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Stereodivergent Silylzincation of α-Heteroatom-Substituted Alkynes

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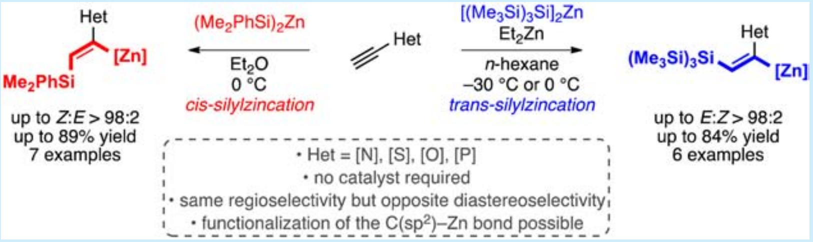
Supporting Information

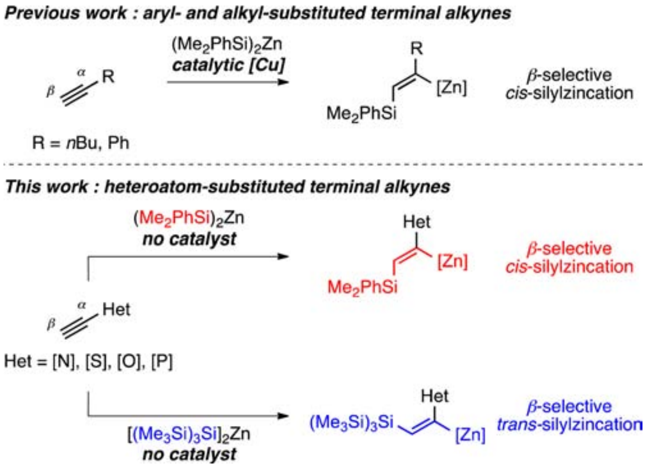


ABSTRACT: Zinc reagents $(Me_2PhSi)_2Zn$ and $[(Me_3Si)_3Si]_2Zn$ undergo highly regio- and stereoselective addition across the carbon−carbon triple bond of nitrogen-, sulfur-, oxygen-, and phosphorus-substituted terminal alkynes in the absence of copper or any other catalyst. Both reagents yield exclusively β-isomers, and the stereoselectivity is determined by the silyl group: Me_2PhSi for *cis* or $(Me_3Si)_3Si$ for *trans*. These stereodivergent silylzincation protocols offer an efficient access to heteroatom-substituted vinylsilanes with either double bond geometry, including trisubstituted vinylsilanes by one-pot electrophilic substitution of the intermediate $C(sp^2)$−Zn bond by copper(I)-mediated carbon−carbon bond formation.

Vinylsilanes are versatile synthetic building blocks, and their regio- and stereocontrolled preparation by carbon−silicon bond formation continues to attract considerable attention.[1] In this context, neutral bis(triorganosilyl) zinc compounds, e.g., $(Me_2PhSi)_2Zn$,[2] have emerged as mild sources of nucleophilic silicon during the past decade.[3] Silicon transfer from $(Me_2PhSi)_2Zn$ is readily achieved through catalytic formation of silicon-based cuprates by zinc to copper transmetalation in the presence of copper(I) salts. This strategy made possible an array of carbon−silicon bond-forming reactions,[3] including a protocol for the copper-catalyzed silylzincation of alkynes (Scheme 1, top).[4] Conversely, reports on reactions involving carbon−silicon bond formation by silicon transfer from $(R_3Si)_2Zn$ in the absence of any transition metal catalyst are still rare. Only conjugate addition to α,β-unsaturated acceptors[5] as well as addition to the tropylium cation,[6] across phenylallenes,[7] and to acetylenic epoxides[8] have been disclosed to date.[9] In this Letter, we disclose the regio- and stereoselective addition of $(Me_2PhSi)_2Zn$ and $[(Me_3Si)_3Si]_2Zn$ across the carbon−carbon triple bond of nitrogen-, sulfur-, oxygen-, and phosphorus-substituted terminal alkynes in the absence of any catalyst (Scheme 1, bottom). Remarkably, either *cis*- or *trans*-selective silylzincation is obtained depending on the zinc reagent used.

