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## Chapter five

# Radical reactions of ynamides

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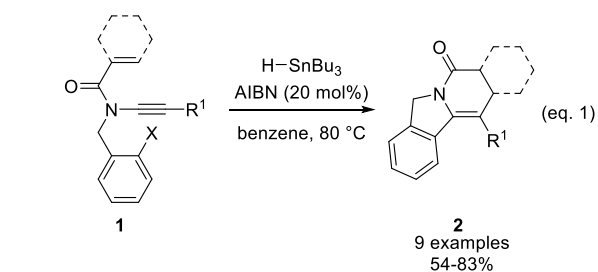
### 1.1 INTRODUCTION

Ynamides are versatile functional groups in modern organic chemistry and they are used in a wide variety of transformations. However, only a few examples of radical reactions of ynamides are known, and their specific reactivity remains mainly underexplored.<sup>1</sup> This chapter will first discuss intramolecular radical reactions of ynamides, which mainly deals with radical cyclizations leading to the straightforward synthesis of nitrogen heterocycles. Next, the intermolecular radical reactions will be exposed, according to the nature of the C-X bond formed during the radical step. A last part will present oxidation reactions of ynamides following a specific reaction with molecular oxygen.

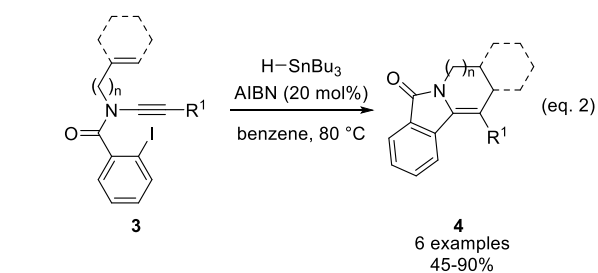
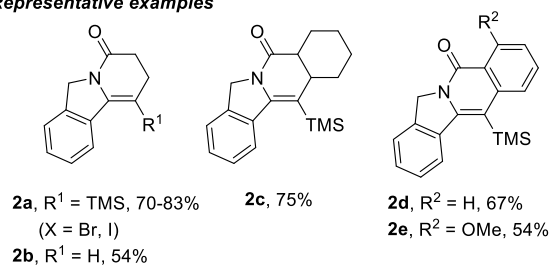
## 1.2 INTRAMOLECULAR RADICAL REACTIONS

### 1.2.1 *Radical cyclization reactions*

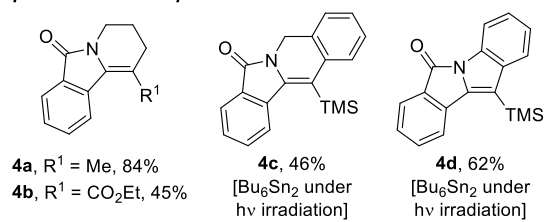
In 2003, Malacria and coworkers reported the first intramolecular radical cyclization reactions of ynamides leading to various nitrogen-containing heterocycles such as isoindoles or isoindolinones (Scheme 1).<sup>[2]</sup> Two classes of radical precursors were studied, **1** and **3**, differing by the position of the carbonyl group. Reaction conditions relied on AIBN (20 mol%) as a radical initiator and tributyltin hydride in benzene at 80 °C. After bromide or iodide abstraction by the tributyltin radical, a highly reactive aryl radical was formed which underwent a 5-*exo*-dig cyclization, followed by a spontaneous 6-*endo*-trig cyclization, delivering the polycyclic compounds **3** and **4** in good yields. Unfortunately, this reaction is not efficient with sulfonyl ynamides. In some cases, a competitive reduction processes took place, but could be minimized using photochemical homolytic cleavage of hexabutylditin.<sup>[3]</sup>



**Representative examples**

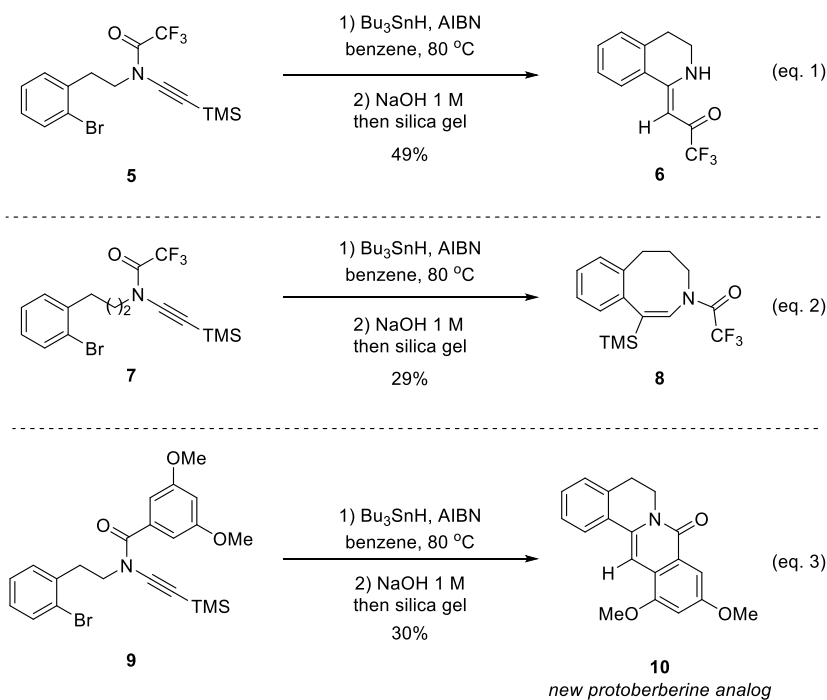


**Representative examples**



**Scheme 1.** Intramolecular cyclization for the synthesis of fused nitrogen heterocycles

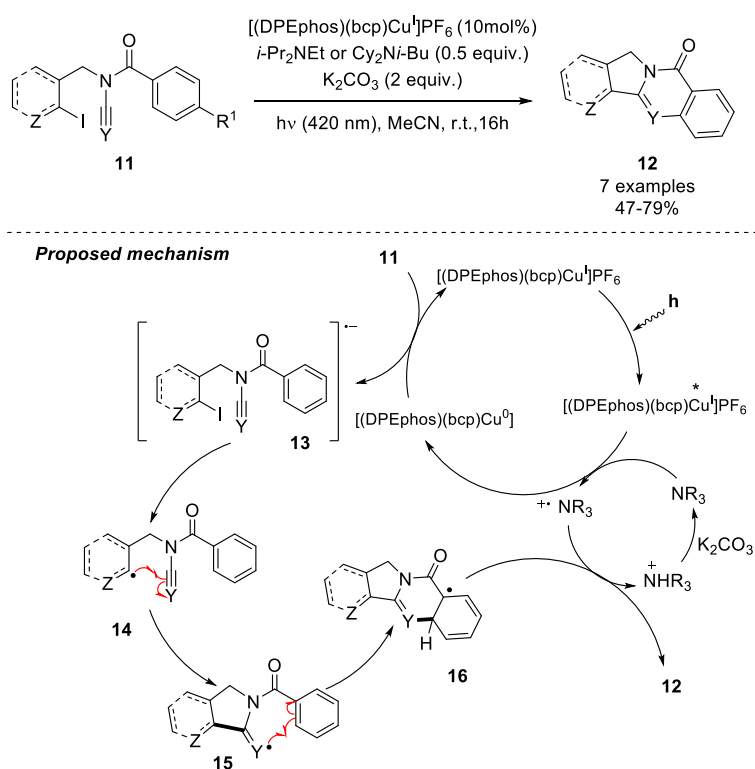
This cyclization strategy was further explored by Balieu, Courillon and co-workers with an ynamide moiety located at a remote position from the halogenated aromatic ring. The radical reactions of ynamides **5**, **7** and **9** gave access to six- and eight-membered rings (**6**, **8** and **10**) in moderate yields using AIBN (50 mol%) as a radical initiator and tributyltin hydride in benzene at 80 °C (**Scheme 2**, eqs. 1-3). Ynamide **5** and **9** underwent a 6-*exo*-dig cyclization whereas in the case of **7** having a three carbons side chain, radical cyclization occurred successfully via an 8-*endo*-dig cyclization delivering the unsaturated eight-membered ring **8**. This protocol has a limited substrate scope, as other ynamides tested led to degradation or competitive dehalogenation processes.<sup>[4]</sup>



**Scheme 2.** Formation of six- and eight-membered rings and total synthesis of a protoberberine analog

Recently, an elegant radical cyclization of ynamides and cyanamides **11** has been reported by the Evano group. The classical tin-based conditions

