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Alkoxyallenes as building blocks for organic synthesis†

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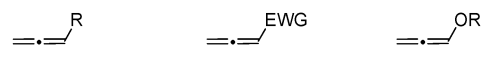
Alkoxyallenes are unusually versatile C3 building blocks in organic synthesis. Hence this tutorial review summarizes the most important transformations, including subsequent reactions and their applications in the synthesis of relevant compounds, *e.g.* natural products. The reactivity patterns involved 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).



R = Alkyl, Aryl (EWG = COR, CO_2R, SO_2R)

Scheme 1 Different classes of allenes (EWG: electron-withdrawing group).

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† Dedicated to Professor Helmut Schwarz on the occasion of his 70th birthday.

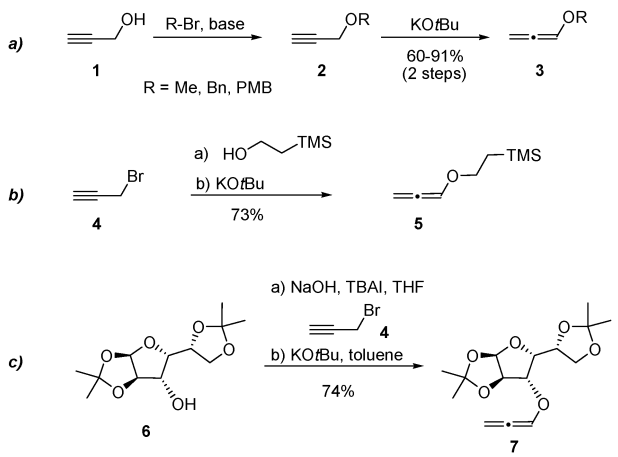
Whereas alkyl and aryl groups modify the reactivity of allenes only moderately, strongly electron-withdrawing substituents such as carbonyl or sulfonyl groups lead to preferred reactions with nucleophiles or to cycloadditions. Compounds from these two major classes of allenes have frequently been used 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 metalation at the carbon next to the oxygen substituent. The combination of these properties makes alkoxyallenes extremely versatile C3 building blocks[3] for the synthesis of acyclic, carbocyclic and heterocyclic compounds, in part with high complexity.[4,5] 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.

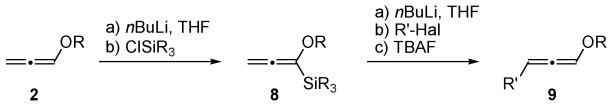
1. Synthesis of alkoxyallenes

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 S_N2-active alkyl halide (Scheme 2, pathway a).[6] 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).[7]



Scheme 2 Different pathways for preparation of alkoxyallenes from propargylic precursors.

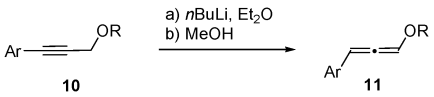
Alternative methods for the synthesis of alkoxyallenes have no general importance.[3] However, C-3 substituted alkoxyallenes are simply accessible starting from unsubstituted alkoxyallenes **2** (Scheme 3). Deprotonation at C-1 (see Section 2.4) followed by C-silylation introduced a protective group that allowed a deprotonation at C-3. The generated lithiated species regioselectively



Scheme 3 Preparation of C-3 substituted alkoxyallenes **9** *via* silylated allenes **8**.

reacts with alkyl halides to give trisubstituted allenes being converted into the desired C-3 substituted alkoxyallenes **9** by subsequent desilylation with fluoride. This route 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 52) so far not very broadly investigated.[8]



Scheme 4 Preparation of 3-aryl-substituted alkoxyallenes **11** from propargylic ethers **10**.

2. Reactions of alkoxyallenes

2.1 General reactivity pattern

At first glance alkoxyallenes are special enol ethers which implies that electrophiles add to the central carbon of the allene moiety. Obviously, this centre is electron-rich due to

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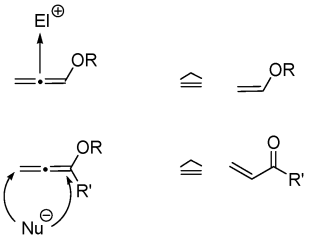
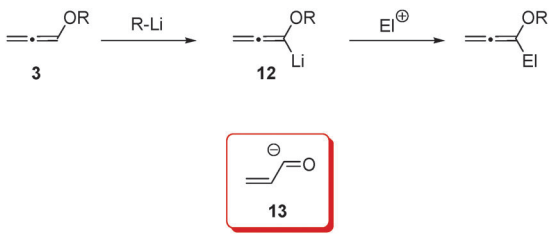
the electron-donating effect of the alkoxy group. As a consequence nucleophiles can add either to carbon C-1 or at the terminal allene carbon C-3 (Scheme 5). The additions of nucleophiles are often catalysed by Brønsted or Lewis acids. This polarisation of alkoxyallenes resembles that of α,β-unsaturated carbonyl compounds and it is also responsible for the regioselectivity of cycloadditions to alkoxyallenes.



Scheme 5 Possible attack of electrophiles and nucleophiles on alkoxyallenes.

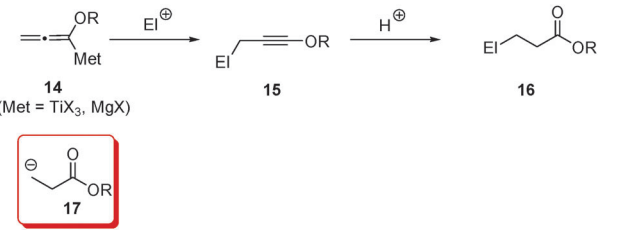
A dramatic change in the reactivity of alkoxyallenes **3** is achieved by the selective deprotonation at C-1.[9] This process generates a fairly strong nucleophile being suitable to react with a variety of electrophiles. In general, lithiated alkoxyallenes **12** add electrophiles to C-1 and hence they can be regarded as an α,β-unsaturated acyl anion synthon **13** (Scheme 6). This kind of umpolung of 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.



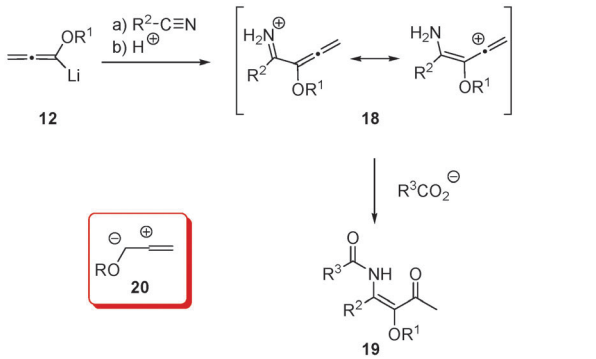
Scheme 6 Deprotonation–addition sequence at C-1 of alkoxyallenes. Lithiated alkoxyallenes **12** as synthetic equivalents of an α,β-unsaturated acyl anion synthon **13**.

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 β-position are generated and therefore these metalated alkoxyallenes **14** serve in this mode of reactivity as an equivalent of homoenolate 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



Scheme 7 Metalated alkoxyallenes **14** as synthetic equivalents of homoenolate synthon **17**.



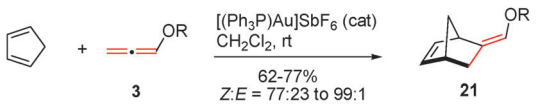
Scheme 8 Formation of β-ketoenamides **19** *via* iminium ion intermediates **18**. Lithiated alkoxyallenes **12** as synthetic equivalents of a 1,2-zwitterionic synthon **20**.

of functionalised β-ketoenamides **19** that are precursors for different classes of heterocycles. In this approach the allene serves as a synthetic equivalent of zwitterionic 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

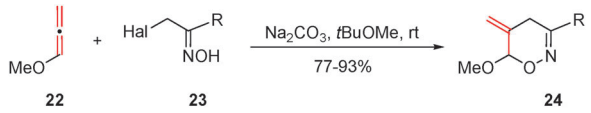
A gold-catalysed Diels–Alder reaction with normal electron-demand has been reported employing several alkoxyallenes **3** and cyclopentadiene as a reactive 1,3-diene.[11] In these transformations the electron-deficient double bond of the allene is engaged in the [4+2] cycloadditions (Scheme 9).



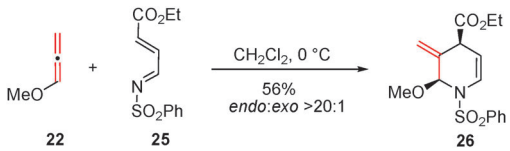
R = Me, *t*Bu, allyl, adamantyl, $(CH_2)_2CMe_2OMe$, (-)-menthyl

Scheme 9 Au-catalysed [4+2] cycloadditions of alkoxyallenes **3** and cyclopentadiene.

