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Copper-Catalyzed Synthesis of Terminal vs. Fluorine-Substituted *N*-Allenamides via Addition of Diazo Compounds to Terminal Ynamides.

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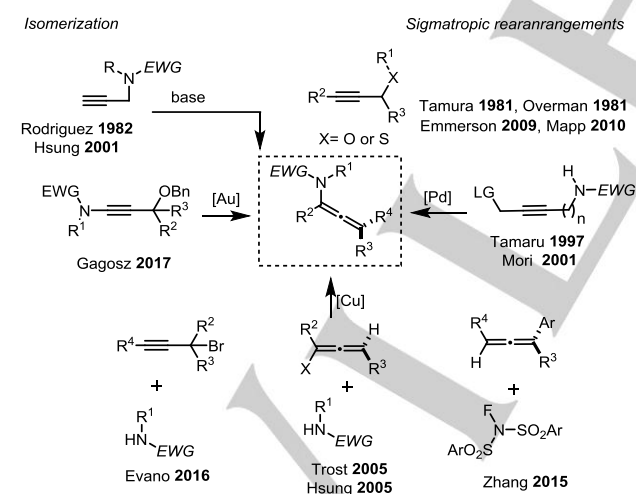
Abstract: A copper-mediated coupling reaction between ynamides and diazo-compounds to produce *N*-allenamides is reported for the first time. This method enables facile and rapid access to terminal *N*-allenamides by using commercially available TMS-diazomethane with wide functional group compatibility on the nitrogen. Furthermore, the ubiquity of molecules containing a fluorine moiety in medicine, in agricultural, and material science requires the continuous search of new building blocks, including this unique surrogate. The CuI/diazo protocol was successfully applied to the synthesis of fluorine-substituted *N*-allenamides. DFT calculations provided insights in the mechanism involved.

N-Allenamides, a subclass of allenes, have become essential motifs in myriad transformations.^[1] Despite their popularity as unique building blocks in organic synthesis the few methods known for their preparation are often hampered by poor substrate scope and a restrained structural diversity.^[2]

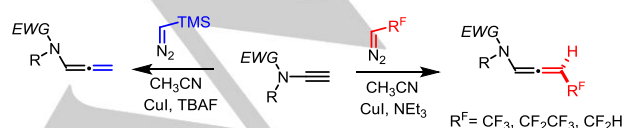
rearrangement of propargylic imidates,^[4] elimination reactions of enol triflates,^[5] as well as intramolecular amino-cyclizations,^[6] only allow the preparation of specific classes of allenamides. The copper-catalyzed allenylation of nitrogen nucleophiles brought a fresh impact to the chemistry of allenamides,^[7] allowing a more general route to these substrates despite the formation of dienes as byproducts. More recently, whereas radical amination of allenes with *N*-fluorodiarenesulfonimides provided aryl-substituted allenamides,^[8] Evano's group published an elegant copper-catalyzed coupling of propargylic bromides and nitrogen nucleophiles, enabling even trisubstituted allenamides to be obtained.^[9] However, the latter strategy is limited to the synthesis of allenamides derived from oxazolidinones and hydantoins (Scheme 1).

Ynamides are known to be particularly suitable compounds for the synthesis of nitrogen-containing molecules. Their attractiveness is undeniably linked to their particular reactivity. These polarized alkynes, which are directly substituted by a nitrogen atom, are strongly activated and stabilized by the electron-withdrawing group on the heteroatom.^[10] Moreover, ynamide substrates are easily accessible through copper catalysis, leading to a large substrate scope.^[11] In this context, ynamides bearing a benzyloxy group at the propargylic position have been efficiently converted into the corresponding allenamides through a 1,5-hydride shift under gold catalysis.^[12] Although the preparation of allenamides is very efficient, the synthesis of allenamides relies on the preparation of peculiar ynamides, and unsubstituted allenamides are obtained with poor yields. In another context, fluorine-containing building blocks have become essential to construct new drug candidates.^[13] Despite the significant advances in fluorine chemistry, fluorine-substituted allenamides are scarce.

