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Polyfunctional Li-Organometallics for Organic Synthesis

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2.1

Introduction

Multifunctional organic molecules can be achieved by reacting functionalized organolithium compounds [1] with electrophilic reagents, this fact makes these intermediates of relevant interest in synthetic organic chemistry [2]. Another remarkable fact concerning organolithium compounds, compared with other organometallic compounds is that they can be prepared following a great number of different methodologies [3]: hydrogen–lithium exchange (deprotonation), halogen–lithium exchange, transmetallation reactions, carbon–heteroatom bond cleavage and carbolithiation of multiple carbon–carbon bonds. However, the highly ionic character of the carbon–lithium bond [4] makes these compounds extremely reactive and also unstable, so the synthetic processes should be carried out in some cases under very mild reaction conditions.

Regarding the stability of functionalized organolithium compounds, it depends mainly on three factors, the most important one being the compatibility of the functional group with the carbon–lithium bond, so in some cases the functionality should be protected. The hybridization of the carbon atom bonded to the lithium atom is also important, so sp derivatives are more stable than the corresponding sp^2 and these are more stable than the sp^3 ones as it happens to the corresponding carbanions. Finally, the relative position of the functionality and the carbanionic center is also relevant, probably the β -functionalized derivatives being the most unstable species due to the existence of two consecutive carbon atoms with opposite polarities, the β -elimination process to give an olefin is extremely favored.

Stabilized organolithium compounds, such as lithium enolate intermediates [5], α -organolithium compounds bearing electron-withdrawing groups (RSO , RSO_2 , CN , NO_2 , etc.) and heteroatoms such as sulfur [6], selenium and phosphorus as well as functionalized aryllithium compounds will not be considered in depth in this chapter due to the limited length of this review.

The following study is ordered based on the relative position of the functionality and the carbanionic center, as well as on the hybridization of that center.

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2.2

α -Functionalized Organolithium Compounds

There are several examples of α -oxygen- and nitrogen-functionalized organolithium compounds with sp^2 and sp^3 hybridization in acyclic and cyclic systems of general structures I–IV. These compounds show a tendency to undergo α -elimination processes to generate carbene intermediates.

2.2.1

sp^3 -Hybridized α -Oxygenated Organolithium Compounds

sp^3 -Hybridized α -oxygenated organolithium compounds of general structure I are accessible mainly through halogen–lithium exchange, tin–lithium exchange and by direct deprotonation of appropriate precursors, which means systems with hydrogens at a benzylic or allylic position. Lithiomethyl alkyl ether **2** has been prepared by chlorine–lithium exchange from the corresponding chloromethyl ether **1**, lithium powder in the presence of a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB) [7], or naphthalene, as well as biphenyl-supported polymers [8], being used as lithiating reagents (Scheme 2.1).

[E = RCHO, R_2CO , CO_2 , PhCN, PhCONMe₂, CyNCO, PhN=CHPh]

Scheme 2.1

In the case of chiral lithiomethyl ethers **4** bearing the menthol unit, the lithiation was performed either in the presence of the electrophile (Barbier-reaction conditions) [9] at 0°C or at -90°C in a two-step process, which means lithiation followed by addition of the electrophile. Low stereoselectivity was observed in the case of using electrophiles with prostereogenic centers [10]. Similar results were obtained also in the case of preparing intermediates **4** and **5** through a tin–lithium exchange [11]. The O-chloroalkyl carbamates **6** were also lithiated by means of lithium in the presence of a catalytic amount of DTBB under Barbier-reaction conditions, because the step by step process at any temperature tried was not effective or gave poor yields. Final hydrolysis with lithium hydroxide or reduction with DIBALH gave 1,2-diols in the case of using carbonyl compounds as electrophiles [12].

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It is possible to transform stereoselectively the anomeric position of a sugar unit into a organolithium compound by chlorine–lithium exchange using a stoichiometric amount of lithium naphthalene as the lithiating reagent [13]. The same kind of intermediates were prepared also by tin–lithium transmetalation [14] and sulfur–lithium exchange in phenyl sulfides and sulfones [15]. In the case of the dianion **8** derived from galactopyranose, the deprotonation of the amide moiety in compound **7** should be performed prior to heteroatom–lithium exchange. The reaction of this intermediate with electrophiles provided α -C-glycosides **9** (Scheme 2.2).

Scheme 2.2

High diastereoselectivity was observed in the reaction of intermediate **11** (prepared by tin–lithium exchange from compound **10**, which derived from L-valine) with benzaldehyde to give the corresponding adducts in a 91:9 diastereomeric ratio. Final hydrolysis yields the 1,2-diol **13** and the chiral auxiliary **12** (Scheme 2.3) [16].

Scheme 2.3

Compounds **14**–**18** have also been prepared from the corresponding stananes. Surprisingly, cyclic α -alcoxy- β -aminoalkyllithium compounds **15** and **16**

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are stable at -78°C , because, taking into account Baldwin's rules along with the microscopic reversibility principle, a β -elimination process (which would lead to a olefin) is the reverse of the *n-endo-trig* cyclization. Thus, the stability of intermediates **15** decreases with increasing ring size [17]. In the case of other α -stannylated hydroxycompounds, the corresponding transmetalation occurs only for their carbamate derivatives [18] but not in the case of O-MOM protected systems [19]. The reaction of intermediates **17** with aldehydes followed by reduction with AlH_3 gave 1,2-diols. The lithiation of enantiomerically enriched α -propargyloxy stannanes proceeds with complete inversion of the configuration and has been applied to study the Wittig rearrangement. In the case of compounds **18** the selectivity of [2,3] versus [1,2] rearrangement is dependent of the nature of the R^2 substituent on the acetylenic moiety [20].

The α -alkoxy alkyl lithium derivative **20**, prepared from compound **19** by tin-lithium exchange with retention of the configuration, undergoes 5-*exo-trig* cyclization to form first the cyclic compound **21** and finally the *trans*-disubstituted tetrahydrofuran **22** through a β -elimination process [21].

Scheme 2.4

The α - and β -configured glycosyl anions **23–26** were prepared by tin-lithium exchange. C-Glycosylated aminoacids were obtained by reaction of intermediate **23** with lactams [14], meanwhile the reaction of compounds **24** and **25** with electrophiles led to α - and β -C-galactosides [22], respectively, intermediate **26** being used in the stereocontrolled synthesis of carba-C-disaccharides [23].

As commented above, this kind of functionalized organolithium compounds can also be prepared through deprotonation processes. The deprotonation can be also performed in a diastereoselective way, for instance, in the presence of (–)-sparteine [24]. Treatment of *O*-alkyl carbamate **27** with *s*-BuLi in the presence of (–)-sparteine at –78 °C gave the organolithium compound **28** with high ee, which upon carboxylation and acidic hydrolysis led to (*R*)-pantolactone **30** (Scheme 2.5) [25].

