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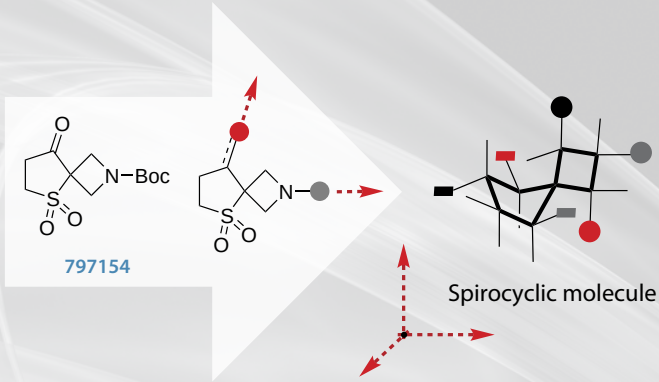
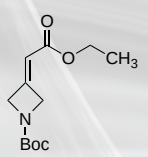
Professor Dr. Erick Carreira



Starting Materials → Spirocyclic Building Blocks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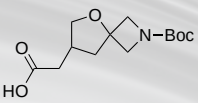
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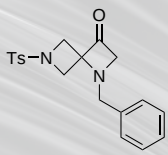
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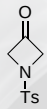
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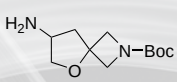
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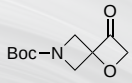
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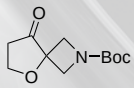
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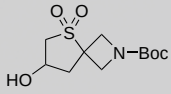
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Dear Fellow Chemists,

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(1) Lauber, M. B.; Stahl, S. S. *ACS Catal.* **2013**, *3*, 2612. (2) Sonobe, T.; Oisaki, K.; Kanai, M. *Chem. Sci.* **2012**, *3*, 3249.

791814

791814	KetoABNO (9-azabicyclo[3.3.1]nonan-3-one-*N*-oxyl)	250 mg 1 g

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Scott Batcheller
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ABOUT OUR COVER

Detail from ***Tamaca Palms***. Photo courtesy National Gallery of Art, Washington, DC.

Tamaca Palms (oil on canvas, 67.9 × 91.3 cm) was painted in 1854 by the famed American landscape artist Frederic Edwin Church (1826–1900). Born to a wealthy family, Church took up art studies at an early age and apprenticed for two years with the renowned British landscape painter Thomas Cole, who had relocated to the U.S. and co-founded the Hudson River School of landscape painting. Church began his artistic career soon after by painting scenes from the northeastern U.S. in the style of the Hudson River School. He won artistic acclaim and achieved commercial success early in his career and, unlike many posthumously famous artists, had assembled a small fortune from the sale of his works by the time he died.

Inspired by the writings of the distinguished naturalist and explorer Alexander von Humboldt, Church travelled extensively in South America, Jamaica, the North Atlantic, the Middle East, Italy, and Greece. It was upon his return from a trip to Colombia in 1853 that Church painted ***Tamaca Palms*** in his New York studio based on meticulous sketches and observations he had made during the trip.* He often painted stunning, large, brightly lit, and detailed panoramas that documented the natural features, plants, and animals of exotic locales. Reminiscent of the romantic tradition in European art, Church's awe of the beauty and majesty of the natural world is unmistakable in his works, where natural features and phenomena are given prominence over the human element.

This painting is part of the Corcoran Collection at the National Gallery of Art, Washington, DC.

** Could Church have used the sketches that he based* ***Tamaca Palms*** *on as an inspiration for later compositions, especially in his later years? To find out, visit* ***Aldrich.com/acta483***

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Despite their huge potential, the inaccessibility and instability of highly reactive nitrogen-substituted alkynes such as ynamines impede numerous synthetic routes.

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Professor Gwilherm Evano, Cédric Theunissen, and Morgan Lecomte (left to right)

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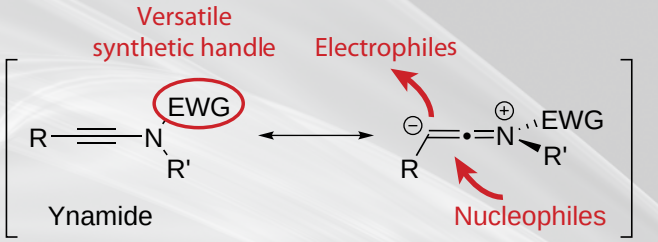

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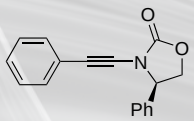
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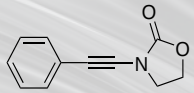
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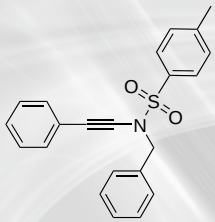
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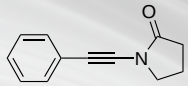
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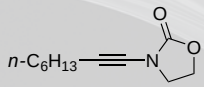
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Ynamides: Powerful and Versatile Reagents for Chemical Synthesis


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Mr. C. Theunissen


Mr. M. Lecomte

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Keywords. ynamides; alkynes; organic synthesis; heterocyclic chemistry; reactivity; reactive intermediates.

Abstract. Ynamides have recently emerged as particularly useful building blocks for chemical synthesis. Their remarkable reactivity has been exploited in the design of a number of novel synthetic processes and for the generation of otherwise inaccessible reactive intermediates. The state of the art of the chemistry of ynamides and its impact on organic synthesis are highlighted in this review, which has been structured according to the nature of both the reactive intermediates generated and the types of reaction they undergo.

Outline

1. Introduction

Organic synthesis is today clearly a central science with significant contributions to, and impact on, various other scientific disciplines such as biology, medicine, and materials science. As a consequence, the high and growing demand for efficient synthetic routes to assemble complex molecules or pharmaceuticals from simple building blocks, as well as the quest for molecular diversity, will continue to challenge the resourcefulness of organic chemists for years to come. In this context, the development of original and versatile starting materials, together with the design of new strategies, will contribute to the selective syntheses of ever larger and more complex systems with increased efficiency.

The need for cleaner, environmentally benign, and more sustainable chemical practices also poses new challenges and requires new ways of carrying out chemical synthesis. Hence, in addition to the development of new reactions, reagents, and catalysts, novel ways to assemble molecules in a more sustainable manner are presently an important factor to consider.

The chemistry of ynamides clearly falls into this category: they display an exceptionally fine balance of stability and reactivity, offer unique and multiple opportunities for the inclusion of nitrogen-based functionalities into organic molecules,[1] and have recently emerged as especially useful and versatile building blocks.[2,3] Indeed, the electron-donating ability of the ynamide nitrogen strongly polarizes the triple bond, which allows for exceptionally high levels of reactivity and regio- and/or stereoselectivities. This reactivity is yet tempered by the electron-withdrawing group, which provides enhanced stability when compared to the highly sensitive ynamines,[4,5] and can also act as an efficient directing group, chiral auxiliary, or can even participate in the reaction (**Figure 1**). These characteristics, coupled with recent breakthroughs in their synthesis,[6–16] have allowed for the increased application of ynamides in synthesis and for their involvement in new and remarkably efficient sequences that are difficult to accomplish otherwise.

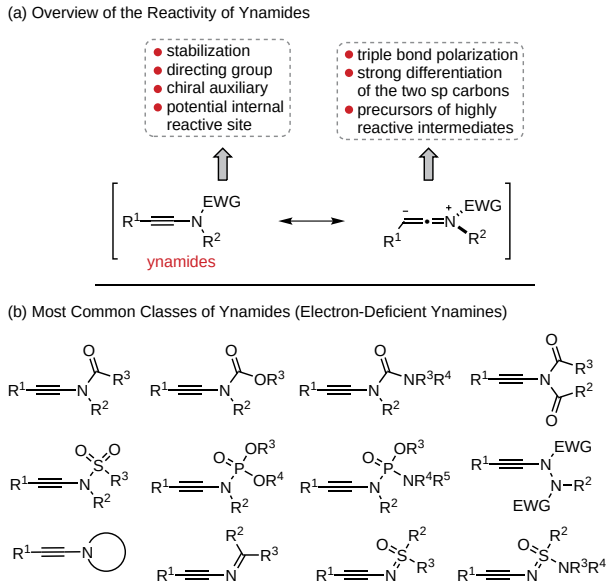


Figure 1. "Ynamides": Structural Types and Chemical Properties.

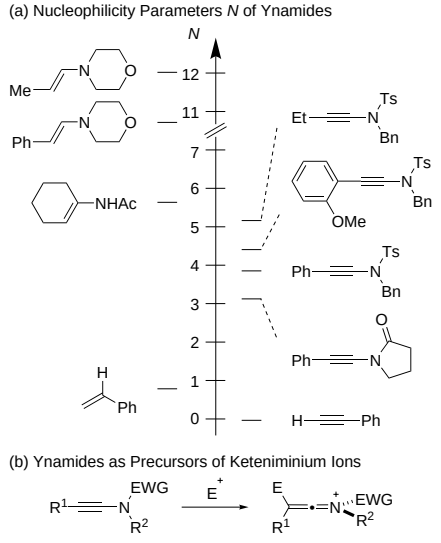


Figure 2. (a) Comparison of the Nucleophilicity Parameters *N* of Ynamides with Those of Related π-Nucleophiles (Mayr Reactivity Scale). (b) Generation of Keteniminium Ions from Ynamides. *(Ref. 18)*

This short review highlights the remarkable reactivity of these building blocks through selected and representative examples of new reactions that have been designed on the basis of the unique behavior of ynamides and other electron-deficient ynamines,[17] which are now also commonly referred to as "ynamides".

2. Ynamides as User-Friendly Precursors

2.1. Of Otherwise Inaccessible Keteniminium Ions

Two characteristic features that are crucial to the reactivity of ynamides are the activation of the triple bond and its strong polarization due to the conjugation of the amine group with the alkyne. Recent studies have shown that ynamides react with electrophiles between 10^3 to 10^5 times faster than regular alkynes (**Figure 2**).[18] The resulting keteniminium ions can participate in a number of transformations including the trapping of these highly reactive and otherwise inaccessible intermediates with nucleophiles. Many electrophile–nucleophile combinations have been employed to access diverse building blocks from ynamides; selected examples will be presented in the next paragraphs.

2.1.1. By Protonation

Brönsted acids have been widely utilized for the generation of keteniminium ions by protonation of ynamides. Depending on the type of acid used and the presence or absence of an additional nucleophile, the conjugated base can act as a nucleophile that traps the keteniminium ion. This yields polysubstituted enamides in a highly stereocontrolled manner, which are valuable building blocks in chemical synthesis and medicinal chemistry. The regio- and stereoselective hydrohalogenation of ynamides is certainly the most representative example of this type of reactivity (**Scheme 1**, Part (a)).[19–21]

Provided that a strong acid is utilized for the protonation of ynamides—which allows the generation of keteniminium ions associated with weakly nucleophilic counterions—additional nucleophiles such as arenes can be used to trap the intermediate keteniminium intermolecularly (Scheme 1, Part (b))[22] or even intramolecularly (which would correspond to a keteniminium version of the Pictet–Spengler cyclization), as exemplified in Scheme 1, Part (c).[23] The generation of highly reactive keteniminium ions by protonation of ynamides, followed by their reaction with a nucleophile, has also been employed to generate intermediate species which can then undergo a [3,3]-sigmatropic rearrangement. Indeed, the protonation of chiral ynamides with *para*-nitrobenzenesulfonic acid, followed by addition of allylic alcohols and subsequent rearrangement of the intermediate allyl vinyl ethers, yields highly substituted homoallylic amides with good levels of diastereoselectivity, which illustrates well the use of chiral ynamides in asymmetric synthesis (Scheme 1, Part (d)).[24] In a similar fashion, the use of arylsulfoxides instead of allylic alcohols provides an efficient (excellent yields within minutes at room temperature) entry into α-arylamides, when catalytic amounts of triflic acid are utilized (Scheme 1, Part (e)).[25]

2.1.2. By Reaction with Electrophiles

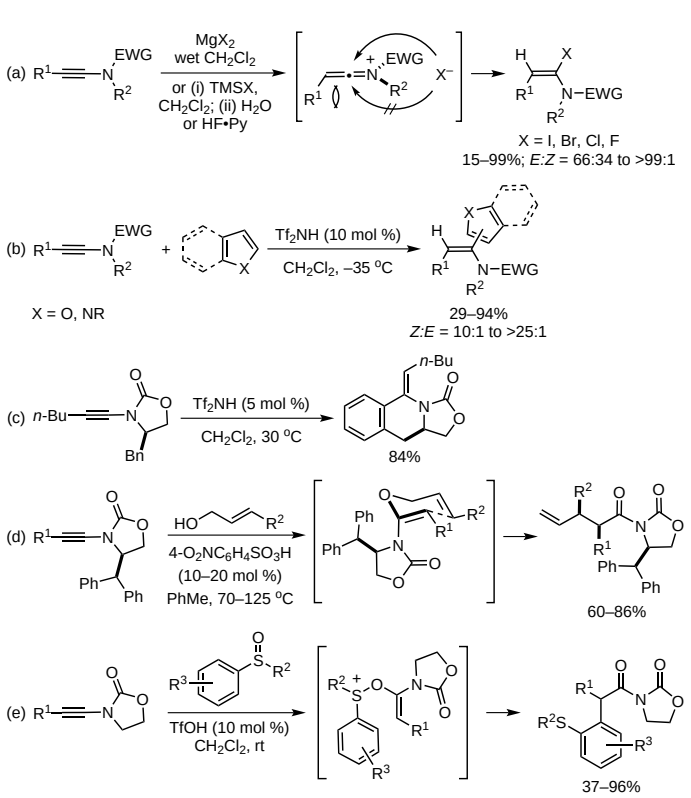
The use of other electrophilic reagents for the generation of keteniminium ions from ynamides is much more challenging since they need to selectively react with the triple bond and not the electron-withdrawing group, which would result in a loss of the stabilization of the ynamides. In addition, the counteranion needs to be a weak nucleophile to avoid trapping the keteniminium ion, which can be circumvented by using an internal nucleophile. The halo-[26] and carbocyclizations[27] of *ortho*-anisole-substituted ynamides yielding highly substituted benzofurans (**Scheme 2**, Part (a)) are representative of this strategy. Other examples that nicely illustrate both the synthetic potential of ynamides and the exceptional reactivity of keteniminium ions generated from these building blocks include the reaction of ynamides with aldehydes, ketones, or enones in the presence of a Lewis acid catalyst. Indeed, upon activation with boron trifluoride or a combination of $CuCl_2$ and $AgSbF_6$, the activated carbonyl derivatives are electrophilic enough to react with ynamides to give intermediate keteniminium ions which can be converted into conjugated amides (Scheme 2, Part (b))[28,29] or into formal [2 + 2] cycloaddition products (Scheme 2, Part (c)).[30] An enantioselective version of the last reaction, now commonly known as the Ficini cycloaddition, has been reported recently.[31]

