ARYNE-MEDIATED SYNTHESIS OF OXYGEN HETEROCYCLES AND APPLICATION TO CYSTEINE-SELECTIVE TRAPPING

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Abstract – The use of arynes as the highly reactive intermediates in organic synthesis has attracted substantial attention. Particularly, the introduction of ortho-(trimethylsilyl)aryl triflates as easily activatable arylene precursors led to growing activity in this field. Most reactions using these arylene precursors proceed through the addition of nucleophiles to arynes and the subsequent trapping with electrophiles to give the multisubstituted arenes with structural diversity and complexity. Based on our studies, this review highlights the insertion of arynes, generated from ortho-(trimethylsilyl)aryl triflates, into C=O π-bond of formamides. Initially, the representative examples for formal [2+2] cycloaddition of arynes with the carbon–heteroatom double bond or the heteroatom–heteroatom double bond are shown. Next, the studies on the insertion of arynes into the N–C and C=O bonds of amide group including our three-component coupling reaction leading to oxygen heterocycles are summarized. The SN2’ reaction of tricyclic oxygen heterocycles, obtained by three-component coupling reaction, was studied by using carbon and sulfur nucleophiles. The SN2’ reaction was expanded to four-component coupling reaction. Finally, the application of tricyclic oxygen heterocycles to cysteine-selective trapping is described.

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1. INTRODUCTION

The use of kinetically unstable arynes in organic synthesis has attracted substantial attention since the 1950s. The strained arynes react with various nucleophiles as powerful electrophiles, leading to the formation of substituted arenes via the protonation of anions (Figure 1). Furthermore, the concerted reactions of arynes such as Diels–Alder reaction and dipolar cycloaddition reaction are the synthetically useful method for preparing bicyclic compounds or benzo-fused heterocycles. In recent years, arynes have been utilized in the transition metal-catalyzed reactions involving [2+2+2] cycloaddition, cross-coupling process and σ-bond insertion.

![Figure 1. Reactions of arynes](image)

In the past decade, arynes have gained increasing attention as highly reactive species for constructing the multisubstituted arenes with structural diversity and complexity. Particularly, the development of ortho-(trimethylsilyl)aryl triflates as easily activatable aryne precursors led to growing activity in this field, resulting in the development of new aryne-based reactions (Figure 2). The generation of arynes can be achieved by treatment of triflates with fluoride ion under the mild reaction conditions. Therefore, the most recent efforts have been directed toward the development of new synthetic reactions leading to ortho-disubstituted arenes from triflates, which comprise the initial addition of nucleophiles to arynes and the subsequent trapping of intermediates with electrophiles. The important feature is that arynes are...
also react with the less reactive substrates having both nucleophilic site and electrophilic site in the same molecule. The initial studies have concentrated on the transition metal-free insertion of arynes A into the σ-bond (X–Y).\textsuperscript{13} Although the insertion reactions of arynes A into the π-bond (X=Y) are relatively limited, the recent works undoubtedly show that formal [2+2] cycloaddition-type reactions of arynes A with X=Y bond are the synthetically important method for constructing ortho-disubstituted arenes. Most of [2+2]-type reactions with X=Y bond would proceed \textit{via} the stepwise [2+2] mechanism involving the formation of zwitterionic species C as intermediates, although the concerted [2+2] mechanism is accepted in some reactions with symmetric C=C bond.\textsuperscript{6} In recent years, the dramatic progresses in aryne-based chemistry are summarized in many review articles.\textsuperscript{3,7,11}

![Reaction of Arynes with Double Bond](image)

