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SYNTHESES OF HETEROCYCLES VIA ALKYNE-CARBONYL METATHESIS OF UNACTIVATED ALKYNES

Akio Saito* and Keiichiro Tateishi

Division of Applied Chemistry, Institute of Engineering, Tokyo University of Agriculture and Technology, 2-24-16 Naka-cho, Koganei, Tokyo 184-8588, Japan.
E-mail address: akio-sai@cc.tuat.ac.jp

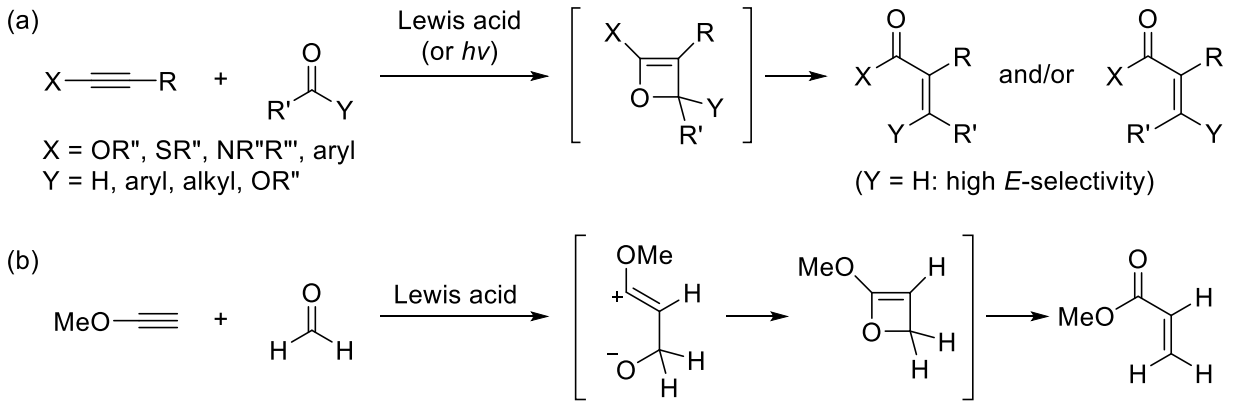
Abstract – The formation of α,β-unsaturated carbonyl compounds by a catalytic alkyne-carbonyl metathesis, which can be catalyzed by both π- and σ-acids, has received attention as an atom economical process alternative to the Wittig reaction. During the last decade, the catalytic alkyne-carbonyl metathesis has provided attractive methods for the construction of various cyclic compounds. This review summarizes synthetic methods of heterocycles with a focus on recent advances in the catalytic alkyne-carbonyl metathesis of the unactivated alkynes.

CONTENTS

1. INTRODUCTION

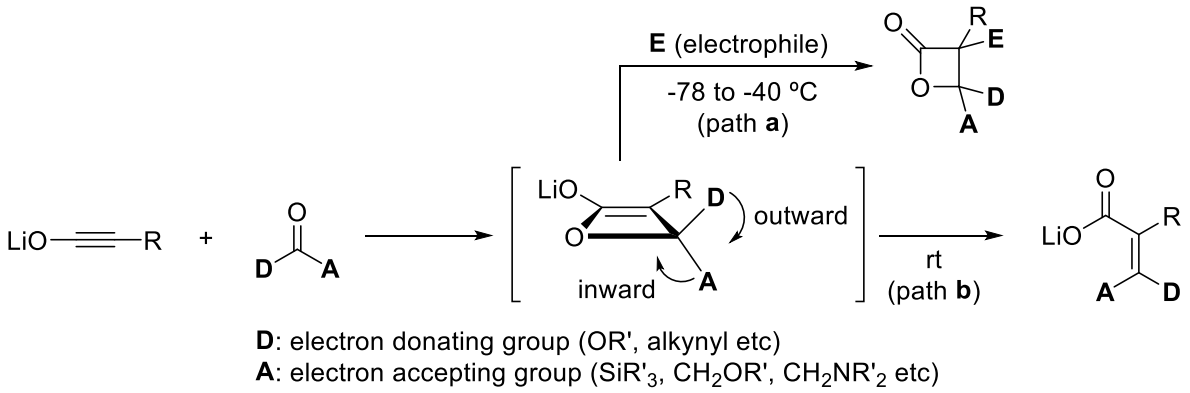
A metathesis reaction between a carbon–carbon triple bond and a carbonyl group, which is called "alkyne-carbonyl metathesis", "hetero-enyne metathesis", and so on, provides an attractive method for the construction of α,β-unsaturated carbonyl compounds (Scheme 1).[1] The alkyne-carbonyl metathesis was discovered from a study on UV-irradiated [2+2] cycloaddition reactions of unactivated alkynes with aromatic aldehydes or ketones in 1956.[2] Although the photoirradiation promoted the intramolecular alkyne-carbonyl metathesis of alkynes with aromatic aldehydes, ketones and quinones,[3] the photoreaction

brought about low yields, low regioselectivities and/or low stereoselectivities of products.[2,3] In 1959, Arens *et al*. first reported the Lewis acid-mediated formation of α,β-unsaturated esters from alkynyl ethers with aldehydes or ketones (Scheme 1a).[4] Since then, Lewis acid such as BF_3•OEt_2 and $TiCl_4$ have been reported to be effective on the alkyne-carbonyl metathesis of heteroatom-substituted alkynes with various carbonyl compounds including acetals and esters.[5,6] These reactions have been considered to proceed via oxetene intermediates because oxetenes were isolated in some cases.[7] On the basis of ab initio studies on alkyne-carbonyl metathesis of methoxyacetylene and formaldehyde, Pons *et al*. proposed that Lewis acid promotes asynchronous formation of the oxetene intermediates and further electrocyclic ring-opening into methyl acrylate (Scheme 1b).[8]



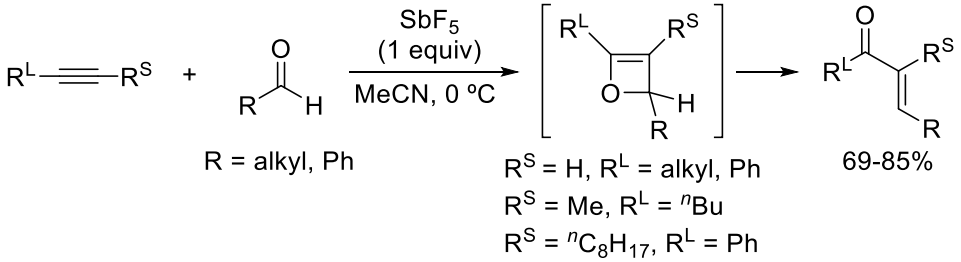
Scheme 1. Alkyne-carbonyl metathesis

Lithium ynolates can react with various carbonyl compounds in the absence of Lewis acid to afford β-lactones (path **a**)[9] or α,β-unsaturated carboxylic acids (path **b**),[10] which are formed from common oxetene intermediates (Scheme 2). In particular, the formation of α,β-unsaturated carboxylic acids from aldehydes,[10] acylsilanes,[10c] α-oxy- and α-amino ketones,[10e] alkynyl ketones,[10g] and esters[10f,h] proceeded with excellent stereoselectivity. Shindo *et al*. explicated that this high torquoselectivity[11] would be attributed to orbital interactions in the electrocyclic ring-opening reactions of oxetene intermediates.[10] Thus, the strong orbital interaction between the nonbonding orbital of the oxygen on the oxetene as well as the cleaving C-O σ-bond with antibonding orbitals such as the Si-C σ*-orbitals, C-Z (Z = O, N) σ*-orbitals makes the electron accepting substituents **A** at C-4 position of oxetene rotate inward. On the other hand, electron donating substituents **D** rotates outward. When such electronic properties of the substituents are not significantly different, steric effects of C-3 and C-4 substituents tend to influence on the torquoselectivity of the ring-opening reactions.



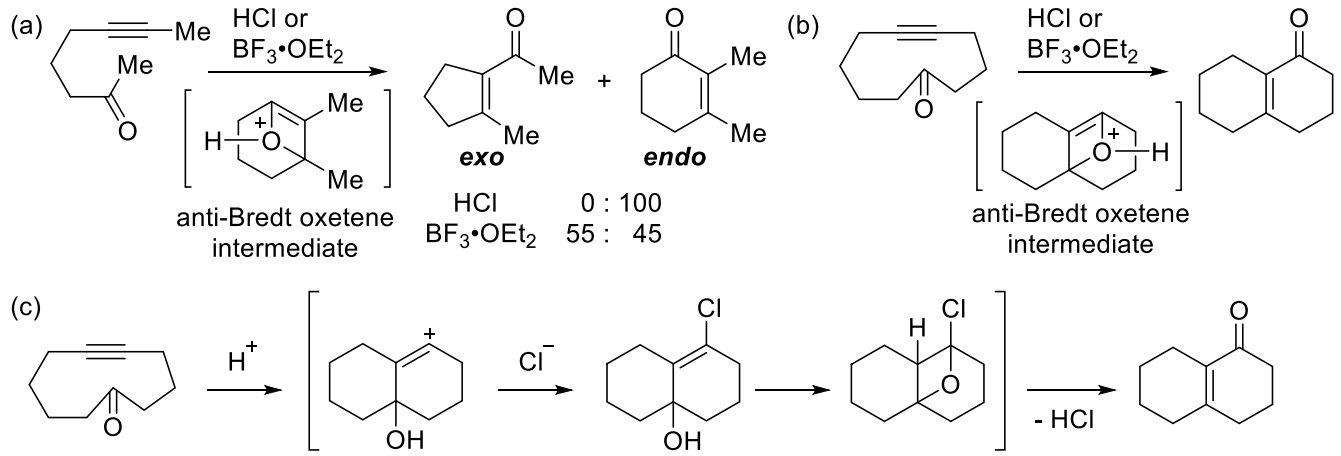
Scheme 2. Reactions of ynolates and carbonyl compounds

Lewis acids can also promote the intermolecular alkyne-carbonyl metathesis of unactivated alkynes and aldehydes (Scheme 1). Although BF_3•OEt_2-mediated reactions of aromatic alkynes were exemplified in the early reports of alkyne-carbonyl metathesis,[12] Yamaguchi *et al.* demonstrated a stoichiometric amount of SbF_5 could be applied not only to aromatic alkynes but also to less reactive aliphatic alkynes (Scheme 3).[13] The regioselectivity of the formation of oxetene intermediates tend to depend on steric effects of substituents of unactivated alkynes ($R^L > R^S$), the case of unsymmetrical aliphatic alkyne bearing no significantly different substituents ($R^L = {}^n$Bu, R^S = Me) even proceeds with high regioselectivity.



