Free carbenes from complementarily paired alkynes

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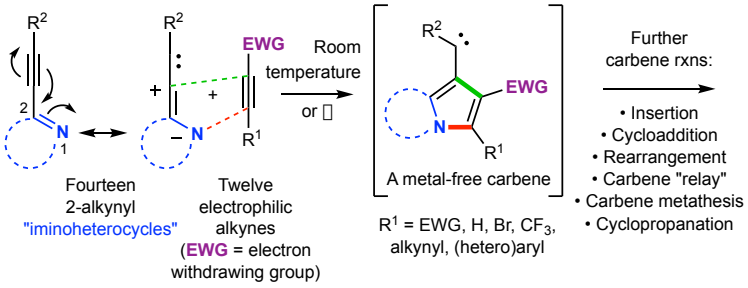
Abstract

Carbenes (R^1R^2C**:**) [like radicals, arynes, and nitrenes] constitute a significant family of neutral, high-energy, reactive intermediates – fleeting chemical entities that undergo rapid reactions. An alkyne ($R^3C{\equiv}CR^4$) is a fundamental functional group that houses a high degree of potential energy; however, the substantial kinetic stability of alkynes renders them conveniently handleable as shelf-stable chemical commodities. The ability to generate metal-free carbenes directly from alkynes, fueled by the high potential (that is, thermodynamic) energy of the latter, would constitute a significant advance. We report here that this can be achieved simply by warming a mixture of a 2-alkynyl-iminoheterocycle (a cyclic compound containing a nucleophilic nitrogen atom) with an electrophilic alkyne. We demonstrate considerable generality for the process: many shelf-stable alkyne electrophiles engage many classes of (2-alkynyl)heterocyclic nucleophiles to produce carbene intermediates that immediately undergo many types of transformations to provide facile and practical access to a diverse array of heterocyclic products. Key mechanistic aspects of the reactions are delineated.



Main Text

Alkynes comprise a fundamental functional group in organic chemistry, prominently appearing among the early chapters in most introductory textbooks on the subject. The parent member, acetylene (HC≡CH), was discovered in 1836.[1] An alkyne is unique because it combines the fundamental property of having an inherently high level of potential energy (thermodynamic instability) yet is relatively slow to engage in chemical transformations (kinetic stability); as such, it resides at the bottom of an energetically high-lying, yet very deep, well on a potential energy surface (cf. ethane vs. ethene vs. ethyne, Fig. 1a). In contrast, reactive intermediates (RIs) in organic chemistry, defined by having relatively short lifetimes (e.g, most carbenes, radicals, nitrenes, and arynes), also possess high levels of potential energy; however, in contrast to alkynes, RIs have inherently low energies of activation (i.e., are situated in shallow wells), causing them to undergo rapid chemical transformations.

The potential energy of an alkyne, once released from its kinetic cage, can serve as thermodynamic fuel to drive many classes of reactions. These include myriad i) transition metal-catalyzed cyclizations such as click reactions,[2,3,4] Larock indole synthesis,[5,6] (2+2+2) cyclizations,[7,8] and Pauson-Khand[9,10,11] reactions and ii) thermal cycloisomerization reactions to generate strained RIs such as arynes,[12,13,14,15] cyclic allenes,[16,17] and α,3-

dehydrotoluenes.[18,19,20] In all of these thermal-only reactions, the intrinsically high potential energy of the alkyne plays a crucial role in powering the formation of RIs by overcoming the energy penalty of forming a strained or valency-deficient entities.

Carbenes are neutral, divalent, electron-deficient species in which the carbon atom contains a pair of non-bonded electrons and has only six rather than the eight valence electrons typical for the vast majority of carbon atoms in molecules. They typically are quite reactive intermediates having only a fleeting lifetime. The earliest report of a reaction involving a free carbene [$EtO_2C(H)C$:] dates to 1903.[21] It was not until 1959 that the simplest carbene, methylene (H_2C:), was first experimentally identified,[22] although an insightful earlier suggestion in the literature of its reactivity was envisioned by Donald Duck ("If I mix CH_2 with NH_4 and boil the atoms in osmotic fog, I should get speckled nitrogen."[23,24]). Free carbenes (cf. **3**) are often generated from the thermal or photochemical activation of diazo compounds (**1**)[25] or diazirines (**2**),[26] where concomitant release of highly stable N_2 gas serves as the thermodynamic driving force (Fig. 1b). In the presence of a transition metal complex, metal-carbenes (i.e., carbenoids, **4**) can be generated from the same precursors.[27,28] Another well-established approach to producing free carbenes is the base-promoted α-elimination of halogenoforms (**5**).[29] The resulting intermediate is a dihalocarbene (**6**). *N*-Heterocyclic carbenes (NHCs, e.g., **8**)[30] are considerably stabilized (and rendered isolable) by donation of non-bonding electron density from the N and Y heteroatoms (Y = NR, O, S[31]). NHCs are typically prepared by the deprotonation of amidinium ion **7** (compare Fig. 1b).

