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The pentadehydro-Diels–Alder reaction

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Abstract

In the classic Diels–Alder (DA) [4+2] cycloaddition reaction[1], the overall degree of unsaturation of the 4π (diene) and 2π (dienophile) pairs of reactants dictates the oxidation state of the newly formed six-membered carbocycle. For example, in the classic DA reaction, butadiene and ethylene combine to produce cyclohexene. More recent developments include variants in which the hydrogen atom count in the reactant pair and in the resulting product is reduced by[2], for example, four in the tetradehydro-DA (TDDA) and by six in the hexadehydro-DA (HDDA[3,4,5,6,7]) reactions. Any oxidation state higher than tetradehydro leads to the production of a reactive intermediate that is more highly oxidized than benzene. This significantly increases the power of the overall process because trapping of the benzyne intermediate[8,9] can be used to increase the structural complexity of the final product in a controllable and versatile manner. In this manuscript, we report an unprecedented *net* 4π+2π cycloaddition reaction that generates a different, highly reactive intermediate known as an α,3-dehydrotoluene. This species is at the same oxidation state as a benzyne. Like benzynes, α,3-dehydrotoluenes can be captured by various trapping agents to produce structurally diverse products that are complementary to those arising from the HDDA process. We call this new cycloisomerization reaction a pentadehydro-Diels–Alder (PDDA) reaction—a nomenclature chosen for chemical taxonomic rather than mechanistic reasons. In addition to alkynes, nitriles (RC≡N), although non-participants in aza-HDDA reactions, readily function as the 2π-component in PDDA cyclizations to produce, via trapping of the α,3-(5-aza)dehydrotoluene intermediates, pyridine-containing products.

The overall oxidation states of the π-bond-containing pair of reactants in Diels-Alder processes can be viewed as the total amount of 'dehydroness' (cf. refs[10,11]) of those species (Fig. 1). This can be identified either from the overall hydrogen atom count *or* by the number of sp-hybridized carbon atoms that engage to create the newly formed six-membered ring (cf. □ and □ in reactants **4** + **5** and **4** + **8**). It occurred to us that a 6π-electron net [4+2] cycloaddition of reactants containing a total of *five* sp-hybridized carbon

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

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atoms—namely, an allenyne + alkyne pair like **11** + **4**—might produce an α,3-dehydrotoluene (cf. **12**, Fig. 1d). The parent species **12** itself has been characterized by photoelectron spectroscopy in the gas-phase[12], and derivatives of **12**, which comprise a little-explored class of reactive intermediate, are generated by the cycloisomerization reaction of allenyl enynes like **14** (Fig. 1e) by the Myers-Saito reaction[13,14,15,16,17] (Fig. 1e). However, we can find no previous examples of the generation of α,3-dehydrotoluene derivatives by a formal cycloaddition event, the process we term here as the pentadehydro-Diels–Alder (PDDA) reaction. We should emphasize that in choosing this nomenclature, we do not mean to imply anything about the mechanism of this net [4+2] cycloaddition. Specifically, it should not be inferred that transformations like **4** + **11** to **12** are required to proceed by a concerted reaction pathway. Finally, it is interesting to note that α,3-dehydrotoluene **12** is merely a tautomer of 3-methyl-1,2-dehydrobenzene (**9**). Accordingly, trapping of **12** leads to a toluene derivative that has been newly functionalized at its benzylic position, whereas capture of the tautomeric benzyne **9** gives rise to a newly substituted benzenoid product.

Our first evidence for a PDDA process came from the reaction of tetrayne **15-Ms** in an ambient temperature solution of piperidine. The benzylic amine **18a** (Fig. 2a) was the only characterizable product formed in this experiment and was isolated in 81% yield following chromatographic purification. Tetrayne **15-Ms** was consumed with a half-life of approximately 15 hours at room temperature. Based on several lines of evidence we have gathered and present below, we believe that the generation of **18a** is best described by (i) initial, rate-limiting piperidine-catalyzed isomerization of **15-Ms** to produce the allenyne **16**, (ii) rapid PDDA cyclization to the dehydrotoluene **17**, and (iii) even more rapid trapping by protic piperidine of that reactive intermediate. Base-promoted isomerization of propargyl to allenyl sulfonamides is known.[18]

This reaction process is quite distinct from the course followed during an HDDA cascade (i.e., sequential benzyne formation and trapping). Formation of a product in which one of the tethering atoms separating the diyne and diynophile has become functionalized has not been observed in any HDDA cascade[7]. We established that, in the absence of base, the tetrayne **15-Ms** is a well-behaved HDDA substrate, but only at elevated temperature (half-life of ca. 4 h at 80 °C in C_6D_6). We have trapped the resulting benzyne **19** with methanol[19,20] or acetic acid[5,19] to produce **20a** or **20b**, respectively (Fig. 2a). Together these observations indicate that formation of the piperidine-trapped product **18a**, occurring at a substantially lower temperature, is not derived from the benzyne **19**. Thus, isomerization of the tetrayne **15-Ms** to the allene tautomer **16** occurs faster than does the thermal HDDA cyclization of **15-Ms**.

