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.
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.](image)

*Insertion into C=O bond of formamides*

![Scheme 3. Activation of amide C=O bond by arynes.](image)

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.
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 4. Reaction of ureas with aryne.**

**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.](image)

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.](image)

The insertion of arynes into the N–C bond of N-phenyltrifluoroacetamides proceeded effectively [25]. In the presence of CsF, the reaction of N-phenyltrifluoroacetamid e 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 CF3 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.
To develop the amide insertion reaction having broad utility, the reaction of \( \text{N-pivaloylaniline} \) \( 26\text{a} \) with triflate \( 23 \) was investigated by changing solvents and fluoride sources \([26]\). Employing tetrabutylammonium triphenyldifluorosilicate (TBTA) as a fluoride source, amide \( 26\text{a} \) underwent the \( \text{N–C insertion} \) in toluene at 50 °C to afford the \( \text{tert-butylketone} \) \( 27\text{a} \) in 64% yield (Scheme 9). Exploration of substrate scope showed that \( \text{N-phenyl derivatives} \) \( 26\text{b} \) and \( 26\text{c} \) were similarly efficient substrates.

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 \( \text{ortho-halobenzamide} \) \( 28 \), with triflate \( 23 \) under microwave irradiation at 120 °C in the presence of TBAT. Acridone \( 29 \) was formed via a route involving the \( \text{N–C insertion} \), followed by the intramolecular \( \text{S}_{\text{NAr}} \) reaction. In contrast, acridine \( 31 \) was synthesized by a one-pot procedure using \( \text{BF}_3\cdot\text{OEt}_2 \) via a route involving the \( \text{N–C insertion} \) of amide \( 30 \) into aryne, followed by a \( \text{BF}_3\)-mediated Friedel-Crafts acylation and dehydration.
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.

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.
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). 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.
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 Et₂Zn in hexane was added to the reaction mixture (Scheme 15). The desired aminophenol 41 was obtained in 71% yield. Diethylzinc 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 diaryliodonium triflate 44 in DMF-facilitated 2-phenoxybenzaldehyde 45 in 87% yield (Scheme 16). In this transformation, diaryliodonium triflate 44 acted as an electrophile by trapping the oxygen atom of a transient intermediate.

![Scheme 16. Trapping reaction using diphenyliodonium salt.](image)

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.](image)

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 2H-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-2H-chromene-3-carboxamide 50 in 81% yield. The synthesis of 4H-chromene derivatives was also achieved by using a three-component coupling reaction involving the hetero Diels-Alder reaction between transient intermediates and dienophiles [37].
The synthesis of benzofurans was also studied [38–40]. The use of α-halogenated enolate, generated from α-chloromalonate 51 and Et₂Zn, 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 Et₂Zn 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 \( n\text{-Bu}_4\text{NF} \), the reaction of \( N\)-phenyltrifluoromethanesulfinamides \( 55\text{a–c} \) with triflate \( 23 \) as an aryne precursor gave the corresponding N–S insertion products \( 56\text{a–c} \) in good yields (Scheme 20).

\[
\begin{align*}
\text{Scheme 20. Reaction of } N\text{-phenyltrifluoromethanesulfinamides with arynes.}
\end{align*}
\]

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 \( 57\text{a–c} \) with triflate \( 23 \) was carried out at 80 °C in a sealed tube (Scheme 21). The ortho-aniline-substituted arylphosphine oxides \( 58\text{a–c} \) were obtained in moderate yields. This transformation proceeded through the addition of the nitrogen atom of \( 57\text{a–c} \) to an aryne, the intramolecular trapping, and the four-membered ring opening. Additionally, the P–N insertion product \( 58\text{a} \) was converted to ortho-amine-substituted arylphosphine \( 59 \) in 96% yield by the reduction using HSiCl₃.

\[
\begin{align*}
\text{Scheme 21. Reaction of diphenylphosphinic amides with arynes.}
\end{align*}
\]
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.

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 SO2 extrusion.

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 heterocycles. I hope that this review will inspire new creative contributions to organic chemists.

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