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Review

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Alkyne-carbonyl metathesis (ACM) as a versatile strategy for the synthesis of α,β-unsaturated carbonyl compounds

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Dedicated to Professor Thomas J. J. Müller for his outstanding contribution in Multicomponent Reactions

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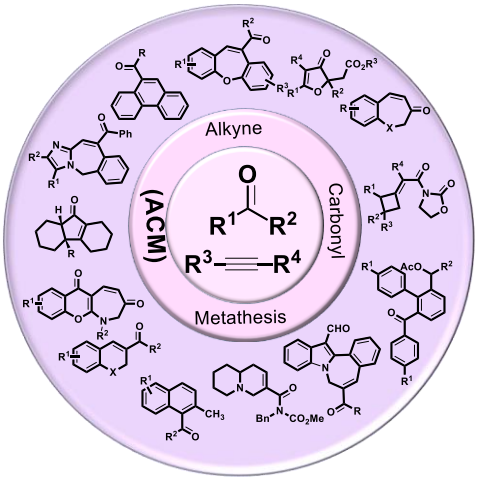
Abstract

Alkyne–carbonyl metathesis (ACM) reactions represent a powerful synthetic strategy for constructing diverse carbocyclic and heterocyclic frameworks. A variety of functional groups can be positioned between the alkyne and carbonyl units within the same molecule, enabling access to structurally diverse products. ACM reactions provide efficient routes to five-, six-, and seven-membered carbocyclic and heterocyclic systems. The choice of catalyst plays a crucial role in directing the reaction pathway and determining the final outcome. This review aims to classify the major types of ACM reactions, outline their underlying mechanisms, and offer guidance on selecting appropriate substrates and reaction conditions to obtain the desired α,β-unsaturated products.



Keywords: Alkyne-carbonyl metathesis; carbocycles; heterocycles; α,β-unsaturated carbonyls; catalysis; photoredox reactions

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1. Introduction

Metathesis reactions particularly olefin metathesis have had a transformative impact on organic synthesis since their accidental discovery in the mid-20th century. This breakthrough revolutionized synthetic planning by providing atom-economical routes to complex molecular architectures.[1] Early developments focused primarily on olefin-based processes, including olefin metathesis,[2-6] ring-closing metathesis (RCM), ring-opening metathesis polymerization (ROMP),[7-9] and cross-metathesis[10-12] (Figure 1), all of which rapidly gained widespread adoption. These methodologies enabled the efficient construction of a broad array of heterocyclic, cyclic, and acyclic structures with excellent functional group tolerance and stereoselectivity.[13-16]

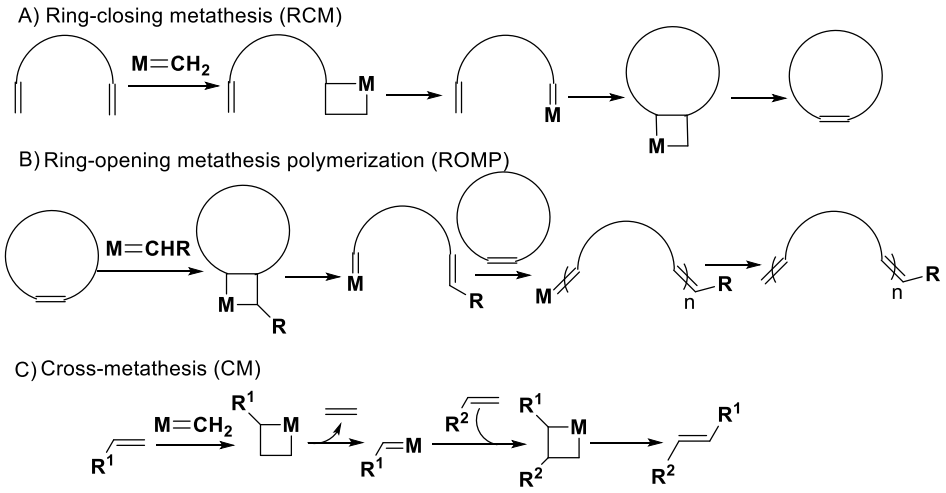


Figure 1. Different types of metathesis reactions.

Olefin–olefin metathesis transformations occur between olefins, proceeding via an initial [2+2] cycloaddition reaction under a metal-based catalytic system, and cycloreversion to produce two new alkenes (Figure **2**A). Carbonyl–olefin metathesis (COM), on the other hand, takes place between an olefin and a carbonyl group, forming a new C=C bond and producing an alkene (Figure 2B).[17] Carbene–alkyne metathesis (CAM) involves the reaction of metal carbene complexes with alkynes to generate vinyl metal carbene intermediates (Figure 2C), which can be transformed into diverse organic structures.[18] Extending metathesis reactivity beyond olefins to carbon–heteroatom bonds has been a major milestone in the evolution of this field.[19] Among these advances, alkyne–carbonyl metathesis (ACM) stands out as an elegant and powerful method for forming C–C bonds through the formal exchange of an alkyne and a carbonyl group (Figure 2D).[20,21] Conceptually, ACM

parallels COM, proceeding through a metal-oxo or metal-carbene intermediate that undergoes [2+2] cycloaddition and subsequent cycloreversion to yield an α,β-unsaturated carbonyl compound. Unlike COM, the higher intrinsic reactivity of alkynes enables access to strained or fused carbocyclic and heterocyclic frameworks.[22]

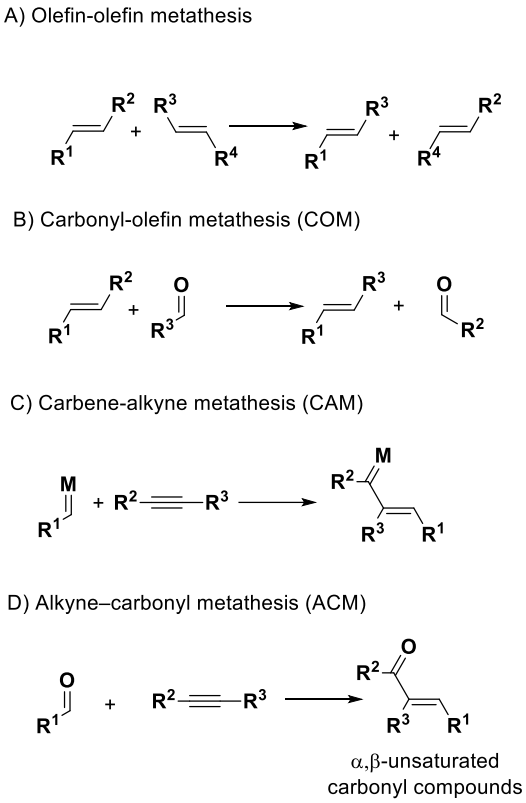


Figure 2. The process of CM, COM, CAM, and ACM reactions.

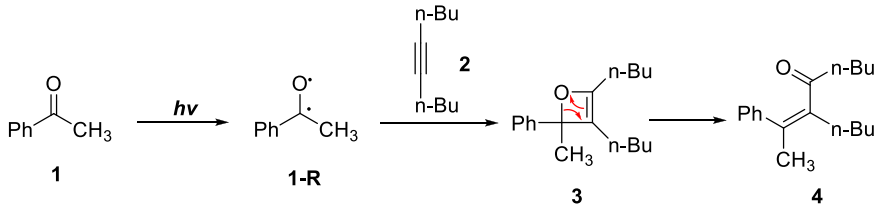
We have previously published two review articles addressing the annulation of 2-alkynylanilines via carbonyl or amide addition to the alkyne moiety, as well as the cyclization of conjugated alkyne–alkene–aldehydes (ynenones) to access a diverse array of carbo- and heterocyclic frameworks.[23,24] In addition, our group has provided a concise overview of the role of ruthenium catalysts in hydrogenative metathesis.[25]

In the present review, we aim to systematize the reactions encompassed by carbonyl–alkyne metathesis, clarify their underlying mechanistic features, and offer guidance for the rational selection of starting materials to construct targeted ring systems. Finally, we outline our perspective on future directions and emerging opportunities in this field.