Scheme 2.5

The organolithium compound **30** was also prepared by an enantioselective deprotonation in the presence of (–)-sparteine. It is configurationally stable, but when reacting with electrophiles retention or inversion of its configuration is observed [26]. The deprotonation can also be performed in the presence of a chiral bisoxazolidine to give benzylic anions **31–33**, which reacted with electrophiles to yield the corresponding reaction products with good stereoselectivity. In this case, the stereoselectivity was explained by a dynamic thermodynamic mechanism instead of through an enantioselective deprotonation [27]. The α -lithiated *O*-protected propargyl alcohol **34** was prepared by deprotonation with *n*-BuLi and used in the synthesis of a cyclic enediyne related to maduropeptin chromophor [28].

Lithiated epoxides [29] of general structure **II** ($X = O$, $n = 0$) were first postulated as intermediates by Cope, and many of them act as carbenoid species: they can undergo (a) β -elimination to give an enolate, (b) α -ring opening followed by

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1,2-hydride shift to give an enolate or (c) α -ring opening followed by attack of an alkyllithium and subsequent elimination of lithium oxide affording an olefin. Only stabilized anions carrying electron-withdrawing or coordinating substituents, or heteroatomic, aromatic or unsaturated groups are stable enough to react with electrophiles. Lithiooxirane **35** was prepared by deprotonation with *s*-BuLi in the presence of TMEDA in THF at -98°C and reacted with electrophiles [30] with retention of the configuration. The same reaction conditions were used in the preparation of oxazolinylloxiranyllithiums **36** [31], which reacted with nitrones to give, after hydrolysis and catalytic hydrogenation, α -epoxy- β -aminoacids [32]. Oxiranyllithium **37** was prepared by lithiation α to the silicon with *n*-BuLi in ether at -116°C with retention of the configuration of the oxirane [33]. Ethynyl oxirane anionic species **38** was prepared by deprotonation with *n*-BuLi at the propargylic position and trapped with electrophiles to give trisubstituted oxiranes [34].

Nonstabilized oxiranyl anions were generated by lithiation of terminal epoxides in the presence of a diamine ligand [35], this methodology being applied to the asymmetric deprotonation of *meso*-epoxide **39** in the presence of (–)-sparteine. The resulting organolithium compound **40** reacted with different electrophiles to give compounds **41** in up to 86% ee (Scheme 2.6) [36].

[E = CD_3OD , PhCHO , PhCONMe_2 , EtCHO , Et_2CO , EtCONMe_2 , EtOCOCl , $n\text{-Bu}_3\text{SnCl}$, Me_3SiCl , MeI]

Scheme 2.6

A α -oxygenated organolithium compound acts as a reaction intermediate in a spiroannulation reaction from 2-cyanotetrahydropyrans. The key feature of this method is the use of a nitrile to facilitate alkylation (to generate the corresponding precursor) and as a precursor of an alkyllithium reagent. Thus, reductive decyanation of compound **42** led to the intermediate **43** [37], which underwent intramolecular carbolithiation and, after carboxylation and reaction with CH_2N_2 , gave spirocyclic ester **44** as a single diastereomer (Scheme 2.7) [38].

Scheme 2.7

2.2.2

 sp^2 -Hybridized α -Oxygenated Organolithium Compounds

Simply vinyl ethers, such as compound **45**, and other vinyloxygenated systems undergo deprotonation with $t\text{-BuLi}$ at low temperatures to give vinyl lithium derivatives of general structure **III** ($\text{X} = \text{OR}$) that react with different electrophiles [39]. For instance, the reaction of the intermediate **46** with chlorotrimethylgermane gave, after acidic hydrolysis, acylgermanane [40] (Scheme 2.8), compound **46** being an acyl anion equivalent [41]. The lithiation of 1-alkoxyallene **47** takes place more easily, using in this case $n\text{-BuLi}$ as base at -78°C in ether or THF as solvents (Scheme 2.8), intermediate **48** being stable at this temperature for several days [42]. Calculations and spectroscopic data suggest a 1,3-bridged structure for the anion **48** [43]. The reaction of this anion with α,β -unsaturated amides, followed by spontaneous Nazarov-type cyclization, gives methylene cyclopentenones [44]. The enantioselective variant of this synthesis was performed with the lithiated allene derived from D-glucose **49** [45].

Scheme 2.8

Cyclic akenyl ethers of general structure **IV** ($\text{X} = \text{O}$), like dihydrofuran and dihydropyran **50** ($n = 1, 2$) are deprotonated by means of either $t\text{-BuLi}$ in a mixture of pentane and THF or with $n\text{-BuLi}$ and TMEDA in hexane or pentane at 0°C [41]. These compounds reacted with a great variety of electrophiles, their reaction with carbonyl compounds, followed by acid treatment, giving spirocyclic ketones after suffering pinacol rearrangement [46]. Enantiomerically enriched spirocyclic compounds were obtained from the intermediate **51** (prepared from tin–lithium exchange) [47], or α -lithiated glucals **52** and **53** (prepared by direct deprotonation with $t\text{-BuLi}$) [48].

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Similarly, 2,3-dihydro-1,4-dioxin can be lithiated at a vinylic position with either *n*-BuLi at 0 °C or *t*-BuLi at –30 to –20 °C [43a]. Related benzocondensed systems **54** were lithiated with LDA at –78 °C to give the dianionic intermediates **55**, which were converted into lactones **56** upon successive reaction with acetaldehyde and propanoic acid [49] (Scheme 2.9).

Scheme 2.9

2.2.3

sp³-Hybridized α -Nitrogenated Organolithium Compounds

There are two types of α -aminoalkyl organolithium compounds of general structures **I** (X = NRR') and **II** (X = NR): those unstabilized (derived from tertiary alkylamines) and those dipole-stabilized.

The stabilized derivatives can be prepared by α -deprotonation of compounds where the nitrogen lone pair of electrons are involved in conjugation with unsaturated systems using strong bases [50]. This situation makes the nitrogen a more electron-withdrawing group, a stabilization of the organolithium compound occurring sometimes by intramolecular coordination of the metal with the functional group that contains the nitrogen atom. In the case of hindered amides α -lithiation to the amide nitrogen leads to stable organolithium compounds. Stereospecific deprotonation with *t*-BuLi of *N*-(α -methylbenzyl)-*N*-isopropyl-*p*-methoxybenzamide gave the corresponding configurationally stable tertiary benzyllithium derivative **57**, which underwent a stereospecific dearomatization-cyclization with >99% retention of the stereochemistry. This methodology was used in the synthesis of kainic acid derivatives [51]. Other stabilized α -nitrogenated organolithium compounds have been prepared by deprotonation of the appropriate precursors. The pyrazole derivative **58** was obtained by deprotonation with *n*-BuLi [2a], whereas in the case of the formamidine derivative **59** *t*-BuLi was used as base [52]. In the case of the lithiated cyclic *N*-nitrosoamine **60**, the deprotonation was performed with LDA to give exclusively the axial lithium derivative, which is stabi-

lized by interaction with the LUMO of the adjacent π -system [53]. Quinuclidine *N*-oxide was lithiated with *t*-BuLi to give the intermediate **61** [54]. All these anionic systems **57–61** reacted with electrophiles to give functionalized molecules in good yields.

