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Ynamides

Ynamides: Versatile Tools in Organic Synthesis

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Ynamides display an exceptionally fine balance between stability and reactivity. They also offer unique and multiple opportunities for the inclusion of nitrogen-based functionalities into organic molecules, and are emerging as especially useful and versatile building blocks for organic synthesis. Recent breakthroughs in the preparation of these substrates have revitalized interest in nitrogen-substituted alkynes, and the beginning of the 21st century has witnessed an ever-increasing number of publications reporting the development of new reactions or synthetic sequences starting from ynamides. This Review highlights major developments in this area.

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1. Introduction: Not Laboratory Freaks Anymore

Heteroatom-substituted alkynes probably represent the most versatile class of alkynes. An especially useful subgroup is the one containing a nitrogen atom directly attached to the triple bond: ynamines.[1] The electron-donating ability of the nitrogen atom strongly polarizes the triple bond, which allows for an exceptionally high level of reactivity together with a strong differentiation of the two sp-hybridized carbon atoms. The first ynamine was isolated by Zaugg et al. after an "*unusual reaction of propargyl bromide with phenothiazine*" in 1958,[2] and five years later the first practical synthesis by Viehe was developed.[3] The synthetic utility of ynamines became apparent within the organic synthesis community and their reactivity was thoroughly explored in the ensuing 20 years. Unlike enamines, their synthetic uses have, however, remained rather limited, and they were still considered as laboratory curiosities by most organic chemists, even if they were shown to participate in elegant, efficient, and selective transformations. Reasons for this probably include their difficult preparation, handling, and their sensitivity.

In contrast, an increasing level of interest in ynamides has become evident over the past decade. They still feature a rather strong polarization of the triple bond by virtue of the ynamine character, but it is tempered by the electron-withdrawing group, which provides enhanced stability (most of them are stable towards aqueous workups, silica gel, heating, etc.) and can also act as an efficient directing group (Figure 1). These characteristics coupled with recent breakthroughs in their synthesis have allowed for increased synthetic use and for the development of highly efficient sequences that otherwise would be difficult to accomplish using traditional ynamines.

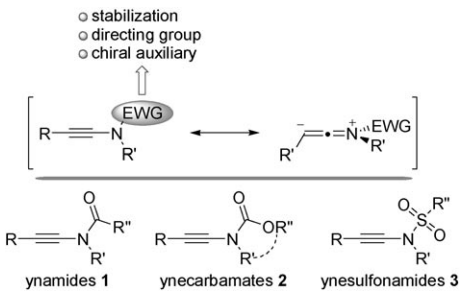

Figure 1. The most common classes of "ynamides". EWG = electron-withdrawing group.

The chemistry of ynamides was extensively and carefully reviewed by Hsung and co-workers in 2001.[1c,4,5] This Review, which was named after Ficini's review "*Ynamines: Versatile Tools in Organic Synthesis*",[1a] will cover developments in the synthesis and reactions of ynamides **1**, ynecarbamates **2**, ynesulfonamides **3**, and related compounds[6] since 2000, with the aim of highlighting contexts where they might be of strong synthetic value. For simplification, all electron-deficient ynamines will be called "ynamides" in this Review.

2. Synthesis of Ynamides: The Emergence of General and Practical Procedures

From a purely historical perspective, the first ynamide, urea derivative **6**, was obtained by Viehe and co-workers in 1972 by elimination of HCl from the corresponding α-chloro-enamide **5**, itself obtained from benzylic amide **4** (Scheme 1).[7]

2.1. Synthesis of Ynamides at the Dawn of the 21st Century

This early study by Viehe and co-workers demonstrated the feasibility of synthesizing ynamides by an elimination reaction from halo-enamides. This procedure was used

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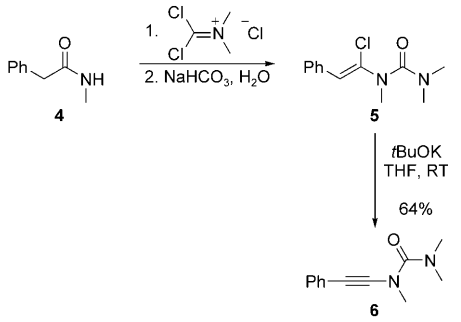
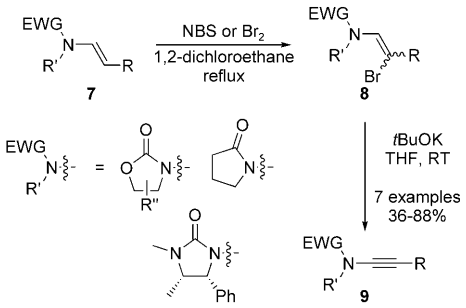


Scheme 1. 1972: The first ynamide synthesis.

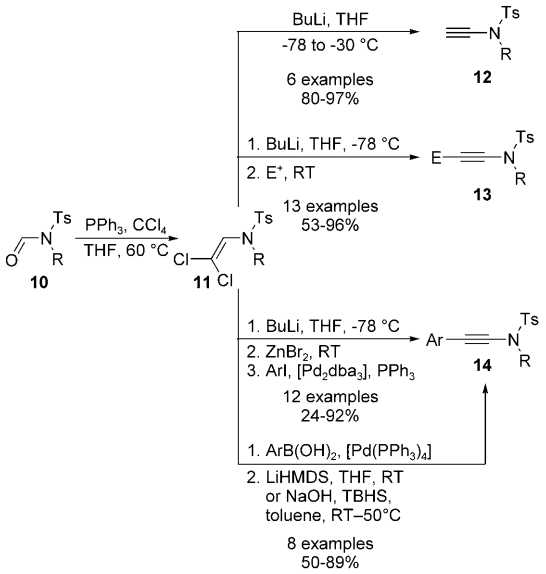
extensively, even though it depends on the availability of the starting halo-enamide and sometimes suffers from restricted substrate scope. In 2001, Hsung and co-workers extended this procedure to the use of β-bromo-enamides **8**, which could be obtained in good yields by bromination of the corresponding enamides **7** (Scheme 2). By using this sequence, pyrrolidi-



Scheme 2. Synthesis of ynamides by elimination from β-bromo-enamides.

none-, oxazolidinone-, and imidazolidinone-derived ynamides **9** could be obtained in useful yields, even though only the *Z* isomers of **8** undergo the elimination process.[8] Elimination from vinyl triflates was also used for the preparation of benzotriazole-derived ynamides.[9]

β,β-Dichloro-enamides **11**, readily obtained by treatment of formamides **10** with triphenylphosphine and tetrachloromethane, were also found to be suitable substrates for the preparation of ynamides (Scheme 3). Reaction with a strong



Scheme 3. Synthesis of ynamides from β,β-dichloro-enamides. E^+ = electrophile, LiHMDS = lithium hexamethyldisilazane, TBHS = tetrabutylammonium hydrogen sulfate, Ts = toluene-4-sulfonyl.

base at low temperature followed by hydrolysis of the resulting metalated alkyne led to **11** being smoothly transformed to the corresponding terminal ynamides **12**.[10] These products can be further transformed to aryl-substituted ynamides **14** by a Sonogashira cross-coupling reaction.[11] The addition of an electrophile before quenching the reaction provides disubstituted ynamides **13**, which are obtained in higher yields than by the direct functionalization of terminal ynamides.[12] Alternatively, transmetalation with zinc bromide and a further Negishi coupling reaction allows for the preparation of aryl-substituted ynamides **14** in reasonable to good yields.[13] Inversion of the reaction sequence (Suzuki–Miyaura coupling followed by elimination of the resulting β-chloro-enamide) also allows for an efficient preparation of aryl-substituted ynamides, as recently demonstrated by Meyer and co-workers.[14]

Another method that met with some success for the preparation of ynamides is based on the isomerization of propargyl amides **15** (Scheme 4).[15] This procedure could be successfully applied to the preparation of methyl-substituted ynamides **16**, but was found to be highly dependent on the

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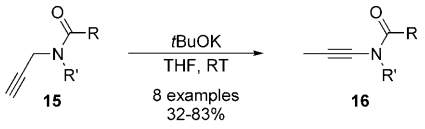
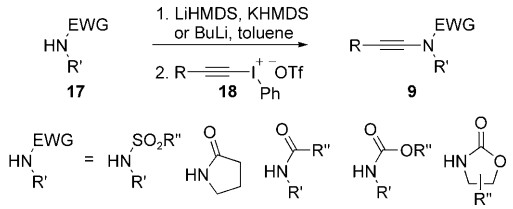
Alexis Coste was born in 1982 and studied chemistry at the Ecole Supérieure de Chimie Organique et Minérale. Since 2007, he has been carrying out PhD research as a National Cancer Institute Fellow under the supervision of François Couty and Gwilherm Evano at the University of Versailles. His work focuses on the development of copper-catalyzed transformations with application in natural product synthesis and the development of new proteasome inhibitors in a tumor-targeting approach.



Scheme 4. Synthesis of ynamides by isomerization of propargylamides.

nature of the electron-withdrawing group. Amides are in fact the only groups tolerated in the isomerization, which otherwise stops at the allenamide.[8]

A last method which ought to be mentioned, especially since it was probably the most popular before the discovery of the copper-catalyzed alkynylation, relies on the use of hypervalent iodonium salts. Following the pioneering work of Stang and co-workers, who showed that push-pull ynamines could be obtained by treating lithium amides with alkynyl iodonium salts **18**,[16] Witulski et al.[17] as well as Rainier and Imbriglio[18] have extended this procedure to the preparation of ynamides (Scheme 5).[19] However, this method still suffers from a major drawback because of the limited availability of the starting iodonium salts, which can only be substituted by silyl, aromatic, or electron-withdrawing groups.



Scheme 5. Synthesis of ynamides from alkynyl iodonium salts. KHMDS = potassium hexamethyldisilazane, OTf^- = trifluoromethanesulfonate.

