The hexadehydro-Diels-Alder reaction: Benzyne generation via cycloisomerization of tethered triynes
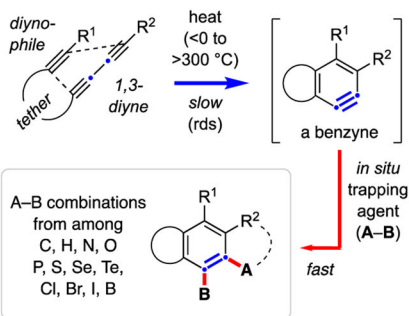
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Abstract

The hexadehydro-Diels-Alder (HDDA) reaction is the thermal cyclization of an alkyne and a 1,3-diyne to generate a benzyne intermediate. This is then rapidly trapped, in situ, by a variety of species to yield highly functionalized benzenoid products. In contrast to nearly all other methods of aryne generation, no other reagents are required to produce a HDDA benzyne. The versatile and customizable nature of the process has attracted much attention due not only to its synthetic potential, but also because of the fundamental mechanistic insights the studies often afford. The authors have attempted to provide here a comprehensive compilation of publications appearing by mid-2020 that describe experimental results of HDDA reactions.

Graphical Abstract

1. INTRODUCTION

1.1. Background: Dehydro-Diels-Alder Reactions (Figure 1)

The Diels-Alder (DA) cycloaddition is one of the most widely known – and powerful – C–C bond forming reactions in organic chemistry.[1] The reaction produces six-membered ring structures in an efficient, customizable, controllable, and predictable fashion, all grounded on a sound mechanistic foundation. The simplest DA reaction is the thermal [4+2] cycloaddition between ethylene (**1a,** the "dienophile") and 1,3-butadiene (**2a**, the "diene") to

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give cyclohexene (**3a**), as shown in Figure 1a. Variations involving progressively more highly oxidized substrates include the didehydro- and tetradehydro-Diels-Alder reactions. [2,3,4] Of course, these result in more oxidized products, namely cyclohexadiene [**3b**, from ethyne (**1b**) and butadiene] and benzene [**3c**, from ethyne and 1,3-butenyne (**2b**)] through the intermediate strained allene 1,2,4-cyclohexatriene. The highest oxidized case – the hexadehydro variant – is exemplified by the reaction of ethyne with 1,3-butadiyne (**2c**) to generate 1,2-dehydrobenzene (or *o*-benzyne). This represents a special situation because benzyne is highly reactive and cannot unimolecularly reorganize to a stable, isolable entity. However, because benzynes (and arynes more broadly) represent one of the most versatile and useful of all reactive intermediates in organic chemistry, this variant offers special opportunity.

A generic version of this triyne-to-benzyne cycloisomerization, now involving a tether linking the 1,3-diyne to a distal diynophile and rendering the reaction intramolecular in nature, is shown in Figure 1b. The resulting benzyne intermediate, **I**, is produced in the presence of suitable trapping agents (oval) that can be either part of substrate **4** (e.g., bonded to R^2) or altogether separate from **4**. These processes lead to structurally complex, highly substituted and/or fused, benzenoid products **5** via intra- (cf. dashed arc in **5**) or intermolecular processes, respectively. The overall transformation involves the initial rate-limiting cycloisomerization of the triyne (blue arrow) followed by rapid *in situ* trapping (red arrow). As demonstrated by the now many examples of published results, the highly customizable nature of both the hexadehydro-Diels-Alder (HDDA) substrate and the trapping reagent(s) provides considerable versatility for the creation of structurally sophisticated benzenoid products. Reviews of the early developments in HDDA chemistry have appeared.[5,6,7]

1.2.   Earliest Examples of Hexadehydro-Diels-Alder Reaction (Figure 2)

The first reports of cyclization of a multiyne to product(s) indicative of a benzyne intermediate came coincidentally and independently from the research groups of Ueda[8] (Figure 2a) and Johnson[9] (Figure 2b) in 1997. Tetrayne **6** was observed to cyclize at ambient temperature in the presence of added anthracene to produce the adduct **7** by way of a transition structure (TS) similar to that shown as **II**. A second minor isomer (not shown) arising from closure of the tetrayne substrate in the complementary sense (see dashed bonds in **6**) was also isolated. This early example, proceeding even at ambient temperature, demonstrated the enhanced reactivity of tetraynes relative to analogous triynes as well as the issue of regioselectivity in the direction of ring closure in unsymmetrical tetraynes. In Johnson's studies the minimalistically tethered triyne **8** was subjected to flash vacuum pyrolysis conditions, giving rise, via **III**, to a mixture of indane (**9**), indene (**10**), and "some soot" – a more or less balanced equation.[9] A dozen years later, the mixed bimetallic tetrayne complex **11** (Figure 2c) was observed by researchers in the Sterenberg group to give rise to a doubly fused benzyne, which was captured by furan to form **12** via TS **IV**.[10] Over a decade, Ueda and coworkers proceeded to study the cyclizations of a number of substrates related to **6**[11,12,13,14,15,16,17,18] in efforts primarily motivated by their interest in using radical character in their *o*-benzyne intermediates to react with DNA[12,18] in analogy to enediyne-derived 1,4-diradicals[19] (i.e., *p*-benzyne). That said, it is now recognized that *o*-benzyne derivatives react

overwhelmingly by polar processes wherein the strained alkyne behaves as a soft (i.e., polarizable) electrophile rather than via single-electron processes involving radical intermediates.

It was not until 2012 that the substantially greater generality of this cycloisomerization transformation became recognized through a report of work done in the Hoye laboratories.[20] It was also in this publication that the term "hexadehydro-Diels-Alder" (HDDA) was coined. The HDDA reaction offers certain advantages over classical methods for generation and trapping of arynes. First, because the initial cyclization event requires only heating, no additional reagents are required. This is in contrast to nearly all other methods of forming arynes, including the most commonly used Kobayashi method.[21] The ability to access this class of reactive intermediate in a pristine environment (i.e., reagent- and byproduct-free) has led to the discovery of some new types of trapping reactions as well as the uncovering of certain mechanistic details that provide new fundamental understanding of aryne reactions. At a strategic level, the HDDA reaction constitutes a de novo construction of the aromatic ring from an acyclic substrate, which is entirely complementary to classical benzyne generation. The latter always starts with a preformed aromatic ring; accordingly, in traditional benzyne chemistry creation and trapping constitutes a net substitution reaction at two adjacent carbons of the benzenoid precursor.

1.3.   Organization of this Review

Here are some organizational and formatting details to help orient readers. Beyond those shown in Figure 2, examples of specific reactions are found in Sections 4 and 5. Those in subsections 4.1–4.13 are categorized according to the types of the two new bonds that are formed at each of the benzyne carbon atoms as a result of the trapping reaction. The HDDA substrates (tethered triynes or tetraynes) and the final, isolated reaction products are designated by Arabic numbers. Intermediates or transition structures (TSs) that are helpful in rationalizing the overall outcome of each reaction are shown within brackets and are distinguished by Roman numerals. Some of these species are well supported by experimental and/or computational experiments, but others are offered by the researchers as their most reasonable rationale to account for the transformation.

We have attempted to include (or at least comment on) at least one reaction from each of the published reports in the last decade in which experimental outcomes are described. Any omission or oversight in achieving that goal is unintentional. Many publications provide multiple examples, in some cases dozens, of the same type of transformation or of trapping reactions that fall into more than one class. The reactions selected for inclusion here are meant to be exemplary of all of the major types of reaction pathways, but by no means do they represent a full compilation of all known HDDA transformations. A Reaxys search of, minimally, a 1,3-diyne mapped to a benzenoid product shows >600 unique reactions.

We typically have elected not to show the reaction solvent unless it explicitly participates in the trapping reaction (e.g., as a member of a 3-component reaction). Some solvents are essentially inert, but others (e.g., benzene or toluene) will, slowly, trap the benzyne if the other trapping processes are relatively slow. The rate of any trapping is a function of both i) the inherent reactivity of the trapping agent and ii) the concentration (or effective molarity)

of that agent. The number of equivalents of an external trapping agent is also not shown, unless only a slight excess was used, implying that an agent of that type is particularly effective at capturing the benzyne. In most instances, trapping agents are trivially available, are used in excess, and the effect of using less has not been explicitly evaluated. The indicated yields are those of isolated material, often for single runs of relatively small-scale experiments; large error bars should be presumed.

2. DIYNE-TO-DIYNOPHILE SUBSTRATE TETHERS (Figure 3)

The tether or linker connects the diyne and diynophile portions of the HDDA substrate. Almost exclusively, tethers are composed of three atoms, which allows for optimum distancing and orientation of the two reacting moieties to enable the cyclization event. The linker atoms are most commonly second-row elements and can be either sp^3- or sp^2-like in geometry. Essentially all of the 3-atom tethers used to date in an HDDA substrate are portrayed in Figure 3. Of these, the most common are of types **13a**, **13k**, and **13q**. This choice is based, in part, on the ease of synthetic access to the triyne or tetrayne substrates. It is not uncommon for the substrates to be prepared by a sequence involving three to seven chemical reactions.

The nature of the tether influences the ease of the initial, rate-determining thermal cycloisomerization event and, therefore, the temperature and time used for the HDDA reaction.[22] A few substrates cyclize at ambient temperature (or even below), many react conveniently in the 70–140 °C range, and a few require even higher temperature. Other than these differences in the rate of cyclization to the corresponding benzyne, there are relatively few instances in which a given trapping reaction would not be expected to be compatible with a given tethering moiety. It also can be anticipated that additional designer tether substructures can be invented to give access to products having specific fused rings of interest in the setting of, e.g., studies of target-directed synthesis of natural products.[23,24,25] The nature of the substituent at the remote terminus of the diyne or diynophile is also known to significantly influence the rate of the HDDA cyclization.[26] Because of these multiple rate-influencing factors, it is difficult to rank the relative rates of cyclization, especially so given that in only a few studies have investigators reported the half-life of the initial, rate-limiting HDDA cyclization. More commonly, the reaction temperature, time, and isolated yield of product are given. However, even if such reactions have been carefully monitored by, e.g., tlc, there is considerable variance in when the observer chooses to stop the reaction. Did that happen after, say, 4, 10, or 20 half-lives? The short answer is that neither the researcher nor the reader can judge without more careful analysis. We would encourage the practice of determining and reporting the half-life of cyclization of a given substrate when possible. Not surprisingly, mechanistic aspects of these cycloisomerizations have also been examined computationally.[27,28,29,30,31,32,33]

3. BENZYNE TRAPPING AGENTS

The trapping agent is the species that (rapidly) captures the reactive benzyne intermediate after the initial (rate-limiting) cyclization event. A wide variety of both inter- and intramolecular traps have been demonstrated. In many cases, the final product arises only

after a series of intermediate events. Additionally, several reports have described the development of multicomponent reactions[34] wherein more than one trapping agent has been engaged to produce structurally more complex products. One consideration for those using or designing new trapping reaction strategies is that the reagent itself cannot undergo reaction with the substrate polyyne faster than its rate of conversion to the HDDA-generated benzyne.[35] Fortunately, such incompatibility is not a serious limitation, and that allows for substantial versatility in trapping strategy.

4. TRAPPING REACTIONS LEADING TO PRODUCTS HAVING NEW TYPES OF ADJACENT σ-BONDS AT THE BENZYNE CARBONS

4.1. Introduction of C–C and C–C bonds

4.1.1 Intramolecular Trap (Figure 4)—Reactions involving trapping agents that lead to the formation of two new carbon-carbon bonds are among the more common HDDA transformations. Representative variants of this process, all of an intramolecular nature, are displayed in Figure 4. Among the initial array of HDDA reactions[20] was an intramolecular trapping of the pendant aromatic moiety present in substrate **14** by a DA reaction of the benzyne with that arene. This yielded adduct **15** via **V** (Figure 4a). It is worth noting that although DA cycloadditions of higher acenes are quite common, arynes comprise one of the very few dienophiles capable of dearomatizing simple benzenoid arenes.[36,37] A similar trapping was observed with the furan-containing substrates **16** and **18** via **VI** and **VII**, respectively (Figures 4b and 4c).[38,] This work demonstrated that a variety of ring sizes, including medium-sized cycles (cf. **17** and **19**), could be formed by intramolecular trapping and that the trapping agent could be appended to an atom within the diyne-to-diynophile tether (cf. **18**).

An interesting intramolecular formation of two C–C bonds by successive elementary mechanistic events was reported by Lee and coworkers, who showed that the toluenesulfonyl group in substrates such as **20** was not innocent, as is evident from the structure of the unusual product **21** (Figure 4d).[39] This is explained through a complex sequence of events in which the benzyne **VIIIa** is proposed to first be captured by the remote, pendant alkene to yield the carbene **VIIIb**. This is sufficiently nucleophilic to engage the electron deficient toluenesulfonamide ring through an ipso attack. Fragmentation and proton transfer produces the dearomatized product **21** (cf. **VIIIc** and **VIIId**). This remarkable process constitutes capture of the benzyne by two separate intramolecular moieties and highlights the level of mechanistic complexity that can be observed in some types of trapping reactions.

Another example of sequential formation of two C–C bonds to the benzyne can be found in a recent report from Shibata et al.[40] The conversion of benzyne **IXa** (from **22**, Figure 4e) to product **23** proceeds via the strained allene **IXb** by way of a tetradehydro-DA (TDDA) reaction. This result also demonstrates the viability of an unusual silicon-containing tether in substrate **22**. Finally, see Figure 24a in the Addendum for an interesting intramolecular trapping of a naphthyne, itself generated by an HDDA reaction in which a classical benzyne functioned as the diynophile.

4.1.2 Intermolecular Trap (Figure 5)—There are numerous examples of processes involving intermolecular reactions with agents that produce two new C–C bonds (Figure 5). A number of these reactions are closely analogous to those shown above in Figure 4. For example intermolecular DA reactions with benzene;[20] 5-membered cyclic dienes (furans,[41] pyrroles,[41] thiophenes, and cyclopentadiene),[42] anthracenes,[43] and isobenzofurans[44] are quite common (cf. **X**–**XIII**, Figure 5a–d). Furans are particularly reactive and efficient traps and are frequently used as probe molecules when examining new types of HDDA substrates. See Figure 24b in the Addendum for an example in which an imidazole was used as the trapping agent, giving, following oxidation, a fused isoindole-1,3-dione product.

Other processes are unique to intermolecular trappings. For example, HDDA-generated benzynes can be trapped with tetraphenylcyclopentadienone (**28** to **31** via CO extrusion from the DA adduct **XIV**, Figure 5e)[45] or perylenes (**28** to **32** via H_2 extrusion from the DA adduct **XV**, Figure 5f[46]). Highly conjugated polycyclic products such as those formed here are of interest for potential application in organic electronic devices.[45] Strained alkenes are known to add in a net [2+2] fashion to benzynes, consistent with what is observed for the HDDA product **33** from **24** (cf. **XVI**, Figure 5g).[20]

Recently, researchers in the Lee lab reported a procedure for coupling two equivalents of an isonitrile with an HDDA aryne in the presence of a silver catalyst (e.g., **34** to **35**; Figure 5h). [47] This was rationalized as involving an initial nucleophilic attack on the aryne by the isonitrile to form **XVIIa**, after which a second molecule attacks the now-electrophilic carbon of that adduct. The intermediate **XVIIb** then cyclizes to form the interesting benzocyclobutene-1,2-diimine **35**. This process was suitable for a variety of aryl (although not alkyl) isonitriles.

Hu and coworkers coupled the HDDA benzyne with stabilized Wittig ylides to introduce adjacent methyl and ethoxycarbonyl groups onto the aryne (e.g., **28** to **36**; Figure 5i).[48] Following nucleophilic attack onto the benzyne **XVIIIa** by the ylide carbon atom, the intermediate **XVIIIb** was envisioned to cyclize to the tetrahedral intermediate **XVIIIc**. Opening of the strained ring to the new, stabilized ylide **XVIIId** and capture by water would then account for formation of **3 I note that the reviewers did not have** A notable aspect of this transformation is its regioselectivity. Normally, nucleophiles would be expected to preferentially attack a fused benzyne such as **XVIIIa** at carbon atom "b" because of the distortion of the aryne ring. That is, DFT computations show that the internal bond angle at atom "b" is significantly larger than that at atom "a". In accord with the distortion analysis of unsymmetrical aryne reactivity,[31,49,50,51] the atom with larger internal angle is more electrophilic (greater p-character in its in-plane π-bond). In the case of addition of the ylide to **XVIIIa**, the large size of that nucleophile makes steric factors override the inherent electronic bias. Namely, the phenyl ring is effectively bulkier than the methylene carbon pinched back into the five-membered ring, steering the attack to atom "a".

In the absence of any other trapping agents in the reaction environment, HDDA polyyne substrates will often cannibalize themselves, producing intractable oligomeric product mixtures. However, in certain instances, the nature of the substrate polyyne is such that its reaction with its progenitor benzyne is selective, leading to dimeric products. For example

(Figure 5j), the ester triyne **37** gave rise to the unsymmetrical dimer **38** in a process envisioned to proceed through a net [2+2] cycloaddition (cf. **XIXa**) to give the benzocyclobutadiene **XIXb**, which is then trapped intramolecularly by a pendant alkyne, giving rise to the penultimate Dewar naphthalene **XIXc**.[52] As an extension of this process, it was found that the added external diyne 2,4-hexadiyne (Figure 5k) could effectively trap the benzyne generated from **28** to produce the transient benzocyclobutadiene **XXa**.[52] When a reactive DA dienophile such as *N*-phenylmaleimide was also present, the final three-component adduct **39** was formed via opening of the strained DA adduct **XXb**.

An interesting intra-annular cyclization of the cyclic triyne **40** gave the dibenzopicene derivative **41** (Figure 5l).[53] Use of furan as the trapping agent for benzyne **XXI** represents another example of how popular it is to employ that very efficient process to benchmark reactions that produce novel HDDA benzynes.

4.2. Introduction of C–C and C–O bonds (Figure 6)

Trapping reactions that form both a C–C and C–O bond are rarer than the C–C and C–C counterparts discussed above. The most common motif in this category is the overall [4+2] trapping of the benzyne by an enal[54] to produce a benzopyran derivative such as **43**,[24] **44**,[55] or **46**[56] (Figures 6a–c). The process begins with a net [2+2] cyclization of the aldehyde carbonyl group with the HDDA benzyne to produce a benzoxetene such as **XXIIb**, **XXIIIa**, or **XIVa**. It is likely that these benzoxetenes are not formed directly by a concerted [2+2] cycloaddition but by a stepwise process, proceeding through a zwitterionic intermediate, shown explicitly as **XXIIa** for the reaction of **42** with, for example, citral enroute to the benzopyran **43**. Under the thermal reaction conditions, the strained oxetene ring undergoes a 4π-electrocyclic ring opening to the dienone **XXIIc**, which, by a 6π-electrocyclic ring closure, generates **43**. Notably, this compound served as the penultimate intermediate in a chemical synthesis of the carbazole-based natural product mahanimbine.[24] This demonstrates a complementary synthesis strategy for the preparation of complex molecules – namely, a de novo construction of the benzenoid core. The reaction of **45** to **46** shows trapping by an exocyclic enal, which produces a spirocyclic product (Figure 6c).[56]

In a related type of reaction, salicylaldehydes and salicylketones can be produced by trapping of the benzyne with tertiary amides (e.g., **47** to **48**, Figure 6d). Initial zwitterion **XXVa** closes to **XXVb**, which is envisioned to be opened through attack by adventitious water to give the tetrahedral intermediate **XXVc**.[57] Note that this is another example in which the steric bulk of the aryl group *ortho* to the benzyne diverts the in-plane attack by the nucleophile, here the amide carbonyl oxygen, preferably to the carbon distal to the aryl (cf. Figure 5i).

In an unusual (and unexpected) mode of reaction, the benzyne produced from **49** (Figure 6e) is thought to engage the natural product colchicine at its ketonic oxygen to generate the tropylium zwitterion **XXVIa**.[58] This collapses to the cycloheptatriene **XXVIb**, which isomerizes to adduct **50** by a final [1.5] hydrogen atom migration to account for product formation.

4.3. Introduction of C–C and C–N bonds (Figure 7)

A variety of traps lead to the formation of products containing new C–C and C–N bonds (Figure 7). Cyclization of **51** in the presence of phenanthridine leads to the relatively rare benzazete derivative **52** (Figure 7a).[59] The intermediate zwitterion **XXVII** is invoked. Such intermediates can be further exploited in three-component fashion, as demonstrated, for example, by the reaction of **51** in the presence of quinoline (or isoquinoline) and electrophiles such as phenylisocyanate (or reactive carbonyls, maleimides, dimethyl acetylene dicarboxylate, etc.) to give **53** (or analogous products, Figure 7b).[59] This implies that the lifetime of the zwitterion **XXVIIIa** is sufficiently long that it can encounter the third component to produce the presumed penultimate precursor **XXVIIIb**.

