The Chemistry of Ynamide and Its Application in Organic Synthesis

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Abstract: Ynamide, is an understudied but attractive class of alkynes, activated by the donating ability of the nitrogen adjacent to alkynes. With the nucleophilicity on β-carbon and the electrophilicity on α-carbon of ynamides, this review summarizes the syntheses of ynamides and miscellaneous reactions - oxidation, rearrangement, cyclization, and cycloaddition to construct complicated heterocyclic rings. The synthetic methodologies were further applied into natural products synthesis, e.g. marinoquinolines A and C, aplidiopsamine A, rigidin A, and 7-azaserotonin derivative.

Keywords: ynamide, yndiamide, thioenamide, haloenamide, keteniminium, Witulski rearrangement, Ullmann coupling, dipolar cycloaddition, α-ketoimide, polycyclic alkaloids.

INTRODUCTION

The carbon-carbon triple bond is one of the most fundamental and valuable functional groups in the organic synthesis. A heteroatom substitution on the triple bond further enriches the reaction versatility. One useful substrate is ynamine, which contains a nitrogen atom directly connected to the triple bond. Conjugation of the nitrogen lone pair readily assists the electrophilic functionalization of the β-position of ynamines, and α-carbocation initiated nucleophilic addition or cyclization reactions (Scheme 1). However, the synthetic utility of ynamines remained limited due to difficult preparation and handling. They are liable to hydrolyse to amides in an expensive manner. The ynamides were therefore tunable by introducing diversified amides, i.e., amides, sulfonamides, carbamates, oxazolidinones, imidazolidinones, and lactams (Scheme 1). Ynamides, with weakened electron-donating electron lone pair of the nitrogens towards the alkylnyl motifs, have been found to be more stable and practicable than conventional ynamines.

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The ynamide chemistry, emerging several decades ago, has been gaining more and more attentions since 2000. Hsung’s group [1, 2] and Evano’s group [3, 4] have published elegant reviews to cover the development. This review focuses on recent developments of syntheses and applications of ynamides after 2010, in order to reveal the value of ynamide chemistry in organic synthesis.

**PREPARATIONS OF YNAMIDES**

**Dehydrohalogenation**

Dehydrohalogenation of halo-substituted enamides was the initial method of preparing ynamides. Viehe et al [5] reported the first case of preparing ynamides. \(N\)-(1-chloroalkenyl)urea 2, generated from secondary acetamide 1 and phosgene immonium chloride, undergoes dehydrochlorination at room temperature with \(t\)-BuOK to afford \(N\)-alkynylurea 3 in moderate yield (Scheme 2).

![Scheme 2: The first case of synthesizing ynamide.](image-url)

Another case is thymine / cytosine [6] derived chloroenamides 4 and 5, obtained by nucleophilic additions of thymines / cytosines to tetrachloroethylene. Dechlorination
(lithium-chlorine exchange) of 4 and 5 with \textit{n}-BuLi occurred smoothly at -70 °C to render ynamides 6 and 7 in 51% and 34% yields, respectively (Scheme 3).

Scheme 3: Lithium-chlorine exchange of chloroenamides to ynamides.

Hsung and co-authors [7] furthered explored the substrate scope to \(\beta\)-bromoenamides, prepared by bromination of the corresponding enamides 8. E2 elimination of hydrobromide from \(\beta\)-bromoenamides 9 with \(t\)-BuOK afforded ynamides 10 in 36–88% yields (Scheme 4), under which conditions, pyrrolidinones, oxazolidinones and imidazolidinones were tolerated. However, transformation of \(E\)-isomers of 9 into ynamides failed.

Scheme 4: Synthesis of ynamides from \(\beta\)-bromoenamides.

Brückner [8, 9] modified the substrates for ynamides via dehydrohalogenation. \(\beta\,\beta\)-Dichloroenamides 12, obtained by Corey-Fuchs reaction of \(N\)-formyl-tosylamides 11, were converted to terminal ynamides 13 in satisfying yields according to lithium-halogen exchange (Scheme 5). \(\beta\,\beta\)-Dibromo-enamides 14, however, were not tolerated, resulting in a mixture of terminal tosylynamides 13 and tosylamides 15.
Scheme 5: Synthesis of ynamides from β,β-dihalogen enamides.

The lithiated ynamide intermediates 16, obtained from the dechlorination of β,β-dichloroenamides 12 with 2 equivalents of n-BuLi, are useful for various transformations (Scheme 6). Transmetalation with ZnBr₂ and Negishi coupling reactions with aryl iodides afforded aryl-substituted ynamides 17 in moderate to good yields, according to Saá’s work [10, 11]. They also found that such lithiated ynamide intermediates could be trapped by diverse electrophiles [12] to render functionalized internal ynamides 18 in high yields. In the case of benzaldehyde as an electrophile, the yield was improved significantly than the direct functionalization of terminal ynamides.

Scheme 6: Functionalization of terminal ynamides with dichloroenamides.

Cossy et al [13] also developed the functionalization of ynamides using Suzuki-Miyaura coupling reaction of β,β-dichloroenamides 19 as the key step (Scheme 7). (Z)-β-chloroenamides 20, which would not undergo a second-round Suzuki-Miyaura coupling reaction, finally delivered ynamides 10 in moderate to good yields, upon treatment with LiHMDS (lithium hexamethyldisilazide) [7].

Recently, Anderson et al [14] reported a modular synthesis of ynamide using TCE (trichloroethene) as an inexpensive two-carbon synthon. A wide range of amides and electrophiles can be converted to the corresponding ynamides in good yields (50~91%) (Scheme 8), through lithium-chlorine exchange of α,β-dichloroenamides 22. This method thus overcomes those limitations mentioned in the above approaches.

Scheme 8: Synthesis of ynamides from TCE-derived α,β-dichloroenamides.

Alkynyliodonium salts

An alternative approach to ynamines / ynamides is to employ the highly electrophilic alkynyliodonium salts. In Stang’s pioneering report [15, 16], the nucleophilic addition of lithium diphenylamine 23 to the β-position of alkynyliodonium salts 24 delivered ynamines 25 in moderate yields, via 1,2-alkyl (or TMS) migration of vinylcarbene intermediate (Scheme 9).

Scheme 9: Synthesis of ynamines from 1,2-alkyl migration of vinylcarbenes.

Witulski and co-authors [17, 18, 19] extended this protocol to access ynamides. Nucleophilic addition of lithiated amides to the readily prepared trimethylsilyl alkynyliodonium salts 26 produced the desired ynamides 28 via 1,2-migration of the silyl group to highly electrophilic vinyl carbene intermediates 27 (Scheme 10).
Deprotection of TMS with TBAF (tetrabutylammonium fluoride) yielded the terminal ynamides $29$ in good to excellent yields. Their later studies [20] demonstrated that the terminal ynamides $29$ could also be synthesized from ethynyliodoniumtriflate $30$ directly.

Scheme 10: Witulski’s rearrangement to ynamides.

Rainer et al [21, 22] also used trimethylsilylethynyliodonium triflate $26$ to prepare the desired yne-ynamides $32$ (Scheme 11).

Scheme 11: Synthesis of yne-ynamides.

A modified procedure of preparing alkynyliodonium salt was to replace PdI(OAc)$_2$ with PhIO (iodosobenzene) by König et al [23] (Scheme 12).

Scheme 12: Synthesis of yne-ynamides.
The above studies establish a valuable strategy for ynamide preparation. However, the alkynyliodonium salts are limited to silyl, aryl and electron-withdrawing substituents.

**Ullmann coupling of amides**

With the renaissance of copper catalysis, Hsung’s group [24] made a breakthrough in ynamide synthesis in 2003 by developing a Cu(I)-catalyzed coupling reaction of alkyne bromides 38 with amides 21, including oxazolidinones, lactams, and carbamates, using DMEDA ($N,N'$-dimethylethlenediamine) as the ligand and K$_3$PO$_4$ as the base (Scheme 13). Upon harsh heating, the ynamides were produced in low to moderate yields.

![Scheme 13: First report of Ullmann coupling to ynamides.](image)

Later in the same year, Danheiser’s group [25] revised the sluggish Hsung’s condition and achieved a mild Ullmann coupling by enhancing the nucleophilicity of amides. Deprotonation of amides 21 under KHMDS and subsequent binding to stoichiometric CuI allowed the formation of stoichiometric amido copper species, which proved to be efficient in Ullmann coupling with bromoalkynes 38 to deliver ynamides in 40–76% yields (Scheme 14). The coupling reactions proceeded well with carbamates, sulfonamides, chiral oxazolidinones and chiral imidazolidinones.

![Scheme 14: Modified Ullmann coupling of amides to ynamides.](image)

The CuSO$_4$•5H$_2$O-1,10-phenanthroline complex has been identified as a robust catalyst [26, 27, 28] to promote Ullmann coupling of amides with bromoalkynes under mild heating condition. A wide range of amides could be converted to the corresponding ynamides, including sulfonamides and imidazolidinones. This method overcame the requirement of the harsh heating and strong base (Scheme 15).
Phosphoramidates have been recognized as the amide surrogates. Hsung et al. [29] described the first synthesis of N-phosphoryl ynamides featuring C- and P-chirality via Cu(I)-catalyzed amidative couplings between phosphoramidates 39 and phosphordiamidates 41 with alkynyl bromides 38, using a readily available catalytic system of a) CuSO₄•5H₂O and 1,10-phenanthroline; b) CuTC and DMEDA (Scheme 16).

Following Hsung’s and Danheiser’s homogeneous catalysis, heterogeneous catalysis in Ullman coupling was then investigated by Pale and co-workers [30]. This study investigated the feasibility of reusing or recycling utility of Cu(I)-ultra stable Y zeolite for the coupling of alkynyl bromides 38 and secondary amides 21 (Scheme 17). This
Cu(I)-ultra stable Y zeolite could be recycled at least five times, with a low loading (0.8-8 mol%) to be a key feature in realizing catalytic turnover.

Scheme 17: Synthesis of ynamides with heterogeneous copper catalyst.

Dibromoalkenes, readily prepared from corresponding aldehydes, were identified as alkynyl bromides surrogates in the Ullmann coupling [31]. Such dibromoalkenes could be coupled with various amides in the catalytic system of CuI and DMEDA (Scheme 18). In the proposed mechanism, amido-copper complex A underwent oxidative addition to the less-hindered C-Br bond of the dibromoalkene 43, followed by amide ligand-exchange and reductive elimination to render (Z)-α-bromoenamide C, which was validated by control experiment. Subsequent dehydrobromination with Cs$_2$CO$_3$ gave the target ynamide 10. The application of Cs$_2$CO$_3$ in 1,4-dioxane or DMF (N,N-dimethylformamide) was the best condition for the Ullmann coupling. Other choices of bases and solvents would lead to nucleophilic addition of amides onto ynamides [32, 33]. However, acyclic secondary amides or ureas did not give the corresponding ynamides.

Scheme 18: Synthesis of ynamides from vinyl dibromides and the proposed mechanism.
In the mean time, replacement of 1,1-dibromoalkenes by 1,2-dibromoalkenes with amides afforded ynamides via Cu(I)-catalyzed amidative cross-coupling [34] (Scheme 19). However, aliphatic 1,2-dibromoalkenes were inefficient for the Ullmann coupling, affording ynamides in poor yields (25~29%). Control experiments indicated that dehydrobromination of 1,2-dibromoalkenes occurred and gave alkynyl bromides prior to coupling with amide moieties, which was different from Evano’s work.

Scheme 19: Synthesis of ynamides from 1,2-dibromo-1-alkenes.

The synthesis and chemistry of yndiamides, acetylenes featuring two amido substituents, is unknown. This class of alkyne would be of considerable interest as a synthetic building block with two nitrogen substituents, yndiamides could exhibit distinct reactivities compared to ynamides. Anderson et al [35] has established the first synthetic route to yndiamides 46, a novel class of bis-aza-substituted alkynes, via Cu(I)-catalyzed cross-coupling of 1,1-dibromoenamides 45 with nitrogen nucleophiles 21 (Scheme 20). Their unique reactivities in Pd(OAc)$_2$, [(C$_{10}$H$_8$)Rh(cod)]SbF$_6$, RhCl(PPh$_3$)$_3$, AuCl(PPh$_3$)$_3$ / AgSbF$_6$, and Brønsted acid-catalyzed cyclizations, suggested significant potential for future applications.

Scheme 20: Synthesis of yndiamides.

(Z)-1-Bromo-2-iodoalkenes 47 were also coupled with carbamates (or oxazolidinones) 21 with catalytic nano-Cu$_2$O-DMEDA complex and delivered corresponding ynamides 10 in good yields [36] (Scheme 21).
**Scheme 21:** Synthesis of ynamides from 1-bromo-2-iodoalkenes.

