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Tandem Michael addition/ylide olefination reaction for the synthesis of highly functionalized cyclohexadiene derivatives

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ABSTRACT

A tandem Michael addition/ylide olefination for the rapid creation of highly functionalized cyclohexadiene is developed. The tandem annulation reactions afford versatile cyclohexadienes in good to excellent isolated yields. This method has been successfully applied to the synthesis of three biologically active molecules.

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1. Introduction

Cyclohexadienes are very important subunits in a number of biologically active compounds[1] such as antibacterially active agent **A**,[1a] antimicrobially active agent **B**,[1c] and calcium channel modulator **C**,[1e] as well as versatile intermediates[2] in organic synthesis (Fig. 1). Although several synthetic methods have been developed,[3,2a] a few are involved in the direct synthesis with high selectivity. Ylide reactions have been developed as one of the powerful approaches for the preparation of alkenes,[4] cyclopropanes,[5] epoxides,[5a,d,6] and aziridines[5b,c,7] due to its unambiguous positioning and good stereoselectivity. Allylic phosphorus ylides have been employed for the construction of cyclohexadiene derivatives via ylide-initiated Michael addition/olefination reaction,[8] however, low yields (<50%) were obtained in the reaction of the corresponding crotonate-derived ylide with α,β-unsaturated carbonyl compounds.[8c] The reactions of crotonate arsonium ylide with conjugate aldehydes were also documented but afforded a mixture of Wittig products and cyclohexadienes (Scheme 1).[8a]

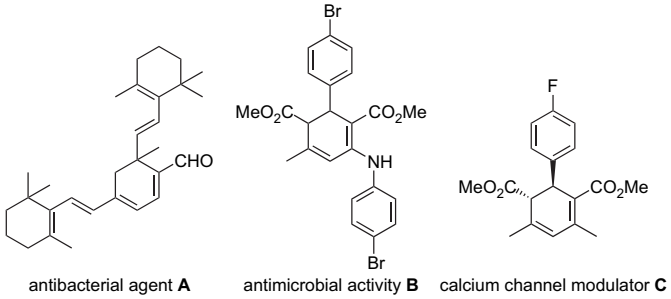
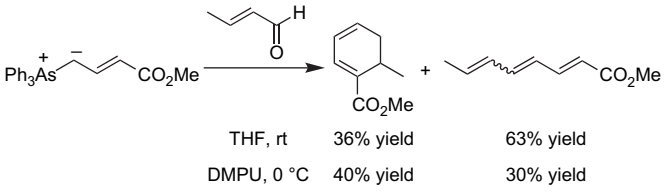


Figure 1. Examples of biologically active compounds containing cyclohexadiene.



Scheme 1. Condensation reaction of crotonate arsonium ylide with crotonal.

In a previous study on ylide chemistry,[9] we developed a tandem reaction of allylic sulfur ylides with α,β-unsaturated ketones for the preparation of functionalized multisubstituted cyclohexadiene epoxides with multiple stereogenic centers (Scheme 2).[10] Very recently, we found that the extension of the sulfur ylide to the corresponding phosphorus ylide in the aforementioned reaction resulted in the formation of versatile cyclohexadienes in good to excellent yields with excellent chemoselectivities and regioselectivities, and the direct Wittig olefination products did not observed at all even when conjugate aldehydes were employed (Scheme 3). Compared with the reaction of the corresponding arsonium ylide,[8a] both the selectivities and the yields of cyclohexadienes have been improved greatly. This reaction proves to be useful in the synthesis of some biologically active molecules such as fungicide. In this paper, we wish to report these results in details.

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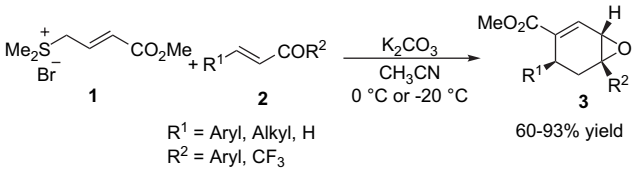
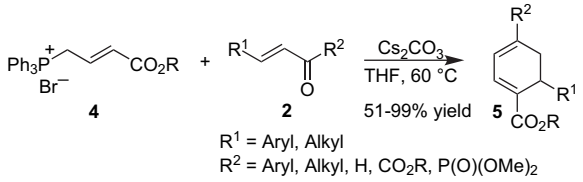


Scheme 2. Tandem Michael addition/ylide epoxidation reaction for the synthesis of highly functionalized cyclohexadiene epoxide derivatives.



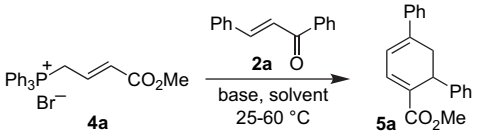
Scheme 3. Synthesis of highly functionalized cyclohexadiene derivatives.

2. Result and discussion

Initially, it was found that allylic phosphonium salt **4a**, after treatment with ^{t}BuOK for 45 min, reacted with chalcone **2a** affording cyclohexadiene **5a** as a single product in 78% yield (entry 1, Table 1). To optimize this tandem Michael addition/ylide olefination reaction, several reaction conditions were investigated using chalcone **2a** as a model substrate. As shown in Table 1, both the base and the reaction temperature influenced the yields. Compared with NaH, both ^{t}BuOK and Cs_2CO_3 were better bases to promote the tandem reaction in THF (entries 2–4, Table 1). Elevating the reaction temperature from 25 to 60 °C increased the yield of **5a** from 84% to 96% (entries 3, 6–7, Table 1). One-pot addition of phosphonium salt **4a**, chalcone, and base resulted in an obvious decrease of the yield (entry 5, Table 1). Although this reaction could be performed in both toluene and acetonitrile, THF was optimal (entries 7–9, Table 1).

