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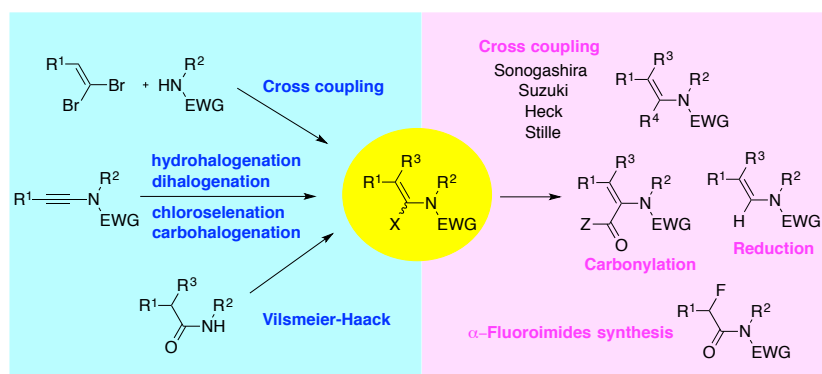
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# $\alpha$ -Haloenamides Synthesis and Subsequent Transformations

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**Abstract** This short review is aimed at giving an updated overview of  $\alpha$ -haloenamides synthesis.  $\alpha$ -Haloenamides constitute a versatile sub-class of enamides. They can be prepared from ynamides, acetamides, or *gem*-dibromo olefins in the presence of *N*-nucleophiles and easily converted into more elaborated structures through halogen-metal exchange and transition metal catalyzed cross-coupling reactions.

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##### 3.4.4 Palladium-catalyzed intramolecular cyclization

### 4 Conclusion

**Key words**  $\alpha$ -Haloenamides, synthesis, ynamides, halogenation, cross-coupling reactions

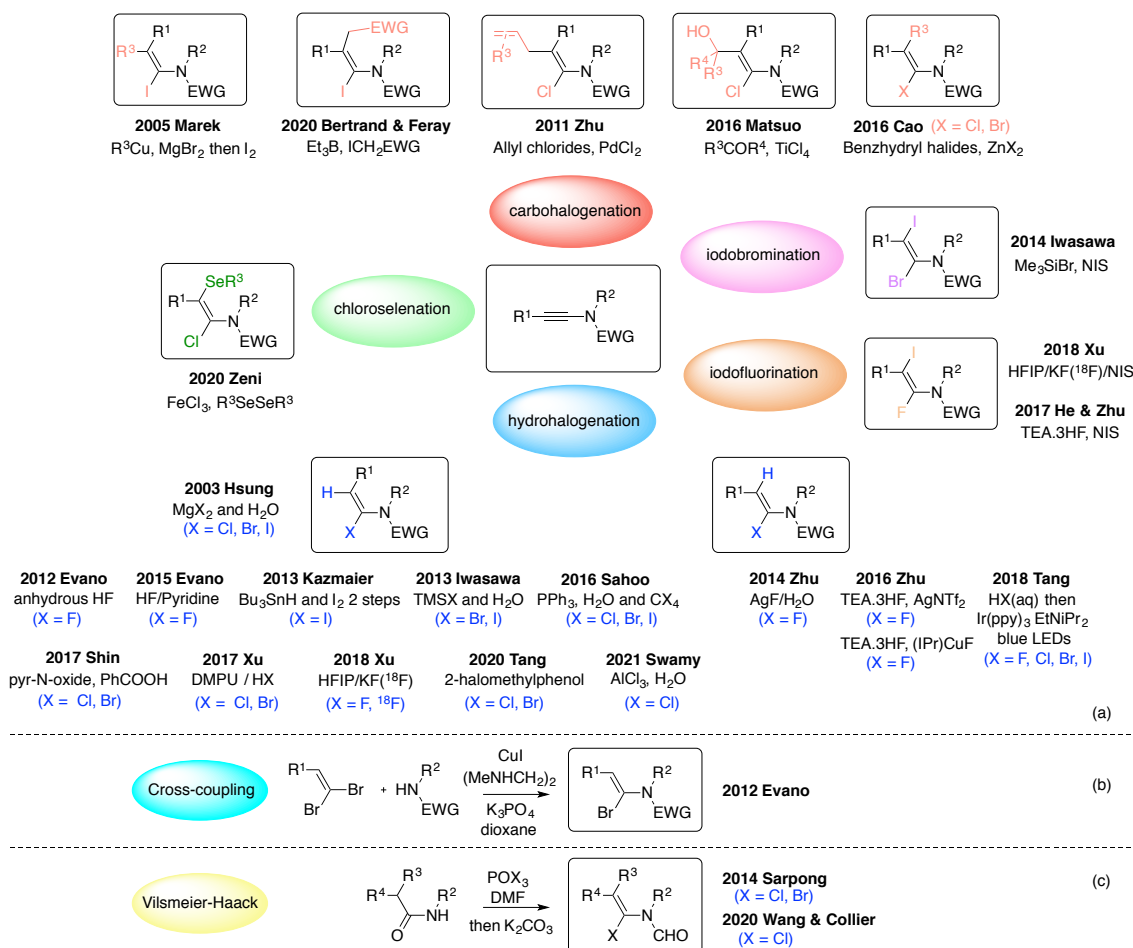
## 1 Introduction

Over the last years, the interest in enamides, powerful synthetic intermediates for organic synthesis, has been growing exponentially. In comparison to enamines, well-known functional groups since the pioneering work realized by Stork in the 1950s,<sup>1</sup> enamides are stable electron rich double bonds that are commonly used in organic synthesis for incorporation of nitrogen functionality.<sup>2</sup> The stability of these units, related to their diminished enaminic reactivity, as the result of the presence of electron-withdrawing group on the nitrogen atom, is well demonstrated by their occurrence in various bioactive natural products.<sup>3</sup>  $\alpha$ -Haloenamides are versatile variants of

enamides. Due to their weakly bonded halogen atom, they can easily be converted into more elaborated structures through halogen-metal exchange and transition-metal-catalyzed cross-coupling reaction. In the first part of this short review, the different methodologies developed for the synthesis of  $\alpha$ -haloenamides are summarized since the pioneering work of Hsung in 2003. The second part focuses on their use for subsequent organic transformations.

## 2 $\alpha$ -Haloenamides synthesis

If one excludes cross-coupling reactions of *gem*-dibromo olefins in the presence of *N*-nucleophiles (Scheme 1(b)) and Vilsmeier-Haack reactions (Scheme 1(c)), all the strategies developed for  $\alpha$ -haloenamides synthesis start from ynamides (Scheme 1(a)).<sup>4</sup>



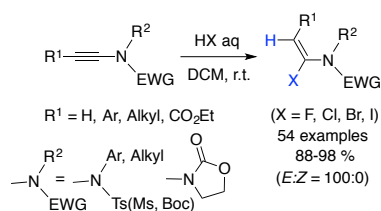
### Scheme 1 $\alpha$ -Haloenamides synthesis. 2.1 Hydrohalogenation of ynamides

#### 2.1.1 *cis*-Hydrohalogenation of ynamides

It has already been pointed out that Hsung and collaborators were the first to develop an efficient method to synthesize  $\alpha$ -iodo, bromo- and chloroenamides (*vide infra*). This section does not respect chronology but rather the nature of the halide and the range of reagents from the simplest to the most sophisticated ones.

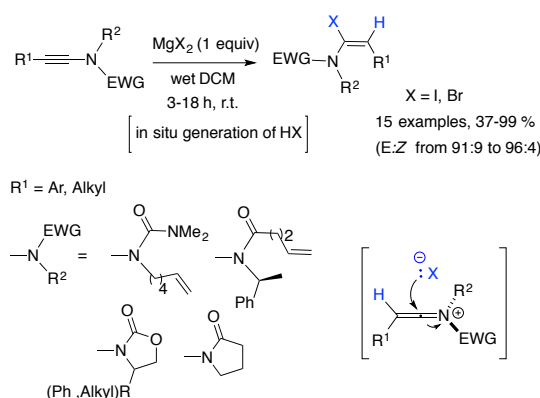
The use of gaseous HCl and HBr in direct hydrohalogenation experiments mostly resulted in poor regio- and stereoselectivity. Commercially available HX reagents solutions exist either in low concentration in ethers or in protic media. The main drawback with the latter is that the protic solvent lowers the nucleophilicity of halide anions and furthermore competes with HX in the nucleophilic addition thus resulting in poor efficacy. In this respect, the use of HX solution in aprotic medium was shown to be the right method to prevent competitive solvolysis reaction and improve reactivity. In fact, as reported in the following paragraph, most efficient methodologies involve hydrogen halides used in biphasic medium or generated in situ in wet solvent, aprotic solvent or even delivered from their association with basic solvent.

Tang and co-workers showed that (*E*)- $\alpha$ -haloenamides can be provided directly via regioselective hydrohalogenation of ynamides using aqueous hydrogen halides in two-phase systems.<sup>5</sup> Notably, the solubility of solvents in water has a significant impact on the yield and reaction time. The highest yield and stereoselectivity were observed using immiscible DCM (dichloromethane), with reaction time between 1.5 to 2 h (Scheme 2). These hydrohalogenation reactions showed high functional-group compatibility.



**Scheme 2**  $\alpha$ -Halogenation in biphasic medium.

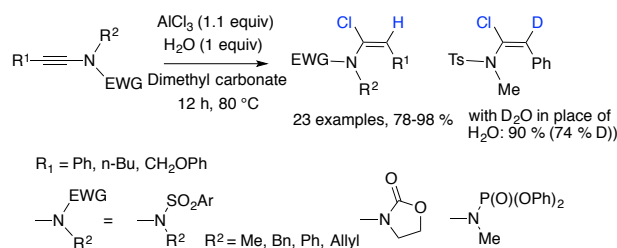
Hsung and co-workers reported the first efficient synthesis of haloenamides from ynamides in 2003.<sup>6</sup> They showed that in situ generation of HX from magnesium halides and traces of H<sub>2</sub>O afforded the corresponding  $\alpha$ -haloenamides with good yields and selectivity (Scheme 3). The stereochemical outcome of the addition is dictated by the polarization of the triple bond caused by nitrogen. As in the previous process, the halide anion automatically unites with the positively charged  $\alpha$ -carbon in the ketene iminium intermediate. The latter possesses a linear geometry, with its upper face sterically hindered by the R<sup>1</sup> group, thus favoring *syn* approach of the nucleophile. Wet DCM was found to be the solvent of choice for this regioselective hydrohalogenation of ynamides allowing the reaction to progress at ambient temperature in the presence of MgI<sub>2</sub> and MgBr<sub>2</sub>.



