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Electrophilic Cyclization of 2-(2′,3′-Allenyl)acetylacetates with Iodine Using Calcium Hydride as the Base

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A facile and efficient protocol for the synthesis of 4,5-dihydrofuran derivatives via iodine-mediated cyclization of various 2-(2′,3′-allenyl)acetylacetates with CaH_2 as the base has been developed. The yields range from moderate to good. The resulting products can be used for further elaboration by palladium-catalyzed coupling reactions.

Introduction

Heterocycles are extremely important in organic chemistry, medicinal chemistry, and natural products chemistry.[1,2] In particular, furan and dihydrofuran derivatives are constituents of a number of biologically active compounds and are also important intermediates in organic synthesis.[3] Thus, the development of efficient methods for the synthesis of dihydrofuran derivatives is still of high interest.[4] Recently, electrophilic cyclizations of functionalized alkynes[5,6] and allenes[7] have been developed as efficient methods for the synthesis of heterocycles under mild conditions. Furthermore, the iodine-containing substrates leave further opportunity for elaboration such as transition-metal-catalyzed transformations. In 2007, Liang reported an electrophilic cyclization of acetylenic malonates and ketones for the synthesis of indene derivatives;[8] Barluenga et al. reported iodocarbocyclization of 2-(3′-alkynyl)acetylacetates to give iodocyclopentenes;[9] Recently, we reported the Pd- and Au-catalyzed cyclization of 2-(2′,3′-allenyl)-acetylacetates to construct cyclic compounds.[10] In our continuous interest in electrophilic iodocyclization of functionalized allenes,[11] we envisioned iodocyclization of 2-(2′,3′-allenyl)acetylacetates. Herein, we disclosed a facile and efficient protocol for the construction of 4,5-dihydrofuran derivatives by iodocyclization of 2-(2′,3′-allenyl)acetylacetates.

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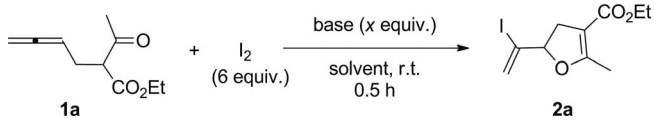
Results and Discussion

The initial electrophilic cyclization experiment was conducted by using 2-(2′,3′-allenyl)acetylacetate (**1a**), I_2 (6 equiv.), and *t*BuOK (1.2 equiv.) in THF at room temperature. We detected the formation of 4,5-dihydrofuran **2a** in only 18% yield, as determined by NMR spectroscopy (Table 1, Entry 1). To improve the yield, a series of bases including K_2CO_3, K_3PO_4, and NaOH were investigated, and they all showed better results than *t*BuOK for the formation of **2a** (Table 1, Entries 2–4). Using bases such as Et_3N and NaH, the reactions afforded **2a** in good yields (Table 1, Entries 5 and 6). Further study revealed that the use of more convenient and user friendly CaH_2 as base afforded the best result, as **2a** was formed in 80% yield under these conditions (Table 1, Entry 7). Subsequent study of the

Table 1. Base and solvent effects of the iodocyclization of 2-(2′,3′-allenyl)acetylacetates.[a]



1a 2a

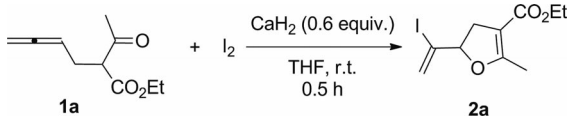
Entry	Solvent	Base (*x* equiv.)	Yield of **2a** [%][b]
1	THF	*t*BuOK (1.2)	18
2	THF	K_2CO_3 (1.2)	28
3	THF	K_3PO_4 (1.2)	54
4	THF	NaOH (1.2)	57
5	THF	Et_3N (1.2)	70
6	THF	NaH (1.2)	75
7	THF	CaH_2 (0.6)	80
8	CH_3CN	CaH_2 (0.6)	67
9	CH_3NO_2	CaH_2 (0.6)	56
10	Et_2O	CaH_2 (0.6)	28
11	toluene	CaH_2 (0.6)	22
12	CH_2Cl_2	CaH_2 (0.6)	37

[a] The reaction was carried out with **1a** (0.2 mmol), I_2 (1.2 mmol), and base in the indicated solvent (2 mL). [b] Determined by ^1H NMR spectroscopic analysis by using 1,3,5-trimethylbenzene as the internal standard.

solvent effects indicated that the solvent was also critical for this reaction (Table 1, Entries 7–12): in comparison with CH_3CN, CH_3NO_2, Et_2O, toluene, and CH_2Cl_2, THF gave the best yield.

