Green Chemistry

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c9gc04184b

Thermal [2 + 2]-cycloaddition between silylalkynes and allenylphenols followed by the nucleophilic addition of water: metal-free and economical synthesis of arylcyclobutenals†

Shohei Ohno,‡ Ramon Francisco Avena,‡ Hiroshi Aoyama, Hiromichi Fujioka and Mitsuhiro Arisawa *

Received 7th December 2019,
Accepted 9th January 2020

DOI: 10.1039/c9gc04184b

rsc.li/greenchem

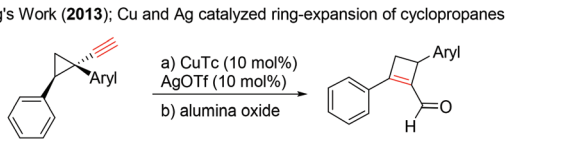
Herein, we report an unprecedented thermal [2 + 2]-cycloaddition between silylalkynes and allenylphenols to form an aromatizing cyclobutachromene intermediate, followed by the nucleophilic addition of water to yield functionalized arylcyclobutenals. This reaction is atom- and pot-economical because all the atoms contained in the starting material are retained in the final product, no other reactants are required, and it proceeds in one-pot.

Introduction

Exploring economical strategies to synthesize the target molecules is one of the most important efforts in both academia and industry, as it can minimize environmental impacts.[1] In this context, chemical transformations with aspects of both atom- and pot-economies are extremely attractive. This is because these strategies maximize the conversion of the starting materials into the target molecules, thereby minimizing the use of reactants and solvents, as well as reducing the generation of chemical wastes.[2] On the other hand, fine chemicals and pharmaceuticals frequently face difficulties in removing heavy-metal catalysts from the final products.[3] Therefore, the combination of metal-free transformations with the atom- and pot-economical concept is generally considered to be green and sustainable,[4] although it still faces considerable challenges.

Meanwhile, four-membered rings are important structural elements of biologically-active compounds,[5] and also serve as versatile synthetic intermediates due to strain-driven chemical reactivities.[6] Among them, arylcyclobutenal may serve as a key intermediate for the synthesis of natural products having a tetra-substituted cyclobutane structure.[7] However, the synthesis method has only one example and requires two toxic metal catalysts: silver and copper (Scheme 1).[8] On the other hand, intramolecular alkyne–allene [2 + 2] cycloadditions leading to bi- or tri-cyclic cyclobutenes have been extensively explored under thermal or transition-metal catalysed conditions (Scheme 2A);[9] however, to the best of our knowledge, there was no example in which this reaction was applied other than the synthesis of bi- or tri-cyclic cyclobutenes until 2017. In 2018, Jiang reported [2 + 2] cycloaddition between alkynes and allenone-esters followed by addition reaction for the synthesis of polycyclic aromatic hydrocarbons, such as nucleophilic addition of water to intermediate **I** (Scheme 2B); however, they did not report unfused monocyclic cyclobutene synthesis.[10]

Based on this research background, we report an unprecedented thermal [2 + 2] cycloaddition between silylalkynes and allenylphenols to form intermediate **II**, followed by the nucleophilic addition of water to yield functionalized arylcyclobutenals **2** (Scheme 2C). When comparing intermediate **I** and intermediate **II**, it becomes clear that intermediate **I** was formed by acid-promoted activation of 2,4-pentadiene-1-one in the system, and that intermediate **II** was formed by aromatization-promoted activation of the cyclobutachromene skeleton. This reaction proceeds only by thermal activation energy, no other reactants are required, and all atoms contained in the starting material **1** were retained in the final product **2**.

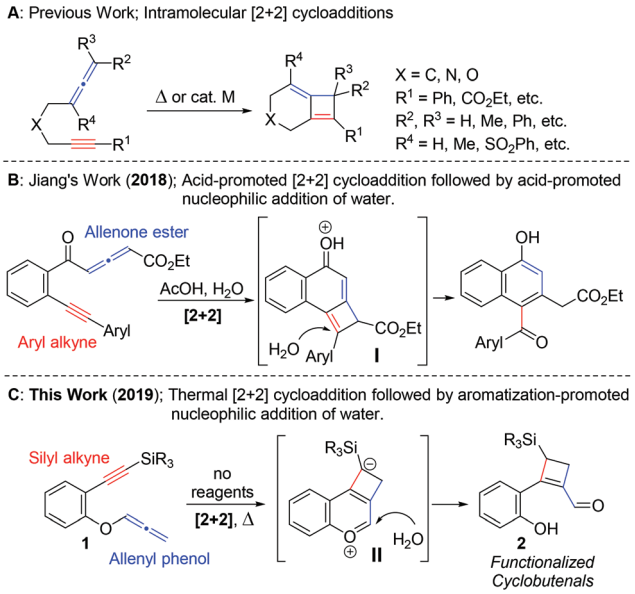


Scheme 1 Previously reported synthesis of arylcyclobutenals.

Graduate School of Pharmaceutical Sciences, Osaka University, Yamada-oka 1-6, Suita, Osaka, 565-0871, Japan. E-mail: arisaw@phs.osaka-u.ac.jp

†Electronic supplementary information (ESI) available. CCDC 1958998. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9gc04184b

‡These authors contributed equally to this work.

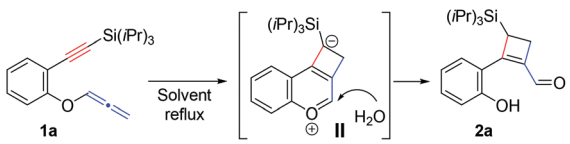


Scheme 2 [2 + 2] Cycloadditions between alkynes and allenes.

Results and discussion

We prepared substrate **1a** and subjected it to several reaction conditions (Table 1). As a result, when refluxing the toluene solution of **1a** for 2 hours, the desired cyclobutene **2a** was obtained in 92% yield (entry 1) and the structure of **2a** was determined by X-ray structure elucidation (Fig. 1).[11] Additionally, using benzene as a solvent, compound **2a** was obtained in a yield of 78%. However, when *para*-xylene with a higher boiling point than toluene was used, a longer reaction time was required, and the yield was decreased (entry 3). When using methanol or ethanol as a solvent, it gave 59% or 63% after 24 hours (entries 4 and 5). In addition, when DMF was used, the yield was reduced due to strong conditions, and many by-products were produced (entry 6). It should also be noted that in the case of acetonitrile or dioxane (entries 7 and 8), we were able to detect the presence of the intermediate

Table 1 Optimization of the reaction conditions



Entry	Solvent	Time (h)	Yield (%)
1	Toluene	2	92
2	Benzene	24	78
3	*p*-Xylene	24	49
4	MeOH	24	59
5	EtOH	24	63
6	DMF	3	33
7	CH_3CN	12	89
8	Dioxane	3	87

