

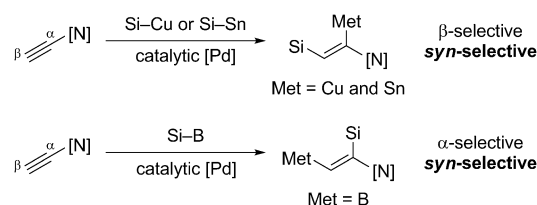
Trans-Selective Radical Silylzincation of Ynamides**

Elise Romain, Carolin Fopp, Fabrice Chemla, Franck Ferreira, Olivier Jackowski, Martin Oestreich,* and Alejandro Perez-Luna*

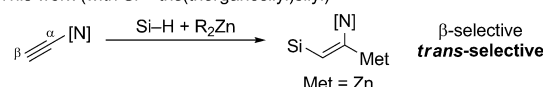
Abstract: The silylzincation of terminal ynamides is achieved through a radical-chain process involving $(\text{Me}_3\text{Si})_3\text{SiH}$ and R_2Zn . A potentially competing polar mechanism is excluded on the basis of diagnostic control experiments. The unique feature of this addition across the $\text{C}\equiv\text{C}$ bond is its *trans* selectivity. One-pot electrophilic substitution of the $\text{C}_{\text{sp}^2}\text{--Zn}$ bond by Cu^{I} -mediated C--C bond formation and subsequent manipulation of the $\text{C}_{\text{sp}^2}\text{--Si}$ bond provides a modular access to $\text{Z-}\alpha,\beta$ -disubstituted enamides.

The addition of Si--Met bonds across $\text{C}\equiv\text{C}$ bonds is an area of intense ongoing research as it offers the possibility to prepare in a single operation 1,2-difunctionalized C=C bonds, i.e., β -metalated vinylic silanes, ideally suited for the subsequent introduction of two different substituents.^[1,2] However, the success of this approach is dependent on the regio- and stereoselectivity of the addition reaction. Popular procedures to perform the silylmetalation of alkynes are the direct silylcupration^[3] and silylzincation^[4] as well as the Cu^{I} -catalyzed silylmagnesianation^[5] and silylzincation.^[6,7] The use of silylstannanes or silylboronic esters for this purpose is also well established.^[1] The classic silylmetalation pathway is entered by transmetalation, whereas oxidative addition chemistry allows for silylstannylation and silylboration reactions. The above-cited methods offer a range of options to control the sense of regiochemistry. By contrast, tuning of stereochemistry is rarely feasible, because these are usually *syn*-addition processes and, hence, provide access to *cis*-silylmetalated alkenes.^[8,9] Thus, finding a method to achieve the silylmetalation of alkynes in a *trans*-stereoselective manner is highly relevant. The demonstration that the *trans* carbocation^[10,11] of alkynes can be achieved by a radical mechanism led us to consider a radical-based silylzincation approach to address this issue.

Previous reports (with $\text{Si} = \text{triorganosilyl}$)



This work (with $\text{Si} = \text{tris(triorganosilyl)silyl}$)



Scheme 1. Diastereocontrolled silylmetalation of terminal ynamides.

Here we focus on ynamides, because the functionalization of these nitrogen-substituted alkynes through addition reactions across their $\text{C}\equiv\text{C}$ bond is currently attracting attention.^[12] A number of protocols was developed for the silylmetalation of ynamides (Scheme 1). Silylcupration^[13] and the Pd^0 -catalyzed silylstannylation^[14] afford α -metalated $\text{Z-}\beta$ -silylenamides. Conversely, the Pd^0 -catalyzed silylboration reaction gives β -metalated $\text{Z-}\alpha$ -silylenamides.^[15] To date, the available synthetic tools only offer the possibility to determine the site selectivity invariably leading to Z- -metalated silylenamides. Here we describe the regio- and stereoselective preparation of α -metalated $\text{E-}\beta$ -silylenamides through the silylzincation of ynamides by reaction with a combination of a hydrosilane and a dialkylzinc reagent. This system leads to an unprecedented *trans* stereoselectivity and represents the first example of a radical-based silylmetalation reaction.^[16] As part of this work, we demonstrate the synthetic potential of this stereodefined construction of orthogonally metalated enamides.