Using CaH_2 (0.6 equiv.) as the base and THF as the solvent, the effect of the loading of I_2 was also investigated. A decrease in the loading of I_2 to 5 or 4 equiv. showed a limited effect on the yield (Table 2, Entries 2 and 3). However, a further decrease in the loading of I_2 influenced the reaction yield dramatically (Table 2, Entries 4–6). By balanced consideration of yield and the amount of I_2, the following optimized reaction conditions were defined for further study: CaH_2 (0.6 equiv.), I_2 (4 equiv.), and THF at room temperature (Table 2, Entry 3).

Table 2. Effect of the amount of I_2 on the iodine-mediated cyclization of 2-(2′,3′-allenyl)acetylacetates.[a]

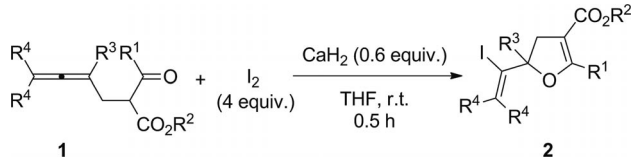


Entry	I_2 [equiv.]	Yield of **2a** [%][b]
1	6	80
2	5	79
3	4	76 (74)[c]
4	3	62
5	2	34[d]
6	1	7[e]

[a] The reaction was carried out with **1a** (0.2 mmol) and CaH_2 (0.12 mmol) in THF (2 mL). [b] Determined by ^1H NMR spectroscopic analysis by using 1,3,5-trimethylbenzene as the internal standard. [c] Number shown in parentheses is the isolated yield. [d] 17% of starting material **1a** remained. [e] 42% of starting material **1a** remained.

To test the versatility of this iodocyclization strategy, the reaction of various 2-(2′,3′-allenyl)acetylacetates **1** with I_2 were studied (Table 3). To our delight, the reaction of **1a** conducted on *one-gram scale* afforded product **2a** in a high yield (Table 3, Entry 2). The reaction of substrates **1b–f** bearing different R^1 groups, such as alkyl, benzyl, and phenyl, afforded the corresponding 4,5-dihydrofurans **2b–f** in moderate to good yields (Table 3, Entries 3–7). An R^3 substituent may also be introduced onto the allene moiety to afford the same type of products with a quaternary carbon atom in good yields (Table 3, Entries 8 and 9). In addition, the reaction of 2-(2′,3′-allenyl)acetylacetates **1i** and **1j** bearing two substituents at the terminal position of the allenyl moiety also afforded the corresponding 4,5-dihydrofurans **2i** and **2j** smoothly (Table 3, Entries 10 and 11).

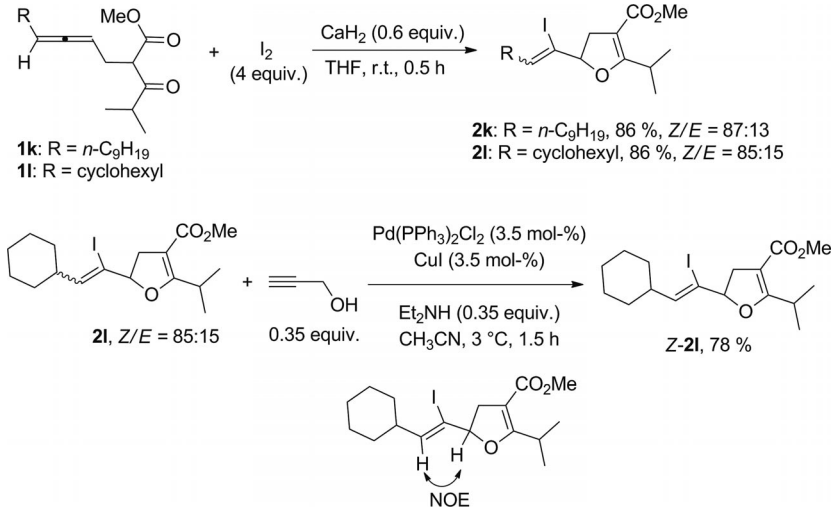
Table 3. Iodine-mediated cyclization of 2-(2′,3′-allenyl)acetylacetates.[a]



