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# Ynamides in Free Radical Reactions

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**Abstract.** In this review we present the transformations that have been developed with ynamides and free radicals. These reactions involve carbon-, heteroatom- or even metalloid-centered radicals and include inter- and intra-molecular reactions. The scope and mechanism of these transformations are discussed in details, including the most recent examples relying on photoredox catalysis.

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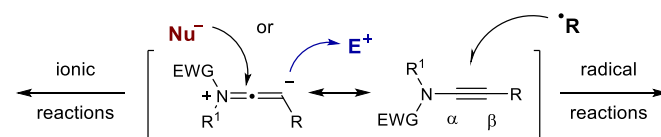
**Keywords:** Ynamides; Free Radicals; Cyclization; Photoredox catalysis; Metalloid radicals

## 1 Introduction

Ynamides are characterized as *N*-alkyne compounds in which the nitrogen atom bears an electron-withdrawing group. In the key monographic reviews published in 2010 by the groups of Hsung<sup>[1]</sup> and Evano,<sup>[2]</sup> they were described as “A Modern Functional Group for the New Millennium” and “Versatile Tools in Organic Synthesis”, respectively, two statements that hold true ten years later in view of the huge amount of research that has been devoted to these compounds.<sup>[3]</sup> The strong polarization of the carbon-carbon triple bond induced by the nitrogen, accounts for most modes of reactivity of ynamides, although a reversal of regioselectivity can be achieved in certain cases.<sup>[4]</sup> The nucleophilic nature of the β carbon and the electrophilic nature of the α carbon can be visualized by drawing the zwitterionic mesomeric form (Scheme 1, left). In particular, the activation of ynamides by electrophilic reagents to generate a key keteniminium intermediate has been the subject of numerous studies.<sup>[5]</sup> Other modes of reaction, such as their anionic chemistry<sup>[6]</sup> or the *in situ* formation of ketenimines,<sup>[7]</sup> as well as specific types of reactions, in particular cyclizations and cycloadditions,<sup>[8–12]</sup> have also been exploited and recently covered in several reviews and highlights.

Nevertheless, despite the myriad of synthetic opportunities conceivable, the use of ynamides in free radical reactions, notably as radical acceptors (Scheme 1, right), has remained relatively underexplored. Yet, with the advent of novel strategies to produce radical intermediates, such as photoredox catalysis,<sup>[13]</sup> this specific field of research is currently undergoing a surge of interest.

The aim of this review is to cover the use of ynamides in free radical reactions involving carbon-, heteroatom- or even metalloid-centered radicals and including inter- and intra-molecular reactions. The scope and mechanism of these transformations will be discussed as well.



**Scheme 1.** Ionic vs. radical reactivity of ynamides.



Capucine Mahe was born and raised in a small city near Paris, Suresnes. She started her undergraduate studies with intensive classes in Lycée Lakanal, Sceaux and then was accepted to Chimie ParisTech in 2015. In 2017, she had the opportunity to do a 5-month internship with Sir Prof. Steve S. G. Davies in Oxford, England.

In 2018, she obtained a joint Sorbonne-Université/Chimie ParisTech master in Molecular Chemistry, during which she did a 6-month internship at Sanofi in Chilly Mazarin. She was awarded a PhD fellowship from Paris-Saclay University under the supervision of Dr. Kevin Cariou at the Institut de Chimie des Substances Naturelles (ICSN), in Gif-sur-Yvette. In 2019 she moved back to Chimie ParisTech., where she will now pursue her thesis. Her work is about the synthesis of novel ynamides and the study of their reactivity, in particular for the generation of ketenimines.

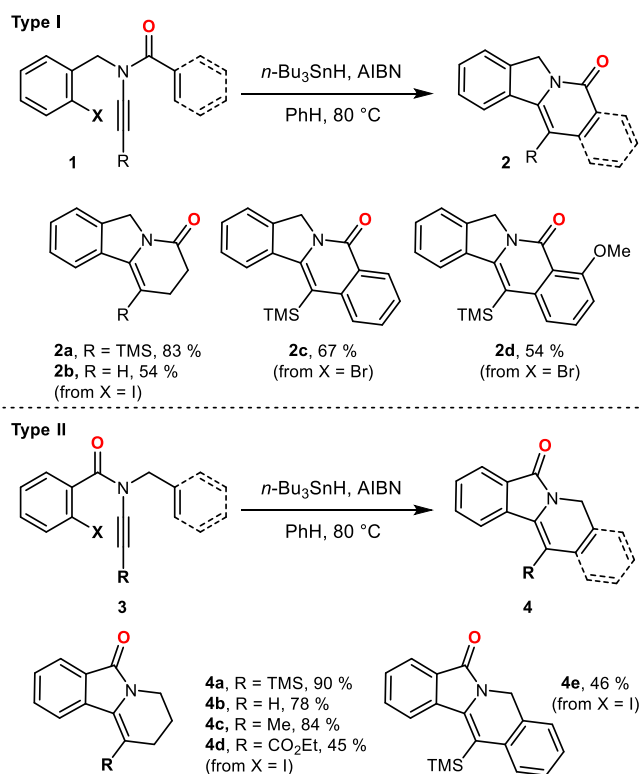


Kevin Cariou graduated from Chimie ParisTech in 2002, he received his PhD in 2006 from the University Pierre and Marie Curie (now Sorbonne Université) under the supervision of Prof. M. Malacria and L. Fensterbank, where he studied Pt- and Au-catalyzed transformations with a joint CNRS-Sanofi fellowship. From 2007 to 2009, including one-year as a Lavoisier fellowship holder, he worked as a postdoctoral researcher in the group of Prof. A. J. Frontier at the University of Rochester (NY, USA) in the field of total synthesis. In 2009 he was appointed as a CNRS Chargé de Recherche at the ICSN. He obtained his Habilitation à Diriger les Recherches (HDR) in 2015 and moved to Chimie ParisTech in 2019. His research interest lie in the development of new synthetic methods, with a focus on iodine(III) reagents and nitrogen-rich building blocks, for applications in medicinal chemistry.

## 2 Intramolecular addition of radicals to the ynamide moiety

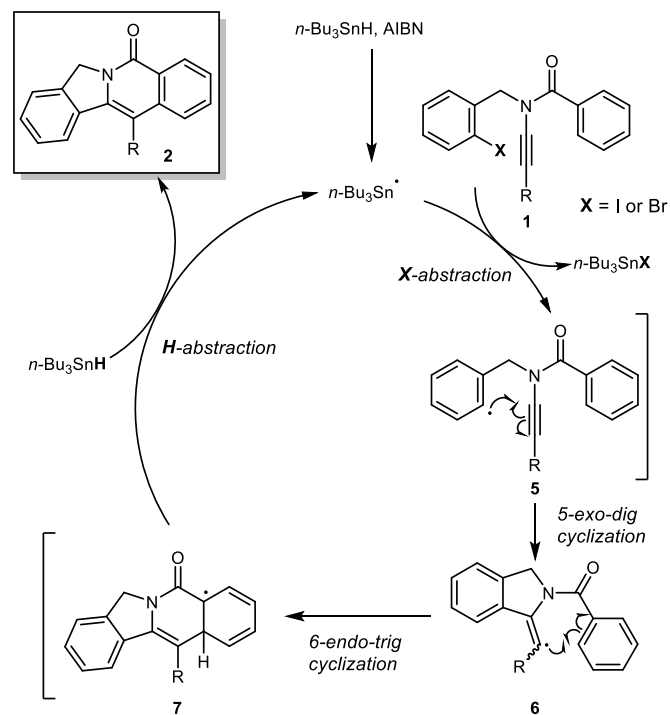
### 2.1 Initiation with AIBN and $n\text{-Bu}_3\text{SnH}$

The first example of a radical reaction involving ynamides was reported by Malacria and co-workers in 2003, who studied radical-cascade reactions to obtain polycyclic derivatives.[14] Two types (I and II) of ynamides (1 and 3) were studied, depending on the position of the carbonyl group (Scheme 2).



