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Angle-Strained Sila-Cycloalkynes

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Second row elements in small- and medium-rings modulate strain. Herein we report the synthesis of two novel oligosilyl-containing cycloalkynes that exhibit angle-strain, as observed by X-ray crystallography. However, the angle-strained sila-cyclooctynes are sluggish participants in cycloadditions with benzyl azide. A distortion-interaction model analysis based on density functional theory calculations was performed.

Angle-strained cycloalkynes¹ are a class of molecules employed to probe the limits of isolable compounds and understand the mechanism of strain-promoted cycloadditions.^{2,3} Incorporation of second-row elements into cycloalkynes influences ring strain, ring conformation, reactivity, and isolability.^{4,5} Replacement of CH₂ with SiR₂ is attractive for the combination of strain alleviation with air-stability and processability, as shown by Fox et al. in the comparison of *trans*-cycloheptene and *trans*-sila-cycloheptene.⁶ Herein, we report the synthesis of two new examples of 7- and 8-membered sila-cycloalkynes, as well as an investigation of their strain-promoted reactivity with azides. Our results demonstrate that measurable angle-strain alone is insufficient for room-temperature cycloaddition, influencing design principles in an area broadly relevant to organic chemists and chemical biologists.

Current approaches to the synthesis of strained sila-cycloalkynes can be low-yielding, reflecting the challenge of synthesizing strained molecules. Ando and coworkers initially synthesized the low strain sila-cyclooctyne **1** (46% yield) and after a photochemical ring contraction accessed the higher strain sila-cycloheptyne **2** (22% yield).⁷ A second ring contraction provided sila-cyclohexyne **3** (20% yield).⁸ While the 7- and 8-membered rings were stable to long-term storage, the

6-membered **3** slowly decomposed at room temperature.⁹ A higher-yielding approach to sila-cyclohexyne **3** employed dilithio- or dimagnesioacetylene and 1,4-dichlorooctamethyltetrasilane to yield the target compound in 55-65% yield.^{8,9} In addition to these compounds containing Si-Me groups, Si-Et^{8,10} and Si-Ph¹¹ side chains have been reported (17% yield).¹⁰ Examples of sila-cycloheptynes with a single CH₂ for SiMe₂ substitution have been reported by Krebs, although the products were not isolable and characterized as their trapped products.^{12,13}

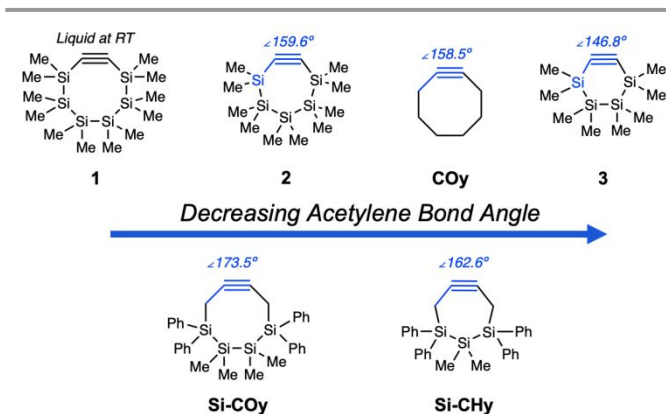


Chart 1. Examples of known sila-cycloalkynes and cyclooctyne, ranked according to extent of distortion from linearity at the alkyne. Energies at ω -B97M-V/def2-TZVPP with implicit toluene solvent.

The distortion of the acetylene bond angle away from linearity (180°), as found by X-ray crystallography, is known as angle strain.¹⁴ Chart 1 summarizes bond angles in known sila-cycloalkynes, with smaller ring sizes resulting in greater distortion. Sila-cycloalkynes are generally less strained than all-carbon rings of the same size. For example, sila-cycloheptyne **2** is less distorted (159.6°) than cyclooctyne **COy** (158.5°), even though it is a smaller ring.