Two examples of hetero Diels–Alder reactions with inverse electron-demand are illustrated in Schemes 10 and 11. Methoxyallene **22** reacts with nitrosoalkenes, *in situ* generated from corresponding α-halogenated oximes **23**, to give highly



Scheme 10 Examples for the synthesis of 5-methylene-substituted 5,6-dihydro-4*H*-1,2-oxazines **24**.

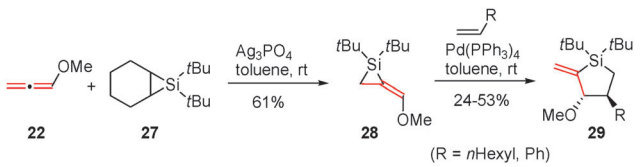


Scheme 11 Synthesis of 5-methylene-substituted 5,6-dihydro-4*H*-pyridine **26**.

functionalised 1,2-oxazine derivatives **24** that are versatile intermediates in organic synthesis.[12] Employing alkoxyallenes with enantiopure auxiliaries at the oxygen such as **7** allows diastereoselective hetero Diels–Alder reactions with the nitrosoalkenes, which subsequently lead to enantio-enriched products.[13]

A similar Diels–Alder reaction proceeds with the α,β-unsaturated imine **25** which combines with methoxyallene **22** to furnish pyridine derivative **26** (Scheme 11).[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 **27** as the precursor was reported by Woerpel.[15] The resulting methylene silacyclopropane **28** undergoes palladium-catalysed cycloadditions to alkenes to afford silacyclopentanes **29** that are useful vinylsilane derivatives suitable for subsequent transformations (Scheme 12).

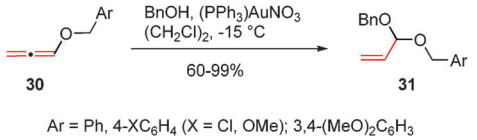


Scheme 12 Synthesis of silacyclopentane derivatives **29** starting from methoxyallene **22**.

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.

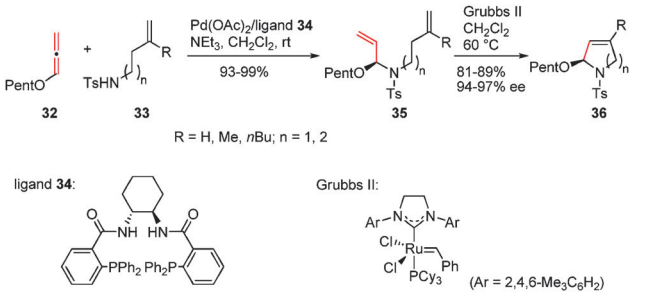
2.3 Additions of nucleophiles to C-1

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 benzyloxyallenes **30** providing under gold-catalysis allylic acetals **31** in good to excellent yields.[16]



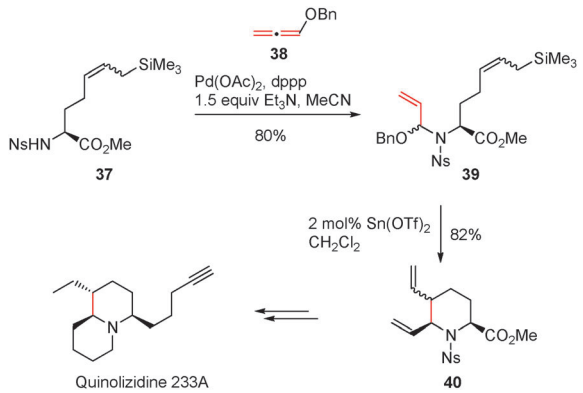
Scheme 13 Au-catalysed hydroalkoxylation of benzyloxyallenes **30**.

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



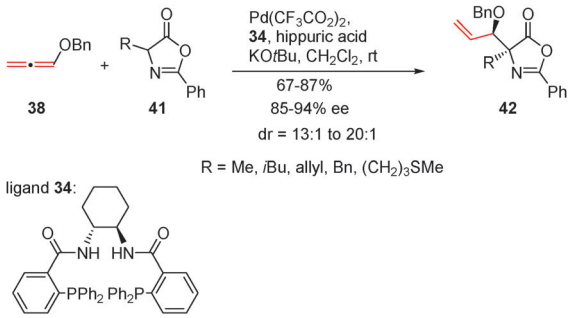
Scheme 14 Enantioselective synthesis of dihydropyrroles **36** employing palladium-catalysed additions of amines **33** to alkoxyallene **32** and olefin metathesis as crucial steps.

An alternative subsequent reaction is achieved with a compound incorporating an allyl silane substructure (Scheme 15). Palladium(II)-catalysed addition of enantiopure nosyl-protected amine **37** to benzyloxyallene **38** affords addition product **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 **40**, a precursor of the alkaloid Quinolizidine 233A.[18]



Scheme 15 Crucial steps in the synthesis of Quinolizidine 233A employing benzyloxyallene **38** as a building block.

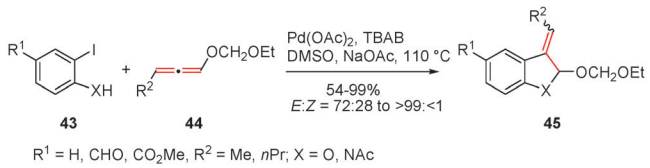
Benzyloxyallene **38** and azalactones **41** combine in the presence of hippuric acid, palladium(II) trifluoroacetate and chiral ligand **34** to form a new carbon–carbon bond between C-1 of the allene and the CH-acidic component (Scheme 16).[19]



Scheme 16 Enantioselective hydrocarbonation of benzyloxyallene **38** with CH-acidic compounds in the presence of ligand **34**.

The resulting allylic ethers **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]



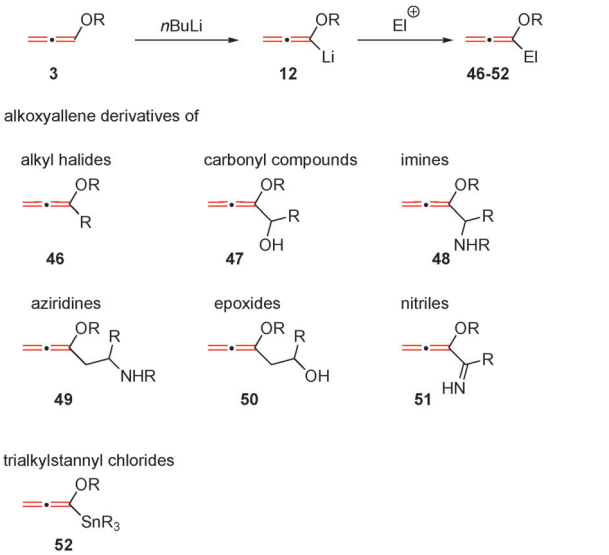
Scheme 17 Example of palladium-catalysed benzannulation reactions using alkoxyallenes **44** and iodo aryl compounds **43**.

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.

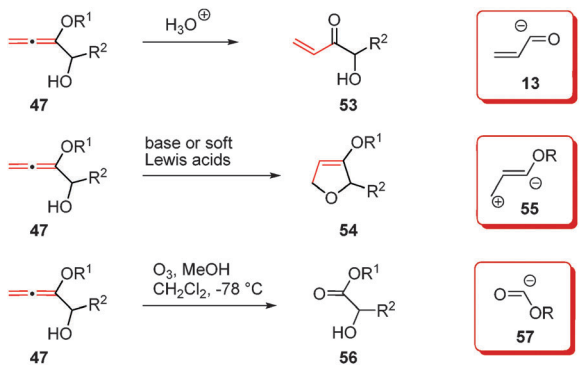
Whereas additions of alkyl halides have been reported they did not become as important as additions of carbonyl compounds and their equivalents such as imines and nitrones (see Scheme 40).



Scheme 18 Generation of lithiated alkoxyallenes **12** and subsequent additions to various electrophiles leading to C-1-substituted alkoxyallenes **46–52**.

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.