Amidative coupling with potassium alkynyltrifluoroborates 48, catalyzed by complex of CuCl₂•2H₂O and 1,2-dimethylimidazole under base-free conditions proceeded smoothly to give a wide range of ynamides bearing oxazolidinones, imidazolidinones, sulfonamides and lactams [37] (Scheme 22).

\[ \text{R}^1 \text{NH} + \text{R}^2 \text{C} \equiv \text{BF}_3 \text{K} \xrightarrow{15 \text{ mol}\% \text{CuCl}_2 \cdot 2\text{H}_2\text{O}} \xrightarrow{4 \text{ Å MS (molecular solvent), O}_2} \text{R}^1 \text{N} \equiv \text{R}^2 \]

**Scheme 22:** Synthesis of ynamides from potassium alkynyltrifluoroborate.

**Oxidative coupling**

Evano’s group developed the methodology of aerobic amidative coupling with copper acetylides [38, 39, 40]. Notably, it obviates the need for a preformed haloalkyne or dihaloalkene. Generated in situ by mixing terminal alkynes 49 with CuI, ammonia, and K₂CO₃, the bench-stable copper acetylides 50 readily coupled with oxazolidinones and lactams 21 to furnish the corresponding ynamides 10 at room temperature (Scheme 23). The reductive copper was then oxidized by oxygen and triggered the next catalytic cycle.

\[ \text{R}^2 \text{C} \equiv \text{Cu} \xrightarrow{\text{CuL, NH}_3 / \text{H}_2\text{O} / \text{EtOH}, \text{or K}_2\text{CO}_3 / \text{DMF}, \text{r.t.}} \xrightarrow{\text{TMEDA, O}_2} \text{MeCN, r.t.} 54-91\% \]

**Scheme 23:** Synthesis of ynamides from copper acetylides.

Stahl et al [41] reported an oxidative amidative coupling with terminal alkynes 49 without utilizing bromoalkynes under harsh condition (Scheme 24). Byproducts were minimized by increasing the amount of nitrogen nucleophile 21 to 5 equivalents. The postulated mechanism rationalized the beneficial effect of using excess of the nitrogen nucleophiles: formation of Cu(II) (alkynyl)(amidate) species was expected to compete over the formation of bis-alkynyl Cu(II) species.
Propiolic acids 51 were identified as a bench-stable “masked” terminal alkynes for oxidative coupling to produce ynamides with yields up to 86%, through Cu-catalyzed decarboxylation [42] (Scheme 25).

Albeit of poor activities in catalyzing homo-coupling, Cu(OH)₂ was found to be efficient in oxidative cross-coupling of a broad range of terminal alkynes 49 and amides 21 to give the corresponding ynamides 10 in moderated to high yields, with a low loading of inorganic base (5 mol%) [43] (Scheme 26). Slow addition of terminal alkynes to the reaction mixture was not required in this protocol.

Interestingly, excess of CuO was found to mediate an “oxidative” amidative coupling of terminal alkynes 49 with 2-oxazolidinones 52 in the absence of oxygen [44] (Scheme 27).
Scheme 27: Synthesis of ynamides from oxidative coupling free of oxygen.

**Functionalization of terminal ynamides**

Sonogashira reaction is usually a good choice to synthesize substituted alkynes. However, when a standard Sonogashira cross-coupling condition was employed to ynamides, dimerization of ynamides was observed [10]. The first Sonogashira coupling was achieved by Hsung’s group via a two-step procedure [45] in which CuI was added after mixing a terminal ynamide, aryl halide, and palladium complex in a solvent. After detailed screening, Wakamatsu’s group [46] developed an efficient copper-free Sonogashira coupling of terminal ynamides 29 and aryl iodides 54 to provide substituted ynamides 55 (Scheme 28).

Scheme 28: Synthesis of ynamides from copper-free Sonogashira coupling.

Wolf’s group has made efforts to functionalize terminal ynamides [47] by addition of N-ethyl-N-phenyl-4-tolylsulfonamide 56 to acyl chlorides 57 and N-heterocycles 59, providing a variety of 3-aminoynones 58 and 1,2-dihydro-N-heterocycles 60 in high yields, respectively [48] (Scheme 29).

Scheme 29: Synthesis of amido-ynone.
They also developed the catalytic enantioselective addition of terminal ynamides 29 to aldehydes 61 [49]. In the presence of catalytic amounts of Zn(OTf)$_2$ and (-)-N-methylephedrine (NME), $N$-substituted propargylic alcohols 62 were formed in good yields and enatioselectivities (Scheme 30).

Scheme 30: Catalytic enantioselective addition of terminal ynamides to aldehydes.

**Strained cyclic ynamide**

Danheiser’s group [50] reported the first synthesis of a strained six-membered cyclic ynamide. $N$-tosyl-3-azacyclohexyne 64 was generated via fluoride-promoted 1,2-elimination of the precursor 63. Diels-Alder adduct 65 was formed after adding dimethylfuran as the trapping agent, which demonstrated the existence of the strained cyclic ynamide. Various nitrogen heterocyclic compounds could be obtained when different reaction partners were used (Scheme 31).

Scheme 31: Diels-Alder reactions of $N$-tosyl-3-azacyclohexynes with dienes.

**REACTIONS OF YNAMIDES**

The first decade of 21st century witnessed the fast growing of ynamide chemistry investigation. Many new transformations have been found during the investigation. In the second decade, researchers keep exploring more to reveal the value of ynamides. This section will discuss the recent advances of reactions of ynamides, including addition, nucleo-metalation, rearrangement, cyclization, and cycloaddition.
**Addition Reaction**

The electrophilicity of α-carbon and nucleophilicity of β-carbon of ynamides allow regioselective addition of nucleophiles or electrophiles onto the triple bond.

**Addition to α-position of ynamides**

*With carbon-halogen bond formation*

Evano, Thibaudeau and co-workers reported a highly regio- and stereo-selective synthesis of α-fluoroenamides through a hydrofluorination of ynamides in a superacid medium [51]. At first, they found that with the presence of appropriate amount of antimony pentafluoride (SbF₅), the ionic composition of HF-SbF₅ could drive the desired reaction to generate α-fluoroenamides. Later, they found that by using anhydrous superacid HF without SbF₅, the hydrofluorination performed more efficiently to achieve 96% yield in 5 minutes in -50 °C. The anhydrous superacid HF allowed the formation of highly reactive keteniminium intermediate and subsequent fluorination and minimized undesired side reactions (e.g. hydrolysis). A wide range of substrates were tolerated, including aryl, alkyl, alkenyl substituted ynesulfonamides, alkynyl carbamates and lactams. This hydrofluorination turned out to be highly stereoselective with (E)-α-fluoroenamides 66 as dominant products (Scheme 32).

With regard to keteniminium A, the steric hindrance between the substituent and the HF chain favored the addition of F⁻ at *trans*-position of R₂. When a directing group was introduced, this stereoselectivity could be tuned. 2-Pyridinyl substituted ynesulfonamide 67 gave (Z)-α-fluoroenesulfonamide 68 as the main product, which might be attributed to the fluorine-ammonium electrostatic interaction (Scheme 33).

![Scheme 32: Hydrofluorination of ynamides in anhydrous HF.](image-url)
Scheme 33: Ammonium assisted hydrofluorination of 2-pyridinyl substituted ynesulfonamides.

As bioisosteres of ureas, α-fluoroenamides could become powerful building blocks for biological and medicinal studies. Evano, Thibaudeau and co-workers continued to investigate hydrofluorination of ynamides [52] using the mixture of HF / pyridine (70 / 30, w / w). The new process avoided handling pure liquid HF and thus allowed the hydrofluorination of some ynamides which could not work in pure HF (Scheme 34).

Zheng, Zhu and co-workers [53] discovered that a new type of fluorination reagent, silver fluoride (AgF), could realize the hydrofluorination of ynesulfonamides 69 to render (Z)-α-fluoroenamides 70 in good yields, compared with (E)-counterparts using HF condition. After activation of triple bond by Ag⁺, F⁻ added to the α-carbon of ynamides from the back side of Ag⁺ to generate intermediate B. Further hydrolysis of B finally delivered product 70 (Scheme 35).

Scheme 33: Hydrofluorination of ynamides in HF/pyridine.

Scheme 34: Silver promoted trans-hydrofluorination of ynesulfonamides.
Zhu’s group [54] reported AgNTf$_2$ catalyzed trans-hydrofluorination of ynamides with Et$_3$N•3HF as the fluorine source, giving the (Z)-α-fluoroenamides 70 as the dominant products in good yields (Scheme 36).

Scheme 36: Ag catalyzed trans-hydrofluorination of ynamides.

It was noticeable that the regioselectivity of fluorination of ynamides was inversed when replacing AgNTf$_2$ with (PPh$_3$)$_3$CuF, presumably due to the existing 5-membered-chelation between Cu and amide groups (Scheme 37).

Scheme 37: Cu catalyzed trans-hydrofluorination of ynamides.

Interestingly, later report [55] showed that the inverse regioselectivity of hydrofluorination of ynamides was observed in the case of (IPr)CuF, with the explanation that the coordination between the Cu center and the carbonyl group of ynamides was disfavored arising from the steric hindrance of IPr group (Scheme 38).

Scheme 38: Cu catalyzed trans-hydrofluorination of ynamides.
As for hydrochlorination, Iwasawa et al [56] reported a facile, metal-free approach to prepare α-haloenamides \( \text{74} \) by the addition of \textit{in situ} generated HX (X = I or Br) to ynamides (Scheme 39) \textit{via} quenching the mixture of TMSX and ynamides with 20 equivalents of water.

![Scheme 39: Hydroiodation and hydrobromination of ynamides.](image)

This approach also worked for terminal ynamides [57]. The \textit{in situ} HX, generated from TMSX (X = Cl, Br, I) and 20 equivalents of water, could add to terminal ynamides \( \text{56} \) and form 1-haloethenamides \( \text{75} \) (Scheme 40). Water served as the key proton source, whereas C-N cleavage was observed when replacing water with methanol.

![Scheme 40: Hydrohalogenation of terminal ynamides.](image)

As for the conjugated ynamides (buta-1,3-diyn-1,4-diamides), the regio- and stereoselective hydrohalogenation proceeded under the same approach [58]. The authors pointed out that the combination of TMSCl and water failed to generate the desired product. A successful hydrochlorination required aqueous NH\(_4\)Cl, which would increase the concentration of chloride in the system, rather than water (Scheme 41). The study of unsymmetrically 1,3-diyn-79 also demonstrated an excellent chemoselective hydrobromination of ynamide in presence of the alkyne.
Iodobromine, with negative charged bromine and positive charged iodine, could add to ynamides to form (E)-α-bromo-β-iodoenamides. Iwasawa’s group [59] proved that this regio- and stereoselective iodobromination proceeded well with commercially available IBr. To improve the handling convenience, they found the combination of TMSBr and NIS (N-iodosuccinimide), which could generate IBr in situ, drove the iodobromination of ynamides to proceed efficiently as well (Scheme 42).

Sahoo’s group [60] developed another metal-free hydrohalogenation of ynamides by using halophosphonium salts which were generated in situ from Ph₃P and CCl₄, CBr₄ or CHI₃. The hydrohalogenation once again showed high regio- and stereoselectivity to afford (E)-α-haloenamides 74 as the major product (Scheme 43). The reaction worked well at room temperature in good-to-excellent yields. It was proposed that the phosphonium salt first added to the ynamide substrate in a concerted manner to yield cationic β-phosphonium-α-haloenamide intermediate B. The nucleophilic attack of water to the cationic intermediate B generated the intermediate C. After the proton transfer and the release of triphenyolphosphate oxide (supported by the ³¹P NMR monitoring), (E)-α-haloenamide was formed as the major product (Scheme 44).
Shin’s group [61] reported a novel synthesis of α-haloenamides with halogenated solvents and pyridine-N-oxide (Scheme 45). The halogen source in this synthesis was halogenated solvents (e.g., dichloromethane, dibromomethane, etc). DCE (1,2-dichloroethane) and 1,3-dibromopropane were found to be the most suitable solvents for the chlorination and bromination, respectively, due to the optimal balance between the reaction rate and the yield. A series of Brønsted acids could trigger the reaction, and benzoic acid was the optimal one. Pyridine-N-oxide was an essential additive to trigger hydrohalogenation. Noticeably, electron-donating group substituted pyridine-N-oxides led to lower yields and the electron-withdrawing substituted ones led to a very slow reaction.

The Brønsted acid HX first added to substrate to form keteniminium intermediate A. In the absence of pyridine-N-oxide, the nucleophilic anion X could further attack the intermediate A to generate the ynamide-acid adduct B, which was demonstrated by
the control experiments. When pyridine-N-oxide was present, those steps could be reversed by trapping keteniminium \(A\) by the halogenated solvent into halonium intermediate \(C\). The substitution of chloromethine by pyridine-N-oxide delivered the desired \(\alpha\)-haloenamide product, with the remaining \(D\) deprotonated into the aldehyde \(E\) (Scheme 46).

![Scheme 46: The proposed mechanism of \(\alpha\)-halogenation.](image)

Allyl and benzyl halides could also be used to realize the \(\alpha\)-halogenation of ynamides. Zhu’s group [62] reported chloro-allylation of ynamides catalyzed by \(\text{PdCl}_2\) at room temperature in good yields, during which process, \(\alpha\)-C-Cl bond and \(\beta\)-C-C bond were formed simultaneously (Scheme 47). The resulting \(\alpha\)-chloroenamide \(86\) could further undergo a Suzuki coupling to provide tetrasubstituted enamides \(87\).

