JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

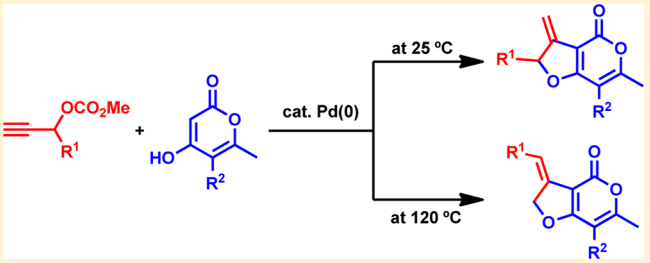
Regiocontrolled Construction of Furo[3,2-*c*]pyran-4-one Derivatives by Palladium-Catalyzed Cyclization of Propargylic Carbonates with 4-Hydroxy-2-pyrones

Masahiro Yoshida,* Tomomi Nakagawa, Kouki Kinoshita, and Kozo Shishido

Graduate School of Pharmaceutical Sciences, The University of Tokushima, 1-78-1 Sho-machi, Tokushima 770-8505, Japan

Supporting Information

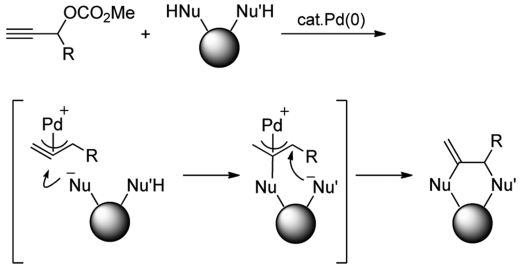
ABSTRACT: The reaction of propargylic carbonates with 4-hydroxy-2-pyrones in the presence of a palladium catalyst is described. By the choice of the reaction temperature, two types of the substituted furo[3,2-*c*]pyran-4-one derivatives were regioselectively synthesized, respectively.



Furo[3,2-*c*]pyran-4-ones are one of the important classes of heteroaromatic molecules which are components in a variety of biologically active natural products.[1] For this reason, considerable effort has been devoted toward developing a novel synthetic method for these compounds.[2,3] However, the number of applications to the synthesis of natural products is limited,[3] and development of a more practical and an efficient methodology for the synthesis of substituted furo[3,2-*c*]pyran-4-ones is still required.

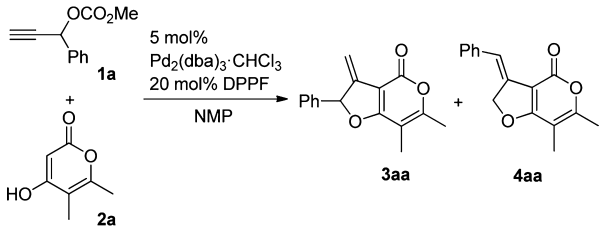
The reactivity of propargylic esters with nucleophiles in the presence of palladium catalyst have received considerable attention and has been extensively studied for the synthesis of complex molecules.[4] The reaction of propargylic compounds with bis-nucleophiles is one of the most studied processes to date.[5] In this reaction, a substrate having two nucleophilic moieties within the molecule reacted sequentially with the (π-propargyl)palladium complex, resulting from propargylic compounds and palladium catalysts, to afford the cyclized product (Scheme 1). Various hetero- and carbocyclic molecules can be synthesized in one step by the choice of adequately designed nucleophilic molecules. In planning our further investigation of this cyclization process, we focused on the nucleophilic activity of 4-hydroxy-2-pyrones. Herein, we describe a novel methodology for the synthesis of furo[3,2-*c*]pyran-4-one derivatives by the palladium-catalyzed reaction of propargylic carbonates with 4-hydroxy-2-pyrones, in which the regioselectivity of the reaction can be completely altered depending on the reaction temperature.

Scheme 1



The initial attempts were employed using methyl 1-phenyl-2-propynyl carbonate (**1a**) and 4-hydroxy-5,6-dimethyl-2*H*-pyran-2-one (**2a**) (Table 1). When **1a** and **2a** were reacted with 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 20 mol % DPPF in NMP at 25 °C, the reaction successfully proceeded to give the 2-phenyl-substituted furopyranone **3aa** in 89% yield as the sole product (Table 1, entry 1). It is interesting to note that the 3-benzylidene-subsituted furopyranone **4aa**[6] was also obtained as the reaction temperature was increased. While the reactions at

Table 1. Effect of Temperature in the Reaction of 1a with 2a



entry	temp (°C)	time (min)	product	total yield (%)
1	25	360	**3aa** only	89
2	50	60	**3aa** only	85
3	80	5	**3aa** only	85
4	100	5	**3aa**:**4aa** = 1:1.9	86
5	120	5	**4aa** only	79

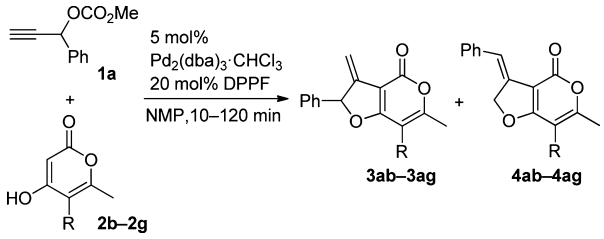
Received: December 12, 2012
Published: January 30, 2013

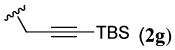
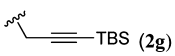
dx.doi.org/10.1021/jo3027092 | *J. Org. Chem.* 2013, 78, 1687−1692

50 and 80 °C afforded the product **3aa** solely (entries 2 and 3), the regioisomer **4aa** was produced together with **3aa** when the reaction was carried out at 100 °C (**3aa**:**4aa** = 1:1.9, 86% yield in entry 4). Furthermore, **4aa** was exclusively obtained in 79% yield in the reaction at 120 °C (entry 5). From these results, it is clear that the regioselectivity of the reaction is completely altered depending on the reaction temperature.

