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Reactions of HDDA benzyne with structurally complex, multifunctional natural products

Sean P. Ross¹ and Thomas R. Hoye^{1,*}

¹Department of Chemistry, University of Minnesota, 207 Pleasant St., SE, Minneapolis, MN 55455

Abstract

The studies reported here were motivated by the desire to probe the extent to which benzyne, one of the classical reactive intermediates in organic chemistry, would react in discriminating fashion with benzyne trapping reagents that contain multiple functional groups and, accordingly, possible modes and sites of reactivity. We deemed that natural products comprise a palette of potential multifunctional compounds with which to address this question. We show that benzyne produced by the hexadehydro-Diels-Alder (HDDA) reaction react with many secondary metabolites with a high preference for one among several potential pathways. Examples demonstrating such selectivity include reactions with: phenolics, through dearomatizing ortho-substitution; alkaloids, through Hofmann-type elimination; tropolone and furan, through cycloaddition; and alkaloids, through three-component fragmentation-coupling reactions. We also demonstrate that the cinchona alkaloids quinidine and quinine give rise to products, some in as few as three steps, that enable subsequent and rapid access to structurally diverse, polyheterocyclic compounds. The results show that benzyne are quite discriminating in their reactivity—a trait perhaps not broadly appreciated.

Nature provides countless examples of complex small molecules in the form of secondary metabolites collectively produced by living organisms. These natural products comprise a rich resource from the perspectives of both structural complexity and functional group diversity. Over 200,000 such substances have been characterized to date. Of growing importance are methods for chemically modifying natural products through a reaction that produces a relatively small change in structure (e.g., C–H hydroxylation¹, hetero-Diels-Alder cycloaddition², O–H functionalization³, arene fluorination⁴, arene bromination⁵, C–H carbenoid insertion⁶, C–H azidation,⁷ C–H amination⁸). The primary motivation for pursuing such methodology has often been to probe the structure-activity profile of a natural substance having a preexisting, valuable biological property. In contrast, chemical transformations that result in more substantial degrees of structural modification, via skeletal

*Correspondence to: hoye@umn.edu.

Author contributions

S.R. and T.H. conceived the experiments, interpreted the data, co-wrote the manuscript, and agreed to the content of the final submission. S.R. executed the experiments and collected the data.

Additional information

Supplementary information is available in the online version of the paper.

Competing financial interests

The authors declare no competing financial interests.

rearrangement and/or reorganization for example, are relatively rare⁹. With the goal of using benzyne that bring considerable structural complexity in their own right to effect such derivatizations, we set out to explore aspects of the reactivity of polyfunctional natural products with some of these reactive intermediates. Efficient processes that enable such substantial reorganization would allow rapid access to compounds having structural motifs that would be otherwise extremely challenging to synthesize. Additionally, we embarked on this study (i) to gain new insights about benzyne chemoselectivity and (ii) to discover new modes of benzyne reactivity. From the outset we viewed the natural product as the derivatizing agent (of the benzyne), rather than the agent being derivatized (by the benzyne). This contrasts with more common approaches in which the secondary metabolite is derivatized by the action of a derivatizing agent or process like those mentioned above^{1–8}.

The hexadehydro-Diels–Alder (HDDA) cycloisomerization reaction of tri- or tetrayne substrates produces fused, bicyclic benzyne derivatives (brackets, Fig. 1a). Benzyne can be trapped in myriad ways, nearly all initiated through attack by a nucleophile at the more electrophilic benzyne carbon atom (Fig. 1b). Even though benzyne (and arynes more broadly) are highly reactive intermediates, such species can still exhibit a high degree of preference for one among several modes of reaction.¹⁰ Here we show that HDDA-generated benzyne¹¹ can be captured by many structural classes of natural products in single-operation, reagent- and catalyst-free processes that produce conjugates having substantially increased structural complexity (Fig. 1a). We also show that, in many instances, these reactions proceed with surprisingly high degrees of chemoselectivity¹².

We selected natural products that contained at least one principle functional group known to productively engage a HDDA benzyne. Our choice of benzyne was guided by two requirements: for any successful HDDA cascade, the trapping agent (i) must not react with the substrate triyne faster than its rate of cyclization to the benzyne and (ii) must engage the benzyne faster than the benzyne reacts with itself, solvent, or additional triyne substrate. To date, we have observed successful HDDA cascades with triyne (or tetrayne) substrates having over 20 different linkers that tether the 1,3-diyne and diynophile units. These fall into two broad classes differing in the nature of the tether—those with and those without a conjugated carbonyl functional group (ketone, ester, or amide). For example, compare **1** and **25** to **6** and **55**. The HDDA cascades reported here are not meant to be exhaustive with the choice of either the benzyne or the NP; they only scratch the surface of possibilities.