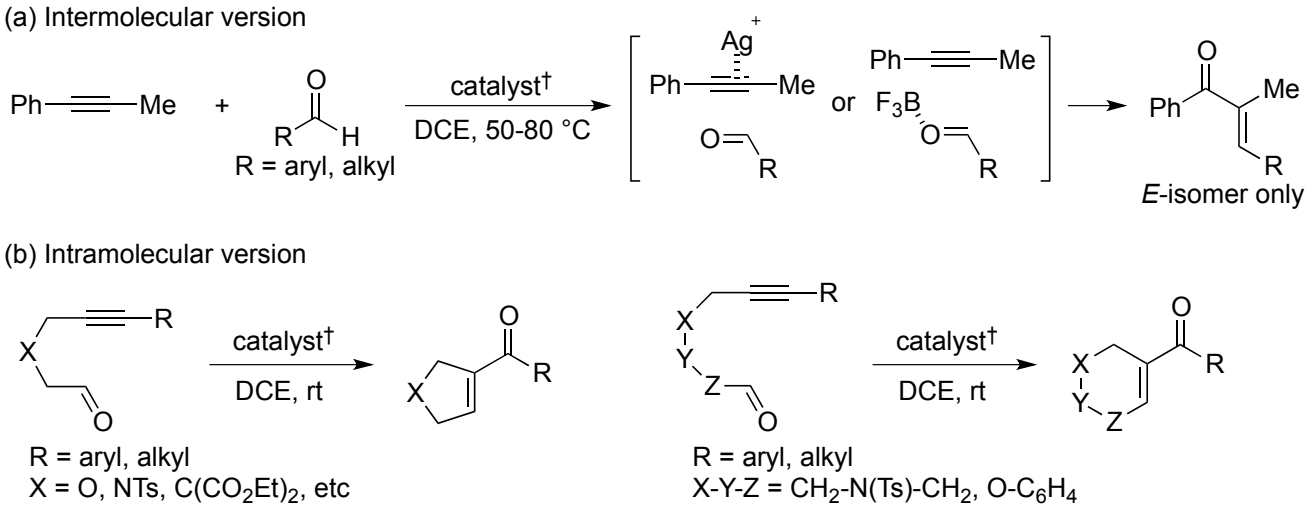
Scheme 3. Alkyne-carbonyl metathesis of aliphatic and aromatic alkynes with aldehydes

As early studies on the intramolecular alkyne-carbonyl metathesis, Hanack, Weiler and others reported that alkynyl ketones underwent both Brønsted and Lewis acid-promoted formation of cyclic enones (Scheme 4a, b).[14] Notably, oxygen-18 labeling experiments by Harding *et al*. showed the complete incorporation of carbonyl oxygen of these starting materials into the final products.[14e] Although previous mechanism for the formation of *endo*-cyclic enones have been considered to involve a highly strained intermediate such as an anti-Bredt oxetene (Scheme 4a, b), Wempe and Grunwell suggested new mechanism via a tricyclic oxetane intermediate (Scheme 4c) on the basis of NMR studies and ab initio calculations.[15]



Scheme 4. Intramolecular alkyne-carbonyl metathesis of alkynyl ketones

In the last decade, the catalytic alkyne-carbonyl metathesis, which provides an atom-economical manner alternative to the Wittig reaction, of unactivated alkynes has been achieved by the use of Lewis acid such as $Yb(OTf)_3$,[16] BF_3•OEt_2, $AgSbF_6$,[17] $AuCl_3$-$AgSbF_6$,[18] Fe(III) halides,[19] SbF_5-alcohol[20] and others,[21] or Brønsted acid.[17,22,23] For example, Krische *et al.* reported the "intermolecular" reaction of aromatic alkynes and aldehydes under Ag(I), BF_3 or HBF_4 catalysis, in which the activation of C-C triple bonds by $AgSbF_6$ was confirmed by ^{13}C-NMR analysis (Scheme 5a).[17] In contrast to $AgSbF_6$, BF_3,[8] SbF_5-alcohol[20] or $In(OTf)_3$-alcohol[21b] catalytic system activates carbonyl group of aldehydes in the reaction of aromatic alkyne and aldehydes. In other words, both π- and σ-acids can catalyze the alkyne-carbonyl metathesis reactions.[24]

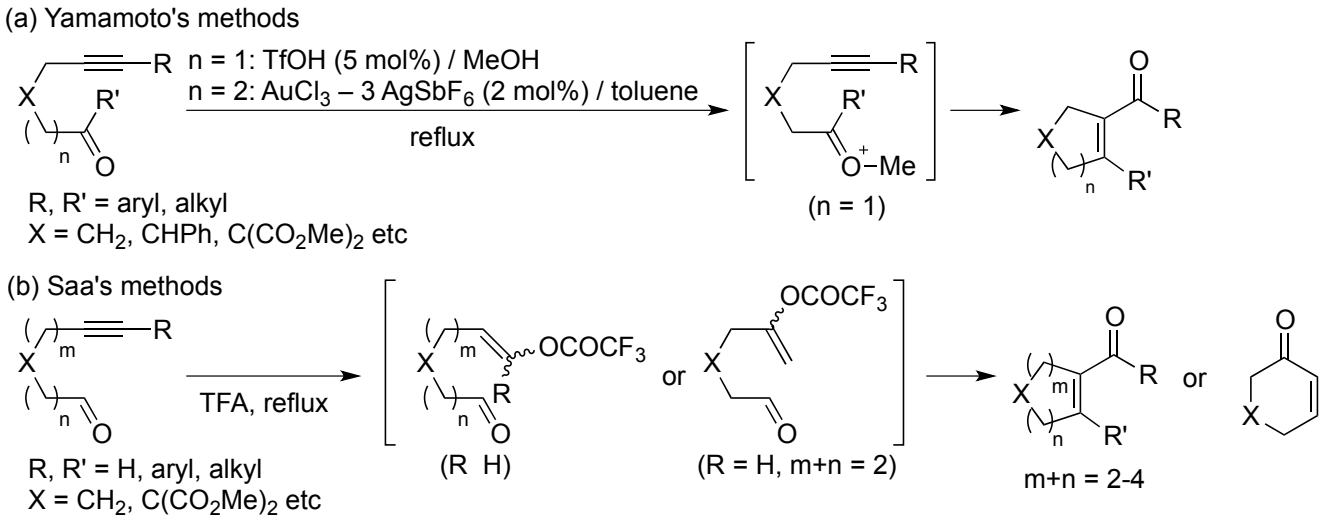


†catalyst: $AgSbF_6$ (10 mol%), HBF_4 (20 mol%), or BF_3•OEt_2 (20 mol%)

Scheme 5. Krische's methods for the catalytic alkyne-carbonyl metathesis of unactivated alkynes

Jin and Yamamoto have succeeded in developing the "intramolecular" reaction of carbon-tethered 6-alkynyl ketones catalyzed by Au(III)[18] and that of 5-alkynyl ketones catalyzed by TfOH (Scheme 6a).[22a] Notably, TfOH catalyst worked well in MeOH solvent, which would be attributed to the formation of reactive oxonium intermediates for alkyne-carbonyl metathesis.[22a] In connection with these reactions, a similar formation of carbocyclic enones from 5-, 6-, and 7-alkynynals in trifluoroacetic acid (TFA) media has been reported by Saá group (Scheme 6b).[25] Interestingly, terminal 5-alkynynals were converted to 6-membered ring products, whereas internal ones were converted to 5-membered ring products. The difference in these cyclization modes would indicate aldol mechanism via the regioselective formation of vinyl trifluoroacetate intermediates as proposed by the authors.

Although these intramolecular reactions have been shown as the synthetic method of carbocylic compounds, the catalytic alkyne-carbonyl metathesis can be applied to heterocyclic syntheses like the reactions of heteroatom-tethered 1,5- and 1,6-ynals by Krische's methods (Scheme 5b).[17] Since these reports, there has been a significant increase in research efforts directed towards the development of novel methods for the construction of heterocycles based on the alkyne-carbonyl metathesis. In this review, we describe an overview of the field, concentrating on recent advances in the catalytic alkyne-carbonyl metathesis of the unactivated alkynes.

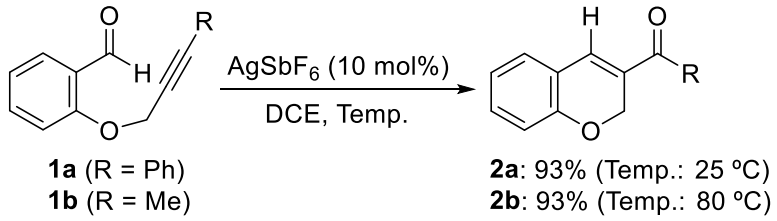


Scheme 6. Yamamoto's and Saá's methods for the formation of carbocyclic cyclic enones

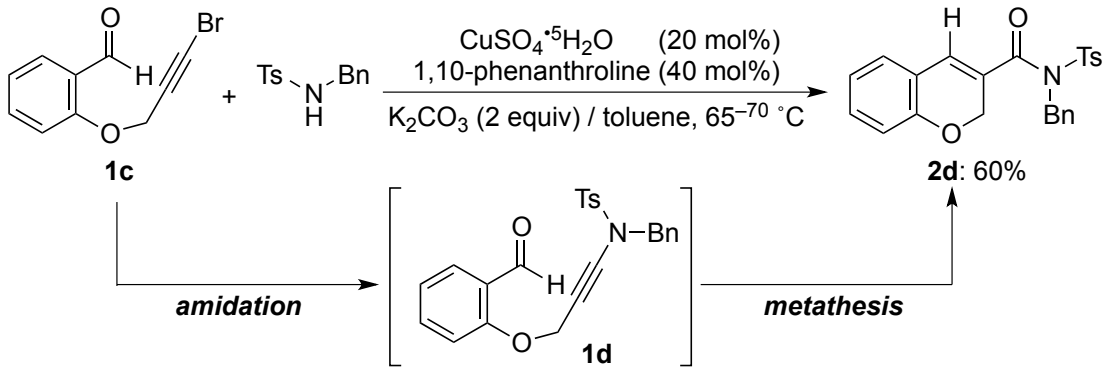
2. SYNTHESES OF HETEROCYCLES VIA INTRAMOLECULAR ALKYNE-CARBONYL METATHESIS

2.1. Ring-closing metathesis and the related reaction of alkynals or alkynones

A ring-closing alkyne-carbonyl metathesis of acyclic heteroatom-tethered precursors provides powerful tools for constructing medium ring-size heterocyclic compounds. Among them, easily available *O*-alkynyl salicylaldehyde derivatives have been relatively well studied as the precursors. As stated above, the ring-closing alkyne-carbonyl metathesis of heteroatom-tethered 1,5- and 1,6-ynals, which is a first reported case of the heterocyclic synthesis by the catalytic alkyne-carbonyl metathesis, has been reported by Krische *et al.* in 2005. In this literature, the authors demonstrated $AgSbF_6$ efficiently catalyzed the reactions of the *O*-propargyl salicylaldehydes **1a, b** compared to BF_3 or HBF_4 (Scheme 7).[17] Later on, Hsung *et al*. have been found out a catalytic ring-closing ynamide-carbonyl metathesis of *O*-alkynyl salicylaldehydes (Scheme 8).[26] Interestingly, the ring-closing metathesis of **1d**, which would be more reactive than the corresponding unactivated alkynes, occurred concomitantly during the amidation of **1c**.