We next conducted the reactions of various 3-substituted 4-hydroxy-2-pyrones **2b–g** with **1a** (Table 2). When the reaction

Table 2. Reactions using Substituted Substrates 2b–g with 1a

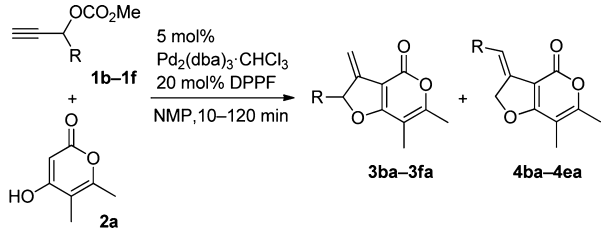


entry	R	temp. (°C)	products	yield (%)
1	H (**2b**)	25	**3ab**	47
2	Et (**2c**)	25	**3ac**	78
3	heptyl (**2d**)	25	**3ad**	64
4	allyl (**2e**)	25	**3ae**	47
5	Bn (**2f**)	25	**3af**	70
6	 (**2g**)	50	**3ag**	71
7	H (**2b**)	120	**4ab**	69
8	Et (**2c**)	120	**4ac**	71
9	*n*-heptyl (**2d**)	120	**4ad**	61
10	allyl (**2e**)	120	**4ae**	68
11	Bn (**2f**)	120	**4af**	64
12	 (**2g**)	120	**4ag**	64

of **2b**, having no substituent on the 3-position of the pyrone ring, was carried out at 25 °C, the 2-phenyl-substituted furopyranone **3ab** was obtained in 47% yield (entry 1). Under the same reaction conditions, the substrates **2c–f** containing an ethyl, a heptyl, an allyl, and a benzyl group, respectively, were converted to the corresponding products **3ac–af** in moderate yields, respectively (entries 2–5). Similarly, the furopyranone **3ag** was successfully obtained in 71% yield from the reaction of the propargyl-substituted substrate **2g** at 50 °C (entry 6). On the other hand, when the 4-hydroxy-2-pyrones **2b–g** were subjected to the reaction at 120 °C, the corresponding 3-benzylidene-subsituted furopyranones **4ab–ag** were produced as the sole products in each cases (entries 7–12).

Table 3 shows the examinations using various propargylic carbonates **1b–f** having a substituent at the propargylic position. Under the reaction conditions at 25 °C, the substrates **1b**,**c** containing a *p*-fluoro- and an *o*-fluorophenyl group successfully reacted with **2a** to produce the 2-aryl-substituted furopyranones **3ba**,**ca** in 90% and 73% yields, respectively

Table 3. Reactions using Substituted Substrates 1b–f with 2a

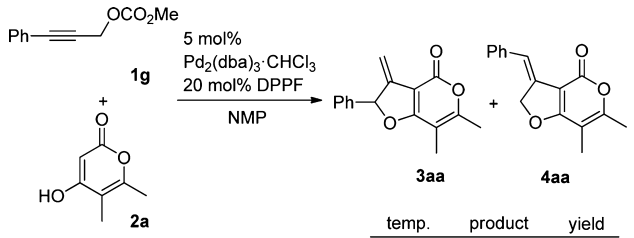


entry	R	temp (°C)	product	yield (%)
1	*p*-fluorophenyl (**1b**)	25	**3ba**	90
2	*o*-fluorophenyl (**1c**)	25	**3ca**	73
3	3-furyl (**1d**)	40	**3da**	82
4	1-naphthyl (**1e**)	25	**3ea**	93
5	pentyl (**1f**)	25	**3fa**	73
6	*p*-fluorophenyl (**1b**)	120	**4ba**	73
7	*o*-fluorophenyl (**1c**)	120	**4ca**	60
8	3-furyl (**1d**)	120	**4da**	50
9	1-naphthyl (**1e**)	120	**4ea**	67
10	pentyl (**1f**)	120		

(entries 1 and 2). Similarly, the corresponding products **3da**,**ea** were obtained in good yields from the reactions using 3-furyl- and 1-naphthyl-substituted substrates **1d**,**e** at low temperature (entries 3 and 4). The reactions of the substrate **1f**, which has a pentyl group, also afforded the cyclized product **3fa** in 73% yield (entry 5). When the substrates **2b–e** were subjected to the reactions at 120 °C, the corresponding regioisomers **4ba–ea** were selectively produced in good yields, respectively (entries 6–9). On the other hand, an unidentified mixture was only obtained from the reaction of pentyl-substituted substrate **1f** at 120 °C (entry 10).

We next attempted the reaction using propargylic carbonate **1g**, which contains a phenyl group at the terminal position (Scheme 2). When the palladium-catalyzed reactions of **1g** with

Scheme 2



temp.	product	yield
25 °C	**3aa**	93%
120 °C	**4aa**	84%

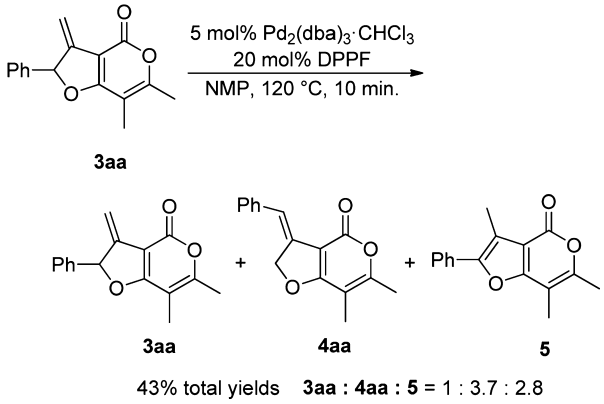
2a were carried out at 25 and 120 °C, the corresponding products **3aa** and **4aa**, which were the same products from the reaction of **1a** with **2a**, were obtained in 93% and 84% yields, respectively. Since in all cases the resulting products **3aa–ag**, **3ba–fa** and **4aa–ag**, **4ba–ea** had been obtained as the sole products, it was determined that the regioselectivity of the reaction can be completely controlled depending on the reaction temperature.

To clarify the regioselective outcome in the cyclization reaction, the reactivity of the resulting product **3aa** with palladium at high temperature was examined. When **3aa** was treated with 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 20 mol % DPPF in NMP at 120 °C, the regioisomer **4aa** was produced as a

dx.doi.org/10.1021/jo3027092 | J. Org. Chem. 2013, 78, 1687–1692

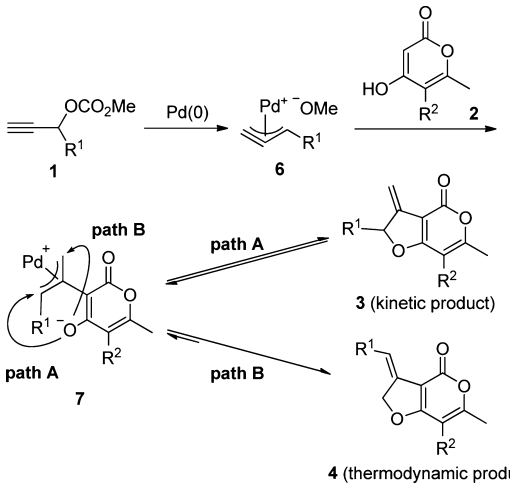
mixture with unreacted **3aa** and the *endo*-olefinic isomer **5** (Scheme 3). The result clearly indicates that conversion of the product **3** to the regioisomer **4** occurred during the reaction.

