doi:10.1038/nature12492

Alkane desaturation by concerted double hydrogen atom transfer to benzyne

Dawen Niu[1], Patrick H. Willoughby[1], Brian P. Woods[1], Beeraiah Baire[1] & Thomas R. Hoye[1]

The removal of two vicinal hydrogen atoms from an alkane to produce an alkene is a challenge for synthetic chemists[1,2]. In nature, desaturases and acetylenases are adept at achieving this essential oxidative functionalization reaction, for example during the biosynthesis of unsaturated fatty acids[3], eicosanoids, gibberellins[4] and carotenoids[5]. Alkane-to-alkene conversion almost always involves one or more chemical intermediates in a multistep reaction pathway; these may be either isolable species (such as alcohols or alkyl halides) or reactive intermediates (such as carbocations, alkyl radicals, or σ-alkyl-metal species). Here we report a desaturation reaction of simple, unactivated alkanes that is mechanistically unique. We show that benzynes are capable of the concerted removal of two vicinal hydrogen atoms from a hydrocarbon. The discovery of this exothermic, net redox process was enabled by the simple thermal generation of reactive benzyne intermediates through the hexadehydro-Diels–Alder cycloisomerization reaction of triyne substrates[6]. We are not aware of any single-step, bimolecular reaction in which two hydrogen atoms are simultaneously transferred from a saturated alkane. Computational studies indicate a preferred geometry with eclipsed vicinal C–H bonds in the alkane donor.

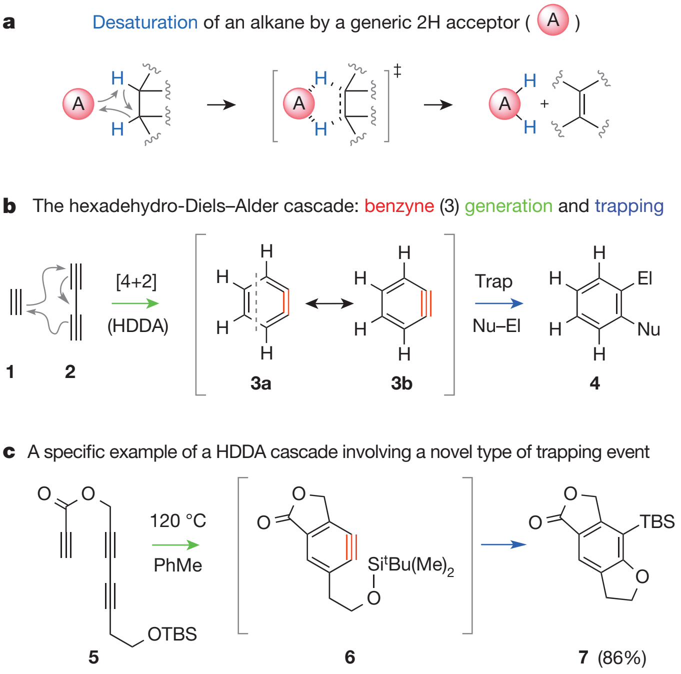


Figure 1 | Introduction and background. a, Species A (red sphere) is a potential double hydrogen atom (2H) acceptor, in which the accepting moiety could be either monoatomic (for example metal, metal-oxo, carbene or nitrene) or polyatomic (for example a π-bonded species) in nature. **b,** The prototypical HDDA cascade. Nu–El, nucleophile–electrophile. **c,** Intramolecular HDDA cycloisomerization followed by silyl ether trapping[6]. TBS, *tert*-butyldimethylsilyl. Here we show that a benzyne (such as **3** or **6**) functions as species A by extracting two hydrogen atoms from adjacent carbon atoms of suitable 2H donor substrates.

