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Palladium-catalysed construction of butafulvenes

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Butafulvene is a constitutional isomer of benzene, comprising a cyclobutene skeleton bearing two exocyclic conjugated methylene units. As a result of the intrinsic high strain energy and anti-aromaticity, the preparation of butafulvene compounds has been a fundamental issue for the development of butafulvene chemistry. Here an efficient palladium-catalysed coupling protocol involving propargylic compounds has been developed, providing a solid and versatile strategy for the rapid assembly of symmetric butafulvene derivatives. Based on mechanistic studies, two complementary mechanisms, both involving palladium catalysis, have been confirmed. With the mechanism unveiled, the synthesis of non-symmetric butafulvenes has also been achieved. Advantages of this strategy include tolerance to a wide range of propargylic molecules, mild reaction conditions, simple catalytic systems and easy scalability. The synthetic potential of the products as platform molecules for cyclobutene derivatives has also been demonstrated.

Since Kekulé proposed a sensible structure for benzene in 1865, landmark achievements have been made in the synthesis and transformation of benzene and its derivatives[1–17]. Owing to the perfect delocalization of six π electrons, benzene is a highly stable aromatic hydrocarbon with all carbon–carbon bonds having an identical length of 1.39 Å (Fig. 1a). In comparison, pentafulvene, a five-membered cyclic isomer of benzene, exhibits very different reactivity[18–22] resulting from the exocyclic double bond (Fig. 1a). If the ring size of the triple-conjugated carbocycle is further contracted, it would form an unusual isomer, anti-aromatic butafulvene, which consists of cyclobutene bearing two exocyclic methylene units. Based on experiments and calculation results, these three isomers—benzene, pentafulvene and butafulvene—may display dramatically different properties (Fig. 1a and Supplementary section 'DFT computations').

In contrast to the well-established synthetic protocols for benzene and pentafulvene derivatives, the synthesis of butafulvenes is still a great challenge owing to its intrinsic high strain energy and anti-aromaticity[23–25], which has become a bottleneck for exploring the potentially exciting and promising butafulvene chemistry[26]. Over 60 years ago, Blomquist et al. reported an eight-step synthesis of butafulvene from truxinic acid (Fig. 1b)[27,28]. Later, Huntsman and colleagues demonstrated that 1,5-hexadiynes could be converted to butafulvene via its isomerization to intermediate 1,2,4,5-hexatetraene and the subsequent four-electron cycloaddition, which required very high energy to overcome the barrier because the reaction was conducted at 350 °C in a flow reactor (Fig. 1c)[29–31]. Inspired by the elegant methods developed on transition metal-catalysed cycloadditions or annulations of allenes and allene-derivatives[32–37], we envisioned a viable catalytic approach from readily available proparylic alcohol derivatives and proparylic/allenylic metal coupling to form bisallenes, which would undergo both cyclometallation and reductive elimination under the influence of transition metal catalysis to enable a mild and efficient synthesis of butafulvenes (Fig. 1d). However, such a protocol was proven to be problematic, with Pasto and colleagues observing that, even with the aid of 0.4 equiv. of nickel complex and 4 equiv. of zinc, butafulvene syntheses remain challenging, with very limited success[38,39]. In addition, Ito, Sawamura and Szabó and colleagues showed that the reaction of propargylic alcohol derivatives with B_2Pin_2 stopped at the stage of allenyl boronates, and the formation of bisallenes or butafulvenes was not observed[40–43]. In this Article we have demonstrated an efficient and comprehensive palladium-catalysed protocol for the rapid assembly of symmetric and non-symmetric butafulvene coupling via the reaction of propargylic compounds.

Results and discussion

Palladium-catalysed construction of symmetric butafulvenes. Initially, we conducted the reaction of propargylic carbonate **1a** in the presence of B_2Pin_2 (1.1 equiv.) under palladium catalysis for the purpose of synthesizing 1,2-allenylic boronates by applying monophosphine ligands[40–43]. A serendipitous formation of highly strained butafulvene **2a** (5% yield) was observed with X-Phos as the ligand, together with a β-H elimination enyne product **3a** in 12% yield (Table 1, entry 1). The yield was slightly improved with PPh_3 (entry 2). Bidentate phosphine ligands such as dppp, dppb and dppf were unsuitable (entries 3–5). A unique reactivity for the highly selective formation of butafulvene **2a** (93% yield) was observed with the use of electron-rich monophosphine Gorlos-Phos **L2**•HBF_4 (ref. [44]) developed in our group (entry 7). LB-Phos•HBF_4 (**L1**•HBF_4) and Zheda-phos•HBF_4 (**L3**•HBF_4)[45,46] were completely ineffective for this transformation (entries 6 and 8). Further solvent screening showed that the reactions in *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) or toluene all delivered poorer results than that in dioxane (entries 9–11). An appropriate amount of water[47] was added to increase the solubility of inorganic base in solvent to improve the selectivity of **2a**/**3a** (entries 12–14). Furthermore, tetrahydrofuran (THF) with H_2O (1.0 equiv.) was found to give better results compared to dioxane with H_2O (1.0 equiv.; entry 13 versus entry 12). When the loading of H_2O was increased to 2.0 equiv., butafulvene **2a** was obtained in 92% yield, exclusively (entry 14). Adding more water or reducing the loading of

