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Ynamides in Ring Forming Transformations

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Conspectus

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.

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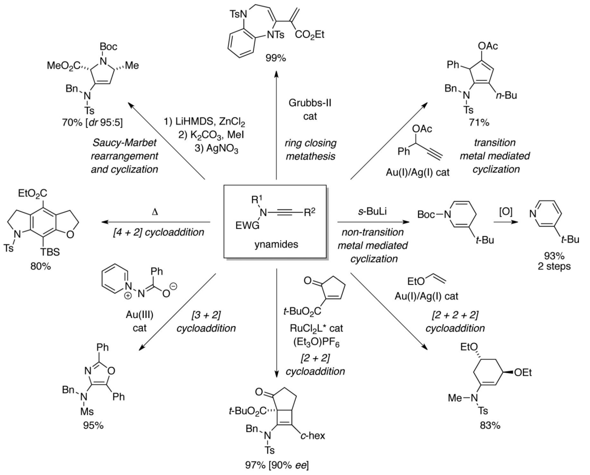

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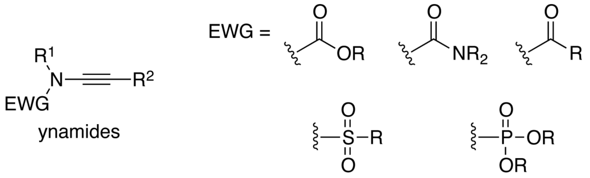
1. Introduction

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 important pharmacophores. These properties have contributed to a continued and dramatic increase in the number of publications in the last 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 analogs 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 and Courillon[7] reported the formation of sixmembered 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 and Perez-Luna[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 and Mori[9] reported further development of their ring-closing metathesis of ene-ynamides, featuring syntheses of 7-membered heterocycles **13**, **15** and 8-membered heterocycles **17** using 2nd-generation Grubbs catalyst (Scheme 3).

4. Non-Transition Metal Mediated Cyclizations

Popik[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 in ring size.

Evano[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[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.

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

Later, Cao[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, NBS, and NCS. This strategy was also used to construct 1-amidonaphthalenes **50** and 1-amidobenzopyrans **52** from ynamides (Scheme 8).

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

Hsung[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 and Hayashi[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, as the carbonyl oxygen might coordinate to the metal during the transformation.

Tang[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).

5.2. Palladium

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

Anderson[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[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 $NaBH_3CN$, 2-indolones **85** were obtained.

5.4. Copper

Chen[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[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).

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[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).

5.5. Silver

Malacria, Fentsterbank, and Aubert[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

Hashimi[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.

Skrydstrup[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[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[30] independently reported a similar gold-catalyzed oxidative ring-expansion (details not shown here).

Liu[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-ketocarbenoid **129**.

Li[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*-allylynamides **132** using pyridine *N*-oxide as the external oxidant (Scheme 25).

Sueda[33] reported both Ag(I)- and/or 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[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[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[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[37] reported the first examples of stereoselective intramolecular cyclopropanations via a de novo class of push-pull carbenes derived from DMDO-epoxidations of chiral ynamides

162 (Scheme 30). This tandem epoxidation-cyclopropanation afforded a series of structurally unique amido-cyclopropanes **165**.

Buono[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 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[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).

Mezzetti[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).

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).

Lam[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).

Takasu and Takemoto[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_2NH 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.

Mikami[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[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[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[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).

Gagosz and Skrydstrup[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[50] reported the synthesis of *δ*-carbolines **220** from 2-iodoanilines **216** and *N*-tosyl-enynamides **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.

Peng[51] reported a AgOTf/Pd$(OAc)_2$ co-catalyzed [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.

Batey[52] reported a series of 1,3-dipole cycloadditions using ynehydrazides **229** that were first synthesized in these authors' lab. This exercise demonstrates the synthetic potential of these novel ynamides (Scheme 44).

6.4. [4 + 1]

Liu[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[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 zwitter ionic intermediate **241**.

Lee[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.

Lee[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[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[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.

Nissen[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 Detert[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, Aubert and Gandon[61] reported a Co(I)-catalyzed regioselective [2 + 2 + 2]-cycloaddition between ynamides **277** and nitriles **278** (Scheme 53). Through adjusting the substituent on the ynamides, regioselectivity of this cycloaddition could be tuned to favor either 3-aminopyridines **279** or 4-aminopyridines **280**.

Saito and Sato[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[63] reported a Au(I)-catalyzed formal [2 + 2 + 2] cycloaddition of ynamides **286** with two equivalents 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[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[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[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 DeKorver[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, as 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 zwitter ionic intermediates **311** that underwent *N*-promoted *H*-shifts (Scheme 59).

DeKorver and Hsung[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.

DeKorver and Hsung[70] showcased a tandem *aza*-Claisencarbocyclization 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[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*-allylynamides **330** and **333** (Scheme 62). Preference of cycloaddition pathways depended upon alkene substitutions.

Meyer and Cossy[72] described an interesting Saucey-Marbet rearrangement of ynamide **336** containing an *N*-Bocglycinate 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 manuscript 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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Biographies

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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, respectively, with Professors Jeff Winkler and Bill Wulff. 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.

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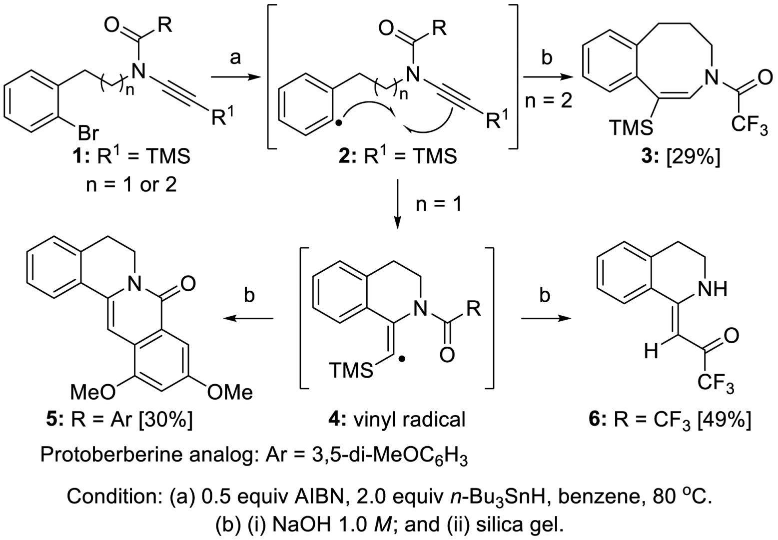
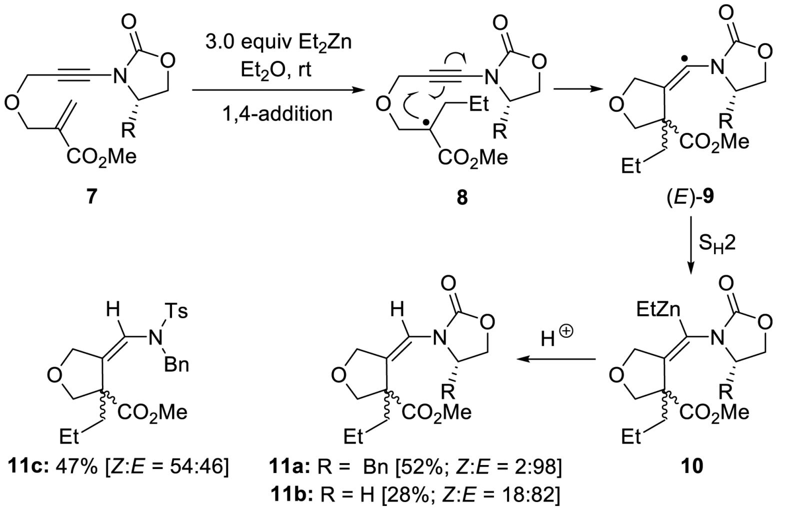
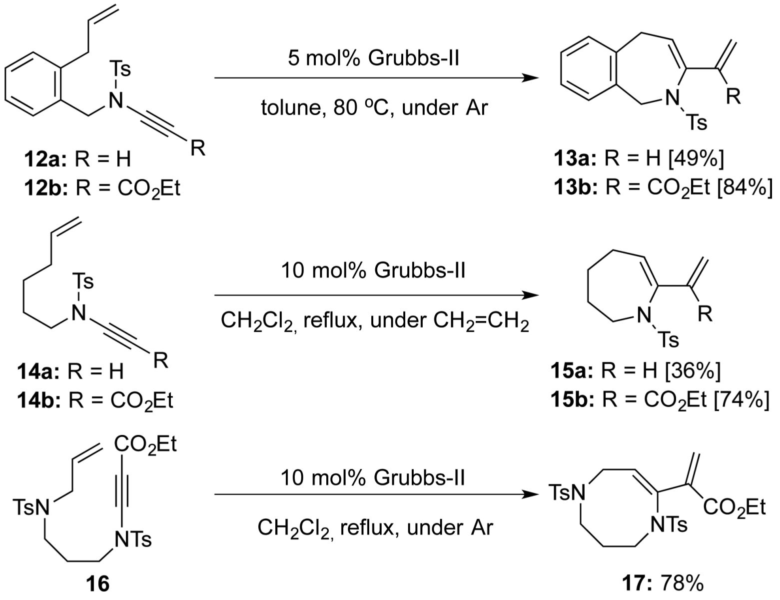

a
b
n = 2
n = 1
b
b
1: R1 = TMS
n = 1 or 2
2: R1 = TMS
3: [29%]
4: vinyl radical
5: R = Ar [30%]
6: R = CF3 [49%]
Protoberberine analog: Ar = 3,5-di-MeOC6H3
Condition: (a) 0.5 equiv AIBN, 2.0 equiv n-Bu3SnH, benzene, 80 °C.
(b) (i) NaOH 1.0 M; and (ii) silica gel.

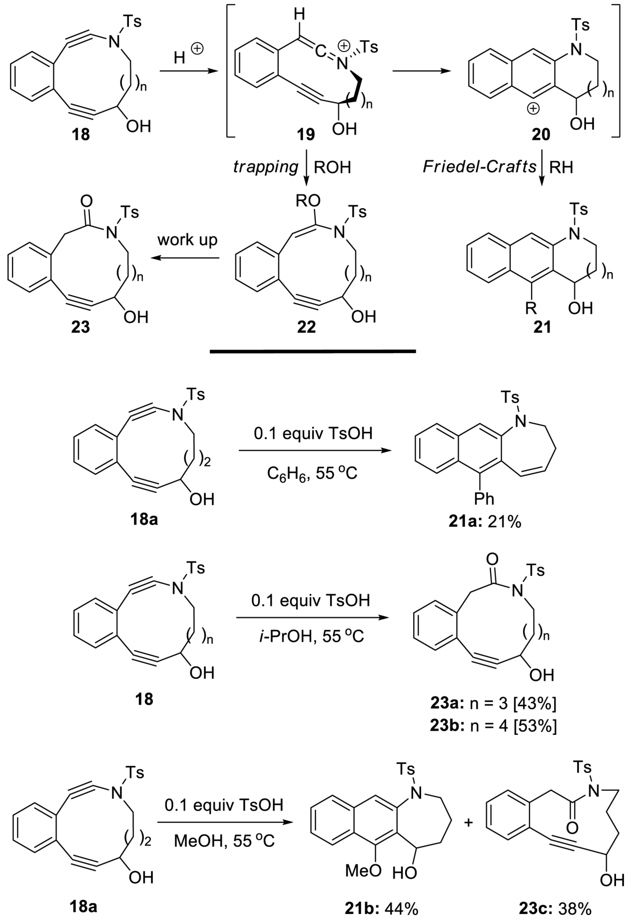
Scheme 1.


3.0 equiv Et_2Zn
Et_2O, rt
1,4-addition
S_H2
$H^{\oplus}$
7
8
(E)-9
10
EtZn
Ts
Bn
Et
R
CO_2Me
11c: 47% [Z:E = 54:46]
11a: R = Bn [52%; Z:E = 2:98]
11b: R = H [28%; Z:E = 18:82]

Scheme 2.

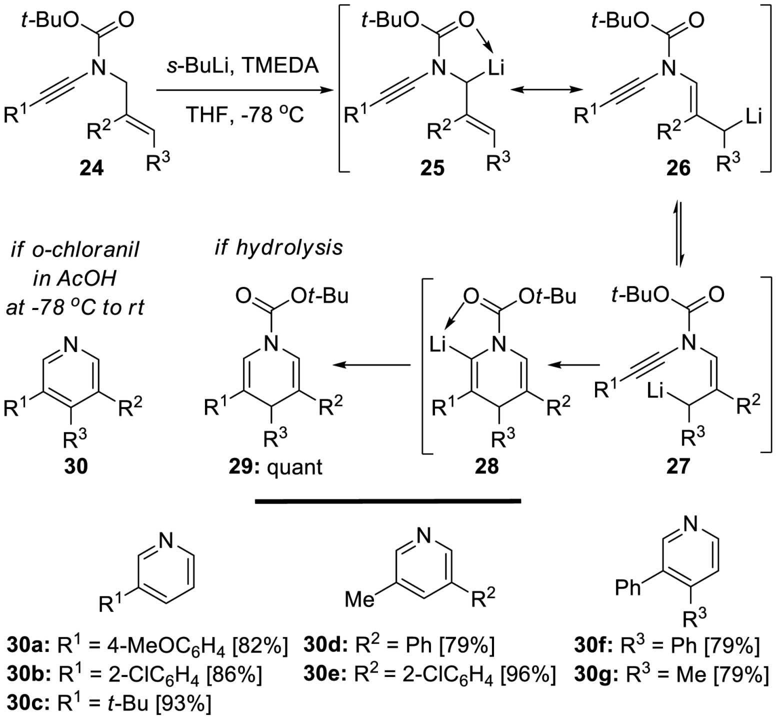

5 mol% Grubbs-II
tolune, 80 ºC, under Ar
12a: R = H
12b: R = CO2Et
13a: R = H [49%]
13b: R = CO2Et [84%]
10 mol% Grubbs-II
CH2Cl2, reflux, under CH2=CH2
14a: R = H
14b: R = CO2Et
15a: R = H [36%]
15b: R = CO2Et [74%]
10 mol% Grubbs-II
CH2Cl2, reflux, under Ar
16
17: 78%
Ts
N
R
CO2Et
TsN
NTs

Scheme 3.

