The remaining allene moiety can subsequently be used for further synthetic elaborations.

Metalated alkoxyallenes \( 14 \) with less electropositive metals such as magnesium and titanium are accessible by transmetalation of \( 12 \) with a suitable metal halide. They may also undergo additions to the terminal C-3 carbon providing functionalised 1-alkoxyalkynes \( 15 \) as products (Scheme 7).\(^{10}\) After hydrolysis carboxylic acid derivatives \( 16 \) with substituents at the \( \beta \)-position are generated and therefore these metalated alkoxyallenes \( 14 \) serve in this mode of reactivity as an equivalent of homo-enolate synthon \( 17 \).

Another reactivity pattern of alkoxyallenes is observed when lithiated alkoxyallenes \( 12 \) are treated with nitriles and subsequently with carboxylic acids. This three component procedure delivers iminium ion intermediates \( 18 \) with an electrophilic character at the central allene carbon. The resulting polarisation is shown in Scheme 8. This kind of reactivity led to the formation of functionalised \( \beta \)-ketoenamides \( 19 \) that are precursors for different classes of heterocycles. In this approach the allene serves as a synthetic equivalent of zwitter-ionic synthon \( 20 \).

After the discussion of the most important features of general reactivity of alkoxyallenes typical and important examples of synthetic applications are presented. In all cases the three carbon atoms derived from the allene precursor are highlighted in red colour to facilitate the understanding of the ongoing reactions.

### 2.2 Cycloadditions to alkoxyallenes

A gold-catalysed Diels–Alder reaction with normal electron-demand has been reported employing several alkoxyallenes \( 3 \) and cyclopentadiene as a reactive 1,3-diene.\(^{11}\) In these transformations the electron-deficient double bond of the allene is engaged in the [4+2] cycloadditions (Scheme 9).

Two examples of hetero Diels–Alder reactions with inverse electron-demand are illustrated in Schemes 10 and 11. Methoxyallene \( 22 \) reacts with nitrosoalkenes, \textit{in situ} generated from corresponding \( \gamma \)-halogenated oximes \( 23 \), to give highly functionalised 1,2-oxazine derivatives \( 24 \) that are versatile intermediates.

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**Scheme 5** Possible attack of electrophiles and nucleophiles on alkoxyallenes.

**Scheme 6** Deprotonation–addition sequence at C-1 of alkoxyallenes. Lithiated alkoxyallenes \( 12 \) as synthetic equivalents of an \( \alpha, \beta \)-unsaturated acyl anion synthon \( 13 \).

**Scheme 7** Metalated alkoxyallenes \( 14 \) as synthetic equivalents of homo-enolate synthon \( 17 \).

**Scheme 8** Formation of \( \beta \)-ketoenamides \( 19 \) via iminium ion intermediates \( 18 \). Lithiated alkoxyallenes \( 12 \) as synthetic equivalents of a 1,2-zwitterionic synthon \( 20 \).

**Scheme 9** Au-catalysed [4+2] cycloadditions of alkoxyallenes \( 2 \) and cyclopentadiene.
in organic synthesis.\textsuperscript{12} Employing alkoxyallenes with enantiopure auxiliaries at the oxygen such as \textsuperscript{7} allows diastereoselective hetero-Diels–Alder reactions with the nitrosoalkenes, which subsequently lead to enantio-enriched products.\textsuperscript{13}

A similar Diels–Alder reaction proceeds with the \(a,b\)-unsaturated imine \textsuperscript{25} which combines with methoxyallene \textsuperscript{22} to furnish pyridine derivative \textsuperscript{26} (Scheme 11).\textsuperscript{14} In the examples of Schemes 10 and 11 the electron-rich double bond of the allene undergoes the cycloaddition with the electron-deficient diene.

A unique \([2+1]\) cycloaddition of a silylene using silacyclopropane \textsuperscript{27} as the precursor was reported by Woerpel.\textsuperscript{15} The resulting methylene silacyclopropane \textsuperscript{28} undergoes palladium-catalysed cycloadditions to alkenes to afford silacyclopentanes \textsuperscript{29} that are useful vinylsilane derivatives suitable for subsequent transformations (Scheme 12).

