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PPh_3-catalyzed ylide cyclization for the controllable synthesis of benzobicyclo[4.3.0] compounds: base effects and scope

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Abstract

A catalytic intramolecular ylide annulation for the controllable construction of benzobicyclo[4.3.0] ring systems with three continuous stereogenic centers is developed in a single manipulation. In the presence of 20 mol % of triphenylphosphine, the reactions of compounds **1a**–**1f** afford benzobicyclo[4.3.0] compounds **3** and **4** as major products, respectively, with excellent diastereoselectivities in good to excellent yields, depending on the base used. In addition, 2-methyl α,β-unsaturated esters **2a**–**2c** also work well to give the corresponding benzobicyclo[4.3.0] compounds with one quaternary carbon center with high diastereoselectivities in good yields under the same conditions.

1. Introduction

The occurrence of the benzobicyclo[4.3.0] subunit in many natural and synthetic biologically active compounds[1,2] has promoted many strategies for its construction.[3,4] Of the synthetic methods developed, most are involved in inter- or intramolecular metal mediated annulation reactions.[4] Recently, ylide cyclizations have been developed for the preparation of five- or six-membered ring as well as such bicyclic compounds.[5–10] Lu demonstrated that phosphines were good catalysts for the construction of cyclopentene derivatives.[5] Zhang, Fu, and Miller independently documented its asymmetric version.[6] Krische developed the first intramolecular variant of the annulation.[7] Aggarwal reported a novel asymmetric synthesis of epoxide- and aziridine-fused heterocycles via a sulfur ylide route.[8] In a previous study on ylide chemistry,[11] we found that α,β-unsaturated esters **1a**–**1f**[12] underwent readily a formal [3+2] cycloaddition to afford benzobicyclo[4.3.0] compounds **3** with excellent diastereoselectivities in good to excellent yields in the presence of 20 mol % of triphenylphosphine.[13,14] On the basis of the result, very recently, we observed a strong base effect and found that using Cs_2CO_3 instead of Na_2CO_3 as a base, the same substrates **1a**–**1f** gave benzobicyclo[4.3.0] compounds **4** as major products. Thus, both benzobicyclo[4.3.0] compounds **3** and **4** could be synthesized controllably from the same starting material just by a choice of the base (Scheme 1). In addition, we also found that α-methyl α,β-unsaturated esters **2** could work well to give the corresponding benzobicyclo[4.3.0] compounds with one quaternary carbon center (Scheme 1). In this paper, we wish to report these results in detail.

2. Result and discussion

In the phosphine-catalyzed intramolecular formal [3+2] cycloaddition of compound **1**, we observed that the desired product **3** was contaminated with **4** in all cases investigated.[12] In addition, when α,β-unsaturated ketone was used as a substrate, product **4** was obtained as a major product. These results suggested that products **4** could be formed probably

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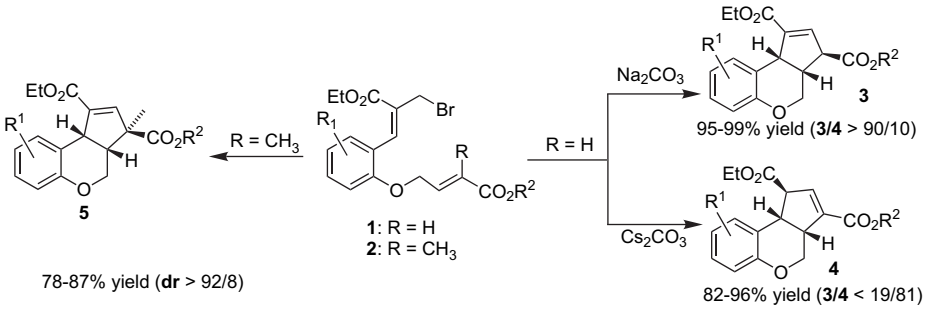


Scheme 1. Base effects on phosphine-catalyzed formal [3+2] cycloaddition.

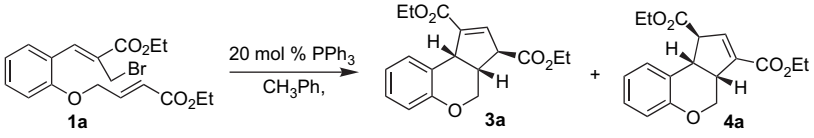
due to the isomerization of products **3** under basic conditions. And it is envisioned that strong base will promote the formation of product **4**. As expected, under a similar reaction condition using Cs_2CO_3 instead of Na_2CO_3 as a base, substrate **1a** gave benzobicyclo[4.3.0] compound **4a** as a major product instead of **3a** in good yield. Thus, benzobicyclo[4.3.0] compounds **3a** and **4a** could be synthesized controllably just by a choice of the base.