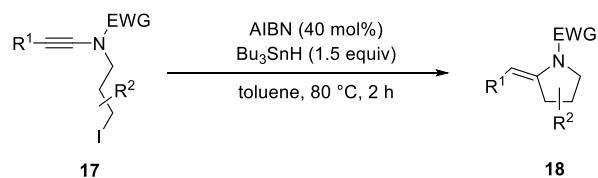
were efficiently replaced by the combination of a photoactivable copper(I) complex, an amine and visible light to generate the radical species involved in the transformation. The copper complex was photoexcited by light, and further underwent reduction by the base generating a transient Cu(0) complex and an amine radical cation. In turn, this Cu(0) complex reduced the C–I bond in **13** and initiated the generation of radical intermediate **14** which underwent 5-*exo*-dig cyclization to the C≡C or C≡N triple bond to form an intermediate vinylic or iminyl radical intermediate **15**. Then, a 6-*endo*-trig radical cyclization with the arene afforded radical intermediate **16**, which upon subsequent aromatization led to complex tri-, tetra- and pentacyclic nitrogen heterocycles **12**. This strategy was applied to the total synthesis of Rosettacin, Luotonin A, and Deoxyvasicinone which are inhibitors of topoisomerase I (**Scheme 3**).<sup>[5]</sup>



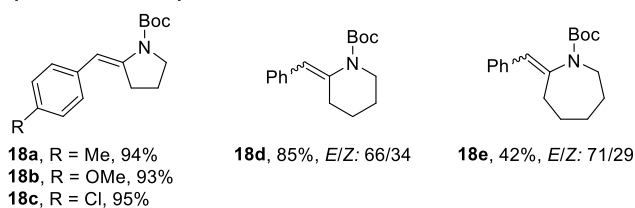
**Scheme 3.** Copper-catalyzed photoinduced radical cyclization of N-

benzoyl-*N*-(*o*-iodobenzyl)cyanamides and ynamines

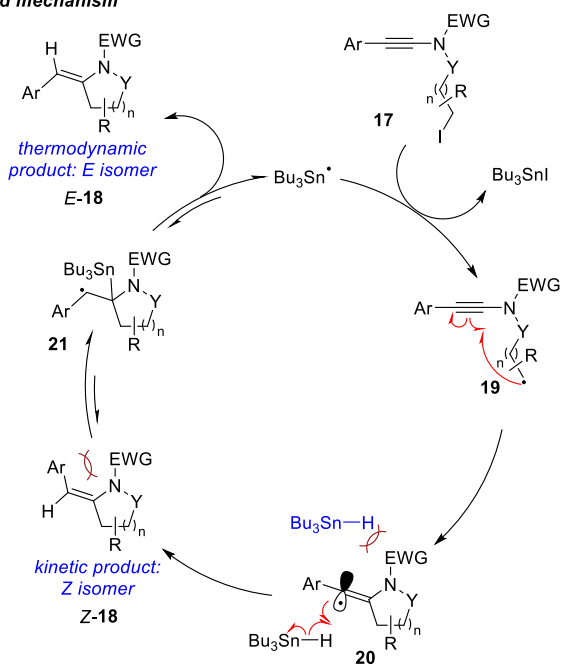
Evano and co-workers recently developed a radical cyclization strategy of ynamides for the versatile synthesis of nitrogen heterocycles **18** bearing an exocyclic double bond. The ynamides bearing an iodoalkyl chain **17** underwent a radical cyclization after initiation with a catalytic amount of AIBN and tributyltin hydride in toluene at 80 °C. Five-, six- and seven-membered ring were obtained (**Scheme 4**). The cyclization was diastereoselective and afforded exclusively the *E*-isomer with the five-membered rings. The transformation was also efficient with the above copper-based photocatalyst, but a lower diastereoselectivity was observed and higher reaction times were required. The transformation displayed broad substrate scope with aryl substituted ynamides. The aryl group on ynamide was found to be necessary as the cyclization was inhibited in its absence; its role was therefore proposed to be a radical stabilizing group. Stereoselectivity decreased upon increasing the chain length between the ynamide and the iodine atom due to low ring strain (**18d-e**). The reaction mechanism started with the homolytic cleavage of C-I bond in **17** to give intermediate **19** which then underwent *n-exo*-dig radical addition on the triple bond, delivering a transient vinylic radical **20**. Upon reduction with tributyltin hydride, this radical gave the kinetically favored *Z* isomer. This kinetic product isomerized to the thermodynamic *E*-product by reversible addition of the tributyltin radical (**21**). Direct formation of *E*-**21** from **20** is not possible because of the steric interaction of the incoming tributyltin hydride and the bulky electron-withdrawing group.<sup>[6]</sup>



**Representative examples**



**Proposed mechanism**

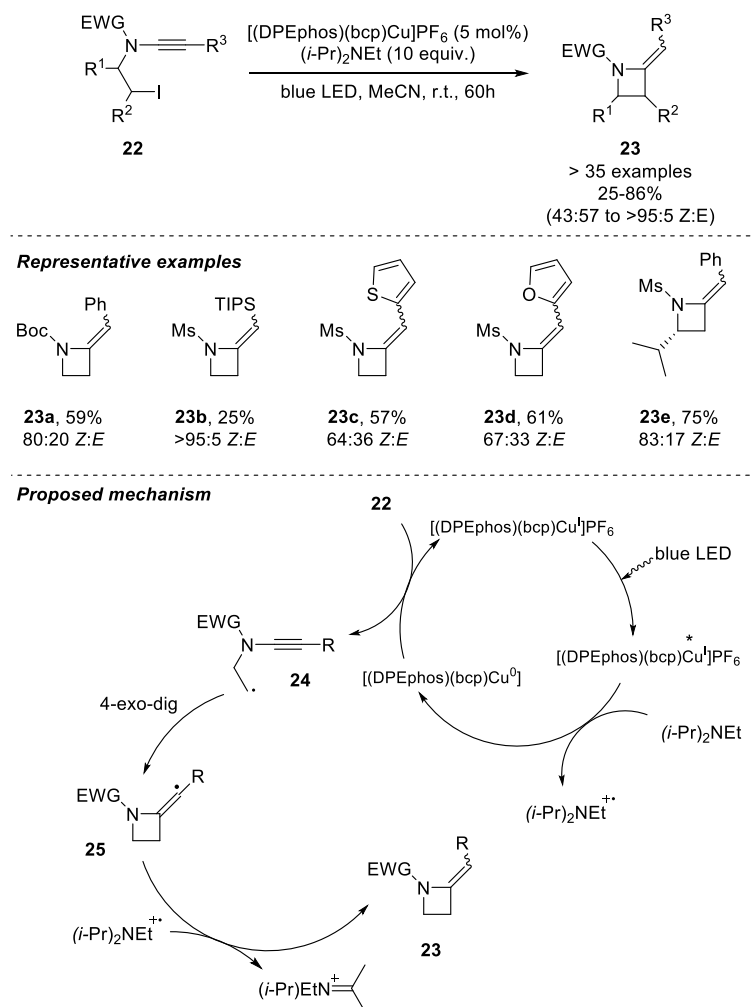


**Scheme 4.** Radical cyclization of ynamides to nitrogen heterocycles



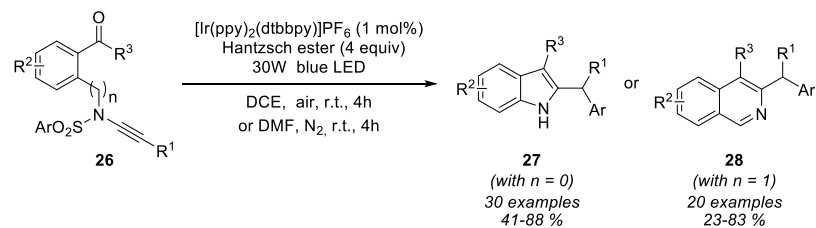
More recently, Moucheron, Van Speybroeck Theunissen and Evano reported the very first anti-Baldwin 4-*exo*-dig cyclization of *N*-iodoethyl-ynamide **22** leading to highly functionalized azetidines **23**. The reaction conditions include [(DPEphos)(bcp)Cu]PF<sub>6</sub> complex (5 mol%) as photocatalyst, Hünig base as sacrificial reductant and blue LED as source of irradiation. They observed an influence of the EWG on the yield of the transformation, since lower yields were obtained with bulky EWG such as Boc whereas yields improved with a mesyl group. The transformation was stereoselective and various substitutions on iodoethyl chain were well tolerated. The nitrogen atom of the ynamide both favored the cyclization by polarizing the triple bond and also stabilized the transient vinyl radical for the cyclization.