**Scheme 3** Magnesium halides for the synthesis of (*E*)- $\alpha$ -iodo, bromo and chloro-enamides.

The use of MgCl<sub>2</sub>•6H<sub>2</sub>O required higher reaction temperatures to complete the reaction, typically from 65 to 100 °C. Thus, in this case 1,2-dichloroethane was the preferred solvent. Attempts to use metallic halides like CuI or ZnCl<sub>2</sub> failed. CuI led to undesired products, ZnCl<sub>2</sub> promoted ynamide hydrolysis, while NaBr induced no reaction. The scope of the transformation was probed using different ynamides as substrates. Ynamides derived from pyrrolidinone or oxazolidinones were converted to the corresponding  $\alpha$ -haloenamides in high yield and with high levels of regio- and stereochemical control. The methodology is compatible with the use of acyclic ynamides. It is to be noted that modest yield was observed in the case of urea-based ynamides due to their slow conversion rate.

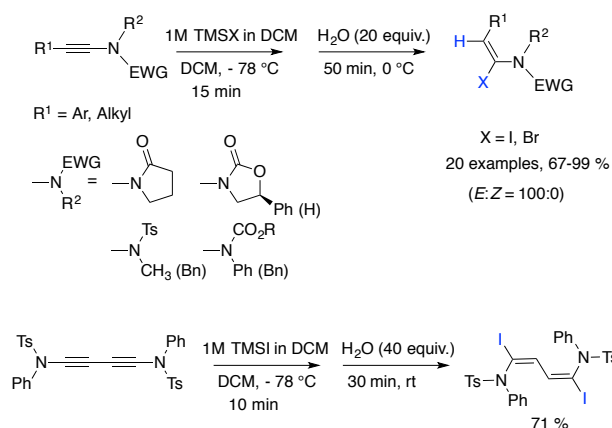
Very recently, Swamy and co-workers have developed a simple approach for the regio- and stereo-selective synthesis of (*E*)- $\alpha$ -chloroenamides by hydrochlorination of ynamides using AlCl<sub>3</sub>/H<sub>2</sub>O as the reagent for hydrochlorination in dimethyl carbonate as solvent (Scheme 4).<sup>7</sup> The method is compatible with ynamides bearing different electron-withdrawing groups. Indeed, replacing the sulfonyl group by a carbonyl or phosphoryl group does not affect the regio- and stereo-selectivity, affording the corresponding products in excellent yields.



**Scheme 4** Hydrochlorination of ynamides using AlCl<sub>3</sub>/H<sub>2</sub>O system.

The reaction conducted in presence of D<sub>2</sub>O instead of H<sub>2</sub>O in dimethyl carbonate suggested the crucial role of water as the proton source in the reaction. In this case, 76 % of deuterated enamide was isolated.

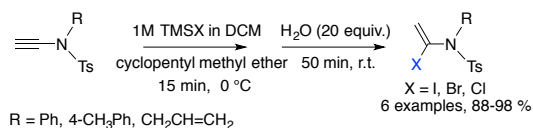
Commercially available TMSI and TMSBr were found to convert ynamides into (*E*)- $\alpha$ -haloenamides in wet solvent, with perfect regio- and stereochemical outcome. This methodology developed by Iwasawa and co-workers showed excellent substrate compatibility. Disubstituted ynamides,<sup>8</sup> terminal tosylynamides<sup>9</sup> were used as starting materials, the protocol also applies to *N*-tosylated buta-1,3-diyne-1,4-diamines.<sup>10</sup>



**Scheme 5** Halotrimethylsilane-mediated hydroiodination and hydrobromination of ynamides.

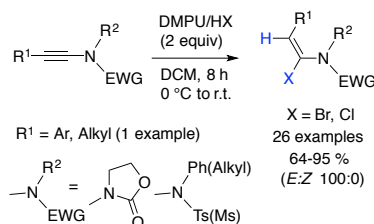
The hydrogen halide (X=I, Br) was generated in situ from mixing 1 M halotrimethylsilane in DCM with several disubstituted-ynamides at  $-78^\circ\text{C}$  for 15 min and then adding 20 equiv of water while allowing the reaction to warm up to  $0^\circ\text{C}$ . The reaction afforded a wide variety of new (*E*)- $\alpha$ -haloenamides in high yields (Scheme 5).<sup>8</sup> It worth noting that the authors applied the same strategy to  $\alpha$ -iodination and bromination of *N*-alkynyl carbomethoxyindoles which can be viewed as vinylogues or phenylogues of ynamides with excellent region and stereoselectivity (Scheme 5).<sup>11</sup>

When TMSCl was used the corresponding chloroenamides were obtained in low yield. The stronger Si-Cl bond TMSCl is more difficult to activate. Surprisingly, TMSCl quickly reacted with tosyl ethynamides (Scheme 6).<sup>9</sup> This points to the importance of complexation between ynamide and TMSX in this process; thus, the sterically unhindered ethynamide tightly coordinates to TMSCl, which readily activates the Si-Cl bond. 1-Iodo- and 1-bromo-ethenamides can also be prepared according to the same procedure, starting with tosyl ethynamides. However, the corresponding products gradually decayed even though they were conserved under argon atmosphere at low temperature.



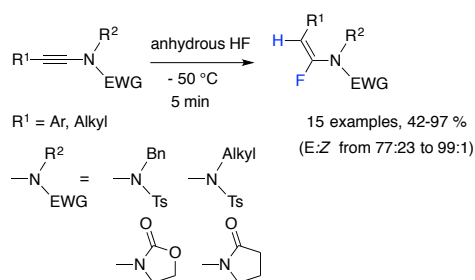
**Scheme 6** Synthesis of 1-haloethenamides.

DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) forms liquid, room temperature stable and highly concentrated complexes with hydrogen chloride and hydrogen bromide. Considering that, DMPU is at the same time a weak Brønsted base, a weak nucleophile but a potent hydrogen bond acceptor, Xu and Hammond assumed that these reagents would exhibit a higher nucleophilicity of halide anions and used them to perform the hydrohalogenation of alkynes.<sup>12</sup> They have then expanded the reactivity of these complexes to achieve the regio- and stereo-selective hydrohalogenation of ynamides (Scheme 7).<sup>13</sup> Despite the fact that ynamides are acid sensitive compounds, the substrate scope was broad. Both aliphatic and aromatic substituted ynamides produced *syn*-addition products in good yields. Acid sensitive functional groups such as nitrile, alkene, allyl and methyl ester survived under these conditions.



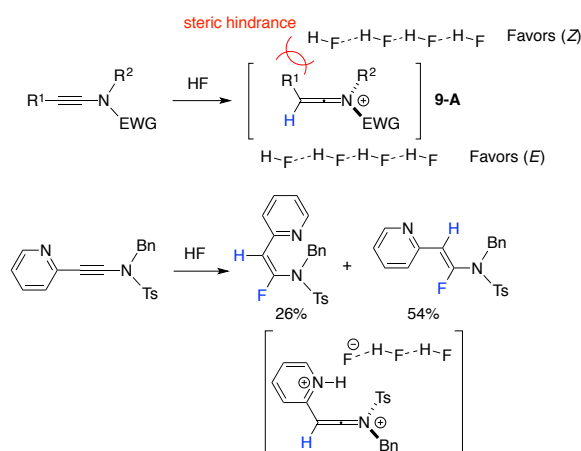
**Scheme 7** DMPU/HX reagents for hydrochlorination and hydrobromination of ynamides.

As regard to the synthesis of fluoroenamides, Evano, Thibaudeau and co-workers proposed the first hydrofluorination of ynamides in 2012.<sup>14</sup> This reaction provides a general entry to  $\alpha$ -fluoroenamides and can easily be applied to a wide range of substrates (Scheme 8). Hydrofluorination can be performed using anhydrous superacid HF leading to high stereocontrol in favor of (*E*)- $\alpha$ -fluoroenamides.



**Scheme 8** Anhydrous HF for (*E*)- $\alpha$ -fluoroenamides synthesis.

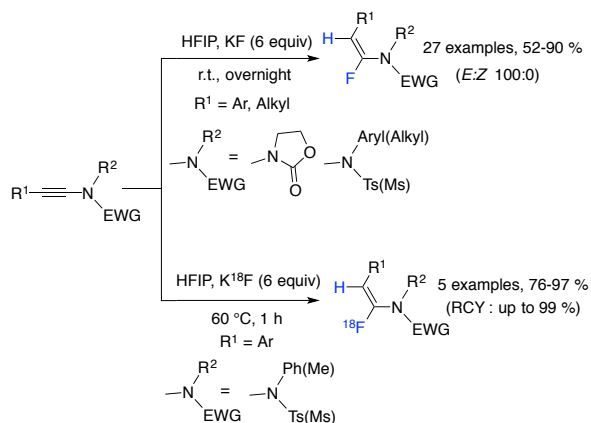
The high stereoselectivity can be rationalized from the structure of liquid anhydrous HF, known to exist as a strongly hydrogen-bonded chain. As shown in Scheme 9, the fluorination of the keteniminium intermediate **9-A**, formed through protonation, occurs at the opposite side of the aromatic group leading to the formation of (*E*)- $\alpha$ -fluoroenamides. Using 2-pyridinyl-substituted ynesulfonamide confirmed this hypothesis. In this case, the electrostatic interaction between HF chains and pyridinium ions switches the stereoselectivity by directing the attack of the fluoride ions to give the (*Z*)- $\alpha$ -fluoroenesulfonamide in 54% yield as the major product.



**Scheme 9** Rationalization for the formation of (*E*)- $\alpha$ -fluoroenamides.

This method was shown to tolerate a large variety of ynamides, however the safety of procedures manipulating pure liquid hydrogen fluoride constitutes a major limitation. Therefore, in 2015, the same group developed a second-generation hydrofluorination process by using a mixture of HF and pyridine at -10 °C (70:30, w:w).<sup>15</sup> The use of aryl- and alkyl-substituted ynesulfonamides, yncarbamates, and ynimides led to the desired nitrogen-substituted fluoroolefins in good yields and stereocontrol favored the formation of the *E*-isomer.

