Trapping of Transient Organolithium Compounds

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Recent Advances in Trapping of Transient Organolithiums

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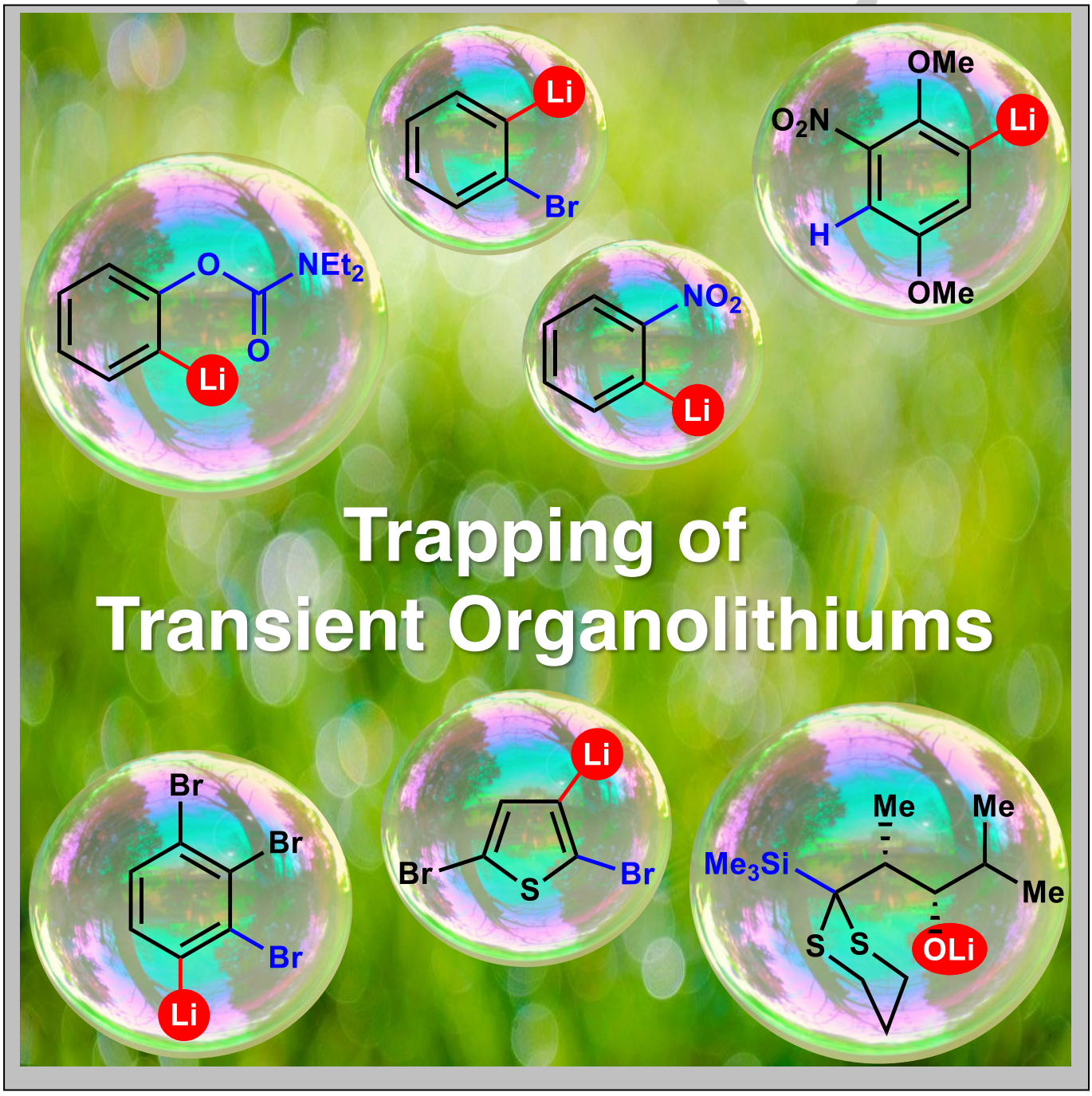

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Abstract: Organolithium chemistry has been widely utilized in organic synthesis as a reliable tool for introducing various functional groups. The intrinsic high reactivity of organolithiums allows rapid chemical transformation; however, the transient organolithiums bearing an electrophilic moiety often cause the undesired reactions such as self-dimerization, isomerization, and decomposition, which prevent further synthetic application. In this minireview, we classify the reactions involving the short-lived organolithiums and focus on the recent progress in flow chemistry, which allows to trap the highly reactive organolithium species. In addition, this review includes other approaches using the related organometallic species that can be performed in a conventional batch reactor. To place the recent development of this field in perspective, the established strategies controlling the reactivities of the short-lived organolithiums provide a short-step, efficient, and protective group-free synthesis of functionalized organic molecules in medicinal, agrochemical, and material chemistry.

1. Introduction

1.1. Organolithium

Organic chemistry has contributed to human activity by providing numerous compounds that are useful as medicines, agrochemicals, functional materials, and natural products. The fundamental approach to access these compounds includes a C–C bond formation because almost all organic compounds contain a carbon chain. Organolithiums have been widely used for the construction of C–C bonds as a carbanion synthon,[1] since the generation method was established by Ziegler,[2] Wittig, and Gilman[3] in 1930s–1940s. The synthetic merits of organolithiums are 1) high reactivity, 2) easy preparation, and 3) commercial availability. These properties meet the demand for versatile functionalization, including the C–C bond formation, which has resulted in the widespread use of organolithiums in modern organic synthesis. However, the high reactivity of organolithiums sometimes causes serious problems regarding the self-reaction and the limited functional group compatibility. In addition, trapping of the short-lived organolithium species during benzyne generation has been a challenging problem. In this minireview, we categorize the types of reactions involving the short-lived organolithiums. We also focus on how each organolithium is selectively trapped to provide the corresponding products. In conclusion, we describe the outlook of this field.

Kengo Inoue was born in Fukuoka in 1997. He received his B.S. in 2020 from Kobe University under the direction of Professors Atsunori Mori and Kentaro Okano. During his M.S. studies, he is working on selective trapping of short-lived heteroaryllithiums in halogen dance and its application to the synthesis of multiply substituted heteroaromatic compounds.

Kentaro Okano received his B.S. in 2003 from Kyoto University under the supervision of Professor Tamejiro Hiyama. He then moved to Professor Tohru Fukuyama's group at the University of Tokyo. In 2007, he joined the faculty at Tohoku University in Professor Hidetoshi Tokuyama's group. In 2014, he visited Professor Amir Hoveyda's group at Boston College as a visiting researcher. In 2015, he moved to Kobe University, where he is currently an Associate Professor in Professor Atsunori Mori's group. His research interests include the development of new synthetic methodologies and natural product synthesis.

1.2. Generation of Organolithiums

The methods used to generate organolithiums can be classified into four types, namely, a) deprotolithiation, b) halogen–lithium exchange, c) reduction of the C–X bond, and d) transmetalation (Scheme 1). During the deprotolithiation process, a strong base (R'–Li or Li–NR^1R^2) is required to deprotonate R–H, which leads to the formation of organolithium R–Li and the corresponding side product such as R'–H (from R'–Li) or H–NR^1R^2 (from Li–NR^1R^2) (Scheme 1a).[4] Deprotonation is considered to be reversible, and the equilibrium depends on the total energy difference between the initial system and the product system. Thus, the deprotonation should be conducted with a strong base, such as R'–Li or Li–NR^1R^2, to drive the equilibrium to the right. Deprotolithiation is the most effective approach to generate organolithiums in terms of atom economy. Halogen–lithium exchange is a reaction during which an organohalide (R–X) and a strong base (R'–Li) react to generate less basic R–Li with the concomitant formation of R'–X (Scheme 1b). The mechanism is considered to be nucleophilic addition of the R'–Li to the halogen atom or single electron transfer (SET).[5] This method requires a strongly basic organolithium such as *n*BuLi and relatively expensive organobromides or organoiodides. Despite their drawbacks, halogen–lithium exchange has been the most widely used method to prepare organolithiums owing to their fast reaction rates.[6] In addition to bromides and iodides, chlorides and sulfides can be converted into organolithiums by reduction with Li metal (Scheme 1c).[7] The reaction requires two equivalents of Li metal to complete the reaction, which proceeds through the SET mechanism. Lithium naphthalenide (LN), lithium 1-(dimethylamino)naphthalenide (LDMAN), and lithium 4,4'-di-*tert*-butylbiphenylide (LDBB) are utilized as electron carriers.[8] Specifically, LDBB is a superior reagent to provide organolithium species by preventing an undesired coupling of the generated radical species R· and 4,4'-di-*tert*-butylbiphenyl (DBB). Organolithium species (R–Li) can be generated by transmetalation of another organolithium (R'–Li) with organotin, organoselenium, and organotellurium (Scheme 1d).[9] Because the reaction proceeds via an ate complex by the nucleophilic attack of organolithium (R'–Li), a lower LUMO level

is desirable for the organometallic compound (R–M). In terms of thermodynamics, the less polarized C–M bond of R'–M is preferable to shift the equilibrium toward the product in a short reaction time. Among these organometallic compounds, organotin is generally employed to meet these demands to obtain the desired organolithium species.

