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Synthesis of complex benzenoids via the intermediate generation of o-benzynes through the hexadehydro-Diels–Alder reaction

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Abstract

The hexadehydro-Diels–Alder (HDDA) cascade enables the synthesis of complex benzenoid products with various substitution patterns via aryne intermediates. The first stage of this cascade involves generation of a highly reactive *ortho*-benzyne intermediate by a net [4+2] cycloisomerization of a triyne substrate. The benzyne can be rapidly 'trapped' either intra- or intermolecularly with a myriad of nucleophilic or π-bond-donating reactants. As a representative example of a general procedure to synthesize highly substituted benzenoids, this protocol describes the synthesis of a typical triyne substrate and its use as the reactant in an HDDA cascade to form a phthalide. The synthetic procedure detailed herein (four chemical reactions) takes 16–20 h of active effort over a several day period for preparation of the triyne precursor and ~2 h of active effort over a 3-day period for generation and trapping of the benzyne and isolation of the phthalide product.

Keywords

HDDA; benzyne; Cadiot-Chodkiewicz; cascade; organic synthesis

Introduction

The pursuit of new methods for synthesizing benzene derivatives (benzenoids) is a longstanding and major theme in organic synthesis research. Benzenoids find important applications in virtually every aspect of human life, including in food additives, dyes, cosmetics, functional materials, agricultural chemicals, and pharmaceuticals. Benzynes (see resonance contributors **2a** and **2b** in figure 1) are one of the oldest and most well studied classes of all reactive intermediates in chemistry (Box 1, top). They are valuable for the synthesis of complex benzenoid products, largely because two carbon atoms within the benzyne ring can be simultaneously functionalized following a trapping reaction with a suitable partner.

Traditional methods of making benzynes typically involve the treatment of a 1,2-disubstituted benzene derivative with a strong base or reducing agent. Thus, benzyne generation followed by trapping amounts to a net replacement of the substituents in the precursor by those in the trapped product. The most widely used procedure for aryne

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generation is the Kobayashi method, which involves the fragmentation of a 2-(trimethylsilyl)phenyl triflate with a fluoride ion source.[1] Except for the simplest of substrates (e.g., 2-(trimethylsilyl)phenyl triflate itself), the benzyne precursor must first be synthesized. The reagents required to generate the benzyne (or the byproducts arising from that generation step) can sometimes limit the types of trapping reactions that can be studied or used. By contrast, the hexadehydro-Diels–Alder (HDDA) reaction—a variant of one of the oldest and most powerful transformations in organic chemistry (Box 1, bottom)—generates a benzyne from a triyne (compound **1** in figure 1) in the absence of any reagents.[2–6] Specifically, [4+2] cycloisomerization between a conjugated 1,3-diyne and a tethered, remote alkyne (the diynophile) forms the benzyne. This strategy for producing the benzyne is orthogonal to all other known methods for aryne generation. A densely functionalized benzenoid compound (see compound **3** in figure 1) is produced following the benzyne trapping event. The HDDA reaction requires only simple thermal activation; hence, it is operationally straightforward. Because no additional reagents or byproducts are present, the HDDA process is tolerant of the presence many functional groups on the triyne precursor (e.g., esters, amides, and alcohols), a feature that enables, in some instances, the discovery, investigation, and exploitation of new intrinsic reactivity.[6] As is the case for accessing the requisite substrates for many traditional benzyne generation reactions, the triynyl HDDA substrate must also be synthesized. Another limiting feature of the HDDA approach is the need for the reacting diyne and diynophile to be present within the same substrate molecule. In other words, thus far, the HDDA reaction has only been observed in intramolecular settings.

We recently reported a variety of HDDA cascades that demonstrate the considerable scope of the process.[6] For example, phthalides (entry 1 in Table 1 and the example in this protocol), isoindolones (entry 2), indenones (entry 3), indolines (entry 4), isoindolines (entry 5), benzofurans (entry 6), and fluorenones (entries 7 and 8) are accessible by modifying the triyne tethering unit. Additionally, silyl ethers (entries 2-4 and 6), alcohols (entry 5), arenes (entry 8), and alkenes can trap the benzyne intermediate intramolecularly to give rise to complex polycyclic aromatics. On the other hand, bimolecular trapping of the short-lived benzyne intermediate is possible using, for example, alcohols (entry 1), amides, carboxylic acids, phenols (entry 7), and ammonium halides.