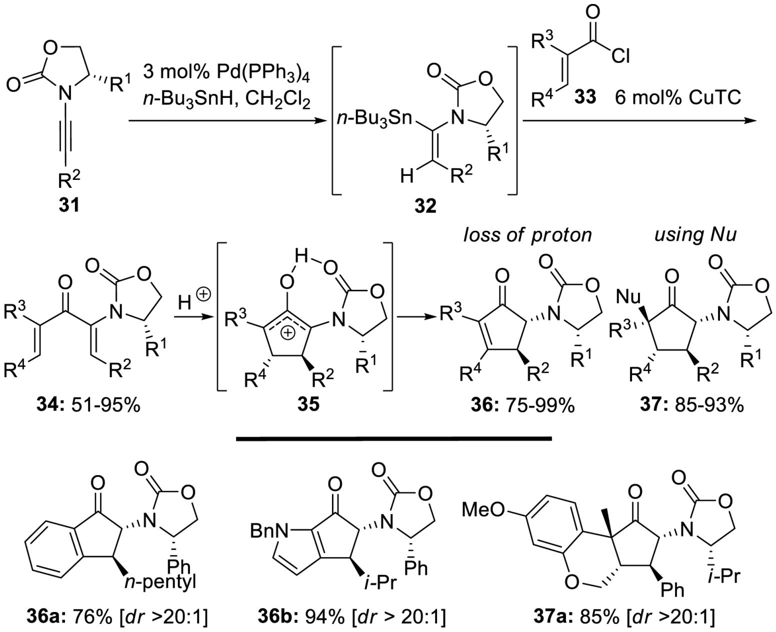


H ⊕
trapping ROH
Friedel-Crafts RH
work up
18
19
20
21
22
23
0.1 equiv TsOH
C6H6, 55 °C
18a
21a: 21%
0.1 equiv TsOH
i-PrOH, 55 °C
23a: n = 3 [43%]
23b: n = 4 [53%]
0.1 equiv TsOH
MeOH, 55 °C
21b: 44%
23c: 38%

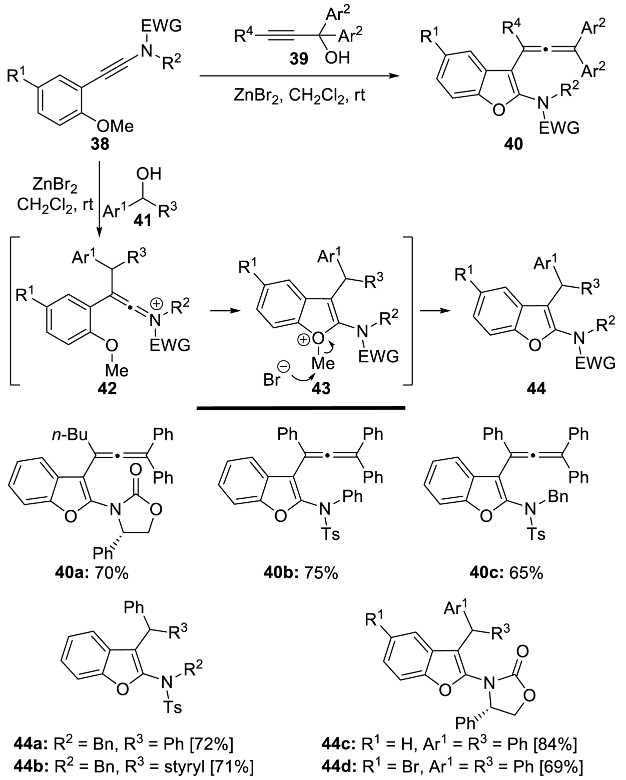
Scheme 4.


t-BuO
O
N
R1
R2
R3
24
s-BuLi, TMEDA
THF, -78 °C
Li
25
26
if o-chloranil
in AcOH
at -78 °C to rt
if hydrolysis
Ot-Bu
30
29: quant
28
27
30a: R1 = 4-MeOC6H4 [82%]
30b: R1 = 2-ClC6H4 [86%]
30c: R1 = t-Bu [93%]
Me
30d: R2 = Ph [79%]
30e: R2 = 2-ClC6H4 [96%]
Ph
30f: R3 = Ph [79%]
30g: R3 = Me [79%]

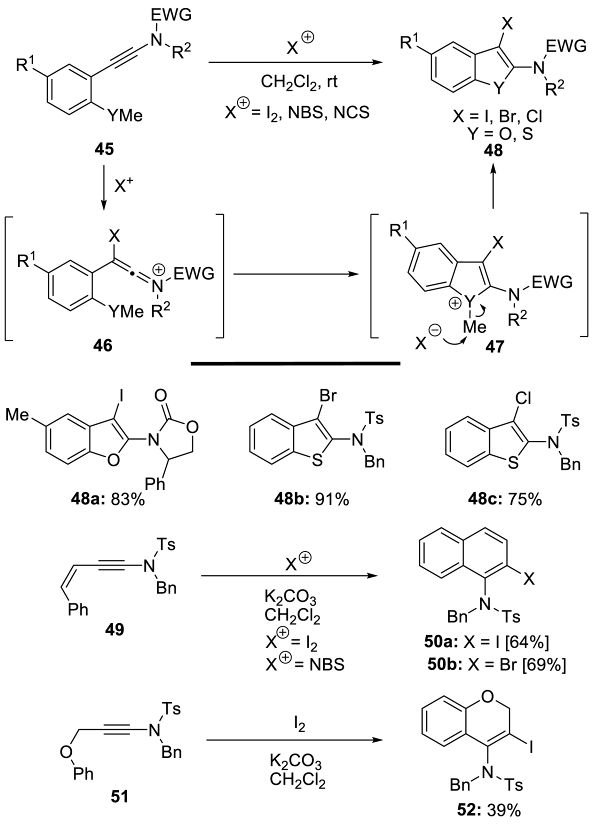
Scheme 5.


3 mol% Pd(PPh3)4
n-Bu3SnH, CH2Cl2
33
6 mol% CuTC
31
32
H⊕
loss of proton
using Nu
34: 51-95%
35
36: 75-99%
37: 85-93%
36a: 76% [dr >20:1]
36b: 94% [dr > 20:1]
37a: 85% [dr >20:1]

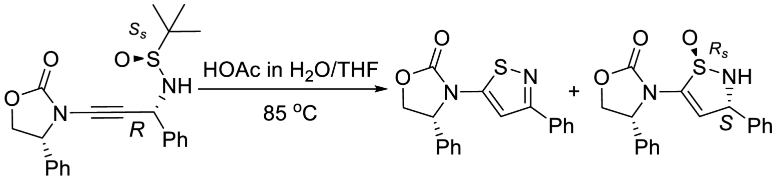
Scheme 6.


39
ZnBr2, CH2Cl2, rt
38
40
ZnBr2
CH2Cl2, rt
41
42
43
44
40a: 70%
40b: 75%
40c: 65%
44a: R2 = Bn, R3 = Ph [72%]
44b: R2 = Bn, R3 = styryl [71%]
44c: R1 = H, Ar1 = R3 = Ph [84%]
44d: R1 = Br, Ar1 = R3 = Ph [69%]

Scheme 7.


45
X⊕
CH2Cl2, rt
X⊕ = I2, NBS, NCS
X = I, Br, Cl
Y = O, S
48
X+
46
47
48a: 83%
48b: 91%
48c: 75%
49
X⊕
K2CO3
CH2Cl2
X⊕ = I2
X⊕ = NBS
50a: X = I [64%]
50b: X = Br [69%]
51
I2
K2CO3
CH2Cl2
52: 39%

Scheme 8.

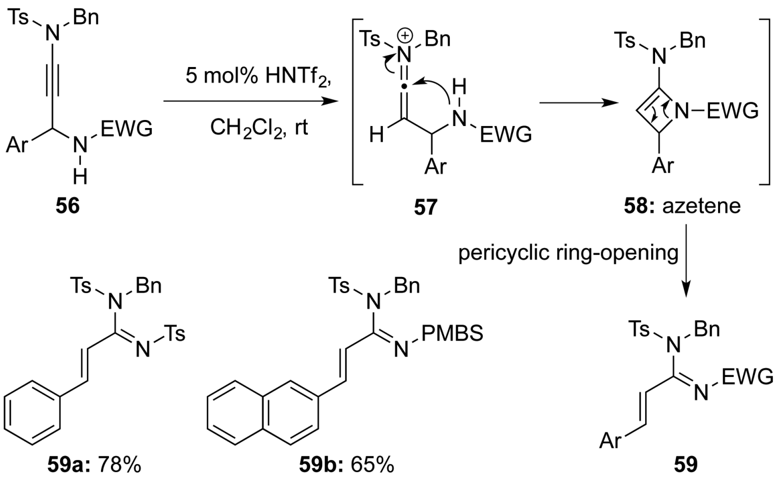


53

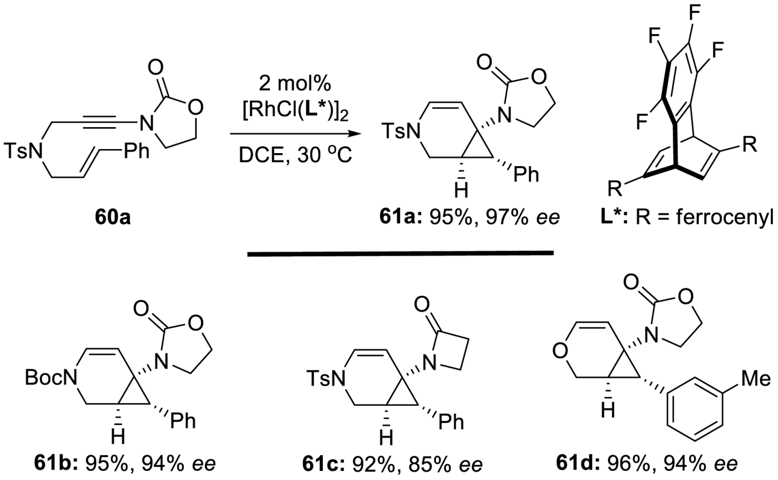
54: 25%

55: 31%

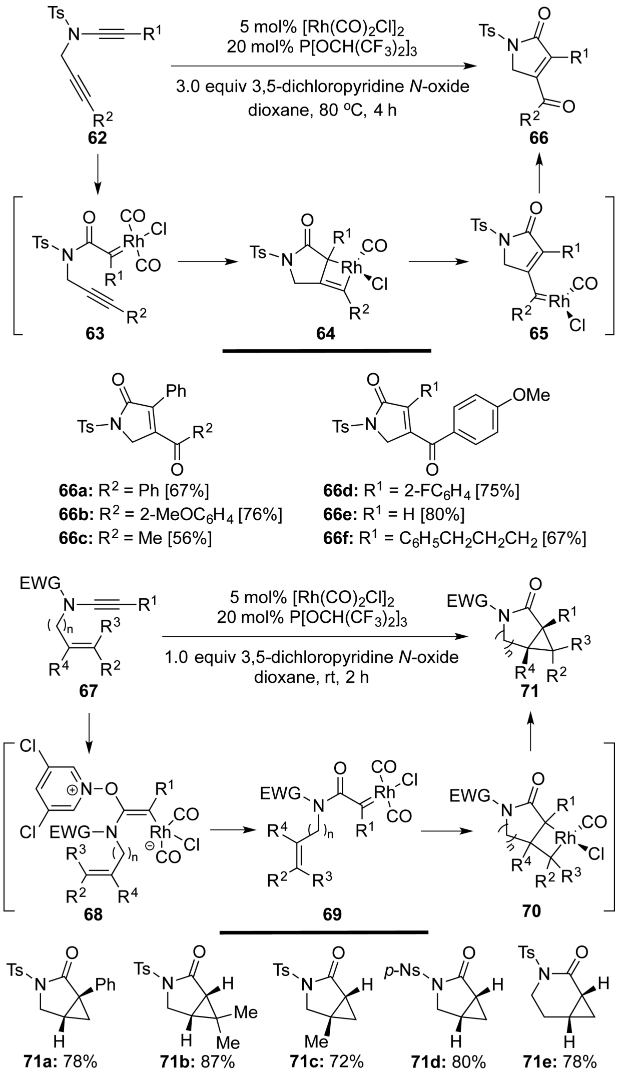
Scheme 9.


Ts
N
Bn
Ar
N
EWG
H
56
5 mol% HNTf2,
CH2Cl2, rt
57
58: azetene
pericyclic ring-opening
59
59a: 78%
59b: 65%
PMBS

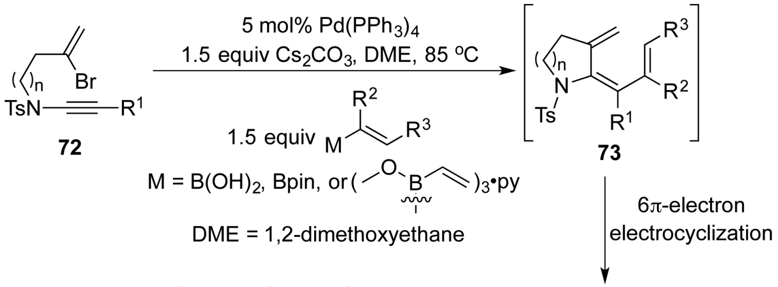
Scheme 10.


2 mol%
[RhCl(**L***)]$_2$
DCE, 30 °C
TsN
Ph
60a
61a: 95%, 97% *ee*
L*: R = ferrocenyl
F
R
BocN
61b: 95%, 94% *ee*
61c: 92%, 85% *ee*
Me
61d: 96%, 94% *ee*

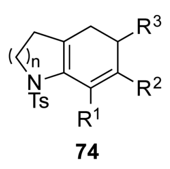
Scheme 11.


5 mol% [Rh(CO)2Cl]2
20 mol% P[OCH(CF3)2]3
3.0 equiv 3,5-dichloropyridine N-oxide
dioxane, 80 °C, 4 h
62
66
63
64
65
66a: R2 = Ph [67%]
66b: R2 = 2-MeOC6H4 [76%]
66c: R2 = Me [56%]
66d: R1 = 2-FC6H4 [75%]
66e: R1 = H [80%]
66f: R1 = C6H5CH2CH2CH2 [67%]
5 mol% [Rh(CO)2Cl]2
20 mol% P[OCH(CF3)2]3
1.0 equiv 3,5-dichloropyridine N-oxide
dioxane, rt, 2 h
67
71
68
69
70
71a: 78%
71b: 87%
71c: 72%
71d: 80%
71e: 78%

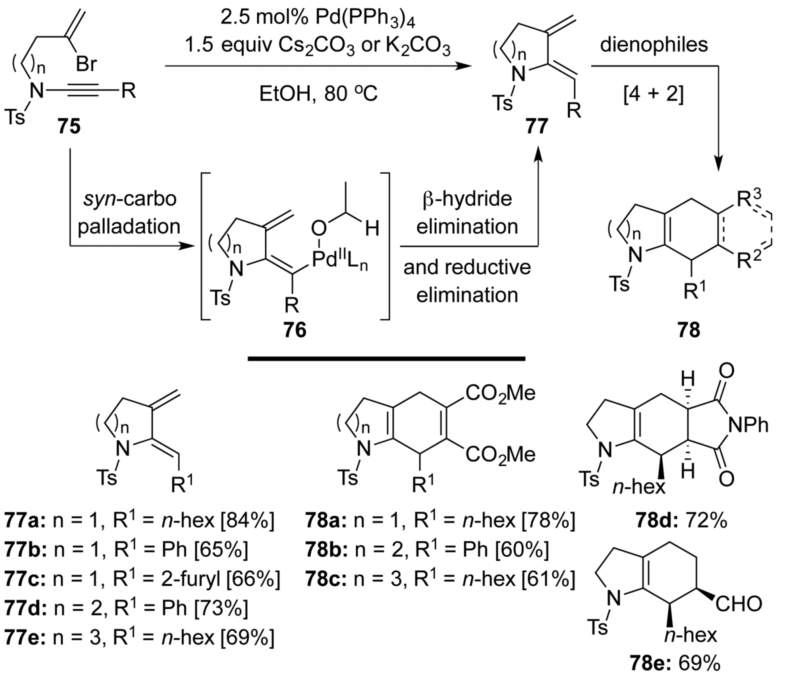
Scheme 12.



