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Reactions of HDDA-derived Benzyne with Sulfides: Mechanism, Modes, and Three-component Reactions

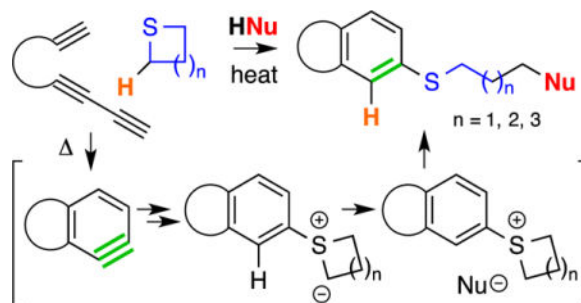
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Abstract

We report here reactions of alkyl sulfides with benzyne thermally generated by the hexadehydro-Diels–Alder (HDDA) cycloisomerization. The initially produced 1,3-betaine (*o*-sulfonium/aryl carbanion) undergoes intramolecular proton transfer to generate a more stable S-aryl sulfur ylide. This can react in various manners, including engaging weak acids (HA) in the reaction medium. This can produce transient ion pairs $\text{ArSR}_2^+\text{A}^-$ that proceed to the products $\text{ArSR} + \text{RA}$. When cyclic sulfides are used, A^- opens the ring and is incorporated into the product, an outcome that constitutes a versatile, three-component coupling process.

Graphical abstract



o-Benzyne (**1**) is the parent member of one of the most versatile of all reactive intermediates in organic chemistry, largely because of its adaptability as an electrophilic agent capable of capture by many different types of external nucleophiles. Its reaction with sulfide trapping agents, largely by way of ylide intermediates (Figure 1), was studied in a number of laboratories in the period 1962¹–1989² but has lain fallow until the recent report of Xu and coworkers. As they pointed out, “nucleophilic attack of alkyl thioether on benzyne followed by an intramolecular 1,4-proton shift has been almost totally neglected since its debut³.”⁴ The majority of those early studies were described in a series of reports from the Nakayama

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Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental details for the preparation of new compounds; spectroscopic data for their characterization, including copies of ¹H and ¹³C NMR spectra; and computed (DFT) geometries of benzyne intermediates and transition state for ylide formation (PDF).

Notes

The authors declare to have no competing financial interests.

laboratory.^{5a} All of this previous work used simple benzyne derivatives, the vast majority of studies being explored with *o*-benzyne (**1**) itself.

The generation of benzyne intermediates by the thermal cycloisomerization reaction of tethered triynes⁶ via the hexadehydro-Diels–Alder (HDDA) reaction⁷ (e.g., **4** to **8**, Figure 2) produces this important class of reactive species in environments free of the reagents and byproducts that necessarily accompany all other methods⁸ of benzyne generation. This permits interrogation of inherent benzyne reactivity at a more fundamental level than is often otherwise possible.⁹ In addition, new modes of benzyne trapping reactions^{10,11,12} can be uncovered that would be otherwise incompatible with most if not all of the more traditional methods of benzyne generation. We describe here results of our investigations of the reactivity between HDDA-generated benzyne derivatives and various sulfides. These studies provide both mechanistic insight as well as novel trapping processes, including new three component reactions.^{8f,13}

To probe details of ylide formation, we first explored reactions between the benzyne **8** and thioanisole (Figure 2). Heating tetrayne **4** with PhSCH₃ in the presence of *p*-chlorobenzaldehyde in *d*₆-benzene produced the diaryl sulfide **5-h** and epoxide **6** [$>60\%$ yield (NMR, see SI)]. Replacing the aldehyde with acetic acid as the additive efficiently produced **5-h** (79% yield following isolation). Both results suggest the intermediacy of ylide **10**; the epoxide would result from a Corey-Chaykovsky-like process⁴ and the outcome with AcOH would arise by protonation of **10-h₃** to give **11-h₃** (not shown) and subsequent methylation^{5b} (ca. one equivalent of MeOAc was observed by NMR spectroscopy).