A plausible mechanism starts with the excitation of [(DPEPhos)(bcp)Cu]PF<sub>6</sub> by irradiation with visible light and subsequent reduction with the amine generated a transient formal copper(0) complex. The latter reduced the C-I bond in ynamide **22** to generate alkyl radical **24** and regenerated the [(DPEPhos)(bcp)Cu]PF<sub>6</sub> catalyst. Then, **24** underwent anti-Baldwin 4-*exo*-dig cyclization and afforded vinylic radical **25** which abstracted an hydrogen atom from the amine radical cation to finally deliver the azetidine product **23** (Scheme 5).<sup>[7]</sup>

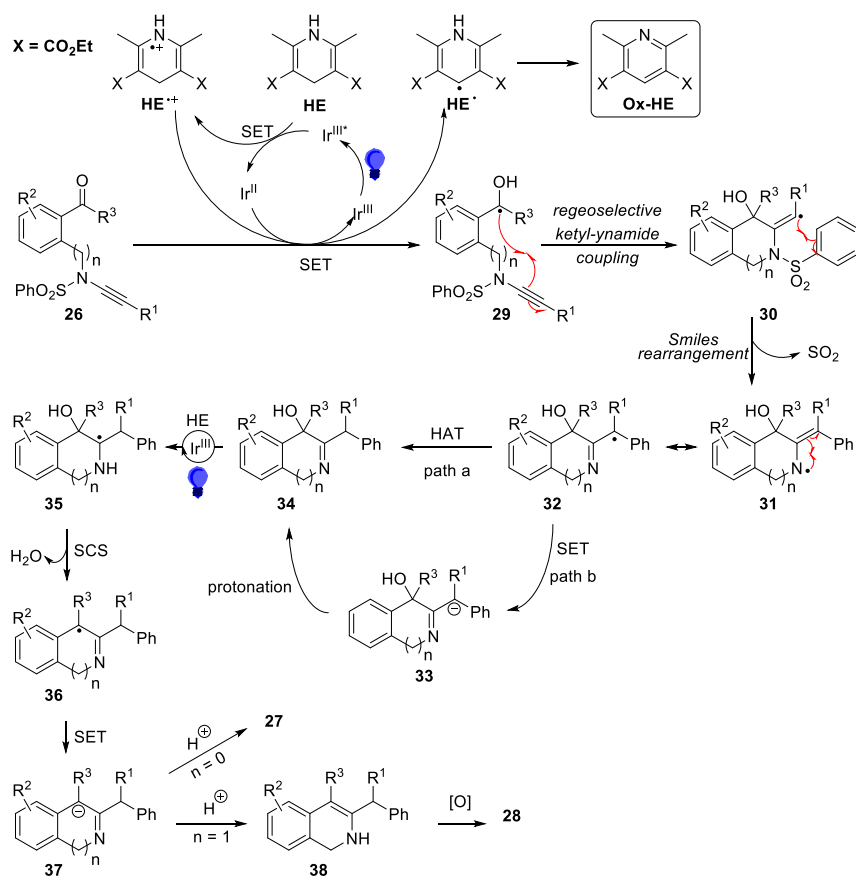


**Scheme 5.** Anti-Baldwin 4-*exo*-dig cyclization for the synthesis of azetidines

In 2020, Ye and coworkers demonstrated a unique photoredox-catalyzed Smiles rearrangement of ynamides **26** to access versatile 2-benzhydrylindoles **27** and 3-benzhydrylisoquinolines **28**. Hantzsch ester was used as reductant in this iridium-based photocatalyzed process, at room temperature for 4 h (**Scheme 6**). The reaction started with the photoactivation of Ir<sup>III</sup> to Ir<sup>III\*</sup> which underwent a SET with the Hantzsch ester (HE) to produce HE<sup>•+</sup> and Ir<sup>II</sup>. The latter then reduced the carbonyl to the corresponding ketyl radical intermediate **29** which underwent a regioselective ketyl-ynamide coupling followed by a Smiles rearrangement, giving access to intermediate **31** via elimination of SO<sub>2</sub> from radical intermediate **30**. Radical **31** is in resonance with radical **32**, which upon SET/protonation or hydrogen atom transfer generated intermediate **34**. This intermediate underwent a second photocatalytic cycle along with spin-center shift and SET, to provide intermediate **39**. For ynamides having n = 0, the protonation of intermediate **39** afforded the indole product **27**, while for n = 1, the protonation followed by dehydrogenative oxidation afforded isoindole product **28**.<sup>[8]</sup>



