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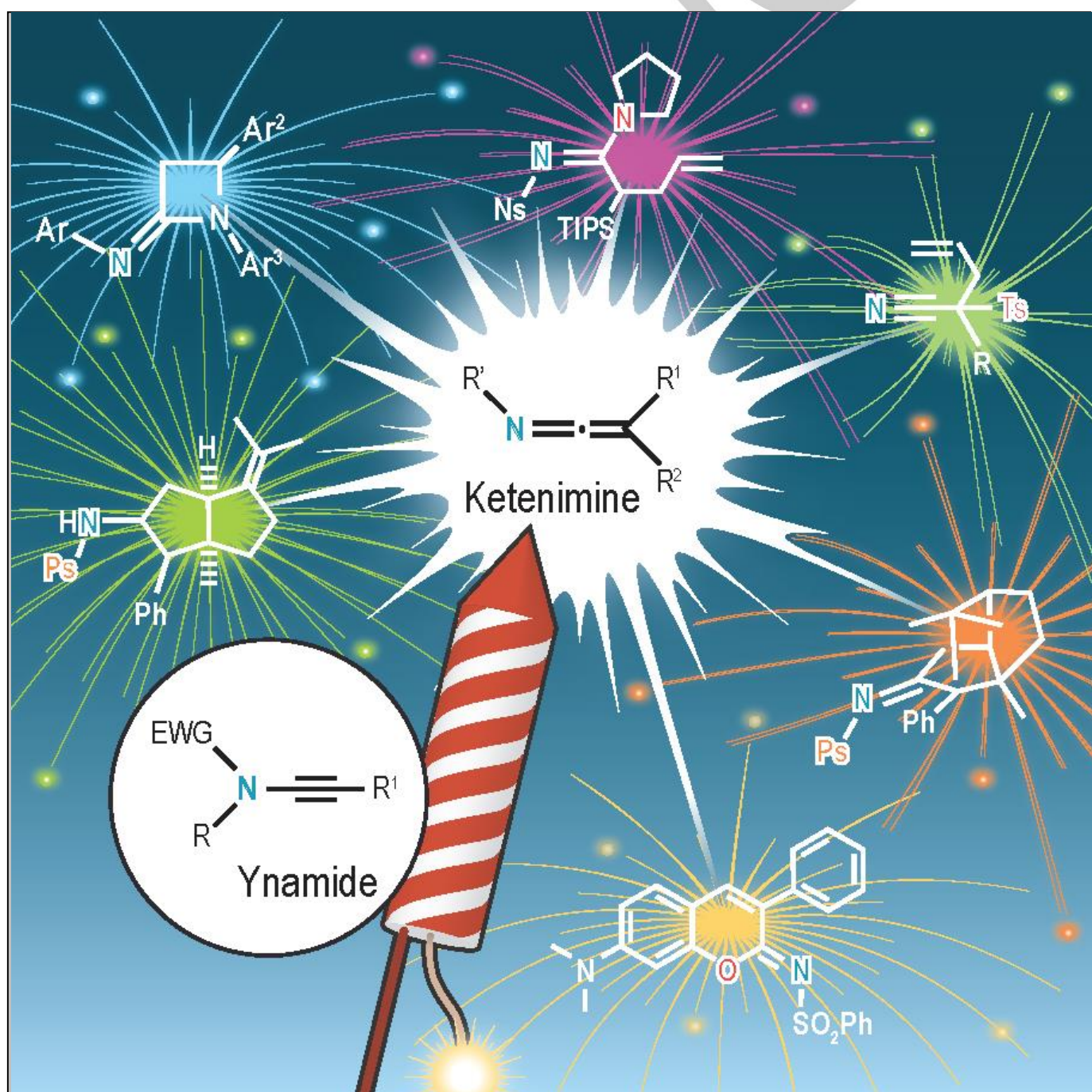
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Ketenimines Generated from Ynamides: Versatile Building Blocks for Nitrogen-Containing Scaffolds

Robert H. Dodd and Kevin Cariou*^[a]

Dedication ((optional))

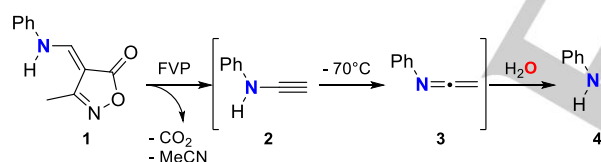


CONCEPT

Abstract: Using ynamides as readily available starting materials, a single step can generate highly reactive ketenimines which can then undergo a variety of transformations. The choice of the method for generating the ketenimine dictates the outcome of the reaction that can, moreover, be precisely steered through minor variations of the starting material. This Concept gives an overview of the different existing methodologies for this objective, showcasing the diverse nitrogen-containing frameworks that can be obtained by this highly versatile strategy.

Introduction

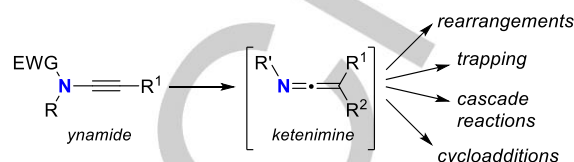
Ketenimines,¹ like ynamines,² are a particularly attractive subclass of unsaturated nitrogen-containing compounds which can serve as versatile building blocks to incorporate an *N*, *C*, *C* triatomic moiety. Both families share some similarities, such as a strong polarization of the carbon backbone or the central *sp*-hybridized carbon and, eventually, ketenimines can be viewed as tautomers of secondary ynamines. This was first demonstrated by the work of Wentrup in the early 80s.³ In this seminal study,^{3a} he showed that flash vacuum pyrolysis (FVP) of methylisoxazolone **1** led to *N*-ethynylaniline **2** which tautomerized to *N*-phenylketenimine **3** (Scheme 1). While this study illustrated how ynamines could be transformed into ketenimines it also showed how unstable these compounds are. Indeed, neither **2** nor **3** were isolated and both could only be characterized by IR spectroscopy at low temperature (-196 °C and -70 °C, respectively). After work-up only *N*-acetylaniline **4**, resulting from the hydrolysis of **3**, was isolated.