We used labeling studies to probe for the intermediacy of a zwitterion like **9**. Tetrayne **4** was heated in C₆D₆ with PhSCD₃ and AcOH. This gave, nearly exclusively, the mono-deuterated sulfide **5-d** and dideuterated methyl acetate (**7**, NMR, see SI). Protonation by AcOH could have occurred at the stage of either the initially formed 1,3-zwitterion **9-d₃** or ylide **10-d₃**. The deuterium labeling pattern of the products **5-d** and **7** clearly indicates the involvement of **11-d₃** and, importantly, establishes the viability of intramolecular proton transfer within **9** (cf. **2** to **3**). Finally, heating **4**, AcOH, and an equimolar mixture of PhSCH₃ and PhSCD₃ gave nearly equal amounts of **5-h** and **5-d** (as well as AcOCH₃ and AcOCHD₂), suggesting that reversal of formation of adduct **9** is slower than the proton transfer that converts **9** to **10**. This result also argues against a concerted event for conversion of **8** directly to ylide **10** (cf., **1** to **3**).

We next explored HDDA-benzyne trapping with a variety of different types of sulfides (Table 1). These studies demonstrated various modes of trapping processes, some precedented and some not. Consistent with our intent, these results establish the viability of each reaction mode in the context of HDDA-generated benzyne. In each case, benzyne **8** from the symmetrical, ether-linked tetrayne **4** (entries 1–3 and Figure 2) gives a mixture of isomeric products arising from competitive trapping at C6 (major, shown) and C7. Details about the structure assignment of these constitutional isomers and DFT calculations showing the extent of ring distortion of the intermediate benzyne¹⁴ are provided in the SI.

Diallyl sulfide trapped the benzyne **8** to provide the desymmetrized diene **15** (Table 1, entry 1), presumably via **15-int**. This is consistent with the outcome of the reaction of **1** with digeranyl³ or diprenyl^{5c} sulfide. The rearrangement of **15-int** to **15** could, in principle, occur either by a [2,3]-sigmatropic process^{3,15} (green arrows) or by a Stevens rearrangement.¹⁶ We therefore carried out analogous reactions with a propargyl sulfide (entry 2) or dibenzyl sulfide^{5d} (entry 3). The former cleanly gave an allene (**16a** or **16b**), showing that [2,3]-Wittig processes (**16-int**) are viable. The latter gave adduct **17**, the product of a Stevens rearrangement (**17-int**).

Given the considerable generality of the HDDA cascade, we were unsurprised to see that sulfide trapping is not unique to benzyne **8**. Those derived from the tetraynes **12–14** participate as well (entries 4–6). In those instances, we happened to use various cyclic sulfides as the trapping agents. Either thiirane or tetrahydrothiophene gave rise to the same product, the vinyl sulfide **18** (entry 4), likely via the fragmentations shown in **18-int** and **18'-int**, respectively. Similar modes of ring-cleavage have been reported.^{2,5e–f,17} In contrast, use of thietane (entry 5) gave rise to the ring-contracted cyclopropane **19**—an apparently unprecedented mode of reaction. Finally, *N*-methylbenzothiazoline (in the presence of acetic acid) gave the aminophenyl sulfide **20** (entry 6), again a new type of trapping reaction.

We then explored the use of cyclic sulfides in the presence of various protic nucleophiles (H–Nu) with the goal of expanding this chemistry into a three-component process.¹³ We are aware of one report in which such a reaction has been described: namely, generation of *o*-benzyne in the presence of (three) cyclic sulfides and aqueous hydrochloric acid produced chloroalkyl sulfides (e.g., 4-chlorobutyl phenyl sulfide from tetrahydrothiophene).^{5c} The HDDA version, via the ion pair **22**, is portrayed generically in the graphic at the top of Table 2. In the products **23**, the tetrayne-derived fragment and nucleophile are linked in a fashion dictated by the structure of the sulfide used. This structural motif is relevant to the field of drug discovery.¹⁸

The reaction is general with respect to the type of benzyne used (see **21a–g**). Two (**21d** and **21e**) represent a previously unreported type of HDDA substrate. It is notable that HDDA cycloisomerization leading to **21e** occurred faster (ca. 5×) than an analog lacking the geminal methyl substituents, presumably a reflection of the bond angle compression that brings the proximal termini of the diyne and diynophile closer to one another.^{12c}

Results of three-component coupling reactions are listed in Table 2. Some highlights are: (i) carbon-, nitrogen- and oxygen-centered nucleophiles, including *N*-heterocycles (entries 7 and 9), will all participate; (ii) hindered (entry 5) or relatively weakly acidic H–Nu species (Brønsted acids) are functional; (iii) the unsymmetrical sulfonium ion intermediate in entry 6 opens selectively at the allylic center; (iv) additional functionality can be tolerated within the cyclic thioether (entries 6 and 8); (v) a number of these nucleophiles are capable of trapping HDDA benzyne directly—the presence of the polarizable sulfide nucleophile outpaces those processes. One limitation is that thiirane has not been an effective participant in the 3-component reaction to date—apparently fragmentation to the vinyl sulfide **18** is so rapid^{5e} that it supersedes protonation by the external protic nucleophile. All told, there is

considerable generality to this process. The preparation of arrays of products from any one benzyne precursor, itself selected from among multiple options, can be envisioned.