Scheme 3



A plausible mechanism for the production of the furopyranones **3** and **4** is shown in Scheme 4. By reaction

Scheme 4



with the palladium catalyst, the propargylic carbonate **1** is transformed to the (π-propargyl)palladium complex **6**, which reacts with the 4-hydroxy-2-pyrone **2** to lead to the (π-allyl) palladium intermediate **7**. The intermediate **7** is further subjected to intramolecular attack of the hydroxy anion to produce the cyclized product **3** or **4**. The observed regioselectivity dependence on the reaction temperature is likely the result of kinetic and thermodynamic control in the cyclization process.[7] In the reaction at low temperature, it is expected that the cyclization occurs via path A, which would be more favorable than path B,[8] leading to **3** as the kinetic product. On the other hand, there would be equilibrium between the products and (π-allyl)palladium intermediate **7** at high temperature. As a result, this reversible process furnished the thermodynamically more stable product **4** via path B. The result from the reaction of the propargylic carbonates **1a,j** to produce the same product **3aa** (Table 1 and Scheme 3) supports a hypothesis that both reactions proceed via the formation of the common (π-allyl)palladium intermediate **7**. As a reason for the formation of the unidentified mixture in the reaction of pentyl-substituted substrate **1f** at 120 °C (entry 10 in Table 3), it is expected that β-elimination of palladium from the corresponding (π-allyl)palladium intermediate would occur prior to the cyclization.[5l]

In summary, the studies described above have resulted in the regioselective synthesis of substituted furo[3,2-*c*]pyran-4-one derivatives by a palladium-catalyzed nucleophilic cyclization of propargylic carbonates with 4-hydroxy-2-pyrones. The regioselectivity of the reaction can be completely controlled depending on the reaction temperature. This methodology provides a new protocol for the synthesis of biologically active natural products containing a furopyranone moiety.

EXPERIMENTAL SECTION

General Considerations. All nonaqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise indicated. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. Solvents were dried and distilled according to the standard protocol. The phrase "residue upon workup" refers to the residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. Propargylic carbonates **1a,d−g**[5b,j] and 4-hydroxy-2-pyrones **2a−g**[9] were prepared according to the procedures described in the literature.

General Procedure for the Synthesis of Propargylic Carbonates 1. Synthesis of 1b. To a stirred solution of 1-(4-fluorophenyl)prop-2-yn-1-ol (660 mg, 4.40 mmol) in CH_2Cl_2 (20 mL) were added methyl chloroformate (0.41 mL, 5.28 mmol), and pyridine (1.10 mL, 13.2 mmol) at 0 °C, and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with aqueous NH_4Cl and extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (1/7 v/v) as eluent to give propargylic carbonate **1b** (844 mg, 4.06 mmol, 92%) as a yellow oil.

*1-(4-Fluorophenyl)prop-2-yn-1-yl Methyl Carbonate (**1b**):* yield: 92%, 844 mg, yellow oil; IR (neat) 1752, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.73 (1H, d, J = 2.4 Hz), 3.82 (3H, s), 6.26 (1H, d, J = 2.4 Hz), 7.05−7.11 (2H, m), 7.52−7.56 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.1 (CH_3), 68.6 (CH), 76.6 (Cq), 79.3 (CH), 115.7 (CH, d, J = 21.5 Hz), 129.8 (CH, d, J = 8.3 Hz), 131.8 (Cq), 154.7 (Cq), 163.2 (Cq, d, J = 247.8 Hz); HRMS (ESI, TOF) m/z calcd for $C_{11}H_{10}O_3F$ $[M + H]^+$ 209.0614, found 209.0614.

*1-(2-Fluorophenyl)prop-2-yn-1-yl Methyl Carbonate (**1c**):* yield 81%, 1.01 g, pale yellow oil; IR (neat) 1756, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.72 (1H, d, J = 2.4 Hz), 3.83 (3H, s), 6.57 (1H, d, J = 2.4 Hz), 7.07−7.12 (1H, m), 7.18−7.22 (1H, m) 7.35−7.41 (1H, m), 7.67−7.72 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2 (CH_3), 63.3 (CH, d, J = 5.0 Hz), 76.4 (Cq), 78.6 (CH), 115.7 (CH, d, J = 20.6 Hz), 123.2 (Cq, d, J = 13.3 Hz), 124.4 (CH, d, J = 3.3 Hz), 129.4 (CH, d, J = 2.5 Hz), 131.3 (CH, d, J = 8.2 Hz) 154.5 (Cq), 160.1 (Cq, d, J = 249.5 Hz); HRMS (ESI, TOF) m/z calcd for $C_{11}H_9O_3FNa$ $[M + Na]^+$ 231.0433, found 231.0433.

General Procedure for the Synthesis of Furopyranones 3. Synthesis of 3aa. To a stirred solution of propargylic carbonate **1a** (50.9 mg, 268 μmol) in NMP (2.0 mL) were added 4-hydroxy-5,6-dimethyl-2*H*-pyran-2-one (**2a**; 45.0 mg, 321 μmol), $Pd_2(dba)_3$·$CHCl_3$ (13.9 mg, 13.4 μmol), and DPPF (29.7 mg, 53.5 μmol) at 25 °C, and stirring was continued for 6 h at the same temperature under an argon atmosphere. After filtration of the reaction mixture using a small amount of silica gel followed by concentration, the residue was chromatographed on silica gel with AcOEt/hexane (1/4 v/v) as eluent to give the 2-phenyl-substituted furopyranone **3aa** (60.7 mg, 239 μmol, 89%) as colorless needles.

*6,7-Dimethyl-3-methylene-2-phenyl-2H-furo[3,2-c]pyran-4(3H)-one (**3aa**):* yield 89%, 60.7 mg, colorless needles (MeOH, mp 92.9−94.9 °C); IR (neat) 3034, 2929, 1728, 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, s), 2.29 (3H, s), 4.76 (1H, d, J = 2.8 Hz),

dx.doi.org/10.1021/jo3027092 | J. Org. Chem. 2013, 78, 1687−1692

5.73 (1H, t, J = 3.2 Hz), 6.18 (1H, dd, J = 2.8 and 3.2 Hz), 7.34−7.42 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (CH_3), 17.5 (CH_3), 90.6 (CH), 101.7 (Cq), 103.4 (Cq), 103.7 (CH_2), 127.6 (CH), 128.8 (CH), 129.2 (CH), 138.1 (Cq), 142.7 (Cq), 159.3 (Cq), 162.2 (Cq), 173.7 (Cq); HRMS (ESI) m/z calcd for $C_{16}H_{14}O_3Na$ $[M + Na]^+$ 277.0841, found 277.0838.

