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Aza Diels-Alder Reactions of Nitriles, *N,N*-Dimethylhydrazones, and Oximino Ethers. Application in Formal [2 + 2 + 2] Cycloadditions for the Synthesis of Pyridines

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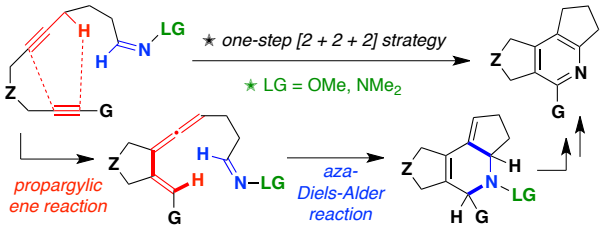
ABSTRACT: Metal-free, formal [2 + 2 + 2] cycloaddition strategies for the synthesis of polycyclic pyridine derivatives are described. The overall transformation proceeds via a two-stage pericyclic cascade mechanism. In the first step, an intramolecular propargylic ene reaction generates a vinylallene that is necessarily locked in the s-cis conformation. This vinylallene exhibits exceptional reactivity as a Diels-Alder reaction partner and engages in [4 + 2] cycloadditions with normally unreactive azadienophiles including unactivated cyano groups and heterosubstituted imine derivatives such as dimethylhydrazones and oximino ethers. Few examples of oximino ether Diels-Alder reactions have been reported previously and normal electron demand [4 + 2] cycloadditions of unactivated dialkylhydrazones are unprecedented. Overall this metal-free formal [2 + 2 + 2] cycloaddition provides access to polycyclic pyridine derivatives and complements transition metal-catalyzed [2 + 2 + 2] strategies.



INTRODUCTION

The development of improved methods for the construction of highly substituted pyridines continues to command great interest due to the prominence of this heterocycle in the structure of numerous natural products, functional materials, and pharmaceutical compounds.[1,2] The rapid assembly of unsymmetrical, multisubstituted pyridines remains a significant challenge in this area, and for this purpose convergent annulation strategies[3] have proven particularly attractive, especially transition metal-catalyzed [2 + 2 + 2] cycloadditions with nitriles[4] and imine derivatives.[5]

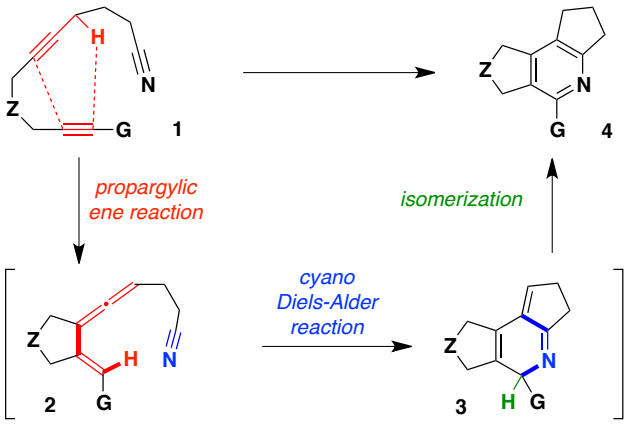
Recently we described a metal-free bimolecular [2 + 2 + 2] cycloaddition strategy for the synthesis of carbocyclic compounds that proceeds in a single synthetic step via a cascade of two pericyclic processes.[6] The first stage involves an intramolecular propargylic ene-type reaction[7] of a 1,6-diyne that generates a vinylallene intermediate, which then engages in an inter- or intramolecular Diels-Alder reaction with an alkenyl or alkynyl dienophile. Overall, this pericyclic cascade sequence provides convenient access to highly functionalized alkylidenecyclohexanes and benzenoid aromatic compounds.

Vinylallenes are intrinsically reactive Diels-Alder dienes,[8,9] and vinylallenes generated via these intramolecular propargylic ene reactions are necessarily locked in an s-cis conformation. These considerations led us to expect that these vinylallenes might exhibit exceptional reactivity as Diels-Alder reaction partners, possibly engaging in cycloadditions with normally unreactive dienophiles. This has proven to be the case, and herein we provide further details on the reactions of unactivated nitriles as dienophiles that we reported previously,[10] and also describe new extensions of this strategy to include reactions of *N*-heterosubstituted imine derivatives such as oximino ethers and dimethylhydrazones.

RESULTS AND DISCUSSION

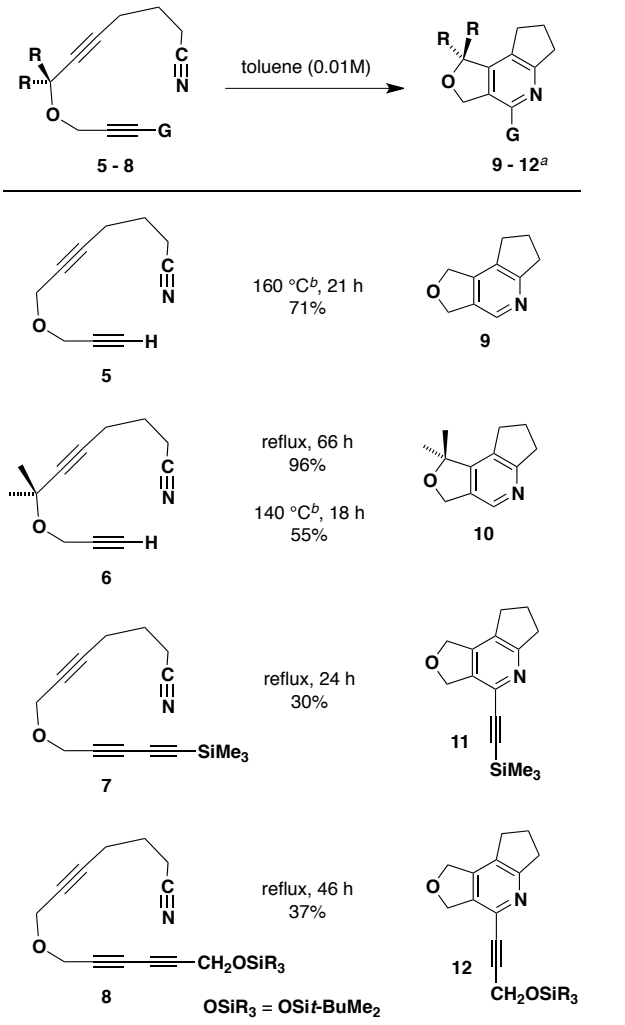
Formal [2 + 2 + 2] Cycloadditions Involving Cyano Diels-Alder Reactions. In our initial studies we focused attention on reactions in which an unactivated cyano group would function as the dienophilic cycloaddition partner. Scheme 1 outlines the proposed strategy. Thermolysis of 1,6-diyne substrate **1** was expected to trigger a propargylic ene reaction, generating a vinylallene (**2**) that would be intercepted by the pendant cyano group in a [4 + 2] cycloaddition leading to **3**. Aromatization via double bond isomerization was then expected to furnish the pyridine product **4**. Although the nitrile functional group rarely participates as a dienophile in Diels-Alder cycloadditions,[11,12] we hoped that the unusual reactivity of vinylallenes of type **2** might render this a feasible process.

Scheme 1. Synthesis of Pyridines via Propargylic Ene/Cyano Diels–Alder Strategy



Tables 1 and 2 present several examples of this variant of our formal [2 + 2 + 2] cycloaddition strategy.[10] Reactions involving terminal alkynes (G = H) as the enophile component proceed at 110 to 160 °C depending on the nature of the tether connecting the two alkynyl triple bonds. As expected, substrates incorporating *gem*-dimethyl substitution undergo reaction at lower temperature due to the *gem*-dialkyl effect.[13] Ambiguity with regard to the regiochemical course of the ene step precludes the use of substrates with G = alkyl, but 1,3-diynes (i.e., G = alkynyl) function as competent enophiles and hydrogenation then provides access to products that would have resulted from reaction of alkyl-substituted acetylenes (vide infra).

Table 1. Formal [2 + 2 + 2] Cycloadditions via Propargylic Ene/Cyano Diels-Alder Reactions

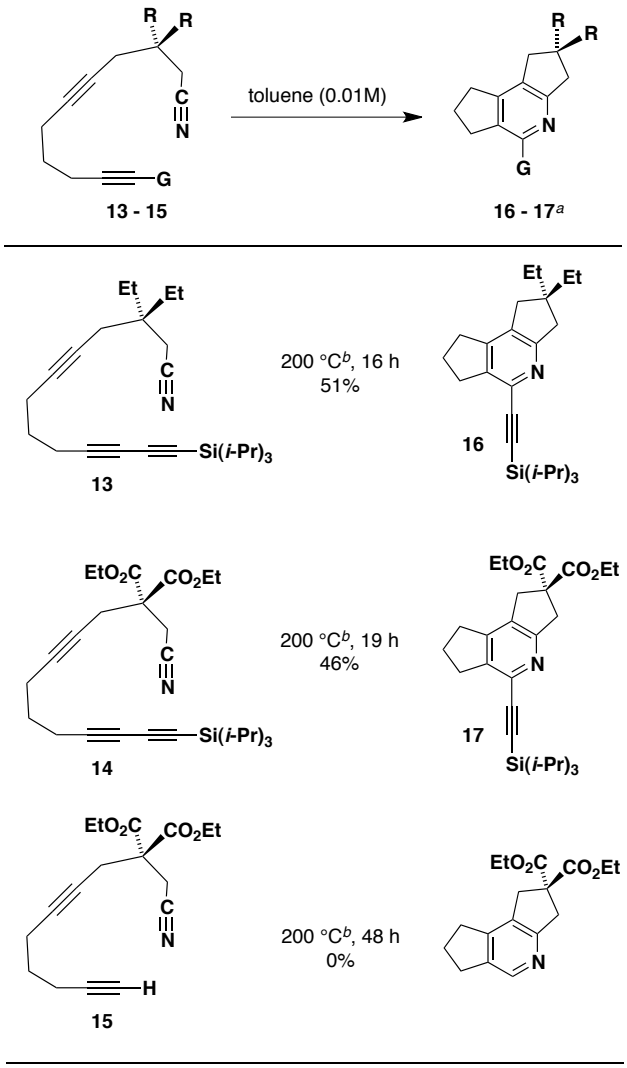


[a] Isolated yield of products purified by column chromatography. [b] Reaction conducted at the indicated bath temperature in a tube sealed with a threaded teflon cap.

Although several alternative mechanisms can be envisioned to account for these formal [2 + 2 + 2] cycloadditions, experimental and computational studies support the mechanistic pathway outlined in Scheme 1. For example, experiments we reported previously rule out an alternative pathway involving a cyano ene reaction followed by an azadiene hetero Diels-Alder reaction leading to the same products.[10] That mechanism was investigated and also excluded through a computational study, which also revealed a considerably lower barrier for the pathway outlined in Scheme 1 as compared to alternatives proceeding via initial cyclization of **1** to form an intermediate 1,4-diradical.[14]

Examples of the formal [2 + 2 + 2] cycloaddition involving substrates with all carbon tethers are shown in Table 2. Higher temperatures are required for these reactions and only complex mixtures were isolated from reactions of compounds with terminal alkynes as enophiles.

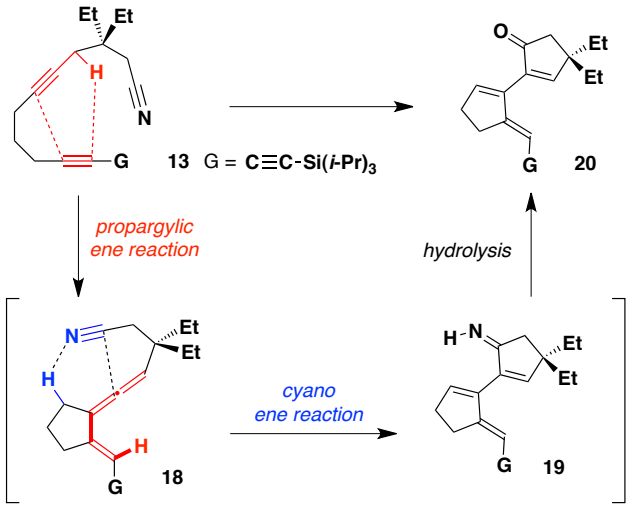
Table 2. Formal [2 + 2 + 2] Cycloadditions via Propargylic Ene/Cyano Diels-Alder Reactions



[a] Isolated yield of products purified by column chromatography. [b] Reaction conducted at 200 °C (bath temperature) in a tube sealed with a threaded teflon cap.

These initial studies served to establish the feasibility of our formal [2 + 2 + 2] cycloaddition strategy, and importantly, confirmed the exceptional Diels-Alder reactivity of vinylallenes generated in this fashion. Unfortunately, from the standpoint of synthetic utility this method suffers from several limitations, most notably low to moderate yields in a number of cases (e.g., **7**→**11** and **8**→**12**). Previously we have observed that the vinylallenes formed by intramolecular propargylic ene reaction undergo rapid [4 + 2] dimerization when generated in the absence of dienophiles.[6] In the case of many of these nitriles, the unactivated cyano group is not sufficiently dienophilic to effectively compete with dimerization. In addition, in a number of cases we also noted the formation of byproducts generated by alternative reaction pathways. For example, thermolysis of **13** (Table 2) led to the desired pyridine **16** (51%) accompanied by a cyclopentenone **20** which was isolated in 29% yield. Scheme 2 outlines the likely mechanism for the formation of this byproduct. Heating **13** effects propargylic ene reaction as usual and furnishes an intermediate vinylallene (**18**) which then undergoes intramolecular *cyano ene reaction* to produce an imine, **19**. Hydrolysis during workup affords the cyclopentenone **20**. Note that to our knowledge the participation of an unactivated cyano group in a thermal ene reaction is unprecedented.[15,16]

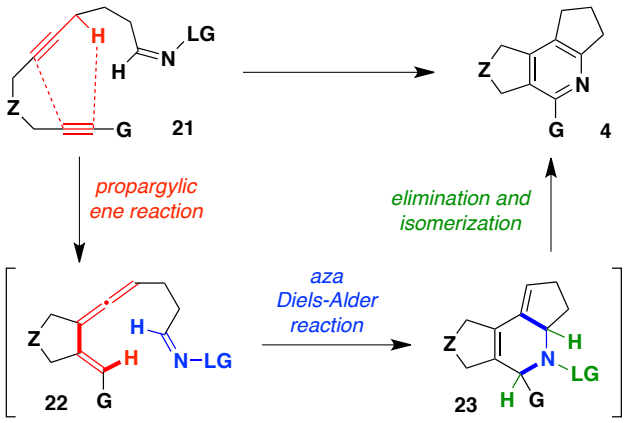
Scheme 2. Formation of Cyclopentenone Side Product via Propargylic Ene/Cyano Ene Pathway



In summary, although this tandem process is certainly mechanistically interesting, the efficiency of the propargylic ene/cyano Diels-Alder [2 + 2 + 2] cycloaddition strategy is not high in the case of some substrates, and the overall scope of the method has proven to be relatively narrow. We consequently undertook the investigation of reactions employing alternative dienophilic functional groups that might have the ability to serve as nitrile surrogates in this strategy for the synthesis of polycyclic pyridines.

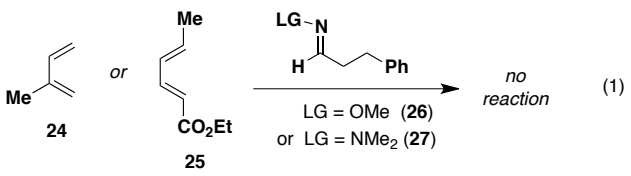
Diels-Alder Reactions of *N*-Heterosubstituted Imines. With the aim of extending the scope of our formal [2 + 2 + 2] cycloaddition strategy, we turned our attention to the tandem strategy outlined in Scheme 3 in which *N*-heteroatom-substituted imines would function as the azadienophiles in the [4 + 2] cycloaddition step. In the proposed strategy, propargylic ene reaction of substrates of type **21** would generate intermediates **22** incorporating vinylallene moieties that we hoped would engage in an efficient [4 + 2] cycloaddition with imine derivatives to afford **23**. Elimination of the *N*-substituent *in situ* followed by isomerization of the exocyclic double bond would then produce the desired pyridines. Overall this strategy would represent a formal [2 + 2 + 2] cycloaddition with imine derivatives and would complement current transition metal-catalyzed variants, which are relatively limited in scope and in some cases suffer from limitations due to unattractive reaction conditions and regiochemical ambiguities.[5]

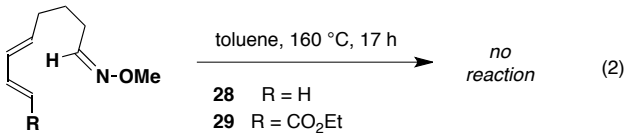
Scheme 3. Synthesis of Pyridines via Propargylic Ene/Imino Diels–Alder Strategy



At the outset of this study we recognized that a key challenge to realizing this scheme would be the identification of imine derivatives that could function as azadienophiles[17] in the key cycloaddition step. After briefly considering *N*-sulfonylimines,[18] we focused our attention on more readily accessible and robust imine derivatives[19] such as dialkylhydrazones and oximino ethers. In this connection it was noteworthy that to our knowledge no prior examples of Diels-Alder reactions of *N,N*-dialkylhydrazones with normal electron demand dienes had been reported,[20,21] and oximino ethers lacking electron-withdrawing groups only engage in cycloadditions with highly reactive dienes such as *ortho*-quinodimethanes.[22,23]

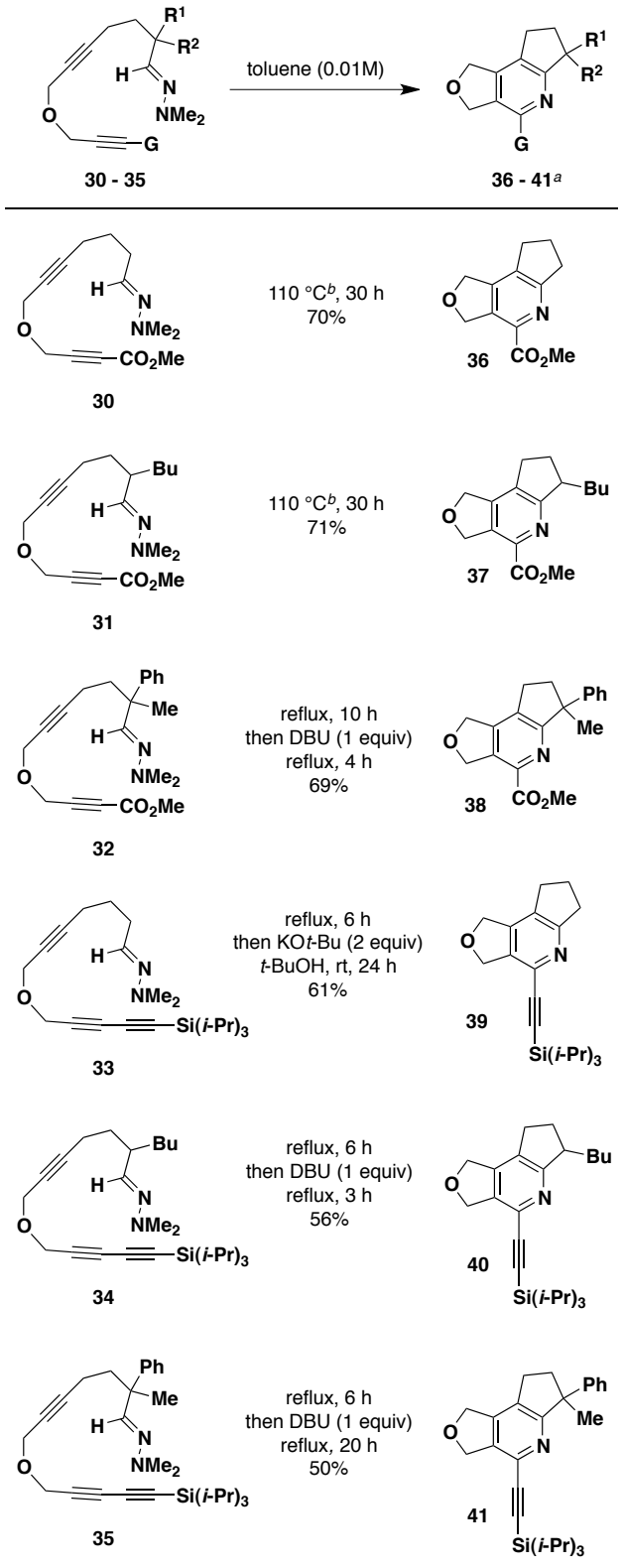
In view of the limited data available in the literature, we carried out a series of experiments to probe the reactivity of "unactivated" hydrazones and oximino ethers in concerted Diels–Alder reactions with simple dienes. As outlined in eq 1, both *O*-methyl oximino ether **26** and *N,N*-dimethylhydrazone **27** failed to react with excess isoprene upon heating overnight in toluene (160 °C, 17 h), and no reaction was observed in the presence of Lewis acids (2.0 equiv Me_2AlCl or $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 15-24 h). In all cases the imine derivatives were recovered in high yield. Inverse electron demand Diels-Alder reactions also failed to take place with these potential dienophiles. Neither **26** nor **27** reacted with ethyl sorbate (**25**) upon heating (toluene, 160 °C, 17 h), and again the imine derivatives were recovered in 90-98% yield. To our surprise, the *O*-methyl oximino ethers **28** and **29** even failed to engage in intramolecular Diels–Alder reactions, and both compounds were recovered in quantitative yield after heating overnight at 160 °C (eq 2).[24] While these experiments served to confirm the relative lack of reactivity of oximino ethers and dialkylhydrazones in conventional Diels-Alder reactions, we hoped that our conformationally constrained vinylallenes would prove to be competent as cycloaddition partners as had been observed in our previous studies with nitrile substrates.





Formal [2 + 2 + 2] Cycloadditions Involving *N,N*-Dimethylhydrazones. It was our hope that the use of exceptionally reactive vinylallenes of type **22** as Diels–Alder reaction partners would enable these normally unreactive imine derivatives to participate as dienophiles in the proposed scheme. The feasibility of this strategy as applied to *N,N*-dimethylhydrazones was examined first. The requisite substrates **30** - **35** (Table 3) were prepared directly from the appropriate aldehyde precursors, in some cases employing well-established hydrazone alkylation chemistry.[25] Special attention was paid to substrates with electron-withdrawing substituents (G = alkyne or CO_2Me) on the enophile alkyne component since these groups can serve as activators for the propargylic ene reaction and also could facilitate the elimination of the dimethylamino substituent from intermediates of type **23**. Table 3 summarizes our results. In some cases heating in toluene[26] at reflux suffices to promote the cascade outlined in Scheme 3, affording the formal [2 + 2 + 2] cycloadducts in good yield. In these reactions the dimethylamine liberated *in situ* may be acting as base to promote the elimination and isomerization steps. Other cases require the addition of base to complete the transformation to the pyridine products, and DBU generally was found to provide optimal results. In the case of pyridine **39**, the desired product could be obtained simply by heating without added base (110 ° C, 5 days, 43%, or 160 °C, 18 h, 51%), but improved yields were obtained by using KO*t*-Bu or DBU to promote the elimination/isomerization steps.

Table 3. Formal [2 + 2 + 2] Cycloadditions with *N,N*-Dimethylhydrazones



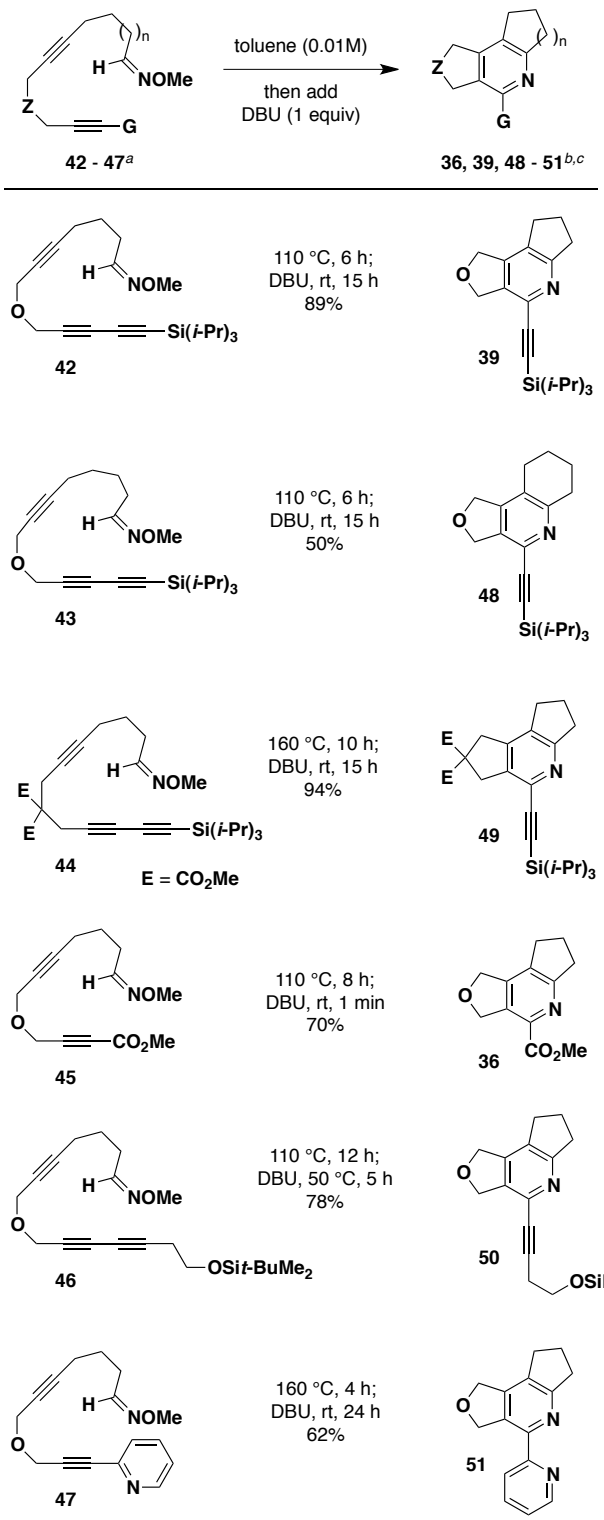
[a] Isolated yield of products purified by column chromatography. [b] Reaction conducted at 110 °C (bath temperature) in a tube sealed with a threaded teflon cap.

Thermal activation is required in these reactions to promote the propargylic ene step; cycloaddition of the resulting vinylallenes takes place rapidly and in no cases were the intermediate vinylallenes detected during the course of the reaction. In general, these reactions also appeared cleaner with fewer side products as compared to reactions of nitrile substrates. To our knowledge, these transformations represent the first examples of *N,N*-dialkylhydrazones functioning as efficient dienophiles in normal electron-demand Diels–Alder reactions.

Formal [2 + 2 + 2] Cycloadditions Involving Oximino Ethers. We next turned our attention to the application of oximes and oximino ethers in the formal [2 + 2 + 2] cycloaddition (Table 4). Heating *O*-methyl oximino ethers **42** - **47** produced cycloadducts of type **23** (LG = OMe) which we found do not undergo significant elimination under these conditions. Elimination and isomerization was therefore effected by cooling the reaction mixtures to room temperature and adding a tertiary amine, among which DBU was found to be most effective. Attempted generation of **36** by using the oxime rather than the corresponding oximino ether gave the desired pyridine in only 30% yield as part of a complex mixture.

As in our previous studies, particular attention was devoted to substrates with alkynes as G groups, since these substituents serve as excellent activators for the propargylic ene step and also function as synthetic equivalents for a variety of substituents on the pyridine ring via further elaboration by hydrogenation, hydration, and hydroboration reactions.[10] Reactions involving these oximino ether substrates proceeded more cleanly as compared to related reactions of nitriles and provided tricyclic pyridine products in improved yield (e.g., compare **7**→**11** and **8**→**12** with **43**→**48** and **46**→**50**). No evidence for ene-type side reactions analogous to that depicted in Scheme 2 was observed in these reactions.

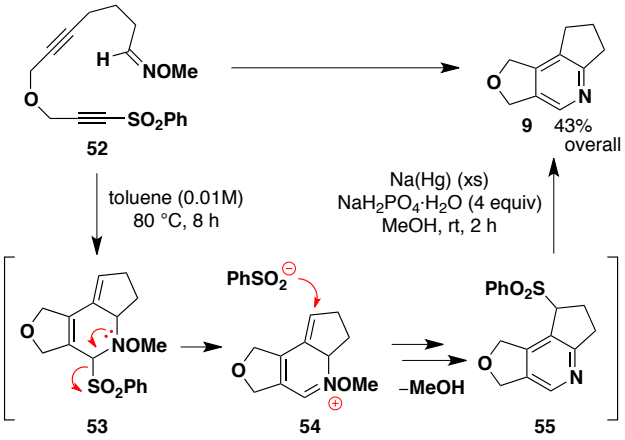
Table 4. Formal [2 + 2 + 2] Cycloadditions with *O*-Methyl Oximino Ethers



[a] Mixtures of E and Z isomers. For details, see Supporting Information. [b] Isolated yield of products purified by column chromatography. [c] Reaction conducted at 110 or 160 °C (bath temperature) in a tube sealed with a threaded teflon cap.

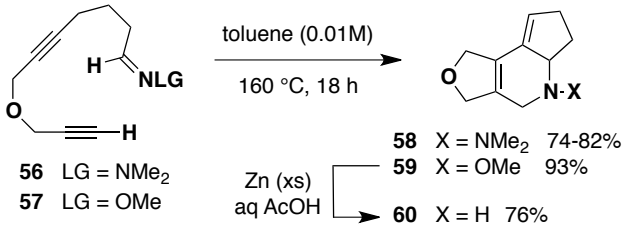
Formal [2 + 2 + 2] cycloaddition of sulfone **52** was also examined with the aim of generating a product that could be desulfonylated to afford the pyridine that would have resulted from reaction of a substrate with an unactivated enophile (i.e., G = H). Interestingly, while this [2 + 2 + 2] reaction proceeded under relatively mild conditions (80 °C), the major product was the sulfonyl migration product **55** rather than the expected cycloadduct. As outlined in Scheme 4, we propose that **55** forms via ionization of the amino sulfone **53** followed by 1,6-addition of sulfinate to the resulting iminium ion and elimination of methanol. In any event, this unanticipated rearrangement was not a concern, since desulfonylation of **55** with sodium amalgam conveniently afforded the desired pyridine **9** in 43% overall yield after purification by chromatography.

Scheme 4. Formal [2 + 2 + 2] Cycloaddition with Alkynyl Sulfone 52



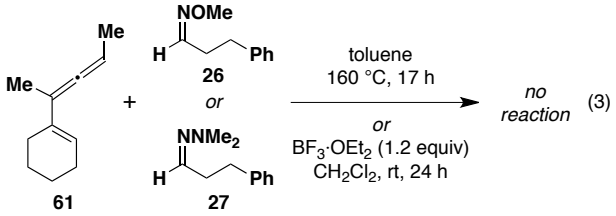
Formal [2 + 2 + 2] Cycloadditions with Terminal Alkynes. It should be noted that formal [2 + 2 + 2] cycloadditions with oximino ethers and *N,N*-dimethylhydrazones lacking enophile G groups (i.e., G = H) can be accomplished in good yield although relatively high temperatures are required in these cases to effect the rate-determining propargylic ene step in the cascade. As illustrated with the examples in Scheme 5, aromatization does not take place in these reactions, and cycloadducts such as **58** and **59** are isolated in good to excellent yield. Reductive cleavage of the N-O bond in **59** with zinc dust in aqueous acetic acid (rt, 48 h) afforded the amine **60** in good yield.

Scheme 5. Formal [2 + 2 + 2] Cycloadditions with Terminal Alkynes



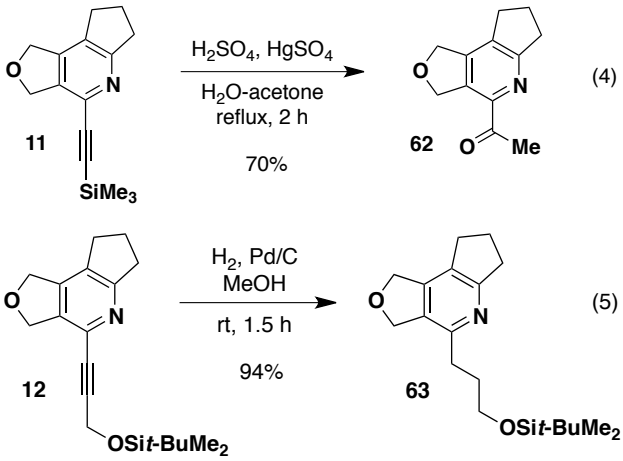
Intermolecular [4 + 2] Cycloadditions Involving Vinylallenes and *N*-Heterosubstituted Imines. The success of the [4 + 2] cycloadditions described here prompted us to ask whether other vinylallenes lacking conformational constraints might engage in efficient Diels-Alder reactions with oximino ethers and dimethylhydrazones. Vinylallene **61** was chosen for our exploratory study since Palenzuela has previously reported that this vinylallene undergoes Diels-Alder reaction with *N*-benzylimines in

the presence of Lewis acids.[27] In the event, no reaction of **26** and **27** with vinylallene **61** was observed either on heating or in the presence of Lewis acids (eq 3), and in all cases the imine derivatives were recovered in 85% to quantitative yield. These results underscore the exceptional reactivity of the vinylallenes generated via the intramolecular propargylic ene reaction which are constrained to be in the highly reactive s-cis conformation.



(3)

Synthetic Elaboration of [2 + 2 + 2] Cycloaddition Products. Throughout the course of our studies particular attention was focused on reactions of substrates incorporating 1,3-diynes as enophiles. In these substrates the alkynyl G groups were found not only to function as excellent activating groups for the propargylic ene and azadiene Diels-Alder reactions, but also can then serve as precursors to a variety of substituents on the pyridine ring. For example, hydration and hydrogenation of formal [2 + 2 + 2] cycloadducts **11** and **12** furnished **62** and **63**, respectively, in good yield (eq 4-5).



(4)

(5)

CONCLUSIONS

In summary, we have described a formal [2 + 2 + 2] cycloaddition strategy for the synthesis of polycyclic pyridines based on a pericyclic reaction cascade incorporating intramolecular propargylic ene and imino and cyano Diels–Alder reactions. In the key [4 + 2] cycloaddition step, the vinylallenes generated *in situ* combine with normally unreactive azadienophiles including nitriles, *O*-methyl oximino ethers, and *N,N*-dimethylhydrazones. Further studies are underway in our laboratory aimed at the development of additional routes to complex multi-substituted pyridines based on the cycloaddition of vinylallenes with other classes of azadienophiles.

EXPERIMENTAL SECTION

General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230-400 mesh).

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. DBU was distilled at 100 °C (20 mmHg) from calcium hydride. Methanol was distilled under argon at atmospheric pressure from calcium hydride. Propargyl alcohol was filtered through neutral alumina and distilled at 54 °C (57 mmHg) from anhydrous potassium carbonate prior to use. *N,N*-Dimethylhydrazine was distilled under argon at atmospheric pressure. Triethylamine was distilled under argon at atmospheric pressure from calcium hydride. Methyl chloroformate was distilled under argon at atmospheric pressure immediately prior to use. Diisopropylamine was distilled under argon from calcium hydride. HMPA was distilled at 70 °C (0.1 mmHg) from calcium hydride. 5-Bromo-1-pentene, 6-bromo-1-hexene, and 2-bromopyridine were filtered through neutral alumina before use. Propargyl bromide (80% w/w in toluene) was filtered through a plug of neutral alumina in a disposable pipette with the aid of argon and its concentration was determined by ^{1}H NMR integration prior to use. *n*-Butyllithium was titrated according to the method of Watson-Eastham using BHT in THF with 1,10-phenanthroline as indicator.[28] 4-Oxadodec-11-en-1,6-diyne **S1**,[6] (*E*)-hexanal 2,2-dimethylhydrazone **S3**, [29] but-3-ynyl trifluoromethanesulfonate **S4**,[30] (*E*)-benzeneacetaldehyde (E)-2-phenylpropionaldehyde dimethylhydrazone **S5**,[31] non-8-en-2-yn-1-ol **S6**,[32] octa-7-en-2-yn-1-ol **S7**,[33] and were prepared as previously reported. 1-Bromo-2-(triisopropylsilyl)acetylene **S2**[34] and 1-bromo-4-(*tert*-butyldimethylsilyloxy)butyne **S8**[35] were prepared as previously reported using the bromination method of Hofmeister and co-workers.[36]

Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured with Inova 500, Inova 300, Bruker 600, and Bruker 400 spectrometers. ^{1}H NMR chemical shifts are expressed in parts per million downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm as standard). ^{13}C NMR chemical shifts are expressed in parts per million downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm as standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 telsa Fourier transform mass spectrometer.

Experimental Procedures for [2 + 2 + 2] Cycloadditions of *N,N*-Dimethylhydrazones.

*Methyl 3,6,7,8-tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine-4-carboxylate (**36**).* A 21-cm, threaded Pyrex tube (47 mm O.D., 41 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with a solution of hydrazone **30** (0.246 g, 0.930 mmol) in 90 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (–196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 110 °C for 30 h and then allowed to cool to rt. The resulting clear yellow solution was concentrated by rotary evaporation (30 °C, 20 mmHg) to afford 0.250 g of a brown oil. Column chromatography on 25 g of silica gel (elution with 50-70% EtOAc-hexanes) afforded 0.142 g (70%) of **36** as a white solid: mp 138-140 °C; IR (KBr) 2956, 1705, 1448, 1346, 1255, 1218, and 1043 cm-1; 1H NMR (500 MHz, CDCl3) δ 5.40 (s, 2 H), 5.05 (s, 2 H), 3.99 (s, 3 H), 3.12 (t, J = 7.5 Hz, 2 H), 2.90 (t, J = 7.5 Hz, 2 H), 2.22 (app quint, J = 7.5 Hz, 2 H); 13C NMR (125 MHz, CDCl3) δ 166.6, 166.5, 147.0, 139.9, 137.6, 135.4, 74.7, 72.1, 53.4, 34.3, 29.9, 23.8; HRMS (DART-FTICR) m/z [M + H]+ calcd for C12H13NO3 220.0968, found 220.0960.

*Methyl 3,6,7,8-tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine-4-carboxylate (**37**).* A 16-cm, threaded Pyrex tube (36 mm O.D., 30 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with hydrazone **31** (0.050 g, 0.16 mmol) and 16 mL of toluene. The reaction mixture was degassed by bubbling argon through the solution for 10 min and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 110 °C (bath temperature) for 30 h and then allowed to cool to rt. The resulting clear orange solution was concentrated by rotary evaporation (30 °C, 20 mmHg) to afford 0.040 g of a brown oil. Column chromatography on 15 g of silica gel (elution with 0-30% EtOAc-hexanes) afforded 0.031 g (71%) of **37** as a colorless oil: IR (NaCl) 2953, 2928, 2856, 1440, 1252, 1203, and 1051 cm-1; 1H NMR (500 MHz, CDCl3) δ 5.39 (s, 2 H), 5.05 (s, 2 H), 3.98 (s, 3 H), 3.18-3.23 (m, 1 H), 2.77-2.91 (m, 2 H), 2.38-2.46 (m, 1 H), 2.08-2.14 (m, 1 H), 1.82-1.89 (m, 1 H), 1.30-1.45 (m, 5 H), 0.92 (t, J = 7.0 Hz, 3 H); 13C NMR (125 MHz, CDCl3) δ 168.7, 166.2, 146.5, 139.8, 137.4, 134.6, 74.3, 71.7, 52.9, 45.3, 34.3, 30.2, 30.0, 27.9, 23.1, 14.4; HRMS (DART-FTICR) m/z [M + H]+ calcd for C16H21NO3 276.1594, found 276.1590.

*Methyl 6-methyl-6-phenyl-3,6,7,8-tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine-4-carboxylate (**38**).* A 100-mL, round-bottomed flask equipped with a condenser fitted with an argon inlet needle was charged with hydrazone **32** (0.175 g, 0.494 mmol, 1.0 equiv) and 50 mL of toluene. The solution was heated at reflux for 10 h, allowed to cool to rt, and DBU (0.08 mL, 0.075 g, 0.49 mmol, 1.0 equiv) was added via syringe. The resulting mixture was stirred at reflux for 4 h and then cooled to rt and concentrated to give ca. 0.3 g of an orange oil. Column chromatography on 30 g of silica gel (elution with 5-30% EtOAc-hexanes) afforded 0.105 g (69%) of **38** as a colorless oil: IR (NaCl) 3057, 3023, 2952, 2862, 1713, 1619, 1600, 1442, 1342, 1255, and 1049 cm-1; 1H NMR (500 MHz, CDCl3) δ 7.21-7.26 (m, 4 H), 7.13-7.17 (m, 1 H), 5.39-5.46 (m, 2 H), 5.04-5.10 (m, 2 H), 3.96 (s, 3 H), 2.78-2.81 (m, 2 H), 2.65-2.70 (m, 1 H), 2.27-2.35 (m, 1 H), 1.80 (s, 3 H); 13C NMR (75 MHz, CDCl3) δ 178.8, 169.7, 166.4, 146.8, 140.5, 137.6, 134.6, 128.5, 126.6, 126.4, 74.4, 71.8, 52.9, 51.6, 41.7, 28.0, 26.7; HRMS (ESI-FTICR) m/z [M + H]+ calcd for C19H19NO3 310.1438, found: 310.1448.

*4-((Triisopropylsilyl)ethynyl)-3,6,7,8-tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine (**39**).* A 100-mL, round-bottomed flask equipped with a condenser fitted with a rubber septum and argon inlet needle was charged with hydrazone **33** (0.200 g, 0.517 mmol, 1.0 equiv) and 52 mL of toluene. The solution was heated at reflux for 6 h and then cooled to rt and concentrated to a volume of ca. 1 mL. t-BuOH (4 mL) and KOt-Bu (0.116 g, 1.03 mmol, 2.0 equiv) were added, and the resulting mixture was stirred at rt for 24 h and then diluted with 10 mL of ether and 10 mL of water. The aqueous phase was separated and extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of satd NaCl solution, dried over MgSO4, filtered, and concentrated to give 0.2 g of a brown oil. Column chromatography on 25 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.107 g (61%) of **39** as a yellow solid: mp 118-119 °C; IR (KBr) 2995, 2865, 2152, 1576, 1460, 1388, and 1054 cm-1; 1H NMR (500 MHz, CDCl3) δ 5.15 (s, 2 H), 5.05 (s, 2 H), 3.01 (t, J = 7.5 Hz, 2 H), 2.83 (t, J = 7.5 Hz, 2 H), 2.15 (app quint, J = 7.5 Hz, 2 H), 1.12 (s, 21 H); 13C NMR (125 MHz, CDCl3) δ 166.3, 145.1, 137.5, 134.8, 130.9, 104.5, 95.7, 73.8, 73.4, 34.5, 29.9, 23.8, 19.3, 11.8; HRMS (ESI-FTICR) m/z [M + H]+ calcd for C12H13NO3 220.0968, found 220.0960.

*6-Butyl-4-((triisopropylsilyl)ethynyl)-3,6,7,8-tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine (**40**).* A 100-mL, round-bottomed flask equipped with a condenser fitted with a rubber septum and argon inlet needle was charged with hydrazone **34** (0.200 g, 0.452 mmol, 1.0 equiv) and 45 mL of toluene. The solution was heated at reflux for 6 h, cooled to rt, and DBU (0.07 mL, 0.069 g, 0.45 mmol, 1.0 equiv) was added via syringe. The resulting mixture was stirred at reflux for 3 h and then cooled to rt and concentrated to give ca. 0.3 g of an orange oil. Column chromatography on 25 g of silica gel (elution with 0-50% CH2Cl2-hexanes) afforded 0.100 g (56%) of **40** as a yellow solid: mp 50-52 °C; IR (NaCl) 2940, 2865, 2361, 2338, 2146, 1458, 1388, and 1054 cm-1; 1H NMR (500 MHz, CDCl3) δ 5.15 (s, 2 H), 5.05 (s, 2 H), 3.08-3.13 (m, 1 H), 2.70-2.85 (m, 2 H), 2.32-2.39 (m, 1 H), 2.04-2.09 (m, 1 H), 1.77-1.84 (m, 1 H), 1.31-1.43 (m, 5 H), 1.13 (s, 21 H), 0.92 (t, J = 7.0 Hz); 13C NMR (125 MHz, CDCl3) δ 168.4, 144.5, 137.2, 134.5, 130.1, 104.3, 95.2, 73.4, 72.9, 45.5, 34.3, 30.2, 29.9, 27.8, 23.1, 18.9, 14.4, 11.4; HRMS (DART-FTICR) m/z [M + H]+ calcd for C25H39NOSi 398.2874, found 398.2861.

*6-Methyl-6-phenyl-4-((triisopropylsilyl)ethynyl)-3,6,7,8-tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine (**41**).* A 100-mL, round-bottomed flask equipped with a condenser fitted with a rubber septum and argon inlet needle was charged with hydrazone **35** (0.19 g, 0.40 mmol, 1.0 equiv) and 40 mL of toluene. The solution was heated at reflux for 6 h, cooled to rt, and DBU (0.06 mL, 0.06 g, 0.40 mmol, 1.0 equiv) was added via syringe. The resulting mixture was stirred at reflux for 20 h and then cooled to rt and concentrated to give ca. 0.4 g of a brown oil. Column chromatography on 25 g of silica gel (elution with 0-100% CH2Cl2-hexanes) afforded 0.085 g (50%) of **41** as a pale yellow oil: IR (NaCl) 3058, 3024, 2943, 2865, 2361, 2153, 1600, 1575, 1463, 1389, and 1053 cm-1; 1H NMR (500 MHz, CDCl3) δ 7.23-7.29 (m, 4 H), 7.16-7.19 (m, 1 H), 5.18-5.24 (m, 2 H), 5.07-5.13 (m, 2 H), 2.75-2.78 (m, 2 H), 2.61 (dt, J = 13.0, 5.5 Hz, 1 H), 2.26 (dt, J = 13.0, 8.5 Hz, 1 H), 1.77 (s, 3 H), 1.16 (s, 21 H); 13C NMR (75 MHz, CDCl3) δ 169.5, 147.1, 144.7, 137.7, 135.1, 130.2, 128.3, 126.6, 126.2, 104.4, 95.4, 73.4, 73.0, 51.7, 41.8, 27.7, 26.6, 18.9, 11.4; HRMS (DART-

FTICR) m/z [M + H]+ calcd for C28H37NOSi 432.2717, found 432.2698.

Experimental Procedures for [2 + 2 + 2] Cycloadditions of Oximino Ethers.

*4-((Triisopropylsilyl)ethynyl)-3,6,7,8-tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine (**39**).* A 16-cm, threaded Pyrex tube (36 mm O.D., 30 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with a solution of oximino ether **42** (0.155 g, 0.414 mmol) in 40 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (–196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 110 °C (bath temperature) for 5 h and then allowed to cool to rt. DBU (0.06 mL, 0.061 g, 0.414 mmol, 1.0 equiv) was added, and the reaction mixture was stirred at rt for 15 h. The resulting clear yellow solution was washed with 20 mL of water and the aqueous phase was extracted with two 20-mL portions of ether. The combined organic layers were washed with 10 mL of satd NaCl solution, dried over MgSO4, filtered, and concentrated by rotary evaporation (30 °C, 20 mmHg) to give 0.210 g of a yellow solid. Column chromatography on 30 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.126 g (89%) of **39** as a white solid: mp 118-119 °C; IR (KBr) 2995, 2865, 2152, 1576, 1460, 1388, and 1054 cm-1; 1H NMR (500 MHz, CDCl3) δ 5.15 (s, 2 H), 5.05 (s, 2 H), 3.01 (t, J = 7.5 Hz, 2 H), 2.83 (t, J = 7.5 Hz, 2 H), 2.15 (app quint, J = 7.5 Hz, 2 H), 1.12 (s, 21 H); 13C NMR (125 MHz, CDCl3) δ 166.3, 145.1, 137.5, 134.8, 130.9, 104.5, 95.7, 73.8, 73.4, 34.5, 29.9, 23.8, 19.3, 11.8; HRMS (ESI-FTICR) m/z [M + H]+ calcd for C12H13NO3 220.0968, found 220.0960.

*4-((Triisopropylsilyl)ethynyl)-1,3,6,7,8,9-hexahydrofuro[3,4-c]quinolone (**48**).* A 21-cm, threaded Pyrex tube (47 mm O.D., 41 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with a solution of oximino ether **43** (0.350 g, 0.902 mmol) in 90 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (–196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 110 °C (bath temperature) for 6 h and then allowed to cool to rt. DBU (0.135 mL, 0.137 g, 0.901 mmol, 1.0 equiv) was added, and the reaction mixture was stirred at rt for 15 h. The resulting clear yellow solution was washed with 30 mL of water and the aqueous phase was extracted with three 25-mL portions of ether. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over MgSO4, filtered, and concentrated by rotary evaporation (30 °C, 20 mmHg) to give 0.440 g of a yellow solid. Column chromatography on 25 g of silica gel (elution with 5-10% EtOAc-hexanes) afforded 0.160 g (50%) of **48** as a white solid: mp 105-107 °C; IR (KBr) 2864, 2155, 1593, 1577, 1461, 1406, and 1052 cm-1; 1H NMR (500 MHz, CDCl3) δ 5.16 (s, 2 H), 5.03 (s, 2H), 2.94 (t, J = 6.5 Hz, 2 H), 2.60 (t, J = 6.5 Hz, 2 H), 1.86-1.91 (m, 2H), 1.80-1.85 (m, 2 H), 1.12 (s, 21 H); 13C NMR (125 MHz, CDCl3) δ 156.9, 147.6, 136.2, 133.4, 126.3, 104.0, 94.9, 73.5, 73.1, 32.6, 26.4, 23.1, 22.4, 18.8, 11.3; HRMS (ESI-FTICR) m/z [M + H]+ calcd for C22H33NOSi 356.2404, found 356.2415.

*Dimethyl 5-((triisopropylsilyl)ethynyl)-2,3,6,8-tetrahydrodicyclopenta[b,d]pyridine-7,7(1H)-dicarboxylate (**49**).* A 16-cm, threaded Pyrex tube (36 mm O.D., 30 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with a solution of oximino ether **44** (0.150 g, 0.307 mmol) in 31 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (–196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 160 °C (bath temperature) for 10 h and then allowed to cool to rt. DBU (0.046 mL, 0.047 g, 0.31 mmol, 1.0 equiv) was added, and the reaction mixture was stirred at rt for 15 h. The resulting clear yellow solution was washed with 20 mL of water and the aqueous phase was extracted with three 10-mL portions of ether. The combined organic layers were washed with 10 mL of satd NaCl solution, dried over MgSO4, filtered, and concentrated by rotary evaporation (30 °C, 20 mmHg) to give 0.251 g of a brown oil. Column chromatography on 25 g of silica gel (elution with 10-20% EtOAc-hexanes) afforded 0.131 g (94%) of **49** as a yellow solid: mp 93-94 °C; IR (NaCl) 3470, 2943, 2865, 2158, 1734, 1607, 1569, 1462, 1271, and 1063 cm-1; 1H NMR (500 MHz, CDCl3) δ 3.77 (s, 6 H), 3.67 (s, 2 H), 3.52 (s, 2 H), 2.97 (t, J = 7.5 Hz, 2 H), 2.84 (t, J = 7.5 Hz, 2 H), 2.11 (app quint, J = 7.5 Hz, 2 H), 1.14 (s, 21 H); 13C NMR (125 MHz, CDCl3) δ 172.3, 165.7, 145.7, 138.1, 137.3, 133.7, 105.2, 95.1, 60.2, 53.9, 40.4, 40.3, 34.7, 29.8, 23.7, 19.4, 11.9; HRMS (ESI-FTICR) m/z [M + H]+ calcd for C26H37NO4Si 456.2570, found 456.2573.

*Methyl 3,6,7,8-tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine-4-carboxylate (**36**).* A 16-cm, threaded Pyrex tube (36 mm O.D., 30 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with a solution of oximino ether **45** (0.150 g, 0.60 mmol) in 60 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (–196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 110 °C (bath temperature) for 8 h and then allowed to cool to rt. DBU (0.089 mL, 0.091 g, 0.60 mmol, 1.0 equiv) was added, and the reaction mixture was stirred at rt for 1 min. The resulting clear amber solution was washed with 20 mL of water and the aqueous phase was extracted with two 20-mL portions of ether. The combined organic layers were washed with 10 mL of satd NaCl solution, dried over MgSO4, filtered, and concentrated by rotary evaporation (30 °C, 20 mmHg) to afford 0.122 g of a yellow solid. Column chromatography on 25 g of silica gel (elution with 80% EtOAc-hexanes) afforded 0.090 g (70%) of **36** as a white solid: mp 138-140 °C; IR (KBr) 2956, 1705, 1448, 1346, 1255, 1218, and 1043, cm-1; 1H NMR (500 MHz, CDCl3) δ 5.40 (s, 2 H), 5.05 (s, 2 H), 3.99 (s, 3 H), 3.12 (t, J = 7.5 Hz, 2 H), 2.90 (t, J = 7.5 Hz, 2 H), 2.22 (app quint, J = 7.5 Hz, 2 H); 13C NMR (125 MHz, CDCl3) δ 166.6, 166.5, 147.0, 139.9, 137.6, 135.4, 74.7, 72.1, 53.4, 34.3, 29.9, 23.8; HRMS (DART-FTICR) m/z [M + H]+ calcd for C12H13NO3 220.0968, found 220.0960.

*4-(4-((tert-Butyldimethylsilyl)oxy)but-1-yn-1-yl)-3,6,7,8-tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine (**50**).* A 16-cm, threaded Pyrex tube (36 mm O.D., 30 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with a solution of oximino ether **46** (0.090 g, 0.24 mmol) in 24 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (–196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 110 °C (bath temperature) for 12 h and then allowed to cool to rt. DBU (0.089 mL, 0.091 g, 0.60 mmol, 1.0 equiv) was added, and the reaction mixture was stirred at 50 °C for 5 h. The resulting clear amber solution was washed with 20 mL of water and the aqueous phase was extracted with two 20-mL portions of ether. The combined organic layers were washed with 10 mL of satd NaCl solu-

tion, dried over MgSO4, filtered, and concentrated by rotary evaporation (30 °C, 20 mmHg) to afford 0.098 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 10-30% EtOAc-hexanes) afforded 0.065 g (78%) of **50** as a colorless oil: IR (NaCl) 2954, 2929, 2856, 2226, 1579, 1472, 1398, 1256, and 1054 cm-1; 1H NMR (500 MHz, CDCl3) δ 5.10 (s, 2 H), 5.02 (s, 2 H), 3.80 (t, J = 7.5 Hz, 2 H), 3.00 (t, J = 7.5 Hz, 2 H), 2.82 (t, J = 7.5 Hz, 2 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.13 (app quint, J = 7.5 Hz, 2 H), 0.88 (s, 9 H), 0.06 (s, 6 H); 13C NMR (125 MHz, CDCl3) δ 165.7, 144.7, 135.6, 134.4, 129.8, 90.8, 79.6, 73.1, 72.8, 61.9, 33.9, 29.4, 26.1, 24.1, 23.3, 18.5, -5.0; HRMS (ESI-FTICR) m/z [M + H]+ calcd for C20H29NO2Si 344.2040, found: 344.2055.

*4-(Pyridin-2-yl)-3,6,7,8-tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine (**51**).* A 21-cm, threaded Pyrex tube (47 mm O.D., 41 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with a solution of oximino ether **47** (0.200 g, 0.740 mmol) in 74 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (–196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 160 °C (bath temperature) for 4 h and then allowed to cool to rt. DBU (0.111 mL, 0.112 g, 0.740 mmol, 1.0 equiv) was added, and the reaction mixture was stirred at rt for 24 h. The resulting clear amber solution was washed with 50 mL of water and the aqueous phase was extracted with two 20-mL portions of ether. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over MgSO4, filtered, and concentrated by rotary evaporation (30 °C, 20 mmHg) to give 0.250 g of a brown oil. Column chromatography on 25 g of silica gel (elution with 50% EtOAc-hexanes) afforded 0.110 g (62%) of **51** as a white solid: mp 136-137 °C; IR (KBr) 3079, 3021, 2933, 2853, 1577, 1470, 1435, 1400, and 1060 cm-1; 1H NMR (500 MHz, CDCl3) δ 8.64 (dd, J = 5.0, 1.0 Hz, 1 H), 8.44 (d, J = 8.0 Hz, 1 H), 7.78 (td, J = 7.5, 2.0 Hz, 1 H), 7.23 (ddd, J = 7.5, 4.5, 1.0 Hz, 1 H), 5.57 (s, 2 H), 5.05 (s, 2H), 3.09 (t, J = 7.5 Hz, 2 H), 2.90 (t, J = 7.5 Hz, 2 H), 2.22 (app quint, J = 7.5 Hz, 2 H); 13C NMR (125 MHz, CDCl3) δ 165.3, 157.8, 149.5, 148.9, 146.9, 137.1, 132.7, 131.0, 123.5, 122.1, 75.8, 72.0, 34.4, 29.7, 24.0; HRMS (ESI-FTICR) m/z [M + H]+ calcd for C15H14N2O 239.1179, found 239.1177.

Experimental Procedure for [2 + 2 + 2] Cycloaddition of Alkynyl Sulfone 52.

*3,6,7,8-Tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine (**9**).* A 250-mL round-bottomed flask equipped with a condenser fitted with an argon inlet needle was charged with oximino ether **52** (0.300 g, 0.90 mmol, 1.0 equiv) and 90 mL of toluene. The solution was heated at 80 °C (bath temperature) for 8 h and then cooled to rt and concentrated. The resulting brown oil was dissolved in 3 mL of CH2Cl2 and 10 mL of ether was added. The beige solids that precipitated and were separated by gravity filtration with the aid of 5 mL of ether. The filtrate was transferred to a 25-mL round-bottomed flask and concentrated. The flask was equipped with a rubber septum fitted with an argon inlet needle and 9 mL of MeOH and NaH2PO4·H2O (0.482 g, 3.60 mmol, 4.0 equiv) were added. The solution was cooled at 0 °C, Na(Hg) (5% Hg by wt., 1.35 g) was added, and the resulting mixture was stirred at rt for 2 h and then diluted with 10 mL of water and 10 mL of EtOAc. The aqueous phase was separated and extracted with three 10-mL portions of EtOAc, and the combined organic phases were washed with 10 mL of satd NaCl solution, dried over MgSO4, filtered, and concentrated to give 0.100 g of a yellow solid. Column chromatography on 25 g of silica gel (elution with EtOAc) afforded 0.062 g (43%) of **9** as a yellow solid with spectral data consistent with that previously reported:[10] 1H NMR (CDCl3, 500 MHz) δ 8.28 (s, 1 H), 5.14 (s, 2 H), 5.03 (s, 2 H), 3.05 (t, J = 7.5 Hz, 2 H), 2.86 (t, J = 7.5 Hz, 2 H), 2.18 (app quint, J = 7.5 Hz, 2H); 13C NMR (CDCl3, 125 MHz) δ 164.7, 145.3, 140.0, 133.2, 130.5, 72.2, 72.1, 33.8, 29.3, 23.4.

Experimental Procedures for [2 + 2 + 2] Cycloadditions of Terminal Alkynes 56 and 57.

*N,N-Dimethyl-4,5a,6,7-tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridin-5(3H)-amine (**58**).* A 21-cm, threaded Pyrex tube (47 mm O.D., 41 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with a solution of hydrazone **56** (0.300 g, 1.45 mmol) in 148 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (–196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 160 °C (bath temperature) for 16 h and then allowed to cool to rt. The resulting clear yellow solution was concentrated by rotary evaporation (30 °C, 20 mmHg) to afford 0.350 g of a brown oil. Column chromatography on 25 g of silica gel (elution with 30-70% EtOAc-hexanes) afforded 0.221 g (74%) of **58** as a yellow solid: mp 75-77 °C; IR (NaCl) 2939, 2845, 1664, 1453, and 1054 cm-1; 1H NMR (500 MHz, CDCl3) δ 5.46 (s, 1 H), 4.74-4.76 (m, 1 H), 4.60-4.69 (m, 3 H), 3.67 (t, J = 8.0 Hz, 1 H), 3.47 (d, J = 15.5 Hz, 1 H), 3.40 (d, J = 15.5 Hz, 1 H), 2.49 (s, 6 H), 2.35-2.47 (m, 2 H), 2.26-2.29 (m, 1 H), 1.76 (ddd, J = 19.5, 9.5, 12.5 Hz, 1 H); 13C NMR (125 MHz, CDCl3) δ 136.2, 135.9, 129.2, 123.4, 76.4, 74.5, 65.9, 40.7, 40.2, 31.9, 31.8; HRMS (DART-FTICR) m/z [M + H]+ calcd for C12H18N2O 207.1492, found 207.1493. In other runs the yield for this reaction ranged from 74-82%.

*5-Methoxy-3,4,5,5a,6,7-hexahydro-1H-cyclopenta[b]furo[3,4-d]pyridine (**59**).* A 21-cm, threaded Pyrex tube (47 mm O.D.; 41 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with a solution of oximino ether **57** (0.193 g, 0.996 mmol) in 100 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (–196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 160 °C (bath temperature) for 18 h and then allowed to cool to rt. The resulting clear yellow solution was concentrated by rotary evaporation (30 °C, 10 mmHg) to afford ca. 0.2 g of a brown oil. Column chromatography on 30 g of silica gel (elution with 10-30% EtOAc-hexanes) afforded 0.185 g (93%) of **59** (70:30 mixture of stereoisomers by 1H NMR analysis) as a yellow oil: For the major stereoisomer: 1H NMR (500 MHz, CDCl3, -30 °C) δ 5.50 (s, 1 H), 4.58-4.74 (m, 4 H), 3.90 (d, J = 15.5 Hz, 1 H), 3.73 (t, J = 7.0 Hz, 1 H), 3.63 (s, 3 H), 3.35 (d, J = 15.5 Hz, 1 H), 2.33-2.51 (m, 3 H), 1.77-1.86 (m, 1 H). For the minor stereoisomer: 1H NMR (500 MHz, CDCl3, -30 °C) δ 5.74 (s, 1 H), 4.84-4.87 (m, 1 H), 4.58-4.74 (m, 3H), 3.94 (t, J = 8.0 Hz, 1 H), 3.83 (d, J = 10.5 Hz, 1 H), 3.54 (s, 3 H), 2.33-2.51 (m, 2 H), 2.15-2.20 (m, 1 H), 1.88-1.96 (m, 1 H). For the mixture: IR (NaCl) 2936, 2850, 1449, 1051, and 1020 cm-1; 13C NMR (125 MHz, CDCl3) δ 134.7, 134.5, 129.4, 124.2, 75.5, 75.7, 71.9, 61.3, 52.6, 31.5, 30.6; HRMS (ESI-FTICR) m/z [M + H]+ calcd for C11H15NO2 194.1176, found 194.1184.

Experimental Procedure for the Reduction of Cycloadduct 59.

*3,4,5,5a,6,7-Hexahydro-1H-cyclopenta[b]furo[3,4-d]pyridine (**60**).* A 25-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with **59** (0.080 g, 0.41 mmol, 1.0 equiv), 3 mL of AcOH, and 1 mL of water. Zinc dust (0.40 g, 6.0 mmol, 15 equiv) was added in one portion and the resulting suspension was stirred at rt for 48 h. The mixture was then filtered through a pad of Celite (washing with ca. 10 mL of AcOH) and the filtrate was concentrated (5 mmHg, 40 °C) to give a beige solid. This material was dissolved in 100 mL of water and the resulting solution was adjusted to ca. pH 9 by the addition of 10% aq NaOH and then extracted with three 50-mL portions of CH2Cl2. The combined organic layers were dried over MgSO4, filtered, and concentrated to give ca. 0.1 g of beige solid. Column chromatography on 25 g of silica gel (elution with 5-10% MeOH-CH2Cl2) afforded 0.051 g (76%) of **60** as an off-white solid: mp 85-90 °C; IR (film) 3277, 2963, 2878, 2847, 1447, 1313, 1043, and 1034 cm-1; 1H NMR (500 MHz, CDCl3) δ 5.43 (s, 1 H), 4.60-4.78 (m, 4 H), 3.77-3.80 (m, 1 H), 3.66 (d, J = 18.0 Hz, 1 H), 3.53 (d, J = 18.0 Hz, 1 H), 3.22 (brs, 1 H), 2.35-2.44 (m, 3 H), 1.45-1.54 (m, 1 H); 13C NMR (125 MHz, CDCl3) δ 135.9, 135.6, 129.4, 122.5, 76.5, 74.6, 62.8, 44.1, 31.8, 31.6; HRMS (DART-FTICR) m/z [M + H]+ calcd for C10H13NO 164.1070, found 164.1060.

Experimental Procedures for the Preparation of [2 + 2 + 2] Cycloaddition Substrates.

*Methyl 4-(oct-7-en-2-yn-1-yloxy)but-2-ynoate (**64**).* A 250-mL, three-necked, round-bottomed flask equipped with two rubber septa, an argon inlet adapter, and a thermocouple probe was charged with alkyne **S1**[6] (4.00 g, 24.7 mmol, 1.0 equiv) and 70 mL of ether. The solution was cooled at -78 °C and butyllithium solution (2.21 M in hexanes, 12.3 mL, 27.1 mmol, 1.1 equiv) was added dropwise via syringe over 5 min. The resulting brown solution was stirred at -78 °C for 30 min. A solution of methyl chloroformate (7.59 mL, 9.32 g, 98.7 mmol, 4.0 equiv) in 70 mL of ether was then added via cannula over 5 min and the resulting orange solution was stirred at -35 °C for 30 min and then allowed to warm to rt over 15 min. The reaction mixture was quenched by addition of 50 mL of saturated aq NH_4Cl solution and the aqueous phase was separated and extracted with two 100-mL portions of ether. The combined organic layers were washed with 50 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give ca. 6 g of an orange oil. Column chromatography on 85 g of silica gel (elution with 10% EtOAc-hexanes) afforded 4.23 g (78%) of **64** as an orange oil: IR (NaCl) 3078, 2943, 2859, 2238, 1721, 1641, 1436, 1258, 1087 and 1059 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H), 5.03 (dtt, *J* = 17.0, 2.0, 1.5 Hz, 1 H), 4.98 (ddt, *J* = 10.0, 1.5, 1.5 Hz, 1 H), 4.37 (s, 2 H), 4.25 (t, *J* = 2.0 Hz, 2 H), 3.72 (s, 3 H), 2.24 (tt, *J* = 7.0, 2.0 Hz, 2 H), 2.14 (dddt, *J* = 14.5, 7.0, 1.0, 1.5 Hz, 2 H), 1.61 (app quint, *J* = 7.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 138.0, 115.5, 88.4, 83.4, 78.2, 74.9, 57.9, 56.0, 53.1, 33.0, 27.9, 18.4; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{13}H_{16}O_3$ 221.1172, found 221.1174. In other runs the yield for this reaction ranged from 76-78%.

General Procedure for the Preparation of Conjugated Diynes. *Triisopropyl(5-(oct-7-en-2-yn-1-yloxy)penta-1,3-diyn-1-yl)silane (**65**).* A 250-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with alkyne **S1**[6] (1.13 g, 6.98 mmol, 1.0 equiv), 80 mL of 30% aq *n*-$BuNH_2$ solution, 40 mL of THF, $NH_2OH{\cdot}HCl$ (0.970 g, 13.96 mmol, 2.0 equiv), and CuCl (0.034 g, 0.349 mmol, 5 mol%). A solution of 1-bromo-2-(triisopropylsilyl)acetylene **S2**[34] (2.19 g, 8.38 mmol, 1.2 equiv) in 40 mL of THF was next added dropwise via cannula over 10 min. The reaction mixture was stirred in the dark at rt for 15 h and then 20 mL of 20% aq NaCN solution was added. The resulting clear yellow solution was extracted with three 100-mL portions of ether and the combined organic layers were washed with 100 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 2.0 g of an orange oil. Column chromatography on 80 g of acetone-deactivated silica gel (elution with hexanes) afforded 1.87 g (78%) of diyne **65** as a pale yellow oil: IR (NaCl) 3078, 2944, 2866, 2223, 2106, 1642, 1463, and 1075 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H), 5.04 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1 H), 4.98 (ddt, *J* = 10.0, 1.5, 1.5 Hz, 1 H), 4.31 (s, 2 H), 4.24 (t, *J* = 2.5 Hz, 2 H), 2.24 (tt, *J* = 7.0, 2.0 Hz, 2 H), 2.15 (dddt, *J* = 7.0, 1.0, 1.0, 7.0 Hz, 2 H), 1.61 (app quint, *J* = 7.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 116.0, 89.6, 88.4, 85.2, 75.8, 73.1, 72.5, 58.2, 57.4, 33.5, 28.4, 19.2, 18.8, 11.9; HRMS (ESI-FTICR) *m/z* $[M + Na]^+$ calcd for $C_{22}H_{34}OSi$ 365.2271, found 365.2260. In other runs the yield for this reaction ranged from 78-86%.

General Procedure for the Ozonolysis of Alkenes. *7-(Prop-2-yn-1-yloxy)hept-5-ynal (**66**).* A 100-mL recovery flask equipped with a rubber septum fitted with an argon inlet needle was charged with alkyne **S1**[6] (2.00 g, 12.3 mmol, 1.0 equiv), 23 mL of MeOH, 8 mL of CH_2Cl_2. A saturated solution of Sudan III in MeOH was added dropwise until the mixture was visibly pink. The resulting solution was cooled at -78 °C and ozone was bubbled through the solution via a glass pipet until the solution turned colorless (10 min). A stream of argon was then bubbled through the solution for 10 min and then dimethyl sulfide (2.72 mL, 2.30 g, 37.0 mmol, 3.0 equiv) was added via syringe. The reaction mixture was allowed to slowly warm to room temperature, and after ca. 15 h was diluted with 50 mL of water. The aqueous phase was separated and extracted with three 50-mL portions of ether, and the combined organic layers were washed with 50 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated (0 °C, 20 mmHg) to give 3.42 g of a pale orange oil. Column chromatography on 60 g of silica gel (elution with 20-30% EtOAc-hexanes) afforded 1.76 g (87%) of **66** as a pale yellow oil with spectral data consistent with that previously reported:[37] ^1H NMR (500 mHz, $CDCl_3$) δ 9.76 (t, *J* = 1.5 Hz, 1 H), 4.18 – 4.19 (m, 4 H), 2.55 (td, *J* = 7.5, 1.5 Hz, 2 H), 2.43 (t, *J* = 2.5 Hz, 1 H), 2.27 (tt, *J* = 7.0, 2.0 Hz, 2 H), 1.81 (app quint, *J* = 7.0 Hz); ^{13}C NMR (125 mHz, $CDCl_3$) δ 202.3, 86.9, 79.7, 76.9, 75.5, 57.7, 57.0, 43.3, 21.6, 18.8.

*Methyl 4-((7-oxohept-2-yn-1-yl)oxy)but-2-ynoate (**67**).* Reaction of alkene **64** (0.670 g, 3.04 mmol, 1.0 equiv), 10 drops of saturated Sudan III solution in MeOH, and dimethyl sulfide (0.67 mL, 0.568 g, 9.13 mmol, 3.0 equiv) in 6 mL of MeOH and 2 mL of CH_2Cl_2 according to the General Procedure provided 0.820 g of a pale orange oil. Column chromatography on 50 g of silica gel (elution with 10-40% EtOAc-hexanes) afforded 0.573 g (85%) of **67** as a pale yellow oil: IR (NaCl) 2956, 2904, 2238, 1721, 1436, 1260, 1087, and 1059 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.5 Hz, 1 H), 4.33 (s, 2 H), 4.20 (t, *J* = 2.0 Hz, 2H), 3.75 (s, 3 H), 2.55 (td, *J* = 7.0, 1.5 Hz, 2 H), 2.28 (tt, *J* = 7.0, 2.5 Hz, 2 H), 1.81 (app quint, *J* = 7.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 153.7, 87.2, 83.2, 78.2, 75.9, 57.8, 56.2, 53.1, 42.9, 21.1, 18.3;

HRMS (ESI-FTICR) *m/z* [M + Na]$^+$ calcd for $C_{12}H_{14}O_4$ 245.0784, found 245.0784.

*7-((5-(Triisopropylsilyl)penta-2,4-diyn-1-yl)oxy)hept-5-ynal (**68**).* Reaction of alkene **65** (1.80 g, 5.25 mmol, 1.0 equiv), saturated Sudan III solution in MeOH, and dimethyl sulfide (1.15 mL, 0.973 g, 15.8 mmol, 3.0 equiv) in 9 mL of MeOH and 3 mL of CH_2Cl_2 according to the General Procedure provided 2.50 g of a pale orange oil. Column chromatography on 60 g of silica gel (elution with 5-15% EtOAc-hexanes) afforded 1.47 g (81%) of **68** as a pale yellow oil: IR (NaCl) 2944, 2866, 2225, 2105, 1726, 1463, 1347, and 1074 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (t, *J* = 7.0 Hz, 1 H), 4.30 (s, 2 H), 4.23 (t, *J* = 2.5 Hz, 2 H), 2.60 (td, *J* = 7.5, 1.0 Hz, 2 H), 2.31 (tt, *J* = 7.0, 2.5 Hz, 2 H), 1.85 (app quint, *J* = 7.0 Hz, 2 H), 1.08 (s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 89.5, 87.3, 85.3, 76.8, 72.9, 72.6, 58.1, 57.6, 43.4, 21.6, 19.2, 18.9, 11.9; HRMS (ESI-FTICR) *m/z* [M + Na]$^+$ calcd for $C_{21}H_{32}O_2Si$ 367.2064, found 367.2058. In other runs the yield for this reaction ranged from 76-81%.

General Procedure for the Formation of *N,N*-Dimethylhydrazones from Aldehydes. *(E)-1,1-Dimethyl-2-(7-(prop-2-yn-1-yloxy)hept-5-yn-1-ylidene)hydrazine (**56**).* A 25-mL recovery flask equipped with a rubber septum fitted with an argon inlet needle was charged with aldehyde **66** (0.300 g, 1.83 mmol, 1.0 equiv) and 7 mL of MeOH. The solution was cooled at 0 °C while *N,N*-dimethylhydrazine (0.200 mL, 0.159 g, 2.74 mmol, 1.5 equiv) was added dropwise via syringe over 2 min. The resulting yellow solution was stirred for 5 min at 0 °C and then concentrated to afford 0.400 g of an orange oil. Column chromatography on 12 g of silica gel (elution with 30-40% EtOAc-hexanes) afforded 0.370 g (98%) of **56** as a pale yellow oil: IR (NaCl) 3288, 2951, 2855, 2282, 2224, 2114, 1607, 1445, and 1078 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (t, *J* = 5.5 Hz, 1 H), 4.21 (d, *J* = 2.5 Hz, 2 H), 4.21 (t, *J* = 2.5 Hz, 2 H), 2.70 (s, 6 H), 2.42 (t, *J* = 2.5 Hz, 1 H), 2.23 (td, *J* = 7.5, 5.5 Hz, 2 H), 2.25 (tt, *J* = 7.0, 2.0 Hz, 2 H), 1.69 (app quint, *J* = 7.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 87.9, 79.8, 76.1, 75.4, 57.8, 56.9, 44.0, 32.9, 27.4, 19.0; HRMS (DART-FTICR) *m/z* [M+H]$^+$ calcd for $C_{12}H_{18}N_2O$ 207.1492, found 207.1489. In other runs the yield for this reaction ranged from 97-98%.

*(E)-Methyl 4-((7-(2,2-dimethylhydrazono)hept-2-yn-1-yl)oxy)but-2-ynoate (**30**).* Reaction of aldehyde **67** (0.400 g, 1.80 mmol, 1.0 equiv) and *N,N*-dimethylhydrazine (0.137 mL, 0.108 g, 1.80 mmol, 1.0 equiv) in 7 mL of THF according to the General Procedure gave 0.549 g of an orange oil. Column chromatograpy on 18 g of silica gel (elution with 50% EtOAc-hexanes) afforded 0.295 g (62%) of **30** as a pale yellow oil: IR (NaCl) 2953, 2856, 2238, 1720, 1609, 1436, 1258, 1087, and 1058 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (t, *J* = 5.5 Hz, 1 H), 4.38 (s, 2 H), 4.25 (t, *J* = 2.0 Hz, 2 H), 3.79 (s, 3 H), 2.73 (s, 6 H), 2.33 (td, *J* = 7.5, 5.0 Hz, 2 H), 2.29 (tt, *J* = 7.0, 2.0 Hz, 2 H), 1.72 (app quint, *J* = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 138.2, 88.7, 83.9, 78.6, 75.6, 58.4, 56.5, 53.5, 44.0, 32.9, 27.3, 19.0; HRMS (DART-FTICR) *m/z* [M + H]$^+$ calcd for $C_{14}H_{20}O_3N_2$ 265.1547, found 265.1551.

*(E)-1,1-Dimethyl-2-(7-((5-(triisopropylsilyl)penta-2,4-diyn-1-yl)oxy)hept-5-yn-1-ylidene)hydrazine (**33**).* Reaction of aldehyde **68** (1.43 g, 4.16 mmol, 1.0 equiv) and *N,N*-dimethylhydrazine (0.346 mL, 0.274 g, 4.57 mmol, 1.1 equiv) in 18 mL of MeOH according to the General Procedure gave 1.70 g of an orange oil. Column chromatography on 60 g of silica gel (elution with 30% EtOAc-hexanes) afforded 1.60 g (85%) of **33** as a pale yellow oil: IR (NaCl) 2945, 2866, 2105, 1608, 1464, 1345, and 1074 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (bs, 1 H), 4.31 (s, 2 H), 4.24 (t, *J* = 2.5 Hz, 2 H), 2.73 (s, 6 H), 2.33 (td, *J* = 7.5, 5.5 Hz, 2 H), 2.28 (tt, *J* = 7.0, 2.0 Hz, 2 H), 1.72 (app quint, *J* = 7.0 Hz, 2 H), 1.08 (s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 89.6, 88.3, 85.2, 76.0, 73.1, 72.5, 58.2, 57.5, 44.0, 32.9, 27.3, 19.2, 19.0, 11.9; HRMS (ESI-FTICR) *m/z* [M + H]$^+$ calcd for $C_{23}H_{38}N_2OSi$ 387.2826; found 387.2829.

*(E)-2-(2-Butylhex-5-yn-1-ylidene)-1,1-dimethylhydrazine (**69**).* A 250-mL, three-necked, round-bottomed flask equipped with two rubber septa, an argon inlet adapter, and a thermocouple probe was charged with 40 mL of THF and diisopropylamine (1.98 mL, 1.42 g, 14.0 mmol, 2.0 equiv). The solution was cooled at 0 °C and butyllithium solution (2.51 M in hexanes, 5.58 mL, 14.0 mmol, 2.0 equiv) was added dropwise via syringe over 15 min. The resulting solution was stirred at 0 °C for 30 min, cooled to -78 °C, and a solution of hydrazone **S3**[29] (1.00 g, 7.03 mmol, 1.0 equiv) in 10 mL of THF was added dropwise via cannula over 5 min (5 mL THF rinse). The resulting solution was stirred at 0 °C for 3 h. The reaction mixture was cooled at -50 °C and HMPA (2.45 mL, 2.25 g, 14.1 mmol, 2.0 equiv) was added dropwise via syringe and the resulting solution was stirred at -50 °C for 10 min. A solution of triflate S4[4] (3.13 g, 15.5 mmol, 2.2 equiv) in 10 mL of THF was cooled to -78 °C and added down the cooled wall of the reaction flask via cannula over 5 min (5 mL THF rinse). The resulting solution was stirred at -50 °C for 10 min. The reaction mixture was quenched by addition of 10 mL of satd aq NH_4Cl and 20 mL of water and the aqueous phase was separated and extracted with three 50-mL portions of ether. The combined organic layers were washed with 50 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give ca. 3 g of a yellow oil. Column chromatography on 80 g of silica gel (elution with 0-10% EtOAc-hexanes) afforded 0.766 g (56%) of **69** as a colorless oil: IR (NaCl) 3312, 2928, 2783, 2361, 2118, 1606, 1468, 1139, and 1016 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (d, *J* = 7.0 Hz, 1 H), 2.70 (s, 6 H), 2.24-2.31 (m, 1 H), 2.11-2.23 (m, 2 H), 1.92 (t, *J* = 3.0 Hz, 1 H), 1.57-1.72 (m, 2 H), 1.33-1.43 (m, 2 H), 1.24-1.33 (m, 4 H), 0.86 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 84.9, 68.4, 43.7, 42.2, 33.6, 32.8, 29.4, 23.0, 16.6, 14.2; HRMS (DART-FTICR) *m/z* [M + H]$^+$ calcd for $C_{12}H_{22}N_2$ 195.1856, found 195.1845. In other runs the yield for this reaction ranged from 52-56%.

*(E)-6-((2,2-Dimethylhydrazono)methyl)dec-2-yn-1-ol (**70**).* A 100-mL, two-necked, round-bottomed flask equipped with two rubber septa and an argon inlet needle was charged with 30 mL of THF and diisopropylamine (0.55 mL, 0.40 g, 3.9 mmol, 1.0 equiv). The solution was cooled at 0 °C and butyllithium solution (2.52 M in hexanes, 1.56 mL, 3.9 mmol, 1.0 equiv) was added dropwise via syringe over 5 min. The resulting solution was stirred at 0 °C for 30 min, cooled to -78 °C, and a solution of hydrazone **69** (0.766 g, 3.94 mmol, 1.0 equiv) in 5 mL of THF was added dropwise via cannula over 5 min (5 mL THF rinse). The resulting solution was stirred at 0 °C for 1 h. Paraformaldehyde (0.236 g, 7.88 mmol, 2.0 equiv) was added in one portion and the resulting suspension was stirred at rt for 5 h. The reaction mixture was quenched by addition of 10 mL of satd aq NH_4Cl solution and 10 mL of water, and the aqueous phase was separated and extracted with three 50-mL portions of ether. The combined organic layers were washed with 20

mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give ca. 1 g of a yellow oil. Column chromatography on 40 g of silica gel (elution with 30-50% EtOAc-hexanes) afforded 0.730 g (83%) of **70** as a colorless oil: IR (NaCl) 3322, 2929, 2857, 2362, 2339, 2223, 1606, 1468, 1138, and 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.49 (d, J = 7.5 Hz, 1 H), 4.10-4.18 (m, 2 H), 3.35 (bs, 1 H), 2.69 (s, 6 H), 2.26-2.33 (m, 1 H), 2.22 (tt, J = 7.0, 2.0 Hz, 2 H), 1.55-1.71 (m, 2 H), 1.32-1.42 (m, 2 H), 1.18-1.32 (m, 4 H), 0.86 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 86.8, 80.2, 51.2, 44.1, 42.9, 33.6, 32.9, 29.4, 23.0, 17.2, 14.2; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{13}H_{24}N_2O$ 225.1961, found 225.1963.

*(E)-2-(2-Butyl-7-(prop-2-yn-1-yloxy)hept-5-yn-1-ylidene)-1,1-dimethylhydrazine (**71**).* A 100-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with alcohol **70** (0.676 g, 3.01 mmol, 1.0 equiv) and 30 mL of THF. The solution was cooled at -78 °C and butyllithium solution (2.52 M in hexanes, 1.20 mL, 3.01 mmol, 1.0 equiv) was added dropwise via syringe over 5 min. The resulting solution was stirred at -78 °C for 15 min. Propargyl bromide (8.0 M in toluene, 0.56 mL, 4.52 mmol, 1.5 equiv) and HMPA (0.58 mL, 0.59 g, 3.31 mmol, 1.1 equiv) were added via syringe in that order, and the resulting mixture was allowed to warm to rt and stirred for 15 h. Satd aq NH_4Cl solution (10 mL) was added followed by 10 mL of water. The aqueous phase was separated and extracted with three 25-mL portions of ether, and the combined organic layers were washed with 25 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give ca. 1 g of a yellow oil. Column chromatography on 60 g of silica gel (elution with 50% CH_2Cl_2-hexanes, and then 0-30% EtOAc-CH_2Cl_2) afforded 0.522 g (70%) of **71** as a yellow oil: IR (NaCl) 3312, 2955, 2929, 2856, 2361, 2339, 2224, 1467, 1457, 1449, 1137, 1079, and 1009 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.38 (d, J = 7.0 Hz, 1 H), 4.23 (d, J = 2.0 Hz, 2 H), 4.22 (t, J = 2.0 Hz, 2 H), 2.71 (s, 6 H), 2.42 (t, J = 2.5 Hz, 1 H), 2.15-2.30 (m, 3 H), 1.56-1.71 (m, 2 H), 1.33-1.43 (m, 2 H), 1.24-1.32 (m, 4 H), 0.87 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 88.0, 79.4, 75.1, 74.9, 57.4, 56.4, 43.6, 42.2, 33.5, 32.8, 29.4, 23.0, 16.9, 14.2; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{16}H_{26}N_2O$ 263.2118, found 263.2115. In other runs the yield for this reaction ranged from 67-70%.

*(E)-2-(2-Butyl-7-((5-(triisopropylsilyl)penta-2,4-diyn-1-yl)oxy)hept-5-yn-1-ylidene)-1,1-dimethylhydrazine (**34**).* Reaction of terminal alkyne **71** (0.519 g, 1.98 mmol, 1.0 equiv) with NH_2OH·HCl (0.275 g, 3.96 mmol, 2.0 equiv), CuCl (0.010 g, 0.099 mmol, 5 mol%), and 1-bromo-2-(triisopropylsilyl)acetylene **S2**[34] (0.775 g, 2.97 mmol, 1.5 equiv) in 40 mL of 30% aq *n*-$BuNH_2$ solution and 40 mL THF according to the General Procedure provided ca. 2 g of a yellow oil. Column chromatography on 60 g of silica gel (elution with 0-30% EtOAc-hexanes) afforded 0.710 g (81%) of **34** as a pale yellow oil: IR (NaCl) 2944, 2866, 2361, 2340, 2106, 1465, 1345, and 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.39 (d, J = 7.0 Hz, 1 H), 4.31 (s, 2 H), 4.23 (t, J = 2.0 Hz, 2 H), 2.72 (s, 6 H), 2.17-2.30 (m, 3 H), 1.57-1.72 (m, 2 H), 1.34-1.46 (m, 2 H), 1.19-1.33 (m, 4 H), 1.08 (s, 21 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 89.1, 88.3, 84.7, 75.1, 72.6, 72.0, 57.7, 56.9, 43.6, 42.2, 33.6, 32.8, 29.4, 23.0, 18.7, 16.9, 14.2, 11.4; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{27}H_{46}N_2OSi$ 443.3452, found 443.3458.

*Methyl (E)-4-((6-((2,2-dimethylhydrazono)methyl)dec-2-yn-1-yl)oxy)but-2-ynoate (**31**).* A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 2 mL of THF and diisopropylamine (0.03 mL, 0.02 g, 0.2 mmol, 2.0 equiv). The solution was cooled at 0 °C and butyllithium solution (2.52 M in hexanes, 0.08 mL, 0.2 mmol, 2.0 equiv) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 30 min, cooled to -78 °C, and a solution of terminal alkyne **71** (0.027 g, 0.10 mmol, 1.0 equiv) in 1 mL of THF was added dropwise via cannula over 1 min (1 mL THF rinse). The resulting mixture was stirred at -78 °C for 3 h. A solution of methyl chloroformate (0.04 mL, 0.05 g, 0.5 mmol, 5.0 equiv) in 1 mL of THF was added dropwise via cannula over 1 min (1 mL THF rinse) and the resulting solution was stirred at -78 °C for 10 min. Satd aq NH_4Cl solution (5 mL) was added, followed by 5 mL of water. The mixture was allowed to warm to rt and the aqueous phase was separated and extracted with three 10-mL portions of ether. The combined organic layers were washed with 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.05 g of an orange oil. Column chromatography on 25 g of silica gel (elution with 0-30% EtOAc-hexanes) afforded 0.020 g (60%) of **31** as a yellow oil: IR (NaCl) 2926, 2855, 2236, 1717, 1436, 1249, 1085, and 1057cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.39 (d, J = 7.0 Hz, 1 H), 4.37 (s, 2 H), 4.24 (t, J = 2.0 Hz, 2 H), 3.78 (s, 3 H), 2.72 (s, 6 H), 2.16-2.30 (m, 3 H), 1.57-1.72 (s, 2 H), 1.34-1.44 (m, 2 H), 1.24-1.33 (m, 4 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 142.8, 89.2, 83.9, 78.6, 75.2, 58.4, 56.5, 53.5, 44.2, 42.7, 34.1, 33.3, 29.9, 23.5, 17.4, 14.7; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{18}H_{28}N_2O_3$ 321.2173, found 321.2166.

*(E)-1,1-Dimethyl-2-(2-methyl-2-phenylhex-5-yn-1-ylidene)hydrazine (**72**).* A 100-mL, three-necked, round-bottomed flask equipped with two rubber septa, an argon inlet adapter, and a thermocouple probe was charged with 30 mL of THF and diisopropylamine (0.805 mL, 0.58 g, 5.73 mmol, 1.01 equiv). The solution was cooled at 0 °C and butyllithium solution (2.51 M in hexanes, 2.28 mL, 5.73 mmol, 1.01 equiv) was added dropwise via syringe over 2 min. The resulting solution was stirred at 0 °C for 30 min, cooled to -78 °C, and a solution of hydrazone **S5**[31] (1.00 g, 5.67 mmol, 1.0 equiv) in 5 mL of THF was added dropwise via cannula over 5 min (5 mL THF rinse). The resulting yellow solution was stirred at 0 °C for 2 h. The reaction mixture was cooled at -50 °C and HMPA (2.00 mL, 2.03 g, 11.3 mmol, 2.0 equiv) was added dropwise via syringe and the resulting orange solution was stirred at -50 °C for 10 min. A solution of triflate **S4**[30] (1.26 g, 6.24 mmol, 1.1 equiv) in 10 mL of THF was cooled to -78 °C and added down the cooled wall of the reaction flask via cannula over 5 min (5 mL THF rinse). The resulting yellow solution was stirred at -50 °C for 10 min. The reaction mixture was quenched by addition of 10 mL of satd aq NH_4Cl and 20 mL of water and the aqueous phase was separated and extracted with three 50-mL portions of ether. The combined organic layers were washed with 50 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 1.5 g of an orange oil. Column chromatography on 80 g of silica gel (elution with 0-10% EtOAc-hexanes) afforded 0.586 g (46%) of **72** as a colorless oil: IR (NaCl) 3296, 3058, 3025, 2957, 2853, 2822, 2784, 2117, 1601, 1493, 1469, 1445, 1263, and 1016 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.35 (m, 4 H), 7.21-7.24 (m, 1 H), 6.66 (s, 1 H), 2.78 (s, 6 H), 2.21-2.27 (m, 1 H), 2.05-2.17 (m, 3 H), 1.92 (t, J = 5.0 Hz, 1 H), 1.46 (s, 3 H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 146.5, 143.6, 129.1, 127.4, 127.0, 85.9, 68.7, 45.5, 44.1, 39.8, 24.8, 14.9; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}N_2$ 229.1699, found 229.1702. In other runs the yield for this reaction ranged from 44-46%.

*(E)-1,1-Dimethyl-2-(2-methyl-2-phenyl-7-(prop-2-yn-1-yloxy)hept-5-yn-1-ylidene)hydrazine (**73**).* A 100-mL, three-necked, round-bottomed flask equipped with two rubber septa, an argon inlet needle and a glass stopper was charged with 30 mL of THF and diisopropylamine (0.86 mL, 0.62 g, 6.1 mmol, 1.0 equiv). The solution was cooled at 0 °C and butyllithium solution (2.52 M in hexanes, 2.4 mL, 6.1 mmol, 1.0 equiv) was added dropwise via syringe over 2 min. The resulting solution was stirred at 0 °C for 30 min, cooled to -78 °C, and a solution of hydrazone **72** (1.4 g, 6.1 mmol, 1.0 equiv) in 5 mL of THF was added dropwise via cannula over 5 min (5 mL THF rinse). The resulting solution was stirred at 0 °C for 1 h. Paraformaldehyde (0.368 g, 12.3 mmol, 2.0 equiv) was added in one portion and the resulting suspension was stirred at rt for 5 h and then cooled to 0 °C. Propargyl bromide (80% in toluene, 1.15 mL, 9.20 mmol, 1.5 equiv) and HMPA (2.13 mL, 2.20 g, 12.3 mmol, 2.0 equiv) were added via syringe in that order and the resulting mixture was allowed to warm to rt and stirred for 15 h. Satd aq NH_4Cl solution (10 mL) was added followed by 10 mL of water. The aqueous phase was separated and extracted with three 50-mL portions of ether. The combined organic layers were washed with 20 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give ca. 2 g of an orange oil. Column chromatography on 120 g of silica gel (elution with 0-10% EtOAc-hexanes) afforded 0.721 g (40%) of **73** as a pale yellow oil: IR (NaCl) 3288, 2853, 2784, 2361, 2224, 2116, 1601, 1445, 1077, and 1016 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.34 (m, 4 H), 7.19-7.23 (m, 1 H), 6.63 (s, 1 H), 4.22 (d, *J* = 2.5 Hz, 2 H), 4.20 (t, *J* = 2.0 Hz, 2 H), 2.76 (s, 6 H), 2.42 (t, *J* = 2.5 Hz, 1 H), 2.05-2.24 (m, 4 H), 1.44 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 143.6, 129.1, 127.4, 127.0, 88.9, 79.9, 75.4, 75.4, 57.9, 56.9, 45.4, 44.0, 39.7, 24.7, 15.2; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{19}H_{24}N_2O$ 297.1961, found 297.1973.

*Methyl (E)-4-((7-(2,2-dimethylhydrazono)-6-methyl-6-phenylhept-2-yn-1-yl)oxy)but-2-ynoate (**32**).* A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 3 mL of THF and diisopropylamine (0.19 mL, 0.14 g, 1.4 mmol, 2.0 equiv). The solution was cooled at 0 °C and butyllithium solution (2.52 M in hexanes, 0.53 mL, 1.4 mmol, 2.0 equiv) was added dropwise via syringe over 2 min. The resulting solution was stirred at 0 °C for 30 min, cooled to -78 °C, and a solution of hydrazone **73** (0.20 g, 0.68 mmol, 1.0 equiv) in 1 mL of THF was added dropwise via cannula over 2 min (1 mL THF rinse). The resulting mixture was stirred at -78 °C for 3 h. A solution of methyl chloroformate (0.26 mL, 0.32 g, 3.4 mmol, 5.0 equiv) in 1 mL of THF was added dropwise via cannula over 2 min (1 mL THF rinse) and the resulting solution was stirred at -78 °C for 10 min. Satd aq NH_4Cl solution (10 mL) was added, followed by 10 mL of water. The mixture was allowed to warm to rt and the aqueous phase was separated and extracted with three 20-mL portions of ether. The combined organic layers were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.30 g of an orange oil. Column chromatography on 50 g of silica gel (elution with 0-30% EtOAc-hexanes) afforded 0.154 g (65%) of **32** as a yellow oil: IR (NaCl) 3057, 2954, 2854, 2361, 2340, 2238, 1719, 1436, 1258, 1086, and 1058 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.33 (m, 4 H), 7.19-7.23 (m, 1 H), 6.63 (s, 1 H), 4.34 (s, 2 H), 4.20 (t, *J* = 2.0 Hz, 2 H), 3.78 (s, 3 H), 2.76 (s, 6 H), 2.05-2.23 (m, 4 H), 1.44 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 146.5, 143.6, 129.1, 127.3, 127.0, 89.6, 83.9, 78.6, 74.9, 58.4, 56.5, 53.5, 45.4, 44.0, 39.7, 24.7, 15.2; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{21}H_{26}N_2O_3$ 355.2016, found 355.2031.

*(E)-1,1-Dimethyl-2-(2-methyl-2-phenyl-7-((5-(triisopropylsilyl)penta-2,4-diyn-1-yl)oxy)hept-5-yn-1-ylidene)hydrazine (**35**).* Reaction of terminal alkyne 73 (0.171 g, 0.577 mmol, 1.0 equiv) with $NH_2OH{\cdot}HCl$ (0.080 g, 1.15 mmol, 2.0 equiv), CuCl (0.003 g, 0.029 mmol, 5 mol%), and 1-bromo-2-(triisopropylsilyl)acetylene **S2**[32] (0.226 g, 0.866 mmol, 1.5 equiv) in 10 mL of 30% aq *n*-$BuNH_2$ solution and 10 mL THF according to the General Procedure provided ca. 1 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with 0-10% EtOAc-hexanes) afforded 0.247 g (90%) of **35** as a pale yellow oil: IR (NaCl) 2944, 2866, 2361, 2339, 2105, 1653, 1457, 1073, and 1018 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ δ 7.29-7.34 (m, 4 H), 7.20-7.23 (m, 1 H), 6.64 (s, 1 H), 4.29 (s, 2 H), 4.20 (t, *J* = 1.5 Hz, 2 H), 2.77 (s, 6 H), 2.08-2.24 (m, 4 H), 1.44 (s, 3 H), 1.09 (s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0, 143.1, 128.6, 126.9, 126.5, 89.1, 88.7, 84.7, 74.8, 72.6, 72.0, 56.7, 56.9, 44.9, 43.5, 39.2, 24.2, 18.7, 14.7, 11.4; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_{30}H_{44}N_2OSi$ 477.3296, found 477.3289.

*9-(Prop-2-yn-1-yloxy)non-1-en-7-yne (**74**).* A 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and an argon inlet adapter was charged with NaH (60% dispersion in mineral oil, 0.362 g, 9.07 mmol, 1.1 equiv). Hexanes (30 mL) was added and the resulting slurry was stirred at rt for 10 min and then allowed to settle. The supernatant hexanes were removed via cannula and 10 mL of THF was added via syringe. The white slurry was cooled at 0 °C while a solution of propargylic alcohol **S6**[32] (1.14 g, 8.24 mmol, 1.0 equiv) in 9 mL of THF was added dropwise via cannula over 20 min (1 mL THF rinse). The reaction mixture was stirred at 0 °C for 1 h and then propargyl bromide (8.2 M in toluene, 1.00 mL, 0.980 g, 8.24 mmol, 1.0 equiv) was added dropwise via syringe over 1 min. The resulting suspension was allowed to warm to rt and stirred for 15 h and then 40 mL of water was added dropwise via syringe over several minutes. The aqueous phase was separated and extracted with three 50-mL portions of ether, and the combined organic layers were washed with 20 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated (0 °C, 20 mmHg) to give 1.50 g of a yellow oil. Column chromatography on 50 g of silica gel (elution with 10% EtOAc-hexanes) afforded 1.21 g (83%) of **74** as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H), 4.98 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1 H), 4.93 (ddt, *J* = 10.0, 1.5, 1.5 Hz, 1 H), 4.22-4.23 (m, 4 H), 2.43 (t, *J* = 2.5 Hz, 1 H), 2.22 (tt, *J* = 7.0, 2.0 Hz, 2 H), 2.03-2.07 (m, 2 H), 1.44-1.55 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 114.9, 87.8, 79.4, 75.3, 74.9, 57.4, 56.4, 33.4, 28.3, 28.2, 18.8; IR (NaCl) 2954, 2924, 2854, 2362, 2341, 1458, 1377, and 1079 cm^{-1}; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{12}H_{16}O$ 177.1274, found 177.1283.

*8-Bromooct-1-en-6-yne (**75**).* A 50-mL, round-bottomed flask equipped with a rubber septum fitted with an argon inlet needle was charged with propargylic alcohol **S7**[33] (1.50 g, 12.1 mmol, 1.0 equiv) and 20 mL of CH_2Cl_2. The solution was cooled to 0 °C and PPh_3 (3.80 g, 14.5 mmol, 1.2 equiv) was added in one portion, followed by CBr_4 (4.80 g, 14.5 mmol, 1.2 equiv) in five portions

over 5 min. The reaction mixture was stirred at 0 °C for 30 min and then diluted with 30 mL of pentane. The resulting white suspension was filtered with the aid of 20 mL of pentane, and the filtrate was concentrated to give 2.3 g of a yellow oil. Column chromatography on 55 g of silica gel (elution with hexanes) afforded 1.93 g (86%) of **75** as a colorless oil: IR (NaCl) 2918, 2232, 1640, 1428, and 1207 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H), 5.02 (dtt, *J* = 17.0, 2.0, 1.5 Hz, 2 H), 3.94 (t, *J* = 2.5 Hz, 2 H), 2.26 (tt, *J* = 7.0, 2.0 Hz, 2 H), 2.15 (dddt, *J* = 7.0, 1.0, 1.0, 6.5 Hz, 2 H), 1.63 (app quint, *J* = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 116.0, 88.6, 76.3, 33.4, 28.2, 19.0, 16.4; HRMS (DART-FTICR) *m/z* $[M + H]^+$ calcd for $C_8H_{11}Br$ 187.0117, found 187.0137.

*Dimethyl 2-(oct-7-en-2-yn-1-yl)malonate (**76**).* A 50-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with NaH (60% dispersion in mineral oil, 0.135 g, 3.37 mmol, 2.0 equiv) and 10 mL of THF. The slurry was cooled at 0 °C while a solution of dimethyl malonate (0.445 g, 3.37 mmol, 2.0 equiv) in 2 mL of THF was added via cannula over 5 min (1 mL THF rinse). The cooling bath was then removed and the reaction mixture was allowed to warm to rt over 1 h. A solution of propargylic bromide **75** (0.315 g, 1.68 mmol, 1.0 equiv) in 2 mL of THF was added via cannula over 5 min (2 mL THF rinse) and the reaction mixture was stirred at rt for 3 h and then quenched by the addition of 5 mL of satd aq NH_4Cl solution and 5 mL of water. The aqueous phase was separated and extracted with three 20-mL portions of ether, and the combined organic layers were washed with 20 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford ca. 1 g of a colorless oil. Column chromatography on 80 g of silica gel (elution with 0-10% EtOAc-hexanes) afforded 0.311 g (77%) of **76** as a colorless oil: IR (NaCl) 3078, 2954, 2856, 2234, 1739, 1641, 1279, 1239, and 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1 H), 5.01 (ddt, *J* = 17.5, 1.5, 1.5 Hz, 1 H), 4.95 (ddt, *J* = 10.5, 2.0, 1.0 Hz, 1 H), 3.75 (s, 6 H), 3.56 (t, *J* = 7.5 Hz, 1 H), 2.47 (dt, *J* = 8.0, 2.0 Hz, 2 H), 2.08-2.14 (m, 4 H), 1.53 (app quint, *J* = 7.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 138.1, 115.3, 82.5, 76.0, 53.0, 51.8, 32.8, 28.1, 19.2, 18.2; HRMS (ESI-FTICR) *m/z* $[M + Na]^+$ calcd for $C_{13}H_{18}O_4$ 261.1097, found: 261.1099.

*Dimethyl 2-(oct-7-en-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (**77**).* A 50-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with NaH (60% dispersion in mineral oil, 0.236 g, 5.91 mmol, 1.1 equiv) and 2 mL of THF. A solution of **76** (1.28 g, 5.38 mmol, 1.0 equiv) in 5 mL of THF was added via cannula over 2 min (4 mL THF rinse) and the resulting mixture was stirred at rt for 1 h. Propargyl bromide (8.20 M in toluene, 0.853 mL, 0.833 g, 7.00 mmol, 1.3 equiv) was then added dropwise via syringe over 1 min and the reaction mixure was stirred for 15 h at rt and then diluted with 20 mL of water. The aqueous phase was separated and extracted with three 30-mL portions of ether, and the combined organic layers were washed with 10 mL of saturated aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 1.55 g of a colorless oil. Column chromatography on 50 g of silica gel (elution with 10% EtOAc-hexanes) afforded 1.18 g (80%) of **77** as a colorless oil: IR (NaCl) 3290, 3078, 3001, 2954, 2844, 2234, 2123, 1741, 1436, 1294, 1213, 1075, and 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.01 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1 H), 4.95 (ddt, *J* = 10.0, 1.5, 1.5 Hz, 1 H), 3.73 (s, 6 H), 2.95 (d, *J* = 2.5 Hz, 2 H), 2.93 (t, *J* = 2.5 Hz, 2 H), 2.07-2.13 (m, 4 H), 2.01 (t, *J* = 2.5 Hz, 1 H), 1.52 (app quint, *J* = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 138.5, 115.8, 84.3, 79.3, 78.0, 74.8, 72.2, 57.5, 53.7, 33.3, 28.7, 23.7, 23.4, 18.7; HRMS (ESI-FTICR) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{20}O_4$ 299.1254, found 299.1257. In other runs the yield for this reaction ranged from 80-83%.

*Dimethyl 2-(oct-7-en-2-yn-1-yl)-2-(5-(triisopropylsilyl)penta-2,4-diyn-1-yl)malonate (**78**).* Reaction of terminal alkyne **77** (1.12 g, 4.06 mmol, 1.0 equiv) with $NH_2OH{\cdot}HCl$ (0.564 g, 8.12 mmol, 2.0 equiv), CuCl (0.401 g, 4.06 mmol, 100 mol%), and 1-bromo-2-(triisopropylsilyl)acetylene **S2**[34] (1.59 g, 6.09 mmol, 1.5 equiv) in 88 mL of 30% aq *n*-$BuNH_2$ solution and 88 mL of THF according to the General Procedure provided 2.40 g of an orange oil. Column chromatography on 55 g of acetone-deactivated silica gel (elution with 5-10% EtOAc-hexanes) afforded 1.22 g (60%) of **78** as a pale yellow oil: IR (film) 3078, 2944, 2866, 2361, 2341, 1745, 1436, 1292, 1210, and 1072 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1 H), 5.03 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1 H), 4.97 (ddt, *J* = 10.0, 1.5, 1.5 Hz, 1 H), 3.76 (s, 6 H), 3.09 (s, 2 H), 2.95 (t, *J* = 2.5 Hz, 2 H), 2.08–2.15 (m, 4 H), 1.53 (app quint, *J* = 7.5 Hz, 2 H), 1.07 (s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 138.1, 115.4, 89.7, 84.1, 81.8, 74.2, 72.6, 68.9, 57.1, 53.4, 32.9, 28.2, 23.8, 23.6, 18.8, 18.2, 11.5; HRMS (ESI-FTICR) *m/z* $[M + Na]^+$ calcd for $C_{27}H_{40}O_4Si$ 479.2588, found 479.2603.

*Triisopropyl(5-(non-8-en-2-yn-1-yloxy)penta-1,3-diyn-1-yl)silane (**79**).* Reaction of terminal alkyne **74** (1.00 g, 5.67 mmol, 1.0 equiv) with $NH_2OH{\cdot}HCl$ (6.78 g, 11.3 mmol, 2.0 equiv), CuCl (0.028 g, 0.283 mmol, 5 mol%), and 1-bromo-2-(triisopropylsilyl)acetylene **S2**[34] (2.22 g, 8.51 mmol, 1.5 equiv) in 84 mL of 30% aq *n*-$BuNH_2$ solution and 84 mL THF according to the General Procedure provided 4.23 g of an orange oil. Column chromatography on 50 g of acetone-deactivated silica gel (elution with hexanes) afforded 1.36 g (67%) of **79** as a pale yellow oil: IR (film) 2943, 2866, 2360, 2341, 2106, 1641, 1463, and 1075 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1 H), 5.02 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1 H), 4.96 (ddt, *J* = 10.5, 2.0, 1.5 Hz, 1 H), 4.32 (s, 2 H), 4.25 (t, *J* = 2.0 Hz, 2 H), 2.24 (tt, *J* = 7.0, 2.0 Hz), 2.07 (dddt, *J* = 7.0, 1.0, 1.0, 7.0 Hz, 2 H), 1.46-1.57 (m, 4 H), 1.09 (s, 19 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 114.9, 89.1, 88.2, 84.7, 75.2, 72.6, 72.0, 57.2, 57.0, 33.5, 28.3, 28.2, 18.9, 18.7, 11.4; HRMS (ESI-FTICR) *m/z* $[M + Na]^+$ calcd for $C_{23}H_{36}OSi$ 379.2428, found 379.2440.

*tert-Butyl((7-(oct-7-en-2-yn-1-yloxy)hepta-3,5-diyn-1-yl)oxy)dimethyl silane (**80**).* Reaction of terminal alkyne **S1**[6] (0.500 g, 3.08 mmol, 1.0 equiv) with $NH_2OH{\cdot}HCl$ (0.428 g, 6.16 mmol, 2.0 equiv), CuCl (0.015 g, 0.154 mmol, 5 mol%), and 1-bromo-4-(*tert*-butyldimethylsilyloxy)butyne **S8**[35] (0.811 g, 3.08 mmol, 1.0 equiv) in 30 mL of 30% aq *n*-$BuNH_2$ solution and 30 mL of THF according to the General Procedure provided 2.10 g of a yellow oil. Column chromatography on 50 g of silica gel (elution with 5% EtOAc-hexanes) afforded 0.881 g (83%) of **80** as a pale yellow oil: IR (film) 3078, 2930, 2857, 2258, 1642, 1472, 1347, 1256, 1109, and 1078 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.5, 10.0, 6.5 Hz, 1 H), 5.04 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1 H), 4.98 (ddt, *J* = 10.0, 1.5, 1.5 Hz, 1 H), 4.29 (t, *J* = 1.0 Hz, 2 H), 4.23 (t, *J* = 2.0 Hz, 2 H), 3.74 (t, *J* = 7.0 Hz, 2 H), 2.49 (tt, *J* = 7.0, 1.0 Hz, 2 H), 2.24 (tt, *J* = 7.5, 2.5 Hz, 2 H), 2.15 (dddt, *J* = 7.0, 1.0, 1.0, 7.0 Hz, 2 H), 1.16 (app quint, *J* = 7.5 Hz, 2 H), 0.89 (s, 9 H),

0.07 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 115.9, 88.3, 78.9, 75.9, 72.2, 72.1, 66.3, 62.0, 57.9, 57.5, 33.5, 28.4, 26.6, 24.4, 19.0, 18.9, -4.6; HRMS (ESI-FTICR) *m/z* [M + Na]$^+$ calcd for $C_{21}H_{32}O_2Si$ 367.2064, found 367.2077.

*2-(3-(Oct-7-en-2-yn-1-yloxy)prop-1-yn-1-yl)pyridine (**81**).* A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with $PdCl_2(PPh_3)_2$ (0.216 g, 0.308 mmol, 0.05 equiv), CuI (0.058 g, 0.308 mmol, 0.05 equiv), and 35 mL of triethylamine. 2-Bromopyridine (0.707 mL, 1.17 g, 7.39 mmol, 1.2 equiv) was added dropwise via syringe over 1 min and the resulting orange slurry was stirred at rt for 5 min. A solution of alkyne **S1**[6] (1.00 g, 6.16 mmol, 1.0 equiv) in 5 mL of triethylamine was added dropwise via cannula over 2 min (1 mL triethylamine rinse). The resulting brown solution was stirred at rt in the dark for 48 h and then diluted with 20 mL of water. The mixture was extracted with three 50-mL portions of ether and the combined organic layers were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 1.61 g of a brown oil. Column chromatography on 80 g of silica gel (elution with 20-30% EtOAc-hexanes) afforded 0.992 g (68%) of **81** as a dark red oil: IR (NaCl) 3077, 2975, 2939, 2854, 2283, 2223, 1641, 1583, 1564, 1464, 1429, and 1078 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 4.5, 1.5, 1.0 Hz, 1 H), 7.63 (td, *J* = 7.5, 2.0 Hz, 1 H), 7.43 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.22 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1 H), 5.77 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H), 5.02 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1H), 4.48 (s, 2 H), 4.30 (t, *J* = 2.0 Hz, 2 H), 2.23 (tt, *J* = 7.5, 2.0 Hz, 2 H), 2.14 (dddt, *J* = 7.0, 1.0, 1.0, 7.0 Hz, 2 H), 1.60 (app quint, *J* = 7.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 143.4, 138.4, 136.8, 127.9, 123.8, 115.9, 88.2, 86.5, 85.4, 76.0, 58.1, 57.4, 33.5, 28.4, 18.9; HRMS (ESI-FTICR) *m/z* [M + H]$^+$ calcd for $C_{16}H_{17}NO$ 240.1383, found 240.1396. In other runs the yield for this reaction ranged from 67-68%.

*8-((5-(Triisopropylsilyl)penta-2,4-diyn-1-yl)oxy)oct-6-ynal (**82**).* Reaction of alkene **79** (1.30 g, 3.65 mmol, 1.0 equiv), saturated Sudan III solution in MeOH, and dimethyl sulfide (0.80 mL, 0.680 g, 10.9 mmol, 3.0 equiv) in 7 mL of MeOH and 3 mL of CH_2Cl_2 according to the General Procedure provided 2.0 g of a pale orange oil. Column chromatography on 50 g of silica gel (elution with 15% EtOAc-hexanes) afforded 1.05 g (81%) of **82** as a pale yellow oil: IR (NaCl) 2945, 2866, 2105, 1726, 1463, and 1074 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.5 Hz, 1 H), 4.31 (s, 2 H), 4.23 (t, *J* = 2.0 Hz, 2 H), 2.47 (td, *J* = 7.5, 2.0 Hz, 2 H), 2.26 (tt, *J* = 7.0, 2.0 Hz, 2 H), 1.71-1.77 (m, 2 H), 1.53-1.59 (m, 2 H), 1.08 (s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 89.1, 87.4, 84.8, 75.7, 72.5, 72.1, 57.7, 57.0, 43.6, 28.1, 21.4, 18.8, 18.7, 11.4; HRMS (ESI-FTICR) *m/z* [M + Na]$^+$ calcd for $C_{22}H_{34}O_2Si$ 381.2220, found 381.2226.

*Dimethyl 2-(7-oxohept-2-yn-1-yl)-2-(5-(triisopropylsilyl)penta-2,4-diyn-1-yl)malonate (**83**).* Reaction of alkene **78** (1.15 g, 2.51 mmol, 1.0 equiv), saturated Sudan III solution in MeOH, and dimethyl sulfide (0.55 mL, 0.468 g, 7.53 mmol, 3.0 equiv) in 5 mL of MeOH and 2 mL of CH_2Cl_2 according to the General Procedure provided 1.55 g of a pale orange oil. Column chromatography on 50 g of silica gel (elution with 15-20% EtOAc-hexanes) afforded 0.766 g (66%) of **83** as a pale yellow oil: IR (NaCl) 2946, 2867, 2227, 2107, 1743, 1436, 1211, and 1072 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.5 Hz, 1 H), 3.76 (s, 6 H), 3.07 (s, 2 H), 2.94 (t, *J* = 2.5 Hz, 2 H), 2.55 (td, *J* = 7.5, 1.5 Hz, 2 H), 2.21 (tt, *J* = 7.0, 2.0 Hz, 2 H), 1.78 (app quint, *J* = 7.0 Hz, 2 H), 1.07 (s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 169.8, 90.1, 83.6, 82.4, 75.7, 72.9, 69.4, 57.4, 53.8, 43.3, 24.4, 24.0, 21.8, 19.2, 18.7, 11.9; HRMS (ESI-FTICR) *m/z* [M + Na]$^+$ calcd for $C_{26}H_{38}O_5Si$ 481.2381, found 481.2381. In other runs the yield for this reaction ranged from 66-75%.

*7-((7-((tert-Butyldimethylsilyl)oxy)hepta-2,4-diyn-1-yl)oxy)hept-5-ynal (**84**).* Reaction of alkene **80** (0.500 g, 1.45 mmol, 1.0 equiv), saturated Sudan III solution in MeOH, and dimethyl sulfide (0.32 mL, 0.270 g, 4.35 mmol, 3.0 equiv) in 3 mL of MeOH and 1 mL of CH_2Cl_2 according to the General Procedure provided 0.650 g of a pale orange oil. Column chromatography on 55 g of silica gel (elution with 10-20% EtOAc-hexanes) afforded 0.280 g (60%) of **84** as a pale yellow oil: IR (film) 2930, 2857, 2258, 1718, 1472, 1361, 1256, and 1107 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (t, *J* = 1.5 Hz, 1 H), 4.28 (t, *J* = 1.0 Hz, 2 H), 4.22 (t, *J* = 2.0 Hz, 2 H), 3.74 (t, *J* = 7.0 Hz, 2 H), 2.60 (td, *J* = 7.0, 1.5 Hz, 2 H), 2.49 (tt, *J* = 7.0, 1.0 Hz, 2 H), 2.31 (tt, *J* = 7.0, 1.0 Hz, 2 H), 1.85 (app quint, *J* = 7.0 Hz, 2 H), 0.89 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 86.6, 78.6, 76.3, 71.8, 71.5, 65.8, 61.5, 57.4, 57.1, 42.9, 26.1, 23.9, 21.1, 18.5, 18.4, -5.1; HRMS (ESI-FTICR) *m/z* [M + Na]$^+$ calcd for $C_{20}H_{30}O_3Si$ 369.1856, found 369.1847.

*7-((3-(Pyridin-2-yl)prop-2-yn-1-yl)oxy)hept-5-ynal (**85**).* Reaction of alkene **81** (0.992 g, 4.15 mmol, 1.0 equiv), saturated Sudan III solution in MeOH, and dimethyl sulfide (0.91 mL, 0.773 g, 12.5 mmol, 3.0 equiv) in 8 mL of MeOH and 3 mL of CH_2Cl_2 according to the General Procedure provided 1.35 g of a pale orange oil. Column chromatography on 80 g of silica gel (elution with 30-50% EtOAc-hexanes) afforded 0.556 g (56%) of **85** as a pale yellow oil: IR (NaCl) 3053, 2941, 2851, 2727, 2225, 1721, 1582, 1562, 1464, 1429, and 1078 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.5 Hz,1 H), 8.56 (ddd, *J* = 5.0, 2.0, 0.5 Hz, 1 H), 7.64 (td, *J* = 7.5, 2.0 Hz, 1 H), 7.42 (dt, *J* = 7.5, 1.0 Hz, 1 H), 7.23 (ddd, *J* = 7.5, 5.0,1.0 Hz, 1 H), 4.46 (s, 2 H), 4.29 (t, *J* = 2.0 Hz, 2 H), 2.58 (td, *J* = 7.0, 1.0 Hz, 2 H), 2.30 (tt, *J* = 7.0, 5.0 Hz, 2 H), 1.83 (app quint, *J* = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 150.2, 142.9, 136.4, 127.4, 123.4, 86.6, 86.1, 84.8, 76.5, 57.6, 57.2, 42.9, 21.1, 18.4; HRMS (ESI-FTICR) *m/z* [M + H]$^+$ calcd for $C_{15}H_{15}NO_2$ 242.1176, found 242.1185.

General Procedure for the Formation of *O*-Methyl Oxime Ethers from Aldehydes. *7-(Prop-2-yn-1-yloxy)hept-5-ynal O-methyl oxime (**57**).* A 100-mL round-bottomed flask equipped with a rubber septum fitted with an argon inlet needle was charged with aldehyde **66** (0.900 g, 5.48 mmol, 1.0 equiv), 50 mL of CH_2Cl_2, *O*-methylhydroxylamine hydrochloride (0.458 g, 5.48 mmol, 1.0 equiv), and sodium acetate (0.899 g, 10.9 mmol, 2.0 equiv). The resulting suspension was stirred at rt for 3 h and then diluted with 25 mL of water. The aqueous layer was separated and extracted with two 50-mL portions of CH_2Cl_2, and the combined organic layers were washed with 25 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 1.13 g of a pale yellow oil. Column chromatography on 30 g of silica gel (elution with 20% EtOAc-hexanes) afforded 0.821 g (78%) of **57** (65:35 mixture of *E* and *Z* isomers by ^{1}H NMR analysis) as a colorless oil: For the *E* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 6.0 Hz, 1 H), 4.22-4.23 (m, 4 H), 3.80 (s, 3 H), 2.43 (t, J = 2.5 Hz, 1 H), 2.24-2.30 (m, 4 H), 1.66-1.74 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 87.2, 79.8, 76.5, 75.5, 62.0, 57.8, 57.0, 29.3,

26.2, 19.0. For the *Z* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (t, J = 5.5 Hz, 1 H), 4.22-4.23 (m, 4 H), 3.85 (s, 3 H), 2.43 (t, J = 2.5 Hz, 1 H), 2.40 (td, J = 7.5, 5.5 Hz, 2 H), 2.24-2.30 (m, 2H), 1.66-1.74 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 87.2, 79.8, 76.5, 75.5, 62.3, 57.8, 57.0, 25.9, 25.5, 19.3. For the mixture: IR (NaCl) 3288, 2941, 2903, 2225, 2116, 1632, 1443, 1347, 1080, and 1051 cm^{-1}; HRMS (ESI-FTICR) *m/z* $[M + Na]^+$ calcd for $C_{11}H_{15}NO_2$ 216.0995, found 216.0991.

*7-((5-(Triisopropylsilyl)penta-2,4-diyn-1-yl)oxy)hept-5-ynal O-methyl oxime (**42**).* Reaction of aldehyde **67** (0.500 g, 1.45 mmol, 1.0 equiv), *O*-methylhydroxylamine hydrochloride (0.121 g, 1.45 mmol, 1.0 equiv), and sodium acetate (0.238 g, 2.90 mmol, 2.0 equiv) in 15 mL of CH_2Cl_2 according to the General Procedure gave 0.600 g of a pale yellow oil. Column chromatography on 30 g of silica gel (elution with 20% EtOAc-hexanes) afforded 0.498 g (92%) of **42** (59:41 mixture of *E* and *Z* isomers by ^{1}H NMR analysis) as a colorless oil: For the *E* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 6.0 Hz, 1 H), 4.31 (s, 2 H), 4.24 (t, *J* = 2.0 Hz, 2 H), 3.82 (s, 3 H), 2.26-2.32 (m, 4 H), 1.67-1.75 (m, 2 H), 1.08 (s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 89.6, 87.6, 85.3, 76.4, 73.0, 72.6, 62.0, 58.1, 57.5, 29.3, 26.2, 19.2, 19.0, 11.9. For the *Z* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (t, *J* = 5.5 Hz, 1 H), 4.31 (s, 2 H), 4.24 (t, *J* = 2.0 Hz, 2 H), 3.87 (s, 3 H), 2.42 (td, *J* = 7.5, 5.5 Hz, 2 H), 2.26-2.32 (m, 2 H), 1.67-1.75 (m, 2 H), 1.08 (s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 89.6, 87.6, 85.3, 76.4, 73.0, 72.6, 62.3, 58.1, 57.5, 25.9, 25.6, 19.3, 19.2, 11.9. For the mixture: IR (NaCl) 2944, 2866, 2223, 2105, 1631, 1463, 1345, 1075, and 1056 cm^{-1}; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{22}H_{35}NO_2Si$ 374.2510, found 374.2511. In other runs the yield for this reaction ranged from 92-95%.

*8-((5-(Triisopropylsilyl)penta-2,4-diyn-1-yl)oxy)oct-6-ynal O-methyl oxime (**43**).* Reaction of aldehyde **82** (1.05 g, 2.93 mmol, 1.0 equiv), *O*-methylhydroxylamine hydrochloride (0.244 g, 2.93 mmol, 1.0 equiv), and sodium acetate (0.481 g, 5.86 mmol, 2.0 equiv) in 29 mL of CH_2Cl_2 according to the General Procedure gave 1.51 g of a pale yellow oil. Column chromatography on 50 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.712 g (63%) of **43** (58:42 mixture of *E* and *Z* isomers by ^{1}H NMR analysis) as a colorless oil: For the *E* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 6.0 Hz, 1 H), 4.30 (s, 2 H), 4.23 (t, *J* = 2.0 Hz, 2 H), 3.81 (s, 3 H), 2.23-2.27 (m, 2 H), 2.20 (td, *J* = 7.5, 6.0 Hz, 2 H), 1.51-1.63 (m, 4 H), 1.08 (s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 89.1, 87.6, 84.7, 75.5, 72.6, 72.1, 61.5, 57.7, 57.0, 29.2, 28.1, 26.1, 18.7, 18.6, 11.4. For the *Z* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (t, *J* = 5.5 Hz, 1 H), 4.30 (s, 2 H), 4.23 (t, *J* = 2.0 Hz, 2 H), 3.86 (s, 3 H), 2.23-2.27 (m, 2 H), 2.23 (td, *J* = 7.5, 5.5 Hz, 2 H), 1.51-1.63 (m, 4 H), 1.08 (s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 89.1, 87.6, 84.7, 75.5, 72.6, 72.1, 61.8, 57.7, 57.0, 28.3, 25.6, 25.2, 18.7, 18.6, 11.4. For the mixture: IR (NaCl) 2866, 2224, 2105, 1634, 1463, 1346, and 1074 cm^{-1}; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{23}H_{37}NO_2Si$ 388.2666, found 388.2687.