![Scheme 47: Chloroallylation of ynamides and Suzuki coupling of \(\alpha\)-chloroenamide.](image)

Cao’s group [63] found that with stoichiometric \(\text{ZnCl}_2\) (or \(\text{ZnBr}_2\)), the addition of benzhydryl chloride (or bromide) \(88\) to ynamide proceeded smoothly in good yields (Scheme 48). Benzyl chloride, benzyl bromide, and trityl chloride were inactive under this condition. The steric hindrance between benzhydryl group and the Zn-ynamide complex favored the trans-carbohalogenation.
Scheme 48: Addition of benzhydryl halides to ynamides.

The cross-reaction experiment showed that the halogen in the α-haloenamide came from both benzhydryl halide and the Lewis acid. In the ZnBr$_2$ mediated reaction of benzhydryl chloride 91 and ynamide 90, α-chloroenamide 92a and α-bromoenamide 92b were both detected in a ratio of 64:36 (Scheme 49).

Scheme 49: The cross-reaction with benzhydryl chloride and ZnBr$_2$.

By using an aldehyde or a ketone as the electrophile to trap the keteniminium intermediate, Matsuo’s group [64] developed a new approach to achieve α-halogenation and β-C-C bond formation of N-sulfonylnamides in one reaction. The reaction occurred smoothly with stoichiometric TiCl$_4$ (or TiBr$_4$) as halide source at -78 °C (Scheme 50). Terminal N-sulfonylnamides 93 could be converted to (Z)-α-halo-γ-hydroxyenamides 95 in moderate to good yields stereoselectively. When the substrate was changed to the internal ynamide 96, the product was a mixture of Z/E isomers 98 and 99 (Z/E = 1 : 1).
Scheme 50: TiX₄ mediated addition of aldehydes or ketones to ynamides.

**With carbon-oxygen bond formation**

In the synthesis or functionalization of ynamides, a hydration would generate undesired amide by-products. Zhu’s group [65] found that the Boc (N-tert-butyloxycarbonyl) substituted ynamides 100 underwent a hydration in TFA (trifluoroacetic acid) at room temperature to afford the N-monosubstituted amides 101 in high yields (Scheme 51). The Boc group was removed in the acidic conditions at the same time. Other kinds of ynamides (oxazolidinone, sulfonamide, and carbamate) were not able to convert into the corresponding amides under TFA condition.

![Scheme 51: TFA mediated hydration of ynamides.](image)

The hydroacyloxylation of ynamides with carboxylic acids could form α-acyloxyenamides. Lam and co-workers [66] developed the first palladium catalyzed hydroacyloxylation of ynamides (Scheme 52). (E)-α-acyloxyenamides 103 were synthesized in moderate to good yields. A diverse range of carboxylic acids and various aryl-substituted ynamides were tolerated.

![Scheme 52: Hydroacyloxylation of ynamides.](image)

Zhao’s group [67] found that when N-methylnemethyl sulfonamide (MYMsA) or N-methylhenetoluene sulfonamide (MYTsA) was used as the substrate, the addition of a series of carboxylic acids gave α-acyloxyenamides 106 nearly quantitatively (92–99%) at room temperature without any catalyst (Scheme 53). α-Acyloxyenamides could undergo amidation conveniently in the presence of aliphatic amines (Scheme 54). Secondary amines reacted with α-acyloxyenamides faster than primary ones due to the increased nucleophilicity. By contrast, aryl amines were inert to amidation.

![Scheme 53: Hydroacyloxylation of ynamides.](image)
Scheme 54: MYTsA-mediated amide bond formation between carboxylic acids and amines.

The authors combined these two reactions into a highly efficient, one-pot strategy to prepare peptides, in which MYMsA and MYTsA worked as crucial coupling reagents. All the chirality of the aminoacids (110 and 111) was well preserved under this one-pot synthesis, and no epimerization or racemization was detected in the peptide products 112 (Scheme 55).

Scheme 55: MYTsA-mediated peptide bond formation.

Clavier and co-workers [68] found that dimerdone 113 could add to ynesulfonamide 56 to form α-alkoxyenamide 114 without catalyst in 34% yield after 96 h. By using Herrmann-Beller phosphapalladacycle (H-B) as the catalyst, the reaction rate and yield notably increased (Scheme 56). This addition showed excellent regioselectivity and various 1,3-diones were suitable nucleophiles to build α-C-O bonds. When internal ynamides were used as the substrates, the enamide products were a mixture of E and Z isomers, in which (E)-enamides were more favorable.

Scheme 56: Addition of 1,3-diones to ynamides.
With carbon-carbon bond formation

To construct C-C bond via addition is another important functionalization of ynamides. Zhu’s group [69] reported that with Pd(OAc)$_2$ as the catalyst and P(3-tol)$_3$ as the ligand, the aryl group in the boronic acid could add to the C-C triple bond of the ynamide via trans-metalation in mild condition. This addition had an excellent α regioselectivity and a high stereoselectivity. (E)-enamides 118 were the major products, indicating that there was an isomerization from intermediate A to C via the palladium carbene species B before protonolysis of the alkenyl C-Pd bond of intermediate C (Scheme 57). Later work [70] showed that when Na$_2$CO$_3$ was applied in this Pd-catalyzed addition, (Z)-enamides 119 turned out to be the major products (Scheme 58), indicating the isomerization of alkenyl palladium intermediate was disfavored.

![Scheme 57: Trans-hydrocarbonation of ynamides.](image)

![Scheme 58: Cis-hydrocarbonation of ynamides.](image)

The regioselectivity was inverted in Lam’s pioneering work [71] on the hydroarylation of ynamides, by taking advantage of the coordination between carbonyl oxygen of the oxazolidinonylynamide and rhodium catalyst, the aryl group favorably added to the β-carbon of ynamide triple bond and generated β,β-disubstituted enamides 121 (Scheme 59).
Hydrovinylation or hydroalkynylation of C-C triple bonds is an atom-economic approach to stereoselectively assemble 1,3-dienes or 1,3-enynes, which can serve as useful precursors to construct conjugated polyenamides. Saito, Sato, and co-workers [72] reported that by using Cp*RuCl(cod) as catalyst, ethylene and ynamides underwent a hydrovinylation-type cross-coupling to give 2-aminobuta-1,3-diene derivatives 122. The excellent regioselectivity and stereoselectivity were attributed to formation of ruthenacyclopentene intermediate A (Scheme 60).

Zhu’s group [73] achieved a Pd-catalyzed trans-hydroalkynylation of N-sulfonylnamides. With Pd₂(dba)₃ as the catalyst, tris(2,6-dimethoxyphenyl)phosphine (TDMPP) as the ligand, Ph₂P(O)OH as the additive, and ethanol as the solvent, a series of alkyl and aryl substituted terminal alkynes 49 could add to the N-sulfonylnamides 123 with excellent α-regioselectivity in good yields (Scheme 61). The resulting C-C double bonds were mainly E configuration.
Reddy and co-workers [74] used Pd(PPh₃)₂Cl₂ as the catalyst and triethylamine as the base to realize cis-hydroalkynylation of oxazolidinone, lactam, and sulfonyl substituted ynamides (Scheme 62). They also found that when the ynamide had aryl substitution on the C-C triple bond and sulfonyl / Boc substitution on the nitrogen atom, the Pd intermediate would suffer a severe steric hindrance between these two substituents, which led to a rotation along the forming C-C double bond and generated Z configured adduct eventually (Scheme 63).

\[
\begin{align*}
\text{Scheme 61: } & \text{Trans-hydroalkynylation reaction of ynamides.} \\
\end{align*}
\]

Lu, Ye, and co-workers [75] developed a novel gold-catalyzed tandem intermolecular ynamide amination and C-H functionalization. A variety of highly functionalized 2-aza-1,3-butadienes 131 were obtained with IPrAuNTf₂ as the optimal catalyst and azides as the amination reagent. The newly formed C-C double bond in the product had a high Z stereoselectivity under optimized reaction conditions (Scheme 64).

**With carbon-nitrogen bond formation**

Lu, Ye, and co-workers [75] developed a novel gold-catalyzed tandem intermolecular ynamide amination and C-H functionalization. A variety of highly functionalized 2-aza-1,3-butadienes 131 were obtained with IPrAuNTf₂ as the optimal catalyst and azides as the amination reagent. The newly formed C-C double bond in the product had a high Z stereoselectivity under optimized reaction conditions (Scheme 64).
Scheme 64: Amination / C-H Functionalization of ynamides.

The reaction pathway was rationalized with assistance of computation. Azide $130^\prime$ attacked the α-position of Au-activated C-C triple bond of the N-sulfonylnynamide to form the Au-substituted alkene intermediate B. Subsequent release of N$_2$ gave the Au carbene intermediate C, which underwent a concerted deprotonation and protodeauration to generate intermediate D with a barrier of 10.5 kcal/mol. However, the transformation from intermediate C to intermediates E and F experienced a barrier of 12.7 kcal/mol and 15.6 kcal/mol, respectively, indicating the insertion of the gold carbene moiety to the C-H bond of 4-Br-phenyl or 4-Me-phenyl group was less favored. Therefore, after ligand exchange with intermediate D, the product $131^\prime$ was generated rather than other kinds of products (Scheme 65).

Scheme 65: Computed reaction pathway.

Using N-H-sulfoximine $132$ as the amination reagent, Chen, Wang, and co-workers [76] developed a Au / Ag-cocatalyzed hydrosulfoximination reaction of ynamides to produce the N-alkenylated sulfoximidoyl derivatives $133$ with E isomer as the main product (Scheme 66). The authors further demonstrated that the C-C double bond of the N-alkenylated sulfoximidoyl derivatives $133$ could be cleaved under Ru-catalyzed oxidative conditions to afford urea-type sulfoximines $134$, which were interesting building blocks in medicinal chemistry.
Scheme 66: Hydrosulfoximination and oxidation reactions of ynamides.

Addition to β-position of ynamides

With carbon-boron bond formation

The addition at the β position of ynamides usually requires suitable electrophiles and metallic species. Organoboranes, with electron deficient boron center, were one kind of such electrophiles. Walsh et al [77] used diethylborane to achieve hydroxyalkylation of ynamides at the β-position (Scheme 67). Diethylborane first underwent a cis-hydroboration of ynamides 135 to form β-amino vinyl boranes A at room temperature. Subsequent boron-to-zinc transmetalation with diethyl zinc generated vinyl zinc intermediates B, which reacted with aldehydes to transform into the desired β-hydroxyalkylenamides 136. The N-tosyl substituted ynamides were proven to be the most robust in this tandem reaction. Other ynamides with Boc, trifluoroacetyl, or imide substituent turned out to be more sluggish.

Scheme 67: Hydroxyalkylation of ynamides.

When enantiomerically pure amino alcohol (-)-MIB was used as the catalyst during the addition to aldehydes, asymmetric products 138 with high enantioselectivities (> 90% ee mostly) were obtained in good yields (Scheme 68).
Scheme 68: Asymmetric generation of (E)-trisubstituted β-hydroxy enamides.

Bis(pinacolato)diboron (B$_2$pin$_2$) was a widely used reagent in Cu-catalyzed hydrobroation process. In the catalytic cycle, the copper boryl complex [LCuBpin], generated from transmetalation between Cu catalyst and B$_2$pin$_2$, was the key active species which made functionalization of C-C triple bond happen. Zhu, Bai, and co-workers [78] found that with CuCl as the catalyst, P(2-furyl)$_3$ as the ligand, t-BuOLi as the base, 2 equivalents of methanol as the additive, and THF as the solvent, a series of ynamides underwent a highly β-selective borylation in good yields (Scheme 69). Ligand and base had notable effects on the regioselectivity. The combination of phosphorus ligands (e.g. PPh$_3$, P(α-tol)$_3$, P(β-tol)$_3$, P(ο-OMePh)$_3$, Xantphos, DPEphos) and t-BuONa favored the β-borylation, which had also been observed and been developed into an efficient methodology by other researchers [79].

Scheme 69: Copper-catalyzed β-hydroborylation of ynamides.

Silylboranes were another kind of reagent to achieve borylation of ynamides. By using commercially available (dimethylphenylsilyl)pinacolatoboron [PhMe$_2$SiB(pin)], Saito, Sato, and co-workers [80] developed a Pd-catalyzed regioselective silaboration of ynamides that led to formation of silyl- and boryl-substituted enamides. In the catalytic cycle, oxidative addition of PhMe$_2$SiB(pin) by Pd(0) formed silyl boryl Pd complex A with appropriate ligand (e.g. isonitrile ligand t-BuCH$_2$CMe$_2$NC), followed by which, the insertion of the C-C triple bond into the Pd-B σ-bond formed the intermediate B. The experimental results indicated this insertion step was regioselective and borylation at β position was favored. Subsequent reductive elimination formed the new C-Si bond to generate the silaborated product (Scheme 70). The silaboratedenamide 143 was further utilized as a coupling partner in
Suzuki-Miyaura coupling reaction. The corresponding coupling products 145 were obtained in good yields (Scheme 71). The borylation of ynamides served as an efficient approach for further C-C bond formation at β position.