Strained sila-cycloalkynes containing both sp³-hybridized C and Si atoms, such as sila-cyclooctyne **Si-COy** and sila-cycloheptyne **Si-CHy**, are less well-precedented. We recently reported the synthesis of low- and high-strain sila-cycloheptenes via a new approach, the alkylation of a silyl dianion.¹⁵ Here, we show that

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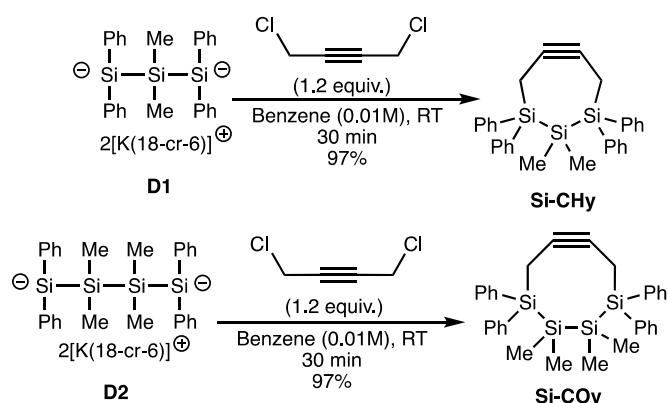
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this synthetic approach is also effective for the synthesis of new examples of sila-cycloalkynes.

We found that sila-cycloheptyne **Si-CHy** and sila-cyclooctyne **Si-COy** could be synthesized by alkylation of an appropriate silyl dianion **D1** or **D2** with 1,4-dichlorobutyne (Scheme 1). The synthesis differs from our previously reported synthesis of *trans*- and *cis*-sila-cycloheptene in employing benzene instead of toluene. While trace amounts of sila-cycloheptyne **Si-CHy** could be obtained in the reaction between **D1** and 1,4-dichlorobutyne in toluene, we found that in benzene we could obtain the desired sila-cycloheptyne **Si-CHy** in 97% crude yield. We hypothesize that the toluene to benzene solvent replacement increased yield by avoiding silanide protonation.¹⁶ By using the 4-membered disilanide **D2**, the sila-cyclooctyne **Si-COy** could also be obtained in 97% crude yield.



Scheme 1. Synthesis of sila-cycloalkynes **Si-CHy** and **Si-COy** via alkylation of dianions **D1** and **D2**.

The molecular structures of the sila-cycloalkynes **Si-CHy** and **Si-COy** were confirmed by single-crystal X-ray crystallography (Figure 1). Single crystals suitable for X-ray diffraction were obtained by the vapor diffusion method. The alkyne bond lengths are typical (ca. 1.20 Å, Table S1). In an unstrained alkyne, a linear geometry (bond angle of 180°) is expected. The extent of ring strain in a cycloalkyne is correlated with the extent of deviation from 180°. In the crystal structures, neither **Si-CHy** nor **Si-COy** possess a linear geometry at the alkyne. The deviation from linearity is greater in sila-cycloheptyne **Si-CHy** (ca. 17°) than in sila-cyclooctyne **Si-COy** (ca. 6°), consistent with greater ring strain in the smaller ring (Table S1). The overall distortion is less than in the smallest known sila-cycloalkyne **3** (33°).⁹

The distortion from linearity in sila-cycloheptyne **Si-CHy** (ca. 17°) is significant but less than cyclooctyne (ca. 28°),¹⁹ the prototypical dipolarophile in strain-promoted azide-alkyne cycloaddition (SPAAC), despite the smaller ring size. This is attributed to the strain-alleviating effect of the longer Si-Si and Si-C bonds. Sila-cyclooctyne **Si-COy** even more clearly shows the strain-alleviating effect of silicon incorporation, as the alkyne is nearly linear.

Heats of hydrogenations were used to estimate reactivity of [3+2] cycloaddition by Bach in 2009.¹⁹ Heats of hydrogenation accounts for the release of strain in the alkyne, alleviation of

ring strain, and the energetically favored reduction in unsaturation. Based on the distorted bond angles in **Si-CHy** and **Si-COy** relative to cyclooctyne, we hypothesized that **Si-CHy** would have a comparable heat of hydrogenation to cyclooctyne, while **Si-COy** should have a smaller heat of hydrogenation due to lower angle strain. Using the ω-B97M-V/def2-TZVPP²⁰ level of theory for energies, we calculated heats of hydrogenation for **COy**, **Si-CHy**, and **Si-COy** and find that the trends are consistent with the acetylene bond angle, with **COy** having the highest heat of hydrogenation, followed by **Si-CHy** and **Si-COy** (Figure 2, See SI for computational details).