2.1.3. By Reaction with Electrophilic Metal Complexes

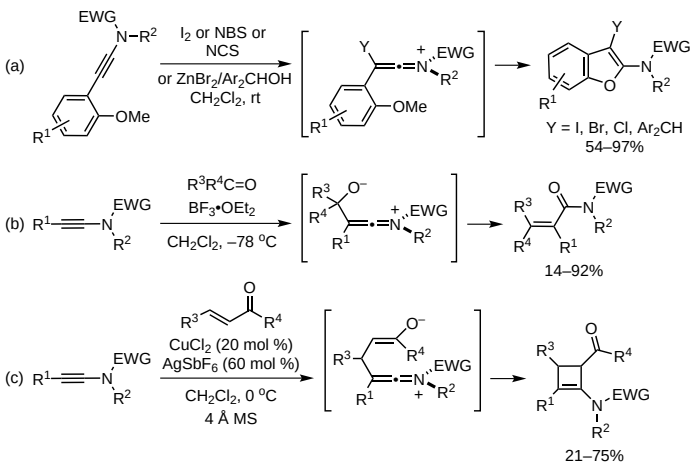
Besides strong acids and other electrophiles; such as halonium ions, carbocations, or activated carbonyl derivatives; electrophilic metal complexes can also be employed for the generation of transient keteniminium ions that can then be trapped by a nucleophile, generally in an intramolecular fashion. In this respect, electrophilic Pd^{II} and Cu^{III} complexes—generated by (formal) oxidative addition of Pd^0 or Cu^I precursors to aryl triflates and diaryliodonium salts respectively—react readily with ynamides, as exemplified by the palladium-catalyzed arylative cyclization of hydroxy-ynamides (**Scheme 3**, Part (a))[32] and the copper-catalyzed carbocyclization of homobenzylic ynamides (Scheme 3, Part (b)).[33]

In addition to these electrophilic palladium and copper complexes, the metal that is probably the most suitable for the activation of the triple bond of ynamides is gold. Indeed, gold complexes have been shown over the years to be excellent electrophilic catalysts for the activation of alkynes, and their use with ynamides, which are more electron-rich than regular alkynes, is therefore ideal. In addition, the polarization of the triple bond ensures high levels of chemoselectivity, as demonstrated by the gold-catalyzed hydroamination of ynamides which proceeds readily at room temperature (Scheme 3, Part (c)).[34]

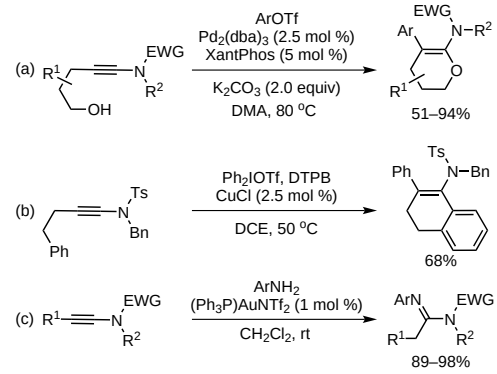
Perhaps more importantly than its use for the regioselective addition of nucleophiles to ynamides, this exceptional affinity between gold complexes and ynamides has found a number of applications in the design of new reactions based on the interception of the auro-keteniminium ions with certain nucleophiles, giving rise to intermediates that can be further elaborated into carbenoid species. Representative examples of such transformations will be discussed in the next section.



Scheme 1. Keteniminium Ions by Protonation of Ynamides and Their Subsequent Transformations. *(Ref. 19–25)*



Scheme 2. Remarkably Reactive Keteniminium Ions by Reaction of Ynamides with Electrophiles. *(Ref. 26–30)*

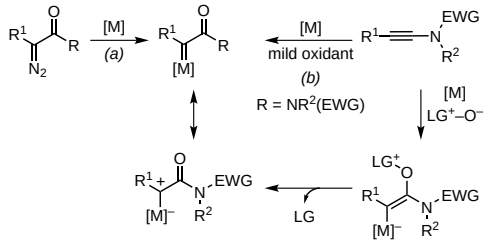


Scheme 3. Cyclization and Functionalization of Ynamides via Keteniminium Ions Promoted by Electrophilic Metal Complexes. *(Ref. 32–34)*

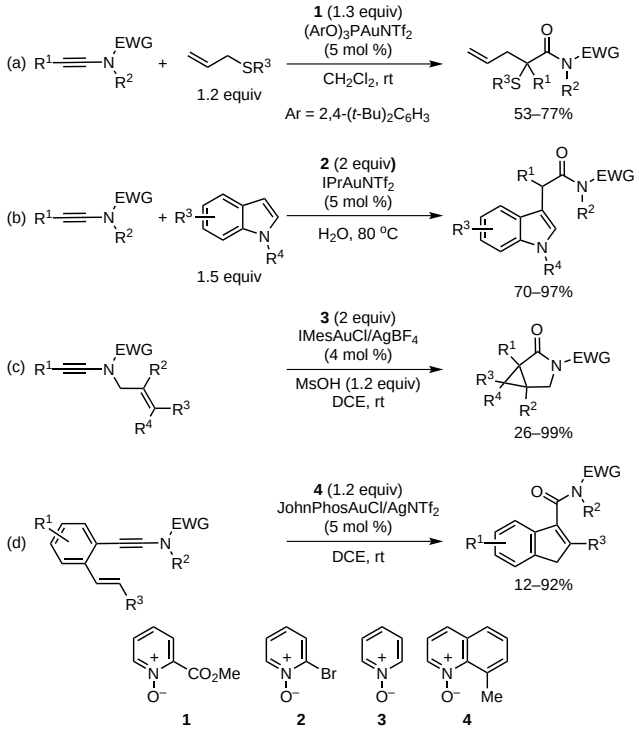
2.2. Of α-Oxo- or α-Imidocarbenes and Carbenoids

α-Oxocarbenes and carbenoids are versatile intermediates that are extensively employed for the development of a wide array of useful transformations. They are, however, typically generated by metal-promoted decomposition of the corresponding potentially hazardous diazo derivatives, which is clearly a severe limitation in terms of efficiency, flexibility, and safety (**Scheme 4**, Part (a)). In an attempt to address this drawback, recent studies have shown that such carbenoids can be readily generated by metal-promoted activation of ynamides in the presence of a suitable mild oxidant. This approach provides an interesting and user-friendly alternative to the use of diazo derivatives (Scheme 4, Part (b)).

Both the inherent reactivity of ynamides and the nature of the oxidant are critical in this approach, since the polarization of the triple bond of the ynamide ensures a total regiocontrol of the π-acidic activation by the metal, and therefore the addition of the nucleophilic external oxidant (LG^+-O^-) α to the nitrogen atom, while the presence of a leaving group in the oxidant enables the generation of the carbenoid.



Scheme 4. Ynamides as Precursors of α-Oxocarbenoids.



Scheme 5. Gold α-Oxocarbenoids from Ynamides and Their Subsequent Inter- and Intramolecular Reactions. *(Ref. 35–38)*

2.2.1. α-Oxocarbenes by Gold-Catalyzed Reaction of Ynamides with Mild Oxidants

This strategy turned out to be especially fruitful by allowing the generation of α-oxocarbenoids under remarkably mild conditions (gold complexes as catalysts and pyridine *N*-oxides as oxidants) from readily available starting materials. In addition, these transformations proceed with impressive levels of chemoselectivity, since the ynamide can be selectively activated in the presence of a wide number of potentially oxidizable functional groups such as alkenes, alkynes, or even sulfides.

Once generated, the α-oxocarbenoids can participate in a number of inter- and intramolecular transformations. Representative examples involving an intermolecular reaction of α-oxocarbenoids include their trapping with allylic sulfides followed by a [2,3]-sigmatropic rearrangement, which leads to highly functionalized α-thioamides (**Scheme 5**, Part (a)),[35] or their reaction with indoles (Scheme 5, Part (b)).[36] Alternatively, the presence of an internal functional group which can react with the intermediate carbenoid can be utilized to access various cyclic and polycyclic molecules. For example, intramolecular cyclopropanation of an appended alkene provides a straightforward entry to fused cyclopropyl-lactams **(**Scheme 5, Part (c)),[37] while a *5-exo-dig* cyclization involving an internal styryl group yields functionalized indenes (Scheme 5, Part (d)).[38] In all cases, the advantage of using ynamides rather than the corresponding diazo compounds as precursors of carbenoids is quite obvious. Following these studies, the use of other oxidants such as sulfoxides[39] or nitrones[40] and the use of rhodium complexes instead of gold catalysts have been reported.[41]

2.2.2. α-Imidocarbenes by Gold-Catalyzed Reaction of Ynamides with Pyridine *N*-Aminidines and Isoxazoles

In all examples mentioned in the previous paragraphs, the pyridine *N*-oxide derivatives only transfer their oxygen atom to generate the oxocarbenoid that is then trapped by a nucleophile, either intramolecularly or intermolecularly. An extension of this strategy relies on the use of nitrogen nucleophiles possessing both a leaving group and a nucleophilic site, masked or not, enabling the generation of electrophilic gold α-imidocarbenes that can react with the internal nucleophile. The gold-catalyzed, formal [3 + 2] cycloaddition between ynamides and pyridine *N*-aminidines is a remarkable application of this reactivity: Reaction of the ynamides with dichloro(pyridine-carboxylato)gold triggers the addition of the pyridine *N*-aminidine ylide to the ynamide. This is followed by cleavage of the pyridine *N*-aminidine N–N bond—generating the key α-imidocarbene—and cyclization involving the *N*-acyl group to yield highly substituted oxazoles (**Scheme 6**, Part (a)).[42] Similarly, isoxazoles can be employed in place of the pyridine *N*-aminidine ylide to give 2-aminopyrroles that result from a formal [3 + 2] cycloaddition (Scheme 6, Part (b)).[43]

As evidenced by all the examples described up to this point, ynamides have evolved as remarkably useful building blocks which act as efficient precursors of highly reactive intermediates such as keteniminium ions or carbenoids that can hardly be accessed from other reagents. This exceptional reactivity, which has ultimately led to the design of original reactions, is mostly based on the electron-rich nature of the ynamides and the polarization of the alkyne. Another facet of their reactivity that has been explored recently is based on their anionic chemistry and, here too, ynamides act as unique building blocks, notably as substrates for carbometallation reactions. These reactions, and the impressive input of ynamides in this chemistry, will be presented in the next section.

3. Carbometallation of Ynamides: New Paradigms in Asymmetric Synthesis and Heterocyclic Chemistry

The carbometallation of ynamides is certainly the most straightforward way to generate, with high levels of regio- and stereoselectivities, metallated enamides. Except in the case where the metal employed is palladium, the presence of the electron-withdrawing group (EWG)—which is also an excellent coordinating group—usually overcomes the polarization of the triple bond (the two effects acting in opposite ways), and controls the regioselectivity of the carbometallation. This results in the selective formation of α-metallated enamides rather than their β-metallated isomers, regardless of the inter- or intramolecular nature of the reaction.