Our idea, outlined in Scheme 2 (top), was inspired by a report on the formation of silyl radicals by the reaction of various silyl-substituted hydrosilanes with dialkylzinc reagents in the presence of radical initiators.^[17] We reasoned that radical **II**, produced in such a way from $(\text{Me}_3\text{Si})_3\text{SiH}$ (**I** $\rightarrow$ **II**),^[18] would add across ynamide **III** to provide regioselectively Z- -configured α -amino vinylic radical **IV** (**II** $\rightarrow$ **IV**).^[19] Reaction of **IV** with the dialkylzinc by homolytic substitution ($\text{S}_{\text{H}}2$) at the Zn atom would afford α -zincated β -silylenamides **V** concomitant with the formation of an alkyl radical that would propagate a radical chain (**IV** $\rightarrow$ **I**). According to this picture, the stereoselectivity of the process would be that of the zincation step. By deliberate installation of a donor group at the ynamide nitrogen atom (Figure 1), we hoped to activate the dialkylzinc reagent toward $\text{S}_{\text{H}}2$ by Lewis pair formation, thereby outcompeting the Z- -to- E- isomerization of the vinylic

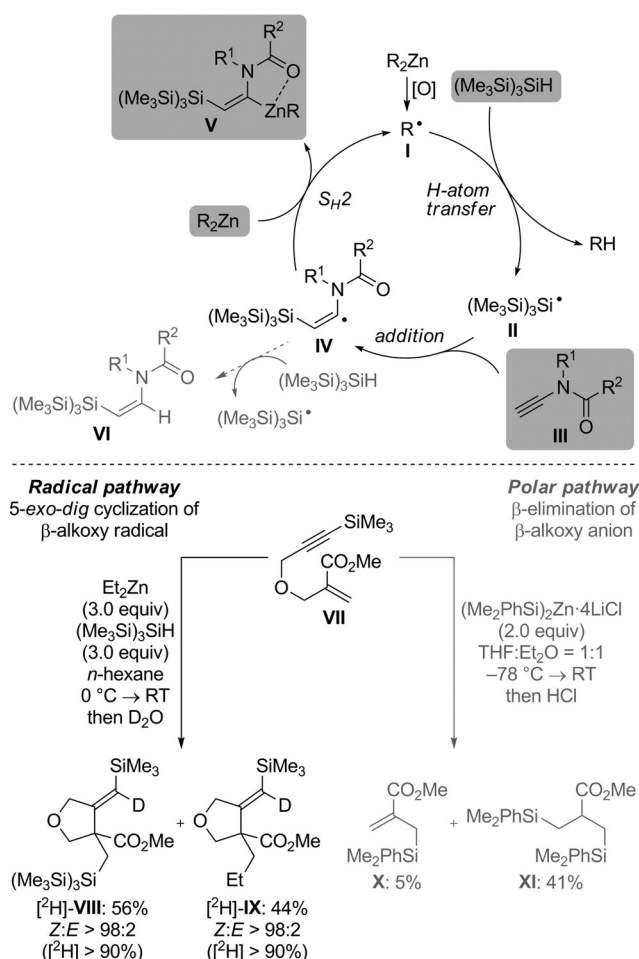
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Scheme 2. Anticipated radical approach to the *trans*-selective silylzincation of ynamides (top) and verification of the radical mechanism (bottom).