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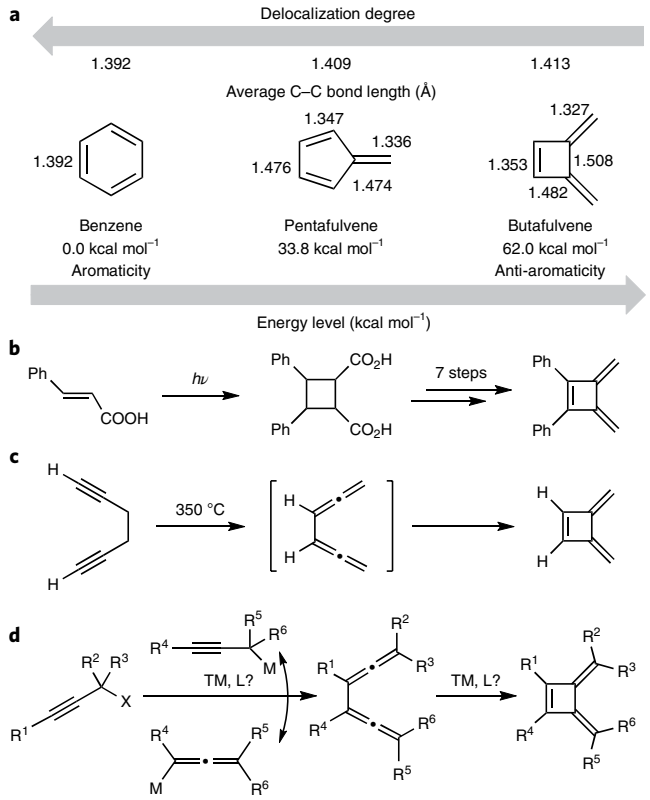


Fig. 1 | Triple-conjugated carbocycles and approaches to strained butafulvenes. a, Triple-conjugated carbocycles with the same formula of C_6H_6 show very different degrees of delocalization, aromaticity and energy storage. **b**, Eight-step synthesis of butafulvene[27,28]. **c**, Four-electron cycloaddition of 1,2,4,5-hexatetraenes at 350 °C (refs. [29–31]). **d**, Proposal: palladium-catalysed reductive coupling/four-electron cycloaddition with propargylic derivatives as the starting materials.

B_2Pin_2 failed to give better results (entries 15–17). From these studies, the optimal conditions have been defined as follows: $Pd(OAc)_2$ (1 mol%), Gorlos-Phos•HBF_4 (4 mol%), B_2Pin_2 (1.1 equiv.), $KHCO_3$ (3.0 equiv.) and H_2O (2.0 equiv.) in THF at 40 °C (entry 14).

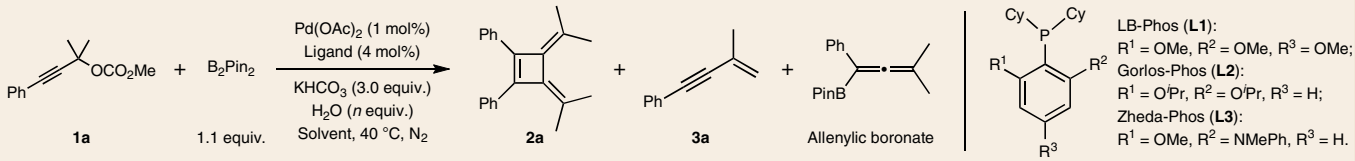
The scope of 3-aryl-substituted propargyl carbonates was first examined on 1 mmol scales; the results are summarized in Table 2 (Conditions A). In addition to the parent phenyl group, the substrates with the aryl groups bearing electron-donating or electron-withdrawing substituents could all be applied, affording the highly strained butafulvenes **2a**–**2f** in 72–85% yields. Synthetically versatile functional groups such as -OMe, -Cl and -CO_2Me could be well tolerated. The 3-thienyl-substituted propargyl carbonate was also compatible, resulting in 80% yield of butafulvene **2g**. In addition to the methyl group, the propargylic substituents may also be tetramethylene (**2h**), pentamethylene (**2i** and **2n**), 4-oxapentamethylene (**2j**), diethyl (**2k**) and dipropyl (**2l**) groups. It is worth mentioning that the reaction could be easily conducted on a gram-scale (**1i**), affording butafulvene **2i** in 75% yield. Several different 3-substituted propargylic carbonates have been tested (**1m**–**1s**). In addition to the butyl and methyl group, allyl and *tert*-butyl(dimethyl)silyl (TBS)-protected hydroxymethyl groups can also be used, affording butafulvenes **2m**–**2p** with 60–69% yields. Interestingly, even the ester functionality could be introduced into the cyclobutene skeleton, affording butafulvene product **2q** in a moderate yield, although a higher catalyst loading was required. It should be noted that the desired products **2r** and **2s** could also be obtained when 3-monosubstituted propargylic carbonates were employed.

However, primary propargyl substrates were not compatible with the current optimal reaction conditions at all. We reasoned that the reactivity of the primary propargylic carbonate toward the in situ-generated Pd(0) is too low, because no product was detected in the reaction of methyl (3-phenylprop-2-yn-1-yl) carbonate with 2-(hepta-1,2-dien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **6i**. After tuning the allenyl precursor[48–55], it is interesting to find that in situ-prepared allenyl-indium reagents could react smoothly with the 3-phenylpropargyl bromide **4a** for the synthesis of terminal butafulvene **5a** in the presence of $Pd(PPh_3)_4$ (Table 2, Conditions B). In addition to propargyl bromide, propargyl iodide and chloride were also suitable coupling partners for this transformation, affording the butafulvene **5a** in 42% and 74% yields, respectively. The reactions of substrates with electron-donating (**4b**–**4e**) and electron-withdrawing substituents (**4f**–**4h**) at the *para* position of the benzene ring all proceeded smoothly to give butafulvene products **5b**–5**h** in 55–87% yields. Substituents at the *meta* position of the phenyl ring of propargyl bromides had no obvious effect on yields (**5i**–**5k**). It is noteworthy that synthetically versatile groups, such as ester, acyl and nitrile, were well tolerated under this protocol, affording butafulvenes **5f**–**5j**. For highly sterically hindered 2,6-disubstituted substrate **4l**, the expected butafulvene product **5l** could also be obtained in 56% yield. It should be noted that **2a** and **5m** could be formed when secondary and tertiary propargyl bromides were employed as substrates, albeit in somewhat lower yields. Substrates with different alkyl or phenylalkyl groups also proceeded smoothly under the standard conditions and delivered products **5n**–5**p** in 42–76% yields. Moreover, propargyl bromides with easily removable benzyloxy groups, either with an electron-donating or electron-withdrawing group, all worked well in this strategy (**5r**–**5w**). Butafulvene **5x** with a phenyl ether was also isolated in 66% yield. In addition, the tethered double bond remained intact, providing the corresponding product **5y** in 56% yield. To highlight the practicability of our protocol, a gram-scale synthesis of **5a** (1.03 g, 89% yield) has been successfully accomplished under the standard conditions.

