

aspects of heteroatom-assisted metalations, and Lever⁷ address early work in this area.

This review is divided into three sections, dealing in order with the chemistry of α -metalated derivatives of (1) acyclic vinyl ethers (**B**), (2) alkoxyallenes (**C**) and (3) non-aromatic cyclic vinyl ethers (**D**). Each section is further subdivided into increasingly more complex or more highly substituted variants of the parent system. The intention of this review is to highlight the practical synthetic applications of these general classes of organometallic reagents. Therefore, within each subclass of α -metalated vinyl ether the discussion will encompass both the generation and the subsequent reactivity of the organometallic species since an analysis of both of these factors is necessary in order to assess its applicability and utility in organic synthesis.

In most cases, the initial formation of the α -metalated vinyl ether involves the lithiation, or deprotonation, of the parent vinyl ether with an alkyllithium base. The commonly used reagents are *n*-BuLi, *s*-BuLi and *t*-BuLi but a combination of *n*-BuLi and *t*-BuOK (the Lochmann–Schlosser base) has also been employed. It is beyond the scope of this review to undertake a detailed discussion of the structure of these lithiating reagents or the mechanism of metalation which are covered in excellent general reviews.^{6,8–11} However, a brief mention must be made of these two important aspects.

It is recognized that alkyllithium reagents are oligomeric species and that the state of aggregation and degree of solvation are highly dependent upon the reaction solvent.^{8–11} Moreover, the concentration, temperature and presence of additives such as TMEDA or HMPA can all have a significant impact on the base strength and the facility of the lithiation reaction. As a result, the reactivity of the alkyllithium can be modulated by the appropriate combination of these effectors. In general, reaction conditions that decrease the aggregate size generate the more reactive lithiating species. The characteristics of each alkyllithium species used in the lithiation reactions have been aptly detailed elsewhere.^{6,8–11} The mechanistic details of vinyl ether lithiation reactions have also been reviewed.^{6,8,9} In general, the vinyl ether oxygen can precoordinate the lithiating reagent and direct it to the adjacent α -hydrogen atom rather than the alternative β -hydrogen atom. In addition, the kinetic acidity of the vinyl hydrogen in the α position is greater than the β -vinyl hydrogen due to the presence of the electronegative oxygen atom. This observation may explain the lithiation regioselectivity without necessarily invoking precoordination or precomplexation phenomena. In practice, it is likely that a combination of the two factors is responsible for the lithiation regioselectivity.

2 α -Metalated acyclic vinyl ethers

2.1 1-Methoxy- and 1-ethoxyvinylolithium ($\text{H}_2\text{C}=\text{Cl}\text{I}\text{OR}$; R = Me, Et)

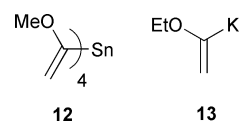
The impetus behind the use of metalated vinyl ethers in organic synthesis began in the early 1970's when Schöllkopf⁴ and Baldwin⁵ recognized that methyl vinyl ether (**7**, MVE) and ethyl vinyl ether (**8**, EVE) could be efficiently converted to 1-methoxyvinylolithium (**9**, MVL) and 1-ethoxyvinylolithium (**10**, EVL), respectively. These species are useful acyl anion equivalents since they readily add to a wide variety of electrophiles and the resulting adducts are converted to the acetyl derivatives **11** under mild acid-catalyzed hydrolysis conditions (Scheme 2).

Interestingly, Paul and Tchelitcheff observed α -metalation of EVE with pentylsodium some 20 years earlier.³

2.1.1 Generation of 1-methoxy- and 1-ethoxyvinylolithium

Baldwin *et al.* demonstrated⁵ that MVE (**7**) is metalated in the α position by the addition of *t*-BuLi in pentane to a cold (-65°C) solution of excess MVE (1.6 equiv. with respect to *t*-BuLi) in THF ($\sim 1.4\text{ M}$) followed by slow warming to 0°C (Scheme 2). The initially produced bright yellow precipitate, shown to be a 2 : 1 *t*-BuLi–THF complex, eventually dissolves ($\sim -45^\circ\text{C}$) and the resulting bright yellow solution becomes colorless (-5 to 0°C) upon formation of MVL (**9**); this solution can be recooled for subsequent use. This procedure, described in an *Organic Synthesis* preparation,¹² has been widely used. Some minor variations have appeared, such as using *n*-BuLi at 0°C in place of *t*-BuLi¹³ and using stoichiometric amounts of MVE and *t*-BuLi.^{14,15} Unfortunately, there are several drawbacks to the preparation of MVL by any of these procedures: (a) MVE (bp $5\text{--}6^\circ\text{C}$) is a gas at ambient temperature and therefore is more difficult to use than EVE (**8**, bp 33°C); (b) the deprotonation of MVE using *t*-BuLi produces small amounts (1–7%) of dilithioacetylene by the formal elimination of methanol.¹⁴ The dilithioacetylene so produced can react with electrophiles and the presence of the resulting acetylenic byproducts can result in purification problems, especially on large scale; (c) by the nature of the synthesis, MVL prepared by the Baldwin procedure is used in the presence of excess MVE which may not be optimum for all subsequent reactions.

To circumvent the last issue, Soderquist^{14,16} developed an alternative procedure for generating MVL. Transmetalation of tetrakis(α -methoxyvinyl)tin **12** with a stoichiometric amount of *n*-BuLi in hexanes at 0°C produces unsolvated MVL which precipitates from the reaction mixture. The precipitate can be purified by washing with hydrocarbon solvent. The tin reagent **12** is prepared in 72% yield by deprotonation of MVE with *t*-BuLi using the Baldwin procedure, reaction with SnCl_4 and distillation and/or recrystallization of the vinyltin reagent **12** from ethanol.¹⁴ The MVL so produced (white solid, highly pyrophoric) is readily soluble in ether or THF and its ^1H NMR spectrum has been obtained in THF-d_8 and C_6D_6 (as a 1 : 1 MVL–THF mixture).



The first deprotonation of EVE was accomplished by Schöllkopf⁴ using *t*-BuLi at -30°C in pentane and a stoichiometric amount of TMEDA. However, the subsequent reaction of EVL with benzaldehyde (43% yield) suggests that this procedure is not optimal and the procedure has rarely been used by others.¹⁷ In addition, the presence of TMEDA is a potential drawback in certain synthetic applications.¹⁸ Alternatively, the Baldwin procedure for the generation of EVL^{19–21} produces a reagent solution that has wide utility in spite of the production of dilithioacetylene ($\sim 3\%$).^{14,22} Unfortunately, the Soderquist preparation of purified, unsolvated EVL from the tetrakis(α -ethoxyvinyl)tin reagent corresponding to **12** is less efficient than the MVL procedure due to the solubility of EVL in pentane.²³ Modifications of the Baldwin procedure for the

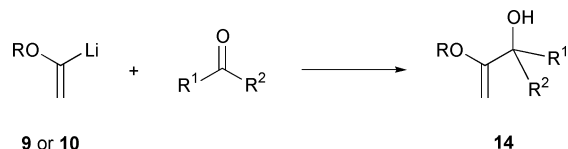
preparation of EVL include (a) the use of *n*-BuLi at 0 °C²⁴ or (b) as reported by Oakes and Sebastian, excess *t*-BuLi²⁵ to effect deprotonation and (c) the slow and careful warming of the mixture undergoing deprotonation to -22 °C.¹⁸ The EVL reagent generated by the Sebastian procedure has been characterized by ¹³C NMR spectroscopy and the vinyl carbon bonded to lithium exhibits the largest downfield shift (61 ppm) with respect to the carbon resonance in the parent EVE.²⁵ Even using these modifications, the resulting EVL solution and subsequent reaction mixtures are often unavoidably contaminated with products resulting from the deprotonation of the THF solvent (acetaldehyde enolate anion and ethylene).^{18,25,26} An interesting modification, introduced by Shimano and Meyers in order to circumvent this latter problem, involves the replacement of THF with tetrahydropyran (THP).^{26,27} The deprotonation of EVE in THP is accomplished by treatment of a -78 °C solution with a slight excess (1.3 equiv.) of *t*-BuLi followed by warming to ~ -3 to -5 °C. The EVL solution so produced is stable at -3 °C for at least 30 minutes and can be used in the normal fashion.²⁶

Brandsma and co-workers²⁸ described another method for preparing EVL which involves the intermediate formation of the potassium anion **13**. Treatment of excess EVE with the base derived from *n*-BuLi-*t*-BuOK (Lochmann-Schlosser base) and TMEDA in hexane or pentane at -20 °C for 15 minutes generates the presumed potassium vinyl ether **13**. This reagent can be used as such or can be transmetalated to EVL by the addition of lithium bromide and THF. A potential advantage to this procedure over all the others described thus far is that it avoids the use of highly flammable *t*-BuLi, an issue which is advantageous on large scale.

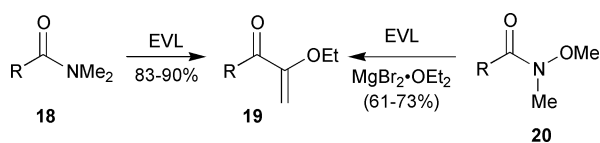
2.1.2 Reactivity of 1-methoxy- and 1-ethoxyvinyl lithium

2.1.2.1 Reaction with electrophiles

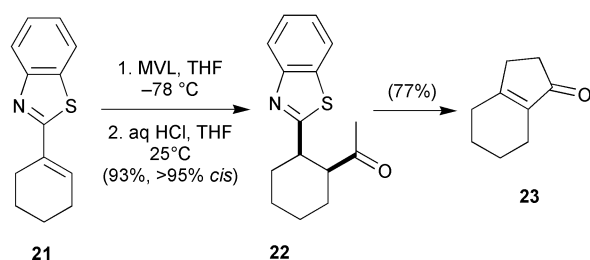
MVL and EVL display reactivity typical of hard carbon nucleophiles and readily add to a variety of electrophiles (Schemes 3–5). Efficient 1,2-addition to aldehydes,^{4,5,29–31} ketones and enones^{4,32–41} is observed in most cases including highly enolizable ketones such as acetophenone (Scheme 3, Table 1). The cerium reagent derived by treating EVL with CeCl₃ has been used for 1,2-addition to a highly enolizable enone when the corresponding lithium reagent itself failed.⁴²



Scheme 3



Scheme 4

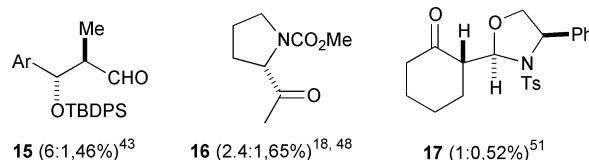


Scheme 5

Table 1 Addition of MVL (**9**) and EVL (**10**) to carbonyl compounds (Scheme 3)

Product	R ¹	R ²	Anion ^a	Yield (%)	Ref.
14a	Me	H	A	90	31
14b	<i>i</i> -Pr	H	A	97	31
14c	<i>n</i> -C ₅ H ₁₁	H	A	75	31
14d	MeCH=CH	H	A	74	5
14e	Ph	H	B	43	4
14f	Ph	H	A	78	5
14g	<i>p</i> -MeC ₆ H ₄	H	A	94	31
14h	Me	Me	A	81	41
14i	Me	Me	C	82	28
14j	PhCH ₂	Me	A	90	5
14k	PhCH ₂ CH ₂	Me	A	76	41
14l	(MOMO)Me ₂ C	Me	A	55 ^b	36
14m	-(CH ₂) ₄ -		A	88	5
14n	-(CH ₂) ₄ -		C	84	38
14o	Me ₂ C=CH	Me	A	75	5
14p	Ph	Me	A	59 ^b	36

^a A = Baldwin procedure: excess MVE or EVE, THF, *t*-BuLi, -65 to 0 °C; B = Schöllkopf procedure: EVE, pentane-TMEDA, -30 °C; C = Brandsma procedure: excess EVE, hexane or pentane, TMEDA, *n*-BuLi-*t*-BuOK, -20 °C. ^b Yield of hydrolysis product.



Substrate controlled diastereoselective addition of MVL and EVL to a number of chiral aldehydes⁴³ and ketones,^{18,44–51} such as **15–17**, has been reported (diastereoselectivity and yield indicated).

Reaction of MVL or EVL with lactones³⁹ or esters⁵ provides the mono- or di-addition products, respectively, the latter of which are useful for the preparation of 4-hydroxyisopyrazoles and 2-pyrazolin-4-ones.⁵² 2-Alkoxyenones **19** (Scheme 4) are obtained in low yields upon treatment of MVL or EVL with acids and nitriles.⁵ Shimano and Meyers²⁶ demonstrated that the low yields can be circumvented by treating the corresponding dimethyl amide **18** with EVL in THP. Similar results are obtained by treating Weinreb amide **20** with the vinyl magnesium reagent obtained upon exposing EVL to MgBr₂·OEt₂ (Scheme 4).⁵³

The alkylations of primary iodides,^{5,54} allyl bromides⁵ and fluoroacetylene⁵⁵ have been reported. MVL and EVL do not react with simple epoxides although an efficient reaction does take place⁵⁶ in the presence of BF₃·OEt₂. Oxetane opening is also possible using this reagent mixture.⁵⁶ In certain cases, MVL and EVL undergo conjugate addition to activated electrophiles including unsaturated acyl ylides,⁵⁷ vinylbenzothiazoles **21** (Scheme 5),⁵⁸ vinyl sulfones,⁵⁹ *exo*-methylene cyclopentadienes^{60,61} and activated 2-vinylindoles.⁶²

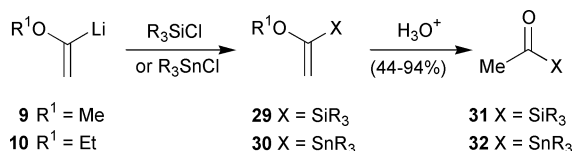
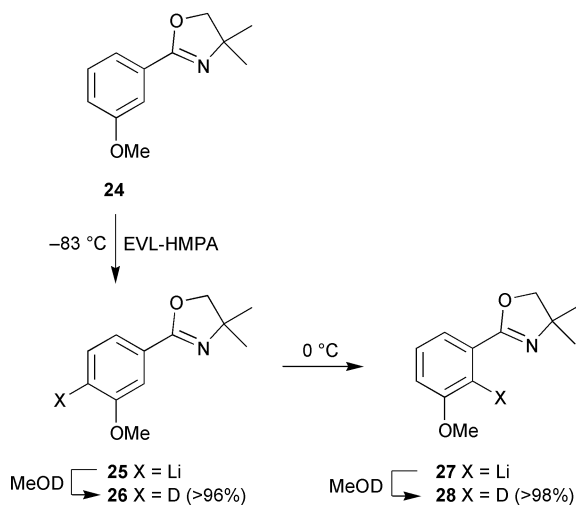
A potentially useful application of a 1 : 1 EVL–HMPA complex was introduced by Shimano and Meyers.²⁷ This complex behaves as a strong base, carrying out aromatic deprotonation in the presence of directed metalation groups (DMG's) (Scheme 6). The metalation regioselectivity of this reagent is particularly noteworthy. In the presence of the traditionally used, but sterically more demanding, diisopropylamide and oxazoline directing groups, metalation *ortho* to methoxy directing groups is preferred under kinetically controlled conditions. Upon warming to 0 °C, the kinetically generated anion **25** rearranges to the thermodynamically more stable position (**27**) *ortho* to the diisopropylamide and oxazoline directing groups.

A versatile and widely used procedure for the synthesis of acyl silanes **31** involves the reaction of MVL or EVL with silyl chlorides followed by hydrolysis of the intermediate

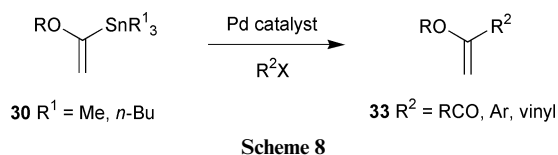
Table 2 Reaction of MVL (**9**) and EVL (**10**) with silyl and stannyl chlorides (Scheme 7)

Substrate	R ₃ MCl	Yield, 29 or 30 (%) ^a	Ref.
MVL	Me ₃ SiCl	88–94 (78–83)	12
	Et ₃ SiCl	89 ^b (93)	65
	TIPSCl	96 ^b (93)	65
	Ph ₃ SiCl	(47)	15
	NphPhMeSiCl	100 (94)	66
	Me ₃ SnCl	85	14
	Bu ₃ SnCl	92	14
	SnCl ₄	72 ^c	14
EVL	Me ₃ SiCl	68	14
	<i>t</i> -BuMe ₂ SiCl	75	64
	Me ₂ SiHCl	(44)	19
	<i>t</i> -Bu ₂ SiHCl	50 (78)	19

^a **9** or **10** prepared using the Baldwin procedure.⁵ Yield of hydrolysis product **31** in brackets. ^b Prepared using the Soderquist procedure.^{14,16} ^c Yield of tetrasubstituted product **12**.



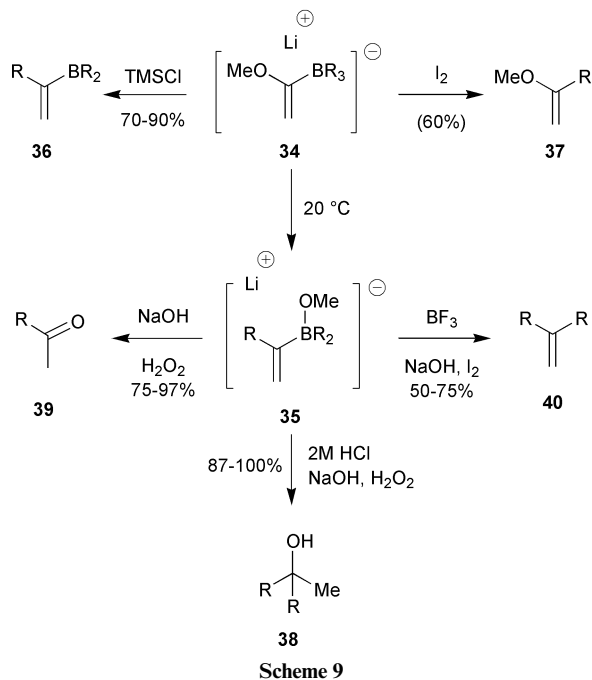
α -alkoxyvinylsilanes **29** (Scheme 7, Table 2).^{12,14,15,19,22,63–66} The corresponding α -alkoxyvinylstannanes **12** and **30** have been prepared by treating MVL or EVL with Me₃SnCl, Bu₃SnCl and SnCl₄ (Scheme 7, Table 2).¹⁴ These vinylstannanes are useful for the generation of unsolvated MVL (the Soderquist procedure) and acylstannanes **32** (upon hydrolysis).¹⁴ They also undergo efficient palladium-catalyzed coupling (Stille reaction) with acid chlorides,⁶⁷ aryl bromides, iodides or triflates,^{† 68,69,70} and vinyl bromides or triflates^{68,69} to generate the α -substituted vinyl ethers **33** (Scheme 8). Carbonylative coupling of **30** with vinyl triflates and aryl iodides has also been reported.⁶⁸



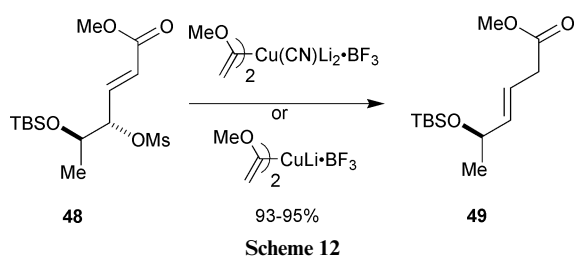
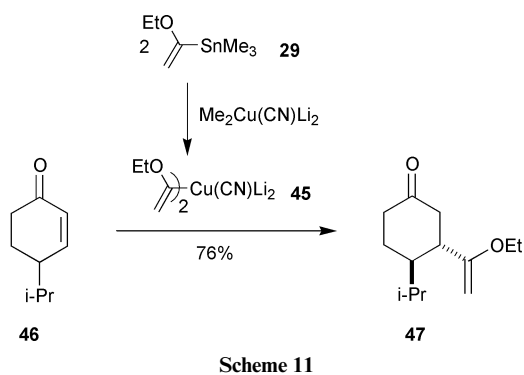
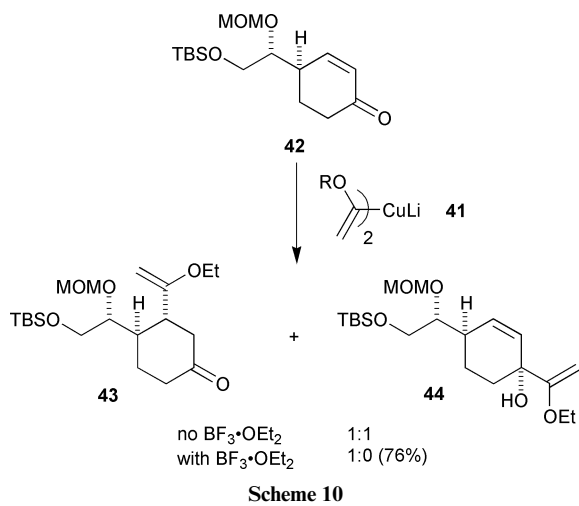
† The IUPAC name for triflate is trifluoromethanesulfonate.

2.1.2.2 Transmetalation

Several groups have described the reaction of MVL and EVL with trialkylboranes. The initially produced vinyl borate salts **34** are stable at -80 °C but undergo alkyl group migration upon warming to room temperature to give alkenyldialkylmethoxyborate salts **35** (Scheme 9).⁷¹ Both of these salts may be used in a variety of ways to form synthetically useful products. For example, treating boronate **34** with either TMSCl or iodine provides the Markovnikov vinyl boranes **36**⁷² or the vinyl ethers **37**,⁷¹ respectively. Exposing the rearranged boronate salt **35** to aqueous acid followed by basic H₂O₂ produces dialkylmethylcarbinols **38**^{71,73} while the alkyl methyl ketones **39** are obtained upon direct treatment with basic H₂O₂.⁷¹ Alternatively, the 1,1-dialkylethylenes **40** are produced in useful yields by reaction of **35** with BF₃·OEt₂ followed by basic aqueous iodine.⁷¹



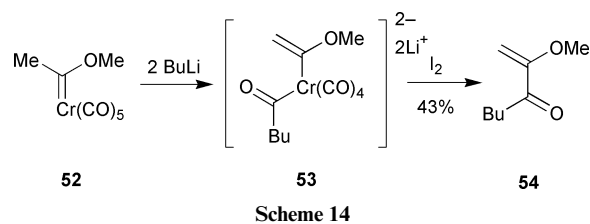
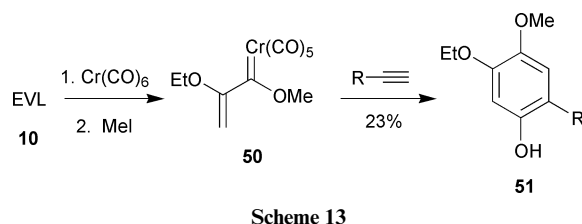
Heathcock, Boeckman, Schut and their respective coworkers have demonstrated that homogeneous lower order (LO) cuprates **41** derived from MVL or EVL and CuI or CuI·SMe₂ undergo 1,4-addition to enones (50–90%)^{20,21,32,74} and alkylate benzyl³² and allylic bromides^{20,74} but not primary, secondary bromides or epoxides. Competing 1,2-addition occurs when hindered enones such as **42** are used as substrates but this undesired reactivity can be overcome by the use of BF₃·OEt₂ in conjunction with the cuprate (Scheme 10).⁷⁵ The LO mixed cuprate formed from EVL and pent-1-ynylcopper transfers the vinyl ether moiety in a conjugate fashion, allowing for its more efficient use.^{20,74} Other reactions of homogeneous LO cuprates include the substitution of β -(phenylseleno)vinyl sulfones to generate 1,3-dienes,⁷⁶ the chemoselective 1,2-addition to aldehydes in the presence of ketones and amides,⁷⁷ and the conjugate addition to vinyl epoxides.⁷⁸ Lipshutz⁷⁹ described the preparation of the higher order (HO) cyanocuprate **45** by a transmetalation process that involves treatment of two equivalents of the α -ethoxyvinyltin reagent **29** with Me₂Cu(CN)Li₂. While this homogeneous HO cuprate efficiently transfers the vinyl ether moiety conjugatively to enones such as **46** (Scheme 11), the HO mixed cuprate (H₂C=COEt)CuMe(CN)Li₂ obtained using only 1 equiv. of **29** preferentially transfers the methyl group.⁷⁹ The HO cyanocuprate analogous to **45**, but prepared by reaction of 2 equiv. of the Soderquist MVL with CuCN, readily alkylates allyl bromide in 60% yield.¹⁶ Both the LO and HO cuprates have been used to induce a stereoselective



reductive elimination of α -methylsulfonyloxy- α,β -unsaturated esters **48** (Scheme 12).⁸⁰

As mentioned earlier, EVL is readily transformed, upon treatment with $\text{MgBr}_2 \cdot \text{OEt}_2$,^{53,81} ZnCl_2 ,^{17,24} or CeCl_3 ,⁴² into the corresponding vinyl-magnesium, -zinc or -cerium reagent, respectively. The vinylmagnesium reagent has been used for addition to Weinreb amides (Scheme 4)⁵³ and 1,2-addition to enones⁸¹ while Hegedus and Negishi have shown that the vinylzincate participates in efficient palladium-catalyzed coupling reactions with aryl and vinyl halides^{17,24} in analogy to the vinyltin reagent **30** (Scheme 8). MVL and EVL undergo reaction with various metal chlorides of the nickel triad to produce well characterized organometallic complexes,¹³ and with $\text{Cr}(\text{CO})_6$ to provide, after reaction with methyl iodide and substituted alkynes, a novel entry into highly substituted phenols **51** (Scheme 13).⁸²

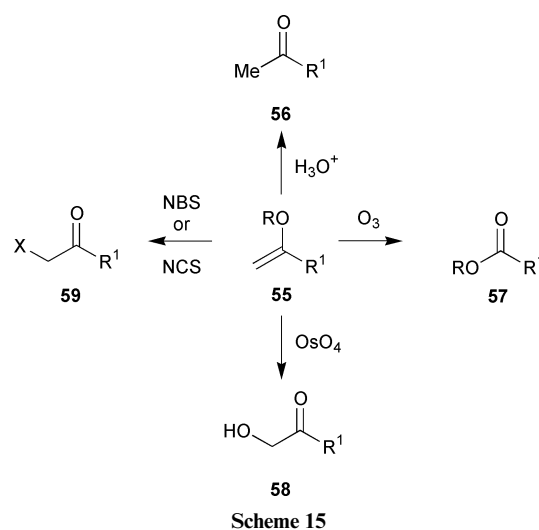
Hegedus⁸³ has described a general route to dianionic (σ -acyl)(σ -vinyl)chromium complexes **53** from [(methoxy)-(methyl)carbene]pentacarbonylchromium(0) **52** (Scheme 14).