3.1. Intermolecular Carbometallation: Easy Access to Metallated Enamides and Beyond

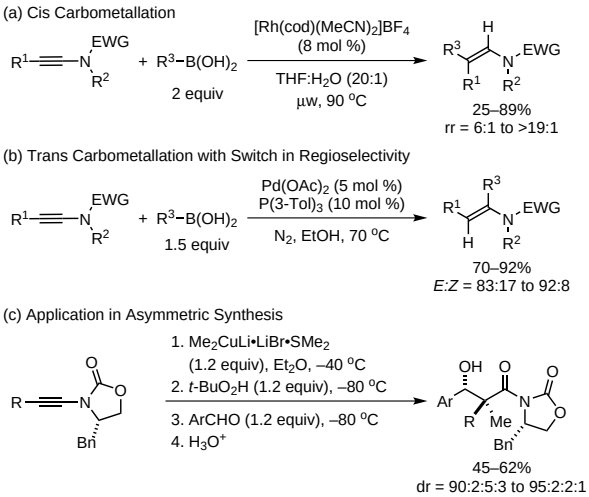
Various organometallic reagents have been employed for the carbometallation of ynamides in the presence or absence of a catalyst. For example, the carbocupration[44,45] and rhodium-catalyzed carbozincation[46] of these building blocks afford straightforward entries to α-metallated enamides, which can be trapped by an array of electrophiles, with total control of both the regio- and stereoselectivities. The carbometallation of ynamides with organoboron reagents is a good illustration of the switch of regioselectivity that can be achieved by the proper choice of the catalytic system. Indeed, while the use of a rhodium catalyst provides the β-functionalized enamides resulting from a cis carbometallation that places the metal next to the nitrogen atom (**Scheme 7**, Part (a)),[47] switching to palladium catalysts reverses both the regio- and stereoselectivity of the reaction (Scheme 7, Part (b)).[48]

Besides providing one of the most efficient entries to multisubstituted enamides, the carbometallation of ynamides has had a dramatic impact in asymmetric synthesis. One of the most striking examples is the carbocupration of chiral ynamides and oxidation of the resulting vinylcopper species. This sequence, the success of which is clearly based on the unique reactivity of ynamides, enables the generation of stereodefined trisubstituted enolates—compounds that are especially challenging to generate otherwise—which are then trapped with aldehydes to yield aldol adducts possessing all-carbon quaternary stereocenters (Scheme 7, Part (c)).[49]

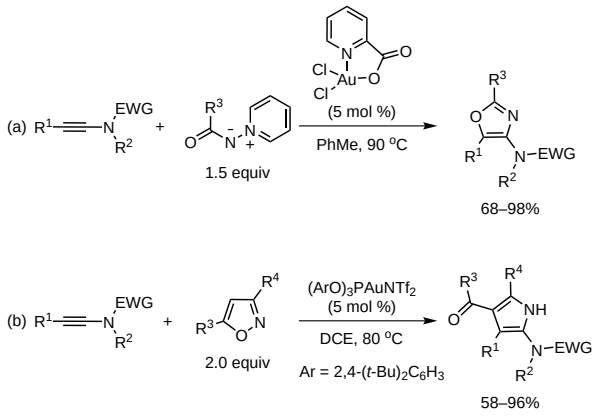
3.2. Intramolecular Carbometallation: New Perspectives in Heterocyclic Chemistry

The unique reactivity of ynamides towards organometallic reagents has also been exploited for the design of new syntheses in heterocyclic chemistry based on intramolecular carbometallation reactions. In this context, the capacity of the electron-withdrawing group to control the regioselectivity of an intramolecular carbolithiation has been used to prepare highly functionalized 1,4-dihydropyridines from *N*-allylynamides by a totally selective deprotonation and 6-*endo*-*dig* cyclization sequence (**Scheme 8**, Part (a)).[50]

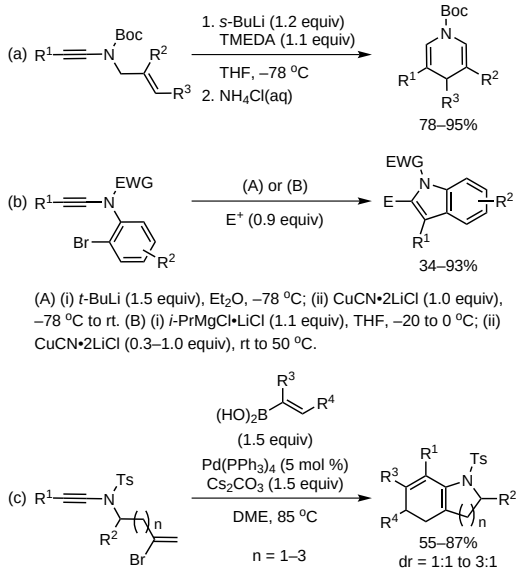
Other heterocycles that can be readily prepared by intramolecular carbometallation of ynamides include functionalized indoles—easily



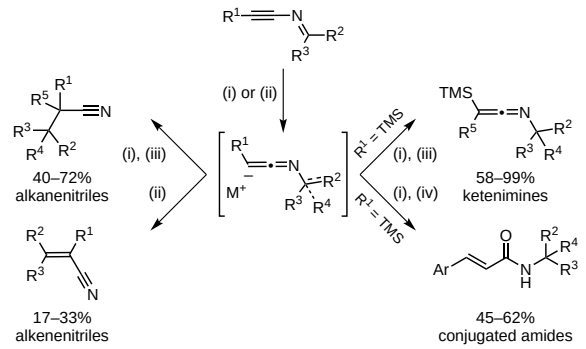
Scheme 7. Intermolecular Carbometallation of Ynamides, Highlighting Control of the Regioselectivity and Remarkable Application in Asymmetric Synthesis. *(Ref. 47–49)*



Scheme 6. Gold-Catalyzed, Formal [3 + 2] Cycloaddition of Ynamides via α-Imidocarbenoids. *(Ref. 42,43)*

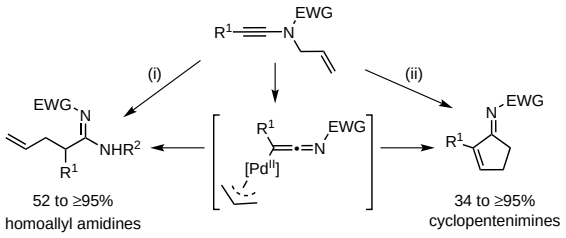


Scheme 8. Synthesis of Heterocycles by Intramolecular Carbometallation of Ynamides. *(Ref. 50–53)*



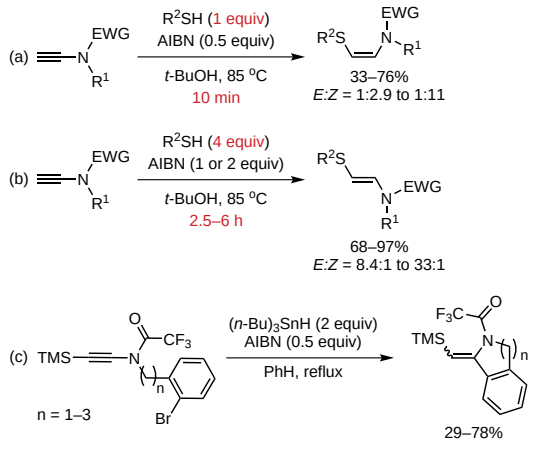
(i) R^4Li, THF, –78 °C. (ii) KHMDS, THF, –78 °C.
(iii) R^5X, –78 °C to rt. (iv) ArCHO, –78 °C to rt.

Scheme 9. Generation and Reactivity of Metallated Ketenimines from Ynimines. *(Ref. 54)*



(i) $Pd(PPh_3)_4$ (5 mol %), K_2CO_3 (1.0 equiv), R^2NH_2 (3.0 equiv), THF, 65 °C
(ii) $Pd(PPh_3)_4$ (5 mol %), PhMe, 70 °C

Scheme 10. Generation and Reactivity of Palladated Ketenimines from *N*-Allylynamides. *(Ref. 55,56)*



Scheme 11. Ynamides as Excellent Radical Acceptors. *(Ref. 59–61)*

obtained by carbocupration of readily available *N*-arylynamides (Scheme 8, Part (b))[51,52]—or their tetrahydro derivatives. Higher ring systems can be accessed from bromoenynamides by a palladium-catalyzed cyclization–cross-coupling–electrocyclization sequence (Scheme 8, Part (c)).[53]

4. Ynamides as Precursors of Metallated Ketenimines

If organometallic reagents and palladium catalysts can be utilized to generate metallated enamides from ynamides, as discussed in the previous paragraphs, they can also be employed to generate metallated ketenimines in situ, another useful class of reactive intermediates that are quite challenging to prepare despite their interesting reactivity.

The first strategy to generate these metallated ketenimines involves either the addition of an organolithium to ynimines or the deprotonation of the latter with a strong base. The metallated ketenimines can then be trapped with electrophiles, which provides a highly divergent and efficient entry to various building blocks, including highly substituted alkanenitriles, alkenenitriles, ketenimines, and conjugated amides (**Scheme 9**).[54]

The second strategy for the generation of metallated ketenimines is based on the palladium-catalyzed oxidative addition to the C–N bond of *N*-allylynamides. The products resulting from this oxidative addition are in equilibrium with the palladated ketenimine, which can then proceed down a number of reaction pathways including reductive elimination and reaction with amines yielding homoallyl amidines,[55] or an aza-Rautenstrauch rearrangement affording cyclopentenimines[56] (**Scheme 10**). The reductive elimination represents a straightforward and efficient entry to ketenimines, while the intermediate palladated ketenimines have found various elegant applications in the synthesis of complex heterocyclic systems.[57,58]

5. Ynamides as Radical Acceptors

Ynamides are also excellent radical acceptors and their use in free radical reactions provides many opportunities for the synthesis of nitrogen-containing molecules. There are still only few examples of intermolecular addition of radical intermediates to ynamides, the most notable being the addition of the electrophilic thiyl radicals. One equivalent of thiol in *tert*-butyl alcohol in the presence of AIBN as the radical initiator provides within 10 minutes the corresponding *Z* β-thioenamide—a moiety that is found in various natural products—as the main product. Employing an excess of thiol and longer reaction times affords mainly the *E* isomer (**Scheme 11**, Parts (a) and (b)).[59]

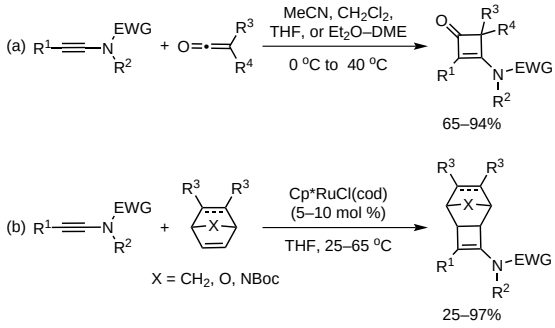
The beneficial use of ynamides as radical acceptors is even more evident in the intramolecular counterparts, since they afford efficient and original entries to nitrogen heterocycles of various sizes. The size of the heterocyclic ring is controlled simply by the length of the tether between the radical center and the ynamide (Scheme 11, Part (c)).[60,61]

6. Ynamides in Cycloaddition Reactions: Diversity-Oriented Syntheses of Heterocycles

The main problem of cycloadditions involving alkynes is that they often yield mixtures of regioisomers due to a poor differentiation of the two sp carbon atoms of the triple bond. This issue can be easily overcome by using ynamides since the inherent polarization of the triple bond ensures that high levels of regioselectivity are typically reached. Another clear advantage of ynamides in cycloaddition reactions lies in the intramolecular variants, which lead to the direct assembly of a wide range of heterocyclic scaffolds. These reactions are efficiently catalyzed by various metals, and representative examples are covered in this section.

6.1. [2 + 2] Cycloadditions

The most notable example of a formal [2 + 2] cycloaddition involving ynamides is the Ficini cycloaddition, which is actually a stepwise process involving the generation of an intermediate keteniminium ion followed by ring closure as described in Section 2.1.2 (Scheme 2, Part (c)). [2 + 2] cycloadditions with ynamides, which efficiently yield aminocyclobutenes, also include their highly regioselective thermal reaction with ketenes (**Scheme 12**, Part (a)).[62] This variant was recently extended to the use of ynesulfoximines,[63] iodoynamides,[64] and vinylketenes,[65] and is now a robust method for the synthesis of 3-aminocyclobutenones. Other examples of [2 + 2] cycloadditions with ynamides are the Ru- or Rh-catalyzed reactions with bicyclic alkenes (Scheme 12, Part (b))[66] and nitrostyrenes.[67]



Scheme 12. [2 + 2] Cycloadditions with Ynamides. *(Ref. 62,66)*

6.2. [3 + 2] Dipolar Cycloadditions

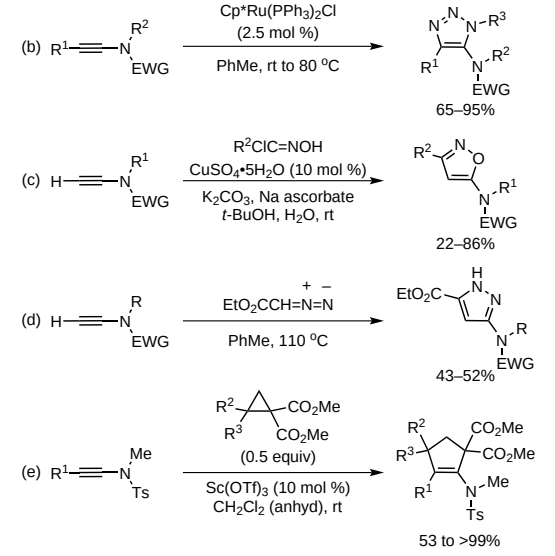
While most alkynes typically afford mixtures of regioisomers in dipolar [3 + 2] cycloaddition reactions, cycloadditions of ynamides with dipoles usually proceed with high levels of regioselectivity, and can therefore be employed for the preparation of an array of amino-substituted carbocycles and heterocycles (**Scheme 13**).[68–71] In addition, terminal ynamides are also remarkably efficient reaction partners for the copper-catalyzed Kinugasa reaction, an iconic route to β-lactams in which the first step involves a [3 + 2] cycloaddition with a nitrone. The use of an ynamide in this reaction offers two main advantages: it can introduce a nitrogen atom on the final β-lactam, or it can control the stereochemistry of the two stereocenters formed by starting from chiral ynamides.[72]

6.3. [4 + 2] Cycloadditions

The intramolecular [4 + 2] cycloadditions of ynamides can be a straightforward entry to various nitrogen heterocycles, and can be conducted either in the presence of a cationic rhodium catalyst from diene-ynamides (**Scheme 14**, Part (a)),[73] or thermally from enyne-containing ynamides (Scheme 14, Part (b)).[74,75]

An interesting extension—which increases the range of heterocyclic systems that can be conveniently synthesized from ynamides using a [4 + 2] cycloaddition strategy—was recently reported, and is based on a hexadehydro-Diels–Alder reaction of diyne-ynamides. This reaction, which can be performed either thermally[76] or in the presence of catalytic amounts of silver triflate (Scheme 14, Part (c)),[77] generates an intermediate aryne which can then be trapped by various nucleophiles to generate highly functionalized indolines.

