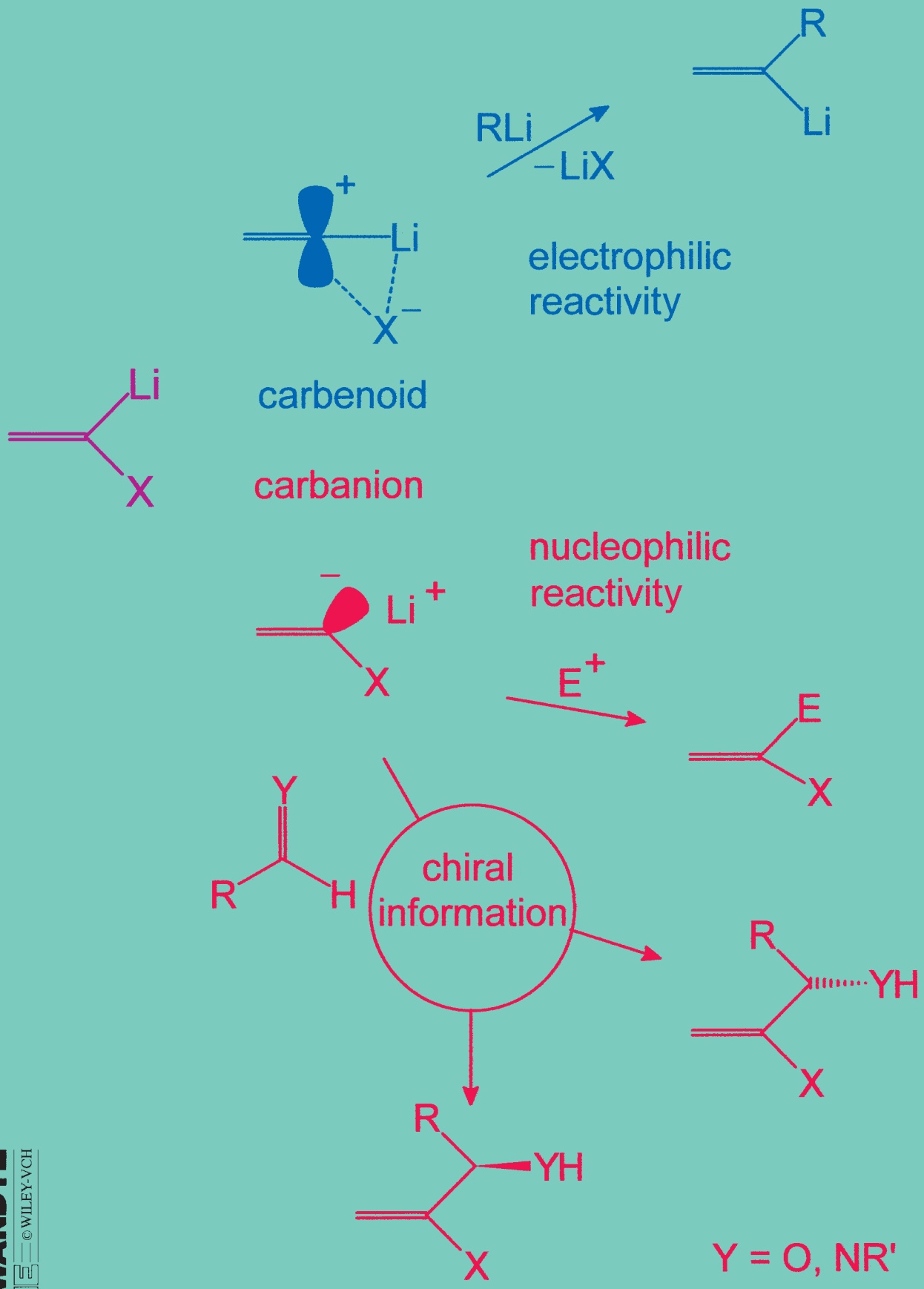


α-Heteroatom-Substituted 1-Alkenyllithium Reagents: Carbanions and Carbenoids for C–C Bond Formation

Manfred Braun*

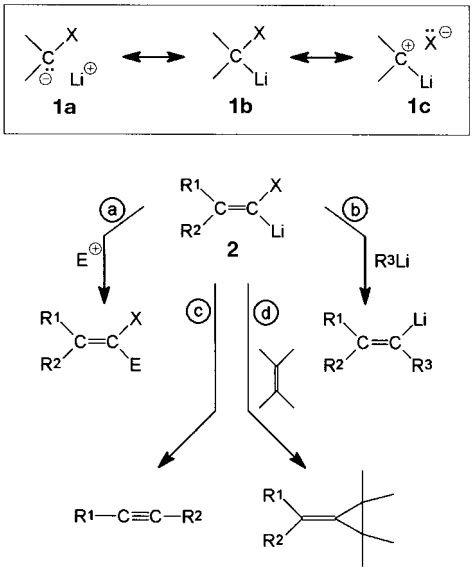
Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

Only the development of low-temperature methods has made it possible to synthesize in solution thermally unstable compounds substituted with a leaving group and a lithium atom at the same carbon center and to exploit their synthetic potential. 1-Alkenyllithium compounds with a heteroatom in the α position (α-heteroatom-substituted 1-alkenyllithium compounds) with geminal substitution of the vinyl carbon atom with an electronegative element and a lithium atom react as electrophilic carbenoids or nucleophilic carbanions depending on the type of heteroatom substituent and the temperature. Newer spectroscopic examinations and X-ray structure analyses, which are summarized here, have contributed substantially towards the understanding of this ambiphilia. After an overview of the most important methods for generating α-heteroatom-substituted 1-alkenyllithium compounds, the carbenoid reactivity of α-lithiated vinyl halides and vinyl ethers is illustrated. In contrast, the many possibilities for C–C bond formation are based on the carbanionic character of the α-heteroatom-substituted 1-lithioalkenes, which are also particularly well suited for carbonyl umpolung. The synthetic potential of such reagents is enlarged substantially with chiral representatives: Lithiated vinyl bromides find application in asymmetric syntheses of α-hydroxy and α-amino carbonyl compounds.

Keywords: asymmetric synthesis · lithium · nucleophilic additions · synthetic methods · umpolung

1. Introduction

Thermal lability and ambiphilic behavior are shown by compounds containing a lithium atom and an electronegative element as a leaving group on the same carbon center. Köbrich, whom we thank for seminal work in this field, used the term "carbenoid" for species **1**, which is usually highly reactive.[1] Whereas the resonance formula **1a** expresses the carbanionic character, the mesomeric structure **1c** highlights the electrophilic reactivity.[2] The ambiphilia is also detectable for alkene derivatives **2**. However, since stabilization of the carbon center increases with growing s content of the corresponding hybrid orbital,[3] the carbanionic reactivity is expressed more strongly in the sp^2-hybridized carbon atom and dominates completely when sulfur, the higher chalcogens, nitrogen, or phosphorus are used as heteroelements X. Numerous reactions with electrophiles prove the carbanionic reactivity (Scheme 1, reaction ⓐ). Since a C–C double bond substituted with a more electronegative element can in principle be converted into a carbonyl group by hydrolysis or ozonolysis, alkenyllithium compounds **2** are suitable equivalents of acyl anions and can be used as reagents for the umpolung of carbonyl reactivity.[4] Marked ambiphilia is



Scheme 1. Reactivities of vinylidene carbenoids **2** as carbanions (a), as electrophiles (b), with rearangement (c), and in cycloadditions (d).

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observed for lithiated vinyl halides and vinyl ethers **2** (X = F, Cl, Br; OR). The surprising reaction of metalated vinyl bromides with alkyllithium compounds makes clear the electrophilic character of these carbenoids: In a nucleophilic, probably metal-supported, substitution the halide is replaced by the alkyl group with inversion of configuration (Scheme 1, reaction ⓑ).[5, 6] As a further feature of carbene-type reactivity, the intramolecular shift of a β-aryl, cyclopropyl, or hydrogen substituent (known as the Fritsch–Buttenberg–Wiechell rearrangement) occurs with the thermolabile α-lithiated vinyl halides **2** (X = Br, Cl; Scheme 1, reaction ⓒ). In the case of β-alkyl-substituted derivatives of **2** (X = Br, Cl), the cyclopropanation typical of carbenoids is also found (reaction ⓓ).[7]

Clearly, this chameleonlike chemical behavior of carbenoids **2** invited structural investigations to reach a better understanding of the different reactivities. Such studies were hampered for a long time by the thermal lability of alkenyllithium compounds, especially those with an α-halogen substituent. It was only in the last few years—in which the interest in carbenes and carbenoids increased[8]—that improved calculations, NMR studies, and finally X-ray structure analyses offered new insight into vinylidene carbenoids **2**. Köbrich had already predicted a larger s content of the C–Li bond and, therefore, a higher p content of the C–X bond in chloro- and bromo-substituted lithioalkenes.[1] Ab initio calculations show that carbenoids **1** and **2** have a comparatively high positive charge at the α-carbon atom and a LUMO that is low in energy.[9] These ideas are confirmed with systematic NMR spectroscopic studies on ^{6}Li-,^{13}C-labeled vinylidene carbenoids **2**:[10] The polarization of the carbon–halogen bond effects a significant deshielding of the α-carbon atom. Therefore, the resonance of the vinyl carbon atom *C in the cyclohexylidene derivative **3** is shifted downfield by $\Delta\delta$ = 101.6 when converted into the alkenyllithium compound **4**. Downfield shifts of $\Delta\delta = 40-280$ are also exhibited by other lithium carbenoids, which shows that the carbocationic structure **1c** has to be taken into account. If a hydrogen-atom substituent in an alkane is replaced by lithium, small upfield shifts of up to $\Delta\delta = 15$ are observed. Downfield shifts also occur to a lesser extent for α-hydrogen- and α-alkyl-substituted alkenyllithium compounds.[11]

The predictions concerning the rehybridization at the carbenoid carbon atom were thoroughly confirmed by an exciting[2] X-ray structure analysis of 1-chloro-2,2-bis(4-chlorophenyl)-1-lithioethene · tmeda · 2 thf (**5**, Figure 1; the second THF molecule is not shown since it is located on a free lattice position and is not bound to the Li atom), the first of a lithium carbenoid.[12] The C1–Cl1 bond is distinctly elongated (by

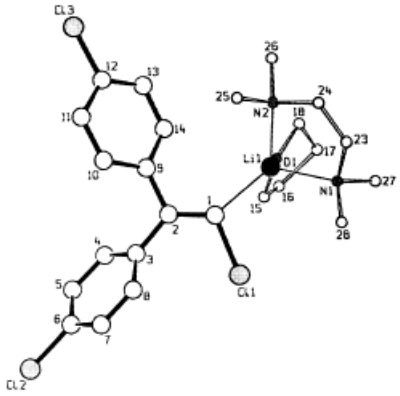
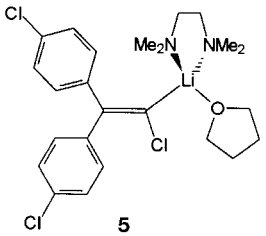


Figure 1. Crystal structure of **5**.



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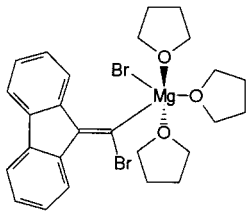

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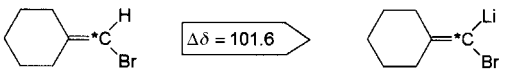
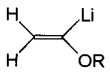
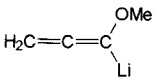


3
δ*C = 99.2

4
δ*C = 200.8



7a: R = Et
7b: R = Me



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Manfred Braun was born in Schwalbach near Saarlouis (Germany) in 1948. From 1966 until 1971 he studied chemistry at the Universität (Technischen Hochschule) Karlsruhe, and in 1975 he completed his doctorate under D. Seebach in Giessen. After a postdoc with G. Büchi at the Massachusetts Institute of Technology in 1975 and 1976 he joined H. Musso's research group at the Universität Karlsruhe and completed the habilitation there in 1981. Since 1985 he has been a professor of organic chemistry at the Heinrich-Heine-Universität Düsseldorf. He received the Liebig scholarship from the Fonds der Chemischen Industrie, the habilitation scholarship as well as the Heisenberg scholarship from the Deutsche Forschungsgemeinschaft, and the Karl Winnacker scholarship. Guest professorships led him to the Université de Rennes (France) and the University of Wisconsin in Madison (USA). His current research interests include the development of new synthetic methods (especially for asymmetric synthesis), organometallic chemistry, and syntheses of natural products.