Treating **52** with 2 equiv. of an organolithium reagent produces the metalated vinyl ether complex **53**, while subsequent oxidation leads to the relatively unstable α -methoxyenone **54** in moderate yields. The corresponding benzyl and *tert*-butyldimethylsilyl vinyl ethers may also be used in this reaction.

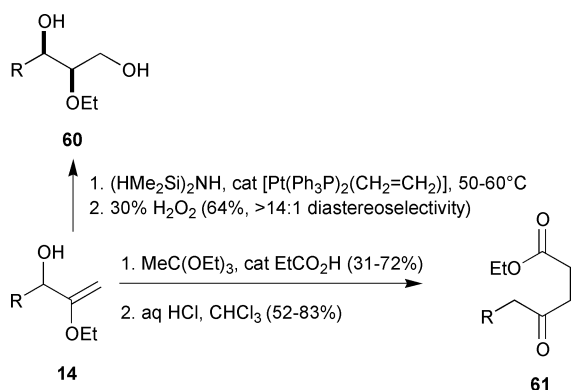
2.1.2.3 Subsequent reactivity

MVL and EVL have been mainly used as the acyl anion umpolung synthon **A**. Therefore, many reports describe the subsequent hydrolysis of the vinyl ether adducts that are produced in the various reactions outlined above. Hydrolysis of **55** (Scheme 15) is readily achieved using a variety of mild acidic conditions, the most common being dilute HCl (0.02 M to 3 M) in methanol,^{5,32,53} THF,^{34,48,58,68} dioxane⁴⁴⁻⁴⁷ or acetone.⁶⁵⁻⁶⁷ Less commonly used procedures include aqueous $\text{H}_2\text{SO}_4/\text{Ag}_2\text{SO}_4$,⁴ 3 M HClO_4 in aqueous methanol,³³ $\text{HgCl}_2\text{-CdCO}_3$ in aq methanol-benzene,⁶³ *p*- TsOH in aqueous acetone,⁶¹ methanol⁸¹ or ethylene glycol,¹⁶ HOAc in aqueous THF,^{50,54} wet silica gel in benzene⁷⁴ or 0.1M oxalic acid in methanol.²⁰ In addition to this principal hydrolysis protocol, other reactions of the vinyl ethers have been described (Scheme 15) including ozonolysis to the corresponding ester **57**,^{30,32,43,53,59,75} treatment with OsO_4 or MCPBA to generate α -hydroxy ketones **58**^{44-47,84} and exposure to NBS or NCS to produce α -halo ketones **59**.^{38,64} Intramolecular hydrosilylation to provide *syn* diols **60** (Scheme 16),²⁹ tandem cationic aza-Cope rearrangement-Mannich cyclization,⁴⁹ Claisen-Johnson rearrangement yielding γ -keto esters **61** (Scheme 16),³¹ intramolecular [2 + 2] photocyclization^{40,41} and intramolecular π -allylpalladium catalyzed cyclization⁷⁷ are other reactions that have been reported for the vinyl ether products **14** generated from the reactions of MVL and EVL. Many of these reactions are key steps in the synthesis of natural products including the allopumiliotoxin A alkaloids 267A and 339B,⁴⁸ the terpenes silphinene⁶¹ and α -cedrene,^{40,41} and taxusin.⁵⁰



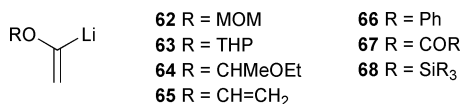
2.2 α -Lithiated species of other simple vinyl ethers ($\text{H}_2\text{C}=\text{C}(\text{LiOR})$)

A number of lithiated vinyl ethers have been explored as potential alternatives to MVL and EVL. These lithiated vinyl ethers

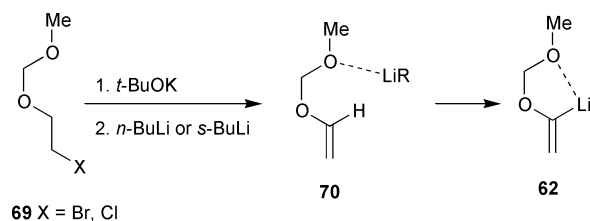


Scheme 16

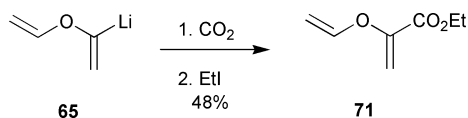
include methoxymethyl (**62**), tetrahydropyranyl (**63**) and ethoxyethyl (**64**) vinyl ethers (more highly oxygenated versions of MVL and EVL), as well as divinyl ether (**65**), phenyl vinyl ether (**66**), acyl vinyl ethers (**67**) and silyl vinyl ethers (**68**). Although some of these vinyl ether anions offer advantages (enumerated below) over MVL, they have not been used as extensively as commercially available MVL or EVL because they have to be synthesized prior to metalation.



While MVE and EVE are most readily deprotonated with *t*-BuLi, the MOM and THP vinyl ethers (prepared by dehydrobromination^{29,85-87} of the corresponding 2-haloethyl ethers such as **69** (bromo or chloro) with *t*-BuOK) are metalated with *s*-BuLi^{86,87} or *n*-BuLi²⁹ to provide **62** and **63** (Scheme 17). This more facile deprotonation suggests that the lithiation may be assisted by chelation of the alkyllithium base with the oxygen atoms of the MOM and THP moieties (as in **70**). The resulting vinylolithium anions **62** and **63** readily add (62–65%) to aldehydes^{29,86,87} and ketones.⁸⁸ Ethoxyethyl vinyl ether⁸⁵ and divinyl ether, the latter prepared by treatment of bis(2-chloroethyl) ether with *t*-BuOK,⁸⁹ have been lithiated with *t*-BuLi in analogy with EVE. The lithiated divinyl ether anion **65** is conveniently transformed to the relatively inaccessible enol pyruvate **71** (Scheme 18) (48%).⁸⁹



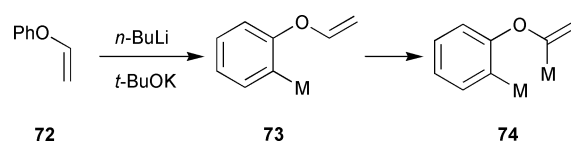
Scheme 17



Scheme 18

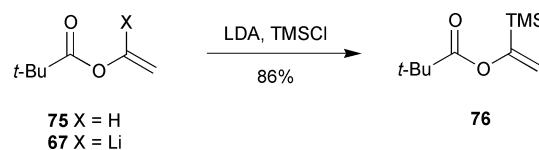
An anomalous reaction occurs when phenyl vinyl ether **72** is metalated with Lohmann–Schlosser base (Scheme 19). In this instance, the vinyl moiety acts as an *ortho*-metalation DMG and deprotonation occurs initially on the aromatic ring.⁹⁰ Exposure to excess base then converts the anion **73** to the dimetalated species **74**. With the exception of carboxylation, this dianion has not been used synthetically.

Wright⁹¹ demonstrated that a class of relatively inaccessible acylsilane enol esters **76** are efficiently prepared (64–93%) by



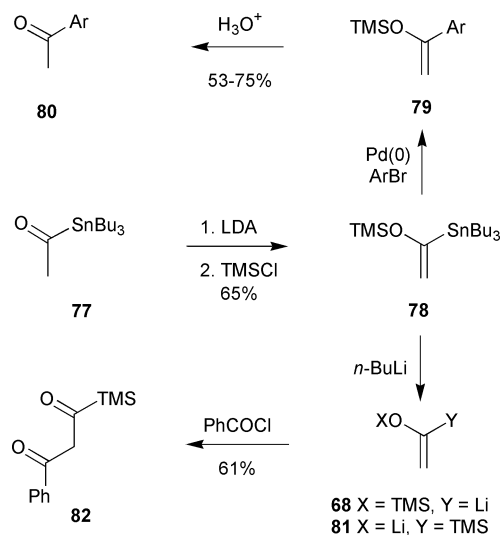
Scheme 19

treating a pre-mixed solution of a vinyl ester **75** (R = 2° alkyl or aryl in place of *t*-Bu) and TMSCl or TESCl with LDA at –78 °C (Scheme 20). Unfortunately, the putative vinyl ether anion intermediate **67** does not react with other electrophiles such as benzaldehyde or methyl iodide.



Scheme 20

The [1-(trimethylsilyloxy)vinyl]tin reagent **78** is prepared (65%) by the lithiation (LDA) and subsequent silylation of acetyltributyltin **77** (Scheme 21).⁹² Verlhac and coworkers⁹² have shown that vinyltin **78** is a useful acyl anion equivalent, readily undergoing reaction with aryl, vinyl and allyl bromides in a Pd(0)-catalyzed coupling reaction to yield the silyl enol ethers **79** which are easily hydrolyzed to the corresponding methyl ketones **80** (53–75%). Alternatively, rapid transmetalation of silyloxyvinyltin **78** is accomplished with *n*-BuLi at –78 °C. The resulting vinylolithium species **68** undergoes a reverse Brook rearrangement to generate a lithium enolate **81** that can be trapped with various electrophiles (benzaldehyde, benzoyl chloride or methyl iodide) to provide access to novel acylsilanes such as **82**.⁹³



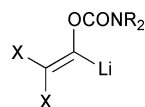
Scheme 21

2.3 α -Lithiated enol carbamates (R₂C=CLiCONR'₂; R = H, F, alkyl)

In the last several years, lithiated enol carbamates such as **83** have been introduced as acyl anion equivalents. Subsequent to the initial lithiation chemistry, the enol carbamate moiety can undergo synthetically useful transformations that are unavailable to simple enol ethers derived from MVL and EVL. Therefore, reagents such as **83** are complementary to the conventional lithiated vinyl ether reagents and may offer potential advantages in terms of synthetic versatility.

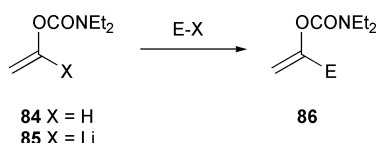
2.3.1 Non-fluorinated enol carbamates

Two routes have been described⁹⁴ for the multi-gram prepar-



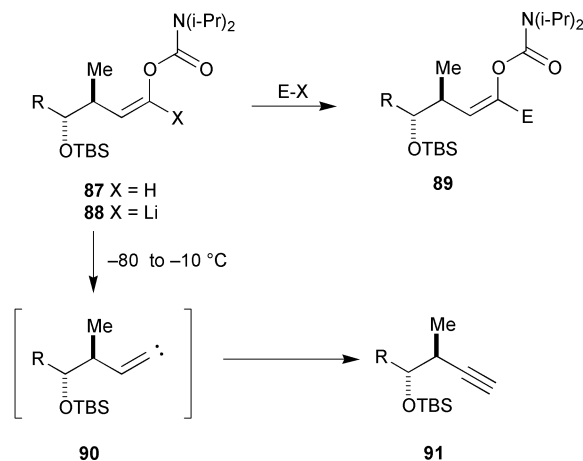
83 X = H, R, F

ation of the simple β -unsubstituted enol carbamate **84** (Scheme 22). The first route involves *O*-carbamoylation of acetaldehyde lithium enolate (80–87%) while in the potentially more general second approach, trimethylsilylamides are quantitatively added to commercially available vinyl chloroformate. The substituted *N,N*-diisopropyl enol carbamates **87** are conveniently prepared by the method of Hoppe^{95–99} which involves treatment of metalated allylic carbamates with aldehydes.



Scheme 22

The Snieckus^{94,100} and Kocienski^{95,96,99,101} groups have shown that the tertiary enol carbamates **84** and **87**, respectively, are readily lithiated, providing access to the metalated vinyl ethers **85** and **88** (Schemes 22 and 23). Lithiation of **84** is accomplished by treatment with *s*-BuLi–TMEDA in THF at $-78\text{ }^\circ\text{C}$ ⁹⁴ while deprotonation of substituted enol carbamate **87** is achieved with *t*-BuLi⁹⁵ or *n*-BuLi–TMEDA⁹⁷ in THF at temperatures from -70 to $-85\text{ }^\circ\text{C}$. The lithio derivative **88** is formed with complete retention of double bond configuration.



Scheme 23

Unsubstituted vinyl lithium reagent **85** reacts readily with a variety of electrophiles (Scheme 22, Table 3), including primary alkyl iodides and triflates, silyl chlorides, epoxides (in the presence of $\text{BF}_3 \cdot \text{OEt}_2$), acid chlorides, isocyanates, sulfonyl fluorides and aldimines, to provide the corresponding vinyl ethers **86** in moderate to good yields.^{94,100} The potentially useful vinyl bromide **86e** is obtained (74%) upon exposure of **85** to $\text{CF}_2\text{BrCF}_2\text{Br}$. Trapping of **85** with aldehydes and ketones generates α -alkoxyketones in moderate yields (65–82%) after carbamoyl transfer. Allyl groups are efficiently introduced by transmetalation of **85** with Cu(I) salts followed by alkylation with allylic halides or epoxides. Formation of the vinylzincate by exposing **85** to ZnBr_2 enables facile Pd(0)-catalyzed cross-coupling with vinyl bromides, aryl and heteroaryl bromides and triflates to be achieved.^{94,102}

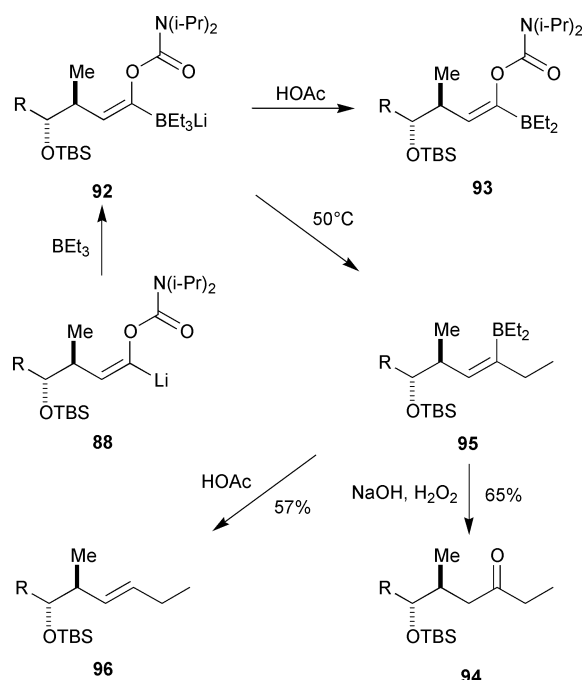
In a similar fashion, the substituted lithiated enol carbamate **88** reacts with several electrophiles (Scheme 23, Table 3) including alkyl iodides, Me_3SnCl ^{95,98,99} and MeSSMe ,⁹⁷ yielding the

Table 3 Reaction of lithiated enol carbamates **85** and **88** with electrophiles (Schemes 22 and 23)

Carbamate	E–X	Product	Yield (%)	Ref.
85	Me–I	86a	82	94
85	<i>n</i> -C ₆ H ₁₃ –I	86b	70	94
85	Me ₃ Si–Cl	86c	85	94
85	TMSCH ₂ –OTf	86d	79	100
85	Br–CF ₂ CF ₂ –Br	86e	74	100
85	PhCO–Cl	86f	40	94
85	PhSe–SePh	86g	54	94
85	H ₂ C=CHMeCH ₂ –Cl	86h	62 ^a	94
85	<i>p</i> -MeC ₆ H ₄ –Br	86i	52 ^b	102
88	Me ₃ Sn–Cl	89a	95	95
88	<i>n</i> -Pr–I	89b	56	95
88	MeS–SMe	89c	95	97

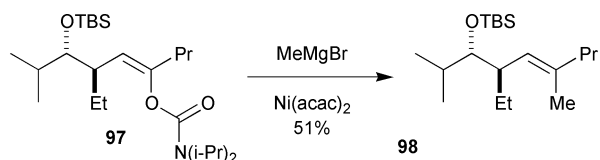
^a Reaction conducted in the presence of 1 equiv. $\text{CuCN} \cdot 2\text{LiCl}$. ^b Via the vinylzincate derived from treatment of **85** with ZnCl_2 and with $\text{PdCl}_2(\text{dppf})$ catalysis.

enol carbamates **89** with retention of olefin geometry. Alternatively, warming of the lithium reagent **88** from -80 to $-10\text{ }^\circ\text{C}$ results in the formation of alkyne **91** via a Fritsch–Buttenberg–Wiechell rearrangement of the initially generated vinyl carbene intermediate **90** (Scheme 23).¹⁰¹ The α -carbamoyloxyborate **92**, readily prepared by treating **88** with BEt_3 ,⁹⁶ is protonated with HOAc to form the chromatographically stable borane **93** (47%). Warming of intermediate **92** to $50\text{ }^\circ\text{C}$ leads to the alkenylborane **95** that is a useful reagent for preparing olefins **96** and ketones **94** (Scheme 24).

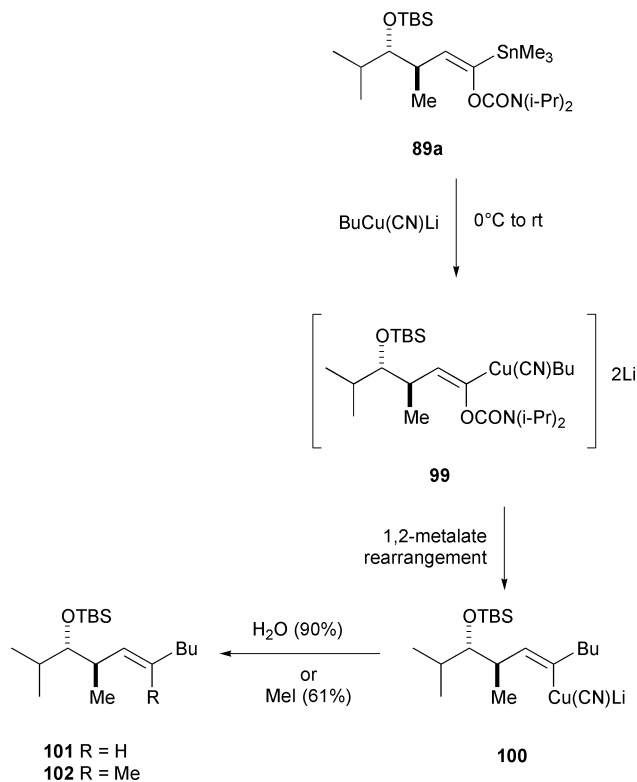


Scheme 24

As mentioned above, one of the powerful features of lithiated enol carbamates is the amenability of the vinyl carbamate moiety to further chemistry that is not possible with the simple vinyl ether products derived from MVL and EVL. For example, Snieckus^{94,100} and Kocienski^{95,99,101} demonstrated that Grignard reagents undergo Wenkert Ni(0)-catalyzed cross-coupling with enol carbamates with retention of olefin stereochemistry to give substituted alkenes of defined geometry (e.g. **97** to **98**, Scheme 25). The versatility of these reagents is demonstrated by the conversion of vinylstannane **89a** to the olefins **101** and **102** via a route which is complementary to the one illustrated in Scheme 24 (Scheme 26).^{95,98,99} Thus, transmetalating **89a** with a LO cuprate provides alkenylcuprate



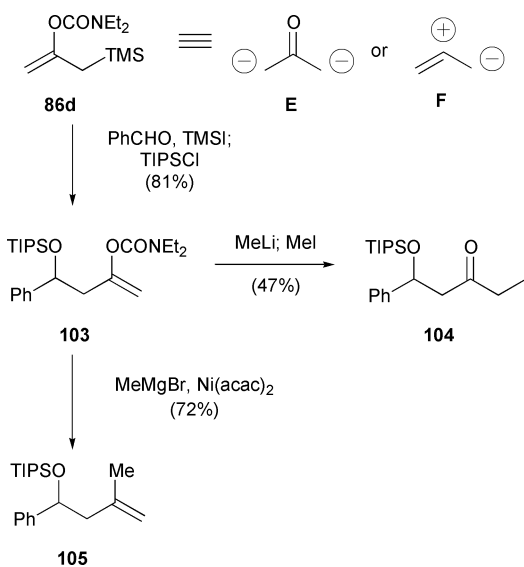
Scheme 25



Scheme 26

100 via 1,2-metalate rearrangement of the initially formed HO cuprate **99**. The di- and tri-substituted alkenes **101** and **102** are produced with >97% stereochemical integrity by quenching **100** with water or an appropriate alkyl halide, respectively.

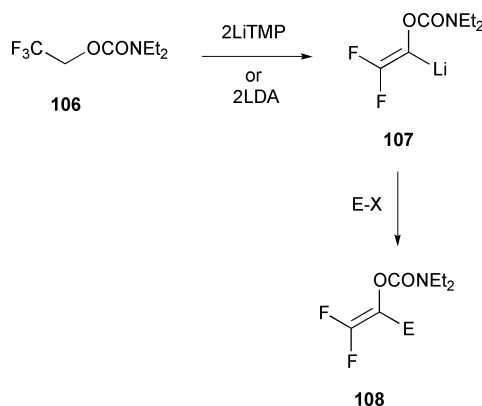
Carbamate **86d** is synthetically equivalent to an α,α' -acetone dianion synthon **E** or an allene 1,2-dipole **F**. Using the unique combination of functional groups, the allylsilane **86d** is readily converted to the ketone **104** or the olefin **105** (Scheme 27).¹⁰⁰



Scheme 27

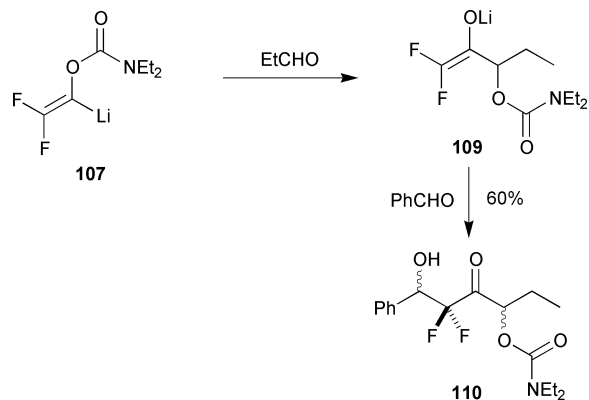
2.3.2 Fluorinated enol carbamates

The fluorinated lithiated enol carbamates **107** and **115** have been prepared by the Percy and Snieckus groups, respectively, and their reactivity investigated.^{103–107} The difluorovinyl lithium reagent **107** is prepared *in situ* by treating the *N,N*-diethyl carbamate derivative of trifluoroethanol **106** with 2 equivalents of LiTMP ¹⁰⁴ or LDA ^{103,104} in THF at -78°C (Scheme 28).