Dipole-stabilized α -aminoorganolithium compounds are less reactive than the unstabilized ones and for that reason more resistant to suffer racemization. Enantioselective deprotonation of *N*-Boc pyrrolidine **62** with *s*-BuLi and (–)-sparteine gave the chiral configurationally stable [55] organolithium compound **63**. Due to the fact that (–)-sparteine is only available in one enantiomeric form, O'Brien et al. reported the synthesis of a (+)-sparteine surrogate, which worked as a successful chiral ligand in the same processes as (–)-sparteine, so both enantiomers are available by choosing the right diamine ligand [56]. The enantio-determining step is the formation of the organolithium derivative, the reaction of this intermediate with electrophiles leading to chiral compounds with high stereoselectivity [57]. For instance, when 1-pyrrolidinecarbonyl chloride was used as electrophile, the corresponding amide **64** was obtained in 85% ee [58] (Scheme 2.10). Intermediate **63** can also be prepared by tin–lithium exchange from the corresponding enantiopure 2-(tributylstannyl)pyrrolidine because tin–lithium exchange takes place with retention of the configuration [59].

Scheme 2.10

The unchelated dipole-stabilized α -aminobenzyl organolithium compound **65** was prepared by deprotonation and used in the synthesis of the azaphenanthrene alkaloid eupolauramine [60]. The *N*-lithiomethylcarbamate **66** was prepared by DTBB-catalyzed lithiation of the corresponding chlorinated precursor in the presence of carbonyl compounds as electrophiles, the resulting adducts being transformed into the corresponding β -aminoalcohols [61]. Chiral *N*-lithiomethylpyrrolidine **67** was prepared through either a tin–lithium exchange with *n*-BuLi or by carbon–sulfur bond cleavage with lithium 4,4'-di-*tert*-butylbiphenyl (LiDTBB) from the corresponding prolinol derivatives. The reaction of the intermediate **67** with aldehydes gave β -aminoalcohols in good yields but poor diastereoselectivity [62]. The corresponding unchelated α -amino organolithium compound was also

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prepared by tin–lithium transmetallation and reacted with electrophiles in moderate yields [63]. Reductive lithiation of a bicyclic oxazolidine with lithium in the presence of a catalytic amount of naphthalene (10 mol%) gave the benzylic organolithium compound **69**, which is stabilized by the alkoxide group. Epimerization at the benzylic position takes place rapidly and one of the diastereomers reacts faster than the other with alkyl halides to give mainly *syn*-products [64]. Nonstabilized aziridinyl anions can be prepared by direct deprotonation of aziridine borane complexes. Thus, deprotonation with *s*-BuLi of 1-(*tert*-butyldimethylsiloxyethyl)-aziridine borane occurred *syn* to the boron substituent to give intermediate **70**, while lithiation of 1-(*tert*-butyldimethylsiloxyethyl)-2-trimethylstannylaziridine borane occurred *anti* to the boron and tin, due probably to steric effects. When the deprotonation was performed in the presence of (–)-sparteine, stereoselectivity went up to 70% ee [65].

A trifluoromethyl stabilizing aziridinyl anion **72** was generated by deprotonation of the optically active *N*-tosyl-2-trifluoromethylaziridine **71** with *n*-BuLi. The organolithium intermediate **72** reacted with electrophiles to give the corresponding adducts **73** in good yields (Scheme 2.11), the whole reaction occurring with retention of the configuration at the stereogenic carbon center [66].

[E = PhCHO, Ph₂CO, PhCOMe, EtO₂CCHO, PhCOCl, MeOCOCl, EtCOCl, BnOCOCl]

Scheme 2.11

2.2.4

sp²-Hybridized α -Nitrogenated Organolithium Compounds

Recently, different α -lithioenamines **75** have been prepared by chlorine–lithium exchange from the corresponding chloroenamines **74** and reacted with electrophiles to give functionalized enamines **76**. A mixture of lithium and a catalytic amount of DTBB was used as the lithiating reagent (Scheme 2.12) [67]. The process can be performed either step-by-step (lithiation–reaction with the electrophile) at -90°C or under Barbier–reaction conditions at -40°C . In the case of using carbonyl compounds as electrophiles, after acidic hydrolysis, α -hydroxyketones were obtained, intermediates **74** acting in this case as acyl anion equivalents [41].

[E = D₂O, Me₃SiCl, PhCOCH=CHPh, CO₂, CyNCO]

Scheme 2.12

Some formamidines underwent lithiation of a vinylic position α to nitrogen, so for instance vinyl lithium compound **77** was prepared by deprotonation with *t*-BuLi of the corresponding formamidine [68]. In the case of hydrazones, a double lithiation occurred leading, for instance, to intermediate **78**, where the second C-lithiation took place at the trigonal carbon atom α to the C=N bond [69]. Lithiated cyclic enamines **79** were prepared by tin–lithium transmetalation and coupled with different electrophiles [70]. Organolithium compounds with a nitrogen at the α -position and sp²-hybridization can be prepared by direct metallation of nitrogen-containing aromatic heterocycles [71]. Thus, direct deprotonation of *N*-methylimidazol gave 2-lithio-*N*-methylimidazol **80** [72]. Direct lithiation of *N*-benzyloxypyrazole with *n*-BuLi gave compound **81**, which reacted with diethyl *N*-Boc-iminomalonate in the synthesis of *N*-hydroxypyrazole glycine derivatives [73]. 2-Lithiobenzothiazole **82** reacted with galactonolactone being used in saccharide chemistry [74]. Selective monobromo–lithium exchange from the corresponding dibromopyridine [75] gave intermediate **83**, which by reaction with a first electrophile and subsequent new lithiation and reaction with a second electrophile was used in the synthesis of a ceramide analog [76]. Using LiTMP as a base, organolithium compound **84** was prepared from 2-chloropyrazine and, after reaction with aldehydes, the resulting products were used in a route to the wheat-disease-impeding growth agent septorin [77]. The pyrazolopyrimidine lithium derivative **85** was prepared by tellurium–lithium transmetalation [78].