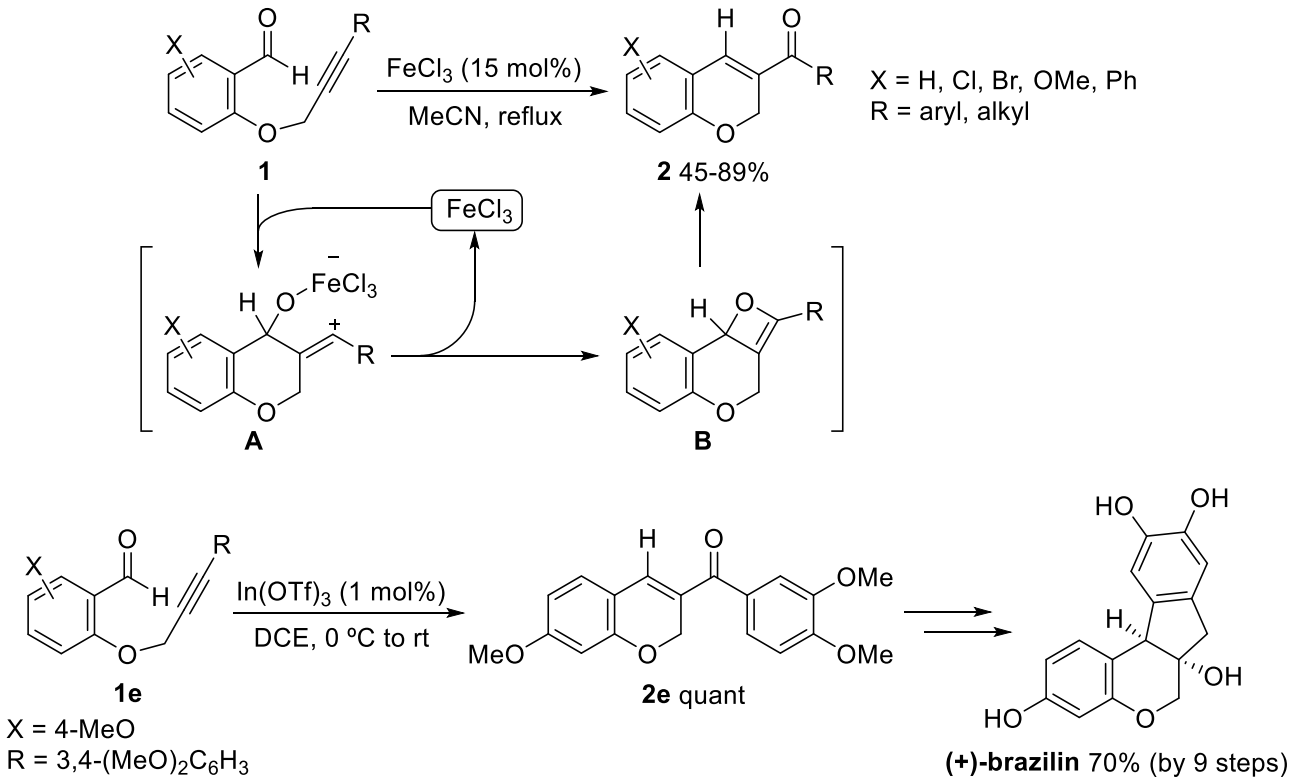
Scheme 7. First example of catalytic ring-closing alkyne-carbonyl metathesis for heterocyclic synthesis



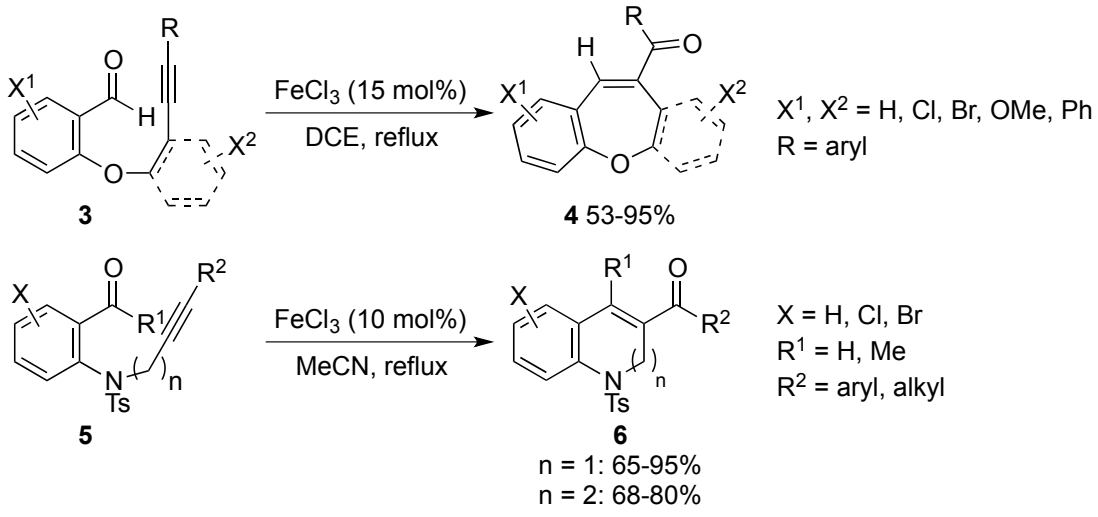
Scheme 8. Ring-closing ynamide-carbonyl metathesis of *O*-propargyl salicylaldehyde derivatives

After these reports, Jana *et al.* reported the environmentally friendly and inexpensive $FeCl_3$ catalyst was effective on the formation of various functionalized 2*H*-chromenes **2** (Scheme 9, upper).[27a] Furthermore, $FeCl_3$ catalyst can be employed for the synthesis of oxepines **4** from the homopropargyl derivatives **3** and for the synthesis of nitrogen-containing heterocycles **6** from the tosylamide-tethered **5** (Scheme 10).[27b,c] As well as the reaction of methoxyacetylene (Scheme 1),[8] these reactions were suggested to procced through stepwise [2+2] cycloaddition reactions (Scheme 9, upper).[27a] Thus, it is crucial to generate vinylic carbocation intermediate **A** efficiently and therefore aryl-substituted alkynes (R = aryl) brought about superior results to alkyl-substituted ones (R = alkyl). Similar observations were shown in Krische's

report, in which the reaction of aromatic alkyne **1a** proceeded at lower temperature than that of aliphatic alkynes **1b** (Scheme 7). Unfortunately, in cases of terminal alkynes (R or R^2 = H), $FeCl_3$ do not catalyze these reactions along with the recovery of starting materials (Scheme 9 and 10).[27] Very recently, Kim *et al*. applied the ring-closing alkyne-carbonyl metathesis of **1a** [X = 4-MeO, R = 3,4-$(MeO)_2C_6H_3$] to construction of brazilin core skeleton, in which $In(OTf)_3$ showed superior result to $FeCl_3$ (Scheme 9, lower).[28]

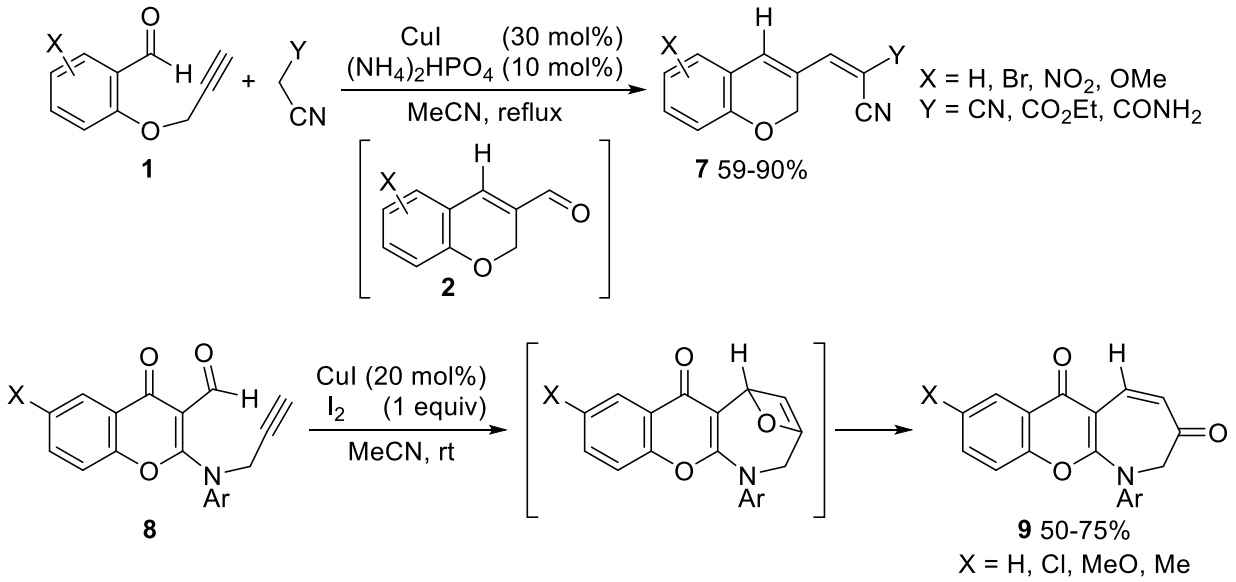


Scheme 9. Ring-closing alkyne-carbonyl metathesis of *O*-propargyl salicylaldehyde derivatives