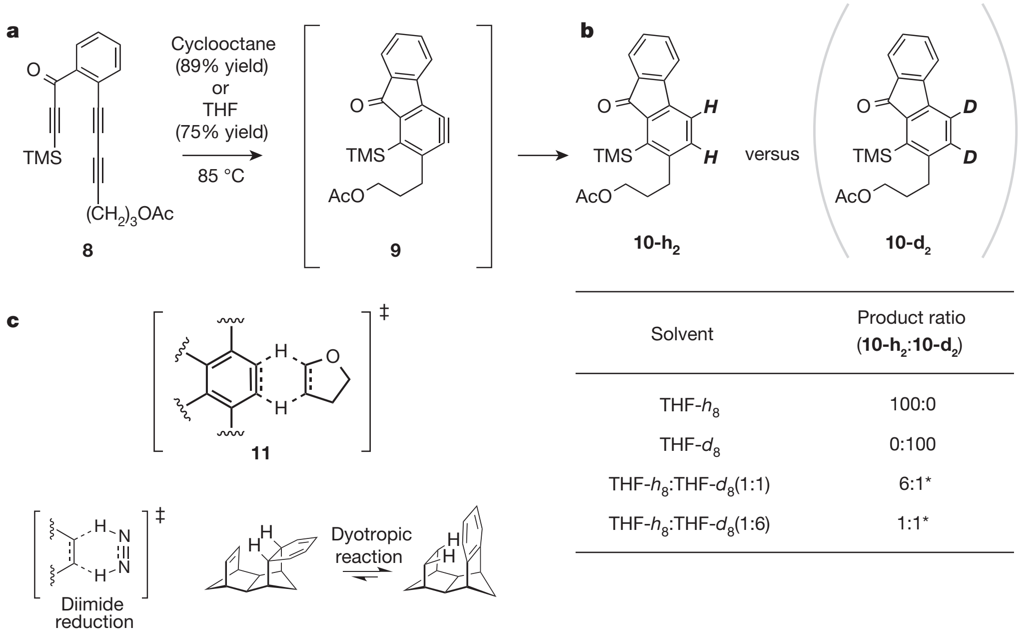
Arynes[7–9] engage in myriad trapping reactions that functionalize adjacent *sp*-hybridized carbons in the *o*-aryne ring. We recently reported a general strategy for the formation and subsequent *in situ* trapping of benzynes by means of the hexadehydro-Diels–Alder (HDDA) reaction[6,10,11]. The simplest imaginable variant (Fig. 1b) is the reaction of 1,3-butadiyne (**2**) with ethyne (**1**, the diynophile) to produce *o*-benzyne (**3**). The free energy change for this process is computed to be exothermic by approximately 50 kcal mol^{-1} (refs 6, 12). Trapping of **3** permits the synthesis of many useful benzene derivatives (**4**). In practice (Fig. 1c), the HDDA cycloisomerization is effected intramolecularly simply by heating a tethered triyne substrate such as **5** to produce a fused bicyclic benzyne intermediate such as **6**. Trapping leads to a highly substituted benzenoid product such as **7**. In addition to the preparative value of this *de novo* generation of benzynes, the HDDA reaction provides the opportunity to uncover previously unprecedented aryne trapping modes[13,14] (for example, the insertion of the strained benzyne into the silyl ether bond as **6** proceeds to **7**). This is largely because HDDA cyclizations produce reactive benzyne intermediates in the absence of added reagents, by-products or catalysts.

Bimolecular desaturation of an alkane by concerted transfer of two vicinal hydrogen atoms to a double hydrogen atom (2H) acceptor is unprecedented (Fig. 1a). We now report a 2H transfer reaction in which a HDDA-generated benzyne simultaneously accepts two vicinal hydrogen atoms from a suitable alkane 2H donor (H–$C_{sp^3}C_{sp^3}$–H). This gives the corresponding (oxidized) alkene and (reduced) benzenoid products. For example, when we heated triyne **8** in cyclooctane to 85 °C, the only isolated product (89%) was the reduced fluorenone derivative **10-h$_2$** (Fig. 2a, b). Using ^{1}H NMR spectroscopy, we observed that a comparable amount of cyclooctene had been formed by desaturation[15] (see Fig. 3b). The only well-characterized example of benzyne reduction by means of the net addition of two hydrogen atoms is a previous study[16] in which a benzyne intermediate derived from a bis-diyne-bridged, dinuclear metal complex was reduced to the arene. They demonstrated that the solvent (tetrahydrofuran; THF) was the source of the hydrogen (and, in the case of THF-d_8, deuterium[17]) atoms that appeared in the reduced benzenoid product. When we heated substrate **8** in THF-h_8, **10-h$_2$** was the only product isolated (75%, Fig. 2a, b). Similarly, when **8** was heated in THF-d_8, the dideuterated analogue **10-d$_2$** (mass spectrometry and ^{1}H NMR) was the only product isolated.