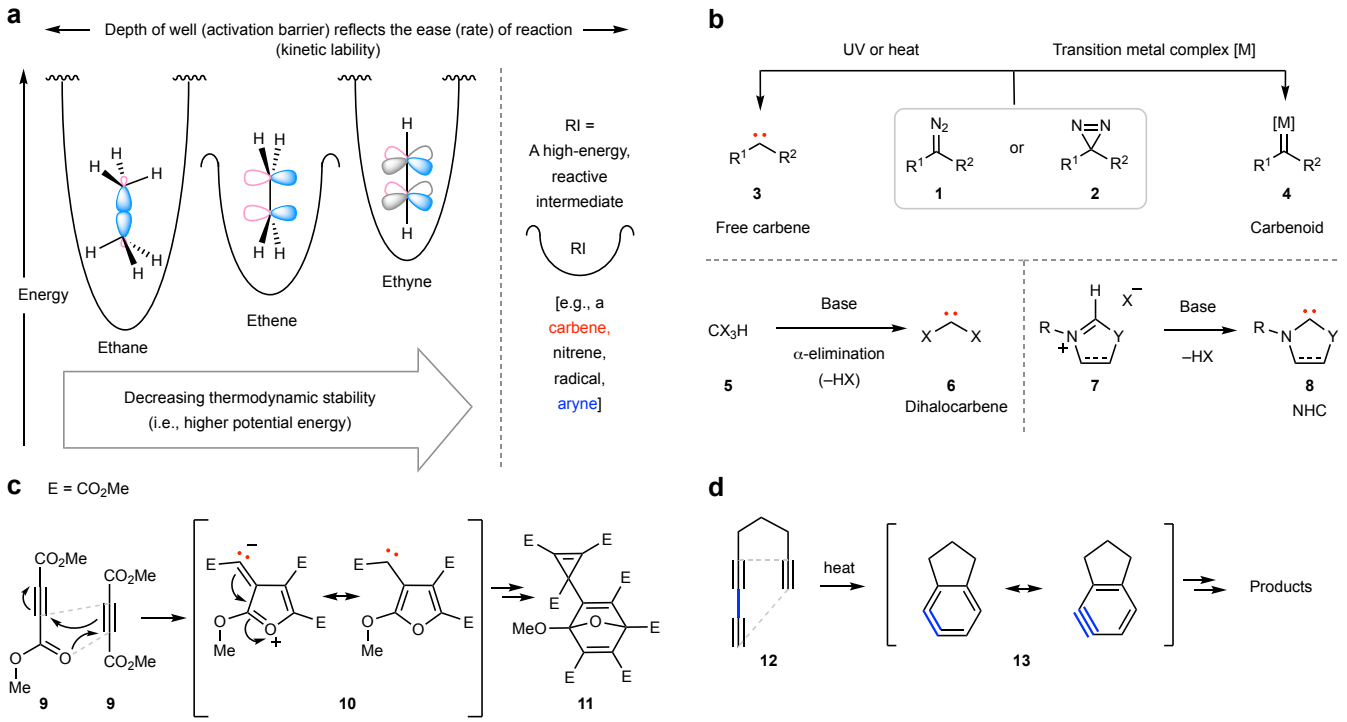


Fig. 1 | The high potential energy (thermodynamic instability) of alkynes can drive the formation of reactive intermediates. a, A C≡C has characteristically high potential energy when compared with its more saturated C=C and C–C analogs; it has relatively higher kinetic stability compared with reactive intermediates (RIs). **b**, Classical methods for carbene generation: Free carbenes and carbenoids are frequently produced with the ejection of N_2 gas as the driving force. Base-promoted eliminations are employed to generate dihalocarbenes and NHCs. **c**, The alkyne units in dimethyl acetylenedicarboxylate molecules can fuel formation of a free carbene intermediate under thermal-only conditions. **d**, Three alkyne units can fuel formation of an (reactive) aryne intermediate under thermal-only conditions. [a]NHC = *N*-heterocyclic carbene

The valency-deficient nature of carbenes confers high reactivity: for example, they readily add to π-bonds to form strained cyclopropanes (from alkenes) or cyclopropenes (from alkynes, cf. **10** to **11**); they can also insert into (strong) σ-bonds (cf., **19** to **17**). Each of these classes of reaction involves formation of two new σ-bonds in the product at the expense of only one π- or σ-bond in the reactants. Despite their high reactivity, carbenes can often be tamed to participate in many useful transformations having a high degree of chemo-, regio-, and/or stereoselectivity; these usually involve the use of carbenoids **4**.[27,28]

In principle, intrinsically high potential energy alkynes can be used to produce high-energy, reactive carbene intermediates. We can locate only two examples of a transformation in which a free carbene has been proposed as an intermediate formed from an alkyne under metal-free reaction conditions.[32,33] The fascinating tetramerization of dimethyl acetylenedicarboxylate (DMAD, **9**) to give the cyclopropene-containing adduct **11** (Fig. 1c) was rationalized as involving the intermediacy of carbene **10**.[32] An analogous multicyclization between (the strained) cyclooctyne and DMAD produced a similar cyclopropene-containing product.[33] The use of alkynes as thermodynamic fuel is further epitomized by the formation of highly strained benzyne intermediates (Fig. 1d). When appropriately tethered, for example, as in the nonatriyne **12**, three alkyne units can engage in a net (4π+2π) cycloisomerization reaction to produce the isomeric benzyne **13**.[12,13] This process has subsequently been shown to have considerable generality.[15]

During the course of an otherwise unrelated study of reactions between hexadehydro-Diels-Alder (HDDA) derived benzynes (e.g., **14** to **16**, Fig. 2a) and conjugated enynes, we attempted to use the enyne in the 2-(1-alkynyl)pyridine **15** as a potential trapping agent for the reactive benzyne **16**. Instead, an unexpected and remarkably clean reaction was observed – namely, the oxasilacycle **17** was formed in an 82% isolated yield when **14** was heated in the presence of **15**, which happened to contain a triisopropylsilyl (TIPS) substituent. Formation of the silacycle can be rationalized by insertion into a tertiary C–H bond of one of the isopropyl groups on the TIPS-ether by the carbon atom denoted by ▲. We propose that the reaction of the electrophilic benzyne **16** begins with nucleophilic attack by the nitrogen atom in the pyridine **15**, giving rise to the zwitterion **18**.[34] A 5-*exo-dig* cyclization converts **18** to the carbene species **19** (cf. the resonance contributors in **10**, Fig 1c), which then converts to the product **17** by an intramolecular 1,5-C–H insertion. In this cascade cyclization, four new C–C bonds, one C–H bond, and one C–N bond are formed, fueled by the consumption of four alkynes.

This result provided an exciting opportunity and led us to hypothesize that other, electrophilic and shelf-stable alkynes would participate in similar processes. If so, this would greatly expand access to free carbene intermediates from alkynes as well as potentially provide novel ways to make structurally diverse, N-containing heterocycles. We elected to first test this idea using the reaction between DMAD (**9**) and 2-(2-isopropylethynyl)pyridine (**20**, Fig. 2b). To our delight, heating these two substances in 1,2-dichloroethane (DCE) at 110 °C quickly produced the indolizine **22** (61% following isolation). This outcome, again, can be rationalized via insertion into the (now vicinal) C–H bond of an isopropyl group in the carbene **21**. The same reaction could also be observed to proceed, albeit more slowly, at room temperature (nearly full conversion after 24 h). A related reaction between 2-(2-phenylethynyl)pyridine and DMAD to produce an indolizine has been reported.[35] In that instance, incorporation of a protic alcohol molecule by net O–H insertion was observed; however, there is no indication that a carbene was considered as an intermediate on the reaction pathway. Numerous reactions of simple pyridine derivatives (not having a 2-alkynyl substituent) with electrophilic alkyne partners proceed by way of initial (and rapid[36,37]) zwitterion formation; however, none then produce carbene intermediates.[38]