To optimize this protocol, several reaction conditions were investigated using compound **1a** as a model substrate. Initially, we examined first the effects of the reaction temperature on this annulation reaction. As shown in Table 1, lowering the reaction temperature increased the selectivity for the formation of **3a** slightly but decreased the yield when using Na_2CO_3 as a base (entries 1–3, Table 1). Base proved to strongly influence the product distribution. For instance, Na_2CO_3 gave compound **3a** as a major product. Using Cs_2CO_3 instead of Na_2CO_3, the reaction selectivity was reversed and benzobicyclo[4.3.0] compound **4a** was obtained as a major product (**4a**/**3a**=82:18) in almost quantitative yield (entry 5, Table 1). K_2CO_3 gave a mixture of **3a** and **4a** with a ratio of 41:59. At 90 °C, the desired product could be furnished in 90% yield even if the catalyst loading was reduced to 10 mol % (entry 6, Table 1). In the absence of PPh_3, the desired product was not observed. In addition, increasing the reaction temperature or prolonging the reaction time could not improve the selectivity for the formation of **3a** and **4a** (entry 7, Table 1).

The generality of the intramolecular annulation reaction was investigated by employing a variety of α,β-unsaturated carbonyl compounds. Substrates **1a**–**1f** are readily accessible from the corresponding salicylaldehydes, as shown in Scheme 2.[15] 2-Chloroethanol reacted with the salicylaldehydes, followed by the Wittig reaction, bromination with NBS, Dess–Martin oxidation, and then Wittig reaction, affording the desired cyclization precursor bromides **1a**–**1f**. In addition, substrate **1** could also be readily available from the corresponding salicylaldehydes in three steps, i.e., a substitution reaction with γ-bromocrotonate and then a Baylis–Hillman reaction, followed by bromination with NBS.

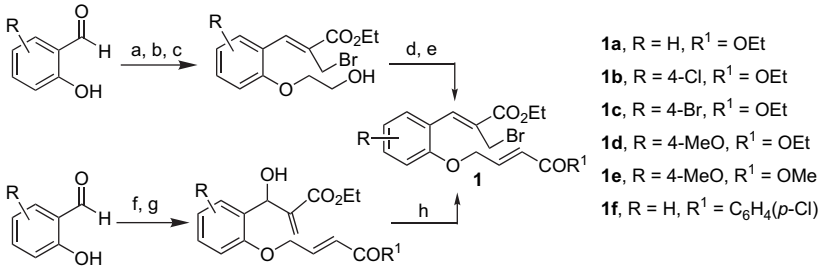
Under the optimal conditions, as shown in Table 2, α,β-unsaturated esters could furnish selectively benzobicyclo[4.3.0] compounds **3** and **4** with excellent stereoselectivity in good to excellent yields, just by a simple choice of the base. Using Na_2CO_3 as a base, compound **3** was obtained as a major product while Cs_2CO_3 gave product **4** instead. The substituents on the benzene ring had slight effects on the yields and

Table 1
Effect of reaction conditions on the formal [3+2] cycloaddition[a]



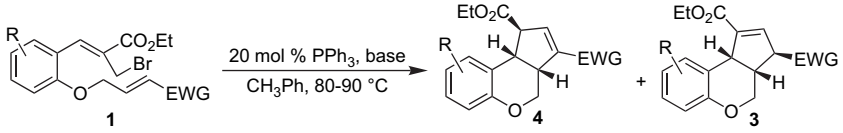
Entry	*T* (°C)	Base	**3a**/**4a**[b]	Yield[c] (%)
1	70	Na_2CO_3	94:6	85
2	80	Na_2CO_3	91:9	95
3	90	Na_2CO_3	88:12	99
4	90	K_2CO_3	41:59	94
5	90	Cs_2CO_3	18:82	96
6[d]	90	Cs_2CO_3	18:82	90
7	110	Cs_2CO_3	18:82	94
8	90	^{t}BuOK	—	<10
9	90	DBU	—	<5
10	90	DABCO	—	<5

[a] Reagents and conditions: PPh_3 (26 mg, 20 mol %), **1a** (199 mg, 0.5 mmol) in CH_3Ph base (1.5 equiv), 70–110 °C, 5–11 h.
[b] Determined by 300 MHz ^{1}H NMR.
[c] Isolated yield.
[d] PPh_3: 10 mol %.