Inspired by the addition of diazo compounds to triple bonds,^[14] we envisioned that terminal ynamides would react with diazo-compounds to form *N*-allenamides. To test this hypothesis, our initial attempts consisted of a coupling reaction between terminal ynamide **1a** and a commercially available surrogate of diazomethane, namely trimethylsilyldiazomethane Me₃SiCHN₂ (2 M in diethyl ether) **2**. At room temperature, after 3 hours, we obtained the desired *N*-allenamides, albeit as a mixture of two compounds, **3a** and **4** (ratio = 57/43) in 68 % yield (Table 1, entry 1). To obtain the silylated allenamide exclusively, we planned to avoid moisture in the reaction mixture. Neither the addition of molecular sieves, nor the use of dry solvent (Table 1,



This work: Addition of diazo-compounds to terminal ynamides

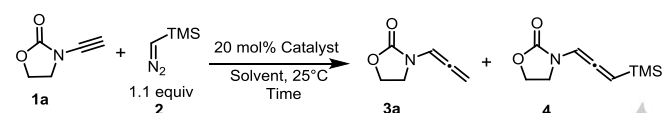


Scheme 1. Typical synthetic routes of *N*-allenamide.

The classical synthesis of allenamides, including base-promoted isomerization of propargylic amides,^[3] sigmatropic

entry 2) nor the addition of a base (Table 1, entry 3) changed the outcome of the reaction; the overall yield remained nearly the same although a slight modification of the ratio of compounds **3a** and **4** in favor of the silylated allenamide **4** was observed when an organic base was added (Table 1, entry 3). Moreover, the addition of an inorganic base as an additive provided only traces of the desired compounds **3a** and **4** (Table 1, entry 4). Changing the copper catalyst or adding a ligand was unproductive, *i.e.*, no reaction or only traces of *N*-allenamides were obtained (Table 1, entries 6-8). However, the use of copper bromide as a catalyst provided the desired *N*-allenamides **3a** and **4**, albeit with a moderate yield of 38% (Table 1, entry 5). Using dioxane as solvent was ineffective (Table 1, entry 9). In contrast, dimethylformamide was impactful and provided *N*-allenamide **3a** along with a small amount of **4** (ratio 99/1) in 52% yield (Table 1, entry 10). Increasing the temperature of the reaction mixture and shortening the reaction time had a positive influence and provided the *N*-allenamides **3a** and **4** in 64% yield (Table 1, entry 11). Increasing the amount of diazo compound **2** resulted in a slight erosion of the yield (Table 1, entry 12). Changing the order of addition decreased the yield by almost half (Table 1, entry 13).

Table 1. Optimization.



Entry	Solvent	20 mol% cat	Time	Ratio 3a/4	Yield
1	MeCN	CuI	3 h	43/57	68%
2	MeCN	CuI / MS	3 h	45/55	37%
3	MeCN	CuI / <i>i</i> Pr ₂ NH	3 h	39/61	[a]
4	MeCN	CuI / Cs ₂ CO ₃	4 h	/	traces
5	MeCN	CuBr	3 h	N.D	38%
6	MeCN	Cu(acac) ₂	4 h	/	[b]
7	MeCN	Cu(MeCN) ₄ PF ₆	3 h	/	Traces ^[c]
8	MeCN	CuI / 1,10-phenanthroline	4 h	/	[b]
9	Dioxane	CuI	3 h	/	traces
10	DMF	CuI	3 h	99/1	52% ^[d]
11	DMF	CuI	1 h 45	99/1	64%
12	DMF	CuI	1 h 45	99/1	60% ^[a]
13	DMF	CuI	2 h	99/1	38% ^[e]
14	MeCN	CuI / TBAF	3 h	100/0	66% ^[f]
15	MeCN	No Cat.	3 h	/	-