*6-Methyl-3-methylene-2-phenyl-2H-furo[3,2-c]pyran-4(3H)-one (**3ab**):* yield 47%, 15.4 mg, colorless needles (Et_2O, mp 95.2−96.3 °C); IR (neat) 3091, 2920, 1732 1572 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 4.78 (1H, d, J = 2.4 Hz), 5.73 (1H, d, J = 3.2 Hz), 6.03 (1H, s), 6.19 (1H, dd, J = 2.4 and 3.2 Hz), 7.34−7.44 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (CH_3), 90.9 (CH), 95.9 (CH), 100.6 (Cq), 101.9 (Cq), 103.9 (CH_2), 127.6 (CH), 128.9 (CH), 129.4 (CH), 138.0 (Cq), 141.9 (Cq), 166.7 (Cq), 173.6 (Cq); HRMS (ESI) m/z calcd for $C_{15}H_{12}O_3$ $[M]^+$ 240.0786, found 240.0782.

*7-Ethyl-6-methyl-3-methylene-2-phenyl-2H-furo[3,2-c]pyran-4(3H)-one (**3ac**):* yield 78%, 60.0 mg, colorless needles (MeOH, mp 87.2−88.5 °C); IR (neat) 2971, 1730, 1560 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.4 Hz), 2.30 (3H, s), 2.41 (2H, q, J = 7.4 Hz), 4.77 (1H, d, J = 2.4 Hz), 5.72 (1H, d, J = 3.2 Hz), 6.19 (1H, dd, J = 2.4 and 3.2 Hz), 7.32−7.42 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 17.1 (CH_3), 17.7 (CH_2), 90.5 (CH), 102.1 (Cq), 103.7 (CH_2), 109.7 (Cq), 127.3 (CH), 128.8 (CH), 129.2 (CH), 138.4 (Cq), 142.7 (Cq), 159.3 (Cq), 162.0 (Cq), 173.6 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{17}H_{16}O_3Na$ $[M + Na]^+$ 291.0997, found 291.0995.

*7-Heptyl-6-methyl-3-methylene-2-phenyl-2H-furo[3,2-c]pyran-4(3H)-one (**3ad**):* yield 64%, 58.0 mg, yellow oil; IR (neat) 2926, 2855, 1732, 1560 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 6.8 Hz), 1.22−1.47 (10H, m), 2.29 (3H, s), 2.37 (2H, t, J = 7.6 Hz), 4.76 (1H, d, J = 2.4 Hz), 5.71 (1H, d, J = 3.2 Hz), 6.17 (1H, dd, J = 2.4 and 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 17.3 (CH_3), 22.5 (CH_2), 24.1 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 31.6 (CH_2), 90.5 (CH), 101.1 (Cq), 103.6 (CH_2), 108.5 (Cq), 127.3 (CH), 128.8 (CH), 129.1 (CH), 138.4 (Cq), 142.8 (Cq), 159.3 (Cq), 162.2 (Cq), 173.8 (Cq); HRMS (ESI) m/z calcd for $C_{22}H_{26}O_3$ $[M]^+$ 338.1882, found 338.1888.

*7-Allyl-6-methyl-3-methylene-2-phenyl-2H-furo[3,2-c]pyran-4(3H)-one (**3ae**):* yield 47%, 38.9 mg, yellow oil; IR (neat) 3064, 1732, 1560 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (3H, s), 3.14 (2H, dt, J = 5.6 and 1.6 Hz), 4.78 (1H, d, J = 2.4 Hz), 5.01 (1H, dq, J = 17.2 and 1.6 Hz), 5.06 (1H, dq, J = 10.4 and 1.6 Hz), 5.72 (2H, d, J = 2.8 Hz), 5.81 (1H, ddt, J = 17.2, 10.4, and 5.6 Hz), 6.19 (1H, dd, J = 2.4 and 2.8 Hz), 7.36−7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3 (CH_3), 27.9 (CH_2), 90.6 (CH), 101.9 (Cq), 103.8 (CH_2), 105.7 (Cq), 115.9 (CH_2), 127.3 (CH), 128.8 (CH), 129.2 (CH), 133.6 (CH), 138.2 (Cq), 142.7 (Cq), 159.1 (Cq), 163.3 (Cq), 173.4 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{18}H_{16}O_3$ $[M]^+$ 280.1099, found 280.1093.

*7-Benzyl-6-methyl-3-methylene-2-phenyl-2H-furo[3,2-c]pyran-4(3H)-one (**3af**):* yield 70%, 37.7 mg, yellow oil; IR (neat) 3030, 1731, 1559 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (3H, s), 3.76 (2H, s), 4.79 (1H, d, J = 2.8 Hz), 5.72 (1H, d, J = 3.2 Hz), 6.18 (1H, dd, J = 2.8 and 3.2 Hz) 7.14−7.38 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 (CH_3), 29.8 (CH_2), 90.6 (CH), 102.1 (Cq), 104.0 (CH_2), 107.4 (Cq), 126.6 (CH), 127.1 (CH), 128.0 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 138.2 (Cq), 138.2 (Cq), 142.6 (Cq), 159.1 (Cq), 163.5 (Cq), 173.5 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{22}H_{18}O_3$ $[M]^+$ 330.1256, found 330.1263.

*7-[3-(tert-Butyldimethylsilyl)prop-2-yn-1-yl]-6-methyl-3-methylene-2-phenyl-2H-furo[3,2-c]pyran-4(3H)-one (**3ag**):* yield 71%, 72.9 mg, colorless needles (MeOH, mp 106.8−108.4 °C); IR (neat) 2952, 2928, 2176, 1735, 1560 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 2.39 (3H, s), 3.34 (2H, s), 4.79 (1H, d, J = 2.8 Hz), 5.73 (1H, d, J = 3.2 Hz), 6.21 (1H, d, J = 2.8 and 3.2 Hz), 7.34−7.41 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6 (CH_3), 15.1 (CH_2), 16.5 (Cq), 17.8 (CH_3), 26.0 (CH_3), 84.3 (Cq), 91.0 (CH), 101.8 (Cq), 102.1 (Cq), 104.1 (CH_2), 104.3 (Cq), 127.5 (CH), 128.9 (CH), 129.3 (CH), 138.1 (Cq), 142.6 (Cq), 158.9 (Cq), 163.9 (Cq), 172.5 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{24}H_{28}O_3SiNa$ $[M + Na]^+$ 415.1705, found 415.1702.