Scheme 28

Vinyl lithium reagent **107** is less reactive than the corresponding defluoro analog **85** (Scheme 22) but nevertheless undergoes reaction with a variety of electrophiles in synthetically useful yields, including silicon, selenium and tin halides^{103,104,107} and alkyl triflates,¹⁰⁴ (Scheme 28, Table 4). Poor reactivity is observed with alkyl halides and carbonyl electrophiles other than CO_2 and simple aldehydes and ketones.^{103,106,107} In the case of aldehyde electrophiles, products resulting from either direct trapping or carbamoyl migration can be obtained and, in the latter case, the lithium difluoroenolate **109** so generated can be used in further reactions (Scheme 29). Interestingly, the lithium reagent **107** generated from **106** by LDA deprotonation (Scheme 30), does not react with epoxides in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. However, transmetalation of vinylstannane **108b** with *n*- BuLi in THF at -78°C produces a vinyl lithium species apparently different from **107** that does react with cyclohexene oxide to afford the alcohol **111** in 65% yield.¹⁰⁷ The vinyl lithium species **107** generated from **108b** may also be converted to the corresponding vinyl copper reagent **112** by reaction with $2\text{LiCl} \cdot \text{CuI}$ in THF at -78 to 0°C .¹⁰⁸ In contrast to **107**, the difluoro-vinyl copper reagent **112** does react with active alkyl halides (40–76%) and with simple acid chlorides (67–77%) (Scheme 30, Table 4).¹⁰⁸



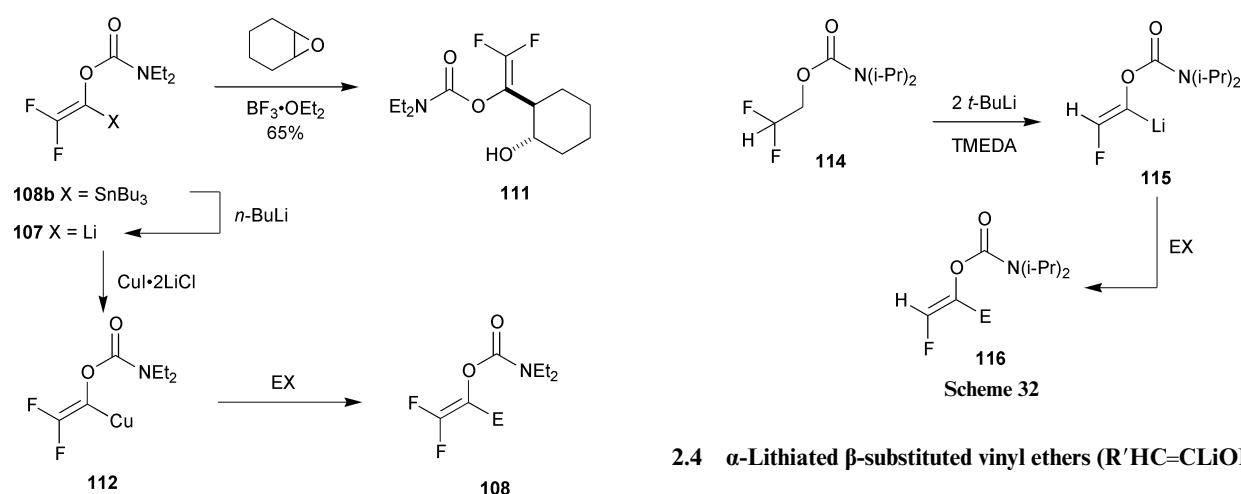
Scheme 29

The vinylsilane **108a** displays unique reactivity since treatment with MeLi , *s*- BuLi , PhLi or LiBEt_3H results in a solvent-dependent addition–elimination process, generating isomeric monofluoro enol carbamate products **113** in a stereoselective fashion (Scheme 31).¹⁰⁴

Table 4 Reaction of metalated, fluorinated enol carbamates **107**, **112** and **115** with electrophiles (Schemes 28, 30 and 32)

Carbamate	E-X	Product	Yield (%)	Ref.
107	Me ₃ Si-Cl	108a	70–80	103,104
107	Bu ₃ Sn-Cl	108b	69	103
107	H-NH ₃ Cl	108c	88	103
107	Me-OTf	108d	71	104
107	Me ₃ SiCH ₂ -OTf	108e	91	104
107	CO ₂	108f	60	103
107	EtCHO	108g	77	103
107	PhSe-Br	108h	58	104
107	I-I ^a	108i	75	107
112	H ₂ C=CHCH ₂ -Br	108j	66	108
112	Bn-Br	108k	53	108
112	EtCO-Cl	108l	76	108
112	PhCO-Cl	108m	77	108
115	TMS-Cl	116a	37	105
115	Bu ₃ Sn-Cl	116b	35	105
115	H-NH ₃ Cl	116c	42	105
115	Me-I	116d	40	105

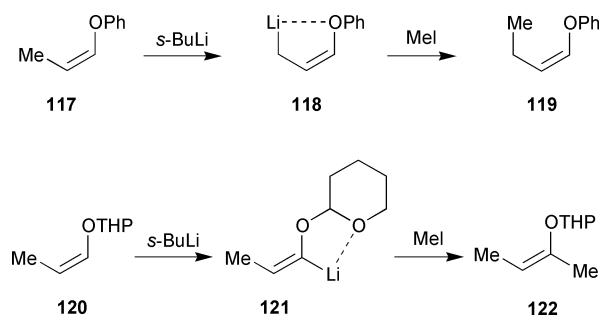
^a Via the zincate derived by treatment of **107** with ZnBr₂.

**Scheme 30****Scheme 32**

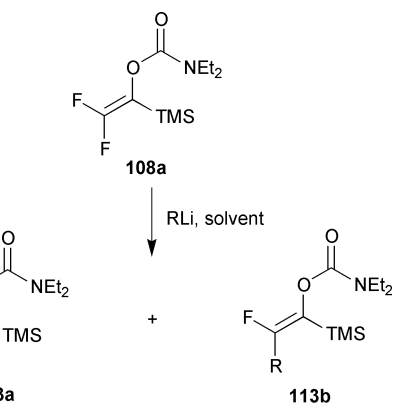
2.4 α -Lithiated β -substituted vinyl ethers (R'HC=CLiOR)

2.4.1 β -Alkyl substituted vinyl ethers

The α -deprotonation of acyclic enol ethers containing β -alkyl substituents is not a general or straightforward reaction but is highly substrate dependent. In 1974, Schlosser¹⁰⁹ demonstrated that treating phenyl propenyl ether **117** with *s*-BuLi in THF results in metalation in the γ -position rather than the α -position, producing the enol ether **119** in 84% yield upon treatment with MeI (Scheme 33). However, Baldwin⁵ showed that an *E/Z*-mixture of the corresponding methyl propenyl ether is readily metalated in the α -position with *t*-BuLi–TMEDA. Furthermore, clean α -metalation (*s*-BuLi) is observed by replacing the phenyl group of **117** with a THP moiety (**120**) and it has been argued that the formation of an intramolecular chelate (**121**) is responsible for the desired α -metalation. The metalated enol ether **121** is trapped by MeI to give **122** in 83% yield.¹¹⁰

**Scheme 33**

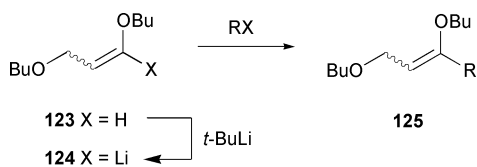
The monofluorovinyl anion **115** is produced stereospecifically by treating the *N,N*-diisopropylcarbamate derivative of difluoroethanol **114** with *t*-BuLi–TMEDA in THF at -78°C (Scheme 32).¹⁰⁵ The use of LDA or the diethylcarbamate analog of **114** leads to complex reaction mixtures. The vinyl lithium reagent **115**, intermediate in reactivity between the defluorovinyl and difluorovinyl enol carbamate anions **85** and **107**, reacts with TMSCl, Bu₃SnCl, MeI and pentanone in low yields (33–42%) (Scheme 32, Table 4).¹⁰⁵



R = *s*-Bu
 THF 9 : 1 (85%)
 Et₂O 1 : 9 (90%)

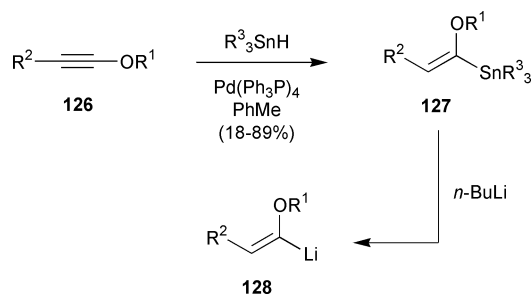
Scheme 31

Gould¹¹¹ and Rossi¹¹² reported that 1,3-dibutoxypropene **123** is another β -substituted vinyl ether that undergoes regioselective α -metalation. Treating either the (*E*)- or (*Z*)-isomer of **123** with *t*-BuLi–HMPA at -65°C preferentially generates the vinyl anion **124**. Alkylation of **124** with primary bromides and iodides proceeds with retention of stereochemistry (70–90%) (Scheme 34). The regio- and stereospecific vinyl lithiation of **123** was postulated¹¹² to be a consequence of the greater kinetic acidity of the α -vinyl C–H bond relative to the allylic C–H bond, a hypothesis that has been supported with MO calculations.



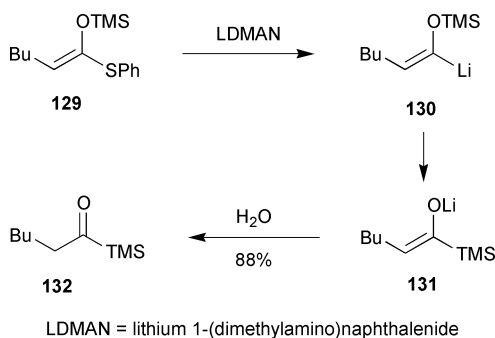
Scheme 34

Kocienski¹¹³ described a potentially general method for the regioselective α -lithiation of vinyl ethers that contain simple β -alkyl substituents. Pd(0)-catalyzed hydrostannylation of 1-alkoxyalk-1-yne **126** ($\text{R}^1 = \text{BOM, THP}$; $\text{R}^2 = \text{alkyl}$; $\text{R}^3 = \text{Me, } n\text{-Bu}$) produces α -alkoxyalkenylstannanes **127** (together with the corresponding β -stannane regioisomers, 100 : 1 to 1 : 3). These vinylstannanes undergo facile transmetalation with *n*-BuLi in THF at -78°C (Scheme 35). This process provided, for the first time, the elusive acyclic α -alkoxyalkenyllithium species **128**.



Scheme 35

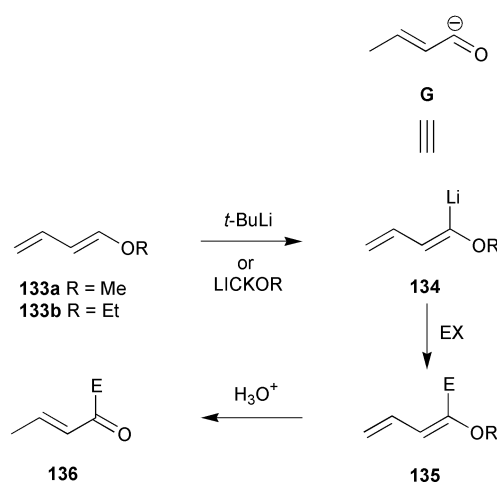
α -Silyloxyvinyl tellurides¹¹⁴ and sulfides **129**^{115,116} serve as substrates for conversion to acylsilanes **132** via a reverse Brook rearrangement of the initially generated β -substituted α -lithiated silyl enol ethers **130** (Scheme 36).



Scheme 36

2.4.2 1,3-Dienyl ethers

In contrast to the large body of work published on the α -metalation of simple vinyl ethers, relatively little data are available on the α -metalation of 1-alkoxydienes **133** (Scheme 37). This may be due to the poor yield (30%) reported by Baldwin⁵ in his original 1974 publication for the metalation (*t*-BuLi), trapping (with PhCHO) and hydrolysis of 1-methoxybutadiene **133a** (unknown stereochemistry). Subsequent to this initial



Scheme 37

report, several groups described the efficient metalation of (*E*)-1-methoxybutadiene **133a** with *t*-BuLi^{117,118} and (*E*)-1-ethoxybutadiene **133b** with *s*-BuLi–*t*-BuOK (LICKOR base),¹¹⁹ both with retention of stereochemistry. In the former case, minor amounts (<5%) of products resulting from the δ -addition of *t*-BuLi to **133a** are observed. The resulting vinyl-metalated species **134** react with electrophiles, such as Me_2HMCl ($\text{M} = \text{Si, Ge}$), Me_3MCl ($\text{M} = \text{Si, Ge, Sn}$), aldehydes and ketones, in moderate to good yields (50–80%). Acid hydrolysis yields the α,β -unsaturated acyl derivatives **136** and thus anion **134** may be considered as an effective crotonyl anion equivalent **G**. Interestingly, the metalated (*E*)-1-ethoxybutadiene **134b** may be generated in a single pot from 1,1-diethoxybut-2-ene upon treatment with 2 equivalents of LICKOR base, obviating the need for isolation of the potentially unstable alkoxydiene **133b**.¹¹⁹ The analogous *Z*-1-methoxy- and phenoxybutadienes are also α -metalated with retention of stereochemistry using the Lohmann–Schlosser base.¹²⁰ The latter example may be contrasted with phenyl vinyl ether **72** which is preferentially metalated on the aromatic ring (Scheme 19).⁹⁰

Soderquist¹¹⁸ described the α -metalation of the isoprenyl system **137** (3 : 1 mixture of *E/Z* isomers). Surprisingly, metalation with *t*-BuLi generates a single methoxydiene isomer (*Z*)-**139** (56–82%) after trapping of the lithiated intermediate **138** with Me_3MCl ($\text{M} = \text{Si, Ge, Sn}$) (Scheme 38). Apparently, the (*E*)-stereoisomer is selectively destroyed in the reaction since it is not isomerized to the (*Z*)-diene, nor does it remain unreacted in the reaction mixture. McDougal and Rico¹²¹ studied the α -metalation of the terminally substituted 1-alkoxydienes **140** and trienes **143**. Both the methyl and methoxymethyl dienyl ethers **140** (~90% *E/E* isomer, ~10% *Z/E* isomer) are deprotonated with *s*-BuLi in THF and the resulting vinyl anion **141** is intercepted with TMSCl (80%) (Scheme 39). In analogy with the observations of Soderquist, the minor *Z/E*-diene component of the substrate is selectively destroyed and thus the reaction products are enriched in the isomer resulting from stereoselective metalation of the *E/E*-diene. An important observation from these results is that the MOM ether **140b** undergoes metalation faster than the methyl ether **140a**. Thus, while the 1-methoxytriene **143a** is not deprotonated under a wide variety of reaction conditions, the MOM trienyl ether **143b** is readily deprotonated with *n*-BuLi presumably due to the rate acceleration imparted by the MOM group. Interestingly, the success of this latter reaction is intimately related to the alkyl lithium base which is used. Efficient metalation is observed with *n*-BuLi–TMEDA in DME at -78°C while the use of *s*-BuLi results in alkyl lithium addition to the trienyl system.

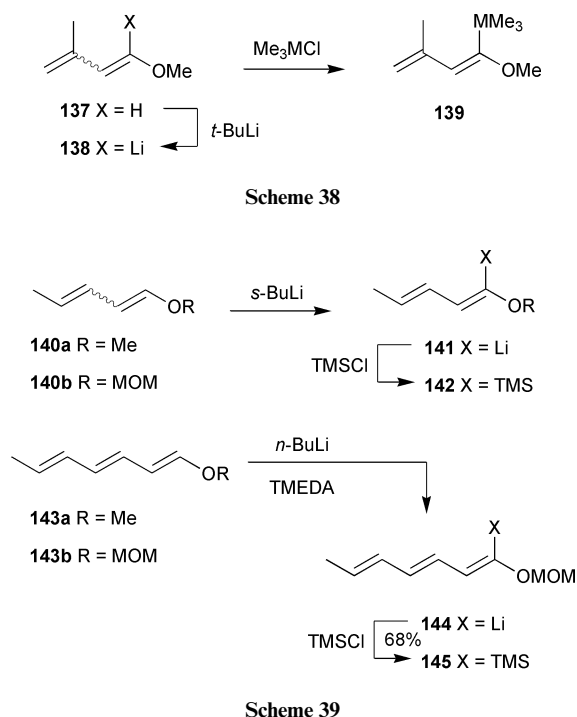
2.4.3 3-Lithio-3-alkoxy acrylates (ROCLi=CHCOX)

The Schmidt group^{122,123} has extensively studied the lithiation

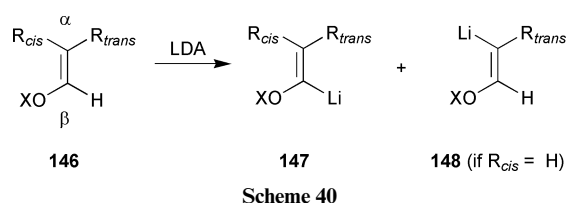
Table 5 Lithiation of acrylic acid derivatives **146** (Scheme 42)

146	X	R _{cis}	R _{trans}	Base	T/°C	t/min ^a	% D ^b	Ratio β/α	Ref.
146a	Me	H	CO ₂ Et	LDA	-90	2	87	95/5	23
				LDA	-90	300	95	57/43	23
146b	Et	H	CN	LDA	-100	2	45	0/100	124
				<i>n</i> -BuLi	-100	30	71	0/100	124
146c	MeO(CH ₂) ₂	H	CO ₂ Et	LDA	-100	2	62	10/90	124
				LDA	-100	120	58	100/0	124
				LDA	-70	10	41	100/0	124
146d	Me	H	CONEt ₂	LDA	-100	30	87	100/0	124
				LDA	-60	10	71	100/0	124
146e	Me	H	CO ₂ H	2 <i>t</i> -BuLi	-80	120	87	^d	129,130
				2 <i>s</i> -BuLi	-100	60	^c	^d	132
146f	Bn	H	CO ₂ H	2 <i>t</i> -BuLi	-80	120	95	^d	130
146g	Me	H	CONHPr	2 <i>t</i> -BuLi	-80	120	95	^d	130
146h	Me	Me	CO ₂ Me	LDA	-80	^d	^c	100/0	125
146i	Et	Me	CN	LDA	-100	2	98	100/0	124

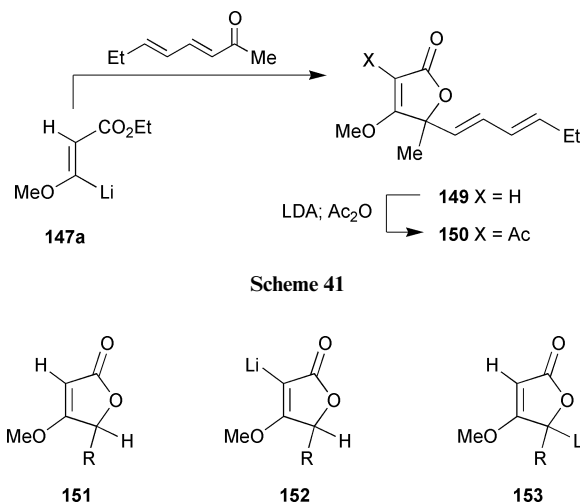
^a THF as solvent. ^b Deuterium incorporation using MeOD quench; starting material as byproduct. ^c Reaction with electrophiles other than MeOD reported. ^d Not reported.



chemistry of β-alkoxy-, β-amino- and β-thio-substituted acrylates. For example, ethyl (*E*)-3-methoxyacrylate **146a** (R_{cis} = H, R_{trans} = CO₂Et, X = Me), is lithiated under kinetically controlled conditions (LDA, -90 °C, 2 min) to give the β-lithiated species **147** in a highly regioselective fashion (**147** : **148** > 95 : 5) (Scheme 40, Table 5). Trapping with MeOD returns the β-deuterated starting material **146** (D in place of H) stereospecifically in 87% yield, the remainder being unreacted starting material. After 5 h at -90 °C, a mixture of the β-lithiated (**147**) and α-lithiated species **148** (~1 : 1, 95% deuteration) is generated, suggesting that the thermodynamic acidities of the vinyl protons are similar.^{23,124} Table 5 lists a number of related alkoxy acrylate derivatives **146** that are lithiated in a similar fashion.



In addition to simple deuteration of the lithiated species, trapping with other electrophiles, such as aldehydes^{125–127} and ketones,^{126,128–130} leads to the preparation of substituted tetronates which are synthetically useful intermediates. For example, treating lithiated intermediate **147a** with (*E,E*)-octa-3,5-dien-2-one yields tetronate **149** (31–45%) (Scheme 41).^{126,128} Metalation of **149** with LDA followed by acetic anhydride (30%)¹²⁶ or methyl acetate (19%)¹²⁸ quench provides *iso*-gregatin B **150**. In the case of tetronates **151** derived from the reaction of **147** with aldehydes, this generally applicable kinetic deprotonation process with LDA leads to direct abstraction of the vinyl proton α to the carbonyl group (**152**) rather than the carbonyl activated γ-methylene protons (**153**).^{126,127}



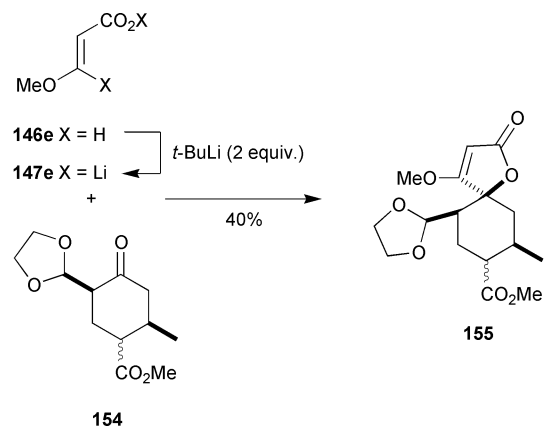
As can be seen from the above example, treatment of the lithiated ester intermediate **147a** with reagents other than reactive electrophiles, such as boranes (48–75%; leading to 1,2-oxaborole betaines)¹³¹ or benzaldehyde (65%),¹²⁶ is not very effective (yields <50%) or does not proceed at all, due to competing proton transfer. In order to achieve reaction with less electrophilic ketones, such as **154** (Scheme 42),^{129,130} the more reactive dilithiated species **147e**, prepared from the acrylic acid derivative **146e** (Table 5), is preferentially used.