The non-nucleophilic base DBU mildly accelerates the initial, rate-limiting isomerization of **15-Ms** to **16**. The rate of formation of adduct **18a** was approximately doubled ($t_{1/2}$ of ca. 7 vs. 15 h) when five equivalents of DBU were added to the initial piperidine solution of **15-Ms**. Other secondary and primary amines participate in this transformation (Fig. 2b, entries 2–5). Other amides in the tether are also compatible (entries 6 and 7), although the reaction is slower with the benzamide **15-Bz**.

Oxygen nucleophiles will also trap the intermediate dehydrotoluene derivative **17** (Fig. 2b, entries 8 and 9). When carried out in methanol or aqueous acetonitrile, DBU-promoted PDDA reaction of the methanesulfonamide **15-Ms** gave the methoxylated or hydroxylated adducts **18h** or **18i**, respectively.

We have also achieved PDDA cyclizations with substrates in which the triply bonded acceptor moiety is a cyano rather than an alkynyl group (Fig. 3a). When dissolved in neat piperidine, diynyl nitriles **21** gave rise to the pyridine derivatives **22**, thereby establishing the viability of an aza-PDDA reaction. The ability of a cyano group to enter into the PDDA cycloisomerization is particularly noteworthy and decidedly distinct from its inertness to HDDA cyclization—we, nor others[21], have ever observed nitriles to engage in that process. This is the case for the nitriles **21** as well. In the absence of base, none gave evidence of cyclizing to a pyridyne such as **23** (a 3,4-dehydropyridine), even upon heating to 150 °C in the presence of an excellent HDDA-aryne trap like acetic acid; only extensive decomposition was observed. Thus, the base-promoted tautomerization to **24** and subsequent PDDA cycloisomerization of that allene to the α,3-dehydroazatoluene (or α,3-dehydropicoline) intermediate **25** is considerably more facile than the HDDA cycloisomerization of its precursor tautomer **21**. This is entirely in parallel with the observation presented earlier—namely, that the PDDA cyclization of **16** is much faster than the HDDA reaction of **15-Ms** (Fig. 2a).

As with the all-alkyne series already discussed (**15**), the nitrile substrates **21** are also competent PDDA precursors when bearing a toluenesulfonyl, methanesulfonyl, or benzoyl electron-withdrawing group on the propargylic nitrogen atom (Fig. 3b). Again, amines (entries 1–4), water (entries 5–6), and alcohols (entries 7–11) are all effective trapping nucleophiles.

We have performed several experiments (Fig. 4) that provide support for the proposed mechanism for these transformations. When either of the substrates **15-Ms** or **21-Ms** was incubated with DBU in a solution of deuterochloroform (Fig. 4a), the major product (**26** or **27**, respectively) was a dichloroalkene in which the arene carbon corresponding to the sp-hybridized center in the putative α,3-dehydrotoluene intermediate was fully deuterated. Presumably, initially formed trichloromethylated adducts like **28** underwent facile elimination induced by the excess DBU present.

In contrast to the behavior of the gem-dimethylated substrates **21** (cf. Fig. 3), the analogous substrate **29** (Fig. 4b) lacking those methyl groups gave a different outcome when held in a piperidine solution at room temperature. No more than a trace amount of the expected PDDA cyclization product was observed. Instead, the enamine **31** was isolated as the principal product formed in this experiment. We presume that this arises by addition of the amine to the central carbon in allene **30** (to give a delocalized allylic/propargylic anion) rather than by direct hydroamination of the starting diyne **29**; we have performed a number of HDDA reactions on diyne substrates, not activated for tautomerization, in the presence of secondary amine trapping agents and never observed amination of a conjugated diyne. The change in reaction course between **21** vis-à-vis **29** can be explained by the Thorpe-Ingold effect;[22] the lack of the geminal substituents results in a widening of the bond angle and

increase in distance (r) between the unsaturated centers in **30**. This significantly slows the rate of the PDDA cyclization, permitting time for the piperidine to intercept the allene. We have observed a similar phenomenon in the rate of HDDA cyclization of an analogous pair of triyne substrates[23] and also have found computational support for this interpretation (see below, Fig. 4c).