Scheme 2. Synthesis of substrates **1a**–**1f**. Reagents and conditions: (a) 2-chloroethanol, $NaOH/H_2O$, 98 °C, 68–77%; (b) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, rt, 81–88%; (c) NBS, AIBN, CCl_4, reflux, 98–100%; (d) Dess–Martin oxidant, CH_2Cl_2, rt, 74–85%; (e) $Ph_3P{=}CHCOR^1$, CH_2Cl_2, rt, 85–95%; (f) $BrCH_2CH{=}CHCOR^1$, NaH, DMF, rt, 56–88%; (g) $CH_2{=}CO_2Et$, DABCO, rt, 52–56%; (h) Me_2S, NBS, CH_2Cl_2, rt, 75–85%.

Table 2
Controllable synthesis of benzobicyclo[4.3.0] compounds[a]

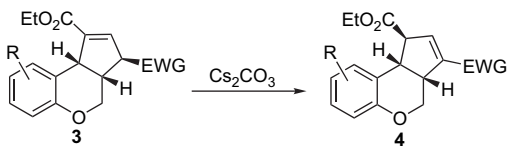


Entry	1	R	EWG	Base	4 or 3 (4/3)[b]	Yield[c] (%)
1	**1a**	H	CO_2Et	Na_2CO_3	**3a** (9:91)	95
2	**1a**	H	CO_2Et	Cs_2CO_3	**4a** (82:18)	96
3	**1b**	4-Cl	CO_2Et	Na_2CO_3	**3b** (6:94)	99
4	**1b**	4-Cl	CO_2Et	Cs_2CO_3	**4b** (83:17)	82
5	**1c**	4-Br	CO_2Et	Na_2CO_3	**3c** (10:90)	96
6	**1c**	4-Br	CO_2Et	Cs_2CO_3	**4c** (82:18)	89
7	**1d**	4-MeO	CO_2Et	Na_2CO_3	**3d** (9:91)	96
8	**1d**	4-MeO	CO_2Et	Cs_2CO_3	**4d** (81:19)	83
9	**1e**	4-MeO	CO_2Me	Na_2CO_3	**3e** (10:90)	99
10	**1e**	4-MeO	CO_2Me	Cs_2CO_3	**4e** (81:19)	85
11	**1f**	H	$COC_6H_4(p\text{-Cl})$	Na_2CO_3	**4f** (81:19)	81
12	**1f**	H	$COC_6H_4(p\text{-Cl})$	Cs_2CO_3	**4f** (86:14)	78

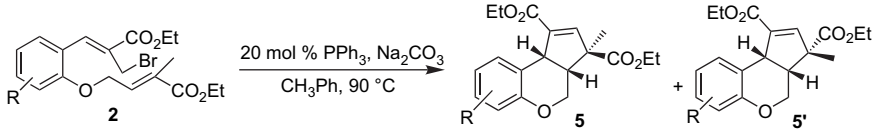
[a] PPh_3 (26 mg, 20 mol %), **1** (0.5 mmol) in CH_3Ph (0.10 M), rt, 15 min, base (1.5 equiv), 80–90 °C, 5–11 h.
[b] Determined by 300 MHz ^1H NMR.
[c] Isolated yield for **3**+**4**.

diastereoselectivities (entries 1–10, Table 2). In addition, α,β-unsaturated ketone **1f** could only give **4f** dominantly whatever Na_2CO_3 or Cs_2CO_3 was used (entries 11 and 12, Table 2). Noticeably, the diastereoselectivity of this reaction is excellent and only one diastereomer was observed in all cases described in Table 2.

In a previous communication,[12] we proposed a mechanism involved in a double Michael addition to explain the formal [3+2] cycloaddition reactions for the formation of product **3**. In the aforementioned reaction, we observed a strong base effect: stronger base gave product **4** more. In particularly, α,β-unsaturated ketone **1f** only produced **4f** as the major product even if Na_2CO_3 was used. On the basis of these results, it is easy to speculate that compound **4** was formed by an isomerization of product **3** under basic conditions (Eq. 1). To demonstrate the hypothesis, we monitored the annulation reaction of **1b** using Cs_2CO_3 as the base by ^1H NMR. As shown in Figure 1, 43 mol % of **1b** was converted into benzobicyclo[4.3.0] compound **3b** after 2 h and **4b** was not observed. Four hours later, 73 mol % of **1b** was converted into **3b** and **4b** remained undetectable. However, more than 80 mol % of **4b** was detected after further 2 h, which should be isomerized from **3b**. Prolonging the reaction time to 9 h, the ratio of **4a/3a** was almost no change, suggesting that there be a balance between **3b** and **4b** under the reaction conditions. To further confirm this isomerization mechanism, we designed α-methyl α,β-unsaturated ester **2** as a substrate and it is expected that, in this case, the desired product would be **5** or **5′** with a quaternary carbon that could block the isomerization (Eq. 2).