As a representative example of the synthetic approach, we provide here details for the conversion of the triyne **4** into phthalide **7** by an HDDA cascade (Figure 2).[6] Cycloisomerization of triyne **4** generates the benzyne intermediate **5**. Our working mechanistic hypothesis is that trapping by the *t*-butyldimethylsilyl ether occurs by nucleophilic addition of the ether oxygen into the electrophilic carbon of the benzyne **5** to form zwitterion **6**. Oxygen-to-carbon silyl transfer gives rise to the phthalide product **7**. We chose this particular example because the synthesis strategy and sequence used to prepare substrate **4** includes many of the essential reaction types (e.g., terminal alkyne bromination, 1,3-diyne synthesis via Cadiot-Chodkiewicz cross-coupling with a terminal alkyne, and a triyne assembly step from the conjugated diyne and monoyne precursors) necessary to prepare a large variety of HDDA substrates, including those in the examples in Table 1. The times required for these representative reactions are quite similar regardless of the specific target substrate one might want to prepare.

Triyne **4** can be prepared in four steps from commercially available reagents by the route outlined in Figure 3. The preparation of **4** and its HDDA cascade conversion to **7** comprise the five reactions for which details are provided in this protocol. 3-Butyn-1-ol (**8**) is converted into its TBS-ether **9** under standard conditions with *t*-butyldimethylsilyl chloride (TBSCl). The alkyne terminus is then brominated with *N*-bromosuccinimide and $AgNO_3$ to give the bromoalkyne **10**. Cross-coupling of **10** with propargyl alcohol gives the diynol **11**.

Dicyclohexylcarbodiimide-mediated esterification of **11** with propynoic acid then provides the triyne substrate **4**. Finally, **4** is heated in toluene to effect the HDDA cascade that leads to the formation of phthalide **7**.

MATERIALS REAGENTS

! CAUTION All chemicals must be handled with care, and thus a lab coat, gloves, and eye protection should be worn, and all operations should be performed in a laboratory hood.

. 3-Butyn-1-ol (Aldrich cat. no. 130850)

. *t*-Butyldimethylsilyl chloride (TBSCl, Aldrich cat. no. 190500)

. Imidazole (Aldrich cat. no. I2399)

. *N*-Bromosuccinimide (NBS, Aldrich cat. no. B81255)

. Silver nitrate ($AgNO_3$, Aldrich cat. no. 209139)

. Piperidine (Aldrich cat. no. 411027)

. Cuprous chloride (CuCl, Aldrich cat. no. 212946)

. Propargyl alcohol (Aldrich cat. no. P50803)

. Propynoic (propiolic) acid (Aldrich cat. no. P51400)

. *N,N'*-Dicyclohexylcarbodiimide (DCC, Aldrich cat. no. D80002)

! CAUTION *N,N'*-Dicyclohexylcarbodiimide is an irritant and can lead to sensitization. Avoid any direct contact with the skin or inhalation of particulates.

. 4-(Dimethylamino)pyridine (DMAP, Aldrich cat. no. 522805)

. Dichloromethane (CH_2Cl_2), ethyl acetate, hexanes, acetone, and toluene, [standard reagent-grade laboratory solvents]

. Chloroform-*d* ($CDCl_3$, e.g., Cambridge Isotopes lab)

. Silica gel (typically 40–63 micrometers diameter particle size with nominal 60 Å pore size)

. Silica gel thin-layer chromatography (TLC) plates (SIL G/UV254, 0.25 mm layer thickness; e.g., Machery Nagel, M805024)

. Reagents used for preparing common stains for visualizing TLC plates:[26] phosphomolybdic acid, anisaldehyde, ceric ammonium molybdate, or potassium permanganate (TCI America, Fischer Scientific, or Aldrich)

- Common inorganic salts used for preparing wash solutions used during extractive workups: sodium chloride and ammonium chloride
- Anhydrous sodium sulfate (Aldrich cat. no. 238597)

Equipment

. Threaded culture tube, 16x150 mm, with Teflon®-lined, threaded, screw-cap (e.g., KIMAX 45066A16150) having a relatively small headspace with respect to the volume of reaction solvent

. Common laboratory glassware (round-bottomed flasks, vials, Erlenmeyer flasks, disposable pipets, test tubes, etc.)

. Vacuum source

. Inert gas (e.g., N_2) line

. Magnetic stirrer plate and Teflon®-coated magnetic stir bars small enough to fit the reaction vessel/flask

. Teflon®-lined caps

. Rubber septa, rubber stoppers, spatula, syringes, and syringe needles

. Silicone oil heating bath, or alternative equipment capable of heating a reaction mixture to 110 °C

. Glass columns for flash chromatography

. TLC developing chamber

. Weighing balance and paper

. Rotary evaporator

. TLC spotters

. UV lamp for visualizing TLC plates

. NMR tubes (5 mm diameter)

. Access to instrumentation for melting point (mp) determination and nuclear magnetic resonance (NMR) spectroscopy

PROCEDURE

Preparation of (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (9)