We have carried out density functional theory (DFT) computations to gain additional mechanistic perspective about the PDDA cycloisomerization. The energy diagram in Fig. 4c shows the relative free energies for four series (**a–d**) of PDDA reactions of allenynes **33a–d**; members of the **a/b** series have an alkyne as the pendant 2π-component and the **c/d** a nitrile. The diagram has been normalized so that each of the four PDDA reactant allenes **33** has the same free energy. The cyclizations proceed to the α,3-dehydro(aza)toluenes **37** by way of diradical intermediates **35**. Houk and coworkers have recently described a DFT analysis of (bimolecular) HDDA reactions and found that the diradical pathway is more favored than the concerted.[24] We have observed the same for a series of *intra*molecular HDDA reactions and found that the (U)B3LYP-D3BJ functional did an excellent job of correlating with our experimentally observed rates.[25] We have not been successful locating transition state structures corresponding to concerted PDDA reactions for **33a–d** at this level of theory.

Some notable points from these calculations are: (i) the free energy differences between the 1,3-diynes **32** and tautomeric allenynes **33** are small, which serves as a reminder that the potential energies of the participating functional groups in **33** are also high, comparable to those in **32**, (ii) as with triyne to benzyne conversions, the overall energies of reaction from **33** to the reactive α,3-dehydrotoluenes **37a/b** are exergonic (by ΔG° of ca. 35 kcal•mol^{-1}), although not to as large an extent as those computed for HDDA cyclizations to benzynes (ca. −50 kcal•mol^{-1})[26,5], (iii) the corresponding energy differences between the nitrile-containing allenynes **33c/d** vis-à-vis the product α,3-dehydroazatoluenes **37c/d** is even smaller, reflecting the inherently lower potential energy of a nitrile triple bond vs. that of an alkyne, (iv) the magnitude of the computed ΔG‡s for the first (and slower) step in the PDDA cyclization [cf. **34** (*TS1*), Fig. 4c] are not inconsistent with the fact that our PDDA cyclizations are proceeding rapidly at less than near-ambient temperatures, and (v) the difference in the computed ΔG‡ for the first step in the PDDA reaction of the nitrile **33c** vs. that of **33d** (23.5 vs. 18.0) is consistent with the differing behavior of allenyne **24** (Fig. 3a) vs. the aza-analog **30** (Fig. 4b). The former, recall, underwent smooth PDDA cyclization to **25** en route to the piperidine-trapped adduct **22b** (Fig. 3a), whereas the latter cyclized so slowly that interception by piperidine interceded to produce the enamine **31**. The optimized geometries computed for the reactive conformers of **33c** vs. **33d** (lacking vs. having gem-dimethyl groups[22]) differ substantially (0.3 Å) in the distance (*r*) between the nitrile and central allene carbons, indicating that the former is better poised for surmounting the *TS1* activation barrier.

Finally, we devised an experiment to unambiguously demonstrate the intermediacy of an allenyne (cf. **40**, Fig. 4d). The hydroxytetrayne **38** reacted readily with chlorodiphenylphosphine to produce the transient phosphinite **39**, which smoothly rearranged[27,14] at sub-ambient temperature to the allenyldiphenylphosphine oxide **40**. This

labile compound was observed to degrade upon handling at room temperature, but could be rapidly purified and characterized. Dissolving **40** in methanol or water/acetonitrile spontaneously gave rise to the corresponding trapped product **42a** or **42b**, respectively. We view this as strong support for the intermediacy of **41** and the PDDA mechanism posited here throughout. That these reactions proceed smoothly *in the absence of base* also argues against a mechanism initiated by nucleophilic attack on the allene terminal carbon of the transient intermediates **16** (Fig. 2a) or **24** (Fig. 3a). The known reaction of methanol with Myers-Saito reaction-derived α,3-dehydrotoluenes in similar fashion is also relevant[28,29,30].

In summary, we have described a new class of reaction—the formal [4+2] cycloaddition of an allenyne with a pendant alkyne (or nitrile) to produce an α,3-dehydro(aza)toluene derivative. We call this a pentadehydro-Diels–Alder (or PDDA) reaction. In the majority of examples reported, the base-promoted isomerization of a precursor *N*-1,3,-diynyl sulfonamide to the reactive allenyl tautomer is overall rate-limiting. The PDDA then proceeds rapidly, far more so than the HDDA cyclization of the precursor 1,3-diyne. We also have shown that the PDDA-derived dehydrotoluene, itself a reactive intermediate, can be trapped by a variety of *N*-, *O*-, and *C*-centered nucleophiles (Figs. 2b and 3b). In one instance the conjugated allenyne has been isolated (**40**, Fig. 4d) and its facile cyclization and *in situ* trapping observed. Finally, nitriles, which do not participate in HDDA reactions, now enter the realm of reactivity, resulting in pyridine-containing products (Fig. 3).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Diels O, Alder K. Synthesen in der hydroaromatischen Reihe. Liebigs Ann. Chem. 1928; 460:98–122.
2. Wessig P, Müller G. The dehydro-Diels-Alder reaction. Chem. Rev. 2008; 108:2051–2063. [PubMed: 18479169]
3. Bradley AZ, Johnson RP. Thermolysis of 1,3,8-nonatriyne: Evidence for intramolecular [2+4] cycloaromatization to a benzyne intermediate. J. Am. Chem. Soc. 1997; 119:9917–9918.
4. Miyawaki K, Suzuki R, Kawano T, Ueda I. Cycloaromatization of a non-conjugated polyenyne system: Synthesis of 5H-benzo[d]fluoreno[3,2-b]pyrans via diradicals generated from 1-[2-{4-(2-alkoxymethylphenyl)butan-1,3-diynyl}]phenylpentan-2,4-diyn-l-ols and trapping evidence for the 1,2-didehydrobenzene diradical. Tetrahedron Lett. 1997; 38:3943–3946.
5. Hoye TR, Baire B, Niu D, Willoughby PH, Woods BP. The hexadehydro-Diels–Alder reaction. Nature. 2012; 490:208–212. [PubMed: 23060191]
6. Yun SY, Wang K-P, Lee N-K, Mamidipalli P, Lee D. Alkane C–H insertion by aryne intermediates with a silver catalyst. J. Am. Chem. Soc. 2013; 135:4668–4671. [PubMed: 23477300]