To probe the mechanism of this process further and, in particular, to distinguish between pathways involving sequential hydrogen atom abstractions from two solvent molecules versus a transfer of two hydrogen atoms from a single molecule, we repeated the generation and trapping of benzyne **9**, this time in the presence of an equimolar mixture of THF-h_8 and THF-d_8. Intriguingly, only the diprotiobenzenoid and dideuteriobenzenoid products **10-h$_2$** and **10-d$_2$** were produced; none of the mono-H/mono-D analogue (**10-hd**) was detected. The observed **10-h$_2$**:**10-d$_2$** product ratio was 6:1, indicating a significant H/D kinetic isotope effect for the 2H transfer. In a complementary experiment, we used a 1:6 molar ratio of THF-h_8:THF-d_8, which gave a nearly 1:1 ratio of products **10-h$_2$**:**10-d$_2$**. The lack of an observable level of monodeuterated

---

[1] Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, USA.



Solvent	Product ratio (**10-h$_2$**:**10-d$_2$**)
THF-h_8	100:0
THF-d_8	0:100
THF-h_8:THF-d_8(1:1)	6:1*
THF-h_8:THF-d_8(1:6)	1:1*

Figure 2 | Both hydrogen atoms come from the same donor molecule. **a**, Dihydrogen transfer reactions between the HDDA-generated benzyne **9** (from the triyne **8**) and the 2H donor solvents cyclooctane and THF give the benzenoid **10-h$_2$**. **b**, Isotope profiling using THF-h_8, THF-d_8 and mixtures thereof shows that both hydrogen atoms in the product originate from a single molecule of 2H donor. Asterisk, mono-deuterated product (**10-hd**) was not observed (^{1}H NMR analysis; estimated limit of detection was 6%). **c**, Representation (**11**) of simultaneous double hydrogen transfer between an aryne and a THF molecule. Analogous six-atom arrays are involved in the transition structures of 2H transfer by diimide to an alkene acceptor[18,19] and in the class of intramolecular reorganizations known as dyotropic reactions[20,21].

