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Reactivity of ynamides in catalytic intermolecular annulations

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Ynamides are unique alkynes with a carbon–carbon triple bond directly attached to the nitrogen atom bearing an electron-withdrawing group. The alkyne is strongly polarized by the electron-donating nitrogen atom, but its high reactivity can be finely tempered by the electron-withdrawing group. Accordingly, ynamides are endowed with both nucleophilic and electrophilic properties and their chemistry has been an active research field. The catalytic intermolecular annulations of ynamides, featuring divergent assembly of structurally important amino-heterocycles in a regioselective manner, have gained much attention over the past decade. This review aims to provide a comprehensive summary of the advances achieved in this area involving transition metal and acid catalysis. Moreover, the intermolecular annulations of ynamide analogs including ynol ethers and thioalkynes are also discussed, which can provide insights into the reactivity difference caused by the heteroatoms.

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1. Introduction

Amino-heterocycles are present in a broad range of active pharmaceutical ingredients and natural products. For example, among the top 200 best-selling pharmaceuticals in 2019, there are about 20 drugs containing the amino-pyrimidine motif.[1] In addition, amino-pyridine can also be found in top selling drugs such as ibrance, pradaxa, orkambi, and lixiana. Natural alkaloids nocarimidazoles[2] and rigidins[3] possess amino-imidazole and -pyrrole cores, respectively. In this context, developing efficient protocols to construct amino-heterocycles is of great significance. Catalytic intermolecular annulation, featuring high atom- and step-economy, is arguably the simplest and most straightforward strategy.

Ynamides are unique alkynes with a carbon–carbon triple bond directly attached to the nitrogen atom bearing an electron-withdrawing group (EWG). The alkyne is strongly polarized by

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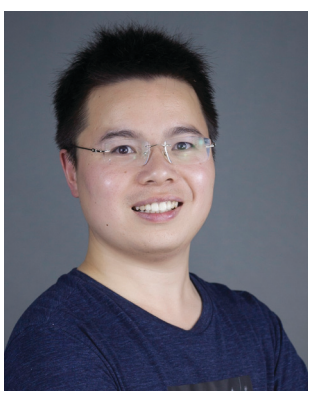


Yan-Cheng Hu

Yan-Cheng Hu was born in Jiangsu Province, China, in 1989. He obtained his BS degree from Nanjing Normal University in 2010 and PhD degree from Dalian Institute of Chemical Physics (DICP) in 2015, under the supervision of Prof. Boshun Wan. He did his postdoctoral research with Prof. Tao Zhang at the same institute from 2015 to 2018. Later, he worked in the group of Prof. Qing-An Chen, where he is currently an associate professor. His research focuses on transition-metal catalyzed transformations of alkynes and alkenes, as well as their applications in the total synthesis of natural products.

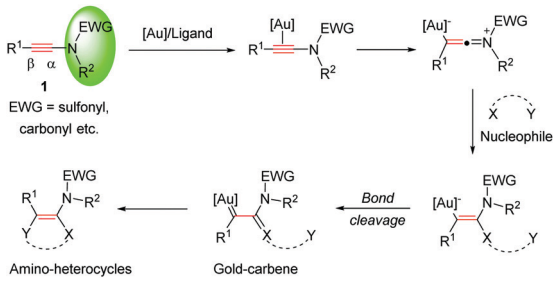
Yingying Zhao

Yingying Zhao was born in Hebei Province, China, in 1990. She received her BS degree from Jiangsu University in 2013 and PhD degree from Dalian Institute of Chemical Physics (DICP) in 2018, under the guidance of Prof. Boshun Wan. Then she began her career at Liaoning Normal University, where she works on acid-catalyzed annulations of ynamides and their applications in the synthesis of biologically relevant molecules.

the electron-donating nitrogen atom, but its high reactivity can be finely balanced by the electron-withdrawing group. As a result, ynamides are endowed with an ambivalent nature, that is, both electrophilic and nucleophilic properties. Since Hsung's seminal work on their preparation was reported in 2003,[4] there has been growing interest in ynamide chemistry. In 2010, two excellent reviews were published to illustrate the discovery and development of ynamide chemistry.[5,6] In recent years, with the deep understanding of the fundamental principles, ynamides have emerged as versatile building blocks in annulation reactions. The studies on the intramolecular cyclizations of ynamides have been carefully reviewed.[7–12] On the other hand, catalytic intermolecular annulations of ynamides, which enable rapid assembly of diverse amino-heterocycles in a regioselective manner, have also gained considerable attention, and the number of publications in this area has increased dramatically. Accordingly, there is a need to give a comprehensive summary on this topic. This review mainly focuses on the advances achieved over the past decade and is organized by the catalytic systems. Nevertheless, to facilitate a better understanding of the progress, some representative studies before 2010 are also discussed. Furthermore, the intermolecular annulations of ynamide analogs including ynol ethers and thioalkynes are covered as well, which can provide insights into the reactivity difference caused by the heteroatoms.

2. Gold catalysis

Gold catalysts, owing to their efficiency in the activation of the triple bond, have been extensively used to facilitate the annulations of ynamides with various unsaturated nucleophiles. On the basis of the reorganization mode of the chemical bonds in nucleophiles, the processes can be classified into six types: N–O bond cleavage, N–N bond cleavage, N–S bond cleavage, C–heteroatom bond cleavage, C–C bond cleavage, and no bond cleavage. In most cases, the bond cleavage of nucleophiles results in the formation of α-oxo/imino gold-carbene, which further reacts with other sites to yield amino-heterocycles (Scheme 1). Thus far, a series of valuable heterocycles such as amino-furans, -pyrroles, -oxazoles, -imidazoles, -pyrimidines, -pyridines, -quinolines, -indoles *etc.* have been synthesized by this strategy.



Scheme 1 A general mechanism involving bond cleavage of nucleophiles in gold catalysis.

2.1 N–O bond cleavage

Prompted by Zhang's pioneering work on the chemistry of α-oxo gold-carbene,[13,14] Liu *et al.* discovered that gold complex JohnphosAuSbF$_6$ [Johnphos = P(^{t}Bu)$_2$(*o*-biphenyl)] could catalyze the annulation of enynamides **2** with quinoline *N*-oxide, leading to amino-furans **4** in good yields (Scheme 2).[15] The mechanism includes the generation of reactive α-oxo gold-carbene species **Int-3** by releasing quinoline and a subsequent oxa-Nazarov cyclization step.

In 2015, Ye's group developed an elegant gold-catalyzed [3+2] annulation of ynamides with isoxazoles for the synthesis of 2-aminopyrroles (Scheme 3).[16] Ynamide is initially activated by Au(I) to form keteniminium ion **Int-5**, which then reacts with isoxazole to generate α-imino gold-carbene **Int-7** *via* cleavage of the N–O bond. A subsequent ring-closure yields five-membered ring **Int-8**. When using 3,5-dimethyl isoxazole as a substrate, 4-acetyl aminopyrrole **7** is obtained *via* an eventual aromatization step, while, in the case of fully-substituted isoxazole, a deacylative aromatization of **Int-8** produces aminopyrrole **8**.

Boshun Wan

Boshun Wan is a full professor at Dalian Institute of Chemical Physics (DICP). His research interests include asymmetric catalysis, catalytic heterocycle synthesis, and energetic material synthesis. He received his BS degree from Nanjing Normal University in 1985 and PhD degree from DICP in 1998. Then he joined DICP as a group leader. He has been a visiting professor at Northwestern University.

Qing-An Chen

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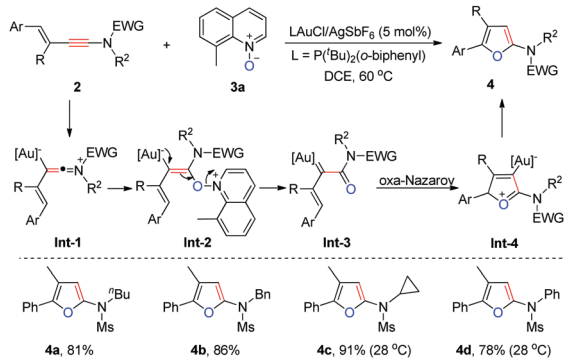
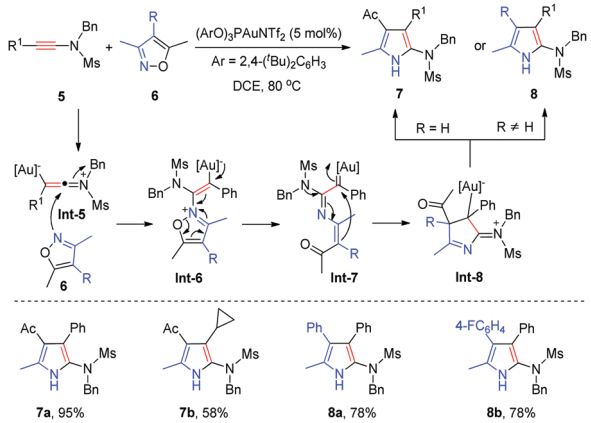


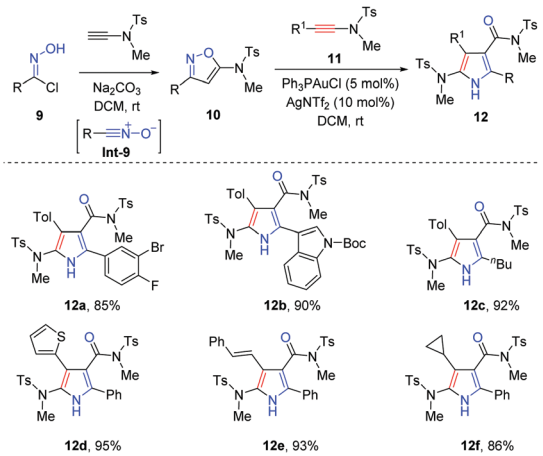
Scheme 2 Gold-catalyzed [4+1] annulation of enynamides with quinoline *N*-oxide.



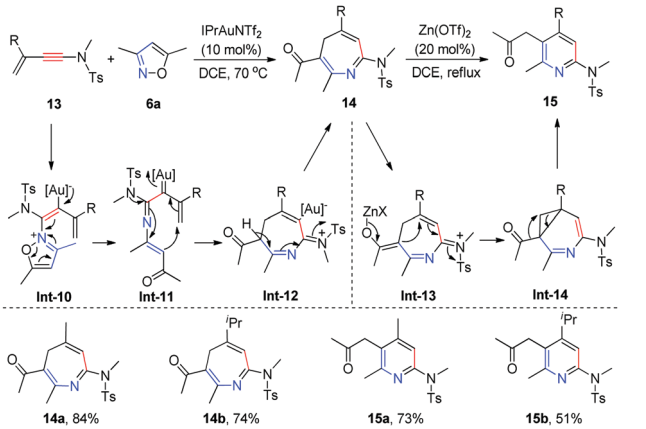
Scheme 3 Gold-catalyzed [3+2] annulation of ynamides with isoxazoles.

Recently, Cui and co-workers developed an annulation of nitrile oxides with terminal ynamides for the synthesis of isoxazoles **10**. By adopting Ye's strategy, **10** could also undergo [3+2] annulation with internal ynamides to generate aminopyrroles **12** in the presence of PPh_3AuCl and $AgNTf_2$ (Scheme 4).[17]

Liu's group disclosed that enynamides and isoxazoles could undergo a [4+3] annulation to furnish amino-azepines **14** in the presence of $IPrAuNTf_2$ (Scheme 5).[18] The success of this



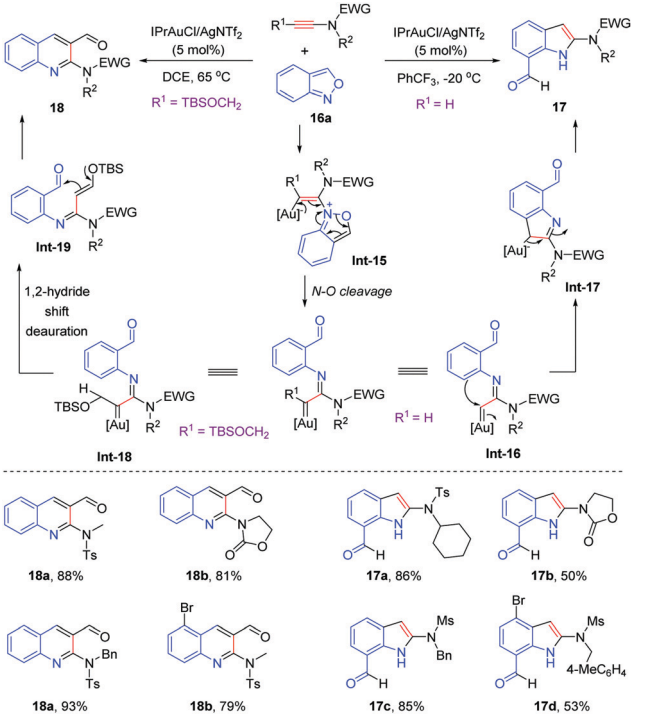
Scheme 4 Gold-catalyzed [3+2] annulation of ynamides with isoxazoles.



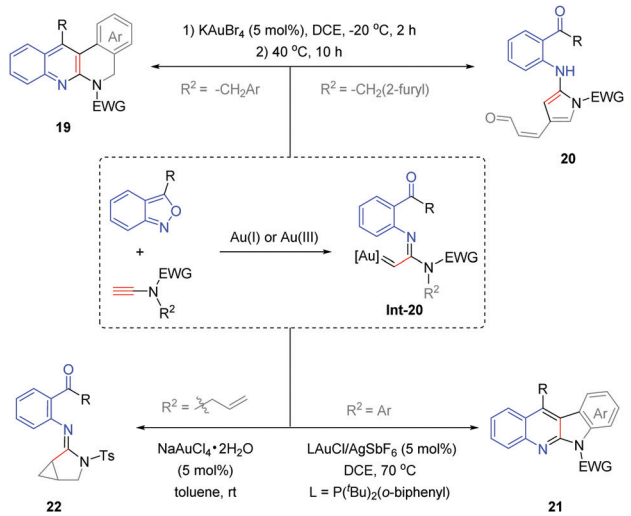
Scheme 5 Gold-catalyzed [4+3] annulation of enynamides with isoxazoles.

protocol relies on a novel 6π electrocyclization of azaheptatrienyl gold-carbene intermediate **Int-11**. When using Lewis acid $Zn(OTf)_2$ as a catalyst, the resulting azepines **14** could be readily converted to amino-pyridines **15** *via* a 1,2-acyl migration step. Notably, the two transformations could be integrated into one step by relay Au(I)/Zn(II) catalysis.

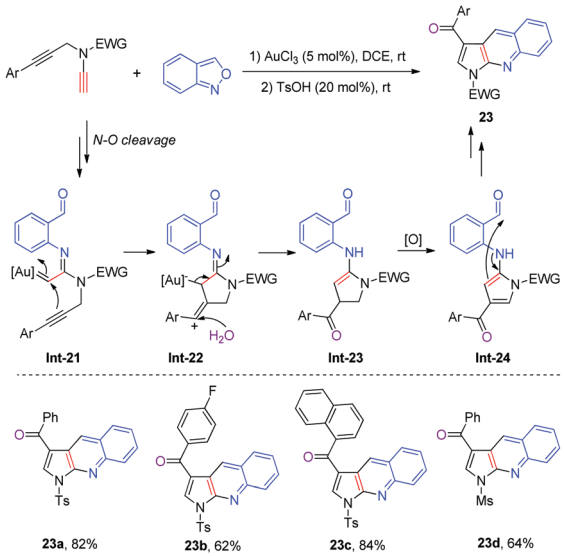
Besides isoxazoles, in 2016, Hashmi *et al.* showcased that anthranil **16a** was also an efficient coupling partner in the annulation of ynamides (Scheme 6).[19,20] The substituents on the ynamides played a crucial role in modulating the annulation pathway. For terminal ynamides (R^1 = H), [3+2]-type products amino-indoles **17** were obtained *via* an *ortho*-aryl C–H insertion into gold-carbene. When silyl ether substituted ynamides ($R^1 = TBSOCH_2$) were used as



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



Scheme 7 Gold-catalyzed diverse annulations of ynamides with anthranils.



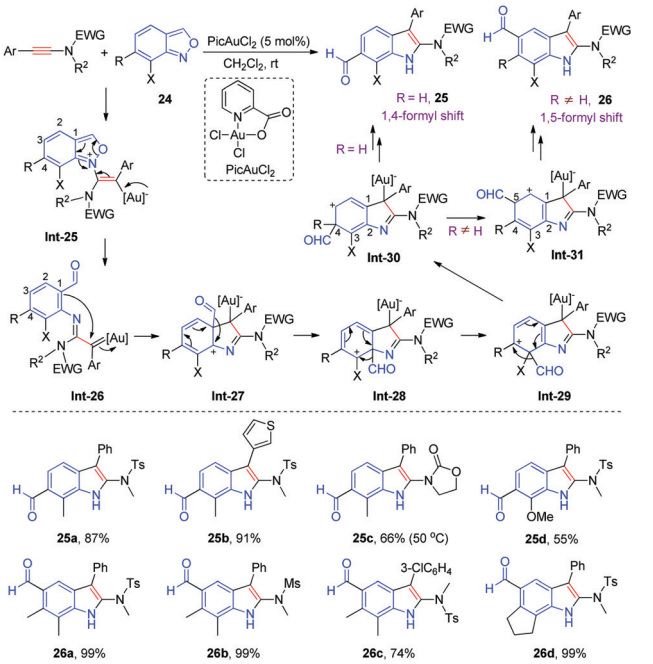
Scheme 8 Gold-catalyzed [4+2] annulation of *N*-propargyl ynamides with anthranils.

substrates, the reactions gave [4+2]-type products amino-quinolines **18** in good yields. It is believed that gold-carbene **Int-15** proceeds through a 1,2-hydride shift and deauration to produce silyl enol ether **Int-19**, which then participates in Mukaiyama aldol condensation to deliver **18**. Interestingly, the substrate scope for both transformations could be extended to non-polarized alkynes *via* a slight adjustment of the reaction conditions.

It is noted that terminal ynamides and anthranils could undergo diverse annulations by tuning the substituents on the nitrogen atom and catalytic system (Scheme 7). For example, in the presence of an Au(III) catalyst ($KAuBr_4$), the gold-carbene intermediate **Int-20** can be intercepted by *N*-Bn of ynamide, followed by deauration, enamine-ketone addition and aromatization to afford quinoline-fused polyheterocycles **19**.[21] Interestingly, under the standard conditions, the annulation of 2-furylmethyl-derived ynamides with anthranils yielded a set of amino-pyrroles **20**, because the electron-rich C2 position of the furan ring serves as a nucleophilic site to trap the gold-carbene intermediate.[21] Following a similar process, the involvement of *N*-aryl terminal ynamides in the annulation led to the formation of indolo[2,3-*b*]quinolines **21**.[22] In the case of *N*-allyl ynamides, capture of gold-carbene with C=C of the allyl motif gave rise to various 3-azabicyclo[3.1.0]-hexan-2-imines **22**.[23]

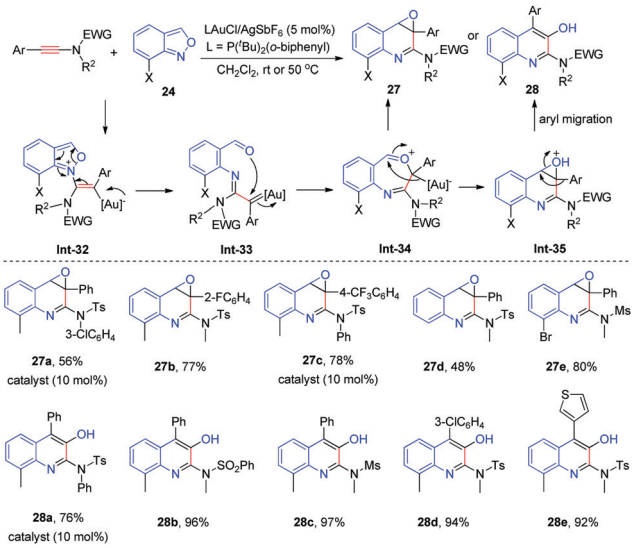
Liu and co-workers described that *N*-propargyl ynamides and anthranil could undergo two sequential annulations to furnish pyrrolo[2,3-*b*]quinolines **23** *via* gold(III)/acid relay catalysis (Scheme 8).[24] ^{18}O-labelling experiments indicate that the oxygen atom of ketone in the product originates from water. The formed reactive gold-carbene **Int-21** could be intercepted by C≡C of the propargyl motif to result in five-membered vinyl carbocation species **Int-22**. Subsequently, nucleophilic attack of water and auto-oxidation yield amino-pyrroles **Int-24**, which can be transformed into **23** *via* a domino acid-catalyzed enamine-aldehyde addition and dehydration process.

More recently, the group of Hashmi found that when 7-substituted anthranils **24** were employed as coupling partners, $PicAuCl_2$-catalyzed annulations of ynamides led to a series of



Scheme 9 Gold(III)-catalyzed [3+2] annulation of ynamides with anthranils.

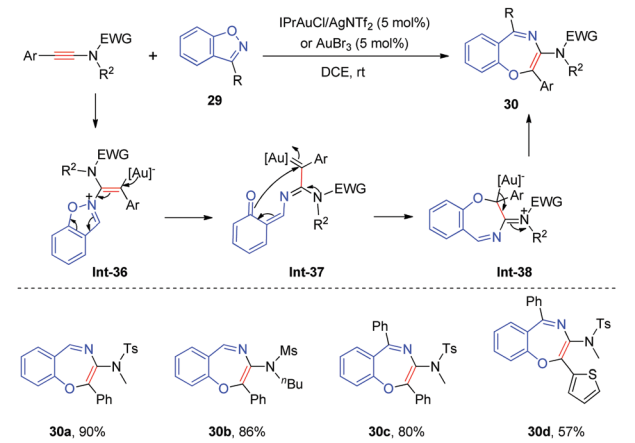
5- (**26**) and 6-formyl amino-indoles (**25**) *via* 1,5- and 1,4-formyl migration, respectively (Scheme 9).[25] The chemoselectivity was diverted to quinoline epoxides **27** and hydroxylquinolines **28** in the presence of $JohnphosAuSbF_6$ (Scheme 10).[25] Aryl groups on the terminus of ynamides proved to be essential for both systems. For gold(III) catalysis, α-imino gold-carbene **Int-26**, *in situ* generated *via* N–O bond cleavage of anthranil, is preferentially trapped by the aryl carbon atom bonded to the carbonyl group. A subsequent formyl shift along the clockwise direction yields amino-indoles **25** or **26**. When varying to a gold(I) catalyst, a nucleophilic attack of the carbonyl group



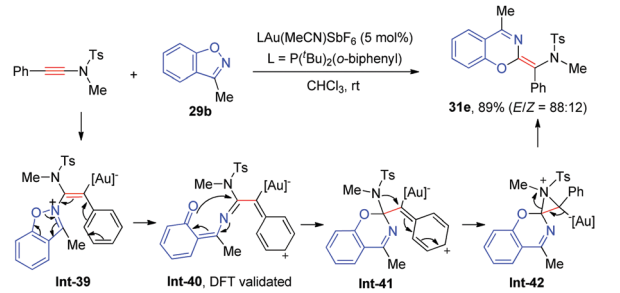
Scheme 10 Gold(I)-catalyzed [4+2] annulation of ynamides with anthranils.

towards gold-carbene **Int-33** preferably takes place, producing seven-membered ring intermediate **Int-34**. A following deauration step affords quinoline epoxides **27**. In some cases, the epoxides would further proceed through aryl migration to result in ring-opening products hydroxylquinolines **28**. DFT calculations were also conducted to explain the catalyst-controlled selectivity. Compared to $PicAuCl_2$, the employment of $JohnphosAuSbF_6$ as a catalyst leads to a lower barrier for the formation of the strained oxirane ring.

Liu and co-workers first employed 1,2-benzisoxazoles **29**, possessing a similar structure to isoxazoles and anthranils, as partners in the gold-catalyzed annulations of ynamides (Scheme 11).[26] Remarkably, the chemoselectivity could be switched by varying the ligand. With $IPrAuCl/AgNTf_2$, the reaction gave [5+2] adducts amino-benzoxazepines **30**, whereas the selectivity was diverted to [5+1] annulation when using Johnphos as a ligand (Scheme 12). For [5+2] annulation, 6π electro-cyclization of gold-carbene intermediate **Int-37** is the



Scheme 11 Gold-catalyzed [5+2] annulation of ynamides with 1,2-benzisoxazoles.

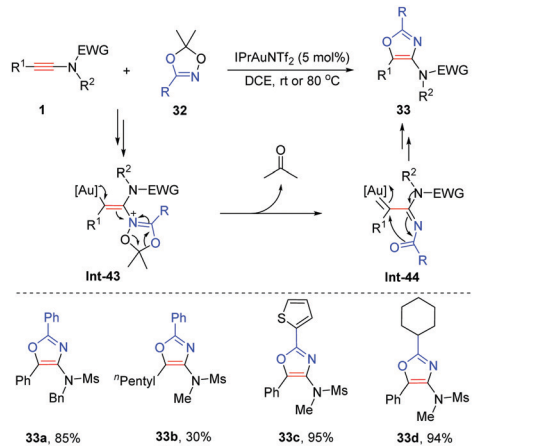


Scheme 12 Gold-catalyzed [5+1] annulation of ynamides with 1,2-benzisoxazoles.

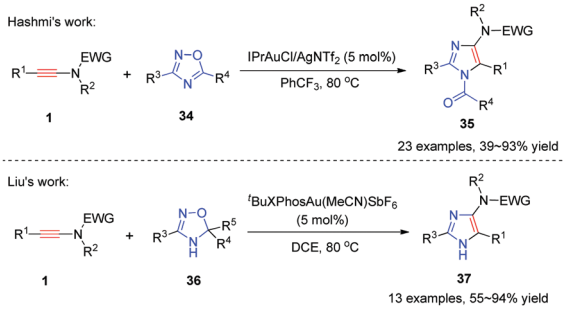
key step. ^{13}C labelling experiments revealed that a 1,2-sulfonamide shift is involved in the [5+1] process. Independently, Liu's group disclosed that the same divergence of annulations could be realized as well by varying the gold catalyst.[27] Meanwhile, the [5+1] annulation was also investigated in-depth by Gandon and Sahoo *et al.*[28] Their DFT calculations revealed that the cleavage of the benzisoxazole N–O bond is trigged by the electron delocalization of the phenyl ring (**Int-40**), followed by ring-closure and a 1,2-sulfonamide shift to furnish the product (Scheme 12).

Dioxazoles **38** could serve as efficient *N*-acyl nitrene equivalents in gold-catalyzed annulation of ynamides, thus allowing for the modular synthesis of 4-aminooxazoles (Scheme 13).[29] Aryl-substituted ynamides worked well under the standard conditions, while the ^{n}pentyl-derived substrate led to a low yield. The substituents on dioxazoles had a negligible effect on the reactivity, affording the desired amino-oxazoles in good yields. The key α-imino gold-carbene intermediate **Int-44** is generated by N–O bond cleavage of dioxazole accompanied by the elimination of acetone.

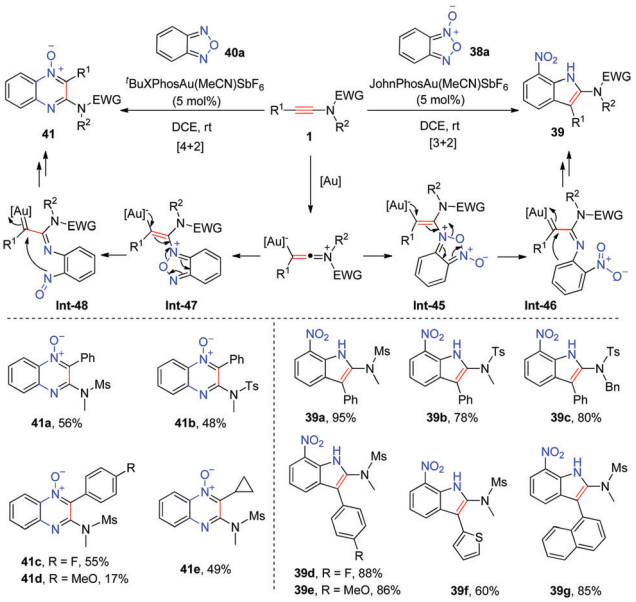
Later, following a similar strategy, 1,2,4-oxadiazoles **40** and dihydro-1,2,4-oxadiazoles **42** could be employed as C3 building units as well (Scheme 14). In Hashmi's work, $IPrAuCl/AgNTf_2$-catalyzed annulations of 1,2,4-oxadiazoles with ynamides resulted in various *N*-acyl amino-imidazoles **35**.[30] In comparison, Liu *et al.* chose dihydro-1,2,4-oxadiazoles as starting materials to synthesize free NH amino-imidazoles **37** using bulky ^{t}BuXPhosAu(MeCN)SbF_6 as a catalyst.[31]



Scheme 13 Gold-catalyzed [3+2] annulation of ynamides with dioxazoles.