**Scheme 70: Silaboration of ynamides.**

**Scheme 71: Suzuki-Miyaura coupling of enamide 143 with aryl iodides.**

**With carbon-carbon bond formation**

Sato’s group [81] demonstrated a nickel-catalyzed addition of oxazolidinone-derived ynamides 146, aldehydes, and triethylsilane to construct new β-C-C bonds on ynamides (Scheme 72). The active catalyst was Ni(0)-NHC (nitrogen heterocyclic carbene) complex, which was generated from Ni(cod)2, IMes•HCl, and t-BuOK. The high regioselectivity was mainly attributed to the oxanickel-cyclic B generated from the oxidative cyclometalation of Ni center, ynamide, and aldehyde. As a result of an electronic match between ynamide and aldehyde. The cleavage of the nickel-oxygen bond by σ-bond metathesis (depicted as intermediate C) of the nickelacycle B with Et3SiH afforded hydridenickel intermediate D. The reductive elimination from D finally produced the γ-silyloxyenamide derivatives 148.
Scheme 72: Nickel-catalyzed multicomponent coupling.

Later, the authors [82] used ynamides 149 with a chiral auxiliary to achieve the asymmetric synthesis of γ-siloxyenamides 150 in high diastereoselectivity. Surprisingly, the methyl group on the oxazolidinone ring induced excellent diastereoselectivity and yield, whereas other bulky groups (e.g. Bn, Ph, i-Bu) led to a decrease of de% (Scheme 73). It was proposed that due to the steric repulsion between the R<sup>2</sup> group in the aldehyde and the bulky SIMes ligand, nickelacycle B was formed preferably. However, when the chiral auxiliary became larger, the steric repulsion between R<sup>2</sup> and R would increase, which made the pathway through nickelacycle D less difficult, thus a decrease of diastereoselectivity was observed (Scheme 74).

Scheme 73: Nickel-catalyzed asymmetric multicomponent coupling.
Gosmini, Gillaizeau, and co-workers [83] developed a cobalt-catalyzed hydroarylation of ynamides 10 in the presence of arylzinc derivatives 146, providing β-aryl enamides 147 as main product in moderate to good yields (Scheme 75). This reaction proceeded through transmetalation between organozinc and cobalt complexes, cis-addition to the C-C triple bond, a second transmetalation from Co to Zn, and protonation. It was assumed that the coordination between EWG and Co center favored the arylation at β-site of ynamides.

Hou et al [84] developed a copper-catalyzed alkylative carboxylation of ynamides with CO₂ and dialkylzinc reagents. In the presence of the optimal catalyst [(IPr)CuCl], a variety of ynamides (oxazolidinone, lactam, and Boc group containing) underwent this transformation to afford the corresponding α,β-dehydroamino acid derivatives.
This reaction would be a desirable method for the synthesis of highly substituted α,β-dehydroamino acid derivatives due to its high regioselectivity (with alkylation at β-position and carboxylation at α-position) and stereoselectivity (cis addition) via one-pot procedure.

**Scheme 76:** Copper-catalyzed alkylative carboxylation of ynamides.

**With carbon-phosphorus bond formation**

Evano, Rabasso, and co-workers [85] found that in the presence of NiBr₂ catalyst, the hydrophosphonylation of ynamides 10 with dialkyl phosphites 155 proceeded efficiently to form β-aminovinylphosphonates 156 with E double bond configurations (Scheme 77). Diphenyl phosphites were inactive however, with ynamides recovered. Pd(PPh₃)₄ was found to give opposite regioselectivity; the phosphonylation occurred at α-position with a poor yield (10%).

**Scheme 77:** Addition of dialkyl phosphates to ynamides.

**With carbon-nitrogen bond formation**

Dodd’s group [86] found that the N-H bond of indole could add to terminal ynamides 29 to form Z-indoloetheneamides 161 without transition metal catalyst (Scheme 78). This reaction required 2 equivalents of strong base (t-BuONa) and 2 equivalents of indole in order to achieve a high conversion of ynamides. Many indolic derivatives (e.g. skatole, gramine, carbazole, azaindole, imidazole, etc.) also reacted quite well. Internal ynamides did not react with indole and led to complex mixture. The addition of indole anion A (after deprotonation by strong base) occurred at the β-position of

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154 (Scheme 76).
the ynamide, which was rather special because nucleophilic attack commonly happened at the α-position.

![Scheme 78: N functionalization of indoles with terminal ynamides.]

By tuning the N-substituents R¹ and EWG, and reducing indole and strong base to 1 equivalent, the reaction pattern changed drastically and the amidine products 162 were obtained (Scheme 79). The sulfonamide, acetamide, and tert-butoxycarbamate substrates, along with N-phenyl substituent, all led to amidine products. The N-Boc and N-benzyl combination also worked the same. It was proposed that the strong base could cleave the EWG of those substrates to give amides C, which were converted to the reactive ketenimine D after tautomerization and protonation. Addition of indole anion A to the α-site of ketenimine D led to the amidine 162 eventually.
With carbon-silicon bond formation

In the presence of Cu catalyst, silylboranes (e.g. PhMe₂SiBpin, Et₃SiBpin) could act as silylation reagent solely to do the β-silylation of ynamides instead of borylation. In the work of Riant, Evano, and co-workers [87], CuF(PPh₃)₃•2MeOH was screened to be the optimal catalyst. A series of ynamides 10 were converted into β-silylenamides 165 or 166 in good yields with excellent E stereoselectivities (Scheme 80). The key step in the catalytic cycle was the silylcupration to the ynamide triple bond. The β-silylation was attributed to the coordination between EWG and Cu center; the single stereoisomer was attributed to the cis-silylcupration. Propiolates 167 also underwent silylcupration to give corresponding β-silylacrylates 168.

Scheme 80: Silylation of ynamides and propiolates.

Radical process
Radicals are electron-deficient, therefore, the addition of radical species to ynamides prefers at the β-position. The addition of a thiol radical to an ynamide would produce a β-thioenamide. Castle’s group [88] reported a stereoselective addition of thiol radicals to terminal ynamides. Both Z- and E-β-thioenamides could be obtained by varying the reaction conditions. When stoichiometric thiol radicals (1 equivalent of thiol and 0.5 equivalent of AIBN as radical initiator) were utilized and the reaction was heated for a short time (10 min) at 85 °C in t-BuOH, Z-β-thioenamides 171 were the major product. When the reaction conditions changed to excess thiol radicals (4 equivalents of thiol and 2 equivalents of AIBN) and longer reaction time (hours), E isomers 170 became the major product (Scheme 81). PhSH and n-BuSH followed these two patterns. The exception was the bulky t-BuSH. The major product was the Z isomer even subjected to the E selective conditions.

**Scheme 81:** Addition of thiol radicals to terminal ynamides.

Regioselective addition of a thiol radical to the terminal ynamide 169 provided vinyl radicals A and B, which would rapidly equilibrate. Radical B had less steric hindrance at the radical center. Its hydrogen abstraction from the thiol afforded the Z-β-thioenamide 171 as the kinetic product (Scheme 82). Excess thiol radical in the reaction mixture allowed the isomerization of 171 to the thermodynamically more stable E isomer via a radical addition-β-thiol radical elimination pathway. The transformation of Z adduct 172 to E adduct 173 under thermodynamic conditions was confirmed by the control experiment.

**Scheme 82:** Proposed radical addition.

Yorimitsu, Oshima, and co-workers [89] used triethylborane (Et₃B) to initiate thiol radicals at low-temperature (-30 °C in CH₂Cl₂). Ethyl radical, generated under oxygen, abstracted the hydrogen from arenethiols and affords the arenethyl radicals. The
addition of these arenethiyl radicals to the \( \beta \)-carbon of internal ynamides 10 finally led to kinetic product, Z-\( \beta \)-thioenamides 175 (Scheme 83).

![Scheme 83: Addition of arenethiols to ynamides.](image)

Similar to diethylborane, dialkyl zinc (e.g. Et\(_2\)Zn), combined with hydrogensilanes [e.g. (Me\(_3\)Si)\(_3\)SiH], could generate silyl radical. Oestreich, Perez-Luna, and co-workers [90] developed a trans-selective silylzincation of terminal ynamides through radical pathway. After quenched with NH\(_4\)Cl, Z-\( \beta \)-silylenamides 176 were obtained as the main product in good yields (Scheme 84). The silyl radical B was demonstrated again to add to the \( \beta \)-carbon of ynamides C and kinetically favored vinyl radical D was formed. The deuterium quenching experiment showed that high percentage of deuterium was incorporated at the \( \alpha \)-position of the product, which supported a more favorable Zn complex E other than the direct hydrogen abstraction from another (Me\(_3\)Si)\(_3\)SiH. The complex E, with coordination between carbonyl group and Zn center, determined the trans stereoselectivity of the resulting enamide.

![Scheme 84: Silylzincation of ynamides and proposed mechanism.](image)

In the presence of CuCN•2LiCl, the silylzincation intermediate could be readily coupled with organohalides to afford the corresponding \( \alpha \)-substituted-\( \beta \)-silylenamides 177 (Scheme 85).
Oxidation

Oxidation of ynamides would generate α-ketoimide or α-ketoamide derivatives, which are biologically active moieties and versatile building blocks in organic synthesis as well. Iodine-mediated oxidation has been developed to overcome the limitations of harsh oxidative conditions and expensive and hazardous transition metals. Iwasawa’s group and Zhu’s group reported this oxidation in the same year.

In Iwasawa’s work [91], treatment of ynamides 10 with 1.2 equivalents of NIS and 2.8 equivalents of DMSO (dimethyl sulfoxide) in CPME (cyclopentyl methyl ether) at 0 °C for 1 h generated the α-ketoimide products 178 (Scheme 86). NIS worked as the I⁺ source to initiate the oxidation, I₂ was less efficient though. DMSO (or other sulfoxides) worked as an oxygen source as the reduction product sulfane was observed. Oxygen in atmospheric air was also found to be another crucial oxidant. When the reaction was subjected to the argon, complex reaction mixture was observed.

It was proposed that I⁺ activated ynamide 10 to provide oxysulfonium A. The addition of molecular oxygen and single electron transfer formed peroxide radical B and thiyl radical cation. The thiyl radical cation could receive one electron from succinimide anion to convert into sulfide byproduct. Intermediate B was then involved with the succinimide radical and generated intermediate C. Cleavage through single electron transfer afforded the final α-ketoimide product 178 (Scheme 87).
In Zhu’s work [92], the oxidation went well under treatment with 1.5 equivalents of NIS or I₂. The optimal solvent was a mixture of CH₃CN and H₂O. When Boc protected ynamides 179 were used as substrates, with TFA as an additive to enhance the acidic environment, Boc-deprotected α-ketoamides 180, were obtained in high yields (Scheme 88). Other ynamides 10 (containing e.g. oxazolidinone, indole, and sulfonyl groups) offered α-ketoimides 181 in moderate yields. Control experiments (Scheme 89) showed that the desired oxidation product was not obtained in the absence of H₂O, as isotope experiment demonstrated ¹⁸O would transfer from H₂¹⁸O to the oxidation product. The reaction yield could be enhanced when combined with molecular oxygen (from 21% to 93%).

Scheme 87: Plausible reaction pathway.

Scheme 88: Oxidation of ynamides.
Scheme 89: Control experiments and proposed mechanism.

I⁺ activated ynamide A was attacked by H₂O to form iodoenol intermediate B in high regioselectivity. Tautomerism gave α-iodo ketone intermediate C, generating radical intermediate D through a homolytic cleavage of the C-I bond. Radical coupling with O₂ converted D into peroxide radical E, which released a hydroxyl radical to afford α-ketoimide 181. The hydroxyl radical might combine with the iodine radical to release HIO (Scheme 89).

Ynamides can also be oxidized (e.g., N-oxides, sulfoxides, nitrones, etc) under transition metal catalyzed-conditions. Davies’s group [93] developed a general route to synthesize α,β-unsaturated imides by a gold-catalyzed intermolecular oxidation of ynamides. The oxide underwent nucleophilic addition selectively to α site of the gold activated ynamide A, generating gold-carbenoid C or D (Scheme 90). As for alkyl substituted ynamide substrates, the gold-carbenoid intermediate would undergo 1,2-insertion to provide the α,β-unsaturated imide product 185. As for phenyl substituted ynamide substrate, double oxidation product 186 was obtained instead.
Scheme 90: Gold-catalyzed intermolecular oxidation of ynamides.

In light of the gold-carbenoid, Davies further coupled the chemoselective oxidation of ynamides with [2,3]-sigmatropic rearrangements of allyl sulfoniumylides to achieve one-pot synthesis of functionalized tertiary thioethers [94]. Using a combination of cationic gold phosphate complex Au-I as the catalyst and methylpicolinate N-oxide 189 as the oxidant, S-aryl, S-benzyl, and S-alkyl allyl sulfides 188 reacted with ynamides 187 to provide imide products 170 bearing sulfur-substituted quaternary carbons in dichloromethane at room temperature (Scheme 91). Phenyl, alkenyl, and electron deficient aryl substituted ynamides were suitable substrates.