HDDA benzynes are excellent 1,3-dipolarophiles, as exemplified by the reaction of **54** in the presence of ethyl diazoacetate (Figure 7c).[60] The initially formed adduct **XXIXb**, formed via the cycloaddition portrayed in **XXIXa**, tautomerizes to the more stable benzopyrazole **55**. This reaction is also notable because the cyclization of **54** (and related diarylated tetrayne substrates) can not only be induced thermally but, at much lower temperatures, by irradiation – a photo-HDDA reaction (discussed further in section 5.1 below).

Simple imines also trap the reactive benzynes. For example, the preparation of the acridine derivative **56** is shown in Figure 7d.[61] In this case the intermediate azetidine ring in **XXXa** is sufficiently fragile to undergo electrocyclic opening to **XXXb**, analogous to the benzoxetene openings shown in Figures 6a–c. Electrocyclization and rearomatization leads to **56**.

Lee group researchers have shown that added Ag(I) salts can promote the three-component reactions of nitriles with HDDA benzynes. For example, triyne **57** incorporated two molecules of benzonitrile to give the quinazoline derivative **58** (Figure 7e).[62] Intermediate species like **XXXIa** and **XXXIb** were proposed to account for this mechanistically intriguing transformation. Even more interesting are reactions in which both a nitrile and an isonitrile are incorporated into a three-component product. For example, substrate **34** produced the unsymmetrical bis-imine **59** (Figure 7f).[47] The complementary and constitutionally isomeric nature of products **59**, **58**, and **35** (cf. Figure 5h) is particularly notable.

Hu and coworkers have recently reported a thorough examination of the trapping of HDDA benzynes with oxazolines. Three variants of this chemistry, each producing a novel product architecture, are shown in Figure 7g–i.[63] The nature of the substituent at the 2-position of the oxazoline is the key factor in determining the reaction pathway. The conversion of **28** to **60** (Figure 7g) shows that oxazolines bearing an alkyl substituent in their 2-position form azetidine and ring-opened o-quinomethide imines like **XXXIIIa** and **XXXIIIb** en route to product. In contrast, oxazolines unsubstituted at C2 add with reversed regiochemical orientation (cf. **XXXIVa** vs. **XXXIIIa**), and the resulting o-quinomethide **XXXIVb** is now sufficiently electrophilic to be captured by the pendent phenyl ring in Friedel-Crafts fashion to give the penultimate **XXXIVc** (Figure 7h). Finally, 2-arylated isoquinolines (Figure 7i) produce products that experience loss of formaldehyde (e.g., **63** from **28**, suggested to proceed via **XXXVa-c**).

4.4. Introduction of C–C and C–H bonds

4.4.1 Intramolecular Trap (Figure 8)—Many reactions produce a C–C and a C–H bond. These again have been segregated into intra- and intermolecular categories (Figures 8 and 9, respectively). HDDA benzynes were used to establish the first high-yielding "aromatic ene" reactions.[64] An example is given in Figure 8a. HDDA cyclization of **64**, which bears a designed placement of a *meta*-alkylated aryl substituent, produces the enophilic benzyne, which abstracts a benzylic hydrogen atom (cf. **XXXVIa**) to yield the isotoluene derivative **XXXVIb**. Water-catalyzed proton shuttle, demonstrated by use of added D$_2$O, rearomatizes this species to give the product **65a**. Alternatively, under anhydrous conditions, an added enophile such as *N*-methylisatin captures the isotoluene in a bimolecular Alder-ene reaction as portrayed in **XXXVIb** to efficiently provide the adduct **65b**.

Lee and coworkers have provided numerous examples of thermal cyclization of substrates bearing pendant alkenes. For example, **66** produced a benzyne that then underwent an intramolecular Alder-ene reaction (cf. **XXXVII**) to produce product **67**.[65] Lee et al. have also exploited silver ion additives[66,67] to identify new modes of HDDA benzyne trapping reactions that lead to net C-H insertion (Figure 8c and 8d). In the case of tetrayne **68**, it is envisioned that the pendant phenyl group is captured by an electrophilic carbon in the benzyne•Ag(I) complex **XXXVIIIa** to produce a phenonium ion **XXXVIIIb** en route to the product **69** (Figure 8c).[68] Alternatively, electrophilic carbene character in the complex **XXXIX** is thought to enable insertion into a methyl C–H bond in the pendant *n*-propyl group to give **71** (Figure 8d).[69,70]

An analogous overall C–H insertion process, this time mediated by boron trifluoride as the additive, was used to convert, for example, **72** into the cyclopentano- and cyclobutanofluorenone derivatives **73a** and **73b** (Figure 8e).[71] The different outcomes imposed by the TBS vs. *t*-Bu substituents in **72** are notable and suggest that differences in the extent of buttressing change the internal bond angles in **XL** in perhaps small but certainly important ways allowing for formation of the strained four-membered ring in product **73b**. The carbene-like character suggested by structure **XL** is unprecedented for a boron-containing species, which further highlights the unique reactivity that can be uncovered by studies of HDDA reactions. For an additional example that demonstrates how subtle structural changes can be exploited to change the course of outcome in a similar carbenoid C–H insertion reaction, see Figure 24c in the Addendum.

4.4.2 Intermolecular Trap (Figure 9)—In the intermolecular mode of C–C and C–H bond-forming processes, some of the same reactivity patterns are observed. Bimolecular versions of the silver-catalyzed net electrophilic aromatic substitution (EAS) with an aromatic solvent molecule (**74** to **75**, Figure 9a)[68] and the Alder ene reaction (**76** to **77**, Figure 9b)[72,73] have both been demonstrated. Phenolic trapping agents capture HDDA benzynes at their *ortho* position (e.g., **49** to **78**, Figure 9c).[74] This process is viewed as a phenol-ene reaction (cf. **XLIIIa** to **XLIIIb**) and is notable because this mode of phenol trapping is not observed for classically generated benzynes, where the presence of basic reagents typically promotes oxygen attack and formation of diaryl ethers.

Net trifluoromethane addition to the benzyne can be accomplished by use of the Prakash reagent (CF_3TMS) in the presence of an equivalent of silver fluoride in acetonitrile solvent (e.g., **79** to **80**, Figure 9d).[75] This conversion is presumed to involve capture of the benzyne by in situ-generated trifluoromethylsilver ($AgCF_3$) to produce **XLIV**.

In another isonitrile-based multicomponent trapping scheme, substrate **34**, when heated in the presence of both PhNC and acetic acid, gives the 1:1:1 adduct **81** (Figure 9e).[76] The initial adduct **XLVa** is protonated and captured by acetate to produce the isoimide **XLVb**, which, finally, rearranges to the imide **81**. Alcohols and sulfonamides were also shown to serve in the capacity of protic nucleophiles in analogous processes.

A Cu(I)-catalyzed process for the hydroalkynylation of HDDA benzynes has been developed (e.g., **82** to **83**, Figure 9f).[77] Initial Cu-acetylide addition to the benzyne is proposed to form the adduct **XLVI**, which then disproportionates with another molecule of alkyne to continue the cycle. In another Cu(I)-promoted reaction of a terminal alkyne, HDDA reactivity expressed itself in an unplanned way (Figure 9g).[78] A mixture of substrates **84** and **85** produced the unusual HDDA substrate **XLVIIa**, which then cycloisomerized to **XLVIIb** and was captured by a third molecule of the terminal diyne **84**.

4.5. Introduction of a C–C and a C–Br, C–S, C–Se, or C–Te bond (Figure 10)

Bromoalkynylation of the HDDA benzyne derived from **82** (Figure 10a) is a complement to the hydroalkynylation shown above in Figure 9f. The Cu(III) species **XLVIII** is proposed to account, following reductive elimination, for the production of products such as **87**. Cross-coupling of the aryl bromide in these products demonstrated the potential for using this transformation to access products having two different types of adjacent C–C bonds (cf. Section 4.1.2).

Thioamides react with HDDA benzynes to produce benzothiazine derivatives (Figure 10b).[79] Initial [2+2] cyclization of the HDDA benzyne from **88** with the thioamide generates adduct **XLIXb** via zwitterion **XLIXa**. Opening of the four-membered ring reveals the *o*-thioquinonemethide **XLIXc**. Proton transfer isomerizes this to the isomeric zwitterion **XLIXe** via **XLIXd**, which collapses to the thiazine ring in **89**.

Hu and coworkers have reported some similarly complicated reaction pathways that produce dibenzo-thiophene, -selenophene, and -tellurophene derivatives (cf. **91**, Figure 10c and 10d). In the first of these (Figure 10c)[80] the benzyne from **90** is generated in the presence of diphenyl diselenide or diphenyl ditelluride, resulting in formation of **91** (X or Se or Te, respectively). It is proposed that the trapping involves addition of a PhX• radical to **La** to produce **Lb**, which then undergoes radical addition to the Ph group. An alternative consideration is the dipolar process implied by intermediates **LIa** and **LIb**. The same type of products were formed with a substantially different trapping agent and mechanism when the tetrayne **28** was heated in the presence of triphenylphosphine sulfide or selenide (Figure 10d).[81] Upon HDDA cyclization of the initial substrate, the P=Y moiety undergoes a [2+2] cyclization to **LIIb**, likely via the zwitterion **LIIa**. This then ring opens to species **LIIc** having zwitterionic character. An unusual ring-closing event then occurs wherein a phosphine phenyl group is engaged by the sulfur or selenium atom to yield the polycyclic

intermediate **LIId**. Aromatization to **LIIe** and loss of diphenylphosphine then accounts for formation of **91**.

4.6. Introduction of C–O and C–Si bonds (Figure 11)

Trapping processes that yield a C–O and a C–Si bond are not known for classically generated arynes. This is the type of reaction in the first (unplanned) HDDA cyclization observed in the Hoye laboratories that propelled investigations revealing the generality of these thermal cyclizations.[20] A typical example is the conversion of **92** to **93** (Figure 11a). Intermediate zwitterion **LIII**, formed from trapping the initial benzyne by the oxygen atom of the pendant OTBS group, was envisioned to proceed via a retro-Brook-like rearrangement. Interestingly, this reaction proceeded not only in solution[22] but also reasonably cleanly as a neat sample in a differential scanning calorimetry pan during DSC monitoring of the onset of exothermic reaction of substrate **92**.[82] This is noteworthy because it shows that intramolecular trapping can be faster than competitive reaction of the benzyne with an alkyne in an additional molecule of the triyne substrate, even at the highest possible substrate concentration.

Computational and experimental studies of related substrates such as **94** suggested that in addition to a stepwise process via the zwitterion **LIVb**, a concerted insertion of the benzyne π-bond into the O–Si bond in benzyne **LIVa** to provide **95** directly was energetically feasible (Figure 11b).[83] This OTBS trapping strategy has often been employed when first probing the feasibility of a new class of HDDA substrate. For example, the carbazolyne derived from the diynamide **96** was converted to **97** via zwitterion **LV** or in the concerted alternative (Figure 11c).[24]

A more unusual and remarkably efficient transformation is shown in Figure 11d.[84] Substrate **98**, bearing a pendant siloxyethyl substituent, presumably undergoes analogous cyclization and intramolecular nucleophilic attack to yield the initial, now strained, zwitterionic intermediate **LVIa**. Ring-opening, perhaps electrocyclic, of the four-membered ring leads to the dearomatized **LVIb**, poised for rapid transfer of the silicon group to provide the *o*-quinonemethide **LVIc**. Intramolecular proton transfer gives the phenolic product **99**.

4.7. Introduction of C–O and C–H bonds (Figure 12)

Although there are many examples of traps that form a C–O and a C–H bond, many proceed by the same basic reaction pathway. As an example, consider the cyclization of tetrayne **100** to the benzofuran derivative **101** (Figure 12a).[20] It is tempting to envision a mechanism that begins in parallel with that for the silyl ether addition (cf. Figure 11a) – namely, initial formation of the zwitterion **LVIIa**. Because unimolecular proton transfer within this species would face a stereoelectronically imposed barrier, a proton shuttle mechanism via a transition structure conveyed by **LVIIb** was thought likely.

A related, diironnonacarbonyl-promoted reaction is shown by the example of **102** to **103** (Figure 12b).[85] A number of additional metal-based additives led to the same outcome. However, results from an important control experiment – that is, heating **102** at the same temperature in the absence of any additive – was not described. Because the same product,

103, would be expected to form at the same reaction temperature, the case for catalysis (cf. **LVIIIa** and **LVIIIb**) may not have been definitively established.

In 2008 Ueda and coworkers reported cyclization of the methyl ether-containing substrate **104**, which produced the demethylated benzopyran derivative **105** (Figure 12c).[86] This reaction is additionally notable because the starting material is a triyne that, upon conversion to the cyano analog **LIXa** (with CuCN), proceeded to undergo the HDDA isomerization to the benzyne **LIXb**. Nucleophilic attack by the methoxy oxygen gives the zwitterion **LIXc**, which proceeds through protonation and demethylation to **105**.

The tetrayne substrate **106** contains *o*-methoxyphenyl substituents. Upon being heated, it is converted to the benzopyranyl product **107** via initial formation of zwitterion **LXa** (Figure 12d).[87] Protonation by chloroform solvent (or adventitious water) and demethylation can account for product formation and the fates of the electrophilic methyl group – MeCl, MeCCl$_3$, MeOH, and MeOMe – were detected as byproducts by direct ^{1}H NMR monitoring of the reaction mixture. In this study, it was also shown that the sulfides in products from these types of bis-diynylsulfide precursors serve as a traceless tether. That is, they could be reductively cleaved (Ra-Ni) to establish an overall process that is the equivalent of an otherwise unknown bimolecular HDDA reaction.[87]

Bimolecular analogs of the unimolecular OH additions given in Figures 12a and 12b are also known (e.g., **108** to **109**, Figure 12e).[20] Later studies,[88] both computational and experimental, support the idea that bimolecular alcohol addition is a process involving alcohol dimers, as suggested by the TS **LXI**. This view is related to the six-atom TSs that can be envisioned for additions of carboxylic acids[89] and 2-pyridone to the benzyne (cf. TSs **LXII** and **LXIII**), which can account for the conversion of, e.g., **76** to **110** (Figure 12f[90]) and **111** to **112** (Figure 12g[24]).

In another Ag(I)-promoted reaction, researchers in the Lee group showed that silver trifluoroacetate promoted addition of trifluoroacetic acid to the benzyne **LXIVa** derived from **113** (Figure 12h).[89] The labile aryl trifluoroacetate **LXIVc**, suggested to arise via **LXIVb**, was cleaved to the phenol **114** upon exposure to silica gel.

An example of a trapping reactions with a glycidol derivative is shown in Figure 12i.[91] Trapping of the benzyne from **51** leads to products such as the ketone **115**, from which it is clear that a carbon skeleton rearrangement has occurred. The zwitterion **LXV**, arising from attack by the epoxide oxygen, is poised to undergo a 1,2-methyl migration to account for the outcome. Several additional rearrangement or cleavage pathways were uncovered for glycidols with various substitution patterns.

4.8. Introduction of a C–N and a C–N or a C–S bond (Figure 13)

Trapping reactions that create both a C–N and a C–N or a C–N and a C–S bond are rare. The only method for the formation of two C–N bonds is the 1,3-dipolar cycloaddition reaction of the HDDA benzyne with an azide, a reaction well known[92] for classically generated[21] arynes. For example, use of trimethylsilyl azide gives the benzotriazole **117** when used to trap the benzyne from **116** (cf. **LXVI**, Figure 13a).[41]

Two methods for producing a C–N and a C–S bond have been described. The first involves intramolecular trapping by an aryl sulfonamide (**118** to **119**, Figure 13b).[93] Nucleophilic attack of the benzyne by the pendant sulfonamide nitrogen gives the zwitterion **LXVII**. The sulfonyl group then migrates to the carbanionic center, a process involving a four-center reaction made possible by access to d-orbital space around the third-row sulfur atom.

The second reaction exploits an unprecedented pseudo-1,3-dipolar cycloaddition of thioamides with HDDA benzyne. The conversion of **51** to the benzothiazoline **120** is exemplary (Figure 13c).[94] Initial nucleophilic attack by the sulfur atom forms the iminium zwitterion **LXVIIIa**. In an unusual elementary event, the positively charged nitrogen is suggested to then be attacked by the anionic arene carbon atom to yield the CF_3-stabilzed nitrogen ylide **LXVIIIb**. All of the thioamides that participated in this pseudo-1,3-dipolar reaction contained an electron withdrawing substituent on the thiono carbon atom. Intramolecular proton transfer extrudes ethylene and accounts for the product **120**.

4.9. Introduction of C–N and C–H bonds (Figure 14)

In contrast to the above category, there is a wide variety of reaction types that make both a C–N and a C–H bond during a trapping reaction. The simple nucleophilic attack of a primary or secondary amine is very common. The examples shown in Figure 14a come from a report that examined in considerable depth the factors that impact the sense and extent of regioselectivity of the addition of amines. For example, *n*-butylamine adds to the benzyne produced from the tetrayne **76** to give the isomeric adducts **121a** and **121b** (R = ^{n}Bu) in a 1:1.5 ratio.[90] Isoindolinynes such as **LXIX** show relatively little distortion and often lead to mixtures of isomers arising from competitive attack at the C_a- vs. the C_b-benzyne atoms. Steric interactions between the attacking nucleophile and the substituents in the 3- and 6-positions *ortho* to the benzyne can then be more influential in directing the incoming trapping agent. When an analogous reaction was performed with the TES-substituted tetrayne **142**, the larger TES group in **LXIX** (R = TES) guided the attack more toward C_a to give the major product **121a** (R = TES). When **142** was trapped by the bulkier tertiary amine Et_3N, the added steric bulk of that nucleophile directed the attack to C_a, giving, solely, the diethylamino analog of **121a** (R = TES) and showing that the steric interactions can completely dominate over the electronic bias imposed by the silyl substituent in the benzyne. An additional directing effect in benzyne **LXIX** (R = TES) stems from the presence of a trialkylsilyl group adjacent to the benzyne, a substituent known to electronically enhance nucleophilic attack at the adjacent rather than remote benzyne carbon.[95,96,97,98] As is often the case in evaluating selectivity of a given reaction outcome, whether before (prediction) or after (rationalization) the fact, when multiple opposing directing effects are in play[90] – here steric vs. electronic vs. distortion – it is not possible to judge which combination will dominate without a more extensive and systematic evaluation of substrate substituent effects (e.g., here, changing the sizes of the trialkylsilyl group).

The mechanism by which tertiary amines trap a HDDA benzyne has been investigated (Figure 14b).[99] Shown here is the reaction of trioctylamine with the tetrayne substrate **122**, which gives an ca. 1:1 mixture of products **123a** and **124b**. When performed in $CDCl_3$ solution, these products are essentially fully deuterated, showing that a solvent molecule

(and not a proton from the β-position of one of the octyl groups) is the source of the hydrogen atom in the product (cf. **LXXa** to **LXXb**). The fate of the departed octyl group was also identified; 1-chlorooctane was produced in nearly stoichiometric amount through dealkylation of **LXXb** [and the elimination product 1-octene was not observed (in situ NMR or GCMS)].

In contrast to isoindolinynes such as **LXIX** , the indolinyne derived from the unsymmetrical tetrayne **49**[33] (not shown) engages the tertiary amine in quinidine highly regioselectively at its C_a to produce, following proton transfer from the adjacent hydroxyl group, the alkoxyammonium ion **LXXI**.[58] Collapse to the epoxyamine leads to formation of **124**. A large number of other reactions between HDDA-generated benzynes and multifunctional natural products[100] were also revealed in this study, which, among other things, revealed a noteworthy high level of kinetic selectivity among multiple potential reaction types.[58]

The conversion of tetrayne **125** to the acetanilide derivative **126** (Figure 14d) is achieved by Ag(I)-catalyzed addition of acetonitrile, the solvent.[101] This Ritter-like reaction is viewed to proceed through the nitrilium ion **LXXIIa**. Water in the reaction mixture then adds to furnish the amide enol **LXXIIb** before final tautomerization to the product.