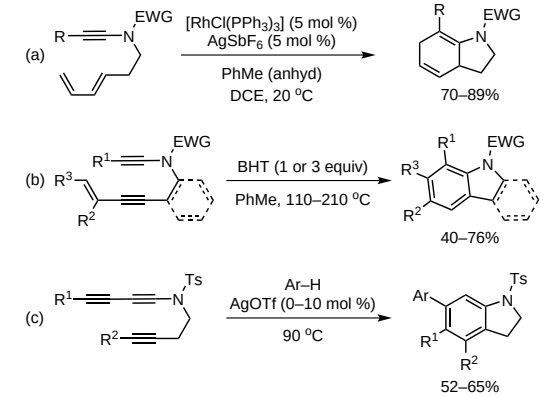
In addition to their remarkable [2 + 2], [3 + 2], and [4 + 2] cycloaddition reactions, ynamides have been elegantly utilized in [2 + 2 + x] reactions, providing entries to other molecular architectures. Here again, the success and the high levels of selectivity of these processes lie in most cases in the exceptional reactivity of ynamides. These reactions will be described in the following paragraphs.



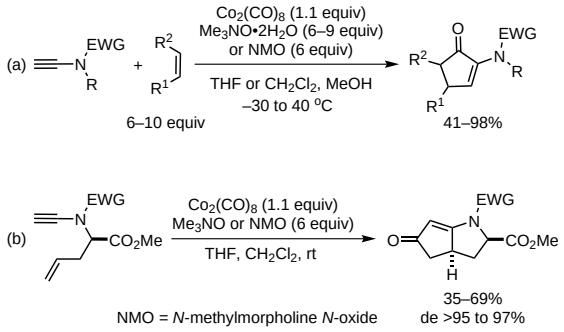
Scheme 13. Formal, [3 + 2] Dipolar Cycloadditions with Ynamides. *(Ref. 68–71)*

6.4. [2 + 2 + 1] Pauson–Khand Cycloadditions

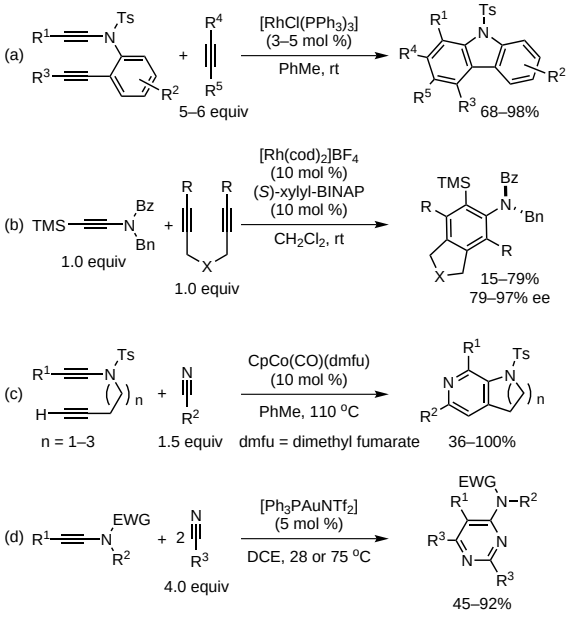
[2 + 2 + 1] reactions of ynamides are mostly associated with the Pauson–Khand reaction. As a gross simplification, the use of ynamides in this venerable reaction can be beneficial mostly in two cases: either in an intermolecular reaction in which the ynamide is utilized to introduce an exocyclic amine (**Scheme 15**, Part (a)),[78] or in intramolecular processes in which the nitrogen is incorporated into one of the rings formed during the cycloaddition. This latter case results in the diastereoselective formation of cyclopentapyrrol-5-one derivatives (Scheme 15, Part (b)).[79] In both cases, the reaction conditions are based on Schreiber's protocol and rely on the use of $[Co_2(CO)_8]$ and trimethylamine *N*-oxide.



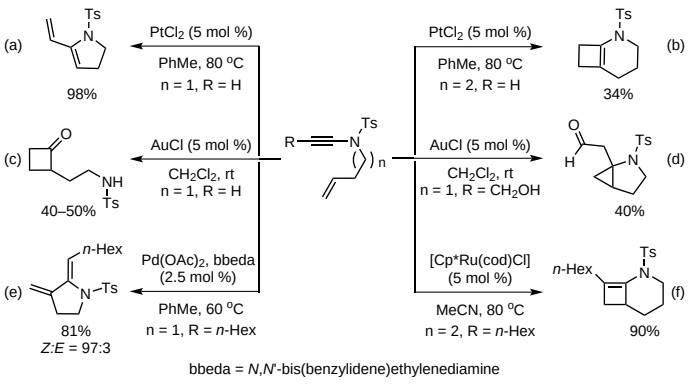
Scheme 14. [4 + 2] Cycloadditions with Ynamides. *(Ref. 73,74,77)*



Scheme 15. Pauson–Khand Reactions with Ynamides. *(Ref. 78,79)*



Scheme 16. [2 + 2 + 2] Cyclotrimerizations with Ynamides. *(Ref. 80–83)*



Scheme 17. Examples of Cycloisomerizations of Enynamides. *(Ref. 84,86,87)*

6.5. [2 + 2 + 2] Cycloadditions

The metal-catalyzed [2 + 2 + 2] cycloaddition of ynamides with alkynes and/or nitriles provides original entries to polysubstituted anilines, aminopyridines, and aminopyrimidines. These reactions have been extensively studied over the past decade and, in most cases, at least two reactants are tethered to ensure high levels of selectivity. Representative examples include the rhodium-catalyzed reaction of yne-ynamides with alkynes yielding polysubstituted carbazoles (**Scheme 16**, Part (a)),[80] the enantioselective cyclization of ynamides with diynes leading to axially chiral anilides (Scheme 16, Part (b)),[81] and the cobalt-catalyzed cyclotrimerization of yne-ynamides with nitriles affording bicyclic 3-aminopyridines (Scheme 16, Part (c)).[82]

While monomolecular versions of these reactions where all reactants are tethered together—which leads to the formation of one additional cycle—have also been reported, the corresponding trimolecular processes, in which serious issues with selectivity often arise, are still rare. One isolated example of such cyclotrimerization was reported in 2014, and is based on the gold-catalyzed, formal [2 + 2 + 2] cycloaddition of an ynamide with two equivalents of a nitrile (Scheme 16, Part (d)).[83] 4-Aminopyrimidines, which are commonly found in many bioactive molecules, are formed in high yields and with remarkable efficiency. The selectivity of this reaction was attributed to the electron-rich nature of the ynamide triple bond, which can be selectively activated by the gold catalyst.

7. Cycloisomerization of Ynamides: Rapid Approaches to Diverse Nitrogen Heterocycles

Heterocyclic scaffolds that are at the core structures of various natural and/or biologically relevant molecules can be accessed by cycloisomerization of ynamides possessing other reactive moieties such as an alkene or an allene. The cycloisomerization of homoallylic ynesulfonamides and their higher homologues is quite representative of the advances recently made in this area, and showcases the dramatic effect that both the metal catalyst and the substitution pattern of the starting ynamide can have on the outcome of the reaction. Indeed, upon reaction with a catalytic amount of $PtCl_2$, a 1,6-enynamide produced a vinyl-substituted dihydropyrrole (**Scheme 17**, Part (a)),[84] a compound which can also be obtained from the same enynamide using a ring-closing metathesis reaction.[85] Under the exact same conditions, a 1,7-enynamide exhibited a different behavior and led to the selective formation of a strained 2-azabicyclo[4.2.0]oct-1(6)-ene (Scheme 17, Part (b)).[84] A skeletal rearrangement of the 1,6-enynamide to an aminoethylcyclobutanone was promoted by a gold catalyst (Scheme 17, Part (c)).[86] The presence of a propargylic alcohol in the starting enynamide had a dramatic influence on the cycloisomerization reaction pathway, which led to the formation of a fused cyclopropylpyrrolidine (Scheme 17, Part (d)).[86] The combination of a 1,6-enynamide and a palladium(II) catalyst resulted in a cycloisomerized product possessing both a five-membered-ring heterocyclic core and an exocyclic diene (Scheme 17, Part (e)).[87] The ruthenium-catalyzed cycloisomerization of the 1,7-analogue afforded a 2-azabicyclo[4.2.0]oct-1(8)-ene (Scheme 17, Part (f)).[87] Since the outcome of these cycloisomerizations is now well understood, they clearly provide excellent opportunities for diversity-oriented synthesis in heterocyclic chemistry.

If enynamides clearly are ideal substrates in cycloisomerization reactions, the cycloisomerizations are not restricted to this subclass of ynamides. Other functional groups on the starting ynamides can be employed to access other types of cycloisomerization products. The silver-catalyzed cycloisomerization of allenynamides (**Scheme 18**,

Part (a))[88] and the gold-catalyzed transformation of furanyl-ynamides (Scheme 18, Part (b))[89] are two examples of this approach.

The reliability of the ynamide reactions described up till now, and the possibility of predicting the regioselectivity in most of them, have recently led to the design of more complex processes in which more than one cycle are formed in a single operation. These efficient polycyclization reactions from ynamides will now be briefly discussed.

8. Polycyclizations of Ynamides: Straightforward Routes to Complex Nitrogen Heterocycles

Most reactions involving ynamides can be taken one step further by carefully tuning the nature and position of substituents to promote cascade processes, leading to the selective formation of complex heterocyclic frameworks. In most cases, the activation of the ynamide triggers the polycyclization, and its presence typically controls the regioselectivity of the process.

The first cationic cascade involving ynamides was reported in 2014, and is based on a keteniminium ion initiated cascade polycyclization of *N*-benzyl- or *N*-allyl-*ortho*-tolylynamides. Upon reaction with excess triflic acid or catalytic amounts of bistriflimide, these ynamides are transformed into the corresponding highly reactive keteniminium ions. This induces a [1,5]-shift of hydrogen, an electrocyclization, and a Friedel–Crafts-type reaction (**Scheme 19**, Part (a)).[90] Polycyclic nitrogen heterocycles possessing up to three stereocenters and seven fused cycles can be easily obtained in a single operation: the comparison of this route with previously reported ones for accessing similar molecular architectures in more than ten steps clearly demonstrates the advantages of using ynamides.

The gold-catalyzed activation of ynamides can also be employed to promote polycyclization reactions via gold carbenoids. Treatment of an *N*-styryl *ortho*-azidophenyl ynamide with a cationic gold catalyst at room temperature generates the key carbenoid (by activation of the ynamide, nucleophilic attack of the azide, and extrusion of dinitrogen), which is trapped by the appended alkene to generate a cyclopropanindoloquinoline with remarkable efficiency (Scheme 19, Part (b)).[91]

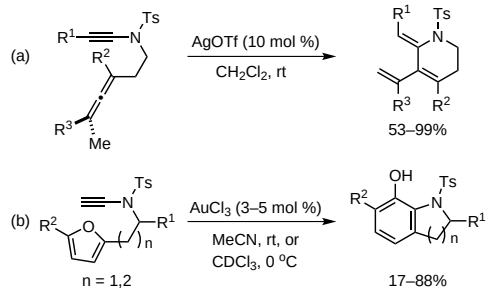
The vinylpalladium complex formed after an initial oxidative addition–carbopalladation sequence of a bromoenynamide (see Scheme 8, Part (c)) can also be utilized in a cascade polycyclization by further intramolecular carbopalladation of a second alkyne group in the starting acyclic precursor (Scheme 19, Part (c)).[92] Reactive aryne intermediates—which are conveniently generated by a silver-catalyzed formal [4 + 2] cycloaddition from diyne-ynamides as discussed in Section 6.3 (see Scheme 14, Part (c))—can also trigger a second cyclization by insertion into a C(sp^3)–H bond, affording multisubstituted cyclopentaindoles in excellent yields (Scheme 19, Part (d)).[93]

9. Ynamides as Building Blocks for the Synthesis of Natural Products: Enabling New and Original Bond Disconnections

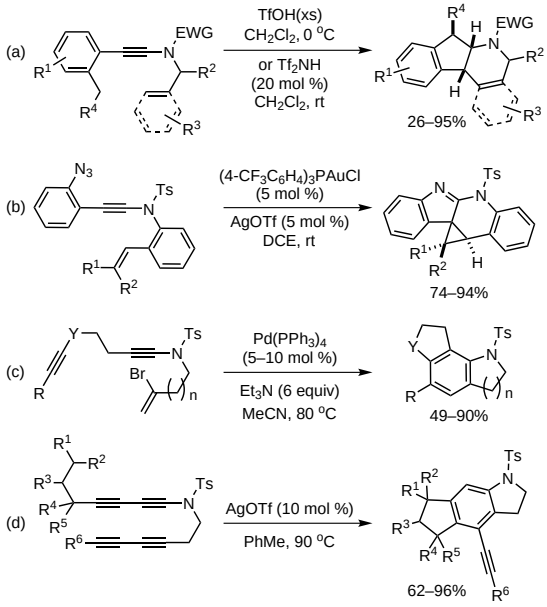
Previous sections demonstrated the tremendous advances recently reported in the chemistry of ynamides. Capitalizing on the remarkable reactivity of ynamides, a number of robust, reliable, and efficient processes have been developed over the past 15 or so years. Simple building blocks, heterocycles, reactive intermediates, as well as complex molecular architectures can efficiently be obtained from various ynamides. The attractiveness and reliability of some of these processes, which often also provide shorter and more efficient synthetic routes as compared to other approaches, have been exploited in the synthesis of various natural products, an area of chemistry where only the most robust and reliable methods can be employed.[94] **Figure 3** showcases a few of the natural and/or biologically relevant molecules that are readily obtained using an ynamide in a key step of the synthesis.[23,95–104] Importantly, ynamides are not only utilized for the introduction of a nitrogen atom, they can also be employed to access key intermediates in a synthetic sequence or to control the regio- and/or stereoselectivity of a reaction. In this latter case, the nitrogen atom of the starting ynamides can be sacrificial and does not necessarily have to be incorporated into the target molecule.