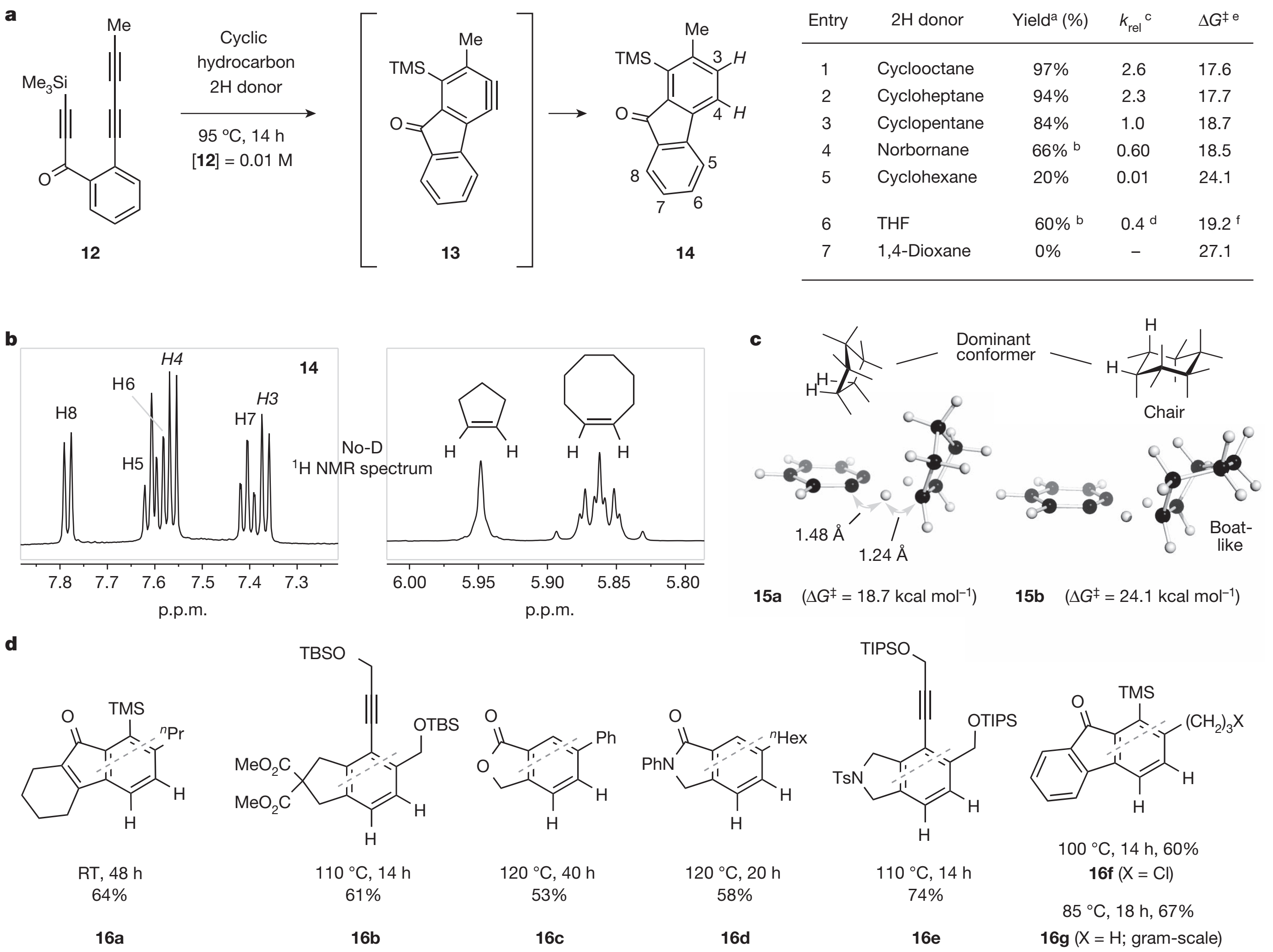
product in any of these experiments is consistent with the concerted transfer to the benzyne of two hydrogen atoms from a single THF molecule as represented in the depiction of the transition structure **11** (Fig. 2c). Although such a description might seem unusual, it can be noted that the generally accepted mechanism for the reduction of alkenes by diimide (HN=NH)[18,19] and for dyotropic reactions in which two hydrogen atoms are shuffled intramolecularly[20,21] (Fig. 2c) involves a similar simultaneous transfer.

We next screened a series of cyclic hydrocarbons to explore their relative ability to engage an aryne in a similar hydrogen transfer reaction (Fig. 3). We were surprised to observe that cyclohexane was significantly less efficient than the other cycloalkanes in its reduction of the benzyne **13** (Fig. 3a, entries 1–5). This was initially seen from simple comparison of the chemical yields after the purification of reduced (benzenoid) product **14**. It is relevant that when the HDDA cyclization is performed in the absence of a suitably good trapping agent, we routinely observe the formation of intractable, dark-coloured mixtures of oligomeric substances. We speculate that this is because the reactive benzyne (for example **13**) engages the conjugated diyne unit in another molecule of substrate triyne (for example **12**) competitively with its abstraction of two hydrogen atoms from a solvent molecule. Thus, for these processes the yield of **14** is a meaningful reflection of the 2H transfer rate from each donor solvent. Use of the acyclic hydrocarbon *n*-heptane as solvent also resulted in the production of **14**, now in 30% (isolated) yield—that is, heptane is intermediate in reactivity between cyclopentane and cyclohexane. When the starting concentration of triyne **12** was decreased tenfold (that is, from 10 mM to 1 mM), the isolated yield of **14** more than doubled for the reaction in cyclohexane (from 20% to 53%) or *n*-heptane (from 30% to 73%). This is consistent with the hypothesis that the rate of the primary decomposition process is dependent on the triyne concentration.