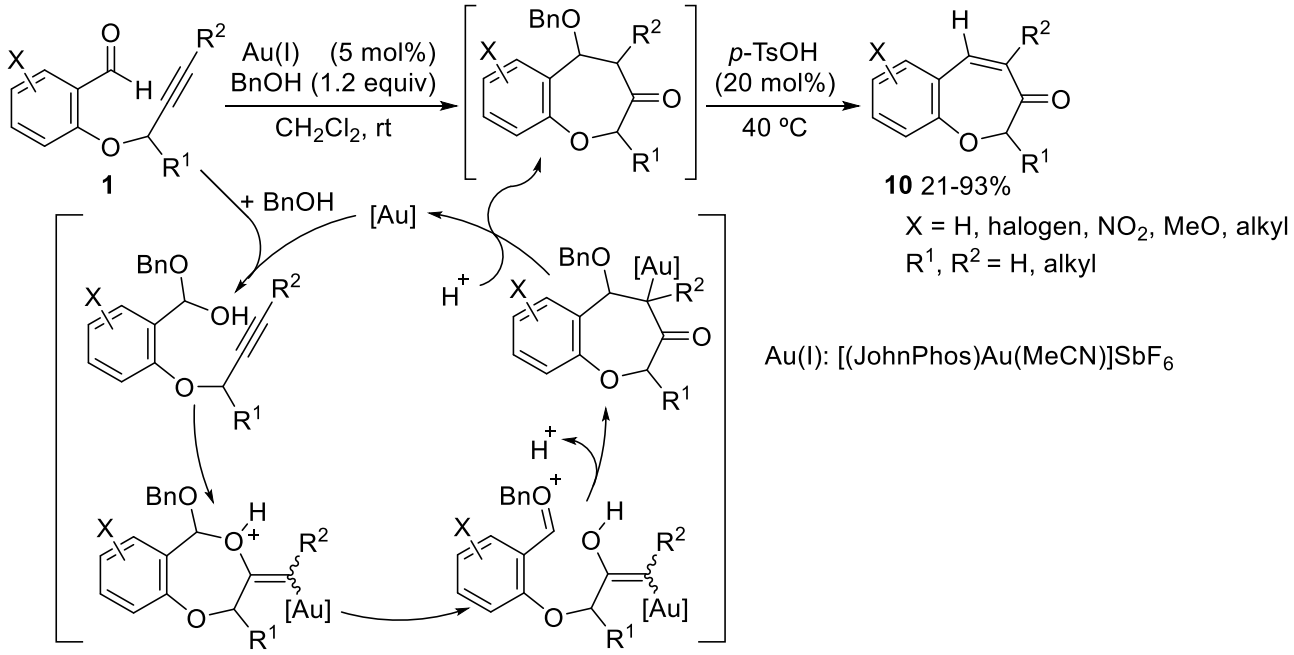
Scheme 10. $FeCl_3$-catalyzed ring-closing alkyne-carbonyl metathesis

As the ring-closing reaction of the terminal propargyl compounds **1**, CuI/$(NH_4)_2HPO_4$-catalyzed formation reaction of chromenes **7** has been published (Scheme 11, upper).[29,30] In contrast to $FeCl_3$, the Cu(I)-catalytic systems have been described to bring about the yield of metathesis products **2**, which as intermediates would lead to **7** by the subsequent Knoevenagel condensation in the presence of active methylene compounds under the similar conditions, although the mechanism analysis for the formation of **2** has been not carried out in detail. On the other hand, chromenone-tethered 6-alkynals **8** can be converted to *endo*-cyclic enones **9** by CuI/I_2 catalytic systems (Scheme 11, lower).[31] Bandyopadhyay *et al*. proposed transannulation-type [2+2] cycloaddition would involve in this reaction, and I_2 would act as a σ-acid to coordinate carbonyl groups of aldehydes as well as CuI would activate the terminal alkyne as a π-acid. However, this procedure is limited to the reaction of terminal alkynes.



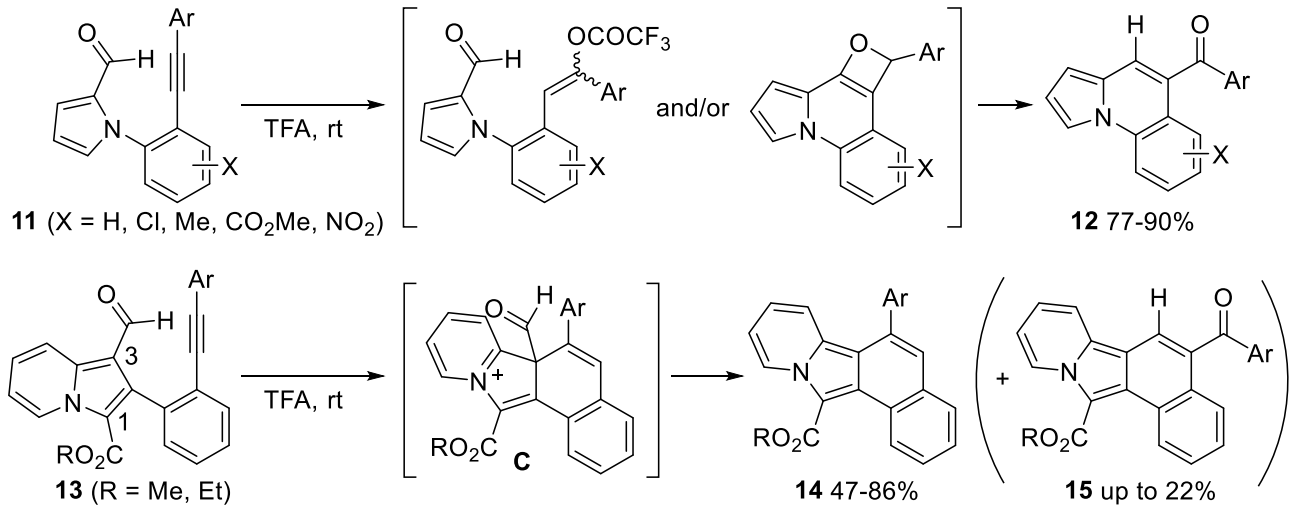
Scheme 11. Cu(I)-catalyzed ring-closing alkyne-carbonyl metathesis of terminal alkynes

An approach to *endo*-cyclic enones, benzoxepinones **10** from the terminal propargyl compounds **1** has been achieved by Au(I)-catalyzed domino reactions, which proceed via heterocyclization of the *in situ* generated hemi-acetals followed by Petasis–Ferrier rearrangement of the resulting intermediates (Scheme 12).[32] Although requiring an additional step of β-elimination of BnOH, this procedure can be applied not only to terminal alkynes (R^2 = H) but also to internal alkynes (R^2 = alkyl). In addition to this protocol, Au(I)-catalyzed ring-closing reactions of alkynyl ketones via difference route in the alkyne-carbonyl metathesis have been known.[33]



Scheme 12. Au(I)-catalyzed formation of cyclic enones

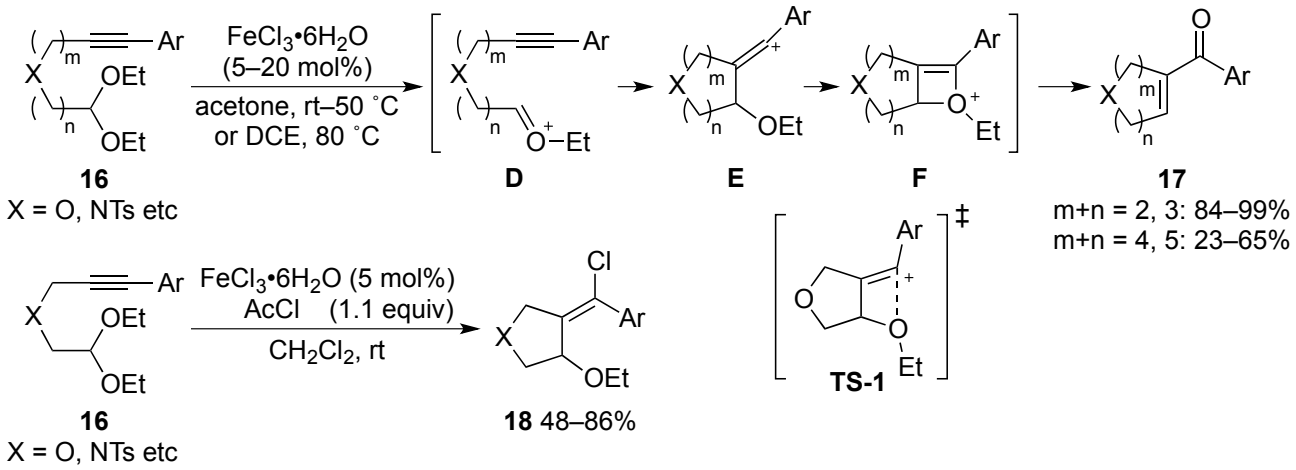
TFA can be used for the synthesis of polycyclic heterocycles via ring-closing reactions of heterocycle-tethered 1,6-ynals (Scheme 13).[34] According to the report by Kim *et al.*, pyrroles **11** were exposed to TFA media affording pyrroloquinolines **12** through the metathesis-type reaction between triple bonds and carbonyl groups.[34a] In addition to aldol mechanism indicated by Saá (Scheme 6b),[25] [2+2] cycloaddition mechanism was suggested to take part in this reaction (Scheme 13, upper). In cases of indolizines **13**, however, benzopyridoindoles **14** are formed prior to the metathesis products **15**.[34b] The formation of **14** was explained to consist of hydroarylation by an attack of the C3 position of indolizine ring to triple bonds, followed by a deformylative aromatization of the intermediate **C**.



Scheme 13. TFA-mediated formation of cyclic enones

2.2. Ring-closing metathesis of alkynyl acetals

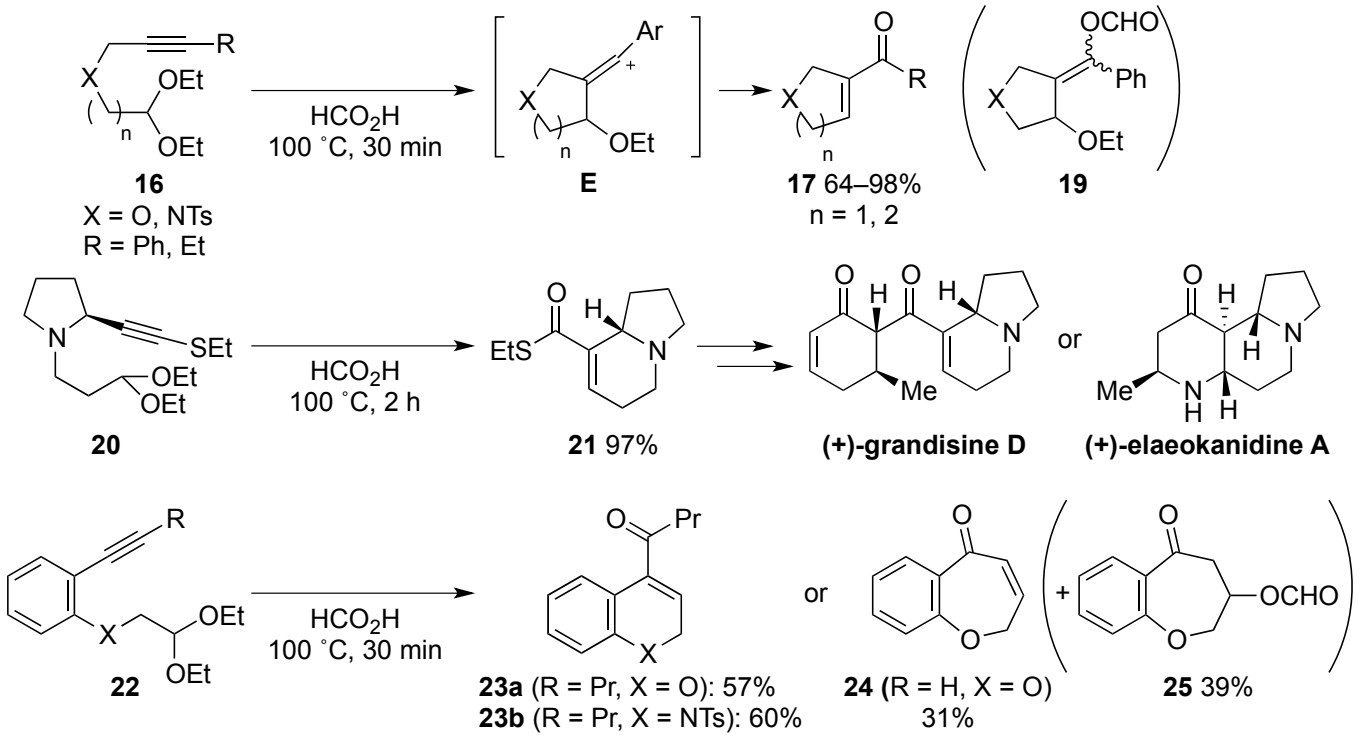
As shown in Scheme 6a, oxocarbenium ions consisting of carbonyl group and alcohol show high reactivity for alkyne-carbonyl metathesis[22a] so that the ring-closing metathesis reactions of alkynyl acetals through the generation of oxocarbenium ions can be realized. Yu and Li group reported a Fe(III)-catalyzed metathesis of alkynyl acetals **16** for the construction of five- to eight-membered heterocycles **17** (Scheme 14, upper).[19a] Computational studies on this reaction mechanism indicated the involvement of the stepwise [2+2] cycloaddition reactions of oxocarbenium **D** followed by the cycloreversion of intermediates **F**. The formation of **F** must overcome a barrier of 17.2 kcal/mol from **E** to transition state **TS-1**, and thus **E** is easily trapped by chloride anion to form product **18** in the presence of AcCl at a relatively low temperature (Scheme 14, lower).[19a] In similar to the formation of **18**, Prins-type cyclization of alkynyl acetals has been known.[19b,35]



