Ynamides: A Modern Functional Group for the New Millennium

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Contents

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1. Introduction

1.1. An Overview on Ynamines

Alkynes represent one of the most important and versatile building blocks in organic synthesis. Heteroatom-substituted alkynes, which can be considered as subgroups of alkynes, have also been vastly utilized in developing synthetic methods. In particular, ynamines [1-amino-alkynes or *N*-alkynyl amines] became the most valuable subgroup of alkynes after the establishment of their practical synthesis in the 1960s. The first attempt at preparation of an ynamine was reported by Bode[1,2] in 1892. While well-characterized ynamines were reported in 1958[3] and 1960,[4] a practical synthesis was not achieved until the effort led by Viehe[5] in 1963 in addition to other subsequent works. In the ensuing

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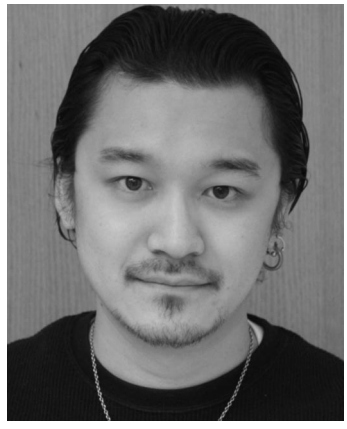
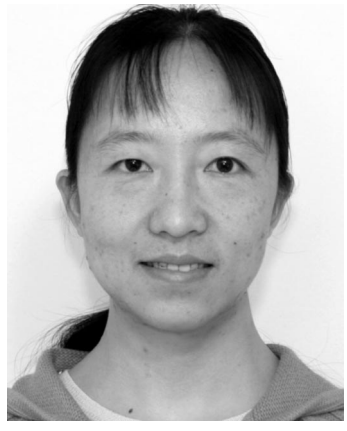


Ryuji Hayashi graduated from Indiana State University in Terre Haute, IN, with his B.S. in Chemistry and Biochemistry in 2003. He then moved to North Dakota State University in Fargo, ND, and obtained his Ph.D. degree in organic chemistry under the supervision of Professor Gregory Cook in 2008. He was a recipient of the NDSU Graduate School Doctoral Dissertation Award 2007−2008. Since 2008, he has been researching as a postdoctoral research associate in Professor Richard Hsung's group at the University of Wisconsin at Madison. He is currently exploring a variety of tandem reactions via allenamide isomerizations.

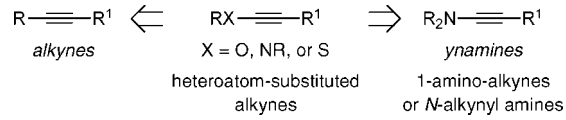


Zhenjie Lu obtained her B.S. degree in chemistry in 1996 from the East China University of Science and Technology in Shanghai, China. She started as a graduate student at Michigan State University under Professor Bill Wulff's direction in 2002 as a graduate student and finished her Ph.D. degree in 2008. Her research involved studies on the optimization and synthetic application of catalytic asymmetric aziridination reactions.

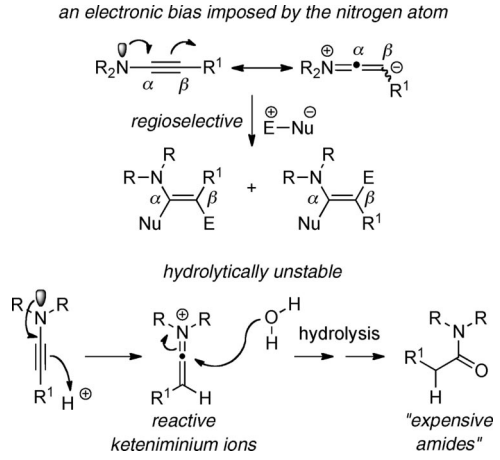
Yu Zhang carried out his undergraduate research at the East China University of Science and Technology in Shanghai, China. He received his B.S. degree in chemistry in 1996, and then in 2000, he joined Professor Bill Wulff's group as a graduate student at Michigan State University. He obtained his Ph.D. degree in 2006 after working in the area of mechanism and methodology development of catalytic asymmetric aziridination. After spending one year at University of Maryland working for Professor Michael P. Doyle, from 2007 to 2009 he was a postdoctoral scholar at the University of Wisconsin at Madison, working with Professor Richard Hsung in the area of ynamide chemistry and natural product synthesis. He is currently a senior chemist in Dow AgroSciences LLC.

Richard P. Hsung obtained his B.S. in Chemistry and Mathematics from Calvin College in Grand Rapid, MI. He then attended The University of Chicago and received his M.S. and Ph.D. degrees in Organic Chemistry in 1990 and 1994, respectively, under the supervision of Professors Jeff Winkler and Bill Wulff. After pursuing a postdoctoral stay with Professor Larry Sita in Chicago and NIH-postdoctoral work with Professor Gilbert Stork at Columbia University, he moved to the University of Minnesota as an Assistant Professor in 1997 and was promoted to Associate Professor in 2002. He was promoted to Professor and moved to the University of Wisconsin in 2006. He was a recipient of the Camille Dreyfus Teacher−Scholar Award and the National Science Foundation Career Award. He has coauthored 200 publications, delivered over 180 invited lectures, and supervised 120 students and postdoctoral fellows with research interests in developing cycloaddition and annulation approaches to natural product syntheses and stereoselective methods using allenamides, ynamides, enamides, and acetals.

20 years, the synthetic significance of ynamines in organic and organometallic chemistry was firmly established by the work of many creative synthetic chemists. These elegant pioneer works have been informatively and carefully reviewed by Viehe in 1967[6] and 1969;[7] by Ficini in 1976;[8] by Pitacco and Valentin[9] in 1979; by Collard-Motte and Janousek[10] in 1986; by Himbert[11] in 1993; and most recently by us[12,13] and Katritzky.[14]



The synthetic eminence of ynamines is well merited because of the predictable regioselectivity in their transformations, as shown by the generalization below, and, more importantly, because they are inherently highly reactive. However, this latter attribute is also the source of the limitation that has seriously hampered the development of ynamine chemistry, thereby shortening the period of its prominence in synthesis. Ynamines are very sensitive toward hydrolysis, as protonation of the electron-rich alkynyl motif affords reactive keteniminium intermediates, which upon trapping with water leads to simple amides in a rather expensive manner (graphic below). This hydrolytic instability has caused much difficulty in the experimental preparation and general handling of ynamines and, more detrimentally, rendered ynamine chemistry inaccessible.

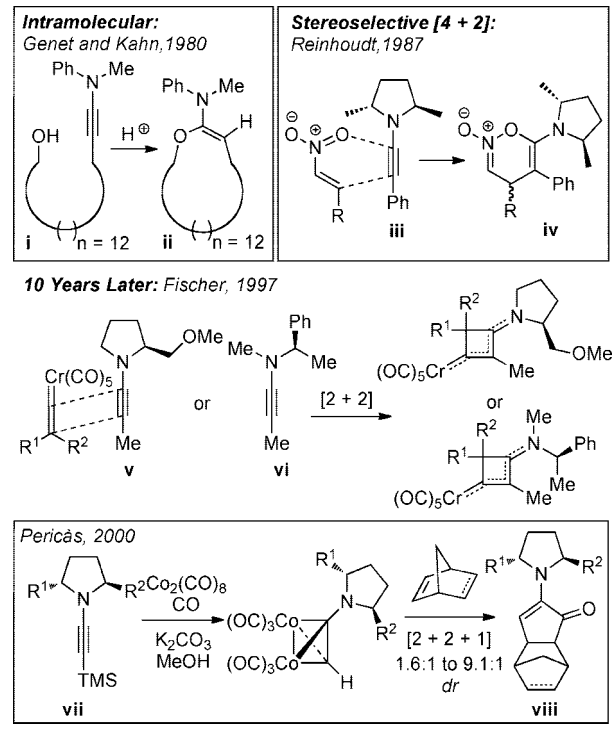


Consequently, the synthetic utility of ynamines has suffered a dramatic decline during the last 30 years.[15] The most glaring limitations have been in the development of intramolecular and stereoselective reactions.[7−14] The only reported intramolecular reaction of ynamines was Genet and Kahn's acid catalyzed addition of a hydroxyl group to an ynamine (**i** → **ii** below) in 1980,[16] and although clever, it constitutes a hydrolytic process.

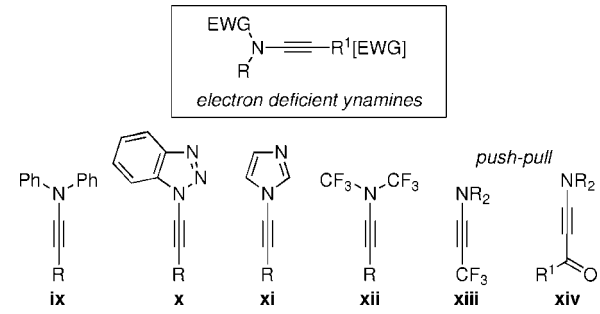
Besides Reinhoudt's[17] sole account in 1987 reporting hetero-[4 + 2] cycloadditions of chiral ynamine **iii** with nitroalkenes that led to cycloadducts **iv** in modest *de*, the only other notable studies were reported 10 years later by Fischer,[18] showcasing [2 + 2] cycloadditions of chiral ynamides **v** and **vi** with vinylidene chromium carbene complexes, and another 3 years later by Pericàs[19] in their Pauson−Khand cycloadditions using chiral ynamines **vii**.

1.2. Emergence of Ynamides

To improve the stability of ynamines and revitalize their synthetic utility, diminishing the electron density by substituting the nitrogen atom and/or the alkyne with electronegative elements would appear to be a logical solution. These could be classified as electron-deficient ynamines [**ix**−**xiv** below], and their reactivities and relative stabilities are known in the literature.[7−14] These would include beautiful recent work by Katritzky[20] using benzotriazole substituted ynamines [**x**] and by Kerwin[21] involving imidazole-substituted ynamines

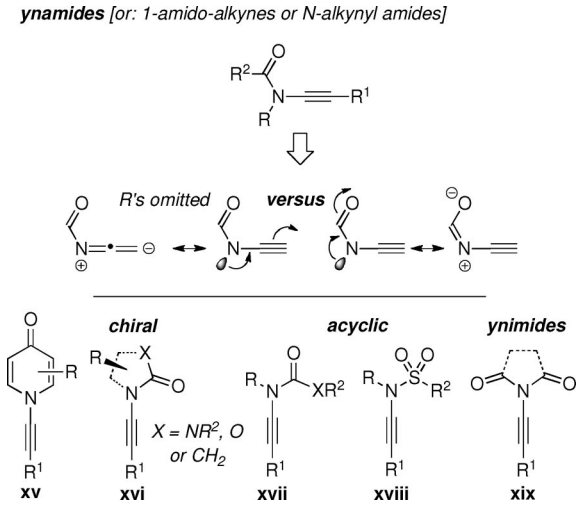


[**xi**]. In addition, elegant chemistry has been reported during the last 30 years using so-called push−pull ynamines or alkynes.[7−14] Ishihara's reports[22] employing *N*,*N*-dialkyl-(3,3,3-trifluoro-1-propynyl)amines **xiii** and Stang's push−pull ynamines **xiv**[23] represent examples of such electron deficient ynamines.



While the aforementioned electron-deficient variants of ynamines [**ix**−**xiv**] depend upon inductive effects, or delocalization of the nitrogen lone pair into an aryl or heteroaryl system, or through the triple bond to reduce the electron density of the ynamine motif, the chemistry of another class of electron-deficient ynamines has emerged in the last 15 years. By simply placing an electron-withdrawing carbonyl group on the nitrogen atom, the donating ability of the nitrogen lone pair toward the alkynyl motif is greatly diminished through resonance delocalization into the carbonyl oxygen (see graphic below). These new electron-deficient ynamines have been called ynamides, or 1-amido-alkynes [or *N*-alkynyl amides]. Not only do they offer superior stability to traditional ynamines, but they also have set the gold standard for balancing reactivity and stability.

Examples of ynamides would include those in which the nitrogen atom is a member of (1) vinylogous amides or pyridones **xv**; (2) imidazolidinones, oxazolidinones, or lactams **xvi**, which can also be chiral; (3) ureas, urethanes, or simple amides **xvii**, and sulfonamides **xviii**, which

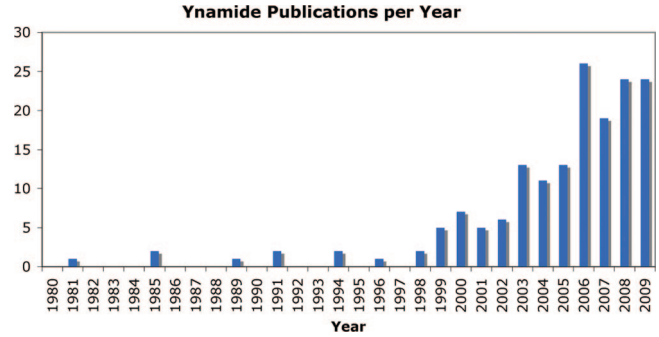


represent acyclic ynamides; or (4) imides **xix**, which remain elusive to date. This very concept of improving thermal stability and stability toward hydrolytic conditions by using an electron-withdrawing carbonyl group should be credited to Viehe, who in 1972 reported the synthesis of the first ynamide [see **xvii**: R = R^2 = Me, R^1 = Ph, X = NMe].[24]

While identifying stable variants of ynamines represents a pressing issue, more important is the need for the new variants to retain high levels of reactivity. In meeting both of these criteria, ynamides may lead to rich new areas of chemistry where their improved thermal and hydrolytic stability could allow access to intramolecular and stereoselective reactions that are not possible with ynamines. Most significantly, while the chemistry of other heteroatom-substituted alkynes is of high impact and value, nitrogen atom-substituted alkynes offer greater advantages. The trivalent nature of the nitrogen atom allows the following: (1) tethering of a chirality-inducing unit for providing asymmetric induction; (2) inclusion of the coordinating unit to provide conformational rigidity; (3) a much greater flexibility in designing intramolecular reactions or tandem processes than with oxygen- or sulfur-substituted alkynes; and, last but not the least, (4) a novel entry to alkaloids if the nitrogen atom can be preserved throughout the transformations. These are remarkably attractive features for developing highly stereoselective methodologies and rapid assembly of structural complexity.

Surprisingly, despite the precedent for ynamide synthesis and documentation of its superior thermal stability by Viehe, reactions involving ynamides remained almost unknown for 25 years (see graphic below).[7−14] It was not until the late 1990s that the chemistry of ynamides began to appear in the literature, commencing with Feldman's synthesis of chiral ynamides,[25] and later, in a series of beautiful works done by Witulski, as well as those of Rainier and Chen. Meanwhile, our lab initially focused on developing an atom-economical way of synthesizing ynamides. These early developments awakened the synthetic community to utilizing nitrogen-substituted alkynes in organic synthesis and led to a Tetrahedron-Symposium-in-Print[26] focused on the chemistry of electron-deficient ynamines and ynamides.

In the last 5 years, the chemistry of ynamides has exploded (see graphic directly below), particularly that involving ynamides **xvi**−**xviii**. It can be stated that the chemistry of ynamines has reemerged in the forms of ynamides. These



efforts demonstrate that ynamides possess the right balance between reactivity and stability and can be employed in a diversified array of stereoselective and intramolecular reactions that were not possible with traditional ynamines. With such compelling evidence for the reemergence of "ynamine" chemistry, it is the purpose of this review to provide proper illustrations of elegant chemistry involving ynamides **xvi**−**xviii** that has come to pass and to illicit a greater interest from the synthetic community, leading to new ynamide chemistry in the future.

1.3. Personal Perspective

Despite working with alkynes extensively in Professor Bill Wulff's lab, my interest in the chemistry of ynamines truly began with Professor Gilbert Stork in the summer of 1996 when a discussion of ours led to the topic of Professor Jacqueline Ficini's dihydroantirhine synthesis,[27] which featured Ficini's ynamine-[2 + 2] cycloaddition to cleverly control the relative stereochemistry at C3, C15, and C20 in dihydroantirhine. It was a memorable discussion because I had not seen Professor Stork this passionate before, and I could sense that he has a profound respect for Jacqueline. I queued into phrases such as, "ynamines are not stable but clearly useful" and "it's an unsolved area and you should look into it." After two more similar conversations, I was into it.

Six months later, I learned something invaluable from an interview trip to Palo Alto. In his office, Professor Barry Trost was quite fascinated with our proposed ynamine chemistry, asking what I had really thought of in terms of improving stability and what the future might hold. Not having found Viehe's paper, I was not sure of a good answer. However, from our conversation, I grasped that, to truly revitalize interest in this functionally rich organic building block, one would need to address issues related not only to stability but, more importantly, to synthetic accessibility in an atom-economical manner, which became our foremost quest.

A few weeks later in Lansing, it was Professor Robert Maleczka who pointed out that our proposed novel ynamines with chiral oxazolidinone and imidazolidinone motifs [see **xvi**] could offer the needed thermal stability given the electron-withdrawing carbonyl group. In hindsight, while having read Viehe's paper would have made my life a little easier, that particular conversation has significance of its own. It led me to focus on these novel oxazolidinone and imidazolidinone substituted ynamides **xvi** instead of sulfone-substituted ynamides **xviii**. The implication is that while the latter could be accessible using the iodonium triflate salt protocol developed by Stang and Zhdankin[28] as a new method for ynamine synthesis from lithium amides, the same protocol was not useful for the former, thereby requiring the development of new methods. Without the conversation with

Professor Maleczka, we might not have embarked on this adventure, which ultimately led to the development of a copper-catalyzed *N*-alkynylation or Ullmann-type amidative cross-coupling.

It is noteworthy that when one digs deep enough into history, one can always find a precedent. In this case, an earlier account related to copper-promoted *N*-alkynylations was reported by Balsamo and Domiano et al. in 1985[29] using $CuCl/O_2$, although the resulting ynamide was a byproduct. Even earlier in 1968, Peterson[30] at Dow-Midland reported the use of $Cu(OAc)_2/O_2$ in the synthesis of ynamines from terminal acetylenes and secondary amines, which is as economical as it gets. I should also note that while we were exploring various possible synthetic approaches toward ynamides, it was Chris Douglas, a college sophomore at the time [now at Minnesota], who suggested the possibility of pursing a Buchwald−Hartwig−Migita type palladium-catalyzed amination to make ynamides.

Lastly, to advance any area or field of interest, it requires creativity from as many people as possible. This perspective remains true here, as the chemistry of ynamides would not be what it is today without these collective innovations. On that note, while we tried our very best to be comprehensive, it is likely that we have inadvertently missed some beautiful work, for which we express our regret here in advance. Overall, this review is intended to highlight ynamide chemistry in the past 10−15 years with the hope that work in the next decade and beyond will truly render ynamides a modern functional group for the new millennium.

2. Synthesis of Ynamides

The first ynamine synthesis was reported more than 50 years ago; however, the very first example of ynamide preparation was not disclosed until 14 years later. One major obstacle for the broader synthetic application of this versatile building block lies in the fact that, until recently, a highly practical, efficient ynamide preparation procedure, which also possesses general substrate scope, remained elusive. While the emergence of alkynyliodonium chemistry greatly helped the development of ynamide chemistry, the more recent discovery of metal-catalyzed ynamide formation provided significant fuel for the explosion of this area since 2003−2004.

2.1. Isomerization

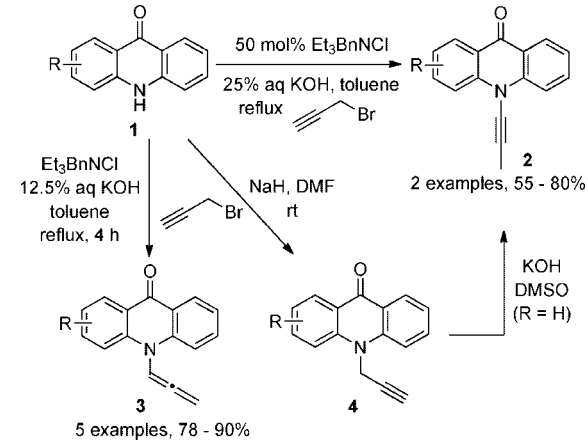
In 1958, Zaugg[3] described the first example of ynamine synthesis via isomerization. Twenty years later, several more syntheses were reported by Galy[31,32] and Katritzky[33] (Scheme 1). Galy initially reported a phase-transfer condition which involved propargylation of acridones **1** followed by *in situ* isomerization to give ynamides **2** in 55−80% yield. The same group later also reported conditions for selective preparation of ynamides **2** and allenamides **3**. Katritzky found that it was more efficient to follow a two-step procedure in which the intermediate **4** was isolated and then rearranged to the desired ynamides.

According to Majumdar's[34] study, propargylation of acridones **1** with propargyl bromide **5** followed by isomerization and elimination under phase-transfer conditions gave various ynamides **8**. Alternatively, **8** could also be accessed by a one-pot procedure using propargyl chlorides **7** (Scheme 2).

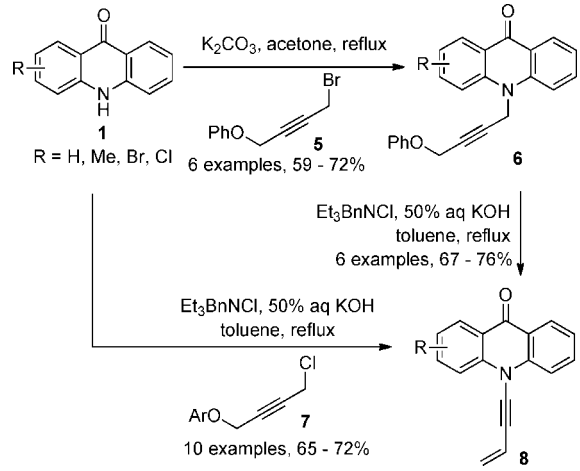
Attempts to extend the scope of isomerization to chiral ynamides were initially met with difficulty. In 2001, Hsung[35a] described that isomerization of **9** failed to give the desired ynamides **10** (Scheme 3). It was later found that the isomerization of propargyl urethanes **11a** and **11b** gave exclusively allenamides **12**, however, the attempted rearrangement of **12** to ynamides **13** was not successful.

However, Hsung[35b] discovered that propargyl amides **14** underwent complete isomerization to ynamides **16** in the presence of a catalytic amount of KO*t*-Bu (Scheme 4). The chiral ynamides were then used in ring-closing metathesis (section 3.3.3).

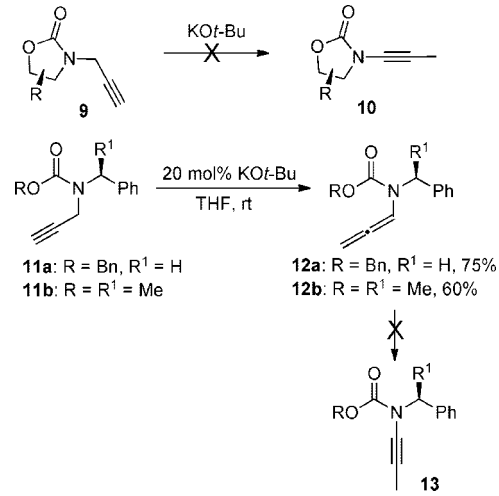
Scheme 1



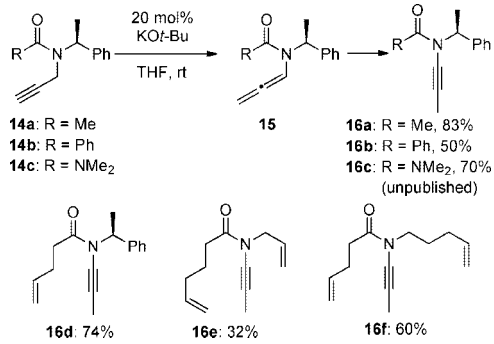
Scheme 2



Scheme 3



Scheme 4



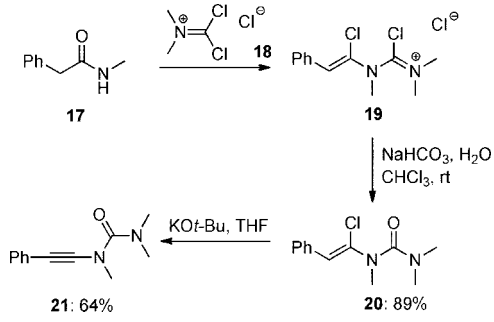
2.2. Elimination

The first example of an elimination protocol was reported by Viehe[36] in 1972 (Scheme 5). A secondary acetamide **17** reacted with phosgeneimmonium chloride **18** gave a chloroformamidinium salt **19**. Upon hydrolysis, **19** afforded urea **20**, which underwent elimination in the presence of base to produce ynamide **21**.

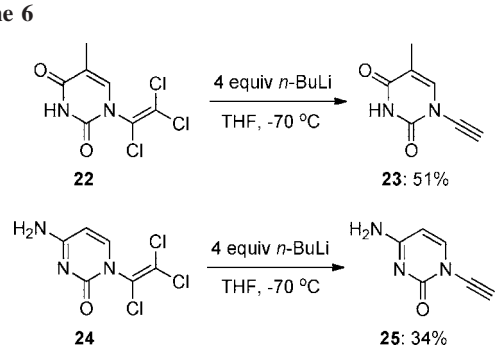
Zemlicka[37] prepared several ynamines/ynamides derived from nucleic acid bases (Scheme 6). Chloroenamines **22** and **24** were prepared in ~20% yield from their respective deprotonated 2-pyrimidinones and tetrachloroethylene. Treatment of **22** and **24** with *n*-BuLi at −70 °C afforded the respective ynamides **23** and **25** in 34−51% yields.

Brückner[38] published a facile elimination protocol via formamides (Scheme 7). Intermediate formamides **27** could be accessed from tosyl amides **26** via coupling reactions with formyl benzotriazole **29**. Alternatively, **27** could be prepared from formamides **28** and alkyl mesylates. Treatment of **27** with CCl_4 and PPh_3 leads to β,β-dichloroenamides **30**, and subsequent elimination with *n*-BuLi afforded various *N*-alkyl, phenyl ynamides **31** in generally excellent yields over two steps in a homologous Corey−Fuchs manner. Brückner also described that the reactions of **27** with CBr_4/PPh_3 were not satisfactory, as the corresponding β,β-dichloroenamides gave mixtures of the desired ynamides **31** and the starting tosylamides **26**.

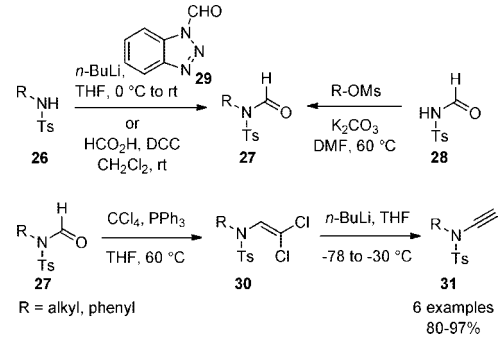
Scheme 5



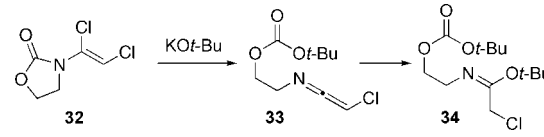
Scheme 6



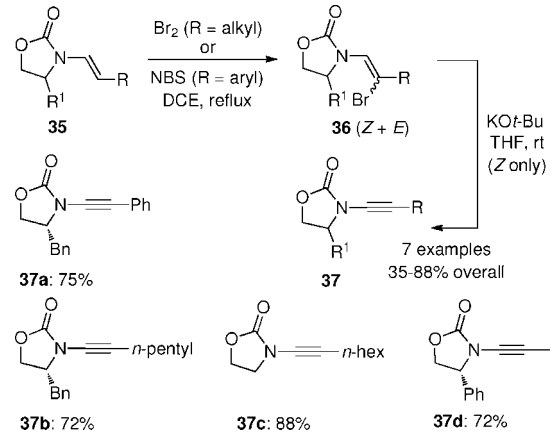
Scheme 7



Scheme 8



Scheme 9



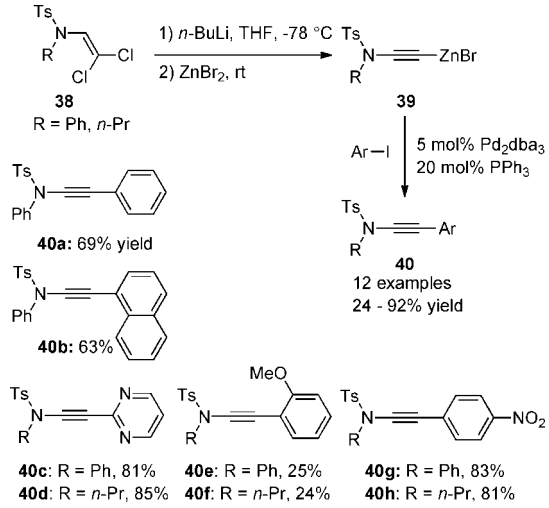
Hsung[35] described an attempt to prepare ynamides via the elimination of α,β-dicholoenamides **32** (Scheme 8); however, the only isolated product was **34**, which presumably resulted from the attack of KO*t*-Bu on chloroketenimine **33**.

In the same article, Hsung disclosed the successful preparation of ynamides **37** via elimination (Scheme 9). It was found that, by either refluxing enamides **35** (R = alkyl) with bromine or refluxing enamides **35** (R = aryl) with NBS in 1,2-dichloroethane (DCE), the desired β-bromoenamides **36** could be isolated in good yields. Subsequent treatment of the *Z*-bromoenamides with KO*t*-Bu afforded ynamides **37** in moderate to excellent yield. The ynamides were found to be quite stable to hydrolysis and could survive silica gel chromatography. It should be noted that while the brominations of **35** typically gave **36** with various *E*/*Z* ratios (1:8 to 1.5:1), efforts to prepare ynamides from *E*-**36** were not successful.

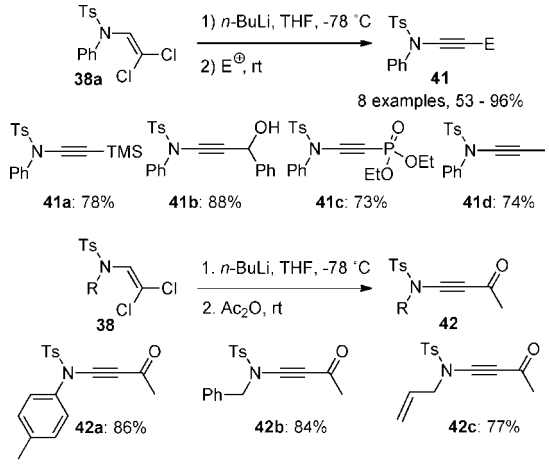
An improved and extended protocol for the elimination process was reported by Saá[39] (Scheme 10). After the treatment of β,β-dichloroenamides **38** with *n*-BuLi, transmetalation with $ZnBr_2$ led to the intermediate zinc acetylide **39**, and a subsequent one-pot Negishi coupling of **39** with various aryl iodides gave the desired ynamides **40** in moderate to excellent overall yields.

