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## Chapter nine

# Pericyclic reactions of ynamides

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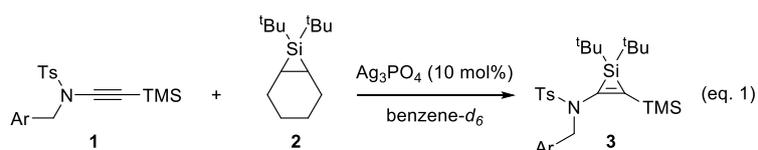
## 1.1 INTRODUCTION

Ynamides are versatile substrates in organic synthesis, the electron-rich character of the polarized  $\pi$ -system makes them ideal substrates for regio-, chemo- and stereoselective transformations. Moreover, ynamides possess good affinity for Lewis and Brønsted acids and they easily form highly reactive keteniminium ions upon reaction with an electrophile. Pericyclic reactions of ynamides have attracted a lot of interest from the synthetic community and are now well-established tools.<sup>[1,2]</sup> Depending on the substitution, the presence (and nature) of a catalyst and the reaction conditions, ynamides can be used as  $2\pi$ -electrons partner ( $C\equiv C$ ),  $4\pi$ -electrons (for aromatic-substituted ynamides) or can even act as a three atoms system sharing  $\pi$ -electrons ( $N-C\equiv C$ ). The present chapter, by no

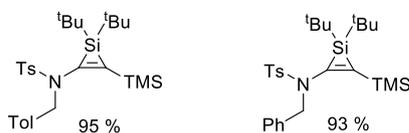
mean exhaustive, gathers pericyclic reactions of ynamides up to 2022 and is organized by classes of cycloaddition: [2+1] cycloadditions will be discussed first followed by [2+2], [3+2], [4+1], [4+2], [4+3], [5+1], [5+2] and finally [2+2+2] reactions.

## 1.2 [2+1] CYCLOADDITIONS

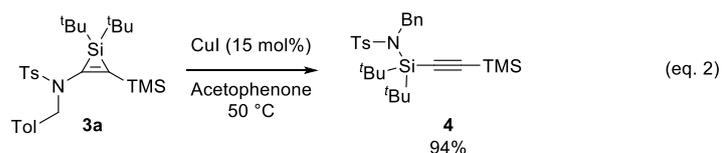
The first [2+1] cycloaddition reaction of ynamide was reported by Woerpel and his group (Scheme 1).<sup>[3]</sup> Silylene transfer from silacyclopropane **2** to ynamides **1** was quite efficient under silver phosphate-catalysis (eq. 1). Silacyclopropenes **3** were obtained in nearly quantitative yield. Moreover, **3** could be further rearranged under copper(I) catalysis leading to disilylalkyne **4** in high yields (eq. 2).



### Representative examples



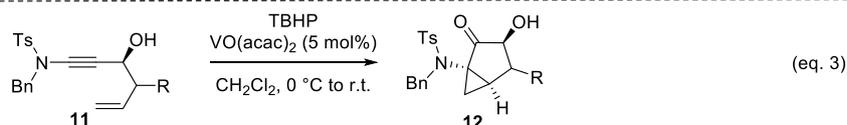
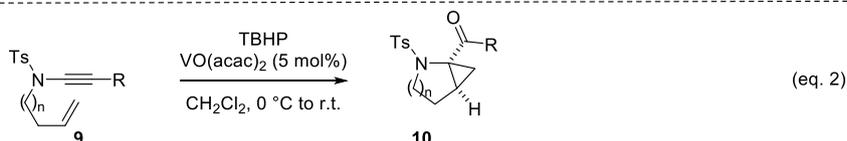
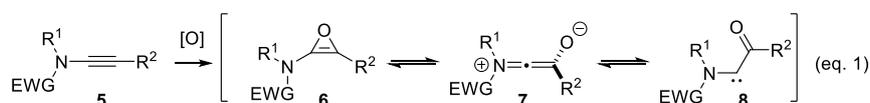
### Cu(I)-rearrangement of **3**



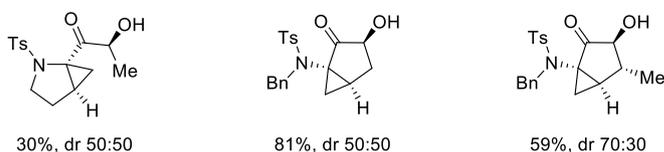
**Scheme 1.** Silver-catalyzed formation of silacyclopropenes from ynamides and further rearrangement under copper catalysis

A few years later, it was discovered that the oxidation of ynamides **5** led to the formation of carbene **8** (Scheme 2, eq. 1). Cossy and Meyer described that this carbene could be intramolecularly trapped by an alkene in an

efficient cyclopropanation reaction. The epoxidation was performed chemoselectively with respect to the alkene, with TBHP and a catalytic amount of VO(acac)<sub>2</sub> (Scheme 2, eq. 2 and 3). Diastereoselective versions were investigated and led to a diastereomeric ratio of 50:50 of adducts **10** from ynamide **6**. On the other hand, ynamide **11** led to an improved diastereoselectivity since bicyclic cyclopentanone **12** was obtained with a diastereomeric ratio of 70:30.<sup>[4]</sup>

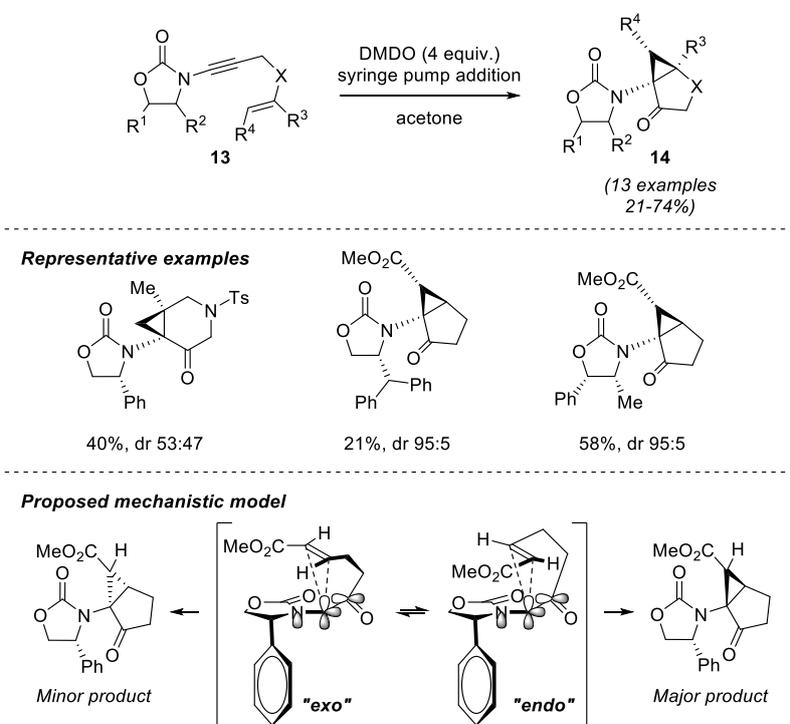


**Representative examples**



**Scheme 2.** Chemoselective epoxidation-intramolecular cyclopropanation of ene-ynamides

Shortly after, Hsung and coworkers reported new examples of stereoselective epoxidation-intramolecular cyclopropanation of ynamides **13** with higher diastereoselectivity (up to 95:5 d.r.) **10** in metal-free conditions (Scheme 3).<sup>[5]</sup> A mechanistic model was developed to explain the selectivity of the cyclopropanation and they concluded that the *endo* approach was favored, delivering **14** in moderate to excellent d.r..<sup>[6]</sup>



**Scheme 3.** Stereoselective epoxidation-intramolecular cyclopropanation of chiral ynamides

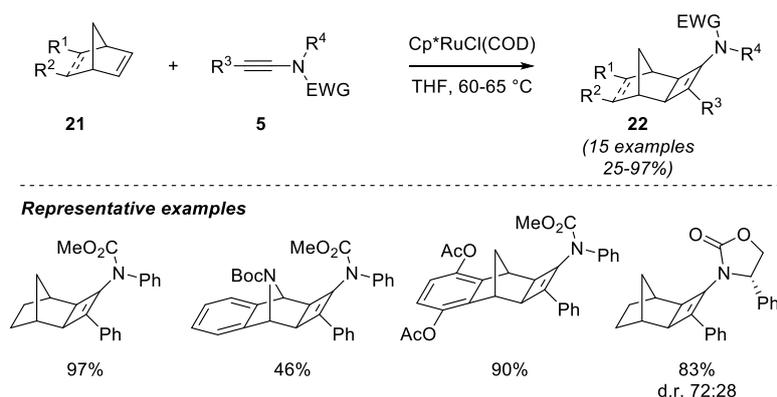
In 2009, the same group reported that other type of carbenes can react with ynamides **5** and can be used for the synthesis of highly substituted 2-amido-furans **16**, via this [2+1] cycloaddition. This reaction consisted in a tandem cyclopropanation followed by rearrangement, thereby resulting in a formal [3+2] cycloaddition. The reaction was catalyzed by  $\text{Rh}_2(\text{OAc})_4$  and the carbene can either be formed from diazo or iodonium salt but diazo species **15** were more reliable and gave better yields (Scheme 4).<sup>[7]</sup>



**Scheme 5.** Pd-catalyzed synthesis of aminomethylenecyclopropanes from terminal ynamide

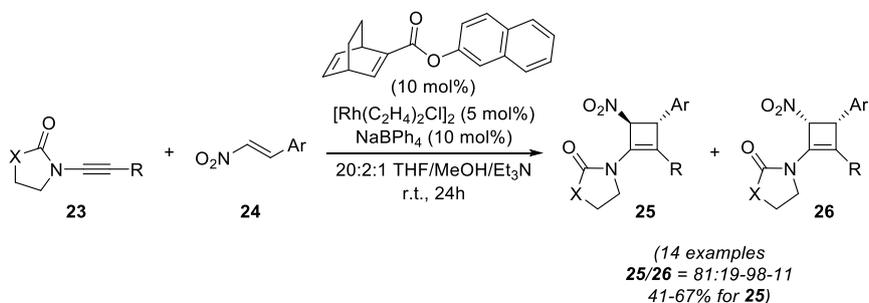
### 1.3 [2+2] CYCLOADDITIONS

Tam and coworkers reported the first case of [2+2] cycloaddition between norbornenes derivatives **21** and ynamides **5**. This ruthenium-catalyzed reaction proceeded with moderate to good yields (Scheme 6). The reaction was sensitive to the substitution of the ynamides: bulky ynamides such as sultam derivatives, hindered R<sup>2</sup> groups such as TIPS, terminal ynamides (R<sup>2</sup> = H) or push-pull system (R<sup>2</sup> = CO<sub>2</sub>Et) did not deliver desired cycloadduct **22**. Ynamides possessing propargylic alcohol or silyl ether gave low yields along with polymeric materials. Chiral ynamides were also tested but unfortunately the diastereomeric ratio was modest (58:42 to 75:25).<sup>[9,10]</sup>



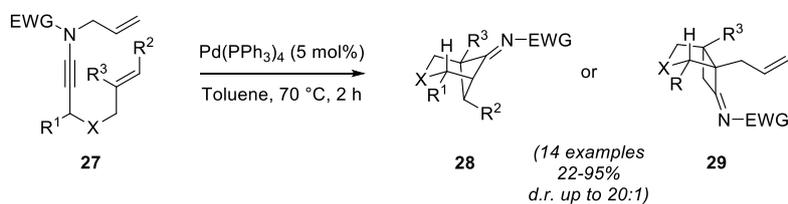
**Scheme 6.** [2+2] cycloaddition between ynamides and norbornenes derivatives

Later, Lam and coworkers reported a rhodium-catalyzed [2+2] cycloaddition between ynamides **23** and nitroalkenes **24** (Scheme 7). The reaction was performed in the presence of a racemic diene and NaBPh<sub>4</sub>, presumably both acting as ligands. The *trans*-nitrocyclobutene **25** was obtained as major product in yield up to 67% and can be separated in most cases from the *cis*-isomer **26**.<sup>[11]</sup>

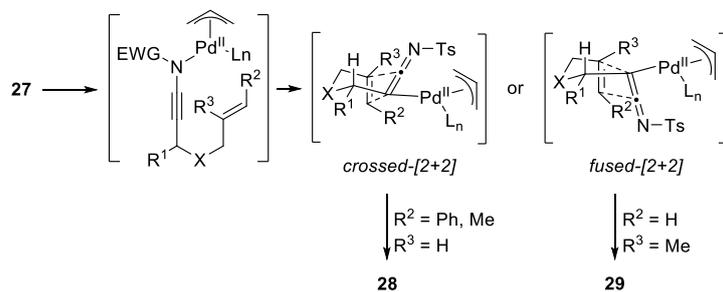


**Scheme 7.** Rhodium-catalyzed [2+2] cycloaddition between ynamides and nitroalkenes

A palladium-catalyzed intramolecular [2+2] cycloaddition of ynamide **27** was reported in 2012 by Hsung and coworkers. The reaction is initiated by the oxidative insertion of Pd(0) into the *N*-allyl bond of the ynamides **27** and is then followed by an isomerization towards the corresponding ketenimides. Crossed or fused intramolecular [2+2] cycloaddition then took place in a diastereoselective fashion depending of the substitution affording the cycloadducts **28** or **29** in good yields and with d.r. up to  $\geq 20:1$  (Scheme 8).<sup>[12]</sup>



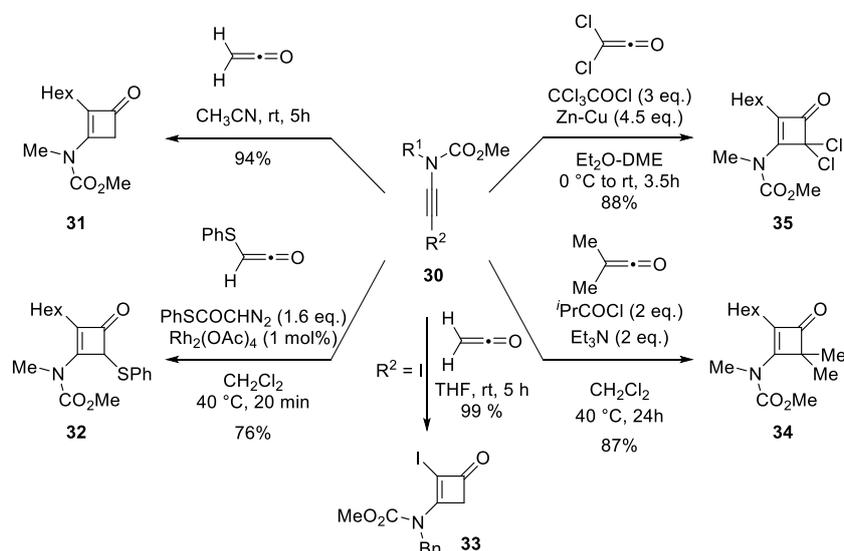
**Proposed mechanism**



**Scheme 8.** Pd-catalyzed tandem isomerization-intramolecular [2+2]

cycloaddition

In 2006, Danheiser and coworkers reported the first cases of [2+2] cycloaddition between ynamides **30** and ketenes (Scheme 9). The cycloaddition proceeded smoothly with various ketenes affording cyclobutenones **31-35** in high yields.<sup>[13]</sup> Interestingly, it was found that iodo-ynamides were suitable substrates for this reaction delivering iodo-cyclobutenone **33** in excellent yield.<sup>[14]</sup> Analogous reaction with iodoalkynes or iodo-alkynylethers failed, probably due to the low stability of those alkynes in contrast to the stability of iodo-ynamides.

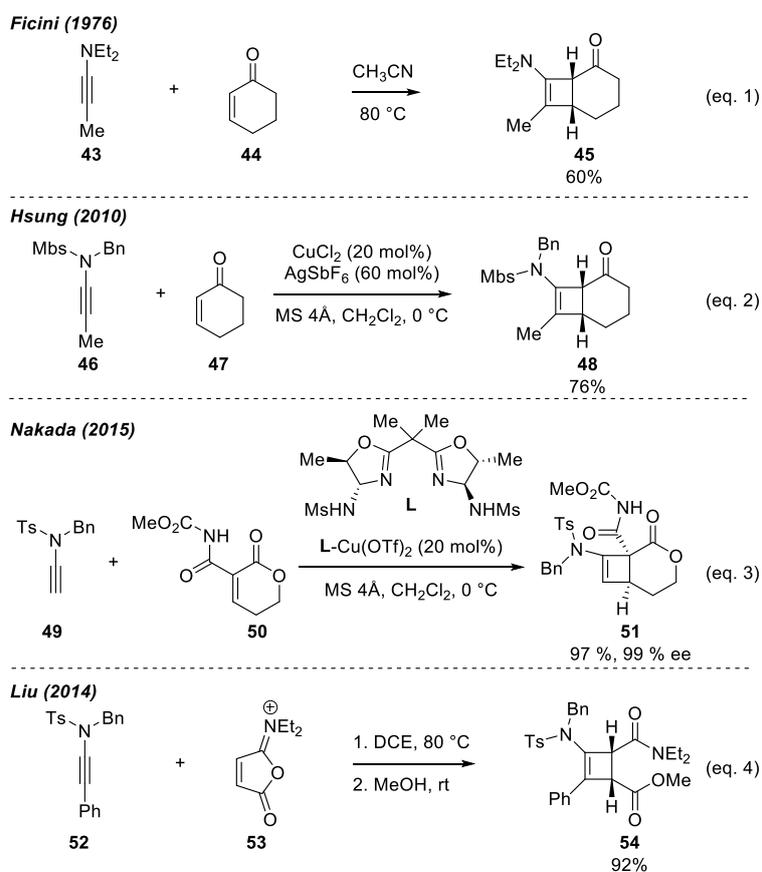


**Scheme 9.** Formation of cyclobutenones and iodo-cyclobutenones from the [2+2] cycloaddition reactions of ynamides with ketenes

Chang, Wang and coworkers reported a Pd-catalyzed [2+2] cycloaddition between ynamides **5** and ketenes generated *in situ* from acyl chloride (Scheme 10). The reaction was efficient and reliable and delivered  $\beta$ -aminocyclobutenones **37** with yields up to 95%.<sup>[15]</sup>



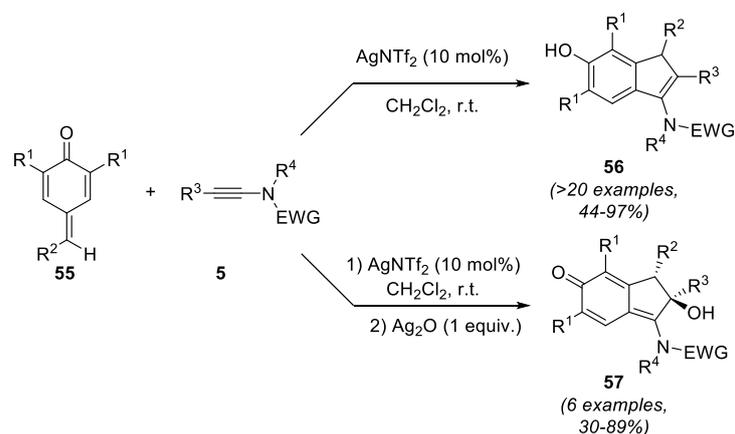
a chiral bisoxazoline ligand, with up to 99% ee (Scheme 12, eq. 3).<sup>[19]</sup> Noteworthy, Liu and coworkers reported the first cases of uncatalyzed Ficini reaction with ynamides using cyclic isoimidium salt **53** as an electron-deficient alkene (Scheme 12, eq. 4).<sup>[20]</sup>



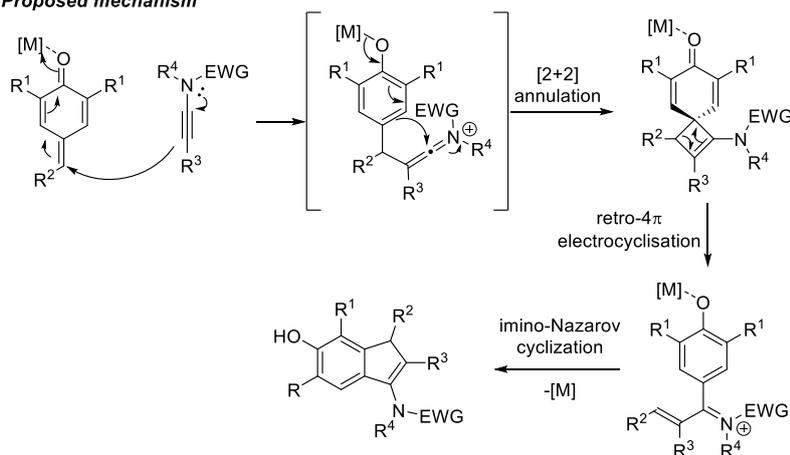
**Scheme 12.** Evolution of the Ficini reaction with ynamides and enones

More recently, Zhao, Fan and coworkers proposed a domino reaction processing through a tandem [2+2] annulation, retro-4 $\pi$  electrocyclicization, and imino-Nazarov cyclization of *p*-quinone methides **55** with ynamides **5** to form aminoindenes **56** (Scheme 13).<sup>[21]</sup> A one-pot oxidation protocol

based on tandem cyclization leading to indenones **57** was also proposed by the same authors.



