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RECENT ADVANCES IN SYNTHETIC HETARYNE CHEMISTRY

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Abstract – Recent advances in synthetic hetaryne chemistry are reviewed. Various methods for the generation of hetaryne intermediates from several types of precursors enabled facile syntheses of a broad range of heteroaromatic compounds including natural products.

CONTENTS

1. INTRODUCTION

Heteroaromatic compounds are widely used in various fields including pharmaceutical science and materials chemistry.[1,2] Due to the importance and different reactivities, which depend on the type of the heteroaromatic skeleton, diverse methods for the synthesis of functionalized heteroaromatics have been developed.[3] In the current review, we summarize recent approaches for the preparation of these compounds, which has been achieved through transformations via heteroaromatic-type aryne intermediates, referred to as hetarynes, categorizing by their generation methods.

As a result of remarkable recent improvements in the field of aryne chemistry, transformations via hetarynes have allowed for efficient and expeditious syntheses of various complex heteroaromatics, including natural products.[4] Furthermore, various types of precursors can be employed, since numerous methods for generating hetarynes have been developed. One of the most conventional approaches involves generation of hetarynes from heteroaryl halides by deprotonation with an appropriate base (Figure 1A, path a). Halogen–metal exchange reaction of precursors including *o*-dihaloheteroarenes and *o*-iodoheteroaryl triflates, which triggers a β-elimination of the leaving group (LG), also results in the generation of hetarynes (Figure 1A, path b). Recently, activation of heteroaromatic silanes such as *o*-silylheteroaryl triflates with a fluoride anion has gained significant attention due to the mild reaction conditions required for the generation of hetarynes (Figure 1A, path c). Moreover, intramolecular [2+4] cycloaddition between 1,3-diyne and alkyne moieties by hexadehydro-Diels–Alder (HDDA) reaction is an emerging method for generating polycyclic hetarynes (Figure 1A, path d). These methods have enabled the generation of a broad range of hetarynes such as didehydropyridines (pyridynes), pyridobenzynes (quinolynes), pyrrolobenzynes (indolynes), thiazolobenzynes, thienobenzynes, furanobenzynes, and others (Figure 1B). These hetarynes have been successfully applied in the synthesis of various bioactive compounds, including some natural products. In addition, recent advances in theoretical analyses based on the density functional theory (DFT) method have enabled practical prediction of regioselectivity in the reactions between hetarynes and unsymmetrical arynophiles.[5]

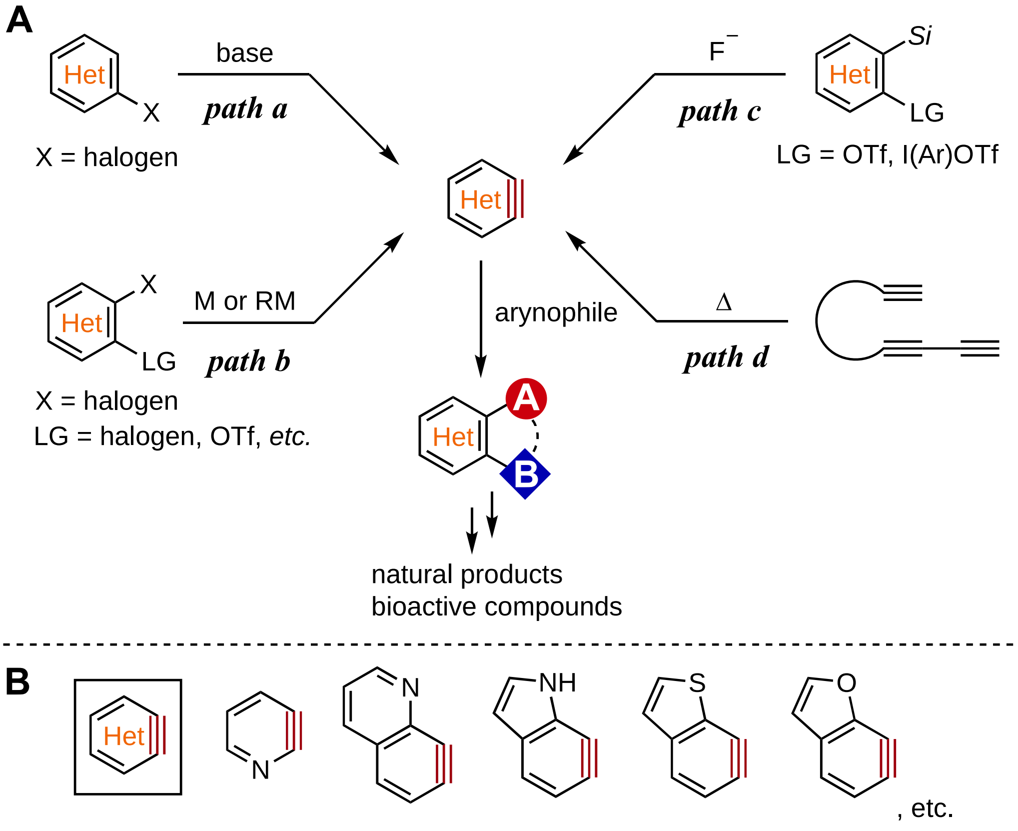
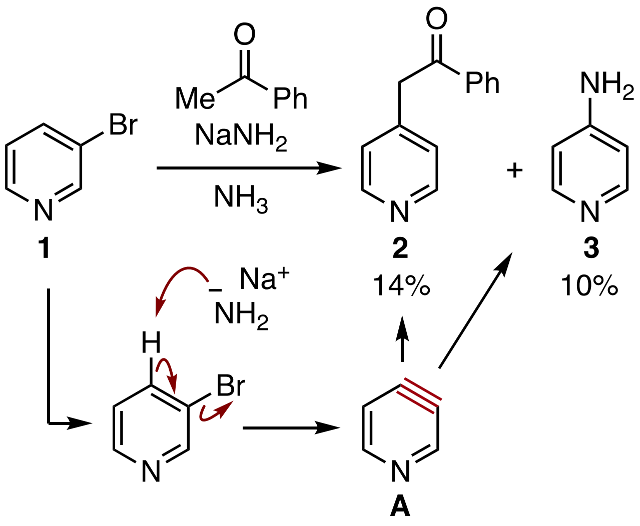


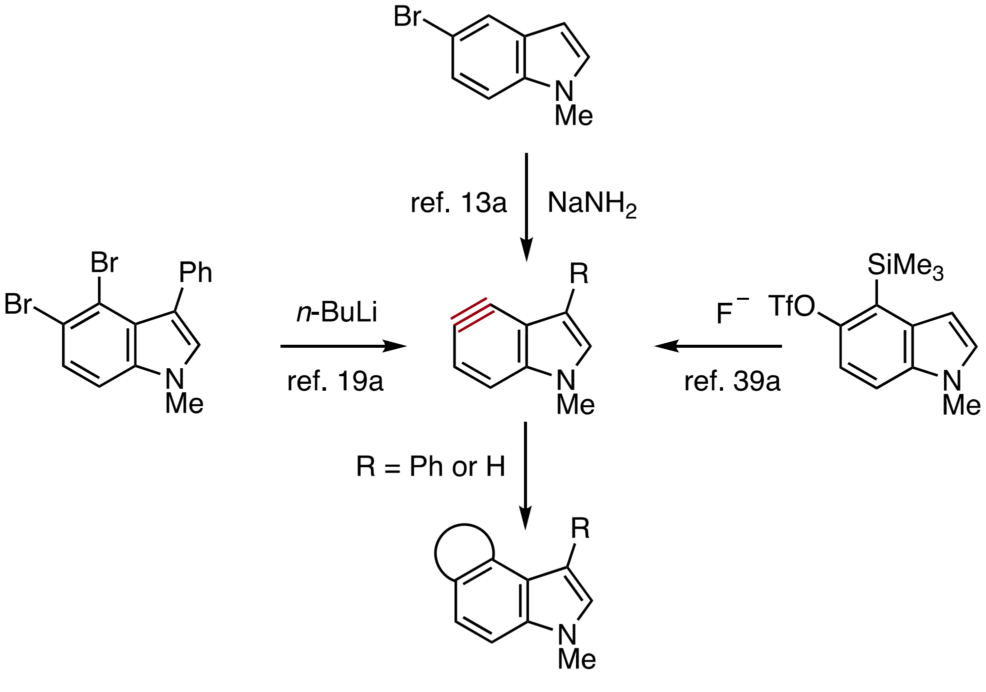
Figure 1

2. OVERVIEW OF SYNTHETIC HETARYNE CHEMISTRY

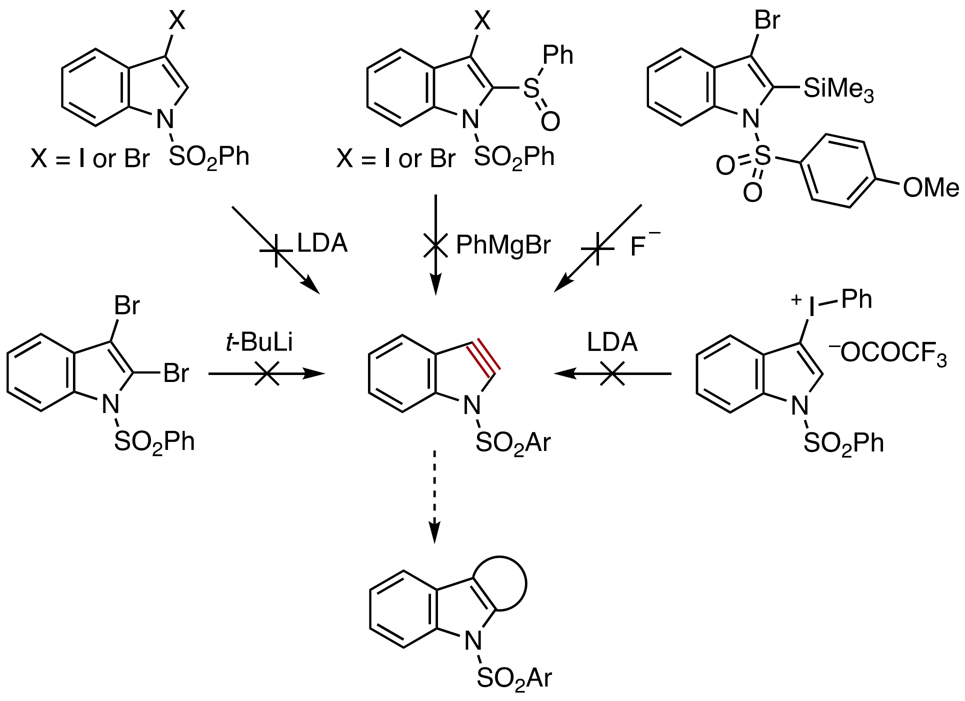
Hetarynes have received widespread attention from organic chemists since more than half a century ago.[6] In 1955, Leake and coworker reported syntheses of α-(4-pyridyl)acetophenone (**2**) and 4-aminopyridine (**3**), which were achieved by the treatment of a mixture of 3-bromopyridine (**1**) and acetophenone with sodium amide albeit in low yields (Scheme 1).[7] These products were recognized to be obtained by the addition to 3,4-pyridyne (**A**) generated by regioselective deprotonation of 3-bromopyridine (**1**) followed by β-elimination of the bromide anion. Subsequently, the generation and transformations involving various hetarynes, including 4,5-indolynes, were accomplished using several types of precursors (Scheme 2), although several attempts to generate a 2,3-didehydroindole species failed (Scheme 3).[8] These early studies particularly provided experimental insights into the regioselectivity of the reactions between different hetarynes and nucleophiles.



Scheme 1



Scheme 2



Scheme 3

Recently, Houk, Garg, and coworkers reported that the reactivity aspects of diverse hetarynes, such as the regioselectivity, can be predicted based on a theoretical calculation based on the DFT method.[5a–d] The aryne distortion model that they demonstrated allowed for reliable prediction of the regioselectivity of the reactions of hetarynes with nucleophiles, enhancing the synthetic utility of hetaryne intermediates.[4] Indeed, it was clearly demonstrated that nucleophilic addition to hetarynes such as pyridynes and

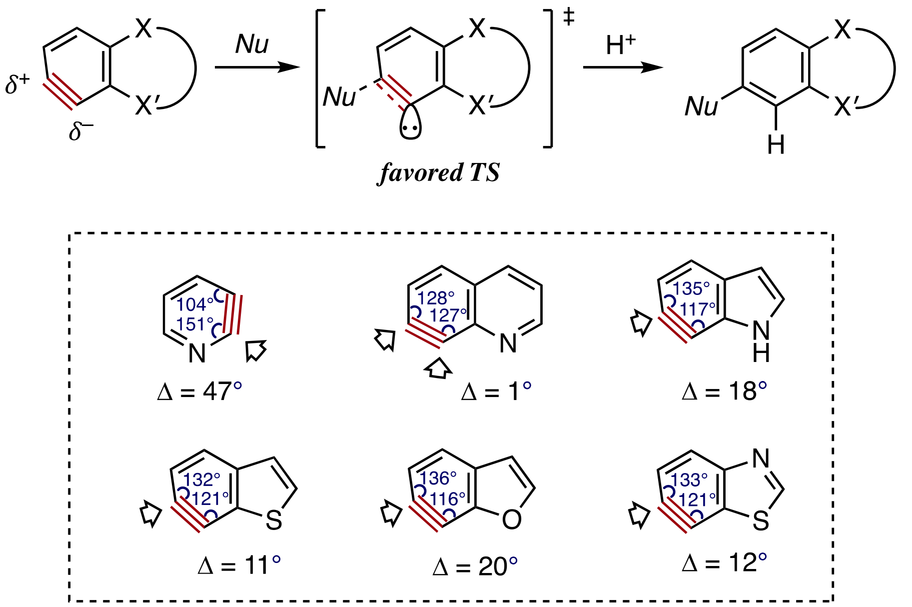


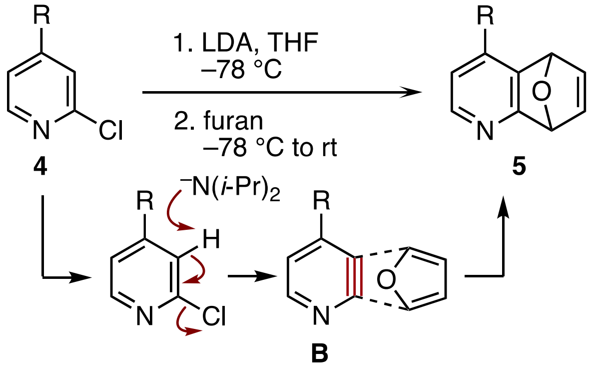
Figure 2

indolynes occurred at the aryne carbon with a larger angle in the distorted hetaryne structure, as obtained by the DFT calculation (Figure 2). Categorizing by the types of precursors, we herein review the recent synthetic methods involving hetaryne intermediates, including the regioselective reactions.

3. HETARYNE GENERATION FROM HETEROARYL HALIDES

3-1. Pyridynes

Generation of pyridynes from pyridyl halides by the treatment with an appropriate strong base, which can also play as a reactive nucleophile, has been achieved and applied practically to the syntheses of various pyridine derivatives since the beginning of the hetaryne chemistry.[7] Recent studies on the transformations via pyridyne intermediates generated from the corresponding halides improved the synthetic utility of pyridynes for the synthesis of complex pyridine derivatives due to the easy availability of pyridyl halides. Although efficient transformations via 3,4-pyridynes generated from 3-bromopyridine derivatives by selective deprotonation at the 4-position have been reported, the generation of 2,3-pyridynes is not easy to achieve due to the instability of the intermediate, which was also demonstrated in a theoretical calculation.[5b] In 2004, Hegarty and coworkers reported that the efficiency for generating 2,3-pyridynes **B** from 2-chloropyridines **4** triggered by deprotonation with lithium diisopropylamide (LDA) was improved by the presence of substituents at the 4-position (Scheme 4).[9] For example, cycloadduct **5f** was obtained in a moderate yield by the treatment of 2-chloro-4-(4-methoxyphenyl)oxypyridine (**4f**) with LDA at −78 °C and subsequent addition of furan and warming the reaction mixture to room temperature, while no desired cycloadduct **5a** was detected when using 2-chloropyridine (**4a**).

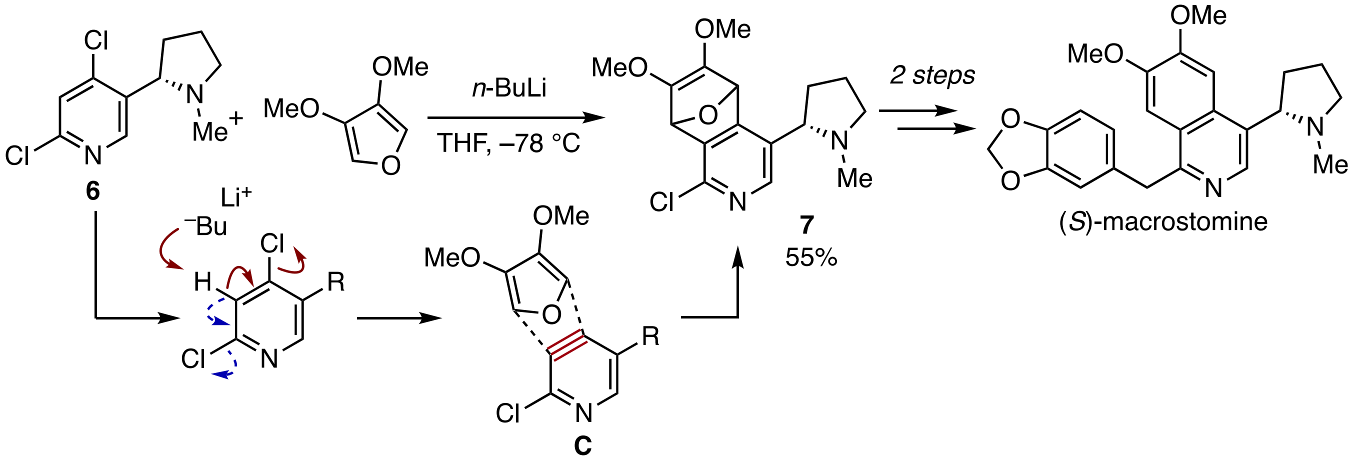


4a	R = H	**5a**	0%
4b	R = Me	**5b**	0%
4c	R = OMe	**5c**	37%
4d	R = OPh	**5d**	25%
4e	R = SPh	**5e**	29%
4f	R = OPMP	**5f**	58%

PMP: *p*-methoxyphenyl group

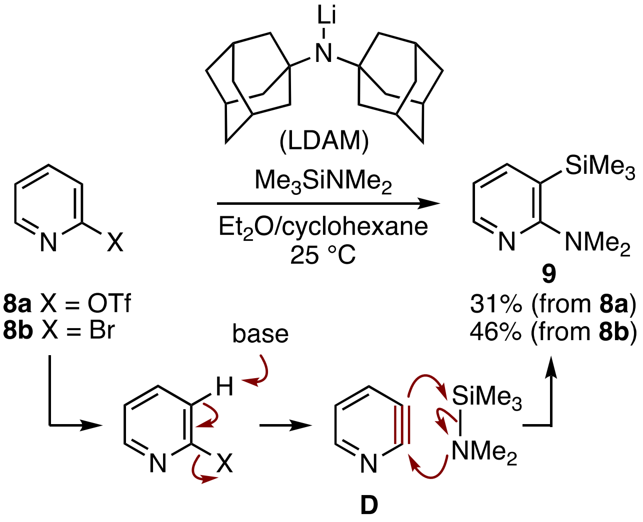
Scheme 4

Selective β-elimination from 2,4-dichloropyridine that enabled efficient generation of the desired hetaryne species was a valuable reaction for the synthesis of multisubstituted pyridine derivatives (Scheme 5). For example, Comins and coworkers achieved a facile synthesis of (*S*)-macrostomine through the generation of 3,4-pyridyne **C** from 2,4-dichloropyridine derivative **6** by deprotonation with butyllithium, followed by a selective β-elimination of the chloro group at the 4-position.[10]



Scheme 5

In 2018, Daugulis and coworkers reported an efficient approach for generating arynes from (psuedo)haloarenes by the treatment with highly bulky lithium di(1-adamantyl)amide (LDAM) (Scheme 6). This method enabled various transformations including silylamination, silylthiolation, and silylphosphanation without affecting electrophilic functional groups such as formyl and cyano groups.[11] For example, regioselective silylamination of 2,3-pyridyne (**D**) generated from 2-(triflyloxy)pyridine (**8a**) or 2-bromopyridine (**8b**) with dimethyl(trimethylsilyl)amine was demonstrated.



Scheme 6

3-2. Indolynes

Indolynes, which are indole-type hetarynes, have been applied in the facile synthesis of indole-type natural products. In 1998, Iwao and coworkers reported that LDA or lithium cyclohexyl(isopropyl)amide(LICA) triggered efficient generation of 4,5-indolyne intermediate **E** from 4-chloroindole derivative **10** by deprotonation (Figure 3A).[12] Intramolecular hydroamination of 4,5-indolyne **E** proceeded smoothly to afford the cyclized product **11**, from which the total synthesis of makaluvamine I was accomplished in 3 steps. Makaluvamines A, D, and K were also prepared through the cyclization of indolyne intermediates (Figure 3B).

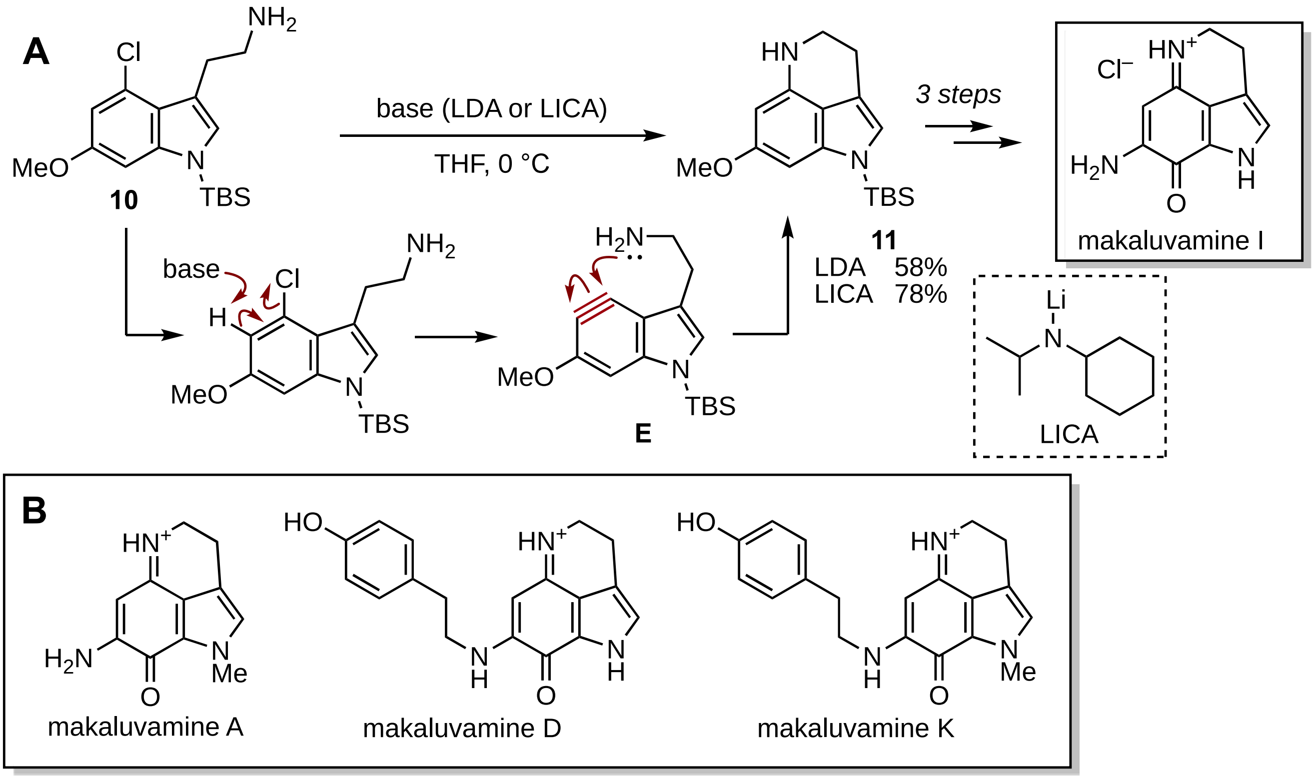


Figure 3

In the last decade, transformations via indolyne intermediates have been extensively studied and elegantly applied by Garg and coworkers in the total syntheses of diverse indole-type natural products.[13] For instance, total synthesis of *N*-methylwelwitindolinone C isothiocyanate was accomplished via 4,5-indolyne intermediate **F** generated from 5-bromoindole derivative **12** by the treatment with sodium amide (Figure 4A).[13b] The generation of indolyne was triggered by selective deprotonation at the 4-position, and following *C*-arylation or *O*-arylation afforded the desired product **13** and ether byproduct **14**, respectively. Further reactions of **13** resulted in the synthesis of *N*-methylwelwitindolinone C isothiocyanate in 13 steps. Since the transformations involving indolyne generation, followed by the ring-closure, allowed for efficient construction of the core skeleton of the welwitindolinone family, Garg and coworkers also achieved total syntheses of various welwitindolinone analogs via indolyne intermediates (Figure 4B).[13c-e]