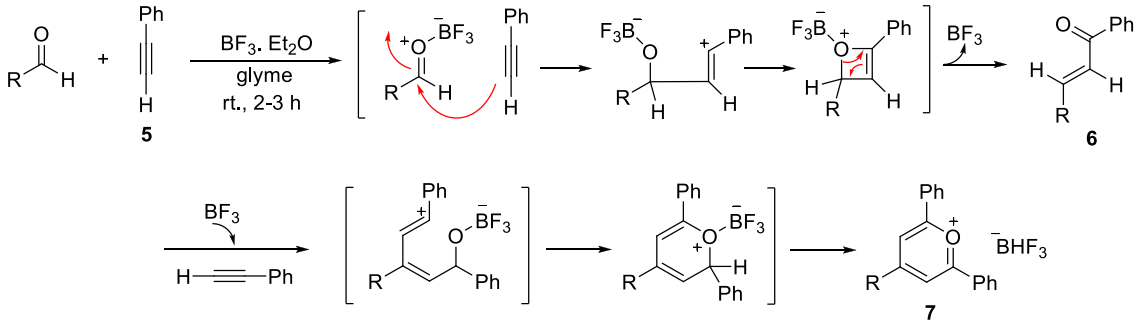
2. Alkyne-Carbonyl Metathesis

The alkyne–carbonyl metathesis (ACM) reaction has arisen as a powerful strategy in modern organic synthesis, particularly for constructing α,β-unsaturated carbonyl compounds (enones). This transformation, involving the formal exchange of a C≡C bond and a C=O bond, provides an atom-economical and direct route to conjugated enones, often with excellent regio- and stereoselectivity. The first example of a carbonyl–alkyne transformation was reported in 1956 by Büchi et al., during their investigation of the photochemical [2+2] cycloaddition

between acetophenone **1** and 5-decyne **2** (Scheme 1). Under irradiation, acetophenone 1 is converted into its biradical triplet state 1-R, which subsequently undergoes cycloaddition to form oxetene **3**. This intermediate then decomposes to afford the substituted 2-octen-4-one.[26] In 1963, Bos and Arens employed BF_3 as a Lewis acid to promote the reaction between an aldehyde and phenylethyne under non-photochemical conditions. However, a significant amount of 2,4,6-triarylpyrylium tetrafluoroborate **7** was formed alongside the desired enone **6** (Scheme 2).[27] When gallium trichloride or indium triflate was used as the catalyst, the reaction instead produced highly conjugated aromatic compounds rather than the expected enone **6**.[28,29] In contrast, cationic silver ($AgSbF_4$) proved to be an effective catalyst, delivering enone **6** as a single geometrical isomer.[30]



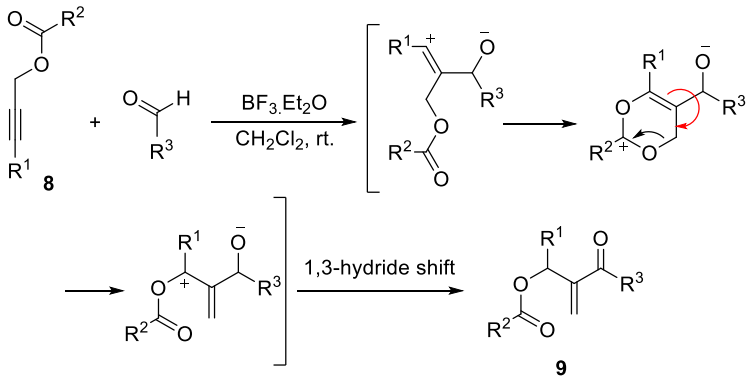
Scheme 1. Photochemical reaction between acetophenone **1** and 5-decyne **2.**



Scheme 2. BF_3-mediated reaction between aldehydes and acetylenes.

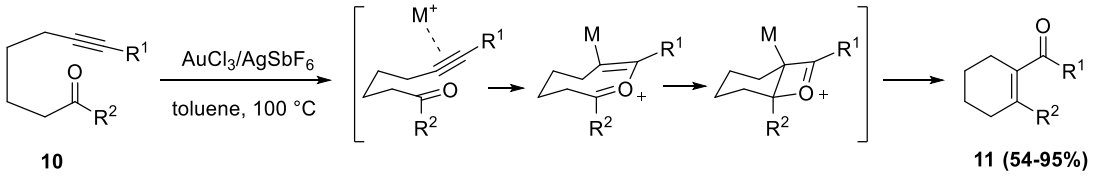
3. The Golden Age of Alkyne-Carbonyl Metathesis

Following the initial discovery of the ACM reaction, extensive studies were undertaken to evaluate the influence of various catalysts on its efficiency, rate, product scope, and overall performance. A wide range of catalytic systems—including trifluoromethanesulfonic acid, trifluoroacetic acid,[31] Barluenga's reagent,[32] ytterbium triflate ($Yb(OTf)_3$),[33] indium(III) triflate ($In(OTf)_3$),[34] $AgNTf_2$,[35] 3,5-dibromopyridinium trifluoromethanesulfonate,[36] and nano-sized ferrite catalysts[37]—have been shown to promote ACM reactions with high specificity and regioselectivity. In 2013, Karpaviciene demonstrated that substituents on the alkyne moiety can significantly influence the course of ACM reactions. In this system, the alkyne–carbonyl metathesis of substrate **8** is accompanied by migration of the carboxylate group, ultimately yielding the corresponding Morita–Baylis–Hillman adducts **9**.[38] Subsequently, Trujillo et al. investigated the intermediates formed in this transformation using ^{18}O-labeled aldehydes and proposed a plausible mechanism, as illustrated in Scheme 3.[39]

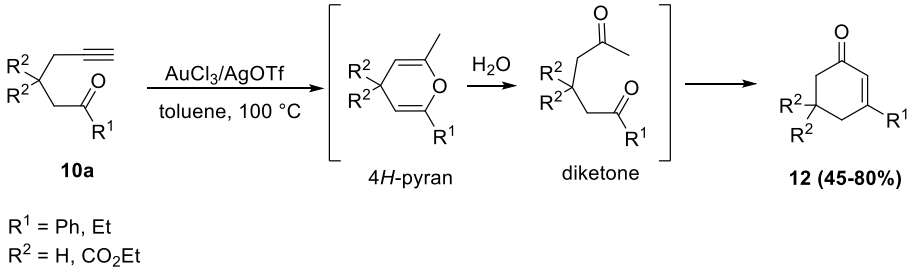


Scheme 3. The proposed mechanism of BF_3-mediated reaction between aldehydes and alkynes.

Early developments in ACM were largely stoichiometric and suffered from narrow substrate scope, low efficiency, and harsh reaction conditions.[20,40] These limitations were progressively overcome through the introduction of catalytic systems based on gold, molybdenum, rhenium, and, more recently, Brønsted acids and organocatalysts.[41-43] Among these advances, gold-catalyzed alkyne–carbonyl metathesis has proven particularly effective, enabling mild, chemoselective transformations with broad substrate compatibility.[44] Intramolecular cyclization of internal alkynes tethered to carbonyl groups **10** was achieved using a bicatalytic $AuCl_3/AgSbF_6$ system, affording cyclic enone **11** via an oxetene intermediate, as shown in Scheme 4. Notably, the use of either metal catalyst alone resulted in poor yields, whereas the bicatalytic system exhibited significantly enhanced efficiency and broad applicability. When the alkyne and carbonyl groups are separated by four carbon atoms, the reaction affords the exocyclic enone 11 as the major product. However, when terminal alkynyl ketones (compound **10a**) are used in the presence of the $AuCl_3$/AgOTf system, a different product **12** is obtained. This outcome likely arises from the involvement of alternative 4H-pyran and diketone intermediates in the reaction pathway, as illustrated in Scheme 5.[45]

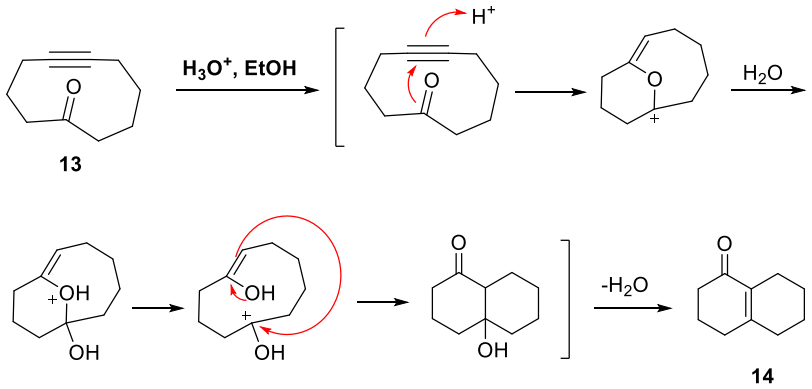


Scheme 4. Au-Ag-catalyzed intramolecular cyclization of internal alkynes.



