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Isoxazoles as efficient alkyne amination reagents in divergent heterocycle synthesis

Xin-Qi Zhu, *[a] Zhi-Xu Meng,[a] Bo Zhou, [b] Ming-Yu Teng [a] and Long-Wu Ye *[abc]

During the past decades, the exploration of new alkyne amination reactions has attracted increasing attention due to the high efficiency in heterocycle synthesis. In addition to the well-established alkyne amination reagents (such as nitrogen ylides and azides), isoxazoles and their derivatives have been proven to be efficient amination reagents, especially the N,O-bifunctional reagents of alkynes, in the transition metal-catalyzed transformation of alkynes through metal carbene intermediates. Isoxazole derivatives have been extensively applied to the rapid synthesis of a diverse range of structurally complex N-containing molecules, especially the valuable N-heterocycles in atom-economic manner. In this review, we summarize the latest trends and developments of isoxazole-enabled alkyne amination reactions and their applications in divergent heterocycle synthesis, including amination of ynamides, amination of ynol ethers, amination of thioynol ethers, amination of electron-deficient alkynes, amination of unpolarized alkynes and asymmetric amination of alkynes. Finally, we list the current challenges and opportunities for potential breakthroughs in this field.

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Key learning points

(1) Overview of current developments in the isoxazoles as efficient alkyne amination reagents.
(2) Strategies for the divergent synthesis of heterocycles employing isoxazoles and alkynes.
(3) Important reaction types in amination of alkynes with isoxazoles.
(4) α-Imino metal carbenes as the key intermediates in amination of alkynes with isoxazoles.
(5) The current challenges and the future directions in amination of alkynes with isoxazoles.

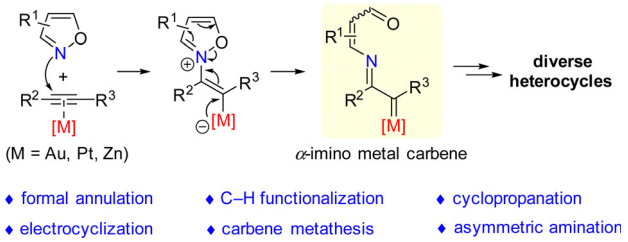
1. Introduction

Transition metal-catalyzed alkyne amination reaction is a powerful methodology for the rapid assembly of valuable N-heterocycles from readily available alkynes *via* α-imino metal carbene intermediates.[1] In the past decades, a variety of amination reagents, including azides,[2] nitrogen ylides,[3] sulfilimines,[4] and others,[5] have been demonstrated in the transition metal-catalyzed intermolecular and intramolecular alkyne amination reactions. In spite of the efficiency of these approaches, the limitation in atom-economy still exists.

Isoxazoles and their derivatives (such as benzo[*c*]isoxazoles and benzo[*d*]isoxazoles) are important skeletons, which could be found in a broad range of natural products, pharmaceuticals and bioactive molecules.[6] However, the reaction of isoxazole derivatives with alkynes was underexplored for a long duration probably due to the weak nucleophilicity of isoxazole derivatives. Compared with the above-mentioned alkyne amination reagents,[2–5] the reaction of isoxazoles with alkynes exhibits unique advantages in heterocycle synthesis. Mechanistically, the labile N–O bonds of isoxazole make it a potential amination reagent in the amination reaction of alkynes, and no waste would be formed in the transformation. Therefore, the development of a new catalytic system and exploration into the electronic properties of alkyne species are important.

In 2015, Ye's group demonstrated a gold-catalyzed reaction of ynamides with isoxazoles, which represents the first example of alkyne amination reaction using isoxazole derivatives.[7] This

[a] *Yunnan Key Laboratory of Modern Separation Analysis and Substance Transformation, College of Chemistry and Chemical Engineering, Yunnan Normal University, Kunming 650500, China. E-mail: xinqizhu@ynnu.edu.cn*
[b] *State Key Laboratory of Physical Chemistry of Solid Surfaces, Key Laboratory of Chemical Biology of Fujian Province, and College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China. E-mail: longwuye@xmu.edu.cn*
[c] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*



Scheme 1 Reaction pathway for the amination of alkynes with isoxazoles.

work provided a new strategy for the amination reaction of alkynes, offering an efficient and divergent method for the synthesis of a wide range of functionalized N-containing heterocycles through an atom-economic pathway. The typical reaction pathway of alkyne amination reaction with isoxazole derivatives is shown in Scheme 1. The nitrogen atom in the isoxazole derivative initially attacks the metal-activated triple bond to afford the vinyl metal intermediate, triggering the fragmentation of N–O bond to generate the key α-imino metal carbene intermediate. The α-imino metal carbene intermediate is regarded as a high electrophilic Fischer-type carbene complex, which could further undergo a series of transformations, such as formal annulation, C–H functionalization, cyclopropanation, electrocyclization, carbene metathesis and other asymmetric aminations, and lead to the assembly of diverse heterocycles.

Considering the wide applications of isoxazoles in alkyne amination reactions, especially as the N,O-bifunctional reagents of alkynes, it is necessary to summarize the latest advances in the amination of alkynes with isoxazoles. During the past years, several relevant reviews on transition metal-catalyzed amination of alkynes have been demonstrated.[8]

Xin-Qi Zhu

Xin-Qi Zhu *was born in 1993 in Ruijin, Jiangxi province of China. He received his BSc degree in chemistry from Nanchang University in 2015. He then obtained his PhD in 2020 from Xiamen University under the guidance of Prof. Long-Wu Ye. After postdoctoral research with Prof. Long-Wu Ye at Xiamen University and with Prof. Jieping Zhu at École Polytechnique Fédérale de Lausanne (EPFL), he joined Yunnan Normal University in 2023 as a full professor. His current research interests include the development of novel asymmetric organocatalyzed and transition-metal-catalyzed reactions.*

Zhi-Xu Meng

Zhi-Xu Meng *was born in Puan, Guizhou Province of China. She earned her BSc from Zunyi Normal University in 2022. She is currently a third-year graduate student in the group of Prof. Ming-Yu Teng of Yunnan Normal University.*

Bo Zhou

Bo Zhou *was born in 1992 in Lu'an, Anhui province of China. He received his BSc in chemistry from Wuhan University of Technology (2013). He then obtained his PhD in 2019 from Xiamen University under the guidance of Prof. Long-Wu Ye. After postdoctoral studies with Prof. Guangbin Dong at the University of Chicago, he joined Xiamen University in 2022 as an associate Professor. His current research interests include asymmetric synthesis based on alkynes and their further applications.*

Ming-Yu Teng

Ming-Yu Teng *was born in 1981 in Tongren, Guizhou province of China. He received his BSc in chemistry from Zhejiang University (2003). He then obtained his PhD in 2009 from Nanjing University, under the guidance of Prof. Yi Pan and Le-Yong Wang. After postdoctoral studies with Prof. You-Xuan Zheng and Bing-Cai Pan at Nanjing University, he joined Yunnan Normal University in 2013 as an assistant Professor. He was promoted to the associate Professor in 2016 and full Professor in 2024. His current research interests include the development of organic optical functional materials, transition-metal catalysis and heterocycle synthesis.*

However, the latest comprehensive summary on the amination of different types of alkynes with isoxazoles has not been reported.

The aim of this review is to provide latest trends and developments of alkyne amination reactions with isoxazoles in divergent heterocycle synthesis, which is organized by different types of alkynes, including amination of ynamides, amination of ynol ethers, amination of thioynol ethers, amination of electron-deficient alkynes, amination of unpolarized alkynes and asymmetric amination of alkynes. In general, ynamides, ynol ethers, and thioynol ethers are considered as electron-rich alkynes, which exhibit α-addition by isoxazoles in the alkyne amination reactions with isoxazoles. In contrast, electron-deficient alkynes, such as propiolates, alkynones and alkynyl sulfones, display β-addition by isoxazoles. The unpolarized alkynes demonstrate relatively poor chemoselectivity in the alkyne amination reactions with isoxazoles. We believe this review will promote the further development of heterocycle synthesis, alkyne chemistry and carbene chemistry.

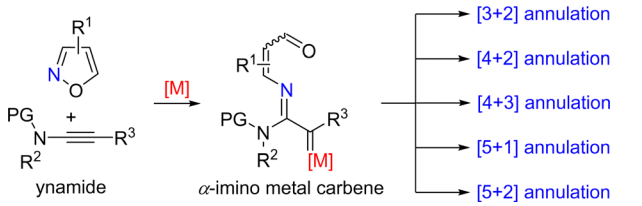
2. Amination of ynamides

2.1. Formal annulation

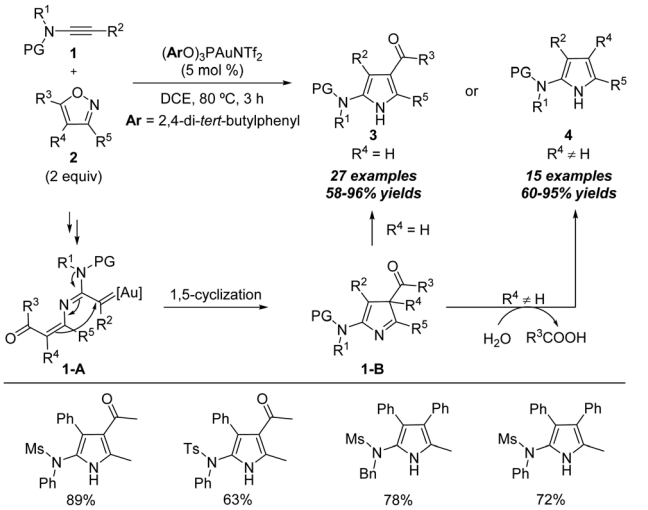
Ynamides are special alkynes directly attached to the nitrogen atom containing an electron-withdrawing group (EWG), which have electron-rich triple bonds and tunable electronic properties. Ynamides have been proven to be versatile synthons in organic synthesis.[9] Since the first report on formal annulation of ynamides with isoxazoles by Ye's group,[7] a series of formal annulation reactions between ynamides and isoxazoles have been developed, such as [3+2], [4+2], [4+3], [5+1] and [5+2] annulations, leading to the construction of diverse N-heterocycles (Scheme 2).

2.1.1. Formal [3+2] annulation. The amination of ynamides by using isoxazoles as alkyne amination reagents was not reported until 2015.[7] As depicted in Scheme 3, Ye and coworkers reported an efficient gold-catalyzed formal [3+2] annulation of ynamides **1** with isoxazoles **2**, leading to the formation of a variety of polysubstituted 2-aminopyrroles **3** and **4** in moderate to excellent yields with a broad substrate scope. Interestingly, the product distributions were achieved due to the substitutions of the isoxazole substrates. 2-Aminopyrroles **3** were generated from the direct [3+2] annulation of 3,5-disubstituted isoxazoles. However, when trisubstituted isoxazoles **2** were used as substrates, the corresponding deacylated products **4** were obtained. Alkyl substituted ynamides are incompatible in this formal [3+2] annulation. It is worth noting that this protocol represents the first amination reaction of alkynes with isoxazoles.

