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Ynamides in Ring Forming Transformations

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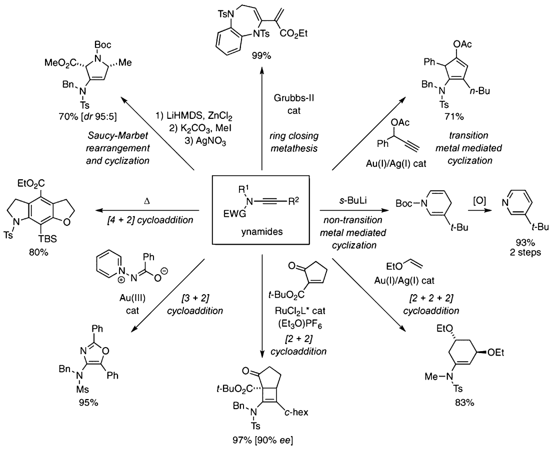

The ynamide functional group activates carbon–carbon triple bonds through an attached nitrogen atom that bears an electron-withdrawing group. As a result, the alkyne has both electrophilic and nucleophilic properties. Through the selection of the electron-withdrawing group attached to nitrogen, chemists can modulate the electronic properties and reactivity of ynamides, making these groups versatile synthetic building blocks. The reactions of ynamides also lead directly to nitrogen-containing products, which provides access to important structural motifs found in natural products and molecules of medicinal interest. Therefore, researchers have invested increasing time and research in the chemistry of ynamides in recent years.

This Account surveys and assesses new organic transformations involving ynamides developed in our laboratory and in others around the world. We showcase the synthetic power of ynamides for rapid assembly of complex molecular structures. Among the recent reports of ynamide transformations, ring-forming reactions provide a powerful tool for generating molecular complexity quickly. In addition to their synthetic utility, such reactions are mechanistically interesting. Therefore, we focus primarily on the cyclization chemistry of ynamides.

This Account highlights ynamide reactions that are useful in the rapid synthesis of cyclic and polycyclic structural manifolds. We discuss the mechanisms active in the ring formations and describe representative examples that demonstrate the scope of these reactions and provide mechanistic insights. In this discussion, we feature examples of ynamide reactions involving radical cyclizations, ring-closing metathesis, transition metal and non-transition metal mediated cyclizations, cycloaddition reactions, and rearrangements. The transformations presented rapidly introduce structural complexity and include nitrogen within or in close proximity to a newly formed ring (or rings). Thus, ynamides have emerged as powerful synthons for nitrogen-containing heterocycles and nitrogen-substituted rings, and we hope this Account will promote continued interest in the chemistry of ynamides.

1. Introduction

Over the past 15 years, ynamides have become a modern functional group that has been prominently featured in a variety of synthetic transformations including natural product total syntheses.[1−3] Fueled by preparative access that is efficient and atom economical,[4,5] the field of ynamide chemistry has rapidly expanded. Ynamides provide a means of activating carbon–carbon triple bonds, giving them both electrophilic and nucleophilic properties. The electronic properties of ynamides are tunable based on selection of the electron-withdrawing group attached to nitrogen, thereby rendering them highly versatile synthons. Furthermore, among all heteroatom-substituted alkynes, ynamides are special because nitrogen is one of the most privileged elements in nature. Consequently, many transformations involving ynamides offer a diverse array of novel structural entities that are not only powerful platforms for further transformations but also prevalent among

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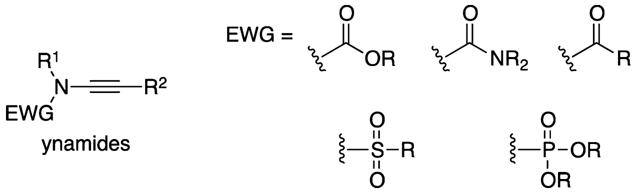
important pharmacophores. These properties have contributed to a continued and dramatic increase in the number of publications in the past few years.



This Account aims to examine the literature from late 2009 through early 2013 related to the use of ynamides in synthetic transformations that form cyclic and polycyclic manifolds. Consequently, the Account is organized by reaction types used in the ring formation, and representative examples are selected to showcase scope and mechanistic insight of each transformation. The intention here is not to comprehensively review the ynamide chemistry that appeared during this period but to highlight major advancements in ynamide chemistry through revelation of its utility in rapid assembly of structural complexity. As a result, some beautiful recent works are not presented here. This includes improved ynamide preparations and syntheses of de novo structural analogues of ynamides. Both topics have been the subject of a thorough review published recently by Evano.[4] In addition, new advances related to in situ generation of ketenimines or metallo-ynamides via Huisgen's azide-[3 + 2] cycloaddition/retro-[3 + 2] are not covered here.[6]

2. Radical Cyclizations

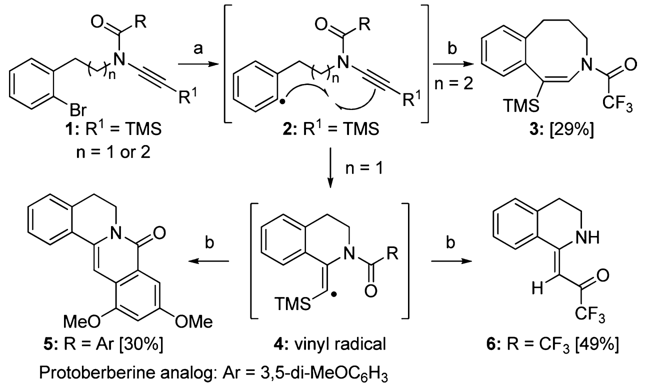
Balieu et al.[7] reported the formation of six-membered rings **5** and **6** and the eight-membered ring **3** via the radical cyclization of ynamides **1** (Scheme 1). A tandem radical cyclization also took place when R was 3,5-dimethoxyphenyl through vinyl radical **4**.

Chemla et al.[8] reported synthesis of 3-alkylidenetetrahydrofurans **11** from ynamides **7** through a 1,4-addition/alkyne carbozincation sequence based on a radical zinc-atom transfer process (Scheme 2). The addition of ethyl radical gave enoxy radical **8**, which underwent 5-*exo-dig* cyclization with the ynamide leading to vinyl radical **9** of *E*-geometry.

3. Ring-Closing Metathesis

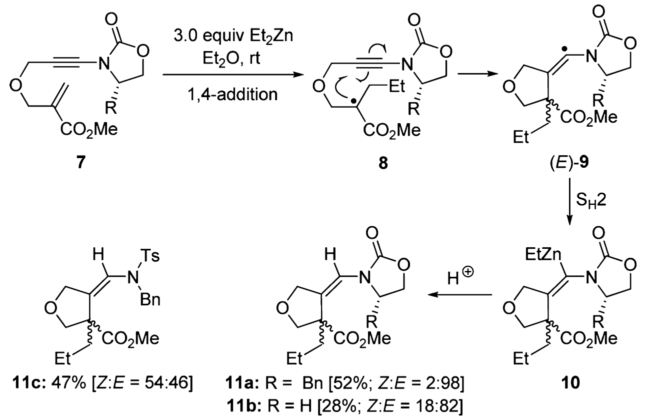
Wakamatsu et al.[9] reported further development of their ring-closing metathesis of ene-ynamides, featuring syntheses of seven-membered heterocycles **13** and **15** and eight-membered heterocycles **17** using second-generation Grubbs catalyst (Scheme 3).

SCHEME 1[a]



[a]Conditions: (a) 0.5 equiv of AIBN, 2.0 equiv of n-Bu_3SnH, benzene, 80 °C; (b) (i) NaOH, 1.0 M; (ii) silica gel.

SCHEME 2



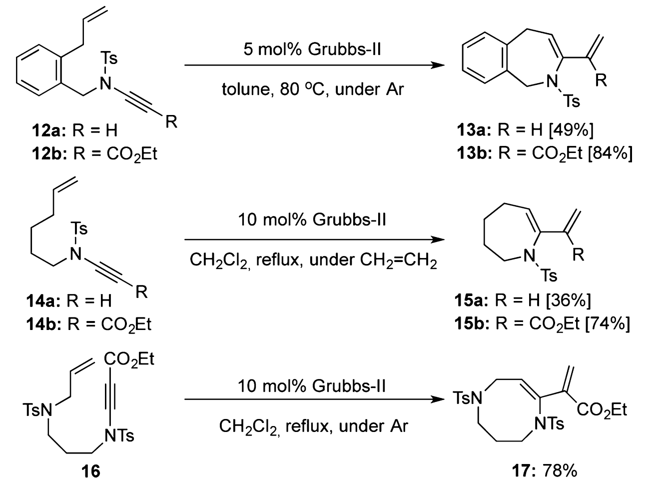
4. Non-Transition Metal Mediated Cyclizations

Popik and co-workers[10] reported acid catalyzed cycloaromatizations of cyclic ynamides **18** (Scheme 4). Protonation of the ynamide followed by addition of the alkyne onto the resulting keteniminium ion **19** provided cation **20**, which underwent Friedel–Crafts additions. Alcoholic solvent trapping of **19** competed with cycloaromatization, especially with increasing ring size.

Evano and co-workers[11] developed a general and efficient approach toward 1,4-dihydropyridines **29** and pyridines **30** from readily available *N*-allyl-ynamides **24** via a tandem lithiation–isomerization–6-*endo-dig* intramolecular carbolithiation sequence (Scheme 5).

Flynn and co-workers[12] reported a highly torquoselective Nazarov cyclization of 2-amido divinyl ketones **34** derived from chiral oxazolidinone-substituted ynamides **31** (Scheme 6). The diastereoselectivity can be very high, and Nazarov arrested products such as **37a** could also be obtained.

SCHEME 3



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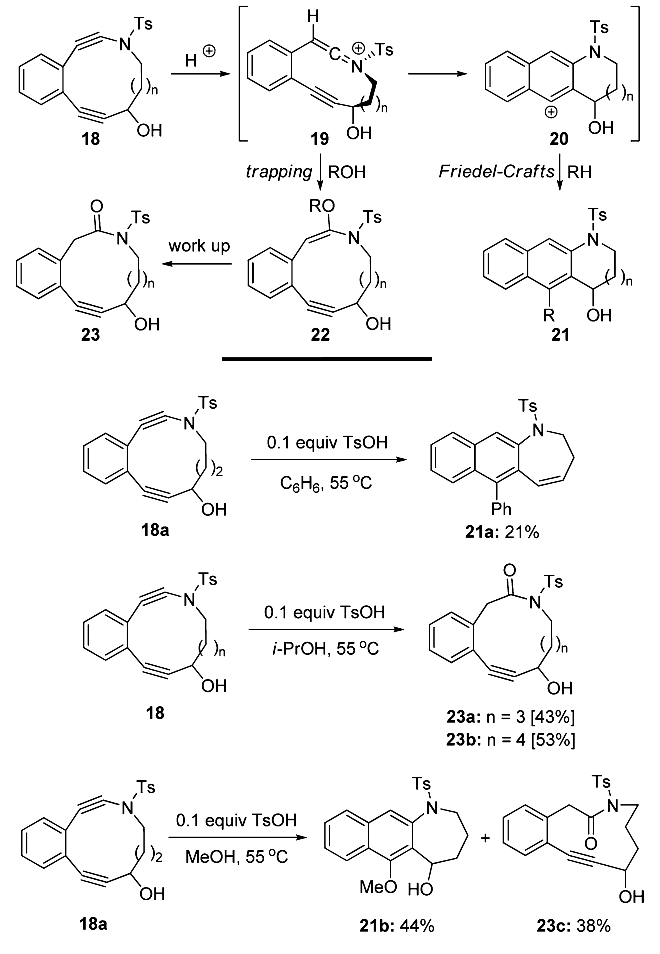

Cao and co-workers[13] described an efficient approach toward 3-allenyl-2-amidobenzofurans **40** and 3-alkyl-2-amidobenzofurans **44** via a novel carbocation-induced electrophilic cyclization of *o*-anisole-substituted ynamides with