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2.2.5

Other sp^2 -Hybridized α -Functionalized Organolithium Compounds

Two general strategies have been followed for preparing α -haloalkyllithiums: (a) α -deprotonation of vinyl halides with strong bases and (b) halogen–lithium exchange in 1,1-dihaloalkenes [43a,79]. In both cases the processes having to be carried out at low temperature (-100°C). The deprotonation of (Z)-1-chloro-1,3-butadiene **86** with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) at -90°C gave (Z)-1-lithio-1-chloro-1,3-butadiene **87**. The reaction with benzaldehyde as electrophile took place with retention of the configuration of the double bond, giving compound **88** after hydrolysis (Scheme 2.13) [80].

Scheme 2.13

Although vinyl bromides and iodides are useful precursors of vinylolithiums by reaction with alkylolithiums through a halogen–lithium exchange, in the case of chlorinated materials, deprotonation occurs preferentially. Thus, treatment of 1,1-diphenyl-2-chloroethylene with *n*-BuLi in THF at -100°C gave the vinylolithium derivative **89** (deprotonation) [81], whereas under the same reaction conditions, chlorotrifluoroethylene gave intermediate **90**, (deprotonation is not possible) so a fluoro-stabilized vinylolithium compound by a chlorine–lithium exchange is formed [82].

2.3

 β -Functionalized Organolithium Compounds

Organolithium compounds bearing a functional group at β -position are unstable species. They show a great tendency to undergo a β -elimination process to give olefins, the better leaving group the higher instability. The hybridization of the carbon atom attached to the metal could be sp^3 (general structures **V** and **VI**) as well as sp^2 (general structures **VII–X**) in both cyclic and acyclic systems.

2.3.1

sp^3 -Hybridized β -Functionalized Organolithium Compounds

One way to prevent the decomposition of β -functionalized organolithium compounds **V-X** ($X = OR, NR_2$) is by diffculting the β -elimination process developing a negative charge on the heteroatom. These intermediates have been prepared following three general strategies: (a) mercury–lithium transmetallation, (b) chlorine–lithium exchange (in both cases oxygen and nitrogen deprotonation should be carried out first) and more recently by (c) reductive opening of epoxides and aziridines [83]. Deprotonation of organomercurials **91** with phenyllithium followed by mercury–lithium transmetallation with lithium metal gave organolithium intermediates **92**, which are stable at -78°C and reacted effectively with electrophiles to give polyfunctionalized compounds **93** (Scheme 2.14) [84]. ■AQ■

Scheme 2.14

Since enantiomerically pure epoxides are easily accessible or commercially available, chiral products can be obtained through a reductive cleavage followed by reaction with electrophiles. The DTBB-catalyzed lithiation of epoxide **94**, derived from D-glucose, led to the organolithium derivative **95**. In the case of unsymmetrically substituted epoxides, the regiochemistry of the ring opening always led to the most stable organolithium compounds, what is the case of the primary intermediate **95**. Its reaction with electrophiles followed by hydrolysis gave the corresponding 3C-substituted D-glucose derivatives **96** (Scheme 2.15) [85].

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Scheme 2.15

Enantiomerically pure intermediates **97** and **98** of type **V** ($\text{X} = \text{OLi}$) were prepared from the corresponding chiral chlorohydrins by deprotonation first with $n\text{-BuLi}$ and subsequent chlorine–lithium exchange with lithium naphthalenide [86]. The reaction of these dianions with prostereogenic carbonyl compounds showed low diastereoselectivity. The same strategy was followed in order to prepare these intermediates but starting from β -(phenylsulfanyl)alcohols through a sulfur–lithium exchange [87]. Oxygen functionalized organolithium compounds **99** [88] and **100** [89] were prepared by reductive opening of the corresponding chiral epoxides with LiDTBB and used in the synthesis of calcitriol lactone and diterpene forskolin, respectively. Dianionic intermediate **101** was also prepared by DTBB-catalyzed lithiation of the corresponding epoxide derived from (–)-menthone and used in the synthesis of functionalized terpenes [90].

Dilithium derivatives **102–105** were generated by reductive opening of epoxides derived from D-glucose, D-fructose, estrone and cholestanone, respectively, and trapped with different electrophiles. In this way, 6C-substituted 6-deoxy-D-glucose, 3C-substituted D-psycose [85], 17C-substituted-17 β -estradiol and 3C-substituted-3 α -cholestanol [91] derivatives were prepared.

As has been described before, one of the most important problems to be overcome in the preparation of sp^3 -hybridized β -functionalized organolithium compounds is their decomposition by a β -elimination process to give olefins. Advantage of this reaction can be taken to prepare olefins starting from organomercurials, chlorohydrins and epoxides by performing the lithiation process at higher temperatures [92].

The reductive opening of aziridines **106** should be performed at -78°C with an excess of lithium in the presence of a catalytic amount of an arene. A limitation in this methodology is that a phenyl or aryl group should be present as a substituent either at the nitrogen or at one of the carbon atoms of the aziridine ring. Regarding the regiochemistry of the process, the most stable primary organolithium intermediate **107** is always formed that by reaction with electrophiles and final hydrolysis led to the corresponding functionalized amines **108** (Scheme 2.16) [93].

[E = H₂O, D₂O, RHal, Me₂S₂, RCHO, R³R⁴CO, (EtO)₂CO, CH₂=CHCO₂Et]

Scheme 2.16

The enantiomerically enriched β -nitrogenated organolithium compound **109** was prepared by reductive opening of the aziridines derived from (–)-ephedrine [93], whereas compounds **110** and **111** were generated from the corresponding chlorinated precursors through a DTBB-catalyzed lithiation by a chlorine–lithium exchange [94]. The same methodology but using lithium naphthanelide was employed to prepare the intermediate **112**. Compound **113** was formed by stereoselective deprotonation of the corresponding *N*-Boc-cyclopropylamines [96]. The reaction of all these intermediates **109**–**113** with electrophiles yielded chiral regioselectively functionalized nitrogenated compounds.

Although allylic organolithium compounds of the type **VI** decompose easily to give allenes, deprotonation of methyl isopropenyl ether with a mixture of *n*-BuLi/*t*-BuOK at -78°C gave the allylic intermediate **114**, which was trapped with electrophiles. At -30°C compound **114** decomposes to give allene [97]. The organolithium derivative **115** was prepared by deprotonation with LDA at 0°C and decomposed immediately to give the corresponding allene [98]. However, cyclic allylic organolithium compounds **116** [99] and **117** [100], which are more stable,

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were also prepared by direct deprotonation with LDA and *t*-BuLi, respectively, intermediate **116** being used in the synthesis of tetrahydropyranones.