X-ray crystallographic analyses were performed to unveil the structural details of butafulvenes **2a** and **5h** (Table 2). Taking **5h** as the specific example, the bond length of exocyclic C=C is ~1.32 Å (C8=C9 and C12=C13), which is close to that of ethylene (1.33 Å, 174 kcal mol^{-1}). The bond length of cyclic C=C (C10–C11, 1.38 Å) is close to that of the adjacent phenyl group (1.37–1.39 Å). The bond length of the exocyclic single bond (C5–C10, 1.43 Å) is shorter than endo single bonds (C9–C10, C9–C12, 1.47–1.49 Å). This difference in bond length probably results from the stronger electron delocalization between the cyclic C=C (C10=C11) and adjacent phenyl ring. All these bond lengths are well consistent with the calculated data for unsubstituted butafulvene (Fig. 1a). Unexpectedly, the X-ray crystallographic analysis shows that the phenyl rings are not coplanar with the butafulvene ring (Supplementary section 'X-ray crystal structures for **2a**, **5h**, **18a**, **19a** and **22**'). The dihedral angles between the butafulvene ring plane and phenyl rings are 22.1° and 33.5°, respectively. Owing to the steric hindrance of the methyl groups on butafulvene **2a**, the bond length of the exocyclic C=C (C9–C17, 1.34 Å) and endo single (C9–C8, 1.49 Å; C9–C10, 1.52 Å) bonds are all longer than those of terminal butafulvene **5h** (Table 2).

Mechanistic discussions. With the aim of unveiling the mechanism of the B_2Pin_2-promoted one-pot synthesis of butafulvene (Table 2), some control experiments were performed (Fig. 2a,b). No relevant bisallene intermediate was detected when the reaction time was shortened in the reaction of **1a**. Similarly, no relevant intermediate was found in the reaction of **4a**, even when the reaction was conducted at a lower temperature (Supplementary section 'Mechanistic studies'). Fortunately, it was found that bisallene **7m**

Table 1 | Optimization for the construction of butafulvenes



Entry	Ligand	Solvent	Time (h)	Yield of 2a/3a (%)[a]	Recovery of 1a (%)[a]
1	X-Phos	Dioxane	18	5/12	68
2	PPh_3	Dioxane	18	10/0	46
3	dppp	Dioxane	16	0/0	100
4	dppb	Dioxane	16	0/0	100
5	dppf	Dioxane	16	0/0	80
6	**L1**•HBF_4	Dioxane	18	2/2	82
7	**L2**•HBF_4	Dioxane	16	93/7	0
8	**L3**•HBF_4	Dioxane	18	0/0	100
9	**L2**•HBF_4	DMF	20	0/3	81
10	**L2**•HBF_4	DMSO	20	9/0	71
11	**L2**•HBF_4	Toluene	20	17/16	46
12	**L2**•HBF_4	Dioxane + H_2O (1 equiv.)	16	89/3	0
13	**L2**•HBF_4	THF + H_2O (1 equiv.)	20	95/1	0
14	**L2**•HBF_4	THF + H_2O (2 equiv.)	20	92/0	0
15	**L2**•HBF_4	THF + H_2O (4 equiv.)	20	89/0	0
16[b]	**L2**•HBF_4	THF	20	91/4	0
17[c]	**L2**•HBF_4	THF	20	78/7	15

[a]Determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard; [b]B_2Pin_2 (0.8 equiv.) was used; [c]B_2Pin_2 (0.6 equiv.) was used.

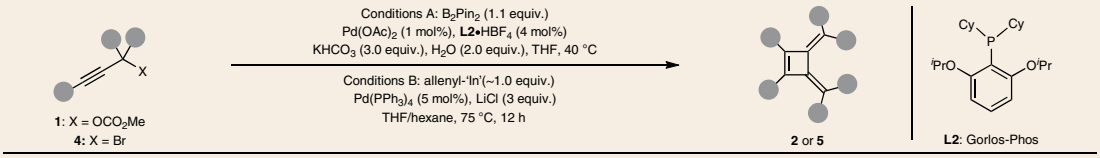
could be isolated in 34% yield when the reaction was stopped after 2 h. Meanwhile, intermediate allenyl borate **6m** and butafulvene **2m** were also observed in the crude reaction mixture (Fig. 2a). To clarify whether bisallene **7m** is the key intermediate of the transformation[39,56–59], bisallene **7m** was subjected to the optimal conditions, and butafulvene **2m** was formed in 99% NMR yield (Fig. 2b, entry 1). Control experiments showed that palladium, $KHCO_3$ and B_2Pin_2 were all crucial for the formation of **2m** (entries 2–5). Butafulvene **2m** was formed in only 2% NMR yield in the absence of B_2Pin_2, although most of bisallene **7m** was consumed (entry 5). Interestingly, the yield of **2m** was positively correlated to the amount of B_2Pin_2, indicating the importance of [B] species in the cyclization process (entries 5–7). Furthermore, to further clarify the role of any [B] species, B_2Pin_2 was replaced with the envisioned by-product, MeOBpin or $B(OMe)_3$, and only 3% or no butafulvene **2m** was formed respectively, indicating that B_2Pin_2 is indispensable (Supplementary section 'Mechanistic studies').

Based on the experimental results above, the mechanism for the synthesis of butafulvenes involving B_2Pin_2 is proposed as shown in Fig. 2c. An initial oxidative addition of Pd(0) catalyst with propargyl carbonate produces allenyl palladium intermediate **A**[60,61], which reacts with B_2Pin_2 to afford allenyl palladium intermediate **B**. After reductive elimination, allenyl boronate **6** was produced and the catalytically active Pd(0) was regenerated[35]. On the other hand, another molecule of allenyl palladium species **A** would couple with allenyl boronate **6** to afford bisallenyl palladium **C**, which would give bisallene **7** after reductive elimination. Subsequently, L_nPd^+Bpin may be generated via the oxidative addition of L_nPd with B_2Pin_2, followed by ligand exchange with $KHCO_3$, as observed in the traditional Suzuki coupling reaction[62]. Insertion of one of the two allene units in bisallene **7** into L_nPd^+–BPin forms **D**, which further undergoes intramolecular carbopalladation to afford cyclobutadiene **E**. Finally, butafulvene **2** is delivered after releasing L_nPd^+–Bpin (Fig. 2c).