The same group later reported a different method for the synthesis of disubstituted ynamides[40] (Scheme 11). It was found that, after the *n*-BuLi mediated elimination of dichlo-

Scheme 10



Scheme 11



roenamides **38**, the corresponding lithium acetylide could be quenched with various electrophiles to afford ynamides **41** and **42**.

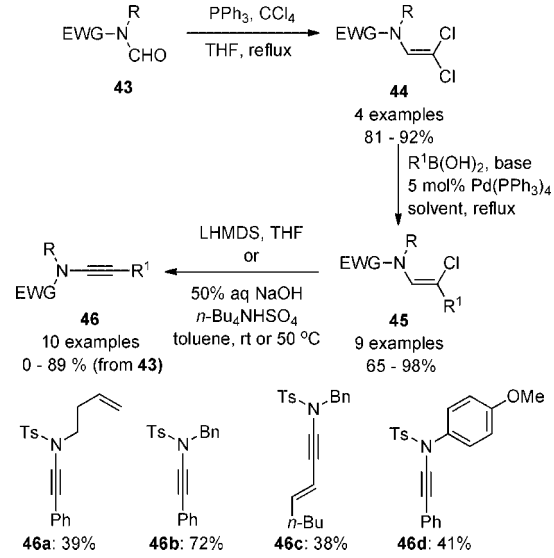
An alternative construction of the key C−C bond in ynamides was published by Cossy.[41] *N*-Formamides **43** were transformed into β,β-dichloroenamides **44** following Brückner's procedure (Scheme 12). Instead of direct elimination of **44** as done by Saá, Cossy reported that Suzuki−Miyaura coupling reactions of **44** with various boronic acids gave (*E*)-β-chloroenamides **45**, which underwent elimination in the presence of LHMDS or NaOH/*n*-Bu_4NHSO_4 to yield ynamides **46**.

2.3. Alkynyliodonium Salts

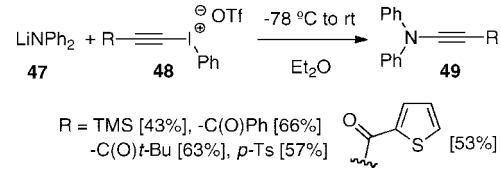
The method involving the reaction of alkynyliodonium salts **48** with lithiated amine **47** was first described in Stang's pioneering work[42] for the synthesis of ynamines **49** (Scheme 13). It is presumed that a vinylcarbene is first generated via nucleophilic addition β to the iodine followed by a 1,2-shift forming the acetylide. This transformation is discussed in more detail below and has proven to be an excellent protocol for synthesizing sulfonyl-substituted ynamides.

In the study of the inter- and intramolecular addition/cyclization of sulfonamide anions with alkynyliodonium triflates, Feldman[43] found that when more electrophilic iodonium triflates **51** and **54** were used, chiral ynamides **52** and **55** were isolated in moderated yields instead of the

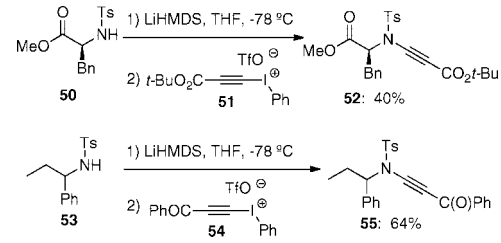
Scheme 12



Scheme 13



Scheme 14



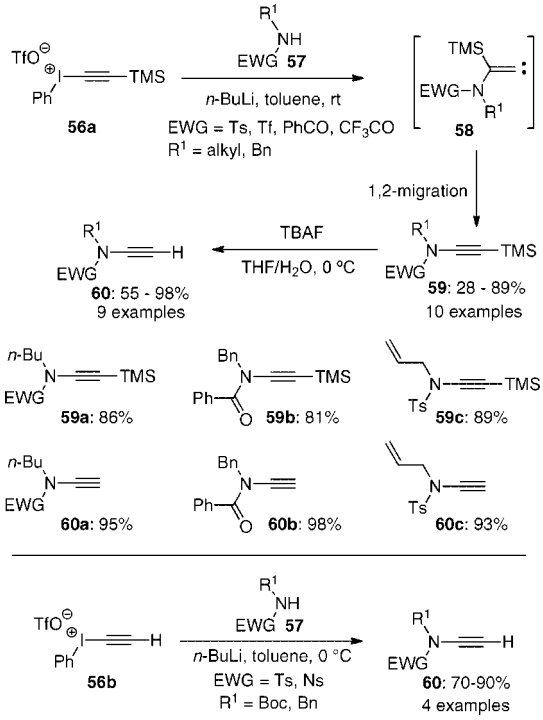
originally desired 1,5-C-H insertion products, representing the first successful synthesis of chiral ynamides (Scheme 14).

Witulski[44] reported a more detailed discussion on the 1,2-migration after *in situ* formation of carbenes **58**. They also discussed the effect of steric hindrance of amides **57** in this methodology for the preparation of ynamides (Scheme 15). A variety of ynamides **59** were obtained in up to 89% yield, with lower yields observed in the cases when *a*-branched amides were used, reflecting an increase of steric hindrance in the nucleophilic addition of **57** to **56**. Upon the treatment of ynamides **59** with TBAF, terminal ynamides **60** could be obtained in good to excellent yields. In their later study, it was found that terminal ynamides could also be synthesized directly by using ethynyliodonium triflate **56b**.

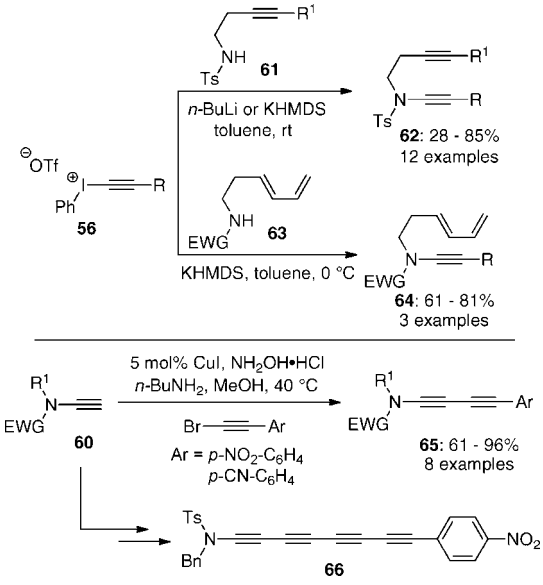
Some highly functionalized ynamides[45] such as **62** and **64** were also generated via this route in variable yields (Scheme 16). These ynamides were poised for metal-catalyzed intramolecular cycloaddition reactions. More recently, it was reported that the conjugated polyynes **65** or **66** could be synthesized via the same route as shown in Scheme 16 followed by a Cadiot−Chodkiewicz cross coupling reaction.

Rainier[46] synthesized three yne-ynamides **69** with different tether lengths using this iodonium triflate strategy (Scheme 17). The ring-opening of aziridine **68** by lithium trimethyl-

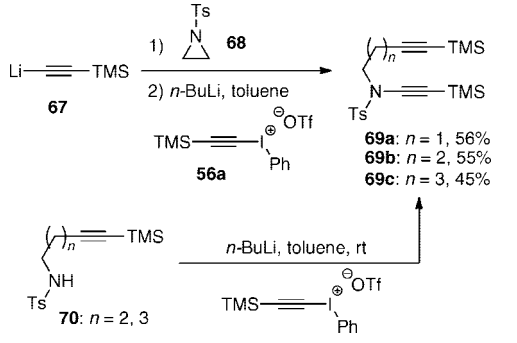
Scheme 15



Scheme 16

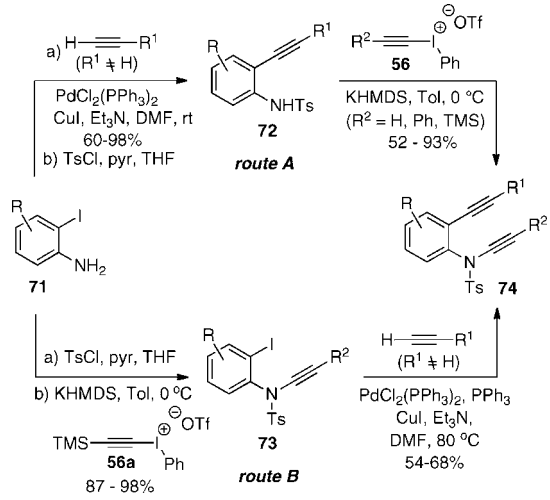


Scheme 17

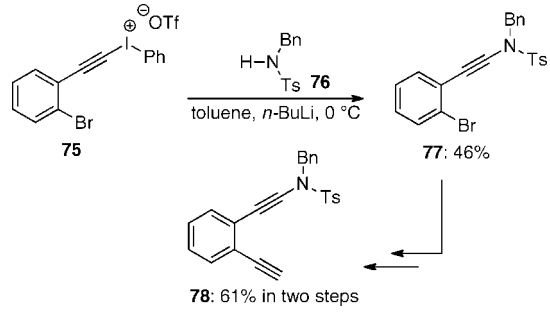


silyl acetylene **67** provided the nitrogen nucleophile for the synthesis of diyne **69a**.

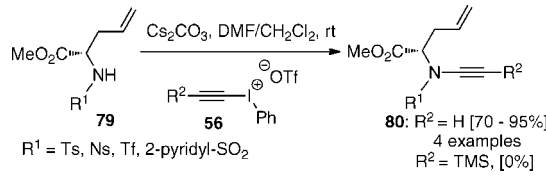
Scheme 18



Scheme 19



Scheme 20



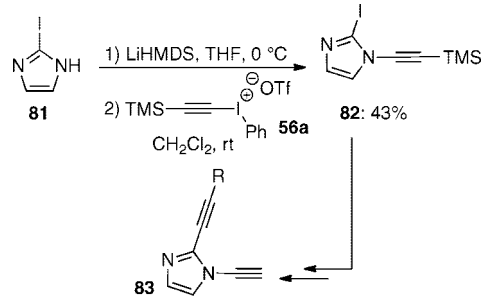
In the study of inter- and intramolecular alkyne cyclotrimerizations, Witulski[47] reported the preparation of other functionalized diynes **74** via two sequences from aniline **71** as shown in Scheme 18. If the Sonogashira coupling reaction was introduced after the ynamide formation (route B), higher reaction temperature was required, probably due to the increased steric hindrance in the intermediate **73**.

König[48] also synthesized ynamide **78** as a target for their study of cyclizations. The reaction of iodonium salt **75** with amide **76** produced ynamide **77**, which was followed by Sonogashira coupling and subsequent desilylation to give ynamide **78** in good overall yield (Scheme 19).

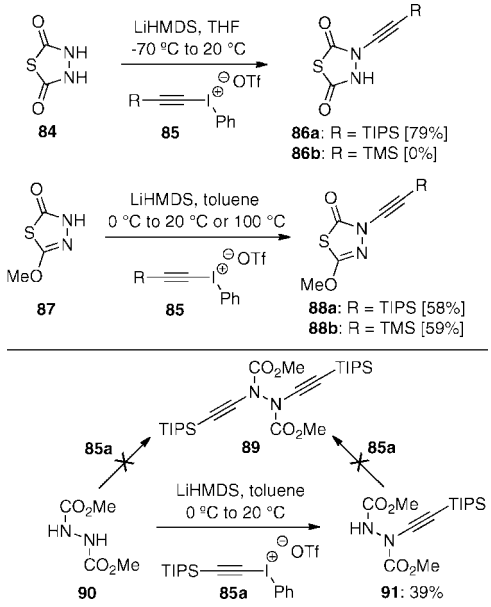
In 1999, Witulski[49] published their results for the synthesis of chiral α-branched ynamides **80** using a similar route. The reaction was only effective when ethynyl(phenyl)iodonium triflate **56b** (R^2 = H) was used (Scheme 20). Lack of reactivity was observed if more sterically hindered iodonium triflate **56a** (R^2 = TMS) was used, which is consistent with their previous results for low yields of achiral ynamides **61** when the α-position of amides is hindered. The increased steric hindrance inherent in α-branched amino acid derivatives **79** interferes with the nucleophilic addition of the amide nitrogen to the *β*-carbon of the alkyne.

The synthesis of 1,2-dialkynylimidazoles **83** was reported by Kerwin,[50] in which the ynamide **82** was synthesized as a

Scheme 21



Scheme 22



common intermediate through the reaction of **56a** with 2-iodoimidazole **81** (Scheme 21).

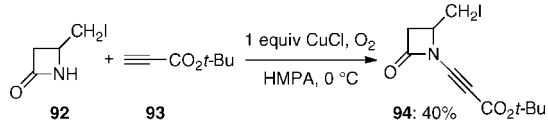
Diederich[51] tried to synthesize azoacetylenes via protected 1,2-bis-ynamides. However, it was found that while the preparation of mono ynamides such as **86a** and **88** was successful, the second ynamide formation via similar chemistry failed (Scheme 22). Hydrazodicarboxylates such as **90** also failed to produce the desired bis-ynamide **89**.

2.4. Amidative Cross-Coupling

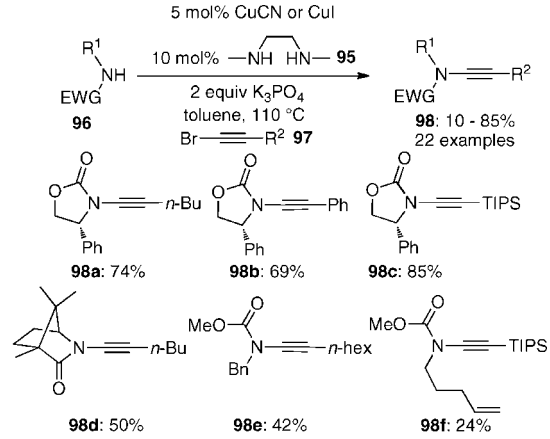
The first synthesis of ynamides using metal-mediated reactions was discovered by Balsamo and Domiano[52] in 1985. The authors attempted to react the copper-acetylide of **93** with amide **92** with an intention to displace the iodine of **92**; however, **94** was found to be the only product and its structure was confirmed by X-ray crystallographic analysis (Scheme 23). It is noteworthy that a stoichiometric amount of CuCl was required in this reaction.

In 2003, Hsung[53] published the first copper-catalyzed ynamide formation reaction, which provided the first direct and atom-economical entry to various ynamides (Scheme 24). In this process 5 mol % CuCN or CuI was used as the catalyst and 10 mol % DMEDA (*N*,*N*′-dimethylethylenediamine) was used as the ligand. The reaction between amides **96** and alkynyl bromides **97** occurs in refluxing toluene in the presence of K_3PO_4 as the base. A wide range of substrates, including oxazolidinones and lactams, were found to be effective substrates and gave corresponding ynamides **98** in good to excellent yields. However, the reactions with imidazolidinones and sulfonamides gave unsatisfactory results. The authors suggested that the course of the catalytic cycle is related to the process proposed by Buchwald[54] for the *N*-arylation of amides.

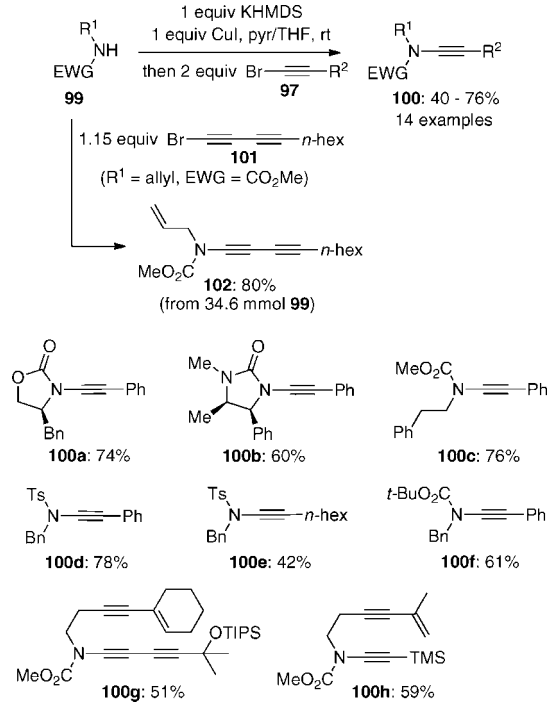
Scheme 23



Scheme 24

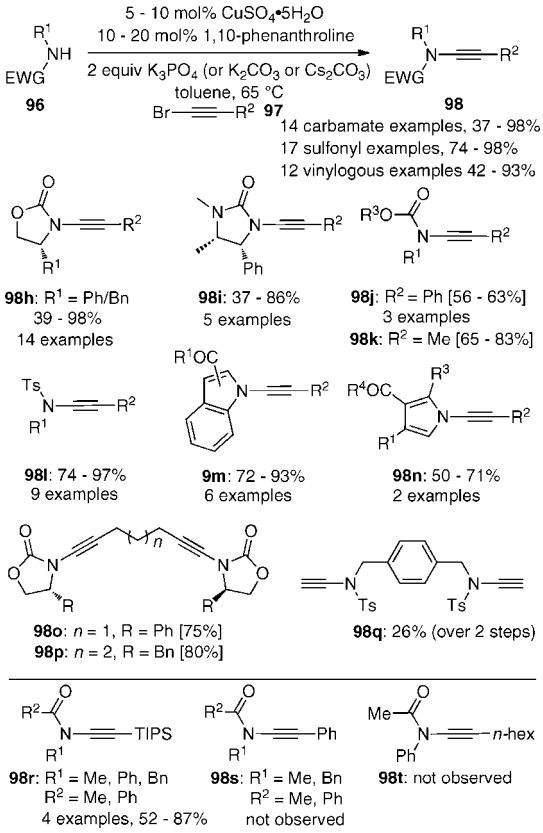


Scheme 25



In the same year, Danheiser[55a] reported a general method for the synthesis of ynamides via copper-mediated coupling of amides with alkynyl bromides. The process involves the conversion of amide substrates **99** to their copper derivatives before the addition of alkynyl bromides **97**. Although a stoichiometric amount of CuI was necessary, the reaction proceeded at room temperature, and in almost all cases the desired ynamides **100** were isolated in good to excellent yields (Scheme 25). The coupling reaction could be conveniently carried out at gram scale to give ynamide **102** in excellent yield.[55b] Preparation of more complex substrates

Scheme 26



such as **100g** and **100h** could also be accomplished in synthetically useful yields.[55c,d]

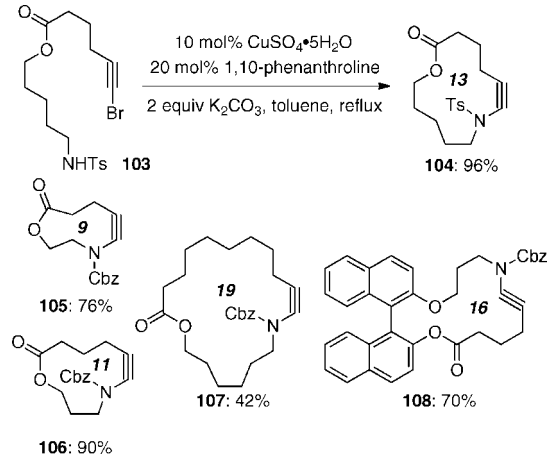
Subsequently, Hsung[56] disclosed an improved, more practical copper-catalyzed cross-coupling process of amides with alkynyl bromides. The new catalyst system applied inexpensive $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline as ligand (Scheme 26) and compares quite favorably with the original CuCN catalyst system, as (1) the new system could be used for a large variety of substrates, including previously unreactive substrates such as sulfonamides and imidazolidinones, and (2) the reaction temperature could be as low as 60 °C, minimizing ynamide decomposition. It was found that the new process could be carried out conveniently at 100 mmol scale and consistently gave excellent yields.[56c] One limitation for Hsung's system is that the coupling conditions were not effective for the preparation of several simple ynamide substrates such as **98s** or **98t**.[56d]

This process was equally effective for intramolecular amidation reactions. As shown in Scheme 27, intramolecular coupling was successfully applied to the synthesis of several unique macrocyclic ynamides **104**−**108** that contain up to a 19-membered ring system.

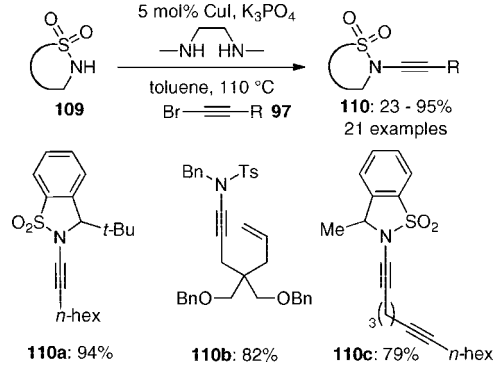
A modified Cu(I)-catalyzed process was described by Urabe[57] for the coupling of sulfonamide **109** employing CuI and DMEDA (Scheme 28), Another interesting modification of Hsung's system was described by Skrydstrup,[58] who discussed in detail about the water content of potassium phosphate and its effect in this $CuSO_4$ catalyzed coupling reaction.

Kerwin[59] published a copper-catalyzed coupling of bromoalkynes **97** with imidazoles **111**, which provided access to novel *N*-alkynylimidazoles **112** (Scheme 29). The authors mentioned that diamine ligands such as 1,10-phenanthroline or DMEDA were not effective. In contrast, a catalyst system

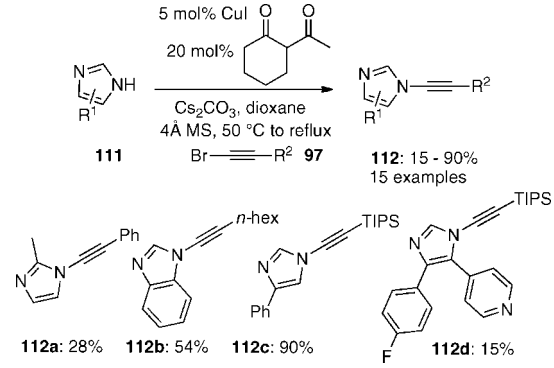
Scheme 27



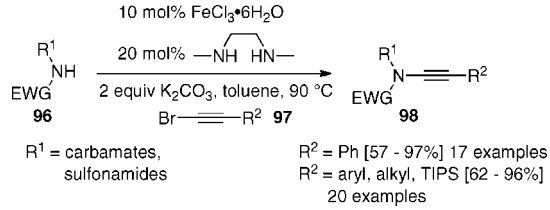
Scheme 28



Scheme 29



Scheme 30

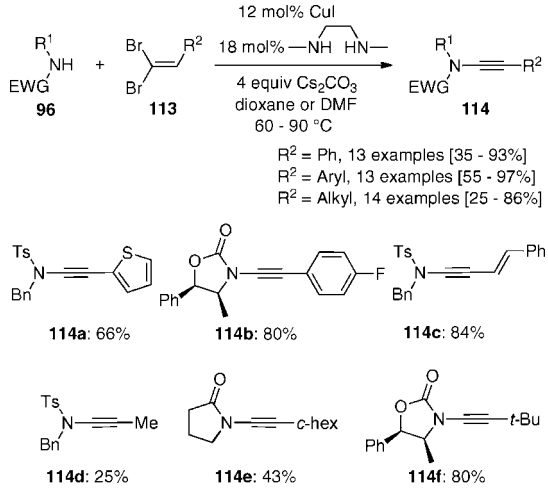


that utilized CuI and using 2-acetylcyclohexanone as the ligand produced the desire products in variable yields.

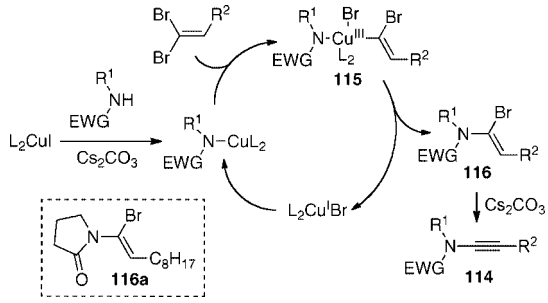
The first iron-catalyzed coupling of amides and alkynyl bromides was recently published by Zhang.[60] It was demonstrated that $FeCl_3 \cdot 6H_2O$, as an inexpensive, environmentally benign alternative to copper salt, was an equally efficient and practical catalyst for ynamide synthesis (Scheme 30).

More recently, Evano[61] documented the direct synthesis of ynamides **114** from 1,1-dibromo-1-alkenes **113**. A com-

Scheme 31



Scheme 32



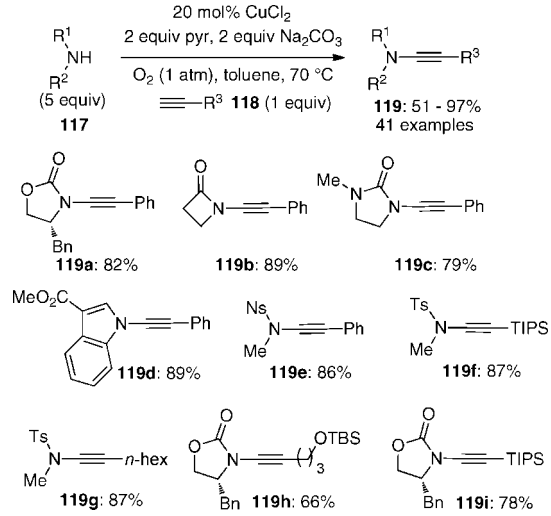
bination of CuI and DMEDA was found to be the best catalyst system for the reaction between **96** and **113**, and Cs_2CO_3 was the optimal base (Scheme 31).

A plausible mechanism is illustrated in Scheme 32. The authors described that (1) a regioselective coupling of the amide and dibromide would produce **115** as a result of the known higher reactivity of the *trans* C−Br bond toward oxidative addition[62] and (2) Cs_2CO_3 mediated elimination of **116** would produce **114**. This step is supported by the fact that an isolated sample of **116a** could be converted to the corresponding ynamide by reaction with only Cs_2CO_3 via E2 elimination.

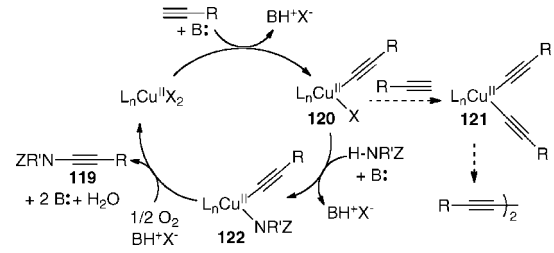
Continuing with the work started by Balsamo, Domiano, and Peterson, *vide supra*, Stahl[63] reported the first copper-catalyzed aerobic oxidative amidation of terminal alkynes. An extensive screening of various Cu sources, Brønsted bases, and solvents led to the optimal conditions shown in Scheme 33. It was found that a wide range of nitrogen nucleophiles **117** and alkynes **118** could be used, and in most cases the desired ynamides **119** were isolated in good to excellent yields. The only shortcoming of this system lies in the fact that 5 equiv of amide was necessary to achieve satisfactory yields.

Stahl[63] proposed a mechanism that involves sequential activation of the alkyne and amide, followed by reductive elimination and regeneration of Cu(II) catalyst via aerobic oxidation (Scheme 34). The authors rationalized that an intermediate **120** may be involved in two possible pathways. The desired formation of the mixed Cu(II)-(alkynyl)(amidate) species **122** was expected to compete with the undesired formation of bis-alkynyl-Cu(II) species **121**. These two pathways thus rationalize the necessity to use an excess amount of amide nucleophile.

Scheme 33



Scheme 34



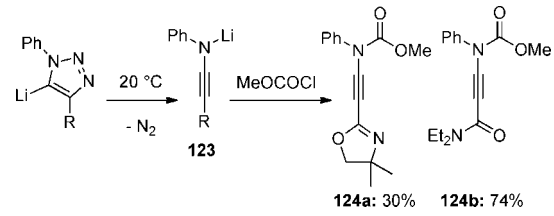
2.5. Other Methods

Gilchrist[64] demonstrated in 1991 that ynamides **124** could be constructed by the electrophilic trapping of lithiated ynamines **123** generated by decomposition of 1,2,3-triazoles with chloroformate (Scheme 35).

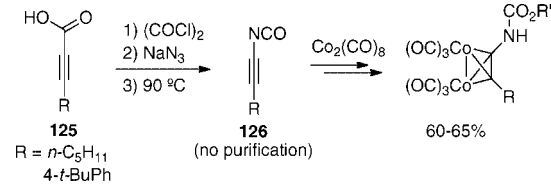
Chen[65] synthesized a variation of ynamides known as alkynyl isocyanates. Two isocyanates **126** were prepared from alkynoic acids **125** (Scheme 36) and were directly protected with octacarbonyl dicobalt without purification before further manipulation. The yields were estimated based on the isolation of the protected alkynylcarbamates.

In a manner similar to Gilchrist's previous work,[64] Masson[66] reported that treatment of *S*-methyl-α-(trimethylsilyl)-ethanimidothiolate **127** with *n*-BuLi led to the formation of *β*-lithiated-*β*-silylated ketenimine **128a** (Scheme 37), which is in equilibrium with *N*-lithiated ynamine **128b**.

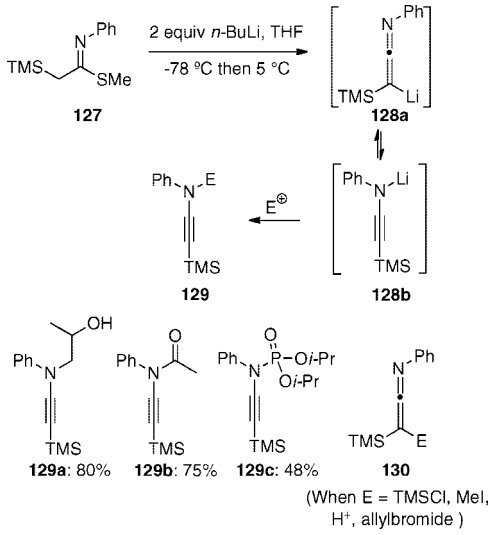
Scheme 35



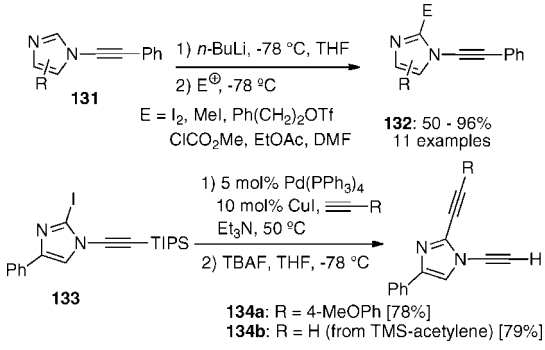
Scheme 36



Scheme 37



Scheme 38



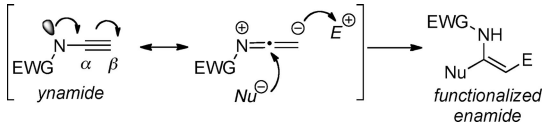
Intermediate **128a** could be selectively protonated, methylated, or allylated, yielding ketenimines **130**. However, if the lithiated intermediate was treated with more reactive electrophiles such as excess propylene oxide, acetyl chloride, or diisopropyl chlorophosphate, the reaction would favor the nitrogen addition to give ynamines or ynamides **129**.

