Complex-Induced Proximity Effect in Lithiation: Unveiling Recent Potentials in Organic Synthesis of Biologically Relevant Heterocyclic Compounds

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Abstract: Reactions that convert carbon–hydrogen (C–H) bonds into carbon–carbon (C–C) or carbon–heteroatom (C–Y) bonds are attractive tools for organic chemists, potentially expediting the synthesis of target molecules via functional group interconversion. More explorative studies have shown Complex Induced Proximity Effect (CIPE) to be a solution-provider for the synthesis of bioactive compounds. This might act as excellent pathfinders to new drugs for combating microorganisms’ resistance challenges to old existing drug. So, a constant review into CIPE and lithiation chemistry is crucial because they offer excellent pathways to new heterocyclic compounds which are essential agents in drug design and discovery.

Keywords: Aziridine, bioactive heterocycles, cipe mechanism, enantioselective, lithiation, stereoselectivity.

1. INTRODUCTION

Over the years, there has been a considerable attention and interest in the aromatic metalation procedure, especially
lithiation reaction which is an efficient synthetic method for heterocycle substitution [1]. A useful strategy for intramolecular cyclization and synthetic information transfer is by using proximity and shape of one part of a molecule to stereoselectively control reaction occurring nearby [2]. This idea in lithiation is known as complex induced proximity effect (CIPE). It originated in 1986, when novel carbanions formation by organolithium bases was described as a two-step process [3] in which the formation of a prelithiation complex brings reactive groups into proximity for directed deprotonation [4]. It is however, very interesting to note that relative ease of lithiation is attributed to a prelithiation phenomenon. This prelithiation phenomenon that occurred in the transition state [2] before deprotonation was achieved was termed the complex induced proximity effect, CIPE [5]. This factor provided alternative way to C-C bond formation which was facilitated by heteroatoms of the substituted organolithium reagents [6]. Among the most widely used are metalated sulfoxides [7], acyclic anion [8], acetic acid dianion [9], cyanohydrin anion [10], homoenoate anion [11] and dithianes [12]. In this regard, reactions in which lithiated secondary amides provide CIPE control of regioselectivity and stereoselectivity have been a recurrent theme in this area [13].

Complex induced proximity effect provides the chemists with a well equipped synthetic toolbox for the functionalization of the aromatic ring and intramolecular cyclization [14]. Organolithium synthesis generally involves an alkylolithium-promoted halogen-lithium exchange or the simple direct deprotonation of the most acidic and stabilizing position of the heterocyclic nucleus with alkylolithium or lithium amides [15]. This is a stabilization which can be produced by an adjacent atom or group in the so-called “directed ortho-metallation” (DoM) [16]. The potential of DoM, as amplified by the versatile lithium species, has been largely exploited in the total synthesis of natural products bearing bioactive heterocyclic cores [16]. Heterocycles are found in all kind of compounds of interest in medicinal chemistry research. They could be inserted in other class of compounds to boost therapeutic efficiency. Among all the possible synthetic methods of achieving this insertion into any structure, probably the use of lithiation chemistry is the most direct strategy [17]. Although, the principal enabling force in the development of organolithium chemistry is the commercial availability of inexpensive stable solutions of n-butylithium [18] and the more potent and selective s-BuLi and t-BuLi, which on the contrary, are expensive and difficult to handle [19]. Nevertheless, the scope of the metation reaction has been expanded by the use of complexing and chelating reagents such as hexamethyolphosphoric triamide (HMPA), N,N'-dimethylpropyleneurea (DMPU) and tetramethylethylenediamine (TMEDA) which increase the rate of metation and thus, extend the range of compounds which can be deprotonated [20].

The aim of this present work is to evaluate recent advance in the CIPE approaches to new compounds via lithiation chemistry covering from year 2000 to 2014. Hence, this review presents CIPE as a resourceful tool in metatation chemistry for the designing of valuable scaffolds which may serve as great opening to new drug discovery and development.

2. MECHANISM IN CIPE

2.1. CIPE: The underlying mechanism behind DOM Methodologies

The direct metalation group (DMG) is typically a Lewis basic moiety that interacts with the Lewis acidic lithium cation allowing for deprotonation by the alkyl-lithium species from the nearest ortho-position on the arene [21]. Applications of CIPE to synthetic goals have been particularly well-developed for directed ortho metalation (DOM) methodologies which involved the use of DMGs as the coordinating functional group necessary for CIPE [22]. Although, DMGs do not function alone in determining the site of metalation, but sterics and other functional groups on the arene also have a great deal of influence [23]. The general CIPE is illustrated in 4, a lithiation/substitution sequence as shown in the Scheme (1) below. The coordinative interaction of 1 with an appropriate organolithium reagent provides the complex 2 which upon subsequent directed lithiation via transition state 3 affords lithio species 4 [24]. The quenching of 4 by addition of an electrophile is highly favoured over traditional electrophilic substitution to achieve 5 because of the regioselective preference displayed. Cases that can be cited for CIPE include not only deprotonative mono- and dilitiations but also hetero atom–lithium exchanges, inventive displacements’ and additions. CIPE process appears to arise in a wide variety of reactions of organolithium compounds [17]. Thus, we have herein reviewed recently reported carbolithiations which are consistent with the general process outlined in Scheme (1).