Although other cycloadditions with alkoxyallenes are known, e.g. \([3+2]\) cycloadditions, they are often not regio- and stereoselective and therefore synthetically not particularly important.

### 2.3 Additions of nucleophiles to C-1

Assisted by electrophilic catalysts, O-, N- or C-nucleophiles generally add to C-1 of alkoxyallenes furnishing allylic acetals, allylic O,N-semiaminals or allylic ethers. The resulting products are versatile precursors for further transformations, e.g. for olefin metathesis. Scheme 13 depicts one of many examples of hydroalkoxylations to benzyloxylallenes \textsuperscript{30} providing under gold-catalysis allylic acetals \textsuperscript{31} in good to excellent yields.\textsuperscript{16}

For nitrogen nucleophiles palladium(\(n\)) seems to be an efficient catalyst as shown by the examples of Scheme 14. By using palladium acetate and the chiral ligand \textsuperscript{34} a very high degree of enantipurity of the intermediates \textsuperscript{35} can be achieved.\textsuperscript{17} These products are efficiently converted into dihydropyrorro derivatives \textsuperscript{36} employing the Grubbs II catalyst.

An alternative subsequent reaction is achieved with a compound incorporating an allyl silane substructure (Scheme 15). Palladium(\(n\))-catalysed addition of enantiopure nosyl-protected amine \textsuperscript{37} to benzyloxylallene \textsuperscript{38} affords addition product \textsuperscript{39} in good yield as a mixture of diastereomers. This O,N-semiaminal is a suitable precursor for a Lewis acid promoted ring closure to \textsuperscript{40}, a precursor of the alkaloid Quinolizidine 233A.\textsuperscript{18}

Benzylloxylallene \textsuperscript{38} and azalactones \textsuperscript{41} combine in the presence of hippuric acid, palladium(\(II\)) trifluoroacetate and chiral ligand \textsuperscript{34} to form a new carbon–carbon bond between C-1 of the allene and the CH-acidic component (Scheme 16).\textsuperscript{19} The resulting allylic ethers \textsuperscript{42} are formed in good yields and with high enantio- and diastereoselectivities.

With nucleophiles containing aryl halide moieties these palladium-catalyzed processes lead to simultaneous formation
of new C–C bonds (by carbopalladation) and of C–O or C–N bonds. As an example, Scheme 17 illustrates the addition of ortho-iodo phenol or aniline derivatives \(^{43}\) and alkoxyallenes \(^{44}\) that afford bicyclic products \(^{45}\) with an exo-alkylidene group. \(^{20}\)

All the examples in this section demonstrate the excellent capability of alkoxyallenes to serve as C3 building blocks for the synthesis of functionalised allylic ether derivatives that are very versatile intermediates for the synthesis of all kinds of heterocycles.

**2.4 Deprotonation of alkoxyallenes and reactions with electrophiles**

The generation of lithiated alkoxyallenes and their first reactions with electrophiles were reported shortly after the discovery of the standard route to alkoxyallenes by the Arens group. \(^{9}\) In general, \(n\)-butyllithium in ethereal solvents such as THF or diethyl ether is used to abstract the proton at C-1 of the alkoxyallene \(^{3}\). The resulting lithiated species is depicted with simplified formula 12 (Scheme 18) that is sufficient to understand most of its reactions with electrophiles. It should also be noted here that lithiated compounds such as 12 are carbenoids since they bear a potential leaving group OR at the metalated centre and hence their thermal stability is limited. Their subsequent reactions should occur at temperatures below \(-20\) °C otherwise decomposition to unknown products complicates the outcome of the transformations.

Whereas additions of alkyl halides have been reported they did not become as important as additions of carbonyl compounds and their equivalents such as imines and nitriles (see Scheme 40). Nitriles, aziridines or epoxides are also suitable electrophiles; the strained small ring compounds are generally attacked at the less substituted carbon by lithiated alkoxyallenes 12 and undergo ring opening. Reactions with electrophiles such as chlorotrialkylsilanes or chlorotrialkylstannanes are also possible.