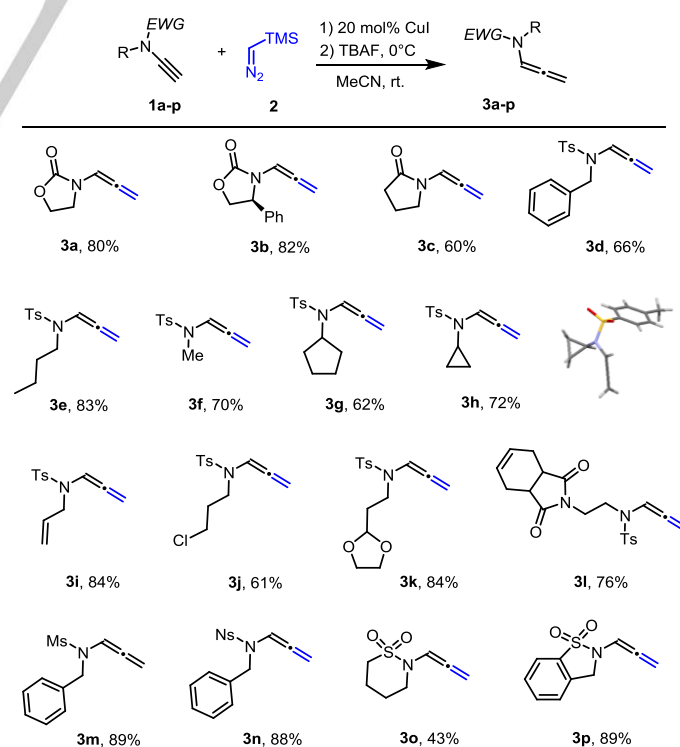
[a] 2 equiv. of diazo compound. [b] 0 °C to rt. [c] -50 °C to rt. [d] 0 °C. [e] Change of the order of addition (diazo compound before ynamide). [f] Addition of TBAF at 0 °C at the end of reaction.

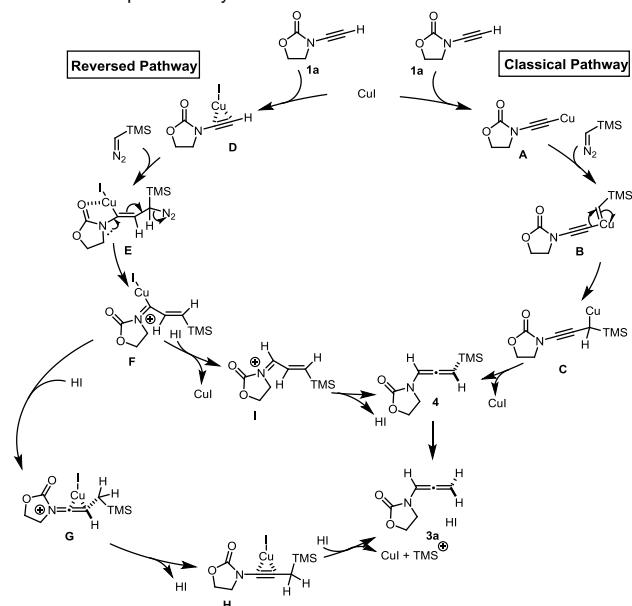
Moreover, when the reaction was performed in acetonitrile in the presence of TBAF, the reaction was oriented to the exclusive formation of the *N*-allenamide **3a** with a higher yield of 66%

(Table 1, entry 14). A control experiment without any copper catalyst showed no transformation of the starting material, thus, illustrating the indispensable role of copper iodide for this transformation (Table 1, entry 15).