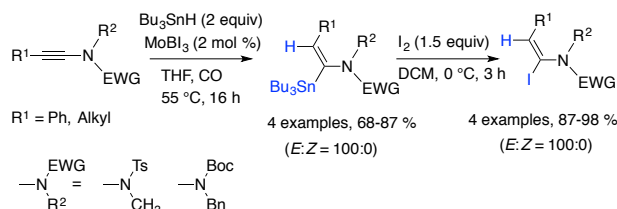
Xu and Hammond<sup>16</sup> selected HFIP (hexafluoro-2-propanol) as hydrogen-bonding activator and proton source. Indeed, hydrogen-bonding network are able to activate easy to handle alkali metal fluorides, such as KF under mild conditions. The H-bond network complexes the alkali metal fluoride and makes it highly soluble. Furthermore, it has been shown that hydrogen bonding media can tune the reactivity of fluoride anion and counter-intuitively can increase its nucleophilicity.<sup>17</sup> The reaction exhibited high functional-group tolerance at room temperature and under ambient atmosphere (Scheme 10). Based on these preliminary studies, the same authors reported a highly valuable expansion of the procedure to nucleophilic (radio)fluoroclick reaction of ynamides with KF(<sup>18</sup>F) leading to labelled  $\alpha$ -fluoroenamides in good yields. Excellent radiochemical yields (RCYs) were observed when K<sup>18</sup>F was used as nucleophile. It is to be noted that this protocol is the first method for <sup>18</sup>F addition to C-C unsaturated bonds with high radiochemical yields.



### Scheme 10 Fluorination and radiofluorination of ynamides.

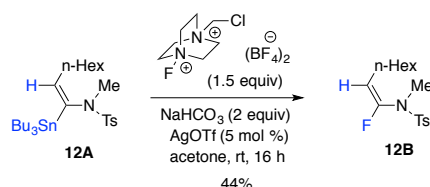
The following methodologies neither proceed by using directly the hydrogen halide as the reagent nor by smoothly generating HX in the reaction medium.

Kazmaier's group reported that  $\alpha$ -iodoenamides could easily be obtained by Mo-catalyzed regio- and stereoselective hydrostannylation of ynamides followed by tin-iodine exchange (Scheme 11).<sup>18</sup>



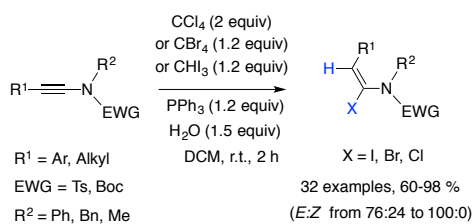
### Scheme 11 Two-step synthesis of $\alpha$ -iodoenamides.

They showed that CO atmosphere is beneficial for the lifetime of the catalyst and under these conditions higher yields are obtained for the hydrostannylation step, especially with 1,2-disubstituted alkynes. The  $\alpha$ -stannylated enamides are stable compounds, which could easily be purified by flash chromatography and converted in  $\alpha$ -iodoenamides through tin-iodine exchange in excellent yields with full retention of the olefin geometry. It is to be noted that tin exchange with bromine and chlorine can be performed by reaction with the corresponding dihalogens or with *N*-halosuccinimides. The tin-fluorine exchange is not so easy to achieve, selectfluor previously used for the synthesis of aryl fluorides from aryl stannanes<sup>19</sup> led to the expected  $\alpha$ -fluoroenamide **12B** in 44% yield in the presence of catalytic silver triflate. (Scheme 12)



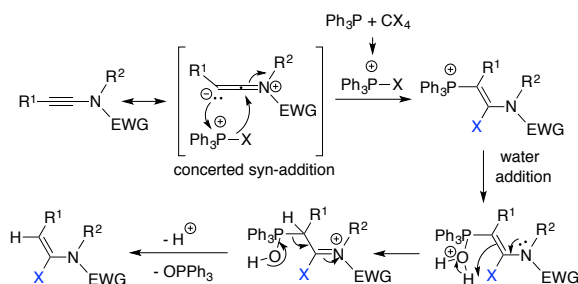
### Scheme 12 Fluorination of stannylated enamide **12A**.

Sahoo and co-workers demonstrated the efficacy of their one-pot construction of  $\alpha$ -haloenamides from tosyl- and *N*-Boc-ynamides using a  $\text{Ph}_3\text{P}/\text{H}_2\text{O}/\text{CX}_4$  system as the halide source (Scheme 13).<sup>20</sup> The efficiency of ynamides chlorination at room temperature is particularly noteworthy.



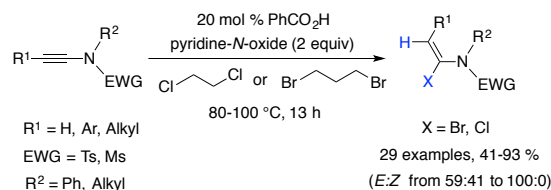
### Scheme 13 $\text{Ph}_3\text{P}/\text{H}_2\text{O}/\text{CX}_4$ system-mediated hydrohalogenation of ynamides.

The mechanism proposed by the authors starts with the *syn*-addition of the phosphonium salt generated *in situ* from triphenylphosphine and halogenating reagent ( $\text{CCl}_4/\text{CBr}_4/\text{CHI}_3$ ) to the reactive ambivalent ynamide (Scheme 14). The subsequent hydrolysis delivers the expected vinyl halide and phosphine oxide.



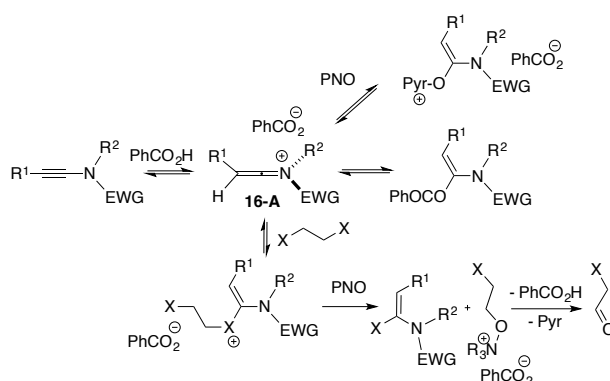
### Scheme 14 *syn*-Addition of phosphonium salt.

Shin and co-workers reported in 2017 a novel benzoic acid-catalyzed hydrohalogenation of ynamides using *N*-oxides/1,2-dihaloethane system (Scheme 15).<sup>21</sup> The reaction tolerates alkyl and aryl substituents at the  $\beta$ -carbon of ynamides. However, terminal alkynes gave poor yields. The *E/Z* ratio depends primarily on the  $R^2$  group with aryl groups giving significantly higher (*E*)-selectivity than alkyl groups.



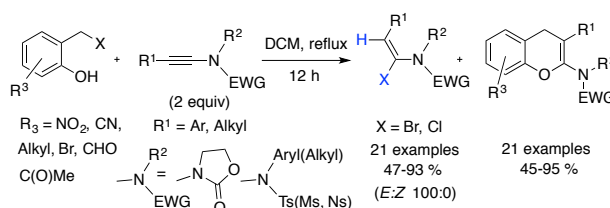
**Scheme 15** Acid-catalyzed  $\alpha$ -halogenation in 1,2-dihalo-ethanes in the presence of pyridine-*N*-oxide.

An interesting aspect of the above method is that, under these peculiar experimental conditions, the activation of the ynamide by acid catalysis result in a situation where multiple nucleophilic species can add to the resulting keteniminium salt (Scheme 16). Ketiminium salt **16-A** forms reversible adducts with both pyridine-*N*-oxide (PNO) and carboxylate. At the same time, the keteniminium ion can also be reversibly trapped, from the side opposite to  $R^1$ , to form a halonium ion. The latter is attacked in the rate-determining irreversible step by pyridine-*N*-oxide to afford the  $\alpha$ -haloenamide.



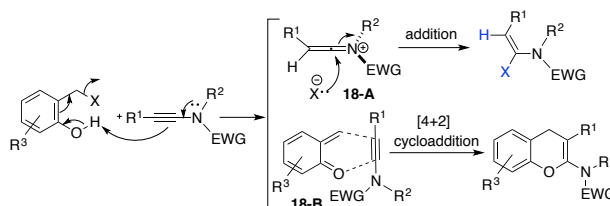
**Scheme 16** Reversible reactions of keteniminium salt and proposed mechanism.

Tang and co-workers reported in 2020 a novel and efficient catalyst-free symbiotic reaction of 2-halomethylphenols (*in situ* source of HX) and ynamides. This process that necessitates the use of 2 equivalents of ynamide provides a general way to construct 2-amino-4*H*-chromenes and  $\alpha$ -bromo- or  $\alpha$ -chloro-enamides simultaneously in one step (Scheme 17).<sup>22</sup>



**Scheme 17**  $\alpha$ -Haloenamides and 2-amino-4*H*-chromenes from ynamides and 2-halomethylphenols.

The authors proposed a mechanism in which, ynamide, acting as a base, reacts with the phenol derivative, leading to keteniminium **18-A** and *o*-methylene quinone **18-B**, (Scheme 18). Subsequently, the keteniminium rearrange via nucleophilic-attack by  $X^-$  from the least hindered face to yield the covalent (*E*)- $\alpha$ -haloenamide. In the meanwhile, intermolecular [4+2] cycloaddition between *o*-methylene quinone **18-B** and another equivalent of ynamide affords 2-amino-4*H*-chromenes.



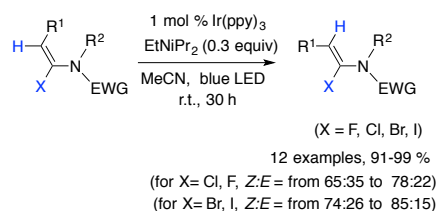
**Scheme 18** Proposed mechanism.

### 2.1.2 *trans*-Hydrohalogenation of ynamides



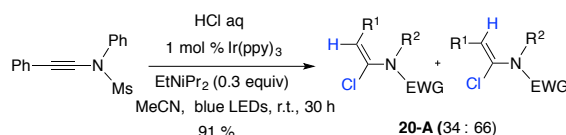
The following section refers to the photochemical double bond isomerization of the previously described *cis*-enamides as routes to *trans*-hydrohalogenated products. Regarding *trans*-hydrofluorination, silver(I) or Cu(I) catalysis provide efficient methodologies.

Following on their achievement of hydrohalogenation in biphasic medium Tang and co-workers<sup>5</sup> have demonstrated that (*E*)- to (*Z*)-isomerization of haloenamides could easily be performed using Ir(ppy)<sub>3</sub> (*fac*-tris[2-phenylpyridinato-C2,*M*] iridium(III)) photocatalysis in the presence of DIPEA (irradiation with blue LED in acetonitrile). Photocatalysis allows to circumvent steric constraints to favor the thermodynamically less stable isomer.<sup>23</sup> The (*Z*)-haloenamides were formed as the main products albeit with moderate stereoselectivity. The halogen type of  $\alpha$ -haloenamides had significant impact on the stereoselectivity and when chlorine/fluorine were replaced with bromine or even iodine, the *Z/E* selectivity could be improved significantly.