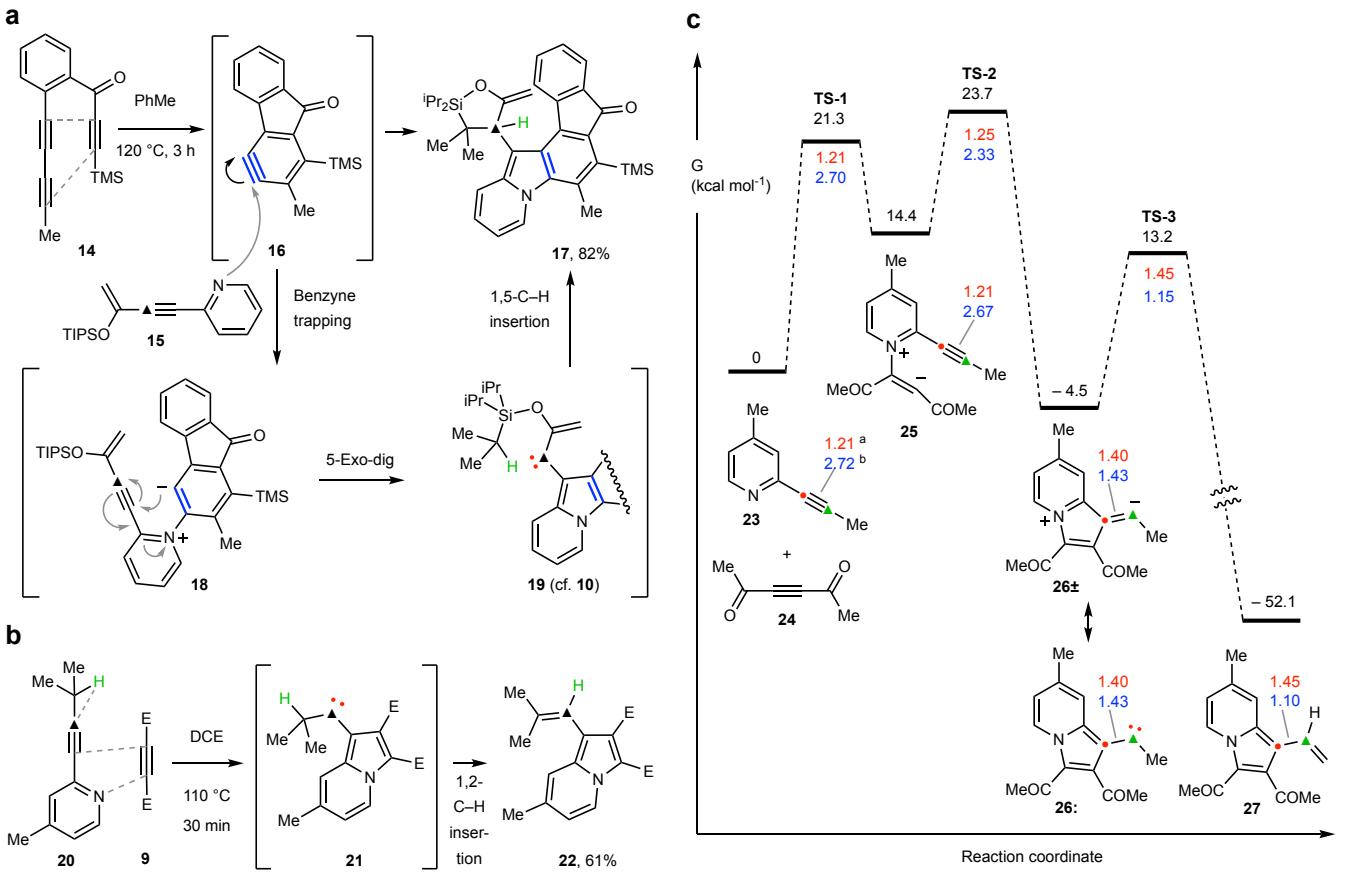


Fig. 2 | Two early reactions suggest the formation of carbene intermediates (further supported by DFT computations) enroute to indolizine-containing products. a, Reaction between the pyridine derivative **15** and the HDDA-benzyne **16** gave rise to the polycyclic product **17** via 1,5-C–H insertion from the carbene **19**. **b**, Reaction between the pyridine derivative **20** and DMAD (**9**) furnished the indolizine **22** via 1,2-C–H insertion from the carbene intermediate **21**. **c**, Potential energy surface of the reaction between model compounds **23** and **24** that leads to the indolizine **27** computed by DFT [SMD (dichloroethane)/B3LYP-GD3BJ/6-311++G(d,p)]. [a]Numbers in red and blue indicate the progression (from **23** to **26** to **27**) in the change in bond length (longer) and bond order (lower) between the red (●) and green (▲) atoms. [b]Bond orders obtained using the Wiberg bond index.[40]

To gain more insight into the reaction pathway, we turned to DFT computations to construct a potential energy surface (Fig. 2c). We chose the model pyridine and ynedione derivatives **23** and **24** to simplify the conformational landscape. The stepwise (3+2) reaction between **23** and **24** begins with the formation of zwitterionic adduct **25** arising via **TS-1** from nucleophilic conjugate addition of the pyridine N-atom to an ynedione alkyne carbon. This zwitterion can then undergo a 5-*exo-dig* cyclization via **TS-2**, giving rise to the hybrid of resonance contributors **26±** and **26:**, formulations that, together, reflect a degree of polarization in this carbene species. Natural bond orbital (NBO)[39] analysis was used to identify the Wiberg bond index,[40] which gave a bond order (blue font) between the red and green carbons in **26** of 1.43. This value is consistent with a hybrid of, in the extremes, strictly zwitterionic character (bond order essentially 2) and localized carbene character (bond order essentially 1). A significant portion of negative charge (–0.22, Hirshfeld) is also observed at the green carbon atom. Notably, despite the valence bond deficiency within the carbene **26**, it has lower Gibbs energy compared to the alkyne precursors **23** and **24**. This transformation is another example in which the high potential energy of alkynes can fuel the formation of a RI, here a divalent carbene. The process is consummated by the

indicated 1,2-C–H insertion event within **26**, which accounts for the formation of the alkene in the indolizine product **27**. A final interesting observation is that the bond order[40] between the alkyne carbons in **23** progressively decreases (from 2.72 to 1.10) across each minimum energy stationary state on the potential energy surface.

These results encouraged us to explore other ways in which the carbene intermediate could be exploited to produce indolizine derivatives containing carbene-derived structural elements (Fig. 3). Five insertion reactions (Fig. 3a-d) and four processes proceeding through carbene-derived 1,3-dipoles (Fig. 3e-g) demonstrate this versatility. Specifically, substrate **28** bears a TIPS ether of a tertiary alcohol, a similar trapping agent to that present in the pyridine **15** used in the initial HDDA trapping reaction. Again, efficient insertion into an isopropyl methine C–H bond was observed in the form of product **29** (Fig. 3a). Each of the 2-ethynylpryidine derivatives **30-O** or **30-S**, having a 2-methoxy- or 2-methylthiophenyl appendage at the ethyne terminus, reacted with DMAD to produce the dihydrobenzofuran **31-O** or dihydrobenzothiophene **31-S** by a 1,5-insertion of the carbene into a methyl C–H bond (Fig. 3b). We next showed that the carbene intermediate could be generated from the 2-ethynyl pyridine derivative **32**, which has no remote substituent (Fig. 3c). In this case the carbene was trapped by insertion into an O–H bond of a judiciously placed carbinol, now as a substituent on the pyridine ring, to give **33**. The TMS group in substrate **34** did not hamper the generation of the carbene (Fig. 3d). When DMAD was used in excess (8 equiv.), a mixture of the strained 5,5,6-tricyclic heterocycle **35** (via 1,5-C–H insertion) along with its MeOH-elimination product **36** was obtained as an ca. 3:1 mixture. When the pyridine substrate **34** was used in excess (2.5 equiv.), the enol ether **36** was isolated as the only product, suggesting that **36** is produced by a base-catalyzed elimination of MeOH from **35**. This hypothesis was supported by the observation that treatment of **35** with pyridine (1 equiv.) in DCE at 110 °C cleanly led to formation of **36**.