Scheme 1. Generation of ynamines by FVP, followed by isomerization to ketenimine.

Yet, while ynamine chemistry has witnessed a tremendous increase in interest from the synthetic community over the last 20 years or so, ketenimines remain rather exotic and under-employed substrates despite their synthetic potential.¹ This can be partly explained by the relatively small number of existing methods to generate them. In contrast, for ynamines, by focusing on the more stable subclass of ynamides,⁴ many robust and general methods have been developed, allowing access to an ever-increasing range of derivatives. Compared with ynamines,

the electron-withdrawing group on the nitrogen of ynamides improves the stability without overly hampering the reactivity. This can be viewed as a particularly seductive entry into ketenimine chemistry since, starting with a readily available ynamide, one single synthetic operation should be sufficient to convert it into a ketenimine (Scheme 2).

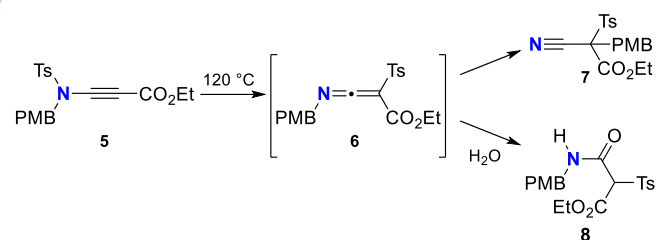


Scheme 2. Generation of ketenimines from ynamides.

This Concept will give the reader a panorama of the methods that start from preformed ynamides to generate ketenimines and their subsequent transformations. Depending on the mode of generation of the intermediate ketenimine various mechanistic pathways can be triggered or shut down and particular attention will be given to present the key steps and how they influence the outcome of the reactions.

Thermal Rearrangements

Twenty-five years after Wentrup's pioneering study of ynamines, the first thermal rearrangement of an ynamide into a ketenimine was reported by the group of Wudl.⁵ By heating compound **5** at 120 °C, *N* to *C* migration of the *p*-tosyl group yielded ketenimine **6** (Scheme 3). The latter could thereafter evolve towards tertiary nitrile **7** through a second *N* to *C* migration, this time of the PMB group, or be hydrolyzed to yield amide **8**.



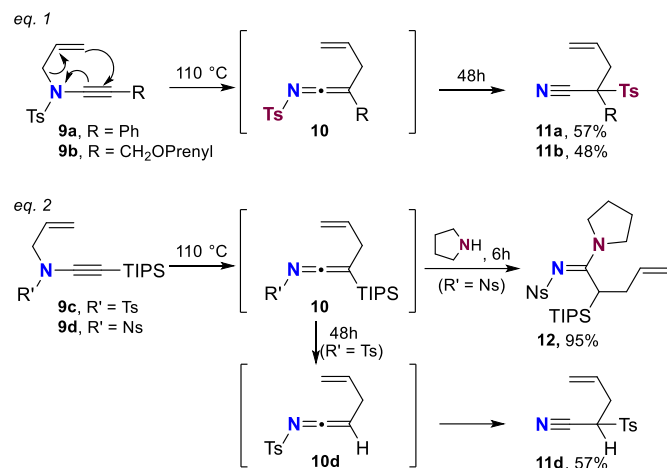
Scheme 3. Thermal rearrangement of sulfonylynamides into ketenimines.

Similar results were obtained by the Hsung group for the thermal rearrangement of *N*-allylsulfonylynamide **9**,⁶ although in this particular case the allyl group is the first one to migrate through an aza-Claisen rearrangement (Scheme 4). The outcome of this process is particularly dependent on the nature of the *R* group. In the case of a phenyl group (**9a**) or a protected primary alcohol (**9b**), the intermediate ketenimine **10** eventually converges towards the corresponding tertiary nitrile **11** by a 1,3-sulfonyl shift (Scheme 4, eq.1). However, a TIPS substituent brings enough

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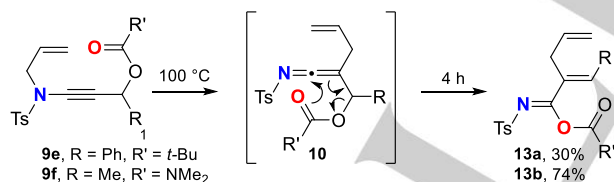
CONCEPT

stabilization to allow isolation of ketenimine **10** or its trapping by nucleophilic addition with pyrrolidine to give amidine **12** (Scheme 4, eq.2). Under prolonged heating, desilylation of the ketenimine occurs thus triggering its rearrangement into secondary nitrile **11d** (Scheme 4, eq.2).



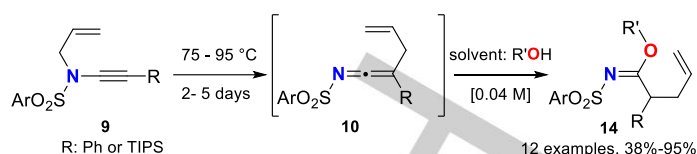
Scheme 4. Aza-Claisen rearrangement of *N*-allylsulfonylaminides into ketenimines.