A recent paper by Kerwin[67] described their efforts on the functionalization of imidazoles **131** at the 2-position (Scheme 38). Their optimized condition allows a successful deprotonation/lithiation strategy on imidazoles with an adjacent *N*-alkynyl substituent to give more functionalized ynamides **132**. When substrate **133** was subjected to a Sonogashira coupling and desilylation to demonstrate the utility of their strategy, 1,2-dialkynylimidazoles **134** could be obtained in good yields.

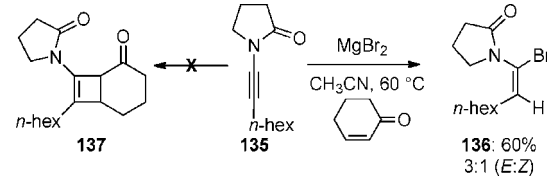
3. Reactions of Ynamides

3.1. Addition Reactions

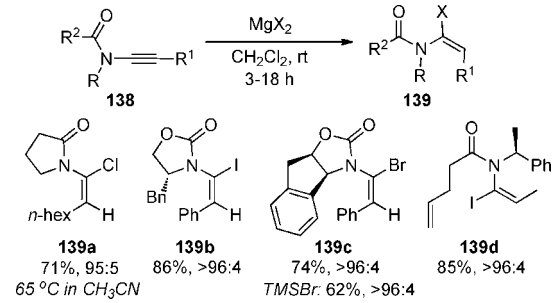
The unique nature of ynamides allows for the regioselective addition of electrophiles or nucleophiles onto the ynamide due to the electron-donating ability of the nitrogen.



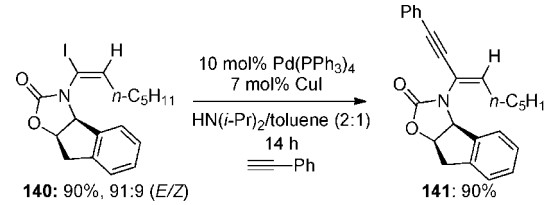
Scheme 39



Scheme 40



Scheme 41



3.1.1. Addition of Heteronucleophiles

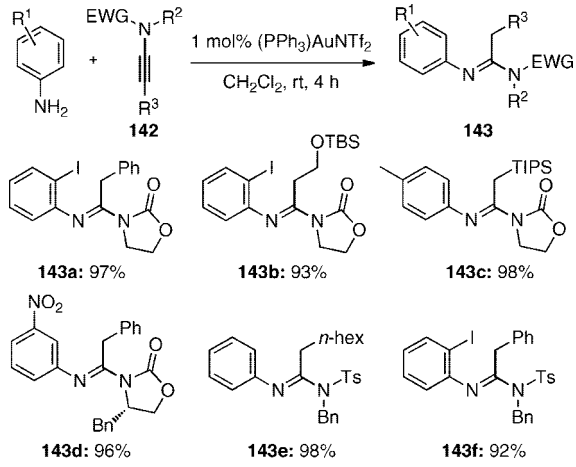
Heteroatom nucleophiles have played a significant role in the addition to ynamides, leading to complex heterocycles as well as providing a route to cross-coupling precursors. In 2003, Hsung[68] reported a highly stereoselective preparation of chiral α-haloenamides via an unexpected hydrohalogenation of ynamides. While attempting to facilitate a Lewis acid-mediated [2 + 2] cycloaddition of ynamide **135** using magnesium salts, the authors obtained α-haloenamide **136** as a 3:1 mixture of *E*/*Z* isomers instead of the desired cycloadduct **137** (Scheme 39). The reaction was highly regioselective, as no *β*-haloenamide was found.

Further optimization found that various magnesium salts in CH_2Cl_2 gave high yields and excellent diastereoselectivity for the (*E*)-α-haloenamide at ambient temperature. As shown in Scheme 40, a number of cyclic and acyclic chiral ynamides **138** gave the corresponding α-haloenamide **139** with *E*/*Z* ratios of ≥96:4 in almost all cases. It is noteworthy that the use of TMSBr also provided **139c** in good yield as a single *E*-isomer; however, attempts to extend this system to include TMSCN and TMSOTf failed. The stereochemistry suggests a *syn*-addition of HX generated from trace amounts of water with the magnesium salt. This was supported by the observation that freshly prepared $MgBr_2$ in distilled CH_2Cl_2 gave a much slower conversion rate for the hydrohalogenation compared with the same reaction run in "wet" CH_2Cl_2 out of a bottle.

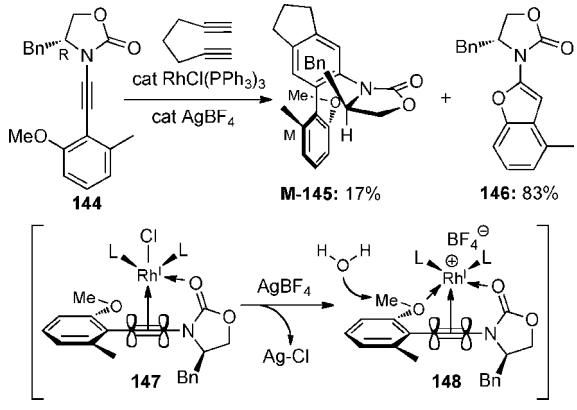
The authors were able to further demonstrate the utility of these α-haloenamides in a Sonogashira coupling reaction (Scheme 41). The α-haloenamide **140** was coupled with phenyl acetylene to give chiral enyne **141**, which could be useful in a number of other applications.

A gold-catalyzed hydroamination of ynamides was recently reported by Skrydstrup[69] for the formation of amidine

Scheme 42



Scheme 43



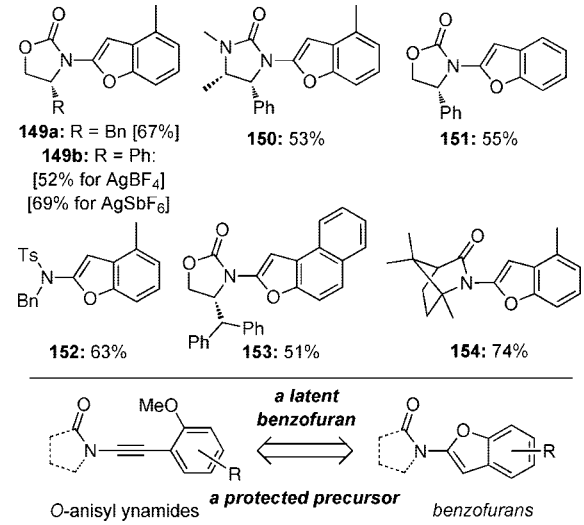
products and their application toward indole synthesis (Scheme 42). Nucleophilic addition of aniline derivatives onto substituted ynamides under mild conditions using the Gagosz catalyst[70] provided amidine products **143** in excellent yields. Cyclic and acyclic ynamides were tolerated with various substituents on the terminal position. Several of the amidines were further used in indole synthesis via Pd(0)-catalyzed ring closure.

Other metals have also been shown to catalyze the addition of heteronucleophiles to ynamides. In Hsung's[71] research using rhodium to catalyze a [2 + 2 + 2] cycloaddition of aryl-terminated ynamides, *vide infra*, silver salts were employed as a key additive to enhance the catalytic efficiency. However, the use of $AgBF_4$ led to a surprisingly different reaction pathway in a tandem Rh(I)-catalyzed demethylation−cyclization of *o*-anisyl ynamides **144**, giving benzofuran **146** as the major product instead of the desired chiral biaryl *M*-**145** (Scheme 43).

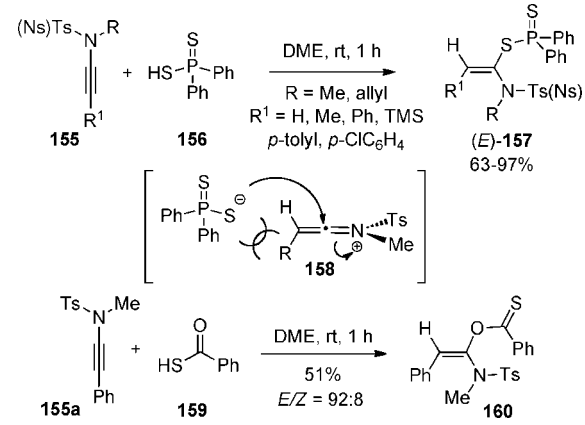
Although the reason for this interesting counteranion effect is unclear, the use of other silver salts also led to benzofuran product in the absence of any diyne. It is reasonable to suggest that the demethylation involves only the cationic rhodium complex **147**, which could possess additional coordination sites for a bidentate complexation with the *o*-methoxy oxygen after being stripped of the ligand present in complex **148**.

Essentially, this methodology allowed *o*-anisyl ynamides to serve as protected benzofuran precursors. Using these conditions, the authors were able to construct a variety of functionalized benzofurans, as shown in Scheme 44.

Scheme 44



Scheme 45

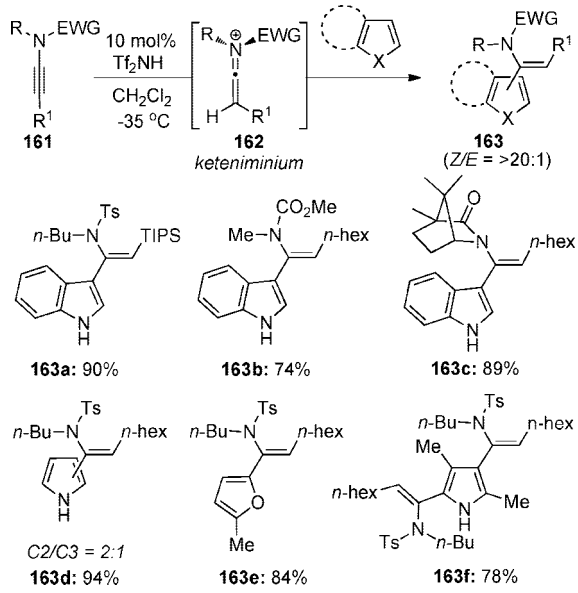


The addition of sulfur nucleophiles to ynamides has been demonstrated by Oshima and Yorimitsu,[72] leading to interesting *N*,*S*-acetal derivatives (Scheme 45). The hydrothiolation of sulfonyl-ynamides **155** with diphenyldithiophosphinic acid **156** led to (*E*)-alkenyl thioesters **157** as single isomers. Deuterium studies suggest the formation of a reactive keteniminium intermediate **158**, whereby addition of the dithiophosphinate anion from the less hindered face leads to the observed (*E*)-isomer. Furthermore, treatment of ynamide **155a** with thiobenzoic acid **159** led to the *O*-addition product **160** while the use of benzenethiols or alkyl thiols as nucleophiles gave no reaction, suggesting the acidity of nucleophiles is important.

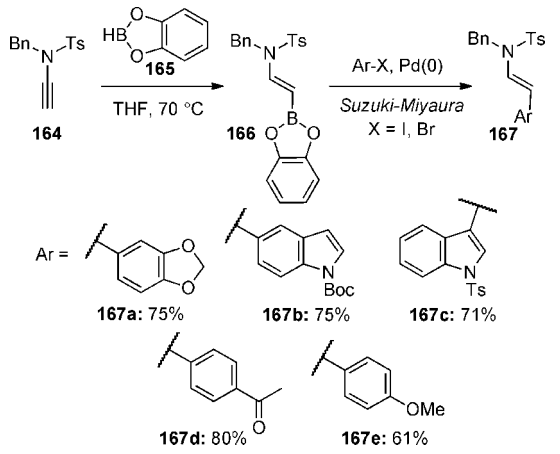
3.1.2. Hydroarylation

Zhang[73,74] has reported a mild Brønsted acid-catalyzed addition of indoles and other heterocycles as an equivalent process to the hydroarylation of ynamides. As shown in Scheme 46, various sulfonyl-substituted ynamides as well as carbamate- and *aza*-camphor-derived ynamides could be coupled with indoles, furans, and pyrroles, giving hydroarylation products **163** in good yields and with high regio- and stereoselectivities favoring the *Z*-isomer. Trifluoromethanesulfone imide (Tf_2NH) proved to be the optimal catalyst for protonation of ynamide **161** to give the reactive keteniminium ion **162**, while platinum and palladium catalysts as well as sulfonic acids were ineffective.

Scheme 46



Scheme 47



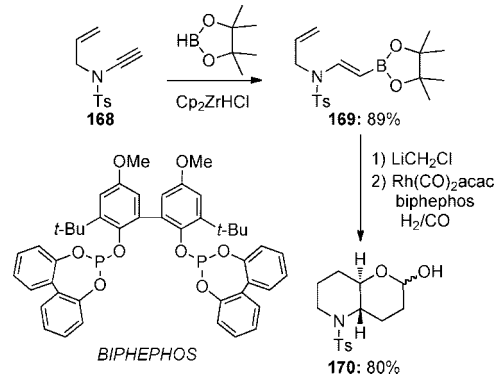
It was noted that no protecting groups were necessary on the indole or pyrrole nitrogen atom and strong electron-withdrawing carbonyl or sulfonyl groups actually led to no desired product formation. However, electron-withdrawing and electron-donating substituents were tolerated on the aryl ring and divinylation products could be obtained when using excess ynamide. When using unsubstituted pyrroles, a 2:1 mixture of C-2 and C-3 vinylation products **163d** was isolated. This method provides a synthetically useful route utilizing ynamides to gain access to substituted enamides.

In a similar process, Hsung reported an intramolecular variant in a Pictet−Spengler cyclization of ynamides catalyzed by Brønsted acids. This example is included in section 3.3.1.

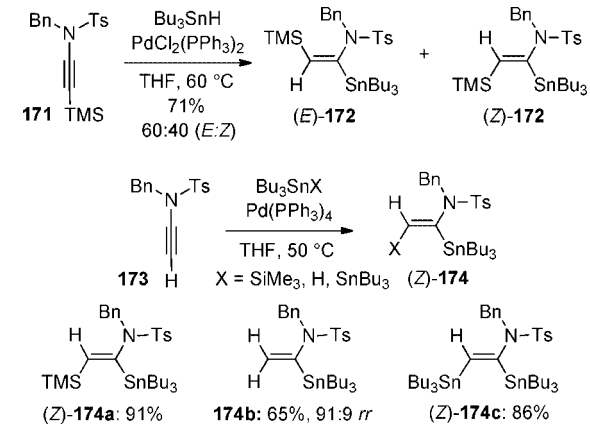
3.1.3. M−H/M−X Additions

The addition of metals to ynamides has allowed for rapid access to a variety of highly functionalized enamides which can be useful in a number of applications and especially in the area of cross-coupling reactions. In 2000, Witulski[75] reported the first hydroboration of *N*-sulfonyl ynamide **164** utilizing catecholborane, giving *E*-vinylborane **166** as the only stereo- and regioisomer (Scheme 47). However, due to the instability and difficulty in isolating the hydroboration product, a one-pot hydroboration/Suzuki−Miyaura coupling

Scheme 48



Scheme 49



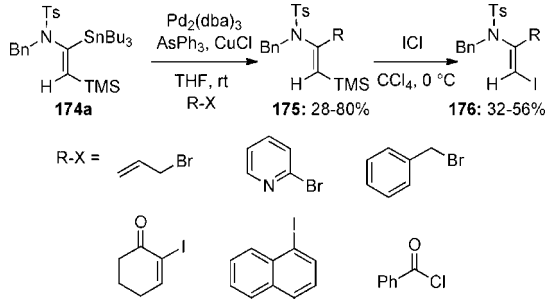
procedure was developed with aryl and indolyl halides as coupling partners, leading to various β-substituted enamides **167**.

Hoffmann[76] was also able to successfully demonstrate a zirconocene-catalyzed hydroboration of ynamide **168** with pinacolborane to generate vinyl boronate **169** in 89% yield (Scheme 48). Further homologation followed by a domino hydroformylation−allylboration−hydroformylation sequence gave the lactol **170** as a 1:1 mixture of anomers. Both hydroboration methods allow for exclusive formation of β-substituted enamides, as addition to the ynamide occurs regioselectively.

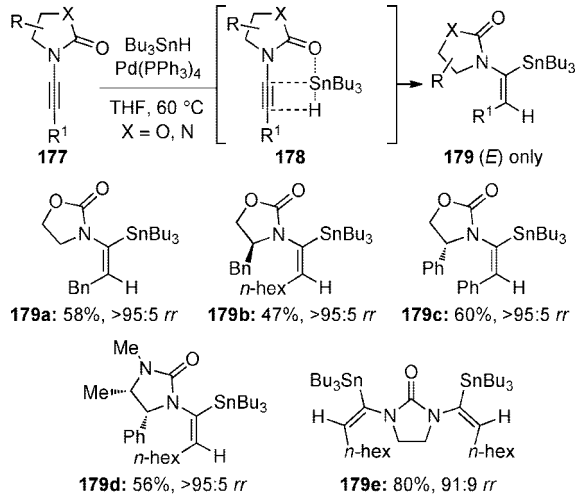
A complementary approach was developed by Cintrat[77] through a palladium-catalyzed hydrostannation of ynamides, thereby gaining access to α-substituted enamides. The first attempt at the hydrostannation of silyl-protected ynamide **171** led to a mixture of (*E*)- and (*Z*)-enamides **172** (Scheme 49). However, the use of terminally unsubstituted ynamide **173** allowed for a facile synthesis of only the (*Z*)-silylstannylated product **174**. The hydrostannation product **174b** was obtained as a 91:9 mixture of regioisomers in favor of the α-stannylated product. The authors also reported significant protodestannylation of the β-isomer when the mixture was subjected to column chromatography.

Furthermore, it was shown that the α-stannylated enamides could be selectively functionalized to give a wide array of products[78] (Scheme 50). Using a modified Stille coupling procedure, a variety of acyl, allyl, and aryl halides could be coupled with silylstannylated enamide **174a** to selectively functionalize the α-position. Iododesilylation at the β-position would then allow for further diversity in the formation of disubstituted enamides **176**. It was noted that, in the absence

Scheme 50



Scheme 51

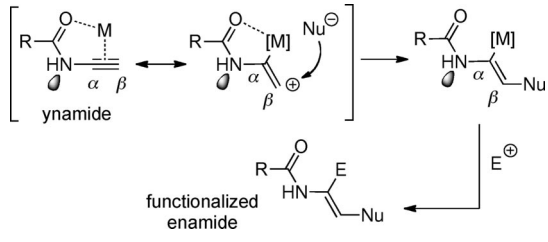


of the silicon group, heating was necessary for complete conversion of the Stille coupling.

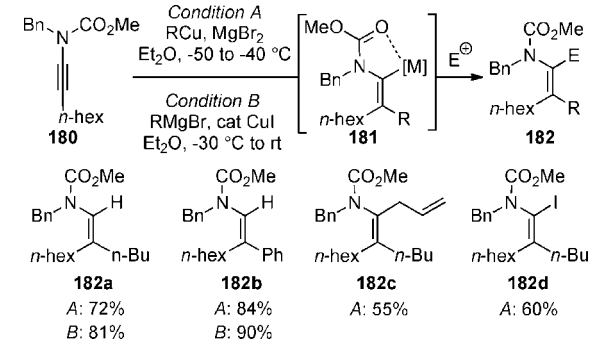
Cintrat[79] later reported an α-selective hydrostannation of terminally substituted ynamides. They found that use of cyclic amide-derived ynamides **177**, specifically with oxazolidinone or imidazolidinone moieties, gave the best selectivity for the α-stannylated enamide **179**, presumably through an intermolecular chelation of the carbonyl oxygen to tin, as shown in **178** (Scheme 51). The hydrostannation worked with a variety of terminal substituents as well as chiral and achiral auxiliaries, giving high regioisomeric ratios (*rr*) in favor of the α-stannylated product with little or none of the (*Z*)-isomer.

3.1.4. Umpolung-Type Additions

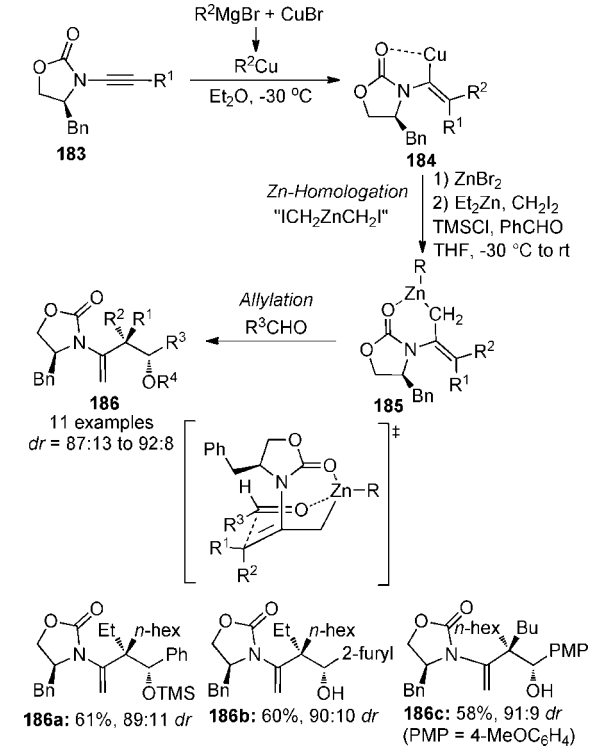
Much of the earlier chemistry involving ynamides has taken advantage of the electron-donating ability of nitrogen for the regioselective addition of nucleophiles and electrophiles to the α- and β-carbons of ynamides, respectively. More recently, several groups have focused on "umpolung-type" additions of nucleophiles to ynamides via metal-catalyzed processes, providing a facile entry to the opposite regioisomeric addition products.



Scheme 52



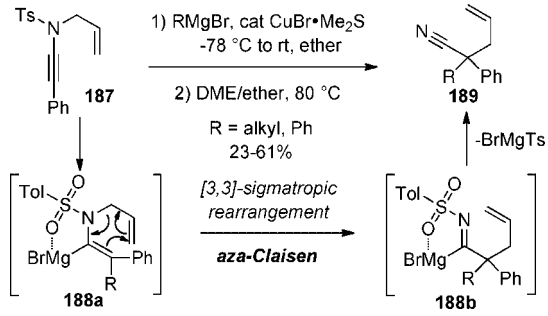
Scheme 53



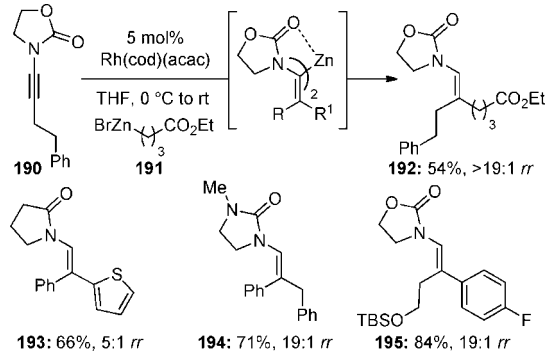
Indeed, the unique nature of ynamides, combining an electron-withdrawing substituent with a chelating moiety, was utilized by Marek[80] in a regiochemically controlled carbometalation of ynamides (Scheme 52). Two sets of conditions could be used in a carbocupration (condition A) or copper-catalyzed carbomagnesiation (condition B) of ynamide **180**. Chelation of the organometal reagent to the carbamoyl moiety controls the regioselective addition of the carbon nucleophile to the β-position. This provides the α-metalated intermediate **181**, which can subsequently be trapped with various electrophiles to give substituted enamides **182**. In general, both conditions gave similar results, with the carbomagnesiation giving slightly higher yields. The carbometalation could also be carried out on *N*-sulfonyl ynamides, although both conditions were slower and required higher temperatures.

Marek[81] further demonstrated the utility of ynamides in an efficient one-pot carbocupration/Zn-homologation/allylation sequence to obtain product **186** with the formation of an all-carbon quaternary stereocenter (Scheme 53). A possible mechanism suggests that, after initial carbocupration with the diethylcuprate, transmetalation of vinyl cuprate intermediate **184** followed by homologation with the

Scheme 54



Scheme 55



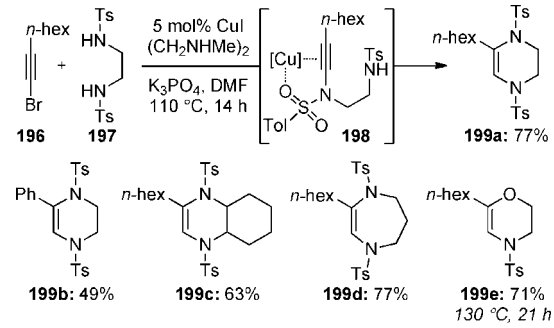
Simmons−Smith−Furukawa[82] zinc carbenoid (generated *in situ*) would give allylzinc species **185**. Subsequent trapping with benzaldehyde then provides the aldol product **186**. Several other aldehydes and organocuprates were also used, giving similar yields and high diastereoselectivities. The absolute stereochemistry of the major isomer of **186** can be rationalized by the Zimmerman−Traxler transition state, in which the benzyl group of the auxiliary shields one face in the chelated six-membered chair conformation.

Oshima and Yorimitsu[83] reported a similar silylcupration and copper-mediated carbomagnesiation of *N*-sulfonyl ynamides followed by an *aza*-Claisen rearrangement (Scheme 54). After the initial carbomagnesiation of ynamide **187**, instead of trapping the α-metalated enamide **188a** with an electrophile, they found that heating the reaction mixture in 1,2-dimethoxyethane (DME) led to 4-pentenyl nitriles **189** via a two-step [3, 3] sigmatropic rearrangement/elimination sequence. While it is unclear whether the elimination occurs before or after the rearrangement, the reaction did not occur with protonated enamides, suggesting the presence of the magnesium metal is essential for the reaction to proceed.

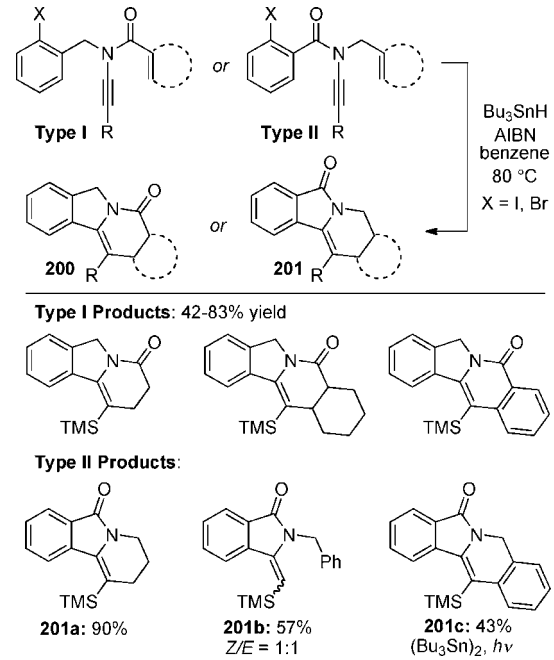
One limitation to these types of carbometalation reactions is the use of Grignard reagents, which limits certain functional groups that can be tolerated on the ynamide. In an effort to improve upon this, Lam[84] recently communicated their efforts on a rhodium-catalyzed carbozincation of ynamides. A representative example is shown in Scheme 55, in which ynamide **190** reacts with alkylzinc bromide **191**, containing an ester moiety yielding the substituted enamide **192**. Using the previous carbometalation conditions with Grignard reagents, the ester functionality would not be tolerated. They were also able to functionalize the vinylzinc intermediate through simple acylations or Negishi couplings.

In addition, nucleophiles other than carbon have been shown to add to ynamides in an umpolung-type manner. In 2008, Urabe[57b] discovered an unexpected copper-catalyzed double amination of 1-bromoalkynes leading to tetrahydropyrazines while attempting an *N*,*N*′-dialkynylation of diamines (Scheme 56). The reaction of bromoacetylene **196** with diamine **197** gave tetrahydropyrazine **199a** using standard coupling conditions at elevated temperatures. Presumably, after the first alkynylation of the sulfonamide, the second amination occurs intramolecularly through a 6-*endo-dig* pathway on the intermediate **198**. The sulfonyl group is thought to play an important role in mediating the *endo*-type pathway through coordination to the copper salt. This method is useful with aliphatic and aromatic acetylenes. Branched 1,2-diamines and 1,3-propanediamines would lead to seven-membered heterocycles, while oxygen nucleophiles require slightly higher temperatures.

Scheme 56



Scheme 57

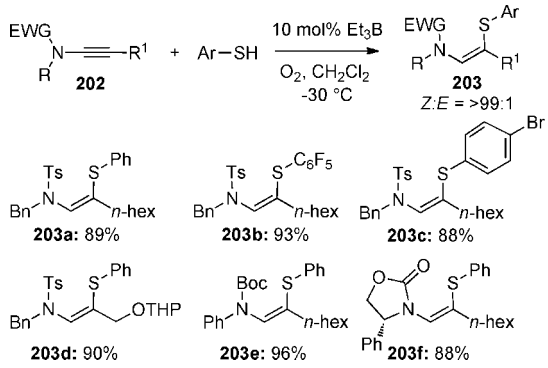


3.1.5. Radical Processes

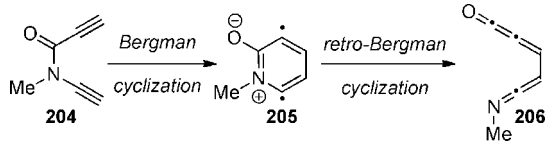
Although only a few radical processes involving ynamides have been reported, they provide another complementary approach toward constructing complex heterocycles and substituted enamides.

Malacria[85] reported a radical cascade reaction of ynamides to gain access to nitrogen heterocycles (Scheme 57). Two types of ynamides were used based on the position of the carbonyl group. The radical cascade occurs through a *5-exo-dig* cyclization followed by a *6-endo-trig* trapping to provide the heterocyclic products. Acyclic or cyclic alkenes could be used with type I (Malacria's classification) ynamides for the *6-endo-trig* radical trapping as well as an aromatic

Scheme 58



Scheme 59



acceptor with varying yields, depending on the rate of hydride addition and the halide used. While simple alkenes also worked for type II ynamides as in **201a**, the cascade reaction was halted after the *5-exo-dig* cyclization when using an aromatic acceptor, giving a 1:1 mixture of the *Z*- and *E*-isoindolinones **201b**. Photolysis of hexa-*n*-butylditin was necessary to obtain the cascade product **201c**, suggesting the carbonyl may have a steric and an electronic effect on the radical trapping.

Yorimitsu and Oshima[86] reported a radical hydrothiolation of ynamides, giving (*Z*)-1-amino-2-thioalkenes **203** (Scheme 58). Cyclic and acyclic ynamides were reacted with various aryl thiols using triethylborane and O_2 as the radical initiator. The reaction is believed to proceed by regioselective addition of the electron-deficient thiyl radical to the more electron-rich 2-position of ynamides **202**. The resulting stereoselectivity for the *Z*-isomer arises from sterics between the terminal substituent and the amide, as smaller terminal substituents led to a mixture of stereoisomers. Furthermore, electron-deficient arenethiols were well tolerated (**203b** and **203c**) while electron-rich arenethiols gave much lower yields, suggesting electron-donation lowers the reactivity of the electrophilic thiyl radical.