Scheme 14 Gold-catalyzed [3+2] annulation of ynamides with oxadiazoles/dihydro-oxadiazoles.

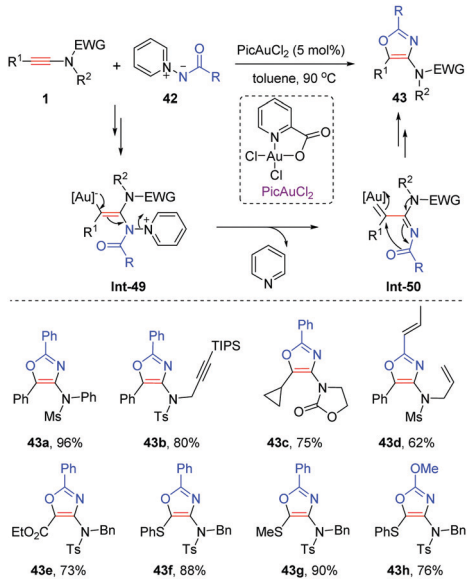


Scheme 15 Gold-catalyzed annulations of ynamides with benzofurazan and its *N*-oxides.

N-Oxides often serve as effective *O*-nucleophiles in gold catalysis; however, in recent work presented by Liu's group, benzofurazan *N*-oxide **38a** was found to act as an *N*-nucleophile in gold-catalyzed annulation of ynamides (Scheme 15).[32] The N–O bond cleavage of benzofurazan *N*-oxide forms α-imino gold-carbene **Int-46**, which can be trapped by the aryl ring to produce [3+2] adducts 7-nitro-2-aminoindoles **39**. In addition, by employing bulky ^{t}BuXPhosAu(MeCN)SbF$_6$ as a catalyst, benzofurazan **40a** could also participate in the annulation of ynamides, delivering diverse quinoxaline *N*-oxides **41** in moderate yields. Independently, the same annulation was also reported by Bao and co-workers.[33]

2.2 N–N bond cleavage

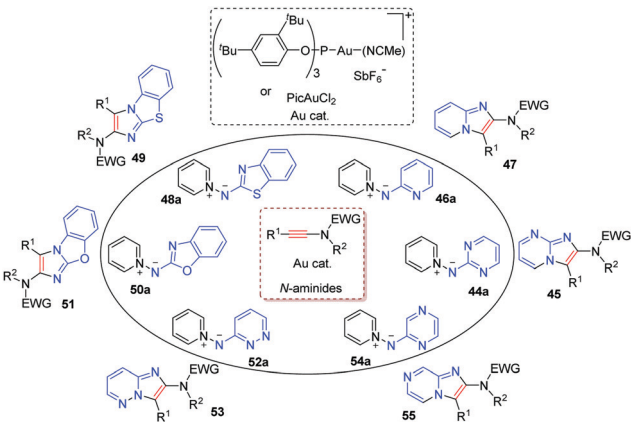
Davies *et al.* made great contributions to the gold-catalyzed annulations of *N*-ylides with ynamides. By using PicAuCl$_2$ as a catalyst, pyridinium *N*-acyl aminides **42**, which can be regarded as *N*-nucleophilic 1,3-*N*,*O*-dipoles, could react with ynamides efficiently to furnish 4-aminooxazoles **43** (Scheme 16).[34,35]



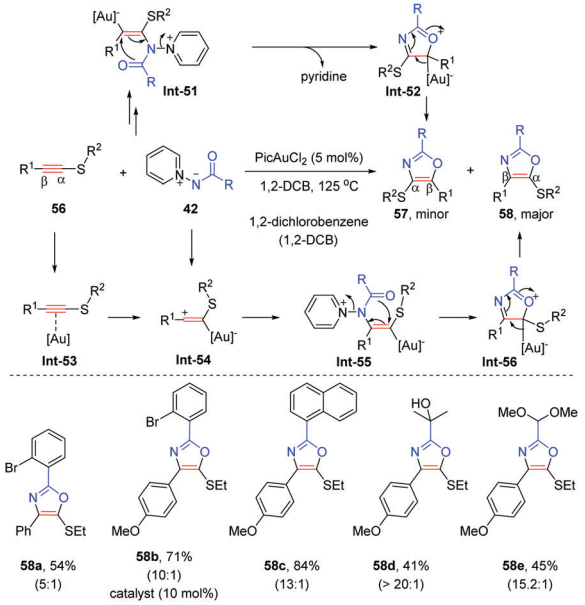
Scheme 16 Gold-catalyzed [3+2] annulation of ynamides with pyridinium *N*-acyl aminides.

The elimination of pyridine enables the formation of α-imino gold-carbene complex **Int-50**. This approach tolerated a wide variety of aryl and alkyl substituents, and was successfully extended to ester- and thio-ynamides.

Later, they employed various pyridinium *N*-heteroaryl aminides as 1,3-*N*,*N*-dipoles in the annulations of ynamides (Scheme 17).[36,37] For example, with (ArO)$_3$PAu(MeCN)SbF$_6$ (Ar = 2,4-(^{t}Bu)$_2$C$_6$H$_3$), pyridinium *N*-(2-pyrimidinyl)aminide **44a** and ynamides underwent [3+2] annulations smoothly to yield imidazo[1,2-*a*]pyrimidines **45**. Other *N*-pyridyl (**46a**), -pyrazinyl (**54a**), and -pyridazinyl (**52a**) aminides were also compatible with the process. PicAuCl$_2$ was proven to be a better catalyst for the annulations of *N*-benzoxazolyl **50a** (or *N*-benzothiazolyl **48a**) aminides with ynamides. This general strategy enables rapid buildup of molecular diversity and structural complexity. Very recently, it was found that sulfenyl substituted ynamides could also participate in such useful transformations.[38]



Scheme 17 Gold-catalyzed [3+2] annulations of ynamides with various pyridinium *N*-aminides.

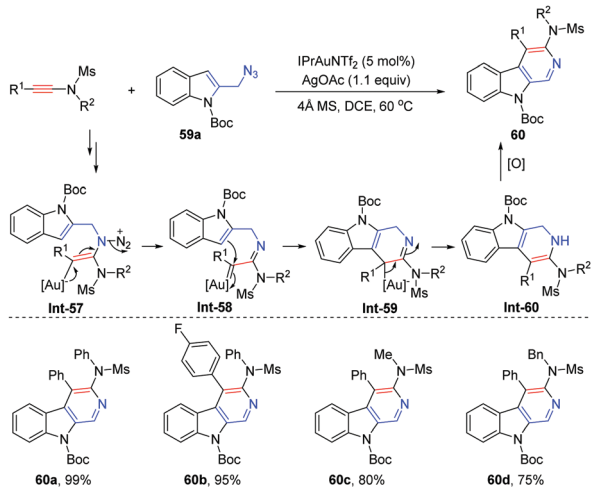


Scheme 18 Gold-catalyzed [3+2] annulation of thioalkynes with pyridinium *N*-acyl aminides.

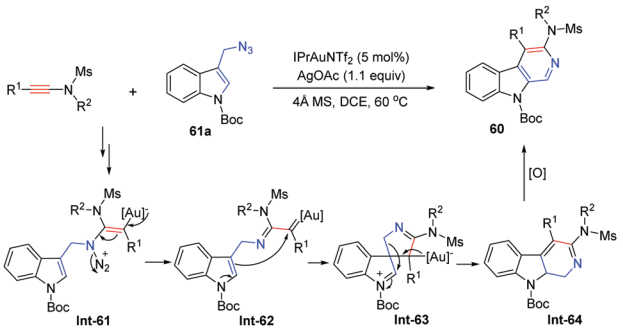
The addition of nucleophiles to ynamides often occurs selectively at the α-position. In comparison, $PicAuCl_2$-catalyzed annulations of thioalkynes **56** with *N*-acyl aminides **42** resulted in an inversion of regioselectivity, providing β-adducts **58** as main products (Scheme 18).[39] It is suggested that the three-membered Au–S dative interaction facilitates a nucleophilic attack of *N*-aminides on the β-site of thioalkynes. The electron-donating group OMe on the phenyl ring of R^1 could reinforce the interactions, thus increasing the regioselectivity. Additionally, the authors also compared the catalytic activities between a gold complex and strong Brønsted acid for the annulation of thioalkyne **56a** and dioxazole **32a**. It is found that $IPrAuNTf_2$ led to reversed selectivity as well, while a normal α-adduct was obtained in the presence of Tf_2NH. Therefore, an alternative explanation is that the ketenethionium ion is much less favored under gold catalysis and the preferential formation of a relatively stable pseudo-benzylic cation triggers a reverse of site selectivity.

In 2015, Lu and Ye *et al.* described that 2-azidomethyl indole **59a** could participate in the gold-catalyzed reactions of ynamides, delivering [4+2] adducts amino-β-carbolines **60** (Scheme 19).[40] Cleavage of the N–N bond in azides generates α-imino gold-carbene species **Int-58**, followed by nucleophilic attack of C3 indole and oxidative aromatization to afford the desired products. Surprisingly, subjecting 3-azidomethyl indoles to the standard conditions yielded the same products (Scheme 20).[41] This result can be ascribed to novel 1,2-alkyl migration in the process.

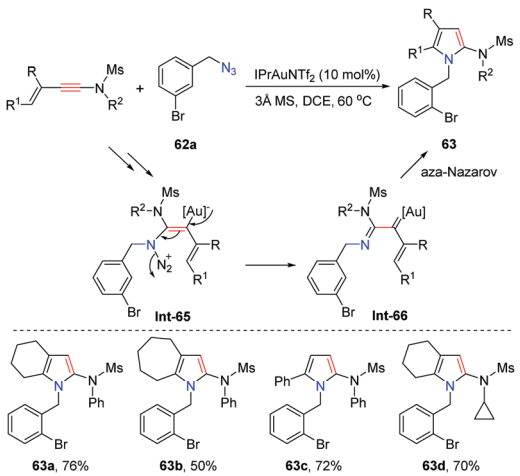
The same group depicted that when enynamides and benzyl azide were employed as substrates, [4+1] annulation took place to yield 2-aminopyrroles **63** in the presence of $IPrAuNTf_2$ (Scheme 21).[42] An aza-Nazarov cyclization of gold-carbene **Int-66** enables the formation of a pyrrole ring.



Scheme 19 Gold-catalyzed [4+2] annulation of ynamides with 2-azidomethyl indole.

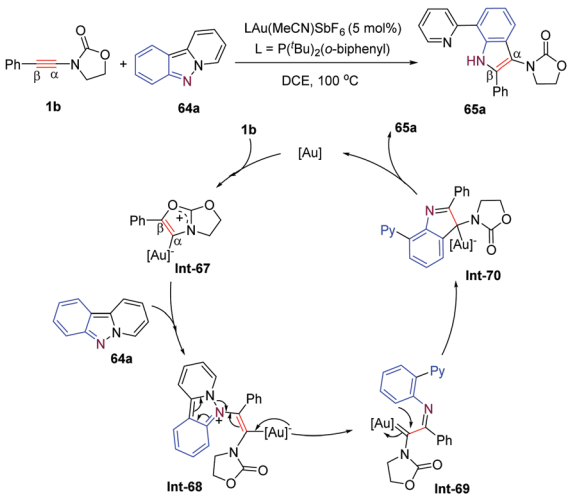


Scheme 20 Gold-catalyzed [4+2] annulation of ynamides with 3-azidomethyl indole.

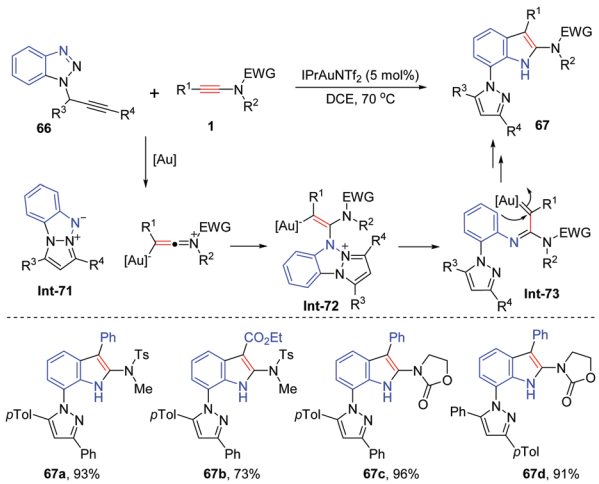


Scheme 21 Gold-catalyzed [4+1] annulation of enynamides with benzyl azide.

In 2016, Huang and co-workers documented an atom-economical gold-catalyzed β-selective [3+2] annulation of ynamide **1b** with pyrido[1,2-*b*]indazole **64a** (Scheme 22).[43] The oxazolidinone group proved to be crucial for this unexpected regioselectivity. Mechanistically, with JohnphosAu(MeCN)SbF_6, an intramolecular cyclization of oxazolidinone-derived ynamide **1b** furnishes a



Scheme 22 Gold-catalyzed [3+2] annulation of an ynamide with pyrido[1,2-*b*]indazole.



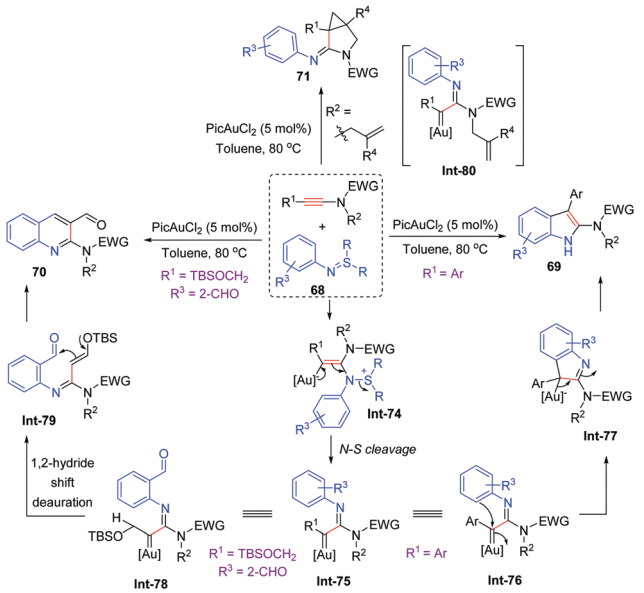
Scheme 23 Gold-catalyzed [3+2] annulation of *N*-propargyl benzotriazoles with ynamides.

five-membered-ring gold complex **Int-67**, which was confirmed by X-ray diffraction analysis. Subsequent nucleophilic attack of **64a** on the β-position and N–N bond cleavage generate gold-carbene intermediate **Int-69**, followed by C–H insertion and aromatization to give the desired product **65a**.

Santamaría and Ballesteros *et al.* reported an alternative for the synthesis of 2-aminoindoles *via* $IPrAuNTf_2$-catalyzed [3+2] annulation of *N*-propargyl benzotriazoles **66** with ynamides (Scheme 23).[44] In this case, *N*-aminide **Int-71** is first formed by a gold-induced intramolecular cyclization of benzotriazole. Subsequently, nucleophilic addition of **Int-71** with the ketenimine ion and N–N bond cleavage afford gold-carbene species **Int-73**. Then, **Int-73** is captured by the aryl C–H bond, followed by aromatization to result in the product.

2.3 N–S bond cleavage

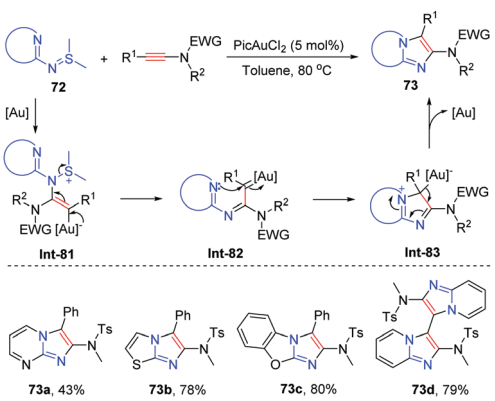
More recently, Hashmi's group exploited a versatile nitrene transfer reagent sulfilimine **68** in the annulations of ynamides



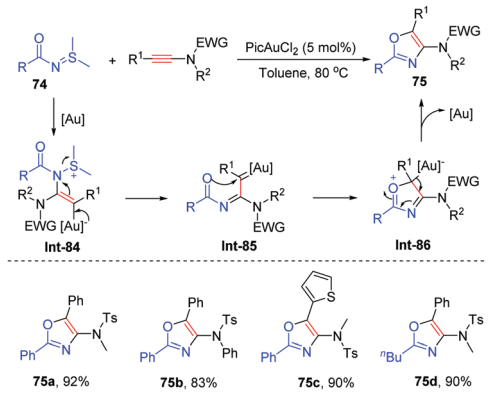
Scheme 24 Gold-catalyzed annulations of sulfilimines with diverse ynamides.

(Scheme 24).[45] Based on the reactions of anthranils (Schemes 6 and 7), similar annulations were also realized by varying the substituents on the ynamides and sulfilimines in the presence of $PicAuCl_2$. Cleavage of the N–S bond in sulfilimine delivers gold-carbene intermediates (**Int-76**, **Int-78** and **Int-80**), which can undergo C–H insertion, a 1,2-hydride shift, and cyclopropanation to form amino-indoles **69**, -quinolines **70**, and 3-azabicyclohexanes **71**, respectively.

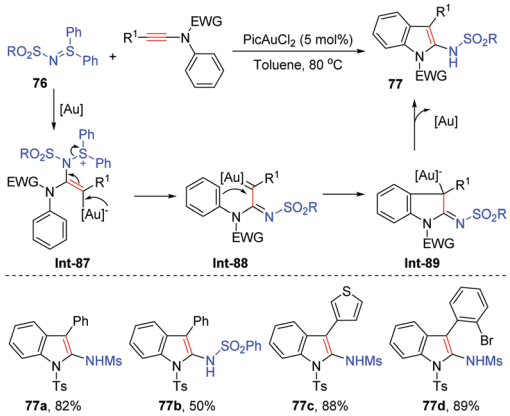
By adopting this strategy, an array of imidazole-fused heterocycles **73** were efficiently produced by a $PicAuCl_2$-catalyzed [3+2] annulation of *N*-heteroaryl sulfilimines **72** with ynamides, in which *N*-heteroaryl sulfilimines act as 1,3-*N*,*N*-dipoles (Scheme 25).[46] Analogously, *N*-acyl sulfilimines **74**, serving as 1,3-*N*,*O*-dipoles, also participated in the process well, providing an alternative for the elaboration of 4-aminooxazoles **75** (Scheme 26).[47] Under the same conditions, *N*-sulfonyl sulfilimines **76** and *N*-aryl ynamides underwent annulation smoothly to yield 2-aminoindoles **77** involving aryl C–H insertion into gold-carbene **Int-88** (Scheme 27).[48]



Scheme 25 Gold-catalyzed [3+2] annulations of *N*-heteroaryl sulfilimines with ynamides.



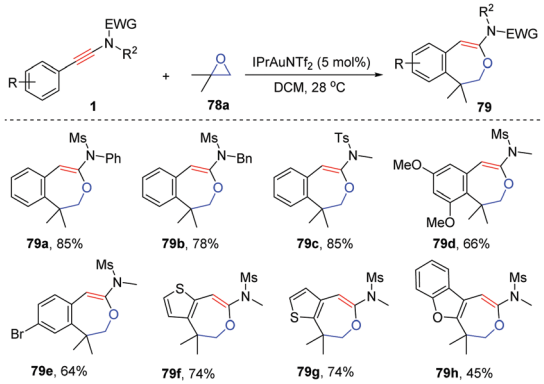
Scheme 26 Gold-catalyzed [3+2] annulations of *N*-acyl sulfilimines with ynamides.



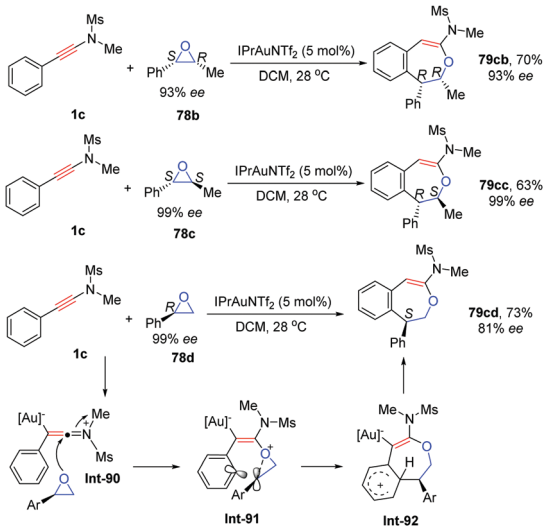
Scheme 27 Gold-catalyzed annulations of *N*-sulfonyl sulfilimines with *N*-aryl ynamides.

2.4 C–heteroatom bond cleavage

In 2012, Liu *et al.* developed a gold-catalyzed [4+3] annulation of ynamides with epoxide for the synthesis of benzoxepines **79** (Scheme 28).[49] An array of heteroaryl-derived ynamides also worked well in the process. Notably, the employment of chiral aryl-substituted epoxides **78b–d** in the reactions resulted in the formation of enantiopure benzoxepines with retention of the stereochemistry (Scheme 29). For example, the chirality of



Scheme 28 Gold-catalyzed [4+3] annulations of ynamides with epoxides.

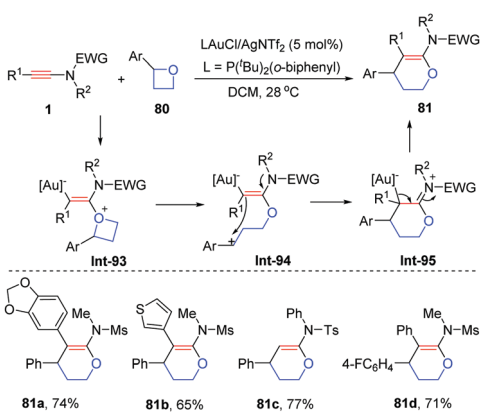


Scheme 29 Gold-catalyzed [4+3] annulations of ynamides with enantiopure epoxides.

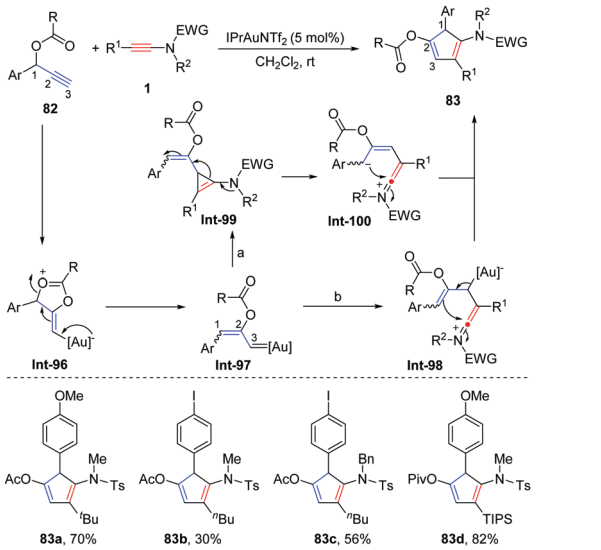
(2*R*,3*S*)-2-methyl-3-phenyloxirane **78b** (93% ee) was successfully transferred to the product. The authors claimed that an S_N2-type front-side attack on the epoxide ring by phenyl is involved in the process. A small degree of racemization was observed in the case of (*R*)-2-phenyloxirane **78d**, which may be ascribed to the epimerization of intermediate **Int-91**. Nevertheless, we think that another possibility is a loose S_N1 pathway *via* memory of chirality where the benzylic carbocation intermediate benefits from association of the oxygen atom.

Later, the same group unveiled that oxetanes **80** could undergo annulations with ynamides in the presence of JohnphosAuCl/$AgNTf_2$, affording [4+2]-type adducts amino-dihydropyrans **81** (Scheme 30).[50] The aryl group on oxetanes accelerates the ring-opening to furnish stable benzylic carbocations **Int-94**. Finally, ring-closure and deauration deliver the target products. Both aryl groups and H at the alkyne terminus were tolerated, whereas alkyl substituents were ineffective.

By taking advantage of the nucleophilicity of ynamides, Hashmi *et al.* documented a gold-catalyzed [3+2] annulation of propargyl carboxylates **82** with ynamides (Scheme 31).[51]



Scheme 30 Gold-catalyzed [4+2] annulations of oxetanes with ynamides.

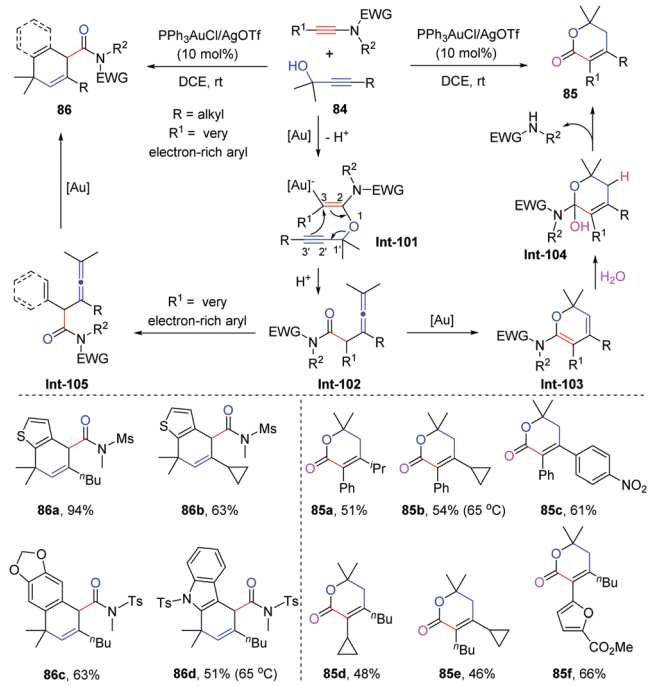


Scheme 31 Gold-catalyzed [3+2] annulation of propargyl carboxylates with ynamides.

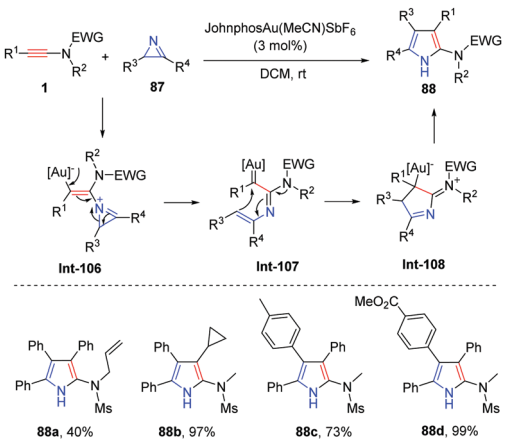
In this case, the gold precursor first activates the propargyl carboxylate to generate vinyl gold-carbene intermediate **Int-97** *via* a 1,2-acyloxy shift. Then, two reasonable pathways were proposed. A cyclopropenation of an electron-rich ynamide with **Int-92** and subsequent ring-opening afford zwitterionic keteniminium ion **Int-100**, which further undergoes cyclization to give the amino-cyclopentadiene **83** (path a). Gold-carbene **Int-97** can be alternatively attacked by the ynamide, followed by ring-closure to deliver **83** (path b).