Scheme 91: Oxidation and sulfur-ylide formation sequence on ynamides.
Ye’s group [95] found that N-sulfonylnamides 191 could also be oxidized into α,β-unsaturated imides 192 under a series of Lewis acid catalysts and N-oxides. The combination of 10 mol% Zn(OTf)₂ and 2 equivalents of 8-ethylquinoline-N-oxide gave the best yields (Scheme 92). Double oxidation could be substantially suppressed. Compared to Davies’ work, in which the product was formed via the 1,2-insertion of gold-carbenoid intermediate, this Zn-catalyzed oxidation underwent an E2-type elimination of the vinyl zinc intermediate A and subsequent protodemetalation of intermediate B to deliver the final product, which was supported by the deuterium studies. In the presence of 3 equivalents of D₂O, > 70% D was incorporated at the alkenyl position under Zn catalysis whereas almost no D was detected under Au(I) catalysis.

![Scheme 92: Zinc-catalyzed oxidation of ynamides and plausible reaction mechanism.](image)

When N-(arylmethyl)-N-sulfonyl ynamides 195 and N-(indolylmethyl)-N-sulfonyl ynamides 197 were subjected to the oxidation system of Zn(OTf)₂ and 2,6-dibromopyridine-N-oxide (or 2-bromopyridine-N-oxide), isoquinolones 196 and β-carbolines 198 were obtained in good yields, respectively, through oxidation / C(sp²)-H functionalization sequence [96] (Scheme 93). The mechanism study and the computation supported the C(sp²)-H functionalization via an intramolecular Friedel-Crafts alkylation to arene rather than metal-carbene insertion.
When external nucleophiles were employed in the Zn-catalyzed oxidation system, they would attack the vinyl zinc intermediate (corresponding to the β-carbon of the ynamide) to help the cleavage of the N-O bond, which therefore led to the formation of α-functionalized imides. Ye and co-workers demonstrated that phenols, thiophenols [97], trimethylsilylazide (TMSN₃), and trimethylsilylisothiocyanate (TMSNCS) [98] were efficient nucleophiles to react with N-sulfonyl ynamides 199 under Zn(OTf)₂ catalyst and proper N-oxides to furnish α-aryloxy, α-arylthio, α-azido, α-thiocyanato imides 200, respectively (Scheme 94). For halogenation, TMSCl and TMSBr only led to the formation of vinyl chloride / bromide 201. By changing the reagents to the combination of TMSN₃ and 2-halopyridine-N-oxide (halo = Cl, Br), the desired α-haloimides 202 were obtained in good yields (Scheme 95). Noticeably, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate (NaBARF) was found to be a better catalyst than Zn(OTf)₂ in the oxidation / bromination sequence.

Scheme 93: Zinc-catalyzed oxidation/C-H Functionalization of ynamides.

Scheme 94: Zinc-catalyzed oxidation of ynamides with nucleophiles.
Chalcogen cations (R-S⁺, R-Se⁺, R-Te⁺) were good electrophiles to activate alkynes. By using DMSO as the oxidant, Zhu, He, and co-workers [99] developed a chalcogen-mediated oxyfunctionalization of ynamides 203 to generate α-chalcogenyl acrylamides 204 (Scheme 96). The chalcogen cation worked as a weak Lewis acid to activate the alkyl substituted ynamide. The resulting keteniminium B could be regioselectively attacked by DMSO to produce intermediate C. Subsequent vinyligous E2-type elimination afforded the α-chalcogenyl acrylamide.

When aryl substituted ynamides were subjected to the arenesulfonyl chloride and DMSO conditions [100], there was no reaction site for the E2-type elimination after the oxothiolylation. Instead, the Cl⁻ would open the oxazolidinone ring and the resulting carboxylic anion would attack the cation counterpart to finish a new ring closure. Therefore, the oxazolidine-2,4-dione 207 bearing sulfur-substituted quaternary carbon were obtained (Scheme 97). For N-alkynyl carbamate substrates...
208, similar cyclization products 210 were obtained as well. However, N-sulfonyl ynamide 157 was transformed into α-ketoimide 211 under open air conditions.

**Scheme 97:** Generation of oxazolidine-2,4-diones.

**Rearrangement**

The ynamide substrates with specially designed substituents can undergo rearrangement reactions to transform into interesting and useful molecules. By reacting with chlorophosphites 213, 3-hydroxy ynamides 212 were transformed directly into allenes 214 through a [2,3]-sigmatropic rearrangement of in situ generated propargyl phosphite A [101] (Scheme 98). This method led to the formation of a series of α-amino allene phosphonates with diverse substituents on the amine, the phosphonate, and the allene moieties.

**Scheme 98:** Preparation of α-amino allene phosphonates.
Cao and co-workers [102] developed a method to synthesize multi-substituted allenamides 217 by Suzuki-Miyaura cross-coupling reaction between 3-alkoxycarbonyloxy ynamides 215 and arylboronic acids 216 (Scheme 99). When subjected to Pd catalyst, 3-alkoxycarbonyloxy ynamides could undergo [3,3’]-sigmatropic rearrangement to form 1-alkoxycarbonyloxy allenamides 218, followed by which, palladium-catalyzed oxidative addition of C-O bond formed intermediate B, which allowed Suzuki coupling to occur at α-position. Interestingly, in the preparation of 3-alkoxycarbonyloxy ynamides 215 from amides and alkynyl bromides, when R² and R³ were both alkyl groups, 1-alkoxycarbonyloxy allenamides 218 were formed instead, probably due to the high steric hindrance (Scheme 100). They were also demonstrated to be effective substrates for the desired Suzuki-Miyaura cross-coupling reaction.

**Scheme 99:** Synthesis of allenamides by Suzuki-Miyaura cross-coupling reaction.

Similar 1,3-acyloxy migration of 3-acyloxy ynamides 220 could occur under Au(I) activation through a [3,3’]-rearrangement [103]. The resulting α-acyloxyallenate intermediate A smoothly reacted with indoles to form γ-indolyl α-acyloxyenamides 222 in good yields and Z-stereoselectivity (Scheme 101). It was found that 4-methoxyaniline, 1,3,5-trimethoxybenzene, and 2-methylfuran were not the effective
nucleophiles as indoles, the α-acyloxyallenamide intermediate A actually underwent an intramolecular proto-deauration to afford enone derivatives 224 (Scheme 102).

Scheme 101: Synthesis of γ-indolyl α-acyloxyenamides.

Carbery’s group [104] found that when the 3-acyloxy ynamide substrates 225 were treated with LiHMDS and TMSCI, amidodienes 226 instead of allenamides were generated, which was presumably via an Ireland-Claisen rearrangement and subsequent decarboxylation (Scheme 103). The methyl substituted alkene of 226 favored Z configuration (Z / E ratios ranging from 2:1 to > 19:1). The authors pointed out that the Z / E ratio varied on the amounts of reagents (LiHMDS, TMSCI) and the initial reaction temperature.

Scheme 102: Effect of other nucleophiles.
**Scheme 103:** Synthesis of 2-amidodienes.

N-Boc glycimates 227 derived from ynamido-alcohols could be converted into functionalized allenamides 228 in high diastereoselectivity through Ireland-Claisen rearrangement when treated with LiHMDS and ZnCl₂ [105] (Scheme 104). In contrast with the previous work, these carboxylic acids were stable and the decarboxylation did not occur. After methylation of the carboxylic acid group, the functionalized allenamides could further undergo a silver catalyzed cyclization to 3-pyrrolines 239, which were useful building blocks.

**Scheme 104:** Synthesis of functionalized allenamides.

Gaunt and co-workers [106] reported the stereoselective [3,3']-rearrangement upon addition of ynamides 230 to the alcohol 231, providing (E)-enolate (in favor of syn-isomer 232) (Scheme 105) [107].

**Scheme 105:** Catalytic addition and [3,3']-rearrangement reactions.

By using chiral sulfoxides, Maulide’s group [108] developed an asymmetric redox arylation of ynamides and thioalkynes to realize an atom-economical 1,4-chirality transfer from sulfur to carbon through a sulfonium [3,3']-rearrangement (Scheme 106).
Under 50 mol% Tf₂NH, the chiral sulfoxide 234 first underwent α-addition to the ynamide 233 (or thioalkyne) and formed sulfonium intermediate A. The following [3,3′]-sigmatropic rearrangement established the chirality (enantio ratio up to 99.5 : 0.5) at the β-position of the ynamide (or thioalkyne) and transferred the oxygen atom to the α-position spontaneously, which efficiently gave access to chiral arylated amides and thioesters 235.

Scheme 106: Asymmetric redox arylation.

N-Allyl ynamides were discovered to rearrange to allyl substituted ketenimines through thermal aza-Claisen rearrangement or Pd-catalyzed allyl transfer. Hsung and co-workers showcased a series of novel chemistry based on this know-how.

The ketenimine intermediate could be trapped by alcohols and transformed into de novo imidates [109]. After condition screening, the authors found that heating of N-allyl ynamides 236 in alcoholic solvents in the presence of 4 Å molecular sieves led to imidates 237 in moderate to excellent yields (Scheme 107). Especially, when allyl alcohol was used, the resulting diallyl imidate 239 could further undergo a [3,3′]-rearrangement in the presence of catalytic PdCl₂(PhCN)₂ and subsequent ring-closing metathesis to afford seven-member ring product azapine-2-one 241.

Scheme 107: Aza-Claisen rearrangements of N-allyl ynamides.

Similarly, simple heating of N-allyl ynamides 242 and amines 243 in toluene at 110 °C afforded amidines 244 in good yields [110] (Scheme 108). When there was no nucleophile in the reaction, a 1,3-sulfonyl shift from N to C took place after the aza-Claisen rearrangement of N-allyl ynamides 242, which led to tertiary nitriles 245.
When $N$-allyl-$N$-phosphoryl ynamides 246 were the substrates, the 1,3-phosphoryl shift of allyl ketenimines A did not occur. Instead, a carbocyclization of allyl ketenimines A took place to form intermediate B, which underwent Meerwein-Wagner 1,2-hydride migration to provide 5-member cyclic products 247 [111] (Scheme 109). With functionalized allyl moieties, such as 4 to 6-member rings, electron-rich arene and terpenes, various bi- and tricyclic scaffolds were afforded (Scheme 110). Regarding 248 bearing an exocyclic alkene, upon enynamide cyclization, the Meerwein-Wagner-type alkyl migration proceeded to deliver ring-expanded product 250 due to the spirocyclic strain, alongside with a hydride migrated 249. When a highly strained 4-membered ring was introduced (251), the alkyl migration was dominated, giving ring-expanded 253 as the sole product. As for 254 with the cyclic alkene, a ring-contracted 255 was afforded through the Meerwein-Wagner-typed alkyl migration, together with the hydride migrated 250. Followed by this, the $p$-methoxyphenyl group in 256 and the dimethyl alkene in 258 served as nucleophiles to undergo Prins-type cyclization, which contributed to tricyclic and bicyclic products.

Scheme 108: Aza-Claisen rearrangement and 1,3-sulfonyl shift.

Scheme 109: Cascade carbocyclization of $N$-allyl-$N$-phosphoryl ynamides.
The rearrangement of $N$-allyl nynamides catalyzed by palladium experienced a different pathway from the thermal aza-Claisen rearrangement (Scheme 111). The $N$-allyl nynamide 242 would undergo an oxidative addition to the Pd(0) catalyst, which led to ynamidino-$\pi$-allyl complex A and ketenimino-$\pi$-allyl complex B. The subsequent formation of amidine 244 would occur in the presence of an amine either through the trapping of ketenimine C, which was derived from B via reductive elimination, or through complex D, which was a result of the amine addition to B prior to the reductive elimination. When the Pd(II) catalyst was used, for example, PdCl$_2$(PPh$_3$)$_2$, PdCl$_2$, and Pd(OAc)$_2$, the deallylative amidine 261 was formed as the major product. This deallylation could occur through excessive amine nucleophilic addition to keteniminium B and releasing allyl amine as byproduct. It could also be envisioned
from keteniminium intermediate E generated from N-allyl ynamide with the Pd(II) species serving as a π-Lewis acid.

Scheme 111: Palladium-catalyzed Amidine formation.

When there was no amine or other external nucleophile, N-allyl-N-sulfonyl ynamides 262 were transformed into α,β-unsaturated cyclopentenimines 263 [112] (Scheme 112) via Rautenstrauch-type cyclization of B or C [112,113].

Scheme 112: Palladium-catalyzed carbocyclization of N-allyl ynamides.

Cyclization
Ynamides are becoming more and more attractive in rapid synthesis of cyclic and polycyclic structures [114] that can be found in natural products and molecules of biological and medicinal interest.