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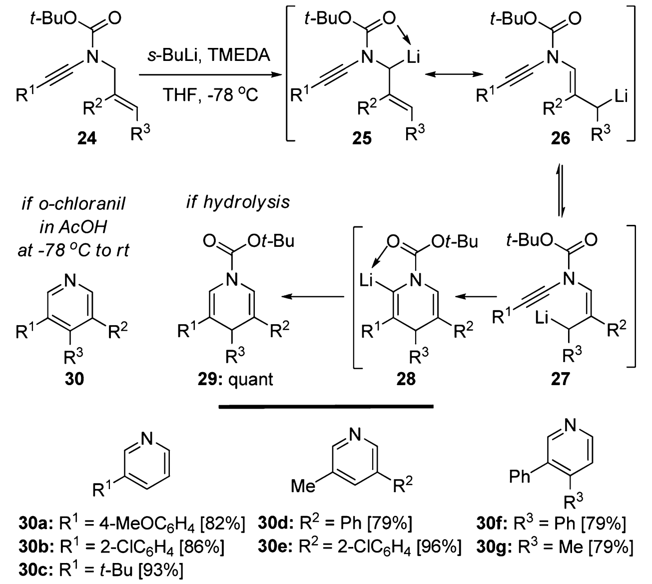

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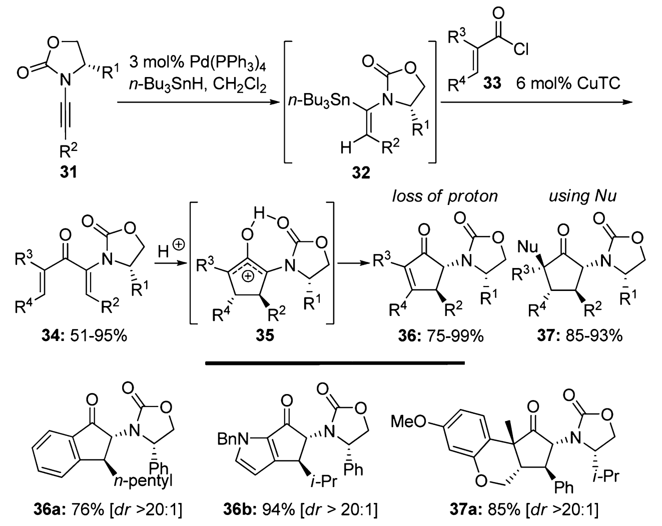

1,1-diaryl-prop-2-yn-1-ol **39** and diarylmethanol **41**, respectively (Scheme 7).

Later, Cao and co-workers[14] developed a novel synthesis of 2-amidobenzofurans and 2-amidobenzothiophenes via electrophilic cyclization of *o*-anisole- and *o*-thioanisole-substituted ynamides **45** with I_2, *N*-bromosuccinimide (NBS), and *N*-chlorosuccinimide (NCS). This strategy was also used to construct 1-amidonaphthalenes **50** and 1-amidobenzopyrans **52** from ynamides (Scheme 8).

Hsung and co-workers[15] unveiled a novel acid promoted 5-*endo-dig* cyclization of chiral γ-amino-ynamide **53** concomitant with the loss of the *t*-Bu group that led to

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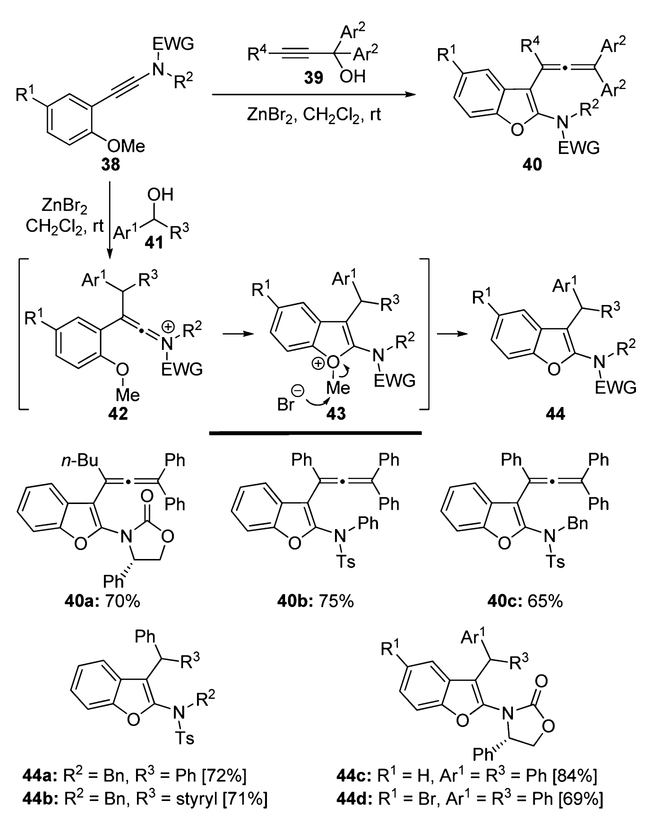

the formation of isothaizole **54** and dihydroisothaizole *S*-oxide **55**. An inversion at the "S" center occurred in **55** (Scheme 9).

Hsung and co-workers[16] featured an *aza*-variant of a Meyer–Schuster rearrangement of γ-amino-ynamides **56**, which involved the formation of azetene intermediate **58** and pericyclic ring-opening (Scheme 10).

5. Transition Metal Mediated Cyclizations

5.1. Rhodium. Nishimura et al.[17] disclosed a rhodium-catalyzed asymmetric cycloisomerization of heteroatom-bridged 1,6-enynamides such as **60** to afford 3-*aza* and oxabicyclo[4.1.0]heptene derivatives such as **61a** (Scheme 11). 2-oxazolidinone and 2-azetidinone substituents of the ynamides were critical for high enantioselectivities, because the carbonyl oxygen might coordinate to the metal during the transformation.

Tang and co-workers[18] developed an efficient method for the generation of α-*oxo* Rh(I) carbenes **63** and **69** from ynamides with 3,5-dichloropyridine *N*-oxide. The resulting Rh(I) carbenes then react intramolecularly with various alkynes or alkenes affording 2-oxopyrrolidines **66** and 3-azabicyclo[3.1.0]hexanes **71**, respectively (Scheme 12).

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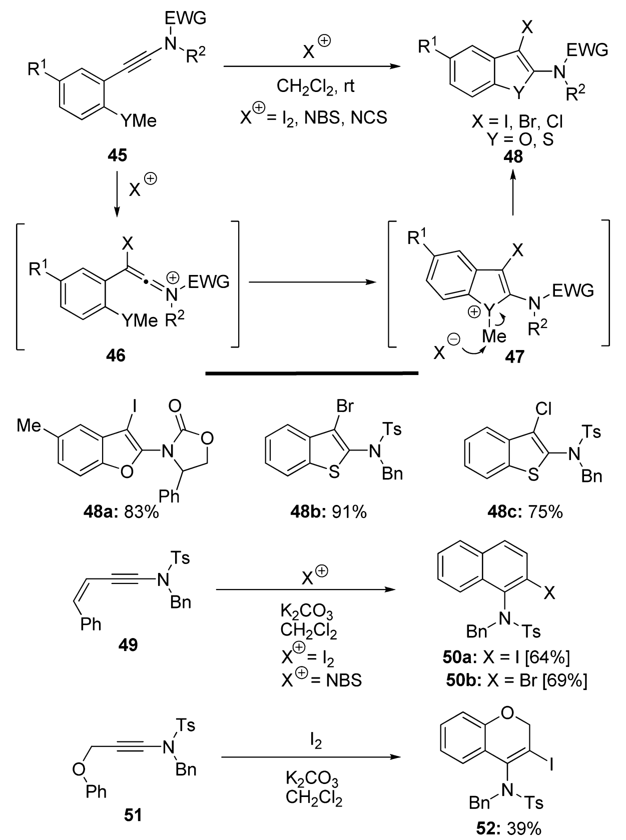

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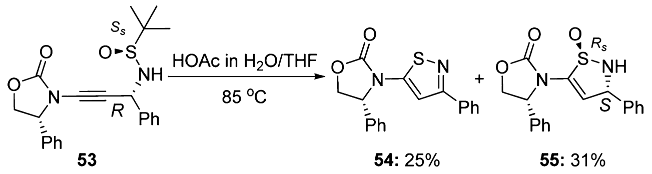
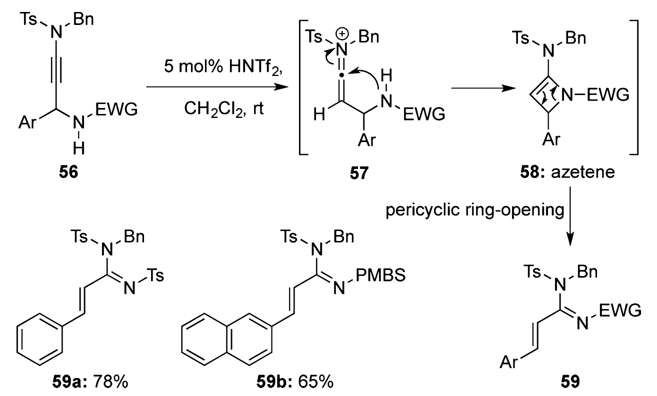


5.2. Palladium. Anderson and co-workers[19] reported a palladium-catalyzed tandem cascade of cyclization–cross-coupling–6π-electron electrocyclization using bromoenynamides **72** (Scheme 13).

Anderson and co-workers[20] subsequently reported a related palladium-catalyzed cascade using bromoenynamides **75** affording cyclic 2-amidodienes **77** that could be used in ensuing Diels–Alder cycloadditions (Scheme 14). An alcohol served as a hydride source to terminate the carbopalladation process.

5.3. Platinum. Liu and co-workers[21] reported an equivalent of Pt(II)-catalyzed *oxo*-arylations of ynamide **79** (Scheme 15). This process employs nitrones **80** and provides imines **83** via intermediates **81** and **82**, and under reductive conditions using NaBH$_3$CN, 2-indolones **85** were obtained.

SCHEME 10



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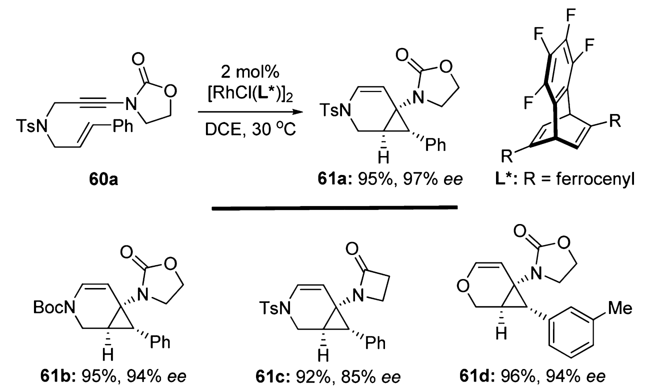

5.4. Copper. Chen and co-workers[22] reported a Cu(I)-catalyzed 1,2-aminothiolation of 1,1-dibromoalkenes **86** with 2-thiobenzoimidazole, leading to thiazolines **90** and **91** (Scheme 16). The regiochemistry of the 1,2-aminothiolation depends on whether it is 5-*endo-dig* cyclization of S- or N-alkynylation intermediates (**88** or **89**).

Hashmi et al.[23] reported a copper-mediated domino reaction of three simple components that included propargylcarboxamide **92**, protected amine **93**, and a chloride source. This cascade provides an efficient construction of highly functionalized oxazines **97** (Scheme 17).

Li and Neuville[24] developed an efficient and regioselective approach to 1,2,4-trisubstituted imidazoles **103** via a copper-catalyzed oxidative diamination of terminal alkynes **99** by amidines **98** (Scheme 18). This transformation employs oxygen as the co-oxidant and proceeds through a direct N-alkynylation of the terminal acetylenes, thereby rendering the process atom economical.

Evano and co-workers[25] reported a modular synthesis of polysubstituted indoles **105** from *N*-aryl-ynamides **104**. A bromine/lithium exchange of *N*-(2-bromoaryl)ynamides **104**, followed by a 5-*endo-dig* carbocupration, afforded the substituted indoles efficiently (Scheme 19).