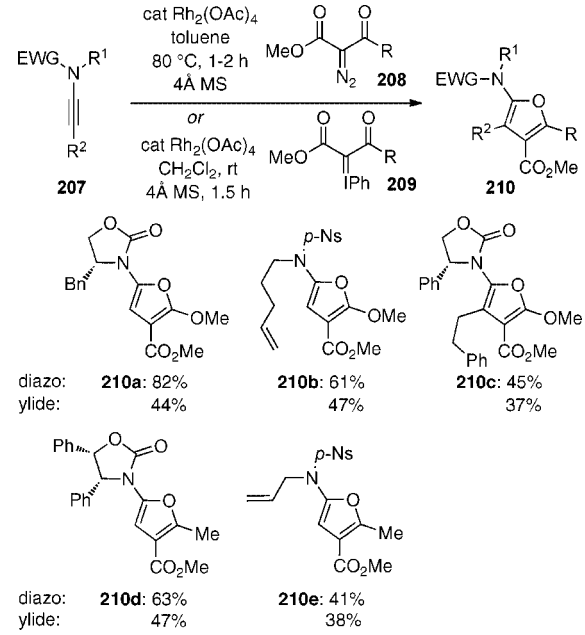
The use of enediynes as potential anticancer drugs is an important area of research because of their ability to cleave DNA through a presumed Bergman cyclization.[87] Kraka and Cremer[88] reported a theoretical investigation of heteroatom-substituted enediynes and the effect on possible Bergman cyclization (Scheme 59). Calculations on ynamide **204** showed very little enediyne character, and the energy barrier for the retro-Bergman cyclization was much lower than that needed for **204** to be useful as a drug candidate.

3.2. Cycloadditions

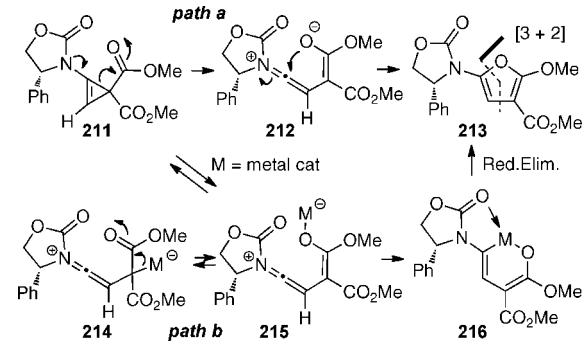
3.2.1. [2 + 1] Cycloadditions

Hsung[89] recently published a Rh(II)-catalyzed cyclopropenation of ynamides, providing facile access to highly substituted 2-amidofurans (Scheme 60). Both diazo dimethyl malonates **208** and phenyl iodonium ylides **209** could be successfully used as the cyclopropenating agent; however, the diazo compounds gave better yields. Unsymmetrical cyclopropenating agents (R = Me) resulted in highly

Scheme 60



Scheme 61



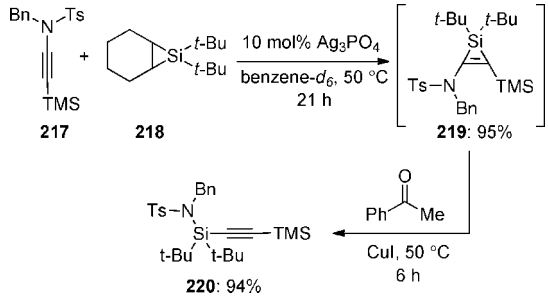
regioselective furan formation. It is noteworthy that this methodology could be applied to terminally substituted ynamides, resulting in tetrasubstituted furans **210**.

The authors suggested that the mechanism for this transformation may proceed through amidocyclopropene **211** formed by a Rh-carbene-mediated [2 + 1] cycloaddition (Scheme 61, path a). Ring-opening of the cyclopropene followed by subsequent ring-closing would yield the observed furan products **213**. Alternatively, **211** may not be involved (path b). Metalloketeniminium **214** could tautomerize to **215** followed by cyclization and reductive elimination to give **213**. Formally, this transformation represents a [3 + 2] cycloaddition.

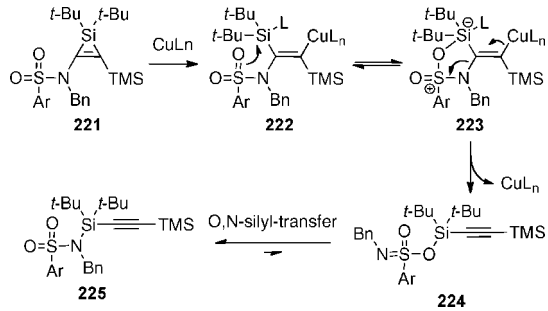
Woerpel[90] found that amido-silacyclopropene **219** could be formed through silver-catalyzed silylene transfer from silacyclopropane **218** to ynamide **217** (Scheme 62). Alternatively, in the presence of CuI and acetophenone, the *in situ* generated silacyclopropene **219** rearranges to alkynylsilane **220** in 94% yield. This silylene transfer may proceed through Cu-mediated ring-opening of **221** to give **222**, which may undergo intramolecular silyl transfer and loss of CuI to generate alkynylsilane **224**. An *O*-to-*N* silyl transfer gives the energetically preferred silyl acetylene **225** (Scheme 63).

Cossy and Meyer[91] reported a novel example of a chemoselective DMDO [methyl(trifluoromethyl)dioxirane] **227** epoxidation of 1,6-ene-ynamide **226** to generate *aza-*

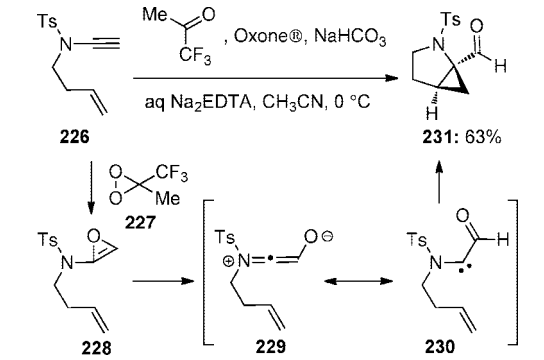
Scheme 62



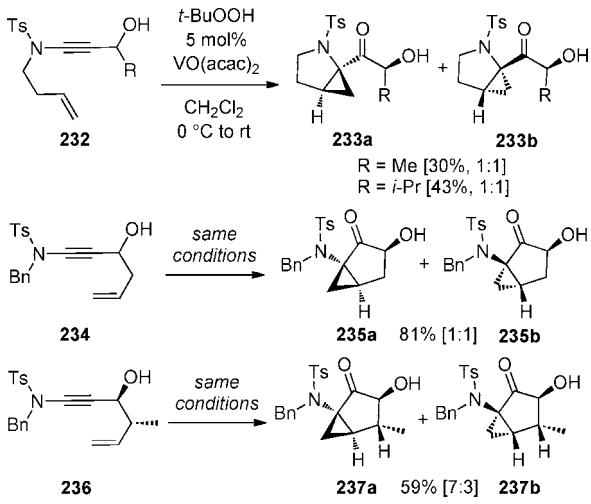
Scheme 63



Scheme 64



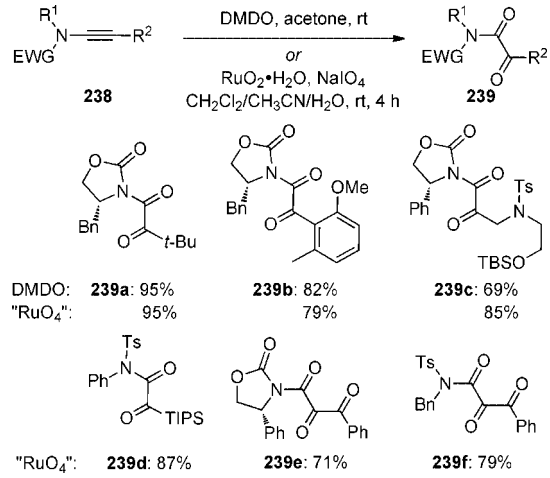
Scheme 65



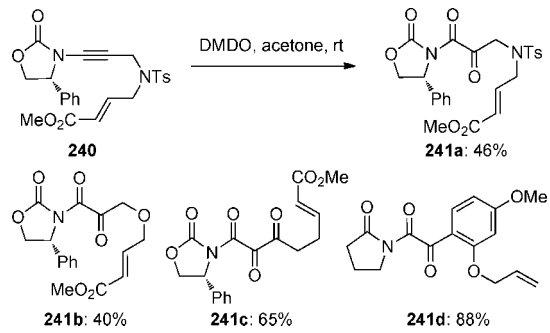
[3.1.0]bicycle **231** through an α-oxocarbene intermediate **229** (Scheme 64).

The above method, however, did not extend well to terminally substituted ynamides (Scheme 65). The authors discovered that the use of *t*-BuOOH with $VO(acac)_2$ could successfully catalyze the epoxidation and subsequent cyclization of ynamides **232**, **234**, and **236**, tethering through

Scheme 66



Scheme 67



either the *N*- or *C*-terminus of the ynamide. Unfortunately, there was no diastereomeric induction with this catalyst; the reaction of **232** gave **233a** and **233b** as 1:1 diastereomeric mixtures. The epoxidation and cyclization of **236** resulted in a 70:30 diastereomeric mixture of **237a**:**237b**.

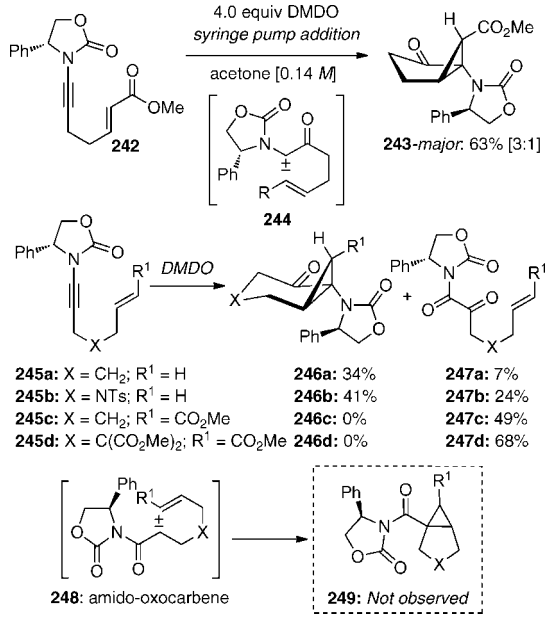
In the same year, Hsung and Al-Rashid[92] described an efficient preparation of α-keto-imides **239** through both RuO_2−$NaIO_4$ and DMDO mediated oxidation of ynamides **238** (Scheme 66). The RuO_2−$NaIO_4$ protocol provided novel syntheses of vicinal tricarbonyl containing **239e** and **239f**, while the DMDO oxidation allowed for the chemoselective oxidation of olefin-tethered ynamides **240** (Scheme 67).

Hsung and Al-Rashid[93] also demonstrated the intramolecular DMDO-mediated cyclopropanation of chiral ene-ynamide **242** through the generation of push−pull carbene **244** (Scheme 68). Amido-cyclopropane **243** was obtained in good yield and 3:1 *dr*, with an α-keto-imide being isolated as a side product.

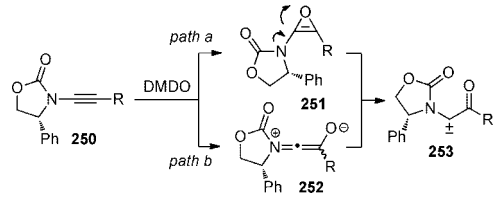
The authors were able to probe the formation of amido carbenes **248** by varying the electronics of the tethered olefin. Ynamides containing electron-deficient olefins gave only α-keto-imides **247c** and **247d**, while with electron-rich olefins the amido-cyclopropanes **246a** and **246b** could be isolated with no traces of bicyclo[3.1.0]hexane **249**, which should result from cyclopropanation via oxocarbene **248**.

The formation of push−pull carbene **253** may proceed through two reaction pathways (path a or b, Scheme 69). In path a, ynamide epoxidation and ring-opening of the intermediate oxirene **251** would give **253**. Alternatively, zwitterionic oxyketeniminium **252** may be involved in the formation of **253** via path b.

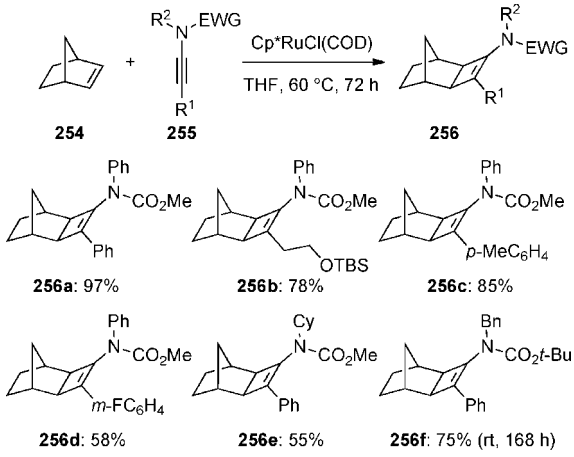
Scheme 68



Scheme 69



Scheme 70



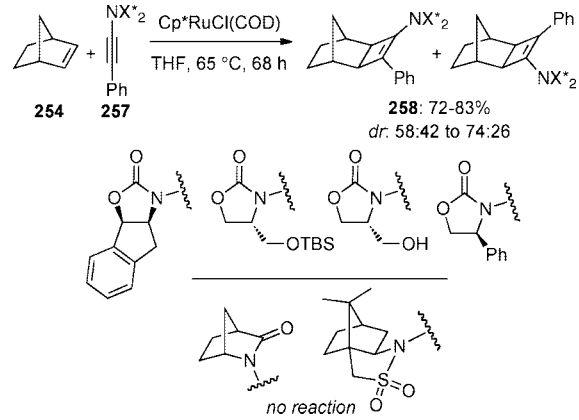
3.2.2. [2 + 2] Cycloadditions

Tam[94] reported the first examples of a ruthenium-catalyzed [2 + 2] cycloaddition between norbornene **254** and ynamides **255** to give amidocyclobutenes **256** (Scheme 70).

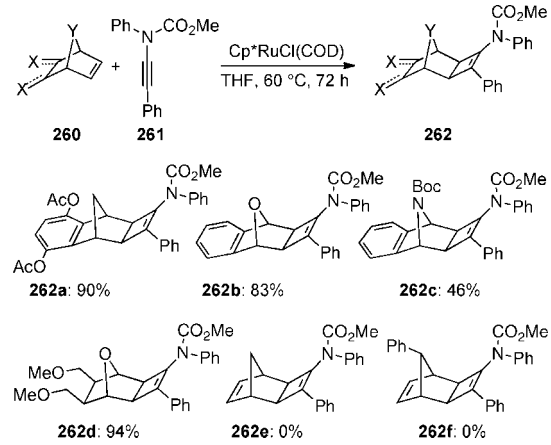
When the authors tried to extend this methodology to include chiral ynamides **257**, the yields of products **258** were good; however, the diastereoselectivity was only moderate, and no reaction was observed using bicyclic amide or sultam derived ynamides, presumably due to the increased steric hindrance (Scheme 71).

Tam[95] later disclosed that a diverse array of bicyclic alkenes **260** could partake in these Ru-catalyzed [2 + 2] cycloadditions, providing functionalized cycloadducts **262** in moderate yields while norbornadienes failed to produce **262e** and **262f** (Scheme 72). The authors believed this could

Scheme 71



Scheme 72



be attributed to chelation of ruthenium to both alkenes of **260e** and **260f** in a bidentate fashion, thereby disfavoring coordination of the ynamide **261**.

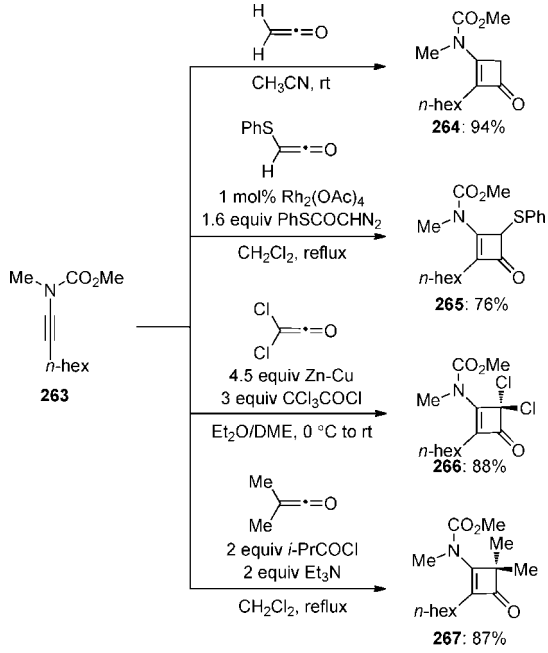
Danheiser[96] has also reported some beautiful [2 + 2] cycloadditions of ynamide **263** with several classes of ketenes, providing substituted 3-amidocyclobutenones **264**−**267** in good yields (Scheme 73).

Hsung[97] explored the reactivity of ynamide **268** with various aldehydes in $BF_3 \cdot Et_2O$-promoted hetero-[2 + 2] cycloaddition reactions (Scheme 74). The resulting amides **269** were obtained in good to excellent yields with high *E*-selectivity. This transformation presumably proceeds through a stepwise [2 + 2] cycloaddition, followed by electrocyclic ring-opening.

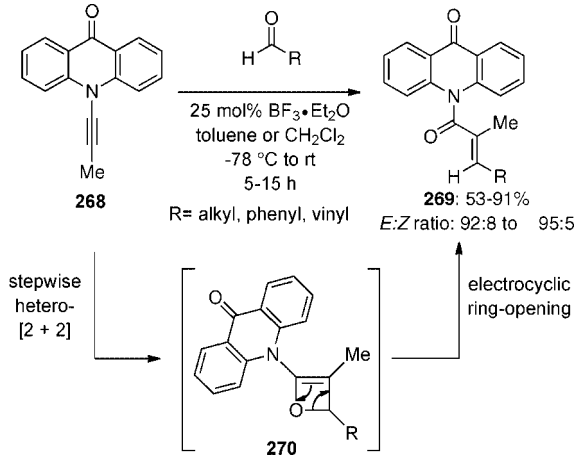
Ynamides **272** bearing a tethered carbonyl could also be utilized in this Lewis acid-catalyzed intramolecular hetero-[2 + 2] cycloaddition, ring-opening sequence to synthesize cyclic α,β-unsaturated amides **273** (Scheme 75). Notably, imide-containing ynamide **274** also led to bicyclic lactam **275** in good yield.

A tandem cross-coupling, cycloaddition, ring-opening sequence[98] was also explored by Hsung (Scheme 76). *In situ* ynamide formation from the cross-coupling of amide with bromide **276** gave chromene **277** in 60% yield. In another case, oxidation of the primary alcohol in **278** could trigger the formation of quinolizidine **280** in 53% yield. The process was also successfully applied to the facile synthesis of the pyrrolizidine motif. The optically enriched bromide **281** was coupled with amide to give ynamide **282** and deprotection of the TBS group, followed by a one-pot tandem oxidation−cycloaddition−ring-opening to produce **284** in good overall yield.

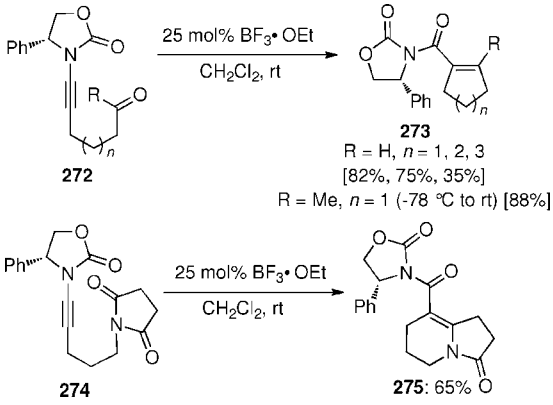
Scheme 73



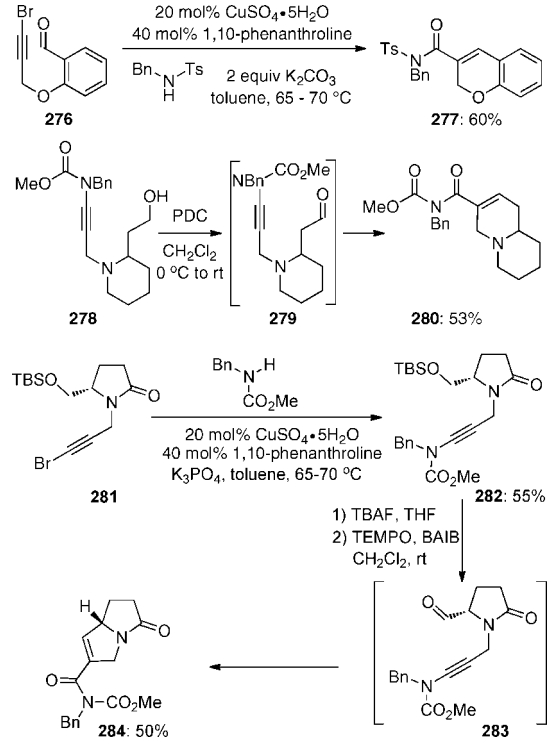
Scheme 74



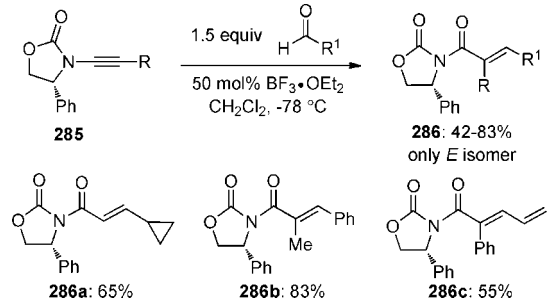
Scheme 75



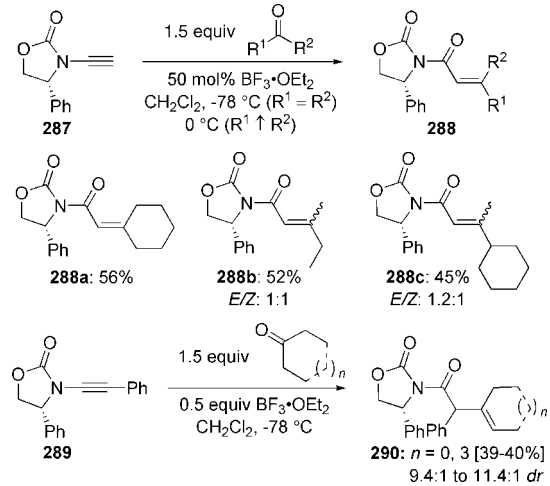
Scheme 76



Scheme 77



Scheme 78

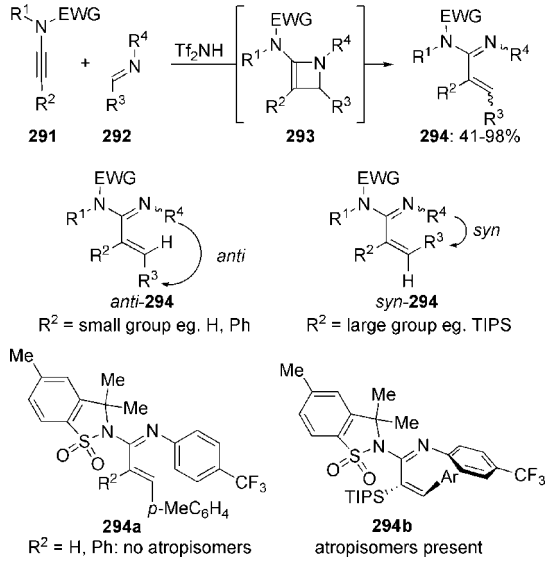


In 2007, Hsung[99] reported a two-carbon homologation of aldehydes and ketones employing ynamides. Ynamides **285** could react with aldehydes under $BF_3 \cdot OEt_2$-promoted conditions to give **286** exclusively as the *E*-isomer (Scheme 77).

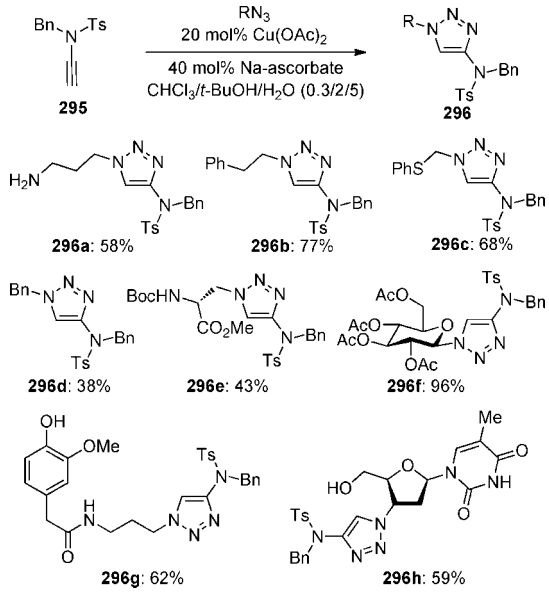
The reaction of terminal ynamide **287** with a variety of ketones also led to unsaturated amides **288** in moderate yields and with low *E*/*Z* selectivity in the examples using unsymmetrical ketones. When phenyl-substituted ynamide **289** was employed in this transformation, deconjugated products such as **290** could be obtained with high diastereoselectivity (Scheme 78).

Takemoto and Takasu[100] described a new method for the synthesis of α,β-unsaturated amidines through a cascade

Scheme 79



Scheme 80



reaction between ynamides **291** and imines **292** consisting of a stereoselective [2 + 2] cycloaddition and a thermal cycloreversion or ring-opening (Scheme 79). When R^2 was small, *anti*-**294** was isolated, whereas when R^2 was large, the product was *syn*-**294**, which existed as a mixture of atropisomers.

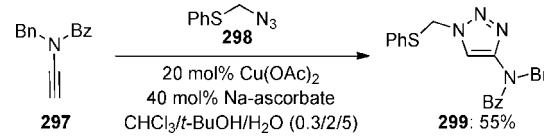
3.2.3. [3 + 2] Cycloadditions

The first examples of "click" chemistry employing ynamides were described by Cintrat[101] in 2006, in which *N*-tosyl ynamide **295** was reacted with alkyl azides to give 4-amino-1,2,3-triazoles **296** with a variety of functionalities at the 1-position (Scheme 80). $Cu(OAc)_2$-Na ascorbate was found to be the best catalytic system for these transformations, while CuI could also be employed.

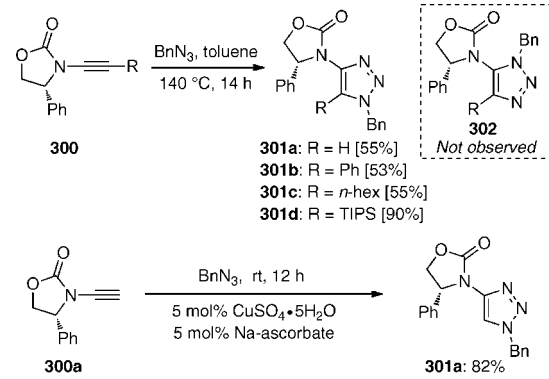
The authors found that although both cyclic carbamate and urea-derived ynamides could not be converted to the expected triazole products, *N*-benzoyl ynamide **297** afforded triazole **299** in 55% yield (Scheme 81)

In the same year, Hsung[102] reported a variation of Huisgen's [3 + 2] cycloaddition involving chiral ynamides

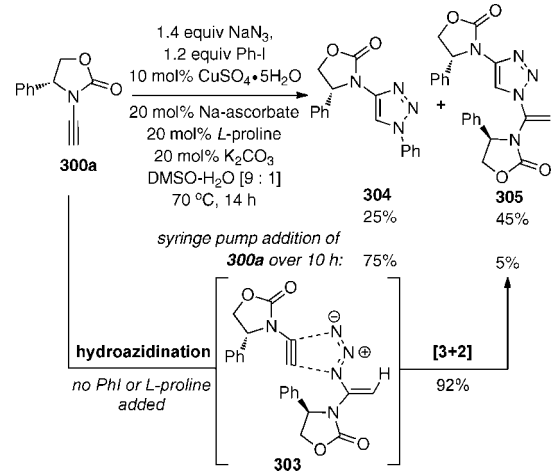
Scheme 81



Scheme 82



Scheme 83

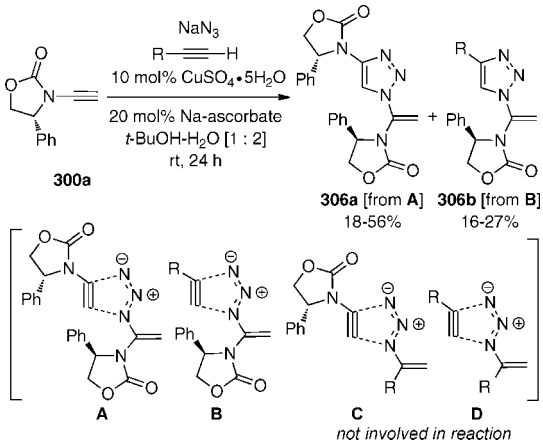


(Scheme 82). The carbamate-derived ynamide **300** reacted with benzyl azide to provide the 1,4-adduct **301** under thermal conditions without observation of the 1,5-adduct **302**. The same 1,4-regioselectivity was also observed in the thermal cycloaddition of internal ynamides. The yield of **301a** was increased to 82% under the Fokin−Sharpless Cu(I) catalytic conditions.

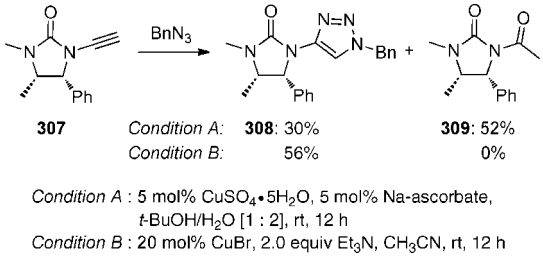
The authors also found an unexpected tandem hydroazidination−Huisgen [3 + 2] cycloaddition of terminally unsubstituted ynamide **300a** that provided vinyl triazole **305** as the major product (Scheme 83). The expected triazole **304** could be preferentially formed by syringe pump addition of the ynamide. By excluding both PhI and L-proline from the reaction mixture, **305** could be isolated in 92% yield, presumably through transition state **303**.

By introducing a second terminal alkyne to the reaction mixture, the authors were able to investigate the electronic sensitivity of this tandem sequence (Scheme 84). In the presence of several alkyl and aryl acetylenes, only **306a** and **306b** were formed, resulting from transition states **A** and **B**, respectively. Under these conditions, there was no formation of products resulting from **C** or **D**, implying that the hydroazidination was chemoselective in favor of the more electron-rich ynamides.

