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

Hideto Miyabe*

School of Pharmacy, Hyogo University of Health Sciences, Minatojima, Kobe 650-8530, Japan; E-mail: miyabe@huhs.ac.jp

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 aryne precursors led to growing activity in this field. Most reactions using these aryne 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 S_N2' reaction of tricyclic oxygen heterocycles, obtained by three-component coupling reaction, was studied by using carbon and sulfur nucleophiles. The S_N2' reaction was expanded to four-component coupling reaction. Finally, the application of tricyclic oxygen heterocycles to cysteine-selective trapping is described.

CONTENTS

1. INTRODUCTION

The use of kinetically unstable arynes in organic synthesis has attracted substantial attention since the 1950s.[1] The strained arynes **A** react with various nucleophiles as powerful electrophiles, leading to the formation of substituted arenes *via* the protonation of anions **B** (Figure 1).[2] Furthermore, the concerted reactions of arynes **A** such as Diels–Alder reaction and dipolar cycloaddition reaction are the synthetically useful method for preparing bicyclic compounds or benzo-fused heterocycles.[3–6] 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.[7–10]

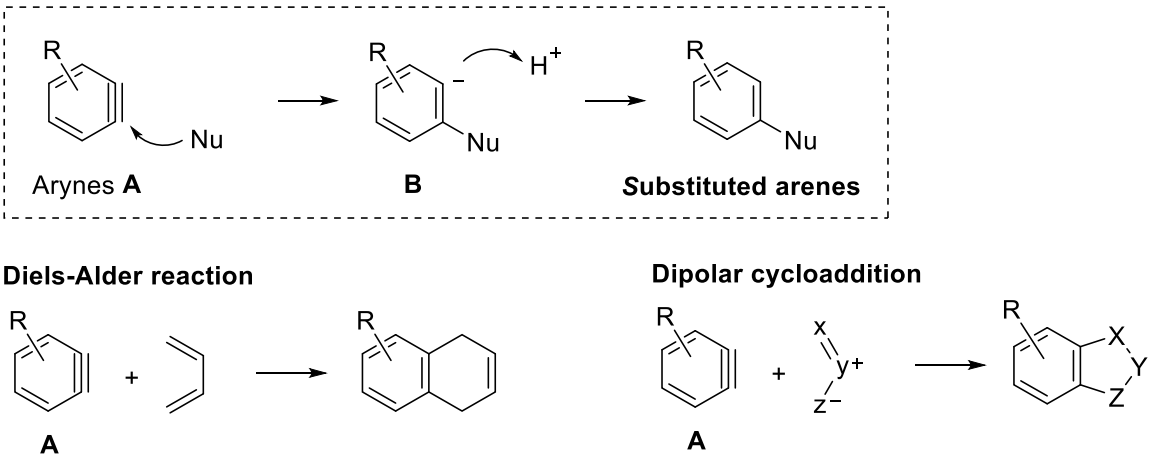


Figure 1. Reactions of arynes

In the past decade, arynes have gained increasing attention as highly reactive species for constructing the multisubstituted arenes with structural diversity and complexity.[11] Particularly, the development of *ortho*-(trimethylsilyl)aryl triflates **1** as easily activatable aryne precursors led to growing activity in this field, resulting in the development of new aryne-based reactions (Figure 2).[12] The generation of arynes **A** can be achieved by treatment of triflates **1** 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 **1**, which comprise the initial addition of nucleophiles to arynes **A** and the subsequent trapping of intermediates **B** with electrophiles. The important feature is that arynes **A**

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).[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 *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.[6] In recent years, the dramatic progresses in aryne-based chemistry are summarized in many review articles.[3,7,11]

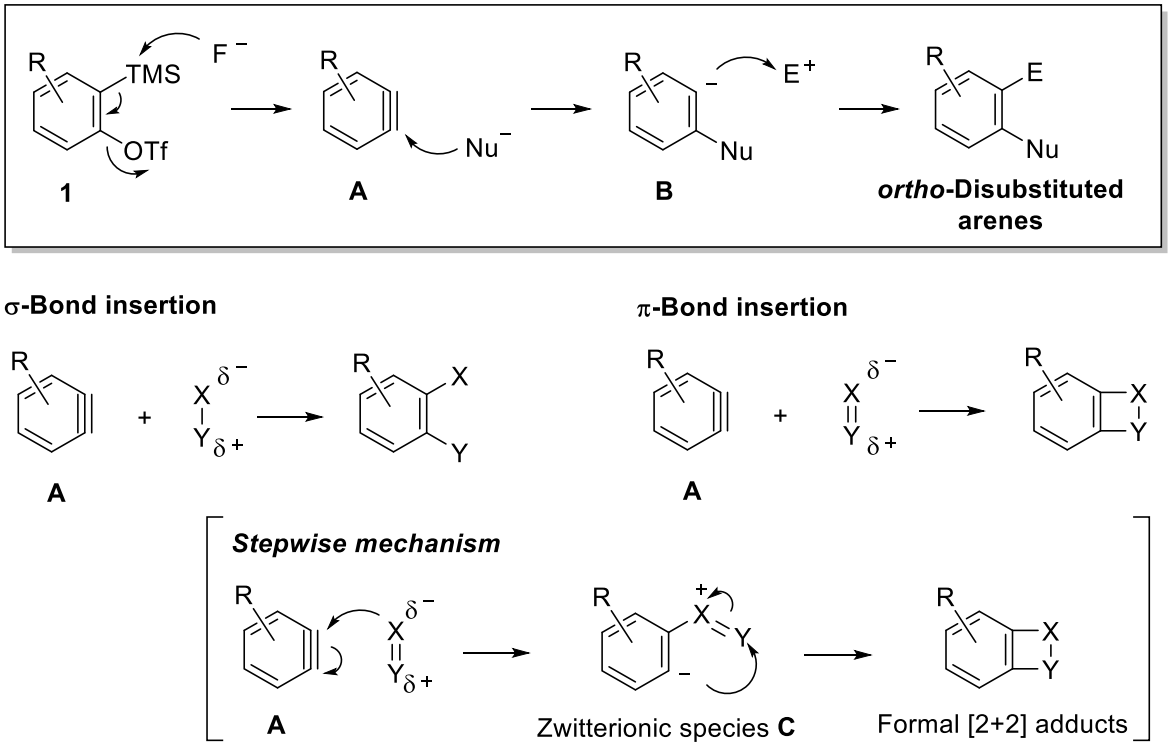
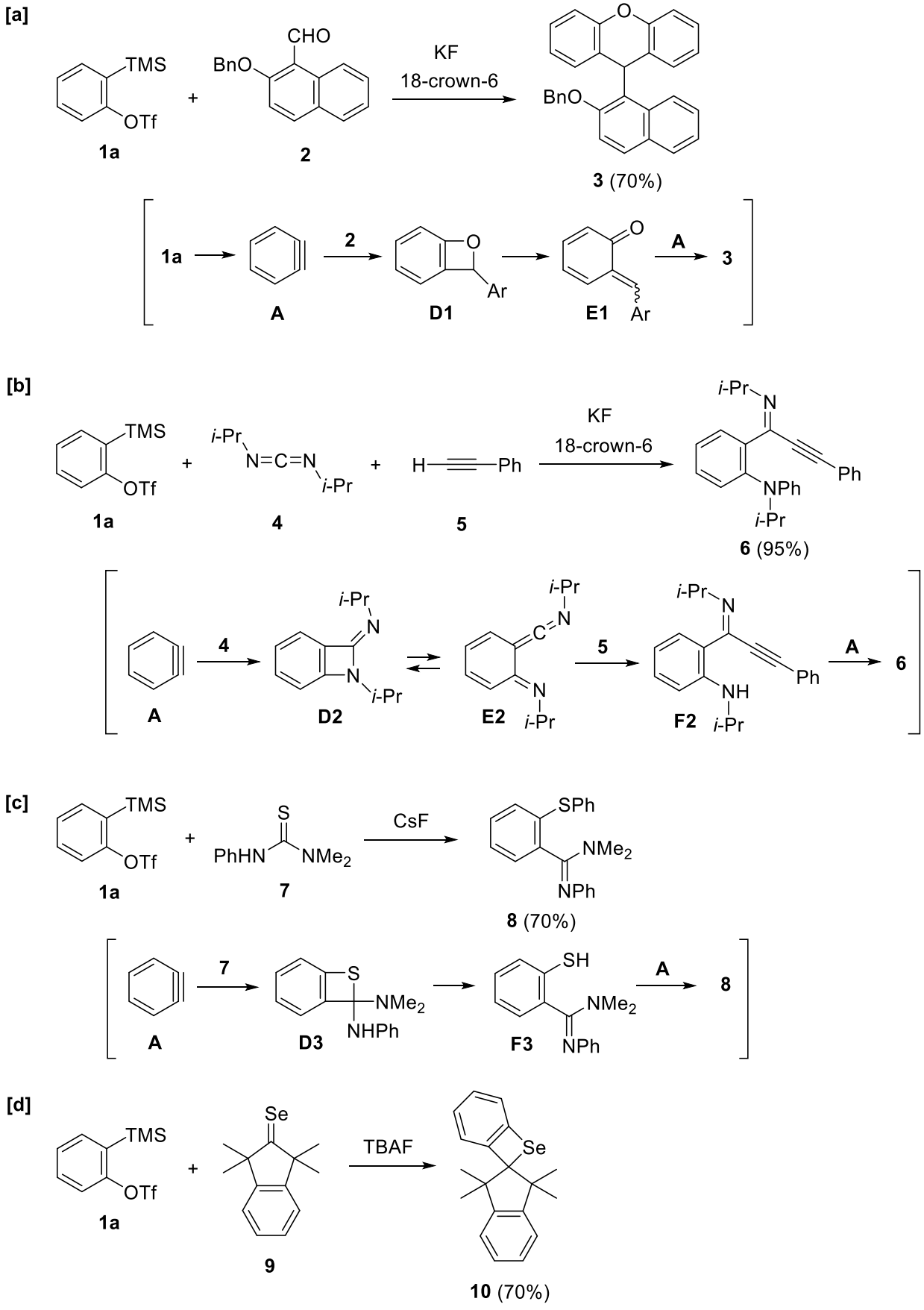