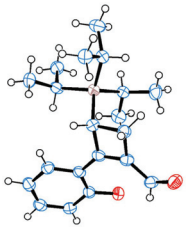
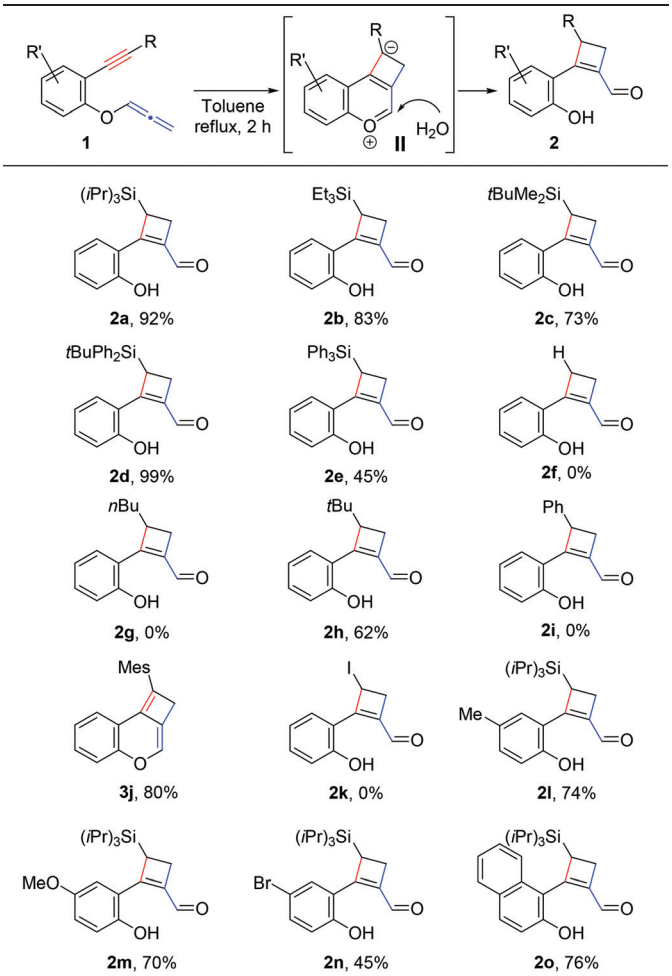


Fig. 1 X-ray structure of **2a**.

based on TLC. However, after purification on silica gel, we noticed that intermediate **II** was subjected to subsequent nucleophilic addition of water. From these data, we concluded that intermediate **II** is water-sensitive, and effects of the solvent are vital to the success of the reaction.

Using the optimum reaction conditions (Table 1, entry 1), we next examined the substrate scope and limitations of this reaction and summarized them in Table 2. Having a silyl group on the alkyne, $SiEt_3$, $SiMe_2tBu$, $SiPh_2tBu$, and $SiPh_3$ derivatives **1b–1e** gave the corresponding cyclobutenes **2b–2e**

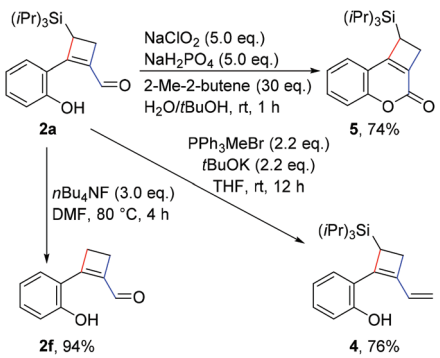
Table 2 Substrate scope and limitations



in 83%, 73%, 99%, and 45% yields, respectively. Also, derivatives with H or alkyl groups on the alkyne, *i.e.*, H derivative **1f**, *n*-butyl derivative **1g**, and *tert*-butyl derivative **1h**, were examined. As a result, **1h** was converted well to **2h** in 62% yield, but **1f** and **1g** were decomposed. Interestingly, in the case of derivative **1j** having a mesityl group on the alkyne, nucleophilic addition of water did not occur after [2 + 2] cycloaddition, and a stable intermediate **3j** was observed. In addition, the reaction did not proceed with substrate **1k** having an iodine on the alkyne. Finally, when the reaction was examined with substrates **1m–1o** having a substituent on the aromatic ring, the yield was slightly reduced for substrate **1n** having a bromo group, but the others were converted to products with good yield. Based on the above results, we thought that the bulkiness and the electron donating properties of the substituents on the alkyne played an important role in the efficient nucleophilic addition of water after [2 + 2] cycloaddition.

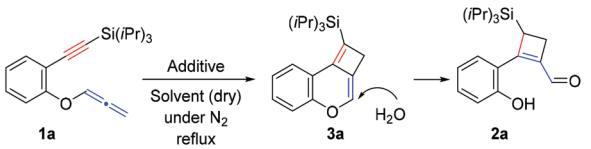
Chemical transformations of **2a** were also possible (Scheme 3). For example, *n*-Bu_4NF was added to **2a** in DMF solution and stirred at 80 °C, and disubstituted cyclobutene **2f** was obtained in 94% yield. Additionally, when the carbonyl of **2a** was subjected to the Wittig reaction, vinyl cyclobutene **4** was obtained in 76% yield. Furthermore, the aldehyde on the cyclobutene of **2a** was oxidized to carboxylic acid by Pinnick oxidation, and intramolecular cyclization occurred subsequently wherein coumarin derivative **5** was obtained in 74% yield. These results have shown that **2a**, efficiently prepared by our reaction, may serve as a good synthetic intermediate.

In order to investigate the solvent effect and intermediate of this reaction, the reaction was examined using dry solvents under a nitrogen atmosphere (Table 3). As a result, almost no product **2a** was obtained in each dry solvent, but instead cyclobutachromene intermediate **3a** was obtained (entries 1–7). Among them, intermediate **3a** was obtained in good yield in benzene, methanol, ethanol, acetonitrile and dioxane (entries 3–7), but the yield of intermediate **3a** was low in toluene and xylene (entries 1 and 2). These results show that intermediate **3a** is stable in benzene, methanol, ethanol, acetonitrile, and dioxane and unstable in toluene and xylene. Therefore, in hydrous toluene solution, an equivalent amount of water was efficiently added to the unstable intermediate **3a** to give



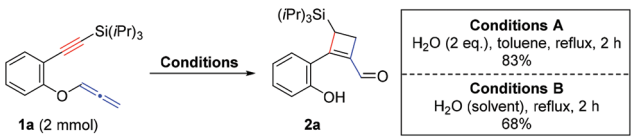
Scheme 3 Chemical transformations.

Table 3 Reactions in dry solvent



Entry	Solvent	Time (h)	Additive	Yield [**3a**, **2a**][a] (%)
1	Toluene	2	None	[15%, 5%]
2	*p*-Xylene	24	None	[9%, 3%]
3	Benzene	24	None	[69%, 3%]
4	MeOH	24	None	[65%, 0%]
5	EtOH	24	None	[73%, 7%]
6	CH_3CN	12	None	[68%, 9%]
7	1,4-Dioxane	12	None	[62%, 4%]
8	Toluene	2	H_2O (1 eq.)	[0%, 92%]
9	Toluene	2	H_2O (2 eq.)	[0%, 92%]

[a] Yields were determined by NMR using 1,3,5-trimethoxy-benzene as an internal standard.

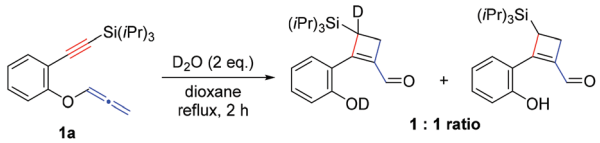


Scheme 4 Scale-up experiment (2 mmol).