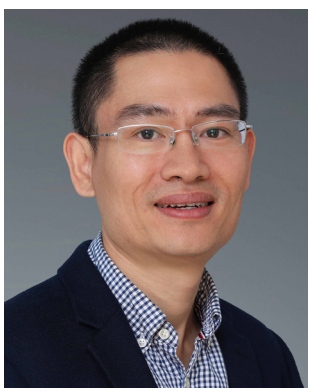
The proposed mechanism of the above gold-catalyzed [3+2] annulation of ynamides with isoxazoles is shown below. First, nucleophilic attack of isoxazole **2** onto the gold-activated triple bond of ynamides and N–O bond cleavage lead to the formation of the α-imino gold carbene intermediate **1-A**. Subsequently, a 1,5-cyclization of **1-A** occurs to form the 3*H*-pyrrole intermediate **1-B** and releases the gold catalyst. Then 3*H*-pyrrole **1-B** readily isomerizes into the 1*H*-pyrrole **3** *via* a 1,3-H shift when the disubstituted isoxazole is used as the substrate. Alternatively, for the trisubstituted isoxazole substrate, a water-assisted deacylative aromatization of **1-B** occurs to afford the final 1*H*-pyrrole **4**.



Scheme 2 Formal annulation reactions of ynamides with isoxazoles.

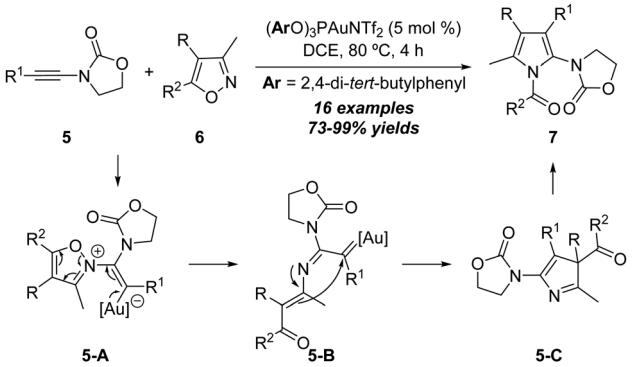


Scheme 3 Gold-catalyzed formal [3+2] annulation of ynamides **1** with isoxazoles **2**.



Long-Wu Ye

Long-Wu Ye *was born in 1981 in Wenzhou, Zhejiang province of China. He received his BSc in chemistry from Zhejiang University (2003). He then obtained his PhD in 2008 from Shanghai Institute of Organic Chemistry with Prof. Yong Tang. After postdoctoral studies with Prof. Subhash Sinha at The Scripps Research Institute and with Prof. Liming Zhang at the University of California at Santa Barbara, he joined Xiamen University in 2011 as an associate Professor. He was promoted to a full Professor in 2012. His current research interests focus on the alkyne transformations and their applications in heterocycle synthesis.*

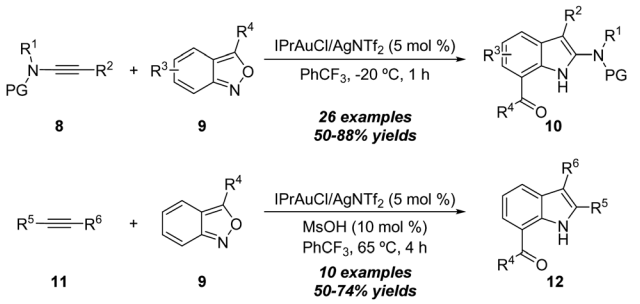


Scheme 4 Gold-catalyzed [3+2] annulation of ynamides **5** with isoxazoles **6**.

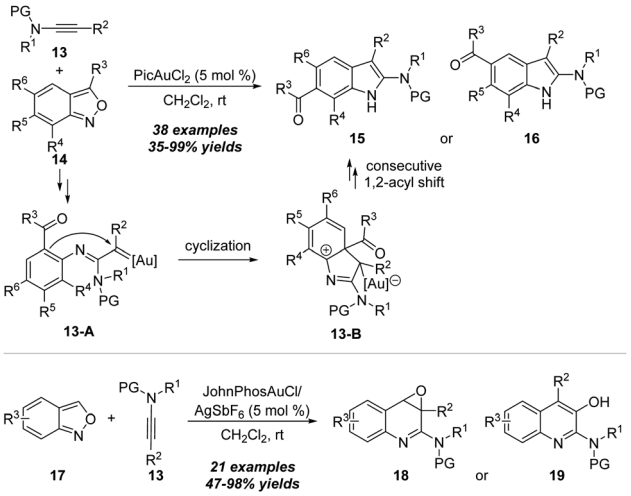
In 2015, the same group disclosed another interesting gold-catalyzed formal [3+2] annulation between ynamides and isoxazoles.[10] The treatment of oxazolinone-type ynamides **5** with isoxazoles **6** in the presence of the $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*tert*-butylphenyl) catalyst afforded a series of *N*-acetylpyrroles **7** in 73–99% yields (Scheme 4). Substrates bearing both electron-donating and -withdrawing groups on the aryl substituents could be well tolerated in this [3+2] annulation. The reaction starts with the coordination of the gold catalyst with ynamide **5**, which is attacked by isoxazole **6** to form the vinyl gold intermediate **5-A**. Then, ring opening of isoxazole moieties in **5-A** happens to deliver the α-imino gold carbene intermediate **5-B** which can be trapped by the intramolecular enamine moiety to form 3*H*-pyrrole intermediate **5-C**. Finally, an intermolecular nucleophilic attack of **5-C** by another intermediate **5-C** occurs to provide the desired product **7**.

Similarly, benzo[*c*]isoxazoles were also developed as amination reagents. In 2016, Hashmi and co-workers reported a gold-catalyzed formal [3+2] annulation of ynamides **8** with anthranils (benzo[*c*]isoxazoles) **9** by employing IPrAuCl/$AgNTf_2$ as the catalyst, affording a variety of 7-acylindoles **10** in generally good yields (Scheme 5).[11] Interestingly, unpolarized alkynes **11** were also proven as suitable substrates in this annulation, and the corresponding 7-acylindoles **12** were produced in 50–74% yields.

In 2020, the same group reported another related gold-catalyzed formal [3+2] annulation/acyl migration of ynamides



Scheme 5 Gold-catalyzed formal [3+2] annulation of ynamides **8** or unpolarized alkynes **11** with anthranils **9**.

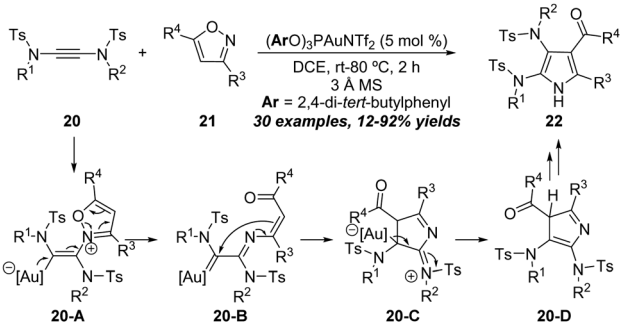


Scheme 6 Gold-catalyzed formal [3+2] annulation of ynamides **13** with anthranils **14** or **17**.

13 with anthranils **14** by employing $PicAuCl_2$ as the catalyst, furnishing the 6-acylindoles **15** or 5-acylindoles **16** in moderate to excellent yields *via* selective 1,4- or 1,3-acyl migration (Scheme 6).[12] Based on the control experiments and density functional theory (DFT) calculations, the mechanism for this selective 1,4- or 1,3-acyl migration is proposed. Initially the α-imino gold carbene intermediate **13-A** is generated from nucleophilic N-attack of anthranil and N–O bond cleavage. After intramolecular cyclization, the consecutive 1,2-acyl shift and anthranil-assisted deprotonation/deauration/protonation process occur to furnish 6-acylindole **15**.

In the same work, the switchable synthesis of quinoline oxides **18** and quinolines **19** from gold-catalyzed amination of ynamides **13** with anthranils **17** was demonstrated through 1,7-cyclization. With 5 mol% JohnPhosAuCl and $AgSbF_6$ in dichloromethane at room temperature, the reaction proceeded smoothly with various functional groups, including electron-withdrawing and electron-donating groups on the aromatic ring, leading to the preparation of a range of quinoline oxides **18** and the rearranged quinoline products **19** in moderate to excellent yields.

Recently, a unique gold-catalyzed formal [3+2] annulation of yndiamides **20** with isoxazoles **21** was demonstrated by Anderson group for the direct synthesis of polysubstituted diaminopyrroles **22** (Scheme 7).[13] By using $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*tert*-butylphenyl) as the catalyst and 3 Å MS as the additive in DCE, a series of functionalized diaminopyrroles **22** were obtained in moderate to good yields. This methodology tolerates a wide range of aryl and alkyl isoxazoles, as well as various symmetrical yndiamides. It is worth noting that the diaminopyrroles could be obtained in good regioselectivities when employing unsymmetrical yndiamide substrates. The reaction starts with the addition of isoxazole **21** onto gold-activated yndiamides to afford the vinyl gold intermediate **20-A**. Subsequent ring opening provides α-imino gold carbene intermediate **20-B**, which can undergo intramolecular cyclization to produce iminium intermediate **20-C**. Next, **20-C** undergoes

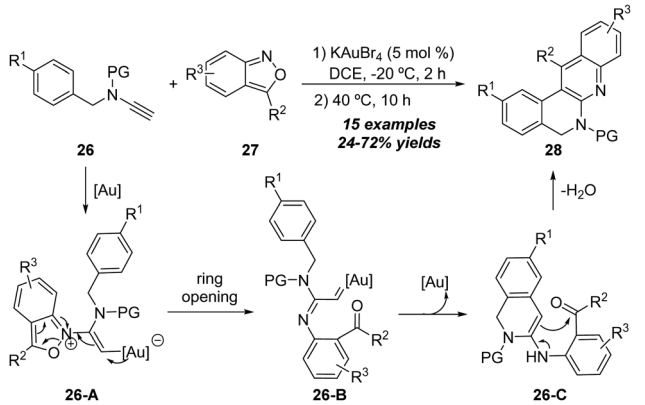


Scheme 7 Gold-catalyzed formal [3+2] annulation of yndiamides **20** with isoxazoles **21**.

protodeauration to afford 3*H*-pyrrole **20-D**. Finally, diaminopyrrole **22** forms *via* double 1,5-H migration.

2.1.2. Formal [4+2] annulation. Different from the above formal [3+2] annulations, the related [4+2] annulations typically require substrates with special substituents. In 2016, Hashmi and co-workers disclosed the first gold-catalyzed [4+2] annulation of alkynes with isoxazoles.[14] As shown in Scheme 8, the treatment of propargylic silyl ethers **23** and anthranils **24** with 5 mol% of IPrAuCl/$AgNTf_2$ at 65 °C allowed the facile synthesis of 2-aminoquinolines **25** in 50–95% yields with a broad functional group tolerance. The reaction mechanism was proposed based on control experiments. First, the vinyl gold intermediate **23-A** is generated from the nucleophilic attack of anthranil **24** onto gold coordinated ynamide, which further undergoes N–O bond fragment to produce α-imino gold carbene intermediate **23-B**. Then, 1,2 C–H insertion of gold carbene takes place to yield silyl enol ether **23-C**. Subsequent Mukaiyama aldol condensation of **23-C** gives rise to final 2-aminoquinoline **25** and releases TBSOH.