The primary addition products still contain alkoxyallene moieties that can be exploited in various reaction modes. The alkoxyallene unit may be just hydrolysed by aqueous acid to afford \(\alpha,\beta\)-unsaturated carbonyl compounds 53 with a heteroatom-substituted carbon adjacent to the carbonyl group (Scheme 19). These enones 53 are good substrates for cycloadditions or Michael additions. More importantly, cyclisation to dihydrofuran derivatives 54 leads to heterocycles with considerable synthetic potential. This cyclisation either occurs under basic conditions or under the influence of soft Lewis acids. Alternatively, the alkoxyallene unit can also be oxidatively degraded by ozonolysis to furnish functionalised alkyl esters 56. \(^{4}\) In these three sequences the lithiated alkoxyallenes serve as synthetic equivalents of an \(\alpha,\beta\)-unsaturated acyl anion synthon 13, of a 1,3-zwitterionic synthon 55 or of an alkoxy carbonyl anion synthon 57. The synthetic value of this type of transformations is evident and has been exploited in numerous applications. \(^{3,4}\)
Although there are quite a number of useful applications employing lithiated alkoxyallenes as synthons \(^{13,55,57}\), the primary products are most often used as precursors for cyclisations to provide heterocyclic compounds such as \(^{54}\). The reaction of lithiated alkoxyallenes \(^{12}\) with imines or with nitrones as electrophiles leads to primary adducts \(^{48}\) and \(^{59}\). The heterocyclic products, dihydropyrroles \(^{58}\) or 1,2-oxazine derivatives \(^{60}\), are formed by spontaneous cyclisations or by application of suitable catalysts (for details, see the following subsections) (Scheme 20).\(^4\)

Primary products derived from lithiated alkoxyallenes and \(\alpha,\beta\)-unsaturated aldehydes or ketones as electrophiles may also undergo cyclisation or rearrangement reactions to deliver products with unique structures not fitting in a general scheme. They will be discussed in a separate section (see Section 2.4.5).

### 2.4.1 Examples of additions to carbonyl compounds and transformations into dihydrofurans.

Arens et al. already demonstrated that lithiated alkoxyallenes smoothly add to carbonyl compounds and that the primary products, e.g. \(^{61}\), can be cyclised under rather specific, strongly basic conditions into dihydrofurans, such as \(^{62}\) (Scheme 21).\(^9\) Subsequent acidic hydrolysis of \(^{62}\) affords the corresponding furanone derivatives \(^{63}\).

The exact mechanism of this seemingly simple cyclisation is still unclear in its details and an electron-transfer mechanism has been proposed by Magnus.\(^21\) Despite this uncertainty this approach to dihydrofuran derivatives has been used in stereoselective synthesis, e.g. for the preparation of an enantiopure primarily helical compound \(^{64}\) by repetitive additions of lithiated methoxyllene to carbonyl groups (Scheme 22).\(^{22}\)

Dihydrofurans of type \(^{66}\) are prone to undergo an oxidative ring-opening delivering enediones \(^{67}\) (Scheme 23) which have been used for the synthesis of the rare carbohydrate L-Cymarose and its stereoisomers starting from l-lactic acid as a chiral pool compound.\(^{23}\) Other enediones \(^{68}\) bearing a CH group next to the internal carbonyl group could be converted into cyclopentenone derivatives \(^{69}\) (Scheme 24).\(^{24}\)