Scheme 5. Au-Ag-catalyzed intramolecular cyclization of terminal alkynes.

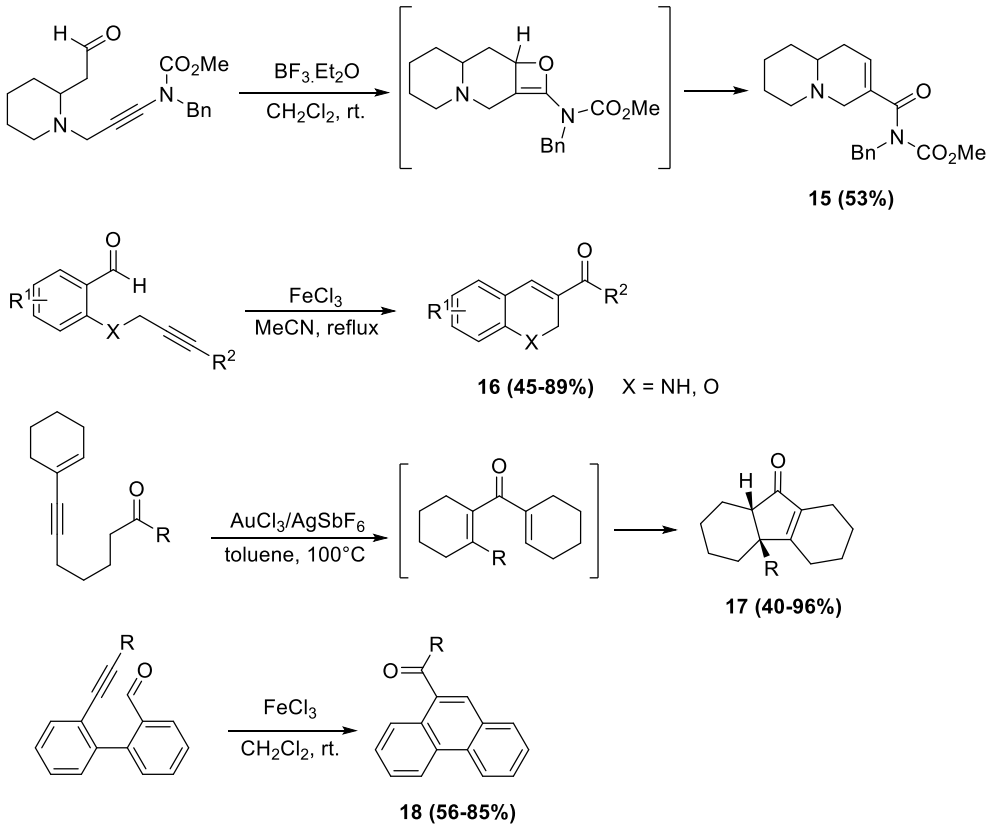
One of the earliest documented examples of an intramolecular alkyne–carbonyl metathesis (ACM) reaction dates back to the early 1970s.[46-48] Although not initially recognized as a metathesis process in the modern sense, the transformation was described as an acid-catalyzed intramolecular cyclization of cyclic alkyne–ketones to form enones. In pioneering studies, Harding and Hanack reported the transannular rearrangement of cyclodecynyl derivative **13**, leading to the formation of bicyclic enone **14** (Scheme 6).[49] Their subsequent investigations using ^{18}O-labeled water ($H_2{}^{18}O$) demonstrated that the reaction proceeds through nucleophilic addition of the carbonyl oxygen to the C≡C bond, as depicted in Scheme 6.[50] When the reaction is carried out in the presence of BF_3, enone **14** is obtained exclusively, with no formation of pyrylium tetrafluoroborates likely due to steric hindrance imposed by the fused ring system.[51]



Scheme 6. Transannular rearrangement of cyclodecynyl derivative **1.**

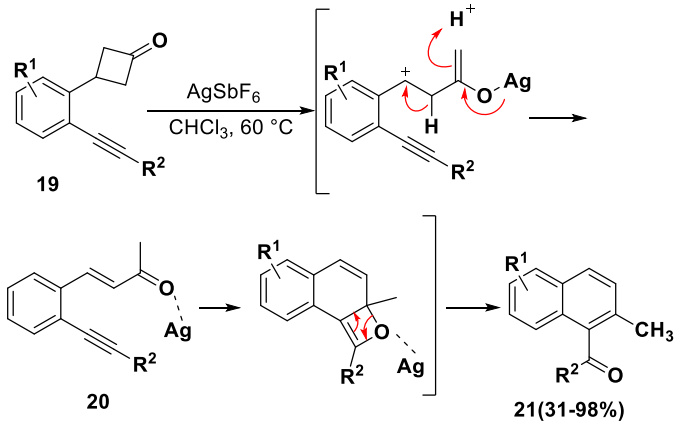
During this period, research activity in the ACM field expanded rapidly. Several groups investigated the reactivity of cyclic alkyne–ketones using catalysts such as HCl, HBr, and HBF_4, aiming to detect and characterize reaction intermediates through spectroscopic techniques including ^{13}C NMR to clarify the underlying mechanism.[52-54] Other researchers examined how the ring size of the starting material, particularly the number of carbon atoms, influenced regioselectivity and the ring-closing outcome of the final products.[55,56]

Subsequently, research in organic synthesis increasingly focused on constructing diverse molecular scaffolds using alkyne-tethered carbonyl systems. In these studies, various carbon-chain lengths and functional groups were introduced between the carbonyl and alkyne units, and the alkyne substituent itself displayed substantial structural diversity. Using this straightforward strategy, numerous heterocycles including quinolizines **15**,[57,58] quinolines, coumarins **16**,[37] and highly conjugated frameworks **17** and **18**—were successfully synthesized (Scheme 7).[64-68]

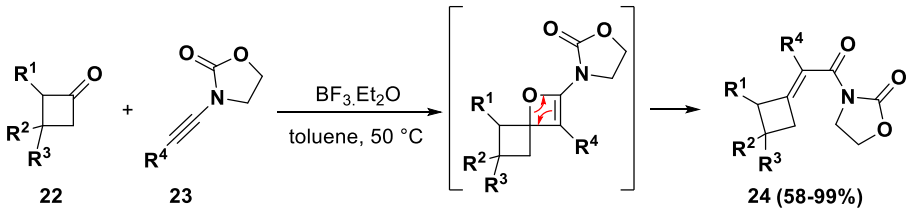


Scheme 7. Intramolecular cyclization of various terminal alkynes.

Alkyne-tethered cyclobutanones **19** serve as suitable substrates for ACM reactions. Ag(I) activates the carbonyl group of the cyclobutanone, promoting ring opening. From the resulting oxetene intermediate, multisubstituted naphthyl ketones **21** are formed (Scheme 8). To clarify the mechanism of this transformation, intermediate **20** was independently synthesized and subjected to the reaction conditions, and the resulting product was compared with that obtained in the main reaction. Additionally, reaction progress and intermediate formation were monitored by NMR spectroscopy in D_2O.[69] Notably, when the alkyne and cyclobutanone are not incorporated within the same molecular framework and instead react as separate molecules, cyclobutanone ring opening does not occur, and the product retains the intact four-membered ring (Scheme 9).[70]

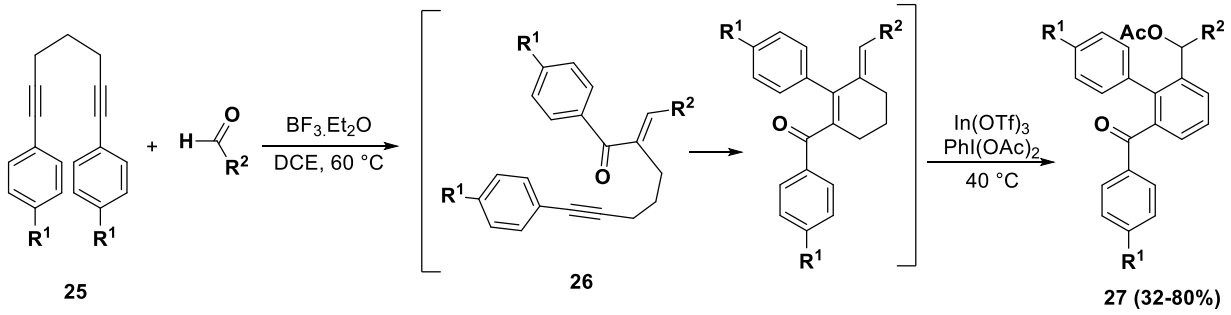


Scheme 8. $AgSbF_6$-catalyzed ring-opening/ACM of alkyne-tethered cyclobutanones.