1. Equip a 250-ml round-bottomed flask with a magnetic stir bar.
2. Transfer 2.8 g of imidazole (41 mmol) to the round-bottomed flask.
3. Dissolve the contents of the flask in anhydrous CH_2Cl_2 (50 ml), cool the reaction mixture to 0 °C in a water–ice bath, and turn on the magnetic stirrer.
4. Add 1.5 ml of 3-butyn-1-ol (**8**, 1.4 g, 20 mmol) to the reaction mixture using a syringe equipped with a steel needle (final concentration of **8** = 0.4M).
5. Transfer 3.6 g of TBSCl (24 mmol) to the reaction mixture.
6. Cap the round-bottomed flask with a rubber septum or stopper.
7. Remove the flask from the water–ice bath and stir the reaction mixture for 2 h. Please note that the mixture remains colorless at this stage, but a white (imidazole•HCl) precipitate forms during the course of the reaction.
8. Filter the reaction mixture through a bed of silica gel (~5 cm d × 15 cm h). Wash the silica gel with ethyl acetate (~150 ml).
9. Evaporate the volatiles under reduced pressure at ambient temperature using a rotary evaporator.
10. Purify the product by flash chromatography on silica gel (~5 cm d × 25 cm h) using a mixture of hexanes and ethyl acetate (19:1 vol:vol; ~250 ml total volume) as eluent. For a detailed procedure for flash chromatography, see Still *et al.*[27]
11. Combine the fractions that contain the product and evaporate the volatiles under reduced pressure at ambient temperature using a rotary evaporator.

12. The product, TBS-ether **9,** is a colorless oil. Confirm the structure and purity of the product by ^{1}H NMR spectroscopy.

■**PAUSE POINT** Compound **9** can be stored indefinitely at ambient temperature (~23 °C) in a closed container to limit exposure to moisture.

Preparation of ((4-bromobut-3-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (10)

13 Place 3.7 g of silyl ether **9** (20 mmol) in a 250-ml round-bottomed flask equipped with a stir bar.

14 Add 100 ml of acetone (final concentration of **9** = 0.2M).

15 Transfer 3.9 g of NBS (22 mmol) and 0.25 g of $AgNO_3$ (1.5 mmol) to the round-bottomed flask. Cap the flask with a rubber septum or stopper and turn on the magnetic stirrer.

16 Stir the reaction mixture for 1 h at ambient temperature.

17 Filter the slurry through a bed of Celite® using CH_2Cl_2 as the eluent.

18 Concentrate the filtrate under reduced pressure on a rotary evaporator at ambient temperature.

19 Repeat steps 10–11 to obtain pure bromoalkyne **10**. Use a mixture of hexanes and ethyl acetate (19:1 vol:vol; ~250 ml total volume) as eluent for the flash chromatography column (~5 cm d × 25 cm h bed of silica gel).

20 The product bromoalkyne **10** is a yellow oil. Confirm the structure and purity of the product by ^{1}H NMR spectroscopy.

■**PAUSE POINT** Compound **10** has been stored for over 3 months in a freezer (~−20 °C) and away from ambient laboratory light. While 1-bromo- and 1-iodoalkynes with conjugating substituents (alkynes, arenes, or alkenes) at C2 are reported to be somewhat unstable,[28] simple 1-haloalkynes are less problematic.

Preparation of 7-((*tert*-butyldimethylsilyl)oxy)hepta-2,4-diyn-1-ol (11)

21 Equip each of two, dry, 6-dram (22 ml) glass vials, labeled A and B, with a stir bar and a rubber septum.

22 Transfer 1.0 g of bromoalkyne **10** (3.8 mmol) to vial A.

23 Transfer 40 mg of CuCl (0.4 mmol) to vial B.

24 Use, in alternating fashion, a vacuum and inert gas line, each terminating with a syringe needle for insertion through the rubber septum, to evacuate and then backfill the headspace of both vial A and vial B.

25 Add via syringe 0.25 ml of propargyl alcohol ($HC{\equiv}CCH_2OH$, 0.26 g, 4.6 mmol), a volatile alkyne, to vial A (which already contains bromoalkyne **10**).

26 Equip a third dry 6-dram (22 ml) glass vial, labeled C, with a rubber septum and a nitrogen inlet needle (~10 cm in length).

27 Transfer via syringe 4.5 ml of anhydrous piperidine to vial C.

28 Insert a needle through the rubber septum of vial C to act as a vent and submerge the nitrogen inlet needle into the piperidine. Gently sparge the solvent with a positive nitrogen pressure for ~1 h.

▲ **CRITICAL STEP** The amount of oxygen present in solution during the subsequent (coupling) operations should be minimal in order to minimize the formation of symmetrical diynes arising from alkyne self-coupling reactions. It is therefore important that the piperidine be sparged thoroughly with nitrogen gas.

29 Transfer via syringe 4 ml of degassed piperidine from vial C to vial A (final concentration of **10** = 1M). Cool vial A to 0 °C in a water–ice bath and turn on the magnetic stirrer to create a homogeneous solution of propargyl alcohol and bromoalkyne **10** in piperidine.