2.3.2

sp²-Hybridized β -Functionalized Organolithium Compounds

Alkenyllithium compounds of type **VII** have been prepared mainly by halogen–lithium exchange. β -Ethoxyvinyl lithium derivatives **118** and **119** were accessible from the corresponding vinyl bromides by stereospecific bromine–lithium exchange with *n*-BuLi at -78°C . The (*Z*)-isomer **119** is much more stable than the (*E*)-isomer **118** because in this case an antiperiplanar elimination of lithium ethoxide is more favorable. In the case of (*Z*)- and (*E*)-diethoxyvinyl lithiums **120** and **121**, they have been prepared by deprotonation with *t*-BuLi at -78°C of the corresponding diethoxyethylenes. The (*Z*)-isomer **121** is also more stable than the (*E*)-isomer **120** due to the previously mentioned antiperiplanar β -elimination of lithium ethoxide. However, compounds **120** and **121** are much more stable than the monoethoxy substituted derivatives **118** and **119** due to the inductive effect of the oxygen atom at the α -position. All these intermediates reacted with electrophiles regio- and stereoselectively [101]. β -(Trimethylsilyl)vinyl lithium **122**, generated from β -(trimethylsilyl)vinyl bromide with *t*-BuLi, reacted with β -alkenoyl acylsilanes to give eight-membered carbocycles [102]. Many vinyl lithium compounds with other functional groups have been described in the literature, for instance, the cyclic β -bromoderivative **123** that was prepared from the corresponding dibromide through a selective monobromo–lithium exchange with *t*-BuLi at -78°C [103]. In this case, decomposition through a synplanar process is obviously inhibited. Intermediates of type **X** are, in general, stable species and therefore useful functionalized organolithium reagents in order to prepare aromatic compounds. They have received much attention and are generated by direct deprotonation [71,104a] or by halogen–lithium exchange [75,104b]. For instance, the aryllithium **124** was prepared by iodo–lithium exchange with *n*-BuLi in toluene and used in the synthesis of antitumor antibiotics duocarmycins [105].

Dianions **126**, alkenyllithium compounds of type **VIII**, have been obtained by halogen–lithium exchange from the corresponding chlorinated or brominated precursors **125** using lithium naphthalenide; it was necessary to carry out a previous deprotonation with PhLi. The reaction of **126** with electrophiles gave regioselective functionalized allyl amines **127** (Scheme 2.18) [106].

Scheme 2.17

Vinyl lithium derivatives **128–131** have been generated through a bromine–lithium exchange with *t*-BuLi. In the case of **128**, used in the synthesis of (–)-wodehiol, a deprotonation of the alcohol functionality was performed prior lithiation [107]. Intermediates **129** were also used in the synthesis of triquinanes [102,108], meanwhile **130** acted as an intermediate in a synthetic route to (+)-pericosine B [109]. Dianionic species **131** showed an unexpected intramolecular carbometallation upon addition of TMEDA to give dilithiated dihydropyrroles, which finally reacted with different electrophiles [110].

Vinyl lithium acetals **142**, compounds of type **IX**, were prepared from the corresponding chlorinated precursor **141** by a DTBB-catalyzed lithiation at low temperature. They reacted with electrophiles to give compounds **143**. In the case of using chiral starting materials (**141**, R = Me), the reaction with prostereogenic carbonyl compounds took place with almost null stereoselectivity (Scheme 2.18) [111].

Scheme 2.18

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2.4

γ -Functionalized Organolithium Compounds

Organolithium compounds with a functional group at the γ position can be represented by a great number of general structures (XI–XX) depending on the hybridization of the carbon atoms bearing both the lithium and the functional group.

2.4.1

γ -Functionalized Alkylolithium Compounds

Functionalized organolithium compounds of type XI can be accessible through a large number of methodologies. They are accessible by halogen–, sulfur–, or selenium–lithium exchange, tin–lithium transmetallation, reductive opening of four-membered heterocycles and also by carbolithiation of cinnamyl systems.

Enantiomerically pure oxygen functionalized organolithium compounds 144–147 have been prepared by halogen–lithium exchange. The precursor of 144 was the corresponding chlorohydrin and lithium naphthalenide the lithiating reagent [86], meanwhile intermediates 145 [112], 146 [113] and 147 [114] were prepared by iodine–lithium exchange by means of *t*-BuLi. All of them reacted with electrophiles to yield polyfunctionalized compounds, compound 146 being used in the synthesis of scopadulcic acid A.

The carbolithiation of cinnamyl methyl ether 148 with an alkylolithium in the presence of TMEDA led to the corresponding benzylic organolithium intermediates 149, which by reaction with electrophiles gave compounds 150 with high diastereoselectivity (Scheme 2.19) [115].

Scheme 2.19

When the carbolithiation of *tert*-butyl cinnamyl ether is performed in the presence of (–)-sparteine, chiral organolithium compounds **151** were obtained, so chiral 2-alkyl-3-phenylpropanols were the reaction products, after hydrolysis [116]. Dianionic species **152–154** were prepared by reductive opening of different heterocycles [83] by an arene-catalyzed lithiation and reacted with electrophiles to give polyfunctionalized molecules in good yields. Enantiomerically pure oxetanes [117,118] (for **152**), 4-phenyl-1,3-dioxolanes [119] (for **153**) and 2-phenyl-substituted azetidines or tietanes [120] (for **154**) were the starting heterocycles used. The reductive cleavage always gave the most stable intermediate: the primary alkyl-lithium compounds for the chiral oxetanes and the benzylic derivatives for the other. Although γ -halogenated organolithium compounds have a great tendency to undergo γ -elimination reactions, the norbornane derivative **155** (prepared from the brominated derivative by treatment with *t*-BuLi at -125°C) could be trapped with carbon dioxide to give the corresponding carboxylic acid in 47% yield [121].

Masked lithium homoenolates of type **XII** are of interest in synthetic organic chemistry and can be considered as three-carbon homologating reagents with umpolung reactivity [122]. The lithiation of the β -chloro orthoester **156** with lithium in the presence of a catalytic amount of DTBB, under Barbier-reaction conditions, and using carbonyl compounds as electrophiles, followed by acidic hydrolysis, led to lactones **158** as reaction products, the masked lithium homoenolate **157** being proposed as a reaction intermediate (Scheme 2.20) [123].

