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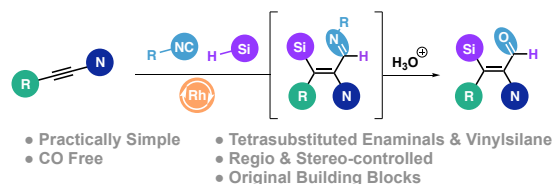
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Versatile Access to Tetrasubstituted 2-Amidoacroleins Through Formal Silylformylation of Ynamides.

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Supporting Information Placeholder



ABSTRACT: In this paper we are reporting the first regio- and stereo-selective silylformylation of ynamides. This reaction is tolerant to a wide range of functional groups around the ynamides. The substitution of CO by an isocyanide makes this reaction safer and more practical than standard silylformylation reactions. It overall represents a versatile and rapid access to various tetrasubstituted 3-silyl-2-amidoacrolein derivatives. The synthetic potential of these new building blocks has been evaluated by performing several post-functionalization.

Among the different small polyfunctionalized building blocks available in organic chemistry, enaminals have demonstrated their high synthetic potential, mainly in heterocyclic chemistry, by being a partner of choice in several multicomponent reactions. However, if 3-aminoacrolein derivatives have been deeply investigated over the past decades, both for their synthesis and for their use,¹ 2-aminoacroleins have attracted much less attention.² This can be mainly explained by a lack of effective and versatile synthetic accesses to this regioisomer. Recently, several groups, including ours, have investigated the regioselective carbonylation of nitrogen-substituted alkynes such as ynamides^{3,4} as an efficient strategy to reach this general motif or its derivatives. However, there is no general and controlled access to noncyclic tetrasubstituted 2-aminoacroleins to date. To the best of our knowledge, Lam and co-workers on one side⁵ and Hou and co-workers on the other side⁶ reported the only examples of ynamide difunctionalization, both through carbocationization strategies, resulting in acyclic tetrasubstituted 2-amidoacrylate derivatives (Figure 1). Notably, these reactions require the use of sensitive organozinc reagents which are not always easy to obtain when they are not commercially available. Thus, to offer a higher degree of versatility, we have decided to focus our attention on silylcarbonylations of ynamides. Indeed, in this case the reaction would lead to fully substituted 2-aminoacroleins incorporating an easily transformable vinylsilane functionality,⁷ thus making this platform particularly tuned to molecular diversity.

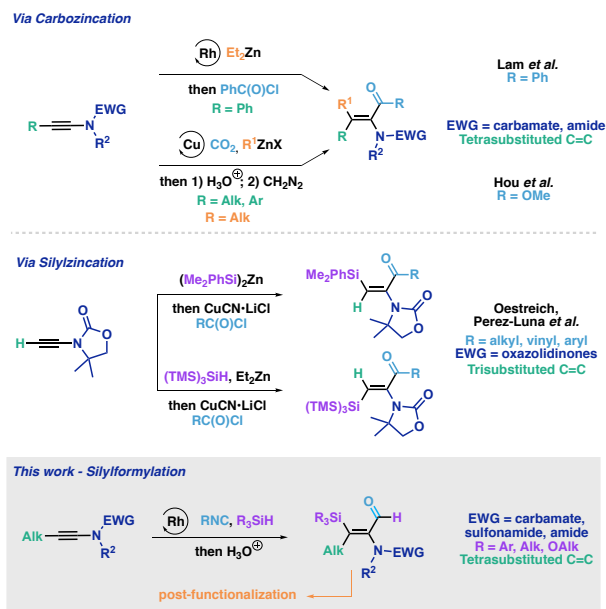


Figure 1 Reported difunctionalization of ynamides leading to 2-amidoacrolein derivatives and proposed strategy

