LITHIUM

ANNUAL SURVEY COVERING THE YEAR 1973

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CONTENTS

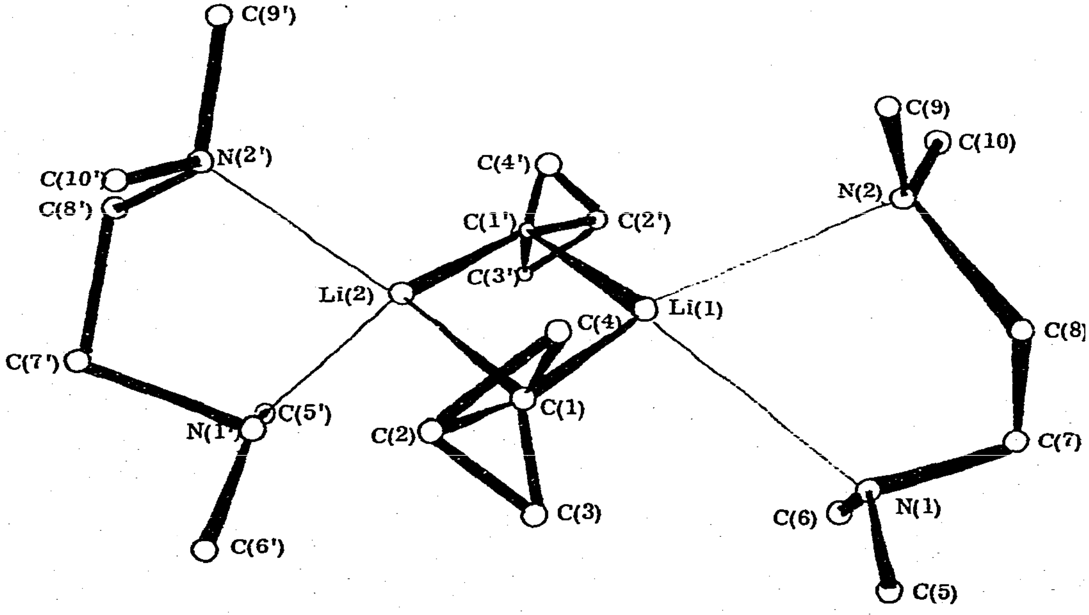
Some general reviews on the utilization of organolithium reagents in synthetic processes have appeared during 1973. Rausch and Sarnelli [1] have summarized the use of chelated organolithium species in synthesis. A recent chapter on the chemistry of carbanions contained much information on the various types and uses of organolithium compounds in general [2]. Of some interest to organolithium chemists may be the medically oriented reviews entitled "Mechanisms of Lithium Action" [3] and "Lithium and Mental Health" [4].

I. Structure and Bonding Studies

An article which considers techniques for the preparation and manipulation of air sensitive organolithium (and magnesium) compounds in nmr sample tubes has been published [5].

Single-determinant SCF-LCAO-MO calculations by the "ab initio" method have been performed for methyllithium and two beryllium species [6]. Using three 2p orbitals on lithium in the calculation, an optimum bond distance in the monomer was predicted to be 2.31A (vs. 2.31A found experimentally for the tetramer). A dimerization energy for methyllithium of 34.9 kcal/mole was calculated. In addition, a theory of bonding and energetics in alkylithium aggregates was proposed.

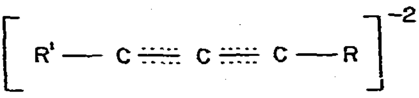
Bicyclobutane was treated with n-butyllithium/TMEDA reagent in hexane; colorless crystals were obtained upon evaporation of solvent and recrystallization [7]. X-ray analysis indicated the electron deficient dimer possessed structure I with a monoclinic space group, C2/m, where a = 8.95Å, b = 15.05Å, c = 9.38Å and



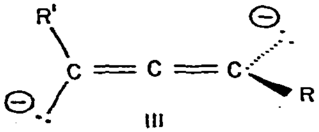
β = 97.90° Z = 4. Refinement of 337 reflections using anisotropic temperature factors for non-hydrogen atoms and a disordered model for the carbon atoms of the TMEDA unit in the space group C2/m gave R 10.8%.

A series of alkali salts of tetraphenylindene have been prepared (alkali metal = Li, Na, K, Rb, Cs) [8]. A detailed structure for the Na salt was obtained. The lithium salt was found to be isostructural with that of the sodium salt [lattice parameters, a = 12.196(6) and c = 6.491(5)Å].

The linear "sesquiacetylenic" geometry for propargylic dianions, II, has been supported (marginally) over that of the allenic dianion structure, III, by all-valence-electron SCF calculations [9]. Dilithiated acetylenes in several solvents can exist as either the sesquiacetylenic or allenic form. This was demonstrated by the observation of a shift from ca. 1800 to 2050 cm^{-1} in the ir spectrum of such compounds with a change to greater coordinating ability of the solvent [10].



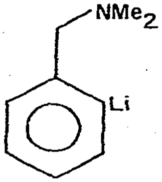
II



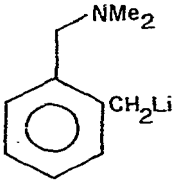
III

A series of α-lithio derivatives of carboxylic acid esters have been prepared by treatment of the ester in hydrocarbon solvent with $LiN(i\text{-}Pr)_2$. Ir spectra of these compounds in general exhibited new, intense absorptions between 700 and 250 cm^{-1} [11].

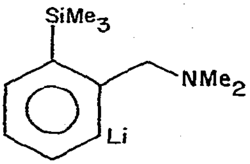
ortho-Lithio-N,N-dimethylbenzylamine (IV), α-lithio-*ortho* methylbenzyldimethylamine (V) and *ortho*-lithio-*ortho*-trimethylsilyldimethylbenzylamine (VI) have been isolated and characterized [12]. Spectral data (ir, uv, nmr) have provided some evidence for intramolecular N-Li association while freezing point depression studies have indicated that all three species exist as dimers at low concentrations and higher oligomers at higher concentrations.



IV



V



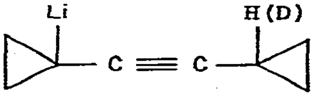
VI

The hydrocarbon solubility of 9-(2-hexyl)fluorenyllithium has permitted evaluation of its aggregation and spectral behavior in nonpolar solvents and comparison to that in polar solvents [13]. Ebulliometry revealed a dimer structure in cyclohexane at 25° over the concentration range of 0.01 to 0.1m. A finite equilibrium between monomeric and dimeric ion pairs over the concentration range 0.002 to 0.04m was indicated in THF at 25°. Lithium-7 and proton nmr spectra recorded in polar and nonpolar solvents showed a regular trend of increasing cation-anion interaction with decreasing solvent polarity. An electronic spectrum in ether solvents has previously been reported; this was found consistent with the description of contact and solvent-separated ion pairs. An apparently striking departure from the predictions of this description was observed in the electronic spectrum of this molecule in hydrocarbon solvents.

The 1,4-addition product of butadiene and _tert_-butyllithium, neopentylallyllithium, has been studied by pmr and uv spectroscopy in ether solvents [14]. Extensive delocalization of the allyl anion was observed in ether solvent as compared to hydrocarbon solvent. _cis_-_trans_ Isomerization occurred slowly in ether at 30°, but was considerably faster in THF.

tert-Butyllithium was reacted with a series of α-methylstyrenes to afford in near quantitative yield the 1:1 addition products [15]. A study of the ring proton chemical shifts in ether, hydrocarbon and hydrocarbon/TMEDA solvents revealed exceptional ring proton shielding which was independent of solvent, metal and substitution on the benzylic carbon. Rates of rotation about the ring-benzyl bond were measured and a solvent to carbon metal coordination transfer mechanism was proposed to explain the rotational dependance upon solvent and metal ion.

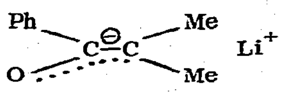
Detailed pmr spectra of the 1-lithiocyclopropyl acetylene (VII) and its deuterated analog in benzene, THF and mixtures thereof revealed some significant information [16]. Whereas the anionic carbon was pyramidal in benzene, configurational inversion was observed in THF *via* a planar transition state. An activation energy for this process of 4 kcal/mole was calculated.



VII

Pmr spectra of lithium, sodium and potassium salts of hydroxymethylene ketones, RCOCH=CHOH were investigated in the solvents H_2O, alcohols, DMSO, HMPT and DME [17]. From interpretation of coupling constant values the salts were proven to be completely dissociated in water; in other solvents the degree of association decreased as the solvent polarity and/or the cation radius decreased.

By study of pmr spectra of lithioisobutyrophenone (VIII) in various ether solvents, a barrier to rotation about the carbon-carbon double bond of >27 kcal/mole has been determined [18].

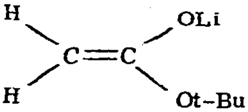


VIII

Several methyl substituted pyridines dissolved in dimethoxyethane have been metalated with n-butyllithium and the pmr spectra of the resulting metalated intermediates recorded [19]. In most compounds metalation occurred at a 2-methyl group. The exceptions were 2,4-lutidine and 2,4,6-collidine where metalation occurred at the 4-methyl substituent. An interesting example of magnetic nonequivalence in the pmr spectra of several of the 2-picolyl carbanions has been observed.

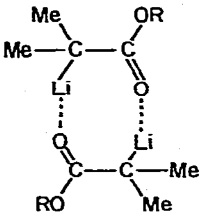
The change in chemical shift of the α-methylene protons of n-butyllithium in hexane upon addition of 1-methoxynaphthalene or anisole has been interpreted in terms of some disruption of alkyllithium oligomer structure in favor of complexation by the respective ethers [20].

Treatment of tert-butylacetate with LiN(i-Pr)$_2$ has resulted in the isolation and characterization of α-lithio-tert-butyl acetate as a stable white solid [21]. Observation of a pair of partially resolved doublets (3.14 and 3.44 ppm downfield from TMS) in the compound's nmr spectrum was interpreted in terms of the O-lithium enolate structure IX.



IX

Vapor phase osmometry was used to determine the degree of association of a series of α-lithio derivatives of carboxylic acid esters [22]. The values obtained in benzene and THF ranged from 1.8 to 6.6 with the higher values being obtained in the hydrocarbon solvent. A possible structure for a dimer interaction is illustrated (X).



X

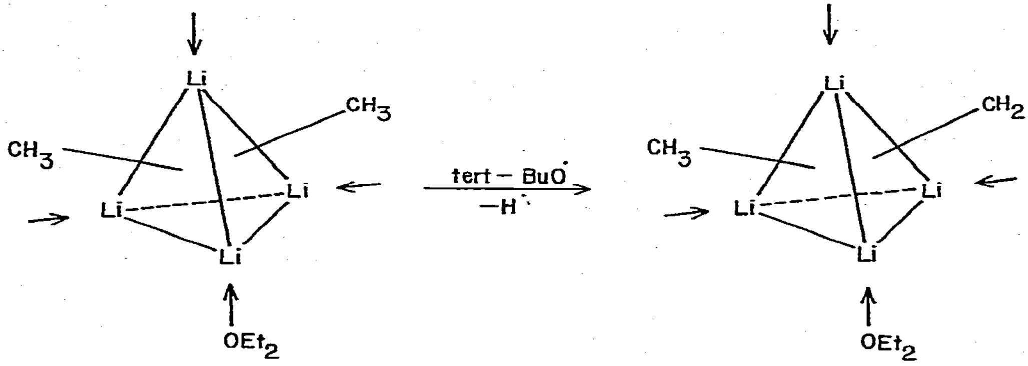
Since Lewis bases often act as catalysts for organolithium reactions, the heats of interaction of THF, tetrahydrothiophene, Et_3N and Et_3P with n-butyllithium in hexane at various base concentrations have been measured by high dilution solution calorimetry [23]. The relative heats found were THF > $Et_3N \sim Et_3P$ > tetrahydrothiophene. Plots of enthalpies of interaction vs. the ratio of added base to lithium atoms revealed a distinct break in THF at a ratio of 0.5. This was interpreted in terms of a hexamer-tetramer conversion.

Addition of methyllithium to NMe_4CN has resulted in the isolation of a 1:1 complex which exists as a tetramer [24].

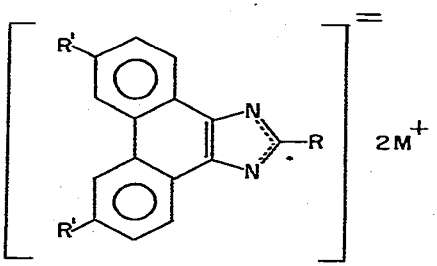
The reduction of dialkylmagnesium compounds with alkali metals proceeded at least partially according to equation 1 in all cases (M = Li, Na, K, Rb, and Cs) [25]. In the case of lithium, our principle interest here, a 3:1 complex, R_5MgLi_3, was also isolated. The observation that when R = sec - butyl or tert-butyl the 1:1 complexes (except Cs) were hydrocarbon soluble was interpreted in terms of a 1:1 alkyl-bridging dimer structure for the complex. Apparently this complexation solubilized and stabilized these alkali metal alkyls.

$$2M + 3R_2Mg \longrightarrow 2R_3MgM + Mg\downarrow \qquad (1)$$

An electron deficient oligomer of methyllithium in ether has been observed to generate an intense esr spectrum upon treatment with di-tert-butyl peroxide [26]. The spectrum exhibited hyperfine coupling of a methyl radical to three equivalent lithium atoms (equation 2).

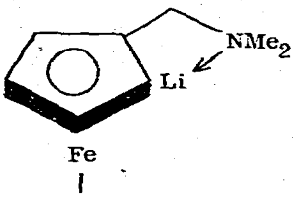


Fourteen radical dianions of general structure XI ($R{=}H$, Ph, C_6D_5, CMe_3 or mesityl; $R'{=}H$ or Me; $M{=}Li$, Na, K) have been studied by ESR at -60° to +30° in dimethoxyethane [27]. When R was aryl the radical electron was not located in the residue probably due to the steric hindrance to coplanarity caused by ion pair formation.



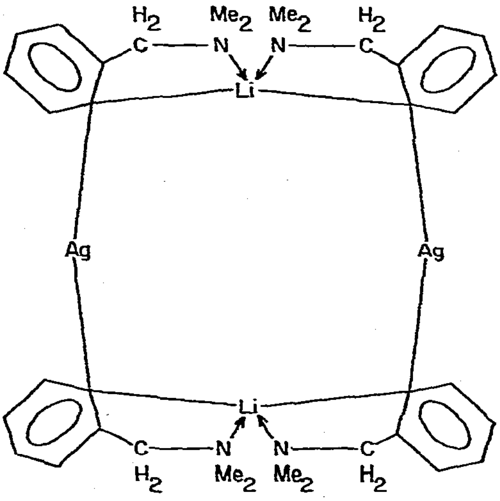
XI

Several solid organolithium species have been isolated and characterized. These include pentachlorophenyllithium, ferrocenyllithium, 1, 1'-dilithioferrocene • 2 TMEDA, ferrocenyllithium • TMEDA and 2-lithio dimethylaminomethylferrocene (XII) [28].



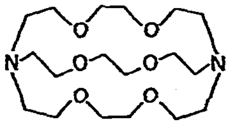
XII

Also, lithiation of dimethylbenzylamine with n-butyllithium followed by treatment with AgBr resulted in isolation of the compound XIII [29].



XIII

n-Butyllithium in hexane did not metalate Ph_3CH or Ph_2CH_2. But addition of a new cryptate (XIV) resulted in immediate formation of the expected carbanion. Condensation with $PhCH_2Cl$, however, gave relatively low yields compared to those when <u>tert</u>-AmONa was used [30].



XIV

II. Kinetics and Mechanisms

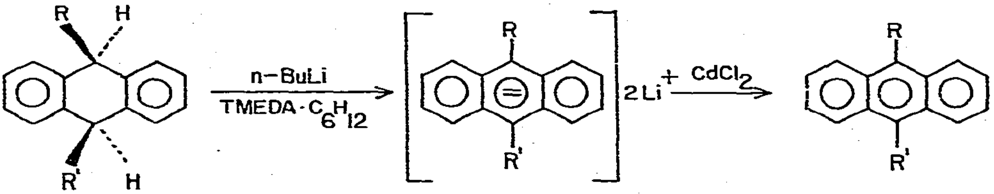
The influence of coordinating solvents on the addition reactions of alkyllithiums with alkenes, where reaction was enhanced, and trialkylaluminums, where reaction was retarded, has been debated [31]. Solvent would tend to coordinate with the remaining site on aluminum, thereby rendering the complex less reactive, while complexation of the alkyllithium specie would tend to increase the carbanionic character of the alkyl group, thereby rendering this reagent more reactive. Since the effective mechanisms of the two reagents are different, comparative analogies should not be drawn.

Ethylene-propylene and ethylene-pentene co-oligomerization catalyzed by a number of alkali metal systems have been observed [32]. Lithium and Group 2A metals provided unusual selectivity for the formation of linear heptenes and nonenes in comparison to other alkali metal systems. It was suggested in the case of the lithium systems that this preference for linearity was a consequence of the preference of the lithium cation to bond to the terminal position of an allylic-type anion.

α- and γ-carbon reactivity of neopentylallyllithium, the 1,4-addition product of tert-butyllithium and 1,3-butadiene, have been studied in THF [33]. Yields of trans olefin from protolysis by water, tert-butanol, 1-hexyne, cyclopentadiene, fluorene and triphenylmethane were essentially constant; yields of cis olefin relative to those from γ-protonation showed dependence on both the steric bulk and the strength of the acid. Addition reactions with ketones were also studied with a much greater preference for reaction at the γ-carbon being noted. Di-tert-butyl ketone, a very bulky ketone, produced adduct resulting from addition by the α-carbon only.

TMEDA can be reacted with ethylene using catalytic amounts of an alkyllithium reagent to give dimethylvinylamine and dimethylethylamine [34]. This same system using propylene afforded dimethylisopropylamine. Competitive reactions of alkyllithium reagents and the alkali amides formed by these reagents reacting with primary or secondary amines in the presence of TMEDA revealed that the diamine further enhanced the addition of such amines to ethylene. Temperatures were 50 - 100° lower and pressures were 1/5th to 1/10th those required when sodium catalysts were utilized. Dimethylamine could be added to propylene, but diethylamine could not. Diethylamine, however, did react with cycloolefins containing strained double bonds.

A new method of dehydrogenation as a convenient, general method of aromatization utilizing an alkyllithium-TMEDA complex has been described (equation 3) [35]. A significant feature of the method is the intermediacy of dianions such as XV, generated in this case from various 9,10-dihydroanthracene systems, and demonstrated by quantitative incorporation of two atoms of deuterium, one each at the 9- and 10-positions, when the dilithio intermediate XV was treated with D_2O. Subsequent oxidation with

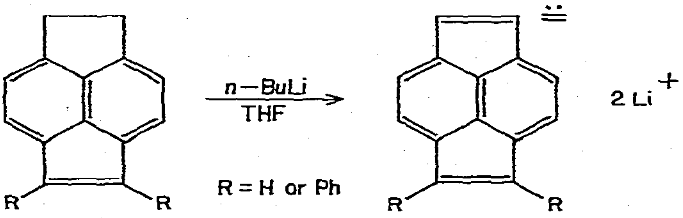


XV

(3)

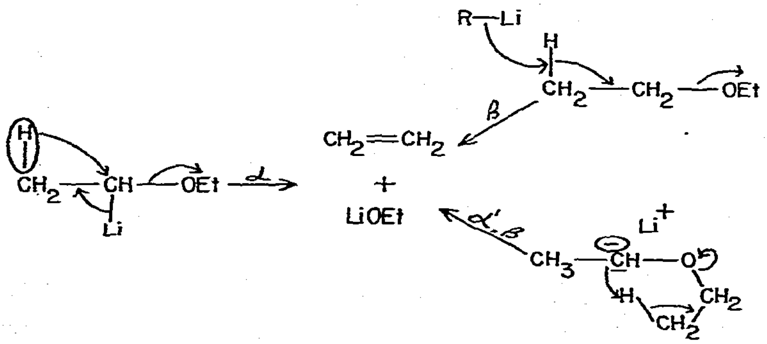
$CdCl_2$ then provided the aromatic hydrocarbon. Subjection of 9,10-dihydrophenanthrene to this same procedure produced phenanthrene, but the final oxidation with $CdCl_2$ was found unnecessary. Evidently a complex was formed that obscured the dianion character of the intermediate but which itself provided oxidation upon hydrolysis.

The pyracyclene dianion has been generated by dimetalation of dihydropyracyclene with butyllithium (equation 4) [36]. Evidence for a 14π electron structure for this dianion perturbed by an internal vinyl crosslink was gained from both deuteration and alkylation experiments. Both Hückel and SCF-PPP charge distribution calculations were in excellent agreement with the experimental observation that these dianions undergo exclusive reaction at the ethylene bridge carbons.



(4)

It has been determined that $(MeCD_2)_2O$ was cleaved by C_2D_5Li solely by a β-elimination mechanism whereas cleavage of $(CD_3CH_2)_2O$ with C_2D_5Li proceeded 4-5 times slower (isotope effects) and by a combination of mechanisms: 55-60% α', β - ca. 35%β- and 5-10% α-elimination (equation 5) [37].



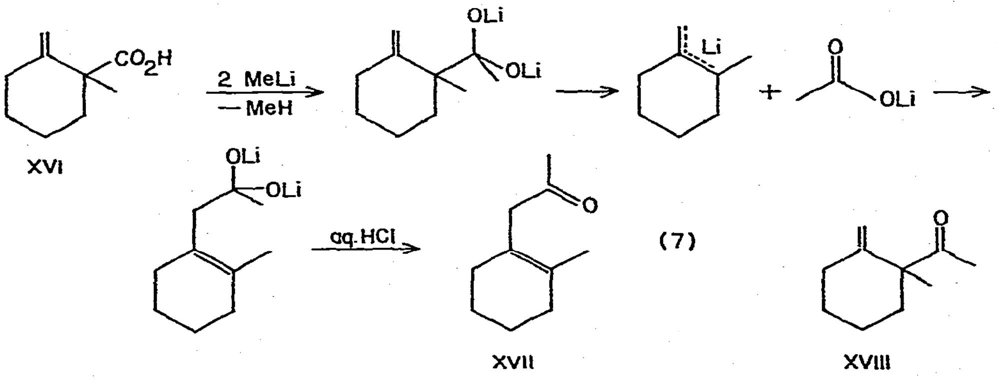
(5)

Nucleophilic ether fission has been investigated by Kobrich and Baumann (equation 6) [38]. Either of the bases 1,1-diphenylhexyllithium or benzhydryllithium functioned satisfactorily as the organolithium reagent. The relative rates of nucleophilic cleavage of C-O bonds by 1,1-diphenylhexyllithium were allyl-O- > vinyl-O- > alkyl-O- > phenyl-O-.

$$R'{-}O{-}R'' + Li{-}R \longrightarrow R'\text{-}OLi + R\text{-}R'' \qquad (6)$$

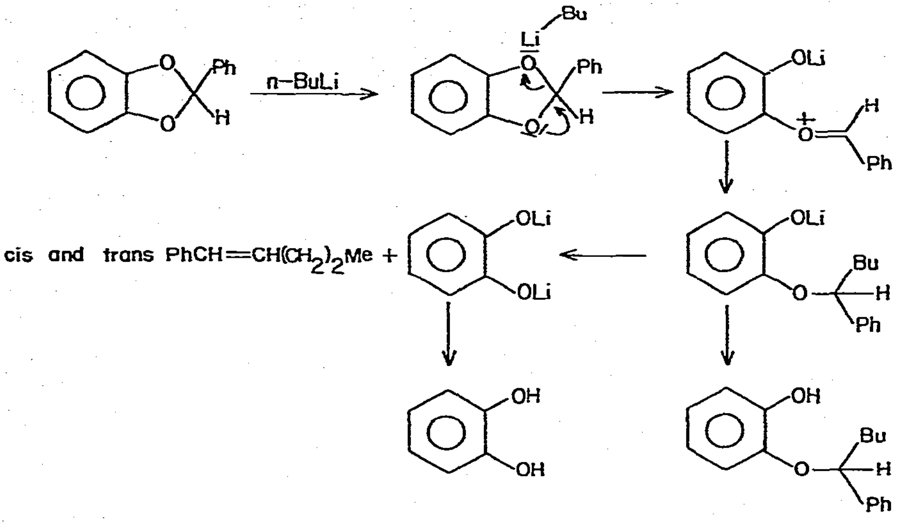
INDO calculations were found to support the previously proposed mechanism for the action of an alkyllithium reagent on tert-butyl phenyl sulfone, namely, that a 3-lithio-1,2-dehydrobenzene species intervened as an intermediate [39].

A novel fragmentation-recombination reaction of β,γ-unsaturated carboxylic acids has been observed by Dalton and Chan (equation 7) [40]. Addition of two equivalents of methyllithium to 2-methyl-2-carboxymethylene-cyclohexane (XVI) in ether afforded 2-methylcyclohexenylacetone (XVII) rather than the expected product, 2-methyl-2-acetylmethylenecyclohexane (XVIII). If the reaction were run in hexane, cyclohexane XVIII was obtained in good yield. It appears that caution should be exercized in the use of ether as a solvent for metalation of β,γ-unsaturated acids.



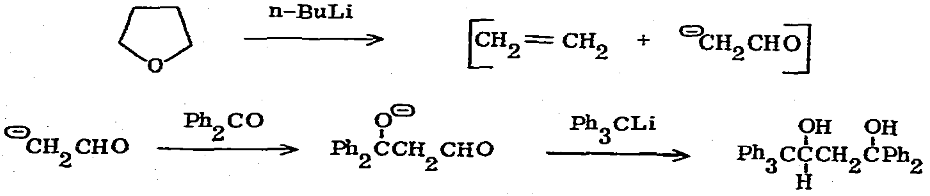
(7)

Fragmentation of cyclic ethers has been investigated. Treatment of 2-phenyl-1,3-benzodioxole with n-butyllithium did not yield benzyne but rather products from the base catalyzed opening of the acetal ring system (equation 8) [41].



(8)

Although ring opening and decomposition of THF in the presence of n-butyllithium has previously been described in the literature, no instance of the isolation of considerable quantities of decomposition products has been reported. In a current study the previously detected enolate ion of acetaldehyde was trapped by condensation with benzophenone and trityllithium to afford 1,1,4,4,4-pentaphenyl-1,3-butanediol (equation 9) [42]. Non-equivalence of the methylene protons in diol XIX was interpreted in terms of significant intramolecular hydrogen bonding.



$$\xrightarrow{n\text{-BuLi}} \left[CH_2{=}CH_2 + {}^{\ominus}CH_2CHO \right]$$

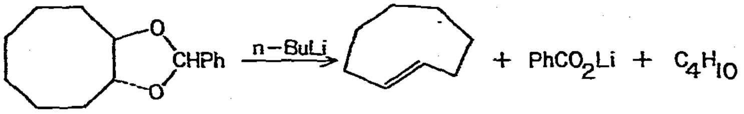
$${}^{\ominus}CH_2CHO \xrightarrow{Ph_2CO} Ph_2\overset{O^{\ominus}}{\overset{|}{C}}CH_2CHO \xrightarrow{Ph_3CLi} Ph_3\underset{H}{\overset{OH}{C}}CH_2\overset{OH}{C}Ph_2$$

XIX

(9

An interesting highly stereospecific synthesis of <u>trans</u>-cyclooctene from <u>cis</u>-cyclooctene has been described (equation

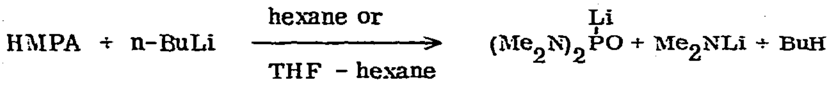
10) [43]. The method consists of formation of the 2-phenyl-1,3-dioxolan derivative (XX) of the diol followed by addition of two equivalents of n-butyllithium. Initial metalation of the dioxolan at the benzyl carbon followed by concerted cycloelimination (fragmentation) to olefin and benzoate ion is proposed to account for these results. Support for this mechanism has been gained by trapping the benzyl anion intermediate as the benzoyl derivative.



XX

(10)

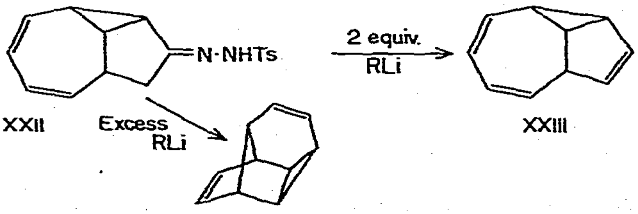
The stability of organolithium agents in HMPA or HMPA-THF has been questioned. Decomposition according to equation 11 was demonstrated by trapping lithio phosphite XXI as its chalcone adduct and as other derivatives [44].



$$\mathrm{HMPA} + n\text{-BuLi} \xrightarrow[\text{THF - hexane}\ 0\text{-}25^{\circ}]{\text{hexane or}} (\mathrm{Me_2N})_2\overset{\mathrm{Li}}{\mathrm{P}}\mathrm{O} + \mathrm{Me_2NLi} + \mathrm{BuH} \qquad (11)$$

XXI

Reaction of tricyclo[5.3.0.0^{2,10}]deca-3,5,-dien-9-one tosylhydrazone XXII with two equivalents of methyllithium afforded triene XXIII while an excess of this reagent gave diene XXIV [45].

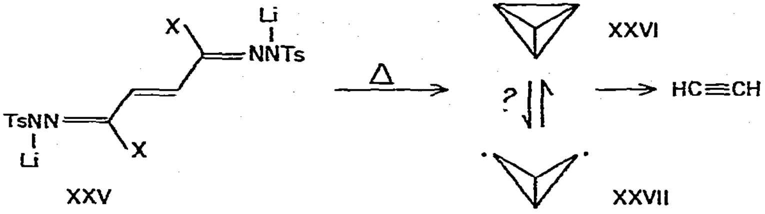


XXII

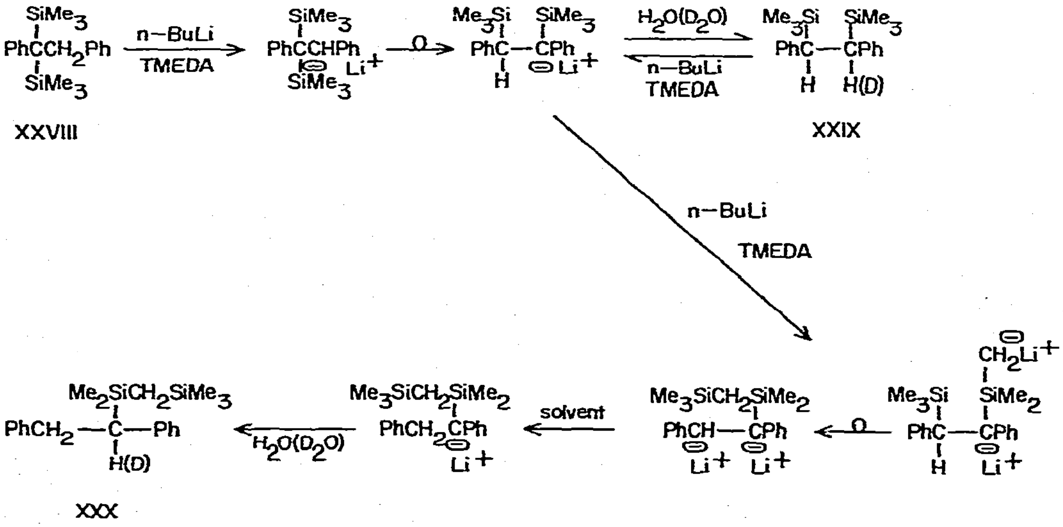
XXIII

XXIV

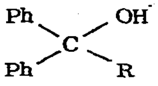
N,N'-Dilithio trans-butenedial bistosylhydrazone (XXV) prepared *via* metalation of the parent compound with n-butyllithium was pyrolyzed to give as the only volatile component, acetylene [46]. It was established by D labeling experiments (X = D) that 37-47% of the acetylene produced was the result of the intervention of either a tetrahedrane (XXVI) or 2,4-bicyclobutyl diradical (XXVII) intermediate



A new anionic carbon to carbon migration in bis(trimethylsilyl) system XXVIII has been discovered [47]. Not only was a 1,2-rearrangement detected to afford XXIX, but also the product of a 1,4-rearrangement, XXX.

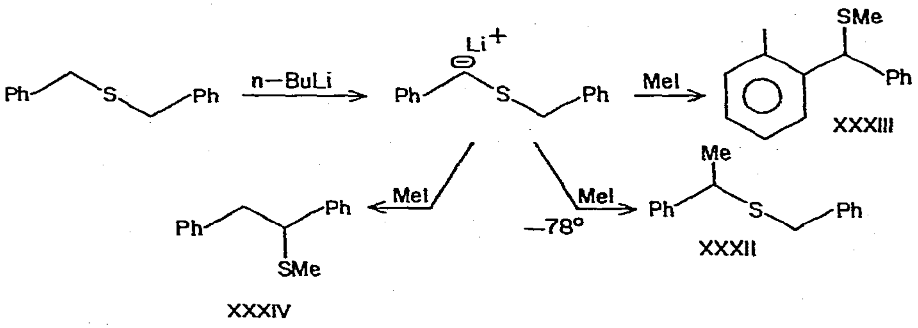


Examination of the Wittig rearrangement and the ketylalkyl iodide reaction has provided new evidence for a partial intermolecular radical pathway for the Wittig rearrangement [48]. Benzhydryl 5-hexenyl ether upon treatment with n-butyllithium afforded 85% Wittig product XXXIa(R = 5-hexenyl) and 15% XXXIb (R = cyclopentylmethyl). The latter product indicated the intermediacy of 5-hexenyl radicals. It was suggested that both the intra- and intermolecular pathway for the Wittig rearrangement proceed by radical pairs with the former occurring <u>via</u> primary recombination of geminate radicals.

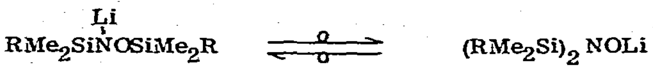


XXXI

Dibenzylthioether in THF/TMEDA can be metalated at an α-position with n-butyllithium to form a relatively stable α-anion which can be alkylated with methyl iodide to give XXXII [49]. At a somewhat increased temperature Sommelet-Hauser product XXXIII was principally observed. At higher temperatures some Stevens rearrangement product XXXIV was also isolated. The role of solvent and its relationship to ion pairing (contact, solvent separated) was discussed.



The first example of an anionic oxygen to nitrogen migration has been demonstrated by West and Bondjouk [50]. One equivalent of an alkyllithium reagent was used to generate the N-lithio derivative of N,O-bis(trimethylsilyl)hydroxylamine (XXXV) which was found to rearrange rapidly to form an equilibrium mixture containing predominantly the rearranged ion XXXVI.



$$\mathrm{RMe_2Si\overset{Li}{N}OSiMe_2R} \xrightleftharpoons[o]{o} \mathrm{(RMe_2Si)_2NOLi}$$

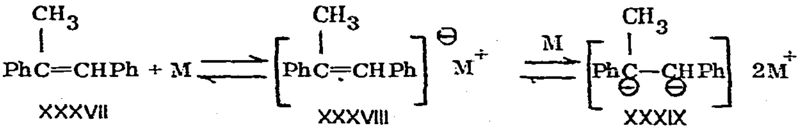
XXXV XXXVI

R = Me, Et, Ph, t-Bu

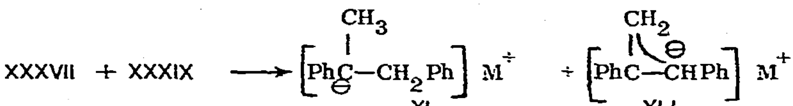
Graphite was vaporized with an electric arc and reacted with atomic lithium [51]. After isolation under argon, hydrolysis and mass spectral analysis, the following 'yields' were recorded: CH_4 (0-10%), C_2H_2 (10-30%), C_2H_4 (∿15%), C_3H_4 (40-65%). The presence of the principle lithium product (or intermediate) was demonstrated by derivatization with Me_3SiCl; a quantity of $C_3(SiMe_3)_4$ was isolated.

Polymetalation of 2-methylpropene, 1-butene and cis/trans-2-butene was accomplished by a system consisting of a combination of n-butyllithium and potassium tert-amyloxide [52]. Extent of metalation was determined by quenching the metalated specie with D_2O and analysis by a gas chromatograph-mass spectrometer combination with the rate of metalation being measured by monitoring the rate of butane evolution. Approximately 20% of cis-2-butene was obtained from the one hour (25°) reaction of 1-butene/n-butyllithium/potassium tert-amyloxide after hydrolysis. A cis/trans-2-butene mixture found 7% being isomerized to 1-butene and the remaining 2-butene enriched in the cis-isomer. That n-butylpotassium was the active metalating agent was confirmed by 1) the similarity to organosodium and organopotassium isomerization of olefins 2) the dependency on the lithium/potassium ratio 3) by rapid reaction with monochlorostyrene at room temperature and 4) the relative ease of decomposition of the organometallic compound at 70°.