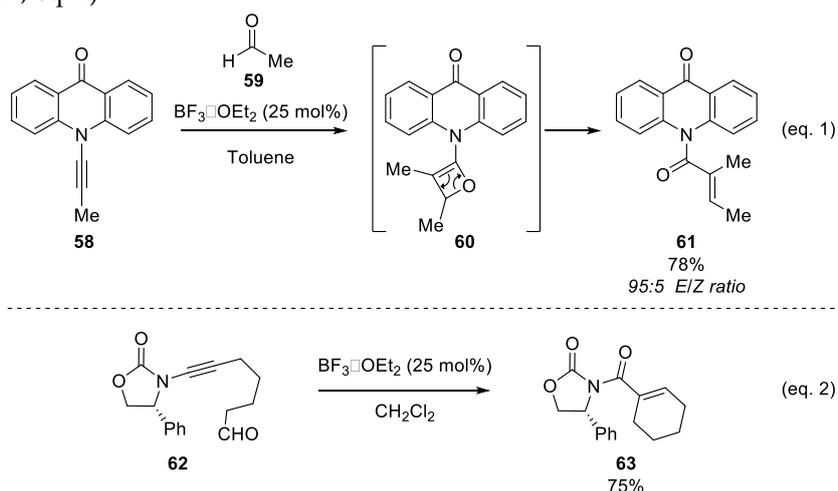
**Proposed mechanism**



**Scheme 13.** Synthesis of aminoindenones and indenones from ynamides

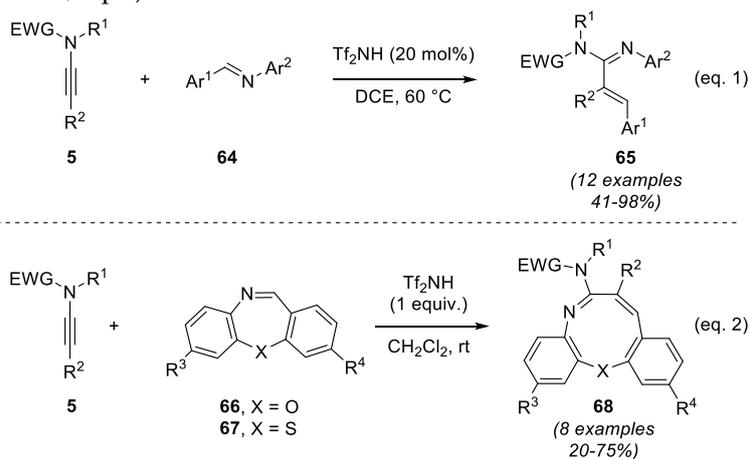
Hsung and coworkers reported a Lewis acid promoted hetero [2+2] cycloaddition between ynamides and aldehydes. Starting from ynamide **58** and acetaldehyde **59**, the primary cycloadduct **60** was obtained. The latter then underwent an electrocyclic ring opening leading to the  $\alpha,\beta$ -unsaturated amide **61** in good yield. Interestingly the electrocyclic opening proceeded selectively with an *E/Z* ratio of 95:5 (Scheme 14, eq. 1).<sup>[22]</sup> Later, Hsung and coworkers reported an intramolecular version as

exemplified in the synthesis of **63** from the ynamide-aldehyde **62** (Scheme 14, eq. 2).<sup>[23]</sup>



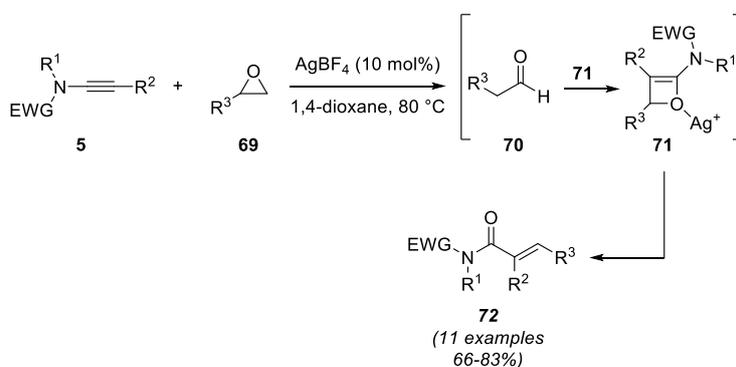
**Scheme 14.** Hetero [2+2] cycloaddition of ynamide and aldehyde leading to  $\alpha,\beta$ -unsaturated amides

A conceptually related reaction between ynamides **5** and imines **64** under bistriflimide catalysis has been disclosed by Takemoto, Takasu and coworkers yielding  $\alpha,\beta$ -unsaturated amidine **65** (Scheme 15, eq. 1).<sup>[24]</sup> Lately, similar reaction was developed with cyclic 7-membered ring imines **66** and **67** resulting in a ring expansion to 9-membered ring **68** (Scheme 15, eq. 2).<sup>[25]</sup>



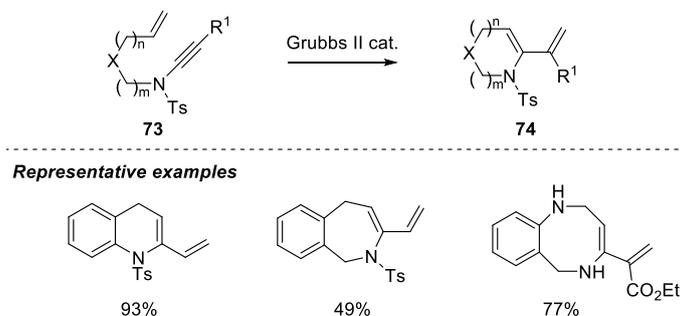
**Scheme 15.** Synthesis of  $\alpha,\beta$ -unsaturated amidines from ynamides and imines

This Lewis acid catalyzed hetero [2+2] cycloaddition can also use epoxides as aldehyde precursors. Indeed, Zhu and coworkers reported that under silver catalysis it was possible to isomerize epoxide **69** to aldehyde **70** *in situ*. As discussed above, the reaction proceeded via a hetero [2+2] cyclization between ynamide **5** and the newly formed aldehyde **70** leading to oxetene **71**, followed by electrocyclic opening generating  $\alpha,\beta$ -unsaturated amides **72** (Scheme 16).<sup>[26]</sup>



**Scheme 16.** Lewis acid catalyzed hetero [2+2] cycloaddition of epoxides and ynamides

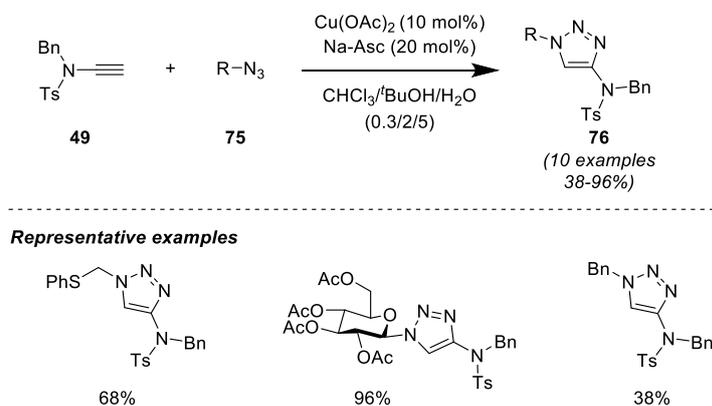
Although not strictly related to pericyclic reactions, the [2+2] cycloaddition of metal-carbenes with ynamides should be mentioned. The intramolecular ring-closing metathesis of ene-ynamides **73** was, for example, reported by Wakamastu, Yoshimura and coworkers using Grubbs II catalyst. With this method 6- to 8-membered rings **74** were synthesized in moderate to good yields (Scheme 17). However, for each substrate the reaction turned out to be sensitive to the quantity of catalyst used, the nature of atmosphere and solvent.<sup>[27]</sup>



**Scheme 17.** Ring-closing metathesis of ene-ynamides

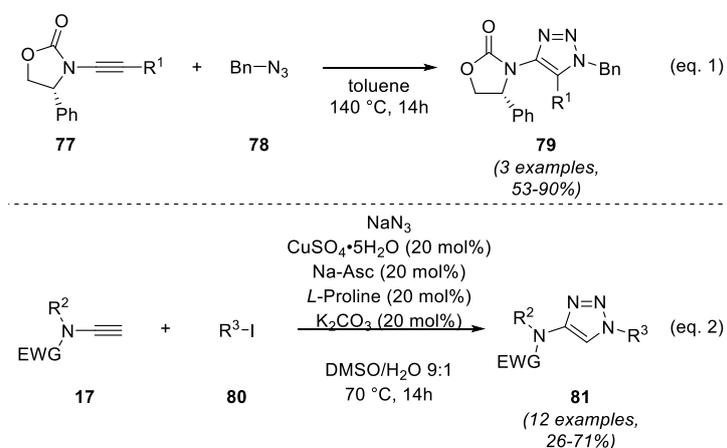
#### 1.4 [3+2] CYCLOADDITIONS

In 2006, Cintrat and coworkers reported the first example of Huisgen [3+2] dipolar cycloaddition of ynamides. In this study, *N*-tosyl-*N*-benzyl terminal ynamide **49** was the only suitable substrate to react with alkyl azides **75** to give 4-amino-1,2,3-triazole **76** (Scheme 18). It was observed that the addition of Cu(I) salts allowed a complete control of the regioselectivity to give the 1,4-disubstituted-1,2,3-triazole **76** as unique product in moderate to good yields.<sup>[28]</sup>

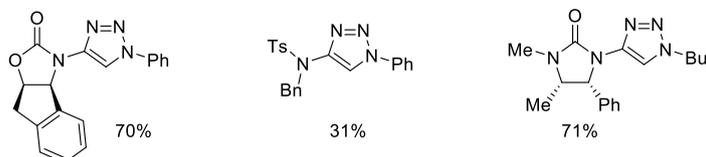


**Scheme 18.** Huisgen [3+2] dipolar cycloaddition of ynamides

The same year, Hsung and coworkers observed a similar 1,4-regioselectivity under thermal conditions (Scheme 19, eq. 1). In addition, a tandem azidination of an electrophile ( $R^3I$ )/ [3+2] cycloaddition procedure was developed for the synthesis of various 4-amino-1,2,3-triazoles **81** from ynamides **17** in moderate to good yields.<sup>[29]</sup>

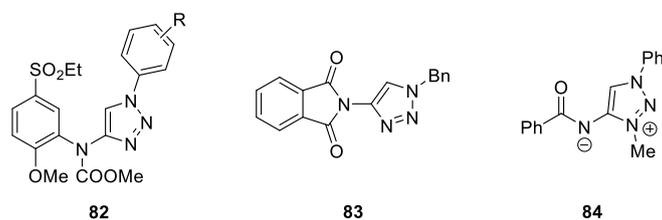


**Representative examples**



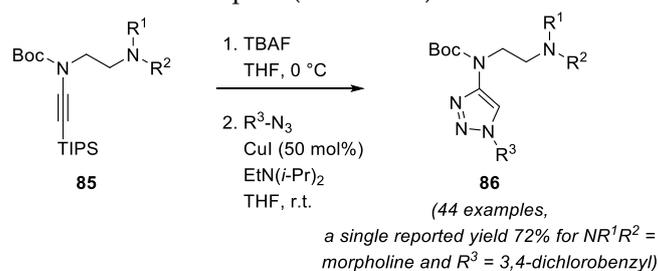
**Scheme 19.** Thermal and tandem Cu(I)-catalyzed azidation-Huisgen [3+2] dipolar cycloaddition of ynamides

These aminotriazoles have been applied as potential inhibitors of VEGFR2 tyrosine kinase **82** (Figure 1).<sup>[30]</sup> Similar conditions have been successfully used with phthalimide derived ynamides,<sup>[31]</sup> a precursor in the synthesis of 1,2,3-triazolium amidate **84** which is used as hydrogen-atom transfer catalyst.<sup>[32]</sup>



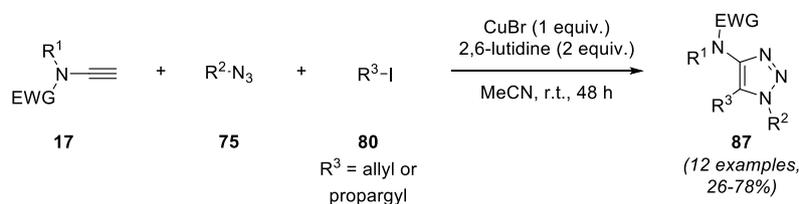
**Figure 1.** Applications of 4-amino-1,2,3-triazoles

To avoid degradation of sensitive terminal ynamides, a one-pot silyl-deprotection of ynamide **85** / [3+2]-cycloaddition sequence was developed by Diaz and co-workers for application as potential selective  $\sigma_1$  receptor ligands for the treatment of pain (Scheme 20).<sup>[33]</sup>



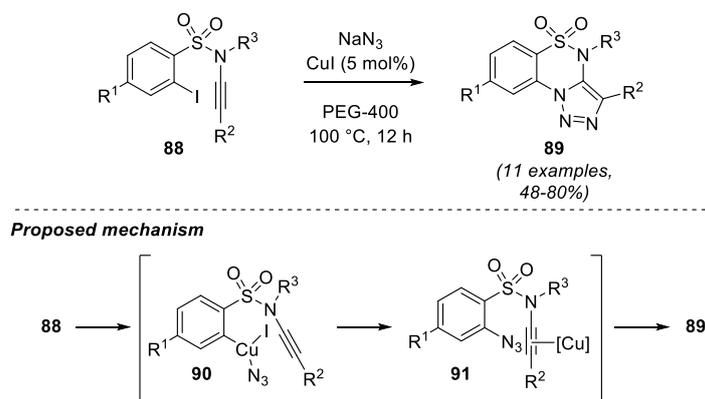
**Scheme 20.** Silylated ynamides as precursors of sensitive terminal ynamides in Huisgen [3+2] cycloadditions

The presence of vinyl copper species as a Huisgen reaction intermediate afforded an opportunity for a tandem Cu-catalyzed [3+2] azide cycloaddition / vinyl-Cu trapping reaction. This strategy was developed by Hsung and coworkers in 2007 from ynamide **17**, azide **75** with allyl- or propargyl iodide **80** as electrophiles to form the trisubstituted triazole **87** (Scheme 21). These scaffolds were further used for the synthesis of novel fused triazoles via ring-closing metathesis.<sup>[34]</sup>



**Scheme 21.** Copper(I)-catalyzed tandem azide-ynamide cycloaddition / electrophilic trapping

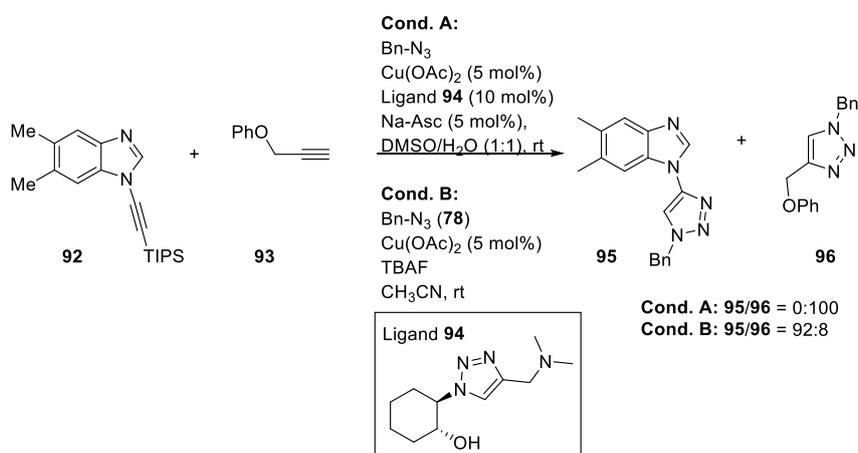
An efficient one-pot approach was developed for the synthesis of fused triazolo 1,2,4-benzothiadiazine-1,1-dioxide **89** derivatives using PEG-400 as solvent.<sup>[35]</sup> The cyclisation process involves an Ullmann type coupling via a C–N bond to form the azide **91** and subsequent intramolecular-cycloaddition allowing the formation of three C–N bonds in a single synthetic step (Scheme 22).



**Scheme 22.** Cu(I)-catalyzed azidation of aryl iodides/intramolecular Huisgen cycloaddition onto ynamides

Burtley, Watson and coworkers studied the origin of rate-independent chemoselectivity in copper-catalyzed azide–alkyne click (CuAAC) reactions of alkyne *vs* ynamides.<sup>[36]</sup> It appeared that the rate determining step of copper-acetylide formation with alkyne is shifted to the azide coordination-ligation step due to the higher acidity of C<sub>sp</sub>-H of ynamides compared to alkynes, which conferred a higher reactivity to terminal

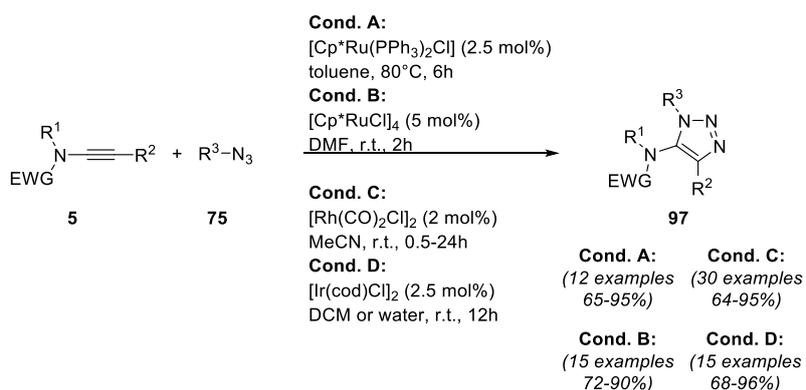
ynamides in CuAAC reaction. By using silyl-protected ynamides, alkynes can react in CuAAC reaction chemoselectively, in the presence of a terminal alkyne. It was demonstrated that ynamide-selective conditions can be developed such as conditions A in Scheme 23. Indeed, a perfect chemoselectivity for **96** was observed (**95/96** = 0:100), while conditions B gave higher chemoselectivity in favor of the Huisgen [3+2] cycloaddition of benzimidazole derived-ynamide **95**. Triazole **95** was obtained as major product (**95/96** = 79:21) (Scheme 23).<sup>[37]</sup>



**Scheme 23.** Alkyne-chemoselectivity in Huisgen reaction, a selectivity switch between silylated ynamides and terminal alkynes

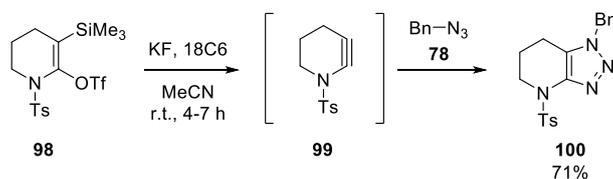
In 2007, Cintrat and coworkers reported a highly regioselective ruthenium-catalyzed Huisgen [3+2] cycloaddition of terminal ynamides ( $R^2 = H$ ) delivering the 5-amido-1,2,3-triazole **97** in high yields (Scheme 24, conditions A).<sup>[38]</sup> Later, the same strategy was proposed by Taddei and coworkers using another ruthenium catalyst and internal ynamides **5** but still with 1,5-regioselectivity (Scheme 24, conditions B).<sup>[39]</sup> High 1,5-regioselectivity was presented by Huang and coworkers using rhodium catalysis (Scheme 24, conditions C). The method is functional group-, air- and moisture tolerant, and it can occur in different solvents. A proposed mechanism supported by DFT calculations implied the oxidative coupling of the azide on the  $\beta$ -carbon of the ynamide with the concomitant formation of a rhodium-carbene intermediate on the  $\alpha$ -position.<sup>[40]</sup> Finally,

Zheng and coworkers reported an exclusive 1,5-regioselectivity using iridium catalysis (Scheme 24, Conditions D).<sup>[41]</sup> The reaction proceeded under very mild conditions (air atmosphere, aqueous media). Biorthogonal conditions were also investigated, due to the low cytotoxicity of the iridium catalyst.