Multicomponent trapping reactions offer an attractive route for introducing structural complexity into HDDA products, some of which involve creation of C–N and C–H bonds (e.g., Figures 14e and 14f[102]). In the first, nucleophilic attack of the benzyne from **51** by aromatic heterocycles of the pyridine class, shown here with quinoline, produces the quinolinium-containing zwitterion **LXXIIIa**. The anionic character of this species is apparently sufficiently basic to deprotonate terminal alkynes also present in the reaction mixture as the third component. The resulting ion pair **LXXIIIb** then collapses to the product **127**. In the second example, substrate **122**, when heated in the presence of the cyclic tertiary amine *N*-phenylpiperidine and acetic acid, gives the 5-acetoxypentylaniline derivative **128**. This can be rationalized by initial formation of the ammonium zwitterion **LXXIVa** [faster, incidentally, than the addition of acetic acid (cf. Figure 12f)], which is then protonated by AcOH to give the ammonium acetate **LXXIVb**. Nucleophilic ring-opening then completes the formation of **128**. A wide assortment of cyclic amines as well as other protic nucleophiles function in these capacities as well.

The methanesulfonamide substrate **129** is an alkyl analog of the arylsulfonamide **118** shown above in Figure 13b. However, the fate of the Ms-containing zwitterion **LXXV** (Figure 14g) is different from that of the NTs analog.[93] Rather than sulfonyl migration to the anionic center, **LXXV** apparently undergoes internal proton transfer with extrusion of sultene to produce the *N*-methylated tetrahydroquinoline derivative **130**.

Finally, an unusual trapping reaction between diaziridines and an HDDA benzyne has been reported (Figure 14h).[103] Following the HDDA cyclization of, e.g., **122**, a nucleophilic diaziridine nitrogen attacks the aryne to give adduct **LXXVIa**. Proton transfer and electrocyclic ring opening forms the new C–H bond and yields the hydrazone product **131a**. Notably, the more hindered but more electron rich nitrogen of mono-*N*-alkylated diaziridines adds preferentially. This likely reflects the expectation that the distance between the

nucleophilic nitrogen and electrophilic carbon atoms is quite long in the TS leading to zwitterions such as **LXXVIa**. Again, a mixture of regioisomeric adducts (cf., **131b**) was formed from this class of benzyne intermediate.

4.10. Introduction of C–H and C–H bonds (Figure 15)

Reactions that create two C–H bonds amount to a net reduction of a benzyne to its benzene analog. Tetrahydrofuran was the first molecule observed to transfer two hydrogen atoms to a thermally generated benzyne; namely, the benzyne shown in **IV** in Figure 2c was reduced by gaining two hydrogens when it was created in THF solution.[10] Viewed at the time as hydrogen atom abstraction events, the net redox reaction with THF was subsequently demonstrated to involve a concerted transfer of two hydrogen atoms as depicted in **LXXVII** (Figure 15a).[104] One key experiment involved heating **24** in an equimolar mixture of THF-d_8 and THF-h_8. Product **132** was formed as a 6:1 ratio of di-protio and di-deuterio isotopomers, but none of the mono-H/mono-D analog was detectable. This is consistent with a single-encounter event like that depicted in TS **LXXVII**; the relatively small kinetic isotope effect for simultaneous cleavage of two C–H bonds reflects the relatively early transition state for this highly exergonic (DFT) process.

Two vicinal hydrogen atoms will also transfer from a saturated, cyclic hydrocarbon, as depicted for the transformation of **133** to **134** in Figure 15b. This key step in the Lee synthesis of selaginpulvilins C and D[23] was carried out by oxidizing a precursor propargylic alcohol, which rapidly cyclized at ambient temperature in cyclooctane solvent. In competition experiments,[104] cyclooctane (and cyclopentane) reduces HDDA benzynes faster than cyclohexane, consistent with the energetically easier access to the more closely eclipsed geometry computed for a concerted transition structure like that shown in **LXXVIII**.

Another instance in which silver(I) has promoted unusual reactivity is shown in Figure 15c.[70] The benzyne-silver complex **LXXIXa** is argued to be sufficiently electrophilic to accept hydride donation from one of the pendant *n*-propyl groups in substrate **135** to produce the carbocation **LXXIXb**, stabilized by the β-silicon atom. Water intervention and extrusion of propene results in the net-hydrogenated silanol product **136**.

Alcohols are also capable of reducing benzynes in a process reminiscent of a Cannizzaro reaction (e.g., **137** to **138**, Figure 15d).[88] A tandem experimental and computational study revealed the ability of primary and secondary alcohols to donate two H atoms in a concerted process similar to the cyclic hydrocarbons. Labeling studies using isomeric mono-deuterated cyclohexanols demonstrated that the process was both concerted and regiospecific, as shown in Figure 15d. Computation of TS geometries for addition of cyclohexanol to benzyne shows a geometry like that shown in **LXXX**. This is consistent with the deuterium labeling pattern in products **138-HD** and **138-DH** and indicates that the CH methine hydrogen atom is transferring as a hydride-like nucleophile and the OH as a proton-like electrophile.

4.11. Introduction of C–H and C–Halogen bonds (Figure 16)

The use of a trapping reagent that produces both C–H and C–halogen bonds yields products with useful handles for further synthetic manipulation. Perhaps the simplest way to

accomplish this is through the net addition of a mineral acid. Although the use of HBr had been demonstrated in a number of publications, the reagents of choice here are ammonium halide salts. For example, triynes **24** or **140** give the bromides **139** or **141** when heated in the presence of primary or tertiary ammonium bromides (Figures 16a[20] or 16b[24]). The soft bromide ion nucleophilically adds to the HDDA benzyne **LXXXIa** or **LXXXIIa** and protonation of the ion pair **LXXXIb** or **LXXXIIb** leads to the product. The level of regioselectivity of nucleophilic addition to each of these benzynes is known to be high.

In one of the Lee group's earliest studies of Ag(I)-enabled chemistry, they developed a method for the net addition of HF across the benzyne using $AgBF_4$ (Figure 16c).[75] Addition of fluoride is a rare outcome for aryne chemistry – consider the thousands of reactions that use the Kobayashi fluoride-induced aryne generation[21] in which F^- does not further engage the reactive intermediate. Presumably this reflects the reluctance of the soft, polarizable aryne bond to accept a hard, compact nucleophile. The silver-benzyne complex **LXXXIIIb**, formed following generation of benzyne **LXXXIIIa** from **142**, presumably accepts a fluoride ion from the (softer) BF_4^- counterion. Protonation – perhaps occurring during workup – yields the product **143**.

Reactions catalyzed by palladium (Figure 16d)[105] and ruthenium (Figure 16e)[25] that result in the net addition of HCl, HBr, and HI to an HDDA benzyne have been reported. In the conversion of, e.g., **47** to **144**, allyl halides serve as the halogen source whereas in the reaction of, e.g., **76** to **145,** dihalomethanes serve that role. In both reactions initial formation of an intermediate benzyne-metal complex (cf. **LXXXIVa** or **LXXVa**/**LXXXVb**) is proposed. In the Pd-variant, a water molecule was demonstrated (D_2O) to be the proton source.

4.12.   Introduction of C–H and C–S bonds (Figure 17)

Sulfides, soft nucleophiles, are quite effective trapping agents. This often leads to products in which adjacent C–S and C–H bonds are introduced at the benzyne carbon atoms. The first example was in the intramolecular setting of the conversion of **146** to **147** (Figure 17a).[14] Intermediates **LXXXVIa-c** were invoked. Subsequent studies have made it clear that proton transfer from an alkyl group within an intermediate such as the zwitterion **LXXXVIb** often generates a sulfur ylide (examples below), likely involved in this reaction as well. An ylide intermediate is supported by a number of experiments, for example the labeling reaction shown in Figure 17b.[106] In the conversion of **148** to **149**, the zwitterion **LXXXVIIa** gives the ylide **LXXXVIIb**, which is then protonated by AcOD also present in the reaction mixture. The acetate in the ion pair **LXXXVIIc** then produces the monodeuterio-methyl acetate, detected by in situ ^{1}H NMR analysis. Notably, the soft sulfur in thioanisole adds to the benzyne in preference to the addition of acetic acid (cf. Figure 12f), even though the latter is a competent trapping agent.

Diallyl sulfide adds to the benzyne from **148** to produce the zwitterion and ylide **LXXXVIIIa** and **LXXXVIIIb**, respectively (Figure 17c).[106] A [2.3]-sigmatropic rearrangement produces the arylsulfide product **150**. Use of cyclic sulfides allows for three-

component reactions (Figure 17d).[106] For example, **82** gives **151** when heated in the presence of thietane and various phenols. Intermediates **LXXXIXa-c** explain that outcome.

Finally, in another silver-catalyzed trapping of HDDA benzynes with a fluorine-containing reagent, the substrate **79** gives rise to the trifluoromethyl sulfide **152** when heated in the presence of AgSCF$_3$ (Figure 17e).[75] Intermediates **XCa** and **XCb** were offered as rationale.

4.13. Introduction of a C–Hal and a C–Hal or a C–O bond (Figure 18)

Dihalogenation represents an example of an HDDA trapping reaction in which compatibility of the polyyne substrate with the trapping reagent envisioned for capturing the benzyne needs to be taken into consideration. For example, elemental dihalogens would react with the alkynes in the substrate before there was any appreciable formation of an HDDA benzyne. Dilithium tetrachlorocuprate (Li$_2$CuCl$_4$) was identified as one solution to this limitation.[107] The tetrayne **142** gave the 1,2-dichlorobenzene derivative **153** (Figure 18a). An associated mechanistic study in which the substrate contained a tethered trapping moiety, which served as an internal clock reaction, allowed determination of the kinetic order of the post-rate limiting trapping step by varying the concentration of Li$_2$CuCl$_4$. The capture is first order in Li$_2$CuCl$_4$; however, this leaves open the question of the detailed mechanism of the reaction. A direct transfer of both chlorine atoms through a TS such as **XCIa** or an intermediate chlorocuprate species such as **XCIb** would both explain the outcome. A related example proceeds through the carbazolyne **XCII** (**154** to **155**, Figure 18b).[24]

Additional variants of silver(I)-promoted reactions lead to either the fluorohalobenzene derivatives **156** (Figure 18c)[75] or *o*-halotriflates such as **158** (Figure 18d).[89] In the first reaction (**125** to **156**), a stoichiometric amount of AgBF$_4$ gave adduct **XCIIIb** by reaction with the initial benzyne **XCIIIa**. Subsequent addition of an *N*-halosuccinimide gave the product dihalides. This represents a rare example in which trapping of an aryne gives a stable intermediate species that then reacts further upon later addition of another reagent. In the second reaction, both silver triflate and an *N*-halosuccinimide (NBS in the example of **157** to **158**) are present from the outset. Here the organosilver species **XCIVb** (from **XCIVa**) is halogenated in situ.

4.14. Introduction of miscellaneous bond pairs (Figure 19)

In this last subsection, several "one-off" examples of some unusual transformations, each fueled by the high potential energy of the reactive benzyne intermediate, are presented. The first of these is a net hydroboration of the HDDA benzyne resulting in the conversion of **159** to **160** (Figure 19a).[108] As with the dihalogens discussed above, hydroboranes as trapping agents would be expected to rapidly consume the substrate alkynes, precluding benzyne formation. In contrast, the indicated carbene-borane complex effects this net hydroboration transformation. The mechanism of this reaction is not obvious. The sense of the (complete) regioselectivity observed for this reaction suggests that the process involves a step in which nucleophilic attack by hydride leads the way. A concerted TS such as **XCV** can be formulated, although it is not clear if the boron atom can sustain this type of bonding and bond reorganization.

The creation of two C–P bonds has been achieved with tetraphenyl diphosphane (**142** to **161**, Figure 19b).[109] A DFT analysis suggested that the intermediate **XCVIa** can progress directly to the bis-phosphine **XCVIb** in a concerted event. A similar reaction with a diaryldisulfane gives the bis-sulfide **162** (Figure 19c).[60] The contrasting behavior between this reagent, which presumably produces the zwitterion **XCVII**, and that of the analogous higher chalcogenides of selenium and tellurium (cf. Figure 10c) is notable. Finally, note that in this instance the substrate **54** was cyclized photochemically, a process discussed in more detail next in section 5.1.

5. STRATEGY-LEVEL DEVELOPMENTS FOR THE HDDA REACTION

There have been several notable conceptual developments that demonstrate important new dimensions of HDDA chemistry. The specific transformations that demonstrate these new strategic advances draw largely from the same pool of substrate tethers and trapping reactions described in Sections 2–4 above. An overview of each development with illustrative examples is presented in Sections 5.1–5.4.

5.1 The Photochemical HDDA Reaction (Figure 20)

The photochemical HDDA reaction, reported in 2017, uses a photon rather than thermal energy to initiate the HDDA cyclization.[60] To date the only class of substrate reported to undergo this transformation is a series of tetraynes bearing two terminal aromatic substituents, as seen from each of the examples in Figure 20. Not surprisingly, substrate **54** can be trapped with a furan derivative to produce **163** (via **XCVIII**, Figure 20a). More informative are the reactions in Figures 20b and 20c in which the intermediate [4+2] adducts were not isolated but lost carbon monoxide (cf. **XCIX**) and dihydrogen (cf. **C**) to give the naphthalene and naphthoperylene derivatives **164** and **165**, respectively. These examples show that those finishing events occur even at ambient temperature, a fact not discernable from the thermal variant of these types of HDDA trapping reactions.

Although most reactions were performed, out of convenience, at ambient temperature, in the case of the substrate **166**, bearing an internal trapping moiety in the form of the *o*-methoxyphenyl substituent, the reaction was shown to proceed also at ca. −70 °C to give **167** (Figure 20d). In this experiment the byproduct methanol was observed, suggesting that a small amount of water in the reaction mixture was providing the proton to zwitterion **CIb** (from cyclization of **CIa**) as well as the nucleophile to subsequently accept the electrophilic methyl group.

Electron rich aryls (cf. **166**, **168**, and **169**) also can be cyclized photochemically. The last two (Figure 20e) are demonstrated by the oft-used furan trapping (cf. **CII**) to produce **170** or **171**, respectively. The latter, where 2,5-dimethylfuran was the trapping agent, was observed by NMR analysis to be a mixture of atropisomers because of hindered biaryl rotation on the NMR time scale.

Finally, important mechanistic information was obtained from study of the reaction of the unsymmetrically substituted tetrayne substrate **172** (Figure 20f). This can be cyclized either thermally (half-life of 12 hours at 75 °C) or photochemically. Under thermal conditions, two

isomeric benzynes, **CIII'a** and **CIII'b**, are formed and give rise to products **173a** and **173b** in a 2.1:1 ratio, respectively. The trapping agent here was cyclooctane (cf. Figure 15b), which made the products easily discernable by NOE experiments. When the same reaction was performed photochemically, the same ratio (within error) of products was observed. This result suggests that the mechanisms leading to formation of the isomeric benzynes converge through a common intermediate, regardless of the means of energization. This is consistent with the view that benzyne formation occurs by a stepwise pathway through a common biradical similar to **CIII**, which then bifurcates during ring closure to either **CIII'a** or **CIII'b**.[24,28,30,32] Further, it suggests that the electronic spin characteristics of this biradical are the same, whether formed by initial thermal or photochemical activation.

5.2 The Domino HDDA Reaction (Figure 21)

If one is good, two (or more) is (often) better. That idea led researchers to hypothesize that an appropriate linear array of multiple tethered diynes would support not one but a series of intramolecular cyclizations wherein each successive aryne would become the diynophile for the next diyne in line – a domino HDDA process.[13] In short, this process initially generates one benzyne that then undergoes subsequent intramolecular HDDA cyclizations with tethered diynes to produce increasingly large members of the acyne family.

The concept was first demonstrated using the pentayne **174** (Figure 21a).[110] This was designed to include a three-atom tether between the first diynophile (the top ynoate) and its proximal 1,3-diyne but with only two atoms (CH_2CH_2 in **174**) separating the pair of 1,3-diynes. As planned, the initial cyclization produced the benzyne **CIVa**, which proceeded to engage the second diyne, now five atoms away from the proximal benzyne carbon, to give the naphthyne **CIVb**. This was trapped by in situ 2,5-dimethylfuran to give essentially nothing but the adduct **175**. Numerous examples of naphthyne trapping were shown to be effective.

The results shown in Figure 21b demonstrate that the process is sequential. That is, the intermediate benzyne **CVa**, produced by initial cycloisomerization of the central tetrayne in substrate **176**, has a finite lifetime. This benzyne is trapped relatively efficiently when the reaction is performed in furan as solvent. As the concentration of furan is systematically lowered, there is a longer lifetime for **CVa**, giving ample opportunity for the second cyclization to occur to produce the naphthyne **CVb** as revealed by the formation of increasing amounts of the naphthalene product **177b**.

The conversion of heptayne **178** to the anthracene derivative **179** (Figure 21c) shows that the two-atom linker between adjacent pairs of diynes also can be a 1,2-disubstituted arene moiety. This particular transformation involves three successive HDDA cyclizations, the last (step iii) converting the naphthyne **CVIa** to the anthracyne **CVIb**.

The most complex substrate examined was the nonayne **180** (Figure 21d). This proceeded through four consecutive events to the tetracyne **CVII**, which was trapped with several agents; shown here is the use of the cyclopentadienone derivative **181**. The initial adduct was desilylated and heated to 180 °C to eject carbon monoxide and produce the dibenzohexacene derivative **182**. This was shown to have a significantly twisted architecture. The highly

conjugated molecules available from these domino HDDA cyclizations have interesting photonic and electronic properties, potentially valuable for use in various electronic devices.

Finally, the domino strategy can be exported into other settings. This was demonstrated by the reaction shown in Figure 21e.[111] As shown by researchers in the Li lab, reactant **183** serves as the equivalent of 1,2-bisbenzyne.[112] When exposed to carbonate and an appropriate nucleophile, this initially forms the benzyne **CVIIIa**, which then engages the nucleophile, here the conjugate base of the triflamide **184**. Net S_N2' displacement of the tosylate leaving group in **CVIIIb** gives the second benzyne **CVIIIc**. This now engages the pendant 1,3-diyne in the HDDA event to give the penultimate intermediate, the naphthyne **CVIIId**. Internal trapping with the tethered TBS ether produces **185**, completing this cascade that marries classical Kobayashi-like with HDDA benzyne formation.

5.3 The Aza-HDDA Reaction (Figure 22)

Replacement of one of the two terminal carbon atoms in a triyne substrate with a nitrogen atom opens the possibility to effect an analogous cycloisomerization to form a pyridyne intermediate. This aza-HDDA reaction has been recently reduced to practice (Figure 22).[113] This represents a fundamentally novel approach towards the construction of highly functionalized pyridines from acyclic precursors. Based on the original location of the nitrile, either a 3,4-pyridyne (**CIXa** to **CIXb**, Figure 22a) or a 2,3-pyridyne (**CXa** to **CXb**, Figure 22b) is formed.

DFT studies of these types of isomeric pyridynes indicate that they have dramatically different levels of geometric distortion. This was shown experimentally by comparing the behavior of these isomeric pyridynes, which exhibit quite different selectivity upon reaction with a nucleophilic trapping agent. For example, substrate **186**, having the nitrile as a diynophile, gives the dienone **187**, but as a mixture of both **187a** and **187b** via the relatively undistorted pyridyne **CXI** (Figure 22c). In contrast, **188**, having an aza-diyne and the precursor to the 2,3-pyridiyne **CXIIa**, reacts with, for example, tropinone (**189**) to give the amine-trapped product **190** (via zwitterion **CXIIb**, Figure 22d). This was the only regioisomer observed; eight other trapping reactions of 2,3-pyridiynes also showed complete regioselectivity, including one with 2,4,6-trimethylphenol.

In many respects the aza-HDDA reaction behaves analogously to the all-carbon HDDA transformation – many of the same traps and tethers can be used. However, the aza variant has several limitations. The aza-HDDA cycloisomerization reaction is considerably slower, with some substrates requiring a reaction temperature in excess of 200 °C. This is consistent with the fact that the bond energy of a C–N triple bond is considerably higher than that of a C–C triple bond. Moreover, product yields of many examples are below 50% and substrate synthesis is not as straightforward as for analogous triynes. Despite a more limited scope, the aza-HDDA variant still represents a novel and potentially useful process for creating certain highly substituted pyridine derivatives.

5.4. Reagent-induced Net HDDA Reactions (Figure 23)

Several reactions have been reported to give products that are HDDA-like, but that do not proceed by way of a benzyne. These are shown in Figure 23. In the first example, the tetrayne **191** was observed to react at ambient temperature in the presence of secondary amines such as morpholine to produce the isoindoline product **192**.[114] Mechanistic studies revealed that the process proceeds by an initial, base-catalyzed isomerization to the allenyne **CXIIIa** that then cyclizes to the strained allene **CXIIIb**. This analog of the known, parent α,3-dehydrotoluene[115] is then captured by the amine.[116] This process was dubbed the pentadehydro-Diels-Alder (PDDA) reaction, signifying that the cyclization occurs via an acyclic intermediate, **CXIIIa**, in which five, not six, of the atoms are sp-hybridized.