We then turned to the use of no-deuterium proton NMR (No-D NMR) spectroscopy[22] to both positively identify the alkene by-product and demonstrate that it was formed in nearly equimolar amounts to the reduced benzenoid product **14**. A typical No-D spectrum, obtained with a sample prepared by heating **12** in an equivolume mixture of cyclooctane and cyclopentane ([**12**] = 0.01 M), is shown in Fig. 3b. The ratio of the alkene resonances of cyclooctene to cyclopentene (adjusted for the molar ratio of solvents) provides the relative rate ratio (k_{rel}) between the two hydrocarbon donors (2.6 for this example). The relative intensity of alkene to arene resonances (from **14**) as well as the absence of resonances indicative of aromatic by-products shows the overall cleanliness of the reaction.

As stated earlier, cyclohexane (Fig. 3a, entry 5 in the inset table) is a considerably poorer 2H donor than the other cyclic hydrocarbons (entries 1–4). We speculated that this implies a preference for an eclipsed geometry for the relevant $\mathrm{HC}_{sp^3}\mathrm{C}_{sp^3}\mathrm{H}$ subunit within the 2H donor molecule. Accordingly, cyclohexane, dominated by the chair conformation, is least disposed towards transfer of two of its hydrogen atoms, whereas the other hydrocarbons all have low-lying conformers with $\mathrm{HC}_{sp^3}\mathrm{C}_{sp^3}\mathrm{H}$ dihedral angles much smaller than 60°. That is, those cyclic hydrocarbons populated to a significant extent by conformers having less highly staggered vicinal C–H bonds are the more reactive 2H donors. To test this thinking further, we examined 1,4-dioxane as a potential 2H donor. Not surprisingly, use of this chair-like compound gave none of the reduced product **14** (Fig. 3a, entry 7). In contrast, norbornane, having a boat-like cyclohexane embedded in its framework (and an associated $\mathrm{HC}_{sp^3}\mathrm{C}_{sp^3}\mathrm{H}$ moiety with a 0° dihedral angle) is a kinetically competent donor (entry 4), even though the product norbornene comprises a strained alkene.

Next, using density functional theory (DFT) methods (see Supplementary Information) we computed the transition structure geometry and the free energy of activation ($\Delta G^{\ddagger}$) for the double hydrogen atom transfer[21] between *o*-benzyne (**3**) and each of the seven cyclic donors shown in entries 1–7 (Fig. 3a). For all 2H donors the calculations indicate a relatively early transition structure (for example, compare the two distances shown in **15a**). This is consistent with the highly exothermic nature of the 2H transfer step (for example, we computed the free energy of reaction to be −65.6 kcal mol^{-1} for *o*-benzyne (**3**) + cyclopentane going to benzene + cyclopentene). The computed geometries for the cyclopentane and cyclohexane transition structures (**15a** and **15b**, respectively) are shown in Fig. 3c. It is not accidental that the energy difference between the chair and boat conformers of cyclohexane (approximately 6 kcal mol^{-1}) is similar to the computed difference in $\Delta G^{\ddagger}$ between **15a**