a) Deprotolithiation

b) Halogen–lithium exchange

(X = Br, I)

c) Reduction of the C–X bond

(X = Cl, Br, I, SPh)

d) Transmetalation

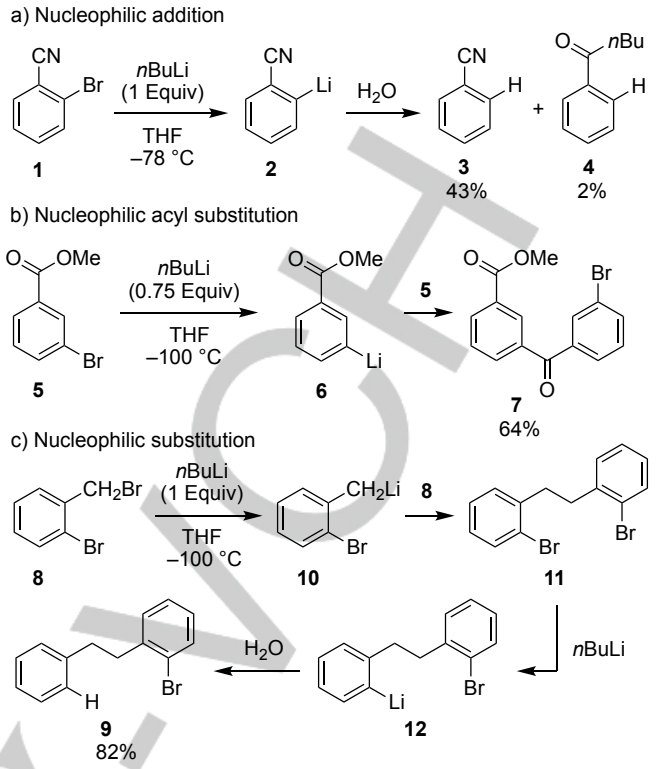
(M = $SnR"_3$, SeR", TeR")

Scheme 1. Representative methods to generate organolithiums.

2. Reactions of Organometallic Species Bearing Electrophilic Functionalities

2.1. Representative Self-reactions of Organolithiums

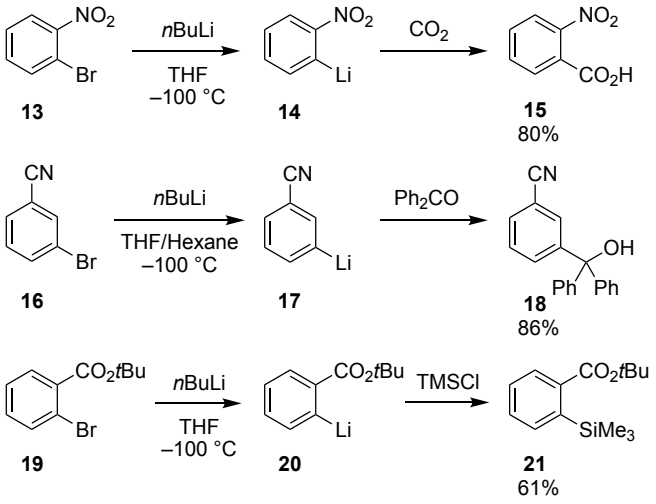
Organolithiums have been widely used in the syntheses of natural products and structurally complex molecules as a significant scaffold. Organolithiums are highly reactive with a wide variety of electrophiles; however, the reaction of organolithiums bearing electrophilic functionalities often causes serious problems owing to their high reactivity toward the electrophilic moiety. Parham *et al.* reported several examples of short-lived organolithiums bearing electrophilic functionalities (Scheme 2). A complicated result was obtained when 2-bromobenzonitrile (**1**) was treated with *n*BuLi at –78 ºC (Scheme 2a).[10] The halogen–lithium exchange of 2-bromobenzonitrile (**1**) resulted in the generation of the corresponding phenyllithium **2**, which was quenched with water to provide benzonitrile (**3**) and ketone **4** in 43% and 2% yields, respectively. The moderate yield can be attributed to the undesired reaction of the electrophilic cyano group. Methyl 3-bromobenzoate (**5**) was converted to phenyllithium **6**, which underwent dimerization even at –100 °C to afford benzophenone **7** through nucleophilic acyl substitution (Scheme 2b).[11] The treatment of 2-bromobenzyl bromide (**8**) with *n*BuLi also resulted in the self-reaction (Scheme 2c).[12] This reaction provided the dimerized compound **9** in 82% yield. The results can be explained by the nucleophilic substitution of the first generated benzyllithium **10** with another benzyl bromide **8** to provide compound **11**, which further reacted with *n*BuLi to generate organolithium **12**.



Scheme 2. Self-reaction of short-lived organolithiums.

2.2. Trapping of Labile Organolithiums

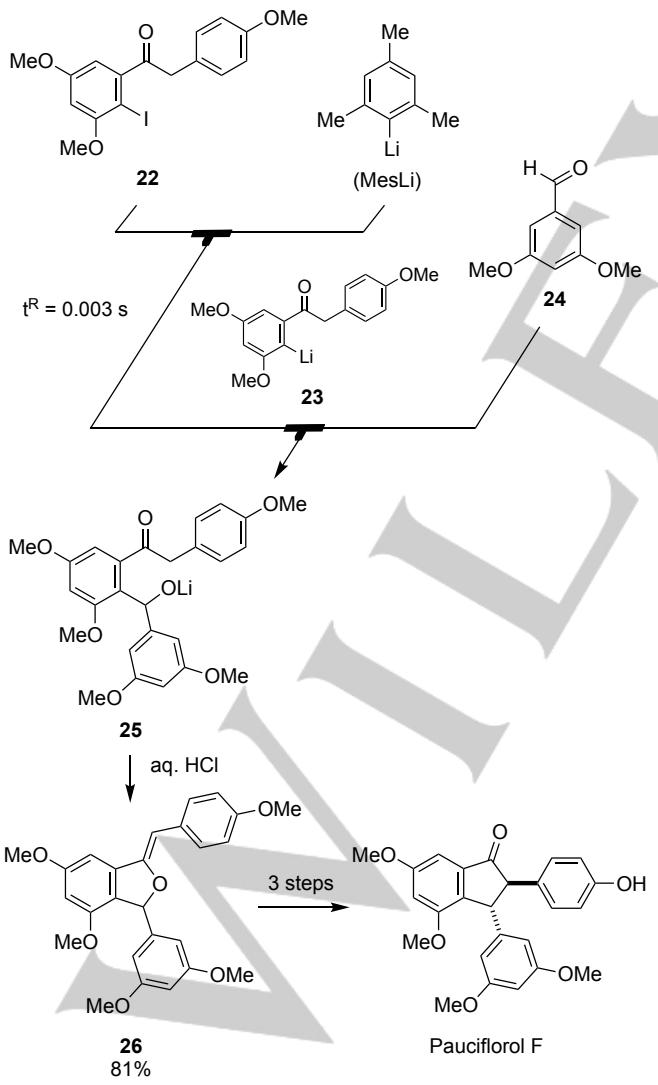
These self-reactions of the labile organolithiums can be avoided in a batch reactor by performing the halogen–lithium exchange at extremely low reaction temperature (Scheme 3). In 1970, Kobrich and Buck reported that the halogen–lithium exchange of 2-bromonitrobenzene (**13**) proceeded smoothly at –100 °C.[13] The generated aryllithium **14** was easily trapped with carbon dioxide to furnish 2-nitrobenzoic acid (**15**) in 80% yield without affecting the electrophilic nitro group.[14] In the case of bromobenzonitrile **16**, aryllithium **17** was trapped with benzophenone to provide the corresponding adduct **18** in 86% yield.[10] Similarly, the halogen–lithium exchange of aryl bromide



Scheme 3. Successful transformations of aryllithium species.

19 was performed at –100 °C to generate aryllithium **20**, which reacted with TMSCl to afford the desired product **21** in 61% yield.[15] The electrophilic nitro, cyano, and *tert*-butyl ester groups were intact within several minutes, when the bromine–lithium exchange was performed at –100 °C; however, aryllithiums bearing more electrophilic ketone and aldehyde moieties cannot be used in a batch reactor under similar conditions. The reaction rate of the halogen–lithium exchange was reported to be much faster than that of subsequent trapping of the resultant aryllithium with an electrophile,[16] which indicates that the transformation should be realized by the precise control of the reaction time in the first reaction on the order of subsecond or millisecond. The recently developed flow reactor technology has paved way for utilizing these short-lived aryllithiums that have not been trapped in a batch reactor without protecting these highly electrophilic functional groups.[17]

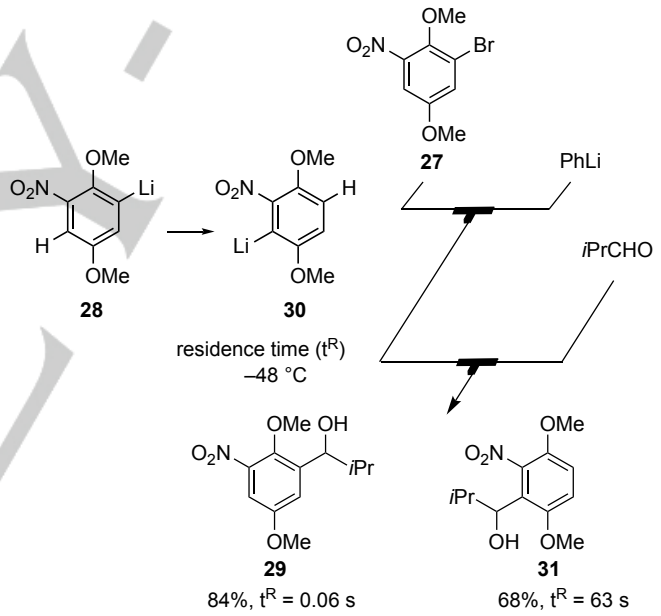
In 2011, Yoshida and Nagaki reported the protective group-free synthesis of pauciflorol F by using the short-lived aryllithium bearing a ketone moiety in a flow microreactor (Scheme 4).[18] The reaction of mesityllithium (MesLi) and 2-iodophenyl ketone **22** led to the formation of the short-lived organolithium **23**, which was successfully trapped with benzaldehyde **24** to furnish the corresponding adduct **25** with the residence time t^R = 0.003 s.