2.2. Two Schools of Thought for One Mechanism: Lithiation

Selective ortho lithiation of aryl rings bearing heteroatom containing functional groups is a powerful synthetic strategy in organic and organometallic synthesis. Two major mechanisms theorized to drive ortho-lithiations: (i) “Coordination only” - substituent coordinates or “complexes” with organolithium reagent to increase kinetic basicity, and directs deprotonation to ortho position. A typical example of which could be explained by the lithiation of dimethylbenzylamine 6 which afforded compound 7 and (ii) “Acid-base” - inductive and/or resonance effects from heteroatomic substituent make ortho proton more acidic [25]. A typical illustration of this mechanism could be explained by why the lithiation of pyrazole 8 gave the 5- lithio derivative 9 and not the 3-lithio counterpart (Scheme 2). Some lithiations are driven entirely by one factor or the other, but the majority of lithiations occur by a combination of both. Organolithiums were thought to coordinate to heteroatoms in α-lithiation of heterocycles [26]. One thing is sure, the mechanistic proposal must explain two main observations which depend on heteroatomic substituent; they are: (a) increase reactivity of substrate and (b) direct regioselectivity of deprotonation.

2.3. CIPE in α-lithiation of amine

The access to α-lithiated amine via direct deprotonation has been established to occur by CIPE mechanism through a pathway of an intermediate complex in which the organolithium compound is pre-coordinated by the amine ligands [27]. Notwithstanding, the bottleneck associated with
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Direct α-lithiation of amine was earlier reported to be due to the destabilization of the carbanions by the interaction with the lone pair electron density of the adjacent nitrogen atom [28]. This had caused unmet demand in the formation of the templates as a desirable synthetic route to polar hetero-organometallics [29]. However, CIPE has been projected as the basic concept in the predicted and investigating basic metalation of which was obtained from partial deprotonation of bis(3-methyl-1,3-diazacyclohex-1-yl)-methane 10 (Scheme 3) [30]. This close proximity of the carbanion C(23) ( tert-butyl group) and the hydrogen atom H(18a) of 10 is also represented as an atomic interaction line in the charge density topology [30]. Kamp and coworkers also demonstrated that the concept of a complex-induced proximity effect can be underlined and supported with charge density topology features [30].

2.4. Kinetically Enhanced Metalation by CIPE Mechanism

Directed lithiations are a topic of considerable deliberation. The selective deprotonation of an ortho or benzylic position assisted by an electron withdrawing group bearing electron lone pairs may be explained through the complex-induced proximity effect (CIPE) model [31]. This mechanism considers the lithiation as a two-step process. First, the coordination of the lithium cation of the base with one Lewis basic heteroatom of the substrate results in the formation of a complex [24]. This complex brings the carbanionic center of the base close to the acidic proton, thus favoring the transfer of the proton in the second step. Ortho-directed deprotonations have been interpreted by an alternative mechanism involving a one-step reaction [32]. In this model, the metalation was described as a kinetically controlled transformation for which the term “kinetically enhanced metalation” has been coined [32]. It was investigated using the reaction of N-alkyl-N-benzyl(diphenyl)phosphinamides 12 with s-BuLi leading to de-aromatized products via the isotopic-labeling and NMR study of the mechanism. This was one of the crucial cases in which pre-lithiation complexes have been structurally identified in the directed deprotonation of a phosphorus-bearing substrate (Scheme 4) [32].

2.5. Trans-esterification mechanistic occurrence by CIPE

Rate enhancements of trans-esterification associated with a second Lewis base centre can be considered as a manifestation of CIPE, which have shown to play an important role in a number of reactions of organic compounds of lithium [17]. The significantly increased

(i). Typical Coordination Only Mechanism

(ii). Typical Acid-Base Mechanism

Scheme (2). Two schools of thought in lithiation mechanism.
reactivity in trans-esterification displayed by the esters containing second Lewis base centre proximal to the ester functionality has been attributed to the CIPE as reported by Jackman and co-workers, 1991. Based on this mechanistic assumption, the free energies of activation for the trans-esterification of six 3,5-dimethylphenyl esters possessing a second Lewis base centre was investigated wherein the predicted and the observed values were compared (Table 1) [33]. It is therefore possible that the presence of other Lewis base centres in the acid moiety of the esters might provide more effective means of attachment [34], even though the electrophilic activation of the carbonyl group associated with coordination of its oxygen to lithium would be lost [33]. The essential role of the pre-equilibrium step is to attach the ester to the tetramer in order to effect electrophilic attack of the putative phenolate ion on the carbonyl carbon atom [33].