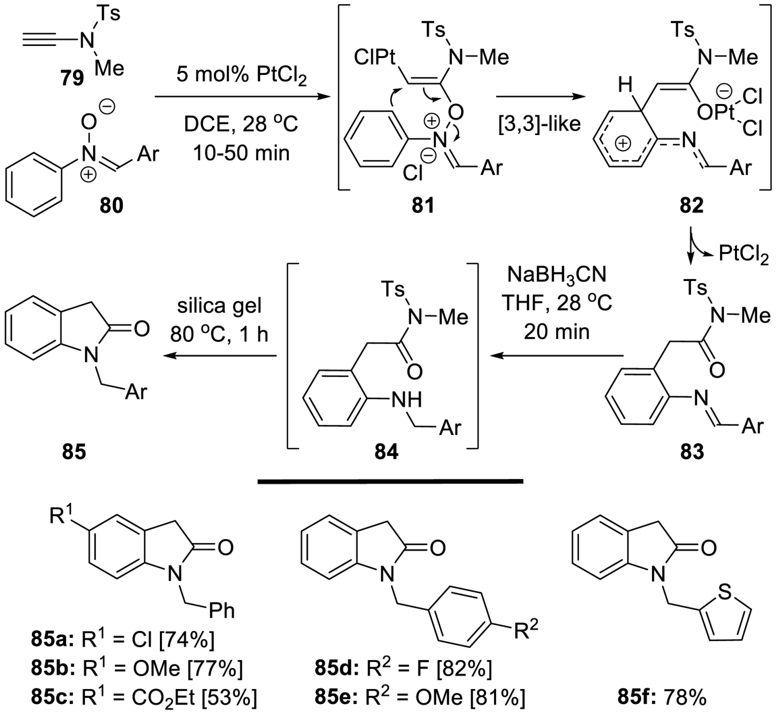
74a: n = 1, R^1 = Ph, R^2 = H, R^3 = Ph [69%]
74b: n = 1, R^1 = *n*-hex, R^2 = H, R^3 = Ph [79%]
74c: n = 3, R^1 = *n*-hex, R^2 = H, R^3 = Ph [74%]
74d: n = 1, R^1 = *n*-hex, R^2 = H, R^3 = *n*-Pr [74%]
74e: n = 1, R^1 = *n*-hex, R^2 = H, R^3 = *c*-hex [70%]
74f: n = 1, R^1 = *n*-hex, R^2 = Et, R^3 = Et [63%]



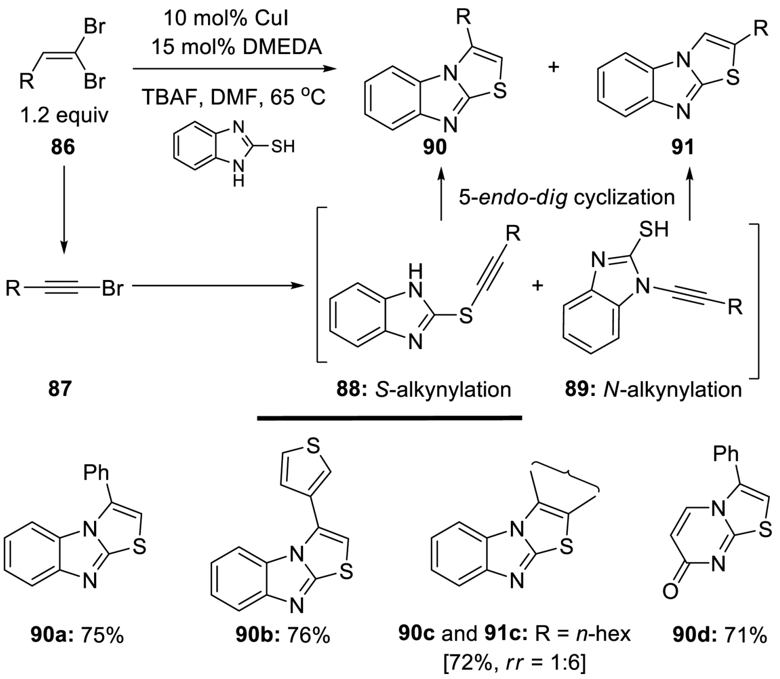
Scheme 13.


2.5 mol% Pd(PPh3)4
1.5 equiv Cs2CO3 or K2CO3
EtOH, 80 ºC
75
77
dienophiles
[4 + 2]
syn-carbo palladation
76
β-hydride elimination
and reductive elimination
78
77a: n = 1, R1 = n-hex [84%]
77b: n = 1, R1 = Ph [65%]
77c: n = 1, R1 = 2-furyl [66%]
77d: n = 2, R1 = Ph [73%]
77e: n = 3, R1 = n-hex [69%]
78a: n = 1, R1 = n-hex [78%]
78b: n = 2, R1 = Ph [60%]
78c: n = 3, R1 = n-hex [61%]
78d: 72%
78e: 69%

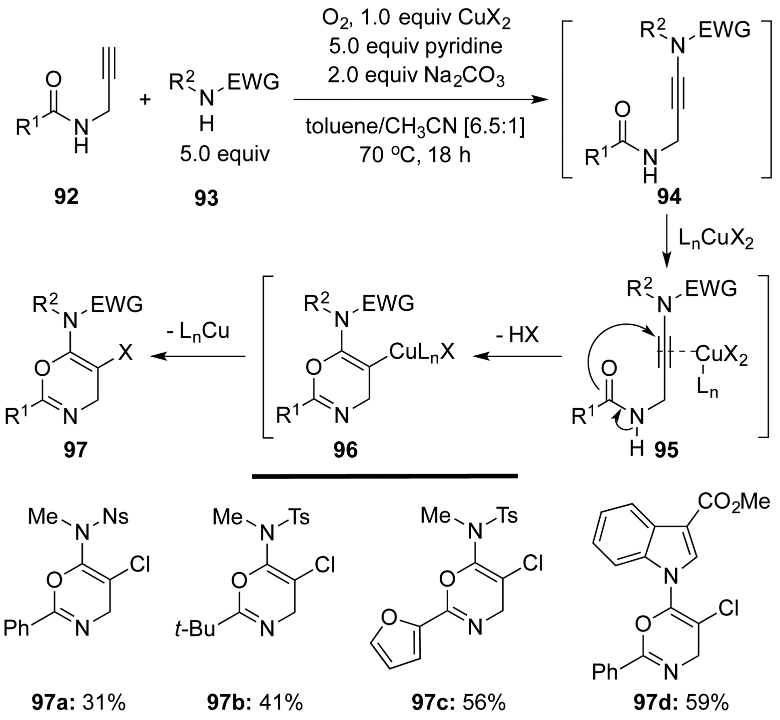
Scheme 14.


Ts
N
Me
79
O
N
Ar
80
5 mol% PtCl$_2$
DCE, 28 °C
10-50 min
ClPt
Ts
N−Me
O
N
Cl
Ar
81
[3,3]-like
H
Ts
N−Me
OPt
Cl
Cl
N
Ar
82
PtCl$_2$
Ts
N−Me
O
N
Ar
83
NaBH$_3$CN
THF, 28 °C
20 min
Ts
N−Me
O
NH
Ar
84
silica gel
80 °C, 1 h
O
N
Ar
85
R^1
O
N
Ph
85a: R^1 = Cl [74%]
85b: R^1 = OMe [77%]
85c: R^1 = CO$_2$Et [53%]
O
N
R^2
85d: R^2 = F [82%]
85e: R^2 = OMe [81%]
O
N
S
85f: 78%

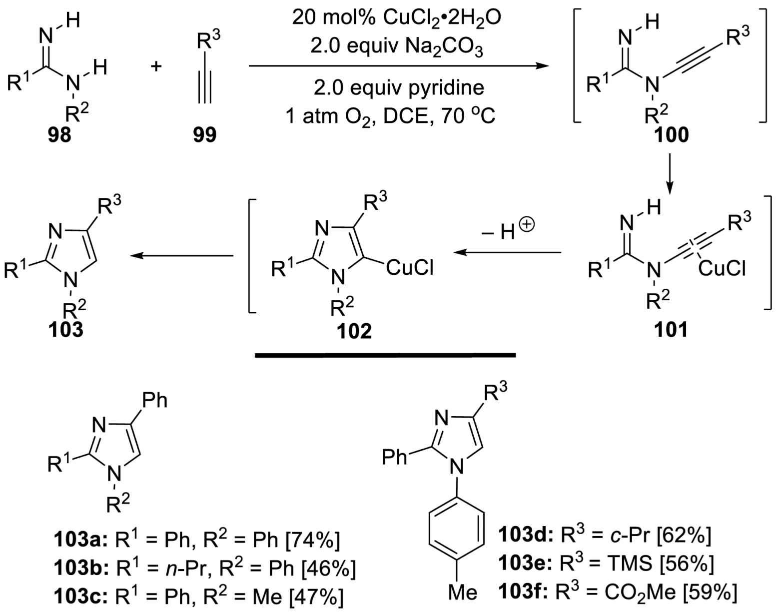
Scheme 15.


10 mol% CuI
15 mol% DMEDA
TBAF, DMF, 65 °C
1.2 equiv
86
87
90
91
5-*endo*-*dig* cyclization
88: *S*-alkynylation
89: *N*-alkynylation
90a: 75%
90b: 76%
90c and **91c:** R = *n*-hex
[72%, *rr* = 1:6]
90d: 71%

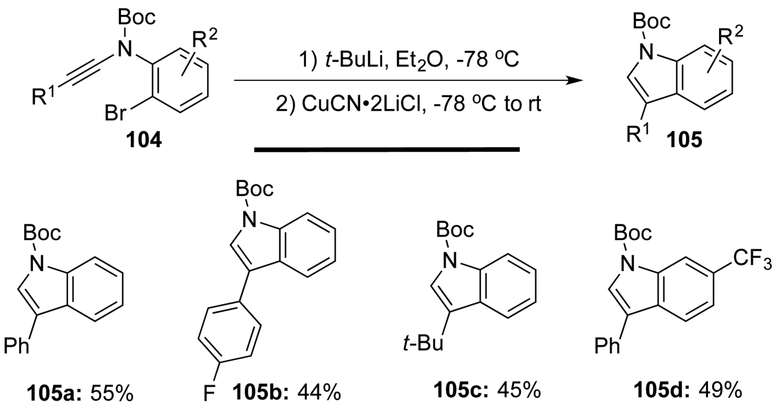
Scheme 16.


O
R^1
N
H
+
R^2 N EWG
H
5.0 equiv
92
93
O$_2$, 1.0 equiv CuX$_2$
5.0 equiv pyridine
2.0 equiv Na$_2$CO$_3$
toluene/CH$_3$CN [6.5:1]
70 ºC, 18 h
R^2 N EWG
O
R^1
N
H
94
L$_n$CuX$_2$
R^2 N EWG
O
R^1
N
H
CuX$_2$
L$_n$
95
- HX
R^2 N EWG
CuL$_n$X
O
R^1
N
96
- L$_n$Cu
R^2 N EWG
X
O
R^1
N
97
Me N Ns
Cl
O
Ph
N
Me N Ts
Cl
O
t-Bu
N
Me N Ts
Cl
O
O
N
CO$_2$Me
N
Cl
O
Ph
N
97a: 31%
97b: 41%
97c: 56%
97d: 59%

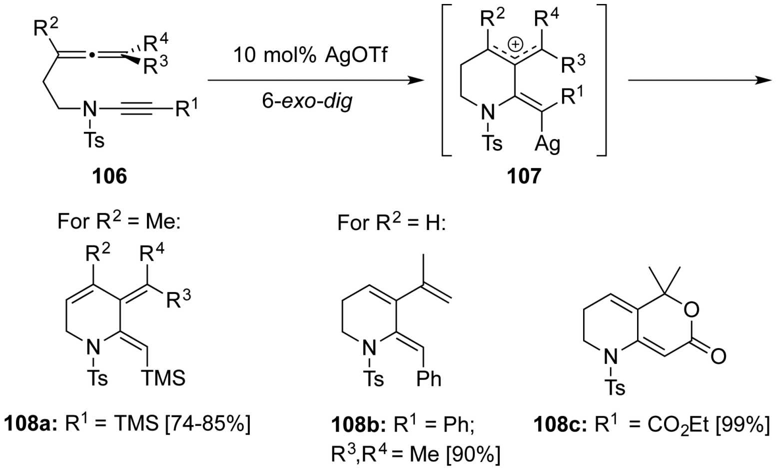
Scheme 17.


20 mol% CuCl2•2H2O
2.0 equiv Na2CO3
2.0 equiv pyridine
1 atm O2, DCE, 70 °C
98
99
100
101
102
103
– H⊕
CuCl
103a: R1 = Ph, R2 = Ph [74%]
103b: R1 = n-Pr, R2 = Ph [46%]
103c: R1 = Ph, R2 = Me [47%]
103d: R3 = c-Pr [62%]
103e: R3 = TMS [56%]
103f: R3 = CO2Me [59%]

Scheme 18.

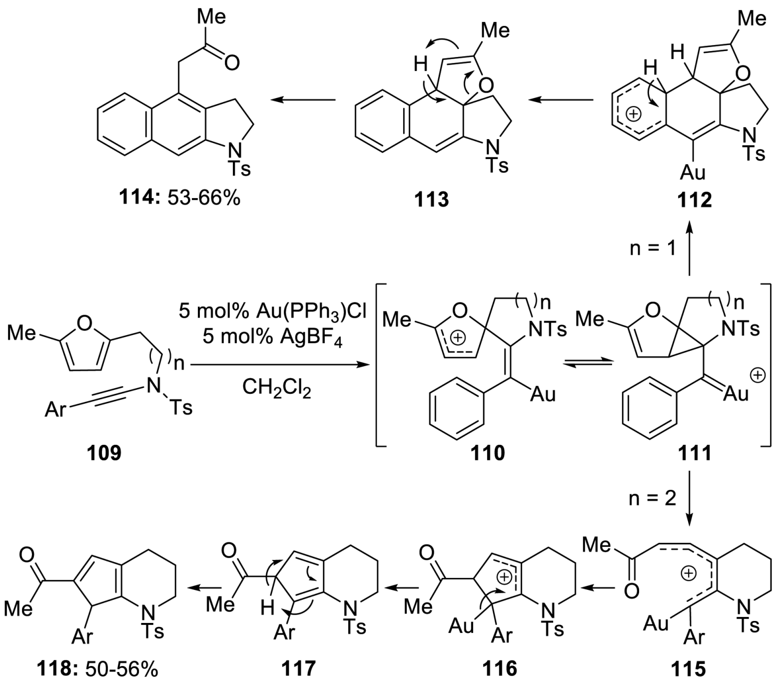

Boc
N
R2
R1
Br
104
1) t-BuLi, Et2O, -78 ºC
2) CuCN•2LiCl, -78 ºC to rt
Boc
N
R2
R1
105
Boc
N
Ph
105a: 55%
Boc
N
F
105b: 44%
Boc
N
t-Bu
105c: 45%
Boc
N
CF3
Ph
105d: 49%

Scheme 19.



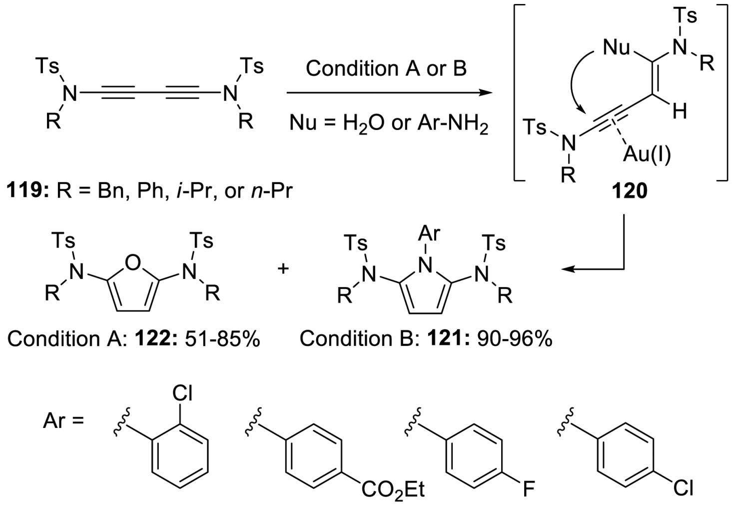
10 mol% AgOTf
6-*exo-dig*
106
107
For R^2 = Me:
For R^2 = H:
108a: R^1 = TMS [74-85%]
108b: R^1 = Ph; R^3,R^4 = Me [90%]
108c: R^1 = CO$_2$Et [99%]

Scheme 20.