Scheme 4. Synthesis of pauciflorol F using a flow microreactor.

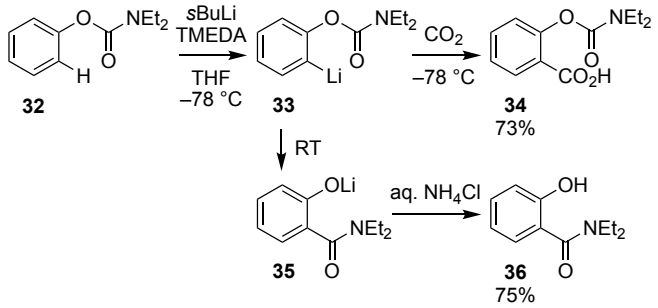
Subsequent acid treatment of **25** provided dehydrated cyclic compound **26** in 81% yield, which was then converted into pauciflorol F in three steps. In addition to the ketone carbonyl group, the trapping of the aryllithium species bearing an aldehyde moiety was achieved with the formyl group remaining intact.[19]

The flow microreactor allows the selective trapping of two isomeric aryllithiums by the precise control of the reaction time. Yoshida and Nagaki utilized the nitro group-containing aryl bromide **27** as a substrate (Scheme 5).[20] The halogen–lithium exchange of bromobenzene **27** with PhLi occurred at –48 °C to generate the corresponding aryllithium **28**. This organolithium was selectively trapped with isobutyraldehyde to afford alcohol **29** in 84% yield, when the residence time was set to 0.06 s. The first generated aryllithium **28** was converted to the thermodynamically favored aryllithium **30**, where the aryllithium was stabilized by the adjacent nitro group. Alcohol **31** was obtained in 68% yield with the residence time set to 63 s. The fine tuning of the residence time cannot be performed in a conventional batch reactor, which fully demonstrates the promising potential of the flow microreactor.



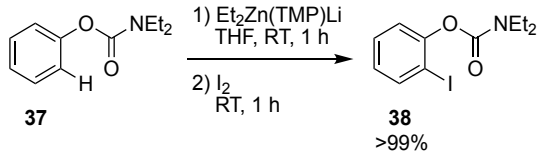
Scheme 5. Selective trapping of organolithiums bearing a nitro group in a flow microreactor.

The anionic Fries rearrangement is another example that involves two organolithium species.[21] In 1983, Snieckus and Sibi reported the first anionic Fries rearrangement (Scheme 6).[22] The reaction started with the deprotolithiation of phenyl carbamate **32** at the *ortho* position directed by the carbamate with the combination of *s*BuLi and TMEDA to generate *ortho*-lithiated *O*-aryl carbamate **33**. This lithiated carbamate **33** could be trapped at –78 °C with carbon dioxide to provide the corresponding benzoic acid **34** in 73% yield. In contrast, by raising the reaction temperature to room temperature, lithiated carbamate **33** underwent the anionic Fries rearrangement to afford *O*-lithiated salicylamide **35**, which was quenched with aqueous NH_4Cl to afford **36** in 75% yield. The results indicate that the aryllithium species bearing the carbamate moiety at the *ortho* position are sufficiently stable to be handled at –78 °C.



Scheme 6. The anionic Fries rearrangement of organolithium.

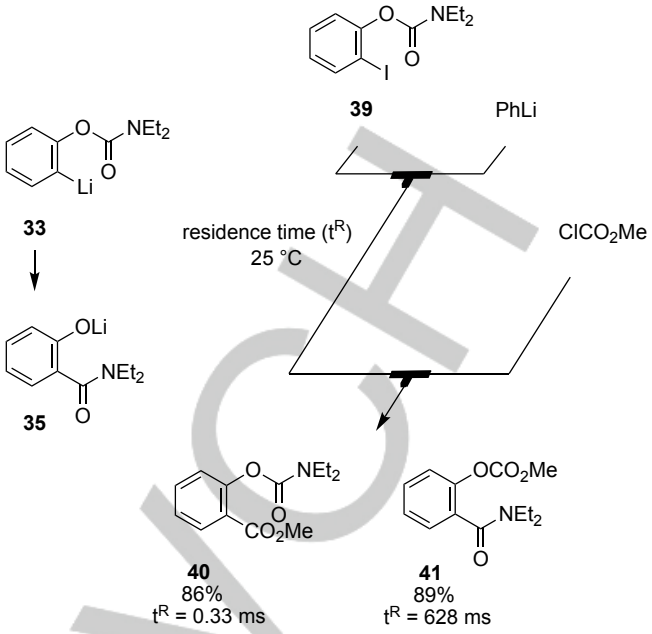
The anionic Fries rearrangement is promoted by the highly reactive organolithium. In 2008, Wheatley and Uchiyama reported the direct iodination of carbamate **37** utilizing $Et_2Zn(TMP)Li$ as a base (Scheme 7).[23] Carbamate **37** underwent a smooth deprotonation at room temperature to generate the corresponding organozinc species, which was transformed to the desired aryl iodide **38** in 99% yield without the anionic Fries rearrangement. The zincation provides direct access to the functionalized aromatic compounds with the combination of recently developed reactions of organozinc species,[24] whereas this example is limited to iodination.



Scheme 7. Suppression of the anionic Fries rearrangement using $Et_2Zn(TMP)Li$.

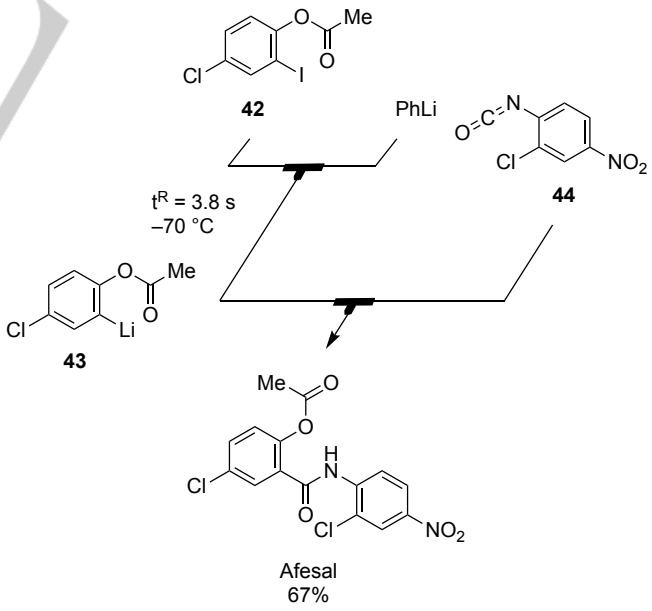
Similar to aryl carbamates, 2-lithioaryl triflates underwent the anionic thia-Fries rearrangement to provide a phenol bearing the sulfonyl group at the *ortho* position.[25] This thia-Fries rearrangement was suppressed by using *i*PrMgCl to generate the organomagnesium reagents from the corresponding aryl iodides, which led to the formation of benzyne through the β-elimination of the triflate.[26] These carbanion intermediates in the anionic Fries rearrangement can be used to react with electrophiles when the reaction involves organozinc or organomagnesium reagents. From a synthetic viewpoint, the method to utilize more reactive organolithiums is still desirable.

Yoshida and Kim have recently reported the trapping of the short-lived organolithium in the anionic Fries rearrangement by the precise control of the reaction time and the reaction temperature in a flow microreactor (Scheme 8).[27] The halogen–lithium exchange of carbamate **39** was conducted at room temperature for 0.33 ms. Subsequent treatment with methyl chloroformate provided benzoic acid ester **40** in 86% yield. In contrast, longer residence time (628 ms) led to the anionic Fries rearrangement to afford carbonate **41** in 89% yield. Compared with the example in Scheme 7, this method allows to use less reactive electrophiles such as methyl chloroformate owing to the high reactivity of organolithiums **33** and **35**. It is worthwhile to point out that both products are available at room temperature on a practical level, simply by changing the residence time in the flow microreactor.



Scheme 8. Selective trapping of the two organolithiums involved in anionic Fries rearrangement in a flow microreactor.

The established method was also applied to the aryl acetate that was more reactive than the aryl carbamate, which allowed direct access to afesal (Scheme 9). The halogen–lithium exchange of aryl acetate **42** with PhLi generated the corresponding organolithium **43** at –70 ºC for 3.8 s, which was successfully trapped with aryl isocyanate **44** to provide afesal in 67% yield, leaving the ester group untouched.