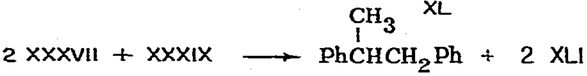
Proton transfer accompanying reductive metalation by alkali metals of trans-1,2-diphenylpropane (equation 12) has been studied as a function of alkali metal (Li,Na,K) and solvent (ether, THF) [53]. The extent of transfer (equations 13 and 14) was assessed by determination of alkali metal consumed, by protonation of the reaction mixture followed by product analysis as well as deuteration of the reaction mixture and spectroscopic determination of deuterium content. For the systems Li/ether, Li/THF and Na/ether the product was the dianion XXXIX, i.e., no proton transfer occurred. Substantial amounts of the substituted allylic anion XLI were formed during Na/THF and K/THF reduction, the latter system undergoing further reduction by dimerization to the tetra-anion of 1,2,5,6-tetraphenylhexane.


XXXVII XXXVIII XXXIX (12)

$$\mathrm{Ph\overset{CH_3}{\overset{|}{C}}{=}CHPh} + M \rightleftharpoons \left[\mathrm{Ph\overset{CH_3}{\overset{|}{C}}{=}CHPh}\right]^{\ominus} M^{+} \xrightleftharpoons{M} \left[\mathrm{Ph\underset{\ominus}{\overset{CH_3}{\overset{|}{C}}}{-}\underset{\ominus}{C}HPh}\right] 2M^{+} \qquad (12)$$


XL XLI (13)

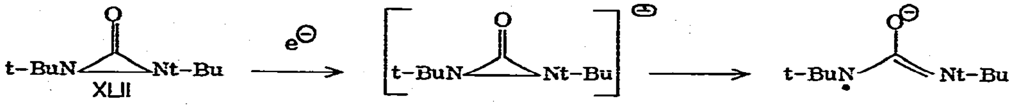
$$\text{XXXVII} + \text{XXXIX} \longrightarrow \left[\mathrm{Ph\underset{\ominus}{\overset{CH_3}{\overset{|}{C}}}{-}CH_2Ph}\right] M^{+} + \left[\mathrm{Ph\overset{CH_2}{\overset{\|}{C}}{-}\overset{\ominus}{C}HPh}\right] M^{+} \qquad (13)$$


(14)

$$2\ \text{XXXVII} + \text{XXXIX} \longrightarrow \mathrm{Ph\overset{CH_3}{\overset{|}{C}}HCH_2Ph} + 2\ \text{XLI} \qquad (14)$$

Study of anthracene anion-radicals of the alkali metals (Li^+, Na^+, K^+) has revealed that the contact ion pairs are more reactive in the reaction with fluorene than are these same ion pairs when separated by a solvent [54]. It was concluded that dissociation of the ion pairs is less important than the effect of desolvation of the cation on the energetics of the reaction.

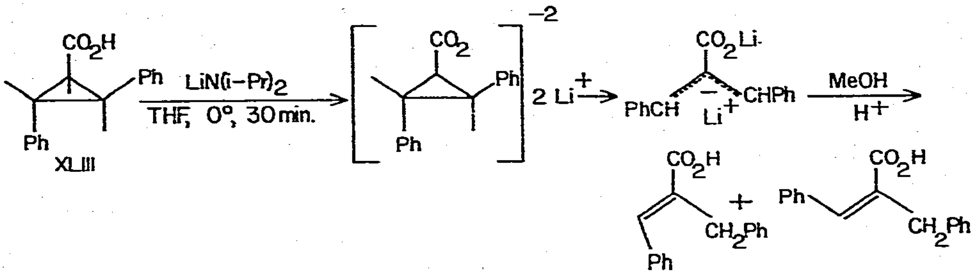
Mechanisms of the reduction of di-tert-butyldiaziridinone (XLII) have centered on an electron transfer process as depicted in equation 15 [55]. Reduction brought about electrochemically as well as that by tert-butyllithium and sodium naphthalenide each gave as product di-tert-butylurea. Cyclic voltammetry indicated that, if the radical anion of XLII were an intermediate, its half-life must be less than 2 msec.



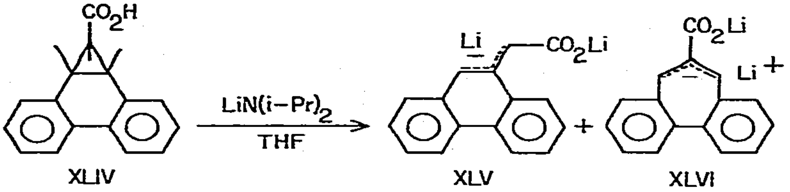
(1

Radical anions of biphenyl and anthracene and potentially of other aromatics can be conveniently prepared by one-electron reductions of the parent hydrocarbon using methyl-, n-butyl- or tert-butyllithium or benzylmagnesium chloride in HMPA solution [56]. It was thought that the high dielectric constant of HMPA facilitated electron transfer in these systems.

cis,trans-2,3-Diphenylcyclopropane-1-carboxylic acid (XLIII) underwent electrocyclic ring opening when treated with lithium diisopropylamide in THF (equation 16) [57]. Hydrolysis and esterification (CH_2N_2) produced cis- and trans-α-benzylcinnamic acids isolated as their methyl esters. From the corresponding trans, trans-2,3-diphenylcyclopropane-1 carboxylic acid the same procedure afforded methyl (E)- and (Z)-3,4-diphenyl-3-butenoates. Similar treatment of 2,3:4,5-dibenzo-2,4-norcaradiene-anti-7-carboxylic acid (XLIV) produced methyl 9-phenanthryl acetate and methyl 3,4:5,6-dibenzocyclohepta-1,3,5-triene-1-carboxylate, arising presumably from the dilithio intermediates XLV and XLVI, respectively. All ring openings should proceed by a conrotatory path according to theory, except for the conversion of norcaradiene anti carboxylic acid XLIV to the dibenzocycloheptatrienecarboxylic acid via dilithio intermediate XLVI which must proceed by a disrotatory path. It was suggested from preliminary kinetic experiments that the rate-limiting step for the ring opening of cis-trans isomer XLIII was metalation of the α-carbon to form the unopened dilithio intermediate while that for the other ring openin may be the actual ring opening step.

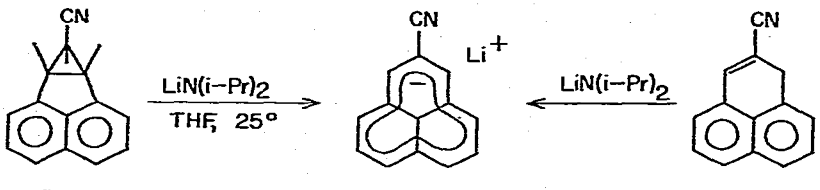


(16)



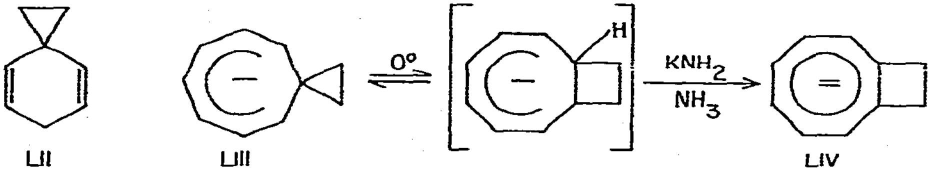
The name dilithium "carboxylate enolate" was proposed for dilithio derivatives of aliphatic carboxylic acids which are formed by loss of protons from oxygen and an α-carbon.

That the conrotatory mode of ring opening was **favored** for cyclopropyl anions has been demonstrated by the following experiments [58]. *cis-trans*-(L) and *trans*, *trans*-2,3-Diphenylcyclopropane-1-carbonitrile (LI) and acenaphthylene XLVII were demonstrated to form α-anions (La and LIa) upon treatment with lithium *tert*-butylamide or lithium diisopropylamide (deuteration with D_2O). The kinetics of the ring openings of these compounds could be followed by the intensities of their respective visible spectra at various concentrations or by glpc. A spectrum of the product formed by treatment of a solution of XLVII in THF with LiN(i-Pr)$_2$ (λ_{max}644nm, log ε 3.89) could also be generated by the identical treatment of 2-cyanophenalene (XLIX), thereby establishing the structure of anion XLVIII. From this it was determined that the ratio of rate constants for the conversion of the cyclopropyl anions La and LIa to the corresponding allyl anion was k_L/k_{LI} = 42 at −25°. Similarly after a number of parameter adjustments $k_L/k_{LI} = 1.4 \cdot 10^4$ at 36°. Thus it was concluded that disrotatory ring opening, the only mode possible for acenaphthylene XLVII, was retarded significantly relative to the ring openings of anions La and LIa, which could have proceeded by a conrotatory path as predicted by theory.



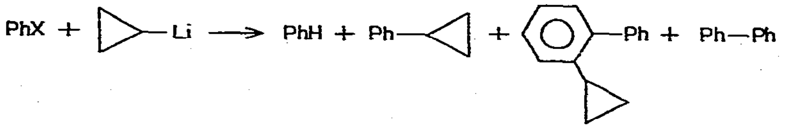
XLVII XLVIII XLIX

Compounds in which cyclopropyl rings are fused to cyclic π-systems containing 4n + 2 electrons should exhibit donation to the cyclopropyl ring while those with 4n π-electrons should exhibit withdrawal [59]. Spiro[2.5]octadiene (LII) when treated with n-butyllithium afforded immediate ring opening to the β-phenethyl anion. In contrast spiro[2.7]decatrienyl anion (LIII) underwent a slow 1,2-migration as demonstrated by further ionization to the dianion LIV followed by hydrogenation to <u>cis</u> bicyclo[6.2.0]decane. Migration was evidently precluded in the spiro[2.5]system since a stable 4n + 2 π-electron array was obtained in the initial bond breaking step.



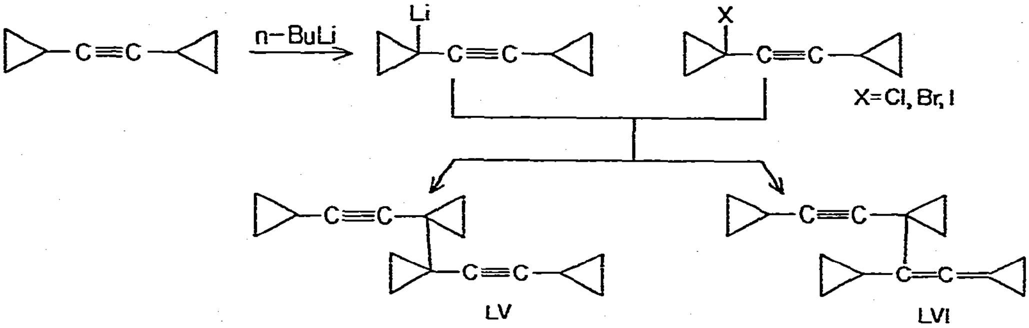
LII LIII LIV

Halobenzenes treated with cyclopropyllithium gave cyclopropylbenzenes and biphenyls after refluxing in ether (equation 17) [60]. Cyclopropylhalobenzenes behaved similarly. Dehalogenation was thought to arise for the bromobenzenes by halogen-metal exchange whereas dehalogenation in the fluoroand chlorobenzenes could occur via benzyne formation followed by hydride transfer. Introduction of the cyclopropyl group as well as biaryl formation may proceed by direct nucleophilic substitution or by a benzyne mechanism. Increased cyclopropyl substitution decreased the rate of benzyne formation but increased the rate of direct substitution.

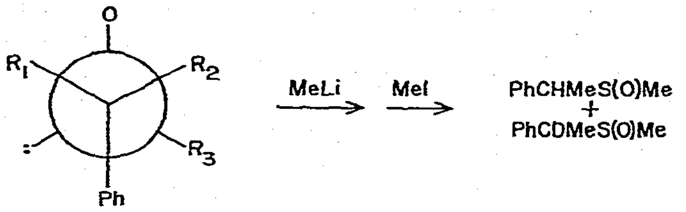


(17)

Cyclopropyl(1-lithiocyclopropyl)acetylene was coupled with cyclopropyl(1-halocyclopropyl)acetylenes to yield the two isomeric compounds LV and LVI [61]. (Cyclopropylethynyl)cyclopropyl radical intermediates were postulated to account for this mixture of products.

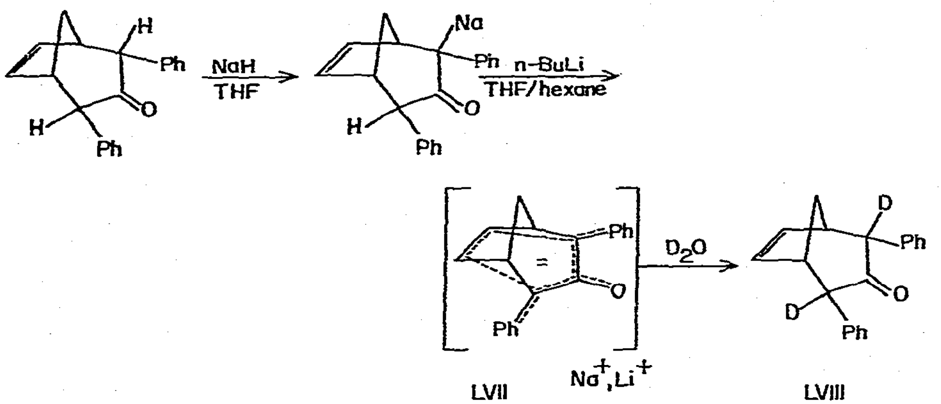


The isotope effect (k_H/k_D) and the selectivity factor (k_{H_R}/k_{H_S}) have been measured for exchange of diastereotopic protons in benzyl methyl- and benzyl tert-butyl sulfoxide (equation 18) [62]. Varying percent mixtures of the (S,S) - and (R,S) - isomers of phenylmethylsulfoxide were subjected to methyllithium treatment for one min. at −60° to produce the two α-methyl derivatives. Suitable calculations from these data gave an isotope effect of 2.5 ± 0.4 and a selectivity factor of 1.7 ± 0.3 for this system. Similarly a selectivity factor of 117 ± 20 was calculated for the tert-butyl system.



(18)

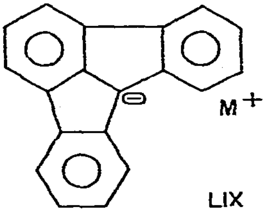
2,4-Diphenylbicyclo[3.2.1]oct-6-en-3-one was converted by sodium hydride to its monoanion and by n-butyllithium to its dianion LVII (equation 19) [63]. Evidence for formation of the dianion was gained by quenching with D_2O to form the dideuterated ketone LVIII. Extensive delocalization in dianion LVII was inferred from a 1.05 ppm upfield shift of the vinylic protons in its nmr spectrum and a 0.43 ppm downfield shift of the bridgehead protons.



(19)

Competitive metalation of indene with tert-butyllithium and isopropyllithium has revealed that the reactions are first order in alkyllithium species [64]. A relationship between the mixed aggregate composition of the alkyllithium species and relative reactivity was established. tert-Butyllithium in mixed aggregate with isopropyllithium was found to be an order of magnitude more reactive than tert-butyllithium tetramer itself. The relative reactivities were determined by adding a limiting amount of indene to a mixture of the two alkyllithiums, quenching the reaction after the desired period with D_2O and measuring the deuterium incorporation of each alkane by quantitative ir analysis.

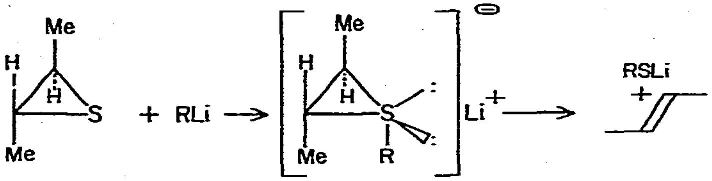
The relatively weakly nucleophilic fluoradenyl carbanions LIX (M = Li, Na, K, Cs) were used to cleave the epoxide linkage in ethylene oxide [65]. Rates were followed by uv-visible spectroscopy. The pseudo-first-order rate constants showed a dramatic increase of about 10^{-5} in going from the Cs to the Li salt. These results were interpreted to mean that ion pairs were the kinetically active species and that the free ion itself was relatively unimportant.



LIX

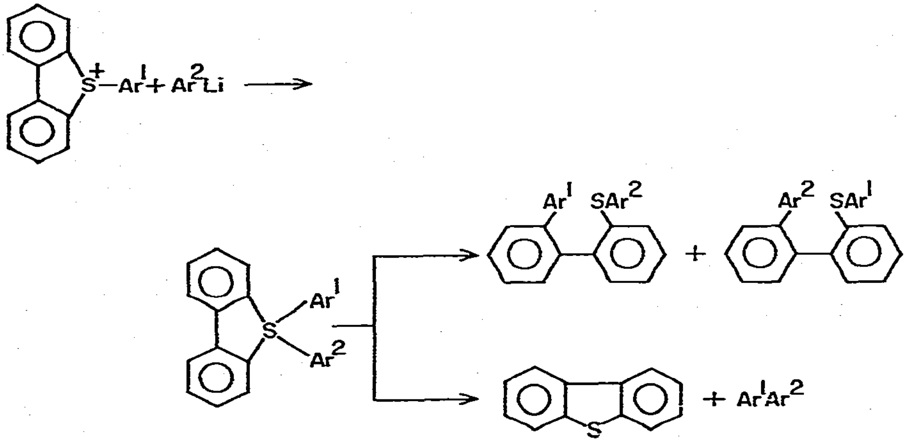
A study of the primary isotope effects for lithium cyclohexylamide-catalyzed exchange in toluene and triphenylmethane has been reported [66]. For both hydrocarbons k_H/k_D was determined to be approximately 11. In addition, kinetic acidities of mono-, di-, and triarylmethanes toward lithium cyclohexylamide have been determined [67].

Generation and utility of sulfuranes has been investigated. Desulfurization of episulfides of cis and trans-2-butene with n-butyllithium has been found to stereospecifically provide the corresponding olefin (equation 20) [68]. Intermediacy of 2-lithio-3-alkylthiobutanes in the reaction was excluded by the observation that independent generation of these intermediates led to olefin products with considerable loss of stereochemistry. Incidental to this study was the conclusion that metal-halogen exchange occurred with greater than 95% stereospecificity.



(20)

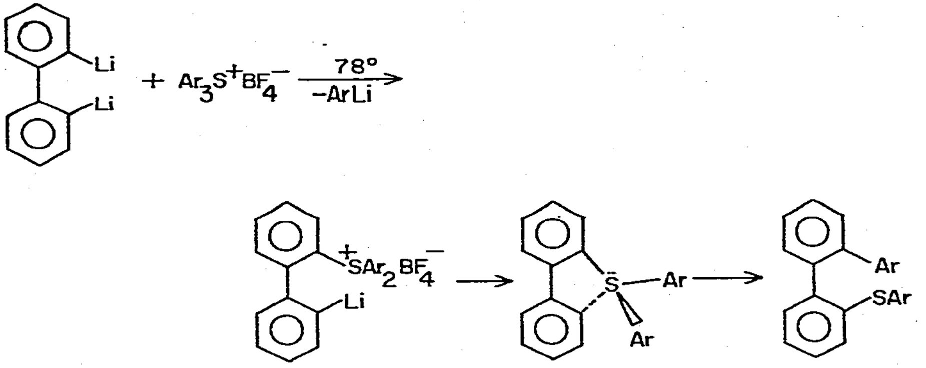
The effect of substituents on the coupling reactions of S-aryldibenzothiophenium fluoroborates with aryllithiums has been studied [69]. Electron-withdrawing groups favored formation of biaryls and dibenzothiophene (equation 22) whereas donating substituents favored formation of 2-arylthio-o-terphenyls (equation 21). Interpretation of this behavior in terms of a sulfurane intermediate was proposed.



(21)

(22)

As part of an investigation into the nature of the transition state for the reaction of sulfur ylides with aromatic carbonium ions, the possibility of a σ-sulfurane intermediate was investigated [70]. Such an intermediate was successfully generated from 2,2-dilithio-biphenyl and a triarylsulfonium salt according to equation 23.

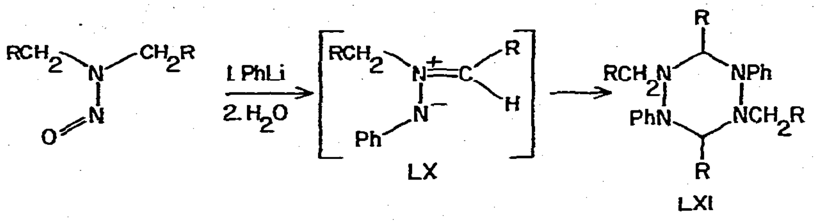


(23)

The reaction of dialkylnitrosamines with organolithium reagents (and Grignards) have been found to provide trisubstituted hydrazines when R' is aryl or the aldehyde hydrazones with R' is alkyl [71]. Formation of the latter product was evidently rapid under all conditions when R' contained an α-hydrogen such that the elements of LiOH could be lost. The addition intermediate shown in equation 24 was thought to be involved.

$$R_2N{-}N{=}O \;+\; R'Li \;(\text{or } R'MgBr) \longrightarrow R_2N\overset{OLi}{N}R' \qquad (24)$$

Reaction of secondary nitrosamines with phenyl or tert-butyllithium afforded N'-alkylated lithium salts which underwent elimination to give azomethine imines LX when treated with H_2O or EtOH [72]. For N-methyl-N-tert-butylnitrosamine, treatment with tert-butyllithium followed by ethanol work-up provided a stable intermediate, 1,2-di-tert-butyl-1-(ethoxymethyl)-hydrazine. On standing the azomethine imines dimerized head to tail to form sym-hexahydrotetrazines LXI or could be trapped with either N-phenylmaleimide or dimethylacetylenedicarboxylate.

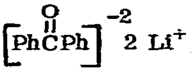


LX

LXI

R=H, Me

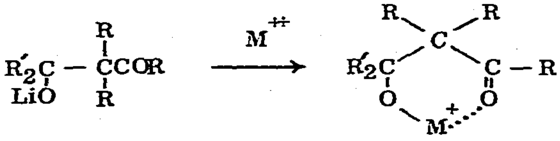
Produced in significant amounts by the reaction of phenyllithium and carbon monoxide were benzophenone, α,α-diphenylacetophenone, α-hydroxyacetophenone, 1,3,3-triphenylpropane-1,2-dione and 1,3,3-triphenylpropan-1-one-2,3-diol [73]. Dilithium benzophenone dianion (LXII) has been determined by spectroscopic studies as the first long-lived intermediate formed in this reaction with the indication that benzoyllithium was a likely precursor of LXII.



$$\left[\mathrm{Ph}\overset{\overset{\displaystyle O}{\|}}{C}\mathrm{Ph}\right]^{-2} 2\,\mathrm{Li}^{+}$$

LXII

Lithium enolates, formed by aldol condensations effected by either methyllithium or $\mathrm{LiN(i\text{-}Pr)_2}$, were found to be stabilized by the process of internal chelation (equation 25) [74]. This process was of synthetic value since higher yields and more convenient experimental conditions were realized.



(25)

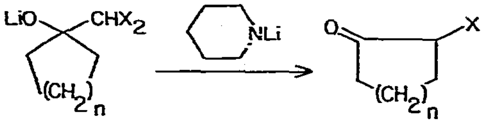
M = Mg , Zn

III. Lithium Carbenoids and other Halogen-substituted Organolithiums.

The chemistry of dichloromethyllithium has been reviewed [75].

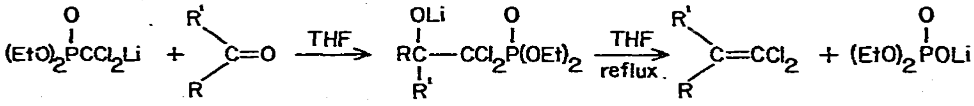
Dibromomethyllithiums ($RCBr_2Li$, where R = H, Bu, Me_3Si and Br) have been prepared by metalation of the corresponding α,α-dibromo compounds with lithium diisopropylamide in THF at low temperature [76]. Alkylations of these intermediates were described as well as new preparations of α-bromoepoxides and α-bromoketones.

A regiospecific synthesis of α-haloketones <u>via</u> rearrangement of carbenoid α-alcoholates has been developed [77]. Notably, lithium cycloalkoxides (X = Cl, n = 2,3,4,5; also X = Br, n = 2) were reacted with lithium piperidide to afford the ring enlargement products (equation 26).



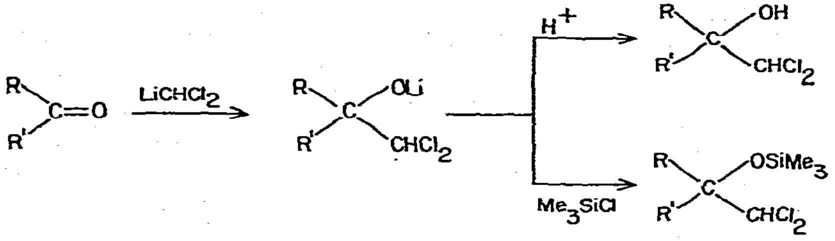
(26)

The preparation and properties of two new halomethyllithium intermediates, namely, $LiCCl_2\overset{O}{P}(OEt)_2$ and $[(EtO)_2\overset{O}{P}]_2CClLi$ have been reported by Seyferth and Marmon [78]. Hydrolysis and alkylation reactions with dimethyl- and diethylsulfate, allyl bromide and trimethylsilyl chloride were described. 1,1-Dichloroolefins were prepared from the dichloro intermediate (equation 27).



$$(EtO)_2\overset{O}{P}CCl_2Li + \begin{matrix}R'\\R\end{matrix}\!\!>C=O \xrightarrow{THF} R\underset{R'}{\overset{OLi}{C}}-CCl_2\overset{O}{P}(OEt)_2 \xrightarrow[reflux]{THF} \begin{matrix}R'\\R\end{matrix}\!\!>C=CCl_2 + (EtO)_2\overset{O}{P}OLi \qquad (27)$$

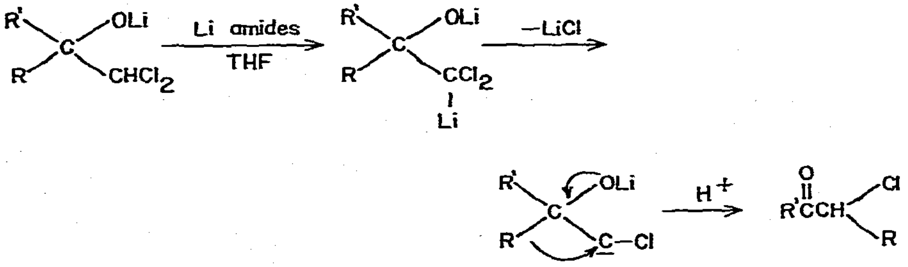
Lithium alkoxides, formed from carbonyl compounds and dichloromethyllithium, yielded alcohols upon protolysis and silylethers upon treatment with trimethylsilyl chloride (equation 28) [79]. These lithium alkoxides could be rearranged at ∿80° into α-chloroxiranes or α-chloroaldehydes.



(28)

The preparations of Me_3SnCHI_2 by use of either CHI_2MgCl or CHI_2Li, of Me_3SiCl_2Me by use of Me_3SiCI_2Li, of $(Me_3Si)_2CI_2$ by use of Me_3SiCI_2Li, of $(Me_3Sn)_2CI_2$ by use of Me_3SnCI_2MgCl and of $CH_2{=}CHCH_2CHI_2$ by use of CHI_2Li have been accomplished [80]. All of these new lithium or magnesium reagents are stable in THF below about -80°.

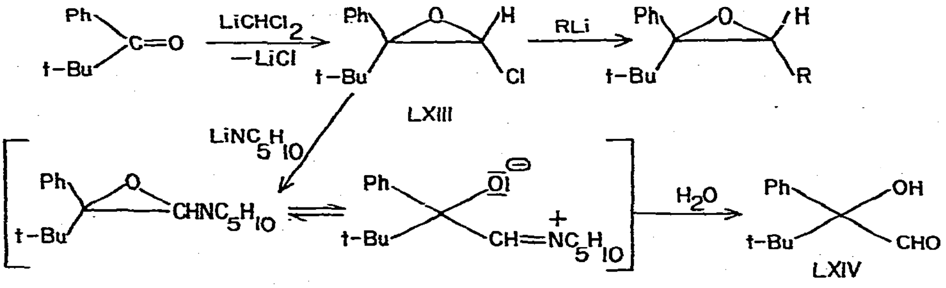
Lithium amide bases promoted α-dehydrochlorination of 1,1-disubstituted 2,2-dichloroethanols which resulted in a new rearrangement of alkyl and aryl groups to give the lithium enolates of α-chloroketones (equation 29) [81].



(29)

2-tert-Butyl-3-chloro-2-phenyloxirane (LXIII) was transformed by organolithium compounds into substituted oxiranes (equation 30) [82]. Lithium piperidide on the other hand converted LXIII into the α-hydroxyaldehyde

LXIV, presumably by the mechanism shown. Speculation as to the mechanism of substituted oxirane formation (equation 30) led to consideration of two alternatives 1) electron transfer and 2) S_N2 with no choice possible from the presented data.

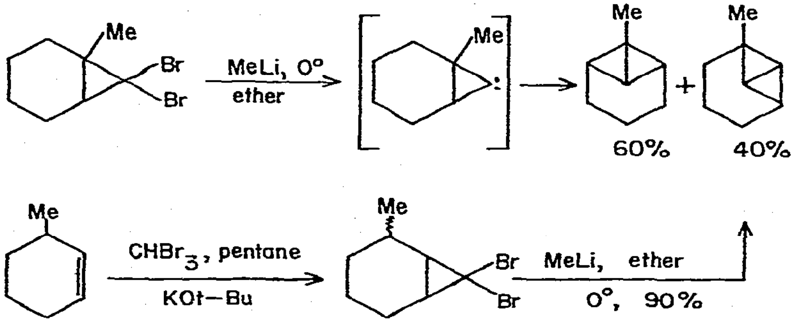


LXIII

LXIV

(30)

Several investigations of cyclopropylidene intermediates were reported. gem-Dibromocyclopropanes, when treated with methyllithium, have been found to produce several bicyclobutane derivates, apparently via cyclopropylidene intermediates (equations 31 and 32) [83].



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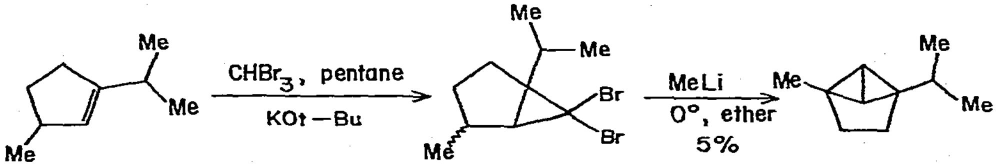
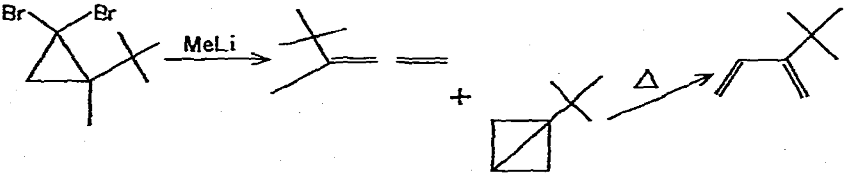


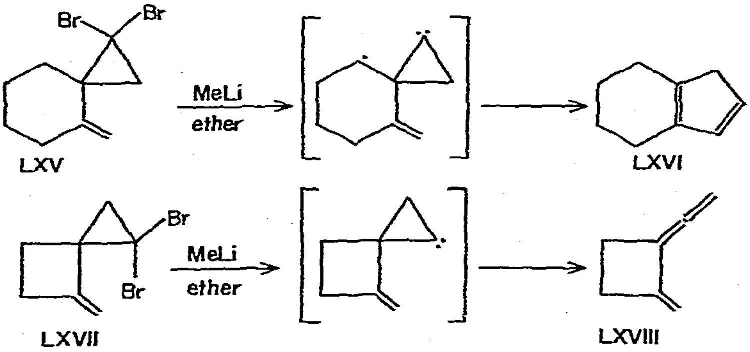
(32)

Previous examination of the effect of strong base on geminate-dibromocyclopropanes had elucidated that allenes were the sole products in the examples of simple alkyl-substituted compounds, but that for 1,1-dibromo-2,2,3,3-tetrasubstituted cyclopropanes, bicyclo[1.1.0]butanes were the products. Jones et al [84] reported the simultaneous production of both types of products, in a ratio of 3/2, formed upon treatment of 1,1-dibromo-2-tert-butyl-2-methyl-cyclopropane with methyllithium (equation 33).

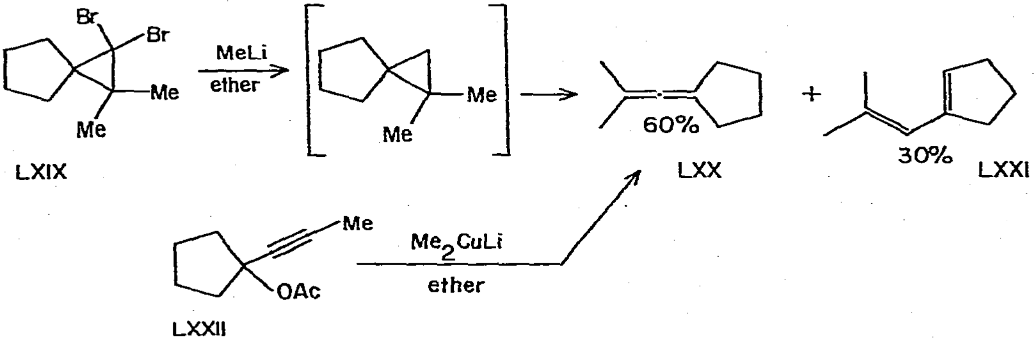


(33)

In the same vein, treatment of 1,1-dibromo-4-methylenespiro [2.5]octane (LXV) or 7,7,-dichloro-1-vinylbicyclo[4.1.0]heptane with methyllithium afforded diene LXVI with no ene-allene being produced [85]. In contrast, 1,1-dibromo-4-methylenespiro [2.3]hexane (LXVII) generated only the ene-allene LXVIII. A conformational analysis of the difference in behavior was offered which examined both the strain inherent in ring size and the geometry of the double bond in relation to the gem-dibromocyclopropane moiety.

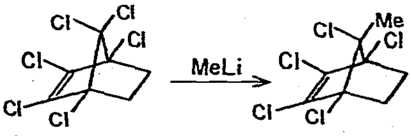


A tetraalkyl-substituted gem-dibromocyclopropane (LXIX) upon treatment with methyllithium was discovered to afford primarily an allene product LXX along with a bicyclic product, LXXI, derived from insertion of the cyclopropylidene intermediate into a C-H bond at C-2 followed by rearrangement [86]. The structure of the allene product was established by an independent synthesis from alkyne LXXII and lithium dimethylcuprate(I).

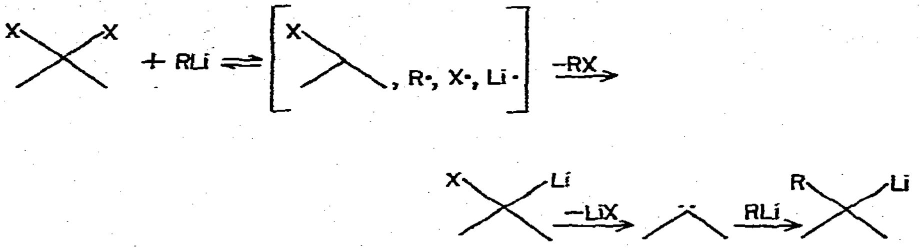


The reaction of phenyllithium with cinnamyl chloride has produced a variety of products which, aside from those stemming from displacement reactions, could be attributed to the intermediacy of an allylic carbene [87]. These include (with percentage yields): cis-1,2-diphenylcyclopropane (0.8), trans-1,2-diphenylcyclopropane (12.8), 1,6-diphenyl-1,3,5-hexatriene (5.6) and benzylacetylene (35.7).