Following these initial findings, Hsung further exemplified both the amidine synthesis (with primary and secondary amines) and the nitrile formation (with diverse substitution patterns on the starting ynamide).⁷ During this latter study, it was also shown that for suitably poised carboxy-substituted ynamides **9e,f** a tandem aza-Claisen/[3,3]-sigmatropic rearrangement reaction could take place to yield imidates **13** (Scheme 5).

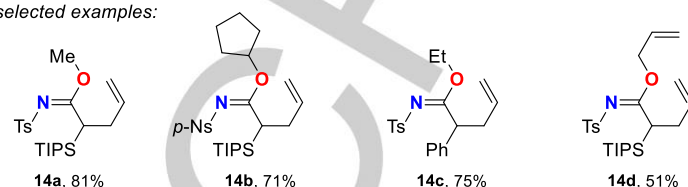


Scheme 5. Tandem aza-Claisen/[3,3] sigmatropic rearrangement.

The same author showed that the synthesis of imidate can also be carried out in an intermolecular fashion by prolonged heating of a highly diluted alcohol solution of ynamides (Scheme 6).⁸ Use of the alcohol as the solvent was necessary to suppress the 1,3-sulfonyl migration that would lead to the corresponding nitriles. Another strategy devised by the Hsung group to prevent the 1,3-shift and explore further synthetic opportunities was to replace the sulfonyl group by a phosphoryl group.⁹

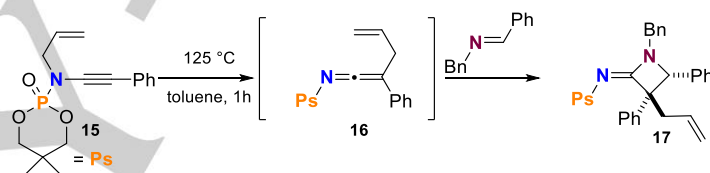


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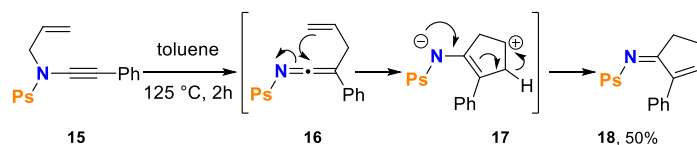
Scheme 6. Intermolecular imidate synthesis.

Thus ynamide **15** bearing a neopentylglycol-derived cyclic phosphoramidate moiety could react thermally to give ketenimine **16** which then furnished azetidimine **17** after a [2+2] cycloaddition with an imine (Scheme 7).



Scheme 7. Use of an *N*-phosphorylamine for the synthesis of an azetidimine.

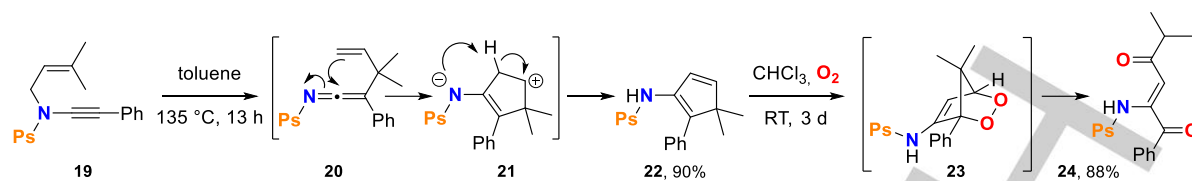
Taking advantage of the relative stability granted to the ketenimine intermediate by the *N*-phosphoryl moiety, a series of carbocyclization cascades leading to intricate structural motifs was developed.¹⁰ First, it was demonstrated that ketenimine **16** was sufficiently electrophilic that a carbocyclization to cyclopentenyl zwitterion **17** could take place (Scheme 8). Secondly, a Wagner-Meerwein 1,2-*H* shift provided cyclopentenimine **18**.



Scheme 8. Carbocyclization/1,2-*H* shift cascade.

This initial finding prompted the authors to probe other possible 1,2 shifts by reacting judiciously substituted ynamides. Thus, aza-Claisen rearrangement of *N*-prenyl ynamide **19** led to ketenimine **20** and cyclization to zwitterion **21** (Scheme 9).

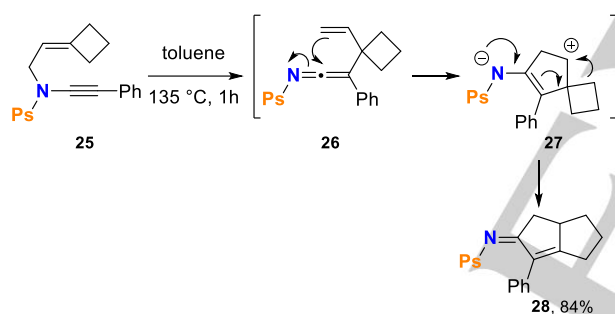
CONCEPT



Scheme 9. Carbocyclization/1,2-*H* shift cascade followed by [4+2] cycloaddition with oxygen.