In the course of these studies, it was discovered that gold-catalysis – well known for other allene cyclisations\(^{25}\) – smoothly converts many of the primary addition products \(^{47}\) (Scheme 19), obtained from lithiated alkoxyallenes and carbonyl compounds into the corresponding dihydrofuran derivatives \(^{54}\). Starting from diacetone glucose-derived allene \(^{7}\) (Scheme 2) the addition to pentadecanal provides allenyl alcohol \(^{70}\) with low diastereoselectivity, which after gold-catalysed cyclisation affords dihydrofuran derivative \(^{71}\) in good yield (Scheme 25). Due to the sensitive carbohydrate substituent this transformation was not efficient under the standard basic cyclisation conditions.
Compound 71 was converted into the cytotoxic natural product Jaspine B in enantiopure form and three of its stereoisomers. Addition of lithiated methoxyallene to functionalised aryl aldehydes such as and subsequent hydrolysis give enones of type that can be employed either in Heck reactions (Scheme 26) or in cuprate additions. This allows the synthesis of precursors like that are highly suitable for the synthesis of benzannulated spiroketales (e.g. 75), a class of compounds important for the synthesis of rubromycin natural products.

2.4.2 Examples of additions to imines and transformation into dihydropyrroles or other heterocycles. Analogously to the additions to carbonyl compounds, imines derived from aldehydes are excellent electrophiles, smoothly reacting with lithiated alkoxylallenes (Scheme 27). The primary allenyl amines with N-alkyl substituents undergo spontaneous cyclisation to give dihydropyrrole derivatives. In contrast, allenyl amines with electron-withdrawing substituents at the nitrogen (aryl, tosyl, and BOC) had to be treated with silver- or gold-catalysts to give the desired heterocycles. This approach is suitable for the synthesis of natural products such as Detoxinine, Anisomycin, Preussin, Codonopsinine and analogues containing highly substituted pyrrolidine rings. With a ketimine as an electrophile the tricyclic compound is available, which is considered to be a possible precursor for the alkaloid FR 901483. The enol ether double bond of the dihydropyrroles of type is suitable for further functionalisations.

Imines may also be generated in situ from aldehydes and lithium bis(hexamethylsilazide) and subsequently treated with lithiated alkoxylallenes. This three-component one-pot protocol efficiently affords the allenyl amines that can be cyclised to give the corresponding dihydropyrrole derivatives 77 in reasonable overall yields (Scheme 28). These heterocycles can be oxidised to electron-rich and fairly sensitive pyrroles such as if stabilised by an electron-withdrawing group at the nitrogen.

After cyclisation either under basic conditions or – in general with better reliability – by gold catalysis, the resulting N-tosyl-substituted dihydropyrroles undergo a base-promoted elimination of potassium sulfinate to provide the electron-rich pyrroles that are not easily accessible by alternative methods (Scheme 29). They have recently been used to prepare BODIPYs such as bearing alkoxyl groups. These dye molecules may be useful for new applications, e.g. fluorescent marker compounds for biomolecules.

An alternative subsequent reaction involves the treatment of the allenyl amines with iodine in nitriles as solvent. The addition of the electrophilic iodine to the central carbon atom...
of the allene generates a stabilised allyl cation which is trapped by the nitrile followed by a cyclisation to dihydroimidazole derivative 84. They undergo an acid-promoted elimination to specifically substituted imidazole derivatives in moderate to good overall yield (Scheme 30).32 The iodovinyl-substituted imidazole derivatives 85 may be used for subsequent reactions such as palladium-catalysed couplings or as starting materials for Grignard intermediates.

Thioisocyanates may also be regarded as special imine derivatives. Fairly early, Brandsma and Nedolya recognized the potential of this type of electrophile for the synthesis of heterocycles from lithiated alkoxyallenes.33 The addition provides an alkoxy-substituted imino allene 86 which after S-alkylation with methyl iodide and subsequent treatment with copper(I) bromide furnishes the 2-thiomethyl-3-alkoxy-substituted pyrrole derivative 87 (Scheme 31). The cyclisation reaction is strongly dependent on the substitution pattern and may also provide pyridine derivatives instead of pyrroles.