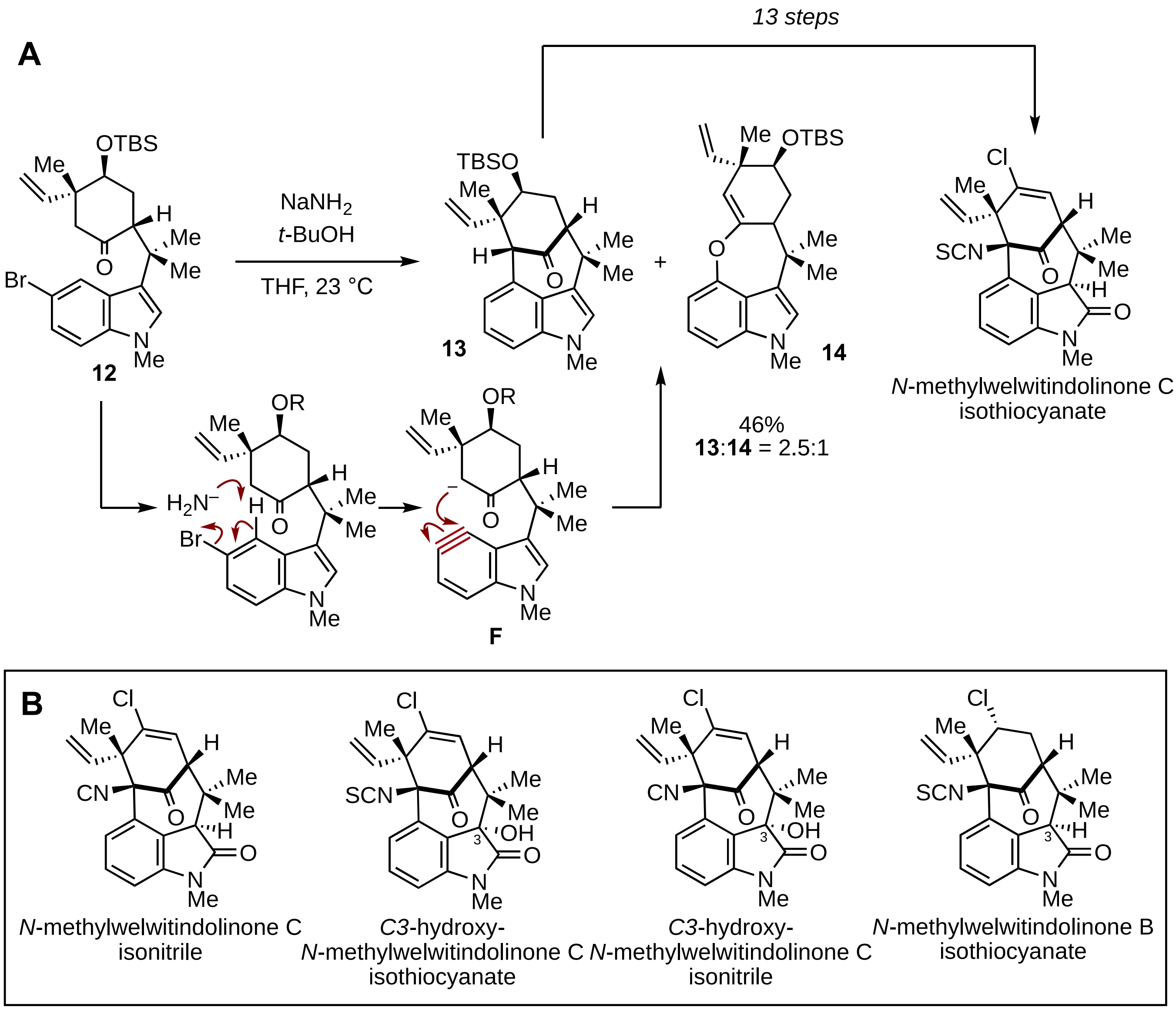
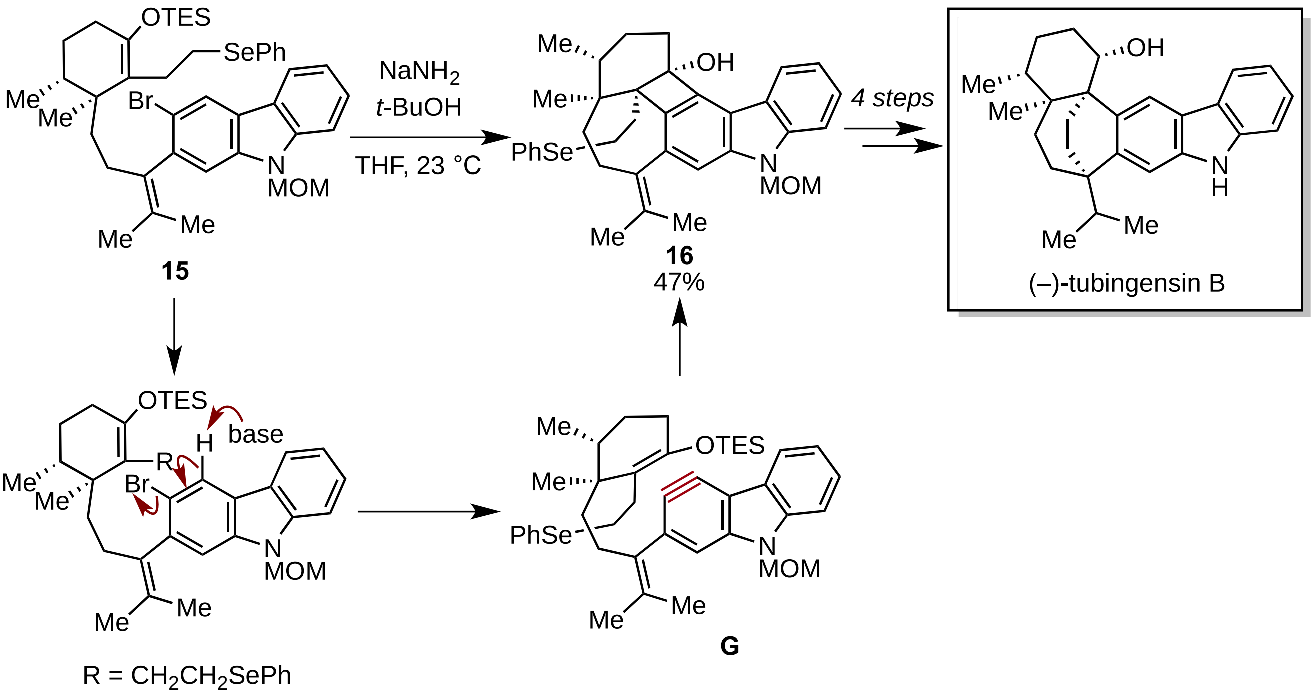


Figure 4

3-3. Indolinobenzynes (Carbazolynes)

Garg and coworkers also succeeded in the total synthesis of (–)-tubingensin B via carbazole-type hetaryne intermediates (Scheme 7).[14a] The key to the success of this synthesis was the effective generation of indolinobenzyne intermediate **G**, which was referred to as carbazolyne, by the treatment of bromocarbazole derivative **15** with sodium amide. The generated carbazolyne **G** smoothly underwent intramolecular [2+2] cycloaddition reaction with the silyl enolate moiety to afford the [2+2] cycloadduct **16**. The same group also achieved the total synthesis of tubingensin A via generation of another carbazolyne intermediate.[14b]



Scheme 7

3-4. Pyrrolidinobenzynes

Synthesis of batzelline C was achieved via a pyrrolidinobenzyne intermediate (Figure 5A). In 2012, Tokuyama and coworkers reported that pyrrolidinobenzyne intermediate **H** was successfully generated

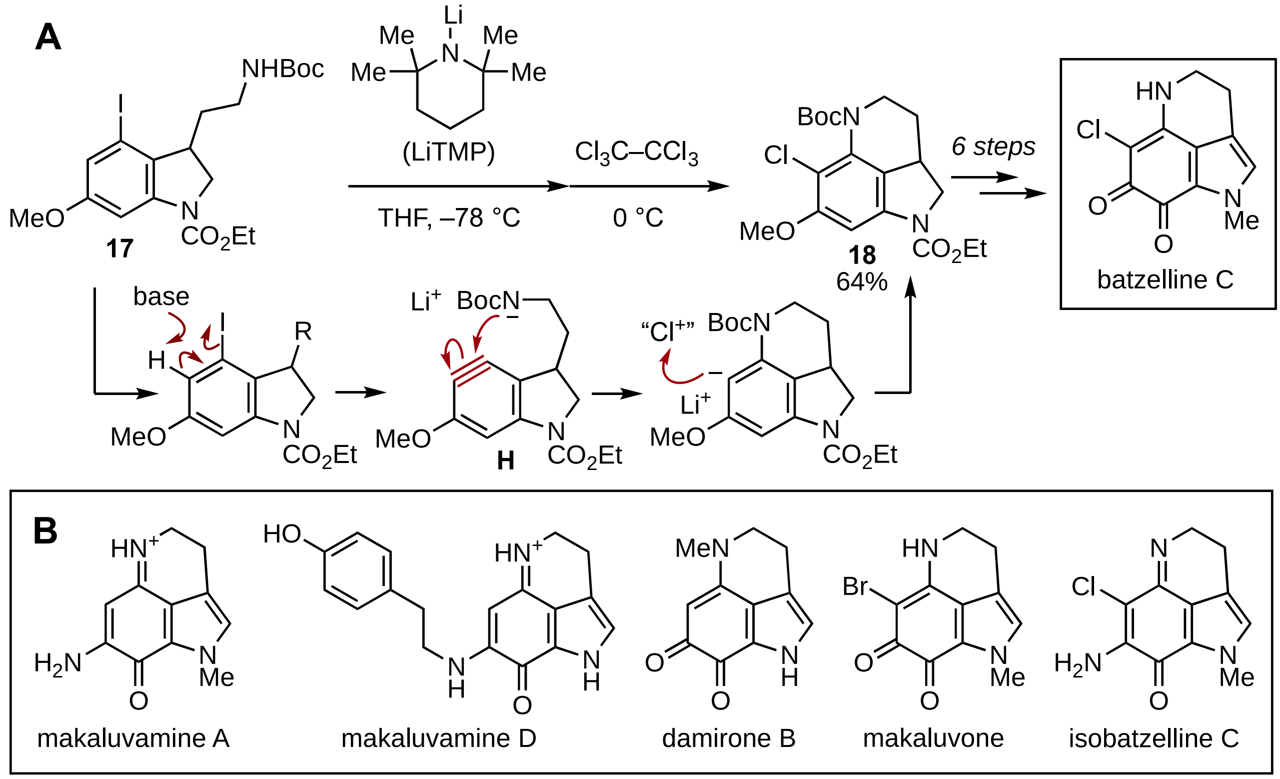
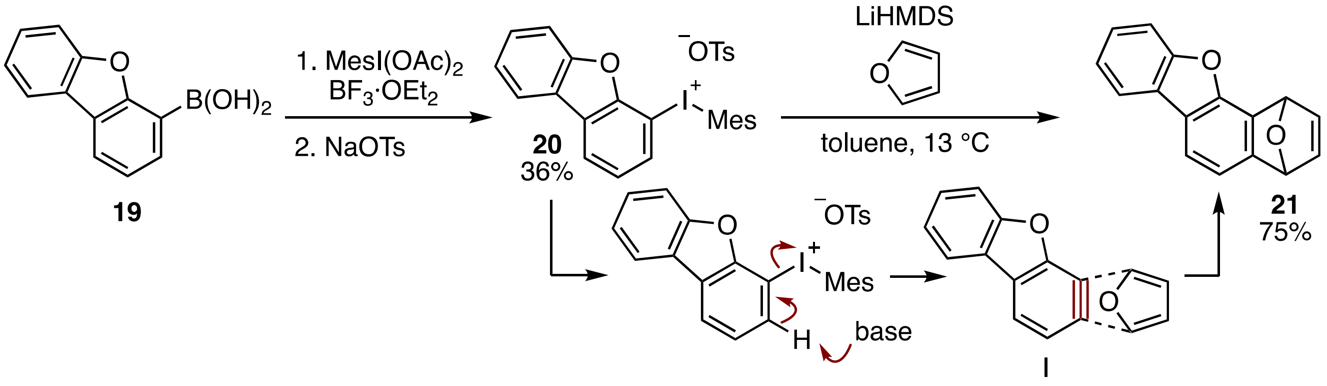


Figure 5

from iodoindoline derivative **17** by the treatment with lithium 2,2,6,6-tetramethylpiperidide (LiTMP). Successive intramolecular C–N formation, followed by electrophilic chlorination, afforded the cyclized product **18**.[15] The same group also accomplished the total syntheses of makaluvamines A and D, damirone B, makaluvone, and isobatzelline C based on the similar skeletal construction (Figure 5B). General method for generating arynes via deprotonation using $(TMP)_2Mg\cdot 2LiBr$ was also developed by the same group.[16]

3-5. Benzofuranobenzyne

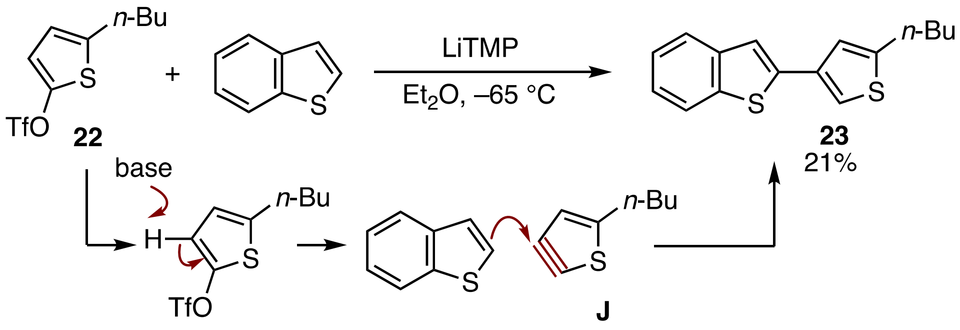
Hetaryne generation by deprotonation of diaryliodonium salts has also been reported. In 2016, Stuart and coworkers developed a novel method for generating arynes from diaryliodonium salts using lithium hexamethyldisilazide (LiHMDS) (Scheme 8).[17] This method was applied for the generation of dibenzofuran-type aryne **I** from diaryliodonium salt **20**, which was prepared from the corresponding arylboronic acid **19**.



Scheme 8

3-6. 2,3-Didehydrothiophene

In 2014, Daugulis and coworkers reported that LiTMP facilitated generation of 2,3-didehydrothiophene intermediate **J** from 2-thienyl triflate **22** by the *ortho* deprotonation (Scheme 9).[18] For instance, treatment



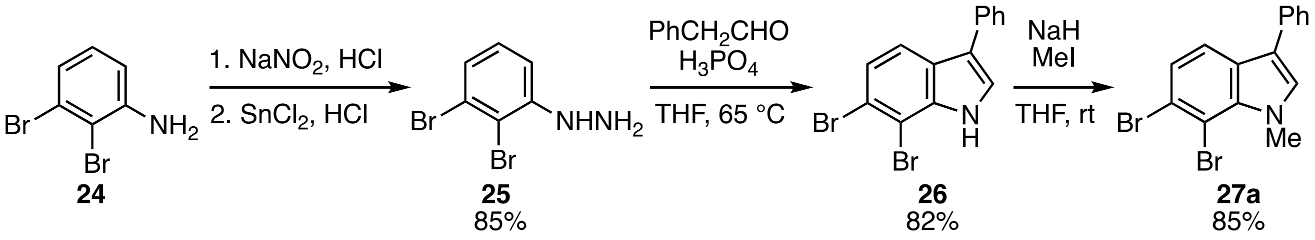
Scheme 9

of a mixture of 2-thienyl triflate **22** and benzo[*b*]thiophene with LiTMP in diethyl ether at −65 °C provided 2-(3-thienyl)benzo[*b*]thiophene **23** albeit in low yield.

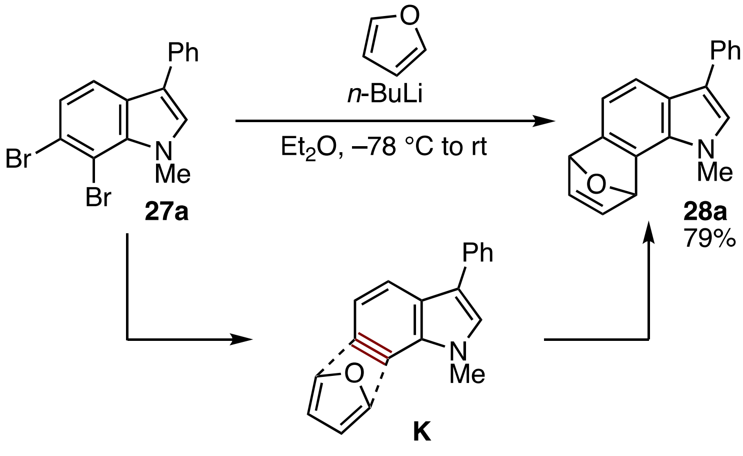
4. HETARYNE GENERATION FROM *o*-DIHALOARENES

4-1. Indolynes

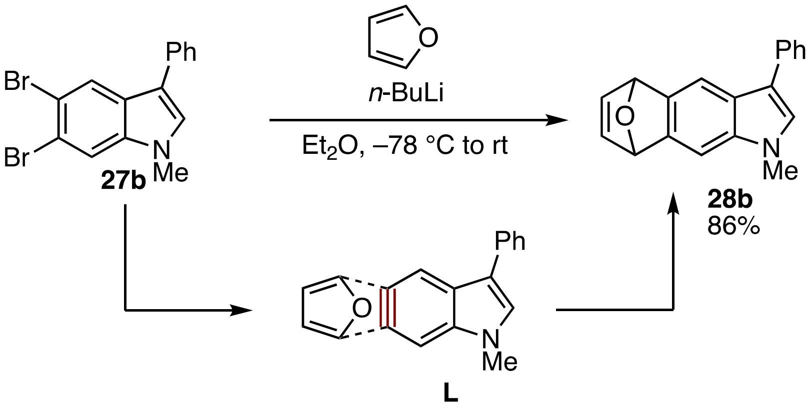
Generation of hetarynes has also been achieved from the corresponding *o*-dihaloarenes by the halogen–metal exchange reaction and subsequent β-elimination of the remaining halogeno group. This exceptionally advantageous method allowed for site-selective generation of hetarynes. Particularly, indolyne generation methods were robustly studied by Buszek and coworkers.[19] For example, the group reported a simple synthesis of 6,7-dibromoindole derivative **27a** from 2,3-dibromoaniline (**24**) via the Fischer indole synthesis (Scheme 10).[19a] Treatment of dibromoindole **27a** with butyllithium in the presence of furan provided the cycloadduct **28a** through efficient generation of 6,7-indolyne intermediate **K** (Scheme 11). Cycloadducts **28b** and **28c** were also obtained under the same reaction conditions from 5,6- and 4,5-dibromoindoles, respectively, through the corresponding indolyne intermediates (Schemes 12 and 13).



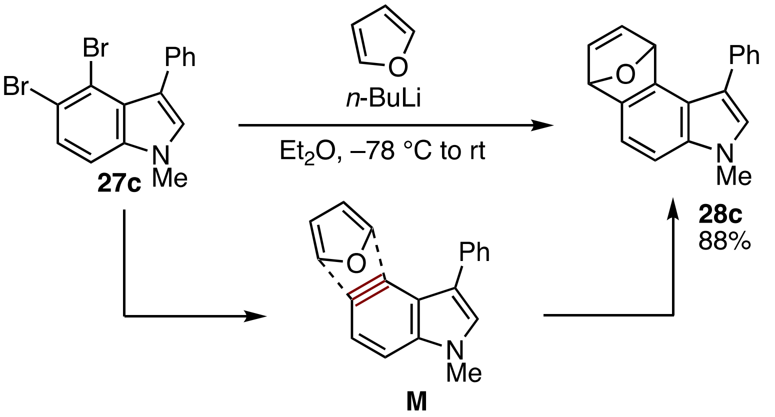
Scheme 10



Scheme 11

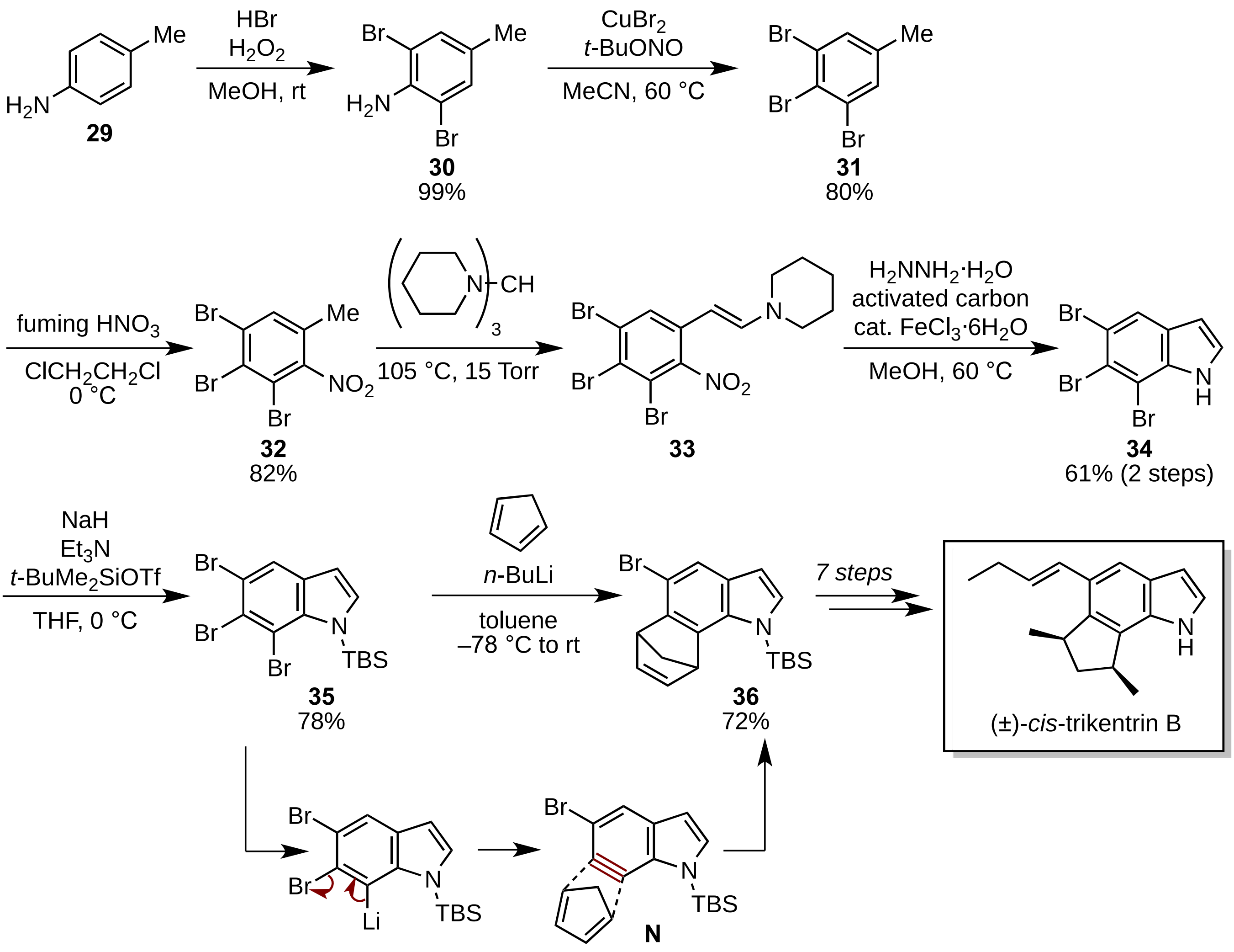


Scheme 12



Scheme 13

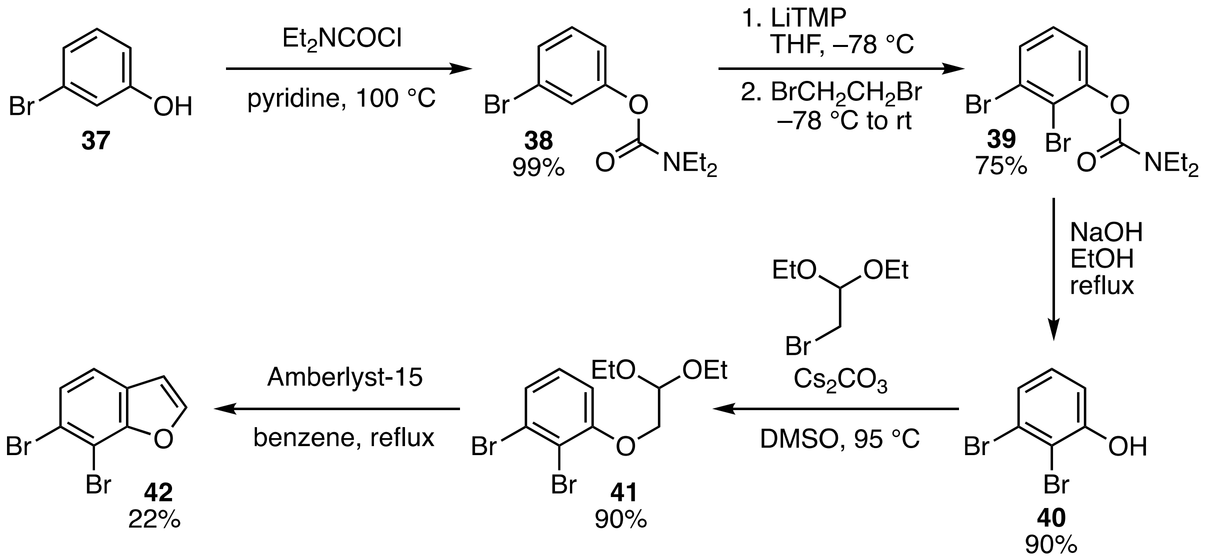
Syntheses of natural products via selective generation of indolynes from 5,6,7-tribromoindole **35** were also achieved by Buszek and coworkers.[19g] Leimgruber–Batcho indole synthesis from 3,4,5-tribromo-2-nitrotoluene (**32**) through enamine formation using tripiperidinylmethane followed by a reaction with hydrazine in the presence of a catalytic amount of $FeCl_3$ furnished 5,6,7-tribromoindole (**34**) (Scheme 14). For instance, the key intermediate for the synthesis of *cis*-trikentrin B was successfully prepared by the selective bromine–lithium exchange of 5,6,7-tribromoindole **35** and resulted in the selective generation of 6,7-indolyne intermediate **N**, which efficiently reacted with cyclopentadiene to afford the cycloadduct **36**. Buszek's group also synthesized *cis*-trikentrin A and herbindole A, B, and C via the generation of indolynes.[19b,d,i]



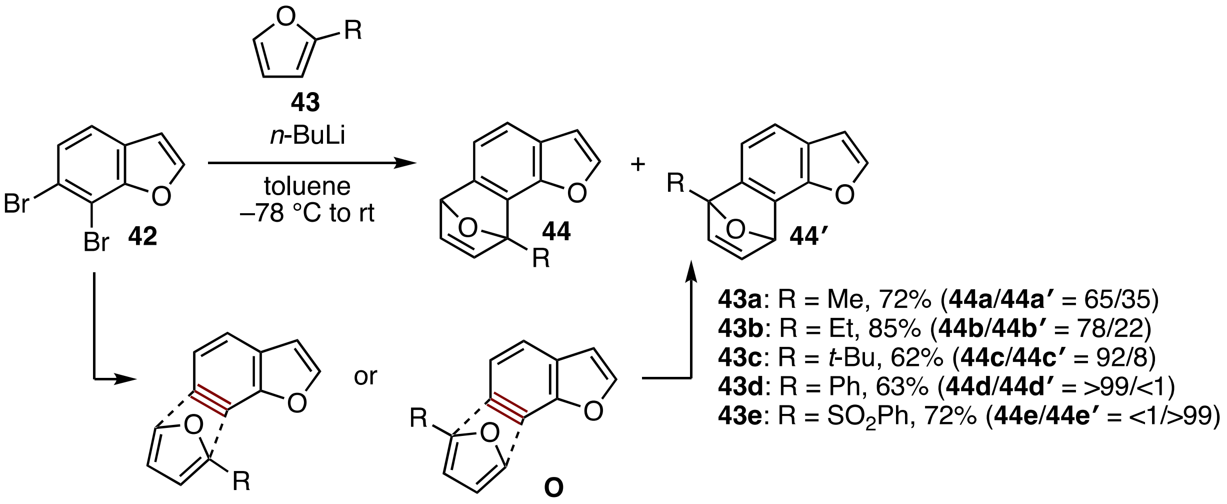
Scheme 14

4-2. Furanobenzyne

Based on the similar approach to the indolyne generation method, Buszek and coworkers also developed a facile synthetic method for fused benzo[*b*]furans by generating furanobenzyne intermediate from 6,7-dibromobenzo[*b*]furan (**42**). This compound was prepared from *m*-bromophenol (**37**) in 5 steps that include introduction of a directing group, selective deprotonative bromination, removal of the directing group, *O*-alkylation, and condensation–cyclization to construct the benzo[*b*]furan skeleton (Scheme 15).[20] Treatment of dibromobenzofuran **42** with butyllithium in the presence of furans **43** provided cycloadducts **44** and **44′** in good yields (Scheme 16). In particular, cycloadditions between furanobenzyne **O** with bulky 2-*t*-butylfuran (**43c**) or 2-phenylfuran (**43d**) resulted in the selective formation of **44c** or **44d**, respectively, while the opposite selectivity was observed in the case of the reaction with 2-(benzenesulfonyl)furan (**43e**) bearing a strong electron-withdrawing group.