Figure 2. Reactions using aryne precursors 1

2. REACTION OF ARYNES WITH DOUBLE BOND

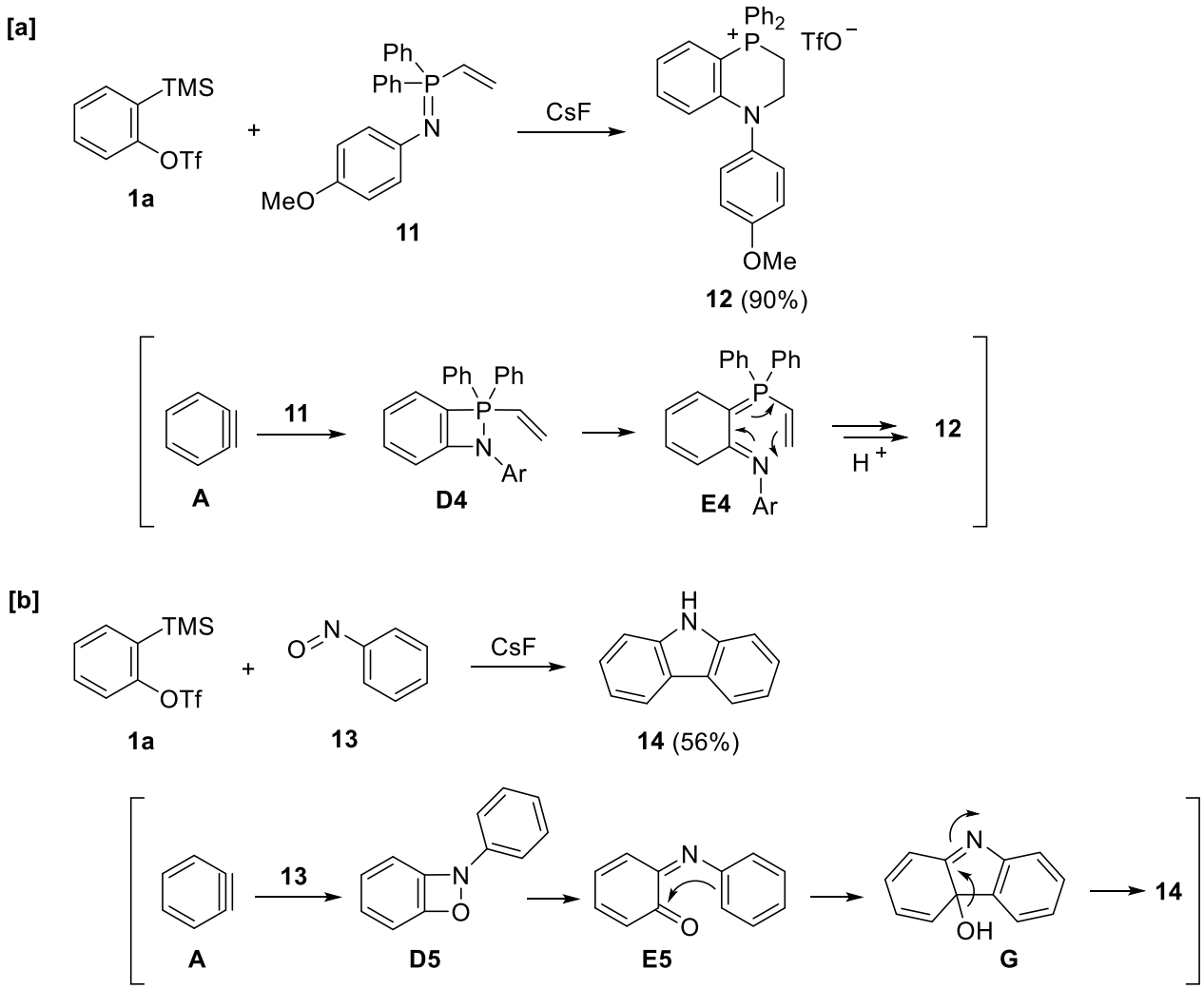
The representative reactions involving the formal [2+2] cycloaddition of arynes with the carbon–heteroatom double bond are shown in Scheme 1. The insertion of arynes into the carbon–heteroatom double bond takes place probably by the stepwise [2+2] mechanism as shown in Figure 2. In general, the insertion 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.[14] 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).[15] When *ortho*-(trimethylsilyl)aryl triflates **1a** as aryne precursor and 2-benzyloxy-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 triflate **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.[16] The reaction of the C=N bond of carbodiimides with arynes was studied by using aryl triflate precursors.[17] As the synthetically useful transformation, three-component coupling reaction using aryne precursor **1a** carbodiimides and terminal alkynes was achieved in the presence of KF and 18-crown-6 (**[b]** in Scheme 1).[17b] 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, phenylethyne **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.[18] The reaction with the C=S bond of thioureas was reported.[18b] 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.[19] Interestingly, 2*H*-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).[19a]

The synthetically useful reactions starting from insertion of aryne **A** to the heteroatom-heteroatom double bond are developed (Scheme 2).[20,21] The [2+2]-type reaction of arynes with the P=N bond was reported.[20a] In the presence of CsF, treatment of *P*-alkenyl-λ^5-phosphazene **11** with aryne precursor **1a** gave 1,4-benzazaphosphorinium triflate **12** in 90% yield (**[a]** in Scheme 2). The phosphorinium triflate **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).[20b] The reaction mechanism involving the [2+2]-type reaction leading to **D5** and the intramolecular electrophilic aromatic substitution of intermediate **E5** was proposed.



Scheme 2. Insertion into P=N and N=O bonds

3. REACTION OF ARYNES WITH AMIDES

Highly reactive arynes can activate both N−C and C=O bonds of amide group, leading to σ-bond insertion or π-bond insertion reactions (Figure 3).[22] When the nitrogen atom of amides acts as a nucleophile, the insertion of aryne **A** into N−C σ-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 π-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 π-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,[23,24] the further transformations can be developed.

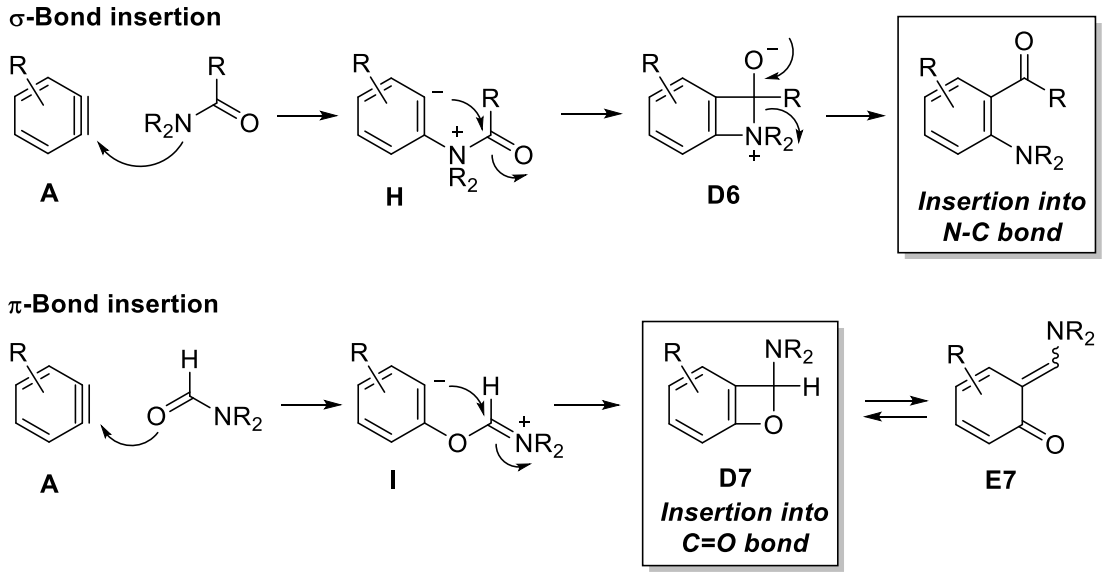
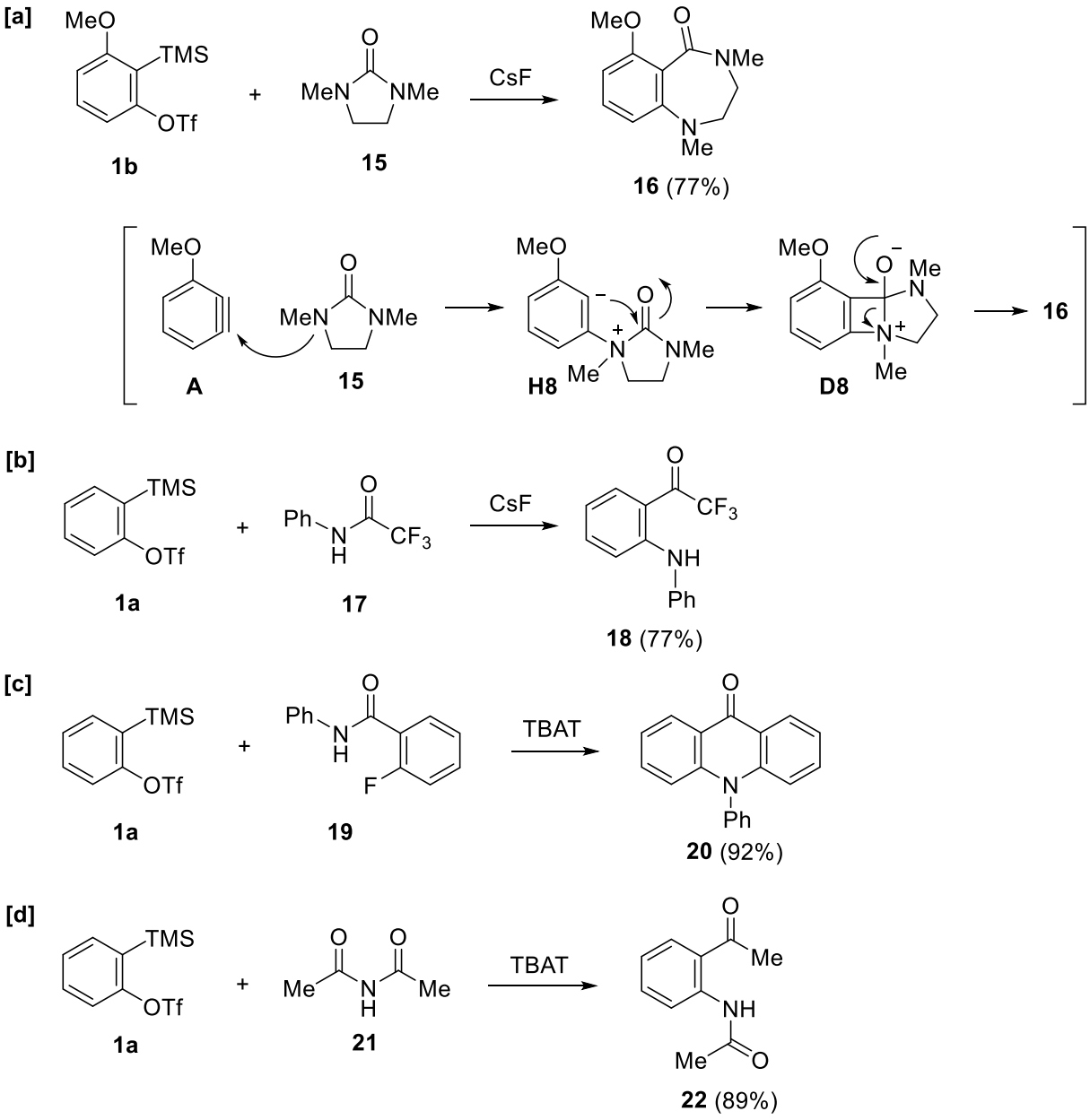