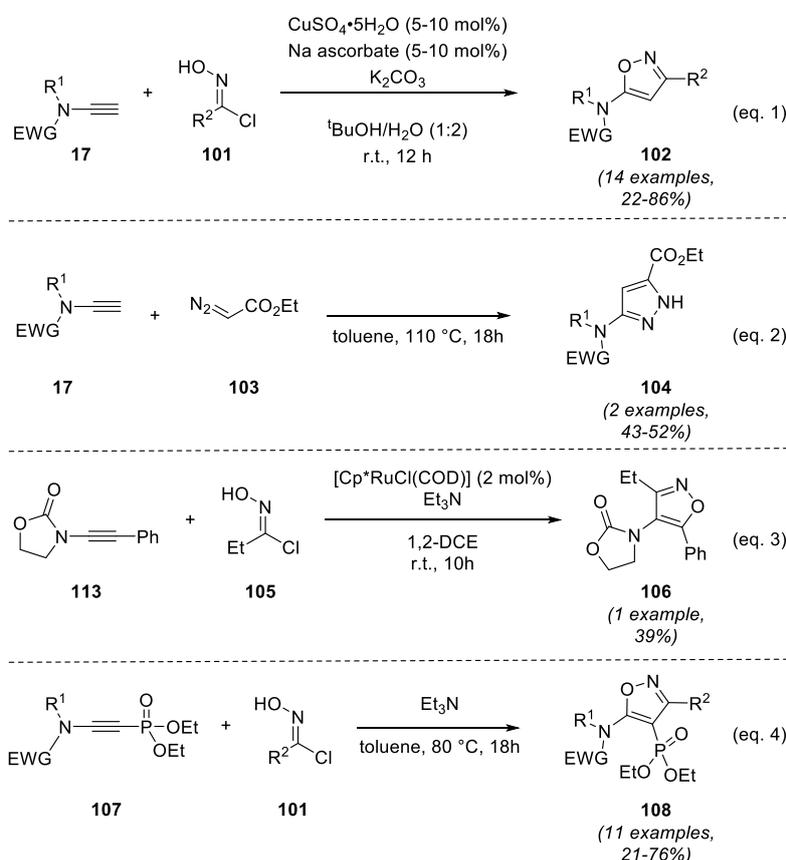
**Scheme 24.** Ru/Rh/Ir-catalyzed 1,5-regioselective Huisgen [3+2] cycloaddition of ynamides

A metal free cycloaddition with highly reactive and *in-situ* generated six-membered cyclic ynamides **99** and benzyl azide **78** has been demonstrated by Danheiser and coworkers in 2014 (Scheme 25).<sup>[42]</sup> The strained *N*-Tosyl-3-azacyclohexyne **99** was generated from cyclic enamine **98** via fluoride-promoted 1,2 elimination under conditions that allowed trapping of the reactive heterocyclic alkyne in a [3+2]cycloaddition leading to triazole **100** in 71% yield.



**Scheme 25.** Metal-free [3+2] Huisgen cycloaddition with *in-situ* generated strained cyclic ynamide

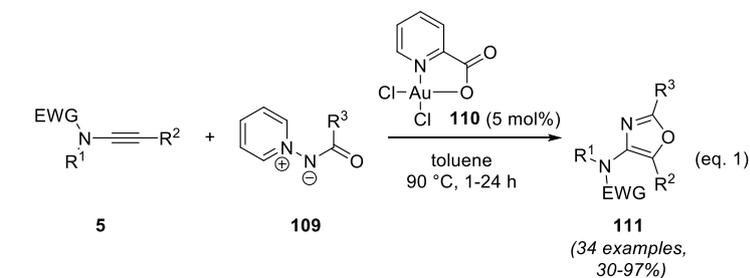
In 2007, Hsung and coworkers reported the highly regioselective copper-catalyzed [3+2] cycloaddition between a terminal ynamide **17** and nitrile oxide generated *in-situ* from  $\alpha$ -chloro oxime **101** affording 5-amido-isoxazoles **102** in moderate to good yields (Scheme 26, eq. 1).<sup>[43]</sup> In the same report, the synthesis of 3-amido-pyrazole **104** by thermal reaction with ethyl  $\alpha$ -diazoacetate **103** was also developed (Scheme 26, eq. 2). A ruthenium-catalyzed approach for the synthesis of 4-amido-isoxazole **106** was proposed by Fokin and coworkers but only a single example of terminal ynamide was disclosed and gave low yield (Scheme 26, eq. 3).<sup>[44]</sup> Nevertheless, this complementary method gave access to the opposite regioselectivity compared to the Hsung's method (**106** vs **102**). Rabasso and coworkers investigated a metal-free [3+2] cycloaddition with push-pull ynamido-phosphonate **107** to provide the fully substituted 5-amido-isoxazoles **108** as single regioisomers in moderate to good yields (Scheme 26, eq. 4).<sup>[45]</sup>



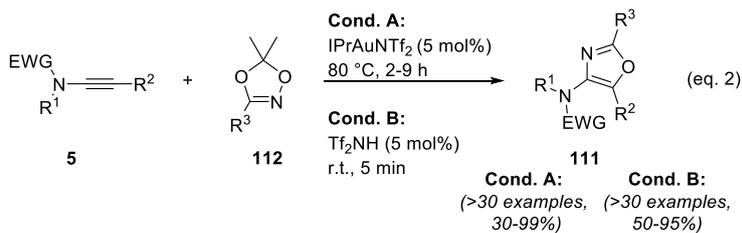
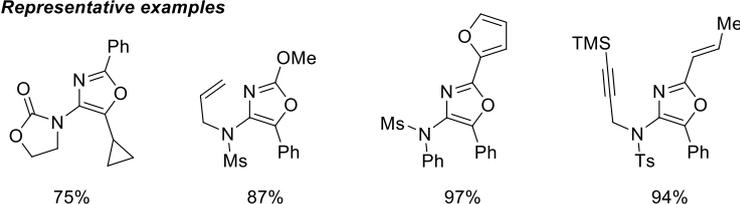
**Scheme 26.** Syntheses of isoxazoles and pyrazoles by [3+2] cycloaddition with ynamides

The formation of 4-amino-oxazole via [3+2] cycloaddition has been largely studied. In 2011, Davies and coworkers reported a regioselective gold-catalyzed intermolecular [3+2] cycloaddition across electronically biased  $\pi$  systems (Scheme 27, eq. 1).<sup>[46]</sup> Ynamides **5** were reacted with *N*-acylpyridinium-*N*-aminides **109** affording the fully substituted 1,3-oxazoles **111** via an intermolecular cycloaddition. The proposed mechanism involved nucleophilic attack of the aminide adjacent to the nitrogen of a gold-activated ynamide, followed by a  $4\pi$ -electrocyclization.<sup>[47]</sup> Another gold-catalyzed strategy was proposed by Liu and coworkers via the

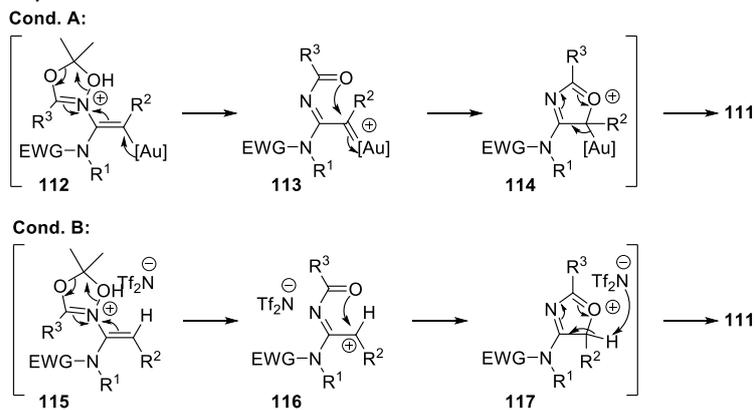
formation of an  $\alpha$ -imino gold-carbene **113** involving a reaction between ynamide **5** and dioxazole **112** to afford the desired 4-amino-oxazole **111** (Scheme 27, eq. 2).<sup>[48]</sup> This method offers several advantages such as easily accessible starting materials, high regioselectivity, wide functional group compatibility and high efficiency. In 2017, Li, Wan and coworkers developed a metal-free version of this transformation using Tf<sub>2</sub>NH as Bronsted acid in very mild reaction conditions and a very short reaction time.<sup>[49]</sup> Indeed, the reaction proceeded efficiently at room temperature within few minutes. In presence of Tf<sub>2</sub>NH, ynamide **5** generated *in situ* a keteniminium ion intermediate which underwent addition of the dioxazole **112** adjacent to the nitrogen of the ynamide, followed by cyclization to **111**.



**Representative examples**

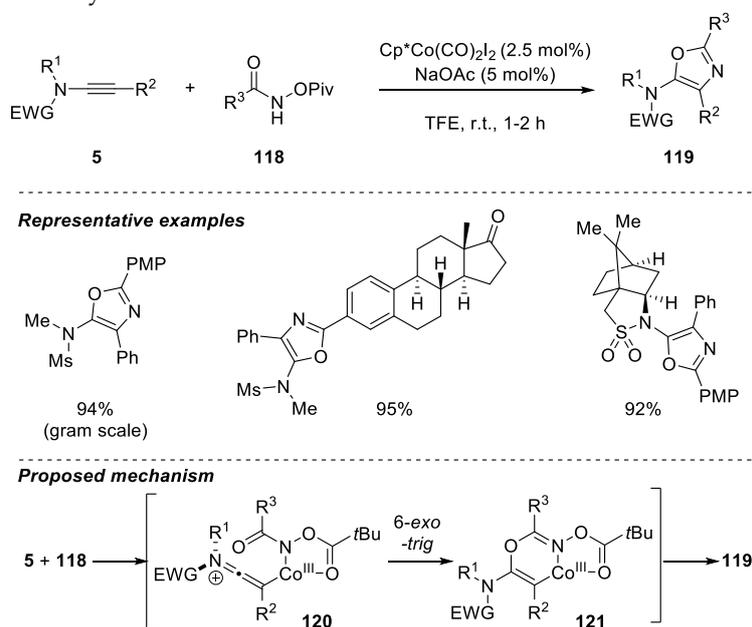


**Proposed mechanisms**



**Scheme 27.** Gold- or Bronsted-acid catalyzed reactions of ynamides and nitrogen nucleophiles for the synthesis of 4-amido-1,3-oxazoles

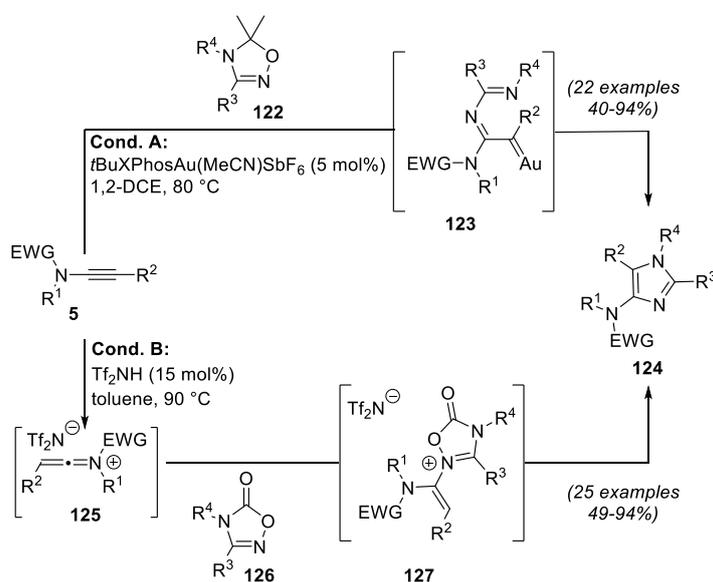
In 2017, Li and coworkers described a fully regioselective synthesis of 5-amido-1,3-oxazole **119** via a redox neutral Co(III)-catalyzed formal [3+2] cycloaddition of *N*-(pivaloyloxy)amides **118** with ynamides **5** (Scheme 28).<sup>[50]</sup> The proposed mechanism implied the formation of keteniminium **120** via nucleophilic attack of ynamide **5** to cobalt complex. Then, an intramolecular 6-*exo*-trig cyclization generated a cyclocobalt species **121** which finally delivered **119**.



**Scheme 28.** Cobalt(III)-catalyzed formal [3+2] cycloaddition of *N*-(pivaloyloxy)amides with ynamides

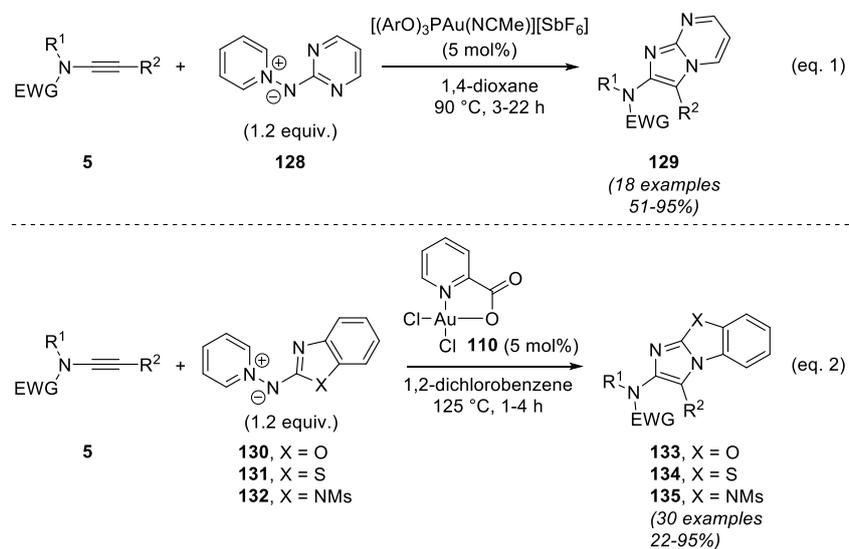
Inspired by their work on gold-catalyzed synthesis of oxazoles from ynamides,<sup>[48]</sup> Liu and coworkers recently explored the formation of functionalized imidazole **124** from ynamides **5** and 4,5-dihydro-1,2,4-oxadiazoles **137** using a gold-catalyzed formal [3+2] cycloaddition.<sup>[51]</sup> The reaction provided a concise and regioselective access to highly functionalized 4-aminoimidazoles **124** likely via the formation of an  $\alpha$ -imino gold carbene intermediate **123** followed by cyclization (Scheme 29, conditions A). Sterically demanding ligands such as *t*-BuXPhos or even

bulky phospholes showed great efficiency for this transformation.<sup>[52]</sup> Similarly, Wan, Li and coworkers extended the metal-free strategy reported for oxazoles<sup>[49]</sup> for the synthesis of aminoimidazoles **124** via a [3+2] cycloaddition of oxadiazolones **126** in the presence of catalytic amounts of Tf<sub>2</sub>NH.<sup>[53]</sup> The reaction followed a similar mechanism: nucleophilic attack of **126** on keteniminium **125** leading to **142**, which spontaneously decarboxylated and cyclized to the desired **124**.



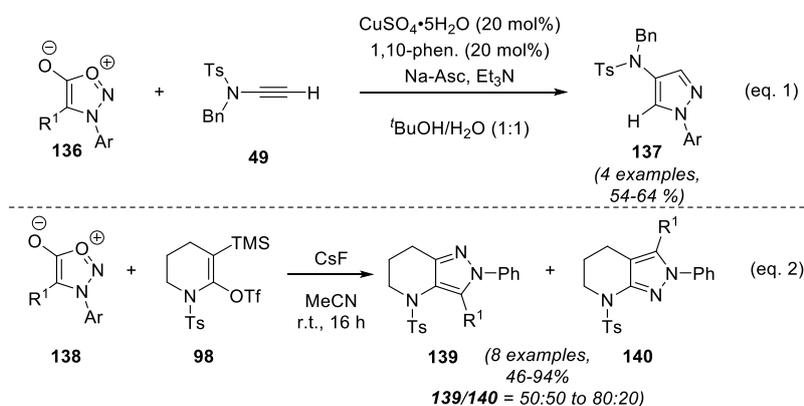
**Scheme 29.** Gold- or Bronsted-catalyzed formal [3+2] cycloaddition between ynamides and 4,5-dihydro-1,2,4-oxadiazoles

Similarly, Davies and coworkers extended the gold-catalyzed strategy for the synthesis of fused imidazoles by modifying the nature of the *N*-heteroaryl-pyridinium-*N*-aminide (**128** or **130-132**) and adapting the catalytic conditions (Scheme 30, eqs. 1 and 2). Formal gold-catalyzed [3+2]-dipolar cycloadditions across ynamides **5** delivered fused heterocycles such as imidazopyrimidines (**129**),<sup>[54]</sup> imidazo[2,1-*b*]-benzoxazoles, imidazo[2,1-*b*]benzothiazole and imidazo[1,2-*a*]benzimidazole (**133-135**).<sup>[55]</sup>



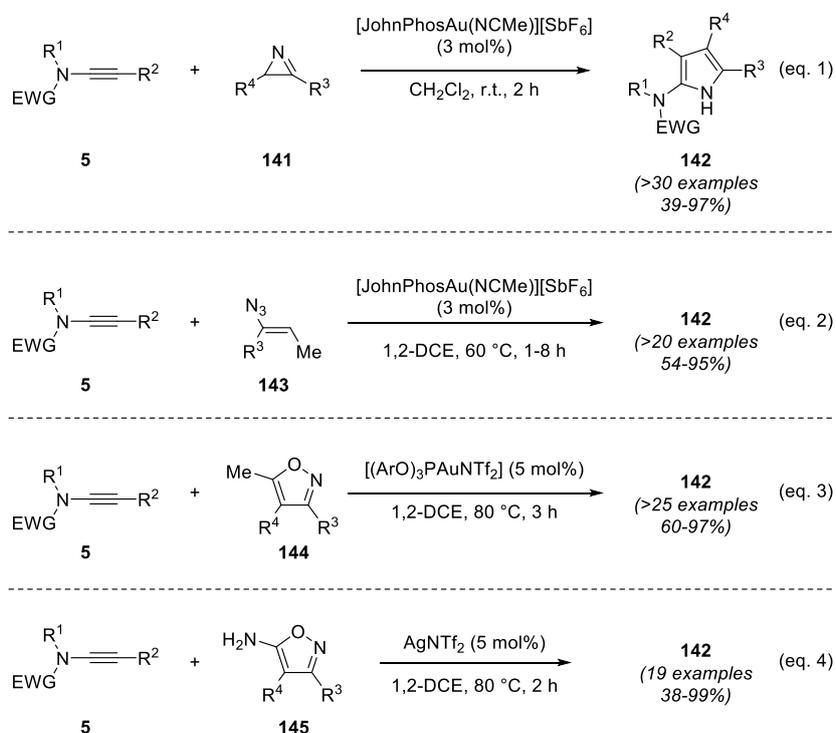
**Scheme 30.** Gold-catalyzed cycloaddition of ynamides and *N*-heteroarylpyridinium-*N*-aminide for the synthesis of fused-imidazoles

In 2017, Bräse and coworkers proposed the synthesis of 4-amidopyrazoles **137** as sole regioisomer via a copper-catalyzed cycloaddition of sydnone **136** with ynamides **49** (Scheme 31, eq. 1).<sup>[56]</sup> Unfortunately, only C4-unsubstituted sydnone is suitable for this transformation. The authors also developed a metal-free cycloaddition with an *in situ* generated strained cyclic ynamides generated from cyclic enamine **98** affording a mixture of 4,3- and 3,4-regioisomers of fused pyrazoles **139** and **140**, respectively, with substrate dependent regioselectivity (Scheme 31).



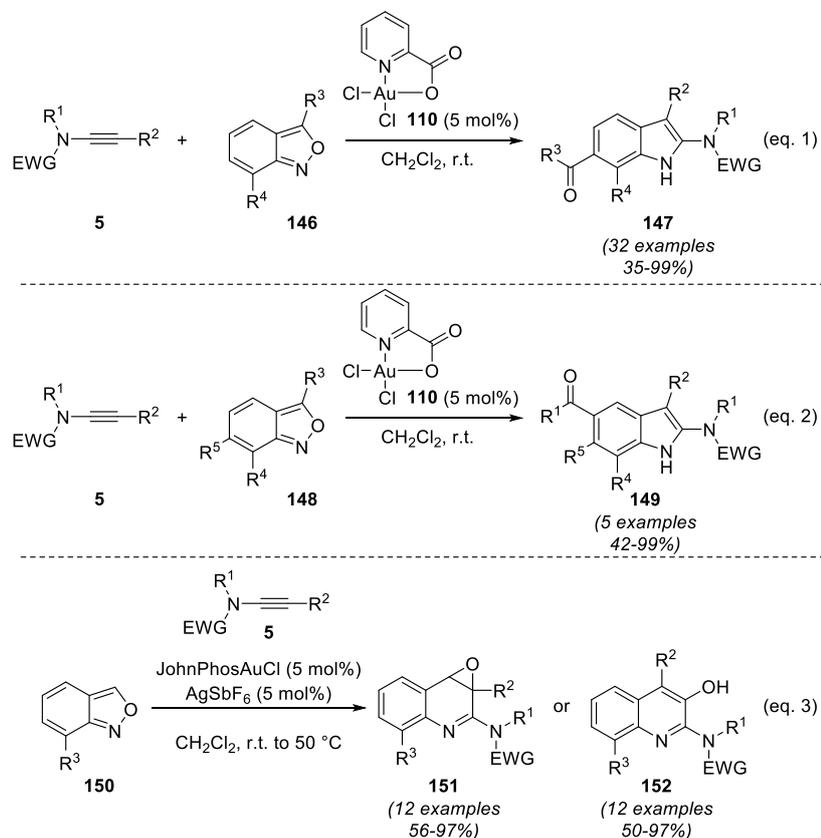
**Scheme 31.** Copper catalyzed [3+2] cycloaddition between ynamides and sydrones for the synthesis of 4-amidopyrazoles

In 2015, Huang and coworkers developed two close methods for the synthesis of polysubstituted 2-amino-pyrroles **142** from ynamides **5** relying on a gold-catalyzed [3 + 2] cycloaddition involving a nitrene transfer process. The latter was based on azirine **141** or on vinyl azide **143** in gold-catalyzed processes (Scheme 32, eqs. 1 and 2).<sup>[57,58]</sup> In the same year, a gold-catalyzed cycloaddition from ynamide **5** and isoxazole **144** was developed by Lu, Ye and coworkers<sup>[59]</sup> and in 2019 an analogous silver-catalyzed reaction was proposed by Cao, Meng and coworkers<sup>[60]</sup> using 5-aminoisoxazoles **145**, both involving an  $\alpha$ -imino-metal-carbene as intermediates.