Scheme 15



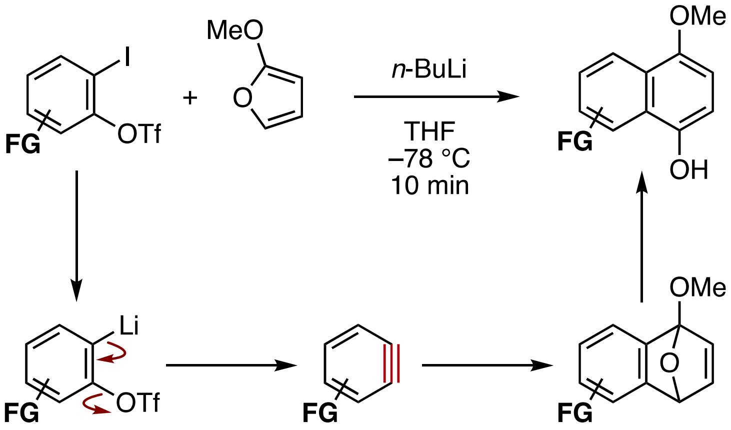
43a: R = Me, 72% (**44a**/**44a′** = 65/35)
43b: R = Et, 85% (**44b**/**44b′** = 78/22)
43c: R = *t*-Bu, 62% (**44c**/**44c′** = 92/8)
43d: R = Ph, 63% (**44d**/**44d′** = >99/<1)
43e: R = SO_2Ph, 72% (**44e**/**44e′** = <1/>99)

Scheme 16

5. HETARYNE GENERATION FROM *o*-HALOARYL SULFONATES

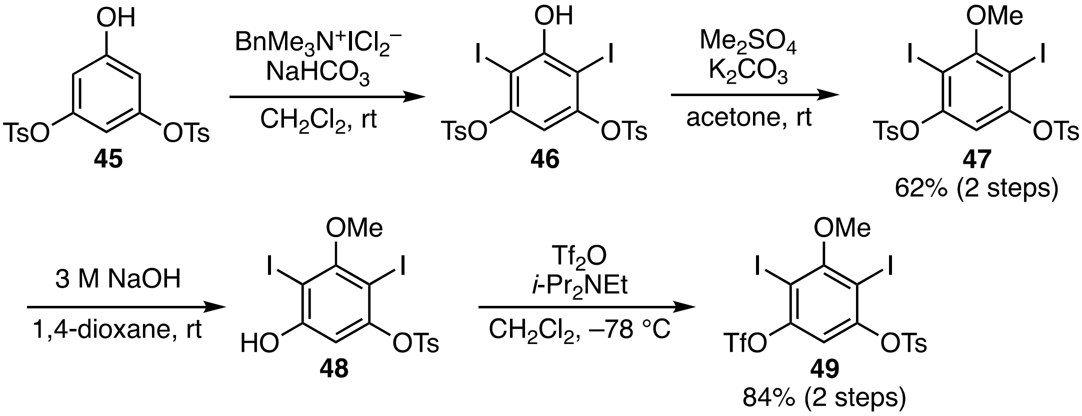
5-1. Various methods for hetaryne generation from *o*-iodoaryl sulfonates

Synthetic aryne chemistry using *o*-iodoaryl triflates as aryne precursors has been extensively investigated by Suzuki and coworkers, who applied these precursors to the syntheses of various natural and non-natural products.[4o] In 1991, Suzuki's group reported rapid generation of arynes by the treatment of *o*-iodoaryl triflates with butyllithium in tetrahydrofuran (THF) at −78 °C (Scheme 17).[21] However, only a few examples for generating hetarynes using this method have been reported so far.

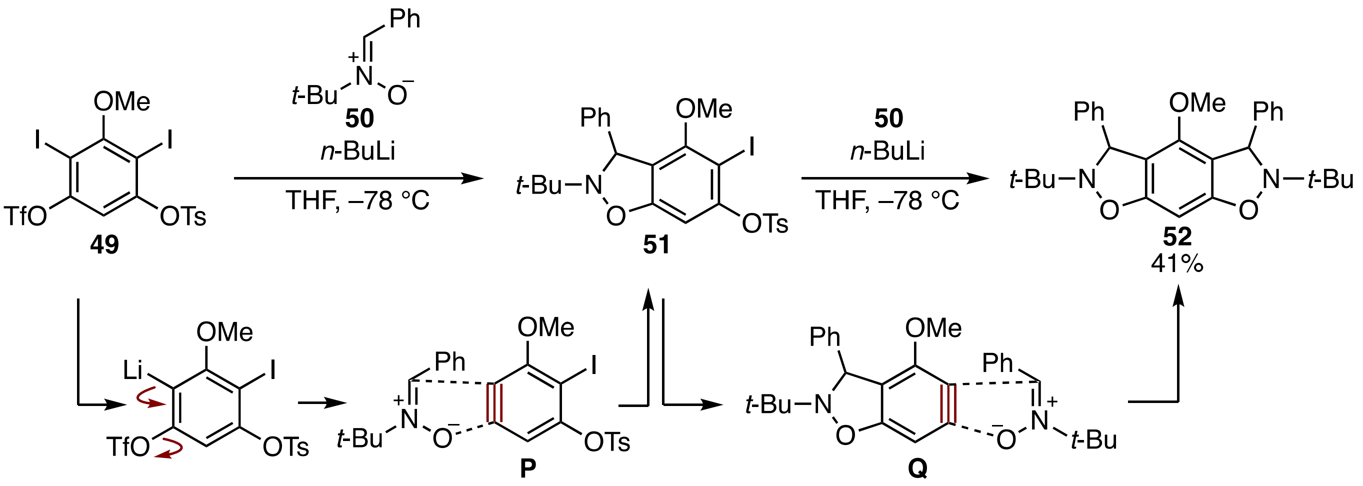


Scheme 17

Suzuki and coworkers also reported cycloaddition of an aryne fused with a dihydroisoxazole ring generated from the corresponding *o*-iodoaryl tosylate **51**, which was prepared via the selective aryne generation from precursor **49** containing two aryne generation moieties (Schemes 18 and 19).[22] This 1,4-benzdiyne equivalent **49** was prepared from C_2-symmetrical 3,5-bis(tosyloxy)phenol (**45**) in 4 steps (Scheme 18). The sequential generation of arynes from 2,6-diiodo-3-(tosyloxy)-5-(triflyloxy)anisole (**49**) was achieved by the selective generation of the first aryne at the *o*-iodoaryl triflate moiety (Scheme 19). This selectivity was a result of the electron-withdrawing effect of the triflyloxy group that triggered the selective iodine–magnesium exchange at the *o*-iodoaryl triflate moiety. Thus, treating the 1,4-benzdiyne equivalent **49** with an appropriate amount of butyllithium at −78 °C in the presence of nitrone **50** initially afforded dihydrobenzisoxazole derivative **51**. Further addition of butyllithium resulted in the generation of hetaryne **Q** that reacted with nitrone **50** to afford tetrahydrobenzodiisoxazole derivative **52**. In these transformations, regioisomers **51** and **52** were selectively obtained due to the strong inductive effect of the methoxy group.

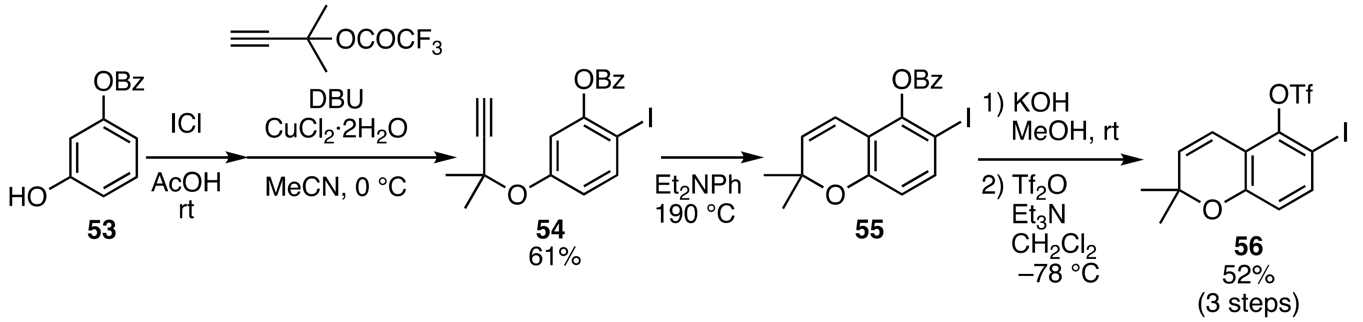


Scheme 18

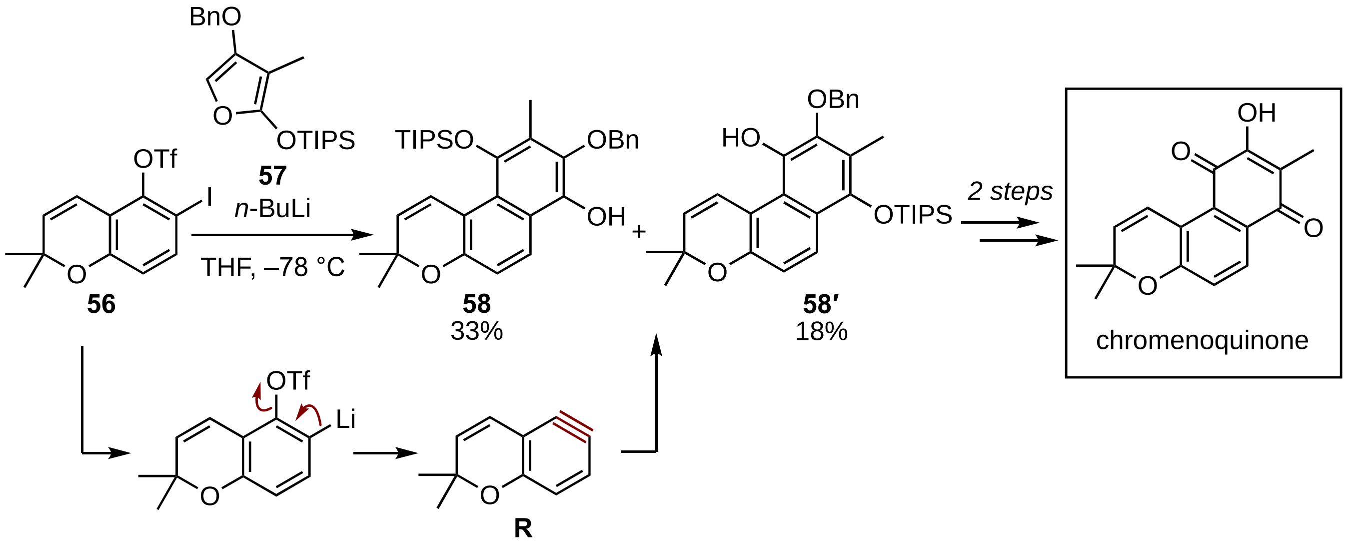


Scheme 19

The useful aryne generation method using *o*-iodoaryl triflates as precursors was applied in the synthesis of chromenoquinone via pyranobenzyne intermediate **R** by Kumamoto and coworkers in 2014 (Schemes 20 and 21).[23a] The pyranobenzyne precursor **56** was prepared from resorcinol derivative **53** in 5 steps including the Claisen-type rearrangement for the construction of the benzopyran scaffold without



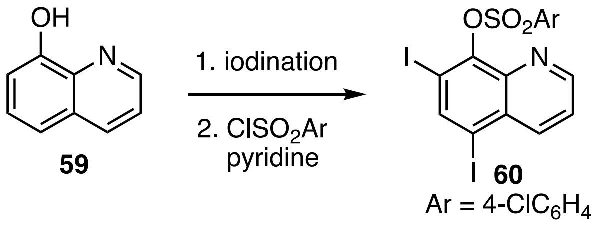
Scheme 20



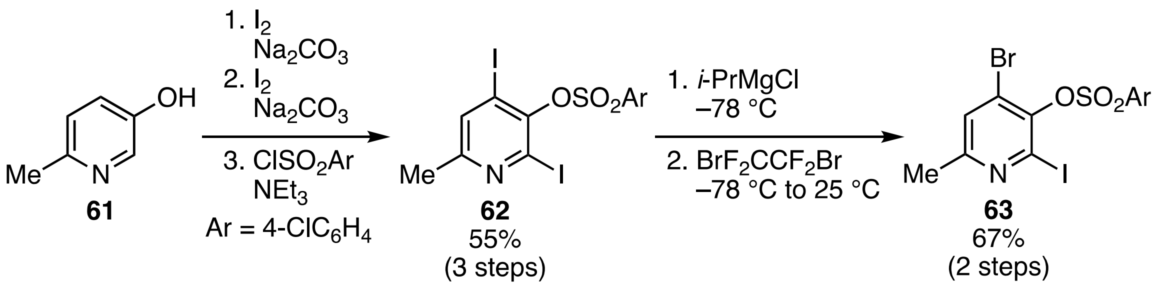
Scheme 21

affecting the iodo group (Scheme 20). Treatment of *o*-iodoaryl triflate **56** with butyllithium in the presence of furan **57** afforded the cycloadduct **58** along with the isomer **58′** (Scheme 21). Chromenoquinone was then successfully synthesized from pyranonaphthalene **58′** in 2 steps. Kumamoto's group also achieved the synthesis of teretifolione B and methylteretifolione B via the pyranobenzyne intermediate.[23b]

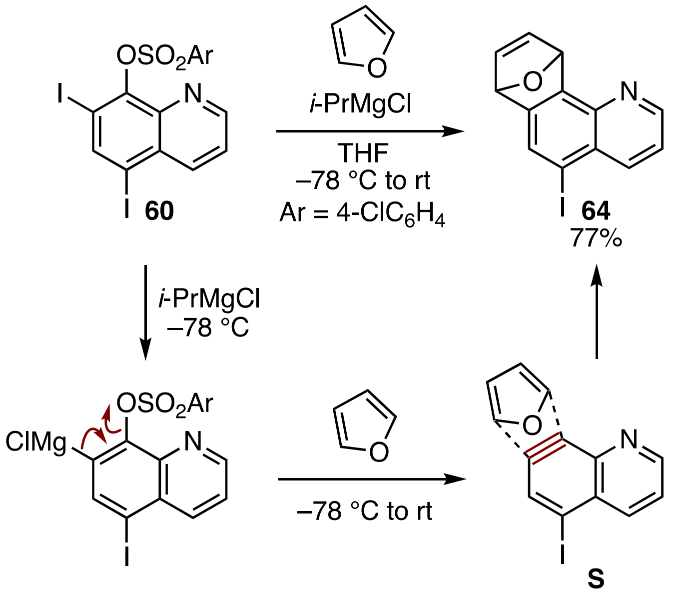
Knochel and coworkers reported a generation method for a wide range of arynes including hetarynes from *o*-iodoaryl *p*-chlorobenzenesulfonate by the treatment with isopropylmagnesium chloride or isopropylmagnesium chloride lithium chloride complex.[24] For example, 7,8-quinolyne precursor **60** and 2,3-pyridyne precursor **63** were prepared from 8-hydroxyquinoline (**59**) and 5-hydroxy-2-methylpyridine (**61**), respectively, thorough electrophilic iodination (Schemes 22 and 23). Efficient cycloaddition with furan proceeded via generation of quinolyne **S** by treating *o*-iodoaryl sulfonate **60** with isopropylmagnesium chloride in THF at −78 °C and then warming the reaction mixture to room temperature (Scheme 24). The group also developed facile synthetic methods for multisubstituted pyridines by transformations of 3,4-pyridynes **T** (Scheme 25). For instance, electrophilic thiolation of 2-iodo-3-(4-chlorobenzenesulfonyloxy)-4-bromopyridine (**65**) by the iodine–magnesium exchange afforded 2-(arylthio)pyridine **66** without generating 2,3-pyridyne. Subsequently, multisubstituted pyridine **67** and **67′** were prepared through pyridyne generation from the remaining *o*-bromoaryl sulfonate moiety, nucleophilic thiolation, and electrophilic iodination.



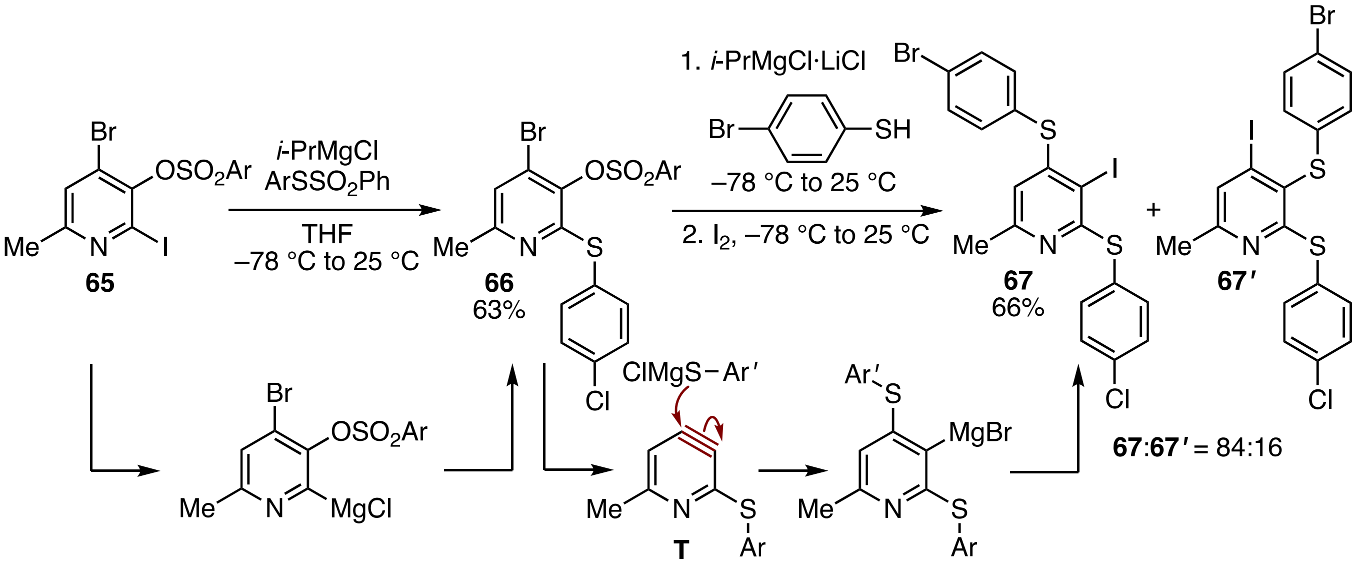
Scheme 22



Scheme 23



Scheme 24



Scheme 25

As mentioned above, several synthetic methods utilizing hetaryne intermediates generated from *o*-iodoaryl triflates have been developed. Although various *o*-iodoaryl triflate-type hetaryne precursors can be prepared easily, their applications in the synthesis of heteroaromatic compounds via the hetaryne intermediates have been somewhat limited, possibly due to side reactions caused by the highly reactive nucleophilic activators such as butyllithium and isopropyl Grignard reagents.

5-2. Hetaryne generation using a silylmethyl Grignard reagent

5-2-1. Aryne generation from *o*-iodoaryl triflate with a silylmethyl Grignard reagent

To improve the synthetic utility of hetaryne intermediates, we recently developed novel methods to generate hetarynes from easily obtainable *o*-iodoaryl triflate-type precursors using a silylmethyl Grignard reagent as a mild activator.[25] In 2014, we found that the silylmethyl Grignard reagent triggered efficient generation of arynes bearing a terminal alkyne moiety from the corresponding *o*-iodoaryl triflates (Figure 6A).[25a] Indeed, treatment of a mixture of 2-iodo-3-(propargyloxy)phenyl triflate (**68**) and benzyl azide (**69**) in THF with (trimethylsilyl)methyl Grignard reagent at −78 °C regioselectively afforded benzotriazole **70** in high yield without affecting the terminal alkyne moiety. In contrast, using butyllithium as an activator resulted in a complex mixture of products. Activation of *o*-iodoaryl triflate-type precursors by the silylmethyl Grignard reagent with low nucleophilicity and low but sufficient reactivity to activate the iodo group, also enabled generation of various aryne intermediates bearing functional groups such as azido,[25b] methoxycarbonyl,[25c] triflyloxy,[25d–g] and halogeno[25h] groups (Figure 6B). Since various *o*-iodoaryl triflate-type aryne precursors can be prepared effortlessly from phenol derivatives, we then applied the method utilizing the silylmethyl Grignard reagent as the activator for the generation and transformations of hetarynes including thiazolobenzynes, thienobenzynes, and furanobenzynes.

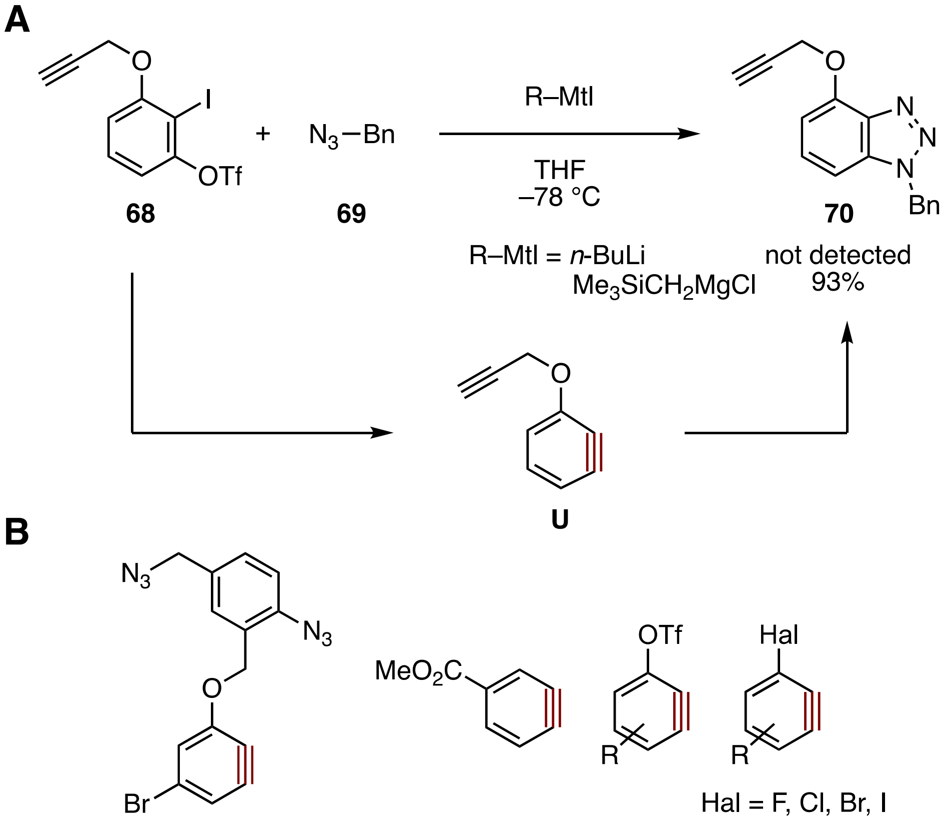


Figure 6

5-2-2. Thiazolobenzynes

Benzothiazoles are an important class of compounds frequently used in broad disciplines such as materials science and pharmaceutical chemistry.[26] To facilitate the availability of multisubstituted benzothiazoles, we examined the generation of thiazolobenzyne intermediates such as **V** and **W**, which are benzothiazole-type arynes, from the corresponding *o*-iodoaryl triflate-type precursors (Figure 7).[27] The 6,7- and 4,5-thiazolobenzyne precursors **75a** and **81a** were easily prepared from 6- and 4-methoxybenzothiazoles **71** and **76** in several steps including iodination, demethylation, and triflation (Schemes 26 and 27). Screening various activators for the reaction of 6,7-thiazolobenzyne precursor **75a** with 2,5-dimethylfuran revealed that cycloadduct **82a** was obtained in optimal yield when the silylmethyl Grignard reagent was employed as the activator (Scheme 28), whereas the turbo Grignard reagent was less efficient due to the nucleophilic attack of the reagent onto thiazolobenzyne **V′**. Similarly, 4,5-thiazolobenzyne intermediate **W′** was efficiently generated from precursor **81a** under the same conditions (Scheme 29).