Figure 3. σ-Bond insertion and π-bond insertion

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.[25] 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 CF_3 group on amides is critical to the success of this transformation.[26] 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 CF_3 group, the N−C bond insertion using simple aryl amides was investigated by changing solvents and fluoride sources.[27] 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_NAr 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

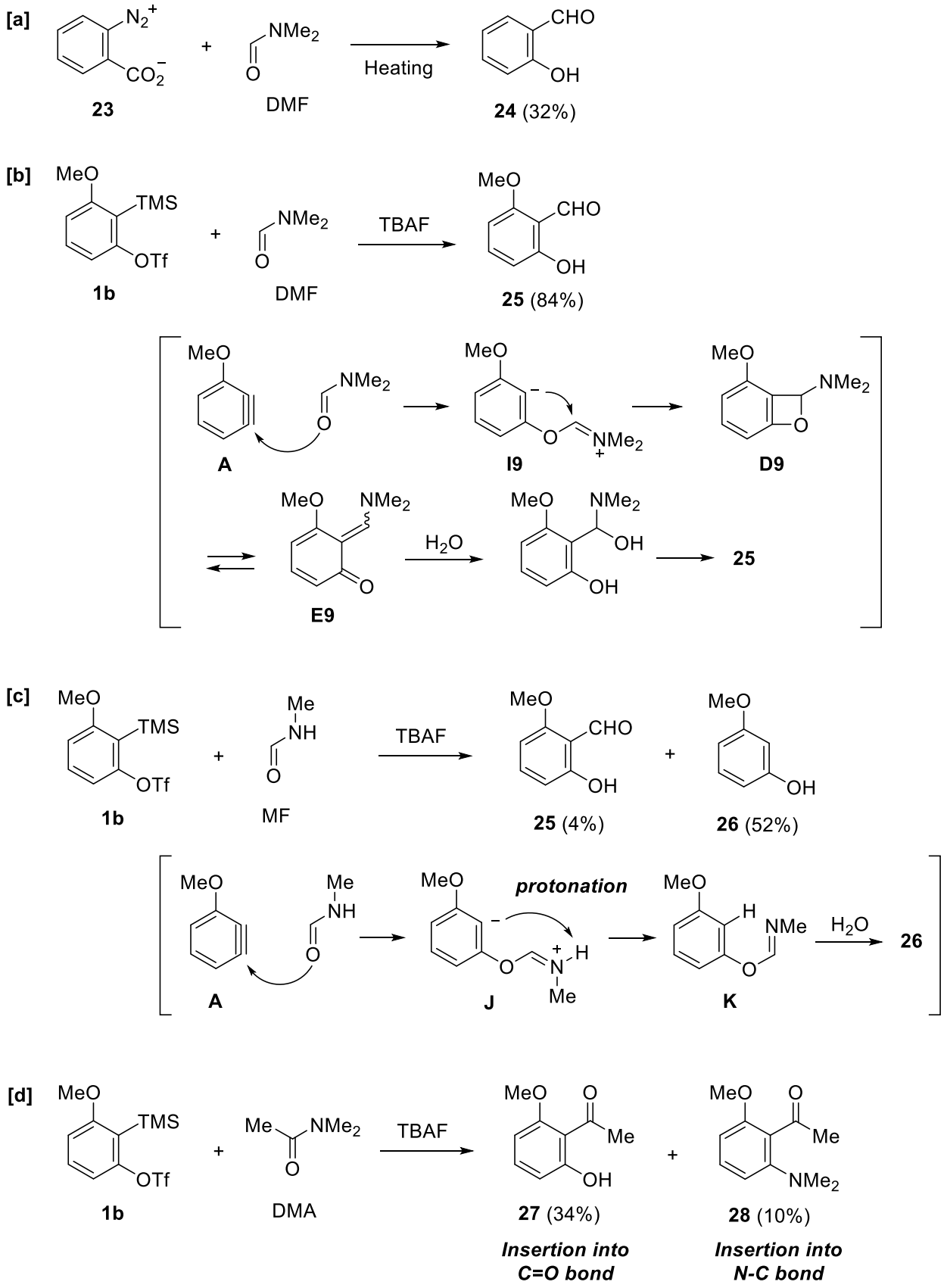
N−C insertion product **22** in 89% yield (**[d]** in Scheme 3).[28] As the effective N−C insertion reaction, the insertion of arynes into the N−C bond of β-lactam was reported.[29]



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

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

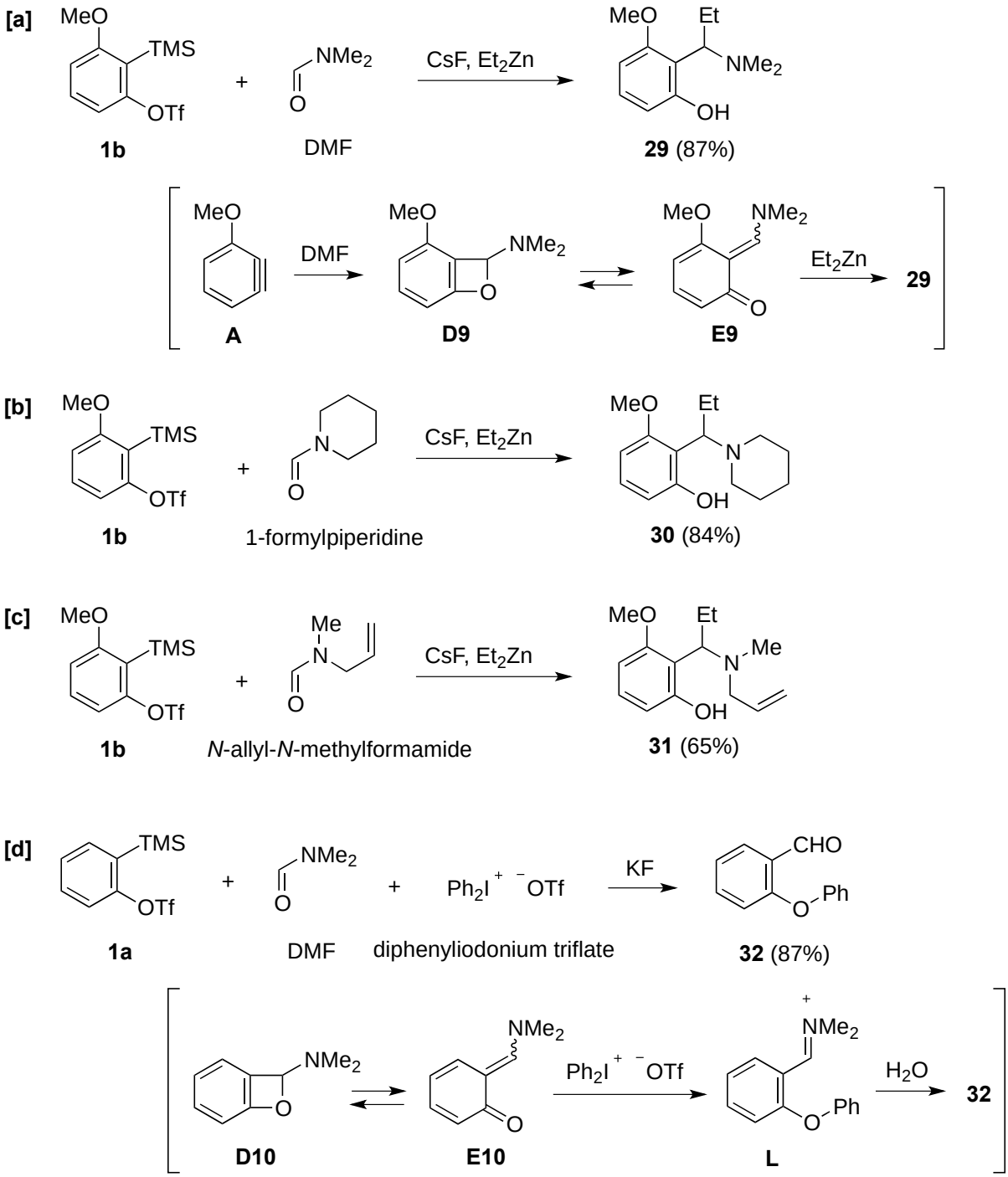
In organic synthesis, *N*,*N*-dimethylformamide (DMF) can react as either an electrophilic or nucleophilic agent.[30] The insertion of arynes into the C=O bond of amide group was studied mainly by the use of DMF as a sterically less hindered formamide.



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 **I9**. 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 Et_2Zn 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 Et_2Zn 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, Me_2Zn and Ph_2Zn 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.



Scheme 5. Trapping reaction of the unstable intermediates

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).[35] 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. in a

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.