10. Conclusion and Outlook

The unique reactivity of ynamides has made them into powerful reagents for chemical synthesis. They are convenient precursors of highly reactive intermediates such as keteniminium ions or carbenoid species. They offer general, reliable, and often straightforward routes to many molecules ranging from simple building blocks and heterocycles to complex polycyclic structures and natural products. Chiral ynamides offer new opportunities in asymmetric synthesis, and various long-



Scheme 18. Other Cycloisomerizations of Ynamides. *(Ref. 88,89)*



Scheme 19. Cascade Polycyclizations of Ynamides. *(Ref. 90–93)*

standing synthetic challenges—such as the generation of stereodefined trisubstituted enolates,[49] the catalytic and stereocontrolled generation of dienolates,[105] and the preparation of an azacyclohexyne derivative[106]—have been, at least partially, solved by taking advantage of ynamide chemistry. In most cases, they do not only react as "nitrogen-substituted alkynes" or "*N*-alkynylamides", but their reactivity is in fact a subtle combination of both functional groups, and the ynamide moiety should in general be considered as a whole. Ynamides have been used recently in coordination chemistry, where they behave as stable equivalents of unstable oxazol-4-ylidenes.[107] Ynamides are also starting to find applications in medicinal chemistry. In spite of the widespread studies of ynamides, many aspects of their reactivity remain largely unexplored. Further understanding and quantification of the exact influence of the electron-withdrawing groups and other substituents on the reactivity of ynamides will facilitate the choice of a class of ynamides for a given application. In any case, this field is anticipated to continue to rapidly expand and mature, and interesting breakthroughs can be expected.

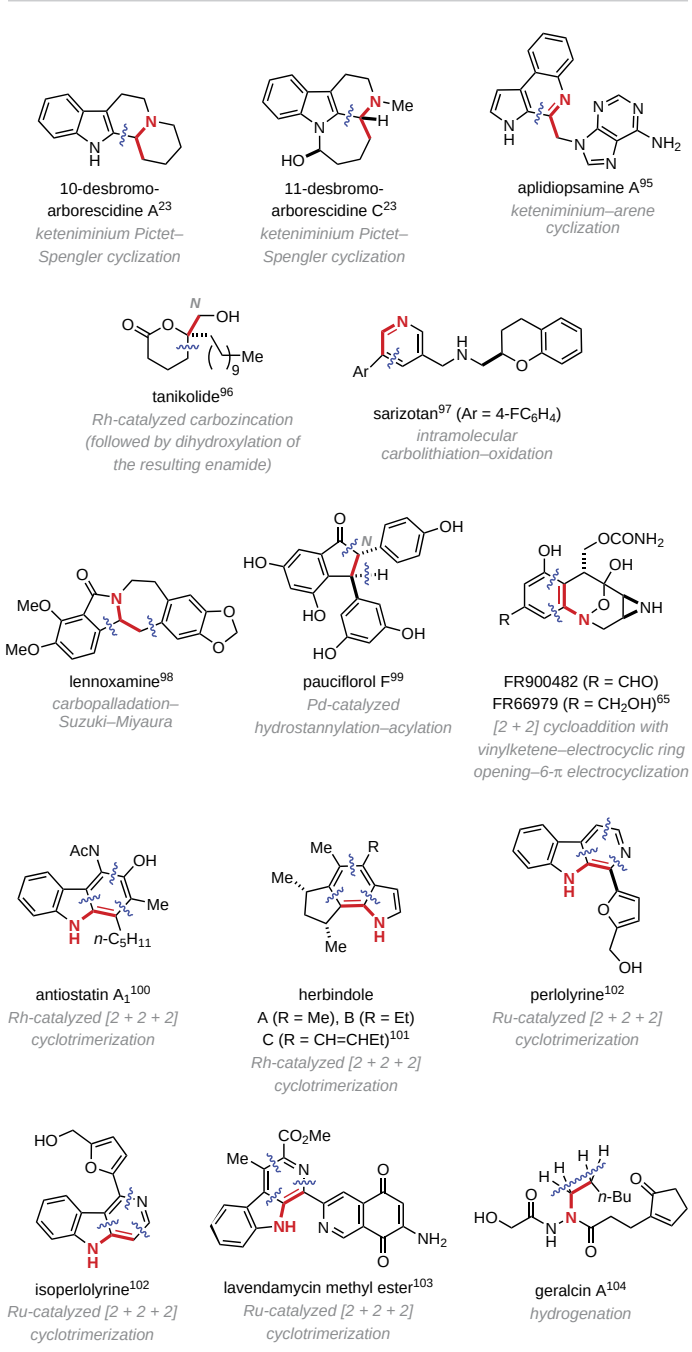


Figure 3. Natural and/or Biologically Relevant Molecules Synthesized from Ynamides (Bonds and Atoms Shown in Red Were Initially Part of the Starting Ynamides. In the Case Where the Nitrogen Atom of the Ynamide Was Not Incorporated in the Final Product, Its Initial Position Is Indicated by a Grey, Italic, and Upper-Case *N*. Key Bond Disconnections Involving the Ynamides Are Shown in Blue).

11. Acknowledgments

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Cédric Theunissen was born in Brussels in 1989 and studied chemistry at the Université Libre de Bruxelles. In 2012, he obtained his master's degree under the supervision of Prof. Cécile Moucheron. His master's thesis research focused on the synthesis of new ruthenium complexes designed to interact with DNA in an anticancer approach. He then obtained an F.R.I.A. fellowship, and started his Ph.D. level research in the group of Prof. Gwilherm Evano. This research focuses on the development of new copper-mediated synthetic transformations and on the study of the reactivity of ynamides.

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PRODUCT HIGHLIGHT

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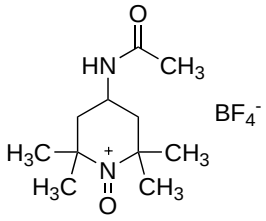

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Reference:
Leadbeater, N. E.; Bobbitt, J. M. *Aldrichimica Acta* **2014**, *47*, 65.

84031-c

Cyclic Sulfamidate Enabled Syntheses of Amino Acids, Peptides, Carbohydrates, and Natural Products


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Keywords. regiospecific; stereospecific; ring-opening; unnatural amino acid; chiral building block; natural product; cyclic sulfamidate.

Abstract. This article reviews the emergence of cyclic sulfamidates as versatile intermediates for the synthesis of unnatural amino acids, chalcogen peptides, modified sugars, drugs and drug candidates, and important natural products.

Outline

1. Introduction

Cyclic sulfamidates are synthetic intermediates that are readily accessible from both amino acids and amino alcohols, and form a versatile set of electrophiles that can undergo facile and regiospecific nucleophilic substitution at the O-bearing carbon center. Synthetically, five- and six-membered-ring sulfamidates are equivalent to aziridines and azetidines. However, cyclic sulfamidates have several advantages over aziridines and azetidines in terms of reactivity and selectivity (**Figure 1**, Part (a)). The present article reviews exciting recent advances in organic synthesis enabled by cyclic sulfamidates.

2. Structural Analysis and Reactivity of Cyclic Sulfamidates

Cyclic sulfites (1,3,2-dioxathiolane 2-oxides, **1**) and cyclic sulfates (1,3,2-dioxathiolane 2,2-dioxides, **2**) are the sulfite and sulfate esters of diols, and are the synthetic equivalents of epoxides. Cyclic sulfamidites (1,2,3-oxathiazole 2-oxide, **3**) and sulfamidates (1,2,3-oxathiazole 2,2-dioxides, **4**) are the corresponding sulfite and sulfate esters of amino alcohols, and are the synthetic equivalents of aziridines (Figure 1, Part (b)). Although compound classes **1**–**4** have been known for a long time,

their general application in synthesis became possible only after the development of efficient methods for their synthesis. Derivatives **3** and **4** can be better alternatives to aziridines, since they are not encumbered with regioselectivity issues; sulfamidates (**4**), an activated form of sulfamidites (**3**), have a great potential as nitrogenous electrophiles for regioselective ring-opening under mild conditions.

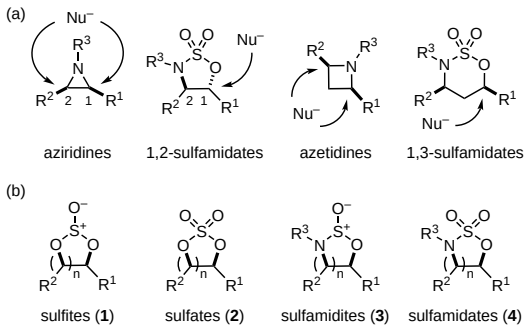
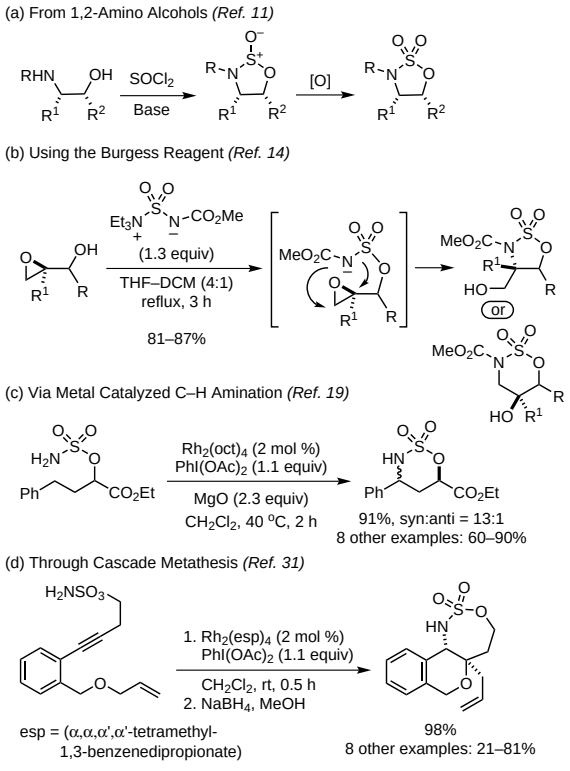


Figure 1. (a) Preferred Sites of Nucleophilic Attack in Aziridines, Azetidines, and Cyclic Sulfamidates. (b) Cyclic Sulfite and Sulfate Derivatives of Diols and Amino Alcohols.



Scheme 1. Syntheses of Cyclic Sulfamidates.

3. Synthesis of Cyclic Sulfamidates

McCombie and Parkes discovered cyclic sulfamidites by accident in 1912.[1] However, they remained little used until 1969, when Deyrup and Moyer's unsuccessful attempt to prepare aziridines from 1,3-amino alcohols led to the formation of cyclic sulfamidites instead.[2] While this became thereafter a practical method for their synthesis,[3] the sluggish reactivity of sulfamidites, and the need to employ drastic conditions in their reactions, prevented their wider use in organic synthesis.[4] The sluggish reactivity of sulfamidites has been overcome by converting them into the corresponding sulfamidates.[5–7]

3.1. From 1,2-Amino Alcohols

Cyclic sulfamidates can be prepared directly in one step from 1,2-amino alcohols by treatment with SO_2Cl_2 or SO_2Im_2.[8] This method, however, found limited success in the case of conformationally constrained 1,2-amino alcohols, such as 2-aminophenols and prolinols,[9] and cannot be utilized as a general preparative method due to competitive aziridination and/or azitidation. Consequently, a two-step approach that mirrors the synthesis of cyclic sulfates[10] has been developed, whereby treatment of 1,2- or 1,3-amino alcohols with $SOCl_2$ leads to the efficient formation of cyclic 1,2- and 1,3-sulfamidites[2] that are then oxidized to the sulfamidates (**Scheme 1**, Part (a)).[11]

3.2. From Diols and Epoxides Using the Burgess Reagent

The Burgess reagent is prepared from chlorosulfonyl isocyanate and triethylamine in a simple, two-step procedure.[12] Nicolaou and co-workers have shown that this reagent can be utilized to synthesize cyclic sulfamidates from diols via a double alcohol activation mechanism,[13] and applied this approach to the synthesis of functionalized chiral sulfamidates from allyl epoxides (Scheme 1, Part (b)).[14] This method allows the direct conversion of diols (1,2-diols, 1,3-diols, etc.) into the corresponding sulfamidates, with the regioselectivity being dependent on the stereoelectronic preferences of the diols. Hudlicky and co-workers have also demonstrated that cyclic sulfamidates can be accessed from epoxides by treatment with the Burgess reagent.[15]

3.3. Via Metal-Catalyzed C–H Amination

Capitalizing on the discovery by Breslow and Gellman,[16] Che and co-workers demonstrated that intermolecular nitrogen insertion into an unactivated C–H bond is possible via Ru- or Mn-catalyzed nitrene insertion.[17] This strategy was applied to cyclic sulfamidates by using the enantioselective intramolecular amidation of saturated C–H bonds catalyzed by a Ru-porphyrin chiral complex.[18] Du Bois and co-workers reported a similar protocol using a Rh-catalyzed reaction (Scheme 1, Part (c)).[19] Che's and Du Bois's methods involved intramolecular cyclization of sulfamate ester wherein the cyclization results most of the time in the formation of six-membered-ring cyclic sulfamidates.[20,21] Some sluggish substrates give five- or even seven-membered-ring sulfamidates.[20] This study led to the development of a modular method for the synthesis of sulfamidates from sulfamate esters.[22] Cui and He have employed silver metal in combination with phenyliodonium acetate for the intramolecular cyclization of sulfamate esters.[23] There have been other strategies utilizing Rh, Cu, and Au metal salts or complexes for the formation of seven-membered-ring sulfamidates, where the nitrogen is also a part of an aziridine ring system.[24–25] Although the metal-catalyzed synthesis of cyclic sulfamidates has been well established using C–H activation, the asymmetric variant has not been generalized. Che[26] employed chiral manganese(III) Schiff-base complexes, while Müller[27,28] attempted the use of rhodium chiral complexes as catalysts for the enantioselective synthesis of

cyclic sulfamidates. However, moderate asymmetric inductions were observed in both cases. In contrast, Du Bois's use of a chiral rhodium carboxamidate complex[29] and Blakey's demonstration of cationic ruthenium(II)-pybox systems[30] have provided a reasonable, practical synthesis of chiral cyclic sulfamidates.

