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Silicon as a powerful control element in HDDA chemistry: redirection of innate cyclization preferences, functionalizable tethers, and formal bimolecular HDDA reactions†

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The 1,3-diyne and diynophile in hexadehydro-Diels–Alder (HDDA) reaction substrates are typically tethered by linker units that consist of C, O, N, and/or S atoms. We describe here a new class of polyynes based on silicon-containing tethers that can be disposed of and/or functionalized subsequent to the HDDA reaction. The cyclizations are efficient, and the resulting benzoxasiloles are amenable to protodesilylation, halogenation, oxygenation, and arylation reactions. The presence of the silicon atom can also override the innate mode of cyclization in some cases, an outcome attributable to a β -silyl effect on the structure of intermediate diradicals. Overall, this strategy equates formally to an otherwise unknown, bimolecular HDDA reaction and expands the versatility of this body of aryne chemistry.

Introduction

The generation of highly versatile, reactive *o*-benzyne intermediates from triyne or tetrayne substrates and their subsequent capture by various trapping agents – *i.e.*, the hexadehydro-Diels–Alder (HDDA) cascade¹ – is a growing area of research.² In essentially all cases, the starting diyne and diynophile have been tethered by a linker unit that consists of C, N, and/or O atoms.² In 2018, we reported a formal bimolecular HDDA reaction using erasable sulfur-based linkers (Fig. 1a, 1 \rightarrow 3).³ This inspired us to explore other heteroatom-based tethers that could be readily accessed, stable to the (thermal) HDDA reaction conditions, and usefully manipulated following cyclization.

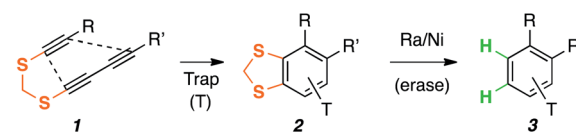
Silicon tethers have long been recognized as versatile linkers to support various intramolecular transformations such as radical cyclization, cycloaddition, and ring-closing metathesis.⁴ Notably, Suzuki and co-workers recently demonstrated the use of silicon tethering to enhance the efficiency of trapping reactions of classically generated benzyne (*e.g.*, by the Kobayashi protocol⁵) by rendering the benzyne capture event intramolecular.⁶ However, silicon-tethered HDDA reactions are an under-explored area of research.⁷ In the lone previous report, an intriguing preference for initial HDDA rather than tetrahydro-Diels–Alder (TDDA) cyclization in substrates capable of either was observed. Here we describe the chemistry of a novel

class of HDDA substrates that contain disposable and/or functionalizable silicon tethers (Fig. 1b, 4 \rightarrow 6). In addition to hypothesized outcomes, several unexpected reaction selectivities were revealed by the studies.

Results and discussion

Initially, silicon-tethered substrates 4a–c were prepared to probe the feasibility of the anticipated HDDA reactions (Fig. 2). Upon heating in decalin, products 5a–c were obtained from the desired HDDA cascade reactions.[‡] The silicon tether was then readily removed *via* desilylation to provide 7 in high yields. However, the HDDA reactions of 4a–c required heating at very

a Formal bimolecular HDDA reaction using erasable sulfur-based linkers



b HDDA reactions using disposable silicon linkers (this work)

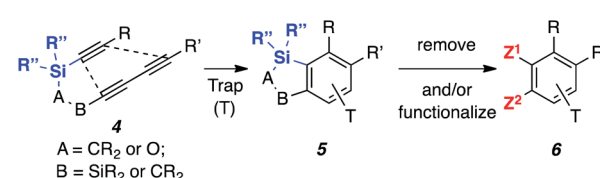


Fig. 1 (a) Previous studies of HDDA cascade reactions using erasable sulfur-based linkers. (b) In this report we disclose formal bimolecular HDDA reactions using disposable and/or functionalizable silicon linkers.