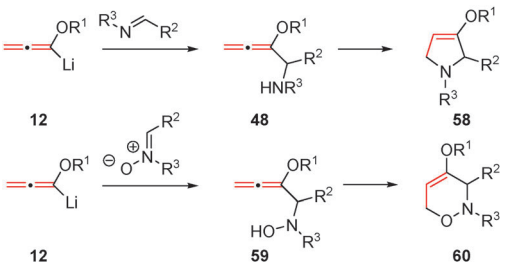
The primary addition products still contain alkoxyallene moieties that can be exploited in various reaction modes. The alkoxyallene unit may be just hydrolysed by aqueous acid to afford α,β-unsaturated carbonyl compounds **53** with a heteroatom-substituted carbon adjacent to the carbonyl group (Scheme 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



Scheme 19 Hydrolysis, cyclisation and ozonolysis of α-hydroxy-substituted alkoxyallenes **47** leading to enones **53**, to dihydrofurans **54** or to alkyl esters **56**. Lithiated alkoxyallene **12** is a synthetic equivalent to synthons **13**, **55** and **57** in these transformations.

lithiated alkoxyallenes serve as synthetic equivalents of an α,β-unsaturated acyl anion synthon **13**, of a 1,3-zwitterionic synthon **55** or of an alkoxycarbonyl 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** and **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]

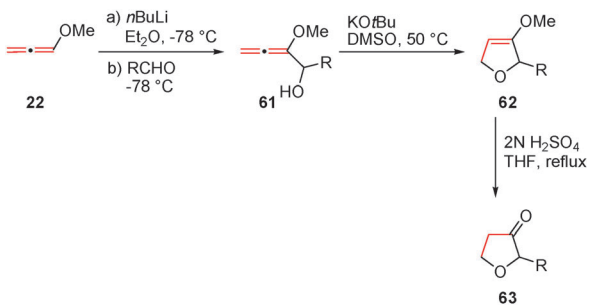


Scheme 20 Additions of lithiated alkoxyallenes **12** to imines and nitrones and subsequent cyclisations leading to dihydropyrroles **58** and 1,2-oxazine derivatives **60**.

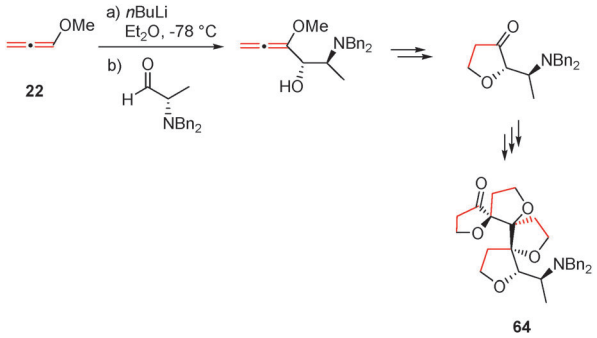
Primary products derived from lithiated alkoxyallenes and α,β-unsaturated aldehydes or ketones as electrophiles may also undergo cyclisation or rearrangement reactions to deliver products with unique structures not fitting in a general scheme. They will be discussed in a separate section (see Section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



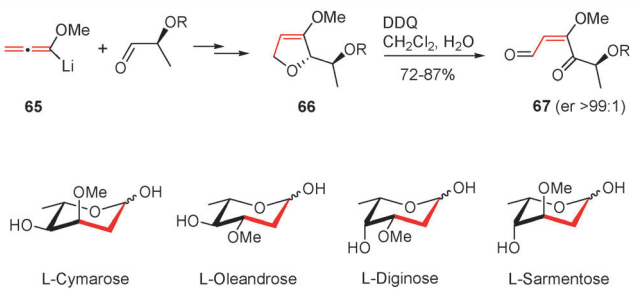
Scheme 21 Conversion of methoxyallene **22** and carbonyl compounds into furanones **63** by an addition–cyclisation–hydrolysis sequence.



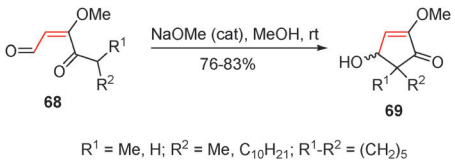
Scheme 22 Synthesis of enantiopure primarily helical compound **64** starting from methoxyallene **22** and enantiopure dibenzyl-protected alaninal.

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 methoxyallene 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]

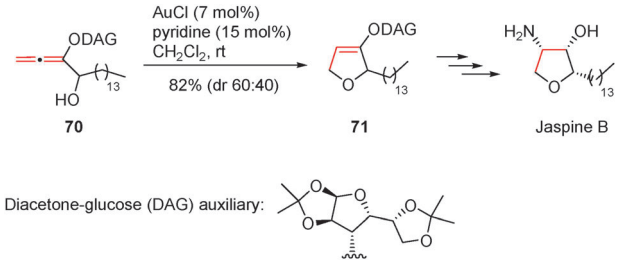


Scheme 23 Oxidative transformation of dihydrofurans **66** into enediones **67** as crucial intermediates for the synthesis of a series of rare methoxy-substituted carbohydrates.



Scheme 24 Intramolecular aldol reaction of enediones **68** to cyclopentenone derivatives **69**.

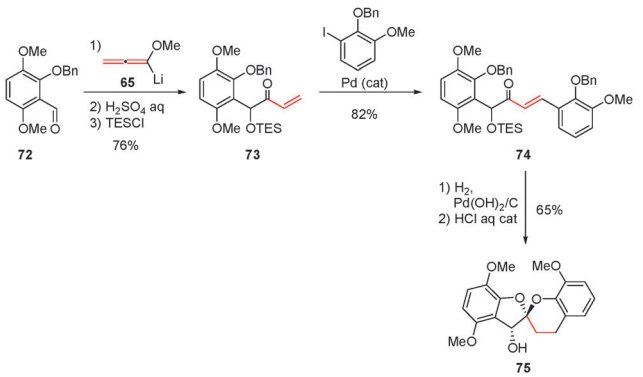
In the course of these studies, it was discovered that gold-catalysis – well known for other allene cyclisations[25] – smoothly converts many of the primary addition products **47** (Scheme 19), obtained from lithiated alkoxyallenes and carbonyl compounds into the corresponding dihydrofuran derivatives **54**. Starting from diacetone glucose-derived allene **7** (Scheme 2) the addition



Scheme 25 Synthesis of enantiopure Jaspine B *via* dihydrofuran derivative **71**.

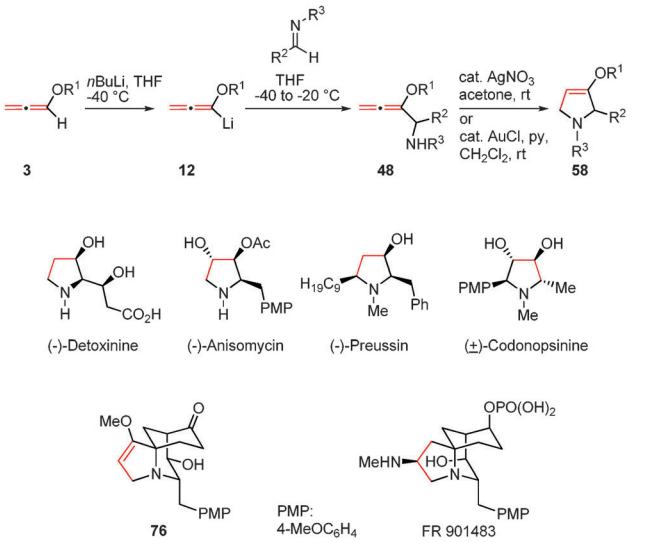
to pentadecanal provides allenyl alcohol **70** with low diastereoselectivity, which after gold-catalysed cyclisation affords dihydrofuran derivative **71** in good yield (Scheme 25). Due to the sensitive carbohydrate substituent this transformation was not efficient under the standard basic cyclisation conditions. Compound **71** was converted into the cytotoxic natural product Jaspine B in enantiopure form and three of its stereoisomers.[26]

Addition of lithiated methoxyallene **65** to functionalised aryl aldehydes such as **72** and subsequent hydrolysis give enones of type **73** that can be employed either in Heck reactions (Scheme 26) or in cuprate additions. This allows the synthesis of precursors like **74** that are highly suitable for the synthesis of benzannulated spiroketals (*e.g.* **75**), a class of compounds important for the synthesis of rubromycin natural products.[27]



Scheme 26 Synthesis of benzannulated spiroketal **75** with the alkoxyallene-derived enone **73** as a crucial intermediate.

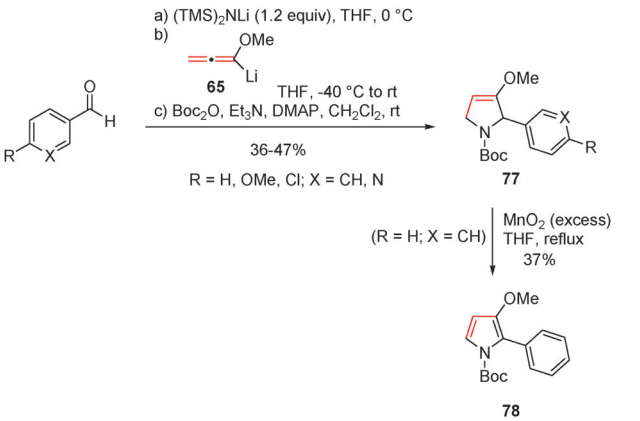
2.4.2 Examples of additions to imines and transformation into dihydropyrroles or other heterocycles. Analogously to the additions to carbonyl compounds, imines derived from aldehydes are excellent electrophiles, smoothly reacting with lithiated alkoxyallenes **12** (Scheme 27). The primary allenyl amines **48** with *N*-alkyl substituents undergo spontaneous cyclisation to give dihydropyrrole derivatives **58**. In contrast, allenyl amines **48** 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.[28] 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



Scheme 27 Synthesis of dihydropyrroles **58** as key intermediates for a series of natural products containing functionalised pyrrolidine rings.

