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A MECHANISTIC STUDY OF LITHIATION SUBSTITUTION REACTIONS AT C-H CENTRES OF HETEROATOM SUBSTRATES

Sneh Lata
Department of Chemistry, SGT University, Gurugram, INDIA

Manisha T Sharma
Babu Banarasi Das University, Lucknow (U.P.) INDIA

Abstract: Lithiation-substitution protocol is a significant tool for the formation of a new C-C bond in heteroatom-containing compounds. This strategy has been extensively explored to synthesize many heterocyclic drugs and drug intermediates. These reactions are always considered very complex and many research groups have worked to explore the regioselectivity and stereoselectivity of these reactions. The feasibility of these reactions is affected by many factors like the nature of the lithiation reagent, solvent and temperature. In this chapter, we will discuss in detail the different lithiating reagents, the effect of solvent, temperature, regioselectivity and stereoselectivity. This chapter will also deal with the different mechanistic aspects involved in the regioselective and stereoselective outcomes of the lithiation-substitution reaction.

Key Words: Lithiation, Heterocyclic compounds, Regioselectivity and Stereoselectivity.

Introduction: Lithiation followed by a reaction with an electrophile is the most widely used methodology for forming a new bond at weakly acidic C-H centres. This protocol is the basic step in the synthetic and mechanistic investigation carried out in the present acquisition. Accordingly, a select a review of aspects of lithiation chemistry based on many papers' reviews and monographs. [1-105] Paraphrasing of this chemistry in introductory chapters of two earlier dissertations from this laboratory has been extensively relied upon,[2a,b] with referencing to the original sources, also recasting and up-dating wherever considered necessary. The first step in lithiation protocol involves the replacement of most acidic protons with lithium when a substrate is treated with an alkyl lithium base. This protocol furnished anion that can be expediently trapped by different electrophiles to introduce new functionalities in the molecule.[3] Major interest in this field has been centred on; the location of metalation, its mechanism with structural and kinetic aspects, and synthetic efficacy. The position of metalation was of primary importance in the earlier years, the subsequent research emphasizes mechanistic studies and the synthetic utility has remained important throughout.[3-4] Although lately, the emphasis has revolved around diastereo and enantioselectivity. The presence of heteroatom in the substrate significantly affects the feasibility and regio-selectivity of the lithiation-substitution protocol. It is due to the electronic effects of heteroatom and its coordination with lithium atoms in the transition state, possibly in a pre-lithiation complex. The position of the heteroatom in a substrate directs the regiochemistry of the lithiation reactions along with its strong accelerating influence.

The present chapter is focused on lithiation/substitution reactions of heteroatom-bearing substrates with special emphasis on tertiary amines and their Lewis acid complexes. It is an effort to explain the effect of nitrogen on the generation and reactivity of carbanionic intermediates in

tertiary amines, especially on benzylic C-H centres. Further, this methodology has been used to synthesize many molecules of potential pharmacological utility. The chapter aims to explain the nature and existence of lithiation reagents, their activity, factors that affect the activity of lithiating reagents, types of different possible lithiation, the mechanism involved, and the influence of different heteroatoms and their effect on the regioselectivity of lithiation, etc.

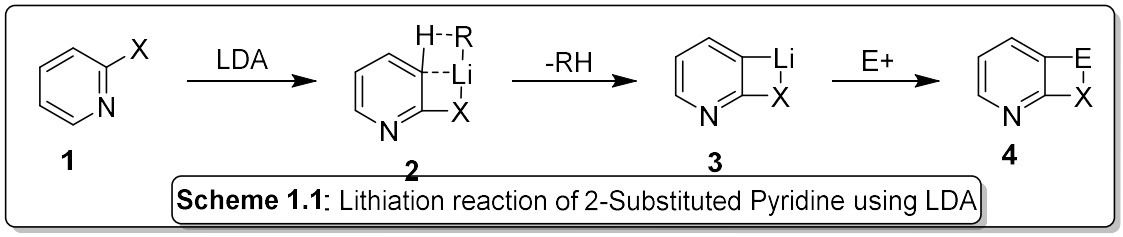
Lithium Reagents: The chemical compounds involving a direct bond between the carbon of the alkyl/aryl group and the Lithium atom, act as lithiation reagents. For any lithiation reagents, we must consider the following points [5,6]-

1. Organolithium bases exist as a polymer and the degrees of polymerization depend upon the nature of the solvent, concentration, and temperature.
2. The reactivity of the organolithium bases can be influenced by the method of preparation, like the presence or absence of halide in the reaction, its concentration, the solvent used, and the extent of polymerization.
3. In lithiation reactions, in situ generated new organolithiums, complexed the reaction kinetics.
4. Organolithium compounds are sensitive to oxygen and moisture which may result in several impurities.

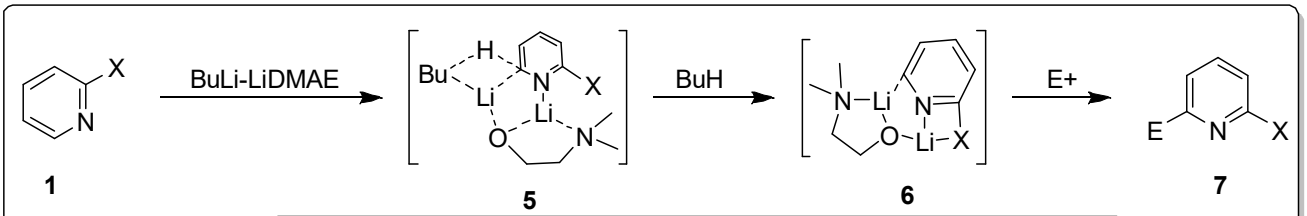
Thus, initially, we will focus on the distinct characteristics of these lithiating agents before any mechanistic discussion. Organolithium compounds are oligomers of varying complexity in solution, gases, and solid phases, many studies have been directed toward elucidating their structure. A partial understanding of the structure of organolithium compounds is necessary therefore only the more significant facts are discussed here.

Aggregation of Lithiation Reagents and the factors affecting aggregation

All the organolithium compounds are polymeric, electron-deficient species,[7-9] and therefore act as a Lewis acid, and can coordinate with Lewis bases like ethers and amines[10] with a consequent degree of depolymerization. Kinetically, the basicity of these reagents increases as the aggregate size must diminish. The perceptible extent of polymerization fluctuates with both the nature of the solvent and the structure of the organolithium reagent. Normally, the extent of polymerization is more for straight chains than for branched-chain compounds. Hence steric hindrance is one of the significant factors in determining the polymeric form and regioselectivity of the reactions. There are many reported reactions in literature where the change in base leads to a complete reversal of regioselectivity. For example, in the case of 2-substituted pyridines **1**, lithiation takes place exclusively at the C-3 position (Scheme-1) when LDA is used as a base,[11] whereas the use of a (1:1) mixture of BuLi-Me_2N $(CH_2)_2OLi$ (BuLi-LiDMAE) resulted in predominant lithiation at the C-6 position (Scheme-2).[12]

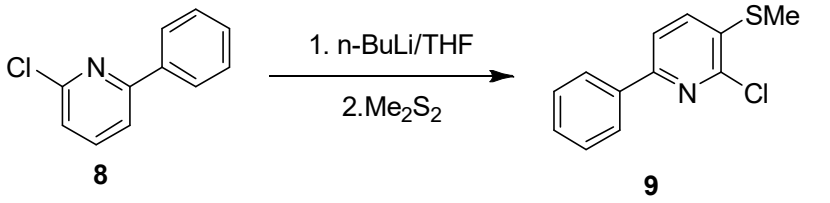


Scheme 1.1: Lithiation reaction of 2-Substituted Pyridine using LDA

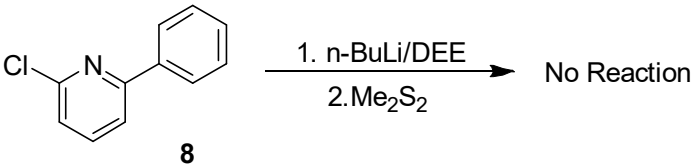


Scheme 1.2: Lithiation reaction of 2-Substituted Pyridine using BuLi-LiDMAE

The nature of solvent also affects many lithiation-substitution reactions and this effect of solvent has been widely studied. For example, lithiation of 2-aryl-6-chloropyridine (**8)** with n-BuLi as a base in THF followed by the reaction with dimethyldisulphide gives 5-substituted product **9** (Scheme-3) but under the same conditions in DEE (Scheme-4) as a solvent, no reaction was observed.[13]



Scheme 1.3: Reaction of 2-Aryl-6-chloropyridine with n-BuLi in THF



Scheme 1.4: Lithiation reaction in DEE as solvent

One of the possible reasons for this could be the solvation of n-BuLi. It exists as a dimmer in THF whereas in DEE it exists as a tetramer.

The organolithium compounds can be of two types; one in which negative charge resides on carbon (e.g., n-BuLi) and the other where the charge is localized on the heteroatom (e.g., LDA). The carbanionic compounds can be further divided into; a) localized anions like aryl and alkyl lithium and b) delocalized carbanions like cyclopentadienyl anion and fluorenyl lithium complexes. In localized carbanionic compounds, the interaction between carbanion and lithium is generally ionic.

Theoretical studies on methyl lithium documented these interactions as 88% ionic and 12% covalent in character.[14] However, the small covalent contribution is very important in structural investigations.

Broadly, in solution organolithium compounds are either present as contact ion pair (CIP) or as solvent-separated ion pair (SSIP) Fig 1. In localized carbanionic compounds, SSIP may be present though in very low concentration. However, they are still important, as the reactivity of SSIPs is much more than CIPs. In solution, these two ion pairs often exist in equilibrium.

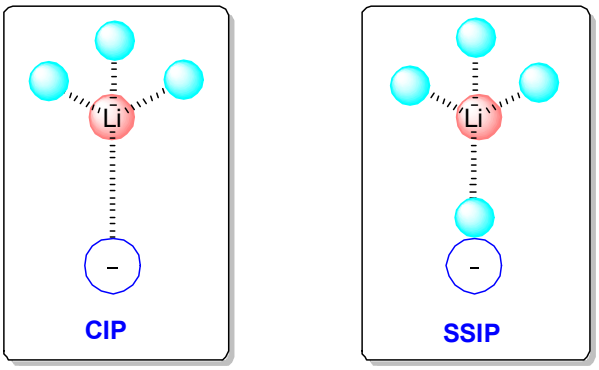


Figure 1: CIP and SSIP form of organolithiums.

The coordination number of lithium can vary from 2-12 but four is the most commonly observed coordination number. Hence lithium is coordinated to several donor atoms from solvent or ligand. The CIPs in localized ion pairs generally exist as aggregates; monomer **10**, dimer **11**, trimer **12**, tetramer **13** and hexamer **14,** etc.

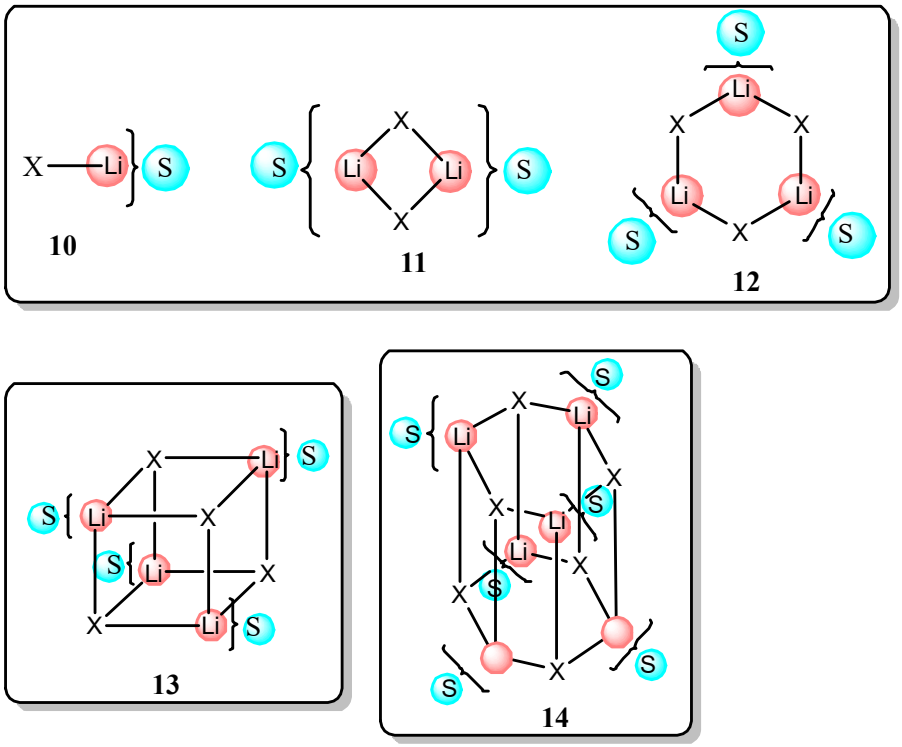


Figure 2: CIP aggregates

The most common coordination number for lithium is four. Therefore, the number of sites available for coordination of solvent or ligand decreases from 3 to 1 as the number of aggregations increases from monomer to tetramer or hexamer as shown. This decrease in the available coordination number of Li causes lower reactivity of higher aggregates in comparison to lower aggregates. In the last three decades, there are many reports on the aggregation effect but the relative reactivity of different aggregates has been determined occasionally.[12,15] Mc Garry et al have studied the relative reactivity of dimeric and tetrameric state of n-BuLi in THF and found that dimer is more reactive than tetramer towards cyclopentadiene and benzaldehyde.[15a]

In the early years of organolithium chemistry, methods of structure determination were limited. Measurement of colligative properties by cryoscopy and ebullioscopy and density measurements were generally employed to establish the degree of aggregation of organolithium reagents in solution.[16] But presently many techniques to determine the structure of organolithium complexes, both in solution and in solid-state, have been developed.

X-ray crystallography and solid-state NMR spectroscopy provide a deep insight into the solid structure as well as the nature of bonding of organolithium reagents.[17] In the solution state, spectroscopic techniques like UV-visible, IR, and NMR are generally employed. UV-visible and IR spectroscopy are based on wavelength shift with the change of aggregation or structure,[18] and can be used to detect low concentrations of complexes and fast dynamic processes at low concentrations. These are of limited use at higher concentrations. NMR spectroscopy has emerged as one of the most important developments for structural studies. There are several, one and two-dimensional experiments like ^{1}H, ^{13}C, ^{7}Li, HOESY, COSY, etc which can be used at room temperature as well as at low temperatures for structural elucidation of organolithiums.[19]

Different aggregation states are possible in a particular solvent under different conditions and are in dynamic equilibrium with each other. For example, in THF as a solvent, n-BuLi exists as tetramer/dimer and s-BuLi as dimer/monomer. Similarly, phenyl lithium exists as a tetramer/dimer in THF.[20] Thus aggregates are often involved in the exchange process, which is both inter-and intra-aggregate. Generally, two mechanisms for exchange have been proposed for inter-aggregation. These are (a) dissociative processes and (b) associative processes. The details of these processes have been discussed by taking the examples of tetramers.[8b,21,22]

Deaggregation of organolithium Reagents

A marked solvation influence was observed on the aggregation state of lithiating reagents. In the presence of Lewis bases like tertiary amines and ethers, a competition arises between anion and Lewis bases for coordination to lithium cation. If the added Lewis base is strong enough, it leads to the deaggregation of the organolithium reagents. This relationship between solvation, degree of aggregation, and reactivity of organolithium chemistry is described in **Figure 1.3**.[23]

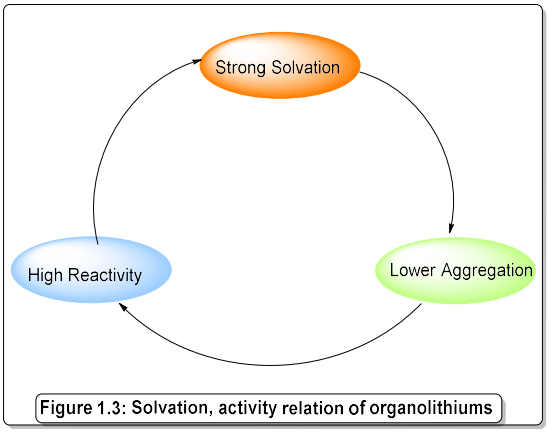


Figure 1.3: Solvation, activity relation of organolithiums

The addition of strong coordinating ligands like TMEDA or PMDTA causes deaggregation of organolithium from tetramer to dimer in case of TMEDA[24a,b,] and monomer in case of PMDTA.[24c] The strong complexing ability of these amines is due to polydentate metal-ligand interactions, which result in a stable chelated substructure as evident from crystallographic studies. This shows that the feasibility of the deaggregation process is dependent on entropy criteria. However, there is some controversy as to whether TMEDA is a good ligand to increase the reactivity of organolithium reagents. Schleyer and co-workers found that in the THF solution of t-BuLi, on the addition of one equivalent of TMEDA, about 97% of amine remains uncomplexed.[20] Collum based on his work on the structure, kinetics, and calorimetric studies of alkyl/aryl lithiums with TMEDA/THF, revealed that; [23]

1. TMEDA has a strong substrate-based affinity for lithium. The magnitude of the interaction between TMEDA and Lithium may be strongest in the less hindered lithium derivatives and least in a more hindered environment.
2. In the absence of donor solvents, TMEDA may influence the structure and reactivity of the organolithium reagents.
3. The higher donicity of TMEDA being a bidentate ligand except for a few exceptions can increase the reactivity of organolithiums by deaggregation.
4. Even if both available monomeric ground states and coordinatively complexed monomeric transition states are both more stable than their highly aggregated counterparts, it will not guarantee an increase in reaction rate.
5. The solvent will be ideal if have no affinity for the ground state but a high attraction for the transition state.
6. The exact mechanism of interaction of TMEDA with organolithium is not known but it acts as a good ligand and enhances the reactivity of organolithium reagents.

The degree of aggregation of aryl/alkyl lithium in different solvents is tabulated in **Table-1.1**.[9]

Table-1.1: Extent of aggregation of organolithiums in different solvents

Organolithiums	Solvent	Aggregates
n-BuLi	Hydrocarbon	Hexamer
	Ether	Tetramer
	THF	Dimer
n-BuLi-TMEDA	Hydrocarbon	Monomer
t-BuLi	Hydrocarbon	Tetramer
	THF	Dimer
C_6H_5Li	Ether	Dimer
	THF	Dimer

The unsaturated compounds like benzene or ethylene (pk_a 36.5-37.0),[25,26] can be thermodynamically deprotonated with alkyl lithiums having □pk_a greater than 5. It is observed that these lithiation reactions are very slow even in ether-solvents e.g., benzene displays negligible lithiation with n-BuLi even after 3h at room temperature.[27,28] However, a remarkable enhancement in the rate of lithiation was observed for heteroatom-containing substrates; e.g., Phenyl methyl ether is 30% Lithiated with n-BuLi in the diethyl ether after 2h.[29]

Conversely, a significant rate enhancement is detected if the benzene is Lithiated with n-butyl lithium coordinated with TMEDA (3h/25°) rather than using n-BuLi alone.[30,28] The TMEDA caused depolymerisation of the normal hexameric BuLi and make the monomeric form kinetically more stable by coordinating the nitrogen atoms with the lithium.