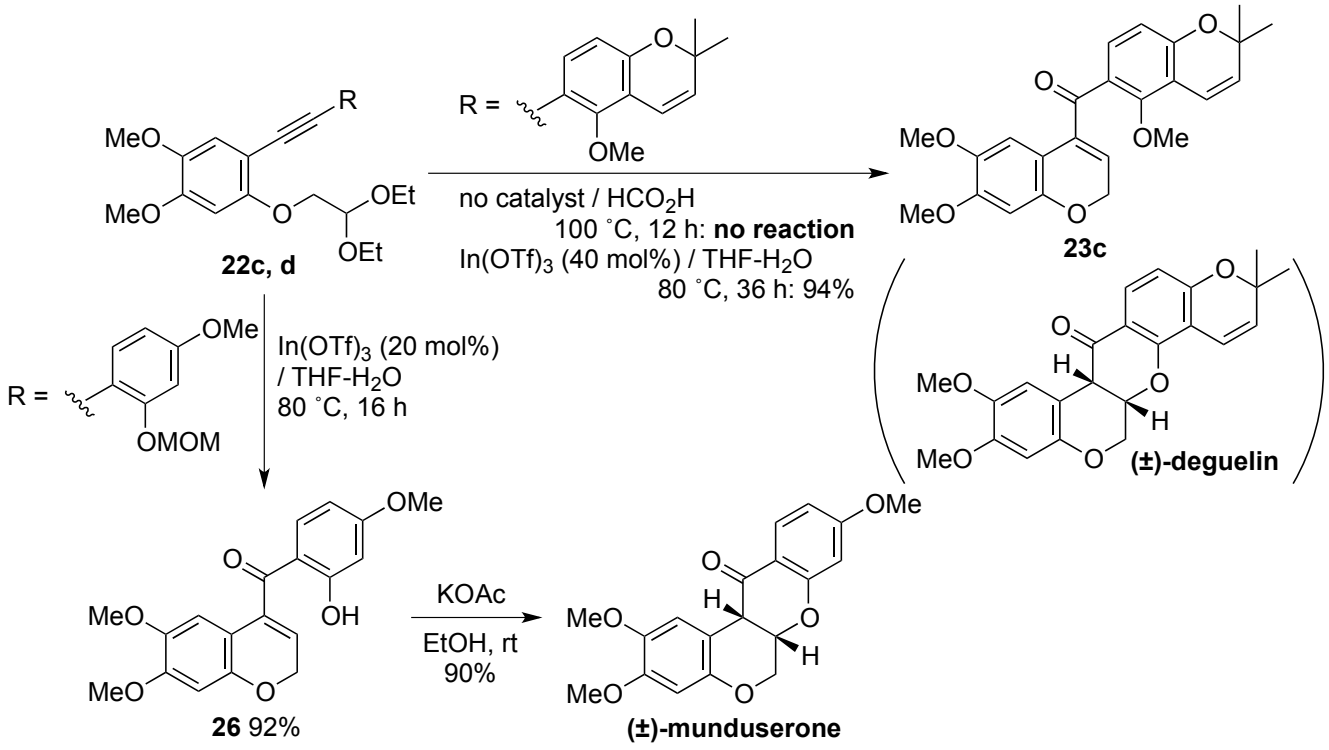
Scheme 14. $FeCl_3$-catalyzed ring-closing reaction of alkynyl acetals

Taylor *et al*. demonstrated formic acid media was effective on the ring-closing reaction of alkynyl acetals.[36] As shown in Scheme 15, **16** were rapidly converted to five- or six-membered cyclic enones **17** in formic acid at 100 ºC.[36a] The reaction of **16** at rt within 30 min led to a potential intermediate **19**, which would be formed by a Prins-type process through an addition of HCO_2H to intermediate **E**. In similar to the formation of **17**, the exposure of **20** in formic acid brought about the formation of indolizidine **21** in excellent yield, and then five-step conversion from **21** gave grandisine D.[36b] **21** has been also used as a synthetic intermediate of elaeokanidine A.[36c] Furthermore, this procedure could be applied to the ring-closing reaction of **22** resulting in not only the yield of chromene **23a** and dihydroquinoline **23b** from internal alkynes (R = Pr) but also the yield of benzoxepins **24** and **25** from terminal alkynes (R = H, X = O).[36a] Very recently, ring-closing reactions of **22c, d** were used for the synthetic approach to rotenoid natural products by Kim group (Scheme 16).[37] In contrast to Taylor's examples, formic acid media did

not promote the formation of **23c**, which is known as a synthetic intermediate of (±)-deguelin.[38] On the other hand, $In(OTf)_3$ in THF-H_2O (4:1) brought about the high yield of **23c** and **26** (with the deprotection of MOM group from **23d**). Furthermore, the obtained **26** could be easily converted to (±)-munduserone.



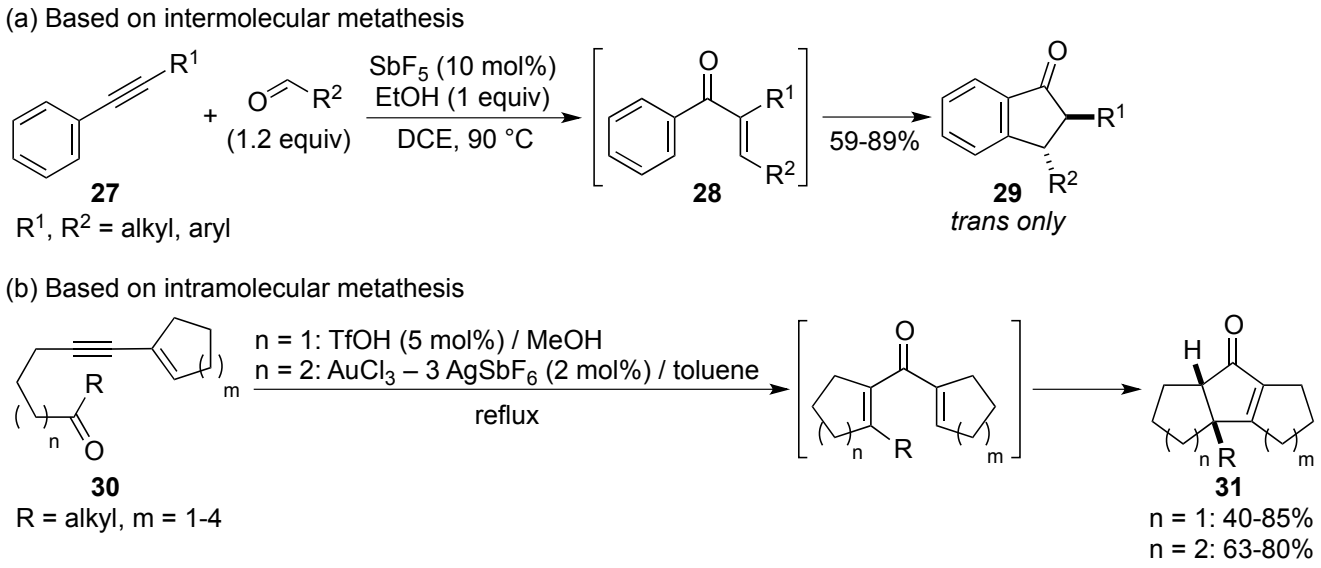
Scheme 15. HCO_2H-mediated ring-closing reaction of alkynyl acetals



Scheme 16. $In(OTf)_3$-catalyzed ring-closing reaction of alkynyl acetals for the total synthesis of rotenoids

2.3. Domino reactions based on intramolecular alkyne-carbonyl metathesis

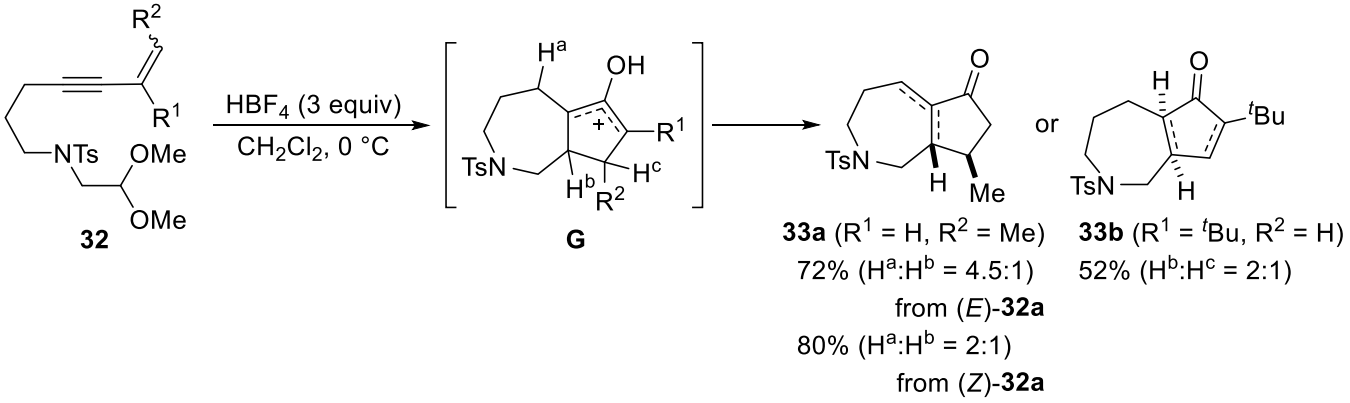
Since α,β-enones are widely used as useful synthons in various conversion reactions catalyzed by Lewis acid and Brønsted acid, domino reactions via an alkyne-carbonyl metathesis has been found.[39] As early examples based on the catalytic alkyne-carbonyl metathesis of unactivated alkynes, domino reactions with a Nazarov cyclization has been known (Scheme 17).[20,40] In 2008, Saito and Hanzawa group reported a highly stereoselective synthesis of *trans*-2,3-disubstituted indanones **29** through the intermolecular metathesis of phenylalkynes **27** and aldehydes, in which SbF_5-alcohol complexes activates the aldehydes and intermediate **28** as a σ-acid catalyst (Scheme 17a).[20] In the same year, Jin and Yamamoto group reported the similar domino reactions via the intramolecular metathesis of 6-alkynyl ketones **30** (n = 2) caused by both σ- and π-acidity of cationic gold (III) catalyst (Scheme 17b).[40] Notable, the formation of polycyclic compounds **31** (n = 1) were efficiently catalyzed by TfOH in MeOH, which was effective for the ring-closing metathesis of 5-alkynyl ketones as shown in Scheme 6a.[22a]