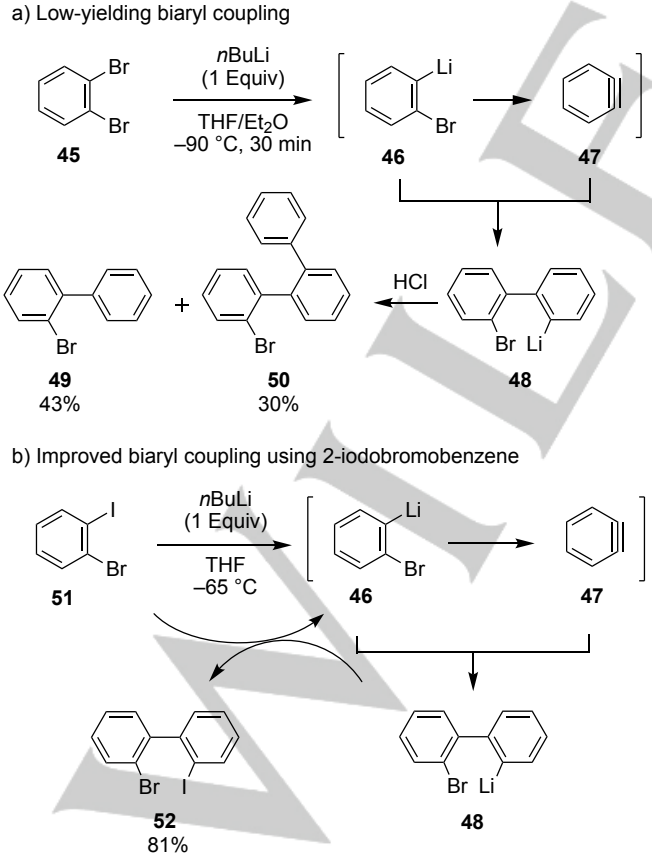


Scheme 9. Synthesis of afesal in a flow microreactor.

In addition to the approach using organolithium species in a flow microreactor, more stable organometallic species such as Grignard reagents or organozinc reagents are employed to avoid the undesired self-reaction. Several accounts and reviews dealing with this topic have been published.[28]

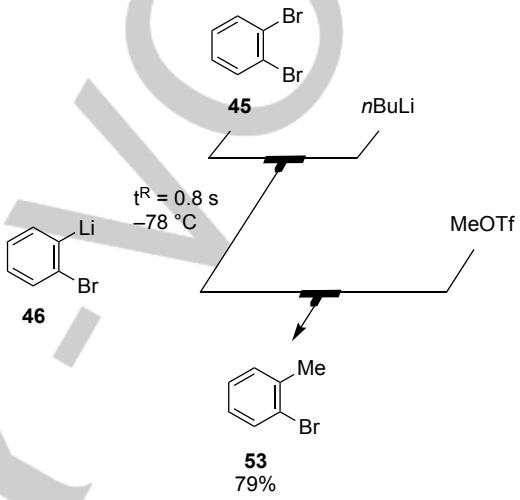
3. Arylmetal Species Bearing a Halogen/Pseudo Halogen at Position 2

Aryllithiums bearing a halogen/pseudo halogen at position 2 are susceptible to β-elimination, which led to the generation of aryne intermediates. In 1980, Chen reported that the treatment of 1,2-dibromobenzene (**45**) with *n*BuLi at −90 °C facilitated the biaryl coupling (Scheme 10a).[29] The halogen–lithium exchange of **45** gave 2-bromophenyllithium (**46**), which was converted to benzyne (**47**) with elimination of LiBr. Benzyne (**47**) was highly electrophilic and reacted with another phenyllithium **46** to generate biaryllithium **48** through the C–C bond formation. Acidic workup provided biaryl compound **49** in 43% yield associated with terphenyl **50** in 30% yield. These results indicated that biaryllithium **48** underwent further nucleophilic addition to benzyne (**47**). In 2002, Schlosser and Leroux reported the considerable effect of the rates of halogen–lithium exchange on improving the yield of the biaryl coupling by using 2-bromo-1-iodobenzene (**51**) (Scheme 10b).[30] The iodine-selective halogen–lithium exchange of **51** occurred to generate organolithium **46**, which was then converted into benzyne (**47**). The reaction of benzyne (**47**) and the organolithium **46** generated biaryllithium **48**, which was the same transformation as that in Chen's report. The generated biaryllithium **48** underwent iodine–lithium exchange with **51** to afford the corresponding biaryl **52** in 81% yield with the regeneration of organolithium **46**. The reaction rate of the bromine–lithium exchange of organolithium **48** is much slower than that of the iodine–lithium exchange, which resulted in further reaction with benzyne (**47**) to provide terphenyl **50** in Scheme 10a.



Scheme 10. Generation of benzyne via 2-substituted phenyllithiums.

As described in Scheme 10, 1,2-dibromobenzene (**45**) and 1-bromo-2-iodobenzene (**51**) serve as a potential scaffolding element to construct the biaryl skeleton that is often found in useful compounds. Nevertheless, trapping of the transient carbanion **46** would offer a straightforward approach toward *ortho*-disubstituted benzene derivatives. In 2007, Yoshida and Nagaki successfully trapped the short-lived carbanion **46** with some electrophiles in a flow microreactor before the generation of benzyne (**47**) (Scheme 11).[31] They performed the halogen–lithium exchange of 1,2-dibromobenzene (**45**) with *n*BuLi at −78 °C to produce benzyne precursor **46** within 0.8 s, which reacted with MeOTf to afford 2-bromotoluene (**53**) in 79% yield.

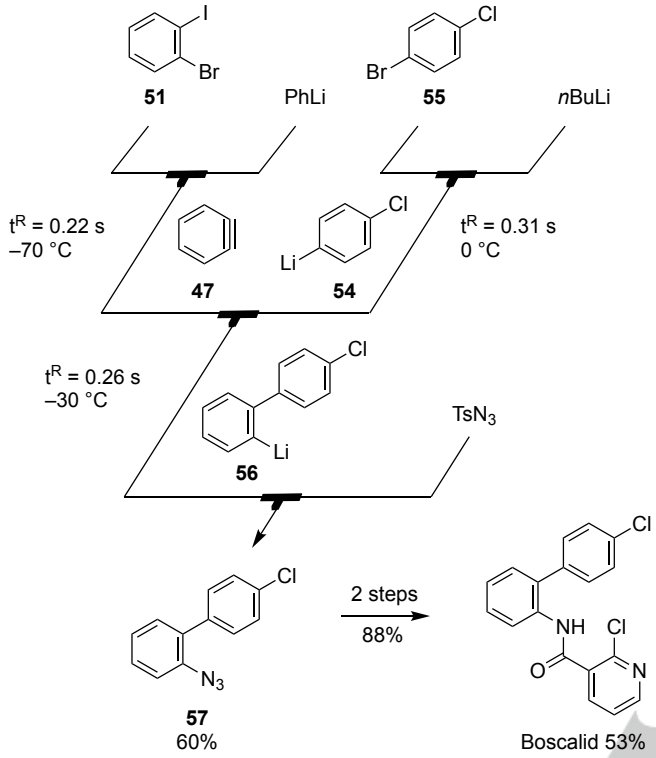


Scheme 11. Trapping of the short-lived organolithium in a flow microreactor.

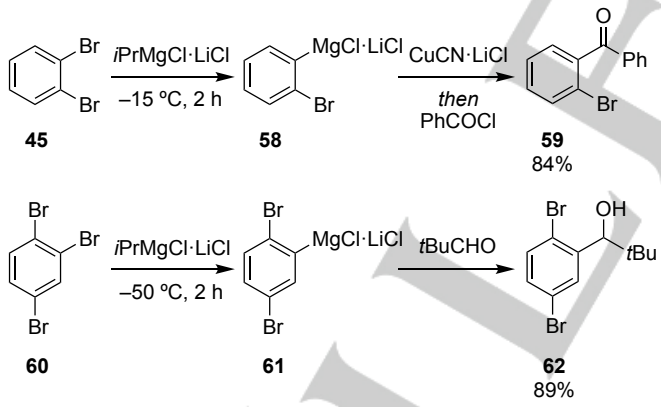
The residence time of 0.8 s allowed to suppress the benzyne formation and utilized the short-lived organolithiums for organic synthesis. The prolonged residence time led to the formation of benzyne that could be handled as a reagent. In 2014, Nagaki and Yoshida reported a three-component coupling through carbolithiation of benzyne with functionalized aryllithiums (Scheme 12).[32] The iodine–lithium exchange of **51** and PhLi at −70 °C for 0.22 s generated organolithium **46**, which was then mixed with another organolithium **54** generated from 4-chloro-bromobenzene (**55**). Upon raising the reaction temperature to –30 °C, the generated benzyne (**47**) reacted with aryllithium **54** to provide biaryllithium **56**. Finally, the reaction was quenched with TsN_3 to afford aryl azide **57** in 60% yield, which was converted into boscalid in 53% yield over two steps. The method allows to utilize benzyne (**47**) for the "cross" coupling reaction with another organolithium, whereas the examples shown in Scheme 10 are "homo" coupling.

Knochel and co-workers have reported that 2-bromophenyl Grignard reagents were sufficiently stable to be functionalized at low reaction temperatures (Scheme 13).[33] They used *i*PrMgCl·LiCl to generate arylmagnesium chloride **58** through halogen–magnesium exchange. After transmetalation with CuCN·LiCN, subsequent reaction with benzoyl chloride provided the desired ketone **59** in 84% yield. This method was also applied to 1,2,4-tribromobenzene (**60**) for the regioselective formation of arylmagnesium **61**, which reacted with pivalaldehyde to afford benzyl alcohol **62** in 89% yield. The halogen–magnesium exchange of **45** and *i*PrMgCl·LiCl

proceeded smoothly without benzyne formation, whereas the related magnesium ate base such as *n*Bu$_3$MgLi accelerated the benzyne formation.[28d]

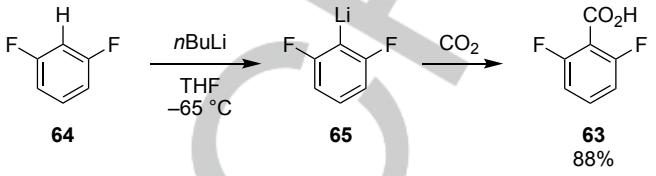


Scheme 12. Three-component coupling via carbolithiation of benzyne in a flow microreactor.