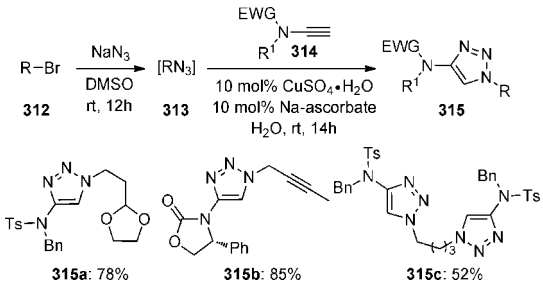
Scheme 84



Scheme 85



Scheme 86



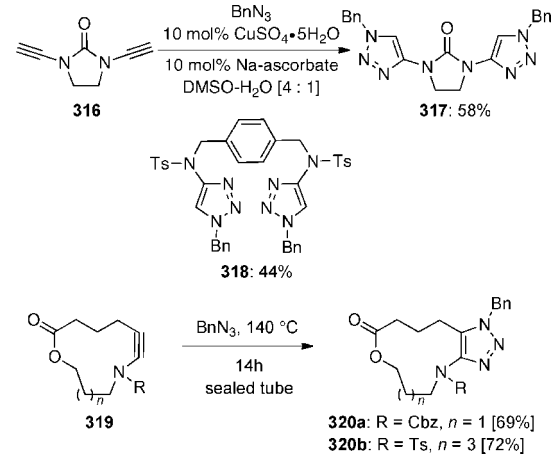
Later, it was found that ynamide hydrolysis could be a competing reaction in this [3 + 2] cycloaddition,[103] especially with less stable ynamides such as **307** (Scheme 85). When **307** was reacted with benzyl azide under $CuSO_4 \cdot 5H_2O$ catalyzed conditions (condition A), only 30% of the expected triazole **308** was isolated, with the major product being **309**, resulting from ynamide hydrolysis. The authors were able to circumvent the hydrolysis issue by using CuBr as the catalytic copper species, providing **308** in 56% yield.

This reaction sequence could also be carried out in one pot by *in situ* formation of the alkyl azides **313** from the corresponding alkyl bromides **312** (Scheme 86). As anticipated from their previous work, the only observed product was the 1,4-disubstituted isomer. Both primary and secondary alkyl bromides could be used while the latter afforded triazoles **315** in a lower yield. This one-pot protocol could also be applied to the synthesis of the novel bis-triazole **315c**.

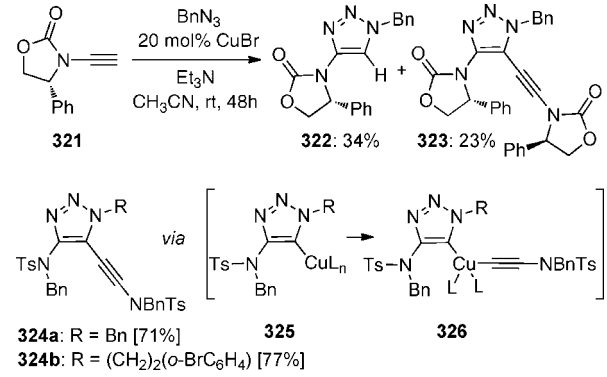
In a similar manner, bis-triazoles **317** and **318** could be prepared in synthetically useful yields from the corresponding bis-ynamides **316** (Scheme 87). As another example of the utility of this transformation, macrocyclic ynamides **319** could be functionalized to the 1,4-disubstituted macrocyclic fused triazoles **320** in good yields.

With the anhydrous CuBr-catalyzed conditions overcoming the problem of ynamide hydrolysis, another intriguing

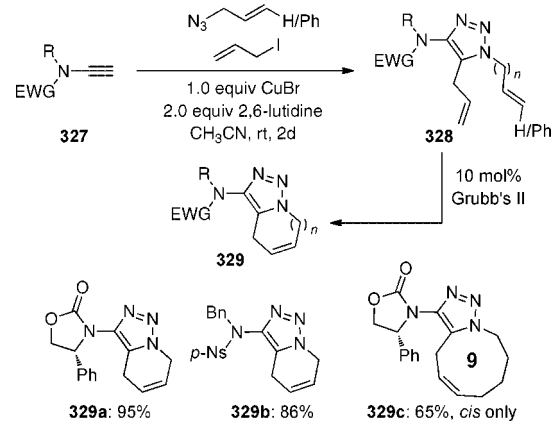
Scheme 87



Scheme 88



Scheme 89

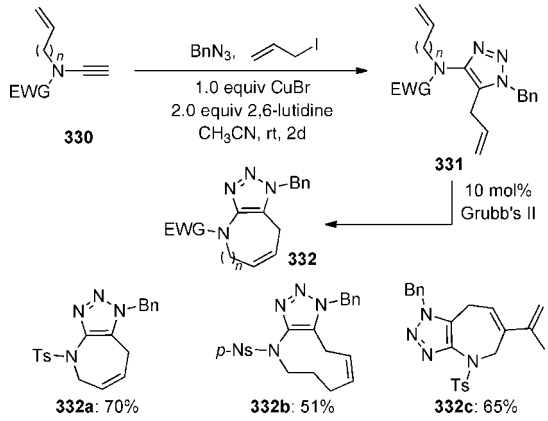


observation was soon discovered[104] (Scheme 88). When ynamide **321** was treated with benzyl azide, a mixture of triazole **322** and alkyne **323** was isolated. *N*-Sulfonyl-substituted ynamides afforded even higher yields of ene-ynamides **324**, which were presumably derived from reductive elimination of intermediate **326**, implying the presence of vinyl copper intermediate **325**.

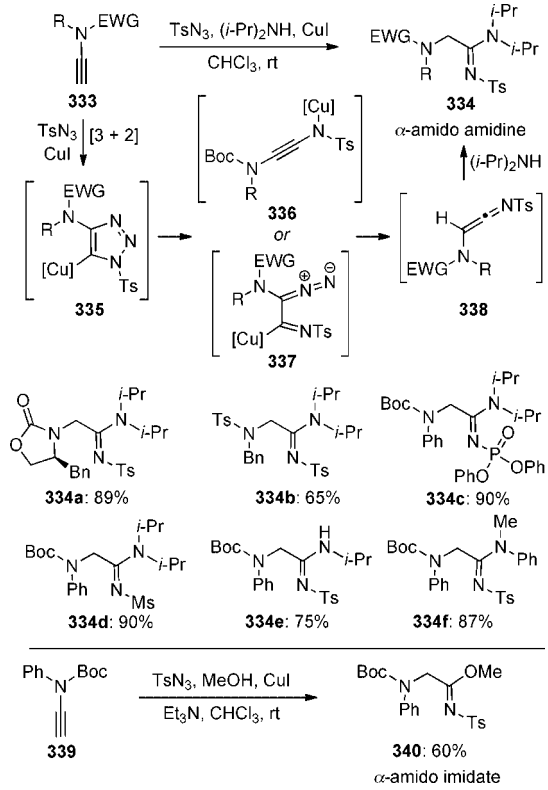
The presence of this vinyl copper species afforded an excellent opportunity to prepare unique trisubstituted-amido-triazoles (Scheme 89). By trapping the vinyl copper intermediate prepared from ynamide **327** with allyl iodide, triazoles **328** could be formed. These diallyl-triazoles could be directly subjected to Grubbs' II catalyzed ring-closing metathesis to construct a variety of bicyclic triazoles **329**.

In a variation of this transformation, the authors found that *N*-allyl ynamides **330** could be functionalized to triazoles

Scheme 90



Scheme 91

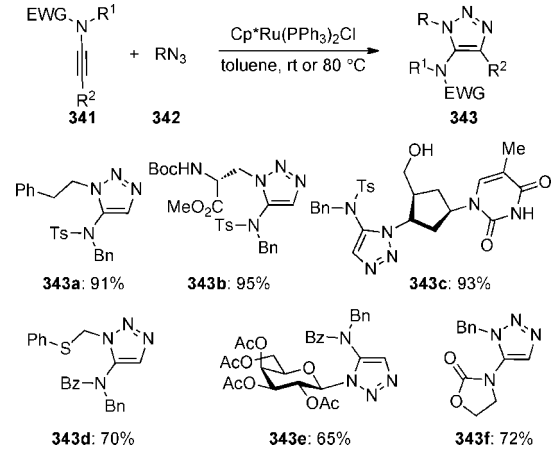


331, allowing subsequent ring-closing metathesis to afford bicyclic triazoles **332** with the amide functionality incorporated into the ring (Scheme 90).

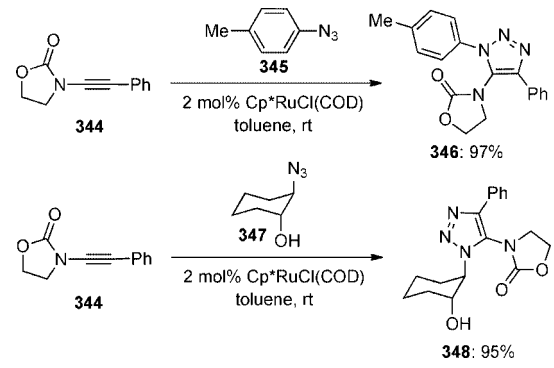
Chang[105] described a copper-catalyzed three-component coupling reaction of ynamides **333**, tosyl azide, and various amines to prepare α-amido amidines **334** (Scheme 91). In this reaction, the 1,2,3-triazol-5-yl copper species **335** was first formed by [3 + 2] cycloaddition, followed by the generation of intermediate **336** or **337**, which would lead to formation of highly reactive amido-ketenimine **338**. The ketenimine could then be trapped by amines to provide α-amido amidines **334** or by methanol to give α-amido imidate **340**.

Cintrat[106] reported a highly regioselective ruthenium-catalyzed [3 + 2] cycloaddition to provide 5-amido 1,2,3-triazoles **343** (Scheme 92). This methodology compliments the copper-catalyzed cycloaddition discussed previously that yields 1,4-substituted triazoles. Both sulfonyl and carbamate-derived ynamides **341** worked well in this system, affording the corresponding triazoles in moderate to excellent yields.

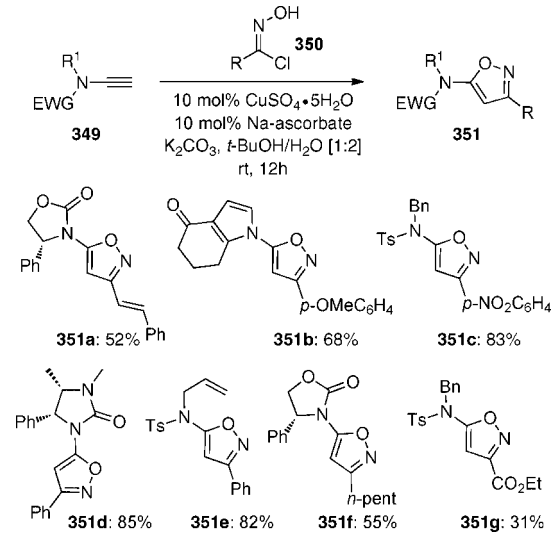
Scheme 92



Scheme 93



Scheme 94

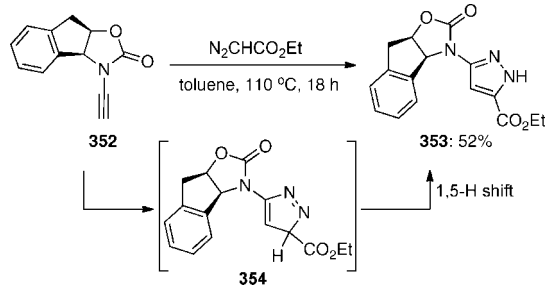


Lin, Jia, and Fokin[107] also reported a similar ruthenium-catalyzed [3 + 2] cycloaddition of ynamide **344** with azides **345** and **347** to efficiently provide 5-amido 1,2,3-triazoles **346** and **348**, respectively (Scheme 93).

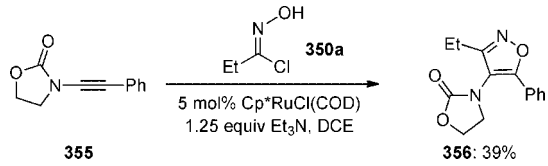
In 2007, Hsung[108] disclosed a highly regioselective [3 + 2] cycloaddition between terminally unsubstituted ynamides and nitrile oxides generated *in situ* from α-chloro oximes **350** to synthesize 5-amido-isoxazoles **351** (Scheme 94). Significantly, no 4-amido-isoxazoles were observed in these reactions, denoting the excellent regioselectivity present in these transformations.

Also discussed was the preparation of 3-amidopyrazole **353** from the [3 + 2] cycloaddition of ynamide **352** and ethyl

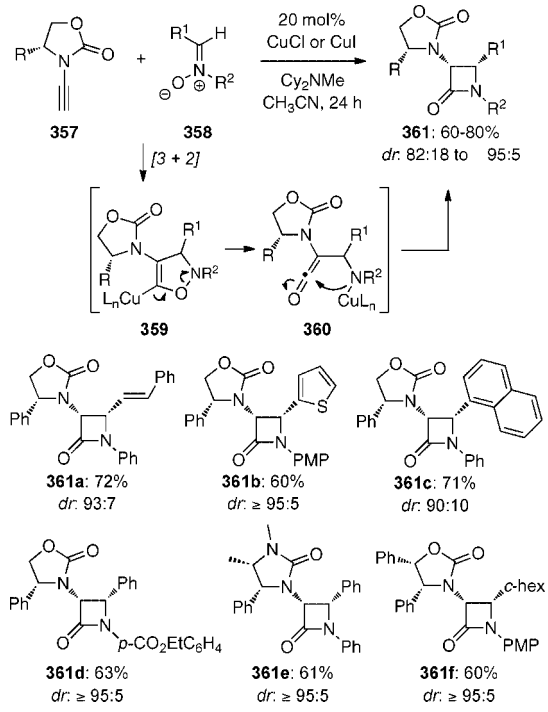
Scheme 95



Scheme 96



Scheme 97



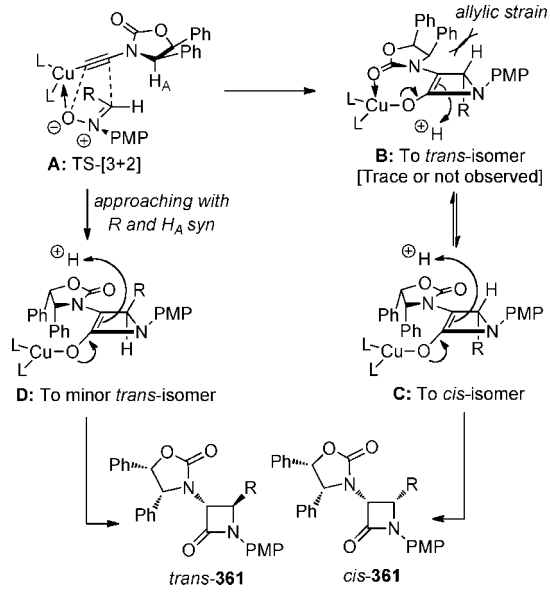
diazoacetate to give intermediate **354** (Scheme 95). An ensuing 1,5-*H* shift results in preferential formation of **353**.

Fokin[109] reported a complementary ruthenium-catalyzed [3 + 2] cycloaddition of ynamide **355** with oxime **350a**, providing isoxazole **356** as a single regioisomer in 39% yield. Notably, this methodology provided the opposite regioisomer to the copper-catalyzed cycloadditions discovered by Hsung (Scheme 96).

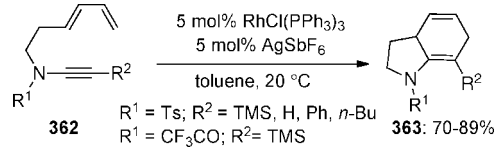
Hsung[110] later demonstrated a highly diastereoselective Kinugasa nitrone-[3 + 2] cycloaddition involving ynamides to synthesize chiral α-amino-*β*-lactams **361** (Scheme 97). The mechanism involves an initial [3 + 2] cycloaddition of nitrone **358** with chiral ynamide **357** to give metalated-isoxazole **359**, which may afford **361** through intramolecular trapping of ketene **360**.

The authors attributed the excellent diastereoselectivity in this Cu(I)-promoted nitrone-[3 + 2] cycloaddition to a divergence in reactivity of intermediate **A**, which could follow two reaction pathways determining the *β*-carbon

Scheme 98



Scheme 99



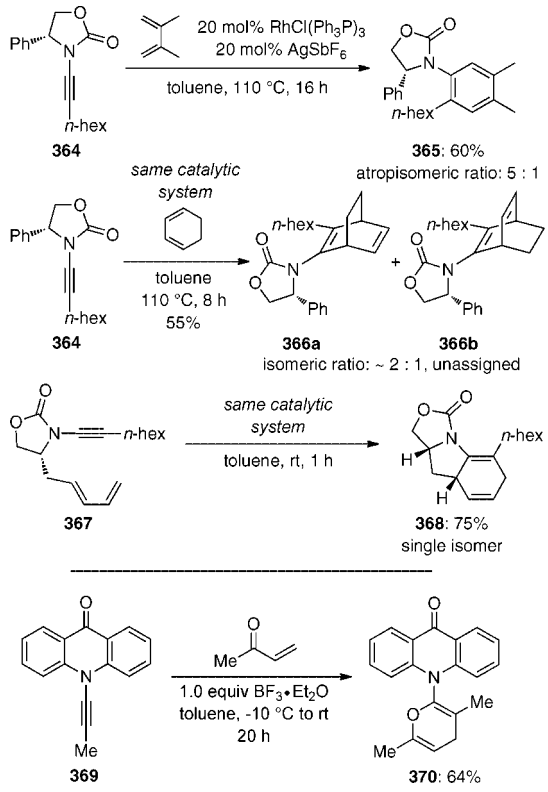
stereochemistry (Scheme 98). The preferred pathway would involve the approaching nitrone, with its vinyl hydrogen being *syn* to H_A on the chiral auxiliary and the larger R group *anti* to H_A to minimize steric interactions. This pathway would lead to intermediate **B** and while **B** could undergo protonation at the more open bottom face away from the phenyl rings, it would lead to *trans*-**361**, which was not observed. Therefore, the authors reasoned that a facially selective protonation took place instead via intermediate **C** on the top face to give *cis*-**361** because **C** is more stable than **B** in light of the allylic strain. On the other hand, the less favorable cycloaddition pathway would involve the larger R group approaching *syn* to H_A and should lead to the minor *trans*-**361** isomer via related intermediate **D**.

3.2.4. [4 + 2] Cycloadditions

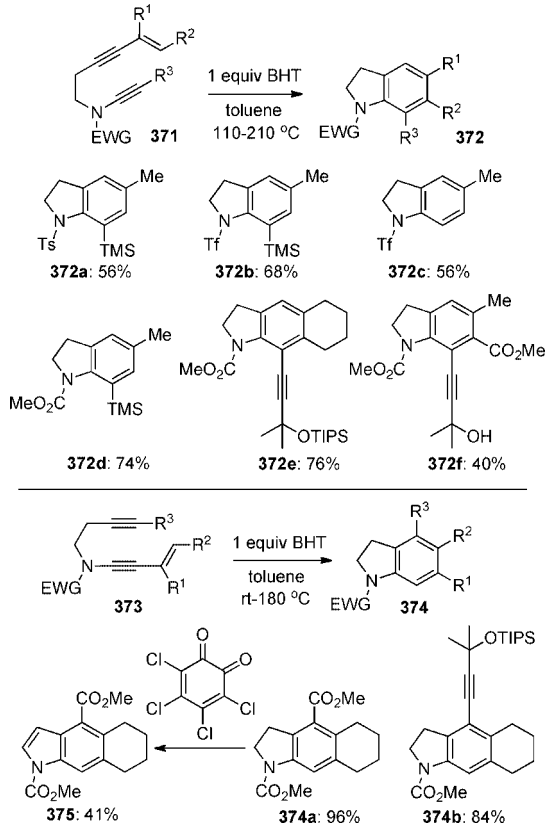
The first intramolecular [4 + 2] cycloaddition employing diene-ynamides **362** was reported by Witulski[45b] in 2003 (Scheme 99). Their protocol provided an efficient and versatile access to functionalized dihydroindolines **363** employing cationic rhodium(I) prepared *in situ* from RhCl(PPh_3)$_3$ and $AgSbF_6$. It is noteworthy that the authors did not observe the typical Diels−Alder side products usually resulting from subsequent isomerization or aromatization under these mild conditions.

Hsung[56b] later expanded on this work with an intermolecular Diels−Alder cycloaddition between chiral ynamide **364** and several symmetrical dienes (Scheme 100). Anilide **365** (5:1 atropisomeric ratio) and bicyclic chiral enamides **366** were obtained in moderate yields. The intramolecular cycloaddition of ynamide **367** proved to be highly diastereoselective, affording dihydroindoline **368** as a single isomer. Hsung[97] also showcased a hetero-Diels−Alder cycloaddition of ynamide **369** with methyl vinyl ketone to give **370**.

Scheme 100

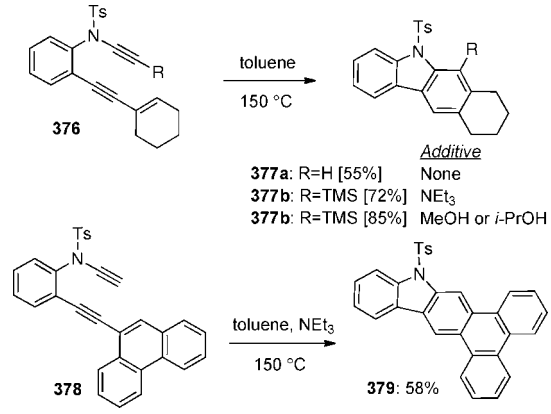


Scheme 101

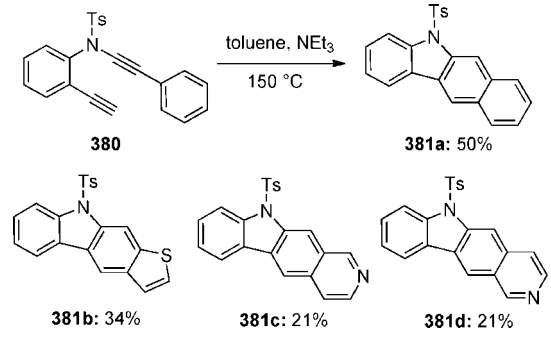


Danheiser[55d] described the first intramolecular thermal [4 + 2] cycloaddition giving highly substituted indolines **372** and **374**, employing enyne-tethered ynamides **371** and yne-tethered ene-ynamides **373** (Scheme 101, BHT = butylated hydroxytoluene). Likewise, interesting acetylene tethered indolines **372e**, **372f**, and **374b** could be prepared from the respective diyne-ynamides. The indoline product could be conveniently oxidized to the corresponding indole **375** by employing *o*-chlorocil.

Scheme 102



Scheme 103



An intramolecular dehydro-Diels−Alder reaction of ynamides **376** and **378** was soon after reported by Saá[111] for the synthesis of several carbazole skeletons (Scheme 102). Depending on the substrate, various additives, including NEt_3, MeOH, and *i*-PrOH, were required for optimal yields.

In 2008, it was discovered that, by introducing various aromatic functionalities to the *C*-terminus of the yne-ynamides **380** instead of to the *N*-terminus, heteroarylcarbazoles **381** could be isolated, albeit in low yield using NEt_3 as an additive (Scheme 103).

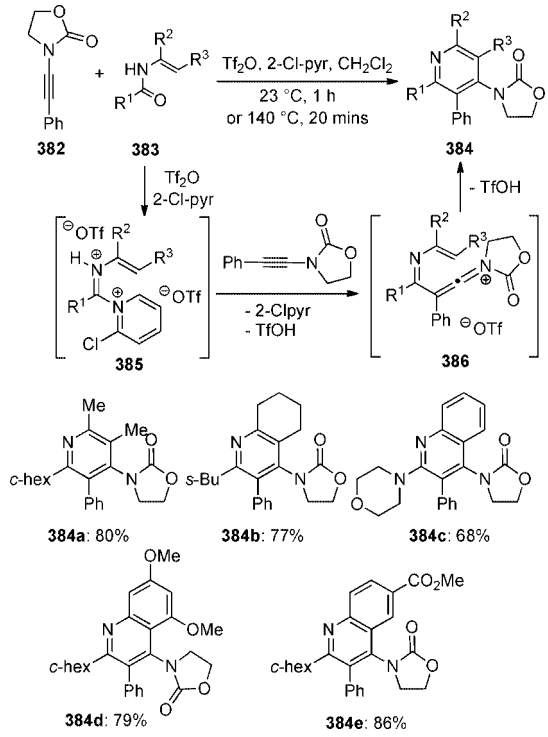
Movassaghi[112] reported an acid-catalyzed *aza*-[4 + 2] cycloaddition of ynamide **382** with enamides **383** to provide a direct synthesis of pyridines **384** (Scheme 104). This methodology proved compatible with a variety of *N*-vinyl and *N*-aryl amides and π-nucleophiles. The authors proposed that the mechanism involves acidic activation of **383** to give bis-iminium **385**, which is subsequently attacked by the ynamide to give keteniminium **386**. The ensuing intramolecular *aza*-[4 + 2] cycloaddition would afford the observed pyridine derivatives.

It is noteworthy that carrying out this reaction with enantiomerically enriched enamide **388** resulted in formation of the cycloadduct **389** with no loss of optical activity (Scheme 105).

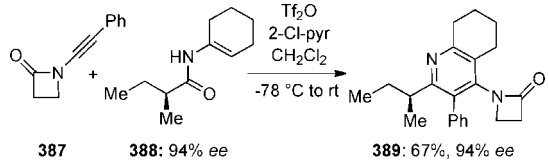
Gagosz[113] reported a formal Au-catalyzed hetero-[4 + 2] cycloaddition of Boc-protected ynamides **390** bearing a tethered trisubstituted alkene to give enamides **392** all as single isomers (Scheme 106).

In the case of ynamide **393** containing a trans-disubstituted alkene, the diastereoselectivity was only moderate. The authors attributed this selectivity to a strong steric interaction between the acetoxy group and R^1 in the intermediate **396**

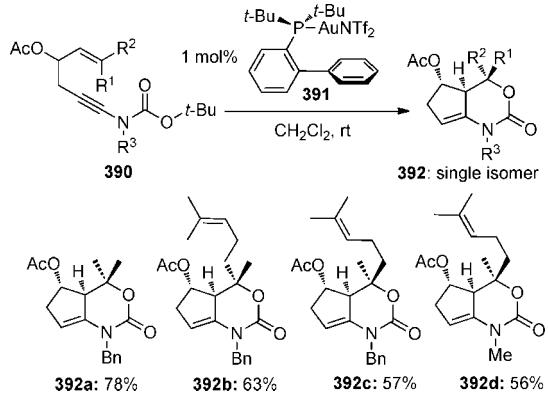
Scheme 104



Scheme 105



Scheme 106

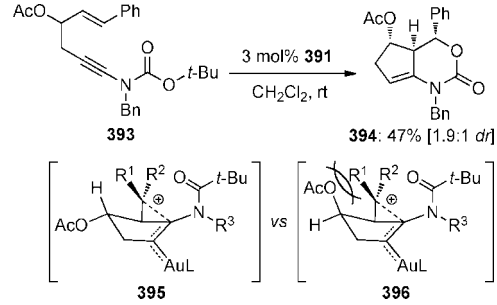


compared to the intermediate **395**. The use of chiral *N*-auxiliaries was also explored; however, no asymmetric induction was observed (Scheme 107).

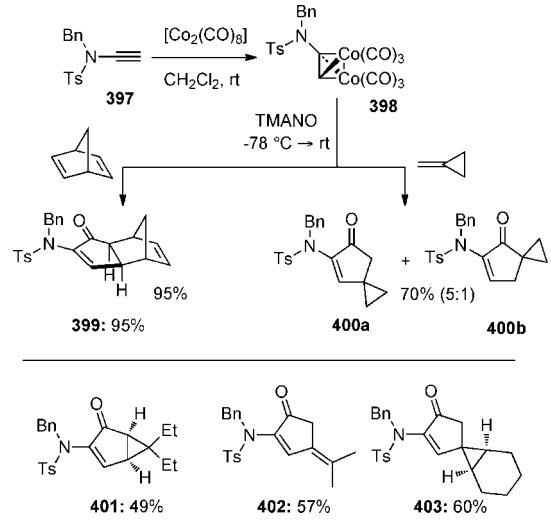
3.2.5. [2 + 2 + 1] Cycloadditions

In 1998, Witulski[44a,114] elegantly demonstrated that ynamides could serve as electron-rich alkynes in highly regioselective Pauson−Khand [2 + 2 + 1] cycloadditions with a variety of olefins (Scheme 108). Initially formed is an isolable dicobalt complex **398**, which when treated with trimethylamine *N*-oxide (TMANO) in the presence of norbornadiene or methylenecyclopropane yielded α-amidocyclopentenones **399** as the single *exo* diastereomer or a 5:1 mixture of **400a** and **400b**, respectively. Several other olefins

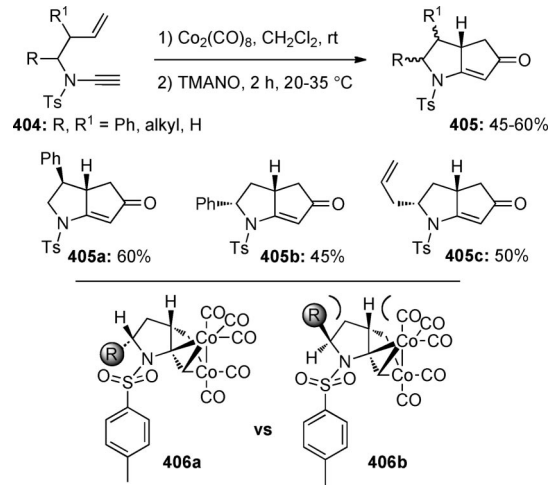
Scheme 107



Scheme 108



Scheme 109

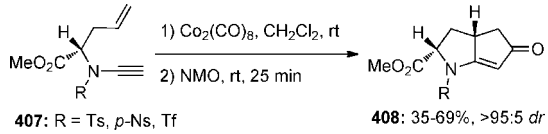


(not shown) also underwent the desired cycloaddition to give cycloadducts **401**−**403** in moderate yields.

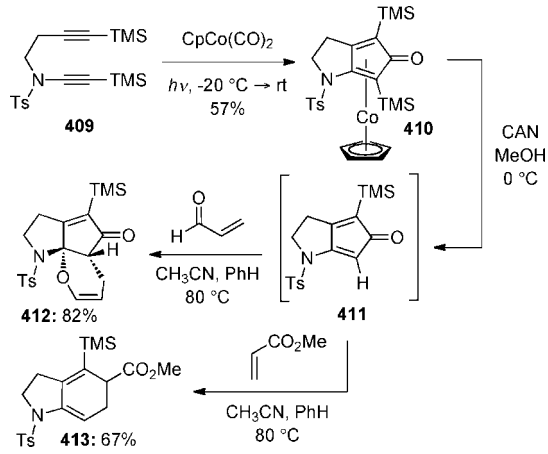
By incorporating an *N*-tethered olefin into ynamides **404**, the authors were able to construct bicyclic vinylogous amides **405** in 45−60% yield (Scheme 109). It is noteworthy that both α and β-branched ynamides afforded the products as single diastereomers. The authors rationalized this exceptional diastereoselectivity by comparing reaction intermediates **406a** and **406b**, where **406b** is less favored due to a pseudodiaxial interaction between the R-group and a carbonyl fragment.