Lithiation of heteroatom-containing cyclic or acyclic compounds

For many years it was assumed for the same reason that heteroatom facilitates the lithiation reaction by coordinating with the electron-deficient organolithium reagent (with consequent depolymerisation).[31] The resulting coordination followed proton abstraction by the carbanionic portion of the organolithium from the nearby C-hydrogen bond, leading to the lithiated product.[32] Although this basic mechanistic aspect is quite valuable to explain and forecast many observations but other aspects like the heteroatom's inductive effect can also play a significant role in these reactions. Accordingly, this is postulated that there are two limiting mechanisms;[9]

1.“Co-ordination only” mechanism

2.“Acid-Base” mechanism

A continuous spectrum of both effects contributes to a varying degree between these two extremes. This concept can be best understood through illustration.

Classification of lithiation reactions

The heteroatom-facilitated lithiation significantly enhances the regioselectivity, and usually takes place at some adjacent carbon atom. Lithiation reactions based on the location of the

heteroatom in the substrate can be classified into three main categories: alpha, beta, and lateral lithiation.

In alpha-lithiation, the lithiating reagent abstracts the proton from the carbon (sp^2, sp^3) atom next (□) to the heteroatom and forms a lithium-carbon bond. Here, sp^3-carbon can be enclosed in the heterocycle or side chain of the heterocyclic system and the sp^2-carbon atom can be associated with an unsaturated or heteroaromatic □-system.

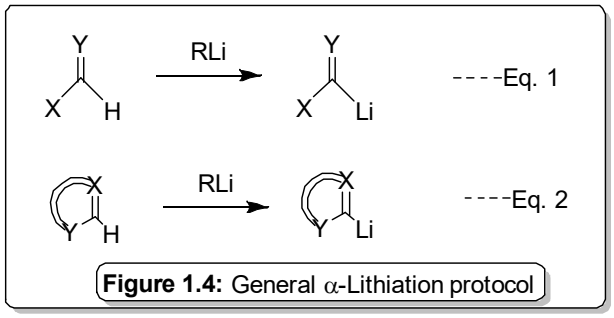


Figure 1.4: General α-Lithiation protocol

The beta lithiation involves deprotonation of the carbon atom (sp^2, sp^3) present at the beta position relative to the heteroatom-containing substituent. The sp^3-carbon atom can be enclosed within the carbocyclic or part of the acyclic system. The designation "ortho-lithiation" is used precisely for the □-lithiation of the carbocyclic aromatic system.

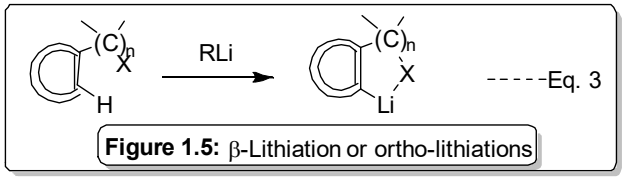


Figure 1.5: β-Lithiation or ortho-lithiations

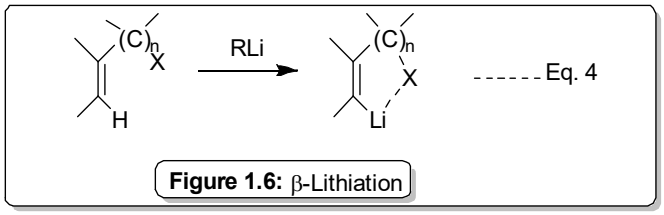


Figure 1.6: β-Lithiation

The lateral lithiation involves lithiation on a benzylic carbon (side chain) that is adjacent to, or skirted by, a heteroatom-containing substituent (G); these substituents facilitate lithiation relative to the parent system without G.

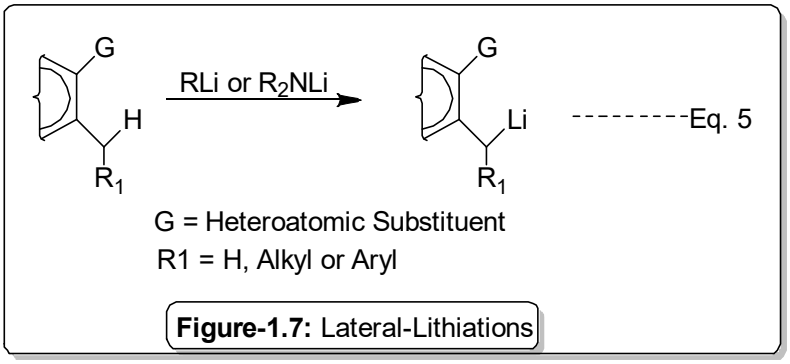


Figure-1.7: Lateral-Lithiations

Nature of Heteroatom and their effect on Lithiation

The ease of carbanion generation depends on other groups attached to the carbon atom and on the nature of the heteroatom. In compounds containing heteroatoms like N, O, S, P, and Se, the relative ease of generation of □- carbanion has been studied through the rate of exchange of □-hydrogen in an acyclic system as shown.[33,2a] It is clear that out of these heteroatoms sulfur is the most and nitrogen is the least effective.

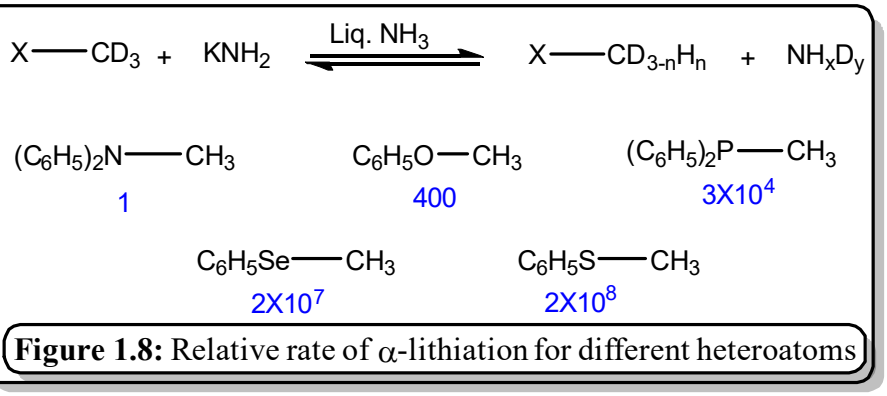


Figure 1.8: Relative rate of α-lithiation for different heteroatoms

Peterson et al reported that □-heteroatom substituted organometallic compounds could be readily generated from the corresponding weakly acidic methane in the case of S, Se, Si and P while □-halomethyl ethers have to be used in the case of oxygen (figure 1.9).[34]

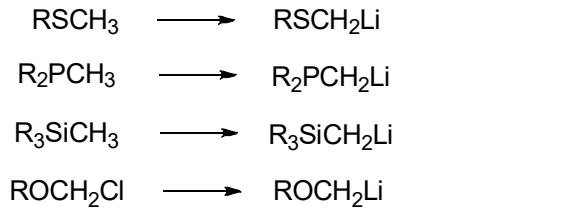


Figure 1.9: α-Lithiation of S, P, Si and O-heteroatoms

Such studies reveal that □-carbanion generation becomes easier:

i) As we move toward the right in the same row of the periodic table.

ii) When the heteroatom belongs to the third row instead of the fourth or second row.

These observations have been explained by two different theories:

A) **d-Orbital Theory**[34b,35]**-** It postulates that the heteroatom stabilizes the □-carbanion by delocalization of the charge in its low-lying d-orbitals. Since the overlapping between 2p□ orbital of carbanion and d_{xy-}□ orbital of heteroatom is better in the case of 3d than 4d orbitals (Fig. 1.10), the stabilizing effect of 3rd-row heteroatom is more pronounced than 2nd and 4th row.

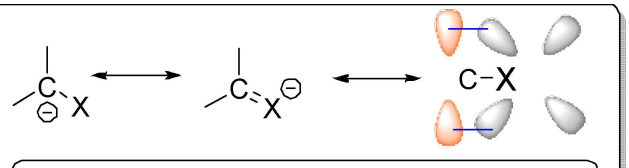


Figure-1.10: Carbanion through d-orbital theory

B) **Polarization Theory** [36]**-** This theory is based on theoretical calculations and the results are explained based on the polarizability or electronegativity of the heteroatom which allows better diffusion of the carbanionic charge. The inductive effect of the □-activator significantly enhances the acidity of the adjacent C-H bond, hence facilitating the □-lithiation. The following heteroatoms are known to enable □-lithiation: N, O, S, Se, P, and Te.

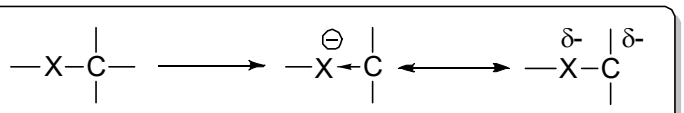


Figure 1.11: Carbanion through polarization

The competitive lithiation studies of five-membered heterocyclic-thiophene, furan, and N-alkyl pyrroles have shown that in the thermal control environments the rate of lithiation is highest with sulfur, and then followed the order: sulfur> oxygen> N-alkyl.[37] In sulfur, the highest □-activation is due to the effective □-d orbital overlap, which overcomes the induced inductive effect by more electronegative oxygen or nitrogen atoms. Similarly, the more swift lithiation of furan in kinetically controlled conditions is dedicated to the better ligating ability of the oxygen.[38] Hence, under the kinetically controlled situation (low temperature) the order becomes; oxygen> sulfur> N-alkyl. The effect of nitrogen is unique because unlike sulfur and phosphorus it neither has low-lying d-orbitals, nor its electronegativity is as high as that of the oxygen atom to disperse the charge. Moreover, the repulsion between the carbanionic electron pair and the lone pair of nitrogen destabilizes the carbanion.[35]

For the primary and secondary amines, □-lithiation can be enabled by connecting the nitrogen with an activating group.[39]

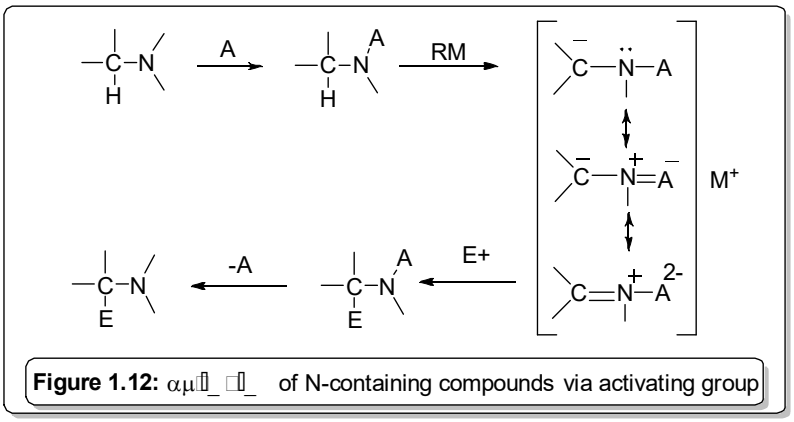


Figure 1.12: αμ[]_ □[]_ of N-containing compounds via activating group

An effective activating group should have the following characteristics-

I. Promote the acidity of □-protons

II. Devoid of any kinetically acidic protons

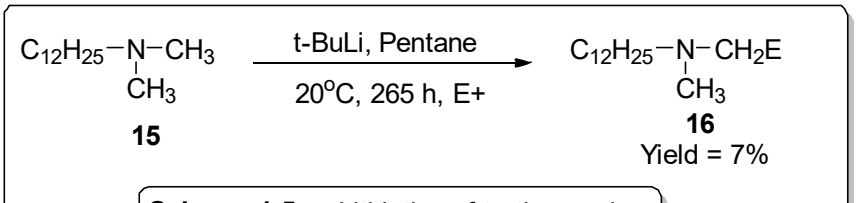
III. Inactive toward electrophilic substitution

IV. Stable toward strongly basic conditions

V. Should be conveniently attached in the first step and removed in the last.

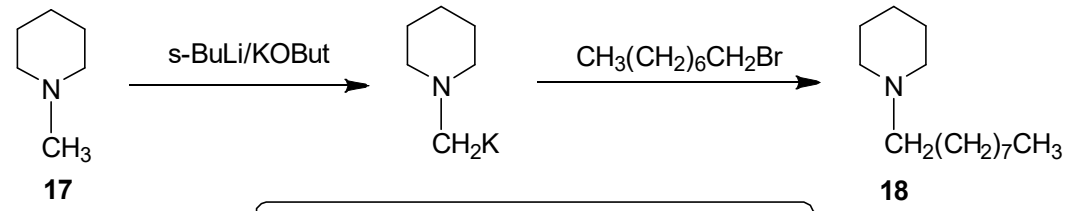
The secondary amines can be effectively activated by functionalities like nitrosamines, amides, formamidines, oxazolidines, carbamates etc. whereas for primary amines effective functionalities are isonitrile, □-(nitrosamine)-alkyl ethers and tert-butyldiphenylmethylhydrazones. The applicability of these functionalities has been discussed in several review articles.[40]

The □-lithiation of tertiary amines is difficult still a few reports of direct metalation are available in the literature. Peterson et al observed that prolonged treatment of dodecyl dimethylamine (**15**) with t-BuLi leads to some □- deprotonation (**16**).[34,41]



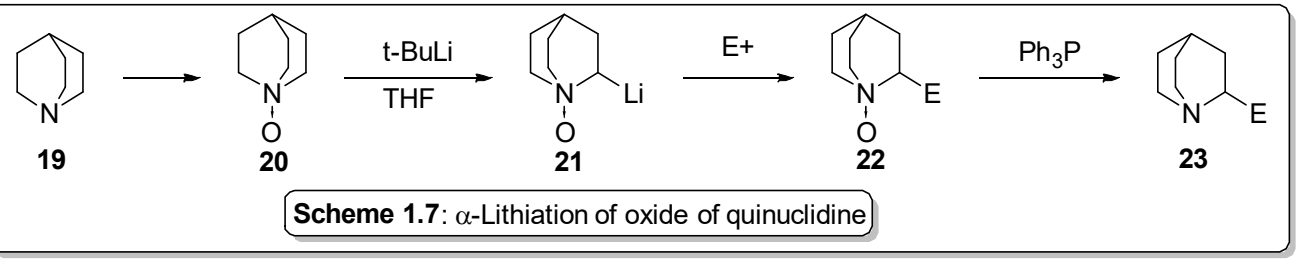
Scheme 1.5: α-Lithiation of tertiary amine

Similarly, Ahlbrecht and Dollinger reported deprotonation of N-methyl piperidine(**17**) with s-BuLi/ KOBu^t to give dialkylamino methylpotassium, which upon reaction with octyl bromide, afforded □-substituted product **18** in 70% yield, only in case N-methyl piperidine itself is used as a solvent.[42]



Scheme 1.6: α-Lithiation N-Methyl pyrrolidine

Barton *et al* showed that oxide **20** of quinuclidine (**19**) after lithiation and subsequent reaction with suitable electrophile could be deoxygenated with triphenylphosphine to give product **23**. But this procedure is limited to bridgehead tertiary amines, otherwise formed lithiated intermediate undergoes rapid LiOH elimination.[43]



Scheme 1.7: α-Lithiation of oxide of quinuclidine

Kessar *et al* developed a widely applicable approach for activating the tertiary amines by complexing with a boron Lewis acid like BF_3, before treatment with a strong base. The success of this methodology relies on averting the reaction between the Lewis acid and the base used, possibly either through steric or HSAB mismatch.[44] The activation by BF_3 is very convenient since protection, lithiation, electrophilic substitution and deprotection all can be carried out in one pot.[45]

In BF_3-complexed tertiary amines, □-deprotonation is promoted and the □-amino carbanions so generated, can be effectively trapped by various electrophiles.[2] For example C-1 deprotonation of N-methyl-1,2,3,4-tetrahydroisoquinoline and subsequent reaction with the electrophile opened up a versatile route to precursors of many isoquinoline alkaloids. The alkaloids synthesized using BF_3-complexation methodology include (±) nuciferidine (**25**), (±) corydaine (**26**), (±) yenhusomidine (**27**), (±) raddeanine (**28**), (±) egenine (**29**) and precursor to domesticine (**30**), Ethylmorphine (**31**), cryptowoline (**32**), crypaustoline (**33**), oliveroline (**34**) and ushinsunine (**35**).[46,47]

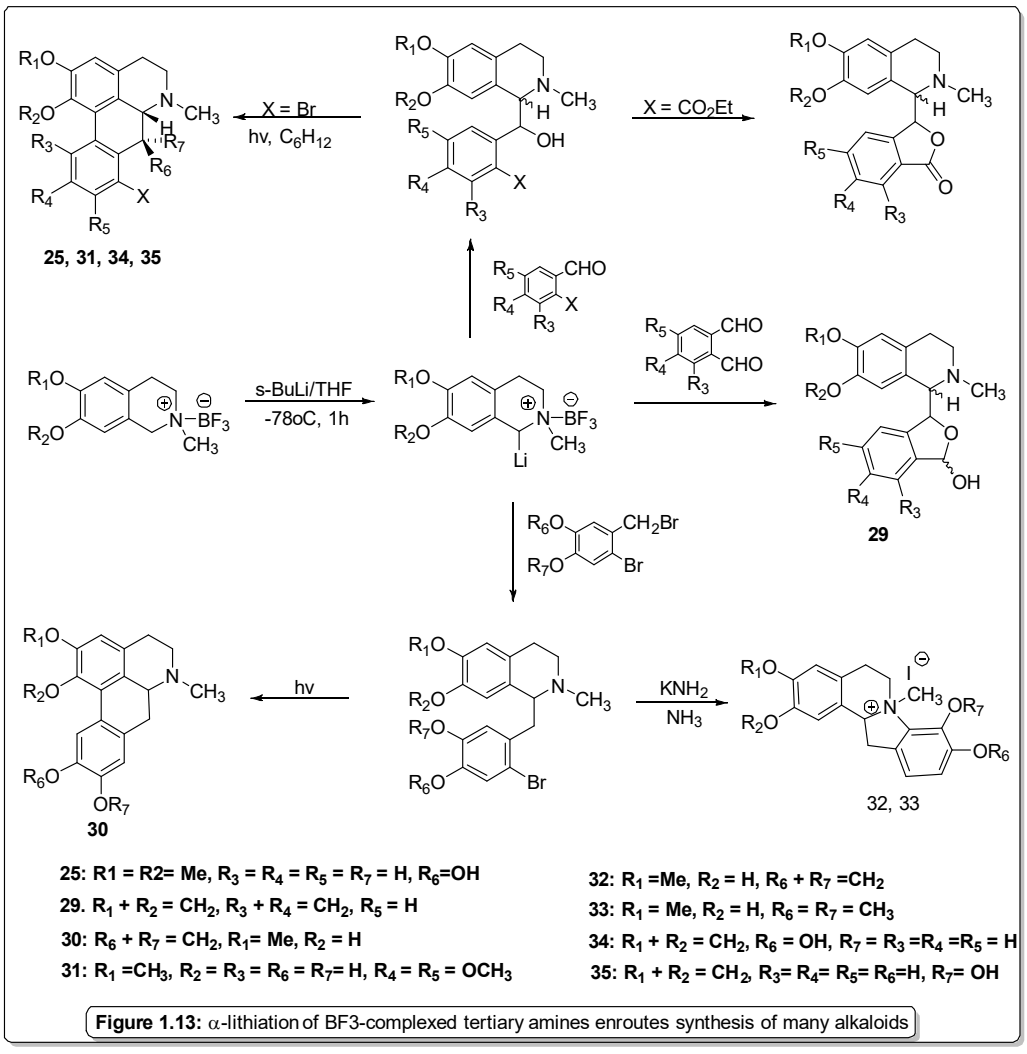


Figure 1.13: α-lithiation of BF3-complexed tertiary amines enroutes synthesis of many alkaloids