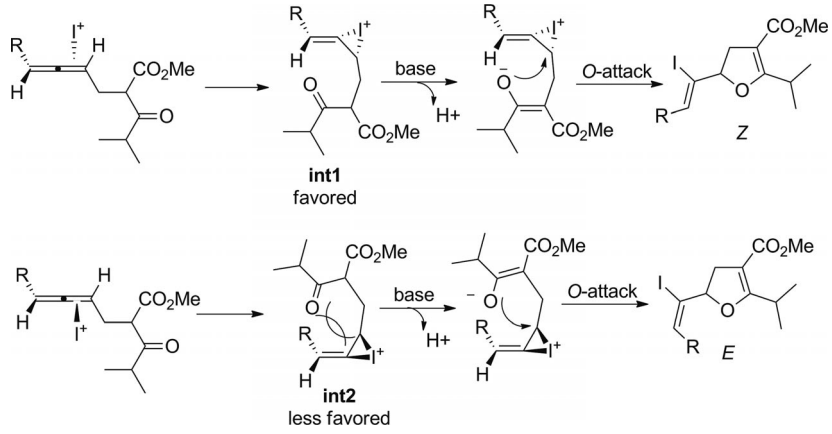
Entry	$R^1/R^2/R^3/R^4$ (**1**)	Yield of **2** [%][b]
1	CH_3/Et/H/H (**1a**)	74 (**2a**)
2	CH_3/Et/H/H (**1a**)	78 (**2a**)[c]
3	CH_3/CH_3/H/H (**1b**)	66 (**2b**)
4	Et/CH_3/H/H (**1c**)	72 (**2c**)
5	*i*Pr/CH_3/H/H (**1d**)	80 (**2d**)
6	Bn/CH_3/H/H (**1e**)	61 (**2e**)[d]
7	Ph/Et/H/H (**1f**)	83 (**2f**)
8	CH_3/Et/Et/H (**1g**)	82 (**2g**)
9	*i*Pr/CH_3/Bn/H (**1h**)	70 (**2h**)
10	*i*Pr/CH_3/H/CH_3 (**1i**)	83 (**2i**)
11	*i*Pr/CH_3/H/$(CH_2)_5$ (**1j**)	52 (**2j**)

[a] The reaction was carried out with **1** (0.2 mmol) and CaH_2 (0.12 mmol) in THF (2 mL). [b] Isolated yield. [c] The reaction was carried out on a 1-g scale. [d] Reaction time: 50 min.

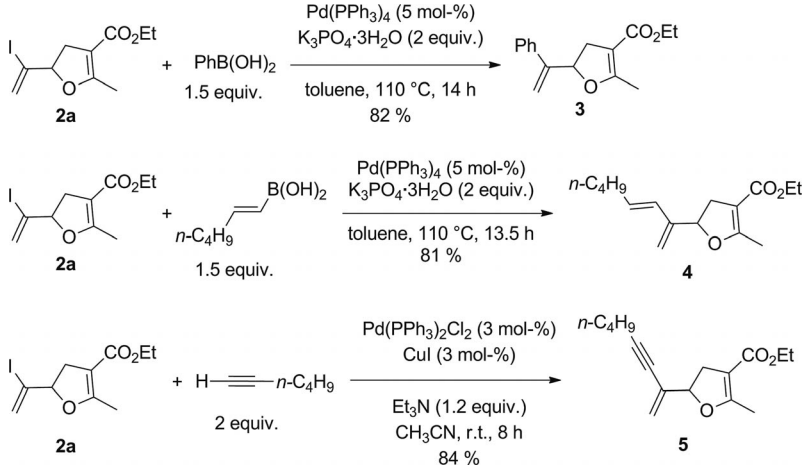
However, when there is only one substituent at the terminal position of the allenyl moiety, the reaction of **1k** and **1l** afforded the corresponding products **2k** and **2l** as a mix-



Scheme 1.