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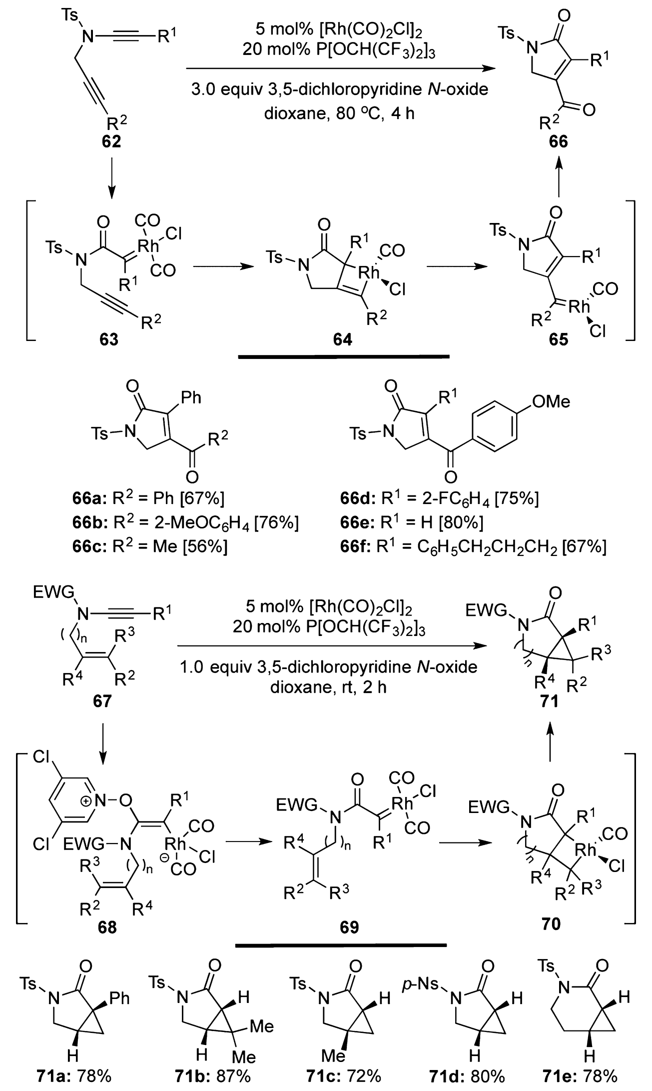

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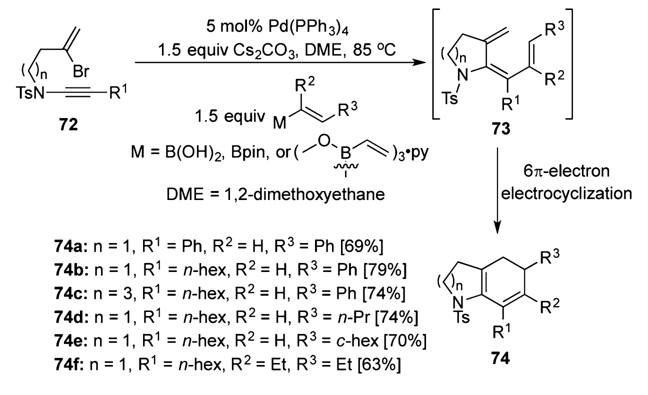

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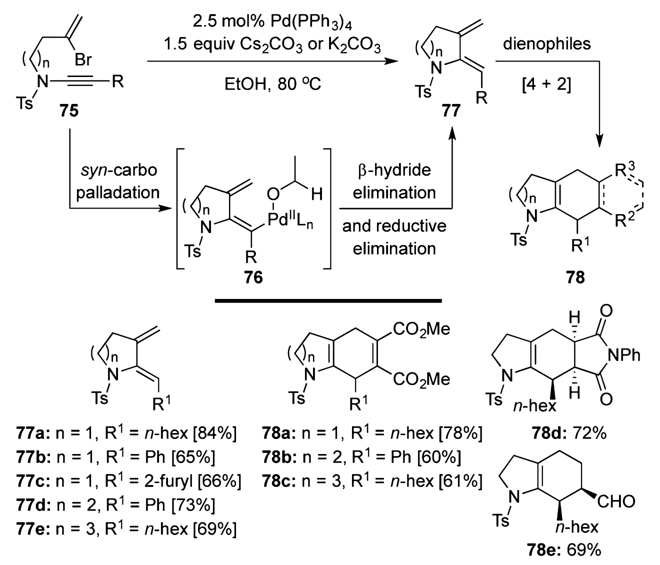
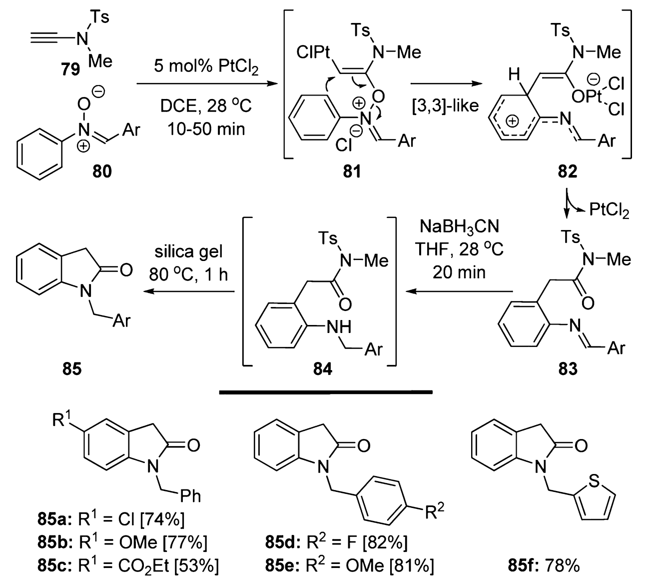


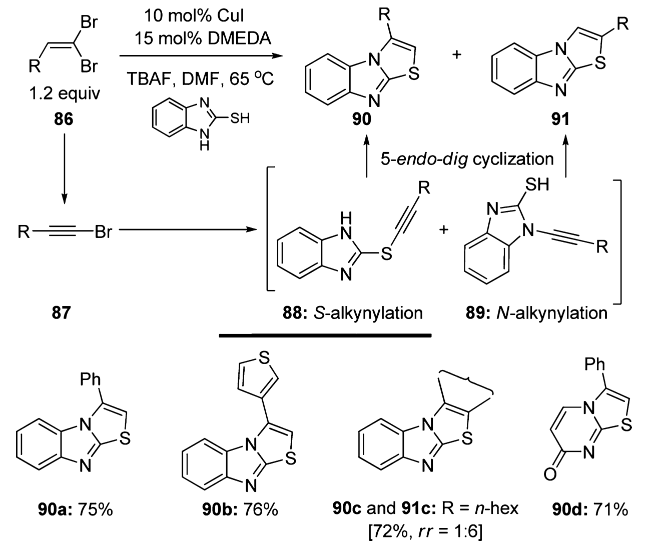
SCHEME 15



5.5. Silver. Malacria and co-workers[26] reported a silver-catalyzed cycloisomerization of de novo allene-ynamides **106**, leading to amide-substituted cross-conjugated trienes **108** that are useful for tandem Diels–Alder cycloadditions (Scheme 20).

5.6. Gold. Hashmi et al.[27] reported a gold-catalyzed cyclization of furanyl-ynamides **109** (Scheme 21). The course of the cyclization depended upon the length of the tether. Benzoanellated heterocycles **114** were produced when $n = 1$, while cyclopentadiene fused piperidines **118** were obtained when $n = 2$.

SCHEME 16



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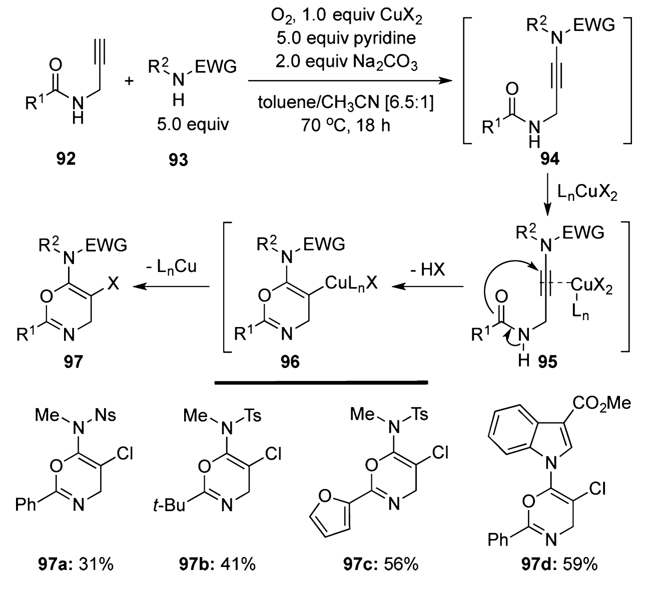
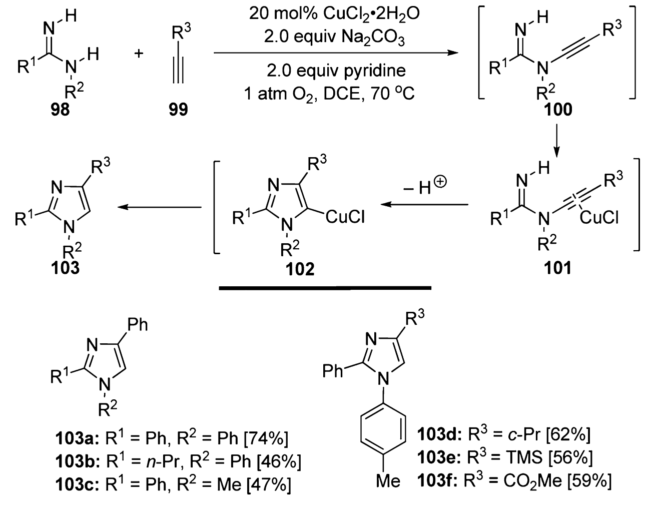


Skrydstrup and co-workers[28] reported Au(I)-catalyzed hydroaminations or hydrations of diynamides **119** to access 2,5-diamidopyrroles **121** and 2,5-diamidofurans **122**, respectively (Scheme 22). This development represents a clever application of diynamides.

Liu and co-workers[29] reported highly regioselective Au(I)-catalyzed oxidative ring expansions of cyclopropyl-substituted ynamides **123** using Ph_2SO (Scheme 23). The ring expansion is not believed to proceed through an α-keto gold carbenoid intermediate but through **124**. Subsequently, Li and co-workers[30] independently reported a similar gold-catalyzed oxidative ring expansion (details not shown here).

SCHEME 18



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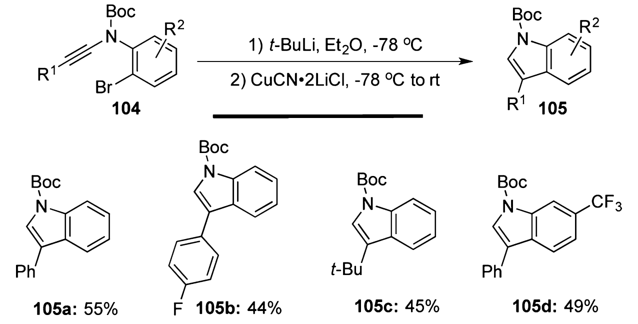

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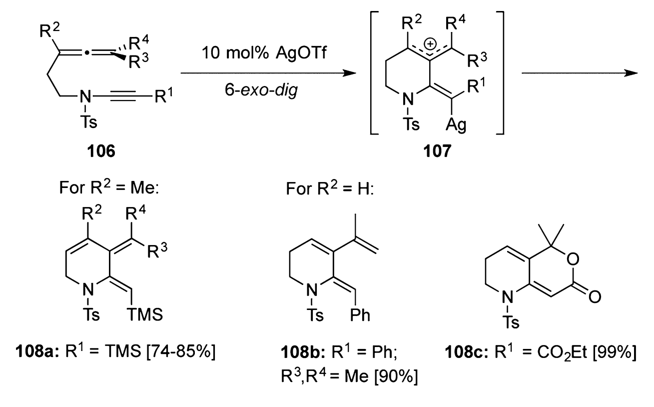

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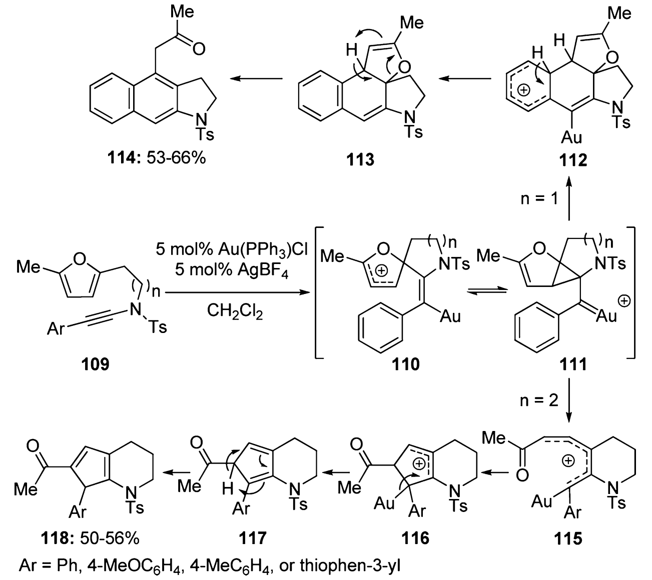