Liu's group discovered that propargyl alcohols **84** could serve as three-carbon or four-carbon synthons in the gold-catalyzed annulation of ynamides (Scheme 32).[52] The chemoselectivity was dependent on the nature of the R^1 motif. When alkyl or electron-deficient aryl was employed in R^1, [4+2] annulation took place, resulting in the formation of dihydropyranones **85**. In the case of very electron-rich aryl-substituted ynamides, [3+3] adduct fused cyclohexenes **86** turned out to be predominant. The process starts with gold-catalyzed hydroalkoxylation, followed by [3,3]-sigmatropic rearrangement and protodeauration to give allenylamide intermediate **Int-102**. Subsequent *O*-attack on the activated allenyl motif, 1,4-addition of water, and elimination of amine deliver **85**. In comparison, very electron-rich aryl R^1 prefers to undergo a Friedel–Crafts reaction to afford **86**.

In 2015, Huang and co-workers reported mild and facile access to 2-aminopyrroles **88** *via* a gold-catalyzed [3+2] annulation of azirines **87** with ynamides (Scheme 33).[53] Mechanistically, a gold-triggered nucleophilic addition of azirine to ynamide forms intermediate **Int-106**. A subsequent azirine ring opening leads to gold-carbene species **Int-107**, followed by an aza-Nazarov cylization to furnish intermediate **Int-108**. A final aromatization results in the product **88**. *N*-Allylic ynamide was compatible with the process (**88a**), and no cyclopropane side-product was observed, illustrating that aza-Nazarov cylization of gold-carbene **Int-107** possibly is a fast step. Besides, they also found that vinyl azides **87′**,

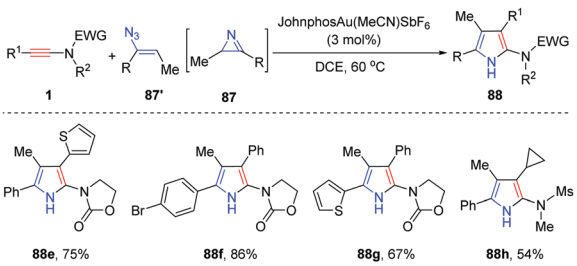


Scheme 32 Gold-catalyzed [3+3] and [4+2] annulations of propargyl alcohols with ynamides.

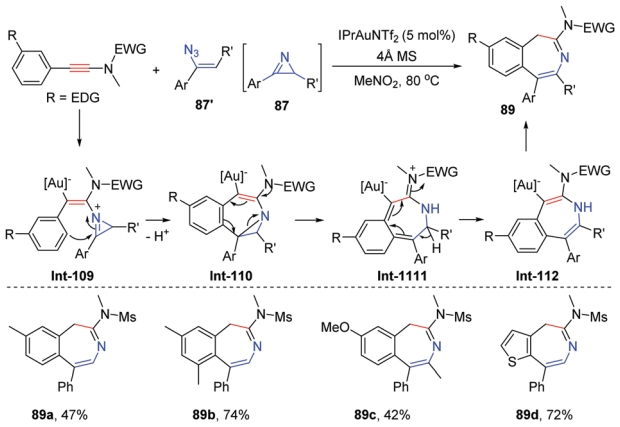


Scheme 33 Gold-catalyzed [3+2] annulations of azirines with ynamides.

which could produce azirines *in situ* by releasing nitrogen, reacted with ynamides as well to give amino-pyrroles (Scheme 34).[54]



Scheme 34 Gold-catalyzed [3+2] annulations of vinyl azides with ynamides.

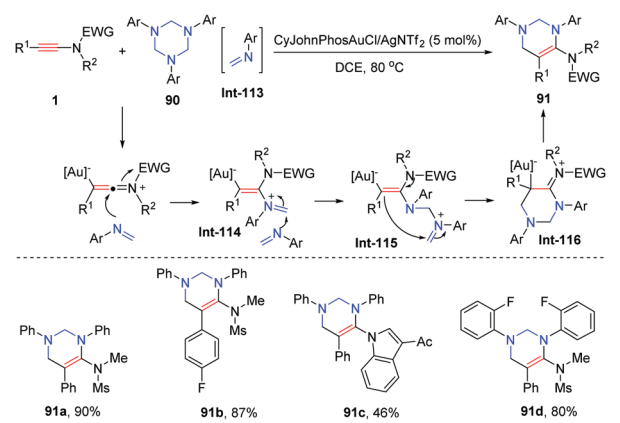


Scheme 35 Gold-catalyzed [4+3] annulations of ynamides with vinyl azides.

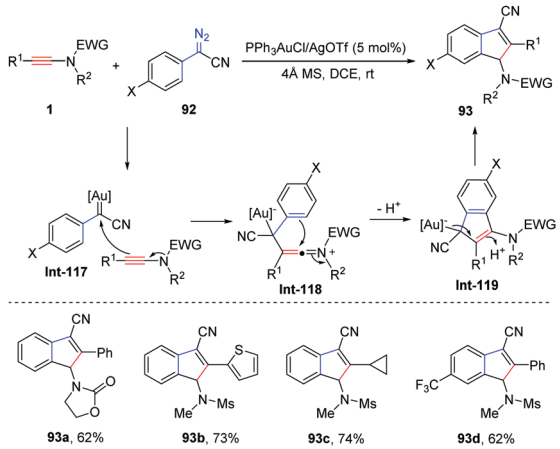
Independently, Liu's group also explored the reactivity of azirines and vinyl azides in the annulations of ynamides.[55] Besides the similar [3+2] pathway, an unexpected [4+3] annulation between electron-donating aryl ynamides and vinyl azides was observed (Scheme 35). The iminium ion in the azirine ring of **Int-109** can be attacked by the electron-rich aryl motif, followed by ring-opening and isomerization to yield amino benzoazepines **89**.

Hashmi and co-workers presented a novel gold-catalyzed annulation between unstrained 1,3,5-triazinanes **90** and ynamides for the synthesis of amino tetrahydropyrimidines **91** (Scheme 36).[56] A variety of aryl substituents in R^1 and 1,3,5-triazinane were suitable for the transformation. The reaction of ynamides with a mixture of two different 1,3,5-triazinanes resulted in a mixture of two normal and two crossover products, revealing that a pseudo three-component [2+2+2] annulation is presumably involved. Formaldimine **Int-113**, *in situ* generated from triazinane, proceeds through nucleophilic addition onto the keteniminium ion to give enamine intermediate **Int-114**. Another formaldimine can react with **Int-114**, followed by ring-closure and deauration to yield the desired product.

Liu *et al.* depicted a mild gold-catalyzed [3+2] annulation between aryl diazonitriles **92** and ynamides (Scheme 37).[57] In this case, the ynamide serves as a nucleophile rather than



Scheme 36 Gold-catalyzed annulations of 1,3,5-triazinanes with ynamides.

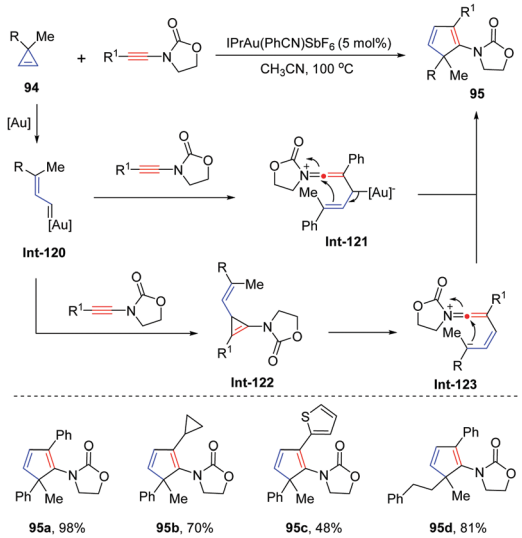


Scheme 37 Gold-catalyzed [3+2] annulations of aryl diazonitriles with ynamides.

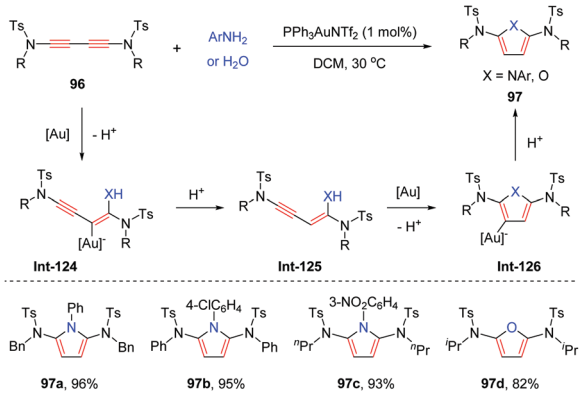
an electrophile. α-Cyano gold-carbene **Int-117**, generated from diazonitrile, is attacked by the ynamide to form keteniminium ion **Int-118**. A subsequent Friedel–Crafts reaction and deauration deliver amino-indenes **93**. The properties of the substituents in the ynamides had little impact on the reactivity. Besides, electron-withdrawing group CF_3 on the phenyl ring of diazonitrile, which may hamper the Friedel–Crafts step, was also tolerated (**93d**).

2.5 C–C bond cleavage

In 2017, Huang and co-workers developed an elegant [3+2] annulation of cyclopropenes **94** with ynamides under gold catalysis, enabling a facile synthesis of amino-cyclopentadienes **95** (Scheme 38).[58] Using IPrAu(PhCN)SbF_6 as a catalyst, substrates possessing various alkyl and aryl groups were all amenable to the conversion. Activation of cyclopropene by the gold catalyst yields vinyl gold-carbene **Int-120**, which can be captured by C≡C of ynamides to furnish cyclopropene intermediate **Int-122**.



Scheme 38 Gold-catalyzed [3+2] annulations of cyclopropenes with ynamides.



Scheme 39 Gold-catalyzed [4+1] annulations of anilines/water with ynamides.

Ultimately, ring-opening and intramolecular cyclization give the target product **95**. Alternatively, the ynamide can act as a nucleophile to attack **Int-120** and subsequent deauration affords **95**.

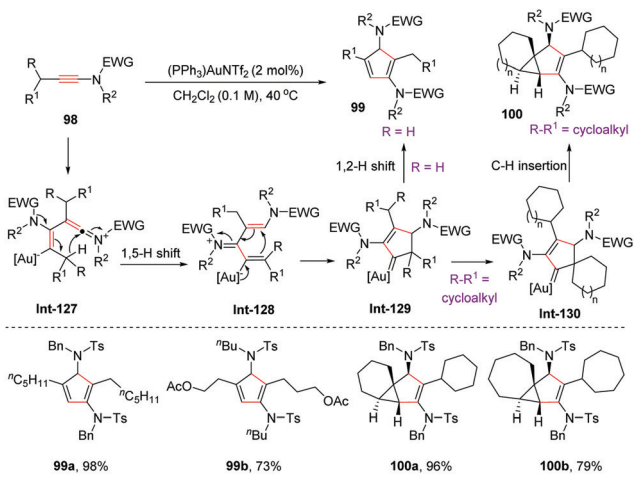
2.6 No bond cleavage

In 2010, Skrydstrup and co-workers disclosed that anilines/water could undergo [4+1] annulation with 1,3-diynamides **96** with PPh_3AuNTf_2 as a catalyst (Scheme 39).[59] The protocol involves initial intermolecular hydroamination/hydration and a subsequent ring closure pathway. It provides a practical and mild alternative for the rapid preparation of 2,5-diaminofurans and 2,5-diaminopyrroles.

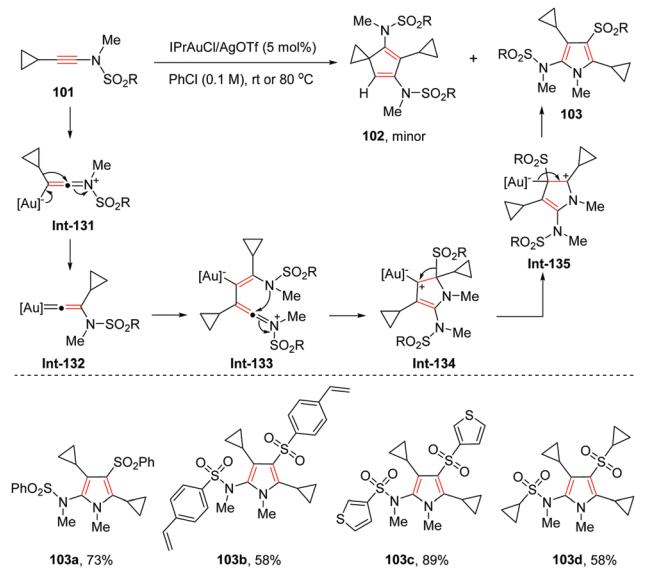
Later, an unexpected gold-catalyzed [3+2] cyclodimerization of ynamides was discovered by the same group (Scheme 40).[60] The success of this procedure depends on the ambivalent nature of ynamides. When linear alkyl groups were located on the ynamide terminus, the dimerization occurred in high efficiencies, leading to the formation of amino-cyclopentadienes **99**. Interestingly, subjecting cycloalkyl-substituted ynamides to the standard conditions produced various fused tricyclic compounds **100**. A nucleophilic attack of the ynamide on the gold-activated ynamide gives a dimeric keteniminium intermediate **Int-127**, which undergoes a 1,5-hydride shift and ring-closure to form five-membered gold-carbene species **Int-129**. In the case of the linear alkyl-derived ynamide, a subsequent 1,2-hydride shift generates cyclopentadiene **99**. In comparison, spirocyclic gold-carbene **Int-130** favors a C–H insertion of the adjacent cycloalkyl moiety.

Based on this work, the group of Shi thoroughly investigated the cyclodimerization of cyclopropyl derived ynamides recently (Scheme 41).[61] Surprisingly, in the presence of IPrAuCl/AgOTf, fully substituted aminopyrroles **103** were dominantly produced with minor normal dimers **102**. A series of (hetero)aryl- and alkyl-sulfonyl groups were amenable to the transformation. The active keteniminium species **Int-131** proceeds through a 1,2-cyclopropyl shift to generate vinyl gold-carbene **Int-132**. Subsequent interception by another molecule of the ynamide gives rise to keteniminium ion **Int-133**, followed by concerted [*N*,*C*]-sulfonyl migration and ring closure to afford intermediate **Int-134**. The second sulfonyl migration and deauration deliver the final products **103**.

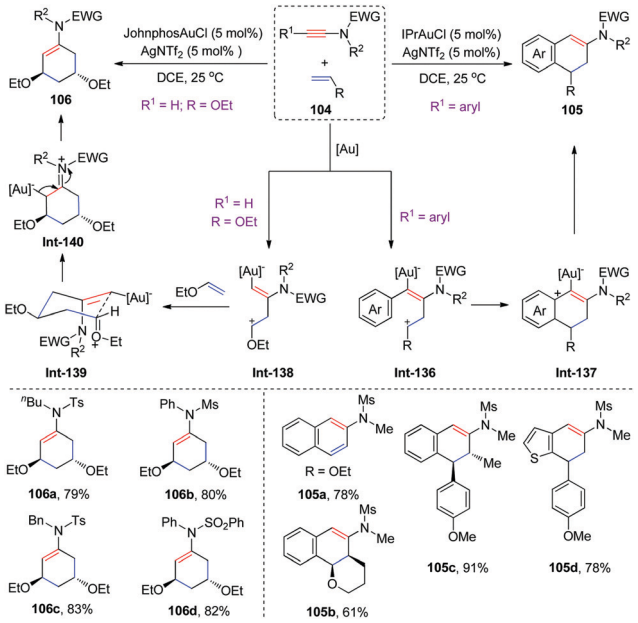
Liu and co-workers realized divergent annulations of ynamides with simple alkenes by gold catalysis (Scheme 42).[62] Using IPrAuCl/$AgNTf_2$ as a catalyst, aryl-derived ynamides could react with alkenes to deliver [4+2] adducts **105**. It is noteworthy that submitting ethoxyethene to the optimized conditions led to aminonaphthalene **105a** by the elimination of ethanol. Surprisingly, the annulation of terminal ynamides with ethoxyethene switched to a [2+2+2] pathway with high selectivity. Both processes are initiated by the nucleophilic addition of alkenes to ynamides, resulting in the formation of carbocation intermediates. For [4+2] annulation, the following Friedel–Crafts-type alkylation and protodeauration give amino-dihydronaphthalene **105**. For [2+2+2] annulation, the carbocation **Int-138** is trapped by another molecule of ethoxyethene to generate an oxonium species **Int-139**. Subsequent ring closure takes place *via* a less-hindered chair-like transition state to deliver **Int-140** with an *anti*-configuration, which finally undergoes deauration to afford product **106**.



Scheme 40 Gold-catalyzed [3+2] cyclodimerization of ynamides.



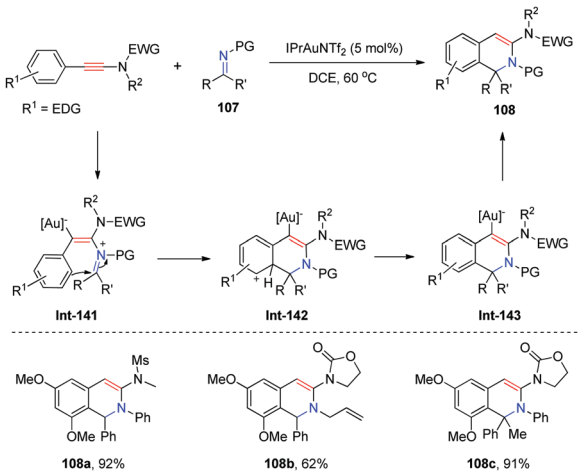
Scheme 41 Gold-catalyzed [3+2] cyclodimerization of ynamides.



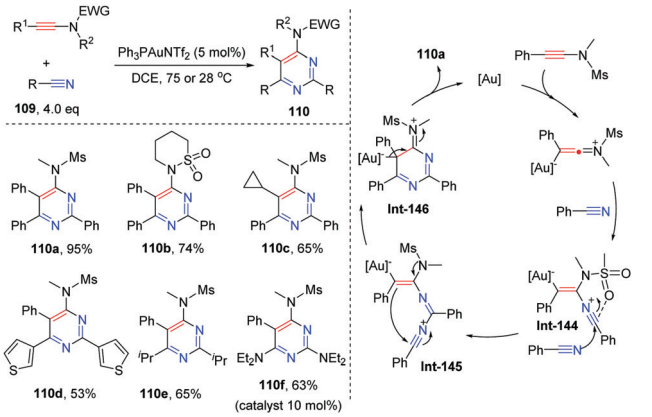
Scheme 42 Gold-catalyzed [4+2] *versus* [2+2+2] annulation of ynamides with alkenes.

Kramer and Skrydstrup *et al.* documented new entry to amino-dihydroisoquinolines **109** *via* an $IPrAuNTf_2$-catalyzed [4+2] annulation of ynamides with imines (Scheme 43).[63] Electron-donating substituents on the phenyl ring of the ynamide were crucial for achieving high yields. Besides aldimines, ketimine was a suitable partner as well (**108c**). The iminium ion **Int-141**, formed by nucleophilic addition of the imine to the ynamide, can be directly attacked by the electron-rich aryl motif, followed by aromatization and protodeauration to furnish the product.

In 2014, an unprecedented gold-catalyzed [2+2+2] annulation of ynamides with nitriles to prepare privileged amino-pyrimidines **110** was documented by Liu *et al.* (Scheme 44).[64] This procedure features mild reaction conditions, excellent regioselectivity, and a broad substrate scope. Notably, electron-rich *N*,*N*-diethylcyanamide



Scheme 43 Gold-catalyzed [4+2] annulation of ynamides with imines.

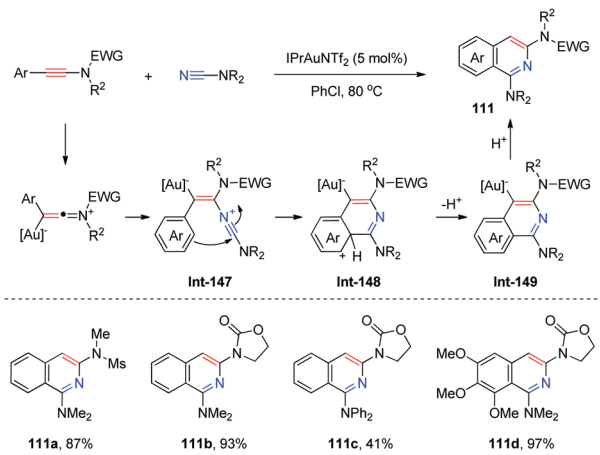


Scheme 44 Gold-catalyzed [2+2+2] annulation of ynamides with nitriles.

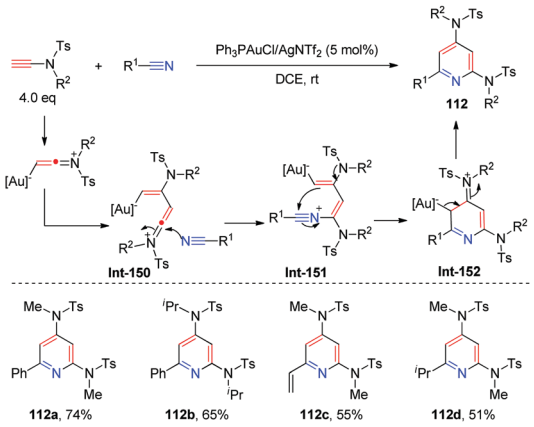
could participate in the annulation as well, providing triamino-pyrimidine **110f** in an acceptable yield. The reaction is initiated by activation of the ynamide. Subsequent nucleophilic attack of two nitriles generates nitrilium species **Int-145**, which undergoes ring-closure and deauration to furnish amino-pyrimidine **110a**. This mechanism is further supported by DFT calculations performed by Bi *et al.* in 2016.[65]

More recently, Dubovtsev and Kukushkin *et al.* studied in depth the annulations between ynamides and cyanamides.[66] They also observed the same annulation as obtained in Liu's group (**110f**, Scheme 44). Interestingly, the [4+2] annulation turned out to be predominant when the reaction was conducted at high temperature (Scheme 45). Under this condition, the active nitrilium ion **Int-147** is preferably attacked by the aryl ring of the ynamide *via* a Friedel–Crafts pathway, followed by protodeauration to produce diaminoisoquinolines **111**.

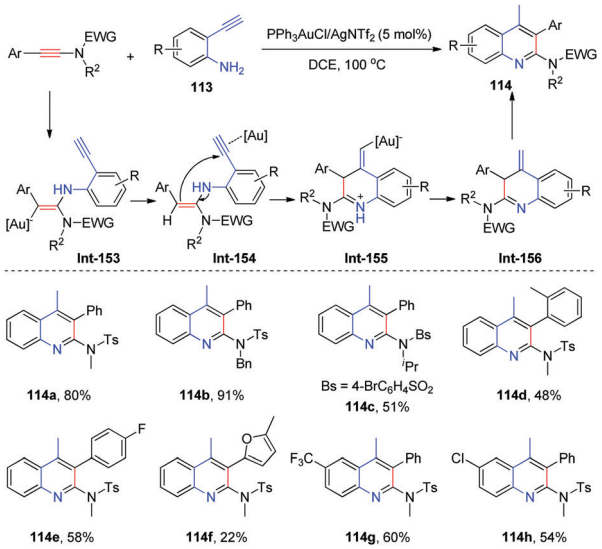
The chemoselectivity of the annulation could be altered to amino-pyridines **112** when *N*-Ts terminal ynamides were employed (Scheme 46).[67] The terminal ynamides, which are better nucleophiles than the substituted ones, prefer to undergo dimerization in the presence of a gold catalyst to give keteniminium species **Int-150**. Eventually, nucleophilic attack of nitriles and deauration form amino-pyridines **112**. It is worthwhile to note that the



Scheme 45 Gold-catalyzed [4+2] annulation of ynamides with cyanamides.



Scheme 46 Gold-catalyzed [2+2+2] annulation of terminal ynamides with nitriles.

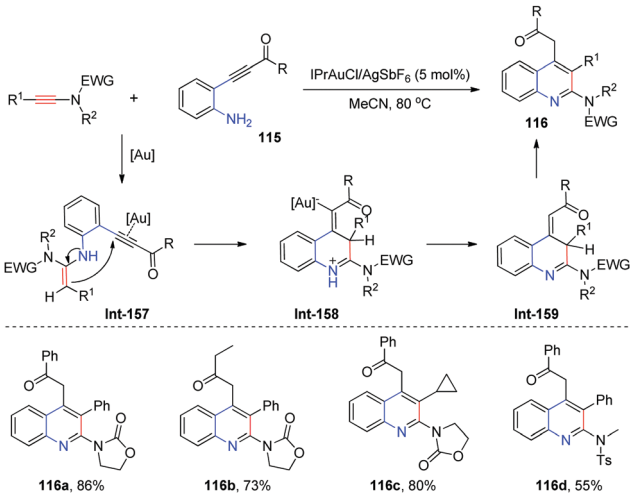


Scheme 47 Gold-catalyzed [4+2] annulation of ynamides with ethynylanilines.

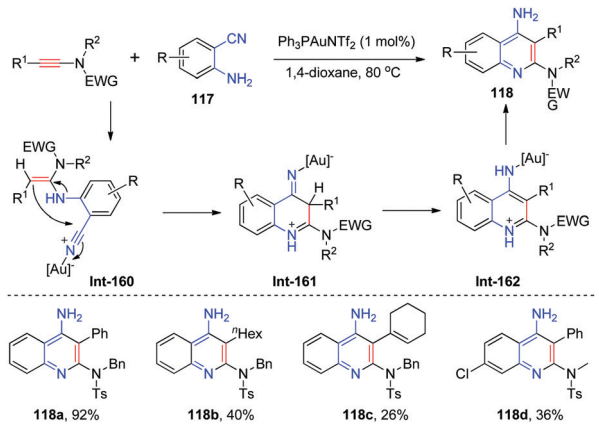
annulation of an *N*-Ms terminal ynamide and nitrile favored the formation of amino-pyrimidine, because Ms could stabilize the competing nitrilium species **Int-144** (Scheme 44).

Hashmi *et al.* reported an expeditious methodology for the assembly of 2-aminoquinolines **114** *via* a gold-catalyzed annulation of ynamides with ethynylanilines **113** (Scheme 47).[68] A variety of aryl groups on the terminus of ynamides were tolerated. The annulation of internal alkynylanilines could not take place under the standard conditions. The process is initiated by gold-catalyzed hydroamination of ynamides. The resulting alkynyl enamines **Int-154** subsequently undergo gold-catalyzed 6-*exo*-dig cyclization, protodeauration and aromatization to yield the products. Following the same strategy, the scope can be expanded to ketone-substituted alkynylanilines **115**[69] and 2-aminobenzonitriles **117**[70] (Schemes 48 and 49).

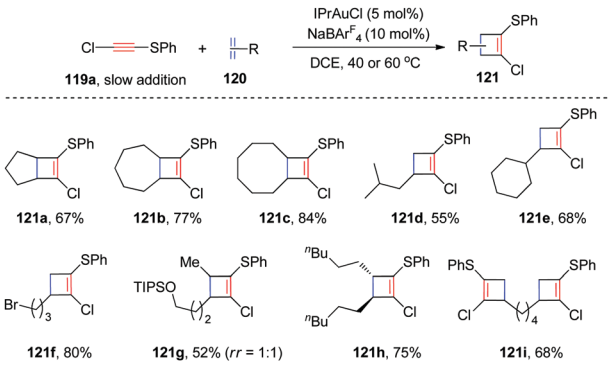
In 2018, Zhang's group accomplished an intriguing [2+2] annulation between chloro-substituted thioalkyne **119a** and unactivated alkenes **120** with gold catalysis (Scheme 50).[71]



Scheme 48 Gold-catalyzed [4+2] annulation of ynamides with ketone-substituted alkynylanilines.



Scheme 49 Gold-catalyzed [4+2] annulation of ynamides with 2-amino-benzonitriles.



Scheme 50 Gold-catalyzed [2+2] annulation of a chloro-substituted thioalkyne with unactivated alkenes.

The monosubtituted alkenes worked well, yielding the expected cyclobutenes (**121d**, **e**, and **i**) with excellent regioselectivities. With symmetrical alkenes including cycloalkenes and 1,2-disubstituted alkene, the reactions proceeded in a stereospecific fashion

(**121a–c**, and **h**). Disappointingly, in the case of an unsymmetrical alkene, a poor regioselectivity was afforded (**121g**). The terminal chloro group is critical for the high efficiency of the annulation, as the electron-withdrawing nature of Cl makes the alkyne strongly polarized and capable of reacting with unactivated alkenes.