7. Holden C, Greaney MF. The hexadehydro-Diels–Alder reaction: A new chapter in aryne chemistry. Angew. Chem. Int. Ed. 2014; 53:5746–5749.
8. Wang K-P, Yun SY, Mamidipalli P, Lee D. Silver-mediated fluorination, trifluoromethylation, and trifluoromethylthiolation of arynes. Chem. Sci. 2013; 4:3205–3211.
9. Niu D, Hoye TR. The aromatic ene reaction. Nature Chem. 2014; 6:34–40. [PubMed: 24345944]
10. Bergman RG. Reactive 1,4-dehydroaromatics. Accts. Chem. Res. 1973; 6:25–31.
11. Johnson RP. Dehydropericyclic routes to reactive intermediates. J. Phys. Org. Chem. 2010; 23:283–292.
12. Logan CF, Ma JC, Chen P. The photoelectron spectrum of the α,3-dehydrotoluene biradical. J. Am. Chem. Soc. 1994; 116:2137–2138.
13. Myers AG, Kuo EY, Finney NS. Thermal generation of α,3-dehydrotoluene from (*Z*)-1,2,4-heptatrien-6-yne. J. Am. Chem. Soc. 1989; 111:8057–8059.
14. Nagata R, Yamanaka H, Okazaki E, Saito I. Biradical formation from acyclic conjugated eneyne-allene system related to neocarzinostatin and esperamicin-calichemicin. Tetrahedron Lett. 1989; 30:4995–4998.
15. Mohamed RK, Peterson PW, Alabugin IV. Concerted reactions that produce diradicals and zwitterions: Electronic, steric, conformational, and kinetic control of cycloaromatization processes. Chem. Rev. 2013; 113:7089–7129. [PubMed: 23600723]
16. Sakai T, Danheiser RL. Cyano Diels-Alder and cyano ene reactions. Applications in a formal [2+2+2] cycloaddition strategy for the synthesis of pyridines. J. Am. Chem. Soc. 2010; 132:13203–13205. [PubMed: 20815385]
17. Karmakar R, Yun SY, Chen J, Xia Y, Lee D. Benzannulation of triynes to generate functionalized arenes by spontaneous incorporation of nucleophiles. Angew. Chem. Int. Ed. 2015; 54:6582–6586.
18. Grigg R, Sansano JM. Sequential hydrostannylation-cyclisation of δ- and ω-allenyl aryl halides. Cyclisation at the proximal carbon. Tetrahedron. 1996; 52:13441–13454.
19. Karmakar R, Yun SY, Wang K-P, Lee D. Regioselectivity in the nucleophile trapping of arynes: the electronic and steric effects of nucleophiles and substituents. Org. Lett. 2014; 16:6–9. [PubMed: 24313272]
20. Willoughby PH, Niu D, Wang T, Haj MK, Cramer CJ, Hoye TR. Mechanism of the reactions of alcohols with *o*-benzynes. J. Am. Chem. Soc. 2014; 136:13657–13665. [PubMed: 25232890]
21. Kimura H, Torikai K, Miyawaki K, Ueda I. Scope of the thermal cyclization of nonconjugated ene–yne–nitrile system: A facile synthesis of cyanofluorenol derivatives. Chem. Lett. 2008; 37:662–663.
22. Beesley RM, Ingold CK, Thorpe JF. The formation and stability of spiro-compounds. Part I: Spiro-compounds from cyclohexane. J. Am. Chem. Soc. 1915; 107:1081–1092.
23. Woods BP, Baire B, Hoye TR. Rates of hexadehydro-Diels–Alder (HDDA) cyclizations: Impact of the linker structure. Org. Lett. 2014; 16:4578–4581. [PubMed: 25153729]
24. Liang Y, Hong X, Yu P, Houk KN. Why alkynyl substituents dramatically accelerate hexadehydro-Diels-Alder (HDDA) reactions: Stepwise mechanisms of HDDA cycloadditions. Org. Lett. 2014; 16:5702–5705. [PubMed: 25329369]
25. Marell DJ, Furan LR, Woods BP, Lei X, Bendelsmith AJ, Cramer CJ, Hoye TR, Kuwata KT. Mechanism of the intramolecular hexadehydro-Diels–Alder reaction. J. Org. Chem. ASAP. 2015
26. Ajaz A, Bradley AZ, Burrell RC, Li WHH, Daoust KJ, Bovee LB, DiRico KJ, Johnson RP. Concerted vs. stepwise mechanisms in dehydro-Diels–Alder reactions. J. Org. Chem. 2011; 76:9320–9328. [PubMed: 21977993]
27. Schmittel M, Strittmatter M, Vollmann K, Kiau S. Intramolecular formal Diels-Alder reaction in enyne allenes. A new synthetic route to benzofluorenes and indeno[1,2-g]quinolines. Tetrahedron Lett. 1996; 37:999–1002.
28. Myers AG, Dragovich PS, Kuo EY. Studies on the thermal generation and reactivity of a class of (σ,π)-1,4-biradicals. J. Am. Chem. Soc. 1992; 114:9369–9386.
29. Cremeens ME, Hughes TS, Carpenter BK. Mechanistic studies on the cyclization of (*Z*)-1,2,4-heptatrien-6-yne in methanol: A possible nonadiabatic thermal reaction. J. Am. Chem. Soc. 2005; 127:6652–6661. [PubMed: 15869286]