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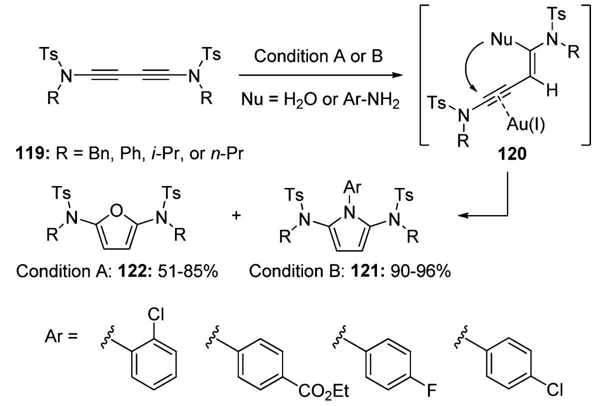

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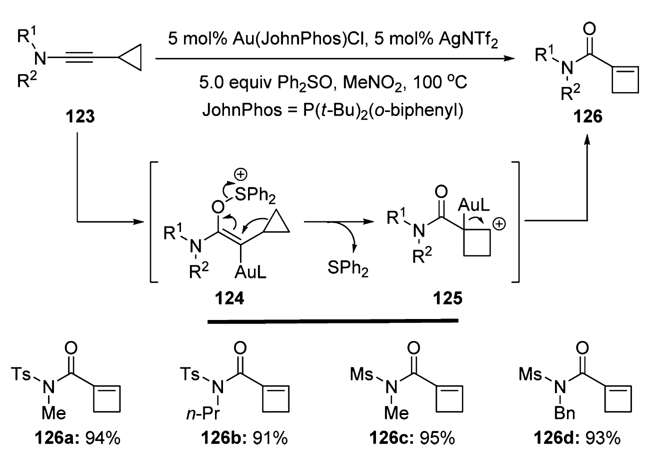
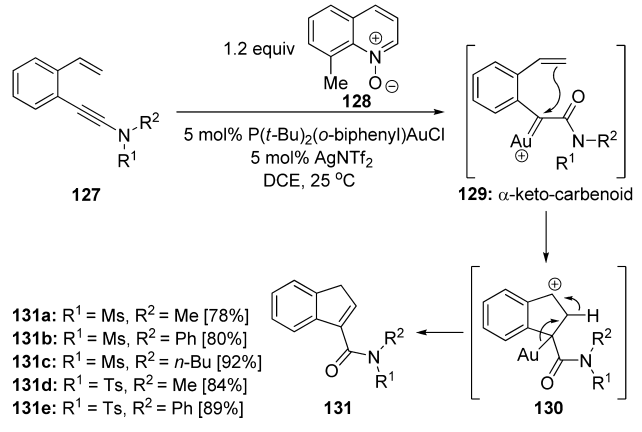


Liu and co-workers[31] then explored 1,5-enynamides **127**, developing a Au(I)-catalyzed oxidative cyclization using 8-methylquinoline *N*-oxide **128** as the external oxidant to construct 3-carboxyamidoindenes **131** (Scheme 24). The transformation is believed to proceed through α-keto-carbenoid **129**.

Li and co-workers[32] reported a clever synthesis of 3-*aza*-bicyclo[3.1.0]hexan-2-one derivatives **135** via Au(I)-catalyzed oxidative cyclopropanations of *N*-allyl-ynamides **132** using pyridine *N*-oxide as the external oxidant (Scheme 25).

SCHEME 24



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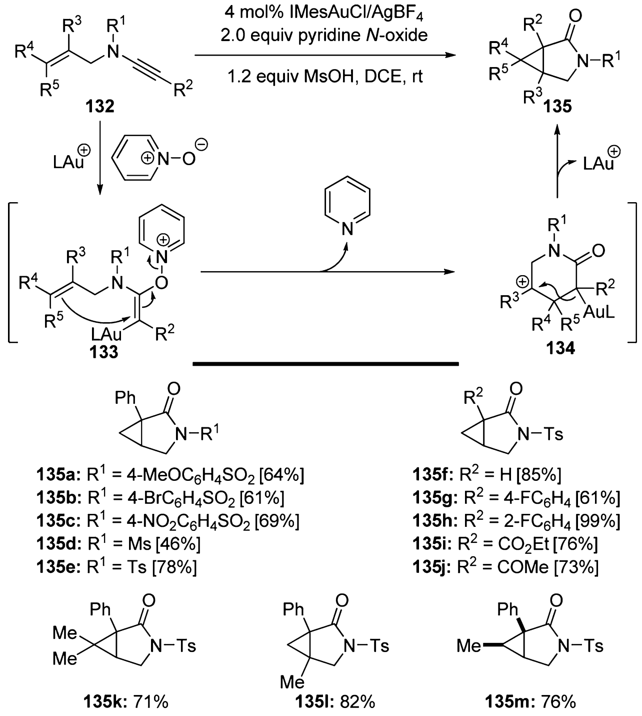

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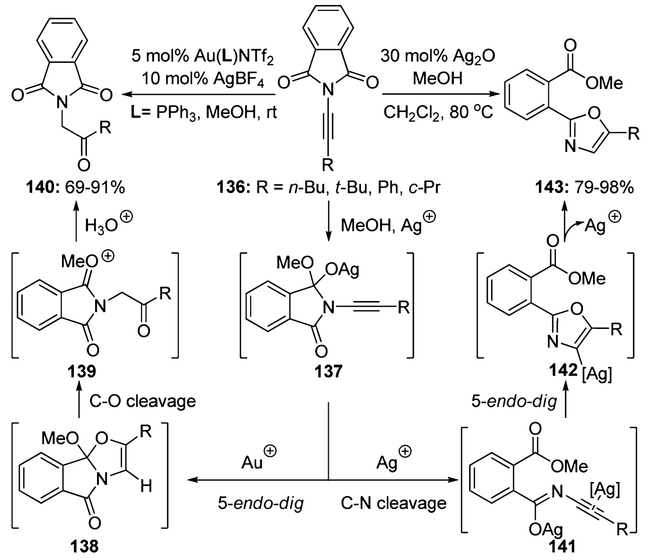

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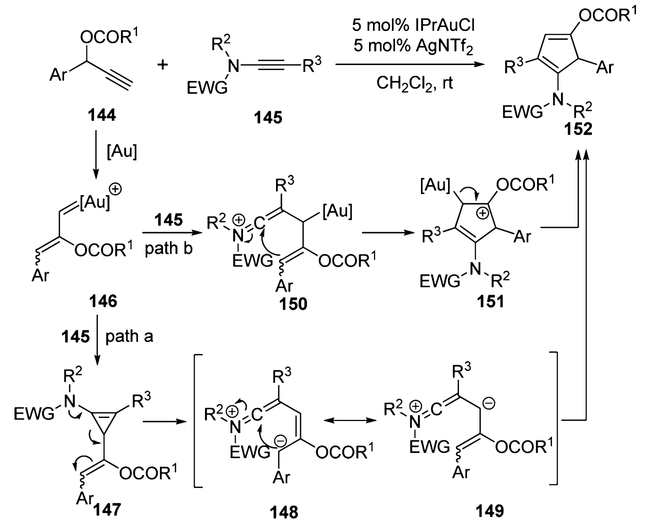

Sueda et al.[33] reported Ag(I) or Ag(I) and Au(I) catalyzed cyclizations of de novo ynimides **136**, which could be accessed for the first time. These cyclizations gave β-ketoimides **140** when using both Au(I) and Ag(I), while providing oxazoles **143** when using only Ag(I) (Scheme 26).

Hashmi and co-workers[34] reported synthesis of highly functionalized cyclopentadienes **152** in moderate to good yields via Au(I)-catalyzed intermolecular cyclization of propargylic carboxylates **144** and ynamides **145** (Scheme 27).

Sahoo and co-workers[35] developed Au(I)-catalyzed hydrative cyclization of easily accessible 5-yne-ynamides **153**, giving substituted 1,6-dihydropyridin-2(3*H*)ones **157** in good to excellent yields (Scheme 28). A mechanism involving a 6-*endo-dig* cyclization of intermediate **155** was proposed.

Bertrand and co-workers[36] reported that deprotonation of oxazolium salt **159** initiated an interesting ring-opening process giving ynamide **160** (Scheme 29). The acyclic ynamide readily reacts with various transition metals affording robust mesoionic carbene complexes **161**.

6. Cycloadditions and Formal Cycloadditions

6.1. [2 + 1]. Hsung and co-workers[37] reported the first examples of stereoselective intramolecular cyclopropanations via a de novo class of push–pull carbenes derived from

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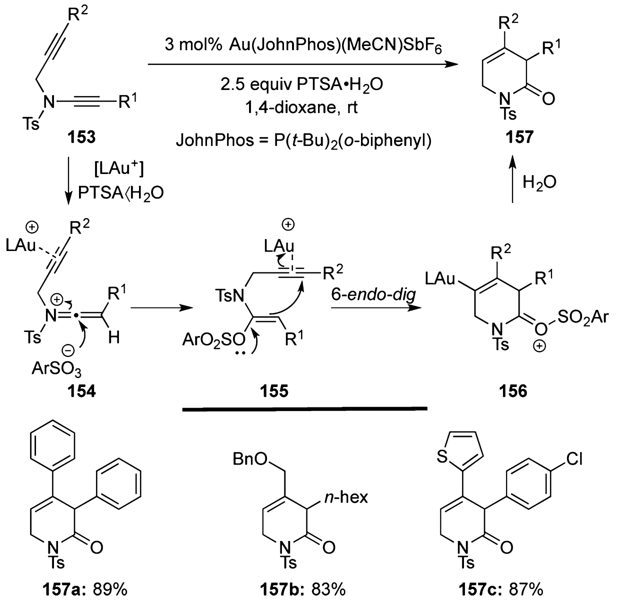

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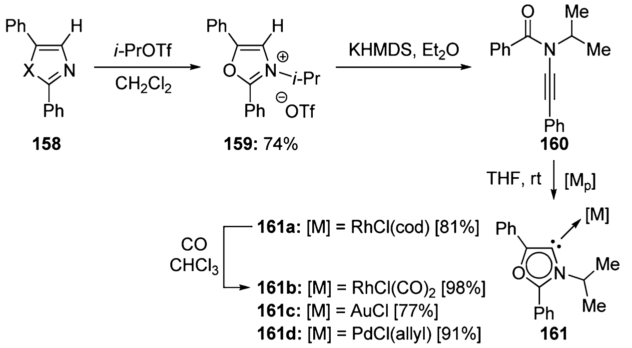
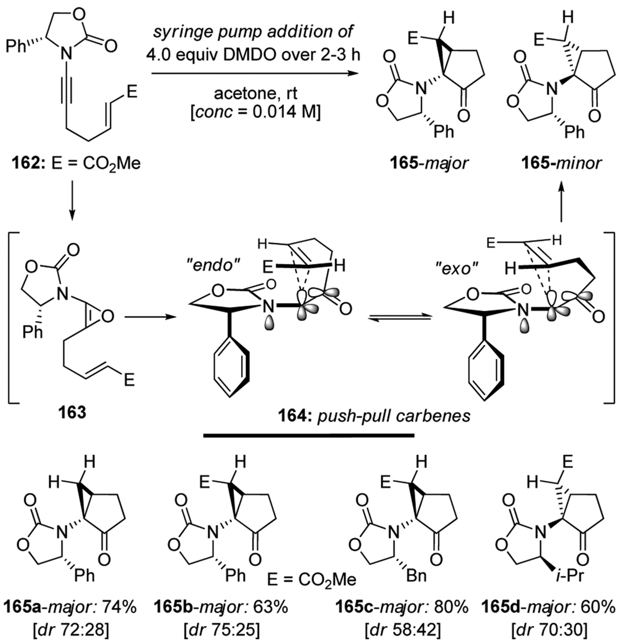


dimethyldioxirane (DMDO) epoxidations of chiral ynamides **162** (Scheme 30). This tandem epoxidation–cyclopropanation afforded a series of structurally unique amido-cyclopropanes **165**.

Buono and co-workers[38] reported an unusual palladium catalyzed [2 + 1] cycloaddition of ynamides **166** with norbornene derivatives **167** giving various substituted aminomethylenecyclopropanes **170** (Scheme 31). Based on their previous study in an alkyne system,[39] this process may involve a [2 + 2] cycloaddition of palladium vinylidene species with the double bonds of norbornene derivatives, followed by reductive elimination to furnish cyclopropanes.