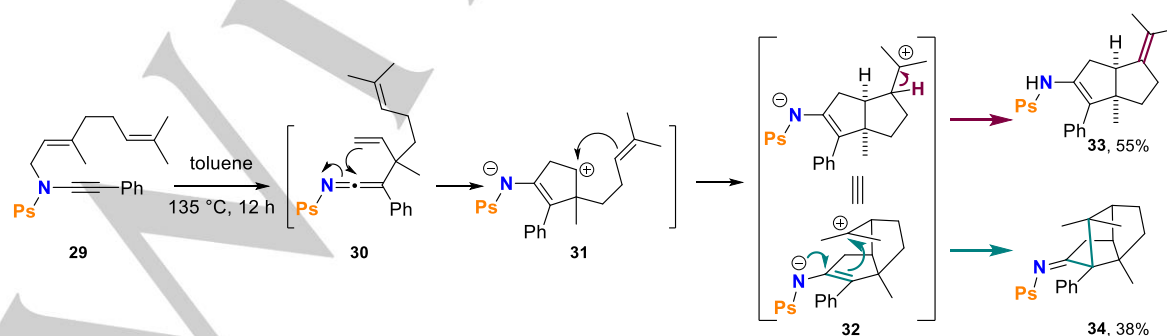
In this case, the Wagner-Meerwein methyl shift was not operative and deprotonation gave enamine **22** (as a 1:1 mixture of tautomers) with an excellent overall yield. Quite interestingly, bubbling air into a solution of **22** in chloroform for three days gave access to diketone **24**, presumably via fragmentation of endoperoxide **23** that results from a [4+2] cycloaddition with oxygen.¹⁰

For ynamide **25** bearing a vinylidenecyclobutane moiety, the aza-Claisen/carbocyclization sequence led to spiro-zwitterion **27** possessing enough ring strain for the 1,2-alkyl shift to take place, furnishing cyclic imine **28** with 84% yield (Scheme 10).¹⁰



Scheme 10. Carbocyclization/ring expansion cascade.

Other complex ring expansions cascades have been developed but, perhaps, the most spectacular results in terms of structural complexity generation came from geranylamine-derived ynamide



Scheme 11. Cationic polyene cascade.

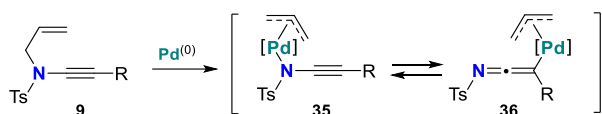
29. After initial isomerization to ketenimine **30**, two carbocyclizations take place to give bicyclic zwitterion **32** (Scheme 11). The latter can then either evolve through simple elimination to give **33** or through a third carbocyclization to give caged tricyclic **34** which exhibits four contiguous stereocenters and three all-carbon quaternary centers. Both compounds were isolated as single diastereoisomers with an almost quantitative combined yield.¹⁰

Metal-Catalyzed Rearrangements

Hsung and coworkers not only explored the thermal aza-Claisen rearrangement of *N*-allyl ynamides but also extensively studied their behavior in the presence of transition metals. The cornerstone of this chemistry was the demonstration that upon treatment with a Pd(0) complex, oxidative addition into the *N*-allyl bond led to ynamide- π -allyl complex **35** that lies in equilibrium with ketenimine- π -allyl complex **36** (Scheme 12).^{11,12}

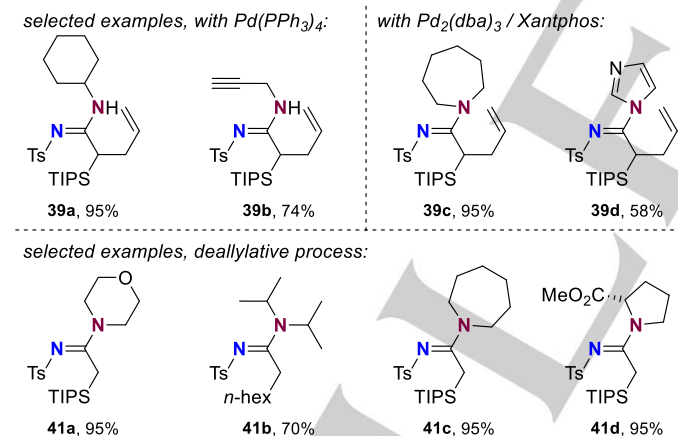
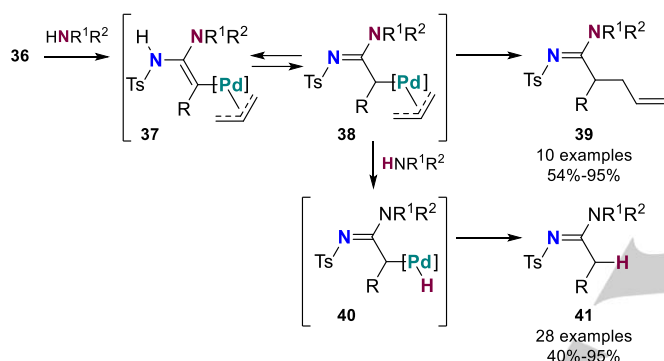
The latter could then react in a variety of ways. In their first study, trapping with a primary or secondary amine was considered. Initial addition (**37**) followed by tautomerization would give amidinyl π -allyl complex **38** (Scheme 13). Reductive elimination eventually led to amidine **39**, 28 examples of which were prepared. When an excess of the amine was used, a competitive pathway could take place. Thus, deallylation gave palladium hydride **40** and, after reductive elimination, amidine **41** in which the allyl group was not transferred.

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Scheme 12. Pd-Catalyzed rearrangement of *N*-allyl ynamides into ketenimines.