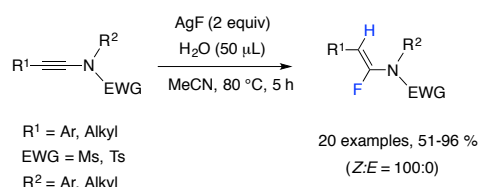
**Scheme 19** (*E*)- to (*Z*)-isomerization under photocatalysis.

It is to be noted that when the procedure was performed in one-pot to give chloroenamide **20-A** by cascade hydrochlorination and photocatalysis performed in acetonitrile, high yield was obtained but with low stereoselectivity (Scheme 20).



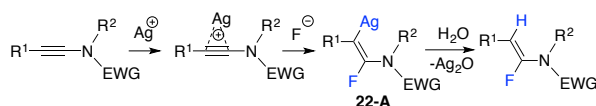
**Scheme 20** One-pot procedure for the synthesis of (*Z*)- $\alpha$ -chloroenamide **20-A**.

Zhu's group reported in 2014 a novel method for the synthesis of (*Z*)- $\alpha$ -fluoroenamides with AgF as the fluorination reagent (Scheme 21).<sup>24</sup> The use of 2 equiv of AgF was required for the full conversion of *N*-sulfonyl ynamides in refluxing wet acetonitrile. In all cases high *Z*-stereoselectivity was observed. However, the reaction conditions were not suitable for the oxazolidinonyl- and imidazolyl-derived ynamides leading to poor *trans-cis* ratios in hydrofluorinated products and thus, revealed synthetically useless (1:1-4:1). It is to be noted that other fluoride sources, including CsF, KF, NaF, and TBAF, almost shut down the reaction.



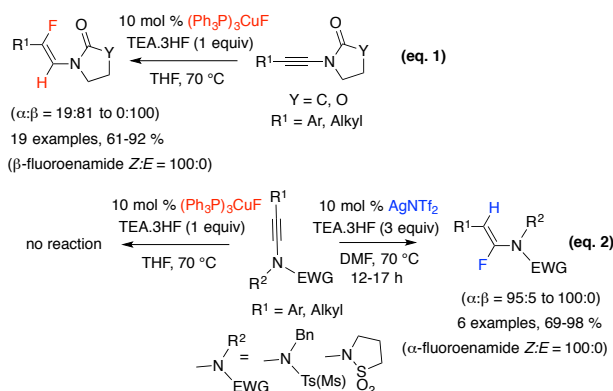
**Scheme 21** Silver-promoted *trans*-hydrofluorination of *N*-sulfonyl ynamides.

The mechanism proposed by the authors is depicted in Scheme 22. The activation of the ynamide triple bond by silver cation followed by the nucleophilic attack of fluoride anion from the opposite side of the complex generates intermediate **22-A**. The polarization of the triple bonds of ynamides caused by the electron-donating property of nitrogen atom probably explains the regioselectivity. Then, the protonolysis of the C—Ag bond affords the *trans*-hydrofluorination products.



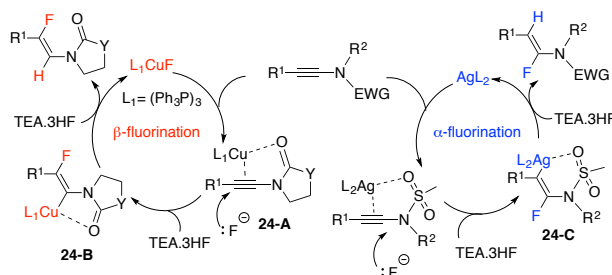
**Scheme 22** Proposed mechanism.

Zhu and co-workers reported copper(I)- or silver(I)-catalyzed regiocontrolled *trans*-hydrofluorination of ynamides with TEA•3HF (Et<sub>3</sub>N•3HF) as the fluorinating reagent.<sup>25</sup> In the presence of 10 mol% of (PPh<sub>3</sub>)<sub>3</sub>CuF and TEA•3HF (1 equiv) in THF, ynamides derived from oxazolidinones and pyrrolidinones were converted in  $\beta$ -fluoroenamides in good yields and high stereoselectivities (Scheme 23 (eq.1)). However, the use of *N*-sulfonyl ynamides as substrate failed under the same reaction conditions. In all likelihood the oxygen atoms of sulfonylamides is not basic enough to complex efficiently the copper catalyst. Conversely, in the presence of TEA•3HF (3 equiv), using AgNTf<sub>2</sub> catalyst in DMF, *N*-sulfonyl ynamides were transformed in  $\alpha$ -fluoroenamides in good yields, showing a completely reversed regioselectivity as compared to the Cu(I)-catalyzed hydrofluorination of yncarbamates and yncpyrrolidinones (Scheme 23 (eq.2)).



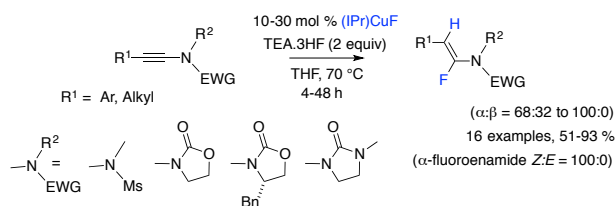
**Scheme 23** Cu(I)- and Ag(I)-catalyzed regio- and stereocontrolled *trans*-hydrofluorination of ynamides.

A plausible mechanism to explain these opposite behaviors is depicted in Scheme 24. The coordination of a copper cation with the carbonyl oxygen of ynamide substrate occurs to generate a copper-alkyne complex **24-A**. Subsequent back-side nucleophilic attack of fluoride on the activated alkyne provides the alkenylcopper intermediate **24-B**. Protonolysis of the carbon-copper bond by TEA·3HF delivers the β-site regiocontrolled (*Z*)-fluoroenamide and regenerates the copper catalyst. In the case of the AgNTf<sub>2</sub>-catalyzed *trans*-hydrofluorination of *N*-sulfonyl ynamides, the formation of α-site regiocontrolled (*Z*)-fluoroenamide possibly proceeds via the six-membered chelated transition state **24-C** resulting from the cooperation of sulfonyl oxygen coordination and polarization of the triple bond of *N*-sulfonyl ynamides. The latter reaction might also proceed without chelate formation like in Scheme 22.



**Scheme 24** Mechanisms proposed for catalyzed α- and β-fluorination.

The same group conducted a detailed study of the Cu(I)-catalyzed hydrofluorination of ynamides. Interestingly, they demonstrated that the use of (NHC) ligand for Cu(I) complex instead of (PPh<sub>3</sub>)<sub>3</sub>CuF led to α-site regio-defined hydrofluorination of ynamides (Scheme 25).<sup>26</sup>



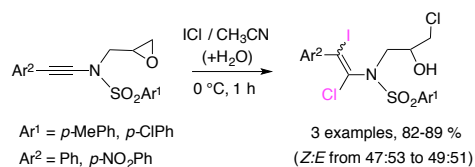
**Scheme 25** (IPr)CuF-catalyzed α-site *trans*-hydrofluorination of ynamides ((IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)

The NHC ligand might increase the electrophilic character of Cu and makes the Cu atom bind to the β-carbon atom of the ynamide, while logically fluoride ion attacks the positively charged α-carbon atom. Alternatively, as proposed by the authors, the NHC ligand would impede by steric effect the binding of Cu atom to the α-carbon. Aryl ynamides derived from oxazolidinone delivered the desired products in good to excellent yields whereas alkyl alkynylated ynamides afforded modest yields and regioselectivities. The methodology is also applicable to urea-based ynamides. Ynesulfonamides which were not reactive in (PPh<sub>3</sub>)<sub>3</sub>CuF-catalyzed hydrofluorination, were also compatible with this process leading to excellent yields and stereoselectivities.

## 2.2 α,β-Dihalogenation

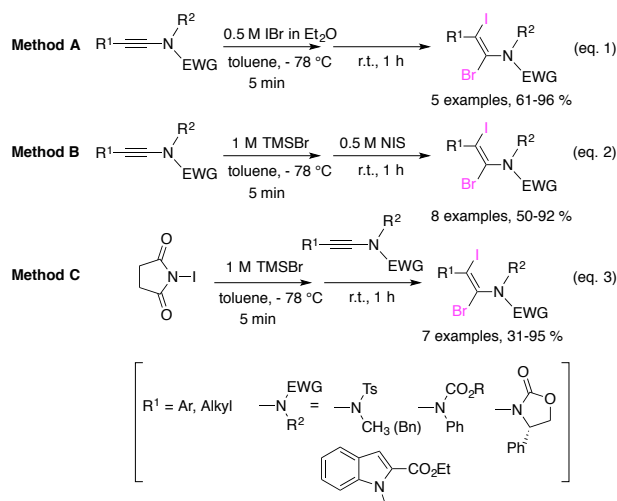
### 2.2.1 Iodochlorination and iodobromination of ynamides

According to Swamy's report the use of ICl as polarized electrophilic reagent to achieve iodochlorination of *N*-sulfonyl ynamides sounds quite limited. Only epoxy-ynamides underwent regioselective β,α-iodochlorination in good yield but with concomitant epoxide ring opening (Scheme 26).<sup>7</sup>



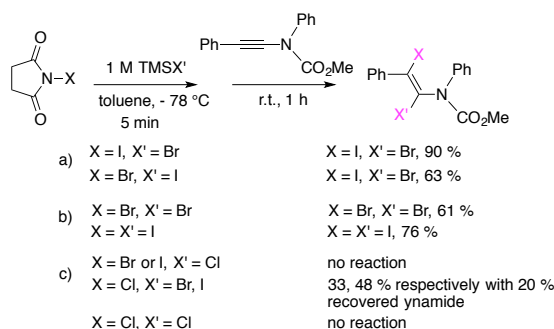
**Scheme 26**  $\beta,\alpha$ -iodochlorination of epoxy-yenamides.

Iwasawa and co-workers reported the first example of an easy one-step synthesis of vicinal bromiodoenamides from ynamides in a highly regio- and stereoselective manner.<sup>27</sup> Commercially available IBr (method A) or in situ generated IBr from bromotrimethylsilane and *N*-iodosuccinimide (methods B and C) can be used to accomplish the reaction (Scheme 27).



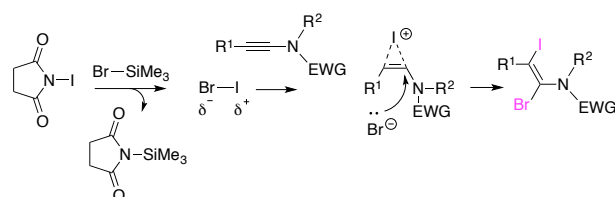
**Scheme 27** Iodobromination of ynamides with "IBr".