2.4.3 Examples of additions to nitriles. The addition of lithiated alkoxyallenes 12 to nitriles was executed in order to directly access electron-rich pyrroles such as 88 (Scheme 32). However, the cyclisation to the sensitive products 48 turned out to be quite capricious, but it could be achieved in several examples employing silver(I) salts. By serendipity, it was discovered that treatment of the primary addition products of lithiated alkoxyallenes 12 and nitriles with trifluoroacetic acid established a new approach to synthesise functionalised β-ketoenamides 89 and as subsequent products pyridines 90 or other heterocycles.34

A mechanistic scenario for the formation of the β-ketoenamides 89 and the pyridines 90 is depicted in Scheme 33. It involves protonation of the primarily formed allenyl imines 48 at the nitrogen and addition of the carboxylate to the central allene carbon atom. Subsequent acyl migration to the nitrogen leads to the β-ketoenamides 89 and an intramolecular aldol-type condensation reaction provides pyridinones 91 which are in equilibrium with the corresponding 4-pyridinol derivatives 90. For the full conversion of 89 to 90 trimethylsilyl triflate and base are suitable condensation reagents. This fairly efficient protocol enables the new three-component synthesis of a variety of highly functionalised pyridine derivatives 89.35
The functional groups in compounds 90 can be employed for subsequent reactions, e.g. all kinds of palladium-catalysed coupling reactions. Sonogashira reactions and subsequent cyclisations led to new furopyridine derivatives. Depending on the position of the coupling either furo[2,3-c]pyridines (92) or furo[3,2-c]pyridines (93) were prepared (Scheme 34).

As an example of the synthesis of a drug intermediate, the preparation of the Glenvastatin precursor 95 is described (Scheme 35).

A series of 2-thienyl-substituted pyridine derivatives such as 97 and 100 is also accessible. Again lithiated methoxallylene 65, thiophene-2-carbonitrile and 2-thiophenecarboxylic acid are the ingredients to deliver the corresponding β-ketoenamide. After cyclisation to the pyridinol 97 and further activation by iodination the resulting pentasubstituted pyridine derivative 98 is used to prepare triflate 99 after several coupling steps (Scheme 36). The resulting final products 100 and 101 (bearing nine thiophene rings!) are interesting due to their photophysical and electrochemical properties.

Intermediate β-ketoenamides 19 are also very versatile starting materials for the synthesis of highly substituted pyrimidines 102 and pyrimidine N-oxides 103 (Scheme 37). The condensation with ammonia sources or with hydroxylamine hydrochloride leads to these heterocycles that can be further transformed into a variety of other derivatives due to the functional groups present (OR group and methyl group).

On the other hand, β-ketoenamides 19 with an acid sensitive OR group undergo a smooth cyclisation to functionalised...
oxazole derivatives 104. These heterocycles contain a methyl ketone moiety that can also be employed in subsequent reactions, e.g. in a Fischer indole synthesis providing compound 106 or the transformation into an alkyne 107 serving as the precursor for the star-shaped compound 108 (Scheme 38). The intriguing self-assembly of compounds of this type on highly oriented pyrolytic graphite has been investigated by scanning tunneling microscopy.

All these examples demonstrate that \( \beta \)-ketoenamides 19 obtained by the novel three-component reaction are extremely versatile intermediates for the synthesis of a broad range of functionalised heterocycles (Scheme 39). The lithiated alkoxyallenes 12 trigger the formation of the \( \beta \)-ketoenamides 19 and provide a functionalised C3-unit allowing all subsequent transformations into highly substituted products.35

### 2.4.4 Examples of additions to nitrones

Nitrones are versatile components of 1,3-dipolar cycloadditions leading to isoxazole derivatives, but they also react with nucleophiles at their electrophilic carbon atom. We found that a variety of nitrones smoothly combine with lithiated alkoxyallenes 12 providing hydroxylamine derivatives that can be isolated only in rare cases, but rather undergo a fast cyclisation to 1,2-oxazine derivatives.39 The stereodivergent behaviour of this \([3+3]\) cyclisation is shown by the addition of lithiated alkoxyallenes to glyceraldehyde derived nitrone 112 (Scheme 40). The standard conditions provide the syn-configured 1,2-oxazines 113 in excellent yields and diastereoselectivities, whereas pre-complexation of the nitrone with diethylaluminium chloride allows a perfect switch to the corresponding anti-configured 1,2-oxazines 113. A similar stereodivergent performance of this nitrone with simple organometallics has earlier been reported and mechanistically interpreted by the Dondoni group.40