3. POLYFUNCTIONAL ORGANOLITHIUM REAGENTS VIA CIPE

The use of Lewis bases to increase the reactivity of lithium organics is an important tool in synthetic chemistry [34]. N,N,N',N'-tetramethyl ethylenediamine (TMEDA), one of the most powerful and most often used Lewis bases, is known to undergo a direct R-lithiation, the regioselectivity of which depends on the used deprotonation agent [20]. The α-lithiation of TMEDA in the presence of t-BuLi was reported to give, after electrophilic quenching, a tridentate ligand 17 according to Scheme (5) [28]. The presence of heteroatoms in close proximity to the carbon-lithium bond facilitates the formation of an organolithium species as long as the various functional groups are tolerated [17]. The direct lithiation with lithium powder in the presence of a catalytic amount of 4,4'-di-tert-butylibiphenyl (DBB), as popularized, proves to be a very convenient method for preparing a broad range of polyfunctional organolithium reagents [35]. Thus, imidoyl 18, carbamoyl 19a, or thiocarbamoyl 19b lithium compounds which are formerly difficult to prepare, could now be generated using this facile approach which was made possible by CIPE. The direct preparation of acyllithium compounds such as 20, either by a direct low-temperature route from RLi/CO or a lithium-tellurium exchange reaction, has been successfully performed [36]. In these direct preparation methods, the acyllithium species are generated in the presence of an electrophile [37].
4. UNVEILING SYNTHETIC POTENTIALS OF METALATION CHEMISTRY

4.1. Diversity of Aziridine and its CIPE accomplice

Aziridines are important compounds because of their widespread use in organic synthesis and their presence in many natural products and biologically active molecules [38]. They have been extensively investigated either from the synthetic or reaction points of view. Concerning the reactivity, the most common transformations of these spring-loaded three-membered ring systems are the ring-opening reactions that can be initiated by both electrophilic and nucleophilic reagents [39]. Numerous synthetic approaches have been developed for the preparation of aziridine due to

![Fig. (1).](image)

Table 1. Observed and predicted free energies of activation for the transesterification, at 30 °C in DME, of 3,5-dimethylphenyl esters possessing a second Lewis base center.

<table>
<thead>
<tr>
<th>Comp. No</th>
<th>R</th>
<th>$\Delta G^\circ$ (kcal mol$^{-1}$)</th>
<th>obsd</th>
<th>pred</th>
<th>diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>16a</td>
<td>CH$_2$OCH$_3$</td>
<td>19.6</td>
<td>21.3</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>16b</td>
<td>CH$_3$CH$_2$OCH$_3$</td>
<td>21.6</td>
<td>22.7</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>16c</td>
<td>CH$_2$CH$_2$CH$_2$OCH$_3$</td>
<td>22.5</td>
<td>22.8</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>16d</td>
<td>2-tetrahydrofuryl</td>
<td>20.4</td>
<td>21.7</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>16e</td>
<td>CH$_3$N(CH$_3$)$_2$</td>
<td>20.9</td>
<td>22.2</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>16f</td>
<td>CH$_3$ (2-pyridyl)</td>
<td>19.9</td>
<td>22.1</td>
<td>2.2</td>
<td></td>
</tr>
</tbody>
</table>

Comp. No = Compound Number; obsd = observed; pred = preserved; diff = difference
their widespread applications in medicinal chemistry. Some of these methods include aza-Darzen approaches [40], transfer of nitrogen to olefins [41], addition across the carbon-nitrogen double bond of aziridines [42], and more recently, metalation approach via CIPE [43-44].

4.1.1. Stereoselective lithiation of N-Alkyl-(o-tolyl)aziridine in Isochromans

Six membered-ring oxygen-bearing aromatic heterocycles with isochromans and related skeletons occur in nature and among bioactive compounds of interest, including drugs (medicines, agrochemicals, etc.) and drug candidates [45]. The lateral lithiation of ortho-tolylaziridine 21 followed by electrophile trapping gave the intermediate ortho-hydroxylated aziridines 22 which has been recently reported as an excellent route towards a range of bioactive isochromans 23 via acid-catalyzed cyclization approach (Scheme 6) [42]. The results of the lithiation/trapping sequence above clearly demonstrated the directing group ability of the aziridine ring [42]. It is likely that the nitrogen-induced stabilization in 21-Li, and CIPE could act synergically making the lateral benzylic position the kinetically and thermodynamically favored one [46]. This work reported a new and convenient methodology for the preparation of ortho-functionalized aziridines based on the benzylic lithiation of simple and easily available o-tolylaziridines [47]. It is, indeed, worth pointing out that the lithiation of the related acyclic derivative, 2-N,N-dimethylaminomethyltoluene, is comparatively much slower requiring more than 6 h at room temperature for complete deprotonation [42].

4.1.2. Regioselective lithiation of Aziridine

Aziridines are widely used as versatile building blocks for the synthesis of a variety of biologically and pharmaceutically important molecules [48]. Data from the literature indicate that N-alkyl-2-phenylaziridines undergo smooth ortho-lithiation [49]. In contrast, trans-N-alkyl-2,3-diphenylaziridines undergo exclusive R-lithiation with a stereochemistry strongly depending on the coordinating ability of the solvents [43]. The aziridino-borane complexes 25a,b were prepared by treating 2-phenylaziridines 24a,b with 1M THF solution of BH₃·THF complex. When 25a was reacted with s-BuLi (1.2 equiv) in THF at -50 °C for 2 h, the corresponding aziridinylithium was generated as proved by its trapping with D₂O to furnish complex 26a (Scheme 7). The BH₃ removal was easily achieved by adding a small amount of H₂O at room temperature and the corresponding 2-deuterated aziridine 27a was recovered almost quantitatively and as a single stereoisomer after the work-up [43]. This showed the ability of the aziridino group to act as a directing metalation group (DMG) [49].
4.1.3. Stereospecific lithiation of arylaziridine