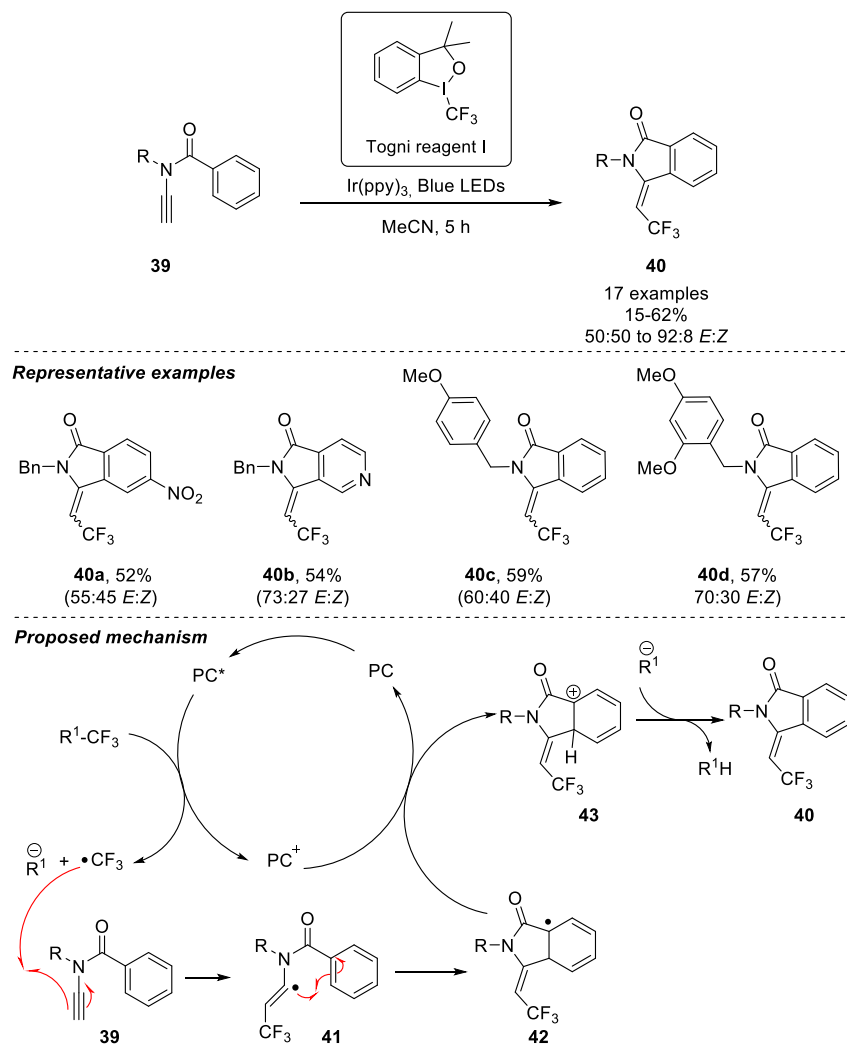
**Proposed mechanism**



**Scheme 6.** Synthesis of 2-benzhydrylindoles and 3-

## benzhydrylisoquinolines

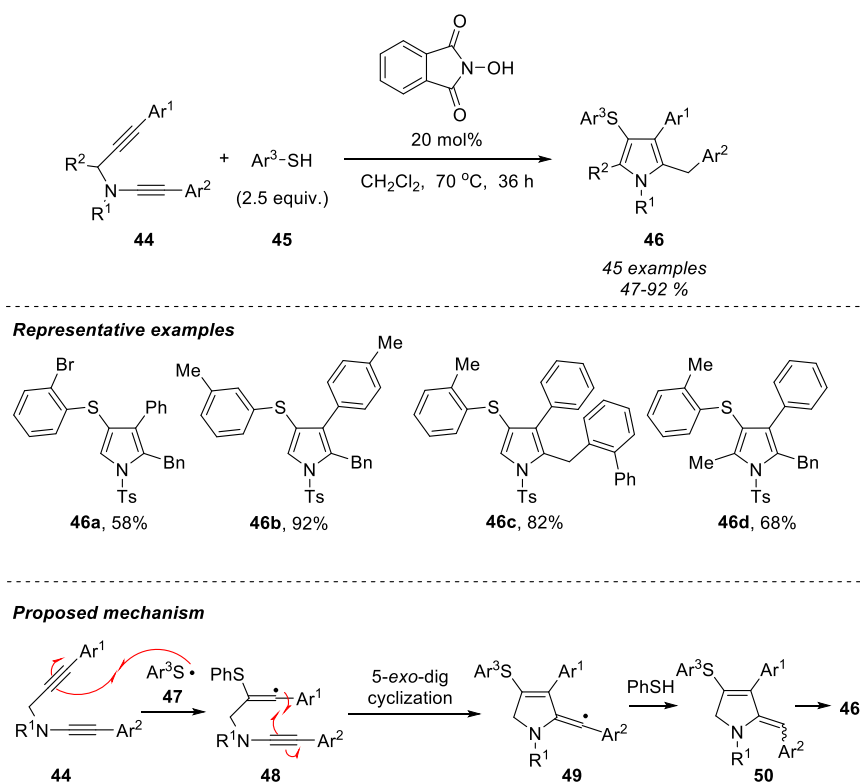
In 2019, Ollivier, Fensterbank and coworkers described a photocatalyzed cyclization reaction triggered by a radical trifluoromethylation of *N*-benzoyl ynamides **39**. The reaction was performed in acetonitrile using iridium photocatalyst and Togni reagent I as the trifluoromethylating reagent (**Scheme 7**). The transformation was highly regioselective, but the *E*-stereoselectivity was relatively modest. The proposed mechanism involved initial photocatalytic generation of CF<sub>3</sub>• radical, which underwent intermolecular addition on *N*-benzoyl ynamides **39** to give vinyl radical **41**. Subsequent radical cyclization took place on the aryl ring affording the isoindolinone product **40** in moderate yields. Theoretical studies revealed that the addition of the CF<sub>3</sub>• radical on the ynamide is a highly exothermic and barrier-free process with  $\Delta G = -33.7$  kcal/mol. The cyclization towards the *N*-benzoyl rather than the *N*-benzyl was calculated to be favored by 9.8 kcal/mol, which explained why cyclization on the benzyl moiety was not observed. However, the *E/Z* configuration of the intermediate radical **41** exhibited only a 1.3 kcal/mol difference.<sup>xl<sup>9</sup></sup>



**Scheme 7.** Photocatalyzed synthesis of trifluoromethyl substituted isoindolinones

Gandon, Sahoo and coworkers have unveiled a sulfur-radical-triggered cyclization of yne-tethered ynamides, wherein the reactivity of simple alkynes exceeded that of ynamides and was supported by DFT

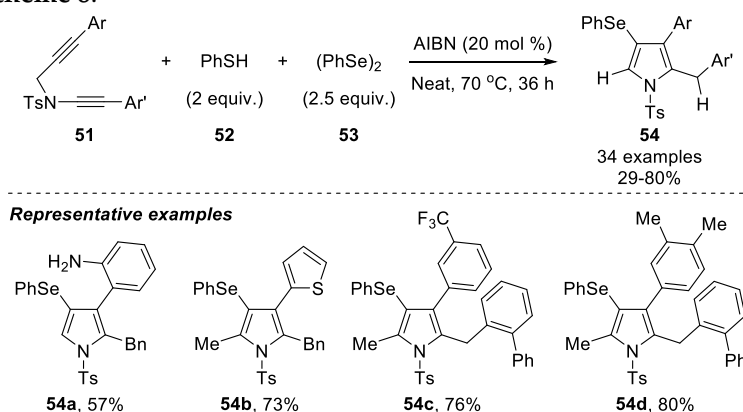
calculations. The reaction of yne-tethered ynamides **44** with arylthiols **45**, initiated by a catalytic amount of *N*-hydroxyphthalimide afforded a variety of 4-thioaryl-pyrroles **46**. The transformation displayed a broad substrate scope and high functional-group tolerance (**Scheme 8**). This radical cyclization started with the initial generation of thiyl radical **47** which attacked the alkyne system of the yne-tethered ynamide **48**, followed by 5-*exo*-dig cyclization with the ynamide core to deliver radical intermediate **49**. This intermediate then abstracted a hydrogen atom from thiophenol to give specie **50** which rapidly tautomerized to the aromatic 4-thioaryl-pyrrole **46**.<sup>[10]</sup>



**Scheme 8.** Thiyl-radical-triggered cyclization of yne-ynamides

Later on, the same authors reported the synthesis of 4-selenylated pyrroles **54** using yne-tethered ynamides **51**, by employing an unconventional

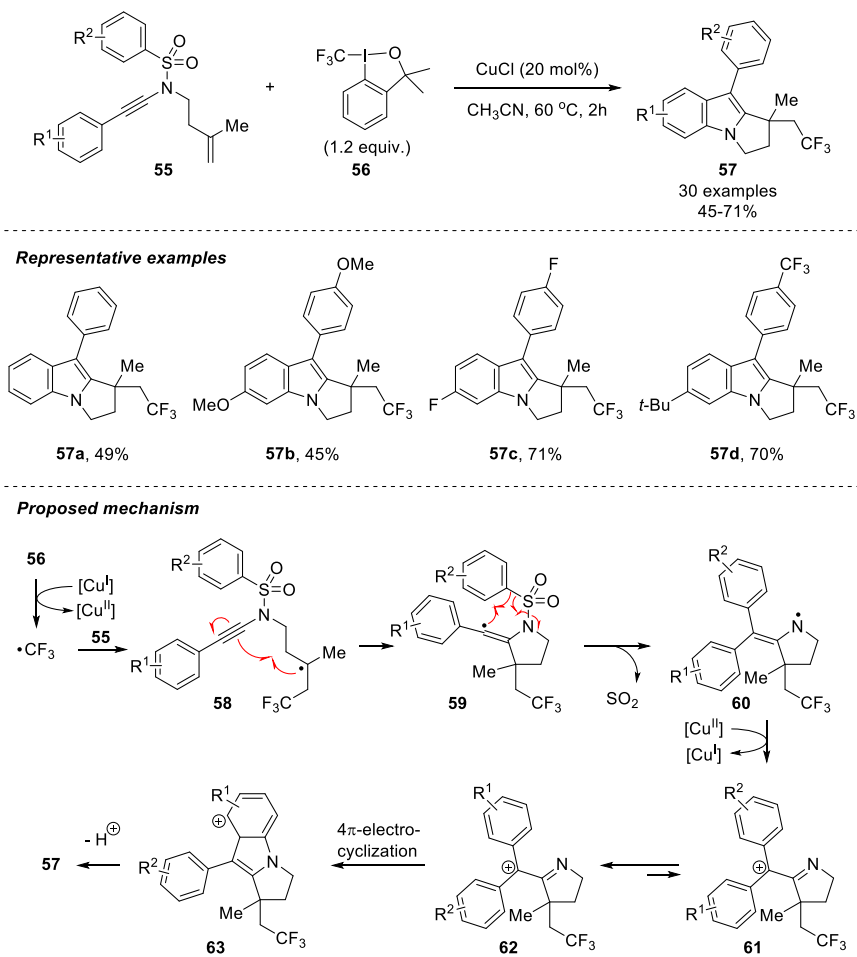
sulfur-to-selenium-to-carbon radical transfer process (**Scheme 9**). They computed that the addition of thiyl radical (derived from **52**) towards the alkyne required 15.8 kcal/mol while the reaction with the diselenide **53** was much more favored (4.0 kcal/mol) and generated preferentially the selenyl radical. Without thiophenol **52**, the reaction did not proceed. Further DFT and HRMS experiments confirmed the necessity of the thiol to generate the selenyl radical which underwent the mechanism depicted in **Scheme 8**.<sup>[11]</sup>



### Scheme 9. Synthesis of 4-selenylated pyrroles

Davies, Shu and co-workers reported the synthesis of [1,2]-annulated indoles **57** by cascade cyclizations of ene-ynamides **55**, promoted by Togni's reagent (**56**) as a trifluoromethyl radical precursor under copper(I) catalysis. The reaction was initiated with a single electron transfer from the Cu(I) catalyst to **56** which led to the  $\text{CF}_3\cdot$  radical and a Cu(II) species. The  $\text{CF}_3\cdot$  radical then reacted with ynamide **55** and afforded radical intermediate **58** which underwent intramolecular cyclization leading to generate radical intermediate **59**. Then an ipso cyclization with arylsulfonamide followed by desulfonylation afforded radical intermediate **60**. The latter was further oxidized with Cu(II) to generate cation **61** and regenerate Cu(I) catalyst. Finally,  $4\pi$ -electrocyclization followed by deprotonation of the cation **63** delivered indole **57**. The mechanism was also studied by DFT calculations, which supported an aza-Nazarov type cyclization following a radical Smiles rearrangement process (**Scheme 10**).<sup>[12]</sup>