The silylmetalation of ynamides offers an entry into the synthesis of stereodefined nitrogen-substituted vinylsilanes.[10−12] In this area, we recently disclosed a radical-based *trans*-selective silylzincation of terminal ynamides employing a combination of Et_2Zn and $(Me_3Si)_3SiH$.[13] In continuation of this work, we became interested in developing a complementary method that would allow for the *cis*-selective silylzincation of the same substrate class. For this, we decided to use our established $(Me_2PhSi)_2Zn$−Cu(I) catalytic system (cf. Scheme 1, bottom).[4,10] To our surprise, we quickly learned that $(Me_2PhSi)_2Zn$[14] reacts with ynamide **1** *in the absence of any*

Scheme 1. Silylzincation of Terminal Alkynes Using Zinc Reagents $(Me_2PhSi)_2Zn$ and $[(Me_3Si)_3Si]_2Zn$ as Silicon Sources



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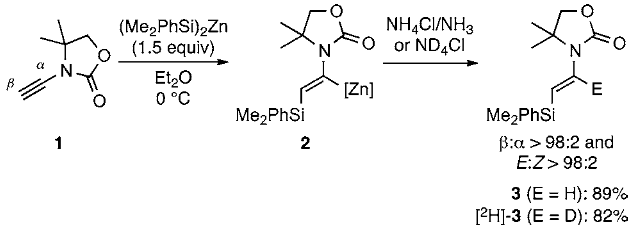
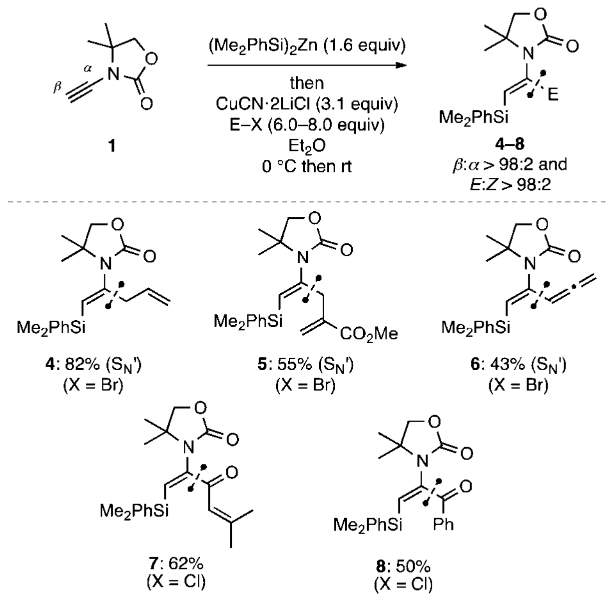
catalyst. Reaction in Et_2O at 0 °C afforded enamide **3** as a single regio- and diastereomer that was isolated in 89% yield after hydrolysis. Deuterium labeling confirmed the formation of vinylzinc intermediate **2** as [^{2}H]-**3** was obtained in 82% yield on quenching with ND_4Cl (Scheme 2).

Scheme 2. Cis-Selective Silylzincation of an Ynamide with $(Me_2PhSi)_2Zn$



Scheme 3. Stereoselective Preparation of *E*-Configured Trisubstituted Vinylsilanes with an Oxazolidinone Substituent



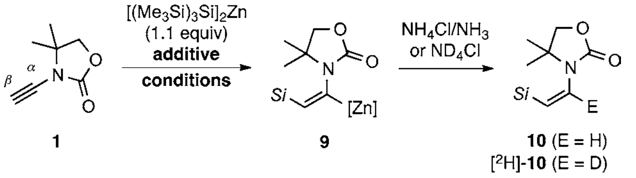
The formation of a C(sp^2)–Zn bond in **2** then serves as a useful linchpin for another bond formation in the same pot to give access to trisubstituted vinylsilanes that cannot be prepared using hydrosilylation chemistry.[1] For example, intermediate **2** reacted with allylic and propargylic bromides as well as with acyl chlorides in the presence of CuCN·2LiCl (Scheme 3). Complete retention of the double bond geometry was observed, and vinylsilanes **4**–**8** having an oxazolidinone group β to the silicon substituent were obtained from **1** in 43–82% yield.