(1)



(2)

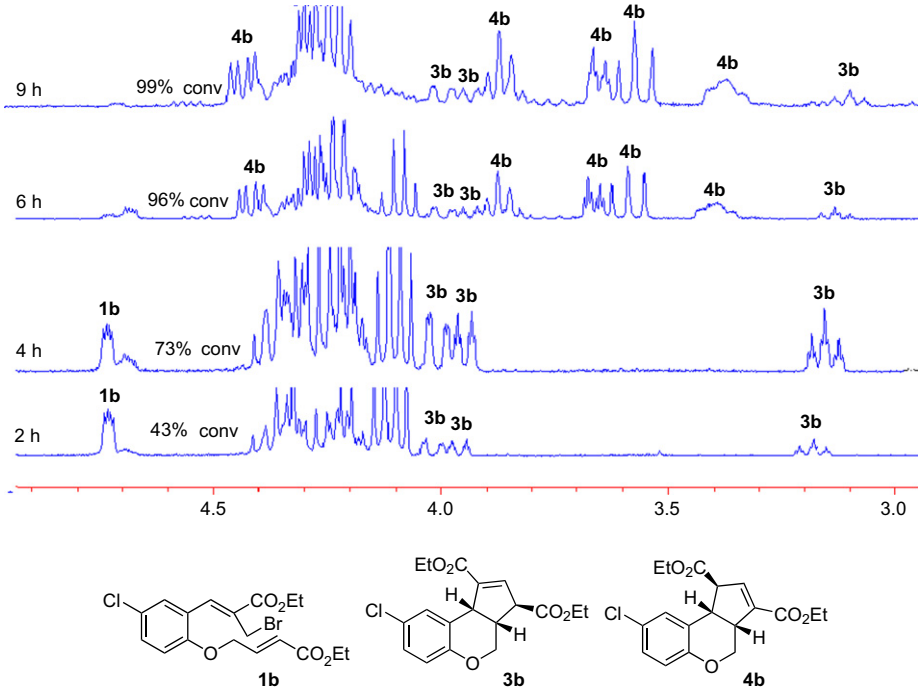
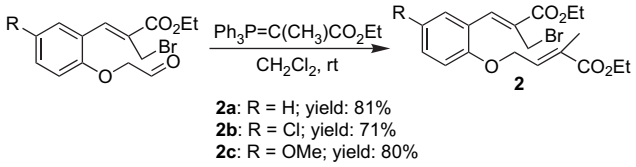


Figure 1. ^{1}H NMR monitoring on the annulation of **1b** using Cs_2CO_3.



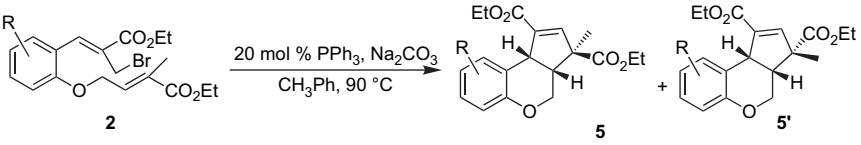
Scheme 3. Synthesis of substrates **2a–c**.

The synthesis of α-methyl α,β-unsaturated esters **2a–c** was shown in Scheme 3. The synthetic method is similar to that of substrate **1** except that different phosphorus ylides were used in the final step (Scheme 3). As expected, substrates **2** gave only benzobicyclo[4.3.0] compounds with a quaternary carbon **5** and **5′** as the products in good yields using Na_2CO_3 as a base. The isomerized products were not observed at all, further supporting the proposed mechanism. As summarized in Table 3, the substituents on the benzene ring had almost no effect on the diastereoselectivities (entries 1–4, Table 3). Noticeably, diastereoisomers **5** and **5′** could be easily separated by flash chromatography. These results, together with the ^{1}H NMR trace in Figure 1, demonstrated clearly that the product **4** was formed by the isomerization of compound **3**.

The structures of compounds **4a–4f** and **5a–5c** were characterized by ^{1}H, ^{13}C NMR, and HRMS or elemental analysis. Compounds **4f**[12] and **5b** were further confirmed by single-crystal X-ray diffraction analysis (Fig. 2).