Scheme 2.



Scheme 3.

ture of stereoisomers in *Z*/*E* ratios of 87:13 and 85:15, respectively, in good yields. Further kinetic resolution via Sonogashira coupling[12] afforded *Z*-**2l** as the only isomer, and the relative C=C bond configuration was confirmed by its ^{1}H–^{1}H NOESY study (Scheme 1 and Supporting Information).

A rationale for the stereoselectivity is shown in Scheme 2: the regioselective facile interaction of I_2 with the C=C bond close to the nucleophilic group leads to the formation of three-membered iodonium intermediates **int1** and **int2**. Due to the steric interaction between the R group and the nucleophilic group, **int2** is less favored than **int1**.[13] Subsequent deprotonation and *anti*-attack of the enolic oxygen would afford the 4,5-dihydrofuran with the *Z* isomer as the major product.

The formation of the C–I bond via this iodocyclization protocol leaves further opportunity for elaboration.[14] For example, the Suzuki–Miyaura coupling of **2a** with phenylboronic acid or (1*E*)-hexenylboronic acid afforded C-substituted derivative **3** or **4** in good yield, respectively;[15] Sonogashira coupling of **2a** with 1-hexyne proceeded smoothly to afford product **5** in 84% yield (Scheme 3).[16]

Conclusions

In conclusion, we have developed a facile and efficient protocol for the synthesis of 4,5-dihydrofuran derivatives via electrophilic cyclization of various 2-(2′,3′-allenyl)acetylacetates with I_2. The reaction proceeds smoothly at room temperature within a short period of time. Subsequent elaboration of the resulting products by palladium-catalyzed coupling reactions leads to some other dihydrofuran skeletons. Further studies in this area are being carried out in our laboratory.

Experimental Section

General Information: All reactions were carried out in oven-dried Schlenk tubes. THF and toluene were distilled from sodium wire with diphenyl ketone as the indicator. CH_3CN was dried with calcium hydride before distillation. NMR spectra were recorded with a Bruker AM-300 instrument. Chemical shifts are reported in ppm relative to TMS or solvent residual peaks [^{1}H: δ = 0.00 ppm (TMS), δ = 7.26 ppm ($CDCl_3$); ^{13}C: δ = 77.0 ppm ($CDCl_3$)]. IR spectra were measured with a Nexus FT-IR spectrometer or a Bruker Ten-

sor27 instrument. MS analyses were performed with an Agilent Technologies 5975C instrument. HRMS analyses were performed with a Waters GCT Premier instrument. Elemental analyses were carried out with a Vario EL III instrument.

Typical Procedure for the Iodine-Mediated Cyclization of 2-(2′,3′-Allenyl)acetylacetates

3-(Ethoxycarbonyl)5-(1′-iodovinyl)-2-methyl-4,5-dihydrofuran (2a): To a flame-dried Schlenk tube was added CaH_2 (5.2 mg, 0.12 mmol) and THF (1 mL). The resulting mixture was stirred at room temperature for 5 min, and then I_2 (205.0 mg, 0.8 mmol), **1a** (36.2 mg, 0.2 mmol), and THF (1 mL) were added to the above solution. The mixture was stirred at room temperature and monitored by TLC. After 0.5 h, the reaction mixture was quenched by a saturated aqueous solution of $Na_2S_2O_3$ (10 mL), extracted with Et_2O (3× 15 mL), and dried with anhydrous Na_2SO_4. After filtration and evaporation of the solvent, chromatography on silica gel (petroleum ether/dichloromethane, 1:1) afforded **2a** (45.2 mg, 74%) as a liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.38 (s, 1 H, one proton of H_2C=C), 5.87 (s, 1 H, one proton of H_2C=C), 4.83 (dd, J = 10.5, 7.8 Hz, 1 H, OCH), 4.17 (q, J = 7.2 Hz, 2 H, CO_2CH_2), 3.07 (dd, J = 13.7, 11.9 Hz, 1 H, one proton of C=CCH_2), 2.76 (dd, J = 14.9, 7.7 Hz, 1 H, one proton of C=CCH_2), 2.22 (s, 3 H, C=CCH_3), 1.28 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 166.9, 165.6, 125.9, 111.1, 101.7, 85.6, 59.6, 36.7, 14.4, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2979, 1696, 1654, 1618, 1445, 1381, 1314, 1255, 1220, 1171, 1142, 1126, 1080, 1017 cm^{-1}. MS (70 eV, EI): m/z (%) = 308 (26.06) $[M]^+$, 43 (100). HRMS: calcd for $C_{10}H_{13}O_3I$ $[M]^+$ 307.9909; found 307.9911.