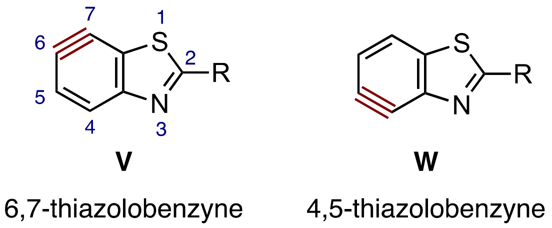
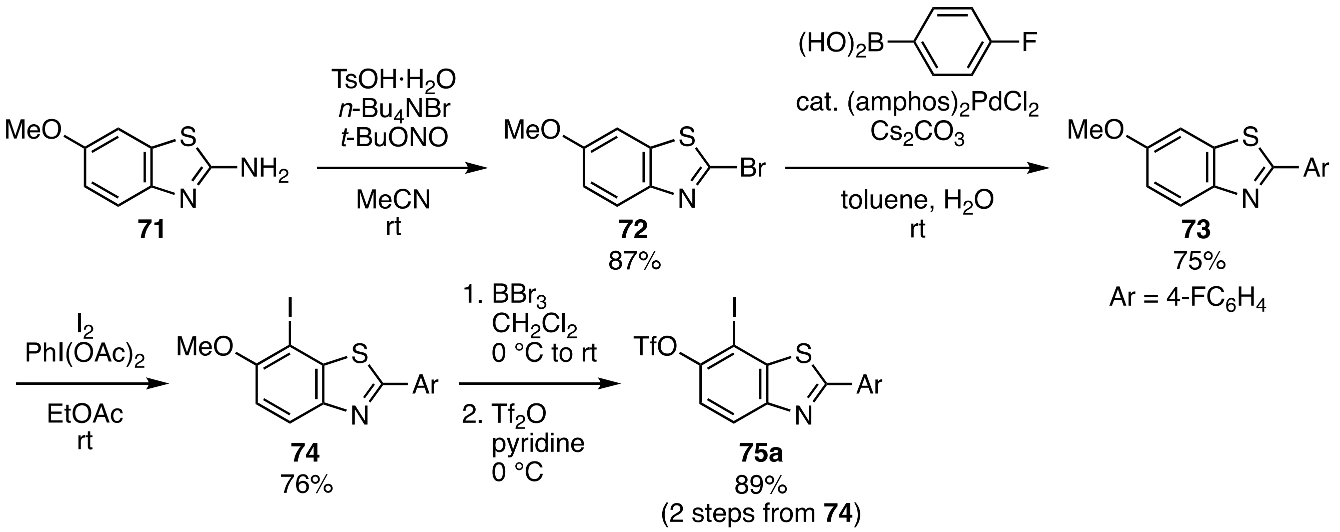
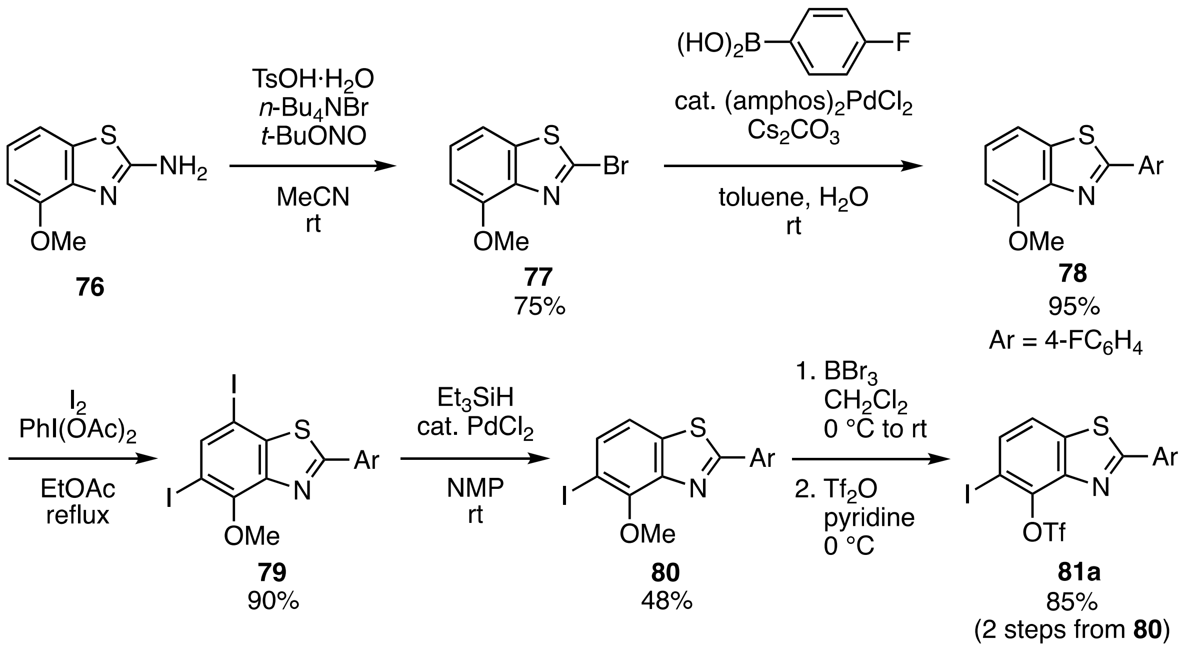


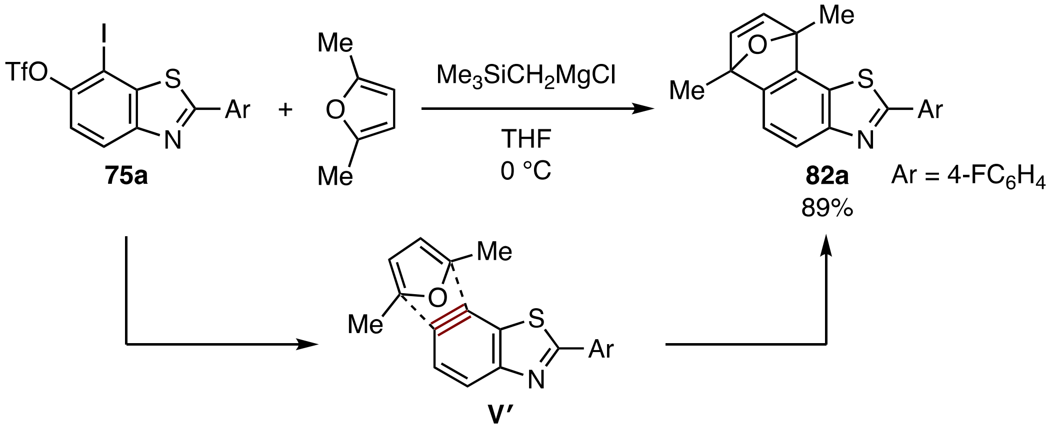
Figure 7



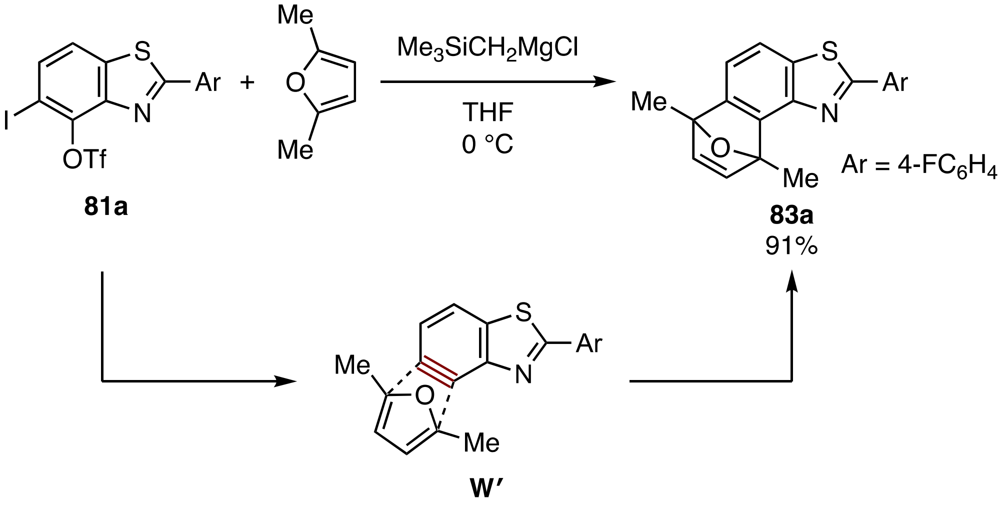
Scheme 26



Scheme 27

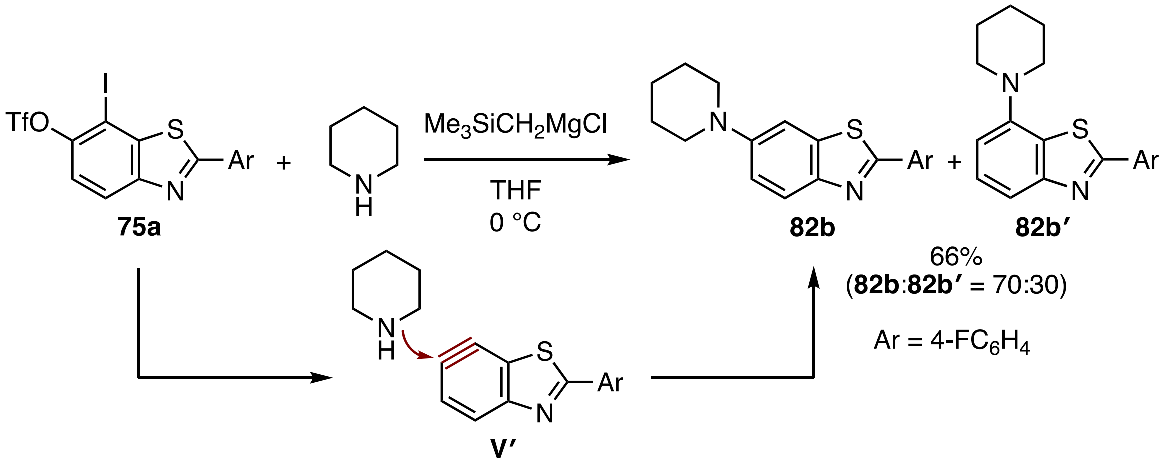


Scheme 28

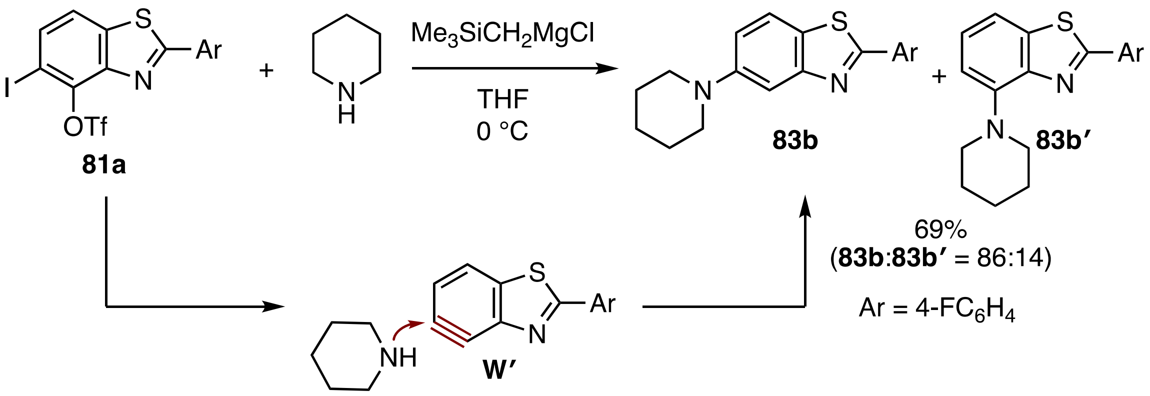


Scheme 29

We also demonstrated that a wide range of multisubstituted benzothiazoles could be obtained from reactions between thiazolobenzynes generated from the corresponding *o*-iodoaryl triflates and diverse arynophiles (Schemes 30 and 31 and Figures 8 and 9). For example, nucleophilic addition of piperidine to 6,7-thiazolobenzyne **V′** and 4,5-thiazolobenzyne **W′** proceeded smoothly to afford 6-piperidinobenzothiazole **82b** and 5-piperidinobenzothiazole **83b**, respectively, with moderate selectivity. The observed regioselectivity was in good agreement with the reported analysis based on the aryne distortion model.[5b] Thiazolobenzynes **V** and **W** also reacted with a broad range of arynophiles (Figures 8 and 9), demonstrating that transformation via thiazolobenzynes is an effective approach for the preparation of diverse benzothiazole derivatives.



Scheme 30



Scheme 31

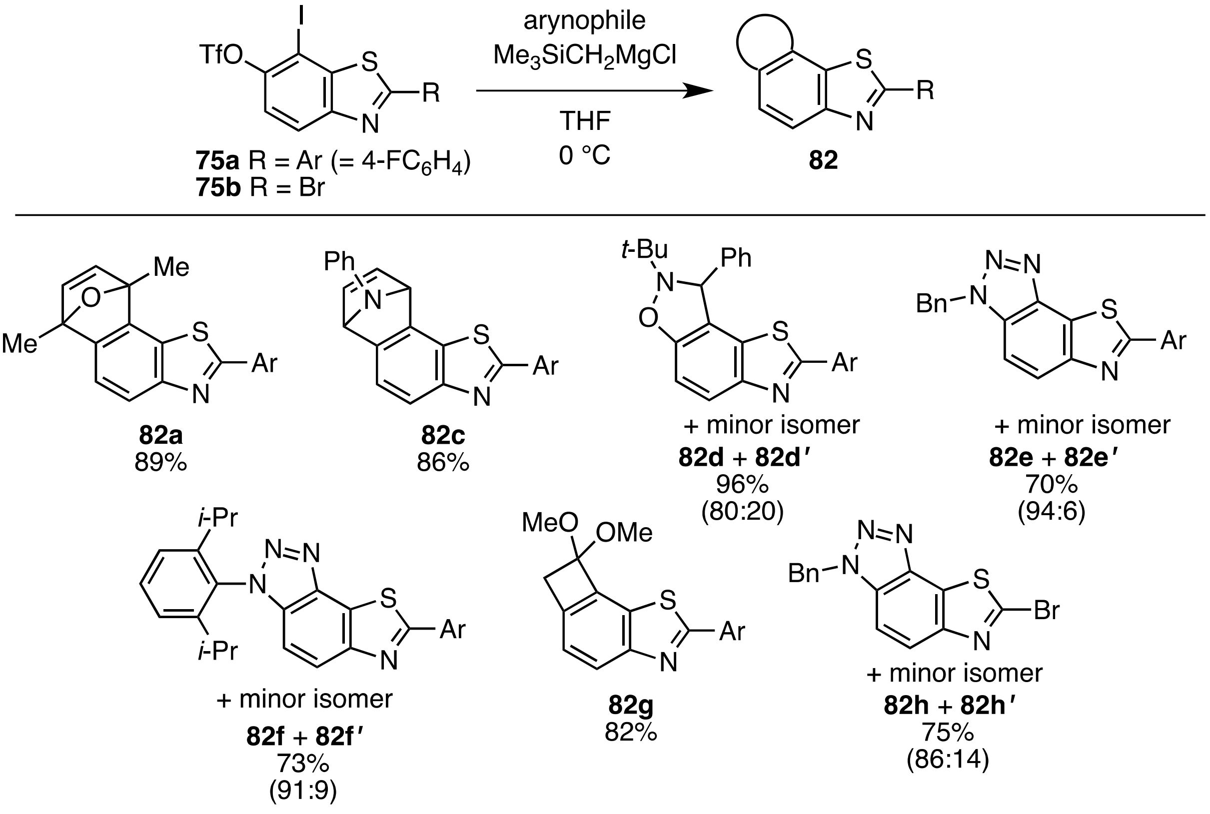


Figure 8

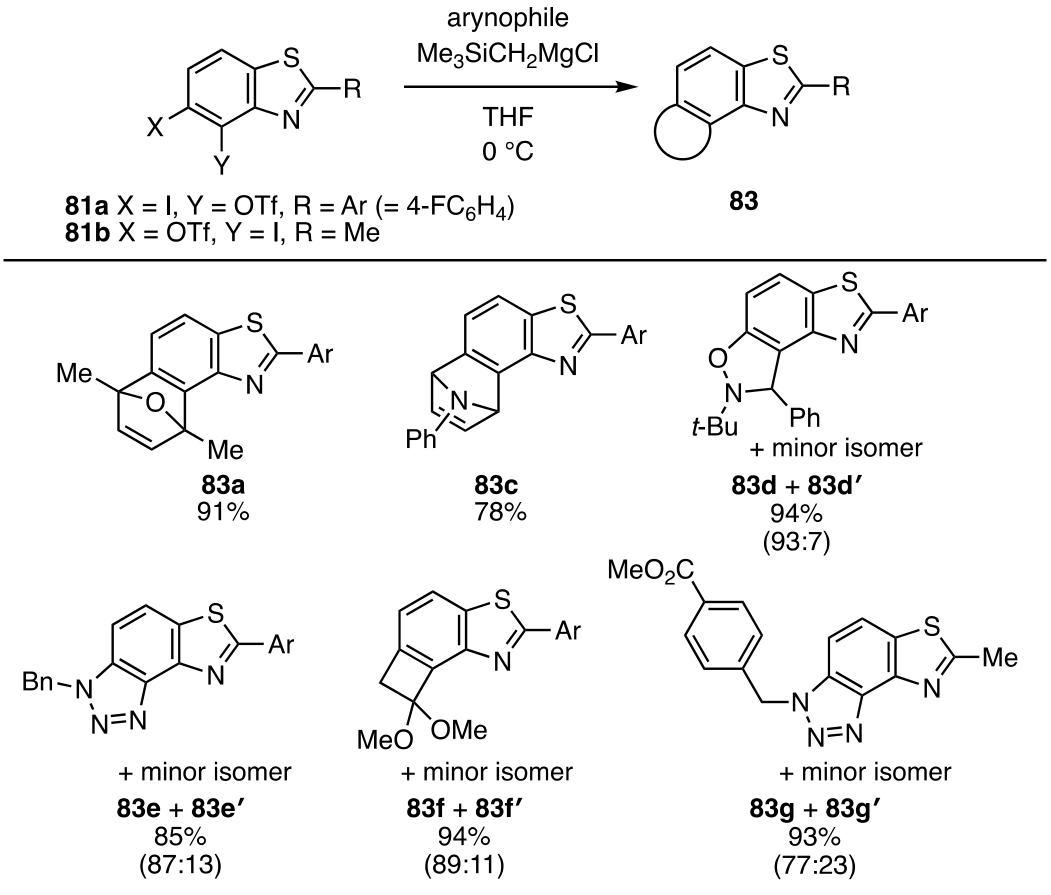
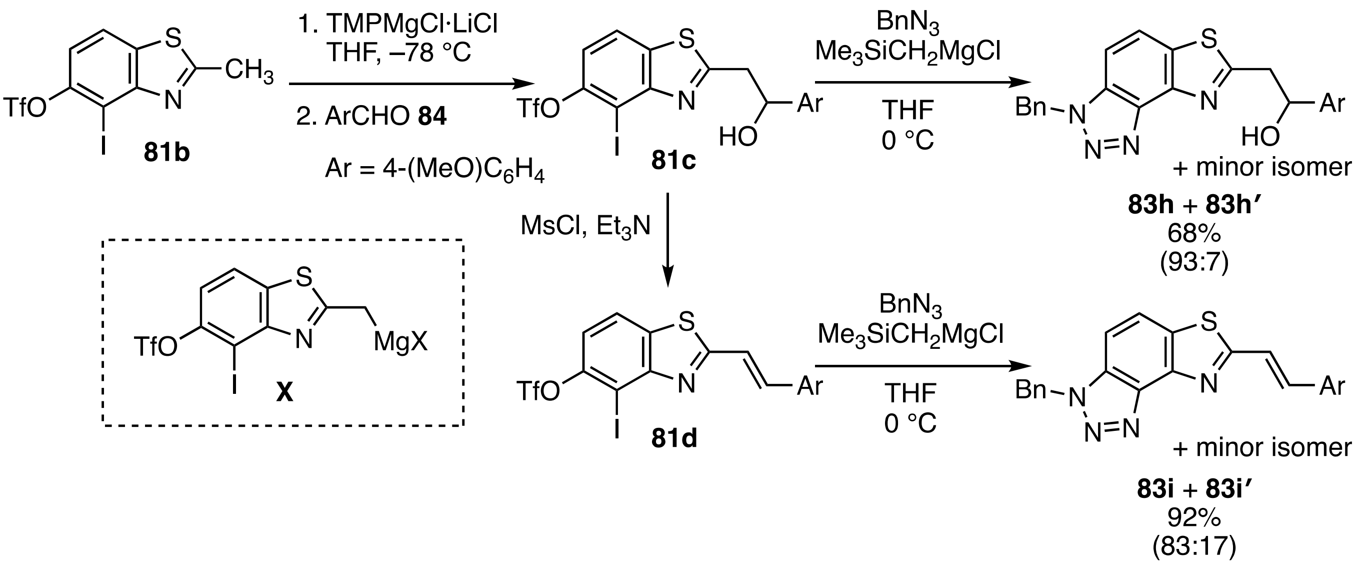


Figure 9

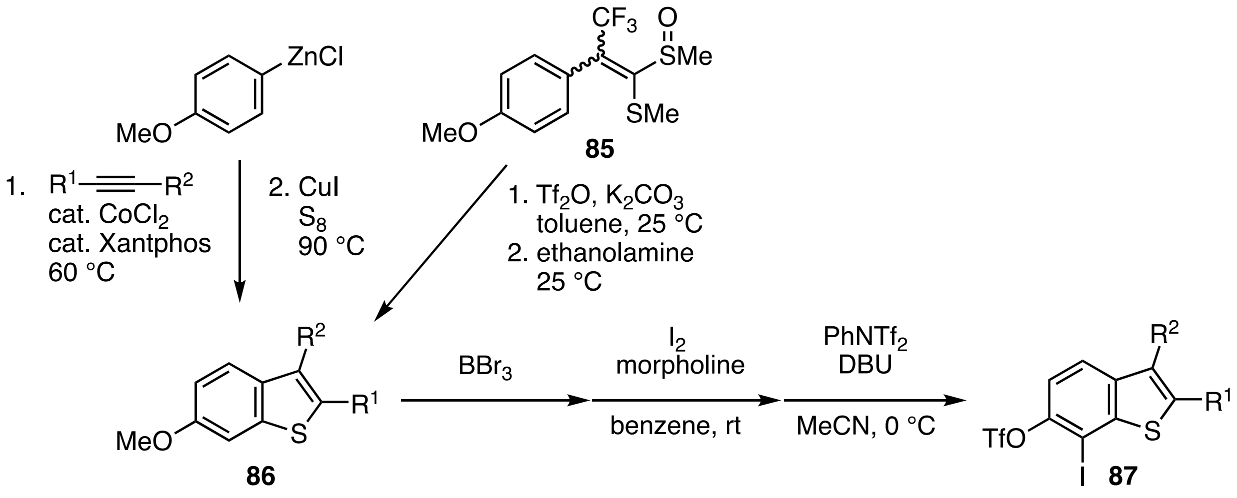
In addition, diversification of a simple thiazolobenzyne precursor **81b** was achieved by deprotonation of the 2-methyl group using the Knochel–Hauser base (2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex; TMPMgCl·LiCl), facilitating the preparation of a wide variety of benzothiazoles (Scheme 32). For instance, thiazolobenzyne precursors **81c** and **81d** were synthesized via metalation of **81b** to generate carbanion species **X**, which was subjected to the C–C bond formation with aldehyde **84**, followed by dehydration of the resulting alcohol **81c** to afford 2-styrylthiazolobenzyne precursor **81d** leaving the iodo and triflyloxy groups unaffected. Synthesis of triazole-fused benzothiazoles **83h** and **83i** was accomplished via the generation of the corresponding 4,5-thiazolobenzynes from these precursors using silylmethylmagnesium chloride. Thus, utilizing other electrophiles and arynophiles in this scheme would allow for efficient synthesis of diverse multisubstituted benzothiazoles.



Scheme 32

5-2-3. Thienobenzynes

Following the successful development of the efficient synthetic method for multisubstituted benzothiazole derivatives via thiazolobenzyne intermediates, we also established several synthetic methods utilizing other hetaryne intermediates. To render multisubstituted benzothiophenes more easily available, we examined efficient generation of thienobenzyne intermediates from the corresponding *o*-iodoaryl triflate-type precursors.[28] Various 2,3-disubstituted 6,7-thienobenzyne precursors **87** were easily prepared in a 3-step sequence involving demethylation, iodination, and triflylation of the corresponding methoxy-substituted benzo[*b*]thiophenes **86**. A variety of methoxybenzo[*b*]thiophenes **86** were readily obtained by cobalt-catalyzed C–C bond formation[29] or Yorimitsu–Oshima benzothiophene synthesis using ketene dithioacetal monoxides **85** (Scheme 33).[30]



Scheme 33

Diverse multisubstituted benzothiophenes were successfully synthesized via the transformation of 6,7-thienobenzyne intermediate generated from precursor **87a** with a wide variety of arynophiles (Figure 10). Various 2,3-disubstituted 6,7-thienobenzyne intermediates also participated in the cycloaddition with azide **89** to afford triazole-fused benzothiophenes without affecting the various functional groups such as amide, chloro, trifluoromethyl, and methylthio groups (Figure 11). The reaction of the 6,7-thienobenzyne

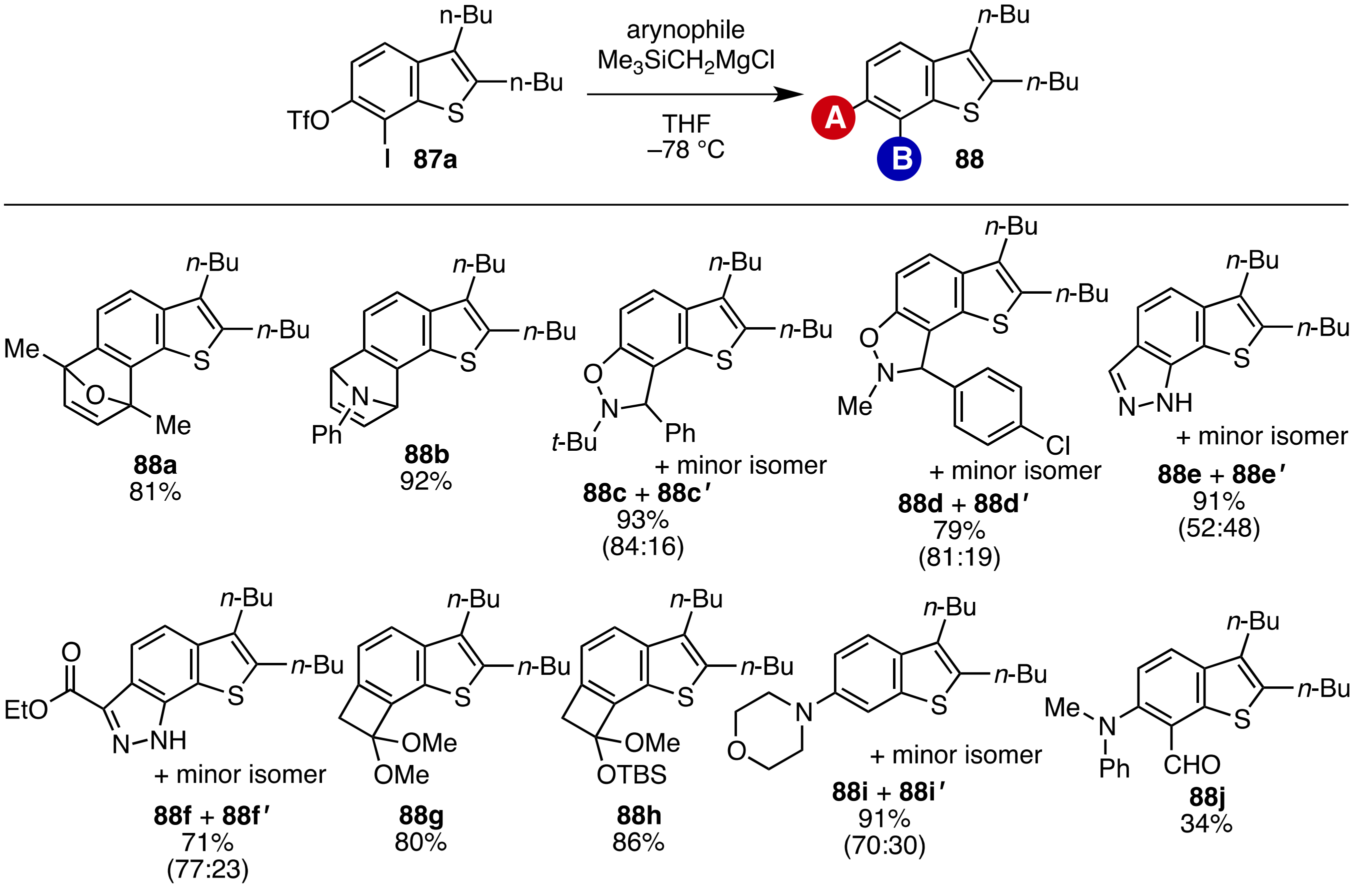


Figure 10

intermediates with azide **89** proceeded to afford a regioisomeric mixture of products with high selectivity, which was predicted by the computed structure of 6,7-thienobenzyne. Since a wide variety of benzothiophene derivatives have played important roles as pharmaceuticals, organic materials, and so on, this novel synthetic method based on the generation of thienobenzynes would be useful for the development of effective compounds in a broad range of research fields.