3. Silver catalysis

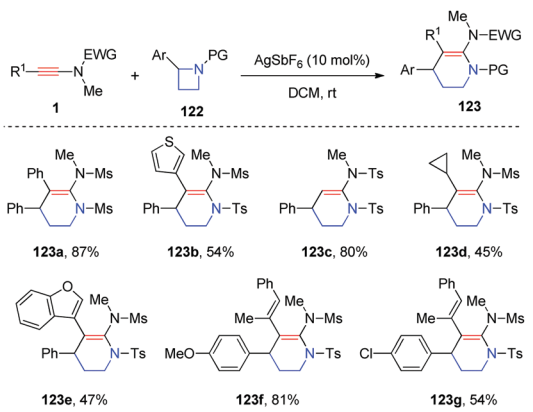
Along with their findings in gold-catalyzed [4+2] annulation of oxetanes with ynamides (Scheme 30), Liu *et al.* showcased that when azetidines **122** were employed as partners, $AgSbF_6$ was demonstrated to be a better catalyst for their annulation (Scheme 51).[50] This mild nature of this strategy makes it compatible with a broad range of aryl and alkyl substituents.

In 2019, Sun's group developed straightforward entry to eight-membered lactams **126** *via* a [6+2] annulation of siloxy alkynes **124** and vinylazetidines **125** (Scheme 52).[72] The protocol features mild reaction conditions, a broad substrate scope and easy access to medium rings. In the presence of an AgOTf or PAr_3 catalyst, the siloxy alkyne is converted to the ketene **Int-163**, which further undergoes addition with vinylazetidine and intramolecular [3,3]-sigmatropic rearrangement to furnish the desired product. It is noted that the annulation of pre-synthesized ketene **124a′** and vinylazetidine could take place spontaneously without any catalyst. This result supports the fact that the catalyst is just responsible for the generation of the active ketene species.

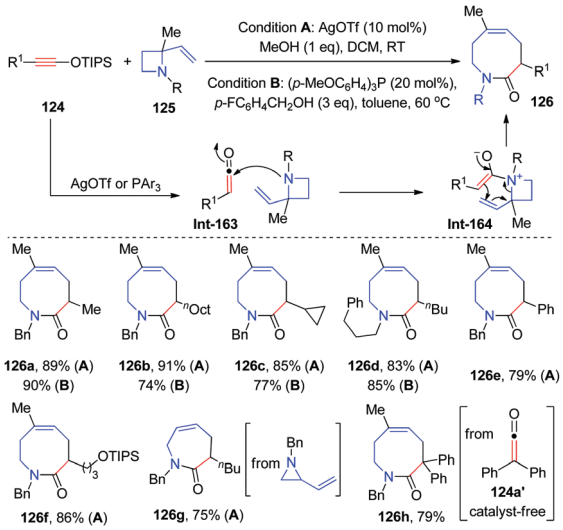
4. Copper catalysis

Huisgen [3+2] annulations of ynamides with azides were independently developed by Cintrat *et al.*[73] and Hsung's group[74,75] (Scheme 53). In Cintrat's work, a variety of organic azides participated in the reactions efficiently, providing diverse functionalized 4-aminotriazoles **127**. In comparison, Hsung *et al.* developed a tandem three-component protocol involving Cu-catalyzed azidination of aryl/vinyl iodides with sodium azide and subsequent [3+2] annulations. Both processes gave 1,4-adducts with complete regiocontrol and no 1,5-adducts were observed. Only terminal ynamides were suitable for the catalytic transformations, while internal ynamides could undergo Huisgen annulations with exclusive 1,4-selectivity under thermal conditions (Scheme 54).[74]

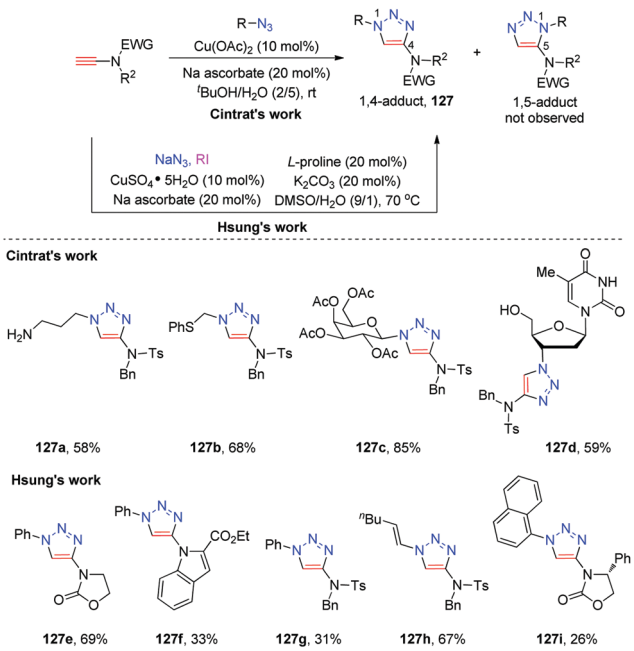
As early as 1969, Ficini *et al.* reported a thermally-driven step-wise [2+2] annulation of cyclic enones with ynamines for the construction of fused aminocyclobutenes.[76] However, the practical problems in the synthesis, storage and handling of highly reactive ynamines hampered the application of the reaction. With the development of ynamide chemistry, in 2010, Hsung's group uncovered the first copper-catalyzed Ficini [2+2] annulation of ynamides with enones (Scheme 55).[77] Slow addition of a mixture of two reactants to the $CuCl_2/AgSbF_6$ system was required to achieve good yields and regioselectivities



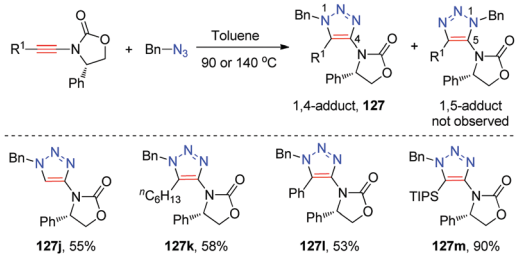
Scheme 51 Silver-catalyzed [4+2] annulation of ynamides with azetidines.



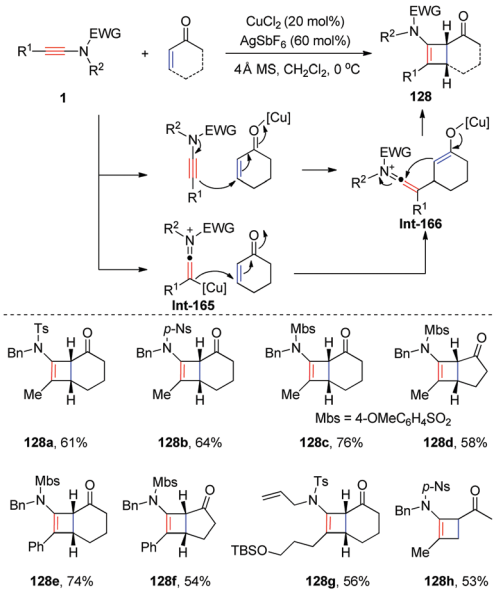
Scheme 52 Silver-catalyzed [6+2] annulation of siloxy alkynes with vinylazetidines.



Scheme 53 Copper-catalyzed [3+2] annulation of terminal ynamides with azides.



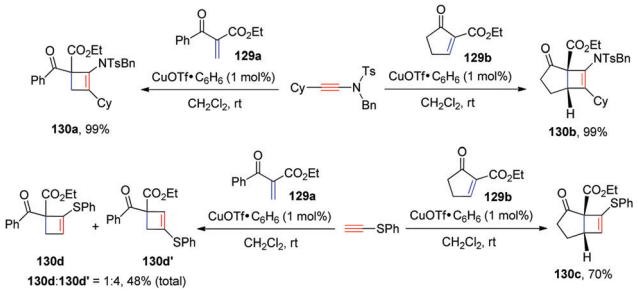
Scheme 54 Thermally-driven [3+2] annulation of ynamides and benzyl azide.



Scheme 55 Copper-catalyzed Ficini [2+2] annulation of ynamides with enones.

of aminocyclobutenes **128**. The copper catalyst first activates the cyclohexenone to facilitate the Michael addition of the ynamide, resulting in the formation of keteniminium ion **Int-166**. An eventual ring-closure generates the [2+2] adduct. It is worthy of note that the pathway consisting of the initial ynamide activation and subsequent 1,4-addition cannot be ruled out.

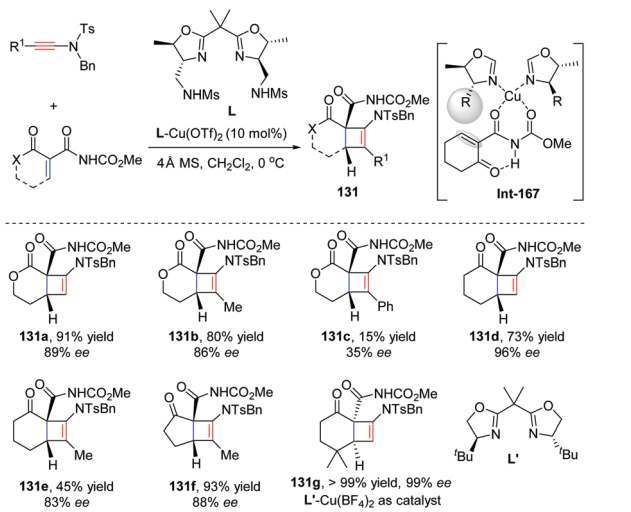
Later, Mezzetti and co-workers realized the Ficini annulation of sterically hindered unsaturated β-ketoesters (**129a** and **b**) with an ynamide (Scheme 56).[78] Besides, the reaction of a terminal thioalkyne with cyclic ketoester **129b** also worked well, whereas in the case of noncyclic ethyl 2-benzoylacrylate **129a** the transformation furnished the adducts (**130d** and **d′**) in moderate regioselectivity and yield.



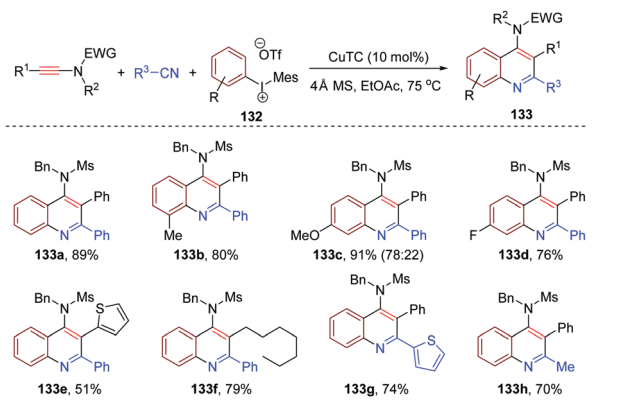
Scheme 56 Copper-catalyzed Ficini [2+2] annulation of an ynamide/thioalkyne with unsaturated β-ketoesters.

Based on these seminal studies, Nakada's group established an asymmetric copper-catalyzed Ficini annulation of ynamides with unsaturated β-oxo imides (Scheme 57).[79] A combination of a chiral bisoxazoline ligand and $Cu(OTf)_2$ led to good stereocontrol of the expected [2+2] adducts. The high efficiency can be explained by the formation of a rigid conformation (**Int-167**), comprising the intramolecular hydrogen bond between the acidic imide hydrogen and β-oxo, and the coordination of two imide carbonyls with the Cu(II) center. Terminal and methyl-substituted ynamides were well tolerated in the process, while a phenyl-derived substrate gave poor results (**131c**). When dimethyl-substituted cyclohexenone imide was employed as a partner (**131g**), ^{t}Bu-derived chiral bisoxazoline was found to be the optimal ligand.

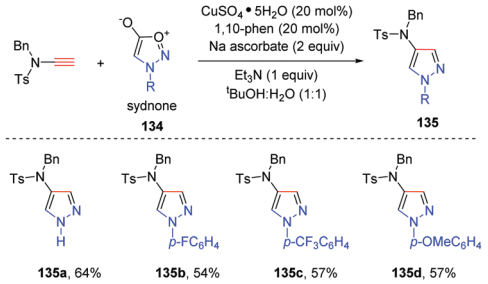
In 2017, Park and co-workers developed expedient access to useful 4-aminoquinolines **133** *via* a copper-catalyzed [2+2+2] annulation of ynamides, nitriles, and aryliodoniums **132** (Scheme 58).[80]



Scheme 57 Asymmetric copper-catalyzed Ficini [2+2] annulation of ynamides with unsaturated β-oxo imides.



Scheme 58 Copper-catalyzed [2+2+2] annulation of ynamides, nitriles, and aryliodoniums.



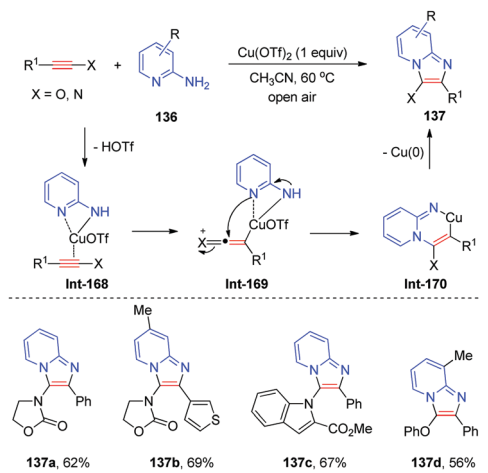
Scheme 59 Copper-catalyzed [3+2] annulation of a terminal ynamide with sydnones.

In general, the process features high regioselectivity and wide functional group tolerance. However, the electron-rich *meta*-OMe substituted phenyliodonium salt gave an inseparable mixture of regioisomers (**133c**). The benzyl and sulfonyl protecting groups on the nitrogen atom of 4-aminoquinolines could be easily removed with ^{t}BuOK.

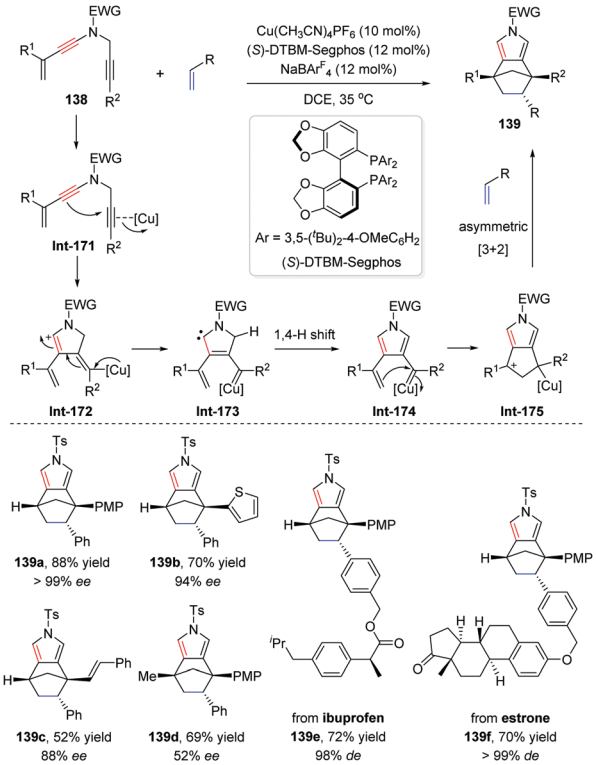
Bräse *et al.* discovered that sydnones **134** could serve as effective 1,3-dipoles in the copper-catalyzed annulation of a terminal ynamide, providing an easy alternative for the elaboration of aminopyrazoles **135** (Scheme 59).[81]

Reddy *et al.* found that 2-aminopyridines **136** and ynamides or ynol ethers could undergo [3+2] annulations in the presence of $Cu(OTf)_2$ to yield diverse imidazo[1,2-*a*]pyridines **137** (Scheme 60).[82] It is suggested that the active Cu(II) catalyst, *in situ* formed by the elimination of HOTf from 2-aminopyridine and $Cu(OTf)_2$, reacts with the ynamide to generate Cu-ketenimine complex **Int-169**. A subsequent nucleophilic attack of the pyridyl nitrogen atom delivers a six-membered copper ring **Int-170**, and a final reductive elimination yields Cu(0) and the product.

Along with the development of gold carbene chemistry, the facile generation of non-noble transition metal carbenes from alkynes also attracted chemists' interest.[83,84] More recently, Ye and co-workers exploited an efficient catalytic system consisting of $Cu(CH_3CN)_4PF_6$, (*S*)-DTBM-Segphos, and $NaBAr^F_4$ to achieve enantioselective annulations of alkenyl *N*-propargyl ynamides



Scheme 60 Copper-promoted [3+2] annulation of ynamides with 2-aminopyridines.



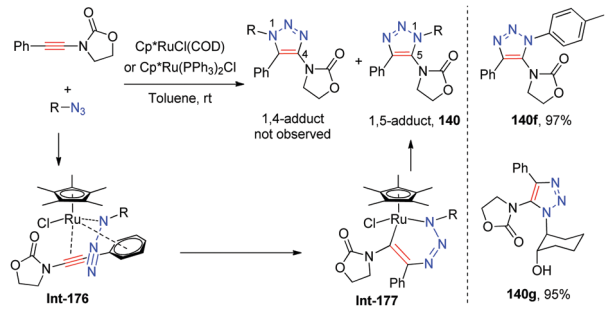
Scheme 61 Asymmetric copper-catalyzed [3+2] annulation of alkenyl *N*-propargyl ynamides with styrenes.

138 with styrenes (Scheme 61).[85] Mechanistically, the ynamide unit serves as a nucleophile to attack the copper-activated alkyne, followed by a 1,4-hydride shift to deliver a donor/donor copper carbene **Int-174**. Then, the copper carbene can be attacked by the alkene motif to generate 1,3-dipolar intermediate **Int-175**. Eventually, a highly diastereo- and enantioselective formal [3+2] cycloaddition of **Int-175** with styrenes furnishes the expected pyrrole-fused bridged [2.2.1] products **139**. In most cases, high yields and enantioselectivities were obtained. Notably, the complex styrenes derived from bioactive skeletons (*e.g.* ibuprofen and estrone) were also compatible with the annulations.

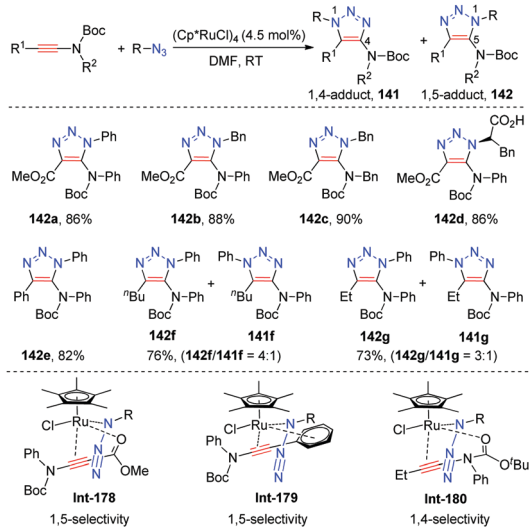
5. Ruthenium catalysis

Inspired by ruthenium-catalyzed azide–alkyne cycloaddition,[86] in 2007, Cintrat *et al.*[87] and Fokin's group[88] independently found that ynamides could participate in the reaction to yield 5-aminotriazoles **140** (Scheme 62). In comparison with the exclusive 1,4-selectivity attained from copper catalysis (Scheme 53), 1,5-adducts turned out to be predominant under ruthenium catalysis. The oxidative cyclization of a ruthenium catalyst, azide and ynamide generates a six-membered ruthenacycle species **Int-177**, followed by reductive elimination to form 5-aminotriazoles.

In 2015, Taddei and co-workers explored the reactivity of *N*-Boc ynamides in ruthenium-catalyzed Huisgen annulations (Scheme 63).[89] Carboxylate and phenyl groups on the alkyne terminus gave 5-aminotriazoles with complete regiocontrol, while alkyl-derived substrates resulted in a mixture of regioisomers



Scheme 62 Ruthenium-catalyzed [3+2] annulation of ynamides with azides.

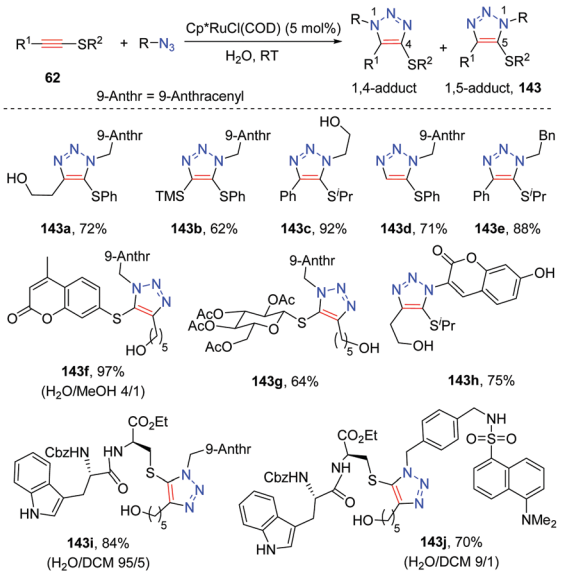


Scheme 63 Ruthenium-catalyzed [3+2] annulation of *N*-Boc ynamides with azides.

(**142f** and **g**). The exclusive 1,5-selectivity might be ascribed to the favorable interaction between the carboxylate/phenyl group and ruthenium center (**Int-178** and **Int-179**). However, in the case of alkyl groups, the coordination of Ru with the Boc substituent can drive the orientation toward 1,4-selectivity (**Int-180**). The resulting products 5-aminotriazole-4-carboxylates **142** could be employed to prepare useful triazole-based peptides.

In 2017, López and Mascareñas *et al.* successfully expanded the scope to thioalkynes, delivering 5-thiotriazoles **142** with high regioselectivity (Scheme 64).[90] By employing Cp*RuCl-(COD) as a catalyst, water was a good reaction medium for the process. Substrates bearing coumarin (**143f** and **h**), 2-thioglucose (**143g**) and a cysteine-based dipeptide (**143i** and **j**) were all well tolerated. Remarkably, the transformation proceeded efficiently in the presence of biomolecular additives (*e.g.* glutathione and amino acids) and under various biologically relevant conditions such as phosphate-buffered saline and living bacteria (*E. coli*).

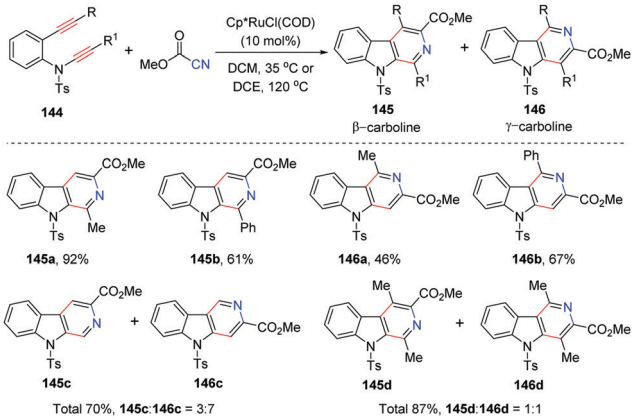
Witulski's group made great contributions to [2+2+2] annulation of yne-ynamides. In 2011, ruthenium complex Cp*RuCl(COD) was used to promote the coupling of yne-ynamides **144** with methylcyanoformate, enabling flexible synthesis of structurally important



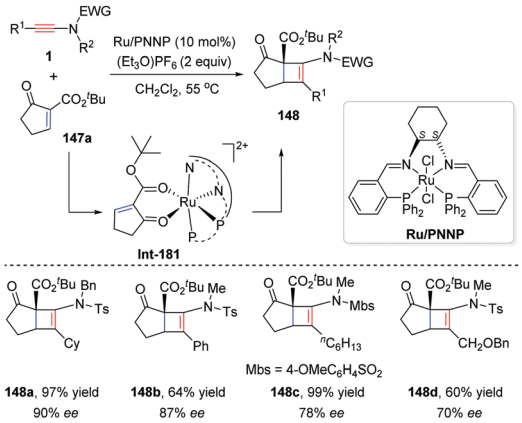
Scheme 64 Ruthenium-catalyzed [3+2] annulation of thioalkynes with azides.

β- and γ-carbolines (Scheme 65).[91] Only mono-substituted yne-ynamides gave the products with complete regiocontrol, while un-substituted (**145c** and **146c**) and di-substituted (**145d** and **146d**) ones afforded a mixture of regioisomers. The engagement of internal ynamides in the process exclusively led to β-carbolines (**145a** and **b**), while the substituents in R switched the selectivity to γ-carbolines (**146a** and **b**).

In 2011, Mezzetti *et al.* developed the first enantioselective Ficini reaction *via* ruthenium catalysis (Scheme 66).[92] The chiral Ru/PNNP complex is activated by $(Et_3O)PF_6$ to form dicationic ruthenium species, whose coordination with two carbonyls of cyclic enone **147a** leads to the clear differentiation of the two enantiofaces (**Int-181**). Ultimately, Michael addition of an ynamide to **Int-181** from the upper face and ring-closure deliver the chiral aminocyclobutenes **148**. Bulky R^1 groups and ^{t}Bu ester were required for achieving high enantioselectivity.



Scheme 65 Ruthenium-catalyzed [2+2+2] annulation of yne-ynamides and methylcyanoformate.

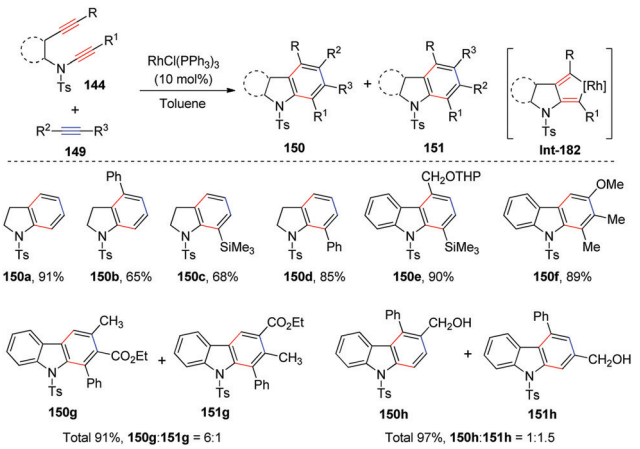


Scheme 66 Ruthenium-catalyzed enantioselective Ficini [2+2] annulation of ynamides with cyclic enone.

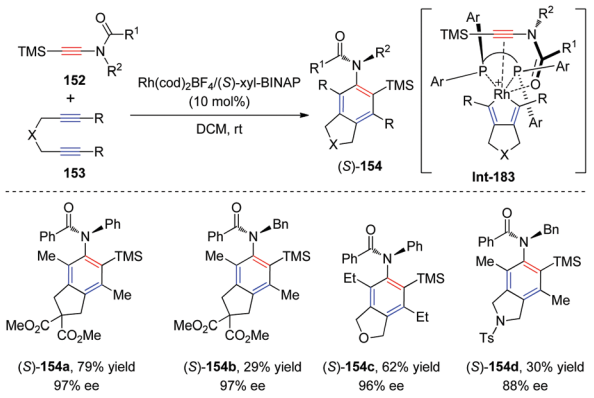
6. Rhodium catalysis

Rhodium-catalyzed [2+2+2] annulations of yne–ynamides **143** with simple alkynes were well investigated by Witulski and co-workers (Scheme 67).[93–95] When acetylene was used as a coupling partner, terminal, mono-substituted, and di-substituted yne-ynamides all resulted in the product indolines or carbazoles with good selectivities (**150a–e**) in the presence of Wilkinson's catalyst [$RhCl(PPh_3)_3$]. A mixture of regioisomers was often obtained for unsymmetrical alkynes, but complete regiocontrol was observed in the case of ynol ether 1-methoxy-1-propyne (**150f**).[90] This unexpected result is likely to be attributed to the coordination between the methoxy group and the rhodacyclopentadiene intermediate **Int-182** during the insertion step.

In 2006, Tanaka *et al.* developed an elegant approach for the synthesis of axially chiral anilides **154** *via* an asymmetric rhodium-catalyzed [2+2+2] annulation of diynes and TMS-ynamides (Scheme 68).[96] By employing $Rh(cod)_2BF_4$/(*S*)-xyl-BINAP as a catalyst, *C*-, *N*-, and *O*-tethered 1,6-diynes were all compatible with the transformation. The coordination of the carbonyl group to the rhodium center and the steric repulsion between



Scheme 67 Rhodium-catalyzed [2+2+2] annulation of yne-ynamides with alkynes.