**Scheme 2.** Radical cyclization cascade involving ynamides and selected examples.

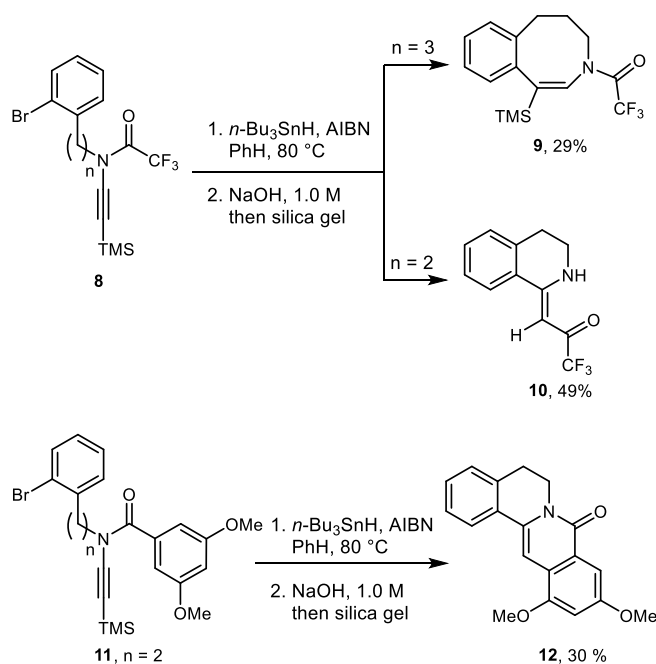
The reaction can lead to a large array of tricyclic and tetracyclic isoindole (2, type I) and isoindolinone (4, type II) derivatives with good to excellent yields, with both terminal and internal ynamides, and different substituted aromatic groups. The yields are generally higher when the starting material is an iodoarene, compared to the analogous bromo derivatives. This study was further exemplified by the same group in 2006,<sup>[15]</sup> while Hsung developed an analogous reaction with allenamides in 2005.<sup>[16]</sup>



**Scheme 3.** Mechanism for the formation of pyridoisindolone derivatives (Type I).

From a mechanistic point of view, a classical initiation step in the presence of AIBN in refluxing benzene generates the tin radical, that reacts with the haloaryl moiety through a halogen abstraction to give the aryl radical **5** (Scheme 3). Then, an intramolecular addition onto the ynamide occurs, via a 5-*exo*-dig cyclization, generating vinyl radical **6**. This is followed by 6-*endo*-trig cyclization with the pendant aromatic ring (**7**). Rearomatization occurs through a hydrogen abstraction from the tin hydride to regenerate the tin radical species.

In 2011, Courillon and coworkers extended the scope of this reaction by expanding the size of the newly formed cycle. By elongating the chain bearing the bromoaryl group (**8**), they managed to synthesize 8-membered (**9**) and 6-membered rings (**10**) as well as, in the latter case, to perform a cascade cyclization to give protoberberine analog **12** (Scheme 4).<sup>[17]</sup>



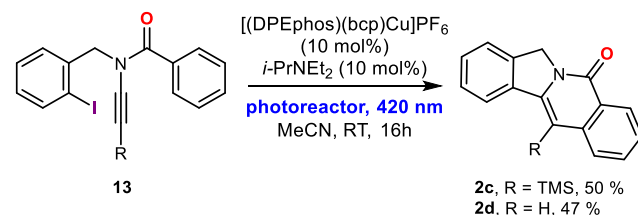
**Scheme 4.** Radical cyclization giving 6- and 8-membered rings.

The mechanism of this reaction is quite similar to the one described above (Scheme 3), the main difference being the nature of the first cyclization, which here can be either an 8-*endo*-dig cyclization or a 6-*exo*-dig cyclization.

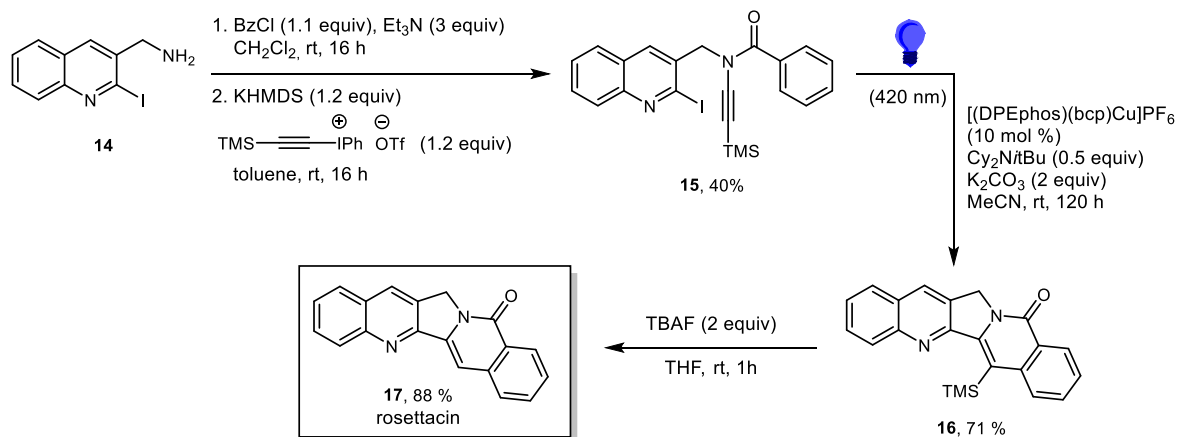
## 2.2 Initiation with photoredox catalysis

In 2018, Evano and co-workers developed a photocatalyzed version of the cyclization previously developed by Malacria for type I ynamides.<sup>[14]</sup> The reaction relies on the use of a copper(I) photocatalyst,<sup>[18,19]</sup> in the presence of a tertiary amine, starting from ynamide **13** the tetracyclic adducts **2c** and **2d** can be obtained in moderate yields (Scheme 5).<sup>[20]</sup>

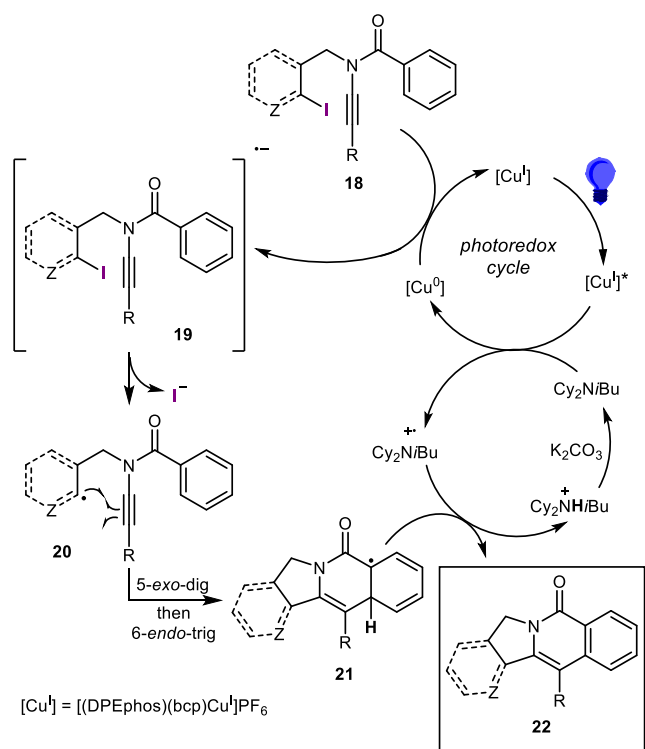
This transformation has also been extended to cyanamides, to allow an efficient and quick access to complex nitrogen-rich molecules, such as luotonin. Additionally, rosettacin **17** (the *de-aza* analogue of luotonin), a potent topoisomerase I poison,<sup>[21]</sup> can be readily obtained in 4 steps from iodo-quinoline **14**. Applying the radical cascade to **15** gives the pentacyclic adduct **16**, which is desilylated to complete the synthesis (Scheme 6).