Scheme 17. Alkyne-carbonyl metathesis/Nazarov cyclization sequence of domino reactions

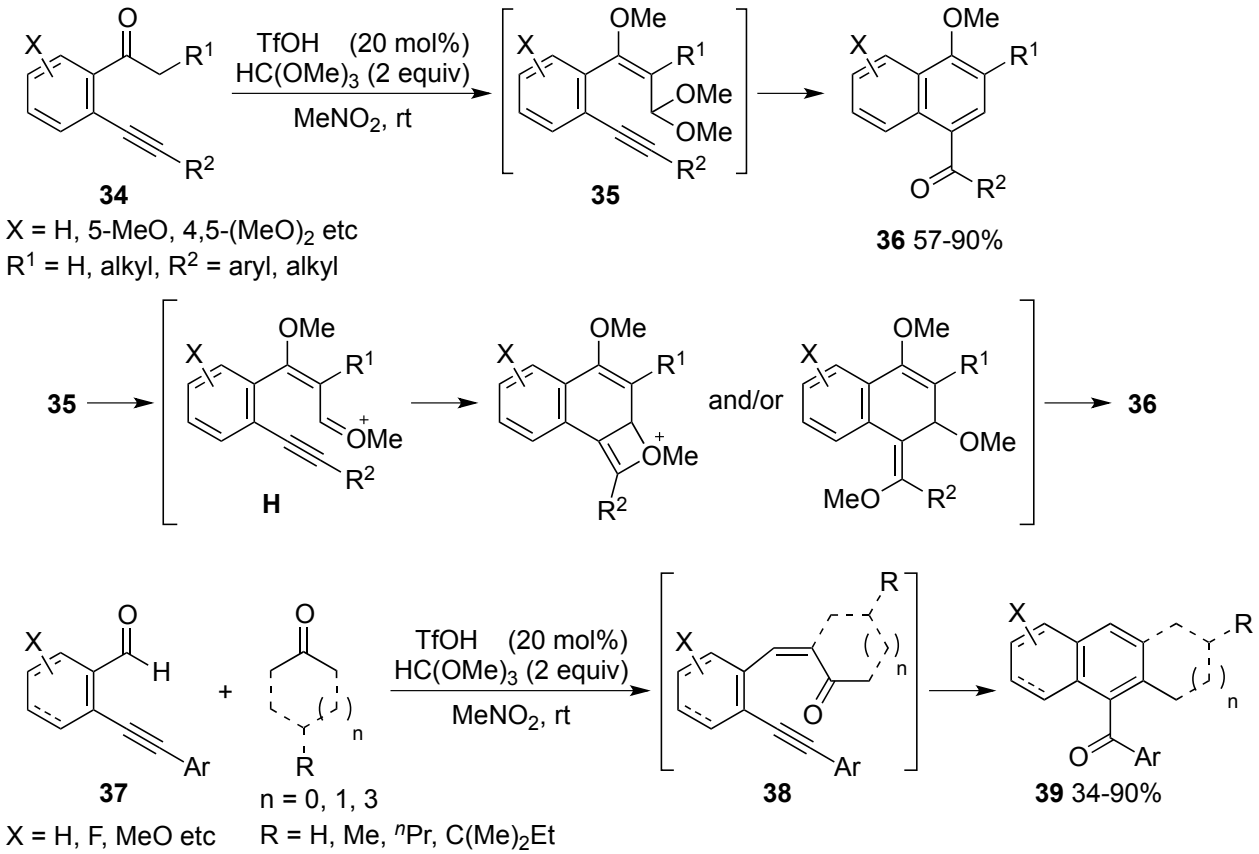
The present domino reaction can be used not only for the formation of carbocycles[21c] but also for the formation of heterocycles (Scheme 18).[41] Thus, Saá *et al.* have succeeded in the developing the synthetic method of bicyclic azepane **33** by means of HBF_4-mediated domino reactions of nitrogen-tethered alkynyl acetals **32**, in which the formation of each product isomer depends on the proton (H^a, H^b, or H^c) removing in the Nazarov intermediate **G**. In cases of β-substituted **33a** (R^1 = H, R^2 = Me), regardless of the geometry of **32a**, the elimination of the proton proceeded preferably in order to H^a and H^b. In cases of α-substituted **33b** (R^1 = ^{t}Bu, R^2 = H), the elimination of H^b proceeded preferably along with the

elimination of H^c. Such an isomeric formation of product was observed in the preparation of **31** (m = 3, 4, Scheme 17b).[22a,40]



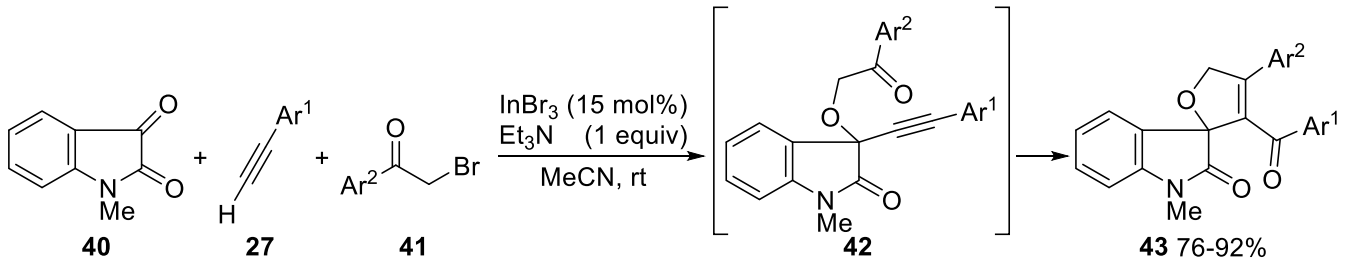
Scheme 18. Alkyne-carbonyl metathesis/Nazarov cyclization sequence for heterocyclic synthesis

Domino alkyne-carbonyl metathesis approaches to polycyclic carbocycles or heterocycles triggered by an incorporation of carbonyl equivalents into alkyne compounds have been achieved by some groups (Scheme 19, 20).[42,43]



Scheme 19. Aldol-type reaction/alkyne-carbonyl metathesis sequence of domino reactions

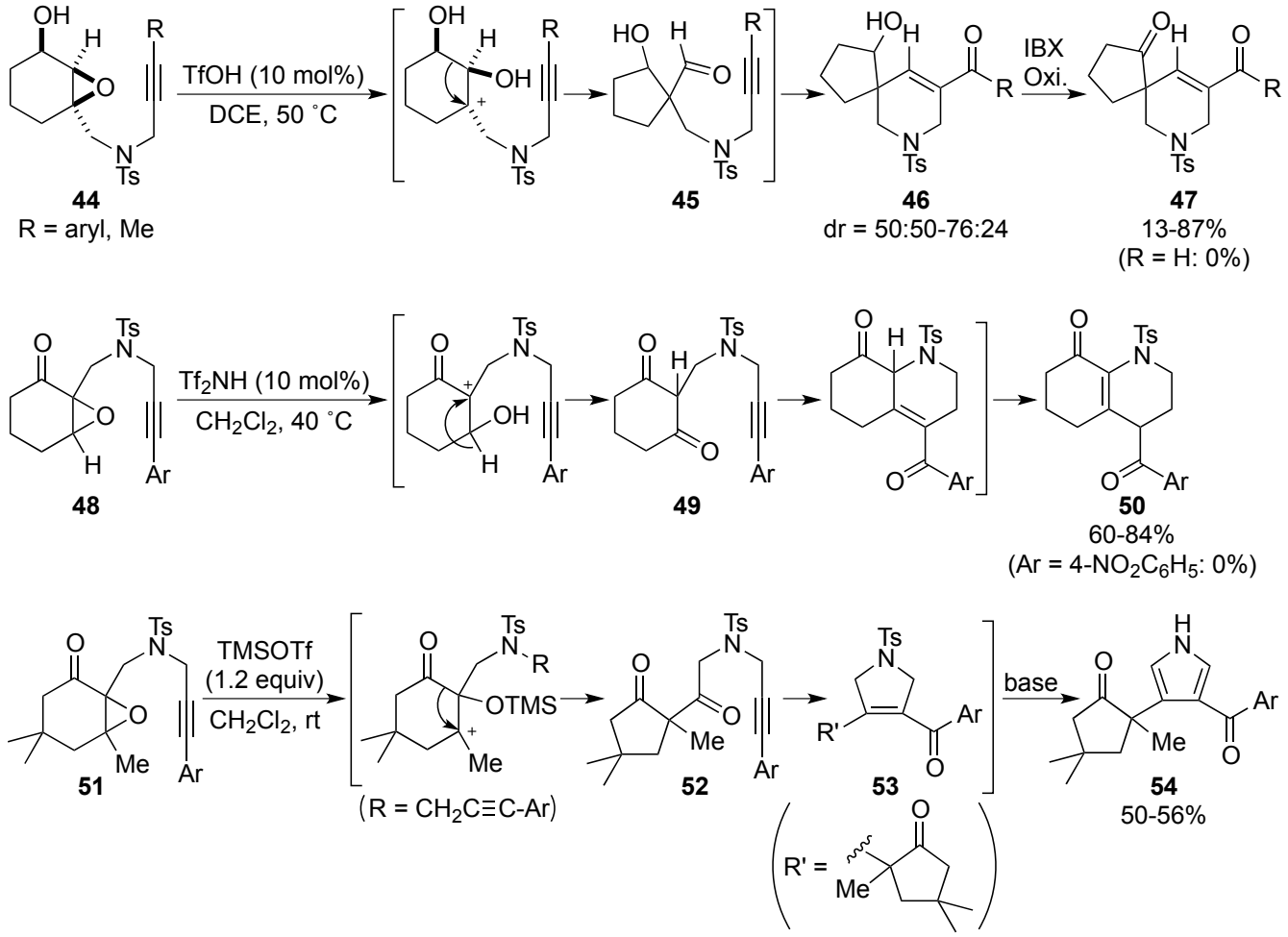
In the synthesis of naphthalene derivatives **36** by Manojveer and Balamurugan, alkynyl acetal intermediates **35** were generated by TfOH-catalyzed aldol-type reactions of *o*-alkynylacetophenone **34** with orthoformate (Scheme 19, upper).[42a] In the ring-closing reaction of intermediates **35**, Prins-type process of oxonium **H** was considered to be involved along with [2+2] cycloaddition pathway. The authors extended the synthetic method of naphthalene derivatives **36** to the formation of bicyclic or tricyclic benzenes **39** from alkynal **37** and ketone, in which the ring-closing reaction of intermediates **38** was also considered to consist of [2+2] cycloaddition and/or Prins-type pathway (Scheme 19, lower).[42b] Siddiqui *et al.* reported In(III)-catalyzed synthesis of spiro dihydrofuran oxindoles **43** by ring-closing metathesis of alkynyl ketone intermediate **42**, which formed by the three-component reaction of isatins **40**, terminal alkynes **27** and phenacyl bromides **41** (Scheme 20).[43]