Shortly thereafter, Witulski[49] demonstrated that the *N*-protecting group of ynamides **407** could be altered, still

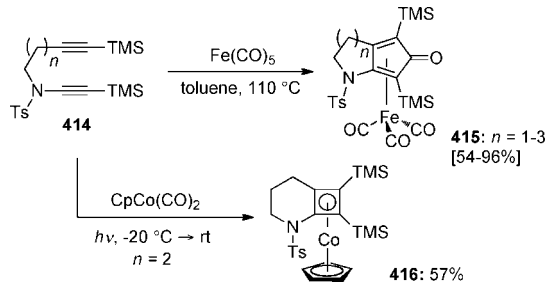
Scheme 110



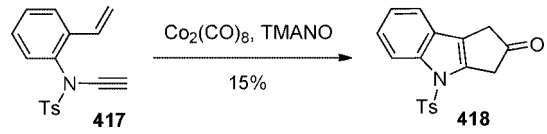
Scheme 111



Scheme 112



Scheme 113



resulting in high levels of diastereoselectivity in **408** in the Pauson−Khand reaction (Scheme 110).

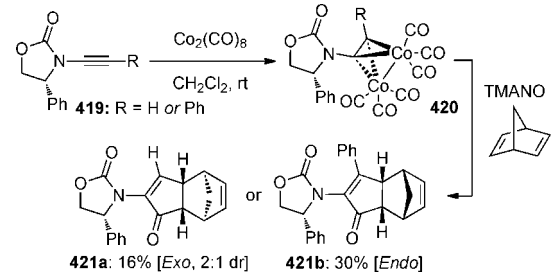
Rainer reported[46a] that when yne-ynamides **409** were subjected to Volhardt's conditions ($CpCo(CO)_2$ in the presence of light), they underwent an intramolecular Pauson−Khand reaction, giving cobalt bound cyclopentadienones **410** in 57% yield (Scheme 111). Oxidative cleavage of the cobalt led to *in situ* generation of cyclopentadienone **411**, which was then trapped by either heterodienes or dienophiles via intermolecular Diels−Alder reactions, yielding products such as **412** or **413** through loss of CO.

Rainer[46b] later discovered in 2000 that the $CpCo(CO)_2$ catalyzed reaction of yne-ynamide **414** resulted in formation of cyclobutadiene complex **416**. In contrast, $Fe(CO)_5$ could be used to catalyze the Pauson−Khand cycloaddition of **414** to give **415** in moderate to excellent yields (Scheme 112). The use of $Fe(CO)_5$ represented a novel catalytic system for these transformations.

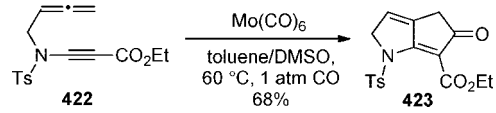
In an attempt to carry out a Pauson−Khand cycloaddition with ynamide **417**, Pérez-Castells[115] was able to isolate the desired annulated indole **418** in low yield (Scheme 113).

Hsung[116] expanded on this body of work by developing intermolecular [2 + 2 + 1] cycloadditions with chiral ynamides **419** (Scheme 114). Interestingly, the *endo* vs *exo* selectivity in product **421** was affected by the alkyne substitution, with terminally substituted ynamides favoring unusual *endo* addition of norbornadiene. The mechanistic rationale for this unusual *endo* selectivity remains unclear.

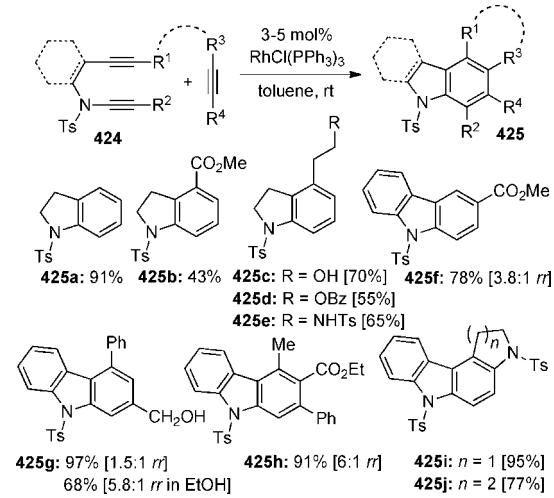
Scheme 114



Scheme 115



Scheme 116



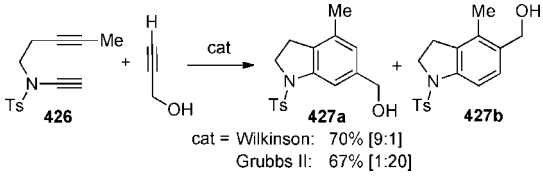
In 2005, Oh[117] reported the use of $Mo(CO)_6$ to catalyze the transformation of allene-ynamide **422** to **423** in 68% yield, as shown in Scheme 115.

3.2.6. [2 + 2 + 2] Cycloadditions

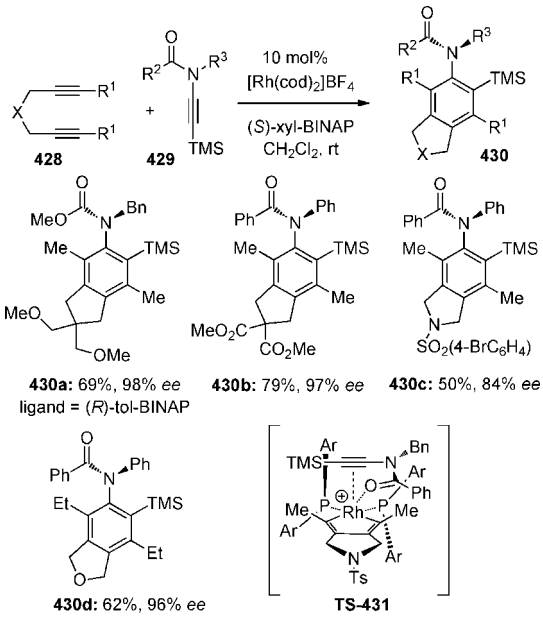
Witulski[47,118] was the first to demonstrate the power of the [2 + 2 + 2] cycloaddition with ynamides. The authors were able to rapidly construct indolines and carbazoles **425** through a Wilkinson's catalyst promoted cyclotrimerization of yne-ynamides **424** with a variety of alkynes (Scheme 116). The regioselectivity of the addition was highly dependent on both steric factors and solvent effects, as demonstrated by the increase in regioselectivity in some cases using ethanol instead of toluene (see **425g**). Diyne-ynamides could similarly be used to construct annulated carbazoles in good to excellent yields.

It was later reported by Witulski[119] that the regioselectivity of the cycloaddition could be completely reversed by using Grubbs' second-generation catalyst instead of Wilkinson's catalyst (Scheme 117). It was proposed that Grubbs' catalyst induces a cascade of metathesis steps beginning by addition of the electrophilic Ru-benzylidene to the electron rich ynamide motif, resulting in the change in regioselectivity.

Scheme 117



Scheme 118



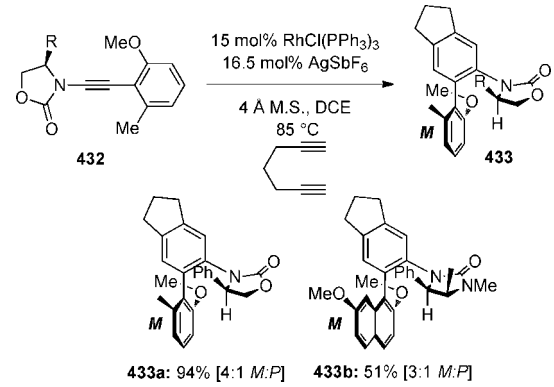
In 2006, Tanaka[120a] reported an asymmetric Rh-catalyzed [2 + 2 + 2] cycloaddition of diynes **428** with ynamides **429**. As shown in Scheme 118, a variety of chiral ligands were screened, with the best being (*R*)-xyl-BINAP, which provided **430** with up to 98% *ee*. They were then able to construct a variety of highly functionalized axially chiral anilides in good yields with good to excellent enantiomeric induction. The yields were heavily dependent on the ynamide's substitution, as terminal ynamides resulted in no reaction.

The authors proposed model **TS-431** to rationalize the observed enantioselectivity, where the ynamide preferentially coordinates to the rhodium center so as to minimize the steric interaction between the benzyl group of **429** and the PAr_2 of the (*S*)-xyl-BINAP.

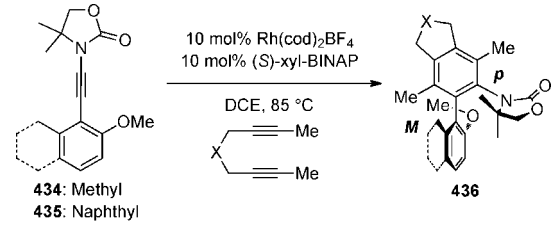
By introduction of a chiral moiety, Hsung[121] was able to use ynamides **432** in a diastereoselective rhodium-catalyzed [2 + 2 + 2] cycloaddition for the synthesis of axially chiral biaryls **433** (Scheme 119). Initial screening revealed a significant counterion effect, as $AgSbF_6$ was essential for complete conversion, as was the addition of molecular sieves to prevent demethylation, *vide supra*. The best diastereoselectivity was observed using phenyl-substituted Evans' auxiliary, resulting in **433a** with a moderate *dr* of 4:1 in favor of the *M* atropisomer. Biaryl **433b** could be synthesized in a 3:1 *dr* using Close's auxiliary. It is noteworthy that there is no interconversion of the *M* and *P* atropisomers under the reaction conditions, as the energy barrier to thermal equilibration was calculated to be 29.4 kcal mol^{-1} and no equilibration was observed even at 120 °C.

Using the rhodium-catalyzed protocol developed by Tanaka with terminally substituted ynamides **434** and **435** in the presence of (*S*)-xyl-BINAP, Hsung[122] was able to construct axially chiral *N*,*O*-biaryls **436** in up to a 6:1 diastereomeric

Scheme 119

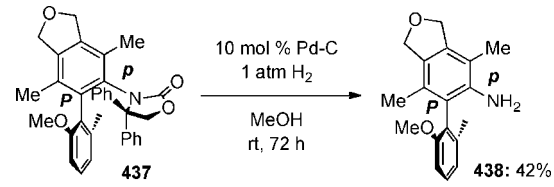


Scheme 120



X	Ynamide	Yield [%]	*dr* [*M*, *p*]: [*P*, *p*] (% *ee*)
O	**434**	92	5:1 (99, 91)
O	**435**	96	3:1 (98, 98)
$C(CO_2Me)_2$	**434**	95	6:1 (99, 99)
$C(CO_2Me)_2$	**435**	78	2:1 (99, 99)

Scheme 121



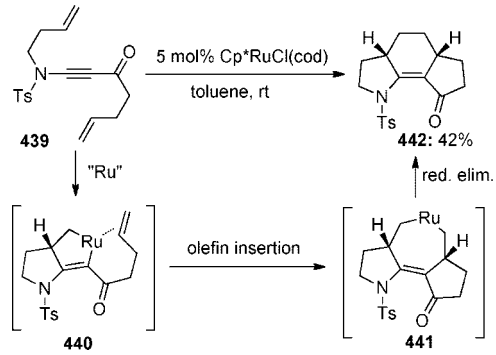
ratio of *M*:*p* to *P*:*p*, with both diastereomers having up to 99% *ee* (Scheme 120). The procedure was general for a variety of aryl-substituted ynamides as well as with diynes containing either a carbon tether or one containing a heteroatom.

Removal of the achiral diphenyl-2-oxazolidinone auxiliary such as in **437** under mild hydrogenation conditions allowed access to interesting chiral *N*,*O*-biaryl compounds (Scheme 121).

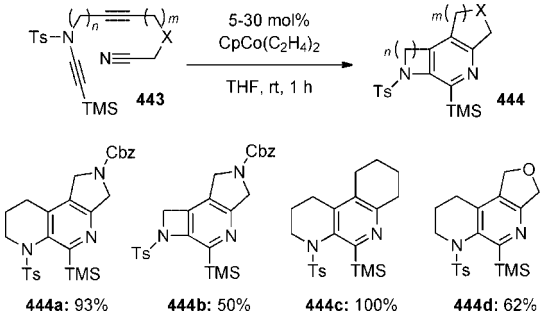
Sato and Mori[123] were able to construct tricyclic vinylogous amide **442** via a [2 + 2 + 2] cyclization of dieneynamide **439** under ruthenium catalyzed conditions (Scheme 122). Initial formation of ruthenacyclopentene **440** is followed by olefin insertion to give **441**, which then undergoes reductive elimination, yielding **442**. The authors discovered in the case of non-ynamide substrates that the carbonyl moiety was not essential for reactivity; however, the carbon-tethering length was. This work provided rapid access to heterocyclic tricycles from linear substrates.

In work recently reported by Aubert and Malacria,[124] yneynamide nitriles **443** were used for the construction of functionalized pyridines **444** by a cobalt-catalyzed intramolecular [2 + 2 + 2] cycloaddition. As shown in Scheme 123, a variety of tethering lengths with or without heteroatom substitution gave the desired product, often in high yield. Furthermore, the mandatory trimethylsilyl group provided a

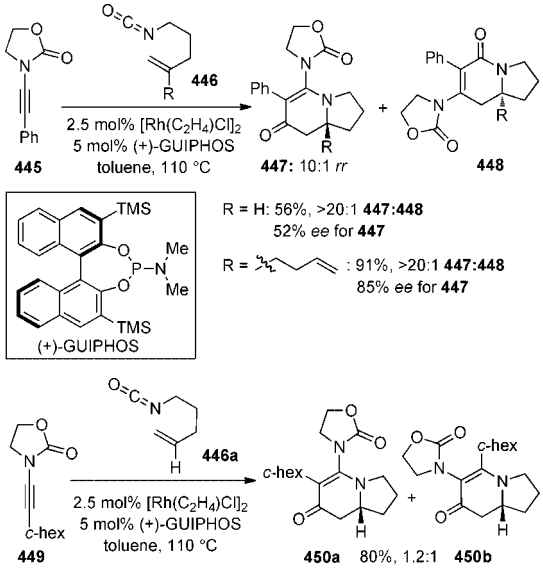
Scheme 122



Scheme 123



Scheme 124

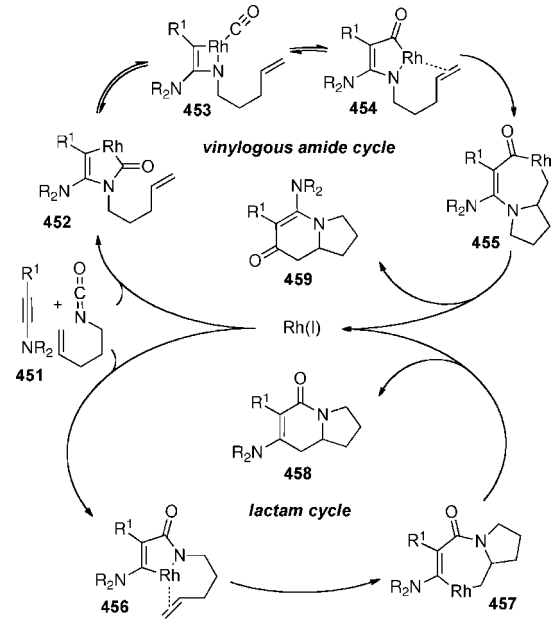


handle for functionalization via Hiyama cross-coupling, allowing access to substituted biaryl compounds.

Rovis[125] demonstrated a rhodium-catalyzed [2 + 2 + 2] cycloaddition of achiral ynamides with alkenyl isocyanates **446** to afford vinylogous amides **447** and **450** with moderate to good enantioselectivity using a chiral GUIPHOS ligand (Scheme 124). With phenyl-substituted ynamide **445**, the ratio of **447** to **448**, resulting from distinct reaction pathways (see Scheme 125), was better than 20:1, with **427** being isolated as an inseparable 10:1 mixture of enamide regioisomers. However, with cyclohexenyl-substituted ynamide **449**, a 1.2:1 mixture of regioisomers **450a**:**450b** was obtained.

The authors proposed that the vinylogous amides and lactams observed originated from different reaction pathways, as shown in Scheme 125. Product selectivity was determined

Scheme 125



in the initial oxidative cycloaddition, which may lead to **452** or **456**. Electronic effects were shown to be significant, as demonstrated by the difference in selectivity using phenyl- or cyclohexenyl-terminated ynamides.

3.3. Cycloisomerization Reactions

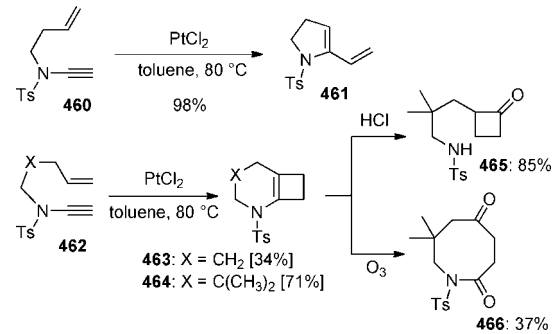
3.3.1. Metal- and Acid-Catalyzed Cyclizations

Over the past three decades, there have been significant advances in the area of transition metal catalyzed cycloisomerization reactions of ene-ynamides.

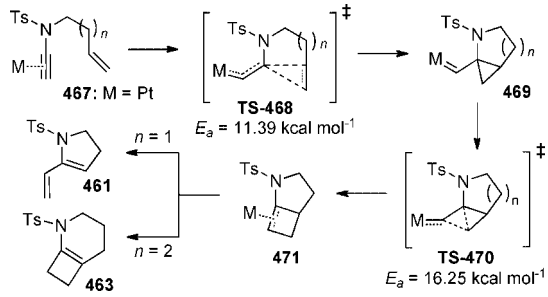
Ene-ynamides were introduced into this field in 2004, when Malacria and Fensterbank[126] developed the first platinum-catalyzed ene-ynamide cycloisomerization, leading to either *aza*-1,3-dienes **461** or *aza*-bicyclo[4.2.0] compounds **463** and **464**, depending on the number of tethering carbons (Scheme 126). Mori had previously observed **461**, obtained through Ru-catalyzed RCM of ynamide **460**, *vide infra*. As the bicyclic products were prone to decomposition, they were directly functionalized via a one-pot hydrolysis or ozonolysis to give **465** or **466**.

Soriano and Marco-Contelles[127] explored the mechanism of this transformation through DFT theoretical calculation (Scheme 127). They proposed initial complexation of the electrophilic metal to the nucleophilic ynamide followed by *exo*-attack of the tethered alkene to give cyclopropyl metallacarbene **469**. A 1,2-alkyl shift into the carbene would

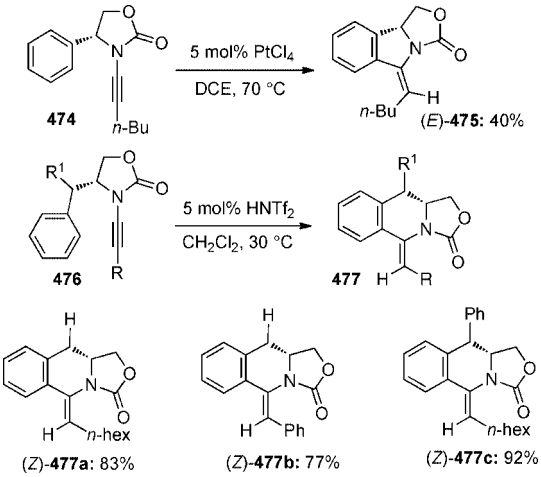
Scheme 126



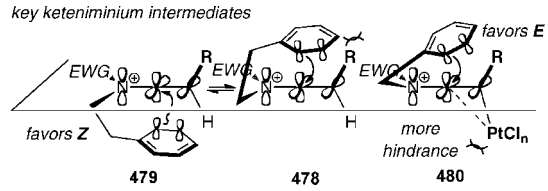
Scheme 127



Scheme 128



Scheme 129



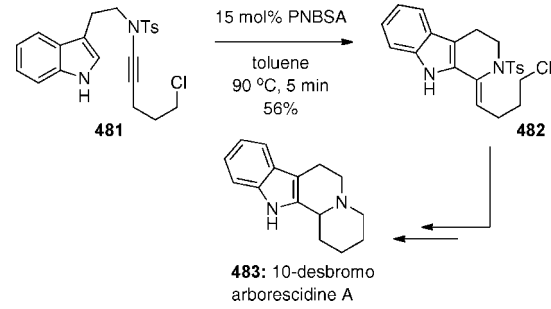
form the key intermediate metallocyclobutene **471**. Depending on the tethering length and ultimately the ring stain, either formal metathesis product **461** or bicyclo[4.2.0]octene **463** is preferentially formed.

Hsung[128] further demonstrated the power of ynamides as functional groups through the synthesis of chiral isoindole and tetrahydroisoquinoline derivatives via acid-catalyzed keteniminium Pictet−Spengler cyclization (Scheme 128). Interesting, the use of an (*R*)-phenyl oxazolidinone as a nucleophile only afforded isoindole **475** with an *E*-exocyclic olefin in moderate yield when using $PtCl_4$. By adding a methylene unit such as in **476**, $HNTf_2$ could catalyze the reaction to give *Z*-olefin containing isoquinolines **477** in good yields with a variety of different functionalities.

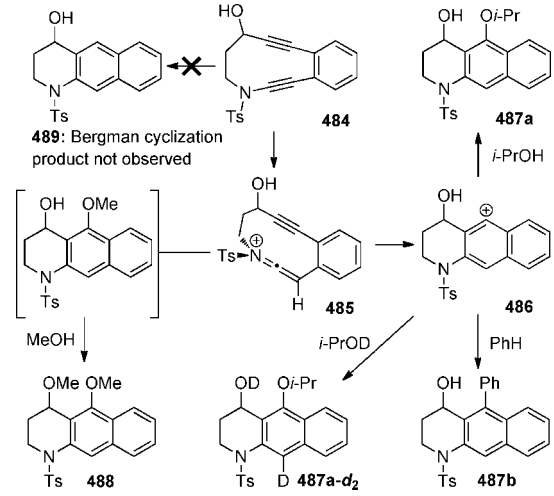
The divergence in selectivity could be rationalized by analyzing the conformations of the keteniminium intermediate in both the Brønsted-acid and Lewis-acid catalyzed cyclizations (Scheme 129). In the Brønsted-acid case, the *Z*-conformation **479** is preferred to minimize steric interaction between the aromatic nucleophile and the R-group. Alternatively, the use of bulky $PtCl_4$ favors the *E*-keteniminium **480**, leading to the observed selectivity.

This methodology was then applied to the total syntheses of two arborescidine alkaloids. Shown in Scheme 130 is a facile total synthesis of 10-desbromo arborescidine A, beginning with the Brønsted-acid catalyzed keteniminium

Scheme 130



Scheme 131



Pictet−Spengler cyclization of ynamide **481** to enamide **482**. This and another related alkaloid synthesis is further discussed in the Ynamides in Total Synthesis of Natural Products section of this review.

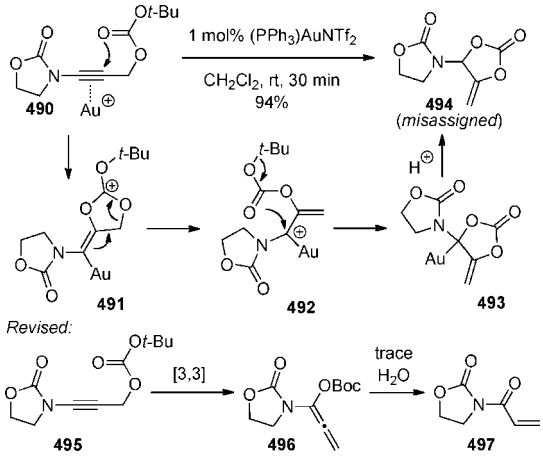
A recent study by Popik[129] showed that cyclic ynamide **484** containing an enediyne moiety could undergo cycloaromatization more than 2 orders of magnitude faster than the analogous carbocyclic enediyne (Scheme 131). This finding supports the theoretical calculations that π-donors and σ-acceptors directly attached to the acetylenic termini of enediynes enhance the rate of Bergman cyclization. Surprisingly, however, **489** was never isolated, implying that, in this system, Bergman cyclization did not occur.

The rate of the cyclization was heavily dependent on solvent polarity, with the half-life of **484** being 105 min in hexane, 65 min in chloroform, and 20 min in 2-propanol. In addition, by running the reaction in benzene, the single major product was **487b** via analogous Friedel−Crafts trapping of the intermediate carbocation. The cycloaromatization was two times slower in 2-propanol-d_1 to give **487a**-d_2, supporting a kinetic isotope effect (k_H/k_D) in the normal direction, consistent with the proton transfer being at least partially rate limiting.

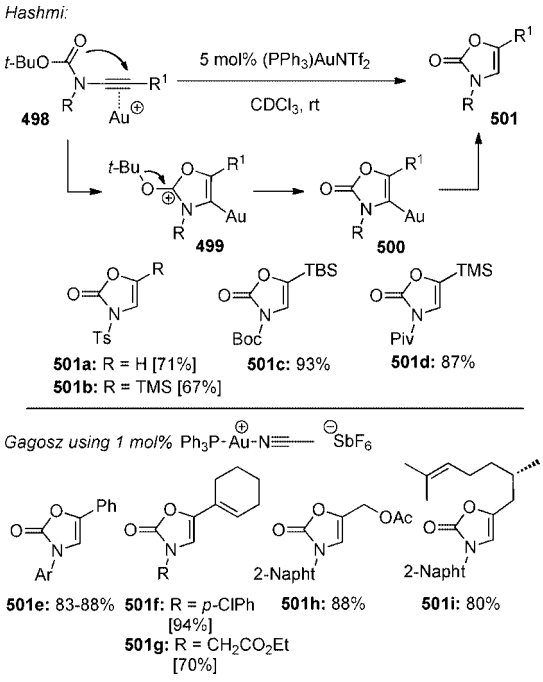
Collectively, these results indicate a polar pathway rather than a diradical one. The initially formed keteniminium **485** is trapped by the nearby alkyne and later by an external nucleophile such as an alcoholic solvent. When methanol was used, **488** was isolated, presumably through displacement of the protonated hydroxyl group.

Gagosz[130] attempted to cyclize ynamide **490**, featuring a tethered carbonate under gold-catalyzed conditions (Scheme 132). They initially reported **494** as the cyclized product, proceeding through nucleophilic attack of the carbonate onto

Scheme 132



Scheme 133

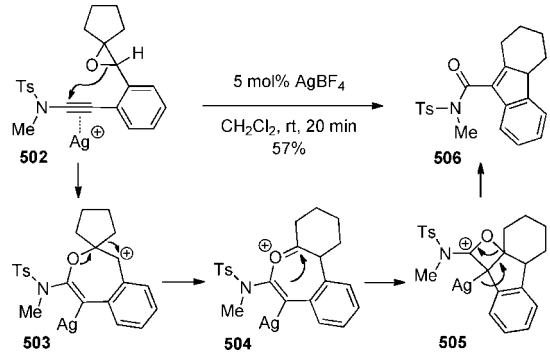


the metal-activated alkyne, followed by olefin migration, cyclization, and loss of isobutene. Upon further investigation,[130b] they recently rescinded their original structure in favor of α,β-unsaturated amide **497**, resulting from 1,3-migration of the carbonate and fragmentation of the resulting allenamide **496**.

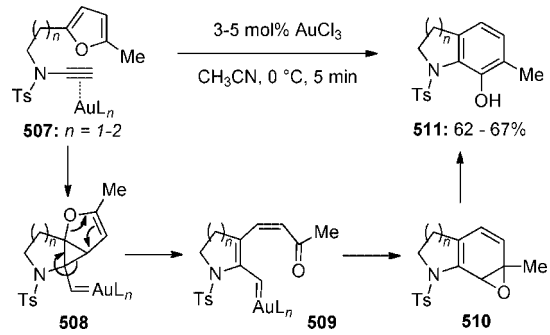
Starting from carbamate-protected ynamides **498**, Hashmi[131] was able to accomplish a similar gold-catalyzed transformation yielding a variety of oxazolidinones **501** (Scheme 133). Mechanistically, this involved 5-*endo-dig* cyclization of the Boc-protecting group onto the gold-activated alkyne, followed by loss of isobutene and protodemetalation. The only reported examples were with terminal or silylated ynamides, limiting the substrate scope.

Hashmi[132] later expanded on this concept employing Echavarren's cationic $[Ph_3P-Au(NCCH_3)]^+SbF_6^-$ catalyst (Scheme 133), improving the generality of the transformation and allowing the authors to isolate oxazolidinones **501e−i** in good to excellent yields. It is noteworthy that the use of $AgNTf_2$ could also catalyze this transformation in some cases; however, the results were not general.

Scheme 134



Scheme 135



In a similar manner, Liu[133] recently reported a silver-catalyzed cycloisomerization of epoxide-alkyne functionalities to quickly generate complex carbocyclic skeletons (Scheme 134). In one such example, treatment of ynamide **502** with $AgBF_4$ triggered a 1,2-alkyl shift ring expansion through intermediate **503**. Consequently, cyclization of **504** and elimination of silver from **505** gave **506**, which could be subsequently reduced to access the core of gibberic acid.

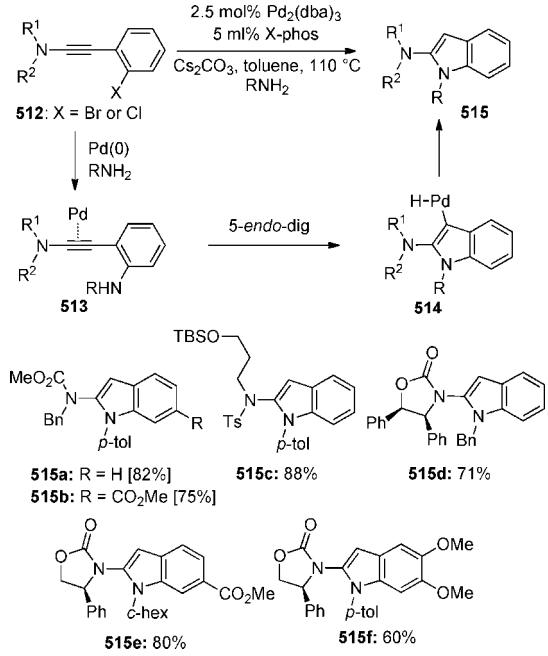
Hashmi[134] found that $AuCl_3$ could be used to catalyze the transformation of ynamido-furans **507** to functionalized indoline or tetrahydroquinoline derivatives **511**, depending on the tether length (Scheme 135). The authors proposed the intermediacy of gold-stabilized carbocation **508**, which may undergo ring opening to give **509**, primed for insertion into the nearby carbonyl to give epoxide **510**. Subsequent tautomerization would result in the formation of **511**.