In conclusion, we have (i) presented evidence supporting the involvement of initial 1,3-zwitterions in reactions of aliphatic sulfides with benzynes (Figure 2), (ii) demonstrated the viability of several new modes of trapping reaction (Table 1), (iii) presented two new types of HDDA-benzynes (**21d** and **21e**, Table 2), and (iv) shown that three-component reactions that engage HDDA-benzynes, cyclic sulfides, and a protic nucleophile have considerable generality.

Supplementary Material

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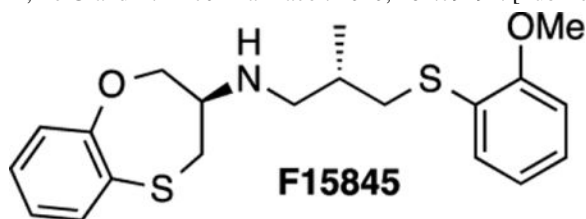
Acknowledgments

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References

1. (a) Hellmann H, Eberle D. *Liebigs Ann Chem.* 1963; 662:188–201. (b) Franzen V, Joschek HI, Mertz C. *Liebigs Ann Chem.* 1962; 654:82–91.
2. Nakayama J, Kumano Y, Hoshino M. *Tetrahedron Lett.* 1989; 30:847–850.
3. Blackburn GM, Ollis WD. *Chem Commun.* 1968:1261–1262.
4. Xu H, Cai M, He W, Hu W, Shen M. *RSC Adv.* 2014; 4:7623–7626.
5. Summarized (pp 400–406) in (a) Nakayama J. *J Sulfur Chem.* 2009; 30:393–468. (b) Nakayama J, Fujita T, Hoshino M. *Chem Lett.* 1982:1777–1780. (c) Nakayama J, Hoshino K, Hoshino M. *Chem Lett.* 1985:677–678. (d) Iwamura H, Iwamura M, Nishida T, Yoshida M, Nakayama J. *Tetrahedron Lett.* 1971; 12:63–66. (e) Nakayama J, Takeue S, Hoshino M. *Tetrahedron Lett.* 1984; 25:2679–2682. (f) Nakayama J, Ozasa H, Hoshino M. *Heterocycles.* 1984; 22:1053–1056.
6. (a) Bradley AZ, Johnson RP. *J Am Chem Soc.* 1997; 119:9917–9918. (b) Miyawaki K, Suzuki R, Kawano T, Ueda I. *Tetrahedron Lett.* 1997; 38:3943–3946.
7. (a) Hoye TR, Baire B, Niu DW, Willoughby PH, Woods BP. *Nature.* 2012; 490:208–212. [PubMed: 23060191] (b) Baire B, Niu D, Willoughby PH, Woods BP, Hoye TR. *Nature Protocols.* 2013; 8:501–508. [PubMed: 23411632]
8. For some recent reviews and commentary on aryne chemistry: (a) Holden C, Greaney MF. *Angew Chem Int Ed.* 2014; 53:5746–5749. (b) Dubrovskiy AV, Markina NA, Larock RC. *Org Biomol Chem.* 2013; 11:191. [PubMed: 23132413] (c) Wu C, Shi F. *Asian J Org Chem.* 2013; 2:116. (d) Peñe D, Peña D, Guitián E. *Eur J Org Chem.* 2013:5981. (e) Tadross PM, Stoltz BM. *Chem Rev.* 2012; 112:3550–3577. [PubMed: 22443517] (f) Gampe CM, Carreira EM. *Angew Chem, Int Ed.* 2012; 51:3766–3778. (g) Bhunia A, Yetra SR, Biju AT. *Chem Soc Rev.* 2012; 41:3140. [PubMed: 22278415] (h) Okuma K. *Heterocycles.* 2012; 85:515. (i) Yoshida H, Ohshita J, Kunai A. *Bull Chem Soc Jpn.* 2010; 83:199. (j) Kitamura T. *Aust J Chem.* 2010; 63:987–1001.
9. (a) Niu D, Willoughby PH, Baire B, Woods BP, Hoye TR. *Nature.* 2013; 501:531–534. [PubMed: 24067712] (b) Hoye TR, Baire B, Wang T. *Chem Sci.* 2014; 5:545–550. [PubMed: 25419449] (c) Niu D, Wang T, Woods BP, Hoye TR. *Org Lett.* 2014; 16:254–257. [PubMed: 24329102] (d) Willoughby PH, Niu D, Wang T, Haj MK, Cramer CJ, Hoye TR. *J Am Chem Soc.* 2014; 136:13657–13665. [PubMed: 25232890] (e) Marell DJ, Furan LR, Woods BR, Lei X, Bendelsmith AJ, Cramer CJ, Hoye TR, Kuwata KT. *J Org Chem.* 2015; 80:11744–11754. [PubMed: 26270857]