Different patterns of *N*-halosuccinimide/halotrimethylsilane were tested (Scheme 28). Interestingly, both combinations of TMSI/NBS and TMSBr/NIS generate in situ IBr to produce the same iodobromo-enamide (Scheme 28 (a)). Various combinations of halogenated reagents, were quite efficient and afforded the desired product. These data point again the difficulty to perform chlorohalogenation. The use of TMSCl showed no reaction (Scheme 28 (c)). When NCS was used in the presence of TMSI or TMSBr, the products resulting from diiodination or dibromination were obtained together with recovered ynamide.



**Scheme 28** Dihalogenation of ynamides.

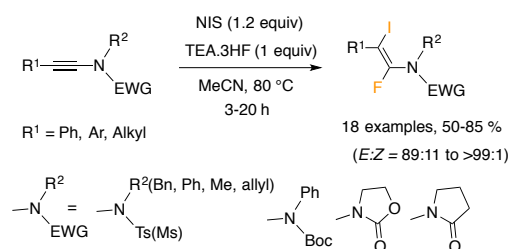
The mechanism proposed by the authors involves *in situ* formation of polarized IBr that undergoes addition via an iodonium ion intermediate to deliver ynamide according to *anti*-ring-opening mode (Scheme 29).



**Scheme 29** Proposed mechanism.

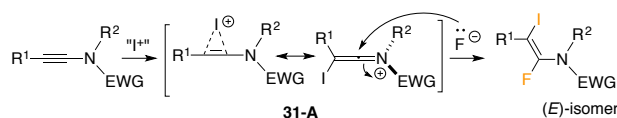
## 2.2.2 Iodofluorination of ynamides

He, Zhu and co-workers reported in 2017 the regio- and stereo-selective iodofluorination of ynamides using TEA•3HF/NIS system.<sup>28</sup> The reaction was compatible with a wide array of ynamides and tolerated a variety of functional groups (Scheme 30).



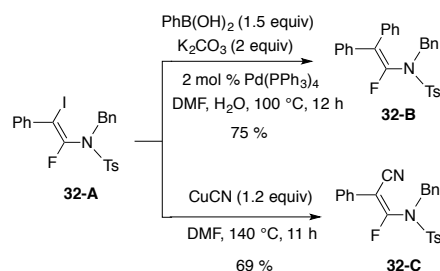
**Scheme 30** Iodofluorination of ynamides using TEA•3HF/NIS system.

The proposed mechanism involves the formation of the iodonium intermediate **31-A**, which is in resonance with the keteniminium ion. Then the nucleophile fluoride ion attacks selectively from the less hindered face of **31-A** to afford (*E*)-isomer as the major product (Scheme 31).



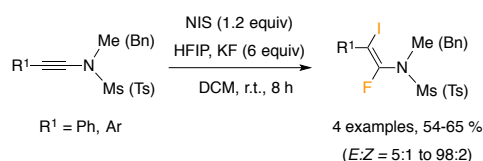
**Scheme 31** Proposed mechanism.

The  $\alpha$ -fluoro- $\beta$ -iodoenamides obtained in this study are useful intermediates for the stereospecific synthesis of  $\alpha$ -fluoroenamides as exemplified in Scheme 32. Fluoroenamides **32-B** and **32-C** can be efficiently prepared in good yields *via* Pd-catalyzed coupling and CuCN-mediated cyanation of fluoro-iodoenamide **32-A**, respectively.



**Scheme 32**  $\alpha$ -Fluoroenamides from  $\alpha$ -fluoro- $\beta$ -iodoenamide **32-A**.

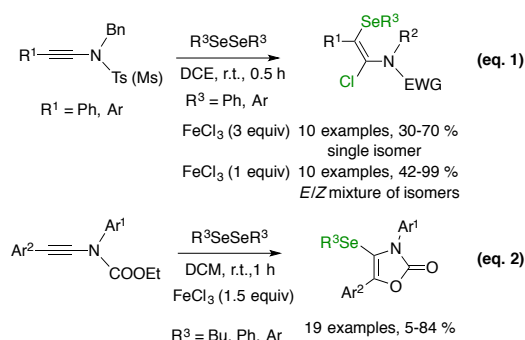
Xu and co-workers extended their hydrofluorination system based on the use of KF/HFIP (Scheme 10) to iodofluorination of sulfonylynamides.<sup>16</sup> When the iodination reagent, *N*-iodosuccinimide, was incorporated in the fluorination medium,  $\alpha$ -fluoro- $\beta$ -iodoenamides were obtained with moderate yields and moderate to good selectivity (Scheme 33).



**Scheme 33** Iodofluorination of sulfonylynamides with NIS/KF/HFIP system.

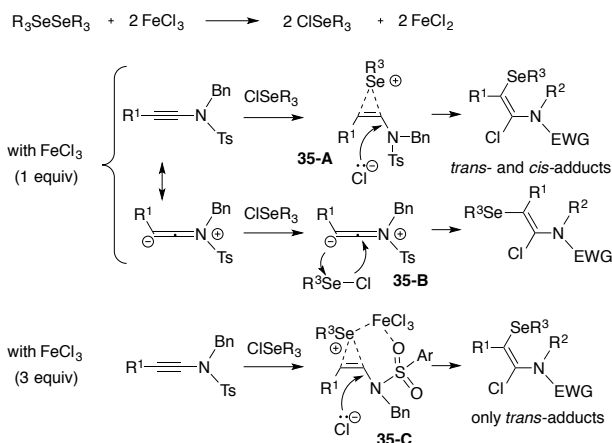
### 2.3 Chloroselenation of ynamides

Very recently Zeni and co-workers proposed a selective approach to (*E*)- $\alpha$ -chloro- $\beta$ -(organoselenyl)enamides using sulfonylynamides as substrates with diorganylselenides as electrophilic selenium reagent and iron(III) chloride as chloride ion source (Scheme 34 (eq. 1)).<sup>29</sup> Although yields were lower than those obtained from the direct use of PhSeCl (or PhSeBr), a significant improvement in selectivity was observed by increasing the loading of iron(III) chloride up to 3 equiv. Under these conditions although enamides were formed in low to acceptable yields, but only (*E*)-isomers were isolated. It is to be noted that, under the same experimental conditions, alkynyl carbamate led to the formation of 4-(organoselenyl)oxazolones as the major product (Scheme 34 (eq. 2)).



**Scheme 34** Diorganylselenides and iron(III) chloride for the chloroselenation of sulfonyl amides and alkynyl carbamates.

The authors proposed that the formation of (*E*)- and (*Z*)-enamides most likely proceeds *via* a selenium electrophilic addition on the carbon-carbon triple bond (Scheme 35). The reaction of the electrophilic selenium species with the tosylamide led to the seleniranium ion **35-A** that should be trapped by chloride anion to afford (*E*)- $\alpha$ -chloro- $\beta$ -(arylselenenyl) enamide. Therefore, the exclusive formation of (*Z*)- $\alpha$ -chloro- $\beta$ -(arylselenenyl) enamide follows from a *syn* addition of the electrophilic selenium species to the keteniminium ion **35-B**. The high selectivity obtained with iron(III) chloride (3 equiv) results from the complexation of the positively charged selenium atom with the oxygen atoms of the sulfonyl group in intermediate **35-C** that impedes approach of the nucleophile from that side.



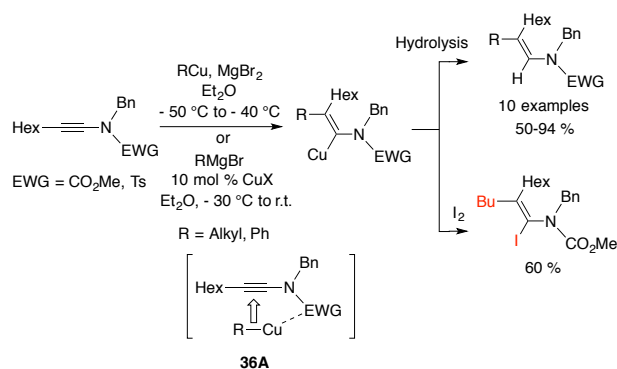
**Scheme 35** Proposed mechanism depending on the number of equivalents of FeCl<sub>3</sub>.

## 2.4 Carbohalogenation of ynamides

### 2.4.1-Carboiodination

#### 2.4.1.1-Carbocupration followed by iodination

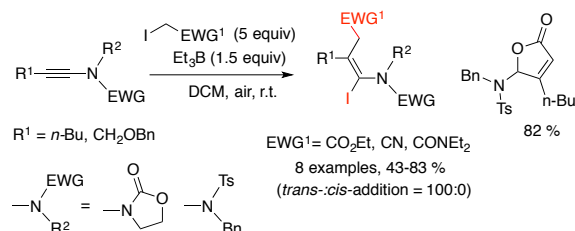
Marek and co-workers reported in 2005 the first carbocupration and copper-catalyzed carbomagnesiation of diversely substituted ynamides.<sup>30</sup> The carbocupration reaction of ynamide with an organocopper leads to the corresponding vinylic organocopper intermediate at low temperature. The latter can be trapped either with a proton or with classical electrophiles used in organocopper chemistry such as iodine, which affords, in this particular case, the corresponding  $\alpha$ -iodoenamide (Scheme 36). The regioselectivity is accounted for by the formation of the key chelated intermediate **36A**.



**Scheme 36** Carbometallation and iodination of ynamide.

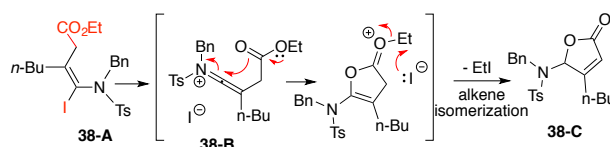
#### 2.4.1.2 Iodine atom transfer radical addition

Very recently our group has shown that intermolecular addition of electrophilic carbon-centered radicals to ynamides using ATRA methodology afforded a new regio- and stereoselective route to persubstituted  $\alpha$ -iodoenamides.<sup>31</sup> The addition of ethyl  $\alpha$ -iodoacetate,  $\alpha$ -iodo-acetonitrile, or  $\alpha$ -iodo-*N,N*-diethylacetamide onto ynamides derived from oxazolidinone and tosylbenzylamine was initiated with triethylborane in DCM. The reactions proceeded with total regio- and stereo-selectivity to give  $\alpha$ -iodoenamides in moderate to good yields (Scheme 37). It is to be noted that the addition is no longer regio- nor stereo-selective when the substituent R<sup>1</sup> at the  $\beta$ -carbon of the triple bond is a phenyl group.