Normally, the presence of an electron withdrawing group (EWG) on the nitrogen or the carbon atoms of the heterocyclic ring is crucial for successful metalation [50]. Recently, lithiation/electrophile trapping of unsubstituted and 2-alkylsubstituted N-Bus-aziridines has been reported [51]. However, no efficient methods for the α-lithiation of N-Bus-substituted monoarylaziridines have been disclosed. In view of this, Musio and coworkers developed stereospecific lithiation route for the synthesis of optically active trisubstituted arylaziridines and further assessed the role of N-Bus in the lithiation reaction [44]. The enantiomerically enriched N-Bus-2-phenylaziridine (R)-28 was prepared from (-)-phenylglycinol by a high-yielding sequence that involved N-sulfinylation, oxidation, o-tosylation, and cyclization (Scheme 8). Upon lithiation / trapping sequencing of (R)-28, a stereospecific route was provided for obtaining α,α-disubstituted aziridines 30a-e as single enantiomers (er > 98:2). This indicates that the intermediate organolithium (R)-29 is configurationally stable [44].

4.2. Enantioselective carbolithiation in heterocyclic construction

The carbolithiation reaction has attracted considerable interest among synthetic organic chemists, as it offers an attractive pathway for the efficient construction of heterocyclic compounds of medicinal interest [52]. These reactions can be carried out either in inter- or intramolecular fashion [50]. (a). Taking advantage of CIP, Woltering and coworkers reported that the deprotonation of racemic (carbamoyloxy)methyl-N-cinnamyl piperidine 31 with s-butyllithium (−)-sparteine (L1), and subsequent anionic 5-exo-trig cyclization, leads to the formation of (2R,8aR)-2-benzyloctahydroindolizin-1-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate 32 with high diastereomeric and enantiomeric ratios, in moderate yield. (Scheme 9) [53]. It is important to note that the resulting benzyllithium can also be trapped with electrophiles in order to achieve other synthetic manipulations [18].

(b). Barluenga and coworkers reported the enantioselective synthesis of benzo fused furan derivative via intramolecular carbolithiation with special regard to CIP [54]. Enantiomerically enriched 2,3-dihydrobenzofurans 34a-d were obtained in moderate to good yields and high enantiomeric purity from intramolecular carbolithiation of 3,5-disubstituted 2-(allyloxy)-1-bromobenzene 33a-d by using (−)-sparteine (L1) as chiral ligand, and diisopropyl ether as solvent (Scheme 10). The resulting organolithium can be trapped with several electrophiles [54]. However, the presence of a substituent at the 3-position of the aromatic ring (R1 ≠ H) is very crucial otherwise, the aryllithium...
intermediate undergoes a tandem carbolithiation–γ-elimination leading to enantio-enriched 2-cyclopropylphenols [55].

(c) The presence of a substituent in the position ortho to the lithium atom of lithio species generated from 35 leads to lower yields and the opposite enantiomer (S)-3-methyl indoline (S)-36 with low enantiomeric excess (22% ee) when (-)-sparteine (L1) is used (Scheme 11) [56]. However, Mealy and coworkers has proved that the (1R,2R)-N,N,N',N'-tetramethylcyclohexane-1,2-diamine (L4) to be a more efficient ligand for lithium, leading to (R)-1-allyl-3,4-dimethyl indoline (R)-36 in 70% ee [56].

(d) The lithiation sequences from 38a-c to 37 and 39 were quite illustrative as shown in Scheme (12). Treatment of 38a with LDA afforded 37, the result of a directed lithiation and an anionic ortho-fries rearrangement [22]. In the case of 38b or 38c, the normal site of metalation was blocked and deprotonation of the remote ring became thermodynamically favoured by the initial formation of a complex between the directing group and the organolithium reagent [50]. Rearrangement and acid catalyzed cyclization followed to provide the dibenzopyranones 40 in good yields [22].

Scheme (9). Carbolithiation of cinnamyl piperidine to indolizidine derivative 32.

Scheme (10). Intramolecular carbolithiated synthesis of 2,3-dihydrobenzofurans 34.

Scheme (11). Comparative study of efficiency of ligands in synthesis of 36.

Scheme (12). Remote carbolithiation toward synthesis of dibenzopyranones 40.
(e) Aliyenne and coworkers has developed a more convenient method for the preparation of chiral saccharins than the earlier one by Soubh and coworkers [57]. Aliyenne and coworkers reported that their process was driven by CIPE and constitutes a mild method for the LDA–HMPA mediated regiospecific conversion of N-arylsulfonyl oxazolidin-2-ones 41a–f readily available from optically pure amino acids into novel chiral analogues of saccharins 42a–f (Table 2) [58]. The resulting optically active benzisothiazolinone 1,1-dioxides 42a–c and naphthaisothiazolinone 1,1-dioxides 42d–f were obtained in good yields [58].