In 2008, Hsung and Zhao[135] reported a sequential Pd-catalyzed C−N bond formation for the synthesis of 2-amidoindoles **515** (Scheme 136). The tandem sequence involves the amination of aryl halides to give intermediate **513**, followed by metal-promoted 5-*endo-dig* cyclization. The generality of this reaction was demonstrated using a variety of primary amines, *N*-functionalized ynamides, and aryl halides.

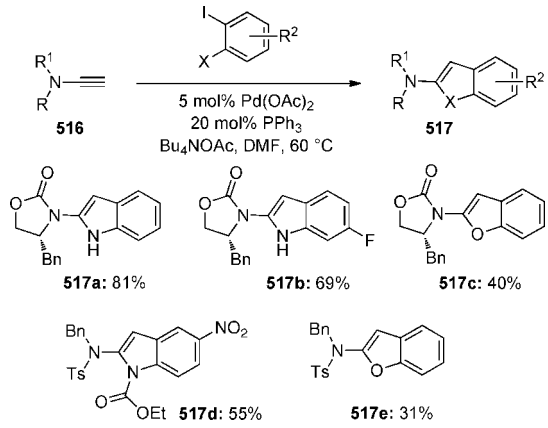
Recently, Skrydstrup[136] developed a very nice variation of this indole synthesis involving the Pd-catalyzed coupling of terminal ynamides **516** with various *o*-iodoaniline and phenol derivatives (Scheme 137). The authors suggested this reaction proceeds through Sonogashira coupling of the terminal ynamide with the aryl iodide, followed by a Pd-mediated hydroamination to yield product **517**.

Cossy[137] elegantly demonstrated the feasibility of constructing substituted cyclobutanones **519**, amido-lactones **520** and **522**, and *aza*-bicycles **524** from ene-ynamides via highly diastereoselective gold-catalyzed cycloisomerizations (Scheme 138). Due to the instability of the resultant aminocyclobutanones **519**, they were directly functionalized via Baeyer−

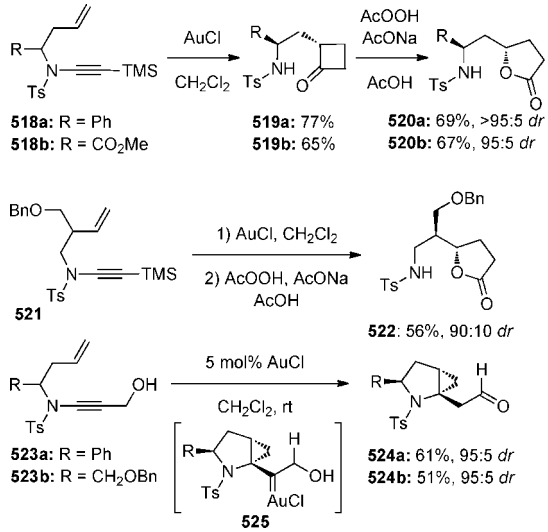
Scheme 136



Scheme 137

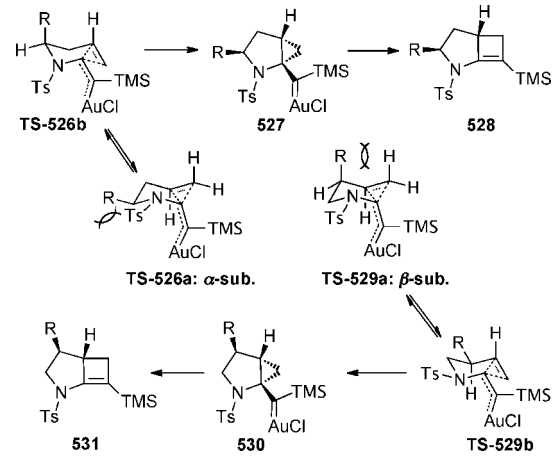


Scheme 138

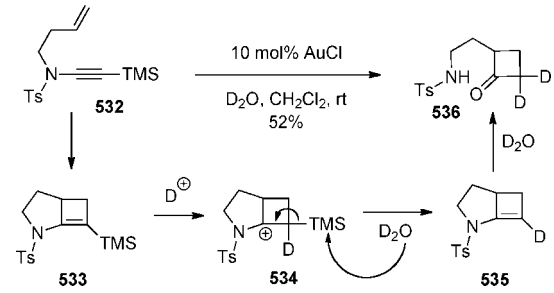


Villiger oxidation to lactones **520** or **522**. Ynamides containing both α- and *β*-substituents were tolerated to give products in good yields and with high diastereoselectivity, as shown from **518** and **521**. Interestingly, a tethered hydroxide functionality

Scheme 139



Scheme 140



in **523** altered the reaction pathway, leading to *aza*-bicycles **524**, presumably through an oxygen-mediated hydride shift.

The authors were intrigued by the mechanism for this transformation and furthermore by the high levels of diastereoselectivity, which must originate during the formation of gold-stabilized carbocations **527** and **530**, as shown in Scheme 139.

Conformational drawings of the two possible chairlike transition states leading to the formation of **527** from α-substituted ynamides reveal a distinct steric preference for **TS-526b**, avoiding the gauche interaction between the sulfonyl and the α-substituent. This preference is further enhanced by nitrogen stabilization of the developing carbocation becoming similar to $A^{1,2}$ strain. In a similar manner, **TS-529b** is favored for *β*-substituted ynamides avoiding 1,3-diaxial interactions. A subsequent 1,2-alkyl shift in both cases would form the respective cyclobutene, maintaining the high level of diastereoselectivity.

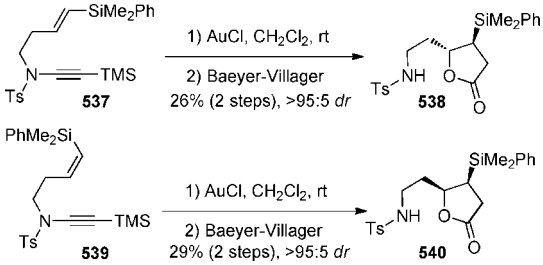
Further analysis[137b] via deuterium labeling supported the initial formation of silylated cyclobutene **533**, followed by desilylation and hydrolysis to afford the isolated dideuterated aminocyclobutanone **536** (Scheme 140).

Cossy also reported the use of *E*- and *Z*-substituted eneynamides **537** and **539** to give *cis*- or *trans*-disubstituted lactones (Scheme 141). As expected from the diastereoselectivity analysis provided above, the relationship across the olefin was conserved in the formation of product.

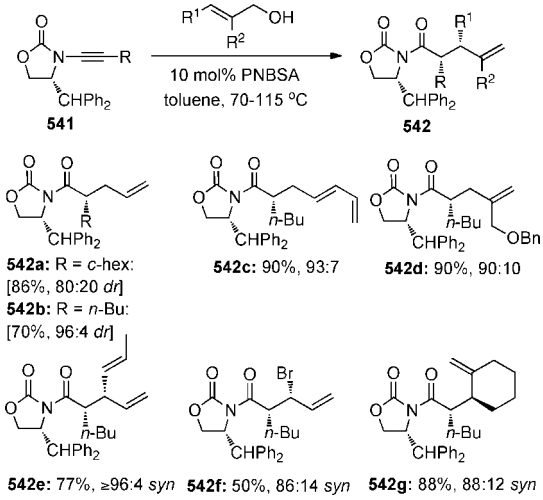
3.3.2. Pericyclic Rearrangements

In 2002, Hsung[138] showcased the first Ficini−Claisen rearrangement with chiral ynamides, proceeding with high levels of diastereoselectivity and in good to excellent yields (Scheme 142). The use of *p*-nitrobenzenesulfonic acid (PNBSA) minimized hydrolysis of the ynamide, allowing

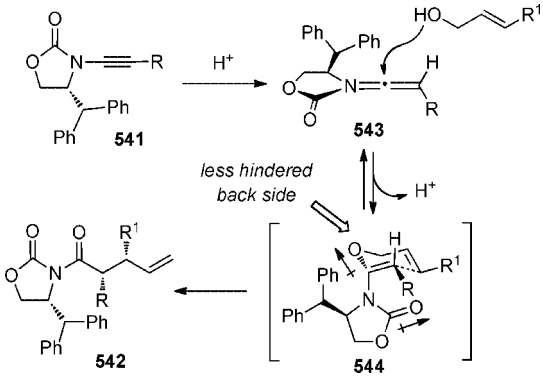
Scheme 141



Scheme 142



Scheme 143

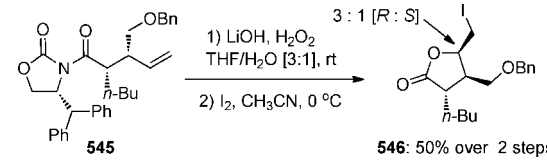


for the optimal yields of **542** to be obtained. The highest level of diastereomeric control was achieved using a benzyl-substituted oxazolidinone auxiliary [up to 96:4 *dr*]. It is noteworthy that a variety of allyl alcohols could be used with good yields and *dr* favoring the *syn* isomers, many of which cannot be accessed through classical Evans' asymmetric alkylation.

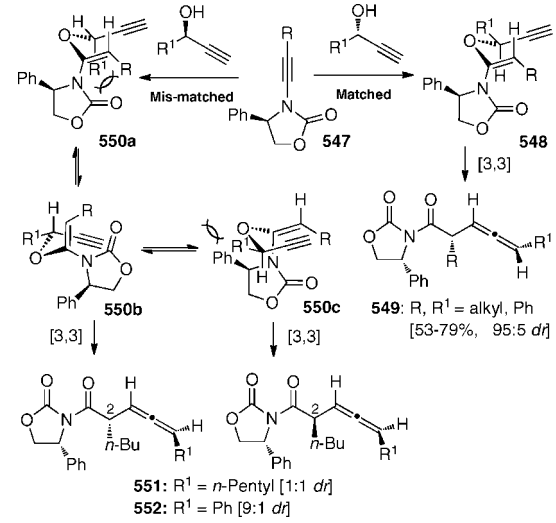
A plausible mechanistic model to explain the stereochemical outcome of this transformation is shown in Scheme 143. Protonation of **541** gives keteniminium **543**, which would be attacked by the allyl alcohol over H rather than over the R group. By comparison to Evan's model for asymmetric aldol chemistry, minimization of the dipole moments in ketene aminal **544** and positioning of the R^1 group equatorial would favor Claisen-rearrangement from the less-hindered back face to give the observed *syn* diastereomer.

Cleavage of the chiral auxiliary and iodolactonization under standard conditions proceeded smoothly to give chiral lactones **546** in 3:1 *dr* favoring the *R*-conformation (Scheme 144).

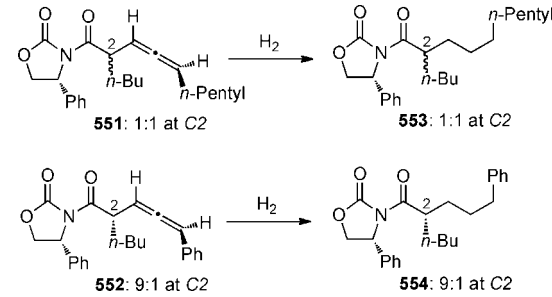
Scheme 144



Scheme 145



Scheme 146

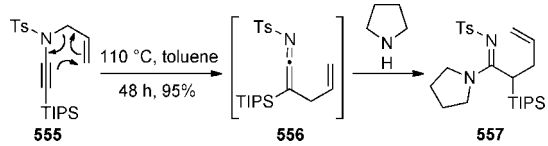


This research was later expanded upon with the first example of a Saucy−Marbet[139] rearrangement of chiral ynamides with chiral propargyl alcohols[140] (Scheme 145). After addition of the alcohol to give either **548** (matched) or **550a** (mismatched), the resulting yne-enamides undergo a concerted [3,3]-sigmatropic rearrangement. In the case where the two chiral entities are sterically matched, the allenyl imides **549** are produced in good yields with excellent diastereoselectivities. For the mismatched examples, the equilibrium between **550b** and **550c** governs the diastereomeric outcome, with a bulky substituent on the chiral alcohol favoring **550b** by minimizing steric interactions between R^1 and the chiral auxiliary.

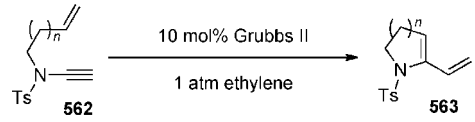
In order to determine the origin of the lower diastereoselectivity in the mismatched examples (i.e., from either C2 or the axial chirality of the allene), the allene was hydrogenated in both **551** and **552**, destroying any axial chirality.[141] As the resultant imides maintained the original diastereomeric ratio, it became clear that the lack of stereochemical control was centered at C2 and the chirality transfer from the chiral alcohol to the allene was in fact high (Scheme 146).

Hsung[142] recently disclosed a thermal *aza*-Claisen rearrangement of silylated ynamides **555** to isolable ketenimines **556**, which can be trapped *in situ* with nucleophilic amines (Scheme 147). In refluxing toluene, the reaction proceeded

Scheme 147

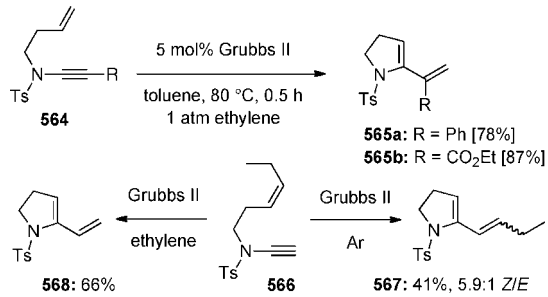


Scheme 148



n =	Conditions	Time	Yield [%]
1	CH_2Cl_2/reflux	4 h	66
1	Tol/80 °C	15 min	83
2	CH_2Cl_2/reflux	6 h	85
2	CH_2Cl_2/reflux/Ar atm	5 h	82

Scheme 149



efficiently to give allylated amidines **557** in high yields as a complementary method to the palladium-catalyzed reaction (section 3.7).

Another pericyclic rearrangement process was described by Oshima;[83] it involves a metal-mediated *aza*-Claisen rearrangement of ynamide following the addition of alkyl or aryl Grignard reagents (Scheme 54 in section 3.1.4).

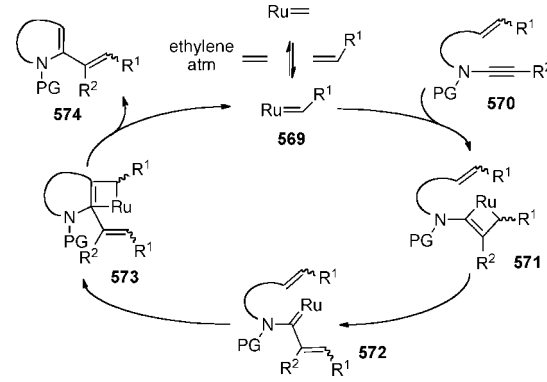
3.3.3. Metal-Catalyzed Ring-Closing Metathesis

In 2002 Mori[143] reported the first ring-closing metathesis (RCM) of ene-ynamides **562** using Grubbs' second-generation catalyst (Scheme 148). When $n = 1$, the reaction proceeded best in toluene at 80 °C under an atmosphere of ethylene; however, with a longer tether ($n = 2$), refluxing dichloromethane led to the highest yields. Intriguingly, the reaction proceeded in similar yield under an argon atmosphere for both substrates.

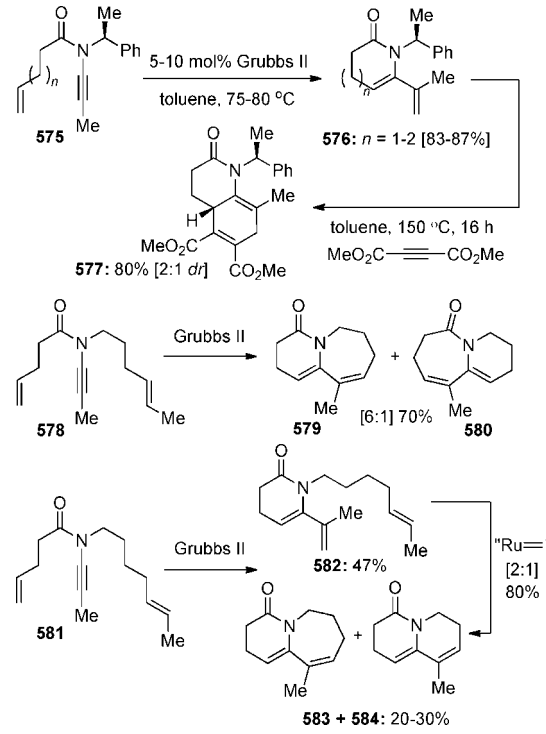
Mori[144] later expanded on the scope of the reaction to include a variety of terminally substituted ynamides **564**. Shown in Scheme 149 are two representative examples. Both electron rich and electron poor substituents could be tolerated, producing the respective *aza*-1,3-dienes **565** in good yields. An interesting reaction dichotomy was observed for (*Z*)-ene-ynamide **566**. Under one atmosphere of argon, the expected metathesis product **567** was isolated in 41% yield as a 5.9:1 mixture of *Z*:*E* isomers. Alternatively, one atmosphere of ethylene gas provided *aza*-diene **568** in 66% yield as a result of ethylene exchange with the ruthenium alkylidene.

Mechanistically, the transformation occurs through a series of [2 + 2] and retro-[2 + 2] cycloadditions initiated at the alkyne to give carbene complex **572** (Scheme 150). Intramolecular cycloaddition and cycloreversion yields the product

Scheme 150



Scheme 151



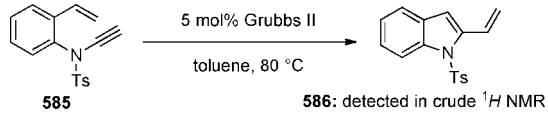
574 and regenerates the reactive ruthenium alkylidene to continue the catalytic cycle.

Soon after Mori reported their initial discovery of the ene-ynamide RCM, Hsung[145] developed a modification by incorporating the tethered alkene into the electron-withdrawing *N*-substituent, allowing the use of a chiral auxiliary as demonstrated by the transformation of **575** to **576** (Scheme 151). This route provided an entry to chiral 2-amido dienes containing either a fused 6- or 7-membered lactam in good yields, which could be further functionalized through Diels−Alder chemistry to give **577** with moderate diastereoselectivity.

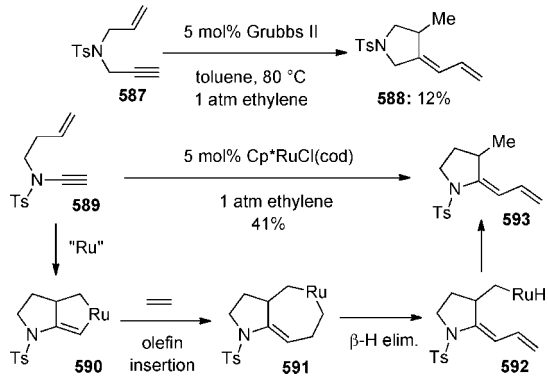
Expanding on this concept, Hsung was able to develop the first tandem RCM of diene-ynamides such as **578** and **581**. The sequence progressed smoothly for **578**, yielding a 6:1 mixture of **579**:**580**, depending on which alkene was involved in the first RCM. By extending the tethering length for one of the alkenes, a mixture of mono-RCM product **582** and double-RCM products **583** and **584** was isolated. However, resubjecting **582** to the reaction conditions provided the double-RCM products in good yield.

Pérez-Castells and co-workers[146] attempted to use the RCM of ene-ynamide **585** for the synthesis of natural product

Scheme 152



Scheme 153



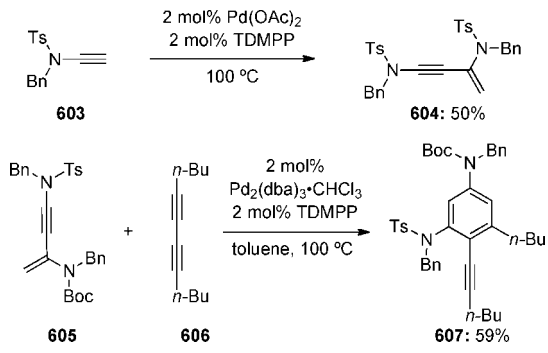
scaffolds; however, they were only able to detect the desired vinyl indole **586** in the crude ^{1}H NMR (Scheme 152). Attempts at isolation were unsuccessful.

While initially probing the reactivity of enynes in RCM, Mori found that enyne **587** yielded a mixture of the formal metathesis product and unprecedented diene **588** (Scheme 153). Six years later,[147] they revisited this issue, and by exploring the use of other ruthenium catalysts, they were able to optimize the yields of 1-azadienes such as **593** from ene-ynamide **589**. They proposed that the mechanism for these transformations occurs through ruthenacyclopentene **590**, into which ethylene can undergo olefin insertion to give ruthenacycloheptene **591**. β-Hydride elimination followed by reductive elimination would yield the observed 1-amido-dienes **593**.

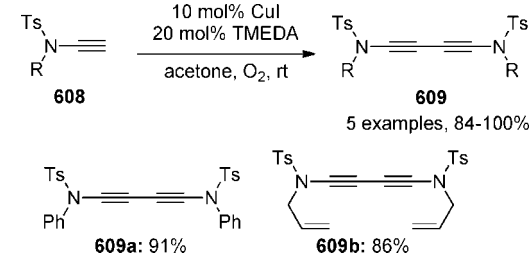
3.4. Metal-Catalyzed Coupling Reactions

One of the most concise methods for synthesizing complex ynamides and enamides has proven to be via metal-catalyzed coupling reactions. Yamamoto[148] demonstrated the synthesis of polysubstituted anilines via Pd-catalyzed cross-benzannulations. The conjugated enyne **604** was prepared in moderate yield by dimerization of ynamide **603** (Scheme 154). Ene-ynamide **605** could similarly be subjected to the cross-benzannulation reaction with conjugated diyne **606** to prepare the highly functionalized aniline **607** in 59% yield with high regioselectivity under relatively mild reaction conditions.

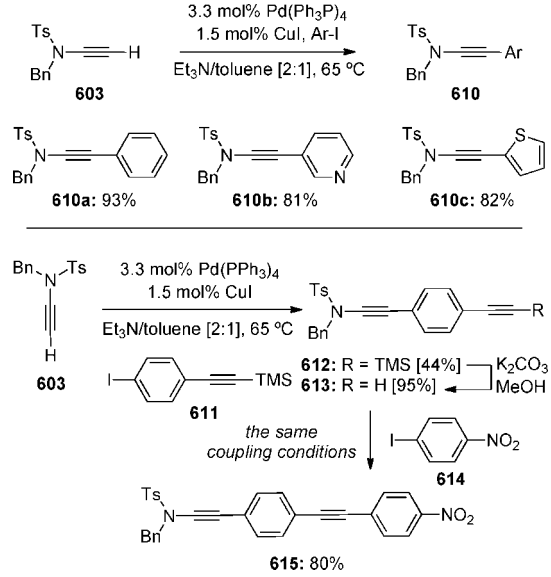
Scheme 154



Scheme 155



Scheme 156



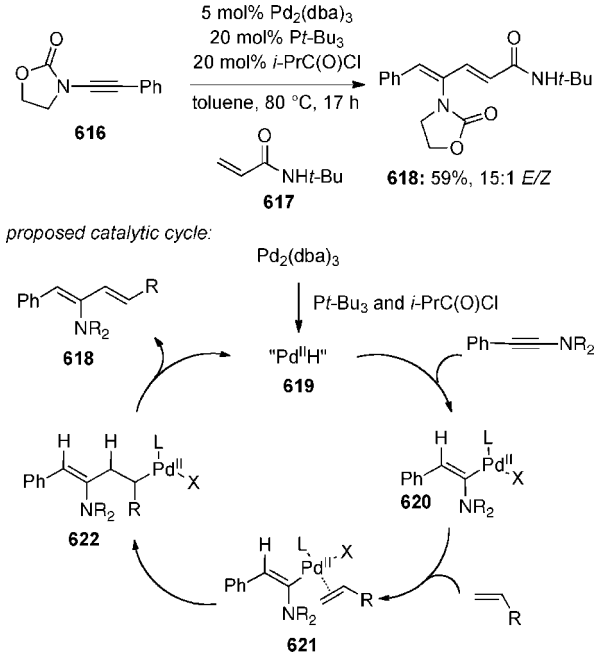
The homocoupling of ynamide **608** was first reported by Saá[149,150] in 2004. The dimerization could be catalyzed by CuI/TMEDA to afford diynes **609** in high yield (Scheme 155).

Later, Hsung[151] succeeded in the first Sonogashira cross-coupling of ynamides with aryl and vinyl iodides under Pd-catalyzed conditions (Scheme 156). This methodology could tolerate a variety of heteroatoms including N, S, and O to give terminally substituted ynamides **610**. Notably, competing dimerization pathways (as shown in Scheme 155) were not observed. Hsung also applied this protocol toward the construction of extended conjugated phenylacetylenic systems. The first coupling reaction between ynamides **603** and aryl iodide **611** afforded TMS-capped acetylenes **612** in 44% yield. Subsequent basic desilylation of **612** and a second Sonogashira coupling of the resulting ynamide **613** with another aryl iodide **614** gave the conjugated yne-ynamide **615** in high yield.

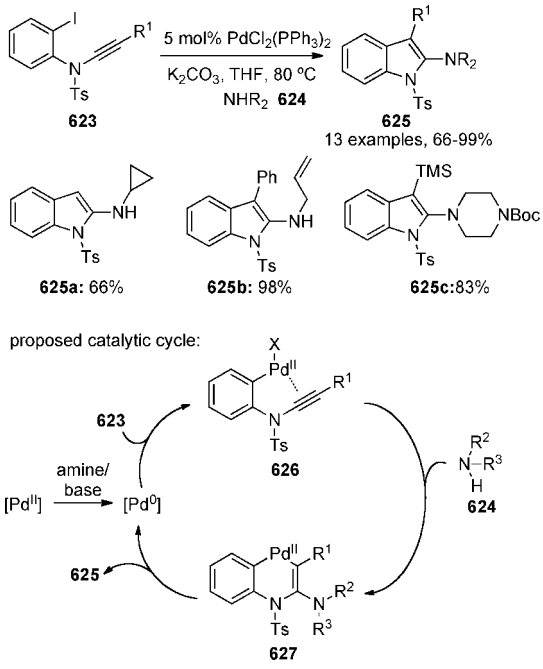
In 2004, Saá[39] demonstrated a ZnBr-mediated Negishi coupling of ynamides to give similar arylated ynamides, which was discussed in Scheme 10.

Skrydstrup[152] accomplished a very interesting intermolecular Mozoroki−Heck-type enyne coupling reaction between electron deficient olefin **617** and ynamide **616** to access synthetically rare push−pull 2-amido-diene **618** in moderate yield with high regioselectivity and *E*/*Z* control (Scheme 157). Mechanistically, the catalytic Pd(II) hydride species **619** was generated from isobutyryl chloride, likely by oxidative addition of Pd^0 into the C−Cl bond, followed by decarbonylation and subsequent β-hydride elimination. The Pd−H complex underwent hydropalladation with alkynes, providing alkenyl Pd(II) intermediates **620**. Association of

Scheme 157



Scheme 158

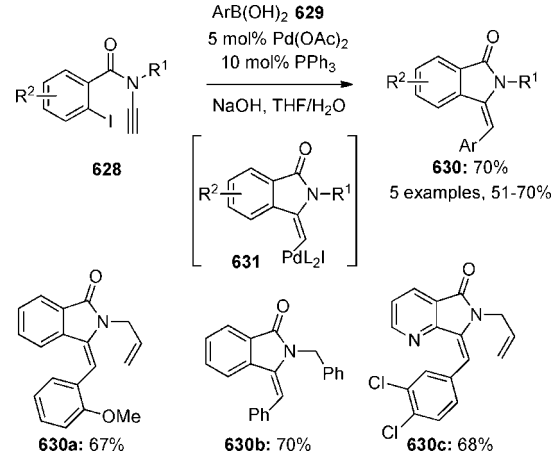


the alkene followed by olefin insertion and β-hydride elimination would afford **618** and regenerate the reactive Pd−H species.

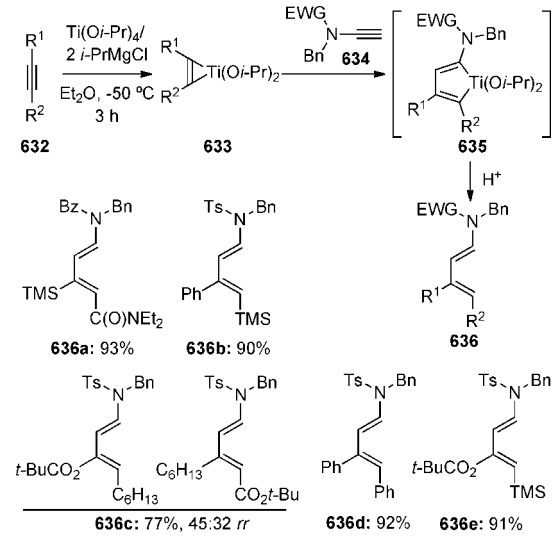
A diversity-tolerant 2-amidoindole synthesis via Pd-catalyzed heteroannulation was reported by Witulski and coworkers.[153] Their catalytic system allowed for the preparation of a wide variety of 2-amidoindoles (Scheme 158). The proposed mechanism involves *in situ* formation of Pd^0, followed by oxidative addition into the C−X bond to give **626**. Addition of amines to the activated ynamide **626** would generate the vinyl-Pd intermediate **627**. Reductive elimination would afford product **625** and regenerate the active Pd^0 catalyst.

Cossy[154] reported a concise access to isoindolinones via a Pd-catalyzed Heck−Suzuki−Miyaura domino reaction of ynamides (Scheme 159). After ynamide **628** underwent

Scheme 159



Scheme 160



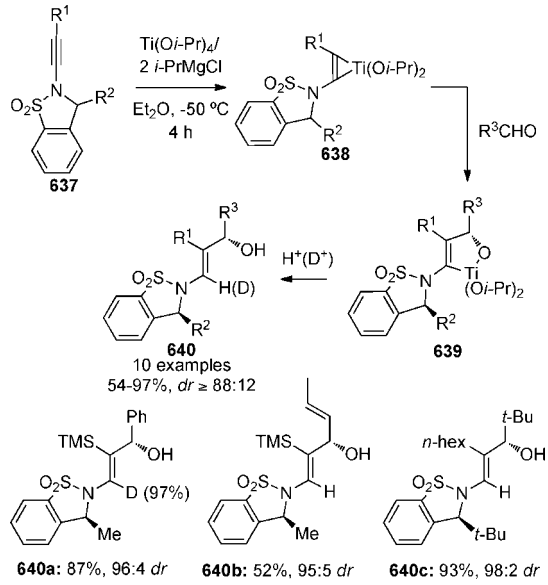
cyclization, the resulting vinyl-Pd intermediate **631** could be transmetalated with various aryl boronic acids **629** to afford 3-(arylmethylene)isoindolinones **630** in good yield with high *E*-selectivity. In the natural product synthesis section of this review, the application of this transformation in total synthesis will be discussed.