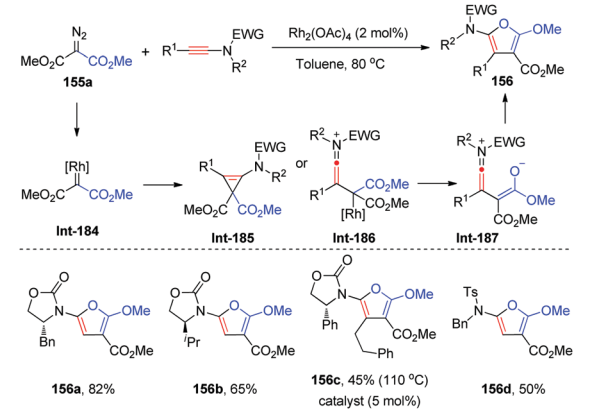


Scheme 68 Enantioselective rhodium-catalyzed [2+2+2] annulation of diynes with TMS-ynamides.

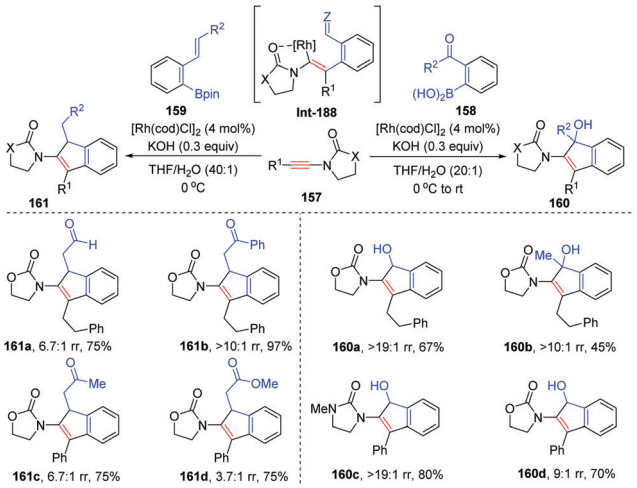
the R^2 group and the PAr_2 motif of (*S*)-xyl-BINAP can account for the high enantioselectivity of the adduct.

Hsung *et al.* uncovered an Rh(II)-catalyzed annulation of diazomalonate **155a** with ynamides for the synthesis of 2-aminofurans **156** (Scheme 69).[97] The diazomalonate is considered as a three-atom synthon in the process. Rhodium-carbene **Int-184**, easily formed *via* the release of nitrogen from the diazomalonate and $Rh_2(OAc)_4$, first reacts with the ynamide to deliver cyclopropene intermediate **Int-185**. Then, ring-opening and *O*-attack on the keteniminium moiety furnish the desired [3+2] adduct. The pathway involving the direct formation of keteniminium ion **Int-186** *via* nucleophilic addition of the ynamide to rhodium carbene cannot be excluded.

In 2010, Lam and co-workers showcased that when using $[Rh(cod)Cl]_2$ as a catalyst, arylboronic acids/esters (**158** and **159**) bearing an electrophilic center at the *ortho*-position could efficiently undergo [3+2] annulation with ynamides to give 2-aminoindenes (**160** and **161**) with moderate to good regioselectivities (Scheme 70).[98] The coordination between the carbonyl group and the rhodium facilitates a regioselective insertion of the ynamide into the initially formed aryl-rhodium species, leading to vinyl rhodium intermediate **Int-188**. A subsequent nucleophilic addition of the Rh–C bond to the carbonyl group or C=C bond yields the adduct.



Scheme 69 Rhodium-catalyzed [3+2] annulation of a diazomalonate with ynamides.

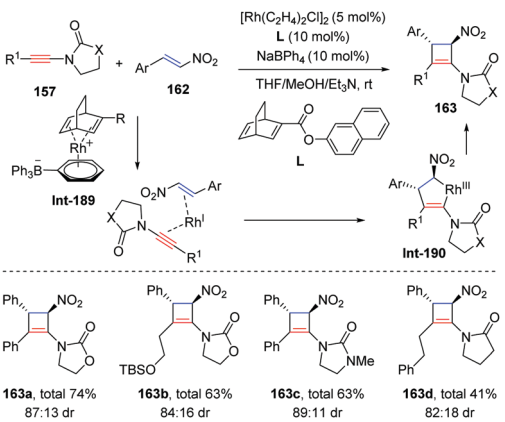


Scheme 70 Rhodium-catalyzed [3+2] annulation of arylboronic acids/esters with ynamides.

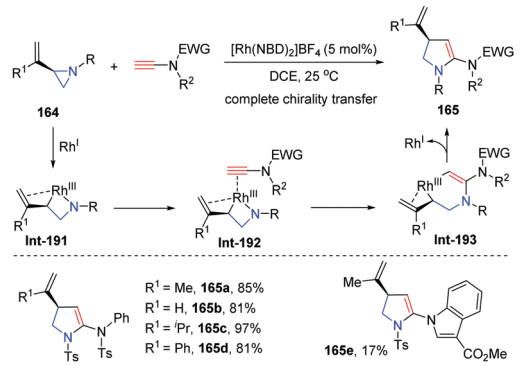
The same group depicted that ynamides and nitroalkenes could proceed through [2+2] annulation in the presence of a diene-ligated rhodium complex and sodium tetraphenylborate (Scheme 71).[99] A set of aminocyclobutenes **163** was obtained with acceptable diastereoselectivities. The Rh(I) precursor is first activated by $NaBPh_4$ to form cationic rhodium species **Int-189**, which undergoes oxidative cyclization with the ynamide and nitroalkene to produce rhodacyclopentene intermediate **Int-190**. An ultimate reductive elimination furnishes the target product and regenerates the Rh(I) catalyst.

Zhang's group developed expedient entry to chiral amino-pyrrolines **165** *via* a rhodium-catalyzed stereospecific [3+2] annulation of vinylaziridines **164** with terminal ynamides (Scheme 72).[100] The chirality of vinylaziridines can be completely transferred to the adducts. An initial oxidative addition of Rh(I) with the aziridine ring delivers four-membered rhodacycle **Int-191**, followed by ynamide insertion and reductive elimination to yield amino-pyrroline.

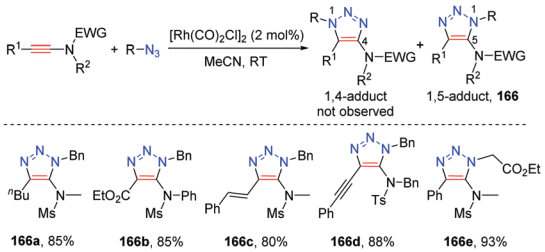
Huang *et al.*, in 2017, presented that Huisgen annulations of ynamides with azides also took place in the presence of



Scheme 71 Rhodium-catalyzed [2+2] annulation of ynamides with nitroalkenes.



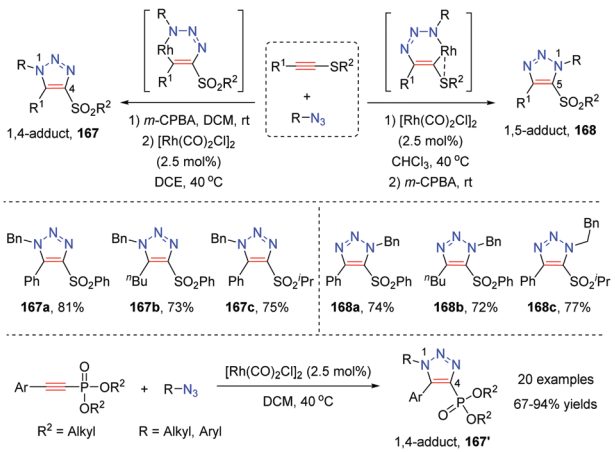
Scheme 72 Rhodium-catalyzed stereospecific [3+2] annulation of vinyl-aziridines with terminal ynamides.



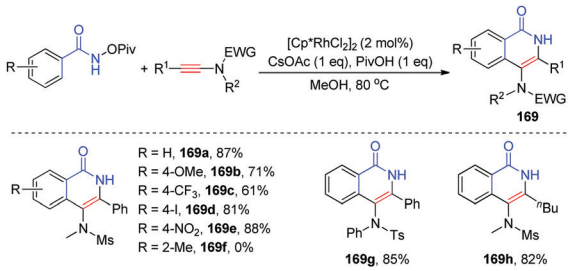
Scheme 73 Rhodium-catalyzed [3+2] annulation of ynamides with azides.

$[Rh(CO)_2Cl]_2$ (Scheme 73).[101] In previous ruthenium catalysis (Scheme 63), alkyl-derived ynamides gave a mixture of regioisomers, while, in this system, 5-aminotriazoles were observed as single isomers. Besides, the reaction could be even carried out in water without a significant loss of yield. The salient advantages of rhodium catalysis include wide substrate scope, exclusive regio-selectivity, air- and moisture-stability, and simple operation.

In 2018, Song's group demonstrated that by tuning the sequence of oxidation and an Rh(I)-catalyzed click reaction, both 4- and 5-sulfonyl triazoles could be selectively synthesized from thioalkynes and azides (Scheme 74).[102,103] When thioalkynes were first oxidized by *m*-CPBA, the resulting sulfur(IV) could not



Scheme 74 Rhodium-catalyzed [3+2] annulation of thioalkynes or alkynylphosphonates with azides.



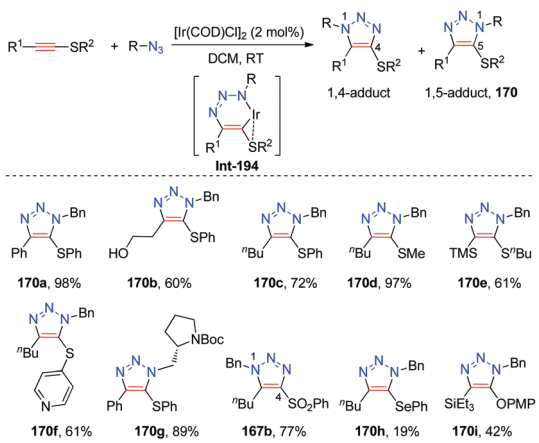
Scheme 75 Rhodium-catalyzed [4+2] annulation of ynamides with *N*-(pivaloyloxy)benzamides.

coordinate with the rhodium center, thus preferentially delivering 1,4-adducts **167**. In comparison, the favorable chelation between the sulfur(II) atom in thioalkynes and the rhodium center leads to the formation of 1,5-adducts **168**. The annulation of alkynylphosphonates and azides also proceeded efficiently in the presence of $[Rh(CO)_2Cl]_2$, giving rise to 1,4-adducts **167'** *via* a non-chelation mechanism.[104] Later, they also successfully realized three-component cascade click/nucleophilic substitution reactions.[105,106]

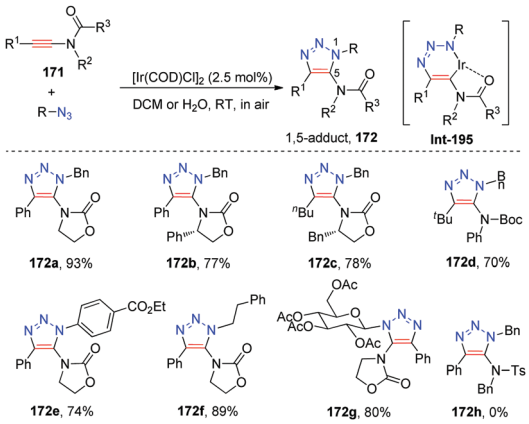
Shi and co-workers unveiled that ynamides could serve as effective coupling partners in the Rh(III)-catalyzed C–H activation of *N*-(pivaloyloxy)benzamides, giving [4+2] adducts 4-amino isoquinolinones **169** with exclusive regioselectivity (Scheme 75).[107] A series of 4-substituted benzamides were applicable to the transformation (**169a–e**), but 2-Me benzamide was not a suitable substrate (**169f**). The substituents on the ynamide had no significant impact on the reaction outcome.

7. Iridium catalysis

In 2014, Jia and Sun *et al.* developed the first Huisgen annulation of thioalkynes with azides *via* iridium catalysis (Scheme 76).[108] This procedure usually exhibits complete 1,5-regioselectivity, good compatibility with air and water, and a wide substrate scope. Subjecting sulfonyl alkyne to the standard conditions gave the opposite regioselectivity and 4-sulfonyl triazole **167b** was afforded. Notably, the annulation was successfully extended to selenyl alkyne and ynol ether, leading to single 1,5-adducts as



Scheme 76 Iridium-catalyzed [3+2] annulation of thioalkynes with azides.



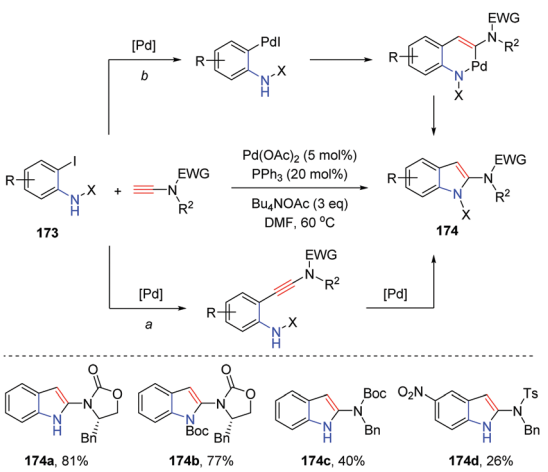
Scheme 77 Iridium-catalyzed [3+2] annulation of ynamides with azides.

well (**170h** and **i**). An oxidative cyclization results in six-membered iridacycle intermediate **Int-194**, which can be further stabilized by the coordination between the sulfur atom and the iridium center. This additional coordination may also contribute to the observed 1,5-regioselectivity. An eventual reductive elimination yields 5-thio triazoles.

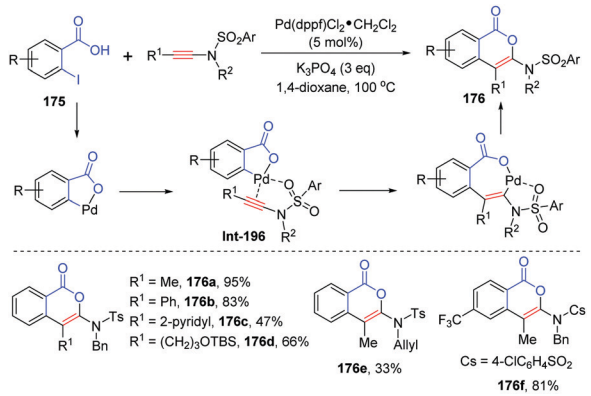
Later, the as-developed iridium system was also employed to promote the annulation of ynamides **171** with azides (Scheme 77).[109] The oxazolidione- and *N*-Boc ynamides were well tolerated, while the reaction of the sulfonyl-substituted ynamide did not occur (**172h**). It reveals that the coordination between the carbonyl group of the ynamide and the iridium center (**Int-195**) is crucial for the excellent regioselectivity. Remarkably, the reaction also worked well under various bioorthogonal conditions, exhibiting significant potential for clinical applications.

8. Palladium catalysis

Ruhland and Skrydstrup *et al.* reported a facile route to access 2-aminoindoles **174** from terminal ynamides and *o*-iodoanilines (Scheme 78).[110] Chiral oxazolidione ynamides could be readily transformed into the corresponding indoles in a regiospecific



Scheme 78 Palladium-catalyzed [3+2] annulation of terminal ynamides with *o*-iodoanilines.

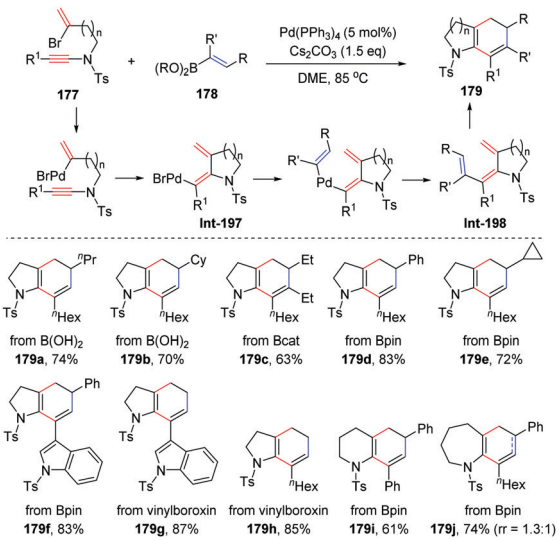


Scheme 79 Palladium-catalyzed [4+2] annulation of ynamides with *o*-iodoaromatic acids.

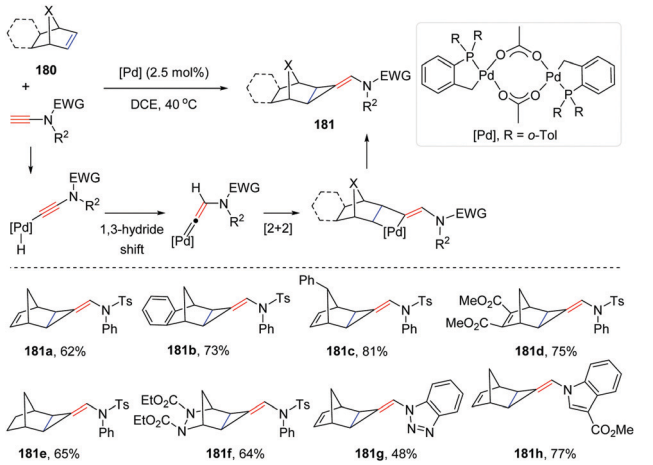
manner (**174a** and **b**). The *N*-sulfonyl and -Boc ynamides also worked well (**174c** and **d**). It is suggested that the reaction proceeds through initial Sonogashira coupling and subsequent cyclization (path a). Nevertheless, we propose an alternative mechanism consisting of oxidative addition, migratory insertion of the ynamide, ligand exchange, and reductive elimination, also known as Larock indole synthesis (path b).

Chang and co-workers showcased the coupling of ynamides and *o*-iodoaromatic acids **175** for the assembly of aminoisocoumarins **176** (Scheme 79).[111] *o*-Iodoaromatic acids act as four-atom synthons in the process. Of note is the chelation between the sulfonyl oxygen atom and the palladium (**Int-193**), which assists the subsequent ynamide insertion into the Pd–C bond with high regioselectivity.

Anderson and co-workers documented that ynamides **177**, bearing a bromoalkene motif, could smoothly undergo [2+2+2] annulation with vinylboronates **178** in the presence of $Pd(PPh_3)_4$ (Scheme 80).[112,113] The process involves intramolecular carbopalladation of bromoenynamides **177** (**Int-197**), Suzuki cross-coupling



Scheme 80 Palladium-catalyzed [2+2+2] annulation of bromoenynamides with vinylboronates.

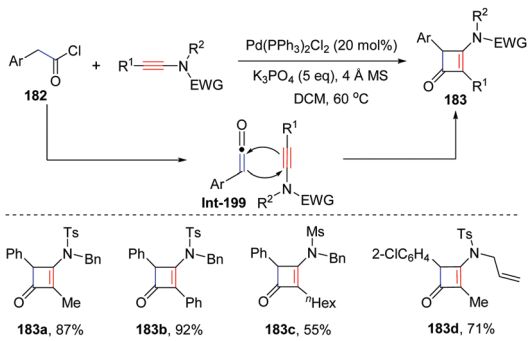


Scheme 81 Palladium-catalyzed [2+1] annulation of terminal ynamides with norbornene derivatives.

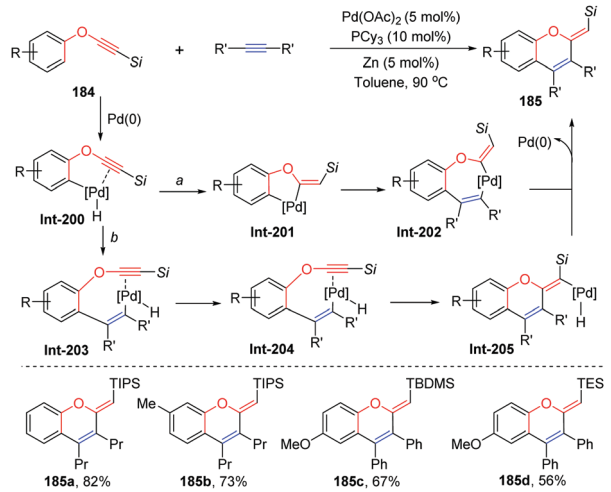
with vinylboronates (**Int-198**) and 6π-electrocyclization. The transformation tolerated an array of alkyl and aryl groups in R^1 and R and the resulting products aminocyclohexadienes **179** could be easily oxidized into indolines or indoles.

In 2013, Clavier and Buono *et al.* employed a bulky phosphapalladacycle complex to promote the coupling of terminal ynamides and norbornene derivatives **180**, giving rise to unexpected [2+1] adducts aminomethylenecyclopropanes **181** (Scheme 81).[114] The reaction exhibited good tolerance to diverse functionalized bicyclo[2.2.1]hept-2-enes and ynamides. Although a detailed mechanism is not given in the original paper, we suggest that an initial C–H activation *via* oxidative addition and a subsequent 1,3-hydride shift generate the palladium vinylidene species, which then undergoes [2+2] annulation with norbornene and reductive elimination to furnish the products **181**.[115]

Chang and Wang *et al.* documented a palladium-catalyzed [2+2] annulation of acyl chlorides and ynamides for the preparation of 3-aminocyclobutenones **183** (Scheme 82).[116] The acyl chlorides **182** are first converted to the active ketenes **Int-199** *via* dehydrochlorination, which then undergo [2+2] annulation with ynamides to give the products. It should be noted that sole K_3PO_4 could also promote the annulation to produce **183a** in 28% yield and most of the ynamide was transformed into the



Scheme 82 Palladium-catalyzed [2+2] annulation of acyl chlorides with ynamides.

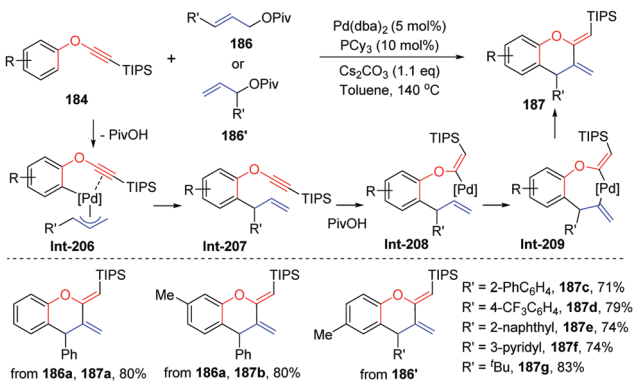


Scheme 83 Palladium-catalyzed [4+2] annulation of ynol ethers and alkynes.

corresponding hydrochlorinated product. This result illustrates that a Pd catalyst is not essential for the first step but can accelerate the subsequent [2+2] annulation.

Minami and Hiyama *et al.*, in 2012, adopted a C–H activation strategy to accomplish the coupling of aryl-substituted ynol ethers **184** and internal alkynes, affording [4+2] adducts 2*H*-chromenes **185** (Scheme 83).[117] An alkyne-directed *ortho* C–H activation generates Ar–Pd–H species **Int-200** *via* an oxidative addition with a Pd(0) catalyst. Subsequent intramolecular alkyne insertion into Pd–H forms five-membered palladacycle **Int-201**, followed by an insertion of an internal alkyne and reductive elimination to yield the product (path a). An alternative pathway involves the first insertion of an internal alkyne into Ar–Pd and then intramolecular ynol insertion into vinyl palladium **Int-204** (path b).

Later, they uncovered that allyl pivalates were also suitable building units in palladium-catalyzed annulation of ynol ethers (Scheme 84).[118] Both linear and branched allyl pivalates (**186** and **186′**) led to the same products, thus illustrating that a π-allyl palladium intermediate **Int-206** is involved in the process. The protocol features a site-selective hydrovinylation



Scheme 84 Palladium-catalyzed [4+2] annulation of ynol ethers with allyl pivalates.

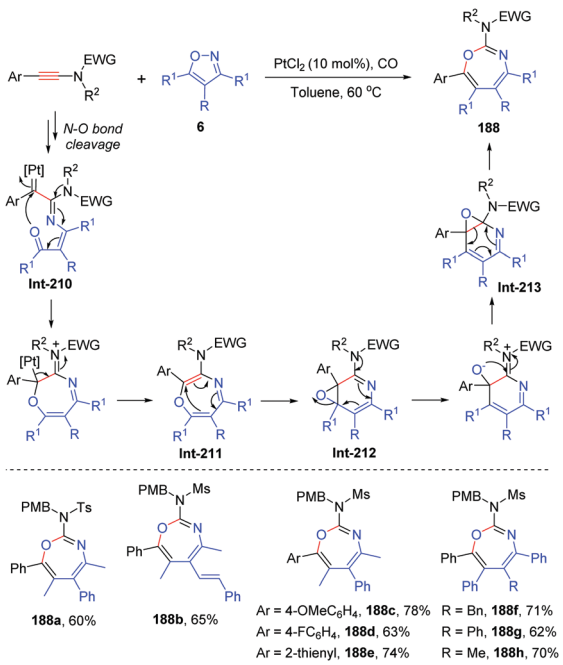
of alkynes, consisting of double C–H activation of two substrates. A broad range of functionalities were tolerated, and of note was the 3-Me substituted ynol ether, which was converted to the target adduct with exclusive regioselectivity as well (**187b**).

9. Platinum catalysis

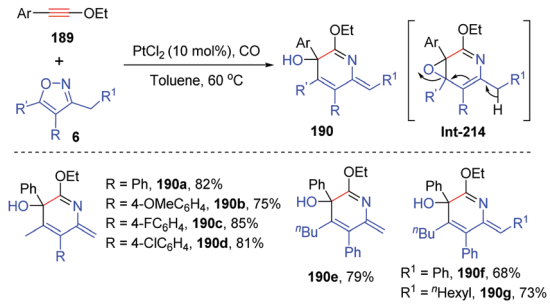
In 2017, Ye and Lu *et al.* developed an elegant strategy for the rapid assembly of amino 1,3-oxazepines **188** *via* a platinum-catalyzed [5+2] annulation of ynamides and isoxazoles (Scheme 85).[119] Distinct from the previous gold catalysis (Scheme 3), isoxazoles act as five-atom synthons in platinum catalysis. The N–O bond cleavage of isoxazole first generates α-imino platinum carbene species **Int-210**, which is captured by the carbonyl group to give 1,4-oxazepine **Int-211** with the release of the platinum catalyst. A subsequent 6π-electrocyclization results in fused epoxide intermediate **Int-212**, followed by ring opening of the epoxide and ring closure to form rearranged epoxide **Int-213**. An eventual 6π-electrocyclic ring opening leads to 1,3-oxazepine **188**. Only aryl-substituted ynamides were compatible with the transformation. Surprisingly, subjecting aryl ynol ethers **189** to the standard conditions afforded unexpected 2,5-dihydropyridines **190** (Scheme 86). In this process, the fused epoxide intermediate **Int-214** prefers to undergo the ring-opening pathway, instead of the rearrangement step.

10. Cobalt catalysis

Malacria, Aubert, and Gandon *et al.*, in 2011, described that by employing [CpCo(CO)(dmfu)] as a catalyst, a wide range of nitriles could participate in the annulation of yne-ynamides, delivering 3- or 4-aminopyridines (**191** and **192**) with high



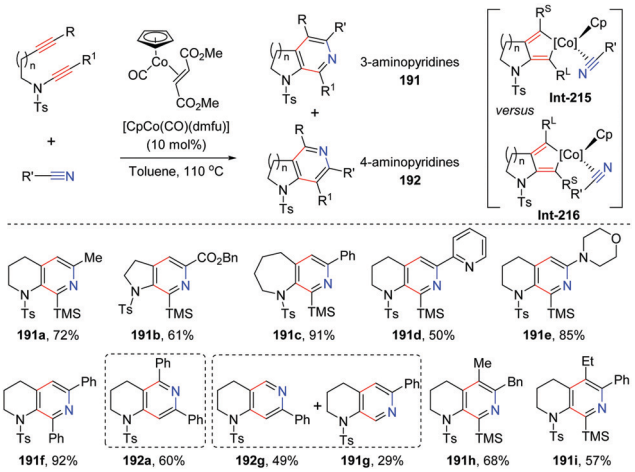
Scheme 85 Platinum-catalyzed [5+2] annulation of ynamides with isoxazoles.