6.2. [2 + 2]. Hsung and co-workers[40] reported the first successful example of Ficini's [2 + 2] cycloaddition of ynamides **171** with enones **172** using $CuCl_2$ and $AgSbF_6$ as catalysts (Scheme 32).

SCHEME 30



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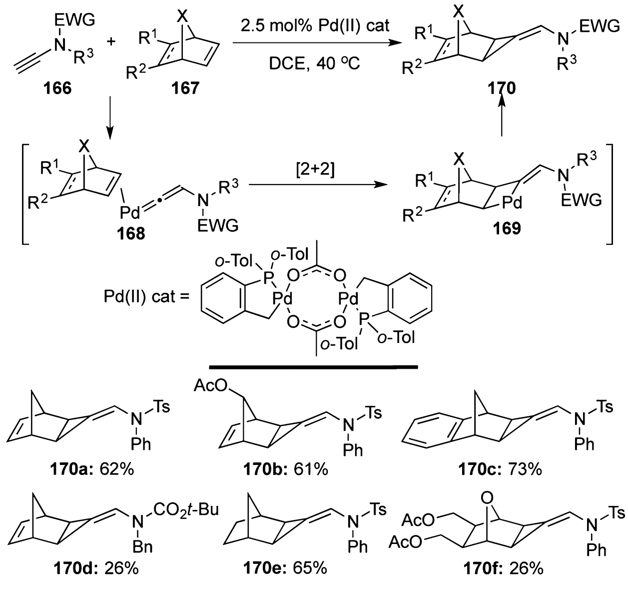
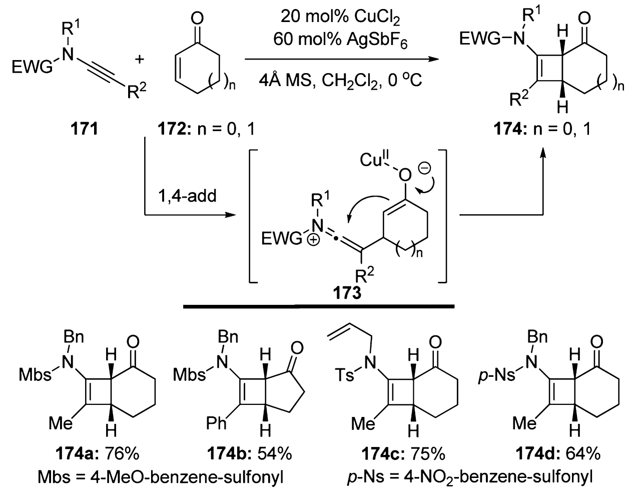


Mezzetti and co-workers[41] subsequently reported $Cu(OTf)_2$ promoted Ficini [2 + 2] cycloadditions of ynamides with unsaturated β-keto esters in addition to a beautiful asymmetric variant using dicationic ruthenium(II)/PNNP complex (Scheme 33).

Wang and Danheiser[42] reported the first examples of thermal [2 + 2] cycloadditions of 2-iodoynamides **181** with ketenes **182**, leading to 3-amido-2-iodocyclobutenones **183** (Scheme 34).

SCHEME 32



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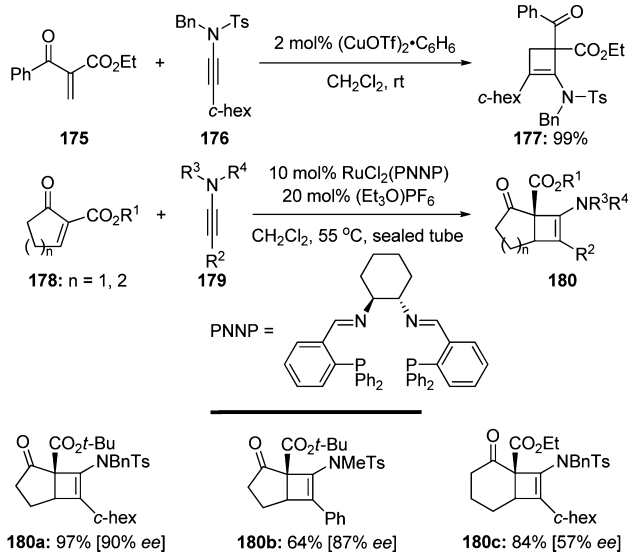

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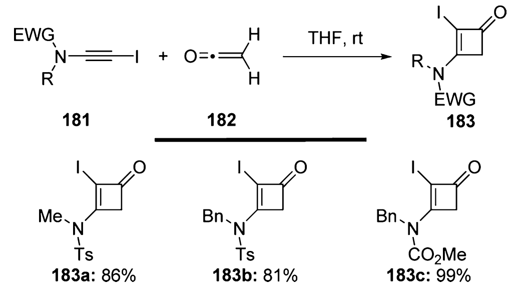
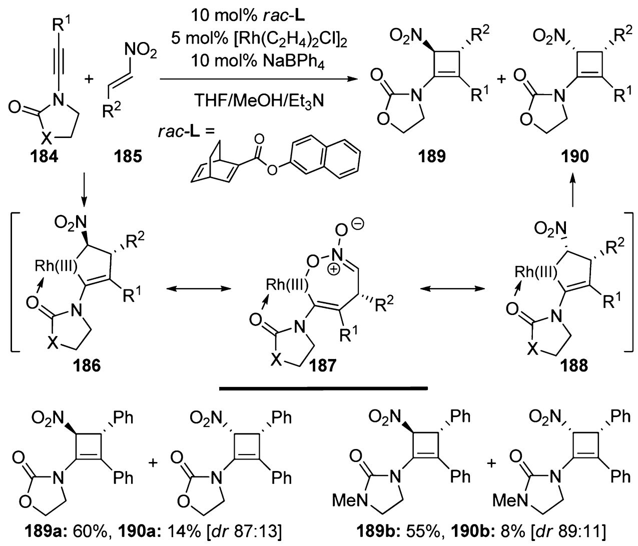
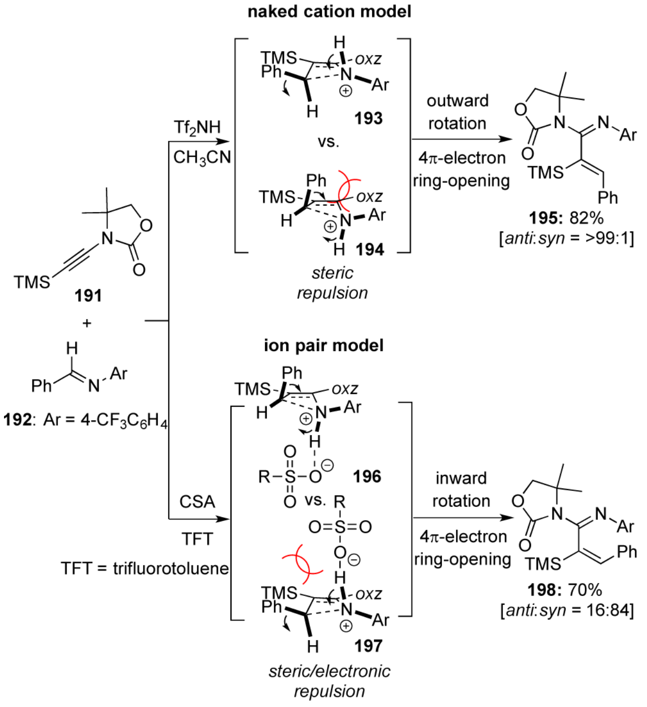


Lam and co-workers[43] reported a [2 + 2] cycloaddition of ynamides **184** with nitroalkenes **185** catalyzed by a dirhodium complex and sodium tetraphenylborate, leading to nitro-substituted cyclobutenamides **189** and **190** (Scheme 35).

SCHEME 35

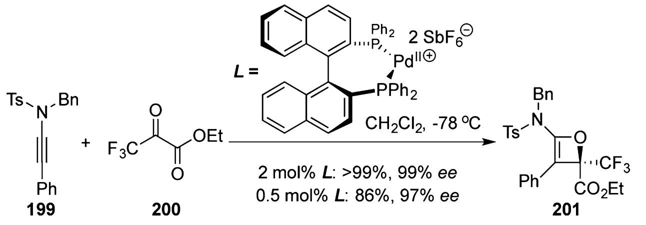


SCHEME 36

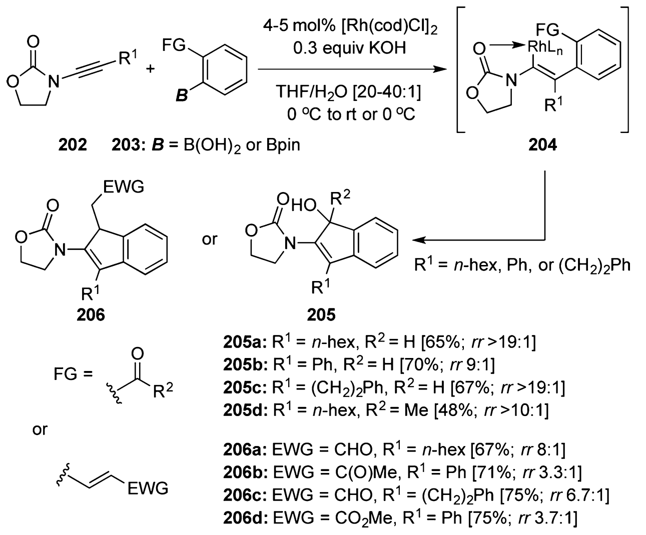


Takasu and co-workers[44] reported selective syntheses of either *syn* or *anti* isomers of α,β-unsaturated amidines **195** and **198** through a tandem cascade of *aza*-[2 + 2] cycloaddition–4π-electron pericyclic ring-opening by using Tf$_2$NH or CSA as catalyst, respectively (Scheme 36). The torquoselectivity of ring-opening was controlled by the Brønsted acidity of the catalyst and the polarity of the solvent.

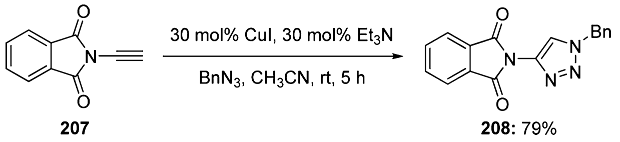
SCHEME 37



SCHEME 38



SCHEME 39



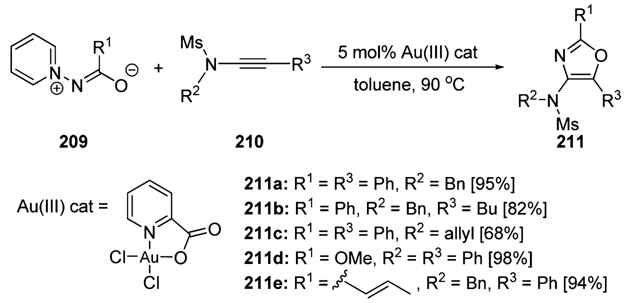
Mikami and co-workers[45] reported an asymmetric [2 + 2] cycloaddition of ynamide **199** with ethyl trifluoropyruvate **200** using a dicationic (*S*)-BINAP-Pd catalyst with excellent yield and enantioselectivity. This is also the first enantioselective synthesis of a stable oxetene derivative (Scheme 37).

6.3. [3 + 2]. Lam and co-workers[46] reported a Rh-catalyzed formal [3 + 2] cycloaddition of ynamides **202** with arylboronic acids or esters **203** containing an electrophilic functional group at the *ortho*-position. This transformation effectively provides 2-amido-indenols **205** or 2-amido-indenes **206** in good regioselectivities (Scheme 38).