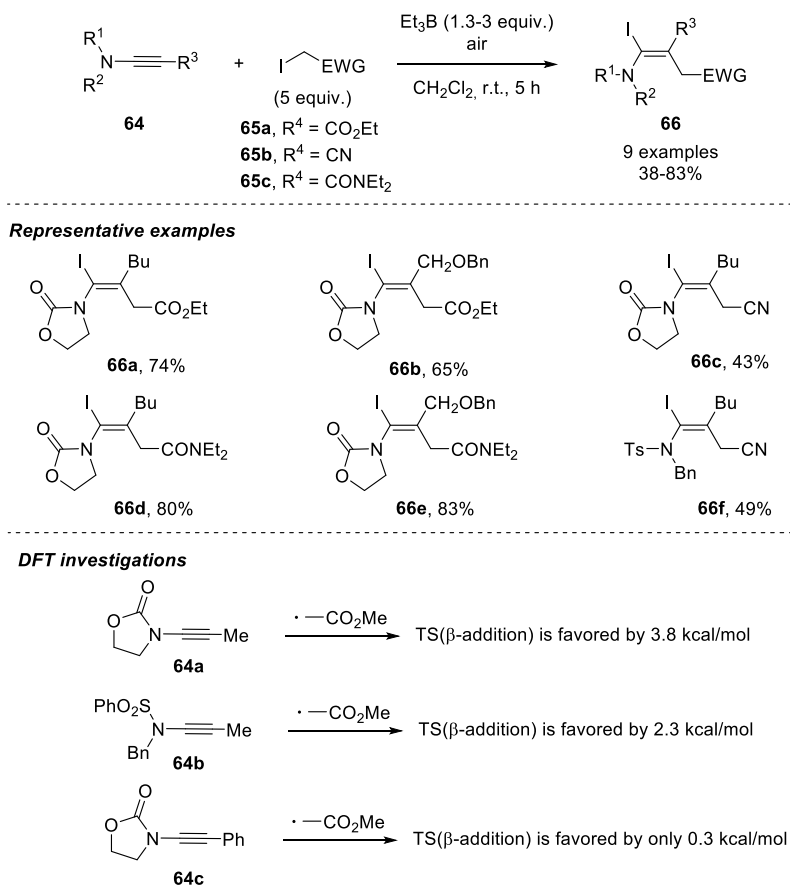
**Scheme 10.** Synthesis of [1,2]-annulated indoles

### 1.3 INTERMOLECULAR RADICAL REACTIONS

### 1.3.1 C-C bond formation

In 2020, Bertrand, Feray and co-workers reported an intermolecular addition of electron-deficient carbon-based radicals on ynamides.<sup>[13]</sup> These electrophilic species, generated from ethyl  $\alpha$ -iodoacetate **65a**,  $\alpha$ -iodoacetonitrile **65b** or  $\alpha$ -iodo-*N,N*-diethylacetamide **65c** in the presence of triethylborane as radical initiator are added in a regioselective manner to the  $\beta$ -position of ynamides **64**. Persubstituted  $\alpha$ -iodo-enamides **66** are obtained in moderate to high yields as single isomer as long as the terminal position of the ynamide is substituted by an alkyl chain. On the other hand, the reaction with phenyl-substituted ynamides is much less selective and yield four different isomers.

DFT investigations of the reaction mechanism demonstrated that  $\beta$ -selective addition was favored by 3.8 kcal/mol in the case to oxazolidinone-based ynamides substituted at the terminal position by an alkyl group (**64a**), whereas 2.3 kcal/mol were calculated in the case of sulfonamide-base-ynamides (**64b**). With the aryl-substituted ynamide (**64c**), the energy difference between the  $\alpha$ -selective and  $\beta$ -selective transition states is only 0.3 kcal/mol, in line with the experimental results (Scheme 11).

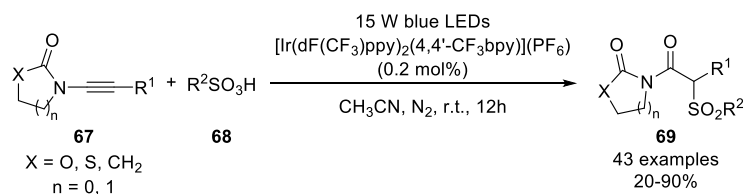


**Scheme 11.** Radical trans  $\alpha$ -iodo- $\beta$ -alkylation of ynamides.

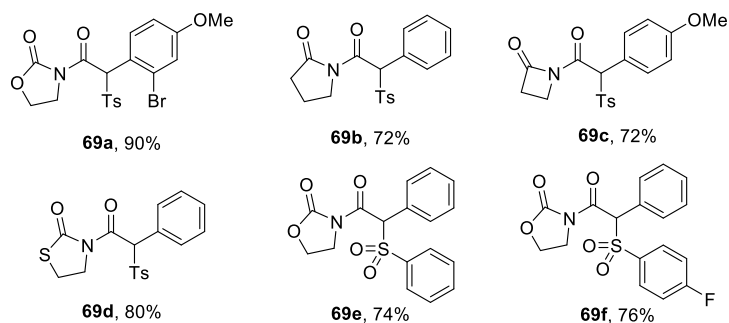
### 1.3.2 C-O bond formation

Yue, Feng and co-workers reported in 2019 an efficient photoinduced oxo-sulfonylation of ynamides with easily-available and inexpensive sulfonic acids.<sup>[14]</sup> A variety of  $\alpha$ -sulfonylated amides **69** were obtained in moderate to high yields by a photoinduced radical cascade electrophilic addition / rearrangement of sulfonyl radical under iridium catalysis. In general, the reaction is favored with aromatic-ynamides substituted with electron-donating groups, while lower yields were obtained with electron-

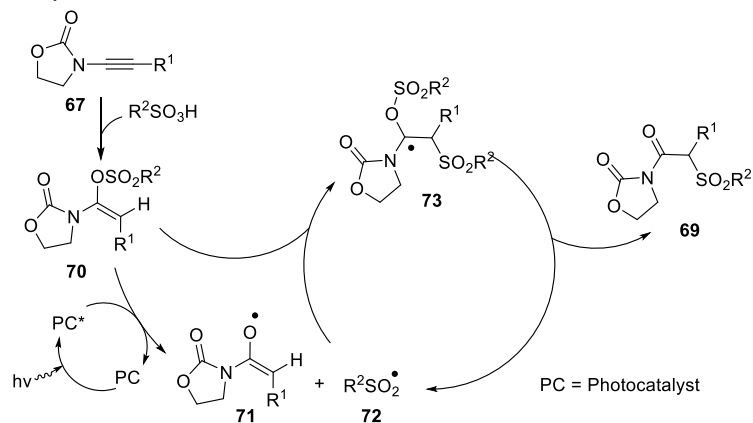
withdrawing groups. The reaction was also applied to fused aromatic and heterocyclic substituents as well as the sulfonic acid partner. The proposed mechanism is based on experimental observations. Initially, electrophilic addition of sulfonic acid **68** to ynamide **67** regioselectively provided vinylsulfonate **70**. Upon reaction with the excited photocatalyst, the C–S bond of **70** underwent homolytic cleavage and generated an enol radical **71** as well as a sulfonyl radical **72**. Subsequently, the electrophilic S-centered radical **72** selectively added to the electron-rich alkene moiety of **70** and promoted the generation of the desired product **69** via a smooth  $\beta$ -scission of radical intermediate **73** while regenerated sulfonyl radical **72** for the next reaction cycle (**Scheme 12**).