30. Peterson PW, Mohamed RK, Alabugin IV. How to lose a bond in two ways — The diradical/zwitterion dichotomy in cycloaromatization reactions. Eur. J. Org. Chem. 2013:2505–2527.

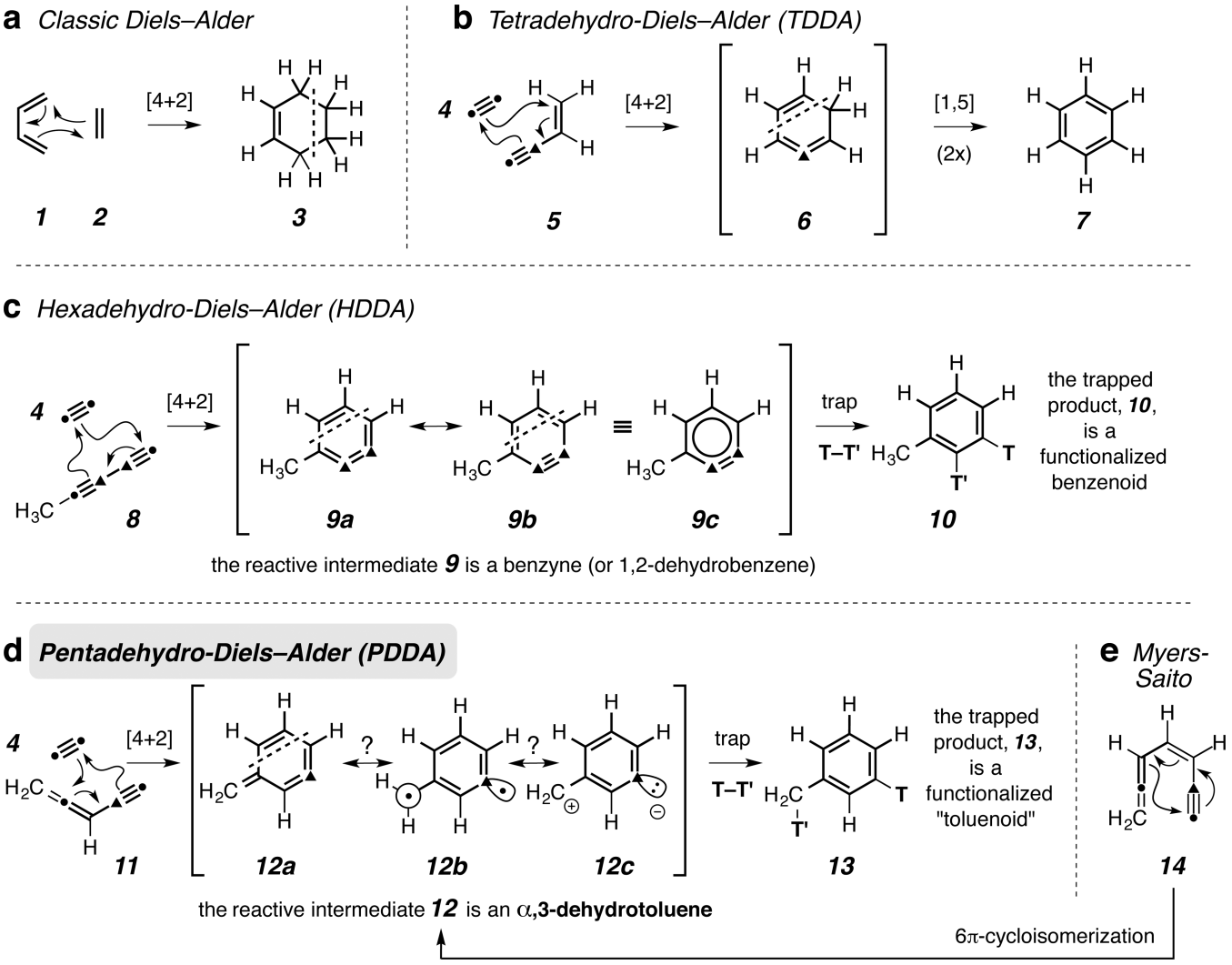
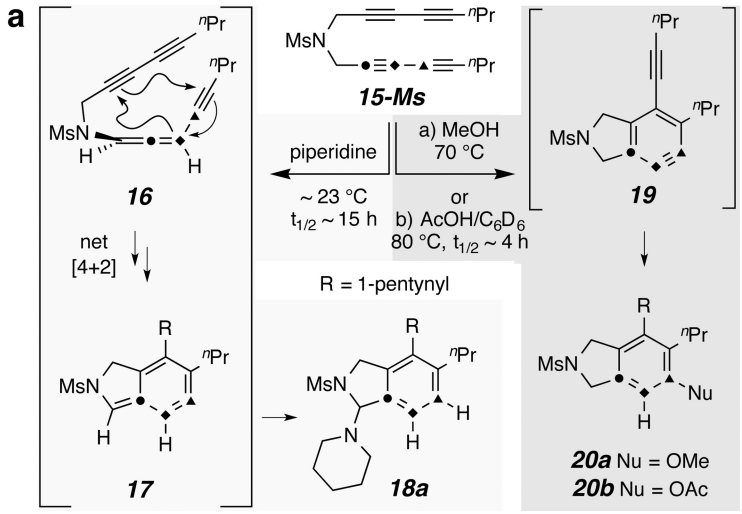
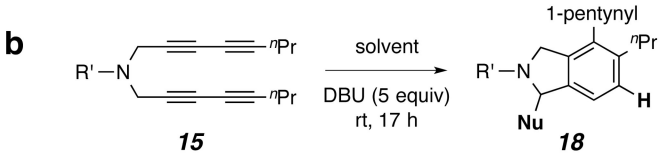