Under the optimized reaction conditions, the scope of the reaction was explored by varying the ynamide (Scheme 2). Addition of TMS-diazo **2** to oxazolidinone derivatives **1a** and **1b** resulted in good yields of *N*-allenamides **3a** and **3b**. Reaction with terminal pyrrolidinone **1c** provided the corresponding *N*-allenamide **3c** with a slight erosion of the yield. Linear alkyl groups [*e.g.*, butyl (**3e**) and methyl (**3f**)] as well as cyclic alkyl groups [(cyclopentyl (**3g**) and cyclopropyl (**3h**))] were also suitable substrates for this transformation. X-Ray analysis of **3h** confirmed the structure of amido-cyclopropyl allene **3h** (CCDC 2082118 contains the supplementary crystallographic data for the structure).^[15] Notably, even alkenes (**3i**), halogens (**3j**), protected aldehydes (**3k**), and imides (**3l**) were also compatible, amplifying substantially the substrate scope. The influence of either more labile electron-withdrawing groups on the nitrogen atom, such as mesyl (**3m**), nosyl (**3n**) or more hindered cyclic sulfonamides (**3o**, **3p**), were revealed to be fully accommodated in this transformation.

To gain insight in the underlying reaction mechanism, calculations based on Density Functional Theory (DFT) were performed (computational details in the Supporting Information (SI)). Ynamide **1a** and TMS-diazomethane served as model substrates for all investigated processes. Inspired by previous literature on copper-catalyzed coupling reactions with alkynes,^[16] we have proposed two different multistep pathways (see Scheme 3): a “classical” catalytic cycle (Figure 1. Cycle I), where the Cu(I) specie exchanges with the hydrogen at the β-carbon of **1a**, and a



Scheme 2. Scope for the synthesis of terminal *N*-allenamides.**Scheme 3.** Possible reaction mechanism.

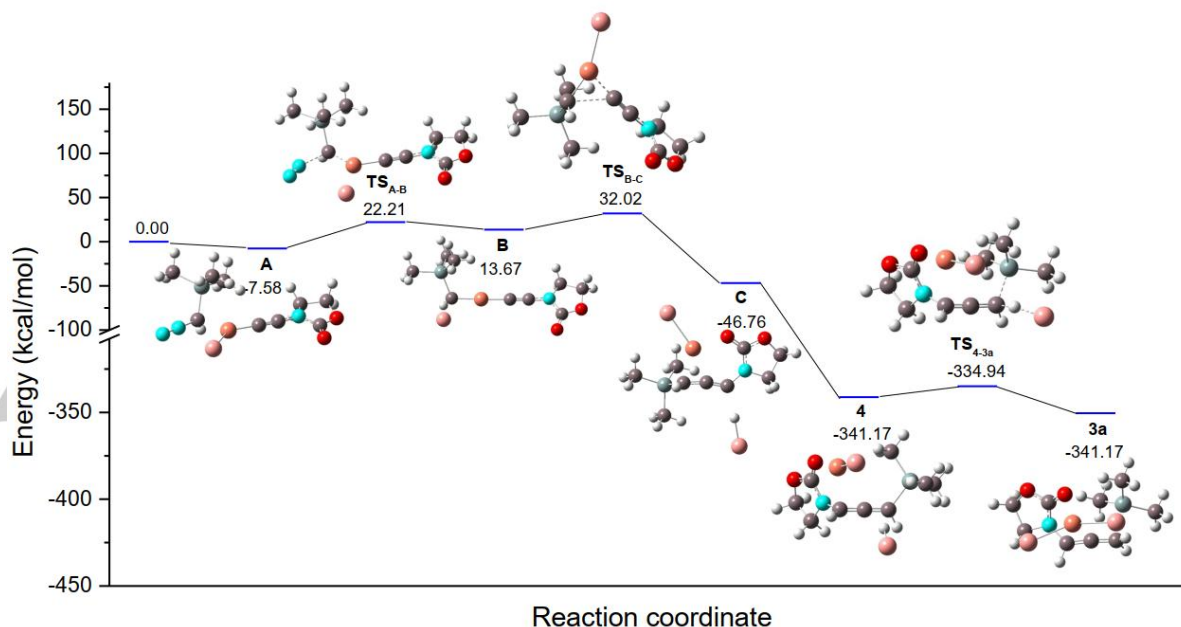
“reversed” catalytic cycle (Figure 2. Cycle II), where the TMS-diazo-compound adds directly to the terminal ynamide at the β position.