**Representative examples**



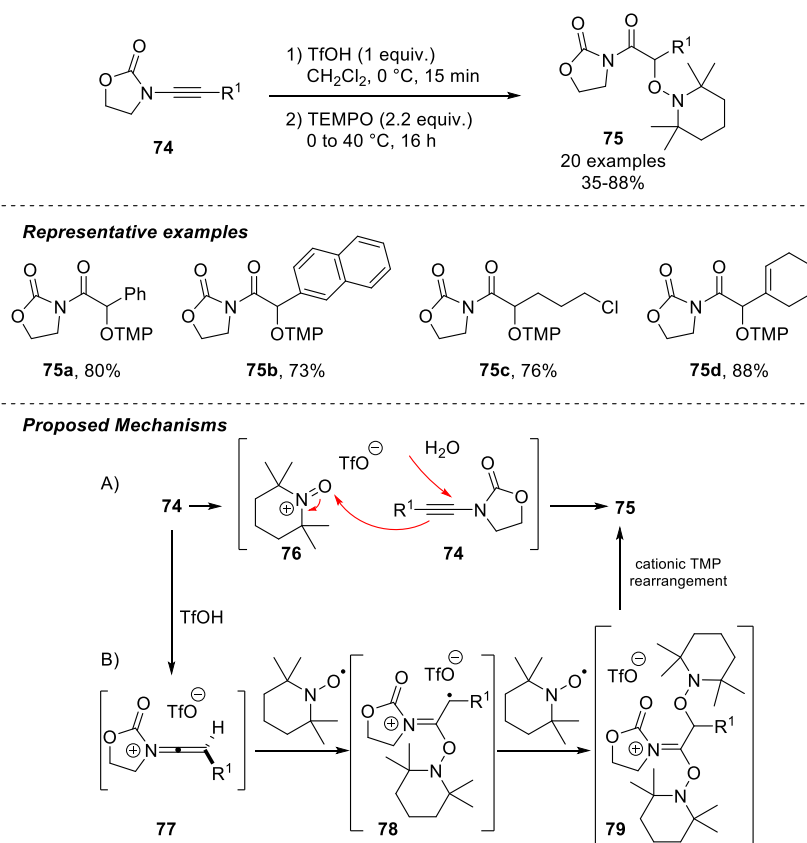
**Proposed Mechanism**



**Scheme 12.** Oxo-sulfonylation of ynamides with sulfonic acids

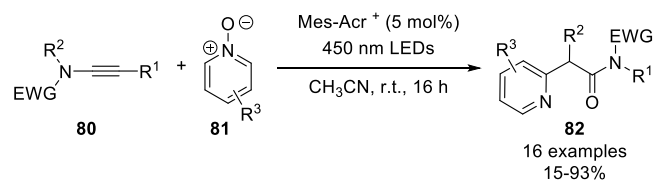
In 2017, Maulide and co-workers reported the hydrative aminoxylation of ynamides **74** with TEMPO under acidic conditions to deliver product **75** in moderate to good yields.<sup>[15]</sup> Two possible reaction mechanisms were experimentally and theoretically identified (**Scheme 13**). In first pathway **A**, it was observed that reaction of TEMPO<sup>+</sup> **76** with ynamide in the

presence of water delivered product **75** in 62% yield. This unexpected reactivity confirmed the ability of **76** to act as a cationic O<sup>+</sup>-donor and to activate ynamides. In pathway **B**, treatment of ynamide **74** with TfOH led to keteniminium ion **77**, which then reacted with TEMPO to give the Pinner type intermediate **78**. This radical recombined with another equivalent of TEMPO to form intermediate **79** and then a cationic rearrangement of the TMP<sup>+</sup> fragment with a thermodynamically favored heterolytic O–N bond cleavage (–95.0 kcal/mol) delivered product **75**.

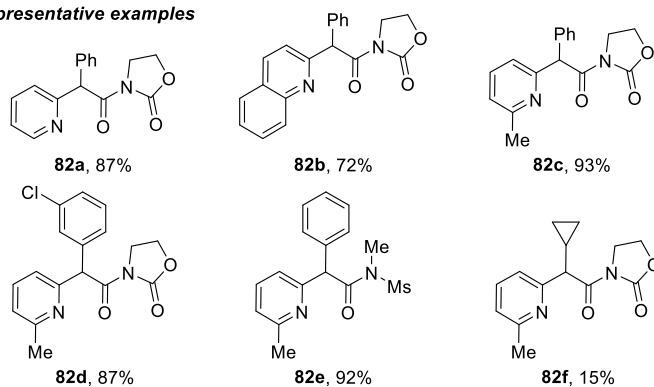


**Scheme 13.** Hydrative aminoxylation of ynamides

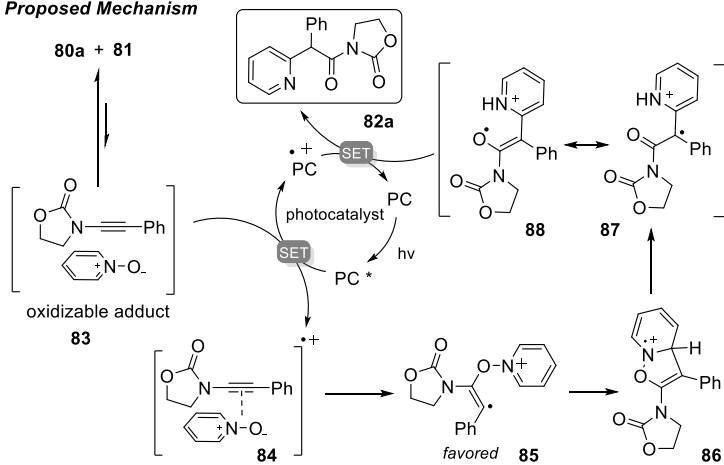
In 2019, Deng and co-workers documented a facile and scalable photocatalyzed ortho-alkylation of pyridine *N*-oxides with ynamides and arylacetylenes.<sup>[16]</sup> Variation of the ynamide **80** and/or pyridine *N*-oxide **81** substitution were well tolerated and the products **82** were obtained in yields ranging from 15 to 93%. The proposed mechanism implied the formation of an oxidizable ynamide/pyridine *N*-oxide adduct **83** with an oxidation onset of 1.32 V. Upon photocatalytic irradiation and SET, it radical cation **84** was formed and underwent nucleophilic attack by the oxygen of pyridine *N*-oxide, leading to radical species **85**. The regioselective formation of this cationic vinyl radical intermediate was favored due to the resonance stabilization imparted by the aromatic group. Then, radical cyclization and N-O bond cleavage delivered intermediates **87** and **88** (in resonance equilibrium). Later, they underwent a second SET event to regenerate the photocatalyst in its ground-state and delivered  $\alpha$ -(2-pyridinyl) benzyl amide product **82** (Scheme 14).



**Representative examples**



**Proposed Mechanism**

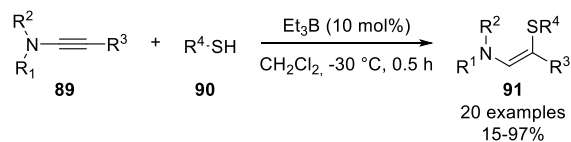


**Scheme 14.** Photocatalysis addition of pyridine *N*-oxides to ynamides

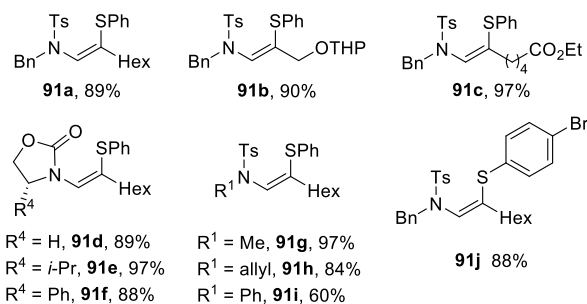


### 1.3.3 C-S bond formation

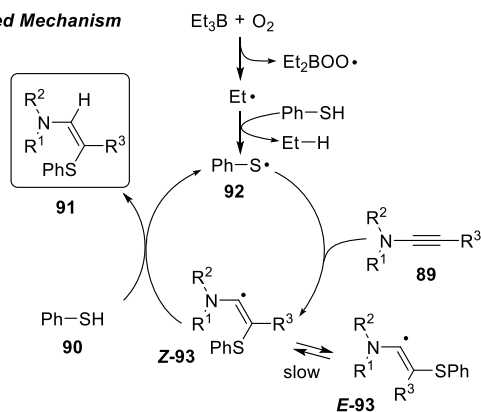
Yorimitsu, Oshima and co-workers developed in 2010 a regio- and stereoselective radical additions of thiols to various ynamides with the aid of triethylborane as a radical initiator. <sup>[17,18]</sup> The experimental study suggested that the radical addition of electron-deficient arenethiols proceeded smoothly in 88-93% yields, while reactions with electron-rich arenethiols were much less efficient. In contrast, the functional group tolerance on the ynamide was very broad and the reaction proceeded smoothly in good yields. From a mechanistic point of view, it was proposed that an ethyl radical (generated from triethylborane in the presence of oxygen) abstracted a hydrogen atom from benzenethiol, leading to thiyl radical **92**. The electron-deficient radical immediately reacted with ynamide **89** to generate vinyl radical **93**. The *Z*-isomer (**93**) selectively abstracted the hydrogen atom from benzenethiol **90** to yield product **91**, and regenerated a thiyl radical to complete the radical chain process (Scheme 15).