We next turned our attention to $[(Me_3Si)_3Si]_2Zn$. Its straightforward preparation from Et_2Zn and $(Me_3Si)_3SiH$ had recently been reported,[15] thereby avoiding any metalation/transmetalation chemistry. However, the potential of $[(Me_3Si)_3Si]_2Zn$ as a silicon-transfer reagent had yet to be demonstrated. To our delight, $[(Me_3Si)_3Si]_2Zn$ was found to react smoothly with **1** in *n*-hexane (Table 1). At room temperature, enamide **10** was formed in 60% isolated yield with Z/E = 81:19, clearly favoring the Z double bond (entry 1). Performing the reaction at 0 °C led to exclusive formation of the Z diastereomer (entry 2). Moreover, the intermediacy of vinylzinc **9** was again verified by quenching with ND_4Cl; [^{2}H]-**10** was obtained in 81% yield with 83% deuterium incorporation (entry 3). Thus, both $(Me_2PhSi)_2Zn$ and $[(Me_3Si)_3Si]_2Zn$ react with excellent β-selectivity in the absence of any catalyst but with opposite diastereoselectivity.[16] We explain the observed reversal of stereoselectivity with a polar mechanism in the case of $(Me_2PhSi)_2Zn$[9] and a radical-chain mechanism in the case of $[(Me_3Si)_3Si]_2Zn$.[17,18]

The preference of $[(Me_3Si)_3Si]_2Zn$ to engage in the radical pathway is ascribed to its expected higher susceptibility toward homolytic cleavage of the silicon–zinc bond.[19] Hence, we added AIBN as radical initiator to improve the efficiency of the process. However, since thermal fragmentation of AIBN requires 80 °C, the Z/E ratio dropped dramatically, and the high temperature also resulted in decomposition (entry 4). We then tested Et_2Zn as additive.[20] The reaction of **1** with $[(Me_3Si)_3Si]_2Zn$ and Et_2Zn in equimolar ratio at 0 °C afforded **10** in 84% yield as a single diastereomer (entry 5). Importantly, on quenching with ND_4Cl, [^{2}H]-**10** was obtained with an excellent level of deuterium incorporation, substantially higher than that without Et_2Zn (96% vs 83%, entries 3 and 6).

We then focused on assessing the value of this new *trans*-selective ynamide silylzincation protocol for the synthesis of trisubstituted vinylsilanes (Scheme 4). Again, a range of carbon–carbon bond-forming reactions of intermediate **9** mediated by CuCN·2LiCl proceeded with immaculate retention of the double

Table 1. Trans-Selective Silylzincation of an Ynamide with $[(Me_3Si)_3Si]_2Zn$ (Si = $Si(SiMe_3)_3$)



entry	additive (equiv)	conditions	enamide	Z/E[a]	yield (%)[b]
1		*n*-hexane, rt	**10**	81:19	60
2		*n*-hexane, 0 °C	**10**	>98:2	83
3		*n*-hexane, 0 °C	[^{2}H]-**10** (83%[d])	95:5	81[c]
4	AIBN (0.16)	benzene, 80 °C	**10**	62:38	nd[e]
5	Et_2Zn (1.1)	*n*-hexane, 0 °C	**10**	>98:2	84
6	Et_2Zn (1.1)	*n*-hexane, 0 °C	[^{2}H]-**10** (96%[d])	>98:2	67

[a] Determined by ^{1}H NMR analysis prior to purification. [b] Isolated yield of both diastereomers. [c] Determined by ^{1}H NMR spectroscopy using 2,3,4-trichloropyridine as internal standard. [d] Deuteration grade estimated by NMR analysis. [e] Not determined.