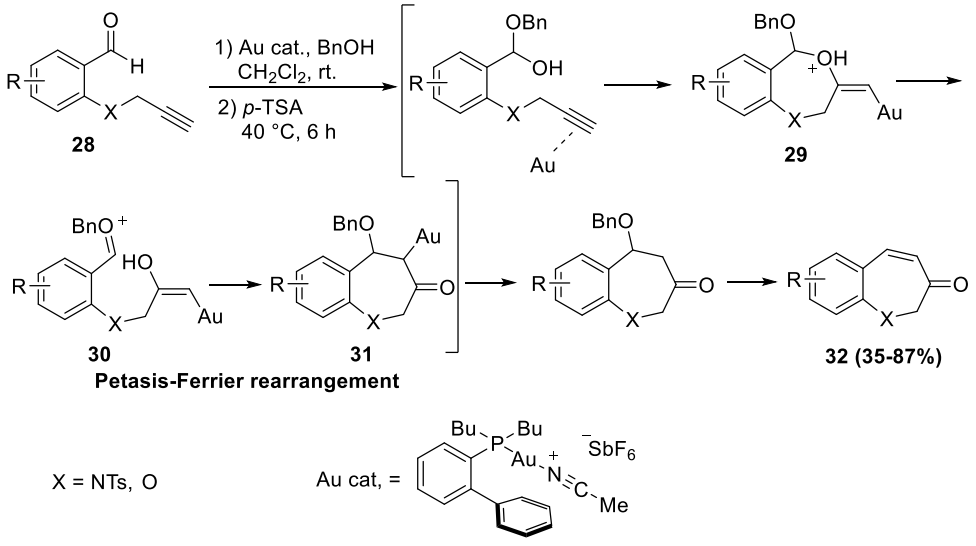
Scheme 9. BF_3-catalyzed ACM reaction between cyclobutanone and alkyne.

Surprisingly, the ACM reaction of a molecule containing two alkyne groups **25** with an aldehyde proceeds through a BF_3-catalyzed intermolecular ACM step, followed by an $In(OTf)_3$-mediated intramolecular ACM cyclization of the resulting adducts **26**. The final biaryl product **27** is then formed through oxidative aromatization in the presence of iodobenzene diacetate (Scheme 10).[71]

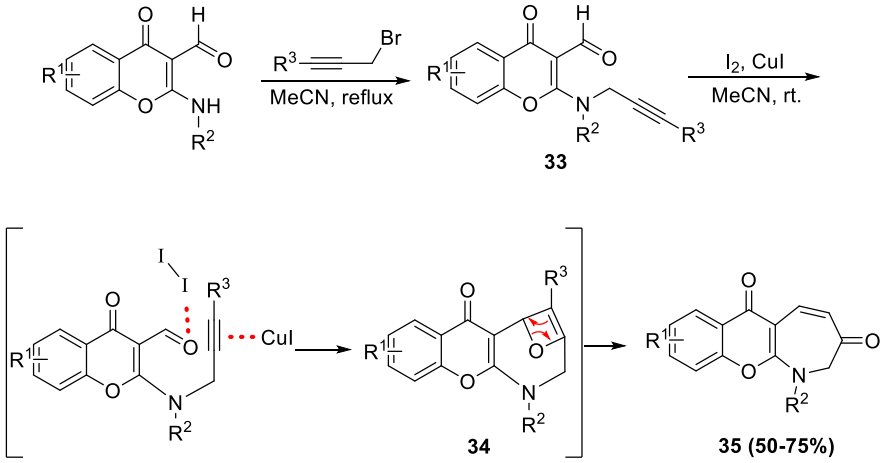


Scheme 10. Inter-/Intramolecular cyclization of a bi-alkyne.

The synthesis of fused oxepinone and azepinone frameworks typically requires highly unstable reactants or harsh reaction conditions. For example, we previously reported the preparation of pyrrolo[3,4-b]azepin-5(4H)-ones from allene-tethered O-propargyl oximes.[2-6] In 2011, Sze et al. discovered that the use of an Au(I) complex in combination with benzyl alcohol significantly alters the reaction pathway. As illustrated in Scheme 11, substrate **28** is first converted into a hemiacetal, which subsequently undergoes cyclization to form intermediate **29**. Owing to the catalytic role of gold, intermediate **30** is generated through a Petasis–Ferrier rearrangement,[73] leading to cyclized adduct **31**. This intermediate ultimately evolves into the desired benzo[b]oxepinone and/or benzo[b]azepinone products **32**.[74,75] As previously demonstrated, the reaction between an alkyne and a carbonyl compound typically proceeds through an oxetene intermediate to furnish a six-membered ring product. In the present case, however, the benzyl alcohol–Au(I) catalytic system, together with the associated rearrangement, directs the reaction toward formation of a seven-membered ring. Subsequently, a related transformation was carried out using N-alkynylated chromenone-3-carbaldehyde **33**,[76] where the strong CuI–I_2 catalytic system enabled an analogous reaction pathway. In this study, the authors proposed that the reaction proceeds through an oxetene intermediate **34** formed by addition of the carbonyl group to the alkyne in a steric orientation distinct from earlier examples. This pathway ultimately delivers the seven-membered fused heterocycle chromeno[2,3-b]azepine-3,6-dione **35** (Scheme 12).[77]

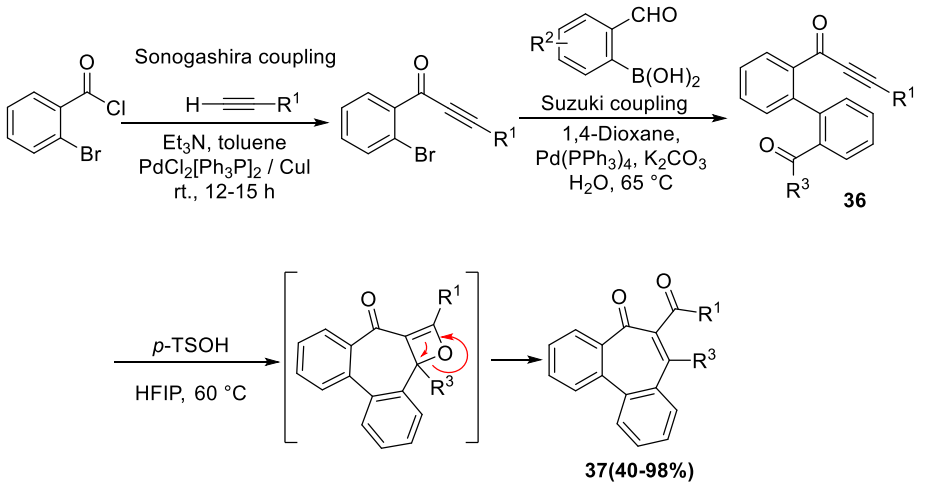


Scheme 11. Gold-catalyzed synthesis of benzo[b]oxepinone and benzo[b]azepinone.