A possible mechanism is proposed as shown in Scheme 4 to explain the aforementioned reactions. Triphenylphosphine **I** reacts with bromide **1** to form phosphonium salt **II**, which is deprotonated by Cs_2CO_3 to generate the corresponding

Table 3
Intramolecular phosphine-catalyzed annulation reaction[a]



Entry	2	R	5 (5/5′)[b]	Yield (%)[c]
1	**2a**	H	**5a** (93:7)	82
2	**2b**	4-Cl	**5b** (95:5)	78
3[d]	**2b**	4-Cl	**5b** (96:4)	90
4	**2c**	4-MeO	**5c** (92:8)	87

[a] PPh_3 (26 mg, 20 mol %), **5** (0.5 mmol) in CH_3Ph (0.10 M), rt, 15 min, then Na_2CO_3 (80 mg, 1.5 equiv), 90 °C, 8–12 h.
[b] Determined by 300 MHz ^{1}H NMR.
[c] Isolated yield.
[d] Using 50 mol % PPh_3.

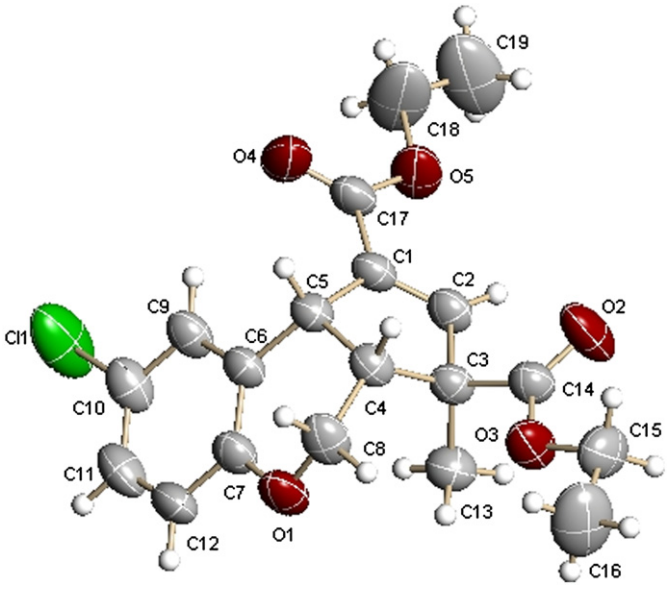
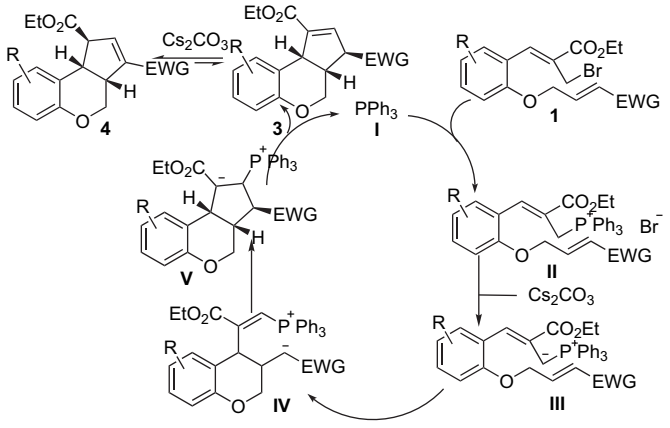


Figure 2. X-ray crystal structure of compound **5b**.



Scheme 4. A possible mechanism for the annulation reaction.

phosphonium ylide **III** in situ. An intramolecular Michael addition of the ylide, followed by a Michael addition of phosphonium salt **IV** and then β-elimination of triphenylphosphine, completes the catalytic cycle.

3. Conclusion

In summary, the controllable synthesis of benzobicyclo[4.3.0] compounds **3** and **4** with three continuous stereogenic centers has been developed. The mechanistic insight of the base effect was investigated by ^{1}H NMR monitoring and chemical experiments in detail. In addition, benzobicyclo[4.3.0] compounds with one quaternary carbon center could also be prepared with high diastereoselectivities in good yields. The high diastereoselectivity, cheap and readily available catalyst, the simple procedure, and the mild conditions make these methods potentially useful in organic synthesis. The development of its asymmetric version is 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. ^{1}H NMR and ^{13}C NMR spectra were recorded in chloroform-d_3 on a VARIAN Mercury 300.