**Metal-free or Lewis acid mediated cyclization**

Carbocations, generated from diarylmethanol 265 and Lewis acid ZnBr₂, initiated an electrophilic cyclization of *o*-anisole substituted ynamides 264 to 3-alkyl-2-amidobenzofurans 266 in good yields [115] (Scheme 113). 1-Arylprop-2-en-1-ol and 1-arylprop-2-yn-1-ol also worked as effective carbocation precursors in this transformation.

**Scheme 113:** Cyclization of ynamides with carbocations.

Benzyl silyl ether 267 could also be used to generate an electrophile - the benzyl carbocation with ZnBr₂ for an electrophilic addition of the ynamide 10. Subsequent intramolecular Friedel-Crafts alkylation led to 1-amidoindene 268 [116] (Scheme 114). In the case of *o*-methoxybenzyl silyl ether 269, cyclization occurred to give 2-amido-4*H*-chromene 270 as the final product.
Scheme 114: Synthesis of 1-amidoindenes and 2-amido-\(H\)-chromenes.

Halogen cations, from I\(_2\), NIS, NBS, and NCS, were able to activate \(o\)-anisole- and \(o\)-thiaoanisole-substituted ynamides 271, and transform these substrates into 3-halogenated-2-amidobenzofurans or 3-halogenated-2-amidobenzothiophenes 272, respectively [117] (Scheme 115). Further Pd-catalyzed cross-coupling reactions could functionalize 3-position of the heterocycle 273.

Scheme 115: Synthesis of 2-amidobenzofurans and 2-amidobenzothiophenes.

Okitsu’s group [118] reported a similar iodocyclization of ynamides 276 to 3-iodo-2-amidobenzofurans 277 (Scheme 116). By appropriately choosing ethoxyethyl ether as the leaving group on the ynamide substrates and bis(2,4,6-collidine)iodonium hexafluorophosphate [I(coll)\(_2\)PF\(_6\)] as the iodonium reagent, this cyclization could complete in several seconds.
When the specially designed N-aryl ynamides 278 was subjected to Brønsted acid, an electrophilic aromatic substitution would occur from the reactive keteniminium intermediate to give arene-fused quinolines 279 in good yields [119]. Yamaoka, Takasu and co-workers further demonstrated this arene-ynamide cyclization enabled facile access to natural products, for example, marinoquinolines A and C and aplidiopsamine A (Scheme 117).
To synthesize highly substituted quinolines, a tandem ynamide benzannulation / iodocyclization strategy was developed by Danheiser’s group [120]. The benzannulation based on the reaction of vinylketenes 280 (in situ generated from cyclobutenones or diazo ketones) and N-propargyl-substituted ynamides 281 proceeded via [2+2] cycloaddition, 4-electron electrocyclic ring opening, and 6-electron electrocyclic ring closure. In the second stage of the tandem strategy, after treatment with triflic anhydride (Tf₂O), the resulting triflate derivatives further underwent iodine promoted cyclization to form quinoline products 283 (Scheme 118).

Scheme 118: Synthesis of highly substituted quinolines.

Aryl t-butyl ynoyl ethers 284 were also found to be convenient precursors to generate ketenes under heating conditions. The arylketenes, resulted from an intramolecular [1,5]-hydrogen shift of 284, react with ynamides 10 via [2+2] cycloaddition-retrocyclization (CA-RE), Friedel-Craft acylation and aromatization to afford 3-amino-1-naphthols 285 in good yields [121] (Scheme 119).

Scheme 119: Synthesis of 3-amino-1-naphthols.

Wang, Chang, and co-workers developed a Sn(IV)-promoted annulation reaction of ynamides 10 with 2-methoxyaroyl chlorides 286 to synthesize 3-substituted
2-aminochromones 287 in mild conditions [122] (Scheme 120). The reaction was proposed to undergo a tandem Friedel-Crafts acylation / oxo-Michael addition / demethylation / dechlorination pathway to furnish the final product, as the intermediate C in this pathway was isolated from the reaction. The authors also mentioned that path b through a cyclization of intermediate B and demethylation was also possible.

Scheme 120: Synthesis of 3-substituted 2-aminochromones.

Under the iodonium activation, N-alkynyl tert-butyloxycarbamates 288 [123] and N-alkynyl benzylxoycarbamates 290 [124] could accept the nucleophilic attack of acetonitrile (or propiononitrile) and further underwent a 6-endo-dig cyclization to offer iodine-substituted 1,3,5-oxadizazin-2-ones 289 and 292, respectively (Scheme 121).
Bräse’s group [125] reported a one-pot procedure to synthesize polysubstituted 4-aminoquinolines 295 from sulfonyl ynamides 293 and electrophilically activated amides (a combination of amides 294, triflic anhydride, and 2-chloropyridine) (Scheme 122). This approach provided full flexibility of substitution at the C2 and C3 positions, which would be valuable from a pharmaceutical point of view.

Evano’s group [126] found that the keteniminium ions, generated from the Brønsted acid activated ynamides 296, were able to initiate a [1,5]-sigmatropic hydrogen shift from an unactivated benzylic position, and then a cationic polycyclization was triggered to give polysubstituted indenotetrahydroisoquinolines 297 as final products (Scheme 123). Further investigation showed that the keteniminium ions were also able to initiate the [1,5]-hydride shift when from a properly placed isopentyl chain, and after the cationic cyclization, functionalized tetrahydropyridines 299 were formed [127] (Scheme 124). Functionalized piperidines 301 could be readily prepared when nucleophiles (1,3-dimethoxybenzene, TMSCN, and Et₃SiH) were introduced in the reaction.
Scheme 123: Synthesis of polysubstituted indenotetrahydroisoquinolines.

Scheme 124: Synthesis of tetrahydropyridines and piperidines.

Ynamides attached with epoxides were versatile synthons [128]. When treated with strong base t-BuOK, the ynamide substrates 302 underwent a 6-exo-dig cyclization to become 1,3-oxazines 303 in good yields with excellent E stereoselectivity of the resulting C-C double bond. When treated with sodium azide NaN₃, the epoxide ring would open from the less hindered site after the nucleophilic attack of N₃⁻, which triggered a different 6-endo-dig cyclization and led to 1,4-oxazines 304 as final products (Scheme 125).
**Scheme 125:** Cyclization of epoxyynamides.

**Gold-mediated cyclization**

Gold complexes are strong alkynophilic species. Various cyclizations of ynamides could occur under gold catalysis. Ynamides 305 containing a tosyl or a methoxybenzenesulfonyl group were found to favor a dimerization [129], in which one molecule of ynamide acted as a nucleophile to react with the electrophilic gold-ynamide complex, and the intermediate A would be transformed into cyclopentadiene derivative 306 via sequential [1,5]-hydride shift / metalla-Nazarov reaction / [1,2]-hydride shift (when R^3 = H) (Scheme 126). Interestingly, when cycloalkyl groups were introduced at the terminus of the alkyne E (R^2-R^3 = cycloalkyl), the insertion of the gold carbene occurred into a C-H bond of the adjacent spirocycloalkyl fragment to deliver tricyclic compounds 307 (79-96%). Aryl-substituted sulfonamide 157 was not able to dimerize, presumably because the aryl group reduces the nucleophilicity of the ynamide. When the N-sulfonyl group was replaced by less electron-withdrawing oxazolidone group, dimerization occurred and more complicated fused ring products 309, 310, and 311 were obtained (Scheme 127).
Scheme 126: Dimerization of ynamides.

In the presence of Au(I) catalyst and TsOH·H$_2$O as the additive, 5-ynyl-ynamides 312 could undergo a hydrative cyclization to give 1,6-dihydropyridin-2(3H)ones 313 in good yields [130]. A 6-endo-dig cyclization of intermediate B was proposed to be the key step in the reaction mechanism (Scheme 128).
Scheme 128: Synthesis of 1,6-dihydropyridin-2(3H)ones.

$o$-Anisole substituted ynamides 314 were good substrates to synthesize benzofurans. When the $O$-substituents ($R^1$) were allylic, benzylic, methoxymethyl groups, etc. they could migrate from O to C3 position via relative stable carbocations following Au(I)-catalyzed 5-endo-dig cyclization of ynamides [131] (Scheme 129).

Scheme 129: Synthesis of benzo[b]furans.

With ($p$-CF$_3$C$_6$H$_4$)$_3$PAuNTf$_2$ catalyst, ynamides 316 could be converted into functionalized indenes 317 in good yields [132] (Scheme 14030). In this reaction, 6-endo-dig cyclization was initiated by the nucleophilic addition of alkoxy group to the electrophilic $\alpha$-carbon of the ynamide, giving the intermediate A. Followed by that, benzyl C-O cleavage by the vinyl gold intermediate B delivered the $\alpha$-hemiaminal gold carbene D, which was terminated by 1,2-$N$-migration to give 317.
Regarding the \(N\)-allyl ynamides 318, the use of \([\text{Au(picolinate)}\text{Cl}_2]\) and appropriate reaction temperature (≥ 50 °C) favored the C-H insertion to the ynamide moiety, which initiated subsequent polycyclization to form new polycyclic products 319 [133] (Scheme 131). This was a different reaction pattern from the previous case. The authors also found that in the presence of CuI, the \(N\)-allyl ynamides 320 would undergo a cascade aza-Claisen rearrangement, [1,5]-hydride shift, and electric cyclization to generate isoquinoline derivatives 321 or 322.

Scheme 131: C-H insertion-cascade cyclization of \(N\)-allyl ynamides.
In the presence of IPrAuNTf₂, benzyl azide 324 would attack the ynamide substrate 323 to form α-imino gold carbene intermediate B [134], which could be trapped by the N-aryl group from the ynamide moiety and yield to the product 2-aminoindole 325 with 2-amino group from azide and the N atom in the indole ring from ynamides (Scheme 132). The authors later found that when indolyl azides 327 were used, the α-imino gold carbene intermediate D would be trapped by the more nucleophilic indolyl part rather than the N-aryl group of the ynamide moiety, which led to 3-amino-β-carbolines 328 as the final products.

Scheme 132: Gold-catalyzed reaction of azides with ynamides.

When 3-en-1-ynamides 329 were used as the substrates, a formal aza-Nazarov cyclization would take place after the Au(I)-catalyzed alkyne amination of 3-en-1-ynamides and benzyl azides, which led to the highly regioselective synthesis of functionalized 2-aminopyrroles 330 [135] (Scheme 133).
Scheme 133: Synthesis of functionalized 2-aminopyrroles.

Hashmi, Ohno, and co-workers [137] developed a novel transformation from $N$-propargyl ynamides 333 to tricyclic pyrroles 334 by the use of a cationic dual-activation gold catalyst (DAC-PF$_6$). The first cyclization started with the $\beta$-addition of a gold acetylide onto the ynamide triple bond. The resulting gold vinylidene B provoked the C-H insertion to finish the second cyclization (Scheme 135). Not only aryl substituted ynamides but also alkyl substituted ynamides could undergo this C-H insertion to form polycyclic pyrroles.
With the catalysis of $[\text{Au(Johnphos)(MeCN)}\text{SbF}_6]$, the 1,6-diynes 338 with an ynamide propargyl ester moiety would undergo a 1,2-acyloxy migration and then a cyclization of vinyl gold carbenoid and the pendant triple bond, providing an attractive route to a diverse-substituted cyclopenta[b]indoles 339 [138] (Scheme 136).

In the presence of $[\text{Au(Johnphos)(MeCN)}\text{SbF}_6]$ catalyst, a cascade cyclization from diyne-tethered ynamides 340 to benzo[f]dihydroisoquinolones 341 was developed by Sahoo’s group [139] (Scheme 137). Based on the isolation of intermediates and on labeling studies as below, the authors proposed the pathway: the addition of TsO-enamide generated the $N,O$-acetal enamide, followed by cleaving the S-O bond to give intermediate C. Finally, enyne cyclization and aromatization afforded the
product. The isotopic labeling study of 340a with \( p \)-TsOH, \( \text{H}_2\text{H}^{18}\text{O} \) delivered 341a without incorporation of \( ^{18}\text{O} \), which further explained the oxygen source should come from \( p \)-TsOH rather than the water.

**Scheme 137**: Synthesis of benzo[\( f \)]dihydroisoquinolones and the control experiments.

Analogously, by taking advantage of the nucleophilicity of the indole ring, Gong, Yang, and co-workers [140] achieved the synthesis of tetracyclic spirocyclic pyrrolidinoindolines 343 bearing an all-carbon quaternary stereocenter from linear indole-ynamide substrates 342 in a single step catalyzed by Au(I) (Scheme 138).
Copper-mediated cyclization

Upon bromine / lithium exchange with t-BuLi and subsequent transmetalation with CuCN•2LiCl, N-(2-bromophenyl)ynamides \(344\) underwent an intramolecular 5-endo-dig carbocupration to give indoles \(345\) in moderate yields [141] (Scheme 139). This method was a modular synthesis of 3-substituted indoles, with no substituent at 2-position.