Synthesis of 3-(Ethoxycarbonyl)-5-(1′-iodovinyl)-2-methyl-4,5-dihydrofuran 2a On One-Gram Scale: To a flame-dried Schlenk flask was added CaH_2 (139.1 mg, 3.3 mmol) and THF (30 mL). The resulting mixture was stirred at room temperature for 10 min, and then I_2 (5.5840 g, 22.0 mmol) and **1a** (1.0014 g, 5.5 mmol) were added to the above solution. After 0.5 h, the reaction mixture was quenched by saturated aqueous $Na_2S_2O_3$ (40 mL), extracted with Et_2O (3× 40 mL), and dried with anhydrous Na_2SO_4. After filtration and evaporation of the solvent, chromatography on silica gel (petroleum ether/dichloromethane, 1:1) afforded **2a** (1.3207 g, 78%) as a liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.39 (s, 1 H, one proton of H_2C=C), 5.86 (s, 1 H, one proton of H_2C=C), 4.83 (dd, J = 10.2, 7.8 Hz, 1 H, OCH), 4.17 (q, J = 7.2 Hz, 2 H, CO_2CH_2), 3.07 (dd, J = 14.4, 11.1 Hz, 1 H, one proton of C=CCH_2), 2.76 (dd, J = 15.0, 7.5 Hz, 1 H, one proton of C=CCH_2), 2.22 (s, 3 H, C=CCH_3), 1.28 (t, J = 7.2 Hz, 3 H, CH_3) ppm.

5-(1′-Iodovinyl)-3-(methoxycarbonyl)-2-methyl-4,5-dihydrofuran (2b): The reaction of CaH_2 (5.0 mg, 0.12 mmol), I_2 (203.6 mg, 0.8 mmol), and **1b** (34.6 mg, 0.2 mmol) in THF (2 mL) afforded **2b** (39.7 mg, 66%) after chromatography (petroleum ether/dichloromethane, 2:1) as a liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.38 (s, 1 H, one proton of H_2C=C), 5.86 (s, 1 H, one proton of H_2C=C), 4.83 (dd, J = 10.5, 7.5 Hz, 1 H, OCH), 3.70 (s, 3 H, OCH_3), 3.06 (dd, J = 13.5, 10.5 Hz, 1 H, one proton of C=CCH_2), 2.76 (dd, J = 14.9, 7.4 Hz, 1 H, one proton of C=CCH_2), 2.22 (s, 3 H, C=CCH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 167.3, 166.0, 126.0, 111.0, 101.4, 85.7, 50.9, 36.7, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2949, 2867, 1706, 1654, 1619, 1438, 1383, 1256, 1223, 1190, 1136, 1088 cm^{-1}. MS (70 eV, EI): m/z (%) = 294 (22.56) $[M]^+$, 43 (100). HRMS: calcd. for $C_9H_{11}O_3I$ $[M]^+$ 293.9753; found 293.9752.