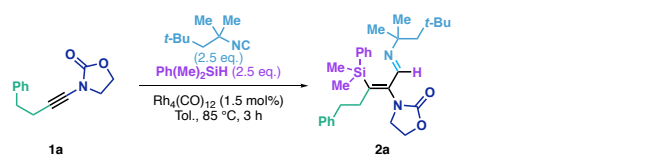
To our knowledge, only the groups of Oestreich and Perez-Luna reported a silylcarbonylation of ynamides based on a key regio- and stereoselective silylzincation step followed by a copper-mediated nucleophilic attack on an acyl chloride.⁸ Nicely, this work allowed either the Z or the E isomer to be obtained selectively. However,

this reaction appeared to be limited to a single terminal ynamide bearing a 2,2-dimethyl-oxazolidinone as a nitrogen substituent. Interestingly, this reaction has been subsequently extended to germylcarbonylations of ynamides with similar limitations.⁹

In this global context, inspired by Fukumoto's and Chatani's work on terminal alkynes,¹⁰ we have decided to develop the formal silylformylation¹¹ of ynamides using readily available reagents such as silanes and isocyanides to make it as practical as possible. Our choice to avoid carbon monoxide was additionally dictated by the dangerousness of this gas as well as by the need to use expensive specific equipment (high-pressure reactor, detector). However, this approach comes with several important challenges. First, we must mention the issues of stereoisomeric mixtures (E/Z) of the products that are frequently reported in the field of alkyne silylformylations. Another classical problem is the competitive hydrosilylation reaction that could easily emerge in the case of electron rich alkynes such as ynamides. Moreover, it is important to note that very few examples of silylformylation of unsymmetrical internal alkynes have been reported due to major regioselectivity problems.¹¹ Finally, as this reaction leads to an intermediate imine that needs to be hydrolyzed at the end of the reaction, it is hard to anticipate the stereostability of the C=C double bond during this last process.

Pleasingly, after optimization, while using ynamide 1a bearing an alkyl chain on the alkyne and an oxazolidinone, we defined our best reaction conditions as follows: toluene as solvent, 2.5 equiv of 1,1,3,3-tetramethylbutyl isocyanide and phenyldimethylsilane, Rh₄(CO)₁₂ (1.5 mol %) as a catalyst. Under these conditions, complete conversion occurred after 3 h at 85 °C to furnish the corresponding silyl-imine product 2a with a very good 93% NMR yield as a single regio- and stereoisomer (Table 1, entry 1).

Table 1 Control Reactions of Optimized Conditions



Entry	Deviations	Yield (%) ^a
1	none	93 (79)
2	THF as solvent	84
3	CH ₃ CN as solvent	37
4	CH ₂ Cl ₂ as solvent	n.r.
5	[Rh(acac)(CO) ₂] (1.5 mol%) Xantphos (3 mol%)	84
6	[Rh(acac)(CO) ₂] (1.5 mol%)	32 ^{b, c}

	PPh ₃ (3 mol%)	
7	Pd(PPh ₃) ₄ (1.5 mol%)	n.r.
8	1 equiv. of isocyanide	27 ^c
9	1 equiv. of silane	13 ^c
10	Room temperature	0 ^d

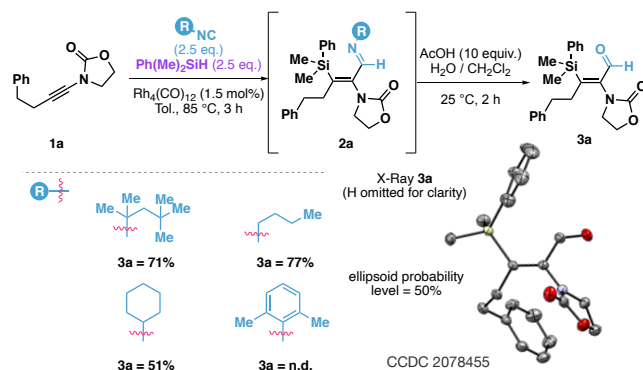
^a Yields determined by ¹H NMR using dimethylterephthalate as an internal standard (isolated yield into brackets); ^b A mixture of two isomers with a ratio of 8:2 was observed; ^c Incomplete conversion; ^d Only starting material and traces of the hydrosilylation product were observed in ¹H NMR.