4.2. Representative procedure for the controllable synthesis of benzobicyclo[4.3.0] compounds

4.2.1. Preparation of 1,3a,4,9b-tetrahydro-cyclopenta-[c]chromene-1,3-dicarboxylic acid diethyl ester ***4a***

To a solution of substrate **1a** (0.50 mmol, 199 mg) in CH_3Ph (5.0 mL) was added triphenylphosphine (0.10 mmol, 26 mg). The resulting mixture was stirred at room temperature for 15 min. Then Cs_2CO_3 (0.75 mmol, 245 mg) was added. The mixture was stirred at 90 °C for 8 h. After the reaction was complete, the mixture was filtered rapidly through a funnel with a thin layer of silica gel and eluted with ethyl acetate. The filtrate was concentrated and the residue was purified by chromatography on silica gel to afford the desired product **4a** as colorless oil. Yield: 96%; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.29 (d, J=7.5 Hz, 1H), 7.18–7.13 (m, 1H), 6.97–6.90 (m, 2H), 6.82 (t, J=1.5 Hz, 1H), 4.46 (dd, J=10.8 and 4.5 Hz, 1H), 4.34–4.23 (m, 4H), 3.97 (t, J=7.8 Hz, 1H), 3.76–3.65 (m, 2H), 3.52–3.47 (m, 1H), 1.38–1.32 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 163.7, 154.8, 141.7, 137.9, 129.7, 127.7, 124.4, 121.5, 117.1, 66.6, 61.6, 60.8, 58.8, 42.8, 39.5, 14.1(9), 14.1(7); IR ν/cm^{-1} 2982 (m), 2933 (m), 1734 (s), 1716 (s), 1631 (m), 1581 (m), 1490 (m), 1246 (m), 758 (m); MS (ESI, positive mode, *m*/*z*) 371 (M+MeOH+Na^+), 339 (M+Na^+), 317 (M+H^+); HRMS (EI) calcd for $C_{18}H_{20}O_5$ (M^+): 316.1311, found: 316.1304.

4.2.2. 8-Chloro-1,3a,4,9b-tetrahydro-cyclopenta[c]-chromene-1,3-dicarboxylic acid diethyl ester ***4b***

Yield 82% (oil, 10 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.31 (d, J=2.7 Hz, 1H), 7.09 (dd, J=9.0 and 2.4 Hz, 1H), 6.85–6.82 (m, 2H), 4.44 (dd, J=11.1 and 4.8 Hz, 1H), 4.36–4.22 (m, 4H), 3.91 (t, J=8.1 Hz, 1H), 3.71 (dt, J=8.1 and 2.4 Hz, 1H), 3.64 (t, J=10.2 Hz, 1H), 3.49–3.42 (m, 1H), 1.37 (t, J=7.2 Hz, 3H), 1.32 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 163.6, 153.5, 141.6, 137.7, 129.4, 127.8, 126.2, 125.9, 118.5, 66.8, 61.8, 60.9, 58.6, 42.5, 39.3, 14.2; IR ν/cm^{-1} 2983 (m), 2937 (m), 1733 (s), 1716 (s), 1632 (m), 1580 (m), 1485 (m), 1247 (m), 818 (m), 748 (m), 640 (m); MS (ESI, positive mode, *m*/z) 407 (M+MeOH+Na^+), 405 (M+MeOH+Na^+), 375 (M+Na^+), 373 (M+Na^+); HRMS (EI) calcd for $C_{18}H_{19}O_5Cl$ (M^+): 350.0921, found: 350.0923.

4.2.3. 8-Bromo-1,3a,4,9b-tetrahydro-cyclopenta[c]-chromene-1,3-dicarboxylic acid diethyl ester ***4c***

Yield 89% (oil, 11 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.45 (d, J=2.4 Hz, 1H), 7.23 (dd, J=9.0 and 2.4 Hz, 1H),

6.83–6.77 (m, 2H), 4.43 (dd, J=10.8 and 4.2 Hz, 1H), 4.36–4.20 (m, 4H), 3.91 (t, J=7.8 Hz, 1H), 3.71 (dt, J=7.8 and 2.4 Hz, 1H), 3.64 (t, J=10.2 Hz, 1H), 3.49–3.41 (m, 1H), 1.37 (t, J=7.2 Hz, 3H), 1.32 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 163.6, 154.0, 141.6, 137.6, 132.4, 130.7, 126.5, 119.0, 113.5, 66.7, 61.8, 60.9, 58.6, 42.5, 39.3, 14.2 (0), 14.1 (8); IR ν/cm^{-1} 2982 (m), 2929 (m), 1734 (s), 1716 (s), 1632 (m), 1581 (m), 1483 (m), 1247 (m), 817 (m), 748 (m); MS (ESI, positive mode, m/z) 451 (M+MeOH+Na$^+$), 449 (M+MeOH+Na$^+$), 419 (M+Na$^+$), 417 (M+Na$^+$); HRMS (EI) calcd for $C_{18}H_{19}O_5Br$ (M$^+$): 394.0416, found: 394.0419.