2-Ethyl-5-(1′-iodovinyl)-3-(methoxycarbonyl)-4,5-dihydrofuran (2c): The reaction of CaH_2 (5.3 mg, 0.12 mmol), I_2 (204.0 mg, 0.8 mmol), and **1c** (36.7 mg, 0.2 mmol) in THF (2 mL) afforded **2c** (44.7 mg, 72%) after chromatography (petroleum ether/dichloromethane, 2:1) as a liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.38 (s, 1 H, one proton of H_2C=C), 5.86 (s, 1 H, one proton of H_2C=C), 4.82 (dd, J = 10.7, 7.4 Hz, 1 H, OCH), 3.70 (s, 3 H, OCH_3), 3.07 (dd, J = 14.9, 11.0 Hz, 1 H, one proton of C=CCH_2), 2.85–2.53 (m, 3 H, one proton of C=CCH_2 and CH_2), 1.16 (t, J = 7.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 171.9, 165.8, 125.9, 111.3, 100.3, 85.4, 50.9, 36.7, 21.1, 11.2 ppm. IR (neat): $\tilde{\nu}$ = 2976, 2945, 2875, 1707, 1647, 1437, 1360, 1331, 1250, 1209, 1190, 1135, 1097, 1017 cm^{-1}. MS (70 eV, EI): m/z (%) = 308 (21.73) $[M]^+$, 57 (100). HRMS: calcd. for $C_{10}H_{13}O_3I$ $[M]^+$ 307.9909; found 307.9908.

5-(1′-Iodovinyl)-2-isopropyl-3-(methoxycarbonyl)-4,5-dihydrofuran (2d): The reaction of CaH_2 (5.2 mg, 0.12 mmol), I_2 (206.0 mg, 0.8 mmol), and **1d** (38.9 mg, 0.2 mmol) in THF (2 mL) afforded **2d** (51.3 mg, 80%) after chromatography (petroleum ether/dichloromethane, 3:2) as a liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.38 (s, 1 H, one proton of H_2C=C), 5.85 (s, 1 H, one proton of H_2C=C), 4.81 (dd, J = 10.8, 7.5 Hz, 1 H, OCH), 3.74–3.55 (m, 4 H, OCH_3 and C=CCH), 3.05 (dd, J = 14.9, 11.0 Hz, 1 H, one proton of C=CCH_2), 2.74 (dd, J = 14.9, 7.7 Hz, 1 H, one proton of C=CCH_2), 1.18 (d, J = 7.2 Hz, 3 H, CH_3), 1.12 (d, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 174.9, 165.8, 125.7, 111.5, 99.0, 85.2, 50.8, 36.7, 26.7, 19.7, 19.5 ppm. IR (neat): $\tilde{\nu}$ = 2971, 2940, 2873, 1706, 1643, 1465, 1438, 1355, 1298, 1258, 1232, 1185, 1119, 1046 cm^{-1}. MS (70 eV, EI): m/z (%) = 322 (29.98) $[M]^+$, 251 (100). HRMS: calcd. for $C_{11}H_{15}O_3I$ $[M]^+$ 322.0066; found 322.0064.

2-Benzyl-5-(1′-iodovinyl)-3-(methoxycarbonyl)-4,5-dihydrofuran (2e): The reaction of CaH_2 (5.4 mg, 0.12 mmol), I_2 (204.0 mg, 0.8 mmol), and **1e** (49.9 mg, 0.2 mmol) in THF (2 mL) afforded **2e** (46.1 mg, 61%) after chromatography (petroleum ether/diethyl ether, 10:1) as a liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.17 (m, 5 H, Ar-H), 6.12 (s, 1 H, one proton of H_2C=C), 5.74 (s, 1 H, one proton of H_2C=C), 4.86 (dd, J = 10.5, 7.5 Hz, 1 H, OCH), 4.06 (d, J = 13.8 Hz, 1 H, one proton of CH_2 of Bn), 3.96 (d, J = 14.1 Hz, 1 H, one proton of CH_2 of Bn), 3.75 (s, 3 H, OCH_3), 3.09 (dd, J = 15.0, 10.8 Hz, 1 H, one proton of C=CCH_2), 2.79 (dd, J = 15.0, 7.2 Hz, 1 H, one proton of C=CCH_2) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 168.3, 165.7, 136.3, 129.1, 128.4, 126.8, 125.7, 110.5, 101.4, 85.6, 51.1, 36.5, 33.6 ppm. IR (neat): $\tilde{\nu}$ = 3026, 2948, 1708, 1645, 1617, 1495, 1435, 1366, 1257, 1234, 1191, 1124, 1078, 1055 cm^{-1}. MS (70 eV, EI): m/z (%) = 370 (61.30) $[M]^+$, 91 (100). HRMS: calcd. for $C_{15}H_{15}O_3I$ $[M]^+$ 370.0066; found 370.0067.