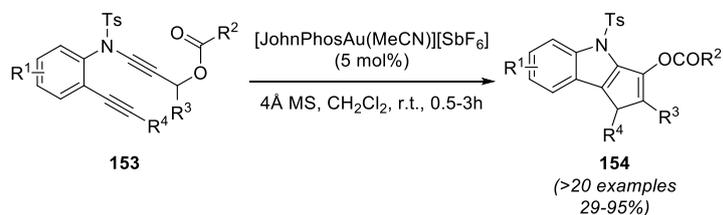
**Scheme 32.** Gold- and silver-catalyzed [3+2] cycloaddition between ynamides and azirines, vinyl azide or isoxazoles for the synthesis of 2-aminopyrroles

In 2020, Ariaifard, Hashmi and coworkers studied the gold-catalyzed formal [3+2] cycloaddition of anthranil **146**, **148** and **150** with ynamides **5**. Interestingly, it was observed that gold(III) complex (such as **110**) gave access to 2-amido-6-acyl indoles **147** or 2-amido-5-acyl indoles **149**, while gold(I) complex give 2-amido-quinoline derived epoxides **151** or 2-amido-3-hydroxyquinolines **152** (Scheme 33).<sup>[61]</sup> A detailed computational study was conducted to explain the formation of 5- or 6-membered rings, and it appeared that both mechanisms relied on the nitrogen attack of the anthranils on the carbon adjacent to the nitrogen of the gold-activated ynamide, resulting in the formation of a  $\beta$ -goldcarbene species which underwent C- or O-oriented cyclization and rearrangement depending on the catalyst.

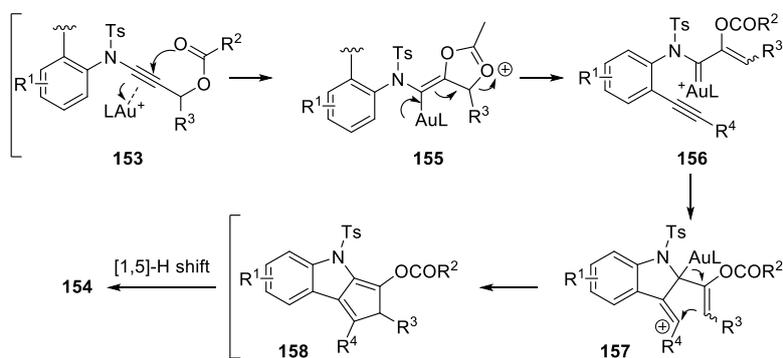


**Scheme 33.** Gold-catalyzed annulations of anthranils and ynamides

The cycloisomerization of aniline-bridged 1,6-diynyl acetate **153** has been reported by Liu and coworkers using gold(I) catalysis. 1,4-Dihydrocyclopenta[*b*]indole **154** were obtained in good yields (Scheme 34).<sup>[62]</sup> The proposed mechanism involved 1,2-acetate migration followed by formal [3+2] cycloaddition of the vinyl gold–carbenoid intermediate **156** with the alkynyl moiety.

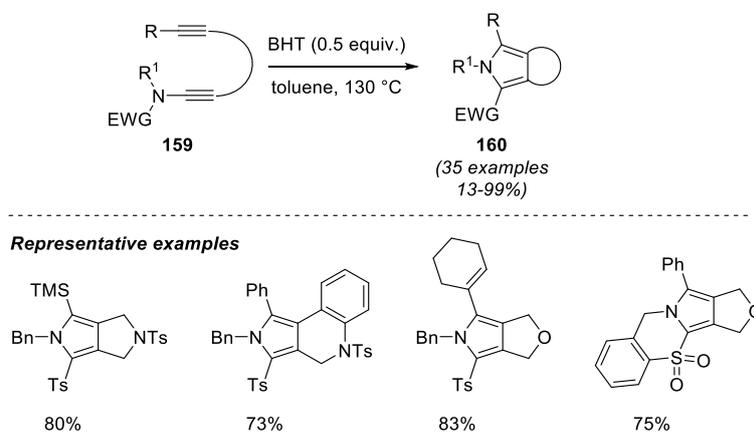


**Proposed mechanism**



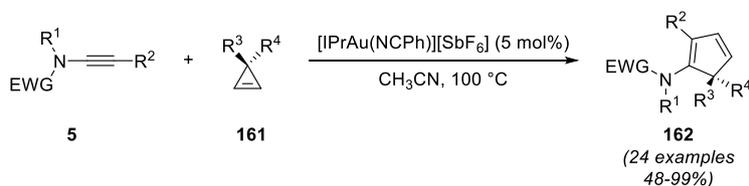
**Scheme 34.** Gold(I)-catalyzed 1,2-acyloxy migration/[3+2] cycloaddition of aniline-bridged 1,6-diyne acetates

In 2021, a metal free [3+2] cycloaddition of yne-ynamide derivatives **159** has been published by Campeau, Gagosz and coworkers.<sup>[63]</sup> This efficient thermal rearrangement into polycyclic pyrroles **160** showed good functional group tolerance since a wide variety of scaffolds can be easily prepared (Scheme 35). Considering experimental observations and DFT calculations, it was postulated that the [3+2] cycloaddition step may occur through a concerted or a singlet diradical pathway, followed by a 1,2-migration of the EWG.



**Scheme 35.** Ynamides as a three-atom partner in intramolecular [3+2] cycloadditions with alkynes

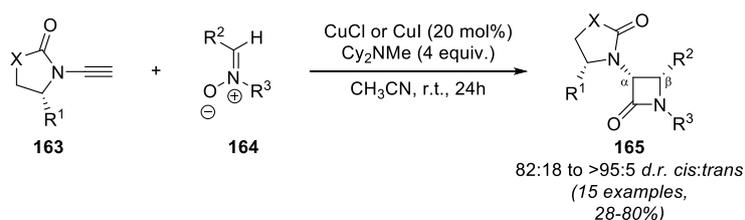
Synthesis of polysubstituted-cyclopentadienes **162** was achieved by Chen, Huang and coworkers under gold(I) catalysis by enyne cycloisomerization of ynamide **5** and cyclopropene **161** (Scheme 36).<sup>[64]</sup> Cross-over experiment confirmed that gold-catalyzed activation of the strained cycloalkene **161** occurred prior to activation of ynamide **5**.



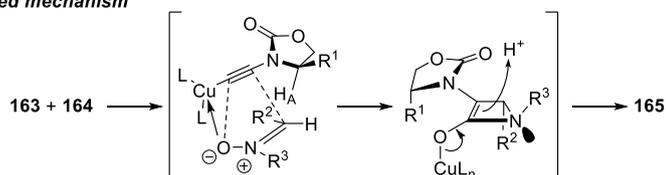
**Scheme 36.** Preferential gold-catalyzed activation of cyclopropenes in the presence of ynamides leading to 1-amino-1,3-cyclopentadienes

A copper-catalyzed Kinugasa reaction between ynamides **163** and nitrones **164** were reported by Hsung and coworkers (Scheme 37). The use of chiral oxazolidinone- or imidazolidinone-based ynamides yielded a mixture of *cis* and *trans*  $\alpha$ -amino- $\beta$ -lactams **165** in favor of the *cis* isomer up to 95:5 d.r. The proposed mechanism supported by DFT calculation indicated that the reaction favored the kinetic *cis* product (by 2.50 to 4.86

kcal/mol difference) and was controlled by both the initial [3+2] cycloaddition and the subsequent facial selective protonation.<sup>[65]</sup>



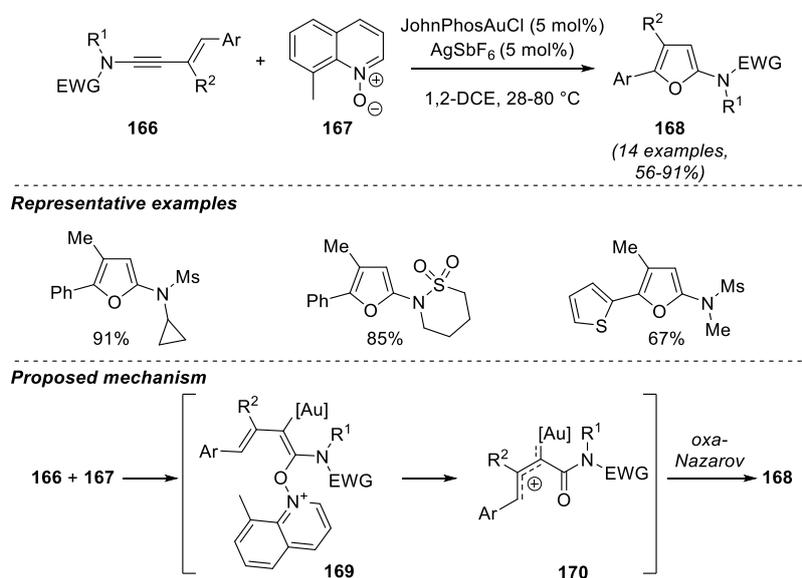
*Proposed mechanism*



**Scheme 37.** Copper-catalyzed Kinugasa reaction with ynamides

## 1.5 [4+1] CYCLOADDITIONS

In 2012, Liu and coworkers reported a new formal [4+1]-cycloaddition of 3-en-1-ynamides **166** using quinoline oxides as oxygen atom donors (Scheme 38).<sup>[66]</sup> The optimized reaction conditions used the classical combination of catalytic amounts of JohnPhosAuCl and AgSbF<sub>6</sub> (5 mol%) and 8-methylquinoline oxide **167**, which led to 2-aminofurans **168** as single products. The proposed mechanism implied the formation of an alkenylgold carbenoid **169** followed by an oxa-Nazarov cyclization of gold-stabilized allylic cation **170**. This study revealed that an R<sup>2</sup> alkyl substituent at the C3 position of ynamides **166** increased the stability of gold-stabilized allylic cation **182** and thus facilitated the oxa-Nazarov cyclization.

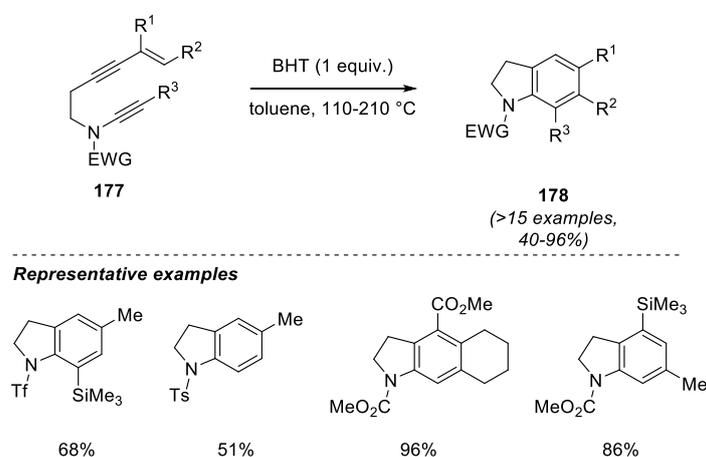


**Scheme 38.** Gold-catalyzed synthesis of 2-aminofurans by [4+1] cycloaddition of ynamides

## 1.6 [4+2] CYCLOADDITIONS

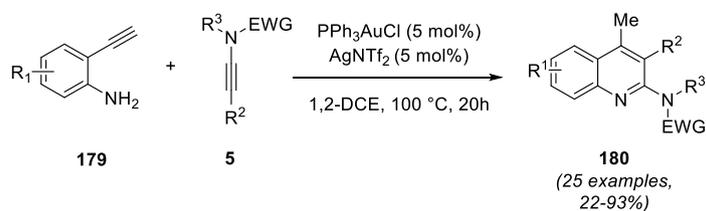
One of the earliest examples of a [4+2] cycloaddition of an ynamide (acting as a  $2\pi$  partner) has been reported by Hsung and coworkers in 1999.<sup>67</sup> An inverse electron demand hetero Diels-Alder reaction between an electron enriched ynamide **171** and a methyl vinyl ketone **172**, mediated by one equivalent of  $\text{BF}_3$ , led to cycloadduct **173** in 64% yield (Scheme 39).



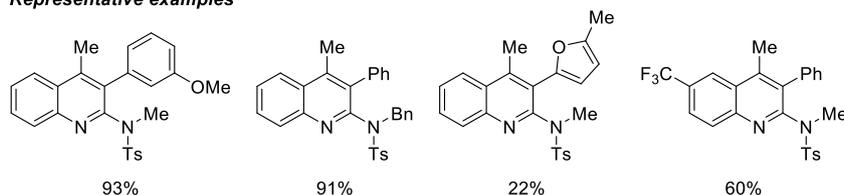


**Scheme 41.** Synthesis of indolines by intramolecular [4+2] cycloaddition of ynamides tethered with 1,3-enynes

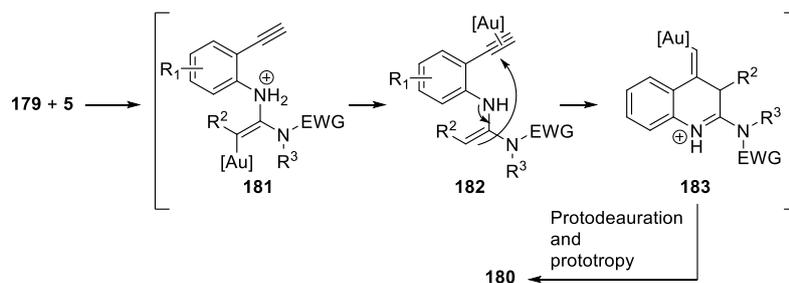
In 2018, the synthesis of 2-aminoquinoline **180** via a [4+2] cycloaddition was reported by Hashmi and coworkers starting from 2-ethynylanilines derivatives **179** and ynamides **5** under gold(I) catalysis (Scheme 33).<sup>[70]</sup> The reaction proceeded through nucleophilic attack of the aniline onto the gold-activated ynamide **5**, followed by a 6-*exo*-dig cyclization leading to **183**. Unfortunately, substituted alkynes were not reactive partners in this transformation.



**Representative examples**

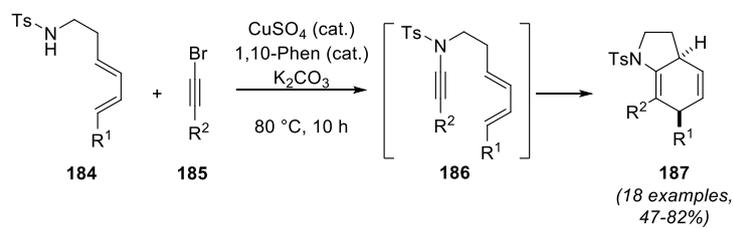


**Proposed mechanism**

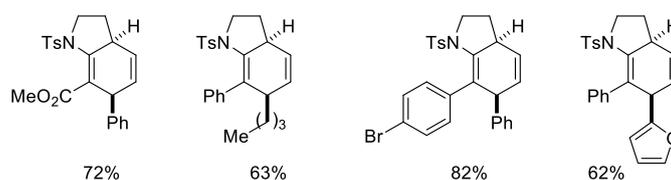


**Scheme 42.** Synthesis 2-aminoquinolines via intramolecular [4+2] cycloaddition of *o*-alkynylanilines with ynamides

Copper is the privileged metal for ynamide synthesis from alkynes (or alkyne surrogates) and nitrogen nucleophiles, but it can also favor [4+2] cycloaddition of ynamides. In 2019, Xu, Shen and coworkers used this strategy to perform a one-pot synthesis of tetrahydroindoles **200** by the *in situ* formation of ynamide **186** from the correspond alkynyl bromides **185** and subsequent intramolecular [4+2] cycloaddition with the pendant diene (installed from sulfonamido-1,3-diene **184**) (Scheme 43).<sup>[71]</sup> Formation of the intermediate ynamide **186** was confirmed experimentally by performing the alkynylation reaction at 45 °C.

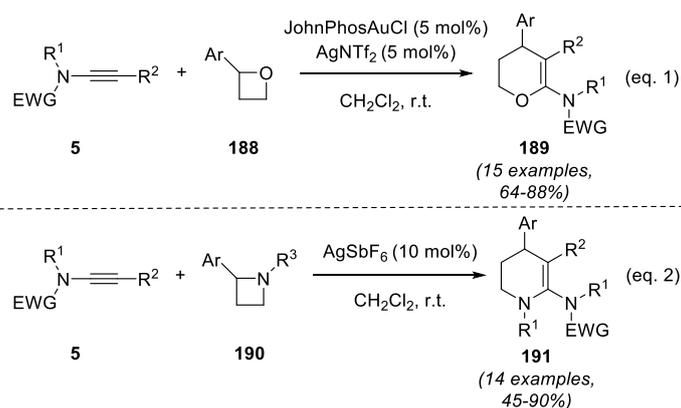


**Representative examples**



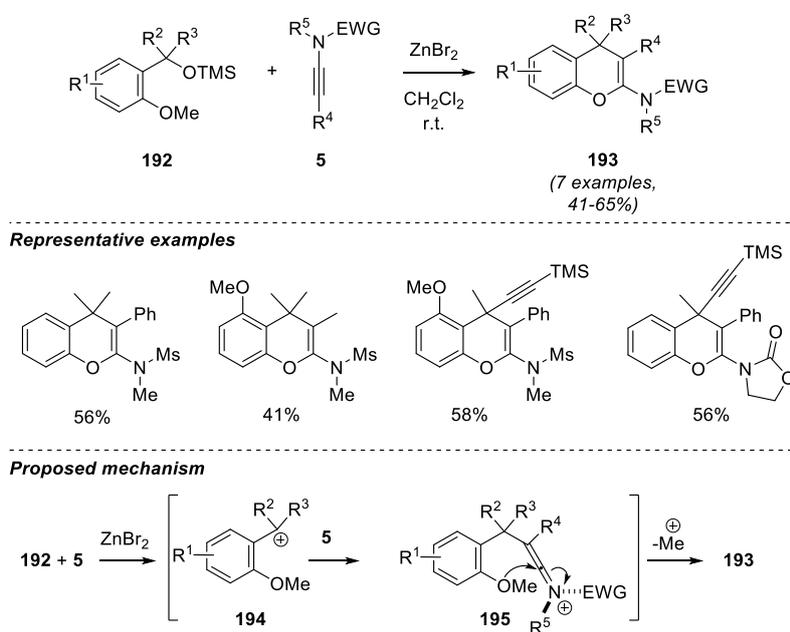
**Scheme 43.** Copper-catalyzed *N*-alkynylation/[4+2] cycloaddition cascade

In 2014, Pawar and coworkers reported the synthesis dihydro-2*H*-pyrans **189** and tetrahydropyridines **191** derivatives by [4+2] cycloaddition of ynamides **5** with oxetanes **188** or azetidines **190**, respectively. Classical gold(I) catalysis proved to be more efficient than silver(I) catalysis to deliver **189** in good yields (Scheme 44, eq. 1). In contrast, the opposite trend was observed for the synthesis of **191**, for which silver(I) catalysis gave higher yields (Scheme 44, eq. 2).<sup>[72]</sup>



**Scheme 44.** [4+2] Cycloaddition of ynamides with oxetanes and azetidines

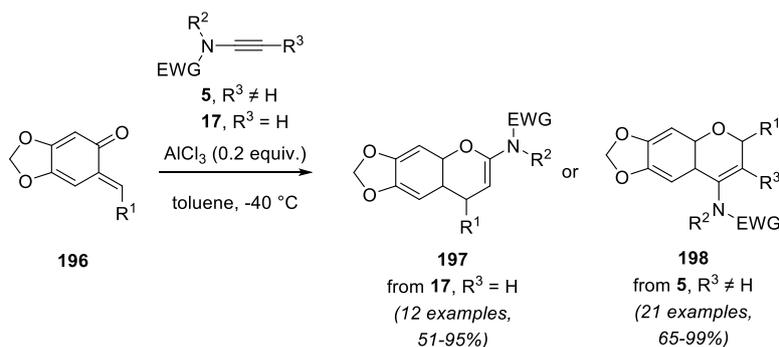
Zinc(II)-promoted [4+2] cycloadditions between benzylethers **192** and ynamides **5**, leading to chromenes **193**, were described by Chen and coworkers in 2016 (Scheme 45).<sup>[73]</sup> Thanks to the Lewis acid character of zinc bromide, a benzyl carbocation **194** can be generated from *o*-methoxybenzyl silyl ethers **192**, which then reacted with ynamide **5** and cyclized to form 2-amido-4*H*-chromenes **193** in moderate yields. Interestingly, the reaction was still effective with benzyl silyl ethers without the methoxy group and 1-aminoindenes were obtained via a formal [3+2] cycloaddition.