**Scheme 5.** Copper catalyzed photoinduced cyclizations.



**Scheme 6.** Total synthesis of rosettacin.

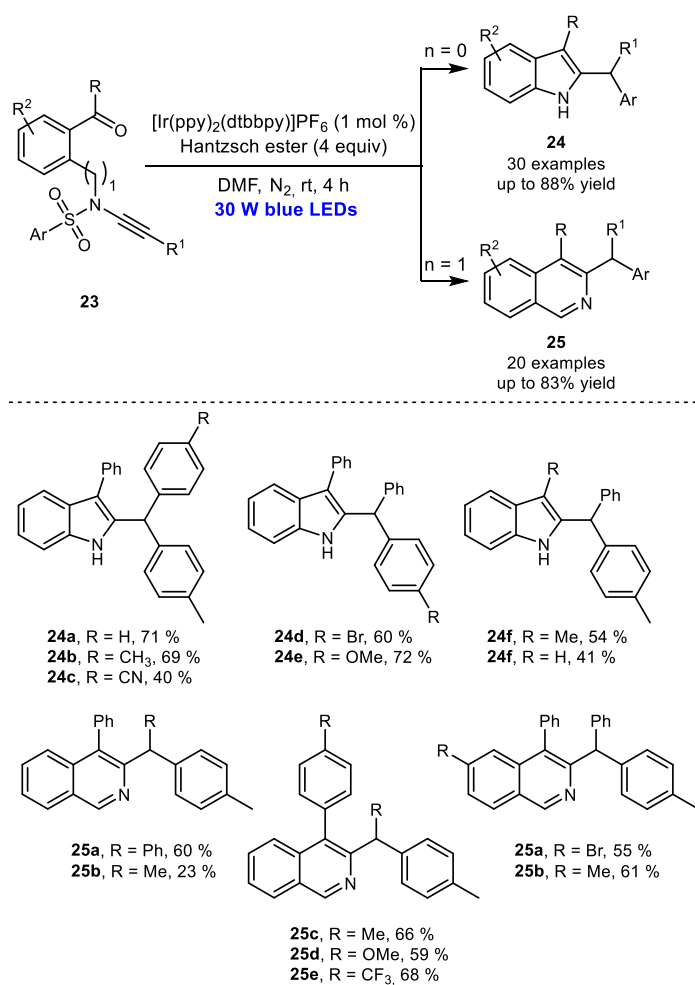


**Scheme 7.** Mechanism of the copper catalyzed photoinduced cyclization.

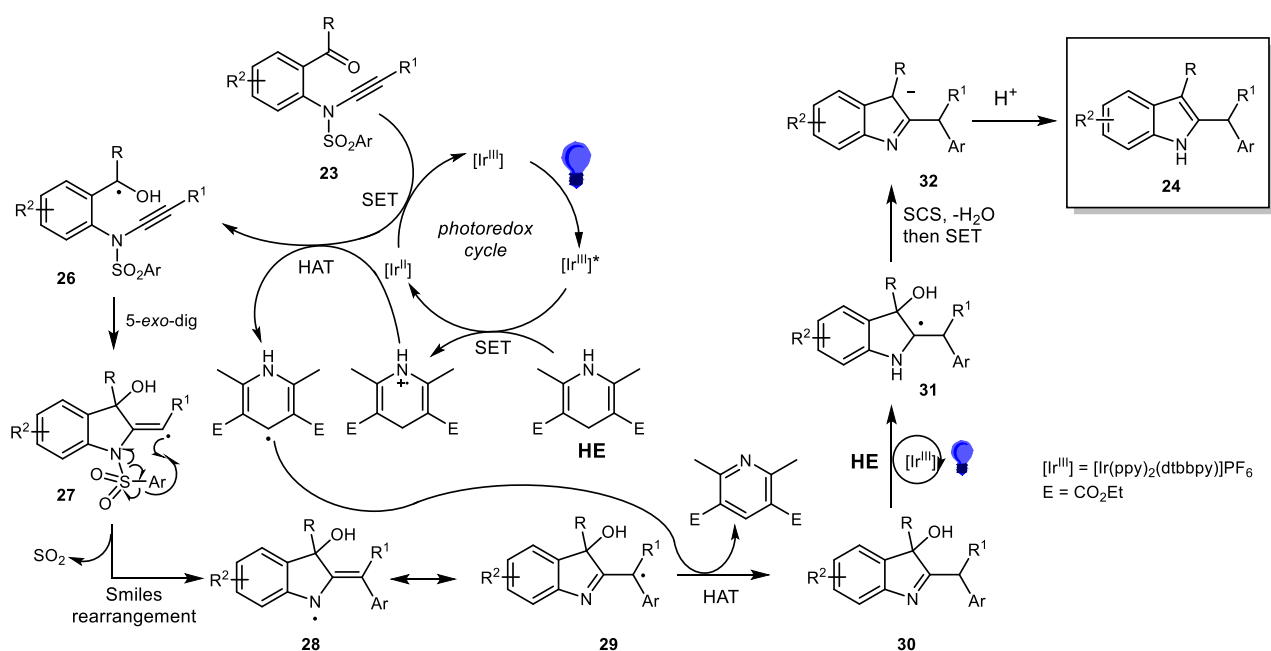
The mechanism of these radical cyclizations shares some similarities with the one proposed above (see Scheme 3) but both the initiation and termination steps are different (Scheme 7). After irradiation of the copper(I) complex at 420 nm, the excited species [Cu<sup>I</sup>]<sup>\*</sup> would be reduced by the tertiary amine Cy<sub>2</sub>Ni-Bu, resulting into the formation of a copper(0) complex and the radical cation of the amine. The former species would be involved in a single electron transfer (SET) with the ynamide substrate **18** thus giving back the Cu(I) complex in its ground state. Reduction of the iodoarene would firstly give radical anion **19** and then aryl radical **20** after the departure of the iodide. A 5-*exo*-dig intramolecular addition on the carbon-carbon triple bond of the ynamide would occur, followed by a 6-*endo*-trig trapping by the aromatic moiety (**21**). Final rearomatization to yield **22** would be enabled by H-abstraction with the amine radical cation to give the ammonium that would be deprotonated by the base to effectively close the tertiary amine catalytic cycle.

In 2020, the group of Ye devised a different approach to the photocatalyzed generation of a radical on an ynamide substrate, through the single-electron reduction of a ketone.<sup>[22]</sup> Depending whether the ynamides **23** are derived from anilines or benzylamines, indoles (**24**) or isoquinolines (**25**) can be obtained, respectively, with generally good yields and functional group tolerance (Scheme 8). The proposed reaction occurs concomitantly with the loss of SO<sub>2</sub>, which was to happen through a Smiles

rearrangement. In this reaction the photocatalytic cycle starts with the excitation of the Ir(III) complex, to Ir(III)<sup>\*</sup> which is thereafter reduced by the Hantzsch ester (HE) (Scheme 9). The resulting Ir(II) complex can reduce the ketone, while HE radical cation can perform a hydrogen atom transfer (HAT) to give both the ketyl radical **26** and the HE radical. The former radical then reacts intramolecularly on the ynamide triple bond in a 5-*exo*-dig fashion to give vinyl radical **27**. A radical Smiles rearrangement releases SO<sub>2</sub> and a 1-aza-allyl radical with two main resonance hybrids: *N*-centered radical **28** and tertiary radical **29**. The latter can undergo an additional HAT with the Hantzsch ester radical giving the eneindolin-3-ol **30**. From there the authors propose another photo-catalyzed formation of a ketyl-type radical from the imine. A photocatalyzed spin-center shift (SCS)<sup>[23]</sup> would lead to the release of water and the formation of a 3-indoyl radical (**31**), that would then be reduced by SET (**32**) and protonated to yield the final product **24**. The mechanism for the formation of the isoquinoline adducts **25** is similar, with an extra oxidative aromatization as the last step.



**Scheme 8.** Synthesis of 2-benzhydrylindoles and selected examples of indoles and isoquinolines obtained.



**Scheme 9.** Mechanism proposal for the radical Smiles rearrangement triggered by a photocatalytic ketyl-ynamide coupling.