The reaction of 1,2,3,4,7,7-hexachloronorborn-2-ene with methyllithium has resulted in the replacement of a bridge chlorine atom by a methyl group (equation 34) [88]. Similar results have been established for halogenated norbornanes and norbornadienes. Diene and tricyclic products were obtained from slightly modified systems. These results have been in-

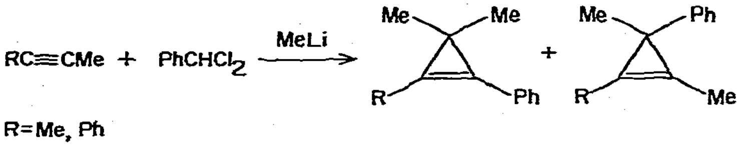


(34)

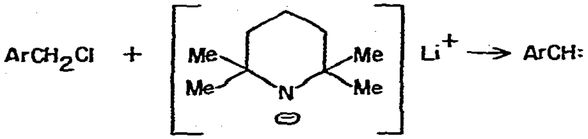

(35)

terpreted in terms of radical pairs as intermediates (equation 35)

Tetrasubstituted cyclopropenes may be conveniently prepared by the reaction of a dichloromethane derivative with methyllithium whereby the base served not only to remove a proton from the dichloromethane moiety but also as an alkylating agent (equation 36) [89].


(36)

A new steric base, lithium 2,2,6,6-tetramethylpiperidide (LiTMP) has been used to effect a safe, economical synthesis of aryl carbenes or carbenoids (equation 37) [90]. Yields of cyclopropanes gained from use of this reagent with a variety of alkenes were 50-87%. The reactions were stereospecific as far as the alkenes were concerned and were also characterized by the usual high syn/anti ratios common to carbenoid reactions.

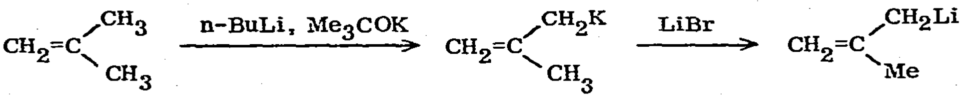

(37)

IV. Metalations (Hydrogen-lithium Exchange Reactions)

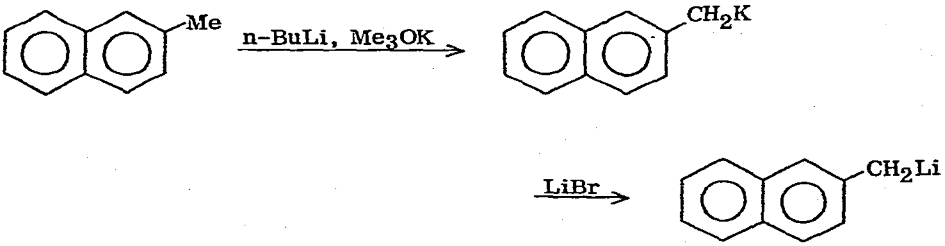
A. At sp^3 Carbon

A series of papers have appeared dealing with the preparation of allyllithium species. The difficult-to-prepare benzyl and allyl lithium reagents were conveniently generated (equations 38-40) by metalation of the appropriate hydrocarbon with n-butyllithium/Me_3COK [91]. The alkyl/aryl potassium salt precipitated allowing its isolation and conversion to the lithium salt by treatment with LiBr.

$$PhCH_3 \xrightarrow{\text{n-BuLi, } Me_3C\text{-OK}} PhCH_2K \xrightarrow{\text{LiBr}} PhCH_2Li \qquad (38)$$

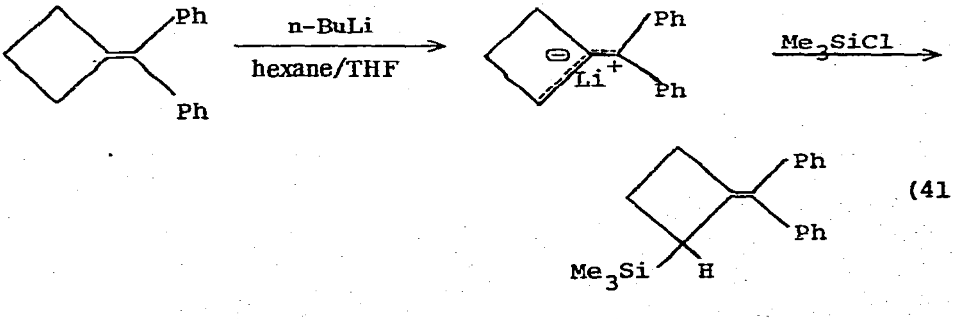


$$CH_2{=}C(CH_3)CH_3 \xrightarrow{\text{n-BuLi, } Me_3COK} CH_2{=}C(CH_2K)CH_3 \xrightarrow{\text{LiBr}} CH_2{=}C(CH_2Li)Me \qquad (39)$$



(40)

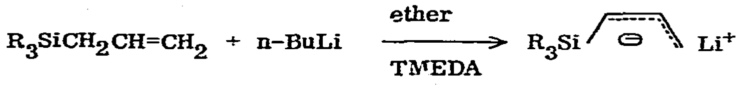
Likewise, lithiation of diphenylmethylenecyclobutane has been found to take place exclusively on the α-carbon of the cyclobutane ring (equation 41) [92].



(41)

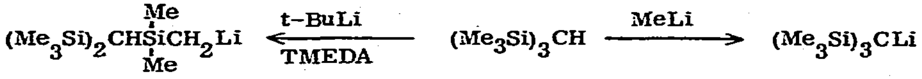
Allyllithium and methallyllithium have been prepared by the expedient method of metalating propene and isobutylene, respectively, with n-butyllithium • TMEDA complex [93]. 1-Alkylindenes, where the alkyl substituent was Me,Et,Pr,Me_2CH, Bu,Me_3C and n-hexyl have been prepared by addition of indenyllithiu in hexane/ether to the appropriate alkylating agent [94].

Alkyl carbons adjacent to silicon can undergo metalation. Treatment of trisubstituted allylsilanes with n-butyllithium has yielded the resonance stabilized anion LXXIII [95]. Mixtures of products formed from the anion LXXIII include those from both α and γ metalation.



LXXIII

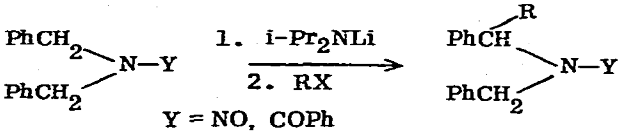
Lithiation of $(Me_3Si)_3CH$ with methyllithium provided the expected tertiary carbon metalation intermediate LXXIV, whereas metalation with tert-butyllithium occurred only at a primary carbon to give LXXV [96].



$$(Me_3Si)_2CH\overset{Me}{\underset{Me}{Si}}CH_2Li \xleftarrow[TMEDA]{t\text{-}BuLi} (Me_3Si)_3CH \xrightarrow{MeLi} (Me_3Si)_3CLi$$

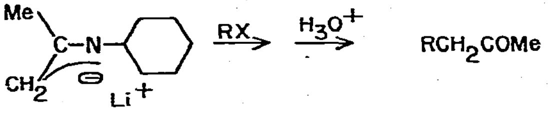
LXXV LXXIV

Metalation of alkyl groups adjacent to or in conjugation with nitrogen has been reported. Direct alkylation of benzylic amines has been carried out via metalation of either the N-nitrosyl or N- benzoyl derivative (equation 42) [97].



(42)

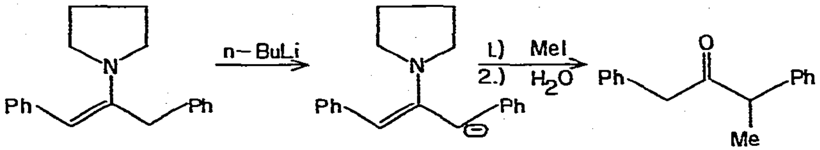
Metalation of the acetonimine gave the lithio derivative LXXVI which was then alkylated and hydrolyzed to produce a series of 15 methyl ketones (equation 43) [98].



LXXVI

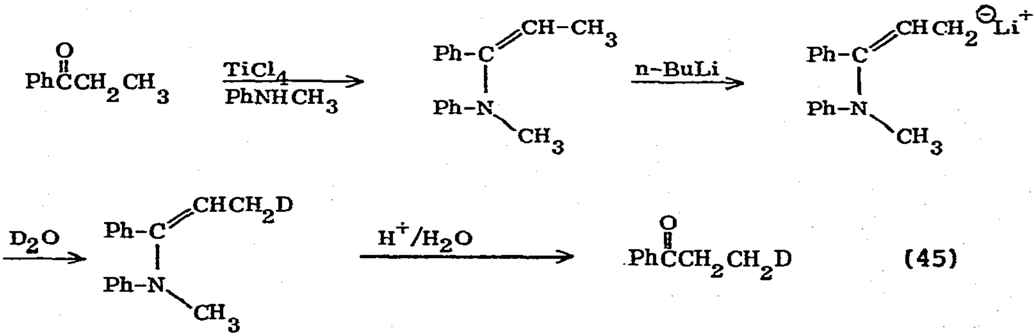
(43)

Many undesirable side-reactions during enamine syntheses were avoided when enamines of ketones having α or β-positioned phenyl groups were deprotonated with n-butyllithium. High yields of the corresponding methyl ketones could be obtained upon alkylation and hydrolysis (equation 44) [99].



(44)

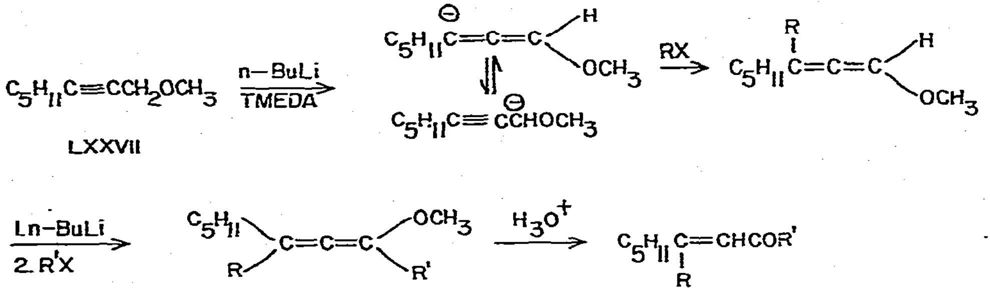
Formation of the N-methylaniline enamine derivative of propiophenone allowed electrophilic substitution of the β-carbon via formation of the lithio species (equation 45) [100]. Several condensation products from this reaction were cyclized to oxygen-containing heterocycles.



(45)

It has been proposed that hard alkylating reagents (Me_3SiCl,

Me_2SO_4, etc.) react with the sp^2 rather than the sp^3 carbanion formed by metalation of the propargylic ether LXXVII with n-BuLi TMEDA. The alkyl derivative can be further metalated and alkylated to give allenic ethers which can, in turn, be hydrolyzed to α,β-unsaturated carbonyl compounds (equation 46) [101].

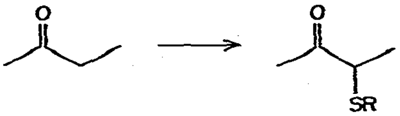


LXXVII

(46)

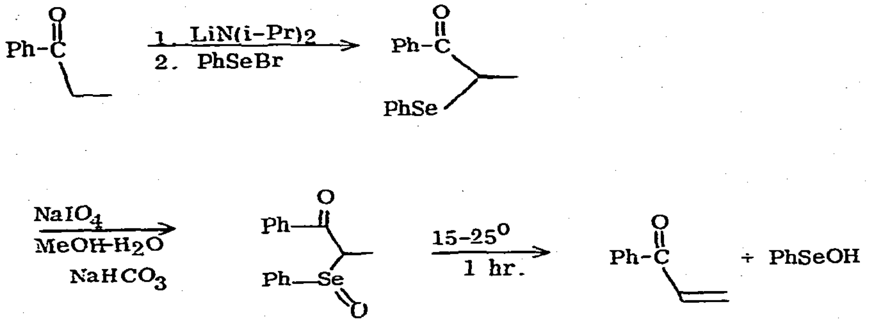
α-Metalation of ketones has been put to a variety of uses. Current interest in the anion chemistry of thioacetals (ketals) and thioethers has prompted an examination of new methods of preparation of these compounds. Seebach and Teschner have studied four successful methods of effecting the substitution shown in equation 47 [102];

1. Preparation of the lithium enolate from the silylether and methyllithium followed by reaction with a sulfenylchloride.
2. Preparation of the enolate of the ketone using lithium-diisopropylamide, followed by reaction with diphenyldisulfide.
3. Same procedure as 2 except the lithium enolate was treated with a sulfenylchloride.
4. Same procedure as 2 except that the lithium enolate was formed by treatment with lithium-cyclohexyl-isopropylamide.



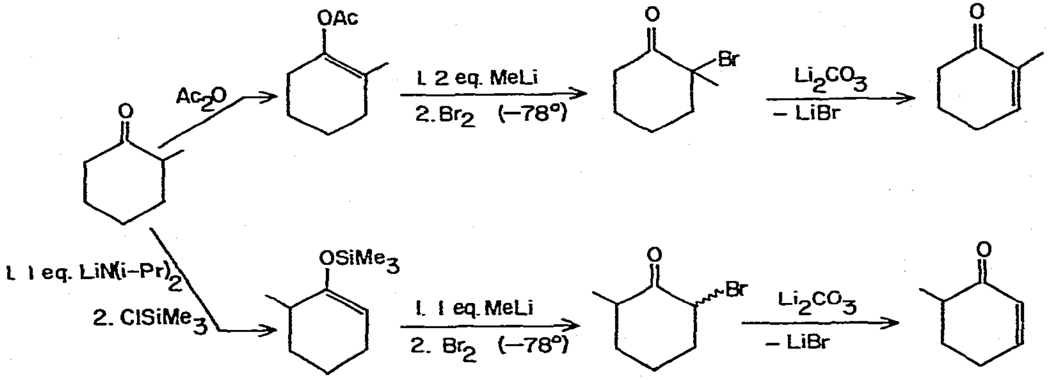
(47)

Conversion of ketones or esters to the corresponding α,β-unsaturated derivatives can be accomplished by α-lithiation with diisopropylamide, formation of the α-phenylseleno derivative followed by oxidation and elimination (equation 48) [103]. These conditions are sufficiently mild that several sensitive α,β-unsaturated ketones have been conveniently prepared.



(48)

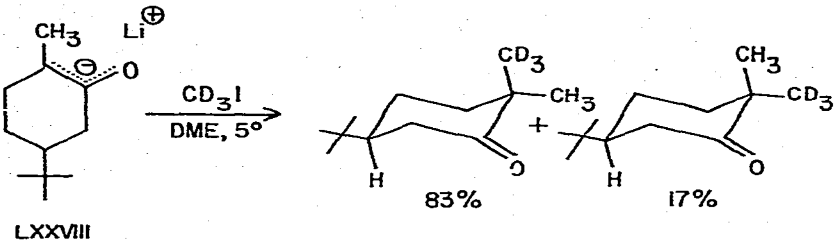
Position-specific generation of α,β-unsaturation in unsymmetrical ketones has been accomplished by position-specific α-bromination of ketone enolates with methyllithium/bromine followed by elimination (equation 49) [104]. No rearrangements or other base catalyzed side-reactions were found to compete.



(49)

Predominant axial substitution with trideuteriomethyl iodide in the lithium-enolate LXXVIII (equation 50) [105] has been interpreted in terms of a transition state geometry which minimizes eclipsing but allows for some bond deformation.

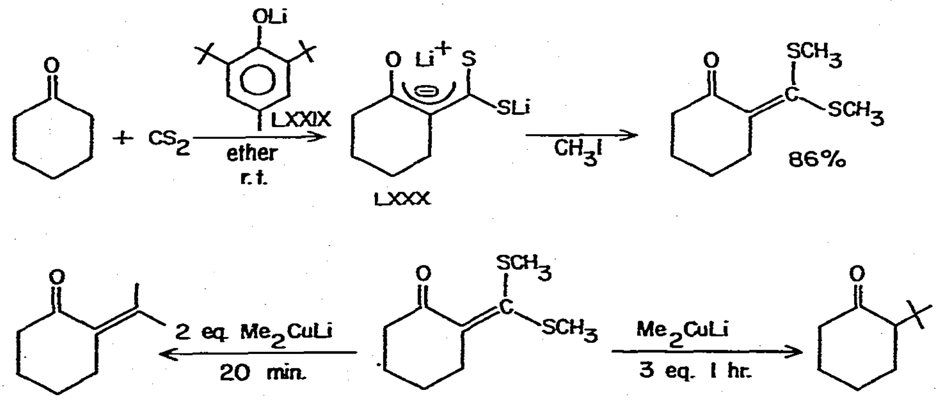
Michael addition of this enolate to methyl acrylate gave a mixture of epimers of nearly the same relative composition.



(50)

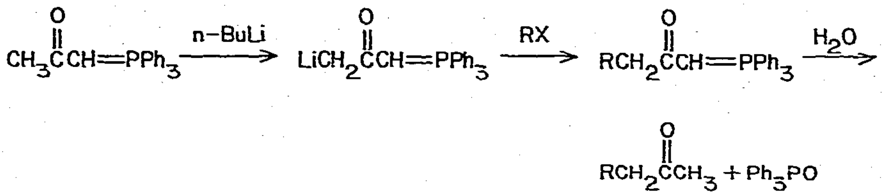
The metal enolate salts of ketones with the metal being mercury(II), lithium, sodium, zinc and magnesium have been studied by House and co-workers [106]. Lithium enolates were found to exist as either contact or solvent separated ions. C-acylation (vs. O-acylation) can become predominant when the metal enolate is in the contact ion pair form.

Lithium 4-methyl-2,6-di-tert-butylphenoxide (LXXIX) can be used to effect α-metalation of ketones which can then be carbonated [107]. α-Dithiomethylene derivatives of ketones can be formed by α-lithiation with this phenoxide base and condensation with carbon disulfide to provide the dithio derivative LXXX which can be methylated to give the dithiomethylene ketone. This derivative can serve as a source of α-isopropylidene and α-tert-butyl groups in the corresponding ketone (equation 51) [108]



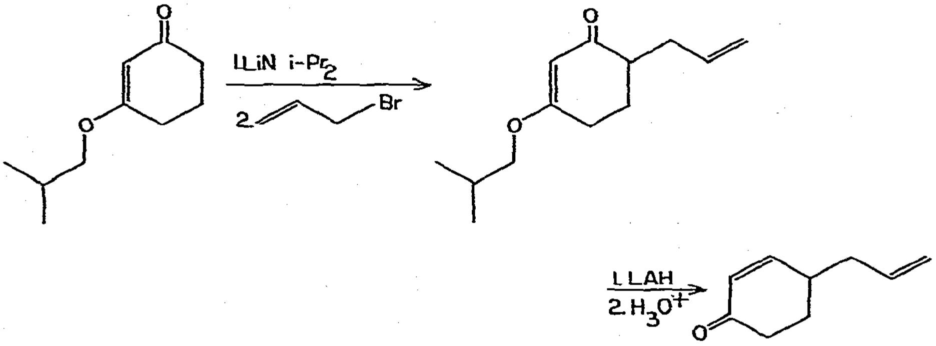
(51)

Lithiotriphenylphosphinioacetonide has been shown to be useful for the introduction of the acetonyl group by nucleophilic displacements on alkyl halides (equation 52) [109].



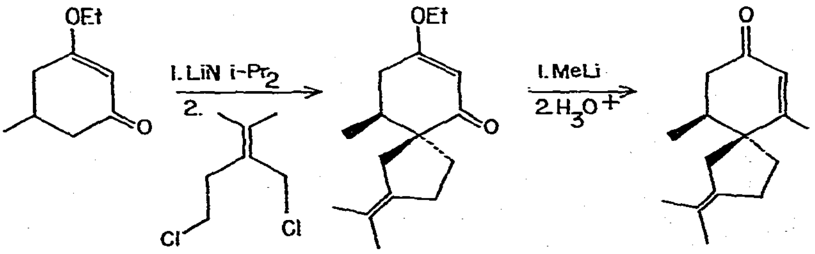
$$CH_3\overset{O}{\overset{\|}{C}}CH{=}PPh_3 \xrightarrow{n\text{-BuLi}} LiCH_2\overset{O}{\overset{\|}{C}}CH{=}PPh_3 \xrightarrow{RX} RCH_2\overset{O}{\overset{\|}{C}}CH{=}PPh_3 \xrightarrow{H_2O} RCH_2\overset{O}{\overset{\|}{C}}CH_3 + Ph_3PO \qquad (52)$$

Alkylation of the kinetic enolates from the enol ether of cyclohexan-1,3-dione produced by metalation with lithium diisopropylamide has led to 6-substituted compounds. Reduction and hydrolysis then afforded 4-substituted cyclohex-2-enones (equation 53) [110].



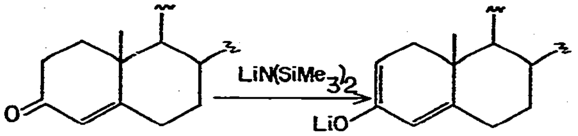
(53)

Utilizing this method Stork and co-workers have developed a simple stereo-specific synthesis of β-vetivone (equation 54) [111].



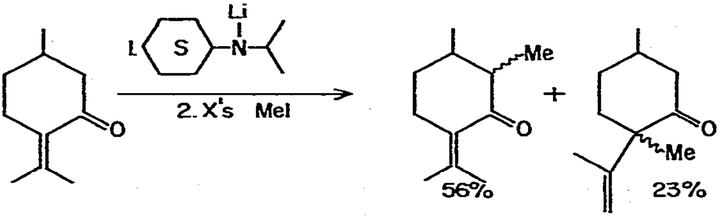
(54)

Metalation of testosterone and 10-nortestosterone 17-tetrahydropyranyl ethers with lithium hexamethyldisilazane gave the lithio-2,4-dienolate ions (equation 55) [112]. These ions could be methylated at C-2 or trapped as 2,4-dienolsilylethers.



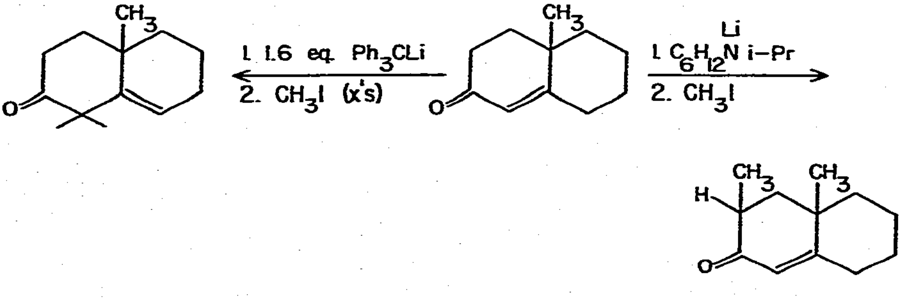
(55)

Most bases with α,β-unsaturated ketones provide α-metalation. Lithium 2°-amide bases have now been observed to provide principally α'-metalation as demonstrated by the metalation and alkylation of pulegone (equation 56) [113].



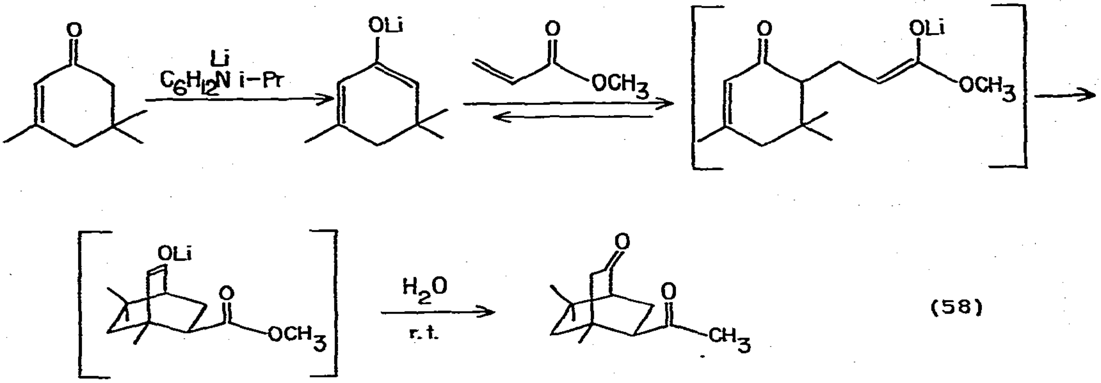
(56)

Significantly different results were obtained from the metalation of a steroidal Δ^4-ene-3-one with cyclohexyl isopropyl lithium (which gave 2-lithiation and alkylation) and trityllithium (which gave dialkylation at the 4-position) (equation 57) [114]. These results were interpreted in terms of an electron transfer mechanism operating during the trityllithium reaction.



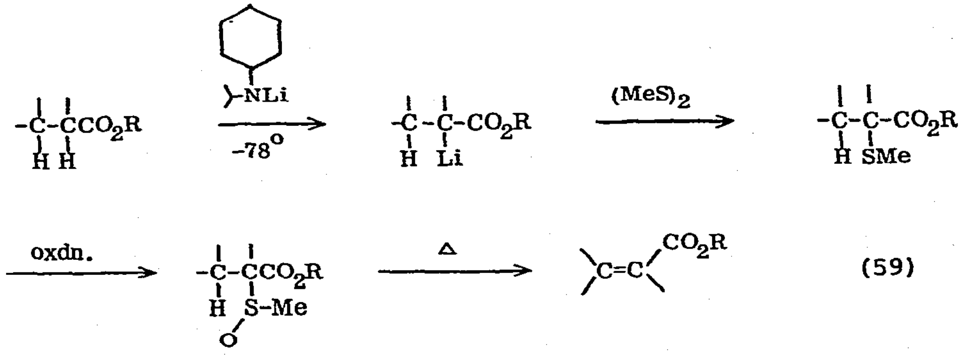
(57)

α-Dienolates formed from lithium dialkylamides can be used in Michael additions with the result that a ready synthesis of bicyclo[2.2.2]octan-2-ones has been developed (equation 58) [115].



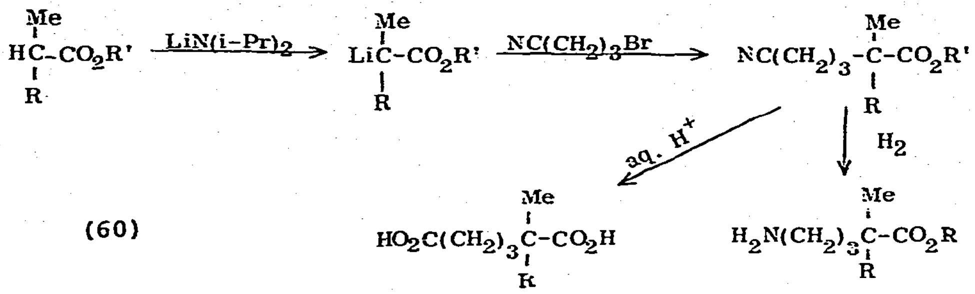
(58)

New methods of α-alkylation of esters have been studied. Sulfenylation of the α-carbon of esters followed by oxidation and thermolysis has provided a novel technique for the introduction of unsaturation (equation 59) [116].



(59)

Use of $LiN(i\text{-}Pr)_2$ to effect ionization of the α-H in esters has been exploited for the preparation of a series of ω-aminoalkanoic and alkanedioc acids (equation 60) [117]. Controlled alkylation of lithium enolates of lactones in greater than 90% yield has been reported [118]. The method

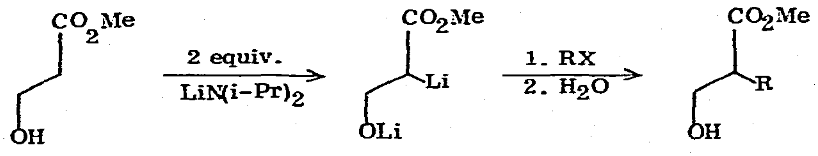


(60)

featured use of lithium di-isopropylamide as the base and use of HMPA as the solvent for the alkylation.

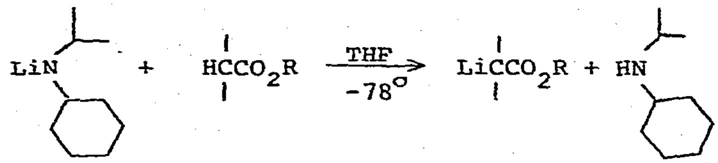
A convenient one flask procedure for ester alkylation which consists of forming the lithium ester enolate by adding the ester (1 equiv.) to a 1 molar THF solution containing 1 equiv. of lithium isopropylamide at −78° has been described [119]. After 20–40 minutes at this temperature, the desired alkylating agent (1.0–1.2 equiv.) dissolved in HMPA was added. Esters with quaternary α-carbons could be constructed by this procedure. A significant advantage of this procedure is the nearly 1:1:1 ratio of the reactants.

α-Substituted hydracrylate esters have been prepared via the dilithio intermediate LXXXI [120]. Apparently, neither O-alkylation nor ester self-condensation competed. Dehydration of several of the hydracrylate esters produced the acrylate analogues.



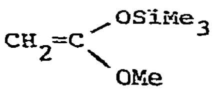
LXXXI

Lithium ester enolates, prepared by metalation of esters with lithium N-isopropylcyclohexylamide, have been found to undergo exclusive C-alkylation using alkylating agents and a mixture of C- and O- alkylation with trimethylsilylchloride (equation 61) [121].



$$LiCH_2CO_2C_2H_5 \xrightarrow{RX} RCH_2CO_2C_2H_5$$

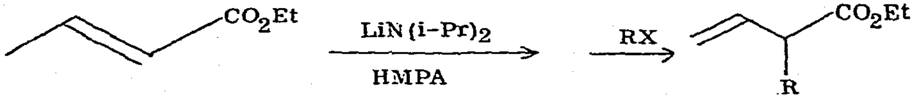
$$LiCH_2CO_2Me + Me_3SiCl \xrightarrow{THF}$$



$$CH_2{=}C(OSiMe_3)(OMe) + Me_3SiCH_2CO_2Me \qquad (61)$$

65% 35%

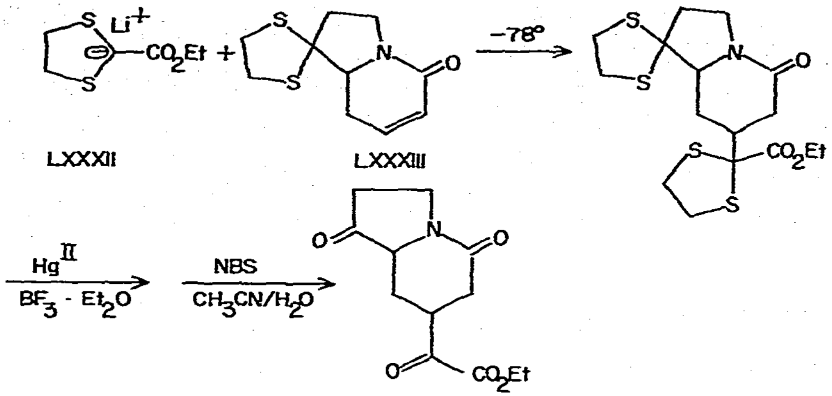
Alkylation of ethyl crotonate can be carried out by α-metalation with lithium isopropylamide followed by alkylation (equation 62) [122]. A second metalation-alkylation sequence to produce products with a quaternary α-carbon was found to be feasible.

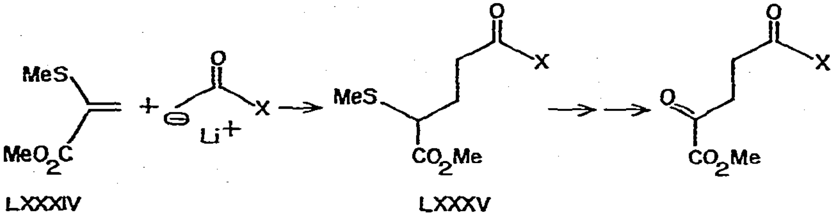


(62)

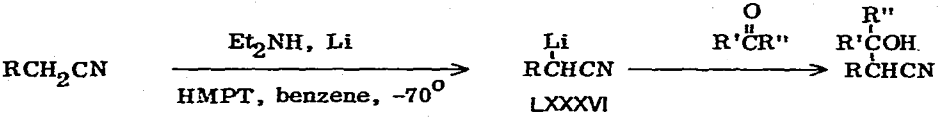
Conjugate addition to the lactam LXXXIII could not be effected by other carbonyl anion equivalents but was accomplished by use of the lithium anion of the dithiolane derivative of ethyl glyoxalate LXXXII [123].

Further investigation into routes to 1,4-dicarbonyl compounds has led Schlessinger and co-workers to examination of the Michael receptor, methyl 2-methyl-thioacrylate (LXXXIV) [124]. Reaction of this compound with weak nucleophiles (enamines) or strong nucleophiles (lithium enolates) produced good yields of the conjugate addition product LXXXV which could be transformed into the corresponding 1,4-dicarbonyl compound.



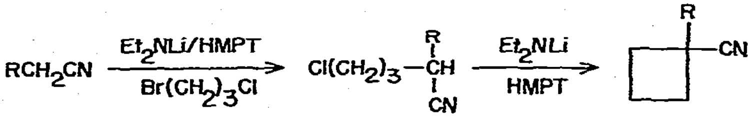


Excellent yields of β-hydroxynitrile derivatives were obtained by condensing the α-lithio intermediate LXXXVI with aldehydes and ketones [125].



$$\mathrm{RCH_2CN} \xrightarrow[\text{HMPT, benzene, }-70^{\circ}]{\mathrm{Et_2NH,\ Li}} \underset{\text{LXXXVI}}{\begin{array}{c}\mathrm{Li}\\ \mathrm{R\dot{C}HCN}\end{array}} \xrightarrow{\mathrm{R'\overset{O}{\overset{\|}{C}}R''}} \begin{array}{c}\mathrm{R''}\\ \mathrm{R'\dot{C}OH}\\ \mathrm{R\dot{C}HCN}\end{array}$$

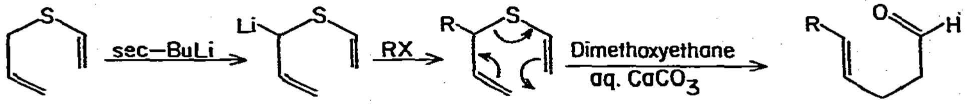
ω-Halogenated nitriles can be both prepared and cyclized by use of lithium diethylamide in HMPT (equation 63) [126]. Cyclobutane derivatives were easily prepared using this method.



(63)

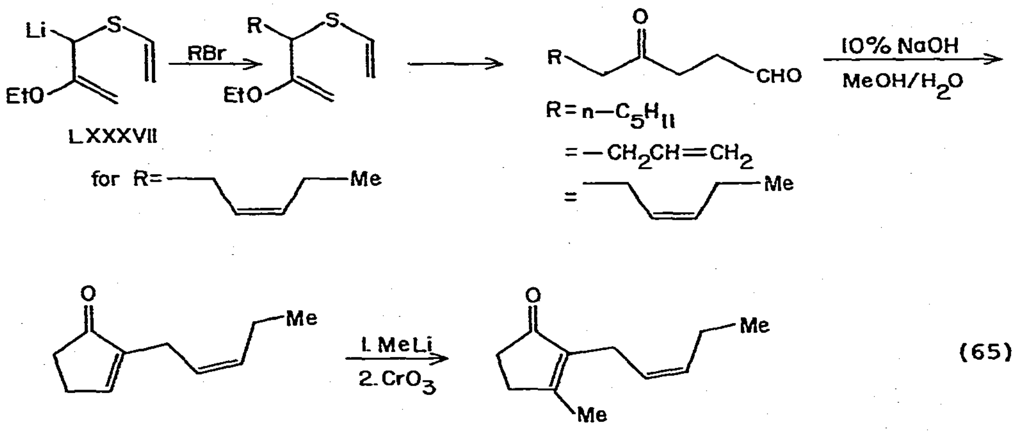
Alkylation of 1-vinylthioallyllithium and subsequent thio-Claisen rearrangement has afforded stereoselective conversion of an alkyl halide to its γ,δ-unsaturated aldehyde (equation 64)

[127]. This technique has provided a facile synthesis of the moth sex attractant, propylure.



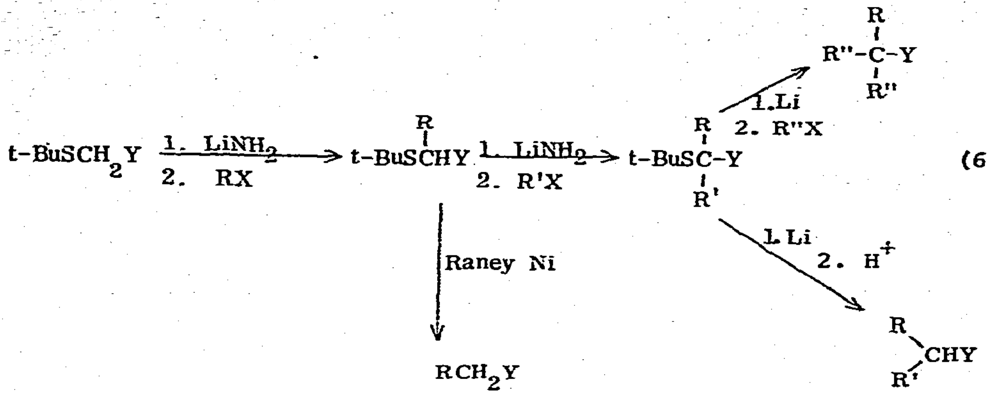
(64)

An alkylation-thio-Claisen rearrangement sequence on the (1-vinylthio)allylithium LXXXVII (prepared by metalation with sec-butyllithium) has been found to provide a route to γ-ketoaldehydes [128]. An illustration of the utility of this procedure has been provided by the synthesis of cis-jasmone (equation 65).