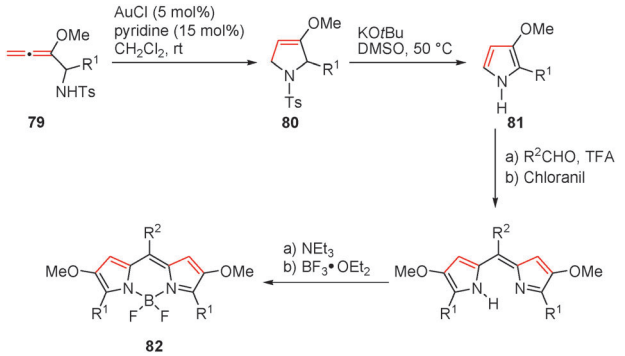
the tricyclic compound **76** is available,[29] which is considered to be a possible precursor for the alkaloid FR 901483.[30] The enol ether double bond of the dihydropyrroles of type **58** is suitable for further functionalisations.

Imines may also be generated *in situ* from aldehydes and lithium bis(hexamethylsilazide) and subsequently treated with lithiated alkoxyallenes. 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).[31] These heterocycles can be oxidised to electron-rich and fairly sensitive pyrroles such as **78** if stabilised by an electron-withdrawing group at the nitrogen.



Scheme 28 Formation of dihydropyrroles **77** and subsequent oxidation to pyrrole **78**.

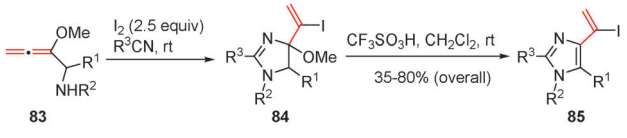
After cyclisation either under basic conditions or – in general with better reliability – by gold catalysis, the resulting *N*-tosyl-substituted dihydropyrroles **80** undergo a base-promoted elimination of potassium sulfinate to provide the electron-rich pyrroles **81** that are not easily accessible by alternative methods (Scheme 29).



Scheme 29 Access to novel BODIPYs of type **82** from alkoxyallene-derived electron-rich pyrroles **81**.

They have recently been used to prepare BODIPYs such as **82** bearing alkoxy 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 **83** 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.

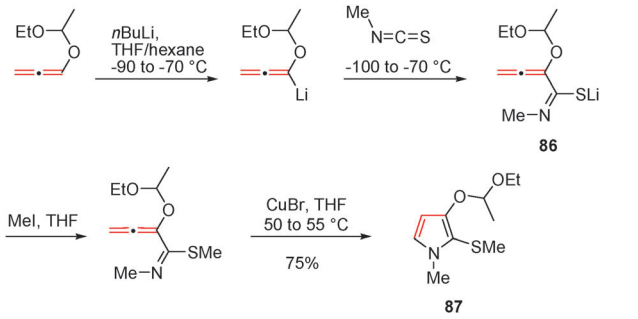


R^1 = *n*Bu, Ph; R^2 = Ph, Ts; R^3 = Me, Et, Ph

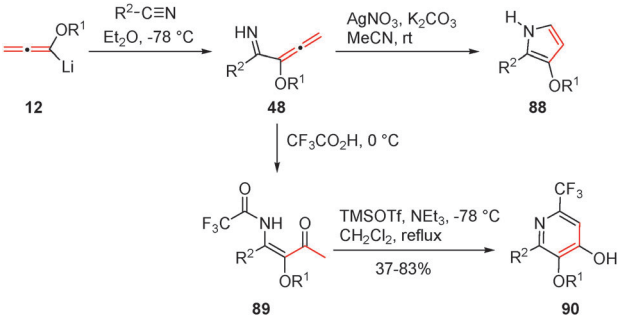
Scheme 30 Synthesis of iodovinyl-substituted imidazole derivatives **85** from allenyl imines **83** and nitriles.

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



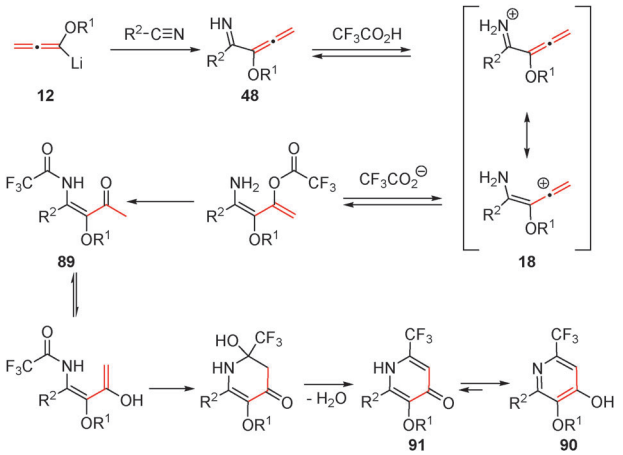
Scheme 31 Synthesis of 2-thiomethyl-3-alkoxy-substituted pyrrole derivative **87** by addition of a lithiated alkoxyallene to methyl thioisocyanate and subsequent reactions.



Scheme 32 Formation of allenyl imines **48** and their silver-catalysed transformation into pyrroles **88** and the three-component reaction with acids to pyridines **90**.

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]

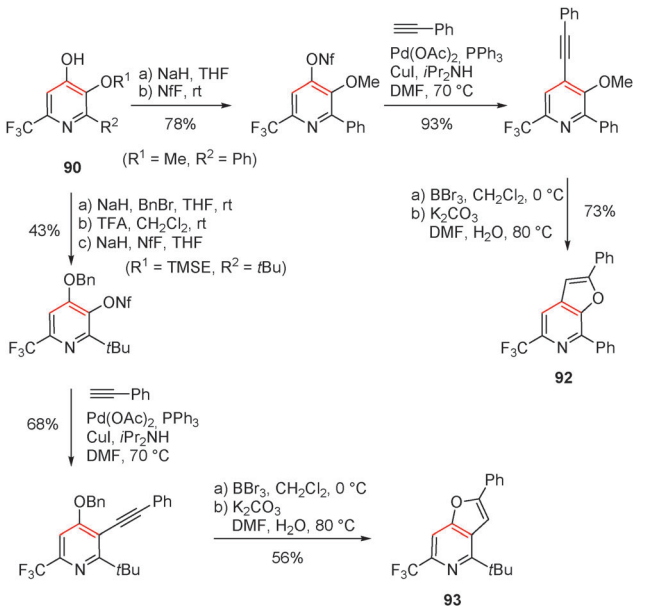
A mechanistic scenario for the formation of the β-ketoenamides **89** and the pyridines **90** is depicted in Scheme 33. It involves protonation of the primarily formed allenyl imines **48** at the nitrogen and addition of the carboxylate to the central allene carbon atom. Subsequent acyl migration to the nitrogen leads to



Scheme 33 Proposed mechanism for the formation of β-ketoenamides **89** and pyridines **90**.

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.[35] 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).

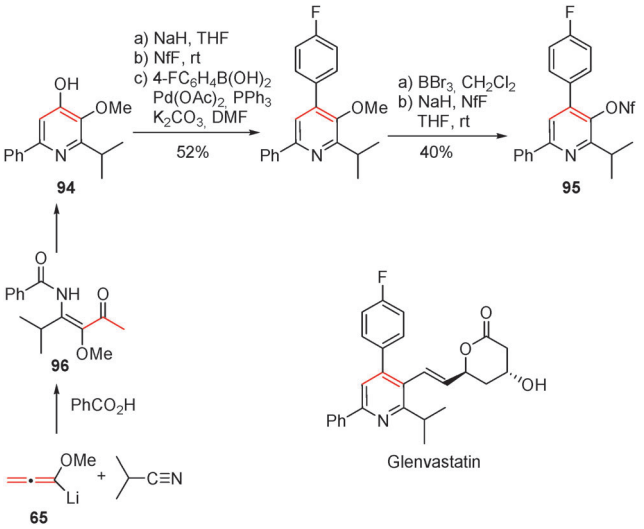


Scheme 34 Synthesis of furo[2,3-*c*]-pyridine (**93**) and furo[3,2-*c*]pyridine (**93**) from 4-pyridinol derivative **90** by a suitable activation/coupling strategy and subsequent cyclisations. Nf = $C_4F_9SO_2$.