**Scheme 45.** Zinc(II)-promoted synthesis of 2-amido-4*H*-chromenes from benzylethers and ynamides

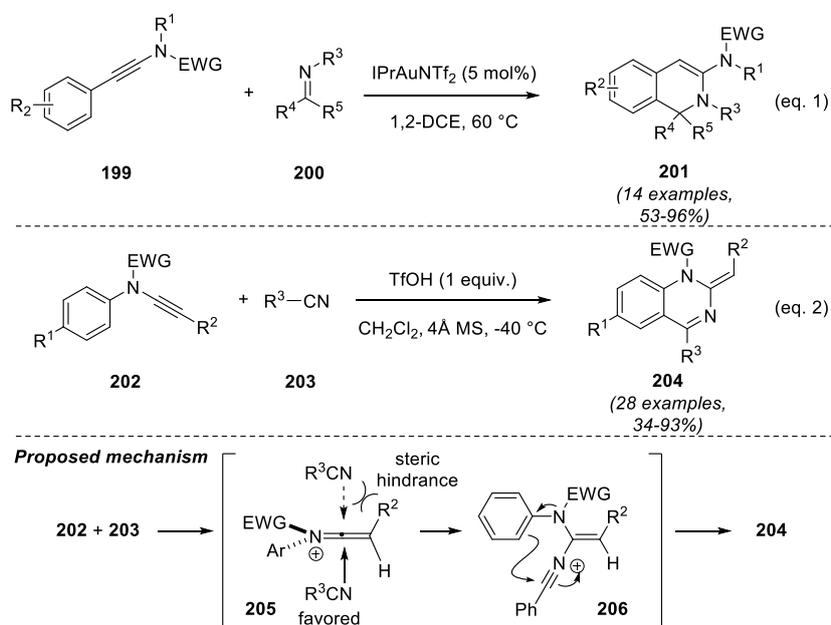
The use of  $\text{AlCl}_3$  to catalyze annulation of terminal ynamides **17** ( $\text{R}^3 = \text{H}$ ) with *o*-quinone methide derivatives **196** has been reported by Yang and coworkers in 2016.<sup>[74]</sup> This method enabled the access to 2-amino-2*H*-chromenes **197** with moderate to excellent yields. Interestingly, with internal ynamides **5** ( $\text{R}^3 \neq \text{H}$ ), reaction favored [2+2] cycloaddition

followed by  $4\pi$ -electrocyclic ring opening and  $6\pi$ - electrocyclic ring closure affording 4-amino-2*H*-chromenes **198** (Scheme 46).



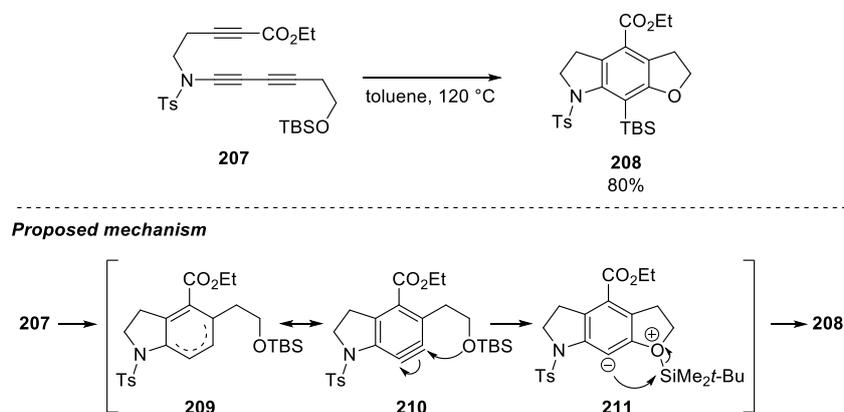
**Scheme 46.** Aluminum(III)-catalyzed divergent synthesis of 2- or 4-amino-2*H*-chromenes from terminal or  $\beta$ -substituted ynamides

In 2014, Xin and coworkers reported the use of ynamides such as **199** in [4+2] cycloaddition with imines **200**. Interestingly in that case, ynamide can play the role of the  $4\pi$ -electrons partner for the synthesis of 1,2-dihydroisoquinolines **201** with good to excellent yield using gold(I) catalysis (Scheme 47).<sup>[75]</sup> Similarly, in 2019 Wu and coworkers demonstrated that reaction of *N*-aryl ynamides **202** with nitriles **203** in the presence of triflic acid delivered isoquinazolines **204** in high yields.<sup>[76]</sup> The reaction showed excellent diastereoselectivity regarding the final configuration of the alkene, probably due to the face preference during the attack of the nitrile on keteniminium **205**.



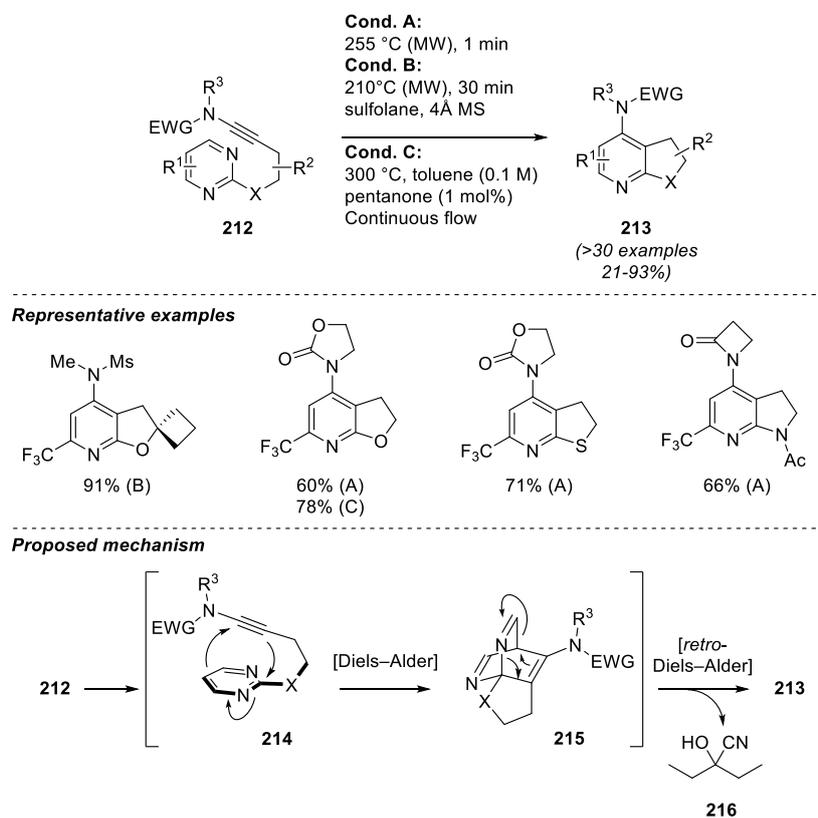
**Scheme 47.** [4+2] Cycloaddition of C- and N-aryl ynamides with imines or nitriles

HexahydroDiels–Alder (HDDA) reactions of ynamides were described by Hoyer and coworkers in 2012.<sup>[77]</sup> Heating ynamide **207** at 120 °C in toluene led to polycycle **208** via the HDDA to **209** followed by cyclization of the silyloxy motif onto the benzyne. A final 1,3-silyl migration delivered the observed adduct (Scheme 48). The reaction is quite simple, and lead to a rather complex structure with a great atom economy.



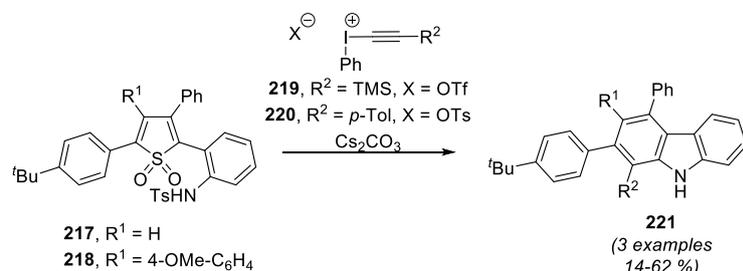
**Scheme 48.** Hexadehydro Diels-Alder reaction of ynamide

In 2017, Blanchard and coworkers reported the first example of an intramolecular inverse electron-demand hetero-Diels-Alder (ihDA)/retro-Diels-Alder (rDA) between an ynamide (acting as the  $2\pi$  partner) and a pyrimidine system (acting as the  $4\pi$  partner) (Scheme 49).<sup>[78]</sup> Heating **212** between 210 and 255 °C (in microwave, conditions A or B) for a short time delivered the fused pyridine **213** in good yields. The method was extended to continuous flow conditions in superheated toluene (conditions C, 300 °C) which enable the synthesis of multigrams of cycloaddition product within very short times ( $t_{R,eff} = 7.4$  min). 3-Pentanone (1 mol%) proved to be central to avoid blocking of the continuous flow system by trapping the cyanide generated from the retro-Diels-Alder step, which otherwise spontaneously polymerized.

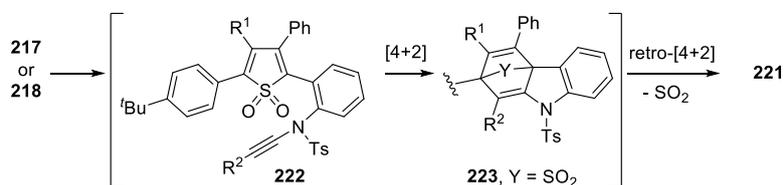


**Scheme 49.** Intramolecular inverse electron-demand hetero-Diels–Alder (ihDA)/retro-Diels–Alder (rDA) between ynamides and pyrimidines

In 2020, Yamaguchi and coworkers reported the formation of pentaarylcarbazoles **221** with different aryl groups on the benzenoid moiety.<sup>[79]</sup> In this method, initial *N*-alkynylation reactions of sulfonamides **217** or **218** with iodonium salts **219** or **220** let to ynamides **222** which spontaneously underwent intramolecular [4+2] cycloaddition between the  $\pi$  system of the ynamide and the thiophene dioxide. After chelotropic extrusion of  $\text{SO}_2$ , carbazoles **221** were obtained in modest to good yields.



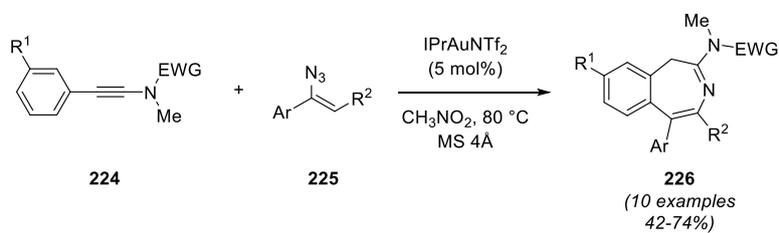
**Proposed Mechanism**



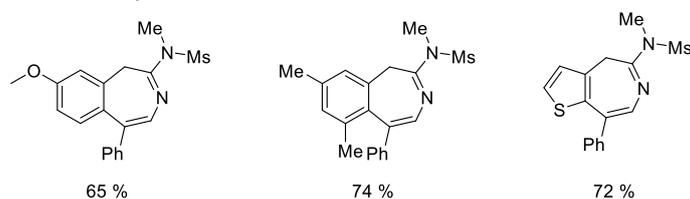
**Scheme 50.** Synthesis of carbazoles by [4+2] cycloaddition of ynamide

### 1.7 [4+3] CYCLOADDITIONS

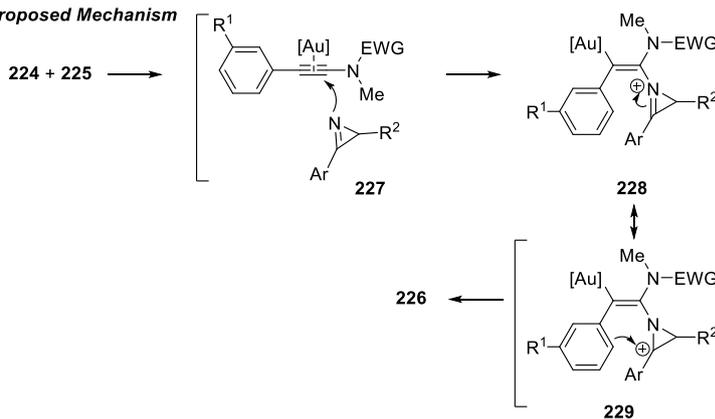
One of the classical methods to access 7-membered rings is the [4+3] cycloaddition reaction.<sup>[80]</sup> In 2015, Liu and coworkers showed that ynamides **224** reacted with azidoalkenes **225** in a gold(I)-mediated [4+3] formal cycloaddition to afford 1*H*-benzo[*d*]azepines **226** (Scheme 51).<sup>[81]</sup> The reaction involved the thermal formation of a stable 2*H*-azirine **227** which attacked the gold-activated ynamide to form an alkenylgold intermediate **228**. The iminium character of the 2*H*-aziridinium then triggered an attack of the adjacent electron-rich phenyl group. Ring-opening of the aziridinyll group and aromatization delivered **226** in moderate to good yields.



**Representative examples**



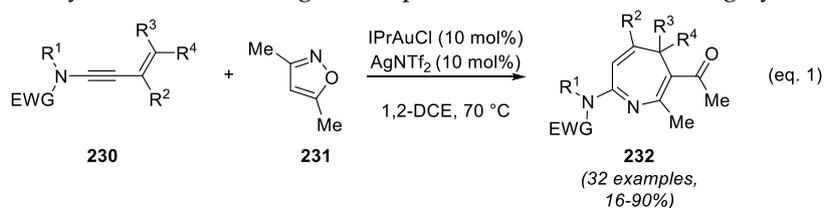
**Proposed Mechanism**



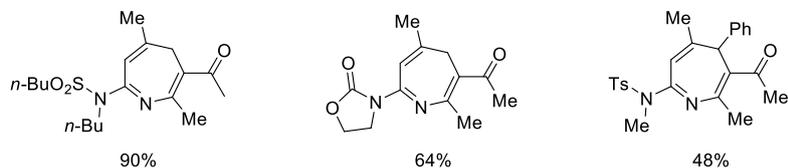
**Scheme 51.** Gold(I)-catalyzed synthesis of 1*H*-benzo[*d*]azepines from ynamides and vinylazides

In 2018, the same group reported the gold-catalyzed [4+3] cycloaddition of enyamides **230** with isoxazoles **231** to form 4*H*-azepines **232**.<sup>[82]</sup> The optimized conditions involved a catalytic amount of IPrAuCl and AgNTf<sub>2</sub> in 1,2-DCE at 70 °C (Scheme 52). The mechanism proposed by the authors starts with the N-attack of the isoxazole **231** onto the gold- $\pi$ -ynamide species to form a gold-carbene **234**, which can be visualized as a gold-stabilized cycloheptatrienyl cation. When R<sup>2</sup> is an alkyl or an aryl

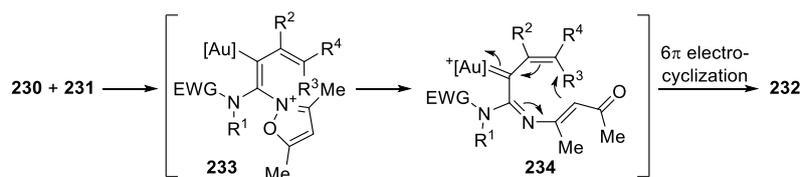
substituent, the preferred geometry of the intermediate **234** induced a  $6\pi$ -electrocyclization delivering *4H*-azepines **232** in moderate to high yields.



**Representative examples**

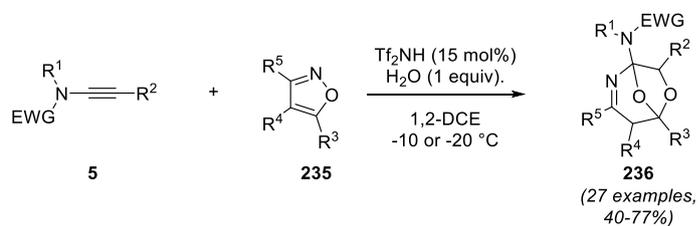


**Proposed mechanism**

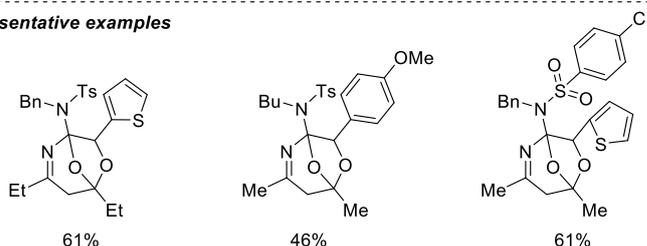


**Scheme 52.** Gold(I)-catalyzed [4+3] cycloaddition of ynamides with isoxazoles

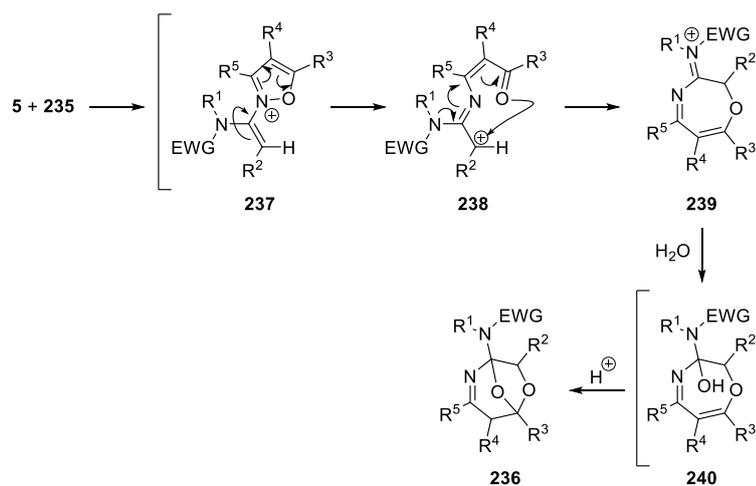
A distinct mechanistic pathway was discovered by Hu, Wan and coworkers for the reaction between ynamides, isooxazoles and water catalyzed by  $\text{Tf}_2\text{NH}$  (Scheme 53). A formal [5+2+1] cycloaddition was proposed, leading to oxygen-bridged tetrahydro-1,4-oxazepines in moderate to good yield.<sup>[83]</sup>



**Representative examples**



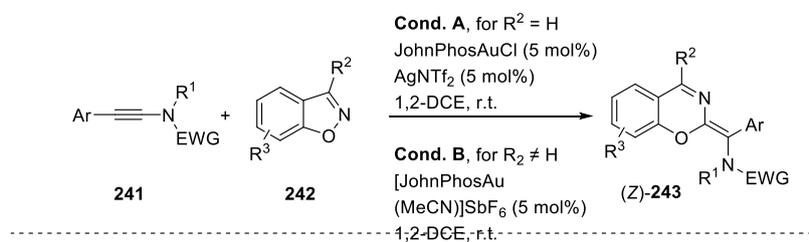
**Proposed mechanism**



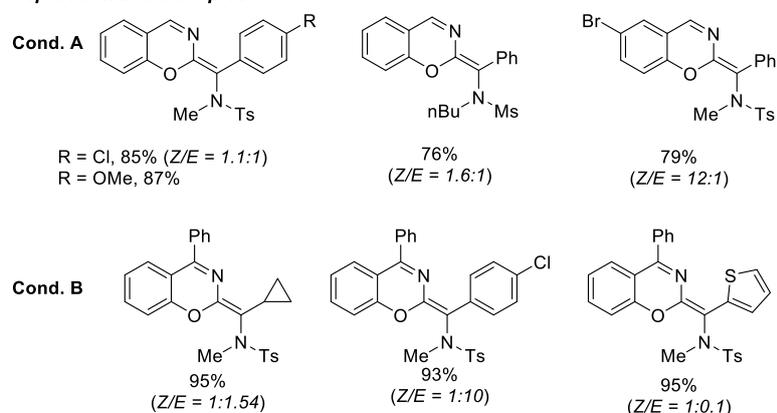
**Scheme 53.**  $\text{Tf}_2\text{NH}$ -catalyzed formal [5+2+1] cycloaddition of ynamides and isoxazoles with water