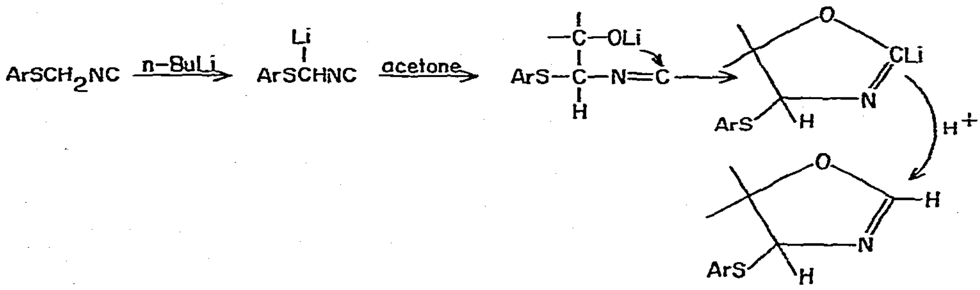


(65)

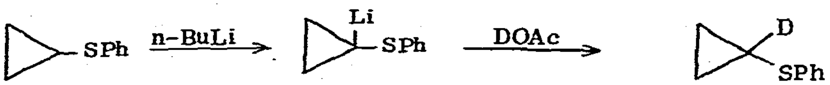
Stepwise, α-alkylation of esters, nitriles and ketones can be accomplished by metalation of their α-tert-butylthio derivatives (equation 66) [129].
α-Lithiated isocyanomethylarylsulfides have proven useful for the preparation of oxazolines and oxazoles via condensation with carbonyl compounds (equation 67) [130].

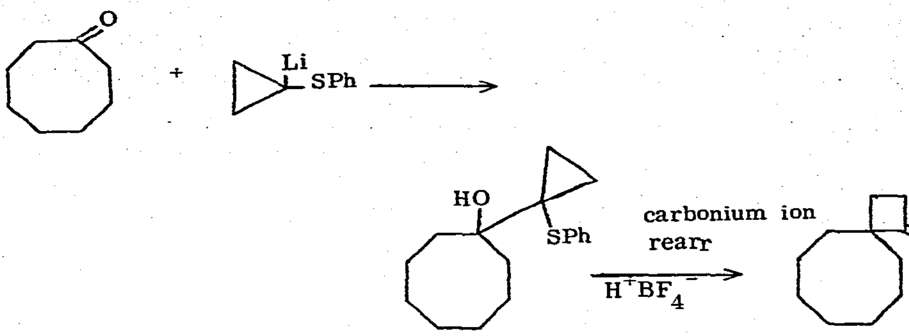

(66)

Y =-CO_2Me, -CO_2t-Bu, -CN, -COMe


(67)

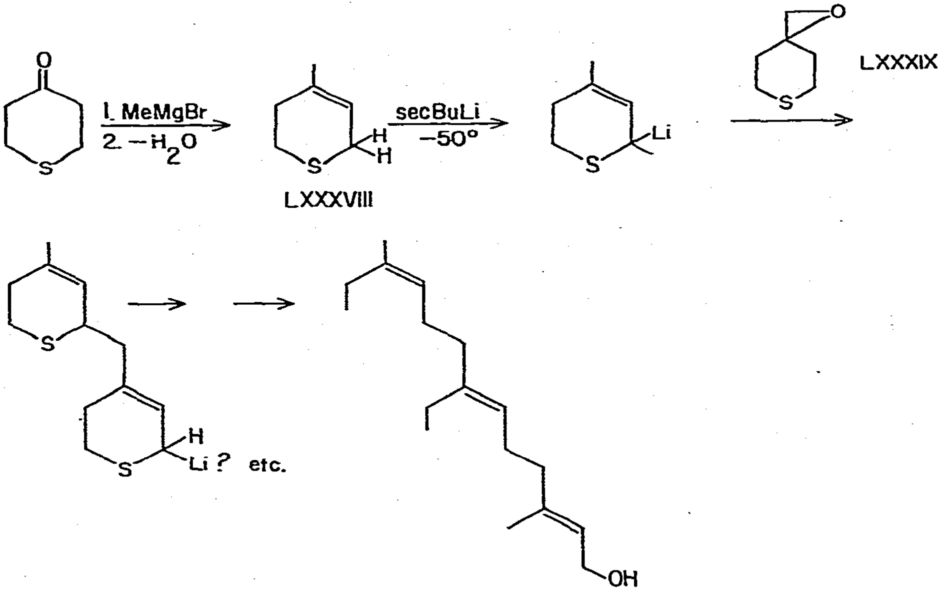
Lithiation of cyclopropyl phenyl sulfide has been found to occur specifically at the 1-carbon of the cyclopropyl group (equation 68) [131]. This observation has been used to develop a new spiroannelating technique involving condensation of the lithio intermediate with a cyclic ketone followed by acid-catalyzed ring expansion (equation 69).


(68)



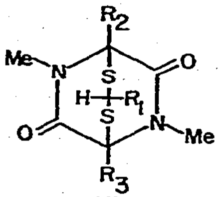
(69)

A trans geometry for the chain of acyclic olefins can be realized by metalation of a 4-thio-1-methylcyclohexene-1 (LXXXVIII) with sec-butyllithium and condensation with epoxide LXXXIX [132]. The C_{17} and C_{18} Cecropia juvenile hormones were synthesized using this technique.

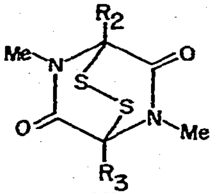


The anisaldehyde thioacetal of 1,4-dimethylpiperazine-2,5-dione-3,6-dithiol (XC, R_1 = p-$MeOC_6H_4$) has been observed to undergo a position specific metalation with n-butyllithium at the R_2 carbon [133]. This monoanion reacted smoothly with primary halides, acid halides and aldehydes in THF at −78°.

These monosubstituted derivatives could also be metalated at the R_3 carbon to produce disubstituted compounds. A two step cleavage sequence of the thioacetal system then afforded epidithiodiketopiperazines (XCI).



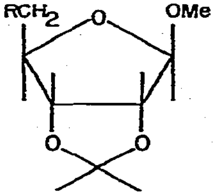
XC



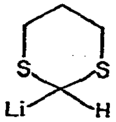
XCI

The fact of a position specific metalation in thioacetal XC has been used in a synthesis of dihydrogliotoxin [134] and sporidesmin A [135].

Methyl 5-deoxy-5-iodo-2,3-O-isopropylidene-β-D-ribofuranoside (XCIIa, R = I) was treated with 2-lithio-1,3-dithiane (XCIII) to afford XCIIb (R = 1,3-dithianyl) [136]. This in turn was hydrolyzed with ceric ammonium nitrate to give XCIIc (R = CHO) which was reduced with $NaBH_4$ to homoribose XCIId (R = CH_2OH). Similar 2-lithio-1,3-dithiane displacement reactions were recorded for 1-deoxy-2,4-O-ethylidene-1-iodo (chloro) erythritol.



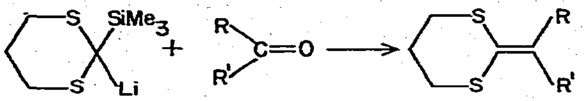
XCII



XCIII

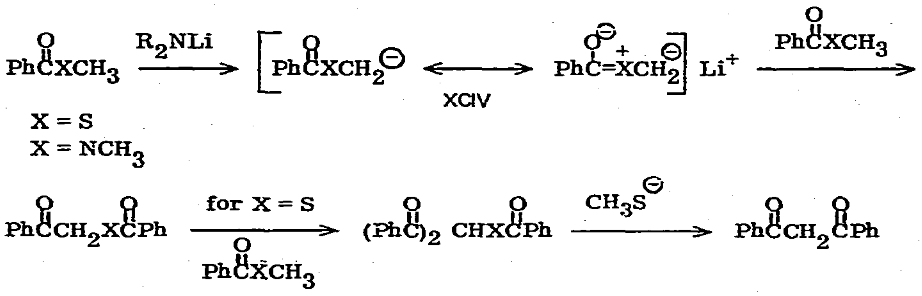
2-Lithio-2-trimethylsilyl-1,3-dithiane can be prepared by metalation with n-butyllithium. The reagent was reacted with ketones to afford alkylidenedithians (equation 70) which are potential intermediates for C_1 homologation (i.e. RR'CO→RR'CHCHO)

[137]. Similar reactions of this lithio intermediate with acetyl chloride, styrene oxide and cis-[$PtCl_2(PPh_3)_2$] were detailed.

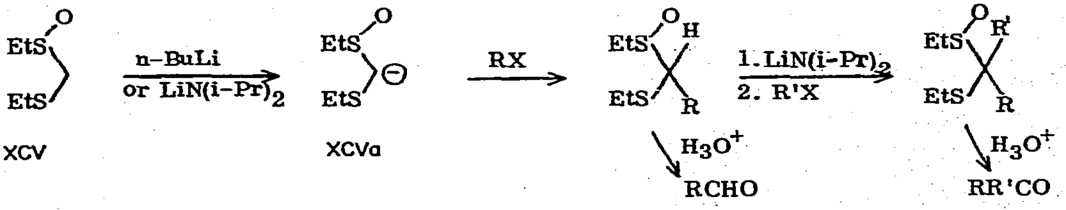


(70)

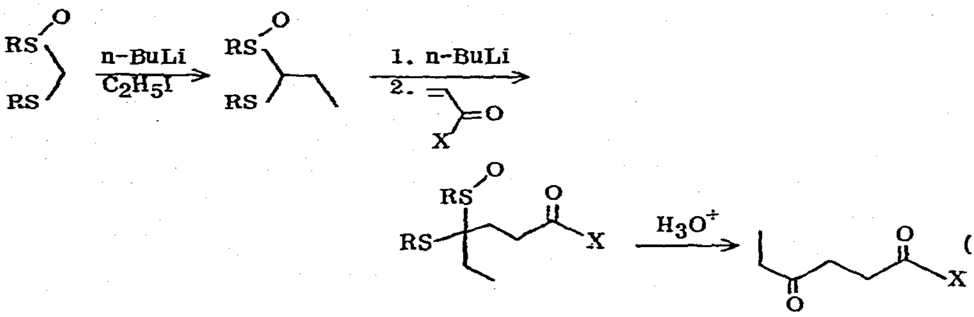
The production of dibenzoylmethane from the treatment of methyl thiobenzoate with lithium 2,2,6,6-tetramethylpiperidide has been interpreted as proceeding via the dipole-stabilized carbanion XCIV [138]. A similar rationale has been used to explain the synthesis of methylphenacylbenzamide from dimethylbenzamide (X = NCH_3).



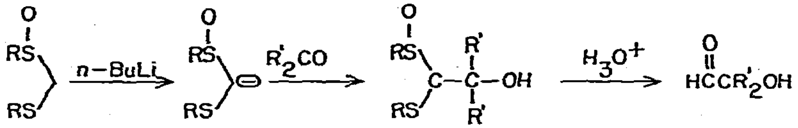
A carbonyl anion equivalent, the thioacetal monosulfoxide XCV, was found to provide quantitative yields of anion XCVa with metalating agents. Alkylation of this anion afforded either aldehydes or ketones [139].

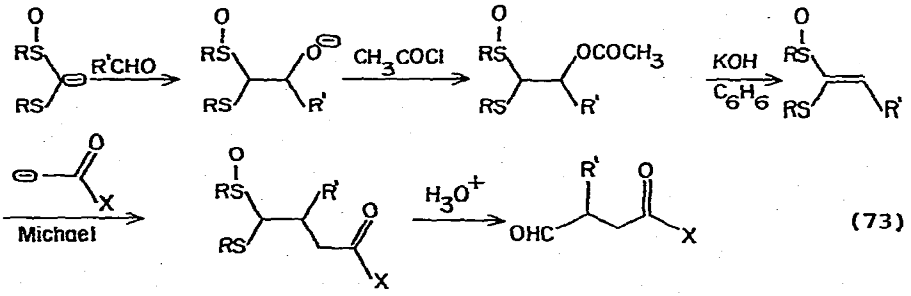


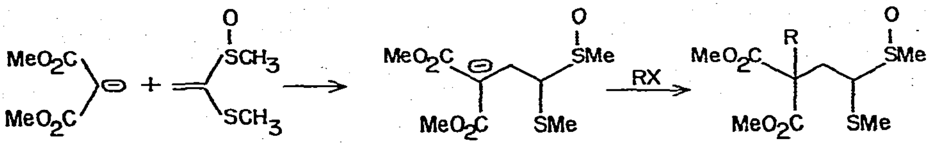
This carbonyl anion equivalent has been found to undergo both alkylation and conjugate addition, thereby realizing the goal of functioning as a "linch-pin" for the construction of unsymmetrically substituted 1,4-dicarbonyl compounds (equation 71) [140]. Utilization of this technique for the synthesis of dihydrojasmone and cis-jasmone has been detailed. [141].


(71)

Treatment of this intermediate with aldehydes or ketones gave intermediates from which the corresponding α-hydroxycarbonyl system could be isolated upon hydrolysis (equation 72) [142]. α-Dicarbonyl systems were formed when the intermediate was treated with acid chlorides or esters followed by hydrolysis. The intermediate can be used to prepare ketone thioacetal monoxides, which can function as Michael receptors (equations 73 and 74) [143,144].

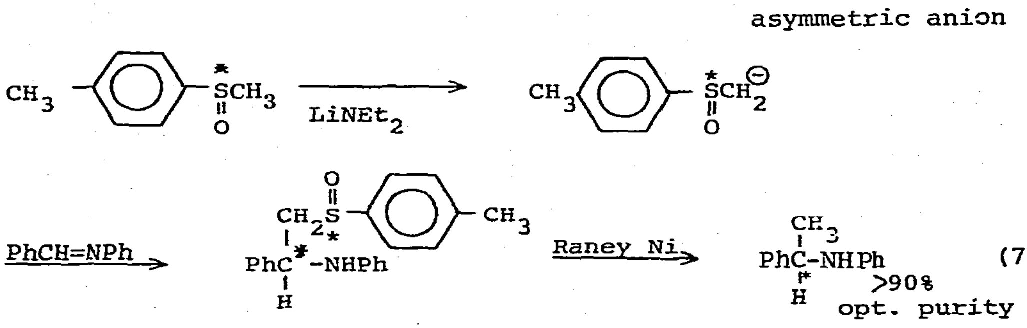

(72)


(73)



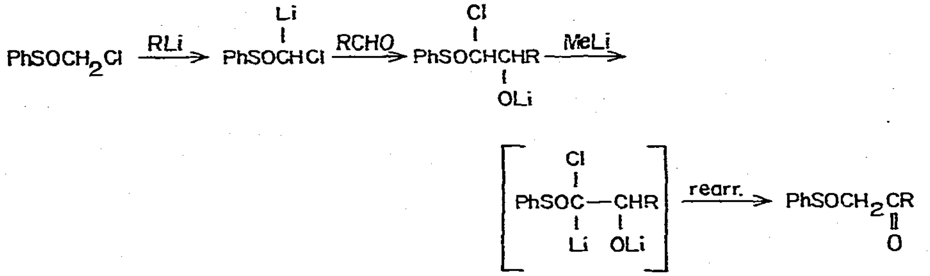
(74)

Optically active amines can be synthesized in high optical purity utilizing the asymmetry induced by the treatment of an imine or nitrile with optically active p-toluenesulfinylcarbanion (equation 75) [145].



(75)

Lithiation of chloromethyl phenyl sulfoxide was observed to take place at the methylene group. Condensation of this intermediate with aldehydes and subsequent treatment of the solution with methyllithium has provided a route to the corresponding phenylsulfinylmethyl ketones (equation 76) [146].

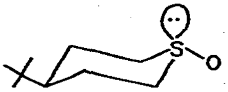


$$\mathrm{PhSOCH_2Cl} \xrightarrow{RLi} \mathrm{PhSO\overset{Li}{C}HCl} \xrightarrow{RCHO} \mathrm{PhSO\overset{Cl}{C}H\underset{OLi}{C}HR} \xrightarrow{MeLi} \left[\mathrm{PhSO\underset{Li}{\overset{Cl}{C}}{-}\underset{OLi}{C}HR}\right] \xrightarrow{rearr.} \mathrm{PhSOCH_2\underset{O}{\underset{\|}{C}}R} \qquad (76)$$

The stereochemistry of methylation and deuteration of cyclic α-lithiosulfoxides has been studied [147]. For model compounds related to XCVI and XCVII the hydrogen <u>cis</u> to the

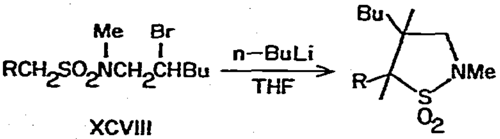
S-O bond was always removed more quickly in the presence of n-butyllithium/THF than those trans. Furthermore methylation with CD_3I occurred only trans to the S-O bond.

XCVI



XCVII

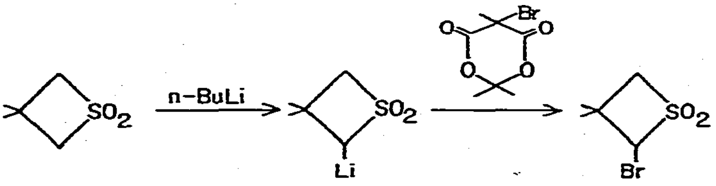
Metalation at the 2-position of a compound containing a sulfonyl group is a well-known technique. Sultams have been prepared by the α-metalation of the sulfonamide XCVIII and subsequent ring closure [148].



XCVIII

R=H,Me

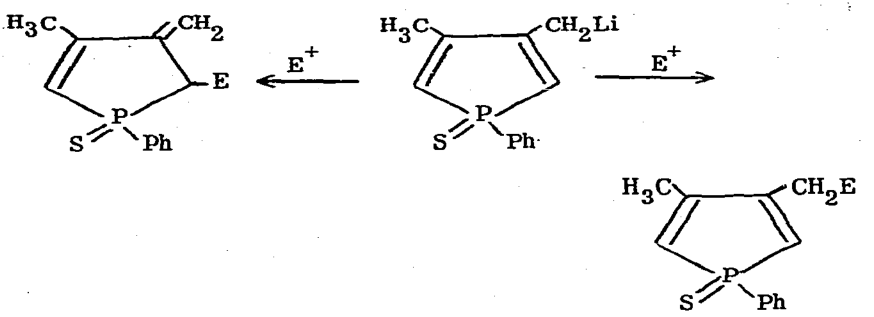
α-Halosulfones have been prepared by metalation of a series of cyclic sulfones with n-butyllithium followed by treatment of the resulting organolithium intermediate(s) with hexachloroethane [149]. Some α,α'-di and/or α,α-di and α,α,α'-trimetalated species were identified. The use of a bromine derivative of Meldrum's acid allowed preparation of the α-bromo thietan-1,1-dioxide derivative C via the α-lithiated intermediate XCIX [150].



XCIX

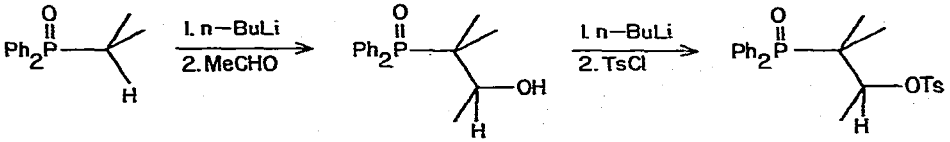
C

Various metalations of phosphorus compounds have been reported. Lithiation of P-thio-P-phenyl-3,4-dimethylphosphole with tert-butyllithium took place at both a 2-position and a methyl group as determined by derivatization (equation 77) [151].



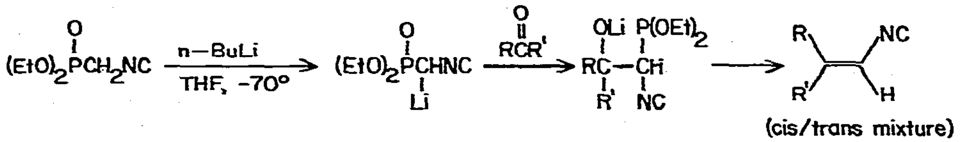
(77)

Metalation α to a phosphine oxide moiety was utilized in the synthesis of the tosylate CI [152].



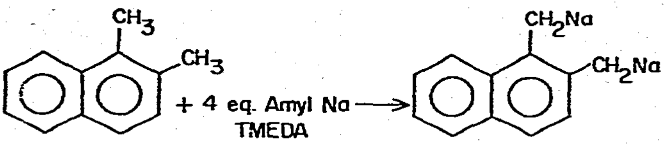
CI

Isocyanomethane phosphonic acid diethyl ester was α-lithiated with n-butyllithium. This α-anion was condensed with aldehydes and ketones to produce vinyl isocyanides (equation 78) [153]. With sodium and potassium bases cyclization and ring opening reactions occurred.



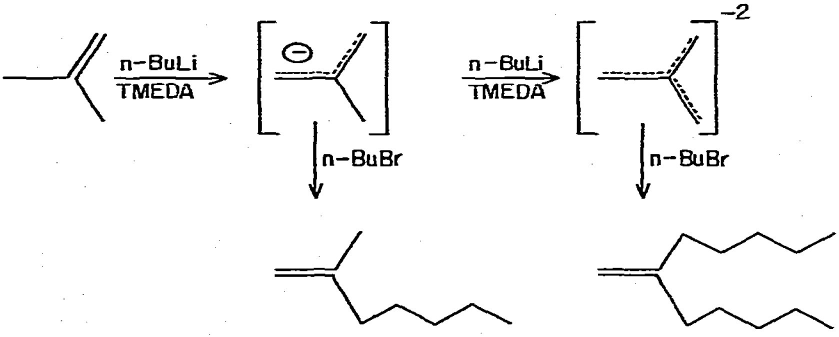
(78)

The following study will be of interest to organolithium chemists. α, α'-Disodiation of 1,2-, 1,3-, 1,6- and 1,8-dimethylnaphthalenes and o- and m-xylene has been effected with amylsodium/TMEDA reagent (equation 79) [154]. These reactions are attributed primarily to a peptizing action by TMEDA.



(79)

Metalation of isobutene with n-butyllithium in TMEDA followed by treatment with n-butyl bromide afforded a mixture of mono- and dialkylated products (equation 80) [155]. The latter product was inferred to have arisen from a trimethylenemethane dianion.



(80)

Polycarbonyl compounds, namely, 1,3,5,7,9,11-hexaketone, 1,3,5,7,9,11,13-heptaketone and 1,3,5,7,9,11,13,15-octaketone have been synthesized by a β-ketoacylation reaction carried out on the appropriate polyanion (equation 81) [156]. These polyketones can be easily cyclized to naphthalene (equation 82) and anthracene derivatives containing specific functional groups that make them convenient sources of polycyclic aromatic metabolites.

β-Keto phosphonates, useful in a modified Wittig olefin synthesis, can be prepared by alkylation of the dianion formed by sequential treatment with 1 equiv. NaH and then 1 equiv. of n-butyllithium (equation 83) [157].

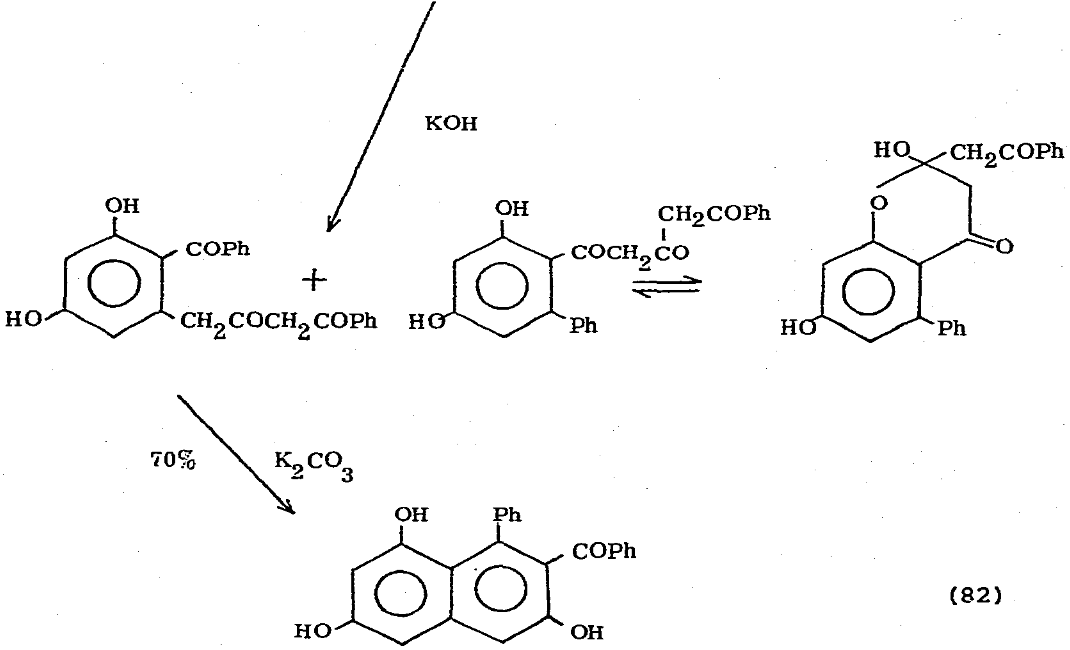
$$\mathrm{PhCOCH_2COCH_2COCH_2COCH_3} \xrightarrow[\text{THF, }0^{\circ}]{\text{4 eq. } \mathrm{LiN}(-\!\!<)_2}$$

$$\mathrm{PhCO\overset{\ominus}{C}HCO\overset{\ominus}{C}HCO\overset{\ominus}{C}HCO\overset{\ominus}{C}H_2} \xrightarrow{\mathrm{PhCO\overset{\ominus}{C}HCO_2Et}\text{ (via NaH)}}$$

$$\mathrm{PhCO\overset{\ominus}{C}HCO\overset{\ominus}{C}HCO\overset{\ominus}{C}HCOCH_2CO\overset{\ominus}{C}HCOPh} \xrightarrow[\text{base}]{\text{addl.}}$$

$$\text{pentaanion} \xrightarrow{\mathrm{H^+}}$$

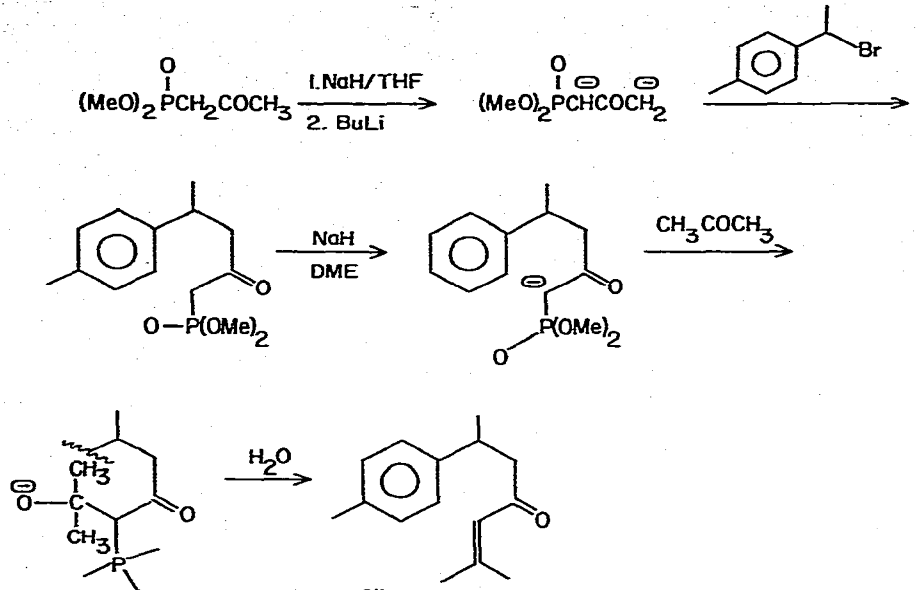
$$\text{hexaketone}\quad \mathrm{PhCOCH_2COCH_2COCH_2COCH_2COCH_2COPh} \qquad (81)$$



(82)

$$\mathrm{(CH_3O)_2\overset{O}{P}CH_2COCH_3} \xrightarrow[\text{THF}]{\text{NaH}} \mathrm{(CH_3O)_2\overset{O}{P}\text{–}\overset{\ominus}{C}HCOCH_3} \xrightarrow{\text{n-BuLi}}$$

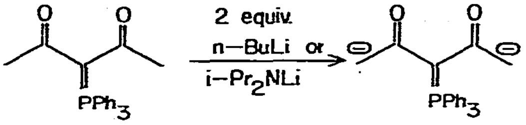
$$\mathrm{(CH_3O)_2\overset{O}{P}\text{–}\overset{\ominus}{C}HCO\overset{\ominus}{C}H_2} \xrightarrow[\text{2. H}^+]{\text{1. RX}} \mathrm{(CH_3O)_2\overset{O}{P}CH_2COCH_2R} \qquad (83)$$



CII

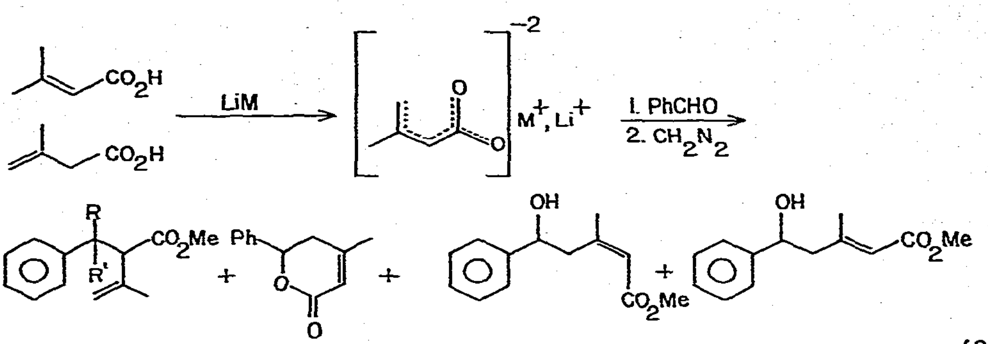
A short route to (±)-ar-tumerone (CII) has been developed utilizing this procedure [158].

Mono- and dialkylation of the dianion of diacetylmethylenetriphenylphosphorane has been observed (equation 84) [159]. Treatment of this dianion with 1,3-diiodopropane resulted in the formation of the anticipated eight-membered ring system.



(84)

Various lithium bases were used to dimetalate 3-methylbut-3-enoic and 3-methylbut-2-enoic acids. Condensation of these dimetalated intermediates with carbonyl compounds brought with certain bases reaction at C_4 of the acids, thereby introducing an isoprene unit into the original carbonyl compound (equation 85) [160].

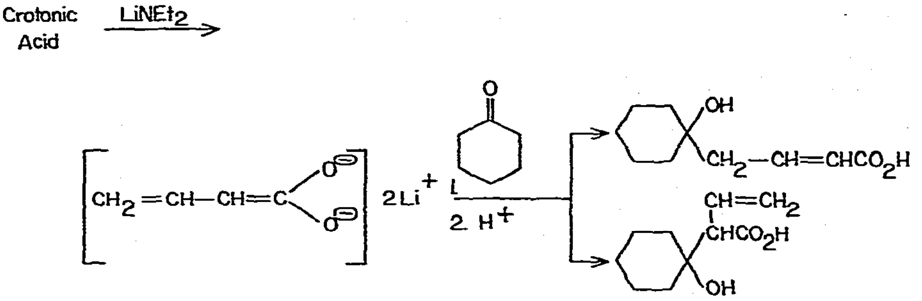


(85)

M=Bu_3Sn, $(i-Bu)_2Al$, Li, Na, K

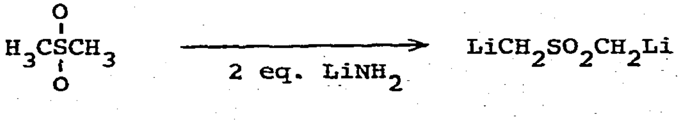
R=OH, R'=H
R=H, R'=OH

Reexamination of the dianion reactions of the crotonate dianion has revealed that a mixture of products from both α- and γ-substitution were obtained (equation 86) [161]. These observations reconciled previous reports in which α- and γ-substitution were each claimed (in separate publications) to lead to a single product.



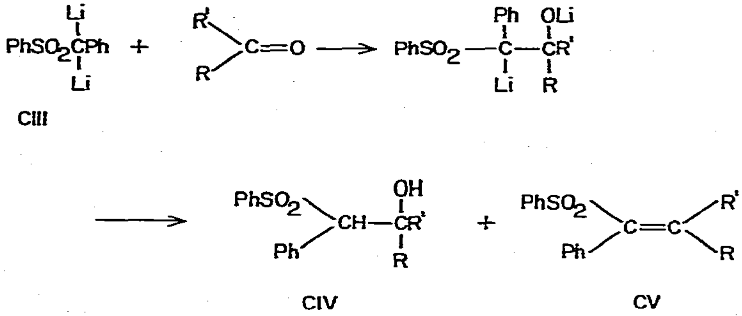
(86)

1,3-Dialkali metal salts of certain sulfones and sulfoxides have been generated (equation 87) [162] and have been found to undergo double aldol-type condensations and double alkylations.



$$H_3C\overset{O}{\underset{O}{S}}CH_3 \xrightarrow[\text{2 eq. LiNH}_2]{} LiCH_2SO_2CH_2Li \qquad (87)$$

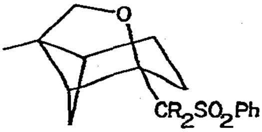
Novel α, α-dilithio species have received attention. An attempt to condense the α, α-dilithio sulfone CIII with propionaldehyde afforded only a very low yield of the anticipated α,β-unsaturated sulfone, the main product being the hydroxyphenyl sulfone CIV (R=H, R'=Pr). This was attributed to the poor leaving-group character of OLi. Good yields of the desired α,β-unsaturated sulfone CV were obtained by treatment of the dilithio intermediate with two equiv. of MgI_2 before condensation [163].


CIII

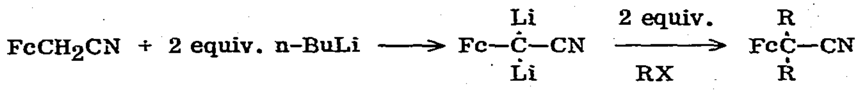
CIV

CV

Treatment of the sulfone CVI (R = H) with excess n-butyllithium at -70° in ether provided essentially quantitative conversion to the sulfone α,α-dianion [164]. This was demonstrated by the complete deuteration of this position (R = D) by addition of deuterium oxide to the presumed dianion. At higher temperatures under these same conditions an elimination product was isolated. An E1cB mechanism was proposed for this process.


CVI

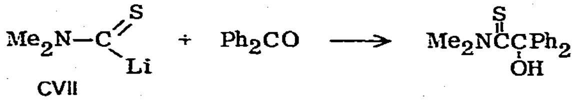
α, α-Dilithiation of ferrocenymethyl cyanide has led to a series of dialkylated derivatives after treatment with benzyl chloride, n-butyl bromide, methyl iodide and 1,2-dichloroethane (equation 88) [165]. Further reaction of certain of these α,α-disubstituted cyanides with n-butyllithium afforded a series of ferrocenylmethyl butyl ketones while $LiAlH_4$ reduction gave the respective amines.



$$\mathrm{FcCH_2CN} + 2\ \text{equiv. n-BuLi} \longrightarrow \mathrm{Fc{-}\overset{Li}{\underset{Li}{C}}{-}CN} \xrightarrow[\mathrm{RX}]{2\ \text{equiv.}} \mathrm{Fc\overset{R}{\underset{R}{C}}{-}CN} \qquad (88)$$

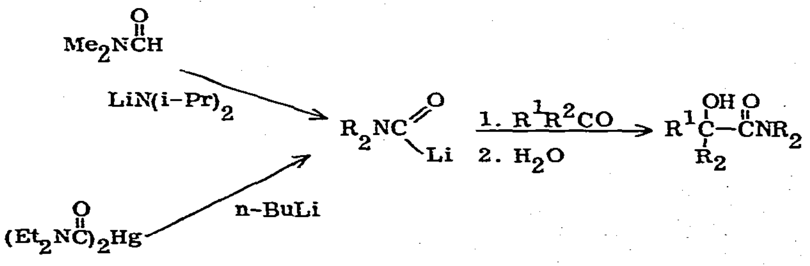
B. At sp^2 and sp Carbon

Upon addition of thioformamide to the THF solution of lithium diisopropylamide at -100°, a solution of dimethylthiocarbamoyllithium (CVII) was formed [166]. The utility of this reagent for the preparation of α-hydroxythioamides was illustrated by its addition to benzophenone as well as to other aldehydes and ketones.