Scheme 2.20

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Cyclopentanone dioxolane lithium homoenolate **159** was prepared by reductive lithiation with LiDTBB of the corresponding β -penylsulfanyl derivative and alkylated with allylic bromides in the presence of copper salts [124]. The acyclic dioxane lithium homoenolate **160** was prepared by bromine–lithium exchange and used for the synthesis of highly functionalized porphyrins [125]. Carbolithiation of a cinnamyl acetal with *t*-BuLi in toluene gave the lithium homoenolate **161**, which reacted with electrophiles to give reaction products with high diastereoselectivity [126]. The chiral benzylic homoenolate **162** was prepared by deprotonation of the corresponding amide with 2 equiv of *s*-BuLi in the presence of TMEDA at -78°C . First deprotonation deactivates the functionality and the second deprotonation is directed to the β -position of the carboxamide by the so-called complex-induced proximity effect (CIPE) [127]. In the reaction of intermediate **163** with electrophiles an almost 1:1 mixture of diastereomers was obtained [128]. Lithiated imines **163**, which were prepared by DTBB-catalyzed lithiation of the corresponding chlorinated derivatives, underwent intramolecular cyclization through an *endo-trig* process to yield 2-substituted pyrrolidines, after hydrolysis [129].

2.4.2

 γ -Functionalized Allyllithium Compounds

Functionalized allyllithium compounds of type **XIII** are also homoenolate equivalents [122,130], but in their reaction with electrophiles sometimes it is not possible to control the regioselectivity. These compounds have been prepared mainly by either deprotonation or tin–lithium exchange. Deprotonation of (*E*)-cinnamyl-*N,N*-diisopropylcarbamate **164** with *n*-BuLi in the presence of (–)-sparteine in toluene gave a configurationally stable lithiated *O*-allyl carbamate (*epi*-**165**), which equilibrates at -50°C to give the (*R*)-intermediate **165**. Whereas the reaction of these compounds with MeI and MeOTs gave the γ -attack, however acylation, silylation and stannylation took place at the α -position (Scheme 2.21) [131].

Scheme 2.21

The allylic intermediate **166** was prepared by deprotonation with LDA and reacted with 1,2-dialkyloxiranes in the synthesis of parasorbic acid [132]. Direct deprotonation of silyl allyl ether with *s*-BuLi gave the allylic compound **167**, which reacted with electrophiles at the γ -position [133]. Tin–lithium transmetalation of a 3-stannylated enamine led to the intermediate **168**, which after reaction with electrophiles and acidic hydrolysis gave 3-functionalized cyclohexenones [134]. The chiral *endo*-aminoallyllithium **169** was also prepared by tin–lithium transmetalation of the corresponding *O*-methylprolinol derivative, and alkylated to give after hydrolysis β -alkylated ketones [135]. Direct deprotonation with *t*-BuLi of *N*-methallylaniline gave the dianionic intermediate **170**, of type **XIV** [136].

Starting from the symmetrical allylic diselenanyl compound **171**, and through a selenium–lithium exchange with *n*-BuLi, methylselenanyl methallyllithium compound **172** was prepared, which after reaction with electrophiles afforded products **173** (Scheme 2.22) [137].

Scheme 2.22

2.4.3

γ -Functionalized Benzyllithium Compounds

Functionalized benzyllithium compounds of type **XV** are prepared by proton abstraction at the benzylic position with appropriate bases. Trilithiated 2,6-dimethylphenol **174** was prepared by deprotonation with *n*-BuLi under hexane reflux and its tetrameric structure was determined by X-ray diffraction [138]. In the case of 2-methoxy benzyl ether, reductive cleavage of the benzylic carbon–oxygen bond by means of a naphthalene catalyzed lithiation at -10 °C in THF gave the benzyllithium derivative **175** [139], other benzyllithium compounds being prepared through this methodology. On the contrary, the benzyllithium derivatives **176** were generated by carbolithiation of *o*-vinyl substituted *N*-Boc protected aniline with *n*-BuLi in diethyl ether at -78 °C. Further reaction with DMF followed by final acidic hydrolysis yielded functionalized indoles in a one-pot process [140]. Dianions **177** [141] and **178** [142] were prepared by double deprotonation with LDA and *n*-BuLi, respectively, the first one being used in the synthesis of β -resorcylic acid derivatives [141].

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Benzylic organolithium compounds are in general configurationally unstable. However, the lateral lithiation of tertiary 2-alkyl-1-naphthamides, such as **179**, was stereoselective and yielded a single diastereomeric atropisomer **180** [143], which reacted with several electrophiles with retention, to give compounds **181** [144], except with trialkyltin halides for which an inversion of the configuration was observed (Scheme 2.23) [144a].

Scheme 2.23

2.4.4

γ -Functionalized Akenyllithium Compounds

Vinylolithium compounds of type **XVI** show *Z/E*-configuration and can be prepared by tin– or halide–lithium exchange, because deprotonation occurs mainly at the allylic position, except in very special cases. *O*-Silyl protected γ -lithiated allyl alcohol **182** has been prepared by iodine–lithium exchange with $t\text{-BuLi}$ in hexane or THF at 0°C , the process being totally stereospecific, so the resulting vinyl-lithium compound kept the configuration of the starting iodide [145]. The silylated compound **183** was prepared by tin–lithium transmetallation and reacted with cyclopentenones in the presence of zinc salts for the synthesis of prostaglandins [146]. Azasilacines and azagermacines were synthesized in a direct way from the trianion **184** [147], which was prepared by a sequential deprotonation at a vinylic position [136,148] followed by a tin–lithium transmetallation from (*Z*)-allyl-3-(tri-*n*-butyltin)allylamine. Reagent **185**, which derived from a protected diol, was prepared by bromine–lithium exchange and used in the synthesis of butenolide fugomycin [149]. The *N*-methoxyimine derived from (*Z*)- β -iodo acrolein was lithiated with $n\text{-BuLi}$ in hexane at -78°C to give vinylolithium intermediate **186**, which was trapped with isocyanates to give the corresponding amides [150].

β -Chloro *E*- α,β -unsaturated ketone acetals **187** underwent stereoselective DTBB-catalyzed lithiation to give vinyl lithium derivatives **188**, which after reaction with electrophiles and final acidic hydrolysis led to regioselectively functionalized α,β -unsaturated carbonyl compounds **189**. In the reaction of enantiomerically enriched starting materials **187** ($R^2 = \text{Me}$) with prostereogenic carbonyl compounds, no diastereoselectivity was observed (Scheme 2.24) [111,151].

Scheme 2.24

Aryllithium compounds of type **XVIII** are generated mainly either by direct deprotonation [71,104] or by halogen–lithium exchange [75,105]. In the case *p*-methoxybenzaldehyde dimethyl acetal, *ortho* lithiation with *n*-BuLi (to give the intermediate **190**), followed by reaction with electrophiles and final acidic hydrolysis, led to polyfunctionalized benzaldehydes in high yields [152]. Vinyl lithium derivatives **191** and **192** (of type **XIX**) have been prepared from the corresponding vinylic halides by treatment with *t*-BuLi. The silyl ether derivative **191** was used in the synthesis of the C1 alkyl side chains of Zaragozic acids A and C [153] and the intermediate **192** was involved in the total synthesis of marine metabolites (+)-calyculin A and (–)-calyculin B [154]. The chlorovinyl lithium derivative **193** was accessible through a tin–lithium transmetalation and used in the synthesis of the marine sesquiterpenoid ($\pm$)-kelsoene [155]. Cyclic vinyl lithium intermediate **194** was used in the construction of *seco*-taxanes, being prepared from the corresponding ketone trisylhydrazone applying the Shapiro reaction [156].