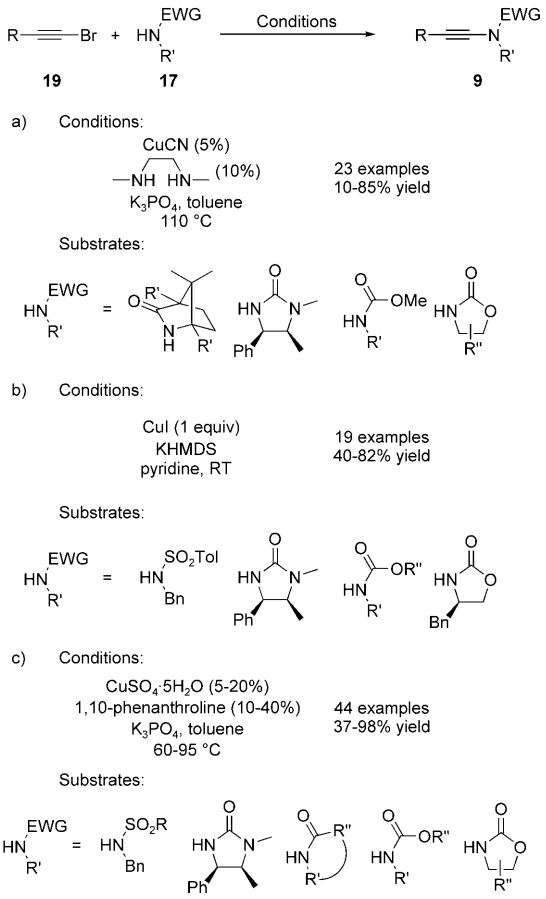
While efficient methods were reported for the preparation of ynamides at the end of the 20th century, all of them still suffered from either low substrate scope, very harsh reaction conditions, or from the requirement for lengthy reaction sequences. This probably accounts for the limited number of research groups involved in the reactivity and reaction design with ynamides. This situation has changed in the past 10 years or so with the development of highly efficient procedures based on copper catalysis. These methods, probably the most efficient to date, will be overviewed in the next section.

Kévin Jouvin was born in 1985 and studied chemistry at the University Joseph Fourier in Grenoble (France) where he did his undergraduate research with Dr. Martine Demeunynck. He is currently carrying out PhD research under the supervision of François Couty and Gwilherm Evano at the University of Versailles on the development of new transformations with ynamides and their application in natural product synthesis as well as the development of copper-catalyzed transformations.

2.2. General Procedures for the Alkynylation of Amides: Copper Showed the Way

2.2.1. Alkynylation of N Nucleophiles with Bromoalkynes

A major breakthrough in the synthesis of ynamides was reported in 2003 by the Hsung research group. Inspired by the renaissance of copper catalysis[20] and by the studies of Buchwald and co-workers on the arylation of amides,[21] Hsung and co-workers first developed a copper-catalyzed coupling of alkynyl bromides with amides by using *N*,*N*′-dimethylethylenediamine as the ligand, which provided an improved synthetic access to ynamides over the existing protocols (Scheme 6a).[22] However, severe limitations remained, such as the use of high temperatures and low substrate scope. Although oxazolidinones were good substrates in the coupling reaction, amides were mostly poor and sulfonamides were not suitable at all. Danheiser and co-workers developed a solution to this problem. The use of stoichiometric amounts of copper iodide along with potassium hexamethyldisilazane resulted in the reactions proceeding at room temperature with carbamates and sulfonamides,



Scheme 6. Copper-mediated synthesis of ynamides from alkynyl halides. a) Hsung et al. (2003);[22] b) Danheiser et al. (2003);[23] c) Hsung et al. (2004).[24] Bn = benzyl, Tol = tolyl.

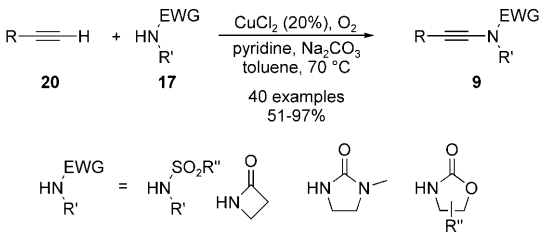
but still required the use of a strong base (Scheme 6b).[23] A general and mild procedure was finally published in 2004 by Hsung and co-workers, who reexamined this coupling protocol by screening a variety of copper sources and ligands. The use of copper sulfate pentahydrate in combination with 1,10-phenanthroline proved to be especially successful, and allowed the reaction to occur at 60–95 °C in the presence of potassium phosphate as the base (Scheme 6c).[24] From a practical point of view, it should be noted that it was later shown that the quality of the potassium phosphate is crucial for the success of the reaction.[25]

Iron trichloride was also shown to be an efficient catalyst for this alkynylation of amides.[26] However, a recent report from Buchwald and Bolm showed that the outcome of the reported $FeCl_3$-catalyzed reactions may in certain cases be significantly affected by trace quantities of other metals, particularly copper.[27]

These procedures are clearly among the most efficient to date for the preparation of ynamides. They require, however, the preparation of the starting bromoalkyne, which can be difficult in some cases, even if the vast majority of these compounds are typically formed in excellent yields by bromination of the corresponding terminal alkynes.

2.2.2. Alkynylation of N Nucleophiles with Terminal Alkynes

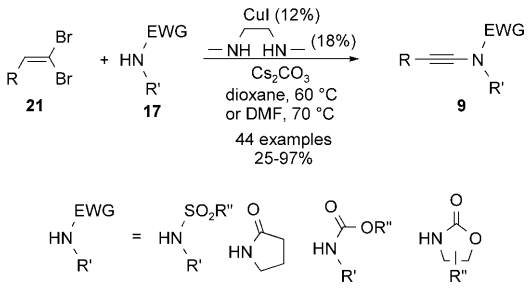
A particularly elegant procedure which relies on an oxidative alkynylation of amides with terminal alkynes **20** (Scheme 7), and thus overcomes the need for a bromoalkyne starting material, was reported by Stahl and co-workers in 2008.[28] Ynamides **9** were obtained in excellent yields by using this procedure, even on a large scale, by simply using oxygen as the terminal oxidant. Limitations of the method, however, are the need to use five equivalents of the nitrogen nucleophile **17**, which is required to reduce the amount of Glaser–Hay dimerized products, and the low reactivity of carbamates, pyrrolidinone, acyclic amides, and ureas.



Scheme 7. Synthesis of ynamides from terminal alkynes.

2.2.3. Alkynylation of N Nucleophiles with Vinyl Dibromides

An efficient alternative to these procedures based on the reaction of nitrogen nucleophiles with vinyl dibromides **21** was recently reported. These vinyl dibromides act as synthetic equivalents of bromoalkynes and are readily available alkynylating agents (Scheme 8).[29] This procedure was found to be rather general, even on a large scale and with



Scheme 8. Synthesis of ynamides from vinyl dibromides.

complex and sensitive substrates. The choice of the base turned out to be crucial to avoid further reaction between the N nucleophile and the formed ynamide **9** (see Scheme 15).[30] The major limitation lies in the nucleophiles that can be used in the coupling reaction: while sulfonamides, oxazolidinones, and pyrrolidinone were found to be excellent substrates, acyclic secondary amides or ureas do not give the corresponding ynamides.

The development of copper-catalyzed reactions for the preparation of ynamides provided efficient, straightforward, and reliable access to these useful building blocks. These procedures are without doubt more convenient than the stepwise sequences, and provided benchmarks for the development of the chemistry of ynamides.

3. Recent Developments in the Chemistry of Ynamides: An Ocean of Possibilities

The number of publications dealing with the use of ynamides for the development of new synthetic transformations and/or for the preparation of complex molecules is increasing exponentially, thus creating what could be qualified as a real "ynamide boom". This section will focus on the chemistry of ynamides since 2000, and the reactions will be overviewed in the following order:

- addition at the α position,
- addition at the β position,
- reduction/reductive coupling,
- oxidation,
- cycloaddition,
- ring-closing metathesis,
- cycloisomerization,
- functionalization of terminal ynamides,
- other reactions.

Such a classification is not completely unambiguous and others might have been more appropriate. The classification of the addition reactions (at the α or β positions) is simply based on the first substituent (other than H) introduced on the ynamide.

The outcome of all these reactions is dictated either by the polarization of the triple bond by the nitrogen atom or by a possible chelation of the reagent with the electron-withdrawing group. Overall, the general reactivity of ynamides can be summarized as shown in Figure 2.

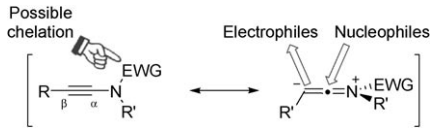


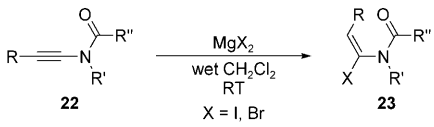
Figure 2. General reactivity of ynamides.

3.1. Addition at the α Position

The addition of various reagents α to the nitrogen atom has been studied extensively. These reactions are in most cases achieved by activation of the ynamide with either a Lewis/Brönsted acid or a transition metal.

3.1.1. ***Brönsted Acid Catalyzed Addition at the α Position***

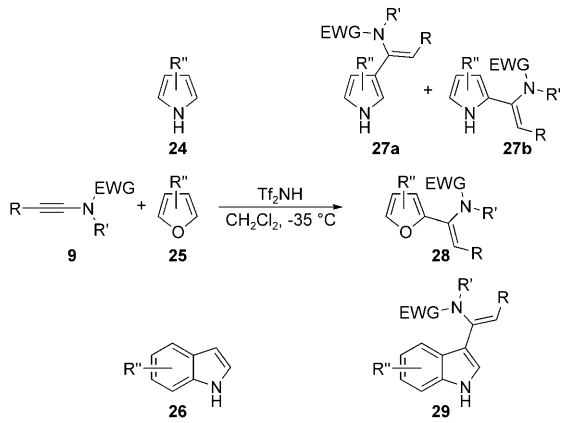
In 2003, Hsung and co-workers reported an efficient and stereoselective hydrohalogenation of ynamides **22** under mild conditions. Treatment with $MgBr_2$ or MgI_2 in wet dichloromethane enabled the corresponding *E*-α-halo-enamides **23** to be obtained in excellent yield and with good selectivity (Scheme 9).[31] The presence of water is crucial to the success of the reaction, which was explained by the in situ generation of HX from the magnesium salt and water.



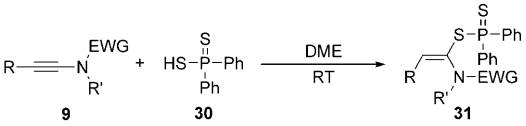
Scheme 9. Stereoselective hydrohalogenation of ynamides.