3.4. Through Cascade Metathesis

Blakey and co-workers disclosed an unconventional method for the synthesis of cyclic sulfamidates using a cascade metallonitrene–alkyne metathesis process.[31] Their study was based on the hypothesis that the metallonitrene species would react with an alkyne, leading to a zwitterionic intermediate; this would be followed by a metal shift that precipitates a cascade cyclization coupled with a concerted imine reduction. The method has been very useful for the synthesis of six- and seven-membered-ring sulfamidates (Scheme 1, Part (d)).[31–32]

3.5. By Hydrogenation and Transfer Hydrogenation

Treatment of α-hydroxy ketones with sulfamoyl chloride (H_2NSO_2Cl) affords the corresponding cyclic imines which can be hydrogenated to sulfamidates. The asymmetric variant gives direct access to enantioenriched cyclic 1,2-sulfamidates as in the case of the Pd/binaphane one (**Scheme 2**, Part (a)).[33] The reaction proceeds efficiently and gives quantitative yields in almost all cases. Lee and co-workers, reported that RhCl(*R*,*R*)-TsDPEN]Cp* catalyzes an asymmetric transfer hydrogenation using formic acid and triethyl amine as the hydrogen source.[34,35]

3.6. By Arylation of Cyclic N-Sulfamidate Alkylketimines

Feng, Lin, and co-workers developed a new route for the enantioselective synthesis of sulfamidates by 1,2-arylation of cyclic *N*-sulfamidate alkylketimines with arylboronate esters. A range of enantiomerically pure substituted cyclic sulfamidates have been prepared in 19–99% yield by this method in the presence of a chiral rhodium–diene complex as a catalyst (Scheme 2, Part (b)) These sulfamidates provide access to biologically interesting and enantiomerically pure β-alkyl-β-aryl amino alcohols.[36]

3.7. Through Aminohydroxylation of Sulfamate Esters

Inspired by the intramolecular aminohydroxylation of carbamates derived from allylic alcohols,[37] Kenworthy and Taylor employed the aminohydroxylation of sulfamate esters derived from homoallylic alcohols for the synthesis of six-membered-ring sulfamidates (Scheme 2, Part (c)).[38]

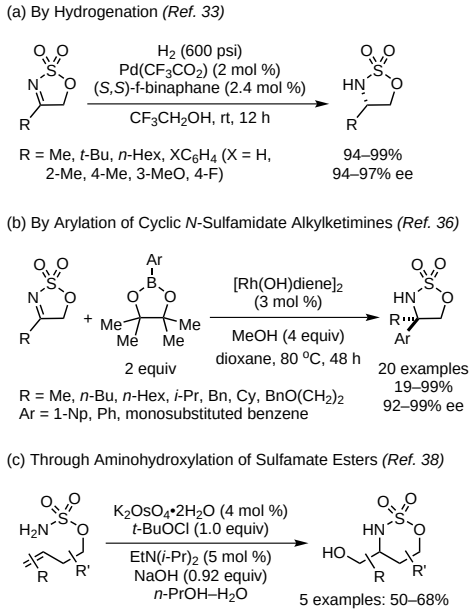
4. Ring-Opening Reactions of Cyclic Sulfamidates

The main driving force in aziridine and azetidine chemistry comes from the ring strain, which is lacking in five- and higher-membered-ring nitrogen heterocycles. In contrast, the reactivity in sulfamidate ring-opening reactions is attributed to the activation of the C–O bond by the SO_2 group, which makes them good electrophiles that can react with a variety of heteroatom and carbon nucleophiles. Moreover, their ability to undergo regioselective ring-opening reactions augments their synthetic value.

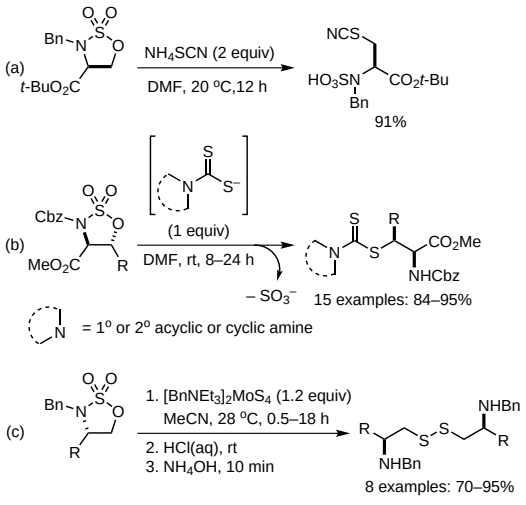
4.1. Heteroatom Nucleophiles

4.1.1. Sulfur Nucleophiles

The ring-opening of sulfamidates with ammonium thiocyanate gives 3-thiocyanate alanine derivatives (**Scheme 3**, Part (a)).[39,40] Lubell and co-workers were able to confirm that the stereoselectivity of the reaction is not compatible with an elimination–addition mechanism which would result in racemization.[3–5] The free thiol group is not a suitable nucleophile for the opening of five-membered-ring sulfamidates bearing an α-carbonyl group; in combination with a base it leads to the formation of dehydro amino acids. Thioacetates, a stabilized form of thiol nucleophiles, serve as masked thiols in reactions with sulfamidates to give amino thioacetate derivatives.[41] Our group has demonstrated the usefulness of in situ generated dithiocarbamates, another type of stabilized sulfur nucleophile, in sulfamidate chemistry (Scheme 3, Part (b)).[42] The addition of in situ generated dithiocarbamate anion to cyclic sulfamidates leads to stereo- and regioselective ring-opening to form



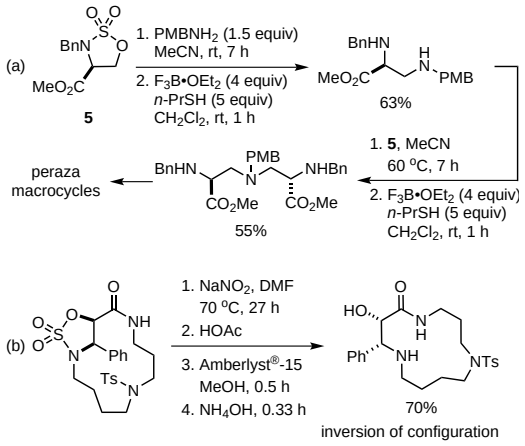
Scheme 2. Additional Syntheses of Cyclic Sulfamidates.



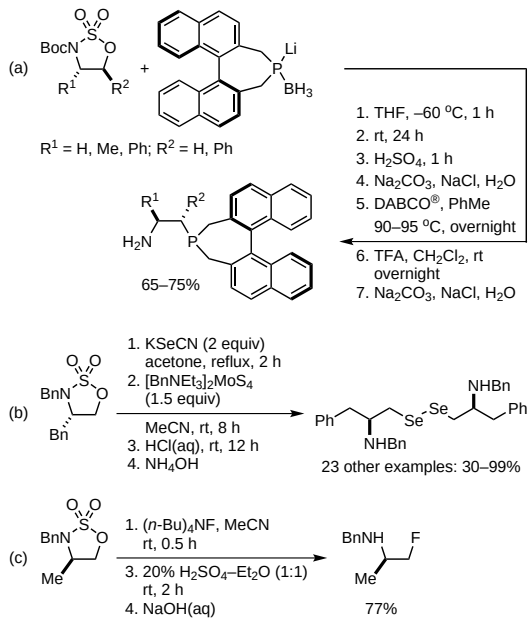
Scheme 3. Ring-Opening of Sulfamidates with Sulfur Nucleophiles. (*Ref. 39,40,42,43*)

the optically pure products in high yield (84–95%). Chandrasekaran and co-workers have effected the ring-opening of sulfamidates using $[BnEt_3N]_2MoS_4$, which acts as a sulfur-transfer reagent via disulfide bond formation. The reaction proceeds efficiently in acetonitrile to give the *N*-alkyl-β-amino disulfides directly (Scheme 3, Part (c)).[43]

Interestingly, $[BnEt_3N]_2MoS_4$ exhibited anomalous behavior in the reaction with sulfamidates derived from diols by using the Burgess reagent. Its reaction with sulfamidates under conditions similar to those shown in Scheme 3, Part (c), resulted in the formation of β-amino thiols instead of β-amino disulfides.[44] This regio- and stereoselective ring-opening of sulfamidates provides an efficient, direct, and altenative route to conventional methods for the synthesis of β-amino thiols via the acid-catalyzed ring-opening of aziridines with hydrogen sulfide or with the sodium or potassium salt of thioacetic acid, followed by deprotection of masked thiols.[45] Five-membered-ring sulfamidates give β-amino thiols, whereas the reaction of six-membered-ring sulfamidates forms γ-amino thiols.[44]



Scheme 4. Ring-Opening of Cyclic Sulfamidates with (a) Nitrogen and (b) Oxygen Nucleophiles. *(Ref. 47,51)*



Scheme 5. Ring-Opening of Cyclic Sulfamidates with (a) Phosphorus, (b) Selenium, and (c) Halogen Nucleophiles. *(Ref. 54–56)*

4.1.2. Nitrogen Nucleophiles

The nucleophilic nitrogen can be that of a primary amine, secondary amine, azide, or even that of a heterocyclic system such as imidazole or related scaffold. Sodium azide reacts with cyclic sulfamidates to give the corresponding amino azide derivatives, with no apparent restriction on substrate structure and substituents.[46] Primary and secondary amines react efficiently with cyclic sulfamidates to give the corresponding diamine derivatives (**Scheme 4**, Part (a)).[47] The ring-opening with a heterocyclic system nitrogen has been employed effectively to prepare chiral 2,3-diaminopropanoate derivatives.[48]

4.1.3. Oxygen Nucleophiles

The ring-opening of sulfamidates has been unsuccessful with most strong oxygen nucleophiles (e.g., sodium methoxide). The possible hydrolysis of serine- or threonine-derived cyclic sulfamidates with sodium bicarbonate in deuterated water (D_2O) has been disappointing,[49] and the ring-opening of α-methylserine-derived sulfamidates gave a very poor yield of ring-opened products.[40] The first successful ring-opening of sulfamidates was achieved with weakly basic oxygen nucleophiles, and was further exemplified using stabilized phenoxy ions.[50] Khanjin and Hesse utilized $NaNO_2$ for the ring-opening of sulfamidates, which was followed by hydrolysis to give macrocyclic alcohols (Scheme 4, Part (b)).[51]

4.1.4. Phosphorus Nucleophiles

The introduction of phosphorus has been very difficult due to its sensitivity to the reaction conditions and substrate structure. Although many N–P chiral ligands have been synthesized, severe problems have been encountered in terms of byproduct formation and purification.[52] Chiral 1-isopropylamino-2-(diphenylphosphino)ethanes can be synthesized through ring-opening of chiral, cyclic sulfamidates with potassium diphenylphosphide ($KPPh_2$).[53,54] This method has been extended to the synthesis of protic aminophosphines with multiple chiral centers by the nucleophilic ring-opening of N-protected cyclic sulfamidates. The introduction of another chiral center into the aminophosphine backbone using nucleophilic phosphide—derived from the reaction of butyllithium and the respective phosphine–borane—was a significant finding that was extended to the synthesis of a wide range of multicenter phosphine ligands (**Scheme 5**, Part (a)).[53,54]

4.1.5. Selenium Nucleophiles

Chandrasekaran and co-workers reported the synthesis of chiral *N*-benzyl-β-aminodiselenides in moderate-to-good yields via a regio- and steroselective ring-opening of sulfamidates with potassium selenocyanates (Scheme 5, Part (b)).[55] The reaction proceeds through selenocyanate intermediates, which, on dimerization with tetrathiomolybdate, afford the *N*-benzyl-β-aminodiselenide products.

