Review

Transition-Metal-Free Activation of Amide Bond by Arynes

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Abstract: Highly reactive arynes activate the N–C and C=O bonds of amide groups under transition metal-free conditions. This review highlights the insertion of arynes into the N–C and C=O bonds of the amide group. The insertion of arynes into the N–C bond gives the unstable four-membered ring intermediates, which are easily converted into *ortho*-disubstituted arenes. On the other hand, the selective insertion of arynes into the C=O bond is observed when the sterically less-hindered formamides are employed to give a reactive transient intermediate. Therefore, the trapping reactions of transient intermediates with a variety of reactants lead to the formation of oxygen atom-containing heterocycles. As relative functional groups are activated, the reactions of arynes with sulfinamides, phosphoryl amides, cyanamides, sulfonamides, thioureas, and vinylogous amides are also summarized.

Keywords: amide; arynes; insertion; activation; heterocycles; organic synthesis; multi-component coupling reaction

1. Introduction

In recent years, the use of arynes as highly reactive and strained intermediates in organic synthesis has attracted substantial attention [1–15]. Arynes have been extensively utilized in transition-metal-catalyzed reactions [16,17]. The development of *ortho*-trimethylsilyl aryltriflates **1** as mild aryne precursors led to growing activity in this field (Scheme 1) [18]. Arynes **A** can be generated in situ from triflate **1** and fluoride ion under mild reaction conditions. Therefore, the aryne chemistry using aryltriflates **1** has achieved some remarkable success, particularly in the transition metal-free reactions.
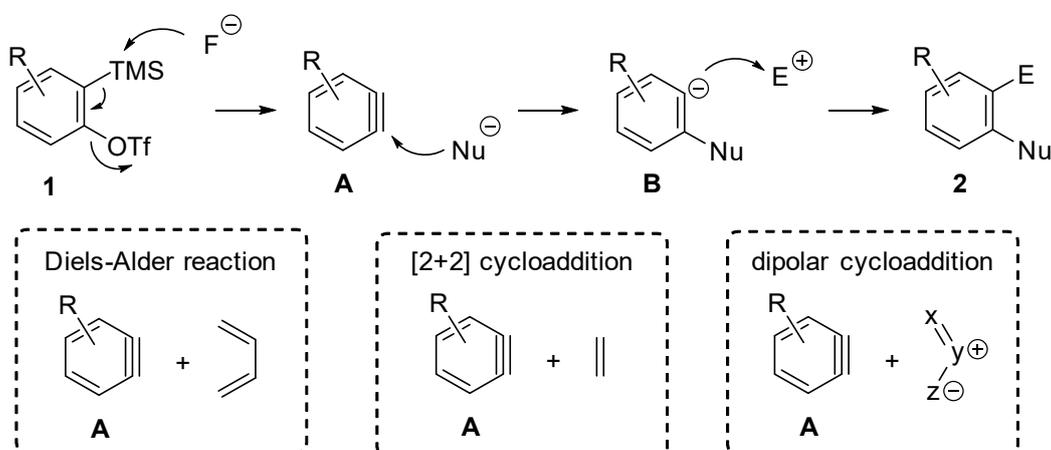

Scheme 1. Transition metal-free reaction of arynes.

Most of transition metal-free reactions proceed through the addition of nucleophiles to arynes **A** and the subsequent trapping of intermediates **B** with electrophiles to give multi-substituted arenes with structural diversity and complexity. The transition metal-free concerted reactions, such as the Diels-Alder reaction, [2 + 2] cycloaddition reaction, and dipolar cycloaddition reaction, are also synthetically useful [6,7,11,12].

When the nitrogen atom of amides acts as nucleophiles toward arynes, the insertion of arynes into the N–C bond is induced to give the N–C insertion products **3**, via the formation of four-membered ring intermediates, **C** (Scheme 2). In contrast, insertion into the C=O bond is promoted by the nucleophilic addition of the oxygen atom of amides to arynes (Scheme 3). In the C=O insertion reaction, the four-membered ring intermediates **D** and *ortho*-quinone methides **E** are highly reactive [19,20]; thus, a variety of further transformations using **D** or **E** have been developed as multi-component coupling reactions [9]. As shown in Section 3 with the C=O bond activation, the suitable amides for C=O insertion are the sterically less-hindered formamides, such as *N,N*-dimethylformamide (DMF).

Insertion into N-C bond of amides
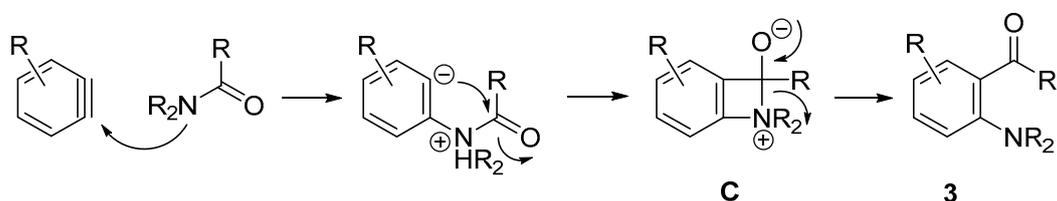

Scheme 2. Activation of amide N–C bond by arynes.

Insertion into C=O bond of formamides

Further Transformations

Multi-component coupling reactions
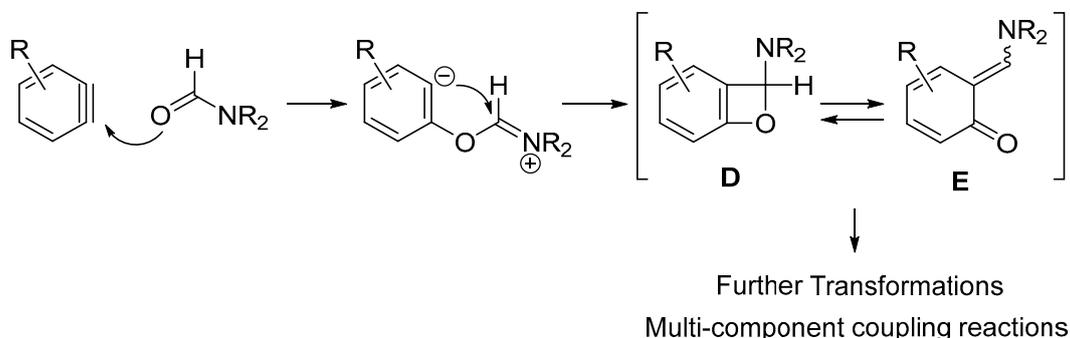
**Scheme 3.** Activation of amide C=O bond by arynes.