Encouraged by these results, the generality of this tandem reaction was examined by evaluating various α,β-unsaturated carbonyl compounds under the optimal conditions. As shown in Table 2, both aryl and alkyl substituted α,β-unsaturated ketones are good substrates to give the cyclohexadiene derivatives with excellent

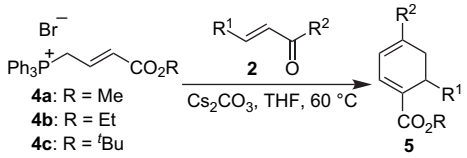
Table 1
Influence of reaction conditions on the tandem Michael addition/ylide olefination reaction[a]



Entry	Solvent	T (°C)	Base	Yield[b] (%)
1[c]	THF	25	^{t}BuOK	78
2	THF	25	^{t}BuOK	83
3	THF	25	Cs_2CO_3	84
4	THF	25	NaH	26
5[d]	THF	25	Cs_2CO_3	43
6	THF	50	Cs_2CO_3	89
7	THF	60	Cs_2CO_3	96
8	CH_3CN	60	Cs_2CO_3	73
9	$CH_3C_6H_5$	60	Cs_2CO_3	48

[a] Reagents and conditions: base (0.40 mmol), **4a** (144 mg, 0.33 mmol) in solvent (2.5 mL), room temperature, 45 min, then **2a** (52 mg, 0.25 mmol) in solvent (2.5 mL) was added and stirred for further 24–48 h at 25–60 °C.
[b] Isolated yield.
[c] Base (1.2 equiv).
[d] One-pot addition of **4a**, Cs_2CO_3, and **2a**.

Table 2
Tandem Michael addition/ylide olefination reaction for the synthesis of highly functionalized cyclohexadiene derivatives[a]

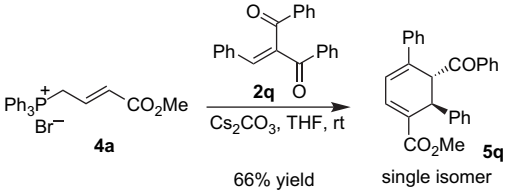


Entry	2	R^1	R^2	5	Yield[b] (%)
1	**2a**	Ph	Ph	**5a**	96
2[c]	**2a**	Ph	Ph	**5a′**	91
3	**2b**	4-Br–C_6H_4	Ph	**5b**	98
4	**2c**	4-OMe–C_6H_4	Ph	**5c**	89
5	**2d**	2-Br–C_6H_4	Ph	**5d**	93
6	**2e**	2-OMe–C_6H_4	Ph	**5e**	91
7	**2f**	4-CH_3–C_6H_4	Ph	**5f**	96
8[d]	**2g**	3,4-$(OMe)_2$–C_6H_3	4-F–C_6H_4	**5g**	99
9	**2h**	Me	Ph	**5h**	86
10	**2i**	Styryl	Ph	**5i**	71
11	**2j**	Ph	Styryl	**5j**	65
12	**2k**	Ph	Me	**5k**	72
13	**2l**	Ph	CO_2Me	**5l**	99
14	**2m**	Me	CO_2Et	**5m**	72
15	**2n**	Me	$P(O)(OMe)_2$	**5n**	51
16[e,f]	**2o**	Ph	H	**5o**	81
17[e]	**2p**	Me	H	**5p**	76

[a] Reagents and conditions: Cs_2CO_3 (130 mg, 0.40 mmol), **4a** (144 mg, 0.33 mmol) in THF (2.5 mL), room temperature, 45 min, then **2** (0.25 mmol) in THF (2.5 mL) was added and stirred for another 44–72 h at 60 °C.
[b] Isolated yield.
[c] Using phosphonium salt **4c**.
[d] Using phosphonium salt **4b**.
[e] At room temperature.
[f] Using 1.6 equiv ^{t}BuOK as a base.

chemoselectivities and regioselectivities in good to excellent yields (65–99%, entries 1–12, Table 2). Chalcones gave excellent results, and both electron-donating and electron-withdrawing groups on the aryl ring proved to be well-tolerated (entries 1–8, Table 2). (*E*)-Methyl-2-oxo-4-phenylbut-3-enoate **2l**, (*E*)-ethyl-2-oxopent-3-enoate **2m**, and but-2-enoyl-phosphonic acid dimethyl ester **2n** also gave the desired cyclohexadienes in good yields (entries 13–15, Table 2). It is worth noting that α,β-unsaturated aldehydes **2o** and **2p** furnished the desired cyclohexadienes in good yields (entries 16–17, Table 2) and the direct Wittig olefination products were not observed. Thus, the current reaction provides a highly efficient method to construct the cyclohexadiene backbone with multifunctional groups in one step.

2-Benzylidene-1,3-diphenyl-propane-1,3-dione **2q** reacted with allylic phosphonium salt **4a** to furnish multisubstituted cyclohexadiene **5q** in 66% yield (Eq. 1). Noticeably, the diastereoselectivity of this reaction is excellent and only one diastereomer was observed.