Trapping with phenolics (Fig. 2)

Because HDDA-derived benzyne are produced thermally, they engage in their subsequent trapping reactions in the absence of the reagents and byproducts that are necessarily associated with the generation of benzyne by classical methods^{13,11}. This circumstance can result in new modes of trapping reactions compared with those seen in traditional benzyne chemistry^{11,14,15}. One example is the trapping by neutral phenols^{11,16}. Under classical conditions, often in the presence of basic reagents, phenols typically form adducts with benzyne by nucleophilic attack through the oxygen atom to produce phenoxy ether products¹⁷ and only rarely by predominant functionalization at the *ortho* carbon atom¹⁸. Phenol (**3a**) traps the thermally generated benzyne **2** (derived from heating triyne **1**) in a

fashion we reported previously¹¹—namely, by adding through its *ortho*-carbon atom to efficiently give the adduct **5** (after rearomatization of the dienone intermediate **4a**, Fig. 2a). Consistent with a mechanistic formulation that involves a phenolic-ene type process (cf. **2** + **3**), trapping by 2,4,6-trimethylphenol (**3b**) leads in high yield to a non-enolizable dienone, **4b**—an unprecedented type of transformation. Yield data, throughout, represent the amount of product obtained following chromatographic purification.

The tetrayne **6** undergoes HDDA cyclization highly regioselectively¹⁹ to produce only the benzyne **8** (Fig. 2b). Because the HDDA reaction to form the benzyne is the rate limiting step in all HDDA cascades, the conditions for all of the reactions using tetrayne **6** as substrate (Figs. 2b–d and 3–6) were identical (see Methods Summary below). We have computed [density functional theory (DFT), M06-2X/6-31+G**] an optimized geometry for **8** and observed it to have a distorted geometry, as indicated by the angles shown in Fig. 2b^{20,21}. Accordingly, we were not surprised to observe that trimethylphenol (**3b**) had engaged the more electrophilic carbon atom in benzyne **8** (•) to give a single 2,4,6-trimethylcyclohexadienone-bearing adduct (71%, see **103** in SI).

Vitamin E (**7**) is a naturally occurring phenol that lacks aromatic hydrogens at positions *ortho* to the hydroxyl. When **7** was heated with **6** (Fig. 2b), an analogous process led to the adducts **9a–d** in a combined yield of 82%. This reaction was not unique to this pair of reactants. The triyne **1**, via benzyne **2**, also efficiently engaged vitamin E (**7**) to give the four separable isomers of ene products **10a–d** (76%). Estrone (**11a**), having the unsymmetrical C3-hydroxylated A-ring, was trapped by benzyne **2** to give the constitutionally isomeric biaryls substituted at C4 (**12a**, **6**, 39%) and C2 [**12b**, **7**, not shown (see SI), 35%]. Estradiol-17*O*-acetate (**11b**) reacted with benzyne **8** in a similar fashion to produce the adducts **13a** (**6**) and **13b** [**7**, not shown, (see SI)] in a combined yield of 48%. In contrast, reaction between vitamin E (**7**) and *o*-benzyne [1.5 equiv, generated from 2-(trimethylsilyl)phenyl triflate and CsF²²] gave a complex mixture of at least five products, most incorporating two benzyne-derived subunits (LCMS). A different mode of reaction was seen when estrone (**11a**) was reacted with *o*-benzyne—namely, estrone phenyl ether (see **104**, Supplementary Information) was cleanly produced (92%). These outcomes serve to emphasize the differences in reaction pathways that can be seen with benzynes used under basic (F⁻) vs. neutral (HDDA) conditions.

In a different vein and prior to studying reactions of HDDA-derived benzynes with alkaloids containing bridgehead nitrogen atoms, we observed that 1,4-diazabicyclo[2.2.2]octane (DABCO, **14**), in the presence of a sufficiently acidic third reactant such as benzotriazole (**15**), will engage benzyne **8** in a three-component coupling reaction (Fig. 2d). When **6** was heated in the presence of only a slight excess of both **14** and **15**, the piperazine-containing adducts **18a** and **18b** were formed in good yield. This presumably arises by way of sequential formation of the 1,3-zwitterion **16** and ammonium-benzotriazolide ion pair **17**, which finally undergoes nucleophilic opening of one of its three equivalent bridges. This can occur through the *N*¹- or *N*²-position of the benzotriazolide anion, which gives rise to the isomers **18a** or **18b**, respectively.

We then explored an analogous three-component reaction involving phenolic natural products. When tetrayne **6** was heated in the presence of DABCO (**14**) and vitamin E (**7**) (Fig. 2e, left) **19** was formed in good yield. Estradiol (**11c**), a substrate with both phenol and alcohol hydroxyl groups, was also examined. It formed only the 1:1:1 adduct **20** in a highly chemoselective reaction. It is notable that the formation of the three-component products **18a–b**, **19**, and **20** (Figs. 2d and 2e) is efficient even when a nearly stoichiometrically balanced set of the three reactants is used. Many multicomponent reactions require the use of at least one reactant in substantial excess, precluding application to trios of reactants where each is precious.

Trapping with alkaloids via Hofmann elimination (Fig. 3)

The ready participation of DABCO in these processes encouraged us to explore alkaloidal natural products having tertiary basic amine groups. When tropinone (**21**, 1.5 equivalents, Fig. 3a) and tetrayne **6** were heated, the 1:1 adduct (\pm)-**23** was efficiently formed (75%). This presumably arises through the intermediacy of zwitterion **22**, which undergoes a Hofmann-type fragmentation to give the cycloheptenone **23**. This mode of reactivity is not unique to HDDA generated benzyne. When α -benzyne²² was heated in the presence of tropinone (**21**), the analogous 1:1 adduct (\pm)-**24** was cleanly formed (66%).