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† Electronic supplementary information (ESI) available: Experimental details for the preparation of new compounds; spectroscopic data for their characterization, including copies of ¹H and ¹³C NMR spectra (PDF). See DOI: 10.1039/d1sc04082k

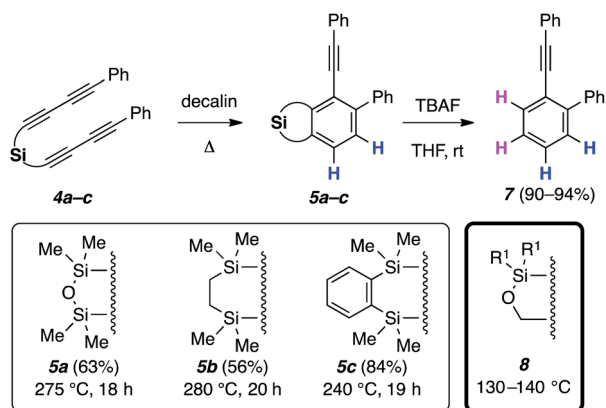


Fig. 2 Preliminary results demonstrating that silicon-tethered HDDA cascades are feasible.

high temperature (240–280 °C) over extended reaction times (*ca.* 20 h), which limited the selection of compatible trapping reagents. Encouraged by these preliminary results, we continued to explore additional silicon tethers and found alkoxy-silanes **8** to be both efficient and more reactive (cyclizations at \sim 100–150 °C lower temperature than **4**) poly-yne substrates (*e.g.*, nearly full conversion at 140 °C after 20 h). We attribute this greater reactivity in the rate-limiting HDDA cycloisomerization for **8** vs. **5a** to the shorter distance between the pair of proximal alkyne carbons⁹ in the former, which has longer bonds to only one third-row Si atom rather than two. Substrates **5b** and **5c** contain four-atom linkers and require formation of benzyne with a fused six-membered ring, here containing two silicon atoms. It is notable that other than these two examples, we know of only one other case in which a 1,3-diyne separated from a diynophile by four atoms gave rise to an intermediate HDDA-benzyne;¹⁰ in that instance the alkynes in the substrate were embedded within a macrocycle, so the HDDA reaction was intramolecular in nature.

Because of their greater reactivity as well as easier and more versatile routes of preparative access, tri- and tetrayne HDDA substrates based on the silyl ether linker motif as seen in **8** were used for the remainder of the studies reported here. As a bonus

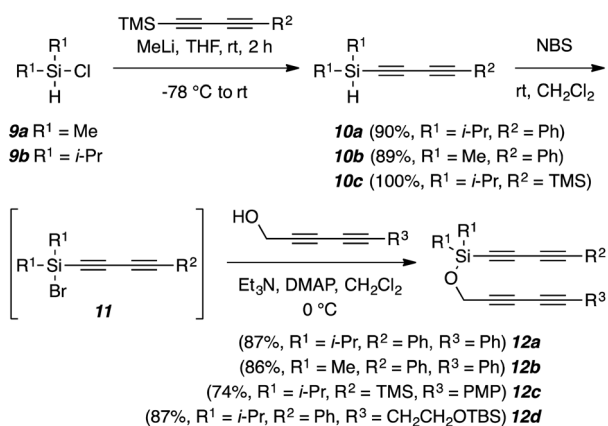


Fig. 3 Preparation of tetraynes **12a-d**. (PMP = *p*-methoxyphenyl).

and as described below, these unsymmetrical substrates demonstrated intriguing (and complete) regioselectivity with respect to their direction of cycloisomerization, including the reversal of inherent reactivity in some instances.

Each of the triyne and tetrayne substrates **12a-g** (Fig. 3, 5, and 9) contains a three-atom alkoxy-silane tether. They can be conveniently prepared¹¹ from dimethyl- or diisopropylchlorosilane (**9a** or **9b**) in two steps and high yield. The diynylsilanes **10a-c** were generated by reacting various diynyllithium species with **9a** or **9b**. In a subsequent one-pot process, each diynylsilane **10** was then converted, *in situ*, to its corresponding bromosilane **11**, which was directly treated with a diynyl alcohol to provide the tetraynes **12a-d**. Triyne