Ar = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, or thiophen-3-yl

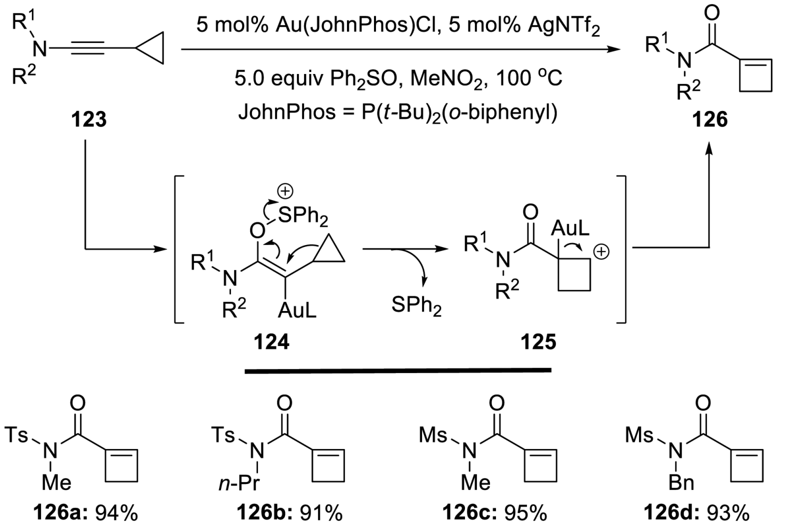
Scheme 21.



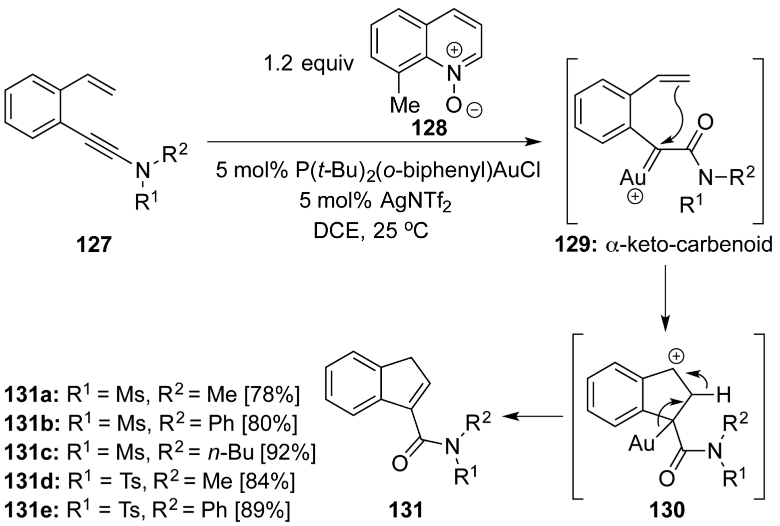
Condition A: 2 mol% $(PPh_3)AuNTf_2$, 1.40 equiv H_2O, THF, 60 °C, 45 min

Condition B: 1 mol% $(PPh_3)AuNTf_2$, 1.05 equiv Ar-NH_2, CH_2Cl_2, 30 °C, 30 min

Scheme 22.

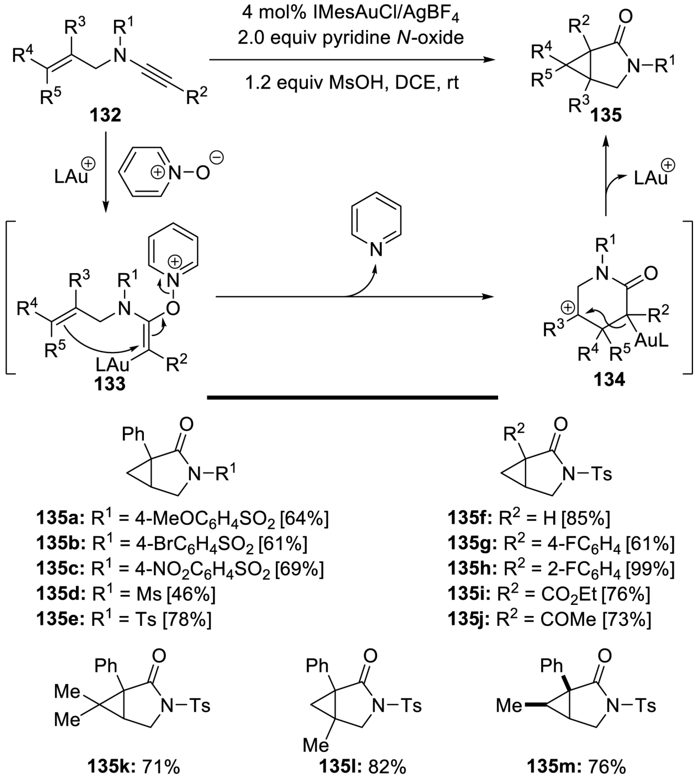

5 mol% Au(JohnPhos)Cl, 5 mol% AgNTf$_2$
5.0 equiv Ph$_2$SO, MeNO$_2$, 100 °C
JohnPhos = P(*t*-Bu)$_2$(*o*-biphenyl)
123
126
124
125
SPh$_2$
AuL
126a: 94%
126b: 91%
126c: 95%
126d: 93%

Scheme 23.

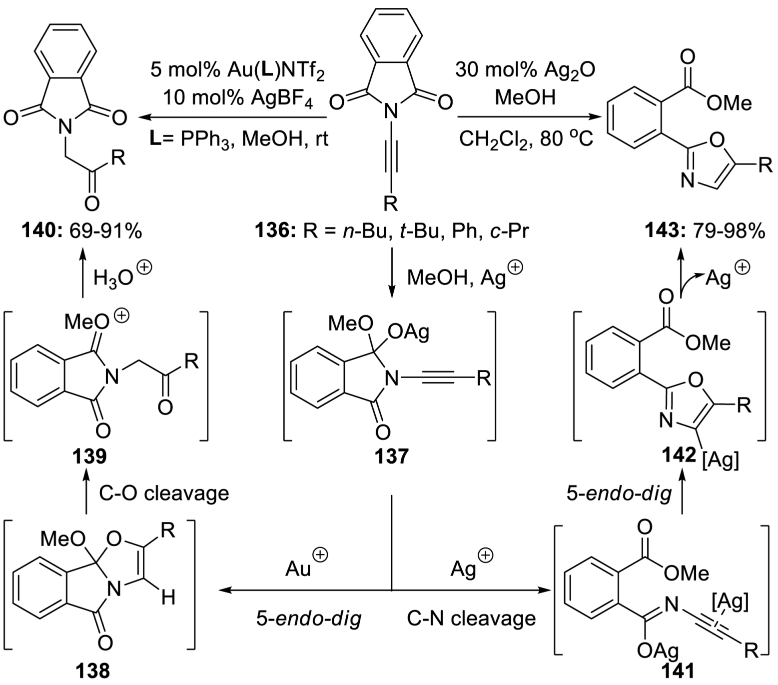


131a: R^1 = Ms, R^2 = Me [78%]
131b: R^1 = Ms, R^2 = Ph [80%]
131c: R^1 = Ms, R^2 = *n*-Bu [92%]
131d: R^1 = Ts, R^2 = Me [84%]
131e: R^1 = Ts, R^2 = Ph [89%]

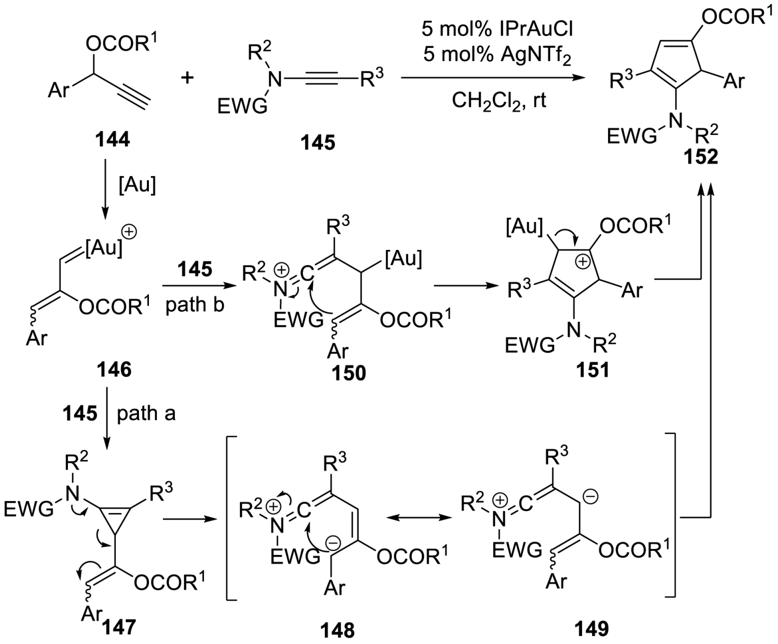
Scheme 24.


4 mol% IMesAuCl/AgBF$_4$
2.0 equiv pyridine *N*-oxide
1.2 equiv MsOH, DCE, rt
132
135
133
134
LAu$^\oplus$
135a: R^1 = 4-MeOC$_6$H$_4$SO$_2$ [64%]
135b: R^1 = 4-BrC$_6$H$_4$SO$_2$ [61%]
135c: R^1 = 4-NO$_2$C$_6$H$_4$SO$_2$ [69%]
135d: R^1 = Ms [46%]
135e: R^1 = Ts [78%]
135f: R^2 = H [85%]
135g: R^2 = 4-FC$_6$H$_4$ [61%]
135h: R^2 = 2-FC$_6$H$_4$ [99%]
135i: R^2 = CO$_2$Et [76%]
135j: R^2 = COMe [73%]
135k: 71%
135l: 82%
135m: 76%

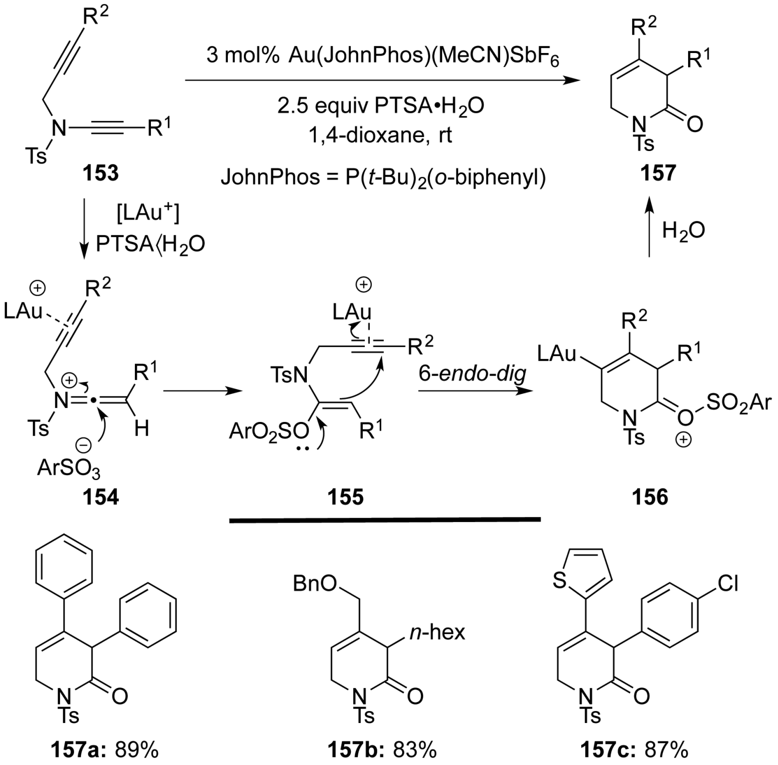
Scheme 25.


5 mol% Au(L)NTf2
10 mol% AgBF4
L= PPh3, MeOH, rt
30 mol% Ag2O
MeOH
CH2Cl2, 80 °C
140: 69-91%
136: R = n-Bu, t-Bu, Ph, c-Pr
143: 79-98%
H3O⊕
MeOH, Ag⊕
Ag⊕
139
137
142
C-O cleavage
5-endo-dig
Au⊕
Ag⊕
5-endo-dig
C-N cleavage
138
141

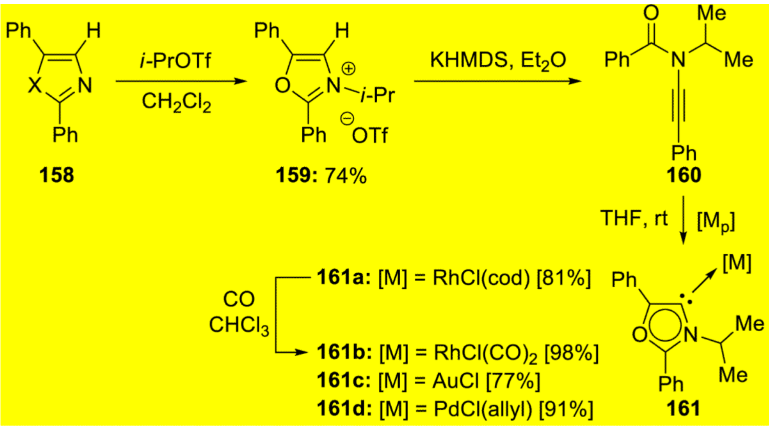
Scheme 26.


5 mol% IPrAuCl
5 mol% AgNTf2
CH2Cl2, rt
144
145
152
[Au]
146
145
path b
150
151
145
path a
147
148
149

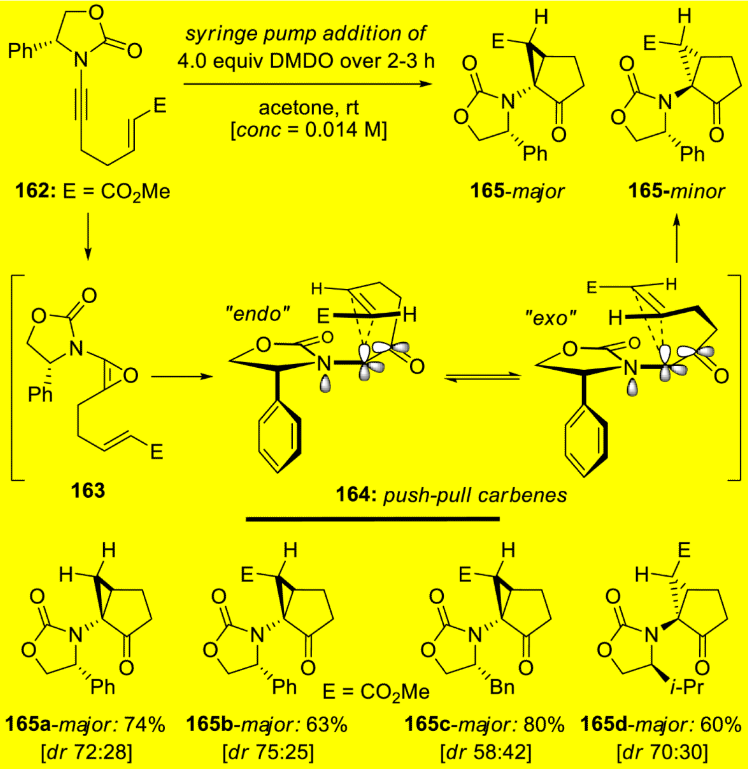
Scheme 27.