Figure 1. Terminology associated with various cyclizations in the Diels–Alder family of 4π+2π reactions

a, The classic example of a diene and dienophile to give a cyclohexene. **b**, The absence of four hydrogen atoms amounts to a tetradehydro (TDDA) variant; the product is at the benzene oxidation state. **c**, The absence of six hydrogen atoms amounts to the hexadehydro Diels–Alder (HDDA) variant. **d**, The unprecedented pentadehydro-Diels–Alder (PDDA) reaction proceeds via an α,3-dehydrotoluene (cf. **12**); importantly, both the HDDA and PDDA reactions result in formation of trappable reactive intermediates. **e**, α,3-Dehydrotoluenes have previously been generated principally by cyclization of allenyl enynes like **14**.





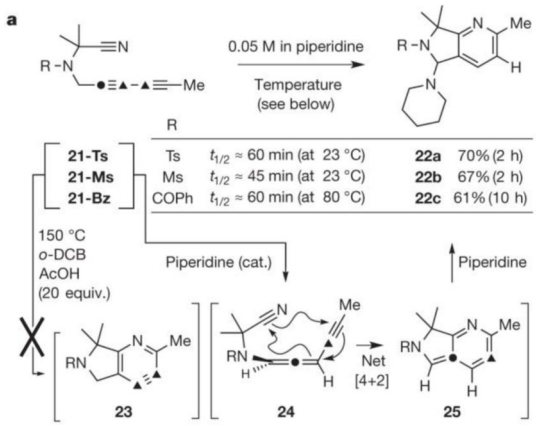
entry	tetrayne substrate	solvent (= Nu–H)	product #	R'[d]	Nu	yield
1	**15-Ms**	piperidine	**18a**	Ms		81%
2	**15-Ms**	pyrrolidine	**18b**	Ms		73%
3	**15-Ms**	morpholine	**18c**	Ms		82%
4	**15-Ms**	diethylamine[a]	**18d**	Ms	Et_2N–	62%
5	**15-Ms**	*n*-butylamine	**18e**	Ms	^nBuNH–	86%
6	**15-Ts**	piperidine[b]	**18f**	Ts		52%
7	**15-Bz**	piperidine[c]	**18g**	Bz		25%
8	**15-Ms**	methanol[a]	**18h**	Ms	MeO–	80%
9	**15-Ms**	MeCN/H_2O	**18i**	Ms	HO–	15%

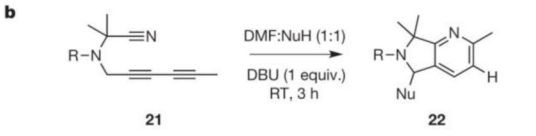
[a] reaction performed at 40 °C for 17 h; [b] reaction performed at 40 °C for 20 h; [c] reaction performed using ^{t}BuOK (1 equiv) in place of DBU as the added base at room temperature (rt) for 17 h. Ms = CH_3SO_2; Ts = *p*-$CH_3C_6H_4SO_2$; Bz = PhCO.