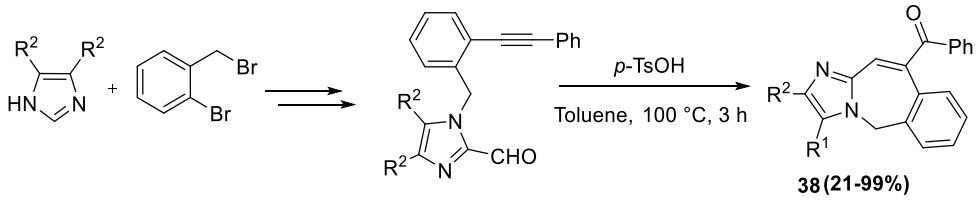
Scheme 12. CuI/I_2-catalytic system for the synthesis of chromeno[2,3-*b*]azepine-3,6-dione.

Langer et al. introduced an alternative acid-catalyzed strategy for synthesizing seven-membered rings through ACM metathesis. In this design, two aromatic rings are positioned between the carbonyl and alkyne groups, directing the carbonyl to approach the alkyne from a defined orientation and ultimately leading to formation of the fused six-membered ring dibenzotropone **37** (Scheme 13). The precursor **36** can be conveniently prepared via Sonogashira coupling, followed by a Suzuki reaction to append the aryl-alkyne fragment to the aryl-aldehyde moiety.[78]

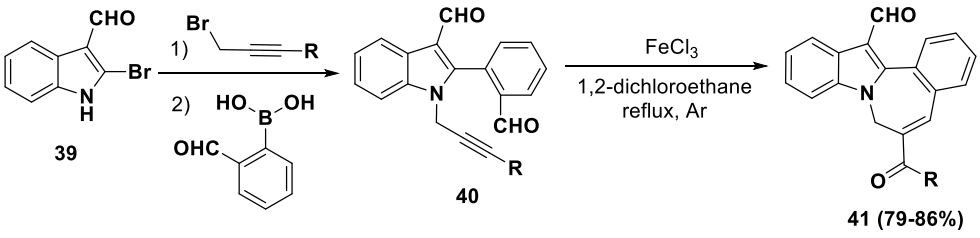


Scheme 13. Brønsted acid-catalyzed synthesis of dibenzotropones.

This synthetic strategy provides a practical route to a variety of fused heterocycles. Previously, imidazoazepines were accessible only under harsh conditions using LDA,[79] or required expensive Pd-based catalysts for cyclization.[80,81] In 2022, Langer et al. reported a more efficient method for preparing fused imidazoazepines **38** (Scheme 14).[82] Starting from 2-bromo-1H-indole-3-carbaldehyde **39**, the authors obtained substrate **40** through N-propargylation, followed by Suzuki coupling with 2-formylphenylboronic acid. The presence of the alkyne on the nitrogen atom and the aldehyde on the adjacent aromatic ring directs the reaction toward formation of the seven-membered fused azepino[1,2-a]indole **41** (Scheme 15).[83]

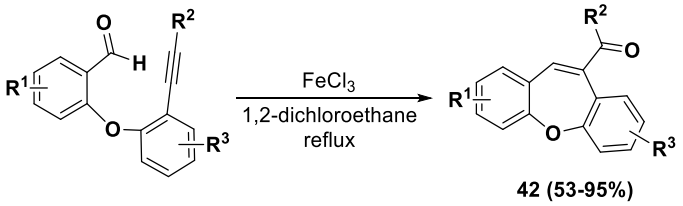


Scheme 14. Brønsted acid-catalyzed synthesis of fused imidazoazepines.



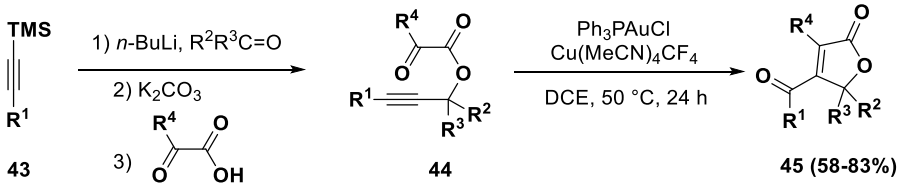
Scheme 15. $FeCl_3$-catalyzed synthesis of fused azepino[1,2-*a*]indoles.

To introduce structural diversity into the products, various heteroatoms can be incorporated between the benzene rings bearing the aldehyde and alkyne functionalities, enabling the formation of a wide array of seven-membered heterocyclic frameworks (Scheme 16).[84] Consequently, this class of ACM metathesis reactions can be efficiently promoted by both Lewis and Brønsted acids.



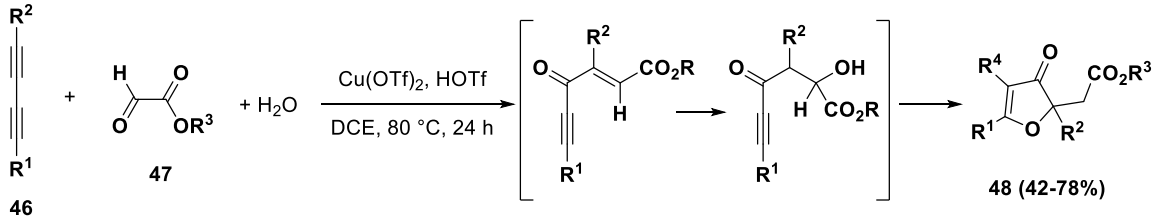
Scheme 16. Lewis acid-catalyzed synthesis of fused dibenzo[*b,f*]oxepines.

The advancement of ACM transformations is not limited to the synthesis of six- or seven-membered rings; more recently, researchers have also succeeded in constructing five-membered rings. For example, compound **44** readily obtained from the reaction of alkyne **43** with an aldehyde, followed by condensation with pyruvic acid derivatives—undergoes ACM cyclization in the presence of a Au/Cu bimetallic catalyst to afford furanones **45** (Scheme 17). This synthetic protocol provides an efficient route to isomuronic acid, a natural product.[85]



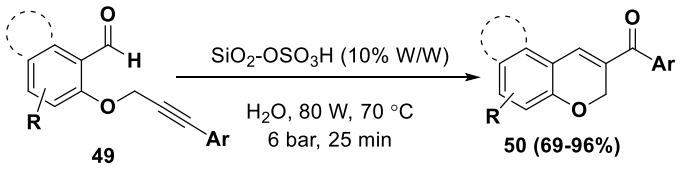
Scheme 17. Au/Cu-catalyzed synthesis of 2(5*H*)-furanones.

3(2H)-Furanones **48** can also be synthesized through a three-component reaction involving 1,3-diynes 46, alkyl glyoxylates **47**, and water. A bicatalytic combination of Lewis and Brønsted acids promotes the ACM transformation followed by an oxa-Michael addition.[86]



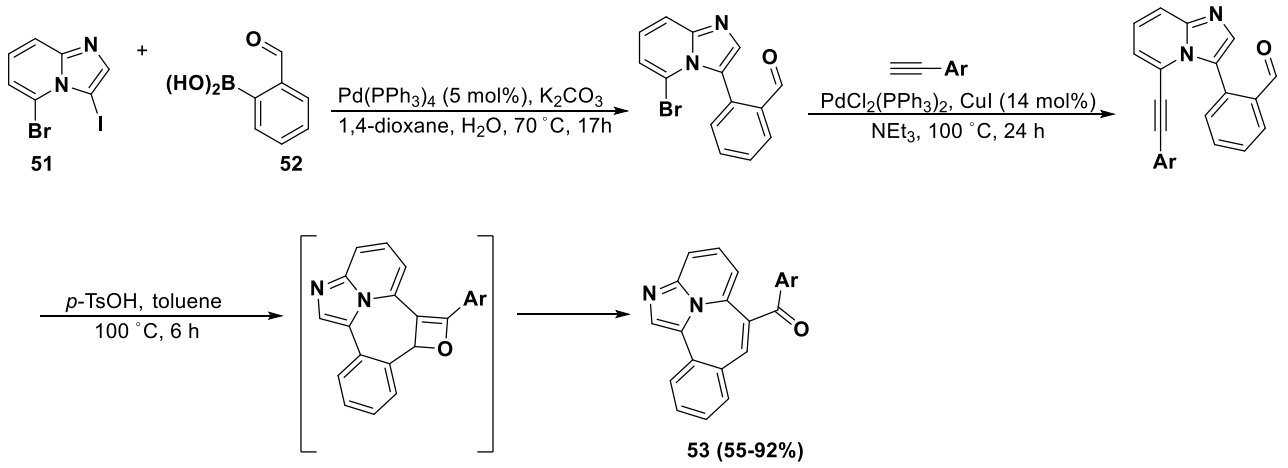
Scheme 18. Cu-catalyzed synthesis of 3(2*H*)-furanones.