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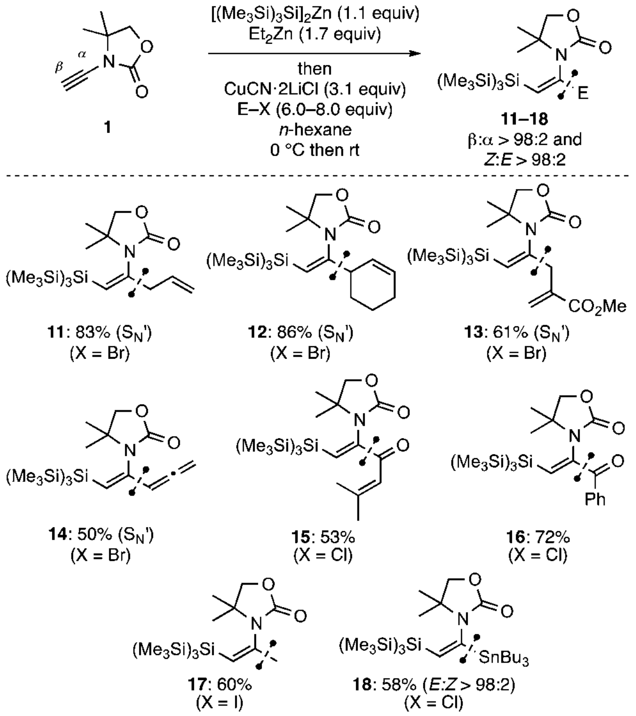
Scheme 4. Stereoselective Preparation of Z-Configured Trisubstituted Vinylsilanes with an Oxazolidinone Substituent

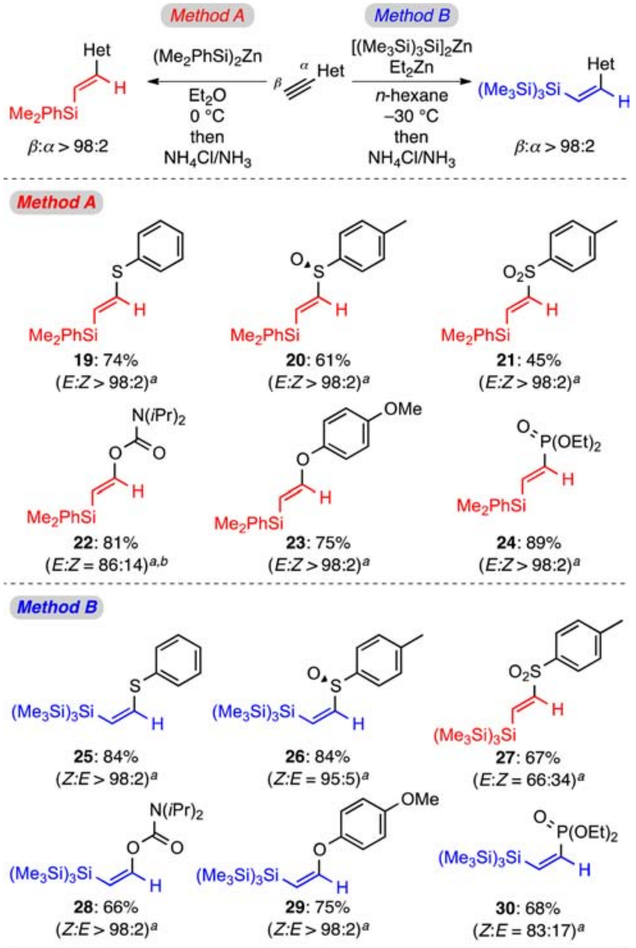


bond geometry. Exposure of **9** to differently substituted allylic bromides, propargylic bromide, and acyl chlorides yielded **11**–**16** in synthetically useful yields as single regio- and diastereomers. Electrophilic trapping was also possible with methyl iodide and tributyltin chloride that had failed to react with intermediate **2** derived from $(Me_2PhSi)_2Zn$; **17** and **18** were both isolated in acceptable yield.

With the stereodivergent silylzincation protocols in hand, we next considered applying them to other α-heteroatom-substituted terminal alkynes (Methods A and B, Scheme 5).[21] The synthesis of *E*-configured 1,2-disubstituted vinylsilanes decorated with an arylsulfide (**19**), arylsulfoxide (**20**), arylsulfone (**21**), *O*-carbamate (**22**), phenoxy (**23**), and phosphonate (**24**) was readily achieved through silylzincation with $(Me_2PhSi)_2Zn$ (Method A). Isolated yields ranged from 45% to 89%, and complete regio- and diastereocontrol was observed in all cases except for carbamate **22** (*E*/*Z* = 72:28). For the latter, performing the reaction at −78 °C gave better results, but the diastereoselectivity was still not complete (*E*/*Z* = 86:14).