In a related reaction, the cyanodiyne **193** was converted to the pyridine derivative **194** under the action of DBU in deuterochloroform (Figure 23b). This was the first instance in which the energetically more demanding cyano group participated in an HDDA-related cyclization. This aza-PDDA reaction likely proceeds via intermediates **CXIVa-c**.

As shown earlier in Figure 5l, the cyclic triyne **40** requires heating for many hours at 70 °C to generate the benzyne **XXI**. Shown in Figure 23c is the reaction of **40** with bromine, which rapidly (<1 h) at room temperature generates the dibrominated product **195**.[53] This strongly suggests that **XXI** is not involved in this "bromine-induced transannular cyclization."[53]

Finally, the hydrometallation product **198** was generated highly efficiently (accompanied by a small amount of the isomeric rhodacycle **199**) when the potential HDDA tetrayne substrate **196** was exposed to a stoichiometric amount of the Rh(I) complex **197**.[117] Based on the known rate of reaction of tetraynes structurally very similar to **196** [e.g., **172** (cf. Figure 20f) cyclizes thermally with a half-life of ca. 4 h at 90 °C[60]], it can be expected that **196** would require elevated temperature to cyclize to the HDDA benzyne **CXV** at any reasonable rate. Therefore, it is most probable that Rh(I) is inducing cyclization leading, ultimately, to the new benzenoid ring in **198** by a pathway that does not include the free benzyne as an intermediate.

6. ADDITIONS MADE DURING MANUSCRIPT REVISION (Figure 24)

Several additions, including a summary of recently published reports, are presented in Figure 24. In a few instances where relevant, these have been referred to (called out) by a comment at an appropriate location in earlier discussion.

Yoshida, Hosoya, and coworkers devised the interesting cascade reaction shown in Figure 24a.[118] This involves initial generation of the benzyne **CXVIa** from substrate **200**, which then functions as the diynophile to engage the tethered diyne. The resulting naphthyne **CXVIb** is then trapped by the tethered furan to produce the polycyclic structure **201**. Hu et al. have described trapping reactions with a series of N-substituted imidazoles (Figure 24b). [119] For example, the benzyne **CXVIIa** from tetrayne **28** adds to 1-methylimidazole in the presence of oxygen to give the imide **202**. The exact sequence of HCN extrusion and oxidation of the suggested initial Diels-Alder adduct **CXVIIb** was not delineated. Xia, Lee, and their coworkers reported the cyclization of **203** to give the strained benzocyclobutene

derivative **204** (Figure 24c).[120] This demonstrates how even subtle changes in structure can impact reaction outcomes. The alcohol-containing substrate **203** gave a higher yield of Alder-ene product than any of a series of similar substrates that lacked a hydroxyl group. The hydrogen bond in the benzyne **CXVIII** is argued to induce bond-angle strain, increasing the proximity of the alkene and benzyne in **CXVIII**. This is an example of a phenomenon that the purely thermal HDDA reaction rendered detectable; it likely would be invisible, if not inoperative, in the presence of the reagents present in virtually all of the methods for generating benzynes by classical methods.

In recent work, researchers in the Yao and Tan labs have described the reaction between HDDA benzynes and the thiolactam **205** (Figure 24d).[121] For example, heating **142** with this oxindole analog gave the thioimino ether product **206** via a process that can be rationalized by the transition structure **CXIX**.

As mentioned earlier, it is often the case that if no trapping agent is present when an HDDA benzyne is formed, an intractable array of products is often formed. However, certain substrate polyynes are exceptional; instead they form structurally complex, unsymmetrical dimers (cf. Figure 5j).[52] Researchers in the Engels and Marder groups have reported an interesting example of this dimerization process. As shown in Figure 24e, the tetrayne **207**, when heated in toluene solution, gave the naphthalene derivative **210** as the major product. [122] It is notable that the initial benzyne **CXXa** was trapped by Diels-Alder reaction with a toluene solvent molecule when the initial concentration of **207** was ca. 0.012 M. Increasing the [**207**]$_0$ to 0.16 M allowed for a more competitive intervention of a second molecule of the tetrayne to proceed, via benzocyclobutadiene **CXXb** and Dewar naphthalene **CXXc**, to the dimer adduct **208**. This study also demonstrates another feature common to a number of HDDA reactions. The identification of additional minor products (not shown here) allowed several other energetically viable pathways to be delineated. It is often the case that the practice of 'digging through' minor products, while of arguable preparative value, expands our awareness and understanding of entirely new mechanistic pathways.

Finally, capitalizing on the photo-HDDA[60] reaction, investigators in the Marder, Mitric, and Brixner labs have recently reported their use of femtosecond transient absorption spectroscopy to provide the first direct evidence for the intermediacy of a benzyne in an HDDA reaction.[123] A body of data from the excitation and decay of species produced by irradiation of a solution of substrate **207** was interpreted to support the existence of a steady state concentration of the benzyne **CXXa** in this fundamentally important study.

7. CONCLUSION

In conclusion, the hexadehydro-Diels-Alder reaction provides a valuable (and intriguing) route for the preparation of complex benzenoids by way of a benzyne intermediate. A wide variety of structurally diverse species are accessible due to the large number of tethers and trapping agents that are compatible with the purely thermal reaction conditions (i.e., in the absence of other reagents). Examples of new tethers and new trapping reagents or reactions will continue to emerge as increasing numbers of investigators contemplate the opportunities provided by this approach to forming benzynes by a protocol that is quite complementary to

and distinct from other aryne-generating methods. Studies of HDDA reactions have also provided new mechanistic understanding and insights about benzyne reactivity, and many additional such results are embedded in the primary publications cited here. Finally, new avenues are also being opened by strategic developments such as the domino-, photochemical-, and aza-HDDA reactions, which adds further versatility to the synthetic utility. Future new strategic advances can also be anticipated.

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Biographies

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a

classical
Diels-Alder
(DA)

didehydro-DA
(DDDA)

tetradehydro-DA
(TDDA)

hexadehydro-DA
(HDDA)

b
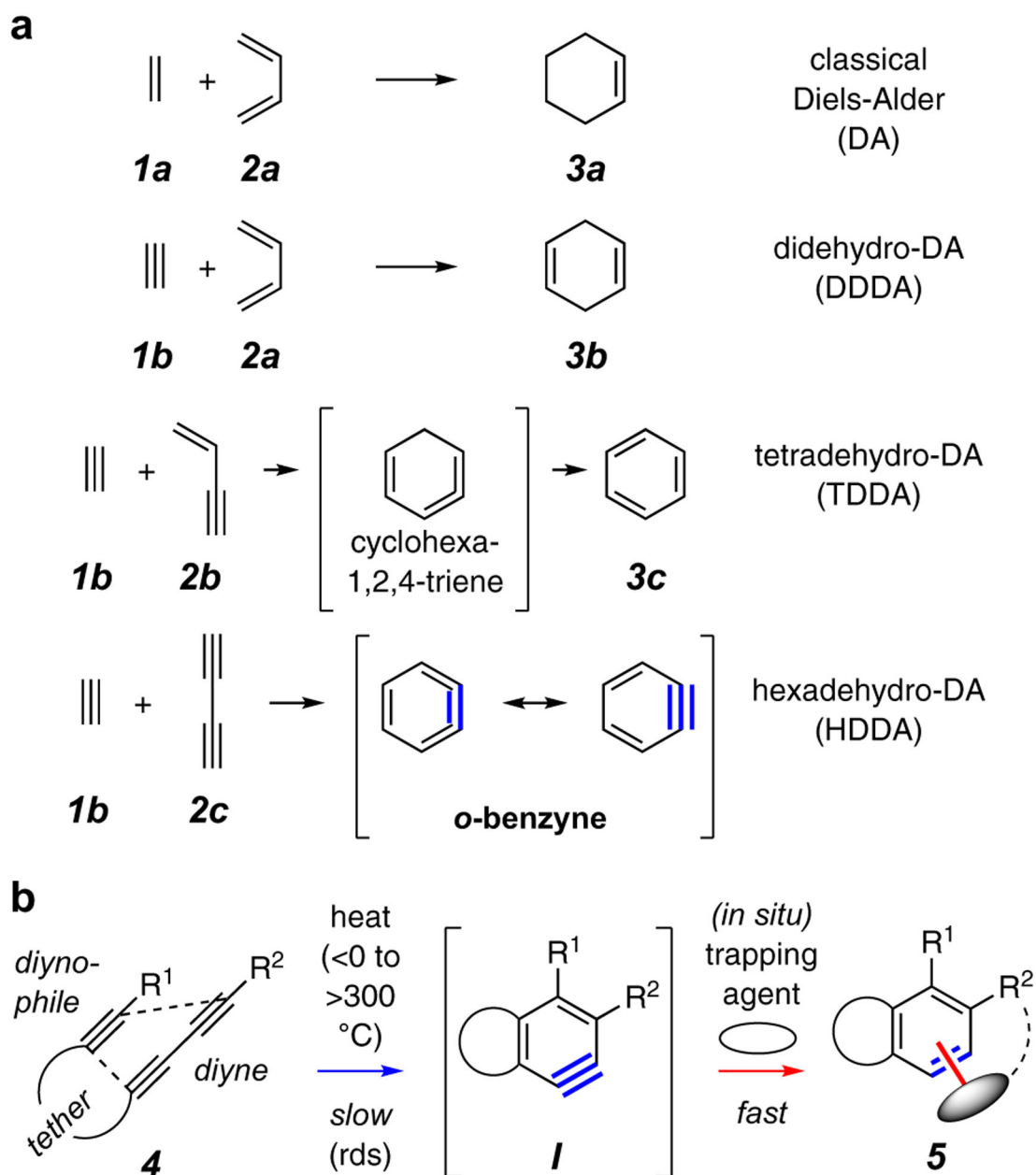
Figure 1.
(a) The family of prototypical classical and various dehydro-Diels-Alder reactions of increasing oxidation states. (b) The generic intramolecular hexadehydro-Diels-Alder (HDDA) cyclization and benzyne-trapping reaction.
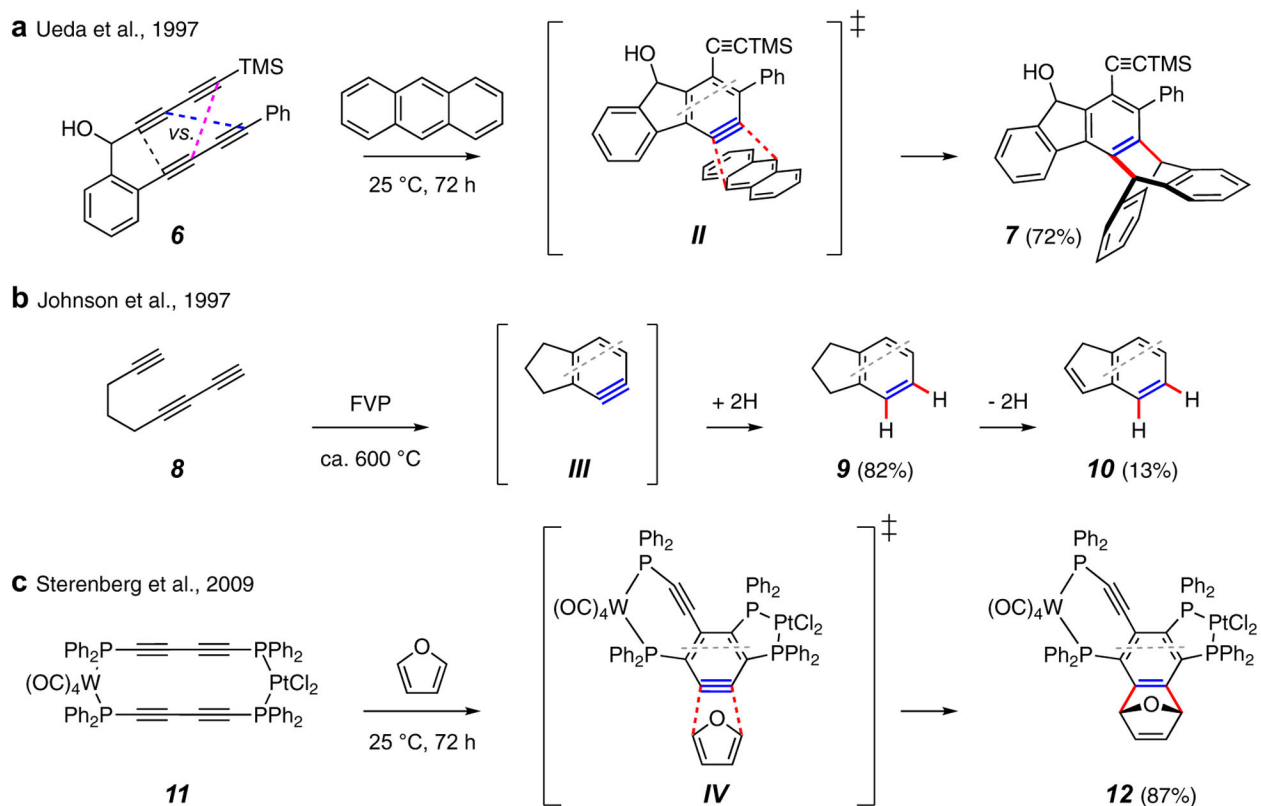
Figure 2.
Earliest reports of cyclization of a triyne to a benzyne intermediate.
(a)formattingasusedbyChemRev Ueda and coworkers (1997): trapping of the benzyne **II**
with anthracene gives the triptycene **7**. (b) Johnson and coworkers (1997): high temperature
(short time) cycloisomerization of **8** to **10** via **III** and **9**. (c) Sterenberg and Tsui (2009):
intra-annular cyclization of dinuclear complex **11** in the presence of furan gives the adduct
12 via **IV**.
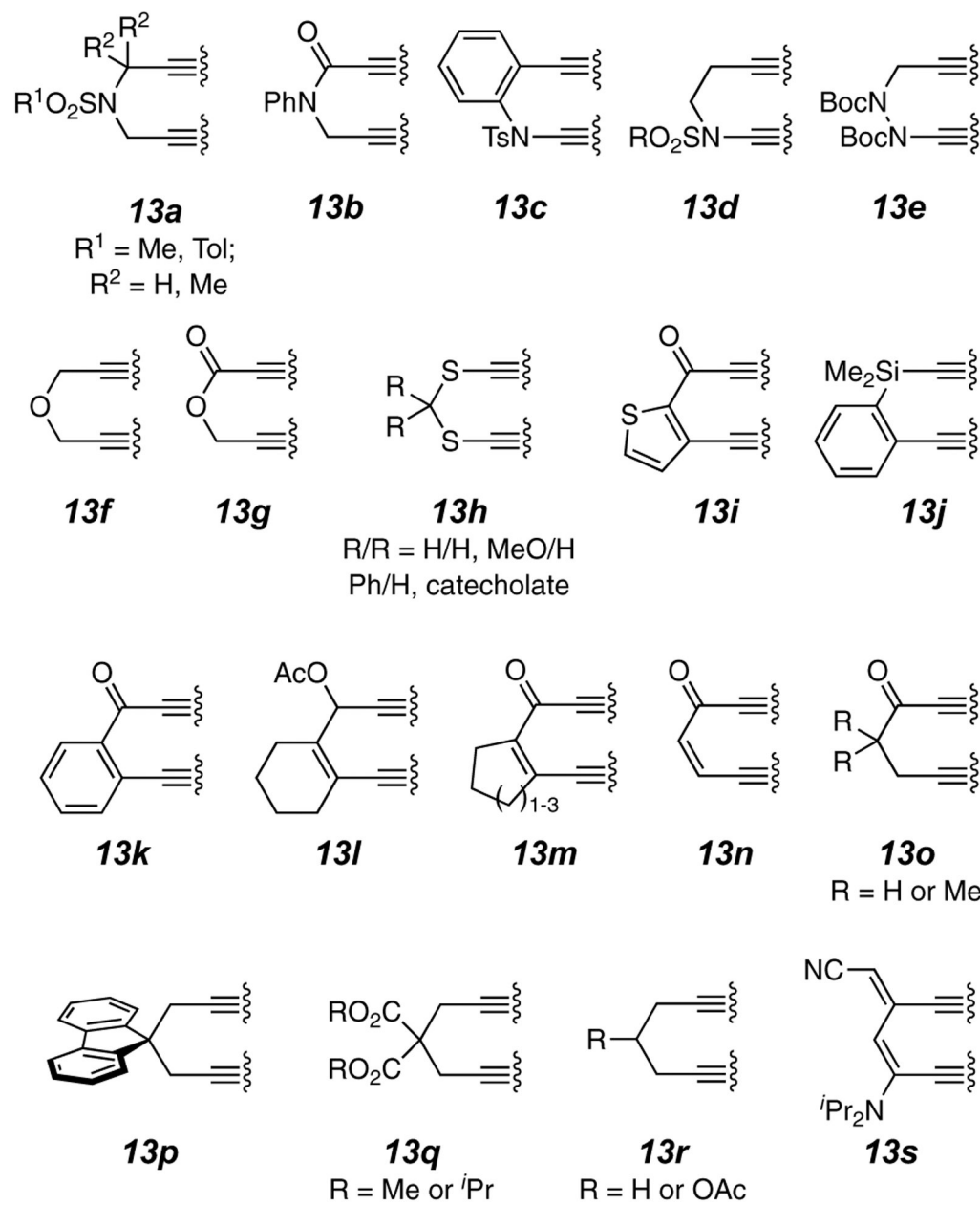
Figure 3.