2. N–C Bond Activation

At first, the insertion of arynes into the N–C bond of the amide group was reported in the reaction of ureas with arynes [21]. In the presence of CsF, treatment of 3-methoxy-2-(trimethylsilyl) phenyl triflate **4** as an aryne precursor with 1,3-dimethyl-2-imidazolidinone (DMI) **5** gave 1,4-benzodiazepine derivative **6** in 77% yield (Scheme 4). Under similar reaction conditions, *N,N′*-dimethylpropyleneurea (DMPU) **7** worked well to give 1,5-benzodiazocine derivative **8**. The insertion of aryne into the N–C bond of acyclic *N,N,N′,N′*-tetramethylurea **9** also proceeded. In these reactions, aryne is generated by the reaction of triflate **4** with the fluoride anion of CsF. The sequential transformation is achieved via a route involving the addition of the urea nitrogen atom to an aryne, followed by the intramolecular nucleophilic attack on the carbonyl carbon atom. The resulting four-membered ring intermediate readily undergoes ring opening to afford the N–C insertion products **6**, **8**, and **10**.
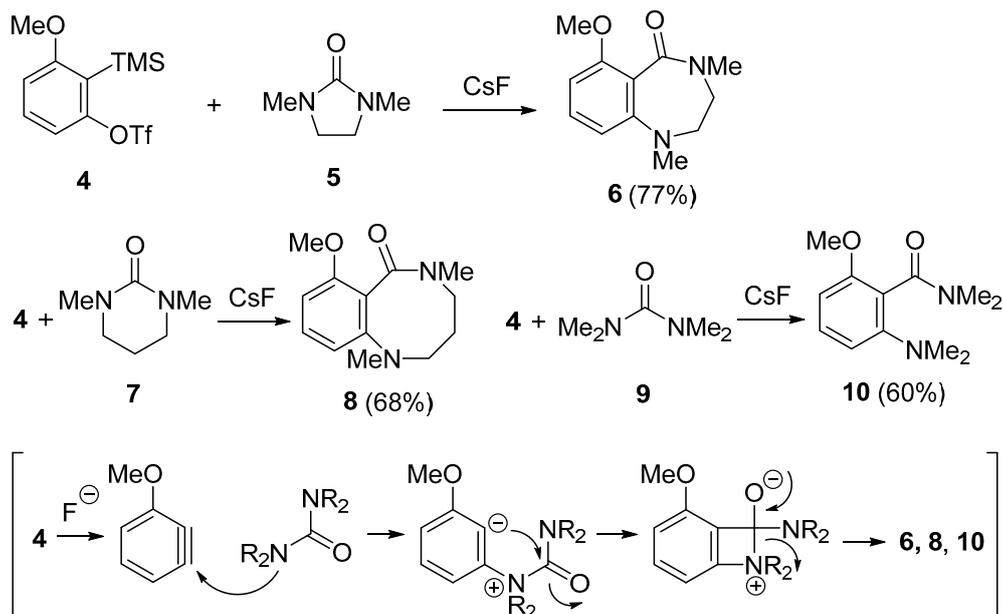
Scheme 4. Reaction of ureas with aryne.

The reaction of pyridynes with ureas was studied [22]. In the presence of CsF, the reaction of 4-triethylsilyl-3-trifluoromethanesulfonyloxypyridine **11** as a 3,4-pyridyne precursor with DMI **5** gave pyridodiazepine derivatives **12** and **13** in 86% yield and a ratio of 65:35 (Scheme 5). High regioselectivity was obtained by using the 3,4-pyridyne precursor **14** having a methoxy group at the 2-position to give the product **15**, selectively. The use of DMPU **7** instead of DMI **5** led to the formation of the corresponding pyridodiazocine, **16**. When 1-methyl-2-oxazolidone **17** was employed, the selective insertion into the N–C bond of **17** proceeded to give pyridooxazepine **18**.
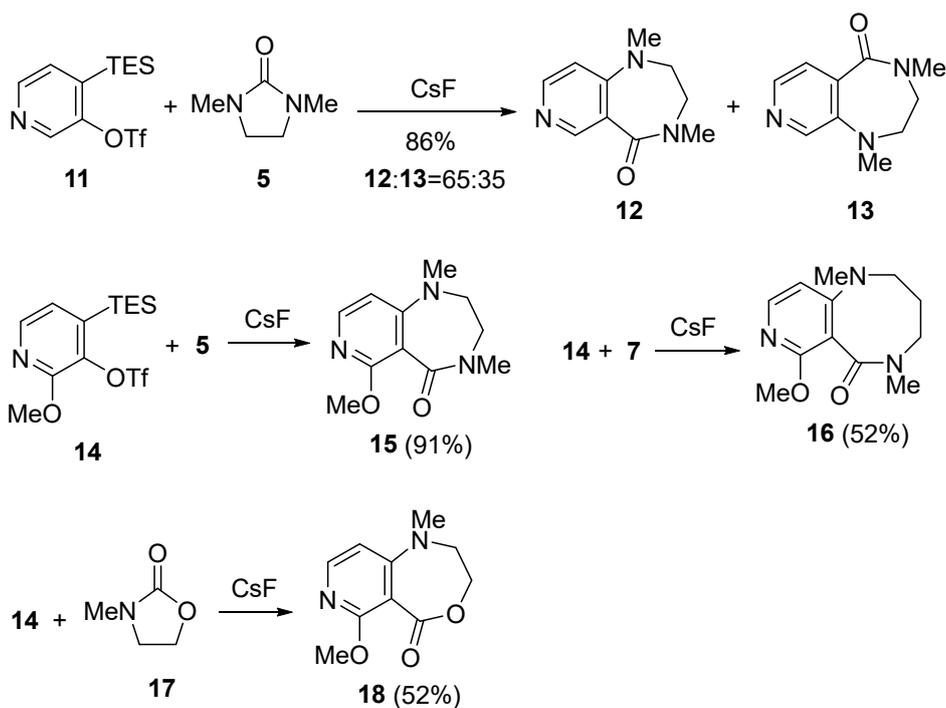

Scheme 5. Insertion of pyridynes into N–C bond.

The reaction of DMI **5** with 4,5-benzofuranyne precursor **19** was also studied (Scheme 6) [23]. The N–C insertion product **20** was regioselectively obtained in 90% yield as a result of the initial attack of DMI **5** at C5 of 4,5-benzofuranyne.
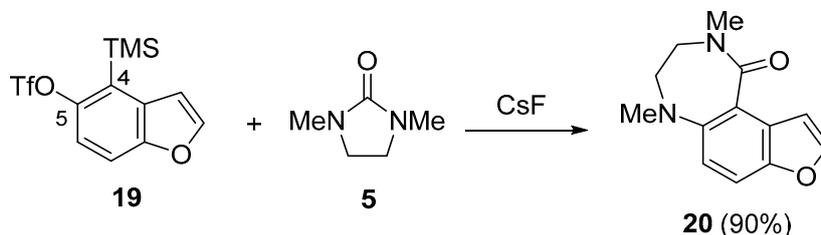

Scheme 6. Insertion of 4,5-benzofuranyne into N–C bond.