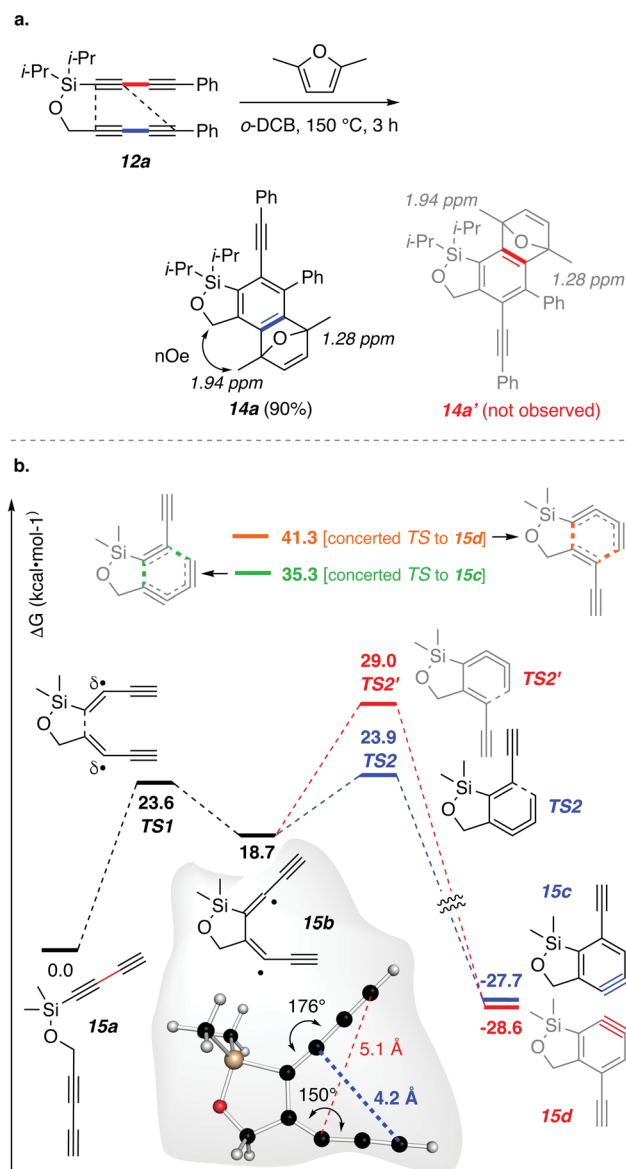


Fig. 4 (a) Exclusive formation of **14a** (via a single benzyne) from the tetrayne substrate **12a**. (b) DFT calculations of the relative free energies (ΔG) of species on the potential energy surface for the reaction of the slightly simplified, model tetrayne **15a** (at 413 K) [SMD(chloroform)/(U) B3LYP-D3BJ/6-311+G(d,p)/(U)M062X/6-311+G(d,p)].



substrates **12e–g** were synthesized in a similar fashion (see ESI†).

In our initial experiment, a solution of tetrayne **12a** and 2,5-dimethylfuran in *o*-dichlorobenzene was heated at 150 °C for 3 h, and product **14a** was produced in 90% yield (Fig. 4a). HDDA reactions of unsymmetrical tetrayne substrates such as **12a** can give rise to two isomeric benzyne involving the same pair of proximal but opposite pairs of distal atoms of the two 1,3-diyne. In this instance, the second possibility would have led to **14a'**. The assignment of structure **14a** was supported by a significant nuclear Overhauser enhancement (NOE) observed between the methyl protons at 1.94 ppm and the methylene protons in the benzoxasilole.

This intriguing selectivity in the benzyne formation prompted us to conduct DFT calculations to gain additional insight to the energy barriers for the formation of each of the two isomeric benzyne. These were performed starting from the simplified model tetrayne **15a** (Fig. 4b). Prior experimental studies¹² have shown that the HDDA cycloisomerization can proceed by a stepwise mechanism *via* a diradical intermediate, at least for

one class of HDDA polyne substrate, although various computational investigations¹³ often indicate similar energies of activation for concerted *vs.* stepwise pathways over a range of different triyne or tetrayne substrates. In the present case, the energy barrier (**TS1**) leading to the diradical intermediate **15b** was computed to be 23.6 kcal mol^{−1}. This diradical, common to the paths leading to both **15c** and **15d**, was seen to then ring-close through the lower energy **TS2** (23.9 kcal mol^{−1}; a 5.2 kcal mol^{−1} barrier) compared to **TS2'** (29.0 kcal mol^{−1}; 10.3 kcal mol^{−1} barrier). Thus, the computations suggest that ring-closure significantly favors formation of benzyne **15c**, consistent with the experimental isolation of only **14a** from the trapping reaction of **12a**. We were also able to identify concerted TSs for cycloaddition of **15a** directly to **15c** and **15d** (top of Fig. 4b). While these also showed a strong preference for the former, both of these concerted pathways were, nonetheless, calculated to be considerably less favorable (higher *E*_{act}s) than that of the stepwise-diradical alternative.