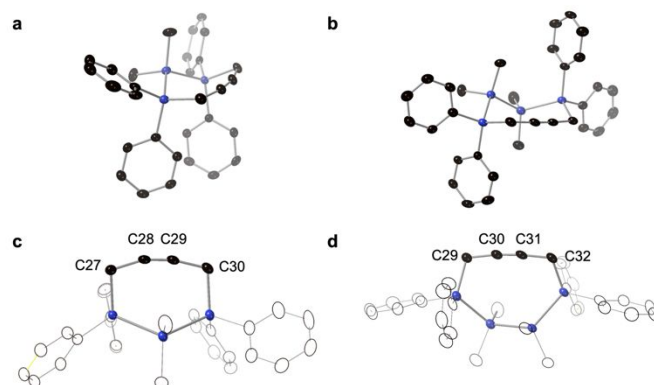


Figure 1. (a-b) Displacement ellipsoid plots (50% probability level) of sila-cycloalkynes **Si-CHy** and **Si-COy** at 110 K. H atoms are removed for clarity. (c-d) View of distortion from linearity at alkyne.

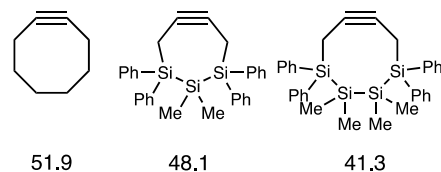
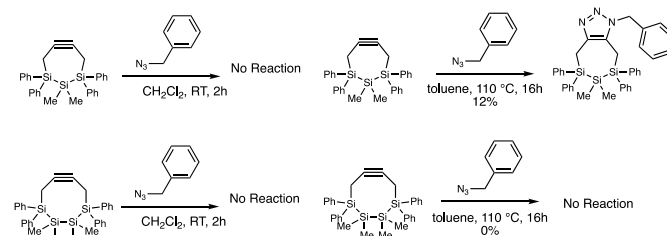


Figure 2. Calculated heats of hydrogenation for **COy**, **Si-CHy**, and **Si-COy** in kcal/mol. Heat of hydrogenation of alkynes were calculated as partial reduction of cycloalkynes to cis-cycloalkenes. Energies at ω-B97M-V/def2-TZVPP with implicit toluene solvent.

Prior work on the mechanism of SPAAC has shown a correlation between reaction rate and strain energy.¹⁹ We evaluated both **Si-CHy** and **Si-COy** in the uncatalyzed [3+2] reaction with benzyl azide (**N₃Bn**) at room temperature and at 110 °C (Scheme 2).



Scheme 2. Attempted azide-alkyne cycloaddition reactions of **Si-CHy** and **Si-COy** with benzyl azide at room temperature in dichloromethane and at high temperature in toluene.

While the overall similarity of the angle strain in sila-cycloheptyne and cyclooctyne might suggest a similar reaction rate in the azide-alkyne cycloaddition, ¹H NMR analysis of the room temperature reaction between **Si-CHy** and **N₃Bn** showed

no conversion to the triazole after 2 hours (Figure 3a). The unreacted **Si-CHy** and N_3Bn could both be detected, indicating that rapid decomposition of one of the reaction partners was not contributing to the lack of cycloaddition. Triazole **4** could be prepared, however, at 110 °C, albeit in only 12% yield (Scheme 2). The crystal structure of triazole **4** could be obtained from single crystal X-ray Crystallography as well (Figure 4). The lower-strain sila-cyclooctyne **Si-COy** did not react with N_3Bn at either room temperature or at 110 °C (Figure 1b and Scheme 2).