Unusual products were formed from the reaction between DMAD and the pyridine derivatives **37**, **38**, **45**, and **48**. Each of the first two of these reactions (Fig. 3e) incorporated two molecules of DMAD to produce the tricyclic ketone **39** (74%) or **40** (73%) as the only isolated product. We rationalize this transformation as follows: following a net (3+2) cyclization between the pyridine substrate and DMAD, the carbene intermediate **41** engages the adjacent ester carbonyl oxygen atom to produce the 1,3-dipole **42**. This then undergoes (3+2) cycloaddition with a second DMAD molecule to generate the bridged cyclic ether **43**. Electron density from the indolizine ring in **43** can assist in the opening of the ether bridge, leading via the zwitterionic species **44** to **39** or **40**, respectively. Substrate **45**, differing from **37** only by the presence of a TMS group on the alkyne terminus, gave rise to a now-isolable polycyclic bridged ether, **46** (cf. **43**). At higher temperature, this was shown to rearrange to the ketone **47**, a direct analog of **39** (Fig. 3f). These observations strongly support the mechanism involving a 1,3-dipolar cycloaddition. We also note that substrates **34** and **45**, differing only in the nature of the substituent at C3 of the pyridine, follow exclusive reaction pathways that diverge in the fate of the carbene – insertion into the acetal C–H bond in the former vs. ester carbonyl interception in the latter. Finally, the diyne **48**, incorporating a properly disposed, 1,3-dipolarophile, was reacted with DMAD (Fig. 3g). The isolated tetracyclic ketone **50** arose via the intramolecular cycloaddition shown in **49**.

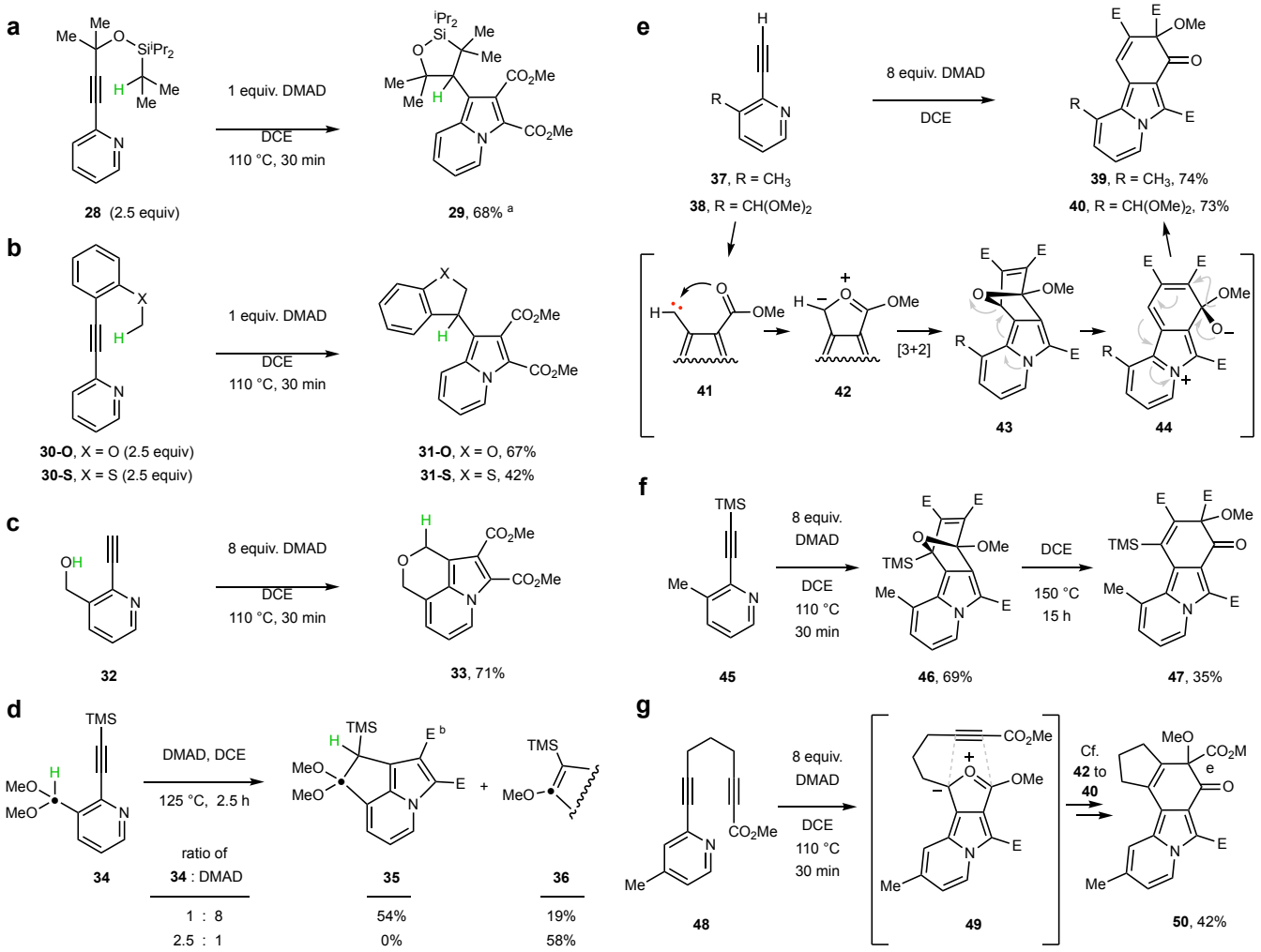


Fig. 3 | Insertion (a-d) and 1,3-dipolar cycloaddition (e-g) reactions of the carbene intermediates. a, Carbene insertion into an isopropyl C–H bond. **b**, Carbene insertion into OMe or SMe C–H bond. **c**, Carbene insertion into an O–H bond. **d**, Formation of a strained 5,5,6-trycyclic product via C–H insertion. **e**, 1:2 Adducts between 2-ethynyl pyridines and DMAD via interception of the carbene by an ester carbonyl oxygen and subsequent 1,3-dipolar cycloaddition. **f**, Isolation of the bridged ether product **46** and its rearrangement to its tricyclic ketone isomer **47** provide support for the proposed reaction pathway. **g**, Intramolecular 1,3-dipolar cycloaddition provides a tetracyclic ketone. [a]##%s indicate the isolated yields following chromatographic purification (silica gel). [b]E = CO_2Me (from DMAD, **9**, EC≡CE).

The smooth reaction between DMAD and 2-ethynyl pyridines motivated us to explore the use of yet other electron deficient alkynes to expand the versatility of the process. As a preliminary step, we first worked to identify a carbene "reporter" group that would efficiently convert the carbene into a robust and stable derivative. After an initial screening of various candidates, we identified a tertiary acetate moiety as an ideal choice for this purpose. The reaction between the pyridine **51a** and DMAD very cleanly produced the enol acetate **54a** (Fig. 4a). Clearly a 1,2-migration of OAc group had occurred (from **52** to **53** to **54**, or, perhaps in a concerted fashion from **52** to **54**). Although similar carbenoid rearrangements are known,[41] we are not aware of any examples of analogous ester rearrangements within a free carbene intermediate. Subsequently, the similar mono-substituted pyridine **51b**[42] was prepared and subjected to a 1-gram scale reaction with a smaller excess of DMAD (1.5 equiv.). This larger scale reaction still proceeded cleanly and delivered the indolizine product **54b** in 82% isolated yield. A control experiment was conducted to check for the intramolecularity of the 1,2-migration of the ester moiety. The

propanoate ester analog of **51b** and DMAD were heated in the presence of added tetrabutylammonium acetate. Only the propanoate ester analog of the indolizine **54b** was observed; the lack of any incorporation of external acetate ion supports the unimolecular nature of the process [Supplementary Fig. 1 and associated text in the Supplementary Information (SI) for details].