**1.8 [5+1] CYCLOADDITIONS**

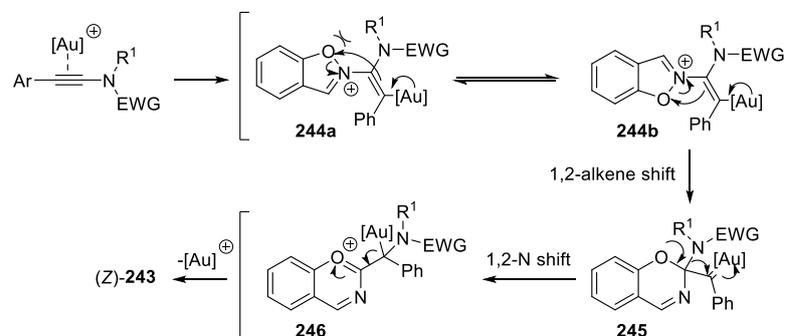
The first examples of [5+1] cycloaddition reactions of ynamides were reported in 2018. Liu and coworkers described a gold(I)-catalysed [5+1] annulation of ynamide **241** with 1,2-benzisoxazoles **242** (Scheme 54, conditions A).<sup>[84]</sup> The reactions were not fully selective, the [5+1] cycloaddition products **243** being obtained in good yields but as a *Z:E* mixture (from 1:1 to >20:1 in favor of the *Z* isomer). Moreover, a by-product resulting from the [5+2] cycloaddition reaction was also observed in small amounts (6 to 19%, not depicted). From a mechanistic perspective, the nucleophilic attack of benzisoxazole **242** onto the gold-activated ynamide led to intermediates **244a,b** that could undergo a 1,2-alkene shift resulting in the formation of **245**. A 1,2-N-shift followed by deauration led **243**. The same year, a closely related study was reported by Liu and coworkers, although with C-3 substituted 1,2-benzisoxazoles **242** ( $R^2 \neq H$ ) and non-aromatic ynamides (Scheme 54, conditions B).<sup>[85]</sup>



**Representative examples**



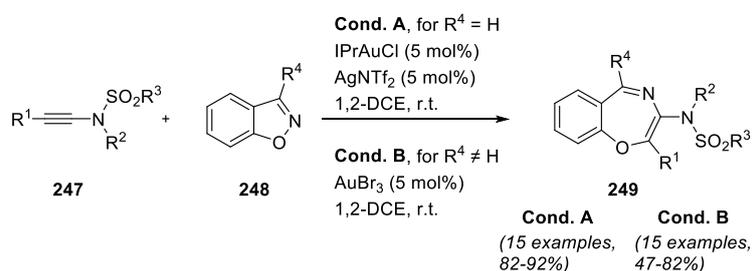
**Proposed mechanism**



**Scheme 54.** Gold-catalyzed [5+1] cycloaddition of ynamides with benzisoxazoles

**1.9 [5+2] CYCLOADDITIONS**

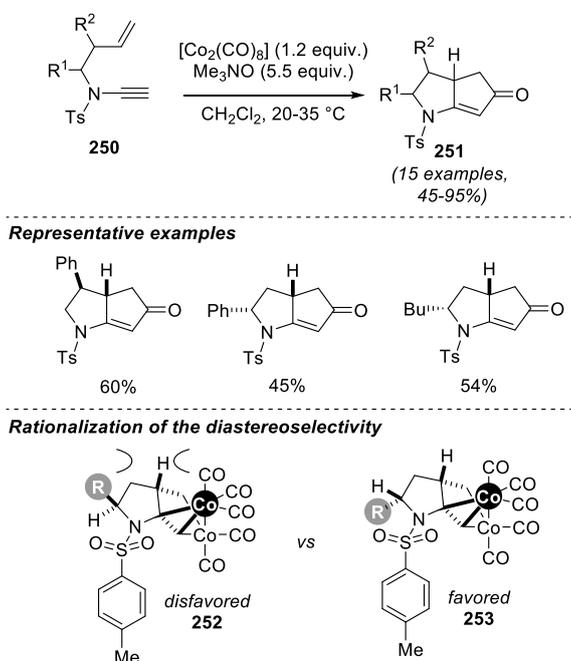
As mentioned above for the [5+1] cycloaddition, the [5+2] cycloaddition of ynamide has been reported by two groups at the same time.<sup>[84,85]</sup> Benzo[*d*]isoxazoles derivatives **248** were competent nucleophiles in gold-catalyzed [5+2] cycloaddition reactions with ynamides **247**, leading to benzo[*f*][1,4]oxazepines **249** (Scheme 55). The selectivity for the formation of 7-membered products **249** was attributed to the less sterically demanding gold catalysts, compared to the [5+1] cycloaddition depicted in Scheme 54.



**Scheme 55.** Gold-catalyzed [5+2] cycloaddition of ynamides with benzoisoxazoles

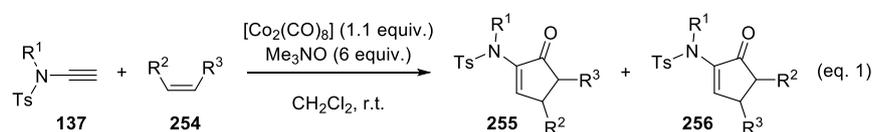
### 1.10 [2+2+1] CYCLOADDITIONS

The first examples of [2+2+1] cycloaddition of ynamides using a Pauson-Khand reaction was described by Witulski and coworkers in 1998 for the synthesis of cyclopentadienone derivatives **251** (Scheme 56) via an intermolecular or an intramolecular pathway using Co<sub>2</sub>(CO)<sub>8</sub> and trimethylamine N-oxide.<sup>[86]</sup> Moderate to good yields were observed and a single diastereoisomer was obtained when using  $\alpha$ - and  $\beta$ - branched enynamides. This observation may be rationalized by the energy difference between **252** and **253** en route to **251**, intermediate **252** being disfavored by pseudoaxial interactions between the R-group and the CO ligand of the cobalt complex.

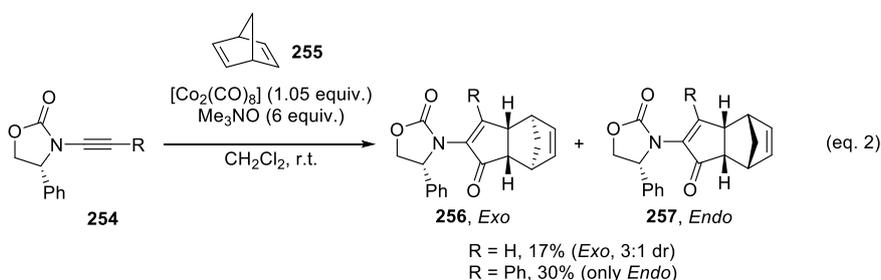
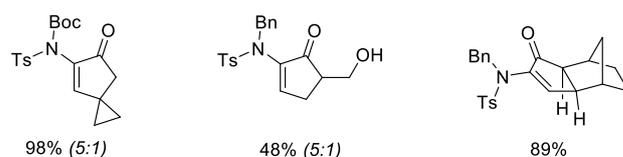


**Scheme 56.** Intramolecular Cobalt-catalyzed Pauson-Khand [2+2+1] cycloaddition of ene-ynamides

For the intermolecular [2+2+1] cycloaddition with non-symmetrical alkenes, regioselectivity for the cyclopentadienone **255** vs **256** can attain 5:1 with moderate to excellent yields (41-98%) (Scheme 57, eq. 1).<sup>[87]</sup> Hsung and coworkers studied the selectivity of the intermolecular Pauson-Khand reaction of chiral ynamides **254** with norbornadiene **263**. Adduct **256** resulting from an *endo* approach was obtained in 3:1 d.r. when a terminal ynamide was used. On the other hand, an unusual *endo* selectivity was observed when the R substituent of **254** was a phenyl group (Scheme 57, eq. 2).<sup>[88]</sup>

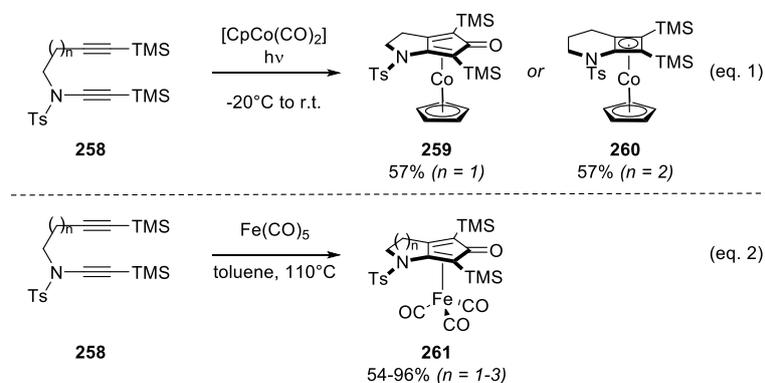


**Representative examples**



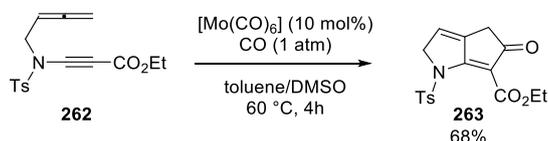
**Scheme 57.** Intermolecular Cobalt-catalyzed Pauson-Khand [2+2+1] cycloaddition of ynamides with alkenes and norbornadiene

In 2000, Rainier and coworkers discovered an intramolecular light mediated Pauson-Khand reaction of yne-ynamides **258** using  $\text{CpCo}(\text{CO})_2$  giving the cyclopentadienone-cobalt complex **259**.<sup>[89]</sup> In a separate report, they observed that those conditions were not applicable to every yne-ynamides, but that the length of the carbon chain separating the alkyne from the ynamide had an impact on the nature of the product. For instance, a [2+2] cycloaddition may be favored, resulting on the formation of the cobalt complex **260**.<sup>[90]</sup> The use of  $\text{Fe}(\text{CO})_5$  in toluene gave the expected [2+2+1] products **261** independently of the chain length (Scheme 58).



**Scheme 58.** Cobalt- and iron-mediated intramolecular Pauson-Khand cycloaddition of yne-ynamides

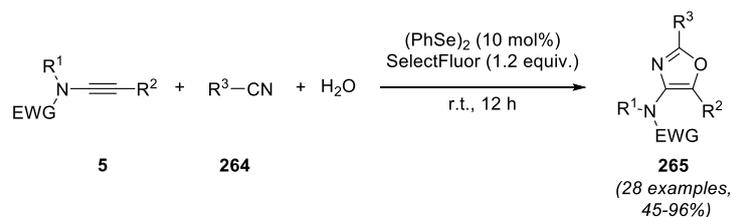
A molybdenum-catalyzed synthesis of cyclopentadienones **263** from allenyl-ynamide derivative **262** was described by Oh and coworkers in 2005. The reaction proceeded efficiently in the presence of a catalytic amount of molybdenum hexacarbonyl under an atmosphere of carbon monoxide **272** (Scheme 59).<sup>[91]</sup>



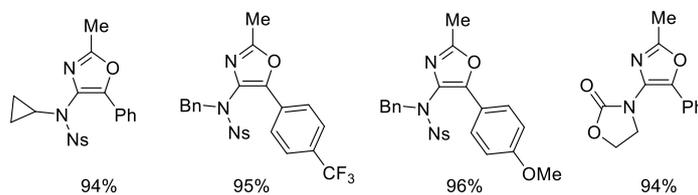
**Scheme 59.** Molybdenum-catalyzed intramolecular [2+2+1] cycloaddition

in 2018, Zhao and coworkers reported a synthesis of multi-substituted oxazoles **265** by a selenium-catalyzed [2+2+1] cycloaddition of ynamide **5** with a nitrile **264** and water (Scheme 60). This methodology is very general and efficient, leading to isolated oxazoles in yields up to 96%. On the other hand, it was observed that yields were moderate but less compatible with terminal ynamides.<sup>[92]</sup> The proposed mechanism demonstrated the importance of SelectFluor in this transformation for the activation of the diselenide by generation and regeneration of the catalytic species Ph-Se-X. The authors proposed the formation of selenirenium salt **266** followed by the highly electrophilic keteniminium salt **267**. Nucleophilic addition

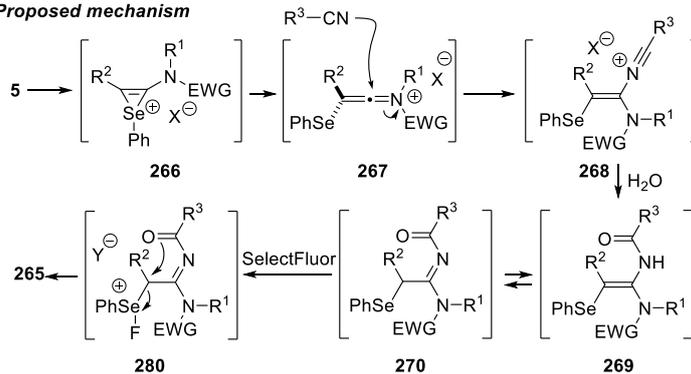
of the nitrile **264** then led to nitrilium **268** which was hydrolyzed to **269**. Prototropy followed by cyclization finally led to **265**, while regenerating PhSeX.



**Representative examples**



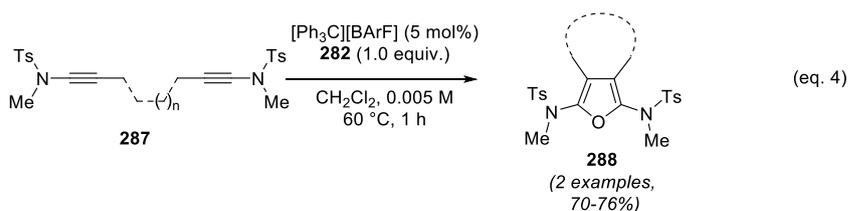
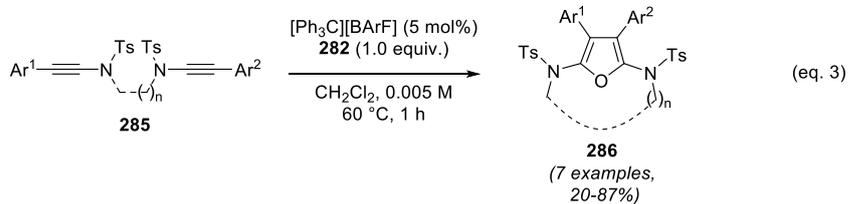
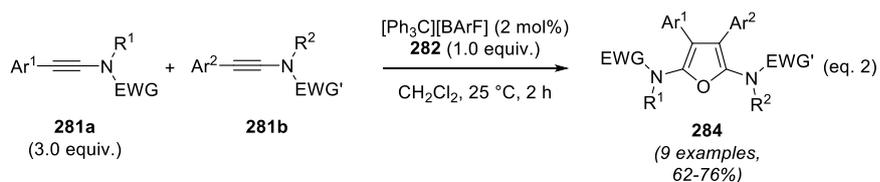
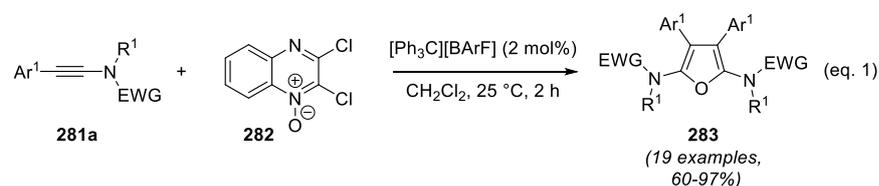
**Proposed mechanism**



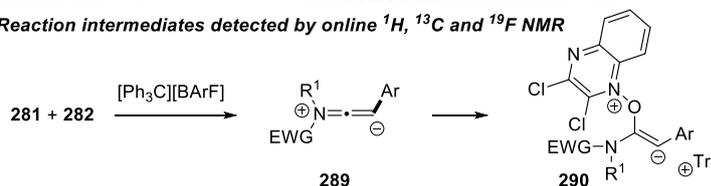
**Scheme 60.** Selenium-catalyzed [2+2+1] cycloaddition of ynamides with acetonitrile and water

Hashmi and coworkers described a metal-free [2+2+1] cycloaddition between two ynamides **281a** and the quinoxaline *N*-oxide **282** for the synthesis of 2,5-diaminofuran derivatives **283**.<sup>[93]</sup> Here, the trityl carbocation acts as a catalyst to activate the triple bond of the ynamide. This process is limited to ynamides substituted with an aromatic and it is more efficient with electron-rich aromatics (Scheme 61, eq. 1). The

synthesis of non-symmetrical diaminofurans **284** was also possible by using an excess of one of the two ynamides, leading to **284** with good yields (Scheme 61, eq. 2). Finally, using highly diluted conditions, an intramolecular pathway was developed for the synthesis of furans **286** and **288** from ynamides **285** and **287**, respectively, with moderate to good yields (Scheme 61, eq. 3-4). Several reaction intermediates were determined by NMR, such as **289** and **290**.



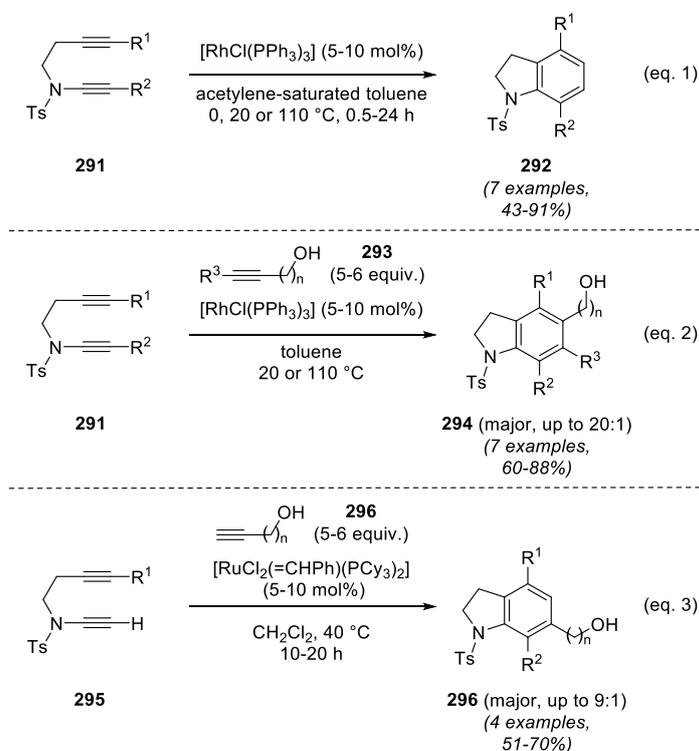
Reaction intermediates detected by online  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR