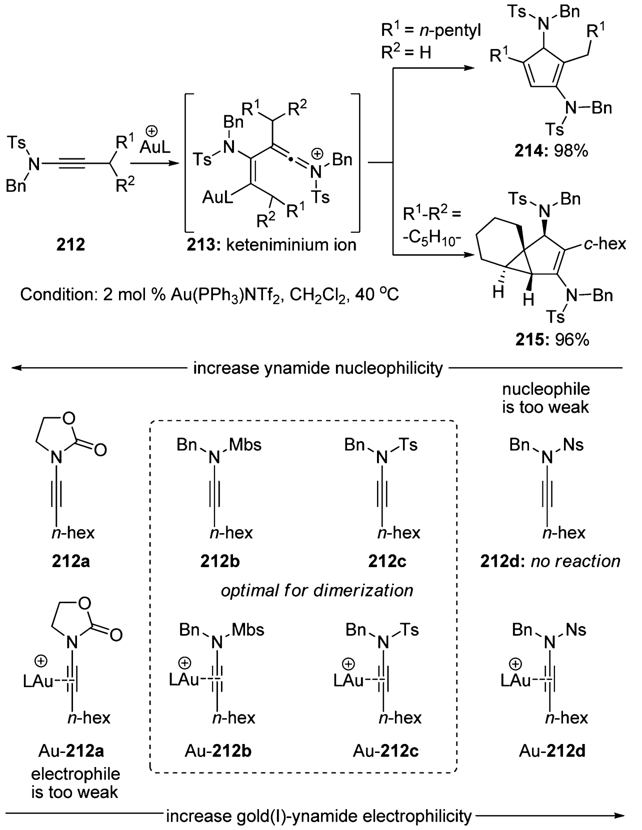
Sueda et al.[47] applied their ynimides **207** to the copper-mediated Huisgen's azide-[3 + 2] cycloaddition giving 4-phthalimido-1-benzyl-1,2,3-triazole **208** (Scheme 39).

Davies et al.[48] reported that 2,4,5-trisubstituted oxazoles **211** could be synthesized from ynamides **210** and 1,3-*N*,*O*-dipole equivalents **209** in a gold(III) catalyzed process (Scheme 40).

SCHEME 40



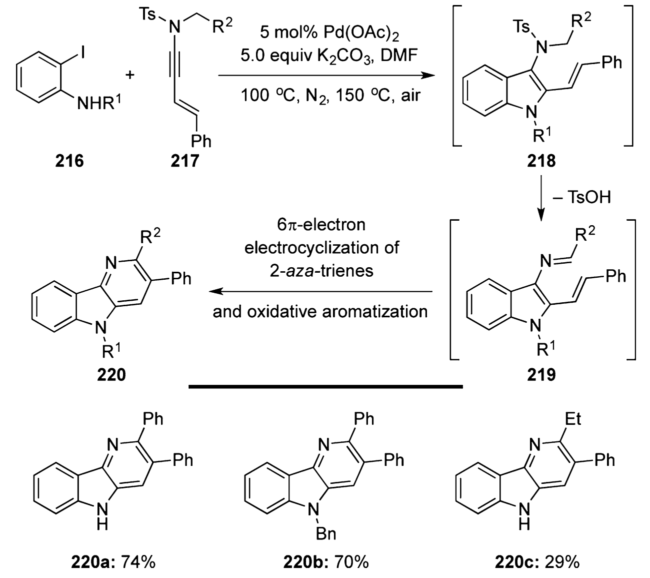
SCHEME 41



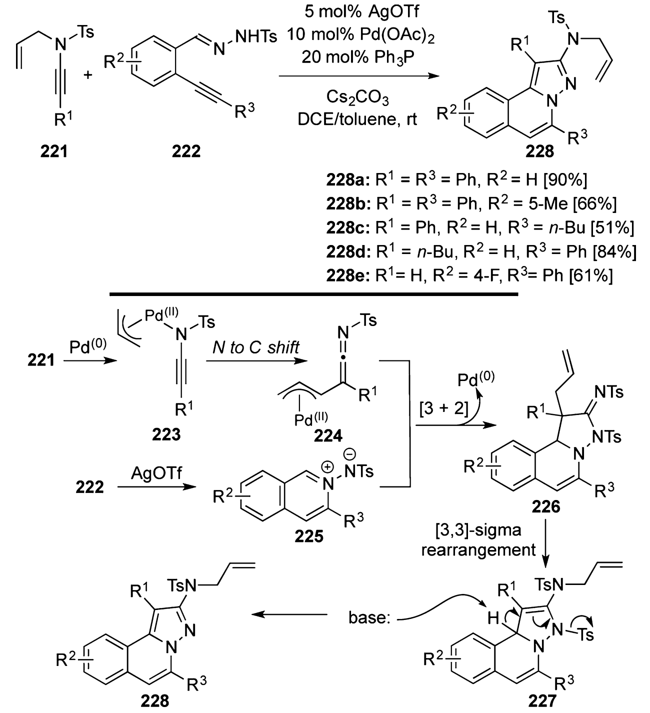
Gagosz and co-workers[49] reported syntheses of cyclopentadienes **214** or tricycles **215** from dimerizations of ynamides **212** in the presence of a Au(I) complex (Scheme 41). While the divergence in this dimerization depends upon the substitution pattern, its efficiency is directly dependent on the electronic properties of the ynamide, which acts both as the electrophile and the nucleophile in the process.

Lai and co-workers[50] reported the synthesis of δ-carbolines **220** from 2-iodoanilines **216** and *N*-tosyl-enynamides

SCHEME 42

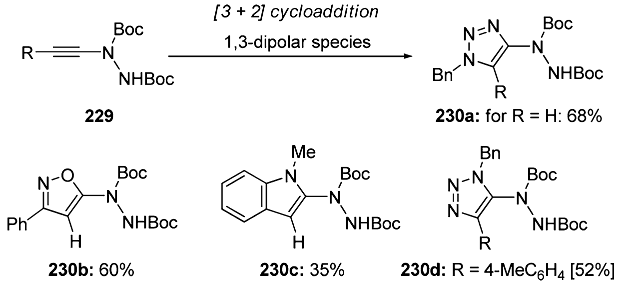


SCHEME 43

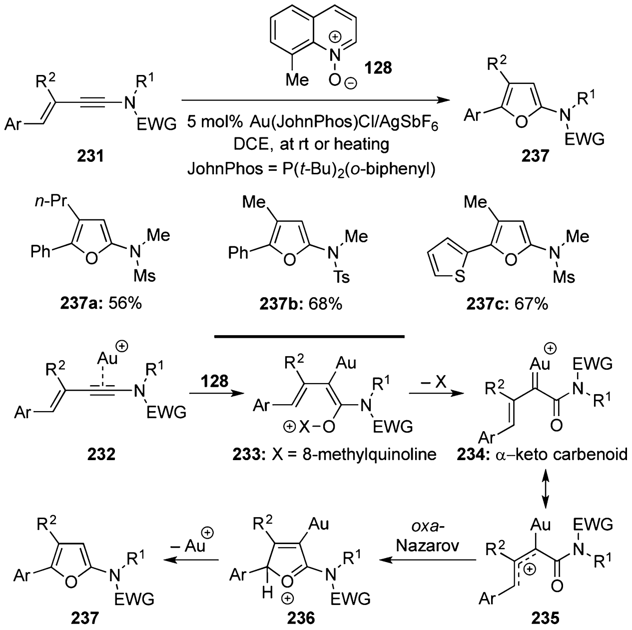


217 via a Pd(0)-catalyzed cascade (Scheme 42). This cascade involves Larock's heteroannulation giving indoles **218** and an electrocyclization of 2-*aza*-trienes **219** after loss of TsOH.

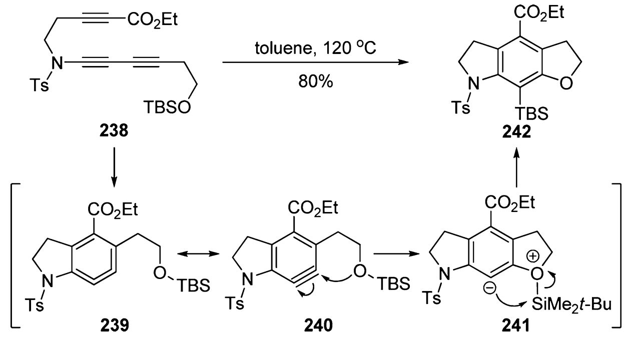
SCHEME 44



SCHEME 45



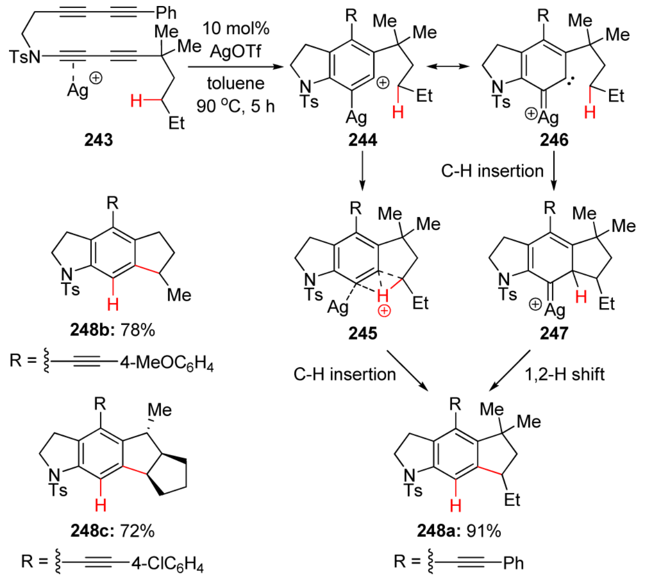
SCHEME 46



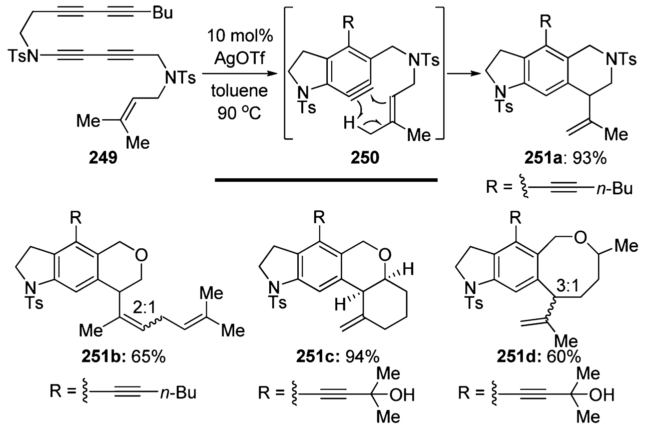
Peng and co-workers[51] reported a AgOTf/Pd(OAc)$_2$ cocatalyzed [3 + 2]-cycloaddition of *N*-allyl-*N*-sulfonyl ynamides **221** with *N*′-(2-alkynyl-benzylidene)hydrazides **222** giving 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines **228** (Scheme 43). The transformation proceeds through 6-*endo-dig* cyclization of **222**, [3 + 2] cycloaddition between **224** and **225**, 3,3-sigmatropic rearrangement, and aromatization.

Beveridge and Batey[52] reported a series of 1,3-dipole cycloadditions using ynehydrazides **229** that were first synthesized in these authors' laboratory. This exercise