It is reported that silylaryl bromides and iodides can be used as aryne precursors under the conditions similar to those employed for silylaryl triflates, such as precursors **4**, **11**, and **19** [24]. The utility of silylaryl bromides **21a–c** was demonstrated in the N–C bond reaction (Scheme 7). In the presence of tetramethylammonium fluoride (TMAF), 1-bromo-3-methoxy-2-(dimethylsilyl) benzene **21a** reacted with DMPU **7** to give **22a** in 64% yield. Silylaryl bromides **21b** and **21c** also worked well.
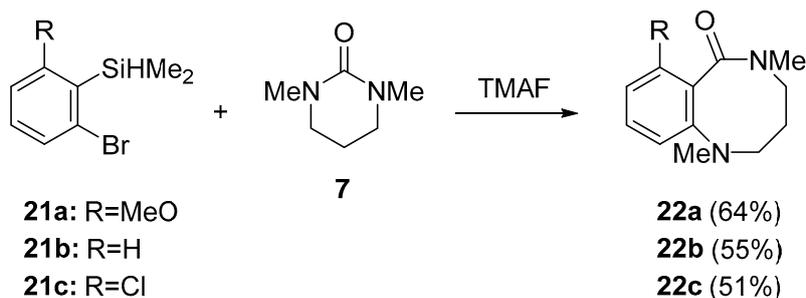

**Scheme 7.** Reaction of silylaryl bromides **21a–c** with DMPU **7**.

The insertion of arynes into the N–C bond of *N*-phenyltrifluoroacetamides proceeded effectively [25]. In the presence of CsF, the reaction of *N*-phenyltrifluoroacetamide **24a** with triflate **23** as an aryne precursor gave the N–C insertion product **25a** in 77% yield (Scheme 8). The substituted *N*-aryltrifluoroacetamides **24b–d** also afforded the corresponding products **25b–d** in good yields. Since the CF$_3$ group on amides is critical to the success of these transformations, they propose the reaction mechanism involving the abstraction of the hydrogen on amide nitrogen by fluoride anion as a base. The products **25a–d** are obtained via the attack of amide nitrogen anion to aryne, the intramolecular trapping process with the carbonyl carbon atom, and the four-membered ring opening.
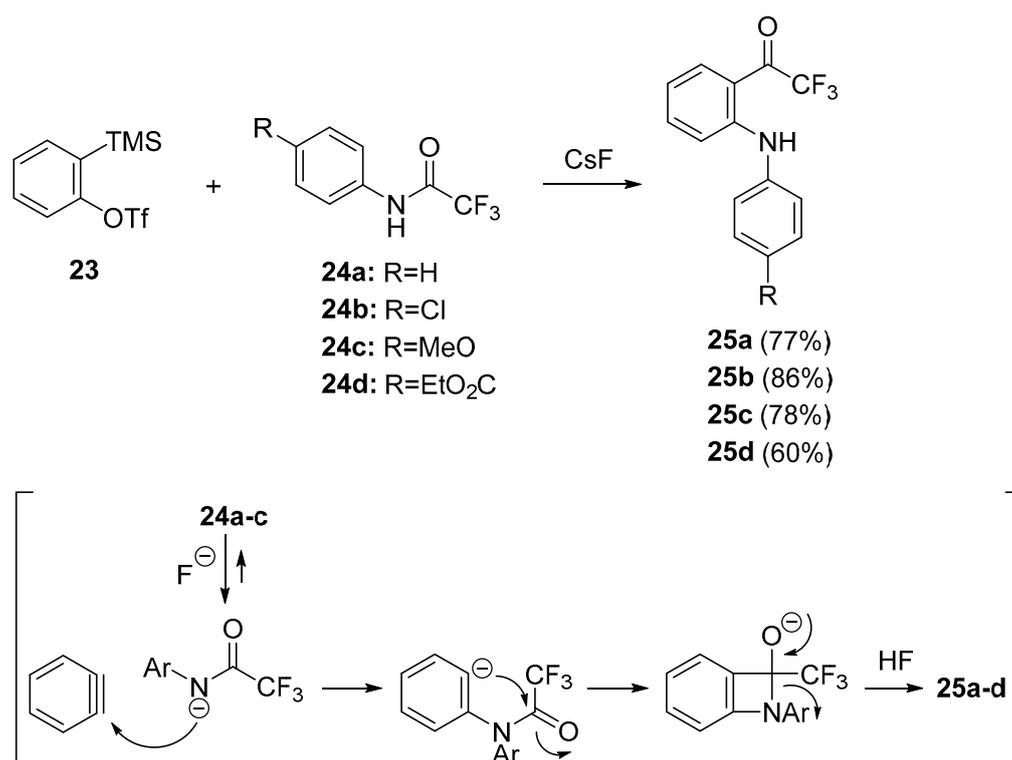
Scheme 8. Reaction of *N*-phenyltrifluoroacetamides with aryne.

To develop the amide insertion reaction having broad utility, the reaction of *N*-pivaloylaniline **26a** with triflate **23** was investigated by changing solvents and fluoride sources [26]. Employing tetrabutylammonium triphenyldifluorosilicate (TBTA) as a fluoride source, amide **26a** underwent the N–C insertion in toluene at 50 °C to afford the *tert*-butylketone **27a** in 64% yield (Scheme 9). Exploration of substrate scope showed that *N*-phenyl derivatives **26b** and **26c** were similarly efficient substrates.
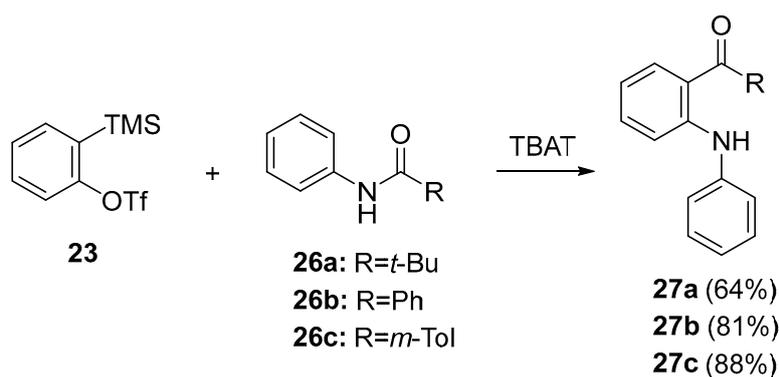

Scheme 9. Reaction of *N*-phenyltrifluoroacetamides with aryne.

Additionally, this reaction was applied to the synthesis of acridones and acridines (Scheme 10). The one-step synthesis of acridone **29** was achieved by the reaction of *ortho*-halobenzamide **28**, with triflate **23** under microwave irradiation at 120 °C in the presence of TBAT. Acridone **29** was formed via a route involving the N–C insertion, followed by the intramolecular S_NAr reaction. In contrast, acridine **31** was synthesized by a one-pot procedure using $BF_3 \cdot OEt_2$ via a route involving the N–C insertion of amide **30** into aryne, followed by a BF_3-mediated Friedel-Crafts acylation and dehydration.
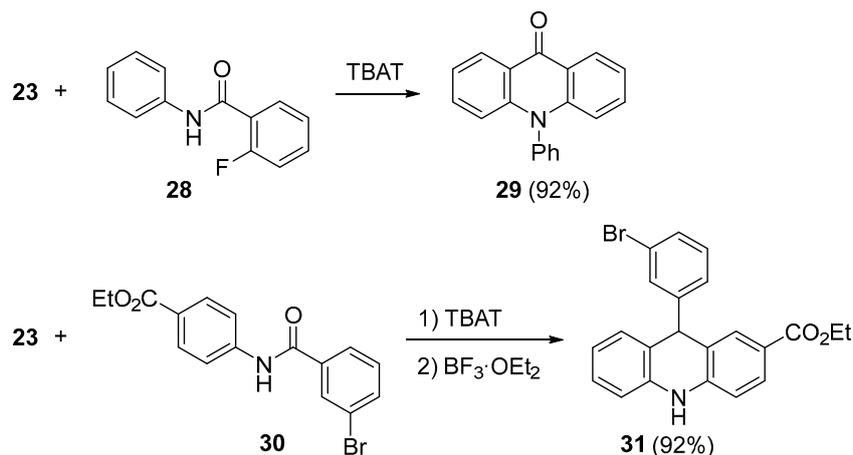
Scheme 10. Synthesis of acridone and acridine.