3-(Ethoxycarbonyl)-5-(1′-iodovinyl)-2-phenyl-4,5-dihydrofuran (2f): The reaction of CaH_2 (5.4 mg, 0.12 mmol), I_2 (202.4 mg, 0.8 mmol), and **1f** (47.7 mg, 0.2 mmol) in THF (2 mL) afforded **2f** (59.7 mg, 83%) after chromatography (petroleum ether/ethyl acetate, 3:2) as a liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.77 (m, 2 H, Ar-H), 7.52–7.34 (m, 3 H, Ar-H), 6.47 (s, 1 H, one proton of H_2C=C), 5.92 (s, 1 H, one proton of H_2C=C), 4.98 (dd, J = 10.7, 8.0 Hz, 1 H, OCH), 4.15 (q, J = 7.2 Hz, 2 H, CO_2CH_2), 3.33 (dd, J = 15.5, 11.0 Hz, 1 H, one proton of C=CCH_2), 3.02 (dd, J = 15.5, 7.7 Hz, 1 H, one proton of C=CCH_2), 1.22 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 164.7, 164.0, 130.4, 129.5, 129.3, 127.6, 126.1, 111.0, 102.1, 85.0, 59.9, 38.4, 14.2 ppm. IR (neat): $\tilde{\nu}$ = 3056, 2979, 2931, 2866, 1709, 1616, 1599, 1576, 1493, 1446, 1395, 1375, 1347, 1305, 1243, 1172, 1148, 1089, 1001 cm^{-1}. MS (70 eV, EI): m/z (%) = 370 (7.61) $[M]^+$, 105 (100). HRMS: calcd. for $C_{15}H_{15}O_3I$ $[M]^+$ 370.0066; found 370.0067.

3-(Ethoxycarbonyl)-5-ethyl-5-(1′-iodovinyl)-2-methyl-4,5-dihydrofuran (2g): The reaction of CaH_2 (5.2 mg, 0.12 mmol), I_2 (203.6 mg,

0.8 mmol), and **1g** (41.5 mg, 0.2 mmol) in THF (2 mL) afforded **2g** (54.5 mg, 82%) after chromatography (petroleum ether/diethyl ether, 20:1) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.36 (s, 1 H, one proton of H_2C=C), 5.85 (s, 1 H, one proton of H_2C=C), 4.15 (q, J = 7.1 Hz, 2 H, CO_2CH_2), 3.00 (d, J = 15.0 Hz, 1 H, one proton of C=CCH_2), 2.70 (d, J = 15.0 Hz, 1 H, one proton of C=CCH_2), 2.21 (s, 3 H, C=CCH_3), 2.06–1.91 (m, 1 H, one proton of CH_2), 1.91–1.77 (m, 1 H, one proton of CH_2), 1.26 (t, J = 7.1 Hz, 3 H, CH_3), 0.88 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 166.3, 165.8, 125.2, 114.3, 101.2, 92.1, 59.5, 41.1, 32.2, 14.4, 14.1, 7.6 ppm. IR (neat): $\tilde{\nu}$ = 2975, 2932, 2872, 1704, 1655, 1613, 1460, 1379, 1332, 1297, 1267, 1240, 1121, 1073 cm^{-1}. MS (70 eV, EI): m/z (%) = 336 (10.04) $[M]^+$, 293 (100). HRMS: calcd. for $C_{12}H_{17}O_3I$ $[M]^+$ 336.0222; found 336.0221.