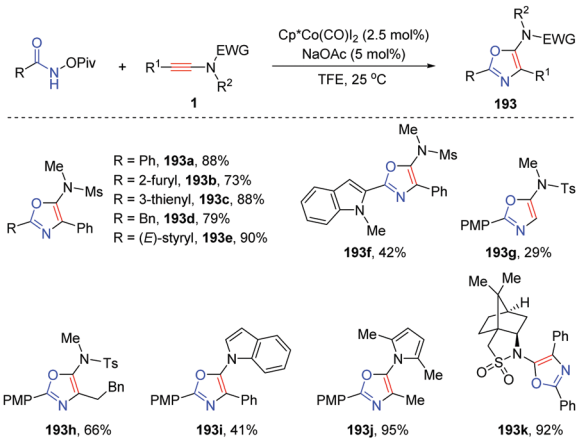
Scheme 86 Platinum-catalyzed [4+2] annulation of ynol ethers with isoxazoles.

regioselectivity (Scheme 87).[120,121] For substrates with a large substituent, TMS for instance, in R^1 and a small one (H, Me, Et) in R, 3-aminopyridines (**191a–f**, **h** and **i**) were exclusively obtained. However, in the case of a terminal ynamide with an internal alkyne (R^1 = H, R = Ph), the chemoselectivity was varied to 4-aminopyridine (**192a**). The reaction of an unsubstituted yne–ynamide led to a mixture of regioisomers (**191g** and **192g**). The regioselectivity stems from the coupling of the nitrile and the cobalta-cyclopentadiene intermediate (**Int-215** and **Int-216**) *via* either an insertion or [4+2] pathway. Further DFT calculations indicated that 3-aminopyridines are formed by [4+2] annulation, whereas 4-aminopyridines arise from an insertion step.

Distinct from Rh(III) catalysis (Scheme 75), Li's group presented that ynamides and *N*-(pivaloyloxy) amides could undergo [3+2] annulation efficiently in the presence of Cp*Co(CO)I_2 (Scheme 88).[122] The assembly of oxazoles from ynamides often gave 4-aminooxazoles (Schemes 13 and 16), while, under cobalt catalysis, unexpected 5-aminooxazoles were exclusively formed. The protocol features unique chemoselectivity, good functional group tolerance, mild reaction conditions, and high yields. Mechanistically (Scheme 89), the amido cobalt complex **Int-217**, formed by the coordination of *N*-(pivaloyloxy) amide to Co(III), is attacked by the nucleophilic carbon of the ynamide to generate the keteniminum ion **Int-218**. A subsequent 6-*exo*-trig cyclization yields the cobaltacycle species **Int-219**. Then, the



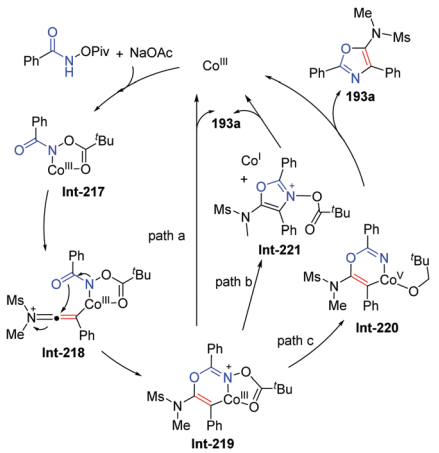
Scheme 87 Cobalt-catalyzed [2+2+2] annulation of yne-ynamides with nitriles.



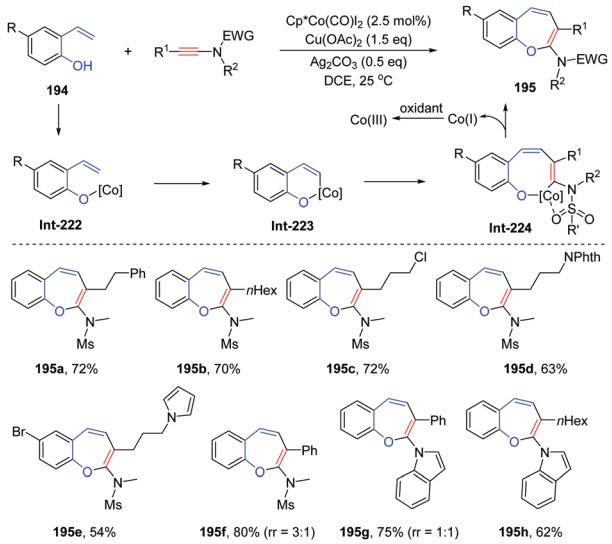
Scheme 88 Cobalt-catalyzed [3+2] annulation of ynamides with *N*-(pivaloyloxy) amides.

N–O bond of **Int-219** is likely to be cleaved by a direct nucleophilic attack of the Co–C bond to afford the product and Co(III) catalyst (path a). Alternatively, a reductive elimination of **Int-219** furnishes the *N*-pivaloyloxy oxazole cation **Int-221** and Co(I) species. A further oxidation of Co(I) by the N–O bond of **Int-221** produces Co(III) with the release of 5-aminooxazole (path b). Another possible pathway involves an oxidation of Co(III) to Co(V) by the N–O bond of **Int-219** and subsequent reductive elimination (path c).

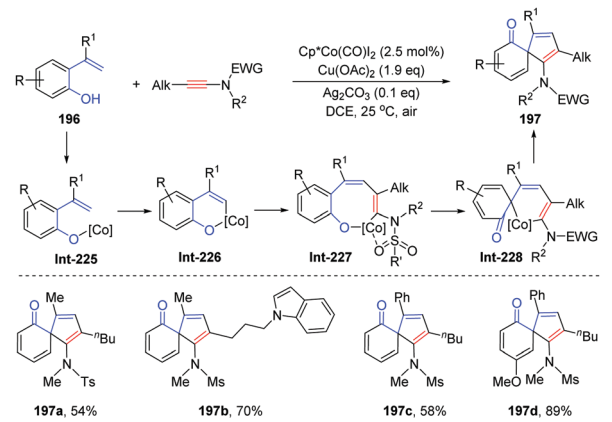
Later, the same group uncovered that vinylphenols **194** could serve as five-atom synthons in the Co(III)-catalyzed annulation of ynamides, leading to the formation of 2-aminobenzoxepines **195** (Scheme 90).[123] The alkyl groups on the terminus of ynamides were well tolerated, while phenyl-substituted substrates resulted in poor regioselectivities (**195f** and **g**). A directed vinyl C–H activation *via* a concerted metalation deprotonation (CMD) pathway generates a six-membered cobaltacycle **Int-223**. Then, migratory insertion of ynamide into the Co–C bond and reductive elimination deliver the product. The resulting Co(I) species is oxidized by $Cu(OAc)_2$ and Ag_2CO_3 to regenerate the Co(III) catalyst.



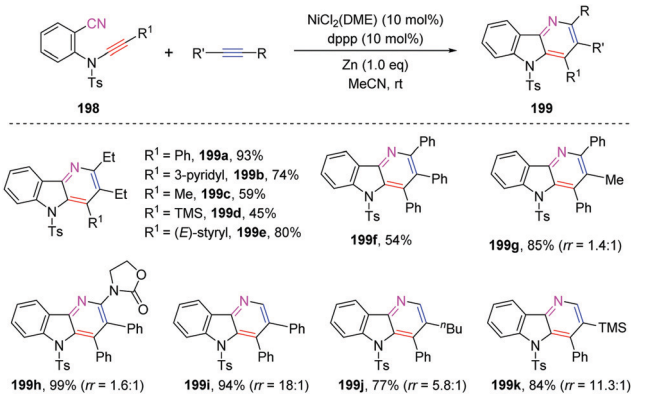
Scheme 89 Cobalt-catalyzed [3+2] annulation of ynamides with *N*-(pivaloyloxy) amides.



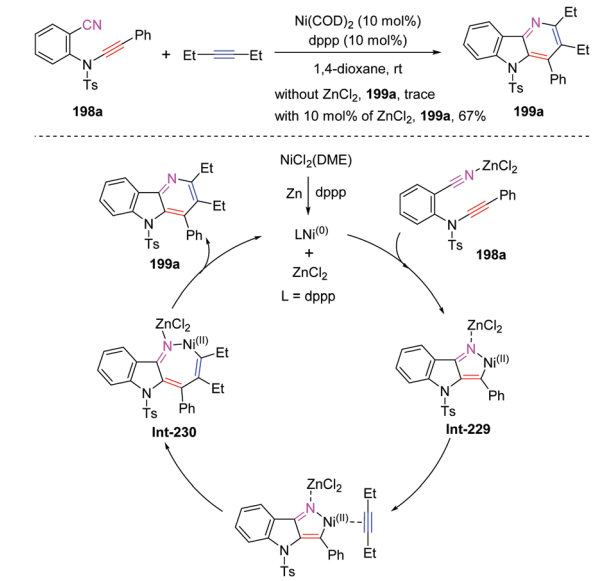
Scheme 90 Cobalt-catalyzed [5+2] annulation of ynamides with *o*-vinylphenols.



Scheme 91 Cobalt-catalyzed [3+2] annulation of ynamides with *o*-vinylphenols.



Scheme 92 Nickel-catalyzed [2+2+2] annulation of nitrile-ynamides and alkynes.



Scheme 93 Nickel-catalyzed [2+2+2] annulation of nitrile-ynamides with alkynes.

Surprisingly, when substituted vinylphenols **196** were engaged in the reaction, dearomative [3+2] spiroannulation took place, giving rise to amino-spiro[4,5]decanes **197** with high regioselectivity (Scheme 91).[124] Only alkyl-substituted ynamides were amenable to the transformation. The substituents in R^1 may increase the strain of the eight-membered cobaltacycle **Int-227**, which tends to isomerize to a six-membered cobaltacycle **Int-228**. Subsequent reductive elimination yields the product and further oxidation of the resulting Co(I) regenerates the catalyst.

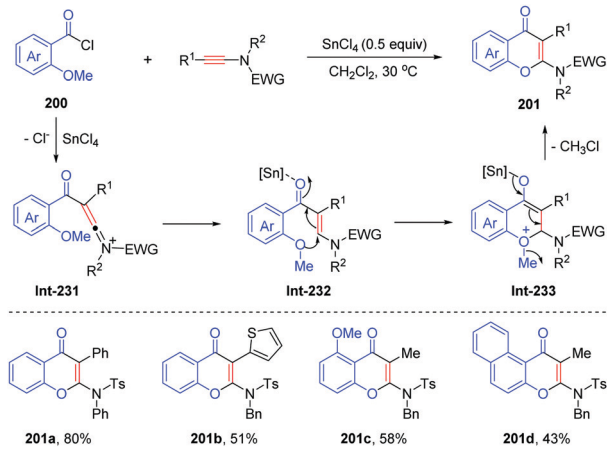
11. Nickel catalysis

In 2017, Liu and co-workers presented a nickel-catalyzed [2+2+2] annulation of nitrile-ynamides **198** and alkynes for the elaboration of δ-carbolines **199** (Scheme 92).[125] A combination of $NiCl_2$(DME), dppp and Zn proved to be the optimal catalytic system. The alkyl and aryl substituted ynamides were all compatible with the protocol. A mixture of regioisomers was obtained for the unsymmetrical internal alkynes (**199g** and **h**). In comparison, the annulation of terminal alkynes led to the desired products with moderate to high regioselectivity (**199i–k**). The reaction did not occur in the presence of $Ni(COD)_2$ and dppp, whereas the addition of Zn to the system could efficiently furnish the target adduct, suggesting that *in situ*-generated $ZnCl_2$ plays a crucial role as a Lewis acid in the process. Mechanistically (Scheme 93), the reduction of $NiCl_2$(DME) with Zn forms the active Ni(0) species and $ZnCl_2$. The nitrile moiety may be activated by $ZnCl_2$, followed by an oxidative cyclization with Ni(0) to yield the nickelacycle complex **Int-229**. Finally, migratory insertion of the alkyne into the Ni–C bond and reductive elimination produce the δ-carboline.

12. Lewis acid catalysis

12.1 Stannum catalysis

Chang and Wang *et al.*, in 2015, documented an $SnCl_4$-catalyzed [4+2] annulation of ynamides and 2-methoxybenzoyl chlorides

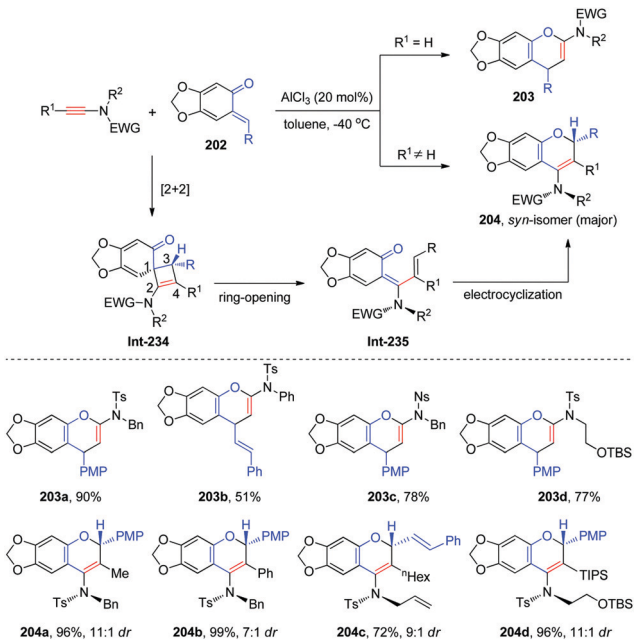


Scheme 94 Stannum-catalyzed [4+2] annulation of ynamides with 2-methoxybenzoyl chlorides.

200 for the assembly of 2-aminochromones **201** (Scheme 94).[126] Both aryl and alkyl substituents on the ynamide were applicable to the transformation. In the presence of $SnCl_4$, a nucleophilic attack of the ynamide on benzoyl chloride *via* Friedel–Crafts type acylation forms the keteniminium ion **Int-231**. Subsequent Michael-type addition of the methoxy group affords six-membered ring intermediate **Int-233**, followed by release of CH_3Cl to yield the product.

12.2 Aluminium catalysis

Later, the same group described that *o*-quinone methides **202** could serve as four-atom building units in the $AlCl_3$-catalyzed annulation of ynamides (Scheme 95).[127] When terminal ynamides were engaged in the reaction, formal Diels–Alder cycloadducts



Scheme 95 Aluminium-catalyzed [4+2] annulation of ynamides with *o*-quinone methides.

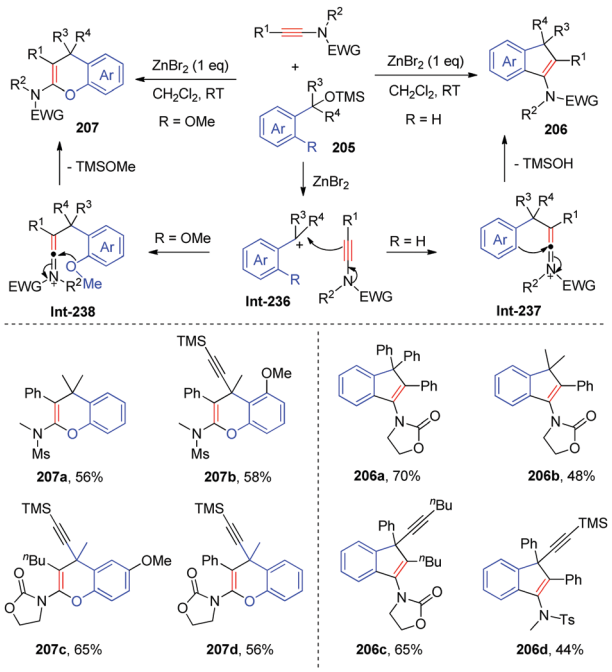
2-amino-chromenes **203** were obtained. In comparison, the chemoselectivity was altered to 4-amino-chromenes **204** when using internal ynamides as substrates and, notably, the diastereoselectivity was also well controlled. The sequence consisting of formal [2+2] cycloaddition, ring-opening and 6π-electrocyclization leads to the formation of **204**.

12.3 Zinc catalysis

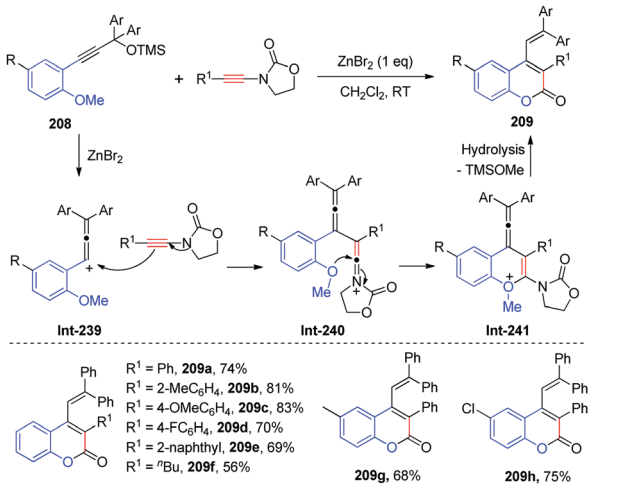
Cao and Xu *et al.*, in 2016, documented a zinc-promoted annulation between ynamides and benzyl silyl ethers **208**, whose selectivity could be diverted by varying the substituent (Scheme 96).[128] Treatment of unsubstituted benzyl silyl ethers (R = H) with ynamides and $ZnBr_2$ led to the formation of the [3+2] adducts amino-indenes **206**. In the case of *o*-methoxybenzyl silyl ethers, [4+2] annulation took place, delivering 2-amino-chromenes **207** with high selectivity. Both transformations start with the formation of benzyl carbocation species **Int-236** from benzyl silyl ether, followed by nucleophilic attack of the ynamide to generate keteniminium ions **Int-237** and **Int-238**. Ultimate capture by the aryl ring and methoxyl group yields the [3+2] and [4+2] adduct, respectively.

They also found that when *o*-anisole-substituted propargyl silyl ethers **208** were employed as substrates, a range of 4-vinyl-coumarins **209** were readily obtained (Scheme 97).[129] In this process, the allenyl carbocation species **Int-239**, generated from propargyl silyl ethers with the assistance of $ZnBr_2$, is trapped by the ynamide, followed by ring-closure and hydrolysis to furnish the target product.

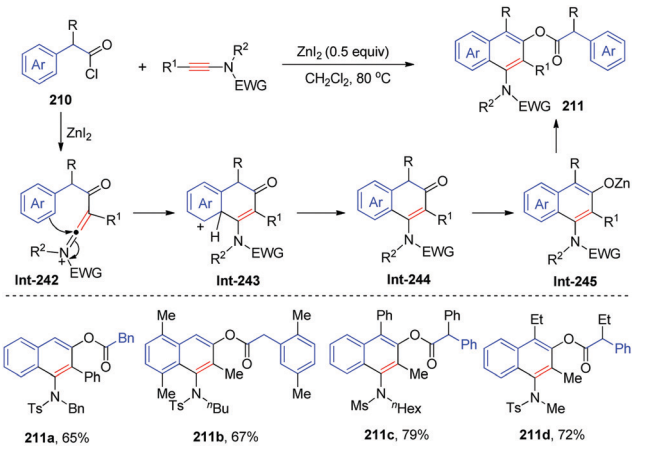
Chang and Wang *et al.* presented that ZnI_2 could promote the annulation of acyl chlorides **210** and ynamides to prepare 2-naphthol derivatives **211** (Scheme 98).[116] The mechanism involves the generation of keteniminium ion **Int-242** *via* acylation



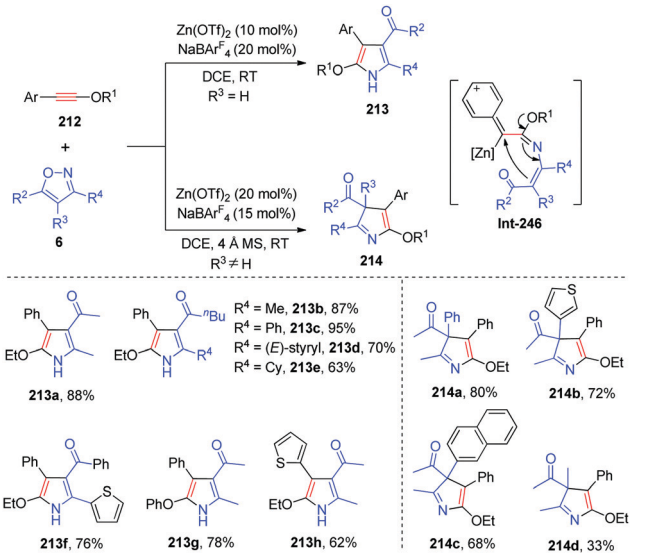
Scheme 96 Zinc-catalyzed [3+2] *versus* [4+2] annulation between benzyl silyl ethers and ynamides.



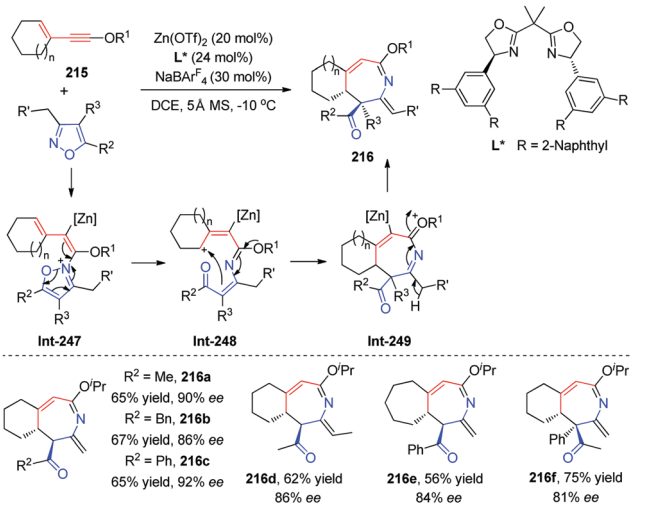
Scheme 97 Zinc-catalyzed [4+2] annulation between propargyl silyl ethers and ynamides.



Scheme 98 Zinc-catalyzed [4+2] annulation between acyl chlorides and ynamides.



Scheme 99 Zinc-catalyzed [3+2] annulation between ynol ethers and isoxazoles.



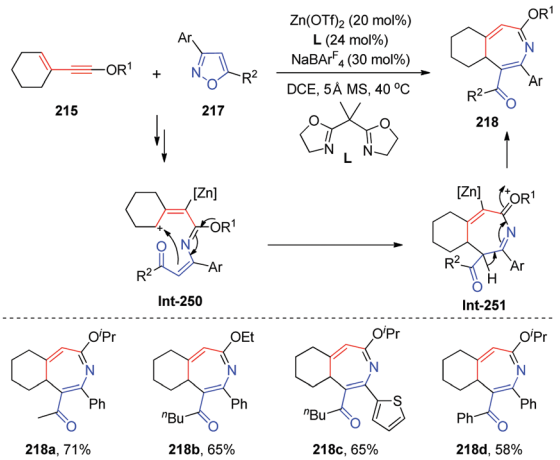
Scheme 100 Enantioselective zinc-catalyzed [4+3] annulation of enynol ethers with isoxazoles.

of the ynamide, nucleophilic attack of the aryl ring, and aromatization.

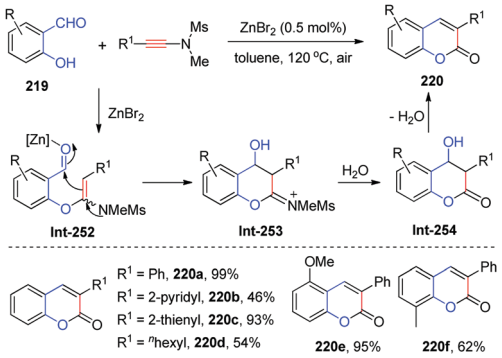
Distinct from their previous platinum catalysis (Scheme 86), Ye's group discovered that a combination of $Zn(OTf)_2$ and $NaBAr^F_4$ could alter the annulation of ynol ethers **212** with isoxazoles to a [3+2] pathway (Scheme 99).[130] The employment of 3,5-disubstituted isoxazoles as substrates resulted in the formation of 2-alkoxyl 1*H*-pyrroles **213**, while trisubstituted isoxazoles switched the selectivity to 3*H*-pyrroles **214**. DFT calculations suggested that the N–O bond cleavage of the isoxazole is trigged by the electron delocalization of the aryl ring, leading to the formation of vinyl carbocation intermediate **Int-246**.

Based on this work, more recently, they developed an elegant asymmetric zinc-catalyzed [4+3] annulation between enynol ethers **215** and isoxazoles (Scheme 100).[131] By employing bulky 2-naphthyl substituted chiral bisoxazoline as a ligand, a set of fused 2*H*-azepines **216** was obtained in acceptable to good enantioselectivities. It is proposed that the N–O bond cleavage of the isoxazole generates vinyl-stabilized carbocation intermediate **Int-248**, which can also be regarded as a heptatrienyl-cation. Finally, an enantioselective 6π electrocyclization of **Int-248** yields the product. When aryl-substituted isoxazoles **217** were used as coupling partners, the chemoselectivity was switched to fused 4*H*-azepines **218** (Scheme 101).

Youn and co-workers reported an expedient approach to access coumarins **220** from ynamides and salicylaldehydes **219** *via* zinc catalysis (Scheme 102).[132] A wide range of alkyl and aryl substituents on the ynamides were well compatible with the reaction. A nucleophilic addition of the phenol oxygen to the zinc-activated ynamide gives an enamine intermediate **Int-252**, followed by ring-closure to form a six-membered iminium ion **Int-253**. Eventually, hydrolysis and dehydration produce the coumarin.



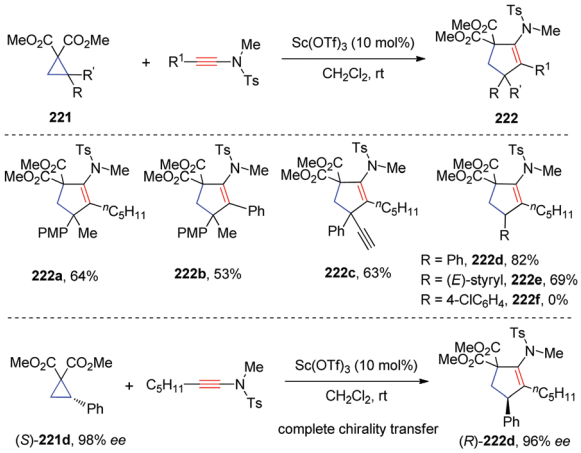
Scheme 101 Zinc-catalyzed [4+3] annulation of enynol ethers with isoxazoles.



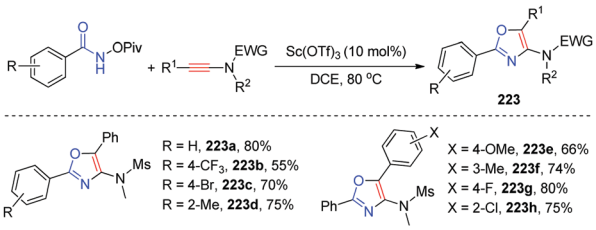
Scheme 102 Zinc-catalyzed [4+2] annulation of salicylaldehydes with ynamides.

12.4 Scandium catalysis

In 2014, Johnson *et al.* first employed donor–acceptor cyclopropanes **221** as coupling partners in the annulation of ynamides (Scheme 103).[133] The reaction proceeded well in the presence of



Scheme 103 Scandium-catalyzed [3+2] annulation of ynamides with donor–acceptor cyclopropanes.



Scheme 104 Scandium-catalyzed [3+2] annulation of ynamides with *N*-(pivaloyloxy)benzamides.

Lewis acid $Sc(OTf)_3$, resulting in the formation of multi-substituted amino-cyclopentenes **222** with exclusive regioselectivity. The electron-withdrawing group on the phenyl ring of cyclopropane totally suppressed the annulation (**222f**). Notably, treatment of the enantioenriched cyclopropane (*S*)-**221d** with the standard conditions furnished the target product with complete inversion of the stereocenter and no significant erosion of ee, thus suggesting that the annulation proceeds in a stereospecific manner.