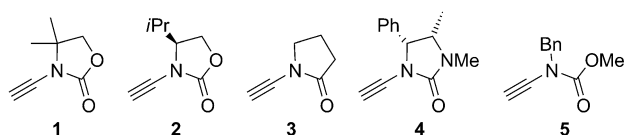


Figure 1. Ynamides considered in this work.

radical **IV**.^[10a] That would secure the *trans* stereoselectivity of the overall process. A key requirement is that radical **IV** must undergo Zn-atom transfer faster than competitive H-atom transfer from $(\text{Me}_3\text{Si})_3\text{SiH}$ ($k_{\text{IV-V}} > k_{\text{IV-VI}}$). If not, hydrosilylation^[20] of **III** will occur (**III** $\rightarrow$ **VI**) and the Zn functionality is lost.

As previously demonstrated by Apeloig and co-workers, the combination of a dialkylzinc reagent, for example, Et_2Zn , and a silyl-substituted hydrosilane such as $(\text{Me}_3\text{Si})_3\text{SiH}$ indeed yields $[(\text{Me}_3\text{Si})_3\text{Si}]_2\text{Zn}$ in the absence of a deliberately added radical initiator.^[17] Hence, its polar addition across triple bonds had to be excluded. To distinguish between radical and polar pathways, we employed **VII** as a mechanistic probe (Scheme 2, bottom). Radical 1,4-addition would proceed through a β -alkoxy radical followed by a 5-*exo-dig* ring

closure (**VII** $\rightarrow$ **VIII**, left), whereas the alternative polar addition would form a fragile β -alkoxy anion prone to rapid β -elimination (**VII** $\rightarrow$ **X**, right). Subjecting **VII** to the later established procedure yielded cyclized $[\text{2H}]\text{-VIII}$ and $[\text{2H}]\text{-IX}$ exclusively (as a result of competing ethyl radical addition). Conversely, $(\text{Me}_2\text{PhSi})_2\text{Zn}$ that is unlikely to form radicals led to quantitative fragmentation (**VII** $\rightarrow$ **X**); **X** reacted with the remaining zinc reagent furnishing **XI**.^[21] In agreement with the requirement for a silyl group at the silicon atom,^[17,18] treatment of **III** with Me_2PhSiH and Et_2Zn was not effective. These findings strongly support the proposed mechanism (Scheme 2, top).

Ynamide **1** was selected as test substrate (Table 1). The initial conditions, involving Et_2Zn (3.0 equiv) and $(\text{Me}_3\text{Si})_3\text{SiH}$ (1.3 equiv) at 0°C in CH_2Cl_2 , led to substrate

Table 1. Optimization of the silylzincation of ynamide **1**.

Reaction scheme showing ynamide **1** reacting with R_2Zn (3.0 equiv), $(\text{Me}_3\text{Si})_3\text{SiH}$ (1.3 equiv), then $\text{NH}_4\text{Cl}/\text{NH}_3$ or ND_4Cl to yield products **Z-6** and **E-6**.

Entry	Conditions	E	Product ^[a]	Yield [%] ^[b]	d.r. (Z:E) ^[c]
1	Et_2Zn , CH_2Cl_2 , 0°C	H	6	6 ^[d]	—
2	Et_2Zn , <i>n</i> -hexane, 0°C	H	6	97	$> 98:2$
3	Et_2Zn , <i>n</i> -hexane, 0°C	D	$[\text{2H}]\text{-6}$	95 ^[e]	$> 98(79\%[\text{f}]):2$
4	Et_2Zn , ^[g] <i>n</i> -hexane, 0°C	D	$[\text{2H}]\text{-6}$	98 ^[e]	$> 98(78\%[\text{f}]):2$
5	$(\text{cHex})_2\text{Zn}$, <i>n</i> -hexane/ Et_2O , 0°C	D	$[\text{2H}]\text{-6}$	95 ^[e]	$> 98(86\%[\text{f}]):2$
6	Me_2Zn , <i>n</i> -hexane, 0°C	H	6	77	$37:63$