In the course of this work, we observed that trapping of HDDA precursors containing electrophilic ynones and ynoates with tertiary amines is sometimes inefficient, presumably due to deleterious events initiated by conjugate addition pathways. However, by a slight redesign of the HDDA substrate, this problem can be mitigated. For example, the triyne **25** contains a bulky *tert*-butyldimethylsilyl (TBS) substituent at the terminal carbon of the ynoate, which renders it compatible with such amines. Thus, when **25** was heated in the presence of tropinone (**21**), the constitutional isomers **27a** (49%) and **27b** (40%) were formed. The near absence of regioselectivity is surprising based on the extent of distortion; benzyne **26** and **8** each show a similarly large deviation of their internal bond angles x and y (DFT). The different outcomes (i.e., a single isomer in Fig. 3a vs. ca. 1:1 ratio of isomers in Fig. 3c) are likely due to the difference in size of the flanking substituents in **8** vs. **26**, having large methanesulfonamide vs. small methylene groups, respectively.

The acidity of the protons α to the ketone in **21** is not a requirement for this Hofmann-like elimination. Thus, scopolamine (**28**, Fig. 3d) gave adducts **30a** and **30b** (via **29**) as a 1:1 mixture of separable diastereomers. The epoxide, even with its allylic activation; the primary alcohol¹⁵; and the ester functionality all remain intact in the product **30**. The more complex alkaloid sinomenine (**31**) was trapped by benzyne **8** to give the separable isomeric dienones **33a** and **33b** in a combined yield of 74% (Fig. 3e), likely via fragmentation of epimers **32a** and **32b**, respectively^{23,24}.

Trapping with brucine and reserpine (Fig. 4)

The proclivity of zwitterionic intermediates such as those in Fig. 3 to preferentially undergo Hofmann-type fragmentations led us to explore alkaloid substrates containing a bridgehead nitrogen. That arrangement should preclude the elimination pathway, thereby affording the

opportunity for three-component couplings. When tetrayne **6** was heated in the presence of both brucine (**34**, 1.5 equiv, Fig. 4a) and 3,5-bis-*tert*-butyl-4-hydroxytoluene (BHT, 1.25 equiv), a single three-component adduct **37a-20** was isolated. To our surprise, alkene migration had occurred²⁵; presumably the initial zwitterion **35** had undergone intramolecular proton transfer to form the unusual aza-allyl ylide **36**, which was then protonated by the hindered BHT at its more sterically accessible C22. The resulting ion pair then cleaved the C-ring C–N bond. Use of less hindered phenols in place of BHT produced varying amounts of the isomeric alkenes **37-20** and **37-21**. In the case of 2,4,6-trimethylphenol, a small amount of the allylic aryl ether **38b**, arising from S_N2' opening of ring-D, was observed. Finally, two different natural products, brucine and a phenol derivative, could be amalgamated into a single three-component product: vitamin E (**7**) gave rise to **37d-20**, **37d-21**, and **38d** while estradiol (**11c**) afforded only **37e-21**.

We next considered members of the yohimbans family—another well-known class of alkaloids that contain a bridgehead nitrogen atom. For example, when the benzyne precursor **6** was heated in the presence of both reserpine (**39**, 1.5 equiv) and 4-*tert*-butylphenol (1.25 equiv), a mixture of diastereomeric indoloazocines **41a** was produced in a combined yield of 35% (Fig. 4b). These presumably arose via electrophilic activation of the basic nitrogen atom followed by cleavage of the C/D ring fusion bond^{26,27}. The iminium ion **40** was then trapped by the phenoxide counterion. Use of benzotriazole as the Nu–H component resulted in formation of the indole/indoline/triazole/azecane-containing adduct **41b** (34%). This reaction proceeded with a very high level of diastereoselectivity; trapping of iminium ion **40** is presumably sensitive to the steric bulk of the trapping nucleophile.

The use of near equimolar loading for each of the seven three-component reactions presented in Fig. 4 is noteworthy. These examples demonstrate the enabling power of using a HDDA cascade to fuse three separate molecules, each of considerable structural complexity.

Trapping via [8+2] or [4+2] cycloaddition (Fig. 5)

We have also explored some net cycloaddition reactions (Fig. 5). Colchicine (**42**) is known to undergo [4+2] cycloaddition reactions with many dienophiles across the 1,3-diene subunit terminated by carbons C8 and C12^{2,28}. However, when heated in the presence of the HDDA substrate **6**, colchicine (1.5 equiv) was engaged by benzyne **8** in a new type of tropolone cycloaddition, giving rise to the benzofuran derivative **45** in good yield (59%, Fig. 5a). This is a formal 8 π + 2 π cycloadduct that can be viewed as proceeding either by a discrete tropylium-containing zwitterion **43** or via an asynchronous concerted process, presumably with a transition state geometry having that character. The primary adduct **44** has undergone rearrangement via [1,5]-hydrogen atom shift en route to the more stable fused benzofuran **45**. We also examined the reaction of **42** with (symmetrical) *o*-benzyne itself²² and, interestingly, observed an entirely different reaction course—namely, the formation of the [4+2] adduct **46** (Fig. 5b). The contrasting behavior for these two benzyne perhaps results from the unpolarized, symmetrical nature of the latter vs. the polarized, distorted character of **8**. This difference in the course of the reaction vis-à-vis *o*-benzyne is not unique to **8**. When triyne **25** was heated in the presence of colchicine (1.5 equiv), again, a benzofuran adduct, **47**, was formed from benzyne **26** (Fig. 5c). Finally, furans are classic dienes used for

aryne trapping²⁹. Heating **6** in the presence of the naturally occurring furan limonin (**48**, 1.1 equiv, Fig. 5d) gave, in excellent overall yield (84%), the mixture of isomeric [4+2] adducts **49**.