*2-(4-Fluorophenyl)-6,7-dimethyl-3-methylene-2H-furo[3,2-c]-pyran-4(3H)-one (**3ba**):* yield 90%, 58.7 mg, yellow needles ($CHCl_3$, mp 220.0−222.1 °C); IR (neat) 2928, 1727, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (3H, s), 2.26 (3H, s), 4.75 (1H, d, J = 2.4 Hz), 5.75 (1H, d, J = 3.2 Hz), 6.17 (1H, dd, J = 2.4 and 3.2 Hz), 7.08−7.12 (2H, m), 7.34−7.37 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (CH_3), 17.5 (CH_3), 89.9 (CH), 101.8 (Cq), 103.4 (Cq), 104.0 (CH_2), 115.8 (CH, d, J = 22.3 Hz), 129.8 (CH, d, J = 8.2 Hz), 134.1 (Cq, d, J = 3.3 Hz), 142.6 (Cq), 159.3 (Cq), 162.4 (Cq), 163.3 (Cq, d, J = 247.0 Hz), 173.6 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{16}H_{13}O_3F$ $[M]^+$ 272.0849, found 272.0848.

*2-(2-Fluorophenyl)-6,7-dimethyl-3-methylene-2H-furo[3,2-c]-pyran-4(3H)-one (**3ca**):* yield 73%, 47.8 mg, colorless plates (MeOH, mp 119.8−121.3 °C); IR (neat) 2928, 2630, 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, s), 2.29 (3H, s), 4.82 (1H, d, J = 2.8 Hz), 5.73 (1H, d, J = 2.8 Hz), 6.50 (1H, t, J = 2.8 Hz), 7.11−7.19 (2H, m), 7.25−7.33 (1H, m), 7.36−7.41 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (CH_3), 17.5 (CH_3), 84.5 (CH, d, J = 3.3 Hz), 101.7 (Cq), 103.4 (Cq), 103.6 (CH_2), 115.8 (CH, d, J = 21.5 Hz), 124.5 (CH, d, J = 3.3 Hz), 125.5 (Cq, d, J = 2.4 Hz), 128.9 (CH, d, J = 3.3 Hz), 131.0 (CH, d, J = 8.3 Hz), 141.9 (Cq), 159.2 (Cq), 160.8 (Cq, d, J = 248.7 Hz), 162.3 (Cq), 173.8 (Cq); HRMS (ESI) m/z calcd for $C_{16}H_{13}O_3F$ $[M]^+$ 272.0849, found 272.0850.

*2-(Furan-3-yl)-6,7-dimethyl-3-methylene-2H-furo[3,2-c]pyran-4(3H)-one (**3da**):* yield 82%, 41.6 mg, colorless needles ($CHCl_3$, mp 130.9−132.6 °C); IR (neat) 3133, 2926, 1723, 1563 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (3H, s), 2.27 (3H, s), 4.87 (1H, d, J = 2.8 Hz), 5.73 (1H, d, J = 3.2 Hz), 6.21 (1H, dd, J = 2.8 and 3.2 Hz), 6.41 (1H, dd, J = 1.6 and 0.8 Hz), 7.45 (1H, t, J = 1.6 Hz), 7.58 (1H, dd, J = 1.6 and 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (CH_3), 17.5 (CH_3), 83.2 (CH), 101.6 (Cq), 103.4 (CH_2), 103.5 (Cq), 109.2 (CH), 123.2 (Cq), 141.5 (Cq), 142.0 (CH), 144.1 (CH), 159.3 (Cq), 162.2 (Cq), 173.6 (Cq); HRMS (ESI) m/z calcd for $C_{14}H_{12}O_4Na$ $[M + Na]^+$ 267.0633, found 267.0639.

*6,7-Dimethyl-3-methylene-2-(naphthalen-1-yl)-2H-furo[3,2-c]-pyran-4(3H)-one (**3ea**):* yield 93%, 60.0 mg, yellow powder (MeOH, mp 149.7−151.5 °C); IR (neat) 2927, 1724, 1563 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (3H, s), 2.30 (3H, s), 4.81 (1H, d, J = 2.4 Hz), 5.81 (1H, d, J = 3.2 Hz), 6.93 (1H, dd, J = 2.4 and 3.2 Hz), 7.47−7.59 (4H, m), 7.90−7.94 (2H, m), 8.01−8.03 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (CH_3), 17.5 (CH_3), 88.5 (CH), 102.1 (Cq), 103.6 (Cq), 104.1 (CH_2), 123.4 (CH), 125.2 (CH), 126.0 (CH), 126.7 (CH), 126.8 (CH), 128.9 (CH), 130.1 (CH), 131.5 (Cq), 132.9 (Cq), 134.0 (Cq), 141.8 (Cq), 159.5 (Cq), 162.3 (Cq), 173.7 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{20}H_{16}O_3$ $[M]^+$ 304.1099, found 304.1097.

*6,7-Dimethyl-3-methylene-2-pentyl-2H-furo[3,2-c]pyran-4(3H)-one (**3fa**):* yield 73%, 36.1 mg, yellow oil; IR (neat) 2931, 1730, 1565 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.2 Hz), 1.31−1.58 (6H, m), 1.69−1.78 (1H, m), 1.81−1.89 (1H, m), 1.95 (3H, s), 2.25 (3H, s), 4.83 (1H, d, J = 2.4 Hz), 5.27−5.31 (1H, m), 5.59 (1H, d, J = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (CH_3), 13.9 (CH_3), 17.4 (CH_3), 22.4 (CH_2), 23.8 (CH_2), 31.5 (CH_2), 36.0 (CH_2,), 89.8 (CH), 100.9 (CH_2), 101.9 (Cq), 103.5 (Cq), 143.0 (Cq), 159.6 (Cq), 161.8 (Cq), 174.1 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{15}H_{20}O_3Na$ $[M + Na]^+$ 271.1310, found 271.1312.