Notably, THF appeared to be the only other solvent that could efficiently be used (Table 1, entry 2). However, while investigating the scope of the reaction we noticed that yields were significantly lower with THF than toluene when ynamides bearing a nitrogen moiety different from oxazolidinone were employed as substrates. Similarly, the only other catalytic system that appeared to be efficient was the combination of [Rh(acac)(CO)₂] as a precursor with Xantphos as ligand (Table 1, entry 5). Again, this system of the nature of isocyanide reagents, and it appeared that noncyclic alkyl isocyanides such as 1,1,3,3-tetramethylbutyl or butyl isocyanide gave the best results with respective yields of 3a of 71% and 77%. Due to its volatility and its very strong odor, we preferred to avoid the use of butyl isocyanide and to continue our study with the more practical 1,1,3,3-tetramethylbutyl isocyanide (Table 2).

With the optimal conditions in hand, we decided to investigate the scope and limitations of this silylformylation reaction (Table 3). First, we demonstrated that the reaction with arylsilanes, such as diphenylmethylsilane or triphenylsilane for instance, was always leading to the targeted aldehyde in good yields (82% (3b) and 79% (3c)). Contrastingly, the use of a trialkylsilane, such as triethylsilane, led to a significant loss of reactivity as the complete conversion was only reached after 72 h. Moreover, the corresponding aldehyde 3d was obtained in a moderate 38% yield as a 3:7 mixture of Z/E isomers. The reaction with ethoxydimethylsilane, to reach a valuable alkoxyvinylsilane that could subsequently be engaged in a Hiyama–Denmark cross-coupling,^{7d,12} led to the intermediate imine product 2e in a good 60% yield (determined by NMR with an internal standard). However, this compound appeared to be extremely sensitive which made its hydrolysis and purification impossible to achieve with an acceptable yield. To follow our investigations, we then evaluated the effect of the ynamide substitutions on the course of the reaction. On the one hand, alkyl groups on the alkyne moiety always gave the targeted aldehydes (3f–3i) in good yields (63–82%). Notably, the bulky tert-butyl substitution totally inhibited the reaction. On the other hand, all ynamides bearing an aryl substituent on the alkyne moiety, such as a phenyl group (1j) for instance, that were investigated led systematically to the hydrosilylated products without traces of the desired imine

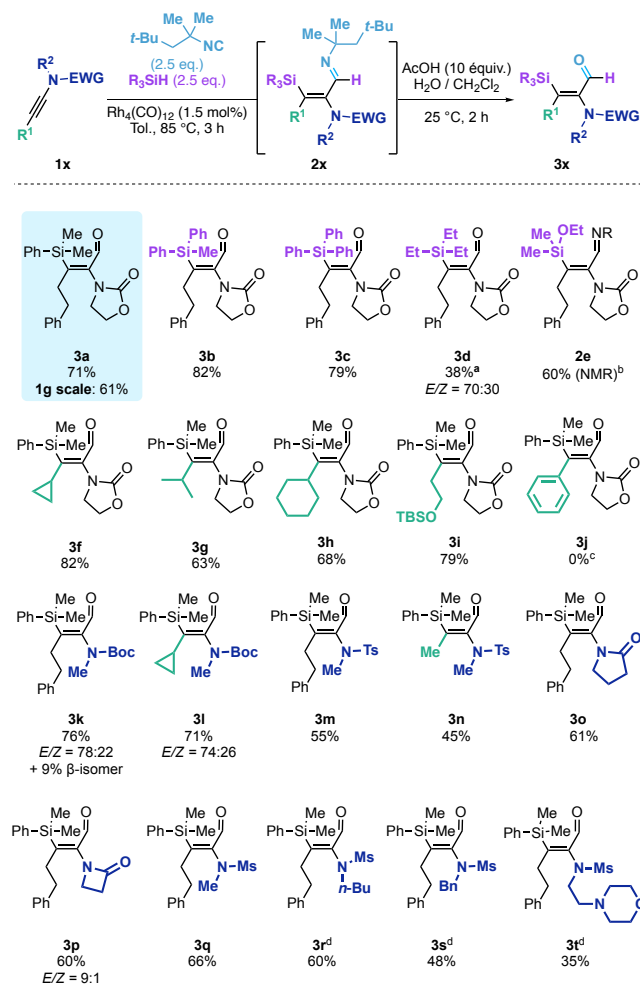
intermediate **2j**.¹³ Regarding the electron-withdrawing groups on the nitrogen of the ynamides, this transformation revealed to be widely permissive, as various groups such as amides, sulfonamides and carbamates appeared to be well compatible with this reaction (**3k–3t**). Interestingly, if a Boc group was allowed to reach the corresponding aldehyde **3k** in a good 76% yield, the products were obtained in a mixture of *E/Z* isomers in a 78:22 ratio.