Khatravath and co-workers reported an efficient microwave-assisted synthesis of 2H-chromenes **50** using readily accessible alkyne-tethered 2-((3-phenylprop-2-yn-1-yl)oxy)benzaldehydes **49** via an intramolecular alkyne–carbonyl metathesis reaction, employing silica sulfuric acid (SiO_2–OSO_3H) as an inexpensive and environmentally benign catalyst (Scheme 19).[87] Under these optimized conditions, a broad range of 2H-chromenes **50** was obtained from substrates bearing both electron-withdrawing (e.g., Cl, F, NO_2, CO_2Me) and electron-donating (e.g., Me, OMe) substituents, with good to excellent yields.



Scheme 19. Synthesis of 2*H*-chromenes.

Diazadibenzo[cd,h]azulene derivatives **53** were synthesized by Langer and co-workers through a three-component reaction involving 5-bromo-3-iodoimidazo[1,2-a]pyridine **51**, (2-formylphenyl)boronic acid **52**, and arylacetylenes (Scheme 20).[88] This strategy integrates chemoselective Suzuki–Miyaura and Sonogashira cross-coupling reactions with an intramolecular alkyne–carbonyl metathesis (ACM), providing efficient access to these polycyclic heterocycles.



Scheme 20. Synthesis of diazadibenzo[cd,h]azulene derivatives.

A comprehensive analysis of these studies shows that ACM reactions can yield markedly different products depending on several key factors, including reaction conditions, the nature of the starting materials, the spatial orientation of the alkyne relative to the carbonyl group, the number of atoms separating these two functionalities within the same molecule, and the type of catalyst employed. From a mechanistic perspective, Lewis acids typically function as oxophilic catalysts that activate the C=O group, whereas Ag-, Au-, and Pd-based catalysts are generally believed to interact with the C≡C bond.[89-91] Table 1 summarizes additional references not explicitly discussed in the main text. Notably, the ACM precursor can be generated in situ through a one-pot multicomponent reaction, after which the ACM process can be promoted in the same vessel by introducing an appropriate catalyst. Moreover, the Ugi reaction provides versatile adducts suitable for metathesis transformations.[92] For example (Table 1, entry 21), the Ugi reaction employing alkynes and ketones offers an effective route to intermediates bearing adjacent alkyne and carbonyl groups. Upon addition of catalysts such as palladium[59] or camphorsulfonic acid,[94] these intermediates undergo cyclization to furnish quinolinone derivatives.

Table 1. The ACM reactions leading to the various products

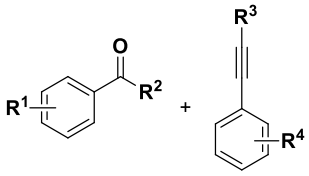
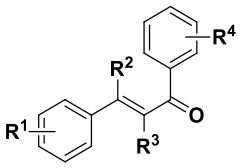
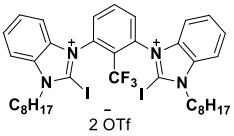
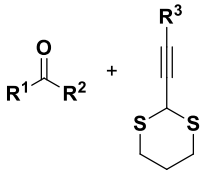
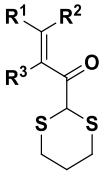
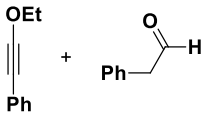
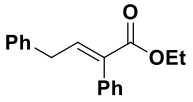
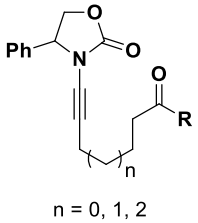
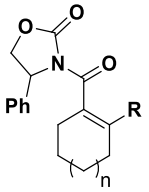
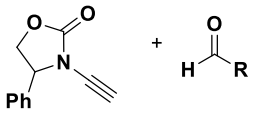
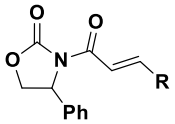
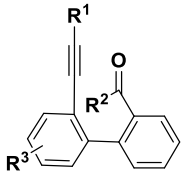
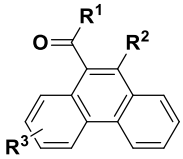
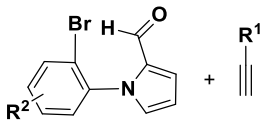
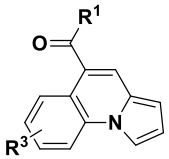
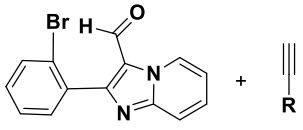
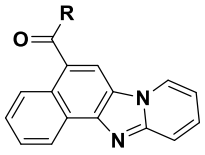
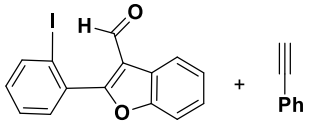
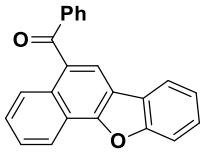
Entry	Reactant(s)	Product	Conditions	Yield (%)	Ref
1			 MeOH, rt., 72 h	65-71	95
2			KO*t*-Bu, rt., DMSO, 10 min	43-79	96
3			$AgBF_4$, 1,4-dioxane, 80 °C	82	97
4	 n = 0, 1, 2		BF_3-OEt_2, CH_2Cl_2, rt.	22-85	57
5			BF_3-OEt_2, CH_2Cl_2, rt.	42-83	98
6			$FeCl_3$, 1,2-dichloroethane, reflux	68-85	99
7			1) $(PPh_3)_2PdCl_2$, CuI, Et_3N, THF 2) TFA, 1,2-dichloroethane, 90°C	33-93	100
8			1) $(PPh_3)_2PdCl_2$, CuI, Et_3N, THF 2) TFA, 80°C	65-84	101
9			1) $(PPh_3)_2PdCl_2$, CuI, Et_3N, THF 2) TFA, 1,2-dichloroethane, 80°C	97	102, 103

Table 1. Continued

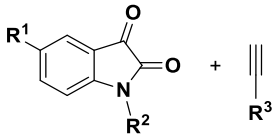
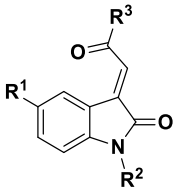
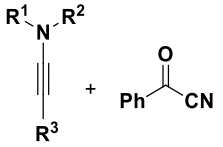
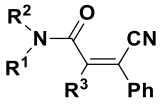
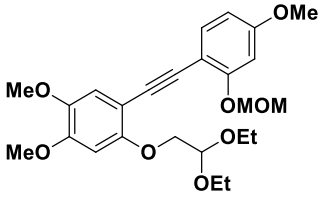
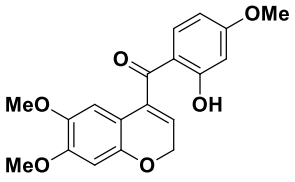
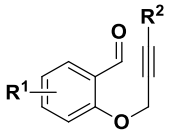
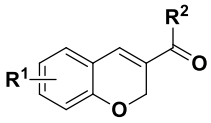
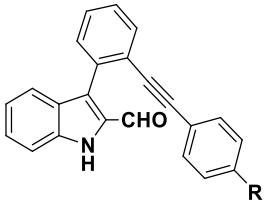
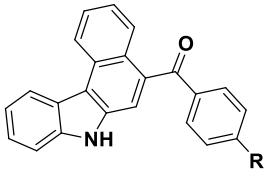
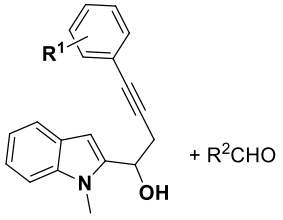
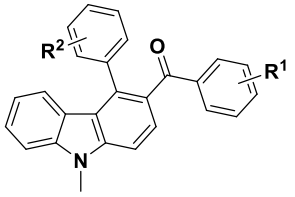
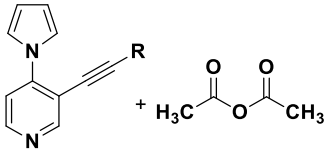
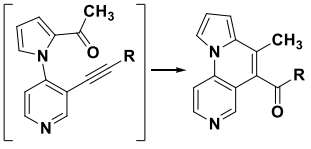
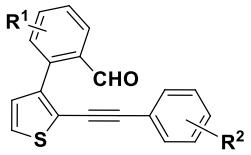
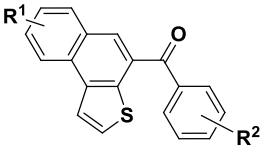
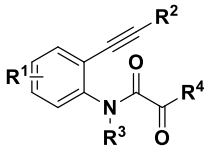
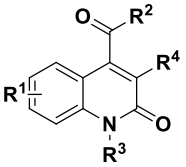
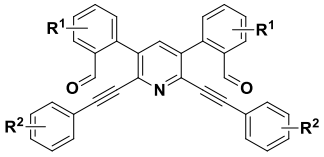
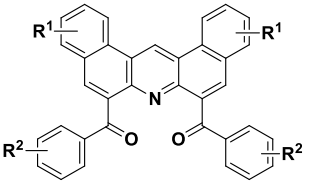
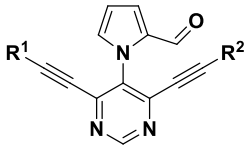
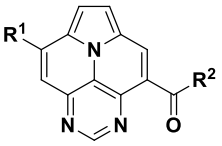
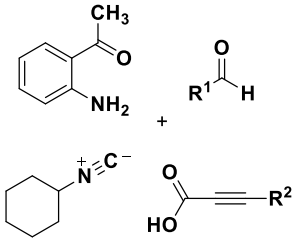
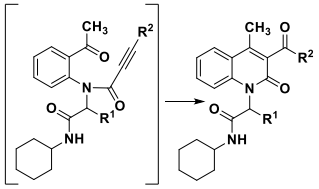
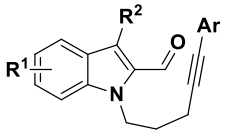
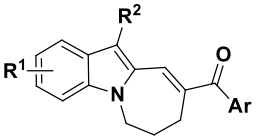
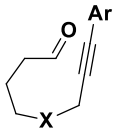
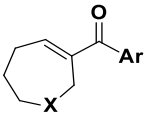
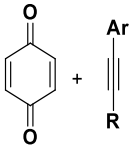
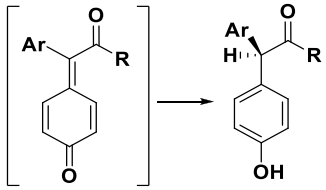
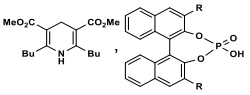
Entry	Reactant(s)	Product	Conditions	Yield (%)	Ref
10			$FeCl_3$, CH_3CN, reflux	10-73	104, 105
11			$Sc(OTf)_3$,$CHCl_3$, N_2, rt.	53-93	106
12			$In(OTf)_3$, THF. H_2O, 80 °C (Then this product was converted into racemic munduserone and deguelin natural products under basic and acidic conditions, respectively.)	92	107
13			I_2, CH_2O, MeOH rt., 24 h $C_7H_7BF_4$, 1,2-dichloroethane, 50 °C	90-97 40-96	108 109
14			$FeCl_3$, 1,2-dichloroethane, Ar, reflux	76-85	83
15			$Pd(bpy)Cl_2$, D-(+)-camphorsulfonic acid, 1,4-dioxane, 75 °C, 6-8 h	40-73	89
16			1) TFFA, xylene, 140 °C; 2) *p*-TSA, xylene, 140 °C	24-95	110

Table 1. Continued

Entry	Reactant(s)	Product	Conditions	Yield (%)	Ref
17			*p*-TSA, toluene, reflux	45-95	111
18			$Sc(OTf)_3$, dioxane, 110 °C	42-93	112
19			$C_7H_7BF_4$, neat, 60 °C, 12 h	31-70	113, 114
20			*p*-TsOH·H_2O, xylene, 120 ℃, 6 h	51-71	115
21			1) EtOH 2) $Pd(OAc)_2$, 1,10-phenanthroline, EtOH/AcOH, 75 °C, 24 h	17-81	93-94
22			$Sc(OTf)_3$, 1,2-dichloroethane, 80 °C	87-90	116
23			TFA, 90 °C	57-90	117
24			 *hv*, CH_2Cl	37-96	118

More critical and comparative evaluation of ACM methodologies by examining mechanistic features, efficiency trends, selectivity profiles, and practical considerations across Au-, Ag-, and Brønsted acid–catalyzed systems. Gold catalysts, which strongly activate alkynes through π-coordination and stabilize cationic intermediates, generally deliver high yields, broad substrate scope, and predictable regioselectivity, though their cost and sensitivity to coordinating groups remain notable limitations.[119-121] Silver catalysts, with weaker π-activation, often exhibit moderate efficiency and less predictable selectivity, and their narrower functional

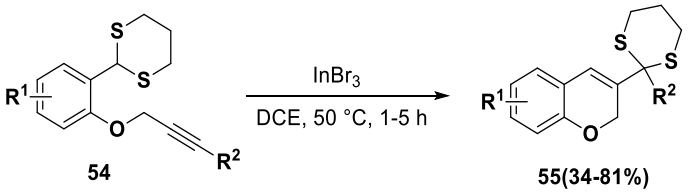
group tolerance can necessitate higher catalyst loadings.[122,123] Brønsted acids provide metal-free activation and strong chemoselectivity under mild conditions, yet may suffer from over-protonation and limited stereocontrol, particularly with acid-sensitive substrates.[124] Meanwhile, there are some key limitations inherent to ACM chemistry, including constraints in substrate scope, regio- and chemoselectivity challenges, competing pathways, and issues associated with oxetene intermediates highly strained species prone to rearrangement, fragmentation, or premature ring opening, which can complicate both selectivity and scalability. Furthermore, intermolecular and intramolecular ACM processes is an important subject, noting that intermolecular reactions often face entropic penalties and competition from side reactions, whereas intramolecular cyclizations benefit from proximity effects that enhance yield, selectivity, and functional group tolerance, albeit at the cost of requiring pre-organized substrates. Finally, scalability and synthetic applicability, emphasizing factors such as reaction robustness, sensitivity to functional groups, and the challenges posed by unstable intermediates during large-scale implementation were clarified. Collectively, these additions provide a more interpretive and mechanistic perspective, strengthening the depth and practical relevance of the reaction.

Table 2. Comparisons between Au-, Ag-, and Brønsted acid-catalyzed ACM reactions

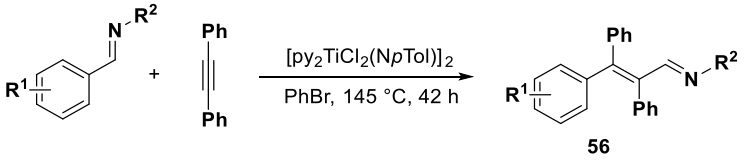
Catalyst Class	Activation Mode	Reaction Efficiency	Selectivity Profile	Functional Group Tolerance	Key Limitations	Ref
Gold (Au)	Strong π activation of alkynes; stabilizes cationic intermediates	Typically high yields; broad substrate scope	Excellent chemoselectivity; predictable regioselectivity	Good tolerance for heteroatoms, aromatics, and electron rich groups	Cost; sensitivity to coordinating groups; potential over activation	119-121
Silver (Ag)	Weaker π activation; promotes cycloisomerization	Moderate efficiency; substrate dependent	Less predictable selectivity; more prone to competing pathways	Tolerates simple alkynes and carbonyls; less robust with complex substrates	Lower reactivity; narrower scope; often requires higher loadings	122-123
Brønsted Acids	Protonation driven activation; metal free	High efficiency for certain substrates; mild conditions	Strong chemoselectivity; pathway control via acid strength	Excellent tolerance for sensitive functional groups; avoids metal contamination	Limited stereocontrol; risk of over protonation; acid sensitive substrates	124