**Scheme 37** Carboiodination of ynamides through ATRA process.

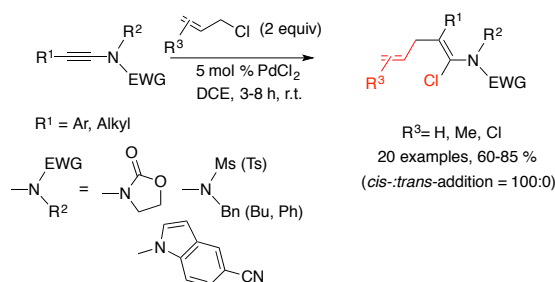
In the case of tosylbenzylamide, the product resulting from carboiodination was unstable. It evolved rapidly toward aminofuran-2-one **38-C**, isolated in 82% yield. Due to the lower mesomeric electron-withdrawing power of the tosyl group compared to the oxazolidinone carbonyl group,  $\alpha$ -iodoenamide **38-A** is likely to give rise more easily to the keteniminium ion **38-B**, precursor of aminofuran-2-one **38-C** via cascade intramolecular nucleophilic attack by the ester carbonyl group, iodine-mediated dealkylation, and double bond migration (Scheme 38).



**Scheme 38** Formation of aminofuran-2-one **38-C** through degradation of iodoenamide **38-A**.

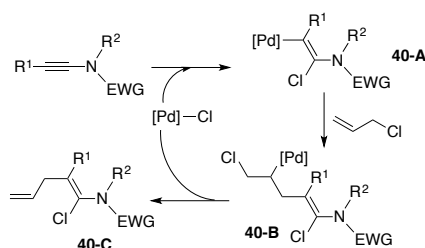
## 2.4.2 Chloroallylation

Zhu and co-workers described the Pd-catalyzed chloroallylation of ynamides at room temperature.<sup>32</sup> DCE was the most suitable solvent for this reaction in the presence of 5 mol % of PdCl<sub>2</sub> at room temperature, producing persubstituted enamides in good yields (Scheme 39). The reaction of aromatics and aliphatic ynamides proceeded nicely to provide the corresponding enamides. Ynamides derived from oxazolidinone, tosyl amines or even indole analogues afforded the desired adducts, while ynamides derived from pyrrolidinone were non reactive even at elevated temperature.



**Scheme 39** Chloroallylation of ynamides.

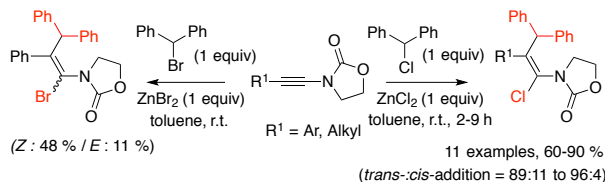
The mechanism proposed by the authors is depicted in Scheme 40. The *cis*-halopalladation of ynamides selectively forms the vinyl palladium intermediate **40-A**. The oxidative addition of allyl chloride yields the  $\beta$ -chloroalkyl palladium **40-B**. Finally,  $\beta$ -Cl elimination produces enamide **40-C** and regenerates the palladium catalyst.



**Scheme 40** Proposed mechanism.

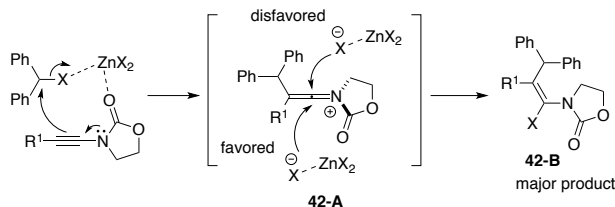
### 2.5.3 Chloro-benzhydrylation

Cao and co-workers have reported a regio- and stereo-selective synthesis of persubstituted  $\alpha$ -chloroenamides *via* zinc chloride mediated direct addition of diphenyl-methyl chloride to ynamides.<sup>33</sup> A stoichiometric amount of Lewis acid was necessary to reach high yield and the use of ynamides derived from oxazolidinone led to high conversion and good stereoselectivity (Scheme 41). Low stereoselectivity were observed when diphenyl-methyl bromide was used instead of the corresponding chloride or when the reaction was conducted onto sulfonylynamides.



**Scheme 41** Chloro-benzhydrylation of ynamides.

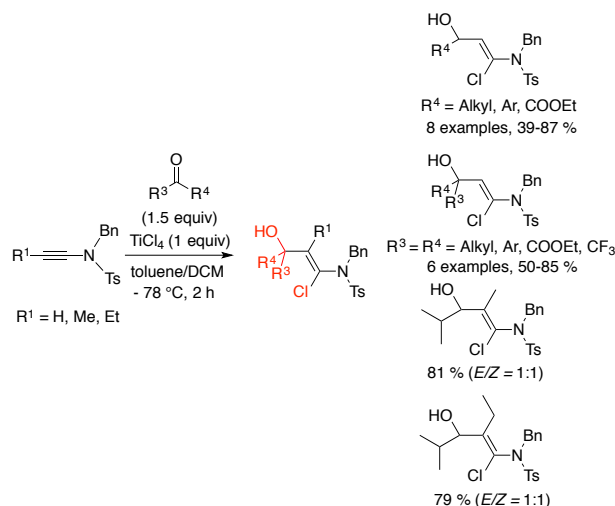
The proposed mechanism involves: *i*) the coordination of zinc halide to both the substrate and the benzylic chloride, *ii*) nucleophilic substitution of the latter by the nucleophilic  $\beta$ -carbon of the enamide leading to the keteniminium **42-A**, *iii*) nucleophilic addition of halide anion to the keteniminium intermediate -selectively from the less hindered face- to afford haloenamide **42-B** as the major product (Scheme 42).



**Scheme 42** Proposed mechanism.

### 2.5.4 Chloro- $\gamma$ -hydroxylation

Matsuo and co-workers have shown that terminal *N*-alkylsulfonamides react with aldehydes or ketones in the presence of  $\text{TiCl}_4$  to give the corresponding (*Z*)- $\alpha$ -chloro- $\gamma$ -hydroxyenesulfonamides with good yields (Scheme 43).<sup>34</sup>

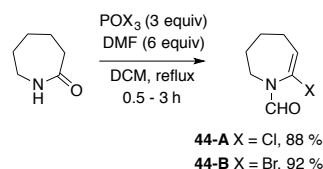


**Scheme 43**  $\text{TiCl}_4$ -mediated  $\alpha$ -chloro- $\gamma$ -hydroxylation of ynamides.

The mechanism, proposed by the authors, involves, after the coordination of titanium tetrachloride to the carbonyl oxygen atom, the addition of the triple bond to the activated carbonyl that releases chloride ion from the  $\text{TiCl}_4$ -aldehyde complex. In the case of terminal ynamide, the chloride ion rapidly reacts from the same face on which aldehyde reacts to give (*Z*)-isomer of the enamide. In opposite, more stabilized carbocations from internal ynamides ( $\text{R}^1 = \text{Me, Et}$ ) react more slowly with chloride ion, which leads to a lack of stereoselectivity.

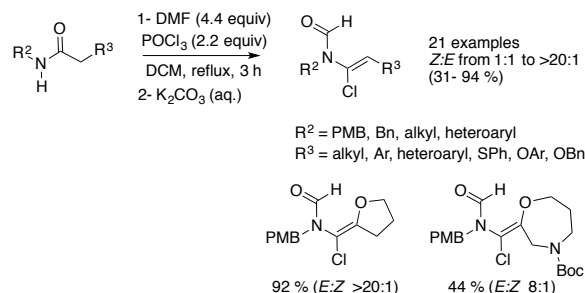
## 2.6 Vilsmeier-Haack reactions

Sarpong and co-workers proposed in 2014 the direct synthesis of  $\alpha$ -halo eneforamides **44-A,B** from caprolactam using Vilsmeier-Haack reaction (Scheme 44).<sup>35</sup>



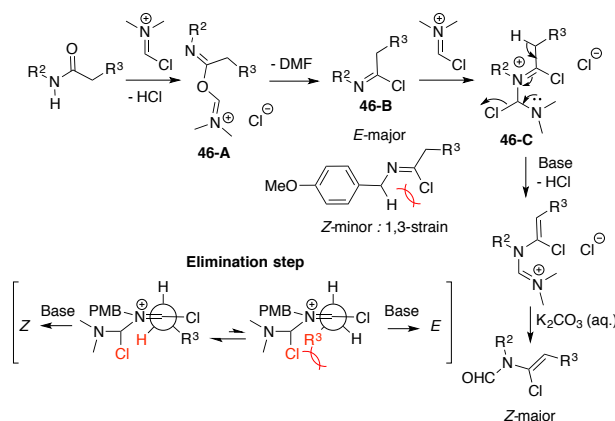
**Scheme 44**  $\alpha$ -Halo eneformamides **44-A,B** from caprolactam using Vilsmeier-Haack reaction.

Wang, Collier and co-workers recently generalized the use of Vilsmeier-Haack reaction to the synthesis of various acyclic  $\alpha$ -chloro eneformamides from  $\alpha$ -substituted secondary acetamides (Scheme 45).<sup>36</sup>



**Scheme 45** Use of Vilsmeier-Haack reaction in the synthesis of various acyclic  $\alpha$ -chloro eneformamides from secondary acetamides.

The reaction was found to be quite general in scope with respect to the acid component of the amide. Electron rich and electron deficient aryl- and heteroaryl-acetamides were well tolerated to give (*Z*)- $\alpha$ -chloro eneformamides with good stereocontrol. Higher yields were obtained with amides derived from  $\alpha$ -alkoxy- and  $\alpha$ -aryloxy-carboxylic acids. The method is compatible with highly substituted amides providing stereodefined enamides with four substituents on the double bond. The stereoselectivity of the reaction is dependent on the *N*-substituent. Indeed, replacing the PMB group by a hindered alkyl group diminished selectivity.



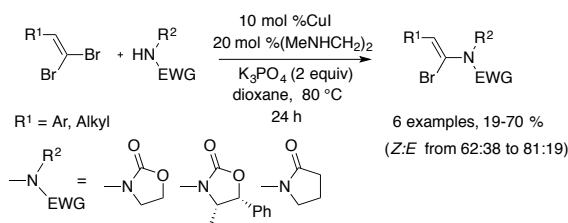
**Scheme 46** Proposed mechanism.