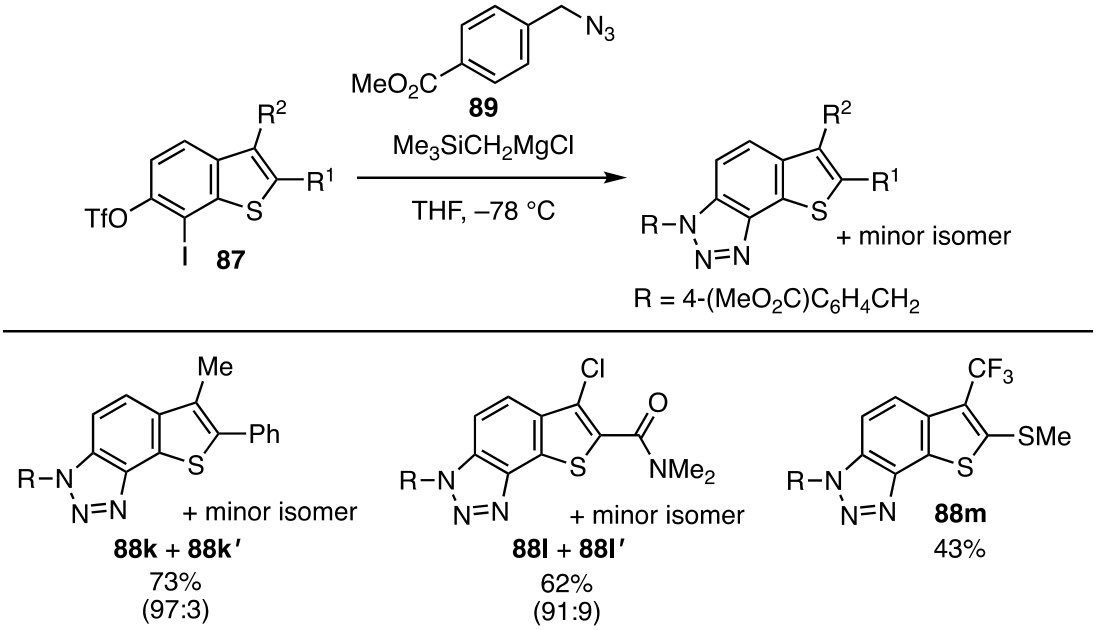


Figure 11

5-2-4. Furanobenzynes

We also applied the described method for generating arynes from *o*-iodoaryl triflate-type precursors by the treatment with the silylmethyl Grignard reagent to the furanobenzyne chemistry.[31] Various 2,3-disubstituted 6,7-furanobenzyne precursors were easily prepared from phenol derivatives by a

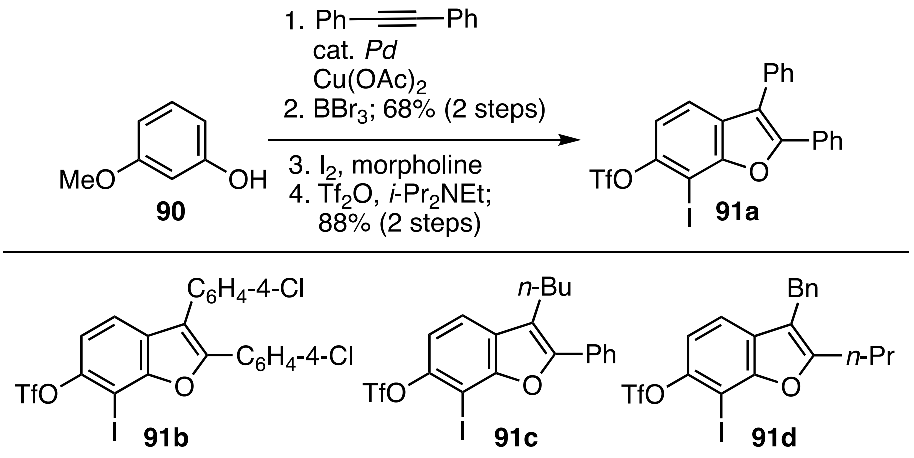
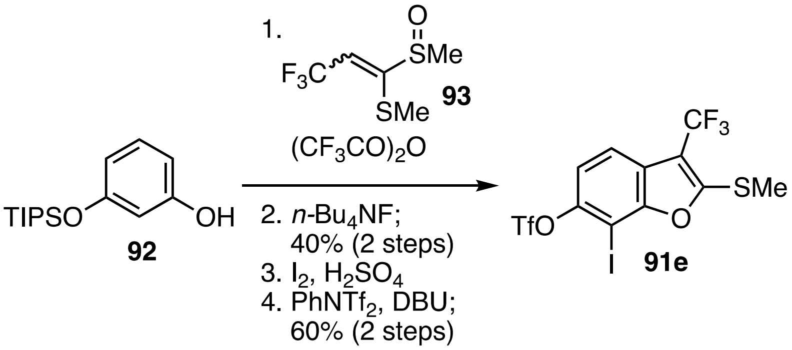


Figure 12

palladium-catalyzed cross-coupling reaction[32] or Yorimitsu–Oshima benzofuran synthesis[33] to construct 2,3-disubstituted hydroxybenzofuran derivatives and the following iodination/triflation sequence (Figure 12 and Scheme 34).



Scheme 34

Several 2,3-disubstituted 6,7-furanobenzynes were efficiently generated from the corresponding *o*-iodoaryl triflate-type precursors by the treatment with the silylmethyl Grignard reagent. The generated furanobenzyne intermediates successfully reacted with a wide range of arynophiles, facilitating the availability of multisubstituted benzofurans (Figures 13 and 14). Notably, nucleophilic addition of

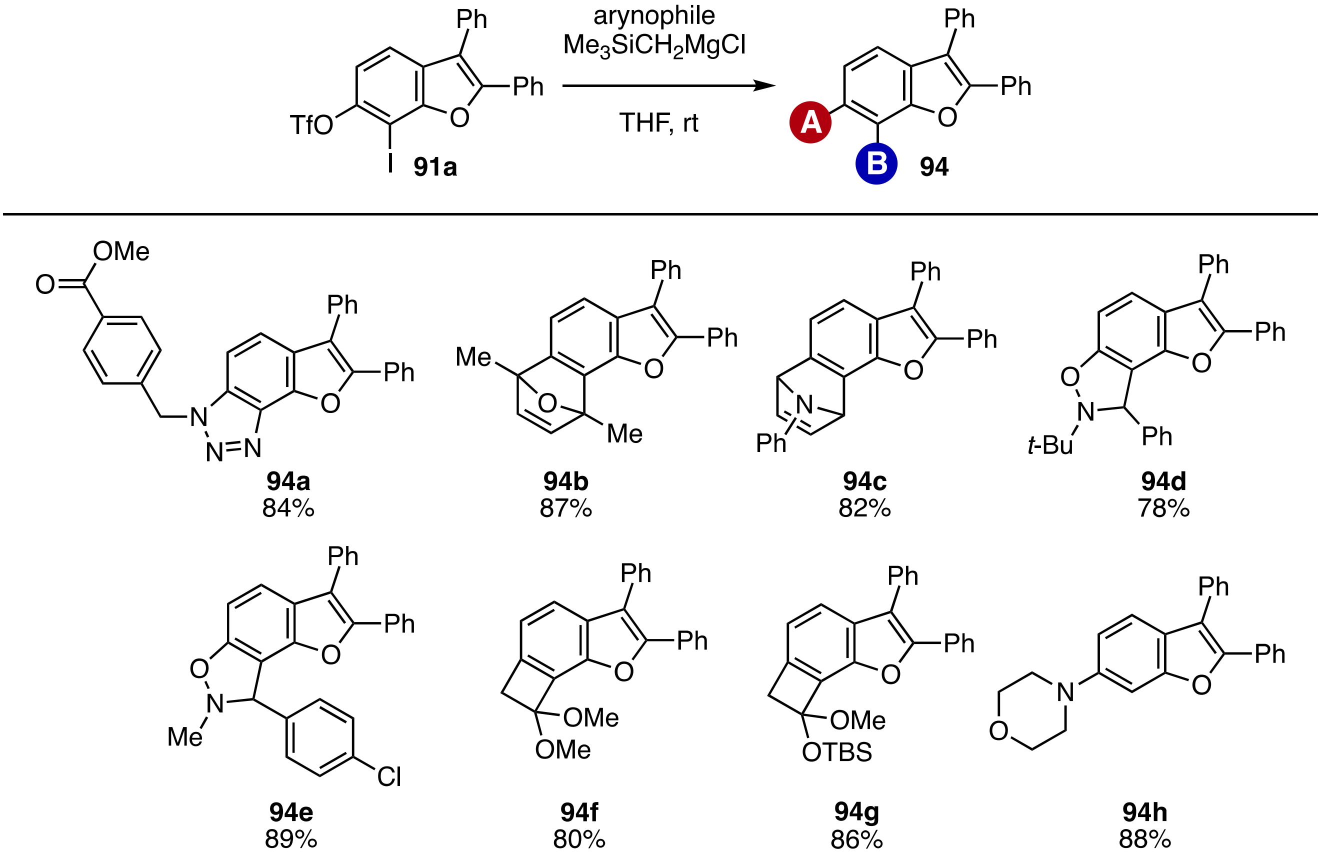


Figure 13

morpholine to the 6,7-furanobenzyne intermediate occurred in a highly selective manner to afford the adduct as a single isomer. This outcome was attributable to the highly distorted structure of furanobenzyne suggested by the optimized structure obtained by the DFT method.

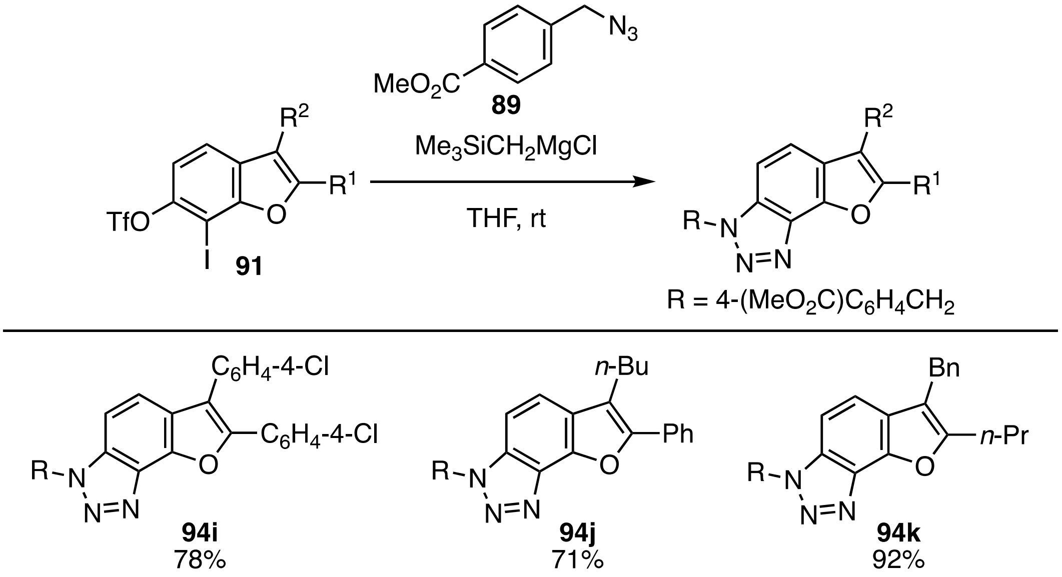
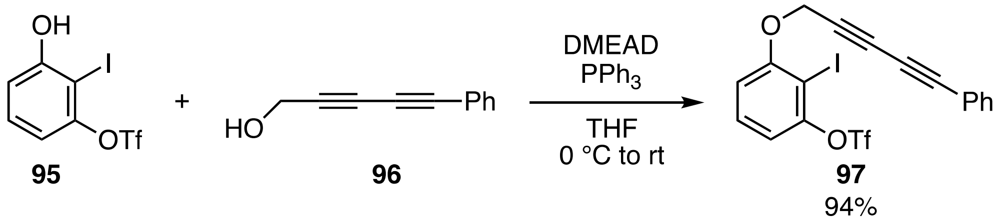


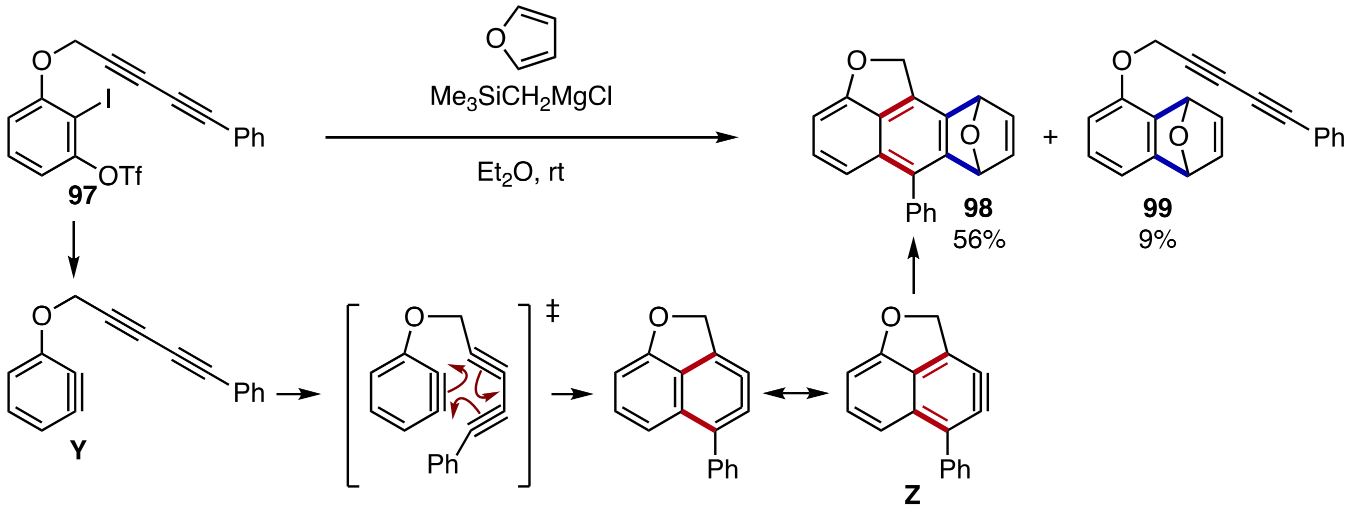
Figure 14

5-2-5. Furanonaphthalynes

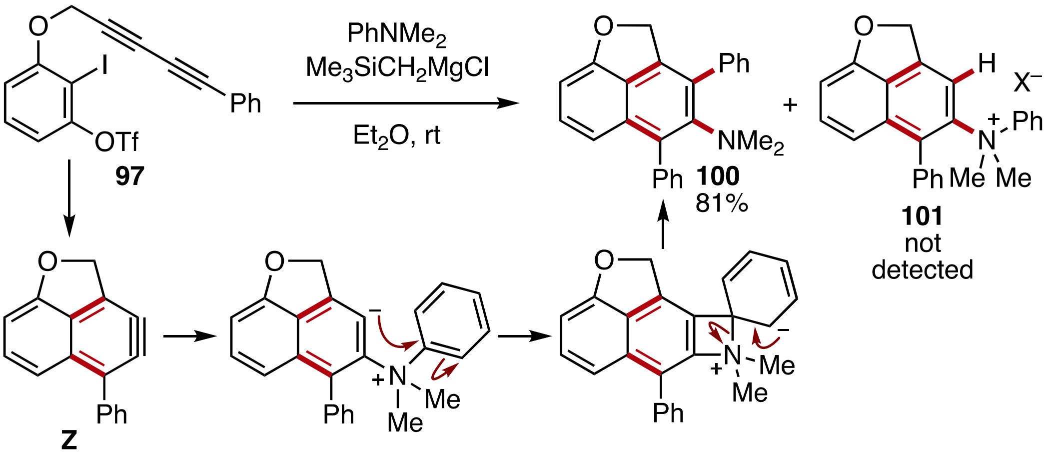
We also found that intramolecular [2+4] cycloaddition of aryne **Y** bearing a 1,3-diyne moiety generated from the corresponding *o*-iodoaryl triflate resulted in the sequential generation of another aryne species, furanonaphthalyne **Z**.[34] The aryne precursor **97** was easily prepared by the Mitsunobu reaction between phenol **95** and 5-phenylpenta-2,4-diyn-1-ol (**96**) (Scheme 35). Treatment of the precursor **97** with the silylmethyl Grignard reagent in the presence of furan afforded anthracene derivative **98** via furanonaphthalyne intermediate **Z** generated via the HDDA reaction, as described later in detail in Chapter 7 (Scheme 36). Moreover, we also unexpectedly found that furanonaphthalyne **Z** reacted with *N*,*N*-dimethylaniline to afford aminoarylated naphthalene **100** in high yield (Scheme 37).



Scheme 35



Scheme 36

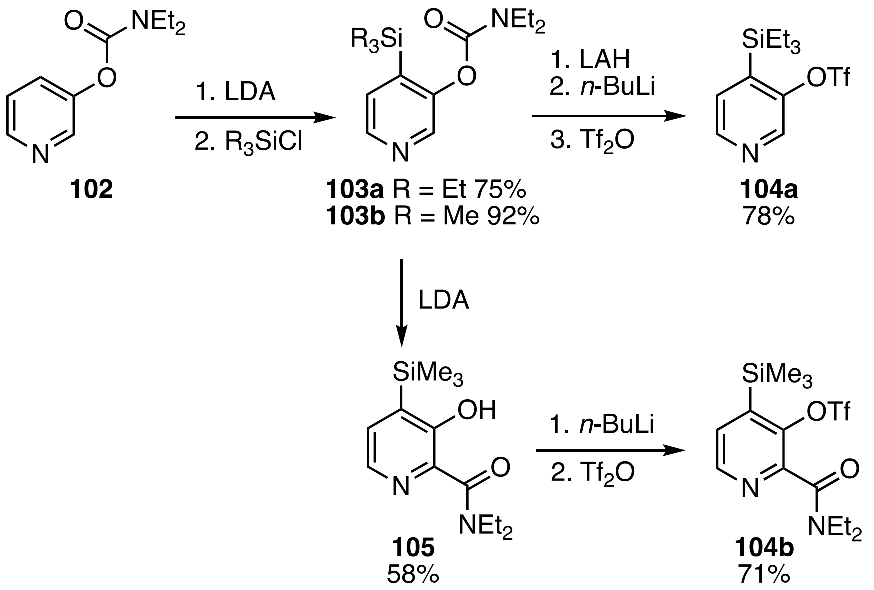


Scheme 37

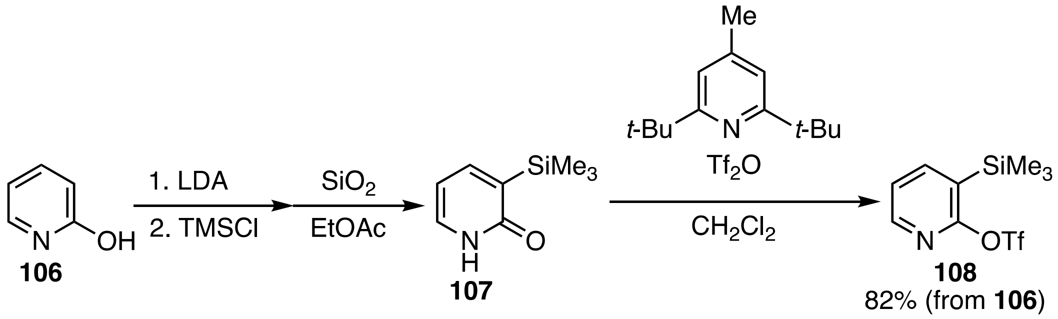
6. HETARYNE GENERATION FROM *o*-SILYLARYL TRIFLATES

6-1. Pyridynes

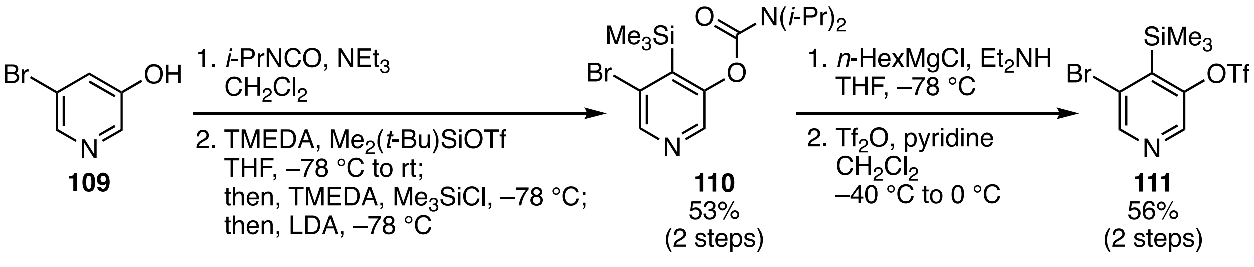
An efficient synthetic approach utilizing pyridyne intermediates generated by the activation of *o*-silylaryl triflate-type pyridyne precursors under mild conditions using fluoride sources has been developed.[35] The precursors were typically prepared from hydroxypyridine derivatives through deprotonative *C*-silylation followed by *O*-triflylation. For example, 3,4-pyridyne precursor **104b** bearing an amide group was synthesized via *C*-silylation, the Fries rearrangement, and *O*-triflation (Scheme 38).[36a] Various 2,3- and 3,4-pyridyne precursors were also prepared by similar methods (Schemes 39–41).[36b–d]



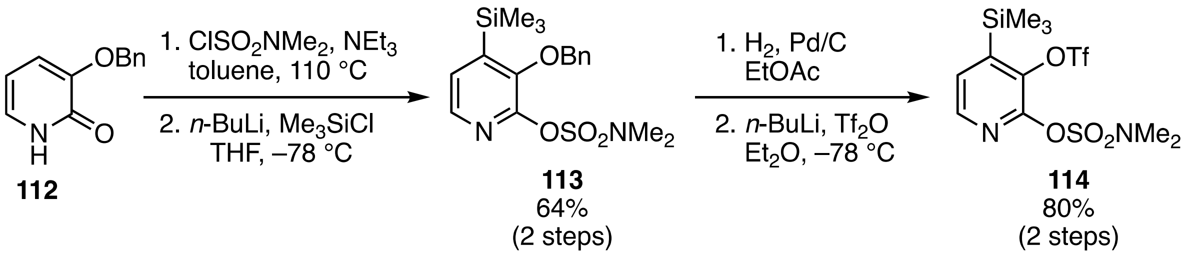
Scheme 38



Scheme 39

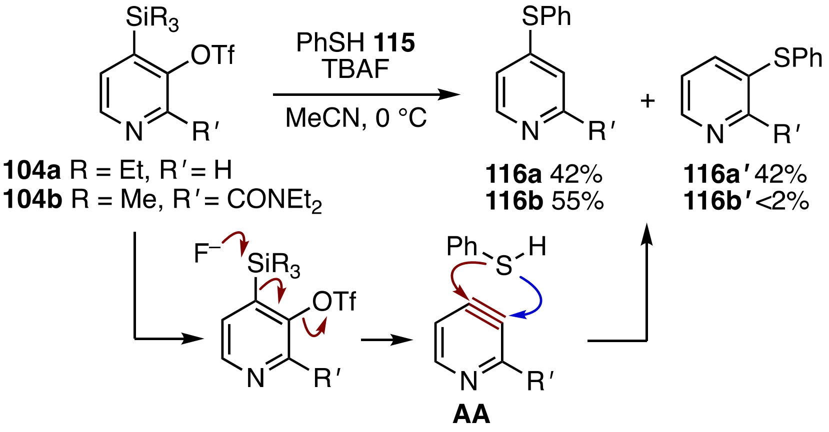


Scheme 40

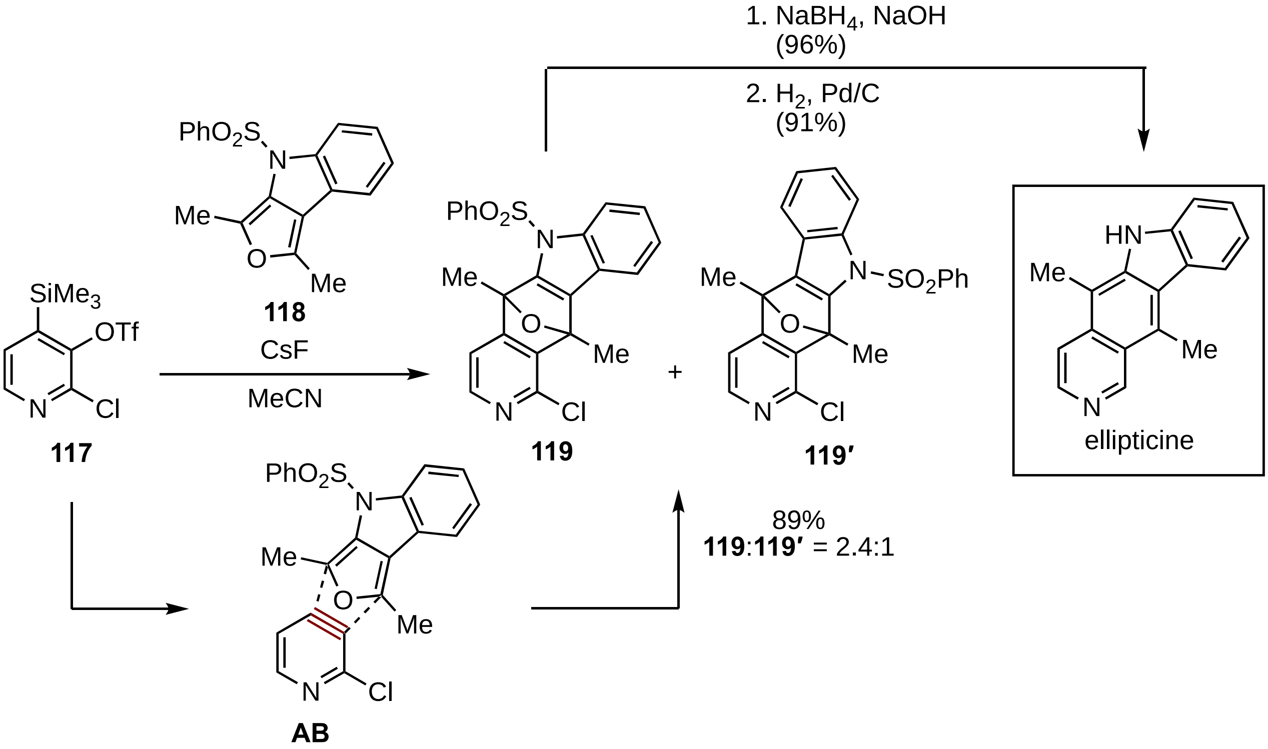


Scheme 41

Nucleophilic additions to pyridynes have been studied particularly in terms of the regioselectivity. For instance, Snieckus and coworker reported a selective addition of benzenethiol (**115**) to 3,4-pyridyne intermediate **AA**, which owing to the electron-withdrawing effect of the amide group at the 2-position afforded 4-thiolated pyridine **116b**, while a 1:1 mixture was obtained from the reaction of 3,4-pyridyne without the amide group (Scheme 42).[36a] Diels–Alder reaction between 2-chloro-3,4-pyridyne (**AB**) generated from precursor **117** and indole-fused furan **118** afforded cycloadducts **119** and **119′** with a moderate regioselectivity that was induced by the electron-withdrawing chloro group (Scheme 43).[36e,f] The resulting cycloadduct **119** was successfully desulfonylated and the subsequent reduction afforded ellipticine.