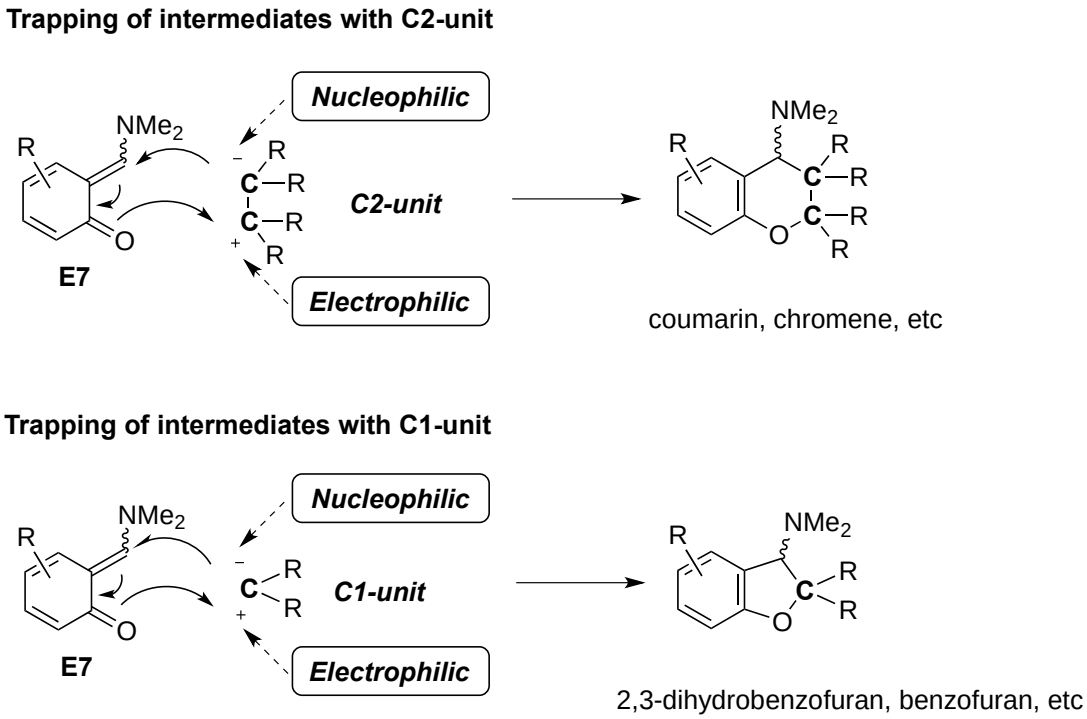
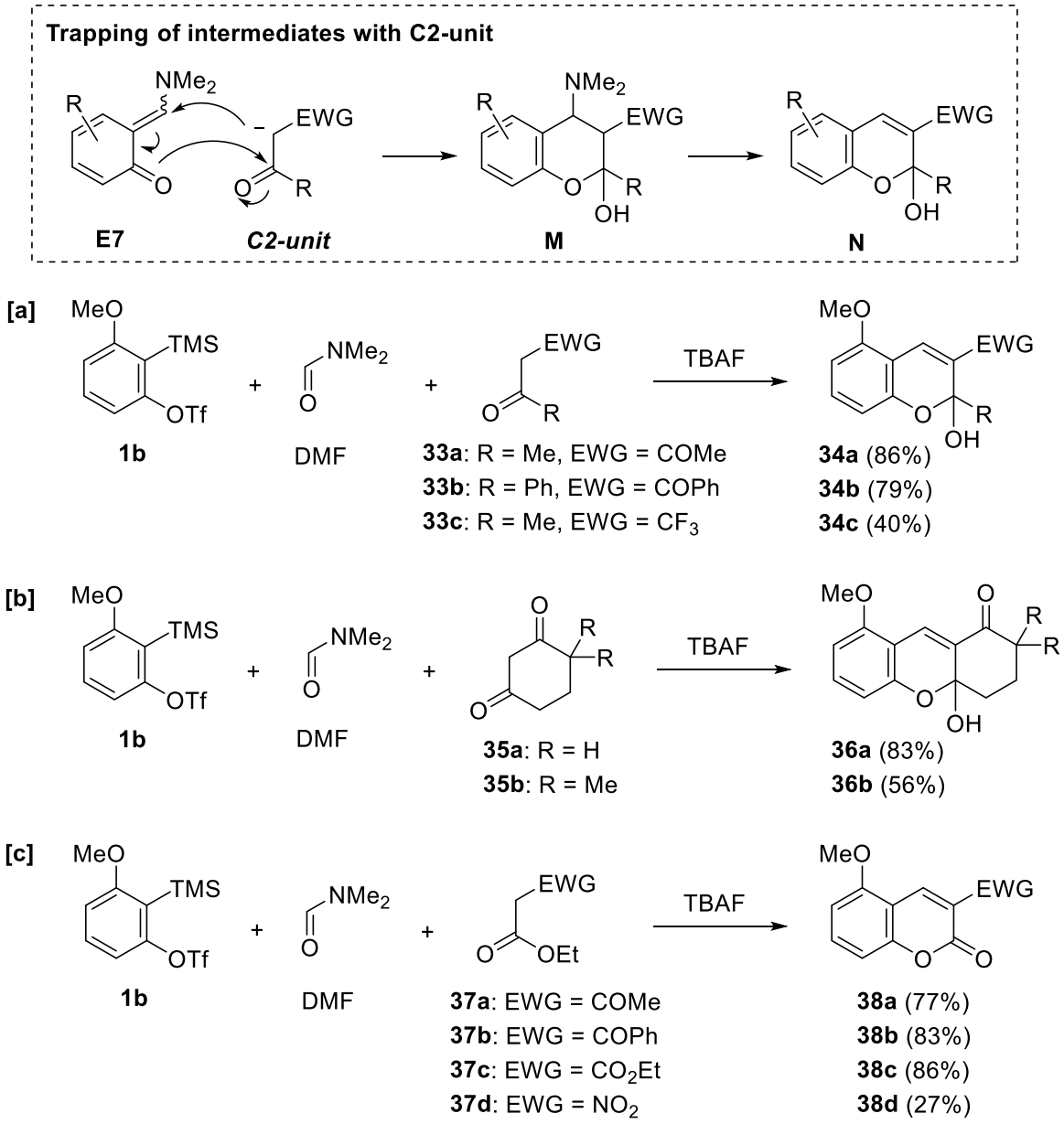


Figure 4. Synthetic approaches to benzo-fused oxygen-heterocycles

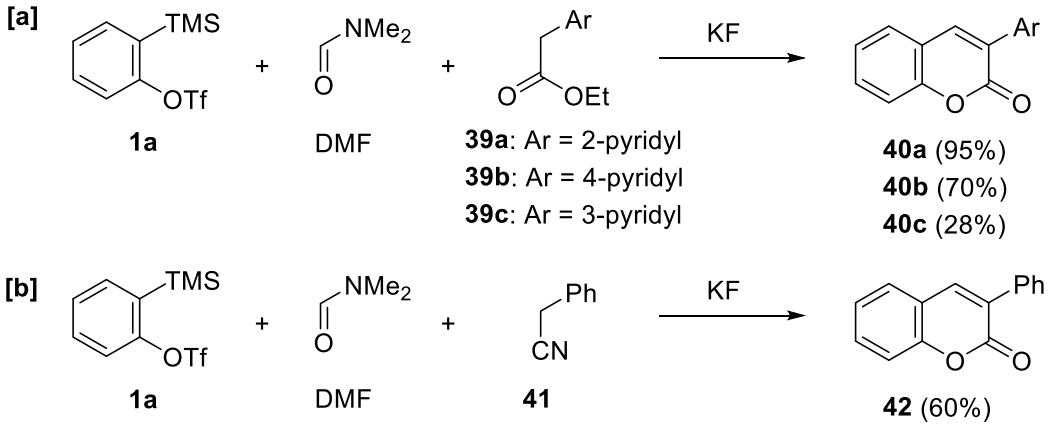
We used the anions of active methylenes as C2-units having both nucleophilic and electrophilic sites (Scheme 6).[35a,c] Trapping the intermediate **E7** with C2-unit leads to the coumarin derivatives **M** and **N**. In the presence of anhydrous TBAF as fluoride ion source, treatment of precursor **1b** with acetylacetone (**33a**) in DMF gave the 2*H*-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_3 group gave the corresponding 2*H*-chromenes **34b** and **34c** in 79% and 40% yields, respectively. When cyclic 1,3-diketone **35a** was employed as C2-unit, the tricyclic 2*H*-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 arynes to give the σ-bond insertion products.[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.



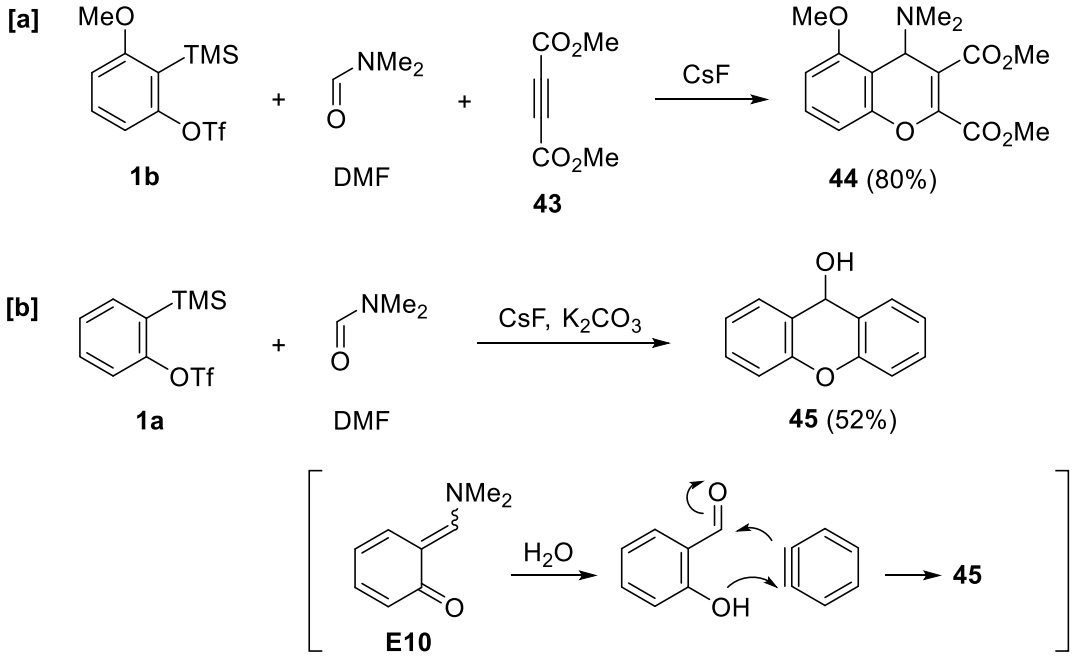
Scheme 6. Trapping reaction with active methylenes as C2-units

Three-component coupling reaction for preparing the coumarin derivatives substituted an aryl group at 3 position was also reported by Yoshida's group.[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).