(1)

The products were characterized by ^{1}H NMR, ^{13}C NMR, elemental analysis, and mass spectra. Products **5d** and **5q** were further confirmed by X-ray analysis (Fig. 2). The relative configuration of **5q** was determined by ^{1}H NMR as well as X-ray analysis, in which the substituted groups are located in trans-position.

This method proves to be very useful in organic synthesis.[11,2a,b,d] As shown in Scheme 4, for example, reduction of **5a** with DIBAL-H,

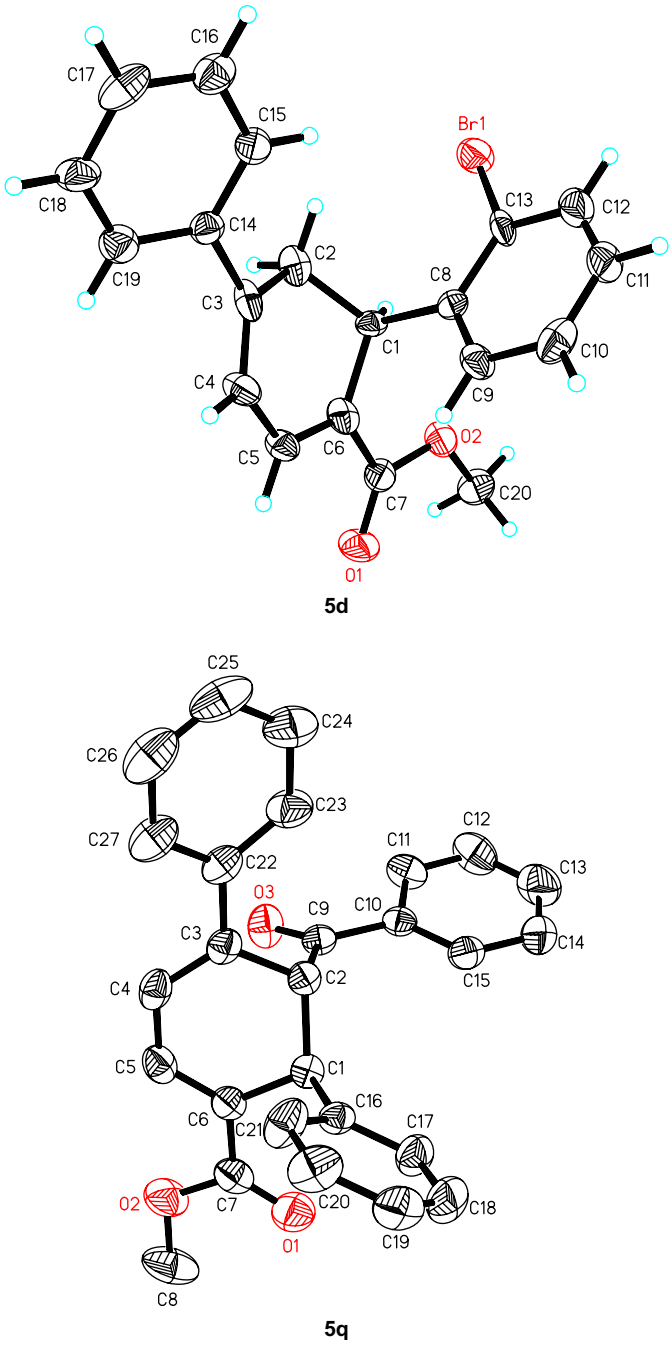
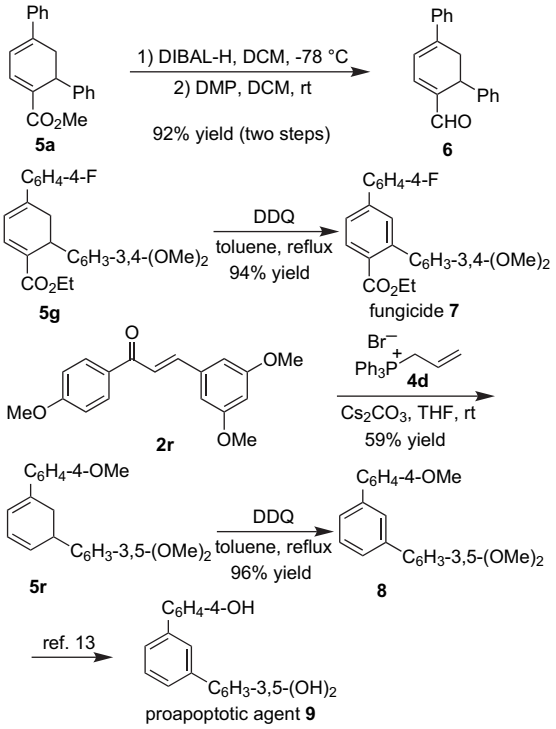


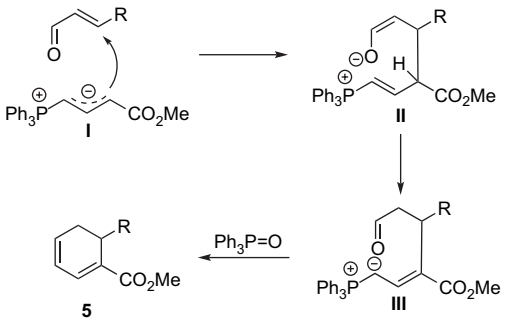
Figure 2. Molecular structure of compounds **5d** and **5q**.