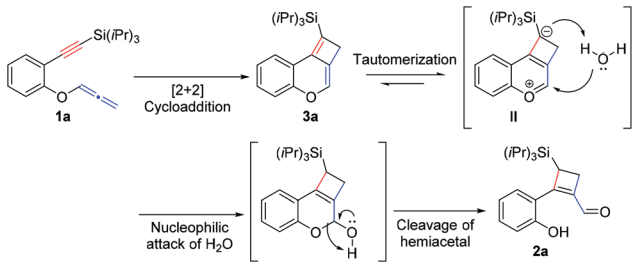
product **2a** in high yield (entries 8 and 9). From these results, it was found that this reaction was caused by the formation of **3a** by thermal [2 + 2] cycloaddition and subsequent nucleophilic addition of water.

In addition, the possibility of using this reaction in a large-scale synthesis was examined by using 2 mmol of **1a** which smoothly resulted in the production of **2a** in 83% yield (Scheme 4, conditions A). Furthermore, this reaction can be performed on a large scale even when water is used as a solvent, and product **2a** was obtained in a yield of 68% (Scheme 4, conditions B).

Finally, in order to validate the mechanism of this reaction, we performed D_2O labeling experiments (Scheme 5). As a result, a mixture of deuterium-labeled and non-labeled products was obtained in a 1 : 1 ratio. This supports the proposed mechanism of this reaction as shown in Scheme 6 wherein **3a** tautomerizes into intermediate **II** which then undergoes nucleophilic addition of H_2O followed by cleavage of the resulting hemiacetal to obtain product **2a**.



Scheme 5 D_2O labeling experiment.



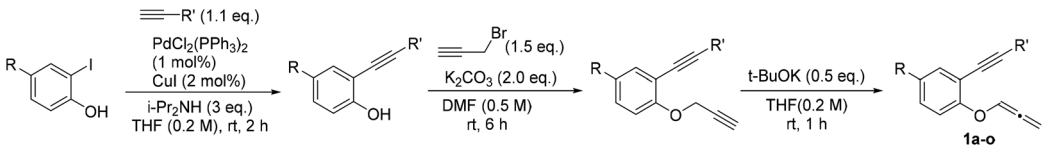
Scheme 6 Proposed mechanism.

Conclusion

This reaction is the first intramolecular [2 + 2] thermal cycloaddition between functionalized allenylphenols and silylalkynes which can further undergo nucleophilic addition of water. This reaction is atom- and pot-economical because all atoms contained in starting material **1** were retained in the final product **2**. Additionally, it is a one-pot reaction that doesn't require other reactants so there is no need for several extensive purification processes. Furthermore, chemical transformations of product **2a** afforded other useful compounds, such as vinyl cyclobutene **4** and coumarin derivative **5**.

Experimental section

General procedure A for the synthesis of compounds 1a–d and 1f–o



A.1: To a round-bottom flask containing 2-iodophenol (1.0 equiv.), mono-substituted acetylene (1.15 equiv.), and diisopropylamine (3.0 equiv.) in THF (0.2 M) were added copper(I) iodide (2 mol%) and bis(triphenylphosphine) palladium(II) dichloride (1 mol%). The mixture was stirred under nitrogen at ambient temperature for 2 h. The mixture was quenched with saturated NH_4Cl solution and the organic compounds were then extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was then subjected to short column chromatography (neutral silica gel, hexane/AcOEt = 20 : 1).

A.2: To a stirred solution of the obtained 2-substituted-ethynylphenol in DMF (0.5 M) were added propargyl bromide (1.5 equiv.) and K_2CO_3 (2.0 equiv.). The mixture was stirred under nitrogen at ambient temperature for 6 h. The mixture was quenched with water and the organic compounds were then extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was then subjected to short column chromatography (neutral silica gel, hexane/AcOEt = 50 : 1).

A.3: To a stirred solution of the obtained *O*-propargyl-2-(substituted-ethynyl)phenol in THF (0.2 M) was added *t*-BuOK (0.5 equiv.). The mixture was stirred under nitrogen at ambient temperature for 1 h. The mixture was quenched with water and the organic compounds were then extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was then subjected to column chromatography (neutral flash silica gel, hexane/AcOEt = 150 : 1) to give compounds **1a–d** and **1f–o**.

***O*-Allenyl-2-[(triisopropylsilyl)ethynyl]phenol 1a.** Following general procedures A.1–3, 2-iodophenol (550 mg, 2.50 mmol) was converted to **1a** (586 mg, 3 steps, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, d, J = 7.8 Hz), 7.28–7.24 (1H, m), 7.07 (1H, d, J = 8.3 Hz), 7.00 (1H, dd, J = 7.6 Hz, 7.6 Hz), 6.91 (1H, t, J = 6.0 Hz), 5.40 (2H, d, J = 6.0 Hz), 1.13 (21H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.22, 157.72, 133.65, 129.21, 122.70, 119.04, 116.92, 114.97, 102.04, 95.71, 89.84, 18.47, 11.51; HRMS (MALDI) calcd for $C_{20}H_{29}OSi$ $(M + H)^+$: 313.1982, found: 313.1974.

***O*-Allenyl-2-[(triethylsilyl)ethynyl]phenol 1b.** Following general procedures A.1–3, 2-iodophenol (550 mg, 2.50 mmol) was converted to **1b** (122 mg, 3 steps, 18%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, d, J = 7.3 Hz), 7.29–7.25 (1H, m), 7.07 (1H, d, J = 8.3 Hz), 7.00 (1H, dd, J = 7.3 Hz, 7.3 Hz), 6.89 (1H, t, J = 6.0 Hz), 5.42 (2H, d, J = 6.0 Hz), 1.05 (9H, t, J = 7.8 Hz), 0.68 (6H, q, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.96, 158.34, 134.41, 129.97, 123.25, 119.33, 117.23, 115.16, 102.07, 97.39, 90.43, 7.96, 4.90; HRMS (MALDI) calcd for $C_{17}H_{23}OSi$ $(M + H)^+$: 271.1513, found: 271.1508.

***O*-Allenyl-2-[(*tert*-butyldimethylsilyl)ethynyl]phenol 1c.** Following general procedures A.1-3, 2-iodophenol (550 mg, 2.50 mmol) was converted to **1c** (360 mg, 3 steps, 53%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (1H, dd, J = 7.6, 1.6 Hz), 7.29–7.25 (1H, m), 7.07 (1H, d, J = 7.8 Hz), 7.00 (1H, dd, J = 7.8 Hz, 7.8 Hz), 6.88 (1H, t, J = 6.0 Hz), 5.42 (2H, d, J = 6.0 Hz), 1.00 (9H, s), 0.18 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.49, 157.88, 133.86, 129.55, 122.79, 118.87, 116.76, 114.62, 100.97, 97.77, 89.99, 26.10, 16.81, −4.64; HRMS (MALDI) calcd for $C_{17}H_{23}OSi$ $(M + H)^+$: 271.1513, found: 271.1502.