In Cycle I, the Cu(I) specie reacts first with **1a** to form a copper acetylide **A**, followed by reaction of **A** with diazo substrate **2**, leading to the copper carbene specie **B**. From intermediate **B**, a migratory insertion into the Cu–carbene bond forms the copper intermediate **C**. Subsequently, a decupration and protonation regenerates copper iodide and forms TMS-allenamide **4**. On the other hand, the metal carbonyl chelation-controlled addition of TMS-diazomethane to the β -position of the ynamide leads to the formation of a copper-alkene specie **E**. Loss of N_2 provides copper-iminium intermediate **F**. Further protonation and decupration of **F** lead to ketene-iminium **G**. A subsequent deprotonation forms ynamide **H**, from which protonation causes elimination of the TMS group, leading to final product **3a**. **Figure 1.** Calculated energy profile for the catalytic cycle I.

Nonetheless, a pathway allowing the formation of product **4** from **F** is possible. This latter, reported in Supporting Information, proceeds via a protodecupration of copper-iminium intermediate **F** to form iminium ion **I**. Finally, deprotonation of **I** leads to *N*-allenamide **4**, which can easily provide terminal *N*-allenamide **3a**.

Catalytic Cycle I (Figure 1).

Catalytic cycle I starts with the activation of the terminal alkyne at the β -position by the Cu(I) specie through a concerted metalation–deprotonation process, thus forming the stable copper acetylide **A** (-7.6 kcal/mol). At this stage, the α -carbon of **A** becomes a nucleophilic site ($\delta^- = -0.61$ |e-|), where TMS-diazomethane can add via **TS_{A-B}** to generate the copper carbene intermediate **B** and release a N_2 molecule. This reaction step is determined to be the rate limiting step, because the calculated activation barrier is 29.8 kcal/mol. The calculated Cu–carbene bond length in intermediate **B** is 1.93 Å. From **B**, a migratory insertion of the alkynyl group into the Cu–carbene bond occurs via a three-membered ring **TS_{B-C}**, forming intermediate **C**. The (Mulliken) partial charge calculated on the TMS-substituted carbon ($\delta^- = -0.88$ |e-|) suggests a facile migratory insertion from the alkynyl group. Indeed, we calculated a corresponding activation energy barrier equal to 18.3 kcal/mol. Finally, a protonation by hydriodic acid of the ynamidic carbon forms the TMS substituted allene **4** and leads to regeneration of the active Cu(I) species. Being barrierless, this step occurs without kinetic impediment. Of note the computed stabilization energy for this step is certainly overestimated due to the fact that it includes also the formation energy of CuI which is fully artificial. Nonetheless, even if the stabilization of **4** is certainly artificial, we can safely affirm that product **4** can easily interconvert to product **3a** via a protonation on TMS-substituted carbon because of the relatively small energy barrier of 6.2 kcal/mol. Furthermore, this reaction step is also favored thermodynamically because product **3a** is found to be more stable than **4** by 9.2 kcal/mol.