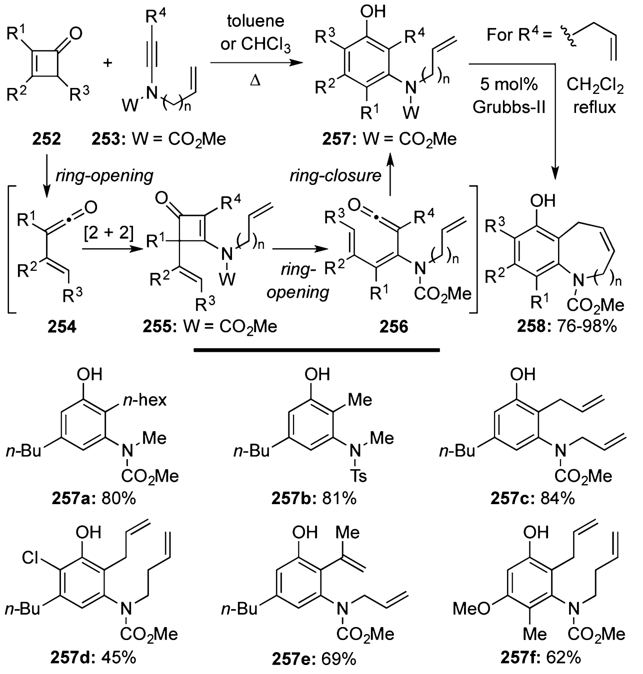
SCHEME 47



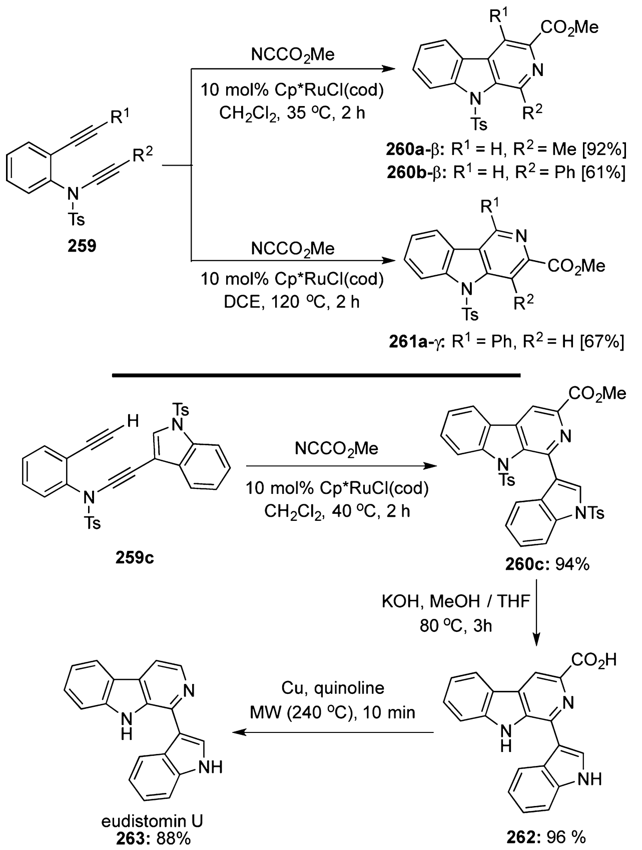
SCHEME 48



SCHEME 49



SCHEME 50

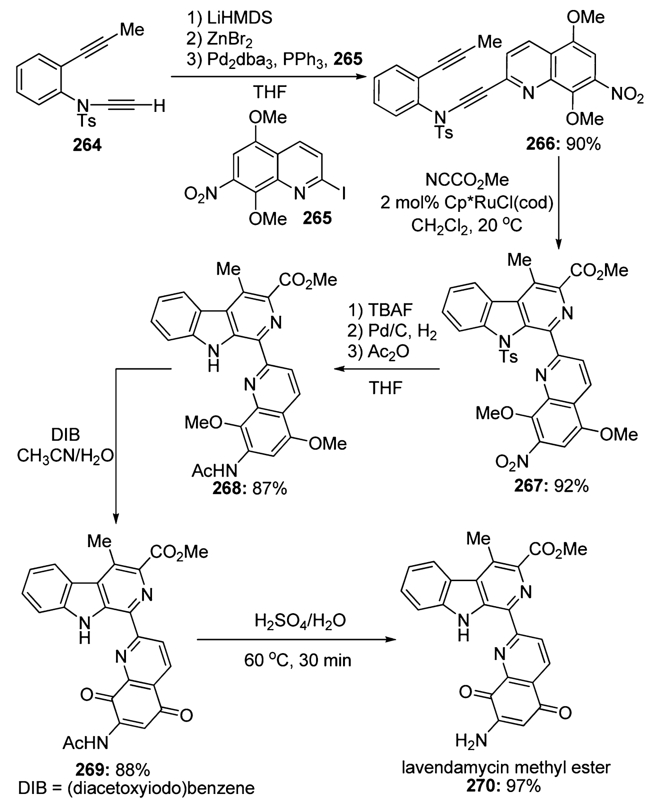


demonstrates the synthetic potential of these novel ynamides (Scheme 44).

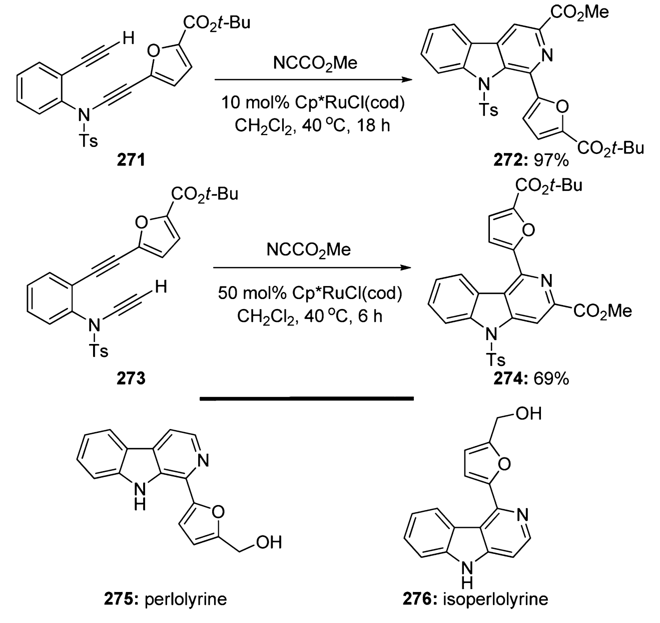
6.4. [4 + 1]. Liu and co-workers[53] reported a gold-catalyzed formal [4 + 1]-cycloaddition of ynamides **231** with 8-methylquinoline oxide **128**, leading to a series of substituted 2-amido-furans **237** (Scheme 45). Mechanistically, this formal cycloaddition likely proceeded through α-keto carbenoid **234** via an initial gold-catalyzed addition of 8-methylquinoline oxide **128** to ynamides **231** followed by an *oxa*-Nazarov cyclization.

6.5. [4 + 2]. Hoye et al.[54] disclosed an intramolecular hexadehydro-Diels–Alder cycloaddition reaction of ynamide **238** (Scheme 46). The hexadehydro-Diels–Alder reaction of **238** led to the key benzyne intermediate **240**, which was trapped by the pendant silyloxy group, giving the tricycle **242** in 80% yield after an *O*-to-*C* silyl migration of the zwitterionic intermediate **241**.

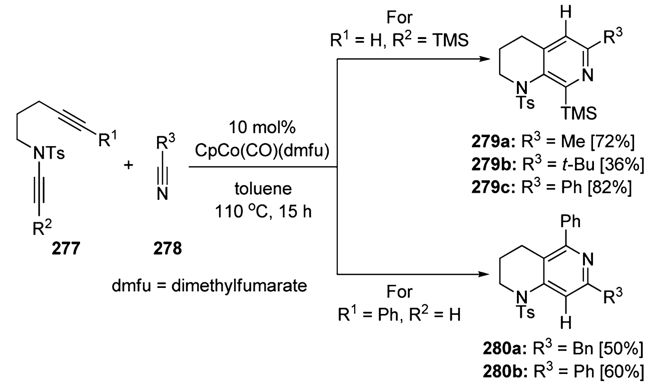
SCHEME 51



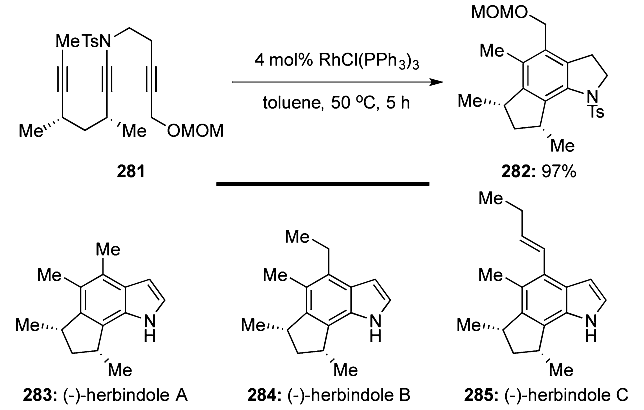
SCHEME 52



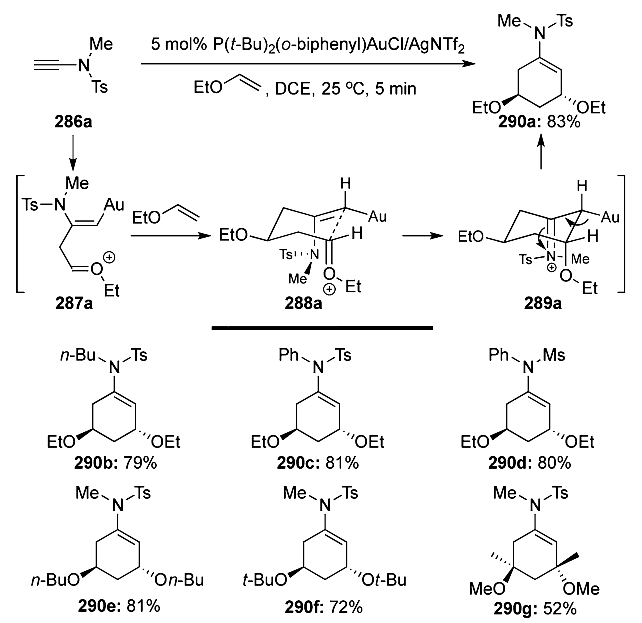
SCHEME 53



SCHEME 54

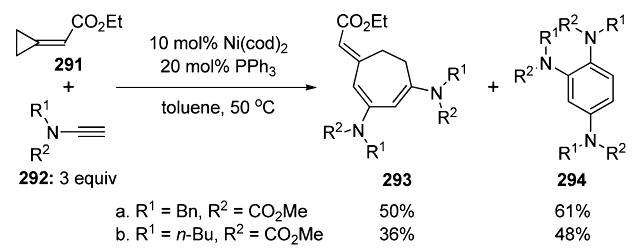


SCHEME 55

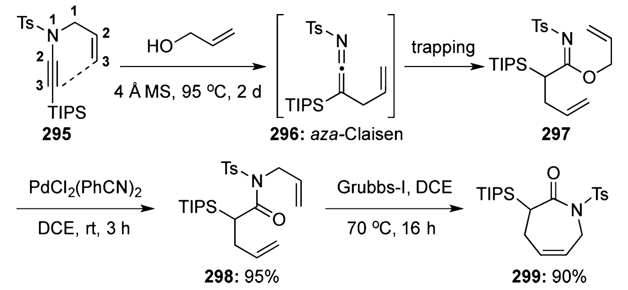


Lee and co-workers[55] independently reported a similar hexadehydro-Diels–Alder cycloaddition of ynamide **243** catalyzed with silver (Scheme 47). What distinguishes this beautiful work from Hoye's is the alkane C–H insertion of the silver complex aryne to form carbon–carbon bonds.

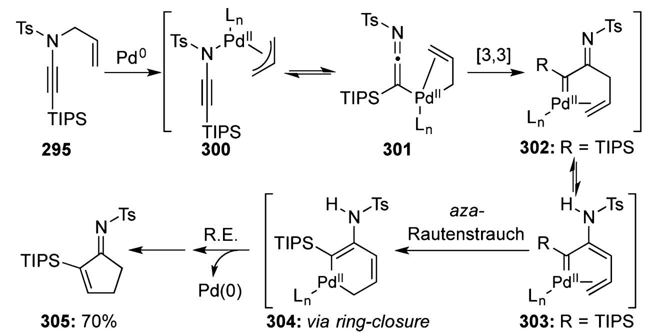
SCHEME 56



SCHEME 57



SCHEME 58

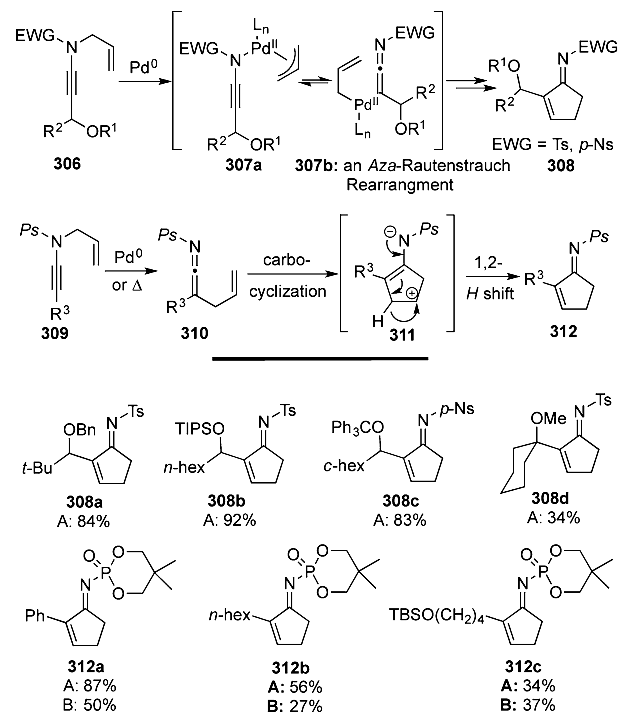


Lee and co-workers[56] subsequently reported a clever use of the Alder-ene process to trap the aryne intermediates derived from hexadehydro-Diels–Alder cycloaddition of ynamide **249** (Scheme 48). The metal catalyst was not essential but increased the reaction's rate.