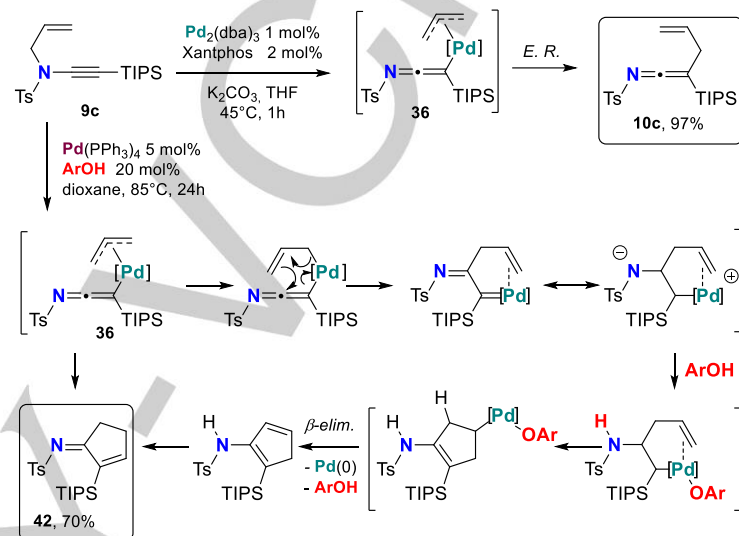
This pathway could be suppressed by adjusting the reaction conditions (slow addition of the amine and use of a ligand such as X-Phos or Xantphos that favors reductive elimination before the deallylation).¹¹ The scope of the deallylative amidine formation was then further exemplified for both primary (8 examples, 30% - 95% yields) and secondary (20 examples, 37% - 95% yields) using $\text{PdCl}_2(\text{PPh}_3)_2$.⁷



Scheme 13. Trapping of the ketenimine π -allyl complex with an amine.

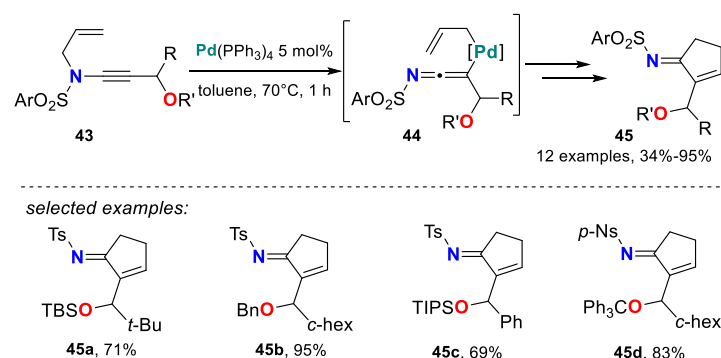
The case of TIPS-substituted ynamide **9c** is noteworthy for how it showcases the influence of the Pd-complex on the course of the reaction after the formation of intermediate **36** (Scheme 14).¹¹ Using $\text{Pd}_2(\text{dba})_3$ with Xantphos favored the reductive elimination and therefore the formation of ketenimine **10c** obtained with a near-quantitative yield thanks to the silyl group's stabilizing effect. In contrast, using $\text{Pd}(\text{PPh}_3)_4$ as catalyst with a phenol additive ultimately led to the formation of cyclopentenimine **42**.⁶ The authors showed that the formation of the 5-membered ring did not

stem from ketenimine **10c** and proposed a series of elementary steps from π -allyl complex **36** to account for its formation. A Pd-[3,3]-sigmatropic rearrangement of the η^1 -form of **36** would yield a palladium carbenoid that can be neutralized by the addition of the phenol. Aza-Rautenstrauch cyclization followed by β -elimination and tautomerization would then give cyclopentenimine **42**.



Scheme 14. Pd-Catalyzed synthesis of ketenimine and cyclopentenimine.

This strategy could be extended to a broad range of γ -branched ynamides **43**, readily accessible from the parent free ynamide and the corresponding aldehyde.¹³ Submitting these to $\text{Pd}(\text{PPh}_3)_4$ catalysis gave a dozen cyclopentenimines **45** with moderate to excellent yields through the aza-Claisen/aza-Rautenstrauch sequence (Scheme 15).

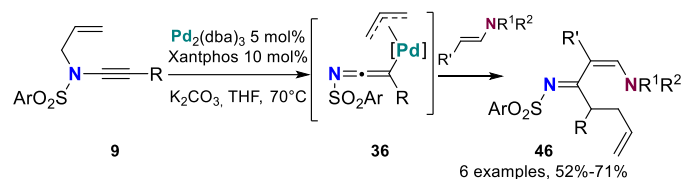


Scheme 15. Aza-Claisen/aza-Rautenstrauch sequence.

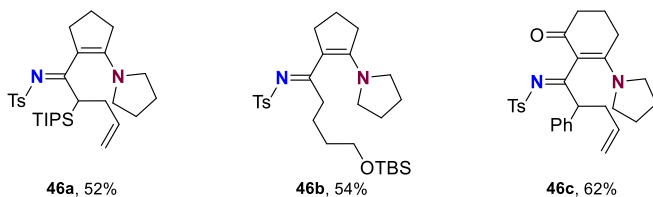
Along with their exploration of the Pd(0)-catalyzed formation of amidines, Hsung also designed a vinylogous amidine synthesis.⁷ Instead of trapping the intermediate Pd-ketenimine with an amine nucleophile, an enamine was used, resulting in the formation of

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imino-enamines **46** (Scheme 16). The yields are generally good although in some cases the reaction follows the deallylative pathway.



selected examples:

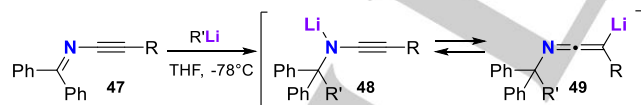


Scheme 16. Vinylogous amidine synthesis.