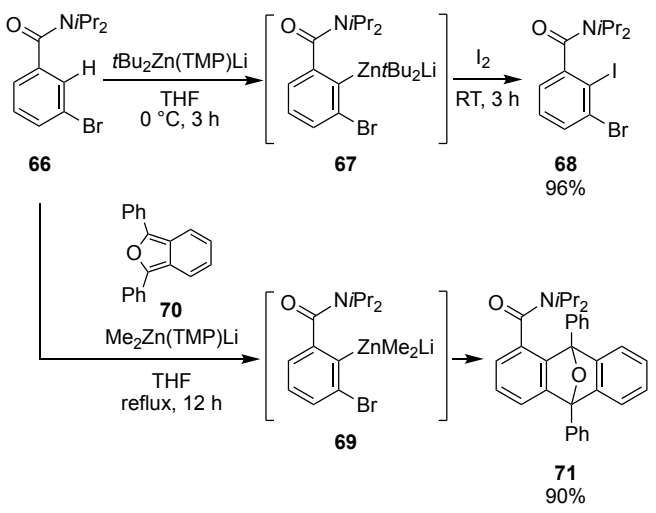
Scheme 13. Suppression of benzyne formation via halogen–magnesium exchange.

The fast halogen–metal exchange is utilized to trap transient carbanions before the formation of benzyne. The slower deprotolithiation can be also employed when the resulting phenyllithium is stabilized by an electron-withdrawing group. Specifically, a fluoro group is often used for this purpose owing to the strong electron negativity and the poor leaving group ability. In 1965, Tamborski and Soloski reported the synthesis of 2,6-difluorobenzoic acid (**63**) (Scheme 14).[34] The treatment of 1,3-difluorobenzene (**64**) with *n*BuLi at −65 °C produced 2,6-difluorophenyllithium (**65**), which was trapped with carbon dioxide to furnish 2,6-difluorobenzoic acid (**63**) in 88% yield without benzyne formation. The fluoro group can be functionalized by S_NAr reaction and several coupling reactions; however, the available reactions are limited compared to those of other halogen atoms, which can be readily converted into various functional groups. From the viewpoint of organic synthesis, the deprotonative approach to utilize organometallic reagents bearing a halogen/pseudo halogen at position 2 without benzyne formation is still required.



Scheme 14. Regioselective lithiation without benzyne formation.

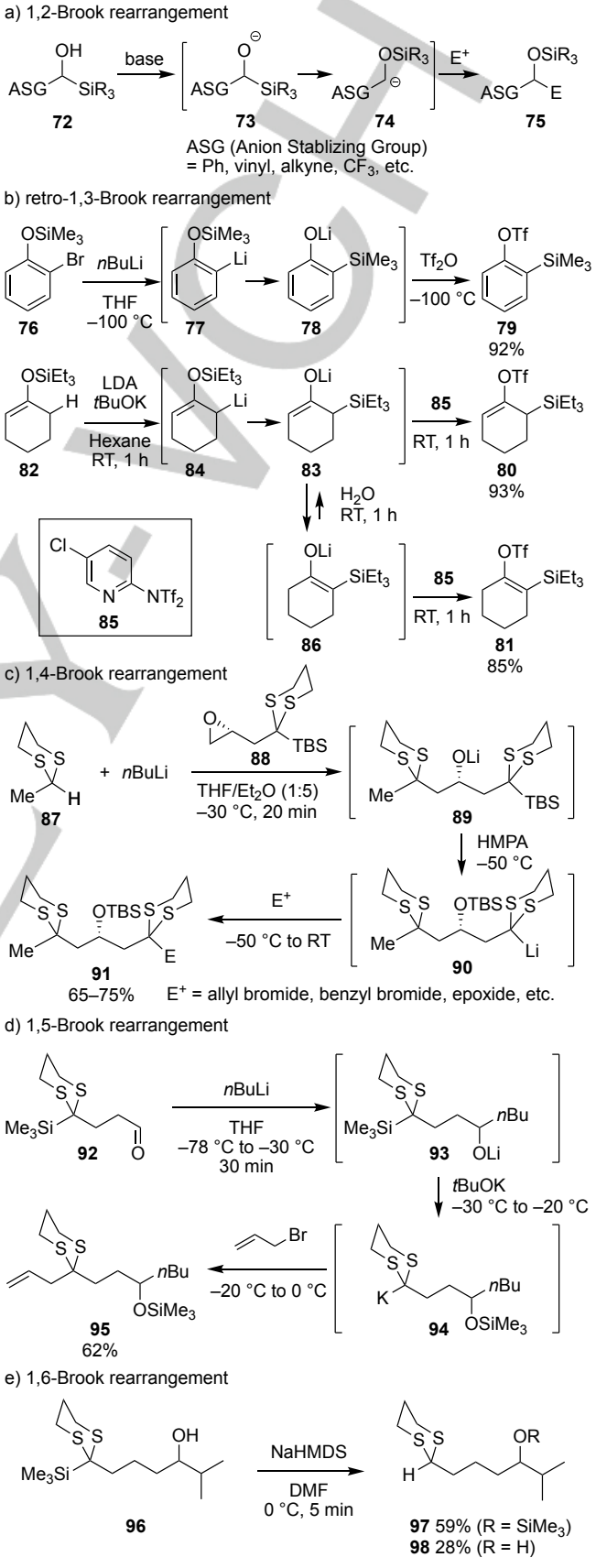
In 2002, Uchiyama and co-workers reported the deprotonation of bromobenzenes bearing a substituent such as an amide or a halogen at position 3, using R$_2$Zn(TMP)Li as a base (Scheme 15)[35]. The deprotonation of bromobenzamide **66** was successfully performed with *t*Bu$_2$Zn(TMP)Li to provide the corresponding zincate **67**, which could be trapped with iodine to afford 1,2,3-trisubstituted benzene derivative **68** in 96% yield. The substituent that assists deprotonation proved important for this reaction, and the method provided direct access to multiply halogenated benzene derivatives that were useful scaffolds for further functionalization. Similarly, bromobenzamide **66** underwent the regioselective deprotonation by Me$_2$Zn(TMP)Li to provide arylzincate **69**, which led to the formation of the corresponding benzyne upon heating. Subsequent cycloaddition with isobenzofuran **70** furnished cycloadduct **71** in 90% yield. In 2004, they also reported an efficient switching between benzyne formation and suppression of benzamide derivative **66** with *t*Bu$_3$Al(TMP)Li by controlling the reaction time and the reaction temperature.[36] Compared to the corresponding aryllithium intermediates, the presented arylzincate and arylaluminate are sufficiently stable to be handled in a batch reactor, which shows a potential to be applied to further chemical transformations.



Scheme 15. Ligand effects of the alkyl group of the zincate for the selective synthesis of 1,2,3-trisubstituted benzene or for the generation of benzyne.