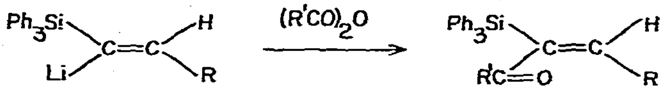
CVII

α-Hydroxy N, N-dimethylcarboxamides (R = Me) have been prepared by treating dimethylformamide with lithium diisopropylamide in THF/ether at -79° [167]. The resulting (dimethylcarbamoyl)-lithium derivative was then added to carbonyl compounds (equation 89). These authors also reported preparation of dimethylthiocarbamoyllithium.



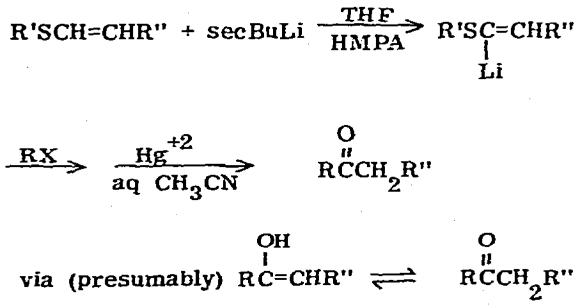
(89)

A new route to α,β-unsaturated ketones having a silyl group attached to the carbon-carbon double bond has been developed [168]. α-Lithiovinyltriphenylsilane (CVIIIa, R = H) and 1-lithio-1-triphenylsilyl-2-phenylethylene-E (CVIIIb, R = Ph) coupled with both acetic (R' = Me) and benzoyl (R' = Ph) anhydrides to provide the corresponding acyl derivatives.



CVIII

A vinyllithium reagent has been developed which, after alkylation and hydrolysis, afforded good yields of ketones (equation 90) [169]. Treatment of the 1-(alkylthio)vinyllithium intermediate with aldehydes (equation 91) and epoxides (equation 92) similarly gave good yields of the respective acyloins and α,β-unsaturated ketones.

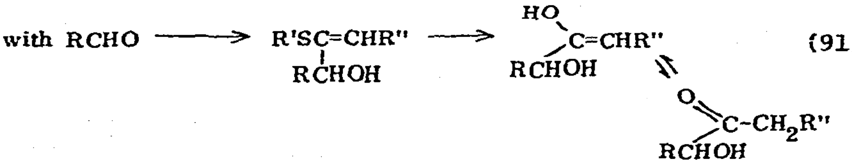


(90)

$$\text{R'SCH=CHR''} + \text{secBuLi} \xrightarrow[\text{HMPA}]{\text{THF}} \text{R'S}\underset{\displaystyle\text{Li}}{\text{C}}\text{=CHR''}$$

$$\xrightarrow{\text{RX}} \xrightarrow[\text{aq CH}_3\text{CN}]{\text{Hg}^{+2}} \text{R}\overset{\displaystyle\text{O}}{\overset{\|}{\text{C}}}\text{CH}_2\text{R''}$$

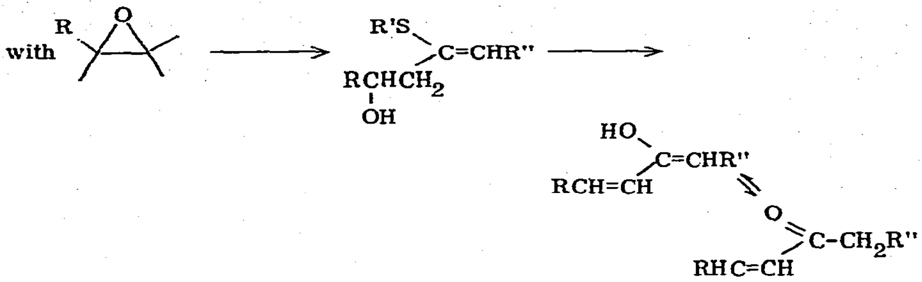
$$\text{via (presumably) } \text{R}\overset{\displaystyle\text{OH}}{\text{C}}\text{=CHR''} \rightleftharpoons \text{R}\overset{\displaystyle\text{O}}{\overset{\|}{\text{C}}}\text{CH}_2\text{R''}$$



(91)

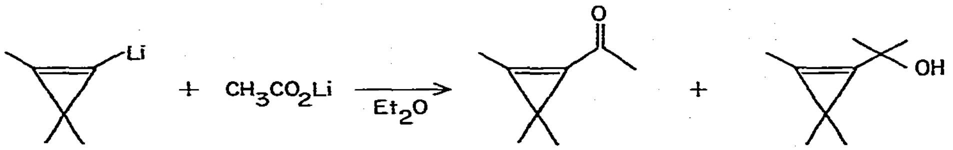
$$\text{with RCHO} \longrightarrow \text{R'S}\underset{\displaystyle\text{RCHOH}}{\text{C}}\text{=CHR''} \longrightarrow \text{HO}(\text{RCHOH})\text{C=CHR''} \rightleftharpoons \text{O=C}(\text{RCHOH})\text{-CH}_2\text{R''}$$

Nearly quantitative and instantaneous formation of the appropriate 1-metallocyclopropene upon addition of at least one equivalent of alkali amide (M = Li, Na, K) in liquid ammonia has been reported [170]. Mono- and dialkylated cyclo-



(92)

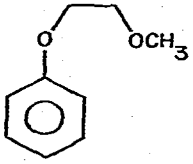
propenes were formed upon alkylation. Standing for 18 hours or much longer produced dimers and trimers of cyclopropene. Among the methods attempted for the preparation of 1-acylcyclopropenes was the alkylation of lithium acetate by the cyclopropenyl lithium intermediate CIX which produced the desired acyl compound CX and the corresponding alcohol (CXI) in a product ratio of 2:1 [171]. When lithio intermediate CIX was treated with dimethylacetamide, a small amount of the alcohol CXI was produced along with the major product, 3,3-dimethyl-2,5-hexanedione.



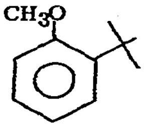
CIX CX CXI

An approximately 14-fold greater extent of lithiation of 1-methoxy-2-phenoxyethane (CXII) over anisole was observed upon competitive metalation in hexane or ether [172]. It was concluded that complexation was a factor in such metalations.

o-tert-Butylanisole (CXIII) has been found to undergo directed metalation at the remaining ortho position to the extent of 7.5% under conditions that gave a 65% yield of ortho metalation in anisole [173]. With TMEDA present a 30% yield of metalation as determined by isolation of the trimethylsilyl derivative was obtained. These results indicated steric interference with the conformation(s) necessary for co-ordination with n-butyllithium in the transition state.

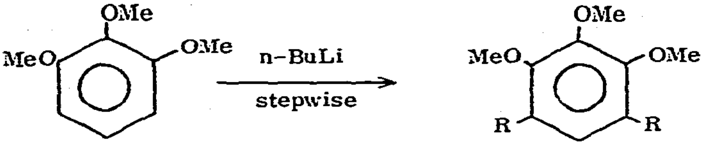


CXII



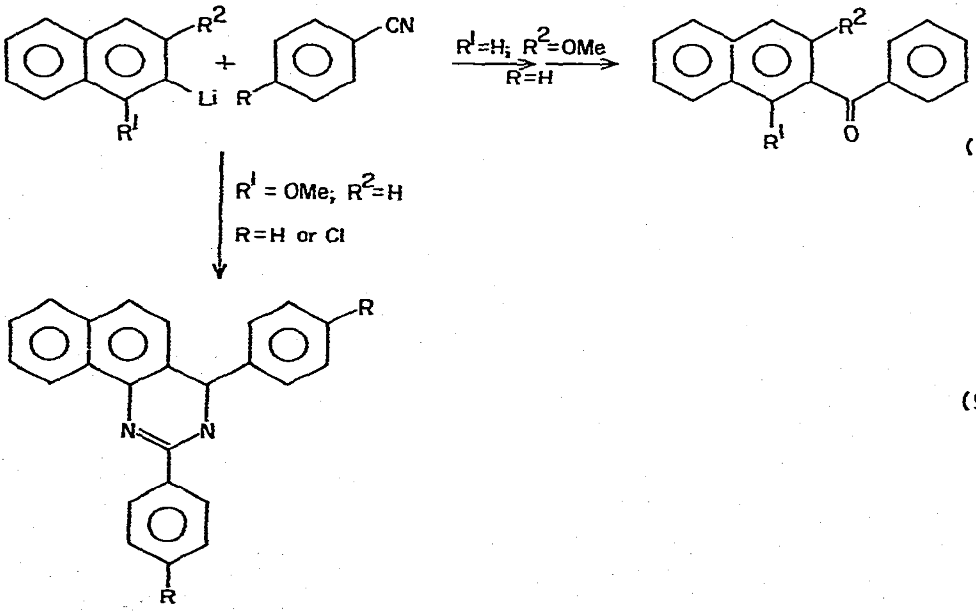
CXIII

Pyrogallol trimethylether has been stepwise metalated and alkylated at the positions ortho to the two methoxy groups (equation 93) [174].



(93)

A novel synthesis of 2,4-diarylbenzo[h]quinazolines beginning with the directed metalation of 1-methoxynaphthalene has been reported (equation 94) [175]. Similar metalation of 2-methoxynaphthalene led only to the benzoylation product (equation 95).

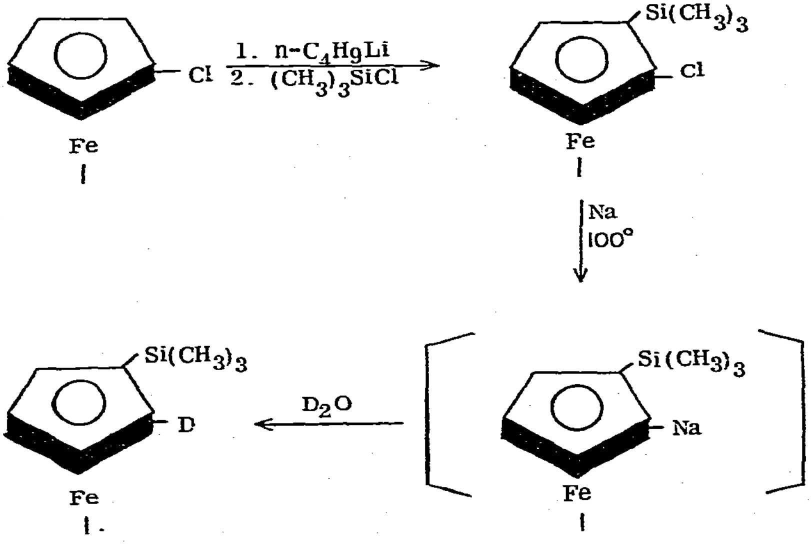


(95)

(94)

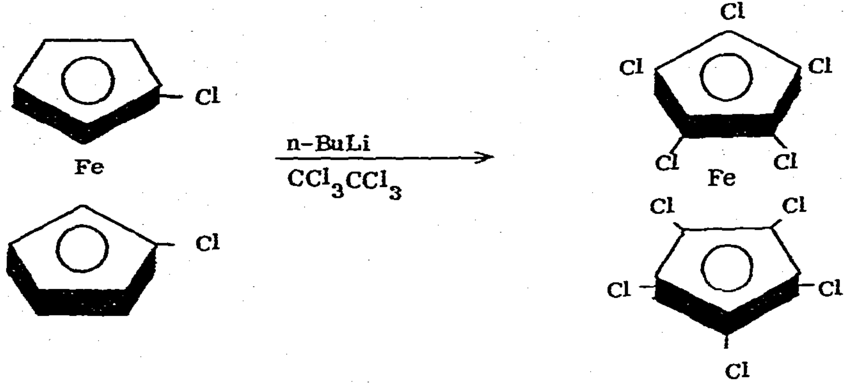
Lithium diisopropylamide metalated the side-chain in N,N-diisopropyl- and N,N-diethyl-o-, m- and p-toluamides [176]. With n-butyllithium, N,N-diethyl-o-toluamide also underwent side-chain metalation, but the m- and p-isomers provided mainly addition to the carbonyl. Lithiation of 1,3-bis(trifluoromethyl)benzene with n-butyllithium occurred at both the 2- and 4-positions while similar metalation of the 1,4-isomer occurred at the 2-position [177]. Sites of metalation were determined by carbonation and subsequent examination of the products by 100 and 220 MHz pmr.

Directed lithiation of chloroferrocene has allowed preparation of the 2-trimethylsilyl derivative [178]. Conversion of the specifically substituted molecule to 2-deuteriotrimethylsilylferrocene (CXIV) has resulted in the identification of the chemical shifts of the 2,5- and 3,4-position protons.



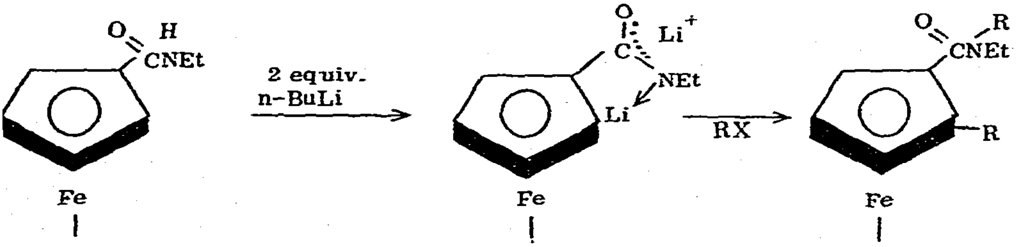
CXIV

Sequential directed metalation of 1,1'-dichloroferrocene has led ultimately to the preparation of decachloroferrocene (equation 96) [179]. A similar route involving seven successive lithiation-chlorination steps was used for the synthesis of the ruthenium analog.



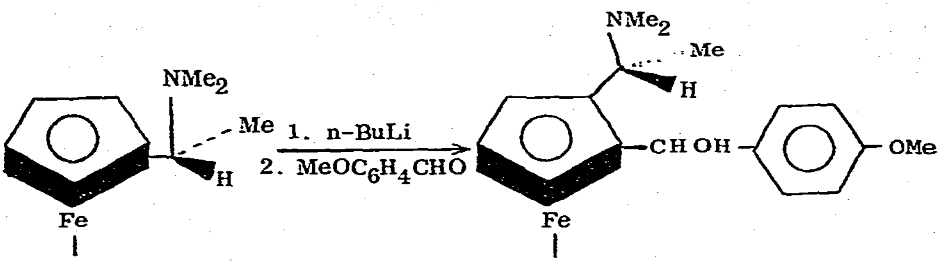
(96)

A series of 2-substituted N-ethylferrocene carboxamides were prepared by directed metalation of N-ethylferrocenecarboxamide (equation 97) [180].



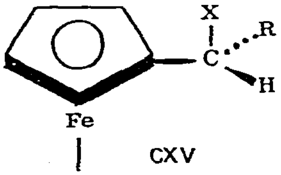
(97)

Directed lithiation of (R)-N,N-dimethyl-1-ferrocenylethylamine followed by condensation with p-anisaldehyde provided asymmetric induction not only at the incipient chiral plane, but also at the incipient chiral carbon (equation 98) [181]. A single crystal X-ray structure of the predominant product from this metalation (S,R,S)-2-(p-methoxyphenyl)hydroxymethyl-N,N-dimethyl-1-ferrocenylethylamine has provided confirmatory evidence for the absolute configurations assigned to a series of 1,2-disubstituted ferrocenes.



(98)

Methoxymethylferrocene (CXV, X= OMe) afforded approximately equal amounts of 2-and 1'-lithiation as determined by derivatization experiments with benzophenone [182]. α-Methoxyethylferrocene (MEF) upon lithiation gave a mixture of all three possible metalation isomers. (+)-MEF, when metalated and condensed with benzophenone, led to the expected mixture of three products, but only the 2-isomer possessed induced ring asymmetry. The activity possessed by this compound was found to be only about 10% of that exhibited by an otherwise identical sample prepared by a route involving asymmetric induction in the ferrocene system where metalation was directed by nitrogen (CXV, X=NMe$_2$).

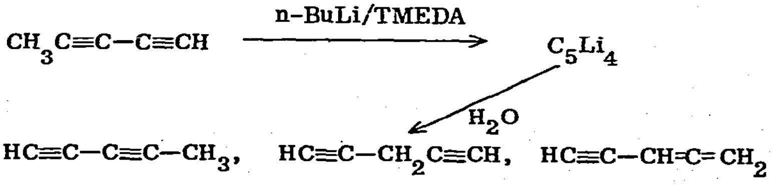


CXV

X = -OMe; R = H

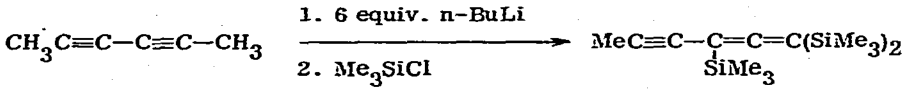
X = -NMe$_2$; R = Me

1,3-Pentadiyne, when treated with n-butyllithium/TMEDA reagent, has been reported to form a tetralithium species which after hydrolysis yielded the three acetylenes shown (equation 99) [183]. An ir spectrum of the C_5Li_4 species suggested that a $Li_2C{=}C{=}C{=}C{=}CLi_2$ structure predominated.



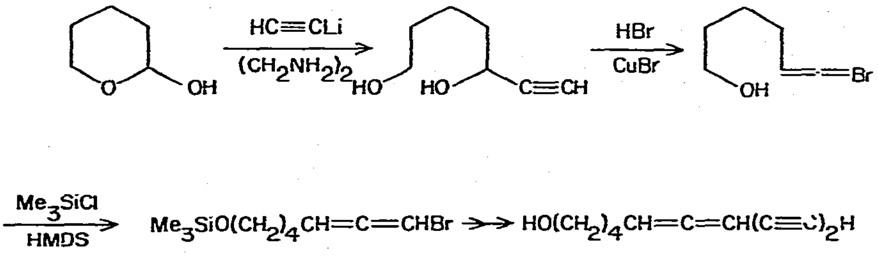
$$CH_3C{\equiv}C{-}C{\equiv}CH \xrightarrow{n\text{-}BuLi/TMEDA} C_5Li_4 \xrightarrow{H_2O} HC{\equiv}C{-}C{\equiv}C{-}CH_3,\ HC{\equiv}C{-}CH_2C{\equiv}CH,\ HC{\equiv}C{-}CH{=}C{=}CH_2 \qquad (99)$$

Hexa -2,4-diyne upon addition of six equivalents of n-butyllithium followed by, after 65 hours, addition of trimethylchlorosilane produced the trisilyl derivative (equation 100) [184]. It was thought the protons were all abstracted from the same carbon. For a shorter metalation period (16 hours) and two equivalents n-butyllithium significant monometalation was observed. Intermediate periods of metalation following otherwise the same procedure brought the unusual cumulene, $Me\underset{SiMe_3}{C}=C=C=C=C(SiMe$



$$CH_3C{\equiv}C{-}C{\equiv}C{-}CH_3 \xrightarrow[\text{2. }Me_3SiCl]{\text{1. 6 equiv. n-BuLi}} MeC{\equiv}C{-}\underset{SiMe_3}{C}{=}C{=}C(SiMe_3)_2 \qquad (100)$$

A synthesis of (±)-undeca-5,6-diene-8,10-diyn-1-ol has been recorded (equation 101) [185]. Novel features of this synthesis were an allenic bromide/butadiynyl(trimethyl)silane coupling reaction and the ring opening reaction of 2-hydroxypyran by lithium acetylide.



(101)

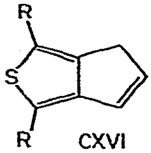
Mg and Li derivatives of phenylacetylene and vinylacetylene were treated with Me_3SiCl and Me_3SiF to afford the expected mono trimethylsilyl derivatives [186].

Ferrocenylacetylene was lithiated and reacted with Et_3SiCl and Et_2SiCl_2 to give $FcC{\equiv}CSiEt_3$ and $(FcC{\equiv}C)_2SiEt_2$, respectively [187].

V. Heterocycles

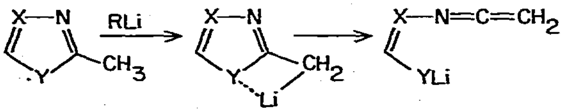
Lithiation of *tert*-butyl-3-thienyl sulfone afforded mainly the 2,4-dilithio intermediate [188]. This was in contrast to the behavior of *tert*-butyl phenyl sulfone which formed benzyne under these conditions.

4H-Cyclopenta[c]thiophene (CXVIa,R=H) and its 1,3-dichloro derivative (CXVIb, R=Cl) have been metalated with n-butyllithium [189]. Analysis of carboxylic acids produced by carbonation of the lithio intermediate(s) showed that CXVIa was metalated 70% at the allylic position and 30% at the two thiophene positions. The dichloro compound (CXVIb) was metalated exclusively at the allylic position. HMO calculation of bond orders and charge distribution for the allylic lithio intermediate, a formal Hückel 10-π-electron system, were provided.



CXVI

Upon treatment with organolithium reagents thiazoles (Y=S), 1,3,4-thiadiazoles (X=N; Y=S) and 1,3,4-oxadiazoles (X=N; Y=O) all rearranged to the ketenimine structure which could be isolated in a dimer form (equation 102) [190].

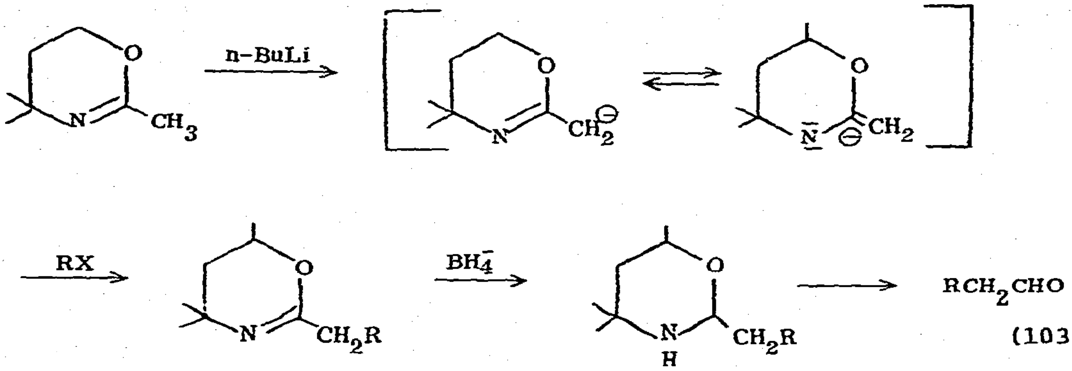


X=N
Y=S,O

(102)

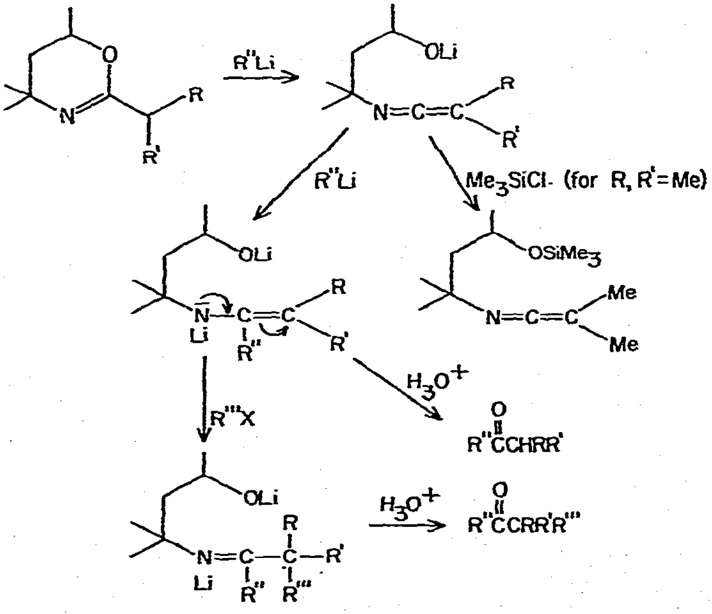
Syntheses *via* alkylations of dihydro -1,3- oxazines and 2-oxazolines has been extensively studied during 1973. A review of this area has been published [191].

The use of dihydro-1,3-oxazines in the synthesis of substituted acetaldehydes has been reported (equation 103) [192]. The scheme amounts to an aldehyde equivalent to the malonic ester synthesis.



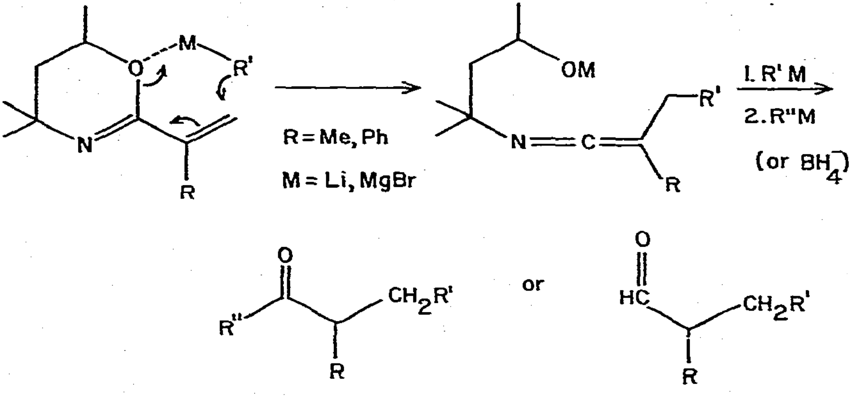
(103)

Starting with 2-isoalkyloxazines, a series of highly substituted ketones could be prepared by treatment with organolithium reagents and alkylation (equation 104) [193]. The presence of a ketone intermediate was varified by isolation of its trimethylsilyl derivative. Essentially the same results have been reported by Lion and Dubois [194].



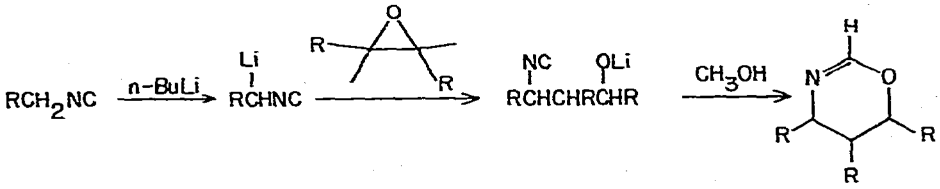
(104)

1,4-Addition of organolithium and Grignard reagents to 2-alkenyloxazines has lead to a synthetic route to α-substituted aldehydes and ketones (equation 105) [195].



(105)

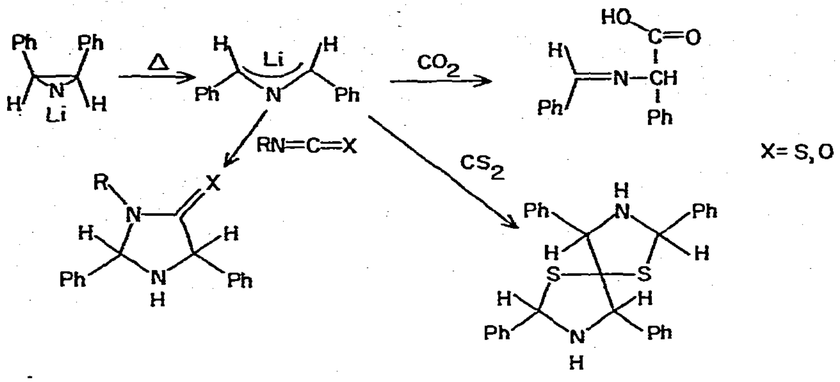
α-Metalation of isocyanides followed by treatment with an epoxide has provided a method for the synthesis of 5,6-dihydro-4H-1,3-oxazines (equation 106) [196].



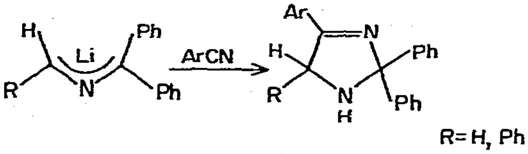
(106)

Anionic cycloaddition reactions have been utilized in the synthesis of heterocycles, trans, trans-1,3-diphenyl-2-azaallyllithium, formed by thermal ring cleavage of N-lithio-2,3-diphenylaziridine, has been observed to undergo cycloaddition reactions with CO_2, CS_2, RN=C=X (X=S,O) and $C_6H_{11}N{=}C{=}NC_6H_{11}$ to produce a variety of heterocyclic derivatives (equation 107) [197].

Cycloaddition of 1,3-azaallyllithium compounds to nitriles has been found to yield 3-imidazolines or, in some cases, imidazoles (equations 108 and 109) [198].



(107



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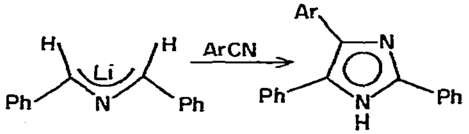
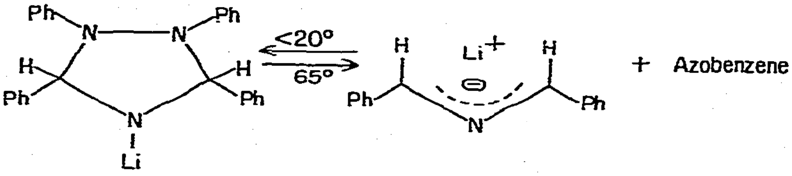


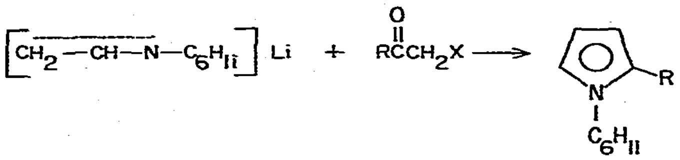
(109)

The reversibility of the cycloaddition reaction shown in equation 110 has been demonstrated. Similar reversibility in the pyrrolidine and pyrazolidine systems were also reported [19



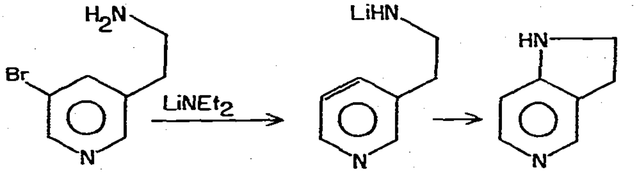
(11

A series of α-haloketones have been reacted with lithiated Schiff bases to afford pyrrole derivatives (equation 111) [200].



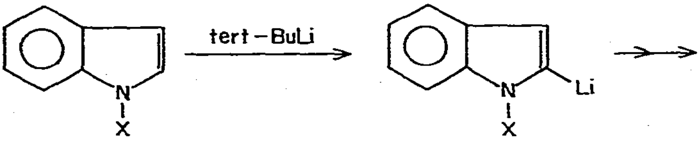
(11

3-(2-Aminoethyl)- (equation 112) and 3-benzoylamino-5-bromopyridine when treated with lithium amides in inert solvents underwent intramolecular cyclization via the respective heteroaryne intermediates [201].



(112)

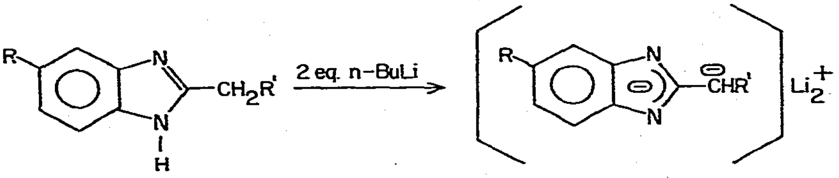
The benzenesulfonyl and methoxymethyl moieties served as N-protecting groups for the lithiation of indole in the 2-position (equation 113) [202]. Reaction of this intermediate with aldehydes, ketones, acid chlorides, esters and nitriles was accomplished. The benzenesulfonyl protecting group was conveniently removed by mild alkaline hydrolysis.



(113)

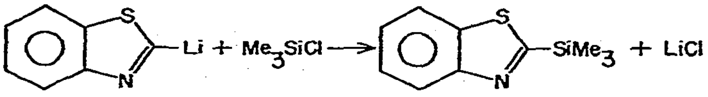
$X = PhSO_2-,\ MeOCH_2-$

Formation of the dilithio derivatives of benzimidazoles allowed reaction with alkyl halides, aldehydes and ketones selectively at the side-chain carbanion site (equation 114) [203].



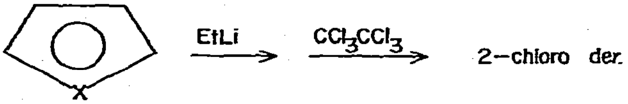
(114)

2-Benzothiazolyl(trimethyl)silane (CXVIII) and a series of di(2-benzothiazolyl)silanes have been prepared by metalation of benzothiazole with n-butyllithium to form the 2-lithiated intermediate CXVII followed by reaction with the appropriate silane. The silicon-carbon bond in these systems was found to be very reactive [204].

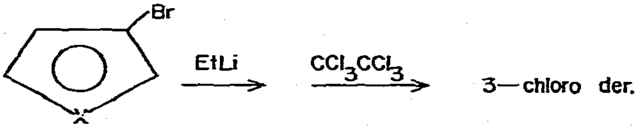


CXVII CXVIII

The preferred route to 2- and 3-chloro furan and selenophene was found to be by reaction of the corresponding lithio derivative with hexachloroethane (equation 115 and 116) [205].

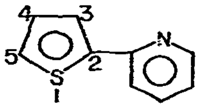


X=O, Se (115)



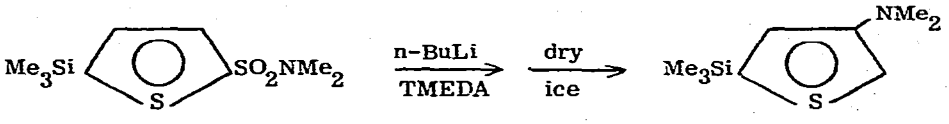
X= O, Se (116)

Metalation of thiophene derivatives has provided some interesting results in 1973. 2-(2'-Thienyl)-pyridine (CXIX) has been observed to undergo metalation not only at the 5-position, but also at the 3-position as determined by derivatization of the mixture of these organolithium intermediates with trimethylchlorosilane [206]. 2-(2'-Thienyl)-quinoline and a pyrimidine derivative of CXIX were also found to exhibit this metalation pattern.



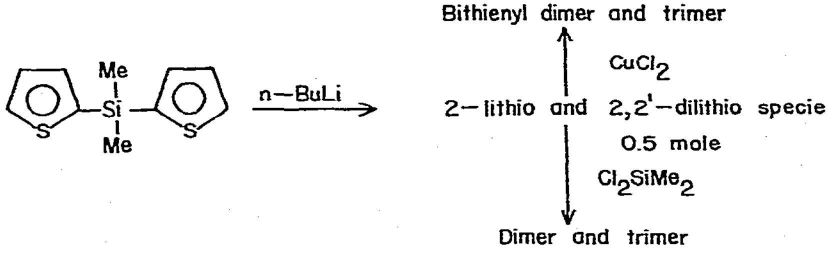
CXIX

Dithiation of 5-trimethylsilyl-2-N,N-dimethylthiophenesulfonamide (CXX) afforded 3-metalation and, in one instance, spontaneous loss of the trimethylsilyl group [207]. When n-butyllithium/ TMEDA reagent was used a rearrangement to produce the amine CXXI was discovered.

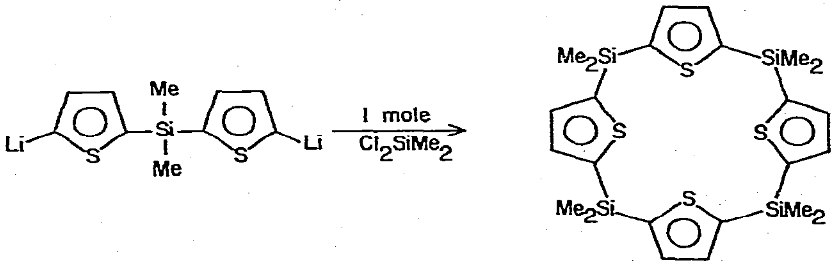


CXX CXXI

Dimethyl-di(2-thienyl)silane was metalated with n-butyllithium to afford a mixture of the 2-lithio- and 2,2'-dilithio intermediates (equation 117) [208]. These were 1) coupled with $CuCl_2$, 2) di- and trimerized with 0.5 mole Cl_2SiMe_2 and 3) transformed into a cyclic dimer with 1.0 mole Cl_2SiMe_2 (equation 118). Nucleophilic substitution of four fluorines on hexafluorobenzene by trichloro-2-thienyllithium in THF has been observed [209]. Tetrakis(trichloro-2-thienyl)difluorobenzene was obtained in good yield. Data to support a contention that the remaining fluorines were para to each other was included.