General Procedure for the Synthesis of Furopyranones 4. Synthesis of 4aa. To a stirred solution of propargylic carbonate **1a** (52.1 mg, 274 μmol) in NMP (2.0 mL) were added 4-hydroxy-5,6-dimethyl-2*H*-pyran-2-one (**2a**; 46.0 mg, 329 μmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (14.2 mg, 13.8 μmol), and DPPF (30.4 mg, 54.8 μmol) at room temperature. The reaction mixture was immediately heated to 120 °C, and stirring was continued for 5 min at the same temperature under an argon atmosphere. After filtration of the reaction mixture using a small amount of silica gel followed by concentration, the residue was chromatographed on silica gel with AcOEt/hexane (1/4 v/v) as eluent to give the 3-benzylidene-substituted furopyranone **4aa** (55.3 mg, 217 μmol, 79%) as colorless blocks.

dx.doi.org/10.1021/jo3027092 | J. Org. Chem. 2013, 78, 1687−1692

*(Z)-3-Benzylidene-6,7-dimethyl-2H-furo[3,2-c]pyran-4(3H)-one (**4aa**):* yield 79%, 55.3 mg, colorless blocks ($CHCl_3$, mp 229.6−231.8 °C); IR (neat) 1712, 1560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.00 (3H, s), 2.29 (3H, s), 5.54 (2H, d, J = 3.2 Hz), 7.16−7.23 (4H, m), 7.35−7.39 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1 (CH_3), 17.4 (CH_3), 77.1 (CH_2), 103.3 (Cq), 103.6 (Cq), 117.9 (CH), 126.4 (CH), 127.7 (CH), 128.7 (CH), 132.1 (Cq), 137.4 (Cq), 159.5 (Cq), 161.4 (Cq), 174.0 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{16}H_{15}O_3$ $[M + H]^+$ 255.1021, found 255.1024.

*X-ray Crystallographic Analysis of Compound **4aa**.* A colorless block crystal having approximate dimensions of 0.80 × 0.50 × 0.30 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite-monochromated Mo Kα radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F was based on 2277 observed reflections ($I > 0.00\sigma(I)$) and 186 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of R = 0.084 and R_w = 0.155. Crystal data for **4aa**: $C_{16}H_{14}O_3$, M_r = 254.28, triclinic, space group $P\bar{1}$ (No. 2), a = 7.3396(6) Å, b = 8.7082(6) Å, c = 9.9553(9) Å, β = 74.592(3)°, V = 611.71(9) Å^3, Z = 2, D_c = 1.380 g/cm^3, $F(000)$ = 268.00, μ(Mo Kα) = 0.95 cm^{-3}.

*(Z)-3-Benzylidene-6-methyl-2H-furo[3,2-c]pyran-4(3H)-one (**4ab**):* yield 69%, 29.4 mg, yellow needles ($CHCl_3$, mp 187.7−190.4 °C); IR (neat) 1720, 1573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (3H, s), 5.54 (2H, d, J = 3.2 Hz), 6.08 (1H, s), 7.16−7.24 (4H, m), 7.35−7.39 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (CH_3), 77.2 (CH_2), 96.0 (CH), 103.4 (Cq), 118.0 (CH), 126.5 (CH), 127.8 (CH), 128.7 (CH), 131.3 (Cq), 137.2 (Cq), 159.5 (Cq), 165.8 (Cq), 173.8 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{15}H_{12}O_3$ $[M]^+$ 240.0786, found 240.0784.

*(Z)-3-Benzylidene-7-ethyl-6-methyl-2H-furo[3,2-c]pyran-4(3H)-one (**4ac**):* yield 71%, 54.0 mg, yellow needles (MeOH, mp 205.5−206.9 °C); IR (neat) 2963, 1720, 1558 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, t, J = 7.6 Hz), 2.31 (3H, s), 2.44 (2H, q, J = 7.6 Hz), 5.55 (2H, d, J = 3.2 Hz), 7.16−7.23 (4H, m), 7.36−7.39 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (CH_3), 17.0 (CH_3), 17.8 (CH_2), 77.0 (CH_2), 103.6 (Cq), 109.9 (Cq), 117.9 (CH), 126.4 (CH), 127.7 (CH), 128.7 (CH), 132.0 (Cq), 137.4 (Cq), 159.5 (Cq), 161.2 (Cq), 173.8 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{17}H_{16}O_3Na$ $[M + Na]^+$ 291.0997, found 291.1004.

*(Z)-3-Benzylidene-7-heptyl-6-methyl-2H-furo[3,2-c]pyran-4(3H)-one (**4ad**):* yield 61%, 55.2 mg, yellow needles (MeOH, mp 152.1−153.9 °C); IR (neat) 2953, 2927, 2855, 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.0 Hz), 1.25−1.53 (10H, m), 2.30 (3H, s), 2.40 (2H, t, J = 7.8 Hz), 5.54 (2H, d, J = 3.2 Hz), 7.16−7.26 (4H, m), 7.35−7.39 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 17.3 (CH_3), 22.6 (CH_2), 24.3 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 31.7 (CH_2), 77.0 (CH_2), 103.5 (Cq), 108.6 (Cq), 117.8 (CH), 126.4 (CH), 127.7 (CH), 128.7 (CH), 132.1 (Cq), 137.3 (Cq), 159.5 (Cq), 161.4 (Cq), 173.9 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{22}H_{26}O_3Na$ $[M + Na]^+$ 361.1780, found 361.1780.

*(Z)-7-Allyl-3-benzylidene-6-methyl-2H-furo[3,2-c]pyran-4(3H)-one (**4ae**):* yield 68%, 47.2 mg, yellow needles ($CHCl_3$, mp 184.1−187.6 °C); IR (neat) 2923, 1720, 1560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (3H, s), 3.18 (2H, dt, J = 5.6 and 1.6 Hz), 5.04 (1H, dq, J = 16.8 and 1.6 Hz), 5.09 (1H, dq, J = 10.4 and 1.6 Hz), 5.54 (2H, d, J = 3.2 Hz), 5.84 (1H, ddt, J = 16.8, 10.4, and 5.6 Hz), 7.16−7.23 (4H, m), 7.35−7.39(2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3 (CH_3), 28.0 (CH_2), 77.1 (CH_2), 103.5 (Cq), 105.9 (Cq), 116.1 (CH_2), 118.0 (CH), 126.4 (CH), 127.7 (CH), 128.7 (CH), 131.9 (Cq), 133.6 (CH), 137.3 (Cq), 159.3 (Cq), 162.5 (Cq), 173.6 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{18}H_{16}O_3$ $[M]^+$ 280.1099, found 280.1089.

*(Z)-7-Benzyl-3-benzylidene-6-methyl-2H-furo[3,2-c]pyran-4(3H)-one (**4af**):* yield 64%, 55.4 mg, yellow needles (MeOH, mp 197.0−198.3 °C); IR (neat) 1728, 1557 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 3.80 (2H, s), 5.54 (2H, d, J = 2.8 Hz), 7.15−7.39 (11H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7 (CH_3), 29.8 (CH_2), 77.2 (CH_2), 103.7 (Cq), 107.3 (Cq), 118.2 (CH), 126.5 (CH), 126.7 (CH), 127.7 (CH), 127.9 (CH), 128.7 (CH), 128.7 (CH), 131.8 (Cq), 137.3 (Cq), 138.1 (Cq), 159.3 (Cq), 162.7 (Cq), 173.6 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{22}H_{19}O_3$ $[M + H]^+$ 331.1334, found 331.1337.