**Scheme 61.** Metal-Free synthesis of 2,5-diaminofurans by [2+2+1] cycloaddition of ynamides

### 1.11 [2+2+2] CYCLOADDITIONS

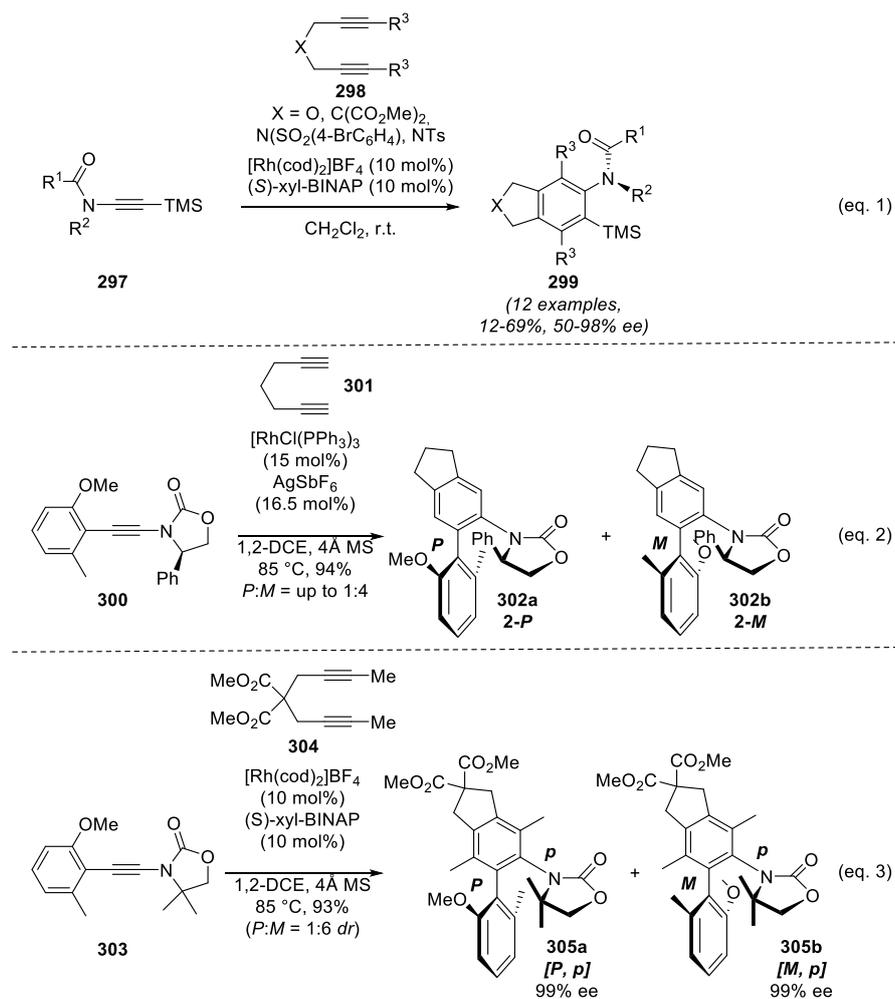
The rhodium- and ruthenium-catalyzed intramolecular [2+2+2] cycloaddition of yne-ynamides **291** and **295** have been studied by Witulski and coworkers (Scheme 62).<sup>[94,95]</sup> Indolines **292**, **294** and **296** were obtained in good yields. Quite interestingly, a switch in regioselectivity was observed between ruthenium-catalyzed reactions (**294** being major, up to 20:1, eq. 2) and rhodium-catalyzed ones (**296** being major, up to 9:1, eq. 3). A similar intra- or intermolecular strategy was also used for the synthesis of unsymmetrical carbazoles.<sup>[96]</sup>



**Scheme 62.** Regioselective rhodium- and ruthenium-catalyzed intramolecular [2+2+2] cycloaddition of yne-ynamides

In 2006, Tanaka and coworkers explored the enantioselective rhodium-catalyzed [2+2+2] of ynamides **297** with 1,6-diynes **298** (Scheme 63, eq. 1). This method gave access to functionalized axially chiral fused-anilides **299** in low to good yields, but with high enantioselectivity (up to 98% ee).<sup>[97,98]</sup> Independently, Hsung and coworkers intensively studied the synthesis of amide-substituted chiral biaryls by rhodium-catalyzed cyclotrimerization. The use of chiral ynamide **300** led to biaryls **302a** and **302b** with a diastereomeric ratio of 1:4 in favor of the 2-M product **302b** (Scheme 63, eq. 2).<sup>[99]</sup> Unfortunately, combination of chiral substrate with a chiral ligand on the rhodium catalyst drastically reduced the diastereoselectivity. Finally, it was found that achiral ynamide **303** can be converted to the corresponding biaryl **305b** using a chiral rhodium

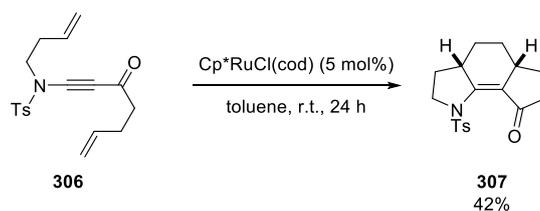
catalyst. A good diastereoselectivity (**305a/305b** = 1:6) and an excellent enantioselectivity (99% ee) was obtained (Scheme 63, eq. 3).<sup>[100,101]</sup>



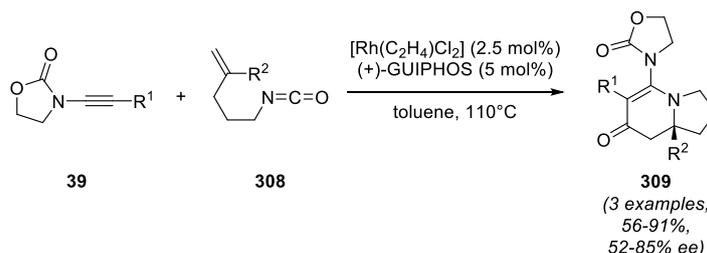
**Scheme 63.** Rh-catalyzed asymmetric [2+2+2] cyclotrimerization

Sato, Mori and coworkers reported the ruthenium-catalyzed intramolecular [2+2+2] cocyclization of diene-ynamide **306**, leading to **307**

in 42% yield (Scheme 64).<sup>[102]</sup> Ynamides **39** were also used by Rovis and coworkers in the enantioselective rhodium-catalyzed cycloaddition with alkenyl isocyanates **308**. An aryl-substituted ynamide gave both good yield and enantioselectivity, but regioselectivity was lost with an alkyl-substituted ynamide (Scheme 65).<sup>[103]</sup>



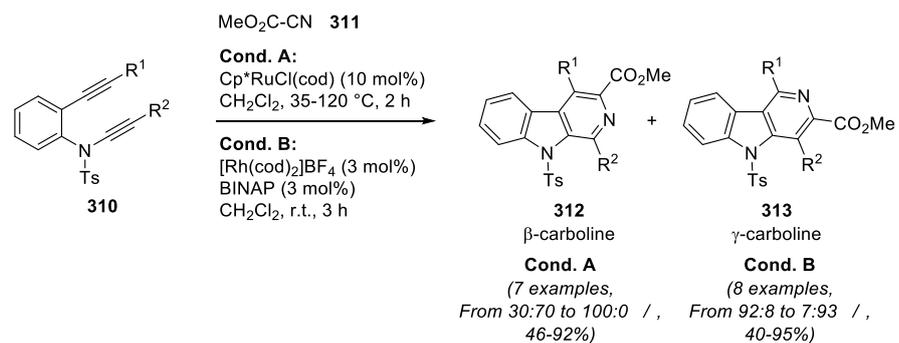
**Scheme 64.** Ru-catalyzed intramolecular [2+2+2] cycloaddition of diene-ynamide



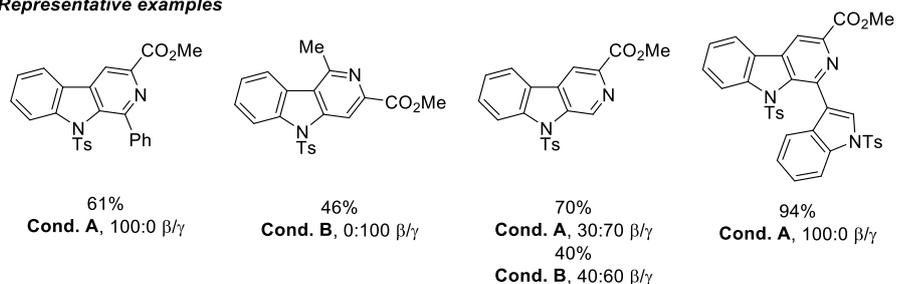
**Scheme 65.** Enantioselective rhodium-catalyzed cyclootrimerization of ynamides and alkenyl isocyanates

In 2011, Witulski and coworkers reported a flexible and regioselective synthesis of  $\beta$ - and  $\gamma$ -carboline **312** and **313** from ynamides **310** and Mander's reagent **311**, using ruthenium or rhodium catalysis (Scheme 66, conditions A or B).<sup>[104]</sup> Unfortunately, the regioselectivity was not controlled by the catalyst but mainly by the substrate substitution. Indeed, when a terminal alkyne was used,  $\beta$ -carboline **312** was favored, while terminal ynamide yielded selectively  $\gamma$ -carboline **313**. However, when both alkyne or ynamide are substituted or unsubstituted, a mixture of **312** and **313** was obtained. This methodology was successfully used in the synthesis of a key intermediate in the total synthesis of the marine natural product Eudistomin U (last example of Scheme 66). In 2011, Nissen and coworkers

used the same method for the synthesis of another  $\beta$ -carboline based natural product, Lavendamycin.<sup>[105]</sup>

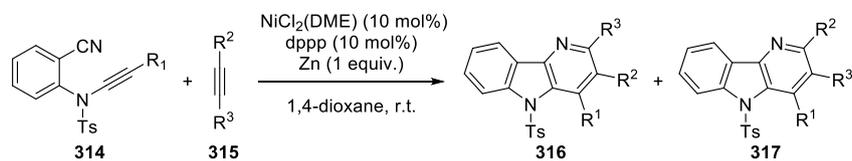


**Representative examples**

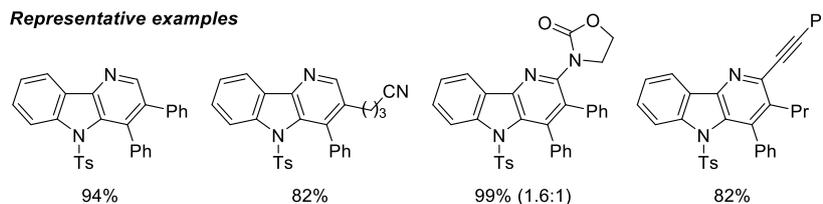


**Scheme 66.** Ru- or Rh-catalyzed intramolecular [2+2+2] cycloaddition of yne-ynamide for the synthesis of carbolines

In 2017, Liu and coworkers reported a nickel-catalyzed intermolecular [2+2+2] cycloaddition methodology for the synthesis of  $\delta$ -carbolines by reaction between a ynamide **314** and alkyne **315** (Scheme 67).<sup>[106]</sup> This methodology presented a regioselectivity challenge which depended mainly on the size of the substituents of **315**. Terminal alkynes led to increased regioselectivity.



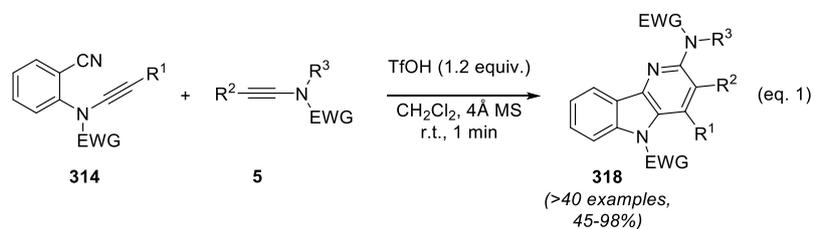
**Representative examples**



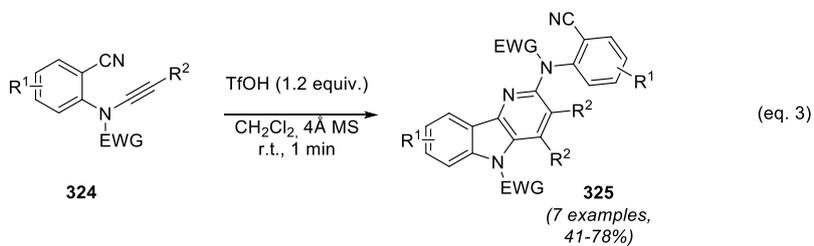
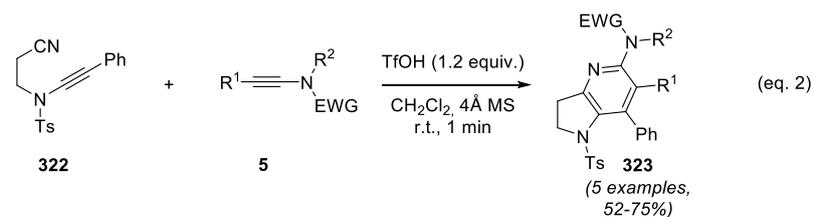
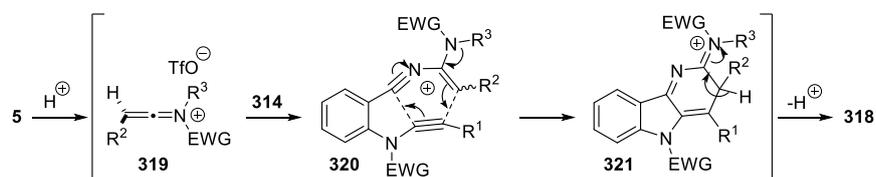
**Scheme 67.** Nickel-catalyzed [2+2+2] cycloaddition of nitrile-containing ynamides and alkynes for the synthesis of  $\delta$ -carbolines

In 2018, Cheng, Tang and coworkers reported the first metal-free [2+2+2] cycloaddition of nitrile-containing ynamide **314** and ynamide **5** for the synthesis of  $\delta$ -carboline derivatives **318**, mediated by  $\text{TfOH}$  as a Brønsted-acid (Scheme 68, eq. 1).<sup>[107]</sup> High regio- and chemoselectivities were obtained. The proposed reaction mechanism proceeded via the protonation of ynamide **319** with triflic acid to form keteniminium **319**, which was then attacked by the nitrile motif of **314** leading to **320**. Electrocyclization reaction of the latter followed by rearomatization afforded carboline **318**. Interestingly, this method can also be applied to the synthesis of 4-azaindolines **323** (Scheme 68, eq. 2) or even carboline **325** by a self-reaction process of ynamide **324** (Scheme 68, eq. 3).

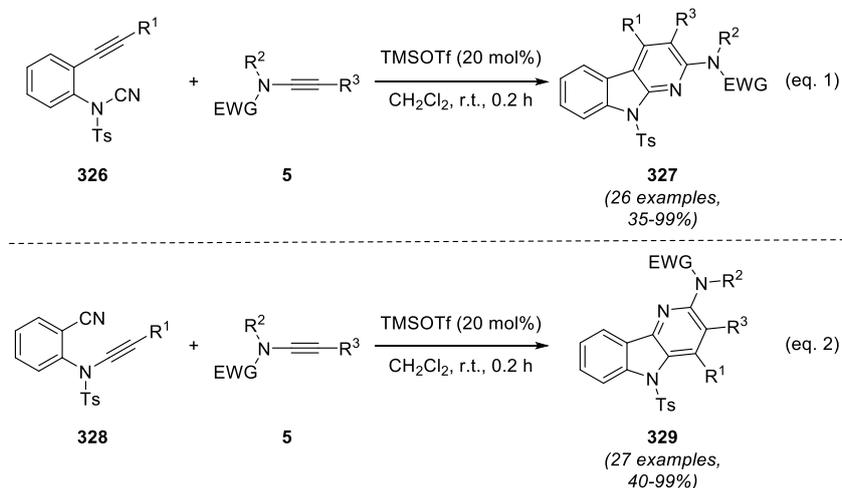
Later on, Wang, Chang and coworkers also succeeded to synthesize  $\delta$ -carboline derivatives, replacing  $\text{TfOH}$  by a catalytic amount of  $\text{TMSOTf}$ . This efficient methodology has been exemplified on more than 50 different 2-amino- $\alpha$ -carboline **329** and 3-amino- $\delta$ -carboline **331** (Scheme 69).<sup>[108]</sup>



**Proposed mechanism**

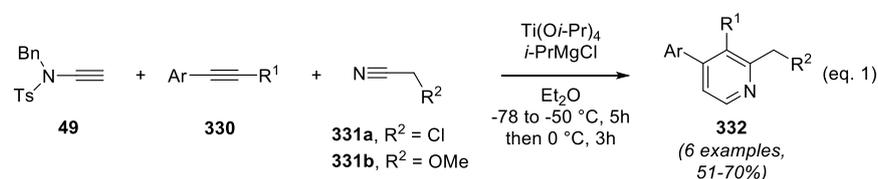


**Scheme 68.** Triflic acid-mediated [2+2+2] cycloaddition of nitrile-containing ynamides and ynamides for the synthesis of  $\delta$ -carboline and 4-azaindolines

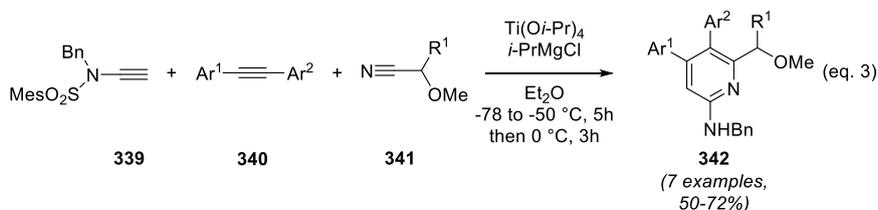
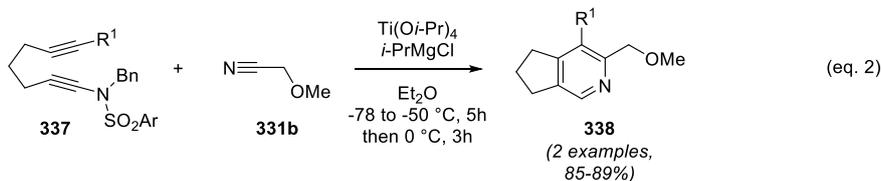
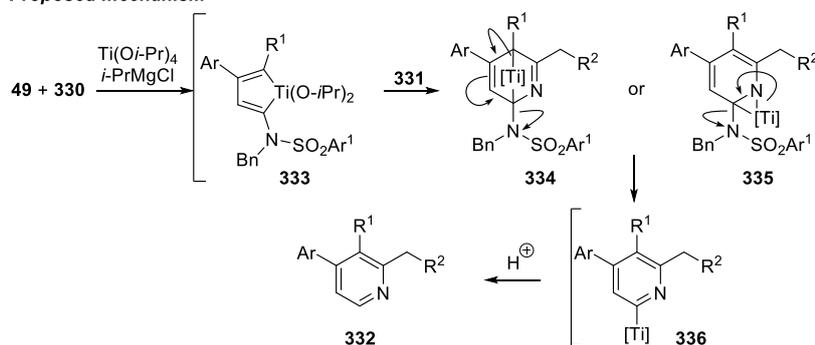


**Scheme 69.** TMSOTf-catalyzed synthesis of 2-amino- $\alpha$ -carboline and 3-amino- $\delta$ -carboline derivatives

In 2005, Sato, Urabe and coworkers reported a divalent titanium alkoxide-mediated [2+2+2] cycloaddition between ynamides, alkynes and  $\alpha$ -heterosubstituted nitriles (Scheme 70).<sup>[109]</sup> Pyridines were obtained and their substitution depended upon the nature of the alkyne and of the bulkiness of the electron-withdrawing substituent of the nitrogen atom in the ynamide. When the alkyne was substituted with one aromatic group, the [2+2+2] cycloaddition led to a titanated pyridine **336** which can be protonated to **332** (eq. 1). With alkyl-substituted alkynes, only the intramolecular version was efficient (eq. 2). Finally, with ynamides **339** and diarylated alkynes **340**, 2-aminopyridines **342** were obtained in moderate to good yields (eq. 3). In the latter case, elimination of the electron-withdrawing substituent of the nitrogen atom was the predominant mechanistic pathway.