12 pm) with respect to that in the non-lithiated compound. The Cl1-C1-C2 angle of 112.6(5)° is smaller than the 120° angle at sp^2-hybridized carbon atoms, whereas the Li1-C1-C2 angle is significantly larger (137.1(6)°). These results are easily explained with the high s character of the C–Li bond and the p content of the C–Cl bond. For a nonsolvated carbenoid **2** (X = Cl, OR), calculations predict a structure[13] in which the C–X bond is bridged by the lithium.[14] This contradiction to the crystal structure of **5** is probably due to the fact that the lithium atom is sufficiently solvated by TMEDA and tetrahydrofuran. The bond angles at the carbenoid carbon atom in **5** offer a simple explanation for the inversion that takes place during nucleophilic substitution at lithioalkenes **2** (Scheme 1, reaction ⓑ): apparently the "open" side (large C2-C1-Li angle) opposite the leaving group X offers the ideal trajectory for the nucleophilic alkyllithium compound. A distinct similarity to the alkenyllithium compound **5** is seen for the Grignard compound **6**, which is not surprising owing to the diagonal relationship in the periodic table. The C–Br bond in **6** is 10 pm longer than that in the corresponding vinyl bromide.[15]

1-Ethoxy-1-lithioethene (**7a**), which in contrast to the monomers **5** and **6** exists as polymeric chains in the crystalline state, also displays carbenoid character: With an average length of 142.8(7) pm, the C1–O bond is significantly elongated with respect to that normally seen in vinyl ethers (136 pm). The asymmetric unit presented in Figure 2 contains six $H_2C{=}C(Li)OEt$ molecules. Four of them form a distorted cubic Li_4C_4 tetramer, and the remaining two a second tetrameric aggregate.[16] According to ^{13}C NMR, ^{6}Li,^{13}C

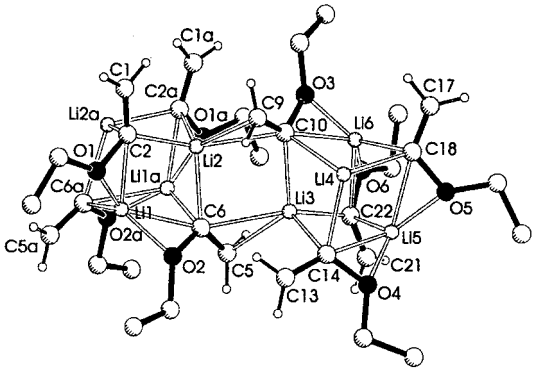
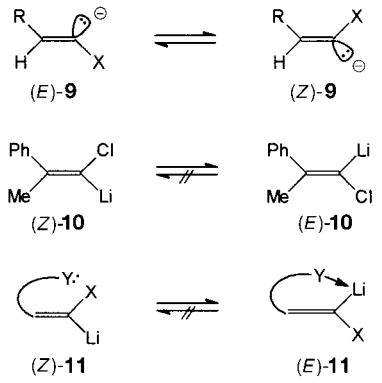


Figure 2. Detail of the crystal structure of polymeric **7a**.

HOSEY NMR, and IR spectroscopic studies, 1-lithio-1-methoxyallen (**8**) in tetrahydrofuran exists in the form of a dimeric nonclassical 1,3-bridged structure; this is also confirmed by ab initio model calculations on α-lithiohydroxyallene.[17]

Unlike alkyl anions, vinyl anions are regarded as configurationally stable; the calculated inversion barrier is about 35 kcal mol^{-1} in the case of the ethenyl anion (*E*)/(*Z*)-**9** (X = H).[18] This value was also experimentally confirmed for a series of 1-lithioalkenes with hydrogen, alkyl, and aryl groups as α substituents.[19] For preparative use, it is of great importance that if generated under mild conditions (low temperatures) the α-substituted 1-alkenyllithium reagents[20]



keep their configuration and react with electrophiles under retention. The lithioalkene (*Z*)-**10**, which is obtained at −110 °C, partially isomerizes to the more stable (*E*)-**10** upon warming to −85 °C, whereas the reverse reaction is not observed.[5] Therefore, two stereoselective transformations are possible: The respective vinylidene carbenoid with the higher energy configuration can be produced at temperatures below −105 °C without inversion and allowed to react under retention. In addition, the diastereomer becomes accessible if the alkenyllithium reagent is allowed to invert by raising the temperature to yield the thermodynamically more stable alkylidene carbenoid. This method can be applied with particular success when there are substituents in the *Z* position with respect to the lithium atom that contain donor centers at the right distance, so that the formation of chelates (*E*)-**11** (X = Cl, Br; Y = OR, NR_2) is possible. Admittedly the temperature can only be increased to about −85 °C because of the thermal lability of α-halogen α-lithioalkenes. On the other hand, metalated vinyl ethers are configurationally stable up to −20 °C for reactions with electrophiles in tetrahydrofuran.[21] Until the onset of decomposition, solutions of 1-ethoxy-1-lithioethene (**7a** · tmeda) show no coalescence of the signals for the vinyl protons in the ^1H NMR spectrum, as would be expected if inversion took place.[22] Also in the case of α-lithiated vinylthioethers, no *E*/*Z* isomerization occurs in tetrahydrofuran up to 0 °C; deprotonated vinyl sulfoxides and vinyl sulfones, on the other hand, are configurationally less stable.[23]

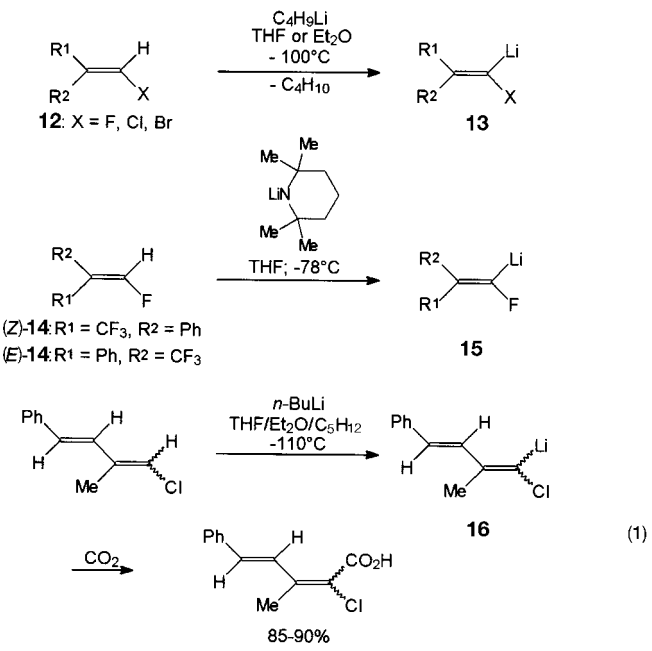
The selective generation of *E* and *Z* vinylidene carbenoids is growing in importance for synthetic applications of α-heteroatom-substituted 1-alkenyllithium compounds. This is particularly true when enantiomerically pure substances are to be produced by stereoselective transformations of such alkenyllithium compounds. This aspect of the chemistry of lithium carbenoids,[1, 2, 20, 24] which has so far received little notice, is the object of particular attention in this review.

2. Generation of α-Substituted 1-Alkenyllithium Compounds

2.1. Hydrogen–Lithium Exchange

α-Heteroatom-substituted 1-alkenyllithium compounds are usually generated quantitatively in solution under inert

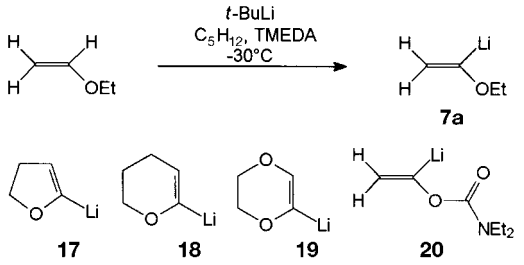
conditions at low temperatures and allowed to react further without isolation.[25] The acidity of vinyl-bound hydrogen atoms is sufficiently high due to the greater s proportion of the C–H bond compared with alkanes,[3] and deprotonation is possible with alkyllithium reagents such as *n*-, *sec*-, or *tert*-butyllithium. If the system to be metalated has one or several protons in the allyl position, the formation of the allyl instead of the vinyl anion can become the dominating rival reaction.[26] In alkenes with heteroatom substituents from Groups 15, 16, and 17, however, the α-hydrogen atom shows a higher acidity. Therefore, 1-halo-1-alkenes **12** can react with *n*- or *tert*-butyllithium in tetrahydrofuran or diethyl ether at $-100\,^{\circ}C$ to yield fluoro-, chloro-, and bromo-substituted 1-lithioalkenes **13**, whose existence can be confirmed in most cases by reaction with electrophiles.[24, 27] With vinyl fluorides and vinyl chlorides, deprotonation is very much faster than



(1)

halogen–lithium exchange, which, however, can occur with bromoalkenes. Lithium-2,2,6,6-tetramethylpiperidide is also suitable for the metalation of vinyl fluorides **14** to form lithioalkenes **15**, which are stable up to $-78\,^{\circ}C$ and also retain their configuration.[28, 29] Particularly labile carbenoids such as the butadiene derivative **16** are advantageously generated[30] in the "Trapp mixture"[1]—a solvent mixture of tetrahydrofuran, diethyl ether, and pentane that has a low freezing point—and allowed to react further [Eq. (1)].

The metalation of an alkyl vinyl ether was first achieved by reaction with *tert*-butyllithium in pentane with TMEDA as a co-solvent [Eq. (2)].[31] 1-Ethoxy-1-lithioethene (**7a**) produced in this way can be characterized by NMR spectroscopy; the typical downfield shift for the carbenoid carbon atom can also be observed in this case ($\delta = 212$).[32] *tert*-Butyllithium in tetrahydrofuran[33] or tetrahydropyran[34] as well as a mixture of potassium *tert*-butoxide and butyllithium are also suitable for deprotonating alkyl alkenyl ethers. A series of α-lithiated vinyl ethers—such as 2-lithio-4,5-dihydrofuran (**17**),[32, 36, 37]



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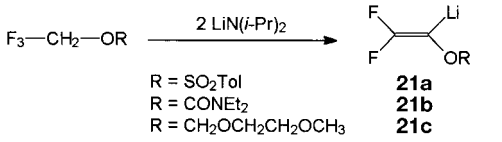
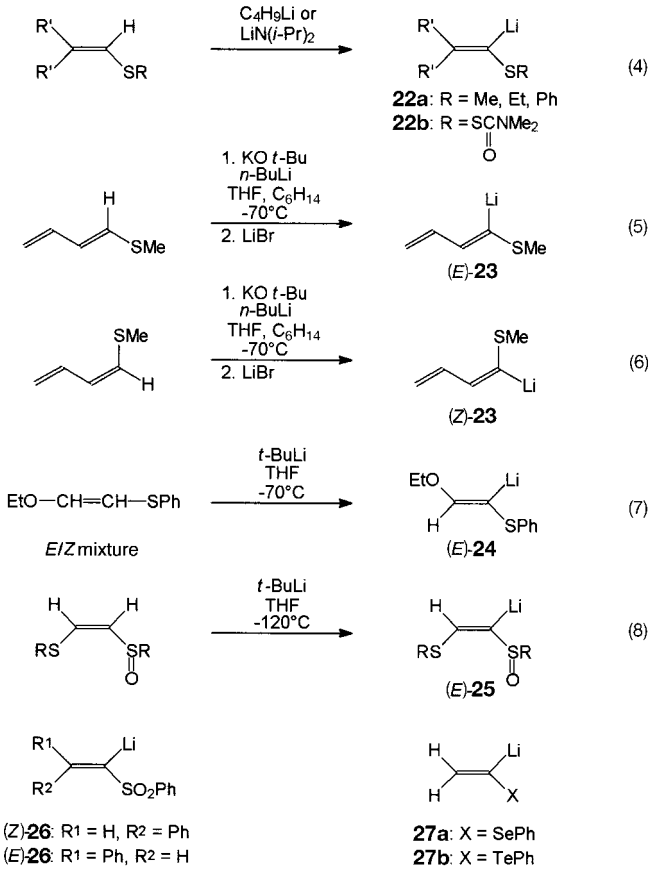