Iron-catalyzed carbolithiation of the internal alkyne **195**, bearing an alkoxy group at the homopropargylic position, led to the vinyl lithium compound **196**,

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which was trapped with electrophiles to give the corresponding functionalized olefins **197** with a defined stereochemistry and in high yields (Scheme 2.25) [157].

Scheme 2.25

2.4.5

 γ -Functionalized Alkynyllithium Compounds

Functionalized alkynyllithium compounds of type **XX** were prepared almost exclusively by deprotonation of the corresponding terminal alkynes and therefore, the functionality sometimes have to be protected in order to tolerate the presence of the base and to resist the conditions for the acetylenic proton to be removed. Functionalized lithium acetylide **198** was prepared by deprotonation of the corresponding O-protected propargyl alcohol and further alkylated with butadiene bis-epoxide in order to prepare dienediyens [158]. The alkynyl anion **199** was used in the synthesis of (–)-lulimalide, a microtube-stabilizing agent [159]. The intermediate **200**, prepared from Garner's aldehyde, reacted with aldehydes in high yields [160] and the orthoester reagent **201** acted as the acetylenic anion of propyolic acid and reacted with carbonyl compounds in good yields [161].

The lithium orthopropiolate **203** was prepared by a silicon–lithium exchange from the trimethylsilylacetylene derivative **202** and reacted with acetylenic aldehydes to give diacetylenic alcohols **204**, which were easily transformed into the corresponding ketones by treatment with manganese dioxide (Scheme 2.26) [162].

Scheme 2.26

2.5

δ -Functionalized Organolithium Compounds

The number of possible structural devices increases as functionality gets further from the anionic center in functionalized organolithium compounds. So, δ -functionalized organolithium compounds can be classified according to the hybridization of the carbon atom bonded to the lithium in alkyllithium compounds (XXI and XXII), allylic and benzylic derivatives (XXIII–XXV) and alkenyl (XXVI–XXVIII) and alkynyl systems (XXIX).

2.5.1

δ -Functionalized Alkylolithium Compounds

Different alcohols and protected alcohols (as hemiacetals, silyl, methoxymethyl or phenyl ethers) were lithiated at the δ -position to give the corresponding organolithium compounds. In the case of alcohols, a previous deprotonation of the hydroxyl functionality is required. The chiral intermediate **206** was prepared from the phenylsulfanyl derivative **205** first by deprotonation followed by carbon–sulfur bond cleavage with LiDTBB at low temperature. The reaction of the dianionic system **206** with γ - and δ -lactones in the presence of cerium(III) salts gave, after hydrolysis, spiroketal pheromones **207** (Scheme 2.27) [163].

Scheme 2.27

Similarly to cinnamyl alcohols and ethers, which undergo carbolithiation by reaction with alkyllithiums [115,116], treatment of (*E*)-4-phenyl-3-buten-1-ol with two equivalents of *n*-BuLi in the presence of (–)-sparteine gave the organolithium compound **208**, which after hydrolysis afforded the corresponding alcohol with 72% ee [164]. The optically active intermediate **209** was prepared by bromine–lithium exchange with *t*-BuLi in ether and was used in the synthesis of the C28–C40 fragment of azaspiracids [165]. Masked bishomoenolates **210** and **211**

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were prepared by means of a DTBB-catalyzed lithiation of the corresponding γ -chloro orthoesters [166] and phenylsulfanyl derivative [167], respectively. Functionalized methyl esters were obtained when the lithiation leading to the intermediate **210** was performed in the presence of electrophiles followed by hydrolysis with methanol and a catalytic amount of *p*-toluenesulfonic acid [166]. The lithio-thioacetal **211** reacted with *N*-phenethylimides, pyrroloisoquinolinones being obtained in good yields after acyliminium ion cyclization [167].

2.5.2

 δ -Functionalized Allyl and Benzyllithium Compounds

Dianion **212** was prepared by double deprotonation of 3-methyl-3-buten-1-ol with *n*-BuLi in the presence of TMEDA and reacted with alkyl halides in the synthesis of different pheromones, the best results being obtained using diethyl ether as solvent [168]. However, the dianionic allylic isomer **213** was prepared through a tin–lithium transmetallation starting from the corresponding tri-*n*-butyltin derivative. The reaction of compound **213** with aldehydes took place at the internal position of the allylic system [169]. Reductive opening of heterocycles bearing the heteroatom at an allylic or benzylic position, as well as cyclic aryl ethers and thioethers, leads to functionalized organolithium compounds in a direct way [83]. The δ -amino functionalized organolithium compound **214** was prepared through an allylic carbon–nitrogen bond cleavage by a DTBB-catalyzed lithiation from *N*-phenyl-2,3-dihydropyrroline and reacted with electrophiles regioselectively [170]. The dilithium derivatives **215** and **216** have also been prepared from 2-phenyltetrahydrothiophene (Y = S) [171], *N*-isopropyl-2-phenylpyrrolidine (Y = NPh) [170], thiophthalan (Y = S) [172] and *N*-phenylisoindoline (Y = NPh) [170] under the same reductive reaction conditions. In all these cases, a benzylic carbon–heteroatom bond cleavage took place, their reaction with electrophiles leading to polyfunctionalized molecules in a regioselective manner.

In addition, the lithiation of phthalan **217** could be directed to the introduction of two different electrophiles at both benzylic positions in a sequential manner. Thus, after the reductive opening of compound **217**, the resulting dianionic inter-

mediate **218** reacted with a first electrophile followed by hydrolysis to give the functionalized alcohols **220**. However, when, after the addition of the first electrophile, the resulting alcoholate **219** was allowed to react in the highly reductive reaction medium at room temperature, a new benzylic carbon–oxygen bond cleavage took place to give a new organolithium intermediate **221**. The addition of a second electrophile and final hydrolysis led to polyfunctionalized *o*-xylene derivatives **222** (Scheme 2.28) [173]. Functionalized benzyllithium compound **218** has found a wide applicability in organic synthesis. Depending on the electrophile it has been used in the synthesis of tetrahydroisoquinolines [174] and structurally modified sugars [85b], steroids [91b] and monoterpenes [175]. In the presence of different metallic salts, intermediate **218** participated in conjugate addition processes, acylation reactions, dimerization and alkylation with allylic systems, as well as in chemoselective additions to carbonyl compounds [176].