3 mol% Au(JohnPhos)(MeCN)SbF6
2.5 equiv PTSA•H2O
1,4-dioxane, rt
JohnPhos = P(t-Bu)2(o-biphenyl)
153
157
[LAu+]
PTSA⟨H2O
H2O
6-endo-dig
154
155
156
157a: 89%
157b: 83%
157c: 87%

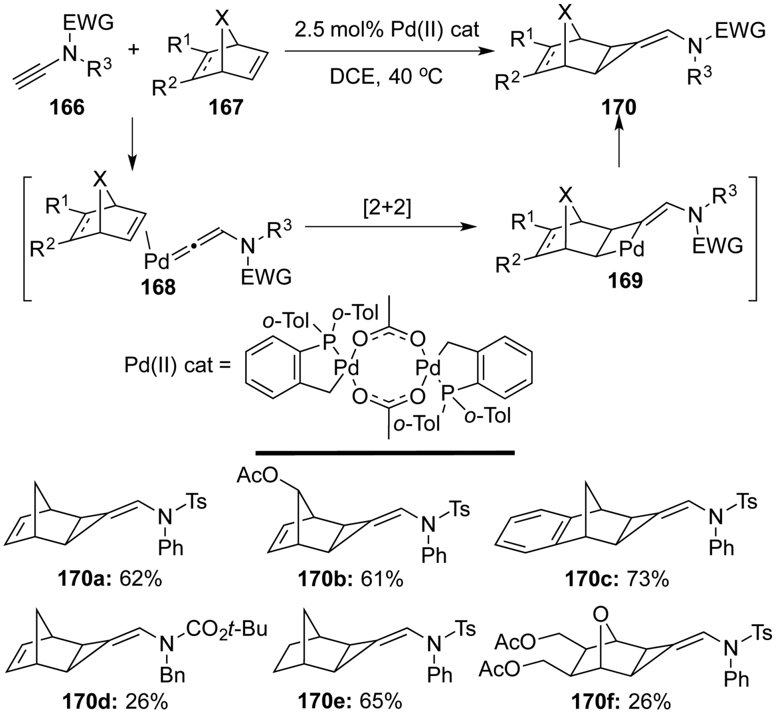
Scheme 28.


Ph
H
X
N
Ph
158
i-PrOTf
CH2Cl2
O
N
i-Pr
OTf
159: 74%
KHMDS, Et2O
Me
Me
160
THF, rt
[Mp]
CO
CHCl3
161a: [M] = RhCl(cod) [81%]
161b: [M] = RhCl(CO)2 [98%]
161c: [M] = AuCl [77%]
161d: [M] = PdCl(allyl) [91%]
[M]
161

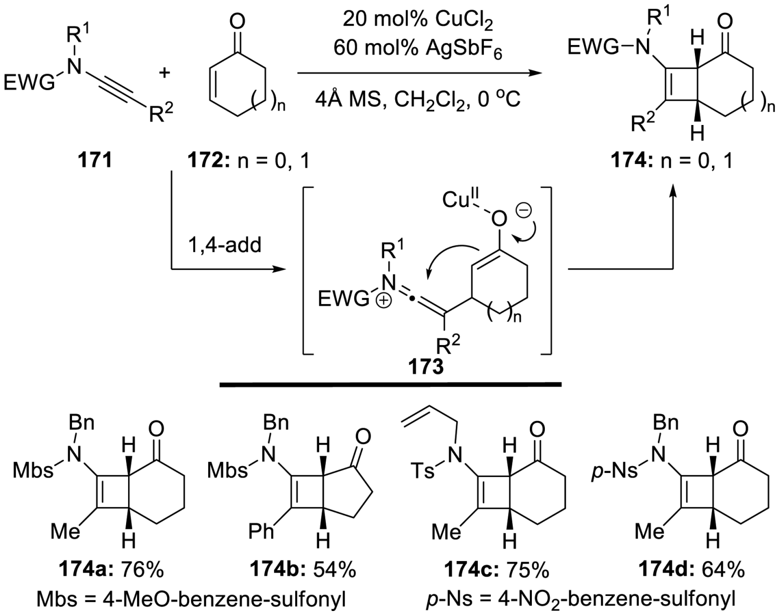
Scheme 29.


syringe pump addition of
4.0 equiv DMDO over 2-3 h
acetone, rt
[conc = 0.014 M]
162: E = CO2Me
165-major
165-minor
163
"endo"
"exo"
164: push-pull carbenes
E = CO2Me
165a-major: 74%
[dr 72:28]
165b-major: 63%
[dr 75:25]
165c-major: 80%
[dr 58:42]
165d-major: 60%
[dr 70:30]

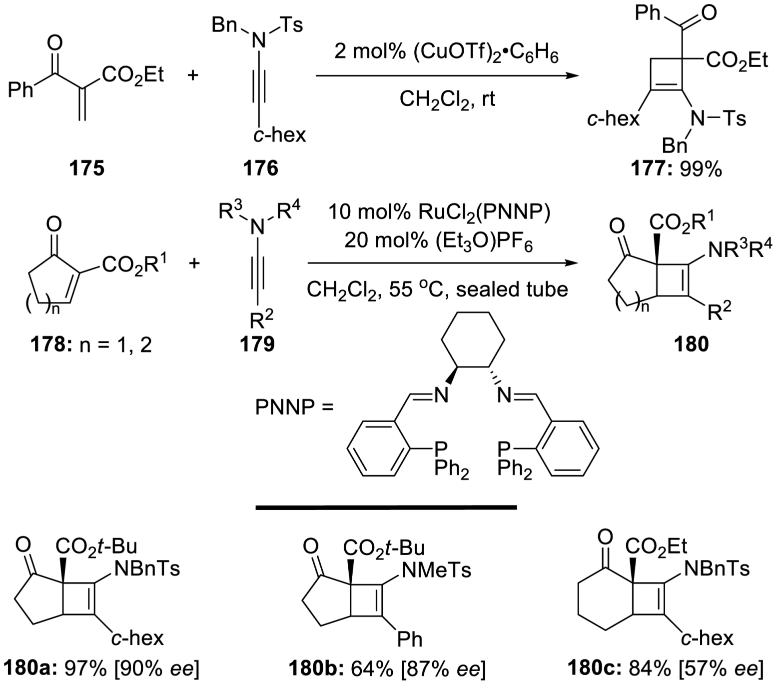
Scheme 30.


EWG
N
R3
166
+
R1
R2
X
167
2.5 mol% Pd(II) cat
DCE, 40 ºC
170
EWG
[2+2]
168
Pd
169
Pd(II) cat =
o-Tol
P
Pd
O
170a: 62%
170b: 61%
AcO
170c: 73%
Ts
Ph
170d: 26%
CO2t-Bu
Bn
170e: 65%
170f: 26%

Scheme 31.

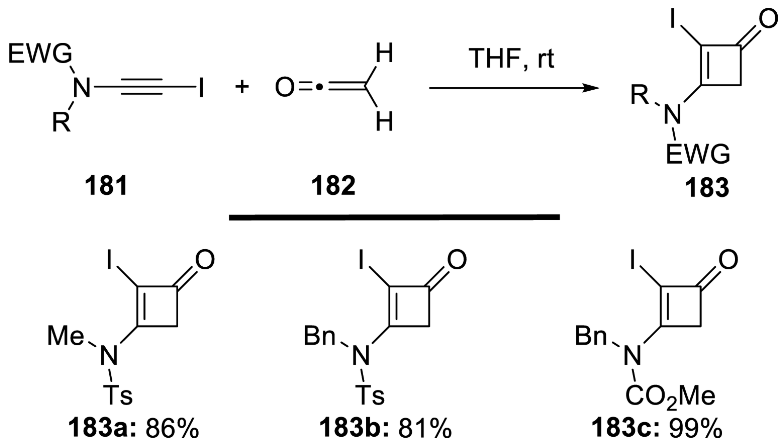

20 mol% CuCl2
60 mol% AgSbF6
4Å MS, CH2Cl2, 0 °C
171
172: n = 0, 1
174: n = 0, 1
1,4-add
173
174a: 76%
174b: 54%
174c: 75%
174d: 64%
Mbs = 4-MeO-benzene-sulfonyl
p-Ns = 4-NO2-benzene-sulfonyl

Scheme 32.

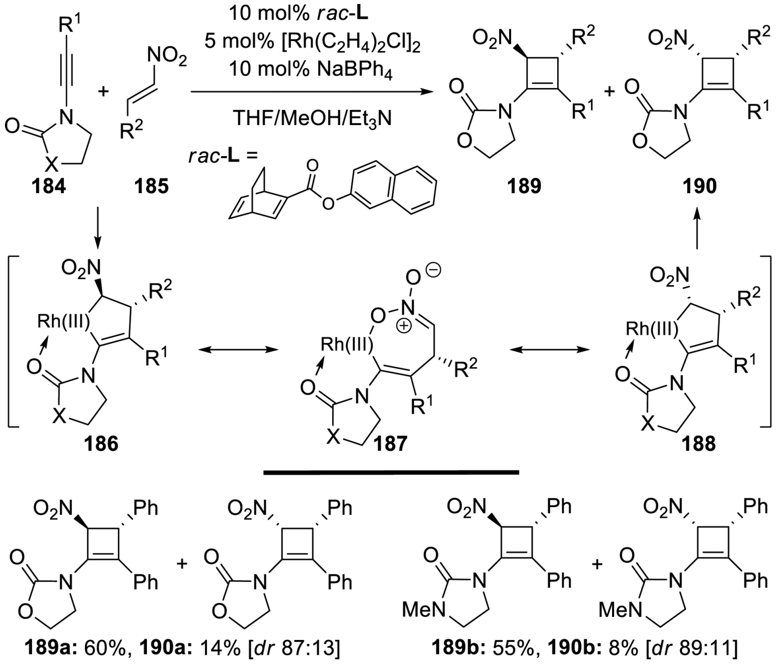


2 mol% $(CuOTf)_2•C_6H_6$
CH_2Cl_2, rt
175
176
177: 99%
10 mol% $RuCl_2(PNNP)$
20 mol% $(Et_3O)PF_6$
CH_2Cl_2, 55 °C, sealed tube
178: n = 1, 2
179
180
PNNP =
180a: 97% [90% ee]
180b: 64% [87% ee]
180c: 84% [57% ee]

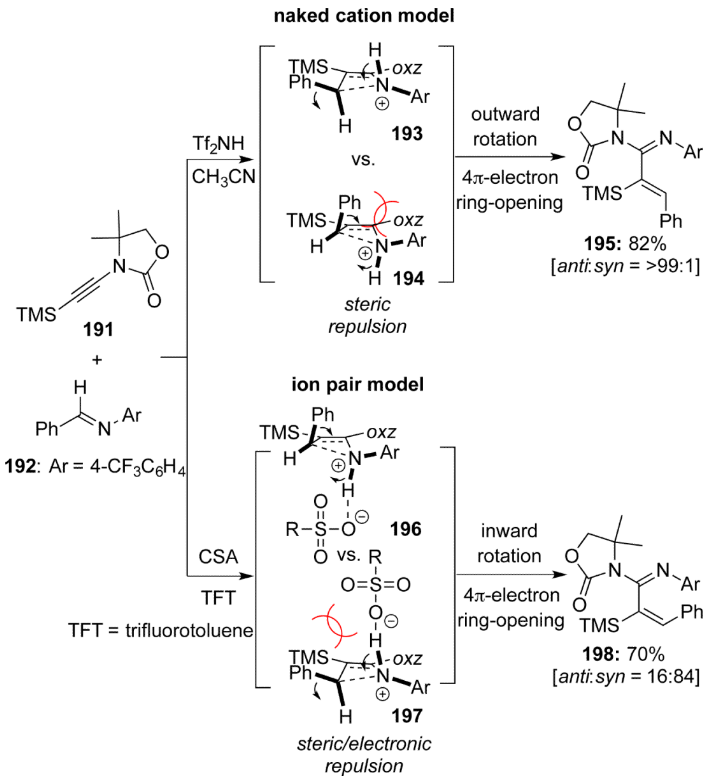
Scheme 33.


EWG
N
R
I
+
O=•
H
H
THF, rt
I
O
R
N
EWG
181
182
183
I
O
Me
N
Ts
183a: 86%
I
O
Bn
N
Ts
183b: 81%
I
O
Bn
N
CO2Me
183c: 99%

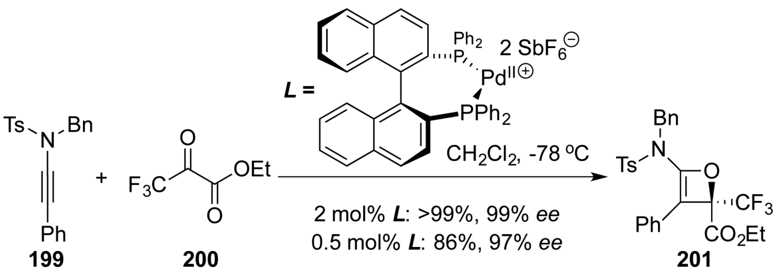
Scheme 34.


10 mol% rac-L
5 mol% [Rh(C2H4)2Cl]2
10 mol% NaBPh4
THF/MeOH/Et3N
rac-L =
184
185
189
190
186
187
188
Rh(III)
189a: 60%, 190a: 14% [dr 87:13]
189b: 55%, 190b: 8% [dr 89:11]

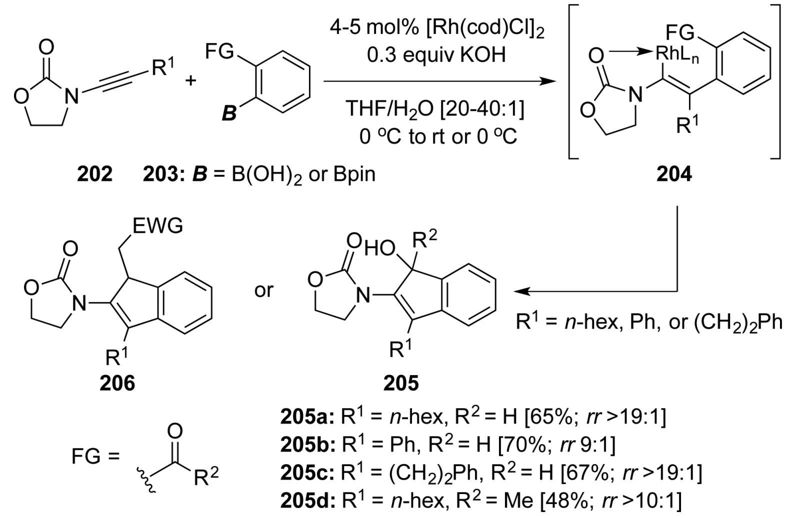
Scheme 35.


naked cation model
TMS
Ph
H
oxz
N
Ar
H
193
vs.
Ph
TMS
oxz
H
N
Ar
H
194
steric
repulsion
Tf2NH
CH3CN
outward
rotation
4π-electron
ring-opening
O
N
N
Ar
O
TMS
Ph
195: 82%
[anti:syn = >99:1]
TMS
N
O
O
191
+
H
Ph
N
Ar
192: Ar = 4-CF3C6H4
ion pair model
Ph
TMS
oxz
H
N
Ar
H
O
R–S–O
O
196
vs.
R
O=S=O
O
H
TMS
Ph
oxz
N
Ar
H
197
steric/electronic
repulsion
CSA
TFT
TFT = trifluorotoluene
inward
rotation
4π-electron
ring-opening
O
N
N
Ar
O
TMS
Ph
198: 70%
[anti:syn = 16:84]

Scheme 36.