(3)

2-lithio-5,6-dihydropyran (**18**),[32, 38] and 2-litho-5,6-dihydro-1,4-dioxin (**19**)[39, 40]—as well as the metalated carbamide **20**[41] are available with this or a similar procedure. The metalated vinyl ethers are much more stable than the 1-halo-1-lithioalkenes; the lithiated dioxin **19** can supposedly be kept in solution at $20\,^{\circ}C$ for several days.[39]

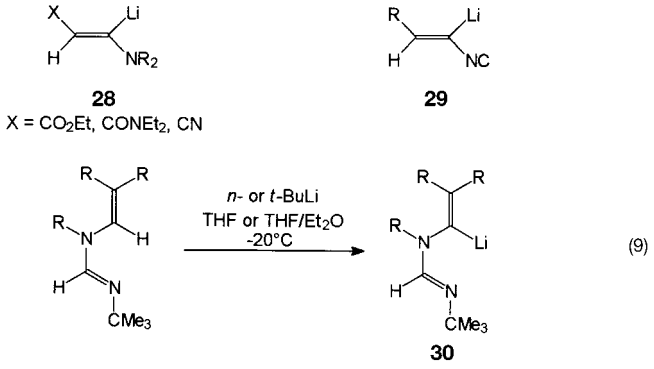
Lithiated enol esters **21a**[42] and **21b**,[43] which are substituted with two fluorides in the β position, are directly available from the corresponding esters of 2,2,2-trifluoroethanol [Eq. (3)]. In the reaction with two equivalents of lithium diisopropylamide the first step is probably elimination to yield the enol ester, which is immediately metalated in situ. Thus, the lithiated enol ether **21c** is also accessible.[44]

Considering the carbanion-stabilizing effect of the thio substituent, it comes as no surprise that alkyl and aryl vinyl sulfides[45–47] as well as thioesters[48] are easily converted into the alkenyllithium reagents **22a** and **22b**, respectively, by metalation [Eq. (4)]. Alkylthio-substituted derivatives of acrylic acid,[49] 1,2-bis(alkylthio)alkenes,[35a, 50] 1,4-dithiins,[51] and tetrathiafulvalene[52] can also be deprotonated in the same way. The lithiation of 1-methylthio-1,3-butadiene, however, can not be effected directly with butyllithium; instead, the potassium compound is produced and then transmetalated with lithium bromide [Eqs. (5), (6)].[53, 54] The diastereomers (*E*)- and (*Z*)-**23** thus available are configurationally stable below $-20\,^{\circ}C$.[54] The acidity of the α-positioned vinylic hydrogen atom is higher in alkylsulfinylalkenes[55, 56] than in the corresponding thioethers, and higher in these than in vinyl ethers. This is clearly shown in the regioselective metalations leading to the heteroatom-substituted lithioalkenes **24**[57] and **25** [Eqs. (7), (8)].[23] As expected, vinyl sulfones[58] and vinyl sulfoximines[59] are metalated even more easily, for example with methyllithium. The 1-arylsulfonyl-1-lithioalkenes thus available show low configurational stability unless they are already present as the thermodynamically favored isomer. Therefore, (*Z*)-**26** almost completely converts into the *E* isomer at $-60\,^{\circ}C$ in tetrahydrofuran.[60] The metalation of vinyl selenides and vinyl tellurides to give **27** is effected with comparatively weak bases such as lithium diisopropylamide or lithium hexamethylpiperidide[61] as well as with a mixture of potassium diisopropylamide and lithium *tert*-butoxide;[62]



apart from the formation of the α-seleno-substituted 1-lithioalkene **27a**,[63] elimination leading to the alkyne can also occur depending on the reaction conditions.[61]

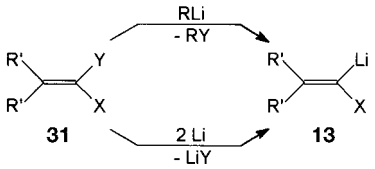
Enamines can only be deprotonated if additional carbanion-stabilizing groups are present either in the alkene skeleton or on nitrogen; in all cases *n*- or *tert*-butyllithium is necessary. Examples for the former substitution pattern are amides, esters and nitriles of β-aminoacrylic acid, whose lithium derivatives **28** ($R_2 = (CH_2)_4$, $(CH_2)_3$) are, however, extremely unstable and must be generated and allowed to react at



$-120\,^{\circ}C$.[64] Lithiated isonitriles **29** are similarly unstable,[65] whereas metalated amidines **30** [Eq. (9)] can be kept in solution at $-78\,^{\circ}C$, some even at $-20\,^{\circ}C$.[66] In contrast, vinyl phosphonates can already be deprotonated with lithium diisopropylamide.[67]

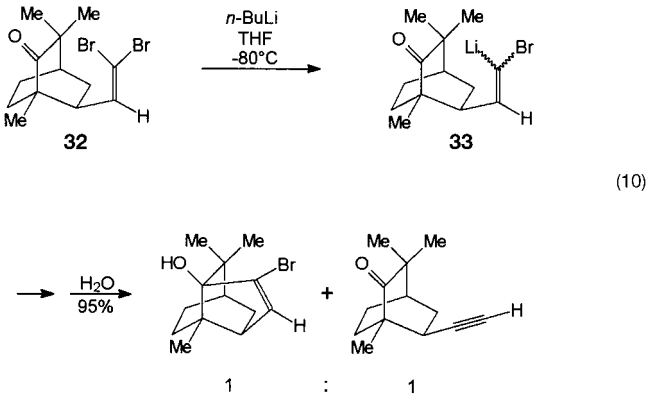
2.2. Halogen–Lithium Exchange

The most common method for generating alkylidene carbenoids **13** is halogen–lithium exchange in dihaloalkenes **31**. Particularly suitable reagents are *n*- or *tert*-butyllithium;



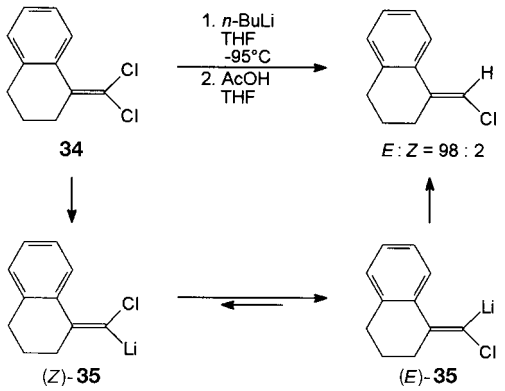
occasionally, metallic lithium is used. The efficiency of this method is documented in numerous examples.[24, 27]

The rate of halogen–lithium exchange increases when going from chlorine to iodine. Thus, only the bromine atom in 1-bromo-1-chloro- and 1-bromo-1-fluoroalkenes is replaced by the metal upon treatment with butyllithium.[6, 68] The reaction with *n*- or *tert*-butyllithium is so fast with the heavier halogens that it can compete with the addition of the alkyllithium compound: In the reaction of the dibromoalkene **32** with *n*-butyllithium, bromine–lithium exchange apparently takes place followed by the intramolecular nucleophilic addition of the lithioalkene **33** at the keto group or elimination to yield the alkyne [Eq. (10)].[69] Owing to the



high reaction rate, the halogen–lithium exchange is particularly suitable for generating the unstable halocarbenoids **13** since the reaction already takes place below $-100\,^{\circ}C$ in a fast and, for the most part, quantitative manner.

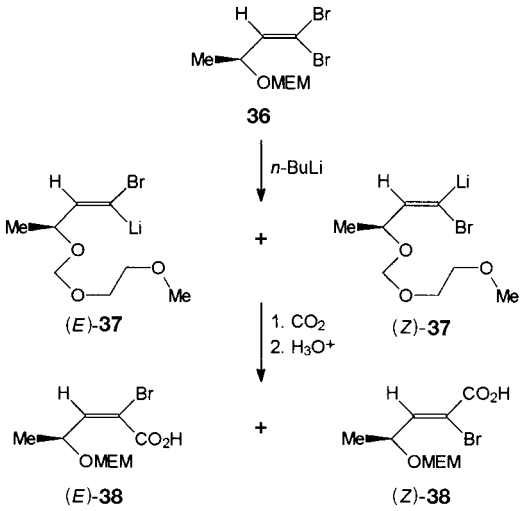
The stereochemistry of the reaction of butyllithium with 1,1-dibromo- and 1,1-dichloroalkenes, by which a halogen atom in a *Z* or *E* position with respect to a β substituent can in principle be replaced, is not uniform. As the example of the tetralin derivative **34** shows, bulky groups seem to favor lithiation in the *Z* position. The vinyl chloride obtained after protonation of **35** shows an *E*:*Z* ratio of over 98:2 [Eq. (11)].[70] As the formation of the diastereomer (*E*)-**35** by kinetically controlled attack on the sterically more hindered chlorine atom of alkene **34** is improbable, an equilibrium between (*Z*)-**35** and (*E*)-**35** is assumed in which



(11)

the *E* diastereomer is strongly favored. Apparently, the lithium atom requires less space than the halogen despite being solvated by the solvent.[71]

The effect a possible chelation has on the stereochemistry of the bromine–lithium exchange was investigated with the dibromoalkene **36**. Of the two diastereomeric lithiation

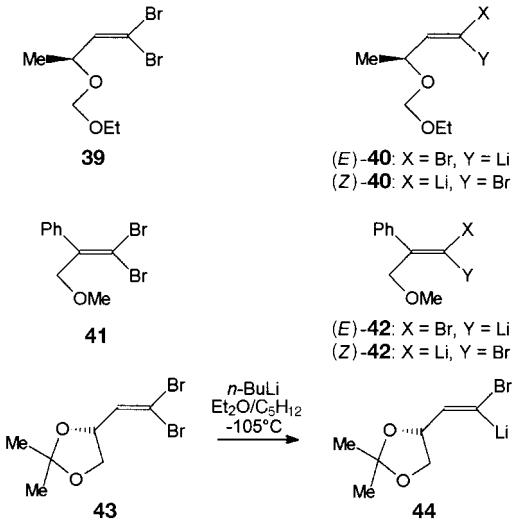


	(*E*)-**38** : (*Z*)-**38**
1.2 *n*-BuLi, THF	32 : 68
0.95 *n*-BuLi, Et_2O	>99 : 1

products **37**, the *E* diastereomer is without doubt thermodynamically more stable because of the lower space requirement of the lithium atom and particularly because of the possibility of intramolecular complexation by the methoxyethoxymethyl (MEM) ether protecting group. Surprisingly, treatment of the dibromoalkene **36** with 1.2 equivalents of *n*-butyllithium in tetrahydrofuran afforded the acids (*E*)- and (*Z*)-**38** in a ratio of 32:68 after carboxylation—apparently as a result of the kinetically favored substitution of the more easily accessible *trans* bromine atom by lithium. On the other hand, exclusive formation of the *E*-configured alkenyllithium compound **37** occurs when slightly less than one equivalent (0.95–0.98 equiv) of butyllithium is slowly added dropwise to a solution of **36** in diethyl ether at $-105\,^{\circ}C$. The diastereomeric carboxylic acids isolated after the reaction with dry ice are formed in a ratio of over 99:1.[72, 73]

The highly stereoselective bromine–lithium exchange in **36** can be explained as an equilibrium in which the two isomeric carbenoids (*E*)- and (*Z*)-**37** as well as the dibromoalkene **36** are involved. Since the latter is present in a slight excess, (*Z*)-**37** can enter into another bromine–lithium exchange with its partner **36**, so that finally the thermodynamically favored isomer (*E*)-**37** results as de facto the only lithioalkene [(*Z*)-**37** + **36** ⇌ (*E*)-**37** + **36**].[73] In an analogue fashion, the selective replacement of the *endo* bromine atom in 7,7-dibromonorcarane was effected.[74]

The outer oxygen atom of the MEM ether apparently plays an important role in the chelation of the lithium atom in the more stable isomer (*E*)-**37**: If the MEM unit is replaced by an ethoxymethoxy group (**39**), the bromine–lithium exchange in the dibromoalkene **39** only leads to an 87:13 mixture of (*E*)-**40** and (*Z*)-**40** under the conditions described for **36**.[73] This