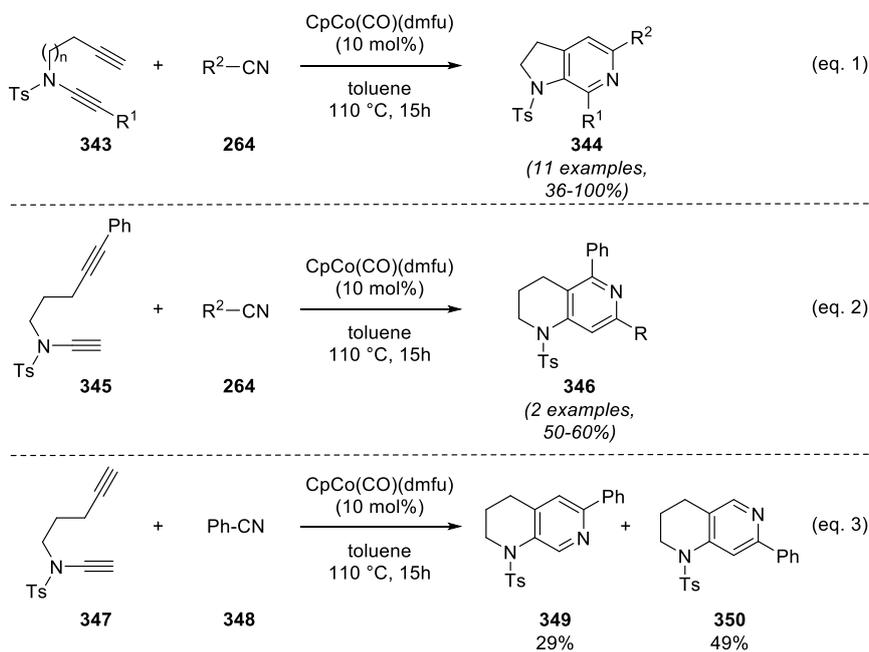
**Proposed mechanism**



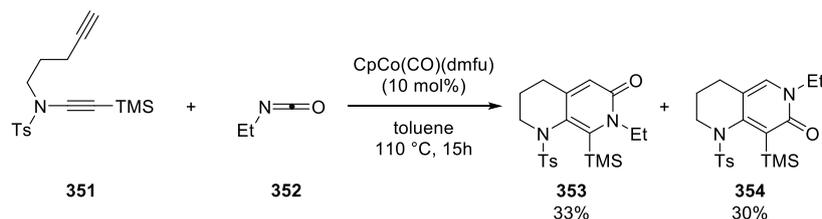
**Scheme 70.** Divalent titanium alkoxide-mediated [2+2+2] cycloaddition of ynamides, alkynes and  $\alpha$ -heterosubstituted nitriles

In 2009, Aubert, Malacria and coworkers reported the first cobalt-catalyzed cyclotrimerization of ynamides for the synthesis of 3-aminopyridines.<sup>[110]</sup> Later on, the method was improved by using the air stable CpCo(dmfu) instead of CpCo(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub> and fused pyridines **344**, **346**,

**349** and **350** were obtained with moderate to excellent yields (Scheme 71). Regioselectivity was mainly controlled by the substitution of the alkyne or ynamide moiety as shown for ynamide **347** which gave a mixture of the regioisomers **349** and **350**.<sup>[111]</sup> The cobalt-catalyzed transformation was further exemplified with isocyanates (Scheme 72), thus delivering to fused pyridones **353** and **354**.<sup>[112]</sup>

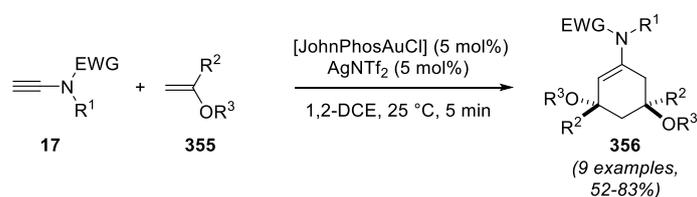


**Scheme 71.** Cobalt-catalyzed [2+2+2] cycloaddition of yne-ynamides with nitriles

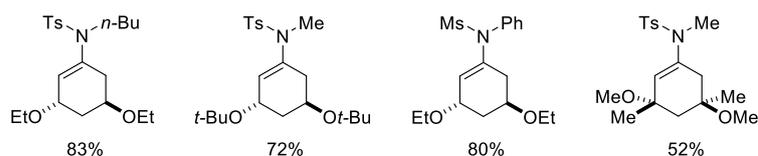


**Scheme 72.** Cobalt-catalyzed [2+2+2] cycloaddition of yne-ynamides and isocyanate

In 2012, Liu and coworkers reported the gold(I)-catalyzed [2+2+2] cycloaddition of ynamides of terminal ynamides **354** with enol ethers **355** leading to cyclic enamines **356** in a regio- and diastereoselective manner (Scheme 73).<sup>[113]</sup>



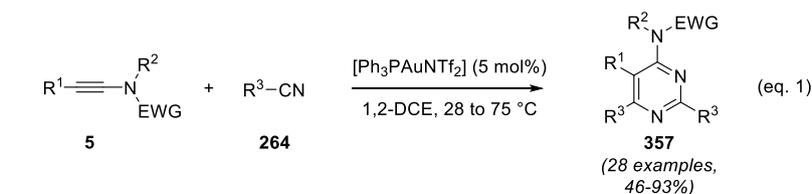
**Representative examples**



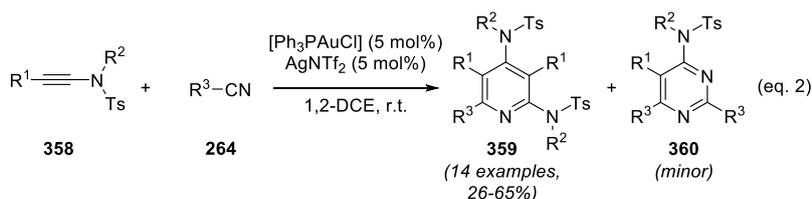
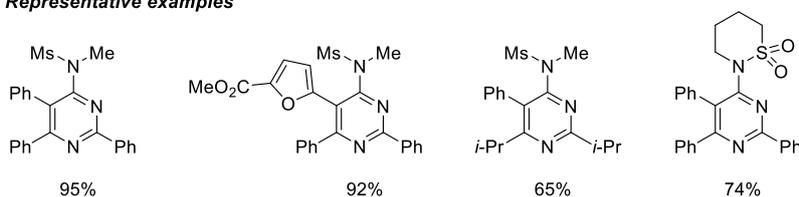
**Scheme 73.** Gold-catalyzed [2+2+2] cycloaddition of ynamides with enol ethers

Later on, the same group reported the gold-catalyzed [2+2+2] cycloaddition of ynamides **5** with two discrete nitriles **264** for the regiocontrolled formation of 4-aminopyrimidines **357** (Scheme 74, eq. 1).<sup>[114]</sup> The proposed mechanism involved the gold-catalyzed dimerization of the two nitriles **264** prior to reaction with ynamide **5**. However, this mechanism was later computed by Bi and coworkers who demonstrated that gold(I) catalyst itself cannot dimerize nitriles. On the other hand, a gold(I)-ynamide complex can effectively induce dimerization and yield a single regioisomer.<sup>[115]</sup> In 2016, Liu and coworkers demonstrated that shifting from N-Ms ynamide (**5**, R = SO<sub>2</sub>R) to N-Ts ynamide **358** changed the reaction outcome and led to 2,4-diaminopyridines **359** as major products, along with 4-aminopyrimidines **360** in a minor proportion (Scheme 74, eq. 2).<sup>[116]</sup> Yields are in general lower than in equation 1. A proposed mechanism suggested that a gold-activated ynamide was

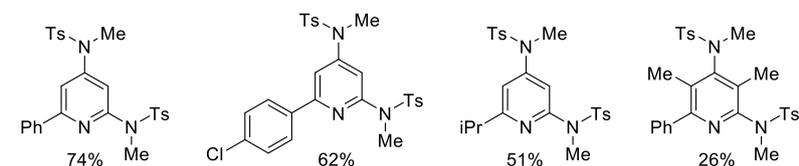
attacked by a nitrile, which was attacked by a second equivalent of ynamide followed by cyclization.



**Representative examples**

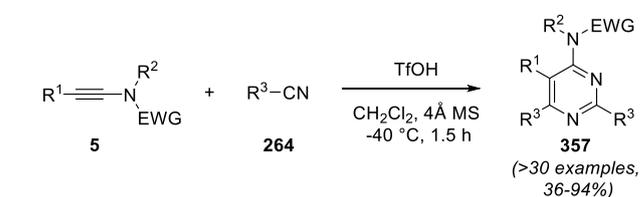


**Representative examples**

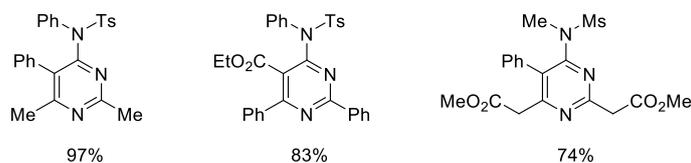


**Scheme 74.** Gold-catalyzed [2+2+2] cycloaddition of ynamides with nitriles leading to amino-pyrimidines and amino-pyridines

In 2016, Tang and coworkers introduced a metal-free synthesis of 4-aminopyrimidines **357** using triflic acid as Brønsted acid (Scheme 75). Acetonitrile can play both roles of solvent and reactant, otherwise dichloromethane was used as solvents for other nitriles.<sup>[117]</sup> Control experiments showed that mixing two different nitriles ended up with the formation of the four possible products without control.

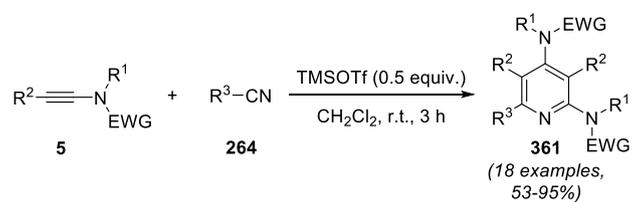


**Representative examples**

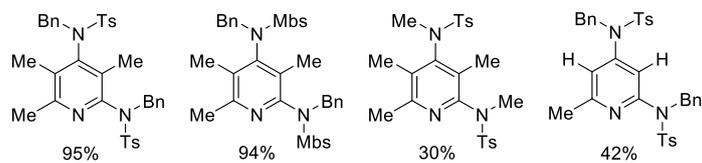


**Scheme 75.** Triflic acid-mediated [2+2+2] cycloaddition of ynamide with nitrile leading to 3-aminopyrimidines

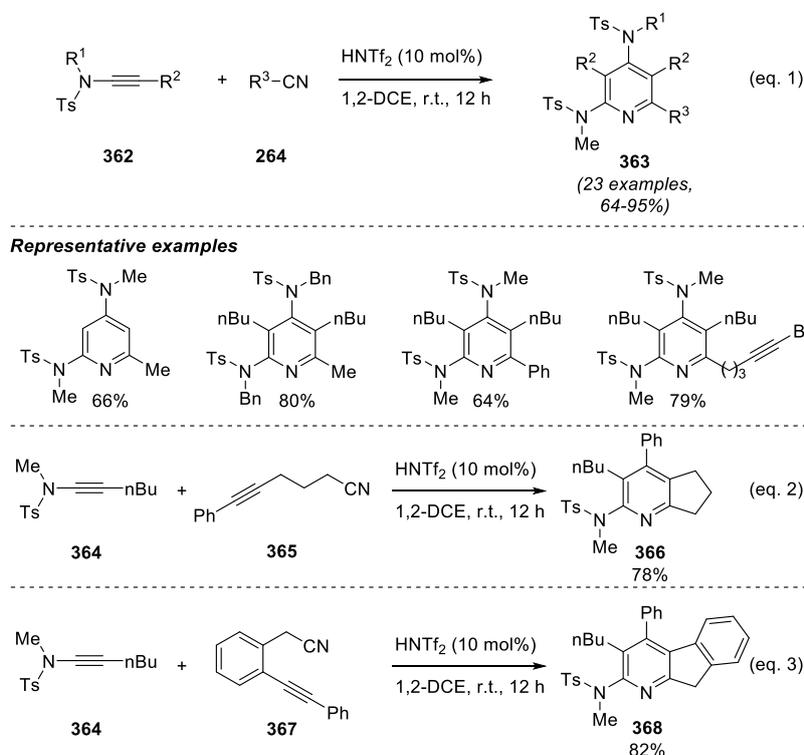
Wang, Chang and coworkers proposed an efficient and alternative metal-free synthesis of 2,4-diaminopyridines **361** using TMSOTf at room temperature (Scheme 76). The electron-withdrawing group of ynamides **5** needs to be an arylsulfonamide, but in contrast to Liu's method with triflic acid,<sup>[116]</sup> the corresponding pyrimidines were not observed as by-products.<sup>[118]</sup> In 2016, Zhang, Sun and coworkers published another metal-free cyclotrimerization of ynamides **362** with nitrile **264** using this time bistriflimide as a catalyst (Scheme 77, eq. 1).<sup>[119]</sup> Even though this method often needed thermal assistance and long reaction time, it can be applied to a large panel of nitriles. Using yne-nitriles **365** and **367**, fused aminopyridines **366** and **368** were obtained in good yields (Scheme 77, eq. 2-3).



**Representative examples**

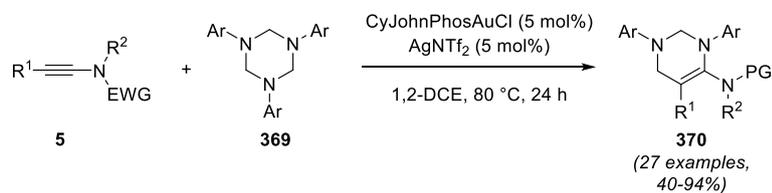


**Scheme 76.** TMSOTf-catalyzed [2+2+2] cycloaddition of ynamides with nitriles for the synthesis of 2,4-diaminopyridines

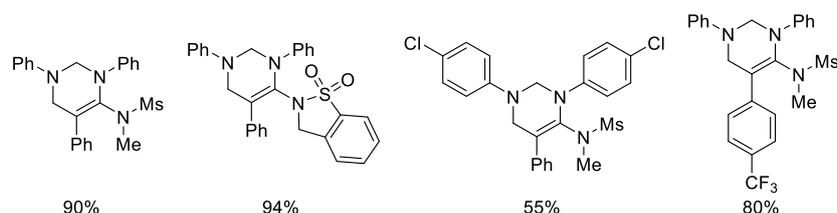


**Scheme 77.** Bistriflimide-catalyzed [2+2+2] cycloaddition of ynamides with nitriles and yne-nitriles

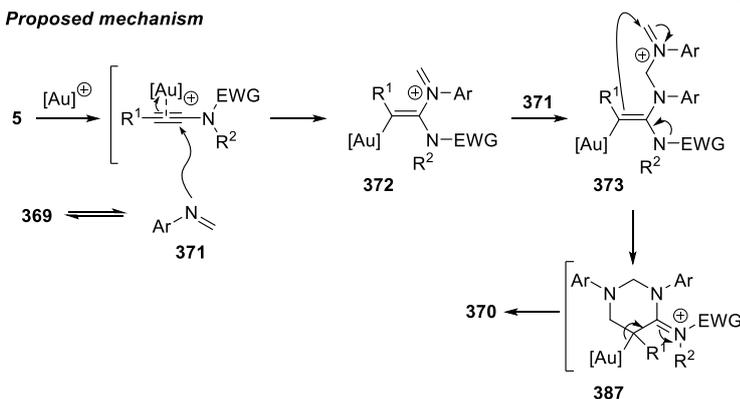
In 2017, Hashmi and coworkers published a [2+2+2] cycloaddition of ynamides **5** with 1,3,5-triazanes **369** as cyclization partners.<sup>[120]</sup> This gold-catalyzed process relied on the *in-situ* generation of imine **371** which attacked the gold-activated ynamide to form intermediate **372**. A second equivalent of imine **371** then attacked iminium **372**. Cyclization followed by deauration yielded **370** in moderate to excellent yields (Scheme 78).



**Representative examples**

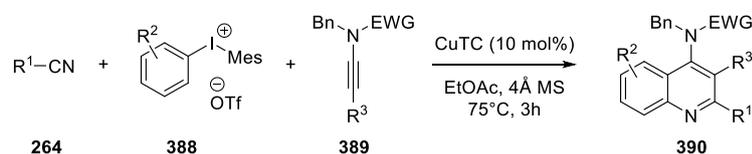


**Proposed mechanism**

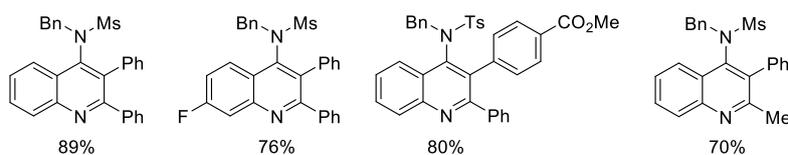


**Scheme 78.** Gold(I)-catalyzed [2+2+2] cycloaddition of ynamides and imines derived from 1,3,5-triazanes

In 2017, Park and coworkers explored another method of cycloaddition of ynamides **389** using diaryliodonium salts **388** and nitriles **264** under copper(I)-catalyzed conditions for the synthesis of 4-aminoquinolines **390** (Scheme 79).<sup>[121]</sup> High to excellent yields were obtained in most cases, except with electron-rich iodonium salt ( $R^2 = \text{OMe}$ ) for which a mixture of regioisomers was observed.

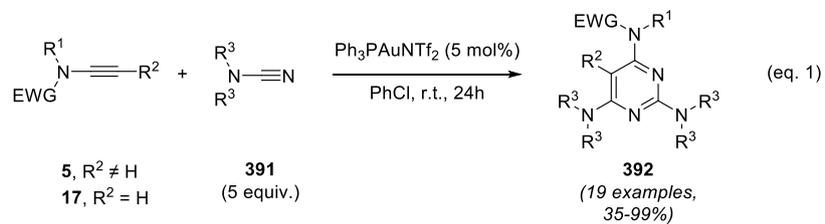


**Representative examples**

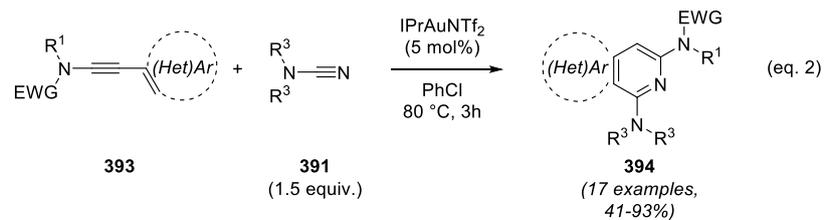
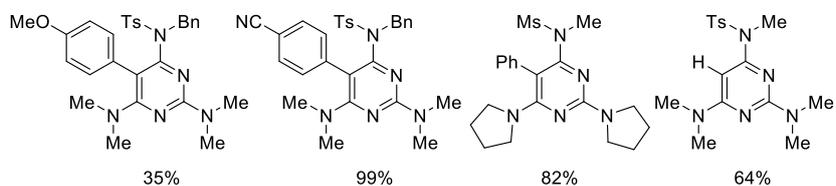


**Scheme 79.** Synthesis of 4-aminoquinoline by copper-catalyzed [2+2+2] cycloaddition

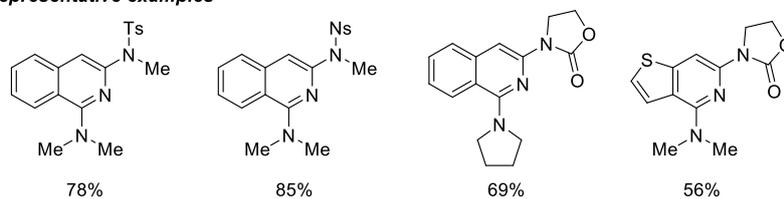
In 2020, Dubovtsev, Kukushkin and coworkers demonstrated that gold(I)-catalyzed [2+2+2] cycloadditions of ynamides with cyanamides could lead to two different *N*-heterocycles depending on the nature of the catalyst, the stoichiometry of the cyanamide and the reaction conditions (Scheme 80).<sup>[122]</sup> Indeed, with Ph<sub>3</sub>PAuNTf<sub>2</sub> (5 mol%) as the catalyst, with 5 equivalents of cyanamide **391** in chlorobenzene at room temperature, 2,4,6-triaminopyrimidines **392** were obtained in moderate to excellent yields (eq. 1). Upon switching to IPrAuNTf<sub>2</sub> as the catalyst, with 1.5 equivalents of cyanamide **391** in chlorobenzene at 80 °C, the 1,3-diaminoisoquinolines **394** were the major products (eq. 2). The proposed mechanism logically relied on the nucleophilic attack of cyanamide **391** on the π-activated ynamide followed by a second attack from cyanamide **391** (when the latter is in excess, bottom path) or from the aromatic ring substituting the π-system of the ynamide (when 1.5 equivalent of cyanamide **391** is used, right path).



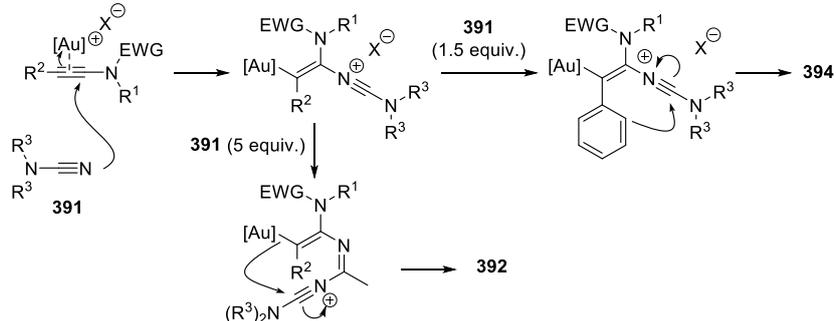
**Representative examples**



**Representative examples**



**Proposed mechanism**



**Scheme 80.** Gold-catalyzed [2+2+2] cycloaddition between ynamides and cyanamides for the synthesis of 2,4,6-triaminopyrimidines or 1,3-diaminoisoquinolines

## 1.12 CONCLUSION

This chapter summarizes intense efforts from the chemical community regarding the reactivity of ynamides in cycloaddition reactions. By no mean exhaustive, this selection of transformations highlights the potential of these nitrogen-substituted alkynes in various [2+1], [2+2], [3+2], [4+1], [4+2], [4+3], [5+1], [5+2] and finally [2+2+2] cycloaddition reactions, leading to a large diversity of heterocycles. Whether transition-metal catalyzed or metal-free transformations, these reactions are reliable, simple to set up, often high yielding and constitute an alternative pathway to classical heteroaromatic chemistry. Current efforts focus on the use of more sustainable transformations of ynamides, avoiding the use of precious metals. Without doubt, exciting new cycloaddition reactions of ynamides are within reach.

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