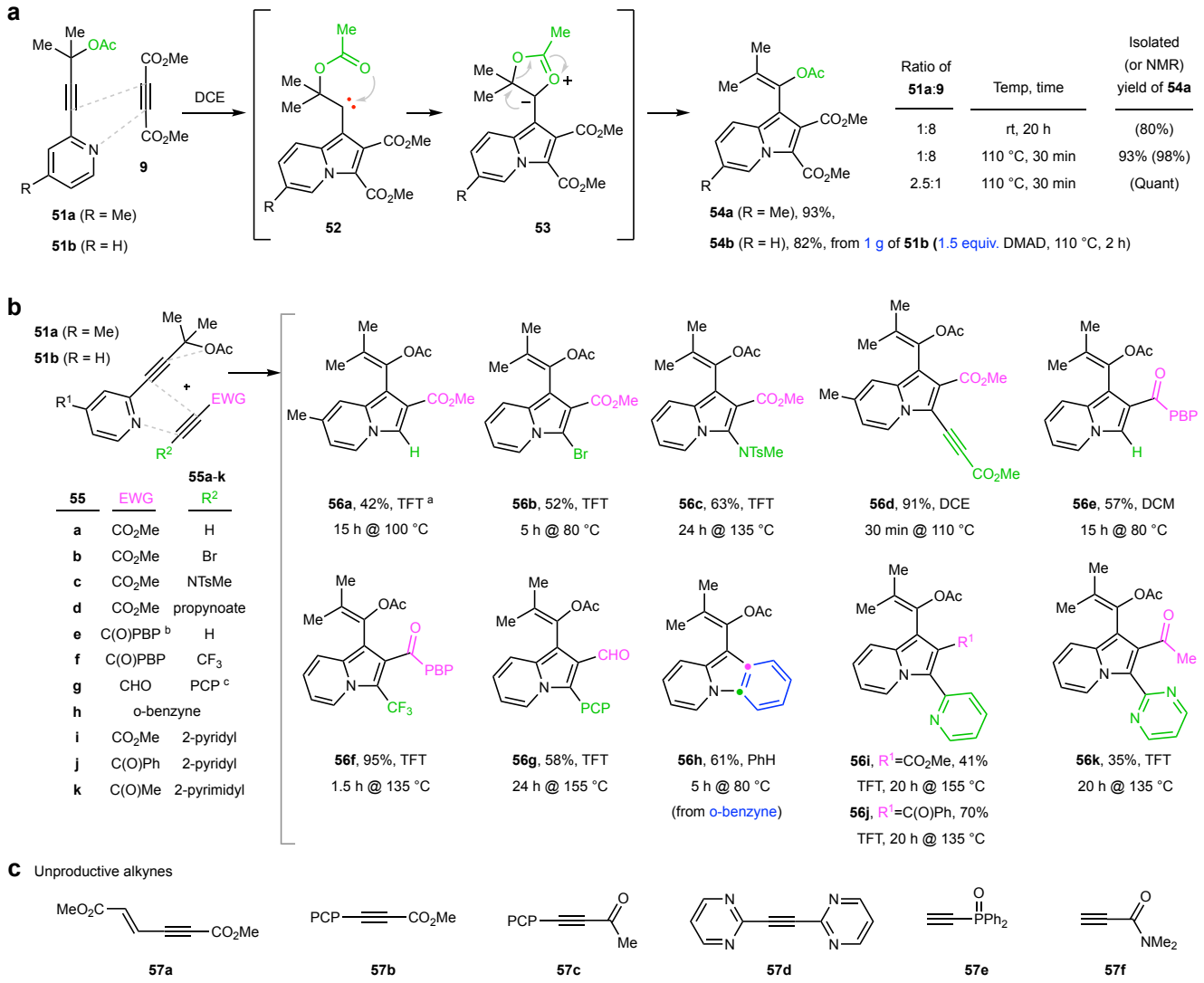


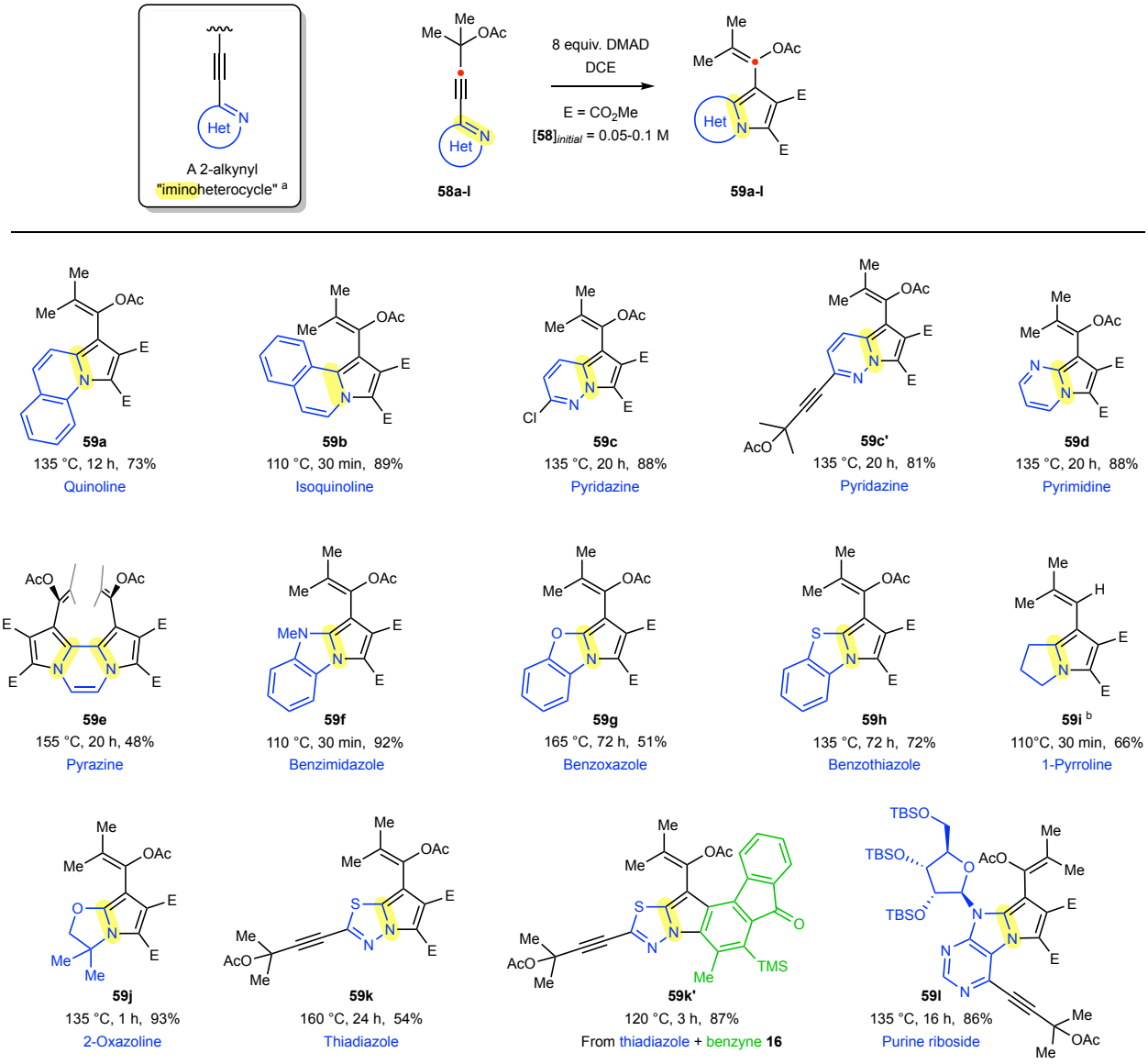
Fig. 4 | Scope of electrophilic alkynes. a, Identification of OAc as an ideal carbene trapping group. **b**, A variety of electrophilic alkynes, including benzyne can engage with 2-ethynyl pyridine derivatives. **c**, Unproductive alkyne substrates. [a]TFT = α,α,α-trifluorotoluene; [b]PBP = *p*-bromophenyl; [c]PCP = *p*-chlorophenyl.