Knochel’s group [142] also reported a similar intramolecular carbocupration of ynamides to synthesize indoles and azaindoles. \(i\)-PrMgCl•2LiCl was used to trigger the bromine / magnesium exchange in the first step. After the 5-endo-dig carbocupration, various electrophiles (e.g. 2-bromomethyl acrylate, cyclopropanecarbonyl chloride, and 4-methylbenzoyl chloride) were used to trap the copper intermediate, which allowed for an easy functionalization at the 2-position of resulting indoles \(347\) (Scheme 140). The authors later applied this methodology to the synthesis of pyrrolo[2,3-d]pyrimidines \(349\) (Scheme 141) and successfully completed the formal synthesis of the marine alkaloid rigidin A and a derivative of 7-azaserotonin [143] (Scheme 142).
Scheme 140: Synthesis of functionalized indoles.

Scheme 141: Synthesis of pyrrolo[2,3-d]pyrimidines.

Scheme 142: Synthesis of Rigidin A and a 7-azaserotonin derivative.

Cu(I)-catalyzed coupling reactions of organo halides and amides is a powerful method to synthesize ynamides. Perumal’s group [144] reported that for certain functionalized precursors, the resulting ynamides could further undergo cyclization under the same catalytic conditions. For example, in the presence of CuI, 1,10-phenanthroline, and Cs$_2$CO$_3$, in situ generated ynamide from the coupling reaction of gem-dibromovinylanilide 350 and sulfonamide 351 would undergo a base-promoted...
intramolecular hydroamination to afford 2-amidoindoles 352 in good yields (Scheme 143). When N-tosyl-o-bromobenzamide 354 was used as the reaction precursor, after the base-promoted intramolecular hydroamination, the N atom on the indole ring would couple with the proximal aryl halide via catalyst to afford the N-arylation product indolo[1,2-α]quinazoline 355.

Scheme 143: Synthesis of 2-amidoindoles and indolo[1,2-α]quinazolines.

The authors also reported another similar one-pot protocol from gem-dibromovinyls 356 (and 358) and sulfonamides to achieve pyrrolo- / indolo[1,2-α]quinolones 357 and naphtha[2,1-b]thiophenes 359 [145] (Scheme 144). The AgOTf-catalyzed intramolecular hydroarylation was crucial in this one-pot reaction to build up fused heterocycles.

Kumara Swamy’s group [146] developed a novel and efficient Cu(I)-catalyzed cyclization of functionalized ynamides, which was achieved through oxidative addition of $N$-alkynyl-2-iodo-benzenesulfonamide 360 to CuI generated intermediate A, ligand exchange with S or Se (possibly in the form of S$_n^2$- or Se$_n^2$-, with the presence of water and base) to B. Reductive elimination of CuI formed the S or Se functionalized intermediate C with subsequent cyclized nucleophilic addition to ynamides and protonation gave the final product benzo[1,4,2]dithiazine-1,1-dioxides or benzo[1,4,2]diaselenazine-1,1-dioxides 361 (Scheme 145). The resulting enamides has an excellent Z configuration.

**Scheme 145**: Tandem cyclization of functionalized ynamides.

**Palladium-mediated cyclization**

It was known that Pd catalyst was crucial for the generation of ketenimine intermediate from $N$-allyl ynamide and AgOTf was an effective catalyst for the cyclization of $N'$-(2-alkynylbenzylidene)hydrazide. Based on that, Chen, Peng, and co-workers [147] developed a Pd and Ag co-catalyzed reaction of $N'$-(2-alkynylbenzylidene)hydrazides 362 and $N$-allyl ynamides 363 to synthesize 2-amino-$H$-pyrazolo[5,1-$a$]isoquinolines 364 in good yields (Scheme 146). The transformation proceeded through 6-endo-cyclization, [3+2] cycloaddition, [3,3]-$\pi$-rearrangement, and aromatization.
To build up 3,4-disubstituted isocoumarins which were of biological value, a Palladium-catalyzed annulation of 2-iodoaromatic acids 366 with ynamides 367 was developed [148] (Scheme 147). Under basic conditions, oxidative addition and ligand exchange with 2-iodobenzoate A provided cyclopalladated intermediate B. Carbopalladation of ynamides regioselectively and reductive elimination furnished the desired isocoumarins 368.

Scheme 147: Synthesis of 3,4-disubstituted isocoumarins.

With CuCl₂ or CuBr₂ as halide source, N-alkynyl alkyloxycarbamates 179 could undergo a Pd(PPh₃)₄-catalyzed intramolecular cyclization to form 4-halo-oxazolones 369 [149] (Scheme 148). It is proposed that halopalladation of the ynamide delivers halo-enamide B, which undergoes the ligand exchange with Boc group and releases the product by reductive elimination of C-O bond, with Pd(0) released, being oxidized by copper (II).

Scheme 148: Synthesis of 4-halo-oxazolones.
The pharmaceutically attractive benzosultams could be synthesized via a Palladium-catalyzed tandem cyclization of N-alkynyl-2-halobenzenesulfonamides and various nucleophiles [150] (Scheme 149). The key step in the proposed pathway highlighted the nucleopalladation of ynamides, offering functionalized product.

Based on the carbopalladation of bromoenynamides (e.g. 373), the Anderson’s group [151] developed a series of cascade cyclizations for diverse azacycles. The resulting Pd intermediate A from the carbopalladation could undergo a Stille cross-coupling with alkenyl tin reagents 374 and a subsequent 6-electrocyclization to generate bicyclic aminodienes 375 (Scheme 150). The Suzuki cross-coupling could also be incorporated in this cascade strategy when the coupling partner was alkenylboronic acids and esters 377 [152], or potassium alkenyltrifluoroborate salts 380 [151].
Scheme 150: Synthesis of bicyclic aminodienes.

With alcohols serving as a hydride source in the reaction, the carbopalladation intermediate A could be transformed into monocyclic dienamide 382 after β-H-Pd elimination and reductive elimination [153,151] (Scheme 151). The resulting monocyclic dienamides could be further used in (hetero) Diels-Alder cycloadditions to build up useful polycyclic compounds 383.

Scheme 151: Synthesis of cyclic dienamides and azacycles.

When the bromoenynamides were installed with another alkyne moiety, the Palladium-catalyzed cascade cyclization afforded azatricyclic products 385 with trikentrin-like framework [154] (Scheme 152).
Scheme 152: Synthesis of azatricycles.

The cycloisomerization of 1,6- and 1,7-enynamides 386 proceeds in the presence of Pd or Ru catalyst. This was another efficient approach to access cyclic dienamides 387 [155] (Scheme 153). In the Pd catalytic cycle, regioselective hydropalladation of enamide affords the alkenylpalladium intermediate A. Carbopalladation of the alkene gives the enamidyl cyclized alkylpalladium species B, which undergoes β-hydride elimination to deliver the diene product 387. Compared with palladium catalysis, Ruthenacyle D is formed via oxidative cyclometallation. When \( n = 2 \), reductive elimination leads to the 6,4-fused cyclobutene product 388. When \( n = 1 \), the ring strain of 5,5-fused ruthenacyle would prohibit the direct reductive elimination, which then favors the β-hydride elimination and a subsequent reductive elimination to yield the diene product 387. Pyrrolidinyl dienals (390 and 393) could also be prepared by this Pd-catalyzed cycloisomerization, followed by desilylation and oxidation. The chiral pyrrolidine catalyst (Jørgensen-Hayashi catalyst) could transform dienal substrates into chiral conjugated trienamine intermediates, which further trigger the Diels-Alder reactions with oxindole to generate polysubstituted hexahydroindoles (391 and 394) in excellent enantioselectivities [156] (Scheme 154).
Scheme 153: Synthesis of cyclic dienamides from 1,1-enynamides.

Scheme 154: Synthesis of polysubstituted hexahydroindoles.

Rhodium-mediated cyclization

Lam’s group once developed a rhodium-catalyzed hydroarylation of ynamides with arylboronic reagents [71]. The regioselective carbo-rhodation of ynamides is assisted by the 5-membered chelation of the oxazolidinone with the rhodium. Terminated by alkenyl rhodium insertion of the ketones / aldehydes, 2-amidoindenols 397 or 2-amidoindenes 399 were released [157] (Scheme 155).

Scheme 155: Annulation of ynamides with bifunctional arylboron reagents.

Hishimura, Hayashi, and co-workers [158] disclosed a rhodium-catalyzed asymmetric cycloisomerization of heteroatom-bridged 1,6-enynamides 400 to yield functionalized 3-aza- and oxabicyclo[4.1.0]heptene derivatives 401 (Scheme 156). The reaction was proposed to undergo a 6-endo cyclization via the electrophilic activation of an alkyne moiety by π-acidic Rh catalyst to form a Rh-carbenoid species C, and a subsequent 1,2-hydrogen shift to furnish the bicyclic backbone. Conformation A1 is favored where the X group (NR or O) is placed at a less bulky site, whilst the conformation
A2 suffers from a repulsion between the X group and the ferrocenyl group of the ligand L*. Therefore, the cyclization of A1 gives the Rh-carbenoid C1, which finally delivers the chiral product 401 in high enantioselectivity.


Cycloaddition

[2+1]

Terminal ynamides 403 could work with one-carbon synthon to achieve a formal [2+1] cycloaddition with strained C-C double bonds (like those in norbornene or its derivatives 402) in the presence of H-B Pd catalyst (Hermann-Beller phosphapalladacycle) [159]. According to the authors’ previous study on the palladium-catalyzed [2+1] cycloaddition of terminal alkynes to norbornene derivatives [160, 161], this reaction might experience a similar [2+2] cycloaddition of Pd vinylidene species with the double bond of norbornene derivatives, and a reductive elimination to afford the cyclopropane rings 404 (Scheme 157).
[2+1] cycloaddition of ynamides with norbornene derivatives.

Hsung’s group [162] did a pioneering work on demonstrating ynamide could act as an effective reaction partner in Ficini [2+2] cycloaddition. With CuCl₂ and AgSbF₆ as catalysts, ynamides reacted with enones smoothly to generate the desired cyclobutene products (Scheme 158).

Mezzetti’s group [163] subsequently developed a ruthenium-catalyzed Ficini cycloaddition of ynamides with unsaturated β-keto esters in good ee by applying chiral PNNP (Scheme 159).
Another asymmetric Ficini cycloaddition of ynamides 137 with cyclic α-alkylidene β-oxo imides 409 was achieved in the presence of chiral Cu complex [164] (Scheme 160).

Scheme 160: Copper-catalyzed asymmetric [2+2] cycloaddition.

The first metal-free Ficini cycloaddition was developed by Liu’s group [165]. Ynamides 10 reacted with cyclic α,β-unsaturated isomidium salts 411 to give stable cyclobutenamides 412 in good to excellent yields (Scheme 161).

Scheme 161: First case of metal-free Ficini cycloaddition.

Bis(trifluoromethylsulfonyl)ethene (Tf$_2$C=CH$_2$), which was in situ generated from 2-(2-fluoropyridinium-1-yl)-1,1-bis(trifluoromethylsulfonyl)ethan-1-ide 413, was an alternative to the α,β-unsaturated carbonyl compound to participate in Ficini cycloaddition with ynamides 10 under metal-free conditions [166] (Scheme 162). As for the aryl ynamides 126, the resulting cyclobutene ring could be attacked by water or alcohols at β-position of enamides, delivering cyclobutenol derivatives 415 by deprotonation.
Scheme 162: Metal-free synthesis of aminocyclobutenes and aminocyclobutenols.

A [2+2] cycloaddition of ynamides 10 and tetracyanoethylene (TCNE) 416 could occur at room temperature, however the labile cycloadducts A would undergo retroelectrocyclization to provide tetracyanobutadienes 417 [167] (Scheme 163).

Scheme 163: Synthesis of tetracyanoethylene.

Lam and co-workers [168] reported [2+2] cycloadditions of ynamides 395 and nitroalkenes 418 to deliver cyclobutenamides 419 and 420 in the presence of Rh-diene and NaBPh₄. The X-ray crystallographic analysis confirmed that product 419 is the major isomer, with the nitro in trans-configuration with the R² groups on the cyclobutene ring. By contrast with Ficini cycloaddition’s pathway, this reaction was proposed to undergo an oxidative cyclization to form rhodacycle A or C and subsequent reductive elimination to release the products (Scheme 164). The five-membered rhodacycle C could be switchable to A with less sterical repulsion between NO₂ and R₂, via a seven-membered rhodacycle B.
Hsung’s group \[169\] found that in situ generated ketenimine from the palladium-catalyzed N-to-C allyl rearrangement could react with an oxygen tethered alkenyl moiety to realize an intramolecular [2+2] cycloaddition (Scheme 165). The substrate 421 is supposed to undergo N-to-C allyl rearrangement to generate keteniminyI intermediate B with a favorable chair-like conformation, as shown in the scheme. Followed by that, a subsequently [2+2] cycloaddition results in the bridged bicycloimine 422. As for gem-disubstituted alkenyl 423, the keteniminyI intermediate favors boat-like conformation D, leading to fused bicycloimines 424.

In the presence of Lewis acid BF$_3$•Et$_2$O, a formal [2+2] cycloaddition between ynamides 425 and propargyl silyl ethers 426 would occur to form alkylidenecyclobutenones 427 [170] (Scheme 166). The cycloaddition of allenyl cation A with ynamides formed iminium intermediate B through either a stepwise or a concerted process. TMSO anion later added back to the intermediate B and eliminated the oxazolinone moiety, yielding cyclobutenones.