4.1.6. Halogen Nucleophiles

Among halogens, fluoride ion has been employed for the nucleophilic ring-opening of sulfamidates to afford, in the case of five-membered-ring

sulfamidates, β-amino fluorides. KF/CaF_2 or ammonium fluorides have been used as sources of nucleophilic fluorines (Scheme 5, Part (c)).[56]

4.2. Carbon Nucleophiles

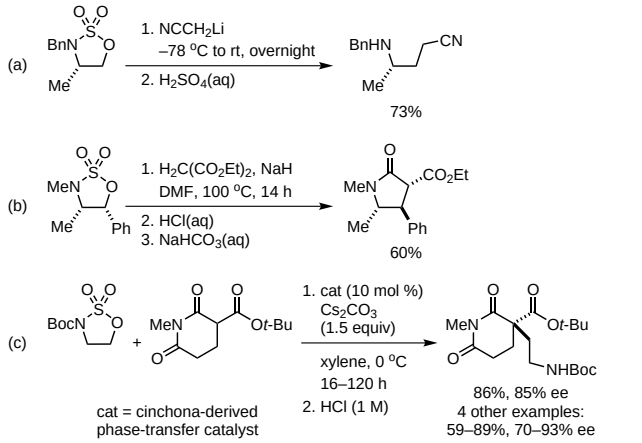
4.2.1. Hard Carbon Nucleophiles

The ring-opening of sulfamidates with aryllithium reagents (e.g., phenyl-, 3,4-dimethoxyphenyl-, and 2-thienyllithium) has been reported.[57] While the reaction of cyclic sulfamidates with alkyllithiums failed initially,[58] the reaction of alaninol-derived sulfamidates with alkyllithiums such as di(*n*-butyl)lithium cuprate, lithiated acetonitrile, and lithiated 1,3-dithiane afforded the corresponding amines (**Scheme 6**, Part (a)).[59] The same reaction with PhLi or *n*-BuLi gave a mixture of products, presumably due to competitive attack at the electrophilic C-5 and S centers. Similarly, the reaction of hard carbon nucleophiles (such as alkyllithium, Grignard reagents, etc.) with serine- and threonine-derived sulfamidates consistently led to mixtures of products due to competitive attack at the reactive carbonyl group.

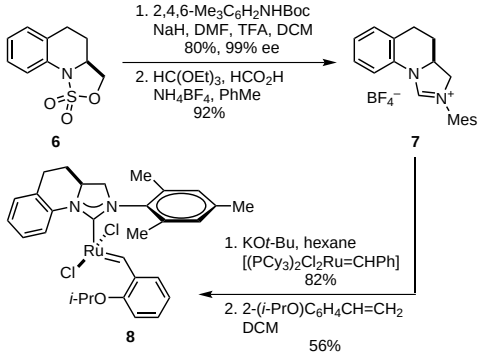
4.2.2. Soft (Stabilized) Carbon Nucleophiles

It is believed that the softening of carbon nucleophiles through conjugation or stabilization would result in increased selectivity. Cyanide ion is the most stable of carbon nucleophiles; it can react with any type of sulfamidates to give the corresponding aminonitrile derivatives.[60] Cyclic sulfamidates react with most of the stabilized carbon nucleophiles (e.g. β-keto esters, diethyl malonates, aryl-substituted enolates, and phosphonate-stabilized enolates) to give the cyclized product in the presence of a proximate ester, ketone, or amine functional group (Scheme 6, Part (b)).[61]

Many natural products bearing aminoethylene and aminopropylene scaffolds at a quaternary stereocenter are known in the literature.[62] These aminoalkenes can be incorporated at quaternary centers through the enantioselective ring-opening of aziridines and azetidines. However, these electrophiles require activation at nitrogen, and, typically, a wide range of activating groups need to be screened along with asymmetric induction. In contrast, the reaction of cyclic sulfamidates with *tert*-butyl 1-methyl-2,6-dioxopiperidine-3-carboxylate in the presence of a cinchona-derived phase-transfer catalyst readily gives the ring-opened product (Scheme 6, Part (c)). The variation in ring size and protecting group at the nitrogen atom in the sulfamidates does not alter the reaction outcome.[63]



Scheme 6. Ring-Opening of Cyclic Sulfamidates with (a) Hard Carbon Nucleophiles and (b, c) Soft Carbon Nucleophiles. *(Ref. 59,61,63)*



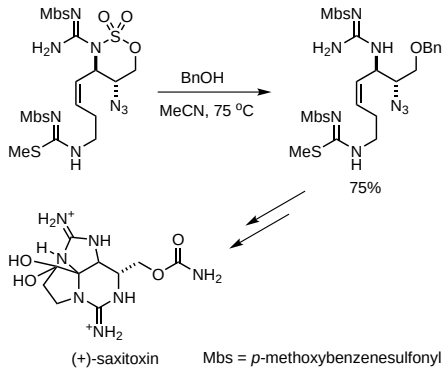
Scheme 7. Cyclic Sulfamidates for the Synthesis of Asymmetric Ligands of Chiral Olefin-Metathesis Catalysts. *(Ref. 64)*

5. Applications of Cyclic Sulfamidates in Heterocycle and Natural Product Synthesis

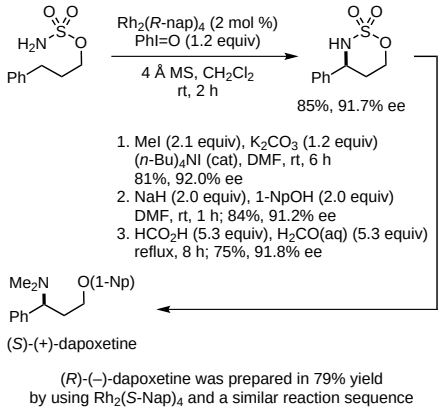
Blechert and co-workers utilized cyclic sulfamidates for the synthesis of asymmetric ligands that are incorporated into highly active, chiral olefin-metathesis catalysts (**Scheme 7**).[64,65] Cyclic sulfamidate **6** was converted into chiral diamine **7**, in high yield and with high enantioselectivity, through a regioselective ring-opening with Boc-mesidine. Chiral diamine **7** was then elaborated into chiral ruthenium catalyst **8** in two straightforward steps.

5.1. (+)-Saxitoxin

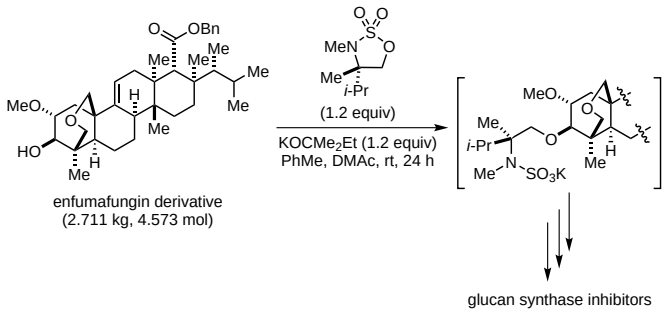
Neurotoxic agents are important pharmacological scaffolds used for understanding protein function associated with the ionic mechanisms of electrical transmission in cells. The guanidinium toxins such as (+)-saxitoxin and (–)-tetrodotoxin are exemplary in this regard, and have been employed for the study of voltage-gated sodium channels along with their identification and characterization. The basic saxitoxin skeleton was assembled from cyclic sulfamidate, and converted into (+)-saxitoxin and its derivatives (**Scheme 8**).[66]



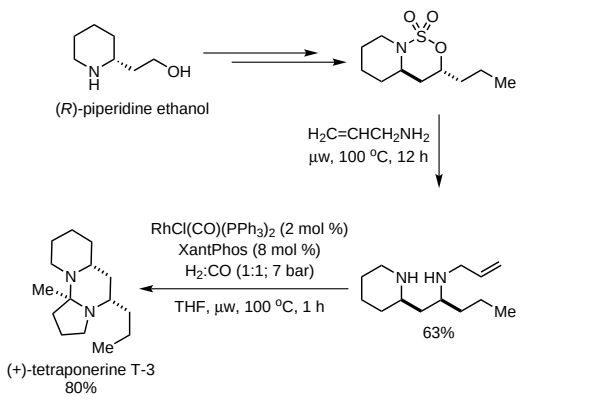
Scheme 8. Cyclic Sulfamidate Ring-Opening as a Key Step in the Synthesis of (+)-Saxitoxin. *(Ref. 66)*



Scheme 9. (*S*)-(+)- and (*R*)-(–)-Dapoxetines from Cyclic Sulfamidates. *(Ref. 67)*



Scheme 10. Cyclic Sulfamidate Allows a Direct and Milder Incorporation of the Side Chain en Route to a Large-Scale Semisynthesis of Enfumafungin Derivatives. *(Ref. 70)*



Scheme 11. Cyclic Sulfamidate as Key Intermediate in the Synthesis of (+)-Tetraponerine T-3 Alkaloid. *(Ref. 71)*

5.2. (S)-(+)- and (R)-(–)-Dapoxetines

(*S*)-(+)-Dapoxetine hydrochloride is a potent and selective serotonin reuptake inhibitor, and is used specifically for the treatment of premature ejaculation. It is obtained from racemic dapoxetine by tartaric acid promoted chiral resolution, or from chiral amino alcohols through enzymatic synthesis. In contrast, Du Bois's method, employing Rh_2(*S*-nap)$_4$ or Rh_2(*R*-nap)$_4$, provides both enantiomers of the cyclic 1,3-sulfamidate precursors, which are easily converted into (*S*)-(+)- and (*R*)-(–)-dapoxetines using a straightfoward reaction sequence (**Scheme 9**).[67]

5.3. Antifungal Glucan Synthase Inhibitors

Enfumafungin, isolated from a fermentation of a *Hormonema* species, is capable of inhibiting fungal glucan synthase, and two novel enfumafungin derivatives have been identified as potent glucan synthase inhibitors.[68] The installation of the side chain was accomplished by S_N2 ring-opening of an N-tosylated aziridine by the in situ generated potassium alkoxide of the starting material.[69] The replacement of aziridine with its synthetic equivalent, a five-membered-ring sulfamidate, allows the direct incorporation of the side chain under milder condition (**Scheme 10**).[70]

5.4. (+)-Tetraponerine T-3

The tetraponerines constitute a family of alkaloids that pseudomyrmecine ants of the genus *Tetraponera* deploy as paralyzing venoms in chemical warfare. Their challenging tricyclic skeleton and biological activities make them attractive targets for total synthesis.[71] Mann and co-workers reported the synthesis of (+)-tetraponerine T-3 starting from chiral (*R*)-piperidine ethanol and using sulfamidate as a key intermediate en route to the strategically important diamine. The diamine was directly converted into (+)-tetraponerine T-3 in a one-pot hydroformylation and cyclization process (**Scheme 11**).[71]

5.5. Pyrrolidinones and Piperidinones

The reactions of five- and six-membered-ring sulfamidates with enolates derived from malonate afford access to C–3 carboxylated lactams, such as pyrrolidinone and piperidinone derivatives, in excellent yields.[61,72] It is important to note that the lactamization is dependent on the ring size: formation of six-membered rings is slower than that of five-membered rings. The reaction of cyclic sulfamidates with phosphonate-stabilized enolates gives α-phosphono lactams,[73] which are amenable to double-bond installation through a Wadsworth–Emmons olefination. Elevated temperatures are required to achieve C–O bond cleavage, which leads to the competitive decomposition of the enolate component possibly due to nucleophilic attack on phosphorus.[74] Gallagher and co-workers have demonstrated the use of α-sulfinyl-substituted nucleophiles in sulfamidate ring-opening reactions, which lead upon hydrolysis to the lactamization product.[75] The strategy could not be extended to other cyclic sulfamidates due to competing sulfoxide elimination at higher temperatures, leading to the formation of complex mixtures. Switching to the α-phenylsulfenyl group [PhS(=O)–] on the enolate component helped generate an array of α-sulfenylated lactams in good-to-excellent yields. The sulfenylated lactams can be easily converted into unsaturated lactams by a Pummerer rearrangement. The strategy was employed for the synthesis of alkylidene pyrrolidines and piperidines starting with cyclic sulfamidates, which undergo ring-opening with the dianion of ethyl acetoacetates, followed by in situ *N*-sulfate hydrolysis and intramolecular condensation onto the intermediate ketone.[76] The most important application of sulfamidate chemistry in this regard has been the enantioselective total synthesis of (–)-paroxetine (**Scheme 12**, Part (a))

and (+)-laccarin.[76] Gallagher also utilized sulfamidates in the synthesis of (–)-aphanorphine, a natural product isolated from the freshwater blue-green algae, *Aphanizomenon flos-aquae* (Scheme 12, Part (b)).[77–81] These syntheses proceed through pyrrolidinone or piperidinone intermediates, which have also been utilized in the synthesis of natural products and their heterocyclic analogues.[76–81]

5.6. Thiomorpholinones and Piperazinones

Cyclic 1,2-sulfamidates, even sluggish ones possessing both primary and secondary electrophilic centers, react with methyl thioglycolate to give chiral thiomorpholinones in excellent yields (**Scheme 13**, Part (a)).[79] Gallagher's group extended this methodology to the synthesis of piperazinones, wherein phenylalanine-derived cyclic sulfamidates provide the corresponding piperazinones (Scheme 13, Part (b)).[79] Bicyclic systems such as praziquantel can be constructed by employing different amino-based nucleophiles;[6] a phenylalanine-derived cyclic sulfamidate reacts efficiently with enantiotopic proline ethyl esters to afford bicyclic piperazinones.[79] The ring-opening of an enantiopure cyclic sulfamidate with the indole nitrogen of indolecarboxylic acid methyl ester provides the corresponding pyrazino-indole with 98% ee.[80]

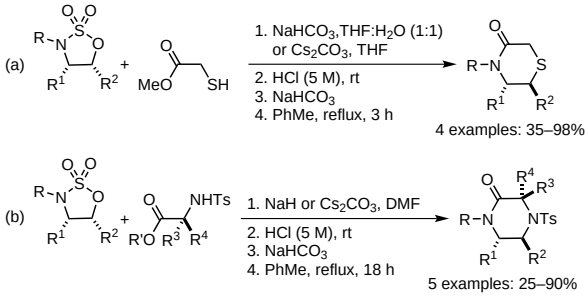
5.7. 1,4-Benzoxazines, Benzothiazines, and Quinoxalines