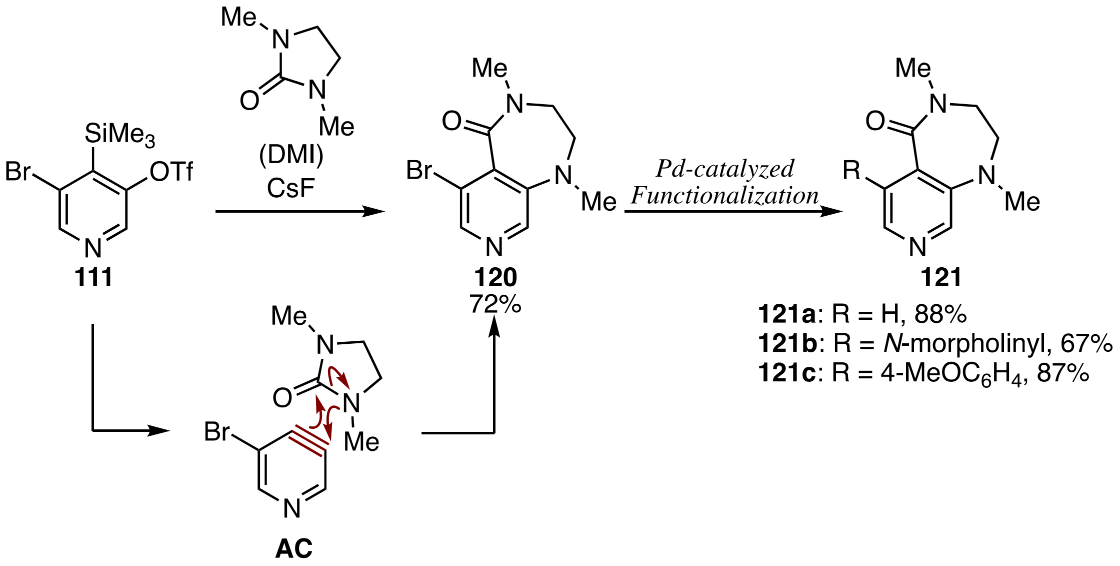


Scheme 42

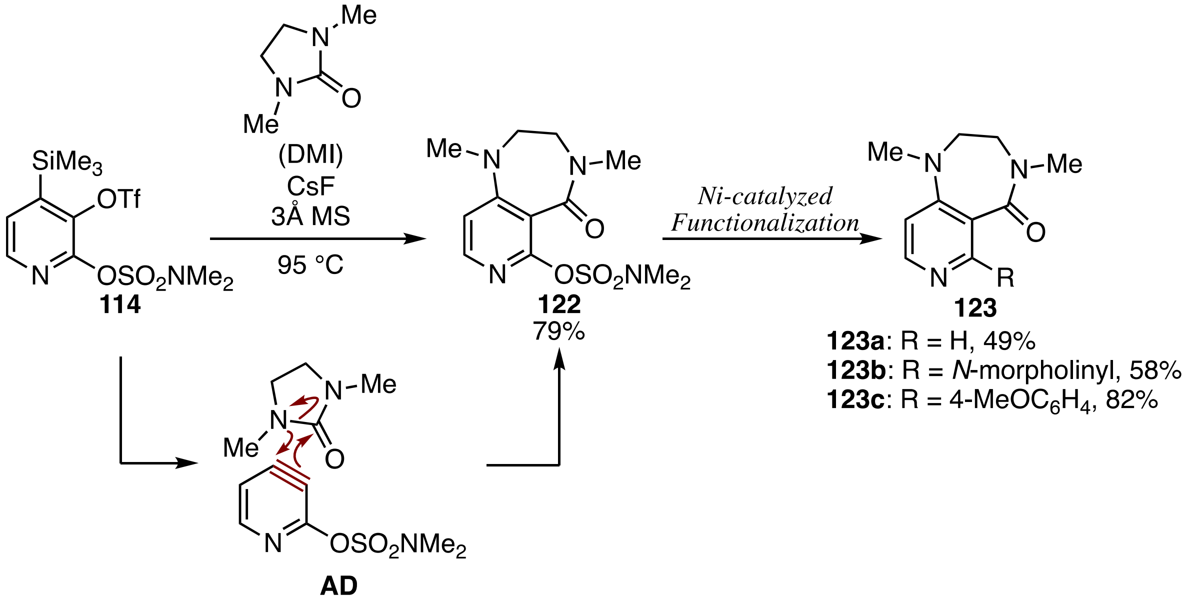


Scheme 43

Regioselective difunctionalization of 5-bromo-3,4-pyridyne (**AC**) was reported by Garg and coworkers, as demonstrated in the reaction of pyridyne precursor **111** with 1,3-dimethyl-2-imidazolidinone (DMI), which selectively afforded the tetrahydropyridodiazepinone derivative **120** owing to the electron-withdrawing effect of the bromo group (Scheme 44).[5c,36d] Subsequent palladium-catalyzed functionalizations of **120** resulted in the synthesis of various tetrahydropyridodiazepinone derivatives **121a**–**c**. The same group also achieved the synthesis of isomeric tetrahydropyridodiazepinone derivatives **123a**–**c** by the regioselective difunctionalization of 2-(dimethylaminosulfonyloxy)-3,4-pyridyne (**AD**) with DMI followed by nickel-catalyzed functionalizations (Scheme 45).

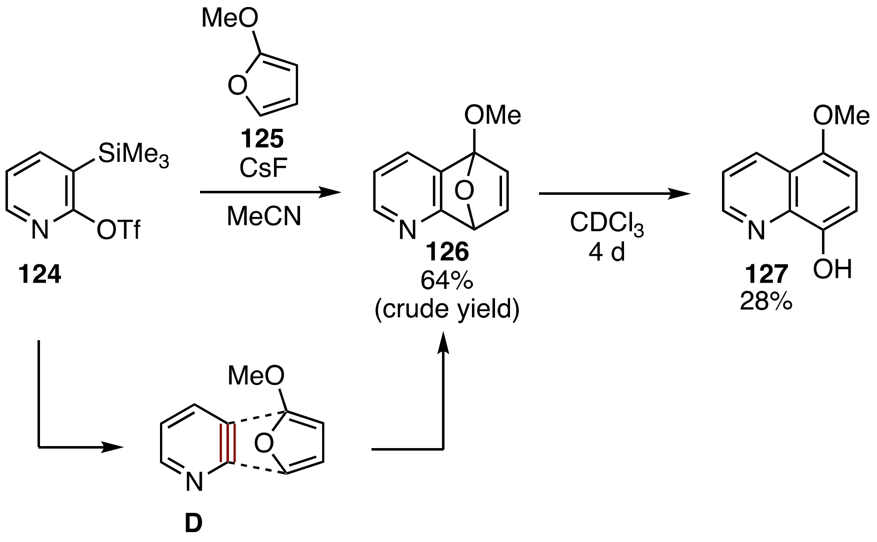


Scheme 44



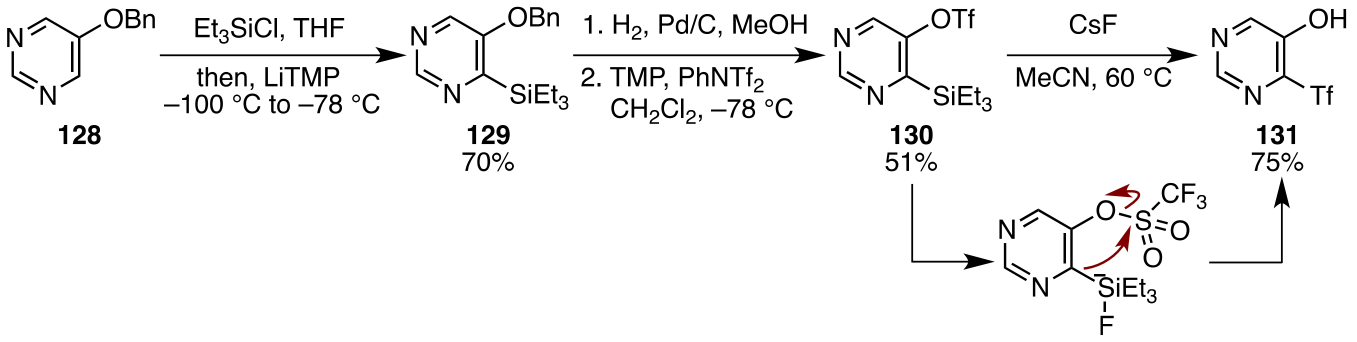
Scheme 45

Furthermore, cycloaddition of 2,3-pyridyne (**D**) with 2-methoxyfuran (**126**) also proceeded regioselectively to afford quinoline derivative **126** in moderate yield (Scheme 46).[36b,c] 5-Methoxy-8-quinolinol (**127**) was obtained by the ring-opening of **126**, which proceeded in $CDCl_3$ without any additive albeit in low yield. Following this report, a variety of reactions such as 1,3-dipolar cycloadditions, insertion reactions, and transition-metal-catalyzed reactions using 2,3- and 3,4-pyridynes were further explored.[37]



Scheme 46

While various efficient transformations of 2,3- and 3,4-pyridynes have been achieved, attempts to generate didehydropyrimidine from the corresponding *o*-silylaryl triflate-type precursors were unsuccessful (Scheme 47 and Figure 15).[38] Although 4-silyl-5-triflyloxypyrimidine **130** and 5-silyl-4-triflyloxypyrimidine **133** were successfully prepared from **128** and **132**, respectively, 4,5-didehydropyrimidine was not generated from either of these potential precursors by the treatment with cesium fluoride in acetonitrile at 60 °C.



Scheme 47

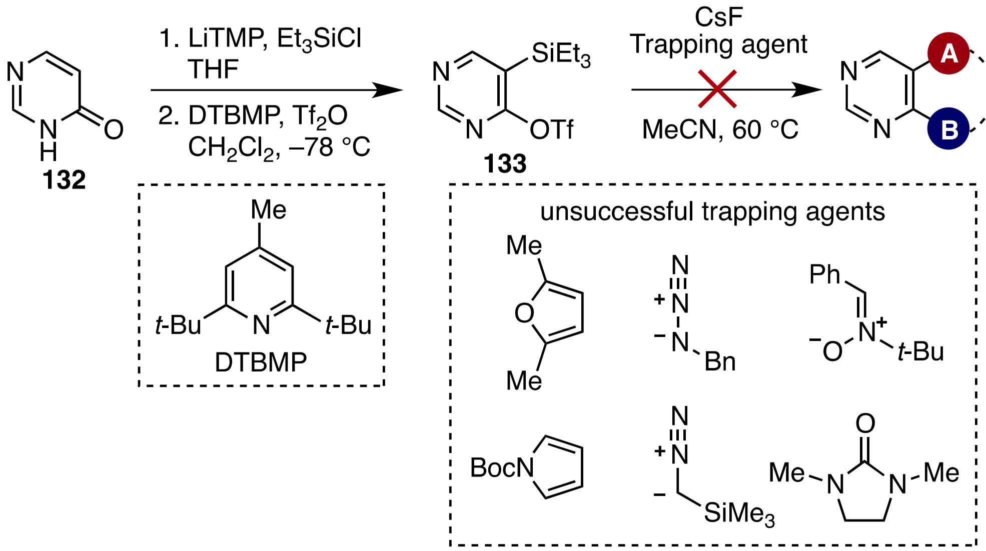
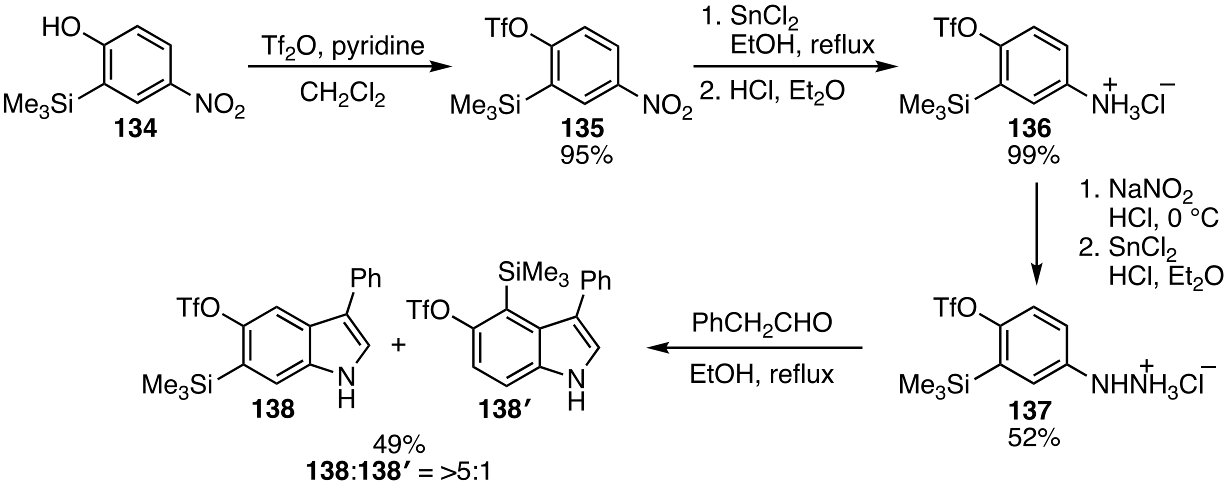


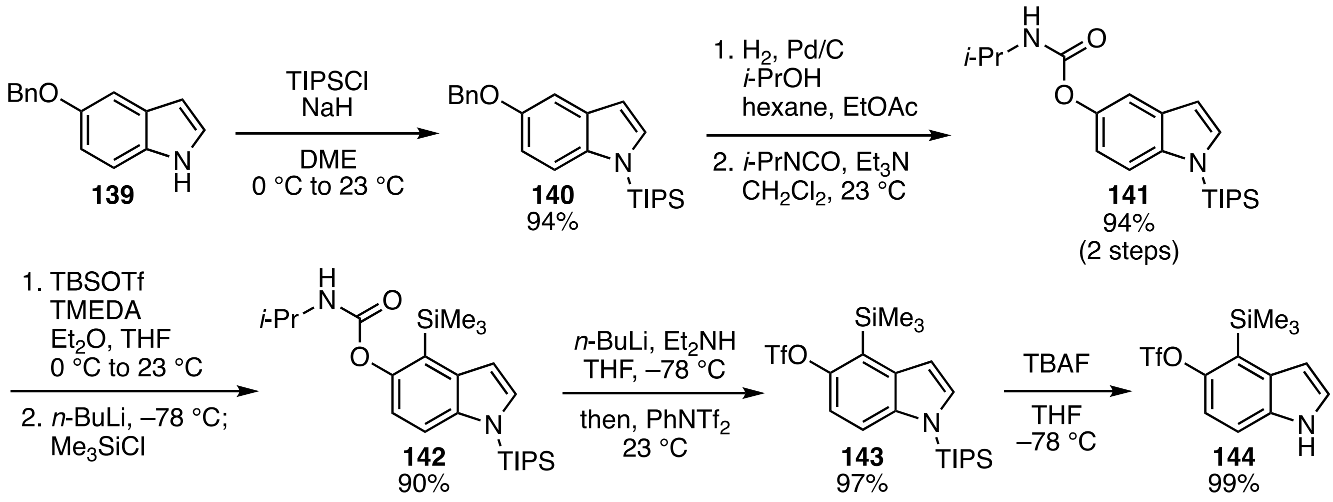
Figure 15

6-2. Indolynes

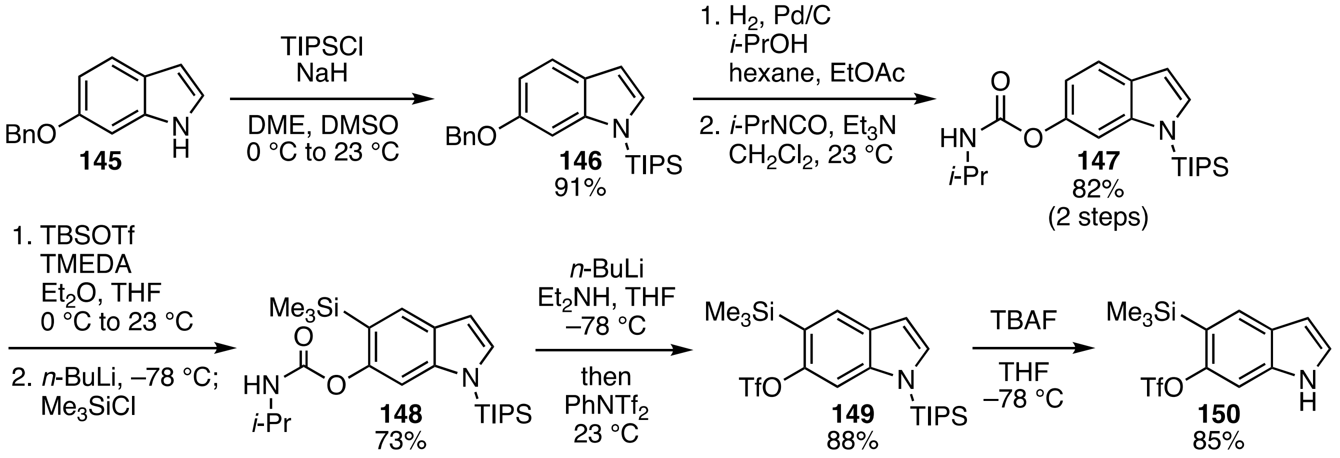
Garg's and Buszek's groups dynamically developed various synthetic methods for multisubstituted indoles employing indolyne intermediates. In 2009, Buszek and coworkers reported the synthesis of a mixture of 4,5- and 5,6-indolyne precursors from 4-nitro-2-silylphenyl triflate **135** in 3 steps involving reduction of the nitro group, transformation to hydrazine **137**, and the Fischer indole synthesis leaving the silyl and triflyloxy groups untouched (Scheme 48).[19c] Moreover, in 2009, Garg and coworkers reported selective syntheses of indolyne precursors **144**, **150**, and **156** via *C*-silylation of *ortho*-lithiated carbamates of *N*-protected indoles and subsequent deprotective *O*-triflylation and *N*-deprotection (Schemes 49–51).[39a,b]



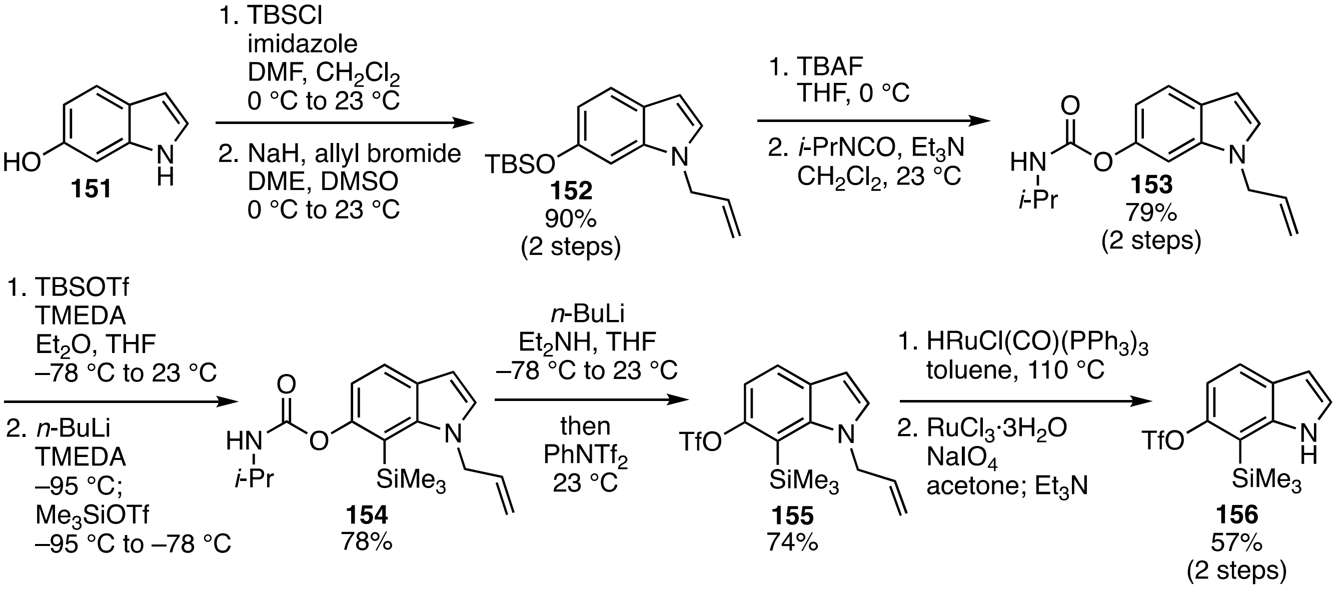
Scheme 48



Scheme 49

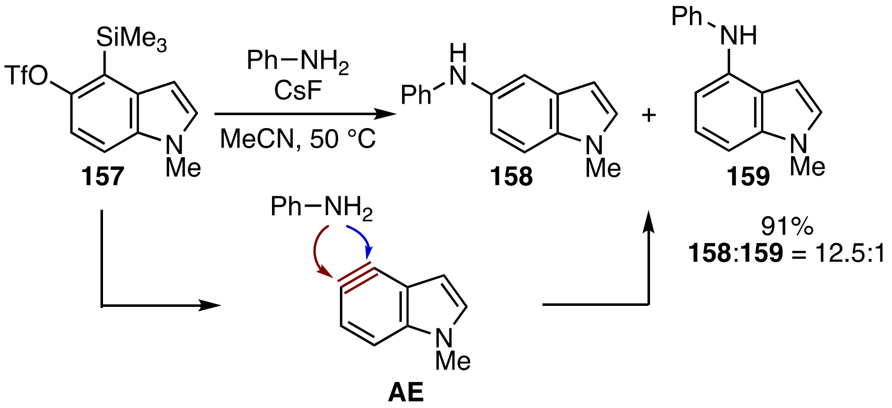


Scheme 50

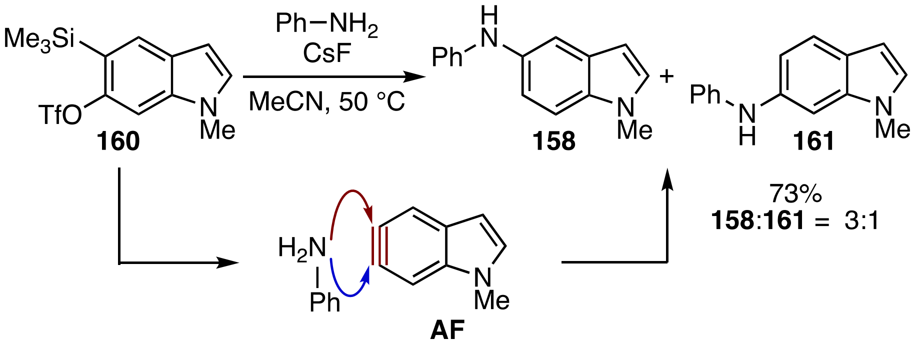


Scheme 51

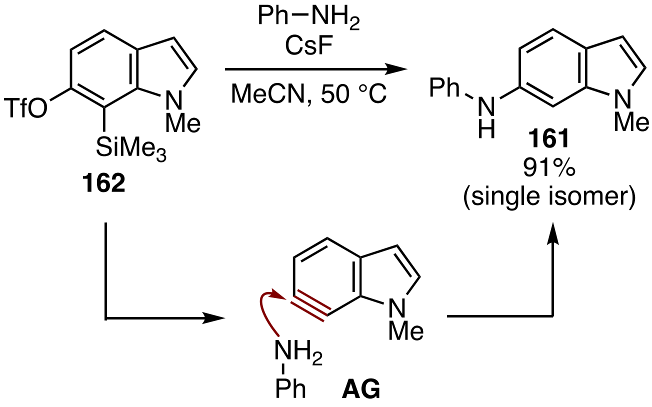
Garg and coworkers also demonstrated that selective nucleophilic addition of aniline to 4,5-, 5,6-, and 6,7-indolyne generated from the corresponding precursors by the treatment with cesium fluoride in acetonitrile at 50 °C proceeded to afford 5-, 5-, and 6-aminoindole, respectively, as the major adducts (Schemes 52–54).[39b,c] The aryne distortion model, which was proposed to rationalize the regioselectivity of the reactions involving aryne intermediates, was generally applicable to predict the regioselectivities of a broad range of aryne reactions. Indeed, nucleophilic attack onto the indolyne carbons with a larger angle took place predominantly in all cases (Figure 16).



Scheme 52



Scheme 53



Scheme 54

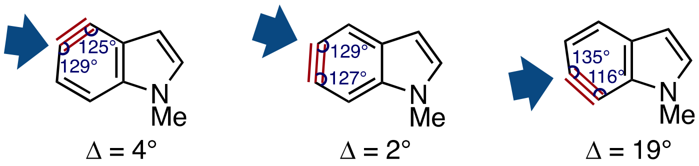
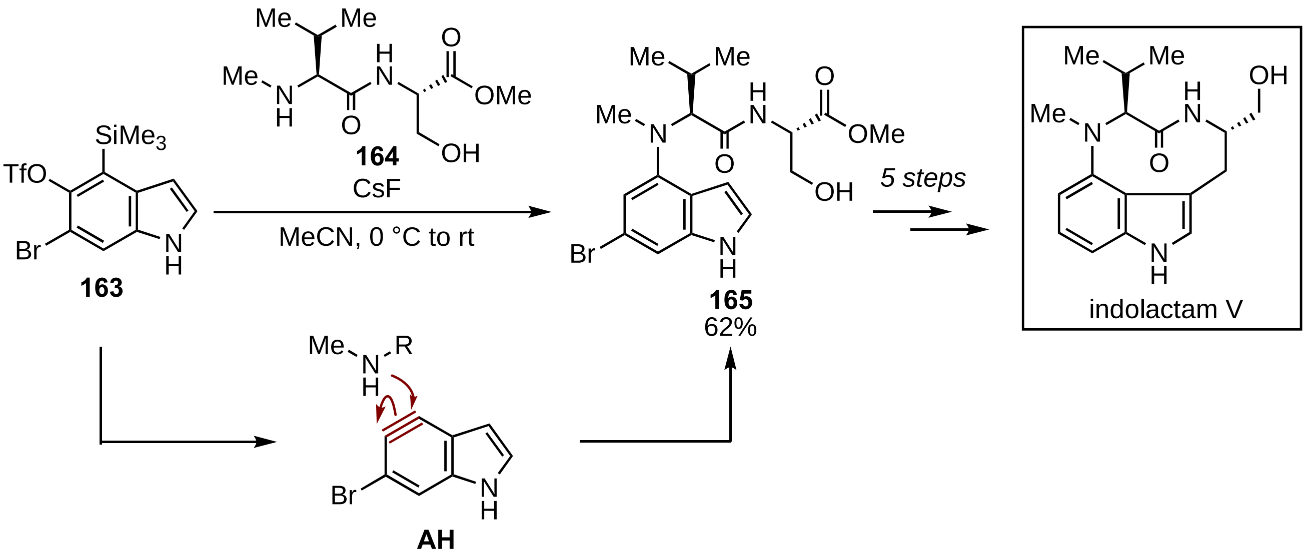


Figure 16

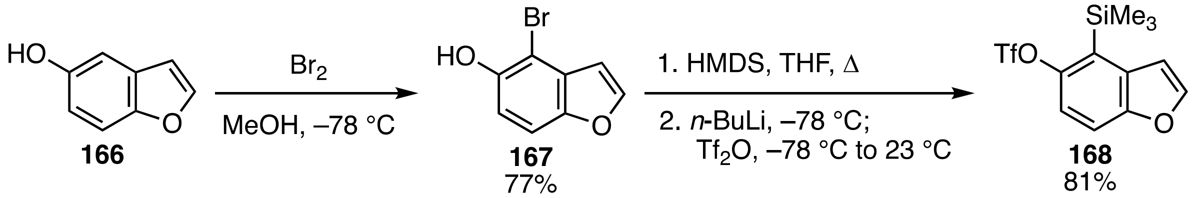
Selective amination of 4,5-indolyne intermediate **AH** at the 4-position was elegantly achieved by introducing an electron-withdrawing bromo group at the 6-position, which was used as a key step in the synthesis of indolactam V (Scheme 55).[39d,e] The easily removable bromo group served as the switch to reverse the regioselectivity of the addition reaction.