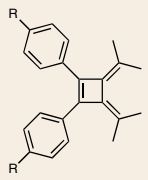
For the indium-involved protocol, bisallene **11** was deliberately prepared from propargylic alcohol **8** through Glaser–Hay coupling/esterification/double S_N2'-type coupling with triethyl aluminium (Fig. 2d). The treatment of bisallene **11** with $Pd(PPh_3)_4$ at 75 °C led to the formation of butafulvene **5q** in 84% yield (Fig. 2e). In addition, no **5q** could be obtained in the absence of palladium catalyst (Fig. 2e). In the meantime, butafulvene **5q** could be obtained in 74% yield when bisallene **11** was treated with B_2Pin_2, $Pd(PPh_3)_4$, **L2**•HBF_4 and $KHCO_3$ (Fig. 2e). These results indicated the essential role of palladium catalyst for the cyclization. Thus, for the indium-mediated process, the oxidative addition of Pd(0) species with propargyl bromide **4** leads to the allenyl Pd(II) intermediate **A′**. Subsequent transmetallation between **A′** and the preformed organoindium reagent **4-In** delivers bisallenyl-Pd(II) species **C′**. Then, the reductive elimination of **C′** affords bisallene intermediate **7′-Pd** complex **F**. Subsequent oxidative cyclometallation of bisallene palladium complex **F** produces a five-membered palladacycle species **G**. A final reductive elimination of species **G** gives the butafulvene product **5** and regenerates the Pd(0) catalyst (Fig. 2f).

Palladium-catalysed construction of non-symmetric butafulvenes. Based on the aforementioned mechanism (Fig. 2c), a route to access non-symmetric butafulvenes **12** has been developed via a cross-coupling reaction between propargyl carbonate **1** and allenylic boronates **6**[40–43] (Fig. 3a). However, the cross-coupling using the allenyl-indium protocol formed an inseparable mixture of symmetric and non-symmetric butafulvenes (Supplementary section 'Synthesis of non-symmetric butafulvenes') due to the reversible exchange of organoindium reagent with propargyl bromide.

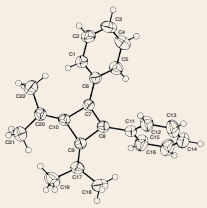
Table 2 | Palladium-catalysed construction of symmetric butafulvenes



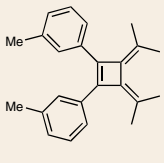
Conditions A



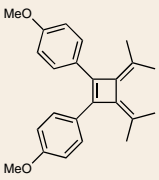
2a (R = H), 85%, 20 h
2b (R = Me), 82%, 20 h



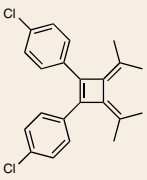
2a (CCDC-1875931)



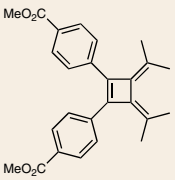
2c, 82%, 20 h



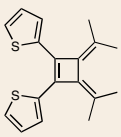
2d, 78%, 17 h



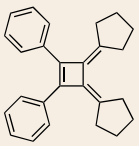
2e, 74%, 20 h[a,b]



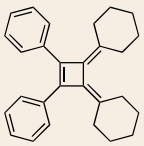
2f, 72%, 20 h



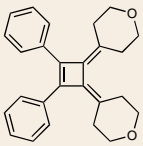
2g, 80%, 20 h



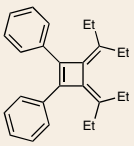
2h, 77%, 20 h



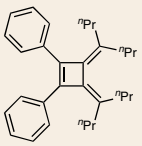
2i, 74%, 17 h
(75%, 19 h)[c]



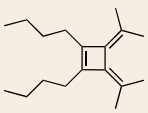
2j, 60%, 46 h[b]



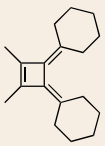
2k, 51%, 16 h[d]



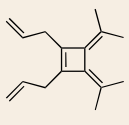
2l, 38%, 18 h[d]



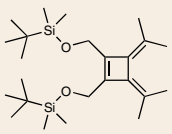
2m, 60%, 12 h[e]



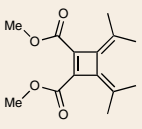
2n, 69%, 12 h[e]



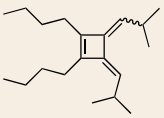
2o, 66%, 10.5 h[e]



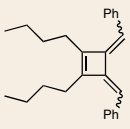
2p, 61%, 12 h[e]



2q, 46%, 20 h[f]

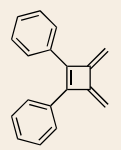


2r, 33%, 12 h[g]
(1.0:0.9)

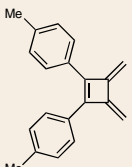


2s, 70%, 16 h[g]
(1:0.4:0.13)

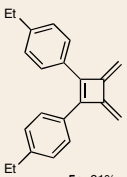
Conditions B



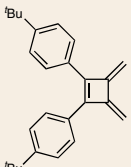
5a, 91%
(1.03 g, 89%)[h]



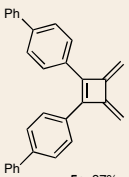
5b, 66%



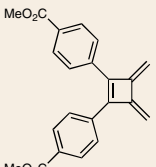
5c, 61%



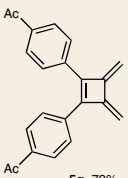
5d, 79%



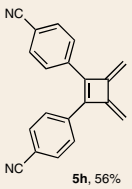
5e, 87%



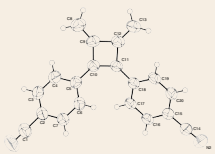
5f, 55%



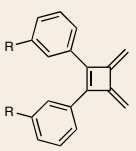
5g, 73%



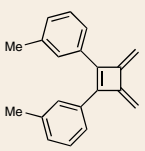
5h, 56%



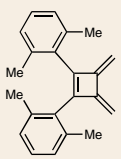
5h (CCDC: 2035320)