In 2018, Hashmi and co-workers realized another gold-catalyzed [4+2] annulation of ynamides with isoxazoles (Scheme 9).[15] In the presence of 5 mol% $KAuBr_4$ catalyst, the reaction proceeded at −20 °C for 2 h, and was then heated to 40 °C. The formal [4+2] annulation of *N*-benzyl ynamides **26** with anthranils **27** led to the desired quinoline-based polyazaheterocycles **28** in 24–72% yields. The plausible mechanism involves the formation of α-imino gold carbene intermediate **26-B**, followed by the subsequent *N*-benzyl C–H insertion of

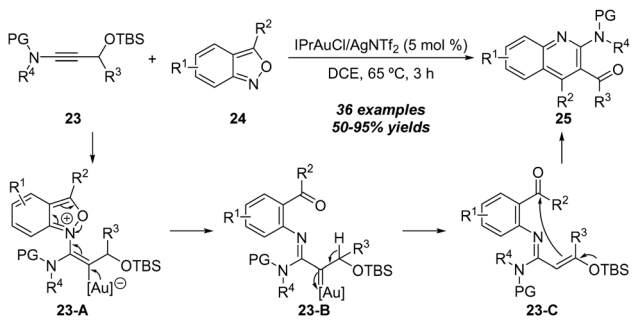


Scheme 9 Gold-catalyzed [4+2] annulation of *N*-benzyl ynamides **26** and anthranils **27**.

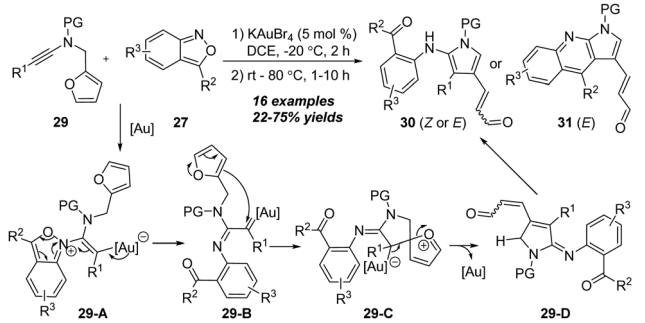
gold carbene, and enamine-aldehyde addition/elimination to generate the expected quinoline-based polyazaheterocycle **28**.

In the same report, the authors demonstrated a gold-catalyzed [4+2] annulation of *N*-furanylmethyl ynamides with anthranils. As shown in Scheme 10, 2-amino pyrroles **30** were initially obtained under the optimized reaction conditions from the amination of *N*-furanylmethyl ynamides **29** with anthranils **27**, which could be readily transformed into thermodynamically more stable pyrrolo[2,3-*b*]quinolines **31**. Mechanistically, the α-imino gold carbene **29-B** is first generated from nucleophilic addition and the fragment of N–O bonds. Then **29-B** is captured by *N*-furanylmethylene species to generate spiro intermediate **29-C**, followed by a C–O cleavage of the furan ring (**29-C**) to form the imine intermediate **29-D**, which can be transformed into 2-amino pyrrole **30** *via* aromatization. Finally, a Friedel–Crafts type cyclization of 2-amino pyrrole **30** affords the desired pyrrolo[2,3-*b*]quinoline **31**.

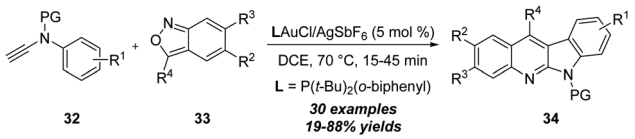
By using a similar strategy, in 2018, Liu and co-workers disclosed a gold-catalyzed tandem [4+2] annulation of *N*-aryl ynamides **32** with anthranils **33**, delivering diverse 6*H*-indolo[2,3-*b*]quinoline derivatives **34** in 19–88% yields (Scheme 11).[16] Similar to the above report,[15] the key *N*-phenyl C–H insertion of gold carbene and the enamine-aldehyde addition/elimination were involved in this [4+2] annulation.



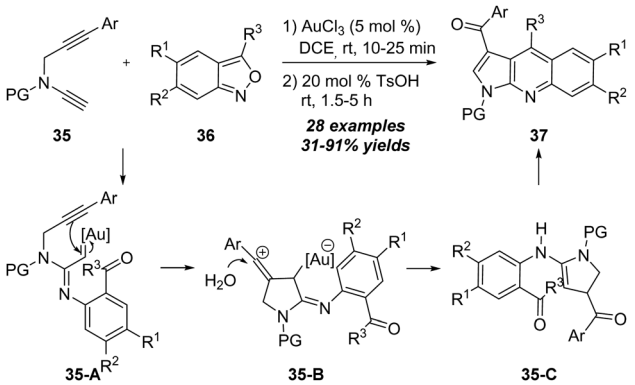
Scheme 8 Gold-catalyzed [4+2] annulation of propargylic silyl ethers **23** with anthranils **24**.



Scheme 10 Gold-catalyzed [4+2] annulation of *N*-furanylmethyl ynamides **29** with anthranils **27**.



Scheme 11 Gold-catalyzed [4+2] annulation of *N*-aryl ynamides **32** with anthranils **33**.

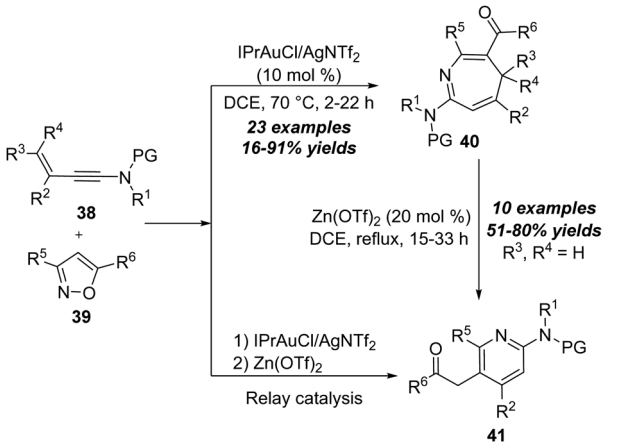


Scheme 12 Gold-catalyzed tandem [4+2] annulation of *N*-propargyl ynamides **35** with anthranils **36**.

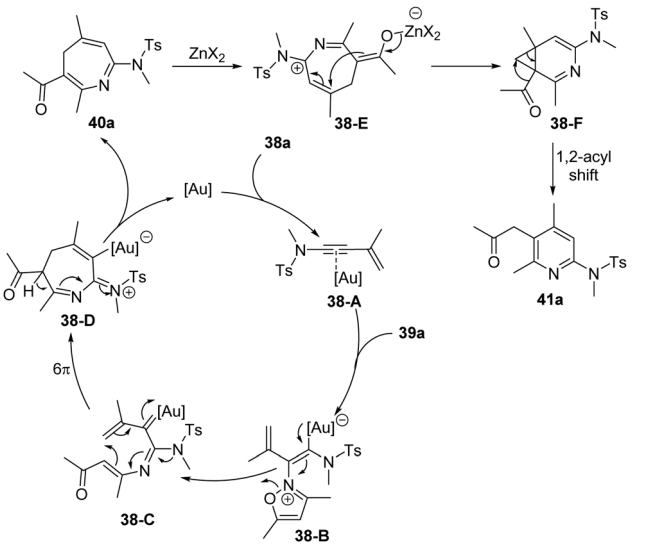
Later in 2019, the same group further reported that this formal [4+2] cycloaddition strategy was also applicable to the reaction of *N*-propargyl ynamides **35** with anthranils **36** under gold catalysis.[17] As outlined in Scheme 12, the reaction of *N*-propargyl ynamides **35** with anthranils **36** took place efficiently in the presence of 5 mol% of $AuCl_3$, and various pyrrolo[2,3-*b*]quinolines **37** could be produced in 31–91% yields after the treatment of 20 mol% TsOH. The reaction of *N*-propargyl ynamide **35** and anthranil **36** first generates α-imino gold carbene intermediate **35-A**, which is trapped by the alkyne moiety *via* carbene/alkyne metathesis, affording vinyl cation intermediate **35-B**. After that, vinyl cation **35-B** is trapped by water, followed by elimination of the gold catalyst, providing intermediate **35-C**. Further oxidation/intramolecular cyclization/elimination occurs to deliver pyrrolo[2,3-*b*]quinoline **37**.

2.1.3. Formal [4+3] annulation. In 2018, Liu and co-workers reported an elegant gold-catalyzed formal [4+3] annulation of alkynes with isoxazoles.[18] As shown in Scheme 13, treatment of 3-en-1-ynamides **38** with isoxazoles **39** in the presence of 10 mol% IPrAuCl/$AgNTf_2$ in DCE delivered 4*H*-azepines **40** in generally moderate to good yields. Interestingly, the resulting 4*H*-azepines **40** could undergo further skeletal rearrangement to furnish 2-amino pyridines **41** in 51–80% yields. Notably, a relay catalysis was also developed using the Au/Zn catalytic system to realize a formal [4+2] annulation from the 3-en-1-ynamides **38** and isoxazoles **39**.

A proposed mechanism for this formal [4+3] annulation is depicted in Scheme 14. The reaction begins with coordination of the gold catalyst with ynamide **38a**, followed by nucleophilic addition with isoxazole **39a**, delivering the vinyl gold intermediate **38-B**. Subsequent ring-opening forms the α-imino



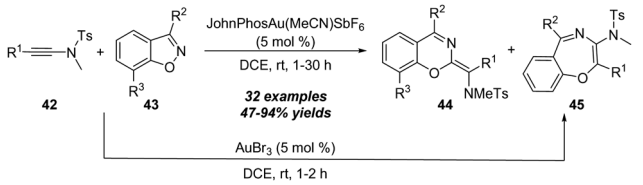
Scheme 13 Gold-catalyzed formal [4+3] annulation of 3-en-1-ynamides **38** with isoxazoles **39**.



Scheme 14 Proposed mechanism for gold-catalyzed formal [4+3] annulation of 3-en-1-ynamides **38** with isoxazoles **39**.

gold carbene **38-C**. Then, a heptatrienyl cation type 6π electrocyclization occurs to produce seven-membered iminium intermediate **38-D**. Subsequent elimination and protodeauration of **38-D** furnish 4*H*-azepine **40a** with the regeneration of the gold catalyst. Further treatment of 4*H*-azepine **40a** with the zinc catalyst generates 2-azapentadienyl cation **38-E**, that undergoes an intramolecular cyclization to afford cyclopropane intermediate **38-F**. Finally, a 1,2-acyl shift of **38-F** takes place to yield 2-amino pyridine **41a**.