Using the tertiary acetate moiety as the reporter, we proceeded to test a variety of electrophilic alkynes for their ability to participate in carbene and indolizine generation (Fig. 4b). Esters, ketones, and aldehydes were all identified as suitably potent electron withdrawing groups (EWGs). The substituent on the β-carbon of the electrophilic alkyne could be a hydrogen atom or a bromo, sulfonamido, alkynyl, trifluoromethyl, aryl, and heteroaryl groups. *o*-Benzyne was also a productive participant (cf. **56h**). The pyridyl and pyrimidyl products **56i-k** are enticing examples because they suggest the ability of this process to deliver biheteroaryl compounds with interesting topology via a streamlined, modular strategy. Their preparation is additionally notable, because each of the electrophilic alkynes **55i/j/k** also contains a 2-ethynyl "iminoheterocyclic" subunit (i.e., a heterocycle that houses a C=N double bond); in principle these could have undergone homodimerization processes. No evidence

of this was seen; the orthogonal cross-engagement of the electronically differentiated, complementary pairs of substrates predominated. Shown in Fig. 4c are several electron deficient alkynes that were briefly screened and observed to be not readily productive reaction partners; no reaction was observed until the reaction mixtures were heated to considerably higher temperatures, where multiple decomposition events were suggested by NMR and thin layer chromatography (TLC) analyses.

In the examples presented thus far, a pyridine ring was always the nucleophile that initiated the process giving rise to the carbene intermediates. We proceeded to screen a variety of analogs containing iminoheterocycles other than pyridine for their ability to participate in these (3+2) cyclizations (Table 1). Many such heterocycles reacted efficiently and cleanly with DMAD as the prototypical electron deficient alkyne, leading to structurally diverse heterocyclic skeletons as seen in products **59a-l**. The following classes of heteroaromatic substrates were competent: quinoline (**58a**), isoquinoline (**58b**), pyridazine (**58c** and **58c'**), pyrimidine (**58d**), pyrazine (**58e**), benzimidazole (**58f**), benzoxazole (**58g**), benzothiazole (**58h**), thiadiazole (**58k**), and a purine riboside (**58l**). In addition, substrates containing the non-aromatic heterocyclic core 1-pyrroline (**58i**) or 2-oxazoline (**58j**) also participated. Four substrates containing a pair of 2-(1-alkynyl)imine motifs were examined; these theoretically could have engaged two DMAD molecules via bis-cyclization. However, only the 2,3-bisalkynyl pyrazine **58e** produced the corresponding bis-cyclized product, **59e**. The substrates **58c'** and **58k** reacted with only one molecule of DMAD, likely because of the increased steric hindrance around the second N-atom following the first cyclization. Finally, the imidazole N-atom in **58l** is more nucleophilic than the purine N-atom for steric and electronic reasons, accounting for the selectivity in its mono-cyclization to give **59l**.

Table 1 | Twelve distinct classes of 2-alkynyl iminoheterocycles were observed to engage DMAD to produce structurally appealing products via a carbene intermediate



[a]The class of heterocycle present in the precursor is indicated in blue. [b]The pyrroline precursor with a propargylic tertiary acetate proved difficult to prepare, so the substrate in this example contained a 2-isopropylethynyl substituent instead.

Above we described, separately, different modes of carbene trapping (between 2-alkynyl pyridines and DMAD, Fig. 3), the involvement of different electron-deficient alkynes (with 2-alkynyl pyridines via acetate migration, Fig. 4), and the participation of various 2-alkynyl iminoheterocycles (with DMAD via acetate migration, Table 1). To demonstrate additional versatility of the overall process, we have varied some of these elements. First, to further probe aspects of O–H insertion reactions, we examined the series of homologous primary alcohols **60a-d** (Fig. 5a) by reacting each with the ynone **61**. Complete regioselectivity was observed in the formation of indolizine products **62a**–**62d** (compare the location of ketone vs. ester substituents). The homologs **60a/b** gave the cyclic ethers **62a/b** via O–H insertion. The two shorter substrates (homopropargylic and

propargylic alcohols **60c** and **60d**) gave the alkene **62c** and aldehyde **62d**, respectively, albeit each with reduced efficiency. Mechanistic considerations for the origin of these two products is given in the SI (Supplementary Fig. 2). Second, the formation of 2:1 adducts via trapping of an intermediate carbonyl ylide by a second molecule of DMAD was further demonstrated by the conversions of the isoquinoline **63** and the thiazole **65** to **64** and **66**, respectively. Thus, iminoheterocycles other than pyridine (cf. Fig 3e-g) participate in the 1,3-dipole formation and cycloaddition. Third, different combinations of the type of iminoheterocycle (other than pyridine) and different electron-deficient alkyne (other than DMAD) that use two different types of C–H insertion processes are demonstrated in Fig. 5c. The non-aromatic, 5-membered 1-pyrroline derivative **58i** with the hexadiynoate **56d** gave the bicyclic pyrrole derivative **67** following 1,2-C–H insertion. And the aromatic, 6-membered pyrimidine **68** with the unsymmetrical ynoate **69** gave the polycyclic product **70** following 1,5-C–H insertion into the OMe group.