The mechanism proposed by the authors is depicted in Scheme 46. The first equivalent of *in situ* generated Vilsmeier-Haack reagent reacts with starting amide to give imidoyl chloride **46-B**. With substrates bearing a PMB group on the nitrogen atom, the formation of the (*E*)-imidoyl chloride, less destabilized by allylic steric strain than (*Z*)-isomer, is favored. The introduction of additional steric strain, even in the (*E*)- isomer, due to the replacement of *N*-PMB group with sterically more demanding *N*-substituent, lowers geometric selectivity. The second equivalent of Vilsmeier-Haack reagent then activates **46-B** to form iminium ion **46-C**. Subsequent elimination provides (*Z*)- $\alpha$ -chloro eneformamides as the major product. In this typical case, the less hindered transition state leads faster to the less strained isomer of the product than to its rotamer.

## 2.7 Cross-coupling reaction of *gem*-dibromo olefins in the presence of *N*-nucleophiles

Evano and co-workers have shown that the synthesis of  $\alpha$ -bromoenamides can be achieved by the cross-coupling between 1,1-dibromoalkenes and nitrogen nucleophiles derived from oxazolidinone and pyrrolidinone in the presence of copper(I) iodide, *N,N*-dimethylethylenediamine and potassium phosphate in 1,4-dioxane at 80 °C (Scheme 47).<sup>37</sup>





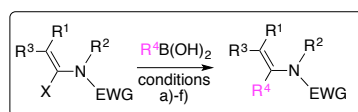
**Scheme 47** Cross-coupling of 1,1-dibromoalkenes with secondary amides and carbamates.

Because of the fast elimination of HBr from (*Z*)-1-bromoenamides in the presence of a base and the ease of the second cross-coupling yielding to the formation of ketene *N,N*-acetals, the reaction was difficult to optimize. The use of an excess of vinyl dibromides in the presence of catalytic amounts of copper(I) iodide was needed. Regarding the number of equivalent of base, the use of just 1 equivalent resulted in low conversion. The use of 3 equivalents favoured the double substitution. In the presence of 2 equivalents the  $\alpha$ -bromoenamides were isolated in reasonable yields as a 2:1 mixture of stereoisomers.

### 3 Subsequent transformations

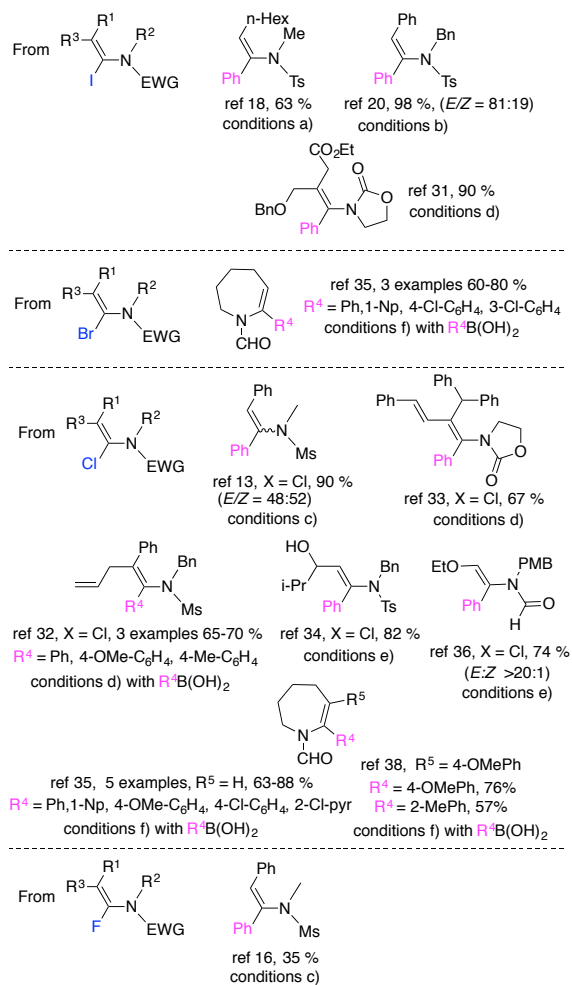
#### 3.1 Suzuki and Sonogashira reactions

The synthetic potential of  $\alpha$ -haloenamides as building blocks was clearly demonstrated in cross-coupling reactions. Indeed,  $\alpha$ -haloenamides are valuable synthetic intermediates for the synthesis of a variety of substituted enamides by palladium-catalyzed coupling reactions such as Suzuki (Scheme 48, Scheme 49) and Sonogashira (Scheme 50, Scheme 51) reactions. In most cases, coupling reactions conducted with  $\alpha$ -chloro-,  $\alpha$ -bromo-, and  $\alpha$ -iodoenamides gave trisubstituted or tetra-substituted enamides with good to excellent yields with retention of the initial geometry of the double bond.<sup>6,9,10,18,31,32,33,34,35,36,38</sup> Isomerization of the double bond during these processes have been reported by Sahoo,<sup>20</sup> Hammond and Xu<sup>13</sup> and Tang.<sup>5</sup> They described that coupling reactions of (*E*)- $\alpha$ -haloenamide led to a mixture of (*E*) and (*Z*) enamides due to partial isomerization that probably occurs during the palladium-catalyzed transformations.

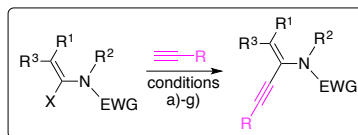


- PhB(OH)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, DME-H<sub>2</sub>O
- PhB(OH)<sub>2</sub>, Pd(P(*o*-tol)<sub>3</sub>)<sub>2</sub>, NaO*t*-Bu, EtOH-H<sub>2</sub>O-THF
- PhB(OH)<sub>2</sub>, Pd(OAc)<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, EtOH-H<sub>2</sub>O
- PhB(OH)<sub>2</sub>, Pd(OAc)<sub>2</sub>, XPhos, K<sub>3</sub>PO<sub>4</sub>, THF
- PhB(OH)<sub>2</sub>, Pd<sub>2</sub>(dba)<sub>3</sub>, *t*-Bu<sub>3</sub>P, Cs<sub>2</sub>CO<sub>3</sub>, dioxane
- PhB(OH)<sub>2</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Et<sub>3</sub>N, DMF

**Scheme 48** Conditions for Suzuki coupling of  $\alpha$ -haloenamides.

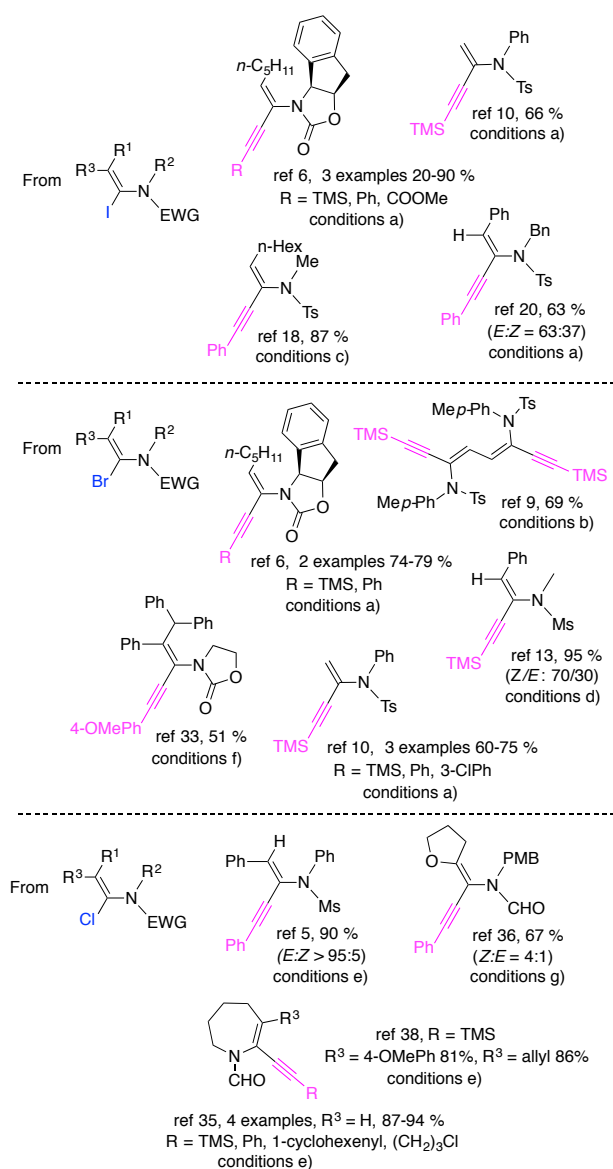


**Scheme 49** Suzuki coupling of  $\alpha$ -haloenamides.



- Pd(PPh<sub>3</sub>)<sub>4</sub>, CuI, HN(*i*Pr)<sub>2</sub>, toluene
- Pd(PPh<sub>3</sub>)<sub>4</sub>, CuI, HN(*i*Pr)<sub>2</sub>, DCM
- Pd(PPh<sub>3</sub>)<sub>4</sub>, CuI, piperidine, benzene
- Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, CuI, Et<sub>3</sub>N, THF
- Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, CuI, Et<sub>3</sub>N, DMF
- Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, CuI, Et<sub>3</sub>N, 1,4-dioxane
- Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, CuI, Cs<sub>2</sub>CO<sub>3</sub>, DMF

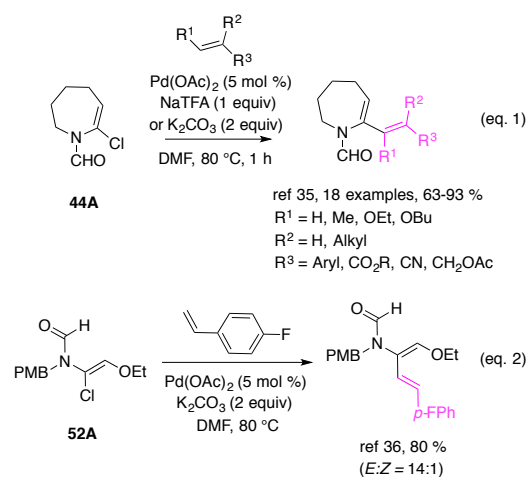
**Scheme 50** Conditions for Sonogashira coupling of  $\alpha$ -haloenamides.