**Figure 2. Reactions using aryne precursors 1**

2. **REACTION OF ARYNES WITH DOUBLE BOND**

The representative reactions involving the formal [2+2] cycloaddition of arynes with the carbon–heteroatom double bond are shown in Scheme 1. The insertion of arynes into the carbon–heteroatom double bond takes place probably by the stepwise [2+2] mechanism as shown in Figure 2. In general, the insertion of arynes into the carbon–heteroatom double bond gives [2+2]-type adducts as the unstable intermediates. Therefore, the subsequent electrocyclic opening of [2+2]-type adducts leads the further transformations.
Scheme 1. Insertion into C=O, C=N, C=S and C=Se bonds
Initially, the reaction of arynes, generated from 2-carboxybenzenediazonium aryne precursors, with the C=O bond of α,β-unsaturated aldehydes was studied by Heaney’s group. More recently, Yoshida and Kunai’s group reported the 2:1 coupling reaction between two molar amounts of aryne and one molar amount of aryl aldehyde ([a] in Scheme 1). When ortho-(trimethylsilyl)aryl triflates 1a as aryne precursor and 2-benzzyloxy-1-naphthaldehyde (2) were employed in the presence of KF and 18-crown-6, the 9-arylxanthene derivative 3 was obtained in 70% yield. The [2+2]-type reaction of aryne A, generated from aryl trflate 1a, with the C=O bond of aldehyde 2 gives the unstable intermediate D1, which is isomerized to ortho-quinone methide E1. The 9-arylxanthene 3 was formed by the [4+2] cycloaddition between ortho-quinone methide E1 and aryne A. The reaction of aryne, generated form 2-carboxybenzenediazonium, with the C=N bond of imines or diimines was reported. The reaction of the C=N bond of carbodiimides with arynes was studied by using aryl trflate precursors. As the synthetically useful reactions starting from aryne A carbodiimides and terminal alkynes was achieved in the presence of KF and 18-crown-6 ([b] in Scheme 1). Aryne A, generated from 1a, reacted with N,N-diisopropylcarbodiimide (4) and phenylacetylene (5) to give the difunctionalized benzene 6 in 95% yield via the [2+2]-type reaction of aryne A with the C=N bond of carbodiimide 4. In this reaction, phenylethane 5 acts as a nucleophile for trapping an intermediate E2; thus, the product 6 is formed through the nucleophilic addition of alkyne 5 to an intermediate E2 and the subsequent N-arylation of intermediate F2 by aryne A. The reaction of arynes with C=S bond has been studied. The reaction with the C=S bond of thioureas was reported. The reaction of aryne A, generated from 1a, with thiourea 7 afforded the product 8 in 70% yield as a result of S-arylation of intermediate F3 by aryne A ([c] in Scheme 1). As the related examples, the reaction of arynes with C=Se bond or C=P bond was also studied. Interestingly, 2H-benzoselenete 10 was obtained as a stable [2+2]-type adduct by treatment of precursor 1a with 1,1,3,3-tetramethylindan-2-selone (9) in the presence of tetrabutylammonium fluoride (TBAF) ([d] in Scheme 1).

The synthetically useful reactions starting from insertion of aryne A to the heteroatom-heteroatom double bond are developed (Scheme 2). In the presence of CsF, treatment of P-alkenyl-λ^5-phosphazene 11 with aryne precursor 1a gave 1,4-benzazaphosphorinium trflate 12 in 90% yield ([a] in Scheme 2). The phosphorinium trflate 12 is formed via the [2+2]-type reaction leading to D4, the electrocyclization of intermediate E4 and the protonation. The insertion of arynes into the N=O bond proceeds by the [2+2] mechanism. In the presence of CsF, treatment of nitrosobenzene (13) with aryne precursor 1a gave carbazole (14) in 56% yield ([b] in Scheme 2). The reaction mechanism involving the [2+2]-type reaction leading to D5 and the intramolecular electrophilic aromatic substitution of intermediate E5 was proposed.
3. REACTION OF ARYNES WITH AMIDES

Highly reactive arynes can activate both N–C and C=O bonds of amide group, leading to $\sigma$-bond insertion or $\pi$-bond insertion reactions (Figure 3).\textsuperscript{22} When the nitrogen atom of amides acts as a nucleophile, the insertion of aryne A into N–C $\sigma$-bond proceeds to give the N–C insertion products via the formation of four-membered ring intermediates D6 by the stepwise mechanism. On the other hand, the insertion of arynes into C=O $\pi$-bond is observed when the sterically less hindered formamides are employed. The nucleophilic addition of the oxygen atom of formamides to aryne A leads to the $\pi$-bond insertion reactions by the stepwise [2+2] mechanism. Since four-membered ring intermediates D7 or ortho-quinone methides E7 are formed as the highly reactive intermediates,\textsuperscript{23,24} the further transformations can be developed.
3-1. Insertion of Arynes into N–C Bond of Amides