followed by Dess–Martin oxidation, provided biologically active compound **6**[1a] in 92% yield. Oxidation of **5g** with dichlorodicyanoquinone (DDQ) afforded the fungicide **7**[12] in 94% yield. In addition, the reaction of allylic phosphonium salt **4d** with chalcone **2r** (THF, 1.6 equiv of Cs_2CO_3, rt; 59%), followed by DDQ oxidation (DDQ, toluene, 120 °C; 96%), afforded compound **8**, which could be easily transformed to proapoptotically active compound **9** by demethylation with BBr_3.[13]

The present reaction could be accounted by a proposed mechanism as shown in Scheme 5. Ylide **I**, generated in situ from the corresponding phosphonium salt **4a**, underwent an intermolecular Michael addition with α,β-unsaturated ketones to form intermediate **II**. Proton transfer of intermediate **III**, followed by an intramolecular ylide olefination afforded the desired cyclohexadiene derivative **5**. A clear mechanism waits for further study.



Scheme 4. The applications of the tandem reaction in the synthesis of biologically active compounds.



Scheme 5. A possible mechanism.

3. Conclusion

In summary, we have developed a tandem Michael addition/ylide olefination reaction, providing an easy access to highly functionalized cyclohexadiene derivatives in good to excellent yields. The reaction displayed a good substrate scope and proceeded with excellent chemoselectivity and regioselectivity. The applications of this reaction in the synthesis of biologically active compounds **6**, **7**, and **9** have been achieved from readily available starting materials under mild conditions. Further investigations on its asymmetric version are in progress in our laboratory.

4. Experimental

4.1. General

All reactions were carried out under N_2 unless otherwise noted. All solvents were purified according to standard methods prior to use. ^1H NMR and ^{13}C NMR spectra were recorded in chloroform-d_3 on a VARIAN Mercury 300.

4.2. Representative procedure for the synthesis of highly functionalized cyclohexadiene derivatives

4.2.1. Preparation of 4,6-diphenyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5a**

Cs_2CO_3 (130 mg, 0.40 mmol) was added to a solution of phosphonium salt **4a** (144 mg, 0.33 mmol) in THF (2.5 mL), and the resulting mixture was stirred at room temperature for 45 min. Chalcone **2a** (52 mg, 0.25 mmol) in THF (2.5 mL) was added and the reaction mixture was stirred at 60 °C for 48 h. After the reaction was complete (monitored by TLC), the reaction mixture was passed through a glass funnel with a thin layer of silica gel, and eluted with ethyl acetate. The filtrate was concentrated and the residue was purified by flash column chromatography to afford cyclohexadiene **5a** as white solid (mp 96–97 °C). Yield 70 mg (96%); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.44–7.13 (m, 11H), 6.53 (dd, J=6.0 and 3.0 Hz, 1H), 4.18 (dd, J=1.8 and 9.9 Hz, 1H), 3.70 (s, 3H), 3.29–3.19 (m, 1H), 3.02 (dd, J=18 and 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 158.7, 142.6, 141.7, 139.7, 134.6, 128.5, 128.4, 128.3, 127.1, 126.6, 125.5, 119.7, 51.7, 36.8, 34.5. IR ν/cm^{-1}: 2948 (m), 1705 (s), 1561 (m), 1493 (m), 1082 (m), 747 (m), 697; MS (EI, m/z, rel intensity): 290 (M^+, 77.4), 231 (100). Anal. calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.83; H, 6.18.

4.2.2. 4,6-Diphenyl-cyclohexa-1,3-dienecarboxylic acid tert-butyl ester **5a′**

Yield 91% (colorless oil, 51 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.42–7.39 (m, 2H), 7.33–7.15 (m, 9H), 6.51 (dd, J=6.0 and 2.7 Hz, 1H), 4.12 (dd, J=2.1 and 9.9 Hz, 1H), 3.27–3.17 (m, 1H), 2.99 (dd, J=17.7 and 2.7 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 143.3, 140.9, 139.9, 133.6, 130.6, 128.5, 128.3, 128.1, 127.1, 126.4, 125.5, 119.8, 80.3, 37.4, 34.6, 28.0. IR ν/cm^{-1}: 2926 (m), 1700 (s), 1561 (m), 1494 (m), 1367 (m), 751 (m), 697 (m); MS (EI, m/z, rel intensity): 332 (M^+, 6.8), 230 (100). HRMS (EI) calcd for $C_{23}H_{24}O_2$ (M^+): 332.1776. Found: 332.1765.

4.2.3. 6-(4-Bromo-phenyl)-4-phenyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5b**

Yield 98% (a white solid, mp 141–142 °C, 57 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.43–7.23 (m, 8H), 7.16 (d, J=8.4 Hz, 2H), 6.52 (dd, J=6.0 and 3.0 Hz, 1H), 4.12 (d, J=9.9 Hz, 1H), 3.70 (s, 3H), 3.27–3.17 (m, 1H), 2.96 (dd, J=17.7 and 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 141.6 (0), 141.5 (8), 139.4, 134.8, 131.5, 128.9, 128.5 (3), 128.4 (7), 128.0, 125.5, 120.5, 119.6, 51.7, 36.4, 34.4. IR ν/cm^{-1}: 2948 (m), 1705 (s), 1561 (m), 1485 (m), 1368 (m), 778 (m), 693 (m), 492 (m); MS (ESI, positive mode, m/z): 425 (M+MeOH+Na$^+$), 423 (M+MeOH+Na$^+$), 393 (M+Na$^+$), 391 (M+Na$^+$), 371 (M+H$^+$), 369 (M+H$^+$). HRMS (EI) calcd for $C_{20}H_{17}O_2Br$ (M^+): 368.0412. Found: 368.0418.