Entry	2H donor	Yield[a] (%)	k_{rel}[c]	$\Delta G^{\ddagger}$[e]
1	Cyclooctane	97%	2.6	17.6
2	Cycloheptane	94%	2.3	17.7
3	Cyclopentane	84%	1.0	18.7
4	Norbornane	66%[b]	0.60	18.5
5	Cyclohexane	20%	0.01	24.1
6	THF	60%[b]	0.4[d]	19.2[f]
7	1,4-Dioxane	0%	–	27.1

Figure 3 | Dihydrogen transfer between arynes and cyclic hydrocarbons. **a**, Relative efficiency (percentage yield and k_{rel} compared with cyclopentane) of various hydrocarbon (and cyclic ether) 2H donors for the reduction of aryne **13** to arene **14**. For notes a–f in the inset table see Supplementary Information. **b**, A representative No-D ^{1}H NMR[22] spectrum (this example is of the reaction solution arising from heating **12** (at 10 mM) in a 1.5:1 molar ratio of cyclopentane:cyclooctane at 95 °C), showing the overall efficiency of the reaction and validating the k_{rel} value (1:2.6) obtained as described in the text. Italicized H3 and H4 denote the resonances for the newly introduced pair of hydrogen atoms in product **14**. **c**, Computed transition structure geometries and $\Delta G^{\ddagger}$ for the transfer of two hydrogen atoms to benzyne (**3**) from cyclopentane (**15a**) and cyclohexane (**15b**). **d**, Reduced benzenoid products **16a–g** generated by heating the triyne precursor in cyclooctane under the indicated conditions (starting substrate concentration 10 mM). RT, room temperature; Ts, *para*-toluenesulphonyl; TMS, trimethylsilyl; TIPS, triisopropylsilyl; ^{n}Pr, *n*-propyl; ^{n}Hex, *n*-hexyl.

and (the boat-like) **15b**. The $\Delta G^{\ddagger}$ values computed for all seven donors are given in the inset table in Fig. 3a. There is a remarkably good correlation between the computed $\Delta G^{\ddagger}$ values and the observed k_{rel} values. These observations are most consistent with the idea of substantial dependence on dihedral angle for the process, which can only be true if the double hydrogen atom transfer event is concerted.

Products **16a**–**g** (Fig. 3d) arose from incubating the corresponding triyne precursor (inferred from the dashed line in each structure; see Supplementary Information for details) in cyclooctane under the indicated conditions. Notable features include the following: a variety of functional groups, present in both the triyne precursor and benzenoid product, are readily tolerant of these benign reducing conditions; benzynes representing a breadth of electronic activation and/or perturbation engage in the reaction; most of the products **16** have a 1,2,3,4-tetrasubstituted motif, a substitution pattern that can be challenging to access by classical aromatic synthesis strategies; the double hydrogen atom transfer process occurs readily even at ambient temperature (compare **16a**); and the reaction is not limited by scale (compare **16g**).

Finally, an ancillary but important practical consideration has emerged. The most common method for generating simple benzyne derivatives, including the parent **3**, is that[23] in which 2-trimethylsilylphenyl triflate (*o*-TMSPhOTf) is exposed to a fluoride ion source (commonly CsF) in, most often, THF as the solvent. We speculated that some known trapping reactions of benzynes generated in THF are compromised in their efficiency as a result of competitive reduction by that solvent. Indeed, when we exposed *o*-TMSPhOTf to CsF in THF-d_8 in the absence of any other trapping agent, we observed the production of benzene ($C_6H_4D_2$, by ^{1}H NMR analysis). Similarly, benzene (and cyclopentene) was seen when CsF and *o*-TMSPhOTf were reacted in CD_3CN that contained cyclopentane (approximately 25 equivalents). We suggest that all traditional benzyne generation methods performed in the presence of a potential 2H donor (most typically, THF) are at risk to the unwanted, benzyne-depleting, 2H transfer process, especially when the benzyne trapping event is inherently slow. Indeed, we infer that this has already been encountered. Recent reports show THF to be an inferior medium (compared with 1,4-dioxane[24] or diethyl ether[25]) for some benzyne trapping reactions. This is consistent with both the results reported above for the relative efficiencies of THF and 1,4-dioxane as a 2H donor (Fig. 3a, entries 6 and 7 in the inset table), and also our arguments for angle dependence during the 2H transfer.