In addition to a number of classic homocoupling and cross-coupling protocols shown in this section, Urabe and Sato[155] discovered a unique coupling protocol via formation of acetylene- or ynamido-titanium complexes (Scheme 160). Treatment of alkyne **632** with $Ti(O\textit{i}\text{-}Pr)_4$/2-*i*-PrMgCl generated the Ti-cyclopropene intermediate **633**, which further reacted with ynamide **634**, providing the titanacyclopentadiene **635**. Acid hydrolysis of **635** afforded dienamides **636** in excellent yields with high functional group tolerance. In several cases involving unsymmetrical alkynes, a mixture of regioisomeric dienes (shown with **636c**) was observed.

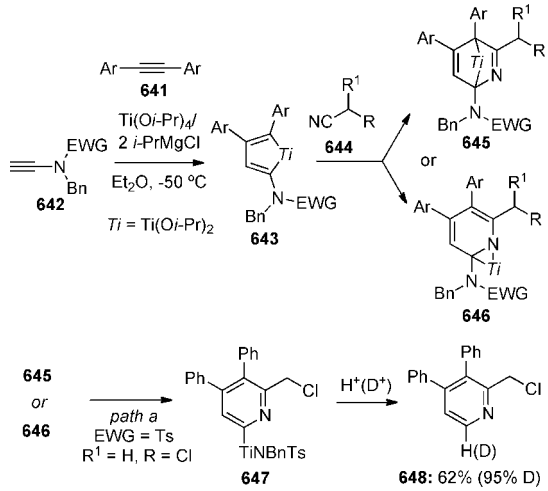
In a similar manner, *N*-substituted Ti-cyclopropene intermediates **638** could be formed from ynamides **637**.[57b,156] This allowed the formation of oxatitanacycles **639** via coupling reactions with a variety of aldehydes. The remaining vinyl-titanium bond in **639** was confirmed by deuteriolysis (97% D in **640a**). Hydrolysis of **639** gave a wide range of amido-substituted allylic alcohols **640** with good diastereoselectivity via notable 1,5-remote asymmetric induction (Scheme 161).

Titanacyclopentadienes **643** were also capable of reacting with nitriles **644** to generate titanacycles **645** or **646**[157]

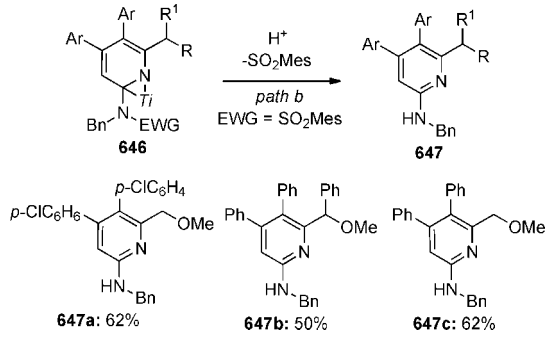
Scheme 161



Scheme 162



Scheme 163

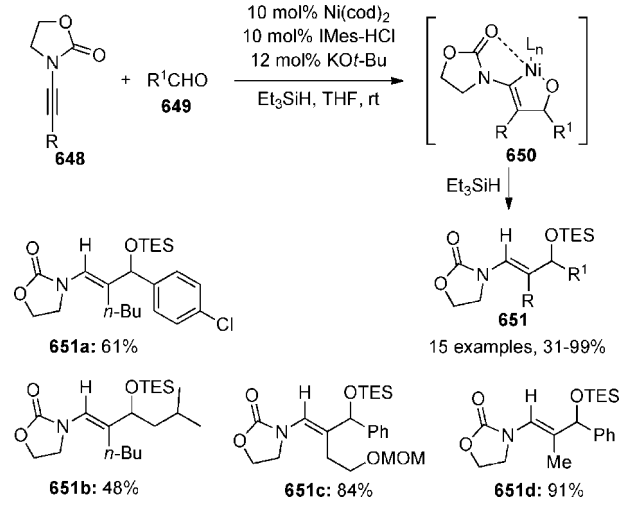


(Scheme 162). Depending on the type of *N*-protecting group, two reaction pathways were observed. From tosyl-protected ynamides, formation of **646** was followed by rearrangement to metalated pyridine **647**, which was confirmed by deuteriolysis (path a).

Using mesyl-protected ynamides, formation of **646** was followed by elimination of the mesyl group to provide 1-amino-pyridines **647** in high yields (path b) (Scheme 163).

Recently, Sato[158] reported a Ni-NHC-catalyzed multicomponent coupling of ynamides, aldehydes, and silanes to

Scheme 164



access functionalized enamides (Scheme 164). Reactions between ynamides **648** and various aldehydes resulted in regioselective formation of oxanickelacycle intermediate **650**, and then hydride reduction of the metallacycle by Et_3SiH gave the desired enamides **651** in high yield with a high degree of *E*/*Z* control.

3.5. Reductions of Ynamides

Hsung[56b] accomplished the first stereoselective reduction of ynamides. A variety of *Z*-enamides **660** could be prepared by Lindlar hydrogenation of ynamides **659** in high yields, or *E*-enamide **662** could be accessed by DIBAL-H reduction at −78 °C in moderate yield (Scheme 165).

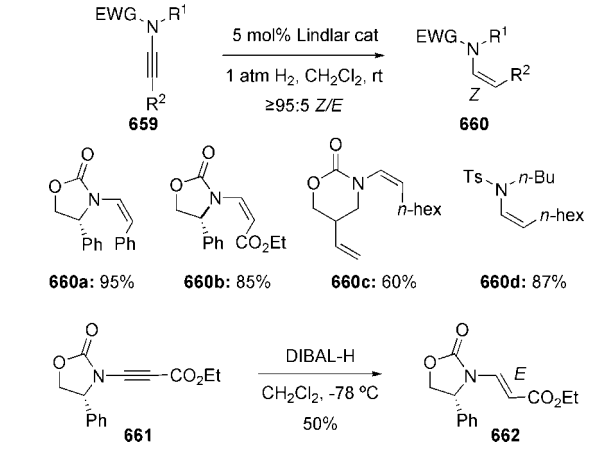
Alternatively, Cossy and Meyer[159,160] prepared *Z*-enamides *Z*-**664** via Ti(II)-mediated reduction of ynamides **663** or *E*-enamides *E*-**664** via Red-Al-mediated reduction (Scheme 166).

3.6. Reactions Involving Ynamido-Metal Intermediates

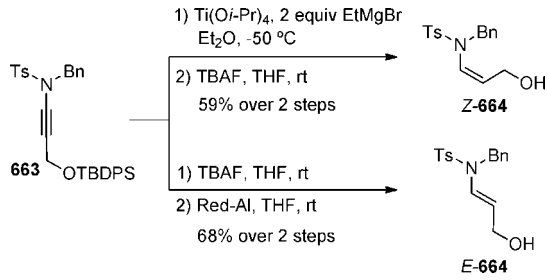
While there have been many recent and notable improvements in ynamide chemistry, perhaps one of the newest and most exciting areas in this field involves the generation and reactivity of ynamido-metal intermediates.

Hsung and Zhang[142] recently reported a possible metalloynamido complex in their work on the synthesis of amidines **668** from *N*-allyl ynamides **665** (Scheme 167). Pd(0) was found to catalyze an N-to-C allyl transfer, presumably

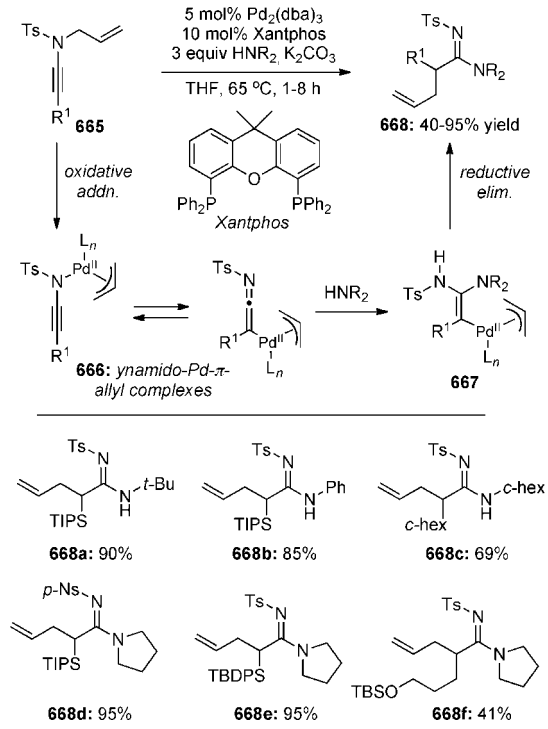
Scheme 165



Scheme 166



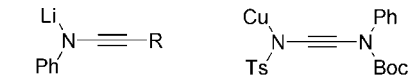
Scheme 167



through oxidative addition into the C−N bond to form an ynamido-Pd-π-allyl complex in equilibrium with the ketenimine-Pd complex **666**. Nucleophilic addition of various amines into the reactive ketenimine complex **666** followed by reductive elimination of **667** provides the allyl-transferred amidine products **668**. Within their work, they found that use of the xantphos ligand was necessary to accelerate reductive elimination, preventing deallylation of the Pd-complex, especially when using more nucleophilic secondary amines.

It was found that a variety of amidines could be prepared using primary or secondary amines and various terminally substituted *N*-sulfonyl ynamides.

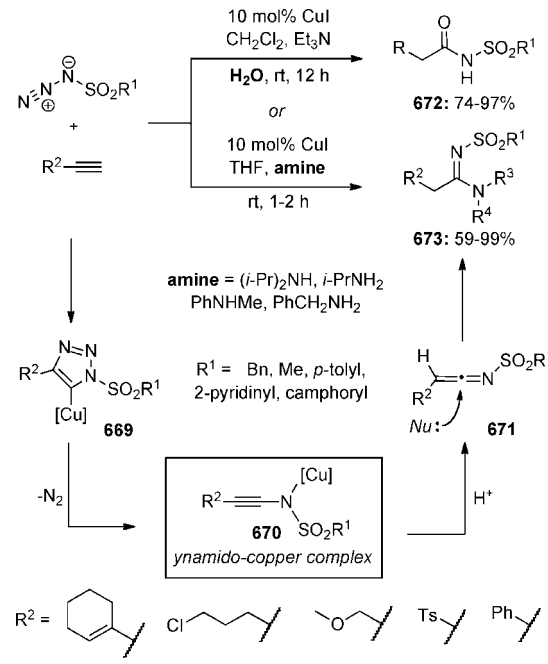
Other metals have also been reported to form ynamido-metal intermediates, as described in previous sections. In particular, ynamido-copper intermediates generated by a formal [3 + 2] cycloaddition have been recognized as a very useful synthon in multicomponent reactions.



Schemes 35 and 37 *Scheme 91*

Chang[161] reported the synthesis of various *N*-sulfonyl amides and amidines via copper(I)-catalyzed "click" chemistry, both of which could be obtained through a common

Scheme 168



ynamido-copper intermediate **670** (Scheme 168). The reaction of various terminal alkynes with alkyl- or arylsulfonyl azides in the presence of Cu(I) salts led to amide products **672** when using water as the nucleophile or amidines **673** with the use of amines. After initial formation of triazole **669**, elimination of N_2 would give the ynamido-copper complex **670**, which could be protonated to give a reactive ketenimine **671**. Addition of the nucleophile to the ketenimine would then lead to the desired product. Various amine nucleophiles could be tolerated as well as a variety of other functional groups such as alkynes and azides.

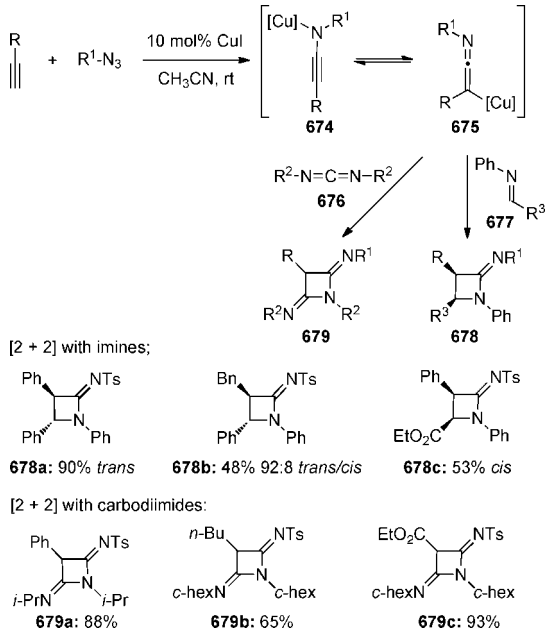
Fokin[162,163] later reported a similar procedure for the formation of amide products, in which the use of tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine was found to accelerate the reaction and sodium ascorbate was used to prevent the formation of oxidation byproducts.

Both Fokin[164] and Xu[165] also cleverly applied the use of these ynamido-copper intermediates in cycloaddition chemistry (Scheme 169). Fokin showed that ketenimine intermediates **675** underwent [2 + 2] cycloaddition reactions with imines **677**, resulting in azetidinimine products **678**. In most cases, the *trans* stereochemistry was observed in the product. However, the *cis*-product could be obtained predominately with electron-deficient imines. Similarly, this key intermediate **675** was shown by Xu[165] to undergo [2 + 2] cycloadditions with carbodiimides **676** to synthesize a variety of 2,4-diiminoazetidines **679**.

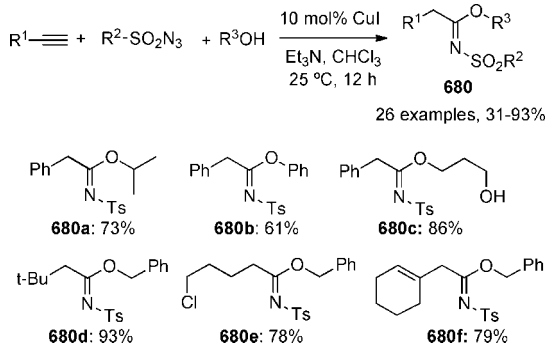
Additionally, Chang[166] reported an efficient three-component reaction of terminal alkynes, sulfonylazides, and alcohols for a facile access to *N*-sulfonylimidates **680**. This reaction proceeded through a similar ynamido-copper intermediate generated through formal [3 + 2] cycloaddition (Scheme 170).

Wang[167] has beautifully demonstrated a variety of multicomponent annulation reactions via equilibration of ynamido-copper intermediate **681** and ketenimine intermediate **682**, which were again generated through a formal [3 + 2] cycloaddition (Scheme 171). In the presence of an amine base, addition of salicylaldehydes **683** provided the intermediate **684**. Subsequent cyclization followed by elimination

Scheme 169



Scheme 170



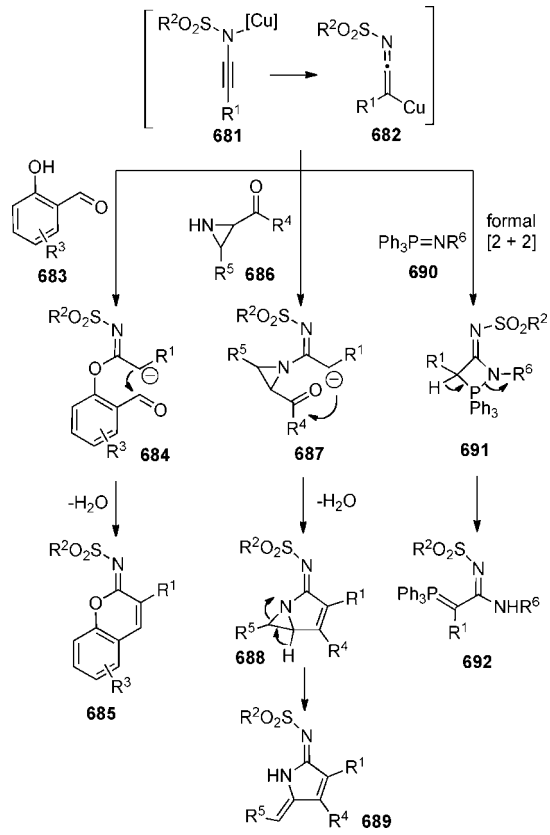
of water efficiently afforded a wide range of coumarins **685**. Notably, this protocol can be applied to ketones to access even further functionalized coumarins. Similarly, aziridines **686** could undergo addition reactions with **682** to give **687**, which could then cyclize and dehydrate to afford 1-*aza*-bicyclo[3.1.0]hexenes **688**. The subsequent ring-opening of **688** would afford pyrrolines **689**. Finally, a formal [2 + 2] cycloaddition of iminophosphoranes **690** and ketenimines **682** was shown to form amidine ylides **692** through ring-opening of the intermediate 1,2-phosphazetidine **691**.

Also, an intramolecular variant was reported by Fu[168] for the formation of medium- and large-sized heterocycles **698** using "click" chemistry. They proposed the intramolecular addition of nitrogen or oxygen nucleophiles to the ketenimine-copper intermediate **697** (Scheme 172). After elimination of nitrogen gas from triazole **695**, it is possible for the ynamido-copper complex **696** to exist in equilibrium with a ketenimine-copper complex **697** rather than being protonated. Trapping of the ketenimine-copper complex by the nucleophile followed by elimination of copper would then give the heterocyclic product. Various-sized macrocycles **698** could be obtained in good yields from the *ortho*-diamides **694**.

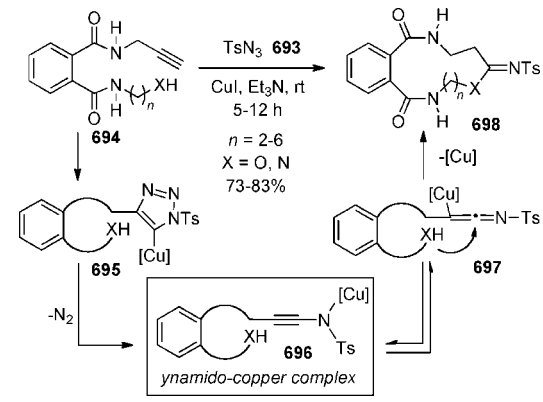
3.7. Other Reactions

Chen[65] discovered in 1998 that isocyanate containing ynamides **699** could be protected as dicobalt complexes **700** (Scheme 173), allowing further functionalization of the

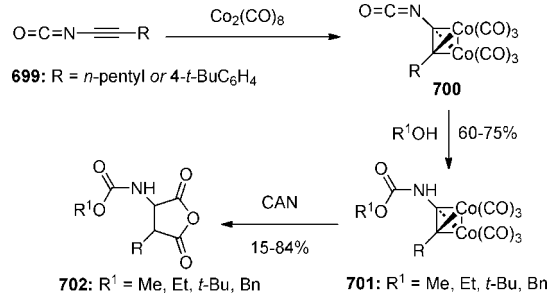
Scheme 171



Scheme 172



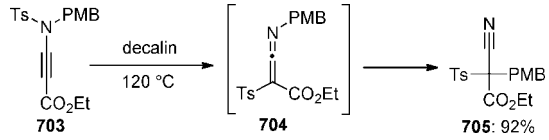
Scheme 173



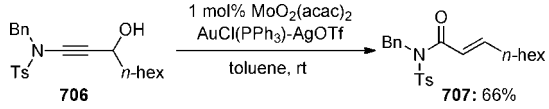
isocyanate moiety. Introduction of an alcoholic nucleophile proceeded in moderate to good yields to give carbamate complexes **701**. The dicobalt protecting group could then be oxidatively cleaved, providing access to functionalized malaeic anhydride derivatives **702**.

In 2005, Wudl[169] published an interesting example of a double-barreled migration of both the tosyl and *p*-methoxy-

Scheme 174



Scheme 175



benzyl groups of ynamide **703** to nitrile **705**, as shown in Scheme 174. The authors proposed that the tosyl transfer should be more facile, giving ketenimine **704** as a reactive intermediate.

Another example of an ynamide rearrangement was reported by Akai,[170] involving the transformation from ynamido-alcohol **706** to α,β-unsaturated amide **707** using a Mo, Au, and Ag tricatalytic system (Scheme 175).

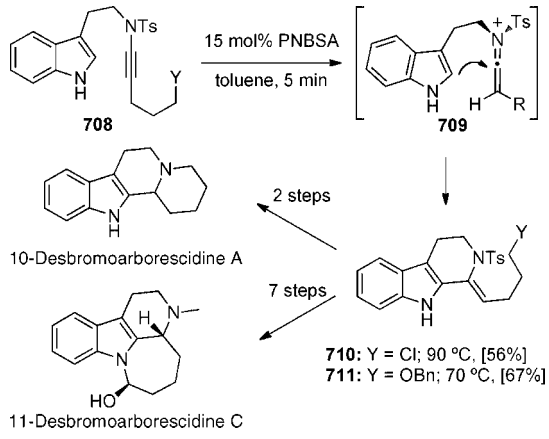
4. Ynamides in Total Synthesis of Natural Products

There have been few reports of natural product syntheses employing ynamides during a key step. Hsung[128] was the first to utilize ynamides in the total syntheses of 10-desbromoarborescidine A and 11-desbromoarborescidine C (Scheme 176). Indole-tethered ynamides **708** were subjected to Brønsted acid-catalyzed Pictet-Spengler cyclization via the keteniminium intermediate **709** to construct the tricyclic core of the desbromoarborescidines **710** and **711**. From **710**, reduction of the enamide followed by intramolecular *N*-alkylation provided 10-desbromoarborescidine A, and 11-desbromoarborescidine C was reached in 7 more steps from **711**.

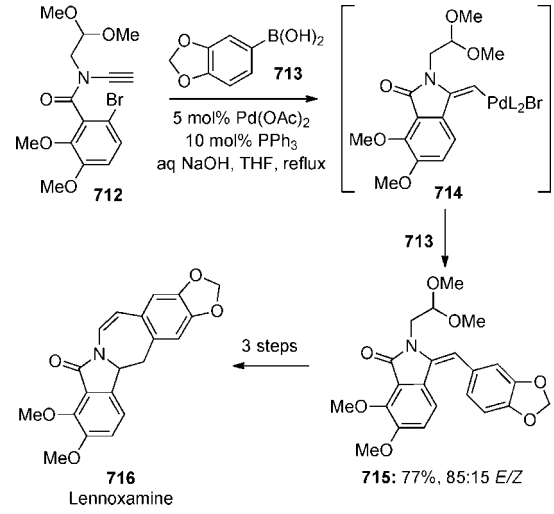
Cossy and Meyer[171] accomplished a total synthesis of lennoxamine (Scheme 177) via tandem intramolecular Heck-type cyclizations of ynamides **712** to generate the vinyl Pd(II) intermediate **714**, which underwent transmetalation with aryl boronic acid **713**, affording the desired product **715** in high yield with moderate *E*/*Z* control. Hydrogenation of the resulting enamide **715** followed by construction of the seven-membered ring via a ring-closing Friedel−Crafts reaction and a second enamide reduction completed the total synthesis of lennoxamine.

Most recently, Witulski[172] completed an elegant total synthesis of antiostatin A_1 (Scheme 178). As a key step, a

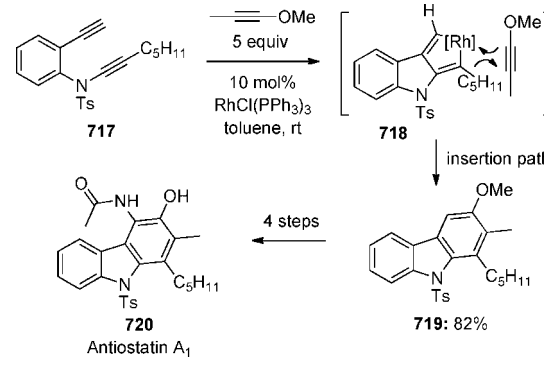
Scheme 176



Scheme 177



Scheme 178

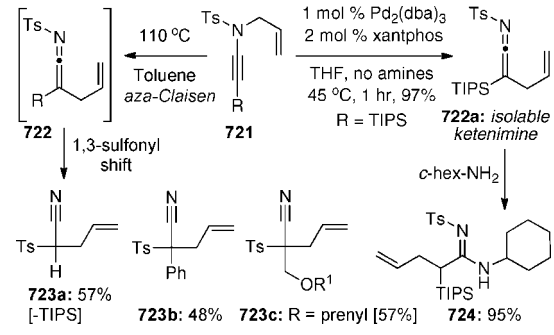


chemo- and regioselective Rh-catalyzed alkyne cyclotrimerization reaction employing ynamide **717** afforded **719** in high yield through trapping of the rhodiacyclopentadiene intermediate **718** with an ynol ether. From the cyclotrimerization product **719**, the total synthesis of antiostatin A_1 **720** was accomplished in four steps.

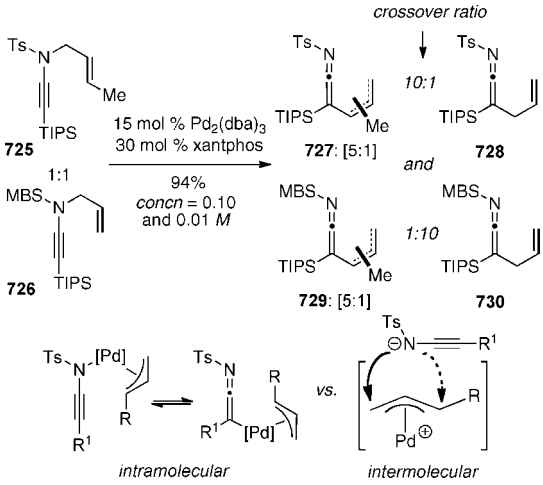
5. Most Recent Developments

After the manuscript of this review was submitted, Hsung and co-workers disclosed an extension of his Pd-catalyzed *N*-allyl ynamide rearrangement for the synthesis of amidines (Scheme 179). They discovered that, under Pd-catalyzed conditions without an amine nucleophile present, the intermediate ketenimine **722a** could be isolated in near quantitative yield even after silica gel chromatography. Upon treatment with cyclohexylamine, amidine **724** was isolated, supporting **722a** as a reactive intermediate. Furthermore,

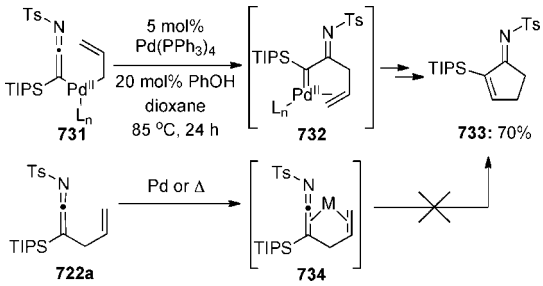
Scheme 179



Scheme 180



Scheme 181



when alkyl- and aryl-terminated ynamides were employed in a thermal *aza*-Claisen variation of this rearrangement, an unusual 1,3-sulfonyl transfer occurred to give nitriles **723** bearing an adjacent quaternary center. In the case of **723a**, the nitrile was formed, presumably after hydrolysis of the silicon group in **722a**.

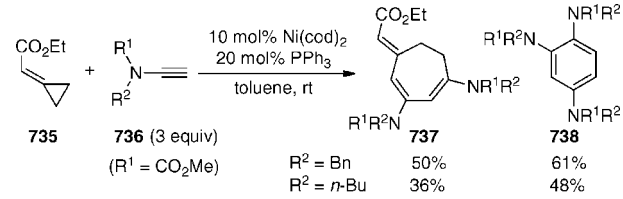
With the isolation of the ketenimine intermediate, it became possible to probe the mechanism of the Pd-catalyzed allyl transfer, namely whether the transfer occurred intra- or intermolecularly (Scheme 180). A crossover experiment employing a 1:1 mixture of *N*-crotyl and *N*-allyl ynamides **725** and **726** resulted in a 10:1 product distribution disfavoring any crossover. This result supports an intramolecular transfer through a tightly coordinated ynamido-Pd-π-allyl intermediate rather than via a dissociative Tsuji−Trost type mechanism.

The authors also demonstrated an *aza*-Rautenstrauch-type cyclization of Pd-ketenimine **731** to give silylated cyclopentenimine **733**, presumably through Pd-carbenoid **732** (Scheme 181). Interestingly, subjection of **722a** to either Pd-catalyzed or thermal conditions resulted in no formation of **733**, implying that the cyclization must occur before reductive elimination and that an imino-Nazarov type cyclization is not in operation.

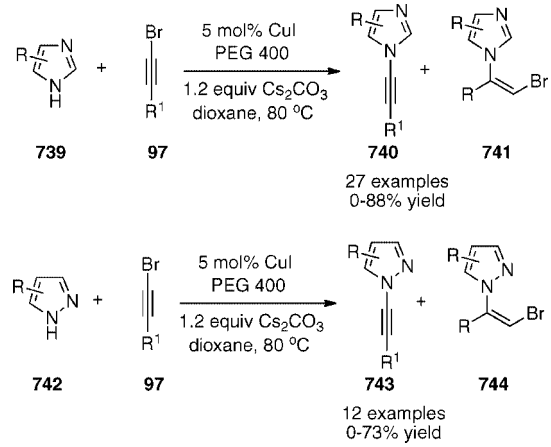
A nickel-catalyzed [3 + 2 + 2] cycloaddition of ethyl cyclopropylideneaceate **735** and ynamides **736** was described by Saito (Scheme 182). The reaction procedure involves slow addition of **735** and **736** over several hours to the mixture of catalyst and ligand. It was found that the cocyclization product **737** could be isolated in 36−50% yield; however, a significant amount of the trisubsituted benzene **738** was also observed. The authors also found that ynamines bearing bulky *N*-substituents were more efficient substrates.

One of the most recent contributions to ynamide chemistry was disclosed by Burley and Davies, who reported a facile

Scheme 182



Scheme 183



and efficient Cu(I)-catalyzed N-alkynylation of imidazoles, benzimidazoles, indazoles, and pyrazoles using poly(ethylene glycol)400 (PEG400) as solvent medium (Scheme 183). It was suggested that PEG can act as a efficient phase transfer solvent by providing a bridge between substrates and inorganic base. Meanwhile, PEG may also act as ligand for a copper catalyst, as it was found that common Cu(I)-stabilizing ligands were not necessary for the success of the reaction. Another improvement of this process involves the use of microwave irradiation, which significantly reduced the reaction time from 24 h to 30 min. The major side-products isolated from the crude reaction mixture were bromoalkenes **741** and **744**, and their formation increased as the steric bulk of the heteroarene increased.

6. Conclusions

The field of ynamide chemistry has experienced rapid expansion in the past decade, fueled by the development of efficient means of preparation. Beautiful work has been accomplished showcasing the unique reactivity of ynamides in a plethora of reactions that have delivered a diverse array of novel carbo- and heterocyclic structures representing prevalent and important pharmacophores in addition to being useful platforms for further transformations. To date, ynamides have yet to be extensively employed in total synthesis; however, with all of the recent methodological advancements, we are very interested to see the work that is surely on the horizon.

Perhaps the most exciting area of current ynamide chemistry is the discovery and exploitation of ynamido-metal intermediates. These methods provide unique modes of reactivity and are sure to play a vital role in establishing ynamides as a powerful synthon for the new millennium.

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