The insertion of arynes into the N–C bond of amide group was widely studied by employing ureas. In the presence of CsF, treatment of aryne precursor 1b with 1,3-dimethyl-2-imidazolidinone (15) gave 1,4-benzodiazepine derivative 16 in 77% yield ([a] in Scheme 3). This σ-bond insertion initiated by the nucleophilic addition of the nitrogen atom of 15 to aryne A. The sequential transformation is achieved via the intramolecular nucleophilic attack on the carbonyl carbon atom of H8 followed by the ring opening of four-membered ring intermediate D8, affording the N–C insertion product 16. It was reported that the insertion into the N–C bond of N-phenyltrifluoroacetamides proceeded effectively and the CF₃ group on amides is critical to the success of this transformation. In the presence of CsF, the reaction of N-phenyltrifluoroacetamide (17) with aryne precursor 1a took place smoothly to give the N–C insertion product 18 in 77% yield ([b] in Scheme 3). In this study, the reaction mechanism involving the abstraction of the hydrogen on amide nitrogen by fluoride anion as a base was proposed. Later, to achieve the insertion reaction without the activation by CF₃ group, the N–C bond insertion using simple aryl amides was investigated by changing solvents and fluoride sources. As more general procedure having broad utility, new reaction conditions using tetrabutylammonium triphenyldifluorosilicate (TBAT) as fluoride source in toluene at 50 °C were developed. Furthermore, the modified reaction conditions led to the one-step synthesis of acridone 20 via a route involving the N–C insertion followed by the intramolecular S_N_Ar reaction ([c] in Scheme 3). In the presence of TBAT, the reaction of ortho-halobenzamide 19 with aryne precursor 1a gave acridone 20 in 92% yield under microwave irradiation at 120 °C. The insertion into the N–C bond of imides was also investigated. In the presence of TBAT, the reaction of imide 21 with precursor 1a was carried out in toluene at 60 °C to give the desired
N−C insertion product 22 in 89% yield ([d] in Scheme 3). As the effective N−C insertion reaction, the insertion of arynes into the N−C bond of β-lactam was reported.

Scheme 3. Insertion of arynes into N−C σ-bond of amides

3-2. Insertion of Arynes into C=O Bond of Amides

In organic synthesis, N,N-dimethylformamide (DMF) can react as either an electrophilic or nucleophilic agent. The insertion of arynes into the C=O bond of amide group was studied mainly by the use of DMF as a sterically less hindered formamide.
Scheme 4. Insertion of arynes into C=O π-bond of amides
In 1965, Yaroslavsky reported that treatment of 2-carboxybenzenediazonium aryne precursor 23 in a 1:1 mixture of DMF–benzene gave salicylaldehyde (24) in 32% yield ([a] in Scheme 4).31 Recently, we reported that the reaction using triflate 1b as a precursor in DMF in the presence of TBAF afforded salicylaldehyde 24 in 84% yield ([b] in Scheme 4).32 In this reaction, DMF was used as a solvent. The insertion into the C=O bond of DMF will proceed via the stepwise mechanism involving the addition of the oxygen atom of amide to aryne followed by the intramolecular nucleophilic attack on iminium 19. In this mechanism, the benzoxetene D9 is formed as formal [2+2] adduct, which would isomerize into ortho-quinone methide E9 as transient intermediate. Salicylaldehyde 24 is obtained by the reaction of ortho-quinone methide E9 with water. When N-methylformamide (MF) was employed as protic amide, the insertion into the C=O bond did not proceed effectively probably due to the rapid intramolecular protonation of anion J ([c] in Scheme 4).33 Although the sterically less hindered MF worked as an oxygen atom nucleophile, the undesired product 26 was predominantly obtained as a result of the hydrolysis of intermediate K. In a consequence, the use of fully substituted formamides is essential for the desired π-bond insertion reaction. Two competitive attacks between nitrogen and oxygen atoms of amide group were observed by changing amide from DMF to sterically hindered N,N-dimethylacetamide (DMA).32,33 The π-bond insertion reaction leading to π-bond insertion product 27 was suppressed, because the steric factor of DMA gave rise to decreasing the nucleophilicity of oxygen atom on DMA and destabilizing the [2+2] intermediate ([d] in Scheme 4). As a result of competitive nucleophilic addition of the nitrogen atom of DMA to an aryne, the formation of the N–C σ-bond insertion product 28 was also observed.