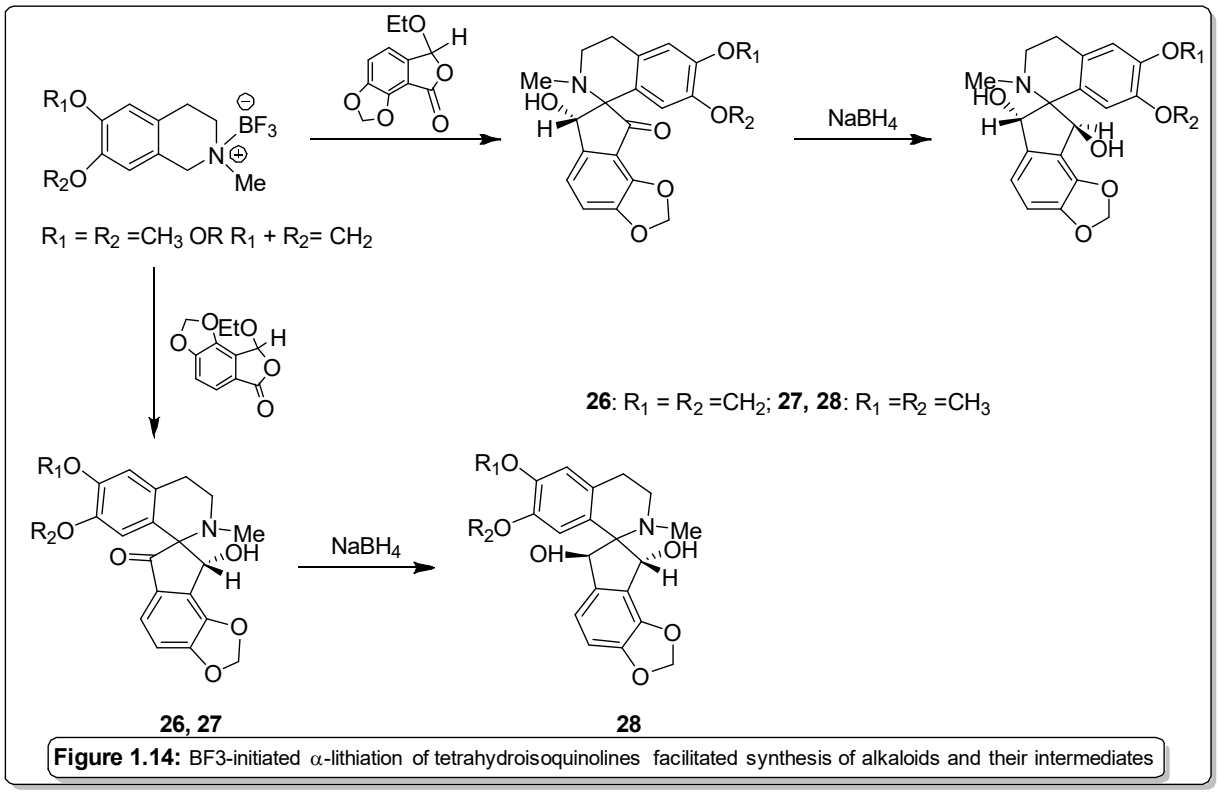
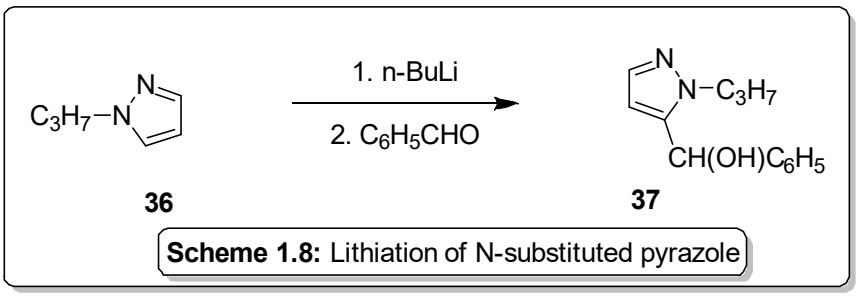


Figure 1.14: BF3-initiated α-lithiation of tetrahydroisoquinolines facilitated synthesis of alkaloids and their intermediates

This methodology is also applicable for tertiary amines devoid of any allylic or benzylic activation like N-methyl piperidine. The BF_3-complex on treating with s-BuLi gets lithiated at the N-methyl group and on subsequent reaction with electrophile gives □- substituted products in 70-80% yield.

Mechanistic Review of Lithiation Reaction

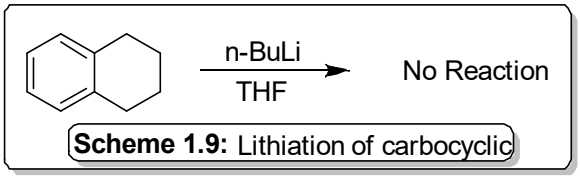
For the □-lithiation of the thiophene, the mechanism initially involves the coordination of the lithiating agent with the heteroatom.[48,9,38] However, it has been demonstrated that thiophene, like benzene, can't be lithiated readily in the ethereal solvent by n-BuLi[49,38]. This evidenced that the sulphur atom in thiophene did not act as a Lewis base like the oxygen atom in anisole, and thiophene did not affect the extent of polymerisation of n-BuLi. The increase in the reaction rate and regioselectivity of most □-lithiation in thiophene was considered to arise due to the "acid-base" mechanism. Further, the acid-base mechanism is supported by the lithiation of the N-substituted pyrazole (36) [50] that occurred at position-5 (37) and not at position-3 which indeed was expected if the pre-coordination of nitrogen positioned second would be a vital factor.



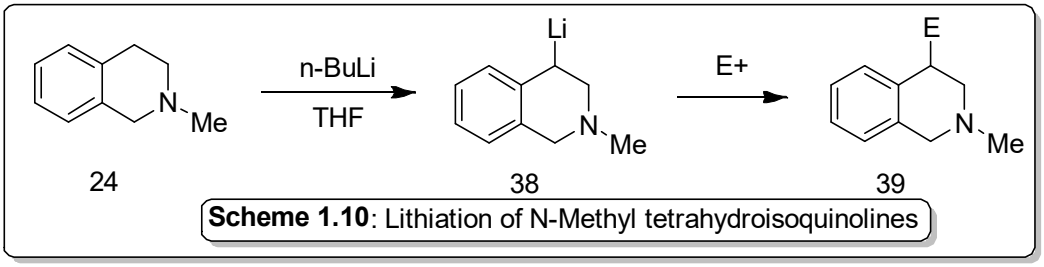
Scheme 1.8: Lithiation of N-substituted pyrazole

In short, it seems that depolymerized/deaggregated lithiating reagents with preferred thermodynamic products resulting the deprotonation of the most acidic proton. In contrast to this, polymerized/aggregated lithiating agents (such as n-butyl lithium in hexane or ethers) gave kinetic products causing deprotonation of the proton closest to the most effective ligand.

Heteroatoms not only facilitate lithiation at □-position but can also affect the generation and reactivity of carbanion away from it. It has been suggested by Davies et al that in the case of N-methyl-1,2,3,4-tetrahydroisoquinoline (**24)**, abstraction of a proton from C-4 is facilitated by the presence of nitrogen in the substrate while there is no deprotonation of benzylic proton in the corresponding carbocyclic system under same conditions.[51,2] This is supposed to occur through RLi association with nitrogen.

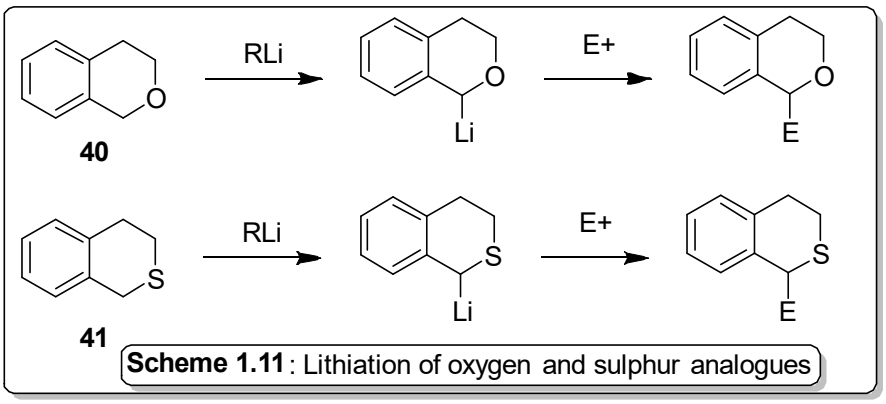


Scheme 1.9: Lithiation of carbocyclic



Scheme 1.10: Lithiation of N-Methyl tetrahydroisoquinolines

In contrast, in the corresponding oxygen[52] and sulfur[53] analogues (**40**, **41**), lithiation and subsequent electrophilic reaction take place at □-position.



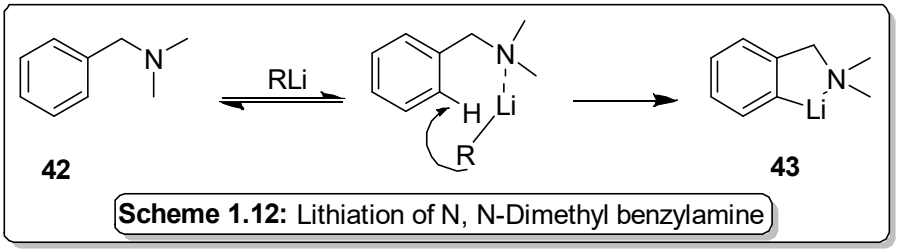
Scheme 1.11: Lithiation of oxygen and sulphur analogues

As aforementioned, □-lithiation involves the substitution of a proton by the lithium atom at the β-position to a functionality having an electron pair. The term "ortho lithiation" is a type of □-lithiation used to designate the deprotonation at the position closer to the directing atom or functionality attached to an aromatic or non-aromatic substrate.

Each functional group has its individual discrete □-directing effect. Therefore, a grading of directing potential was required for the systems bearing more than one directing group. Many research groups have worked on this and their conclusions, combined with additional illative understandings, recommend the following:

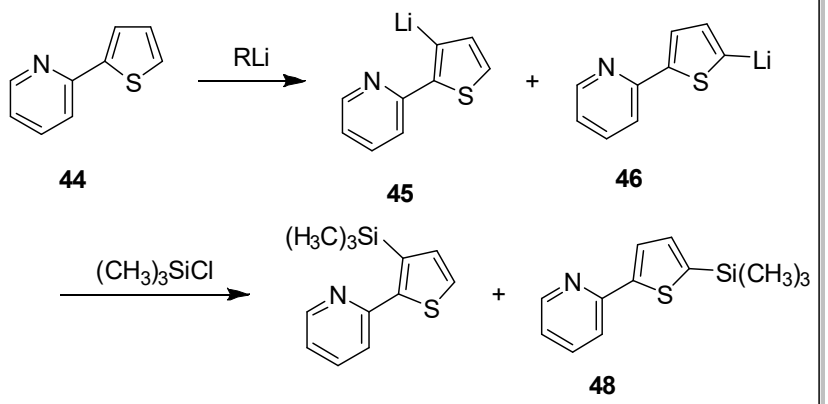
1. For lithiation at low temperature (kinetic conditions), the strongest □-directing group is a good ligand and strongly electron-withdrawing.
2. For a directing heteroatom attached to a □-system through a saturated carbon atom, without any electron-withdrawing effect, the basicity of the nitrogen directs the lithiation.
3. If used deaggregated or depolymerized lithiating agents are, the ranking of the directing group is evaluated from their inductive or acidifying effect.

The "co-ordinative only" mechanism[9] can be best understood by the ortho lithiation of N, N-dialkylbenzylamine[54] (**42**). Here the benzylic -CH2 group imposes a +I-effect on the ortho position and reduces its acidity, still, the lithiation regioselectively occurred at position-2 and at a rate faster than lithiation of benzene.[55,56] It was assumed that initially, the lithium of the reagent coordinates with the lone pair of the nitrogen. Then closely accessible ortho-proton facilitates deprotonation, resulting in internally coordinated isolable organolithium **43**.



Scheme 1.12: Lithiation of N, N-Dimethyl benzylamine

Some interesting lithiation reactions are observed in case both a □- and □-directing functionalities are present in one molecule. Though □-lithiation is preferred over □-lithiation but in some specific cases, both reactions can effectively contend. A pragmatic selection of conditions for the reactions can allow the preference of one over the other. For example, lithiation of 2-(2'-thienyl)-pyridine **44** has two possible sites, the position-3 (corresponding to the □-directing of the pyridine nitrogen) and position–5 (corresponding to the □-lithiation). Selecting appropriate conditions of solvent, temperature, and lithiating reagent, either of the two possible positions can be lithiated preferentially to report the preferential formation of the silane (**47**) or (**48**)[57]. As aforementioned □-lithiation is preferred under kinetically controlled conditions to product **45** which at higher temperature (thermodynamically controlled conditions) slowly equilibrates to the more stable **46** (α-lithiation). At low temperature (kinetic conditions), ethereal n-butyl lithium prefered ligating with the nitrogen and abstracts the nearest proton leading to □-lithiation(**45)**. Conversely, lithiation with dimeric n-butyl lithium in tetrahydrofuran acts as a stronger base and removes most acidic proton(□-positioned) of the thiophene. Similarly, the LDA in ether also furnishes the same result as dimeric n-BuLi which further supports this rationale bearing negligible Lewis acid character.



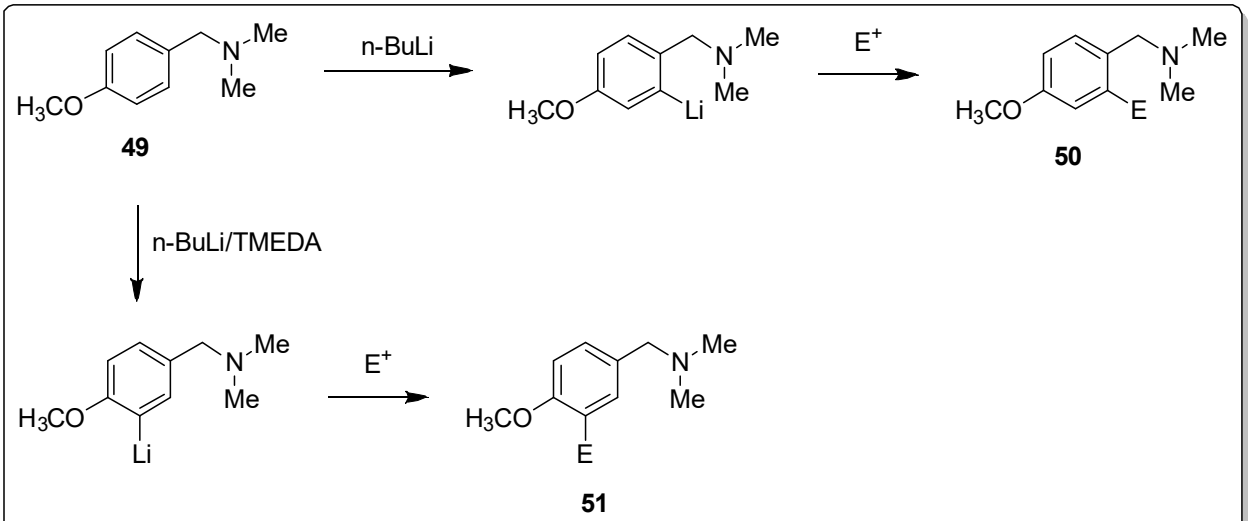
RLi	Solvent	Temperature (° C)	Yield (%) 47	48
n-BuLi	THF	0	4	93
LDA	Ether	0	1	74
n-BuLi	Ether	0	62	13

47

Scheme 1.13: Lithiation of 2-(2'-thienyl)-pyridine

Similarly, in the lithiation reaction of p-methoxy-N, N-dimethylbenzylamine,[58] (**49**) having an α-directing group (methoxy) and a β-directing functionality (N, N-dimethyl), [55,56] lithiation with a polymerized/aggregated lithiating reagent (n-butyl lithium in ether) exclusively prefer at position-2(α-lithiation)**50** due to the higher basicity of the nitrogen ("co-ordination only" mechanism). But

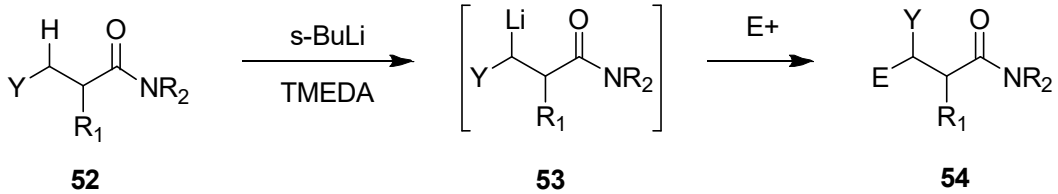
lithiation with n-butyl lithium-TMEDA complex (depolymerized/deaggregated) deprotonates the most acidic proton from position-3(α to methoxy) **51** following the "acid-base" mechanism.[58]



Scheme 1.14: Lithiation of p-Methoxy-N, N-dimethyl benzylamine

With due course of time the concept of the "coordination only" mechanism metamorphosed to lithiation by CIPE (complex induced proximity effect), which extensively and effectively evaluated the stereochemical and regiochemical outcome of varied lithiation reactions.[59,2a]

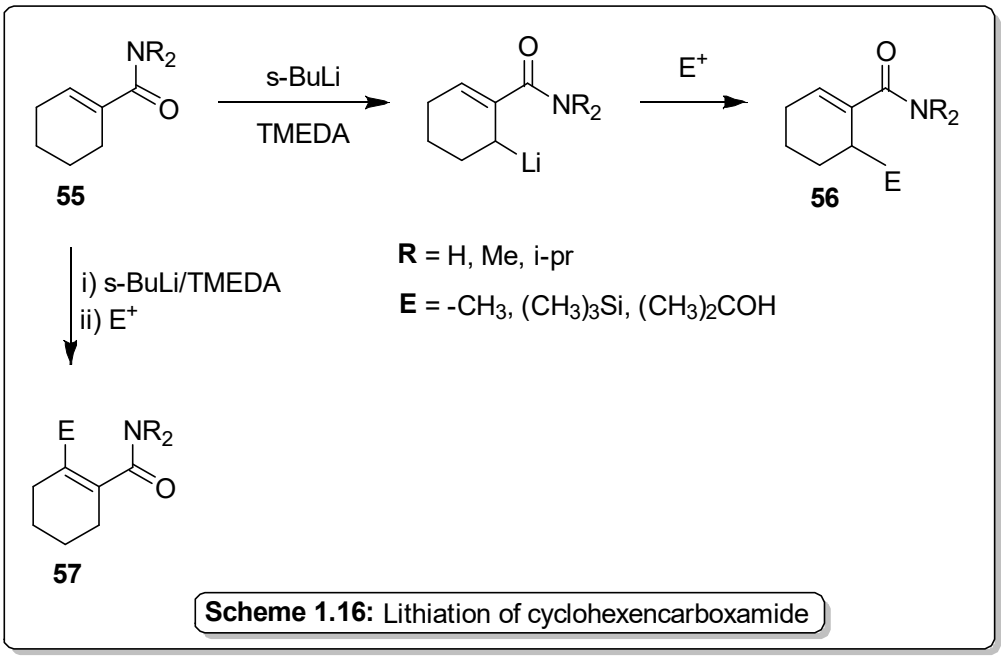
The CIPE is transition state-dependent and was used as a heuristic model irrespective of the detailed reaction mechanism. The concept was used to explicate unanticipated lithiation at the formally distant positions that conformationally have the proximity to the functionality likely to be complexed with a lithiating reagent. The CIPE-directed lithiation can be explained with the help of the following examples; Deprotonation of 52 at the □-position using alkyl lithium reagents provided one of the early reactions which can be explained by the CIPE (**52→53→54**). Although secondary amides have been extensively explored as the complexing group for directing lithiation, the tertiary amides are also equally effective in synthetic applications.[60-62]



Scheme 1.15: CIPE directed Lithiation

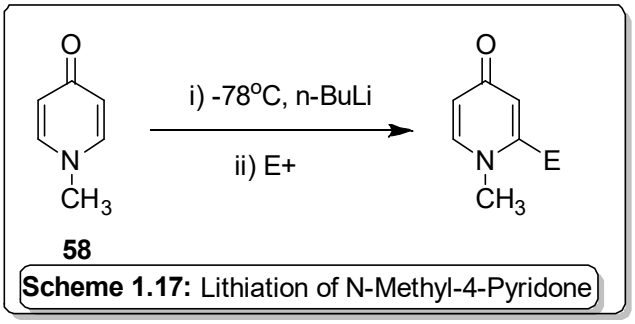
Similarly, in the case of cyclohexencarboxamide (**55**), despite the presence of three possible deprotonation sites i.e., □, □` and □`, lithiation occurs only at the □-position which is governed by

the CIPE of the carboxamide group.[63,2a] After the addition of electrophiles, only product **56** is formed and the formation of **57** was never observed.