Base-Mediated Transformations

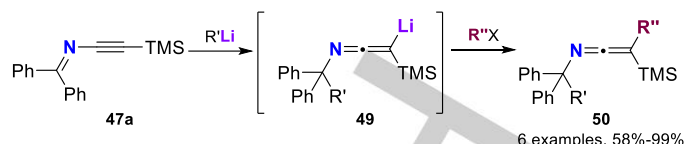
Acidic or electrophilic activation of ynamides can give birth to keteniminium ions which have recently witnessed a surge in attention by the synthetic community due to their high electrophilicity and broad reactivity.¹⁴ Much less explored but equally promising is the anionic activation of ynamides to generate ketenimines,¹⁵ usually through a reaction at the electron-withdrawing group under basic conditions.

Evano's group has developed efficient procedures to access ynamines, a particular class of ynamides for which the stability is provided by the imino substituent, and subsequently explored their unusual reactivity. They showed that adding an organolithium on ynamine **47** generates ynamide/ketenimine lithium anion **48/49** (Scheme 17), which can then evolve following three distinct reaction pathways.¹⁶

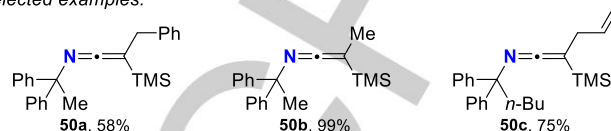


Scheme 17. Carbolithiation of ynamines.

If the starting ynamine is substituted by a silyl group (**47a**), trapping by an alkyl halide leads to ketenimines **50** that, as previously observed by Hsung,¹¹ are stable enough to be isolated with good yields (Scheme 18).¹⁶

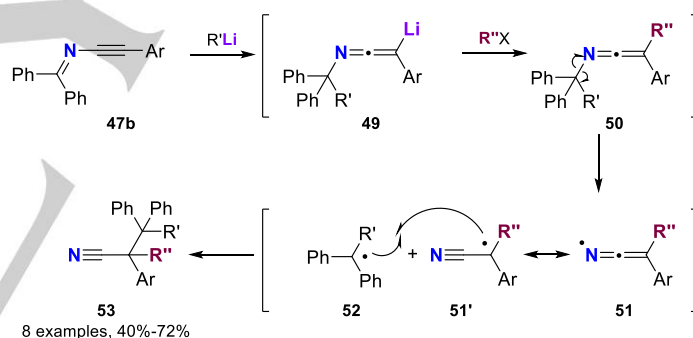


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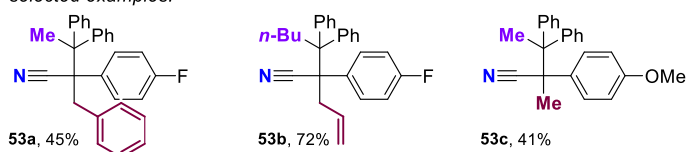


Scheme 18. Synthesis of stable silyl-ketenimines.

The outcome is different when the starting ynamine is substituted by an aryl group (**47b**, Scheme 19). In this case, ketenimine **50** is no longer stable enough to be isolated and homolytically fragments to ketenimine radical **51** and the highly stabilized tertiary radical **52**. The latter can recombine with the more stable captodative radical **51'** to furnish nitrile **53**. The whole dichotomy between silyl- and aryl-substituted ketenimine that can, respectively, be isolated or collapse to the corresponding nitrile is in total agreement with the previous observations of Hsung for the aza-Claisen rearrangement of *N*-allyl-ynamides.



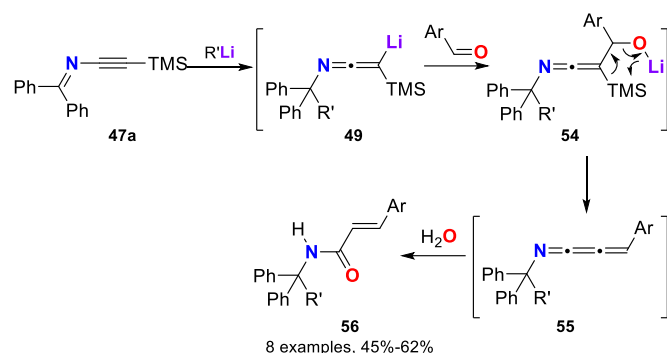
selected examples:



Scheme 19. Homolytic fragmentation/recombination to give nitriles from ketenimines.

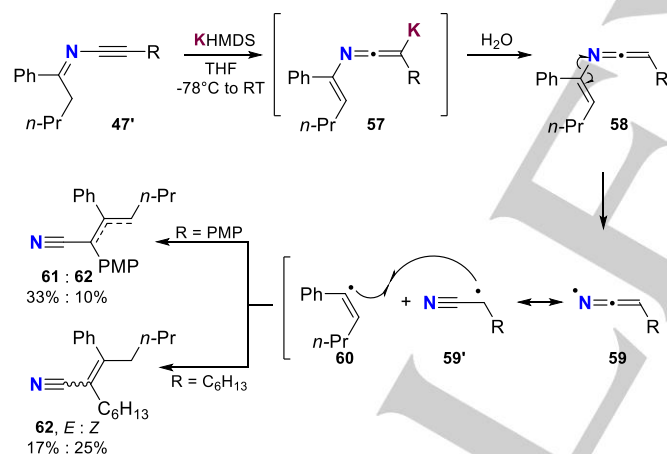
The third reaction pathway requires the use of silylated ynamine **47a** as the starting material and of an aldehyde as the electrophile (Scheme 20). Addition of the ketenimine anion to the aldehyde yields ketenimine **54** bearing a β -silyl alkoxide moiety that can undergo a Peterson elimination. This olefination results in the formation of aza-cumulene **55**, which, after hydrolysis, delivers α,β -unsaturated amide **56**.¹⁶

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Scheme 20. Peterson olefination/hydrolysis to give conjugated amides.