4.2.4. 8-Methoxy-1,3a,4,9b-tetrahydro-cyclopenta[c]-chromene-1,3-dicarboxylic acid diethyl ester **4d**

Yield 83% (oil, 11 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 6.86–6.81 (m, 3H), 6.72 (dd, J=9.0 and 3.0 Hz, 1H), 4.40 (dd, J=10.5 and 4.5 Hz, 1H), 4.32–4.23 (m, 4H), 3.93 (t, J=8.1 Hz, 1H), 3.75–3.71 (m, 4H), 3.63 (t, J=10.2 Hz, 1H), 3.48–3.45 (m, 1H), 1.37–1.30 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 163.8, 154.1, 148.8, 141.6, 137.9, 125.1, 117.8, 113.9 (1), 113.8 (7), 66.9, 61.6, 60.8, 58.9, 55.6, 42.9, 39.8, 14.2(2), 14.1(8); IR ν/cm^{-1} 2982 (m), 1734 (s), 1717 (s), 1629 (m), 1499 (m), 1246 (m), 1033 (m), 862 (m), 817 (m), 749 (m); MS (ESI, positive mode, m/z) 401 (M+MeOH+Na$^+$), 369 (M+Na$^+$), 347 (M+H$^+$); HRMS (EI) calcd for $C_{19}H_{22}O_6$ (M$^+$): 346.1416, found: 346.1417.

4.2.5. 8-Methoxy-1,3a,4,9b-tetrahydro-cyclopenta[c]-chromene-1,3-dicarboxylic acid 1-ethyl ester 3-methyl ester **4e**

Yield 85% (oil, 11 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 6.87–6.82 (m, 3H), 6.72 (dd, J=9.0 and 3.0 Hz, 1H), 4.38 (dd, J=10.8 and 4.5 Hz, 1H), 4.28 (q, J=7.2 Hz, 2H), 3.93 (t, J=8.1 Hz, 1H), 3.80 (s, 3H), 3.78–3.71 (m, 4H), 3.65 (t, J=10.2 Hz, 1H), 3.48–3.45 (m, 1H), 1.34 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 164.2, 154.1, 148.8, 142.0, 137.5, 125.1, 117.8, 113.9 (1), 113.8 (8), 66.8, 61.6, 58.9, 55.6, 51.8, 43.0, 39.8, 14.2; IR ν/cm^{-1} 2984 (m), 1732 (s), 1616 (m), 1499 (m), 1249 (m), 1031 (m), 864 (m), 817 (m), 748 (m); MS (ESI, positive mode, m/z) 387 (M+MeOH+Na$^+$), 355 (M+Na$^+$), 333 (M+H$^+$); HRMS (EI) calcd for $C_{18}H_{20}O_6$ (M$^+$): 332.1260, found: 332.1266.

4.2.6. 3-(4-Chloro-benzoyl)-1,3a,4,9b-tetrahydro-cyclopenta[c]chromene-1-carboxylic acid ethyl ester **4f**

Yield 78% (oil, 5 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.72 (d, J=8.7 Hz, 2H), 7.44 (d, J=8.7 Hz, 2H), 7.30 (d, J=7.5 Hz, 1H), 7.19–7.13 (m, 1H), 6.99–6.89 (m, 2H), 6.46 (dd, J=2.1 and 0.9 Hz, 1H), 4.47 (dd, J=11.4 and 4.2 Hz, 1H), 4.31–4.25 (m, 2H), 4.02 (t, J=6.9 Hz, 1H), 3.94–3.88 (m, 1H), 3.82 (dt, J=6.9 and 2.1 Hz, 1H), 3.76–3.69 (m, 1H), 1.33 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0, 171.8, 155.0, 144.7, 143.0, 139.1, 136.1, 130.5, 129.8, 128.7, 127.8, 124.4, 121.6, 117.3, 66.1, 61.7, 59.9, 44.2, 39.5, 14.2; IR ν/cm^{-1} 2982 (m), 1731 (s), 1646 (m), 1585 (m), 1489 (m), 1248 (m), 1014 (m), 832 (m), 760 (m), 579 (m); MS (ESI, positive mode, m/z) 437 (M+MeOH+Na$^+$), 405 (M+Na$^+$), 383 (M+H$^+$); HRMS (EI) calcd for $C_{22}H_{19}O_4Cl$ (M$^+$): 382.0972, found: 382.0968.