4.2.4. 6-(4-Methoxy-phenyl)-4-phenyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5c**

Yield 89% (a yellow solid, mp 157–158 °C, 56 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.43–7.19 (m, 8H), 6.75 (d, J=8.7 Hz, 2H), 6.52 (dd, J=6.0 and 3.0 Hz, 1H), 4.13 (d, J=9.6 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.27–3.17 (m, 1H), 2.99 (dd, J=17.4 and 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 158.3, 141.7, 139.8, 134.8, 134.3, 128.9, 128.5, 128.3, 128.1, 125.6, 119.6, 113.8, 55.1, 51.7, 36.1, 34.7. IR ν/cm^{-1}: 2949 (m), 1709 (s), 1608 (m), 1560 (m), 1510 (m), 1435 (m), 1082 (m), 831 (m), 760 (m), 696 (m); MS (ESI, positive mode, m/z): 375 (M+MeOH+Na$^+$), 343 (M+Na$^+$). Anal. calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.80; H, 6.29.

4.2.5. 6-(2-Bromo-phenyl)-4-phenyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5d**

Yield 93% (a white solid, mp 143–144 °C, 66 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.58–7.55 (m, 2H), 7.37–7.22 (m, 5H), 7.17–7.08 (m, 2H), 7.04–6.98 (m, 1H), 6.54 (dd, J=6.3 and 3.0 Hz, 1H), 4.67 (dd, J=10.8 and 1.8 Hz, 1H), 3.68 (s, 3H), 3.25–3.15 (m, 1H), 2.99 (dd, J=17.7 and 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 141.7, 140.0, 139.6, 136.0, 133.3, 128.5, 128.4, 128.3, 128.2, 127.6, 127.3, 125.5, 123.7, 119.5, 51.8, 35.9, 32.9. IR ν/cm^{-1}: 2950 (m), 1707 (s), 1560 (m), 1435 (m), 1269 (m), 751 (m), 692 (m), 671 (m); MS (ESI, positive mode, m/z): 425 (M+MeOH+Na$^+$), 423 (M+MeOH+Na$^+$), 393 (M+Na$^+$), 391 (M+Na$^+$), 371 (M+H$^+$), 369 (M+H$^+$). Anal. calcd for $C_{20}H_{17}O_2Br$: C, 65.05; H, 4.64. Found: C, 64.72; H, 4.69.

4.2.6. 6-(2-Methoxy-phenyl)-4-phenyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5e**

Yield 91% (a white solid, mp 161–162 °C, 68 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.51 (d, J=5.7 Hz, 1H), 7.36–7.21 (m, 5H), 7.13 (t, J=7.8 Hz, 1H), 7.05 (d, J=7.8 Hz, 1H), 6.85 (d, J=8.1 Hz, 1H), 6.76 (t, J=7.5 Hz, 1H), 6.50 (dd, J=5.7 and 2.4 Hz, 1H), 4.66 (d, J=8.7 Hz, 1H), 3.89 (s, 3H), 3.67 (s, 3H), 3.19–3.09 (m, 1H), 2.95 (dd, J=17.7 and 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 156.5, 142.2, 140.0, 135.7, 129.1, 128.3, 128.1, 127.9, 127.5 (0), 127.4 (6), 125.5, 120.1, 119.5, 110.7, 55.5, 51.6, 33.1, 29.7. IR ν/cm^{-1}: 2950 (m), 1709 (s), 1565 (m), 1488 (m), 1433 (m), 1028 (m), 856 (m), 760 (m), 699 (m); MS (ESI, positive mode, m/z): 375 (M+MeOH+Na$^+$), 343 (M+Na$^+$), 321 (M+H$^+$). Anal. calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.88; H, 6.29.

4.2.7. 4-Phenyl-6-p-tolyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5f**

Yield 96% (colorless oil, 66 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.41–7.38 (m, 3H), 7.38–7.16 (m, 5H), 7.02 (d, J=8.1 Hz, 2H), 6.53–6.50 (m, 1H), 4.15 (d, J=9.9 Hz, 1H), 3.70 (s, 3H), 3.27–3.17 (m, 1H), 3.00 (dd, J=17.7 and 1.5 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 141.7, 139.7 (3), 139.6 (7), 136.1, 134.4, 129.1, 128.7, 128.4, 128.2, 127.0, 125.5, 119.6, 51.6, 36.5, 34.6, 20.9. IR ν/cm^{-1}: 2948 (m), 1718 (s), 1688 (m), 1560 (m), 1434 (m), 1081 (m), 818 (m), 759 (m), 693 (m); MS (ESI, positive mode, m/z): 359 (M+MeOH+Na$^+$), 327 (M+Na$^+$), 305 (M+H$^+$). HRMS (EI) calcd for $C_{21}H_{20}O_2$ (M^+): 304.1463. Found: 304.1465.