***O*-Allenyl-2-[(*tert*-butyldiphenylsilyl)ethynyl]phenol 1d.** Following general procedures A.1–3, 2-iodophenol (550 mg, 2.50 mmol) was converted to **1d** (710 mg, 3 steps, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.88 (4H, m), 7.56 (1H, d, J = 7.3 Hz), 7.40–7.31 (7H, m), 7.12 (1H, d, J = 8.2 Hz), 7.05 (1H, t, J = 7.6 Hz), 6.95 (1H, td, J = 6.0, 0.9 Hz), 5.43 (2H, d, J = 6.0 Hz), 1.14 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.43, 158.28, 135.67, 133.76, 133.35, 129.97, 129.42, 127.67, 122.80, 118.82, 116.63, 114.42, 104.56, 94.48, 90.08, 27.08, 18.77; HRMS (MALDI) calcd for $C_{27}H_{26}OSiNa$ $(M + Na)^+$: 417.1645, found: 417.1641.

***O*-Allenyl-2-ethynylphenol 1f.** Following general procedures A.1–2, 2-iodophenol (550 mg, 2.50 mmol) was converted to

O-propargyl-2-((trimethylsilyl)-ethynyl)phenol using trimethylsilylacetylene. Next, following general procedure A.3, the obtained crude compound was converted to **1f** (160 mg, 3 steps, 41%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (1H, dd, J = 9.5, 2.0 Hz), 7.34–7.29 (1H, m), 7.11 (1H, dd, J = 10.3, 1.2 Hz), 7.02 (1H, ddd, J = 9.5 Hz, 1.2 Hz, 1.2 Hz), 6.86 (1H, t, J = 7.4 Hz), 5.46 (2H, d, J = 7.4 Hz), 3.31 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.13, 158.58, 134.62, 130.45, 123.12, 118.40, 116.34, 113.31, 90.58, 82.20, 79.74; HRMS (MALDI) calcd for $C_{11}H_9O$ $(M + H)^+$: 157.0648, found: 157.0645.

***O*-Allenyl-2-(*tert*-butylethynyl)phenol 1h.** Following general procedures A.1–3, 2-iodophenol (550 mg, 2.50 mmol) was converted to **1h** (277 mg, 3 steps, 53%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, dd, J = 7.5, 1.6 Hz), 7.24–7.19 (1H, m), 7.05 (1H, d, J = 7.8 Hz), 6.98 (1H, dd, J = 7.5 Hz, 7.5 Hz), 6.88 (1H, t, J = 6.0 Hz), 5.42 (2H, d, J = 6.0 Hz), 1.32 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.65, 157.42, 133.64, 128.64, 123.06, 119.34, 117.23, 115.59, 103.66, 90.04, 74.61, 31.10, 28.34; HRMS (MALDI) calcd for $C_{15}H_{17}O$ $(M + H)^+$: 213.1274, found: 213.1270.

***O*-Allenyl-2-(phenylethynyl)phenol 1i.** Following general procedures A.1–2 and a modified procedure A.3 wherein the reaction was performed at 0 °C, 2-iodophenol (550 mg, 2.50 mmol) was converted to **1i** (294 mg, 3 steps, 51%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.51 (3H, m), 7.36–7.28 (4H, m), 7.13 (1H, dd, J = 8.7, 0.9 Hz), 7.05 (1H, ddd, J = 7.6 Hz, 1.4 Hz, 1.4 Hz), 6.91 (1H, t, J = 6.0 Hz), 5.46 (2H, d, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.80, 157.55, 133.69, 131.80, 129.57, 128.75, 128.40, 125.56, 123.01, 118.69, 116.63, 114.53, 94.11, 90.20, 85.20; HRMS (MALDI) calcd for $C_{17}H_{13}O$ $(M + H)^+$: 233.0961, found: 233.0963.

***O*-Allenyl-2-(mesitylethynyl)phenol 1j.** Following general procedures A.1–2 and a modified procedure A.3 wherein the reaction was performed at 0 °C instead of room temperature, 2-iodophenol (550 mg, 2.50 mmol) was converted to **1j** (466 mg, 3 steps, 68%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, dd, J = 7.8, 1.4 Hz), 7.28 (1H, td, J = 7.8, 1.4 Hz), 7.12 (1H, d, J = 8.2 Hz), 7.06 (1H, dd, J = 7.8, 7.8 Hz), 6.94 (1H, t, J = 5.8 Hz), 6.88 (2H, dd, J = 0.5, 0.5 Hz), 5.43 (2H, d, J = 6.0 Hz), 2.49 (6H, s), 2.29 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.51, 157.08, 140.25, 137.74, 132.98, 128.95, 127.51, 122.90, 120.15, 118.88, 116.64, 115.41, 92.55, 92.17, 89.97, 21.34, 20.94; HRMS (MALDI) calcd for $C_{20}H_{18}O$ M^+: 274.1352, found: 274.1355.

***O*-Allenyl-4-methyl-2-[(triisopropylsilyl)ethynyl]phenol 1l.** Following general procedures A.1–3, 2-iodo-4-methylphenol (585 mg, 2.50 mmol) was converted to **1l** (530 mg, 3 steps, 65%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (1H, d, J = 2.3 Hz), 7.04 (1H, d, J = 2.3 Hz), 6.95 (1H, d, J = 8.7 Hz), 6.89 (1H, t, J = 6.0 Hz), 5.38 (2H, d, J = 5.5 Hz), 2.28 (3H, s), 1.13 (21H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.70, 156.18, 134.54, 133.04, 130.51, 120.39, 118.05, 115.49, 102.88, 95.86, 90.58, 20.90, 19.12, 11.79; HRMS (MALDI) calcd for $C_{21}H_{31}OSi$ $(M + H)^+$: 327.2139, found: 327.2132.

***O*-Allenyl-4-methoxy-2-[(triisopropylsilyl)ethynyl]phenol 1m.** Following general procedures A.1–3, 2-iodo-4-methoxyphenol (625 mg, 2.50 mmol) was converted to **1m** (608 mg, 3 steps, 71%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (1H, d, J = 8.6 Hz), 6.94 (1H, d, J = 2.8 Hz), 6.88 (1H, t, J = 5.7 Hz), 6.81 (1H, dd, J = 9.1, 2.8 Hz), 5.35 (2H, d, J = 5.7 Hz), 3.78 (3H, s), 1.13 (21H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.37, 155.57, 152.19, 121.44, 120.22, 118.06, 116.82, 116.00, 102.52, 96.23, 90.87, 56.08, 19.04, 11.72; HRMS (MALDI) calcd for $C_{21}H_{31}O_2Si$ $(M + H)^+$: 343.2088, found: 343.2088.

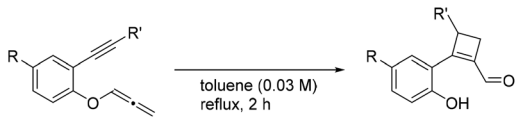
***O*-Allenyl-4-bromo-2-[(triisopropylsilyl)ethynyl]phenol 1n.** Following general procedures A.1–3, 4-bromo-2-iodophenol (747 mg, 2.50 mmol) was converted to **1n** (460 mg, 3 steps, 47%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, d, J = 2.3 Hz), 7.36 (1H, dd, J = 8.7, 2.3 Hz), 6.95 (1H, d, J = 8.7 Hz), 6.86 (1H, t, J = 6.0 Hz), 5.41 (2H, d, J = 6.0 Hz), 1.12 (21H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.26, 157.13, 136.21, 132.35, 119.20, 118.91, 117.33, 115.17, 100.75, 97.86, 90.65, 18.77, 11.41; HRMS (MALDI) calcd for $C_{20}H_{28}OSiBr$ $(M + H)^+$: 391.1087, found: 391.1090.