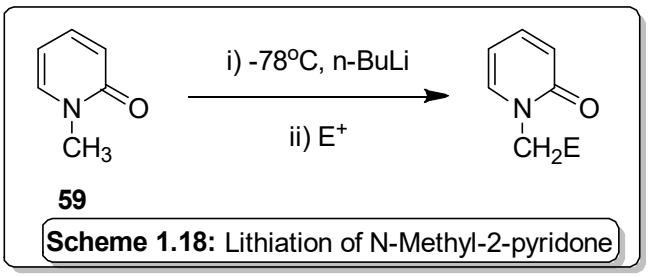


Scheme 1.16: Lithiation of cyclohexencarboxamide

Lithiation in the case of 4-pyridone (**58)** takes place exclusively in the ring to give a dipole stabilized carbanion but in the case of 2-pyridone (**59)**, under the same conditions, lithiation takes place at the N-methyl group via a CIPE process.[64]



Scheme 1.17: Lithiation of N-Methyl-4-Pyridone



Scheme 1.18: Lithiation of N-Methyl-2-pyridone

As mentioned earlier, ortho lithiation is a well-established example of complex induced lithiation. [65,66a] According to the proposed mechanism, the directed ortho metalation (DoM) process follows a sequential three-step process (**figure 1.15**):

1. The interaction of the aggregates of lithiating reagent with the heteroatom of the directed metalation Group (DMG),
2. Abstraction of ortho-proton to give the ortho Lithiated intermediate
3. Subsequent treatment with an electrophile to give the product.

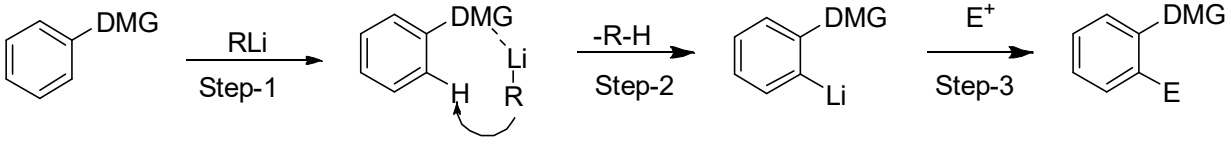
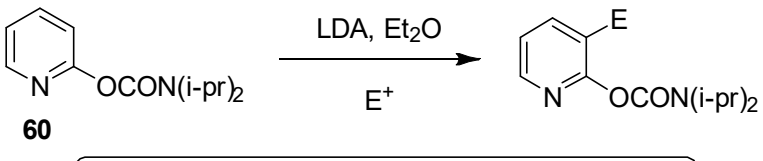


Figure 1.15: Sequences in DoM

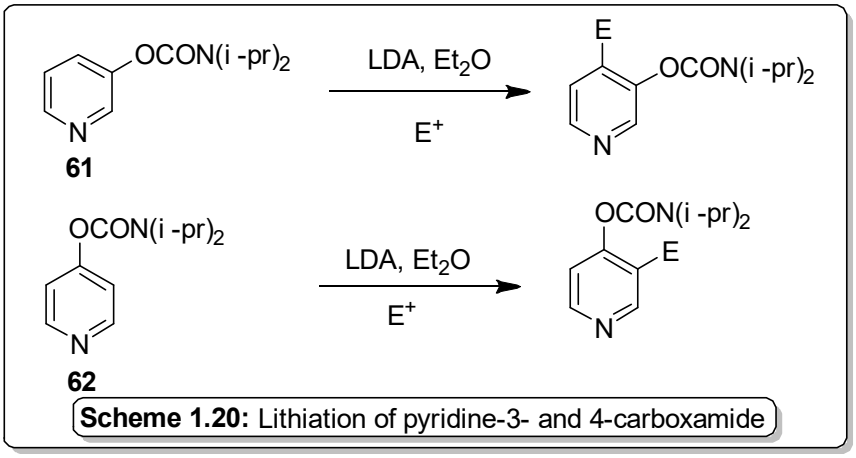
The potential of ortho lithiation depends on the chemical properties of the substituent and the relative competencies of different functional groups in directing ortho lithiation. The relative efficiencies of various DMG have been experimentally evaluated and established by many research groups and laboratories [66-68] $-OCONR_2 > -SO_2Bu^t \approx SOBu^t > CONR_2\ CON^-R > SO_2NR_2 \approx SO_2N^-R > CO_2^- > OMOM > N^-BOC \approx N^-COBu^t > -(CH_2)_n NR_2 > -F > -OCH_3 > -CH_2CH_2NR_2 > -NR_2 > -CF_3$.

The effect of the ortho directing group is not limited to the benzene ring but these are equally effective in inducing ortho-lithiation in heteroaromatic systems.[69,70] There are many examples in the literature where the CIPE of the DoM (Direct ortho metalation) group governs the ortho lithiation in various heteroaromatic systems. It is reported that lithiation in the case of various pyridine carboxamide (**60**-**62**) takes place always at a position ortho to the carboxamide group and there is no effect of ring acidity as well as the position of directing group with respect to nitrogen of pyridine ring on lithiation position.[71]



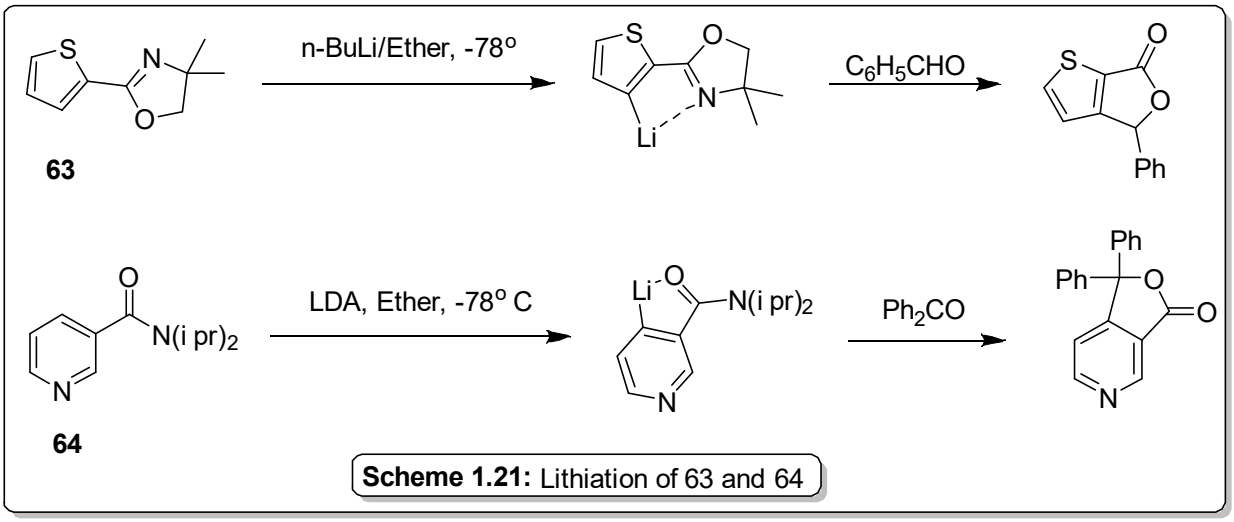
60

Scheme 1.19: Lithiation of Pyridine-2-carboxamide



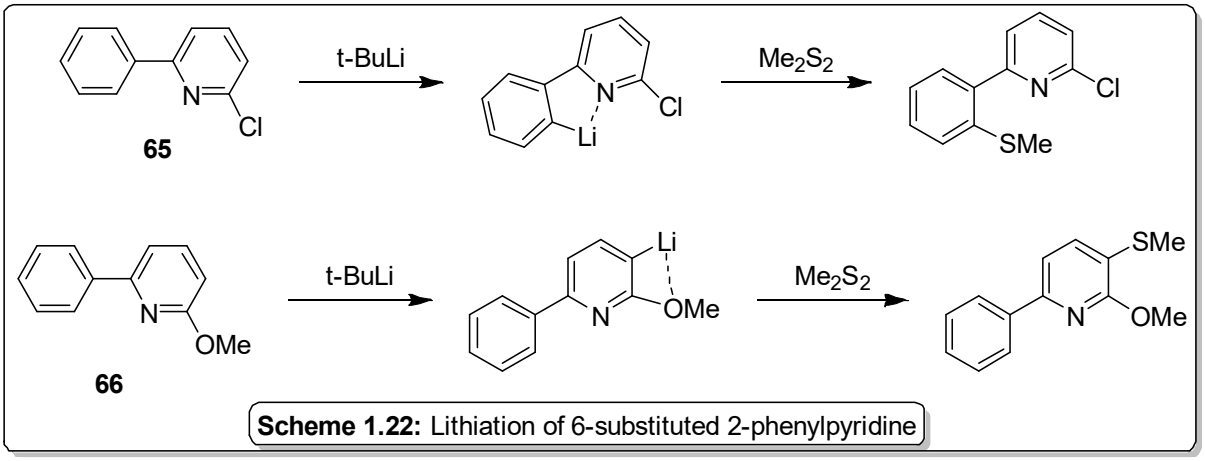
Scheme 1.20: Lithiation of pyridine-3- and 4-carboxamide

The methodology of heteroaromatic ortho lithiation finds good use in the synthesis of mono or poly substituted heterocyclic and bicyclic compounds with one or more heteroatom in the ring.[70] It also provides an easy and short route to many naturally occurring compounds, alkaloids, steroids etc.[69,72]



Scheme 1.21: Lithiation of 63 and 64

Yves Fort and Rodrigue reported that lithiation of 2-aryl-6-chloropyridine (**65)** with t-BuLi in diethyl ether and cumene (1:1) takes place exclusively on the benzene ring and at a position ortho to the pyridine group but when –OMe replaces -Cl in **66**, lithiation takes place in the pyridine ring ortho to the –OMe.[73]



Scheme 1.22: Lithiation of 6-substituted 2-phenylpyridine

Lateral lithiation[74] is another class of heteroatom-facilitated lithiation reaction which plays a significant role in the synthetic elaboration of aromatic and heteroaromatic structures. Mechanism of lateral lithiation is also co-ordination assisted in most cases. Several groups are reported in the literature which induce lateral lithiation, for example, carboxylic acid derivatives, secondary and tertiary amides, nitriles, oxazolines, tetrazoles, dialkyl carbamates, ethers, carboxamide etc.[74]

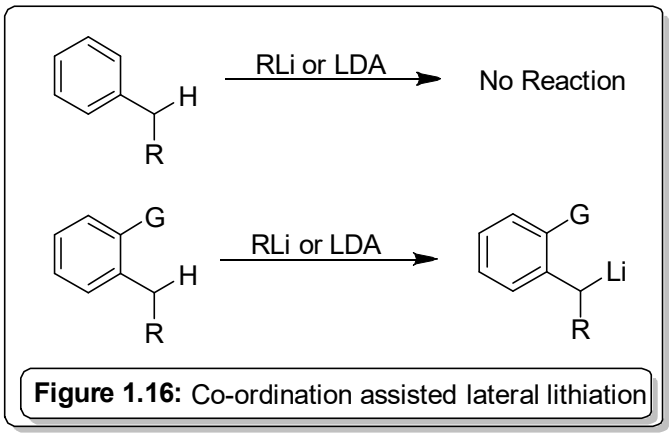
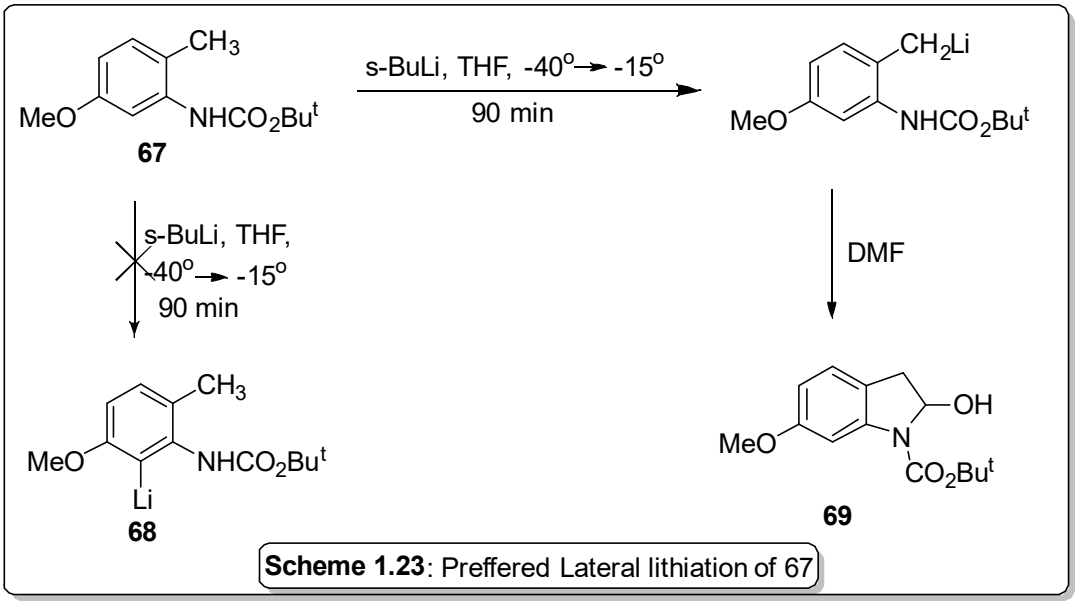


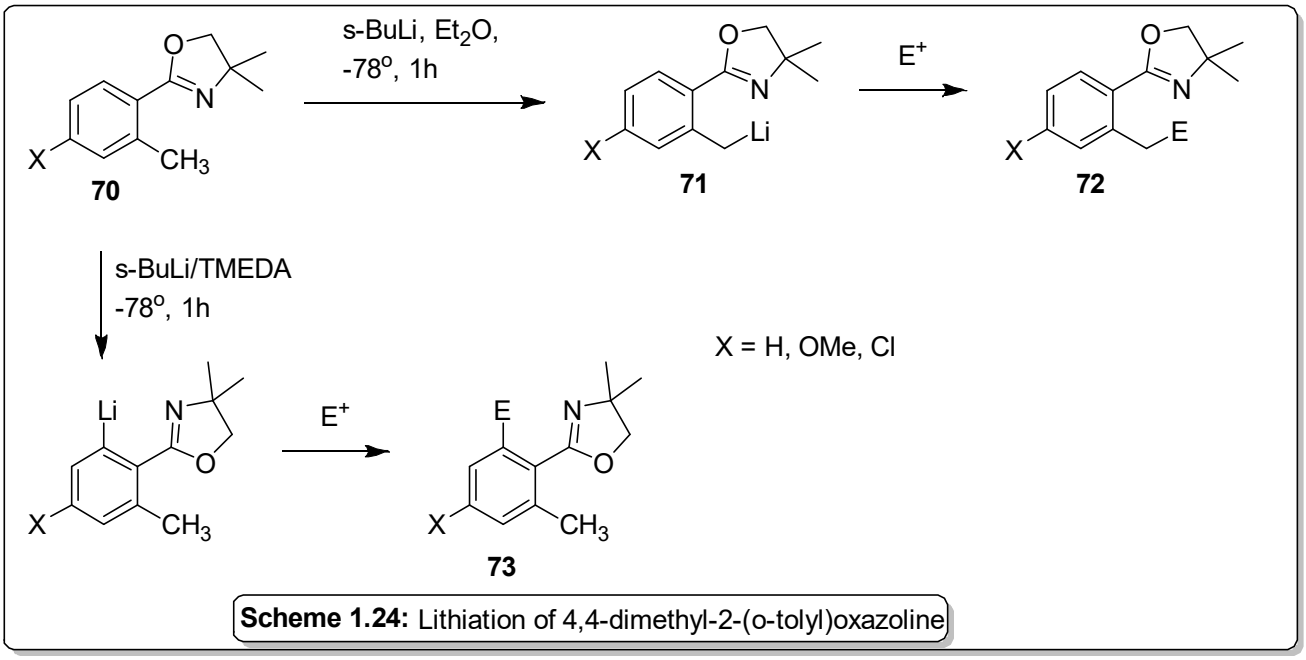
Figure 1.16: Co-ordination assisted lateral lithiation

There is always a competition between lateral and ortho-lithiation and generally, lateral lithiation is preferred over ortho-lithiation. Lithiation of BOC-*o*-toluidine (**67**) can take place either at position-6 or at lateral position i.e. at $–CH_3$. The ortho position appears to be more reactive as it is doubly activated by the combined effect of $–OCH_3$ and Boc Group. However, product **68** of lithiation at the position-6 is not observed and only product **69** is obtained which is a result of lateral lithiation.[75]



Scheme 1.23: Preffered Lateral lithiation of 67

Moreover, one can even control regioselectivity at ortho or lateral position for the same directing group by using different reaction conditions for lithiation. It has been reported that in the case of 4,4-dimethyl-2-(*o*-tolyl)oxazoline (**70)** the reaction with s-BuLi in diethyl ether induces lateral lithiation (**72**), but the addition of TMEDA shifts the lithiation to the ortho-position (**73**).[76]

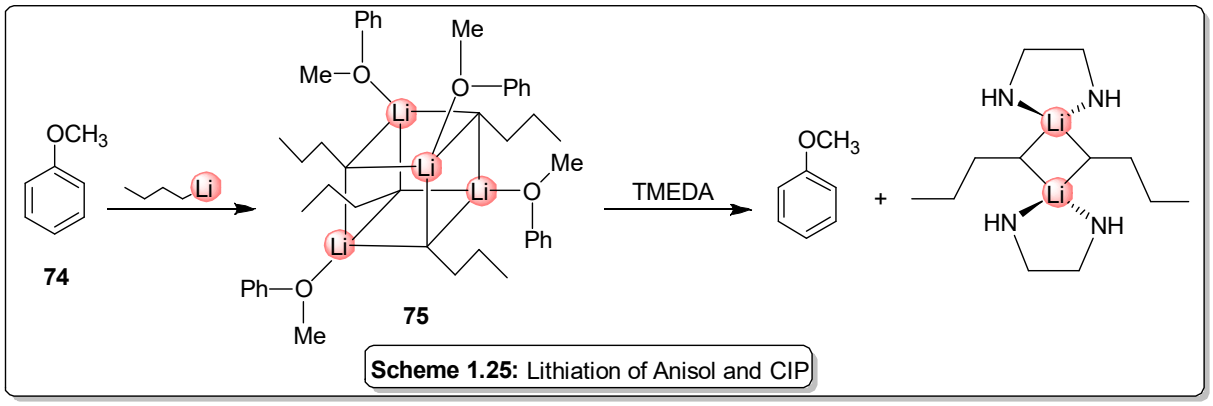


Scheme 1.24: Lithiation of 4,4-dimethyl-2-(o-tolyl)oxazoline

From the above-mentioned examples, it could be inferred that the substrate heteroatom can affect the course of the lithiation-substitution reaction and may control the regioselectivity of metalation by coordination with the lithium. However many aspects of the mechanism of complex induced lithiation are still not very clear. Despite numerous studies, some controversies and uncertainties are still present in the two prevalent concepts. According to one concept[31] lone pair of the heteroatom of the substrate coordinates with the lithium to form a pre-lithiation complex. As a

result, the complex brings the lithiating reagent in close vicinity to the acidic proton furnishing the observed regioselectivity. Beak[59,77] and Saa[78] and many other researchers have tried to establish this mechanism with the help of various studies.