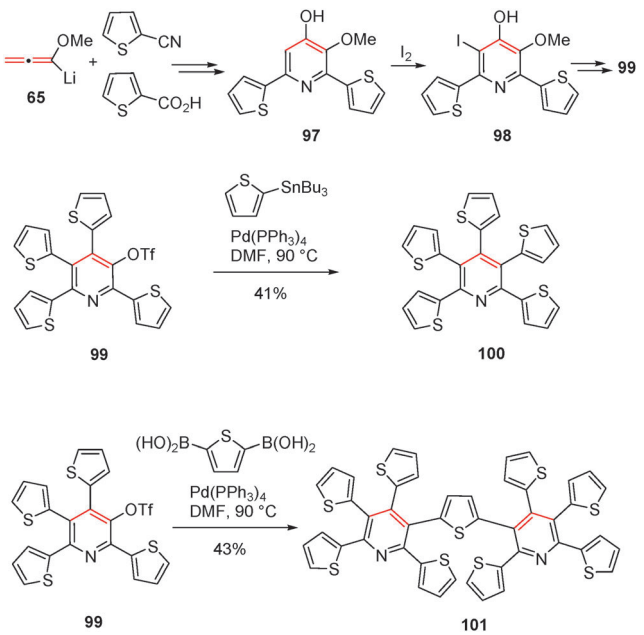
As an example of the synthesis of a drug intermediate, the preparation of the Glenvastatin precursor **95** is described (Scheme 35).[36] Here lithiated methoxyallene **65**, isobutyronitrile and benzoic acid serve as simple starting materials for the synthesis of the crucial β-ketoenamide **96**. Cyclisation and subsequent coupling provide **95** in moderate overall yield.

A series of 2-thienyl-substituted pyridine derivatives such as **97** and **100** is also accessible. Again lithiated methoxyallene **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).[37] 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**



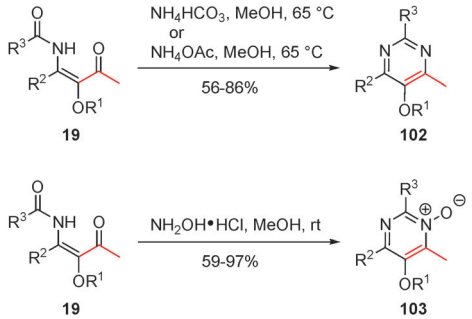
Scheme 35 A formal synthesis of Glenvastatin. Nf = $C_4F_9SO_2$.



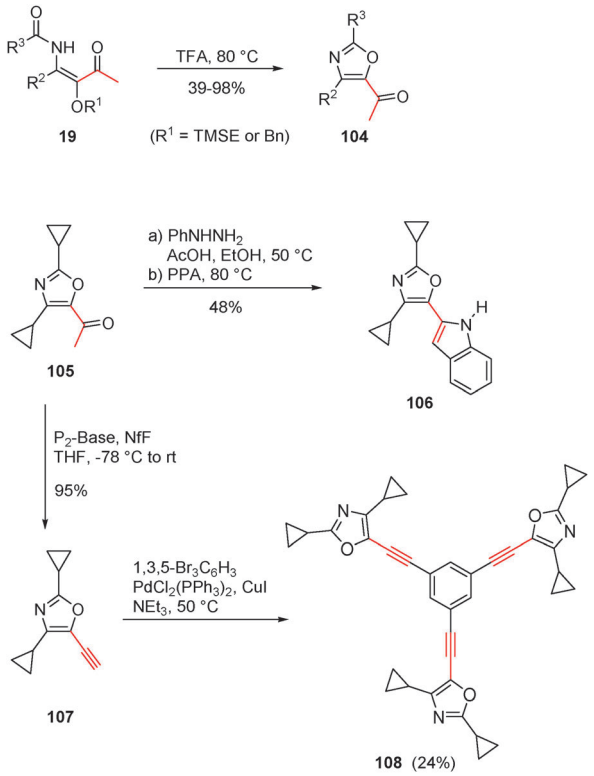
Scheme 36 Synthesis of poly(2-thienyl)-substituted pyridine derivatives.

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).[35]

On the other hand, β-ketoenamides **19** with an acid sensitive OR group undergo a smooth cyclisation to functionalised oxazole derivatives **104**.[38] 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



Scheme 37 β-Ketoenamides **19** as starting materials for the synthesis of pyrimidines **102** and pyrimidine N-oxides **103**.

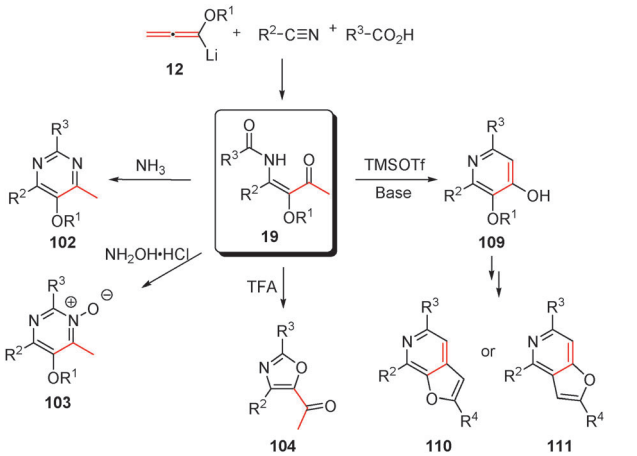


Scheme 38 Synthesis of 5-acetyl-substituted oxazole derivatives **104** and transformation of oxazole **105** into subsequent products.

oriented pyrolytic graphite has been investigated by scanning tunneling microscopy.

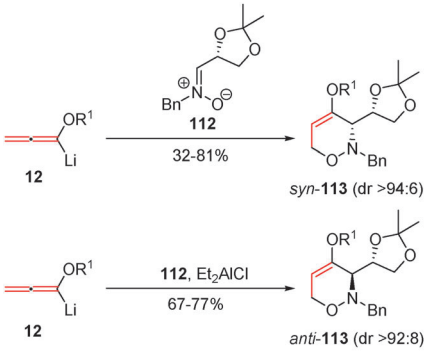
All these examples demonstrate that β-ketoenamides **19** obtained by the novel three-component reaction are extremely versatile intermediates for the synthesis of a broad range of functionalised heterocycles (Scheme 39). The lithiated alkoxyallenes **12** trigger the formation of the β-ketoenamides **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



Scheme 39 Heterocycles accessible by alkoxyallene-derived β-ketoenamides **19**.

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]

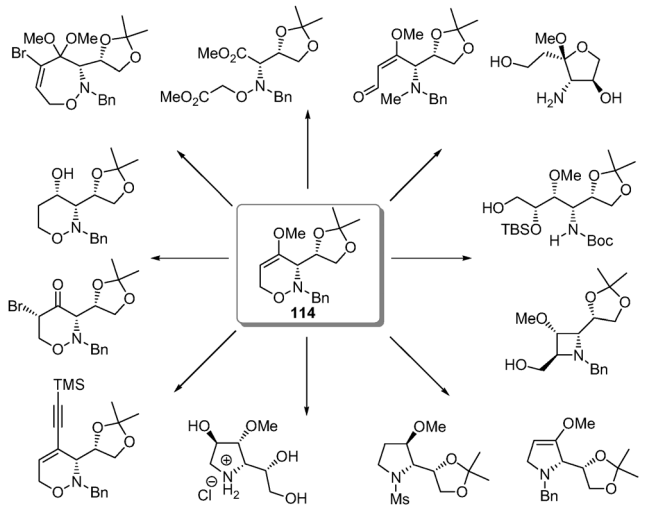


R1 = Me, Pr, Bn, PMB, TMSE

Scheme 40 Stereodivergent preparation of *syn*- and *anti*-configured 1,2-oxazines **113** by addition of lithiated alkoxyallenes **12** to glyceraldehyde-derived nitrone **112**.

