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Highly regioselective, ligand-differentiated platinum-catalysed hydrosilylation of propynamides

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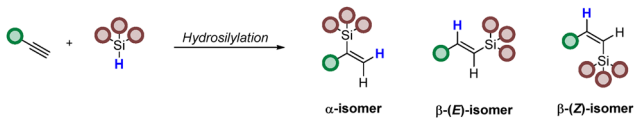
We present, for the first time, a highly regio- and stereoselective ligand-divergent hydrosilylation reaction. The methodology produces diverse amido-vinyl silanes from readily available propynamides. Employing platinum catalysis utilizing commercially available ligands, silyl-α,β-unsaturated amides are produced in synthetically useful yields (up to 91%). This methodology allows, for the first time, an unprecedented ligand differentiated hydrosilylation methodology to form β-(*E*)-silyl-α,β-unsaturated amides in high regioselectivity and α-silyl-α,β-unsaturated amides with complete regioselective control (>99 : 1).

Vinyl silanes have firmly established themselves as important building blocks within synthetic chemistry.[1] Outside their extensive use in polymer chemistry, their use as a low cost, easily handled reactive partner has attracted sustained efforts over the past several decades.[2,3] In particular, their participation in Hiyama cross-couplings to form carbon–carbon bonds,[4] as well as their use in the formation of carbon–oxygen bonds through Tamao–Fleming oxidation reactions,[5,6] showcases their diverse utility. Given their usefulness, it is not surprising that efforts towards their synthesis has resulted in a wide range of elegant methods including dehydrogenative silylation of alkenes,[7] cross-metathesis[8] and silylative Negishi cross-couplings.[9] However, by far the most utilized method for the installation of vinyl silanes is the transition metal catalysed hydrosilylation of alkynes (Scheme 1),[10] which has been the method of choice since the inception of Speir's[11] and Karstedt's catalyst in the middle of the last century.[12]

Although very well established, the hydrosilylation of alkynes continues to suffer from two key issues: (a) general regiochemical control and (b) a lack of tolerance toward amine containing substrates.[13] The first of these issues has seen a wealth of excellent methods developed to access both α and β isomers individually, notably including work by Trost,[14–16] and Ding[17] who have all shown that access to the less favorable α-isomer is possible through judicious design of catalytic systems. On the other hand, few reports exist of a general hydrosilylation reaction when the parent alkyne contains amine or amide derivatives.[18] Recently, our group reported a regioselective hydrosilylation of propargyl amines, in which a bidentate phosphine ligand was required to retard catalyst poisoning through coordination with the amine scaffold.[19] This method exclusively produced the β-(*E*)-vinyl silane, which was subsequently used to access a range of aziridine scaffolds. In saying that, to the best of our knowledge, a method detailing the switching between the isomers through ligand design has not been reported. Furthermore, the lack of Lewis basic functional groups in many of these methods limits their usefulness in terms of complex target synthesis and medicinal chemistry. As such, we set out to explore the feasibility of designing a catalyst system that would allow access to both α and β-isomers from a single starting material and catalyst salt. We reasoned that by careful choice of ligand, we could optimise a hydrosilylation of propynamides to give novel, high value silicon containing acrylamide scaffolds.

To assess the feasibility of our approach, and to set a benchmark for our optimization, we subjected **1a** to well established hydrosilylation conditions ($PtCl_2$, $HSiMe_2Bn$), and observed the product vinyl silane in a 67 : 33 α : β ratio and 81 : 19 β-(*E*) : β-(*Z*) (Scheme 2).

This result was a surprise, given that in a vast majority of cases, the favoured isomer is almost always the β-(*E*) isomer. We reasoned that the switch in selectivity could arise from a



Scheme 1 General alkyne hydrosilylation showing all possible isomers.

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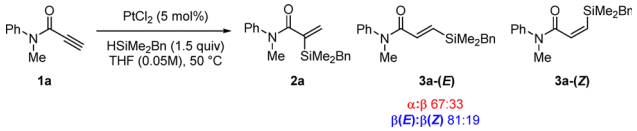


Scheme 2 Platinum catalysed hydrosilylation of propynamides.

coordination effect between the platinum and amido functionality and wondered if we could take advantage of this (Fig. 1).