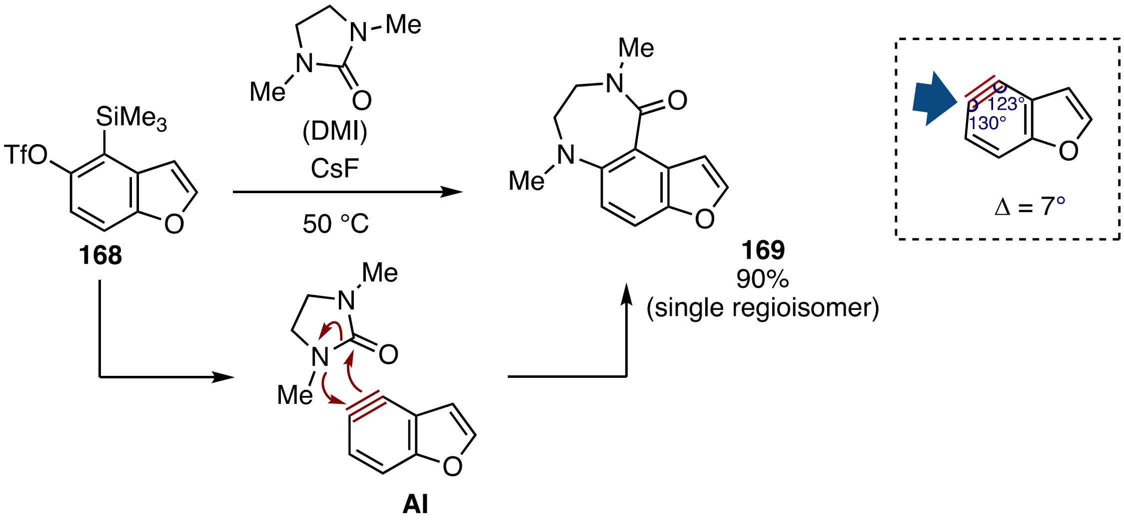
Scheme 55

6-3. Furanobenzyne

Garg's group also developed a synthetic method for various benzo[*b*]furans via furanobenzynes generated from *o*-silylaryl triflate-type precursors.[40] For example, 4,5-furanobenzyne precursor **168** was prepared by 4-bromination of 5-hydroxybenzo[*b*]furan (**166**) followed by *O*-silylation, retro-Brook rearrangement, and *O*-triflylation (Scheme 56). Regioselective reaction between 4,5-furanobenzyne **AI** and DMI proceeded smoothly to afford tetrahydrobenzofurodiazepinone derivative **169** as a sole isomer (Scheme 57).



Scheme 56



Scheme 57

6-4. Thienobenzynes

We developed various *o*-silylaryl triflate-type 6,7-thienobenzyne precursors, which were readily synthesized from 2,3-disubstituted 6-hydoxybenzo[*b*]thiophenes.[41] For instance, 6,7-thienobenzyne precursors **172a**–**c** were successfully synthesized in 4 steps including carbamate formation, deprotonative *C*-silylation, removal of the carbamate group, and *O*-triflation (Figure 17). Another 6,7-thienobenzyne precursor **172d** containing amide and chloro groups was prepared by 7-iodination of 6-hydoxybenzo[*b*]thiophene **171d**, *C*-silylation via magnesiation, and *O*-triflation (Scheme 58).

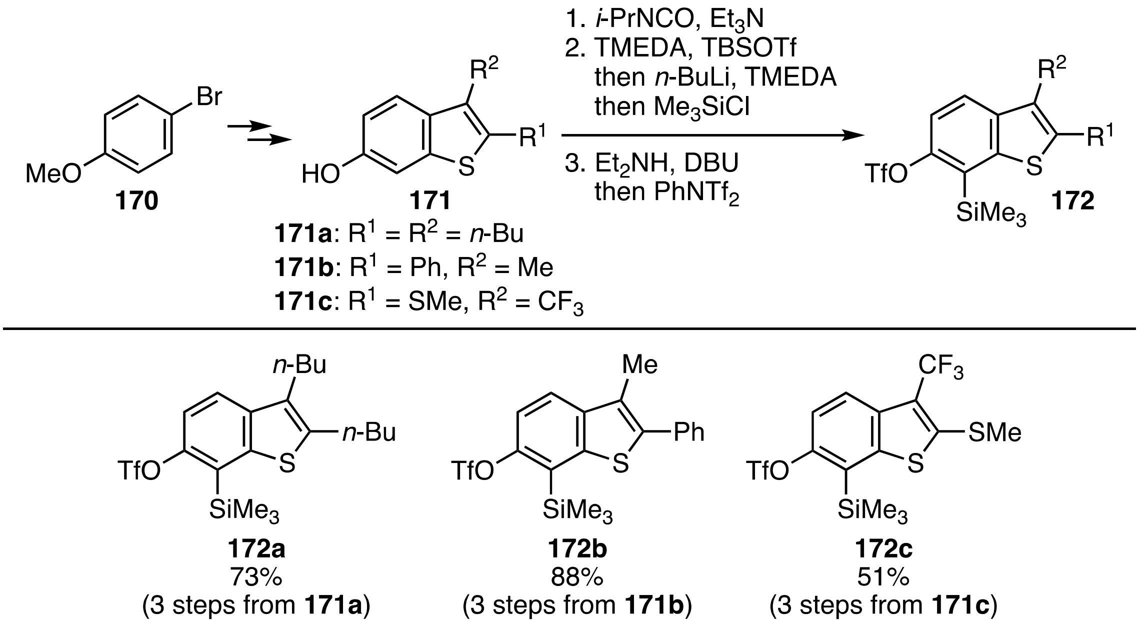
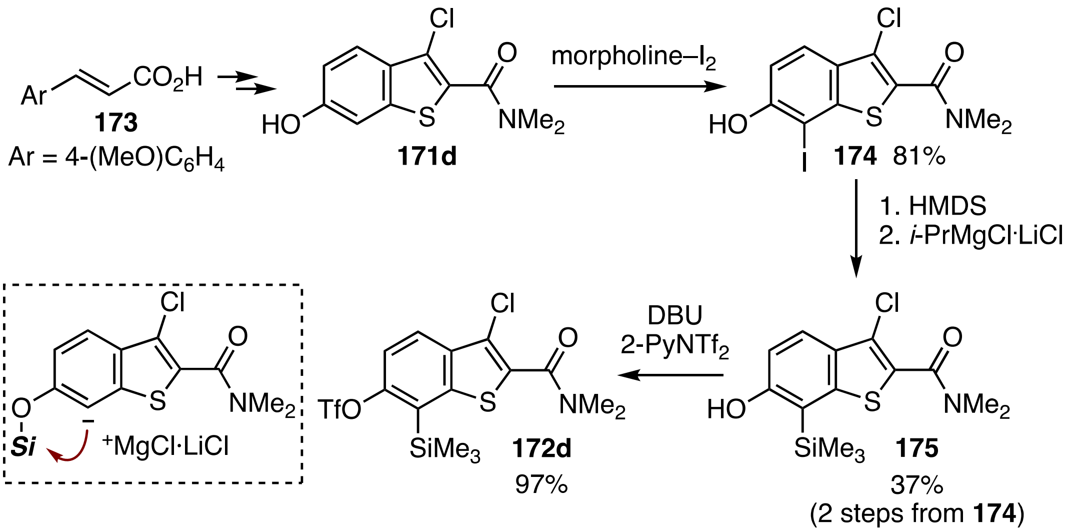


Figure 17



Scheme 58

Generation of 2,3-disubstituted 6,7-thienobenzynes was efficiently achieved by the treatment of precursors **172b**–**d** with a fluoride anion source (Figure 18). This approach was successfully applied to various transformations including cycloaddition with azide **89**, the Michaelis–Arbuzov-type reaction[42] (Scheme 59), and difunctionalizations with sulfilimine **178**,[43] sulfoximine **179**,[44] and sulfoxide **180**[45] (Scheme 60), enabling efficient preparation of diverse multisubstituted benzo[*b*]thiophene derivatives. In addition, using this method, we accomplished the synthesis of a potent analog of prostaglandin E receptor subtype 4 (EP4) antagonist.[46]

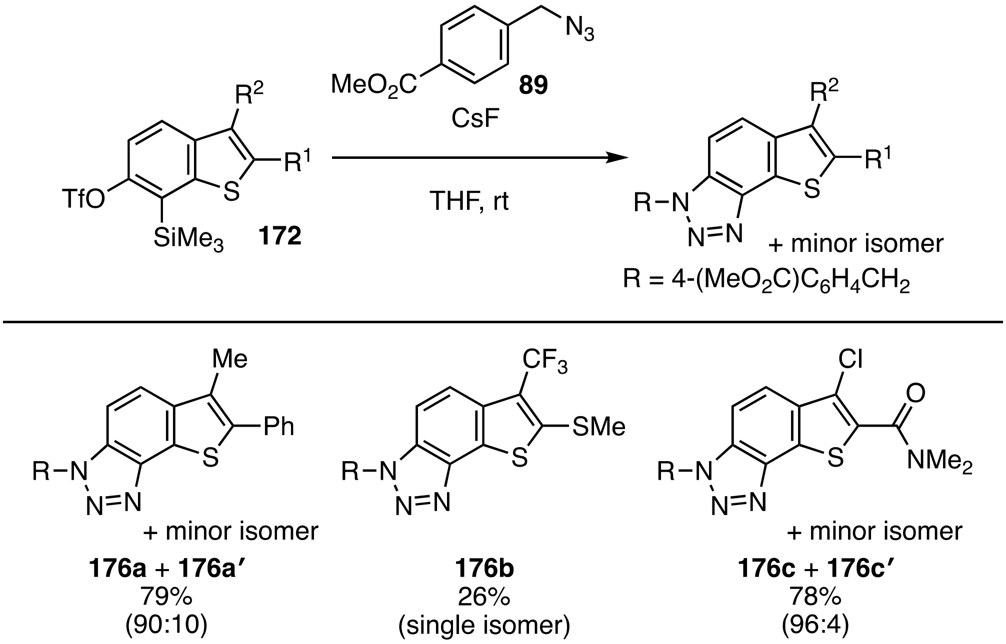
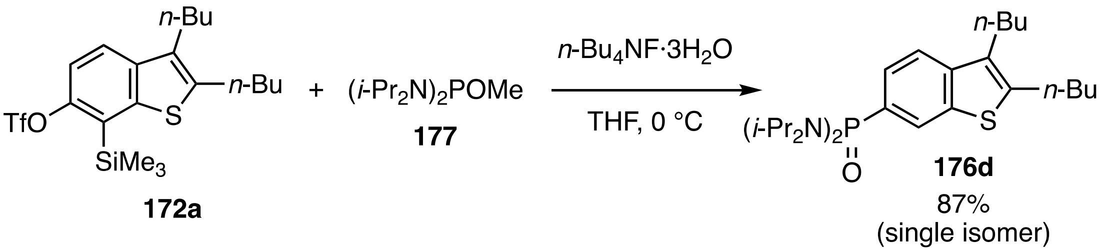
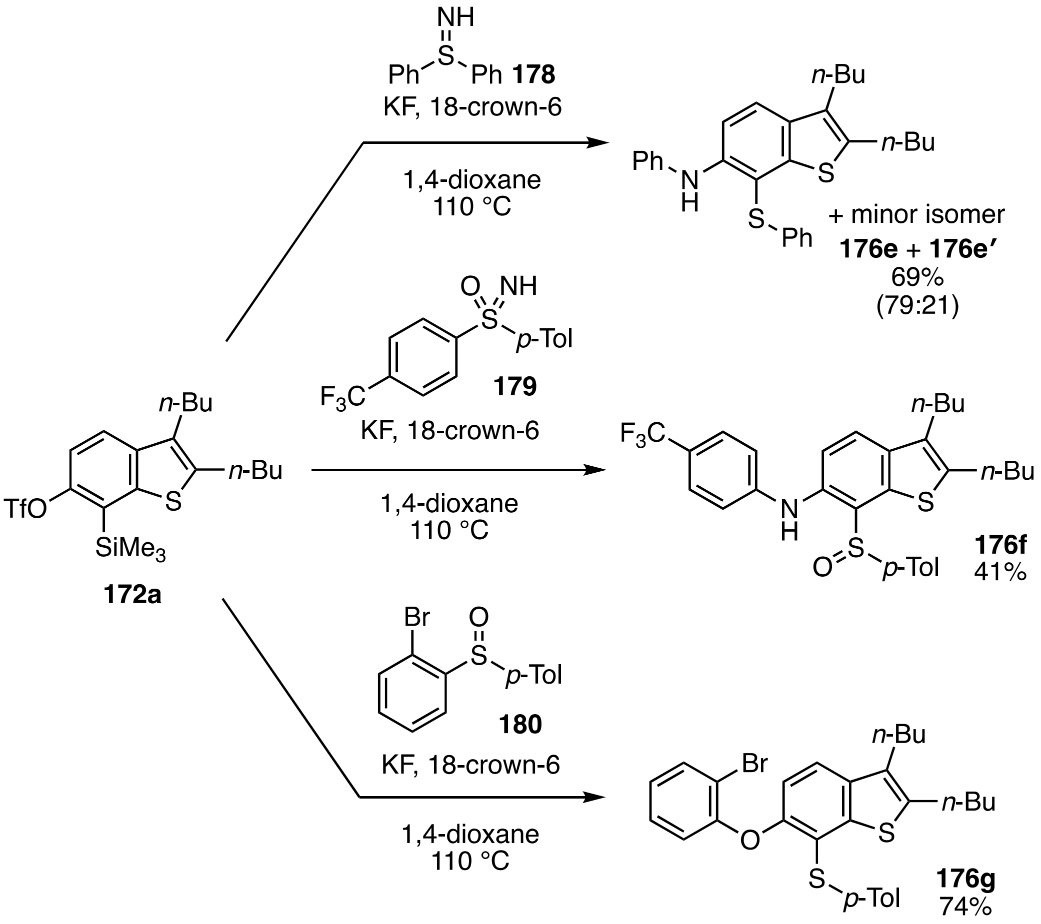


Figure 18



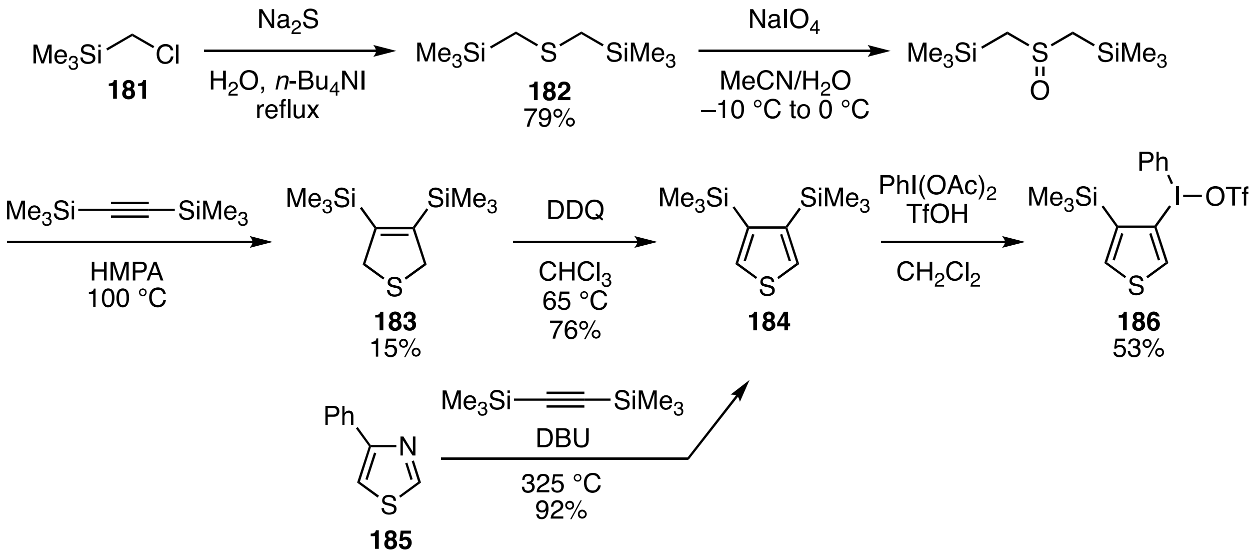
Scheme 59



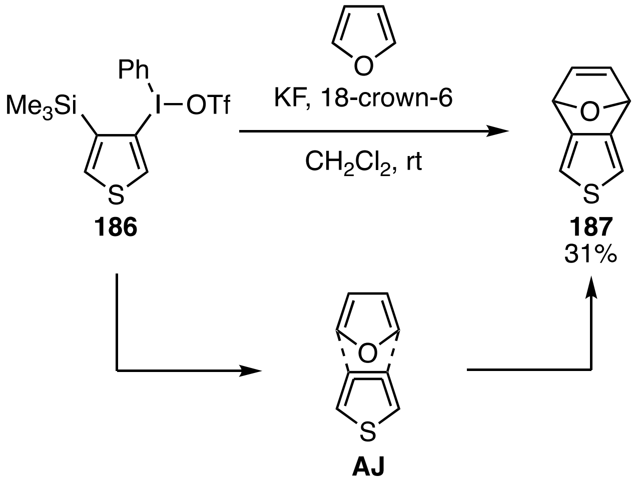
Scheme 60

6-5. 3,4-Didehydrothiophene generation from phenyl[4-(trimethylsilyl)-3-thienyl]iodonium triflate

Wong and coworkers reported that 3,4-didehydrothiophene (**AJ**) could be generated from phenyl[4-(trimethylsilyl)-3-thienyl]iodonium triflate (**186**), which was prepared from chloromethylsilane **181** or 4-phenylthiazole (**185**) (Scheme 61).[47] Treatment of the precursor **186** with potassium fluoride and 18-crown-6[48] in the presence of furan afforded cycloadduct **187** (Scheme 62).



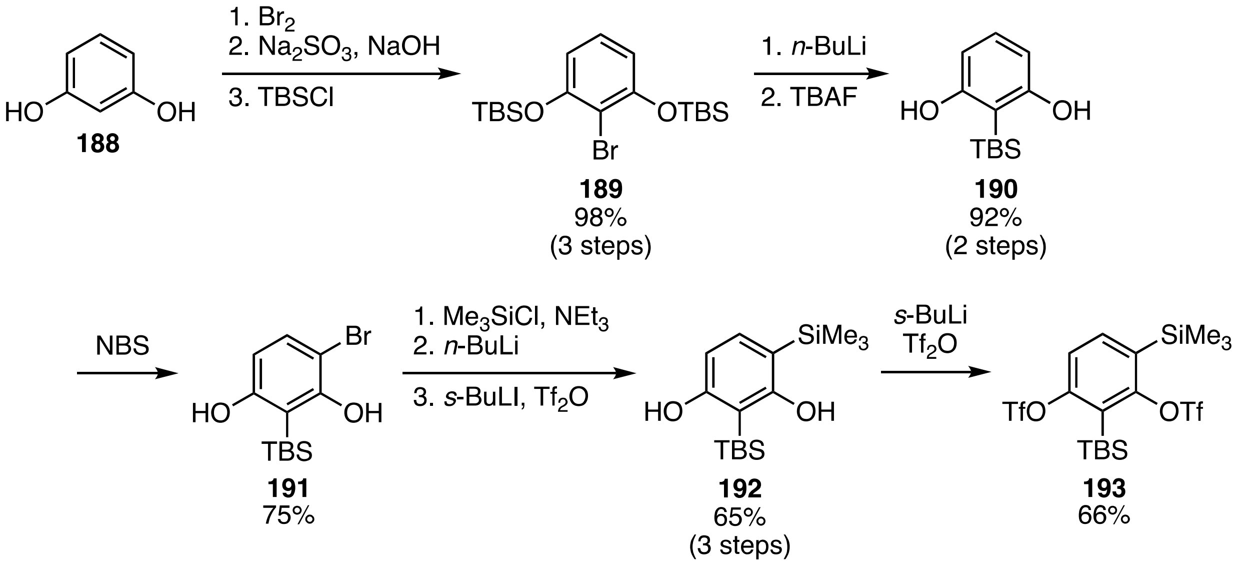
Scheme 61



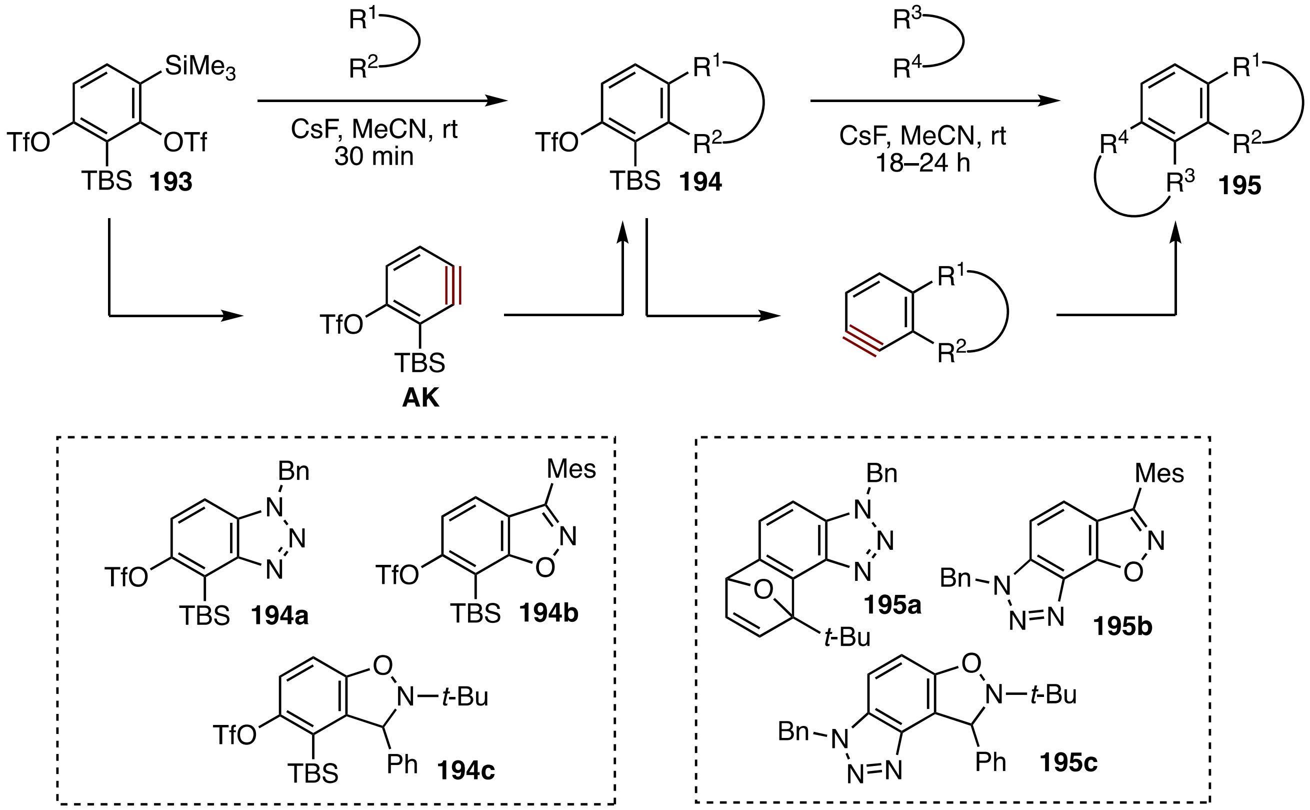
Scheme 62

6-6. Sequential aryne generations via hetarynes

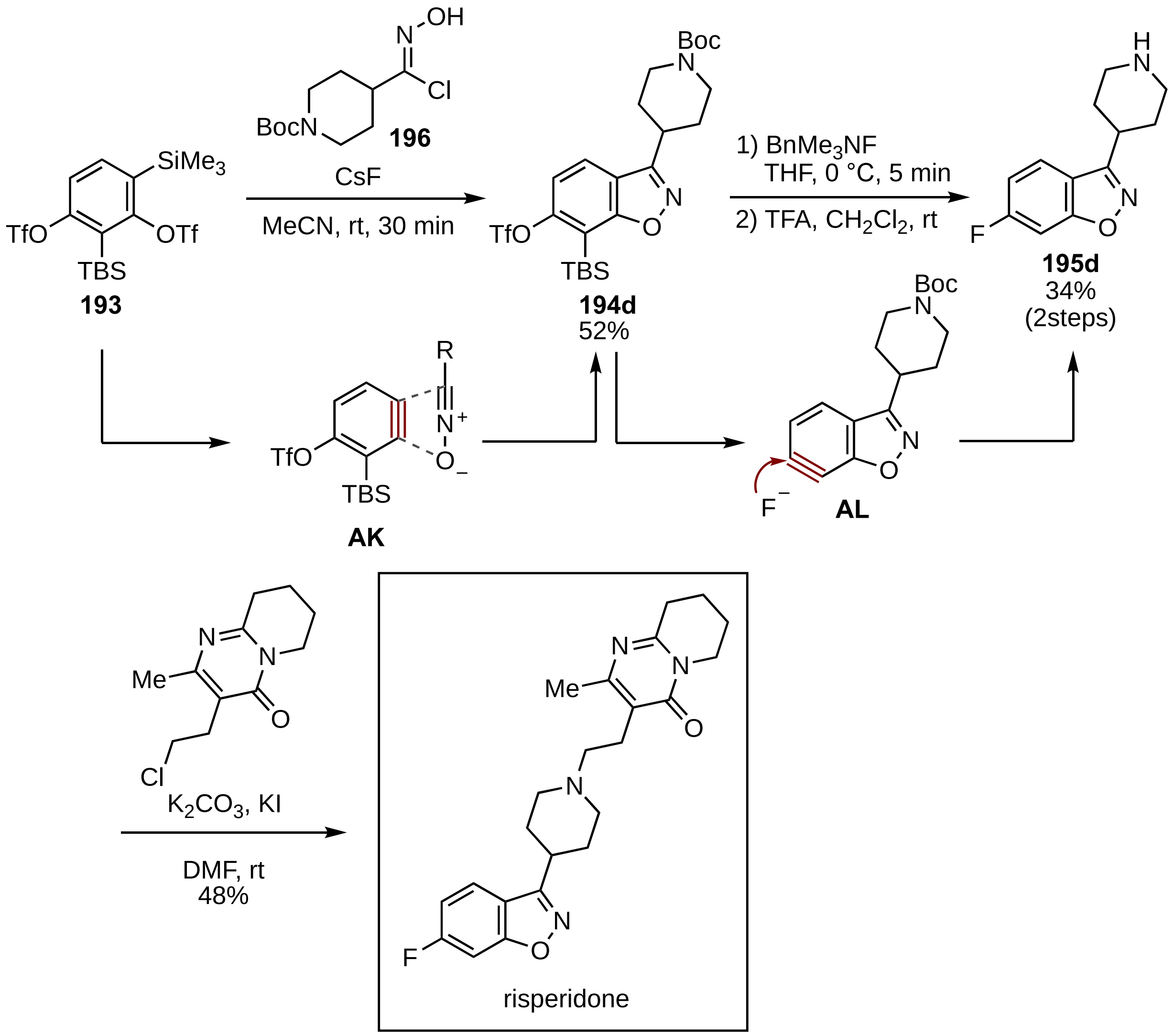
Since various heterocyclic skeletons can be constructed via the reactions of aryne intermediates, transformations of benzdiyne equivalents, which contain two aryne generation sites on the same benzene ring, enabled facile syntheses of complex heteroaromatic compounds via sequential generations of aryne species as shown in Chapter 5-1. Ikawa, Akai, and coworkers reported the synthesis of 1,3-benzdiyne equivalent **193** with two *o*-silylaryl triflate moieties from resorcinol (**188**) in 10 steps (Scheme 63).[49] They achieved transformations via benzotriazole-, benzisoxazole-, and dihydrobenzisoxazole-type arynes generated from precursors, which were obtained by cycloadditions of 3-silyl-4-(triflyloxy)benzyne **AK** selectively generated from 1,3-benzdiyne equivalent **193** by the treatment with cesium fluoride (Scheme 64). The group also demonstrated the utility of the method by the efficient synthesis of risperidone (Scheme 65).