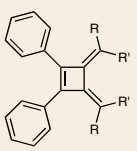
5i (R = CN), 42%
5j (R = CO_2Me), 64%



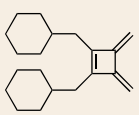
5k, 71%



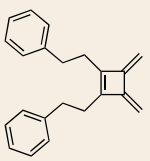
5l, 56%



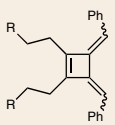
2a (R, R' = Me), 26%
5m (R = Me, R' = H), 19% (0.50:1:0.63)



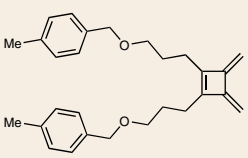
5n, 42%



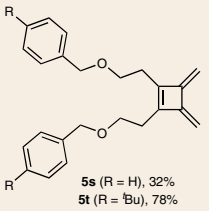
5o, 76%



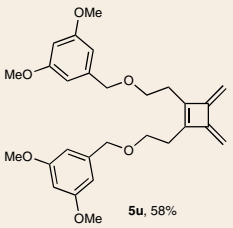
5p (R = Me), 47% (1:0.9:1.2)



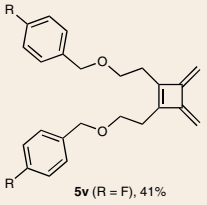
5r, 63%



5s (R = H), 32%
5t (R = ^{t}Bu), 78%



5u, 58%

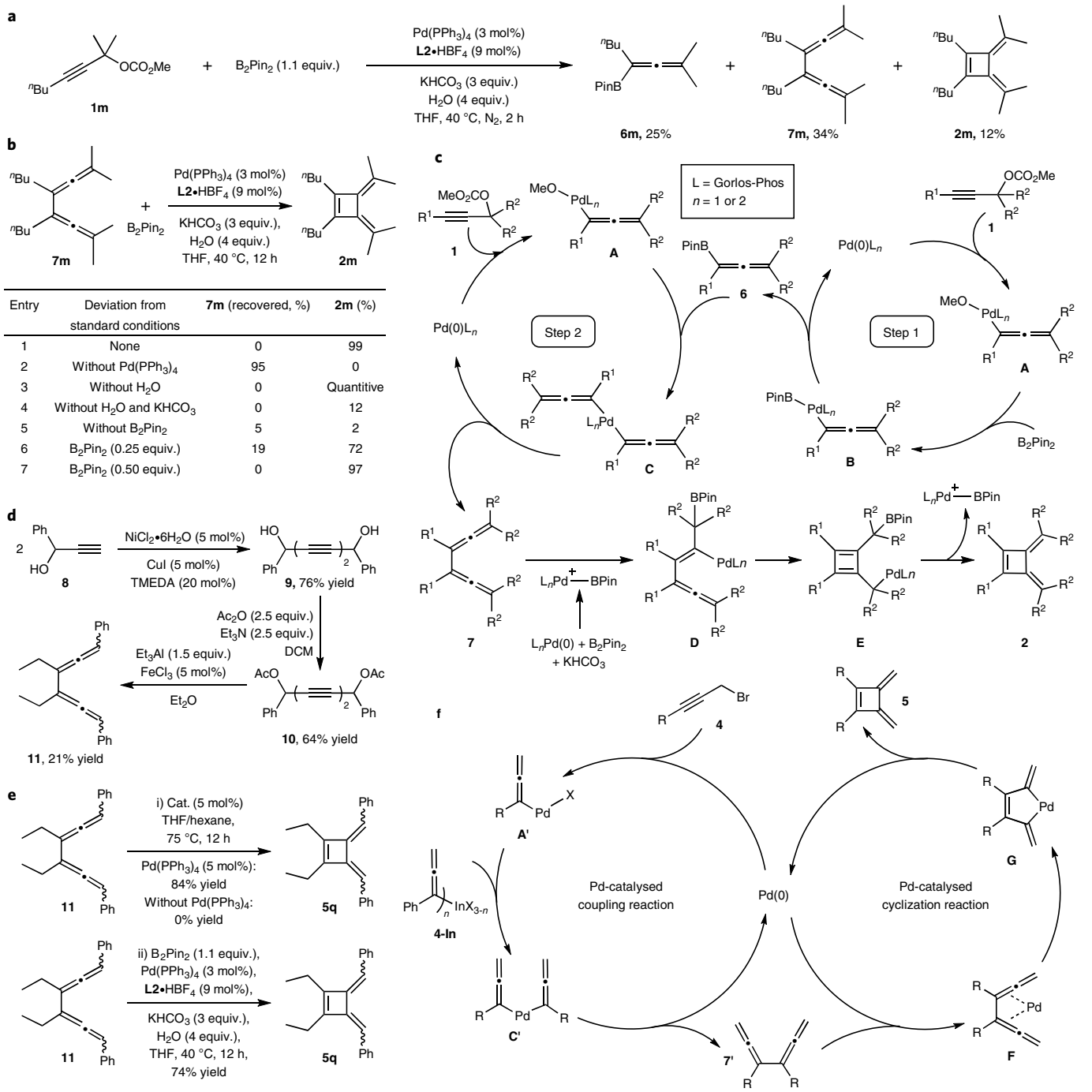


5v (R = F), 41%
5w (R = CF_3), 67%

5x, 66%

5y, 56%

Isolated yields are given. [a]The reaction was conducted on a 0.5 mmol scale. [b]$Pd(OAc)_2$ (2 mol%) and Gorlos-Phos•HBF_4 (6 mol%) were used. [c]The reaction was conducted on 1-g scale. [d]$Pd(PPh_3)_4$ (9 mol%), Gorlos-Phos•HBF_4 (12 mol%) and H_2O (4 equiv.) were used. [e]$Pd(PPh_3)_4$ (3 mol%), Gorlos-Phos•HBF_4 (9 mol%) and H_2O (4 equiv.) were used. [f]$Pd(PPh_3)_4$ (5 mol%), Gorlos-Phos•HBF_4 (15 mol%) and H_2O (4 equiv.) were used. [g]$Pd_2(dba)_3$ (3 mol%), Gorlos-Phos•HBF_4 (9 mol%) and H_2O (4 equiv.) were used. [h]5 mmol scale.