**Representative examples**



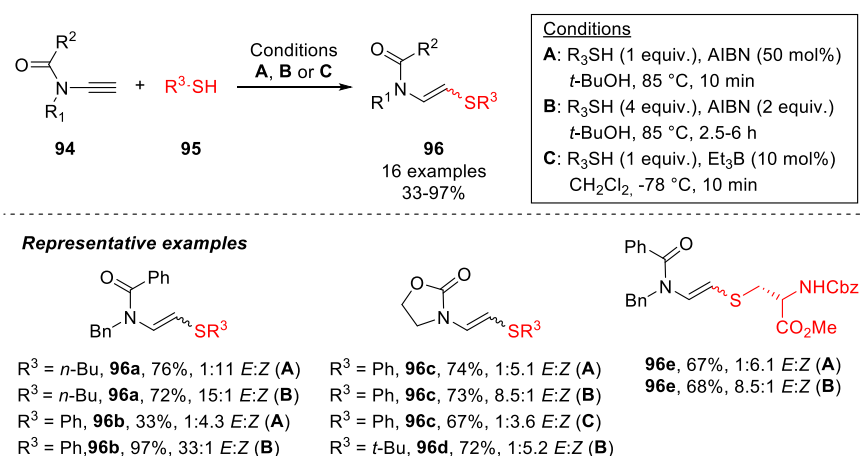
**Proposed Mechanism**



**Scheme 15.** Radical additions of thiols to ynamides

In 2010, Castle and co-workers explored a method for radical additions of thiols **95** to terminal ynamides **94**.<sup>[19]</sup> This approach provides an advantageous way to selectively furnish both *cis*- and *trans*- $\beta$ -thioenamides **96** by choosing the appropriate conditions (**Scheme 16**). Addition of excess thiol **95** (4 equiv) to acyclic amide-derived ynamide **94a** in refluxing *t*-BuOH with AIBN as initiator afforded the (*E*)- $\beta$ -thioenamide **96a** as major product in 72% yield with 15:1 *E*:*Z* ratio after 3–6 h. In contrast, the use of only 1 equiv. of thiol and 0.5 equiv of AIBN led

to (*Z*)-**96a** in 76% yield with 1:11 *E*:*Z* ratio after only 10 min. Mechanistic study showed that this reaction involved vinyl radicals intermediates that were in rapid equilibrium, and that the less hindered radical abstracted an hydrogen atom from the thiol. The reason for this difference might be that the *Z* adduct predominated under kinetically controlled conditions (1 equiv. of thiol and short reaction times), whereas the *E* adduct emerged under thermodynamically controlled conditions (excess of thiol and longer reaction times). The proposed mechanism was confirmed by control experiment subjecting a 1:3.6 *E*:*Z* mixture of **96a** to thermodynamic conditions **B**, and isomerization was observed up to 5.3:1 *E*:*Z*.



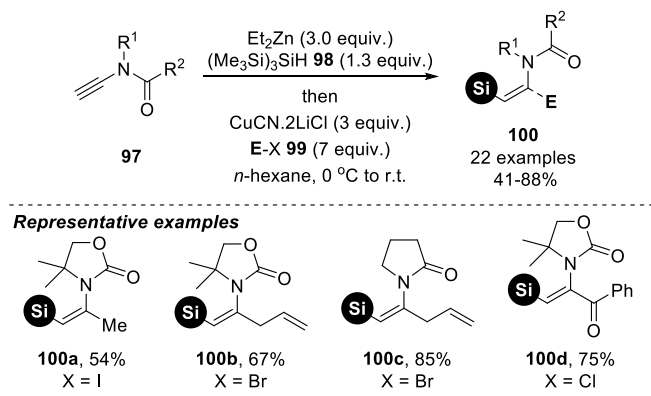
**Scheme 16.** Additions of thiyl radicals to terminal ynamides

### 1.3.4 *C-Si* and *C-Ge* bond formation

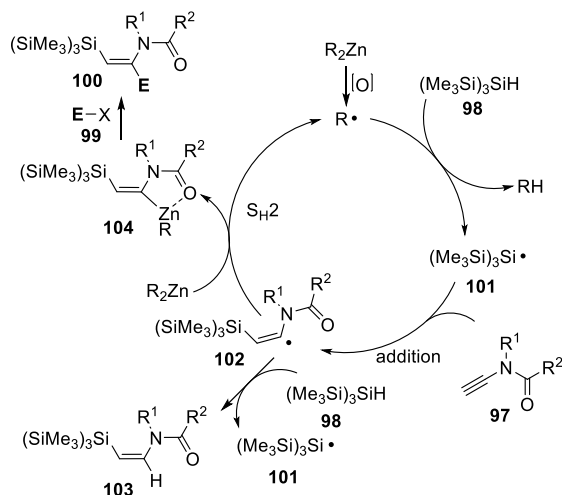
In 2014, Perez-Luna and co-workers described the silylzincation of terminal ynamides **97** through a radical-chain process involving (Me<sub>3</sub>Si)<sub>3</sub>SiH **98** and R<sub>2</sub>Zn.<sup>[20]</sup> This *trans*-selective silylzincation protocol of C=C multiple bonds provided a straightforward access to (*Z*)- $\alpha,\beta$ -disubstituted enamides via subsequent functionalization of the intermediate Csp<sup>2</sup>-Zn and Csp<sup>2</sup>-Si bonds (**Scheme 17**).

The reaction proceeded smoothly with terminal ynamides **97** bearing amides or carbamates fragments and delivered the corresponding

enamides **103** in good to excellent yields with high stereoselectivities, after aqueous workup. As a side note, this method was limited to terminal ynamides. The reactivity of the zinc intermediates **104** as nucleophiles in the formation of C-C bond reactions was further explored. Experiments showed that in the presence of CuCN·2LiCl, these reagents reacted smoothly with a range of electrophiles, leading to the corresponding products **100** in 41 to 88% yields. The proposed mechanism started with the formation of a silyl radical **101** via H-atom transfer between silane **98** and ethyl radical, which then added regioselectively at the terminal position of the C≡C bond to form the radical intermediate **102**. In the presence of water or upon aqueous workup, the *Z*-hydrosilylated product **103** was formed. Alternatively, **102** could react with Et<sub>2</sub>Zn by homolytic substitution (SH<sub>2</sub>) at the zinc atom to afford β-zincated vinylsilane compound **104** (and then **100** upon reaction with electrophile) along with ethyl radical that could propagate the radical chain.



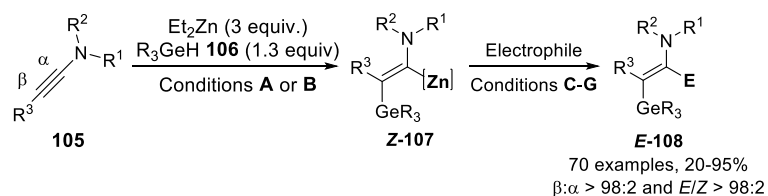
**Proposed Mechanism**



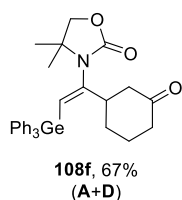
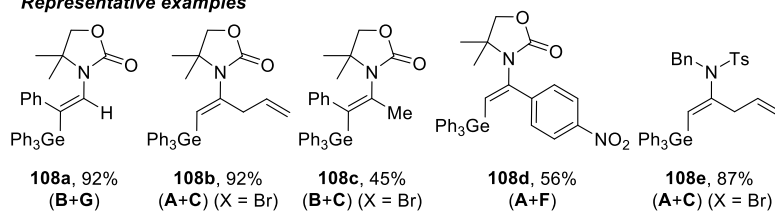
**Scheme 17.** *Trans*-selective radical silylzincation of ynamides

In 2018, this method was further extended to the gerymlyzincation of ynamides **105** using a combination of a germanium hydride **106** and diethylzinc in THF.<sup>[21]</sup> A wide scope of 70 examples was reported and the reaction was efficient with both terminal and internal ynamides. Several sets of conditions (**A-G**) were disclosed, allowing the *cis*-stereoselective gerymlyzincation (**Z-107**), however the  $\beta$ -regiocontrolled gerymlyation was achieved exclusively with triphenylgermane. Interestingly, the vinyl-zinc intermediate **Z-107** generated in-situ can be subjected to Cu(I) or Pd(0)

catalyzed transformations (**E-108**) such as halogenation, nucleophilic substitution, cross-coupling or 1,4-addition, with complete retention of the double bond configuration (**Scheme 18**). The difference of stereoselectivity observed between silylzincation and germylzincation (**E-104** vs **Z-107**) was attributed to the change of solvent from *n*-hexane to THF between the two procedures and it was confirmed experimentally by performing the silylzincation in THF with a 10:90 *Z*:*E* ratio. A similar reaction mechanism was proposed: it started with the formation of the germyl radical which upon addition on ynamide generated the vinyl radical **Z-109** which was in equilibrium with its isomer **E-109**. In that case, THF prevented the Lewis-pair formation and the *Z*-to-*E* interconversion was faster than Zn-atom transfer, which favored the Zn-atom transfer to **E-109** to form **Z-107** and regenerated the ethyl radical.