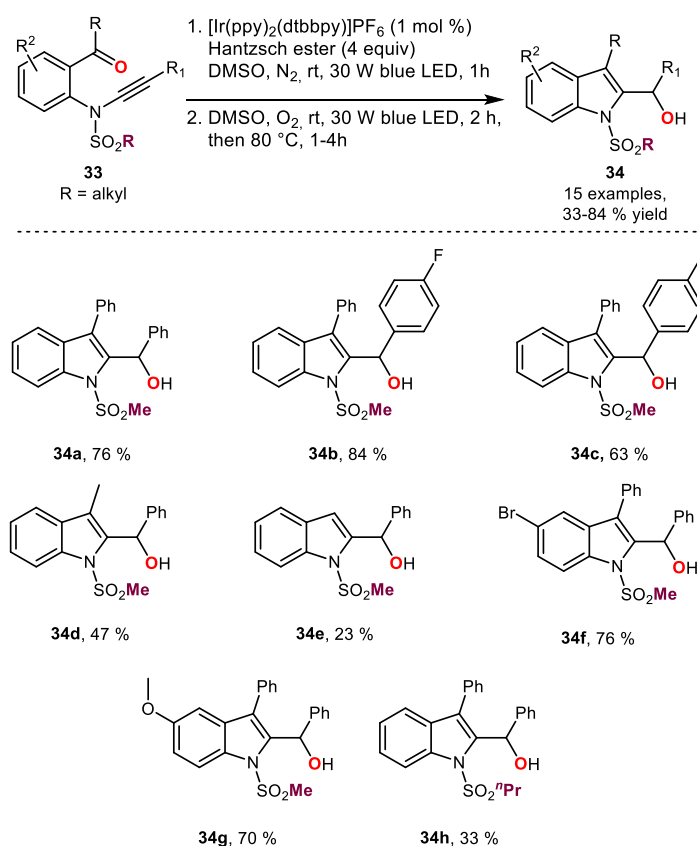
Ye and co-workers then extended the ketyl-ynamide coupling to alkyl-sulfonyl ynamides **33**.<sup>[24]</sup> Using this type of sulfonyl derivatives implies that the vinyl radical intermediate cannot undergo a Smiles rearrangement. Therefore the sulfonyl group remains on the nitrogen and indolic derivatives **34** are eventually obtained (Scheme 10). The yields are good to excellent for ketone derived substrates, but decrease for benzaldehydes (**34e**, 23%). The reaction has also been tested using *n*-propyl sulfonyl group instead of methanesulfonyl, giving the desired product with 33% yield.

The mechanism of this transformation relies on the same photoinduced coupling using  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  as the photocatalyst (Scheme 11). The ketyl radical **35** is first generated following the same pathway as in their previous work (see Scheme 9). Then the radical reacts on the ynamide C-C triple bond in a regioselective manner by a 5-exo-dig cyclization. Vinyl radical intermediate **36** is formed and, as the Smiles rearrangement is no longer possible, is trapped *via* a HAT. This gives eneindolin-3-ol **37** that is converted to 2-hydroxymethylindole **34** by a 1,3 transposition. This transposition was found to perform optimally when the reaction system was charged with  $\text{O}_2$ , still under irradiation with the same blue LED, and heated up to  $80^\circ\text{C}$ , which also lead to the conversion of any remaining HE into the corresponding pyridine.

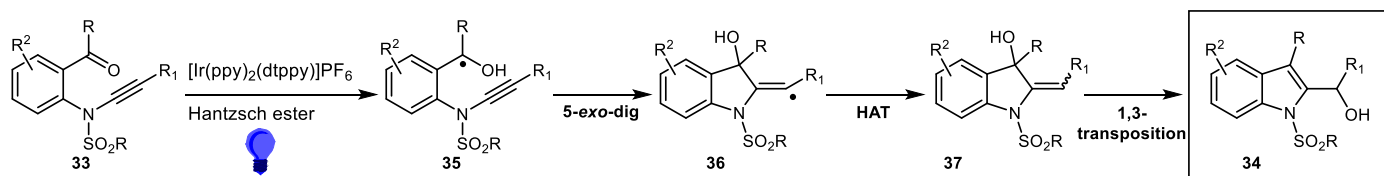
### 2.3 Initiation through the addition of an external radical species

An alternative for generating the radical from the ynamide substrate is to generate an external radical species that would add intermolecularly onto the substrate to initiate a cyclization on the ynamide triple bond. Incorporating a substituent in the molecule that

could they serve as a trapping moiety for radical addition, such as an alkene or an alkyne, would also add more complexity, eventually leading to more densely functionalized molecules.

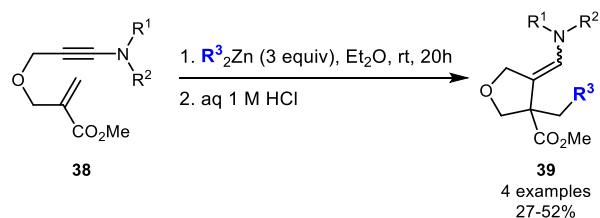


**Scheme 10.** Synthesis of 2-benzhydrylindoles and selected examples of indoles and isoquinolines obtained.

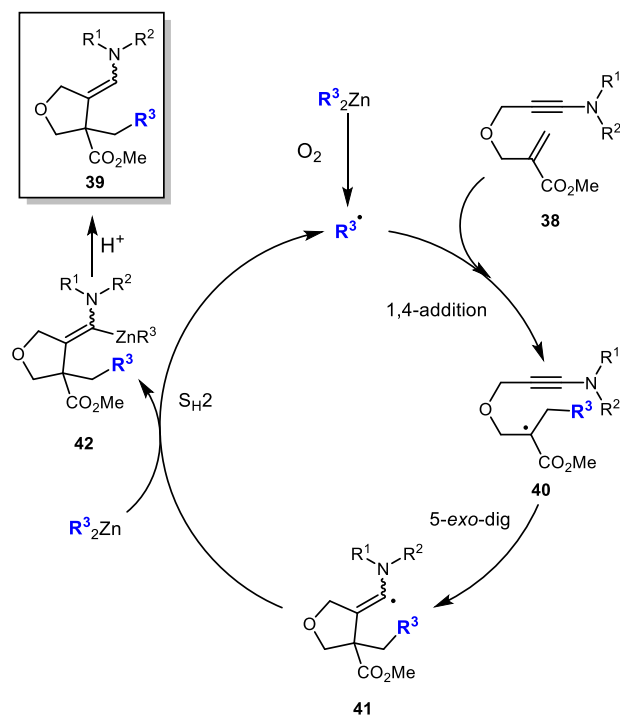


**Scheme 11.** Mechanism proposal for the synthesis of 2-hydroxymethylindoles triggered by a photocatalytic ketyl-ynamide coupling.

The first instance of this strategy was reported in 2011 by the group of Chemla and Perez-Luna who designed ynamides bearing an acrylate moiety as the radical acceptor (**38**).<sup>[25]</sup> In the presence of a dialkylzinc reagent, the reaction gives cyclized product **39** with the addition of the alkyl group on the acrylate (Scheme 12). The initiation step is believed to occur through the oxidation of the dialkylzinc by traces of dioxygen to give the alkyl radical (Scheme 13).