The δ-lactone **157** is formed (46%) by the diastereoselective addition (19 : 1) of **147e** to α-chloropropionaldehyde followed by cyclization of **156** (Scheme 43).¹³²

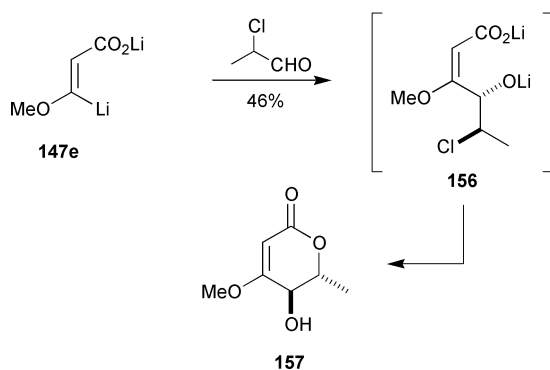
Yoshii and coworkers¹³³ described an alternative and potentially general solution to the poor reactivity of the lithiated ester **147j** (Scheme 44). The cerium reagent **158**, formed by treating **147j** with CeCl₃, undergoes reaction with ketone **159** to

Table 6 Addition of β -lithio acrylates **161** and **162** to aldehydes (Scheme 45)

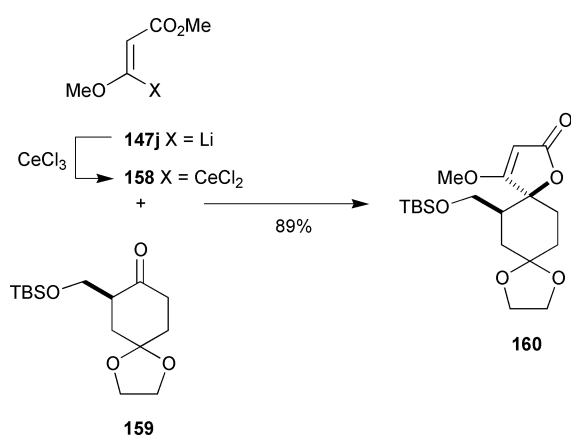
R ¹	R ²	Aldehyde	163 – 164	Yield (%)	Ref.
H	Me	MeCHO	5 : 1	67	134
Me	Et	MeCHO	$\geq 17 : 1$	68	135
H	Me	PhCHO	10 : 1	82	134
Me	Et	PhCHO	2 : 1	66	135



Scheme 42



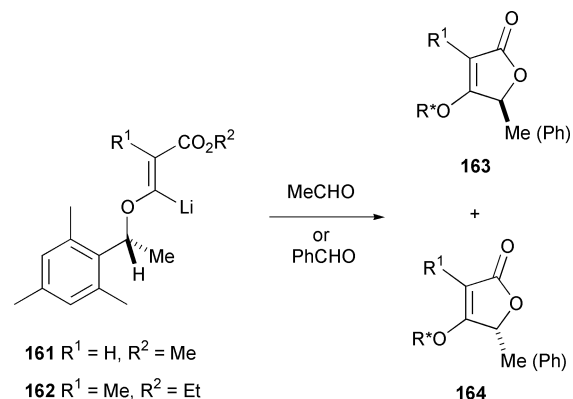
Scheme 43



Scheme 44

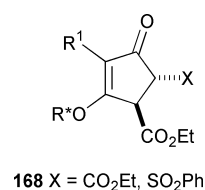
provide spiro-tetronate **160** (89%), which is a precursor to the upper fragment of tetronolide.

Schmidt and co-workers have explored the reaction of chiral lithiated β -alkoxyacrylates such as **161** and **162** (generated by LDA deprotonation of the parent acrylates) with aldehydes^{134,135} and ketones¹³⁶ (Scheme 45, Table 6). Optimum diastereoselectivity in products **163**–**164** using the demethyl species **161** is observed with benzaldehyde (10 : 1),¹³⁴ while lower diastereoselectivity is observed with acetaldehyde (5 : 1)¹³⁴ and ethyl levulinate **165** (4.5 : 1) (Scheme 46).¹³⁶ However, the



Scheme 45

reaction products are still useful for the synthesis of natural products as illustrated by the preparation of (–)-vertinolide **167**. In contrast, 5-substituted 3-methyltetronates are obtained with high diastereoselectivity by treating chiral acrylate **162** with alkyl aldehyde substrates ($>17 : 1$) (Scheme 45, Table 6).¹³⁵ Functionalized cyclopentenones **168** are obtained by a Michael addition–ring closure process, albeit with low diastereoselectivity (2 : 1, 47–62%), by treatment of β -lithiated acrylates **161** and **162** with fumarates and sulfonylacrylates.¹³⁷ The benzylic ether chiral auxiliary is readily removed from the tetronate products by exposure to iodotrimethylsilane at room temperature.^{134,135}



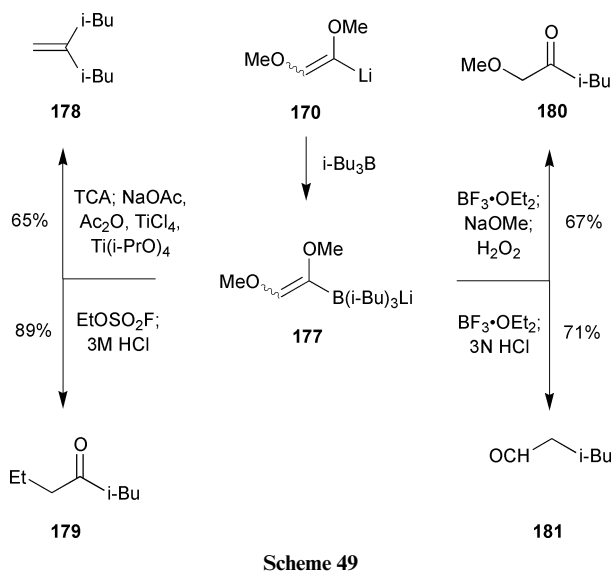
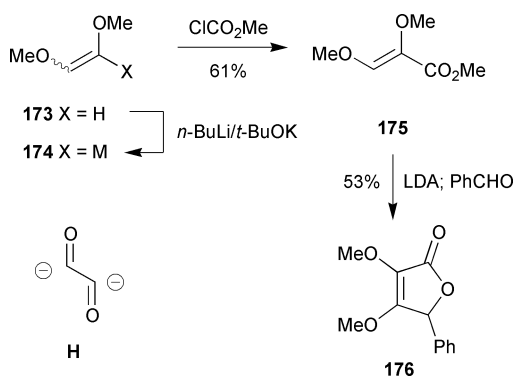
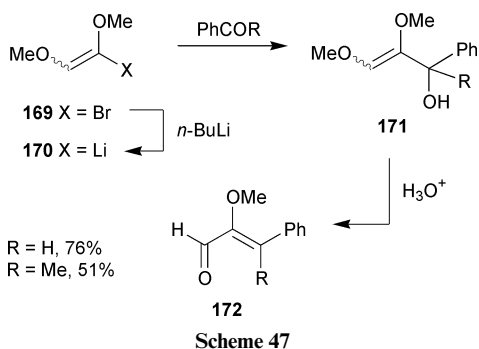
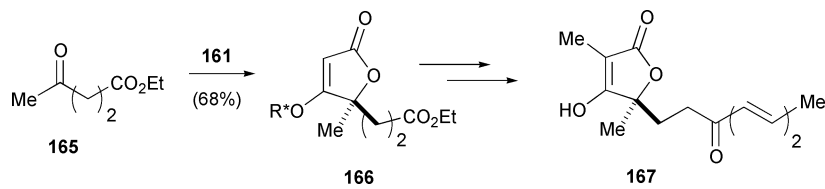
2.4.4 1,2-Dimethoxyvinyl lithium (MeOCH=CLiOMe)

In 1953, McElvain and Stammer¹³⁸ reported that treating 1-bromo-1,2-diethoxyethylene with $n\text{-BuLi}$ in ether at -35°C produces 1,2-diethoxyethylene as a mixture of *E/Z*-isomers when quenched with ethanol. The chemistry of the putative vinyl lithium intermediate was not explored until 1976 when Skold¹³⁹ demonstrated that, in a similar manner, an isomeric mixture of the 1,2-dimethoxyvinyl lithium species **170**, generated from 1-bromo-1,2-dimethoxyethylene **169** and $n\text{-BuLi}$ in ether at -70°C , undergoes reaction with aldehydes and ketones to yield allylic alcohols **171** (Scheme 47). Purification and hydrolysis of the allylic alcohols (6 M HCl, THF) affords α -methoxy- α,β -unsaturated aldehydes **172** in yields of 51–86%.^{139,140}

Schmidt and Betz reported¹⁴¹ that an analogous but stereochemically homogeneous vinyl anion **174** may be prepared by treating *Z*-1,2-dimethoxyethylene **173** with $t\text{-BuOK}$ – $n\text{-BuLi}$ in THF at -80°C (Scheme 48). Trapping **174** with methyl chloroformate provides methyl (*Z*)-2,3-dimethoxyacrylate **175** in 61% yield. The dimethoxy ester **175** can be utilized as a substrate for the further generation and reaction of α -methoxyvinyl lithium species as described previously for substituted acrylates, completing a synthetic sequence that corresponds to a diacyl dianion (**H**) equivalency.

1,2-Dimethoxyethenyl lithium **170**, prepared as in the Skold procedure, undergoes reaction with trialkylboranes to generate borates **177**,^{142–145} versatile synthons that can be transformed into 1,1-dialkylethylenes **178**,¹⁴² unsymmetrical ketones **179**,¹⁴³ 1-methoxyalkan-2-ones **180**¹⁴⁴ and aldehydes **181**¹⁴⁵ in synthetically useful yields (Scheme 49).

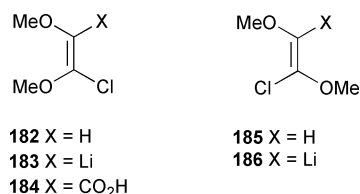
Well-characterized pentacarbonyl [(*Z*)-1,2-dimethoxyvinyl]-carbene complexes are formed stereospecifically by treating an



E/Z-mixture of dimethoxyvinyl lithium **170** with $M(\text{CO})_6$ ($M = \text{Cr}, \text{W}$).¹⁴⁶

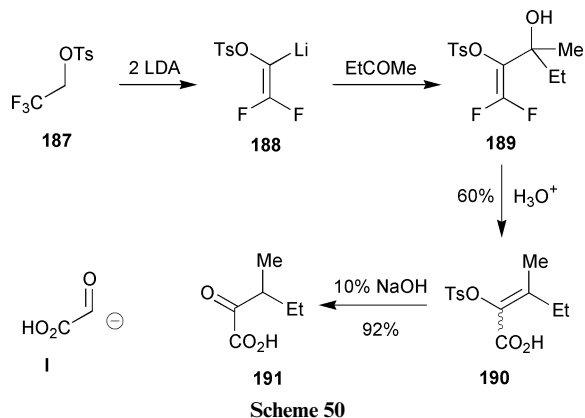
In an interesting study, O'Connor¹⁴⁷ described the reactions of *E*- and *Z*-1,2-dimethoxy-1-chloroethylene **182** and **185** with *s*-BuLi or *n*-BuLi, respectively, in THF at -100°C . The anion **183** generated by deprotonating the (*E*)-isomer **182** is stable for up to 2 h at -80°C (75% recovery upon quenching with HCl) and can be trapped with CO_2 to give 2,3-dimethoxy-3-chloroacrylic acid **184** (45%). However, the anion **186**, similarly derived from (*Z*)-isomer **185**, is less stable and cannot be trapped efficiently with CO_2 . Methyl methoxyacetate is

obtained (50–80%) by adding dilute aqueous acid to **186**, indicating that dimethoxyacetylene is formed in the reaction mixture by elimination of lithium chloride. These observations suggest that the *trans* isomer **186** is less stable than **183** and that *anti* elimination is more facile than *syn* elimination.

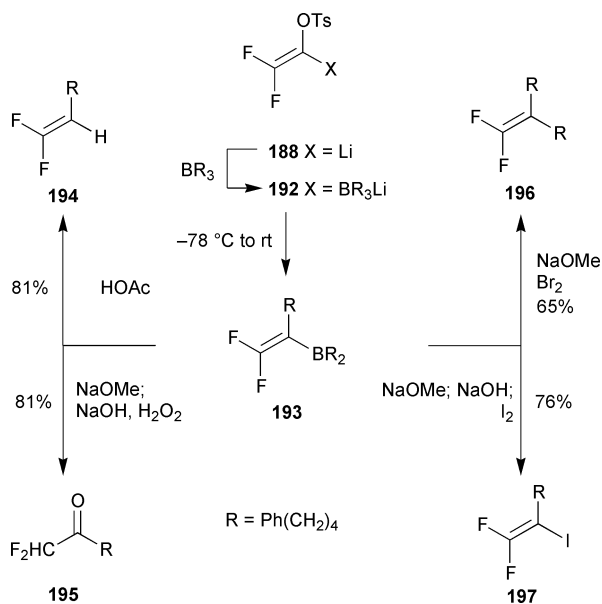


2.5 2,2-Difluoro-1-alkoxyvinyl lithium ($\text{F}_2\text{C}=\text{C}(\text{OR})\text{Li}$; R = Ts, MEM)

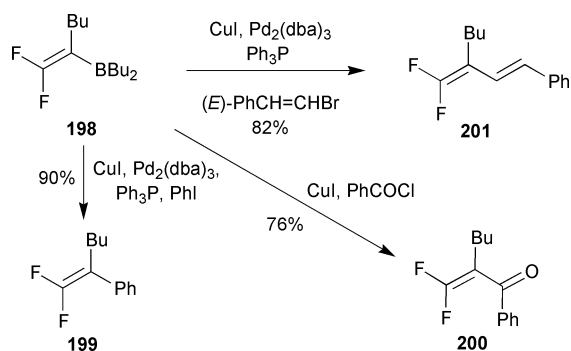
2,2-Difluoro-1-tosyloxyvinyl lithium **188** (Scheme 50) is readily formed from commercially available 2,2,2-trifluoroethyl tosylate **187** and 2 equivalents of LDA at -78°C in THF.¹⁴⁸ The original use of this reagent in synthesis was as the acyl anion equivalent **I**. Quantitative addition of **188** to aldehydes and ketones provides carbinols **189** that are hydrolyzed (95% H_2SO_4) to unsaturated acids **190** (60–78%; 1 : 1 *E/Z*-isomers with ketones and (*Z*)-isomers with aldehydes) and subsequently (10% aq NaOH) to α -keto acids **191** (89–98%).¹⁴⁸



Due to the increased interest in fluorinated molecules for applications in biological and medicinal chemistry, an effort was made to retain the fluorine atoms in **188** in subsequent reactions. In the first of a series of papers published since 1989, Ichikawa's group¹⁴⁹ described the reaction of the vinyl lithium reagent **188** with trialkylboranes. The initially produced ate-complex **192** undergoes rearrangement upon warming to room temperature to give the *gem*-difluoroalkenylborane **193** by a mechanism that involves 1,2-metalate rearrangement (Scheme 51). This class of reagent displays exceptional synthetic versatility and has been used by Ichikawa for the preparation of a wide range of compounds containing the difluorovinylidene and difluoromethylene moiety as illustrated in Schemes 51 and 52. For example, simple protonolysis (HOAc, reflux) provides 1,1-difluoroolefins **194** (41–90%).¹⁴⁹ In the presence of base (MeOH-free NaOMe) and either basic hydrogen peroxide, bromine or iodine, the corresponding difluoromethyl ketones **195** (27–81%),¹⁵⁰ disubstituted 1,1-difluoroalkenes **196** (54–65%),¹⁵¹ and 1,1-difluoro-2-iodoalk-1-enes **197** (51–76%),¹⁵¹



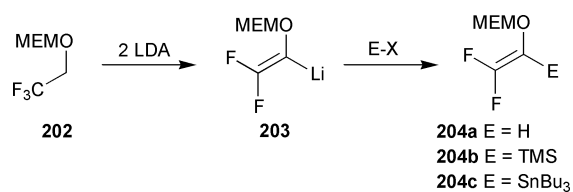
Scheme 51



Scheme 52

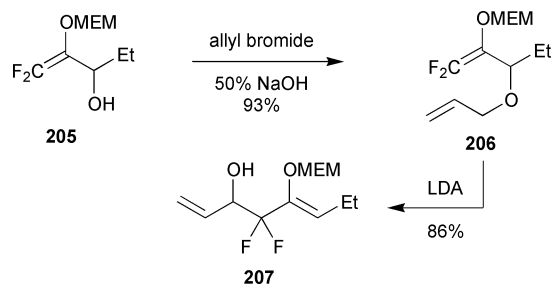
respectively, are obtained. An additional series of difluoro derivatives is available using palladium-catalyzed coupling procedures as exemplified by the reactions of 1-alkyl-2,2-difluorovinylborane **198** (Scheme 52), obtained from **192** in a fashion similar to **193**. Vinylborane **198** can be transformed to alkyl aryl disubstituted 1,1-difluoroalk-1-enes **199** (63–94%),^{152,153} 2,2-difluorovinylcarbonyl compounds **200** (54–84%)^{154,155} and 1,1-difluoro-1,3-dienes **201** (77–86%)¹⁵⁶ by coupling with aryl iodides, acid chlorides and vinyl bromides or iodides, respectively.

In conjunction with work on lithiated difluoroenol carbamates (see Scheme 28), Percy and coworkers^{157,158} described the preparation and reactivity of the methoxyethoxymethyl (MEM) ether carbanion **203** (Scheme 53). This carbanion, readily prepared by the addition of LDA (2 equiv.) to MEM-protected trifluoroethanol **202** in THF at $-78\text{ }^\circ\text{C}$, is stable at this temperature but decomposes above $-65\text{ }^\circ\text{C}$. It undergoes reaction with a range of electrophiles, including Me_3SiCl (79%), Bu_3SnCl (70%), aldehydes (61–94%) and ketones (44–79%) as well as $\text{NH}_4\text{Cl-MeOH}$, which efficiently generates the difluoroenol acetal **204a** (Scheme 53). However, vinyl lithium **203** does not undergo reaction with alkylating agents such as MeI, presumably due to the deactivating effect of the electron-withdrawing fluorine atoms. The stannylated derivative **204c** does not participate in Stille Pd(0)-catalyzed coupling reactions but it is effectively transmetalated ($n\text{-BuLi}$, $-78\text{ }^\circ\text{C}$) to provide an amine-free source of vinyl lithium reagent **203**.¹⁵⁸ Vinylsilane **204b** undergoes reaction with $n\text{-BuLi}$ in TMEDA at $-45\text{ }^\circ\text{C}$ to provide an *E/Z*-mixture of monofluoroenol silanes by an addition–elimination process (Scheme 31).¹⁵⁸ The addition of **203** to propanal provides **205**



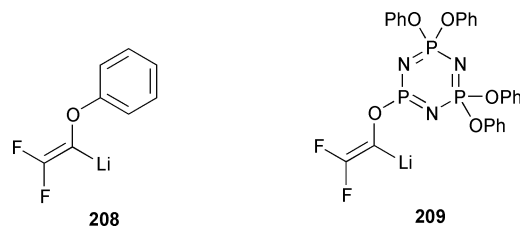
Scheme 53

(83%) and allylic alcohols such as these are useful synthons. For example, [2,3]-Wittig^{159,160} and [3,3]-Claisen¹⁶¹ rearrangements of derivatives of **205** yield highly functionalized products such as **207** that contain a difluoromethylene moiety (Scheme 54). Additionally, difluoroalcohol **205** is reduced with Red-Al® to a monofluoro olefin derivative (mixture of isomers) which can be used in similar rearrangement reactions for the introduction of monofluoromethylene subunits.¹⁶¹



Scheme 54

Two related vinyl lithium reagents **208**¹⁶² and **209**¹⁶³ are prepared by reaction of the phenyl and phosphazene trifluoroethanol derivatives with $n\text{-BuLi}$ and LDA, respectively. The nucleophilic reactivity of these reagents has only been briefly explored due to the limited synthetic potential of the resulting products.

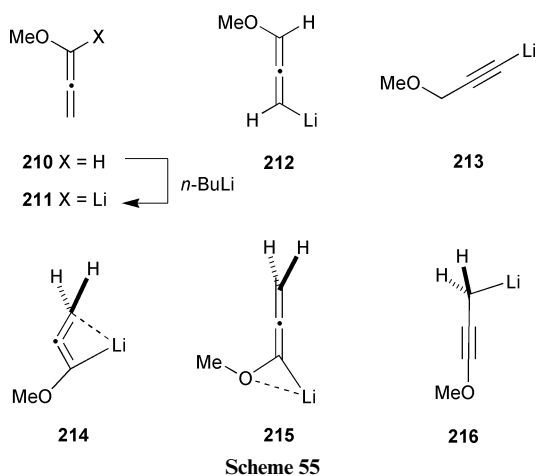


3 α -Metalated alkoxyallenes (allenyl ethers)

3.1 1-Methoxyallenyl lithium ($\text{H}_2\text{C}=\text{C}=\text{ClOMe}$)

The chemistry of 1-methoxyallenyl lithium **211** (Scheme 55) predates that of MVL or EVL discussed in the previous section, probably due to the facility of deprotonation of methoxyallene compared to methyl or ethyl vinyl ether. The parent methoxyallene **210** is readily prepared from propargyl ‡ alcohol by methylation (aq NaOH, Me_2SO_4) and isomerization (0.1 equivalent $t\text{-BuOK}$, $70\text{ }^\circ\text{C}$, 2–3 h).^{164–166} Arens and coworkers¹⁶⁴ first described the generation of **211** from methoxyallene **210** by a procedure that has been used with only minor modifications since its introduction. Thus, treatment of an ether or THF solution of **210** with 1 equiv. of $n\text{-BuLi}$ at -30 to $-40\text{ }^\circ\text{C}$ instantaneously provides the desired α -lithiated allene **211**. Anion **211** is stable at $-30\text{ }^\circ\text{C}$ for several days but rapidly decomposes above $-20\text{ }^\circ\text{C}$, presumably forming the corresponding γ -lithiated and acetylenic isomers **212** and **213**, respectively. Metalation of methoxyallene **210** with lithium, sodium or potassium amide in liquid NH_3 , followed by treating the mixture with an electrophile, yields products derived from all of the anions **211–213**. The ratio of products

‡ The IUPAC name for propargyl is prop-2-ynyl.

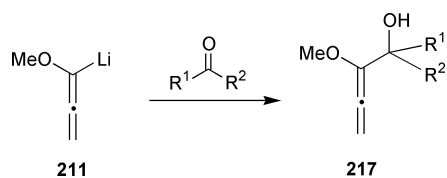


depends on the length of time the mixture is aged prior to quenching and the base (MNH₂, M = Li, Na, K) used for deprotonation.¹⁶⁴

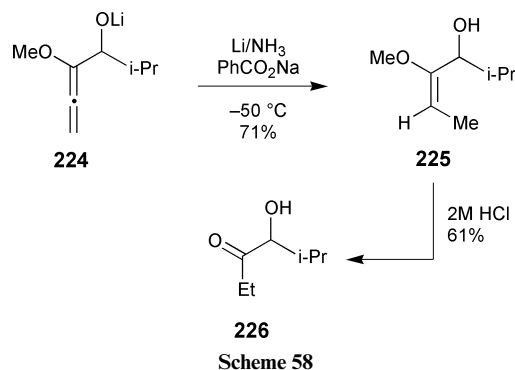
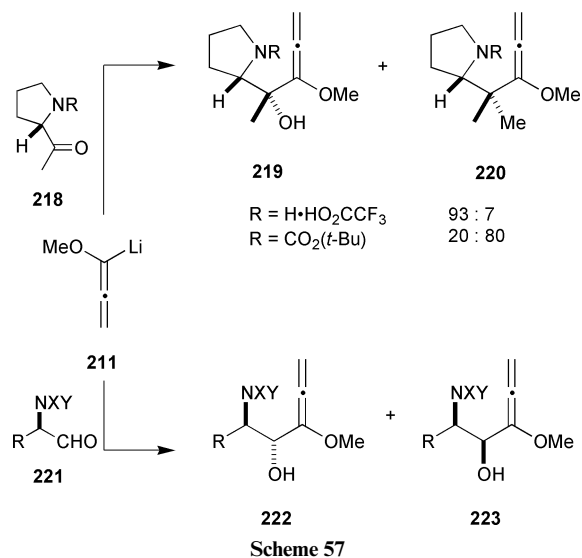
Minor variations of the standard Arens deprotonation procedure include (a) the use of lower reaction temperatures (−78 °C),^{18,167} (b) the use of THF–hexane as solvent¹⁶⁸ and (c) the replacement of *n*-BuLi with MeLi.¹⁶⁹ Surprisingly, the higher temperature (0 °C) that is required for metalation using MeLi is not problematic and byproducts such as **212** and **213** are not observed.

Schleyer and co-workers investigated the structure of α -lithiomethoxyallene **211** using ¹³C, ⁶Li, ¹H-HOESY NMR and IR spectroscopy.¹⁷⁰ These definitive studies proved that **211** exists in a non-classical 1,3-bridged structure **214** rather than an oxygen-coordinated structure **215** or an acetylenic resonance form **216**. The key observations include (a) the relatively unchanged ¹³C NMR resonance frequency of the internal C2 carbon (*ca.* 195 ppm) in the parent methoxyallene **210** and the lithiated species **211** and (b) a heteronuclear Overhauser correlation between the C3 protons and the lithium atom in the lithiated species **211**.¹⁷⁰ *Ab initio* model calculations on α -lithiohydroxyallene provided results that support the conclusions made from these experimental observations. The calculations further suggest that treatment of **211** with an electrophile using kinetically controlled conditions would favour α -substitution over γ -substitution. In addition, it was concluded from the spectra that α -lithiomethoxyallene **211** exists as a dimer in THF and a tetramer in Et₂O.