30 Cool vial B to 0 °C in a water–ice bath and turn on the magnetic stirrer.

31 Use a cannula to transfer the solution in vial A into vial B (which contains the solid CuCl).

32 Transfer the degassed piperidine remaining in vial C (0.50 ml) to vial A via syringe. Swirl vial A to dissolve the residual solution of alkynes and transfer the contents of vial A once more into vial B by cannula.

33 Stir the resulting slurry in vial B at 0 °C for 1 h. Please note that the reaction mixture quickly takes on a light green color and a solid precipitate, presumably piperidinium bromide, appears over time.

34 Transfer the contents of vial B to a separating funnel containing ~20 ml of saturated aqueous NH_4Cl.

35 Extract the aqueous solution with ethyl acetate (3 × ~10 ml) and wash the combined organic layers once with ~20 ml of saturated aqueous NaCl (brine).

36 Dry the combined organic extracts by adding to them ~5 g of anhydrous Na_2SO_4, briefly swirl the resulting mixture, filter the mixture into a round-bottomed flask, and concentrate the filtrate under reduced pressure using a rotary evaporator at ambient temperature.

37 Repeat steps 10–11 to purify the crude product. The silica gel bed size should now be ~2.5 cm d × 15 cm h. Use a mixture of hexanes and ethyl acetate (5:1 vol:vol; ~100 ml total volume) as eluent for the flash chromatography column.

38 The product diyne alcohol **11** is a viscous, pale yellow oil. Confirm the structure and purity of the product by ^1H NMR spectroscopy.

■**PAUSE POINT** Compound **11** can be stored indefinitely; as a precaution, storage in a freezer (~−20 °C) is recommended.

Preparation of 7-((*tert*-butyldimethylsilyl)oxy)hepta-2,4-diyn-1-yl propynoate (4)

39 Transfer 119 mg of the diyne alcohol **11** (0.50 mmol), 39 mg of propynoic acid (also known, trivially, as propiolic acid, $HC{\equiv}CCO_2H$, 0.55 mmol), 6 mg of DMAP (0.05 mmol), and 3 ml of anhydrous CH_2Cl_2 (final concentration of **11** = 0.17M) to a dry 6-dram (22 ml) glass vial equipped with a stir bar and rubber septum or Teflon®-lined screw cap.

40 Cool the vial to 0 °C in a water–ice bath and turn on the magnetic stirrer.

41 Add 110 mg of solid DCC (0.55 mmol) to the vial and stir the reaction mixture for 2 h.

! CAUTION DCC is an irritant and can lead to sensitization. Avoid any direct contact with the skin or inhalation of particulates.

42 Filter the white precipitate, which is largely the unwanted byproduct *N,N'*-dicyclohexylurea, through a bed of Celite®. Wash the Celite® three times with CH_2Cl_2.

43 Concentrate the filtrate under reduced pressure with the aid of a rotary evaporator at ambient temperature and repeat steps 10–11 to purify the product ester **4**. The silica gel bed size should now be ~2.5 cm d × 15 cm h. Use a mixture of hexanes and ethyl acetate (12:1 vol:vol; ~100 ml total volume) as eluent for the flash chromatography column.

44 The triyne ester **4** is a viscous, colorless to pale yellow oil. Confirm the structure and purity of the product by ^{1}H NMR spectroscopy.

■**PAUSE POINT** Compound **4** can be stored indefinitely in a freezer (~–20 °C).

Preparation of 8-(*tert*-butyldimethylsilyl)-2,3-dihydrobenzo[1,2-*b*:4,5-*c'*]difuran-5(7*H*)-one (7) via the HDDA cascade

45 Transfer 29 mg of the triyne ester **4** (0.10 mmol) and 4 ml of anhydrous toluene to a screw-capped, 16 × 150 mm threaded glass culture tube (final concentration of **4** = 0.025M).

46 Cap the vial with a Teflon®-lined screw-cap and immerse the vial in a silicone oil bath (or alternative heat source) at 110 °C. Please note that the reaction solution remains at a constant volume because this apparatus does not permit headspace exchange.

47 Periodically monitor the progress of the HDDA cascade reaction by thin layer chromatographic (TLC) analysis on silica gel TLC plates. The retardation factors (R_F) of the substrate triyne **4** and product **7** in hexanes/ethyl acetate (5:1 vol:vol) are ~0.8 and ~0.2, respectively.

48 Once the substrate **4** is judged to be fully converted to product **7** (~2 days), concentrate the contents of the vial under reduced pressure with the aid of a rotary evaporator in an ~40 °C water bath.

49 Repeat steps 10–11 to purify the product **7** using hexanes/ethyl acetate (4:1 vol:vol; ~50 ml total volume) as eluent for the flash chromatography column. The silica gel bed size should now be ~1 cm d × 10 cm h).

50 The tricyclic phthalide **7** is a colorless solid, mp = 167–169 °C. Confirm the structure and purity of the product by ^{1}H NMR spectroscopy.