As the method trapping the unstable intermediates such as formal [2+2]-type adduct D9 or ortho-quinone methide E9, the reaction of aryne precursor 1b and DMF with Et2Zn was studied in the presence of CsF (Scheme 5).32,33 We found that dialkylzincs had the sufficient reactivity toward these intermediates and the compatibility of DMF. Because CsF is a moisture-sensitive fluoride ion source, a solution of Et2Zn in hexane was initially added to a suspension of CsF in freshly distilled DMF to remove a trace amount of water in the reaction mixture. Next, aryne precursor 1b was added to the reaction mixture. As expected, the aminophenol 29 was obtained in 87% yield ([a] in Scheme 5). Under the similar conditions, Me2Zn and Ph2Zn worked well, allowing facile incorporation of structural variety. Additionally, the one-pot reaction using 1-formylpiperidine and N-allyl-N-methylformamide gave the desired products 30 and 31, respectively ([b] and [c] in Scheme 5). The trapping reaction using diaryliodonium salts as electrophiles was reported.34 In the presence of KF, the reaction of precursor 1a and diphenyliodonium triflate in DMF gave 2-phenoxybenzaldehyde (32) in 87% yield ([d] in Scheme 5). In this transformation, the oxygen atom of quinone methide E10 was effectively trapped by diphenyliodonium triflate.
3-3. Three-Component Coupling Reaction
To develop the domino three-component reactions for preparing the benzo-fused oxygen atom-containing heterocycles, we studied two synthetic approaches for trapping ortho-quinone methide E7 (Figure 4). The sequential transformations can be achieved by the initial addition of carbon nucleophiles to the transient intermediate E7 and the subsequent trapping process with carbon electrophiles. The trapping reaction with C2-unit having both nucleophilic and electrophilic sites gives coumarin, chromene, etc.
single operation. When nucleophile and electrophile belong to the same carbon atom as C1-unit, three-component reaction leads to 2,3-dihydrobenzofuran, benzofuran, etc.

**Figure 4. Synthetic approaches to benzo-fused oxygen-heterocycles**

We used the anions of active methylenes as C2-units having both nucleophilic and electrophilic sites (Scheme 6).\textsuperscript{35ac} Trapping the intermediate E7 with C2-unit leads to the coumarin derivatives M and N. In the presence of anhydrous TBAF as fluoride ion source, treatment of precursor 1b with acetylacetone (33a) in DMF gave the 2H-chromene 34a in 86% yield ([a] in Scheme 6). We were gratified to observe the sufficient reactivity of acetylacetone (33a) toward intermediate E7 in the absence of typical base. Similarly, three-component coupling reactions using the bulky 1,3-diketone 33b bearing two phenyl groups and the acetone 33c having an CF\textsubscript{3} group gave the corresponding 2H-chromenes 34b and 34c in 79% and 40% yields, respectively. When cyclic 1,3-diketone 35a was employed as C2-unit, the tricyclic 2H-chromene derivative 36a was obtained in 83% yield ([b] in Scheme 6). In the case of unsymmetrical diketone 35b, the compound 36b was obtained as a major regioisomer. Three-component coupling reaction using β-keto esters 37a–37d as C2-units leads to the formation of coumarin derivatives 38a–38d. In the presence of anhydrous TBAF, the reaction using precursor 1b and β-keto ester 37a in DMF proceeded effectively to give coumarin 38a in 77% yield ([c] in Scheme 6). Good chemical yields were observed when β-keto ester 37b and diethyl malonate (37c) were employed, although the use of ester 37d having a nitro group led to the relatively lower yield. It is well known that the active methylenes such as...
malonates react with aryne to give the σ-bond insertion products.\textsuperscript{36} To suppress this competitive σ-bond insertion, it is important that sufficient amount of DMF is employed as a solvent for this three-component coupling reaction.