We therefore began our investigation by screening simple phosphine ligands, given their previously described success in other hydrometallation reactions coupled with phosphines' well-known propensity to interact with oxygen atoms, which may invoke a more stabilized 5-membered chelate (Fig. 1). After extensive experimentation (see SI) we found that the highly electron deficient phosphine ligand tris(pentafluorophenyl)phosphine provided the desired α-isomer exclusively, which does indeed fit with our hypothesis of chelation control. We then reasoned that a more sterically encumbered ligand might work to break this coordination, and we focused on Buchwald and bis-amine ligands, which stemmed from our previous experience in the area.[19,20] Once again after in-depth experimentation (see SI) we identified JohnPhos as the optimal ligand to afford the β-(*E*)-isomer as the preferred product (α : β-(*E*) 12 : 18). Importantly, only the *E* isomer was formed in this case, and each of the isomers was easily separated by column chromatography. With optimal conditions in hand to access both regioisomers, we turned our attention to establishing the limits of reaction concentrating initially on the synthesis of α-silyl-α,β-unsaturated amides 2 (Table 1). To further determine if chelation control played a role, a reaction was conducted with phenylacetylene with both ligands, and saw a 1 : 1 α : β ratio for $(C_6F_5)_3P$ and a 10 : 1 β : α ratio for Johnphos which does indeed support the formation of an advantageous chelate for the α-product.

The reaction was tolerant of mixed aryl functionality (**2a–2d**), affording good yields and delivering the products as single regioisomers. It also accommodated bulky alkyl groups (**2d–2g**), providing moderate to good yields with excellent regioselectivity. Nitrogen-containing heterocycles (**2h**), including those bearing electron-donating substituents (**2i**), were well tolerated, affording the α-isomer exclusively. Similarly, oxygen-containing heterocycles (**2j** and **2k**) were compatible, giving good yields with complete regiochemical control. Substrate **2l**, featuring a bulky pyrrolidine moiety, was also formed in excellent yield and with high regioselectivity. In contrast, the reaction did not tolerate simple bisphenyl systems (**2m**), sterically demanding

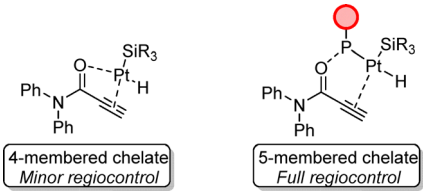
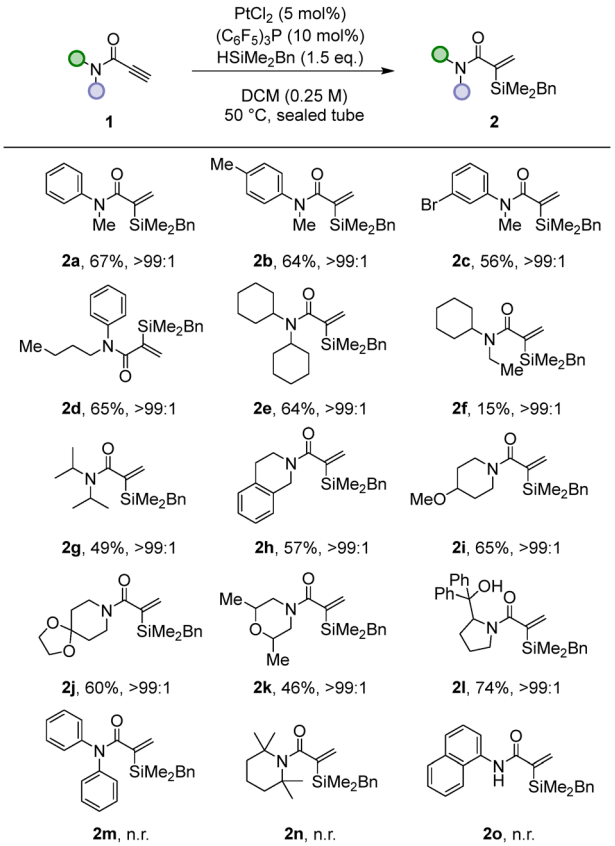


Fig. 1 Potential origin of selectivity *via* chelation control.