***O*-Allenyl-1-[(triisopropylsilyl)ethynyl]naphthalen-2-ol 1o.** Following general procedures A.1–3, 1-iodonaphthalen-2-ol (675 mg, 2.50 mmol) was converted to **1o** (544 mg, 3 steps, 60%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (1H, d, J = 8.7 Hz), 7.78 (2H, t, J = 9.1 Hz), 7.56 (1H, dd, J = 8.2, 7.3 Hz), 7.44 (1H, dd, J = 8.2, 6.9 Hz), 7.34–7.26 (1H, m), 7.06–7.03 (1H, m), 5.69 (2H, dd, J = 6.0, 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.58, 157.24, 134.91, 130.35, 130.04, 128.54, 127.77, 126.30, 125.62, 118.89, 120.73, 110.92, 102.13, 100.48, 90.99, 19.22, 11.87; HRMS (MALDI) calcd for $C_{24}H_{31}OSi$ $(M + H)^+$: 363.2139, found: 363.2137.

Preparation of 1e from 1f

***O*-Allenyl-2-[(triphenylsilyl)ethynyl]phenol 1e.** To a flame-dried round-bottom flask containing compound **1f** (200 mg, 1.28 mmol) in THF (0.2 M) at −78 °C was slowly added *n*-BuLi (1 equiv.). The mixture was stirred under nitrogen for 15 minutes before adding triphenylsilylchloride (2 equiv.) and allowing the mixture to warm to room temperature. After 3 hours, the mixture was quenched with saturated NH_4Cl solution and the organic compounds were then extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was then subjected to column chromatography (neutral silica gel, hexane/AcOEt = 100 : 1) to give compound **1e** (397 mg, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (6H, dd, J = 7.6, 1.6 Hz), 7.55 (1H, dd, J = 7.6, 1.6 Hz), 7.44–7.30 (10H, m), 7.11 (1H, d, J = 7.8 Hz), 7.03 (1H, td, J = 7.6, 0.9 Hz), 6.92 (1H, t, J = 6.0 Hz), 5.44 (2H, d, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.53, 158.38, 135.66, 133.90, 133.61, 130.20, 129.83, 127.90, 122.72, 118.57, 116.39, 113.99, 105.14, 94.06, 90.05; HRMS (MALDI) calcd for $C_{29}H_{22}OSiNa$ $(M + Na)^+$: 437.1332, found: 437.1336.

General procedure B for the synthesis of compounds 2a–e, 2h, 2l–o, and 3j



A solution of compound **1a–o** (50 mg, 0.16 mmol) in toluene (commercially available, not dry, 0.03 M) was placed in a test tube, purged with nitrogen and sealed. After refluxing for 2 h, the solution was cooled to room temperature and concentrated *in vacuo*. The obtained residue was then subjected to column chromatography (neutral silica gel, hexane/AcOEt = 10 : 1 to 5 : 1).

2-(2-Formyl-4-triisopropylsilylcyclobut-1-enyl)phenol 2a. Following general procedure B, compound **1a** (50 mg, 0.16 mmol) was converted to **2a** (49 mg, 92%) as a light yellow prism. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (1H, s), 8.88 (1H, s), 7.37–7.32 (1H, m), 7.27 (1H, d, J = 1.84 Hz), 7.02 (1H, dd, J = 8.2, 1.4 Hz), 6.94–6.90 (1H, m), 3.29 (1H, dd, J = 5.0, 1.8 Hz), 3.07 (1H, dd, J = 13.5, 5.0 Hz), 2.85 (1H, dd, J = 13.7, 1.8 Hz), 1.07 (18H, s), 0.97 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.36, 165.07, 156.67, 133.12, 132.37, 130.51, 124.35, 120.46, 120.29, 32.45, 27.84, 19.19, 12.21; HRMS (MALDI) calcd for $C_{20}H_{29}O_2Si$ (M − H)$^+$: 329.1931, found: 329.1930; m.p. 126–128 °C (from hexane/ethyl acetate).

2-(2-Formyl-4-triethylsilylcyclobut-1-enyl)phenol 2b. Following general procedure B, compound **1b** (43 mg, 0.16 mmol) was converted to **2b** (38 mg, 83%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (1H, s), 9.13 (1H, s), 7.36–7.31 (1H, m), 7.26–7.22 (1H, m), 7.02 (1H, d, J = 4.1 Hz), 6.91 (1H, td, J = 7.5, 1.2 Hz), 3.09 (1H, dd, J = 5.0, 1.6 Hz), 3.01 (1H, dd, J = 13.3, 5.0 Hz), 2.65 (1H, dd, J = 13.5, 1.6 Hz), 0.88 (9H, t, J = 7.8 Hz), 0.50 (6H, q, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.29, 163.89, 156.76, 133.06, 131.10, 130.59, 123.34, 120.09, 119.92, 32.69, 26.51, 7.52, 2.74; HRMS (MALDI) calcd for $C_{17}H_{23}O_2Si$ (M − H)$^+$: 287.1462, found: 287.1463.

2-[2-Formyl-4-(*tert*-butyldimethylsilyl)cyclobut-1-enyl]phenol 2c. Following general procedure B, compound **1c** (43 mg, 0.16 mmol) was converted to **2c** (37 mg, 73%) as a light yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (1H, s), 8.82 (1H, s), 7.35–7.31 (1H, m), 7.22 (1H, dd, J = 7.8, 1.4 Hz), 7.02 (1H, dd, J = 8.26, 0.9 Hz), 6.94–6.89 (1H, m), 3.1 (1H, dd, J = 5.0, 1.4 Hz), 3.00 (1H, dd, J = 13.76, 5.0 Hz), 2.69 (1H, dd, J = 13.5, 1.6 Hz), 0.90 (9H, s), −0.10 (3H, s), −0.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.90, 163.56, 156.40, 132.69, 131.70, 130.73, 123.22, 120.07, 119.79, 32.92, 27.20, 26.82, 17.77, −5.61, −8.92; HRMS (MALDI) calcd for $C_{17}H_{23}O_2Si$ (M − H)$^+$: 287.1462, found: 287.1461. M.p. 118–121 °C (from hexane/ethyl acetate).