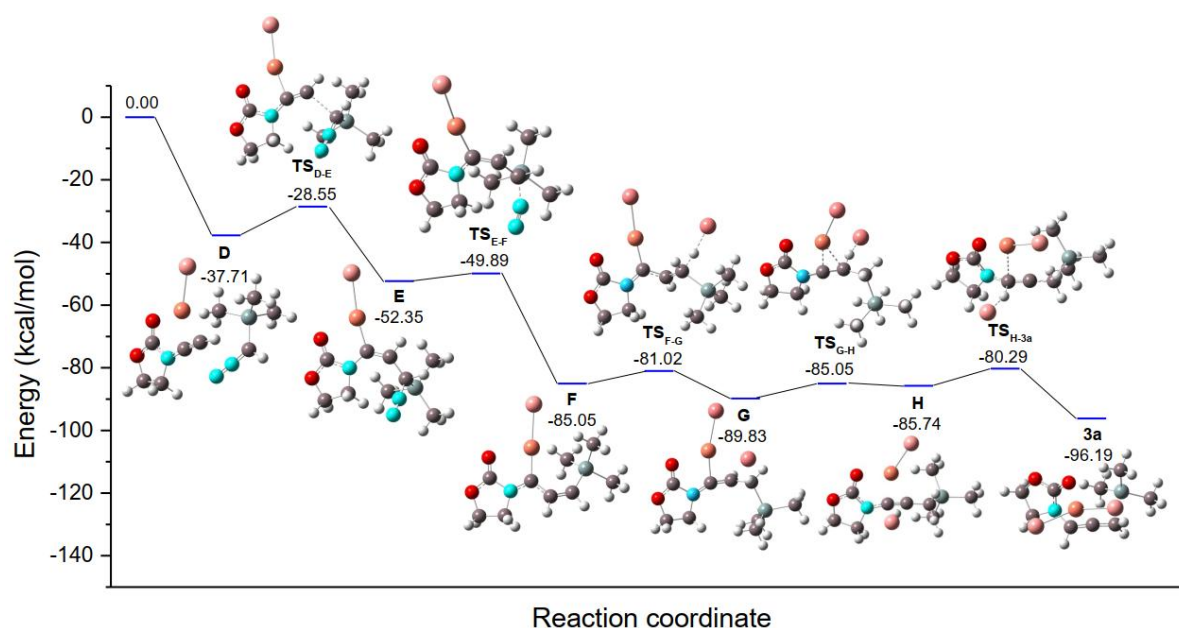


Figure 2. Calculated energy profile for the catalytic cycle II.

Catalytic Cycle II (Figure 2).

The electron-withdrawing carbonyl group of **1a** can not only enhance the stability of intermediate **D** (-37.7 kcal/mol), but also the metal-carbonyl chelation can induce a regioselective β -addition, because in this case the β -carbon is particularly nucleophilic ($\delta^- = -0.70$ |e-|).^[17] The consequent “reversed” addition of **2** forming the copper-alkene intermediate **E** then becomes particularly favorable. Indeed, the energy barrier of **TS**_{D-E} is only 9.2 kcal/mol higher than **D**. From **E**, the ynamidic nitrogen lone pair delocalizes over the alkene skeleton, allowing the release of a N_2 molecule to easily generate intermediate **F**. The activation energy barrier of this step is only 2.4 kcal/mol and leads to a very stable copper-iminium intermediate.

From here, two reaction mechanisms can be envisaged:

1) the β -carbon on the intermediate **F** being nucleophilic (-0.68 |e-|) can be decuprated and protonated by hydroiodic acid leading to intermediate **I** via **TS**_{F-I}. This step results to be effectively kinetically favored since the energetic barrier is of 2.3 kcal/mol. In turn, **I** undergoes deprotonation of the H-substituted alkene carbon by iodide. The process **I** \rightarrow **TS**_{I-4} \rightarrow **4** requests only 2.5 kcal/mol and opens the way not only to the formation of product **4**, but also to the production of **3a**, since **4** interconverts to product **3a**, as already seen for cycle I (see Figure 4 in Supporting Information). 2) The copper moiety migrates from the iminium carbon to the H-substituted alkene carbon, favoring protonation of the TMS-substituted carbon via **TS**_{F-G}, transforming then into the keteneiminium intermediate **G**. The process **F** \rightarrow **TS**_{F-G} \rightarrow **G** is kinetically and thermodynamically favored because the energy barrier is about 4.0 kcal/mol and intermediate **G** is lower than intermediate **F** by 5.0 kcal/mol. Comparing the atomic (Mulliken) charges computed for the **TS**_{F-G} and **G**, it is found that H-substituted keteneiminium C(sp²) becomes more electrophilic (from -0.68 |e-| to 1.29 |e-|). This makes it possible to envisage a proton transfer from carbon of **F** to the iodide anion present in the reaction environment. The low energy barrier (4.8 kcal/mol) computed for this proton transfer confirms the hypothesis and provides the formation of hydroiodic acid and ynamide **H**, where the lone pair returns to the nitrogen,