Examination of the geometry computed for the intermediate diradical **15b** allows us to offer a reason for the exclusive

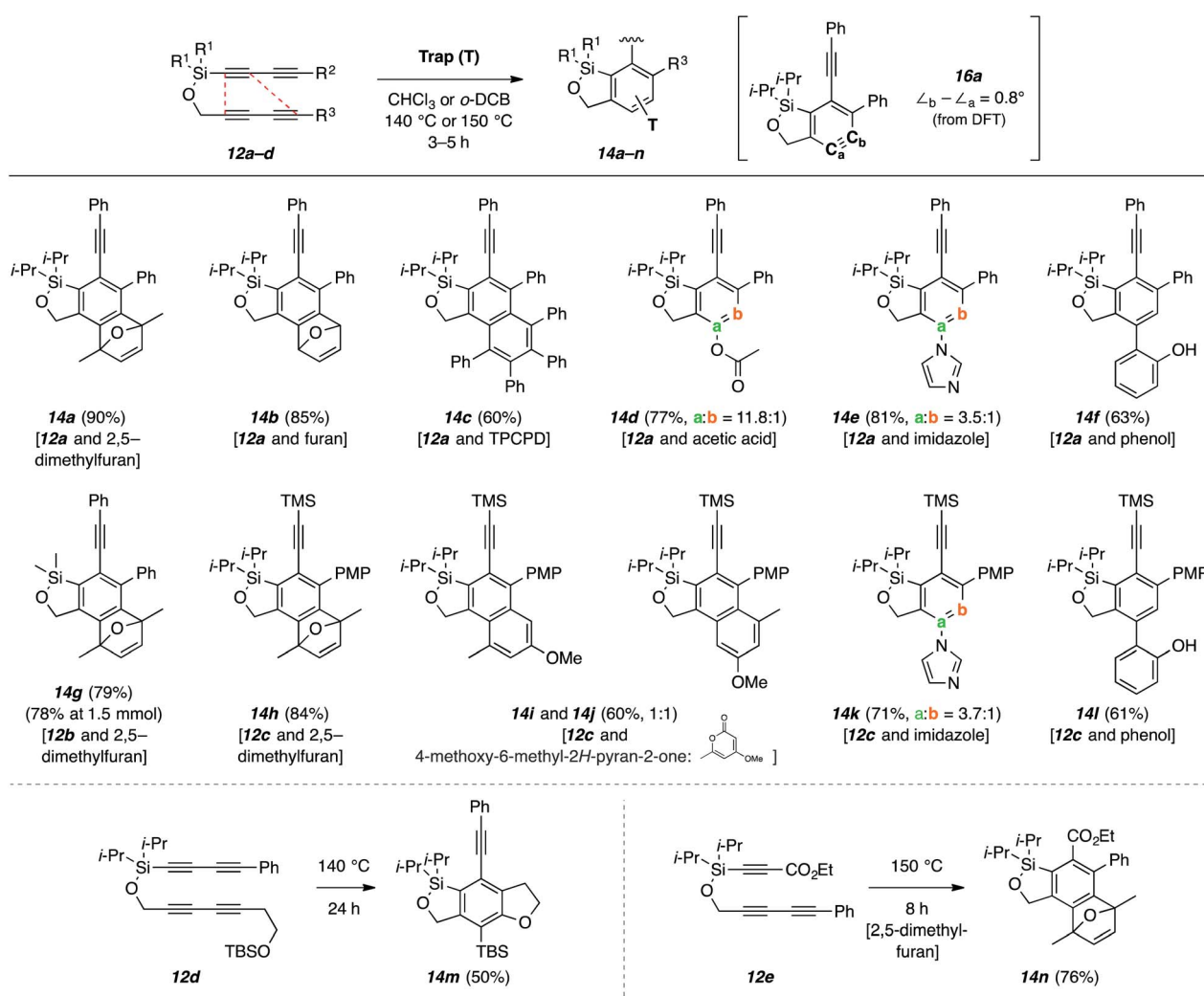


Fig. 5 Products **14** from HDDA cascades using alkoxyisilane-tethered tetraynes/triynes **12** and various trapping agents. (TPCPD = tetraphenylcyclopentadienone).