In agreement with the calculations, α -lithiomethoxyallene **211** readily adds to carbonyl compounds at low temperatures (−20 °C or less) to provide α -allenic alcohols **217** in good yields (Scheme 56, Table 7).

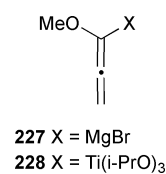


Several reports^{18,48,171,172} describe the substrate-controlled diastereoselective addition of α -lithiomethoxyallene **211** to chiral ketones such as **218** to give mixtures of adducts **219** and **220** (Scheme 57). Reissig and co-workers^{173–175} studied the addition of **211** to protected α -amino aldehydes **221** (Table 8). The *anti*-amino alcohols **222**, resulting from Felkin–Anh addition to **221**, are obtained with good diastereoselectivity. A highly stereoselective and regioselective synthesis of (*E*)-1-hydroxymethyl methyl propenyl ethers **225** (52–83%) is achieved by treating **211** with aldehydes followed by reduction of the intermediate lithium alkoxide **224** with Li–NH₃ (Scheme 58).¹⁷⁶



Hydrolysis provides the corresponding α -hydroxyethyl ketones *e.g.*, **226** (40–83%).

α -Lithiomethoxyallene **211** is converted to the Grignard reagent **227** by the addition of MgBr₂. Compared to the lithio species **211**, the addition of **227** to chiral ketones results in increased chelation-controlled diastereoselectivity but with a corresponding decrease in yield.¹⁷¹ Presumably, the decrease in yield is due to competing γ -substitution of the allene as might be expected based on the theoretical calculations of Schleyer and co-workers.¹⁷⁰ In a similar fashion, the titanated methoxyallene **228**, obtained by treating **211** with Ti(*i*-PrO)₃Cl at −100 to −78 °C, adds to α -amino aldehydes **221** with high γ -selectivity providing methoxyalkynes.¹⁷⁷



The α -hydroxyallenes **217** have been used for the preparation of a number of synthetically useful compounds as illustrated in Scheme 59. For example, hydrolysis (5% H₂SO₄, 0 to 5 °C) provides α,β -unsaturated- α' -hydroxyketones **229** (85–90%),¹⁷⁸ equating α -lithiomethoxyallene **211** with an acyl crolein anion. Exposure to catalytic *t*-BuOK in DMSO¹⁷⁹ or catalytic *t*-BuOK in *t*-BuOH–18-crown-6^{167,180} provides 3-methoxy-2,5-dihydrofurans **230** (42–96%) *via* a 5-*endo-dig* process. As a consequence of deuterium labelling and kinetic studies, Magnus and Albaugh–Robertson¹⁸⁰ suggested that this reaction proceeds *via* a single electron transfer mechanism. Vermeer and co-workers¹⁸¹ demonstrated that transformation of alcohols **217** to their methanesulfinic esters (>95%) followed by reaction with an organocopper(I) reagent produces 3-methoxy-1,3-dienes **231**

Table 7 Addition of α -lithiomethoxyallene **211** to carbonyl compounds (Scheme 56)

α -Allenic alcohol 217	R ¹	R ²	Yield (%)	Ref.
217a	H	H	70	179
217b	Me	H	80	178
217c	Ph	H	87	197
217d	PhMeCH	H	84 ^a	173
217e	Me	Me	82	178
217f	Me	CH ₂ Br	75 ^b	182
217g	Ph	Ph	67	197
217h		-(CH ₂) ₅ -	90	167
217i		-CH=CH(CH ₂) ₃ -	80	167

^a Ratio 86 : 14 *anti* : *syn*. ^b For two-step procedure to epoxide.

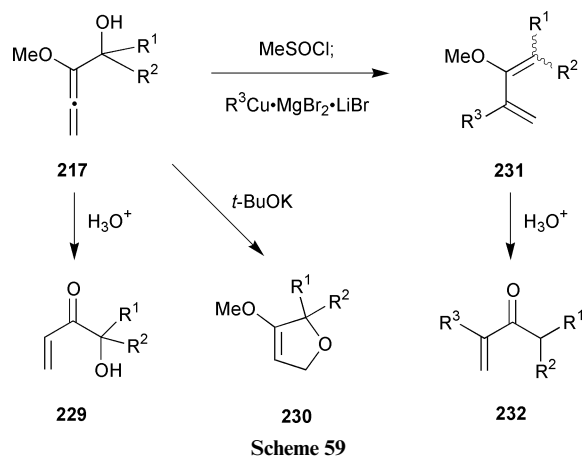
Table 8 Addition of α -lithiomethoxyallene **211** to α -amino aldehydes **221** (Scheme 57)

Amino aldehyde 221	R	X,Y	<i>anti</i> - <i>syn</i>	Yield 222 (%)	Ref.
221a	Me	Bn,Bn	95 : 5	94	173,175
221b	Me	Bn,Boc	89 : 11	—	174
221c	<i>i</i> -Bu	Bn,Bn	80 : 20	77	173,175
221d	<i>i</i> -Bu	Bn,Boc	86 : 14	—	174

Table 9 Alkylation of α -lithiomethoxyallene **211** with electrophiles (Scheme 60)

Product 233	E-X	Solvent ^a	Yield (%)	Ref.
233a	Me-I	A	^b	184
233b	<i>n</i> -Pr-Br	B	47	164
233c	<i>n</i> -Bu-Br	B	67	164
233d	Bn-Br	B	64	164
233e	EtOCH ₂ -Cl	C	78	186
233f	Ph(CH ₂) ₂ -Br	B	^b	190
233g	TBDMSO(CH ₂) ₄ -I	A	99	185
233h	MeS-SMe	C	75	178
233i	Ethylene oxide	C	72	179
233j	I-I	C	95	169
233k	Me ₃ Si-Cl	C	81	196
233l	Me ₃ Sn-Cl	C	61	197
233m	(-)-TolSO-OR	A	90	198

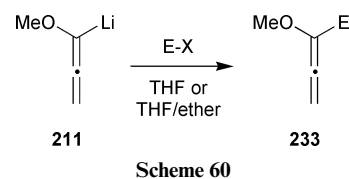
^a A = THF; B = THF-Et₂O; C = Et₂O. ^b Yield not given.



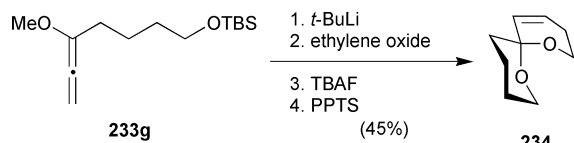
(*E/Z* 1 : 1 to 95 : 5) which may be readily hydrolyzed to α -alkylidene ketones **232** (70–90%). The hydroxyallene substrates **217** have also been used for the synthesis of tetrasubstituted furans,¹⁸² spiroalkanones,¹⁸³ octahydroindolizines,^{18,48} 5-hydroxy-5-vinylcyclopent-2-en-1-ones¹⁷² and α -hydroxy esters *via* ozonolysis.¹⁷⁴

The alkylation of α -lithiomethoxyallene **211** with alkyl halides proceeds in synthetically useful yields as summarized in Table 9 (Scheme 60), provided that THF^{184,185} or THF-Et₂O,¹⁶⁴ and not Et₂O alone, is used as the solvent.

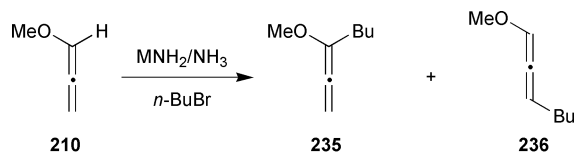
Presumably this reactivity difference is a reflection of the



aggregation state of the lithium species **211** as described by Schleyer and co-workers,¹⁷⁰ the more reactive dimer being formed in THF solution. Interestingly, ether alone is a suitable solvent for the alkylation of reactive electrophiles such as α -chloroethers¹⁸⁶ but not methyl iodide.¹⁸⁴ Kocienski elegantly used the products of these alkylation reactions, such as **233g**, for the synthesis of 1,7-dioxaspiro[5.5]undec-4-enes **234** (Scheme 61). The spiro compounds are precursors for the synthesis of a variety of natural products including talaromycins A and B^{168,185} and lacrimin A.^{187,188} As described above, the deprotonation and alkylation of methoxyallene **210** using MNH₂ (M = Li, Na, K) in ammonia leads to mixtures of α - and γ -alkylated products **235** and **236**, respectively, in low yields (Scheme 62).¹⁶⁴ α -Lithiomethoxyallene **211** also reacts with several other electrophiles as indicated in Table 9. A number of these products have been used in novel reactions to provide synthetically useful compounds such as 3-methoxyalk-3-en-1-yne **237** (82–92%) (Scheme 63),¹⁸⁶ alk-1-ynyl ethers **238** (65–85%) (Scheme 64),¹⁶⁹ methoxycyclopropanes **239** (63–79%) (Scheme 65)¹⁸⁹ and *E*-1-substituted-2-methoxybutadienes **240** (39–53%) (Scheme 66).¹⁹⁰

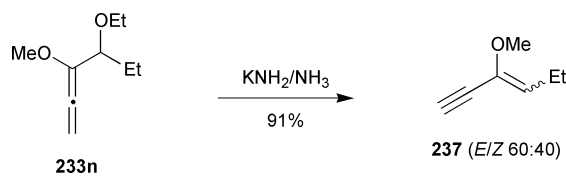


Scheme 61

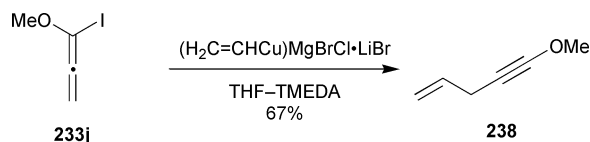


M = Li 55 : 45 (45%)
 M = Na 53 : 47 (44%)
 M = K 56 : 44 (5%)

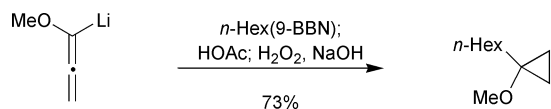
Scheme 62



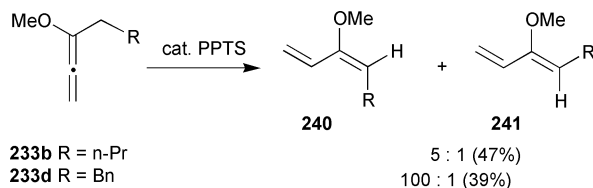
Scheme 63



Scheme 64



Scheme 65



Scheme 66

α -Lithiomethoxyallene **211** participates in Pd(0)-catalyzed cross-coupling reactions with aryl iodides,¹⁹¹ while the allenyl zincate derived by reaction with ZnCl₂ couples in a similar fashion with aryl iodides, benzyl bromide and vinyl halides (bromides and iodides).²⁴ Knochel and co-workers¹⁹² have shown that the allenyl copper reagent obtained by treating **211** with CuI·2LiCl reacts with (iodomethyl)zinc iodide and carbonyl compounds in a novel polymethylene homologation reaction (Scheme 67).

Linstrumelle^{193–195} and Magnus¹⁹⁶ demonstrated that 1-substituted-1-methoxyallenes **246** can be metalated with *n*-BuLi in THF at $-50\text{ }^\circ\text{C}$, or more cleanly with *t*-BuLi in THF at $-78\text{ }^\circ\text{C}$.¹⁹⁶ The γ -lithiated species **247** so produced react with a variety of electrophiles (*e.g.*, Scheme 61).

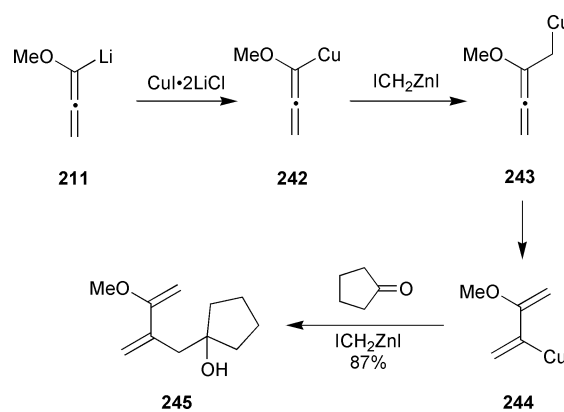
3.2 α -Lithio derivatives of other simple alkoxyallenes (H₂C=C=ClIOR)

The ethoxyethyl (EE)^{15,199–202} and methoxymethyl (MOM)^{88,203–210} allenyl ethers **250** and **248** are deprotonated with *n*-BuLi in THF or THF : Et₂O (1 : 1), respectively, at -78 to

Table 10 Silylation/stannylation and hydrolysis of α -lithioallene **251** (Scheme 68)

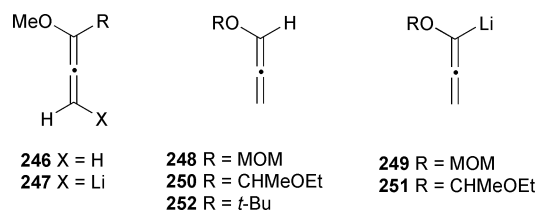
R ₃ MCl	Yield 253 (%)	Yield 254 (%)	Ref.
Me ₃ SiCl	81	65	200
<i>t</i> -BuMe ₂ SiCl	86 ^a	84	200
Et ₃ SiCl	—	65 ^b	15
PhMe ₂ SiCl	—	35 ^b	15
(MeCC)Ph ₂ SiCl	—	29 ^b	15
Ph ₃ SiCl	—	67 ^b	15
Me ₃ SnCl	83	91	202

^a HMPA required for alkylation. ^b Overall yield for two steps.



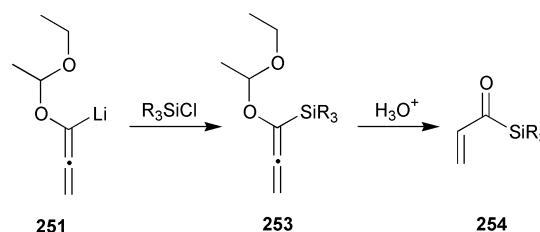
Scheme 67

$-95\text{ }^\circ\text{C}$ to produce the α -lithiated allenes **249** and **251**. In some cases, the addition of a radical inhibitor is advantageous.¹⁵ The *tert*-butoxyallene **252**, which bears a sterically hindering alkoxy moiety, is deprotonated with (*c*-hex)₂NLi predominantly in the γ -position (γ : α 68 : 12).¹⁹³



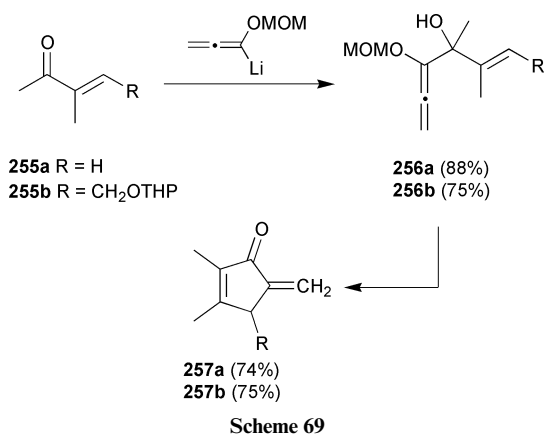
246 X = H
247 X = Li
248 R = MOM
250 R = CHMeOEt
252 R = *t*-Bu
249 R = MOM
251 R = CHMeOEt

Reich^{199,200} and Buynak¹⁵ have trapped the anion **251** with a variety of silyl chlorides to generate the allenyl silanes **253**. The silanes **253** are hydrolyzed (0.1 M H₂SO₄, aq THF or 2 M HCl, Me₂CO) to the vinyl silyl ketones **254** (Scheme 68, Table 10). The propenylstannanes analogous to **254** are prepared in a similar manner (Table 10).²⁰² Stork and Nokamura²⁰¹ have used the lithiated EE ether **251** in a synthesis of the cytochalasins by preparing an enyne in analogy to the reaction shown in Scheme 63.



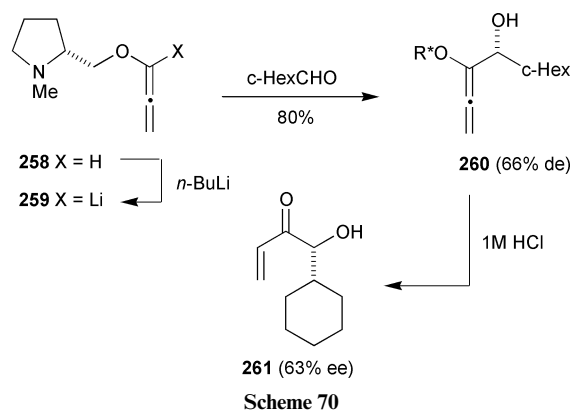
Scheme 68

Tius described the reaction of the lithiated MOM ether **249** with α,β -unsaturated ketones **255** (Scheme 69).^{88,203–210} The resulting alkylated products **256** are obtained in good yields and are useful substrates that undergo acid-catalyzed (BF₃·OEt₂ or Tf₂O–2,6-lutidine) rearrangement to



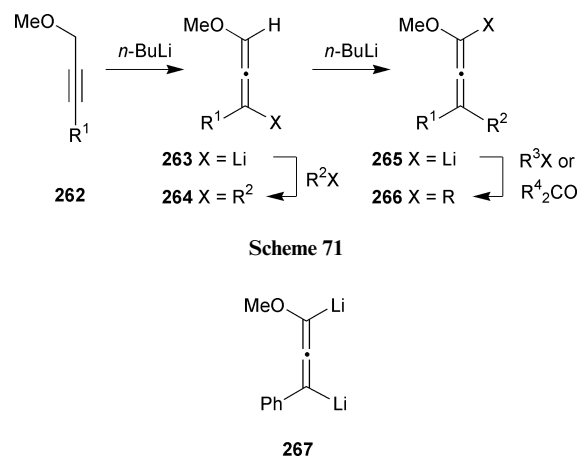
the corresponding α -methylene-cyclopentenones **257** (~75%). This cationic cyclopentannulation reaction is the key step in the synthesis of methylenomycin B (**257a**), methylenomycin A^{88,204,205,207} and xanthocidin.²⁰⁹

Vatèle and co-workers^{211,212} extended the methodology illustrated in Schemes 56 and 59 to the preparation of enantiomerically enriched α -hydroxy enones **229**. A series of alkoxyallenes bearing chiral alkoxy groups were metalated with *n*-BuLi at various temperatures (0 to -80°C) and in various solvents. The resulting α -lithio derivatives were treated with a variety of simple aldehydes. The reagent **259** (Scheme 70) derived from *S*-(-)-*N*-methylprolinol, using *n*-BuLi in ether at -40°C for deprotonation, is the optimal reagent for producing satisfactory and consistent diastereoselectivity in products **260** (de 45–70%). A chiral diacetoneglucose-derived reagent related to **258** gives highest diastereoselectivity upon addition to benzaldehyde (de 85%). The α -hydroxy enone product in this latter reaction was used in a synthesis of (+)-goniodiol.²¹² Notably, the α -hydroxyallene products **260** are hydrolyzed (1 M HCl) to the hydroxy enones **261** without racemization.



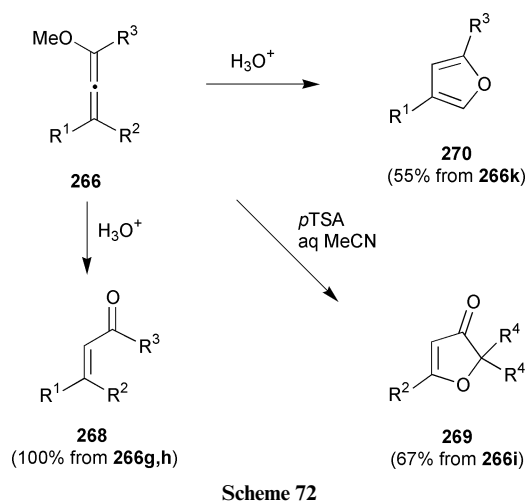
3.3 3,3-Disubstituted 1-methoxyallenyllithium ($\text{R}_2\text{C}=\text{C}=\text{CLiOMe}$)

Treating methyl propargylic ethers **262** ($\text{R}^1 = \text{Ph}, \text{SiMe}_3, \text{SMe}, \text{alkyl}$) with 1 equiv. of *n*-BuLi at -40 to -75°C provides an allenic anion **263** which may be alkylated with a variety of electrophiles ($\text{Me}_3\text{SiCl}, \text{RBr}, \text{MeI}$) to produce the methoxyallenes **264** in good yields (50–95%) (Scheme 71).^{213–219} These allenes are metalated with another equivalent of *n*-BuLi,^{213–216} *t*-BuLi²¹⁸ or LiNH_2 ²¹⁷ in ether or THF at temperatures from -40 to -75°C . The α -lithiated methoxyallenes **265** so formed are alkylated to provide highly substituted methoxyallenes **266** in good yields (Scheme 71, Table 11).^{213–219} The addition of HMPA accelerates the reaction with unreactive electrophiles such as alkyl bromides.²¹⁶ In the case of $\text{R}^1 = \text{Ph}$, the original



propargylic ether **262** reacts with 2 equiv. of *n*-BuLi at -75°C in Et_2O to generate an allenic dianion **267** that may be trapped by electrophiles first at the γ -position and then α to the methoxy group (Table 11).²¹³

The polysubstituted methoxyallenes **266** (Scheme 72) have been used for the preparation of ethylenic ketones **268** by hydrolysis (20% HCl) (61–100%),²¹⁶ furan-3-ones **269** (67–93%),²¹⁷ and 1,3-disubstituted furans **270** (39–67%).²¹¹



Finally, an excellent review by Zimmer¹⁶⁵ summarizes the general synthetic chemistry of alkoxyallenes, including α -lithiomethoxyallene **211**.

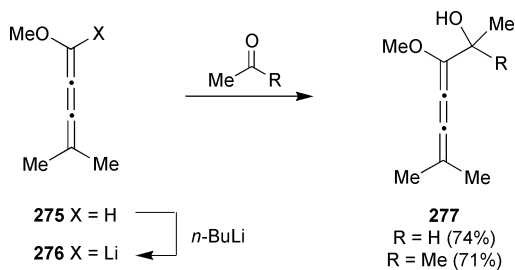
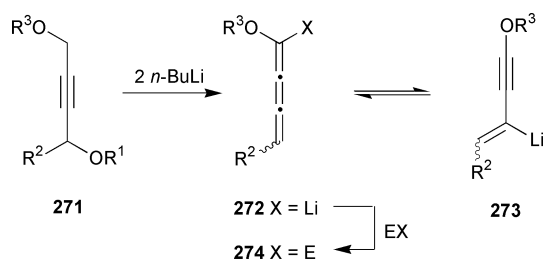
3.4 α -Lithiated cumulenyl ethers

1-Alkoxy-1,2,3-trienyllithiums **272** are readily generated by treating the parent acetylenic bis-ethers **271** with 2.5 equiv. of *n*-BuLi at -20 to -50°C in Et_2O ($\text{R}^2 = \text{H}, \text{Me}, \text{i-Pr}, \text{C}_5\text{H}_{11}$).^{220,221} These anions presumably exist in equilibrium with the lithiated enyne tautomer **273**. They undergo reaction with water or D_2O (60–75%), MeI (with HMPA) (65–70%), acetone (70–75%) and α -chloroethers to give the cumulenyl ethers **274** as mixtures of *E/Z* isomers (Scheme 73). Products resulting from alkylation of the enyne form **273**, or from alkylation of the δ -lithiated cumulenyl ether, are not observed. In a similar fashion, cumulenyl methyl ether **275** bearing two methyl groups at the δ -position is obtained by treating the requisite acetylenic bis-ether **271** with 2 equiv. of NaNH_2 in liquid NH_3 .²²² The methyl ether **275** is deprotonated using *n*-BuLi in Et_2O or THF at -30°C and treating the resulting lithiated species **276** with aldehydes or ketones produces the carbinols **277** (55–90%) (Scheme 74).²²³ Again, products from isomerization of the lithiated cumulene **276** to the enyne tautomer are not observed. The synthetic utility of these

Table 11 Alkylation of 3,3-disubstituted 1-methoxyallenyllithium **265** with electrophiles (Scheme 71)

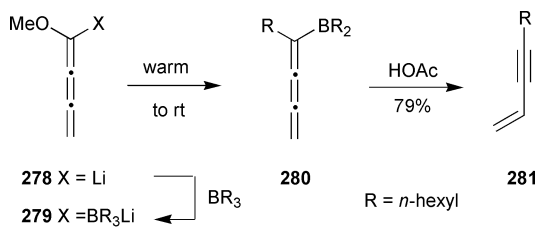
Product 266	R ¹	R ²	R ³ -X or R ⁴ CO	Yield (%)	Ref.
266a	Ph	Et	MeI	76 ^a	213,215
266b	Ph	Me ₃ Si	MeI	70 ^a	213,215
266c	Ph	Me ₃ Si	Me ₂ CO	80 ^a	215
266d	Me ₃ Si	Me	MeI	75	219
266e	Me ₃ Si	Me ₃ Si	MeOCH ₂ Cl	70	219
266f	Me ₃ Si	Me ₃ Si	Me ₂ CO	70	219
266g	C ₅ H ₁₁	Me ₃ Si	Me ₂ SO ₄	100	216
266h	C ₅ H ₁₁	Me	TMSCl	100	216
266i	MeS	Et	Me ₂ CO	67 ^b	217
266j	MeS	Me	PH ₂ CO	93 ^b	217
266k	C ₆ H ₁₃	CH ₂ OH	MeI	55 ^c	218
266l	C ₆ H ₁₃	CH ₂ OH	MeCH=CHCH ₂ Cl	15 ^c	218

^a Via a sequential alkylation of the dianion **267**. ^b Overall yield for conversion to the corresponding furan-3-ones **269**. ^c Overall yield for conversion to 1,3-substituted furans **270**.



compounds is limited since the cumulenic ethers are highly combustible in air and explosive when heated above 50 °C.^{221,223} The extreme air-sensitivity of these compounds requires that the water and ether solvents used for washing and extraction in the workup procedures be perfused with nitrogen prior to use.