Table 2 Influence of the isocyanide structure



With our best conditions in hands, we decided to investigate the scope and limitations of this silylformylation reaction (**Table 3**). Firstly, we demonstrated that the reaction with arylsilanes, such as diphenylmethylsilane or triphenylsilane for instance, was always leading to the targeted aldehyde in good yields (82% (**3b**) and 79% (**3c**)). Contrastingly, the use of a trialkylsilane, such as triethylsilane, led to a significant loss of reactivity as the complete conversion was only reached after 72 hours. Moreover, the corresponding aldehyde **3d** was obtained in a moderate 38% yield as a 3:7 mixture of *Z/E* isomers. The reaction with ethoxydimethylsilane, to reach a valuable alkoxyvinylsilane that could subsequently be engaged in a Hiyama-Denmark cross-coupling,^{7d,12} led to the intermediate imine product **2e** in a good 60% yield (determined by NMR with an internal standard). However, this compound appeared to be extremely sensitive which made its hydrolysis and purification impossible to achieve with an acceptable yield. To follow our investigations, we then evaluated the effect of the ynamide substitutions on the course of the reaction. On the one hand, alkyl groups on the alkyne moiety always gave the targeted aldehydes (**3f–3i**) in good yields (63–82%). Notably, the bulky *tert*-butyl substitution totally inhibited the reaction. On the other hand, all ynamides bearing an aryl substituent on the alkyne moiety, such as a phenyl group (**1j**) for instance, that were investigated led systematically to the hydrosilylated products without traces of the desired imine intermediate **2j**.¹³ Regarding to the electron-withdrawing groups on the nitrogen of the ynamides, this transformation revealed to be widely permissive as various groups such as amides, sulfonamides and carbamates appeared to be well compatible with this reaction (**3k–3t**). Interestingly, if a Boc group allowed to reach the corresponding aldehyde **3k** in a good 76% yield, the products were obtained in a mixture of *E/Z* isomers in a 78:22 ratio.

Table 3 Scope of the reaction



^a In this case the kinetic of the reaction is very slow and the mixture had to be left for 72 h to reach complete conversion resulting in the formation of several byproducts; ^b the imine **2e** was too sensitive to be hydrolyzed into the corresponding aldehyde and an NMR yield has been performed using dimethylterephthalate as internal standard; ^c the reaction led only to the formation of the hydrosilylation product (**4 - Figure 2**); ^d butyl isocyanide was used instead of 1,1,3,3-tetramethyl butyl isocyanide.

Notably, about 10% of the β -E isomer has been also detected. This loss of selectivity can reasonably be attributed to the significant steric hindrance of the Boc group. Similarly, in a less intuitive way, a β -lactam moiety as the nitrogen part of the substrate also led to a light erosion of the stereoselectivity as the corresponding aldehyde **3p** was obtained in 61% yield as a 9:1 *E/Z* mixture. Remarkably, switching a tosyl group (**3m**) to a mesyl group (**3q**) as the nitrogen protecting group increased the yield by approximately 10% presumably due to its relative smaller steric hindrance. Inversely, a bigger substituent on the nitrogen such as a butyl group induced a significant erosion of the yield, but not of the stereoselectivity, in comparison to an equivalent substrate bearing a methyl group. To overcome this limitation, the use of the less hindered butyl isocyanide

allowed a significant increase in the efficiency of the transformation, and the corresponding aldehyde **3** was obtained in a good 60% yield. Pleasingly, the use of this alternative isocyanide allowed extension of the scope of this transformation to substrates bearing various substituents on the nitrogen such as a benzyl group (**3s**) or an ethyl-morpholine chain (**3t**). Various terminal ynamides were also tested but were systematically degraded under our silylformylation conditions.