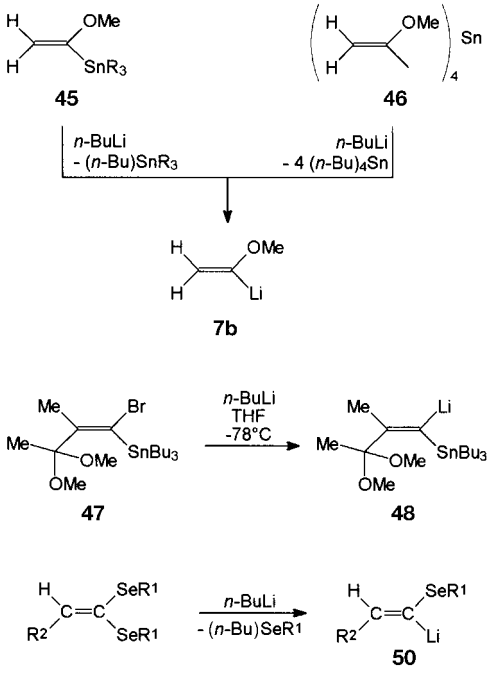
result is in accordance with lithiation of the methyl ether **41**, which affords the diastereomeric carbenoids (*E*)-**42** and (*Z*)-**42** in a ratio of 90:10 in a similar application of thermodynamic reaction control.[71a] On the other hand, the selective bromine–lithium exchange in the dibromoalkene **43** derived from isopropylidene glyceraldehyde is remarkable and leads predominantly (95:5) to the *E*-configured carbenoid **44**, as proven after protonation and carboxylation.[75]

Halogen–lithium exchange is also a method for producing 1-lithioalkenes with oxygen, sulfur, or nitrogen[57, 76] as the α heteroelements. However, it is in general only of preparative importance in special cases, such as with 1,2-dimethoxy-1-lithioethene.[77]

2.3. Metal–Lithium Exchange and Special Methods

Whereas the replacement of mercury, tin, or tellurium by lithium plays an important part in the synthesis of highly unstable di- and polylithiated alkenes,[78] the metal–lithium exchange leading to vinylidene carbenoids is limited to

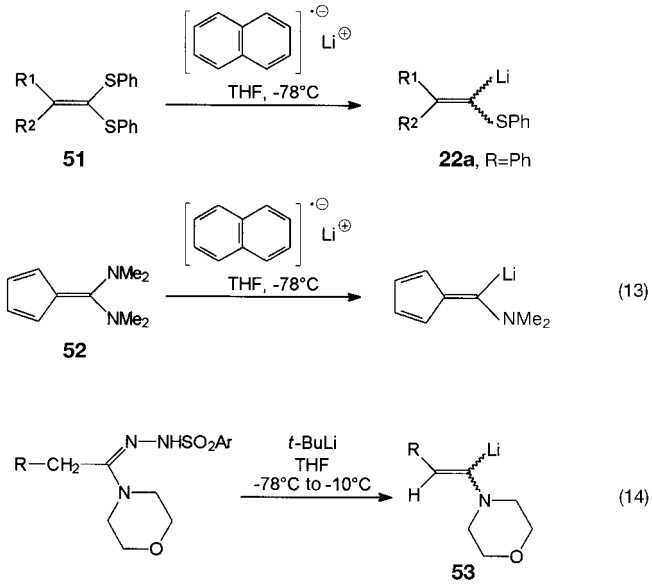
vinylstannanes and vinyl selenides. An alternative to metalation that is seldom used is the reaction of the vinylstannanes **45** and **46** with *n*-butyllithium to form 1-methoxy-1-lithioethene (**7b**) with concomitant formation of the appropriate tetraalkyltin compound.[79] Various α-lithiated vinyl sulfides



(12)

22a are also available by this method.[80] It is, however, unsuitable for generating 1-bromo-1-lithioalkenes **13** (X = Br): The corresponding alkenes, such as **47**, react with butyllithium by way of a bromine–lithium exchange to give metalated vinylstannanes **48**.[81] Clearly, the relatively slow and in principle reversible tin–lithium exchange cannot compete with the halogen–lithium exchange. The substitution of lithium by selenium is used merely for producing lithiated vinyl selenides **50** [Eq. (12)].[80, 82]

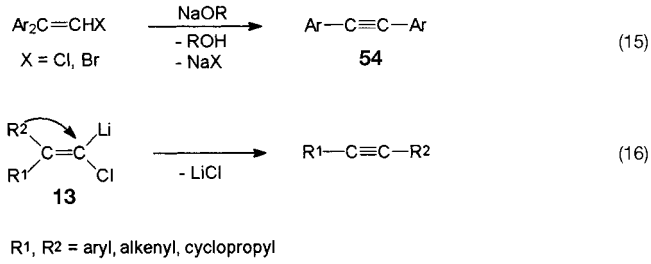
An efficient approach to lithiated vinyl sulfides **22a** is presented by reductive metalation of 1,1-bis(arylthio)ethenes **51** with lithium naphthalenide.[83, 84] The same reagent can also be used to metalate bis(dimethylamino)fulvene **52** [Eq. (13)].[85] The Shapiro reaction, which has found numerous applications in the generation of vinyl anions containing hydrogen or alkyl groups as α substituents,[86] seems to be the only efficient method for access to α-lithiated enamines **53**, which have no anion-stabilizing substituents [Eq. (14)].[87]



3. Reactions of 1-Alkenyllithium Reagents

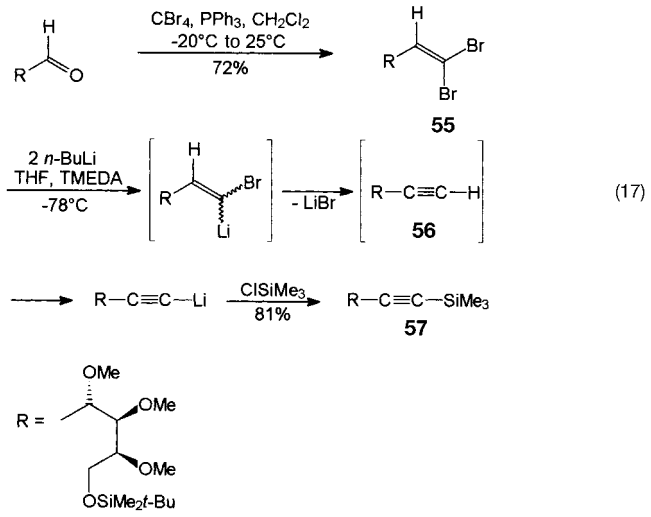
3.1. Reactions Typical of Carbenoids

Only the α-halo- and, to a lesser extent, the α-oxygen-substituted alkenyllithium compounds permit reactions that are typical of carbenoids; alkenyllithium compounds with α-sulfur and nitrogen atoms show carbanionoid reactivity exclusively. Whether 1-halo-1-lithioalkenes react as carbenoids or carbanions depends on the respective partner and, above all, on the reaction temperature. Long before α-halo vinyl anions were established as intermediates, products typical for carbenoid reactions were obtained and characterized: Fritsch, Buttenberg, and Wiechell independently observed at the end of the last century that tolanes **54** are formed upon treatment of 2,2-diaryl-1-haloethenes with sodium alkoxide [Eq. (15)].[88] This intramolecular rearrangement



also occurs in 1-halo-1-lithioalkenes **13** when at least one of the two β substituents is an aryl, alkenyl, or cyclopropyl group [Eq. (16)].[1] If two substituents are capable of undergoing this rearrangement, that in the *trans* position with respect to the halogen atom migrates almost exclusively.[89] The crystal structure of the carbenoid **5** (see Figure 1)[12] gives a plausible explanation for the stereochemistry of the Fritsch–Buttenberg–Wiechell rearrangement. The aryl moiety *cis* to Cl1 makes space for the chlorine atom (C1-C2-C3 129.5°), while that in the *trans* position is bent towards C1 (C1-C2-C9 116.5°). Therefore, migration of the *trans* aryl substituent becomes inevitable, and the free vinylidenecarbene can be ruled out as the intermediate.

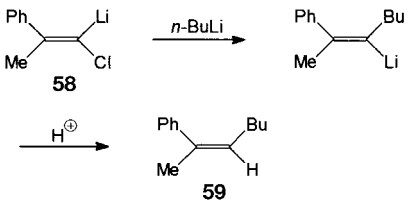
The hydride shift in 1-bromo- and 1-chloro-1-lithioalkenes that is analogous to this rearrangement also takes place at temperatures above $-70\,^{\circ}C$. The reaction is often used to transform aldehydes, which are initially converted into a dihalogenalkene (e.g. **55**) by carbonyl olefination,[90] into alkynes **56** with homologization [Eq. (17)]. If an excess of



(17)

butyllithium is used the deprotonation of the alkyne is already effected in situ, and the reaction with an electrophile directly becomes possible.[90b, d, e, 91] This is illustrated by the formation of the silyl acetylene **57**.[90d]

The carbenoid, electrophilic character of 1-halo-1-lithioalkenes is seen clearly in their reaction with aryl or alkyllithium reagents. Köbrich and Ansari observed that alkene **59** is formed from the *E*-configured alkenyllithium compound **58** with excess butyllithium [Eq. (18)].[5] The



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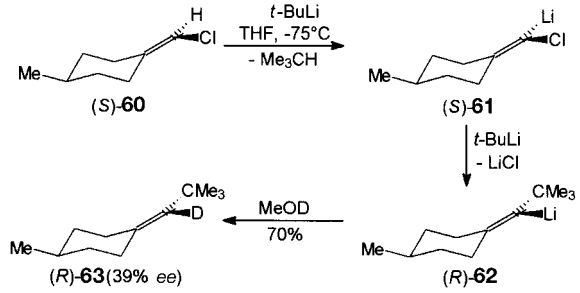
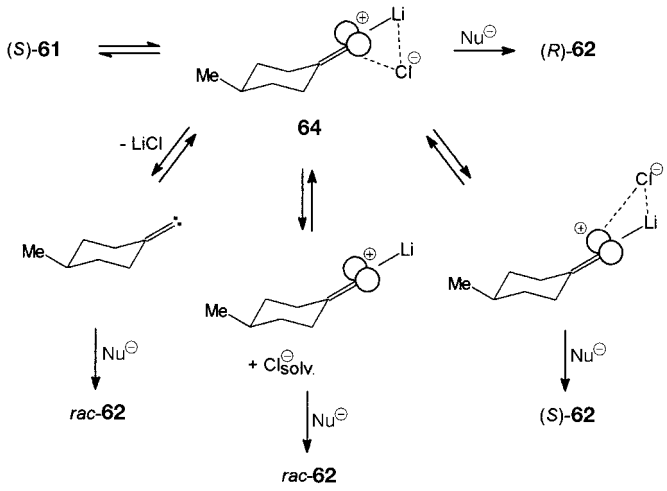


stereochemistry of the surprising reaction was investigated for the chiral chlorolithiocarbenoid **61** (and the corresponding bromine derivative).[6] Metalation of the (*S*)-vinyl chloride **60** with *tert*-butyllithium leads to the likewise *S*-configured carbenoid **61**. This reacts further with *tert*-butyllithium to the alkenyllithium compound **62**, which was detected by deuterolysis to alkene **63** with *R* configuration; this, however, exhibits an enantiomeric excess of only 39%.