4.2.8. 6-(3,4-Dimethoxy-phenyl)-4-(4-fluoro-phenyl)-cyclohexa-1,3-dienecarboxylic acid methyl ester **5g**

Yield 99% (pale yellow oil, 63 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.40–7.35 (m, 3H), 7.02–6.78 (m, 4H), 6.70 (d, J=8.4 Hz, 1H), 6.45 (dd, J=2.7 and 6.0 Hz, 1H), 4.22–4.09 (m, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.25–3.15 (m, 1H), 2.96 (dd, J=17 and 1.8 Hz, 1H), 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 148.5, 147.5, 140.5 (d, J=0.9 Hz), 135.8 (d, J=3.5 Hz), 135.3, 133.6, 129.0, 127.1 (d, J=7.5 Hz), 119.1 (d, J=2.1 Hz), 118.8, 115.4, 115.1, 110.8, 110.3, 60.3, 55.5 (0), 55.4 (8), 36.3, 34.6, 14.0. IR ν/cm^{-1}: 2934 (m), 1700 (s), 1599 (m), 1561 (m), 1509 (m), 1464 (m), 1230 (m), 1028 (m), 830 (m), 771 (m); MS (EI, m/z, rel intensity): 382 (M^+, 100), 309 (92.9). HRMS (EI) calcd for $C_{23}H_{23}FO_4$ (M^+): 382.1580. Found: 382.1578.

4.2.9. 6-Methyl-4-phenyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5h**

Yield 86% (colorless oil, 44 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.42 (d, J=7.2 Hz, 2H), 7.31–7.17 (m, 3H), 7.05 (d, J=6.3 Hz, 1H), 6.36 (dd, J=5.7 and 2.7 Hz, 1H), 3.70 (s, 3H), 2.94–2.76 (m, 2H), 2.54 (d, J=17 Hz, 1H), 0.95 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 141.3, 140.3, 132.8, 131.5, 128.5, 128.1, 125.4, 119.0, 51.5, 33.3, 26.5, 17.7. IR ν/cm^{-1}: 2954 (m), 1705 (s), 1560 (m), 1435 (m), 1089 (m), 753 (m), 693 (m); MS (ESI, positive mode, m/z): 229 (M+H$^+$). HRMS (EI) calcd for $C_{15}H_{16}O_2$ (M^+): 228.1150. Found: 228.1147.

4.2.10. 4-Phenyl-6-styryl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5i**

Yield 71% (colorless oil, 60 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.52 (d, J=6.9 Hz, 2H), 7.39–7.13 (m, 9H), 6.52–6.44 (m, 2H), 6.23

(dd, *J*=15.9 and 7.5 Hz, 1H), 3.78 (s, 3H), 3.71 (t, *J*=7.5 Hz, 1H), 3.07–2.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 141.8, 139.7, 137.3, 133.9, 129.9, 128.7, 128.6, 128.4, 128.3, 127.8, 127.1, 126.2, 125.6, 119.5, 51.7, 34.8, 32.0. IR ν/cm^{-1}: 2948 (m), 1705 (s), 1557 (m), 1434 (m), 1267 (m), 1085 (s), 757 (m), 693 (m); MS (ESI, positive mode, *m*/*z*): 371 (M+MeOH+Na$^+$), 339 (M+Na$^+$), 317 (M+H$^+$). HRMS (EI) calcd for $C_{22}H_{20}O_2$ (M$^+$): 316.1463. Found: 316.1458.

4.2.11. 6-Phenyl-4-styryl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5j**

Yield 65% (a white solid, mp 113–114 °C, 58 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.43–7.12 (m, 11H), 6.89 (d, *J*=16.5 Hz, 1H), 6.67 (d, *J*=16.2 Hz, 1H), 6.24 (d, *J*=6.0 Hz, 1H), 4.17 (t, *J*=5.7 Hz, 1H), 3.70 (s, 3H), 2.97 (d, *J*=5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 143.2, 140.4, 136.8, 134.5, 130.7, 129.6, 129.4, 128.9, 128.7, 128.4, 128.1, 127.1, 126.7, 124.1, 51.7, 36.7, 31.2. IR ν/cm^{-1}: 2948 (m), 1704 (s), 1542 (m), 1434 (m), 1263 (m), 1074 (s), 750 (m), 697 (m); MS (ESI, positive mode, *m*/*z*): 371 (M+MeOH+Na$^+$), 339 (M+Na$^+$), 317 (M+H$^+$). HRMS (EI) calcd for $C_{22}H_{20}O_2$ (M$^+$): 316.1463. Found: 316.1465.

4.2.12. 4-Methyl-6-phenyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5k**

Yield 72% (a white solid, mp 70–71 °C, 72 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.26–7.17 (m, 6H), 5.92–5.90 (m, 1H), 4.00 (d, *J*=10.2 Hz, 1H), 3.67 (s, 3H), 2.88 (dd, *J*=18.0 and 10.8 Hz, 1H), 2.36 (d, *J*=18.0 Hz, 1H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 143.5, 142.7, 134.9, 128.3, 127.0, 126.5 (1), 126.4 (6), 118.9, 51.5, 37.4, 36.7, 23.8. IR ν/cm^{-1}: 2949 (m), 1709 (s), 1589 (s), 1435 (m), 1076 (m), 760 (m), 699 (m); MS (ESI, positive mode, *m*/*z*): 283 (M+MeOH+Na$^+$), 251 (M+Na$^+$), 229 (M+H$^+$). HRMS (EI) calcd for $C_{15}H_{16}O_2$ (M$^+$): 228.1150. Found: 228.1152.