*(Z)-3-Benzylidene-7-[3-(tert-butyldimethylsilyl)prop-2-yn-1-yl]-6-methyl-2H-furo[3,2-c]pyran-4(3H)-one (**4ag**):* yield 64%, 64.9 mg, yellow needles ($CHCl_3$, mp 109.9−112.5 °C); IR (neat) 2952, 2927, 2856, 2171, 1718, 1560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.91 (9H, s), 2.40 (3H, s), 3.38 (2H, s), 5.56 (2H, d, J = 3.2 Hz), 7.16−7.26 (4H, m), 7.36−7.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7 (CH_3), 15.0 (CH_2), 16.5 (Cq), 17.7 (CH_3), 26.0 (CH_3), 77.3 (CH_2), 84.4 (Cq), 101.8 (Cq), 103.6 (Cq), 104.3 (Cq), 118.2 (CH), 126.5 (CH), 127.8 (CH), 128.7 (CH), 131.8 (Cq), 137.2 (Cq), 159.0 (Cq), 163.1 (Cq), 172.6 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{24}H_{29}O_3Si$ $[M + H]^+$ 393.1886, found 393.1885.

*(Z)-3-(4-Fluorobenzylidene)-6,7-dimethyl-2H-furo[3,2-c]pyran-4(3H)-one (**4ba**):* yield 73%, 62.3 mg, colorless needles ($CHCl_3$, mp 220.0−222.1 °C); IR (neat) 2922, 1710, 1563 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.00 (3H, s), 2.29 (3H, s), 5.50 (2H, d, J = 3.2 Hz), 7.04−7.16 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1 (CH_3), 17.4 (CH_3), 76.9 (CH_2), 103.2 (Cq), 103.6 (Cq), 115.7 (CH, d, J = 21.4 Hz), 116.8 (CH), 129.2 (CH, d, J = 7.3 Hz), 131.6 (Cq), 133.6 (Cq), 159.5 (Cq), 161.3 (Cq, d, J = 246.2 Hz), 161.5 (Cq), 173.9 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{16}H_{14}O_3F$ $[M + H]^+$ 273.0927, found 273.0927.

*(Z)-3-(2-Fluorobenzylidene)-6,7-dimethyl-2H-furo[3,2-c]pyran-4(3H)-one (**4ca**):* yield 60%, 45.1 mg, yellow needles ($CHCl_3$, mp 208.6−212.1 °C); IR (neat) 2360, 1719, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.99 (3H, s), 2.29 (3H, s), 5.45 (2H, d, J = 3.2 Hz), 7.05−7.27 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (CH_3), 17.5 (CH_3), 77.2 (CH_2), 103.2 (Cq), 103.6 (Cq), 110.0 (CH, d, J = 5.0 Hz), 115.8 (CH, d, J = 23.1 Hz), 124.0 (CH, d, J = 4.1 Hz), 125.2 (Cq, d, J = 13.2 Hz), 128.1 (CH, d, J = 9.1 Hz), 128.3 (CH, d, J = 3.4 Hz), 134.3 (Cq), 159.3 (Cq), 159.7 (Cq, d, J = 248.6 Hz), 161.8 (Cq), 174.6 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{16}H_{13}O_3F$ $[M]^+$ 272.0849, found 272.0850.

*(Z)-3-(Furan-3-ylmethylene)-6,7-dimethyl-2H-furo[3,2-c]pyran-4(3H)-one (**4da**):* yield 50%, 43.0 mg, yellow needles ($CHCl_3$, mp 186.3−190.2 °C); IR (neat) 2357, 1708, 1568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.99 (3H, s), 2.29 (3H, s), 5.35 (2H, d, J = 3.2 Hz), 6.34−6.36 (1H, m), 6.94 (1H, t, J = 3.2 Hz), 7.36−7.38 (1H, m), 7.43−7.45 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (CH_3), 17.4 (CH_3), 77.1 (CH_2), 102.9 (Cq), 103.7 (Cq), 107.4 (CH), 109.7 (CH), 123.5 (Cq), 130.8 (Cq), 140.2 (CH), 143.5 (CH), 149.5 (Cq), 161.2 (Cq), 174.2 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{14}H_{12}O_4$ $[M]^+$ 244.0736, found 244.0740.

*(Z)-6,7-Dimethyl-3-(naphthalen-1-ylmethylene)-2H-furo[3,2-c]-pyran-4(3H)-one (**4ea**):* yield 67%, 53.1 mg, yellow powder ($CHCl_3$, mp 198.8−202.3 °C); IR (neat) 2360, 1702, 1560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.00 (3H, s), 2.32 (3H, s), 5.48 (2H, d, J = 3.2 Hz), 7.21−7.22 (1H, m), 7.44−7.55 (3H, m), 7.74−7.76 (1H, m), 7.80−7.86 (2H, m), 8.21−8.23 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1 (CH_3), 17.5 (CH_3), 77.2 (CH_2), 103.3 (Cq), 103.7 (Cq), 114.8 (CH), 123.9 (CH), 124.6 (CH), 125.2 (CH), 126.1 (CH), 126.2 (CH), 127.4 (CH), 128.4 (CH), 131.4 (Cq), 133.8 (Cq), 134.2 (Cq), 134.4 (Cq), 159.6 (Cq), 161.6 (Cq), 174.5 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{20}H_{16}O_3$ $[M]^+$ 304.1099, found 304.1096.

*3,6,7-Trimethyl-2-phenyl-4H-furo[3,2-c]pyran-4-one (**5**):* yield 16% from **3aa**, 5.0 mg, colorless needles ($CHCl_3$, mp 157.0−158.2 °C); IR (neat) 2360, 2341, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.20 (3H, s), 2.32 (3H, s), 2.57 (3H, s), 7.31−7.37 (1H, m), 7.45−7.52 (2H, m), 7.68−7.71 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.2 (CH_3), 10.0 (CH_3), 16.8 (CH_3), 103.3 (Cq), 110.3 (Cq), 115.0 (CH_q), 126.0 (CH), 127.9 (CH), 128.7 (CH), 130.3 (Cq), 149.8 (Cq), 155.4 (Cq), 160.4 (Cq), 161.1 (Cq); HRMS (ESI, TOF) m/z calcd for $C_{16}H_{15}O_3$ $[M + H]^+$ 255.1021, found 255.1020.

dx.doi.org/10.1021/jo3027092 | J. Org. Chem. 2013, 78, 1687−1692

■ ASSOCIATED CONTENT

Supporting Information

A CIF file and figures giving X-ray crystallographic data for **4aa** and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yoshi@tokushima-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was supported in part by a Grant-in-Aid for the Encouragement of Young Scientists (B) from the Japan Society for the Promotion of Science (JSPS) and the Program for the Promotion of Basic and Applied Research for Innovations in the Bio-oriented Industry (BRAIN).