**Scheme 12.** Addition of an alkyl radical on an ene-ynamide to initiate radical cyclization.

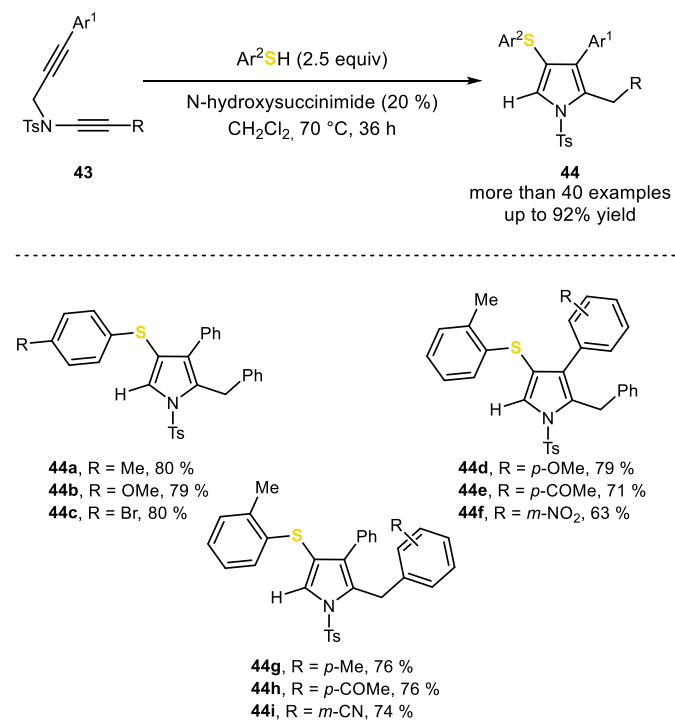


**Scheme 13.** Mechanism of the radical addition/cyclization cascade.

Conjugate addition on the acrylate then gives the ester-stabilized tertiary radical **40** that can undergo a 5-*exo-dig* cyclization on the ynamide to yield enamine radical **41**. The termination occurs through a homolytic substitution with the dialkylzinc, thus regenerating the alkyl radical and yielding a vinylzinc species (**42**) that is hydrolyzed to form the final product.

Although thiyl radicals can readily add on ynamides (see section 3.1 below), in 2019, Sahoo and co-workers took advantage of a preferred addition of a thiyl radical to the alkyne rather than the ynamides to trigger a cascade reaction leading to the formation of pyrrole derivatives from *N*-propargyl ynamides **43** (Scheme 14).<sup>[26]</sup>

With optimized conditions, this transformations enables to synthesize an impressive array of 4-thioaryl pyrroles (**44**). It shows excellent compatibility towards substituted arylthiol derivatives, as well as the aryl groups in both the alkyne and the ynamide termini.



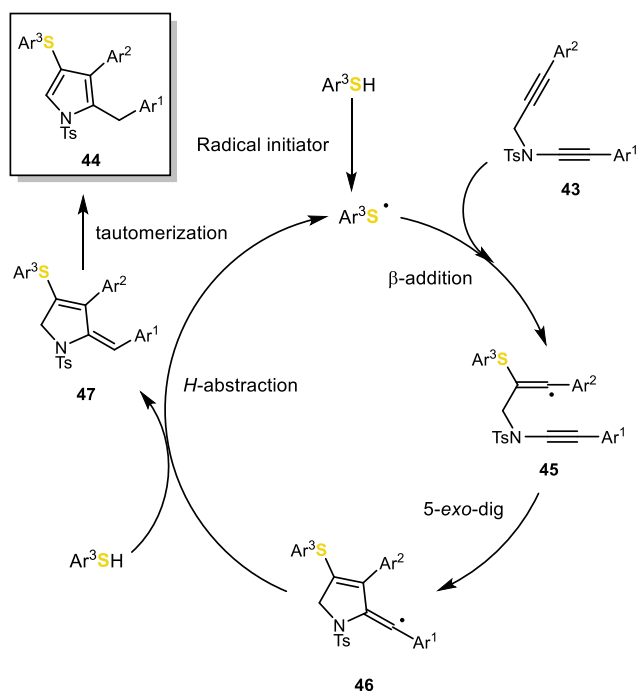
**Scheme 14.** Synthesis of functionalized pyrroles initiated by a thiyl radical and selected examples.

Forty-five examples have been synthesized, with good yields, from 47 % to 92 %. Further functionalizations of these compounds, was also reported, for example by oxidation of the sulfur, followed by rearrangement or cyclization. The initiation step takes place between the radical initiator, *N*-hydroxyphthalimine, and the arenethiol to give the thiyl radical (Scheme 15). DFT computations by Gandon confirmed that the preferred pathways would go through the attack of the radical on the alkyne moiety to give vinyl radical **45**, which is then followed by a 5-*exo*-dig intramolecular attack on the ynamide moiety. The thiyl radical is regenerated through an H-abstraction by **46**. The final aromatized compound is obtained after tautomerization of **47**.

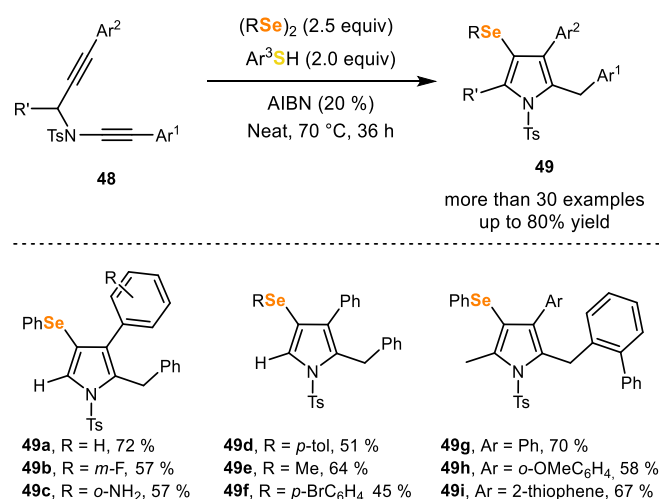
In 2020, the same group extended this strategy to the synthesis to 4-selenylated pyrroles **49**, starting from aryl-ynamides **48** (Scheme 16).<sup>[27]</sup> The reaction conditions are quite similar but the thiyl radical, generated with AIBN, reacts with diphenylselenide to give a selenyl radical instead.

Calculation by Gandon showed that the attack of the selenyl radical is indeed favored over the attack of the thiyl radical and, once again, that initial addition on the alkyne is the preferred pathway. Thirty-four molecules have been synthesized using this method.

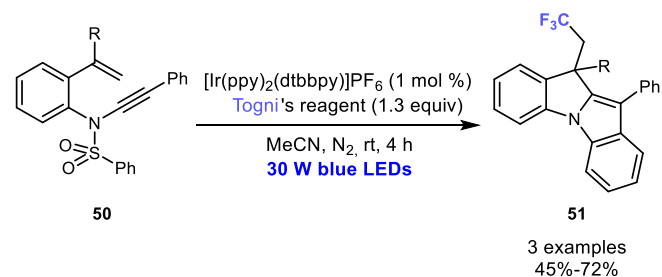
Finally, in addition to their studies on the photogeneration of a ketyl radical, the group of Ye also developed the addition of a photogenerated radical on the alkene analogue **50** of their carbonyl substrate **23** (see Scheme 9).<sup>[22]</sup> The use of Togni's reagent as a source of CF<sub>3</sub>• radical was first explored (Scheme 17) and other carbon-centered radicals could also be introduced using a different Ir(III) catalyst.



**Scheme 15.** Mechanism of the thiyl radical-induced cyclization cascade.



**Scheme 16.** Synthesis of 4-selenylated pyrroles and selected examples.



**Scheme 17.** Synthesis of 2-benzhydrylindoles.

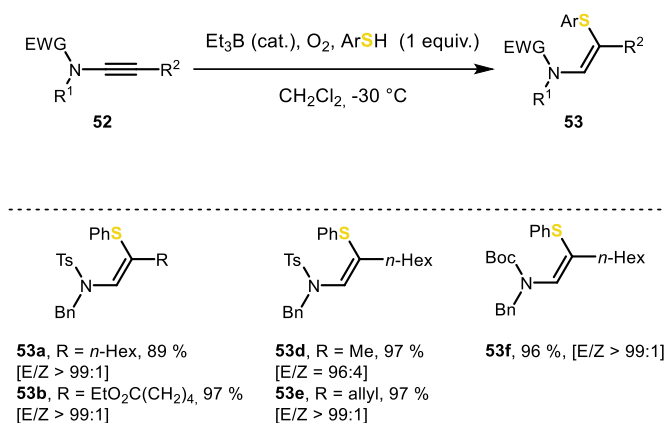
The authors assumed that, after initial addition of the radical to the styryl moiety, the resulting tertiary radical would induce the same cascade as the ketyl radical (see Scheme 9). The cascade conclusion would diverge after the Smiles rearrangement, as the trapping of the nitrogen-centered radical by the transferred phenyl ring occurs to give the tetracyclic adduct **51**.