2.1.4. Formal [5+1] annulation. Alternatively, the reaction of benzo[*d*]isoxazoles could demonstrate new pathway. In 2018, Liu and co-workers disclosed a gold-catalyzed formal [5+1] annulation of ynamides **42** with benzo[*d*]isoxazoles **43**, delivering a variety of functionalized polysubstituted 2*H*-benzo[*e*][1,3]oxazines **44** in moderate to excellent yields (Scheme 15).[19] In addition, the benzo[*f*][1,4]oxazepines **45** could be selectively achieved from the

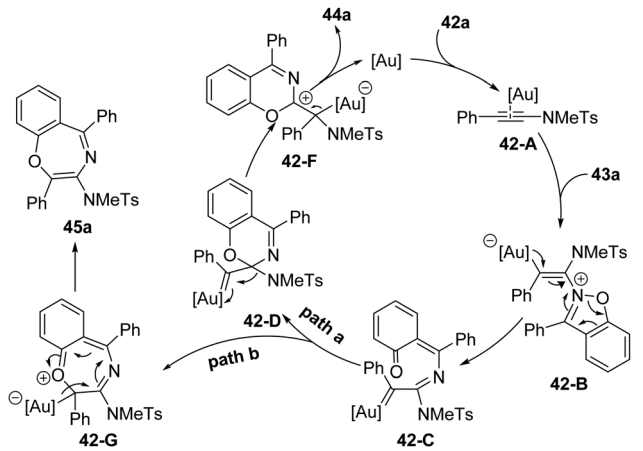


Scheme 15 Gold-catalyzed formal [5+1]/[5+2] annulation of ynamides **42** with benzo[*d*]isoxazoles **43**.

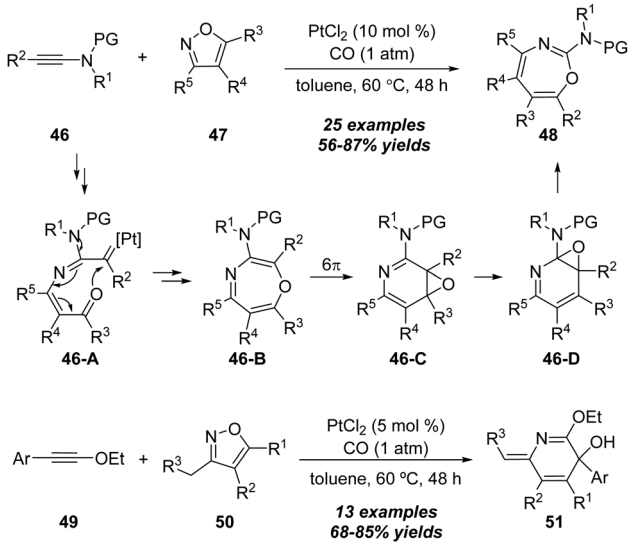
same substrates through a gold catalyst control (using $AuBr_3$ as the catalyst). Ynamides and benzo[*d*]isoxazoles bearing both electron-donating or electron-withdrawing groups on the aromatic ring were compatible with this selective annulation.

The proposed mechanism for this gold-catalyzed cascade formal [5+1]/[5+2] annulation is depicted in Scheme 16. The reaction commences with the coordination of the gold catalyst with ynamide **42a** followed by nucleophilic attack, furnishing vinyl gold intermediate **42-B**. A N–O bond fragment of isoxazole moiety leads to α-imino gold carbene intermediate **42-C**. Then, there are two possible pathways for the intermediate **42-C**. In path a, 6-membered intermediate **42-D** is produced through a 6π electrocyclization. Subsequent 1,2-amino migration of **42-D** followed by the elimination of the gold catalyst provides the 2*H*-benzo[*e*][1,3]oxazine **44a**. Alternatively, in path b, a 1,7-cyclization *via* O-attack to gold carbene **42-C** occurs to deliver 7-membered intermediate **42-G**. Finally, the elimination of the gold catalyst yields the final benzo[*f*][1,4]oxazepine **45a**. Such a type of protocol on gold-catalyzed formal [5+1] annulation of ynamides with benzo[*d*]isoxazoles was also nicely demonstrated by Sahoo and co-workers in 2019.[20]

2.1.5. Formal [5+2] annulation. In 2017, Ye and co-workers realized the first platinum-catalyzed formal [5+2] annulation of ynamides **46** with isoxazoles **47** through the generation of α-imino platinum carbene intermediates, leading to the facile formation of 1,3-oxazepines **48** in 56–87% yields (Scheme 17).[21] Reaction scope studies showed that ynamides and full-substituted isoxazoles bearing both electron-rich



Scheme 16 Proposed mechanism for gold-catalyzed formal [5+1]/[5+2] annulation of ynamides **42** with benzo[*d*]isoxazoles **43**.



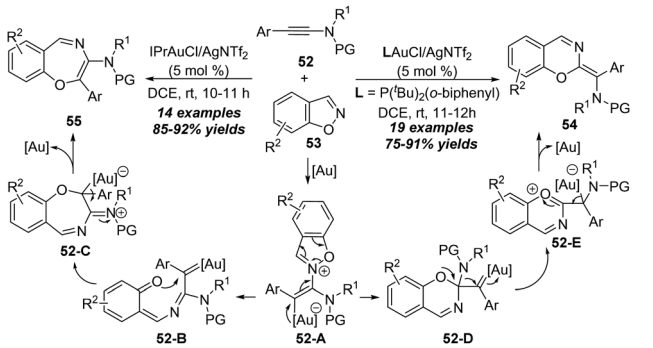
Scheme 17 Platinum-catalyzed formal [5+2] annulation of alkynes with isoxazoles.

and -deficient substituents on the aromatic ring reacted well to produce the desired products in excellent yields. Of note, the reactivity of the platinum-catalyzed protocol was dramatically different from that observed during gold catalysis. The reaction starts with the formation of α-imino platinum carbene **46-A** from platinum-catalyzed nucleophilic addition of isoxazole onto platinum-coordinated ynamide and ring-opening. After O-attack of the platinum-carbene *via* a 1,7-cyclization, the 7-membered intermediate **46-B** forms with the regeneration of the platinum catalyst. Subsequent 6π-electrocyclization and skeleton rearrangement afford the epoxide intermediate **46-D**. Finally, ring-opening of epoxide **46-D** furnishes the desired 1,3-oxazepine **48**.

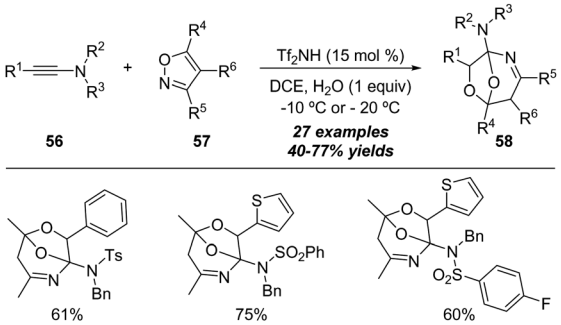
In the same work, a selective platinum-catalyzed formal [4+2] annulation was also achieved when the ynol ethers **49** were used as substrates. As outlined in below, the reaction of ynol ethers **49** with various isoxazoles **50** in the presence of $PtCl_2$ (5 mol%) under CO atmosphere in toluene led to the construction of 2,5-dihydropyridines **51** in generally moderate to excellent yields.

In 2018, Liu group reported gold-catalyzed formal [5+2] and [5+1] annulations between ynamides **52** and 1,2-benzisoxazoles **53** (Scheme 18).[22] A series of 2*H*-benzo[*e*][1,3]oxazines **54** and benzo[*f*][1,4]oxazepines **55** could be selectively synthesized in high yields through the ligand-controlled chemoselectivity. By employing IPrAuCl/$AgNTf_2$ as the catalyst, aryl-substituted ynamides underwent the formal [5+2] annulation *via* a 1,7-cyclization; however P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/$AgNTf_2$ changed the chemoselectivity to a formal [5+1] annulation. Control experiments indicated that a 1,2-sulfonamide shift was involved in the formal [5+1] annulation process.

In 2018, Wan and Hu reported an interesting Brønsted acid-catalyzed formal [5+2+1] annulation of ynamides and isoxazoles with water.[23] As described in Scheme 19, a variety of oxygen-bridged tetrahydro-1,4-oxazepines **58** were isolated in generally



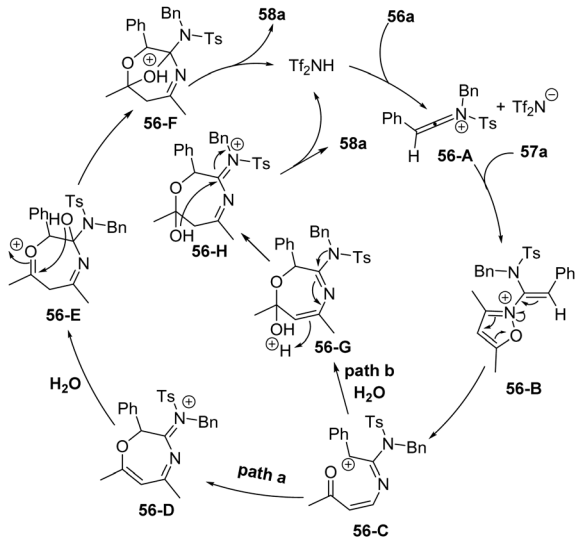
Scheme 18 Gold-catalyzed formal [5+2] and [5+1] annulations between ynamides **52** and 1,2-benzisoxazoles **53**.



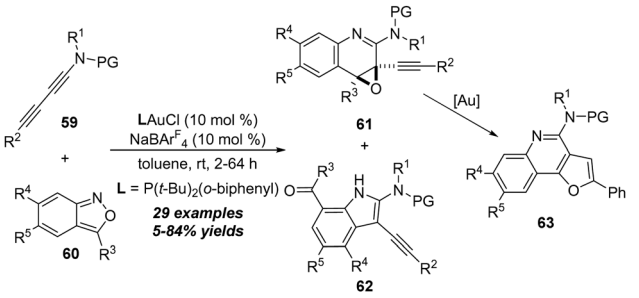
Scheme 19 Brønsted acid-catalyzed formal [5+2+1] cycloaddition of ynamides **56** and isoxazoles **57** with water.

moderate to good yields by employing ynamides **56**, isoxazoles **57** and water using 15 mol% $HNTf_2$ as the catalyst. It is worth noting that this protocol represents the first metal-free reaction of isoxazoles with alkynes.

The proposed mechanism is shown in Scheme 20. First, ynamide **56a** reacts with $HNTf_2$ to give keteniminium



Scheme 20 Proposed mechanism for Brønsted acid-catalyzed formal [5+2+1] cycloaddition of ynamides **56** and isoxazoles **57** with water.



Scheme 21 Gold-catalyzed formal [5+2] annulation of 1,3-diynamides **59** with anthranils **60**.

intermediate **56-A**, which was attacked by isoxazole **57a** to afford intermediate **56-B**. Then carbocation **56-C** is generated from ring-opening, and the carbocation **56-C** may go through two pathways. For path a, a subsequent intramolecular 1,7-cyclization of **56-C** delivers the seven-membered intermediate **56-D**. Ultimately, the addition of H_2O to the iminium **56-D** and subsequent acid-catalyzed ketalization afford the bridged tetrahydro-1,4-oxazepine **58a**. In path b, water may attack the carbonyl group of **56-C** first to assist the intramolecular cyclization, affording the seven-membered intermediate **56-G**. The desired product **58a** forms by the acetal formation step with the regeneration of the catalyst.