Scheme 20. Three-component reaction/alkyne-carbonyl metathesis sequence of domino reactions

Yeh *et al*. have succeeded the development of domino reactions based on a semipinacol rearrangement, which led to conversion of alkynyl epoxides to alkynyl ketone intermediates (Scheme 21).[44] For example, alkynyl epoxides **44** were treated with TfOH catalysts to afford spiropiperidines **46**, in which ring-opening of oxirane of **44** brought about the ring contraction of cyclohexanol parts followed by the ring-closing metathesis of alkynals **45** (Scheme 21, upper).[44a] Due to the isolation of the alkynal **45a** (R = Ph) in the model reaction, **45** would take part into these reactions as a key intermediate. Since spiropiperidines **46** were obtained as a diastereomer mixture, **46** were subject to IBX oxidation and characterized as ketone **47**. In cases of alkynyl epoxides **48**, the C-O bond at the quaternary α-carbon was cleaved in the presence of Tf_2NH to form 6-alkynyl ketones **49**, which were converted to fused piperidines **50**, via H-1,2-shift (Scheme 21, middle).[44b] On the other hand, alkynyl epoxides **51** bearing quaternary carbons at both α- and β-position underwent the cleavage of C-O bond at β-position in the presence of a catalytic amount of TMSOTf (10 mol%) giving rise to the yield of 5-alkynyl ketones **52**.[44b] Since the ring-closing metathesis of **52** requires a small excess amount of Lewis acid, 1.2 equiv of TMSOTf was used in the domino reaction for the formation of metathesis products **53**, which were isolated as pyrroles **54** after the basic workup (Scheme 21, lower). In these reactions, substituent effects

of alkyne were observed and thus terminal, aliphatic and electron-deficient aromatic alkynes showed little or no conversion to desired product (Scheme 21).[44]

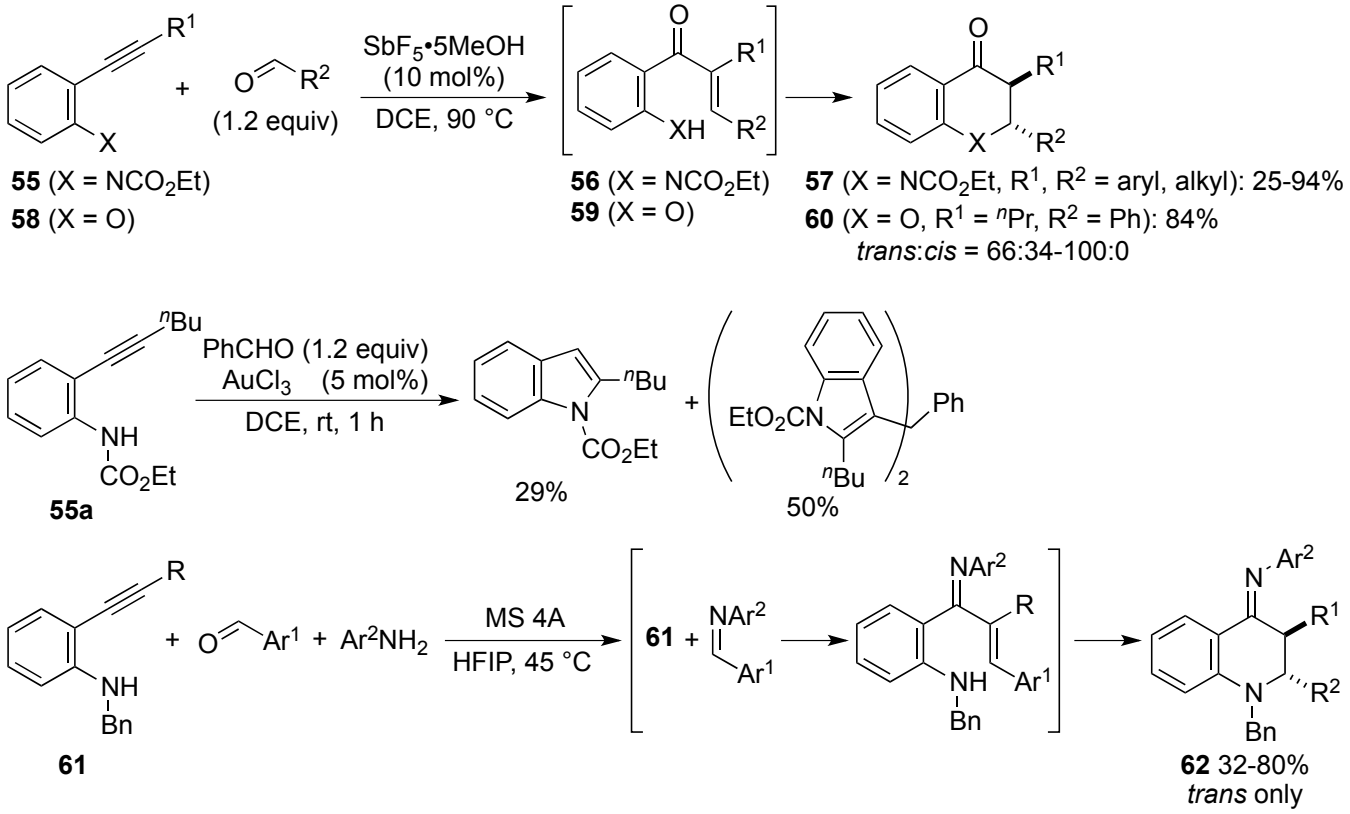


Scheme 21. Semipinacol rearrangement/alkyne-carbonyl metathesis sequence of domino reactions

3. SYNTHESES OF HETEROCYCLES VIA INTERMOLECULAR ALKYNE-CARBONYL METATHESIS

For the extension of intermolecular alkyne-carbonyl metathesis to synthetic methods of cyclic compounds, the development of domino reactions with cyclization of metathesis product is required.[45] As shown in Scheme 17a, Saito and Hanzawa group developed the domino approach to indanones from phenylalkynes and aldehydes catalyzed by SbF_5-alcohol complexes.[20] And then the authors applied the domino reaction to the synthesis of heterocycles from *o*-alkynylaniline (Scheme 22).[46] In the synthesis of dihydroquinolinones **57**, SbF_5•5MeOH, which can be prepared from a 1:5 mixture of SbF_5 and MeOH, efficiently catalyzed the intermolecular metathesis of *o*-alkynylanilines **55** with aldehydes and the subsequent cyclization of enone intermediates **56**.[46a] The key intermediates **56** can be isolated under

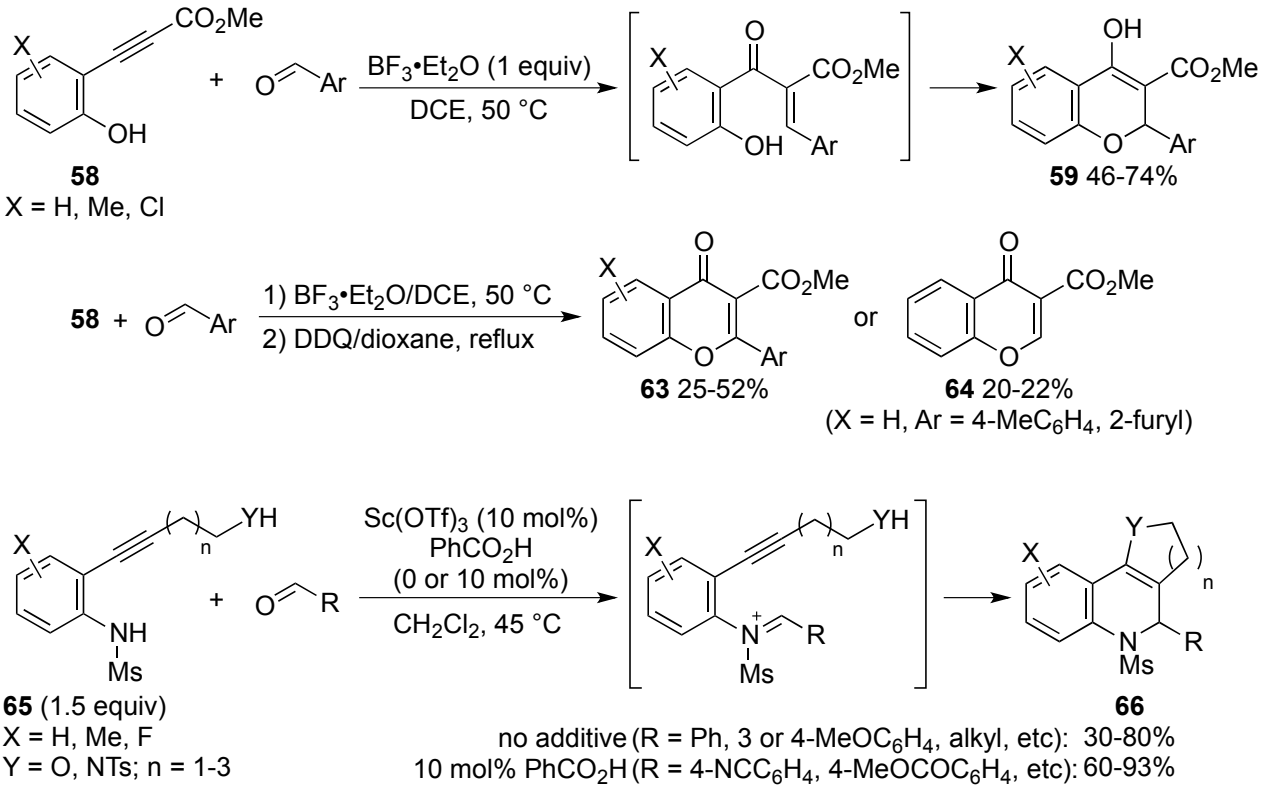
similar conditions at lower temperature. The σ-acidity of the catalyst is crucial for these reactions because π-acid catalysts including $AuCl_3$ have promoted the cyclization of **55** to indole compounds prior to the intermolecular reaction between **55** and aldehydes. SbF_5•5MeOH can be employed for the synthesis of 4-chromanone **59** from the oxygen analogue **58** and aldehydes.[47] Since iminoquinolines is generally difficult to be synthesized by the imination of low electrophilic dihydroquinolinones, three-component synthesis of iminoquinolines **62** have been found on the basis of synthetic method of dihydroquinolinones **57**.[46b] These three-component reactions proceed smoothly by hexafluoroisopropanol (HFIP, pKa = 9.3) media without any catalyst rather than SbF_5•5MeOH to give **62** with complete *trans*-selectivities. The present mechanism was proposed to consist of (1) formation of imine from aldehyde and aromatic amine, (2) metathesis of alkyne **61** and imine, and (3) cyclization of α,β-unsaturated imine intermediate.