formation of constitutional isomer **14a** in the cycloisomerization of **12a**. In **15b** the distal pair of atoms leading to **15c** (blue line) are *ca.* 1 Å closer than those leading to **15d** (red line). This is a consequence of the more pronounced bend in the propargylic radical in the bottom fragment compared to that in the top (150° vs. 184° , gray box in Fig. 4b). We further suggest that this difference in distortion is due to enhanced orbital overlap between the carbon–silicon sigma bond and the radical character at the adjacent sp-hybridized carbon atom in the more linear orientation. It is relevant that hyperconjugative stabilization of radicals by β -silyl substituents has been demonstrated.¹⁴

The reactions of these alkoxy-silane-tethered tetraynes are quite general (Fig. 5). Products **14a–f** were all produced from tetrayne **12a**. These examples demonstrate trapping reactions through 4π -cycloaddition (**14a–c**), nucleophilic addition (with imidazole to **14d** and acetic acid to **14e**), and a phenol–ene reaction¹⁵ (**14f**). The last three examples, each involving an unsymmetrical nucleophilic trapping agent, show a preference for addition to C_a of the benzyne **16a**. DFT calculation [M062X/6-311+G(d,p)] shows that this benzyne has a nearly symmetrical geometry; the internal bond angles at C_a and C_b are essentially the same ($\Delta \angle_{b-a} = 0.8^\circ$). This contrasts with many benzynes having five-membered rings comprising all second-row atoms in the same position of the ring fusion, which are significantly distorted, leading to selective nucleophilic addition to C_b. In the case of benzyne **16a** the regioselectivity of attack by an external nucleophile is, therefore, likely governed more by steric rather than distortion factors; that is, the aryl substituent is effectively larger than the methylene group in the fused ring, allowing easier access to C_a. The dimethylsilyl-containing substrate **12b** was also shown to be viable (*viz.* formation of **14g**). The tetrayne substrate **12c** gave rise to **14h–l** through similar reactions. The naphthalene derivatives **14i** and **14j** were formed when an α -pyrone derivative was used as the trapping agent. The intermediate $[4 + 2]$ adduct ejects carbon dioxide under the reaction conditions; the 1 : 1 mixture of products presumably reflects a similar extent of steric hindrance in the two possible orientations by which the pyrone can engage the intermediate benzyne **16a**. Substrate **12d** contains a tethered TBS ether that serves to trap the benzyne intramolecularly, producing **14m**. Finally, the triyne **12e** was also a viable substrate; its conversion to the adduct **14n** proceeded somewhat more slowly than that of analogous tetraynes, consistent with the accelerating effect of a bystander alkynyl substituent, present in each of **12a–d**, arising from its greater radical stabilizing effect relative to a carboxy ester.^{11,16}

We next sought to demonstrate ways of further functionalizing the various products from these HDDA cascade reactions. First, the oxabenzonorbornadiene products **14a**, **14b**, **14g**, and **14n** (*cf.* Fig. 5) could be readily converted to the corresponding naphthalene derivatives (**17a–d**, Fig. 6) by reductive deoxygenation with TMSI.¹⁷ In the case of the TMS-substituted terminal alkyne **14h**, concomitant hydroiodination¹⁸ provided iodoalkene **17e**.