Table 1 Substrate scope of α-silyl-α,β-unsaturated amides



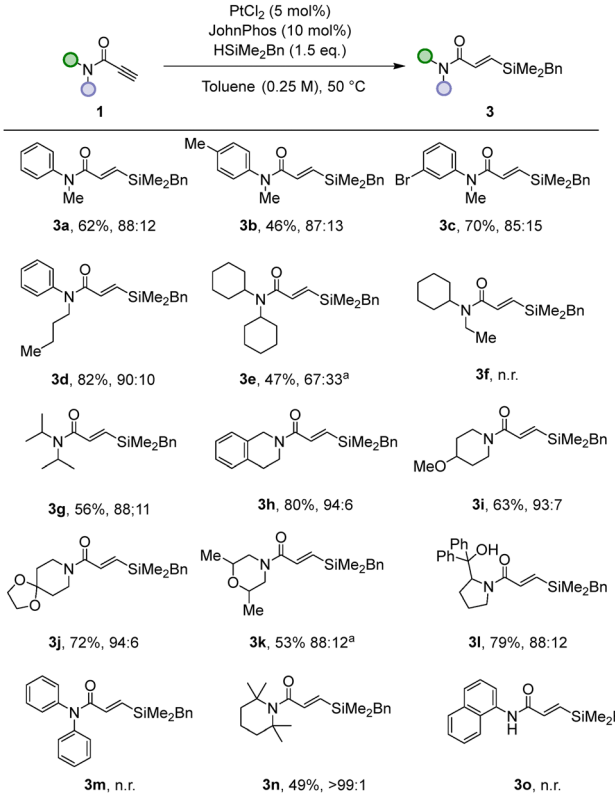
Note: α : β ratio determind *via* analysis of ^{1}H NMR of the crude reaction. Yield are isolated yield of only the α-vinylsilane.

piperidines (**2n**), or secondary amide substrates (**2o**), which we attribute to potential catalyst deactivation pathways.

We next turned our attention to the synthesis of the β-(*E*)-isomer (Table 2). As with the α-series, the reaction tolerated mixed aryl substrates (**3a–3c**), affording slightly higher yields and maintaining high regioselectivity. Bulky alkyl groups (**3d**, **3e**, and **3g**) were also well tolerated, yielding the desired products in good yields. Nitrogen- and oxygen-containing heterocycles (**3h–3l**) performed well under the reaction conditions, again exhibiting good yields and high regiochemical control. Interestingly, in contrast to the α-series, the bulky piperidine derivative **3n** was tolerated, affording the desired product in good yield and with near-perfect regioselectivity. However, bisphenyl **3m** and secondary amide **3o** substrates remained incompatible.

We then investigated the effect of silane structure on the reaction (Table 3). Beginning with the α-isomer series, both dimethylphenyl- and triethylsilane delivered products **4a** and **4c** in good yields with full regiochemical control. The dimethylethylsilane derivative **4b** was also formed in excellent yield, albeit with a slight erosion in regioselectivity. In contrast, more reactive silanes and those with increased steric bulk (**4d–4f**) failed to afford the desired products, resulting instead in complete recovery of starting material.

Table 2 Substrate scope of β-(*E*)-silyl-α,β-unsaturated amides



Note: β : α ratio determind *via* analysis of ^{1}H NMR of the crude reaction, (*Z*)-isomer was not observed, Yield are isolated yield of the β-(*E*)-vinylsilane. [a] Isolated yield of α and β-(*E*)-isomer as an inseparable mixture.

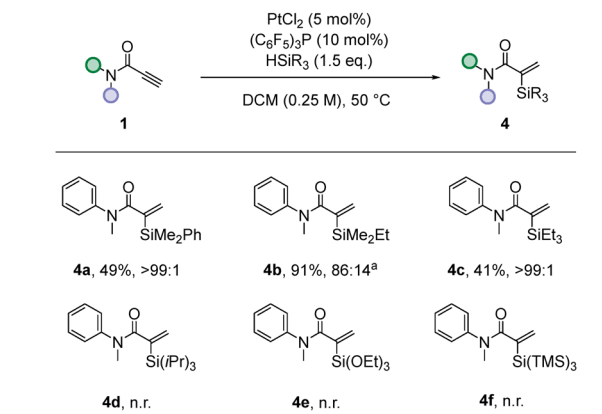
A similar trend was observed for the β-isomer series (Table 4). Dimethylphenyl- and triethylsilanes again afforded the desired products (**5a** and **5c**) in good yields with high regiochemical control. Use of dimethylethylsilane led to formation of **5b** in 59% yield, but with significantly reduced regioselectivity, favoring formation of the α-isomer. Attempts using more reactive or sterically hindered silanes (**5d–5f**) were unsuccessful, with no product formation observed.

As mentioned, vinyl silanes are important building blocks in synthetic organic chemistry, with a plethora of well-established uses within literature. However, incorporation of vinyl silane motifs *via* hydrosilylation of course relies upon the pre-installation of the parent alkyne, which may be difficult or even impossible in complex molecules. Therefore, employing a Weinreb amide as a general reagent that could be used as a vinyl silane lynchpin reagent,[21] facilitating installation of this high value functional group into a range of motifs. As this work showcases, for the first time, hydrosilylation of propargylic amido scaffolds, we decided to install a Weinreb amide **6**, which under the optimised conditions produces both the α **7** and β **8** isomers in good yields and excellent regiocontrol (Scheme 3).