Figure 2. PDDA cascades of tetraynes

a, The first example: substrate **15-Ms** undergoes base-promoted PDDA reaction and *in situ* trapping by piperidine to provide the adduct **18a**; the HDDA cyclization of **15-Ms** is slower. **b,** Examples indicating some of the scope of the PDDA cascades of substrates **15**.

Cyclizations of nitrile-containing diynes—the aza-PDDA





Entry	Tetrayne substrate	NuH	Product No.	R	Nu	Yield*
1	**21-Ts**	Piperidine	**22a**	Ts	pip-	71%
2	**21-Ms**	Piperidine	**22b**	Ms	pip-	69%
3	**21-Ts**	Diethylamine	**22d**	Ts	^{n}BuNH-	71%
4	**21-Ts**	*n*-Butylamine	**22e**	Ts	Et_2N-	46%
5	**21-Ts**	Water†	**22f**	Ts	HO-	57%
6	**21-Ms**	Water†	**22g**	Ms	HO-	60%
7	**21-Ts**	*t*-Butanol	**22h**	Ts	^{t}BuO-	18%
8	**21-Ts**	2-Propanol	**22i**	Ts	^{i}PrO-	45%
9	**21-Ts**	Methanol	**22j**	Ts	MeO-	72%
10	**21-Ms**	Methanol	**22k**	Ms	MeO-	84%
11	**21-Bz**	Methanol‡	**22l**	Bz	MeO-	70%

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Figure 3. Cyclizations of nitrile-containing diynes: the aza-PDDA

a, Substrates **21**, non-competent reactants in HDDA cyclizations, undergo smooth, base-promoted PDDA reactions to give the piperidine-trapped adducts **22a-c**. **b**, Examples indicating some of the scope of the aza-PDDA cascade.