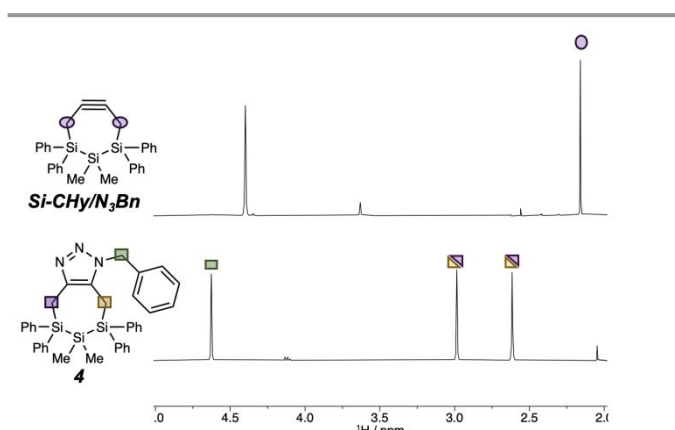


Figure 3. Cropped ¹H NMR spectra (400 MHz, CD₂Cl₂) comparing the results of the SPAAC reaction of **Si-CHy** and N_3Bn (top) to a sample of **4** (bottom). Benzylic and allylic protons are indicated.

After cycloaddition, the endocyclic bond angles in **4** (Figure 4a) are ca. 130°, close to the ideal 120° bond angle of a sp²-hybridized carbon atom. This suggests that significant release of angle strain should be occurring for the [3+2]-cycloaddition reaction between **Si-CHy** and N_3Bn .

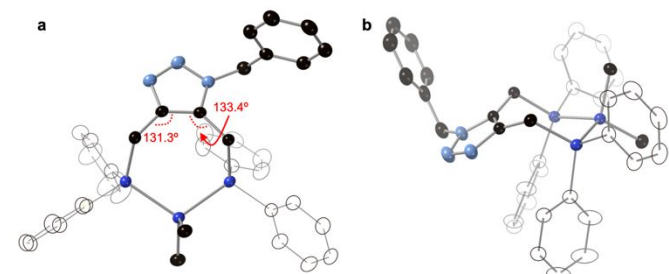


Figure 4. Displacement ellipsoid plot (50% probability level) of triazole **4** at 110 K. Disorder and H atoms are removed for clarity a) View highlighting endocyclic bond angles. b) View highlighting ring conformation. Hydrogens omitted and exocyclic phenyl rings shown in wireframe for clarity. Black = carbon, blue = silicon, light blue = nitrogen.

We sought a kinetic explanation for the lack of strain-accelerated cycloaddition reaction at room temperature. In Bertozzi's pioneering work on room-temperature strain-promoted azide-alkyne cycloaddition reactions, both strain and electronic activation contribute to rate acceleration. Angle strain promotes the cycloaddition reaction by distorting the alkyne bond angles close to the geometry required in the transition state. Electron-withdrawing groups proximal to the alkyne contribute to rate acceleration by lowering the energy of the lowest unoccupied molecular orbital (LUMO), as in the case of fluorinated cyclooctynes.^{21,22}

We hypothesized that the sluggish rate of dipolar cycloaddition at room temperature for the strained sila-cyclooctyne **Si-COy** could arise from both modest alkyne distortion and the electron-donating effect of the silicon atom, especially at the β-position.²³ A free energy profile was calculated using density functional theory (DFT), with complete details in the ESI. Methyl azide was chosen for the computational studies to facilitate comparison to prior published work.²⁴