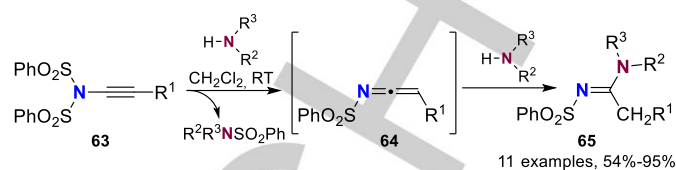
Finally, ynamines **47'** bearing an alkyl group were subjected to potassium bis(trimethylsilyl)amide to give potassium bis(trimethylsilyl)amide to give potassium ynamide **57** (Scheme 21). Hydrolysis led to transient enamidyl-ketenimine **58** which, according to the authors' proposal, would fragment to a ketenimine radical (**59**) and a styryl radical (**60**). Recombination of the latter with α -nitrile radical **59'** then gives mixtures of nitriles **61** and **62** with moderate combined yields. If R is an aryl (*para*-methoxyphenyl) group, then a 3 : 1 ratio of the allylic (**61**) and conjugated (**62**) nitriles is obtained. If R is an alkyl (cyclohexyl) group, an *E,Z* mixture of conjugated nitrile **62** is observed.¹⁶



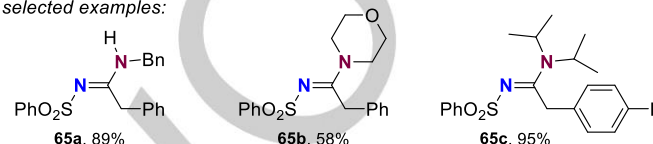
Scheme 21. Synthesis of stable silyl-ketenimines.

Anionic conditions can also be used to remove the electron-withdrawing group of the ynamide that will eventually generate the corresponding ketenimine. This approach has been simultaneously developed by the groups of Cao and of Dodd & Cariou using different types of starting ynamides. In order to facilitate the cleavage of the protecting group Cao studied the behavior of bis-phenylsulfonyl ynamides **63** in the presence of an excess of amine (Scheme 22).¹⁷ A first equivalent of amine deprotects the ynamide to give ketenimine **64** which reacts with a second equivalent of amine to give amidine **65**. The reaction conditions are remarkably mild although the process is sensitive

to steric hindrance on the amine partner, presumably for the initial sulfonyl cleavage step.

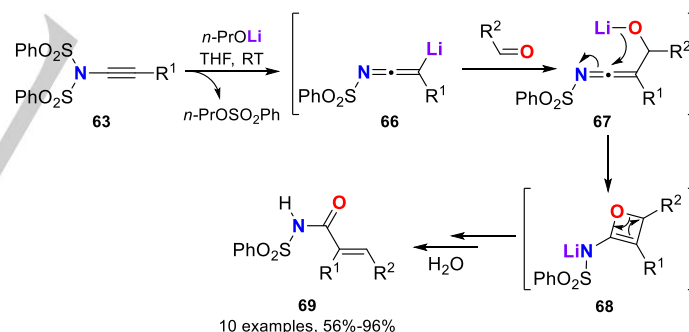


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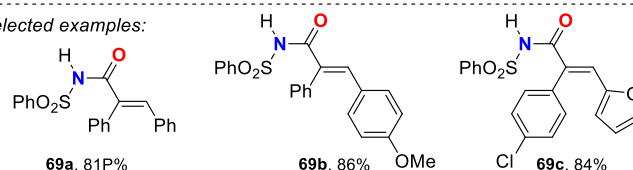


Scheme 22. Sulfonyl cleavage followed by nucleophilic addition.

Following up on their initial report, Cao implemented a similar reaction with aldehydes (Scheme 23).¹⁸ A lithium alkoxide base was used to trigger the formation of a ketenimine anion **66** which then added to an aldehyde to give lithium alkoxide **67**. The authors propose that this intermediate evolves through intramolecular addition to the ketenimine to give oxetene **68**. Conrotatory ring opening followed by hydrolysis then gives rise to α,β -unsaturated amide **69**. Contrary to the case of silylated ynamide developed by the Evans group, the Peterson elimination cannot take place here yet the outcome is similar.



selected examples:

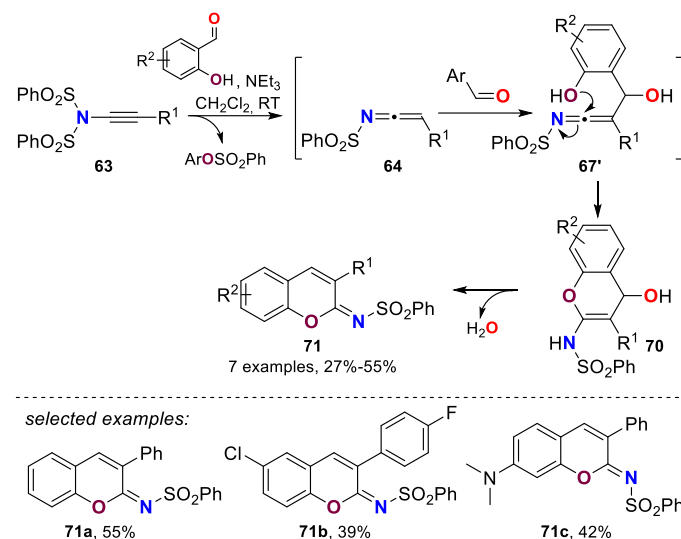


Scheme 23. Oxetene formation/ring opening to give conjugated amides.