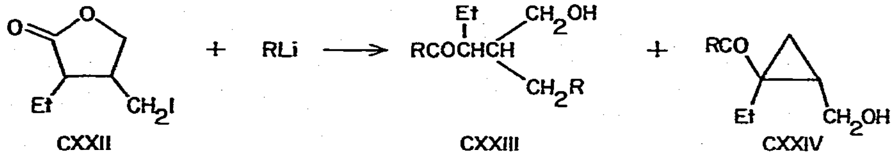


(117)

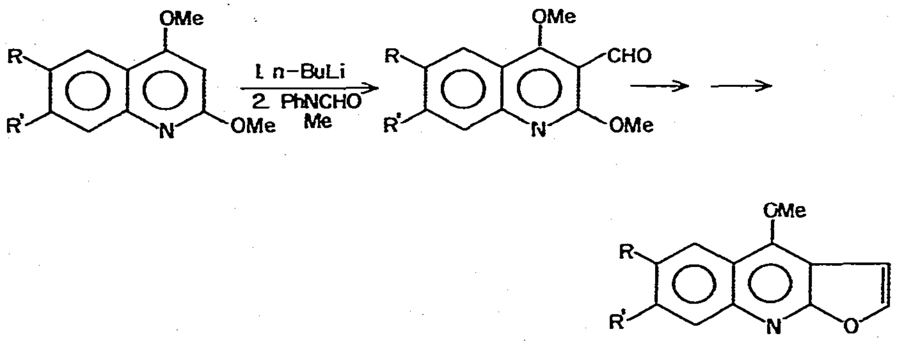


(118)

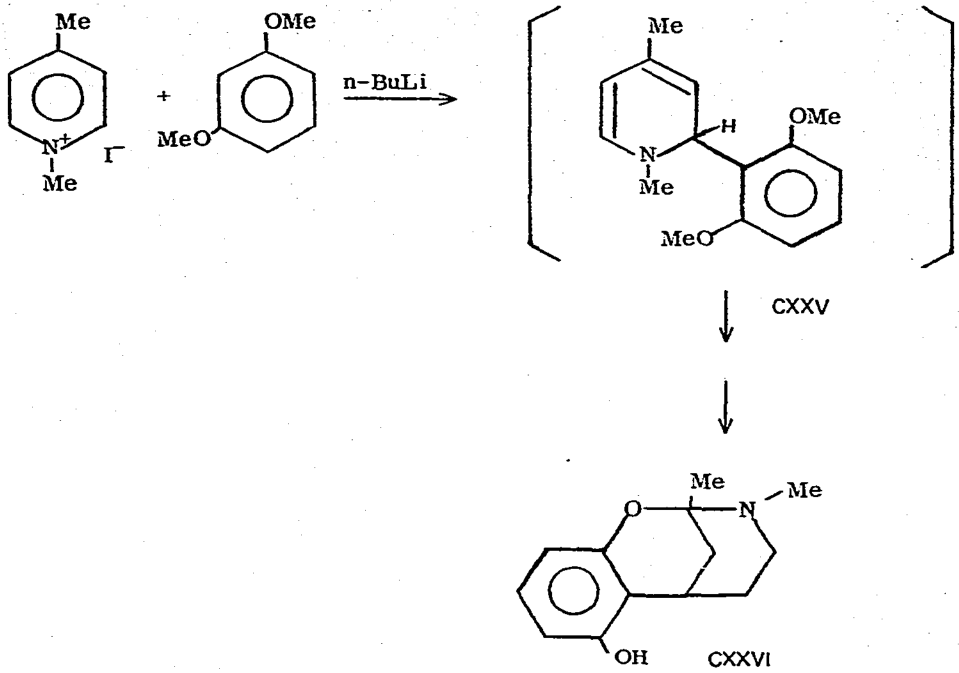
RLi(R = 5-chloro-1-methyl-2-imidazolyl) in ether was added to the lactone CXXII with the ring-opened product CXXIII being isolated after hydrolysis [210]. Cyclopropane CXXIV was a by-product.


CXXII CXXIII CXXIV

A new synthesis involving directed metalation of a 2,4-dimethoxyquinoline system of the furoquinoline alkaloids, dicatamine(R,R' = H), pteleine(R = OMe,R' = H) and evolitrine (R = H, R' = OMe) has been developed [211]. The method was extended to the synthesis of a b-naphthofuran (equation 119), b-naphthocoumarin and oxaphenalene.


(119)

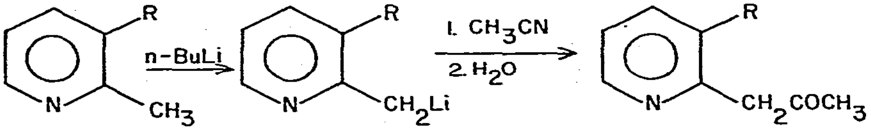
Directed metalation of 1,3-dimethoxybenzene produced the 2-lithio intermediate which, after treatment with 1,4-dimethylpyridinium iodide, afforded a high yield of the crude 1,2-dihydropyridine derivative CXXV [212]. Subsequent reactions in this series culminated in the synthesis of derivatives of 1,5-benzoxazocine and its 1,3-isomer CXXVI.



CXXV

CXXVI

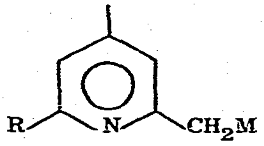
A series of (3-substituted-2-pyridyl)-2-propanones was synthesized by lithiation of the appropriate 3-substituted 2-picoline with n-butyllithium followed by acylation with acetonitrile (equation 120) [213].



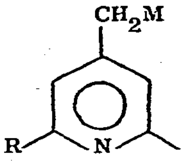
(120)

R = OMe, OEt, $OCHMe_2$, Me

2,4-Lutidine, 2,4,6-collidine and 2,4-dimethylquinoline gave exclusive metalation at the 2-methyl group (CXXVII) with n-butyllithium. On the other hand, with alkali amides in liquid NH_3 or $LiN(i\text{-}Pr)_2$, only metalation at the 4-methyl position (CXXVIII) was observed [214].



CXXVII



CXXVIII

VI. Addition Reactions of Olefins, Carbonyl Compounds and Similar Substrates.

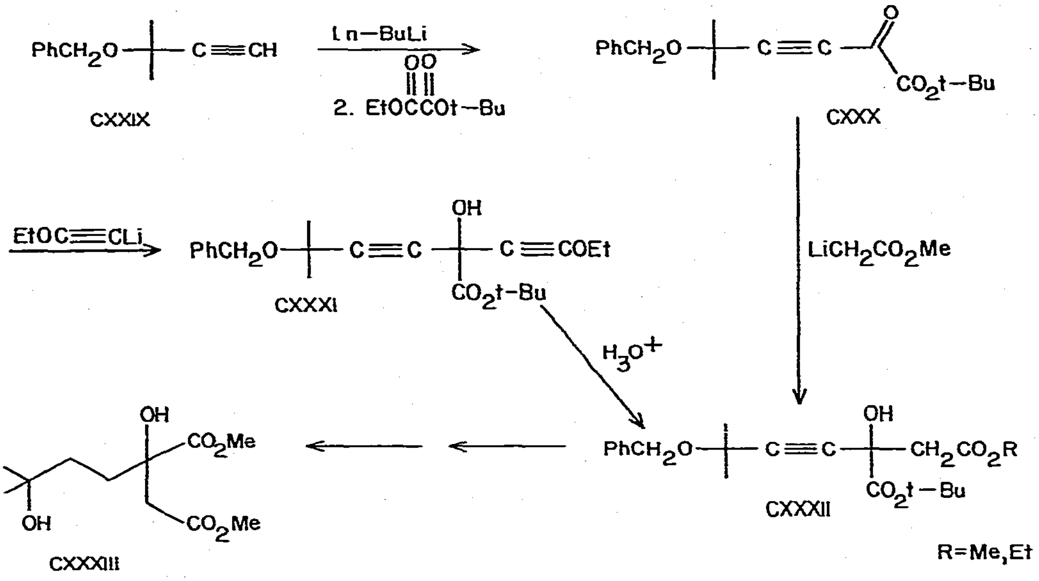
A review article on the addition of alkali metal reagents to unsaturated systems has been published [215].

A study of the reactivity of propynyllithium and propynylsodium in aprotic solvents has resulted in the delineation of conditions that allow a high yield of products to be obtained [216]. A maximum yield (91%) of 1-(1-propynyl) cyclohexanol was obtained from the lithio intermediate and cyclohexanone while the maximum yield (87%) of 2-butynoic acid was obtained from the sodio intermediate and carbon dioxide.

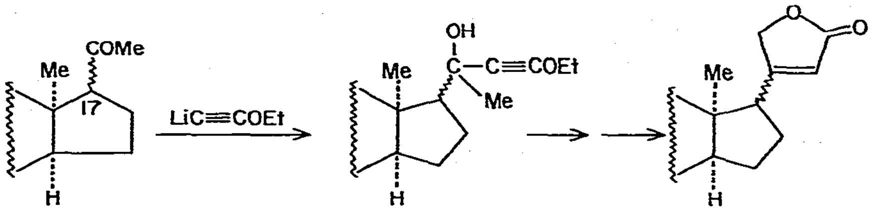
The addition reaction of alkyllithium reagents with aldehydes and ketones was examined in detail [217]. Optimum conditions involved addition of the carbonyl compound to the organolithium species at -78°. Only small losses in yield due to enolization and reduction pathways were discerned for any of the systems. An improved synthesis of carboxamides from addition of organolithium compounds to isocyanates derived from the Curtius reaction has been reported [218].

Addition of excess tert-butylethyloxalate to the lithium salt of the acetylene derivative CXXIX gave the keto ester CXXX which, when reacted with lithium ethoxyacetylide, afforded CXXXI. This compound could be hydrolyzed to the diester CXXXII but this ester could also be prepared directly from keto ester

CXXX by treatment with α-lithio methylacetate. These compounds were found useful in a regiospecific synthesis of the acyl portion of harringtonine CXXXIII [219].

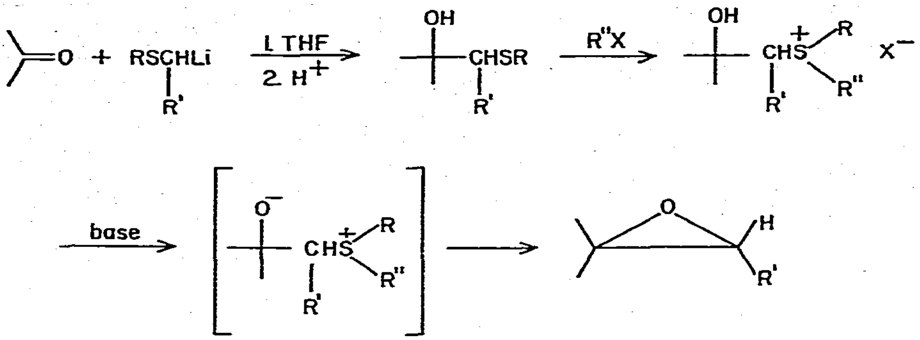


Synthesis of C-17 epimeric 5α, 13α-cardenolides was accomplished by means of the route shown (equation 121) [220].



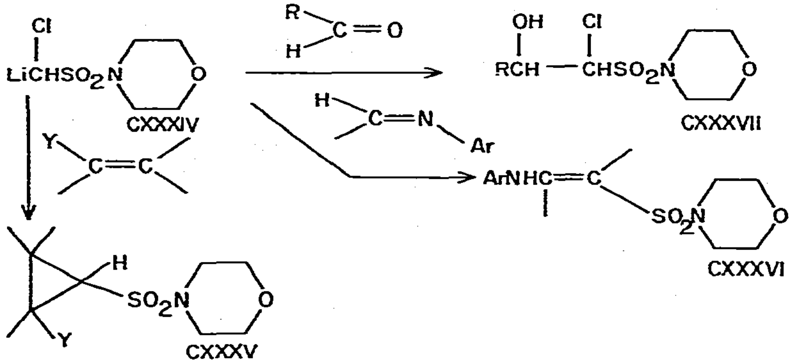
(121)

Treatment of ketones with RSCHR'Li afforded 41 - 100% yields of β-hydroxy sulfides. Alkylation of these sulfides with MeI or $Me_3O^+BF_4^-$ gave the corresponding oxiranes in from 43 to 98% yields (equation 122) [221]. It is advantageous to use this reagent for reaction with highly enolizable and sterically hindered ketones.

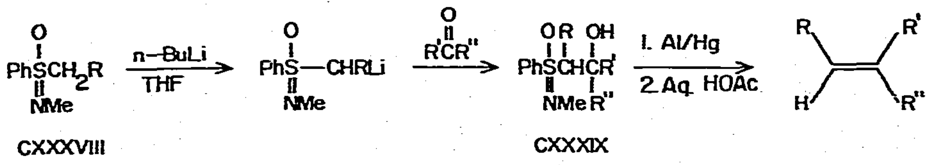


(122

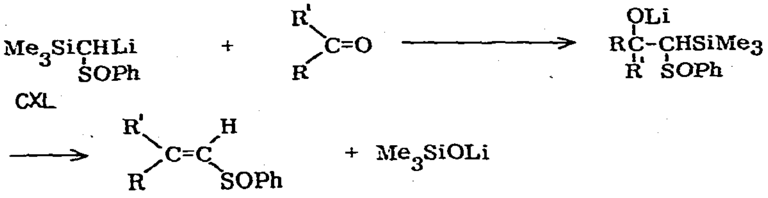
α-Lithiochloromethanesulfonomorpholide (CXXXIV) reacted with CC, CN and CO unsaturated linkages to afford the corresponding cyclopropane (CXXXV), enamine (CXXXVI) and hydroxy derivatives (CXXXVII), respectively [222].



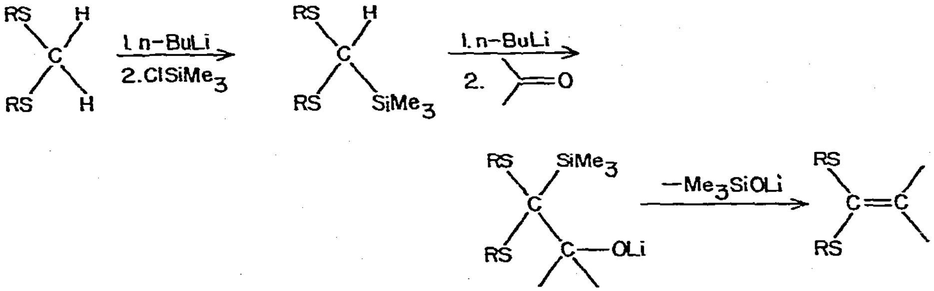
Sulfoximines CXXXVIII (R = H, Me, Pr) have been α-lithiated with n-butyllithium and the lithio intermediate condensed with aldehydes and ketones. Treatment of the resulting β-hydroxysulfoximines CXXXIX with aluminum amalgam followed by aqueous acetic acid provided reductive elimination [223]. A series of 16 olefins was prepared by this technique.



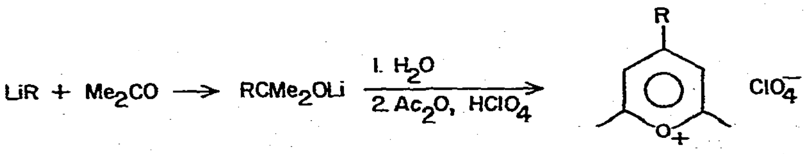
Condensation of the α-lithiosulfoxide intermediate CXL with various carbonyl compounds such as acrolein, adamantanone, benzaldehyde, benzophenone, cinnamaldehyde, cyclohexanone and isobutyraldehyde gave good yields of the corresponding vinylsulfoxides [224].


CXL

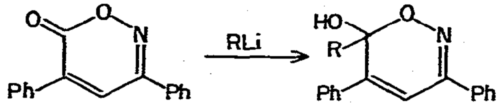
Ketone thioacetals can be prepared in high yield by the reaction of aldehydes, ketones and formamides of secondary amines with 2-lithio-2-(trimethylsilyl)-1,3-dithiane and related intermediates (equation 123) [225].


(123)

Condensation of LiR(R = 2-benzothiazolyl and 2-thienyl) with acetone followed by hydrolysis and dissolution in acetic anhydride/perchloric acid afforded 4-substituted 2,6-dimethylpyrylium perchlorates (equation 124) [226]. These were converted into the corresponding pyridines <u>via</u> treatment with ammonia.

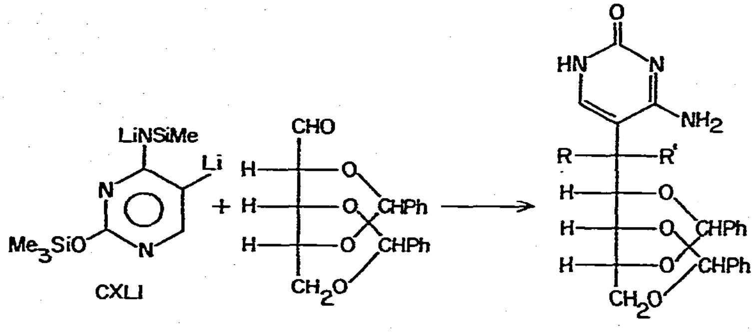

(124)

A series of aryloxazinols (R = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, p-$EtOC_6H_4$, p-BrC_6H_4, m-MeC_6H_4) has been prepared by the addition of RLi to the parent oxazinone (equation 125) [227].



(125)

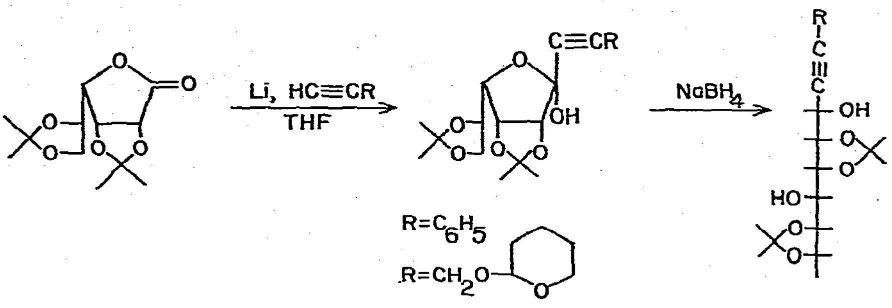
Dilithio cytosine derivative CXLI was condensed with 2,4: 3,5-di-O-benzylidene-D-ribose to give a mixture of the pentitols CXLIIa (R = H, R' = OH) and CXLIIb (R = OH, R' = H) [228]. Acid hydrolysis provided a mixture of 4-amino-2-hydroxy-5-(β-and α-D-ribofuranosyl)pyrimidines.



CXLII

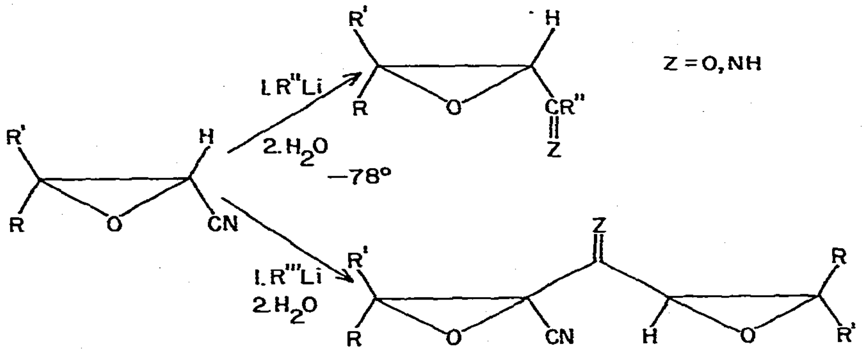
2,3-O-isopropylidene-D-ribonolactone with lithium and PhC≡CH in THF gave a 32% yield of the 1-phenylethynyl derivative CXLIII [229]. Reduction with $NaBH_4$ provided the acyclic heptyne CXLIV. Similarly, 1-octyne-L-glycero-L-talo-3,4,5,6,7,8-hexol derivatives were prepared. Benzothiazole or 1-benzylbenzimidazole upon treatment with lithium in THF afforded 40% 2,2'-bibenzothiazole and 45% 1,1-dibenzyl-2,2'-bibenzimidazole, respectively.

Epoxynitriles upon reaction with organolithium reagents afforded a series of products resulting from addition to the nitrile function (equation 126) [230]. Dimerization of the epoxynitriles was found to compete effectively with addition



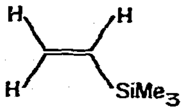
CXLIII CXLIV

in several cases and was attributed to the relative basicities of the organolithium reagents. The weaker bases, MeLi, PhLi, $LiCH_2CN$ and $LiCH_2CO_2Et$ promoted addition while the stronger bases, n-BuLi, $LiCH_2Cl$, $LiCHCl_2$ and $LiCH{=}CH_2$ provided dimerization.

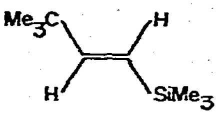


(126)

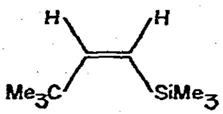
Treatment of vinyltrimethylsilane (CXLV) with <u>tert</u>-butyllithium/TMEDA afforded only addition of the <u>tert</u>-butyllithium reagent to the double bond while similar treatment of the <u>trans</u> isomer CXLVI caused metalation exclusively at the silylmethyl group. Under these same conditions, the <u>cis</u> isomer CXLVII gave a mixture of α-silylvinyl proton and silyl methyl group metalation [231].



CXLV



CXLVI

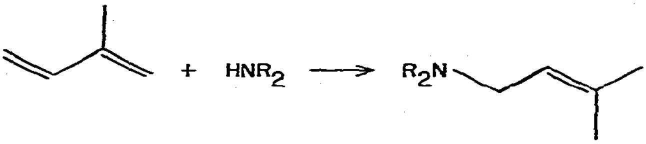


CXLVII

A series of allene amines, $RCH_2CH{=}C{=}CHCH_2NEt_2$ (where R = Et, n-Pr, Me_2CH) have been prepared by the addition of RLi or RCaI to $CH_2{=}CHC{\equiv}CCH_2NEt_2$ [232]. Combining the allyl organometallic agent CXLVIII with aldimines (R = Me, Ph; R' = Me, Me_2CH, Me_3C) afforded reversible 1,2-additon and some 1,4-addition (M = ZnBr, MgBr) [233]. 1,4-Addition was not preferred for these organometallics but was the exclusive pathway when M = Li.

$$RCH{=}CHCH{=}NR' + \underset{\text{CXLVIII}}{EtCH{=}CHCH_2M} \longrightarrow \text{1,2- and 1,4- addition}$$

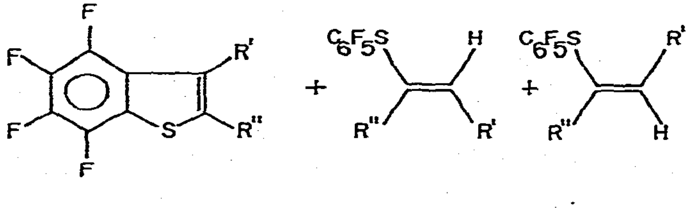
Alkali naphthalenides (alkali = Li, Na, K) in THF have been reported to effect addition of amines to conjugated olefins (equation 127) [234].



(127

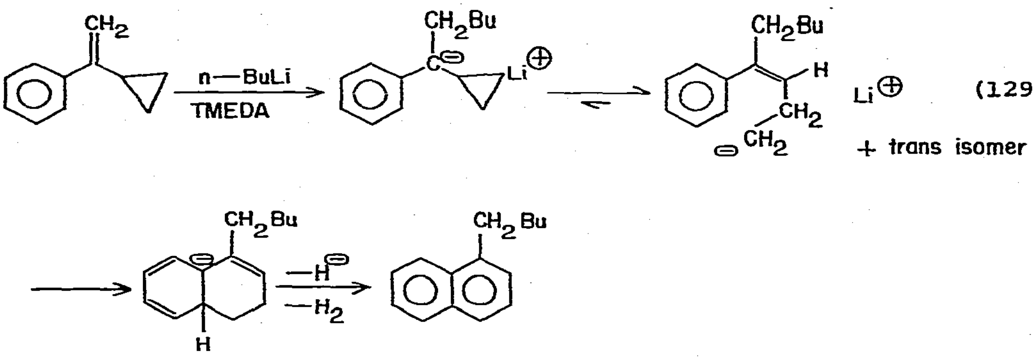
Lithium pentafluorobenzenethiolate was added to various acetylenic compounds to give benzo[b]thiophene derivatives and/or olefins (equation 128) [235].

$$C_6F_5S^-Li^+ + R'C{\equiv}CR'' \longrightarrow$$



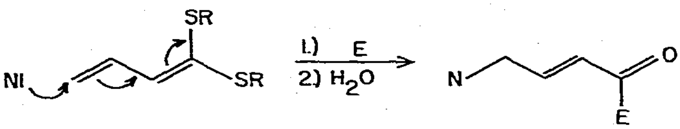
(128)

n-Butyllithium in the presence of TMEDA has been observed to add to α-cyclopropylstyrene to form a cyclopropylcarbinyllithium derivative which undergoes a ring-opening-cyclization-oxidation sequence to give 1-pentylnaphthalene (equation 129) [236].



(129)

A process which allows a Michael-type addition reaction to a four-carbon unsaturated system has been described (equation 130) [237]. The necessary thioacetals can be prepared from 2-lithio-2-(trimethylsilyl)-1,3-dithiane.

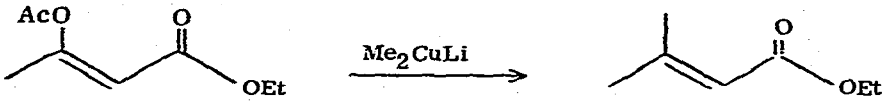


(130)

VII. Copper-Lithium Reagents and Their Reactions

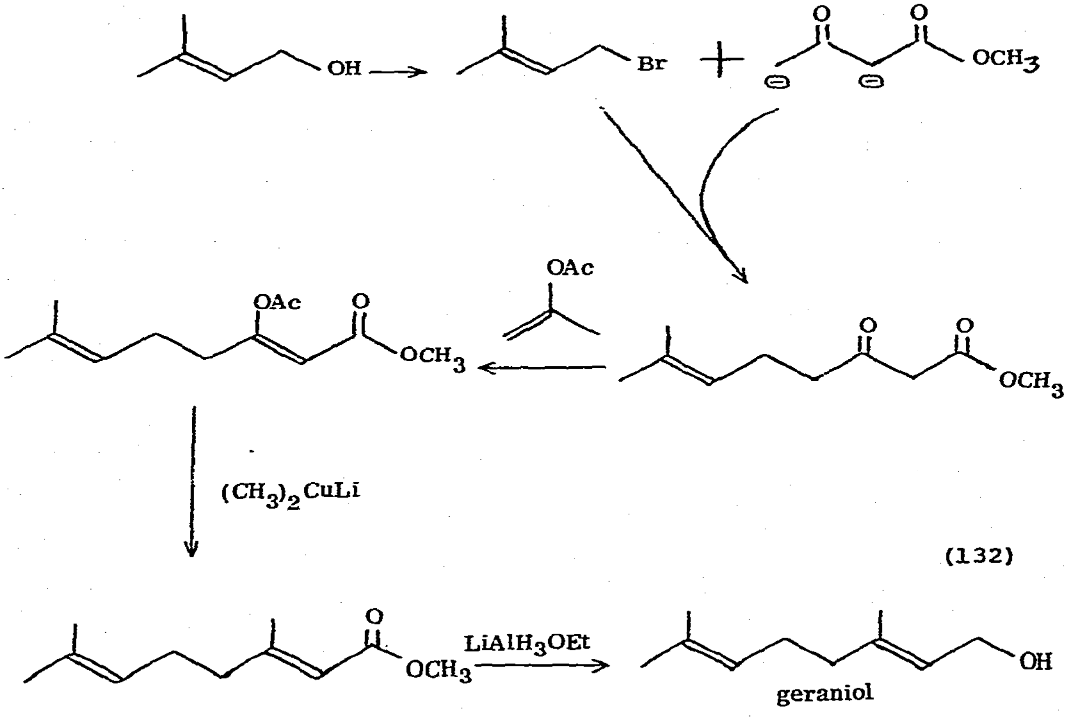
Five new alkylhetero-and arylhetero (alkyl) cuprate(I) reagents, Het(R)CuLi, where Het = t-BuO, PhO, t- BuS, PhS and Et_2N have been prepared [238]. These reagents allow selective alkyl transfer to acid chlorides, α,α-dibromo ketones, alkyl halides and α,β-ethylenic ketones.

Replacement of a β-acetoxy group in a series of α,β-unsaturatec carbonyl compounds using Me_2CuLi has been reported (equation 131) [239].



(131

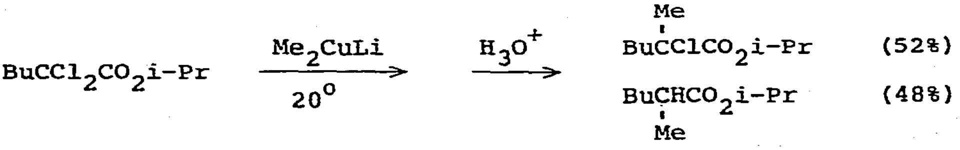
This reaction of lithium dialkylcuprates with β-acetoxy-α,β-unsaturated esters which provides stereoselective synthesis of β-alkyl-α,β-unsaturated esters was successfully utilized in a 5-step synthesis of geraniol (equation 132) [240].



(132)

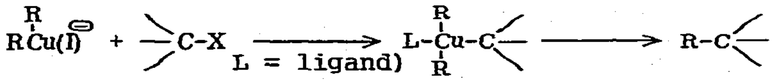
Primary tosylates combined with a wide variety of lithium diorganocuprates (I) to afford substitution products in 70-100% yields [241]. 2-Octyl tosylate reacted with Me_2CuLi to give an 87% yield of 2-methyloctane but other secondary tosylates gave lower yields of the coupling product because of competition by an E_2 process. The coupling reaction of such tosylates was found to proceed at a significantly lower temperature than the analogous couplings with alkyl bromides; in addition the tosylate couplings were noted to proceed faster in ether than in THF. Coupling reactions of difunctional substrates where both functional groups could compete for reagent were examined; preferential reaction at the tosylate of a keto tosylate, some selectivity at the tosylate of a bromo tosylate and little selectivity in an epoxy tosylate were observed.

α,α-Dichloro esters when treated with lithium dimethyl cuprate afforded a mixture of α-chloro-α-methyl ester and the reduced α-methyl ester (equation 133) [242]. At -70° α-chloro ester enolates were produced which upon warming to 20° gave α-methyl ester enolates.



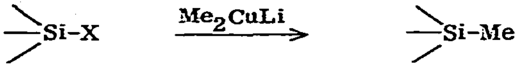
$$\mathrm{BuCCl_2CO_2i\text{-}Pr} \xrightarrow[20^{\circ}]{\mathrm{Me_2CuLi}} \xrightarrow{\mathrm{H_3O^+}} \begin{array}{ll} \mathrm{Bu}\overset{\mathrm{Me}}{\mathrm{C}}\mathrm{ClCO_2i\text{-}Pr} & (52\%) \\ \mathrm{Bu}\underset{\mathrm{Me}}{\mathrm{C}}\mathrm{HCO_2i\text{-}Pr} & (48\%) \end{array} \qquad (133)$$

(+)-(S)-2-Butyl tosylate or mesylate, when treated with Ph_2CuLi in ether, afforded (-)-(R)-2-phenylbutane of such rotation as to indicate 100% inversion of configuration (equation 134) [243]. Likewise the reaction of Me_2CuLi with <u>cis</u> and <u>trans</u> -4-<u>tert</u>-butylcyclohexyl tosylate and with <u>endo</u>-2-norbornyl tosylate also afforded complete inversion but with varying amounts of elimination. With <u>exo</u>-2-norbornyl tosylate considerable loss of stereospecificity was discovered. A second-order rate constant of $2.8 \cdot 10^{-3}$ ℓ/mol.sec. was determined for the reaction of n-octyl tosylate with Me_2CuLi in ether at -42°. It was concluded that these transformations proceed by an "Sn2-like" mechanism and that a triorgano Cu(III) intermediate was likely involved.



(134)

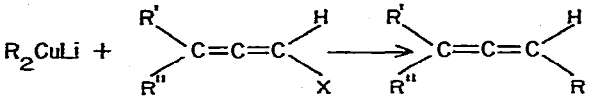
Displacement of a series of substituents from mono- and difunctional silanes has been effected with Me_2CuLi. When the silicon atom was asymmetric, displacement took place with retention of configuration (equation 135) [244].



(135)

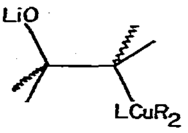
X = H, OMe, F, Cl, OMenthyl

Dialkylcopper lithium reagents at low temperatures can be used to replace a halogen on an allene to produce the alkylated allene (equation 136) [245].



(136)

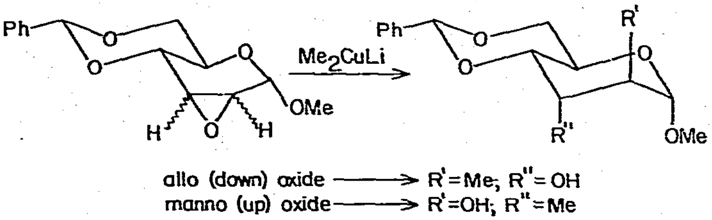
trans-Nucleophilic ring opening of oxiranes can be effectivel accomplished by lithium diorganocuprates [246]. A triorganocopper (III) intermediate CXLIX was discussed. Correspondence was noted on the concept of hard and soft acids and bases with the selectivit of lithium diorganocuprates in reactions containing epoxide and other electrophilic sites.



CXLIX

Epoxides with neighboring oxygen functions (HO, MeO, AcO, EtO_2C) were found to exhibit little regiospecificity in their ring-opening reactions with lithium dimethylcuprate [247].

A stereospecific ring opening cleavage of an oxirane in carbohydrates which utilized Me_2CuLi has been reported (equation 137) [248].

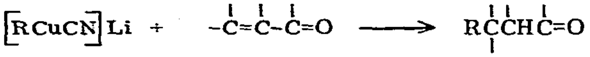


(137)

An unsymmetrical lithium cuprate reagent has been prepared which offers the advantage of utilizing only one equivalent of RLi in its preparation (equation 138) [249]. This reagent has been examined in both substitution and conjugate addition reactions (equations 139 and 140).

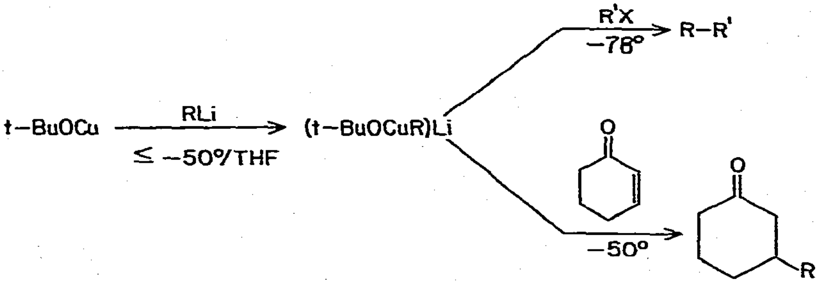
$$\mathrm{CuCN} + \mathrm{RLi} \longrightarrow [\mathrm{RCuCN}]\mathrm{Li} \tag{138}$$

$$[\mathrm{RCuCN}]\mathrm{Li} + \mathrm{R'Br} \longrightarrow \mathrm{R{-}R'} + \mathrm{CuCN} + \mathrm{LiBr} \tag{139}$$



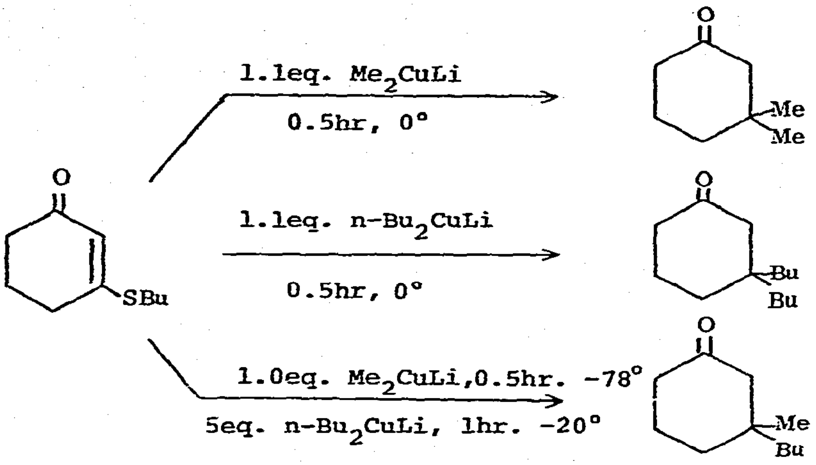
$$[\mathrm{RCuCN}]\mathrm{Li} + -\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}{-}\overset{|}{\mathrm{C}}{=}\mathrm{O} \longrightarrow \mathrm{R}\underset{|}{\overset{|}{\mathrm{C}}}\overset{|}{\mathrm{C}}\mathrm{H}\overset{|}{\mathrm{C}}{=}\mathrm{O} \tag{140}$$

A new copper lithium reagent, (t-BuOCuR)Li, has been found quite effective in substitution and conjugate addition reactions (equation 141) [250]. This is important in that much lower excesses of this reagent as compared to other such reagents were sufficient for high conversion. Also important was the fact that R in (t-BuOCuR)Li could be a secondary or tertiary alkyl group.