Trapping with quinidine and quinine (Fig. 6)

The significant degree of selectivity observed for many of the reactions already described encouraged us to explore a substrate possessing an even greater number of potential sites and/or modes of reactivity. Quinidine (**50**) and quinine (**54**) both meet this criterion. Engagement with a benzyne could occur via: the quinoline nitrogen³⁰, insertion into the hydroxylic O–H bond¹⁵, dihydrogen transfer from either the secondary alcohol or one of the (four) pairs of eclipsed H–CC–H units¹⁵, Alder ene reaction of the alkene³¹, $4\pi+2\pi$ cycloaddition with the anisole-like moiety³², or nucleophilic attack by the bridgehead tertiary amine (Figs. 2–4). When **6** was heated in the presence of quinidine (1.5 equiv), remarkably, even with this wide array of possibilities, trapping proceeded to generate a single isolable material, the epoxide **52** in 49% yield (Fig 6a)³³. This presumably arose via initial attack on the benzyne **8** by the tertiary amine in **50** followed by proton transfer, now intramolecularly from the alcohol hydroxyl group, to give the zwitterion **51**. Collapse of this β -oxido ammonium ion through C–N bond cleavage led to the trans-substituted [$J_{vic-epox} = 1.8 \text{ Hz}^{34}$], *S,S*-epoxide **52**. Likewise, quinine gave the analogous *R,R*-epoxide **53** (45%, Fig. 6a; 2.5 mmol scale).

The degree of selectivity exhibited by the transformations shown in Fig. 6a leads us to suggest that benzyne should be considered as one of the more discriminating of all reactive intermediates. That is, they can preferentially exit even a complex reaction manifold of possible trapping events largely via one channel. Indeed, this feature may be responsible for the remarkable versatility (and preparative value) that has been a hallmark of aryne chemistry from its outset^{35,36}.

With utility in diversity-oriented synthesis approaches in mind, we also examined the reaction of quinine (**54**) with the symmetrical tetrayne **55**, a substrate that can be prepared in two reactions. The derived benzyne **56** often undergoes nucleophilic capture competitively at both benzyne carbon atoms,¹⁹ consistent with the relatively small difference between its two internal bond angles (DFT)³⁷. When **55** (1.2 g, 5 mmol) was heated in toluene with **54** (1.5 equiv), indeed, a (separable) mixture of adducts **57a** and **57b** was cleanly formed (67% combined, Fig. 6b). Although the details are beyond the scope of what is presented here, the benzyne **56** was reacted with most of the natural products described in Figs. 2–5. It consistently engaged in the same mode of reactivity, but, as with the outcome to produce both **57a** and **57b**, led to a mixture of various ratios of constitutional isomers because of the inherently low degree of selectivity in the trapping of **56**. *o*-Benzyne itself reacts with members of the quinine family in the same fashion. For example, hydroquinine produced the *N*-phenyldihydro analog of **57** in good yield (76%, see **107** in SI).

The array of orthogonally reactive functional groups in the readily available adducts **52**, **53**, and **57** makes each well suited for additional diversifying derivatizations. Examples of such transformations are shown in Fig. 6c. These demonstrate: (i) epoxide ring-opening by

nucleophiles (**58**, **59**, and **60**), (ii) successive oxidative cleavage and reductive amination of the vinyl group (**61**), (iii) installation of an additional heterocyclic appendage (**59**), and (iv) *de novo* construction of a new heterocycle (**61** to **62**). The structures represented in Fig. 6c are reminiscent of the multiply linked, mono- and bi-heterocyclic motifs found in many kinase inhibitor lead compounds and drugs.³⁸ Myriad variations and combinations of these themes can be imagined.

Conclusion

By way of example, we have shown that HDDA-derived benzynes can be captured by complex reaction partners belonging to a variety of different classes of secondary metabolites. These trapping agents typically present multiple potential reaction sites or modes, yet the processes often occurred with remarkable levels of selectivity. This underscores the fact that reactive intermediates of the aryne family are quite discriminating.¹⁰ These reactions proceed under mild conditions, often with close to equimolar loading and perfect atom economy, and give natural product derivatives that have been extensively modified in their topology. We have also demonstrated that the products of some of these HDDA cascades can be modified in straightforward fashion to achieve further diversification. The majority of all the new compounds reported here were produced in just 3–4 chemical transformations (and none more than 6) from commercially available chemicals. We also note that numerous other triyne HDDA-substrates, differing in the constitution of the linker atoms that tether the 1,3-dyne and diynophile subunit^{11,37}, could be used to confer additional variety to the molecular structures arising from this approach. Overall, this work provides a new strategy for capitalizing upon nature's bounty of structurally fascinating and complex secondary metabolites.