Scheme 6. Trapping reaction with active methylenes as C2-units

Three-component coupling reaction for preparing the coumarin derivatives substituted an aryl group at 3 position was also reported by Yoshida’s group.\textsuperscript{37} In the presence of KF, treatment of precursor 1a with acetates 39a–39c having an aryl group in DMF gave the coumarin derivatives 40a–40c ([a] in Scheme 7). Interestingly, phenylacetonitrile (41) acted as a nucleophile for trapping ortho-quinone methide to afford the coumarin 42 in 60% yield ([b] in Scheme 7).
Next, the hetero Diels–Alder reaction for trapping ortho-quinone methides with dienophiles was investigated ([a] in Scheme 8). In the presence of CsF, treatment of precursor 1b with dimethyl acetylenedicarboxylate (43) in DMF gave 4H-chromene 44 in 80% yield. The concerted mechanism is rationalized by considering the overlap of HOMO of ortho-quinone methide (−5.20 eV) with LUMO of dienophile 43 (−1.89 eV). As a relative example, the 2:1 coupling reaction of two molar amounts of aryne and one molar amount of DMF was reported. In the presence of CsF and K$_2$CO$_3$, the reaction of precursor 1a (1.2 mol) with DMF (0.5 mol) in MeCN afforded 9-hydroxyxanthene (45) in 52% yield ([b] in Scheme 8). It is assumed that 9-hydroxyxanthene (45) is formed as a result of trapping aryne by salicylaldehyde generated by the hydrolysis of ortho-quinone methide E10.
Next, three-component coupling reaction leading to the formal [4+1] adducts such as 2,3-dihydrobenzofuran derivatives \textbf{O1} was investigated. In this transformation, the α-halogenated active methines must be employed as C1-units for trapping intermediate \( \textbf{E7} \). The desired α-halogenated enolate can be prepared by the reaction of α-chloromalonate \( \textbf{46} \) with \( \text{Et}_2\text{Zn} \). In the presence of CsF and \( \text{Et}_2\text{Zn} \), treatment of precursor \( \textbf{1b} \) with α-chloromalonate \( \textbf{46} \) in DMF gave 2,3-dihydrobenzofuran \( \textbf{47} \) in 86% yield ([a] in Scheme 9). Consequently, ortho-quinone methide \( \textbf{E9} \) was trapped by zinc α-chloroenolate, generated from \( \textbf{46} \), to give dihydrobenzofuran \( \textbf{47} \) via the intermediate \( \textbf{P} \). Moreover, ethyl α-chlorophenylacetate \( \textbf{48} \) participated in three-component coupling reaction to give two diastereomers.
49 and 50 ([b] in Scheme 9). When 1-formylpiperidine was used as formamide instead of DMF, 2,3-dihydrobenzofuran 51 was obtained in 75% yield under similar reaction conditions ([c] in Scheme 9).

The synthetic approach leading to benzofuran O3 via 2,3-dihydrobenzofuran O2 was also studied by trapping ortho-quinone methide E7 with C1-unit. For this study, α-halogenated enolates were employed as nucleophilic and electrophilic C1-units. When ethyl iodoacetate (52) was employed at the high temperature, the desired benzofuran 53 was obtained in 40% yield ([a] in Scheme 10).35c Recently, it was reported that benzofuran 55 was obtained by using 2-bromoacetophenone (54) as a nucleophilic and electrophilic reactant in the presence of KF, 18-crown-6 and K₂CO₃ ([b] in Scheme 10).40

![Trapping of intermediates with C1-unit](image)

Scheme 10. Synthesis of benzofuran derivatives

The one-pot synthesis of benzofurans through the retro-aldol type reaction was achieved by using the α-halogenated active methines having a ketone group as C1-unit.35b,c In the presence of CsF, treatment of active methine 56 with Et₂Zn and precursor 1b in DMF led to the formation of benzofuran 57 in 59% yield ([a] in Scheme 11). This transformation proceeds via the addition of ethyl anion, generated from Et₂Zn, to a ketone moiety of 2,3-dihydrobenzofuran Q followed by the retro-aldol type reaction of R. Similarly, the active methine 58 having ketone and ester groups worked well to give benzofuran 59 ([b] in Scheme 11). The desired benzofuran 61 was obtained even when the methine 60 having a bulky phenyl ketone group and amide group was used ([c] in Scheme 11).
The 2,3-dihydrobenzofuran 63 having a hydroxy group can be prepared by using α-bromomalonate 62 together with a small amount of water instead of Et₂Zn ([a] in Scheme 12). The 2,3-dihydrobenzofuran 63 was obtained in 77% yield, when three-component coupling reaction using precursor 1b and α-bromomalonate 62 in DMF was carried out in the presence of CsF and water (1.0 equiv). Moreover, the effective transformation of 2,3-dihydrobenzofuran 63 to benzofuran 53 was achieved by treatment of 63 with potassium bis(trimethylsilyl)amide (KHMDS) as a base. This transformation would proceed through the generation of cyclic intermediate S followed by the decarboxylation of S. Additionally, the conversion of 2,3-dihydrobenzofuran 47 having N,N-dimethylamino group into benzofuran 53 was also achieved by treatment of 47 with EtMgBr followed by SiO₂ ([b] in Scheme 12). The desired benzofuran 53 was obtained in 77% yield without the isolation of adduct T. This transformation proceeds via a route involving the retro-aldol type reaction of adduct T followed by the elimination of N,N-dimethylamino group of intermediate U.
4. REACTION OF TRICYCLIC OXYGEN HETEROCYCLES