### 4.3. Natural Product Synthesis

(a) Recently, Tricotet and coworkers successfully applied vinyl-lithiation/electrophile trapping/ring closure reaction sequence for the synthesis of the medicinally important natural product Coumestan 45 [59] which is a potential anticancer agent [60]. Vinyl lithiation of bis-ortho-methoxy cis-stilbene 43 followed by CO$_2$ quench provided routine access to intermediate 44 upon which demethylation with BBr$_3$, treatment with base, and oxidative cyclization completed the synthesis of 45 as shown in Scheme (13) [59].

The vinyl lithiation which resulted into the formation of key intermediate 44 was made possible by kinetically favoured CIPE mechanism.

(b) The combination of amide and o-carbamate DreM strategies was illustrated in the synthesis of dengibsin 49 [24], a member of the rare class of naturally occurring fluorenones [61]. Thus, the differentially protected biaryl o-carbamate 46 (available by Suzuki–Miyaura cross-coupling followed by DoM-mediated silylation) was treated with excess LDA under vigorous conditions to afford the amide 47. Protection and desilylation leads to 48, which upon the second LDA-mediated reaction (under milder conditions) and subsequent de-isopropylation afforded the natural product 49 as shown in Scheme (14) [22, 24].

(c) Compound 54 which is coded as RS-42358 and its analogs are a class of 5-HT3 receptor antagonists that show promise as anti-emetic agents. The total synthesis of this biologically active compound 54 was achieved by Kowalsky as shown in Scheme (15) [62]. This involved synthetic conversion of acid 50 to the intermediate N,N-diethyl substituted amide 51 which was lithiated, followed by formylation to afford 52. Lateral lithiation was the key step towards closure of the intermediate 53 which upon condensation with amine generated the targeted compound 54 [62].

### Table 2. Cyclization of 3-N-Arylsulfonyloxazolidin-2-ones 41a–f to 42a–f.

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Ar</th>
<th>$\left[\alpha\right]_D$</th>
<th>Typical Conditions</th>
<th>Mp °C</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Temp. °C</td>
<td>Additive</td>
<td></td>
</tr>
<tr>
<td>42a</td>
<td>Me</td>
<td>C$_6$H$_5$</td>
<td>+45</td>
<td>–78</td>
<td>HMPA</td>
<td>132–134</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–78</td>
<td>TMEDA</td>
<td>–</td>
</tr>
<tr>
<td>42b</td>
<td>s-Bu</td>
<td>C$_6$H$_5$</td>
<td>–53.57</td>
<td>–78</td>
<td>HMPA</td>
<td>73–75</td>
</tr>
<tr>
<td>42c</td>
<td>Bn</td>
<td>C$_6$H$_5$</td>
<td>–55.0</td>
<td>–78</td>
<td>HMPA</td>
<td>107–109</td>
</tr>
<tr>
<td>42d</td>
<td>Me</td>
<td>2-Naphthyl</td>
<td>+40</td>
<td>–78</td>
<td>HMPA</td>
<td>156–158</td>
</tr>
<tr>
<td>42e</td>
<td>s-Bu</td>
<td>2-Naphthyl</td>
<td>+38</td>
<td>–78</td>
<td>HMPA</td>
<td>141–143</td>
</tr>
<tr>
<td>42f</td>
<td>i-Pr</td>
<td>2-Naphthyl</td>
<td>+55.55</td>
<td>0</td>
<td>HMPA</td>
<td>99–101</td>
</tr>
</tbody>
</table>

n.r. = no reaction
(d) As a foray into the synthetic potential of metalation, the versatile CIPE concepts of Beak & Meyers led, as a direct consequence, to the establishment of Directed remote Metalation (DreM)-induced reaction to afford the naphthobenzopyrone 55 which is an essential building block to the antitumor natural product defucogilvocarcin V, 57 via the intermediate Stille product 56 (Scheme 16) [63]. Defucogilvocarcin V 57 is also reported as a new antibiotic from Streptomyces arene with potential activity against lung cancer cell line [64]. In these processes, the effective use of the carbamate moiety as a carbonyl dictation equivalent was demonstrated [65]. These examples demonstrated that the DoM reaction has not only a recognized potential in the modification of a DMG’s ortho-environment but, through its privileged connections with rapidly growing methods (metal-catalyzed cross coupling, RCM, DreM, direct arylation) imposes the choice and exploration of new synthetic routes [66]. In a similar manner, enantioselective total synthesis of (-)-hyperforin was reported in 18 steps starting from ortholithiation of 1,3-dimethoxybenzene [19].