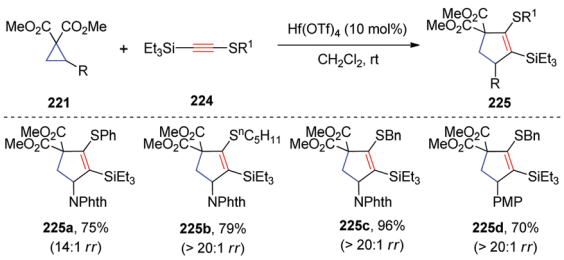
Besides Rh(III) and Co(III) catalysis (Schemes 75 and 88), Lewis acid $Sc(OTf)_3$ could also promote the annulation of *N*-(pivaloyloxy)-benzamides with ynamides, furnishing [3+2] adducts 4-amino-oxazoles **223** (Scheme 104).[107] The steric and electronic factors of the substituents on the phenyl ring had a negligible impact on the results.

12.5 Hafnium catalysis

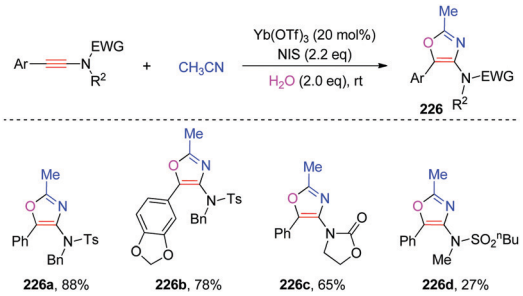
Waser's group discovered that silyl thioalkynes **224** could undergo [3+2] annulation with donor–acceptor cyclopropanes as well in the presence of Lewis acid $Hf(OTf)_4$ (Scheme 105).[134] The bulky silyl group proved to be essential for achieving high regioselectivity. The electron-donating phthalimide and PMP on the cyclopropane gave good results.

12.6 Ytterbium catalysis

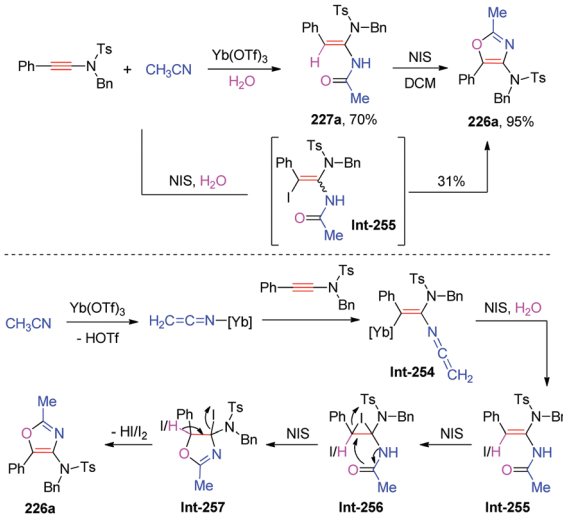
Sahoo's group, in 2017, developed a mild alternative for the synthesis of 4-aminooxazoles *via* a three-component coupling of ynamides, acetonitrile, and water promoted by $Yb(OTf)_3$ and NIS (Scheme 106).[135] The aryl substituted ynamides were well compatible with the procedure. The control experiments revealed that the process is initiated by iodo- or hydro-amidation of the ynamide with acetonitrile (**Int-255**) (Scheme 107). Then, NIS-promoted cyclization and aromatization afford the product.



Scheme 105 Hafnium-catalyzed [3+2] annulation of thioalkynes with donor–acceptor cyclopropanes.



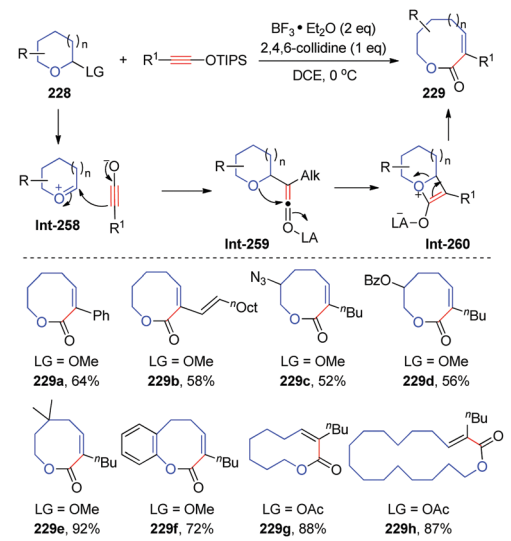
Scheme 106 Ytterbium-catalyzed [2+2+1] annulation of ynamides and acetonitrile with water.



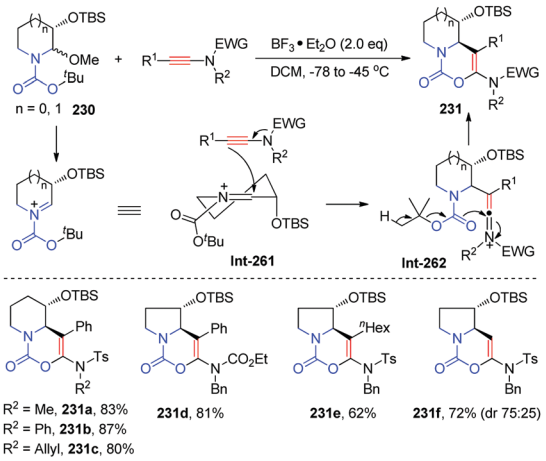
Scheme 107 Ytterbium-catalyzed [2+2+1] annulation of ynamides and acetonitrile with water.

11.7 Boron catalysis

Sun *et al.*, in 2013, developed a novel ring-expansion strategy to assemble medium ring lactones **229** from siloxy alkynes and cyclic acetals **228** (Scheme 108).[136] In the presence of $BF_3{\cdot}Et_2O$,



Scheme 108 BF_3-promoted annulation of siloxy alkynes with cyclic acetals.

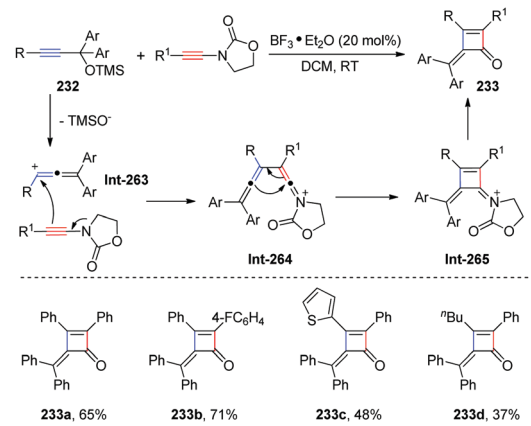


Scheme 109 BF_3-promoted [4+2] annulation of ynamides with cyclic *N,O*-acetals.

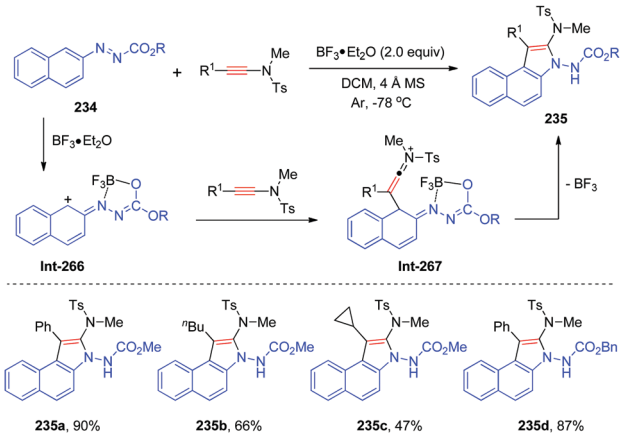
a cyclic oxocarbenium ion **Int-258** is first generated from cyclic acetal *via* releasing the leaving group. **Int-258** further undergoes [2+2] annulation with siloxy alkyne to yield the active oxetenium species **Int-260**. Eventually, ring-expansion and desilylation afford the desired product. It is believed that 2,4,6-collidine can stabilize the oxocarbenium ion **Int-258** through the formation of a pyridinium adduct, which still maintains sufficient reactivity for the subsequent process.

Lewis acid $BF_3{\cdot}Et_2O$ could also promote the annulation of cyclic *N,O*-acetals with ynamides, leading to the formation of [4+2] adducts pyrido- or pyrrolo[1,2-*c*][1,3]oxazines **231** (Scheme 109).[137] The approach features wide functional group tolerance and good regio- and diastereoselectivities. The mechanism consists of the generation of cyclic iminium ion intermediate **Int-261**, nucleophilic addition of the ynamide, and ring-closure. Recently, it was discovered that cyclic *N,O*-hemiacetals and ynamides could also undergo the same annulation but with gold catalysis.[138]

Cao and Xu *et al.* uncovered a mild methodology for the construction of functionalized cyclobutenones **233** *via* a BF_3-catalyzed [2+2] annulation of propargyl silyl ethers and ynamides (Scheme 110).[139] The process starts with the



Scheme 110 BF_3-catalyzed [2+2] annulation of propargyl silyl ethers with ynamides.



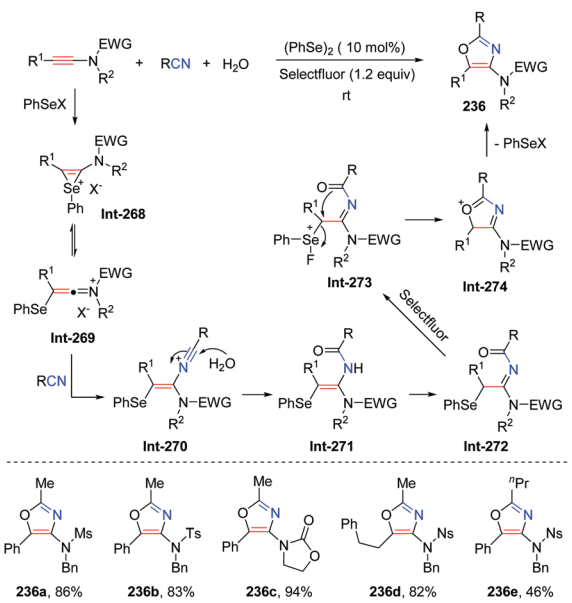
Scheme 111 BF_3-promoted [3+2] annulation of ynamides with azonaphthalenes.

formation of allenyl carbocation intermediate **Int-263** from propargyl silyl ether, followed by nucleophilic attack of the ynamide, ring-closure and hydrolysis to deliver the adduct.

Cui and co-workers reported that in the presence of $BF_3{\cdot}Et_2O$, azonaphthalenes **234** could react with ynamides to synthesize *N*-substituted benzoindoles **235** *via* [3+2] annulation (Scheme 111).[140] Initially, azonaphthalenes are activated by $BF_3{\cdot}Et_2O$ to facilitate the attack of ynamides on the naphthalene ring, resulting in the formation of species **Int-267**. Subsequent ring-closure and release of $BF_3{\cdot}Et_2O$ yield the expected products.

12.8 Selenium catalysis

In 2018, the group of Zhao unveiled an interesting selenium-catalyzed [2+2+1] annulation of ynamides, nitriles and water, which offers another alternative for the synthesis of 4-aminooxazoles (Scheme 112).[141] The additive selectfluor is critical for the efficiency of the transformation. The ynamide is first activated by selenium-π-acid to generate selenirenium ion **Int-268**, which is a resonance form of keteniminium ion **Int-269**. Subsequent nucleophilic attack of nitrile and hydrolysis furnish enamide **Int-271**, which can be tautomerized to imine **Int-272**. A further oxidation with selectfluor delivers species **Int-273**, followed by an S_N2 substitution of the selenium group with the oxygen atom and isomerization to yield the final product **236**.



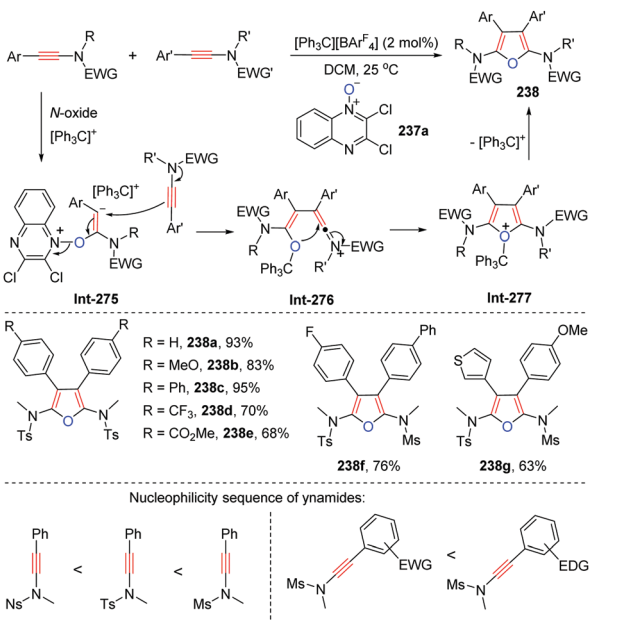
Scheme 112 Selenium-catalyzed [2+2+1] annulation of nitriles, ynamides and water.

12.9 Carbocation catalysis

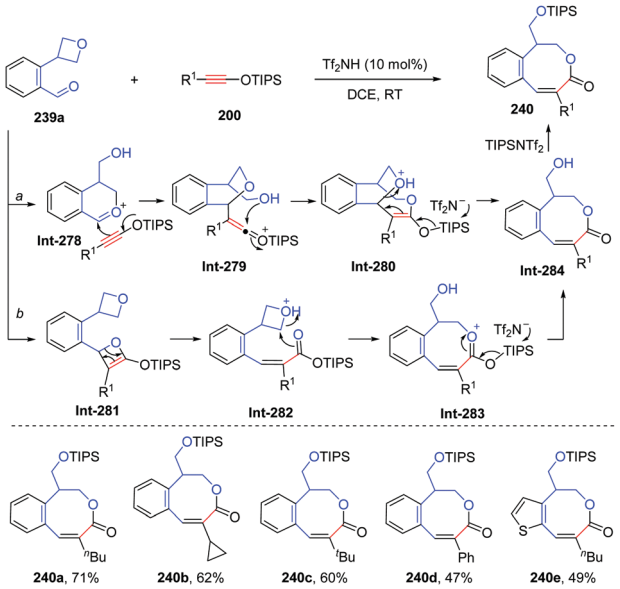
Recently, Hashmi's group documented a highly efficient [2+2+1] annulation between 2,3-dichloroquinoxaline *N*-oxide **237a** and ynamides with carbocation catalysis (Scheme 113).[142] The less nucleophilic 2,3-dichloroquinoxaline *N*-oxide **237a**, which could prevent the overoxidation of the ynamides, gave the best result. A wide variety of symmetrical furans were prepared *via* this strategy, but the electron-deficient ynamides gave slightly decreased yields (**238d** and **e**). Gratifyingly, unsymmetrical furans could also be afforded by tuning the ratio of two different ynamides. Based on the nucleophilicity difference, the less nucleophilic ynamide (*e.g.* 4-fluorophenyl ynamide for **238f**; 3-thienyl ynamide for **238g**) needs to be in 3 fold excess of the other one. The polarized triple bond is first activated by Ph_3C^+ to facilitate the *O*-attack of *N*-oxide, followed by nucleophilic addition of another ynamide to afford keteniminium ion species **Int-276**. A final ring closure gives rise to the product with the regeneration of the carbocation catalyst.

13. Brønsted acid catalysis

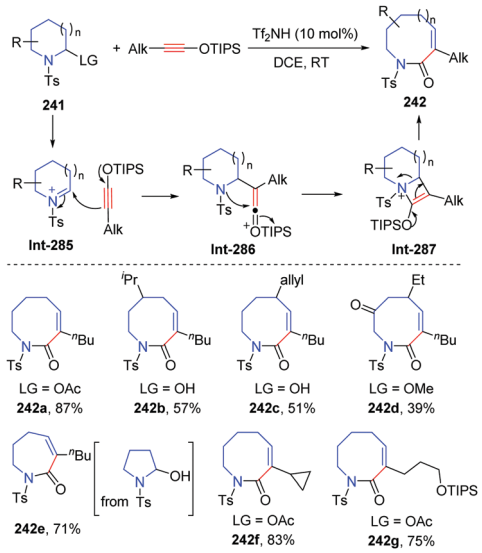
In 2012, Sun and co-workers designed a new type of amphoteric molecule featuring a benzene-tethered oxetane ring and aldehyde



Scheme 113 Carbocation-catalyzed [2+2+1] annulation of *N*-oxides with ynamides.



Scheme 114 Tf_2NH-catalyzed [6+2] annulation of siloxy alkynes with oxetane aldehyde.

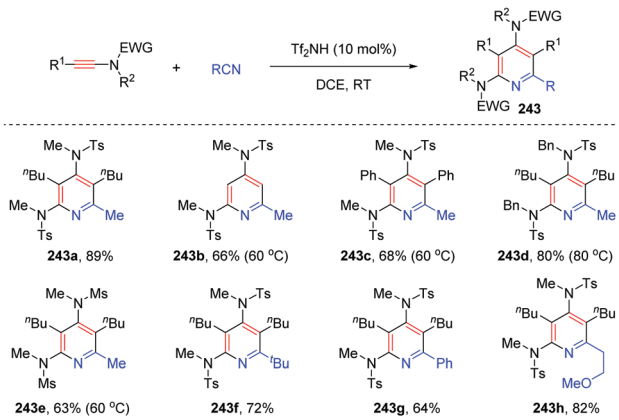


Scheme 115 Tf_2NH-catalyzed [6+2] annulation of siloxy alkynes with cyclic *N,O*-acetals.

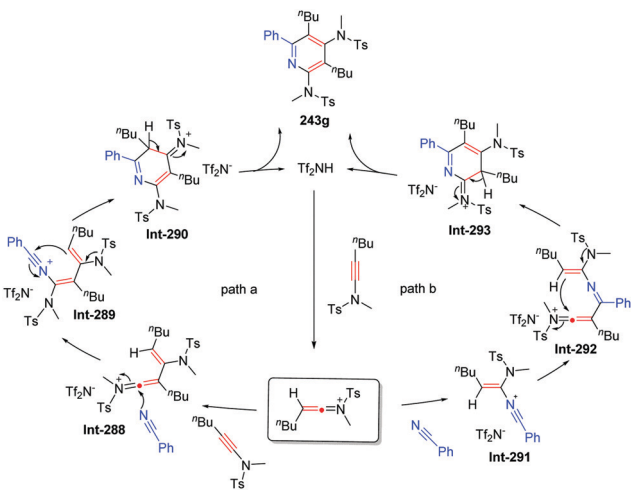
group (**239a**), which could act as a six-atom building unit in the Tf_2NH-catalyzed reaction of siloxy alkynes (Scheme 114).[143] Both alkyl and aryl substituents on the alkyne terminus were amenable to the conversion, delivering eight-membered lactones in acceptable yields. The strong acid Tf_2NH can promote the attack of the aldehyde on the oxetane ring, resulting in the formation of cyclic oxonium species **Int-278** (path a). A subsequent nucleophilic addition of siloxy alkyne gives rise to the ketene intermediate **Int-279**, which is trapped by the hydroxyl group to produce *O*-bridged eight-membered ring **Int-280**. Then, acid-catalyzed ring-opening and silylation yield the product. It is worthwhile to mention that the sequence comprising [2+2] annulation between the aldehyde and siloxy alkyne, ring-opening of the formed oxetene, and acid-promoted ring-closure is another possibility (path b).

Later, the scope of the protocol was successfully extended to cyclic *N,O*-acetals **241**, providing a flexible strategy to access eight-membered lactams (Scheme 115).[144] Alkyl-substituted alkynes were well compatible with the transformation. A stepwise [2+2] annulation between siloxy alkyne and the formed iminium ion produces the azetidinium species **Int-287**, followed by ring-expansion and desilylation to result in the target product.

In 2016, the same group realized a metal-free [2+2+2] annulation between ynamides and nitriles with acid catalysis, providing a complementary method to construct aminopyridines (Scheme 116).[145] While attaining the same chemoselectivity as gold catalysis (Scheme 46), the salient features of this strategy include mild reaction conditions, broad functional group compatibility, excellent regiocontrol, and low cost of the catalyst. Two possible pathways were proposed (Scheme 117). The active keteniminium ion, generated by the protonation of the ynamide, can be trapped by another ynamide to afford vinyl keteniminium ion **Int-288** (path a). The following nucleophilic



Scheme 116 Tf_2NH-catalyzed [2+2+2] annulation of ynamides and nitriles.



Scheme 117 Tf_2NH-catalyzed [2+2+2] annulation of ynamides and nitriles.

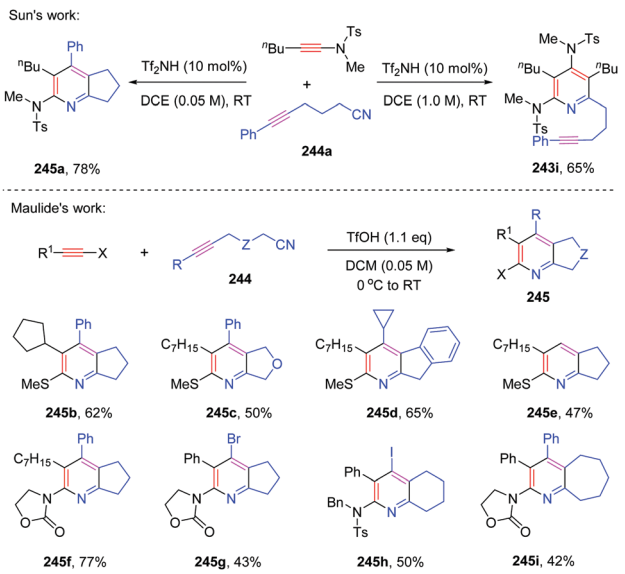
addition of the nitrile, ring-closure and aromatization deliver the product with regenerating the catalyst. Alternatively, the keteniminium ion is likely first attacked by the nitrile, and then reacts with another ynamide, followed by ring-closure and aromatization to form the pyridine (path b). DFT calculations indicated that path a is kinetically more favorable than path b. It is worth noting that Lewis acid TMSOTf could also catalyze this trimolecular assembly of pyridines.[146]

Of note was the annulation of 5-hexynenitrile **244a** and ynamides, whose chemoselectivity could be controlled by the concentration (Scheme 118).[145] The expected trimolecular annulation occurred at a high concentration. Surprisingly, at a lower concentration, the alkyne of 5-hexynenitrile itself could serve as a coupling partner as well, thus leading to bicyclic pyridine **245a** *via* a bimolecular [2+2+2] annulation process. Independently, such a transformation was studied in-depth by Maulide *et al.* and they found that besides ynamides, thioalkynes were suitable substrates as well (Scheme 118).[147]

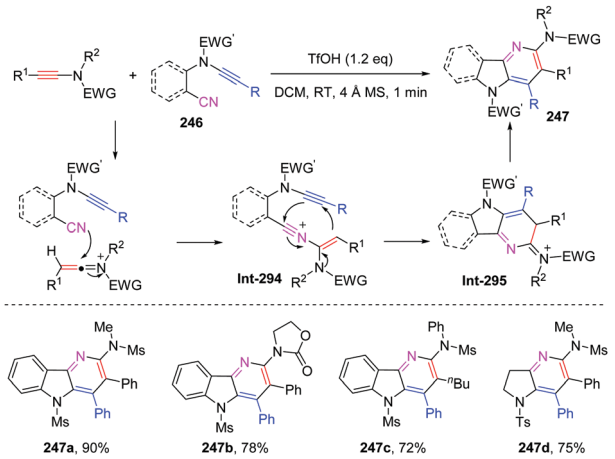
Later, Chen and Tang *et al.* extended the scope to nitrile-ynamides **246**, which could be efficiently coupled with ynamides to elaborate δ-carbolines **247** *via* a bimolecular [2+2+2] annulation (Scheme 119).[148] A variety of alkyl and aryl-derived ynamides were suitable in the process, and, notably, most of the reactions completed within 1 min. The formed keteniminium ion is trapped by the nitrile motif, followed by ring-closure and aromatization to yield the product.

Recently, by employing TMSOTf as a catalyst, the same transformation was accomplished by Wang and Chang *et al.* (Scheme 120).[149] Additionally, the treatment of alkyne-cyanamides **250** with the standard conditions led to α-carbolines **251.** The terminal and internal substrates were amenable to both reactions. It is proposed that the coordination between TMSOTf and the sulfonyl group facilitates the nucleophilic attack of nitrile in a regioselective manner (Scheme 121). But it would be hard to rule out the formation of a small amount of TfOH in this reaction from TMSOTf hydrolysis.

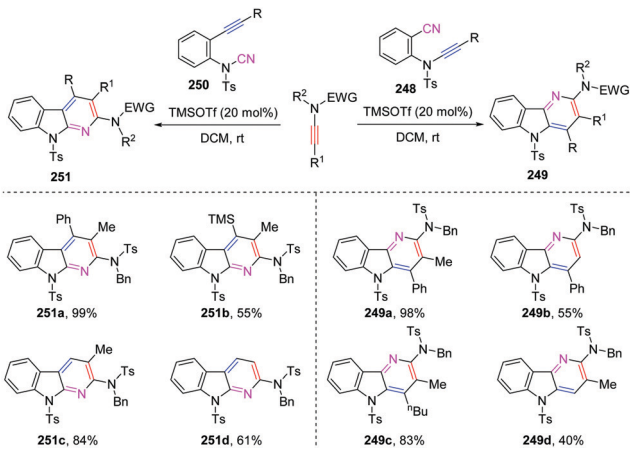
Maulide's group discovered that in the presence of TfOH, aryl-substituted ynamides and nitriles could undergo divergent annulations by varying the concentration (Schemes 122 and 123).[150] Submitting equimolar amounts of two substrates to dichloroethane



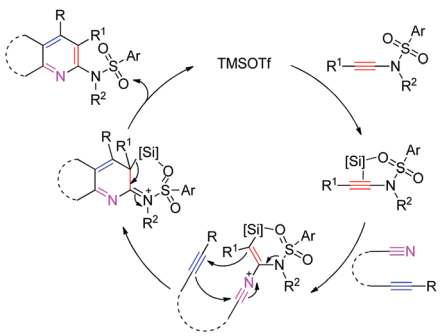
Scheme 118 Tf_2NH- and TfOH-promoted bimolecular [2+2+2] annulation of nitrile-alkynes with ynamides or thioalkynes.



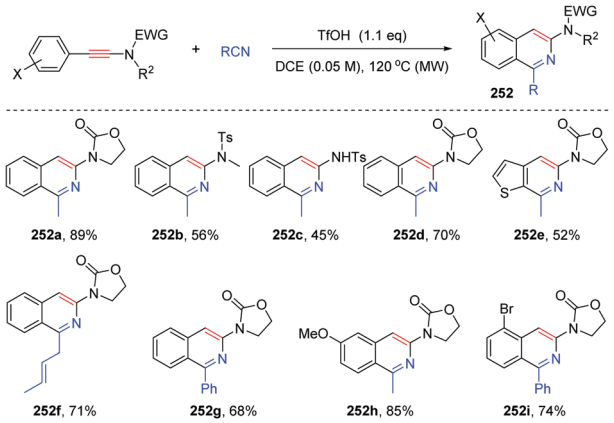
Scheme 119 TfOH-promoted bimolecular [2+2+2] annulation of nitrile-ynamides with ynamides.



Scheme 120 TMSOTf-catalyzed bimolecular [2+2+2] annulation of nitrile-ynamides with ynamides.



Scheme 121 TMSOTf-catalyzed bimolecular [2+2+2] annulation of nitrile-ynamides with ynamides.

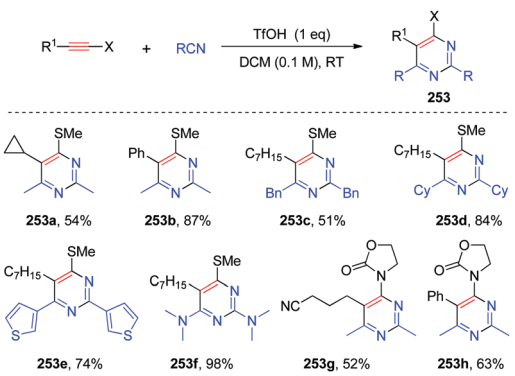


Scheme 122 TfOH-promoted [4+2] annulation of ynamides with nitriles.