Danheiser and co-workers[57] developed an ynamide-benzannulation using cyclobutenones **252** to synthesize highly substituted anilides **257** (Scheme 49). This benzannulation proceeds beautifully via four consecutive pericyclic processes, thereby constituting a formal [4 + 2] annulation. With olefin substitutions in R^4 and on the nitrogen atom, these anilides could undergo ring-closing metathesis to generate complex N-heterocycles such as **258**.

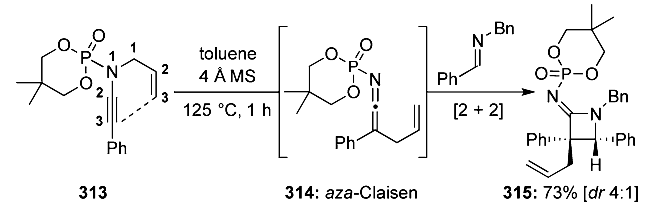
6.6. [2 + 2 + 2]. Witulski and co-workers[58] reported a ruthenium-catalyzed hetero-[2 + 2 + 2] cycloaddition of yne-ynamides **259** with Mander's reagent giving β- and γ-carbolines **260** and **261** (Scheme 50). The regioselectivity could be controlled by the steric hindrance of substitutions to the alkynes and ynamides. A total synthesis of eudistomin U **263** was achieved using regioselective β-carboline synthesis.

SCHEME 59



Method A: 5 mol% $Pd(PPh_3)_4$, toluene, 70 °C; Method B: toluene, 125 °C

SCHEME 60

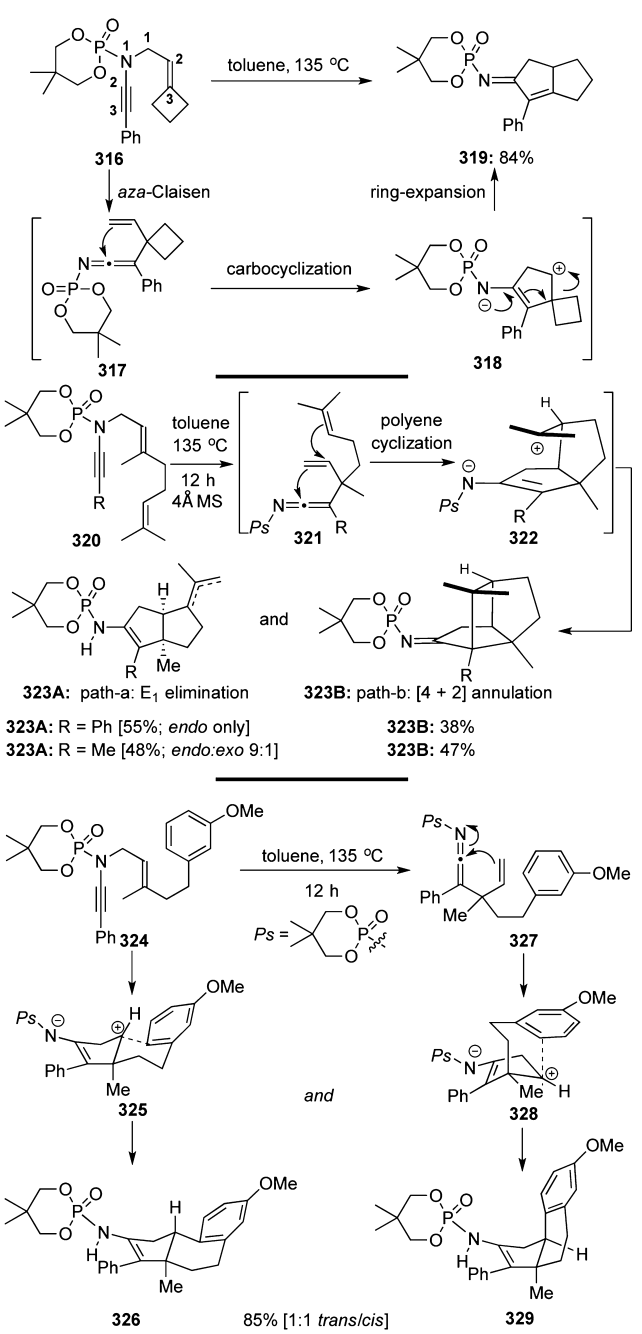


Nissen and Detert[59] subsequently reported the total synthesis of lavendamycin by Ru(II)-catalyzed hetero-[2 + 2 + 2] cycloaddition of ynamide **266** and an electron deficient nitrile to prepare the carboline scaffold (Scheme 51).

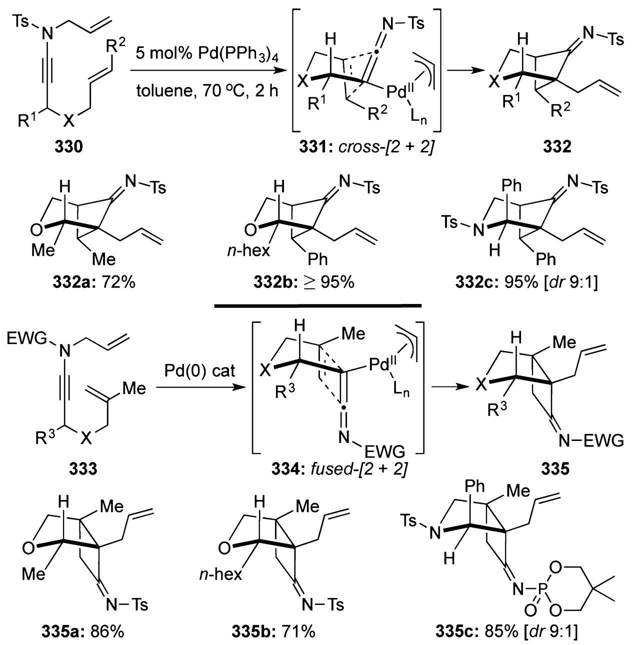
Witulski and co-workers[60] later reported the total syntheses of perlolyrine **275** and isoperlolyrine **276**, featuring this Ru(II)-catalyzed hetero-[2 + 2 + 2] cycloaddition using yne-ynamides **271** and **273** (Scheme 52).

Malacria and co-workers[61] reported a Co(I)-catalyzed regioselective [2 + 2 + 2] cycloaddition between ynamides **277** and nitriles **278** (Scheme 53). Through adjustment of the substituent on the ynamides, regioselectivity of this

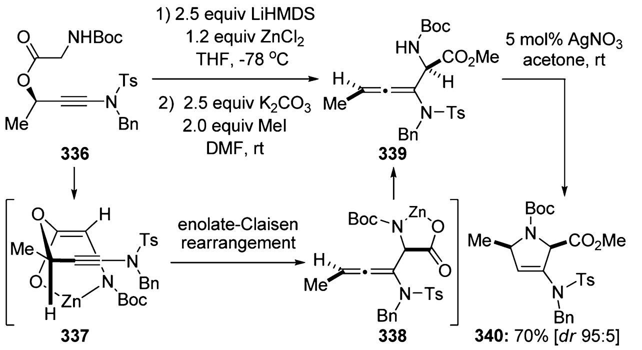
SCHEME 61



SCHEME 62



SCHEME 63



cycloaddition could be tuned to favor either 3-aminopyridines **279** or 4-aminopyridines **280**.

Saito et al[62] reported divergent total syntheses of (−)-herbindoles A−C through intramolecular [2 + 2 + 2] cycloaddition of ynamide **281** catalyzed by Wilkinson's catalyst (Scheme 54). All three herbindoles could be constructed from the common indoline intermediate **282**.

Liu and co-workers[63] reported a Au(I)-catalyzed formal [2 + 2 + 2] cycloaddition of ynamides **286** with 2 equiv of enol ethers (Scheme 55). Under activation by gold, two consecutive nucleophilic attacks by the enol ether followed by Prins-type cyclization furnished cyclic enamides **290** stereoselectively.

6.7. [3 + 2 + 2]. Saito and co-workers[64] unveiled a novel Ni(0)-catalyzed [3 + 2 + 2] cycloaddition of ethyl cyclopropylideneacetate **291** with ynamides **292** (Scheme 56). The desired cycloadducts **293** were obtained in moderate yields with significant amounts of trisubstituted benzenes **294** resulting from trimerizations of the corresponding ynamides.

7. Rearrangements

Hsung and co-workers[65] communicated the synthesis of azapin-2-one **299** via a sequence of *aza*-Claisen rearrangement, Pd(0)-catalyzed Overman rearrangement after trapping of ketenimine **296** with allyl alcohol, and ring-closing metathesis (Scheme 57).

Hsung and co-workers[66] reported a novel synthesis of α,β-unsaturated cyclopentenimine **305** via a Pd-catalyzed *aza*-Rautenstrauch-type cyclization[67] (Scheme 58). It was proposed that the ynamido-π-allyl complex **301** derived from the oxidative addition of TIPS-terminated ynamide **295** underwent a Pd-[3,3] sigmatropic rearrangement giving the α-imino palladium carbenoid **302**, which is related to the key intermediates proposed in the Rautenstrauch cyclization.

Later, Hsung and co-workers[68] discovered that the substrate scope for the Pd-catalyzed carbocyclization was quite broad. A variety of functionalized *N*-allyl-γ-branched ynamides were employed in cyclopentenimine synthesis. With *N*-sulfonyl ynamides **306**, palladium catalysis is required, because facile 1,3-sulfonyl shifts dominate under thermal conditions. However, since no analogous 1,3-phosphoryl shift is operational, *N*-phosphoryl ynamides **309** were used to prepare similar cyclopentenimines under thermal conditions through zwitterionic intermediates **311** that underwent N-promoted H-shifts (Scheme 59).

Hsung and Dekorver[69] described a moderately stereoselective Staudinger-type ketenimine–imine [2 + 2] cycloaddition using *N*-phosphoryl ynamide **313** giving azetidin-2-imine **315** bearing a quaternary carbon center (Scheme 60). The ketenimine intermediate **314** was generated in situ via an *aza*-Claisen reaction.

Hsung and Dekorver[70] showcased a tandem *aza*-Claisen-carbocyclization of *N*-phosphoryl-*N*-allyl-ynamides that included possibilities such as ring-expansion via Meerwein–Wagner rearrangement and polyene-type cyclizations, thereby rapidly building structural complexity leading to fused bi- and tricyclic scaffolds (Scheme 61).

Hsung and co-workers[71] communicated a stereoselective synthesis of bridged or fused bicycloimines through a crossed or fused intramolecular [2 + 2] cycloaddition of ketenimines via palladium-catalyzed *aza*-Claisen rearrangements of *N*-allyl-ynamides **330** and **333** (Scheme 62). Preference of cycloaddition pathways depended upon alkene substitutions.

Meyer and co-workers[72] described an interesting Saucey–Marbet rearrangement of ynamide **336** containing an *N*-Boc-glycinate motif, providing stereoselective access to functionalized allenamide **339**[73,74] (Scheme 63). These de novo allenamides underwent silver catalyzed cyclization affording 3-pyrrolidine derivatives **340** having 2,5-*syn* relative stereochemistry.

8. Conclusion

This Account has highlighted recent advances in ynamide cyclization reactions that are useful in the rapid synthesis of cyclic and polycyclic structural motifs. The transformations presented are significant due to their rapid assembly of structural complexity and inclusion of nitrogen within or in close proximity to the newly formed ring or rings. Thus, ynamides have emerged as powerful synthons for nitrogen-containing heterocycles and nitrogen-substituted rings. We hope this Account will help promote continued interest in the chemistry of ynamides.

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Brant L. Kedrowski obtained a B.S. in chemistry in 1994 and Ph.D. in organic chemistry in 2000 with Professor Wayland Noland at the University of Minnesota. He did postdoctoral work with Professor Clayton Heathcock at the University of California, Berkeley, before his appointment as an assistant professor at the University of Wisconsin Oshkosh in 2002. He was promoted to associate professor in 2008 and to full professor in 2013.

Richard P. Hsung obtained his B.S. in chemistry and mathematics from Calvin College and attended The University of Chicago for his M.S. and Ph.D. degrees in organic chemistry with Professors Jeff Winkler and Bill Wulff, respectively. After postdoctoral stays with Professor Larry Sita in Chicago and Professor Gilbert Stork at Columbia University, he moved to University of Minnesota as an assistant professor in 1997. He was promoted to associate professor in 2002 and to full professor after moving to University of Wisconsin in 2006. He has coauthored over 200 publications and supervised over 150 students and postdoctoral fellows with research interests in developing stereoselective methods using allenamides, ynamides, enamides, and cyclic acetals and applications in natural product syntheses.

FOOTNOTES

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The authors declare no competing financial interest.

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