Scheme 166: Lewis acid-catalyzed formal [2+2] cycloaddition.

[3+2]

In general, ynamides serve as a two-carbon reaction partner to react with various three-atom (4π electron) synthons (e.g. 1,3-dipoles and their equivalents) in [3+2] cycloadditions.

Kumara Swamy’s group [171] achieved an intramolecular cycloaddition to synthesize triazolo-1,2,4-benzothiadiazine-1,1-dioxides 429 (Scheme 167). One main attractive feature of this reaction was using low loading air-stable catalyst (5 mol% CuI) and eco-friendly solvent PEG-400 (polyethylene glycol 400). The control experiment of phenyl iodide with NaN$_3$ in the presence of CuI demonstrates that the azidobenzene was formed, however the Huisgen cycloaddition of ynamide with NaN$_3$ did not occur in the absence of phenyl iodide. This implies that the aryl iodide 360 would be essential to generate the azido substituted C via oxidative addition to CuI, azide exchange, and reductive elimination of CuI. Intramolecular Huisgen cycloaddition of ynamides with the azides affords the fused triazoles 429.
Another case of 1,3-dipolar synthons is cyclopropanes. With oxophilic Lewis acid Sc(OTf)₃, cyclopropanes 430 reacted with ynamides 431 to provide cyclopentene sulfonamides 432 in good to excellent yields [172] (Scheme 168).

Franchini and co-workers [173] reported the first example of a 1,3-dipolar cycloaddition between tert-butyl-N-ethynyl-N-phenylcarbamate 433 and C-carboxymethyl-N-phenylnitrilimine 435, which was generated in situ from hydrazonoyl chloride 434, with Ag₂CO₃ as base (Scheme 169). Product 436 was the only regio-isomer that was obtained due to an electronic match between two partners.
Scheme 169: 1,3-Dipolar cycloaddition of ynamide with nitrilimine.

Electron-deficient ynamides 439, possessing an ynoate or ynone moiety, could undergo a 1,3-dipolar cycloaddition with stabilized pyridinium ylides 438, which was generated in situ from pyridinium salts 437 with base [174]. Sequential aromatization provided a convenient access to highly functionalized 2-aminoindolizines 440 (Scheme 170).

Scheme 170: 1,3-Dipolar cycloaddition of ynamides with pyridinium ylides.

Gold catalyst has been demonstrated as a powerful catalyst to activate ynamide’s C-C triple bond and the resulting gold carbenoid is a versatile intermediate to realize diverse transformations. Davies’ group [175, 176] used N-acylpyridinium-N-aminides 441 as the 1,3-N,O-dipole equivalent to react with ynamides 10 with AuCl₂(picolinate). After the nucleophilic attack of aminide to the gold activated ynamide, the gold carbenoid B would be captured by the acyl oxygen intramolecularly with release of a pyridine, which finally led to the cycloadduct 4-aminooxazole 442 (Scheme 171). Similarly, the 1,3-N,N-dipole equivalents, pyridinium N-(heteroaryl)aminides 443, were also able to react with ynamides 10 to form imidazo-fused heteroaromatics 444 [177] (Scheme 172).

Scheme 171: Synthesis of 4-aminooxazoles.
Both Huang’s group [178] and Liu’s group [179] disclosed an atom-economical synthesis of polysubstituted 2-aminopyrroles 446 (and 449) from 2H-azirines 445 (and 448) and ynamides 10 (and 447) through a gold-catalyzed nitrene transfer process (Scheme 173). Alkenyl azides 450, a “masked” 2H-azirines by losing N2 at elevated temperature, could be used directly in the gold-catalyzed cycloaddition as well [179, 180] (Scheme 174).

Scheme 172: Synthesis of imidazo-fused heteroaromatics.
Ye, Lu, and co-workers [181] found that isoxazoles could also be used in the gold-catalyzed formal [3+2] cycloaddition to form 2-aminopyrroles. After the nucleophilic attack of isoxazole to the gold-activated ynamide, the isoxazole ring would be opened to form a linear gold carbenoid. Subsequent cyclization of the carbenoid led to the formation of the new pyrrole ring system. When fully-substituted isoxazoles were used, de-acylated 2-aminopyrroles was formed instead (Scheme 175). Furthermore, when N-alkynyl oxazolidinones were used as the ynamide substrates, the reaction with fully-substituted isoxazoles would give N-acylpyrroles as the major products and de-acylated pyrroles as the minor products [182] (Scheme 176).

Scheme 175: Cycloaddition of ynamides with isoxazoles.

Scheme 176: Cycloaddition of N-alkynyl oxazolidinones with fully-substituted isoxazoles.

Such reaction pattern could be extended to the reaction of 1,2,4-oxadiazoles with ynamides by Hashmi’s work [183]. It was regarded as an atom-economic access to fully substituted 4-aminimidazoles (Scheme 177).
Scheme 177: Synthesis of fully substituted 4-aminoimidazoles.

Liu’s work [184] demonstrated dioxazole 460 was another five-membered ring precursor that could undergo a gold-catalyzed cycloaddition with ynamides 10 for the synthesis of functionalized oxazoles 461 (Scheme 178) with one molecular acetone released. Li, Wan, and co-workers [185] further developed a metal-free version. By using 5 mol% Tf$_2$NH, the reaction afforded the desired 4-aminooxazoles in good yields.

Scheme 178: Cycloaddition of ynamides with dioxazoles.

[4+1]

A gold-catalyzed formal [4+1] cycloaddition to synthesize substituted 2-aminofurans 464 was developed by Liu’s group [186] (Scheme 179). In the reaction, 3-en-1-ynamides 462 worked as the four-carbon reaction partner and was oxidized by 8-methylquinoline oxide 463 to generate alkenylgold carbenoid B, which would undergo an oxa-Nazarov cyclization to furnish the final products.

Scheme 179: Gold-catalyzed formal [4+1] cycloaddition.

[4+2]

Liu’s group [187] demonstrated that 2-aryl-1-ynamides 465 could also serve as the four-carbon reaction partner to react with various electron-rich alkenes 466 by gold catalyst to complete a formal [4+2] cycloaddition (Scheme 180). It was proposed that the electron-rich alkene would add to the α-position of the Au-activated ynamide to form the cyclopropyl gold carbenoid intermediate B, which was then attacked by the tethered phenyl group to furnish the formation of a new 6-membered ring.
Inspired by Liu’s work, Kramer, Skrydstrup, and co-workers [188] successfully used imines 469 to realize a similar gold-catalyzed formal [4+2] cycloaddition with 2-aryl-1-ynamides 468, providing a new strategy to synthesize 1,2-dihydroisoquinolines 470 (Scheme 181).

Liu’s group [189] further reported a gold-catalyzed [4+2] cycloaddition between oxetanes 471 and ynamides 199 to access 6-membered oxacyclic compounds 472. During the reaction, alkenyl gold species A was proposed to be a key intermediate for the following 4-membered ring opening, which was accelerated by the adjacent aryl group, and a 6-membered ring closure led to the desired oxacycles (Scheme 182). Azetidines 474 were another kind of 4-membered ring reactant to implement this [4+2] cycloaddition, and AgSbF₆ was found to be the most efficient catalyst.
Cao, Xu, and co-workers [190] disclosed a carbocation-initiated [4+2] cycloaddition of \( \sigma \)-anisole-substituted propargyl silyl ethers 476 and ynamides 477 to 4-vinylcoumarins 478 (Scheme 183). In the presence of stoichiometric amount of ZnBr\(_2\), propargyl silyl ethers would be transformed to carbocation A with elimination of TMSO. Subsequent cyclization with ynamide generated intermediate C, which was converted into the final product after demethylation and hydrolysis of the oxazolidinone ring. The 4-vinylcoumarins could be further transformed into polycyclic coumarin derivatives 479 via electrocyclization by photo-irradiation.

Ma’s group [191] developed a three-component reaction of terminal alkynes 49, sulfonyl azides 481, and \( N \)-sulfonyl-1-aza-1,3-butadienes 480 to access functionalized 1,4-dihydropyridines 482 (Scheme 184). Initial CuI-catalyzed cascade reaction of terminal alkyne and azides with stoichiometric amount of Cs\(_2\)CO\(_3\) generated cesium ynamidates A, which acted as dienophiles to undergo an inverse hetero-Diels-Alder reaction with azadienes to afford the [4+2] cycloadducts.
**Scheme 184:** Inverse hetero-Diels-Alder reaction for the synthesis of 1,4-dihydropyridines.

Gandon, Blanchard, co-workers [192] developed an intramolecular inverse hetero-Diels-Alder reaction for the synthesis of 4-aminopyridines 484, possessing various fused O-, S-, N-containing heterocycles (Scheme 185). The pyrimidine moiety was selected as electron-deficient heterodiene to react with the ynamide moiety and then sequential retro-Diels-Alder reaction occurred to construct [6-5] pyridines.

**Scheme 185:** Inverse hetero-Diels-Alder reaction for the synthesis of 4-aminopyridines.

[2+2+2]

Yne-ynamides 485 and nitriles 486 could undergo a Co-catalyzed [2+2+2] cycloaddition to afford bicyclic 3-aminopyridines 487 [193] (Scheme 186). The cycloisomerization of the yne-ynamide with Co catalyst would generate cobaltacyclopentadiene A as the key intermediate in the reaction. The insertion pathway was more favorable for the addition of nitrile to the cobaltacyclopentadiene than the concerted [4+2] pathway according to the calculated reaction barriers [194]. When the substitution pattern of yne-ynamides changed, the regioselectivity of the addition of nitriles would change, resulting in bicyclic 4-aminopyridines 490 and 492 as a major product.
Scheme 186: Synthesis of bicyclic 3- and 4-aminopyridines.

Under the catalytic system of NiCl₂(DME) / dppp / Zn, ynamide-nitriles 494 (or alkyne-cyanamides 497) and alkynes 495 could undergo [2+2+2] cycloaddition to give δ-carbolines 496 or α-carbolines 498 (pyridine-fused indoles), which were of biological interests [195]. The in-situ generated ZnCl₂ played an important role on increasing the electrophilicity of the nitrile moiety for the successful transformation. Subsequent oxidative addition of the activated ynamide-nitrile to the Ni center led to the azanickelacycle B. Insertion of the alkyne to the azanickelacycle B followed by reductive elimination delivered the desired product (Scheme 187).
Scheme 187: Synthesis of δ- and α-carbolines.

In the work of gold-catalyzed cycloaddition between 2-aryl-1-ynamides and electron-rich alkenes, Liu’s group [186] also reported a [2+2+2] cycloaddition of terminal ynamides 29 with enol ethers 499 to deliver 6-membered carbocycles 500 (Scheme 188). The authors postulate the enol ether proceeds a nucleophilic addition to the ynamide activated by Au(i), and forms the cyclopropyl gold-carbenoid A, followed by a second equivalent of the enol ether addition to give an oxonium species B (or B’). Conformation B, with less 1,3-axial strain between the amino group and the oxonium moiety, leads to the product 500 in a high diastereoselectivity.

Scheme 188: Cycloaddition of terminal ynamides with enol ethers.
Later, nitriles 501 were introduced to this gold-catalyzed cycloaddition with ynamides 199 [196], which was demonstrated to be an efficient way to construct 4-aminopyrimidine frameworks 502 (Scheme 189). By increasing the ynamide loading to 4 equivalents with 1 equivalent nitrile, the cycloadduct 2,4-diaminopyridines 504 were formed as the main product from the cycloaddition of two discrete ynamides 503 and one nitrile 501 [197].

\[
\begin{align*}
R^2 &= N \quad \text{SO}_2 R \\
R^1 &= N \\
R^3 &= N
\end{align*}
\]

Scheme 189: Gold-catalyzed [2+2+2] Cycloadditions of ynamides with nitriles.

Further studies showed that the [2+2+2] cycloaddition of ynamides and nitriles could also proceed well in the presence of Brønsted acids (e.g. TfOH [198], Tf$_2$NH [199]) and TMSOTf [200] (Scheme 190).

\[
\begin{align*}
R^2 &= N \quad \text{EWG} \\
R^1 &= N \\
R^3 &= N
\end{align*}
\]

Scheme 190: Metal-free [2+2+2] Cycloadditions of ynamides with nitriles.

\[5+2\]

The Anderson’s group [201] demonstrated that ynamides 506 featuring a pendant vinylcyclopropane could undergo an intramolecular [5+2] cycloaddition to form [5.3.0]-azabicycles 507. With the help of computational ligand design, the target products could be obtained in high enantio- and diastereoselectivities as well (Scheme 191).
CONCLUSION

The ynamide chemistry has been witnessed to blossom in the past decade with established efficient ways of preparation and unique reactivities. We anticipate that the ynamide chemistry will continue to flourish in the future and the ynamide will turn to be a wider popular synthon in synthesis of alkaloids and diverse molecules that are of biological or pharmaceutical values.

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CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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