We have described the essential mechanistic features of a double hydrogen atom transfer process. Both (vicinal) hydrogen atoms come from the same donor molecule. There is substantial dependence on dihedral angle: donors with a greater degree of eclipsing among their low-energy conformers are more reactive. This is reinforced by the nearly planar geometry of the six reacting atoms in the computed transition structures. Our observations support a pathway in which both hydrogen atoms are transferred simultaneously from the saturated alkane to the benzyne carbon atoms—a process that could be viewed as a metal-free, double C–H activation event[26].

METHODS SUMMARY

A typical double hydrogen atom transfer reaction comprised heating a solution of HDDA triyne precursor (substrate) in cyclooctane (approximately 0.01 M) in a closed glass reaction vessel (for example, a screw-capped vial or culture tube). After the specified time, the reaction mixture was loaded directly onto a bed of silica gel and eluted first with hexanes to remove the excess cyclooctane and then with ethyl acetate to capture the reduced benzenoid products. These were further purified by chromatography on silica gel. Relative rate data (Fig. 3a, b) were collected by ^{1}H NMR spectroscopy at 500 MHz using No-D NMR[22] and quantitative NMR[27] techniques. Details are given in Supplementary Information. Details for the preparation of all new compounds, their full spectroscopic characterization data and the computational methods used are also provided in Supplementary Information.

Received 9 March; accepted 18 July 2013.