The reaction of β-lactam **32** with aryne gave acridone **29** in 50% yield by employing 3.5 equivalents of the aryne precursor **23** in the presence of CsF (Scheme 11) [27]. In this transformation, 2,3-dihydroquinolin-4-one **33** is formed as an intermediate as a result of N–C bond insertion of aryne into β-lactam **32**. In fact, **33** reacted under the same reaction conditions to give acridone **29** in 77% yield. The conversion of **33** into **29** will proceed through the *N*-arylation of **33** with second aryne, the subsequent cyclization, the extrusion of ethylene, and the final *N*-arylation with third aryne.
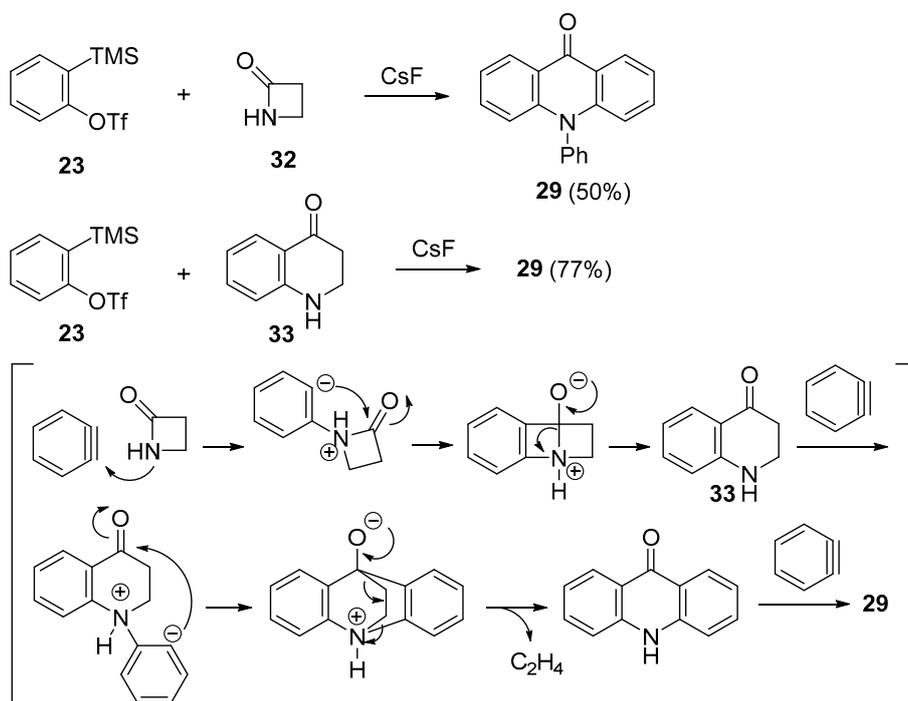
Scheme 11. Reaction of β-lactam with aryne leading to acridone.

The insertion of arynes into the N–C bond of imides was investigated [28]. The formation of simple *N*-arylated products could be suppressed when the reactions of imides **34a–d** with triflate **23** were carried out in toluene at 60 °C in the presence of TBAT (Scheme 12). The desired N–C insertion products **35a–d** were selectively obtained. Additionally, this reaction was applied to the one-pot synthesis of quinolone **36** through Camps cyclization using KOH and 18-crown-6.
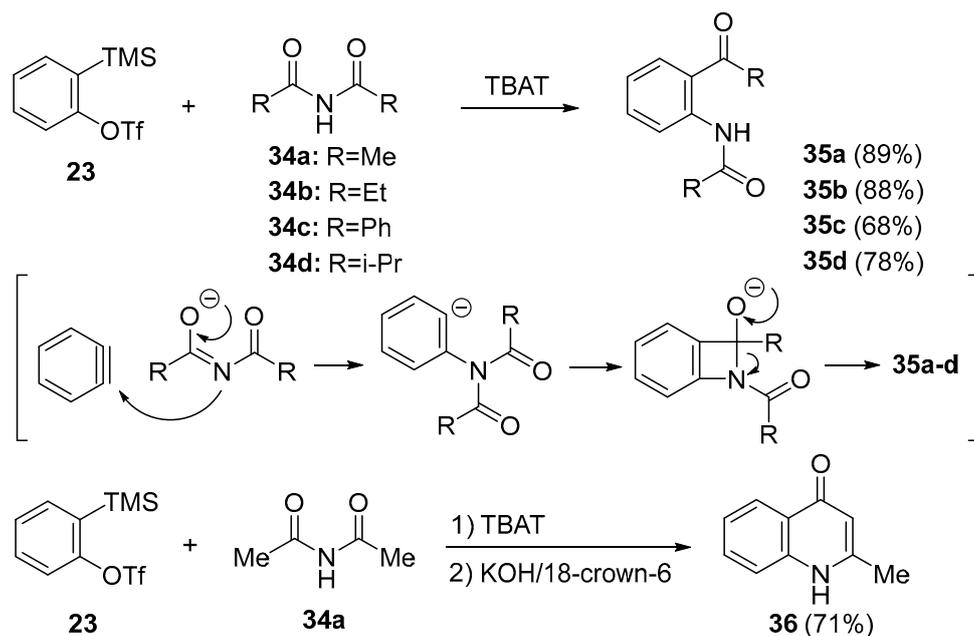
Scheme 12. Reaction of imides with aryne.

## 3. C=O Bond Activation

At first, the insertion of arynes into the C=O bond of the amide group was reported [29]. Aryne, generated from precursor **37**, reacted with *N,N*-dimethylformamide (DMF) to give salicylaldehyde **38** in 32% yield (Scheme 13).
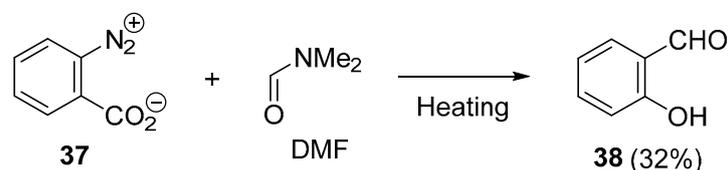
Scheme 13. Reaction of *N,N*-dimethylformamide with aryne.