• TIMING

Preparation of (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (9)

Steps 1–6: 1 h

Step 7: 2 h

Steps 8–12: 1–2 h

Preparation of ((4-bromobut-3-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (10)

Steps 13–15: 1 h

Step 16: 1 h

Steps 17–20: 1–2 h

Preparation of 7-((*tert*-butyldimethylsilyl)oxy)hepta-2,4-diyn-1-ol (11)

Steps 21–25: 1 h

Steps 26–28: 2 h

Steps 29–32: 1 h

Step 33: 1 h

Steps 34–36: 1 h

Steps 37–38: 1–2 h

Preparation of 7-((*tert*-butyldimethylsilyl)oxy)hepta-2,4-diyn-1-yl propynoate (4)

Steps 39–40: 1 h

Step 41: 2 h

Steps 42–44: 1–2 h

Preparation of 8-(*tert*-butyldimethylsilyl)-2,3-dihydrobenzo[1,2-b:4,5-c']difuran-5(7H)-one (7)

Steps 45–47: 1 h

Step 48: 48 h

Steps 49–50: 1 h

ANTICIPATED RESULTS

Typical Yields

(But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (9): 95–99%

((4-Bromobut-3-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (10): 85–95%.

7-((*tert*-Butyldimethylsilyl)oxy)hepta-2,4-diyn-1-ol (11): 70–90%.

7-((*tert*-Butyldimethylsilyl)oxy)hepta-2,4-diyn-1-yl propynoate (4): 45–65%.

8-(*tert*-Butyldimethylsilyl)-2,3-dihydrobenzo[1,2-*b*:4,5-*c'*]difuran-5(7*H*)-one (7): 85–95%.

Analytical Data (see the Supplementary Information associated with reference 6 for copies of most of the following NMR spectra)

(But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (9): **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.74 (t, J = 7.1 Hz, 2H, CH_2OSi), 2.40 (td, J = 7.1, 2.7 Hz, 2H, CH_2C≡CH), 1.96 (t, J = 2.7 Hz, 1H, C≡CH), 0.90 [s, 9H, SiC(CH_3)$_3$], and 0.08 [s, 6H, Si(CH_3)$_2$]. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 81.7, 69.4, 61.9, 26.0, 23.0, 18.5, and -5.1.

((4-Bromobut-3-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (10): **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.73 (t, J = 7.0, 2H, CH_2OSi), 2.42 (t, J = 7.0 Hz, 2H, CH_2C≡CBr), 0.90 [s, 9H, SiC(CH_3)$_3$], and 0.08 [s, 6H, Si(CH_3)$_2$]. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 77.7, 61.6, 39.2, 26.0, 24.1, 18.5, and −5.2.

7-((*tert*-Butyldimethylsilyl)oxy)hepta-2,4-diyn-1-ol (11): **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.32 (dt, *J* = 6.3, 1.1 Hz, 2H, C*H*$_2$OH), 3.74 (t, *J* = 6.9 Hz, 2H, C*H*$_2$OSi), 2.50 (dt, *J* = 6.9, 1.1 Hz, 2H, C≡CC*H*$_2$CH$_2$), 1.55 (t, *J* = 6.3 Hz, 1H, CH$_2$O*H*), 0.90 [s, 9H, SiC(C*H*$_3$)$_3$], and 0.08 [s, 6H, Si(C*H*$_3$)$_2$]. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 78.9, 73.9, 70.9, 65.6, 61.4, 51.7, 26.0, 23.9, 18.5, and −5.2.

7-((*tert*-Butyldimethylsilyl)oxy)hepta-2,4-diyn-1-yl propynoate (4): **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.83 (t, *J* = 1.1 Hz, 2H, CO$_2$C*H*$_2$), 3.74 (t, *J* = 6.9 Hz, 2H, OC*H*$_2$), 2.94 (s, 1H, C≡C*H*), 2.50 (tt, *J* = 6.9, 1.1 Hz, 2H, OCH$_2$C*H*$_2$), 0.90 [s, 9H, SiC(C*H*$_3$)$_3$], and 0.07 [s, 6H, Si(C*H*$_3$)$_2$]. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.9, 79.9, 76.1, 74.0, 72.7, 68.1, 65.3, 61.3, 54.2, 26.0, 23.9, 18.4, and −5.2.

8-(*tert*-Butyldimethylsilyl)-2,3-dihydrobenzo[1,2-*b*:4,5-*c'*]difuran-5(7*H*)-one (7): **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.67 (t, *J* = 1.4 Hz, 1H, Ar*H*), 5.20 (s, 2H, ArC*H*$_2$O), 4.64 (t, *J* = 8.7 Hz, 2H, ArCH$_2$C*H*$_2$), 3.25 (td, *J* = 8.7, 1.2 Hz, 2H, ArC*H*$_2$CH$_2$), 0.89 [s, 9H, SiC(C*H*$_3$)$_3$], and 0.33 [s, 6H, Si(C*H*$_3$)$_2$]. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.5, 171.4, 155.3, 128.7, 123.2, 117.9, 111.4, 71.9, 71.2, 28.7, 26.7, 18.6, and 3.8.