Since glyceraldehyde is easily available in both enantiomeric forms, the enantiomers of syn- and anti-1,2-oxazines 113 are also accessible. From these four stereoisomers a variety of enantiopure subsequent products are easily prepared as summarised for the transformations of syn-1,2-oxazine 114 in Scheme 41.4

Many of the products depicted in Scheme 41 still contain the methoxy group that in general cannot be converted into a hydroxyl group under mild conditions. Alternatively, (2-trimethylsilyl)ethoxy- (TMSEO) or benzyloxy-substituted 1,2-oxazine derivatives are also available with similar selectivities and efficacy. They allow the removal of the O-protective group under mild and specific conditions. As an example the synthesis of N-acetyl neuraminic acid 116 is shown in Scheme 42 employing benzyloxyallene 38 as key C3-building block.41 In this case methoxyallene 22 is additionally employed in the late stage of the synthesis to

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**Scheme 38** Synthesis of 5-acetyl-substituted oxazole derivatives 104 and transformation of oxazole 105 into subsequent products.

**Scheme 39** Heterocycles accessible by alkoxyallene-derived \( \beta \)-ketoenamides 19.

**Scheme 40** Stereodivergent preparation of syn- and anti-configured 1,2-oxazines 113 by addition of lithiated alkoxyallenes 12 to glyceraldehyde-derived nitrone 112.
introduce the methoxycarbonyl group as a nucleophile. Hence in this sequence lithiated alkoxyallenes are used as 1,3-zwitterionic synthon and as alkoxycarbonyl anion synthon.

A general feature of the 1,2-oxazine intermediates is that the enol ether double bond undergoes highly stereoselective addition reactions. The stereoselective hydroboration is an example and was the key step for the preparation of enantiopure pyrroolidine, pyrrolizidine and azetidine derivatives with high selectivity. A collaboration with the Goti group established a short, efficient and stereodivergent synthesis of the pyrrolizidine alkaloids Casuarine and Australine starting from benzyloxyallene as a C3 building block and α-arabinose derived nitrone.43

Whereas many transformations of the enantiopure 1,2-oxazines proceed in a straightforward and foreseeable manner, a serendipitous discovery led to a new scenario. During the attempt to convert TMSEO-substituted 1,2-oxazine into the corresponding 1,2-oxazinone by treatment with Lewis acids we discovered that a novel process occurred. It incorporates the “protective group” into the isolated product generating bicyclic 1,2-oxazinones in good to excellent yields. The mechanism of this rearrangement involves coordination of the Lewis acid (LA) to the dioxolane oxygen, ring-opening to provide a stabilized carbenium ion and attack of this intermediate to give the enol ether moiety of the 1,2-oxazine ring. The resulting new carbenium ion undergoes a fast fragmentation into the corresponding ketone, ethylene and a trimethylsilyl-X species. The carbon–carbon bond forming step can be considered as a Lewis acid-promoted aldol-type addition of an acetal to an enol ether or as Prins reaction. The fast fragmentation of the TMSEO group is a prerequisite for a smooth course of this kind of transformation.

A variety of bicyclic 1,2-oxazines were accessible by this method. Due to their high degree of functionalisation they are excellent starting materials for the synthesis of enantiopure polyhydroxylated aminopyran and aminooxepane derivatives that can be considered as analogues of carbohydrates.
extremely high affinities to \( \lambda \)- and P-selectins, carbohydrate recognising proteins involved in inflammation processes.\(^{44}\)

By introduction of a thiophenyl group into the dioxolane moiety bicyclic 1,2-oxazine derivatives such as 126 can be generated in an analogous manner. They are equivalents of pyrans containing an anomeric centre (Scheme 47) and they allowed the straightforward preparation of branched carbohydrate derivatives and the corresponding di- and trisaccharides of types 129 and 130.\(^{42}\)