When the bulky *N,N*-dimethylacetamide (DMA) was used, competitive insertion into the C=O and N–C bonds of DMA was observed [30]. In the presence of TBAF, treatment of **4** with DMA gave the C=O insertion product **39** in 34% yield, and the N–C insertion product **40** in 10% yield (Scheme 14). This result indicates that the sterically less-hindered formamides are the suitable nucleophiles for C=O insertion. The insertion into the C=O bond will proceed via the stepwise mechanism involving the addition of the oxygen atom of amide to an aryne, followed by the intramolecular nucleophilic attack on the iminium.
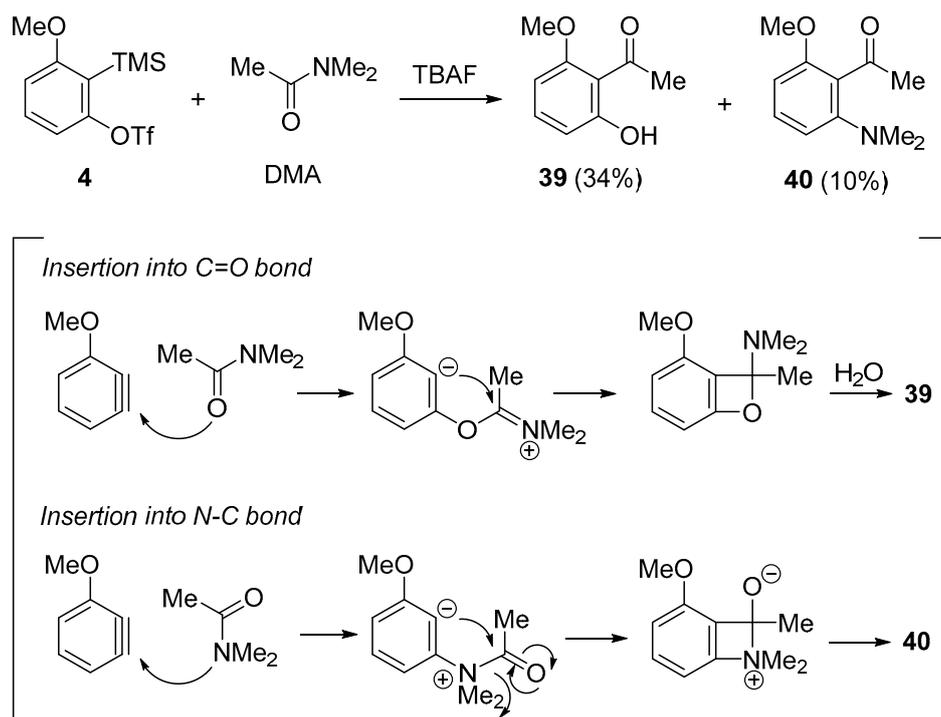
Scheme 14. Reaction of *N,N*-dimethylacetamide with aryne.

The sequential reaction involving the trapping process of transient intermediates with organometallic reagents was studied [30,31]. After a solution of triflate **4** in DMF was stirred in the presence of CsF, a solution of Et$_2$Zn in hexane was added to the reaction mixture (Scheme 15). The desired aminophenol **41** was obtained in 71% yield. Diethyllzinc also trapped the transient intermediate generated from triflate **4** and formamide **42,** to give the aminophenol **43** by a one-pot procedure.
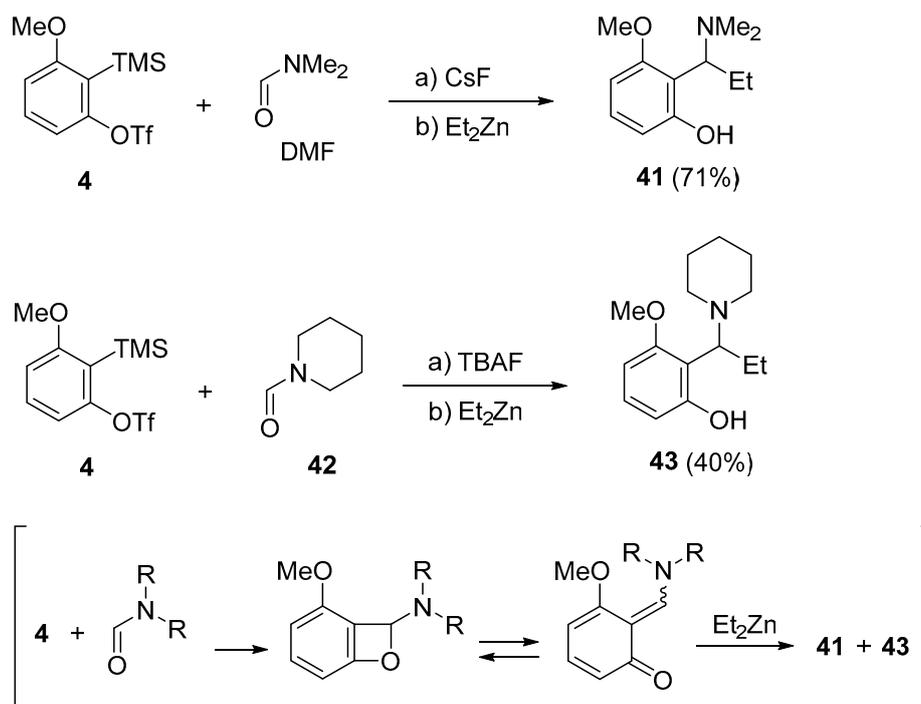
Scheme 15. Reaction for trapping the transient intermediates.

Three-component sequential coupling of arynes, DMF, and diaryliodonium salts was studied [32]. In the presence of KF, a three-component coupling reaction was found using triflate **23** and diphenyliodonium triflate **44** in DMF-facilitated 2-phenoxybenzaldehyde **45** in 87% yield (Scheme 16). In this transformation, diphenyliodonium triflate **44** acted as an electrophile by trapping the oxygen atom of a transient intermediate.
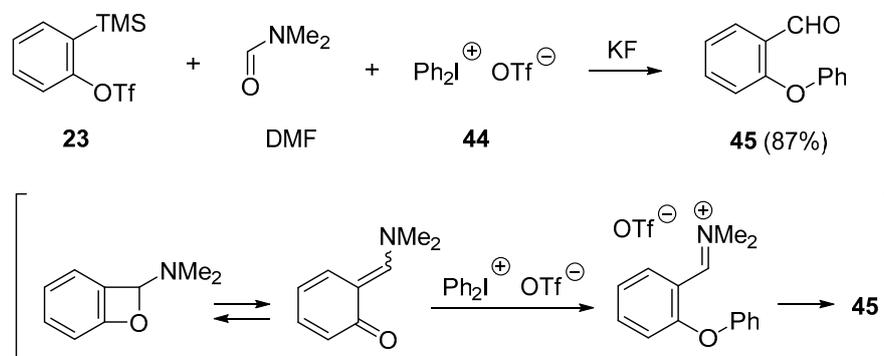
Scheme 16. Trapping reaction using diphenyliodonium salt.