Ts
N
Bn
Ph
199
+
O
F3C
OEt
O
200
L =
Ph2
P
2 SbF6⊖
PdII⊕
PPh2
CH2Cl2, -78 °C
2 mol% L: >99%, 99% ee
0.5 mol% L: 86%, 97% ee
Bn
N
Ts
O
CF3
Ph
CO2Et
201

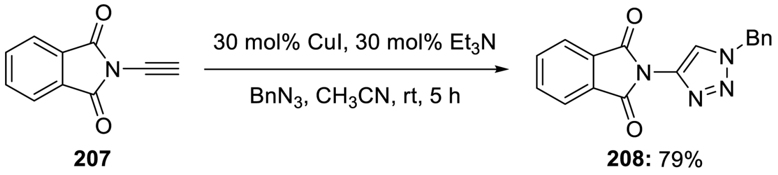
Scheme 37.



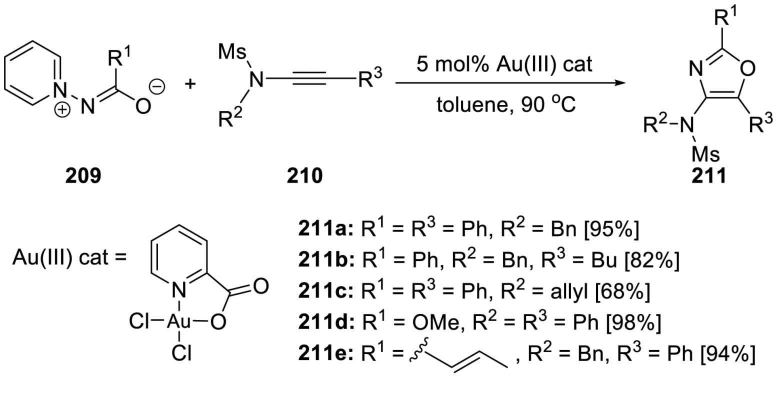
205a: R^1 = n-hex, R^2 = H [65%; *rr* >19:1]
205b: R^1 = Ph, R^2 = H [70%; *rr* 9:1]
205c: R^1 = (CH$_2$)$_2$Ph, R^2 = H [67%; *rr* >19:1]
205d: R^1 = n-hex, R^2 = Me [48%; *rr* >10:1]

206a: EWG = CHO, R^1 = n-hex [67%; *rr* 8:1]
206b: EWG = C(O)Me, R^1 = Ph [71%; *rr* 3.3:1]
206c: EWG = CHO, R^1 = (CH$_2$)$_2$Ph [75%; *rr* 6.7:1]
206d: EWG = CO$_2$Me, R^1 = Ph [75%; *rr* 3.7:1]

Scheme 38.



Scheme 39.



211a: $R^1 = R^3 = Ph$, $R^2 = Bn$ [95%]

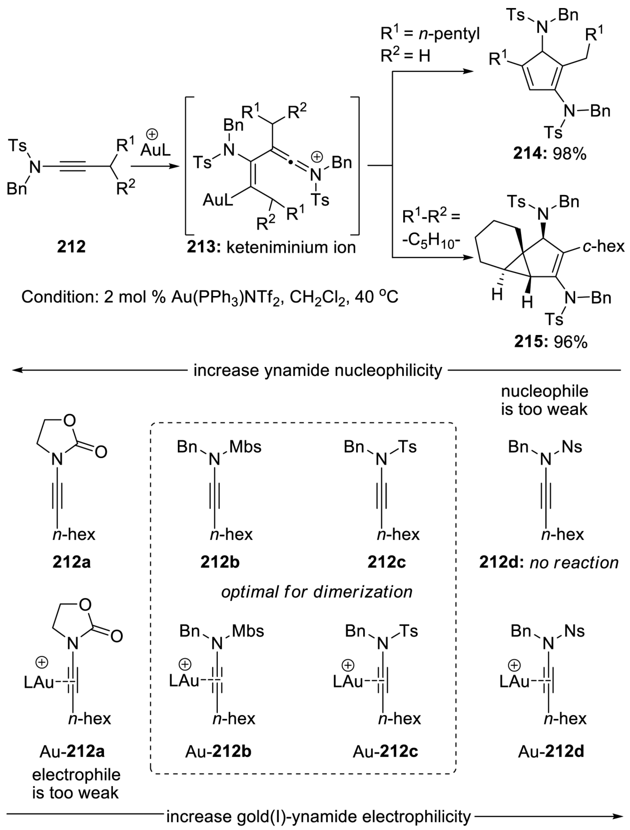
211b: $R^1 = Ph$, $R^2 = Bn$, $R^3 = Bu$ [82%]

211c: $R^1 = R^3 = Ph$, $R^2 =$ allyl [68%]

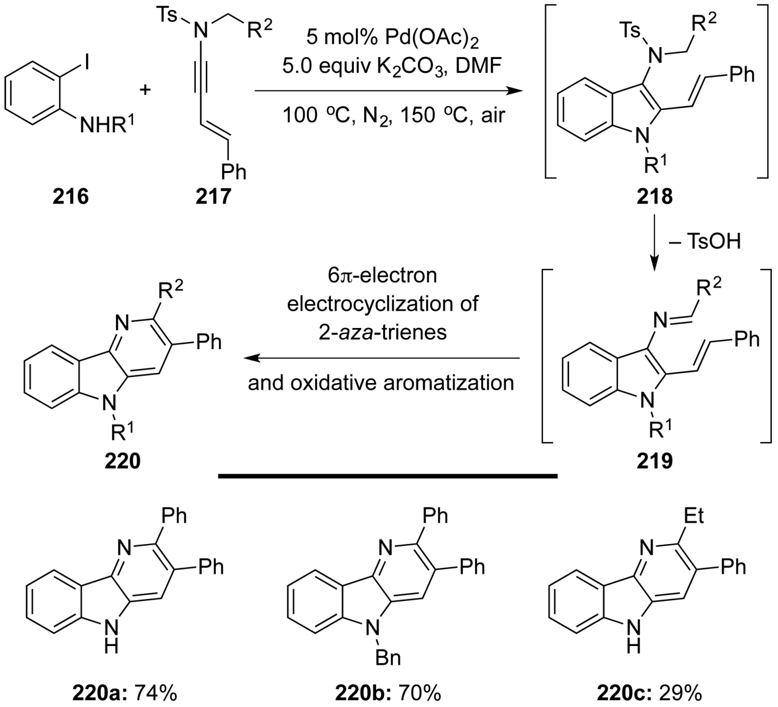
211d: $R^1 = OMe$, $R^2 = R^3 = Ph$ [98%]

211e: $R^1 =$, $R^2 = Bn$, $R^3 = Ph$ [94%]

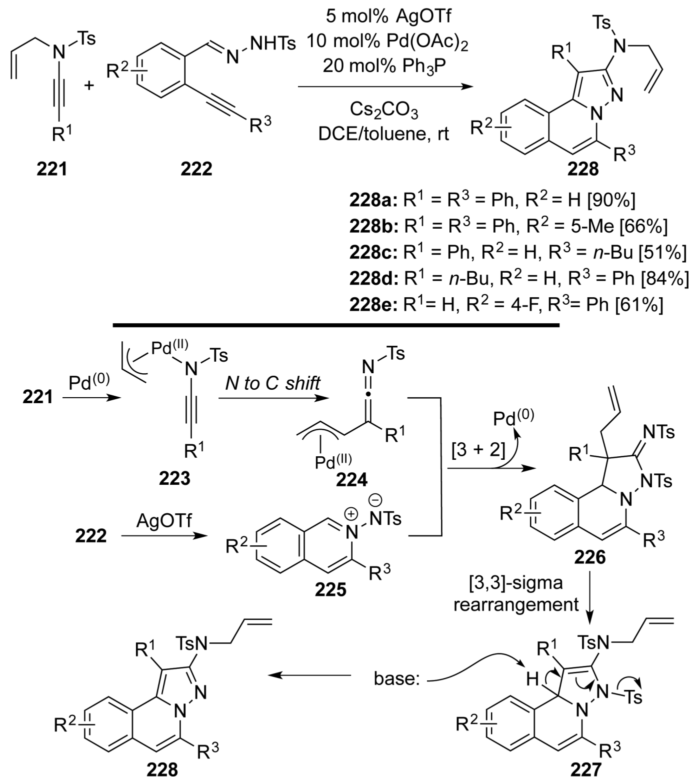
Scheme 40.


212
AuL
213: keteniminium ion
R1 = n-pentyl
R2 = H
214: 98%
R1-R2 = -C5H10-
c-hex
215: 96%
Condition: 2 mol % Au(PPh3)NTf2, CH2Cl2, 40 °C
increase ynamide nucleophilicity
nucleophile is too weak
212a
212b
212c
212d: no reaction
optimal for dimerization
Au-212a
Au-212b
Au-212c
Au-212d
electrophile is too weak
increase gold(I)-ynamide electrophilicity

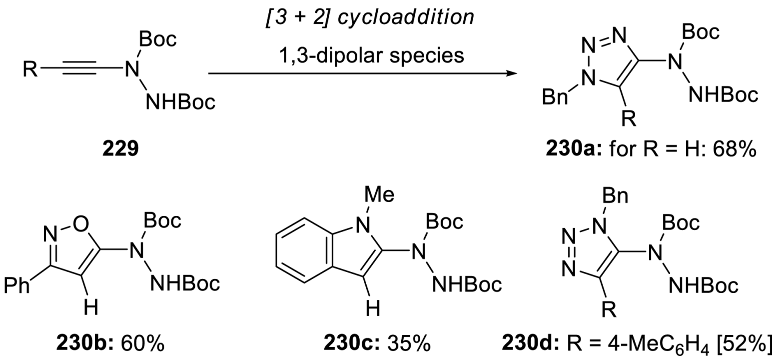
Scheme 41.


I
NHR¹
+
Ts
N
R²
Ph
216
217
5 mol% Pd(OAc)₂
5.0 equiv K₂CO₃, DMF
100 °C, N₂, 150 °C, air
Ts
N
R²
Ph
N
R¹
218
– TsOH
6π-electron
electrocyclization of
2-aza-trienes
and oxidative aromatization
N
R²
Ph
N
R¹
219
R²
N
Ph
N
R¹
220
Ph
N
Ph
N
H
220a: 74%
Ph
N
Ph
N
Bn
220b: 70%
Et
N
Ph
N
H
220c: 29%

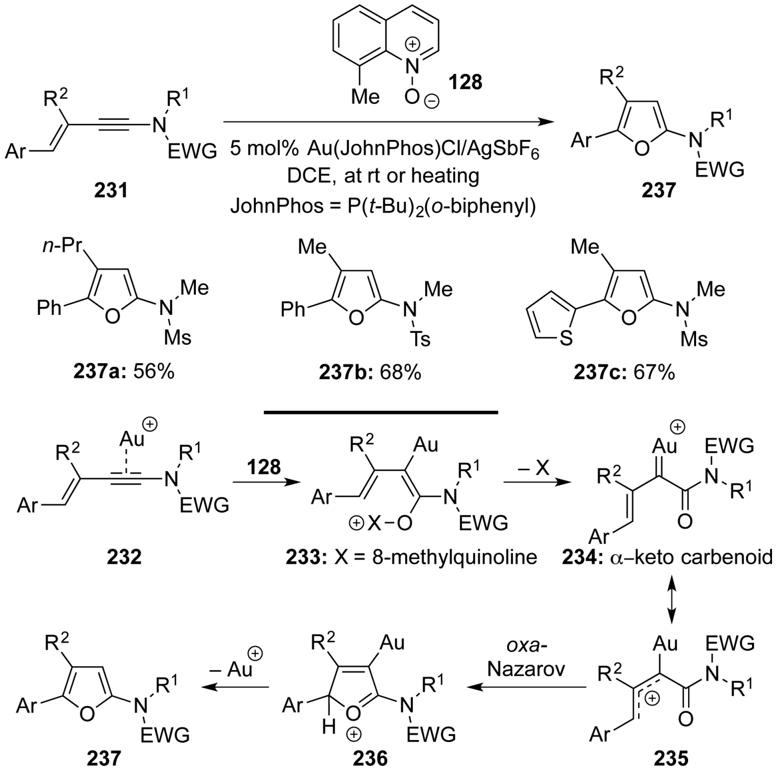
Scheme 42.


221
222
+
5 mol% AgOTf
10 mol% Pd(OAc)2
20 mol% Ph3P
Cs2CO3
DCE/toluene, rt
228
228a: R1 = R3 = Ph, R2 = H [90%]
228b: R1 = R3 = Ph, R2 = 5-Me [66%]
228c: R1 = Ph, R2 = H, R3 = n-Bu [51%]
228d: R1 = n-Bu, R2 = H, R3 = Ph [84%]
228e: R1 = H, R2 = 4-F, R3 = Ph [61%]
Pd(0)
N to C shift
223
224
AgOTf
225
[3 + 2]
226
[3,3]-sigma rearrangement
227
base:
228

Scheme 43.

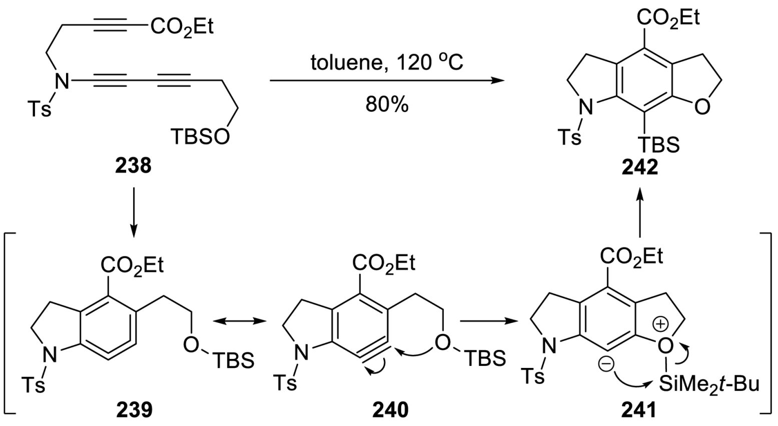

[3 + 2] cycloaddition
1,3-dipolar species
R
Boc
N
NHBoc
229
N=N
N
Bn
R
Boc
N
NHBoc
230a: for R = H: 68%
N-O
Ph
H
Boc
N
NHBoc
230b: 60%
Me
N
H
Boc
N
NHBoc
230c: 35%
Bn
N-N
N
Boc
N
NHBoc
R
230d: R = 4-MeC6H4 [52%]

Scheme 44.