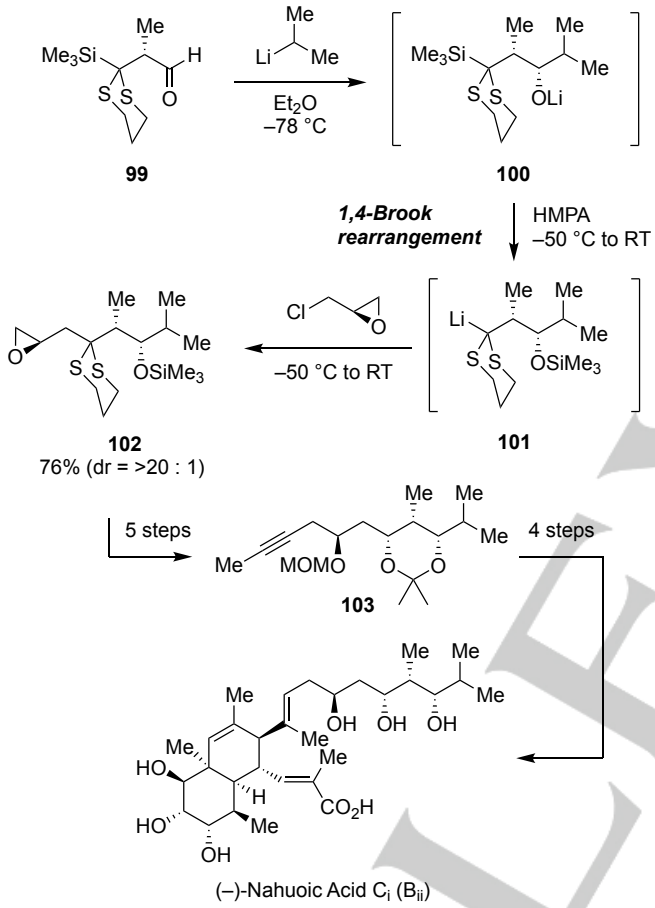
4. Brook Rearrangement

Brook rearrangement is a reliable method for the generation of a carbanion by the transfer of a silyl group from the carbon atom to the proximal oxygen atom, which is promoted by the formation of a strong Si–O bond.[37] For 1,2-Brook rearrangement, the treatment of alcohol **72** with a base (e.g., NaH, RLi, and R_3N) generated alkoxide **73**, which rearranged to carbanion **74** bearing the anion stabilizing group (ASG) at the carbanion center. Following treatment with electrophiles provided **75** (Scheme 16a).[38] This rearrangement proceeds in an intramolecular manner; therefore, silyl migration can occur at a longer distance. The retro 1,3-Brook rearrangement is sometimes preferred when an alkoxide is stabilized as a phenoxide or an enolate, which is used as an efficient method to obtain a precursor of benzyne, cyclohexyne, and 1,2-cyclohexadiene (Scheme 16b).[39] Guitián and co-workers have reported that silyl ether **76** underwent halogen–lithium exchange at –100 ºC followed by the retro 1,3-Brook rearrangement of **77** to provide phenoxide **78**, which was trapped with Tf_2O to afford benzyne precursor **79** in 92% yield from 2-bromophenol. Okano and co-workers have recently reported the divergent synthesis of silyl enol triflates **80** and **81**.[40] Silyl enol ether **82** was subjected to the combination of LDA and *t*BuOK to generate lithium enolate **83** via retro 1,3-Brook rearrangement of the first generated allyllithium **84**, which reacted with Commins' reagent **85**[41] to furnish 1,2-cyclohexadiene precursor **80** in 93% yield. The trisubstituted lithium enolate **83** could be isomerized to tetrasubstituted lithium enolate **86** in the presence of stoichiometric amount of water. The thermodynamically favored **86** was converted to the corresponding cyclohexyne precursor **81** in 85% yield. Smith and co-workers have developed "Anion Relay Chemistry" (ARC), which is an efficient method for the iterative construction of C–C bonds involving 1,4-Brook rearrangement.[42] A silyl group and an ASG such as dithiane proved essential for the anion relay. An early study by Smith has shown a successful example of ARC using dithiane **87** and epoxide **88** (Scheme 16c).[43] The deprotonation of dithiane **87** followed by nucleophilic addition to **88** provided alkoxide **89**. The addition of HMPA assisted 1,4-Brook rearrangement to generate **90**, which was treated with an electrophile such as allyl bromide, benzyl bromide, and epoxide to afford the corresponding products **91** in 65–75% yields. The complete consumption of epoxide **88** was required to prevent the undesired reaction of carbanion **90** and epoxide **88**, which was circumvented by the addition of HMPA triggering 1,4-Brook rearrangement after the completion of the ring opening of epoxide **88**. The elegant method allowed the three-component reaction in one pot including the formation of the two C–C bonds, which provided the appropriately protected acyclic compounds for the synthesis of complex molecules. They also reported that the 1,5-Brook rearrangement smoothly occurred in an intramolecular manner (Scheme 16d).[44] The reaction started with the nucleophilic addition of *n*BuLi to aldehyde **92** bearing a *tert*-butyldimethylsilyl (TBS) group. Upon the addition of *t*BuOK, the transfer of the silyl group in **93** was promoted to afford carbanion **94**, which reacted with allyl bromide to furnish desired product **95** in 62% yield. The 1,6-Brook rearrangement led to the lower yield of the product, presumably owing to the unfavored seven-membered transition state. Smith and co-workers chose dithiane **96** as a substrate for the 1,6-Brook rearrangement (Scheme 16e). The treatment of **96** with NaHMDS provided the desired product **97** with desilylated starting material **98** in 59% and 28% yields, respectively. The authors asserted that this 1,6-Brook rearrangement also involved an intermolecular pathway, which was confirmed by the crossover experiments.



Scheme 16. The reaction types of Brook rearrangement.

Smith has demonstrated the synthetic potential of ARC in the total syntheses of several natural products.[42d] In 2017, they reported the first synthesis of (–)-nahuoic acid C_i (B_{ii}) (Scheme 17).[45] The key transformation began with the diastereoselective addition of isopropyllithium to aldehyde **99** to generate the corresponding adduct **100**, which underwent the 1,4-Brook rearrangement to provide organolithium **101** with the assistance of HMPA. Organolithium **101** reacted with (*R*)-epichlorohydrin to afford the desired product **102** in 76% yield with a >20:1 diastereomeric ratio. The obtained product included the epoxide moiety for further transformations; dithiane **102** was converted into the key synthetic intermediate **103** in five steps, which led to the synthesis of (–)-nahuoic acid C_i (B_{ii}) in another four steps.

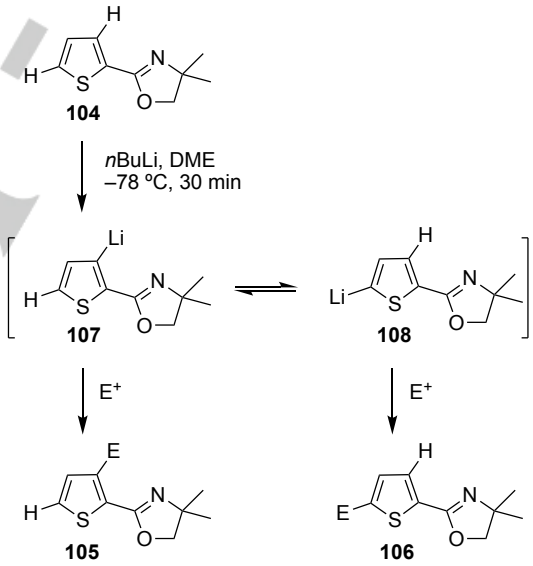


Scheme 17. Total Synthesis of (–)-nahuoic acid C_i (B_{ii}).

5. Isomerization of Organometallic Reagents Generated by Deprotonation

In addition to Scheme 5, several examples of isomerization of organometallic reagents have been reported. When deprotonation is performed using the directing group such as oxazoline, ester, amide, and other functional groups with a coordination site to the base, the kinetically generated organometallic species are sometimes converted into thermodynamically more stable carbanions. In this section, the four insightful examples are described, which serve as a guideline for designing the reactions to obtain multiple constitutional isomers from a single substrate. The kinetically generated carbanions can be selectively trapped by the appropriate choice of solvent and base, the appropriate mixing of reagents, and in situ transmetalation as organozinc species.

In 1985, Chadwick and Carpenter reported that deprotolithiation/deuteration of thiophene **104** bearing an oxazoline at position 3 led to the formation of two constitutional isomers **105** and **106** (Scheme 18).[46] The ratio of products ranged from 2:1 to 2:3, depending on the electrophiles. The authors explained that D_2O and MeOD were reactive electrophiles and that the ratios of products **105** and **106** thus indicated those of thienyllithiums **107** and **108**. In the case of iodomethane, thienyllithium **107** is inherently less reactive than thienyllithium **108** owing to the steric effects of the oxazoline. The slight increase of product **106** suggests an equilibrium between the thienyllithium species **107** and **108**. They also optimized the reaction conditions for the selective generation of each thienyllithium species; *n*BuLi in hexane for **107** and LDA in THF for **108**. The selective generation of thienyllithium **107** would be achieved by increasing the relative effects of the coordination of the oxazoline to *n*BuLi and by lowering the reactivity of thienyllithium **107** as oligomeric structure using the solvent effects of hexane.[47]

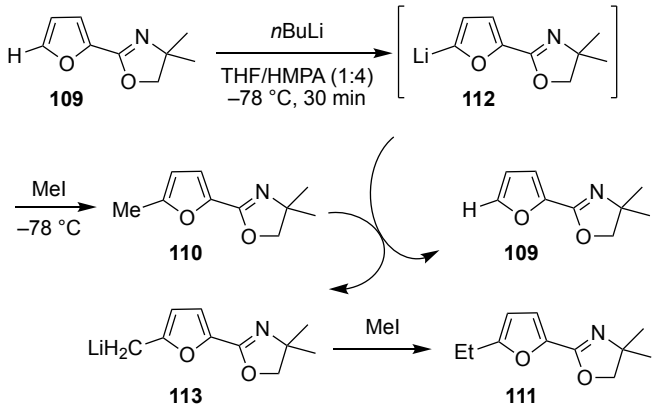


E^+	E		
D_2O	D	60%	32%
MeOD	D	58%	35%
TMSCl	$SiMe_3$	59%	41%
MeI	Me	29%	46%

Scheme 18. Isomerization of thienyllithiums bearing an oxazoline moiety.

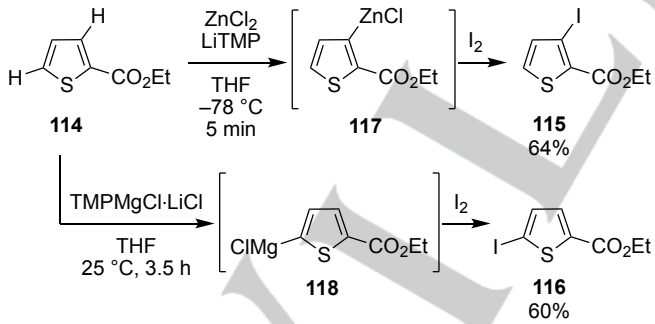
The reactive organolithium species often caused an undesirable overreaction. In 1994, Quéguiner and co-workers reported regioselective deprotolithiation of oxazolidine-substituted furan **109** (Scheme 19).[48] Deprotonation at position 5 was performed by *n*BuLi in THF/HMPA (1:4) at −78 °C. Subsequent addition of iodomethane provided a mixture of 5-methylfuran **110** and 5-ethylfuran **111**. The authors speculated that the unexpected ethylation proceeded through deprotolithiation of the first generated 5-methylfuran **110** by the unreacted organolithium **112** followed by the methylation of the organolithium **113**. They resolved this overreaction by employing the inverse addition; the generated furyllithium **112** was added to

a vigorously stirred solution of iodomethane to afford 5-methylfuran **110** in 85% yield.