[a] Only β -silylated regioisomers were detected ($\beta:\alpha > 98:2$). [b] Combined yield of isolated diastereomers. [c] Determined by ^1H NMR analysis prior to purification. [d] 33% of starting material recovered. [e] Yield determined by ^1H NMR spectroscopy using butadiene sulfone as internal standard. [f] Deuterium grade estimated by NMR analysis. [g] 5.0 equiv Et_2Zn were used.

degradation, and the desired β -silylenamide **6** was isolated in 6% yield at 67% conversion (entry 1). A significant improvement was obtained in *n*-hexane, and **Z-6** was formed in 97% yield as a single regio- and diastereoisomer (entry 2). We emphasize here that the *Z* double bond geometry of **6** ($^3J_{\text{cis}} = 11.2\text{ Hz}$) is opposite to that of the product of the polar addition of $(\text{Me}_2\text{PhSi})_2\text{Zn}$ across **1** ($^3J_{\text{trans}} = 17.9\text{ Hz}$, not shown), lending clear evidence for the radical mechanism. To discriminate between the two possible reaction pathways leading to **Z-6**, that is, silylzincation (**IV** $\rightarrow$ **V**) versus hydrosilylation (**IV** $\rightarrow$ **VI**), the reaction was quenched with ND_4Cl . $[\text{2H}]\text{-6} was recovered with 79% deuterium incorporation at the α -position (entry 3), thereby providing strong evidence for zinc intermediate **V**. We attribute the strong solvent effect to a more favorable complexation of Et_2Zn to the carbonyl group of the oxazolidinone. The formation of such a complex would provide a more efficient radical chain by activating the starting ynamide toward silyl radical addition and at the same$

time by facilitating the S_H2 step. Whereas an increase of the amount of Et_2Zn did not make any difference (entry 4), the ease of the dialkylzinc reagent to undergo Zn-atom transfer was important. With $(cHex)_2Zn$, a secondary dialkylzinc reagent, more susceptible toward S_H2 than Et_2Zn , **Z-6** was obtained as a single isomer with a slightly improved level of zincation (entry 5). In turn, the use of Me_2Zn gave enamide **6** as a mixture of double bond isomers (entry 6), consistent with a more difficult S_H2 step that is not fast enough to occur prior to Z -to- E isomerization of **IV**. Finally, it is worthy of mention that in every case, the initiation of the silylzincation process by oxidation of the dialkylzinc reagent by traces of oxygen present in the reaction media is sufficient to achieve full conversion, and the introduction of additional air or radical initiators is not required. This indicates that the radical chain involved in the process is remarkably efficient.

We next considered the scope of this new silylzincation reaction. Ynamides substituted at the alkyne terminus by a phenyl or an alkyl group failed to react. Conversely, the modification of the nitrogen group was well tolerated (Table 2). Ynamides **2-4** reacted smoothly in the presence

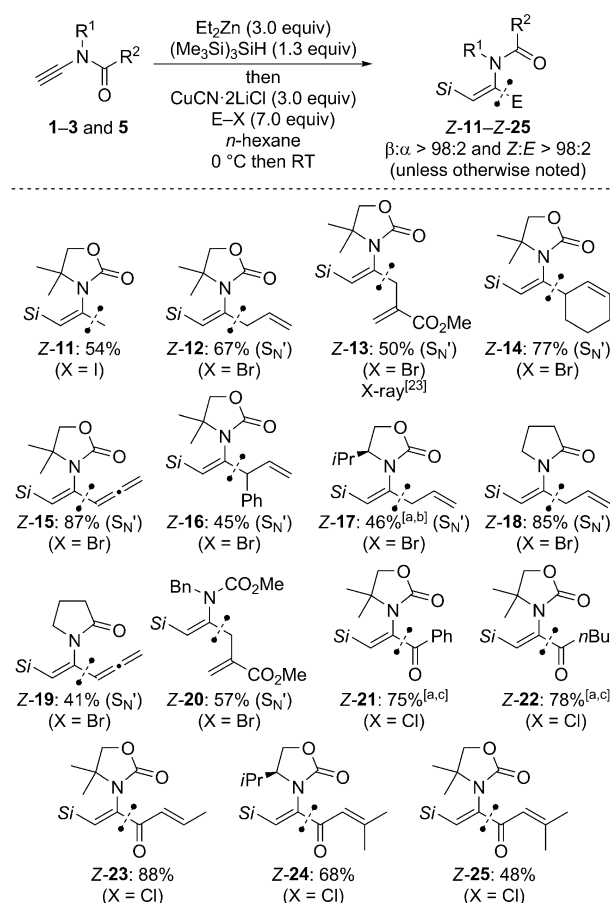
Table 2: Reaction scope for the silylzincation of ynamides.