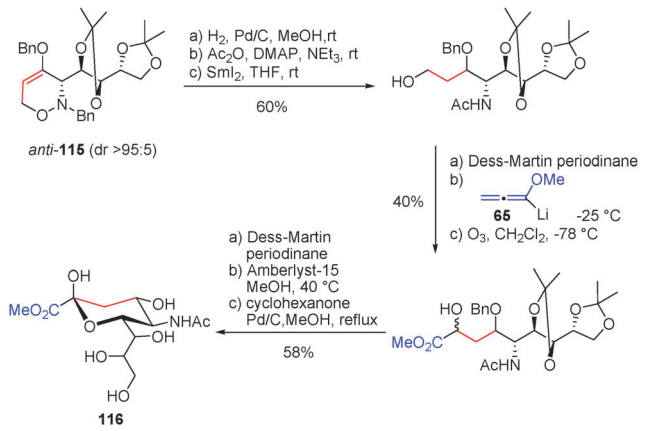
Since glyceraldehyde is easily available in both enantiomeric forms, the enantiomers of *syn*- and *anti*-1,2-oxazines **113** are also accessible. From these four stereoisomers a variety of enantiopure subsequent products are easily prepared as summarised for the transformations of *syn*-1,2-oxazine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



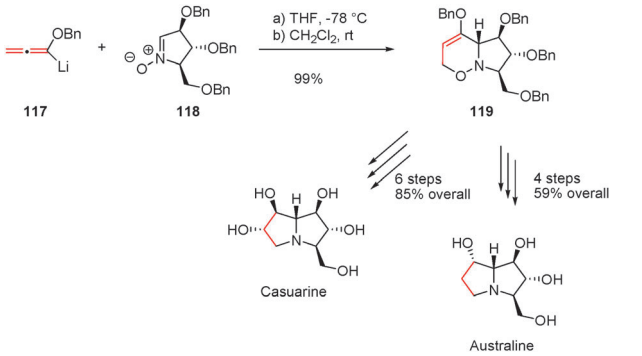
Scheme 41 Acyclic and cyclic products derived from methoxyallene-derived *syn*-1,2-oxazine **114**.

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 introduce the methoxycarbonyl group as a nucleophile. Hence in this sequence lithiated alkoxyallenes are used as 1,3-zwitterionic synthon **55** and as alkoxycarbonyl anion synthon **57**.



Scheme 42 Synthesis of a *N*-acetyl neuraminic acid derivative **116** from *anti*-configured benzyloxy-substituted 1,2-oxazine derivative **115** using lithiated alkoxyallenes as 1,3-zwitterionic synthon **55** and alkoxycarbonyl anion synthon **57**.

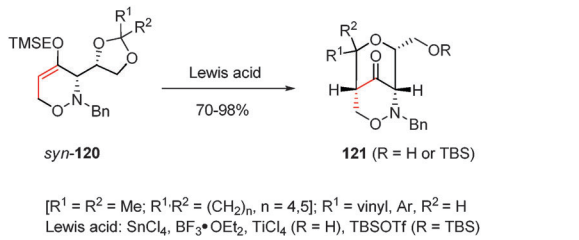
A general feature of the 1,2-oxazine intermediates is that the enol ether double bond undergoes highly stereoselective addition reactions. The stereoselective hydroboration is an example and was the key step for the preparation of enantiopure pyrrolidine, pyrrolizidine and azetidine derivatives with high selectivity.[42] A collaboration with the Goti group established a short, efficient and stereodivergent synthesis of the pyrrolizidine alkaloids



Scheme 43 Stereoselective synthesis of the pyrrolizidine alkaloids Casuarine and Australine starting from benzyloxyallene as a C3 building block and D-arabinose derived nitrone **118**.

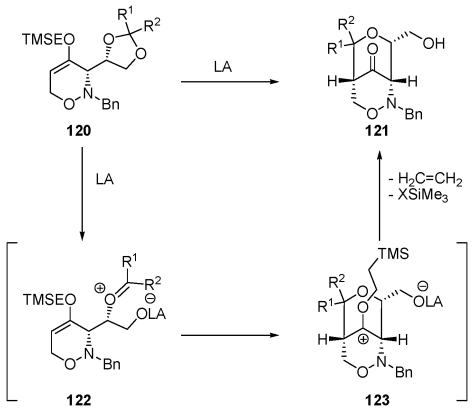
Australine and Casuarine. Lithiated benzyloxyallene **117** was employed as the crucial C3 building block (Scheme 43). Its addition to D-arabinose derived nitrone **118** provided bicyclic 1,2-oxazine **119** in essentially quantitative yield. Depending on the subsequent steps different sides of the intermediates were attacked either leading to Australine in a few steps or to Casuarine.[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 **120** 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 **121** in good to excellent yields (Scheme 44).[42]



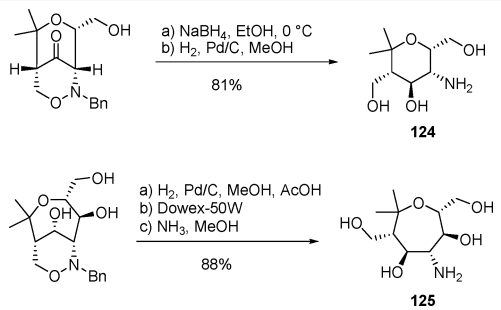
Scheme 44 Lewis acid-promoted transformation of TMSEO-substituted 1,2-oxazines **120** into bicyclic 1,2-oxazinones **121**. TMSEO = (2-trimethylsilyl)-ethoxy.

The mechanism of this rearrangement involves coordination of the Lewis acid (LA) to the dioxolane oxygen, ring-opening to provide a stabilized carbenium ion **122** that attacks the enol ether moiety of the 1,2-oxazine ring (Scheme 45). The resulting new carbenium ion **123** undergoes a fast fragmentation into the corresponding ketone **121**, 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. With simple alkyl groups side reactions leading to different products are observed.



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

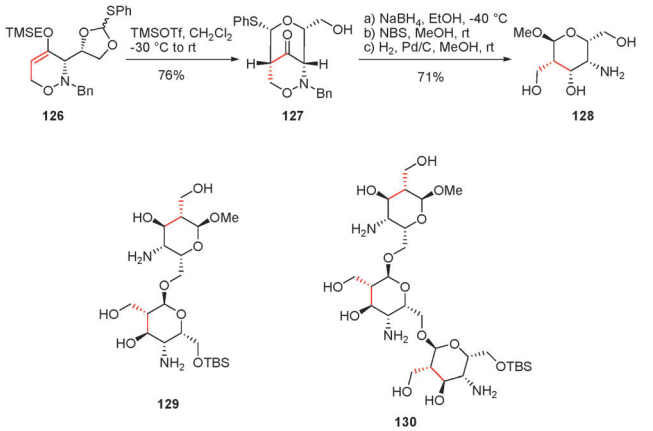
A variety of bicyclic 1,2-oxazines **121** were accessible by this method. Due to their high degree of functionalisation they are excellent starting materials for the synthesis of enantiopure polyhydroxylated aminopyran and aminooxepane derivatives that can be considered as analogues of carbohydrates (Scheme 46).[42] These carbohydrate mimetics, *e.g.* **124** and **125**, have found application as crucial components of multivalent conjugates showing extremely high affinities to L- and P-selectins, carbohydrate recognising proteins involved in inflammation processes.[44]



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

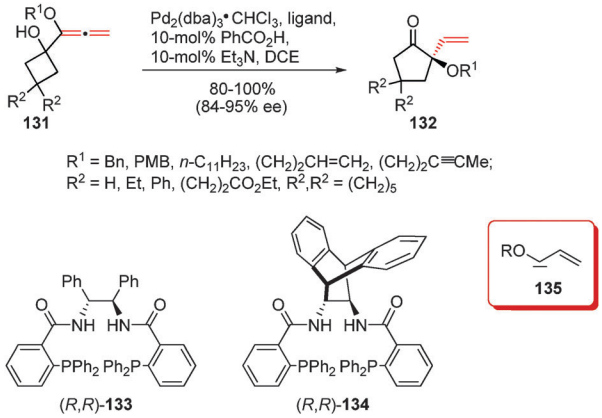
By introduction of a thiophenyl group into the dioxolane moiety bicyclic 1,2-oxazine derivatives such as **126** can be generated in an analogous manner. They are equivalents of pyrans containing an anomeric centre (Scheme 47) and they allowed the straightforward preparation of branched carbohydrate 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



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

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 **135** formally inserting into the carbon–carbon bond next to the carbonyl group of the starting cyclobutanone.

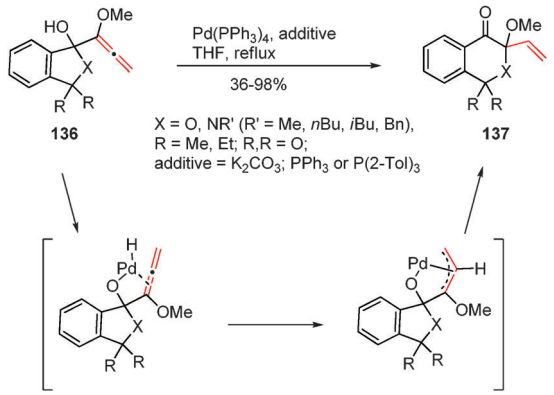


Scheme 48 Synthesis of enantio-enriched cyclopentanones **132** by rearrangement of alkoxyallene–cyclobutanone adducts **131**.