Likewise, the complementary protocol involving $[(Me_3Si)_3Si]_2Zn$ was successfully applied to the same substrates (Method B). To achieve optimal yields, the reaction temperature had to be lowered from 0 °C to −30 °C. The regioselectivity was generally excellent, while with this method the diastereoselectivity was dependent on the heteroatom at the alkyne terminus. The *Z* selectivity was superb for vinylsilanes **25**–**26** and **28**–**29**, but **27** with an arylsulfone and **30** with a phosphonate were exceptions to this general trend. Compound **27** was isolated with the opposite double bond geometry, and **30** showed eroded diastereoselectivity yet still in favor of the *Z* diastereomer. Nevertheless, separation of those diastereomers by flash column chromatography on silica gel was straightforward, and **27** and **30** were obtained as pure *Z* diastereomers in 27% and 55% yield, respectively.

Scheme 5. Stereodivergent Silylzincation Across Various α-Heteroatom-Substituted Alkynes



[a]Determined by ^1H NMR analysis prior to purification. Only β-silylated regioisomers were deleted. [b]Reaction at −78 °C.

In conclusion, we have described the stereodivergent silylzincation of terminal α-heteroatom-substituted alkynes[22] by reaction with $(Me_2PhSi)_2Zn$ and $[(Me_3Si)_3Si]_2Zn$ in the absence of any catalyst. Both protocols offer a direct regio- and stereocontrolled access to both *E*- and *Z*-configured heteroatom-substituted vinylsilanes. As illustrated for the synthesis of an array of trisubstituted vinylsilanes, the $C(sp^2)$−Zn bond formed during the addition event provides a suitable handle to introduce, with complete retention of the double bond geometry, an additional substituent by copper(I)-mediated electrophilic substitution. The stereodivergence in these silylzincation reactions is indicative of a mechanistic dichotomy between the two zinc reagents. While the *E* selectivity observed with $(Me_2PhSi)_2Zn$ is consistent with a conventional anionic silicon transfer, the *Z* selectivity predominantly obtained with $[(Me_3Si)_3Si]_2Zn$ points to an uncommon radical transfer.[13,17]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00680.

Experimental data, product characterizations, and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(16) Reversal of stereoselectivity was not related to a solvent effect; in *n*-hexane at 0 °C, $(Me_2PhSi)_2Zn$ reacted *cis*-selectively with **1** to afford **3** in 70% yield as a single regio- and diastereomer ($\beta/\alpha > 98{:}2$, $E/Z > 98{:}2$).

(17) This is reminiscent of the *trans*-selective radical carbozincation of alkynes with dialkylzinc reagents: (a) Maury, J.; Feray, L.; Bertrand, M. *Org. Lett.* **2011**, *13*, 1884. (b) Chemla, F.; Dulong, F.; Ferreira, F.; Nüllen, M.; Pérez-Luna, A. *Synthesis* **2011**, 1347. (c) Chemla, F.; Dulong, F.; Ferreira, F.; Pérez-Luna, A. *Beilstein J. Org. Chem.* **2013**, *9*, 236.

(18) In the case of $[(Me_3Si)_3Si]_2Zn$, initiation of a radical process likely results from oxidation with residual dioxygen as in the case of dialkyl zinc reagents (cf. ref 17). However, photolysis could be an alternative entry: Kratish, Y.; Molev, G.; Kostenko, A.; Sheberla, D.; Tumanskii, B.; Botoshansky, M.; Shimada, S.; Bravo-Zhivotovskii, D.; Apeloig, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 11817.

(19) Trimethylsilyl substitution at silicon makes the formation of the $(Me_3Si)_3Si^\bullet$ radical highly favorable. Processes involving this radical found numerous applications in synthesis, see: Chatgilialoglu, C. *Chem. - Eur. J.* **2008**, *14*, 2310.

(20) Et_2Zn could influence the process at several levels. Amid others it might (i) favor initiation by oxidation with residual dioxygen, (ii) participate as alkylzinc group donor, or (iii) lead to mixed zinc compounds such as $[(Me_3Si)_3Si]ZnEt$ by Schlenk equilibria.

(21) Phenylacetylene reacted regioselectively but with no control of the double bond geometry: 51% yield, $E/Z = 54{:}46$ (Method A) and 33% yield, $E/Z = 62{:}38$ (Method B).

(22) A few experiments with terminally substituted systems, particularly derived from the sulfoxide, showed that these do not react cleanly.

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