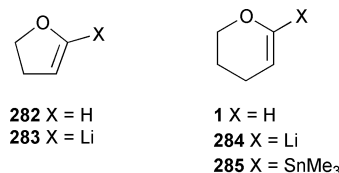
In spite of these limitations, Suzuki²²⁴ has used the unsubstituted lithiated 1-methoxybuta-1,2,3-triene **278** for the synthesis of alk-1-en-3-yne **281** (Scheme 75). Exposing 1,4-dimethoxybut-2-yne to 2 equiv. of *n*-BuLi in Et₂O at -78 to -45 °C provides the lithium anion **278**, which undergoes reaction with R₃B at low temperature (-78 °C) to generate the intermediate cumulenic borate **279**. Alkyl migration occurs upon warming to room temperature and protonolysis-hydrolysis of the intermediate borate **280** provides the enyne **281** (88–91%).



4 α -Metalated cyclic vinyl ethers

4.1 α -Lithiodihydrofuran (Li-DHF) and α -lithiodihydropyran (Li-DHP)

Many groups have studied the metalation of 2,3-dihydrofuran **282** (DHF) and 2,3-dihydro-4*H*-pyran **1** (DHP) and the resulting α -lithiated species **283** (Li-DHF) and **284** (Li-DHP) have been widely used in organic synthesis.



4.1.1 Generation of Li-DHF and Li-DHP

In 1951, Paul and Tchelitcheff¹⁻³ first noted the α -metalation of DHP with pentylsodium in petroleum ether at -10 °C. Reaction of the putative intermediate sodium derivative **2** with CO₂ gave the acid **4** (61%) along with the expected alkyne **5** (39%) (Scheme 1). However, it was not until 1977 that Boeckman and Bruza²²⁵ recognized the potential synthetic utility of the α -lithiated cyclic vinyl ethers and described their use as cyclic acyl anions. Since that time, a wide range of procedures has been reported for the deprotonation of DHF and DHP. Some of the more widely used procedures are summarized in Table 12.

From this diverse group of lithiation procedures, it is apparent that not any one method is appropriate for all intended applications. However, two basic preparative methods are recognized depending on the base used. The first procedure, described by Boeckman,^{85,225} has seen the widest utility and involves the deprotonation of the cyclic vinyl ether with *t*-BuLi in pentane and a small amount of THF (Table 12, first entry). The use of DME or ether as solvent in the deprotonation reaction is ineffective. The presumed metalating species is a *t*-BuLi dimer (2RLi·THF) and both DHF and DHP are efficiently lithiated to form Li-DHF and Li-DHP, respectively. The lithiation of DHF is described in an *Organic Synthesis* procedure.²³² The organolithium solutions of **283** and **284** are stable for several hours at 0 °C and solutions suitable for subsequent use are obtained by diluting with THF or Et₂O and recooling to -78 °C. Boeckman also studied the relative rate of deprotonation of DHF and DHP using this base system and observed that the α -proton in DHF is slightly less kinetically acidic. Meyers and co-worker²⁶ described a potentially useful modification of the Boeckman procedure that involves substitution of the traditionally used THF solvent with THP. This modification is

Table 12 Reaction conditions for formation of Li-DHF (283) and Li-DHP (284) by the α -lithiation of DHF and DHP

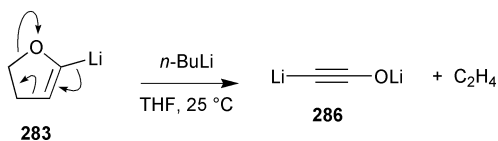
Substrate	RLi	Solvent ^a	Additive	Temp/°C	Ref.
DHF–DHP	<i>t</i> -BuLi	P	THF ^b	–10 to 0	85,225
DHF–DHP	<i>n</i> -BuLi	H	TMEDA ^c	0 to 25 ^d	25,226
DHF	<i>n</i> -BuLi : <i>t</i> -BuOK ^e	H or P	TMEDA ^c	–40 to –10	28
DHF	<i>n</i> -BuLi	Et ₂ O	—	0	227
DHP	<i>n</i> -BuLi	Et ₂ O	TMEDA ^f	–27 to 25 ^d	227,228
DHF	<i>n</i> -BuLi	THF	—	25	229
DHP	<i>n</i> -BuLi	THF–H	—	25 to 50	229–231

^a H = hexane; P = pentane. ^b 2 : 1 THF : *t*-BuLi. ^c Catalytic amount (0.1 equiv.). ^d Lithium species precipitates. ^e Molar ratio of *n*-BuLi : *t*-BuOK : TMEDA = 1 : 1 : 1. ^f Et₂O : TMEDA = 10 : 1.

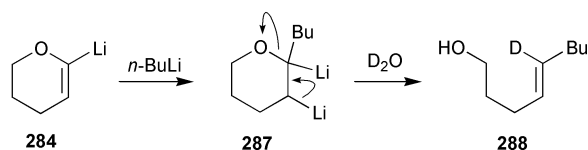
useful in those instances requiring enolate-free environments since *t*-BuLi decomposes THF to acetaldehyde enolate anion. Another related but less-utilized method for forming Li-DHP involves treating stannylated DHP **285** with *n*-BuLi in THF.^{233,234}

The second general method for generating Li-DHF and Li-DHP, introduced by Sebastian and co-workers,^{25,226} involves deprotonating DHF or DHP with *n*-BuLi and a catalytic amount of TMEDA in hexane or pentane at 0 °C to room temperature (or slightly above for DHP) (Table 12, second entry). In the absence of TMEDA, α -lithiation takes place only at elevated temperatures (50–60 °C).^{230,231} The resulting Li-DHF and Li-DHP species precipitate from the reaction mixture as white solids that can be centrifuged, washed with hexane and then redissolved in THF or Et₂O. The ¹³C NMR spectra of Li-DHF and Li-DHP prepared in this manner reveal that the resonance of the vinyl carbon bonded to lithium experiences the greatest downfield shift (~57 ppm) compared to the corresponding resonances of DHF and DHP.²⁵ Furthermore, from the measured coupling constants in the NMR spectra of the parent vinyl ethers, it is possible to estimate the percentage of *s* character of the vinyl ether α -protons. These data suggest that the relative kinetic acidities of the α -protons are in the order DHF > DHP, opposite to that observed experimentally by Boeckman.

No allylic deprotonation or β -metalation is observed in either of these general lithiation procedures and α -metalation regioselectivity has been rationalized based on molecular orbital calculations as well as steric and electronic arguments.^{25,85,226} However, both DHF and DHP are known to undergo cleavage reactions with *n*-BuLi under the appropriate reaction conditions. Li-DHF fragments to ethylene and dilithioynolate **286** after 34 h at 25 °C in the presence of 2 equiv. *n*-BuLi (in THF) (Scheme 76).²³⁵ Li-DHP fragments upon treatment with 2 equiv. of *n*-BuLi in Et₂O at 0 °C for 8 h. The reaction proceeds by a stereospecific ($\geq 98\%$) addition–elimination sequence to form the (*E*)-alkenol **288** (Scheme 77).^{236,237}

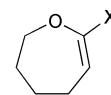


Scheme 76



Scheme 77

Lithiation of 2,3,4,5-tetrahydrooxepin **289** with *n*-BuLi in THF–benzene takes place at room temperature and after 3 days provides the α -lithiated species **290** that has been characterized by ¹³C NMR spectroscopy.²³⁶

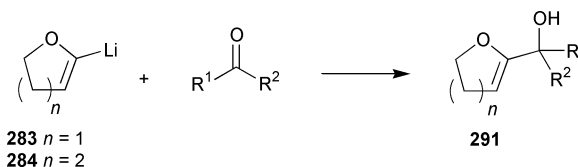


289 X = H
290 X = Li

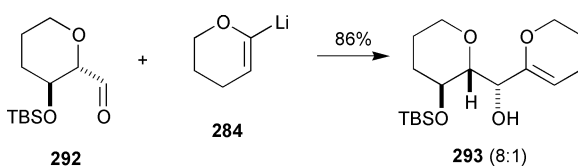
4.1.2 Reactivity of Li-DHF and Li-DHP

4.1.2.1 Reaction with electrophiles

The reactivity of Li-DHF and Li-DHP toward carbonyl containing substrates is typical for that of hard, unstabilized organometallic reagents. Li-DHF and Li-DHP readily add to simple aldehydes and ketones,^{85,225,231,238–241} generally at low temperatures (–78 to 0 °C), generating the corresponding carbinols **291** in good to excellent yields (Scheme 78, Table 13). Regioselective 1,2-addition occurs in reactions with α,β -unsaturated ketones^{85,225,231,239} and substituted quinones.²⁴² Substrate-controlled diastereoselective addition results from reaction with chiral aldehydes such as **292** (Scheme 79)^{234,243} and bicyclic ketones such as norcamphor and fenchone.^{244,245} Simple aldehydes and ketones are not enolized using the lithium reagents **283** or **284**. However, in more complex systems in which this competing reaction is problematic, the cerium reagents **294** and **295** (obtained by treating **283** and **284** with CeCl₃) may be used to cleanly add in a stereocontrolled fashion to give mixtures of **296** and **297** (Scheme 80).^{245–247} Using THF–TMEDA as the solvent increases the reactivity of Li-DHF towards sterically hindered ketones.²⁴⁸



Scheme 78

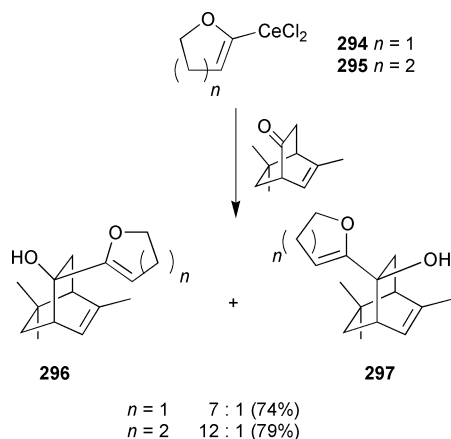
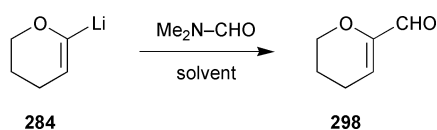


Scheme 79

Li-DHF and Li-DHP add twice to reactive acylating agents, such as CO₂, acid chlorides or anhydrides, providing the dialkylated carbinols in moderate yields (41–67%).^{85,231} Treatment of Li-DHP with γ -lactones produces the corresponding alkylated γ -hydroxy ketones.²⁴⁹ Boeckman and Bruza⁸⁵ have shown that the addition of Li-DHP to *N,N*-dialkylcarbamides proceeds in low yields. However, the yield of ketone **298** improves significantly by replacing the THF–pentane solvent with THP as described by Meyers²⁶ (Scheme 81). Adding Li-DHF and Li-DHP to nitriles in hexane solvent affords the imine adducts in moderate yields.⁶² Reacting

Table 13 Reaction of Li-DHF (**283**) and Li-DHP (**284**) with aldehydes and ketones (Scheme 78)

Substrate	R ¹	R ²	Yield of 291 (%)	Ref.
Li-DHF (283)	<i>n</i> -Bu	H	81	241
	<i>i</i> -Pr	H	100	241
	Me	Me	78	85,225
Li-DHP (284)	H	H	50	231,238
	Me	H	70	231,238
	H ₂ C=CH	H	63	231,238
	Me ₃ SiCH=CH	H	77	239
	Ph	H	68	231,238
	Me	Me	82–86	85,225,231,238
	Me	(CH ₂) ₂ CO ₂ Et	68	85,225
	–(CH ₂) ₃ CH=CH–	68	85,225	

**Scheme 80**

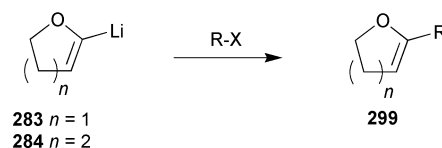
THF/pentane: 30%
THP: 70%

Scheme 81

Li-DHP with acylsilanes results in a novel Brook rearrangement–fragmentation sequence leading to silyloxyalenes.²³³ As described for EVL (Scheme 13), Li-DHP undergoes reaction with Cr(CO)₆ to provide, after methylation and condensation with acetylenes, a novel route to highly substituted phenols.^{81,250} In certain cases, Li-DHP adds in a conjugate fashion to α,β -unsaturated sulfones.⁵⁹

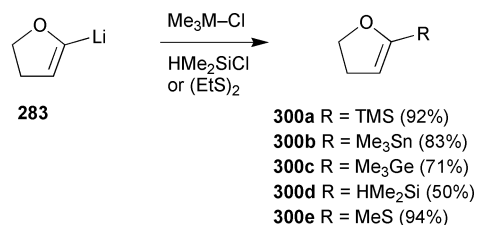
Reaction of Li-DHF and Li-DHP with alkyl halides represents the most extensively studied and widely used application of these reagents in organic synthesis.^{85,225,230,232,240,241,251–264} A wide range of alkylations are feasible as illustrated in Table 14 (Scheme 82). The early alkylation reactions described by Boeckman^{85,225} employed THF–HMPA solvent mixtures at moderate temperatures (–78 to 25 °C) while subsequent alkylations were conducted at elevated temperatures (25 to 50 °C) without HMPA.^{252,255,256} As implied from their absence in Table 14, secondary alkyl halides, alkyl chlorides and tosylates are unreactive towards Li-DHF and Li-DHP.⁸⁵ Allyl bromide and iodide undergo preferential α -metalation rather than alkylation.⁸⁵ As is typical of organolithium reagents, the reaction of Li-DHF and Li-DHP with epoxides proceeds in poor yield (~20%).⁸⁵ Recourse is made in these cases to alternative organometallic derivatives such as cuprates (see following section). Treating Li-DHP with fluoroacetylene (generated by reacting 1,1-difluoroethylene with alkyllithium reagents at –110 °C) produces the DHP–acetylene adduct (75%, see Table 14).

In many cases, the crude alkylation reaction product is sufficiently pure for subsequent reactions. The low isolated yields

**Scheme 82**

occasionally observed in these alkylation reactions are likely due to purification losses resulting from the water solubility, volatility or acid sensitivity of the enol ether products.⁸⁵ The alkylation products **299** derived from Li-DHF, although stable at –20 °C in base-washed glassware, are prone to rearrangement. Prolonged heating or mildly acidic conditions (CDCl₃ at 20 °C in 1 h) produce isomers in which the double bond has migrated into the exocyclic position.²⁴¹

In related reactions, Li-DHF and Li-DHP readily undergo alkylation with silyl chlorides,^{228,241,265–267} germanyl chlorides,²⁶⁶ stannyl chlorides^{234,241,268} and disulfides^{28,85} to produce the substitution products **300** (Scheme 83). Some of the silylated derivatives such as **300d** are novel hydrosilylation reagents.^{265,267}

**Scheme 83**

The utility of Li-DHF and Li-DHP as cyclic acyl anion equivalents is readily apparent from Scheme 84. The carbinol **291** and alkylated products **299** and **300** are easily transformed into synthetically useful compounds, including substituted alkenes, spiroketals and keto acids or alcohols. Thus, hydrolysis (2 M HCl, aq THF, 25 °C) or Jones oxidation (H₂CrO₄, 0 to 25 °C) of **299** provides hydroxy ketones **301** (77–97%)^{85,225} or keto acids **302** (59–69%).^{232,264} When the R substituent contains an alcohol moiety, the cyclization of **299** takes place under acidic conditions (pyridinium tosylate in CH₂Cl₂ or HCl in Et₂O) to yield spiroketals such as **303** (~70%).^{243,249,252,260}

Kocienski and co-workers^{240,241,255–258} extensively studied the Ni(0)-catalyzed coupling reaction of 5-alkyl DHF derivatives **304** with Grignard reagents (Scheme 85, Table 15). Under optimized conditions (catalytic NiCl₂(Ph₃P)₂, refluxing Et₂O : PhH 1 : 5), ring cleavage occurs with retention of stereochemistry ($\geq 94\%$) and provides trisubstituted alkenols **305** (R² = alkyl, aryl) in good to excellent yields. The organometallic partner in the reaction is limited to Grignard reagents, primarily those that lack β -hydrogens. However, Wenkert and co-workers have

Table 14 Reaction of Li-DHF (**283**) and Li-DHP (**284**) with alkyl halides (Scheme 82)

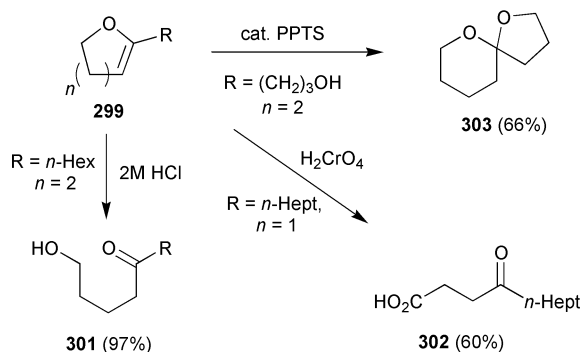
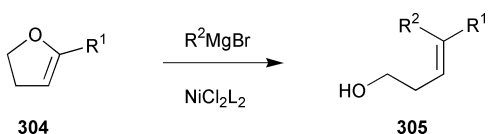
Substrate	R-X	Conditions ^a	Yield of 299 (%)	Ref.	
Li-DHF (283)	C ₃ H ₇ -Br	B	65	241	
	C ₅ H ₁₁ -I	B	96	241	
	Cl(CH ₂) ₃ -Br	A	80	254	
	Me ₂ C=CHCH ₂ -Br	A	67	225	
	H ₂ C=CMe(CH ₂) ₃ -I	B	89	240,257	
	Me ₂ C=CH(CH ₂) ₂ -I	B	97	259	
	BnOCH ₂ -Cl	B	38 ^b	264	
	BnO(CH ₂) ₃ -I	B	94	241	
	TBSO(CH ₂) ₃ -I	B	69	241	
	<i>t</i> -BuO(CH ₂) ₃ -Br	B	90	241,258	
	Li-DHP (284)	Me-I	B	35–75	230
		C ₄ H ₈ -I	B	95	262
		Cl(CH ₂) ₃ -Br	A	80	254
Me ₂ C=CH(CH ₂) ₂ -I		A	52	85	
HO(CH ₂) ₃ -I		B	>90	252	
THPO(CH ₂) ₃ -I		B	>90	252	
TBSO(CH ₂) ₄ -I		B	>90	252	
PhS(CH ₂) ₃ -Br		B	50	260	
HCC-F		C	75	55	

^a A = THF-HMPA (1 equiv.), 0 to 25 °C. B = THF, 25 to 50 °C. C = -80 °C. ^b Yield after subsequent Jones oxidation to 4-keto-5-benzyloxypentanoic acid.

Table 15 Nickel-catalyzed cleavage of 5-alkyl DHF **304** (Scheme 85)

Olefin 305	R ¹	R ²	Conditions ^a	Yield (%)	Ref.
305a	Me	Ph	A	85	256
305b	Me	Bn	A	91	256
305c	Me	Me ₃ SiCH ₂	B	85	256
305d	<i>n</i> -Pr	Me	A	79	256
305e	Me ₃ Si	Me	A	97	241
305f	Me ₃ Sn	Me	A	62	241
305g	Me ₂ C=CH(CH ₂) ₂	Me	A	89	259
305h	TBDMSO(CH ₂) ₃	Me	A	73	241
305i	Me	H	A (R ² = Et)	51	256
305j	Bu	H	C	60	262

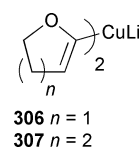
^a A = R²MgBr, NiCl₂(Ph₃P)₂. B = R²MgBr, NiCl₂(dppp). C = *i*-PrMgBr, NiCl₂(*n*-Bu₃P)₂.