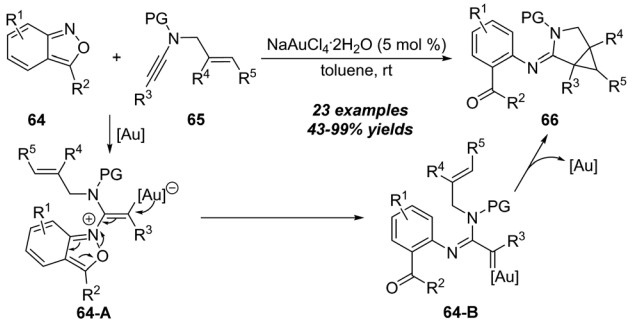
In 2021, Liu and co-workers reported another related gold-catalyzed formal [5+2] annulation of 1,3-diynamides **59** with anthranils **60** for the efficient synthesis of functionalized quiniline oxides **61**.[24] The [3+2] annulation adducts 7-formylindoles **62** were also generated as minor products. Interestingly, the furoquinoline derivatives **63** could be obtained from quiniline oxides **61** through a gold-catalyzed intramolecular cyclization/aromatization sequence (Scheme 21).

2.2. Cyclopropanation

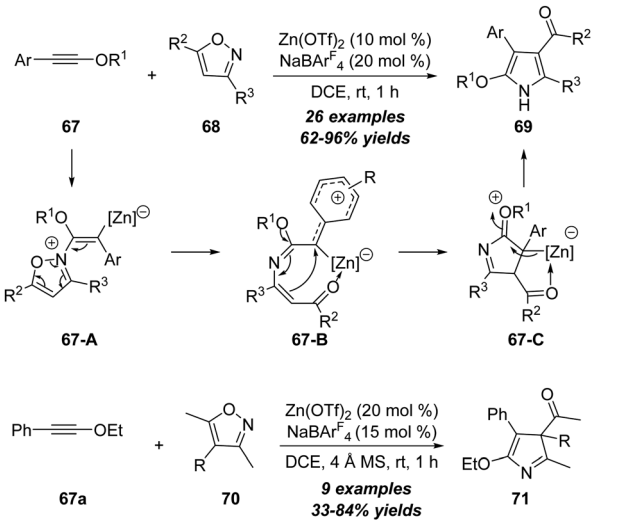
In the amination of alkynes, the key metal carbene intermediates could also undergo cyclopropanation to give cyclopropane-fused heterocycles. In 2019, Hashmi and co-workers demonstrated a gold-catalyzed cyclopropanation between readily available *N*-allylynamides **65** and anthranils **64** (Scheme 22).[25] This protocol features simple conditions, high efficiency, and excellent functional group compatibility. However, the alkene moieties on *N*-allylynamides are limited to di- and trisubstituted alkenes. The mechanism of this intermolecular tandem reaction is postulated to involve the formation of vinyl gold intermediate **64-A**, followed by ring-opening of **64-A**, leading to the formation of α-imino gold carbene **64-B**. Finally, intramolecular cyclopropanation of **64-B** delivers the corresponding 3-azabicyclo[3.1.0]hexane-2-imine **66**.

3. Amination of ynol ethers

In 2018, Ye, Lu and co-workers reported a zinc-catalyzed [3+2] annulation reaction of ynol ethers **67** with 3,5-disubstituted isoxazoles **68** under mild reaction conditions, leading to the



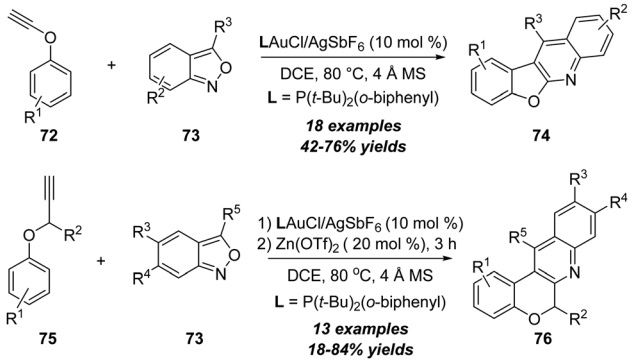
Scheme 22 Gold-catalyzed cyclopropanation between *N*-allylynamides **65** and anthranils **64**.



Scheme 23 Zinc-catalyzed [3+2] annulation reaction of ynol ethers **67** with 3,5-disubstituted isoxazoles **68** or **70**.

atom-economic synthesis of 2-alkoxyl 1*H*-pyrroles **69** in 62–96% yields (Scheme 23).[26] Interestingly, the scope of the above zinc-catalyzed transformation could be extended to the reaction of ynol ether **67a** with trisubstituted isoxazoles **70**, and 3*H*-pyrroles **71** were selectively formed in moderate to excellent yields under similar reaction conditions. Notably, this protocol represents the first example of non-noble metal-catalyzed reaction of ynol ethers with isoxazoles. The reaction starts with the nucleophilic attack of isoxazole **68** on the zinc-activated ynol ether to afford the vinyl zinc intermediate **67-A**, which is further transferred into the carbocation intermediate **67-B** upon the cleavage of the N–O bond. Then, a 1,5-cyclization takes place to form intermediate **67-C**, which undergoes deprotonation and 1,3-H shift to give the final product **69**. Of note, the zinc-catalyzed reaction showed significant difference with platinum catalysis.[21] In addition, theoretical calculations provided further evidence for the proposed reaction mechanism, especially for the distinct selectivity.

In 2019, Liu's group further realized a gold-catalyzed annulation of ynol ethers **72** with anthranils **73**, leading to the

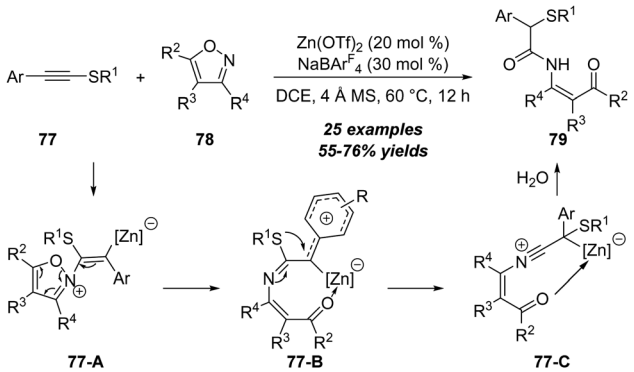


Scheme 24 Gold-catalyzed annulation of ynol ethers **72** or **75** with anthranils **73**.

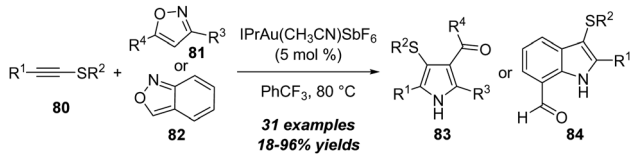
formation of benzofuro[2,3-*b*]quinolines and 6*H*-chromeno[3,4-*b*]quinolines **74** efficiently (Scheme 24).[27] This new synthetic method employed readily available starting materials through a one-pot reaction for the synthesis of biologically significant benzofuro[2,3-*b*]quinolines. Mechanistically, the formation of the α-imino gold carbene intermediate and intramolecular C–H insertion are the key for this reaction. In the same work, the authors also assessed the scope of a one-pot transformation for the direct synthesis of 6*H*-chromeno[3,4-*b*]quinolines from a series of propargyl ethers **75** and anthranils **73**. In the presence of 10 mol% of gold(I) and 20 mol% of zinc(II) as catalysts, the annulation delivered the desired 6*H*-chromeno[3,4-*b*]quinolines **76** in 18–84% yields.

4. Amination of thioynol ethers

Different with ynamides and ynol ethers, the amination reaction of thioynol ethers demonstrated unique reactivities due to the special properties of sulfur atoms. In 2018, Ye, Lu and co-workers reported a novel zinc-catalyzed reaction of thioynol ethers **77** with isoxazoles **78**, leading to the preparation of β-keto enamides **79** in moderate yields, which could be readily converted to diverse heterocycles (Scheme 25).[28] The reaction proceeded through an unprecedented 1,2-sulfur migration based on thioynol ethers. Importantly, this protocol not only represents the first example of the non-noble metal-catalyzed



Scheme 25 Zinc-catalyzed reaction of thioynol ethers **77** with isoxazoles **78**.



Scheme 26 Gold-catalyzed formal [3+2] annulation of alkynyl thioethers **80** with isoxazoles **81** or **82**.

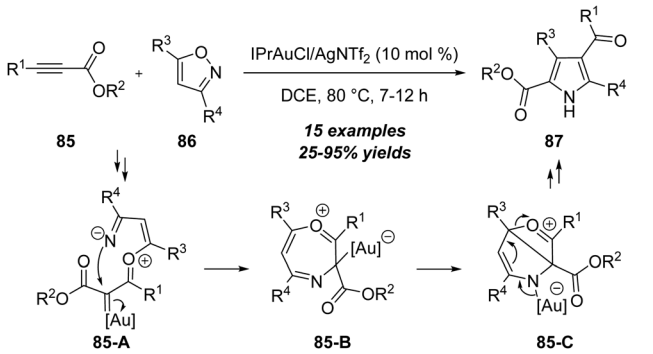
reaction of isoxazoles with alkynes, but also represents the first non-noble metal-catalyzed alkyne amination by an N–X bond nucleophile (X = N or O). The reaction begins with the nucleophilic attack of isoxazole **78** onto the zinc-coordinated thioynol ether to provide a vinyl zinc intermediate **77-A**, which can isomerize into the phenyl-stabilized carbocation intermediate **77-B** upon cleavage of the isoxazole N–O bond. Followed by 1,2-sulfur migration to produce migrated intermediate **77-C**. Through DFT calculations, it is found that 1,2-sulfur migration is kinetically favorable, which eventually furnishes β-keto enamide **79** *via* H_2O addition, proton transfer and proton demetallization.

By employing the amination of thioynol ethers, Davies group extended this strategy to the synthesis of sulfenyl pyrroles **83** and indoles **84**. In the presence of 5 mol% of gold(I) as the catalyst, the [3+2] annulation of alkynyl thioethers **80** with isoxazoles **81** or **82** led to the convergent and efficient synthesis of the corresponding sulfenylated pyrroles **83** or indoles **84** in moderate to excellent yields (Scheme 26).[29] This reaction showed broad structural and functional group tolerance. Initial investigations into the annulation with trisubstituted isoxazoles also revealed the unique reactivity for alkynyl thioethers. Different from typical α-addition of alkynyl thioethers, the observed results and isotopic labelling studies matched with the β-selective addition pathway.