10. (a) Yun SY, Wang K, Lee N, Mamidipalli P, Lee D. *J Am Chem Soc.* 2013; 135:4668–4671. [PubMed: 23477300] (b) Karmakar R, Mamidipalli P, Yun SY, Lee D. *Org Lett.* 2013; 15:1938–1941. [PubMed: 23540274] (c) Wang K, Yun SY, Mamidipalli P, Lee D. *Chem Sci.* 2013; 4:3205–3211. (d) Mamidipalli P, Yun SY, Wang K, Zhou T, Xia Y, Lee D. *Chem Sci.* 2014; 5:2362–2367. (e) Lee N, Yun SY, Mamidipalli P, Salzman RM, Lee D, Zhou T, Xia Y. *J Am Chem Soc.* 2014; 136:4363–4368. [PubMed: 24579690] (f) Karmakar R, Yun SY, Wang K, Lee D. *Org Lett.* 2014; 16:6–9. [PubMed: 24313272] (g) Karmakar R, Yun SY, Chen J, Xia Y, Lee D. *Angew Chem Int Ed.* 2015; 54:6582–6586. (h) Karmakar K, Ghorai S, Xia Y, Lee D. *Molecules.* 2015; 20:15862–15880. [PubMed: 26334266]
11. (a) Vandavasi JK, Hu W, Hsiao C, Senadia GC, Wang JJ. *RSC Adv.* 2014; 4:57547–57552. (b) Liang Y, Hong X, Yu P, Houk KN. *Org Lett.* 2014; 16:5702–5705. [PubMed: 25329369] (c) Nobusue S, Yamane H, Miyoshi H, Tobe Y. *Org Lett.* 2014; 16:1940–1943. [PubMed: 24627980] (d) Kerisit N, Toupet L, Larini P, Perrin L, Guillemin J, Trolez Y. *Chem Eur J.* 2015; 21:6042–6047. [PubMed: 25761250] (e) Watanabe T, Curran DP, Taniguchi T. *Org Lett.* 2015; 17:3450–3453. [PubMed: 26114804]
12. (a) Niu D, Hoyer TR. *Nature Chem.* 2014; 6:34–40. [PubMed: 24345944] (b) Chen J, Baire B, Hoyer TR. *Heterocycles.* 2014; 88:1191–1200. [PubMed: 24910496] (c) Woods BP, Baire B, Hoyer TR. *Org Lett.* 2014; 16:4578–4581. [PubMed: 25153729] (d) Woods BP, Hoyer TR. *Org Lett.* 2014; 16:6370–6373. [PubMed: 25470072] (e) Pogula VD, Wang T, Hoyer TR. *Org Lett.* 2015; 17:856–859. [PubMed: 25671804] (f) Luu Nguyen Q, Baire B, Hoyer TR. *Tetrahedron Lett.* 2015; 56:3265–3267. [PubMed: 26028780]
13. Roy T, Baviskar DR, Biju AT. *J Org Chem.* 2015; 80:11131–11137. and references therein. [PubMed: 26444249]
14. (a) Hamura T, Ibusuki Y, Sato K, Matsumoto T, Osamura Y, Suzuki K. *Org Lett.* 2003; 5:3551–3554. [PubMed: 14507170] (b) Cheong PHY, Paton RS, Bronner SM, Im GYJ, Garg NK, Houk KN. *J Am Chem Soc.* 2010; 132:1267–1269. [PubMed: 20058924] (c) Garr AN, Luo D, Brown N, Cramer CJ, Buszek KR, VanderVelde D. *Org Lett.* 2010; 12:96–99. [PubMed: 19961152]
15. Baldwin JE, Hackler RE. *J Am Chem Soc.* 1969; 91:3646–3647.
16. Bhakat S. *J Chem Pharm Res.* 2011; 3:115–121.
17. Brewer JPN, Heaney H, Jablonski JM. *Tetrahedron Lett.* 1968; 9:4455–4456.
18. E.g., the linked sulfide F15845 has been in Phase I and II clinical trials for treatment of angina: (a) Le Grand B, Pignier C, Létienne R, Cuisiat F, Rolland F, Mas A, Vacher B. *J Med Chem.* 2008; 51:3856–3866. [PubMed: 18529044] (b) Pignier C, Rougier J-S, Vié B, Culié C, Verscheure Y, Vacher B, Abriel H, Le Grand B. *Brit J Pharmacol.* 2010; 161:79–91. [PubMed: 20718741]