Methods

General procedure for the HDDA-trapping reactions of natural products

An oven-dried culture tube containing the tetrayne precursor in organic solvent (initial concentration of 0.02–0.03 M) and the indicated number of equivalents of trapping component(s) was closed with a Teflon-lined cap and the solution was heated at 85–90 °C for 16 h. The half-life for conversion of each of the polyynes used here to the corresponding benzyne was ca. 3–4 h. The product(s) was(were) separated/purified by chromatography on silica gel. Full experimental details and characterization data for all new compounds (polyyne HDDA substrates and products) and a description of the computational methods and results are provided in the Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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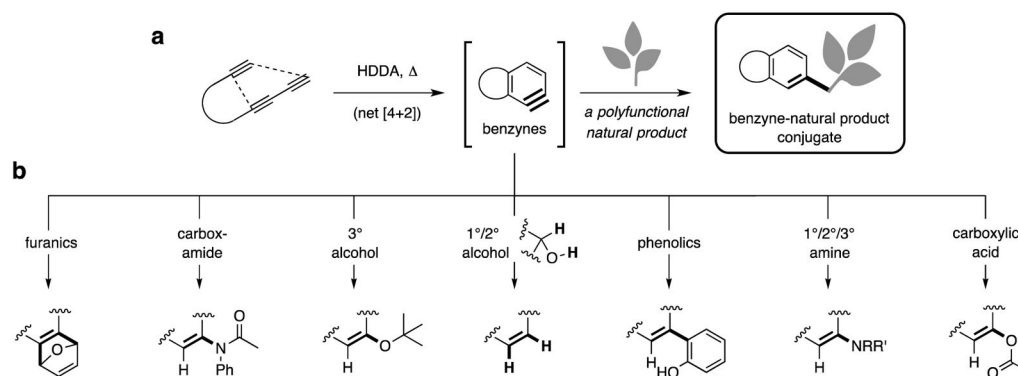


Figure 1. The two-stage hexadehydro-Diels-Alder (HDDA) cascade

Thermal activation of appropriate triene substrates leads, through initial (and rate limiting) cycloisomerization, to highly reactive benzyne intermediates (stage I) that efficiently engage trapping agents (stage II) by reaction with a variety of common functional groups. **a**, This work: the benzyne trapping agents comprise various, multifunctional natural products that present multiple potential sites for reaction. **b**, Representative, known examples of trapping reactions of HDDA-benzyne¹¹ with common functional groups.