**Scheme 84****Scheme 85**

shown that a synthetically useful reduction rather than substitution results when using *i*-PrMgBr and NiCl₂(*n*-Bu₃P)₂ in THF or dioxane. The disubstituted olefins **305** (R² = H) are obtained with good stereoselectivity (10–25 : 1) (Table 15).²⁶² Kocienski and others have applied this reaction to the synthesis of numerous natural products including zoapatanol,^{240,257} premonensin B,²⁵⁸ homogeraniol, homofarnesol and homogeranylgeraniol,²⁵⁹ the pine sawfly pheromone²⁶³ and recifeioliide.²⁶²

4.1.2.2 Transmetalation

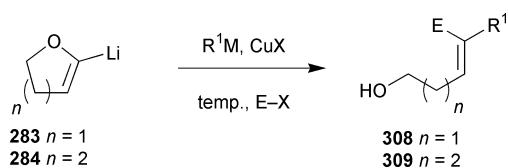
Reactions of the simple organocopper derivatives of Li-DHF and Li-DHP have been reported. The LO homocuprates **306** and **307**, derived from the reaction of CuI and 2 equiv. of Li-DHF²⁶⁹ or Li-DHP,²⁷⁰ undergo reaction with epoxides in THF at 0 to 20 °C to form the alkylated products **299** (analogous to Scheme 82). The corresponding homocuprate derived from EVL (**41**, R = Et) does not alkylate epoxides in a similar manner.²⁷⁰ The mixed cuprate obtained by mixing Li-DHP and a copper acetylide readily adds DHP in a 1,4-fashion to cyclohexenone to afford the conjugate addition product (91%).²²⁵



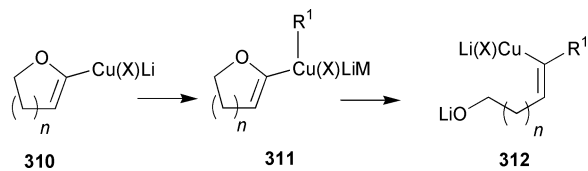
Ring cleavage occurs by treating Li-DHF or Li-DHP with an organolithium or Grignard reagent and a copper salt. Quenching the reaction mixture with an appropriate electrophile produces di- or trisubstituted hydroxy alkenes **308** and **309** with excellent control ($\geq 97\%$) of stereoselectivity (Scheme 86, Table 16). Originally described by Fujisawa and co-workers in 1982,²⁷¹ this method has been further developed and refined by Kocienski^{98,272,273} so that a variety of organometallic reagents can be used (including silyl and stannyl lithium) as summarized in Table 16. Presumably, the reaction proceeds through the

Table 16 Copper-mediated cleavage of Li-DHF (**283**) and Li-DHP (**284**) with organolithium and Grignard reagents (Scheme 86)

Substrate	R ¹ M ^a	CuX ^a	Temp/°C	EX	Yield 308 or 309 (%)	Ref.
Li-DHF	<i>n</i> -BuLi (5)	CuI (1)	0	H ₂ O	91	271
	<i>n</i> -BuLi (2.4)	CuCN (0.1)	0	D ₂ O	82	272
	<i>n</i> -BuLi (2.4)	CuCN (1)	0	allylBr	78	272
	<i>n</i> -BuMgBr (1)	CuBr·DMS (1)	-70	H ₂ O	31	273
	PhLi (2.5)	CuI (0.4)	0	H ₂ O	30	271
	PhMgBr (1)	CuBr·DMS (1)	-70	H ₂ O	50	273
	Bu ₃ SnLi (4)	CuCN (1)	0	MeI	85	275
LiDHP	<i>n</i> -BuLi (2.4)	CuCN (1)	0	D ₂ O	78	272
	H ₂ CCMeLi (2.4)	CuCN (0.07)	0	H ₂ O	79	272
	PhMe ₂ SiLi (2.4)	CuCN (0.2)	0	H ₂ O	92	272
	Me ₃ SnLi (2.4)	CuCN (0.2)	0	H ₂ O	78	272
	allylMgBr (1)	CuBr·DMS (0.5)	-30	H ₂ O	44	273
	PhMgBr (1)	CuBr·DMS (0.5)	-30	H ₂ O	46	273

^a Number of equiv. in brackets.**Scheme 86**

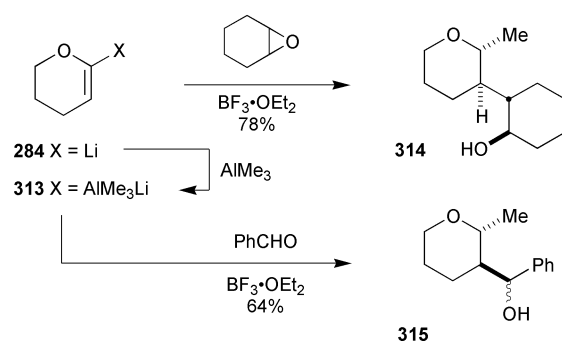
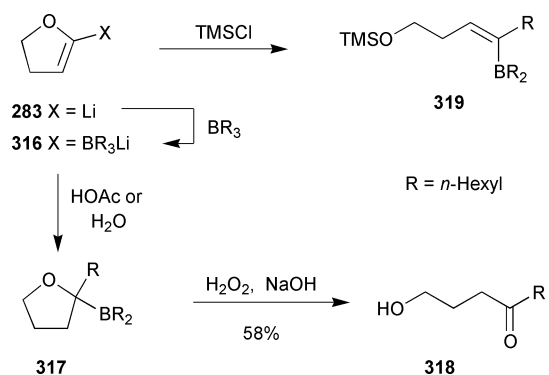
intermediacy of organocopper species **310** which, upon reacting with the organolithium or Grignard reagent, forms a HO cuprate **311** that rearranges with ring fragmentation to the vinyl cuprate **312** (Scheme 87). Trapping of this intermediate leads to the final olefinic products **308** and **309**. The overall transformation is thus conceptually similar to the Ni(0)-catalyzed process described above (Scheme 85, Table 15) and offers additional versatility in synthetic planning.

**Scheme 87**

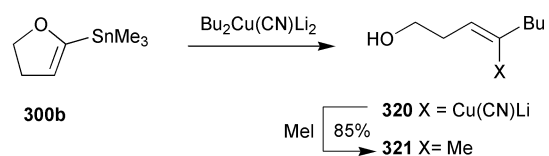
Treating Li-DHP with a triorganoaluminium reagent at -78 to -20 °C generates an intermediate aluminate species **313**.²⁷⁴ In the absence of BF₃·OEt₂, no reaction occurs with added electrophiles such as benzaldehyde or cyclohexene oxide. However, in the presence of stoichiometric BF₃·OEt₂, a novel 1,2-migration followed by nucleophilic attack on the electrophile produces the substituted DHP derivatives **314** and **315** (Scheme 88). Similar reactions are observed using Li-DHF **283** although the reactions with Li-DHP are more efficient. Interestingly, without added electrophile, the aluminate adduct derived from Li-DHF ring opens upon exposure to BF₃·OEt₂ to provide products analogous to those observed by Kocienski in the copper mediated reactions (Scheme 86, E = H).

The reaction of Li-DHF with trialkylboranes in THF at -78 °C affords α -alkoxyvinylborates **316** (Scheme 89) that are stable in refluxing THF for 24 h.⁹⁶ Unlike the corresponding aluminates, these borates undergo 1,2-alkyl shift and ring fragmentation by one of two mechanisms. Simple protonolysis and oxidative workup generate the γ -hydroxy ketones **318** (18–58%) while heating in the presence of Me₃SiCl yields an alkenylborane **319**. Vinylborane **319** participates in reactions that are typical of alkenylboranes (Schemes 9, 24, 51 and 52).

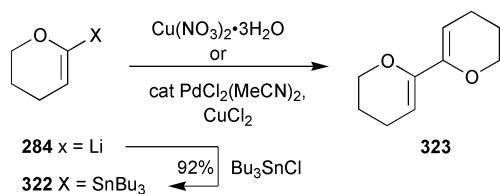
The stannylated DHF and DHP derivatives **300b** and **322** serve as substrates for several novel reactions. Treating **300b**

**Scheme 88****Scheme 89**

with the higher order cyanocuprate Bu₂Cu(CN)Li₂ followed by trapping of the intermediate vinyl copper species **320** provides the (*E*)-olefin **321** in 62–85% yield (Scheme 90).^{98,272,275} This reaction is related, both mechanistically and in the type of olefin product that is formed, to the organometallic-copper mediated ring opening of Li-DHP described previously (Scheme 87).

**Scheme 90**

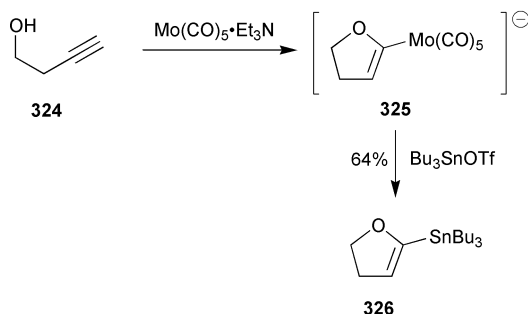
The vinylstannane **322** undergoes oxidative dimerization in the presence of stoichiometric Cu(NO₃)₂·3H₂O, producing the DHP dimer **323** in 80% yield (Scheme 91).²⁶⁸ The reaction is thought to proceed through the intermediacy of a DHP-Cu(II) species, possibly by the generation and homocoupling of free



Scheme 91

radicals. In a related reaction that bypasses the requirement for the formation of the stannylated intermediate, Li-DHF itself dimerizes (80%) in the presence of catalytic $\text{PdCl}_2(\text{MeCN})_2$ and 1 equiv. of CuCl_2 .²⁷⁶ Ley²⁷⁶ has shown that the diene **323** is a novel protecting group for vicinal diols. Vinylstannanes **300b** and **322** participate in Stille cross-coupling reactions with aryl iodides or vinyl halides (bromide or iodide) and the dienes so generated (33–84%) are novel Diels–Alder substrates.²⁷⁷

DHF and DHP complexes of the nickel triad are prepared by treating Li-DHF and Li-DHP with metal chlorides ($\text{C}_6\text{Cl}_5\text{-(Me}_2\text{PhP)}_2\text{MCl}$; M = Ni, Pd, Pt) (45–60%).^{227,229,278} Treatment of these complexes with amines yields crystalline cationic alkoxy carbenes. A novel $\text{Mo}(\text{CO})_5\text{-Et}_3\text{N}$ mediated alkynol cyclization generates a molybdenum Fischer carbene anion **325** that is protonated or trapped with tin triflate to yield unsubstituted (52–71%) or stannylated (45–65%) DHF derivatives (Scheme 92).^{279,280}



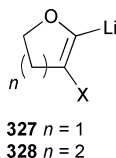
Scheme 92

4.2 Substituted α -lithiodihydrofurans and α -lithiodihydropyrans

With the realization that Li-DHF and Li-DHP are easy to prepare and exhibit useful reactivity, many research groups began investigating the preparation and reactivity of their substituted analogs. In many cases, these investigations were driven by specific needs in natural product total synthesis. The following sections will describe, according to substitution type, some of the substituted cyclic vinyl ethers that have been metalated and their subsequent reactivity.

4.2.1 β -Heterosubstituted Li-DHFs and β -heterosubstituted Li-DHPs

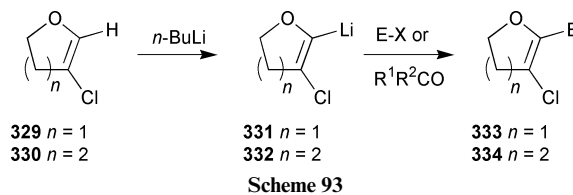
Several β -heterosubstituted (X = Cl, OR, SO_2R) α -lithiated DHF and DHP derivatives **327** and **328**, respectively, are described in the literature.



Schlosser and Riobé independently obtained the lithio derivatives of 4-chloro-2,3-dihydrofuran **331** and 5-chloro-3,4-dihydro-2H-pyran **332** by deprotonating the parent compounds **329** and **330** with *n*-BuLi in THF at -78°C (for DHF)^{281–283} or room temperature (for DHP)^{230,231} (Scheme 93). These condi-

Table 17 Reaction of 4-Cl-5-Li-DHF **331** and 5-Cl-6-Li-DHP **332** with electrophiles (Scheme 93)

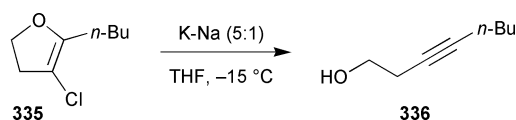
Substrate	E-X or R ¹ R ² CO	Yield (%)	Ref.
331	Me-I	74	281
	PhCHO	77	281
332	Me-I	65	230
	CH ₂ O	80	231
	MeCHO	70	231
	PhCHO	85	231
	Me ₂ CO	80	231



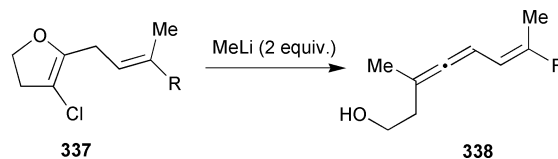
Scheme 93

tions are milder than those required for the lithiation of the dechloro derivatives, which require elevated temperatures or the use of *t*-BuLi or *n*-BuLi in the presence of TMEDA (Table 12). The facility of lithiation was rationalized by arguing that the β -chlorine atom activates the α -position *via* inductive effects and stabilizes the resulting α -lithio species, possibly *via* complexation. An alternative method for generating **331** involves dealkoxylation of 2-alkoxy-3-chlorotetrahydrofurans with excess phenyllithium in Et_2O at room temperature²⁸⁴ through an E1cb mechanism. The lithiated species **331** and **332** react with a variety of electrophiles including alkyl iodides, aldehydes and ketones to produce the substitution products **333** and **334** in good yield (Scheme 93, Table 17).

Allylic chlorides are also alkylation substrates but in these cases, the initially formed vinylolithium species must be converted into the corresponding organocopper reagent by treatment with CuI.^{282,283} The substitution products participate in novel fragmentation reactions (Schemes 94 and 95). Thus, exposing **335** to potassium–sodium alloy (5 : 1) in THF at -15°C produces the alkynol **336** (56%).^{231,281} The diene **337** undergoes reaction with 2 equiv. of MeLi to form the allenol **338** (55%) by a ring opening-substitution process (Scheme 95).^{282,283} This compound serves as a synthon for the synthesis of a variety of isoprenoid natural products.

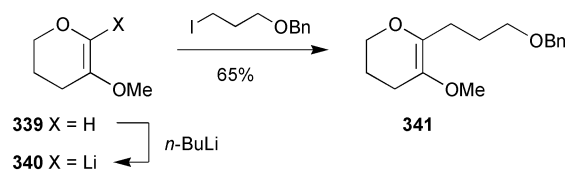


Scheme 94



Scheme 95

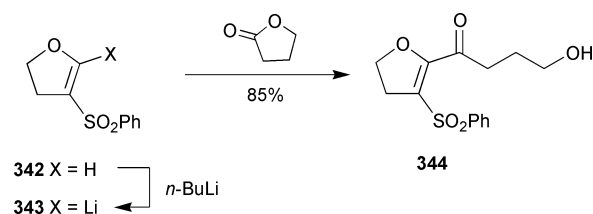
Gallagher^{285,286} has described the preparation and lithiation of 5-methoxy-3,4-dihydro-2H-pyran **339**. Although formation of the lithiated species **340** takes place in a variety of solvents (DME, Et_2O or hexane) using either *n*-BuLi or *t*-BuLi, the optimal conditions involve heating (0 to 50°C) a mixture of **339** and *n*-BuLi in THF. Anion **340** undergoes reaction with alkyl iodides (54–65%), aldehydes and ketones (53–60%) to yield the expected substitution products such as **341** (Scheme 96). Depending on the type of substituent introduced, these compounds serve as substrates for conversion to bicyclic



Scheme 96

hemiketals^{285,286} or spiroketals.²⁸⁶ In the absence of electrophile and upon exposure to CuI, the lithiated species **340** dimerizes when warmed to room temperature (~50%) in analogy to the unsubstituted Li-DHP (Scheme 91).

The preparation and lithiation of 4-phenylsulfonyl-2,3-dihydrofuran **342** have been investigated by Carretero.^{287,288} Deprotonation occurs by exposing **342** to $n\text{-BuLi}$ in THF at $-78\text{ }^\circ\text{C}$. The resulting lithiated species **343** reacts with electrophiles such as MeI (100%), TMSCl (68%) and carbonyl compounds such as γ -butyrolactone (85%) (Scheme 97).^{287,288} Adducts of the type **344** serve as precursors for base-induced and thermodynamically-controlled cyclization to functionalized 1,6-dioxaspiro[4.5]decanes.

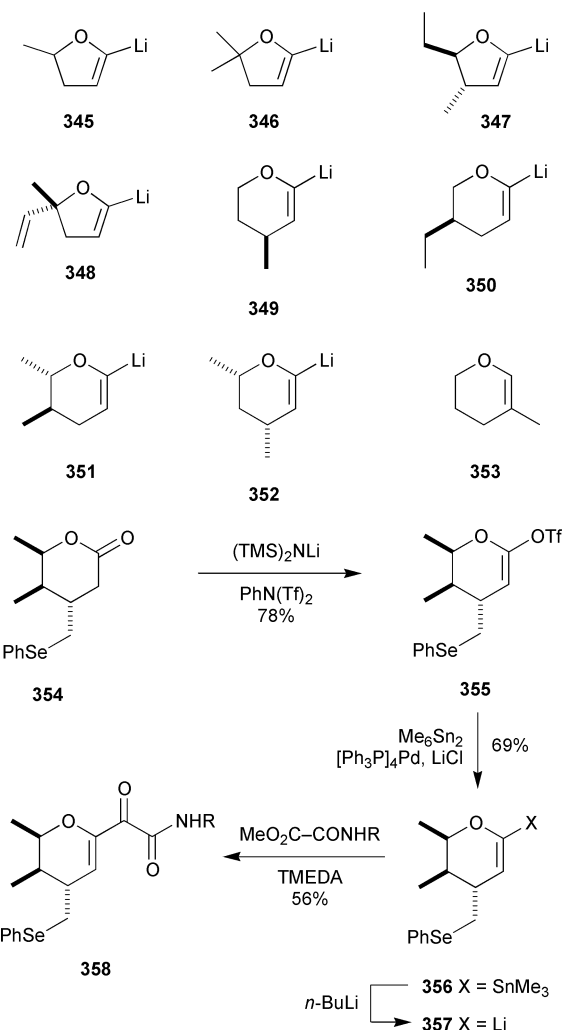


Scheme 97

4.2.2 Alkyl substituted Li-DHFs and Li-DHPs

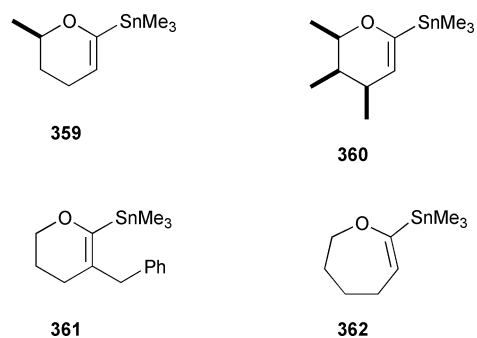
Typically, simple alkyl substitution of DHF and DHP does not alter the expected reactivity of these cyclic vinyl ethers toward alkyllithium bases and they are readily α -lithiated by the standard reagents. The resulting lithiated substrates have mainly been used for natural product total synthesis as exemplified by the alkyl-substituted α -lithiated cyclic vinyl ethers **345**–**352**. In each of these examples, deprotonation is accomplished by applying Boeckman's procedure^{85,225} which involves treating the parent vinyl ether with $t\text{-BuLi}$ in THF at -78 to $0\text{ }^\circ\text{C}$. Subsequent direct trapping with alkyl iodides (**345**, **349**),^{262,258} aldehydes and ketones (**345**, **346**)^{289,290} leads to the expected substitution products. Alternatively, initial conversion to the corresponding copper reagents by reaction with CuI (**350**)^{291,292} or copper acetylide (**351**)^{293,294} makes coupling with epoxides feasible. Condensation with readily enolizable ketones is problematic and, in these cases, transmetalation to the vinylcerium reagent by treating the lithio reagent with CeCl_3 proves to be advantageous (**348**).^{295–298} The lithium reagents **347**²⁷⁵ and **352**⁹⁹ have been used in copper-mediated 1,2-metalate rearrangements similar to the reaction illustrated in Scheme 87.

There are, however, exceptions to the simple lithiation reactions described above. While Boeckman⁸⁵ reported that the β -methyl DHP derivative **353** does not α -metalate upon exposure to $t\text{-BuLi}$ under the standard conditions, Kocienski²⁹⁹ has effected this lithiation, suggesting that the lithiation reaction is highly capricious. All attempts to prepare the lithium species **357** by direct lithiation of the parent dihydropyran were unsuccessful due to preferential reaction of the alkyllithium at the selenium atom.³⁰⁰ To circumvent this difficulty, Kocienski^{300,301} developed an alternative route to the α -lithium species **357** as outlined in Scheme 98. The lactone **354** is first converted to the vinylstannane **356** via the intermediacy of the corresponding enol triflate derivative **355** (61% for two steps).

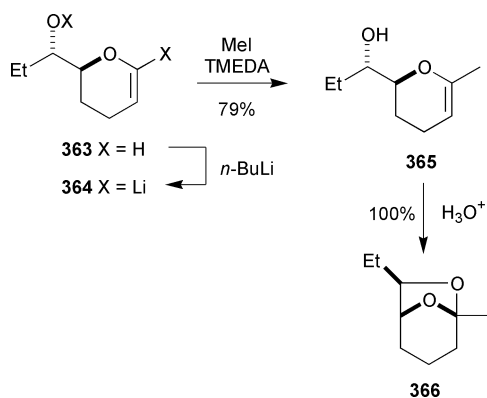


Scheme 98

Transmetalation of the α -stannylated enol ether **356** with $n\text{-BuLi}$ in THF at $-80\text{ }^\circ\text{C}$ proceeds smoothly providing the requisite vinylstannane derivative **357** that reacts with a methyl oxamate ester in the presence of TMEDA to provide the keto amide **358** (55%). This lactone→triflate→vinylstannane sequence is useful in other contexts, including the preparation of the vinylstannane derivative of **352**⁹⁹ and the vinylstannanes **359** (75%), **360** (70%), **361** (36%) and **362** (78%).²⁹⁹ However, the sequence is not applicable to five-membered rings since the triflate intermediates cannot be prepared.²⁹⁹



DHP derivatives that contain an alcohol-bearing moiety at C¹, such as **363**, are deprotonated with slightly greater than 2 equiv. of either $n\text{-BuLi}$ in hexane–TMEDA at $25\text{ }^\circ\text{C}$ ^{302,303} or $t\text{-BuLi}$ in THF at $0\text{ }^\circ\text{C}$.³⁰⁴ The resulting vinylstannane reagent **364** reacts with alkyl iodides to give the substitution product **365** which is cyclized to *exo*-brevicomine **366** upon exposure to acid (Scheme 99).

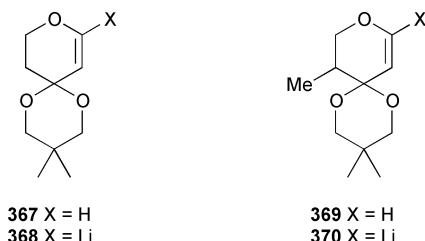


Scheme 99

The range of natural products that have been synthesized by using the lithiated derivatives described in this section is extremely broad and includes: **345**: recifeiolide²⁶² and theaspirane;²⁹⁰ **346**: 20-hydroxyecdysone;²⁸⁹ **347**: rosaramycin;²⁷⁵ **348**: dactyloxene B/C^{295,297} and grindelic acid;^{296,298} **349**: premonensin B;²⁵⁸ **350**: talaromycin B;^{291,292} **351**: milbemycin β_3 ;^{293,294} **352**: jaspamide;⁹⁹ **357**: pederin;^{300,304} **364**: *exo*-brevicommin^{302,303} and the sex pheromone of the Douglas Fir Tussock moth.³⁰⁴

4.2.3 Dihydropyran ketals

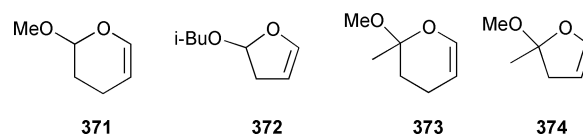
Both of the dihydropyran ketals **367**^{244,305,306} and **369**^{306–308} are readily deprotonated with *t*-BuLi in THF at -78 to 0°C , generating the corresponding α -lithio derivatives. Condensation of both **368** and **370** with aldehydes proceeds smoothly in the presence of HMPA.^{305–308} Smith has used this reaction sequence in the total synthesis of phyllanthoside^{305–307} and breynolide.³⁰⁸ Although vinyl anion **368** does undergo reaction with chiral ketones, initial conversion to the dichlorocerium reagent (using CeCl_3) results in improved diastereoselectivity compared to the lithium reagent.²⁴⁴



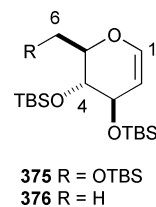
4.2.4 Lithiated glycals and other highly oxygenated Li-DHF and Li-DHPs

The previous sections show that DHF, DHP and their simple alkylated derivatives are readily lithiated using only a slight excess of *t*-BuLi (THF, -78 to 0°C) according to Boeckman's procedure.^{85,225} However, the extension of the procedure to cyclic vinyl ethers containing oxygen substituents is much less straightforward. For example, Boeckman^{85,225} studied the α -metalation reactions of a series of 1-alkoxy DHF and DHP derivatives. He noted that less than 5% of 1-methoxy DHP **371** was α -lithiated under the standard deprotonation conditions (1 equiv. *t*-BuLi, THF, 0°C). In addition, deprotonation of **371** was slow compared to DHP (relative rate = 0.77) and the *t*-BuLi reagent was dissipated by a competing reaction with the THF solvent. However, by replacing the ethereal solvent with pentane and using only a small amount of THF (at least 2 equiv. THF : *t*-BuLi in order to deaggregate the unreactive tetrameric *t*-BuLi), **371** was quantitatively deprotonated at a reasonable rate with 2 equiv. of *t*-BuLi. The complexation of *t*-BuLi to the extra oxygen atom in the substrate is a possible explanation for the requirement of excess base. The Lochmann–Schlosser base has also been used to deprotonate **371** in pentane at -78 to

-20°C .³⁰⁹ Similarly, the α -lithiation of 1-alkoxy DHF **372** requires the use of 3 equiv. of *t*-BuLi, while the methylated analogs **373** and **374** are deprotonated using 2 and 3 equiv., respectively. All of these oxygenated derivatives undergo metalation 2–4 times slower than the parent DHF and DHP substrates. The lithiated species, once formed, react with a variety of electrophiles including aldehydes and ketones (30–86%), allyl bromides and primary alkyl iodides (33–80%). Interestingly, Meyers²⁶ demonstrated that DHP derivatives **371** and **373** are lithiated with only 1.3 equiv. of *t*-BuLi at -5 to -3°C provided that the reaction is carried out in THP rather than THF.