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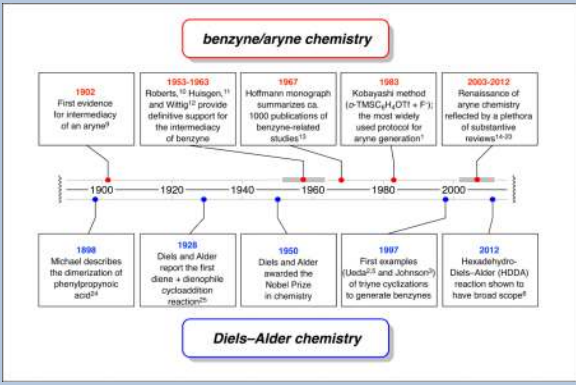
Box 1 LANDMARK EVENTS IN THE CENTURY-OLD HISTORY OF ARYNE AND DIELS–ALDER CHEMISTRIES

Arynes, of which benzynes are a subset, comprise one of the most versatile and well-studied classes of reactive intermediates in organic chemistry. The Diels-Alder [4+2] cycloaddition reaction, which typically creates a six-membered carbocyclic product, is arguably the most venerable transformation in all of chemistry and is described in every introductory organic chemistry textbook. The first reports of aryne[7] and Diels–Alder[8] chemistry appeared over a century ago. Other key events in the development of the understanding of these two fields are summarized on the timeline below.

Benzynes: The first experimental evidence now interpreted as involving the formation of an aryne intermediate was reported in 1902.[9] Experiments reported in the 1950s, and now regarded as classic, provided compelling evidence for the intermediacy of benzyne via clever isotope scrambling and trapping reactions (including, coincidentally, Diels–Alder cycloaddition).[10–12] The ensuing explosive growth of benzyne chemistry is evident by the hundreds of examples of reactions assembled in a 1967 monograph.[13] The most recently developed (and now most widely used) general protocol for generating benzynes is that reported by Kobayashi nearly three decades ago.[1] The convenience of this method for preparing arynes has fueled a remarkable rebirth of interest in aryne trapping chemistry. This resurgence is perhaps best exemplified by the plethora of major reviews on benzyne/aryne chemistry that have appeared over the past few years (ten, appearing since 2010, are cited here).[14–23]



Diels–Alder: Several [4+2] cycloaddition reactions, including an example in 1898 of what now could be called a tetradehydro-Diels–Alder (TDDA) reaction,[24] predate the initial 1928 report by Diels and Alder,[25] from which the reaction takes its name. The keen insights and extensive body of work by these investigators was recognized by the award of the Nobel Prize in chemistry in 1950. In 1997[2,5] the Ueda research group published their first of a series of reports describing the cycloisomerization of tetraynes to give products whose formation can be explained by pathways involving benzyne intermediates. In the same year, Johnson provided convincing evidence for the formation of a benzyne derivative during the flash vacuum pyrolysis (580 °C) of 1,3,8-nonatriyne.[3] The considerable preparative potential of the HDDA cascade had not otherwise been developed prior to the report in 2012.[6]

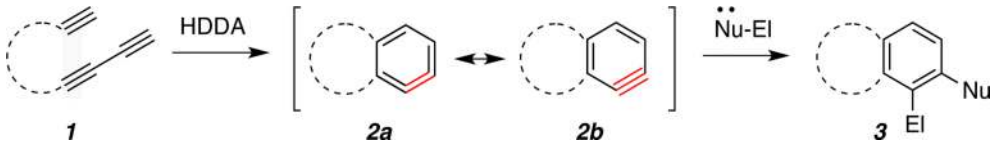


Figure 1.
The hexadehydro-Diels–Alder (HDDA) cascade. Triyne **1** cycloisomerizes to form a benzyne (structures **2a** and **2b**), which is subsequently trapped to produce benzenoid **3**. Nu, nucleophile; El, electrophile.