The 2:1 coupling reaction of two molar amounts of aryne and one molar amount of DMF was reported (Scheme 17) [33]. Initially, the reaction of precursor **23** and DMF gives salicylaldehyde **38** via the hydrolysis of a transient intermediate. 9-Hydroxyxanthene **46** is formed by the reaction of salicylaldehyde **38** with aryne.
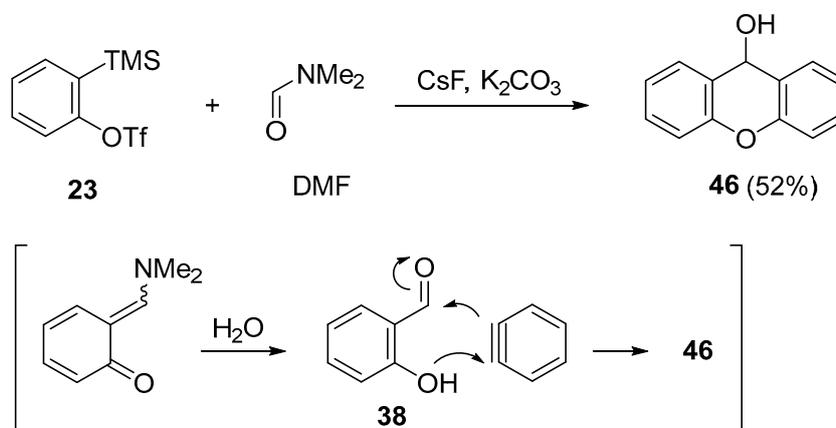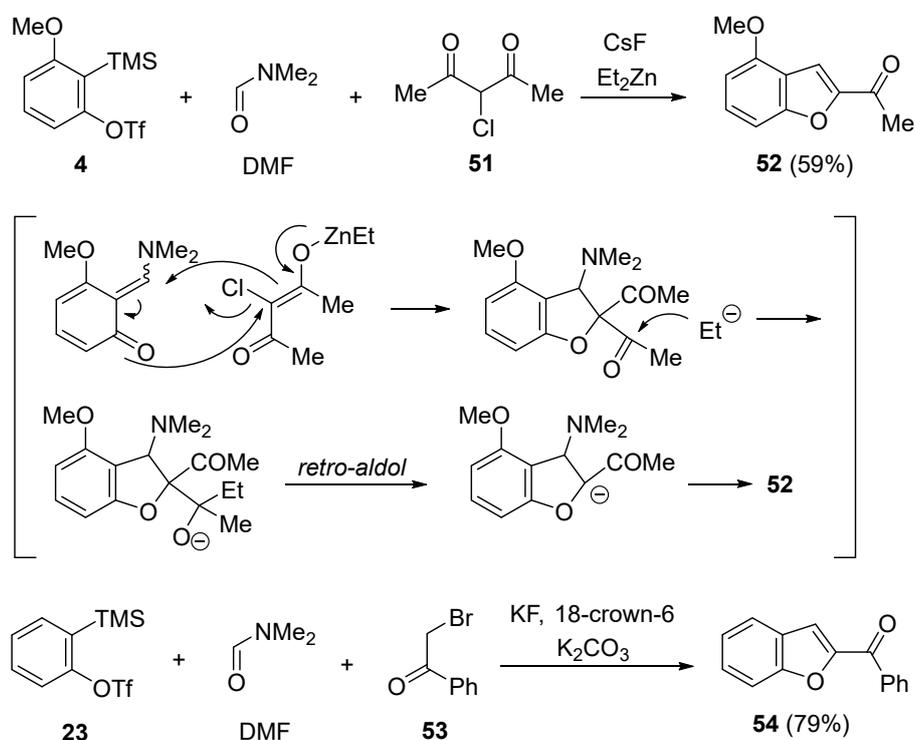
Scheme 17. 2:1-Coupling reaction.

The trapping reactions of transient intermediates generated from arynes precursors and DMF with a variety of reactants have been widely studied as being synthetic approaches to oxygen atom-containing heterocycles [34–43]. The synthesis of 2*H*-coumarin derivatives was also studied [34–36]. Three-component coupling reactions leading to chromene **48** was achieved by the use of acetate **47,** having an aryl group as a nucleophile for trapping the unstable intermediate (Scheme 18). In the presence of KF, the reaction of triflate **23** and acetate **47** was carried out in DMF at 80 °C to give the coumarin **48** in 95% yield [35]. The synthesis of 2-aryliminochromene skeleton of biologically active compounds was studied by using a three-component coupling reaction [36]. A transient intermediate, generated from triflate **23** and DMF, could be trapped by *N,S*-keteneacetal **49** to give the biologically important arylimino-2*H*-chromene-3-carboxamide **50** in 81% yield. The synthesis of 4*H*-chromene derivatives was also achieved by using a three-component coupling reaction involving the hetero Diels-Alder reaction between transient intermediates and dienophiles [37].
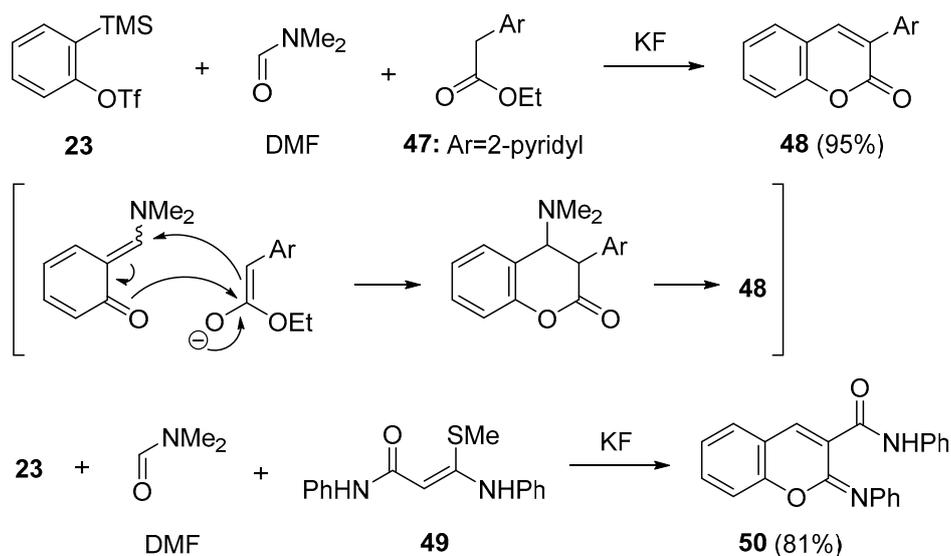
Scheme 18. Synthesis of coumarin derivatives.

The synthesis of benzofurans was also studied [38–40]. The use of α-halogenated enolate, generated from α-chloromalonate **51** and Et$_2$Zn, led to the formation of benzofuran **52** (Scheme 19) [38]. In the presence of CsF, treatment of aryne precursor **4** and α-chloromalonate **51** with Et$_2$Zn in DMF gave **52** in 59% yield. In this transformation, α-chloromalonate acts as a nucleophilic and electrophilic one carbon-unit for trapping a transient intermediate. Benzofuran **52** will be formed via a route involving the retro-aldol type reaction. The simple one-pot synthesis of benzofurans was also reported [40]. When 2-bromoacetophenone **53** was used as a nucleophilic and electrophilic reactant, benzofuran **54** was obtained in 79% yield.


Scheme 19. Synthesis of benzofurans.

Additionally, the trapping reaction of transient intermediates was successfully applied to a four-component coupling reaction for the convenient synthesis of xanthene derivatives [34,41,42].

4. Activation of Relative Bonds

The insertion of arynes into the N–S bond of sulfinamides was studied [25]. In the presence of *n*-Bu$_4$NF, the reaction of *N*-phenyltrifluoromethanesulfinamides **55a–c** with triflate **23** as an aryne precursor gave the corresponding N–S insertion products **56a–c** in good yields (Scheme 20).