4-1. Reaction with Carbon Nucleophiles

Further transformations of benzo-fused oxygen heterocycles, obtained by three-component coupling reaction of arynes with DMF and active methylenes, were investigated. The $S_{N2'}$ reaction of tricyclic oxygen heterocycles with nucleophiles led to the formation of xanthene derivatives. In this study, cyclic 1,3-diketone 35a was used as carbon nucleophile. However, bicyclic substrate 34a did not react with 1,3-diketone 35a ([a] in Scheme 13). In marked contrast, tricyclic substrate 36a has shown the excellent reactivity toward 1,3-diketone 35a. The $S_{N2'}$ reaction of tricyclic substrate 36a with 35a proceeded smoothly to give the xanthene derivative 64 in 79% yield ([b] in Scheme 13). The calculation studies indicate that the pseudo-axial direction of hydroxy group in tricyclic substrate 36a is crucial for the efficiency of $S_{N2'}$ process. In the case of bicyclic substrate 34a, the stable intramolecular hydrogen bond between the hydroxy group and the carbonyl group suppresses the $S_{N2'}$ reaction of 34a with 1,3-diketone 35a.
The $S_{N}2'$ reaction of tricyclic oxygen heterocycles was successfully expanded into the one-pot four-component coupling reaction which involves the formation of two C–O and three C–C bonds. In the presence of anhydrous TBAF, the four-component coupling reaction using two different 1,3-diketones $35c$ and $35a$ proceeded effectively to give the xanthene derivative $65$ in 69% yield by the one-pot procedure ([a] in Scheme 14).$^{35a}$ This transformation involves the trapping reaction of ortho-quinone methide with 1,3-diketone $35c$ followed by the $S_{N}2'$ reaction of tricyclic oxygen heterocycle with 1,3-diketone $35a$. When 2-hydroxy-1,4-naphthoquinone $66$ was used as the nucleophilic reactant for $S_{N}2'$ reaction, the xanthene derivative $67$ was obtained in 67% yield ([b] in Scheme 14).$^{43}$
4-2. Reaction with Sulfur Nucleophiles

Thiols also acted as nucleophiles for the reaction of tricyclic substrate 36a, allowing facile incorporation of structural variety (Scheme 15). The effective transformation using thiols was achieved by employing acetic acid, which will activate the hydroxy group as leaving group. In the presence of acetic acid (0.5 equiv.), the reaction of 36a with thiophenol gave xanthene derivative 68a having phenylthio group at 9 position in 89% yield. Under the similar reaction conditions, tricyclic substrate 36a reacted with ethanethiol to afford 68b in 97% yield.

The reaction using thiols was also applied to the one-pot four-component coupling reaction involving the formation of C–S, two C–O and two C–C bonds. After triflate 1b (1.2 equiv) was reacted with DMF and 1,3-diketone 35a in the presence of TBAF, a solution of thiols and acetic acid in MeCN was added to the reaction mixture ([a] in Scheme 16). The desired xanthenes 68a and 68b were isolated in 71% and 72%
yields, respectively. Similarly, the reaction giving xanthene 69 proceeded by one-pot procedure (b) in Scheme 16.

Scheme 16. One-pot four-component coupling reaction

The further conversion of the four-component coupling product 69 having phenylthio group at 9 position was studied. The use of diethylzinc led to the replacement of phenylthio group to ethyl group, affording the ethylated xanthene 70 in 96% yield (a) in Scheme 17. The reaction of 69 with diethyl malonate (37c) and Et2Zn gave the replacement product 71 via the formation of zinc complex as nucleophile (b) in Scheme 17.