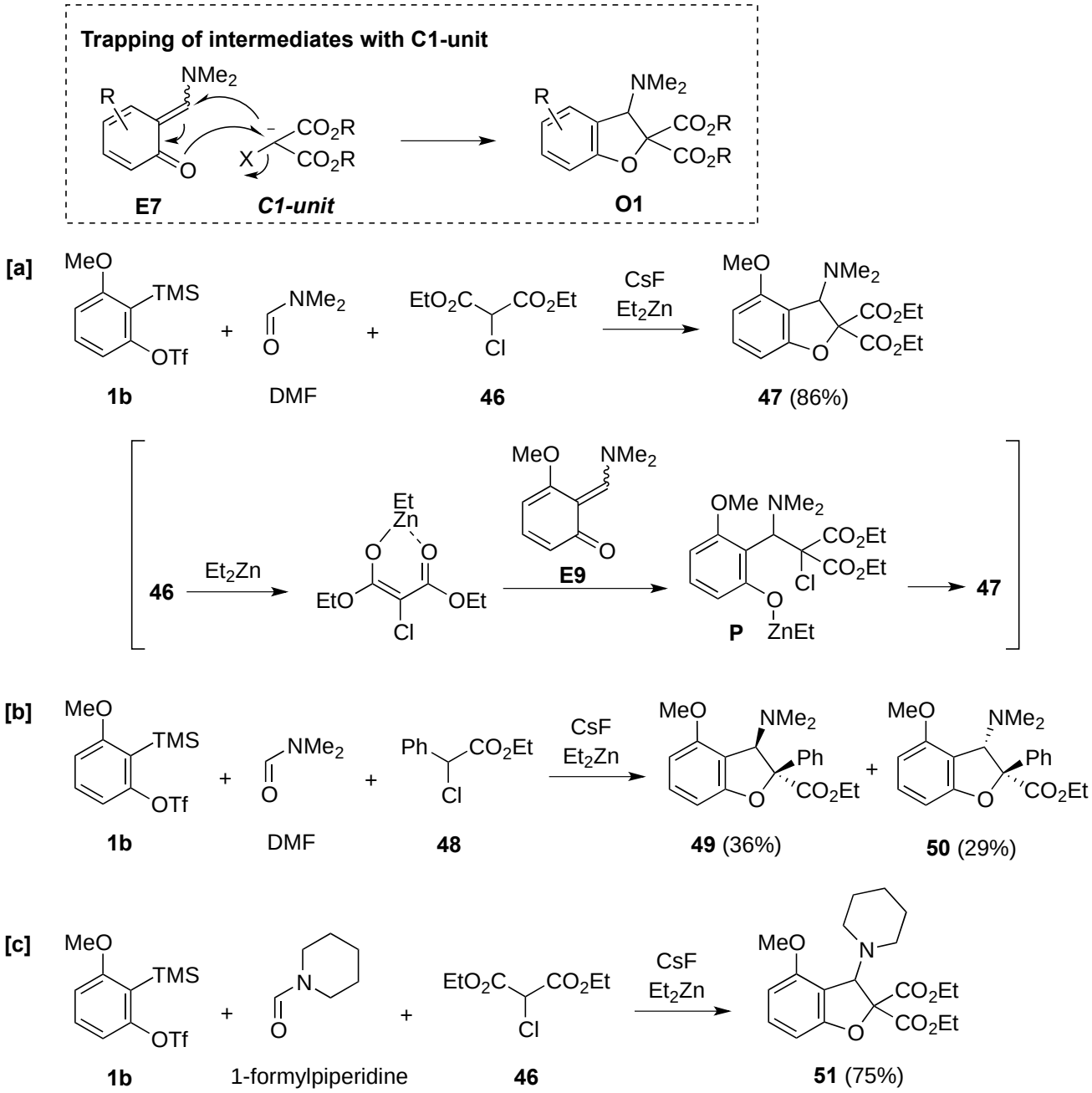


Scheme 7. Synthesis of coumarin derivatives

Next, the hetero Diels–Alder reaction for trapping *ortho*-quinone methides with dienophiles was investigated (**[a]** in Scheme 8).[38] In the presence of CsF, treatment of precursor **1b** with dimethyl acetylenedicarboxylate (**43**) in DMF gave 4*H*-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.[39] In the presence of CsF and K_2CO_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**.



Scheme 8. Hetero Diels-Alder type reaction

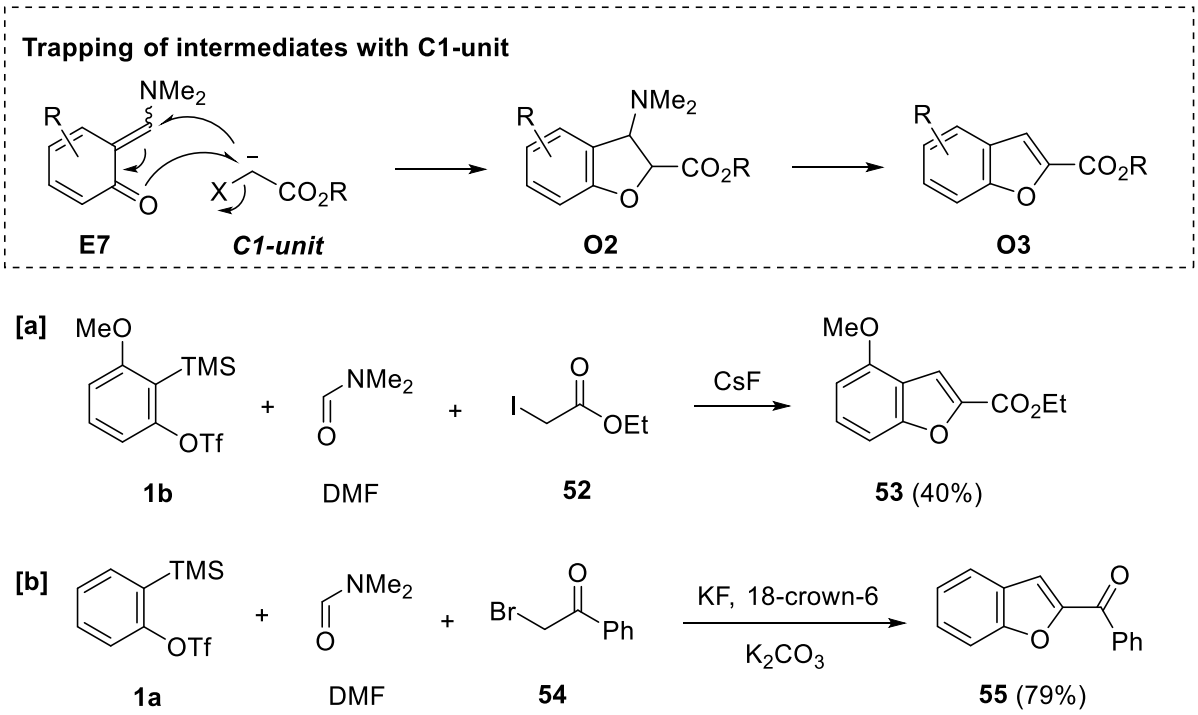


Scheme 9. Trapping reaction with active methines as C1-units

Next, three-component coupling reaction leading to the formal [4+1] adducts such as 2,3-dihydrobenzofuran derivatives **O1** was investigated.[35b] In this transformation, the α-halogenated active methines must be employed as C1-units for trapping intermediate **E7**. The desired α-halogenated enolate can be prepared by the reaction of α-chloromalonate **46** with Et_2Zn. In the presence of CsF and Et_2Zn, treatment of precursor **1b** with α-chloromalonate **46** in DMF gave 2,3-dihydrobenzofuran **47** in 86% yield (**[a]** in Scheme 9). Consequently, *ortho*-quinone methide **E9** was trapped by zinc α-chloroenolate, generated from **46**, to give dihydrobenzofuran **47** *via* the intermediate **P**. Moreover, ethyl α-chlorophenylacetate (**48**) participated in three-component coupling reaction to give two diastereomers

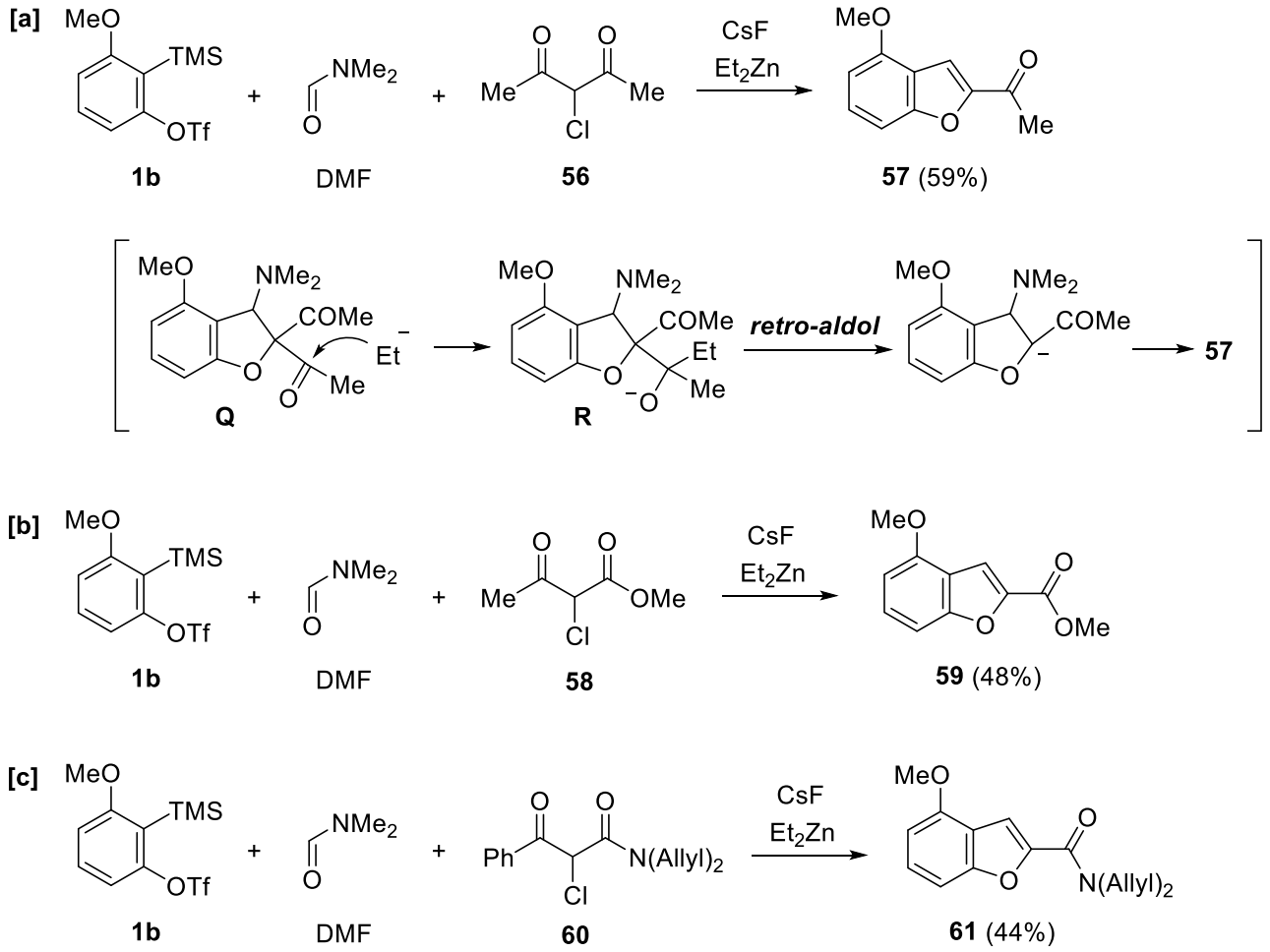
49 and **50** (**[b]** in Scheme 9). When 1-formylpiperidine was used as formamide instead of DMF, 2,3-dihydrobenzofuran **51** was obtained in 75% yield under similar reaction conditions (**[c]** in Scheme 9).