23

55a: R=H
55b: R=I
55c: R=MeO

56a (80%)
56b (81%)
56c (91%)
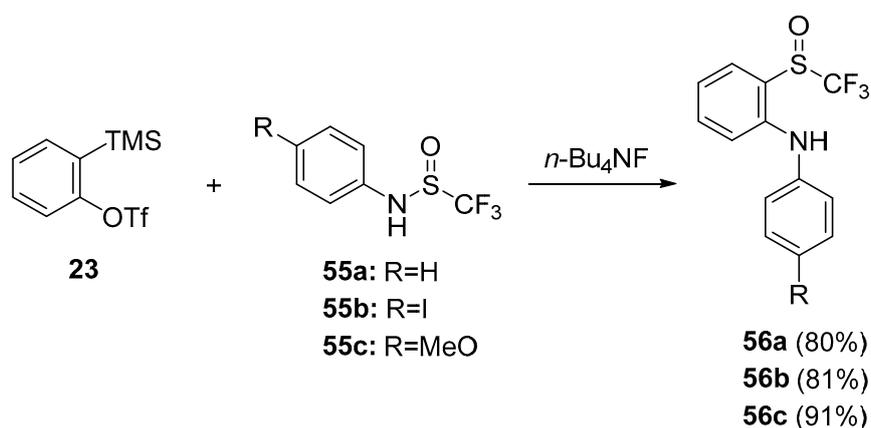
Scheme 20. Reaction of *N*-phenyltrifluoromethanesulfinamides with aryne.

The insertion of arynes into the P–N bonds of arylphosphoryl amides was studied [44]. In the presence of KF and 18-crown-6, the reaction of diphenylphosphinic amides **57a–c** with triflate **23** was carried out at 80 °C in a sealed tube (Scheme 21). The *ortho*-aniline-substituted arylphosphine oxides **58a–c** were obtained in moderate yields. This transformation proceeded through the addition of the nitrogen atom of **57a–c** to an aryne, the intramolecular trapping, and the four-membered ring opening. Additionally, the P–N insertion product **58a** was converted to *ortho*-amine-substituted arylphosphine **59** in 96% yield by the reduction using HSiCl$_3$.

23

57a: Ar=Ph
57b: Ar=4-MeO-C$_6$H$_4$
57c: Ar=4-Cl-C$_6$H$_4$

58a (44%)
58b (42%)
58c (71%)

58a

59 (96%)
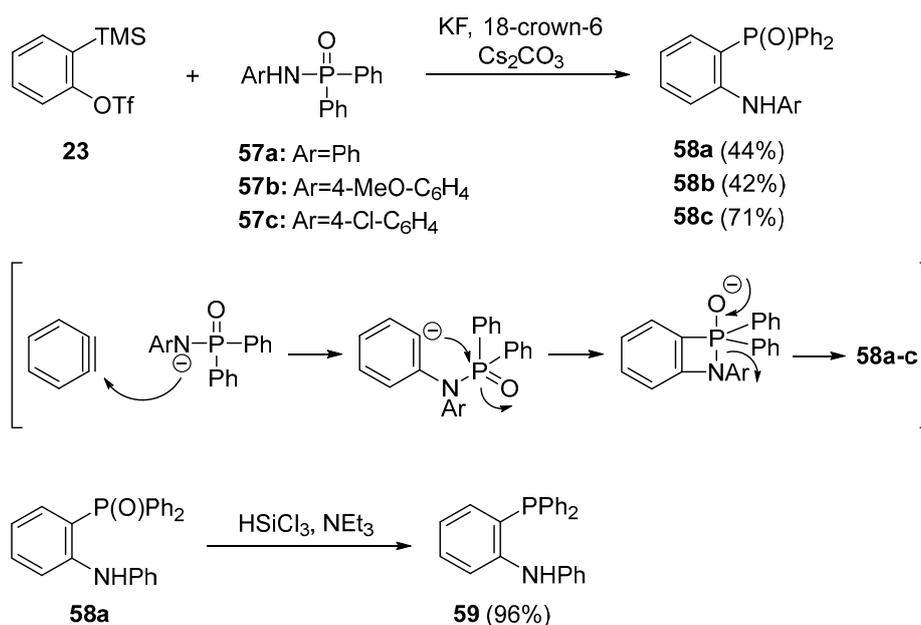
Scheme 21. Reaction of diphenylphosphinic amides with aryne.

The insertion of arynes into the N–C bonds of aryl cyanamides was reported [45]. In the presence of CsF, triflate **23** reacted with aryl cyanamides **60a**–**e** to give the 1,2-bifunctional aminobenzonitriles **61a**–**e** in good yields (Scheme 22). This N–C bond insertion also proceeds via the formation of the four-membered ring intermediates.

60a: R=H
60b: R=4-MeO
60c: R=2-MeO
60d: R=4-MeO$_2$C
60e: R=3-NO$_2$

61a (70%)
61b (72%)
61c (65%)
61d (79%)
61e (79%)
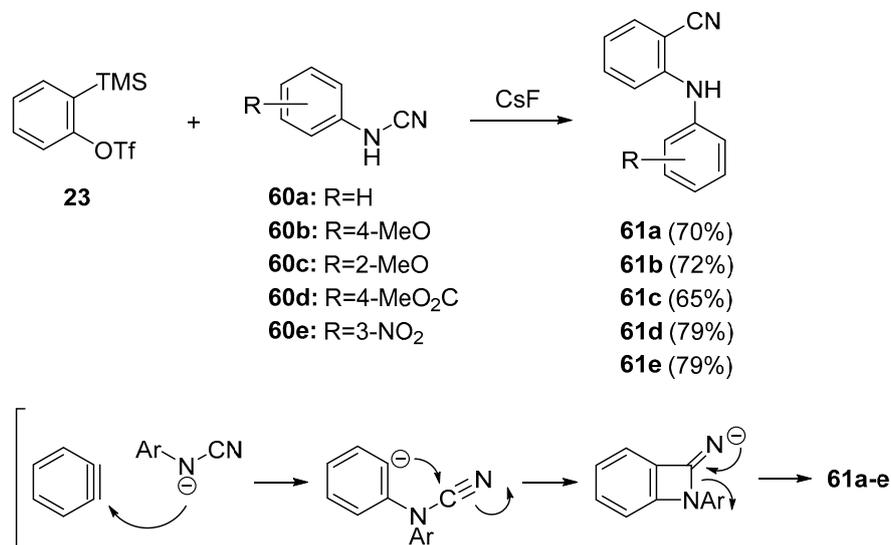
**Scheme 22.** Reaction of aryl cyanamides with aryne.

The synthesis of biaryl compounds was achieved by using the reaction of aryl sulfonamides with arynes [46]. In the presence of KF and 18-crown-6, aryl sulfonamides **62a**–**c** having an electron-withdrawing group reacted with aryne to afford 2-amino-biaryls **63a**–**c** (Scheme 23). This reaction involves the addition of sulfonamides to aryne, and the subsequent Smiles-type *ipso*-substitution with sulfur dioxide SO$_2$ extrusion.