Scheme 17. Further conversion using dialkylzincs
5. APPLICATION TO CYSTEINE-SELECTIVE TRAPPING

Chemical modification of proteins has attracted extensive attention in the biochemical or biomedical chemistry. In particular, the site-specific modification of proteins and peptides has attracted substantial attention, since 20 different amino acids are incorporated to proteins. Cysteine is a relatively rare α-amino acid in natural proteins. Therefore, the cysteine-selective trapping methods are of particular importance for the site-specific modification. For examples, maleimides, α-halocarbonyls and vinyl sulfones are employed as cysteine-selective trapping reagents (Figure 5). Therefore, our laboratory is interested in studying the potential of benzo-fused tricyclic oxygen heterocycles as the trapping reagents for cysteine and its related thiols.

![Figure 5. Cysteine-selective modification methodology](image)

To survey the reactivity of tricyclic oxygen heterocycles as thiol-trapping reagents, the competitive reaction using oxygen heterocycle 72 and maleimide 73 was studied ([a] in Scheme 18). The desired adduct 74 was obtained in 39% yield from oxygen heterocycle 72 accompanied with the adduct 75 in 58% yield from maleimide 73; thus, the oxygen heterocycle 72 has the sufficient reactivity comparable with a typical trapping reagent 73. The selectivity of oxygen heterocycle 72 toward thiols was evaluated by employing benzylthiol and benzylamine in 1:1 ratio ([b] in Scheme 18). As expected, the thiol-adduct 74 was selectively formed in 89% yield without the detection of another amine-adduct. In the case of maleimide 73, a small amount of the amine-adduct 76 (12% yield) was also obtained ([c] in Scheme 18). These results show that oxygen heterocycle 72 has the excellent thiol-selectivity.
The reaction trapping of L-cysteine by oxygen heterocycle 72 was examined under the mild and aqueous reaction conditions ([a] in Scheme 19). When phosphate-buffered saline (PBS) was employed as aqueous co-solvent, the reaction proceeded with the excellent yield and selectivity even in the absence of acetic
The desired thiol-adduct 77 was obtained in 97% yield by using MeCN–PBS (5:1, v/v) as mixed solvent. The high cysteine-selectivity of oxygen heterocycle 72 was confirmed by the competition experiment using L-cysteine and L-lysine monohydrochloride ([b] in Scheme 19). As expected, L-lysine did not react with oxygen heterocycle 72 leading to the selective formation of cysteine-adduct 77.

Scheme 20. Reaction of oxygen heterocycle with other thiols

Oxygen heterocycle 72 reacted with bulky d-penicillamine, although the adduct 78 was unstable ([a] in Scheme 20). The reaction trapping of captopril with oxygen heterocycle 72 took place without any problems to give the adduct 79 almost in quantitative yield ([b] in Scheme 20). The use of glutathione as
an acidic peptide nucleophile led to the formation of 80 with the excellent yield and selectivity ([c] in Scheme 20).

Scheme 21. Reaction of other oxygen heterocycles

The oxygen heterocycles 36a and 82 having the substituent on aromatic ring were employed. Despite the steric hindrance increasing around the reaction site on oxygen heterocycle, oxygen heterocycle 36a worked well as a trapping reagent to give the adduct 81 in 98% yield ([a] in Scheme 21). The reaction of oxygen heterocycle 82 with glutathione led to the complex adduct 83 ([b] in Scheme 21).

6. CONCLUDING REMARKS

Recent aryne-based chemistry has achieved the remarkable success. The synthetic strategies based on the aryne-mediated domino reaction offer the advantage of multiple carbon–carbon and/or carbon–heteroatom bond formations in a single operation. As described above, the insertion of arynes into the C=O bond of formamides has studied as a powerful method for preparing the oxygen heterocycles. These multi-component coupling reactions offer the opportunities for further exploration with intriguing possibilities in arylene chemistry. As the successful application of the oxygen heterocycles obtained by the
aryne-based multi-component coupling reaction, the utility of tricyclic oxygen heterocycles as trapping reagents for cysteine and its related thiols is shown.

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