2-[2-Formyl-4-(*tert*-butyldiphenylsilyl)cyclobut-1-enyl]phenol 2d. Following general procedure B, compound **1d** (63 mg, 0.16 mmol) was converted to **2d** (66 mg, 99%) as a light yellow prism. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (1H, s), 7.84 (1H, s), 7.49 (2H, dd, J = 8.0, 1.1 Hz), 7.46 (2H, dd, J = 8.0, 1.7 Hz), 7.40–7.29 (4H, m), 7.24 (2H, dd, J = 7.5, 7.5 Hz), 7.18 (1H, td, J = 7.8, 1.7 Hz), 6.95 (1H, dd, J = 8.0, 1.7 Hz), 6.89 (1H, dd, J = 8.6, 1.1 Hz), 6.59 (1H, td, J = 7.4, 1.1 Hz), 3.67 (1H, dd, J = 5.2, 1.7 Hz), 3.12 (1H, dd, J = 13.8, 5.2 Hz), 2.80 (1H, dd, J = 13.8, 1.7 Hz), 1.04 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.28, 162.97, 155.48, 136.13, 136.04, 133.75, 133.10, 132.72, 132.02, 130.65, 129.42, 129.35, 127.67, 127.40, 122.90, 119.97, 119.01, 32.69, 28.40, 28.29, 19.35; HRMS (MALDI) calcd for $C_{27}H_{28}O_2SiNa$ (M + Na)$^+$: 435.1751, found: 435.1752; m.p. 112–115 °C (from hexane/ethyl acetate).

2-(2-Formyl-4-triphenylsilylcyclobut-1-enyl)phenol 2e. Following general procedure B, compound **1e** (66 mg, 0.16 mmol) was converted to **2e** (31 mg, 45%) as a light yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (1H, s), 8.77 (1H, s), 7.43–7.37 (9H, m), 7.32–7.25 (6H, m), 7.13 (1H, dd, J = 7.8, 7.8 Hz), 6.91 (1H, d, J = 8.3 Hz), 6.78 (1H, dd, J = 8.0, 1.6 Hz), 6.29 (1H, dd, J = 7.6, 7.6 Hz), 3.75 (1H, dd, J = 5.0, 1.8 Hz), 3.21 (1H, dd, J = 13.3, 5.0 Hz), 2.71 (1H, dd, J = 13.3, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.07, 161.44, 156.37, 135.77, 132.60, 132.45, 131.39, 131.16, 129.88, 127.91, 122.22, 119.61, 119.34, 33.21, 27.71; HRMS (MALDI) calcd for $C_{29}H_{24}O_2SiNa$ (M + Na)$^+$: 455.1438, found: 455.1430; m.p. 103–107 °C (from hexane/ethyl acetate).

2-(2-Formyl-4-*tert*-butylcyclobut-1-enyl)phenol 2h. Following general procedure B, compound **1h** (34 mg, 0.16 mmol) was converted to **2h** (23 mg, 62%) as a light brown powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (1H, s), 7.59 (1H, s), 7.31–7.25 (2H, m), 7.00 (1H, d, J = 1.15 Hz), 6.99–6.91 (1H, m), 3.23 (1H, dd, J = 4.6, 1.7 Hz), 2.76 (1H, dd, J = 13.75, 4.6 Hz), 2.47 (1H, dd, J = 13.75, 1.7 Hz), 0.87 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.44, 161.43, 155.23, 136.17, 131.76, 131.03, 123.16, 120.36, 118.82, 52.62, 33.24, 27.35, 27.02; HRMS (MALDI) calcd for $C_{15}H_{17}O_2$ (M − H)$^+$: 229.1223, found: 229.1225. M.p. 110–112 °C (from hexane/ethyl acetate).

1-Mesityl-2*H*-cyclobuta[*c*]chromene 3j. Following general procedure B, compound **1j** (44 mg, 0.16 mmol) was converted to **3j** (35 mg, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.17 (1H, m), 7.01 (1H, d, J = 8.2 Hz), 6.95–6.90 (4H, m), 6.47 (1H, s), 3.47 (2H, s), 2.32 (6H, s), 2.30 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.86, 136.86, 136.77, 134.43, 132.41, 129.56, 128.23, 126.18, 126.04, 124.99, 123.03, 122.52, 118.46, 117.45, 38.93, 21.03, 20.72; HRMS (MALDI) calcd for $C_{20}H_{18}O$ M$^+$: 274.1352, found: 274.1356.

2-(2-Formyl-4-triisopropylsilylcyclobut-1-enyl)-4-methylphenol 2l. Following general procedure B, compound **1l** (52 mg, 0.16 mmol) was converted to **2l** (41 mg, 74%) as a light yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (1H, s), 8.77 (1H, s), 7.15 (1H, dd, J = 8.5, 2.31 Hz), 7.07 (1H, d, J = 1.83 Hz), 6.92 (1H, d, J = 8.25 Hz), 3.29 (1H, dd, J = 5.04, 1.35 Hz), 3.06 (1H, dd, J = 13.7, 5.04 Hz), 2.84 (1H, dd, J = 13.5, 1.83 Hz), 2.26 (3H, s), 1.08 (18H, s), 0.98 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.73, 164.55, 153.95, 133.39, 131.32, 130.05, 128.91, 123.38, 119.49, 31.72, 27.13, 20.06, 18.58, 11.59; HRMS (MALDI) calcd for $C_{21}H_{31}O_2Si$ (M − H)$^+$: 343.2088, found: 343.2087. M.p. 112–114 °C (from hexane/ethyl acetate).

2-(2-Formyl-4-triisopropylsilylcyclobut-1-enyl)-4-methoxyphenol 2m. Following general procedure B, compound **1m** (55 mg,

0.16 mmol) was converted to **2m** (40 mg, 70%) as a light yellow flake. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (1H, s), 8.33 (1H, s), 6.98–6.93 (2H, m), 6.73 (1H, d, J = 2.85 Hz), 3.76 (3H, s), 3.27 (1H, dd, J = 4.87, 1.8 Hz), 3.07 (1H, dd, J = 13.45, 5.0 Hz), 2.85 (1H, dd, J = 13.75, 1.7 Hz), 1.08 (18H, s), 0.98 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.68, 163.95, 152.91, 150.41, 131.89, 124.45, 121.32, 119.75, 112.77, 55.61, 31.97, 27.37, 18.38, 11.70; HRMS (MALDI) calcd for $C_{21}H_{33}O_3Si$ $(M + H)^+$: 361.2194, found: 361.2195. M.p. 130–132 °C (from hexane/ethyl acetate).

4-Bromo-2-(2-formyl-4-triisopropylsilylcyclobut-1-enyl) phenol 2n. Following general procedure B, compound **1n** (63 mg, 0.16 mmol) was converted to **2n** (30 mg, 45%) as an orange powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (1H, s), 9.18 (1H, s), 7.41–7.36 (2H, m), 6.91 (1H, d, J = 8.72 Hz), 3.25 (1H, dd, J = 5.04, 1.84 Hz), 3.07 (1H, dd, J = 13.72, 5.04 Hz), 2.85 (1H, dd, J = 13.72, 1.8 Hz), 1.08 (18H, s), 0.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.38, 162.76, 155.74, 135.42, 132.59, 132.20, 125.69, 122.16, 112.22, 32.36, 27.66, 16.67, 11.91; HRMS (MALDI) calcd for $C_{20}H_{28}O_2SiBr$ $(M - H)^+$: 407.1036, found: 407.1030. M.p. 163–165 °C (from hexane/ethyl acetate).