Entry	Deviation from standard conditions	**7m** (recovered, %)	**2m** (%)
1	None	0	99
2	Without $Pd(PPh_3)_4$	95	0
3	Without H_2O	0	Quantitive
4	Without H_2O and $KHCO_3$	0	12
5	Without B_2Pin_2	5	2
6	B_2Pin_2 (0.25 equiv.)	19	72
7	B_2Pin_2 (0.50 equiv.)	0	97

Fig. 2 | Mechanistic studies on reaction intermediates and proposed mechanism for the two developed strategies. a, Intermediate tracing experiments. **b**, Control experiments for the palladium-catalysed cycloisomerization of bisallene **7m**. **c**, Proposed three-step boronate-mediated mechanism. First, allenyl borate **6** was produced via boronation of propargyl carbonate. Then, coupling of allenyl borate **6** with propargyl carbonate **1** could afford bisallene **7**, which was further transformed to the target product via 4e cycloaddition. **d**, Synthesis of bisallene intermediate **11** through Glaser–Hay coupling/esterification/double S_N2'-type coupling with triethyl aluminium. **e**, Experiments for the palladium-catalysed cycloisomerization of bisallene **11**. First, palladium was found to be crucial to the transformation in conditions B of Table 2. Furthermore, bisallene **11** could also be converted to butafulvene **5q** in a decent yield when conditions A of Table 2 were employed. **f**, Proposed mechanism for the indium-involved process. The oxidative addition of Pd(0) species with propargyl bromide **4** leads to the allenyl Pd(II) intermediate **A′**. Subsequent transmetallation between **A′** and the preformed organoindium reagent **4-In** delivers bisallenyl-Pd(II) species **C′**. The target product **5** could be obtained after reductive elimination and cyclometallation.

Interestingly, Heck reaction of **5a** with aryl iodides has been developed to afford the non-symmetric butafulvenes **13a–c** with moderate yields and decent stereoselectivities (*E*/*Z* 10:1, Fig. 3b). Furthermore, it was found that non-symmetric butafulvenes **15** could also be formed from the reaction of tertiary propargylic acetates with propargylic bromides (Fig. 3c). Generally, tertiary 3-aryl-substituted propargyl acetates with different electronic nature for the phenyl substituents (R^1) were found to be compatible with this strategy (**15a–15e**), and other 3-alkyl-substituted propargyls also worked to afford the corresponding products **15g**