## 3 Intermolecular addition of radicals on the alkyne moiety

### 3.1 Addition of thiyl radicals

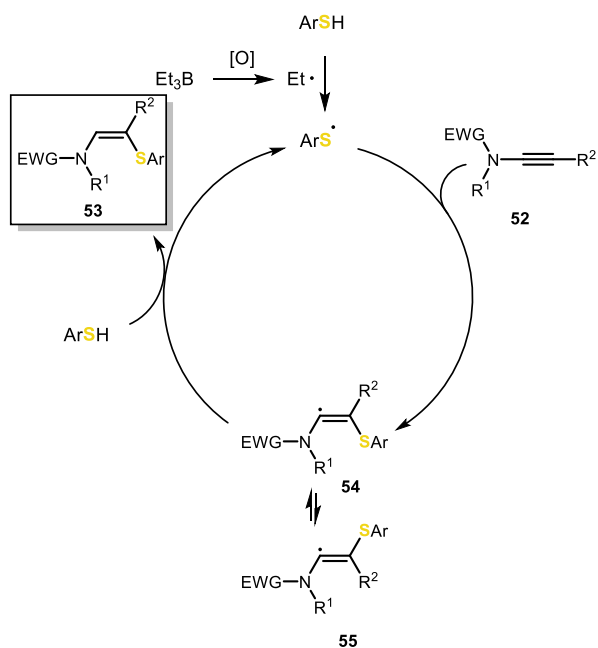
In 2009, Yorimitsu and Oshima reported the first addition of thiyl radicals to ynamides **52**<sup>[28,29]</sup> (Scheme 18). The 1-amino-2-thio-1-alkenes **53** are obtained with moderate to excellent yields and the *Z* stereoisomer is the major one (usually above a 96:4 *Z*:*E* ratio). The reaction tolerates different arylthiols, either sulfonyl or carbamate (EWG) protecting groups, aryl or alkyl groups (R<sup>1</sup>) on the nitrogen and various alkyl chains (R<sup>2</sup>) on the triple bond.





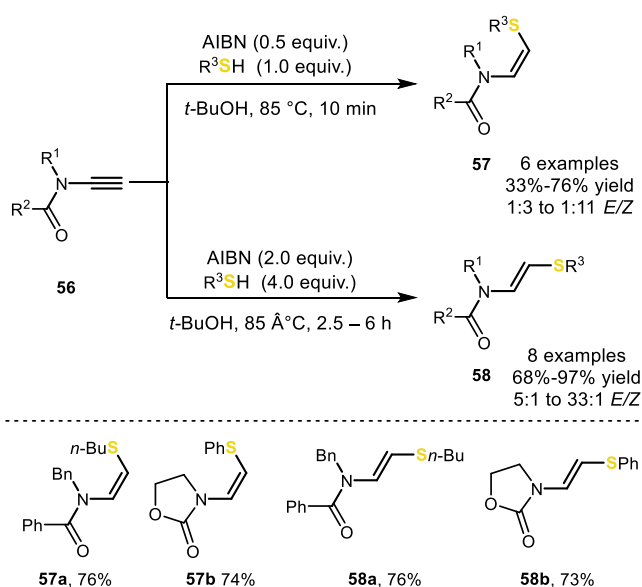
**Scheme 18.** Hydrothiolation of internal ynamides and selected examples.

To initiate the radical species formation, a catalytic amount of triethylborane is used under aerobic conditions (Scheme 19). This leads to the formation of an ethyl radical that can react with the arenethiol to form the arylsulfanyl radical by H-abstraction. Addition to the ynamide at the  $\beta$  position leads to a vinyl radical **54** that is predominantly in its *Z* form **55** to minimize steric interactions between R<sup>2</sup> and the amino group. Selective HAT with the arenethiol then gives the hydrothiolation product **53**.



**Scheme 19.** Mechanism of the hydrothiolation of ynamides.

Following this example, in 2010, Castle and co-workers developed a method to perform the controlled radical hydrothiolation of terminal ynamides **56**.<sup>[30]</sup> Instead of triethylborane, AIBN [2,2'-azobis(isobutyronitrile)], is used as the radical initiator to generate the arylsulfanyl radical. When using only one equivalent of arenethiol during a short reaction

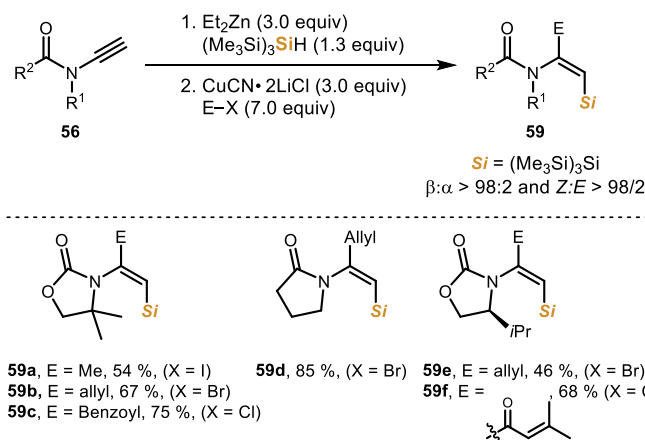


**Scheme 20.** Hydrothiolation of terminal ynamides and selected examples.

time, the *Z* isomer **57** is formed predominantly as the kinetic product (Scheme 20). On the contrary, extended reaction times with an excess of thiol and AIBN led to the *E* isomer **58** as the major product.

### 3.2 Addition of silyl and germyl radicals

Building upon their previous work on the generation of radicals with dialkylzinc (see Section 2.3) the group of Perez-Luna, in collaboration with the team of Oestreich, reported the radical *trans*-silylzincation of ynamides in 2014.<sup>[31]</sup> The addition of a silyl radical proceeds with excellent regio- and diastereoselectivity and can be combined with a one-pot transmetalation with a cyanocuprate, followed by various electrophilic trappings to access a broad range of doubly substituted enamides **59** (Scheme 21).

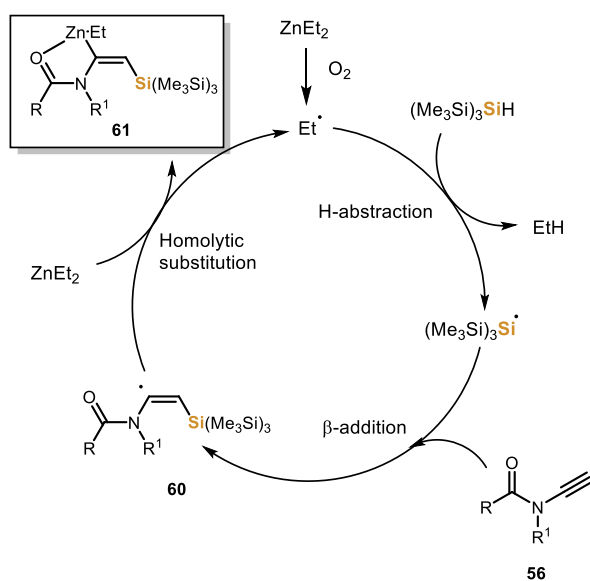


**Scheme 21.** Radical silylzincation, transmetalation and electrophilic addition and selected examples.

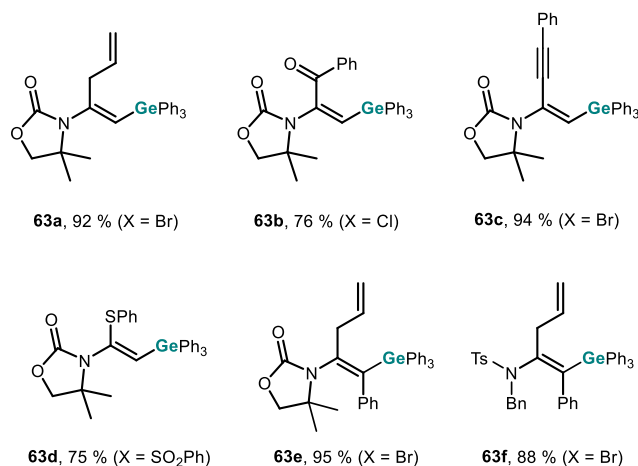
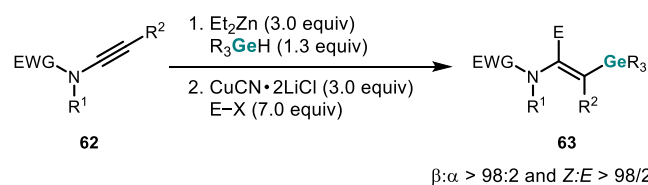
This method has been applied to different ynamides, with various allylic halides, propargyl bromide, or acylchlorides, for a total of sixteen molecules synthesized, with excellent regio- and stereo-selectivity. The vinylsilane itself can also undergo a bromo-desilylation to give diversely substituted vinyl bromides that can be engaged in cross-coupling reactions.