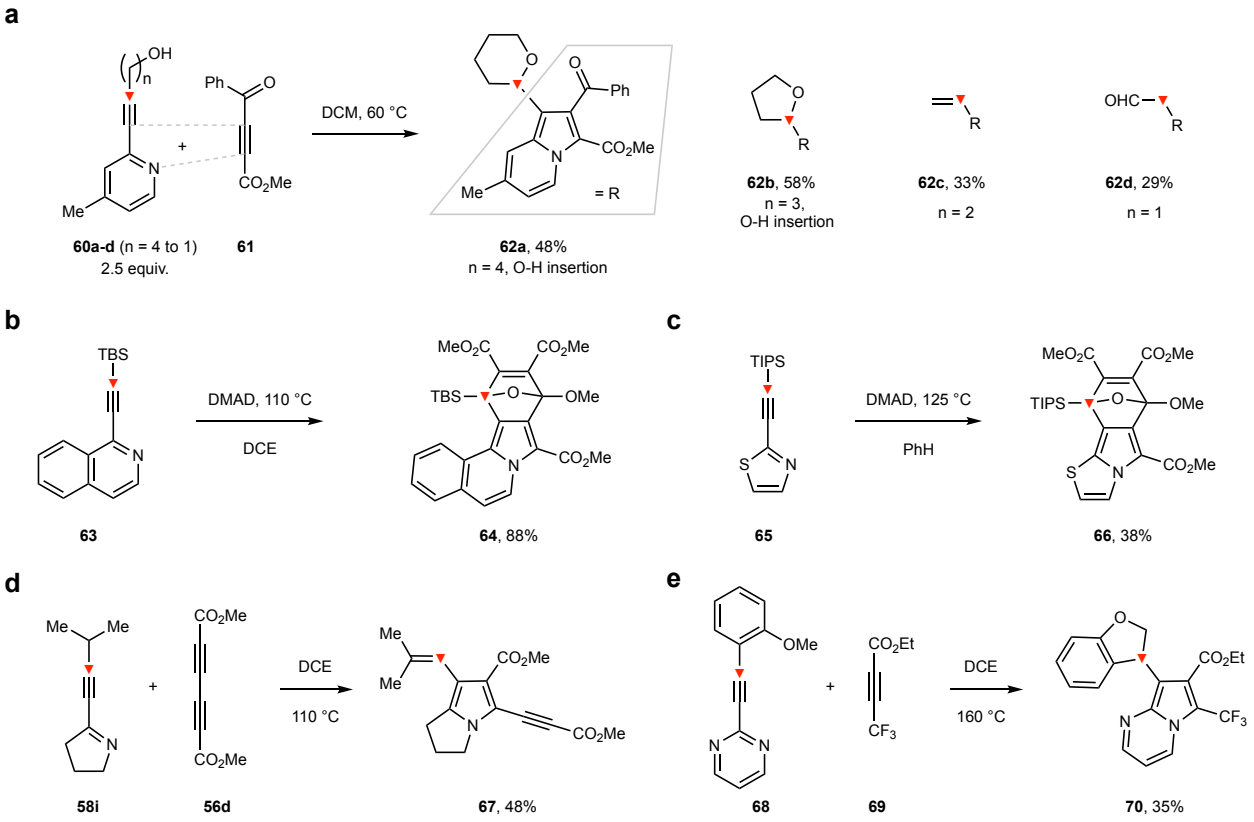


Fig. 5 | Examples in which various arrays of a carbene-capture process, of an electron-deficient alkyne, and of an alkynyl iminoheterocycle are melded. a, O–H insertion reactions of a series of homologous alkynol substrates **60a–d** engaged by an ynone **61**. **b**, 1,3-Dipolar cycloaddition reaction between isoquinoline substrate **63** and DMAD. **c**, 1,3-Dipolar cycloaddition reaction between thiazole substrate **65** and DMAD. **d**, 1,2-C–H insertion using 2-alkynyl pyrroline **58i** and a diyne **56d**. **e**, 1,5-C–H insertion using pyrimidine substrate **68** and ynoate **69**.

We carried out a concluding set of experiments that show unusual reactivity of these N-heterocycle-derived free carbenes. First (Fig. 6a), we used the symmetrical diyne **71** to investigate the possibility of sequential generation of two carbene intermediates from one substrate. Pleasingly, **71** formed a 1:3 adduct with DMAD to cleanly produce the furan derivative **74**. This reaction presumably began with the formation of the ketone intermediate **72** via the first carbene (cf. **38** to **40**, Fig. 3e). The subsequent, now allylic, carbene in **73** was then trapped by a proximal ester carbonyl group to furnish the furan product **74**. Second (Fig. 6b), because a carbene

conjugated to an alkyne [i.e., a propynylidene[43,44,45](cf. propynylidenoids[46,47,48])] is a hybrid of two principal carbene resonance contributors (cf. **76a** and **76b**,), we designed **75**, an ethynylog of the earlier-used substrate **28** (that is, having an additional alkyne unit inserted between two moieties in **28**), to react with DMAD. The carbene character on the ● carbon was captured by the proximal ester carbonyl group and underwent transformation to the ketone **77** as the major product. Competitively, the carbene character on the ▼ carbon inserted into the C–H bond of an isopropyl group in the remote TIPS-ether to afford the oxasilolane **78** as a minor product. Third (Fig. 6c), when the diyne **75** was reacted with the benzyne derived from the triyne **14**, the oxasilolane **80** was obtained as the sole product. The comparative results in Fig. 6b and 6c unambiguously confirmed the delocalized nature of the carbene within the propynylidene derivative **79**; this was further supported by model DFT computations (Supplementary Fig. 4 and associated text). Fourth (Fig. 6d), we discovered a very efficient, three-component reaction between the 2-ethynyl pyridine derivative **81**, DMAD, and trimethyl orthoformate (solvent), which led to the net MeO–H insertion product **84**. This reaction might proceed by the carbene metathesis pathway shown as **82** + $HC(OMe)_3$ (via **83**) to **84** + dimethoxymethylene; this carbene exchange was computed to be exergonic by ca. 24 kcal mol^{-1} (Supplementary Fig. 5). Several experiments aimed at trapping $(MeO)_2C$: were unsuccessful. When a D-enriched (60%) sample of trimethyl orthoformate was used for this reaction (50 vol% in DCM), 14% of D-incorporation at the methoxylated carbon was observed in the product **84-D**. This indicates a kinetic isotope effect of 4.5 if all of the new hydrogen atoms in product **84** come from the orthoformate. Finally (Fig. 6e), the three-component reaction between **85**, DMAD, and vinylidene chloride (**86**) was culminated by a cyclopropanation event leading to **86** as the only observed product. Although several other alkynyl pyridines were not productive in an analogous process, this cyclopropanation chemistry is currently under further investigation.