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 K_2CO_3 (**[b]** in Scheme 10).[40]



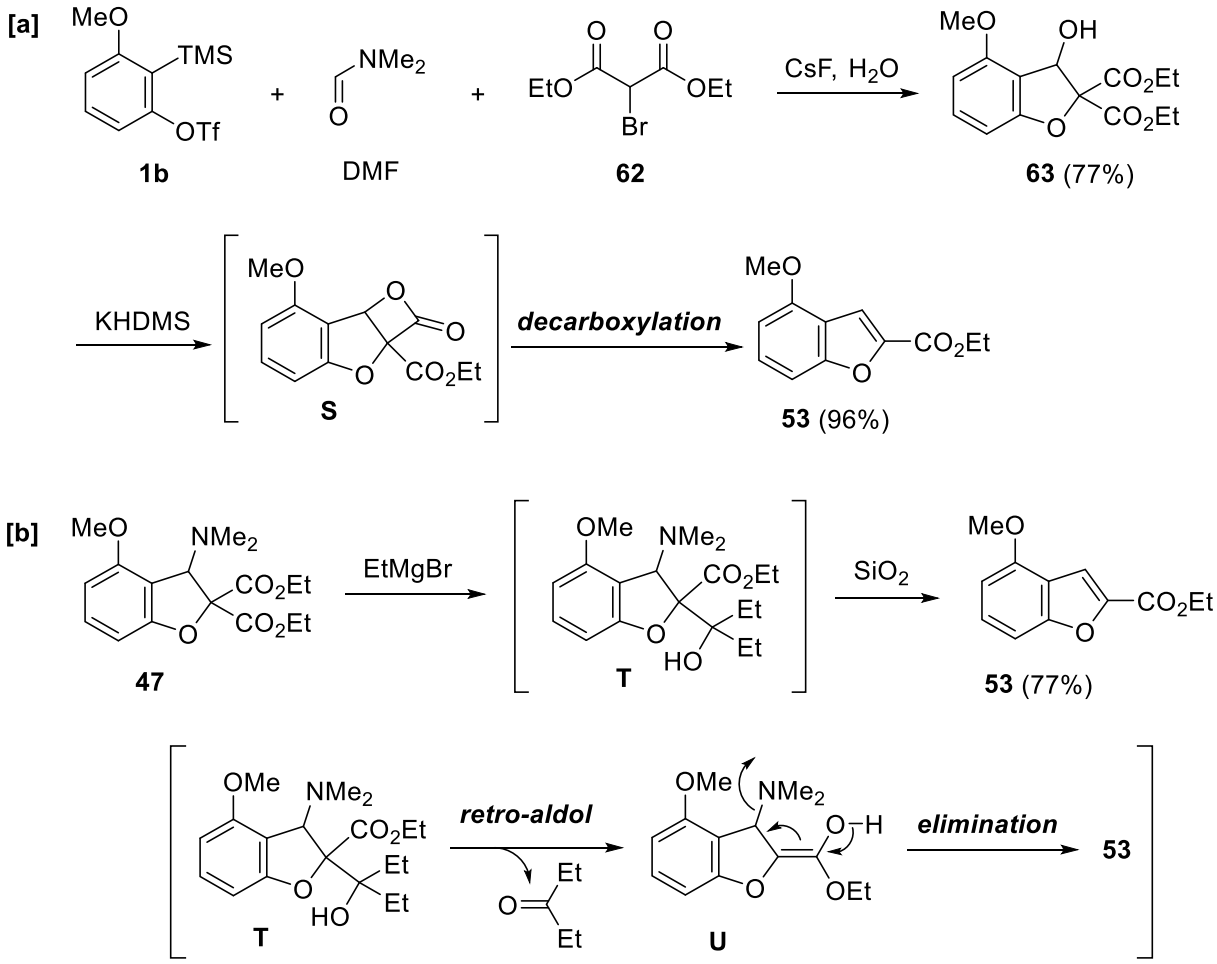
Scheme 10. Synthesis of benzofuran derivatives

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 Et_2Zn 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 Et_2Zn, 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).



Scheme 11. Synthesis of benzofurans *via* retro-aldol type reaction

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 Et_2Zn (**[a]** in Scheme 12).[35c] 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**.[41] 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 SiO_2 (**[b]** in Scheme 12).[35b,c] 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**.

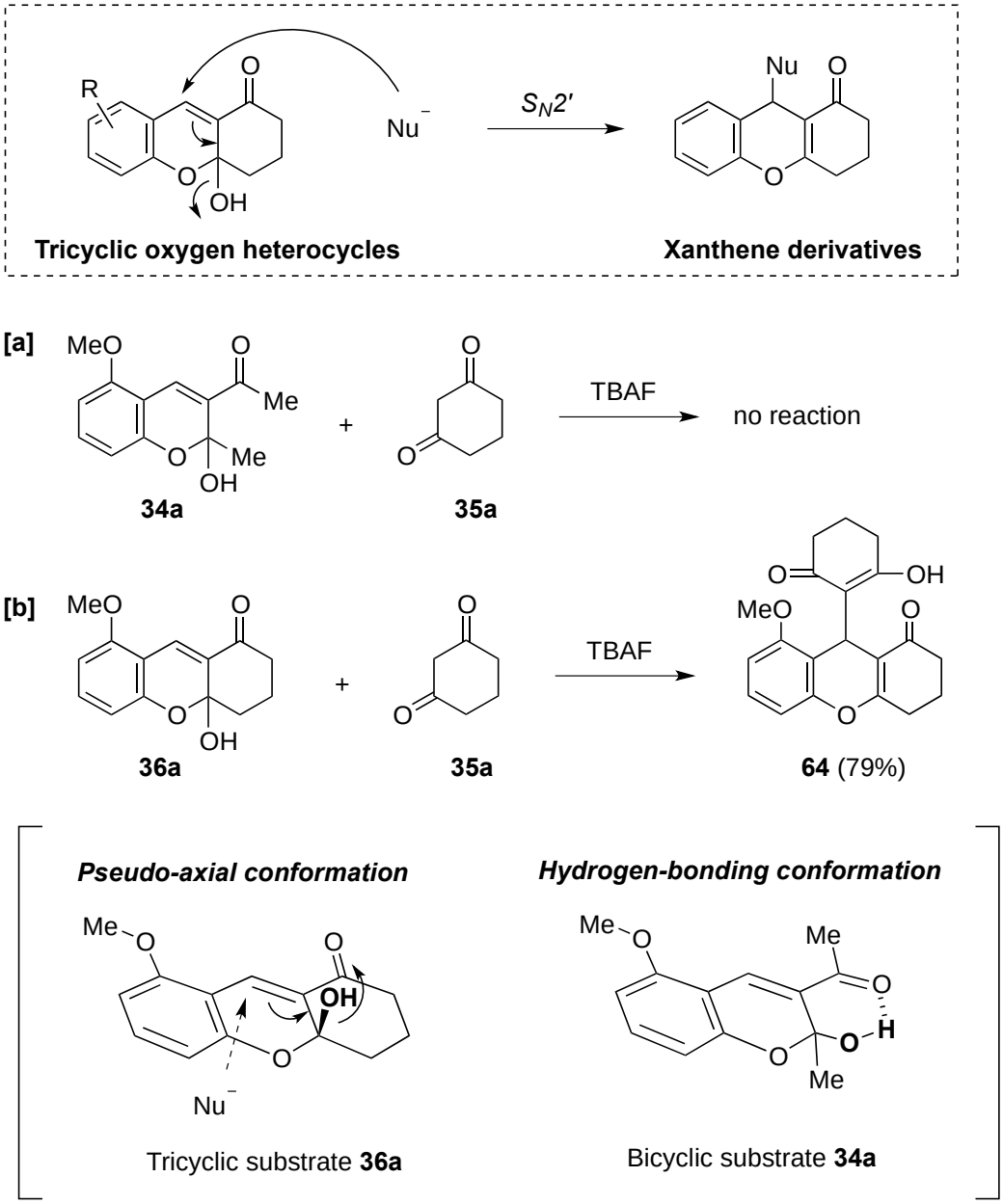


Scheme 12. Other methods for synthesis of benzofuran

4. REACTION OF TRICYCLIC OXYGEN HETEROCYCLES

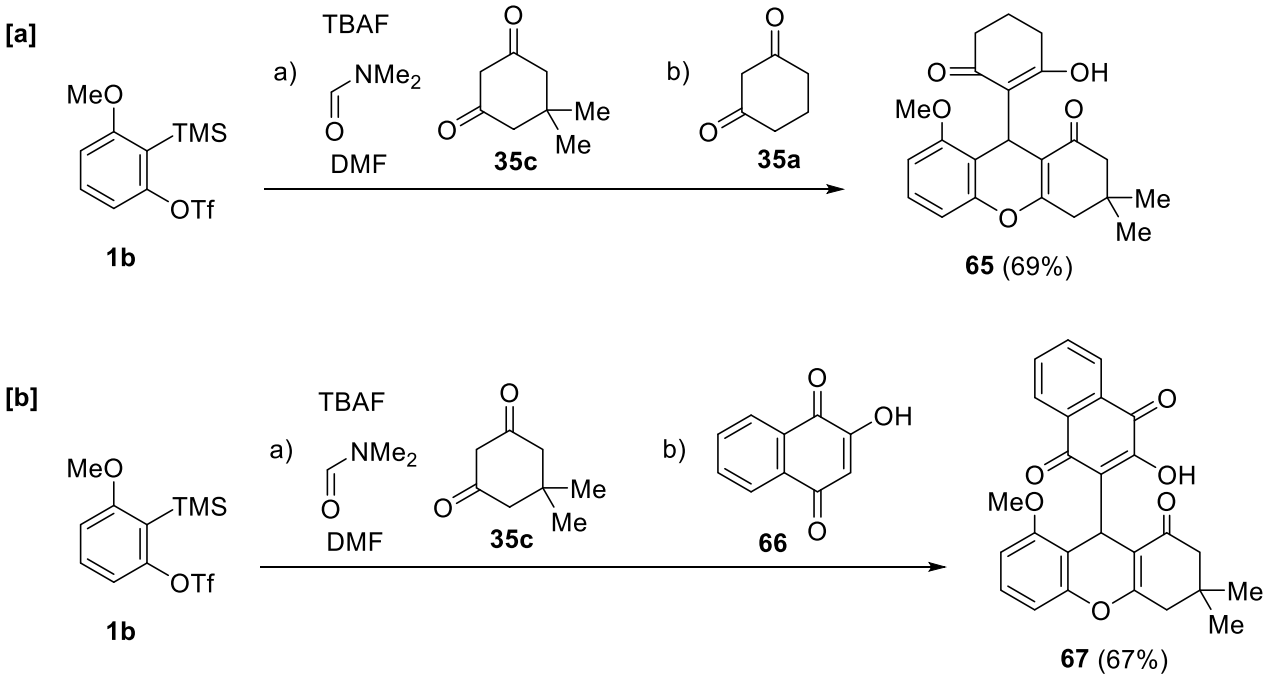
4-1. Reaction with Carbon Nucleophiles

Further transformations of benzo-fused oxygen heterocycles, obtained by three-component coupling reaction of arynes with DMF and active methylenes, were investigated.[42] 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**.