Because of the considerable breadth and versatility of organosilicon chemistry—indeed, a significant subdiscipline of the

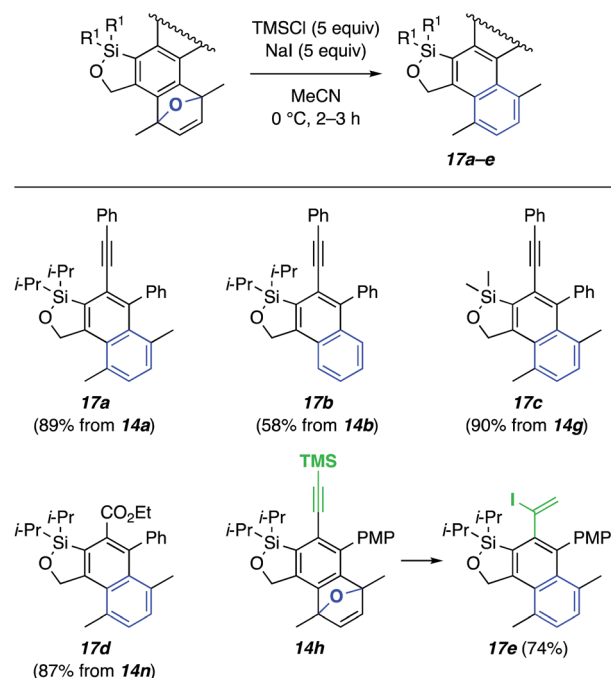


Fig. 6 Synthesis of naphthalene derivatives **17** via deoxygenation of benzoxanorbornadiene derivatives.

entirety of organic chemistry—the C–Si bond in these products offers a host of opportunities for further transformations. We have demonstrated a few. For example, halo-desilylation reactions of the benzoxasilole in **14g** were effective, giving **18a–b** upon treatment with AgF and NIS or NBS (Fig. 7). Interestingly, the

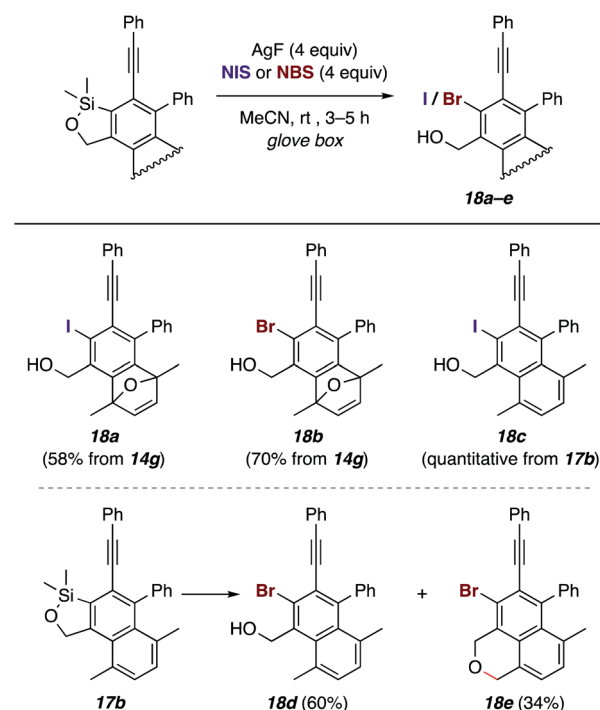


Fig. 7 Iodination and bromination of the C–Si bond (with concomitant cleavage of the tether).