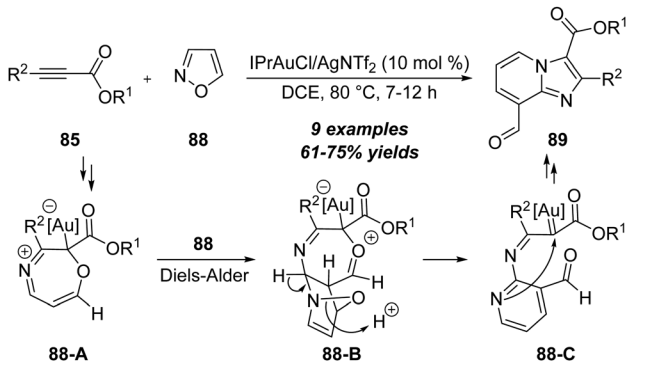
5. Amination of electron-deficient alkynes

Apart from the above electron-rich alkynes, electron-deficient alkynes were also suitable substrates to react with isoxazoles and led to the synthesis of heterocycles. In 2017, Liu group first disclosed a gold-catalyzed [4+1] annulation between propiolate derivatives **85** and isoxazoles **86**, leading to facile synthesis of 2,4-dicarbonylpyrroles **87** in generally moderate to excellent yields (Scheme 27).[30] Both aromatic and alkyl substituted propiolates **85** were suitable substrates to produce the target pyrrole products. The reaction mechanism involves the formation of α-oxo gold carbene intermediate **85-A**, ring closure (**85-B**), intramolecular cyclization and ring-opening of **85-C**.

In the same report, the authors found that the unsubstituted isoxazoles **88** could proceed through the N-attack onto propiolates **85** in the presence of 10 mol% IPrAuCl/$AgNTf_2$, and led to the formation of 3,8-dicarbonylimidazo[1,2-*a*]pyridines **89** in 61–75% yields *via* a formal [2+2+1]/[4+2] annulation (Scheme 28).[30] As shown below, a similar formal [5+2]



Scheme 27 Gold-catalyzed [4+1] annulation between propiolate derivatives **85** and isoxazoles **86**.

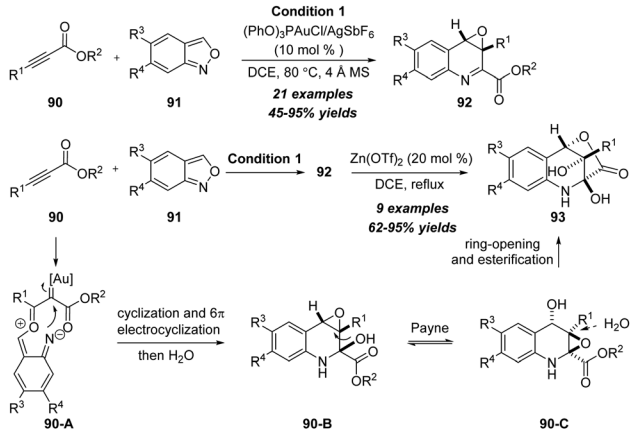


Scheme 28 Gold-catalyzed formal [2+2+1]/[4+2] annulation.

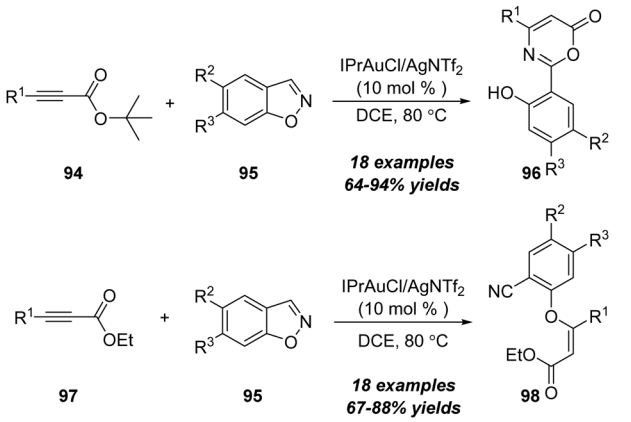
annulation of propiolate **85** with isoxazole **88** first occurs to furnish the 7-membered intermediate **88-A** through a N-attack. Further Diels–Alder reaction with another isoxazole **88** affords the bridged intermediate **88-B**. An aromatization of intermediate **88-B** forms α-imino gold carbene **88-C** by the loss of water, which is attacked by the pyridine moiety and isomerized to afford the desired imidazo[1,2-*a*]pyridine **89**.

In the same year, Liu and co-workers extended the reaction to readily available anthranil substrates and developed a gold-catalyzed formal [4+2] annulation/cyclization cascade of propiolate derivatives **90** with anthranils **91**, delivering quinoline oxides **92** in moderate to excellent yields with excellent diastereoselectivities (Scheme 29).[31] Significantly, a novel relay catalysis using gold and zinc catalysts was also achieved to produce bridged oxygenated tetrahydroquinoline derivatives **93** in high yields with good to excellent diastereoselectivities. Mechanistically, the reaction of alkyne with anthranil first gives α-oxo gold carbene **90-A**, followed by 1,7-cyclization, 6π electrocyclization, water attack and Payne rearrangement to produce expoxide **90-C**. Finally, product **93** forms *via* ring-opening and lactonization.

Later in 2018, the same group demonstrated a gold-catalyzed formal [4+2] annulation between propiolates and 1,2-benzisoxazoles (Scheme 30).[32] When using *tert*-butyl propiolates **94** as substrates, this reaction preferably underwent formal [4+2] annulation, providing 6*H*-1,3-oxazin-6-one



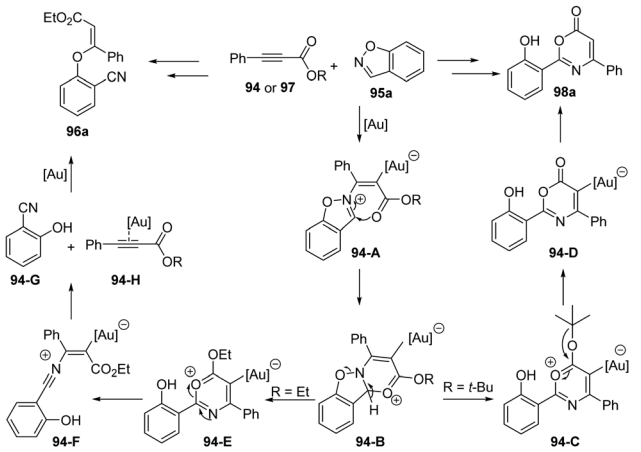
Scheme 29 Gold-catalyzed formal [4+2] annulation/cyclization cascade of propiolate derivatives **90** with anthranils **91**.



Scheme 30 Gold-catalyzed formal [4+2] annulation between propiolates **94** or **97** and 1,2-benzisoxazoles **95**.

derivatives **96** in generally high yields. Alternatively, a direct Michael-type addition occurred when using ethyl propiolates as substrates. In addition, gold-catalyzed Michael-type reactions of ethyl propiolates **97** with 1,2-benzisoxazoles **95** led to assembly of ethyl phenoxyacrylates **98** in 69–88% yields.

The proposed reaction mechanism of above gold-catalyzed formal [4+2] annulation is depicted in Scheme 31. First, nucleophilic attack of 1,2-benzisoxazole **95a** onto gold-activated aryloxy alkyne **94** or **97** results in vinyl gold **94-A**, which can be trapped by the ester group to form tricyclic intermediate **94-B**. After the fragment of N–O bond of **94-B**, there are two pathways depending on the substituents. For the ethyl propiolate **97**, the **94-E** underwent ring-opening to produce the nitrium intermediate **94-F**. Then the dissociation of nitrium intermediate **94-F** forms gold-coordinated alkyne species **94-H** and 2-hydroxybenzonitrile **94-G**, which further react to furnish the observed 3-phenoxyacrylate **96a**. For the *tert*-butyl propiolate **94**, a loss of the *tert*-butyl cation moiety in **93-C** generates stable 6*H*-1,3-oxazin-6-one derivative. Subsequent deauration takes place to afford the desired 6*H*-1,3-oxazin-6-one **98a**.

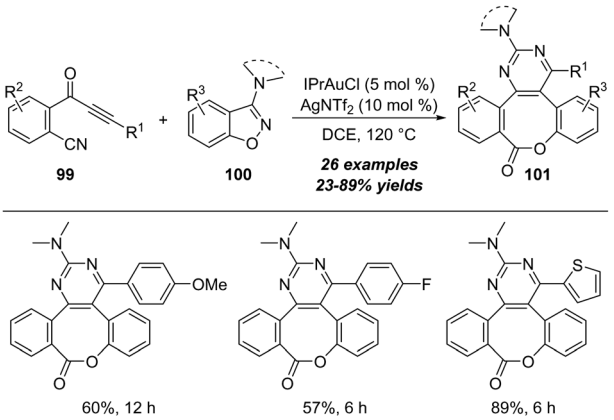


Scheme 31 Plausible mechanism for gold-catalyzed formal [4+2] annulation between propiolates **94** and 1,2-benzisoxazoles **95**.

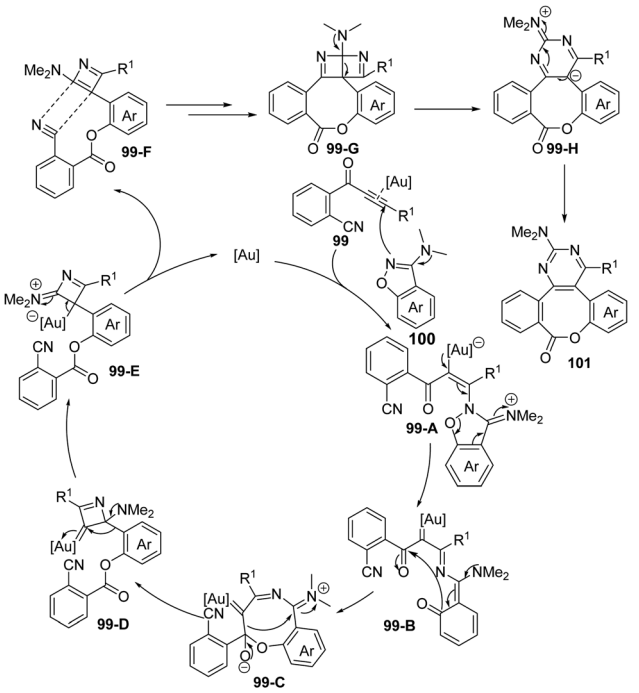
Another interesting protocol on gold-catalyzed cyclization/cascade skeletal rearrangement of *o*-cyanophenylalkynones **99** with 3-amino-benzo[*d*]-isoxazoles **100** was described by Liu and co-workers in 2021.[33] As outlined in Scheme 32, this protocol provides an efficient approach for the construction of medium-sized benzolactones **101** in moderate to excellent yields.

In the proposed reaction mechanism (Scheme 33), an initial attack of benzo[*d*]isoxazole **100** onto gold-activated ynone affords vinyl gold intermediate **99-A**, which undergoes ring-opening to yield the α-imino gold carbene intermediate **99-B**. Then intramolecular cyclization of **99-B** provides the cyclized intermediate **99-C**. Subsequently, carbene transfer of **99-C** *via* C–C bond cleavage followed by 1,2-aryl migration gives the 4-membered ring intermediate **99-E**, which can be converted into **99-F** after the elimination of the gold catalyst. Finally, a formal [2+2] cycloaddition of **99-F** occurs to deliver fused ring intermediate **99-G**, and the desired product **101** forms through ring expansion.