4.2.13. 5-Phenyl-cyclohexa-1,3-diene-1,4-dicarboxylic acid dimethyl ester **5l**

Yield 99% (a white solid, mp 77–78 °C, 46 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.36 (d, *J*=6.3 Hz, 1H), 7.27–7.16 (m, 6H), 4.17 (dd, *J*=9.9 and 2.4 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.08–2.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 166.6, 141.4, 134.5, 132.3, 131.2, 128.5, 127.1, 126.9, 52.0 (4), 51.9 (6), 36.5, 30.7. IR ν/cm^{-1}: 2951 (m), 1712 (s), 1641 (m), 1435 (m), 1092 (m), 734 (m), 700 (m); MS (EI, *m*/*z*, rel intensity): 272 (M$^+$, 44.8), 213 (100). HRMS (EI) calcd for $C_{16}H_{16}O_4$ (M$^+$): 272.1049. Found: 272.1052.

4.2.14. 5-Methyl-cyclohexa-1,3-diene-1,4-dicarboxylic acid 1-ethyl ester 4-methyl ester **5m**

Yield 72% (colorless oil, 54 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.09–7.03 (m, 2H), 4.25 (q, *J*=7.2 Hz, 2H), 3.78 (s, 3H), 3.01–2.90 (m, 1H), 2.71–2.50 (m, 2H), 1.33 (t, *J*=7.2 Hz, 3H), 0.99 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8 (7), 166.8 (5), 137.9, 131.4, 130.4, 60.8, 51.9, 29.2, 26.3, 17.8, 14.2. IR ν/cm^{-1}: 2959 (m), 1709 (s), 1437 (m), 1259 (m), 1095 (m), 740 (m); MS (EI, *m*/*z*, rel intensity): 224 (M$^+$, 14.0), 91 (100). HRMS (EI) calcd for $C_{12}H_{16}O_4$ (M$^+$): 224.1049. Found: 224.1042.

4.2.15. 4-(Dimethoxy-phosphoryl)-6-methyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5n**

Yield 51% (colorless oil, 52 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.06–6.90 (m, 2H), 3.82 (s, 3H), 3.79 (d, *J*=6.0 Hz, 3H), 3.75 (d, *J*=5.7 Hz, 3H), 3.00–2.93 (m, 1H), 2.61–2.50 (m, 1H), 2.45–2.36 (m, 1H), 1.02 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6 (d, *J*=4.0 Hz), 135.1 (d, *J*=10.4 Hz), 132.0 (d, *J*=11.3 Hz), 129.5 (d, *J*=19.3 Hz), 126.8, 52.5 (t, *J*=5.1 Hz), 52.0 (d, *J*=0.9 Hz), 29.8 (d, *J*=7.9 Hz), 25.6 (d, *J*=8.3 Hz), 17.3 (d, *J*=1.1 Hz). IR ν/cm^{-1}: 2956 (m), 1709 (s), 1438 (m), 1258 (m), 1054 (m), 827 (m); MS (ESI, positive mode, *m*/*z*): 315 (M+MeOH+Na$^+$), 283 (M+Na$^+$), 261 (M+H$^+$). HRMS (EI) calcd for $C_{11}H_{17}O_5P$ (M$^+$): 260.0814. Found: 260.0818.

4.2.16. 6-Phenyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5o**

Yield 81% (colorless oil, 56 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.29–7.17 (m, 6H), 6.18–6.12 (m, 1H), 6.02–5.96 (m, 1H), 4.01 (dd, *J*=10.5 and 1.2 Hz, 1H), 3.68 (s, 3H), 2.95–2.83 (m, 1H), 2.61–2.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 142.6, 133.8, 131.7, 129.1, 128.3, 127.2, 126.6, 123.7, 51.7, 35.6, 32.1. IR ν/cm^{-1}: 2950 (m), 1709 (s), 1575 (m), 1435 (m), 1092 (m), 699 (m); MS (EI, *m*/*z*, rel intensity): 214 (M$^+$, 13.8), 57 (100). HRMS (EI) calcd for $C_{14}H_{14}O_2$ (M$^+$): 214.0994. Found: 214.0992.

4.2.17. 6-Methyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5p**[8f]

Yield 76% (colorless oil, 65 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 6.98–6.96 (m, 1H), 6.03 (t, *J*=3.0 Hz, 2H), 3.76 (s, 3H), 2.85–2.75 (m, 1H), 2.57–2.48 (m, 1H), 2.22–2.14 (m, 1H), 0.99 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 132.2, 131.9, 131.6, 122.9, 51.5, 30.6, 25.2, 17.6.

4.2.18. 5-Benzoyl-4,6-diphenyl-cyclohexa-1,3-dienecarboxylic acid methyl ester **5q**

Yield 66% (a white solid, mp 125–126 °C, 70 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 8.07 (d, *J*=7.2 Hz, 2H), 7.67–7.42 (m, 6H), 7.39–7.24 (m, 8H), 6.92 (d, *J*=6.0 Hz, 1H), 4.95 (s, 1H), 4.38 (s, 1H), 3.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.7, 166.6, 141.7, 139.2, 138.9, 134.5, 134.0, 133.5, 129.0, 128.9 (3), 128.9 (2), 128.6, 128.5, 127.5, 127.2, 127.1, 125.6, 123.0, 52.1, 51.7, 41.3. IR ν/cm^{-1}: 2948 (m), 1707 (s), 1596 (m), 1436 (m), 1260 (m), 1082 (s), 751 (m), 697 (m); MS (ESI, positive mode, *m*/*z*): 395 (M+H$^+$). Anal. calcd for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62. Found: C, 82.58; H, 5.59.