1-(2-Formyl-4-triisopropylsilylcyclobut-1-enyl)naphthalene-2-ol 2o. Following general procedure B, compound **1o** (58 mg, 0.16 mmol) was converted to **2o** (46 mg, 76%) as an orange flake. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (1H, s), 7.95 (1H, d, J = 8.25 Hz), 7.67 (2H, d, J = 8.7 Hz), 7.50–7.33 (2H, m), 7.18 (1H, d, J = 8.7 Hz), 3.66 (1H, dd, J = 5.0, 1.83 Hz), 3.25 (1H, dd, J = 13.7, 5.0 Hz), 2.97 (1H, dd, J = 13.7, 1.83 Hz), 0.91 (18H, s), 0.76 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.54, 163.15, 153.25, 138.53, 132.63, 131.90, 129.26, 128.57, 127.12, 124.78, 124.14, 119.91, 116.73, 28.70, 18.73, 18.56, 11.38; HRMS (MALDI) calcd for $C_{24}H_{33}O_2Si$ $(M + H)^+$: 381.2244, found: 381.2246. M.p. 188–190 °C (from hexane/ethyl acetate).

Preparation of 2f from 2a (Scheme 3)

2-(2-Formylcyclobut-1-enyl)phenol 2f. To a round-bottom flask containing compound **2a** (150 mg, 0.45 mmol) in DMF (0.06 M) was added tetrabutylammonium fluoride trihydrate (3.0 equiv.) and was stirred under nitrogen at 80 °C for 4 h. The mixture was then quenched with 0.1 N HCl and the organic compounds were extracted with AcOEt. The combined organic layer was washed with $NaHCO_3$ and brine, and then dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was then subjected to column chromatography (neutral silica gel, hexane/AcOEt = 3 : 1) to give compound **2f** (74 mg, 94%) as an orange powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (1H, s), 9.34 (1H, s), 7.34–7.31 (2H, m), 6.99 (1H, dd, J = 8.0, 1.15 Hz), 6.92 (1H, td, J = 7.5, 1.15 Hz), 2.93 (2H, t, J = 3.7 Hz), 2.82 (2H, t, J = 3.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.33, 156.86, 156.31, 133.27, 132.33, 130.49, 122.00, 120.28, 119.02, 28.99, 23.81; HRMS (MALDI) calcd for $C_{11}H_{11}O_2$ $(M + H)^+$: 175.0754, found: 175.0752. M.p. 160–162 °C (from hexane/ethyl acetate).

2-(4-(Triisopropylsilyl)-2-vinylcyclobut-1-enyl)phenol 4. To a round-bottom flask containing methyltriphenylphosphonium bromide (2.2 equiv.) in THF (0.2 M) at 0 °C was added *t*-BuOK (2.2 equiv.). The mixture was stirred at room temperature for 30 minutes and then it was cooled to 0 °C again before adding compound **2a** (100 mg, 0.3 mmol). It was then stirred under nitrogen overnight and then quenched with water. The organic compounds were then extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was then subjected to column chromatography (neutral silica gel, hexane/AcOEt = 20 : 1) to give compound **4** (75 mg, 76%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.11 (2H, m), 6.90–6.87 (2H, m), 6.49 (1H, dd, J = 5.15, 10.8 Hz), 5.26 (1H, s), 5.24–5.10 (2H, m), 3.06–3.04 (1H, m), 2.82 (1H, dd, J = 13.2, 5.2 Hz), 2.74 (1H, dd, J = 13.4, 2.0 Hz), 1.00 (21H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.37, 140.49, 139.57, 129.86, 129.08, 128.48, 123.12, 120.16, 115.55, 114.90, 28.46, 28.44, 18.86, 11.50; HRMS (MALDI) calcd for $C_{21}H_{31}OSi$ $(M - H)^+$: 327.2139, found: 327.2137.

1-(Triisopropylsilyl)-1,2-dihydro-3*H*-cyclobuta[*c*]chromen-3-one 5. To a round-bottom flask containing compound **2a** (100 mg, 0.3 mmol) in *tert*-butanol (0.05 M) were added 2-methyl-2-butene (30 equiv.) and an aqueous solution of $NaClO_2$ (5 equiv.) and NaH_2PO_4 (5 equiv.) in 1.0 ml of H_2O. The mixture was stirred under nitrogen at ambient temperature for 1 h. It was then quenched with water and the organic compounds were then extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was then subjected to column chromatography (neutral silica gel, hexane/AcOEt = 20 : 1) to give compound **5** (73 mg, 74%) as a dark orange prism. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, t, J = 7.5 Hz), 7.26–7.22 (1H, m), 7.02 (1H, d, J = 8.2 Hz), 6.92 (1H, t, J = 7.4 Hz), 3.16 (1H, d, J = 5.0 Hz), 2.98 (1H, dd, J = 14.0, 5.0 Hz), 2.77 (1H, d, J = 14.2 Hz), 1.04 (18H, s), 0.96 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.05, 165.97, 154.99, 132.30, 129.61, 123.93, 123.45, 120.24, 120.08, 30.37, 28.20, 18.69, 11.61; HRMS (MALDI) calcd for $C_{20}H_{29}O_2Si$ $(M + H)^+$: 329.1931, found: 329.1930. M.p. 145–147 °C (from hexane/ethyl acetate).

1-Triisopropylsilyl-2*H*-cyclobuta[*c*]chromene 3a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, dd, J = 8.0, 1.6 Hz), 7.23 (1H, dd, J = 8.0, 1.4 Hz), 7.06–7.02 (2H, m), 6.36 (1H, s), 3.17 (2H, s), 1.13 (18H, s), 1.11 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.15, 148.78, 129.99, 127.24, 126.25, 125.11, 124.32, 123.52, 119.71, 118.40, 38.68, 19.19, 12.40.

Procedure for the scale-up synthesis of compound 2a (Scheme 4)

Condition A. To a round-bottom flask containing compound **1a** (625 mg, 2 mmol) in dry toluene (0.03 M) was added H_2O (2 equiv.) and the mixture was sonicated for 10 minutes. It was then refluxed under nitrogen for 2 hours, cooled to room temperature and concentrated *in vacuo*. The obtained residue was then subjected to column chromatography (neutral silica gel, hexane/AcOEt = 5 : 1) to give compound **2a** (549 mg, 83%) as a light yellow prism.

Condition B. A solution of compound **1a** (625 mg, 2 mmol) in H_2O (0.03 M) was sonicated for 10 minutes. It was then

refluxed under air for 2 hours, cooled to room temperature and extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was then subjected to column chromatography (neutral silica gel, hexane/AcOEt = 5 : 1) to give compound **2a** (450 mg, 68%) as a light yellow prism.

Procedure for deuterium labeling using D_2O (Scheme 5)

A solution of compound **1a** (50 mg, 0.16 mmol) in dioxane (0.03 M) was placed in a flame-dried test tube, purged with nitrogen and sealed. Using a microsyringe, D_2O (2 equiv.) was added to the solution which was then sonicated for 10 minutes. After refluxing for 2 hours, the solution was cooled to room temperature and concentrated *in vacuo*. The obtained residue was then subjected to column chromatography (neutral silica gel, hexane/AcOEt = 5 : 1) to give a 1 : 1 mixture of deuterium-labeled **2a** and unlabeled **2a**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was partially supported by a Grant-in-Aid from the JSPS KAKENHI for Precisely Designed Catalysts with Customized Scaffolding (Grant No. JP 18H04260), T15K149760, and T15KT00630, by a Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from the AMED under Grant Number JP18am0101084 and JP19am0101084, and by the Cooperative Research Program of "Network Joint Research Center for Materials and Devices" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Notes and references

1 (*a*) B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695; (*b*) S. Kotha, D. Goyal and A. S. Chavan, *J. Org. Chem.*, 2013, **78**, 12288; (*c*) K. Banert and O. Plefka, *Angew. Chem., Int. Ed.*, 2011, **50**, 6171; (*d*) B. M. Trost, F. D. Toste and K. Greenman, *J. Am. Chem. Soc.*, 2003, **125**, 4518; (*e*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259.