An interesting variation was also described when the aldehyde is a salicylaldehyde derivative. In the presence of triethylamine, a first equivalent reacts as a phenol to initiate the formation of ketenimine **64** (Scheme 24). Addition to the carbonyl moiety of a second equivalent would yield alcohol **67'** which could cyclize on

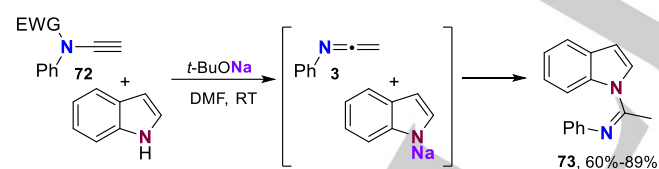
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the ketenimine moiety through the phenol to give iminocoumarin **71** after dehydration of bicycle **70**.¹⁸ An alternative pathway from **64** to **71** would involve the addition of the phenol followed by cyclization of the resulting enamide on the aldehyde.



Scheme 24. Synthesis of iminocoumarins through a formal [4+2] cycloaddition.

For their part, Dodd and Cariou studied the reaction between indoles and unsubstituted ynamides **72** under basic conditions (Scheme 25).¹⁹ Using sodium *tert*-butoxide in dimethylformamide triggered the cleavage of the electron-withdrawing group to give phenylketenimine **3**, presumably through the intermediacy of sodium indolide as the nucleophile.²⁰

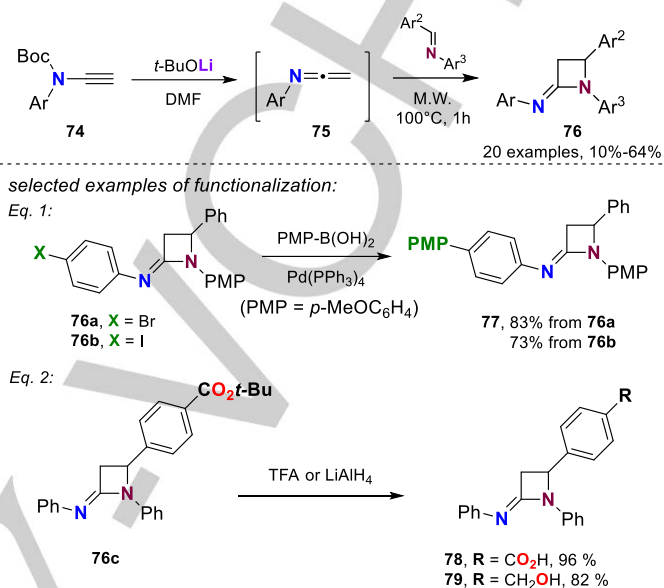


Scheme 25. Synthesis of indolic amidines.

Addition of the anion to the ethenimine then led to indolic amidine **73** in good yields that vary depending on the nature of the electron-withdrawing group.

In order to further expand the potential of this straightforward access to phenylethenimine, Dodd and Cariou sought to trap it in a [2+2] cycloaddition.²¹ Subjecting *N-tert*-butylcarbamate ynamide **74** to lithium *tert*-butoxide in dimethylformamide in the presence of an imine under microwave heating led to azetidinimines **76** in moderate to good yields (Scheme 26). This imino-Staudinger synthesis using arylothenimines **75** is complementary to Fokin's method that provides *N*-sulfonyl-azetidinimines.^{12b} The compounds obtained can also be further functionalized to access more complex scaffolds, using cross-coupling reactions (Scheme

26, Eq. 1 to give biaryl azetidinimine **77**) or strongly acidic or reductive conditions (Scheme 26, Eq. 2, trifluoroacetic acid giving free acid **78** and lithium aluminum hydride yielding benzylic alcohol **79**).



Scheme 26. Synthesis of azetidinimines through a [2+2] cycloaddition.

Summary and Outlook

Overall, the use of ynamides as bench-stable feedstock to access ketenimines is a convenient strategy to tame their instability while taking advantage of their reactivity. This is particularly useful to initiate cascade processes such as tandem sigmatropic rearrangements which, as demonstrated by Hsung, can take place through thermal or metal-catalyzed pathways. Using this approach, ionic or radical manifolds can be operative and unusual scaffolds, that would be difficult to prepare otherwise, are within reach. Yet this probably represents only the tip of the iceberg as the chemistry of ketenimines is richer than that summarized in this Concept. Of particular interest for further studies in the field will probably be the implementation of asymmetric variations of these transformations, a challenge which has yet to be taken up.

Acknowledgements

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Keywords: ketenimines • ynamides • rearrangement • cycloaddition • building blocks

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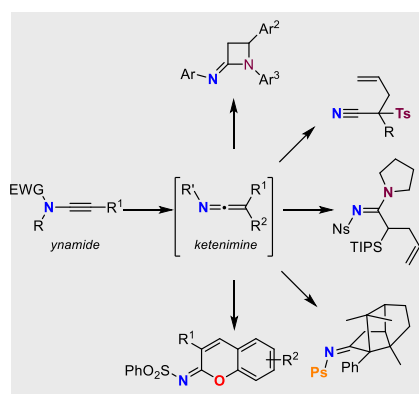
CONCEPT

Entry for the Table of Contents (Please choose one layout)

Layout 1:

CONCEPT

Here Ketenimine: Ketenimines are highly reactive, though sometimes elusive, building blocks that can undergo many transformations. Using bench-stable ynamides as precursors of ketenimines opens robust synthetic routes to build diverse nitrogen-containing scaffolds. A panorama of the methods that follow this strategy is given herein.



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