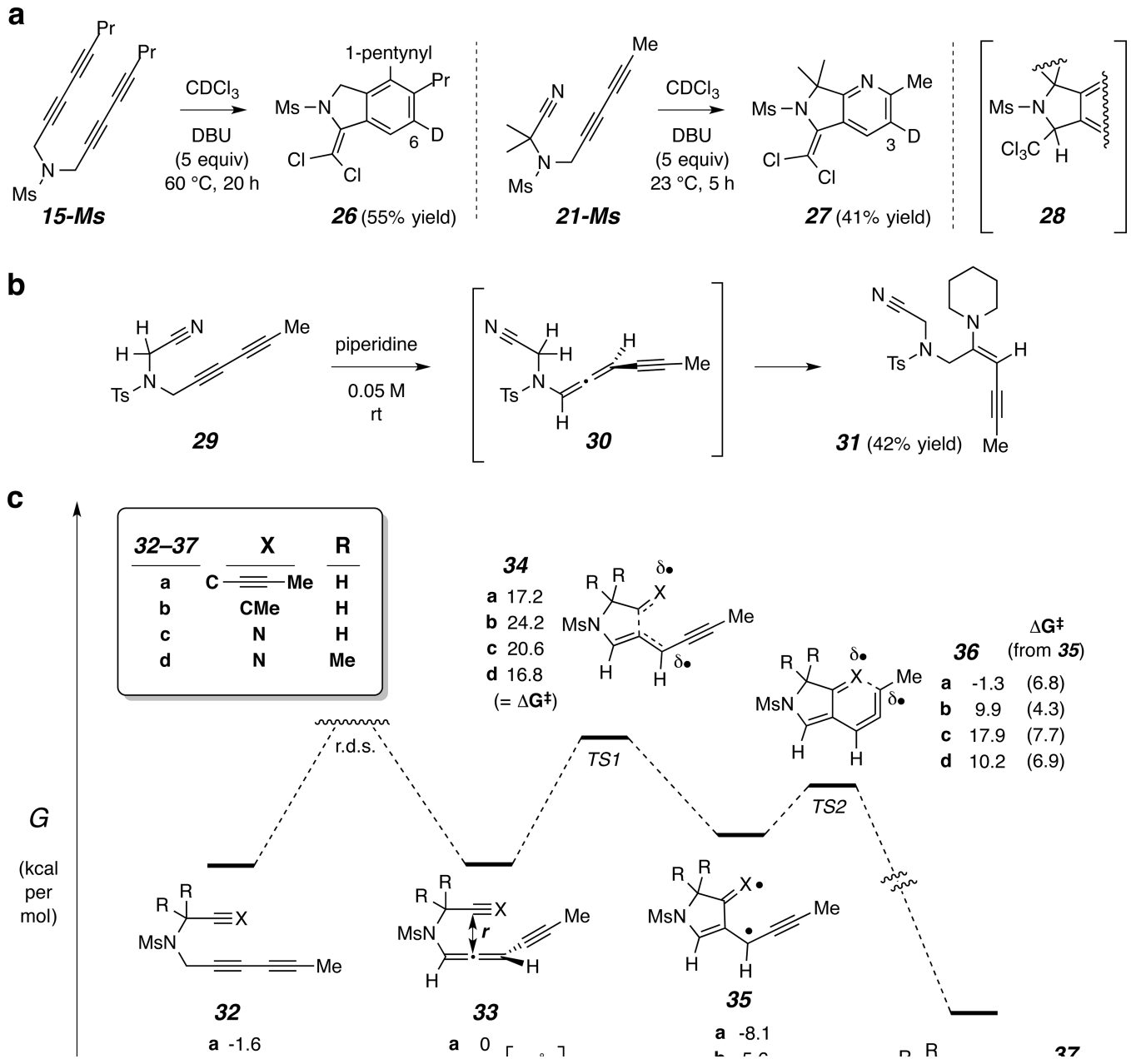

Figure 4a

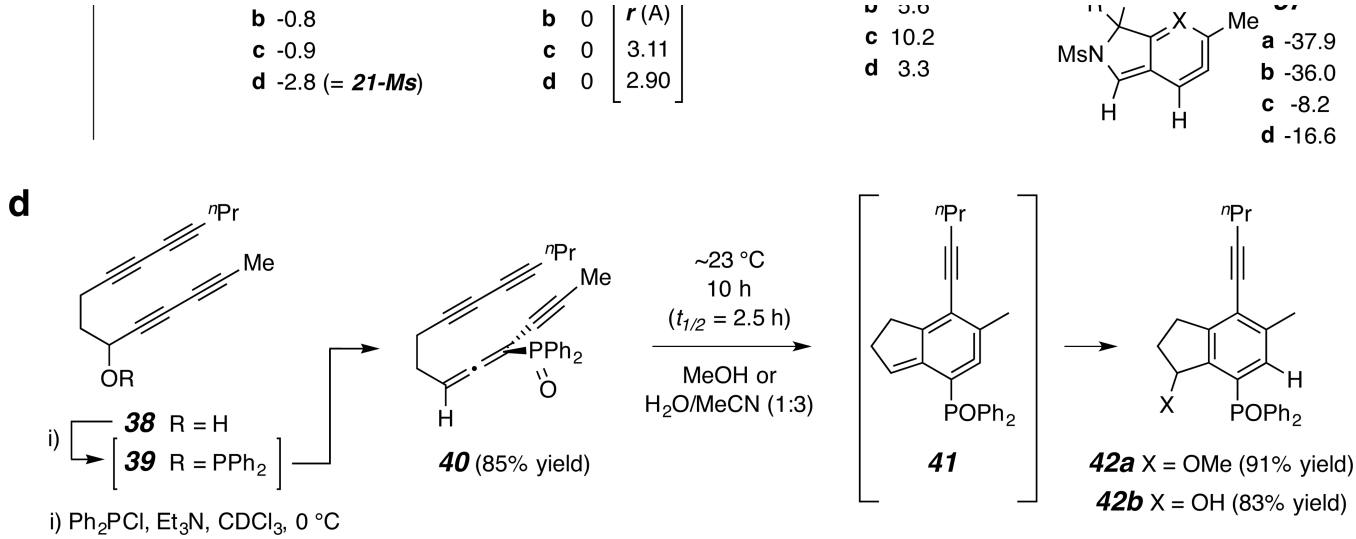

Figure 4b

Figure 4. Mechanistic aspects of the PDDA reaction

a,**b**, Indirect evidence for intermediacy of α,3-dehydrotoluenes and allenes. **c**, Relative free energies (G) from DFT calculations [(U)B3LYP−D3BJ/6−311+G(d,p); a solvation model (using Et_2NH) was employed (see SI)] of the directly relevant minima (**32**, **33**, **35**, and **37**) and two transition state structures [**34** (*TS1*) and **36** (*TS2*)] for the PDDA cyclization via the diradical intermediate **35**. Values beside "**a–d**" for each of **32–37** are the computed energies (G) in kcal•mol^{-1}. The 2π C≡X component is either an alkyne (**a**,**b**) or a nitrile (**c**,**d**). (r.d.s. = rate-determining step.) **d**, An (isolable) allenyne, the phosphine oxide **40**, readily cyclizes to the benzenoid product **42**.