Scheme 13. Reaction of oxygen heterocycles with carbon nucleophile

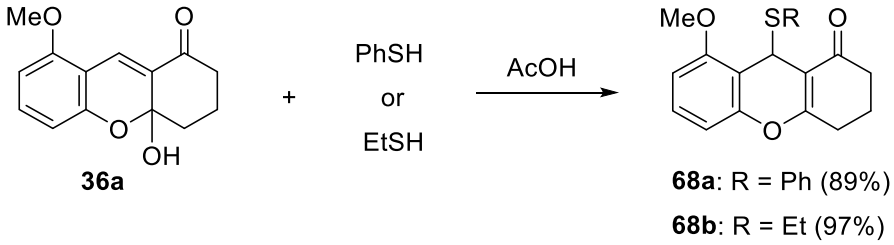
The S_N2' reaction of tricyclic oxygen heterocycles was successfully expanded into the one-pot four-component coupling reaction which involves the formation of two C–O and three C–C bonds. In the presence of anhydrous TBAF, the four-component coupling reaction using two different 1,3-diketones **35c** 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_N2' 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_N2' reaction, the xanthene derivative **67** was obtained in 67% yield (**[b]** in Scheme 14).[43]



Scheme 14. One-pot four-component coupling reaction

4-2. Reaction with Sulfur Nucleophiles

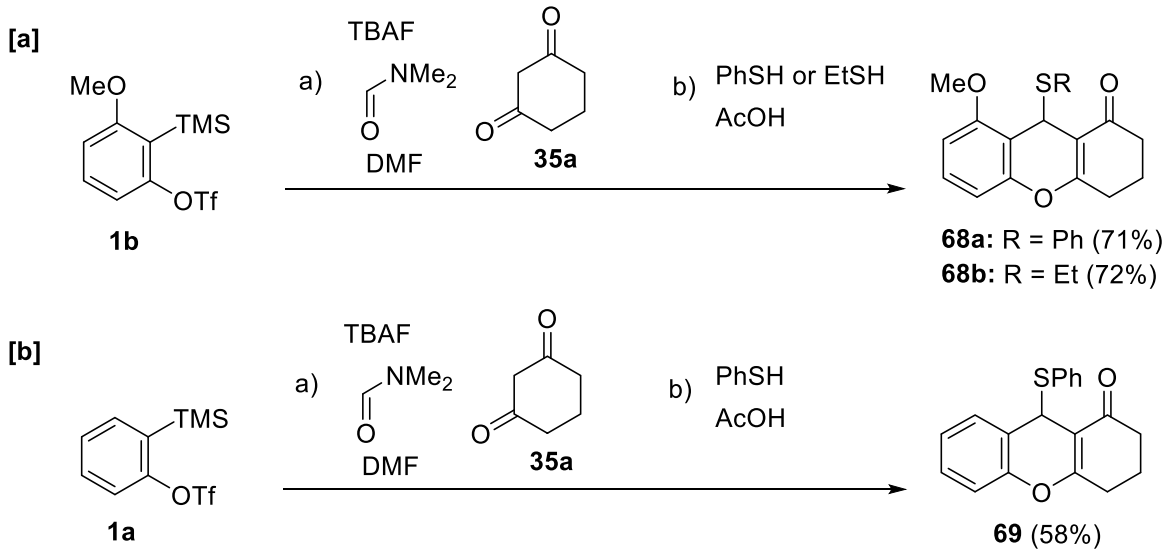
Thiols also acted as nucleophiles for the reaction of tricyclic substrate **36a**, allowing facile incorporation of structural variety (Scheme 15).[42] The effective transformation using thiols was achieved by employing acetic acid, which will activate the hydroxy group as leaving group. In the presence 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.



Scheme 15. Reaction of tricyclic oxygen heterocycle with thiols

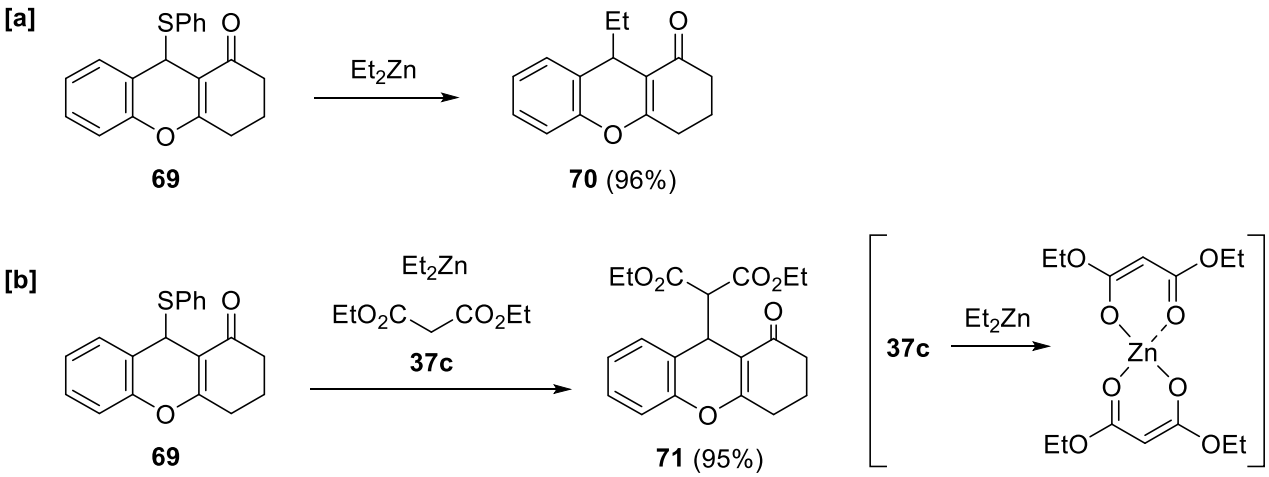
The reaction using thiols was also applied to the one-pot four-component coupling reaction involving the formation of C–S, two C–O and two C–C bonds. After triflate **1b** (1.2 equiv) was reacted with DMF and 1,3-diketone **35a** in the presence of TBAF, a solution of thiols and acetic acid in MeCN was 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 Et_2Zn 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.[44] In particular, the site-specific modification of proteins and peptides has attracted substantial attention, since 20 different amino acids are incorporated to proteins.[45] 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.[46] For examples, maleimides,[47] α-halocarbonyls[48] and vinyl sulfones[49] 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.

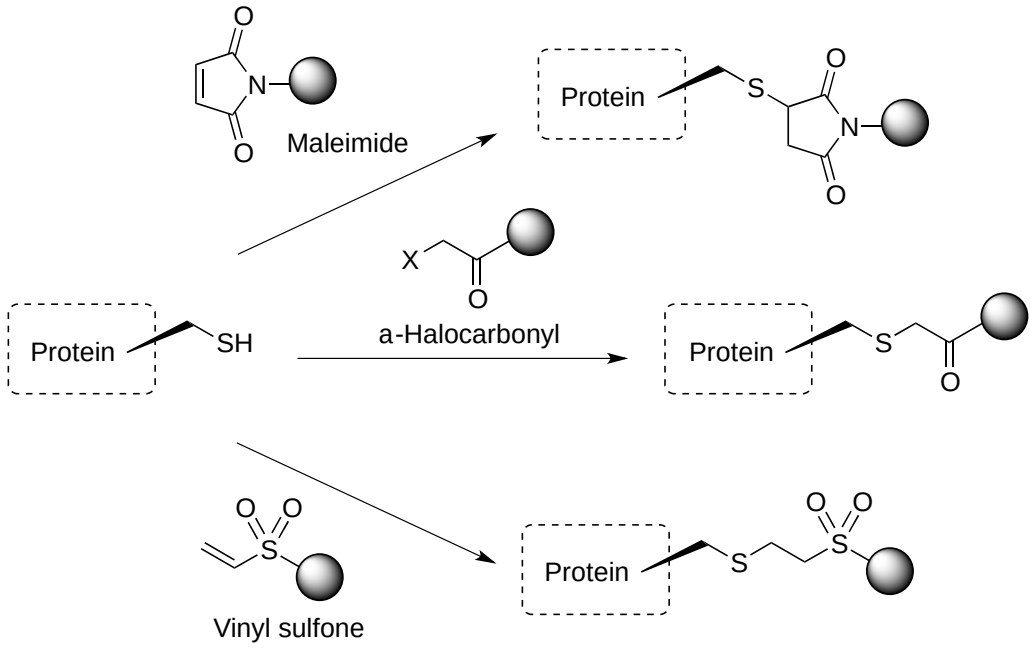
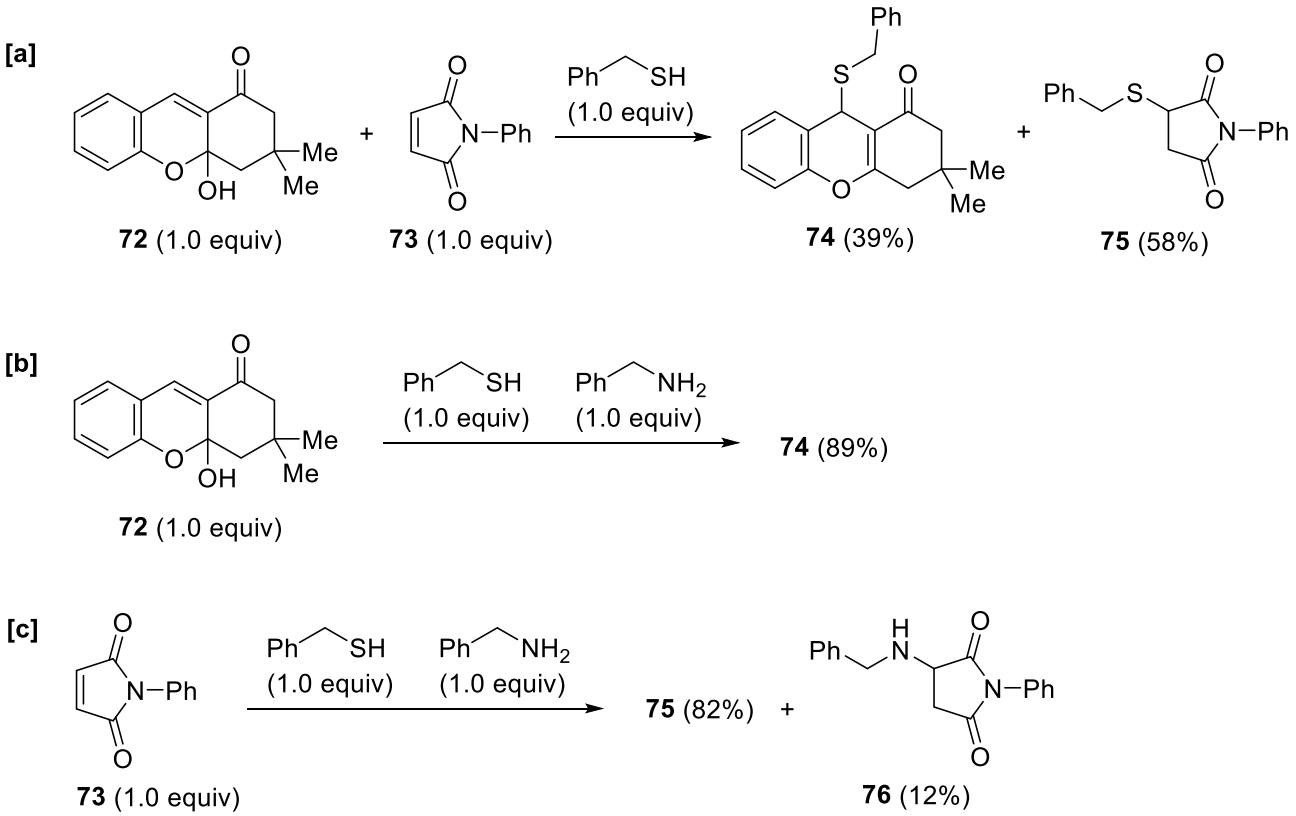
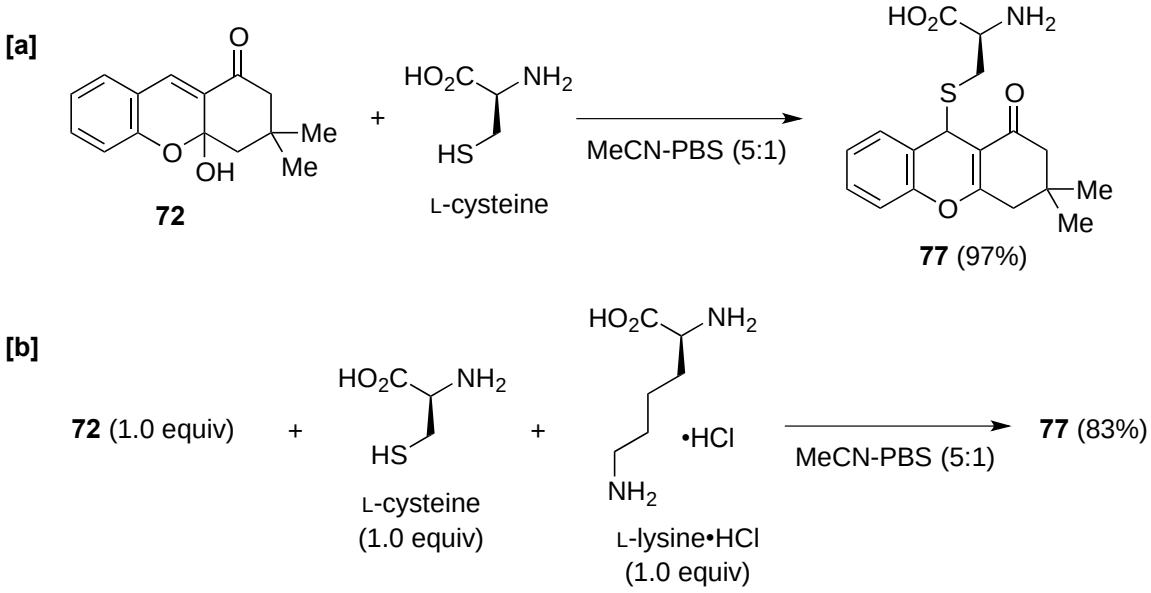