Scheme 22. Alkyne-carbonyl metathesis/cyclization sequence of domino reactions

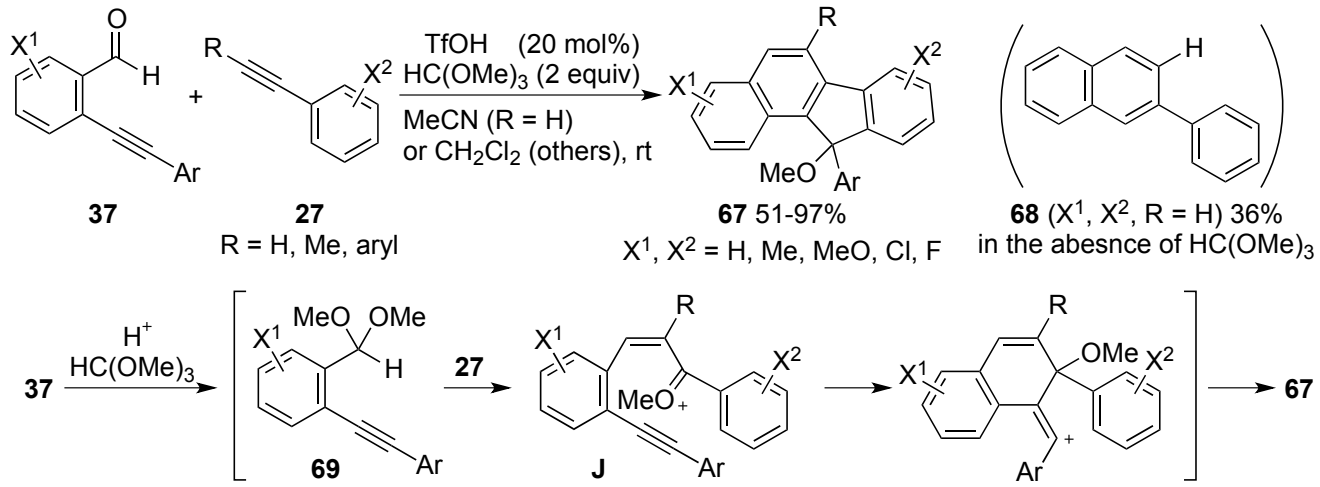
Recently, two groups independently published domino reactions of *o*-alkynylphenols or -anilines with aldehydes (Scheme 23). In the analogue manner by Saito and Hanzawa group,[20] Lu and Wang group developed the BF_3-mediated synthesis of 4-chromanone **59** from *o*-alkynylphenols **58** having the electron-withdrawing group.[48] In this report, the domino reaction has been extended to a one-pot synthesis of 4-chromenone **63** with DDQ oxidation of **59**, although 4-chromenone **63** having electron-rich

aromatic rings (Ar = 4-MeC_6H_4, 2-furyl) were converted to products **64** by the removal of aromatic rings. On the other hand, the synthesis of fused dihydroquinolines **66** by Ma *et al*. was considered to proceed through a Prins-type cyclization of iminium intermediates derived from **65** and aldehydes, which can be regarded as an alternative reaction pathway from *o*-alkynylanilines and aldehydes.[49] For these reactions, $Sc(OTf)_3$ catalytic systems were effective, and particularly the dual catalysts of $Sc(OTf)_3$ and $PhCO_2H$ showed good yields of products from electron-deficient aldehydes (R = 4-NCC_6H_4, 4-$MeOCOC_6H_4$, etc). Such a dual catalyst showed its efficiency in the intermolecular alkyne-carbonyl metathesis.[21c]



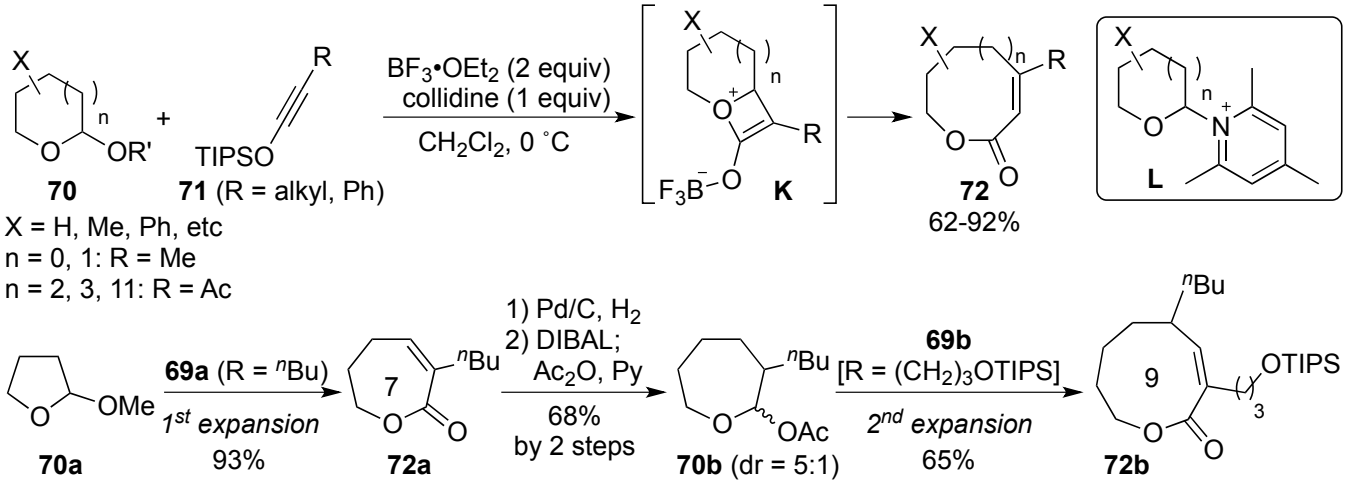
Scheme 23. Domino approach to heterocycles from *o*-alkynylphenols or -anilines and aldehydes

In connection with alkyne-carbonyl metathesis/cyclization sequence of domino reactions, Balamurugan *et al.* found the TfOH-catalyzed domino approach to benzofluorenes **67** from *o*-alkynylbenzaldehydes **37** with aromatic alkynes **27** (Scheme 24).[50] The addition of orthoformates is essential for the formation of **67**, whereas the use of TfOH only afforded naphthalene **68**. The isolated acetals **69** were treated with TfOH to form **67** regardless of the presence of orthoformates, and thus **69** would be initially formed as an intermediate. From results of some control experiments, the authors suggested metathesis intermediates **J** derived from **69** and **27** would undergo consecutive electrophilic cyclization reactions to yield **67**.



Scheme 24. Domino approach to benzofluorenes from *o*-alkynylbenzaldehydes and alkynes

Recently, as an efficient method for the construction of medium and large ring lactones, which does not require high-dilution conditions and a slow addition of substrates, ring-expansion metathesis of cyclic acetals **70** and silyloxy alkynes **71**[51] was found out by Sun *et al*. (Scheme 25).[52] Interestingly, this reaction would involve an unprecedented ring conjunction mode of oxetene such as intermediates **K**, which led to seven- to ten-, and eighteen-membered lactones **72**. In addition to BF_3•Et_2O as a promoter, collidine worked well as an additive for the reversible formation of pyridinium **L** with the highly unstable cyclic oxocarbenium intermediate derived from **70**. Thus, **L** would be considered as a reservoir of the oxocarbenium intermediate to prevent its decomposition before reacting with **71**. Furthermore, this lactone formation reaction could be applied to iterative ring expansions with hydrogenation and reductive acylation of the first obtained lactone **72a**. Therefore, this protocol is in principle capable of assembling various medium and large lactones from a small ring acetal.



Scheme 25. Ring-expansion metathesis of alkyne and cyclic acetals

4. CONCLUSION

We have described a variety of procedures for the synthesis of heterocycles based on the catalytic alkyne-carbonyl metathesis of the unactivated alkynes. The progress of the alkyne-carbonyl metathesis chemistry for the last decades has brought about not only various ring-closing metathesis reactions but also domino approaches with the cyclization of metathesis intermediates and ring-expansion metathesis reactions, which are limited to the examples of silyloxy alkynes. These strategies have been successfully applied to the total syntheses of some important molecules. However, there is still a room for the improvement of the intermolecular metathesis of unactivated alkynes with simple ketones and other low electrophilic carbonyl compounds,[12] although some groups reported [2+2] reactions of unactivated alkynes with trifluoroketones[53] or electron-deficient alkynes with simple ketones.[54] In the future, the alkyne-carbonyl metathesis chemistry would be further improved and a brilliant success would be brought to organic syntheses.

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Akio Saito was born in Tokyo, Japan in 1975. He received his B.S. (1997) and M.S. (1999) degrees from Tokyo University of Pharmacy and Life Sciences under the supervision of Professor Takeo Taguchi. After he spent two years as a Ph. D. student, he was appointed Research Associate in Professor Taguchi's group and then received his Ph.D. degrees from Tokyo University of Pharmacy and Life Sciences in 2003. In 2005, he joined the Showa Pharmaceutical University, where he worked as an Assistant Professor with Professor Yuji Hanzawa. In 2012, he moved to the present position as an Associate Professor in the Tokyo University of Agriculture and Technology. He received the Pharmaceutical Society of Japan Kanto Branch Award for Young Scientists in 2008. His current research interests include the development of domino reactions and multicomponent reactions based on transition metal catalysis or hypervalent iodine chemistry.

Keiichiro Tateishi was born in Saitama, Japan in 1990. He received his B. Sc. (2013) and M.S. (2015) degree from Tokyo University of Agriculture and Technology under the supervision of Professor Takeshi Takeda. In 2015, he began a Ph. D. student of Tokyo University of Agriculture and Technology under the supervision of Professor Akio Saito. His current research is focused on the development of new methods for the stereoselective synthesis of dienes and heterodienes.