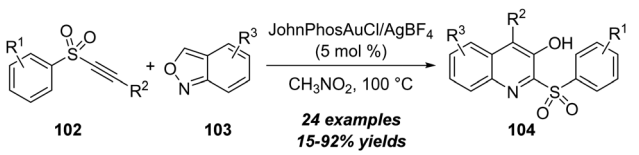
Besides ynones, alkynyl sulfones were also employed as appropriate alkynes in the amination with isoxazoles. In 2022, Hashmi and co-workers reported a gold-catalyzed formal



Scheme 32 Gold-catalyzed cyclization/cascade skeletal rearrangement of *o*-cyanophenylalkynones **99** with 3-amino-benzo[*d*]-isoxazoles **100**.



Scheme 33 Proposed mechanism for gold-catalyzed cyclization/cascade skeletal rearrangement of *o*-cyanophenylalkynones **99** with 3-amino-benzo[*d*]-isoxazoles **100**.

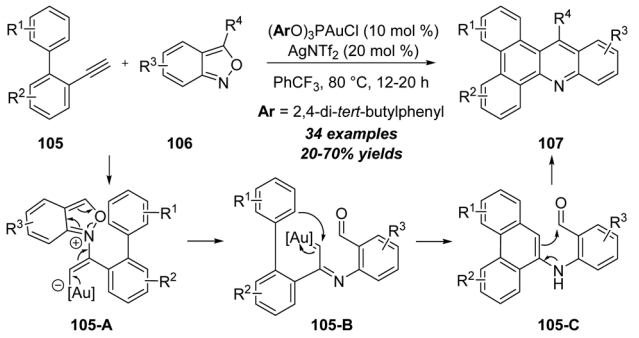


Scheme 34 Gold-catalyzed formal [4+2] annulation of alkynyl sulfones **102** with anthranils **103**.

[4+2] annulation of alkynyl sulfones **102** with anthranils **103**, for the assembly of diverse 3-hydroxyquinolines **104** in moderate to excellent yields (Scheme 34).[34]

6. Amination of unpolarized alkynes

Apart from the above-mentioned polarized alkynes, some specific unpolarized alkynes could also react with isoxazole derivatives in the presence of metal catalysts. In 2018, Hashmi group made a seminal contribution in gold-catalyzed regiospecific C–H annulation of unpolarized alkynes with anthranils (Scheme 35).[35] The gold-catalyzed reaction of *o*-ethynylbiaryls **105** with anthranils **106** produced diverse N-doped polycyclic aromatic hydrocarbons (PAHs) **107** in 20–70% yields. First, the gold-coordinated alkyne is regioselectively attacked by anthranil **106** to produce the α-imino gold carbene intermediate **105-B**, which can be further trapped by the phenyl group through C–H functionalization and deliver the six-membered intermediate **105-C**. Subsequent enamine–aldehyde addition/elimination of **105-C** affords the final product **107**.

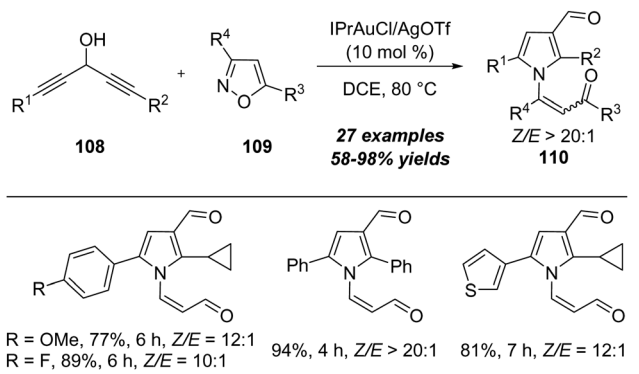


Scheme 35 Gold-catalyzed regiospecific C–H annulation of unpolarized alkynes **105** with anthranils **106**.

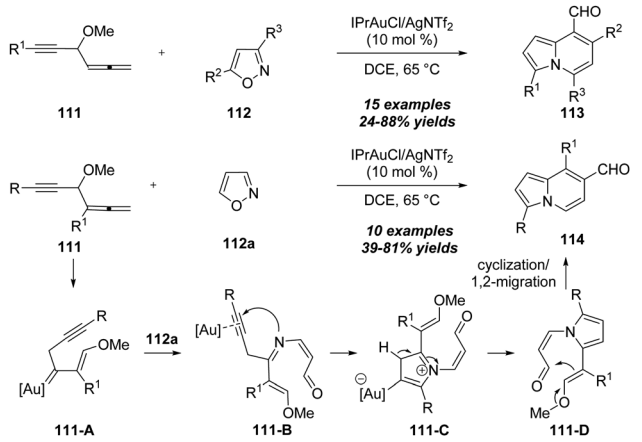
In 2018, a gold-catalyzed [4+1] annulation of 1,4-diyn-3-ols with isoxazoles was disclosed by Liu's group.[36] As shown in Scheme 36, in the presence of 10 mol% of IPrAuCl/AgOTf, the reaction of 1,4-diyn-3-ols **108** with isoxazoles **109** proceeded smoothly, allowing the efficient formation of multisubstituted pyrroles **110** in mostly good to excellent yields. Interestingly, the gold carbene-enabled 1,2-alkyne shift is the key for the transformation.

In 2019, the same group described an elegant protocol for the gold-catalyzed bicyclic annulations of 4-methoxy-1,2-dienyl-5-ynes **111** with isoxazoles **112**.[37] As shown in Scheme 37, it was found that the treatment of 4-methoxy-1,2-dienyl-5-ynes **111** with disubstituted isoxazoles **112** using IPrAuCl/$AgNTf_2$ as the catalyst could afford various 8-formylindolizines **113** in moderate to excellent yields under mild reaction conditions. In addition, the use of non-substituted isoxazole **112a** under the standard conditions led to the formation of the 7-formylindolizines **114**. The reaction begins with the nucleophilic attack of alkyne moiety onto gold-activated allene to provide gold carbene intermediate **111-A**, followed by the attack of isoxazole **112a** to produce alkynyl intermediate **111-B** through a ring-opening of the isoxazole. The subsequent N-attack and protodeauration take place to generate pyrrole intermediate **111-C**, which undergoes a carbonyl-ene reaction and elimination/1,2-acyl migration to deliver the final product **114**.

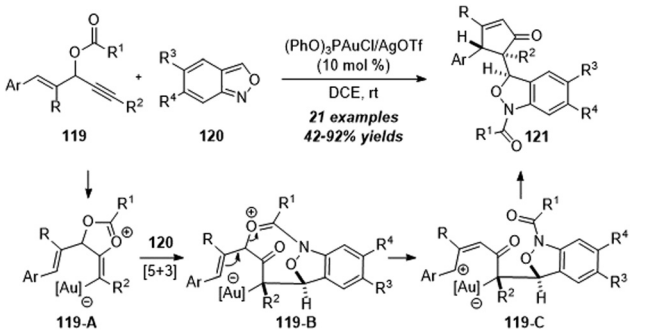
By using a similar strategy, in 2019, Liu and co-workers disclosed the efficient construction of tetrahydro-1*H*-benzo[*b*]-azepine derivatives from gold-catalyzed [4+3] annulation of



Scheme 36 Gold-catalyzed [4+1] annulation between 1,4-diyn-3-ols **108** and isoxazoles **109**.



Scheme 37 Gold-catalyzed bicyclic annulations of 4-methoxy-1,2-dienyl-5-ynes **111** with isoxazoles **112**.



Scheme 39 Gold-catalyzed 1,3-carbofunctionalization of vinyl propargyl esters **119** with anthranils **120**.

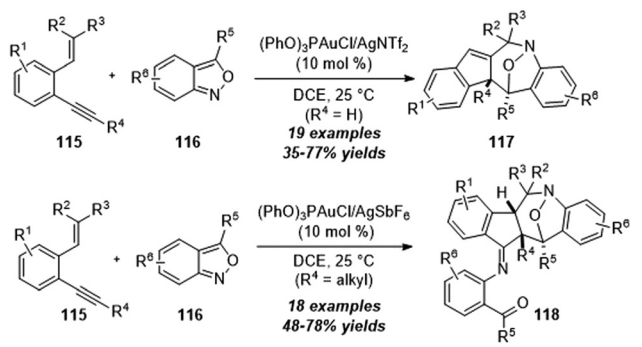
2-alkenyl-1-alkynylbenzenes **115** with anthranils **116**.[38] As shown in Scheme 38, terminal alkynes (R^4 = H) reacted well to furnish benzo[*b*]azepine derivatives **117** *via* a novel skeletal rearrangement, while internal 1,5-enynes (R^4 = alkyl) afforded products **118** in moderate to good yields without the rearrangement process.

In the same year, a gold-catalyzed 1,3-carbofunctionalization of vinyl propargyl esters **119** with anthranils **120** was achieved by Liu and co-workers, leading to the convenient synthesis of 1,3-dihydrobenzo[*c*]-isoxazoles **121** in 42–92% yields with excellent diastereoselectivities (Scheme 39).[39] The proposed mechanism of gold-catalyzed 1,3-carbofunctionalization of vinyl propargyl esters **119** with anthranils **120** is shown below. First, a gold-assisted intramolecular cyclization of gold-activated alkyne takes place to afford vinyl gold intermediate **119-A**. A formal [5+3] annulation of intermediate **119-A** with anthranil **120** furnishes the 8-membered intermediate **119-B**. Further ring-opening of the oxonium moiety yields benzylic cation intermediate **119-C**. Finally, the desired product **121** is obtained through a further intramolecular cyclization.

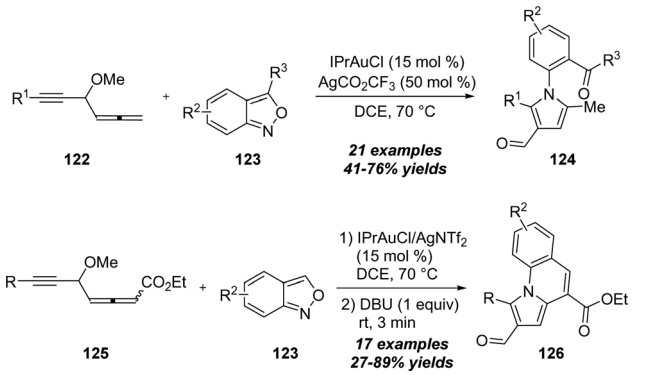
A related gold-catalyzed [4+1] annulation of 4-methoxy-1,2-dienyl-5-ynes **122** with anthranils **123** was also explored by Liu and co-workers in 2019, enabling the preparation of pyrroles **124** (Scheme 40).[40] For the allenyl ester substrates **125**, the formed pyrroles could further undergo intramolecular aldol reaction by the treatment of DBU, and produced diverse pyrrolo[1,2-*a*]quinoline derivatives **126**.