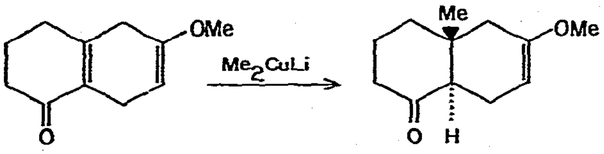
(141)

Conversion of β-alkoxy and β-alkylthio α,β-unsaturated carbonyl compounds into their respective β-alkyl and β,β-dialkyl derivativ has been observed (equation 142) [251].



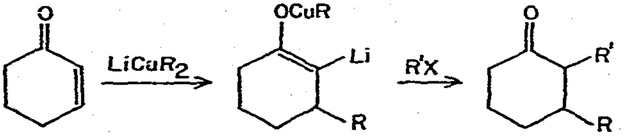
(142

Addition of a methyl group to the α,β-ethylenic ketone system in bicyclic ketone CL was observed to take place stereospecifically in 50% yield to give the <u>trans</u> decalin compound CLI [252]



CL CLI

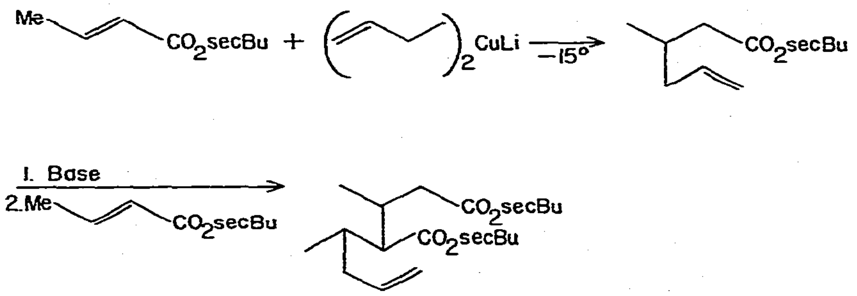
Unhindered intermediate enolates may be alkylated regiospecifically at the α-carbon (equation 143) [253]. These enolates can be formed by conjugate addition of a lithium organocuprate reagent to an α,β-unsaturated carbonyl system. When the β-position was already substituted, various amounts of equilibration of the α-positions was observed.



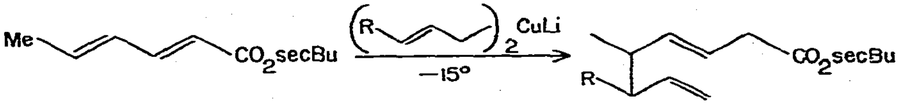
(143)

Preparation of allyllithium reagents was accomplished by means of the technique illustrated in equation 144, followed by preparation of the copper lithium reagent. Addition of the allyl cuprate to sec-butyl crotonate gave a mixture of mono and di conjugate addition product (equation 145). Reaction of such reagents with sec-butyl sorbate produced 1,6-addition product (equation 146). Similarly, only 1,6-addition of the allylcuprate reagent was observed with N,N-diethylsorbamide [254].

$$\mathrm{RCH{=}CHCH_2OPh + 2Li \xrightarrow[-10^{\circ}]{THF} RCH{=}CHCH_2Li + PhOLi} \qquad (144)$$



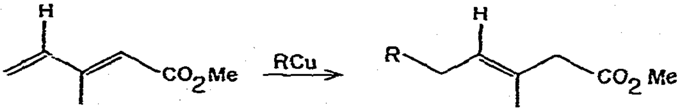
(145)



(146)

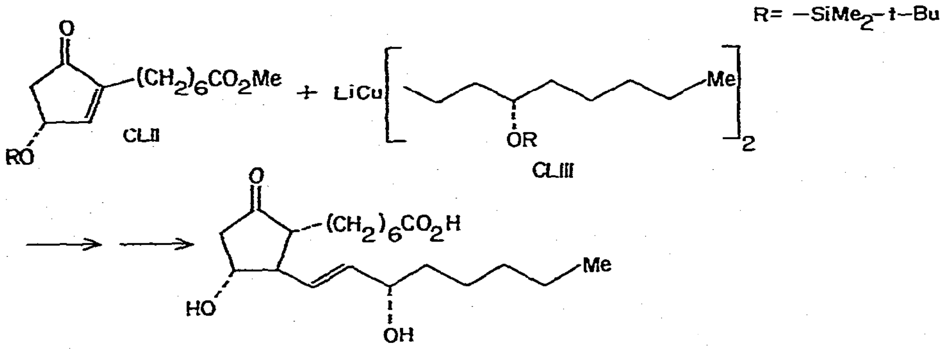
Methyl crotonate, methyl cinnamate, benzalacetone, benzalacetophenone, 2-methoxy-3,5,5-trimethyl-2-cyclohexenone and 4-tert-butyl-1-cyclohexenyl methyl ketone have each undergone a successful conjugate addition with lithium dimethylcuprate [255]. For the cyclohexenyl compound, 92% of the additon product was found in the axial position. $[\mathrm{Me_3CC{\equiv}CCuR}]\mathrm{Li}$ (R is Me or vinyl), a new mixed organocuprate reagent, has been described.

A stereoselective addition (>95% purity) of RCu (R is n-butyl or vinyl) to $\Delta^{2,4}$-dienoic esters that is useful in the preparation of tri- and tetra- substituted olefins has been reported (equation 147). In contrast, the corresponding R_2CuLi reagent did not give stereoselective addition [256].

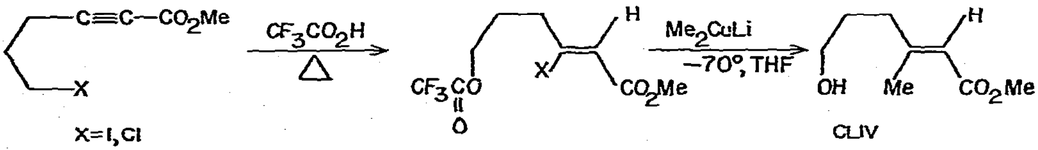


(147)

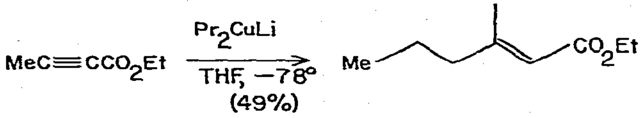
Synthesis of Prostaglandin E_1 by a stereospecific synthesis has been accomplished with one of the key steps being the joining of the cyclic ester CLII and the organocuprate reagent CLIII [257].



Investigation of routes to afford specifically substituted trans olefins has led to utilization of a 1,4-halogen shift to a triple bond followed by treatment with Me_2CuLi [258]. This has yielded the trans olefin CLIV with a stereoselectivity of about 95%.

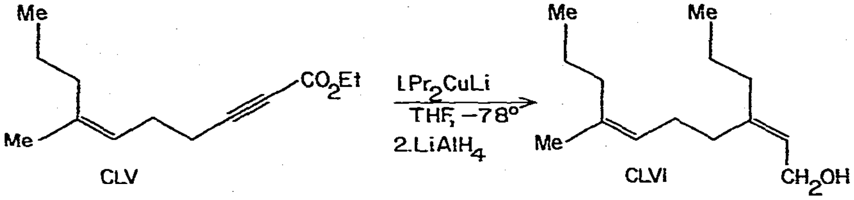


Two separate examples of conjugate addition to an α,β-acetylenic carboxylate were utilized in the six-step synthesis of (2Z,6E)-7-methyl-3-propyl-2,6-decadien-1-ol of which the following (equation 148) is the first step [259]. This material was not identical to the terpenoid alcohol, believed to be a sex pheromone, isolated from the codling moth, although this had been the proposed structure.

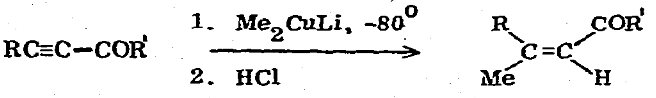


(148)

The natural material CLVI (2Z, 6Z configuration), purportedly a pheromone, isolated from the codling moth, as well as the 2E, 6Z; 2Z, 6E and 2E, 6E configurations have been synthesized [260]. Routes to these substances started with ester CLV or its 6Z isomer and involved the stereospecific addition of or coupling with Pr_2CuLi.



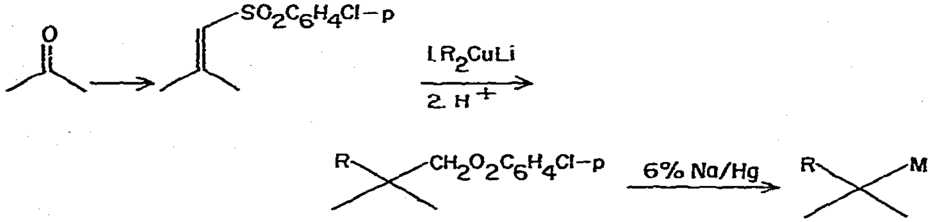
Treatment of α,β-acetylenic carbonyl compounds with Me_2CuLi at −80° afforded products derived from stereospecific cis-addition to the alkyne feature (equation 149) [261]. Allowing the solution to reach room temperature before hydrolysis resulted in virtually complete isomerization to the trans isomer. These observations were interpreted in terms of an sp^2 carbon-copper bond which retained its sterochemistry at −80°, but isomerized to the trans isomer at room temperature. Addition of methyllithium to either the −80° or the room temperature solution before treatment with HCl brought an addition product with complete loss of stereospecificity, i.e., a 50-50 cis-trans mixture. It was concluded that the lithium derivatives formed by this procedure possess an sp hybridized α-carbon.



R	R'
Ph	OMe
Ph	OH
Ph	Me
Me	OMe

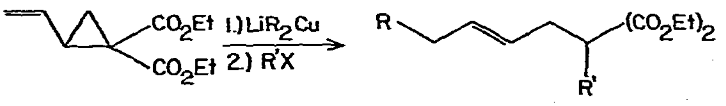
(149)

A reaction sequence has been described that permits conversio of aldehyde carbonyls to tertiary carbon atoms where the three alkyl groups may be different and certain ketone carbonyl groups to quaternary carbon atoms (equation 150) [262, 263]. The essential features involve addition of a lithium organo copper reagent to the β-carbon of an alkenyl aryl sulfone followed by hydrogenolysis with sodium amalgam. Other types of saturated sulfur compounds were found to be unsatisfactory for this procedure

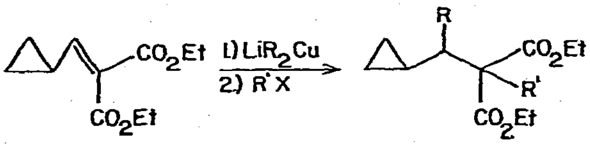


(150)

LiCuR$_2$ (R is Me or Bu) specifically added 1,7 to the vinyl cyclopropane system (equation 151) [264]. In contrast, the isomeric cyclopropylvinyl system underwent 1,4-addition (equation 152). α-Alkylation of those systems was accomplished by treating the α-lithio intermediates with an alkyl halide (R'X).

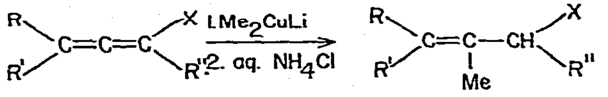


(151)



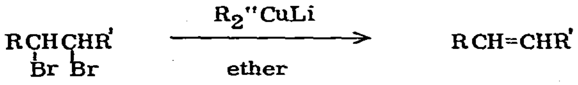
(152)

Me_2CuLi added to the heteroatom-substituted double bond in allenes (X = aryl sulfoxide or sulfone) to give, presumably, the sulfoxide- or sulfone- stabilized carbanionic intermediate. This intermediate could be derivatized with methyl iodide and chalcone (equation 153) [265].



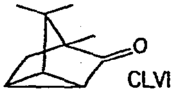
(153)

Organocuprate(I) reagents and organolithium reagents have been used for the reductive elimination of bromine from 1,2-dibromoalkanes (equation 154) [266]. A notable elimination of the bromine from a bromoester [R = H; R' = $(CH_2)_8CO_2Me$] was accomplished using n-Bu_2CuLi.



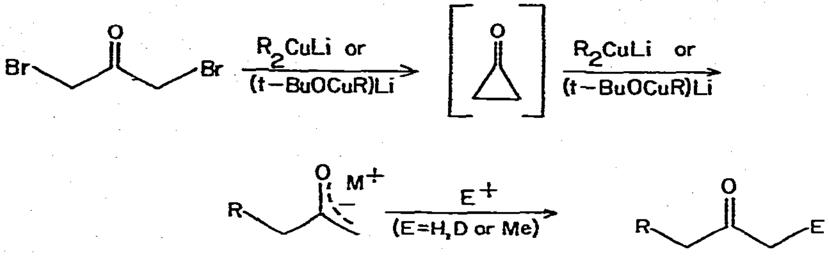
$$\underset{Br}{RCH}\underset{Br}{CHR'} \xrightarrow[\text{ether}]{R_2''CuLi} RCH{=}CHR' \qquad (154)$$

A series of reductions using Me_2CuLi reagent have been carried out [267]. For several steroidal α-epoxyketones direct alkylation of the epoxy group was observed; instead β-hydroxyketones were obtained as the primary products. Pericyclocamphor (CLVII) was reduced to the secondary alcohol with Me_2CuLi, MeMgCl and MeLi whereas Bu_2CuLi added to the carbonyl to afford the tertiary alcohol [268].



CLVII

Treatment of α,α'-dibromo ketones with lithium dialkylcuprate(I) reagents has provided a new route for the α-alkylation of ketones (equation 155) [269].

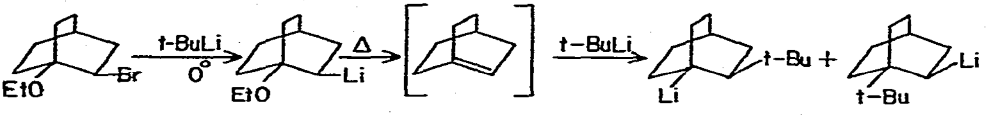


(155)

2-Acetylindene was prepared from indene-2-carboxylic acid *via* treatment of the acid chloride with lithium dimethyl copper [270]. Correction of the structure incorrectly reported in the literature as 2-acetylindene was noted.

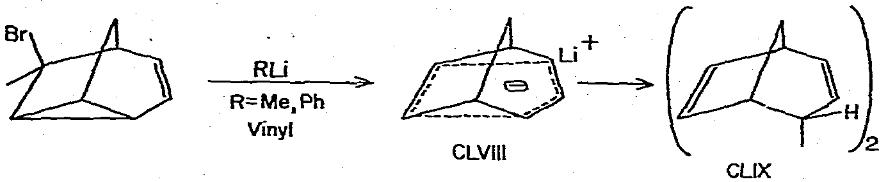
VIII. Halogen-Lithium Exchange Reactions

Exchange of the bromine atom with lithium in 2-bromo-1-ethoxy[2.2.2]bicyclooctane gave an intermediate which eliminated LiOEt to give the anti-Bredt olefin bicyclo[2.2.2] oct-1-ene. The olefin was unstable, its presence being inferred by products formed by the addition of *tert*-butyllithium to the double bond (equation 156) [271].



(156)

Halogen-lithium exchange of *exo* bromotricyclooctene with excess methyllithium, phenyllithium or vinyllithium in ether for two days at room temperature under nitrogen afforded bis-*endo*-bicyclo[3.2.1]-octa-2,6-dien-4-yl(CLIX) in each case [272]. These results were interpreted in terms of the intermediacy of a bishomocyclopentadienide anion (CLVIII).

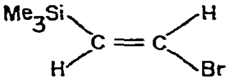


CLVIII CLIX

Although both the α-bromo compound CLX and the trans β-bromo derivative CLXI react rapidly with lithium in ether, the actual lithium intermediate in the case of CLXI could only be demonstrated by in situ trapping with $ClSiMe_3$ to yield trans -bis(trimethylsilyl) ethylene in >80% yield [273]. Prolonged reaction of the trans compound with lithium lead to formation of 2,2,4,4,7,7-hexamethyl-6-(trimethylsilyl)-2,4,7-trisilaoctane.

$Me_3SiCBr = CH_2$

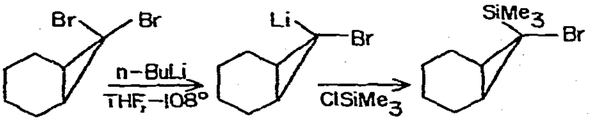
CLX



CLXI

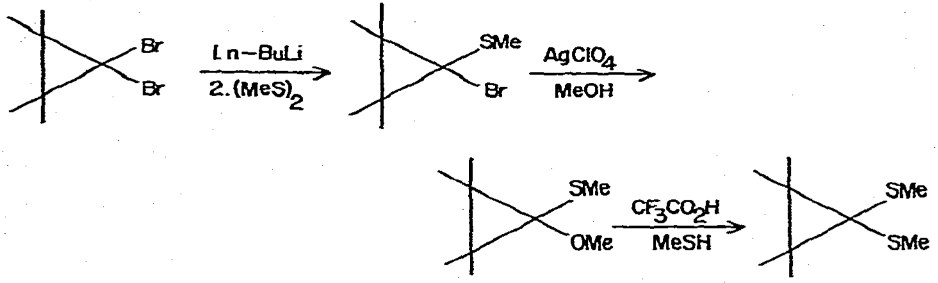
The reaction of lithium metal surfaces with optically active 1-halo-1-methyl-2,2-diphenylcyclopropane led to the formation of the corresponding lithium derivative which was partially racemized [274]. The amount of racemization observed was a function of the halide used (I>Br>Cl), the sodium content of the lithium metal as well as its particle size.

7,7-Dibromonorcarane can be successfully transformed into a single stereoisomer, anti-7-bromo-syn-7-lithionorcarane when treated with n-butyllithium at low temperature in THF (equation 157) [275]. Other derivatives prepared stereospecifically were those with Me_3SnCl, CO_2 and C_2Cl_6.



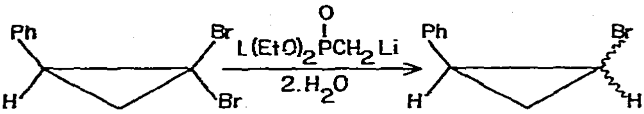
(157)

Cyclopropanethioacetals have proven useful in the preparation of ketones. A new method by which such thioacetals could be synthesized involved preparation of substituted dibromocyclopropanes by carbene addition to an appropriate olefin followed by conversion to the thioacetal (equation 158) [276].



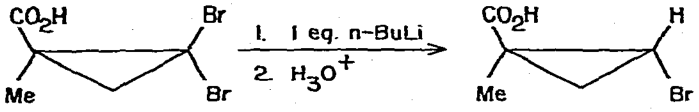
(158)

O,O-Diethyl α-lithiomethylphosphonate *functioned* as a half-reducing agent for the reduction of gem-dihalocyclopropanes (equation 159) [277]. Dimerizations occurred when this reagent was added to cinnamyl chloride and trans-β-bromostyrene, since 3-chloro-1,6-diphenyl-1,5-hexadiene and 1,4-diphenyl-3-buten-1-yne, respectively, were produced.



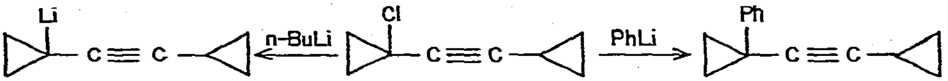
(159)

Treatment of the gem dibromocyclopropane compound CLXII with n-butyllithium and quenching with dilute HCl resulted in a 22% recovery of starting material and 58% yield of the reduced product CLXIII [278]. It was considered that this meant the original compound underwent halogen-metal exchange about 2.5 times faster than carboxylic acid proton abstraction.



CLXII CLXIII

A divergence in reaction between n-butyllithium and phenyllithium with (1-chlorocyclopropyl)cyclopropylacetylene has been observed; with the former halogen-metal exchange was effected but with the latter simple substitution took place (equation 160) [279].

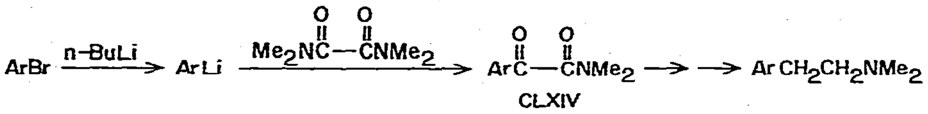


(160)

Theoretical evaluation of the activation energy of group exchange reactions of bromobenzene and phenyllithium has been published [280]. Activation energies of the exchange reaction of PhBr-^{14}C with RC_6H_4Li (R = H, m-Me, p-Me, p-Br and p-Cl) were discussed. Also reported were LCAO calculations of the orienting effect during group exchange of halobenzenes and phenyllithiums [281]. For PhBr, m- and p-BrC_6H_4Cl, m- and p-MeC_6H_4Br exchanged with PhLi, p-ClC_6H_4Li in various combinations showed that in halobenzenes the halogen was the subject of nucleophilic attack whereas the halogen carbon atom was the site of electrophilic attack. Energy level calculations in terms of transition states for bromobenzene and phenyllithium derivatives showed that the aromatic sextet of the reactants was nonuniformly perturbed during electrophilic attack [282].

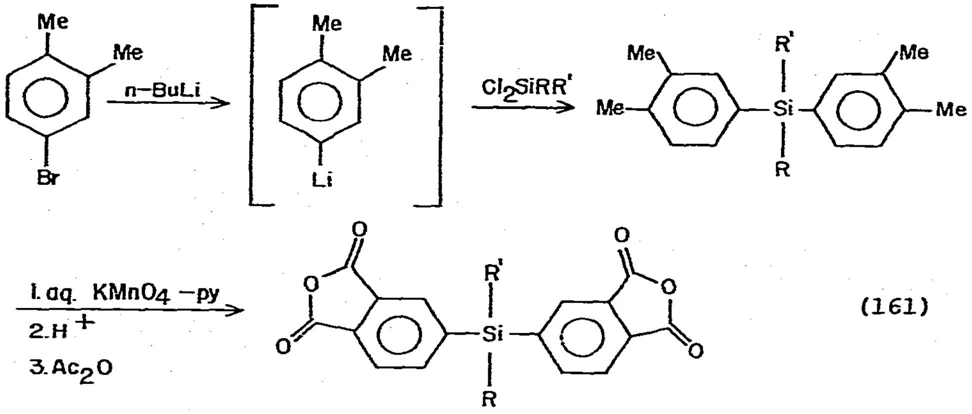
A series of substituted pyridines have been prepared from 2-bromo-and 2,6-dibromopyridine <u>via</u> the halogen-lithium exchange reaction [283]. Apparently this route avoided the normal addition reaction that took place when direct metalation with n-butyllithium was attempted.

A convenient synthesis of β-dimethylaminoethyl derivatives of aryl compounds has been developed by Campaigne and coworkers [284]. The key step following formation of the aryllithium intermediate from the arylbromide by halogen-metal exchange involved reaction of the intermediate with tetramethyloxamide to form the corresponding dimethylglyoxylamide (CLXIV). Reduction then provided the α-hydroxy β-dimethylaminoethyl moiety while further reduction afforded the β-dimethylaminoethyl group itself.



$$\mathrm{ArBr} \xrightarrow{\text{n-BuLi}} \mathrm{ArLi} \xrightarrow{\mathrm{Me_2N\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}NMe_2}} \underset{\text{CLXIV}}{\mathrm{Ar\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}NMe_2}} \longrightarrow \longrightarrow \mathrm{ArCH_2CH_2NMe_2}$$

Halogen-lithium exchange of 4-bromo-o-xylene has been used in the preparation of a series of silicon containing dianhydrides (equation 161) [285].

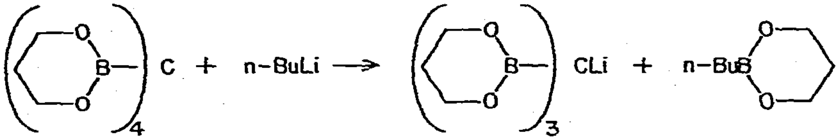


(161)

IX. Reactions of Inorganic and Organometallic Compounds

$Li^+1,2\text{-}B_{10}C_2H_{11}^-$ and $Li^+1,7\text{-}B_{10}C_2H_{11}^-$, prepared by metalation with n-butyllithium of the appropriate carborane, were reacted with $Me_3N\text{-}BH_2I$ to form $1\text{-}Me_3N{\cdot}BH_2\text{-}1,2\text{-}B_{10}C_2H_{11}$ and $1\text{-}Me_3N{\cdot}BH_2\text{-}1,7\text{-}B_{10}C_2H_{11}$, respectively [286]. These materials were resistant to hydrolysis by acid or base. A second metalation-substitution process was also demonstrated at the remaining C-H group for each of the isomers.

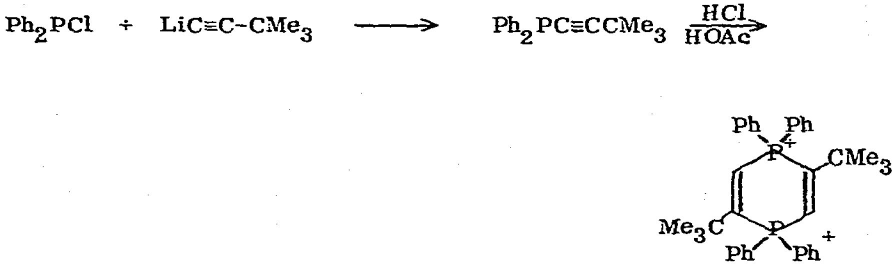
Tetrakis(trimethylenedioxyboryl)methane(CLXV), when treated with n-butyllithium in THF at −70°, precipitated the lithium salt of the methide anion CLXVI [287]. The lithium salt, CLXVI, was reacted with Ph_3SnCl to give the expected triphenylstannyl derivative and with bromine to give the bromo compound. It also could abstract a proton from DMSO to give tris(trimethylenedioxyboryl)methane.



CLXV CLXVI

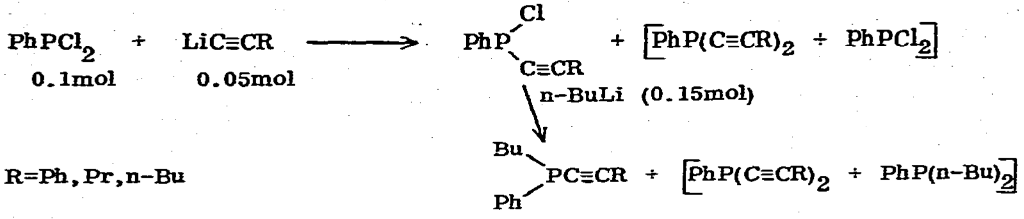
Further reactions of the lithium salt CLXVI were described in a later paper [288]. Treatment with Ph_3MCl formed $Ph_3MC(BO_2C_3H_6)_3$ where M was Ge and Pb in addition to Sn described above. Repetition of these processes led to $(Ph_3M)_2C(BO_2C_3H_6)_2$, where the Group IV metal M may be the same or different. The series was extended to include $(Ph_3Sn)_3CBO_2C_3H_6$. Iodination of the appropriate lithium salt intermediates afforded $Ph_3SnCI(BO_2C_3H_6)_2$ and $(Ph_3Sn)_2CIBO_2C_3H_6$.

Some new types of phosphines and phosphorus heterocycles have been prepared by displacement reactions of lithium alkynes on phosphinous chlorides (equation 162 and 163) [289].



$$Ph_2PCl + LiC{\equiv}C\text{-}CMe_3 \longrightarrow Ph_2PC{\equiv}CMe_3 \xrightarrow[HOAc]{HCl}$$

(162)



$$\underset{0.1\,\mathrm{mol}}{\mathrm{PhPCl_2}} + \underset{0.05\,\mathrm{mol}}{\mathrm{LiC{\equiv}CR}} \longrightarrow \mathrm{PhP(Cl)(C{\equiv}CR)} + [\mathrm{PhP(C{\equiv}CR)_2} + \mathrm{PhPCl_2}]$$

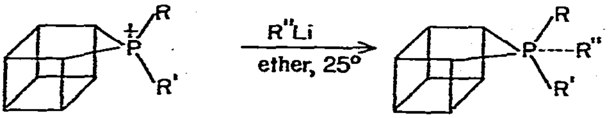
$$\mathrm{PhP(Cl)(C{\equiv}CR)} \xrightarrow{\text{n-BuLi (0.15mol)}} \mathrm{Bu(Ph)PC{\equiv}CR} + [\mathrm{PhP(C{\equiv}CR)_2} + \mathrm{PhP(n\text{-}Bu)_2}]$$

R=Ph,Pr,n-Bu

(163)

The first stable pentaalkylphosphorane and some phenyl-substituted analogs have been synthesized by treatment of the corresponding phosphonium salt with either methyl- or phenyllithium (equation 164) [290]. Relief of ring-strain was proposed as an explanation for the ease with which this new class of compound was formed. Phosphine oxides CLXVII (R = O; R' = Me and R = O; R' = Ph) afforded the phosphonium salts when treated with methyl and phenyllithium.

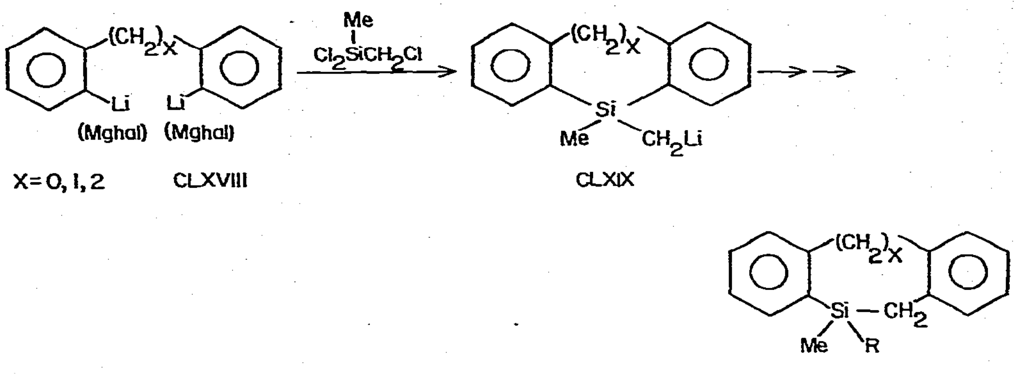
A series of silicon heterocycles were prepared by treatment of the dilithio or diGrignard intermediates CLXVIII with $\mathrm{Cl_2SiMeCH_2Cl}$ to produce CLXIX. Rearrangement to the ring system CLXX was effected by $\mathrm{Al(hal)_3/C_6H_6}$ with the final product CLXX (R = OMe, OH, H or an Si—O—Si bridged dimer) being produced after a reduction step [291].



CLXVII

(164)

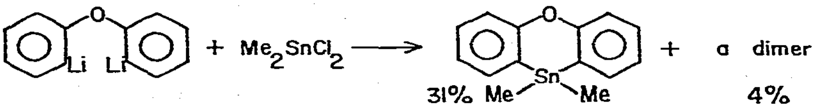
R = Ph; R' = Ph; R" = Ph
R = Ph; R' = Me; R" = Ph
R = Me; R' = Me; R" = Ph
R = Me; R' = Me; R" = Me



CLXVIII CLXIX

CLXX

Somewhat similar heterocycles were formed when bis(2-bromophenyl) ether was converted to the dilithio intermediate CLXXI with n-butyllithium. Treatment of the dilithio intermediate with dimethyl-(or diethyl)tin dichloride afforded 10,10-dimethyl- (or 10,10-diethyl)phenoxastannin, respectively [292]. The sulfur and sulfone analogs of the dimethyl compound CLXXII were prepared by similar routes.

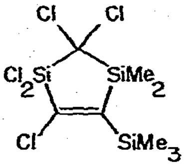


CLXXI CLXXII

A series of silyl-substituted anions have been formed as illustrated in equation 165 [293]. Condensation with ketones afforded a number of highly substituted olefins.

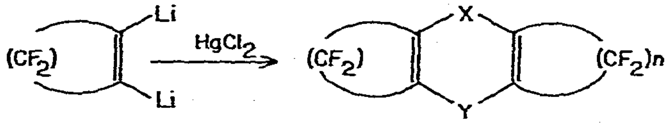
$$(\text{Me}_3\text{Si})_3\text{CH} + \text{LiOMe} \xrightarrow{\text{HMPA}} (\text{Me}_3\text{Si})_2\text{CH}^{\ominus}\text{Li}^{+} \xrightarrow[\text{2.-LiOSiMe}_3]{\text{1. Ph}_2\text{CO}} \text{Ph}_2\text{C}{=}\text{CHSiMe}_3 \tag{165}$$

Reaction of disilacyclopentene CLXXIII with 8 moles of methyllithium afforded $\text{Me}_3\text{SiCCl}_2\text{SiCl}_2\text{C}{\equiv}\text{CSiMe}_3$ which underwent cleavage to give $\text{Me}_3\text{SiCMe}_2\text{SiMe}_3$ and the Si - methylated derivatives, $\text{Me}_3\text{SiC}{\equiv}\text{CSiMe}_3$ and Me_4Si [294].



CLXXIII

Treatment of dihalopolyfluorocycloalkenes with organolithium reagents followed by reaction with $HgCl_2$ afforded the mono mercuri derivative (X = Hg, Y = 2 halogens, n = 3,4) and the dimercuri compound (X,Y = Hg, n = 2,3) (equation 166) [295]. Some similar compounds were isolated using Me_2GeCl_2 and $MeAsI_2$.

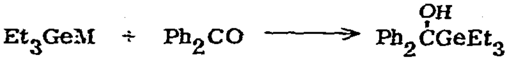


(166)

Trialkylgermyl alkali metal species were prepared according to equation 167 and utilized in the syntheses described in equation 168-170 [296].

$$(R_3Ge)_2Hg \;+\; M \longrightarrow R_3GeM \qquad (167)$$

$$M = Li,\ Na,\ K$$



$$Et_3GeM \;+\; Ph_2CO \longrightarrow Ph_2\overset{OH}{C}GeEt_3 \qquad (168)$$

$$Me_3SiCl \;+\; R_3GeM \longrightarrow Me_3SiGeR_3 \qquad (169)$$

$$R_3GeM \;+\; C_2H_4 \xrightarrow[\text{Hydrolysis}]{\text{after}} R_3GeEt \;+\; MOH \qquad (170)$$

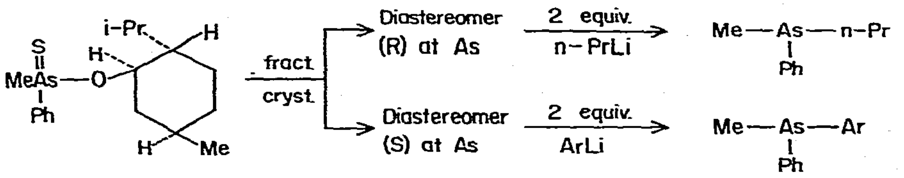
Organolithium reagents (R = Me,Bu,Ph) when reacted with halogenomethinyltricobalt enneacarbonyls (CLXXIV) under a pressure of CO afforded mainly the carboxylic acid (CLXXV) if hydrolysis was with water or the corresponding ester if an alcohol were used [297]. These results were interpreted in terms of CO insertion, probably by way of rearrangement of an unstable carbene intermediate.

$$\underset{\text{CLXXIV}}{XCCo_3(CO)_9} \xrightarrow[2.\,H_2O]{1.\,RLi,\,CO} \underset{\text{CLXXV}}{HO_2C{-}CCo_3(CO)_9}$$

$X = Cl, Br$

Treatment of $X(SiH_3)_2$ in ether at 227° where X = O,S,Se and $Z(SiH_3)_3$ where Z = P,As with methyllithium has resulted in the preparation of colorless crystals of $LiXSiH_3$ and $LiZ(SiH_3)_2$, respectively [298]. Further reaction of $LiXSiH_3$(X = S,Se) with Me_3SiCl afforded $H_3SiXSiMe_3$.

Menthyl methylphenylthioarsinate, derived in 76% yield from the reaction of methylphenyliodoarsine with sodium menthoxide and subsequent sulfurization, can be separated by fractional crystallization into its two diastereomers [299]. Treatment of the (R)-diastereomer with n-propyllithium (equation 171) and the (S)-diastereomer with α-naphthyllithium (equation 172) afforded the appropriate optically active arsine. Study of the stereochemistry of the organolithium step in each case brought the conclusion that the reaction proceeded with retention of configuration.