■ REFERENCES

(1) Representative examples: (a) Cho, J.-Y.; Kwon, Y.-J.; Sohn, M.-J.; Seok, S.-J.; Kim, W.-G. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1716. (b) Lee, I.-K.; Han, M.-S.; Lee, M.-S.; Kim, Y.-S.; Yun, B.-S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5459. (c) Yang, Y.-L.; Liao, W.-Y.; Liu, W.-Y.; Liaw, C.-C.; Shen, C.-N.; Huang, Z.-Y.; Wu, S.-H. *Chem. Eur. J.* **2009**, *15*, 11573. (d) Lee, I.-K.; Seok, S.-J.; Kim, W.-K.; Yun, B.-S. *J. Nat. Prod.* **2006**, *69*, 299. (e) Mo, S.; Wang, S.; Zhou, G.; Yang, Y.; Li, Y.; Chen, X.; Shi, J. *J. Nat. Prod.* **2004**, *67*, 823. (f) Macías, F. A.; Varela, R. M.; Simonet, A. M.; Cutler, H. G.; Cutler, S. J.; Ross, S. A.; Dunbar, D. C.; Dugan, F. M.; Hill, R. A. *Tetrahedron Lett.* **2000**, *41*, 2683. (g) Macías, F. A.; Varela, R. M.; Simonet, A. M.; Cutler, H. G.; Cutler, S. J.; Dugan, F. M.; Hill, R. A. *J. Org. Chem.* **2000**, *65*, 9039. (h) Ishiguro, K.; Nagata, S.; Fukumoto, H.; Yamaki, M.; Isoi, K.; Yamagata, Y. *Phytochemistry* **1994**, *37*, 283.

(2) (a) Hikem-Oukacha, D.; Rachedi, Y.; Hamdi, M.; Silva, A. M. S. *J. Heterocycl. Chem.* **2010**, *48*, 31. (b) Rueping, M.; Parra, A.; Uria, U.; Besselievre, F.; Merino, E. *Org. Lett.* **2010**, *12*, 5680. (c) Ye, Y.; Wang, L.; Fan, R. *J. Org. Chem.* **2010**, *75*, 1760. (d) Majumdar, K. C.; Biswas, A.; Mukhopadhyay, P. P. *Can. J. Chem.* **2005**, *83*, 2046. (e) Takikawa, H.; Hirooka, M.; Sasaki, M. *Tetrahedron Lett.* **2002**, *43*, 1713. (f) Kobayashi, K.; Sakashita, K.; Akamatsu, H.; Tanaka, K.; Uchida, M.; Uneda, T.; Kitamura, T.; Morikawa, O.; Konishi, H. *Heterocycles* **1999**, *51*, 2881. (g) Hagiwara, H.; Sato, K.; Suzuki, T.; Ando, M. *Heterocycles* **1999**, *51*, 497. (h) Hagiwara, H.; Sato, K.; Suzuki, T.; Ando, M. *Tetrahedron Lett.* **1997**, *38*, 2103. (i) Dauzonne, D.; Josien, H.; Demerseman, P. *Tetrahedron* **1990**, *46*, 7359. (j) Saalfrank, R. W.; Guendel, J.; Rossmann, G.; Hanek, M.; Rost, W.; Peters, K.; Von Schnering, H. G. *Chem. Ber.* **1990**, *123*, 1175. (k) Effenberger, F.; Ziegler, T.; Schoenwaelder, K. H. *Chem. Ber.* **1985**, *118*, 741.

(3) (a) Yokoe, H.; Mitsuhashi, C.; Matsuoka, Y.; Yoshimura, T.; Yoshida, M.; Shishido, K. *J. Am. Chem. Soc.* **2011**, *133*, 8854. (b) Takikawa, H.; Hirooka, M.; Sasaki, M. *Tetrahedron Lett.* **2003**, *44*, 5235. (c) Takikawa, H.; Imamura, Y.; Sasaki, M. *Tetrahedron* **2006**, *62*, 39. (d) Hagiwara, H.; Sato, K.; Nishino, D.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2946.

(4) (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 1995; p 453. (b) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Wiley: Chichester, U.K., 2004; p 543. (c) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589. (d) Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.* **2011**, *44*, 111 and references therein. (e) Yoshida, M. *Chem. Pharm. Bull.* **2012**, *60*, 285.

(5) (a) Tsuji, J.; Watanabe, I.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196. (b) Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organomet. Chem.* **1987**, *334*, 225. (c) Geng, L.-F.; Lu, X.-Y. *Chin. J. Chem.* **1993**, *11*, 91. (d) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025. (e) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Org. Lett.* **2000**, *2*, 527. (f) Damez, C.; Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **2003**, *44*, 557. (g) Duan, X.-H.; Liu, X.-Y.; Guo, L.-N.; Liao, M.-C.; Liu, W.-M.; Liang, Y.-M. *J. Org. Chem.* **2005**, *70*, 6980. (h) Yoshida, M.; Higuchi, M.; Shishido, K. *Tetrahedron Lett.* **2008**, *49*, 1678. (i) Yoshida, M.; Higuchi, M.; Shishido, K. *Org. Lett.* **2009**, *11*, 4752. (j) Yoshida, M.; Higuchi, M.; Shishido, K. *Tetrahedron* **2010**, *66*, 2675. (k) Yoshida, M.; Sugimura, C.; Shishido, K. *Org. Lett.* **2011**, *13*, 3482. (l) Yoshida, M.; Ohno, S.; Shishido, K. *Chem. Eur. J.* **2012**, *18*, 1604.

(6) The structure of the resulting product **4aa** was confirmed by an X-ray crystallographic analysis.

(7) For other examples of regio- or stereochemical control depending on the reaction temperature, see: (a) Blaskovich, M. A.; Rickards, R. W. *Tetrahedron Lett.* **1998**, *39*, 3617. (b) Arai, Y.; Nakazaki, J.; Segawa, H. *Tetrahedron Lett.* **2008**, *49*, 5810. (c) Alonso, F.; Davies, S. G.; Elend, A. S.; Smith, A. D. *Org. Biomol. Chem.* **2009**, *7*, 518.

(8) It is known that intramolecular nucleophilic attack at the (π-allyl) palladium predominantly occurs at the more substituted carbon.[4,5]

(9) Yoshida, M.; Takai, H.; Shishido, K. *Heterocycles* **2010**, *82*, 881.