Over the past five years, a wide range of nucleophiles have been shown to be incorporated cleanly at the α position of ynamides by using activation with an appropriate acid to form an intermediate keteniminium ion. This reaction is especially valuable when aromatic compounds are used, since products resulting from a formal hydroarylation are formed with high levels of regio- and stereoselectivity. In this context, Zhang showed that 1-azavinylpyrroles **27**, -furans **28**, and -indoles **29** could be obtained in excellent yields by using trifluoromethanesulfonimide for the activation step (Scheme 10). Although the reaction was highly regioselective with furans and indoles and afforded the C2- and C3-vinylation products **28** and **29**, respectively, reactions with pyrroles were less selective. In all cases, the enamides were mostly formed as their *Z* isomers.[32] An elegant intramolecular variant in which ynamides with an arene group tethered to the nitrogen atom were used has also been reported, and was further implemented in a straightforward synthesis of (±)-desbromoarborescines A and C (see Section 5).[33] In this last case, simple aromatic compounds can also be used for the formal hydroarylation.

Similarly, treatment of ynamides with diphenyldithiophosphinic acid (**30**) affords *E*-ketene-N,S-acetals **31** (Scheme 11). The addition, which proceeds through protonation of the electron-rich alkyne and subsequent nucleophilic addition of the diphenyldithiophosphinate anion, also proceeds in a *syn* fashion.[34]

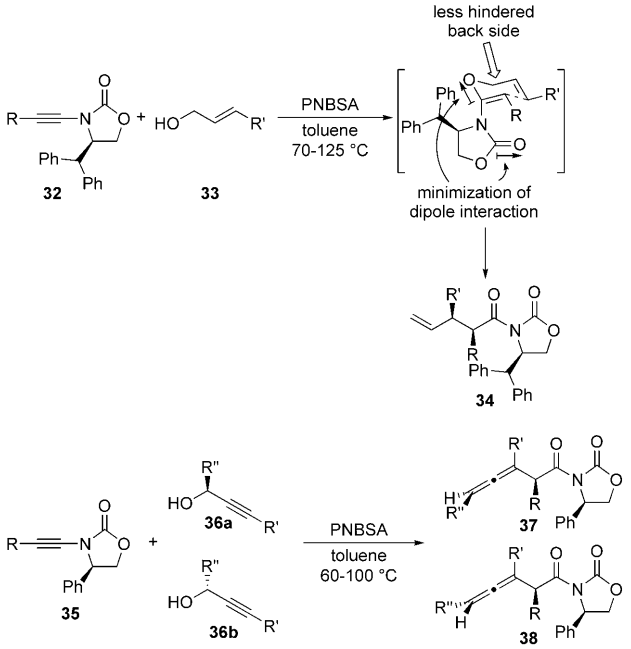


Scheme 10. Stereoselective hydroarylation of ynamides.



Scheme 11. Stereoselective hydrothiolation of ynamides. DME = 1,2-dimethoxyethane.

When allylic alcohols **33** or propargylic alcohols **36** are used as nucleophiles together with chiral, oxazolidinone-derived ynamides such as **32** or **35**, a diastereoselective [3,3] sigmatropic shift follows the addition to the triple bond (Scheme 12). The best catalyst for these highly efficient Ficini–Claisen[35] and Saucy–Marbet[36] rearrangements was *p*-



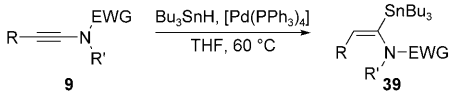
Scheme 12. Stereoselective Ficini–Claisen and Saucy–Marbet rearrangements with chiral ynamides. PNBSA = *p*-nitrobenzenesulfonic acid.

nitrobenzenesulfonic acid, which gave homoallylic amide **34** and homoallenyl amides **37**/**38**, respectively, with useful levels of diastereoselectivity. These rearrangements nicely highlight the use of chiral ynamides for the development of efficient asymmetric reactions.

3.1.2. Transition-Metal-Catalyzed Addition at the α Position

Ynamides are excellent substrates for transition-metal-catalyzed transformations because of their polarization by the nitrogen atom and the possibility of chelation with the electron-withdrawing group. The reactions have been perfomed with various catalysts and have been shown over the years to be particularly efficient for introducing a substituent at the α carbon atom of ynamides, thereby providing straightforward and stereocontrolled entry to polysubstituted enamides or heterocycles.

In this context, Buissonneaud and Cintrat reported a highly regio- and stereocontrolled synthesis of α-stannylenamides **39** by hydrostannylation of ynamides **9** (Scheme 13).[37] Simply heating the latter with tributyltin hydride in the presence of $[Pd(PPh_3)_4]$ in THF at 60 °C led to

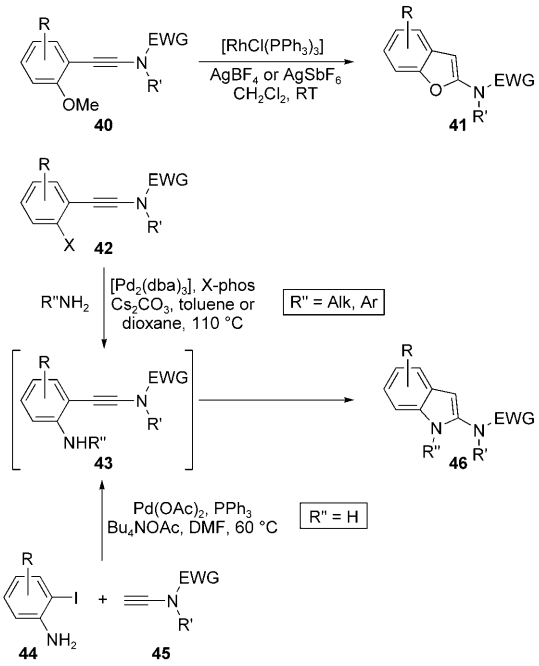


Scheme 13. Hydrostannylation of ynamides.

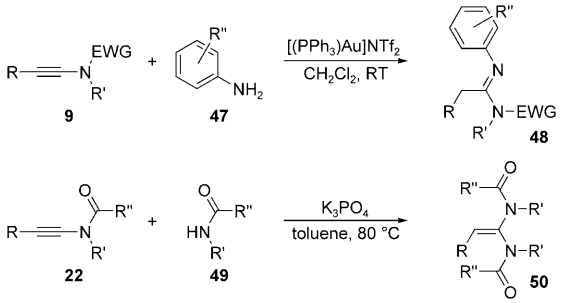
enamides **39** in good yield and selectivity; only in the case of *N*-tosylynamines were larger amounts of the β isomers obtained. These stannyl enamides **39** were shown to be excellent partners for cross-coupling and transmetalation reactions. The reactivity of other organotin reagents such as $Bu_3SnSiMe_3$ or tetraalkyltin derivatives has also been evaluated.[38]

By starting from properly functionalized substrates, intramolecular addition reactions to ynamides are especially efficient for the preparation of various heterocycles, such as 2-aminobenzofurans **41** or -indoles **46**. Compounds **41** can be obtained by a rhodium-catalyzed demethylation/cyclization of *o*-anisole-substituted ynamides **40** (Scheme 14).[39] Additional silver tetrafluoroborate, which functions synergistically with Wilkinson's catalyst for the demethylation step, is required in this cyclization. The 2-aminoindoles **46** can be obtained by using related strategies; the key step involves an intramolecular hydroamination of intermediate *o*-aminoarylynamides **43**. These compounds can be obtained either by amination of the corresponding *o*-halo derivatives **42**[40] or by a palladium-catalyzed copper-free Sonogashira coupling between terminal ynamides **45** and *o*-iodoanilines **44**.[41]

In connection with this work, the Skrydstrup research group next considered the intermolecular hydroamination with anilines **47**. This reaction was found to be catalyzed efficiently by $[(PPh_3)Au]NTf_2$ to give imidoyls **48** with, as usual, excellent regioselectivity (Scheme 15).[42] Skrydstrup and co-workers as well as us showed that carbamates[25] and



Scheme 14. Synthesis of benzofurans and indoles by intramolecular addition to ynamides. dba = dibenzylideneacetone.

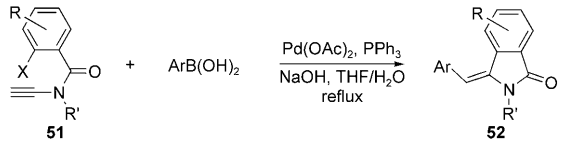


Scheme 15. Intermolecular hydroamination of ynamides.

lactams[30] **49** are also excellent reaction partners. The stable ketene *N*,*N*-acetals **50** were obtained in good yields by simple reaction with potassium phosphate in toluene at 80 °C. No catalyst or additional activation was needed in this case.

Functionalization with an aromatic group at the α position can be achieved by intramolecular carbopalladation starting from intermediates such as **51**. Further reaction of the resulting σ-vinylpalladium complex with boronic acids provides efficient access to 3-(aryl methylene)isoindolinones **52** in a stereoselective manner (Scheme 16).[43] This method has been applied successfully to the total synthesis of lennoxamine (see Section 5). Substrates structurally related to **51** can also be cyclized after generation of a radical: this will be briefly discussed in Section 3.1.3.

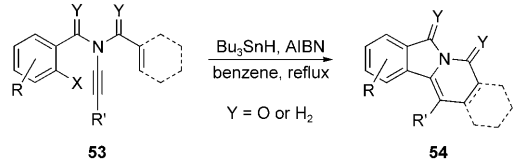
Other possibilities to achieve substitution at the α position of ynamides involve gold cyclization of ynamides possessing a propargylic *tert*-butyl carbonate moiety[44] and their palladium-mediated coupling with alkenes,[45] although a single example was reported in each case.



Scheme 16. Intramolecular carbopalladation of ynamides: efficient synthesis of isoindolinones. X = Br, I.

3.1.3. Radical Addition at the α Position

Malacria and co-workers evaluated the reactivity of ynamides **53** in radical transformations. They showed that the aryl radicals generated from ynamides **53** underwent a reaction cascade involving 5-*exo*-dig cyclization followed by a 6-*endo*-trig radical trapping. This strategy is especially efficient to access various heterocycles such as isoindoles or isoindolines **54** (Scheme 17).[46]

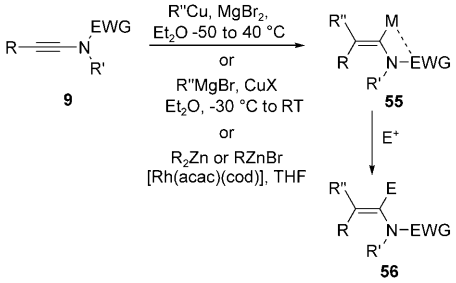


Scheme 17. Intramolecular radical addition at the α position. X = Br, I.