Nucleophilic substitution at the vinylidene carbenoid **61**, which takes place with at least partial inversion, can be explained by the following mechanism: At a temperature

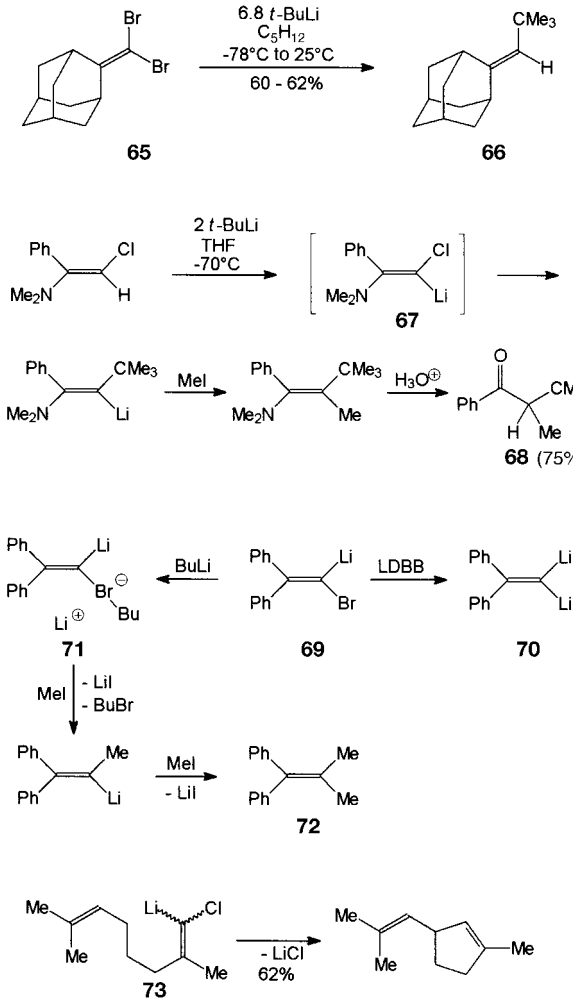


which is typical for every carbenoid, a loosening of the carbon–halogen bond takes place supported by the lithium atom, which remains bonded to the carbon atom ("metal-assisted ionization"). Thus, the nucleophilic vinyl anion **61** is transformed into an electrophilic species, the carbenoid **64**. Rehybridization occurs along with the ionization, and the positive charge is localized in the p orbital of the intimate ion pair. Whereas the lithium atom is colinear with the double bond, the chiral information is preserved by the chloride ion, which occupies one of the enantiotopic faces. The nucleophile Nu^- (in this case *tert*-butyllithium) enters on the side facing away from the chloride, resulting in inversion of configuration in **62** and, after deuterolysis, **63**. The observed partial racemization—that is, the formation of *rac*-**62**—could be caused by the separation of cation and anion by the solvent, the formation of an achiral carbene by completed α-elimination, or the migration of the chloride ion associated with the lithium atom to the enantiotopic face. The latter would lead to inversion of the configuration for **61**.

The ^{13}C NMR spectroscopic studies by Seebach et al.[10] are compatible with an assumed intimate ion pair **64**, which verifies the electrophilic character of the carbenoid carbon atom. The low-temperature crystal structure analysis of the vinylidene carbenoid **5** by Boche et al.[12] comes closer to the idea of the alkenyllithium compound **61** (nonlinearity of the C-C-Li bond); however, the beginning rehybridization is already indicated in this structure.

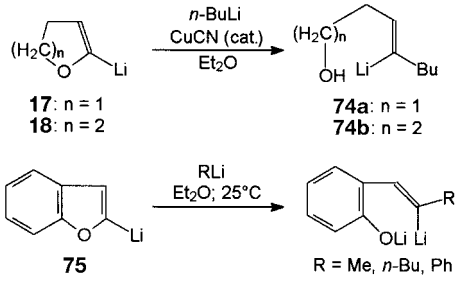
The nucleophilic attack of *tert*-butyllithium on the highly reactive vinylidene carbenoids allows the synthesis of sterically hindered alkenes: Thus, the reaction of the dibromoalkene **65**, which is available from adamantanone, affords neopentylideneadamantane **66**, with three bulky substituents at the double bond, in 62% yield.[92] A *tert*-butyl group can also be introduced into β-chloro enamines by making use of the carbenoid reactivity of the lithium compound formed in the primary deprotonation step. After hydrolysis of the enamine, the ketone **68** is finally obtained via **67** [Eq. (19)].[93]

There has been no lack of attempts to replace the remaining halogen atom by lithium in 1-bromo-1-lithioalkenes in order to acquire geminally dimetalated alkenes. This exchange is possible by, for example, the reaction of **69** with lithio-4,4'-di-*tert*-butyl biphenyl (LDBB) to form **70**. However, the



dilithium compound **70** is not formed in the reaction of **69** with butyllithium, as the alkylation to alkene **72** seems to show [Eq. (20)]. Rather in this case, the reaction with iodomethane proceeds successively with the participation of a quasi-dianion complex ("QUADAC") **71**.[2, 78]

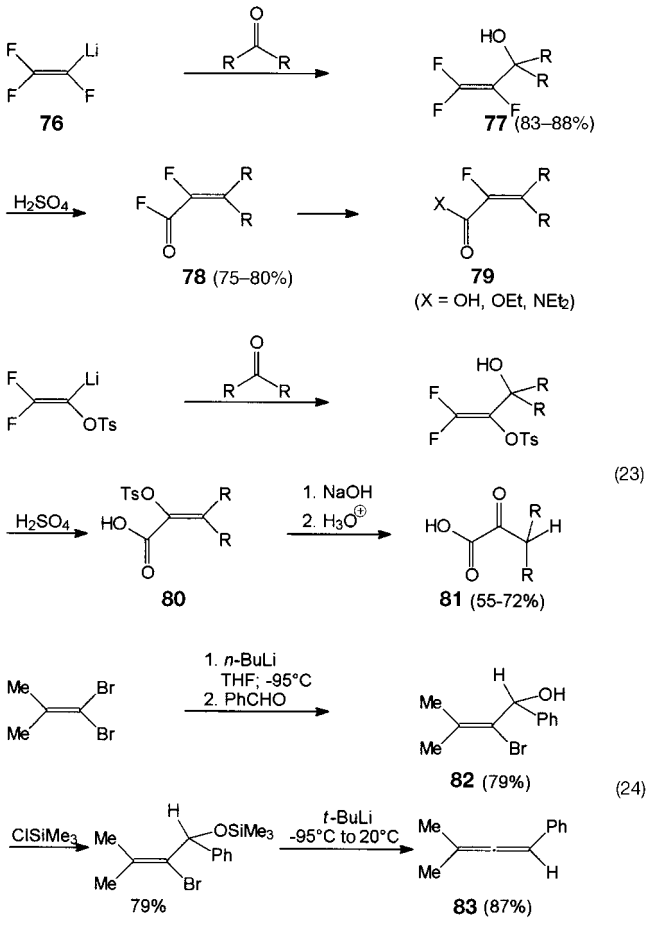
Finally, the carbenoid character of α-lithiated vinyl halides shows itself also in the formation of 1,2,3-butatrienes[94] as well as in the C–H insertion [for example with diene **73**,[95] Eq. (21)] and intramolecular cyclopropanations.[96] Reactivity typical of carbenoids is also displayed by α-lithiated vinyl ethers. For example, the metalated heterocycles **17** and **18** react with *n*-butyllithium to provide the substitution products **74a** and **74b**, respectively, with inversion of configuration at the carbenoid carbon atom.[97] For preparative purposes, the addition of catalytic amounts of CuCN is recommended.[98, 37c] α-Lithiated benzofuran (**75**) undergoes an analogous ring-opening reaction with alkyllithium compounds [Eq. (22)].[97]



3.2. Reactions Typical of Carbanions

α-Heteroatom-substituted 1-alkenyllithium compounds are usually employed as nucleophilic reagents with suitable electrophiles. In the case of the α-halo- and α-oxygen-substituted derivatives, the carbenoid reactivity can be suppressed by maintaining appropriately low temperatures (see **61** and **64**). No attempt will be made to list the reactions of the alkenyllithium reagents **2** with standard electrophiles; instead, synthetically important conversions of vinyl anions **2** and their follow-up reactions will be presented.

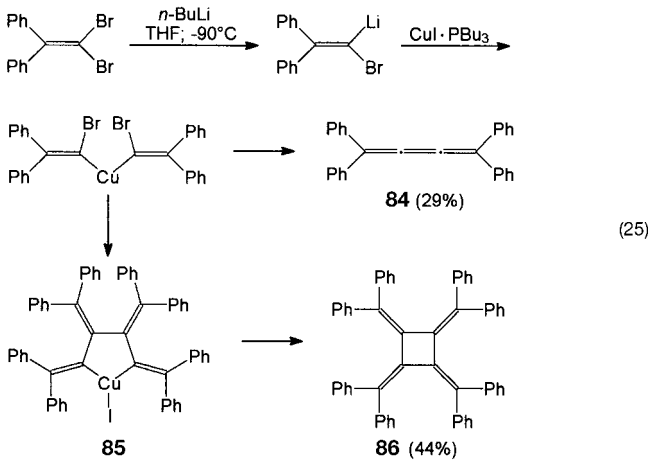
Trifluorovinyllithium **76**, which is available by deprotonation or chlorine–lithium exchange, reacts with ketones to carbinols **77**, as expected. Upon treatment with sulfuric acid,



the carbinols rearrange to acyl fluorides **78**, which can react further to yield α-fluoro-substituted acrylic acid derivatives **79**.[28] The α-sulfonyloxypropenoic acids **80** [Eq. (23)] available in a similar manner can be hydrolyzed to α-oxocarboxylic acids **81** in 55–72% overall yield [based on 2,2,2-trifluoroethyl *p*-toluenesulfonate, Eq. (23); see Section 2.1.].[42] The benzaldehyde adduct **82** of lithiated 1,1-dibromo-2-methyl

propene (**82**) serves as a precursor for an allene synthesis [Eq. (24)]: The hydroxy group is transformed into a leaving group by silylation; a second bromine–lithium exchange affords the allene **83** under spontaneous β-elimination.[20]

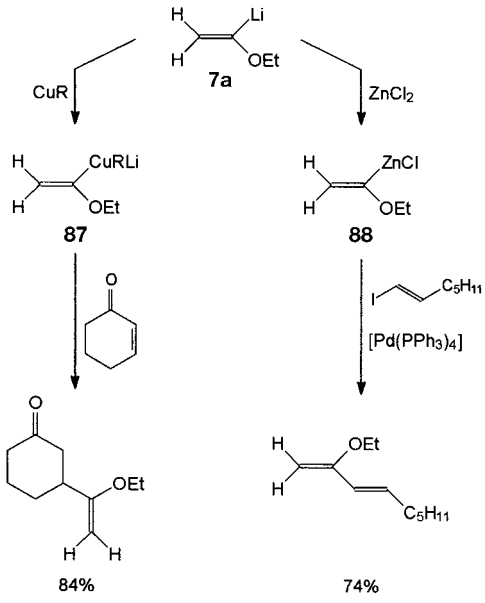
A simple synthesis of the [4]radialene skeleton starts from 1-bromo-2,2-diphenyl-1-lithioethene [Eq. (25)]. Transmetalation with $CuI \cdot PBu_3$ affords, in addition to cumulene **84**, tetramethylene cyclobutane **86** as the main product, whose formation is postulated to proceed via the cuprate **85** as an intermediate.[99]



(25)

The metalation of vinyl ethers followed by reaction with electrophiles and hydrolysis is a simple and efficient method for carbonyl umpolung.[31] The range of applications is considerably increased by the possibility of transmetalating 1-lithioethenes **7a** and **7b**: Cuprates **87** allow 1,4-additions to α,β-unsaturated carbonyl compounds,[100] the zinc reagent **88** can be coupled with aryl or alkenyl iodides under palladium catalysis [Eq. (26)],[101] and the ate complex **89** produced in situ with trialkylborane reacts with transfer of an alkyl group upon warming [Eq. (27)].[102] Starting from an *E*/*Z* mixture of 1,2-dimethoxylithioethene, the tungsten and chromium carbene complexes **90** and **91** can be obtained [Eq. (28)], which, according to NMR spectroscopy, are present in the form of diethyl ether or tetrahydrofuran adducts as pure *Z* isomers.[77b] Further examples for the metalation of 1-alkenyl ethers with electrophiles and follow-up reactions are given in Table 1; it becomes clear that the versatility of the method is guaranteed especially by a particularly broad spectrum of substrates that ranges from simple vinyl ethers over methoxyallene[103, 104] to glucals.[105] In the case of the latter, tin–lithium exchange is used in addition to deprotonation.