Entry	Substrate	E	Product ^[a]	Yield [%]	d.r. (Z:E) ^[b]	[² H] ^[c] [%]
1	2	H	Z-7	87	> 98:2	—
2	2	D	Z-[²H]-7	85 ^[d]	> 98:2	85
3	3	H	Z-8	93 ^[d,f]	97:3	—
4	3	D	Z-[²H]-8	72 ^[d]	95:5	75
5	4	H	Z-9	83 ^[d,g]	87:13	—
6	4	D	Z-[²H]-9	64 ^[d]	78:22	88
7	5	H	Z-10	62	96:4	—

[a] Only β -silylated regioisomers were detected (β : α > 98:2). [b] Determined by 1H NMR analysis prior to purification. [c] Deuteration grade estimated by 1H NMR spectroscopy. [d] Determined by 1H NMR spectroscopy using butadiene sulfone as internal standard. [e] 37% of **Z-8** and 56% of **E-8** were isolated after silica gel chromatography. [f] 26% of **Z-9** and 57% of **E-9** were isolated after silica gel chromatography.

of $(Me_3Si)_3SiH$ and Et_2Zn to provide the corresponding enamides **Z-7**, **Z-8**, and **Z-9** in good to excellent yields and stereoselectivity after aqueous quench (entries 1, 3, and 5). Formation of **V** rather than **VI** was again established by deuterium labeling (entries 2, 4, and 6). The silylzincation reaction was also well-suited for acyclic ynamides such as **5** (entry 7); the regio- and stereoselective formation of **Z-10** was observed in 62 % yield. It must be noted that, as a general trend, the sensitivity of the Z - β -silylenamides toward acid made them prone to Z -to- E isomerization. For **Z-8** and **Z-9**, significant isomerization during purification by chromatography on silica gel could not be avoided and led to a decrease in the isolated yields of the stereochemically pure adducts.

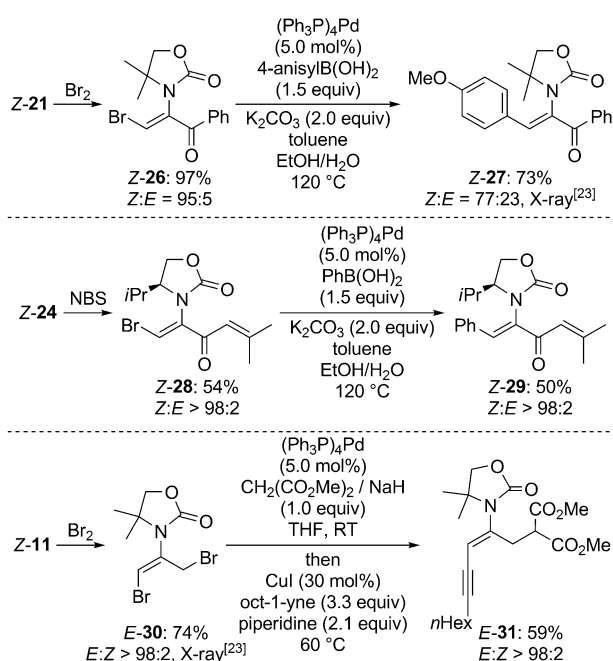
Our next efforts were then devoted to assess the value of zinc intermediates **V** as nucleophiles in C–C bond-forming reactions. In the presence of $CuCN \cdot 2LiCl$, these reagents