3.2. Addition at the β Position

Depending on both the substrate and the transformation, the regioselectivity of the addition can be reversed so that the β position can be functionalized. Here again, this classification is based on the first substituent introduced on the ynamide, even if further functionalization at the α position is possible (and often used in the case of metalation reactions). In most cases, the reversal of regioselectivity compared to the reactions discussed in Section 3.1 is either due to steric considerations, especially for intramolecular reactions, or to chelation with the electron-withdrawing group.

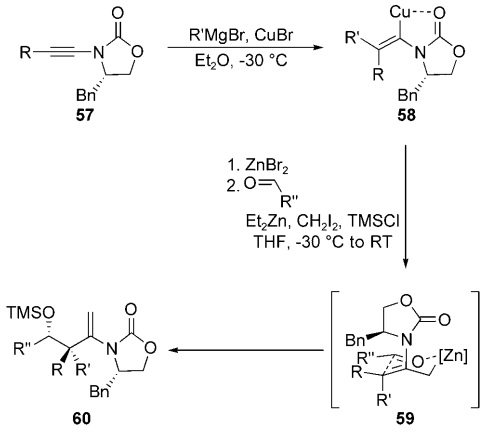
Carbometalation reactions with ynamides, which have been studied in detail by Marek and co-workers, fall into this category. Chelation with the electron-withdrawing group, which acts as an especially efficient directing group, results in carbocupration and copper-catalyzed carbomagnesiation reactions of ynamides that lead to a single regioisomer **56** after trapping of the intermediate vinylcopper **55** with an electrophile (Scheme 18).[47] Interestingly, the regioselectivity of the carbometalation is completely reversed compared to ynamines, which shows the crucial role of the carbonyl or sulfonyl groups. An alternative procedure has recently been reported by Gourdet and Lam, who demonstrated that the carbozincation of ynamides could be smoothly catalyzed by [Rh(acac)(cod)] and that the resulting metalated enamides **55** could be further trapped with electrophiles or involved in Negishi coupling reactions.[48] The reaction course can be altered to hydrozincation when a tri(2-furyl)phosphine-modified rhodium catalyst is used and diethylzinc is employed as the organozinc reagent.[49]



Scheme 18. Carbometalation of ynamides. acac = acetylacetonate, cod = cycloocta-1,5-diene.

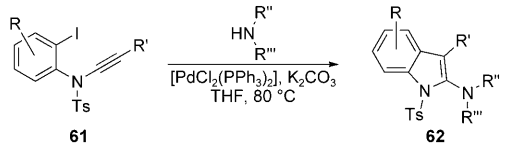
In the case of *N*-allyl-ynamides, an aza-Claisen rearrangement follows the carbomagnesiation to afford homoallylic nitriles upon heating.[50] Silyl cupration has also been studied and provides *E*-β-silylenamides in good yields and with high regio- and stereoselectivity after protonolysis.[51]

This carbometalation of ynamides has recently been implemented by Marek and co-workers in an especially elegant one-pot sequence that leads to the formation of quaternary all-carbon stereocenters.[52] Regioselective carbometalation of chiral ynamide **57** and transmetalation followed by homologation with a zinc carbenoid gives an allylzinc intermediate. Its reaction with an aldehyde via a six-membered chairlike transition state **59** produces, after quenching with TMSCl, aldol surrogate **60** in good yield and excellent selectivity (Scheme 19). This alternative synthetic approach to aldol products should definitely find many applications in organic synthesis.



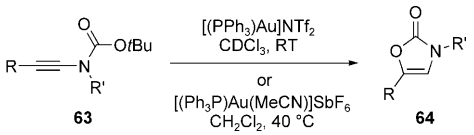
Scheme 19. Carbometalation of ynamides for the preparation of quaternary all-carbon stereocenters. TMS = trimethylsilyl.

Starting from 2-iodoaryl-ynamides such as **61**, an aryl group can also be transferred to the β-carbon atom. 3-Substituted-2-aminoindoles **62** are formed in excellent yields in the presence of catalytic amounts of palladium(II) and a secondary amine (Scheme 20).[53] This procedure nicely complements other ynamide-based methods for the preparation of 2-aminoindoles (Scheme 14).



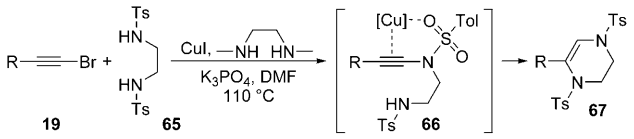
Scheme 20. Palladium-catalyzed synthesis of indoles from ynamides.

In addition to stabilizating the ynamine, the electron-withdrawing group can also be involved in the intramolecular functionalization of ynamides. The *tert*-butoxycarbonyl (Boc) group has been shown to be particularly suitable for such transformations, as demonstrated by the research groups of Hashmi[54] and Gagosz[55] with the preparation of oxazolones **64** by gold-catalyzed cyclization of ynecarbamates **63** (Scheme 21).



Scheme 21. Synthesis of oxazolones by gold-catalyzed cyclization of *N*-Boc-ynamines.

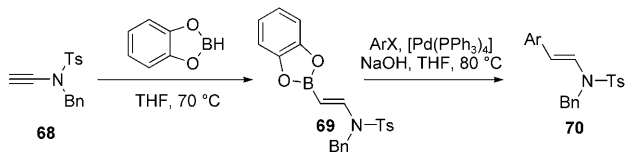
Sulfonamides can also be used for intramolecular addition at the β position, as shown by Urabe and co-workers. They reported a one-pot alkynylation/hydroamination with bissulfonamides to yield tetrahydropyrazines **67** via intermediate ynamides **66** (Scheme 22).[56] The regioselectivity of this



Scheme 22. Synthesis of tetrahydropyrazines.

intramolecular hydroamination is in sharp contrast to the intermolecular version that leads to ketene *N*,*N*-acetals (Scheme 15), where a reversed selectivity was observed. This exclusive 6-*endo*-dig cyclization was attributed to a chelation of the copper salt by the sulfonylamino group.

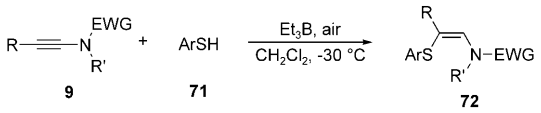
As shown in Scheme 23, ynamides can also be functionalized at their β carbon atom through hydroboration. Reaction with catecholborane gives the unstable monohydroboration product **69** stereoselectively. In situ cross-coupling with aryl halides then gives protected styryl amides **70**.[57] Unfortunately, only ynamide **68** was used in this study and the



Scheme 23. Hydroboration of ynamides.

reactivity of other classes of ynamides, including nonterminal ones, still remains to be evaluated. An additional example of metal-catalyzed hydroboration with pinacolborane was reported a year later.[58]

A regio- and stereoselective radical addition of thiols to ynamides was reported by Yorimitsu and co-workers. The reaction with aryl thiol **71** and triethylborane under air afforded *E*-β-thiophenyl-enamides **72** in excellent yield and selectivity (Scheme 24).[59] The reaction would proceed through addition of the electron-deficient thiyl radical at the β position of the ynamide, where the higher electron density resides. The *Z* isomer of the vinyl radical would then selectively abstract a hydrogen atom from the aryl thiol.

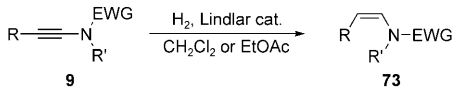


Scheme 24. Stereoselective hydrothiolation of ynamides.

In most of the transformations described above, the triple bond of the starting ynamide is transformed to a double bond after the addition, thereby yielding polysubstituted enamides, or heterocycles in the case of intramolecular transformations. Enamides with different substitution patterns can also be obtained from ynamides by reduction or reductive coupling. These reactions will be overviewed in Section 3.3.

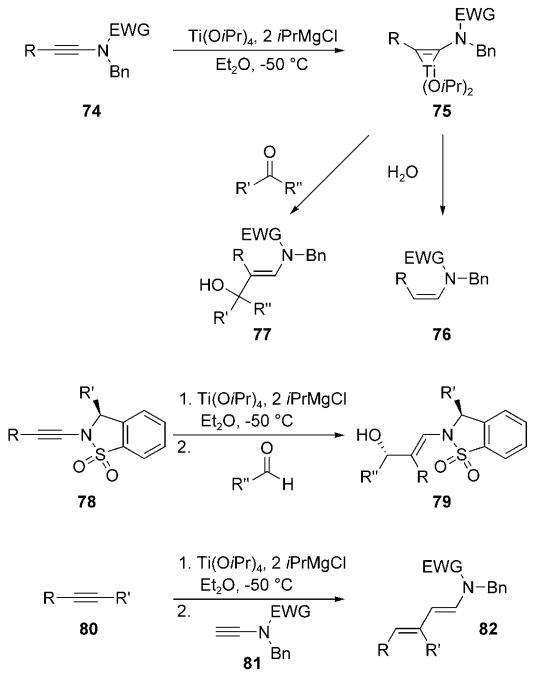
3.3. Reduction/Reductive Coupling

One of the simplest transformations of ynamides is their reduction to *Z*-enamides **73** by Lindlar-type hydrogenation. As a result of the recent advances in the preparation of ynamides, this method now offers an attractive option for the preparation of enamides. An extensive study was reported in 2006 by Hsung and co-workers, who demonstrated that this strategy enables the preparation of Z-enamides in good yield and selectivity, except when bulky substituents are attached to the ynamide (Scheme 25).[24b]



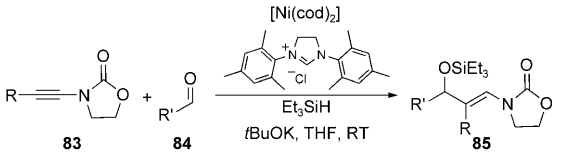
Scheme 25. Hydrogenation of ynamides.