Figure 5. Cysteine-selective modification methodology

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).[50] 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.



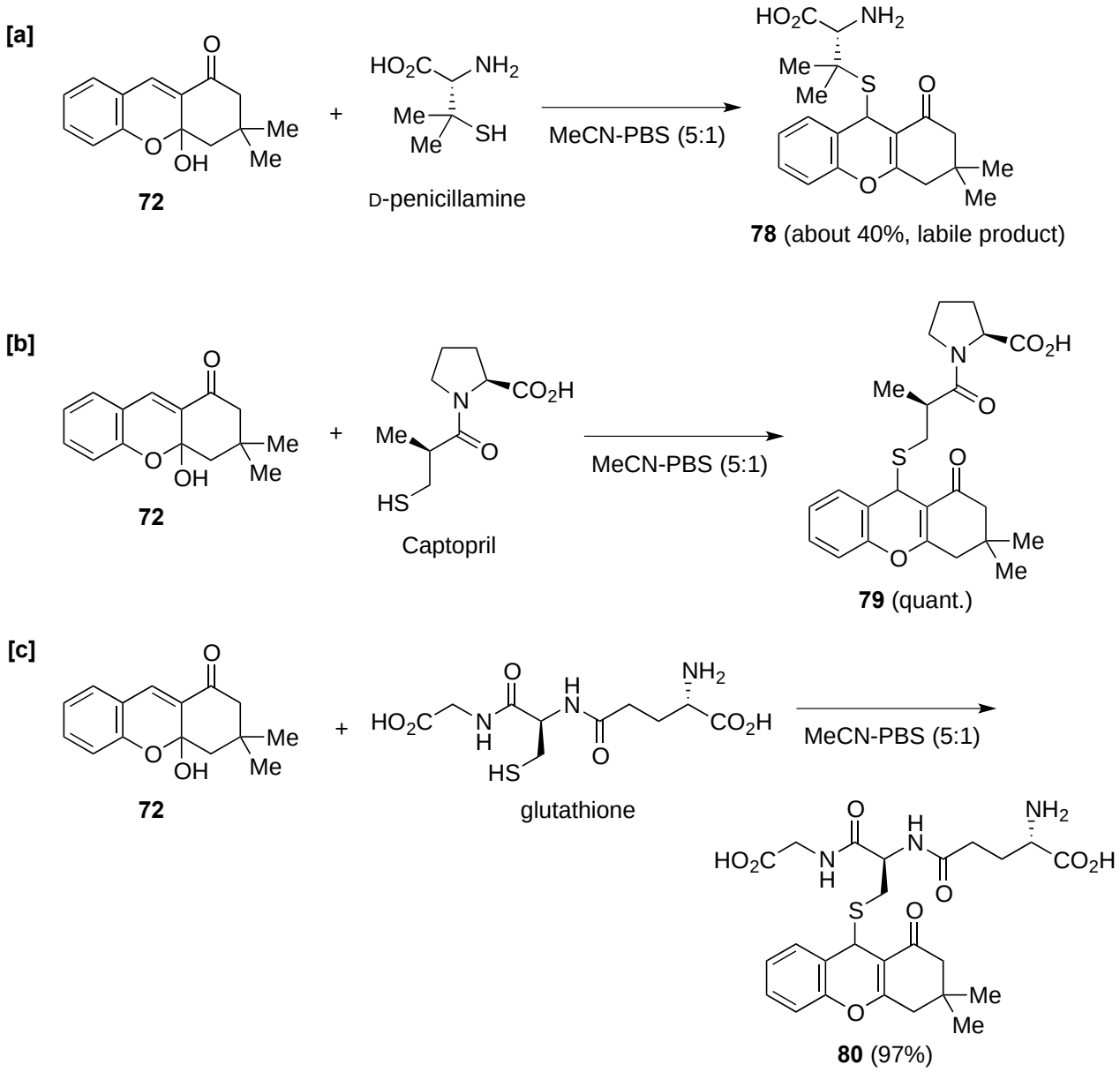
Scheme 18. Reactivity and selectivity of oxygen heterocycle toward benzylthiol



Scheme 19. Cysteine-selective reaction of oxygen heterocycle

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

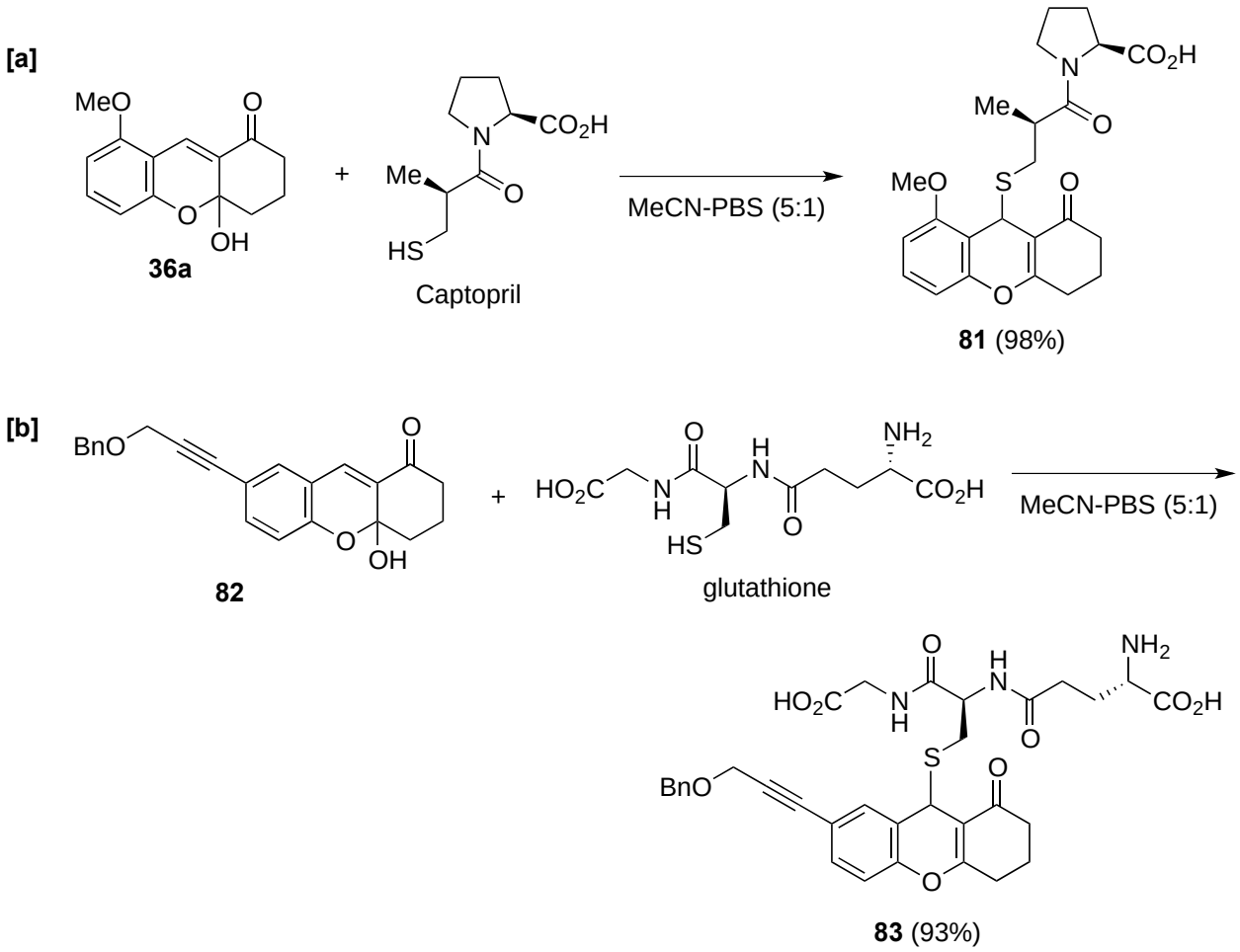
acid. The desired thiol-adduct **77** was obtained in 97% yield by using MeCN–PBS (5:1, v/v) as mixed solvent. The high cysteine-selectivity of oxygen heterocycle **72** was confirmed by the competition experiment using L-cysteine and L-lysine monohydrochloride (**[b]** in Scheme 19). As expected, L-lysine 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.[50b] 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 aryne 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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Hideto Miyabe is professor at School of Pharmacy, Hyogo University of Health Sciences. He received B. Sc. (1991) and Ph. D. degree (1996) from Osaka University. He joined Kobe Pharmaceutical University as assistant professor in 1996. He worked as a JSPS postdoctoral fellow with Prof. Mukund P. Sibi at North Dakota State University in 2001. He moved to Graduate School of Pharmaceutical Sciences, Kyoto University, as lecturer in 2002 and was promoted to associate professor in 2004. He moved to School of Pharmacy, Hyogo University of Health Sciences, as professor in 2007. He received The Nissan Chemical Industries Award in Synthetic Organic Chemistry, Japan in 1999, The Pharmaceutical Society of Japan Kinki-Branch Award for Young Scientists in 2000, and The Pharmaceutical Society of Japan Award for Young Scientists in 2003.