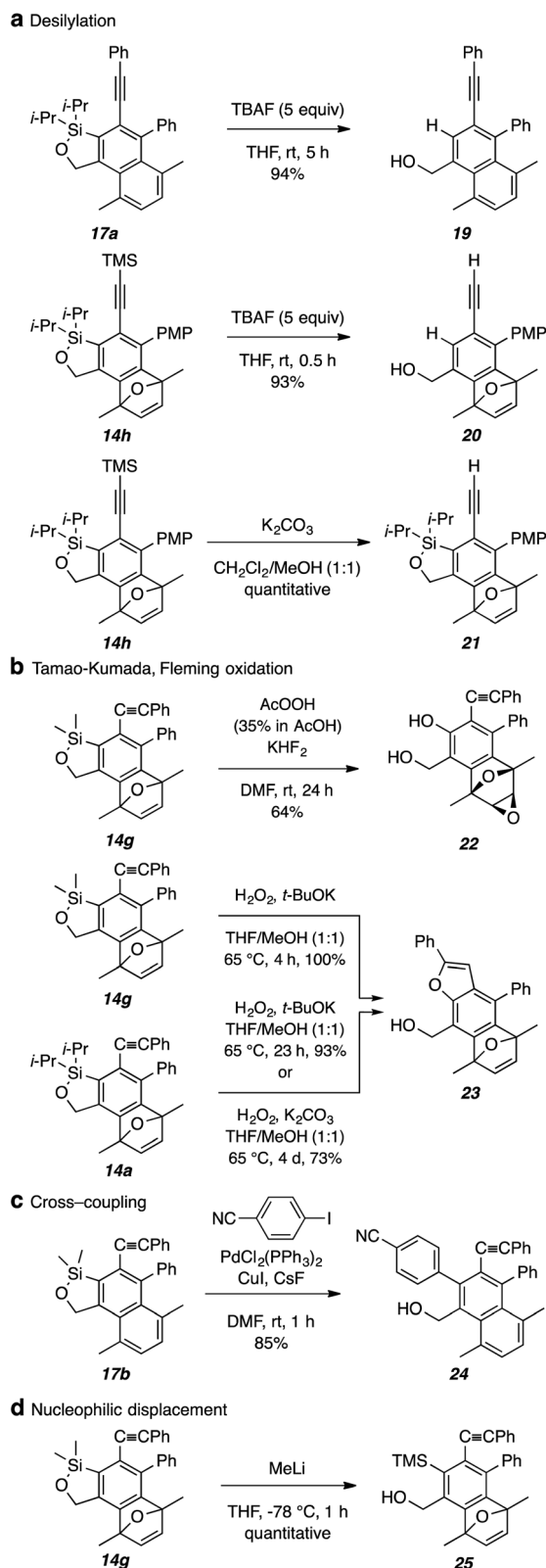


Fig. 8 Synthetically useful transformations of benzoxasiloles (with concomitant cleavage of the tether).

iodination of naphthalene 17b to give 18c was quite clean, but treatment with AgF/NBS gave rise to both the naphthyl bromide 18d and the brominated benzoisochromene 18e.

As demonstrated by the examples in Fig. 8, the aryl-silicon bond can be replaced by bonds to hydrogen, oxygen, or carbon substituents. Simple disposal by protodesilylation with TBAF is straightforward, giving, for example, 19 and 20 (Fig. 8a). If desired, the alkynyl trimethylsilyl group in 14h can be selectively cleaved by treatment with K_2CO_3 in MeOH/THF leaving the Ar-Si bond intact. Oxygenation of the Ar-Si bond is also feasible (Fig. 8b). Upon subjection to peracetic acid, 14g afforded the diol 22 with concomitant epoxide formation. On the other hand, the alkene in either 14g or 14a survived treatment of those substrates with basic hydrogen peroxide to give the substituted benzofuran 23. A cross-coupling reaction (Fig. 8c) was demonstrated in the case of the dimethylated oxasilole 17b using conditions like those effective for arylation of alkenyloxasiloles [$\text{PdCl}_2(\text{PPh}_3)_2$, CuI, CsF, DMF, room temperature].¹⁹ Lastly, nucleophilic displacement of 14g with MeLi occurred smoothly to generate the *ortho*-TMS-substituted benzyl alcohol 25 (Fig. 8d).

In the discussion above accompanying Fig. 4, we described the observation that 12a gave, exclusively, product 14a, indicating that the silicon substituent was serving as an unanticipated control element to guide the HDDA cycloisomerization in only one of two possible directions. Seeing this, we prepared substrate 12f to explore another possible unique directing effect by a silicon substituent (Fig. 9). There is ample evidence^{3,20} that triynes analogous to 12f but in which each of the linking atoms is C, O, N, and/or S will undergo highly preferential cycloisomerization *via* a tetrahydro-Diels-Alder (TDDA) pathway (blue). In contrast, upon heating the silyl-containing triyne 12f, we observed a complete reversal; namely, none of the TDDA product 14o' was detected and the furan-trapped HDDA adduct 14o was isolated in excellent yield (*viz.* red, not blue, Fig. 9a). This type of reactivity reversal was preceded in the silicon-linked triynes studied by the Shibata group.⁷ The silicon atom in the tether is clearly capable of redirecting the