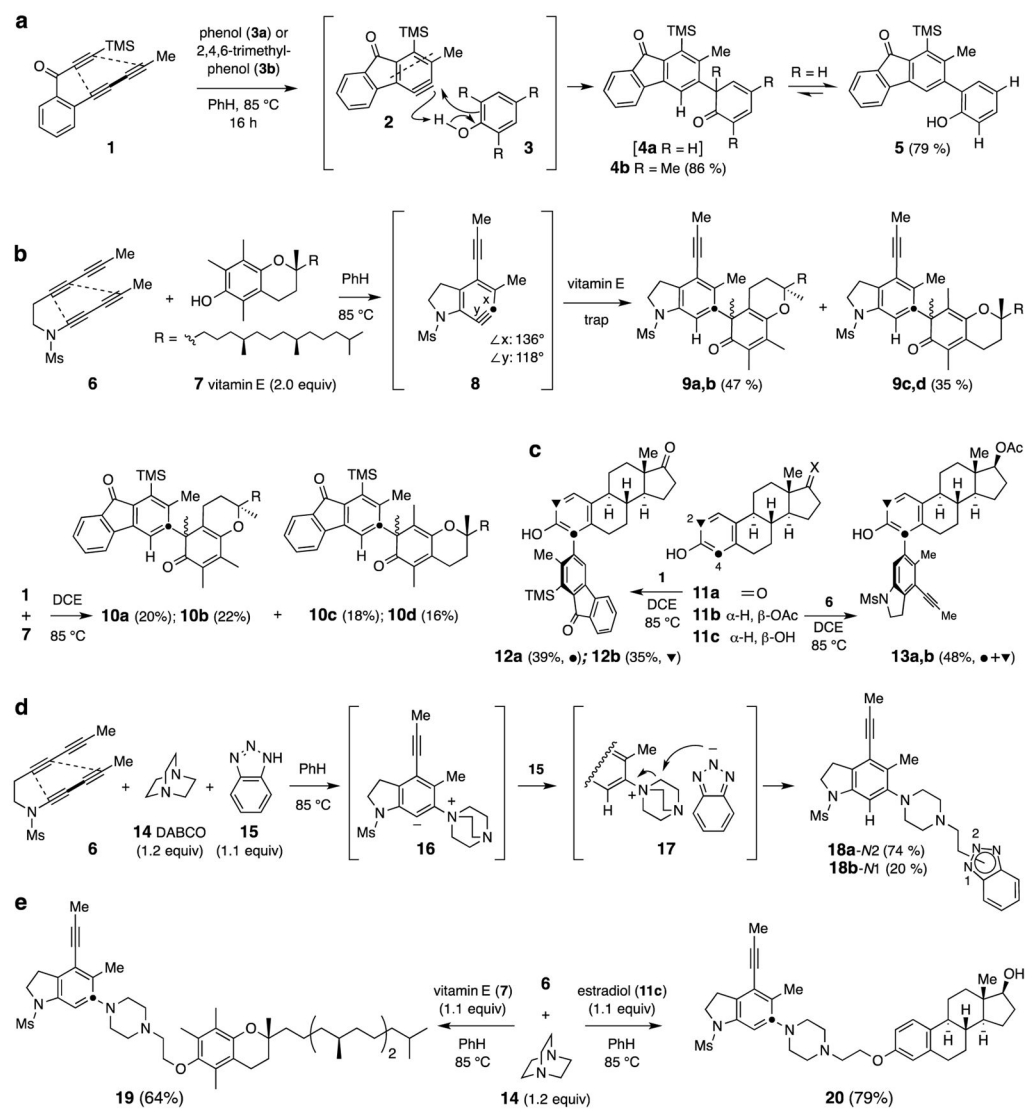


Figure 2. Different modes of reaction between a benzyne (**2** or **8**) and various phenolics. Phenols react with HDDA benzynes by either a phenol-ene type of process¹⁶ or, in the presence of a tertiary amine that outcompetes this ene reaction, by providing a proton that then leads to a three-component reaction. **a**, Phenol (**3a**) or 2,4,6-trimethylphenol (**3b**) is trapped by benzyne **2** through a phenol-ene-like reaction. **b**, Vitamin E (**7**) is engaged by both benzynes **8** and **2** in the same manner; the internal bond angles x and y at the sp-hybridized carbon atoms in benzyne **8** were computed by density functional theory (DFT, M06-2X/6-31+G**). **c**, Estradiol derivatives **11a** and **11b** are trapped by **2** and **8**, respectively, to produce phenolic ene adducts **12** and **13**. **d**, In a three-component process initiated by attack of 1,4-diazabicyclo[2.2.2]octane (DABCO, **14**), zwitterion **16** is protonated by, in this case, benzotriazole (**15**); ring-opening within the ion pair **17** gives **18**. **e**, In the presence of DABCO, vitamin E (**7**) [or estradiol (**11c**)] plays a new role, that of proton-donor and nucleophile to capture the more rapidly formed zwitterion **16**; ring-

cleavage of the quaternary ammonium ion (cf. **17**) by the phenoxide counterion then gives **19** (or **20**).

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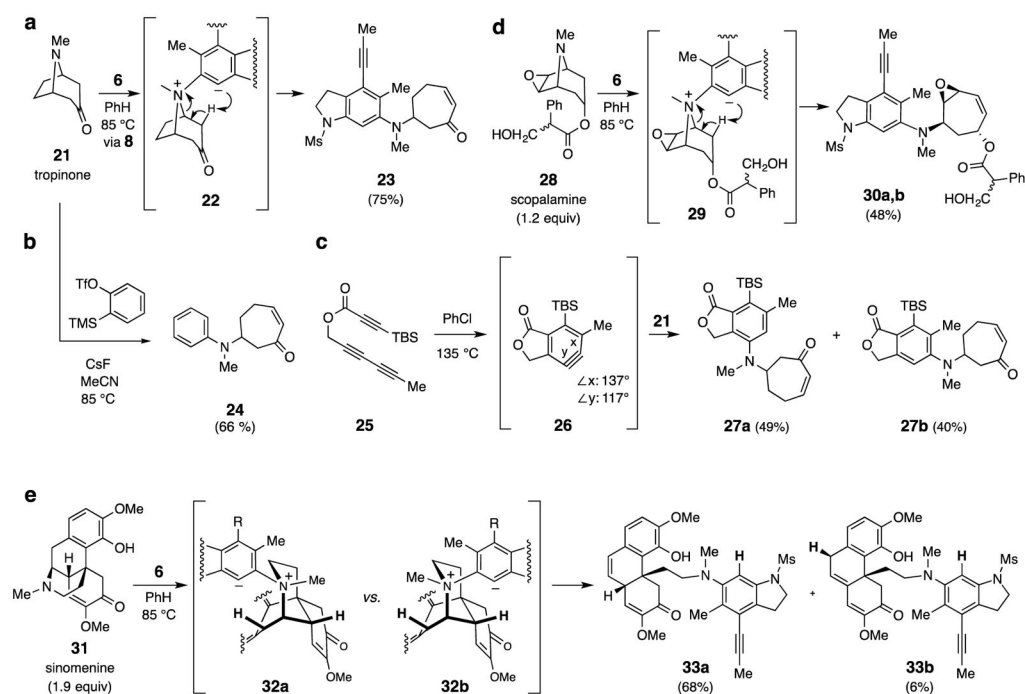


Figure 3. Reactions with tertiary amines

Alkaloids with tertiary amines are fragmented via Hofmann-type elimination reactions. **a**, **b**, **c**. Tropinone (**21**) reacts with **6** (via **8**), *o*-benzyne, or **25** (via **26**) to give adduct **23**, **24**, or **27a–b**; each of these products contains a substituted cycloheptenone, a relatively rare substructural moiety, that is functionalized in a manner that allows for subsequent chemical modification. **d**. Scopolamine (**28**) and **8** give diastereomeric adducts **30a** and **30b** (ca. 1:1) via zwitterion **29**; this shows the compatibility of alcohols as well as vinylic epoxides in the reaction medium. **e**. Sinomenine (**31**) and **8** give the isomeric dienone adducts **33a** and **33b** via the diastereomeric 1,3-zwitterions **32a** and **32b**, respectively.