(171)

(172)

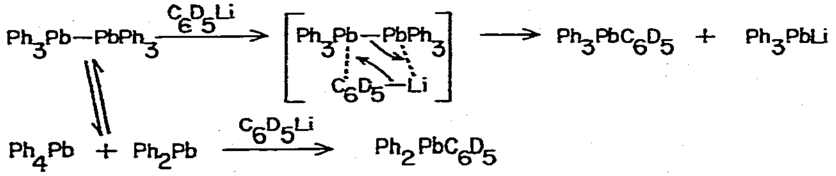
In ether solution below -20° anhydrous $FeCl_3$ underwent reaction with methyllithium to form Li_2FeMe_4. The complex can also be isolated as the etherate or dioxanate [300]. WCl_6 was reacted with Me_4Sn or MeLi to give unstable organotungsten compounds which catalyze olefin disproportionation [301]. Li_2WMe_4? Reaction of methyllithium with $TiMe_4$ afforded isolable adducts of $LiTiMe_5$ [302]. Similarly, $LiMe_4TiR$ (R = Ph, CH_2Ph), $LiMe_2TiPh_3$ and $LiTiR'_4Cl$(R' = Me, Ph) were prepared.

The reaction of all-trans-1,5,9-cyclododecatriene-nickel(O) with phenyllithium has afforded a stable complex which contained π-bonded nitrogen (equation 173) [303]. Ethylene quantitatively liberated nitrogen from the complex. One unusual feature was that the N-N bond was 1.35A, as compared to 1.097A in free N_2.

$$2\ \mathrm{CDT}\cdot\mathrm{Ni} + 6\ \mathrm{PhLi} + \mathrm{N_2} \xrightarrow[0^0]{\mathrm{Et_2O}} \left\langle\left[(\mathrm{PhLi})_3\mathrm{Ni}\right]_2\mathrm{N_2}\cdot 2\,\mathrm{Et_2O}\right\rangle_2 + 2\ \mathrm{CDT} \qquad (173)$$

2-(Dimethylaminomethyl)phenylsilver, its silver bromide complex, bis[2-(dimethylaminomethyl)phenyl]silver • silver bromide, (2,6-dimethoxyphenyl)silver and (2,4,6-trimethoxyphenyl) silver have been prepared from their corresponding organolithium precursors [304]. It is likely that these compounds exist in oligomeric forms. These arylsilver complexes exhibit greater thermal, oxidative and hydrolytic stability than phenylsilver itsel

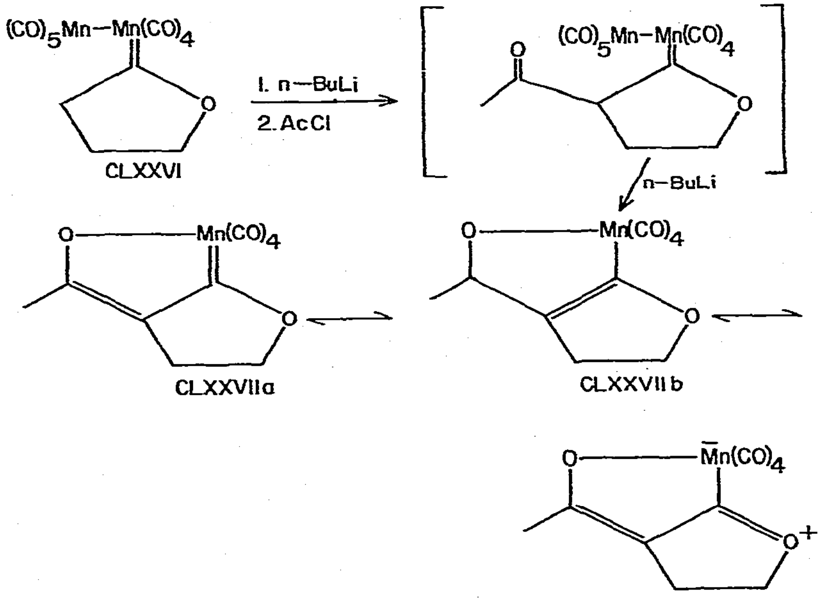
The results of the reaction of pentadeuterophenyllithium (PDPLi) and hexaphenyldilead have cast doubt on the validity of the equilibrium shown in equation 174 [305]. Diphenyllead, if present, would be expected to react rapidly with PDPLi to afford Ph_2PbPDP. No such product was found; instead, Ph_3PbPDP and Ph_3PbLi were isolated suggesting a four-centered nucleophilic mechanism.



(174)

An intermediate acylated derivative of the carbene complex CLXXVI was apparently generated by treatment of the complex with n-butyllithium followed by acetyl chloride [306]. The complex reacted further with base to afford the monomanganese complex

CLXXVII whose structure was determined by x-ray crystallography. It was best formulated as a resonance hybrid of canonical forms CLXXVII a-c.



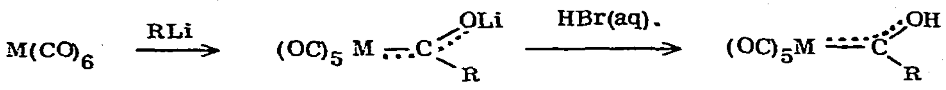
CLXXVI

CLXXVIIa

CLXXVIIb

CLXXVIIc

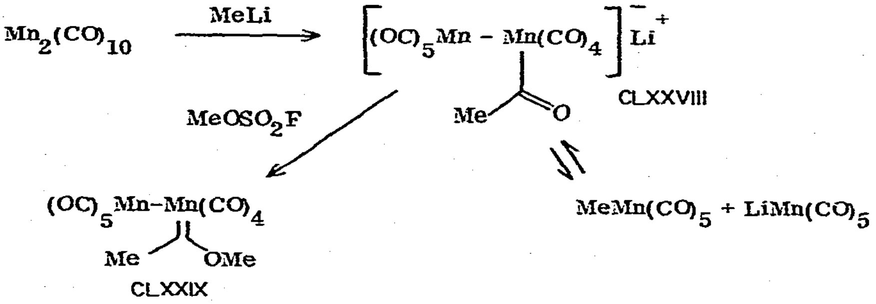
A series of transition metal carbene complexes have been prepared from methyl- and phenyllithium (equation 175) [307]. Isolation and characterization of the hydroxy complex from each organolithium reagent has proven possible when the metal was chromium or tungsten.

 (175)

$$M(CO)_6 \xrightarrow{RLi} (OC)_5M\cdots C\begin{smallmatrix}OLi\\R\end{smallmatrix} \xrightarrow{HBr(aq).} (OC)_5M\cdots C\begin{smallmatrix}OH\\R\end{smallmatrix} \qquad (175)$$

R=Me; M=Cr
R=Ph; M=Cr
R=Me; M=W
R=Ph; M=W

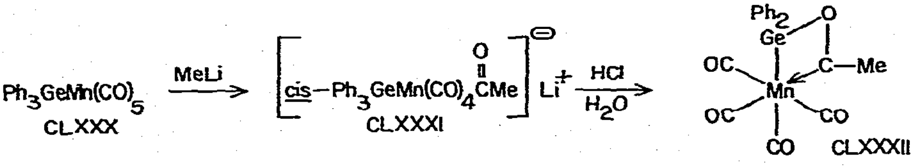
Methyllithium generated the anionic metal acyl compound CLXXVIII which was transformed into the carbene complex CLXXIX using methylfluorosulfonate as the alkylating agent [308]. The improvement in yield of the complex was attributed to two factors, 1) the alkylation could be run at higher concentration than by other methods which served to shift the equilibrium in the equation towards the acyl anion (CLXXVIII) and 2) the extreme capability of methylfluorosulfonate to transfer an alkyl group.



The behavior of onium salts containing carbonylmetalate anions (M = Cr, Mo, W) towards deprotonation has been studied (equation 176) [309]. It was concluded that their reactivity was comparably to that of onium halides.

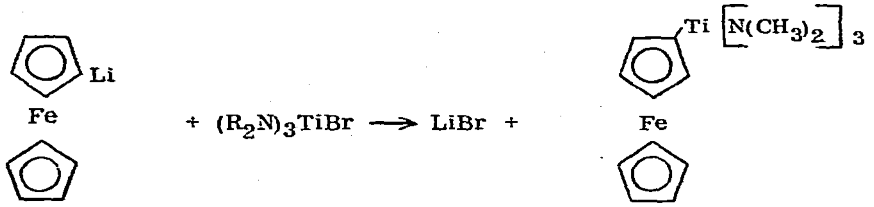
$$\left[Me_3PCH_2SiMe_3\right]^{+}\left[M(CO)_3-\pi-C_5H_5\right]^{\ominus} \xrightarrow{n-BuLi} Me_3P{=}CHSiMe_3\cdot Li\left[M(CO)_3-\pi-C_5H_5\right] \qquad (176)$$

Pentacarbonyl compound CLXXX, when reacted with methyllithium, afforded the acetyl derivative CLXXXI which was isolated as a tetraethylammonium salt [310]. $Et_3O^+BF_4^-$ with the lithium salt gave the ethoxycarbene complex, cis-$Ph_3GeMn(CO)_4\overset{Me}{C}OEt$. Treatment of the acetyl complex CLXXXI with acid precipitated the new complex CLXXXII.



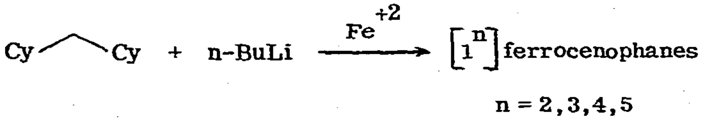
Evidence has been produced that the electrophilicity of the peroxy oxygen atoms of d^6 and d^8 transition metal-oxygen complexes is much lower than that of similar d^0 complexes [311]. The actual order determined was $MoO(O_2)_2 \cdot HMPA$, $CrO(O_2)_2 \cdot Py > (Ph_3P)_3PtO_2$, $(Ph_3P)_2Ir(CO)(O_2)_2I >> Na_2O_2$ by measurement of the ease of formation of lithium n-butoxide upon treatment of each complex with n-butyllithium.

Lithio- and 1,1'-dilithioferrocene were prepared by the halogen-metal exchange reaction from bromo- and 1,1'-dibromoferrocene and n-butyllithium. These reagents were reacted with dialkylamidotitanium bromides to yield ferrocenyl titanium dialkylamides (equation 177) [312].

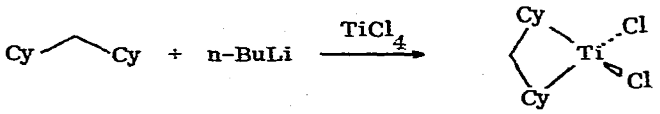


(177)

A series of cyclic oligomers of ferrocene prepared from bis (cyclopentadienyl)methane dianion have been prepared (equation 178) [313]. This same dianion has been used to synthesize 1, 1'-methylenetitanocene dichloride (equation 179) which has been utilized (with lithium naphthalenide) to fix nitrogen and with diethylaluminum chloride to polymerize ethylene.

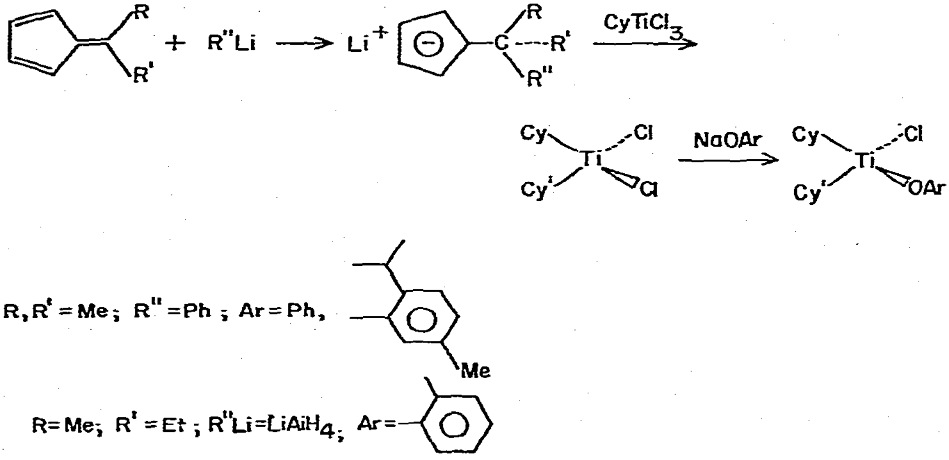


(178)



(179)

Titanocene complexes which exhibit novel stereochemical properties have been prepared by reduction of dialkylfulvenes with phenyllithium or lithium aluminum hydride (equation 180) [314]. The phenoxy and thymol complexes exhibited diastereotopic methyl groups in their respective pmr spectra. In the case of the ortho-cresol complex, an asymmetric titanium atom was apparently formed. Pmr evidence for two diastereoisomers of this complex was presented, but the isomers could not be conveniently separated. There was some evidence of epimerization at titanium.



(180)

A number of relatively stable metal alkyls have been prepared from the new class of ligand R_3MCH_2- [315]. Complexes such as those illustrated in equations 181 and 182 were accessible by reaction of transition metal chlorides with the lithium (or magnesium) derivative of a member of the new class of ligands.

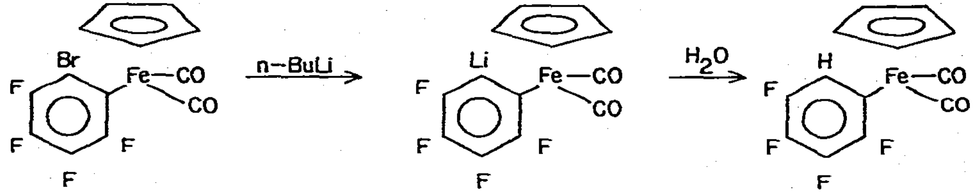
$$Cy_2MCl_2 + Me_3M'CH_2Li \longrightarrow Cy_2M(CH_2M'Me_3)_2 \qquad (181)$$

M=Ti,Zr,Hf M'=Si,Ge

$$Me_3SiCH_2Li + MCl_4 \longrightarrow (Me_3SiCH_2)_4M \qquad (182)$$

Halogen-metal exchange of the ortho bromo compound CLXXXIII afforded the relatively stable ortho-lithio derivative CLXXXIV

[316]. This did not undergo elimination of LiF to produce the benzene derivative as had been observed for the meta and para isomers of CLXXXIII.



CLXXXIII CLXXXIV

X. Miscellaneous Organic Reactions

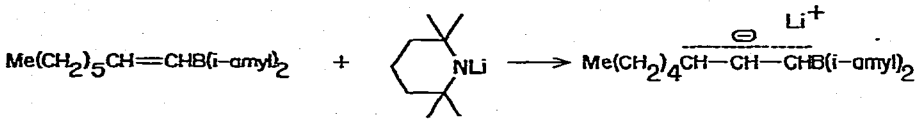
A review article "Some Aspects of Alkylation with Carbanions" [317] and a book "The Ionization of Carbon Acids" [318] were published during the year 1973. Although neither deals for the most part with organolithium compounds, they should be of interest to the organolithium chemist.

A new method of preparation of acetylenes has been developed involving first the formation of the lithium salt and then reaction with a trialkylborane (equation 183) [319]. Migration of an alkyl group from boron to carbon was accomplished by the addition of iodine.

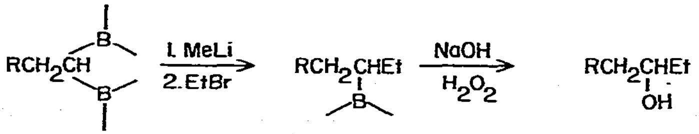
$$HC{\equiv}CR + n\text{-}BuLi \longrightarrow LiC{\equiv}CR$$

$$\xrightarrow{R_3'B} Li\left[R_3'BC{\equiv}CR\right] \xrightarrow{I_2} R'C{\equiv}CR \qquad (183)$$

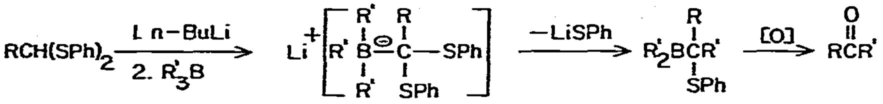
Boron-stabilized carbanions were formed by metalation of vinylboranes with lithium 2,2,6,6-tetramethylpiperidide (equation 184) [320]. Reaction of this anion with acetone or trimethylchlorosilane took place at the γ-carbon and with methyl iodide or water at the α-carbon. The dialkylboron group can be oxidatively cleaved to provide the corresponding alcohols.


(184)

A convenient procedure for the synthesis of secondary alcohols from 1-alkynes has been proposed (equation 185) [321]. The key step involved metalation of the methine carbon to form a boron-stabilized carbanion which could be alkylated. Boracyclanes appeared to be the most suitable hydroborating agents for preparation of the appropriate diborylalkanes.


(185)

The reaction of trialkylboranes with the α-lithio derivatives of bis(phenylthio)methane and 1,1-bis(phenylthio)pentane has resulted in the synthesis of a series of aldehydes and ketones (equation 186) [322].


(186)

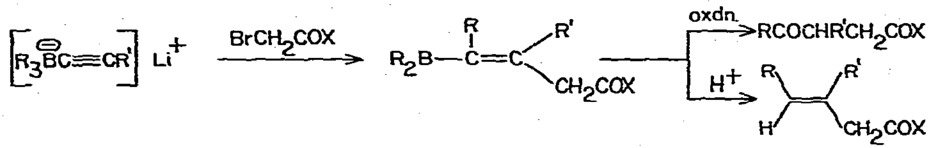
$$RCH(SPh)_2 \xrightarrow[2.\ R'_3B]{1.\ n\text{-}BuLi} Li^{+}\left[R'\overset{R'}{\underset{R'}{B}}\overset{\ominus}{-}\overset{R}{\underset{SPh}{C}}-SPh\right] \xrightarrow{-LiSPh} R'_2B\overset{R}{\underset{SPh}{C}}R' \xrightarrow{[O]} R\overset{O}{\overset{\|}{C}}R' \qquad (186)$$

Also, terminal alkynes have been transformed into ketones by the route shown in equation 187 [323].


(187)

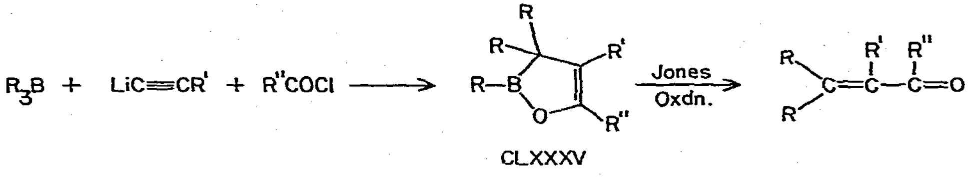
$$R_3B + LiC{\equiv}CR' \longrightarrow R_3\overset{\ominus}{B}C{\equiv}CR'\ \overset{Li^{+}}{} \xrightarrow{R''X} R_2B\overset{R}{\overset{|}{C}}{=}CR'R'' \xrightarrow{H_2O_2} RCOCHR'R'' \qquad (187)$$

A novel synthetic route to 1,4-dicarbonyl compounds has been developed [324]. Treatment of α-halocarbonyl compounds with trialkylalkynylborates has lead to intermediates that can be oxidized or hydrolyzed to 1,4-dicarbonyl compounds or β,γ-unsaturated ketones and esters, respectively (eqation 188).

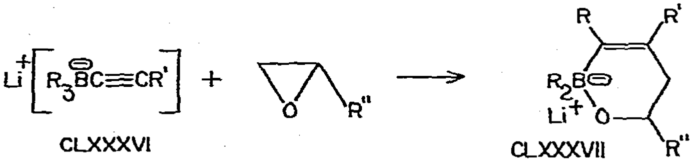


(188)

2-Oxa-3-bororenes (CLXXXV), prepared from trialkylboranes, 1-alkynyllithium and acyl chlorides in THF/hexane solution gave, after oxidation with Jones reagent, the corresponding α,β-unsaturated ketones in moderate yields [325].

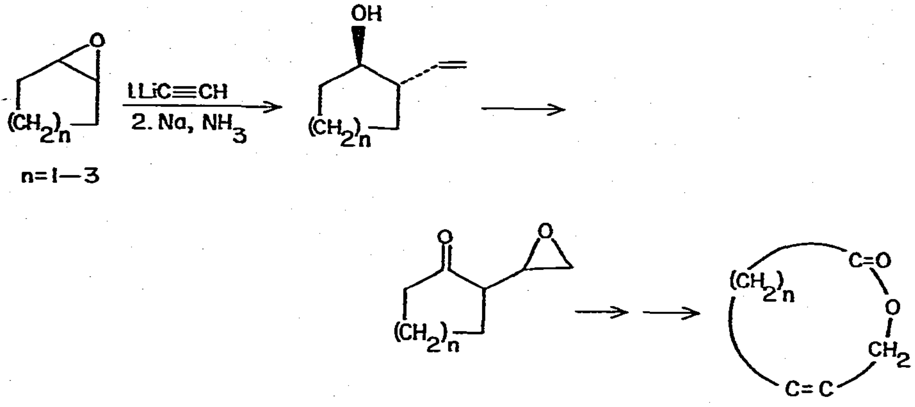


Lithium trialkyl-1-alkynylborates CLXXXVI, prepared by treatment of an alkyne with an alkyllithium reagent followed by addition of a trialkylborane can be used to prepare unstable cyclic borates of general formula CLXXXVII [326]. These cyclic borates upon appropriate work-up afforded 1) γ-hydroxyketones and 2) trisubstituted olefins of rigorous stereochemistry.



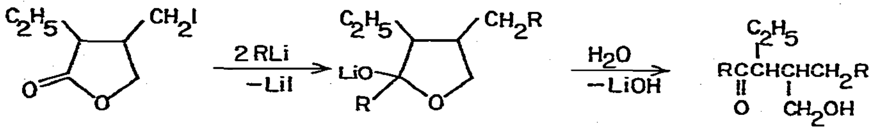
Reaction of lithium trialkylvinylborates, synthesized from vinyllithium and a trialkylborane, with oxiranes followed by oxidative work-up produced 1,4-alkanediols [327]. A cyclic borate was thought to be a relative stable intermediate.

Nucleophilic ring opening of a series of cyclic epoxides with lithium acetylide has afforded the corresponding vinyl alcohols which were transformed into β,γ-epoxyketones [328]. Photolysis of these ketones promoted a three-atom ring expansion (equation 189).



(189)

The reaction of γ-lactone CLXXXVIII with 1-methyl-5-chloro-imidazolyl-2-lithium (RLi) has produced a novel ring opening reaction (equation 190) [329].



CLXXXVIII

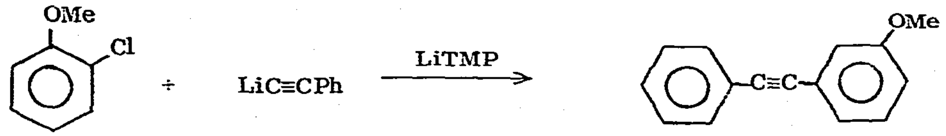
(190)

A one-step synthesis of 1,4-and 1,5-diketones, involving reaction of a variety of organolithium compounds with N,N,N',N'-tetramethylamides of succinic and glutaric acids has been described (equation 191) [330].

$$2\,\mathrm{RLi} + \mathrm{Me_2NCO(CH_2)_nCONMe_2} \xrightarrow{-78^{o}} \mathrm{RCO(CH_2)_nCOR} \qquad (191)$$

Aldehydes and ketones, RCOR' (where R = Ph, Et, n-heptyl and R' = H, Ph, Me, n-Bu) have been synthesized in 10-79% yields by addition of RLi (prepared by the appropriate halogen-lithium exchange reaction) with R'CONX$_2$ (where X = Me, Et, Ph) [331].

Further demonstration of the selectivity of proton removal and low nucleophilicity of LiTMP (lithium tetramethylpiperidide) has been reported [332]. Synthesis of m-methoxytolan was accomplished in 80% yield using LiTMP and in somewhat lower yields with related bases (equation 192). Similarly, benzoylation of the tertiary carbon in CLXXXIX, considered to be a stringent test of the effectiveness of a base, was accomplished in yields of 89% (R = Me) and 86% (R = Et).

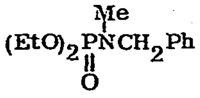


(192)

$$\underset{\text{CLXXXIX}}{R_2CHCO_2Et} \overset{\text{LiTMP}}{\rightleftharpoons} \left[R_2\bar{C}CO_2Et\right] \xrightarrow{\text{PhCOCl}} \underset{\text{R=Me, Et}}{PhCOCR_2CO_2Et}$$

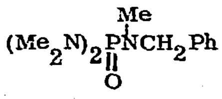
Reaction of at least two equivalents RLi(R = Me, Et, n-Bu) with phenylallene has produced the dilithio species, PhCHLiC≡CLi, at -40° which was alkylated at the softer sp^3 position to give PhCHRC≡CH(R = Me, Bu) [333].

(Diethoxy)-N-methyl-N-benzylphosphoramide (CXC) when treated with n-butyllithium, methyllithium or lithium diisopropylamide, underwent elimination of $(EtO)_2\overset{O}{P}\text{-H}$ whereas the bis(dimethylamino) analog CXCI afforded metalation at the benzyl carbon [334]. Derivatization of this metalated intermediate provided several alkylation and addition products.



$$(EtO)_2\underset{O}{\underset{\|}{P}}\overset{Me}{\overset{|}{N}}CH_2Ph$$

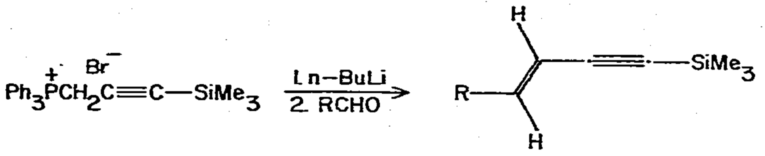
CXC



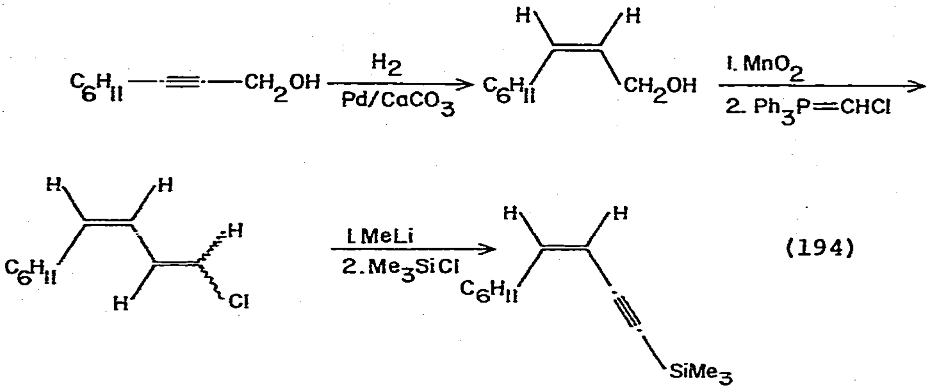
$$(Me_2N)_2\underset{O}{\underset{\|}{P}}\overset{Me}{\overset{|}{N}}CH_2Ph$$

CXCI

Methods for the stereoselective synthesis of trans (equation 193) and cis enynes (equation 194) have been reported [335]. The terminal trimethylsilyl propargylic phosphonium salt was prepared and converted into the protected trans enyne by treatment with n-butyllithium followed by condensation with an aldehyde. The cis enyne unit was formed by a route incorporating as the key step its conversion of chloroolefins into acetylenes. Quantitative removal of the trimethylsilyl group could be effected by treatment of a THF solution of the trans enyne with an excess of $(n\text{-Bu})_4N^+F^-$ or $KF\cdot 2H_2O$ in DMF solution.



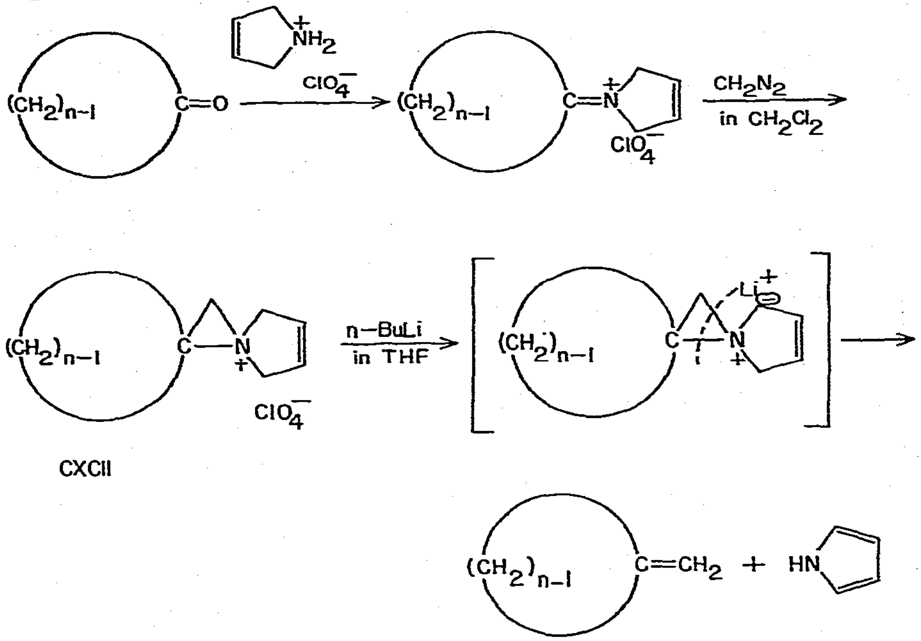
(193)



(194)

In contrast to the rearrangement of α-vinylbenzyl alcohol to propiophenone which had been reported to occur under the influence of n-butyllithium in THF or DME, the reaction in hexane solvent took a different course [336]. Two equivalents of n-butyllithium in the presence of TMEDA in this case afforded 1-phenyl-2-methyl-1-hexanol (68%) and 5-benzyldecane (22%) by various additions to the double bond.

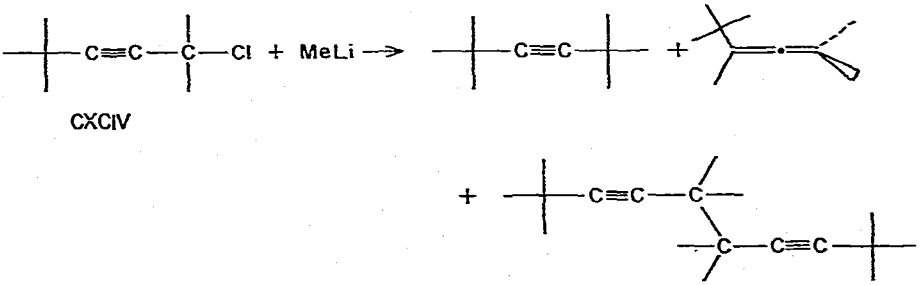
A new method of preparing methylene derivatives from carbonyl compounds has been introduced [337]. A key step in the synthesis was the fragmentation of the aziridinium salt CXCII with loss of pyrrole to give the methylene compound CXCIII. The method was used particularly to synthesize a number of exo methylene compounds.



CXCII

CXCIII

Reaction of the propargyl chloride CXCIV with methyllithium produced three compounds in significant yield [338]. The preferred mechanism for the formation of the dimer CXCV involved initial halogen-metal exchange followed by nucleophilic attack by a tertiary carbanion on a tertiary halide.

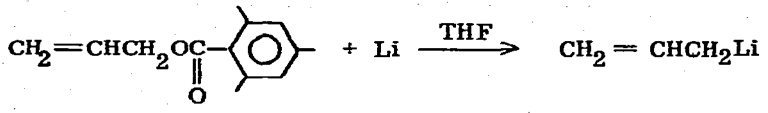


CXCIV

CXCV

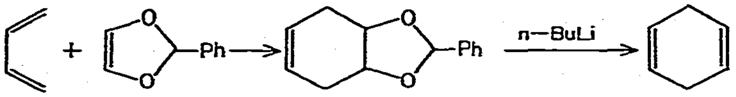
Allylic mesitoates undergo alkyl-O fission upon reduction by lithium metal in THF at 0° to give allyllithium (equation 195)

[339]. Reaction of this intermediate in situ with allylic bromides produced 1,5-dienes; with aldehydes and ketones moderate yields of allylic carbinols were prepared. The latter method was used to synthesize a component of the Ips confusus pheromone.



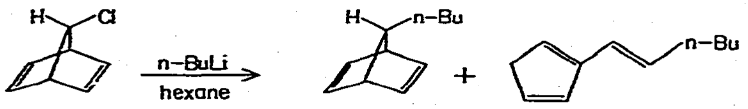
(195)

2-Phenyl-1,3-dioxolene (CXCVI) has been used as an alternative to acetylene in a Diels-Alder type synthesis of 1,4-cyclohexadiene [340]. The key step was the fragmentation of the adduct CXCVII with n-butyllithium.



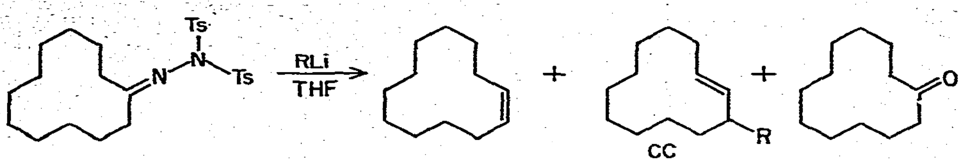
CXCVI CXCVII

Addition of n-butyllithium to the double bond of 7-chloronorbornadiene resulted in the product CXCVIII in small yield and a significant yield of the ring-opened product CXCIX [341]. These results were interpreted in terms of a novel rearrangement mechanis of norbornadienyl anion. An interesting solvent effect on the structure(s) of the products of the reaction was described.



CXCVIII CXCIX

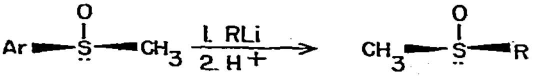
The reaction of representative members of a new class of compounds, N,N-ditosylhydrazones, with methyl and tert-butyllithium has been studied [342]. The products from such treatment of cyclododecanone N,N-ditosylhydrazone are shown in equation 196. Of particular interest was the 29% yield of the alkylation product CC from tert-butyllithium since examples of such direct alkylation reactions are rare.



CC

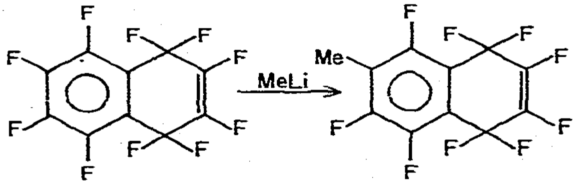
(196)

Aryl alkyl sulfoxides, when treated with alkyllithium reagents, have been found to undergo a reaction other than simple ionization of an α-hydrogen [343]. Exchange of the alkyl group of the organolithium reagent with the aryl group of the sulfoxide took place, apparently with inversion of configuration (equation 197).



$$\mathrm{Ar}-\overset{\mathrm{O}}{\underset{\cdot\cdot}{\mathrm{S}}}-\mathrm{CH_3} \xrightarrow[2.\ \mathrm{H}^+]{1.\ \mathrm{RLi}} \mathrm{CH_3}-\overset{\mathrm{O}}{\underset{\cdot\cdot}{\mathrm{S}}}-\mathrm{R} \qquad (197)$$

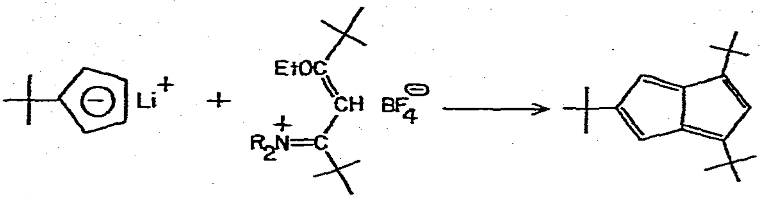
Reaction of decafluoro-1,4-dihydronaphthalene with methyllithium yielded the monomethyl derivative CCI and a series of dimethyl derivatives [344].



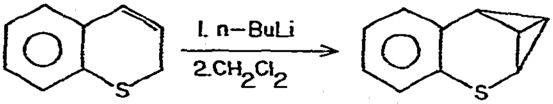
CCI

Sodium salts of linear fatty acids ($RCH_2CH_2CO_2Na$ where R = Me, n-Pr, n-C_5H_{11}, n-C_9H_{19}) can be treated with lithium diisopropylamide in THF/HMPT and subsequently with 2,3-dichloro-5,6-dicyanobenzoquinone to afford the corresponding α,β-unsaturated acids [345].

The synthesis of 1,3,5-tri-*tert*-butylpentalene has been readily accomplished by reaction of lithium *tert*-butylcyclopentadienide with a ketimonium salt (equation 198) [346]. This was the first example of a relatively stabilized pentalene system.


(198)

4,5-Benzo-3-thiatricyclo [4.1.0.0^{2,7}] heptene, a valence bond isomer of the unknown heterocyclic 12-pi electron system, benzo[b]thiepin, has been synthesized by a metalation, methylation sequence (equation 199) [347].


(199)

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