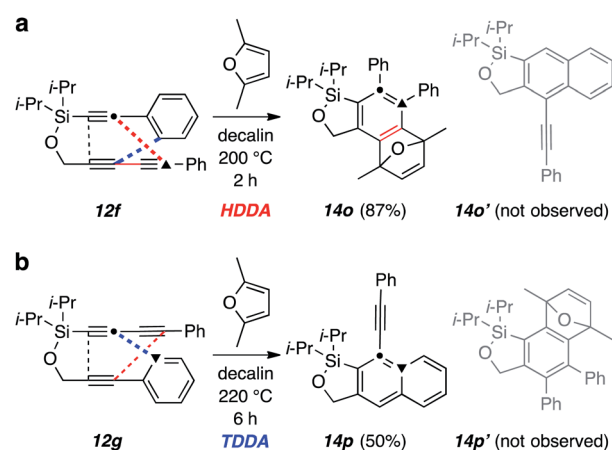


Fig. 9 Triyne substrates 12f and 12g show complementary modes of ring-closing selectivity, dictated by the relative position of diyne and monoyne relative to the silicon atom. (a) The first (12f) proceeds through HDDA cyclization. (b) The second (12g) proceeds through TDDA cyclization. In each case (as with 12a), the alkyne carbon beta to the silicon atom (●) participated in the closure to the new six-membered ring.



innate regioselectivity of dehydro-DA reactions for this type of triyne. Finally, the complementary triyne **12g** was also examined. This produced only the TDDA product **14p** and none of the benzyne trapped, HDDA product **14p'** (blue, not red, Fig. 9b). In all three instances of **12a**, **12f**, and **12g**, the sp-carbon beta to the silicon atom (dot, top) closes to the terminus of the 4 π -component (triangle, bottom), consistent with the rationale and calculations associated with Fig. 4b and explained by radical stabilization by the β -silyl substituent.

Conclusions

We have discovered that hexadehydro-Diels–Alder substrates in which the diyne and diynophile are linked by a tether containing a silicon atom provides new strategic opportunities and practical versatility to HDDA chemistry. The cycloisomerization reactions are often quite efficient. The product benzoxasiloles can be erased through protodesilylation or functionalized by replacement with halide, hydroxyl, or aryl groups. In an intriguing outcome and of fundamental mechanistic interest, the presence of the silicon atom completely biases the direction of cyclization, providing a control element for overriding the inherent regioselectivity of some dehydro-Diels–Alder reactions. We suggest that this arises from the (DFT-computed) geometry of an initially formed diradical intermediate, in turn a manifestation of the stabilization of radical character by the β -silyl substituent. In sum, the presence of a silicon atom-containing tether provides elementary control of these polyyne cyclizations and the benzoxasilole products provide opportunity for further, versatile derivatization.

Experimental

Typical procedure for the cyclization of a silicon-tethered substrate (here, **12a** trapped with furan to give **14b**, Fig. 5): A solution of tetrayne **12a** (28 mg, 0.071 mmol) and furan (0.15 mL, 2.1 mmol) in ethanol-free CHCl₃ (3.5 mL, 0.02 M) was placed in a threaded culture tube and the headspace was flushed with N₂. The tube was fitted with an inert, Teflon®-lined cap, firmly sealed, and heated in an oil bath that had been pre-equilibrated to 140 °C; this mixture was heated for 3 h, cooled to rt and concentrated. The crude product was purified by passage through a small plug of silica gel (15% EtOAc/hexanes as eluent), and the residue was purified by medium pressure liquid chromatography (20% EtOAc/hexanes) to give compound **14b** (28 mg, 85%) as a pale-yellow, crystalline solid.

Author contributions

M. P. S. prepared and established the cyclizations of the initial substrates **4a–c**. M. L. carried out the bulk of the experimentation and co-wrote the early drafts of the manuscript. All authors reviewed and edited the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

† We note that benzoxadisiloles^{aa} such as that in **5a**, as well as 1,2-disilylated benzenes,^{ab} (viz. **5b–c**) are known precursors to benzyne *via* derived iodonium species.

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- 21 Generic tetrahydro-Diels–Alder (TDDA) reaction of **i** to **iii** (via the strained allene **ii**), typically favoured over the possible HDDA reaction of the triyne:

