Alkynes to (Free) Carbenes to Polycyclic Cyclopropanes

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Supporting Information Placeholder

ABSTRACT: Carbenes and carbenoids are commonly employed for the synthesis of cyclopropane-containing compounds. Here we report the metal-free, intramolecular cyclopropanation of tethered alkenes by free carbenes derived from alkynes to construct structurally unique, multicyclic cyclopropanes with perfect atom economy. The nature of the tether influences both the rate of carbene formation as well as subsequent competing reaction events. Some of the substrates lead to metastable cyclopropane intermediates that further fragment to furnish interesting isomeric products by mechanistically novel processes. A removable siloxane tether can be utilized to achieve formal *inter*molecular cyclopropanations and to access cyclopropanol derivatives.

Cyclopropane-containing compounds have long been of interest from a variety of perspectives due to their status as the simplest strained hydrocarbon, their methods of preparation,[1] and the unique reactivity they instill as a consequence of their strained nature.[2] They also have played a prominent role in propelling pharmaceutical drug development[3] [cf. the examples of heterocyclic cyclopropanes shown in the small sampling of the preclinical, clinical, and approved (tasimelteon) pharmaceuticals; Figure 1a].

Free carbenes (R_2C:), distinct from their invaluable metal-complexed carbenoid counterparts,[4] are typically generated through fragmentation of appropriately functionalized precursors and are often employed in the synthesis of cyclopropanes. The most common methods of free carbene formation are by thermal or photochemical (including recent visible light-induced processes[5]) loss of nitrogen from diazo compounds ($R_2C{=}N_2$) or diazirenes or by alpha-elimination of hydrogen halide from (R_2CHX). By contrast, the generation of a free carbene (hereafter, simply, carbene) by a process that conserves all of the elements of the reactant(s) (i.e., is 100% atom economical) is rare. The earliest examples of such a reaction are the oxidative dimerization[6a] and the tetramerization[6b] of dimethyl acetylenedicarboxylate (**1**, DMAD). A related example is the reaction of DMAD with cyclooctyne.[7] Photolysis of acylsilanes can result in C-to-O silyl migration and this represents another method of carbene generation that conserves all atoms.[8] Finally and starting with the initial report of Nakatani and Saito,[9a] a number of instances involving the conversion of an alkyne to a heteroaryl-substituted free carbene[9b] are intramolecular in nature. One case of note here, involves formation and trapping of several (3-indolizinyl)methylcarbenes from 2-enynylpyridines.[10]

We recently disclosed that appropriately paired alkynes can engage one another to produce carbene intermediates (Figure 1b).[11] A wide variety of shelf-stable, electrophilic alkynes **B** (EWG = electron-withdrawing group) were shown to engage the nitrogen atom of many different classes of nitrogen heterocycles containing the 2-alkynyl imine substructure shown in **A** to produce the generic carbene **C**.[12] This intermediate has the character of its two principal resonance contributors [zwitterionic (**C**±) and carbenic (**C:**)]. Carbene **C** demonstrated a host of reactivities that are hallmarks of

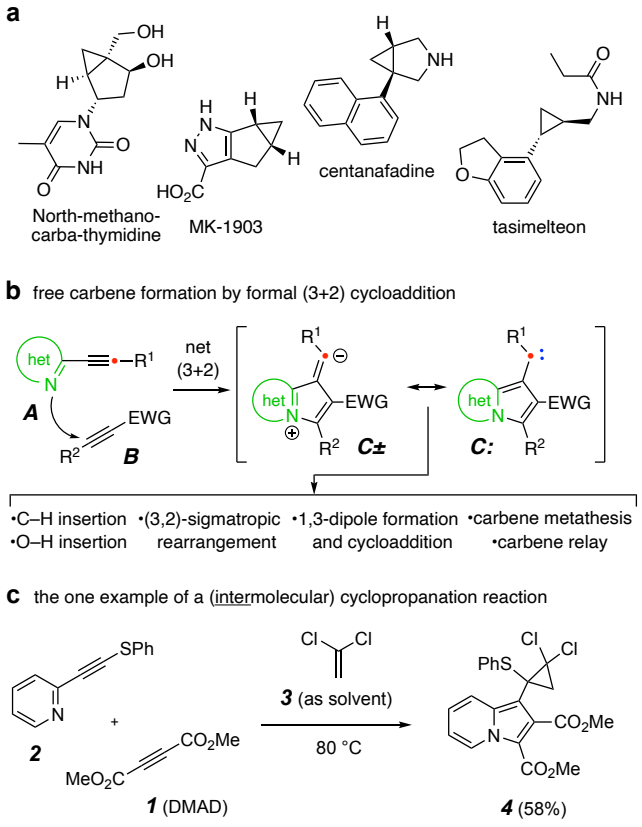

Figure 1. a) Heterocyclic cyclopropanes representative of a large number of compounds pursued in drug-discovery campaigns.[3] **b)** 2-Alkynyl iminoheterocycles **A** react with electron-deficient alkynes **B** in a formal (3+2) reaction giving rise to intermediate free carbenes **C**. **c)** Our first example of a cyclopropanation reaction initiated by a free carbene derived from an alkyne.

carbene character. We reported there a lone example of a cyclopropanation reaction of one of the free carbenes (Figure 1c). When the 2-alkynylpyridine derivative **2** was warmed with DMAD (**1**) in a 1,1-dichloroethene (**3**) solution, the cyclopropane **4**, the result of

an intermolecular capture of the free carbene, was formed as the only isolable product.

In view of this proof-of-principle cyclopropanation reaction, we were naturally drawn to study analogous intramolecular variants (Figure 2) and report our results here. For most of these new cyclopropanations, we purposely chose to hold constant the DMAD (**1**) and 2-alkynylpyridine scaffold as the substrate pair to better focus attention on potential variations in efficiency associated with the nature of the tethering and the alkene on the remote terminus of the 2-alkynylpyridine (see **5a-j**, Figure 2). When each of these pyridine derivatives was warmed in a 1,2-dichloroethane (DCE) solution, it gave rise, via carbene **D**, to the corresponding indolizine-containing product **6a-j** as the only isolated product, formed in generally good yield. Substrates **5a-f** are all based on a gem-dimethylated[13,14] ether linkage connecting the alkynyl pyridine to its tethered alkene. The degree of substitution on an unactivated alkene does not appreciably change the outcome (**6a** vs. **6b**). Both 5- and 6-membered oxasilacycles were formed with similar efficiency (**6c** vs. **6d**). The heteroaromatic "alkenes" in the furan **5e** and the indole **5f** both engaged the carbene, producing **6e** and **6f**, although the latter in more modest yield compared with all of the other reactions of **5a-j**. Several additional substrates containing other types of tethers were shown to be effective. The *N*-diallyl amide **5g** reacted somewhat more slowly than any of the other pyridines, likely a reflection of slightly reduced nucleophilicity of the pyridine nitrogen atom (see later discussion), but still proceeded smoothly. Substrates **5h-j** whose tethers contain embedded aryl groups behaved well, leading to benzofuran (**6h** and **6j**) or benzopyran (**6i**) derivatives. The hindered cyclopropane product **6j** could be isolated as a pair of diastereomeric atropisomers. Heating each individually resulted in slow degradation but gave no sign of their interconversion. Nearly all of the other products **6a-i** showed atropisomerism in their NMR spectra but were indistinguishable on the "chromatographic timescale."

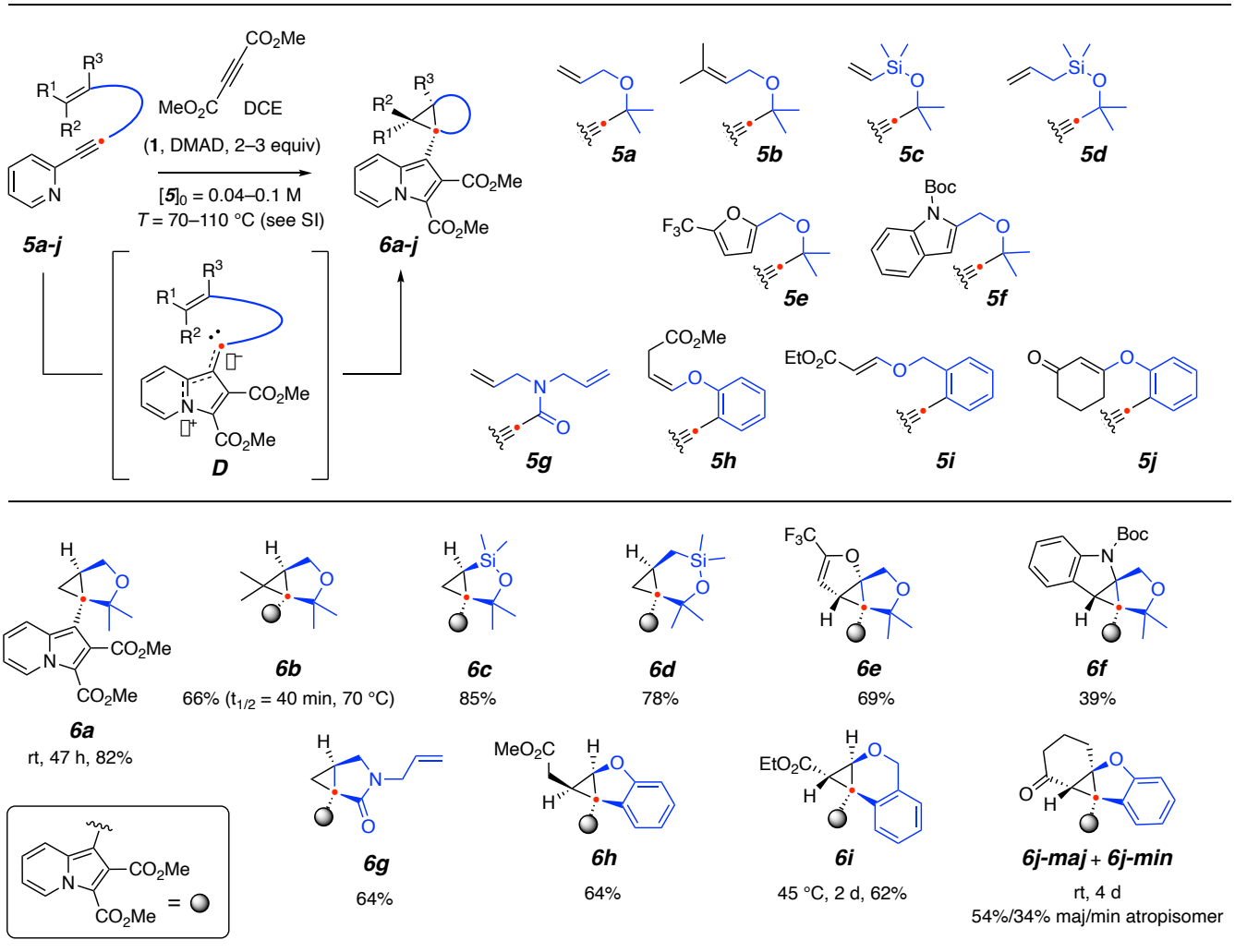

Figure 2. 2-Alkylypyridines containing tethered alkenes (**5a**–**j**) reacting with DMAD to produce a series of structurally diverse fused cyclopropanes **6a**–**j**.

The cyclopropanation reaction is by no means limited to pyridine derivatives or to DMAD (Xu showed[11] that 13 different types of iminoheterocycles **A** and 11 different types of electrophilic alkynes **B** participated in the generic carbene forming reaction shown in Figure 1b). Other 2-alkynyl iminoheterocycles are demonstrated here by derivatives of a thiazole (**7**), an *N*-methylbenzimidazole (**9**), a quinoline (**11**), and a pyridazine (**13**) (Figure 3a). Each participated in the overall cyclopropanation process in good to

excellent yields (Figure 3a). The thiazole, quinoline, and pyridazine precursors reacted more slowly, likely a reflection of reduced nucleophilicity of the heterocyclic nitrogen atom. We also showed that DMAD was not required as the electrophilic alkyne partner (Figure 3b). When heated under similar conditions to the analogous reaction using DMAD, **5g** reacted with the trifluorobutynoate **15** to afford the trifluoromethyl functionalized indolizine cyclopropane product **16** (62%). *o*-Benzynes are also electron-deficient alkynes; therefore, we hypothesized that when heated in the presence of allyl ynoate **18**, the hexadehydro-Diels–Alder (HDDA) precursor **17** would initiate a HDDA/formal (3+2)/cyclopropanation cascade. Through the intermediacy of HDDA benzyne **E**, triyne **17** could in fact be converted to the cyclopropane product **19** (36%). We also explored the behavior of the butadiynyl pyridine **20**, the ethynylog of the monoyne **5c** (Figure 3c). This substrate led to the formation of, mostly, the alkyne substituted cyclopropane **21** (76%) via a propynylidene species (**F**) as well as a small amount of a 2:1 adduct[11] **22** (see SI for a mechanistic rationale).

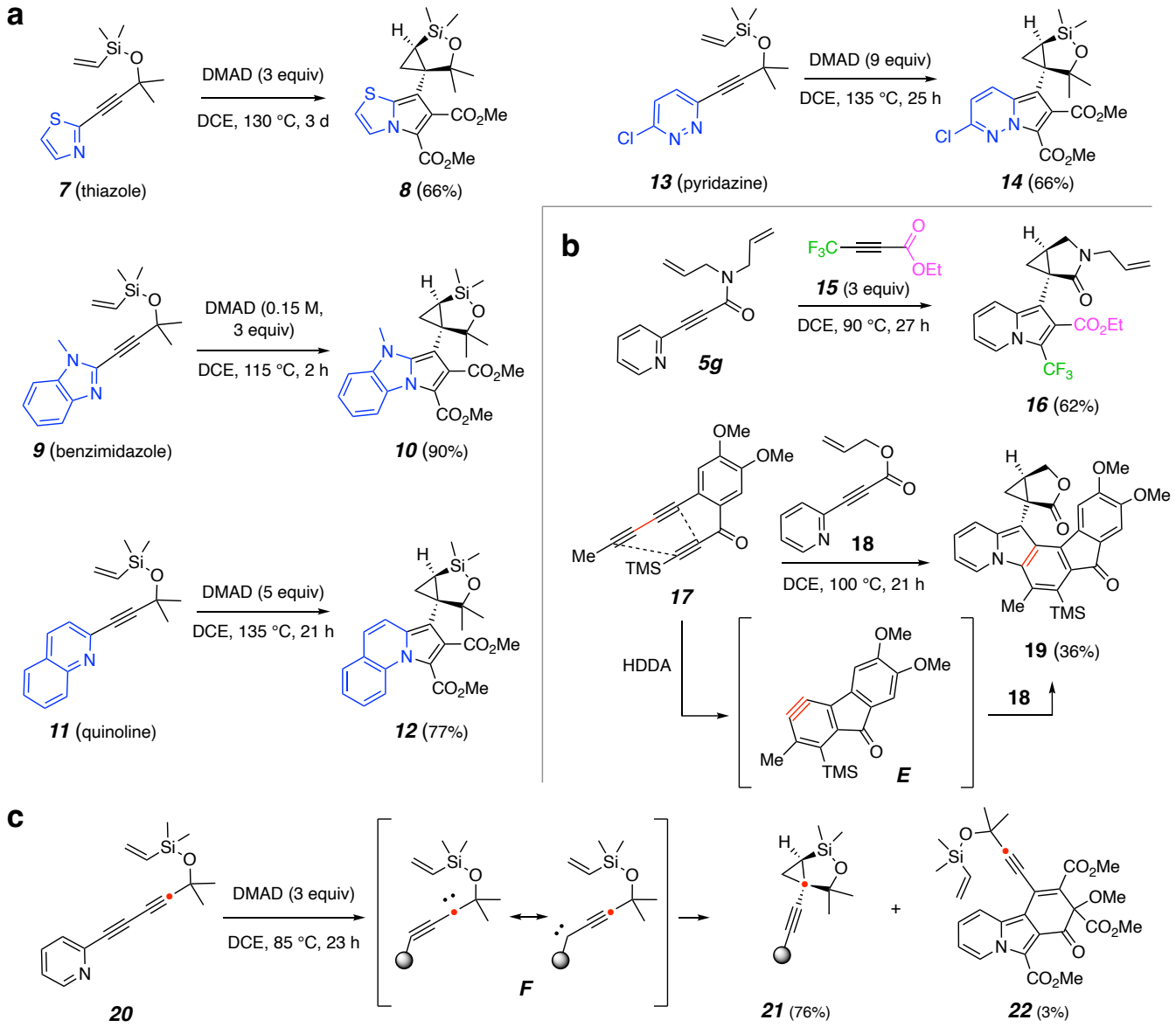

Figure 3. Cyclopropanation reactions involving **a)** other iminoheterocycles, **b)** non-DMAD electron-deficient alkynes, and **c)** a diyne (ethynylog) precursor.

Two substrates with an ester embedded within the alkene tether were examined. Each demonstrated a type of reaction process that competes with the cyclopropanation. The acrylate **23** (Figure 4a) was used to probe whether an electron-deficient alkene would engage the carbene. However, a faster [2,3]-sigmatropic rearrangement of the carbene[11] **G** occurred instead, giving **24** as the only product isolated following purification of the reaction mixture. The allyl ynoate **18** (Figure 4b), like the amide substrate **5g**, has an electron-withdrawing group directly bound to the alkyne terminus. Like **5g**, it reacted somewhat more slowly than most of the other substrates ($t_{1/2}$ ca. 15 h for **18** vs. 40 min for **5b**, both at 70 °C; see SI, Section III). Presumably the reduced nucleophilicity of the pyridine nitrogen atom in **18** (or **5g**) slows the rate of engagement of a DMAD molecule. The ynoate **18** gave the cyclopropane **25** as the predominant product, but this was accompanied by a small amount of the unusual 2:1 adduct **26**. Assigning the structure of this unexpected side product was initially perplexing until we learned that allylic-allylic, 5-bond couplings (both trans and cis) in

1,4-cyclohexadiene (and, presumably, its derivatives) is surprisingly large: 8.0 and 9.6 Hz, respectively.[15] The allylic methine proton in **26** shows coupling to each of the remote methylene protons of 8.3 Hz. Formation of this side product can be rationalized by a C–H insertion event within the carbene **H** that is competitive with the cyclopropanation. The resulting β-lactone **I** can then eject carbon dioxide giving the diene **J**, whose [4+2] Diels-Alder reaction with a second molecule of DMAD accounts for formation of **26**.

The concentration of DMAD can influence the rate of events that compete with carbene formation. For example, the benzimidazole **9**, in the presence of a higher concentration of DMAD (0.5 vs. 0.15 M in the Figure 4c vs. 3a reactions), formed predominately the previously unobserved 2:1 adduct **27** (77%) in addition to the (now) minor cyclopropane product **10** (23%). The zwitterionic intermediate **K** may proceed to a carbene intermediate via a 5-*exo-dig* cyclization or engage a second equivalent of DMAD in a formal (4+2) cycloaddition to generate **27**.

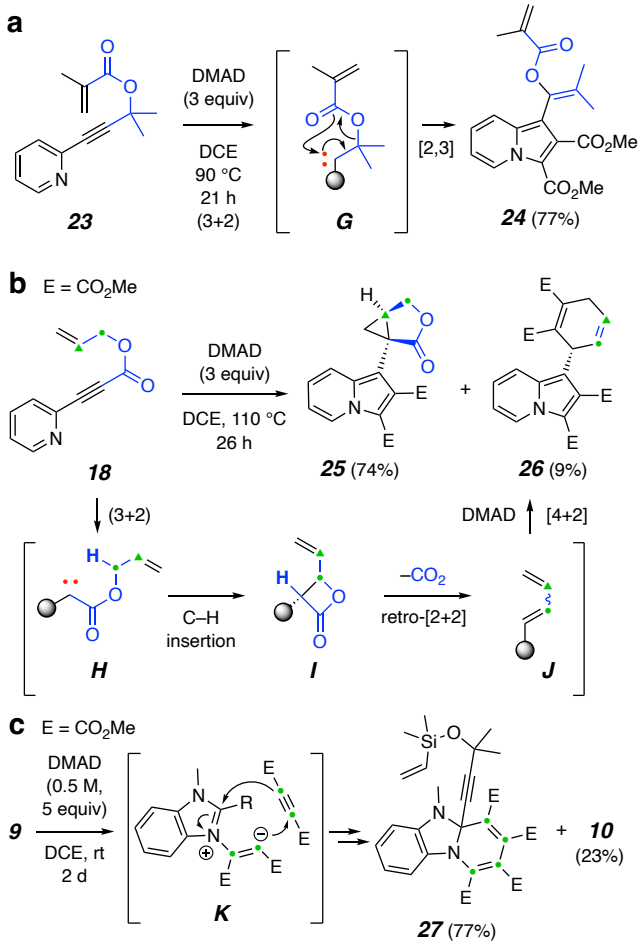

Figure 4. Substrates reacting to give non-cyclopropane-containing products arising from: **a)** 1,2-ester migration, **b)** an intramolecular CH insertion leading to the minor product **26**, which has incorporated two equivalents of DMAD and lost CO_2, and **c)** cycloaddition of zwitterionic intermediate **K** with DMAD to generate the 2:1 adduct **27**.

The furan-containing precursor **28** was designed to further explore aspects of dearomative cyclopropanations (Figure 5a). This ynone substrate required heating at 60 °C for several days to reach high conversion. Instead of a cyclopropane-containing product, we isolated the pair of enal geometric isomers **29-Z** (54%) and **29-E** (4%). Wenkert and co-workers had reported similar reactivity using rhodium carbenoid complexes of substrates bearing pendant furans.[16] They suggested that cyclopropane intermediates were not formed; rather, that the purported metallacyclic intermediates cleaved to generate the enal products. We propose here that the free carbene *does* cyclopropanate the tethered furan (cf. **6e**, Figure 2) to produce, now, the transient species **L**. However, this intermediate, a donor-acceptor (push-pull) activated cyclopropane,[17] is susceptible to facile ring-opening and readily proceeds under the thermal reaction conditions to the fragmentated dienal **29-Z** either in a concerted fashion or, perhaps, via the intermediate zwitterion **M**. We also observed that the cis enal isomer **29-Z** readily photoisomerizes in ambient light to the more thermodynamically stable trans enal **29-E**, a phenomenon that Wenkert and co-workers also had seen.

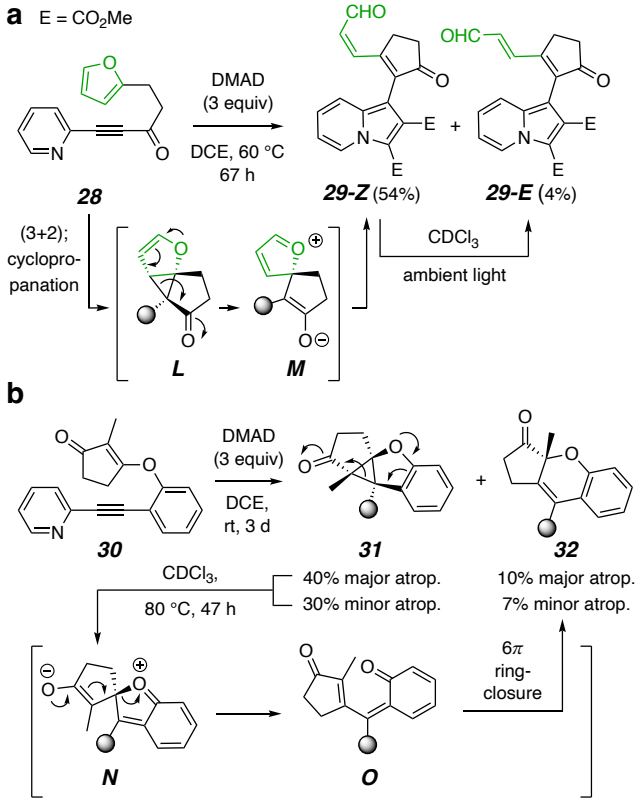

Figure 5. Donor-acceptor cyclopropanes as labile intermediates that proceed to fragmentation products. (gray ball = the 2,3-dicarbomethoxy-1-indolizinyl moiety)

The vinylogous ester **30** was prepared next to examine whether a tetrasubstituted and highly polarized alkene would participate in the cyclopropanation reaction (Figure 5b). When the reaction with DMAD was carried out at room temperature, the fully substituted, hindered cyclopropane **31** was isolated as two, chromatographically separable atropisomers in a 70% combined yield. Additionally, a minor amount of the isomeric benzopyran derivatives **32** was isolated (10% and 7%), again as a separable pair of atropoisomers. When the major isomer of the cyclopropane, **31-maj**, was heated at 80 °C for 47 h in $CDCl_3$, it fully transformed to the same 10:7 equilibrium ratio of **32-maj**:**32-min**. The **31-min** at the same temperature also converted to the same ratio of products **32**, albeit more slowly than its diastereomer, **31-maj**. Thus, the cyclopropane is indeed an intermediate enroute to **32**. To account for this conversion, the cleavage of the strained ring in either of the atropisomeric push-pull cyclopropanes is accompanied by loss of benzenoid aromatic character. The spirocyclic zwitterion **N** can then ring-open to the ortho-quinone methide derivative **O**, now a common inter-

mediate from either of the precursors **31-maj** or **31-min**. A final 6π electrocyclization step generates **32**.