Quantum evidence supports the coordination of the lithium to the heteroatom in the ground state.[79] In the case of anisole (**74**)[80] and 1-methoxynaphthalene[81] co-ordination of butyl lithium with oxygen **75** is well established by NMR spectroscopic studies. But no reaction takes place under these conditions. Ortho lithiation was observed on the addition of TMEDA but no complexation was detected under these conditions.



Scheme 1.25: Lithiation of Anisol and CIP

In the case of N, N-dimethyl benzylamine, it was established with the help of NMR studies that there are strong interactions between Li and nitrogen atom of the substrate even in the presence of coordinating solvents like THF, TMEDA, PMDTA and HMPA.[72b,82b] It has been observed that these chelating groups stabilize the dimeric state more than the monomeric one.[82]

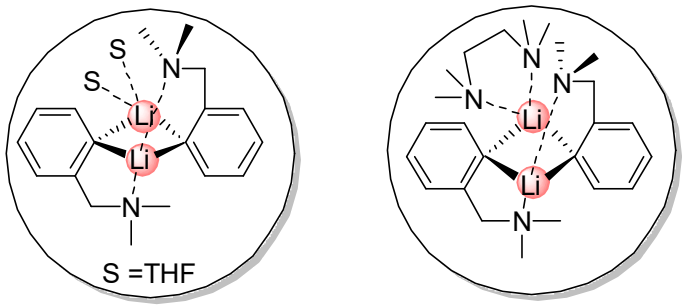
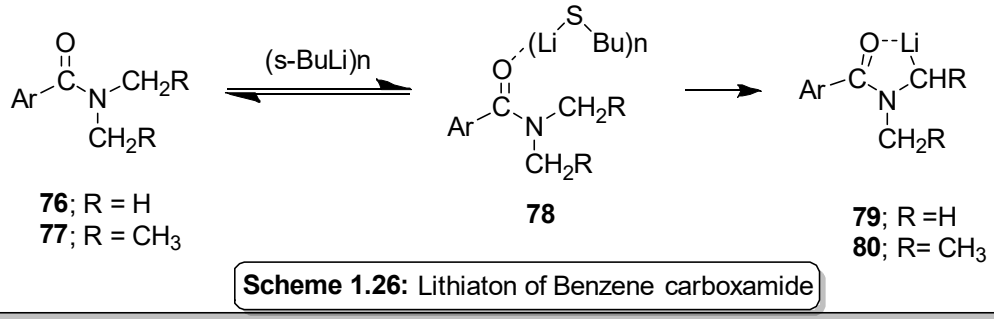


Figure 1.17: Chelating group stabilizing lateral lithiation of N, N-Dimethylbenzyl amines

The evidence for the involvement of pre-lithiation complexes in the reaction pathway is limited. Over the last two decades, many research groups have tried to establish its existence with the help of various spectroscopic and kinetic studies.

The spectroscopic studies on □`-lithiation of carboxamide **76** and **77** were carried out by Beak and Smith.[83] Kinetics of the reaction was followed by stopped-flow IR spectroscopy. The IR band at 1645-1655 cm^{-1} was assigned to the carboxamide **76**, **77**, 1618-1625 cm^{-1} band was assigned to the pre-lithiation complex **78** and 1560-1590 cm^{-1} band was assigned to the carbanion **79**, **80**. It

was concluded from the kinetic data that the rate of disappearance of amide **76** and the complex **78** is the same as the rate of the appearance of □`-lithiated product **79**.



Scheme 1.26: Lithiaton of Benzene carboxamide

Parallelly, the CIP-directed lithiation was also observed during the lithiation of 76 with s-BuLi in cyclohexane as solvent at room temperature to furnish **79**.[83] The reaction involves the instant formation of differentially complexed tetrameric s-BuLi with favourable equilibrium constants. Lithium complexed substrate **81** shows only one amide complexed structure for clarity, though in actuality there are three more amides complexed to the tetrameric form of organolithium and are 1000 times more activated in comparison to the normally complexed tetramers. The increased concentration of s-BuLi decreases the initial rate constant for the formation of **79**. This is because the increased concentration of s-BuLi decreases the concentration of **81**. The proton transfer is favoured by the transition structure **82** resulting from the high reactivity of **81**. The best part of this is that even the addition of TMEDA does not interrupt the s-BuLi tetramer rather it endorses deprotonation by supporting the exclusion of the carbanion in the transition state by deprotonation, similar to that of **82**.[22]

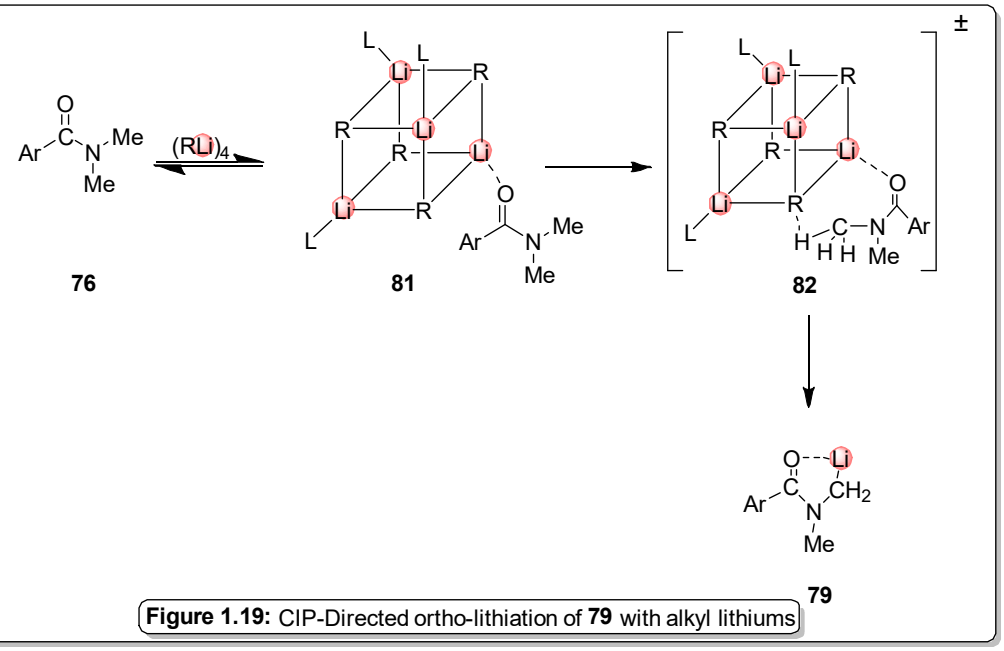
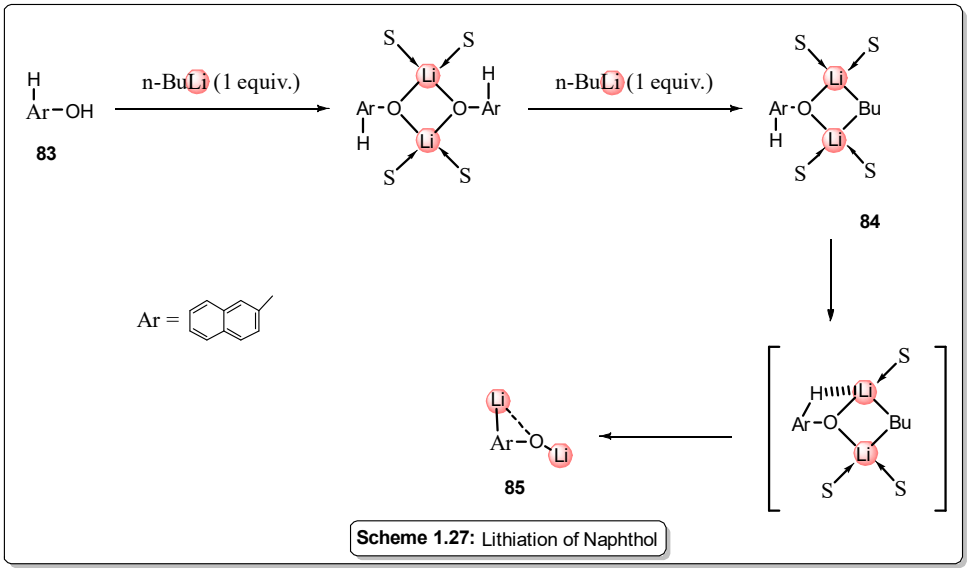


Figure 1.19: CIP-Directed ortho-lithiation of **79** with alkyl lithiums

As discussed earlier, in the case of anisole (**74**) there is direct NMR evidence of co-ordination between oxygen and lithium in the ground state but surprisingly no lithiation occurred under these conditions.[80] On the other hand, a study on the reaction of naphthol (**83**) with n-BuLi by J. M. Saa gave definitive evidence of the existence of a mixed aggregate of type $[(ArOLi)_m.(RLi)_n]$ as an intermediate in the lithiation reaction [84]. Various ratios of naphthol and n-butyllithium in TMEDA like 1:1 (A), 1:2(B), 1:3(C), 1:4(D) etc have been studied. Only one set of signals was observed in ^{1}H NMR in the case of (A) but for all other mixtures (B), (C) and (D) duplicate signals were present both in ^{1}H and ^{13}C spectra. ^{7}Li NMR of (B), (C) and (D) showed three signals assigned to **83**, **84**, and **85** respectively and for (A) there was only one signal in ^{7}Li NMR. From ^{7}Li-^{1}H HOESY spectra of mixed aggregates, it is indicated that peri-hydrogen is closest to the lithium atom and lithiation takes place at the same position.



Scheme 1.27: Lithiation of Naphthol

It was believed that a better insight into the number of steps involved in proton abstraction during lithiation reaction could be extracted from the proton/deuterium isotope effects. For a symmetrical proton transfer, at low temperature, the value of the primary H^+/D^+ isotopic effect is around 25±5 expected. A low value of the H/D isotopic effect indicates either a highly asymmetric proton transfer or that deprotonation is not a rate-limiting step. Reactions involving the transfer of two available symmetrical protons can be specifically more revealing as a direct evaluation of inter and intra-molecular isotope effects can be done.[85,86] In an intermolecular relative experiment, the rate of proton and deuteron abstraction in undeutrated and dideutrated substrates are measured and compared while an intra-molecular experiment involves the replacement of one of the two potential hydrogens with deuterium and the relative selectivity of proton or deuteron abstraction is measured.

Intermolecular:

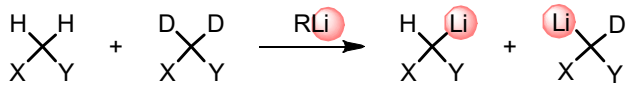


Figure-1.20: Intermolecular relative experiment

Intramolecular:

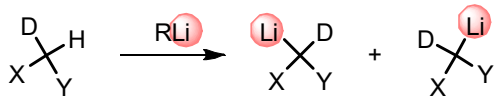


Figure-1.21: Intramolecular relative experiemnts

The lithiation reactions can be envisaged to involve two reaction sequences.

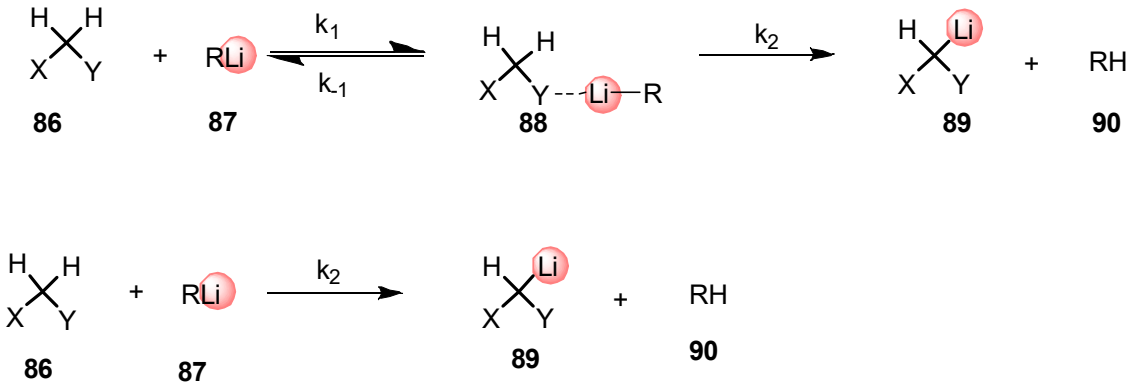
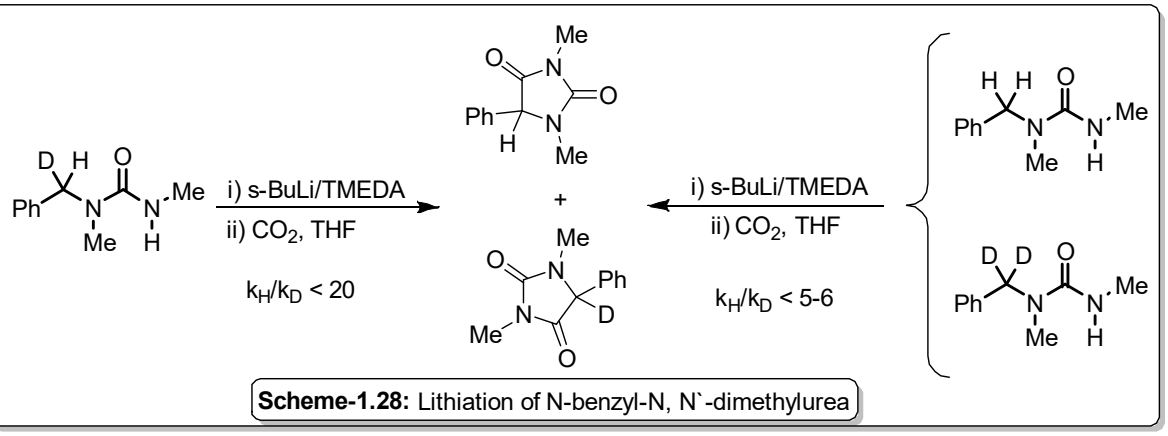


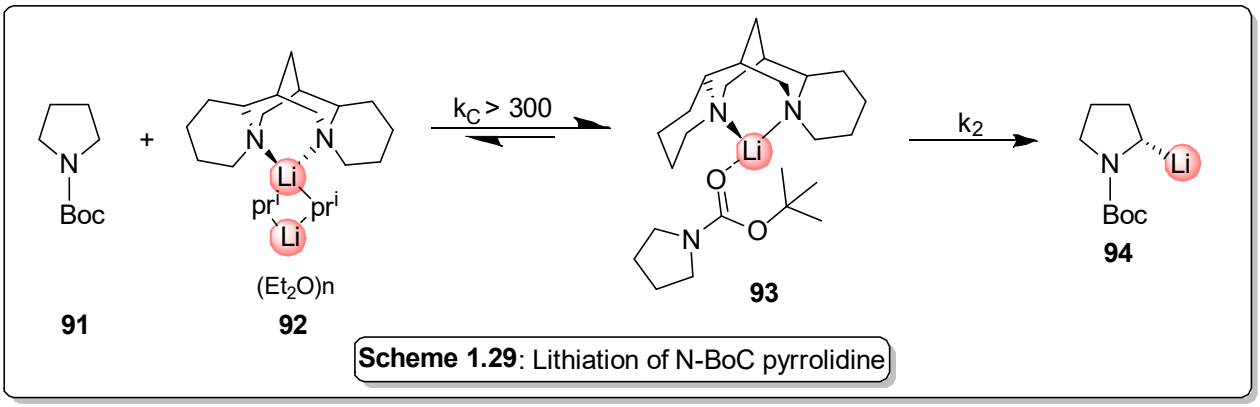
Figure-1.22: Two possible reaction sequences in lithiation

Beak et al have studied inter and intra-molecular isotope effect for benzylic lithiation of N-benzyl-N, N`-dimethylurea by treating it with s-BuLi/TMEDA at –78° and reacting with electrophiles like CO_2 and dimethyl sulphate.[85,86] based on the magnitude of isotopic effect for Intra (>20) and inter (5-6) molecular reactions, it was concluded that the complexation process is rapid and is followed by a slower deprotonation step.



Scheme-1.28: Lithiation of N-benzyl-N, N`-dimethylurea

To order to evaluate the reaction kinetics, the □-lithiation of N-Boc-pyrrolidine (**91**) with diethyl ether complexed diisopropyl lithium-(-)-sparteine (**92**) was carried out to obtain **94,** an excess concentration of organolithium is used (under pseudo-unimolecular conditions).[87] During the lithiation reactions of **91** and 2, 2, 5, 5-tetradeutrated **91**, a high value of the intermolecular-isotope-effect specifies deprotonation as the slowest rate controlling step. The exact structure of **92** complexes, which act as a base, was confirmed by ^{1}H, ^{13}C and ^{7}Li NMR spectroscopic studies. These observations are also consistent with the formation of the prelithiation complex 93 with an equilibrium constant $k_c > 300$.