The ring-opening of sulfamidates with aromatic amines, phenols, or thiophenols under basic conditions, in combination with a Pd-catalyzed Buchwald-type amination, opens a new avenue for the synthesis of 1,4-benzoxazines, benzothiazines, and quinoxalines. For example, when the ring-opening of cyclic sulfamidates with 2-bromophenols is followed by *N*-sulfate hydrolysis and Pd-catalyzed amination, substituted and enantiopure 1,4-benzoxazines are obtained in good-to-high yields (**Scheme 14**, Part (a)).[81]

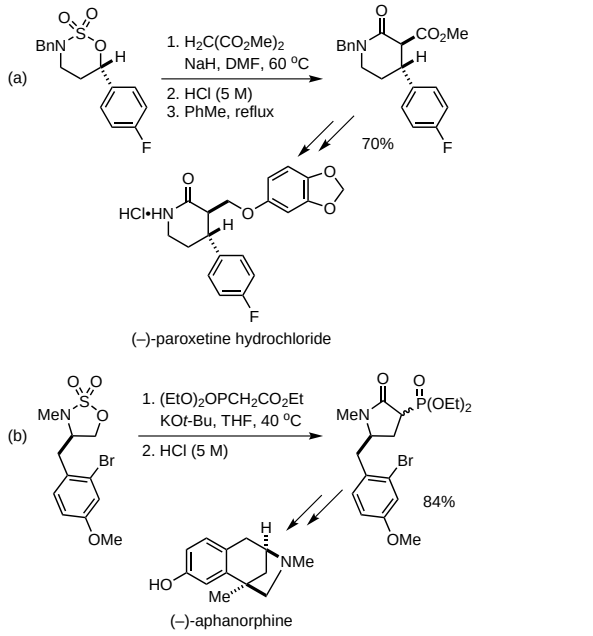
(–)-Levofloxacin is one of the major antibiotic drugs used to treat a wide range of infections, and is active against both gram-positive and gram-negative bacteria. The crucial step in its preparation was the asymmetric synthesis of the chiral benzoxazine core from the sulfamidate. The benzoxazine intermediate was then easily converted into (–)-levofloxacin in a few simple steps.[81,82] The seven-membered-ring variants of benzoxazine are important in pharmaceutical applications.[83] Tetrahydro-1,4-benzothiazepines S107 and JTV519 are being evaluated for treating conditions linked to the stabilization of cardiac ryanodine receptors (RyR1) that leak Ca^{2+} when subjected to stress.[84,85] The usefulness of cyclic sulfamidates in this area was proven by the synthesis of relevant seven- and eight-membered-ring heterocycles (Scheme 14, Part (b)).[85]

5.8. Carbohydrates

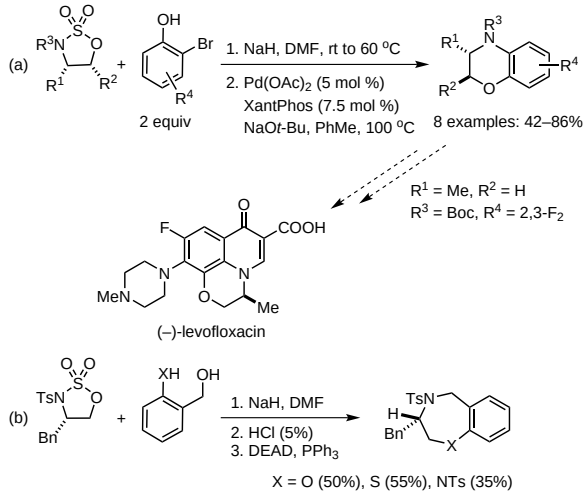
A wide range of diols on different carbohydrate scaffolds (e.g., D-Glc, D-Gal, L-Rha, D-Rib, etc.) can be converted into the corresponding sulfamidates by using the Burgess reagent.[86] Nucleophilic ring-opening of these sulfamidates with sodium azide permits the synthesis of α-glycosylamines.[86] The ring-opening of carbohydrate-derived sulfamidates with non-carbon strong nucleophiles of low basicity proceeds efficiently, while the use of carbohydrate-derived soft



Scheme 13. Thiomorpholinones and Piperazinones by Ring-Opening of Cyclic Sulfamidates. *(Ref. 79)*



Scheme 12. Cyclic Sulfamidates in the Synthesis of Piperidinones and Pyrrolidinones en Route to (–)-Paroxetine and (–)-Aphanorphine. *(Ref. 76,77)*



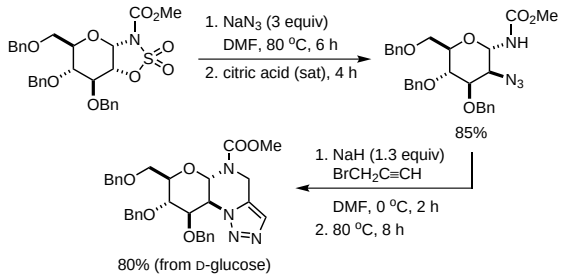
Scheme 14. Cyclic Sulfamidates as Convenient Precursors of 1,4-Benzoxazines, Benzothiazepines, and Benzodiazepines. *(Ref. 81,85)*

nucleophiles results in the successful synthesis of di- and trithiosaccharide analogues.[87] Chandrasekaran and co-workers effected the synthesis of carbohydrate-fused triazole heterocycles in a one-pot tandem process. The reaction proceeds via azido ring-opening propargylation and subsequent intramolecular cycloaddition of the alkyne and azide to deliver the carbohydrate-fused triazole derivative (**Scheme 15**).[46] The same group also reported that the reaction of D-glucose-derived sulfamidates with bis(benzyltriethylammonium) tetrathiomolybdate {$[BnNEt_3]_2MoS_4$} results in the formation of 2-thiolglucosamine derivatives.[44,88]

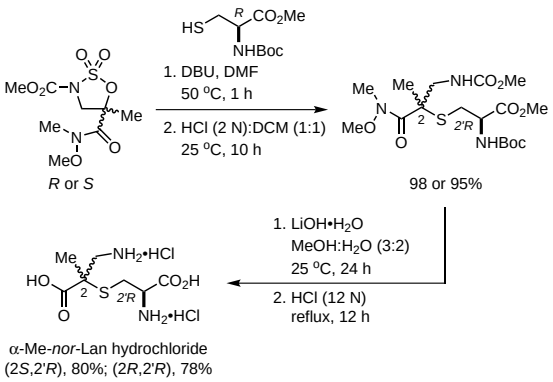
5.9. Unnatural Amino Acids

Interest in unnatural amino acids has been growing due to their application in peptide research.[89] Cyclic sulfamidates provide a unique opportunity to modify natural amino acids into a wide range of unnatural analogues by simple reaction sequences and in fewer steps. Chandrasekaran's group converted serine and threonine derivatives into unnatural cystine and selenocystine amino acids via cyclic sulfamidate intermediates.[43,55] Our group has demonstrated that the reaction of cyclic sulfamidates with in situ generated dithiocarbamate anions can be used for the synthesis of unnatural amino acids containing dithiocarbamate side chains.[42a] We have also utilized sulfamidates for the synthesis of triazole-modified unnatural amino acids in 71–86% yields through the nucleophilic ring-opening of sulfamidates with azide, followed by azido–alkyne cycloaddition.[89]

Lubell and co-workers synthesized *N*-(9-(9-phenylfluorenyl))-homoserine-derived cyclic sulfamidates, and showed that they could be used for the synthesis of functionalized, enantiopure γ-amino acids. The reactions were successful with nitrogen, sulfur, and stabilized oxygen nucleophiles, providing the corresponding unnatural, γ-substituted amino acids in >97% ee's.[90] Peregrina's group reported that the five-membered-ring, α-methylisoserine-derived (*R*)-sulfamidate could be used as an excellent chiral building block that undergoes ring-opening with sulfur nucleophiles at the quaternary carbon.[91] They developed a protocol for the synthesis of (2*S*,2'*R*)- and (2*R*,2'*R*)-α-methylnorlanthionines (α-Me-*nor*-Lan) in diastereomerically pure forms by using the corresponding α-methylisoserine-derived cyclic sulfamidate as a chiral building block (**Scheme 16**).[92]



Scheme 15. Carbohydrate-Derived Fused Heterocycles Through the Intermediacy of Cyclic Sulfamidates. *(Ref. 46)*



Scheme 16. Diastereomerically Pure (2*S*,2'*R*)- and (2*R*,2'*R*)-α-Methyl-norlanthionines (α-Me-*nor*-Lan) from Chiral Cyclic Sulfamidates. *(Ref. 92)*

6. Conclusion

This review highlighted the important role cyclic sulfamidates are playing in natural product synthesis and method development. Their reactions are highly regioselective and stereospecific with inversion of configuration at the reaction center. Even though cyclic sulfamidates had not been extensively studied because of their reactions with carbon nucleophiles had led to complex mixtures and/or decomposition products, recent investigations have overcome most of these limitations by softening the carbon nucleophiles. This approach has resulted in new synthetic strategies in organic chemistry with no limitations in terms of reactivity. We believe that cyclic sulfamidates offer a unique synthetic potential, and can provide practical solutions to the synthesis of challenging drug targets that are sought after by both academia and industry.

7. Acknowledgments

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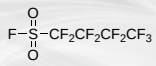

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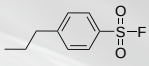

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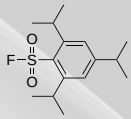

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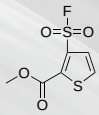

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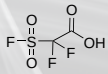

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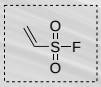

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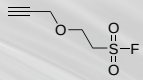

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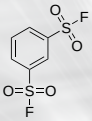

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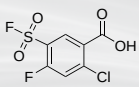

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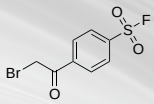

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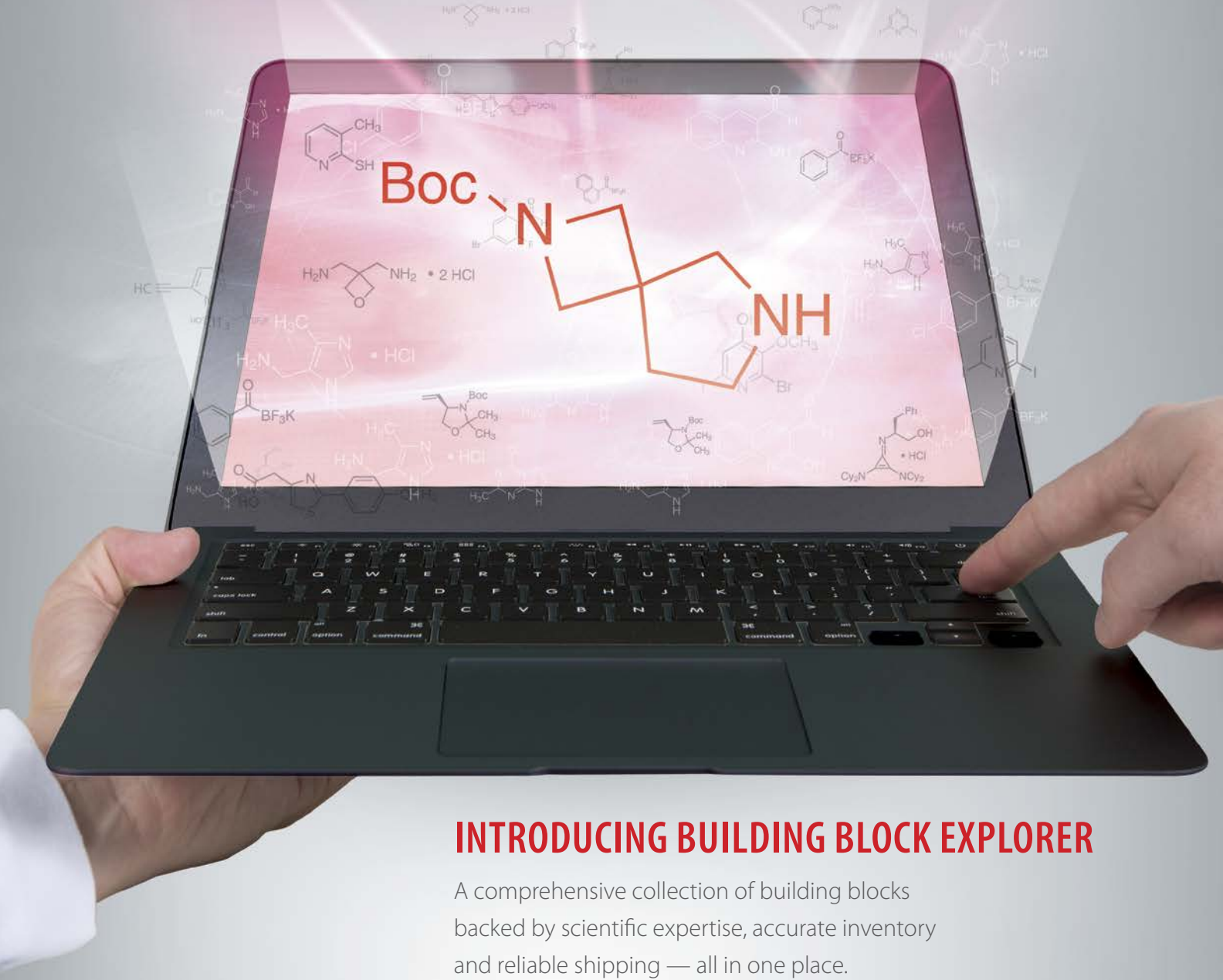

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