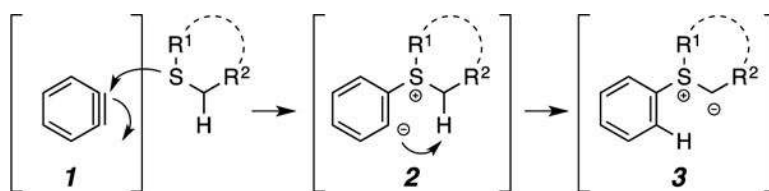


Figure 1. Trapping of α -benzyne (**1**) with an alkyl sulfide produces ylide **3**, presumably via the zwitterionic betaine **2**.

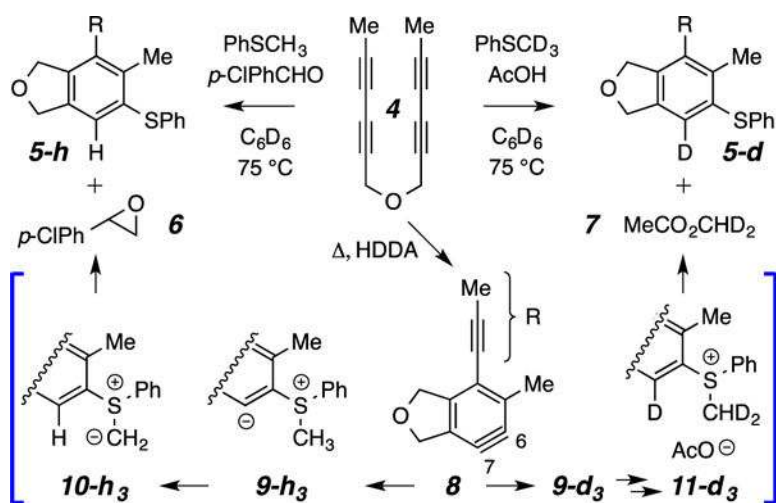


Figure 2. Trapping of HDDA-generated benzyne **8** by thioanisole: epoxidation of $p\text{-ClPhCHO}$ by ylide **10-h₃** and alkylation within the sulfonium acetate ion pair **11-d₃**.

Table 1

Various modes of trapping of HDDA-generated benzynes by sulfides^a

| entry | reactants | key intermediate/event | product, isolated yield |
|-------|--|-------------------------------------|--|
| 1 | 4 + | 15-int | 15 52% (17%) ^c |
| 2 | 4 + X = C≡CH X = CO ₂ Me | 16-int | 16a 39% (10%) X = C≡CH ^c 16b 63% (12%) X = CO ₂ Me ^c |
| 3 | 4 + | 17-int | 17 25% (5%) ^c |
| 4 | 12 + | 18-int 18'-int | 18 90% (via 18-int) 40% (via 18'-int) |
| 5 | 13 + | 19-int | 19 40% |
| 6 | 14 + | 20-int | 20 35% R' = Boc |