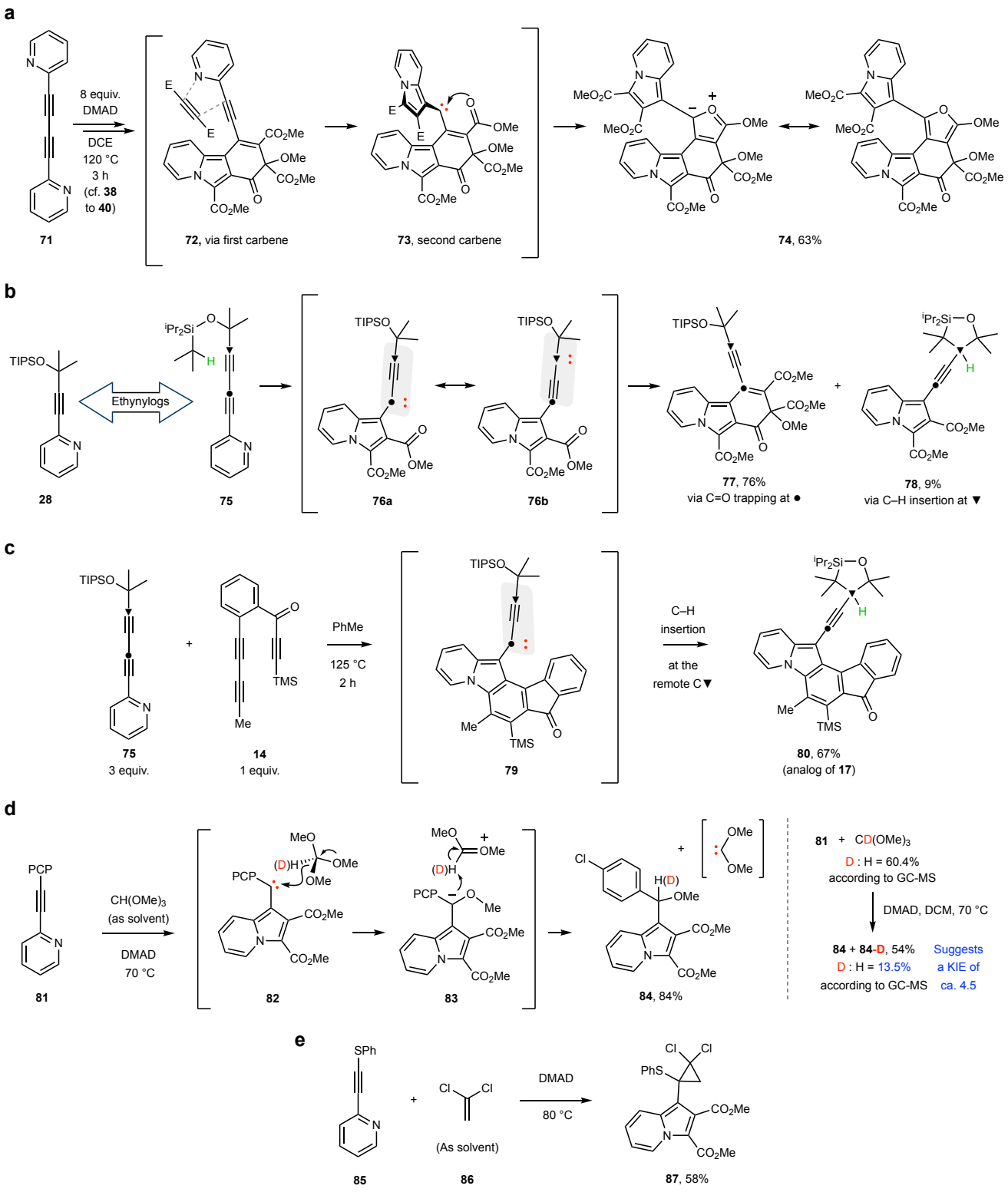


Fig. 6 | A series of unusual transformations. **a**, Sequential generation of two carbene intermediates from the reaction between bipyridine **71** and DMAD. **b**, Formation of two distinct products **77** and **78** provides experimental evidence for the delocalization of the carbene character onto both C● and C▼. **c**, Selective and exclusive propynylidene carbene trapping at the remote carbon (C▼) within **79** can be achieved by using an HDDA benzyne (derived from **14**) as the electrophile. **d**, Formation of **84** and **84-D** indicates a carbene metathesis process that has a significant H/D kinetic isotope effect. **e**, An example of a three-component, cyclopropanation reaction.

This study began with the serendipitous observation of the net (3+2) cycloaddition between a transient benzyne and a 2-ethynyl pyridine derivative (**16** + **15** ➞ **17**, Fig. 2a). Key intermediates were conjectured to be the zwitterion **18** and free carbene **19** enroute to **17**. DFT computations provided support for this mechanistic interpretation (Fig. 2c). Importantly, this initial hit reaction using a benzyne was smoothly expanded to a variety of shelf-stable, electrophilic alkynes (Fig. 4), thereby considerably increasing the applicability of the process. Additionally, the carbene character of the key intermediate was demonstrated by various insertion, cycloaddition, and rearrangement processes (Figs. 3 and 4a). We further showed that a large assortment of 2-alkynyl iminoheterocycles are competent participants (Table 1). Notably, "carbene relay" reactivity of metal-free propynylidene intermediates was demonstrated. To our knowledge this is the first instance of i) generation of propynylidenes under thermal conditions[43,44,45] and ii) demonstration of their efficient trapping (Fig. 6b,c). An unprecedented metal-free carbene metathesis reaction was also discovered (Fig. 6d). Finally, an enticing bimolecular cyclopropanation event was uncovered that has warranted further study. Overall, it can be expected that considerable versatility in product structure is achievable through this chemistry by selecting one of myriad combinations of i) the electrophilic alkyne, ii) the 2-alkynyl iminoheterocycle derivative, and iii) the carbene trapping components that comprise this one-pot, thermal, uncatalyzed, and fully atom-economical[49] reaction. Several examples show the potential of this "mix-and-match" approach (Fig. 5). Both the mechanistic features of this novel transformation as well as its ability to effectively provide access to manifold heterocyclic structural motifs in a modular fashion are appealing attributes. This facile access to carbenes under thermal, additive-free conditions provides a platform for the further exploration of new reactivities of metal-free carbenes.

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Author contributions Q.X. discovered the first reaction and performed the experimental and computational studies; Q.X. and T.R.H. designed the experiments, interpreted the data, and wrote the manuscript together.

Competing interests The authors declare no competing interests.

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Methods

A. General procedure for the iodination of heterocycles to prepare the 2-iodoheterocycles

To a solution of the heterocycle in DMF (0.3 M) was added 1.5 equiv. of $^{n}C_4F_9I$ and then 1.0 equiv. of $NaO^{t}Bu$. The reaction mixture was stirred at room temperature. After TLC analysis indicated the complete consumption of the starting heterocycle, the reaction mixture was quenched by the addition of H_2O, extracted with Et_2O, dried ($MgSO_4$), concentrated, and purified by flash column chromatography.

B. General procedure for the Sonogashira coupling to prepare the 2-alkynylheterocycles

Under an atmosphere of N_2, a round-bottomed flask containing $Pd(PPh_3)_2Cl_2$ (0.02 equiv.) and CuI (0.04 equiv.) was placed into an ice bath. A solution of the halogenated heterocycle (1.0 equiv., 0.1 M in solvent), terminal alkyne (1.5 equiv.), and Et_3N (3 equiv.) was added to the reaction vessel. The reaction mixture was stirred at elevated temperature overnight. After the completion of the reaction according to TLC, the mixture was concentrated in vacuum and passed through a short column of silica gel (same eluant as for the subsequent MPLC purification). The eluted solution was concentrated in vacuum, and the residue was purified by flash column chromatography.

C. General procedure for the acetylation of the propargylic alcohol

To a solution of the alcohol in DCM (0.3 M) was added 5 equiv. of Et_3N and 0.1 equiv. of DMAP. The reaction flask was placed into an ice bath. Ac_2O (3 equiv.) was added to the reaction mixture. Once TLC analysis indicated the full consumption of the alcohol substrate, the reaction mixture was quenched by the addition of sat aq Na_2CO_3 solution, extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified by flash column chromatography.

D. A representative example of a carbene generation and trapping reaction

The pyridazine derivative **58c** (15 mg, 0.063 mmol) and DMAD (72 mg, 0.50 mmol, 8 equiv.) were dissolved in 1.5 mL of DCE in a threaded glass culture tube. The tube was closed with a Teflon-lined screw cap. The reaction mixture was stirred at 135 °C for 20 hours and then eluted using 2:1 Hex/EtOAc through a pipet column of silica gel. After removal of solvent under vacuum, the residue was purified by medium pressure liquid chromatography (2:1 hexanes/ethyl acetate) to afford **59c** (20.9 mg, 87%) as a yellow oil. See the Supplementary Information for full spectroscopic characterization data for this and all other new compounds prepared in this study.

Data availability Preparation procedures and characterization data for all new compounds, computational methodology and data, and copies of all NMR spectra are provided in the PDF of Supplementary Information.