2 (*a*) Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866; (*b*) D. Bonne, T. Constantineux, Y. Coquerel and J. Rodriguez, *Chem. – Eur. J.*, 2013, **19**, 2218; (*c*) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe and B. Wendt, *Angew. Chem., Int. Ed.*, 2007, **46**, 467; (*d*) C. M. R. Chandra, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390; (*e*) L. Albrecht, H. Jiang and K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2011, **50**, 8492; (*f*) P. A. Clarke, S. Santosa and W. H. C. Martin, *Green Chem.*, 2007, **9**, 438; (*g*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*h*) S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137.

3 (*a*) Y.-F. Liang, S. Song, L. Ai, X. Li and N. Jiao, *Green Chem.*, 2016, **18**, 6462; (*b*) C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889; (*c*) C. J. Welch, J. A. Walker, W. R. Leonard, M. Biba, J. DaSilva, D. Henderson, B. Laing, D. J. Mathre, S. Spencer, X. Bu and T. Wang, *Org. Process Res. Dev.*, 2005, **9**, 198; (*d*) L. Wang, L.-X. Shi, L. Liu, Z.-X. Li, T. Xu, W.-J. Hao, G. Li, S.-J. Tu and B. Jiang, *J. Org. Chem.*, 2017, **82**, 3605.

4 (*a*) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289; (*b*) W. Qiand and D. Su, *ACS Catal.*, 2014, **4**, 3212; (*c*) C.-L. Sun and Z.-J. Shi, *Chem. Rev.*, 2014, **114**, 9219; (*d*) C. Allais, J.-M. Grassot, J. Rodriguez and T. Constantieux, *Chem. Rev.*, 2014, **114**, 10829; (*e*) R. A. D. Arancon, C. S. K. Lin, C. Vargas and R. Luque, *Org. Biomol. Chem.*, 2014, **12**, 10; (*f*) M. Rueping, J. Dufour and F. R. Schoepke, *Green Chem.*, 2011, **13**, 1084; (*g*) S. Roscales and A. G. Csákÿ, *Chem. Soc. Rev.*, 2014, **43**, 8215; (*h*) A. J. K. Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489; (*i*) M.-Z. Zhang, Q. Chen and G.-F. Yang, *Eur. J. Med. Chem.*, 2015, **89**, 421.

5 (*a*) V. M. Dembitsky, *J. Nat. Med.*, 2008, **62**, 1; (*b*) V. M. Dembitsky, *Phytomedicine*, 2014, **21**, 1559.

6 (*a*) J. C. Namysloand and D. E. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485; (*b*) T. Seiser, T. Saget, D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2011, **50**, 7740; (*c*) G. Fumagalli, S. Stanton and J. F. Bower, *Chem. Rev.*, 2017, **117**, 9404.

7 (*a*) R. Liu, M. Zhang, T. P. Wyche, G. N. W. McPherson, T. S. Bugni and W. Tang, *Angew. Chem., Int. Ed.*, 2012, **51**, 7503; (*b*) W. R. Gutekunst, R. Gianatassio and P. S. Baran, *Angew. Chem., Int. Ed.*, 2012, **51**, 7507.

8 R. Liu, M. Zhang, G. W. McPherson and W. Tang, *Chem. Commun.*, 2013, **49**, 4376.

9 (*a*) Q. Shen and G. B. Hammond, *J. Am. Chem. Soc.*, 2002, **124**, 6534; (*b*) C. H. Oh, D. I. Park, S. H. Jung, V. R. Reddy, A. K. Gupta and Y. M. Kim, *Synlett*, 2005, 2092; (*c*) K. M. Brummond and D. Chen, *Org. Lett.*, 2005, **7**, 3473; (*d*) C. H. Oh, A. K. Gupta, D. I. Park and N. Kim, *Chem. Commun.*, 2005, 5670; (*e*) H. Ohno, T. Mizutani, Y. Kadoh, K. Miyamura and T. Tanaka, *Angew. Chem., Int. Ed.*, 2005, **44**, 5113; (*f*) C. Mukai, Y. Hara, Y. Miyashita and F. Inagaki, *J. Org. Chem.*, 2007, **72**, 4454; (*g*) H. Ohno, T. Mizutani, Y. Kadoh, A. Aso, K. Miyamura, N. Fujii and T. Tanaka, *J. Org. Chem.*, 2007, **72**, 4378; (*h*) T. V. Ovaska and R. E. Kyne, *Tetrahedron Lett.*, 2008, **49**, 376; (*i*) O. Buisine, V. Gandon, L. Fensterbank, C. Aubert and M. Malacria, *Synlett*, 2008, 751; (*j*) N. Saito, Y. Tanaka and Y. Sato, *Org. Lett.*, 2009, **11**, 4124; (*k*) B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Soc. Rev.*, 2010, **39**, 783; (*l*) A. K. Mailyan, I. M. Krylov, C. Bruneau, P. H. Dixneuf and S. N. Osipov, *Synlett*, 2011, 2321; (*m*) B.-L. Lu and M. Shi, *Angew. Chem., Int. Ed.*, 2011, **50**, 12027.

10 (*a*) J.-Y. Wang, P. Zhou, G. Li, W.-J. Hao, S.-J. Tu and B. Jiang, *Org. Lett.*, 2017, **19**, 6682; (*b*) F. Liu, J.-Y. Wang,

P. Zhou, G. Li, W.-J. Hao, S.-J. Tu and B. Jiang, *Angew. Chem., Int. Ed.*, 2017, **56**, 15570; (*c*) P. Zhou, J.-Y. Wang, T.-S. Zhang, G. Li, W.-J. Hao, S.-J. Tu and B. Jiang, *Chem. Commun.*, 2018, **54**, 164; (*d*) H.-K. Sha, F. Liu, J. Lu, Z.-Q. Liu, W.-J. Hao, J.-L. Tang, S.-J. Tu and B. Jiang, *Green Chem.*, 2018, **20**, 3476; (*e*) H. Li, W.-J. Hao, M. Wang, X. Qin, S.-J. Tu, P. Zhou, G. Li, J. Wang and B. Jiang, *Org. Lett.*, 2018, **20**, 4362; (*f*) H.-K. Sha, T. Xu, F. Liu, B.-Z. Tang, W.-J. Hao, S.-J. Tu and B. Jiang, *Chem. Commun.*, 2018, **54**, 10415; (*g*) H. Li, P. Zhou, F. Xie, J.-Q. Hu, S.-Z. Yang, Y.-J. Wang, W.-J. Hao, S.-J. Tu and B. Jiang, *J. Org. Chem.*, 2018, **83**, 13335.

11 The structure of **2a** was determined by X-ray structure analysis. CCDC 1958998.†