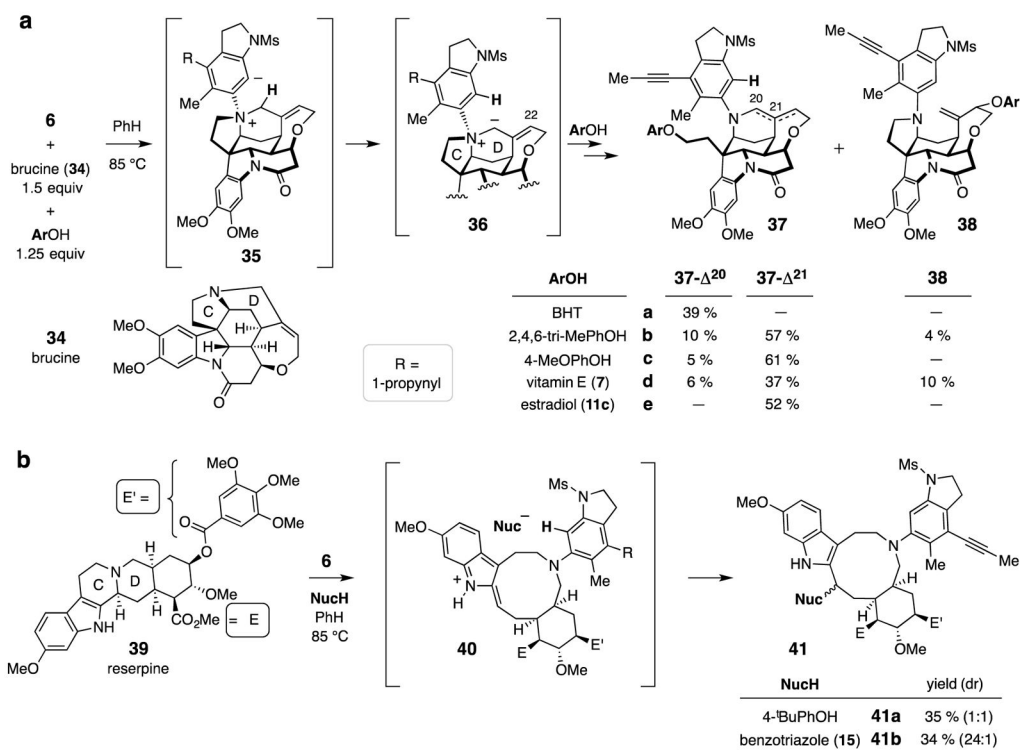


Figure 4. Three-component reactions involving complex alkaloids

Three component reactions similar to those described above for DABCO (Fig. 2d and 2e) can be extended to structurally complex tertiary amine nitrogen centers such as those present in brucine (**34**) and reserpine (**39**). **a**, Brucine (**34**) and one of various phenols give adducts **37- Δ^{20}** and/or **37- Δ^{21}** (and **38**) via **35** and the allylic aza-ylide **36**. **b**, The HDDA-bzynes activates the CD-fusion bond in reserpine (**39**) toward cleavage; the iminium ion **40** is then trapped by the in situ-generated Nuc⁻ counterion from a phenol or benzotriazole to produce the azecane derivative **41**.