The majority of the three-atom tethers present in reported HDDA polyyne substrates.
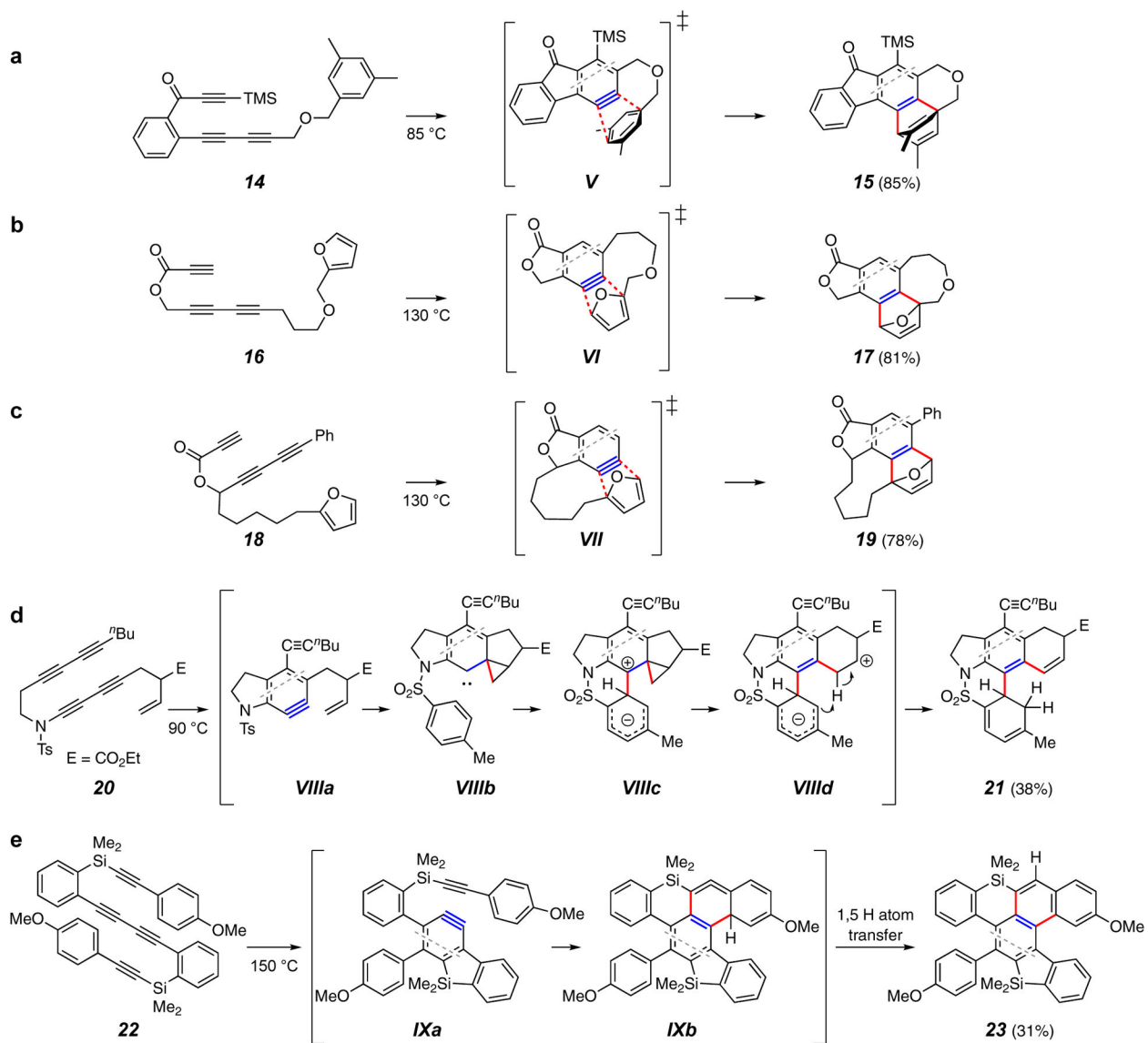
Figure 4.
<u>Intramolecular</u> traps forming two C–C bonds.

a

24

X

25 (70%)

b

X = NTs, O, S, CH₂

80 °C

26

XI

27 X = O, 90%; NTs, 81%; S, 30% (extruded prod.); CH₂, 84%

c

100 °C

28

XII

29 (83%)

d

100 °C

28

XIII

30 (84%)

e

80 °C

28

XIV

−CO

31 (82%)

f

85 °C

28

XV

− H₂

32 (56%)

g

85 °C

24

XVI

33 (63%)
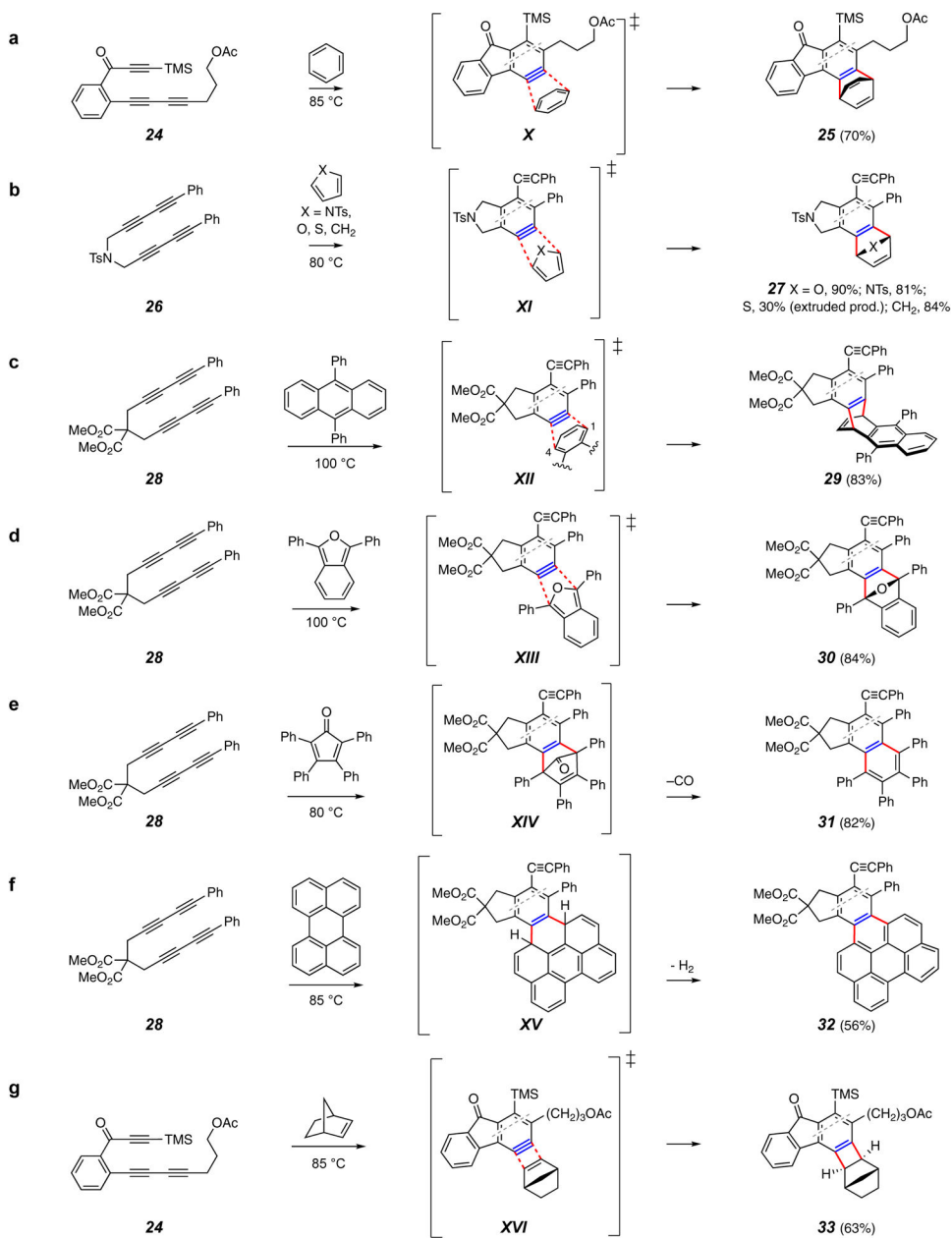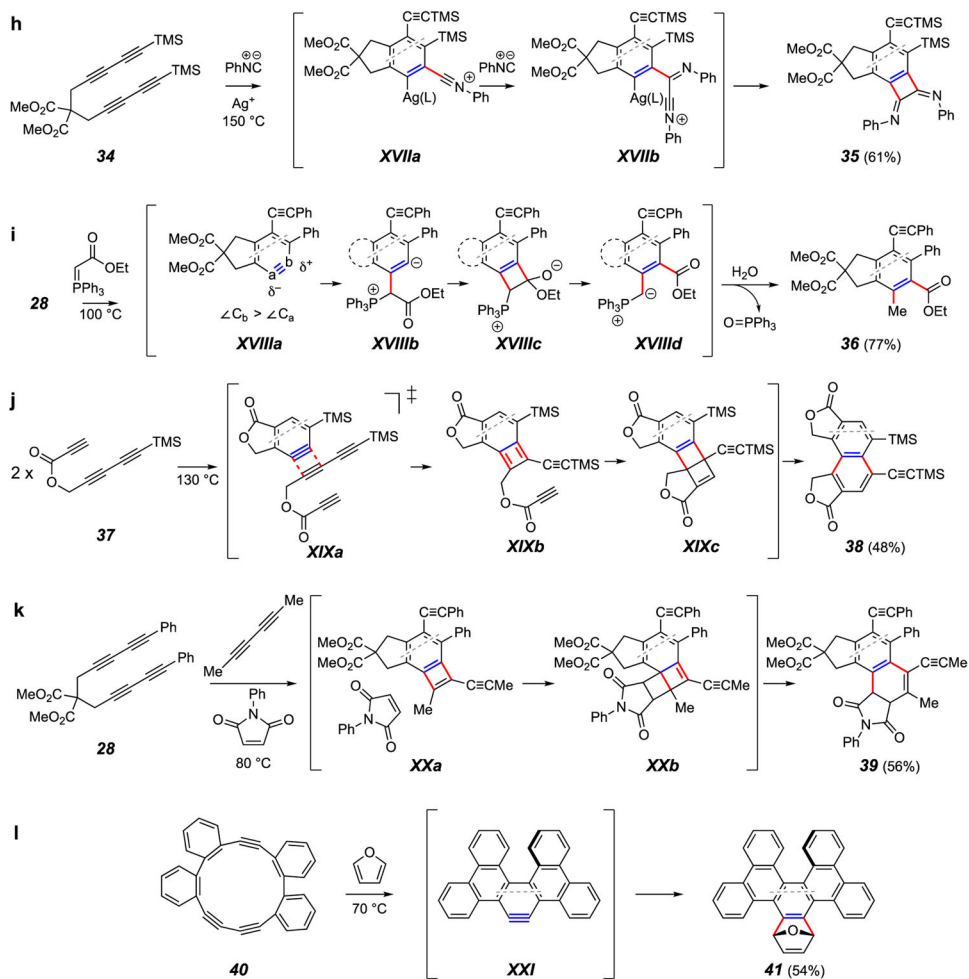
Figure 5.
<u>Intermolecular</u> traps forming two C–C bonds.
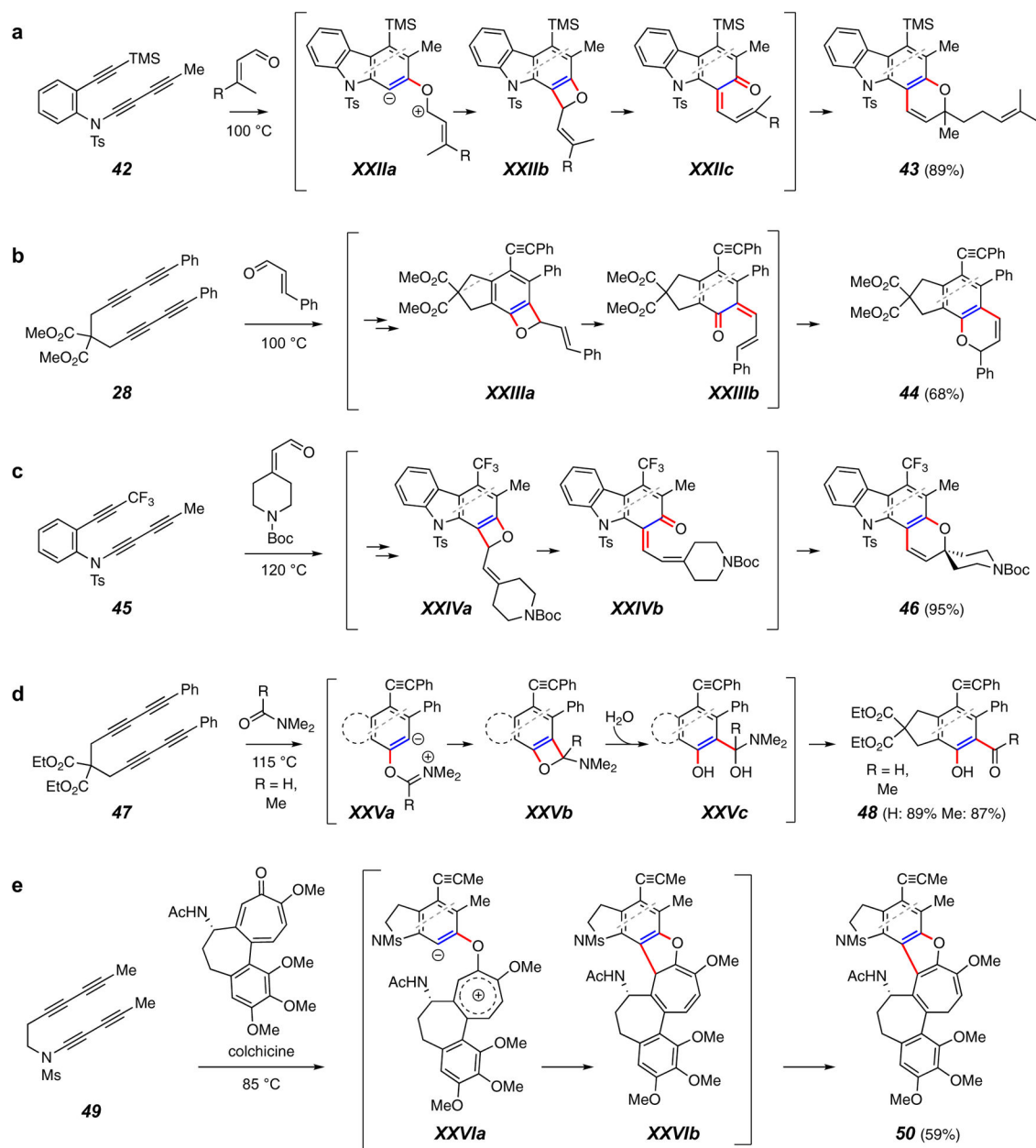
Figure 6.
Trapping reactions forming a C–C and a C–O bond. (a-c) Reactions with enals begins with benzoxetene formation prior to electrocyclic opening and reclosure to produce benzopyrans. (d) Nucleophilic amides capture benzynes to product *o*-hydroxy aldehydes and ketones such as **48**. (e) The cycloheptatrienone in colchicine captures an HDDA-produced benzyne to give the benzofuran derivative **50**.
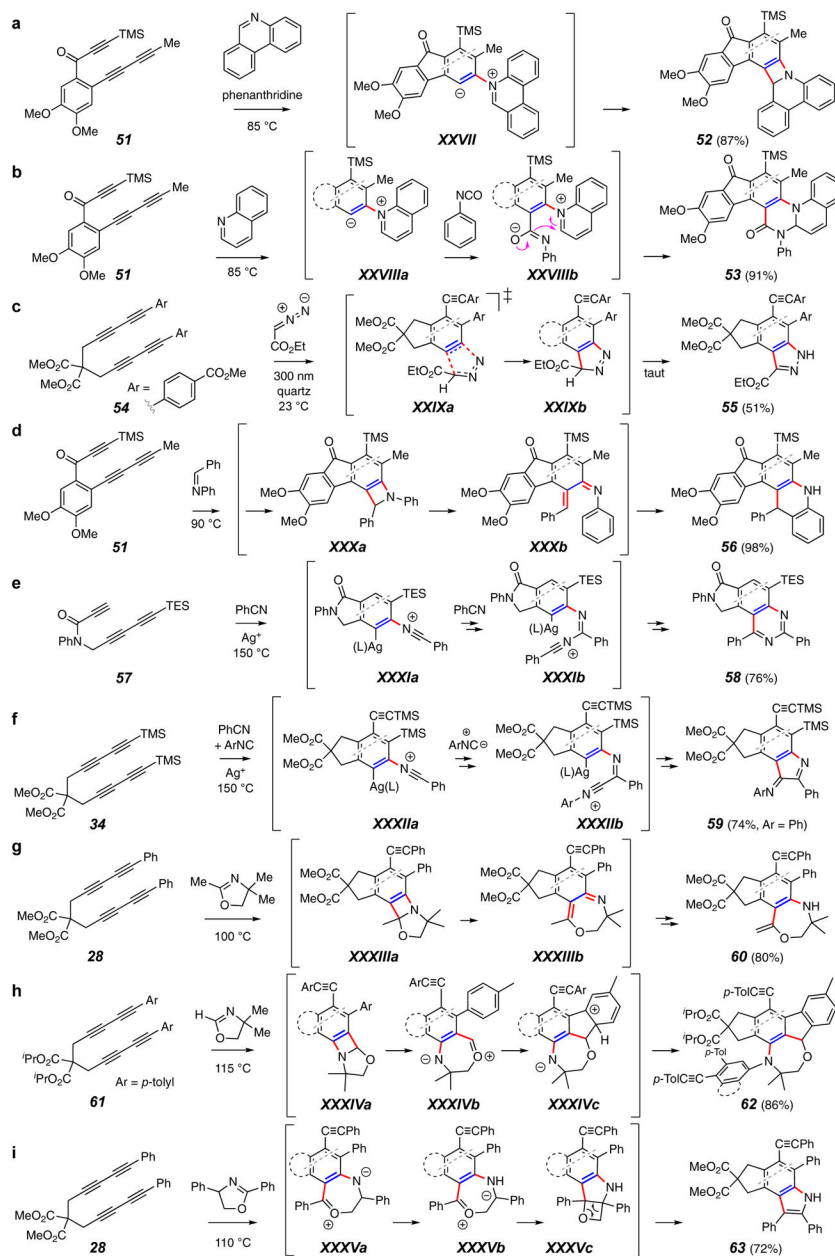
Figure 7.
Trapping reactions forming a C–C and a C–N bond.
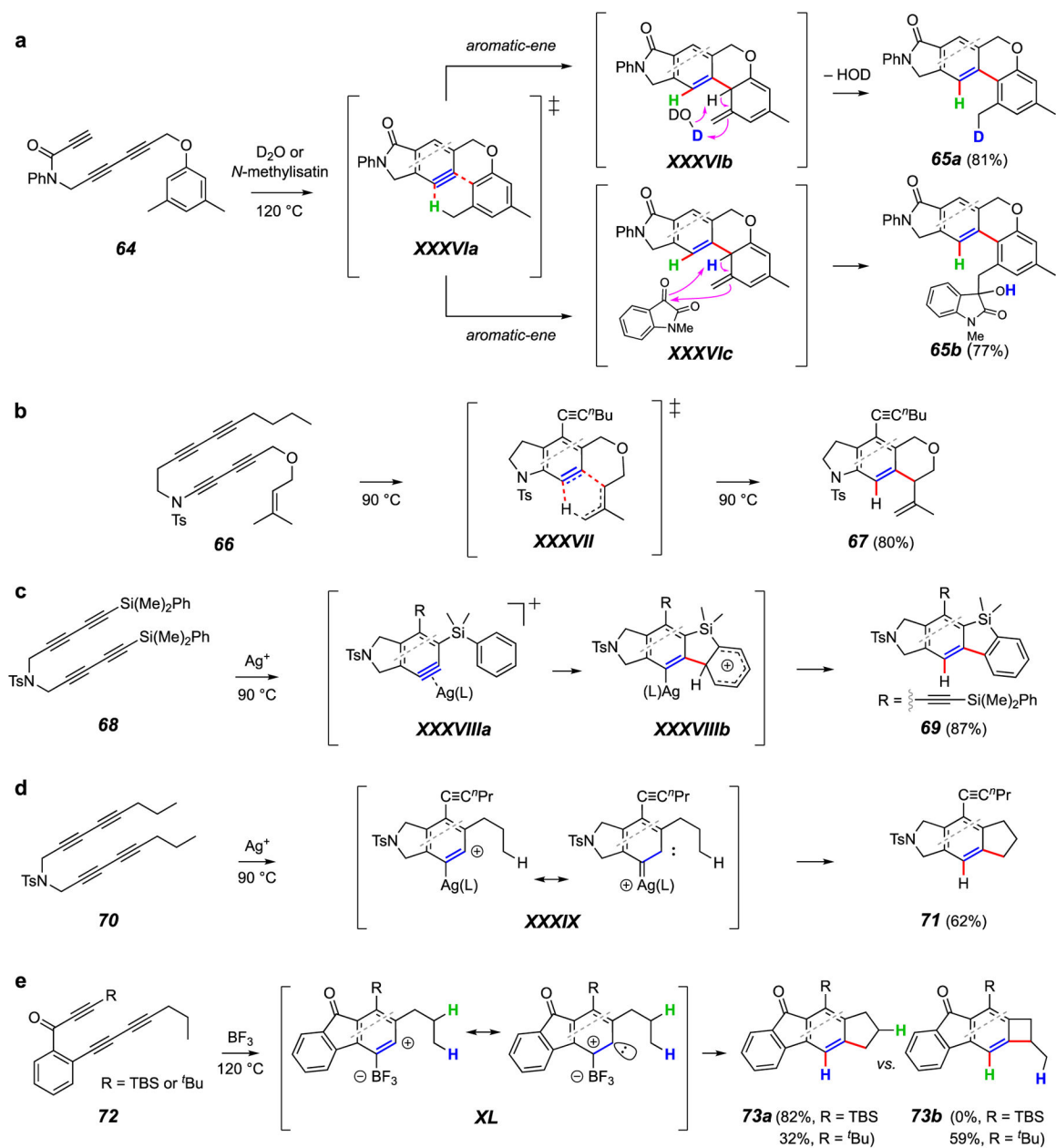
Figure 8.
(Intramolecular) trapping reactions forming a C–C and a C–H bond.
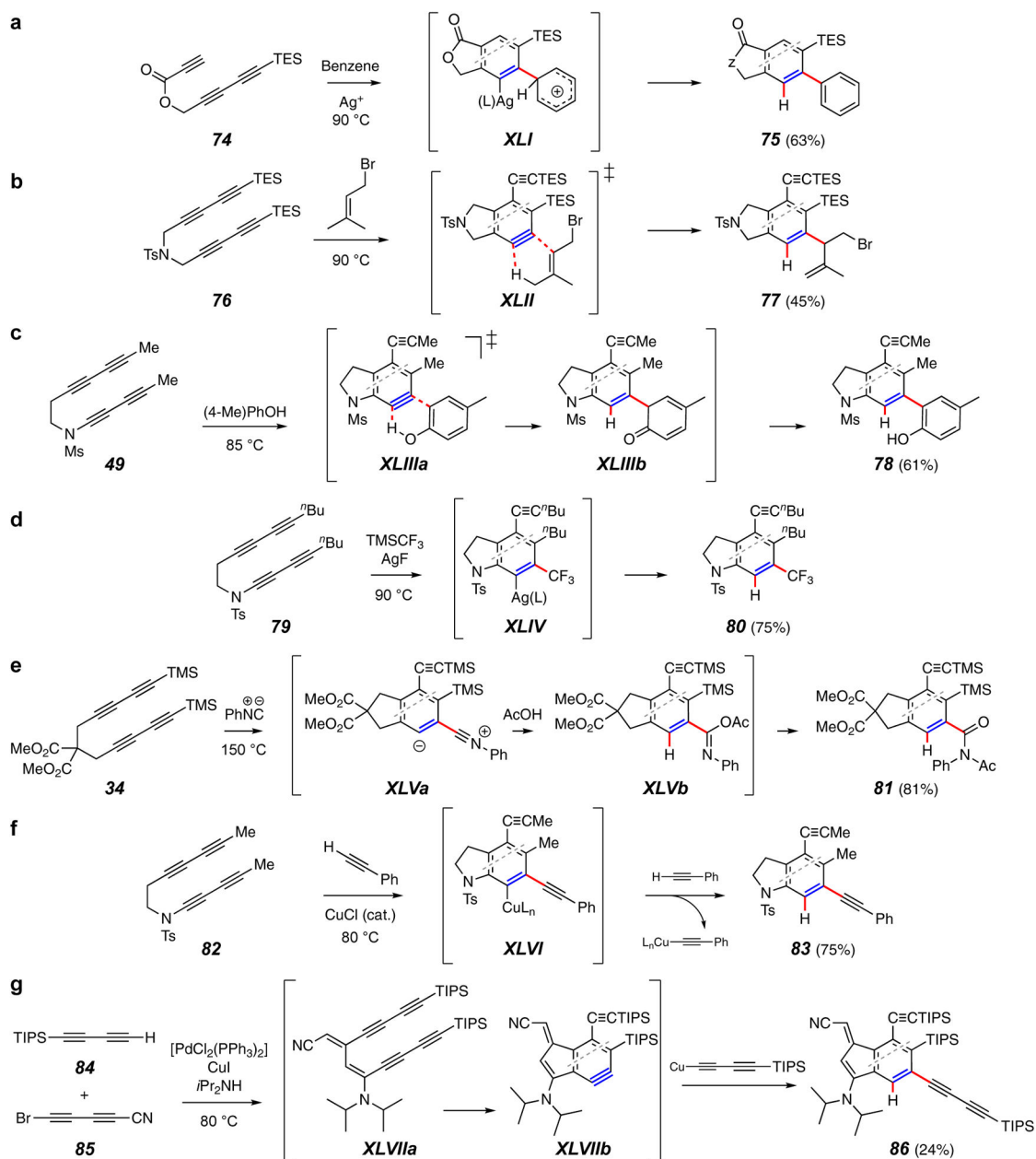
Figure 9.
(Intermolecular) trapping reactions forming a C–C and a C–H bond.
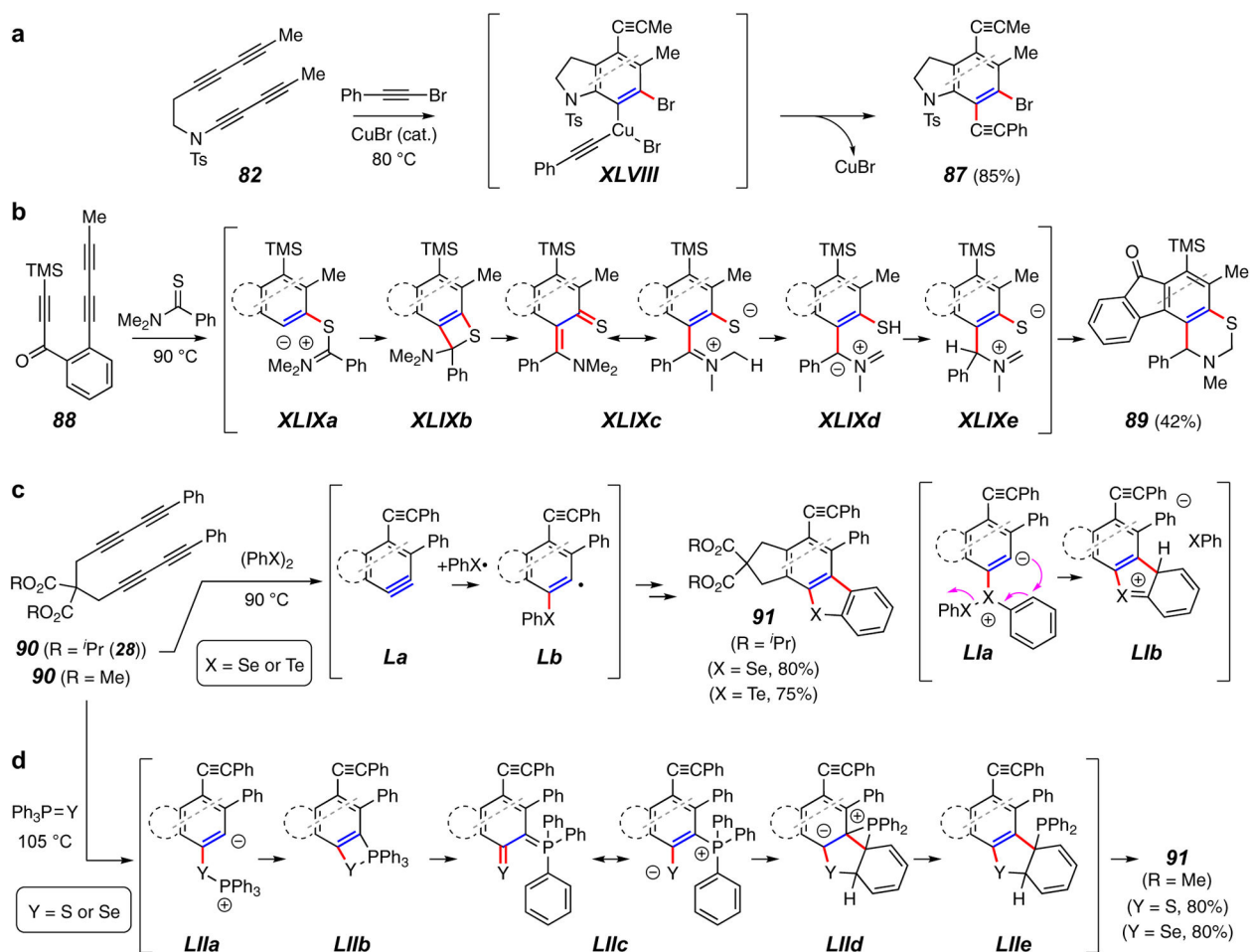
Figure 10.
Trapping reactions forming a C–C and a C–Br, C–S, C–Se, or C–Te bond.
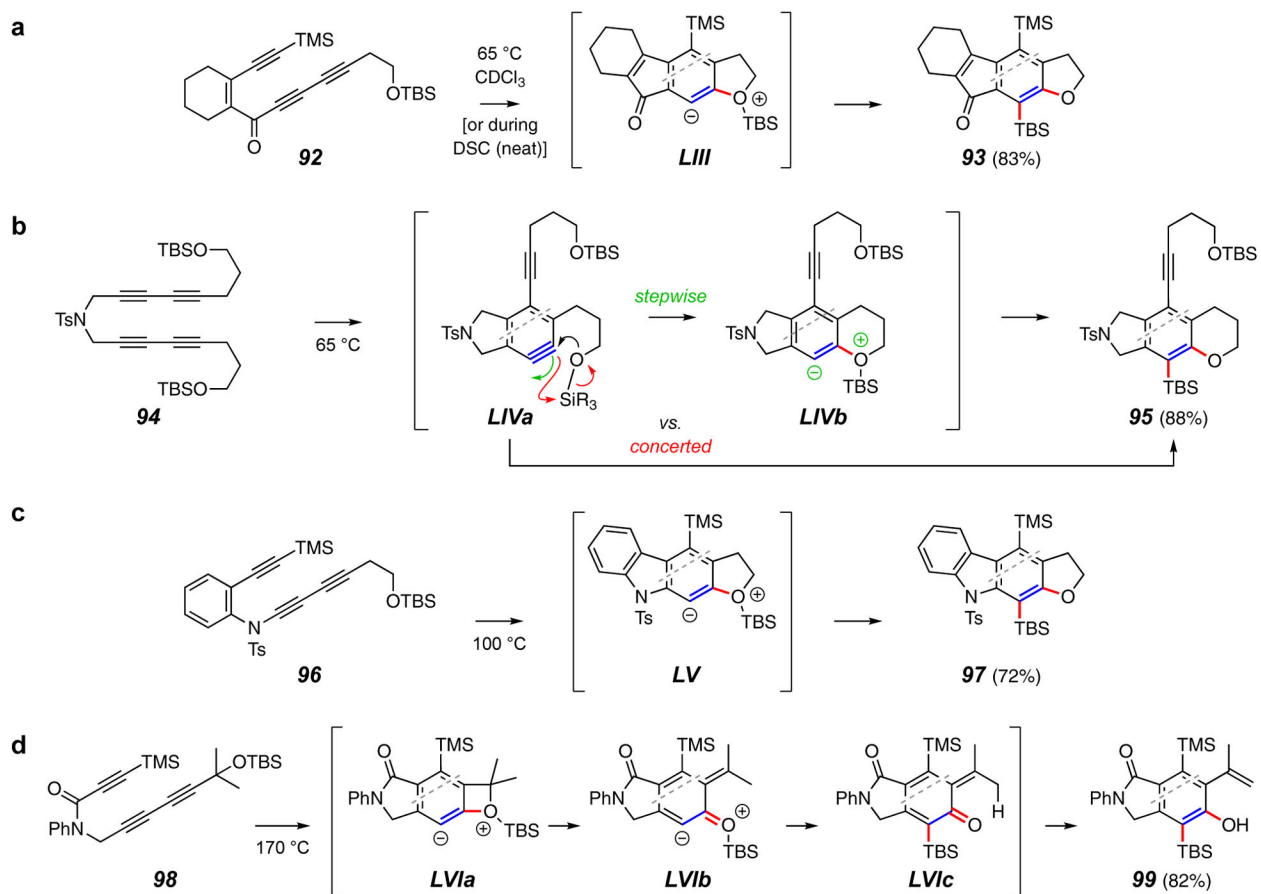
Figure 11.
Trapping reactions forming a C–O and a C–Si bond.