Ynamides **74** can also be reduced stereoselectively to enamides **76** by conversion into a [$Ti^{II}(\eta^2$-alkyne)] complex **75** followed by hydrolysis. Complex **75** also reacts with aldehydes and ketones to afford stereodefined hydroxymethyl-enamides **77** (Scheme 26).[60] This reaction could be performed with high levels of 1,5-asymmetric induction when starting from *N*-alkynylsultams **78**.[60b,61] Alternatively, dienamides **82** could be generated by the coupling of terminal ynamides **81** with a variety of alkyne–titanium complexes.[60] These sequences allow the highly efficient preparation of polysubstituted enamides that would otherwise be quite difficult to obtain.



Scheme 26. Titanium-mediated reduction and coupling of ynamides.

Related substrates can also be obtained by hydroalumination of ynamides possessing a propargylic alcohol[60c,62] or by multicomponent nickel-catalyzed coupling of ynamides with aldehydes and triethylsilane (Scheme 27).[63] This coupling reaction occurred best when catalytic amounts of $[Ni(cod)_2]$ and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) as the ligand were used, and gave the corresponding α-silyloxy-enamides **85**. To rationalize this reaction, the authors invoked coordination of the aldehyde to the nickel complex followed by reaction with the ynamide to form an oxanickelacycle that would finally be cleaved through σ-bond metathesis by the triethylsilane.

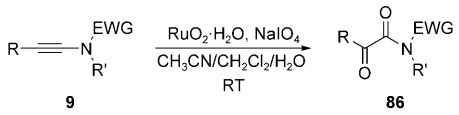


Scheme 27. Three-component coupling of ynamides, aldehydes, and triethylsilane.

While the reduction and reductive coupling of ynamides provides straightforward and elegant regio- and stereocontrolled entry to polysubstituted enamides, the oxidation of ynamides can have a great affect on their skeleton. These oxidative processes, which provide further support for the synthetic utility of ynamides, will be discussed in Section 3.4.

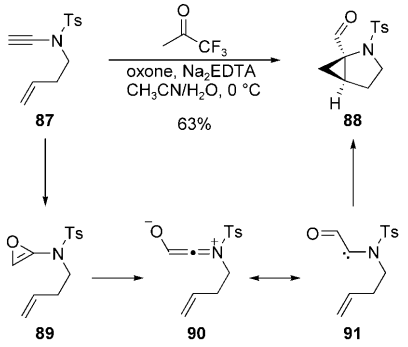
3.4. Oxidation of Ynamides

In 2008, Hsung and co-workers reported the preparation of α-ketoimides by the oxidation of ynamides. Among all the conditions screened for this oxidation, $RuO_2/NaIO_4$ as well as 3,3-dimethyldioxirane were found to be the most efficient systems.[64] While the former was found to give higher yields in most cases, the reaction with the dioxirane led to high levels of chemoselectivity with olefin-containing ynamides (Scheme 28).



Scheme 28. Oxidation of ynamides.

A number of reaction pathways can be invoked to explain the formation of ketoimides and, more generally, for the oxidation of ynamides. The intermediacy of push-pull carbenes was demonstrated almost simultaneously by Meyer, Cossy, and co-workers as well as by Al-Rashid and Hsung by using ene-ynamides such as **87** (Scheme 29).[65] Treatment with the appropriate oxidant results in a chemoselective epoxidation of the ynamide, which is slightly more electron rich than the alkene because of delocalization of the lone pair of electrons on the nitrogen atom. The unstable oxirene **89** would then undergo ring opening to generate the α-oxo-α-azacarbene **91** which is trapped by the alkene. These reactions were, however, found to be quite substrate-dependent, except in the case of ynamides bearing a propargylic alcohol moiety: the use of *tert*-butylhydroperoxide in the presence of vanadyl acetylacetonate enabled a wide range of substrates to be transformed into the corresponding fused cyclopropanes in good yields.



Scheme 29. Push-pull carbenes as intermediates in the oxidation of ynamides—efficient access to fused cyclopropanes. EDTA = ethylenediaminetetraacetate.

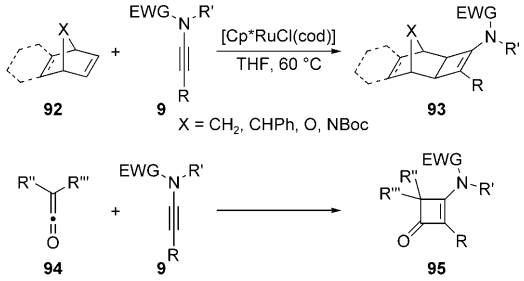
The reactions discussed above have been reported only quite recently and have been specifically designed for ynamides. In contrast, cycloaddition reactions with ynamines have been extensively studied in the past. Such reactions have been applied to ynamides and have been shown over the past decade to be terribly powerful tools for the preparation of an ever-increasing number of carbo- and heterocycles. These reactions will be described in Section 3.5.

3.5. Cycloadditions with Ynamides

Ynamides have been used in all kinds of cycloadditions and related processes. Cycloadditions provide a powerful method for the direct assembly of a wide range of scaffolds, and can be efficiently catalyzed by various transition metals. They will be briefly overviewed in the following order: [2+2], [4+2], [3+2], [2+2+1], and [2+2+2] cycloadditions.

3.5.1. [2+2] Cycloadditions

In a continuation of their studies on ruthenium-catalyzed [2+2] cycloadditions, Tam and co-workers reported the reaction of bicyclic and tricyclic alkenes **92** with ynamides **9**.[66] The latter were found to be compatible with the conditions used for ruthenium-catalyzed cycloaddition and gave the corresponding aminocyclobutenes **93** in moderate to good yields (Scheme 30). The diastereoselectivity of the



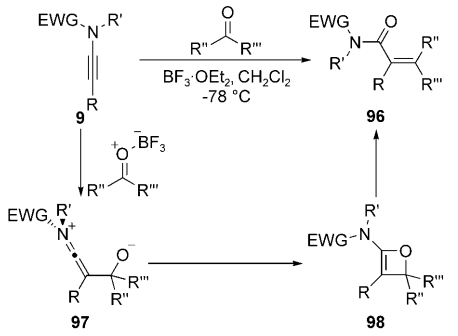
Scheme 30. [2+2] Cycloaddition with ynamides. Cp* = C_5Me_5.

reaction in the presence of chiral, oxazolidinone-derived ynamides was also studied, but was found to be rather modest. Ynamides were also shown to react readily with ketenes **94** in [2+2] cycloadditions to give a variety of aminocyclobutenones **95**, as shown by the Danheiser research group.[67] The reaction is more efficient than the one involving ynamines, which is often complicated by the formation of allene by-products arising from stepwise addition pathways.

A formal [2+2] cycloaddition between ynamides and aldehydes or ketones activated by a Lewis acid has also been described by Hsung and co-workers. This approach was used for the two-carbon homologation of aldehydes and ketones[68] as well as intramolecular ring-closing yne-carbonyl metathesis.[69] In this process, an intermediate oxetene **98** would be formed through a stepwise cycloaddition. Its ring opening would then account for the formation of α,β-unsaturated amides **96** (Scheme 31). A similar reaction leading to α,β-unsaturated amidines from ynamides and imines has also been reported.[70]

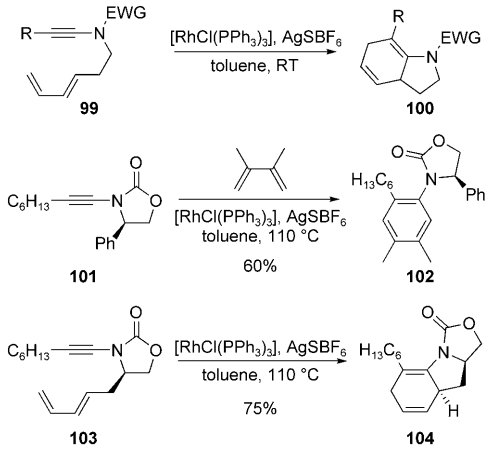
3.5.2. [4+2] Cycloadditions

[4+2] Cycloaddition reactions with ynamides have been reported only quite recently. This transformation, which has long been an invaluable tool in organic synthesis, is especially efficient with ynamides, thereby allowing the incorporation of



Scheme 31. Stepwise [2+2] cycloaddition with carbonyl compounds.

a nitrogen atom into the final molecule. The first examples were reported by Witulski et al., who showed that the use of a cationic rhodium complex was able to catalyze the reaction at room temperature to afford tetrahydroindoles **100** in high yields (Scheme 32; lower yields were obtained under uncata-



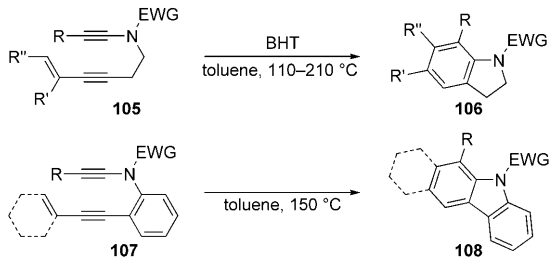
Scheme 32. Rhodium-catalyzed [4+2] cycloaddition with ynamides.

lyzed thermal conditions).[71] Hsung and co-workers later demonstrated that this system was also an efficient catalyst for intermolecular reactions (for example, for the formation of **102**), although heating in toluene at reflux was required. Additionally, the use of oxazolidinone-derived ynamides allowed for a diastereoselective cycloaddition (formation of **104** as a single isomer).[24b]

Finally, Dunetz and Danheiser[72] as well as Saá and co-workers[13b,73] devised original approaches to indolines **106** and carbazoles **108** by thermal cycloaddition of ynamides bearing an enyne moiety (Scheme 33). Intramolecular cycloaddition of alkynes and conjugated enynamides were also used for the preparation of 4-substituted indolines.