In principle, vinyl sulfides are also suitable as equivalents of acyl anions;[45–48] however, the liberation of the carbonyl group is in general more difficult than with vinyl ethers. An exception is given in the simple acid-catalyzed transformation of vinyl sulfide adducts with aldehydes to α-thiolated ketones **92** [Eq. (29)].[46a, 47a] Starting with the *ortho* lithiation of the benzamides **93**, deprotonation of the intermediate vinyl sulfide **94** offers a possibility for a quinone anellation in a one-pot reaction.[106]



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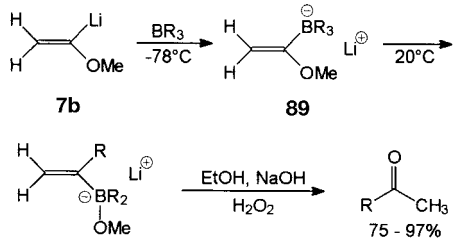

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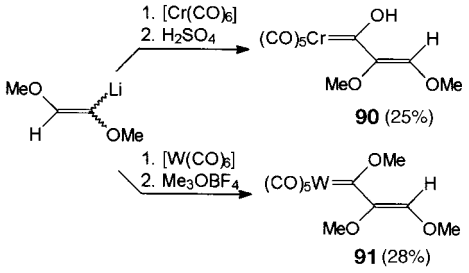
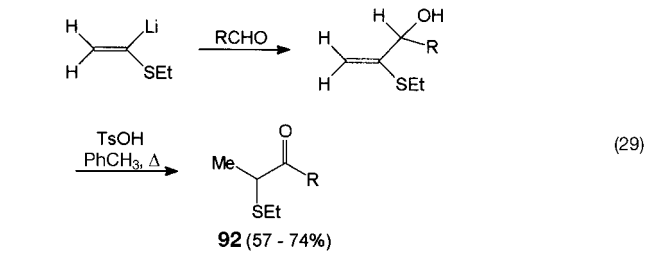


(28)

A new stereocenter is generated when α-heteroatom-substituted 1-alkenyllithium reagents are added to chiral aldehydes or ketones, and the formation of two diastereomeric products has to be anticipated. Reactions which proceed with high stereoselectivity and use enantiomerically pure carbonyl compounds as substrates are of particular interest ("substrate-induced stereoselectivity"[116]). It is hardly surprising that high diastereoselectivities in such reactions were only achieved with cyclic ketones; representative examples are shown in Table 1. The addition of the alkenyllithium compounds normally follows the same course as for other nucleophiles on the corresponding substrate.[117] Thus, estrone methyl ether is attacked by 1-methoxy-1-lithioethene (**7b**) exclusively from the α face[106]—a nucleophilic addition that is typical for 17-ketosteroids.[118] When polar organometallic compounds are allowed to react with α-alkoxy



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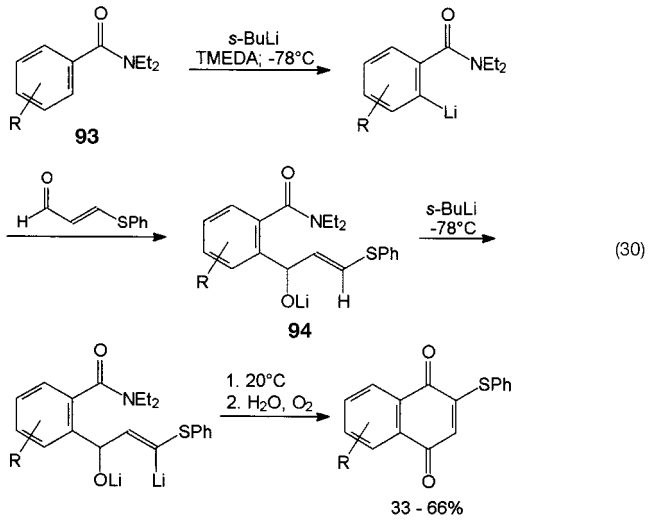
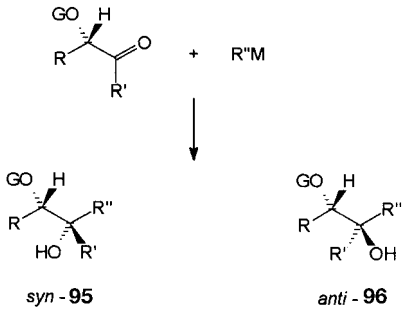


(30)

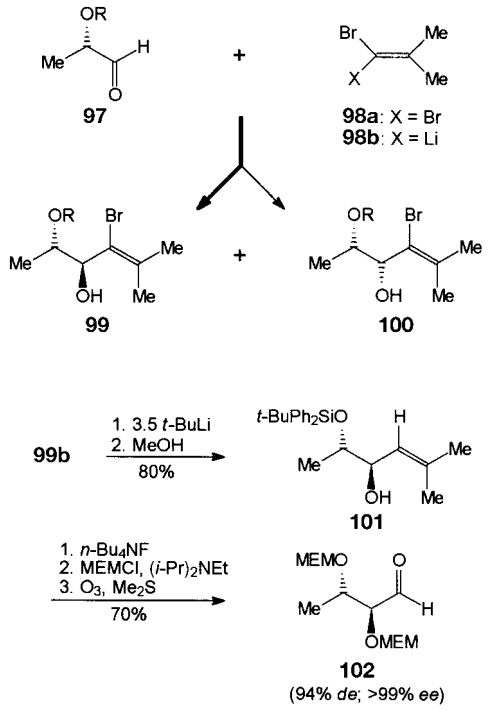
aldehydes or ketones whose carbonyl group is not integrated in a ring, the transformation to the alcohols **95**[117] is more or less stereoselective in the sense of "chelate control" (Scheme 2).[119] This result can plausibly be explained with



Scheme 2. Stereochemical process of the addition of polar organometallic compounds R″M to α-alkoxyaldehydes and -ketones (G = protecting group). Products of chelate control (left) and nonchelate control (right).

Cram's cyclic model.[120] "Nonchelate control"[119] leading to the diastereomeric carbinols **96**, sometimes referred to as Felkin – Anh selectivity,[121] can only be achieved with difficulty by adding lithiumorganic compounds to α-alkoxyaldehydes.[117] Therefore, the reactions of alkenyllithium compounds with chiral aldehydes are still characterized by unsatisfactory diastereoselectivity,[123] despite great progress in the area of acyclic stereoselection;[122] examples for this are also given in Table 1.

For some time now, we have used α-bromo-substituted 1-alkenyllithium reagents as nucleophilic acylating agents which allow stereoselective additions of formyl, formiate, and acyl d^1 synthons ($^-$CHO, $^-$COOH, $^-$COR) to aldehydes and imines.[72, 73, 124–130] The reaction of achiral 1-bromo-1-lithio-2-methyl-1-propene (**98b**), generated from the dibromoalkene **98a** by bromine – lithium exchange, with the MEM-protected enantiomerically pure (*S*)-lactaldehyde **97** is expected to result in the formation of the *syn* alcohol **100a** since the α-MEM ether moiety seems predestined to direct the reaction in the sense of chelate control (Scheme 3).[132] Surprisingly,



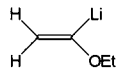
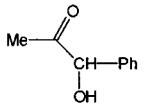
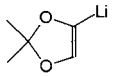
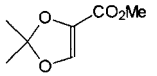
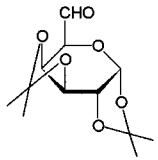
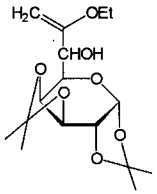
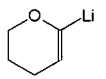
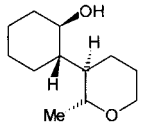
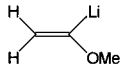
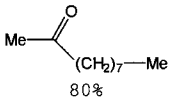
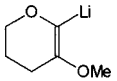
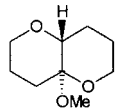
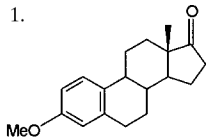
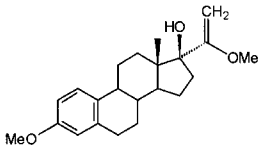
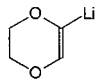
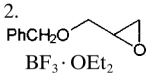
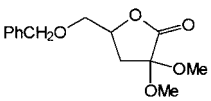
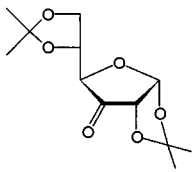
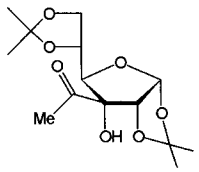
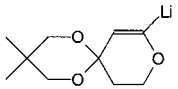
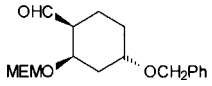
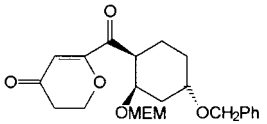
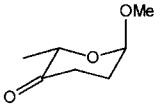
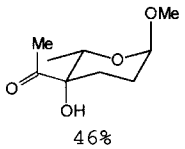
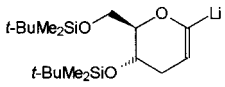
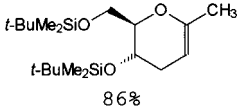
	R	99 : 100	99+100
97, 99, 100 a	MEM	92 : 8	92%
b	t-BuPh$_2$Si	>97 : 3	84%
c	ThexMe$_2$Si	95 : 5	93%

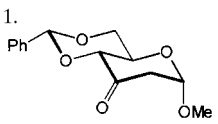
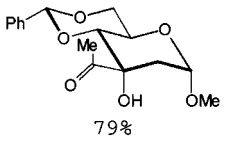
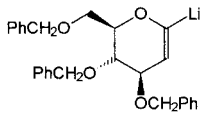
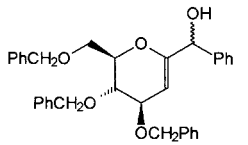
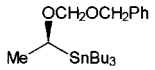
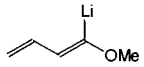
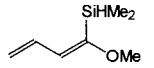
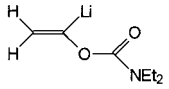
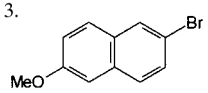
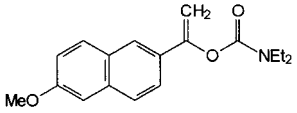
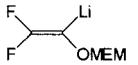
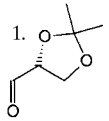
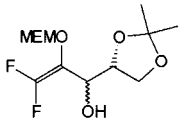
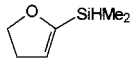
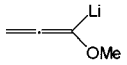
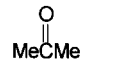
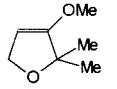
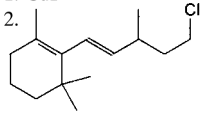
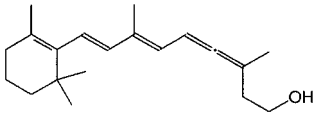
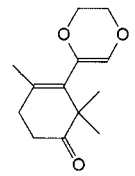
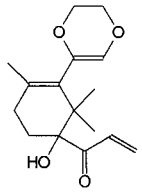
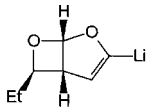
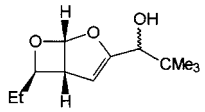
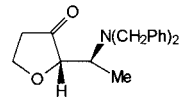
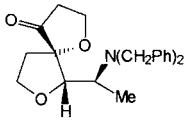
Scheme 3. Diastereoselective introduction of the formyl d^1 synthon $^-$CHO into lactaldehyde **97** by reaction with the lithioalkene **98b**. MEM = $MeOCH_2CH_2OCH_2$, Thex = $Me_2CH{-}CMe_2$.

however, the *anti*-carbinol **99a** is the favored product as a result of Felkin – Anh selectivity (*anti*:*syn* = 92:8). When the MEM group is replaced by silyl ethers (**97b**, **c**) the selectivity can be increased in favor of the nonchelate-controlled products (**99b**, **c**).[124, 126] To illustrate that the carbenoid **98b** can serve as an equivalent of a formyl d^1 synthon, the silyl ether **99b** (95% *de*) was transformed into the alkene **101** by another bromine – lithium exchange followed by protonation. Subsequent desilylation to the diol, protection of both hydroxy groups as MEM ethers, and ozonolysis led to the α,β-dialkoxyaldehyde **102** with a diastereomeric excess of 94%. Since the reaction starts with enantiomerically pure lactaldehyde and no racemization occurs during the course of the sequence, the enantiomeric excess is greater than 99%.[126]

The alkene **99c**, which is obtained with 90% *de* by the stereoselective reaction of the alkenyllithium compound **98b**,

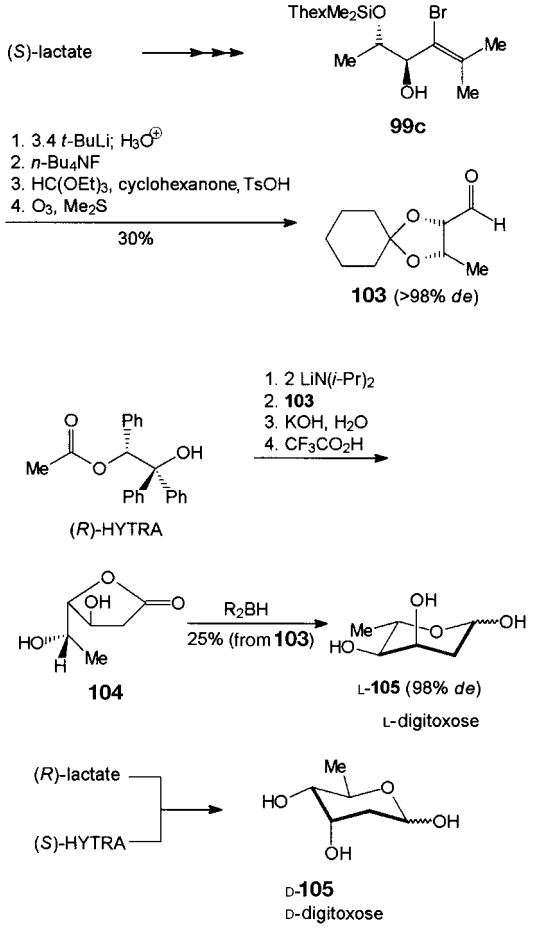
Table 1. Reactions of α-lithiated vinyl ethers.