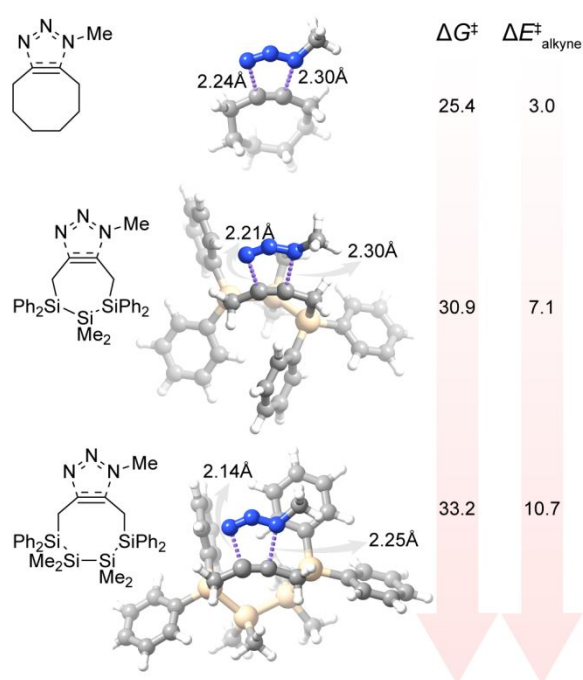


Figure 5. Optimized geometries, activation Gibbs free energies, and alkyne strain energies of [3+2] cycloaddition transition states of **COy** (top), **Si-CHy** (middle), and **Si-COy** (bottom). All energies are in kcal/mol. Energies at ω -B97M-V/def2-TZVPP with implicit toluene solvent.

A distortion/interaction model decomposes activation energies into the sum of strain and interaction energies and has been used to study a wide range of pericyclic reactions,^{25,26} including the [3+2]-cycloaddition.^{24,27} The distortion energy, which describes the energy needed to distort the reactants from their ground state to the transition state geometry, has a positive value (destabilizing) and increases the barrier to reactivity. The rate-acceleration observed with angle-strained cycloalkynes compared to linear alkynes can be attributed to smaller alkyne distortion energy ($\Delta E^\ddagger_{\text{alkyne}}$) and a smaller overall activation energy barrier ("pre-paying" the distortion energy). The interaction energy has a negative value (stabilizing) and depends on the reactants' electronic structure and relative orientation.

We calculated the activation energies ($\Delta G^\ddagger$) of methyl azide addition to **COy**, **Si-CHy** and **Si-COy**, which are 25.4 kcal/mol, 30.9 kcal/mol, and 33.2 kcal/mol. The increasing activation energy across this series matches our experimental relative rates (e.g., **COy** > **SiCHy** > **SiCOy**). We then decomposed the electronic energy of activation into alkyne strain energy ($\Delta E_{\text{strain-alkyne}}$), azide strain energy ($\Delta E_{\text{strain-azide}}$), and an interaction energy ($\Delta E_{\text{interaction}}$). We find that $\Delta E_{\text{strain-alkyne}}$ is consistent with

the reactivity and calculated heats of hydrogenation energies (Figure 5 and Table 1). As the angle deformation decreases, larger positive alkyne strain energies were observed. Surprisingly, azide strain also increased across the series. This was attributed to the transition state becoming progressively later and more product-like; transition state geometries also showed shorter bond distances in **Si-COy** than **Si-CHy** or **COy**. The cycloaddition reaction became less exothermic across the series of three cycloalkanes ($\Delta G = -67.8$ for **COy**, -61.1 for **Si-CHy**, -56.3 for **Si-COy**). A later transition state accounts for the increasingly negative interaction energies (Table 1).

Table 1. Distortion/Interaction analysis of [3+2] activation energies of **COy**, **Si-CHy**, and **Si-COy** with methyl azide. All energies are in kcal/mol.

	COy	Si-CHy	Si-COy
ΔG	-67.8	-61.1	-56.3
$\Delta G^\ddagger$	25.4	30.9	33.2
$\Delta E^\ddagger$	12.7	16.9	18.9
$\Delta E_{\text{strain-alkyne}}$	3.0	7.1	10.7
$\Delta E_{\text{strain-azide}}$	15.8	17.5	20.6
$\Delta E_{\text{interaction}}$	-6.2	-7.7	-12.5

We report a new approach to the synthesis of silicon-containing angle-strained cycloalkynes. X-ray crystal structures showed significant deviation from linearity, although were less deformed than carbocycles of the same atom number. The sila-cycloalkynes were sluggish participants in azide-alkyne cycloadditions. A calculated free energy profile pointed to an interplay between reaction exothermicity and angle-strain so that as a transition state became later, or more product-like, the requisite distortion energy increased for both alkyne and azide. Our results indicate that measurable angle strain alone is an insufficient predictor of room-temperature SPAAC.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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