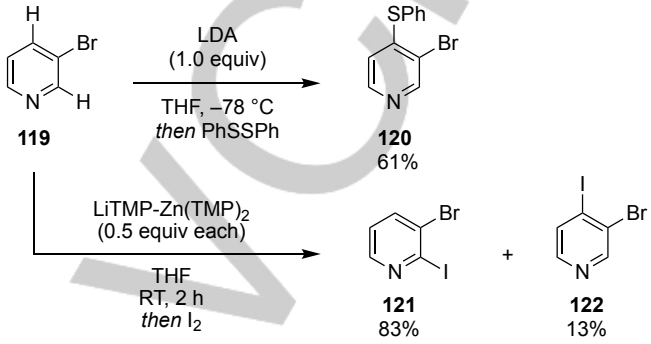
Scheme 19. Unexpected homologation during the methylation of furyllithium.

The appropriate control of such isomerization of organolithiums allows to obtain several constitutional isomers from a single substrate. In 2014, Knochel and co-workers developed a method to transform the short-lived thienyllithium into thienylzinc through in situ transmetalation (Scheme 20).[49] A mixture of thiophene **114** and $ZnCl_2$ was treated with TMPLi at −78 °C for 5 min, and subsequent addition of iodine afforded 3-iodothiphene **115** in 64% yield. In contrast, the reaction with TMPMgCl·LiCl at 25 °C for 3.5 h followed by iodine provided 5-iodothiphene **116** in 60% yield. In the former reaction, the kinetically favored 3-lithiothiophene, which was generated by the ester-directed deprotolithiation, was immediately trapped with $ZnCl_2$ to generate the stable organozinc reagent **117**. In the latter reaction, the first deprotonation occurred probably at the same position; however, the thermodynamically favored reaction conditions led to the exclusive formation of 5-magnesiated thiophene **118** rather than 3-magnesiated thiophene.



Scheme 20. Deprotonative formation of two regioisomeric organometallic species from thiophenecarboxylic acid ethyl ester.

In 1980, Gribble reported the deprotolithiation of 3-bromopyridine (**119**) followed by the reaction with diphenyl disulfide to provide 4-phenylthiopyridine **120** in 61% yield (Scheme 21).[50] In 2011, Mongin and co-workers successfully trapped the kinetic carbanion of the same substrate **119** by the combination of LiTMP (1.5 equiv) and $ZnCl_2$·TMEDA (0.5 equiv) as a base that forms 0.5 equivalents of LiTMP–$Zn(TMP)_2$.[51] The reaction conditions provided 3-bromo-2-iodopyridine (**121**) and 3-bromo-4-iodopyridine (**122**) in 83% and 13% yields, respectively. This in situ transmetalation of the generated 2-lithiated pyridine with $Zn(TMP)_2$ is promoted by forming the thermodynamically more stable C–Zn bond than the C–Li bond. The transmetalation of organolithium to organozinc is much faster than the deprotolithiation of substrate. This in situ transmetalation is essential in driving the equilibrium of the deprotolithiation of substrate toward the generation of the corresponding organolithiums, which are immediately trapped as organozinc species.[52]



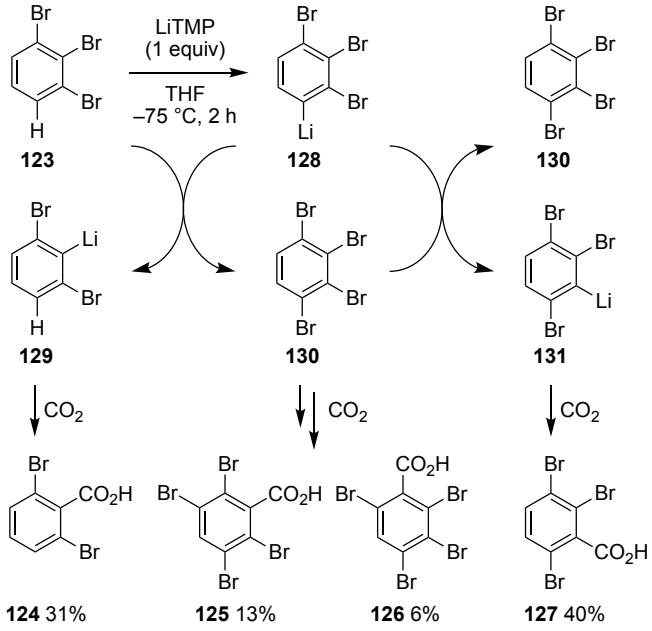
Scheme 21. Stereodivergent transformation of 3-bromopyridine.

6. Halogen Dance

Among halogen atoms, the bromo group on the aromatic ring can be converted to various functional groups by the reliable methods. In this context, a multiply brominated aromatic compound is a promising scaffold for the convergent synthesis of a variety of the highly functionalized compounds. The base-promoted halogen migration, which is known as halogen dance reaction, is the method of choice to provide a series of the brominated compounds that cannot be prepared by the conventional electrophilic bromination. The history of halogen dance of multiply brominated benzenes can be traced to the report by Bunnett in 1963.[53] Thereafter, seminal works including the reaction pathway have been reported by Bunnett, Gronowitz, Quéguiner, Fröhlich, and Stanetty.[54]

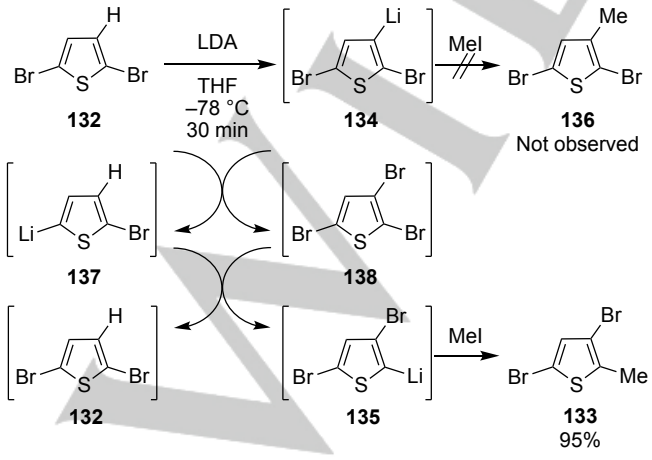
In 2002, Schlosser and Mongin reported the detailed investigation of halogen dance using 1,2,3-tribromobenzene (**123**) (Scheme 22).[55] The treatment with LiTMP followed by carbon dioxide provided the four benzoic acids **124**–**127**. Organolithium **128** underwent halogen–lithium exchange with **123** to afford 2,6-dibromophenyllithium (**129**) and 1,2,3,4-tetrabromobenzene (**130**). Subsequent halogen–lithium exchange of the generated **130** and **128** provided tribromo phenyllithium **131** and tetrabromobenzene **130**. On the basis of the experimental results that two major products were benzoic acids **124** and **127**, the first generated organolithium **128** is more reactive than 2,6-dibromophenyllithium (**129**) that is stabilized by the two vicinal bromo groups. Halogen–lithium exchange at the inside bromo group of tetrabromobenzene **130** occurs with organolithium **128** to provide the thermodynamically more stable organolithium **131**, which is converted to benzoic acid **127**. Benzoic acids **125** and **126** are formed through halogen dance of tetrabromobenzene **130**. These results indicate that the control of the product distribution is challenging in halogen dance of multiply brominated benzene derivatives owing to the

small difference in the relative stabilities of these phenyllithium species, which provides a mixture of multiple products.



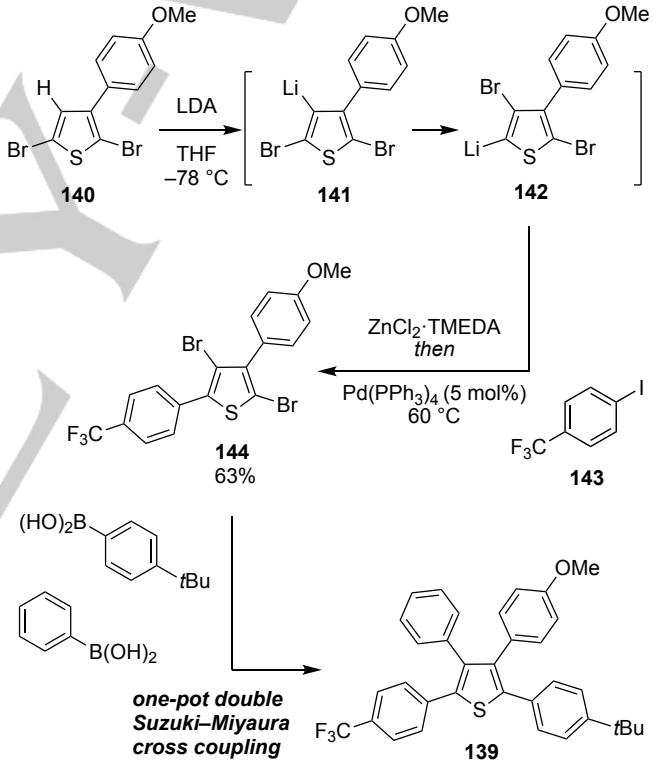
Scheme 22. Plausible reaction pathway of the halogen dance of 1,2,3-tribromobenzene.