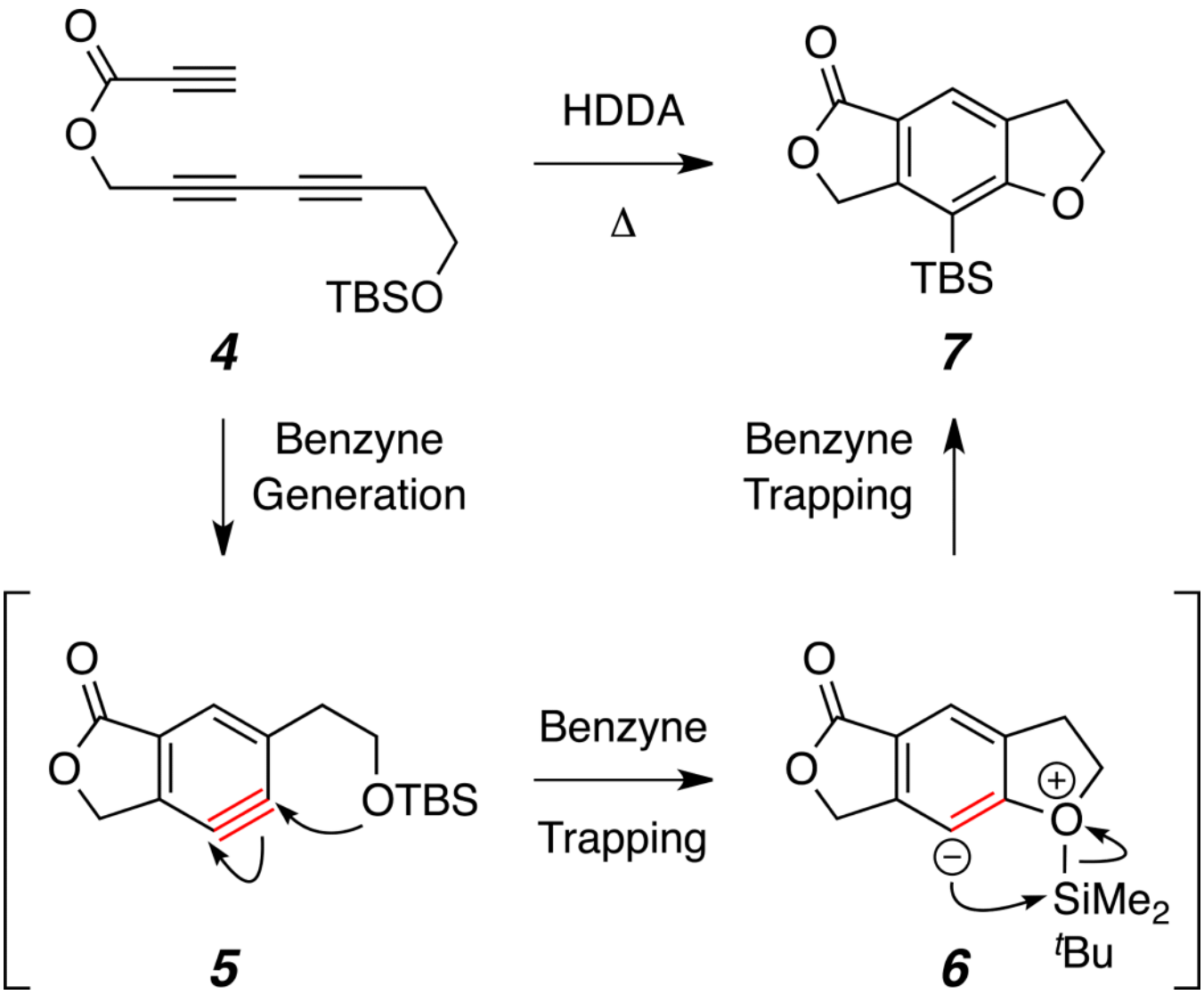


Figure 2.
Intermediates involved (benzyne **5** and zwitterion **6**) in the HDDA cascade conversion of triyne **4** to phthalide **7**. TBS: *t*-butyldimethylsilyl.