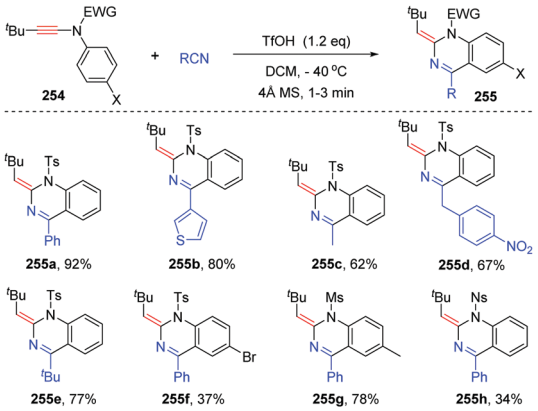
(0.05 M) at 120 °C resulted in the formation of [4+2] adducts isoquinolines **252** with good regiocontrol (Scheme 122). Even in the case of the 3-OMe substituted ynamide, only one isomer was afforded (**252h**). In comparison, when the reaction was conducted in acetonitrile (0.1 M) or dichloromethane (0.1 M), [2+2+2] annulation of nitriles with ynamides preferably took place, providing aminopyrimidines **253** in acceptable yields (Scheme 123). This reaction displays the same chemoselectivity as Liu's gold catalysis (Scheme 44). Notably, thioalkynes were amenable to the trimolecular process as well. Independently, this [2+2+2] annulation was also reported by Tang *et al.*, in which diverse *N*-sulfonyl ynamides were employed as reactants.[151]

Following a similar process, Chen and Tang *et al.* described that when *N*-aryl ynamides **254** were used as substrates, [4+2] annulation also occurred in the presence of TfOH but various dihydroquinazolines **255** were afforded (Scheme 124).[152] The bulky ^{t}Bu on the ynamide terminus is responsible for the exclusive formation of (*Z*)-enamide products due to facially selective attack on the intermediate keteneiminium ion. An array of (hetero)aryl and alkyl nitriles were applicable to this method.

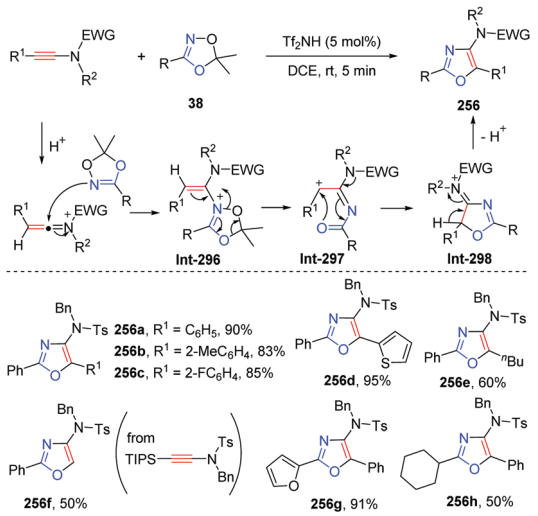
In 2017, our group employed strong acid Tf_2NH to catalyze the coupling of ynamides with dioxazoles, resulting in the formation of [3+2] adducts 4-aminooxazoles **256** (Scheme 125).[153] This metal-free protocol features a broad substrate scope, mild reaction



Scheme 123 TfOH-promoted [2+2+2] annulation of ynamides or thioalkynes with nitriles.



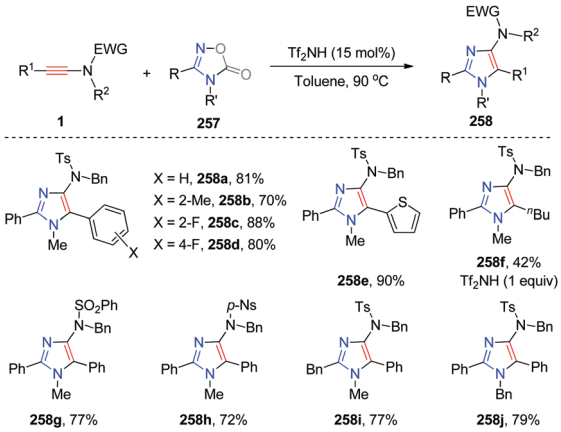
Scheme 124 TfOH-promoted [4+2] annulation of *N*-aryl ynamides with nitriles.



Scheme 125 Tf_2NH-catalyzed [3+2] annulation of ynamides with dioxazoles.

conditions, a very short reaction time (5 min), and low catalyst cost. Of note was the reaction of TIPS-derived ynamide, which resulted in a desilylated product (**256f**). While obtaining the same chemoselectivity as Liu's gold catalysis (Scheme 13), this methodology can serve as an economical alternative for the assembly of oxazoles. The process commences with the formation of the keteniminium ion, which is captured by the nitrogen atom of the dioxazole to obtain enamine **Int-296**. A subsequent N–O bond cleavage generates α-imino carbocation intermediate **Int-297** accompanied by the elimination of acetone. Finally, intramolecular cyclization and aromatization deliver the target product and regenerate the acid catalyst. This cationic-type mechanism was supported by the fact that the annulation of aryl-substituted ynamides gave higher yields (**256a–d**) than that of alkyl substrates (**256e** and **f**), because the formed benzyl carbocation intermediates (**Int-297**) are more stable than the alkyl ones.

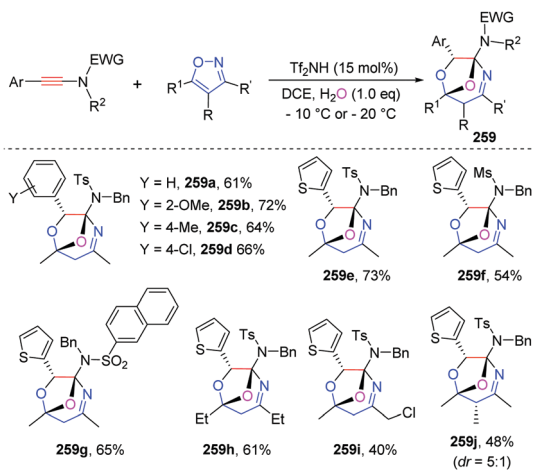
Analogously, oxadiazolones **257** could act as efficient three-atom building units in Tf_2NH-catalyzed annulation of ynamides, enabling a flexible synthesis of amino-imidazoles **258** (Scheme 126).[154] The protecting group on the nitrogen atom of oxadiazolone proved



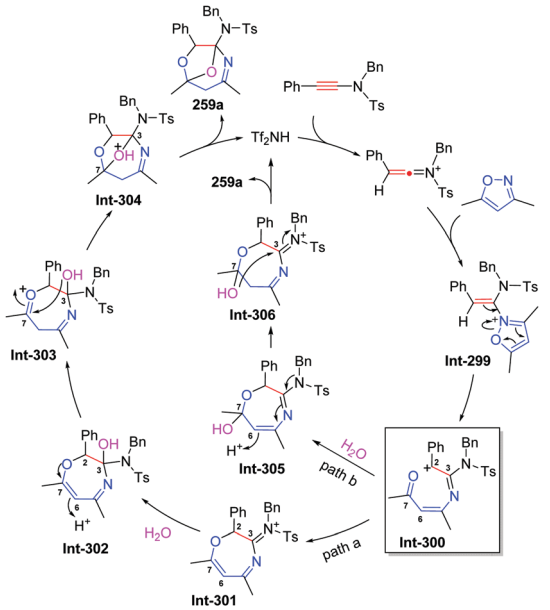
Scheme 126 Tf_2NH-catalyzed [3+2] annulation of ynamides with oxadiazolones.

to be essential for the efficiency of the annulation because, when free NH oxadiazolone was engaged in the reaction, the formed NH imidazole would further undergo addition with the ynamide in the presence of an acid.

The above-mentioned acid-catalyzed annulations of ynamides usually led to the same chemoselectivity as gold catalysis. Therefore, developing new acid systems that can show distinct reactivity from gold catalysis is highly appealing. To this end, we found that isoxazoles and ynamides preferably underwent [5+2+1] annulation with water, instead of the previous [3+2] annulation in gold catalysis (Scheme 3) and [5+2] annulation in platinum catalysis (Scheme 85), providing expeditious entry to oxygen-bridged tetrahydro-1,4-oxazepines **259** (Scheme 127).[155] More recently, theoretical studies of these three catalytic systems (Pt, Au, and Tf_2NH), performed by Fang and Yang *et al.*, revealed that the unique nature of acid catalysts enables water to participate in the annulation.[156] Only aryl-derived ynamides were applicable to the conversion. The ^{18}O-labelling experiment illustrated that the pink oxygen atom originates from water. Mechanistically (Scheme 128), the key α-imino carbocation intermediate **Int-300**, formed by the N–O bond cleavage of isoxazole, can be trapped by



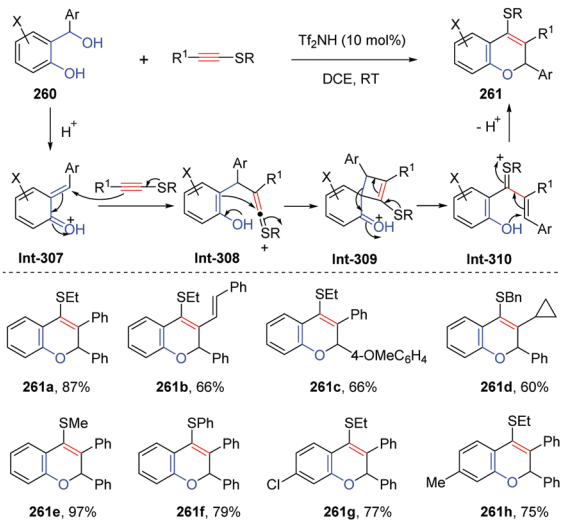
Scheme 127 Tf_2NH-catalyzed [5+2+1] annulation of ynamides and isoxazoles with water.



Scheme 128 Tf_2NH-catalyzed [5+2+1] annulation of ynamides and isoxazoles with water.

the carbonyl group to give seven-membered ring **Int-301** (path a). Subsequent addition of H_2O to the iminium ion and acid-catalyzed ketalization deliver the adduct. Alternatively, H_2O might attack the carbonyl group to promote the ring-closure of **Int-300**, followed by acid-catalyzed *N*,*O*-acetal formation to yield the target product (path b).

Very recently, a novel [4+2] annulation of thioalkynes and *o*-hydroxybenzyl alcohols **260** with Tf_2NH catalysis was documented by Ye and co-workers (Scheme 129).[157] This approach provides an expedient route to synthesize useful 2*H*-chromenes **261** in moderate to good yields under mild conditions. The reaction begins with the acid-promoted formation of active *o*-quinone methides **Int-307**, followed by Michael addition with



Scheme 129 Tf_2NH-catalyzed [4+2] annulation of thioalkynes with *o*-hydroxybenzyl alcohols.

Table 1 A summary of intermolecular annulations of ynamides

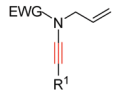
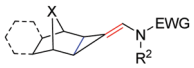
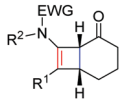
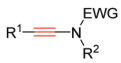
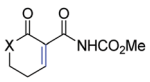
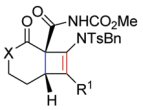
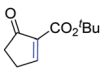
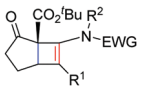
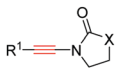
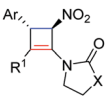
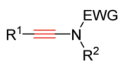
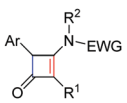
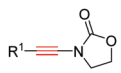
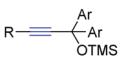
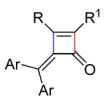
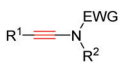
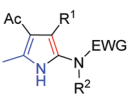
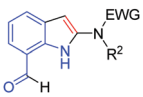
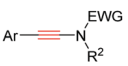
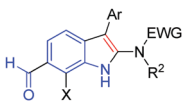
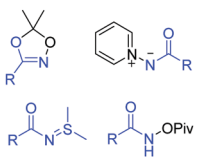
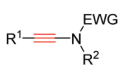
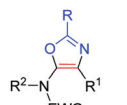
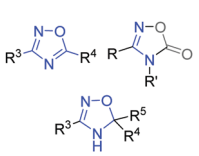
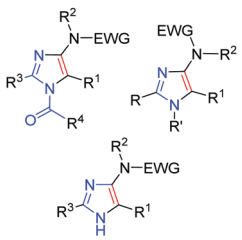
Annulation pattern	Ynamide	Coupling partner	Product	Catalyst
[2+1]				Au; Scheme 7 and ref. 23
				Pd; Scheme 81 and ref. 114
				Cu; Scheme 55 and ref. 77
				Cu; Scheme 57 and ref. 79
[2+2]				Cu, Ru; Schemes 56, 66 and ref. 78, 92
				Rh; Scheme 71 and ref. 99
				Pd; Scheme 82 and ref. 116
				BF_3; Scheme 110 and ref. 139
				Au; Schemes 3, 4 and ref. 16, 17
				Au; Scheme 6 and ref. 19
				Au; Scheme 9 and ref. 25
[3+2]			 4-aminooxazole	Au, Sc, Tf_2NH; Schemes 13, 16, 26, 104, 125 and ref. 29, 34, 35, 47, 107, 153
			 5-aminooxazole	Co; Scheme 88 and ref. 122
				Au, Tf_2NH; Schemes 14, 126 and ref. 30, 31, 154

Table 1 (*continued*)

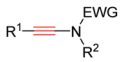
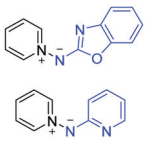
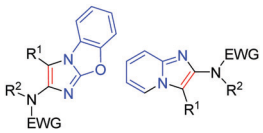
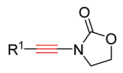
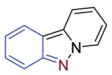
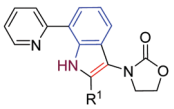
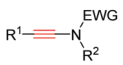
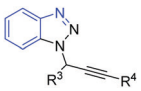
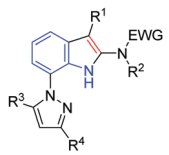
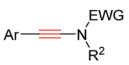
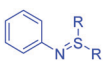
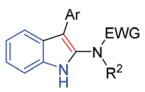
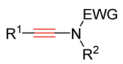
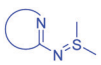
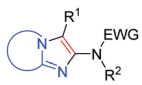
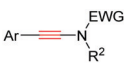
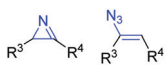
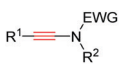
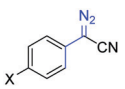
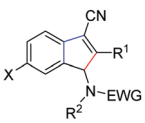
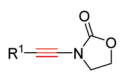
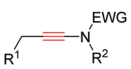
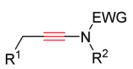
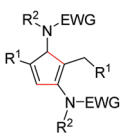
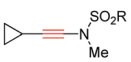
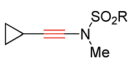
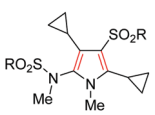
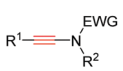
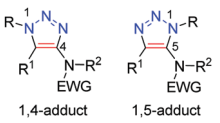
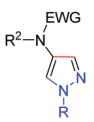
Annulation pattern	Ynamide	Coupling partner	Product	Catalyst
				Au; Scheme 15 and ref. 32, 33
				Au; Scheme 17 and ref. 36, 37
				Au; Scheme 22 and ref. 43
				Au; Scheme 23 and ref. 44
				Au; Scheme 24 and ref. 45
				Au; Scheme 25 and ref. 46
				Au; Scheme 31 and ref. 51
[3+2]				Au; Schemes 33, 34 and ref. 53–55
				Au; Scheme 37 and ref. 57
				Au; Scheme 38 and ref. 58
				Au; Scheme 40 and ref. 60
				Au; Scheme 41 and ref. 61
				Cu, Ru, Rh, Ir; Schemes 53, 54, 62, 63, 73, 77 and ref. 74, 75, 87–89, 101, 109
				Cu; Scheme 59 and ref. 81

Table 1 (*continued*)

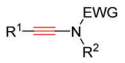
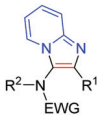
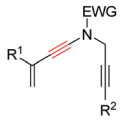
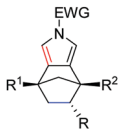
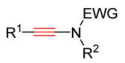
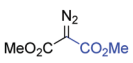
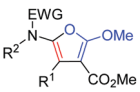
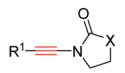
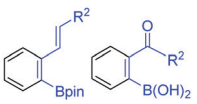
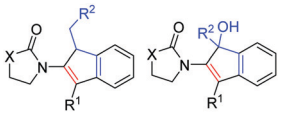
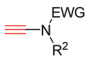
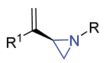
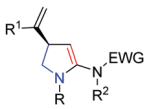
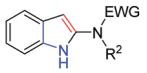
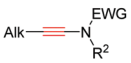
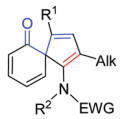
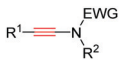
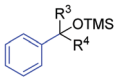
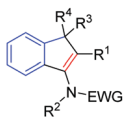
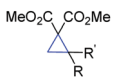
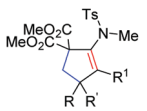
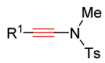
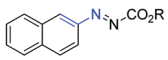
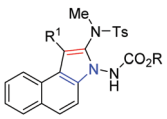
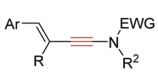
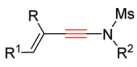
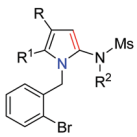
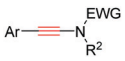
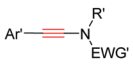
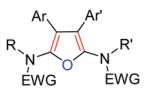
Annulation pattern	Ynamide	Coupling partner	Product	Catalyst
				Cu; Scheme 60 and ref. 82
				Cu; Scheme 61 and ref. 85
				Rh; Scheme 69 and ref. 97
				Rh; Scheme 70 and ref. 98
				Rh; Scheme 72 and ref. 100
				Pd; Scheme 78 and ref. 110
[3+2]				Co; Scheme 91 and ref. 124
				$ZnBr_2$; Scheme 96 and ref. 128
				$Sc(OTf)_3$; Scheme 103 and ref. 133
				$BF_3{\cdot}Et_2O$; Scheme 111 and ref. 140
				Au; Scheme 2 and ref. 15
[4+1]				Au; Scheme 21 and ref. 42
				$Yb(OTf)_3$, $(PhSe)_2$; and Schemes 106, 112 and ref. 135, 141
[2+2+1]				$[Ph_3C]^+$; Scheme 113 and ref. 142

Table 1 (*continued*)

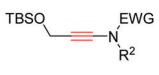
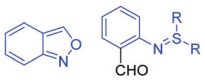
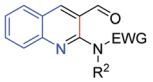
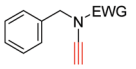
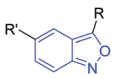
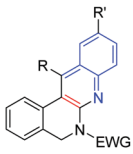
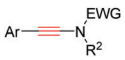
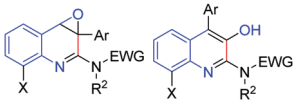
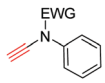
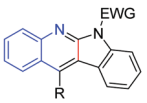
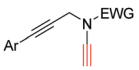
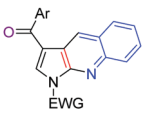
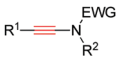
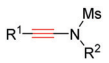
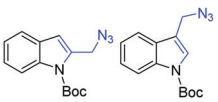
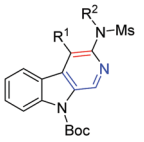
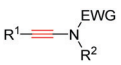
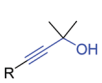
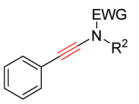
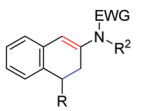
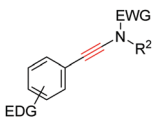
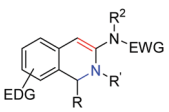
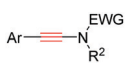
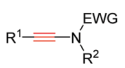
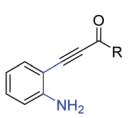
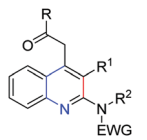
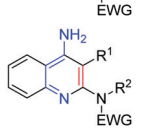
Annulation pattern	Ynamide	Coupling partner	Product	Catalyst
[4+2]				Au; Schemes 6, 24 and ref. 20, 45
				Au; Scheme 7 and ref. 21
				Au; Scheme 10 and ref. 25
				Au; Scheme 7 and ref. 22
				Au; Scheme 8 and ref. 24
				Au; Scheme 15 and ref. 33
				Au; Schemes 19, 20 and ref. 40, 41
				Au, Ag; Schemes 30, 51 and ref. 50
				Au; Scheme 32 and ref. 52
				Au; Scheme 42 and ref. 62
				Au; Scheme 43 and ref. 63
				Au; Scheme 47 and ref. 68
				Au; Scheme 48 and ref. 69
				Au; Scheme 49 and ref. 70

Table 1 (*continued*)

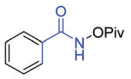
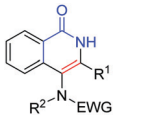
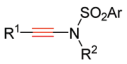
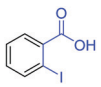
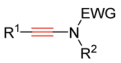
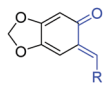
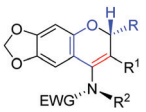
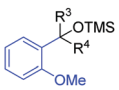
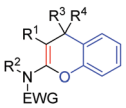
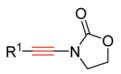
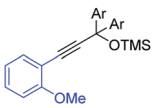
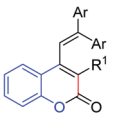
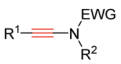
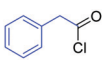
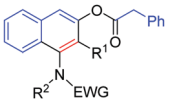
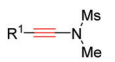
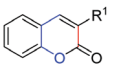
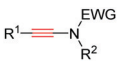
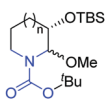
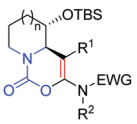
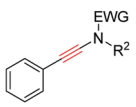
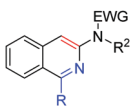
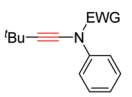
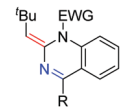
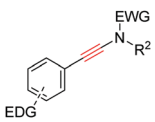
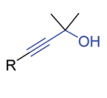
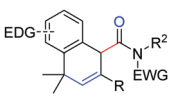
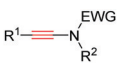
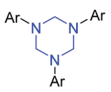
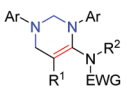
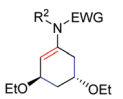
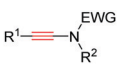
Annulation pattern	Ynamide	Coupling partner	Product	Catalyst
				Rh; Scheme 75 and ref. 107
				Pd; Scheme 79 and ref. 111
				$SnCl_4$; Scheme 94 and ref. 126
				$AlCl_3$; Scheme 95 and ref. 127
				$ZnBr_2$; Scheme 96 and ref. 128
				$ZnBr_2$; Scheme 97 and ref. 129
				ZnI_2; Scheme 98 and ref. 116
				$ZnBr_2$; Scheme 102 and ref. 132
				BF_3; Scheme 109 and ref. 137
				Au, TfOH; Schemes 45, 122 and ref. 66, 150
				TfOH; Scheme 124 and ref. 152
[3+3]				Au; Scheme 32 and ref. 52
				Au; Scheme 36 and ref. 56
[2+2+2]				Au; Scheme 42 and ref. 62
				Au, TfOH; Schemes 44, 123 and ref. 64, 65, 150, 151

Table 1 (*continued*)

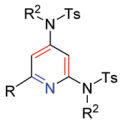
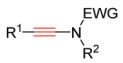
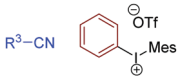
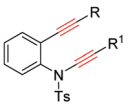
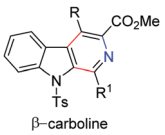
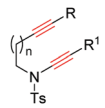
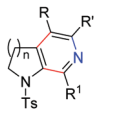
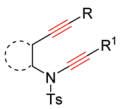
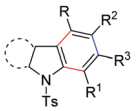
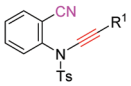
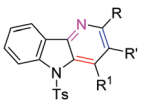
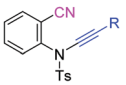
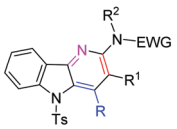
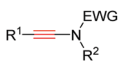
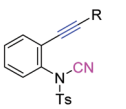
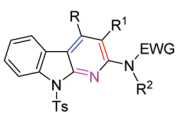
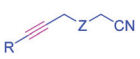
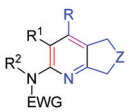
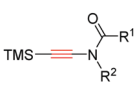
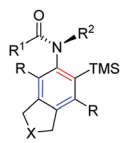
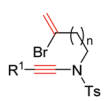
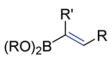
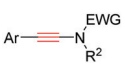
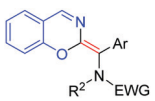
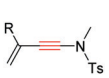
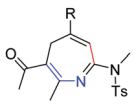
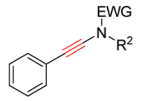
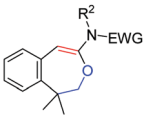
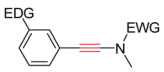
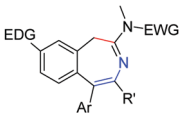
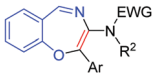
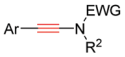
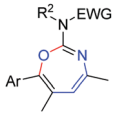
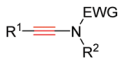
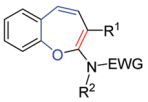
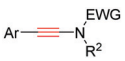
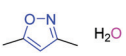
Annulation pattern	Ynamide	Coupling partner	Product	Catalyst
				Tf_2NH, TMSOTf; Scheme 116 and ref. 145, 146
				Au; Scheme 46 and ref. 67
				Cu; Scheme 58 and ref. 80
			 β–carboline	Ru; Scheme 65 and ref. 91
				Co; Scheme 87 and ref. 120, 121
				Rh; Scheme 67 and ref. 93–95
				Ni; Scheme 92 and ref. 125
				TfOH, TMSOTf; and Schemes 119, 120 and ref. 148, 149
				
[2+2+2]				Tf_2NH, TfOH; Scheme 118 and ref. 145, 147
				Rh; Scheme 68 and ref. 96
				Pd; Scheme 80 and ref. 112, 113
[5+1]				Au; Scheme 12 and ref. 26–28
[4+3]				Au; Scheme 5 and ref. 18

Table 1 (*continued*)

Annulation pattern	Ynamide	Coupling partner	Product	Catalyst
				Au; Scheme 28 and ref. 49
				Au; Scheme 35 and ref. 55
				Au; Scheme 11 and ref. 26, 27
[5+2]				Pt; Scheme 85 and ref. 119
				Co; Scheme 90 and ref. 123
[5+2+1]				Tf_2NH; Scheme 127 and ref. 155

thioalkynes to form the sulfonium species **Int-308**. Subsequent nucleophilic addition of the enolate motif affords a spirocyclobutene intermediate **Int-309**, which further undergoes ring-opening and another Michael addition to furnish the product.

14. Conclusions and outlook

Ynamides, owing to their ambivalent nature, have emerged as a versatile building block in catalytic intermolecular annulations, which can rapidly elaborate diverse amino-functionalized hetero- and carbo-cycles in a regioselective manner. The past decade has witnessed substantial achievements in this field. A variety of annulation paradigms have been developed with transition-metal and acid catalysis (Table 1). Nevertheless, some notable issues still remain:

(1) Among those catalytic systems, Brønsted acid-catalyzed intermolecular annulations of ynamides often lead to the same chemoselectivity as gold catalysis. Consequently, there is still enough room for the discovery of new acid systems that can show distinct selectivity. Besides, theoretical investigations will be also needed to clarify the catalyst-controlled divergence, which can provide guidance for rational design of new annulations.

(2) As the carbon–carbon triple bond of ynamides is strongly polarized by the nitrogen atom, their annulations often result in the formation of α-cycloadduts *via* an initial α-addition with unsaturated nucleophiles. In this regard, developing efficient strategies to realize inverted regioselectivity of the annulation (β-cycloadduts) would be highly desirable.[158]

(3) Most of the protocols give rise to five- and six-membered rings, whereas the assembly of medium rings from ynamides remains limited. Therefore, future attention will be paid to this direction by designing suitable amphoteric building units.

(4) While some progress has been made, the enantioselective intermolecular annulation of ynamides is still in its infancy. Hence, exploiting chiral ligands and Brønsted acids to realize asymmetric variants will be another important research area.

We believe that this review will arouse intensive research interest in ynamide chemistry and encourage chemists to apply the developed methodologies to drug design and natural product synthesis.

Conflicts of interest

There are no conflicts to declare.

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