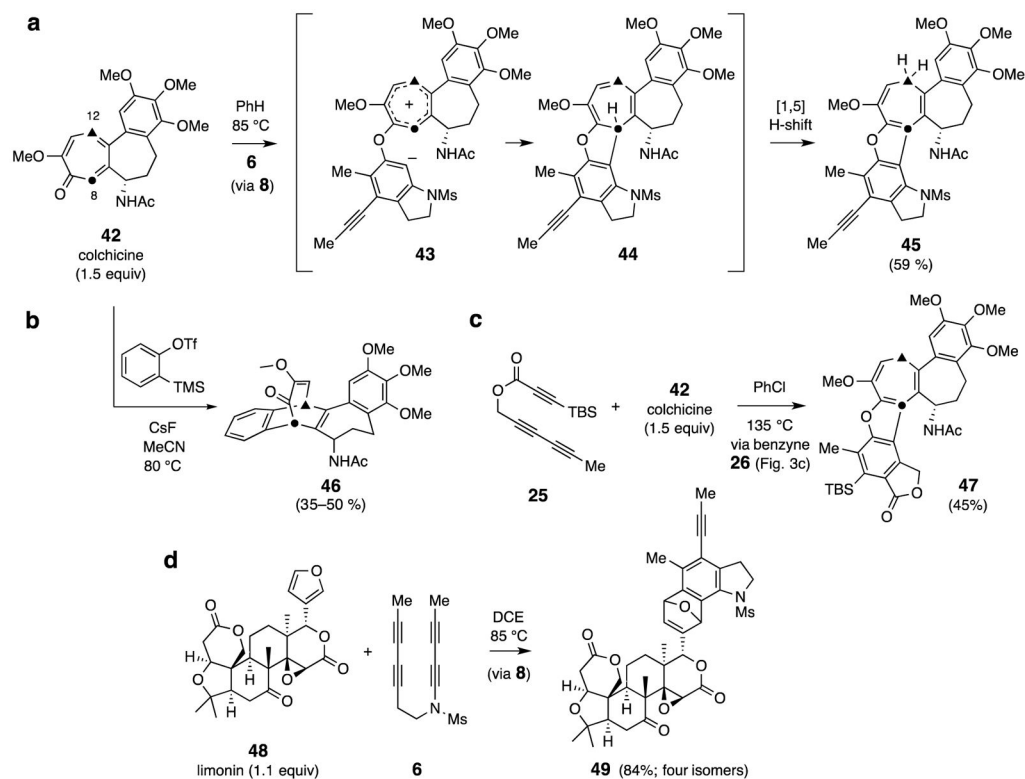


Figure 5. Net cycloaddition reactions between benzyne and conjugated π -systems

The cycloheptatrienone in colchicine (**42**) reacts in an unexpected fashion with a HDDA benzyne, whereas the furan in limonin (**48**) behaves in a well-precedented²⁹ mode. **a**, Tropolone-containing colchicine (**42**) and the HDDA-benzyne **8** gives the all-fused hexacycle **45**. **b**, Colchicine and *o*-benzyne [via Kobayashi generation²²] leads, instead, to a product, **46**, having a bridged motif. **c**, Colchicine and triyne **25** gives the benzofuran **47** (via benzyne **26**). **d**, The furan in limonin (**48**) is efficiently trapped by the benzyne **8** to give the DA cycloadducts **49**.

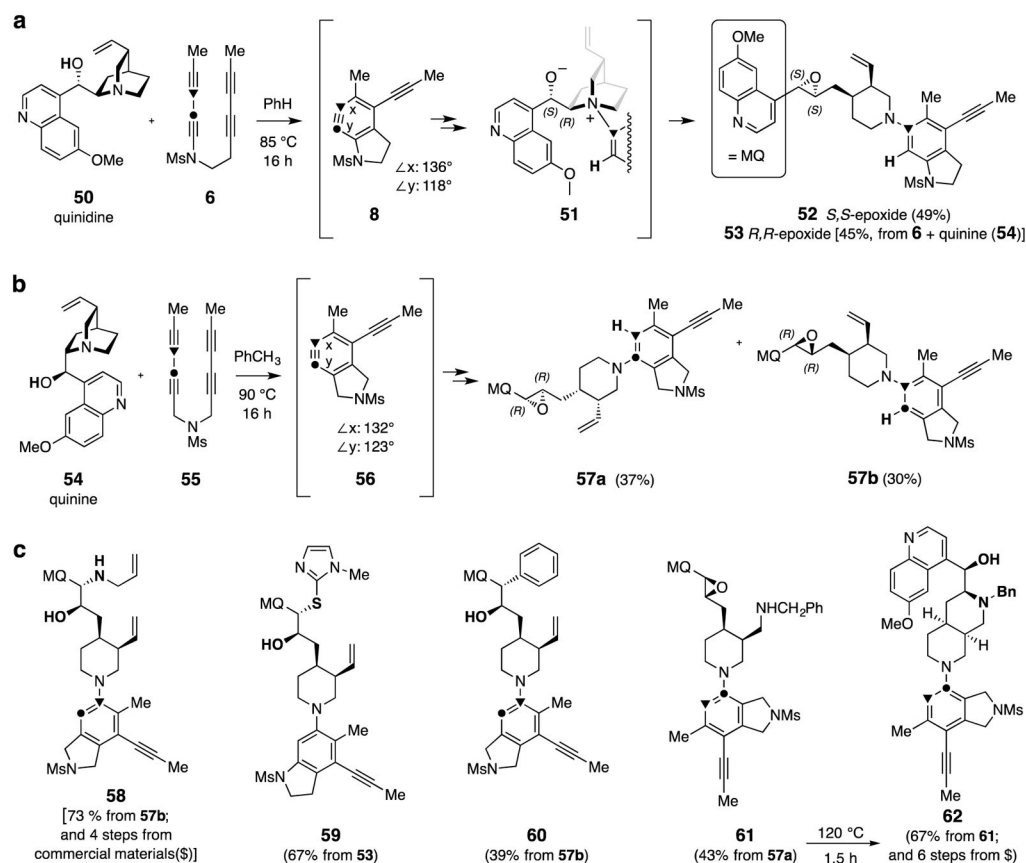


Figure 6. Quinidine (50) and quinine (54) derivatizations via benzynes 8 and 56

Cinchona alkaloids present at least six different sites for reaction with an HDDA benzyne, so it is remarkable that they react largely through a single mode. **a**, Quinidine (50) is trapped by the distorted benzyne 8 to give the epoxide 52 as the predominant product, presumably through the intermediate 51; similarly quinine (54) leads to the bis-epimeric epoxide 53 (not explicitly shown, see SI). **b**, Quinine traps the less distorted benzyne 56 competitively at both benzyne carbon atoms to give the (easily separable) constitutional isomers 57a and 57b. **c**, Examples of products having diverse substructural units that arise from straightforward modification of 57b (58 and 60), 53 (59), or 57a (61 and 62).