4.2.19. 1,3-Dimethoxy-5-[5-(4-methoxy-phenyl)-cyclohexa-2,4-dienyl]-benzene **5r**

Yield 59% (a white solid, mp 74–75 °C, 31 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.37 (d, *J*=9.0 Hz, 2H), 6.85 (d, *J*=8.7 Hz, 2H), 6.50 (d, *J*=2.4 Hz, 2H), 6.35–6.28 (m, 2H), 6.22–6.16 (m, 1H), 5.85 (dd, *J*=9.6 and 3.3 Hz, 1H), 3.79 (s, 3H), 3.77–3.65 (m, 7H), 2.92–2.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.7, 158.9, 148.0, 135.3, 133.2, 128.5, 126.1, 125.5, 118.5, 113.7, 105.6, 98.2, 55.2, 41.4, 34.6. IR ν/cm^{-1}: 2930 (m), 1606 (s), 1512 (m), 1460 (m), 1154 (m), 1065 (m), 831 (m), 750 (m); MS (EI, *m*/*z*, rel intensity): 322 (M$^+$, 100), 171 (53.8). Anal. calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.20; H, 6.94.

4.3. Representative procedure for the synthesis of 4, 6-diphenyl-cyclohexa-1,3-dienecarbaldehyde 6

4.3.1. Preparation of 4,6-diphenyl-cyclohexa-1,3-diene-carbaldehyde **6**

DIBAL-H (1.0 M in toluene, 1.5 mL, 1.5 mmol) was added dropwise to a solution of **5a** (145 mg, 0.50 mmol) in dry dichloromethane (2 mL) at −78 °C. After 1 h, the reaction mixture was warmed to 0 °C and quenched with 5 mL of Rochelle's salt solution. The mixture was stirred vigorously for 2 h, the layers were separated, and the aqueous layer was extracted with dichloromethane (2×10 mL). The organic layers were dried with sodium sulfate and concentrated to give the crude alcohol, which was used directly in the next step.

In a flame-dried round bottom flask, a solution of the obtained crude alcohol was dissolved in dichloromethane (5 mL), Dess–Martin periodinane (DMP) (254 mg, 0.60 mmol) was added to the solution directly and the solution was then allowed to stir at ambient temperature for 10 min. The solution was filtered through Celite 545 and then concentrated in vacuo. The residue was subjected to column chromatography to provide **6**[1a] as pale yellow liquid. Yield 119 mg (92%); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 9.58 (s, 1H), 7.45 (dd, *J*=8.1 and 1.8 Hz, 2H), 7.36–7.05 (m, 9H), 6.63 (dd,

J=6.0 and 2.4 Hz, 1H), 4.22 (dd, J=9.0 and 2.1 Hz, 1H), 3.24–3.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0, 145.3, 143.4, 142.3, 139.2, 138.3, 128.9, 128.6, 128.4, 127.0, 126.7, 125.7, 119.7, 34.2, 33.9. IR ν/cm^{-1}: 2811 (m), 1667 (s), 1553 (m), 1493 (m), 1172 (m), 758 (m), 698 (m); MS (EI, m/z, rel intensity): 260 (M^+, 100), 231 (72.1).

4.4. Representative procedure for the DDQ oxidation

4.4.1. Preparation of fungicide **7**

DDQ (70 mg, 0.31 mmol) was added to a mixed solution of **5g** (96 mg, 0.25 mmol) in toluene (11 mL) and the resulting mixture was stirred at 120 °C for 35 h. After the reaction was complete (monitored by TLC), the reaction mixture was passed through a glass funnel with a thin layer of silica gel, and eluted with ethyl acetate. The filtrate was concentrated and the residue was purified by flash column chromatography to afford **7**[12] as pale yellow oil. Yield 94%; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.87 (d, J=7.5 Hz, 1H), 7.62–7.55 (m, 4H), 7.15 (t, J=8.4 Hz, 2H), 6.92–6.89 (m, 3H), 4.14 (q, J=7.2 Hz, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 1.08 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 148.4 (d, J=2.1 Hz), 142.7 (d, J=7.7 Hz), 135.9 (d, J=3.2 Hz), 134.0, 130.3, 130.0, 129.1, 128.9, 128.8, 128.7, 125.3, 120.6, 115.9, 115.6, 111.7, 110.7, 60.9, 55.8 (2), 55.7 (9), 13.8. IR ν/cm^{-1}: 2936 (m), 1709 (s), 1604 (m), 1508 (m), 1028 (m), 830 (m); MS (EI, m/z, rel intensity): 380 (M^+, 100), 220 (12.5).

4.4.2. Preparation of compound **8**[13]

Yield 96% (pale yellow oil, 17 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.66 (d, J=1.2 Hz, 1H), 7.65–7.39 (m, 4H), 7.16–7.06 (m, 1H), 6.90 (d, J=9.0 Hz, 2H), 6.69 (d, J=2.1 Hz, 2H), 6.39 (t, J=2.4 Hz, 1H), 3.75 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 143.5, 141.7, 141.3, 133.5, 129.1, 129.0, 128.2, 126.0, 125.7, 125.5, 114.2, 105.5, 99.3, 55.4, 55.3. IR ν/cm^{-1}: 2960 (m), 1594 (s), 1517 (m), 1461 (m), 1247 (m), 1155 (m), 1038 (m), 794 (m), 695 (m), 574 (m); MS (EI, m/z, rel intensity): 320 (M^+, 100), 305 (10.5).

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Supplementary data

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