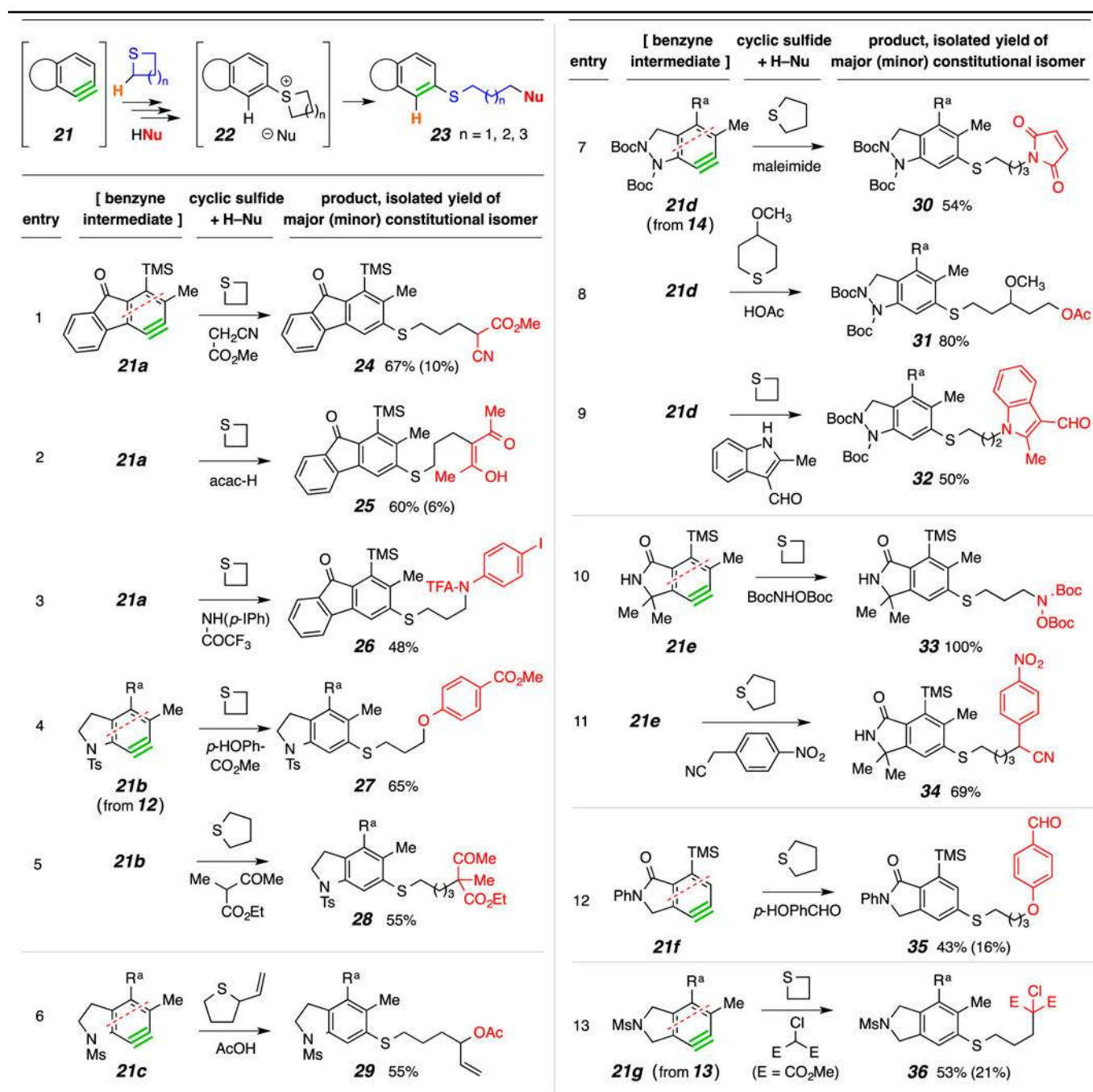
^aReaction conditions: Substrate tetrayne in PhH (0.1 M) containing the indicated sulfide (1.5–2 equiv) was heated in a sealed culture tube (see SI for reaction temperatures and times). For entry 5, five equiv of *o*-NO₂PhCH₂CO₂Me was present. For entry 6, five equiv of AcOH was present.

^bR = 1-propynyl.

^cBenzyne **8** (from **4**) is trapped by sulfides competitively at C6 and C7 to give separable major and minor (yield in parentheses) isomers, respectively.

Table 2

Three-component reactions of HDDA benzynes (21, green), cyclic sulfides (blue), and H-nucleophiles (red)

^aR = 1-propynyl.