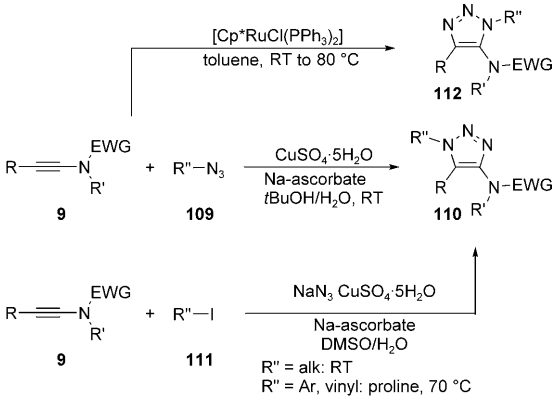
3.5.3. Dipolar [3+2] Cycloadditions

Dipolar [3+2] cycloadditions between ynamides and azides was reported only in 2006 by Hsung and co-workers[74] and by Ijsselstijn and Cintrat.[75] The inherent polarization by the nitrogen atom plays an important role in this trans-



Scheme 33. [4+2] Cycloaddition with enyne-containing ynamides. BHT = butylhydroxytoluene.

formation since a single regioisomer (**110**) is usually observed under thermal conditions (Scheme 34). The Fokin/Sharpless catalytic conditions are, however, milder and allow for the



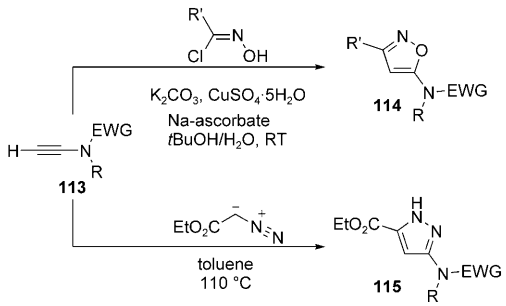
Scheme 34. Huisgen cycloaddition with ynamides.

preparation of a wide range of 4-amino-1,2,3-triazoles **110**. A tandem azidination/cycloaddition sequence can also be used for the preparation of these heterocycles starting from aryl, vinyl,[74] or alkyl iodides **111**[76] and sodium azide. In the first two cases, additional proline is required for the copper-catalyzed azidation step. Furthermore, an in situ reaction of the vinylcopper intermediate with allyl/propargyl iodides allows for functionalization at the C-5 position in **110** when starting from terminal ynamides.[77] The use of tosyl azide and an additional amine enables α-amino-amidines to be isolated at the end of the reaction.[78] As observed with other alkynes, the regioselectivity of the Huisgen cycloaddition can be reversed by switching from the copper-based catalyst to $[Cp^*RuCl(PPh_3)_2]$, which favors the formation of 5-amino-1,2,3-triazoles **112**.[79]

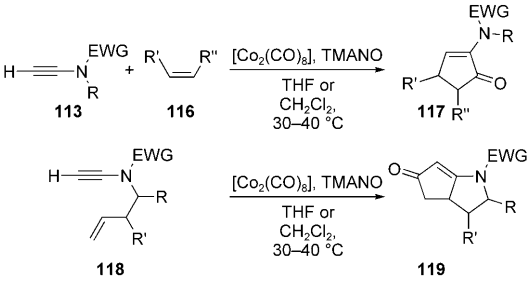
Other dipolar reagents such as nitrile oxides and diazoacetates have also been used in the [3+2] cycloaddition with ynamides. They produce isoxazoles **114** and pyrazoles **115**, respectively, in moderate to good yields (Scheme 35).[80]

3.5.4. *[2+2+1] Cycloadditions: Pauson–Khand Reaction*

The inter- and intramolecular Pauson–Khand reactions with ynamides, which afford functionalized cyclopentenones such as **117** or **119** (Scheme 36), have been studied extensively



Scheme 35. [3+2] Cycloaddition of ynamides with nitrile oxides and diazoacetates.

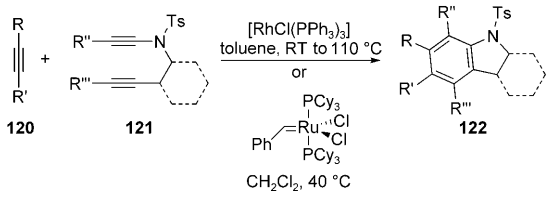


Scheme 36. Pauson–Khand reactions with ynamides. TMANO = trimethylamine *N*-oxide.

by the Witulski and Rainier research groups, and was carefully overviewed in the 2001 review by Hsung and coworkers.[1c] More recently, it has been shown that an unsual *endo* addition was observed with norbornadiene.[81]

3.5.5. *[2+2+2] Cycloadditions*

Ynamides are also interesting reaction partners for cyclotrimerization or—more generally—[2+2+2] cycloadditions because the polarization of the triple bond can greatly affect the regiochemical outcome of such transformations. Indolines or carbazoles **122** are formed with high efficiency when starting from yne-ynamides **121** (Scheme 37).[17c,f] The

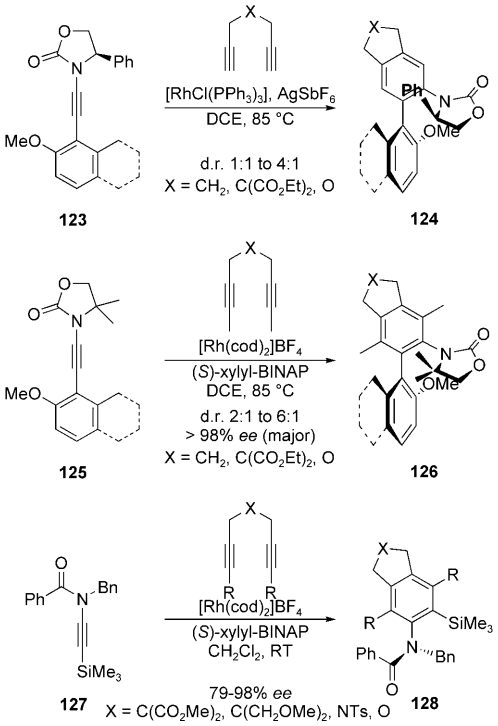


Scheme 37. Formation of indolines and carbazoles by [2+2+2] cycloaddition of yne-ynamides. Cy = cyclohexyl.

regioselectivity of the reaction, which was shown to depend on steric interactions with the substituents of the yne-ynamide, could be elegantly reversed by switching from the Wilkinson to the Grubbs catalyst, thereby producing 4,5- or 4,6-disubstituted indolines selectively from terminal ynamides (**121**, R'' = H) and alkynes (**120**, R or R' = H).[17e]

The combination of ynamides with 1,5-diynes together with a rhodium catalyst leads to the formation of anilides. In

this case, and provided that the substituents on the ynamide are sufficiently bulky, two atropoisomers can be obtained. Hsung and co-workers examined the cyclotrimerization of chiral ynamides **123** possessing a bulky aryl group (Scheme 38),[82] and obtained chiral N,O-biaryls **124**, although

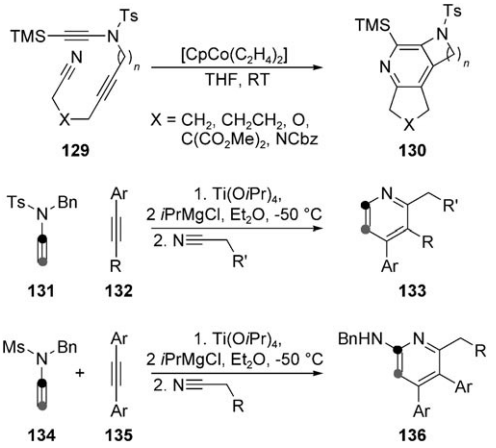


Scheme 38. Stereoselective cyclotrimerization of diynes and ynamides. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, DCE = 1,2-dichloroethane.

with modest diastereoselectivity. The use of enantioselective cyclotrimerizations turned out to be more efficient, as demonstrated successively by Tanaka et al. and Hsung and co-workers, respectively, for the synthesis of axially chiral anilides **128**[83] and biaryls **126**.[84]

Nitriles can also participate in cyclotrimerization reactions with ynamides, as recently shown by Aubert and co-workers: starting from acyclic precursors **129**, which contains a nitrile, an internal alkyne, and an ynamide, a cobalt-catalyzed [2+2+2] cocyclization leads to tricyclic fused 3-aminopyridines **130** in excellent yields (Scheme 39).[85] An especially elegant intermolecular titanium-mediated reaction between a nitrile, a terminal ynamide, and an alkyne was reported by Sato and Urabe. Pyridines **133** or 2-aminopyridines **136** could be obtained selectively, depending on the nature of the sulfonyl group on the ynamine **131** or **134**. Finally, a push-pull diene-ynamide was shown to undergo a ruthenium-catalyzed [2+2+2] cycloaddition to give a tricyclic decahydro-1-aza-*as*-indacene, although in modest yield.[86b]

As demonstrated with these selected examples, ynamides and alkynes are excellent reaction partners for the formation of various cyclic systems by [2+2+2] cycloaddition strategies. Electron-deficient ynamines can also react well with alkenes

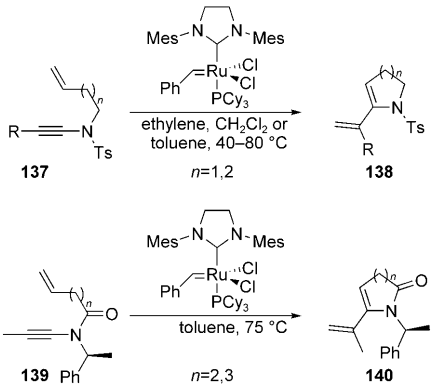


Scheme 39. Synthesis of pyridines from ynamides. Cbz = benzyloxycarbonyl, Cp = cyclopentadienyl.

in the presence of the correct metathesis catalyst. Examples of ring-closing metathesis with ene-ynamides will be overviewed in the Section 3.6.