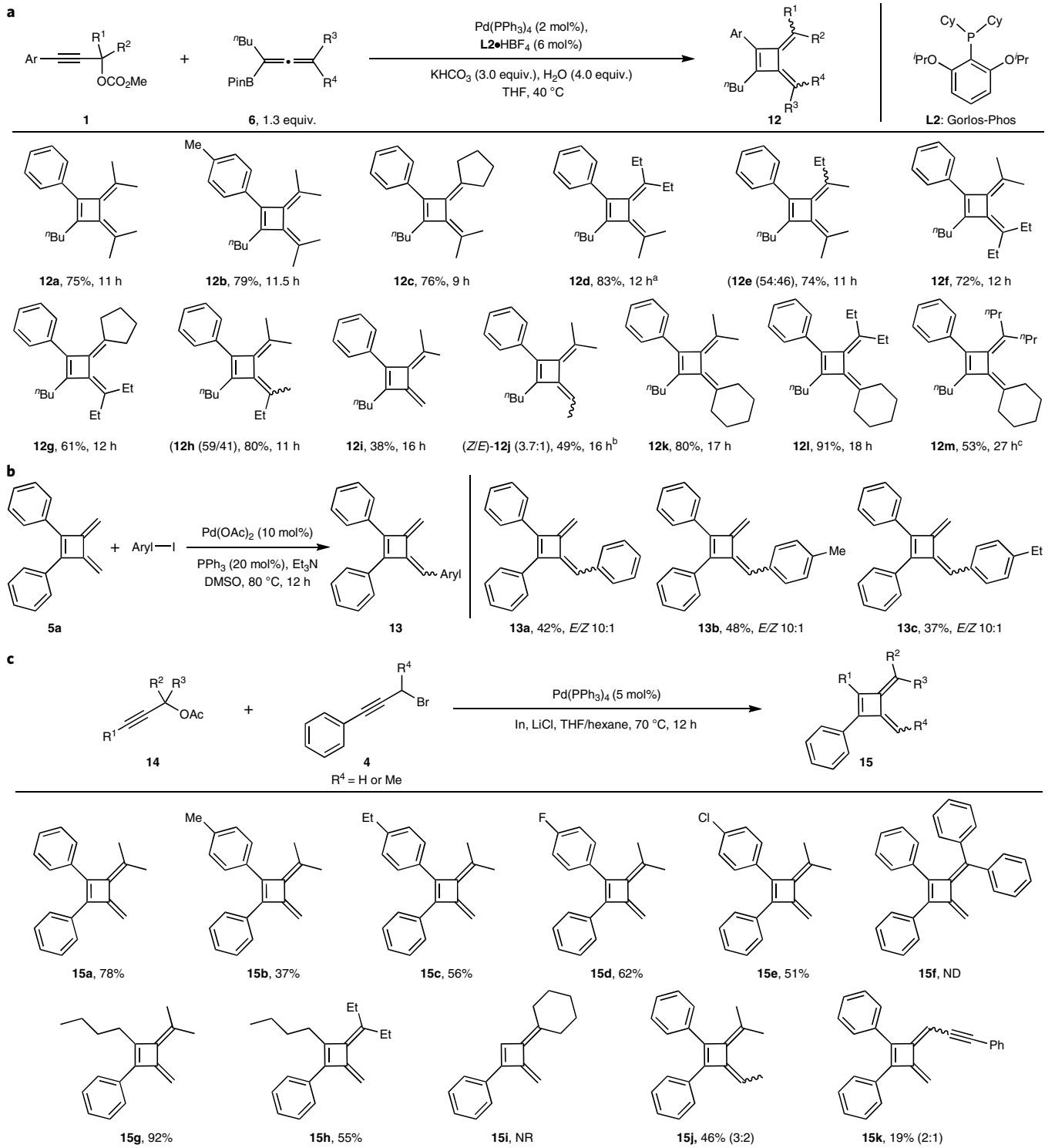


Fig. 3 | Scope of non-symmetric butafulvenes via three different strategies. a, Cross-coupling reaction between propargylic carbonate **1** and allenylic boronate **6**. **b**, Heck reaction of **5a** with aryl iodides. **c**, Reaction of tertiary propargylic acetate **14** with propargylic bromide **4**. Isolated yields are given. [a]$Pd(PPh_3)_4$ (3 mol%) and Gorlos-Phos•HBF_4 (9 mol%) were used. [b]$Pd(PPh_3)_4$ (9 mol%) and Gorlos-Phos•HBF_4 (12 mol%) were used. [c]$Pd_2(dba)_3$ (3 mol%) and Gorlos-Phos•HBF_4 (9 mol%) were used.

and **15h**. However, triphenyl-substituted or terminal propargylic acetate propargyl acetate did not give the target products **15f** or **15i**. It should be noted that the reaction of secondary propargylic bromide **4j** and secondary propargylic acetate **14k** afforded the corresponding products **15j** and **15k**, respectively.

Synthetic transformations of butafulvenes. The synthetic transformations of butafulvenes have also been studied (Fig. 4). Interestingly, the [2 + 2] cycloaddition of butafulvene **5a** with a benzyne intermediate afforded highly strained spirocycle **16** with two four-membered rings, leaving extra terminal C=C bonds for

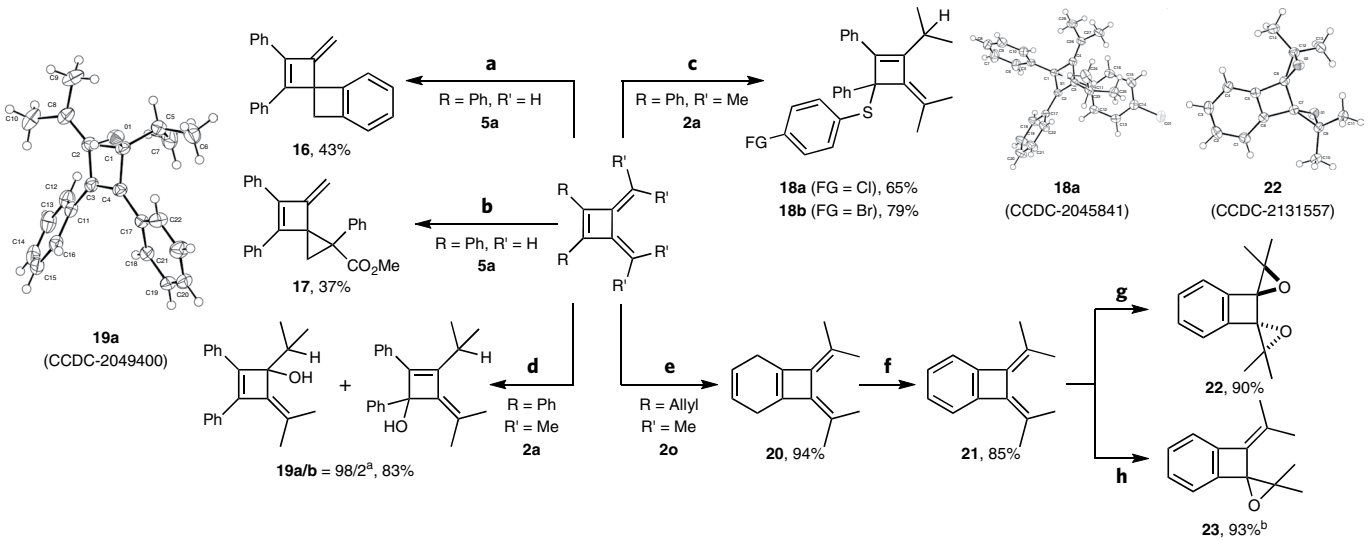


Fig. 4 | Synthetic transformations of butafulvenes. a, The [2 + 2] cycloaddition of butafulvene **5a** with benzyne**: 5a** (0.10 mmol), benzyne precursor (0.30 mmol), CsF (0.30 mmol), toluene/CH_3CN 1:1, 100 °C, 3 h. **b**, Cyclopropanation of butafulvene: **5a** (0.10 mmol), $Rh_2(OAc)_4$ (2.5 mol%), methyl 2-diazo-2-phenylacetate (1.2 equiv.), dichloromethane (DCM), r.t., 2 h. **c**, Visible-light-induced thiol-ene reaction: **2a** (0.30 mmol), [Ir(dFCF$_3$ppy)$_2$dtbbpy (PF_6)] (0.3 mol%), 4-chloro or 4-bromo-benzenethiol (1.1 equiv.), MeCN, 10-W light-emitting diode, 440 nm, 10 h, r.t. **d**, Hydrohydroxylation of **2a: 2a** (0.40 mmol), aqueous HBr (48 wt%, 4.0 equiv.), *n*-hexane/HOAc (2/1), 5 °C, 2 h. **e**, Ring-closing metathesis of **2o**: **2o** (0.30 mmol), Grubbs II cat. (7 mol%), DCM, 27 °C, 5 h. **f**, Oxidative aromatization of **20**: **20** (0.16 mmol), 1,2-dichloro-4,5-dicyanobenzoquinone (DDQ, 1.2 equiv.), DCM, r.t., 12 h. **g**, Double-epoxidation of **21**: **21** (0.2 mmol), *m*-CPBA (3 equiv.), DCM, 0 °C, 10 min. **h**, Mono-epoxidation of **21**: **21** (2 equiv.), *m*-CPBA (0.1 mmol), DCM, 0 °C, 10 min. [a]Determined by ^{1}H NMR analysis of the crude product using mesitylene (0.1 mmol) as the internal standard. [b]Containing ~1.5% **22**.