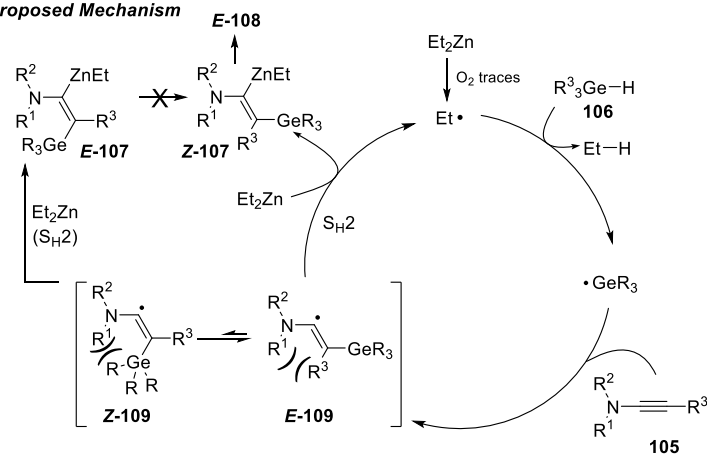
**Representative examples**



**Conditions**

- A:** R<sup>3</sup> = H, THF, 0 °C  
**B:** R<sup>3</sup> ≠ H, *n*-Hexane, 40 °C  
**C:** CuCN.2LiCl (2.0 equiv.), E-X, THF, -30 °C to 0 °C / r.t.  
**D:** CuCN.2LiCl (3.0 equiv.), cyclohexenone (7.0 equiv.), Me<sub>3</sub>SiCl (14.0 equiv.), -78 °C to r.t.  
**E:** CuTC (10 mol%), THF, -30 °C to r.t.  
**F:** Pd<sub>2</sub>dba<sub>3</sub> (5 mol%), (2-Fur)<sub>3</sub>P (10 mol%), THF, 65 °C  
**G:** E = H/D, NH<sub>4</sub>Cl/NH<sub>3</sub> or ND<sub>4</sub>Cl/D<sub>2</sub>O

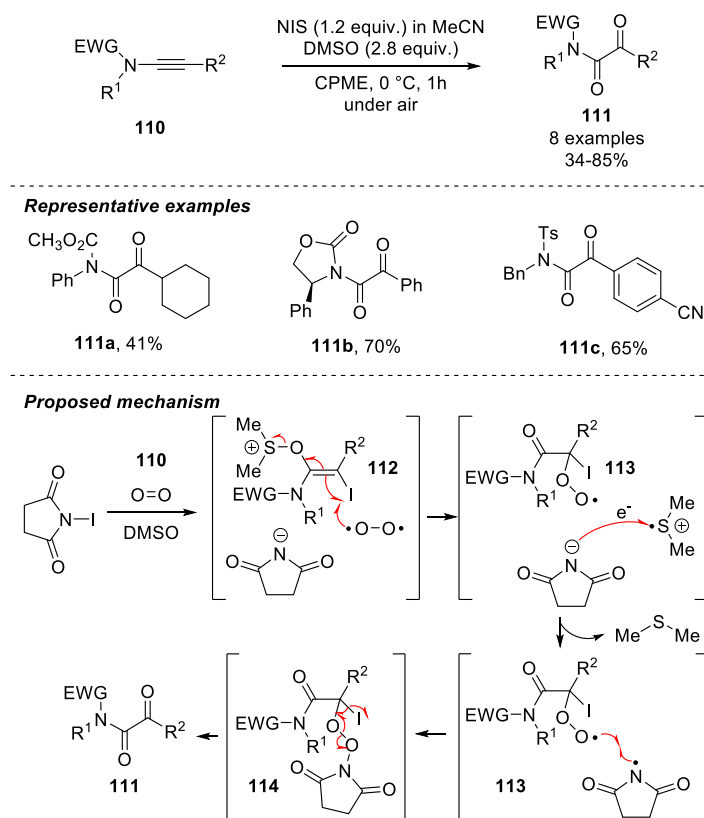
**Proposed Mechanism**



**Scheme 18.** Regio- and stereoselective radical germylzincation of ynamide

## 1.4 OXIDATION OF YNAMIDES

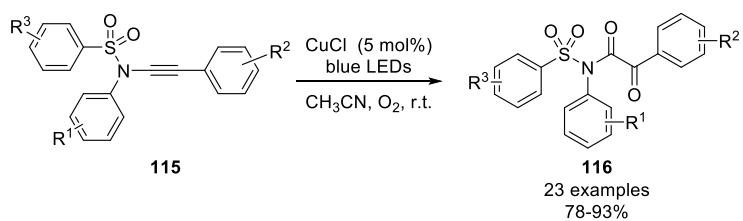
In 2014, an oxidation of ynamides involving a radical process was reported by Iwasawa and co-workers.<sup>[22]</sup> In the presence of *N*-iodosuccinimide, DMSO and air, ynamides **110** were smoothly oxidized to  $\alpha$ -keto-imides **111** in moderate to good yields (**Scheme 19**). The proposed reaction mechanism started with the reaction of NIS as  $I^+$  source to activate the ynamide, leading to oxysulfonium **112**. This intermediate further reacted with molecular oxygen to form peroxide **113** and a thiyl radical cation. The succinimide anion delivered an electron to the thiyl radical and the succinimide radical combined with the peroxide **113** to give the intermediate **114**, and then  $\alpha$ -keto-imide **111**.



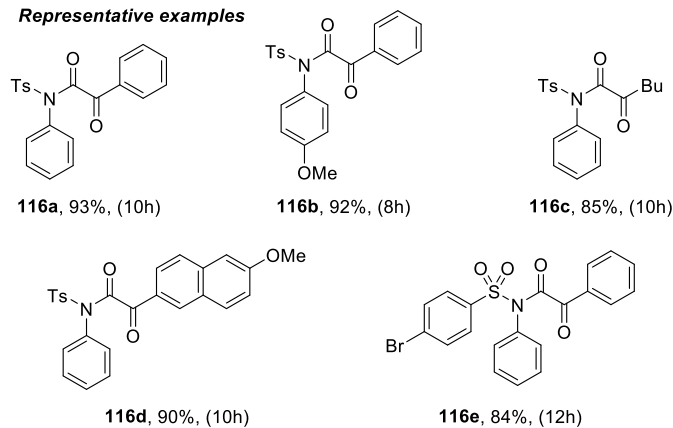


**Scheme 19.** Oxidation of ynamides for the synthesis of  $\alpha$ -keto-imides

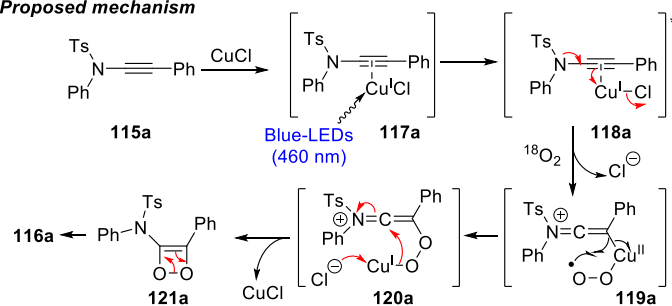
In 2017, Hwanga and co-workers proposed a visible light-mediated, Cu-catalyzed aerobic oxidation of ynamides at room temperature using molecular oxygen as the oxidant.<sup>[23]</sup> The reaction was effective with sulfonamide derived ynamides **115**, it was compatible with a wide range of functional groups, and was scalable to gram scale still with high yields (78–92%). The proposed mechanism involved coordination of the Cu(I) complex to the  $\pi$ -system of ynamide (**117**), then under blue light irradiation, the photo-excited Cu(I)- $\pi$ -complex **118** reacted with oxygen to deliver a Cu(II) peroxo-complex **119**. This complex rearranged to form the Cu(I) species **120**, which next underwent cyclization into the intermediate **121**, and regenerated the CuCl catalyst. Subsequent O–O bond cleavage gave the desired compound **116** (Scheme 20).



*Representative examples*



*Proposed mechanism*



**Scheme 20.** Visible light-mediated copper(I)-catalyzed aerobic oxidation of ynamides

Overall, radical reactions of ynamides are powerful tools that allow creation of carbon-carbon and carbon-heteroatom bonds, either intramolecularly or intermolecularly, with excellent control over the regio- and stereoselectivity. Classical initiation conditions were initially explored but more recent research demonstrated the uniqueness of photocatalytic conditions (including reactions catalyzed by precious metal- or organic photocatalysts, or even EDA-complexes) especially in terms of functional group compatibility and unprecedented cyclization pathways. Radical chemistry of ynamides is still relatively confidential but the diversity of reaction mechanisms should continue to open exciting new avenues.

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