a

b

c

d
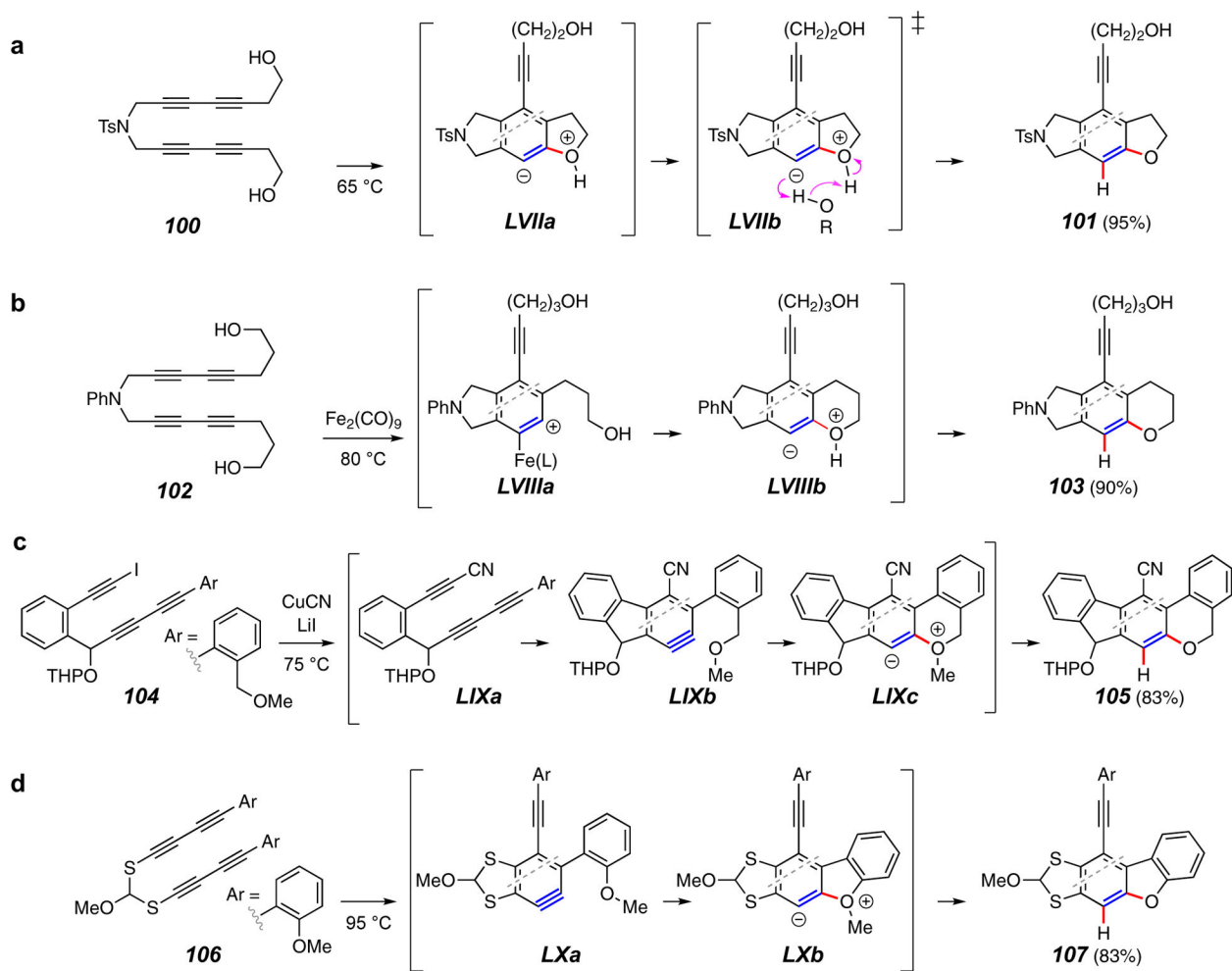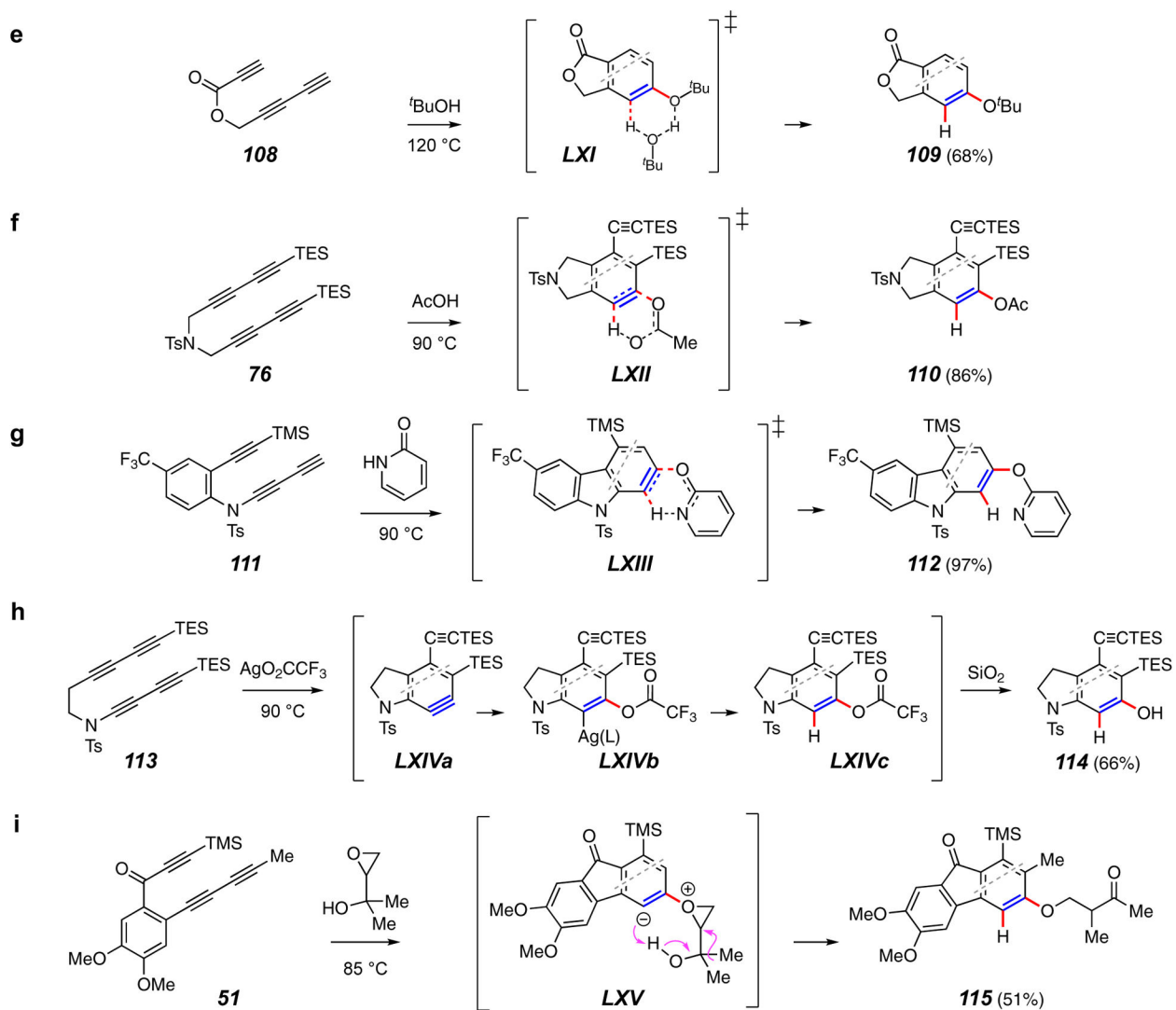
Figure 12.
Trapping reactions forming a C–O and a C–H bond.
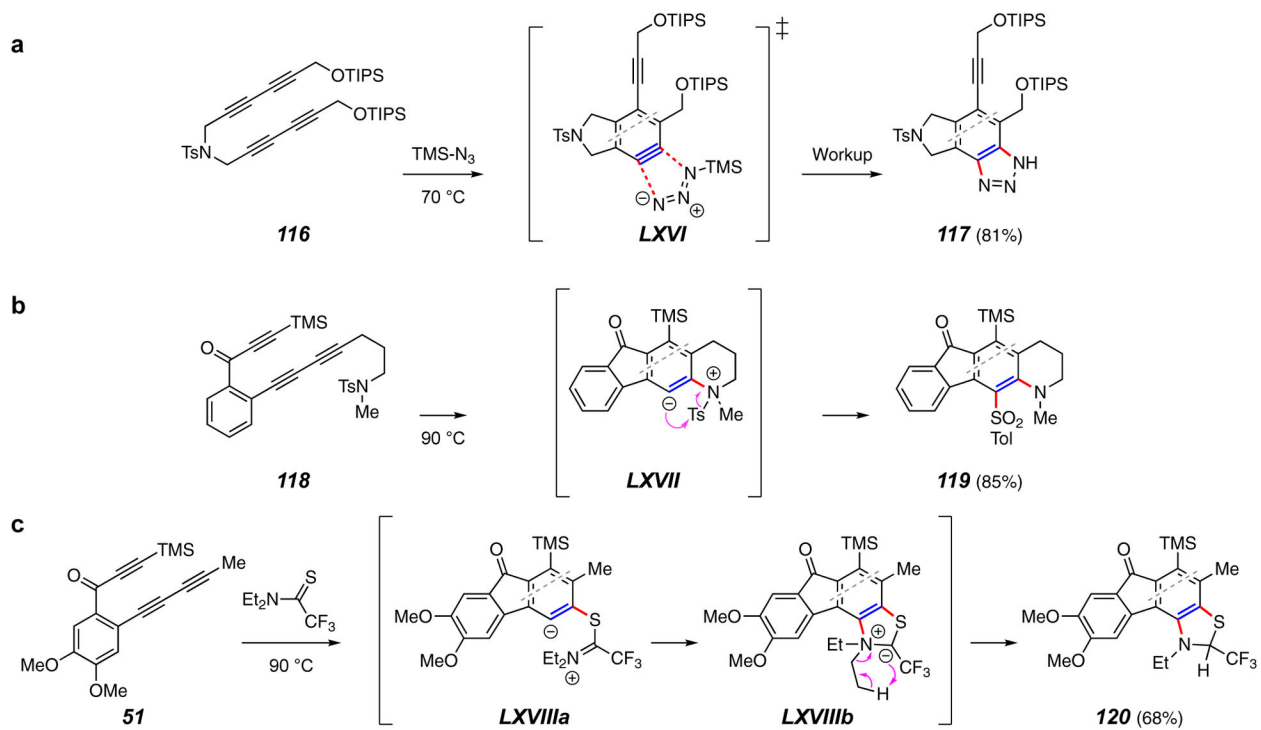
Figure 13.
Trapping reactions forming two C–N bonds or a C–N and a C–S bond.
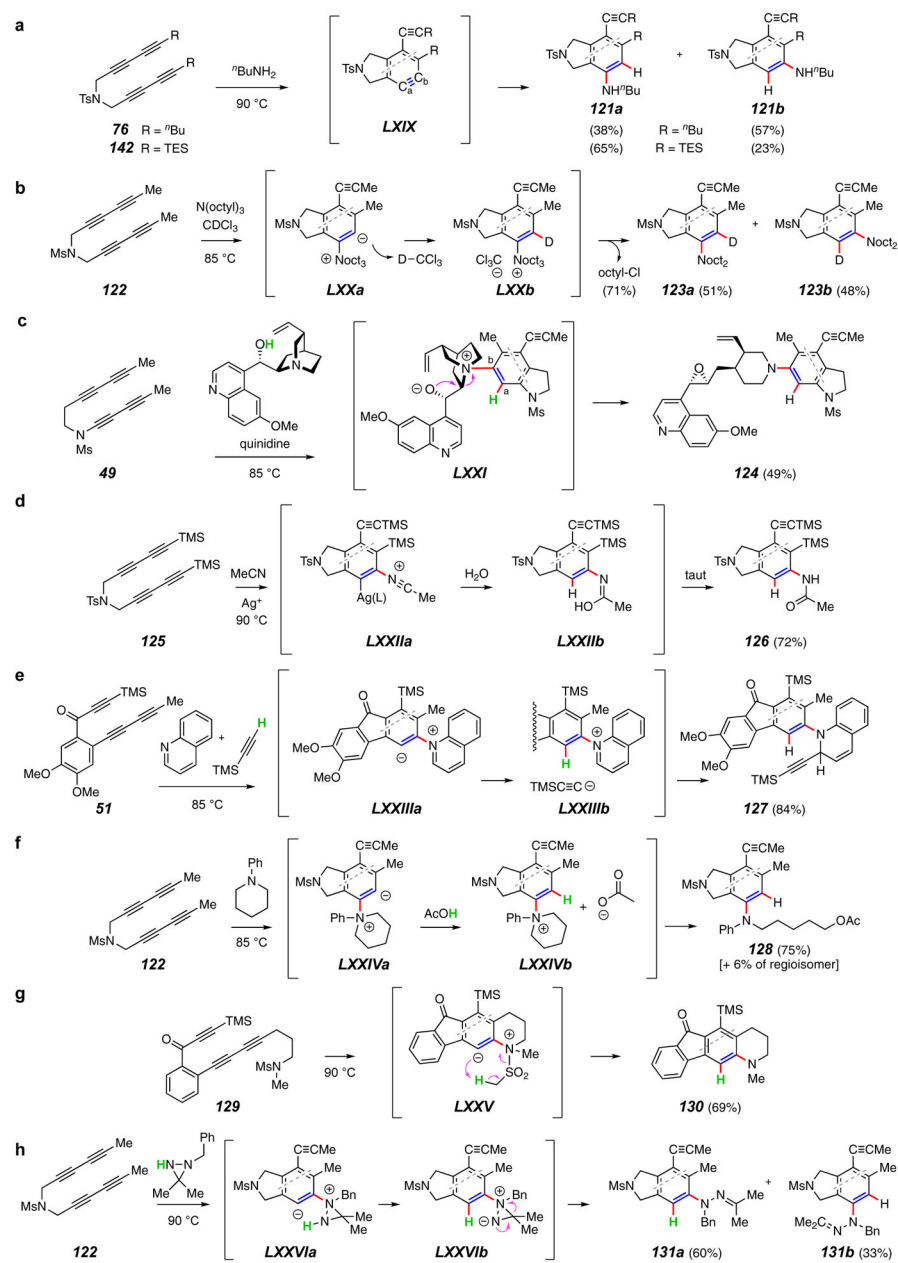
Figure 14.
Trapping reactions forming a C–N and a C–H bond.
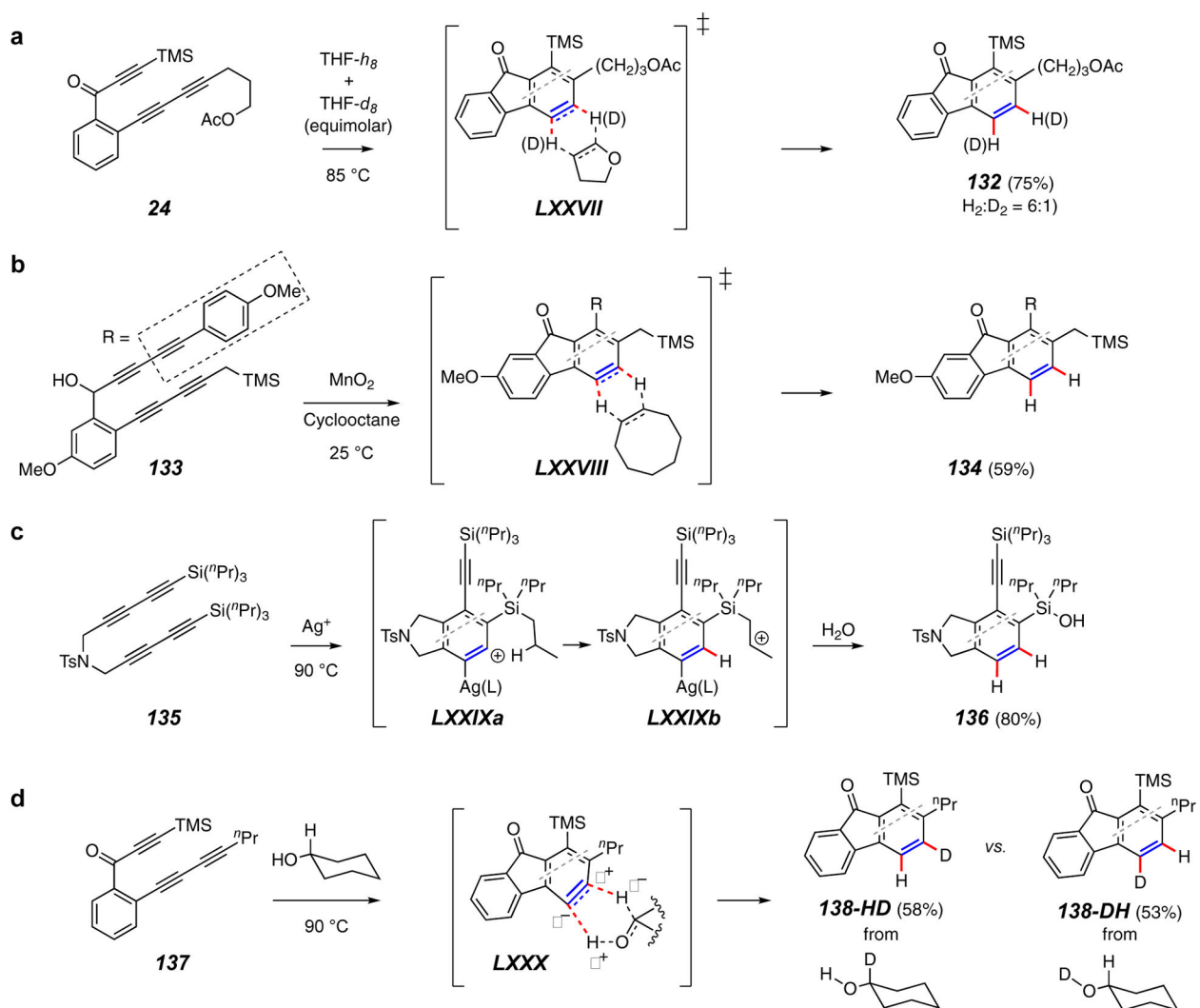
Figure 15.
Trapping reactions forming two C–H bonds.
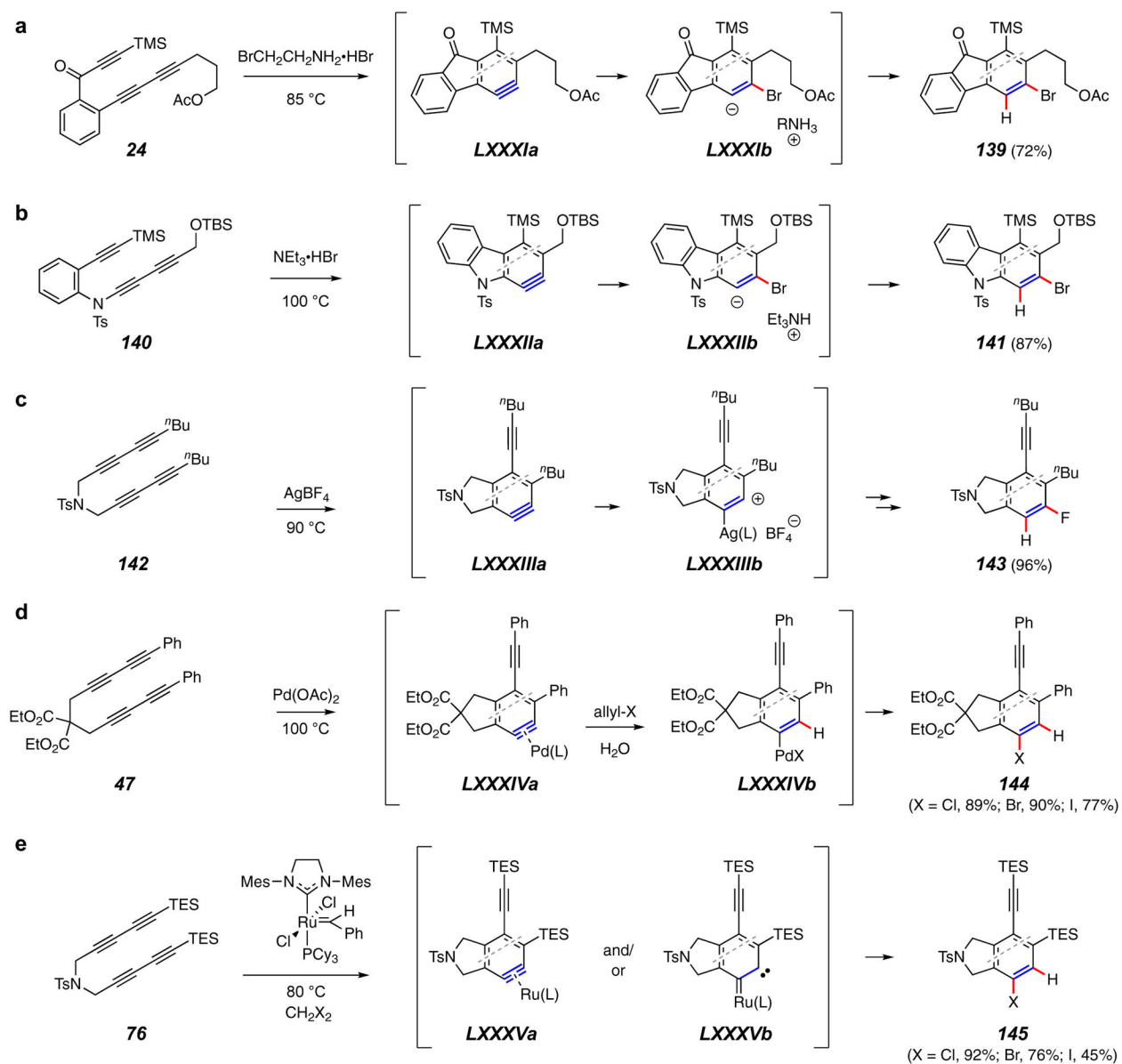
Figure 16.
Trapping reactions forming a C–H bond and a C–Hal bond.
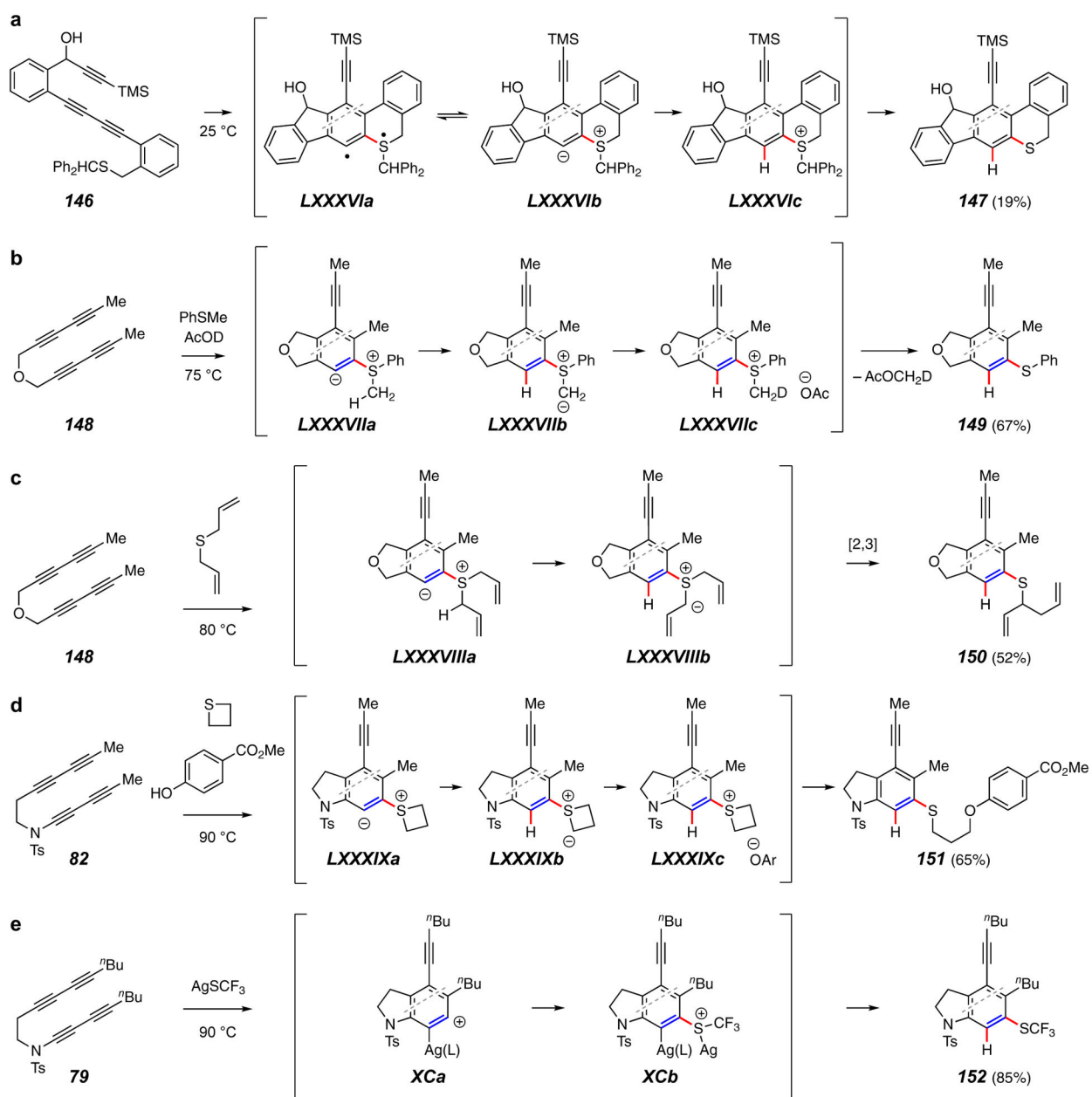
Figure 17.
Trapping reactions that form a C–H bond and a C–S bond.
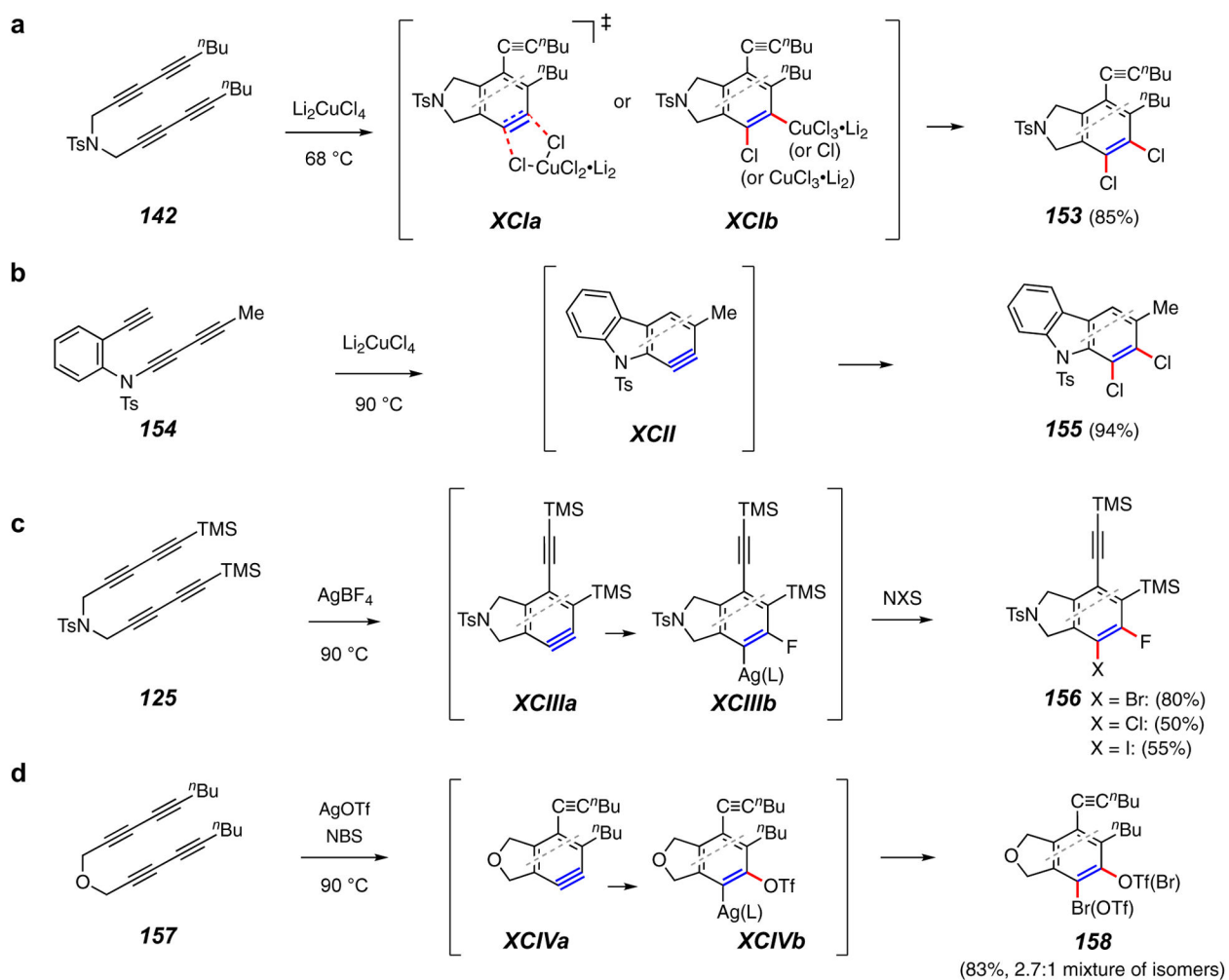
Figure 18.