Based on previous reports on silylformylation reactions, a speculative mechanism can be proposed (Figure 2).^{10,11,14}

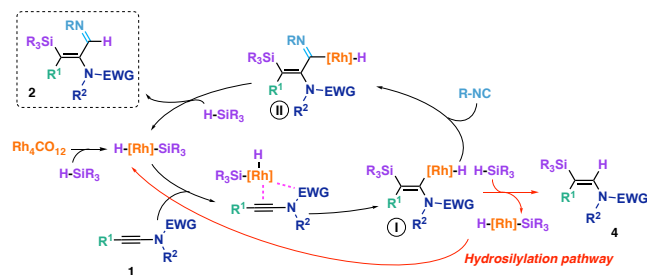


Figure 2 Speculative mechanism for the formation of **2** & **4**

After an activation step of $\text{Rh}_4(\text{CO})_{12}$ precatalyst, the $[\text{Si}-\text{Rh}]$ newly formed complex could proceed to a silylmetalation to lead to the intermediate I. The high regioselectivity could be explained by a combined effect of the polarization of the C–C triple bond and a possible coordination of rhodium to the electron-withdrawing group carried by the nitrogen of the ynamides.^{4f,15} Then the insertion of the isocyanide could lead to the acylrhodium II which can then react with the silane to form a complex that will undergo a reductive elimination to form the targeted imine **2** while regenerating the active $[\text{Si}-\text{Rh}]$ catalyst. On its side, the competitive hydrosilylation product that has been observed while using a phenyl substituted ynamides (i.e., to reach the product **3j** for instance) could come from the direct reaction of intermediate I with the silane without previous insertion of the isocyanide (red pathway in Figure 2)

Finally, to investigate the synthetic potential of our new building blocks, several postfunctionalizations have been performed to selectively change different positions around the double bond (Figure 3). To start, by means of an NBS-mediated bromodesilylation reaction, we obtained the tetrasubstituted vinyl bromide **5a** in a nonoptimized yield of 64% and a 58:42 E/Z ratio. Then various transformations of the aldehyde moiety have been performed. Nicely, a Wittig reaction with the (carbethoxymethylene)triphenylphosphorane led efficiently to the diene **6a** as a single isomer in 84% yield. It has also been possible to obtain the allylic alcohol **7a** in 79% yield thanks to a classical reduction reaction using NaBH_4 in methanol. Subsequently, we performed a protodesilylation reaction on this compound

to obtain the corresponding alcohol **8a** in 84% yield. Notably, the protodesilylation reaction directly applied to the substrate **3a** led to a complex mixture. Finally, a two-step reductive amination allowed us to form the allylic amine **9a** in 40% yield.

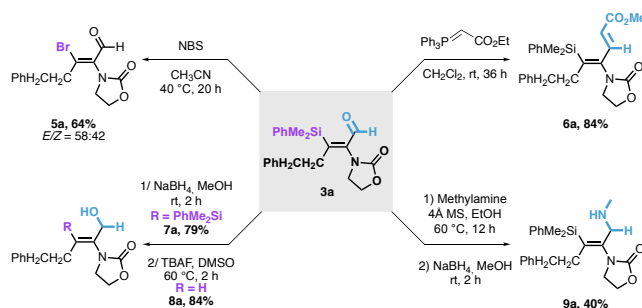


Figure 3 Follow-up chemistry

In conclusion, we have developed the first silylcarbonylation of ynamides selectively leading to tetrasubstituted 2-amidoacroleins. This difunctionalization proved to be highly regio- and stereoselective with variously substituted substrates in the alkyne or nitrogen position. The main limitation proved to be the use of arylsubstituted ynamides, as these substrates mainly lead to the corresponding hydrosilylation products. Furthermore, as long as they carried at least one aromatic substituent, all silanes tested were evaluated as effective in this reaction. Finally, in order to evaluate the synthetic potential of these new molecular building blocks, different transformations were performed to provide selectively highly functionalized molecules.

ASSOCIATED CONTENT

Accession codes

CCDC 2078455 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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