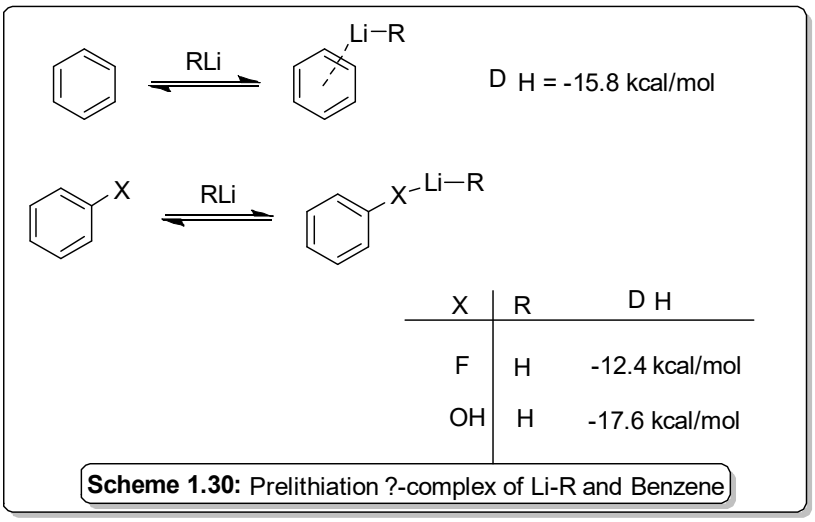


Scheme 1.29: Lithiation of N-BoC pyrrolidine

The complex induced lithiation was associated with some anomalies[80,89-91] and this can be further explained by a different advanced concept termed "kinetically enhanced metalation". [88a] According to it, heteroatom kinetically enhances the deprotonation of the hydrogen adjacent to the organolithium base by coordinating with it in the transition state. According to this concept, no isolable intermediate formed during the reaction pathway before the deprotonation. Any stable coordinated species, if formed, may be intricated in a side-product process.[88]

In support of the proposed mechanism, Schleyer has given results of ab intio calculations [MP^2/6-31+G*//6-31G*] by taking benzene, fluoro-benzene and phenol as substrates and lithium hydride as a base. Some of the important results are:

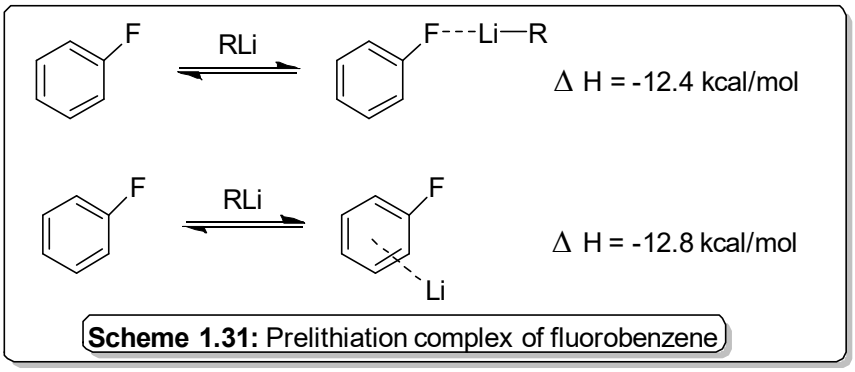
If a pre-lithiation complex is considered as an active intermediate in lithiation reaction then the □-complex of Li-H and benzene is -15.8 kcal/mol more stable than starting material. Similarly complex of LiH with phenol and fluorobenzene is -17.6 kcal/mol and -12.4 kcal/mol more stable than the respective separated species.



X	R	D H
F	H	-12.4 kcal/mol
OH	H	-17.6 kcal/mol

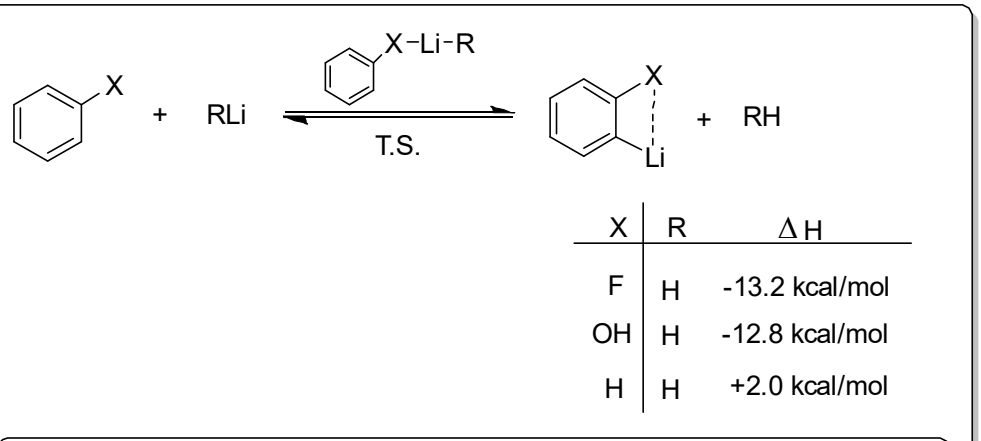
Scheme 1.30: Prelithiation ?-complex of Li-R and Benzene

Similarly, the complex in the case of fluorobenzene is 0.4 kcal/mol more stable when Li is complexed with benzene than when it is complexed to F. Hence one can expect benzene to be more reactive than fluorobenzene, and fluorobenzene to be metallated at para-position if the complex formation is the determining factor for reactivity and regioselectivity.



Scheme 1.31: Prelithiation complex of fluorobenzene

But if the reaction occurs through a single-step mechanism, the calculated overall energy supports the experimental observations. For phenol and fluorobenzene it is -12.8 kcal/mol and –13.2 kcal/mol whereas for lithiation of benzene and para-lithiation of fluorobenzene it is +2.0 and +0.3 kcal/mol respectively.



X	R	ΔH
F	H	-13.2 kcal/mol
OH	H	-12.8 kcal/mol
H	H	+2.0 kcal/mol

Scheme 1.32: Energy changes during lithiation reaction of substituted benzene

The natural charges present on lithium, ipso carbon C-1, the drifting hydrogen atom and the halide ion are also very comparable to the transition state. Moreover, the charge on the migrating hydrogen atom is very low. Hence, metalation should be considered as a transfer of hydrogen rather than the proton.

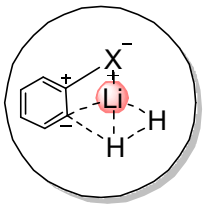


Figure 1.23: Natural charges on atom in Transition state

All these calculated values support a single-step mechanism and counter the concept of lithiation through a pre-lithiation complex. Several similar types of studies have also been carried out by taking anisole, benzene, fluorobenzene and N, N-dimethylaniline as substrate and methyl lithium as a base. To study the effect of aggregation, a mixed aggregate of methyl lithium and lithium hydride was chosen as the base. The result of the ab initio calculations [88b] is quite similar to the earlier results but is important because the substrates and the base chosen for this study are more close to the actual system.

In density functional computational studies by Collum in 2006, several issues of interest in lithiation have been addressed. The influence of electron-withdrawing groups in the lithiation of fluoro aryl carbamates was investigated. When compared with the carbamates without the fluorine, the presence of the halogen was estimated to cause a 5kcal/mol reduction in ΔG^{*}. It was considered to be an inductive effect of fluorine. By comparison, metalation in which the lithiating agent is associated with fluorine is slightly less favourable (**Figure 1.2 A, B** and **C** below). Most surprisingly, a meta methoxy substituent does not seem to facilitate the carbamate lithiation (**Figure 1.2 D** and **E**). In this computational study, Me_2NLi was used as the model base and Me_2O as the model solvent. The absence of activation by ancillary (non-coordinating) meta methoxy moiety seems to be general [92a] and has been further observed by Kessar and *etal*.[92b]

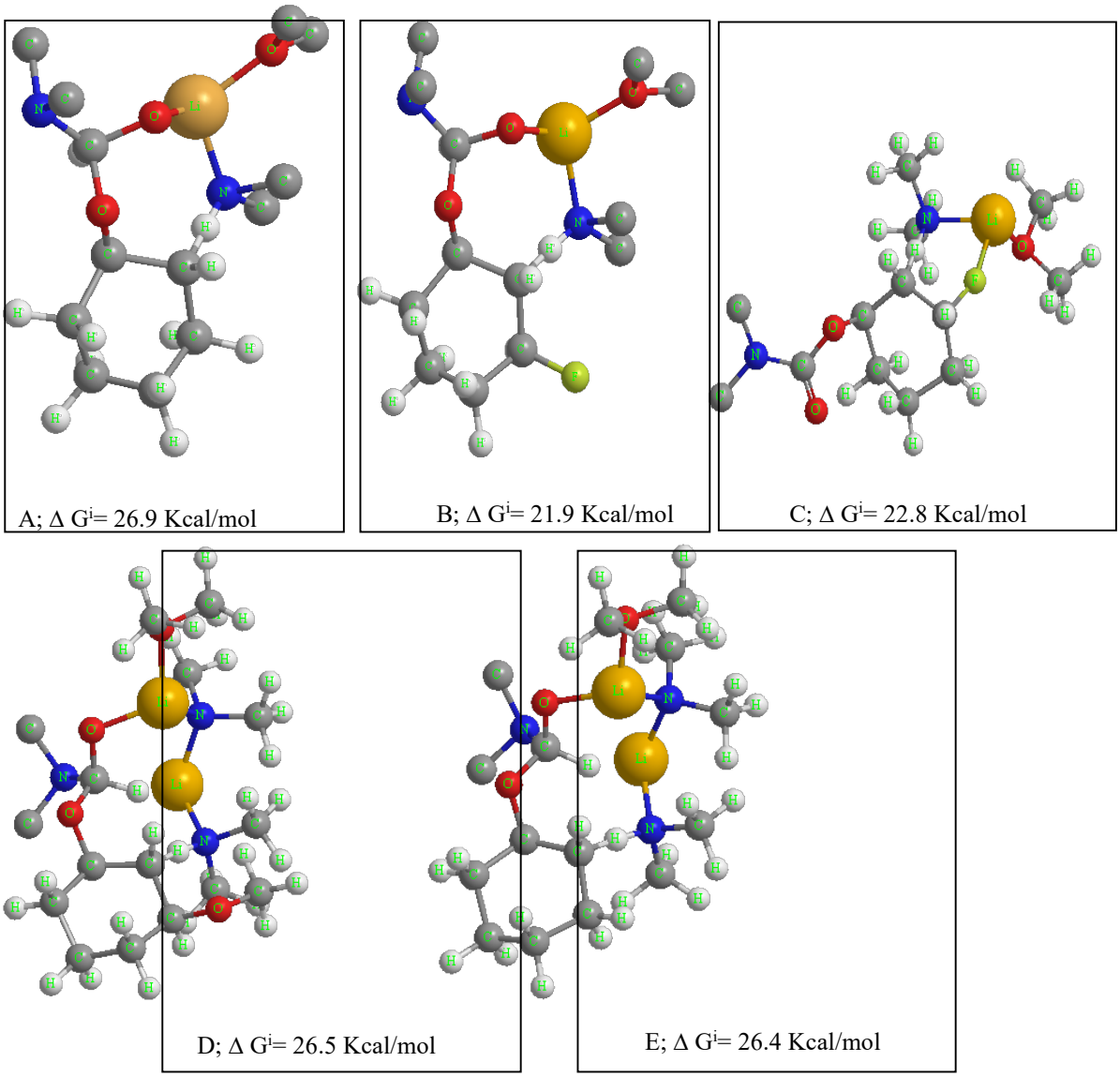


Figure 1.24: Transition Structures of monomer (**A, B** and **C**) and dimer (**D**, **E**) based ortho lithiation of unsubstituted (**A, D**) and substituted (**B, C** and **E**) carbamates.

Asymmetric Lithiation Reactions and the mechanism involved

The other important aspect of these lithiation/substitution reactions is the induction of chirality i.e., enantioselectivity can be induced through chiral ligand-mediated lithiation/substitution reactions. This strategy focuses on the interaction between a lithium-ion bearing a chiral ligand and a developing or previously formed carbanion. This intermediate is forced into a specific configuration, either through a preferred diastereomeric transition state in the course of deprotonation or because of the establishment of a state of equilibrium. The efficiencies of several chiral ligands have been studied and Lupin alkaloid (-)-sparteine seems to be of particular interest in this protocol. It not only

has remarkable suitability as an asymmetric bidentate ligand but has unsurpassed efficiencies and the scopes of application.[93,2b]

Enantioselective synthesis is the transformation of a symmetric substance R_1 selectively into one isomer out of the two possible asymmetric isomers i.e. **CP1** or **epi-CP1**. The stereoselectivity of these reactions depends on the three aspects [94];

a. Selectivity at the stage of formation of the chiral metal intermediate **CM1** or **epi-CM1**;
b. The relative rate of Epimerization between **CM1** and **epi-CM1** and the subsequent reaction (substitution) with electrophiles;
c. The mechanism followed in the substitution by an electrophile.

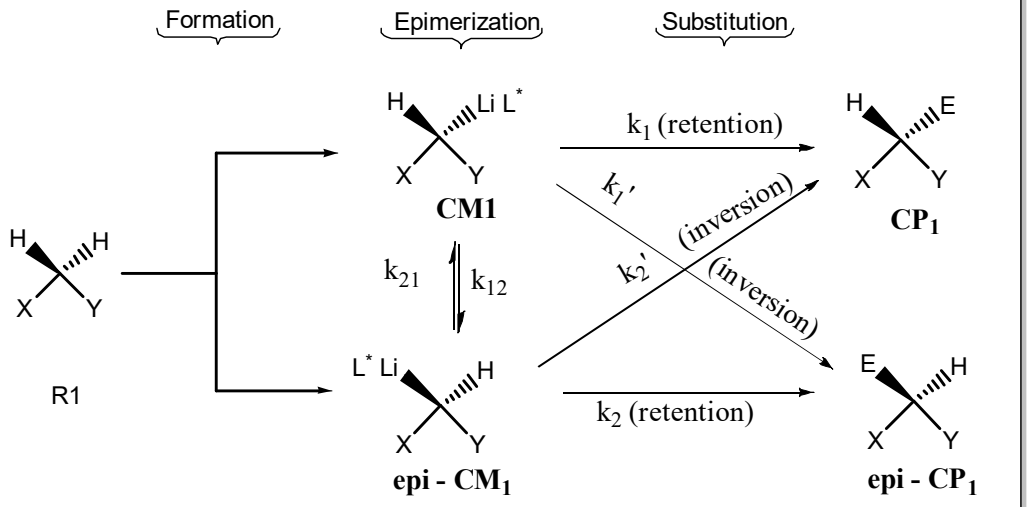
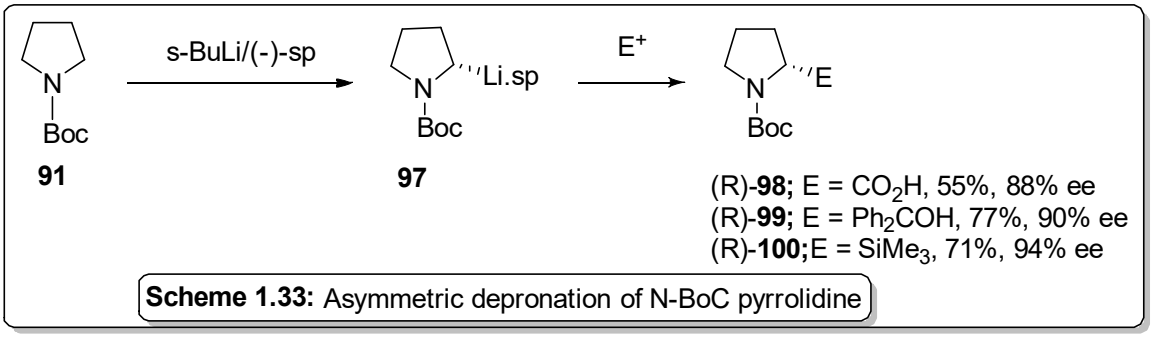


Figure 1.25: Three aspects of stereochemistry in lithiation-substitution reaactions

Any variation in the aforementioned factors can change the stereochemical result of these reactions. The stereochemistry can be transformed by any of these three available limiting pathways:

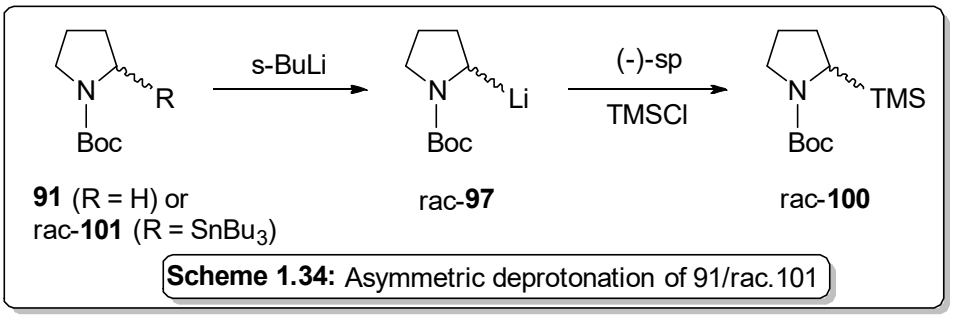
i) **Asymmetric Deprotonation-** A stereoselective formation of the **CM1** or **epi-CM1** by asymmetric deprotonation provides a configurationally stable intermediate; which on stereoselectively reacting with the electrophile, provides the enantioenriched product. The second step involving the reaction with electrophile may not influence the enantioinduction.[93]

For example, the stereoselective deprotonation reaction of N-Boc-pyrrolidine (**91**) is carried out with s-BuLi/(-)-sparteine complex giving stereoselective intermediate (R)-**97**, and this reacts with electrophiles to afford products **98-100** with a good enantiomeric excess of 88-94%.