Trapping reactions that form a C–Hal bond as well as a (second) C–Hal or a C–O bond.
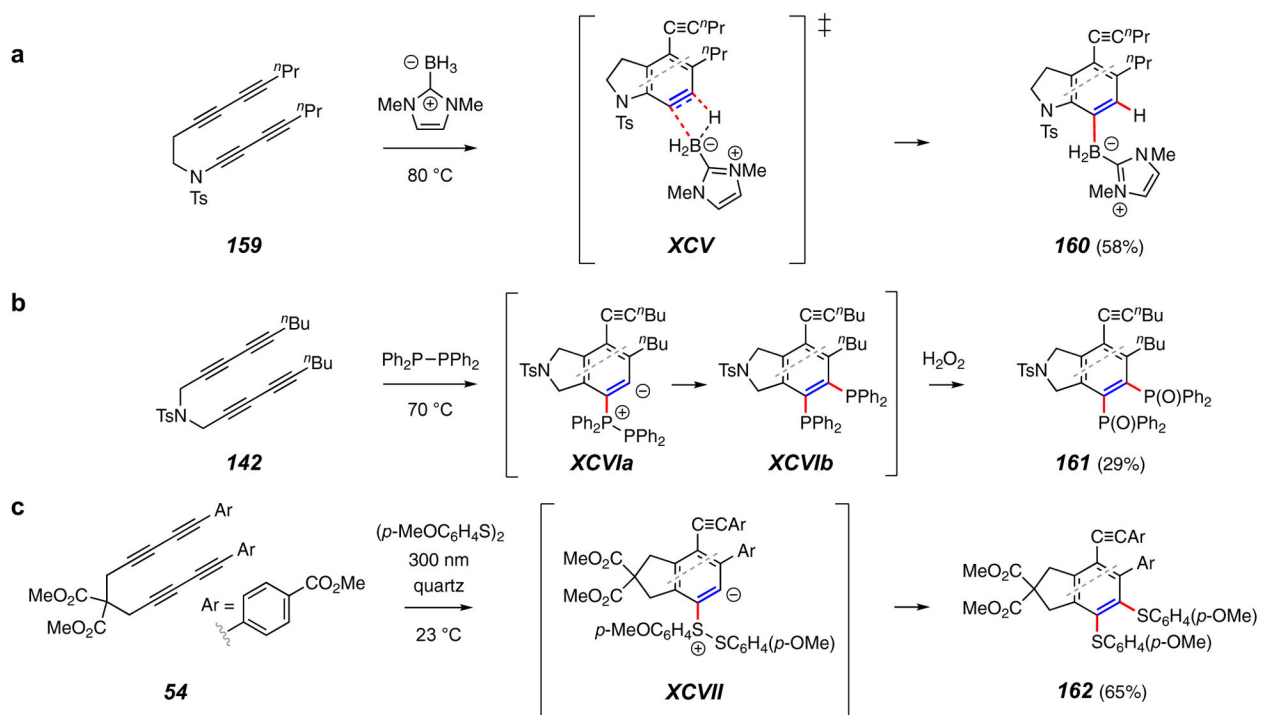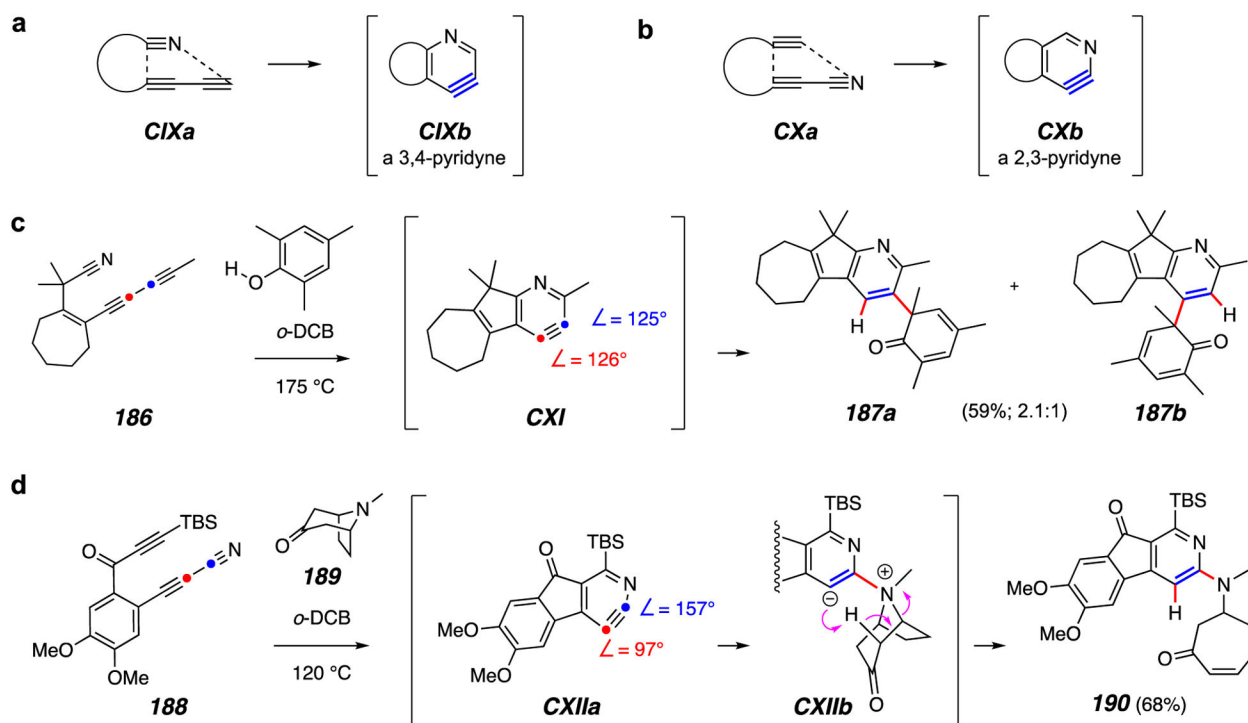
Figure 19.
Trapping reactions that form (a) a C–H and a C–B bond, (b) two C–P bonds, and (c) two C–S bonds.
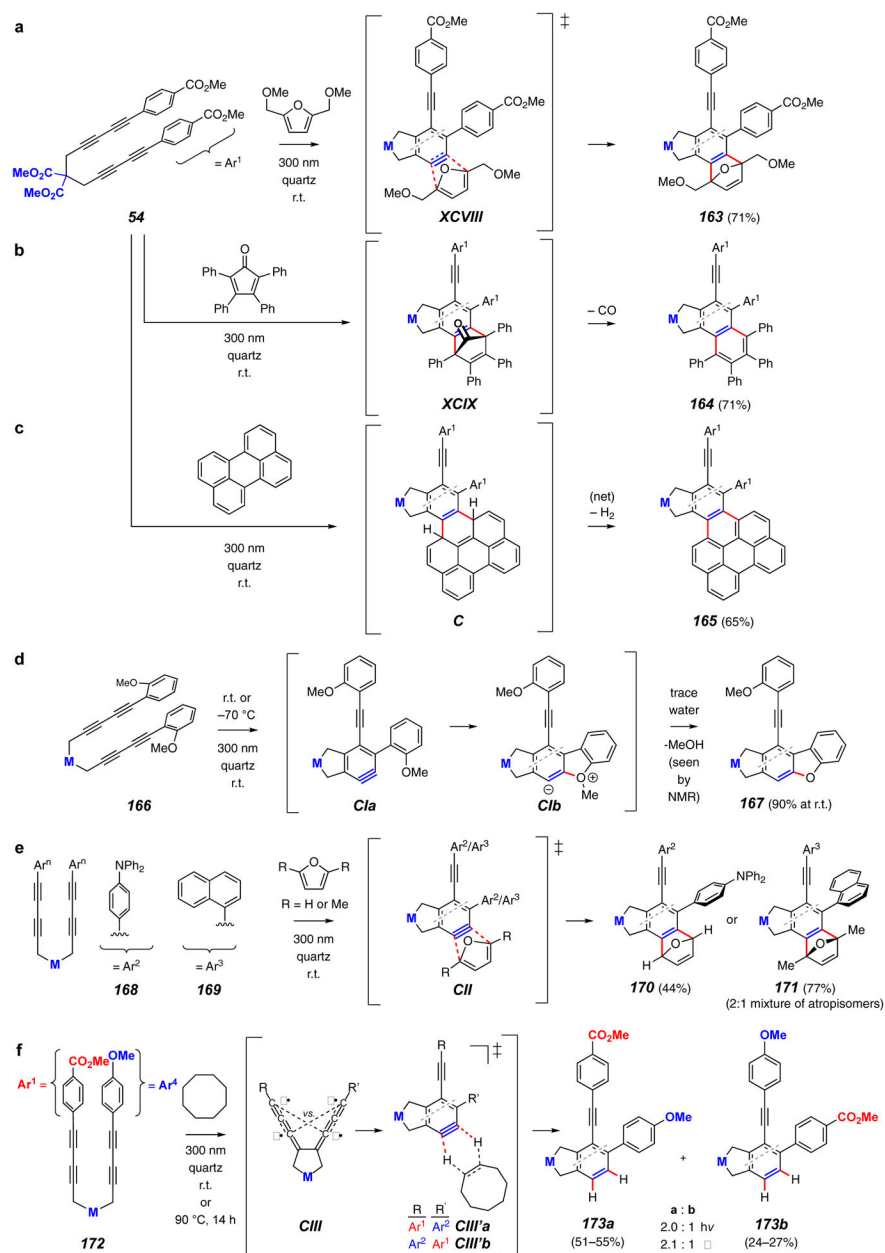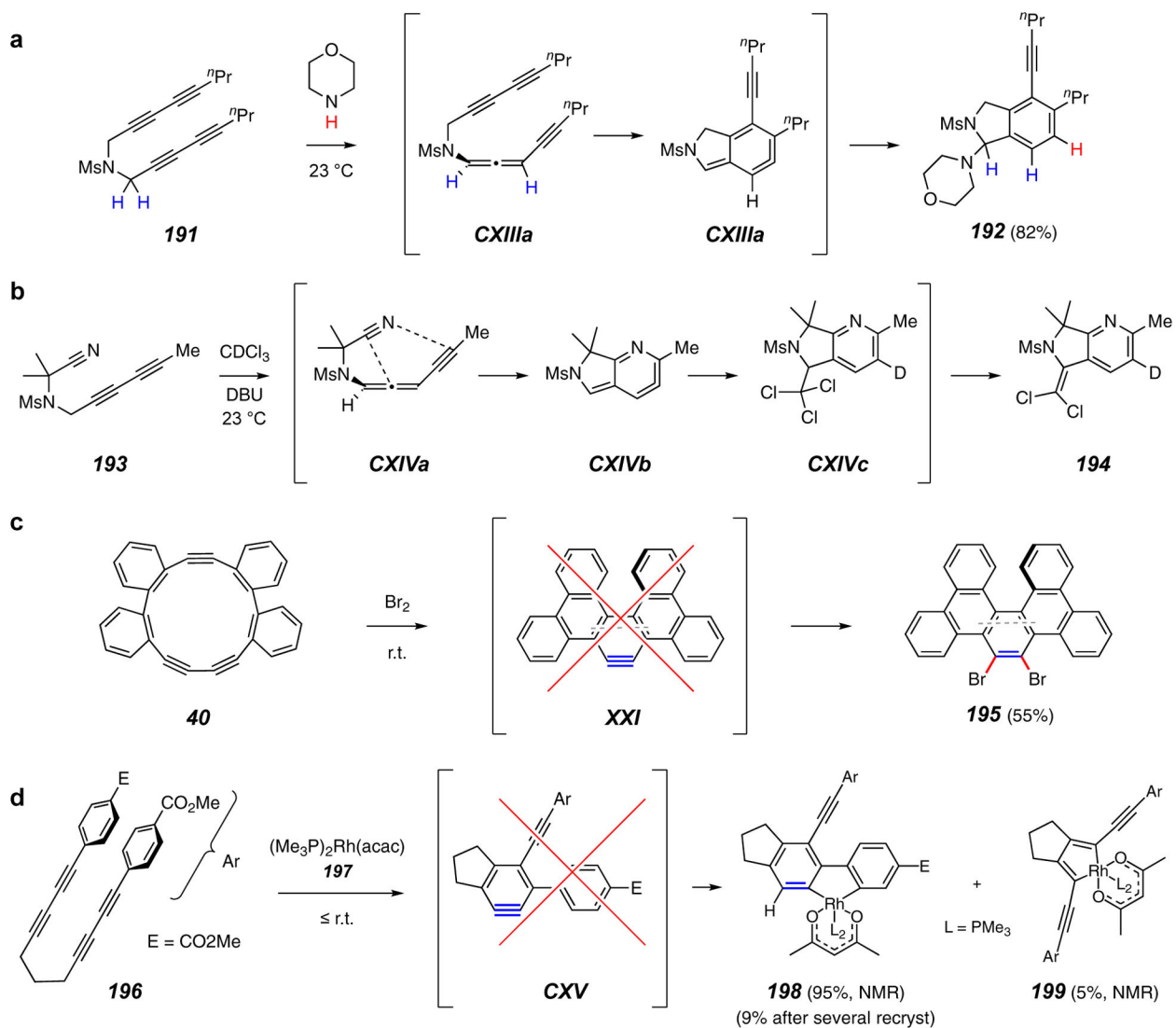
Figure 20.
Examples of the photochemical HDDA (h*v*-HDDA) reaction.
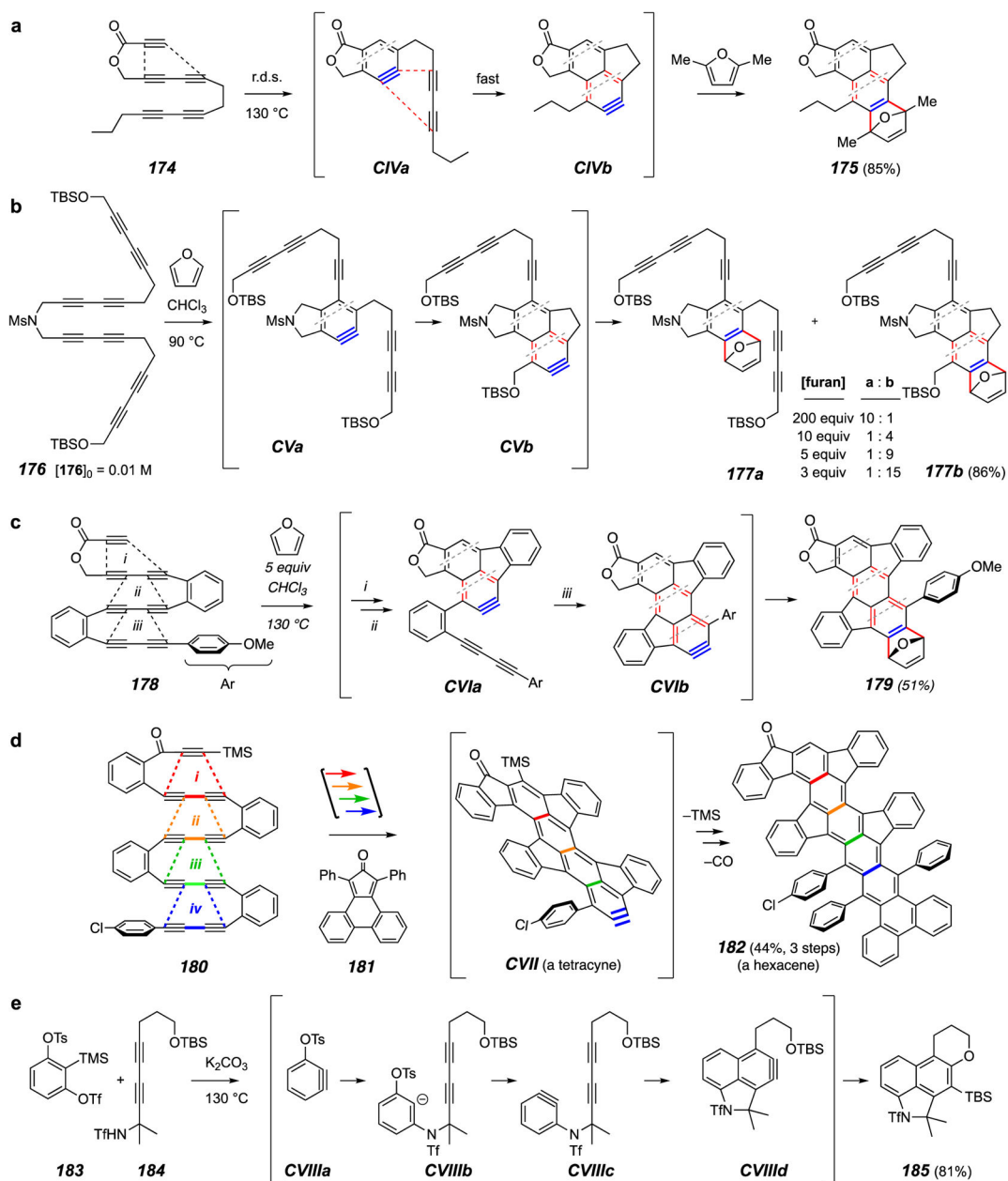
Figure 21.
Examples of the domino HDDA reaction. (a) Benzyne to naphthyne. (b) Evidence for the intermediacy of a benzyne. (c) Benzyne to naphthyne to anthracyne. (d) Benzyne to naphthyne to anthracyne to tetracyne. (e) A domino cascade involving benzynes generated by both classical and HDDA processes.