(e) An iodination reaction for the synthesis of 6-aza-L-tryptophan [67] and 4-alkoxy carboxylations in the preparation of pyridopyrimidinones [68] are recent examples of synthetic application of lithiation technique. In the case of 3-bromopyridine, LDA has been used as metaling agent for the generation of the corresponding brominated 4-pyridyllithium reagent, which has been employed in an addition reaction to acrolein in the synthesis of restricted nicotine analogues [69]. An illustrative example of a DoM reaction for preparing a synthetically useful 4-pyridyllithium species is the one-pot synthesis shown in Scheme (17). Thus, 3-pyridyl carboxylic acid 58 was treated with n-butyllithium to give the corresponding carboxylate anion 59, and further lithiation with LiTMP afforded the organolithium species 60. Subsequent reaction with acetone gave the dilithium salt 61.
which was transformed into a lactopyridone after acid treatment. Final N-methylation under basic conditions gave the pyridinone alkaloid cerpegin 62 (Scheme 17) [70] which is an anti-inflammatory and selectively inhibits the post-acid activity of mammalian 20S proteasomes [71].

(f) 5-Stannylated N-Boc-protected 2,3-dihydro-1H-pyrrole 63 has been recently obtained by direct lithiation-stannylation of the corresponding N-Boc-pyrroline, and has been used in a Stille cross-coupling reaction with the vinyl triflate 64 to give the trienecarbarbamate 65. This compound has been heated to effect an electrocyclic ring closure and oxidized in situ with manganese(IV) oxide to give the marine sponge metabolite (±)-cis-trikentrin A (66) after Boc-deprotection and aromatization (Scheme 18) [72]. Starting from a related stannylated pyrroline, (±)-cis-trikentrin B has been obtained [72].

4.4. Unprecedented Approach of CIPE to 3,4-fused Pyridine-2-one

The synthesis of the 3,4-fused pyrimidine skeleton is limited to three general methods, which include (i) intermolecular annulation and intramolecular cyclization of 3- or 4-substituted pyrimidine derivatives (route i) [73] (ii) [3+3] annulation of a C–C–N fragment, such as an α-acidic imine derivative, with a C–N–C fragment, such as an acyl heterocumulene derivative (route ii) [74]; and (iii) [5+1] annulations of an N–C–C–C–N fragment with a C-1 unit, such as a carbonyl compound or a heterocumulene (route ii) [75]. However, these methods are limited by the fact that they often require the isolation of intermediates, the synthesis of starting materials, high reaction temperatures, and a prolonged reaction time, which decreases product yield [76]. Hence, Sasada and coworkers recently identified a
practical three-component coupling reaction via CIPE using a picoline derivative 67, a nitrile 68, and triphosgene 69 as a C-1 unit that produced 3,4-fused pyrimidin-2-one 70 in a direct, one-pot synthesis as shown in route iv of Scheme (19) [76].

4.5. De-protonative Metalation of Nicotine

In earlier study, Gros and coworkers reported a new base composed of n-BuLi and Me₂N(CH₂)₂OLi [77]. This unimetal superbase called n-BuLi-LiDMAE induced a regioselective lithiation of pyridine derivatives even when an ortho-directing group was present on the heterocyclic ring [78]. Further investigation by Gros and coworkers, revealed that bidentate tertiary diamines such as TMEDA led also to addition products as well as sterically hindered aminoalkoxides such as 2-diisopropylaminomethoxide. The aggregates were also found to be highly sensitive to solvents [77]. Later, a variety of novel, as well as known, C-2- and C-6-substituted nicotines have been synthesized directly from (S)-nicotine 71 in moderate to high yield with the help of conceptual information from CIPE in unimetal superbase [79]. The complete inhibition of the DoM effect of the C-2 chlorine of 72 with n-BuLi-LiDMAE was explained by the formation of aggregates between n-BuLi-LiDMAE and the substrate via lithium complexation by the pyridine nitrogen atom which upon quenching with electrophile afforded 73 (Scheme 20) [79]. It has also been shown that t-BuLi in Et₂O promotes an exclusive regioselective metalation of 2-aryl-6-chloropyridine compounds at the aromatic ortho position [80].

4.6. Ortho-lithiation of N-Benzoyl Iminophosphoranes

Ortho-lithiation is most commonly achieved through deprotonation reactions with organolithium bases [81]. According to the CIPE model, the polar group linked to the aromatic ring directs the approach of the base to the deprotonation site by coordination to the lithium atom and contributes to the stabilization of the ortholithiated species through intramolecular coordination [82]. Although, regioselective ortho-deprotonation of iminophosphoranes 74...
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4.7. Accessibility of New Polyphosphazenes

The degree of accessibility of the reactive centers to the incoming reagents largely dictated by the behavior of the polymers in solution is one of the great determining factors toward new functionalized polymeric material [85]. In view of this, Carriedo and Valenzuela reported that the halogenations of their earlier synthesized precursor phosphazene \([\text{NP(O}2\text{C}12\text{H}_8)]_n\) \(81\) led to a new type of well-defined chemically regular chlorinated- \(82a\) or iodinated polyphosphazenes \(82b\) which upon silylation afforded \(83a\) and \(83b\) respectively (Scheme 23) [87]. There is an evidence of prelithiation disparity as \(82a\) could not be substitutionally silylated on the chlorine position, but have to occur on the trimeric group as seen in \(83a\). However, because of large atomic size of iodine and the lithium charge effect, the silylation occurred on the dimeric position to replace the iodine to afford \(83b\) [87]. Thus, Carriedo and Valenzuela stated clearly that the chemical reactivity of polyphosphazenes with 2,2'-dioxybiphenyl phosphorus rings in the repeating units is limited by conformational changes induced by the new groups incorporated to the ring carbons and by the proximity of the reaction centers to the main chain [87].