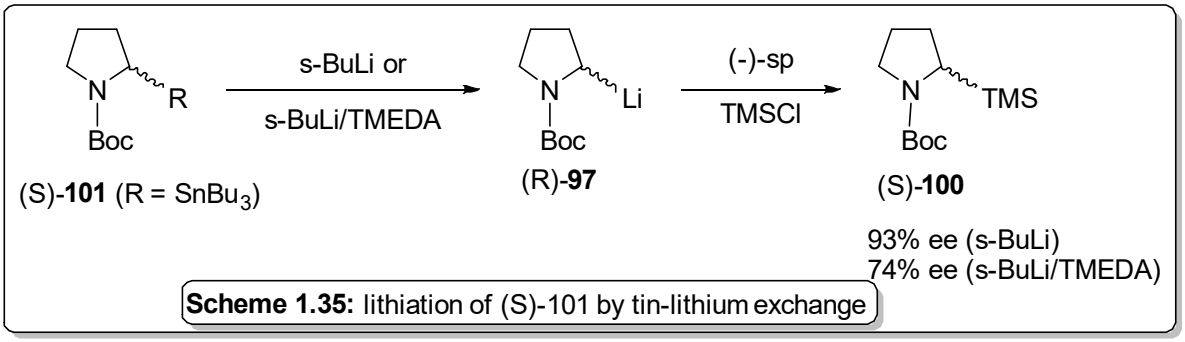
Scheme 1.33: Asymmetric depronation of N-BoC pyrrolidine

If the sequence of asymmetric deprotonation involves the addition of (-)-sparteine followed by the subsequent addition of TMSCl into the racemic 2-lithio-N-Boc-pyrrolidine (rac-**97)**, which is prepared either directly lithiating of **91** with s-BuLi or doing the tin-lithium exchange on rac-**101**, affording only racemic **100**.[95]



Scheme 1.34: Asymmetric deprotonation of 91/rac.101

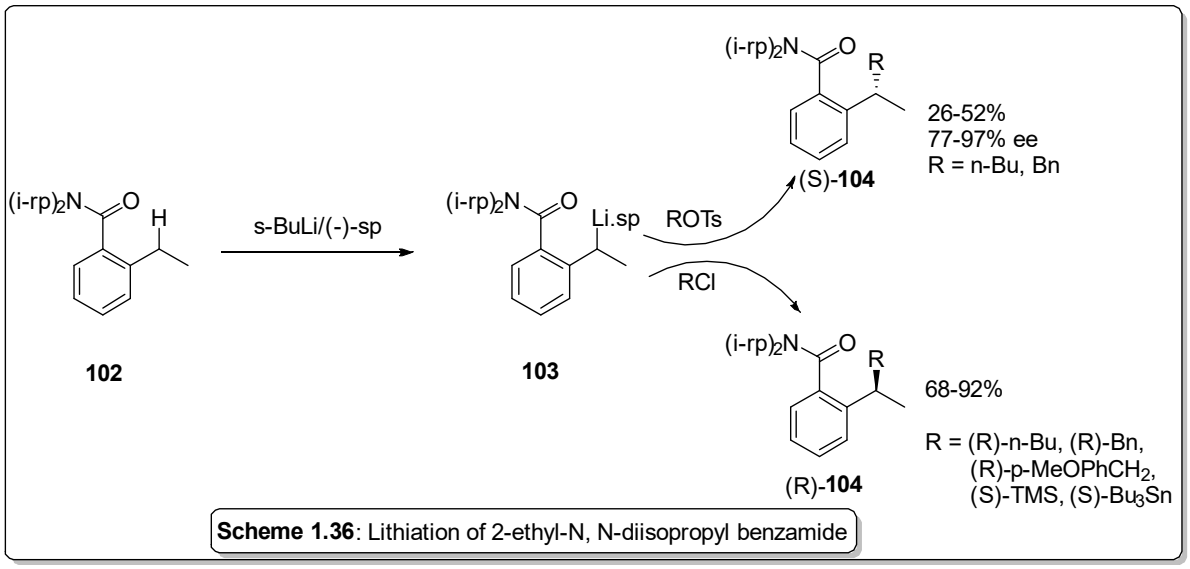
Further, the configurational stability of the intermediate **97** was also assessed by the stereoselective formation of (R)-**97** using the Tin-lithium exchange reaction of (S)-**101** (96% ee) in both the absence and presence of TMEDA. The resulting (R)-97 is treated with (-) sp followed by the addition of trimethyl silyl chloride. The obtained product (S)-**100** was highly enantioenriched.[96]



Scheme 1.35: lithiation of (S)-101 by tin-lithium exchange

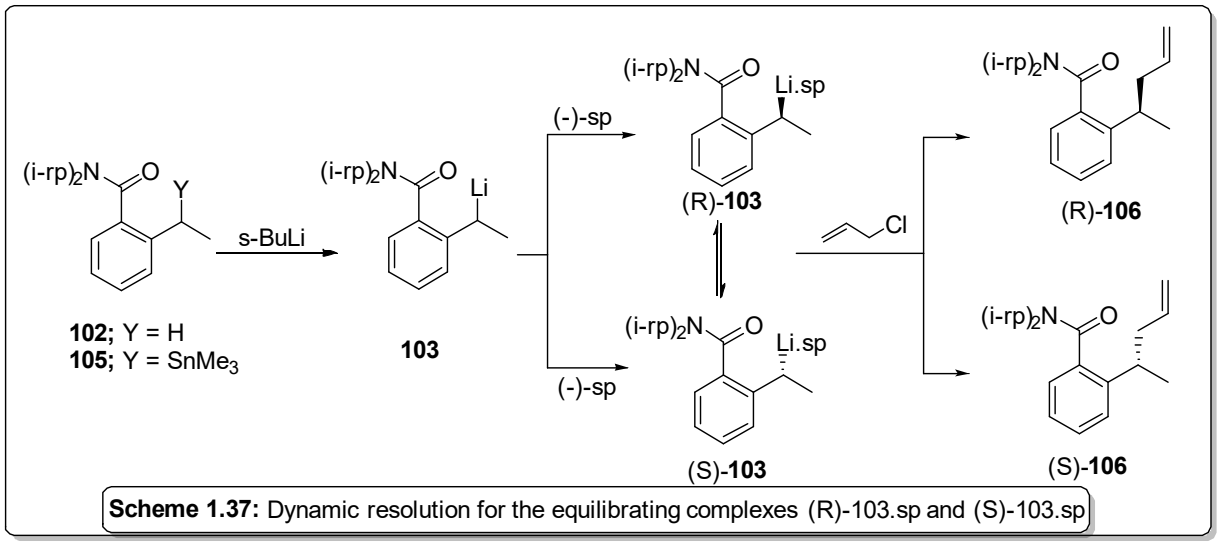
ii) **Dynamic Kinetic Resolution-** When the lithiated intermediate is configurationally labile means both the stereoisomers (CM_1 and epi-CM_1) are in equilibrium with each other then stereoselectivity can arise if the transition state energy for each diastereomeric intermediate (CM1 and epi-CM1) is different at the stage of electrophilic substitution. Under these conditions, stereoselectivity can be achieved if the rate of reaction of one of the diastereomers with electrophile is faster than its rate of epimerization under the given reaction conditions.

During the lithiation of 2-ethyl-N, N-diisopropyl benzamide (**102)** with s-BuLi/(-)-sparteine, generated the **103**.sp reacted with different electrophiles to obtain the product **104** in appreciable yields and excellent stereoselectivities.[97] The nature of leaving group also influences the stereoselectivity of these reactions. For instance, in the case of alkyl halides the products (R)-**104** were obtained with 80%, 74%, and 28% ee respectively. While with alkyl tosyl as an electrophile (S)-**104** was obtained with a much enhanced 97% ee.



Scheme 1.36: Lithiation of 2-ethyl-N, N-diisopropyl benzamide

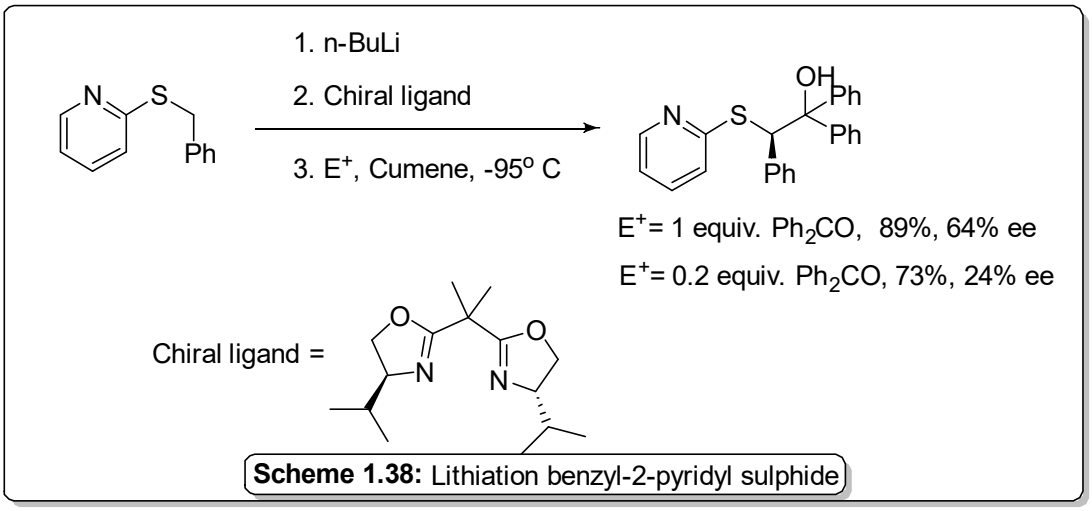
These different enantiomeric excess values with different electrophiles indicate that the enantiomer ratio of the products is different from the diastereomer ratio of intermediates **103**. Sp. The extent of enantioselectivity depends on the difference in transition state energies of the diastereomeric intermediates with the electrophiles. The pathway of dynamic resolution for the equilibrating complexes (R)-**103**.sp and (S)-**103**.sp is shown below-



Scheme 1.37: Dynamic resolution for the equilibrating complexes (R)-103.sp and (S)-103.sp

Toru et al have shown that when a sub-equivalent amount of electrophile is added in the reaction of lithiated benzyl-2-pyridyl sulfide the enantioselectivity obtained is lower.[98] This can be

explained by assuming that the minor diastereomeric complex involves lesser activation energy during the electrophilic substitution. In general, it can be said that if the observed enantioselectivity increases on using a sub-equivalent amount of electrophile then the minor diastereomeric complex has high activation energy and reacts at a slower rate than the major diastereomer and vice-versa.



Scheme 1.38: Lithiation benzyl-2-pyridyl sulphide

The above interpretation of the reaction of diastereomeric complexes with a sub-equivalent amount of electrophile is a modified "elegant Hoffmann test" performed to check the organolithium configurational stability.[99] Observed difference in enantiomeric excess with the non-substantial quantity of the electrophile can be used to test the configurational stability of the complexes but an identical enantiomer ratio does not confirm configurational lability. [100]

Another protocol for detecting the configurational stability of the diastereomeric complex has been proposed by Hoffmann and co-workers based on the kinetic resolution of the electrophilic substitution step.[99b,101,102] In the Hoffmann test two parallel reactions were carried out. The 1st reaction is a reference reaction, where a racemic mixture of the organolithium compound is reacted with a racemic electrophile. In the other reaction, this racemic mixture of the organolithium compound is reacted with an enantiomerically pure electrophile. And the configurational stability is elucidated by comparing the obtained diastereomeric ratio in both the reactions as follows:

1. the same diastereomeric ratio of the product in both experiments indicates configurationally labile organolithium with respect to the rate of reaction with an electrophile.
2. If the ratios of the product are different in both the experiments then it indicates that organolithium is at least partly configurationally stable.
3. When the diastereomeric ratio of the second reaction is one but not equal to the reference reaction then the organolithium compound is completely configurationally stable

For this test, mostly Reetz aldehyde (N, N-dibenzylalaninal) is used as electrophiles.[103]

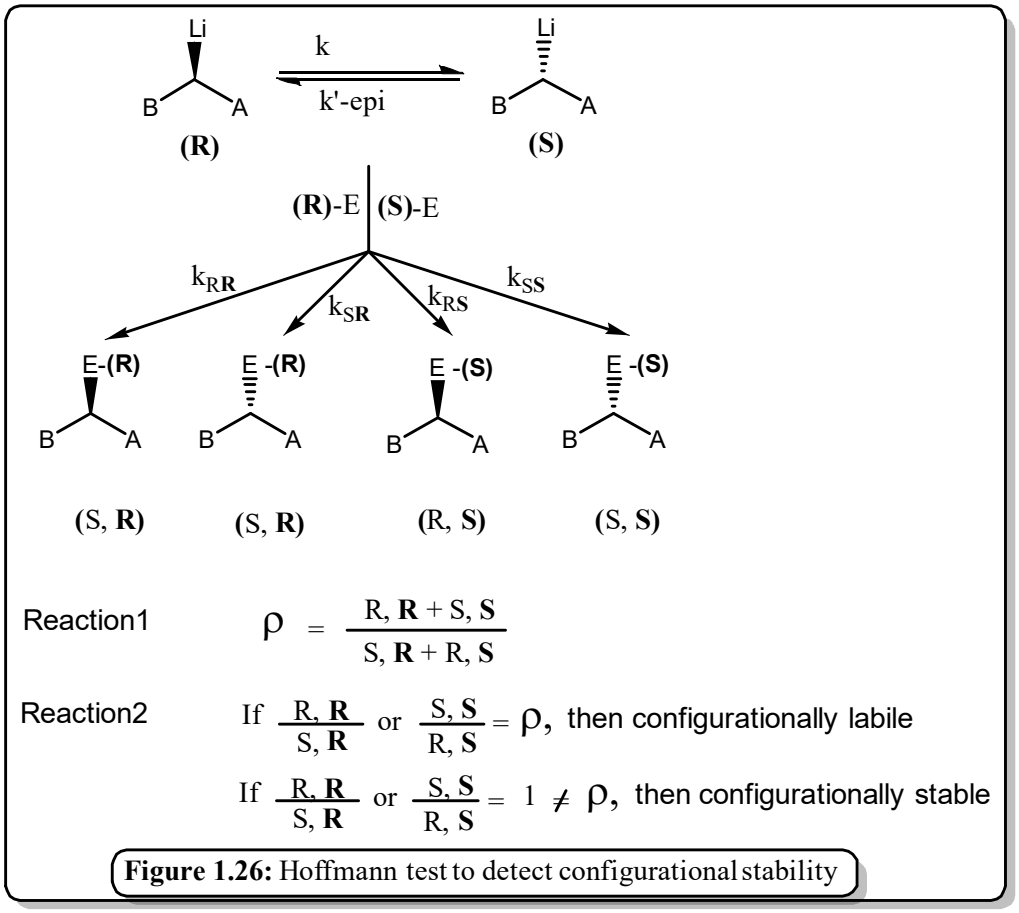


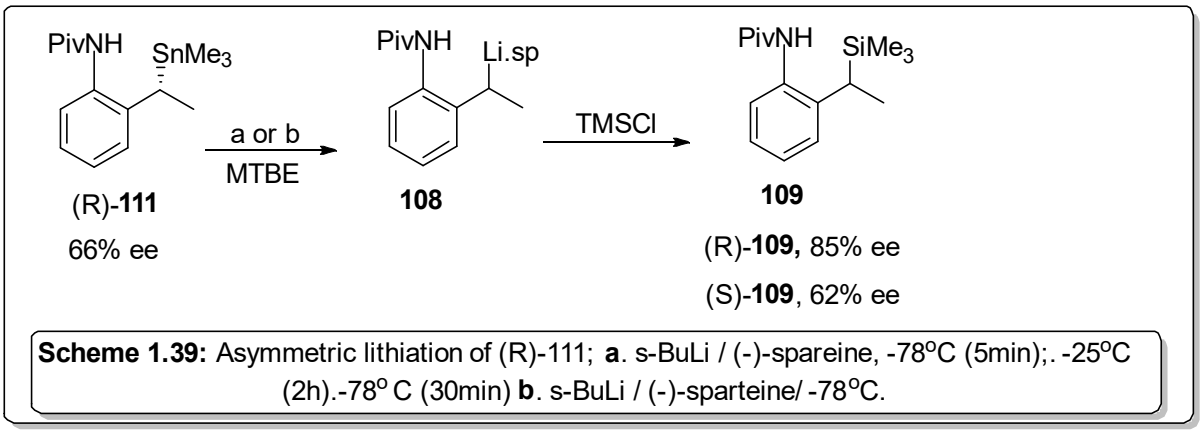
Figure 1.26: Hoffmann test to detect configurational stability

iii) **Dynamic Thermodynamic Resolution-** In this pathway, the configurational stability of the diastereomeric intermediates depends on the temperature of the reaction, which will eventually affect the stereochemical outcome of the ratios of the two products.

Beak et al was the first to reveal the dynamic thermodynamic control during the conversion of **107** (racemic mixture of **111**) to **109** in the year 1996.[104] He carried out asymmetric lateral-lithiation of o-ethyl-N-pivanilide (**107**) using s-BuLi as a base at –25ºC to furnish a diastereomeric intermediate **108**. He added (-)-sparteine and trimethylsilyl chloride to 108 after cooling to –78ºC, this temperature variation gave (R)-**109** with 21% ee. But, if the sequence of addition changed by adding (-)-sparteine at –25º and continued stirring for 45 minutes and then cooled reaction to –78º to add trimethylsilyl chloride, the afforded product (R)-**109** was obtained with 82% ee. The results were equally convincing with other electrophiles using this warm-cool protocol to afford enantioenriched compound **110** in terms of obtained yield and enantiomeric excess.

When the lithiation of **107** was carried out with s-BuLi/(-)-sparteine complex without a warm-cool cycle at –78º C but using trimethyl silyl chloride in sub-equivalent amount (0.1equiv.) as an electrophile, 82% ee observed for (R)-**109**. This outcome was different from the 21% ee which was noticed for the same temperature conditions but with an excess of trimethyl silyl chloride. The difference in the ratio resulted because of the involved kinetic resolution pathway of the diastereomeric complexes **108**.sp in reaction with the electrophile.

Further clarification of this pathway was evident from the tin-lithium exchange reactions.[104] Here, enantiomerically enriched (R)-**111** was lithiated with s-BuLi/(-)-sparteine at -78° and then warm up to –25° for two hours and then cooled to –78°, followed by the addition of trimethylsilyl chloride to obtain 85% ee of (R)-109. However, without any warm-cool cycle during lithiation of (R)-**111** with s-BuLi/(-)-sparteine, and subsequently adding (TMS)Cl at –78° resulted in the same enantiomer S-**109** with similar ee as that of the reactant used. These findings indicate that in the course of the warm-cool cycle, the reaction pathway leads to a thermodynamic ratio due to the equilibration between the diastereomeric complexes formed between 108 and (-)-sparteine at -25°C, and this ratio remained steady even on cooling to –78° as equilibrium ceases at reduced temperature.[104c] Henceforth, the tin-lithium exchange of (R)-**111** without a warm-cool cycle maintained fidelity in transferring stereo information but the incorporation of a warm-cool protocol gives the same thermodynamic ratio. So in the overall conclusion, the enantioselectivity of the product is dependent on the ratio of the non-equilibrating diastereomeric intermediate complex at –78°.



Scheme 1.39: Asymmetric lithiation of (R)-111; **a**. s-BuLi / (-)-spareine, -78°C (5min);. -25°C (2h).-78° C (30min) **b**. s-BuLi / (-)-sparteine/ -78°C.

Finally, a special case of dynamic reaction known as "asymmetric transformation of second order" can occur in post deprotonation stage when one of the diastereomers crystallizes preferentially so that the reaction mixture is converted into essentially one diastereomer.[93a,104]

To further reconfirm the stereochemical aspect of asymmetric lithiation reactions, the structure and dynamic properties of chiral organolithiums, and the kinetic restriction in the enaniomerization of N-BoC-pyrrolidines were further experimentally investigated. [105] It was found that sparteine, as well as TMEDA, greatly lowers both the enthalpy and the entropy of activation for enantiomerisation, whereas, under otherwise identical conditions N, N-diisopropylbispyridine has little effect. These observations suggest a subtle change in the mechanism of enantiomerization.[105a]

Several density functional calculations have also been carried out to identify possible pathways of inversion for such chiral organolithium species. The intervention of both monomeric and dimeric transition states. However, the DFT calculations disfavour a bimolecular mechanism.[105b]

"They conquer who believe they can" is well suited for Graeme barker and *etal* as he successfully established lithiation substitution reaction on 1,3,4-oxadiazolidone under flow conditions at -50°C.[105c]

It may be appropriate to end this chapter with the mechanistic variations in lithiation/substitution chemistry in general by quoting Collum, an established contemporary investigator in the area[92a] that "In case of lithiation substitution reactions, persistent complexity can irritate those who are seeking for swift and simple answers as the principles and conclusions evolved from detailed organolithium mechanistic studies are very rational, even informative, but neither reliability nor simplicity is certain".

Acknowledgement

I acknowledge all the peer groups and laboratories who have done tremendous work on lithiation reactions to create an understanding of its mechanism and explored its applications. I especially thank D. B. Collum, Peter Beak, and Dr S. V. Kessar for their incredible contribution to the field of lithiation chemistry. I am grateful to SGT University for their encouragement and support to write this chapter.