Figure 22.
Aza-HDDA reactions. (a) Generic formation of a 3,4-pyridyne. (b) Generic formation of a 2,3-pyridyne. (c) A relatively unselective trapping of a 3,4-pyridyne. (d) A highly selective trapping of a 2,3-pyridyne.

Figure 23.
Reactions of polyyne substrates that proceed under conditions that would not promote appreciable levels of HDDA benzynes, indicating that the co-reactant is promoting cyclization by engaging the substrate prior to the thermal HDDA cycloisomerization.
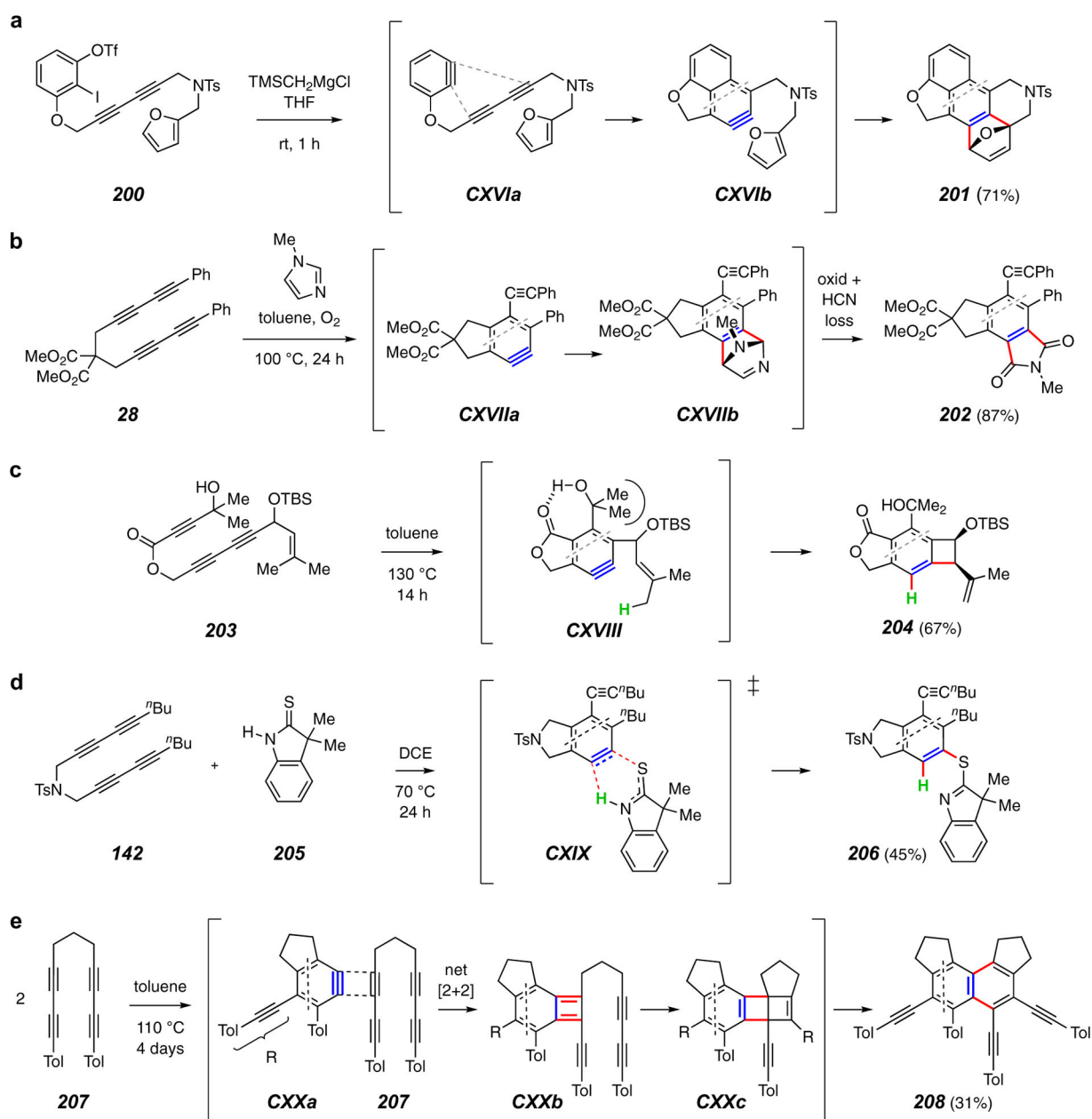
Figure 24.
Reactions identified during manuscript review or published since initial submission.