3.6. Ring-Closing Metathesis of Ene-Ynamides

Of all the ring-closing metathesis (RCM) reactions, intramolecular enyne metathesis is an especially appealing reaction since the double bond of the enyne is cleaved and the alkylidene part of the alkene migrates to the alkyne carbon atom to yield a cyclized product containing a 1,3-diene moiety. Many examples of enyne RCM have been published over the past decades. The first examples using ene-ynamides **137**, which were converted smoothly into unsaturated pyrrolidines or piperidines **138** using the Grubbs second generation catalyst, were reported by Mori and co-workers in 2002 (Scheme 40).[87] The same year, Hsung and co-workers demonstrated that ene-ynamides such as **139** were also excellent substrates for RCM. They next studied the tandem cyclization of ynamides possessing two olefins, a reaction that was found to give various bicyclic lactams and to be—rather logically—highly dependent on the substitution pattern of the two alkenes.[88] Cyclic amido-dienes such as **138** and **140** were

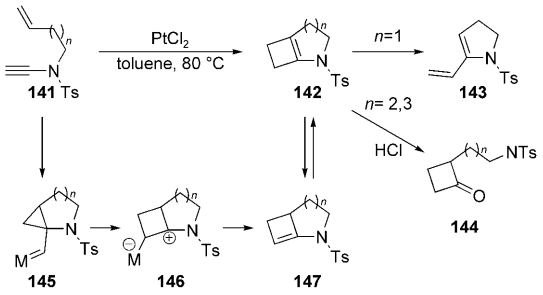


Scheme 40. RCM of ene-ynamides. Mes = 2,4,6-trimethylphenyl.

shown to be excellent partners in Diels–Alder reactions. Replacement of the Grubbs catalyst by another ruthenium complex, [Cp*RuCl(cod)], allows for a completely different reaction, since an alkenylative cyclization occurs in this case.[89]

3.7. Gold- and Platinum-Catalyzed Cycloisomerization

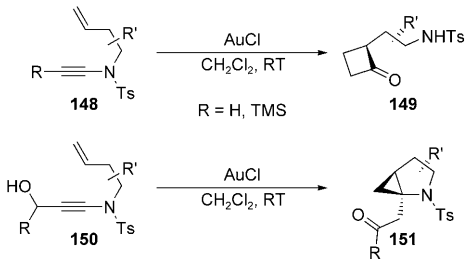
Ene-ynamides are also attractive substrates for cycloisomerization reactions. Fensterbank and co-workers demonstrated that the transformation in the presence of platinum(II) chloride in toluene at 80 °C leads to bicyclic cyclobutenes **142**. When starting from a homoallylic ynamide ($n=1$), **142** underwent electrocyclic ring-opening to give the formal metathesis product **143**. With higher homologues ($n=2$, 3), bicyclic cyclobutenamides **142** or **147** could be hydrolyzed in situ to cyclobutanones. Alkyl substitution is tolerated on both the triple bond and the alkene, even if the opening of the aminocyclobutene might stop at the aminal stage in the latter case. The aminocyclobutene was assumed to originate from an initial π complexation of the alkyne to yield cyclopropylplatinum carbene **145** ($M=PtCl_2$), followed by ring expansion/demetalation/isomerization (Scheme 41).Ozonolysis of bicyclic cyclobutenamides **147** has also been described.[46b,90]



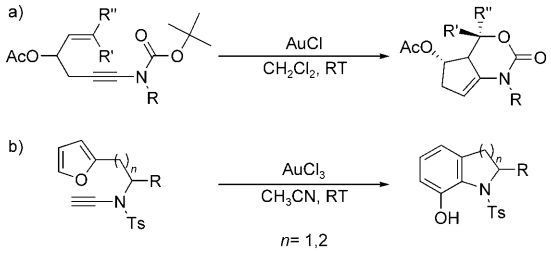
Scheme 41. Platinum-catalyzed cycloisomerization of ene-ynamides.

The reaction was carried out under milder reaction conditions using gold chloride as the catalyst to avoid the ring opening of cyclobutene **142** ($n=1$) and/or skeletal rearrangement of **145**. The stereocenter generated in the cycloisomerization process could now be preserved, and cyclobutenones **149** were formed efficiently with excellent levels of diastereoselectivity for ene-ynamides bearing substituents at the α or β position (Scheme 42).[91] In addition, the use of 1,2-disubstituted alkenes allows for the diastereoselective formation of 2,3-disubstituted cyclobutenones.[92] The structure of the intermediate cyclopropylpyrrolidine **145** ($M=AuCl$) can be retained when starting from ene-ynamides possessing a propargylic alcohol **150**. The ring expansion is suppressed with these substrates, and a 1,2-hydride shift produces bicyclic compounds **151** with excellent stereocontrol.

In the case of the ene-ynamides shown in Scheme 43a, which possess a Boc group on the nitrogen atom, the cationic intermediate generated after reaction with gold chloride is



Scheme 42. Gold-catalyzed cycloisomerization of homoallylic ynamides.

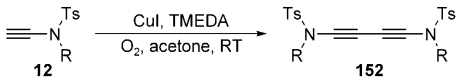


Scheme 43. Gold-catalyzed cycloisomerization of ene-ynamides.

trapped by the carbamate which acts as an internal nucleophile, thereby yielding urethanes with good stereoselectivity.[93] Finally, replacement of the alkene by a furan, as shown in Scheme 43b, allows for the efficient synthesis of dihydroindoles and tetrahydroquinolines, as elegantly demonstrated by Hashmi et al.[94]

3.8. Functionalization of Terminal Ynamides

In addition to the reactivity involving the polarized triple bond, terminal ynamides can participate in various coupling reactions involving abstraction of the acidic hydrogen atom. As mentioned at the beginning of this Review, metalated ynamides have been shown to be excellent partners in Sonogashira[13] and Negishi coupling reactions (Scheme 3).[11] Furthermore, they can also be homocoupled to bisynamides **152** upon treatment with copper(I) iodide and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine in acetone under an atmosphere of oxygen (Scheme 44).[13b,95]

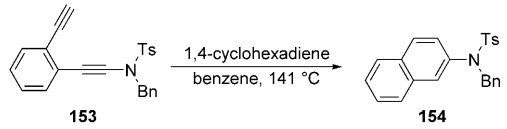


Scheme 44. Homocoupling of terminal ynamides.

3.9. Other Reactions with Ynamides

When writing a review article, the choice of classification is not always a trivial task, since some transformations simply do not fall into any categories, which accounts for the "Miscellaneous" section found in most reviews. Before concluding this Review with a brief overview of heteroaromatic ynamines and applications of ynamides in natural

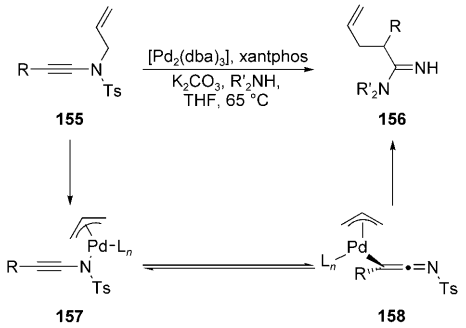
product synthesis, we will briefly comment on other reactions involving ynamides that have recently been published. Aromatic alkynes **153** possessing an ynamide in the *ortho* position have, for example, been shown to cyclize thermally to give the Bergman products **154** (Scheme 45).[96] In the case of compounds possessing a tether of three carbon atoms between the alkyne and the ynamide, the cycloaromatization readily proceeds at 40 °C by a polar rather than the classical diradical pathway.[97]



153 154

Scheme 45. Bergman cyclization of ynamides.

Hsung and co-workers recently reported an efficient palladium-catalyzed N-to-C allyl transfer from *N*-allylynamides **155**. After insertion of the palladium atom into the C–N bond to give **157**, migration of the palladium would allow for the formation of ynamido-π-allylpalladium complex **158**, which is trapped by a secondary amine to give amidines **156** in excellent yield (Scheme 46).[98] While this formal aza-Claisen reaction allows for the migration of the allyl group, an uncatalyzed thermal migration of the two substituents from the nitrogen atom to the β-carbon atom to afford a nitrile has been observed.[99]

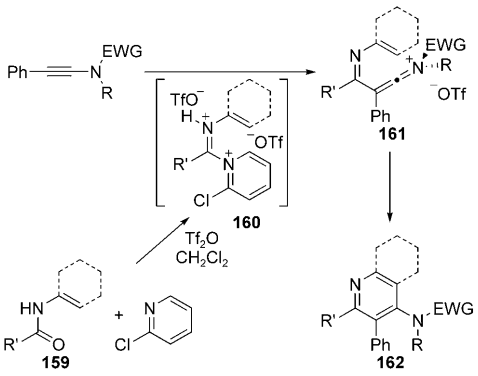


155 156 157 158

Scheme 46. Palladium-catalyzed allyl transfer from ynamides.

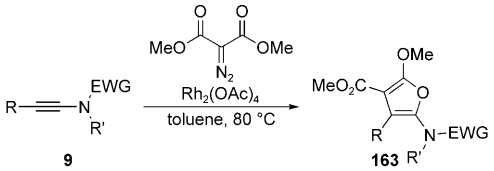
As mentioned in Section 3.1.1, ynamides are also excellent precursors of keteniminium ions, especially when they are in the presence of a strong electrophile. In this context, they have been shown to react with activated electrophiles **160**, generated from enamides **159**, 2-chloropyridine, and triflic anhydride, to give keteniminium ions **161**. Annulation of these intermediates allows for the efficient synthesis of pyridines or quinolines **162**, as demonstrated by Movassaghi et al. (Scheme 47).[100]

Another innovative transformation lies in the reaction of an ynamide and a diazomalonate in the presence of rhodium(II) salts, which could allow, at least in theory, for the formation of amidocyclopropenes. This reaction provides an



Scheme 47. Synthesis of 4-aminopyridines from ynamides.

especially elegant entry to polysubstituted 2-amidofurans **163** (Scheme 48). Other diazo compounds or iodonium ylides can



9 163

Scheme 48. Rhodium-catalyzed cyclopropenation of ynamides.

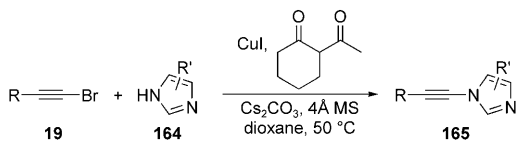
also be used for this formal [3+2] cycloaddition.[101] While the intermediacy of 2-amidocyclopropenes could not be determined directly in this case, Clark and Woerpel demonstrated that their silyl homologues can be formed cleanly by silylene transfer between an ynamide and cyclohexene-derived silacyclopropane in the presence of silver phosphate.[102]

Finally, an ynamide bearing a propargylic alcohol was shown to undergo a Meyer–Schuster rearrangement in the presence of gold and molybdenum complexes to give the corresponding α,β-unsaturated amide, although a single example was reported.[103]

It should be clear at this point of the Review that the chemistry of ynamides is especially diverse, rich, and allows for the development of original and straightforward synthetic methods. In general, *N*-alkynylheterocycles display a reactivity that is quite similar to that of ynamides[6]—except in the case of *N*-alkynylheteroaromatic compounds, whose properties will be briefly overviewed in Section 4.