There are numerous reports of poor results being realized in the α -lithiation of highly-substituted and oxygenated DHF and DHP systems using the standard Boeckman metalation protocol.^{310–320} The problems appear to be associated with either (a) the initial formation of the α -lithiated species or (b) the poor reactivity of the vinylolithium reagent once formed. In some cases, the use of Lochmann–Schlosser base (*n*-BuLi–*t*-BuOK), a stronger and more reactive reagent than *t*-BuLi, overcomes the problem of anion generation in unreactive substrates.^{244,310–312,316} However, when the Lochmann–Schlosser base is used in THF, products resulting from deprotonation of the solvent at C2 have been observed in some cases.³¹⁰ In many oxygenated DHF and DHP substrates, the chief problem associated with generating the vinylolithium species is not only the decrease in reactivity of the vinyl proton towards deprotonation, but also to interference by oxygen protecting groups. Thus, the choice of protecting group becomes critical to the success of the deprotonation reaction. Oxygenated substrates bearing benzyl^{244,310,314,315,317} and TBS^{244,313,318–332} protecting groups are especially problematic since deprotonation of the protecting group (benzylic protons or methyl protons α to silicon) competes with α -lithiation. Generally, trityl,³²¹ MOM^{311,312} and TIPS or TBDPS^{299,319,323–324} protecting groups are suitable, although there have been failures reported using both MOM²⁴⁴ and TIPS^{311,312} moieties.



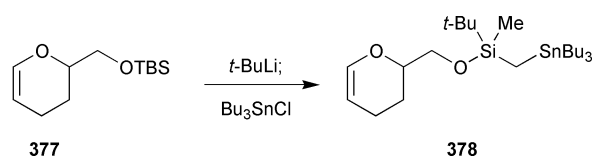
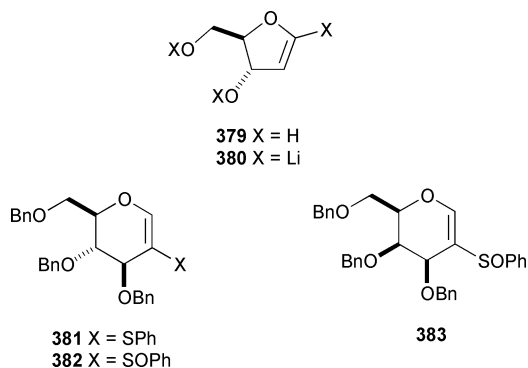
Friesen *et al.*^{319–320} demonstrated (using deuterium incorporation and NMR experiments) that the requirement for excess base in the lithiation of TBS protected glucal **375** (*t*-BuLi, THF at 0°C ; D_2O quench) is partially due to competing lithiation α to silicon on the TBS methyl groups. This competing α -silyl deprotonation is site-selective and lithiation occurs only on the C6 and C4 (glucal numbering) silyloxy moieties. The complete C1-lithiation of **375** requires the use of 3–4 equiv. of *t*-BuLi (Table 18).^{319,320} In contrast, the corresponding TIPS-protected glucal is cleanly deprotonated at C1 with *t*-BuLi.³¹⁹ The lithiation of the 6-deoxy TBDMS-protected glycal **376** is also much less problematic^{320,325–327,242,244} but at least a portion of the excess base (~ 2 equiv.) required to effect complete C1 metalation is due to competing deprotonation α to silicon on the TBS protecting group at C4 (Table 18).³²⁰ Quayle and co-workers³¹³ have shown that deprotonation α to silicon occurs even in the simple DHP derivative **377**. Exposing **377** to 1 equiv.

Table 18 Lithiation of glycols **375** and **376** with *t*-BuLi³²⁰

Glycol	Equiv. of <i>t</i> -BuLi	D incorporation at C1 (%) ^a	D incorporation α to silicon (%) ^b	
			C6	C4
375	2.2	55	27	4
375	3.2	84	57	6
375	4.0	>98	77	11
375	8.0	>98	85	25
376	2.2	>98	—	3
376	4.0	>98	—	8
376	8.0	>98	—	11

^a By inspection of the integrated H¹ and H² resonances in the ¹H NMR spectra. ^b From integration of the D¹ and SiCH₂D resonances in the proton decoupled ²H NMR spectra.

of *t*-BuLi (THF, 0 °C) and *n*-Bu₃SnCl forms the mono-stannylated derivative **378** (64%) along with a ditin product (16%) (Scheme 100). A rationalization of the site-selectivity of lithiation in both **375** and **377** invokes the internal delivery of *t*-BuLi to the silyloxy moieties through a pre-coordinated complex involving the pyran oxygen and/or the primary C6 oxygen atom. This alternative lithiation pathway effectively competes with vinyl ether deprotonation. Daves and co-workers³²¹ demonstrated that the complete absence of protecting groups in the lithiation of oxygenated DHF derivatives may be of some utility since the α -lithiated species **380** produced from **379** (3.5 equiv. of *t*-BuLi in THF at 0 °C) may be trapped with Bu₃SnCl. In a series of papers, Schmidt^{315,328–331} showed that glycol derivatives containing benzyl protecting groups can serve as useful substrates for α -lithiation provided that the C2 position bears a functional group for activation of the C1 position *via* inductive effects and stabilization of the resulting α -lithio species *via* complexation. The synthetically most useful substrates, glucals **381** and **382** and galactal **383**, bearing C2 phenyl sulfide or sulfoxide moieties, are lithiated at C1 using LDA in THF at –100 °C. The resulting vinylolithium species react with aldehydes to provide the expected carbinol products which are converted into *C*-disaccharides^{328,331} and the antibiotic ezomycin A.³³⁰ In the case of sulfoxides, both sulfoxide diastereoisomers can be used and varying degrees of diastereoselectivity are observed (1 : 1 to 100 : 1).

**Scheme 100****Scheme 101**

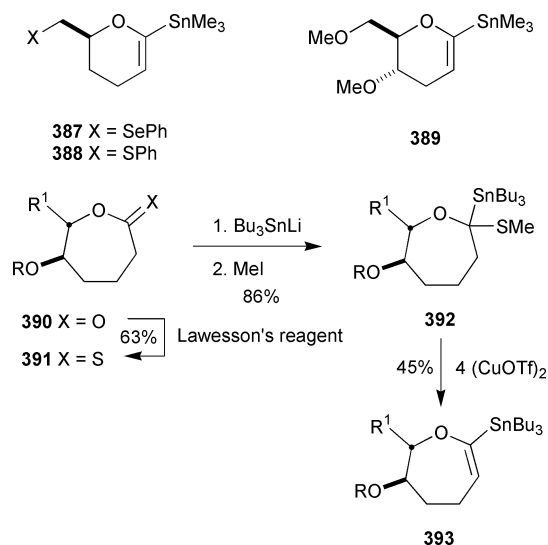
As was mentioned above, excess *t*-BuLi or Lochmann–Schlosser base (2–4 equiv.) is typically necessary to effect quantitative conversion of oxygenated DHF or DHP substrates to the desired vinylolithium reagents. Unfortunately, the presence

of excess base is often problematic in the subsequent reaction of the vinyl ether anion with electrophiles. In addition, the vinyl anion generated by deprotonation with Lochmann–Schlosser base is quite basic and problems are often encountered upon reaction with base-sensitive substrates such as readily enolizable ketones or allylic halides.

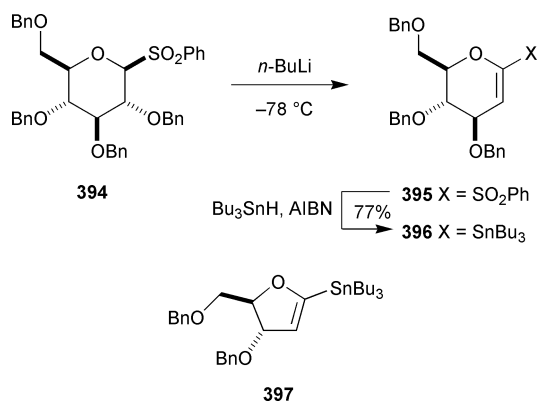
In an effort to overcome some of these problems in reactivity, an alternative strategy for generating the vinylolithium species has been devised.^{244,310–312,316,321} Rather than direct deprotonation, this process involves the initial formation and purification of a vinyltrialkylstannane. Tin–lithium exchange results from exposing the vinylstannane to *n*-BuLi, cleanly generating the desired vinylolithium species. For example, Hanessian and co-workers³¹⁶ deprotonated the TBS glucal **375** using the Lochmann–Schlosser base. Subsequent trapping of the α -metalated species with Bu₃SnCl, desilylation (TBAF) and re-protection with benzyl bromide provides the C1 stannylglucal **384** in 55% overall yield (Scheme 101). Treating **384** with *n*-BuLi in THF at –78 °C cleanly regenerates the α -lithiated glucal **385**, which reacts with methyl iodide (76–88%), aldehydes (49–98%), cyclohexenone (77%), dimethyl carbonate (36%) and Me₃SiCl (92%) to afford the expected substitution products **386**.^{316,317} In the presence of BF₃·OEt₂, the C1-lithiated glucal **385** also undergoes reaction with epoxides (50–80%).³³² Other oxygenated, α -stannylated cyclic vinyl ethers have been prepared in a similar fashion and, upon transmetalation with *n*-BuLi, undergo reaction with a range of electrophiles including primary alkyl bromides (in the presence of HMPA). Boeckman employed this strategy in the total synthesis of the polyether antibiotic (–)-calcimycin.^{311,312}

These synthetically useful stannylated cyclic vinyl ethers have been prepared using several alternative strategies. One of these protocols, developed by Kocienski,²⁹⁹ has been mentioned previously and involves converting a lactone to the corresponding vinylstannane through the intermediacy of an enol triflate (see Scheme 98). Substituted, α -stannylated DHP derivatives **387–389** were prepared in this manner (69–82% overall yield from the corresponding lactone). A related procedure (to **393**) devised by Nicolaou and co-workers³³³ proceeds by cuprous triflate-induced elimination of methanethiol from the stannylated methylthio ether **392**, itself derived from the lactone **390** (Scheme 102). A third method discovered by Beau and co-workers³¹⁷ involves a vinyl sulfone–vinylstannane interconversion (Scheme 103). Thus, base-induced elimination of the benzyl protected glycosyl sulfone **394** provides vinyl sulfone **395** (92%) which, after treating with *n*-Bu₃SnH and AIBN in refluxing toluene, affords the desired vinylstannane **396** (77%). The benzyl protected C1-stannylated DHF derivative **397** was prepared in a similar fashion.³²¹

The vinylstannanes obtained from any of these procedures possess much more synthetic versatility than acting as substrates for simple regeneration of the corresponding vinylolithium species with *n*-BuLi. The vinylstannanes **396**, **397** and **398** participate in Stille Pd(0)-catalyzed cross-coupling reactions with aryl bromides,^{321,334–337} benzyl bromide, allyl bromide and acid chlorides.^{336,337} For example, the syntheses of the

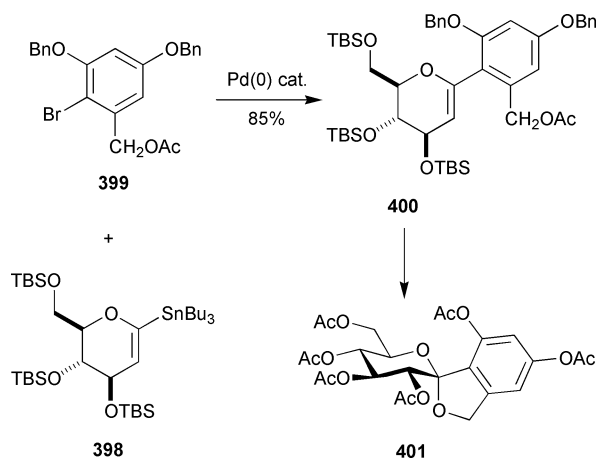


Scheme 102



Scheme 103

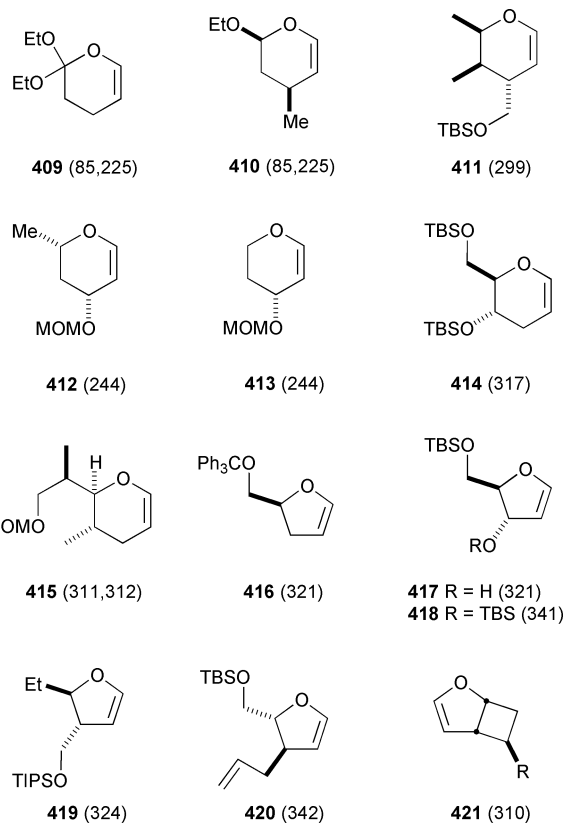
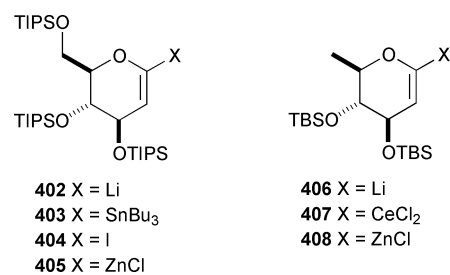
C-aryl glycoside moieties of the papulacandins (**401**)^{338,339} and chaetiaccandins^{339,340} proceed *via* the Cl-aryl glycal **400** that is obtained by coupling **398** and **399** (Scheme 104).



Scheme 104

Treating the vinylstannane **403**, obtained from **402**, with I₂ in CH₂Cl₂ provides the corresponding vinyl iodide **404** (89–100%). In a Pd(0)-catalyzed coupling protocol complementary to the one shown in Scheme 104, reaction of the vinyl iodide **404** with metalated aromatics, such as arylzincs, arylboronic acids and arylstannanes, generates Cl-aryl glycals analogous to **400**.^{323,335}

It is possible to transmetalate the vinyl lithium species derived from oxygenated DHP derivatives. Thus, Paquette and Oplinger²⁴⁴ found that the dichlorovinylcerium reagent **407**, obtained by treating the α -lithio glycal **406** with CeCl₃, gives



superior yields compared to the parent lithium anion in reactions with enolizable ketones. Tius and co-workers used the vinylzinc species **408**, produced by reacting the α -lithiated anion **406** with ZnCl₂, in Pd(0)-catalyzed cross-coupling reactions with aryl iodides.^{325,326} This reaction constitutes the key step in the synthesis of the antitumor antibiotic vineomycinone B² methyl ester. The sequential addition of ZnCl₂ and I₂ or NIS to **402** generates the vinyl iodide **404** through the intermediacy of the vinylzincate **405** (67–81%).^{323,335}

Finally, the wide range of substituted cyclic vinyl ethers from which α -lithiated species are formed, either by direct deprotonation or one of the other related routes described above, include **409–421** (references in brackets).

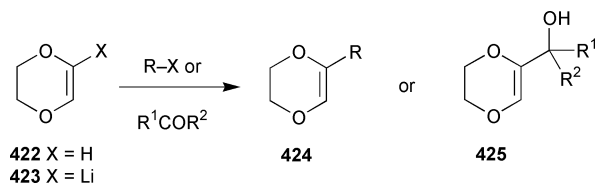
4.3 2-Lithio-1,4-dioxene and related reagents

Neat 1,4-dioxene **422** (Scheme 105) is readily lithiated by exposure to *n*-BuLi at 0 °C³⁴³ or *t*-BuLi at –30 to –20 °C.³⁴⁴ The resulting 1,4-dioxen-2-yl lithium **423** precipitates as a white solid and is stable at room temperature for 24 h. In subsequent reactions, electrophiles are typically added to this precipitate as solutions in THF. Other reaction conditions described for the deprotonation of **422** involve the use of *t*-BuLi at 0 °C in either dioxane–pentane (1 : 5)³⁴³ or THF.^{345,346} The ¹³C NMR spectrum of **423** exhibits the expected and characteristic downfield shift (~40 ppm) of the lithiated vinyl carbon resonance with respect to the corresponding carbon resonance in the parent compound.³⁴³

In analogy with metalated 1,2-dimethoxyethylene **170** and **174** (see Schemes 47 and 48), 2-lithio-1,4-dioxene **423**

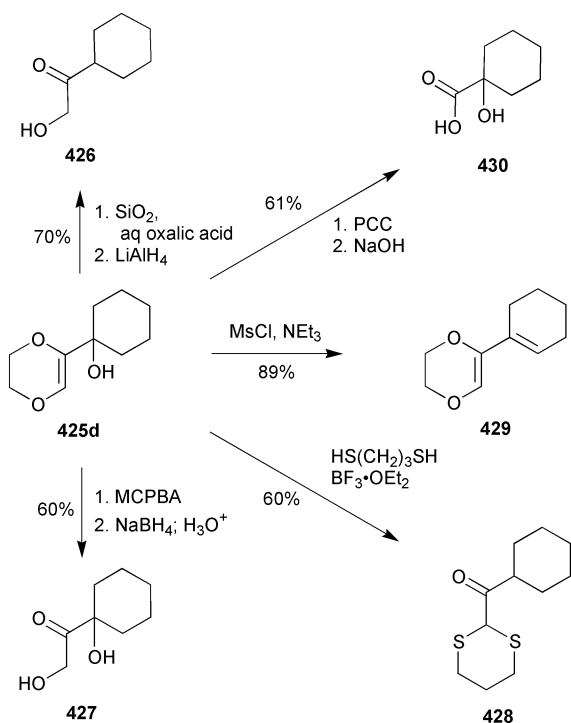
Table 19 Reaction of 2-lithio-1,4-dioxene **423** with electrophiles (Scheme 105)

R-X or R ¹ R ² CO	Product	Yield (%)	Ref.
D ₂ O	424a	93	343
Me-I	424b	79	343
Me ₃ Sn-Cl	424c	82	353
PhCHO	425a	52	349
Acetone	425b	53	351
Butan-2-one	425c	66	351
Cyclohexanone	425d	66	351



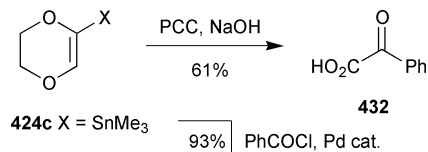
Scheme 105

undergoes reaction with a variety of electrophiles, such as alkyl and stannyl halides, aldehydes and ketones, to provide the expected substitution (**424**) and carbinol products (**425**) (Scheme 105, Table 19). Fetizon and co-workers³⁴⁷ extensively studied the reactions of the carbinol addition products **425** and prepared a variety of useful synthetic intermediates (Scheme 106). Simple transformations provide α -hydroxymethyl ketones **426** (40–85%),^{344,348} α,α' -dihydroxyketones **427** (45–90%),^{348,349} 2-oxoalkanal 1-dithioacetals **428** (55–89%),³⁵⁰ dienes **429** (62–89%)³⁵¹ or α -hydroxy acids **430** (39–61%).³⁵² Pd(0)-catalyzed coupling reactions of the stannylated dioxene **424c** with acid chlorides provide the acylated derivatives **431** (82–95%) that can be oxidized to α -keto acids **432** (Scheme 107).³⁵³ As shown in Scheme 14 for ethoxyvinyl lithium, exposing the lithiated dioxene **423** to Mo(CO)₆ and Cr(CO)₆ generates molybdenum and chromium carbenes that react with acetylenes³⁴⁵ and enynes³⁴⁶ to generate a variety of polycyclic products, such as highly substituted phenols.



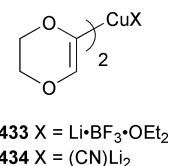
Scheme 106

2-Lithio-1,4-dioxene **423** is a precursor for preparing vinyl-copper reagents. Treatment of **423** with CuI or CuBr·DMS and

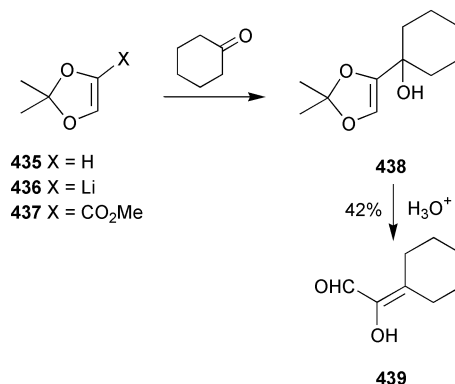


Scheme 107

BF₃·OEt₂ generates the LO cuprate **433** while exposure to CuCN–LiCl provides the HO cuprate **434**.³⁵⁴ Although these cuprates are less reactive than the corresponding di(alkoxyvinyl) analogs **41** and **45**, they undergo reaction with epoxides to give the substitution products (13–75%),³⁵⁴ and with enones to give the expected 1,4-addition adducts (63–94%).^{354,355} The preferred choice of cuprate reagent varies with substrate. For example, the LO and HO cuprate reagents undergo reaction with styrene oxide in yields of 67% and 41%, respectively, while conjugate addition to cyclohexen-2-one proceeds in 75% and 94% yield, respectively.



Lithiation of the dioxole **435** (Scheme 108) with *t*-BuLi in THF (with or without TMEDA) at –80 °C generates a related reagent, 4-lithio-2,2-dimethyl-1,3-dioxole **436**.^{141,356} This vinyl anion undergoes reaction with aldehydes and ketones to provide addition products **438** which may be readily hydrolyzed to the enols of α -keto aldehydes **439** (41–46%).³⁵⁶ Trapping of **436** with methyl chloroformate provides dialkoxy acrylate **437** (72%). Transformation of **437** into butenolides (51–55%) proceeds *via* a reaction sequence analogous to that described in Scheme 48.¹⁴¹

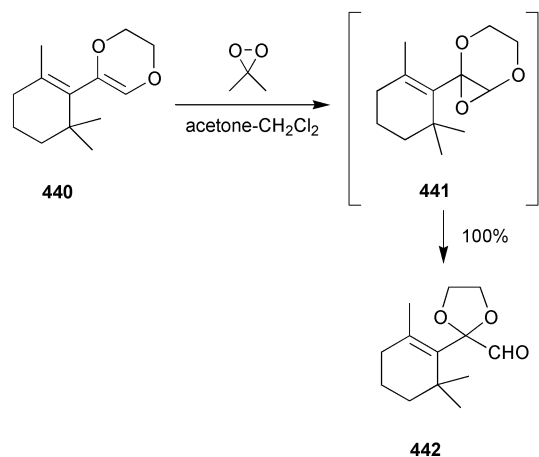


Scheme 108

Hanna demonstrated that oxidation of diene **440** (see Scheme 106) with dimethyldioxirane yields epoxide **441** that readily undergoes rearrangement to the α -ketal aldehyde **442** (Scheme 109).^{357,358} This strategy has been applied to the synthesis of a functionalized AB taxane ring system.³⁵⁹

5 Conclusions

An enormously wide range of α -metalated derivatives of acyclic vinyl ethers, alkoxyallenes and non-aromatic cyclic vinyl ethers is readily available. The subsequent reactions of these organometallic reagents with electrophiles yield an amazing array of substitution products, generally in good to excellent yields. From the simplest α -metalated vinyl ether reagent, MVL, to the highly substituted C1-lithiated glycol derivatives, the synthetic utility of the metalated vinyl ether reagents is



Scheme 109

readily apparent. The demonstrable applicability of many of these reagents to natural and unnatural product synthesis, and even the unexpected observations that have led to fascinating new discoveries, all suggest that this field of synthetic organometallic chemistry will continue to flourish. Finally, in an attempt to comprehensively review the chemistry of α -metalated vinyl ethers from 1951–1996, it is inevitable that some references were overlooked due to the widespread use of this class of reagent by the synthetic organic community. It is a comment on the degree of acceptance and applicability of these organometallic reagents that the scope of references in the present review are such that this oversight is possible.

6 Acknowledgements

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