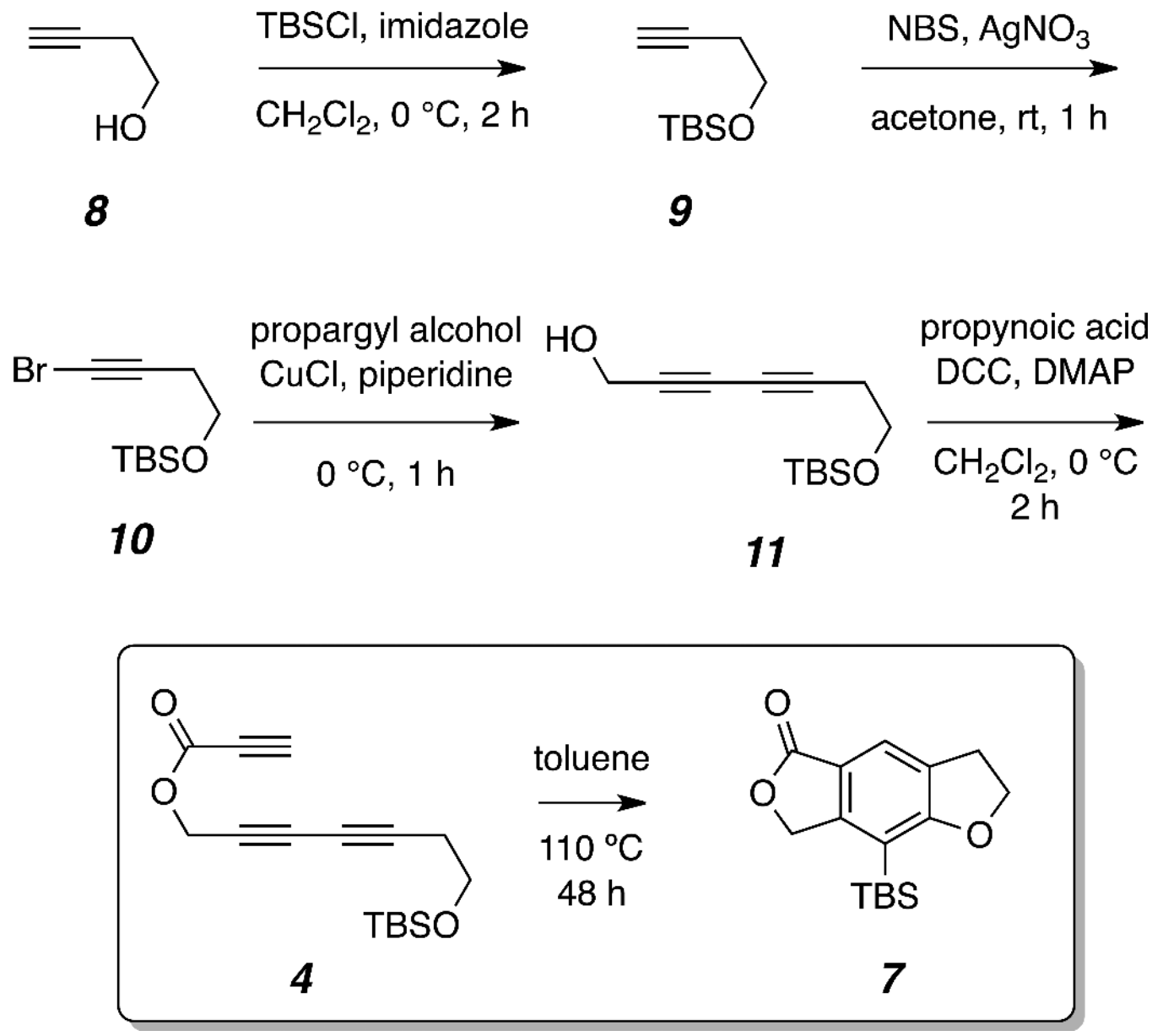
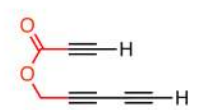
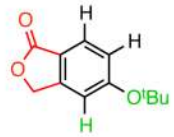
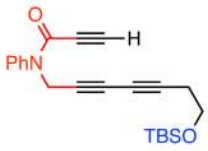
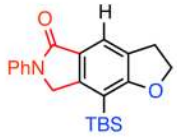
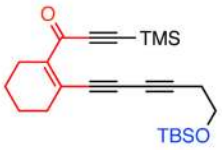
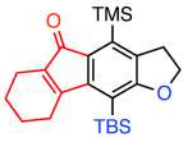
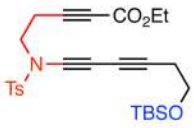
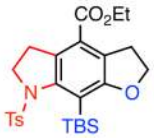
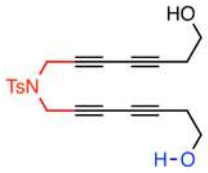
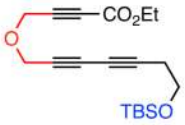
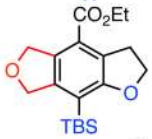
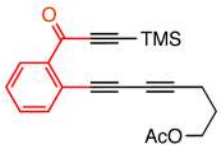
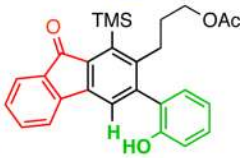
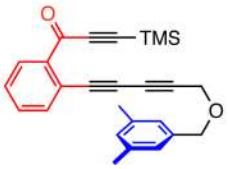


Figure 3.

Synthesis route to obtain substrate **4** and its HDDA cascade to produce the tricyclic phthalide derivative **7**. NBS: *N*-bromosuccinimide; DCC: dicyclohexylcarbodiimide; DMAP: 4-(dimethylamino)pyridine; TBS: *t*-Butyldimethylsilyl.

Table 1

Examples of HDDA cascade processes, including both inter- and intramolecular trapping reactions.

Entry	Substrate	Conditions	Product
1		120 °C 40 h ^{t}BuOH **68%**	
2		120 °C 15 h PhMe **92%**	
3		26 °C 46 h $CDCl_3$ **93%**	
4		120 °C 18 h PhMe **80%**	
5		65 °C 20 h $CDCl_3$ **95%**	
6		110 °C 20 h d_8-PhMe **86%**	
7		85 °C 18 h $CHCl_3$ phenol **85%**	
8		85 °C 18 h $CHCl_3$ **85%**