4.3. Representative procedure for the phosphine-catalyzed synthesis of benzobicyclo[4.3.0] compounds with one quaternary carbon center

4.3.1. Preparation of 3-methyl-3,3a,4,9b-tetrahydro-cyclopenta[c]chromene-1,3-dicarboxylic acid diethyl ester **5a**

To a solution of substrate **2a** (0.50 mmol, 206 mg) in CH_3Ph (5.0 mL) was added triphenylphosphine (0.10 mmol, 26 mg). The resulting mixture was stirred at room temperature for 15 min. Then Na_2CO_3 (0.75 mmol, 80 mg) was added. The mixture was stirred at 90 °C for 12 h. After the reaction was complete, the mixture was filtered rapidly through a funnel with a thin layer of silica gel and eluted with ethyl acetate. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel to afford the desired product **5a** as colorless oil. Yield: 82%; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.60 (d, J=7.8 Hz, 1H), 7.12–7.07 (m, 1H), 6.90–6.79 (m, 2H), 6.74 (s, 1H), 4.47–4.41 (m, 2H), 4.30–4.15 (m, 5H), 3.10 (dt, J=9.0 and 3.0 Hz, 1H), 1.44 (s, 3H), 1.34 (t, J=6.9 Hz, 3H), 1.29 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 165.3, 154.1, 145.5, 138.3, 129.9, 127.6, 123.0, 121.1, 117.3, 64.7, 61.2, 60.8, 56.9, 43.1, 41.2, 20.3, 14.2, 14.1; IR ν/cm^{-1} 2980 (m), 2933 (m), 1734 (s), 1716 (s), 1631 (m), 1580 (m), 1489 (m), 1238 (m), 759 (m); MS (ESI, positive mode, m/z) 385 (M+MeOH+Na$^+$), 353 (M+Na$^+$), 331 (M+H$^+$); HRMS (EI) calcd for $C_{19}H_{22}O_5$ (M$^+$): 330.1467, found: 330.1467.

4.3.2. 8-Chloro-3-methyl-3,3a,4,9b-tetrahydro-cyclopenta[c]chromene-1,3-dicarboxylic acid diethyl ester **5b**

Yield 78% (solid, 10 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.63 (d, J=2.7 Hz, 1H), 7.04 (dd, J=9.0 and 2.4 Hz, 1H), 6.75 (t, J=9.0 Hz, 2H), 4.46–4.13 (m, 7H), 3.09 (dt, J=9.0 and 3.0 Hz, 1H), 1.42 (s, 3H), 1.37 (t, J=7.2 Hz, 3H), 1.30 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 165.0, 152.8, 146.2, 137.8, 129.6, 127.7, 125.8, 124.5, 118.7, 64.9, 61.4, 61.0, 56.9, 42.8, 41.2, 20.3, 14.2, 14.1; IR ν/cm^{-1} 2981 (m), 2936 (m), 1733 (s), 1716 (s), 1630 (m), 1486 (m), 1240 (m), 820 (m), 640 (m); MS (ESI, positive mode, m/z) 421 (M+MeOH+Na$^+$), 419 (M+MeOH+Na$^+$), 389 (M+Na$^+$), 387 (M+Na$^+$); HRMS (EI) calcd for $C_{19}H_{21}O_5Cl$ (M$^+$): 364.1078, found: 364.1075.

4.3.3. 8-Methoxy-3-methyl-3,3a,4,9b-tetrahydro-cyclopenta[c]chromene-1,3-dicarboxylic acid diethyl ester **5c**

Yield 87% (oil, 8 h); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.22 (d, J=3.0 Hz, 1H), 6.76–6.66 (m, 3H), 4.46–4.39 (m, 2H), 4.31–4.12 (m, 5H), 3.72 (s, 3H), 3.07 (dt, J=9.0 and 3.0 Hz, 1H), 1.45 (s, 3H), 1.34 (t, J=6.9 Hz, 3H), 1.30 (t, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 165.4, 153.7, 148.0, 145.9, 138.0, 123.6, 118.0, 114.3, 113.6, 64.9, 61.2, 60.8, 57.0, 55.5, 43.1, 41.6, 20.4, 14.2,

14.1; IR ν/cm^{-1} 2980 (m), 1732 (s), 1713 (s), 1628 (m), 1498 (m), 1238 (m), 1067 (m), 947 (m), 818 (m); MS (ESI, positive mode, *m*/z) 415 (M+MeOH+Na$^+$), 383 (M+Na$^+$), 360 (M+H$^+$); HRMS (EI) calcd for $C_{20}H_{24}O_6$ (M$^+$): 360.1573, found: 360.1577.

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Supplementary data

General synthetic procedures and characterization and spectral data for key compounds, CIF for compound **5b**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.11.052.

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15. For details, please see the Supplementary data.