As described above (see Scheme 13), in the presence of traces of oxygen, diethylzinc can lead to the formation of an ethyl radical, which is the initiator in this transformation (Scheme 22). This radical reacts with  $(\text{Me}_3\text{Si})_3\text{SiH}$  by a H-abstraction to give the stabilized silyl radical that can add onto the  $\beta$ -position of ynamide **56**. Diethylzinc then reacts with the Z-vinyl radical intermediate **60** via an homolytic substitution. The combined effects of the steric hindrance of the silyl group and the chelation of the zinc by the electron-withdrawing group on the ynamide induces an excellent *trans*-selectivity of the reaction. The zinc species **61** can then be transmetalated by addition of cyanocuprate and the resulting vinyl-copper can add on a variety of electrophile to give the 1,2-transdisubstituted alkene.

In 2018 the group of Perez-Luna continued their investigation of the metalloid radical addition onto ynamides (**62**) and developed a germylzincation reaction.<sup>[32]</sup> The conditions are similar as the ones used for the silylzincation, here the radical addition is done by using  $\text{R}_3\text{GeH}$ , which gives the corresponding germyl radical in the presence of diethylzinc and traces of oxygen. The resulting vinyl-zinc intermediate can then be directly trapped by an electrophiles or undergo a transmetalation with copper to give a broad range of tri- or tetra-substituted alkenes **63** (Scheme 23). The reaction initially developed on ynamides was also extended to sulfur-, oxygen-, and phosphorus-substituted terminal alkynes, overall more than fifty examples were reported in this study.



**Scheme 22.** Mechanism of the radical silyl-zincation.

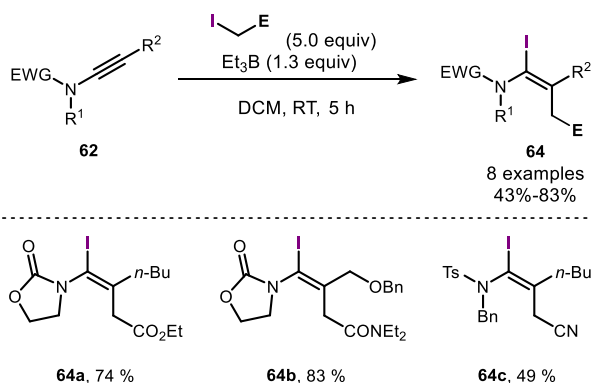


**Scheme 23.** Radical germylzincation, transmetalation and electrophilic addition and selected examples.

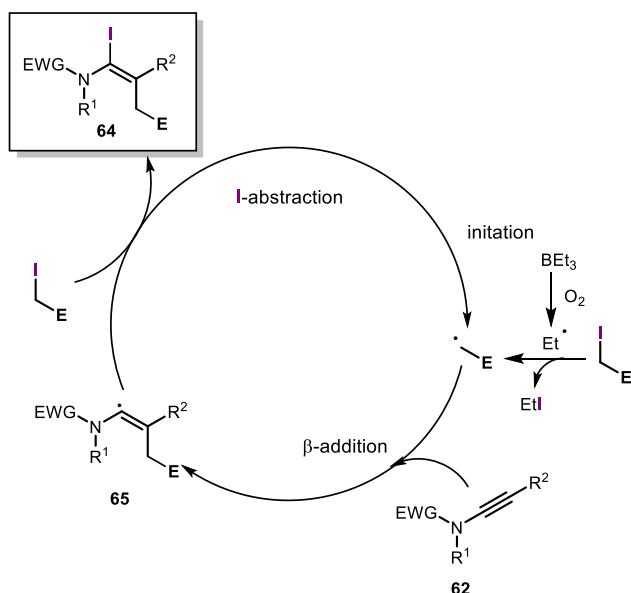
The mechanism is similar to the silylzincation described previously (Scheme 22) although the reaction evolves towards a formal *cis*-germylzincation as opposed to the *trans* selectivity observed with the silyl radical addition. This is particularly interesting as the germyl function can also be used as an intermediate for halodegermylation, thus rendering both approaches fully complementary.

### 3.3 Addition carbon centered radicals

The direct addition of a carbon-centered radical onto ynamides **62** was recently investigated by the group of Bertrand and Feray, using an iodine atom transfer radical addition with  $\alpha$ -iodo-esters, -amide and -nitrile (Scheme 24).<sup>[33]</sup>



**Scheme 24.** Radical carbo-iodination of ynamides and selected examples.

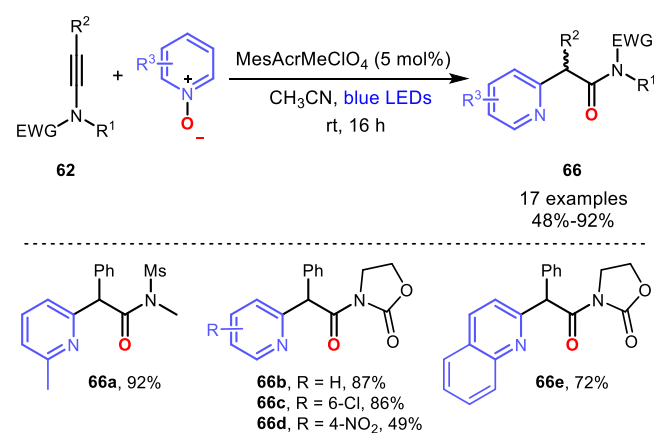


**Scheme 25.** Mechanism of the radical carbo-iodination of

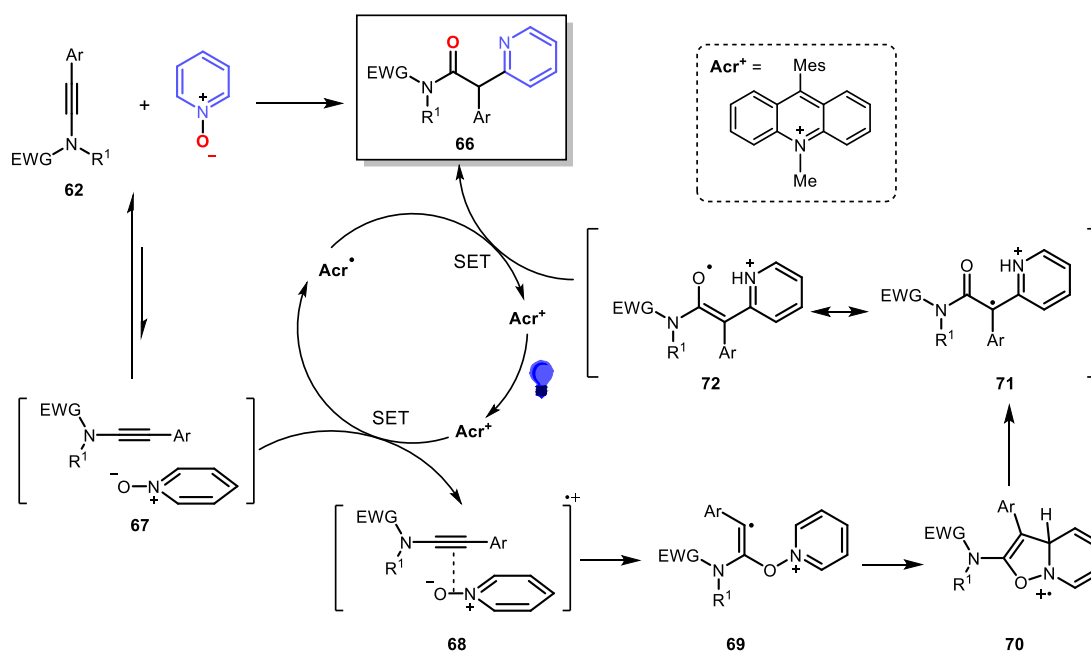
The tetrasubstituted enamides **64** are obtained with good to excellent yields and perfect regio- and diastereo- selectivities. The initiation step with triethylborane and dioxygen would lead to the formation of the carbonyl-stabilized radical, which would add onto the ynamide (Scheme 25). The addition proceeds majorly on the  $\beta$  position, which was rationalized by DFT computations, and the resulting vinyl radical **65** then reacts with the iodo compound yielding to the final product and regenerating the carbon-centered radical ynamides.