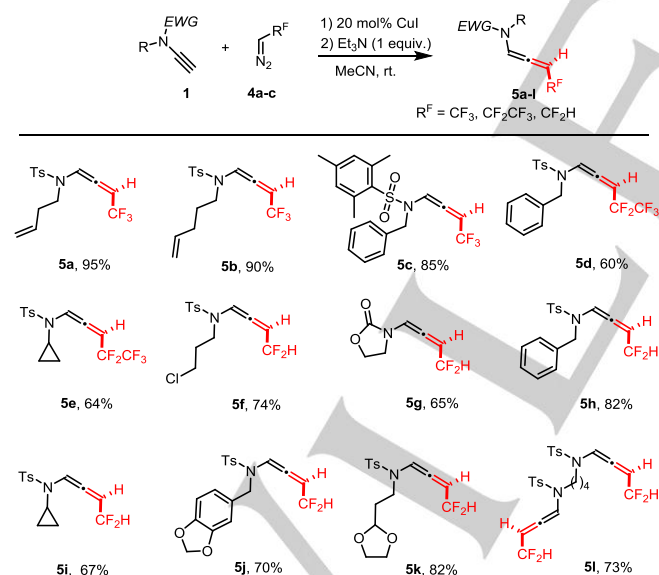
as confirmed by a decrease of the partial charge (from +0.33 |e-| in **G** to +0.08 |e-| in **H**). Finally, the reaction terminates via a protonation of the nucleophilic ynamide carbon ($\delta^- = -0.11$ |e-|), from the hydroiodic acid forming product **3a** and consequent decupration via **TS**_{H-3a} with an activation barrier of 5.4 kcal/mol: the C-H bond decreases, achieving a value of 1.42 Å while the C-Cu is elongated to 2.84 Å, suggesting that there is no more back-donation from the π orbital of the carbon-carbon triple bond to the σ^* antibonding orbital of the C-Cu bond, characteristic of a metal-alkyne bond. Notably, at this stage the TMS group spontaneously eliminates, meaning that it is possible to form solely the most stable product **3a** by catalytic cycle II.

Although catalytic cycle I has been proposed as the classical mechanism for cross-coupling reactions of diazo compounds with alkynes, the formation of copper-carbene intermediate **B** step presents a very high energy barrier (about 30 kcal/mol), whereas the production of copper-substituted alkene **E** in the “reversed” cycle II requires only about 10 kcal/mol. Therefore, considering the energy barriers of the overall copper-catalyzed coupling reaction, we can conclude that the β -addition is preferred and allows the formation both product **4** and **3a**, whose formation is both thermodynamically and kinetically favored, thus explaining the experimental ratio 3a/4 (see Table 1).

Finally, since the stabilization effect provided by the adjacent carbonyl group plays a role driving the reaction towards a “reversed” pathway, in order to understand the high yields obtained for sulfonyl group-protected substrates we have also investigated the first step of each of the two catalytic cycles (*i.e.* **TS**_{A-B} and **TS**_{D-E} of the I and II catalytic cycle, respectively), in the case of the ynamide **1m**. This latter has been considered as model substrate (leading to product **3m**, see Scheme 2), featuring a mesyl-group on the nitrogen in order to see its impact in the first step of the reaction. These data are reported in Supporting Information. As in the case of **1a**, the metal-oxygen chelation induces an enhanced stabilization of the transition state involved in the formation of the copper-alkene intermediate **E** (**TS**_{D-E}) of cycle II thereby making the β -addition effectively preferred since the copper-substituted alkene **E** production

requires 20 kcal/mol less than the formation of copper-carbene intermediate **B**.