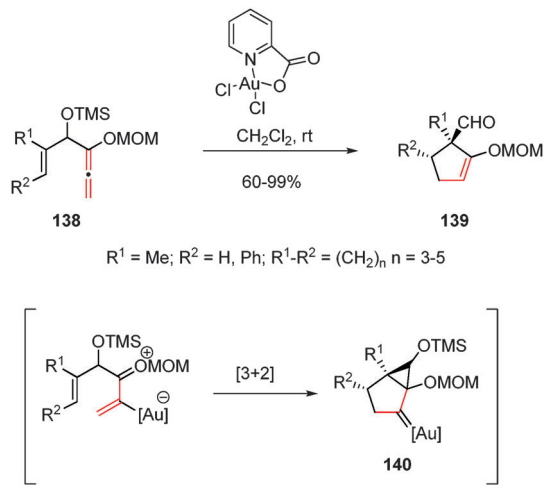
Similar benzannulated compounds **136** lead to ring-expanded bicyclic products of type **137** employing tetrakis(triphenylphosphine) palladium as a catalyst (Scheme 49).[46]

A gold(III)-catalysed process starts from TMS-protected allenyl alcohols **138** and provides cyclic enol ethers **139** as 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.

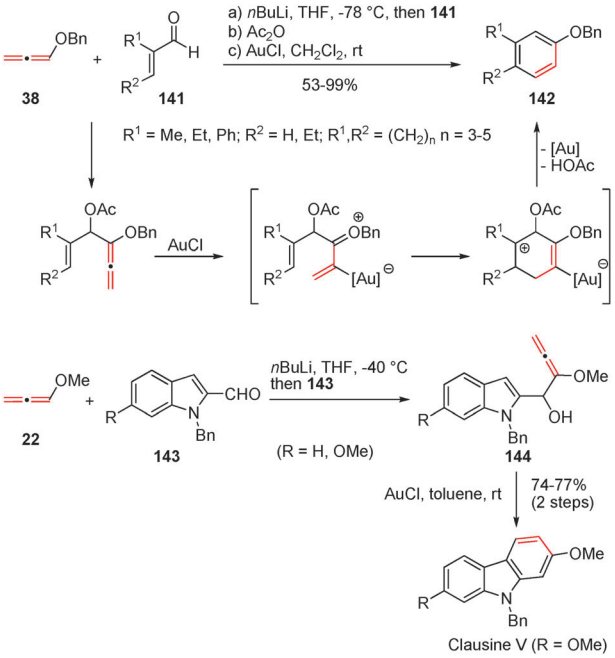
A different method generates benzene rings from alkoxyallenes and α,β-unsaturated aldehydes (Scheme 51). Addition of the lithiated alkoxyallene to the carbonyl group provides the corresponding allenyl alcohols that were subsequently converted into the aromatic unit by gold(I)-catalysis.[48] Among the carbazole derivatives prepared from the corresponding 2-formyl-substituted indole was the natural product Clausine V.[49]



Scheme 49 Palladium-catalysed ring expansion of methoxyallene adducts **136**.



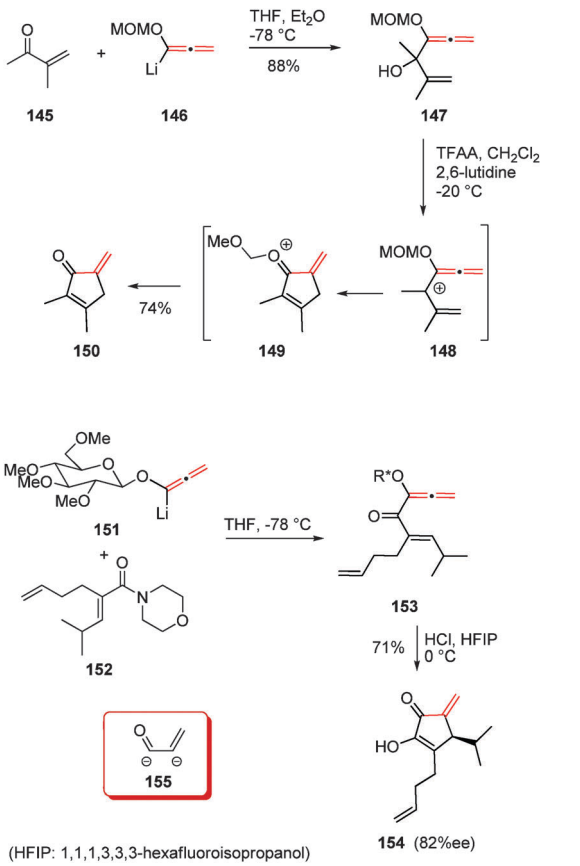
Scheme 50 Au(III)-catalysed cyclisation of TMS-protected alkoxyallene adducts **138** to cyclopentene derivatives **139**.



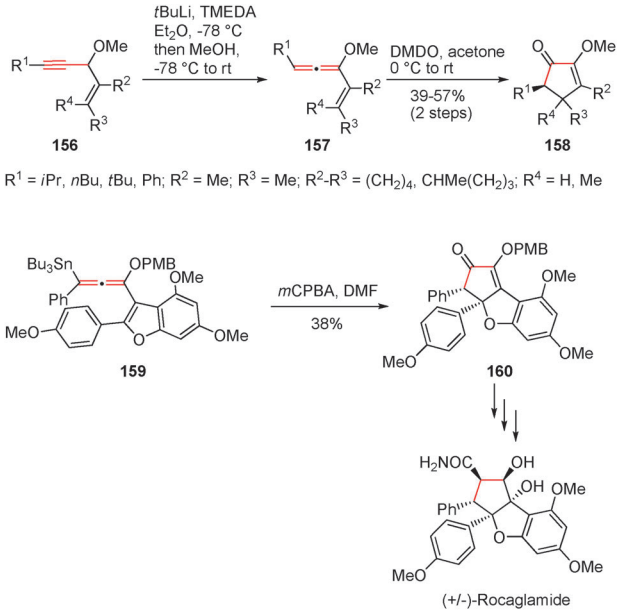
Scheme 51 Formation of benzene rings **142** and **144** from alkoxyallenes and α,β-unsaturated aldehydes **141** and indole-2-carbaldehydes **143**.

Nazarov-type cyclisations involving alkoxyallenes have systematically been studied by the Tius group and also summarized in reviews.[8] Two examples are depicted in Scheme 52. In the first case, addition of the lithiated alkoxyallene **146** to an α,β-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**.[50] 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 α,β-unsaturated ketone **153**. Treatment with acid in hexafluoroisopropanol converts **153** into cyclisation product **154** bearing a hydroxyl group at C2.[51] In these applications the alkoxyallene served as a dianionic synthon **155**.

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



Scheme 52 Nazarov-type cyclisations of alkoxyallene intermediates **147** and **153** leading to cyclopentenone derivatives **150** and **154**. Equivalence of alkoxyallenes with a dianionic synthon **155**.

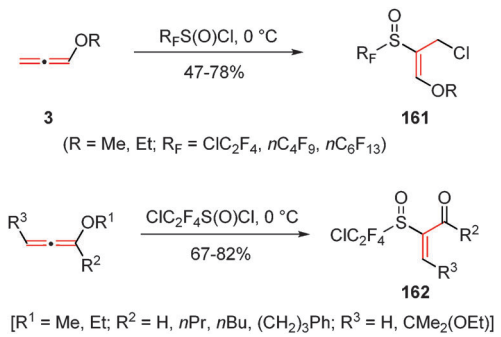


Scheme 53 Oxidation of alkoxyallene derivatives **157** and oxidative Nazarov-type cyclisation of **159**.

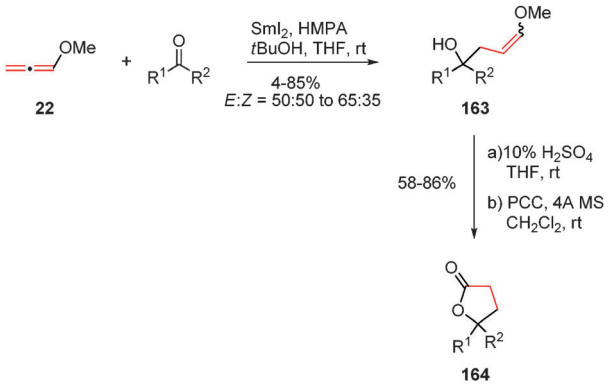
dimethyldioxirane (DMDO) as the oxidising reagent.[52] The resulting species is a 2-oxoallyl cation that undergoes the Nazarov cyclisation to the products **158**. This elegant method has been employed to the synthesis of the natural product Rocaglamide in its racemic form.[53]

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 sulfinyl chlorides to alkoxyallenes furnishes the alkenyl sulfoxides **161** under mild conditions (Scheme 54).[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.