We demonstrated a formal *inter*molecular cyclopropanation by disassembling the tether between the carbene and engaging alkene: namely, desilylation of the siloxane **6c** (Figure 6). Treatment with TBAF afforded alcohol **33** (94%), a process that included desilylation of the cyclopropane ring.[18] Alternatively, the cyclopropane ring could be derivatized to the corresponding cyclopropanol **34** under Fleming–Tamao oxidation conditions in excellent yield (98%).

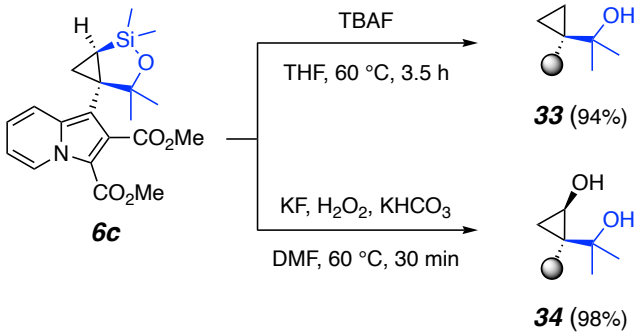

Figure 6. Silicon-containing tether removal via **a**) net protodesilylation or **b**) Fleming-Tamao oxidative cleavage to produce a cyclopropane or cyclopropanol derivative.

In conclusion, a series of multicyclic, fused-ring cyclopropane derivatives has been synthesized via the capture of intermediate free carbenes by pendant alkenes. Various 2-alkynyl iminoheterocycles engage electron-deficient alkynes to produce the transient carbenes that undergo the intramolecular cyclopropanation. Notably, the metal-free carbenes and the derived cyclopropane products retain all of the atoms of the reactants and arise simply by combining reactivity-matched pairs of shelf-stable alkyne substrates; the high potential energy of those alkynes fuels the formation of the reactive carbene intermediate. A 2-(1,3-diynyl)pyridine substrate bestowed carbenic reactivity at the more remote alkyne to produce an alkynyl cyclopropane via a propynylidene, a rare carbene species that has been studied principally for its fundamental reactivity and spectroscopic properties[19] rather than for its synthetic utility. Furan and indole dearomatizations were demonstrated. In some instances, further fragmentation products derived from labile donor-acceptor cyclopropane species were observed. A removable siloxane tether could be excised to achieve formal *inter*molecular cyclopropanations and the synthesis of cyclopropanol derivatives.

ASSOCIATED CONTENT

Supporting Information

Details for the preparation and characterization of all new compounds (**S2**, **S4**–**S7**, **S9**, **S11**, **S13-E**, **S13-Z**, **S14-E**, **S14-Z**, **S15**, **S16-E,E**/**S16-Z,E**, **S16-E,Z**/**S16-Z,Z**, **S17**, **S19**, **S20**, **5a**–**5j**, **6a**–**6i**, **6j-maj**, **6j-min**, **7**–**14**, **16**, **18**–**28**, **29-Z**, **29-E**, **30**, **31-maj**, **31-min**, **32-maj**, **32-min**, **33**, and **34**) and copies of their 1D and selected 2D NMR spectra (^{1}H and ^{13}C) (PDF).
FAIR Data (FID for Publication) of the raw NMR data files for the above new compounds (.zip) and a master metadata file (Word).

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Notes

None of the authors has a conflict with any of the work reported here.

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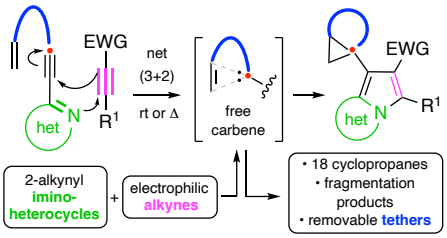
TOC Graphic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