Scheme 3. CuI -mediated electrophilic trapping of vinylic zinc intermediate **V**. [a] Partial isomerization observed on silica gel. [b] 14 % of the E isomer isolated. [c] Contaminated with approx. 5 % of the E isomer. $Si = Si(Me_3Si)_3$.

readily reacted with various electrophiles to afford the corresponding α -substituted β -silylenamides (Scheme 3).^[22] Methyl-substituted **Z-11** was obtained by electrophilic trapping with MeI . Primary and secondary allylic halides as well as propargyl bromide were particularly well-suited and proved to be useful to introduce an array of alkene functionalities (**Z-12–Z-20**, Scheme 3). Full regiocontrol was observed for the allylic and propargylic displacements leading to **Z-15**, **Z-16**, and **Z-19**, this being indicative of S_N' -selective processes. Finally, α -carbonylated β -silylenamides **Z-21–Z-25** were prepared by reaction with aromatic, vinylic, or aliphatic acyl chlorides. The Z configuration of **Z-13** was established by X-ray crystallographic analysis^[23] (see the Supporting Information).

Finally, the $(Me_3Si)_3Si$ group was used as a linchpin for the installation of carbon substituents in the β position of selected enamides by means of a two-step bromodesilylation/ Pd^0 -catalyzed cross-coupling sequence (Scheme 4).^[24] Reaction of **Z-21** with Br_2 in CH_2Cl_2 afforded **Z-26** in 97 % yield with almost complete retention of the double bond geometry. Conversely, NBS emerged as a better alternative to achieve the transformation of **Z-24** to **Z-28** because the competitive allylic bromination was avoided. Full retention of configuration was observed. Moreover, the reaction of Br_2 with β -



Scheme 4. The C_{sp^2} -Si bond as a linchpin for the elaboration of the β position of selected α -substituted Z - β -silylenamides. NBS = *N*-bromosuccinimide.

silylenamide **Z-11** allowed combining bromodesilylation and allylic bromination to afford dibromide **E-30** in 74% yield. Its *E*-configuration was confirmed by X-ray crystallographic analysis.^[23,25] The prepared β -bromo enamides participated readily in Suzuki–Miyaura-type cross couplings. Reaction of **Z-26** with 4-anisylboronic acid afforded α -carbonyl β -substituted enamide **Z-27**^[23,26] in 73% isolated yield in spite of a partial isomerization during the coupling reaction. **Z-29** was prepared similarly from **Z-28** and phenylboronic acid in 50% yield, and no isomerization was observed. Additionally, the potential of dibrominated **E-30** as a template for stereoselective enamide synthesis by means of sequential intermolecular cross-coupling reactions was demonstrated.^[27] We combined an allylic alkylation reaction and a Sonogashira cross-coupling reaction in a one-pot sequence to obtain **E-31** in 59% yield.

In conclusion, we described here the completely regio- and stereoselective silylzincation of terminal ynamides using a combination of $(Me_3Si)_3SiH$ and a dialkylzinc reagent. The procedure is operationally simple, utilizes readily available reagents, and provides a straightforward and modular access to *Z*-configured α,β -disubstituted enamides by means of subsequent sequential functionalization of the C_{sp^2} -Zn and C_{sp^2} -Si bonds introduced. Most significantly, with this reaction we uncover a new entry to the silylzincation of C–C multiple bonds based on the merger of silyl radical chemistry and radical Zn-atom transfer chemistry. The decisive feature of this approach is the possibility to achieve *trans* selectivity in the addition across the C=C bond.

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