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



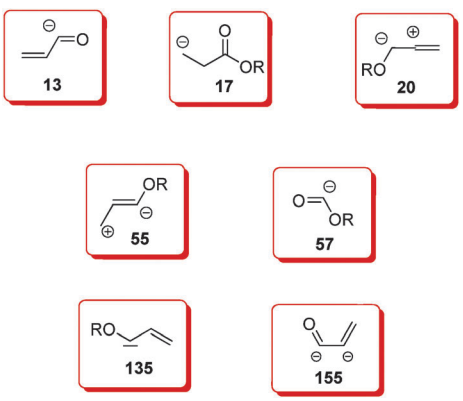
Scheme 55 Synthesis of γ-lactones **164** *via* a samarium diiodide induced coupling reaction of methoxyallene **22** and carbonyl compounds.

The nucleophilic samarium ketyls, 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).[55] These compounds are valuable intermediates and enable the synthesis of a variety of γ-lactones **164.** The regioselective additions of the ketyls 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 valuable.

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 functionalised five-membered and six-membered



Scheme 56 C3 synthons derived from alkoxyallenes as discussed in this tutorial review.

heterocycles. Here the deprotonated alkoxyallenes serve as building blocks operating as 1,3-zwitterionic C3 synthon **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 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 thioethers 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.[2]

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Notes and references

1 *Modern Allene Chemistry*, ed. N. Krause and A. S. K. Hashmi, Wiley-VCH, Weinheim, 2004, vol. 1 and 2.
2 T. Lechel, F. Pfrengle, H.-U. Reissig and R. Zimmer, *ChemCatChem*, 2013, **5**, 2100–2130.
3 R. Zimmer, *Synthesis*, 1993, 165–178.
4 M. Brasholz, H.-U. Reissig and R. Zimmer, *Acc. Chem. Res.*, 2009, **42**, 45–56.
5 N. A. Nedolya, O. Tarasova, O. G. Volostnykh, A. L. Albanov, L. V. Klyba and B. A. Trofimov, *Synthesis*, 2011, 2192–2204.
6 S. Hoff, L. Brandsma and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1968, **87**, 916–924.
7 A. Hausherr, B. Orschel, S. Scherer and H.-U. Reissig, *Synthesis*, 2001, 1377–1385.
8 M. A. Tius, *Chem. Soc. Rev.*, 2014, DOI: 10.1039/c3cs60333d.
9 S. Hoff, L. Brandsma and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1969, **88**, 609–619.
10 S. Hormuth, H.-U. Reissig and D. Dorsch, *Angew. Chem.*, 1993, **105**, 1513–1514 (*Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1449–1450).
11 G. Wang, Y. Zou, Z. Li, Q. Wang and A. Goeke, *Adv. Synth. Catal.*, 2011, **353**, 550–556.
12 R. Zimmer, M. Collas, R. Czerwonka, U. Hain and H.-U. Reissig, *Synthesis*, 2008, 237–244.
13 R. Zimmer, B. Orschel, S. Scherer and H.-U. Reissig, *Synthesis*, 2002, 1553–1563.
14 D. L. Boger and A. M. Kasper, *J. Am. Chem. Soc.*, 1989, **111**, 1517–1519.
15 K. M. Buchner and K. A. Woerpel, *Organometallics*, 2010, **29**, 1661–1669.
16 D.-M. Cui, Z.-L. Zheng and C. Zhang, *J. Org. Chem.*, 2009, **74**, 1426–1427.
17 H. Kim, W. Lim, D. Im, D.-g. Kim and Y. H. Rhee, *Angew. Chem.*, 2012, **124**, 12221–12224 (*Angew. Chem., Int. Ed.*, 2012, **51**, 12055–12058).
18 S. S. Kinderman, R. de Gelder, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra and F. P. J. T. Rutjes, *J. Am. Chem. Soc.*, 2004, **126**, 4100–4101.
19 B. M. Trost, J. Xie and J. D. Sieber, *J. Am. Chem. Soc.*, 2011, **133**, 20611–20622.
20 T. Boi, A. Deagostino, C. Prandi, S. Tabasso, A. Toppino and P. Venturello, *Org. Biomol. Chem.*, 2010, **8**, 2020–2027.
21 P. Magnus and P. Albaugh-Robertson, *J. Chem. Soc., Chem. Commun.*, 1984, 804–806.
22 S. Hormuth, W. Schade and H.-U. Reissig, *Liebigs Ann.*, 1996, 2001–2006.
23 M. Brasholz and H.-U. Reissig, *Eur. J. Org. Chem.*, 2009, 3595–3604.
24 M. Brasholz, B. Dugovič and H.-U. Reissig, *Synthesis*, 2010, 3855–3864.
25 N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994–2009.
26 V. M. Schmiedel, S. Stefani and H.-U. Reissig, *Beilstein J. Org. Chem.*, 2013, **9**, 2564–2569.
27 S. Sörgel, C. Azap and H.-U. Reissig, *Org. Lett.*, 2006, **8**, 4875–4878.
28 M. Okala Amombo, A. Hausherr and H.-U. Reissig, *Synlett*, 1999, 1871–1874.
29 S. Kaden and H.-U. Reissig, *Org. Lett.*, 2006, **8**, 4763–4766.
30 For the most recent total synthesis, see: H.-H. Huo, X.-E. Xia, H.-K. Zhang and P.-Q. Huang, *J. Org. Chem.*, 2013, **78**, 455–465.
31 O. Flögel and H.-U. Reissig, *Synlett*, 2004, 895–897.
32 M. Gwiazda and H.-U. Reissig, *Synthesis*, 2008, 990–994.
33 N. A. Nedolya, L. Brandsma, O. A. Tarasova, A. I. Albanov and B. A. Trofimov, *Russ. J. Org. Chem.*, 2011, **47**, 659–677.
34 O. Flögel, J. Dash, I. Brüdgam, H. Hartl and H.-U. Reissig, *Chem.–Eur. J.*, 2004, **10**, 4283–4290.
35 T. Lechel and H.-U. Reissig, *Pure Appl. Chem.*, 2010, **82**, 1835–1844.
36 T. Lechel, J. Dash, C. Eidamshaus, I. Brüdgam, D. Lentz and H.-U. Reissig, *Org. Biomol. Chem.*, 2010, **8**, 3007–3014.

37 S. L. Gholap, P. Hommes, K. Neuthe and H.-U. Reissig, *Org. Lett.*, 2013, **15**, 318–321.
38 T. Lechel, M. Gerhard, D. Trawny, B. Brusilowskij, L. Schefzig, R. Zimmer, J. P. Rabe, D. Lentz, C. A. Schalley and H.-U. Reissig, *Chem.–Eur. J.*, 2011, **17**, 7480–7491.
39 W. Schade and H.-U. Reissig, *Synlett*, 1999, 632–634.
40 A. Dondoni, S. Franco, F. Junquera, F. L. Merchán, P. Merino, T. Tejero and V. Bertolasi, *Chem.–Eur. J.*, 1995, **1**, 505–520.
41 B. Bressel and H.-U. Reissig, *Org. Lett.*, 2009, **11**, 527–530.
42 L. Bouché and H.-U. Reissig, *Pure Appl. Chem.*, 2012, **84**, 23–36.
43 C. Parmeggiani, F. Cardona, L. Giusti, H.-U. Reissig and A. Goti, *Chem.–Eur. J.*, 2013, **19**, 10595–10604.
44 F. Pfrengle and H.-U. Reissig, *Chem. Soc. Rev.*, 2010, **39**, 549–557.
45 B. M. Trost and J. Xie, *J. Am. Chem. Soc.*, 2008, **130**, 6231–6242.
46 Y. Nagao, A. Ueki, K. Asano, S. Tanaka, S. Sano and M. Shiro, *Org. Lett.*, 2002, **4**, 455–457.
47 X. Huang and L. Zhang, *J. Am. Chem. Soc.*, 2007, **129**, 6398–6399.
48 X. Huang and L. Zhang, *Org. Lett.*, 2007, **9**, 4627–4630.
49 Y. Qiu, D. Ma, C. Fu and S. Ma, *Org. Biomol. Chem.*, 2013, **11**, 1666–1671.
50 M. A. Tius, D. P. Astrab, A. H. Fauq, J. B. Ousset and S. Trehan, *J. Am. Chem. Soc.*, 1986, **108**, 3438–3442.
51 P. E. Harrington and M. A. Tius, *Org. Lett.*, 2000, **2**, 2447–2450.
52 W. T. Spencer III, M. D. Levin and A. J. Frontier, *Org. Lett.*, 2011, **13**, 414–417.
53 J. A. Malona, K. Cariou, W. T. Spencer III and A. J. Frontier, *J. Org. Chem.*, 2012, **77**, 1891–1908.
54 L.-J. Chen and J.-T. Liu, *J. Fluorine Chem.*, 2009, **130**, 329–331.
55 A. Hölemann and H.-U. Reissig, *Chem.–Eur. J.*, 2004, **10**, 5493–5506.