*7-((7-((tert-Butyldimethylsilyl)oxy)hepta-2,4-diyn-1-yl)oxy)hept-5-ynal O-methyl oxime (**44**).* Reaction of aldehyde **83** (0.722 g, 1.57 mmol, 1.0 equiv), *O*-methylhydroxylamine hydrochloride (0.131 g, 1.57 mmol, 1.0 equiv), and sodium acetate (0.257 g, 3.14 mmol, 2.0 equiv) in 16 mL of CH_2Cl_2 according to the General Procedure gave 0.828 g of a pale yellow oil. Column chromatography on 50 g of silica gel (elution with 10-20% EtOAc-hexanes) afforded 0.615 g (81%) of **44** (53:47 mixture of *E* and *Z* isomers by ^{1}H NMR analysis) as a colorless oil: For the *E* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 6.0 Hz, 1 H), 3.81 (s, 3 H), 3.76 (s, 6 H), 3.08 (s, 2 H), 2.94 (t, *J* = 2.5 Hz, 2 H), 2.24 (td, *J* = 7.5, 6.0 Hz, 2 H), 2.15-2.20 (m, 2 H), 1.60-1.68 (m, 2 H), 1.07 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 150.5, 90.1, 83.8, 82.3, 75.3, 73.0, 69.4, 61.9, 57.5, 53.8, 29.2, 26.5, 24.3, 24.0, 19.2, 18.8, 11.9. For the *Z* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (t, *J* = 5.5 Hz, 1 H), 3.86 (s, 3 H), 3.76 (s, 6 H), 3.08 (s, 2 H), 2.94 (t, *J* = 2.5 Hz, 2 H), 2.37 (td, *J* = 7.5, 5.5 Hz, 2 H), 2.15-2.20 (m, 2 H), 1.60-1.68 (m, 2 H), 1.07 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 151.3, 90.1, 83.8, 82.3, 75.3, 73.0, 69.4, 62.3, 57.5, 53.8, 26.2, 25.4, 24.3, 24.0, 19.2, 19.1, 11.9. For the mixture: IR (NaCl) 2946, 2867, 2227, 2107, 1744, 1635, 1436, 1292, 1211, and 1053 cm^{-1}; HRMS (ESI-FTICR) *m/z* $[M + Na]^+$ calcd for $C_{27}H_{41}NO_5Si$ 510.2646, found 510.2643.

*Methyl 4-((7-(methoxyimino)hept-2-yn-1-yl)oxy)but-2-ynoate (**45**).* Reaction of aldehyde **68** (1.00 g, 4.49 mmol, 1.0 equiv), *O*-methylhydroxylamine hydrochloride (0.376 g, 4.49 mmol, 1.0 equiv), and sodium acetate (0.736 g, 8.98 mmol, 2.0 equiv) in 44 mL of CH_2Cl_2 according to the General Procedure gave 1.43 g of a pale yellow oil. Column chromatography on 40 g of silica gel (elution with 20% EtOAc-hexanes) afforded 0.828 g (74%) of **45** (60:40 mixture of *E* and *Z* isomers by ^{1}H NMR analysis) as a colorless oil: For the *E* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 6.0 Hz, 1 H), 4.37 (s, 2 H), 4.42 (t, *J* = 2.0 Hz, 2 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 2.26-2.31 (m, 4 H), 1.67-1.75 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 150.4, 88.0, 83.8, 78.7, 76.0, 62.0, 58.3, 56.6, 53.5, 29.3, 26.2, 18.9. For the *Z* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (t, *J* = 5.5 Hz, 1 H), 4.37 (s, 2 H), 4.25 (t, *J* = 2.0 Hz, 2 H), 3.87 (s, 3 H), 3.79 (s, 3 H), 2.41 (td, *J* = 7.5, 5.5 Hz, 2 H), 2.26-2.31 (m, 2 H), 1.67-1.75 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 151.2, 88.0, 83.8, 78.7, 76.0, 62.3, 58.3, 56.6, 53.5, 25.9, 25.5, 19.3. For the mixture: IR (NaCl) 2954, 2903, 2238, 1720, 1633, 1436, 1259, 1087, and 1056 cm^{-1}; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{13}H_{17}NO_4$ 252.1230, found 252.1234. In other runs the yield for this reaction ranged from 74-77%.

*7-((7-((tert-butyldimethylsilyl)oxy)hepta-2,4-diyn-1-yl)oxy)hept-5-ynal O-methyl oxime (**46**).* Reaction of aldehyde **84** (0.250 g, 0.721 mmol, 1.0 equiv), *O*-methylhydroxylamine hydrochloride (0.060 g, 0.721 mmol, 1.0 equiv), and sodium acetate (0.118 g, 1.44 mmol, 2.0 equiv) in 10 mL of CH_2Cl_2 according to the General Procedure gave 0.300 g of a pale yellow oil. Column chromatography on 20 g of silica gel (elution with 10-20% EtOAc-hexanes) afforded 0.186 g (68%) of **46** (53:47 mixture of *E* and *Z* isomers by ^{1}H NMR analysis) as a colorless oil: For the *E* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 6.0 Hz, 1 H), 4.27 (t, *J* = 1.0 Hz, 2 H), 4.21 (t, *J* = 2.0 Hz, 2 H), 3.80 (s, 3 H), 3.73 (t, *J* = 7.0 Hz, 2 H), 2.48 (tt, *J* = 7.0, 0.5 Hz, 2 H), 2.24-2.30 (m, 4 H), 1.66-1.74 (m, 2 H), 0.88 (s, 9 H), 0.61 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 87.4, 78.9, 76.4, 72.2, 72.1, 66.3, 62.0, 61.9, 57.9, 57.5, 29.3, 26.5, 26.3, 24.4, 19.0, 18.9, -4.6. For the *Z* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (t, *J* = 5.5 Hz, 1 H), 4.27 (t, *J* = 1.0 Hz, 2 H), 4.21 (t, *J* = 2.0 Hz, 2 H), 3.86 (s, 3 H), 3.73 (t, *J* = 7.0 Hz, 2 H), 2.48 (tt, *J* = 7.0, 0.5 Hz, 2 H), 2.40 (td, *J* = 7.5, 5.5 Hz, 2 H), 2.24-2.30 (m, 2 H), 1.66-1.74 (m, 2 H), 0.88 (s, 9 H), 0.61 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 87.4, 78.9, 76.4, 72.2, 72.1, 66.3, 62.3, 62.0, 57.9, 57.5, 26.5, 25.9, 25.6, 24.4, 19.3, 19.0, -

4.6. For the mixture: IR (NaCl) 2932, 2856, 2258, 1472, 1348, 1256, 1108, 1077, and 1054 cm^{-1}; HRMS (ESI-FTICR) *m/z* $[M + Na]^+$ calcd for $C_{21}H_{33}NO_3Si$ 398.2122, found: 398.2122.

*7-((3-(pyridin-2-yl)prop-2-yn-1-yl)oxy)hept-5-ynal O-methyl oxime (**47**).* Reaction of aldehyde **85** (0.521 g, 2.16 mmol, 1.0 equiv), *O*-methylhydroxylamine hydrochloride (0.180 g, 2.16 mmol, 1.0 equiv), and sodium acetate (0.354 g, 4.32 mmol, 2.0 equiv) in 21 mL of CH_2Cl_2 according to the General Procedure gave 0.600 g of a pale yellow oil. Column chromatography on 30 g of silica gel (elution with 40% EtOAc-hexanes) afforded 0.522 g (89%) of **47** (50:50 mixture of *E* and *Z* isomers by ^1H NMR analysis) as a pale yellow oil:. For the *E* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 5.0, 2.0, 0.5 Hz, 1 H), 7.66 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.44 (d, *J* = 7.5 Hz, 1 H), 7.37 (t, *J* = 6.0 Hz, 1 H), 7.24 (ddd, *J* = 7.5, 4.5, 1.5 Hz, 1 H), 4.49 (s, 2H), 4.31 (t, *J* = 2.0 Hz, 2 H), 3.81 (s, 3 H), 2.26-2.32 (m, 4 H), 1.67-1.75 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 150.0, 142.9, 136.4, 127.4, 123.3, 86.9, 86.0, 84.8, 76.1, 61.5, 57.6, 57.1, 28.8, 25.8, 18.5. For the *Z* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 5.0, 2.0, 0.5 Hz, 1 H), 7.66 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.44 (d, *J* = 7.5 Hz, 1 H), 7.24 (ddd, *J* = 7.5, 4.5, 1.5 Hz, 1 H), 6.64 (t, *J* = 5.5 Hz, 1 H), 4.49 (s, 2H), 4.31 (t, *J* = 2.0 Hz, 2 H), 3.86 (s, 3 H), 2.26-2.32 (m, 2 H), 2.42 (td, *J* = 7.5, 5.5 Hz), 1.67-1.75 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 150.2, 142.9, 136.4, 127.4, 123.3, 86.9, 86.0, 84.8, 76.1, 61.8, 57.6, 57.1, 25.5, 25.1, 18.8. For the mixture: IR (NaCl) 3052, 2939, 2901, 2282, 2225, 1632, 1583, 1562, 1464, 1429, 1349, 1078, and 1050 cm^{-1}; HRMS (ESI-FRICR) *m/z* $[M + H]^+$ calcd for $C_{16}H_{18}N_2O_2$ 271.1441, found 271.1447.

*(3-(Oct-7-en-2-yn-1-yloxy)prop-1-yn-1-yl)(phenyl)sulfide (**86**).* A 100-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with alkyne **S1**[6] (1.00 g, 6.16 mmol, 1.0 equiv) and 45 mL of THF. The solution was cooled at -78 °C and butyllithium solution (2.60 M in hexane, 2.32 mL, 6.78 mmol, 1.1 equiv) was added dropwise via syringe over 5 min. The resulting brown solution was stirred for 30 min at -78 °C. A solution of phenyl disulfide (1.61 g, 7.39 mmol, 1.2 equiv) in 10 mL of THF was then added via cannula over 2 min (5 mL THF rinse) and the resulting orange solution was allowed to warm to rt over 15 min. The reaction mixture was quenched by addition of 10 mL of satd aq NH_4Cl solution and 20 mL of water, and the aqueous phase was separated and extracted with three 20-mL portions of ether. The combined organic layers were washed with three 30-mL portions of satd aq K_2CO_3 solution and 30 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give ca. 2 g of an orange oil. Column chromatography on 60 g of silica gel (elution with 25-50% CH_2Cl_2-hexanes) afforded 1.49 g (89%) of **86** as an orange oil: IR (NaCl) 3076, 2939, 2854, 2182, 1641, 1583, 1479, 1442, 1346, and 1078 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 2 H), 7.32-7.36 (m, 2 H), 7.32 (tt, *J* = 7.5, 1.0 Hz, 1 H), 5.79 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H), 5.01 (dtt, *J* = 17.0, 2.0, 1.5 Hz, 2 H), 4.49 (s, 2 H), 4.28 (t, *J* = 2.5 Hz, 2 H), 2.25 (tt, *J* = 7.0, 2.0 Hz, 2 H), 2.16 (dddt, *J* = 14.5, 7.0, 1.0, 1.5 Hz, 2 H), 1.63 (app quint, *J* = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 133.0, 129.9, 127.4, 127.0, 116.0, 95.6, 88.2, 76.0, 74.6, 58.0, 57.8, 33.5, 28.4, 18.9; HRMS (ESI-FTICR) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}OS$ 293.0971, found 293. 0994. In other runs the yield for this reaction ranged from 80-89%.

*2-(6-((3-(Phenylsulfonyl)prop-2-yn-1-yl)oxy)hex-4-yn-1-yl)oxirane (**87**).* A 25-mL round-bottomed flask equipped with an argon inlet adapter was charged with sulfide **86** (0.425 g, 1.57 mmol, 1.0 equiv) and 15 mL of CH_2Cl_2. The solution was cooled at 0 °C and *m*-CPBA (0.812 g, 4.71 mmol, 3.0 equiv) was added in one portion. The reaction mixture was stirred at rt for 5 h and then diluted with 10 mL of satd aq $NaHCO_3$ solution and 10 mL of water. The aqueous phase was separated and extracted with three 20-mL portions of CH_2Cl_2, and the combined organic layers were washed with 10 mL of satd aq $NaHCO_3$ solution and 10 mL of satd NaCl solution, dried with $MgSO_4$, filtered, and concentrated to give ca. 1 g of a colorless oil. Column chromatography on 60 g of silica gel (elution with 50% EtOAc-hexanes) afforded 0.413 g (83%) of **87** as a colorless oil. IR (NaCl) 2942, 2202, 1583, 1339, and 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.5, 1.0 Hz, 2 H), 7.70 (tt, *J* = 7.5, 1.5 Hz, 1 H), 7.59 (t, *J* = 7.5 Hz, 2 H), 4.36 (s, 2 H), 4.16 (t, *J* = 2.0 Hz, 2 H), 2.89-2.93 (m, 1 H), 2.75 (dd, *J* = 5.0, 4.0 Hz, 1 H), 2.47 (dd, *J* = 5.0, 3.0 Hz, 1 H), 2.26-2.30 (m, 2 H), 1.61-1.73 (m, 3 H), 1.52-1.58 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 135.2, 130.2, 128.2, 90.9, 88.9, 83.6, 75.3, 58.8, 56.5, 52.5, 47.6, 32.2, 25.6, 19.2; HRMS (ESI-FTICR) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}O_4S$ 341.0818**,** found 341.0814. In other runs the yield for this reaction ranged from 83-84%.

*7-((3-(Phenylsulfonyl)prop-2-yn-1-yl)oxy)hept-5-ynal (**88**).* A 100-mL round-bottomed flask equipped with a rubber septum fitted with an argon inlet needle was charged with epoxide **87** (1.30 g, 4.08 mmol, 1.0 equiv) and 15 mL of THF. A solution of periodic acid (1.12 g, 4.90 mmol, 1.2 equiv) in 5 mL of H_2O was added dropwise via syringe and the resulting colorless solution was stirred at rt for 3 h and then diluted with 10 mL of water and 20 mL of ether. The aqueous layer was separated and extracted with two 10-mL portions of ether, and the combined organic layers were washed with 10 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give ca. 2 g of a yellow oil. Column chromatography on 50 g of silica gel (elution with 50% ether-hexanes) afforded 1.01 g (81%) of **88** as a pale yellow oil: IR (NaCl) 2941, 2361, 2202, 1718, 1448, 1333, 1164, and 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (t, *J* = 1.5 Hz, 1 H), 8.01 (dd, *J* = 8.5, 1.0 Hz, 2 H), 7.71 (tt, *J* = 7.0, 2.0 Hz, 1 H), 7.60 (t, *J* = 7.5 Hz, 2 H), 4.37 (s, 2 H), 4.18 (t, *J* = 2.0 Hz, 2 H), 2.58 (td, *J* = 7.0, 1.0 Hz, 2 H), 2.30 (tt, *J* = 7.0, 2.0 Hz, 2 H), 1.84 (app quint, *J* = 7.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 141.8, 135.2, 130.2, 128.2, 90.8, 88.3, 83.7, 75.9, 58.8, 56.6, 43.3, 21.5, 18.8; HRMS (DART-FTICR) *m/z* $[M + NH_4]^+$ calcd for $C_{16}H_{16}O_4S$ 322.1108, found 322.1110. In other runs the yield for this reaction ranged from 70-81%.

*7-((3-(Phenylsulfonyl)prop-2-yn-1-yl)oxy)hept-5-ynal O-methyl oxime (**52**).* Reaction of aldehyde **88** (0.986 g, 3.24 mmol, 1.0 equiv), *O*-methylhydroxylamine hydrochloride (0.271 g, 3.24 mmol, 1.0 equiv), and sodium acetate (0.352 g, 6.48 mmol, 2.0 equiv) in 20 mL of CH_2Cl_2 according to the General Procedure gave ca. 1 g of a yellow oil. Column chromatography on 50 g of acetone-deactivated silica gel (elution with 30-50% EtOAc-hexanes) afforded 0.969 g (90%) of **52** (59:41 mixture of *E* and *Z* isomers by ^1H NMR analysis) as a yellow oil: For the *E* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.0, 1.0 Hz, 2 H), 7.71 (tt, *J* = 7.5, 1.5 Hz, 1 H), 7.60 (t, *J* = 7.0 Hz, 2 H), 7.37 (t, *J* = 6.0 Hz, 1 H), 4.37 (s, 2 H), 4.18 (t, *J* = 2.0 Hz, 2 H), 3.18 (s, 3 H), 2.24-2.30 (m, 4 H), 1.66-1.74 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 141.8, 135.1, 130.1, 128.2, 90.8, 88.6, 83.6, 75.6, 62.0, 58.8, 56.5, 29.3, 26.1, 18.9. For the *Z* isomer: ^1H NMR (500 MHz,

$CDCl_3$) δ 8.02 (dd, *J* = 8.0, 1.0 Hz, 2 H), 7.71 (tt, *J* = 7.5, 1.5 Hz, 1 H), 7.60 (t, *J* = 7.0 Hz, 2 H), 6.64 (t, *J* = 5.5 Hz, 1 H), 4.37 (s, 2 H), 4.18 (t, *J* = 2.0 Hz, 2 H), 3.86 (s, 3 H), 2.40 (td, *J* = 8.0, 5.5 Hz, 2 H), 2.24-2.30 (m, 2 H), 1.66-1.74 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 141.8, 135.1, 130.1, 128.2, 90.8, 88.6, 83.6, 75.6, 62.4, 58.8, 56.5, 25.8, 25.5, 19.3. For the mixture: IR (NaCl) 2939, 2361, 2339, 2202, 1653, 1448, 1339, 1164, and 1086 cm^{-1}; HRMS (ESI-FTICR) *m/z* $[M + H]^+$ calcd for $C_{17}H_{19}NO_4S$ 334.1108, found 334.1121.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Schemes describing the synthesis of [2 + 2 + 2] cycloadditions substrates.

Characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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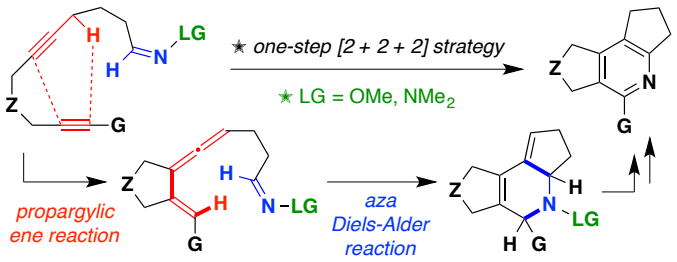
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