4. Future Perspectives on Alkyne-Carbonyl Metathesis Reactions

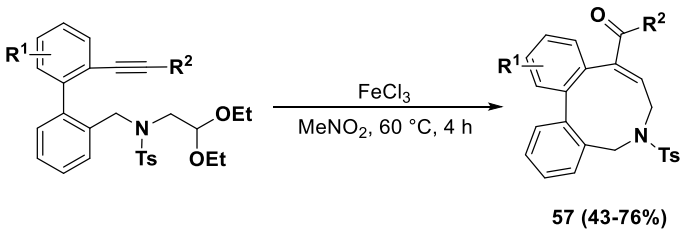
Based on the ACM reactions developed to date, it is reasonable to anticipate that, in the near future, a broad range of heterocycles and complex fused carbocyclic architectures will be accessible through this strategy. Moreover, replacing the oxygen atom of the carbonyl group with other heteroatoms opens the door to metathesis reactions of entirely new substrate classes. Recent studies, for example, have described alkyne–dithianyl, alkyne–acetal, and alkyne–carboamination metathesis processes. [125] Chen et al. recently reported an indium-catalyzed alkyne–dithianyl metathesis of substrate **54**, enabling the construction of 3-(2-methyl-1,3-dithian-2-yl)-2H-chromene **55** (Scheme 21).[126] Koby and Tonks reported an alkyne–carboamination transformation catalyzed by Ti-imido halide precatalysts, affording α,β-unsaturated imines 56 (Scheme 22).[127] The synthesis of 6,7-dihydro-5H-dibenzo[c,e]azonines **57** represents a notable example of an alkyne–acetal metathesis transformation (Scheme 23).[128]



Scheme 20. Indium-catalyzed synthesis of 3-(2-methyl-1,3-dithian-2-yl)-2*H*-chromene.

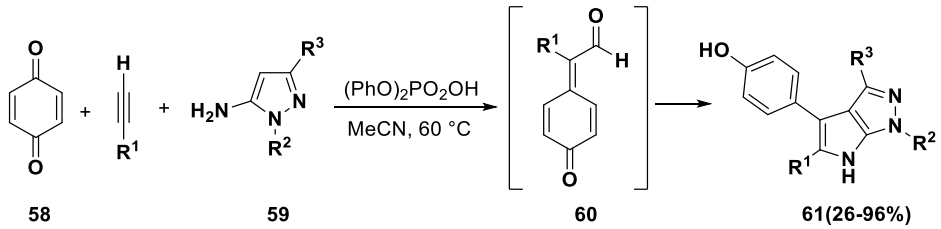


Scheme 21. Ti-catalyzed alkyne-carboamination transformation.



Scheme 22. Fe(III)-catalyzed alkyne-acetal transformation.

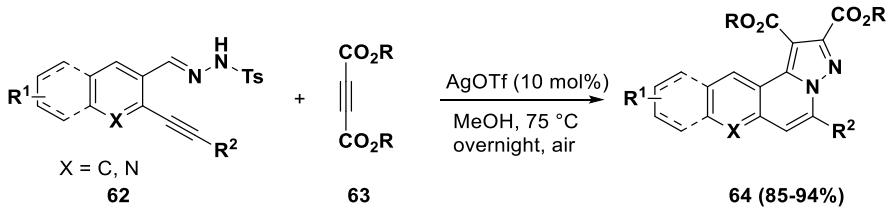
In some cases, the ACM product itself can serve as a reactive intermediate for subsequent transformations, ultimately leading to additional products. [129] Such processes can occur in the same reaction vessel, where the in situ-generated ACM adduct undergoes further reactions with other components present in the mixture. For example, the three-component reaction of *p*-benzoquinone **58**, acetylenes, and 2-aminopyrazoles **59** proceeds through ACM intermediate **60**, followed by a [3+2] cycloaddition and 1,2-aryl migration, to furnish fused pyrrolopyrazoles **61** (Scheme 24). [130]



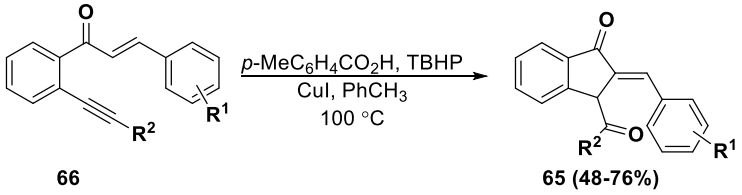
Scheme 23. Acid-catalyzed ACM/cycloaddition/aryl migration transformation.

Our research group developed a novel strategy for accessing diverse fused heterocyclic frameworks through a sequential silver(I)-catalyzed reaction between readily available N-amidonaphthyridin ylide **62** and dialkyl acetylenedicarboxylates **63**. This protocol efficiently furnished a series of tetracyclic ring-fused 1,6-naphthyridine and isoquinoline derivatives **64** in good to high yields. Notably, these compounds represent an intriguing class of luminophores exhibiting tunable emission solvatochromicity (Scheme 25). [131]

In another study, we investigated the formation of 1-indanones **65**, α,β-unsaturated carbonyl compounds via the transformation of ynenones **66** under a copper catalytic system, employing 4-methylbenzoic acid as a cocatalyst and TBHP as both oxidant and reactant. A broad range of ynenones **66** was well tolerated under these conditions, delivering the desired products in moderate to good yields (Scheme 26). [132]



Scheme 24. Silver-catalyzed synthesis of tetracyclic ring-fused 1,6-naphthyridines and isoquinolines.



Scheme 25. Copper-catalyzed synthesis of α,β-unsaturated carbonyl compounds.

Recent advances have greatly expanded the scope and applicability of ACM transformations. Photoredox-assisted ACM reactions have introduced new activation modes that enable radical pathways, milder conditions, and improved functional group compatibility. Green chemistry approaches including aqueous micellar media, solvent-free protocols, and recyclable catalytic systems address sustainability concerns while maintaining high efficiency. In parallel, metal-free and organocatalytic ACM variants have emerged as powerful alternatives to traditional transition-metal catalysis, offering enhanced selectivity, reduced environmental impact, and improved tolerance toward sensitive functional groups. Together, these developments represent important modern directions that broaden the synthetic utility and mechanistic diversity of ACM chemistry.

Table 3. Modern ACM achievements

Methodology	Activation Mode	Advantages	Limitations	Ref
Photoredox-Assisted ACM	Visible-light excitation; radical generation	Mild conditions; new bond-forming pathways; excellent FG tolerance	Requires light setup; radical side reactions	133-134
Green Chemistry ACM	Micellar catalysis; solvent-free; recyclable catalysts	Sustainable; reduced waste; compatible with sensitive substrates	Sometimes lower yields; optimization needed	135-136
Metal-Free / Organocatalytic ACM	Brønsted acid activation; chiral phosphoric acids	Metal-free; high chemoselectivity; potential enantioselectivity	Limited stereocontrol in some systems; acid-sensitive substrates	137-138

Conclusion

ACM transformations have emerged as powerful and versatile synthetic tools for constructing structurally diverse organic frameworks. When carbonyl and alkyne functionalities are incorporated within the same molecule, a wide range of substituents can be positioned between them, enabling fine-tuning of reactivity and access to a broad spectrum of products. The unique reactivity of oxetene intermediates in these transformations provides efficient entry to α,β-unsaturated carbonyl compounds and polycyclic scaffolds.

The development of catalytic systems based on gold, molybdenum, rhenium, and, more recently, Brønsted acids and organocatalysts has significantly improved the yield, chemoselectivity, and substrate scope of ACM reactions. These advances have addressed many of the initial limitations of the transformation, including stoichiometric reagent requirements, narrow substrate scope, low efficiency, and harsh reaction conditions. Moreover, catalyst choice plays a critical role in directing the reaction pathway and selectivity, offering opportunities to steer the transformation toward specific synthetic outcomes. Because variations in catalyst, counterion, or solvent can dramatically influence the reaction profile, mechanistic studies conducted under synthetically relevant conditions will be essential for improving the predictability of ACM transformations. Continued progress in catalyst design and mechanistic understanding is expected to further expand the applicability of ACM chemistry in complex molecule synthesis and materials development.

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