62a: EWG=NO$_2$
62b: EWG=CN
62c: EWG=COMe

63a (66%)
63b (50%)
63c (69%)
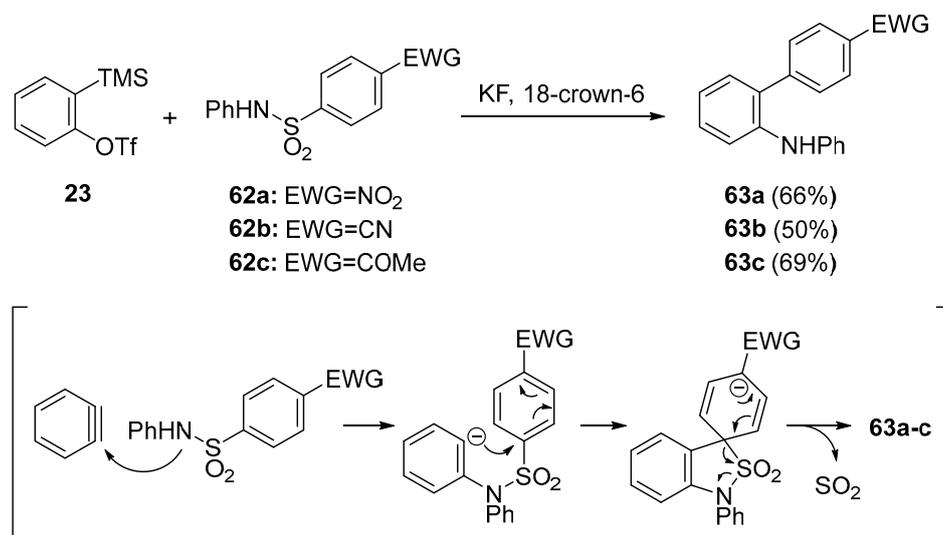
Scheme 23. Reaction of aryl sulfonamides with aryne.

Formal π-insertion into the C=S bond was observed in the reaction of thioureas with aryne [47]. When a solution of triflate **23** and thiourea **64** in toluene/MeCN was heated in the presence of CsF, amidine **65** was formed in 70% yield, accompanied with the simple *S*-arylated product **66** in 20% yield (Scheme 24). The sequential transformation leading to **65** was started by the reaction of the sulfur

atom of **64** with an aryne, which was followed by intramolecular trapping to give a four-membered ring intermediate. The amidine **66** was obtained via the four-membered ring opening and subsequent *S*-arylation by an aryne.
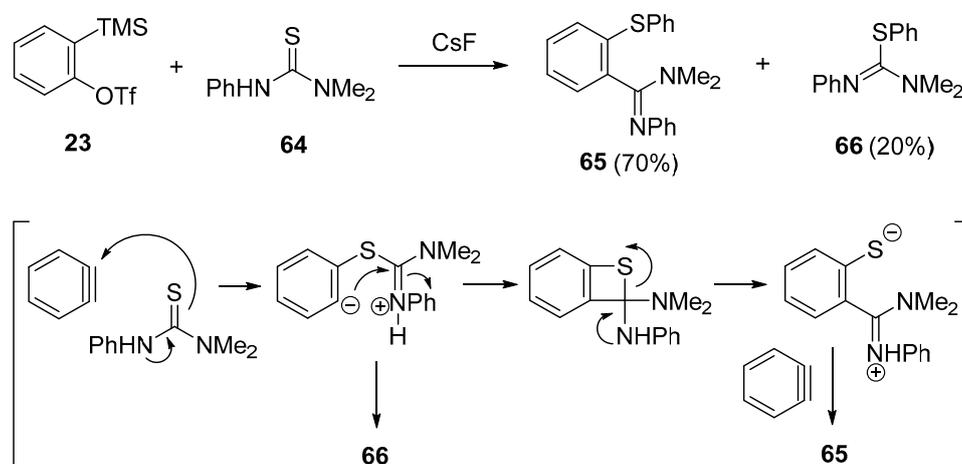
Scheme 24. Reaction of thiourea with aryne.

The C=C double bond of vinylogous amide derivatives reacted with aryne [48,49]. In the presence of CsF, the reaction of vinylogous amide derivatives **67a–b** with aryne gave the carbonyl compounds **68a–b** in good yields (Scheme 25). This transformation proceeded via the [2 + 2] cycloaddition between aryne and **67a–b** and the four-membered ring opening. The bulky vinylogous amides **69a–c** having ester, ketone, or cyano group as an electron-withdrawing group reacted well with aryne to give the corresponding products **70a–c** in good yields.
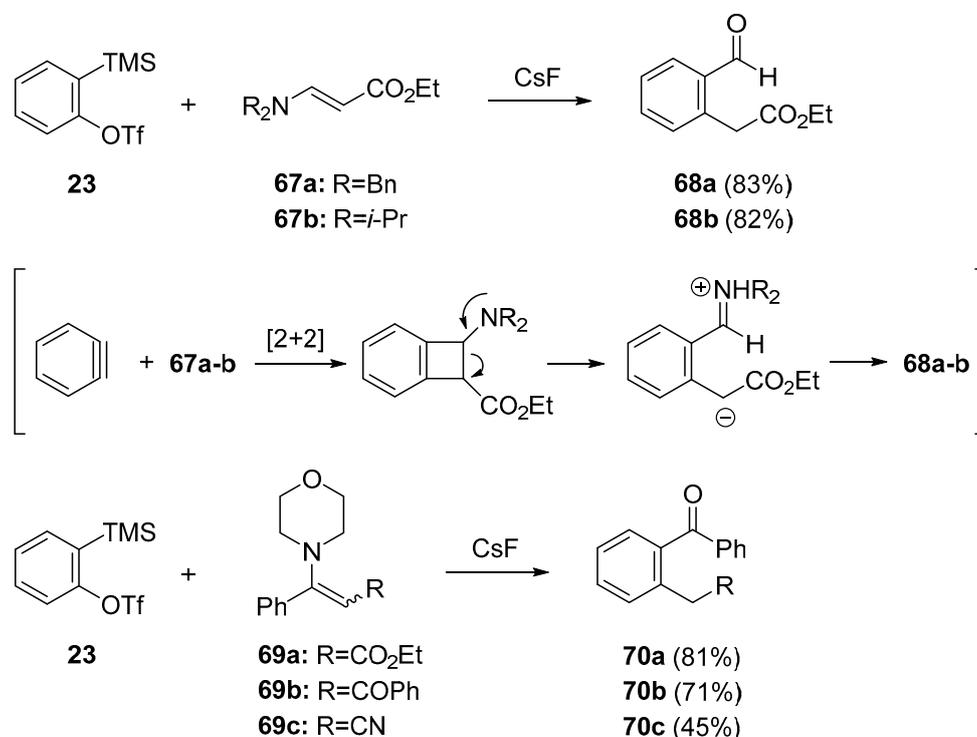
Scheme 25. Reaction of vinylogous amides with aryne.

5. Concluding Remarks

Arynes are highly reactive intermediates that can activate the N–C and C=O bonds of an amide group under transition-metal-free conditions. As described above, the insertion of arynes into the N–C bond has been studied as a powerful method for preparing *ortho*-disubstituted arenes. In contrast, the selective insertion of arynes into the C=O bond proceeds when sterically less-hindered formamides are employed. Moreover, the trapping reactions of transient intermediates with a variety of reactants, leading to the multi-component coupling reaction, disclosed a broader aspect of the utility of N–C bond insertion for the synthesis of oxygen atom-containing heterocycle**s**. I hope that this review will inspire new creative contributions to organic chemists.

Conflicts of Interest: The author declares no conflict of interest.

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