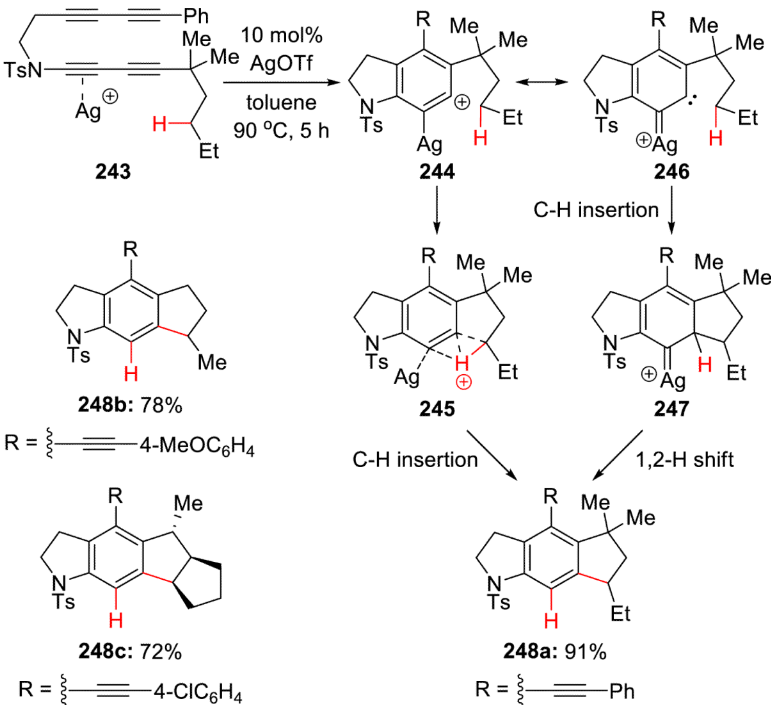


Me
128
231
237
5 mol% Au(JohnPhos)Cl/AgSbF6
DCE, at rt or heating
JohnPhos = P(t-Bu)2(o-biphenyl)
237a: 56%
237b: 68%
237c: 67%
232
128
233: X = 8-methylquinoline
– X
234: α–keto carbenoid
235
oxa-Nazarov
236
– Au
237

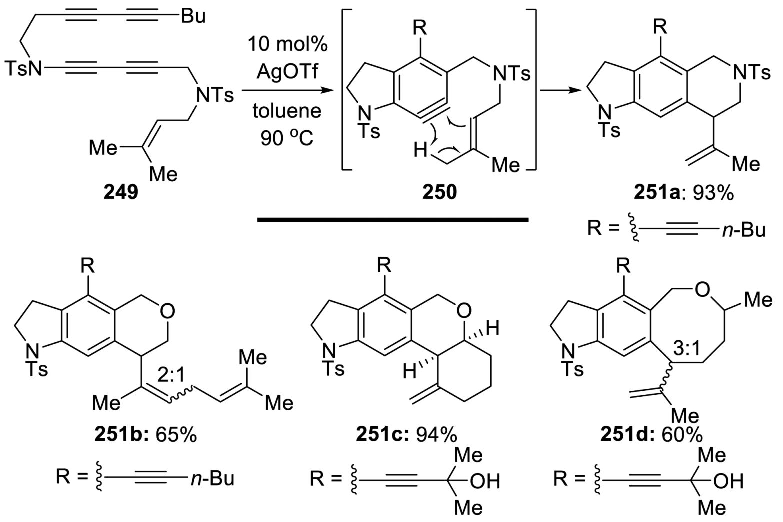
Scheme 45.


CO2Et
N
Ts
TBSO
238
toluene, 120 °C
80%
CO2Et
N
Ts
O
TBS
242
CO2Et
N
Ts
O
TBS
239
CO2Et
N
Ts
O
TBS
240
CO2Et
N
Ts
O
SiMe2t-Bu
241

Scheme 46.

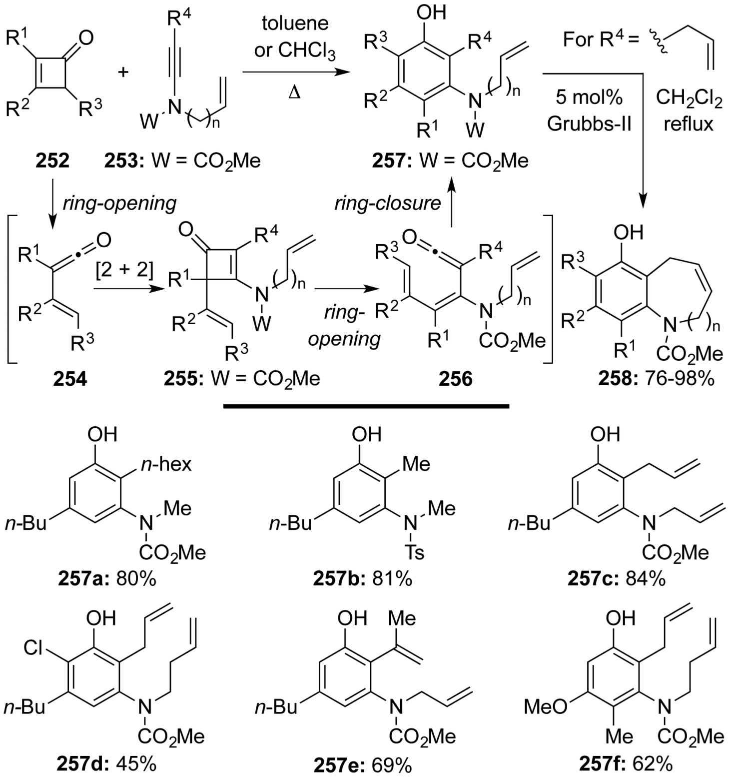

10 mol%
AgOTf
toluene
90 °C, 5 h
C-H insertion
C-H insertion
1,2-H shift
243
244
245
246
247
248b: 78%
R = 4-MeOC6H4
248c: 72%
R = 4-ClC6H4
248a: 91%
R = Ph

Scheme 47.

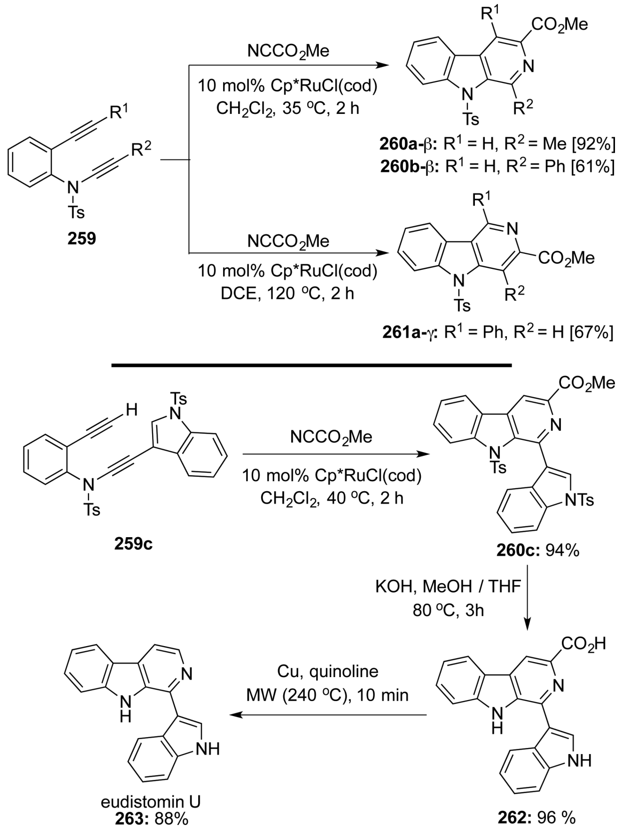


Bu
TsN
NTs
Me
Me
249
10 mol%
AgOTf
toluene
90 °C
R
NTs
N
Ts
H
Me
250
R
NTs
N
Ts
Me
251a: 93%
R = n-Bu
R
O
N
Ts
2:1
Me
Me
Me
251b: 65%
R = n-Bu
R
O
H
N
Ts
H
251c: 94%
R = Me OH Me
R
O
Me
N
Ts
3:1
Me
251d: 60%
R = Me OH Me

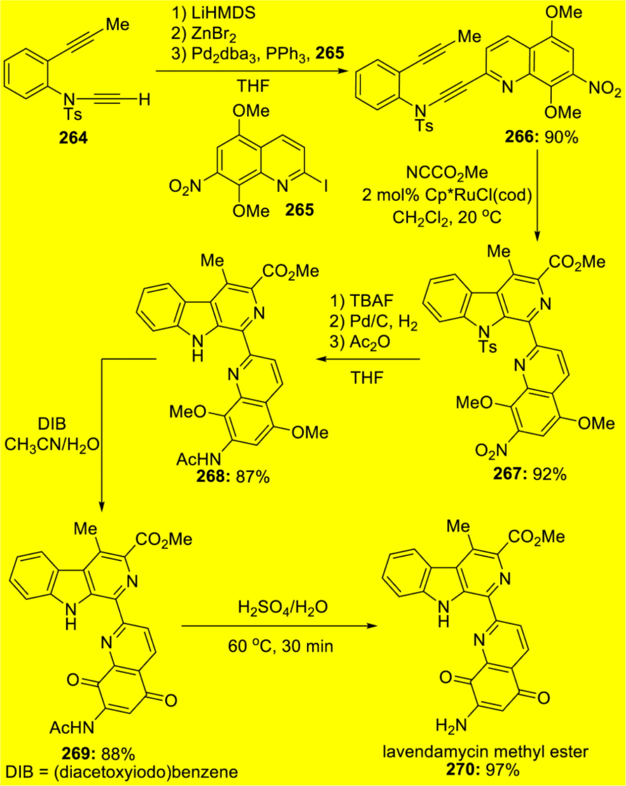
Scheme 48.


252
253: W = CO2Me
toluene or CHCl3
Δ
257: W = CO2Me
For R4 =
5 mol% Grubbs-II
CH2Cl2 reflux
ring-opening
ring-closure
[2 + 2]
ring-opening
254
255: W = CO2Me
256
258: 76-98%
257a: 80%
257b: 81%
257c: 84%
257d: 45%
257e: 69%
257f: 62%

Scheme 49.

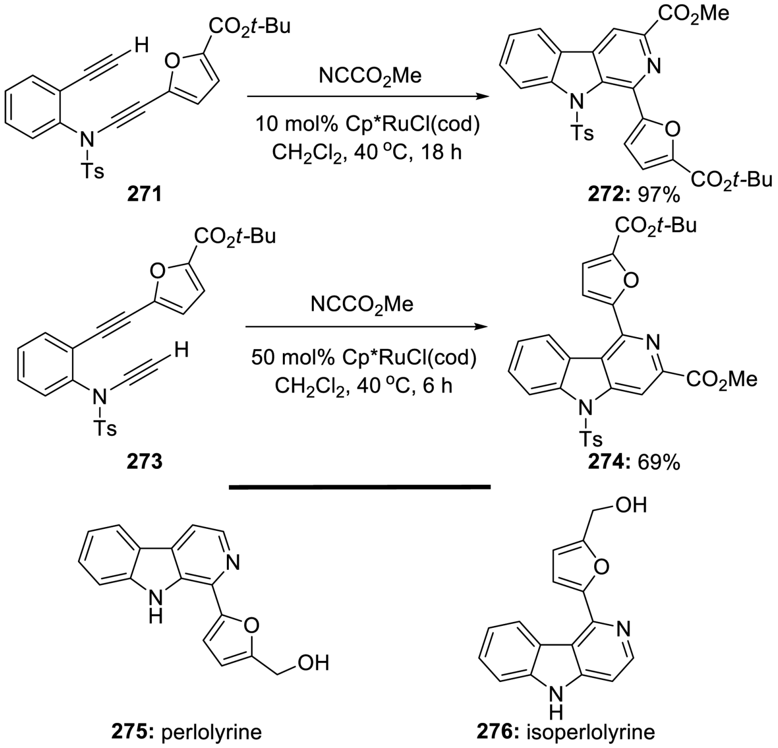

NCCO$_2$Me
10 mol% Cp*RuCl(cod)
CH$_2$Cl$_2$, 35 °C, 2 h
R^1
R^2
N
Ts
259
CO$_2$Me
260a-β: R^1 = H, R^2 = Me [92%]
260b-β: R^1 = H, R^2 = Ph [61%]
NCCO$_2$Me
10 mol% Cp*RuCl(cod)
DCE, 120 °C, 2 h
261a-γ: R^1 = Ph, R^2 = H [67%]
H
259c
NCCO$_2$Me
10 mol% Cp*RuCl(cod)
CH$_2$Cl$_2$, 40 °C, 2 h
NTs
260c: 94%
KOH, MeOH / THF
80 °C, 3h
CO$_2$H
NH
262: 96 %
Cu, quinoline
MW (240 °C), 10 min
eudistomin U
263: 88%

Scheme 50.

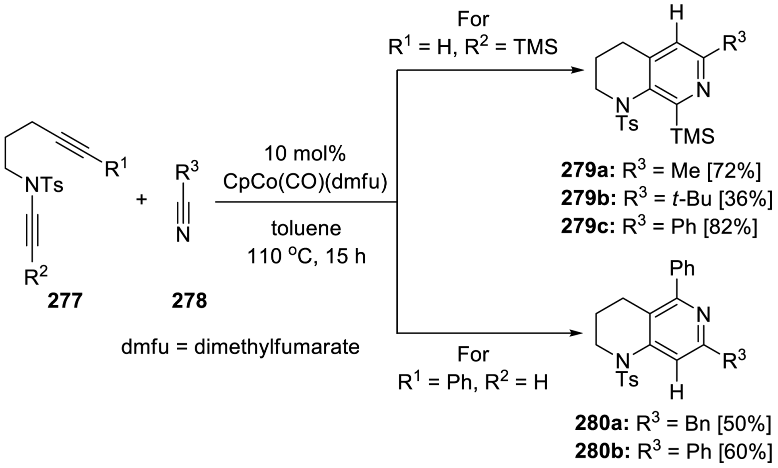


1) LiHMDS
2) ZnBr$_2$
3) Pd$_2$dba$_3$, PPh$_3$, **265**
THF
264
265
266: 90%
NCCO$_2$Me
2 mol% Cp*RuCl(cod)
CH$_2$Cl$_2$, 20 °C
267: 92%
1) TBAF
2) Pd/C, H$_2$
3) Ac$_2$O
THF
268: 87%
DIB
CH$_3$CN/H$_2$O
269: 88%
DIB = (diacetoxyiodo)benzene
H$_2$SO$_4$/H$_2$O
60 °C, 30 min
lavendamycin methyl ester
270: 97%

Scheme 51.

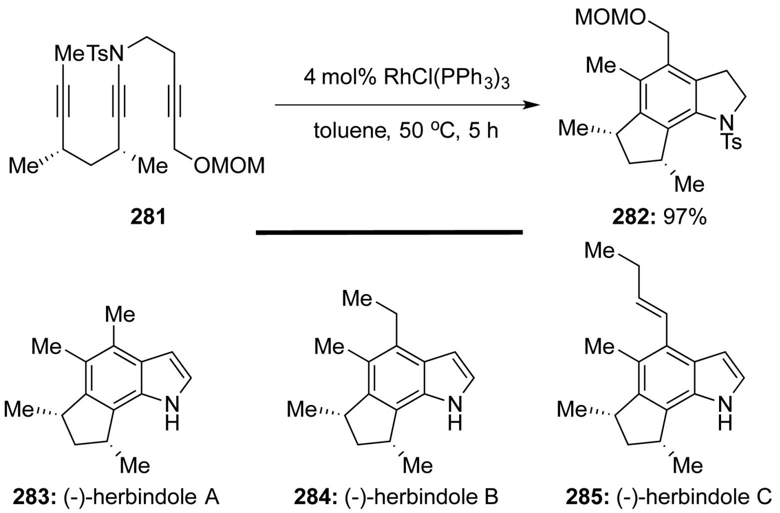

CO2t-Bu
H
O
N
Ts
271
NCCO2Me
10 mol% Cp*RuCl(cod)
CH2Cl2, 40 °C, 18 h
CO2Me
N
N
Ts
O
CO2t-Bu
272: 97%
CO2t-Bu
O
H
N
Ts
273
NCCO2Me
50 mol% Cp*RuCl(cod)
CH2Cl2, 40 °C, 6 h
CO2t-Bu
O
N
CO2Me
N
Ts
274: 69%
N
N
H
O
OH
275: perlolyrine
OH
O
N
N
H
276: isoperlolyrine

Scheme 52.