Scheme 2.28

2.5.3

 δ -Functionalized Alkenyllithium Compounds

Vinyl lithium compounds with a functional group at the δ -position have been prepared stereospecifically from the corresponding vinylic precursors, mainly by halogen– or tin–lithium exchange. They are not accessible by direct deprotonation due to the lack of influence of the functional group, which is located too far away from the vinylic proton to be removed. The alkenyllithium derivative **223** (of type **XXVII**) was prepared from the corresponding ketone by means of a Shapiro reaction, acting as an intermediate in the synthesis of the antibiotic nodusmicin [177]. Meanwhile, the (*E,E*)-dienyllithium compound **224** (of type **XXVIII**) has been generated from 1-(tri-*n*-butylstannyl)-4-ethoxy-1,3-butadiene by a tin–lithium exchange and used in the synthesis of a polyene macrolide roflamycoin [178]. Reductive opening of benzofuran with lithium and a catalytic amount of DTBB at 0 °C gave the (*Z*)-organolithium derivative **225** that reacted with electrophiles in a regio- and stereoselective manner and was applied to the synthesis of substituted *o*-vinylphenol derivatives. In the case of using carbonyl compounds as electrophiles, the resulting diols gave substituted chromenes in high yields, after dehydration under acidic conditions [179].

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2.5.4

 δ -Functionalized Alkynyllithium Compounds

As previously commented for other acetylenic anions, functionalized alkynyllithium compounds of the type **XXIX** were prepared almost exclusively by deprotonation of the corresponding terminal alkynes. Thus, the dihydropyran derivative **226** has been used for the convergent synthesis of *trans*-fused polytetrahydropyrans, which are present in marine toxins by coupling with triflates [180].

A different strategy towards δ -functionalized alkynyllithium compounds consists in the treatment of *gem*-dibromoalkenes (accessible from the corresponding aldehydes) with an excess of *n*-BuLi. Following this methodology, intermediate **228** was prepared from the dithiane derivative **227** and alkylated with methyl iodide to give the corresponding alkyne (Scheme 2.29) [181].

Scheme 2.29

2.6

Remote Functionalized Organolithium Compounds

The influence of the functional group on the reactivity and the stability of functionalized organolithium compounds decreases as it gets further from the carbanionic center, so these compounds behave in many cases as normal organolithium compounds and can be prepared through classical methodologies. They can be classified according to the hybridization of the anionic carbon as in the previous section.

2.6.1

Remote Functionalized Alkylolithium Compounds

In general, organolithium compounds bearing a leaving group at the ϵ -position undergo an intramolecular nucleophilic substitution to give the corresponding cyclic

systems. Treatment of the iodinated methoxy compound **230** with two equivalents of *t*-BuLi in heptane at -78°C gave the ϵ -functionalized organolithium compound **231**, which upon addition of TMEDA, suffered intramolecular $\text{S}_{\text{N}}2'$ cyclization to give the vinylcyclopropane **232** in almost quantitative yield (Scheme 2.30) [182].

Scheme 2.30

On the other hand, the silyl-substituted vinylolithium **233**, prepared by bromine–lithium exchange, did not cyclize and reacted with 3-fluoro-3-buten-2-one to give the corresponding alcohol, which was used in the synthesis of ($\pm$)-dammarenediol [183]. The ϵ -oxido functionalized intermediate **234** was prepared from the corresponding chlorohydrine by a chlorine–lithium exchange with lithium naphthalenide after deprotonation, and reacted with iodoarenes to give the expected coupling products [184]. The organolithium compound **235**, containing a masked acylsilane functionality, was prepared from the corresponding iodinated precursor by treatment with *t*-BuLi, and reacted with substituted cyclopent-2-enones to give the expected 1,2-addition products. This strategy was used for the synthesis of isocarbacyclin, a stable analog of prostacyclin [185].

2.6.2

Remote Allyl and Benzylolithium Compounds

The allyllithium compound **236** was generated from the phenylsulfanyl precursors by means of lithium naphthalenide in THF at -78°C in the presence of TMEDA and underwent an irreversible retro-[1,4]-Brook rearrangement to give an almost 4:1 mixture of *syn,trans* and *anti,trans* diastereomers [186].

A diastereomeric mixture of isopentenyl dimethylcyclopentanol **239** was obtained through a lithium-ene cyclization starting from the oxido allylic intermediate **238**, which was generated by LiDTBB carbon–sulfur bond cleavage of **237**, the lithium oxide unit facilitating the cyclization. The corresponding magnesium derivatives participated in the same cyclization process (Scheme 2.31) [187].

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Scheme 2.31

Dianionic benzylic intermediates **240** [171], **241** (Y = O [188], Y = S [189], Y = NPh [170]), **242** (Y = O [190], Y = S [191], Y = NMe [190]), and **243** (Y = O [190], Y = S [190,192], Y = NMe [190]), were all prepared through a benzylic carbon–heteroatom bond cleavage from the corresponding heterocycles by an arene-catalyzed lithiation and reacted with electrophiles to give polyfunctionalized molecules in a regioselective manner. In a similar way to phthalan **217** (Scheme 2.28), after the reaction with a first electrophile intermediates **242** (Y = S) [191] and **243** (Y = O) [192], underwent a second benzylic carbon–heteroatom bond cleavage to give a new organolithium compound, which reacted with a second electrophile, yielding polyfunctionalized biphenyls and naphthalenes, respectively after hydrolysis.

2.6.3

Remote Functionalized Alkenyl- and Alkynyllithium Compounds

As an example of a remote functionalized alkenyllithium compound, the alkoxy functionalized polyenyllithium **245** (prepared by bromine–lithium exchange with *t*-BuLi) reacted with carbonyl compounds to give after acidic hydrolysis the corresponding polyenic aldehydes **246** (Scheme 2.32) [193].

Scheme 2.32

Lithium (Z)-5-lithio-5-methyl-4-penten-1-olate **247** was also prepared by bromine–lithium exchange, after the deprotonation of the hydroxy unit, and acylated with amides in the synthesis of the enantiomer of natural epolactaene [194]. Di-enyllithium **248** containing a masked carbonyl functionality (prepared by a bromine–lithium exchange) reacted with a lactam being used in the synthesis of trisporic acids [195]. Meanwhile, the lithium acetylide **249** with a remote oxide functionality was prepared by double deprotonation of the corresponding alkynol with *n*-BuLi and alkylated with 1-iodooctane, the resulting product being an intermediate in the synthetic route to the marine sponge natural products *R*-strongylidiols A and B [196]. Finally, the silyl enediyne lithium derivative **250** was prepared by deprotonation of the corresponding monoprotected enediyne with LiHMDS at $-78\text{ }^{\circ}\text{C}$ and used in the synthesis of antitumor agent ($\pm$)-calicheamicinone [197].

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