### 3.4 Photocatalyzed generation of radicals

In 2019, Deng *et. al* studied the photocatalyzed ortho-alkylation of pyridine *N*-oxides with ynamides (**62**), which was also applied to arylacetylenes.<sup>[34]</sup> Under blue irradiation in the presence of an acridinium dye, the reaction between various oxazolidinone- and sulfonamide-based ynamides and pyridine or quinolone *N*-oxides leads to the formation of  $\alpha$ -(2-pyridinyl) benzyl amides **66** (Scheme 26). Herein, the pyridine *N*-oxide has three purposes: it enables the photocatalyzed single electron transfer oxidation process, it serves as an oxygen transfer agent, and acts as a trap for the highly reactive vinyl radical formed on the ynamide. Voltammetry studies have shown that the oxidation potential of the ynamide is significantly lower in presence of pyridine *N*-oxide.

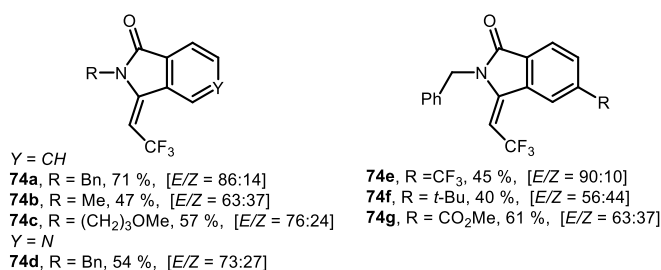
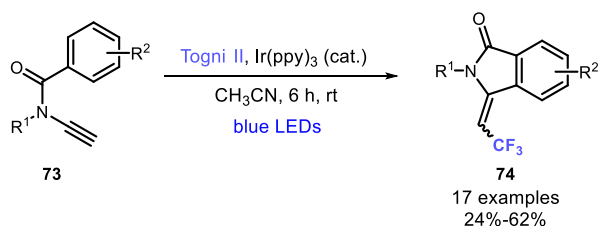


**Scheme 26.** Photocatalyzed simultaneous oxidation and arylation of ynamides and selected examples.



**Scheme 27.** Mechanism proposal for photocatalyzed ortho-alkylation of pyridine *N*-oxides with ynamides.

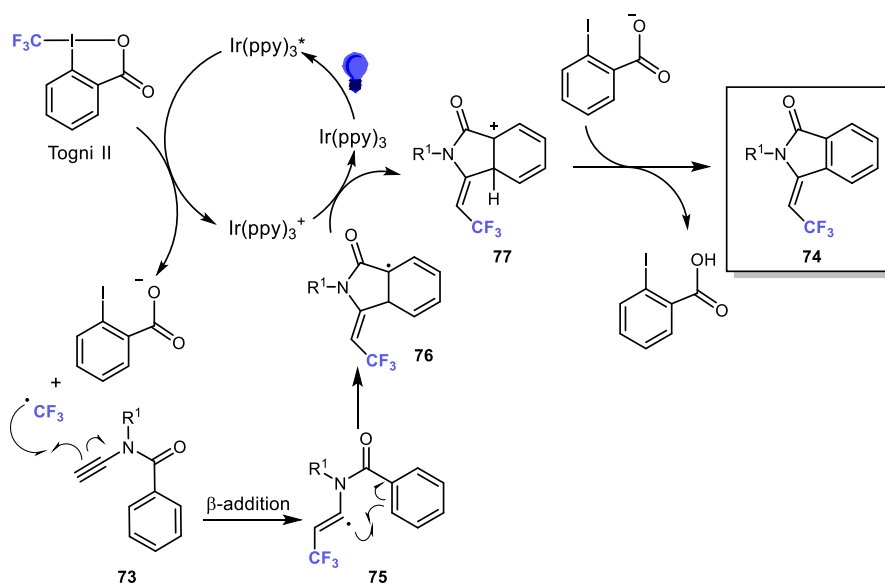
This led to several hypotheses, such as the formation of an electron donor-acceptor (EDA) complex **67**, through  $\pi$ - $\pi$  interaction between the phenyl and triple bond of the ynamides with the pyridine. Although studies are still going to explore this process, it remains the privileged hypothesis. The EDA complex could then be oxidized by SET with the photo-excited acridinium to give a radical cation adduct **68** (Scheme 27). This would evolve via the nucleophilic attack of the oxygen atom of pyridine *N*-oxide. The attack on the  $\alpha$  position would be favored because of the stabilization of the radical near the phenyl group.



**Scheme 28.** Photocatalyzed functionalization and cyclization of ynamides; selected examples.

The vinyl radical **69** would react *via* an intramolecular Minisci-type pathway to give the bicyclic aminyl radical cation intermediate **70**. This would undergo a 1,2-electron shift, with a  $\beta$ -N-O bond scission and proton transfer on the nitrogen atom to give the stabilized tertiary radical **71**, with the pyridine rearomatized. To close the photocatalytic cycle, the enol radical **72** would be reduced by the Acr<sup>\*</sup> to deliver the final product and the acridinium in its ground state.

In 2019, the group of Ollivier and Fensterbank developed a photocatalyzed trifluoromethylation of benzoyl ynamides (**73**), which led to the formation of various isoindolinones **74** after cyclization on the benzoyl fragment (Scheme 28).<sup>[35]</sup> The reaction proceeds under blue light irradiation with an iridium(III) photocatalyst using Togni II trifluoromethylation reagent. After irradiation of the catalyst, the excited species [Ir(ppy)<sub>3</sub>]<sup>\*</sup> can reduce the Togni II reagent to generate the CF<sub>3</sub><sup>•</sup> radical and the *o*-iodobenzoate anion (Scheme 29). Then, intermolecular addition of the trifluoromethyl radical on the triple bond of ynamide **73** takes place on the  $\beta$  position, as it is an electrophilic radical species. DFT-calculations showed that the *Z* and *E* intermediates (**75**) are similar in terms of stability but the 5-*exo* cyclization from the *Z*-isomer is higher in energy. This explains why the *E/Z* ratio of the final product tends to be in favor of the *E*-isomer. The resulting bicyclic radical **76** can then be oxidized by the Ir(IV) complex to regenerate the photocatalyst in its ground state and a tertiary carbocation **77**. Finally, rearomatization takes place through the elimination of a proton by the benzoate.



**Scheme 29.** Mechanism of the tandem trifluoromethylation/cyclization of ynamides.

## 4 Conclusion

Although radical reactions with ynamides have been pioneered more than 17 years ago, they remained rather underexplored for almost 15 years. Yet, since 2018, a surge in publications reporting highly innovative synthetic methodologies involving ynamides in free radical reactions was witnessed. This is mostly due to the emergence of novel strategies to generate radicals such as photoredox catalysis or of the use of metalloid radicals. Complex transformations have been devised in this fashion, from sequential selective additions to cascades yielding complex polycyclic frameworks. Yet there are certainly more to come in the future, as the versatility of ynamides make them ideal substrates for controlled for selective reactions with free radicals.

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