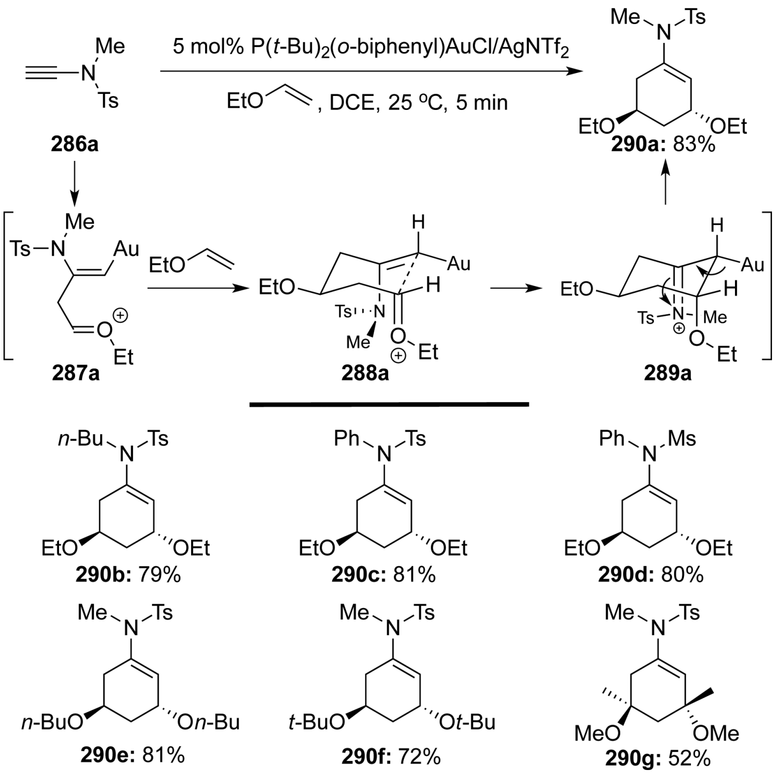


R1
NTs
R2
277
+
R3
N
278
10 mol%
CpCo(CO)(dmfu)
toluene
110 °C, 15 h
dmfu = dimethylfumarate
For
R1 = H, R2 = TMS
H
R3
N
N
Ts
TMS
279a: R3 = Me [72%]
279b: R3 = t-Bu [36%]
279c: R3 = Ph [82%]
For
R1 = Ph, R2 = H
Ph
N
R3
N
Ts
H
280a: R3 = Bn [50%]
280b: R3 = Ph [60%]

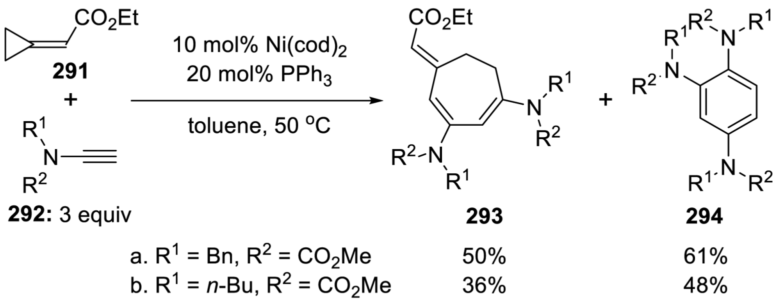
Scheme 53.


MeTsN
Me
Me
OMOM
281
4 mol% RhCl(PPh3)3
toluene, 50 °C, 5 h
MOMO
Me
Me
N
Ts
Me
282: 97%
Me
Me
Me
N
H
Me
283: (-)-herbindole A
Me
Me
Me
N
H
Me
284: (-)-herbindole B
Me
Me
Me
N
H
Me
285: (-)-herbindole C

Scheme 54.

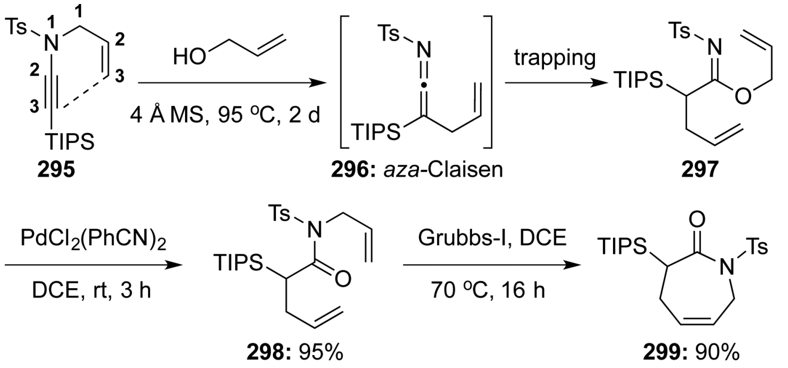

5 mol% P(t-Bu)2(o-biphenyl)AuCl/AgNTf2
EtO, DCE, 25 °C, 5 min
286a
290a: 83%
287a
288a
289a
290b: 79%
290c: 81%
290d: 80%
290e: 81%
290f: 72%
290g: 52%

Scheme 55.



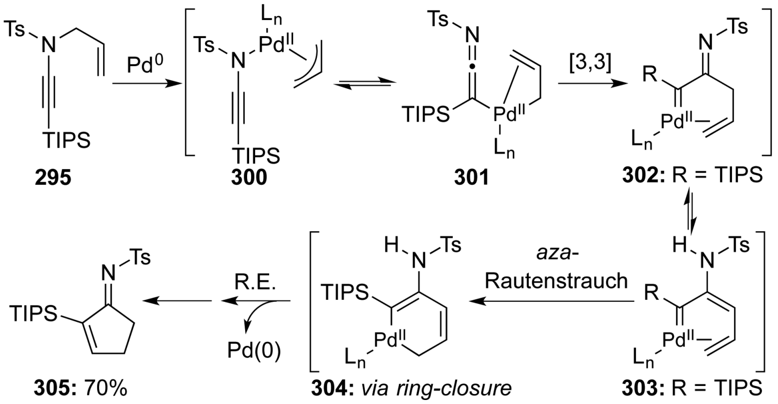
CO2Et
291
+
R1
N
R2
292: 3 equiv
10 mol% Ni(cod)2
20 mol% PPh3
toluene, 50 °C
CO2Et
R1
N
R2
R2-N
R1
293
+
R1
R2
N
R1
R2
N
N
R1
R2
294
a. R1 = Bn, R2 = CO2Me
50%
61%
b. R1 = n-Bu, R2 = CO2Me
36%
48%

Scheme 56.



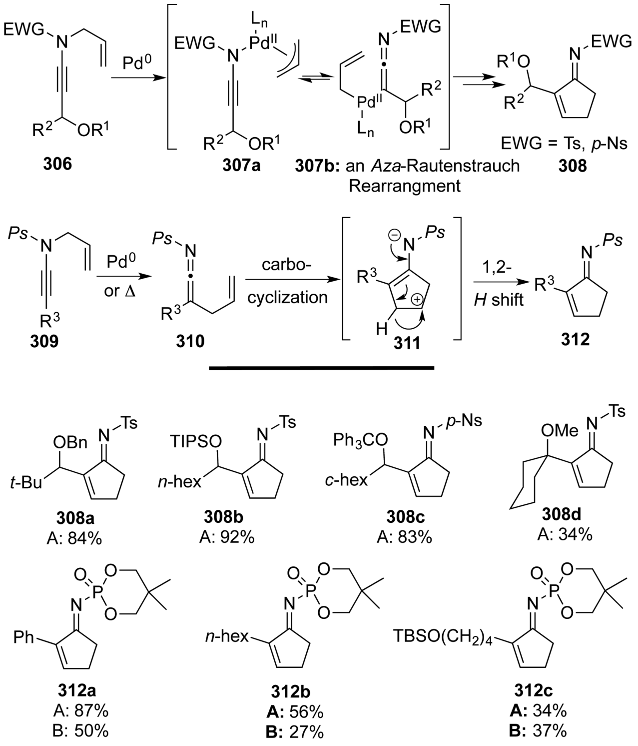
Ts
N
1
1
2
2
3
3
TIPS
295
HO
4 Å MS, 95 °C, 2 d
Ts
N
TIPS
296: aza-Claisen
trapping
Ts
N
TIPS
O
297
PdCl2(PhCN)2
DCE, rt, 3 h
Ts
N
TIPS
O
298: 95%
Grubbs-I, DCE
70 °C, 16 h
O
TIPS
N
Ts
299: 90%

Scheme 57.



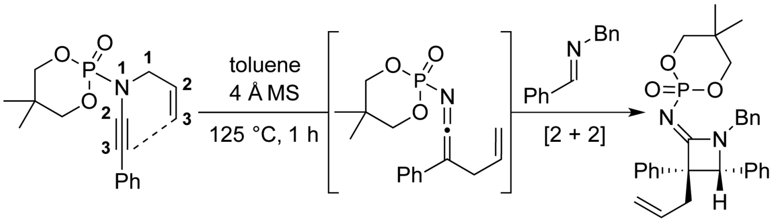
Ts
N
TIPS
295
Pd⁰
Ln
Pdᴵᴵ
300
Ts
N
TIPS
301
[3,3]
R
302: R = TIPS
aza-Rautenstrauch
H
303: R = TIPS
304: via ring-closure
R.E.
Pd(0)
305: 70%

Scheme 58.



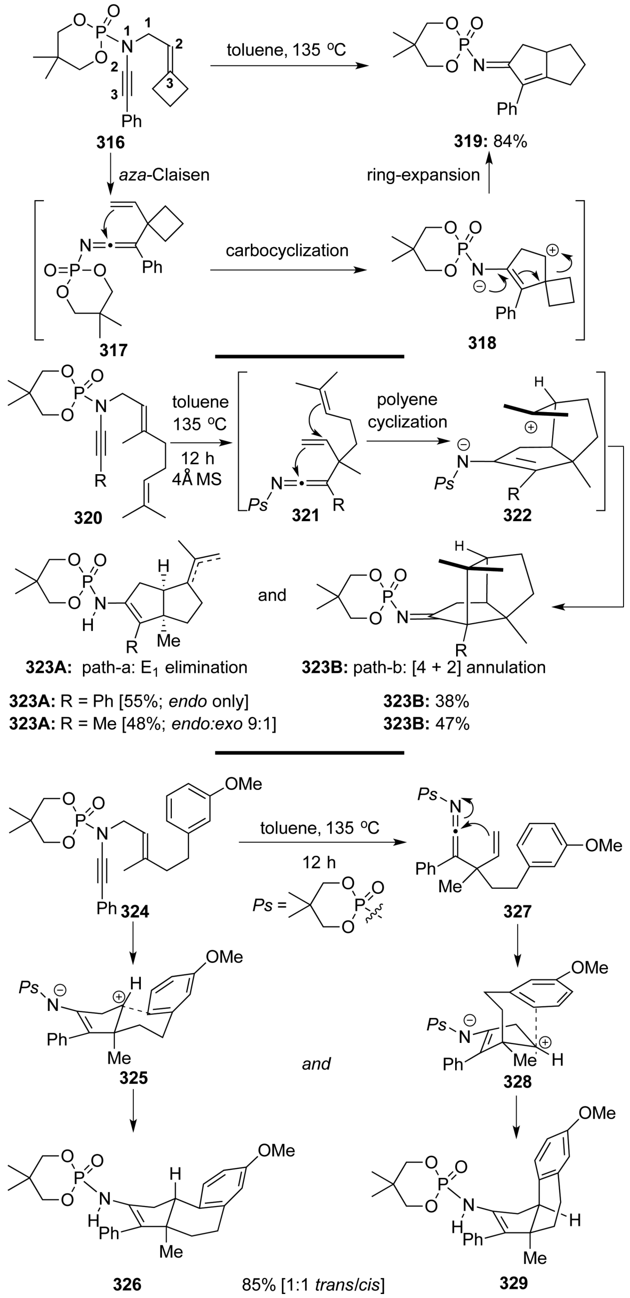
Method A: 5 mol% Pd(PPh$_3$)$_4$, toluene, 70 °C; Method B: toluene, 125 °C

Scheme 59.

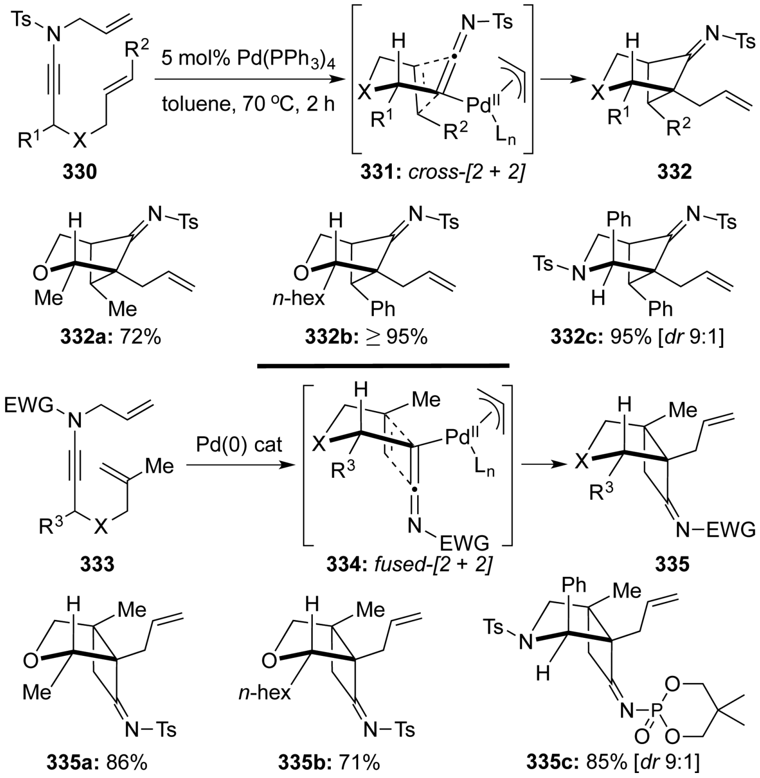


313 **314:** *aza*-Claisen **315:** 73% [*dr* 4:1]

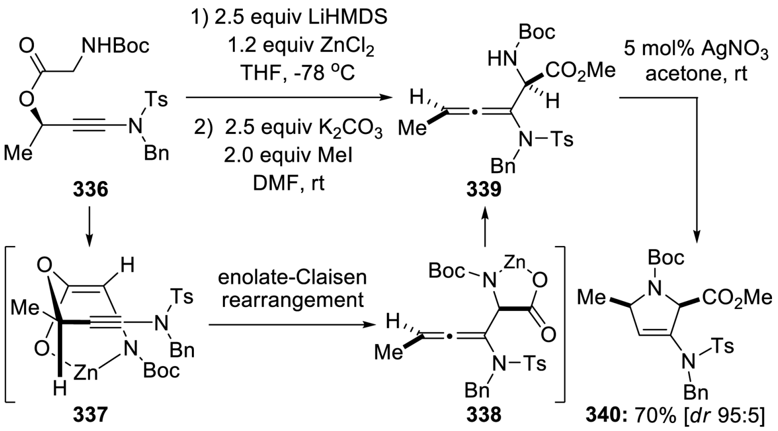
Scheme 60.


316
toluene, 135 °C
319: 84%
aza-Claisen
ring-expansion
carbocyclization
317
318
320
toluene
135 °C
12 h
4Å MS
polyene cyclization
321
322
and
323A: path-a: E1 elimination
323B: path-b: [4 + 2] annulation
323A: R = Ph [55%; endo only]
323A: R = Me [48%; endo:exo 9:1]
323B: 38%
323B: 47%
324
toluene, 135 °C
12 h
Ps =
327
325
and
328
326
85% [1:1 trans/cis]
329

Scheme 61.


5 mol% Pd(PPh3)4
toluene, 70 °C, 2 h
330
331: cross-[2 + 2]
332
332a: 72%
332b: ≥ 95%
332c: 95% [dr 9:1]
Pd(0) cat
333
334: fused-[2 + 2]
335
335a: 86%
335b: 71%
335c: 85% [dr 9:1]

Scheme 62.


1) 2.5 equiv LiHMDS
1.2 equiv ZnCl2
THF, -78 °C
2) 2.5 equiv K2CO3
2.0 equiv MeI
DMF, rt
5 mol% AgNO3
acetone, rt
enolate-Claisen rearrangement
336
337
338
339
340: 70% [dr 95:5]

Scheme 63.