With Weinreb amides **7** and **8** in hand, we pursued further functionalisation, affording a novel class of vinyl silane products (**9**/**10**) (Table 5). These transformations yielded enynones in good to excellent yields without any loss of stereo- or regioselectivity.

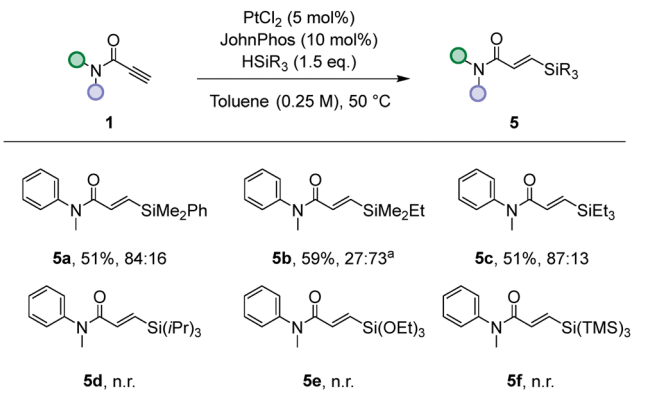
In conclusion, we have developed a regiodivergent hydrosilylation protocol of propynamides, enabling access to both α- and β-(*E*)-vinyl silane isomers under mild conditions in excellent regioselectivity. The reaction shows broad substrate scope,

Table 3 Differentiation of the silane functional group of α-silyl-α,β-unsaturated amides

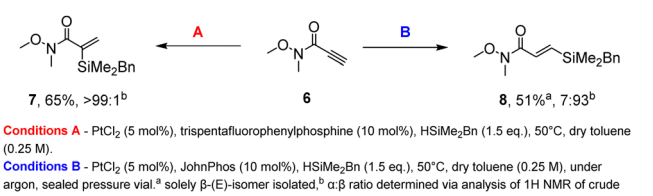


Note: α : β ratio determind *via* analysis of ^{1}H NMR of the crude reaction. [a] Isolated yield of α and β-(*E*)-isomer as an inseparable mixture.

Table 4 Differentiation of silane functional group of β-(*E*)-silyl-α,β-unsaturated amides



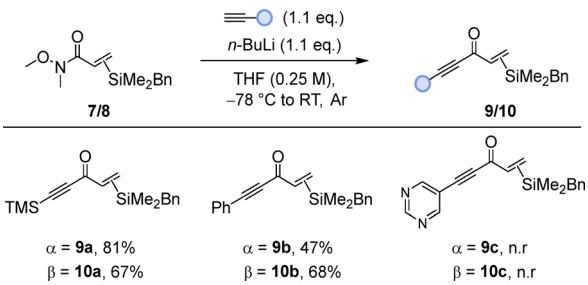
Note: β : α ratio determind *via* analysis of ^{1}H NMR of the crude reaction, (*Z*)-vinylsilane was not observed. [a] Isolated yield of α and β-(*E*)-isomer as an inseparable mixture.



Conditions A - $PtCl_2$ (5 mol%), trispentafluorophenylphosphine (10 mol%), $HSiMe_2Bn$ (1.5 eq.), 50°C, dry toluene (0.25 M).
Conditions B - $PtCl_2$ (5 mol%), JohnPhos (10 mol%), $HSiMe_2Bn$ (1.5 eq.), 50°C, dry toluene (0.25 M), under argon, sealed pressure vial.[a] solely β-(E)-isomer isolated,[b] α:β ratio determined via analysis of 1H NMR of crude reaction

Scheme 3 Regioselective hydrosilylation of Weinreib amides.

Table 5 Synthesis of enynones *via* lynchpin Weinreib amide vinyl silane reagent



tolerating diverse aryl, alkyl, and heterocyclic groups with good yields and high regioselectivity. The influence of silane structure on reaction outcome was systematically explored, highlighting the importance of steric and electronic factors. Additionally, Weinreb amides were employed, and the resulting products were further transformed into enynone derivatives, demonstrating the synthetic utility of the approach. Ongoing work within the group is looking to confirm a stereochemical model and rationale to explain the outcome of these reactions, and this will be reported in due course.

ELRL and MEB carried out experimental work and conducted data analysis, GRA conducted data and formal analysis and MGM conceptualised the project, supervised the work and drafted the manuscript. All authors were involved in subsequent writing.

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Conflicts of interest

There are no conflicts to declare.

Data availability

All experimental and characterisation data including copies of ^{1}H and ^{13}C NMR spectra are available in the SI. See DOI: **https://doi.org/10.1039/d5cc03832d**

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