Abbrevations

S. No.	Abbreviation	Full form
01.	n-BuLi	1-Butyl Lithium
02.	BuLi-LiDMAE	1-Butyl Lithium-Lithium-N, N-Dimethyl aminoethoxide
03.	THF	Tetrahydrofuran
04.	DEE	Diethyl ether
05.	CIP	Contact Ion Pair
06.	SSIP	Solvent-separated ion pair
07.	NMR	Nuclear magnetic Resonance
08	UV	Ultra-Visible
09	IR	Infra-Red
10.	HOESY	Heteronuclear over Hauser effect spectroscopy
11.	COSY	Homonuclear correlation spectroscopy
12.	TMEDA	Tetramethyl ethylenediamine
13.	PMDTA	Pentamethyl diethylenetriamine
14.	LDA	Lithium Diisopropyl amide
15.	sp	Sparteine
16.	ee	Enantiomeric excess
17.	TMSCl	Trimethyl silyl chloride
18.	BoC	t-Butyl carboxylate
19.	DFT	Density Function Theory
20	n-BuCl	N-butyl chloride
21	n-BuBr	n-Butyl Bromide
22.	n-BuOTs	Tosyl protected n-Butanol

References

1. (a) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. In. Ed.* **2007**, 46, 3802. (b) Wu, G.; Huang, M. *Chem. Rev.* **2006**, 106, 2596. (c) Najera, C.; Yus, M. *Tetrahedron* **2005**, 61, 3125. (d) Rappaport, Z.; Mark, I. Eds. *The Chemistry of Organolithium Compounds*; Wiley, New York, **2004**.
2. (a) Kapoor, R. *Ph. D. Thesis*, Panjab University, India, **2005**. (b) Kaur, A. *Ph. D. Thesis*, Panjab University, India, **2004**.
3. Mallan, J. M.; Bebb, R. L. *Chem. Rev.* **1969**, 69, 693.
4. Hommes, N. J. R. v. E.; Schleyer, P. v. R.; *Tetrahedron* **1994**, 50, 5903.
5. (a) Dessy, R. E.; Kitching, W. *Advan. Organometal. Chem.* **1966**, 4, 267. (b) Dessy, R. E.; Poulik, F. *J. Chem. Educ.* **1963**, 40, 185.
6. Brown, T. L.; *Advan. Organometal. Chem.* **1965**, 3, 365.
7. Viswanathan, C. T.; Wilkie, C. A. *J. Organometal. Chem.* **1973**, 54, 1.
8. Brown, T. L.; Dickerhoof, D. W.; Bafus, D. A. *J. Am. Chem. Soc.* **1962**, 84, 1371.
9. Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1984**, 26, 1.
10. (a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*, Pregamon Press, New York, **1974**, pp. 38. (b) Schollkopf, U. in *Houben-Weyl Methoden der Organischen Chemie*, Vol. 13/1, Georg Thieme Verlag Suttgart, **1970**, pp. 7.
11. (a) Marasais, F.; Queguiner, G. *Tetrahedron* **1983**, 39, 2009. (b) Trecourt, F.; Marasais, F.; Queguiner, G. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2409. (c) Comins, D. L.; La Munyon, D. *Tetrahedron Lett.* **1988**, 29, 773.
12. Gros, P.; Choppin, S.; Mathieu, J.; Fort, Y. *J. Org. Chem.* **2002**, 67, 234.
13. Fort, Y.; Rodriguez, A. L. *J. Org. Chem.* **2003**, 68, 4918.
14. Kaufmann, E.; Raghavachari, K.; Reed, K.; Schleyer, P. v. R. *Organometallics* **1988**, 7, 1597.
15. (a) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. R. *J. Am. Chem. Soc.* **1985**. 107, 1810. (b) Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, 107, 2805. (c) Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, 110, 5524.
16. Bauer, W.; Seeback, D. *Helv. Chim. Acta.* **1984**, 67, 1972.
17. Dietrich, H. *Acta Cryst.* **1963**, 16, 681.
18. (a) Leung, S. S. W.; Streitwieser, A. *J. Am. Chem. Soc.* **1998**, 120, 10557. (b) Fraenkel, G.; Adams, D. G.; Dean, R. R. *J. Phys. Chem.* **1968**, 72, 944.

19. (a) Gunther, H.; Moskau, D.; Bast, P.; Schmalz, D. *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 1212. (b) Gunther, H. in " *Advanced Applications of NMR to Organometallic Chemistry*", Gielen, M.; Willem, R.; Wrackmeyer, Eds,. John Wiley & Sons Ltd, **1996**, Ch. 9.

20. Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, 6, 2371.

21. (a) Seeback, D.; Hassig, R.; Gabriel, *J. Helv. Chim. Acta.* **1983**, 66, 308. (b) Heinzer, J.; Oth, J. F. M.; Seebach, D.; *Helv. Chim. Acta.* **1985**, 68, 1848. (c) Fraenkel, G.; Henrichs, M.; Hewitt, J. M.; Su, B. M.; Geckle, M. J. *J. Am. Chem. Soc.* **1980**, 102, 3345. (c) Bauer, W.; Clark, T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, 109, 970.

22. Thomas, R. D.; Clarke, M. T.; Jensen, R. M.; Young, T. C.; *Organometallics* **1986**, 5, 1851.

23. Collum, D. B. *Acc. Chem. Res.* **1992**, 25, 448.

24. (a) Hope, H.; Power, P. P. *J. Am. Chem. Soc.* **1983**, 105, 5320. (b) Thoennes, D.; Weiss, E. *Chem. Ber.* **1978**, 111, 3157. (c) Schumann, U.; Kopf, J.; Weiss, E. *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 215.

25. Cram, D. J. *Fundamentals of carbanion Chemistry,* Academic Press, New York, **1965**.

26. (a) Butin, K. P.; Beletskaya, I. P.; Kashin, A. N. and Reutov, O. A. *J. Organomet. Chem.* **1967**, 10, 197. (b) Ebel, H. F. *Houben-Weyl Methoden der Organischen Chemie*, Vol. 13/1, George Thieme Verlag, Stuttgart, **1970**, p. 32.

27. Gilman, H.; Morton, J. W. Jr., *Org. Reaction*, **1954**, 8, 258.

28. Rausch, J. D.; Ciappenelli, D. J. *J. Organomet. Chem.* **1967**, 10, 127.

29. Ellison, R. A.; Kotsonis, F. N. *J. Org. Chem.* **1973**, 38, 4192.

30. Langer, A. W.;Jr, *N. Y. Acad. Sci.,* **1965**, 27, 741.

31. Roberts, J. D.; Curtin, D. Y. *J. Am. Chem. Soc.* **1946**, 68, 1658.

32. Bryce-Smith, D. *J. Chem. Soc.* **1954**, 1079.

33. (a) Doering, W. V. E.; Hoffmann, A. K.; J. Am. Chem. Soc. **1955**, 77, 521. (b) Slaugh, L. H.; Bergman, E. *J. Org. Chem.* **1961**, 26, 3158.

34. (a) Peterson, D. J.; Hays, J. R. *J. Org. Chem.* **1965**, 30, 1939. (b) Peterson, D. J. *J. Organomet. Chem.* **1967**, 9, 373.

35. (a) Seebach, D.; Peleties, N. *Chem. Ber*. **1972**, 105, 511. (b) Coulson, C. A. *Nature* **1969**, 97, 2209. (c) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Drucker, G. E.; Gerhold, J.; Mccallum, G. J. *J. Org. Chem.* **1977**, 42, 326.

36. (a) Streitweiser, A.; Williams, J. E. *J. Am. Chem. Soc.* **1975**, 97, 191. (b) Bernardi, F.; Csizmadia, I. G.; Mangini, H. B.; Wolf, S. *J. Am. Chem. Soc.* **1975,** 97, 2209. (c) Lehn, J. M.; Wipff, G.; Demuynck, *J. Helv. Chim. Acta* **1977,** 60, 1239.

37. Shirley, D. A.; Goan, J. C. *J. Organomet. Chem*. **1964**, 2, 304

38. Chadwick, D. J.; Willbe, C. *J. Chem. Soc. Perkin Trans. I,* **1977**, 887.

39. Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, 84, 471.

40. (a) Seebach, D.; Enders, D. *Angew. Chem. Int. Ed. Engl.* **1975**, 14, 15. (b) Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 239. (c) Beak, P.; Zajdel, W. J. Reitz, D. B. *Chem Rev*. **1978**, 78, 275. (d) Katritzki, A. R.; Qi, M. *Tetrahedron* **1998**, 54, 2647. (e) Katritzki, A. R.; Sengupta, S. *Ind. Acad. Sci.* **1988**, 100, 187.

41. Peterson, D. J. *J. Am. Chem. Soc.* **1971**, 93, 4027.

42. Ahlbrecht, H.; Dollinger, H. *Tetrahedron Lett.* **1984,** 25, 1353.

43. Barton, D. H. R.; Beugelmans, R.; Young, R. N. *Nouv. J. Chim.* **1976**, 2, 363.

44. Yamamoto, Y. *Angew. Chem. Int. Ed. Engl*. **1986**, 25, 947.

45. Kessar, S. V.; Singh, P.; Vohra, R.; Kaur, N. P.; Singh, K. N. *J. Chem. Soc. Chem. Commun.* **1991**, 568.

46. (a) Kessar, S. V. *Pure Appl. Chem.* **1996**, 68, 509. (b) Kessar, S. V. Vohra, R.; Kaur, N. P. *Tetrahedron Lett*. **1991**, 32, 3221. (c) Kessar, S. V.; *Pure. Appl Chem.* **1990**, 62, 1397. (d) Kessar, S. V.; Vohra, R.; Kaur, N. P.; Singh, K. N.; Singh, P. *J. Chem. Soc. Chem. Commun.* **1994,** 1327.

47. (a) Kessar, S. V.; Singh, P.; Singh, A. K.; Kaul, V. K. *Indian J. Chem.* **1994,** 33b, 818. (b) Gillespie, J. P.; Amoros, L. G.; Stermitz, F. R. *J. Org. Chem*. **1974**, 39, 3239.

48. Shirley, D. A.; Barton, K. R. *Tetrahedron,* **1966**, 22, 515.

49. Screttas, C. G.; Eastham, J. F. *J. Am. Chem. Soc.* **1965**, 87, 3276.

50. Butler, D. E.; Alexander, S. M. *J. Org. Chem.* **1972**, 37, 215.

51. (a) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, 104, 7609. (b) Blagg, J. Coote, S. J.; Davies, S. G. *J. Chem. Soc. Perkin Trans. I* **1987**, 689.

52. Tomooka, N.; Nakai, T.; Wang, L. F.; Okazaki, F. *Tetrahedron Lett.* **2000**, 41, 6121.

53. Horst, B.; Nurgand, S. P. *Phosphorus Sulphur* **1987**, 13, 235.

54. Jones, F. N.; Zinn, M. F.; Hauser, C. R. *J. Org. Chem.* **1963**, 28, 663.

55. Shatenshtein, A. I. *Tetrahedron*, **1962**, 18, 95.

56. Huisgen, R.; Mack, W.; Herbig, K.; Ott, N.; Anneser, E. *Chem. Ber.* **1960**, 93, 412.

57. Kauffmann, T.; Mitschker, A. *Tetrahedron lett.* **1973**, 4039.

58. Sloccum, D. W.; Jennings, C. A. *J. Org. Chem*. **1962**, 41, 3653.

59. (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, 19, 356. (b) Klumpp, G. *Recl. Trav. Chim. Pays-Bas* **1986**, 105, 1. (c) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, 93, 1307. (d) Whisler, M. C.; Neil, S. M.; Sneikus, V.; Beak, P. *Angew. Chem. Int. Ed. Engl*. **2004**, 43, 2206.

60. Pippel, D. J.; Curtis, M. D.; Du, H.; Beak, P. *J. Org. Chem.* **1998**, 63, 2.

61. Beak, P.; Hunter, J. E.; Jun, Y. M.; Wallin, A. P. *J. Am. Chem. Soc.* **1987**, 109, 5403.

62. Lutz, B. P.; Du, H.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, 61, 4542.

63. Beak, P.; Kempf, D. J.; Wilson, K. D. *J. Am. Chem. Soc.* **1985,** 107, 4745.

64. (a) Patel, P.; Joule, J. A. *J. Chem. Soc. Chem. Commun.* **1985**, 1021. (b) Beak, P.; Monroe, E. M.; *J. Org. Chem.* **1969,** 34, 589.

65. Maggi, R.; Schlosser, M. *J. Org. Chem*. **1996**, 61, 5430.

66. (a) Snieckus, V. *Chem. Rev.* **1990,** 90, 879. (b) Chauder, B.; Green, L.; Snieckus, V. *Pure Appl. Chem.* **1999,** 71, 1521.

67. (a) Quesnelle, T.; Lihama, T.; Aubert, H.; Perrier, V.; Sneickus, V. *Tetrahedron Lett.* **1992**, 33, 2625. (b) Watanabe, M.; Date, K.; Kawanishi, T.; Hori, S.; Furnkawa, *Chem. Pharm. Bull.* **1990**, 38, 2637.

68. (a) Bridges, A. J.; Lee, E. C.; Maduakor, C. E.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, 33, 7495. (b) Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett.* **1992**, 360. (c) Mukherjii, C.; De, A. *Synlett* **2002**, 325.

69. Narsimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957.

70. (a) Iddon, B. *Heterocycles* **1994**, 37, 1263. (b) Green, L.; Chaunder, B.; Sneickus, V. J. *Heterocyl. Chem.* **1999,** 36, 1453.

71. (a) Epsztajn, J.; Berski, Z.; Brzezinski, J. Z.; Jozwiak, A. *Tetrahedron Lett.* **1983**, 24, 4735. (b) Epsztajn, J.; Berski, Z.; Brzezinski, J. Z.; Joziak, A.; *Tetrahedron Lett.* **1980**, 21, 4739.

72. (a) Mongin, F.; Queguiner, G. *Tetrahedron* **2001**, 57, 4059. (b) Thomas, G. G.; Meyers, A. I. *Tetrahedron* **1994**, 50, 2297.

73. Fort, Y.; Rodriguaze, A. L. *J. Org. Chem.* **2003**, 68, 4918.

74. Clark, A. D.; Jahangir, A. *Org. React.* **1995**, 47, 1.

75. Clark, A. D.; Muchowski, J. M.; Fischer, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991**, 871.

76. Tahara, N.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* **2002**, 43, 9069.

77. Gross, B. M. K.; Beak, P. *J. Am. Chem. Soc.* **2001**, 123, 315.

78. (a) Saa, J. M.; Deya, P. M.; Suner, G. A.; Frontera, A. *J. Am. Chem. Soc.* **1992**, 114, 9093. (b) Saa, J. M.; Morey, J.; Frontera, A.; Deya, P. M. *J. Am. Chem. Soc.* **1995**, 117, 1103.

79. (a) Setzer, W.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, 24, 353. (b) Slesher, V.; Izatt, R. M.; Bradshaw, J. S.; Delley, N. K. *Chem. Rev.* **1991**, 91, 137. (c) Hey, D. R.; Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, 118, 11391.

80. Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, 111, 7191.

81. Bauer, W.; Betz, J. *J. Am. Chem. Soc.* **2002**, 124, 8699.

82. (a) Wehman, E.; Jastrzebski, J. T. B. H.; Ernsting, J. M.; Grove, D. M.; Van Koten, G. *J. Organomet. Chem.* **1988**, 353, 145. (b) Reich, H. J.; Gudmundsson, B. O. *J. Am. Chem. Soc.* **1996**, 118, 6074.

83. Beak, P.; Smith, G. S.; Song, z.; Hay, D. R. *J. Am. Chem. Soc.* **1988**, 110, 8145.

84. Saa, J. M.; Martorell, G.; Frontera, A. *J. Org. Chem.* **1996**, 61, 5194.

85. Resek, J. E.; Beak, P. *J. Am. Chem. Soc.* **1994**, 116, 405.

86. Anderson, D. R.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, 121, 7553.

87. Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, 60, 7092.

88. (a) Hommes, N. J. R. van Eikema; Schleyer, P. v. R. *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 755. (b) Hommes, N. J. R. van Eikema; Schleyer, P.v. R. *Tetrahedron* **1994**, 50, 5903. (c) Kremer, T.; Junge, M.; Schleyer, P.v. R. *Organometallics* **1996**, 15, 3345.

89. Vessieres, A.; Top, S.; Ismail, A. A.; Butler, I. S. Louer, M.; Jaouen, G. *Biochemistry* **1988**, 27, 6659.

90. (a) Witing, G.; Pieper, G.; Fuhrmann, G. *Chem. Ber.* **1940**, 73, 1193. (b) Gilman, H.; Soddy, T. *J. Org. Chem.* **1957**, 22, 1715.

91. Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett*. **1991**, 731.

92. (a) Singh, K. J.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, 128, 13753. (b) Kessar, S. V.; Singh, P.; Singh, K. N.; Bharatam, P. V.; Sharma, A. K.; Lata, S.; Kaur, A. *Angew. Chem. Int. Ed.* **2008**, 47, 4703.

93. (a) Hoppe, Dieter, Hense, Thomas *Angew. Chem. Int. Ed.* **1997**, 36, 2282. (b) Kasten, K., Seling, N. and O'Brien, P. (**2019**). Enantioselective Lithiation–Substitution of Nitrogen-Containing Heterocycles. In *Organic Reactions,* 255.

94. Basu, A.; Thayumanavan, S. *Angew. Chem. Int. Ed.* **2002**, 41, 716.

95. Beak, P.; Kerrick, S. T.; *J. Am. Chem. Soc.* **1991**,113, 9708.

96. Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, 116, 3231.

97. Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, 116, 9755.

98. Nakamura, S.; Nakagana, R.; Watanabe, Y.; Toru, T. *J. Am. Chem. Soc.* **2000**, 122, 11340.

99. (a) Klute, W.; Dress, R.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1409. (b) Hoffmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, D. *Tetrahedron* **1994**, 50, 6049. (c) Hoffmann, R. W.; Dress, R. K.; Ruhland, T.; Wenzel, A. *Chem. Ber.* **1994**, 50, 6049.

100. Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, 29, 552.

101. Hoffmann, R. W. *Organic synthesis via organometallics* (Eds: Enders, D; Gais, H. J.; Keim, W.) Vieweg, Wiesbaden, **1994**.

102. Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, 125, 975.

103. Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1531.

104. (a) Basu, A.; Gallagher, D.; Beak, P. *J. Org. Chem.* **1996**, 61, 5718. (b) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, 118, 1575. (c) Nadeem S. Sheikh, Daniele Leonori, Graeme Barker, James D. Firth, Kevin R. Campos, Anthony J. H. M. Meijer, Peter O'Brien, and Iain Coldham; *Journal of the American Chemical Society* **2012** *134* (11), 5300-5308

105. (a) Yousaf, T. I.; Williams, R. L.; Coldham, L.; Gawley, R. E. *Chem. Comm.* **2008**, 97. (b) Ashweek, N. J.; Brandt, P.; Coldham, L.; Dufour, S.; Gawley, R. E.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2005**, 127, 449. (c) Wong, J. Y. F.; Tobin, J. M.; Vilela, F. and Barker, G.; *Chem. Eur. J.* **2019**, *25*, 12439.