Scheme 63

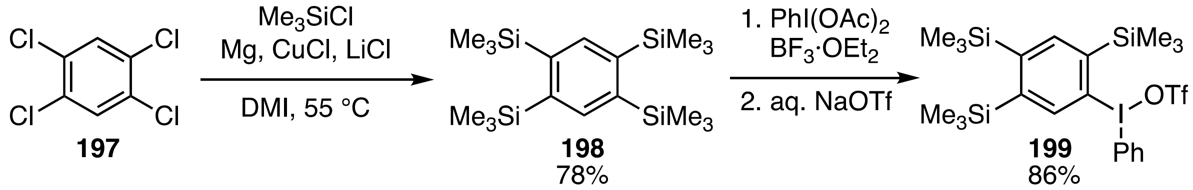


Scheme 64

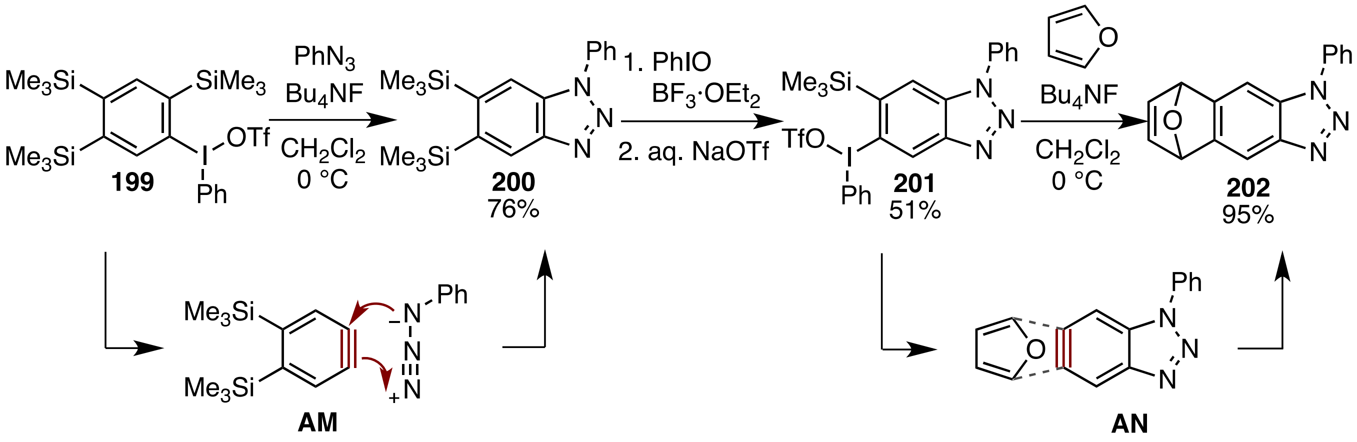


Scheme 65

Kitamura and coworkers developed a similar type of 1,4-benzdiyne equivalent **199**, which was prepared from 1,2,4,5-tetrachlorobenzene (**197**) in 3 steps (Scheme 66).[50a,b] Following the generation of 4,5-disilylbenzyne **AM** from **199** by fluoride activation in the presence of phenyl azide, the resulting disilylbenzotriazole **200** was transformed to *o*-silylaryliodonium triflate-type hetaryne precursor **201**, from which the hetaryne **AN** was efficiently generated to react with furan to afford naphthotriazole derivative **202** (Scheme 67).[50c]

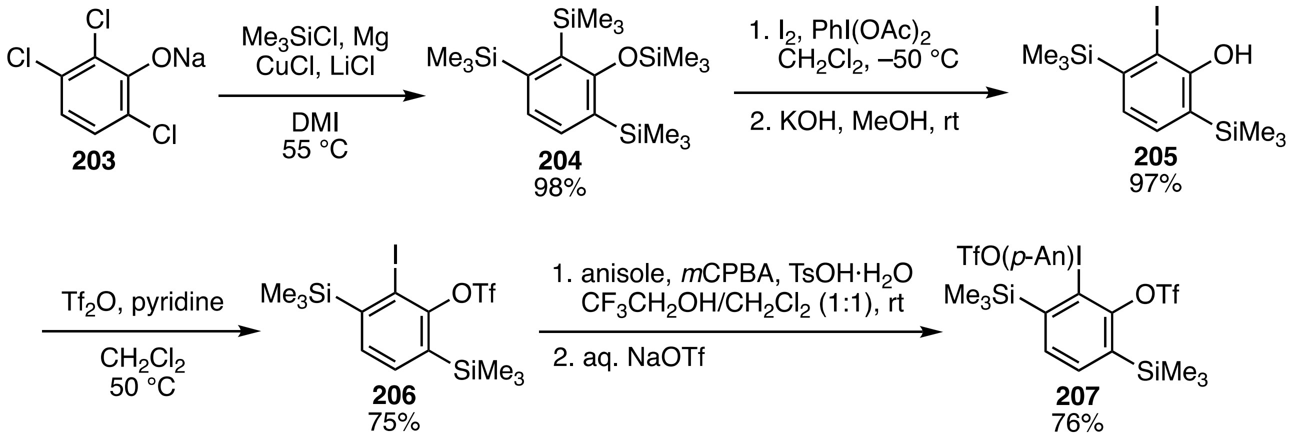


Scheme 66

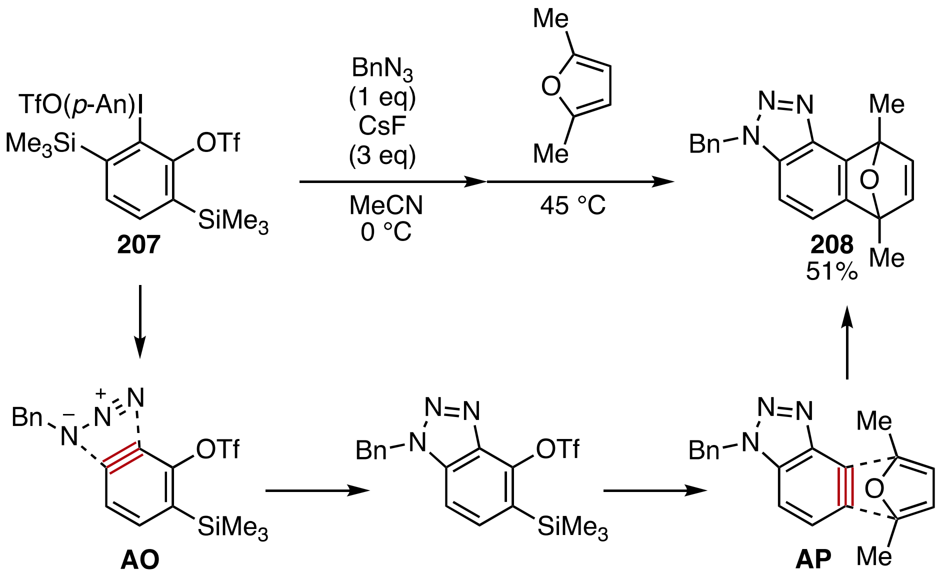


Scheme 67

Kitamura and coworkers also developed 1,3- and 1,4-benzdiyne equivalents containing *o*-silylaryliodonium triflate-type and *o*-silylaryl triflate-type aryne generation moieties, which enabled sequential generation and transformations of arynes in one-pot. For example, 1,3-benzdiyne equivalent **207** was prepared from sodium 2,5,6-trichlorophenoxide (**203**) in 6 steps (Scheme 68).[51] Treatment of **207** with a fluoride anion at 0 °C resulted in a selective generation of aryne at the *o*-silylaryliodonium triflate moiety to react with the first arynophile such as benzyl azide (Scheme 69). Successive addition of the second arynophile, such as furan, and heating the reaction mixture at 45 °C resulted in generation of a second aryne intermediate, such as triazolobenzyne **AP**, to afford the doubly cyclized product **208**.



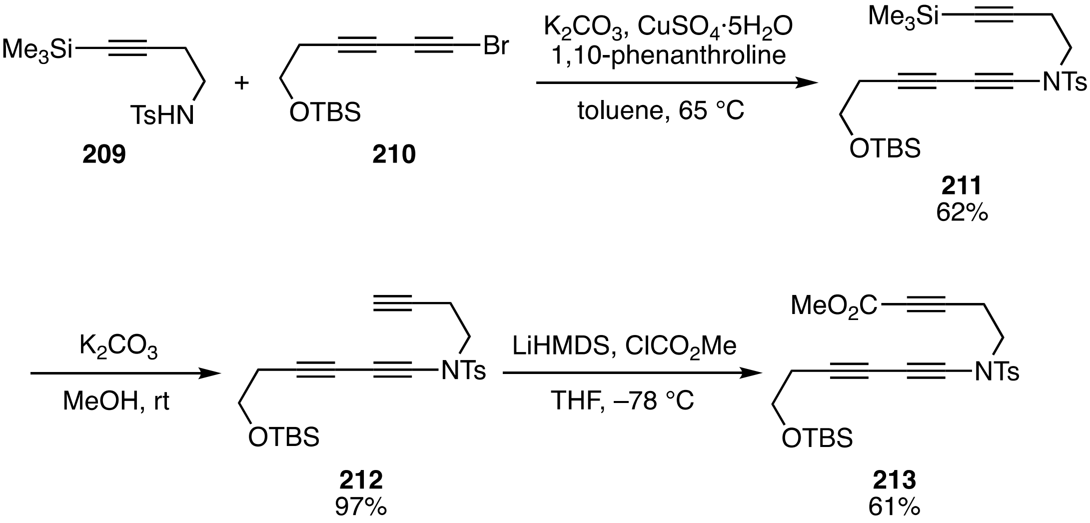
Scheme 68



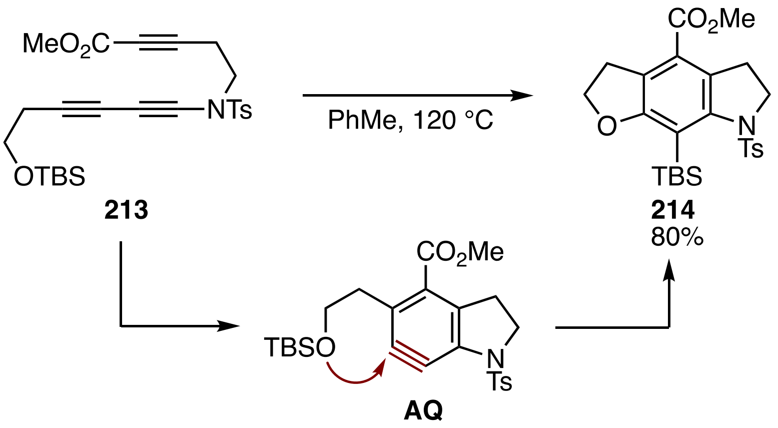
Scheme 69

7. HETARYNE GENERATION BY HEXADEHYDRO-DIELS–ALDER REACTION

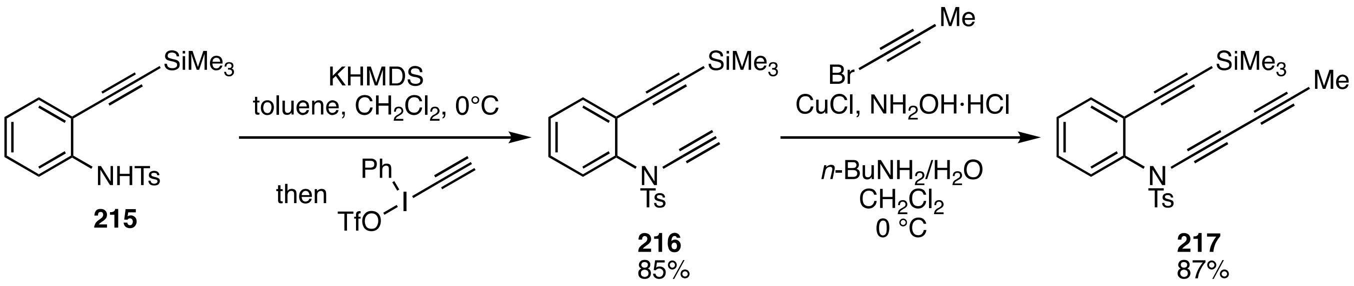
Recent improvements concerning transformations via the HDDA reaction also allowed for the synthesis of a wide range of heterocyclic compounds through various hetarynes. For instance, Hoye and coworkers reported that the HDDA reaction of ynamide-type triyne **213**, prepared from amide **209** and 1-bromo-1,3-diyne **210** (Scheme 70), proceeded at 120 °C to form indoline-type aryne **AQ**, which underwent intramolecular oxysilylation to afford tricyclic compound **214** (Scheme 71).[52a]



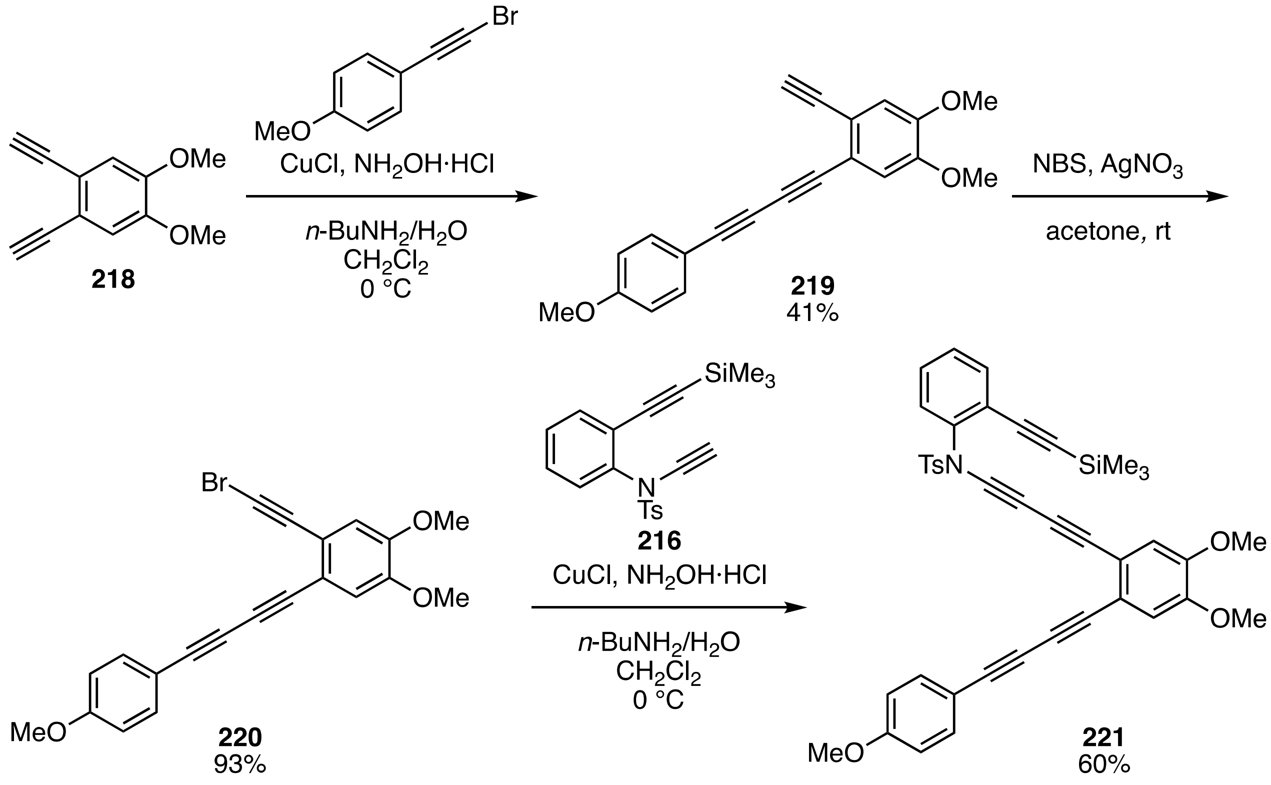
Scheme 70



Scheme 71

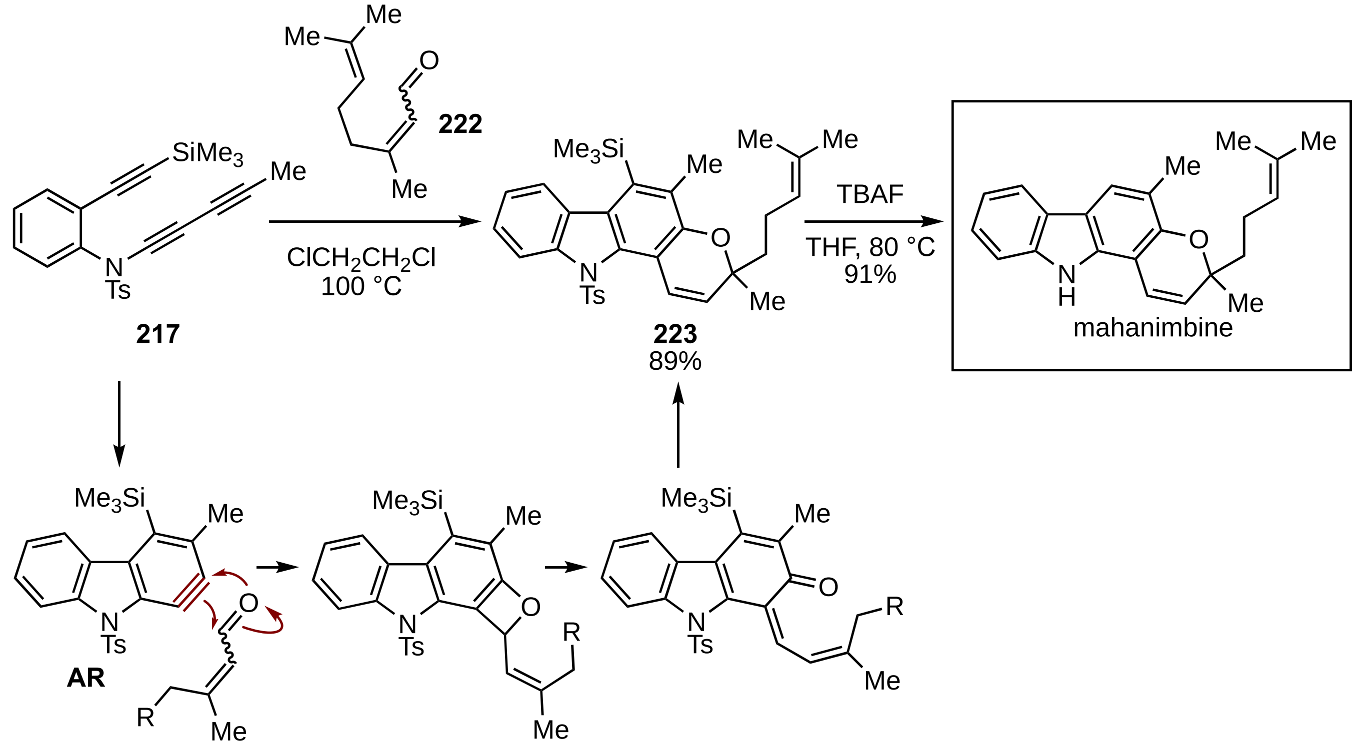


Scheme 72

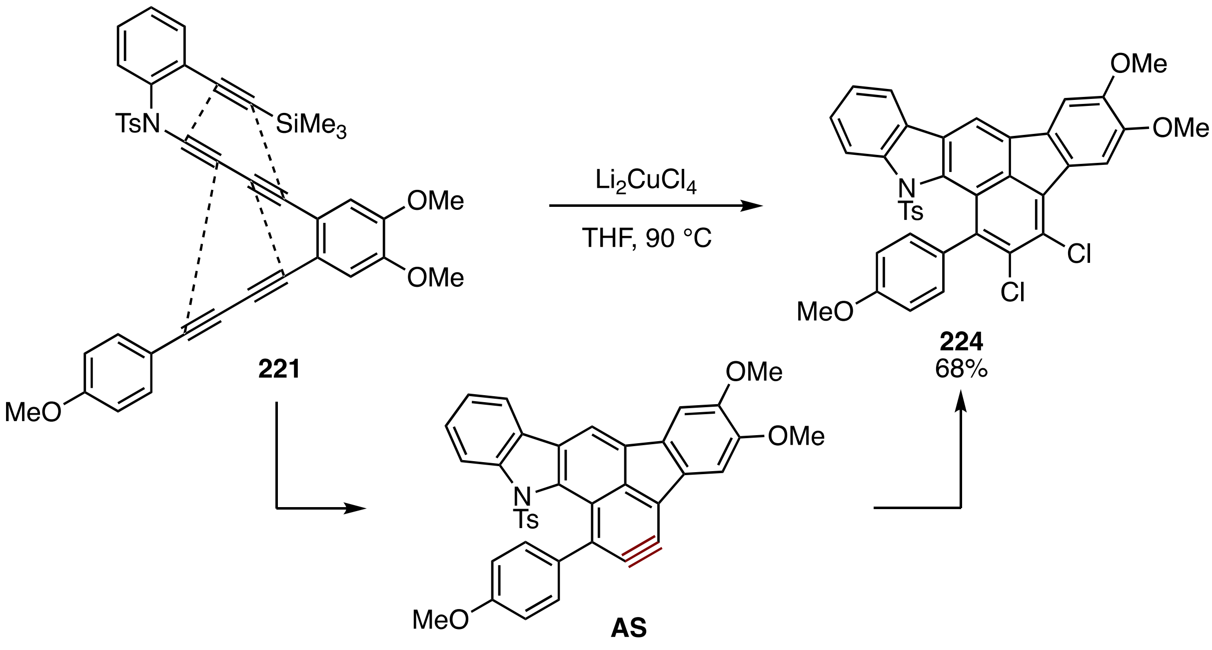


Scheme 73

Moreover, heating the ynamide-type triyne **217** and pentayne **221**, prepared from *N*-tosylanilide **216** (Schemes 72 and 73), also resulted in the generation of carbazole-type arynes **AR** and **AS**, respectively, enabling the synthesis of carbazole derivatives such as **223** and **224** (Schemes 74 and 75).[52b,c] These results clearly indicate the utility of HDDA reaction for the generation of a wide variety of complex hetarynes.



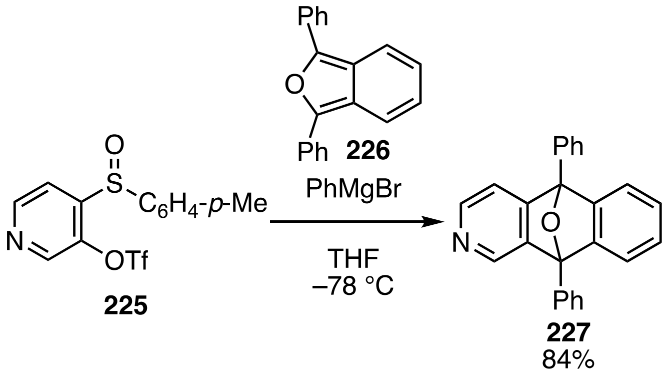
Scheme 74



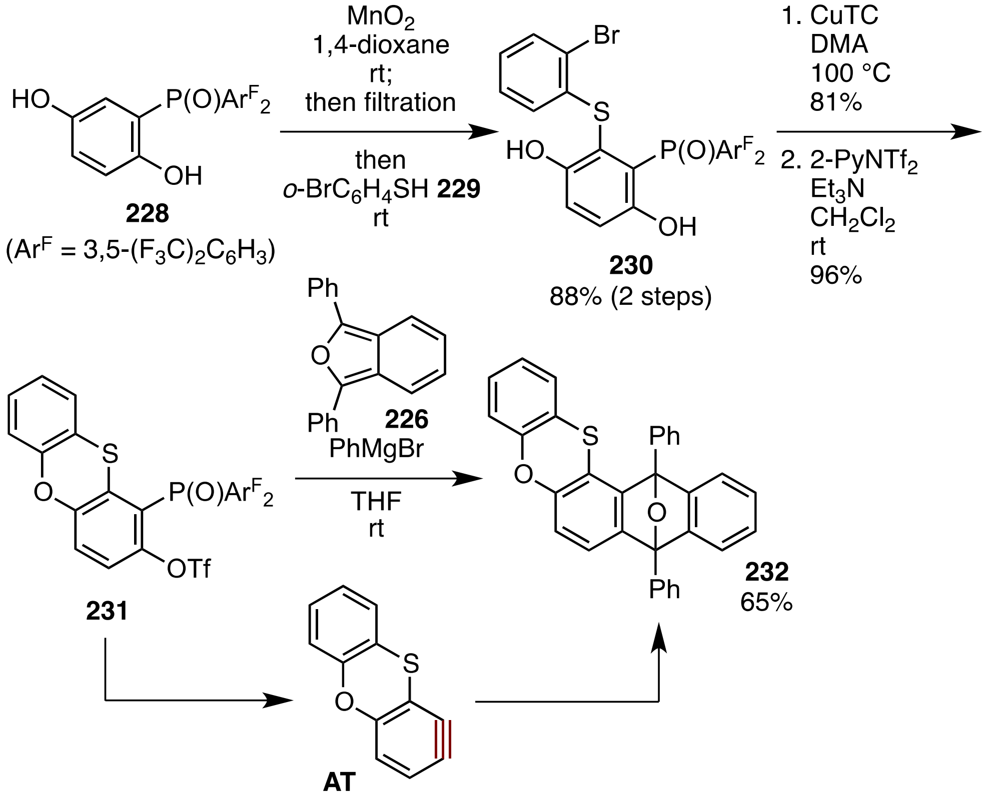
Scheme 75

8. OTHER HETARYNE GENERATION

Our original aryne generation methods were applicable to the generation of several hetarynes. For instance, 3,4-pyridyne could be efficiently generated from *o*-sulfinylaryl triflate-type precursor **225** by the treatment with a phenyl Grignard reagent (Scheme 76).[53] We also developed an aryne generation method involving a C–P bond cleavage, which was successfully applied for the generation and transformation of phenoxathiin-type aryne **AT** (Scheme 77).[54] Since the aryne precursor **231** was prepared easily from 2-phosphinyl-1,4-dihydroquinone **228** by a regioselective 1,4-addition of thiol **229** and subsequent copper-mediated cyclization followed by triflylation, this method would be useful for the synthesis of a broad range of heterocyclic compounds.



Scheme 76



Scheme 77

9. CONCLUSION

The present review summarized remarkable recent advances in the synthetic hetaryne chemistry, which have enabled facile preparation of multisubstituted heteroaromatic compounds. Since a wide variety of transformations involving aryne intermediates have also been developed in recent years, diverse heteroaromatic compounds have become readily accessible utilizing the hetaryne toolbox. In particular, various orthogonal methods to generate hetarynes from different types of precursors would enable syntheses of complex heteroaromatic products in a modular manner.

ACKNOWLEDGEMENTS

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