further synthetic manipulation. The cyclopropanation of butafulvene **5a** with methyl 2-diazo-2-phenylacetate could proceed successfully to afford a more stained bicyclic product **17**. In addition, a visible-light-induced reaction between the diene unit in **2a** with 4-chloro or 4-bromo-benzenethiol exclusively afforded the 1,4-adducts[63] **18a** and **18b** in decent yields, with the structure of **18a** confirmed by X-ray diffraction analysis. Furthermore, we found that one of the two exo-C=C bonds in **2a** could be hydrohydroxylated in aqueous HBr with a remarkable regioselectivity to form cyclobut-2-enol **19a** with the conjugate addition product **19b** as the very minor product. When the R group was an allyl unit, ring-closing metathesis of **2o** could provide [4.2.0]-bicyclic product **20** in 94% yield, which may further undergo aromatization to afford benzocyclobutane **21**. Interestingly, epoxidation of **21** could provide highly strained benzocyclobutadispiro-oxirane **22** and benzocyclobutamonospiro-oxirane **23** in the presence of different amounts of *m*-CPBA (chloroperoxybenzoic acid), respectively.

Conclusion

In summary, we have developed a practical and comprehensive palladium-catalysed construction of highly strained symmetric or non-symmetric anti-aromatic butafulvenes, using readily available propargylic carbonates or bromides as the starting materials. The salient advantages of the developed methods include mild reaction conditions, wide functional group tolerance, easy scalability and two simple catalytic systems. This contribution will foster the development of butafulvene chemistry. Further studies on expanding the scope and application of butafulvene products are now in progress in our laboratory.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-022-01017-9.

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Methods

Commercially available reagents were used without further purification. Solvents were treated before use according to standard methods. Unless otherwise stated, all reactions were conducted under an inert atmosphere using standard Schlenk techniques or in a nitrogen-filled glovebox. ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and ^{19}F NMR spectra were recorded at room temperature (r.t.) in $CDCl_3$ or C_6D_6 on a 300-MHz, 400-MHz, 600-MHz or 700-MHz instrument with tetramethylsilane (TMS; 1H, $\delta = 0$), residual $CHCl_3$ (7.26 ppm) or $CFCl_3$ (^{19}F, $\delta = 0$) as internal standards. Flash column chromatography was performed on silica gel. All reactions were monitored by thin-layer chromatography or NMR analysis. High-resolution mass spectrometry was performed with a Finnigan MAT 8430 system, Bruker APEXIII instrument, Micromass HPLC-Q-TOF mass spectrometer (electrospray ionization) or Agilent 6540 Accurate-MS spectrometer (quadrupole time-of-flight). Elemental analyses were carried out with a Carlo–Erba EA1110 elementary analysis instrument. X-ray crystal structures were determined with a Bruker D8 Venture diffractometer.

General procedure for the synthesis of butafulvene, Table 2, conditions A. To a flame-dried Schlenk tube (dried under vacuum with a heating gun) were added $Pd(OAc)_2$ (2.4 mg, 0.01 mmol), Gorlos-Phos•HBF_4 (19.3 mg, 0.04 mmol), $KHCO_3$ (297.9 mg, 3.0 mmol), B_2Pin_2 (279.9 mg, 1.1 mmol), **1a** (221.6 mg, 1.0 mmol)/THF (4.0 ml) and H_2O (36.0 µl, $d = 1.0$ g ml^{-1}, 36.0 mg, 2.0 mmol) sequentially under a N_2 atmosphere. The tube was then heated to 40 °C in a preheated oil bath. After 20.0 h, the reaction was complete, as monitored by thin-layer chromatography. On completion of the reaction, the reaction mixture was diluted with ethyl ether, filtered through a short column of silica gel, concentrated and purified by flash silica gel column chromatography using petroleum ether/ethyl acetate as eluent to afford the pure products.

General procedure for the synthesis of butafulvene, Table 2, conditions B. Propargyl bromides (0.3 mmol), indium (23.0 mg, 0.2 mmol), LiCl (25.4 mg, 0.6 mmol) and THF (2 ml) were added to a flask equipped with a septum and stirred with a magnetic stir bar at r.t. in a glovebox for 10 min. To the residue were added propargyl bromides (0.2 mmol), $Pd(PPh_3)_4$ (11.6 mg, 5 mol%) and hexane (1 ml), then the reaction mixture was stirred at 75 °C for 12 h. After rotary evaporation, the reaction mixture was directly purified by flash silica gel column chromatography using petroleum ether/ethyl acetate as eluent to afford the pure products.

Because of their highly strained ring, butafulvenes, especially non-aryl-substituted ones, are generally not sufficiently stable at r.t. It is better to adopt a low-temperature chromatography technique to isolate these products, and also to keep the products in a fridge. It should be noted that the palladium source played a key effect on the yield of **2** (Table 2a). Freshly made $Pd(PPh_3)_4$ could provide better results.

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC1875931 (**2a**), 2035320 (**5h**), 2045841 (**18a**), 2049400 (**19a**) and 2131557 (**22**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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Author contributions

S.M. and Q.-A.C. conceived and supervised the project. S.M., Q.-A.C., J.Z., X.H. and B.-Z.C. designed the experiments. X.H., B.-Z.C., P.L., D.-W.J., J.L., H.Z., S.-N.Y., Y.-C.H., B.W., X.-P.H., C.F., Y.H. and J.Z. performed the experiments and analysed the data. All authors discussed the results and commented on the article.

Competing interests

The authors declare no competing interests.

Additional information

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