Scheme (20). Evidence for regiospecificity at C-6 of 2-heterosubstituted pyridine.

and 75 at either side of the PNCO moiety is feasible, the synthetic usefulness of these anions is rather limited due to the intramolecular quench observed for the ortho-PN anion of the parent compound 74 to afford the benzophenone 76 (Scheme 21a) [83] and the poor performance in the case of the ortho-CO anion arising from the methoxy derivative 75 to give the ortho-methylated product 77 (Scheme 21b) [84].

Moreover, owing to these drawbacks encountered in 74 and 75 above, Aguilar and coworkers pressed further and attempted halogen/lithium exchange reactions on 78 as a method for accessing ortholithiated iminophosphoranes 79. This attempt was not only successful in producing 79 but also served as opening to various new compounds 80a-h because of tolerable electrophile quenching attributable to intermediate 79 as shown in Scheme (22) [84]. It is interesting to note that the trapping reactions with a representative series of electrophiles allowed the transformation of the C-Li bond of 79 into a wide variety of C-X (X = Hg, I, P, Sn, Si) and C-C bonds, providing access to new stabilized iminophosphoranes 80a-h not easily accessible through other synthetic pathways [84].

Scheme (21). (a). Ortho-PN deprotonation of 74 and intramolecular quench (b). Ortho-CO deprotonation of 75 and subsequent methylation.
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4.8. Variation of Directing-Group Orientation

For deprotonative lithiation reactions, the geometrical constraints within a complex in the transition state for transfer of the proton to the lithiating reagent have been shown to be important for efficient reaction [23]. For reactions that provide α-lithioamine derivatives of amides an orthogonal relationship between the lithio carbanion and the pi system of the amide has been established to be favorable. These results along with semi-empirical calculations suggested that a small dihedral angle and a calculated distance of 2.78 Å between the carbamate carbonyl oxygen and the proton to be removed were favorable for a carbamate-directed lithiation. Based on the careful study of the effect of directing-group orientation, new series of selected bicyclic carbamates were obtained. The direct lithiation of N-Boc pyrrolidine 84 and reaction with diisopropyl ketone or di-tert-butyl ketone afforded intermediate alkoxide which underwent cyclization upon warming up to room temperature to afford the bicyclic carbamates 85a and 85b respectively [88]. The pyrrolidine-derived oxazolidinones 85a and 85b, upon treatment with sec-butyllithium (s-BuLi)/TMEDA at -78 °C followed by electrophiles provided the substituted products 86a1 – 86b1 in good yields as shown in Table 3 [88]. Recently, the reactions of Hoppe’s lithiated carbamates with appropriately substituted vinylboranes or boronic ester have been reported [89].

4.9. Essentiality of DoM in Scale-up

In the past decade, the DoM reaction has enjoyed increasing application in large-scale process chemistry for the preparation of required amounts for advanced drug discovery studies and commercial drugs. By way of illustration, the synthesis of 2-bromo-6-chlorobenzoic acid 88 on a 60 kg scale and in excellent yields (89–90%) was achieved by Merck chemists [90] via painstaking optimi-
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zation study of the experimental conditions in metalation of 3-chloro bromobenzene 87 followed by quenching with CO₂ as the suitable electrophile (Scheme 24a). Similarly, at Novartis, a pilot plant synthesis of the lead tricyclic compound 91 was devised in large scale [91]. This involved the metalation of the 1,7-dimethoxynaphthalene 89 and electrophilic quenching to give the intermediate 90 in 83% yield which upon further transformation afforded the targeted 6-trimethylsilyl-9-methoxy-1-methyl-3,4,4a,5,10,10-a-hexahydro-2H-benzo[g]quinoline, 91 [91] (Scheme 24b) which was a dopamine D2/D3 agonist useful as antidepressant and anti-psychotic agent [92]. In one pot, chemists at BMS were able to use DoM to synthesize a tetrazole boronic acid 93 from the tetrazolo-starting material, 92 in the first step of the preparation of Losartan™ 94, an antihypertensive drug which is produced 1000 kg/Year [93] (Scheme 24c).

Table 3. Stereoselective lithiation-substitutions of bicyclic carbamate.