The use of thiophenes avoids multiple products owing to the different stabilities of the carbanions at the α and β positions. In 1983, Shibuya and Kano reported the halogen dance of 2,5-dibromothiophene (**132**) (Scheme 23).[56] Dibromothiophene **132** was treated with LDA at –78 °C, and subsequent addition of iodomethane provided 3,5-dibromo-2-methylthiophene (**133**) in 95% yield. The first generated thienyllithium **134** was immediately converted to isomeric thienyllithium **135** at –78 °C within 30 min without providing **136**.[54h] The reaction started with the halogen–lithium exchange of thienyllithium **134** with another dibromothiophene **132** to afford **137** and **138**, which further underwent halogen–lithium exchange to provide the thermodynamically most stable thienyllithium **135** with the regeneration of dibromothiophene **132**.



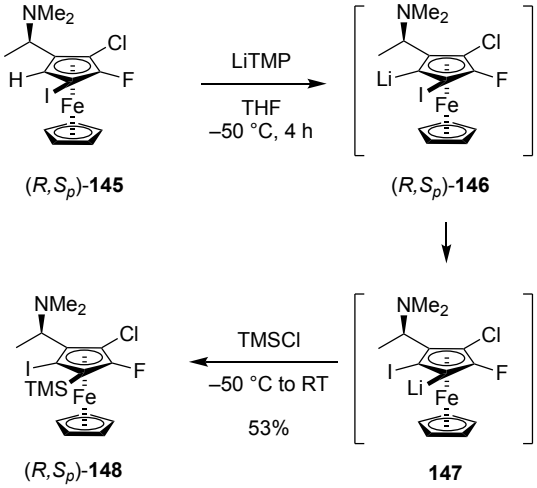
Scheme 23. Plausible reaction pathway of halogen dance of 2,5-dibromothiophene.

In 2016, Okano and co-workers reported the regiocontrolled synthesis of tetraarylated thiophene **139** utilizing one-pot halogen dance/Negishi cross coupling (Scheme 24).[57] The readily available monoarylated 2,5-dibromothiophene **140** was deprotonated with LDA to provide **141**, which was transformed to the thermodynamically favored 3,5-dibromothienyllithium **142**. After transmetalation to the corresponding organozinc species, Negishi coupling proceeded with aryl iodide **143** to afford diarylated 3,5-dibromothiophene **144** in 63% yield. It is worth noting with regard to the synthetic utility of halogen dance that the resulting thiophene has the two bromo groups at the α and β positions after the halogen dance of the thiophene bearing the two bromo groups at each α position. In short, the regioselective functionalization of the α bromo group can be performed based on the superior reactivity of the α bromo group to that of the β group. Subsequent Suzuki–Miyaura cross coupling was consecutively performed in one pot to install the two different aromatic groups to afford the tetraarylated thiophene **139**. This method can be utilized for the regioselective synthesis of various multiply arylated thiophenes.



Scheme 24. Regioselective synthesis of tetraarylated thiophene.

In 2019, Erb and Roisnel reported the asymmetric synthesis of 1,2,3,4,5-pentasubstituted ferrocenes using the halogen dance (Scheme 25).[58] They obtained optically active (*R,Sp*)-**145** from a commercially available chiral ferrocene in three steps. Deprotolithiation with LiTMP generated the corresponding organolithium (*R,Sp*)-**146**, and subsequent halogen dance gave lithiated ferrocene (*R,Sp*)-**147**, which was stabilized by the vicinal fluoro group. The reaction was quenched with TMSCl to afford 1,2,3,4,5-pentasubstituted ferrocene (*R,Sp*)-**148** in 53% yield. The established method has paved the way for the synthesis of the highly substituted ferrocenes in optically pure forms as an unprecedented chemical space.

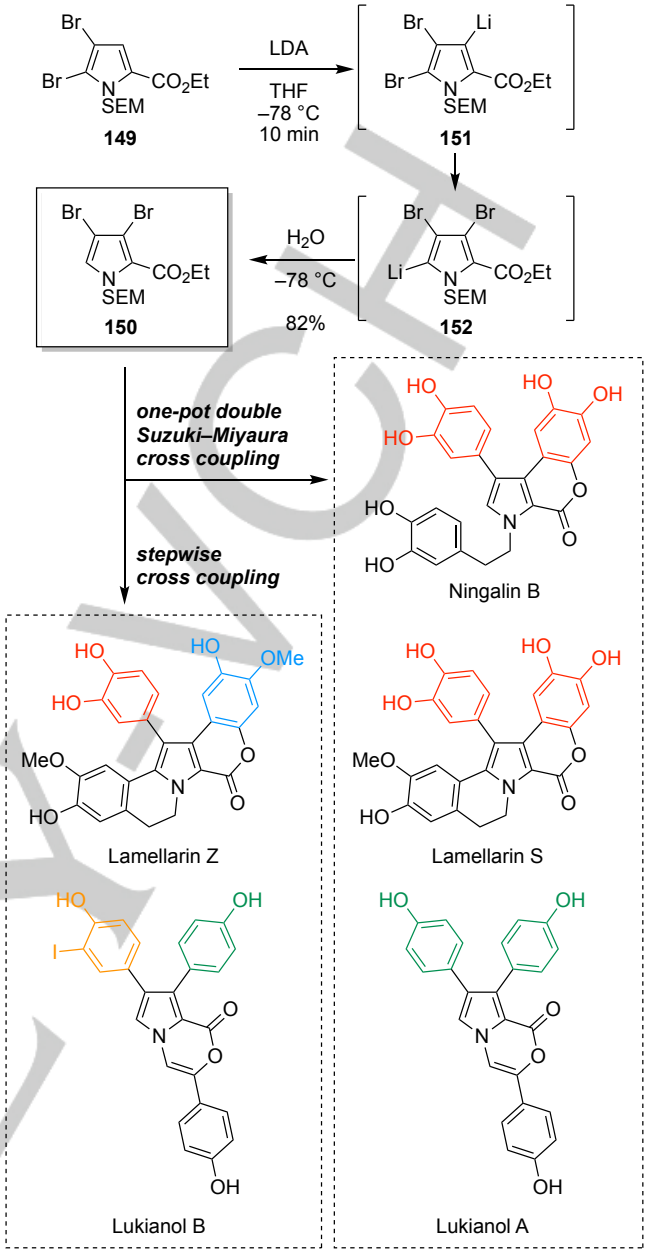


Scheme 25. Stereoselective synthesis of 1,2,3,4,5-pentasubstituted ferrocene using the halogen dance.

Recently, Okano and co-workers reported an unprecedented halogen dance of pyrrole and its application to the total syntheses of lamellarins and their congeners (Scheme 26).[59] The synthesis started with the readily prepared α,β-dibromopyrrole derivative **149**. Similar to their previous work that an ester group promoted halogen dance,[60] this compound was converted to provide β,β-dibromopyrrole **150** in 82% isolated yield on a gram scale. The first generated organolithium **151** was transformed to the thermodynamically more stable organolithium **152**. The two bromo groups and the ester moiety proved essential to the halogen dance. These bromo groups were then transformed to the aryl groups, and the synthetic intermediate was converted into the five natural products bearing multiple aromatic groups attached to the pyrrole core.

7. Summary and Outlook

Organolithium reagents bearing the labile electrophilic functionalities are tolerated at low reaction temperatures in a batch reactor. The recently developed flow microreactor allows the transformation of organolithiums, including highly electrophilic ketone carbonyl and formyl groups, without protection. This method can be utilized for suppressing benzyne formation. The ARC strategy for controlling Brook rearrangement is a powerful tool for the synthesis of the functionalized acyclic systems. In the isomerization of organometallic species, in situ transmetalation is emerging to trap the kinetically generated organolithium species, as another tool to control the reaction of organolithium intermediates. The recently established synthetic methods using halogen dance provide direct access to multiply substituted aromatic compounds. The trapping of the short-lived organolithiums, which are generated by deprotolithiation, is still challenging compared to halogen–lithium exchange, because the deprotonation is generally slower than the halogen–lithium exchange. In this viewpoint, the selective trapping of short-lived organolithiums generated by deprotolithiation will provide an efficient strategy for the stereocontrolled syntheses of the multiple constitutional isomers in an atom-economical manner.



Scheme 26. Total syntheses of lamellarins and their congeners.

Acknowledgements

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Keywords: arenes • carbanions • flow chemistry • in situ transmetalation • lithiation

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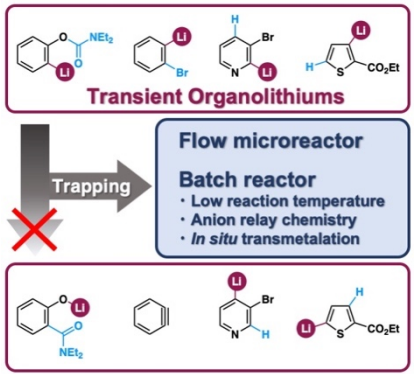

Organolithium chemistry is still developing as a powerful synthetic tool in organic chemistry. The recently established methods including the flow reactor, the anion relay chemistry, and the in situ transmetalation allow to utilize the unexplored short-lived organolithium species that have not been trapped. In this minireview, we shed light on the promising synthetic potential of the recent progress in the organolithium chemistry.