Next, our idea was to investigate the synthesis of fluorinated allenamides using fluorinated diazoalkanes. In this context Blanchard, Evano *et al.* reported a synthesis of γ -trifluoromethylated allenamides from trifluoromethylated propargylic carbamates.^[18] First, we examined the more studied trifluorodiazooethane.^[19] An ethereal solution of trifluorodiazooethane was prepared according to Gilman and Jones.^[20] Addition of trifluorodiazooethane to the terminal ynamides under copper-catalysis in acetonitrile provided the corresponding ynamides with very good yields, provided triethylamine was added to the reaction mixture (compounds **5a-c**). Another highly fluorinated compound, the pentafluoroethyl group, also adapted perfectly to the formation of *N*-allenamides (compounds **5d-f**). Judging by the results obtained, the strategy appeared to be viable. Consequently, we investigated more challenging fluorine substituents, namely the CF₂H-group.^[21] Known to be a metabolically stable bioisostere of a hydroxyl group or a thiol group,^[22] the difluoromethyl group (CF₂H) has emerged as one of the most important fluorine moieties in pharmaceutical, agricultural, and material science. Mykhailiuk reported an elegant *in situ* generation of difluoromethyl diazomethane from difluoroethylamine^[23] for the synthesis of difluorinated pyrazoles via [3+2] cycloadditions. Whereas these authors observed a [3+2] cycloadditions when CF₂HCHN₂ was added to electron deficient alkynes, we obtained CF₂H-substituted *N*-allenamides from terminal ynamides. Oxazolidinone (**5g**), cyclic alkyls groups [cyclopropyl (**5h**)], aryl groups (**5i**, **5j**) as well as protected aldehydes (**5k**) and amides (**5l**) were accommodated (Scheme 4).



Scheme 4. Scope for the synthesis of fluorinated-*N*-allenamides.

To conclude, we present a straightforward method to obtain *N*-allenamides through copper-catalyzed addition of diazo-compounds to terminal ynamides. DFT-calculations showed that this transformation relies on an uncommon “reversed” mechanism that, regardless of the polarization of the triple bond of the ynamide, favors the addition of the diazo compound at the β -position of the ynamide. The protocol tolerates a wide range of

functional groups on the ynamide moiety, but also fluorinated diazo-compounds were accommodated, thus providing access to fluoro-substituted *N*-allenamides. This copper-catalyzed process represents the first synthesis of tri-, di- or per-fluorinated *N*-allenamides from ynamides.

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Supporting Information

CCDC 2082118 (3h) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Experimental procedures and spectral data for all these new compounds are available in Supporting Information.

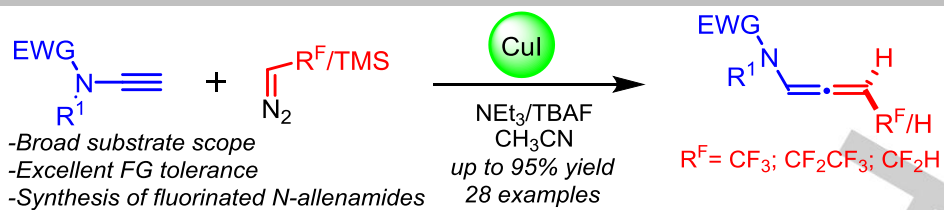
Conflict of interest

The authors declare no competing financial interest.

Keywords: Ynamides • *N*-allenamides • Diazo-compounds • Fluorinated-*N*-allenamides • Copper Catalysis

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A CuI-catalyzed robust synthesis of *N*-allenamides from ynamides by the reaction with various diazo-compounds was developed. DFT-calculations showed that this transformation relies on an uncommon reversed mechanism that, regardless of the polarization of the ynamide, favors the addition of the diazo compound at the β -position of the ynamide. The protocol tolerates a wide range of functional groups. This copper-catalyzed process represents the first synthesis of tri-, di- or per-fluorinated *N*-allenamides from ynamides.