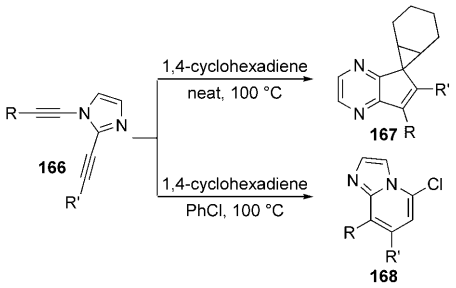
4. N-Alkynylheteroaromatic Compounds

N-Alkynylimidazoles and *N*-alkynylbenzotriazoles are interesting variations on ynamines and share with ynamides the increased stability engendered by delocalization of the lone pair of electrons on the nitrogen atom. While the latter have been reviewed by Katritsky et al.,[6] the reactivity of imidazole derivatives has only been studied quite recently by Kerwin and co-workers, who developed a practical synthesis based on the alkynylation of imidazoles with bromoalkynes (Scheme 49).[104]



Scheme 49. Copper-mediated synthesis of *N*-alkynylimidazoles.

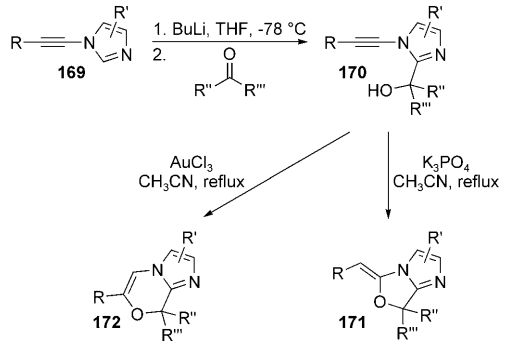
Among the reactions that are specific to these electron-deficient ynamines, the thermolysis of 1,2-dialkynylimidazoles **166** has been studied extensively: instead of the expected aza-Bergman products, cyclopentapyrazines **167** or imidazopyridines **168** are formed, although in rather low yields (Scheme 50).[105]



Scheme 50. Thermolysis of 1,2-dialkynylimidazoles.

Another interesting reaction involving *N*-alkynylimidazoles is the metalation of the heterocycle. Indeed, the carbon atom at the 2-position of these heterocycles can undergo a clean lithiation, and the resulting intermediate can be trapped with various electrophiles including aldehydes and ketones (Scheme 51). While quenching the reaction with water resulted in addition of the resulting alkoxide to the ynamine moiety, (hydroxymethyl)alkynylimidazoles **170** could be obtained in excellent yields when using 1M HCl rather than water.[106] These intermediates have been shown to selectively undergo 5-*exo*-dig or 6-*endo*-dig cyclization, respectively, under base or gold catalysis.

Ynamides offer multiple opportunities for the inclusion of nitrogen-containing groups into organic systems. The recent development of efficient synthetic methods for their preparation allowed for the design of new reactions which are now being used for the preparation of various natural products.

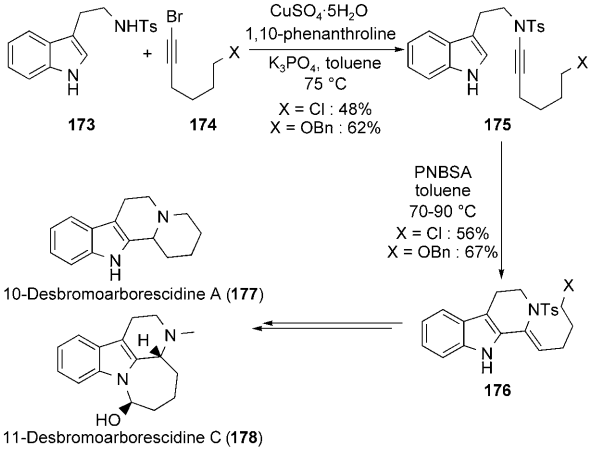


Scheme 51. Lithiation/trapping/cyclization of *N*-alkynylimidazoles.

5. Ynamides in Natural Product Synthesis

The use of an ynamine as a key intermediate during the course of a total synthesis was clearly a decision that bore considerable risk, and might even have seemed counter-intuitive. In contrast, the greater stability and the exceptional reactivity of ynamides make them appealing substrates for the preparation of heterocyclic natural products and allows for very efficient and original disconnections, as will be shown with the following examples.

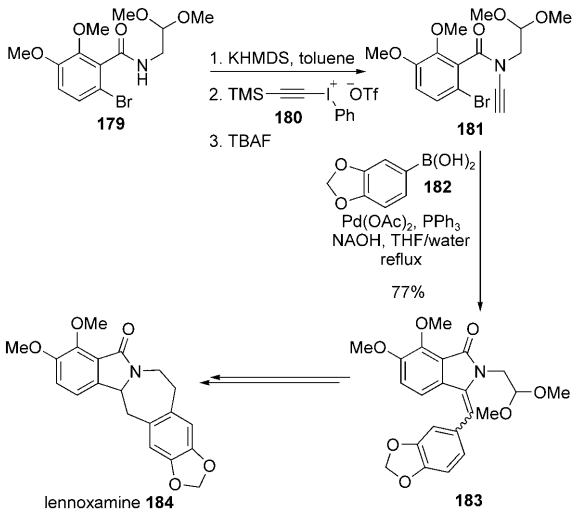
In 2005, Hsung and co-workers reported an elegant synthesis of desbromoarborescidines A (**177**) and C (**178**) through an efficient arene-ynamide cyclization. The synthesis started with the mild alkynylation of *N*-tosyltryptamine (**173**) with bromoalkynes **174** to yield the required ynamides **175** in moderate to good yields. These arene-ynamides **175** then served as keteniminium precursors (generated upon activation with *para*-nitrobenzenesulfonic acid), which underwent a Pictet–Spengler-type cyclization to give tricyclic heterocycles **176** (Scheme 52).[33] These highly efficient cyclizations of arene-ynamides represent one of the first applications of ynamides in natural product synthesis.



Scheme 52. Ynamides in the synthesis of desbromoarborescidines.

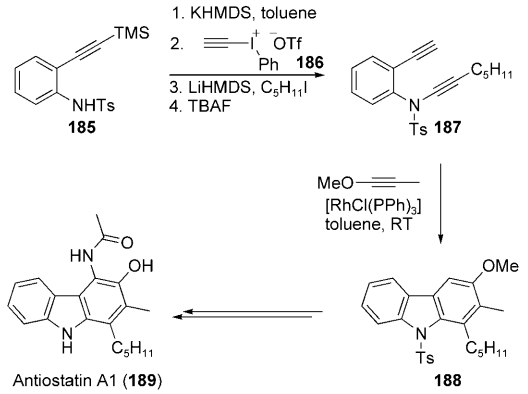
As described in Section 3.1.2, 3-(aryl methylene)isoindolin-1-ones can be obtained efficiently by using palladium-catalyzed domino Heck–Suzuki–Miyaura reactions in the presence of an aryl boronic acid (Scheme 16). This sequence has recently been implemented in an elegant synthesis of lennoxamine (**184**), an isoindolobenzazepine alkaloid.[43b,107] The ynamide **181** required for the key cyclization step was obtained by alkynylation of benzamide **179** with alkynyliodonium triflate **180** followed by desilylation (Scheme 53). The cyclization was then promoted by a combination of palladium acetate and triphenylphosphine, and the resulting vinylpalladium species was coupled with boronic acid **182**, thus allowing the formation of the isoindolinone core of lennoxamine (**184**). The target molecule was obtained after hydrogenation of the enamide and formation of the seven-membered ring.

Finally, a [2+2+2] cycloaddition of a diyne-ynamide was used for the total synthesis of the natural antioxidant antiostatin A_1 (**189**) by Witulski and co-workers



Scheme 53. Ynamides in the synthesis of lennoxamine. TBAF = tetra-*n*-butylammonium fluoride.

(Scheme 54). The acyclic precursor was formed by alkynylation of aromatic sulfonamide **185** with iodonium salt **186** followed by alkylation of the terminal ynamide and desilylation of the alkyne. A highly regioselective rhodium-catalyzed cyclotrimerization then allowed for the formation of the carbazole core of antiostatin A_1 (**189**). The target molecule was obtained after functionalization of the carbazole.[108]



Scheme 54. Ynamides in the synthesis of antiostatin A_1.

6. Conclusions and Future Prospects

In the last ten years, a number of reliable and efficient syntheses of ynamides have allowed their synthetic value to be realized. It is now evident that these compounds can be easily prepared on multigram scales (Figure 3), and no-one should be afraid to prepare such molecules. Furthermore, their stability allows them to be easily handled (they are stable towards aqueous workups, silica gel, heating …), and one should keep in mind that a lot of them can even be stored for months at room temperature without degradation (except in the case of alkyl-substituted ynesulfonamides, which are often readily hydrolyzed to the corresponding amides and cannot be stored for a long time). Of course, there is still no

Figure 3. Synthesis of ynamides on a gram scale: an easy thing to do …

ideal method for their preparation, and there is still a lot of room for improvement.

Their reactivity is quite astonishing: the polarization of the triple bond allows for highly regioselective transformations, and the electron-withdrawing group on the nitrogen atom can act as a very efficient directing/chelating group. The utility of ynamides has now been demonstrated in an impressive range of reactions, including pericyclic, ionic, and radical transformations. The number of publications on their chemical properties is growing continuously (Figure 4). As

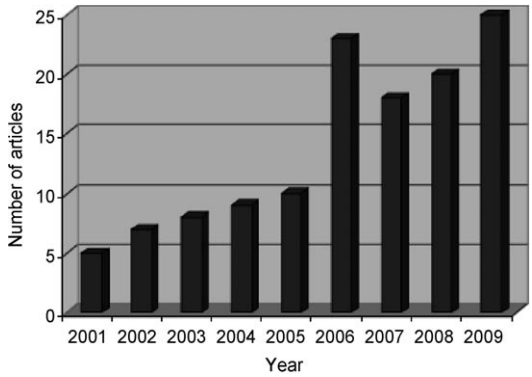


Figure 4. Number of publications on ynamides per year since 2001. (The peak in 2006 is due to the publication of the special issue in Tetrahedron on "Chemistry of Electron-Deficient Ynamines and Ynamides".)

pointed out by an author of one review, an important point has, however, remained rather unexplored, since there is no precise quantification of their reactivity. At this stage in the development of these useful building blocks, a quantitative analysis between all classes of ynamides (charge densities, reaction rates, nucleophilicities) as well as a comparison with other heteroatom-substituted alkynes (including ynol ethers and ynamines) would probably be most helpful. This specific point is currently under investigation by our research group. Our goal is to better understand the reactivity of ynamides, which would serve as a basis for the development of new and exciting transformations.

To conclude this Review, we just remind the reader that the area of ynamides is most probably in its infancy. There is

no doubt that creative efforts will be made to use ynamides for the development of new reactions in organic synthesis. Just wait and see!

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