**Scheme 51** Sonogashira coupling of  $\alpha$ -haloenamides.

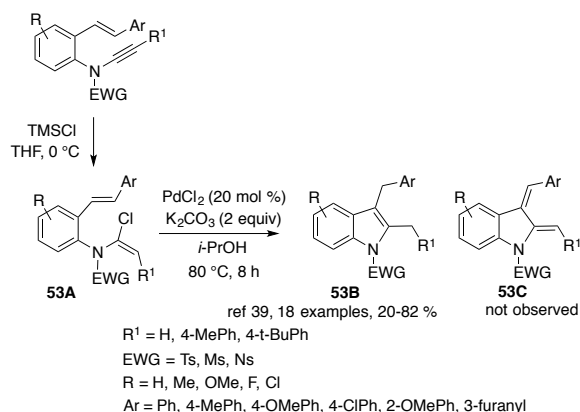
### 3.2 Heck reaction

Sarpong and co-workers reported the first intermolecular Heck coupling reactions of  $\alpha$ -halo eneforamides in 2014.<sup>35</sup> Under the conditions described in Scheme 52, eq (1), other leaving group at C-2 of the eneforamide such as triflates or phosphates fail to undergo the Heck coupling. Furthermore,  $\alpha$ -bromo eneforamides were less reactive, highlighting the uniqueness of the more stable  $\alpha$ -chloro eneforamides as coupling partners. Wang and Collier<sup>36</sup> showed that Heck reaction of  $\alpha$ -chloro eneforamide **52A** with 4-fluorostyrene gave the desired enamide in good yield and high stereochemical fidelity (Scheme 52, eq (2)).



**Scheme 52** Pd-catalyzed Heck alkenylation of  $\alpha$ -chloroeneformamides **44A** and **52A**.

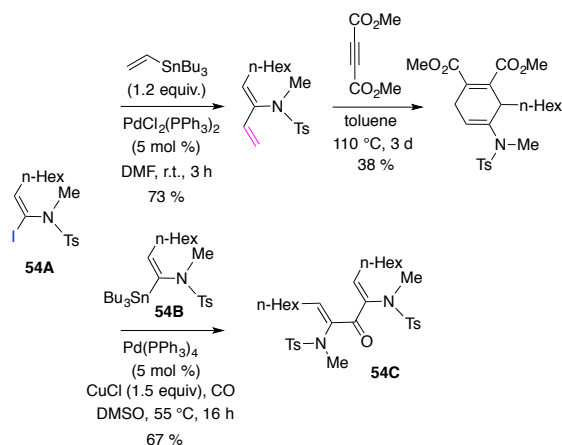
Wu and co-workers<sup>39</sup> showed recently that when in situ generated  $\alpha$ -chloro tosylamides **53A** was submitted to Heck conditions, it led to reduced Heck cyclized product **53B** rather than the expected diene **53C** (Scheme 53). Isopropanol is likely to play the role of reducing agent facilitating the in situ formation of palladium hydride. The potential of this process for the synthesis of azacyclic target compounds was evaluated by using several-substituted tosyl-, mesyl- and nosyl-namides.



**Scheme 53** Pd-catalyzed reductive Heck cycloisomerisation.

### 3.3 Stille reaction

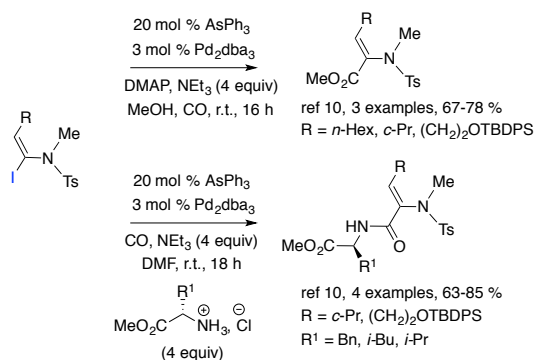
An example of Stille coupling involving  $\alpha$ -iodo tosylenamide **54A** was reported by Kazmaier and co-workers (Scheme 54).<sup>18</sup> When vinyl stannane was used as the coupling partner, an amide-substituted 1,3-diene was formed, which could be subjected to further transformations such as Diels-Alder reactions. When  $\alpha$ -stannylated enamide **54B** was used as coupling partner, interesting building blocks as tosylamide substituted-divinylketone **54C** were prepared under carbonylative Stille coupling conditions. This is directly connected to the next paragraph.



**Scheme 54** Stille coupling of  $\alpha$ -iodotosylenamides.

### 3.4 Miscellaneous applications

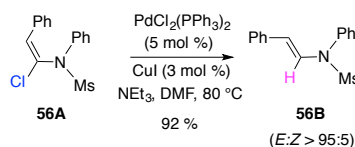
#### 3.4.1 Carbonylation



**Scheme 55** Synthesis of  $\alpha,\beta$ -dehydroamino acids and peptides.

Kasmaier's group<sup>18</sup> also showed that dehydroamino acid esters could be obtained from  $\alpha$ -iodo tosylenamides under carbonylative conditions in the presence of amino acid esters as nucleophiles in methanol or DMF as solvent.

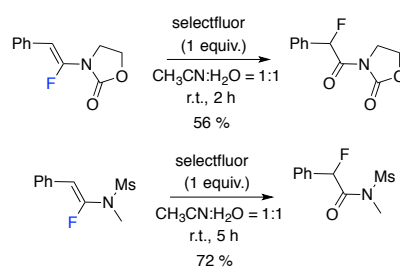
#### 3.4.2 Reduction



**Scheme 56** Reduction of  $\alpha$ -chloroenamide **56A**.

Tang and co-workers reported the direct reduction of  $\alpha$ -chloroenamide **56A** to enamide **56B** using triethylamine as the reductant (Scheme 56).<sup>5</sup> The reaction conducted under Sonogashira conditions, in the absence of a triple bond, occurs with isomerization of the double bond leading to the (*E*)-configured enamide as the major compound.

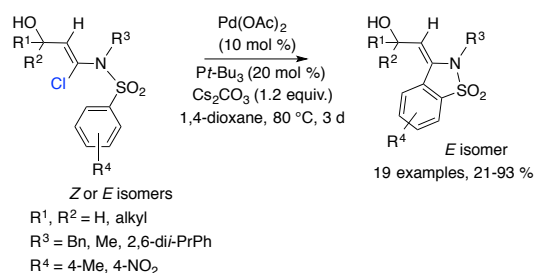
#### 3.4.3 Synthesis of $\alpha$ -fluoroimides



**Scheme 57**  $\alpha$ -Fluoroimides synthesis.

He and Zhu<sup>26</sup> reported that  $\alpha$ -site fluorinated alkenylamides could be transformed into the corresponding  $\alpha$ -fluoroimides in modest to good yields at room temperature under oxidative conditions (Scheme 57).

#### 3.4.4 Palladium-catalyzed intramolecular cyclization



## Scheme 58 Intramolecular cyclization of *N*-arylsulfonyl- $\alpha$ -chloroenamides promoted by a $\gamma$ -hydroxy group.

Matsuo and co-workers<sup>40</sup> reported in 2018, Palladium-catalyzed stereoselective intramolecular cyclization of *N*-arylsulfonyl- $\alpha$ -chloroenamides promoted by a  $\gamma$ -hydroxy group. They showed that both (*E*)- and (*Z*)-isomers reacted stereoselectively to give the corresponding (*E*)-2,3-dihydrobenzothiazole 1,1-dioxides (Scheme 58). In these processes, the  $\gamma$ -hydroxy group was found to accelerate the palladium-catalyzed carbon-carbon bond-forming step.

## 4-Conclusion

$\alpha$ -Haloenamides are available regio- and stereoselectively from a large panel of methodologies. Apart from the limited use of Vilsmeier-Hack reaction and cross coupling of *gem*-dibromoalkenes with secondary amides and carbamates, most procedures involve ynamides as starting material. As far as hydro-iodination, -bromination and -chlorination are concerned, these latter go from the obvious use of HX reagents, already available in solution, notably in basic aprotic solvent like DMPU, or more often generated in situ from hydrolysis of metal halides or TMSX, up to more sophisticated methods. The more anecdotic use of 2-halophenol as *in situ* precursor of HX is worth being mentioned. All these reactions involve ketene iminium salts as intermediates. The linear geometry of the ketene iminium salt and the resulting steric strain governs the stereo selectivity. Most methods favour *syn*-addition. Methods, involving other electrophilic addition of phosphonium halides or pyridinium *N*-oxides as nucleophiles after activation by catalytic benzoic acid, have also been devised. As regard to the synthesis of  $\alpha$ -fluoroenamides the main concern is safe manipulation of HF. Progresses have been made, the procedure evolved from the use of liquid anhydrous HF at low temperature to the use of admixture of HF and pyridine. An interesting advance came from the use of KF in hexafluoro-2-propanol, a highly protic medium, which due to its strong hydrogen bonding web structure modifies significantly the reactivity of fluoride anion. *Anti*-addition need the use of catalytic copper(I)- or silver(I)-catalysts whose ligation with the basic oxygen of the amide function leads to a reversal of stereoselectivity. In each case, the few limitations due to structural parameters, most particularly the nature of the electron withdrawing group attached to nitrogen have been mentioned.

The review also covers difunctionalization, making use of dihalides or other electrophilic halonium sources like *N*-halosuccinimides and selenyl halides. Several regio- and stereoselective carbohalogenation involving organometallic carbocupration, radical addition of electrophilic radicals according to iodine transfer methodology, chloropalladation, and ZnCl<sub>2</sub> catalyzed activation of benzylic halides have been reported. Finally, TiCl<sub>4</sub> was shown to offer an entry to hindered  $\gamma$ -hydroxylated  $\alpha$ -chloroenamides. Perfluoroalkylhalogenation has not been investigated yet.

In the field of synthetic applications, organometallic chemistry with reactions like Suzuki, Sonogashira, Stille, Heck, and carbonylative variants can be viewed as a highway opened towards a very large variety of highly functionalized sterically hindered enamides. Metallaphotoredox catalysis methodology that would expand chemical diversity in coupling reactions is still underdeveloped for these particular substrates. Only one example has been reported. Due to the huge interest drawn in photocatalysis over recent years, even fundamental studies regarding the involvement of single electron transfer or two-electron reduction of the C-X bond should be addressed.

Enamides constitutes one the most valuable precursor class for the synthesis of chiral amines via asymmetric hydrogenation. Would some  $\alpha$ -haloenamides be compatible with these asymmetric methodologies? Enamides are also important building blocks for the synthesis of heterocyclic targets. In short, their synthetic applications, although expanding constantly, remain a challenging field.

It is important to point out that access to axially chiral enamides is still largely uncovered<sup>41</sup> and deserves further exploration to develop new axially chiral platforms.

In summary, this short review was designed to provide a clear updated information about the chemistry of  $\alpha$ -haloenamides. As such, it may sound as if this issue had been quite largely explored to date. However, scope and limitations have not been fully investigated and further studies are still warranted. The future will tell.

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