2.4.5 Examples of rearrangements involving alkoxyallene adducts. Alkoxyallenes with a hydroxyalkyl group adjacent to C1 of the allene moiety are very easily accessible by adding the lithiated species to carbonyl compounds (see above, e.g. Scheme 21). The primary products such as 131 obtained from cyclobutanones as electrophiles undergo a smooth palladium-catalysed ring-expansion to 2-vinyl-substituted cyclopentanone derivatives 132.\(^{45}\) If this pinacol-type rearrangement is executed in the presence of enantiopure ligands \((R,R)-133\) and \((R,R)-134\), respectively, the resulting cyclopentanones 132 are formed with up to 95% ee (Scheme 48). In this process the alkoxyallenes deliver a vinyl carbene synthon formally inserting into the carbon–carbon bond next to the carbonyl group of the starting cyclobutanone.

Similar benzannulated compounds 136 lead to ring-expanded bicyclic products of type 137 employing tetrakis-(triphenylphosphine) palladium as a catalyst (Scheme 49).\(^{46}\)

A gold\((III)\)-catalysed process starts from TMS-protected allenyl alcohols 138 and provides cyclic enol ethers 139 a different type of rearrangement product (Scheme 50).\(^{47}\) As a crucial intermediate the vinyl gold species is assumed to undergo \([3+2]\) cycloaddition to siloxycyclopropane 140 which ring-opens to give the final product.

A different method generates benzene rings from alkoxyallenes and \(\alpha,\beta\)-unsaturated aldehydes (Scheme 51). Addition of

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**Scheme 45** Proposed mechanism for the Lewis acid-promoted transformation of TMSEO-substituted 1,2-oxazines 120 into bicyclic 1,2-oxazines 121. TMSEO = \((2\text{-trimethylsilyl})\text{ethoxy}\).

**Scheme 46** Synthesis of carbohydrate mimetics 124 and 125.

**Scheme 47** Thiophenyl-substituted 1,2-oxazine derivative 126 as a precursor for the synthesis of bicyclic 1,2-oxazine 127 and amino pyran 128 as well as di- and trisaccharide 129 and 130. TMSEO = \((2\text{-trimethylsilyl})\text{ethoxy}\).

**Scheme 48** Synthesis of enantio-enriched cyclopentanones 132 by rearrangement of alkoxyallene–cyclobutanone adducts 131.

**Scheme 49** Palladium-catalysed ring expansion of methoxyallene adducts 136.
the lithiated alkoxyallene to the carbonyl group provides the corresponding allenyl alcohols that were subsequently converted into the aromatic unit by gold(I)-catalysis. Among the carbazole derivatives prepared from the corresponding 2-formyl-substituted indole was the natural product Clausine V. Nazarov-type cyclisations involving alkoxyallenes have systematically been studied by the Tius group and also summarised in reviews. Two examples are depicted in Scheme 52. In the first case, addition of the lithiated alkoxyallene 146 to an a,b-unsaturated ketone furnished intermediate 147 in excellent yield. Its treatment with trifluoroacetic acid anhydride induces the formation of a stabilised carbenium ion 148 which undergoes the Nazarov cyclisation to 149 finally giving exo-methylene cyclopentenone 150. The MOM group is essential for achieving smooth transformations. In a different variation, the carbohydrate-derived lithiated allene 151 and amide 152 combine to give the a,b-unsaturated ketone 153. Treatment with acid in hexafluoroisopropanol converts 153 into cyclisation product 154 bearing a hydroxyl group at C2. In these applications the alkoxyallene served as a dianionic synthon.

A related method to generate cyclopentenone derivatives from highly substituted alkoxyallenes involves the oxidation of the allenes either with dimethyldioxirane or with meta-chloroperbenzoic acid (Scheme 53). The alkoxyallenes 157 were prepared from the corresponding propargylic ethers 156 by a deprotonation–protonation-sequence and then treated with dimethyldioxirane (DMDO) as the oxidising reagent. The resulting species is a 2-oxoallyl cation that undergoes the Nazarov cyclisation to the products 158. This elegant method has been employed to the synthesis of the natural product Rocaglamide in its racemic form.