α-Lithiated vinyl ether	Electrophile Follow-up reagents	Product Yield	Ref.	α-Lithiated vinyl ether	Electrophile Follow-up reagents	Product Yield	Ref.
	1. PhCHO 2. HCl, H_2O, MeOH	 57%	[31a]		1. $ClCO_2Me$	 72%	[67]
	1. 	 67% (1:1 diastereomeric mixture)	[31b]		1. Me_3Al 2.  3. $BF_3 \cdot OEt_2$	 78%	[38c]
	1. $Me(CH_2)_7I$ 2. HCl, H_2O, MeOH	 80%	[33]		1. $I(CH_2)_3OCH_2Ph$ 2. Me_3SiCl, NaI, MeCN 3. H_2, Pd/C 4. MeOH, H^+	 41%	[113]
	1. 	 83%	[107]		1. CuCN, LiCl 2.  $BF_3 \cdot OEt_2$ 3. 3-chloroperbenzoic acid 4. TsOH, MeOH 5. Ag_2CO_3, celite	 60%	[40e]
	1.  2. HCl, H_2O, dioxane	 37%	[108]		1.  2. H_3O^+ 3. Swern oxidation	 71%	[114]
	1.  2. HCl, H_2O, dioxane	 46%	[109]		1. CH_3I	 86%	[105a]

	1.  2. HCl, H_2O, dioxane	 79%	[109]		1. PhCHO	 89% (1:1 diastereomeric mixture)[b]	[105a]
	1. Bu_3SnCl 2. (*R*)-BINAL-H 3. $PhCH_2OCH_2Cl$, iPr_2NEt	 90% *ee*	[110]		1. Me_2SiHCl	 77%	[115]
	1. $ZnBr_2$ 2. $[PdCl_2(dppf)]$[a] (cat.) 3. 	 88%	[41d]		1. 	 26% (6:4 diastereomeric mixture)	[44b]
	1. Me_2SiHCl	 50%	[37a]		1.  2. KO*t*Bu, DMSO	 78%	[103a]
	1. CuI 2.  3. 2 MeLi	 55%	[111]		1.  2. TsOH, H_2O, acetone	 90%	[103e]
	1. Me_3C–CHO	 72% (1:1 diastereomeric mixture)	[112]		1.  2. KO*t*Bu, DMSO 3. H_2SO_4, THF	 84%[c]	[114]

[a] dppf = bis(diphenylphosphanyl)ferrocene. [b] Synthesized by tin–lithium exchange. [c] Diasteromeric ratio: 93:7.

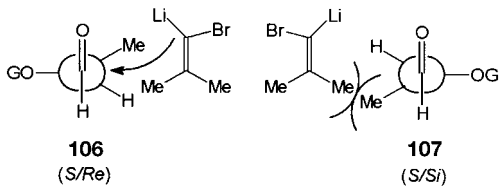
serves as the starting material for the synthesis of digitoxose (**105**) represented in Scheme 4.[127] As this carbohydrate is present in different organisms in both enantiomeric forms, a synthesis was conceived which leads to D- and L- digitoxose. The bromoalkene **99c** was first converted into the aldehyde



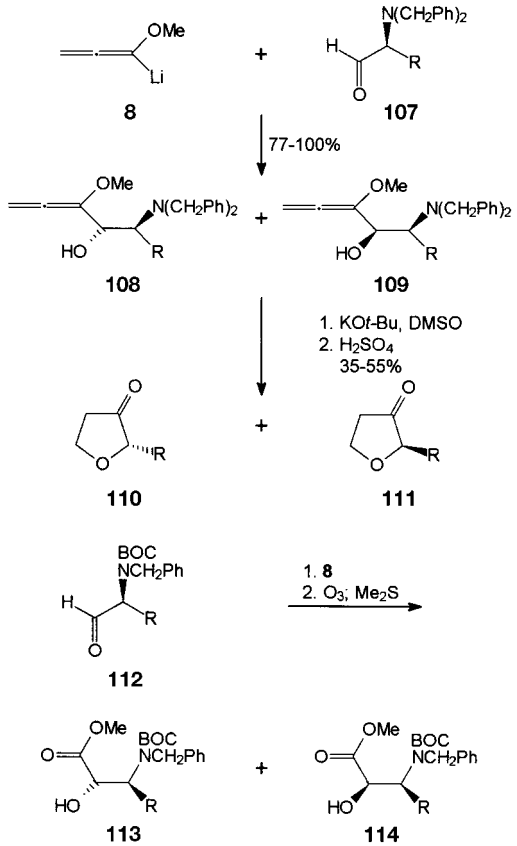
Scheme 4. Synthesis of L- and D-digitoxose.

103 (whose diastereomeric excess is increased to 98% *de* after distillation) by dehalogenation, transformation of the protecting group, and ozonolysis. Lengthening of the carbon backbone by introducing an acetate group proceeds successfully with (*R*)-HYTRA.[131] After removal of the minor diastereomer, the lactone **104** was transformed to L-digitoxose (L-**105**). Since both (*R*)-lactate (*ent*-**97c**) and (*S*)-HYTRA are easily available, D-digitoxose (D-**105**) was obtained in the analogous, enantiomeric sequence.

The extremely strong tendency of 1-bromo-1-lithio-1-alkenes to react in a nonchelate-controlled way, which stands in striking contrast to the low diastereoselectivity with α-unsubstituted 1-lithioalkenes, could be caused by the special structural properties of the carbenoid. Bearing in mind the high p character of the carbon–halogen bond as well as the small X–C=C angle involved, the Felkin–Anh model for the transition state (**106**) could offer an explanation for the preferred *ul* topicity[133] (i.e., attack at the *Re* face of the carbenoid **98b** on (*S*)-**97**): It seems plausible that the alternative reactive conformation **107** is less favored because of steric interaction between the methyl group of the chiral center in the aldehyde and the alkene.[126]



Similar stereochemical behavior with regard to chiral aldehydes is shown by the lithiated methoxyallene **8**, which also reacts with N,N-dibenzylated α-amino aldehydes **107** preferably with nonchelate control to yield *anti*-carbinols **108** (Scheme 5). Diastereomeric ratios **108**:**109** for these reactions

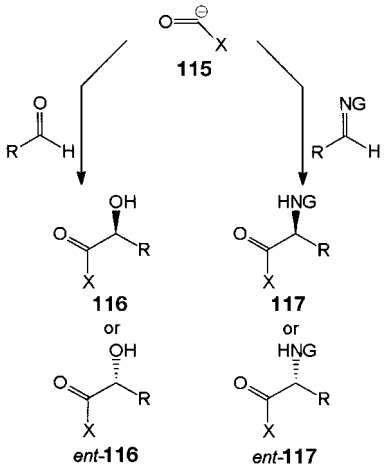


Scheme 5. Addition of lithiated methoxyallene **8** to N-protected α-amino aldehydes **107**. R = Me, $PhCH_2$, $Me_2CH–CH_2$.

can reach 80:20 to 95:5. Reaction with potassium *tert*-butoxide and subsequent acid hydrolysis enables the transformation of allenes **108**/**109** to furanones **110**/**111**.[103d, 134] On the other hand, ozonolysis of the adducts of **8** to the aldehydes **112** (diastereomeric ratios 74:26 to 85:15) offers an approach to N-protected α-hydroxy β-amino esters **113**/**114**.[135] The Felkin–Anh model also offers a plausible explanation for the nonchelate-controlled addition of the metalated allene **8**.

The enantioselective introduction of synthons **115** with umpoled carbonyl reactivity (d^1 reactivity[4]) into *achiral* aldehydes and imines was an unsolved problem of asymmetric

synthesis for a long time. This is surprising considering the large number of α-heteroatom-substituted carbanions[136] which serve as equivalents for the aforementioned synthons and have become extremely important reagents for carbon–carbon bond formation, however, leading to racemic products with aldehydes and imines. Enantiomerically pure acyloins and α-hydroxy carboxylic acids (**116** and *ent*-**116**, respectively) as well as α-amino acids and α-amino aldehydes (**117** and *ent*-**117**, respectively) can be obtained either by using chiral d^1 reagents or by combining achiral substrates with chiral additives (Scheme 6). With the second concept, the addition

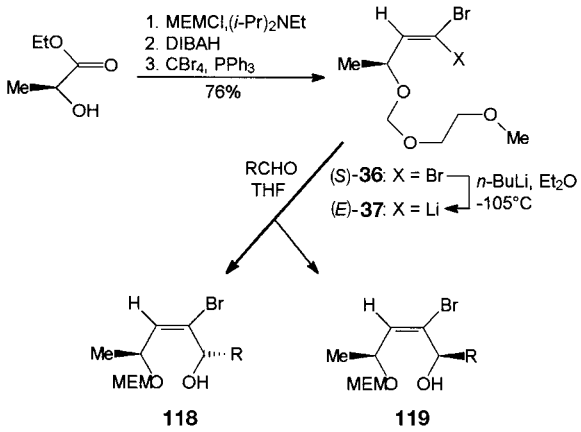


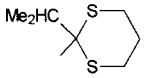
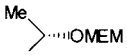
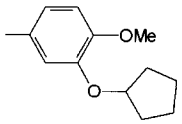
Scheme 6. Synthesis of enantiomerically pure α-hydroxy and α-amino-carbonyl compounds by the addition of chiral d^1 synthons **115** to aldehydes and imines. X = H, OH; G = protecting group.

of nucleophilic acylating agents in the presence of chiral ligands, only modest enantioselectivities are achieved for the most part.[137] On the other hand, α-heteroatom-substituted carbanions with covalently bound chiral auxiliaries are also rare;[138, 139] in some cases the chiral information is not easily introduced and is destroyed upon liberation of the target molecules, and in other cases the extent of stereoselectivity is modest.[140] More successful are different approaches which are not based on the direct addition of chiral synthons to aldehydes, but still lead to nonracemic α-hydroxy[141] and α-amino carbonyl compounds[142] in a roundabout way.

In the search for alkenyllithium reagents that serve as equivalents for d^1 synthons and can be enantioselectively introduced into aldehydes and imines, we followed the concept of a covalently bound auxiliary. Therefore, the chiral information should be localized in the allyl position of the vinyl anion and mediated by an ether group that chelates the lithium atom. These structural features are present in the 1-bromo-1-lithio-1-alkenes (*S*)- and (*R*)-**37**, which are available from the (*R*) and (*S*) lactates. Considerable stereoselectivity can only be expected for the addition to aldehydes or imines if the lithium atom is in the *Z* position with respect to the chelating ether group. This "conditio sine qua non" is met by the selective bromine–lithium exchange to (*E*)-**37** described in Section 2.2.