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Electrophile</th>
<th>E</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>86a₁</td>
<td>i-Pr</td>
<td>PhMe₂SiCl</td>
<td>SiMe₂Ph</td>
<td>4.5</td>
<td>43</td>
</tr>
<tr>
<td>86a₂</td>
<td>i-Pr</td>
<td>Me₂SO₄</td>
<td>Me</td>
<td>3</td>
<td>68</td>
</tr>
<tr>
<td>86a₃</td>
<td>i-Pr</td>
<td>Me₃SnCl</td>
<td>SnMe₂</td>
<td>5</td>
<td>78</td>
</tr>
<tr>
<td>86a₄</td>
<td>i-Pr</td>
<td>Bu₂SnCl</td>
<td>SnBu₁</td>
<td>3.5</td>
<td>67</td>
</tr>
<tr>
<td>86a₅</td>
<td>i-Pr</td>
<td>TMSCl</td>
<td>SiMe₂</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>86a₆</td>
<td>i-Pr</td>
<td>i-Pr₂CO</td>
<td>C(OH)i-Pr₂</td>
<td>2.5</td>
<td>68</td>
</tr>
<tr>
<td>86b₁</td>
<td>i-Bu</td>
<td>PhMe₂SiCl</td>
<td>SiMe₂Ph</td>
<td>2</td>
<td>77, 8⁺</td>
</tr>
<tr>
<td>86b₂</td>
<td>i-Bu</td>
<td>Me₂SO₄</td>
<td>Me</td>
<td>5</td>
<td>77</td>
</tr>
<tr>
<td>86b₃</td>
<td>i-Bu</td>
<td>Ph₂CO</td>
<td>C(OH)Ph₂</td>
<td>3</td>
<td>48⁺</td>
</tr>
<tr>
<td>86b₄</td>
<td>i-Bu</td>
<td>PhCO</td>
<td>CH(OH)Ph</td>
<td>5</td>
<td>66⁺</td>
</tr>
</tbody>
</table>

* A careful search for diastereomers in each case did not reveal their presence. It was estimated that at least 2% of any diastereomers would have been detected by GC analyses. * A compound tentatively identified as the trans diastereomer was isolated in 8% yield. + Additional product was present but was not separated from benzophenone. ** Two diastereomers were formed in a 1.5:1 ratio.

Scheme (24). Large scale production and industrial application of DoM in metalation.
4.10. Hydroxymethylation via Deprotonation

Since the availability of α-silyl carbanion played a significant role in the first stage of the reactions, many synthetic strategies have been developed in order to access this synthon [94]. Among these α-silyl carbanion-generating methods, deprotonation by butyllithium is by far the most convenient way and easily accessible technique, since α-halosilanes, α-heteroatom substituted silanes, and vinylsilanes are not always readily available. The deprotonation of 2-pyridyltrimethylsilane using t-BuLi in diethyl ether was reported to proceed through CIPE strategy of the 2-pyridyl group on silicon [95]. This is because, in most cases, together with the stabilization of the carbanion by the α-silyl group, additional stabilization effects by neighboring heteroatoms or electron withdrawing groups have been exploited for their generation [95]. In the second stage, the lithiated species of 2-pyridyltrimethylsilyl (2-PyMe$_2$Si) 96 formed was quenched with appropriate electrophiles to afford substrates 97a-e which were considered to be excellent hydroxymethylating agents because they possessed versatile silyl group that could be converted to the hydroxyl group with much milder conditions compared to the well-known PhMe$_2$Si group [95]. The oxidative cleavage of carbon-silicon bonds were performed using 30 % H$_2$O$_2$ (30 equiv), KF (2.0 equiv), and KHCO$_3$ (2.0 equiv) in MeOH/THF (1/1) at 50 °C to afford the corresponding alcohols 98a-e in excellent yields (Table 4). Hence, this two-step transformation provided an efficient method for the nucleophilic hydroxymethylation [95].

4.11. Fluorenone: Carbo cyclic Ketone from CIPE

Other reported cipe-based techniques have been reported to include lithiation of a silyl ether in the preparation of...
ortho-Fries hydroxyketone \[96\], directed remote aromatic metatation to access carbocyclic compounds \[97\], regioselective ring lithiation of BF₃-complexed 3-picoline \[98\], benzyne intermediate product formation via media effect on n-BuLi reactivity \[99\], enolate formation for one step synthesis of an optically active β-substituted ketone \[100\] and LDA-mediated ortho metatation of N,N-dialkyl-2-biphenyl carboxamides for the synthesis of cyclic ketone \[101\]. A typical cyclic ketone produce via this route is called fluorenone which is reported to be achieved through the pathway presented in Scheme (25) below according to the investigation by Tilly and coworkers \[101\]. In the absence of an electrophile, \( \text{100} \) undergoes equilibration via \( 99^\text{°} \) with \( \text{102} \), whose fate is instantaneous cyclization to a stable tetrahydrocarbinolamine oxide \( \text{103} \) which, only upon hydrolysis, affords fluorenone \( \text{104} \) \[101\].

**CONCLUSION**

In summary, heteroatom-facilitated lithiation reactions have assumed an increasingly important role in the elaboration of carbocyclic aromatic and heteroaromatic systems. The reactivity profile of the lithio species in a variety of C–C-bond-forming reactions is quite broad and useful. The complex-induced proximity effect (CIPE) in deprotonation may serve as a heuristic to discover new modes for C-H activation, which could be extended to carbonization chemistry. CIPE is an area that demands more careful examination in order to gain insight into the design of highly active and synthetically useful heterocyclic compounds via metatation chemistry. This review underlined the importance of initial lithiation site knowledge to understand the course of a metatation reaction as well as the crucial role of selective site complexation in directed lithiations. It therefore, provides a vista of opportunity towards constructing new biologically active heterocyclic compounds for present and future drug design and development.

**CONFLICT OF INTEREST**

The authors hereby declare that there is no conflict of interest as regard this present work.

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Declared none.

**REFERENCES**