### 2.5 Examples of other reaction types

Simple addition reactions to one of the two bonds of alkoxyallenes may also provide useful products for further synthetic endeavours. For example, addition of simple electrophiles such as fluorinated sulfanyl chlorides to alkoxyallenes furnishes the
alkenyl sulfoxides 161 under mild conditions (Scheme 54). This process is likely to occur via a reasonably stabilised allylic cation. The product 161 still contains an enol ether moiety suitable for further transformations. The second example of Scheme 54 is a related process, but due to a different substitution pattern of the allene the product 162 contains two electron-withdrawing groups at the double bond. Compounds of this type should be excellent Michael acceptors.

The nucleophilic samarium ketyl's, generated from carbonyl compounds and samarium diiodide, add to the terminal carbon of alkoxyallenes generating vinyl radicals. They trap either a hydrogen atom from THF or HMPA or they are further reduced by samarium diiodide and protonated to give enol ethers of type 163 (Scheme 55). These compounds are valuable intermediates and enable the synthesis of a variety of γ-lactones 164. The regioselective additions of the ketyl's demonstrate that alkoxyallenes react preferentially at the terminal carbon with nucleophilic species. Other allenes, e.g. phenylallene are usually attacked by radicals at the central carbon.

3. Conclusions

This tutorial review summarises synthetically important examples which impressively demonstrate the broad applicability of alkoxyallenes in organic synthesis. There are many addition reactions and cycloadditions where alkoxyallenes play the role of acrolein or acrolein acetal substitutes. Although these examples of use seem simple they are nevertheless synthetically very useful.

The most versatile use of alkoxyallenes involves their deprotonation at C1 followed by reactions with electrophiles. Often a cyclisation is the (spontaneous) subsequent step, leading to a series of highly functionalized five-membered and six-membered heterocycles. Here the deprotonated alkoxyallenes serve as building blocks operating as 1,3-zwitterionic C3 synthons 55 (Scheme 56). The functional groups installed in the heterocycles allow many transformations, in particular by exploiting the remaining enol ether double bond. The addition of lithiated alkoxyallenes to nitriles followed by treatment with carboxylic acids establishes a 1,2-zwitterionic C3 synthon 20 that also allowed syntheses of a series of unusually functionalised heterocycles.

The alkoxy group of the allenes can easily be varied and thus allows modulation according to the synthetic problem in the

Scheme 53 Oxidation of alkoxyallene derivatives 157 and oxidative Nazarov-type cyclisation of 159.

Scheme 54 Addition of perfluoroalkanesulfinyl chlorides to alkoxyallenes providing α,β-unsaturated sulfoxides of type 161 or type 162.

Scheme 55 Synthesis of γ-lactones 164 via a samarium diiodide induced coupling reaction of methoxyallene 22 and carbonyl compounds.

Scheme 56 C3 synthons derived from alkoxyallenes as discussed in this tutorial review.
subsequent products, including selective deprotection in complex products. Use of enantiopure alcohols from the pool of chiral compounds allows the preparation of alkoxyallenes with auxiliaries and as a consequence the stereoselective preparation of enantiopure products, including a series of natural products.

Another important use of specifically substituted alkoxyallenes concerns Nazarov-type cyclisations to cyclopentenone derivatives. These and other metal-promoted transformations illustrate the potential of alkoxyallenes to be incorporated into carbocyclic compounds serving as synthons [135 and 155].

The use of axially chiral alkoxyallenes is still a field to be fully explored. Finally, it should be noted that heteroatom analogues of alkoxyallenes, such as allenyl thiocarboxylates or allenyl amides, are also valuable building blocks in organic synthesis. Their reactivity shows many similarities, but also shows distinct differences compared to alkoxyallenes and thus nicely complements the rich chemistry of this type of allenes.

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Notes and references