In 2020, the same group reported a unique gold-catalyzed aminoaromatization of 1,5-diynes with anthranils.[41] As described in Scheme 41, the aminoaromatization of 1,5-diynes **127** with anthranils **128** in the presence of 10 mol% (*o*-biphenyl)di-*tert*-butylphosphine gold chloride and $AgSbF_6$ as the catalyst afforded the corresponding 1-amino-2-napthaldehyde derivatives **129** in generally moderate to good yields. Based on the control experiments, a proposed mechanism is demonstrated. First, α-imino gold carbene intermediate **127-B** is generated from the gold-catalyzed addition of 1,5-diyne **127** with anthranil **128** through vinyl gold intermediate **127-A**. Subsequent 1,2-H shift of gold carbene affords α,β-unsaturated 3-hydroxy-enimine **127-C**. Finally, gold-catalyzed intramolecular cyclization, protodeauration and aromatization take place to produce the desired 1-amino-2-napthaldehyde **129**.

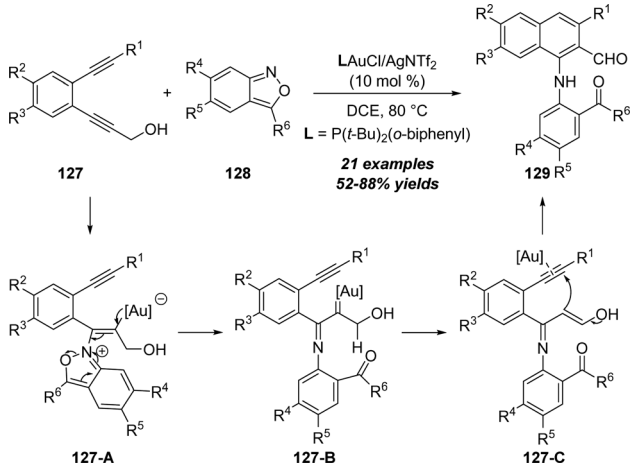
In 2017, Liang and co-workers disclosed a copper-catalyzed [4+2] annulation between propargylic alcohols **130** with benzo[*d*]isoxazoles **131** for the preparation of functionalized quinoline derivatives **132** in good yields under mild conditions. (Scheme 42).[42] Notably, this protocol represents a rare example of non-noble-metal catalyzed reaction of unpolarized alkynes with isoxazole derivatives.



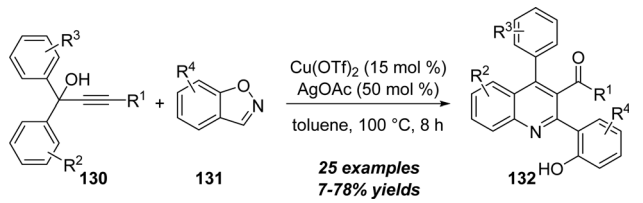
Scheme 38 Gold-catalyzed [4+3] annulations of 2-alkenyl-1-alkynylbenzenes **115** with anthranils **116**.



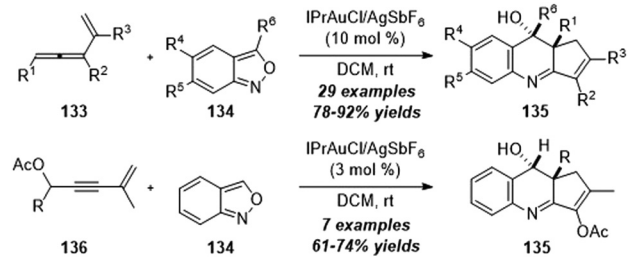
Scheme 40 Gold-catalyzed [4+1] annulation of 4-methoxy-1,2-dienyl-5-ynes **122** or **125** with anthranils **123**.



Scheme 41 Gold-catalyzed aminoaromatization of 1,5-diynes **127** with anthranils **128**.



Scheme 42 Copper-catalyzed [4+2] annulation of propargylic alcohols **130** and benzo[*d*]isoxazoles **131**.

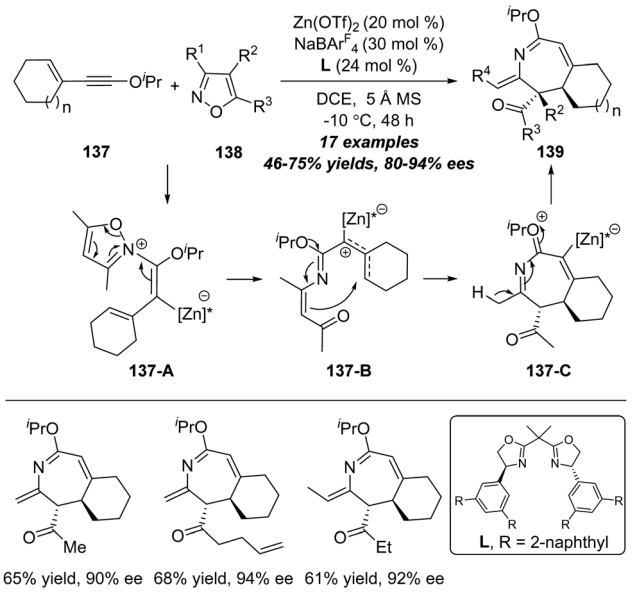


Scheme 43 Gold-catalyzed formal [4+2] annulation of vinylallenes **133** or enyne acetates **136** with anthranils **134**.

By changing the structures of alkynes, Liu group also reported a gold-catalyzed formal [4+2] annulation of vinylallenes **133** or enyne acetates **136** with anthranils **134**, providing an efficient method for the synthesis of various valuable 3,4-dihydroquinoline derivatives **135** (Scheme 43).[43] Of note, this protocol involves the α-alkyl gold carbene intermediates and presents the alkyl C–H reactivity of α-alkyl gold carbenes with an external nucleophile.

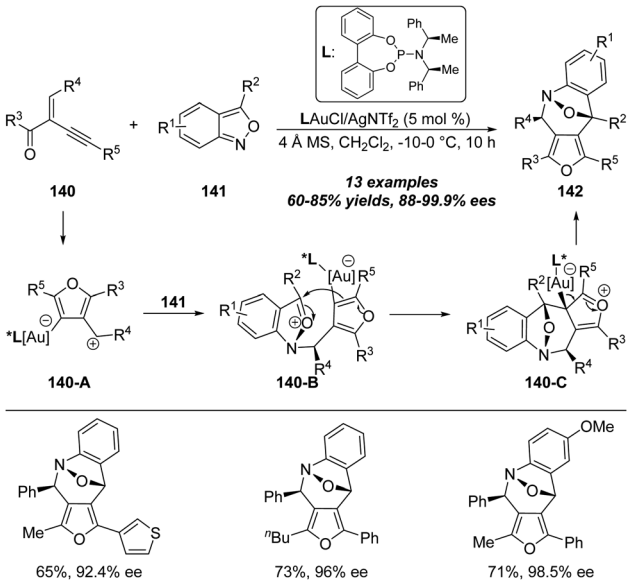
7. Asymmetric amination of alkynes

Although significant advances have been achieved in the amination reaction of alkynes with isoxazoles, the catalytic asymmetric amination was not realized until in 2020 attribute to the impediment in the asymmetric alkyne functionalization.[44] Ye and co-workers realized the first example of catalytic asymmetric reaction of isoxazoles with alkynes.[45] As shown in Scheme 44, the functionalized chiral 2*H*-azepines **139** could be achieved in good yields with moderate to excellent enantioselectivities through a zinc-catalyzed enantioselective formal [4+3] annulation of enynol ethers **137** with isoxazoles **138**. It is worth noting that this protocol not only represents the first asymmetric heptatrienyl cation type 6π electrocyclization, but also constitutes the first asymmetric reaction of ynol ethers. Based on experimental studies and DFT calculations. The plausible reaction mechanism is proposed based on the model substrates. The reaction commences with the nucleophilic attack of isoxazole **138** onto the zinc-activated ynol ether to afford vinyl zinc intermediate **137-A**. Then, the N–O bond cleavage of isoxazole produces zinc-stabilized allyl cation species **137-B**, which is transformed into 7-membered intermediate **137-C** through a heptatrienyl cation type 6π electrocyclization. Notably, the 6π electrocyclization step is the enantiodetermining step. At Last, the deprotonation of intermediate **137-C** delivers the desired chiral 2*H*-azepine **139**.



Scheme 44 Zinc-catalyzed enantioselective formal [4+3] annulation of enynol ethers **137** with isoxazoles **138**.

In 2019, Liu and co-workers reported a gold-catalyzed asymmetric formal [4+3] annulation of enynones **140** with anthranils **141** by employing the chiral phosphine ligand, producing enantioenriched bridged epoxybenzoazepines **142** in moderate to excellent yields with 88–99% ees through an enantioselective dearomatization process (Scheme 45).[46] The proposed mechanism for this gold-catalyzed asymmetric formal [4+3] annulation is shown below. Initially, the gold catalyzed cyclization and tautomerization of enynone **140** occur to provide the 3-furyl methyl cation intermediate **140-A** which can serve as a 1,3-all carbon dipole. Then, nucleophilic addition of anthranil **141**



Scheme 45 Gold-catalyzed asymmetric formal [4+3] annulation of enynones **140** with anthranils **141**.

onto 1,3-dipole **140-A** affords oxonium ion intermediate **140-B**, which could be the enantio-determining step. Moreover, **140-B** undergoes further intramolecular cyclization to deliver the bridged intermediate **140-C**. Finally, the desired chiral bridged epoxybenzoazepine **142** is obtained from aromatization with the regeneration of the gold catalyst.

8. Conclusion

In summary, isoxazoles and their derivatives, as the N,O-bifunctional reagents of alkynes, have attracted more and more attention during the past decades in the development of alkyne amination reactions, providing an efficient and divergent way for the synthesis of a wide range of functionalized heterocycles, especially for valuable N-containing heterocycles. Divergent metal carbene-mediated cascade aminations, including formal annulation, C–H functionalization, cyclopropanation, electrocyclization, carbene metathesis and other asymmetric aminations, could be achieved by exploiting the flexible properties of metal carbene intermediates.

Despite these achievements, there are still considerable challenges that should arouse more research in the near future. Firstly, the developed amination reactions of alkynes with isoxazoles are mostly limited to transition-metal catalysis, especially for noble metal catalysts. Therefore, non-noble metal catalyzed and metal-free protocols need to be further developed for the goal of green synthesis. Secondly, most amination reactions require special alkyne substrates, such as electron-rich alkynes (such as ynamides, ynol ethers and thioynol ethers), electron-deficient alkynes, and conjugated alkynes. Thus, catalytic systems with higher efficiency and selectivity are still in great demand to uncover the amination of simple alkynes. Thirdly, the catalytic asymmetric amination reaction of isoxazoles with alkynes has been rarely demonstrated. Thereby, more types of asymmetric catalytic systems are needed. Finally, further synthetic applications in the synthesis of natural products, bioactive molecules and pharmaceuticals by using this strategy are highly desirable. We anticipate that the amination reactions of alkynes with isoxazoles summarized here will attract more research interest into this field. It is our expectation that the amination of alkynes could be developed as an efficient tool for the assembly of various functional molecules in organic synthesis and other related areas.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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