1. Linstead, R. P., Braude, E. A., Mitchell, P. W. D., Wooldridge, K. R. H. & Jackman, L. M. Transfer of hydrogen in organic systems. *Nature* **169,** 100–103 (1952).
2. Bloomfield, D. K. & Bloch, K. The formation of Δ^9-unsaturated fatty acids. *J. Biol. Chem.* **235,** 337–345 (1960).
3. Buist, P. H. Fatty acid desaturases: selecting the dehydrogenation channel. *Nat. Prod. Rep.* **21,** 249–262 (2004).
4. Bhattacharya, A. *et al.* Characterization of the fungal gibberellin desaturase as a 2-oxoglutarate-dependent dioxygenase and its utilization for enhancing plant growth. *Plant Physiol.* **160,** 837–845 (2012).
5. Moran, N. A. & Jarvik, T. Lateral transfer of genes from fungi underlies carotenoid production in aphids. *Science* **328,** 624–627 (2010).
6. Hoye, T. R., Baire, B., Niu, D., Willoughby, P. H. & Woods, B. P. The hexadehydro-Diels–Alder reaction. *Nature* **490,** 208–212 (2012).
7. Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes* (Organic Chemistry Vol. 11) (Academic, 1967).
8. Tadross, P. M. & Stoltz, B. M. A comprehensive history of arynes in natural product total synthesis. *Chem. Rev.* **112,** 3550–3577 (2012).
9. Baire, B., Niu, D., Willoughby, P. H., Woods, B. P. & Hoye, T. R. Synthesis of complex benzenoids via the intermediate generation of *o*-benzynes through the hexadehydro-Diels–Alder reaction. *Nature Protocols* **8,** 501–508 (2013).
10. Miyawaki, K., Suzuki, R., Kawano, T. & Ueda, I. Cycloaromatization of a non-conjugated polyenyne system: synthesis of 5*H*-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. *Tetrahedr. Lett.* **38,** 3943–3946 (1997).
11. Bradley, A. Z. & Johnson, R. P. Thermolysis of 1,3,8-nonatriyne: evidence for intramolecular [2+4] cycloaromatization to a benzyne intermediate. *J. Am. Chem. Soc.* **119,** 9917–9918 (1997).
12. Ajaz, A. *et al.* Concerted vs. stepwise mechanisms in dehydro-Diels–Alder reactions. *J. Org. Chem.* **76,** 9320–9328 (2011).
13. Hoffmann, R. W. & Suzuki, K. A 'hot, energized' benzyne. *Angew. Chem. Int. Ed.* **52,** 2–4 (2013).
14. Yun, S. Y., 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.* **135,** 4668–4671 (2013).
15. Voica, A.-F., Mendoza, A., Gutekunst, W. R., Fraga, J. O. & Baran, P. S. Guided desaturation of unactivated aliphatics. *Nature Chem.* **4,** 629–635 (2012).
16. Tsui, J. A. & Sterenberg, B. T. A metal-templated 4 + 2 cycloaddition reaction of an alkyne and a diyne to form a 1,2-aryne. *Organometallics* **28,** 4906–4908 (2009).
17. de Almeida, G., Townsend, L. C. & Bertozzi, C. R. Synthesis and reactivity of dibenzoselenacycloheptynes. *Org. Lett.* **15,** 3038–3041 (2013).
18. Hünig, S., Müller, H. & Thier, W. Reduktionen mit diimid. *Tetrahedr. Lett.* **2,** 353–357 (1961).
19. Corey, E. J., Pasto, D. J. & Mock, W. L. Chemistry of diimide. II. Stereochemistry of hydrogen transfer to carbon–carbon multiple bonds. *J. Am. Chem. Soc.* **83,** 2957–2958 (1961).
20. Fernández, I., Cossío, F. P. & Sierra, M. A. Dyotropic reactions: mechanisms and synthetic applications. *Chem. Rev.* **109,** 6687–6711 (2009).
21. Fernández, I., Sierra, M. A. & Cossío, F. P. In-plane aromaticity in double-group transfer reactions. *J. Org. Chem.* **72,** 1488–1491 (2007).
22. Hoye, T. R., Eklov, B. M., Ryba, T. D., Voloshin, M. & Yao, L. J. No-D NMR (no deuterium proton NMR) spectroscopy: a simple yet powerful method for analyzing reaction and reagent solutions. *Org. Lett.* **6,** 953–956 (2004).
23. Himeshima, Y., Sonoda, T. & Kobayashi, H. Fluoride-induced 1,2-elimination of *o*-trimethylsilylphenyl triflate to benzyne under mild conditions. *Chem. Lett.* **12,** 1211–1214 (1983).
24. Ma, Z.-X., Feltenberger, J. B. & Hsung, R. P. Total syntheses of chelidonine and norchelidonine via an enamide–benzyne–[2+2] cycloaddition cascade. *Org. Lett.* **14,** 2742–2745 (2012).
25. Sumida, Y., Kato, T. & Hosoya, T. Generation of arynes via ate complexes of arylboronic esters with an *ortho*-leaving group. *Org. Lett.* **15,** 2806–2809 (2013).
26. Davies, H. M. L., Du Bois, J. & Yu, J.-Q. C–H functionalization in organic synthesis. *Chem. Soc. Rev.* **40,** 1855–1856 (2011).
27. Paul, G. F., Jak, B. & Lankin, D. A. Routine experimental protocol for qHNMR illustrated with taxol. *J. Nat. Prod.* **70,** 589–595 (2007).

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

Acknowledgements We thank C. J. Cramer for helpful discussions about the computational studies. D.N. and P.H.W. thank the University of Minnesota Graduate School Doctoral Dissertation Fellowship and National Science Foundation Graduate Research Fellowship program, respectively. Financial support from the National Institute of General Medical Sciences (GM65597) and the National Cancer Institute (CA76497) of the US Department of Health and Human Services is acknowledged. Portions of this work were performed with hardware and software resources available through the University of Minnesota Supercomputing Institute (MSI).

Author Contributions D.N. made the initial key observations and performed most of the scope studies. P.H.W. performed most of the mechanistic studies. B.P.W. and B.B. also performed aspects of the experimental work. All authors interpreted the data and wrote the manuscript.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to T.R.H. (hoye@umn.edu).