The dibromoalkene (*S*)-**36** is accessible in three steps from (*S*)-ethyl lactate on a 150-g scale by introduction of the MEM protecting group, reduction to the O-protected lactaldehyde,[143] and carbonyl olefination (Scheme 7).[90] (*R*)-Isobutyl



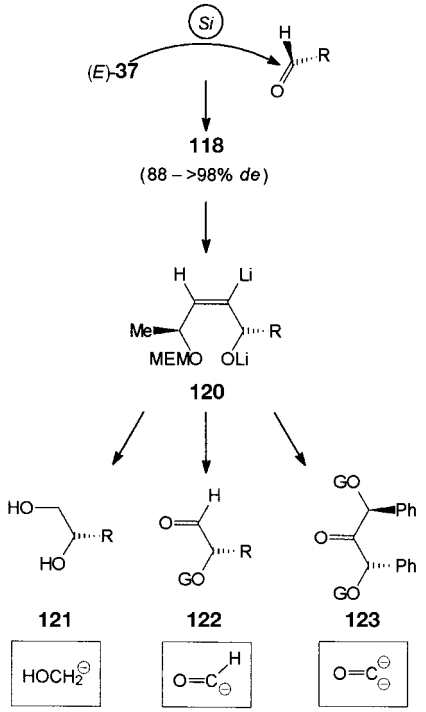
	R	118 : 119	118+119
118, 119 a	Me_2CH	94 : 6	87%
b	Me_2HC 	99 : 1	71%
c		95 : 5	92%
d		98 : 2	76%
e		96 : 4	95%
f	Ph	>99 : 1	93%
g		>99 : 1	92%

Scheme 7. Production and stereoselective addition of the lithioalkene (*E*)-**37** to aldehydes.

lactate is the analogous starting material for the enantiomeric sequence. The alkenyllithium reagent (*E*)-**37** generated from (*S*)-**36** at $-105\,^{\circ}C$ in diethyl ether adds to aliphatic and aromatic aldehydes with good diastereoselectivities after the addition of tetrahydrofuran. In all instances the *S*-configured lithioalkene **37** preferentially attacks the aldehyde from the *Re* face (*ul* topicity), and the predominant to almost exclusive formation of the diastereomers **118** results. In the case of the chiral *S*-configured aldehydes, combination with **37** leads to "matched pairs".[144] The tendency of the aldehydes to react with 1-bromo-1-lithioalkenes under nonchelate-control (substrate-induced) and the *ul* topicity displayed by the reagent (*S*)-**37** (reagent-induced) amplify each other, and allow the formation of carbinols **118c–e** with diastereomeric excesses of 90–96%. Whereas the reactions of (*E*)-**37** proceed with high stereoselectivity, those of analogous alkenyllithium compounds (H, Ph, SO_2Ph instead of Br in (*E*)-**37**) display only little differentiation between the enantiotopic faces of an aldehyde. Only the lithiated thioether (SMe instead of Br in (*E*)-**37**)[46c] shows a comparable diastereoselectivity.[145] If one

takes into account the importance of the outermost oxygen atom of the MEM ether group for the chelation of the lithium atom, it comes as no surprise that the bromolithioalkene (*E*)-**40** with a shorter ether protecting group only affords a 6:1 diastereomer mixture for the reaction with benzaldehyde.

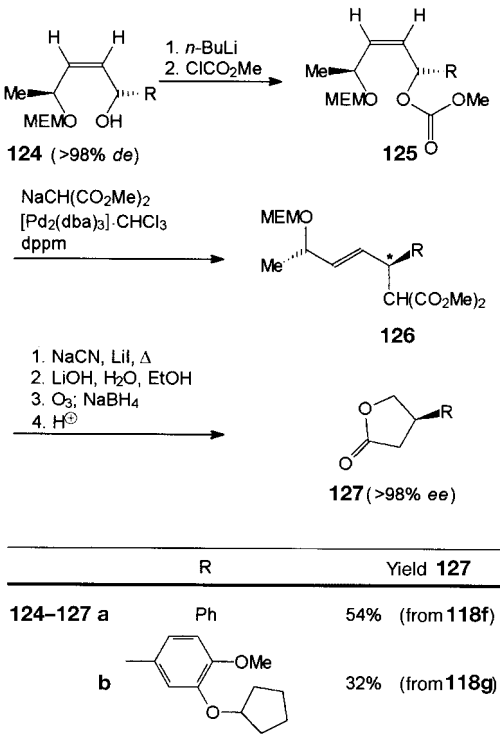
The dilithium compounds **120** can be obtained after one more halogen–lithium exchange in tetrahydrofuran from the bromoalkenes **118** (Scheme 8), which are available in 88 to



Scheme 8. Synthesis of 1,2-diols **121**, O-protected α-hydroxyaldehydes **122** and α,α'-dialkoxyketones **123** by stereoselective attack of the lithioalkene (*E*)-**37** on the *Si* face of aldehydes.

over 98% *de*. This step takes place under complete retention of configuration of the double bond, as proven by protonation to (*Z*)-alkenes.[146] Depending on the workup conditions of the subsequent ozonolysis, (*S*)-diols **121** or—after introduction of a protecting group at the alkene stage—O-protected α-hydroxyaldehydes (*S*)-**122** can be obtained. When the dilithium compound **120** (R = Ph) is allowed to react with benzaldehyde instead of a protic compound, the analogous sequence leads to C_2-symmetrical ketones **123**.[128] The enantiomeric excesses of products **121**, **122**, and **123** (the stereoselectively introduced synthon is given under each formula in Scheme 8) correspond to the respective diastereomeric excesses of the monobromoalkenes **118**.

The aryl-substituted allyl alcohols **124a**, **b**, which are obtained with over 98% *de* and an optical purity of 99% *ee* by protonation of **120**, serve as starting materials for an efficient palladium-catalyzed chirality transfer (Scheme 9).[130] For this the free hydroxy group of the alkenes **124**, which are present as pure *Z* isomers (this is essential, as shown below), is transformed into a leaving group by conversion into the carbonates **125**. The subsequent substitution with sodium dimethyl malonate in the presence of 4–5 mol% of the

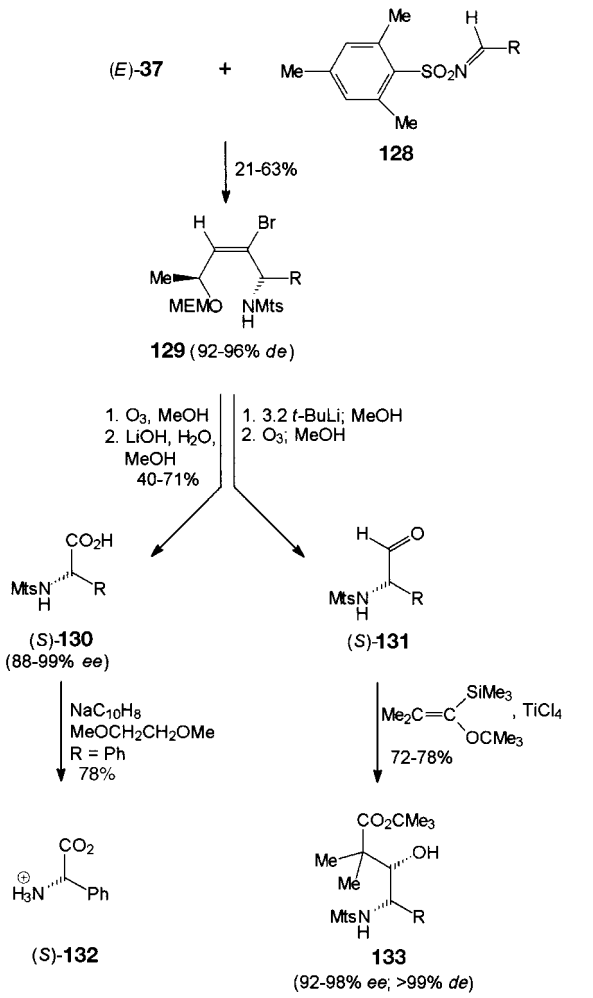


	R	Yield **127**
124–127 a	Ph	54% (from **118f**)
b	OMe	32% (from **118g**)

Scheme 9. Synthesis of chiral lactones **127** from allyl alcohols **124** by palladium-catalyzed chirality transfer.

dibenzylideneacetonepalladium complex $[Pd_2(dba)_3]\cdot CHCl_3$ and bis(diphenylphosphino)methane (dppm) affords the alkenes **126** as single isomers. This course of the reaction is unusual with respect to its stereo- and regiochemistry. Whereas palladium-catalyzed allylic substitutions usually proceed with overall retention due to the double inversion,[147] the stereochemical outcome of the conversion of **125** into **126** is in accordance with an inversion at the *C atom combined with rotation about the C–C double bond. These findings can plausibly be explained by assuming a displacement of the carbonate group (which fragments to sodium ethoxide and CO_2 in the process) by the metal with concomitant formation of a palladium π complex, rotation with a π-σ-π transformation,[148] and finally substitution of the palladium, once more with inversion, by the nucleophilic malonate. The completely regioselective exchange of carbonate for malonate without allyl shift, although the latter would lead to conjugation of the double bond with the aromatic system, is also unusual. Model studies[149] suggest that the MEM ether group is responsible for this, possibly by chelating the palladium atom. The lactones **127** can be obtained with over 98% enantiomeric purity from the alkenes **126** by decarboxylation and ozonolysis; derivative **127b** serves as an intermediate in the synthesis of the antidepressant (*R*)-rolipram.

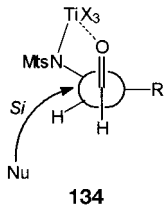
The *S*-configured lithioalkene (*E*)-**37** also adds to mesitylenesulfonylimines **128**, obtained from the corresponding aldehydes RCHO,[150] with preferred attack on the *Re* face with high diastereoselectivity to yield bromoalkenes **129** (Scheme 10). The cleavage of the double bond by ozonolysis in methanol leads directly to the methyl esters,[151] which are saponified without racemization to α-*N*-mesitylsulfonylcarboxylic acids (*S*)-**130**. The possibility of removing the



Scheme 10. Synthesis of N-protected α-amino acids (*S*)-**130** and α-amino alcohols (*S*)-**131** by stereoselective addition of lithioalkene (*E*)-**37** to sulfonylimines **128** and diastereoselective Mukaiyama aldol reaction of the α-amino aldehydes *(S)*-**131** to **133**.

mesitylsulfonyl (Mts) protecting group is shown with the example of the transformation into phenylglycine [(*S*)-**132**]; sodium in ammonia or sodium naphthalenide[152] proved to be the optimal reagents for deprotection without racemization.

As in the case of the allylic alcohols **118**, replacement of the bromine substituent by hydrogen by bromine–lithium exchange and protonation is also possible for the N-protected allylamines **129**. The subsequent ozonolysis then leads to α-sulfonylamino aldehydes (*S*)-**131**, which show the expected conformational lability but can nevertheless be isolated and used in further reactions. To illustrate their synthetic potential these compounds were used as substrates in Mukaiyama aldol reactions[153] with the silyl ketene acetal of *tert*-butyl isobutyrate in the presence of $TiCl_4$. This addition proceeds with very high diastereoselectivity in the sense of chelate control and affords diastereomerically pure alcohols **133** with enantiomeric purities of 92 to 98 % *ee*. The exclusive attack of the silyl ketene acetal on the *Si* face of the N-protected amino aldehyde can be plausibly explained with the transition state model **134**. The efficient chelate control of the Mts protecting group,[154] which was seldom used so far for amines, could also prove worthwhile in other substrates.



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Whereas numerous enantioselective syntheses of α-amino acids are known[142] and a few possibilities for obtaining N-protected α-amino aldehydes[155] have become available, the direct approach by addition of chirally masked formyl or formiate d^1 synthons ($^-$CHO and $^-$COOH) to imines has not been attempted so far. Starting from dibromoalkene **36** or its enantiomer, which are both available from the enantiomerically pure lactates, it is clear that this concept leads to the target molecules with *R* or *S* configuration. For synthetic purposes the N-protected α-amino aldehydes **131** should be of even greater importance than the amino acids themselves.

4. Outlook

The exotic alkenyllithium compounds with electronegative heteroatom substituents in the α position, initially postulated to be short-lived intermediates in α-eliminations, have become useful reagents which can be readily generated in solution and whose chemical behavior is easily understood with the aid of new structural investigations. Owing to their ambiphilia they react with nucleophiles and, far more often, with electrophiles under formation of C–C bonds. Because of the structural unit of the heteroatom-substituted C–C double bond they are suitable for the umpolung of carbonyl reactivity. The possibilities for applying these reagents in asymmetric syntheses have already been demonstrated; further developments in this area can undoubtedly be expected. As far as the carbanionic reactions of the α-heteroatom-substituted alkenyllithium reagents are concerned, an essential future development should lie in the enantioselective control of nucleophilic additions by chiral complexing agents and ligands.

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