5-Benzyl-5-(1′-iodovinyl)-2-isopropyl-3-(methoxycarbonyl)-4,5-dihydrofuran (2h): The reaction of CaH_2 (5.4 mg, 0.12 mmol), I_2 (204.0 mg, 0.8 mmol), and **1h** (57.4 mg, 0.2 mmol) in THF (2 mL) afforded **2h** (57.9 mg, 70%) after chromatography (petroleum ether/dichloromethane, 3:1) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.19 (m, 5 H, Ar-H), 6.21 (d, J = 1.5 Hz, 1 H, one proton of H_2C=C), 5.75 (d, J = 1.2 Hz, 1 H, one proton of H_2C=C), 3.73–3.51 (m, 4 H, OCH_3 and C=CCH), 3.25 (d, J = 14.1 Hz, 1 H, one proton of CH_2), 3.13 (d, J = 14.7 Hz, 1 H, one proton of CH_2), 3.08 (d, J = 15.3 Hz, 1 H, one proton of CH_2), 2.84 (d, J = 15.3 Hz, 1 H, one proton of CH_2), 1.16 (d, J = 6.6 Hz, 3 H, CH_3), 1.13 (d, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 173.8, 165.8, 135.2, 130.6, 127.8, 126.8, 125.7, 114.4, 98.7, 90.9, 50.8, 44.6, 41.1, 26.9, 19.9, 19.8 ppm. IR (neat): $\tilde{\nu}$ = 3030, 2970, 2947, 2872, 1705, 1646, 1614, 1497, 1468, 1455, 1435, 1360, 1351, 1285, 1245, 1190, 1126, 1099, 1065, 1038 cm^{-1}. MS (70 eV, EI): m/z (%) = 412 (5.67) $[M]^+$, 321 (100). HRMS: calcd. for $C_{18}H_{21}O_3I$ 412.0535; found 412.0536.

5-(1′-Iodo-2′-methyl-1′-propenyl)-2-isopropyl-3-(methoxycarbonyl)-4,5-dihydrofuran (2i): The reaction of CaH_2 (5.2 mg, 0.12 mmol), I_2 (203.5 mg, 0.8 mmol), and **1i** (43.9 mg, 0.2 mmol) in THF (2 mL) afforded **2i** (56.9 mg, 83%) after chromatography (petroleum ether/ethyl acetate, 30:1) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.08 (t, J = 9.5 Hz, 1 H, OCH), 3.73–3.55 (m, 4 H, OCH_3 and C=CCH), 2.95 (dd, J = 14.7, 10.8 Hz, 1 H, one proton of CH_2), 2.67 (dd, J = 14.7, 8.4 Hz, 1 H, one proton of CH_2), 2.00 (s, 3 H, CH_3), 1.96 (s, 3 H, CH_3), 1.18 (d, J = 6.9 Hz, 3 H, CH_3), 1.10 (d, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.0, 166.0, 140.4, 105.2, 99.5, 80.4, 50.7, 37.2, 31.6, 26.7, 20.8, 19.61, 19.55 ppm. IR (neat): $\tilde{\nu}$ = 2970, 2932, 2869, 1699, 1637, 1463, 1435, 1361, 1352, 1261, 1229, 1189, 1118, 1062, 1045 cm^{-1}. MS (70 eV, EI): m/z (%) = 350 (30.77) $[M]^+$, 223 (100). HRMS: calcd. for $C_{13}H_{19}O_3I$ $[M]^+$ 350.0379; found 350.0380.

2-Isopropyl-3-(methoxycarbonyl)-5-(2′,2′-pentamethylene-1′-iodovinyl)-4,5-dihydrofuran (2j): The reaction of CaH_2 (5.2 mg, 0.12 mmol), I_2 (206.0 mg, 0.8 mmol), and **1j** (52.6 mg, 0.2 mmol) in THF (2 mL) afforded **2j** (40.6 mg, 52%) after chromatography (petroleum ether/dichloromethane, 2:1) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.16 (t, J = 9.6 Hz, 1 H, OCH), 3.73–3.55 (m, 4 H, OCH_3 and C=CCH), 2.94 (dd, J = 14.6, 10.8 Hz, 1 H, one proton of CH_2), 2.69 (dd, J = 14.6, 8.9 Hz, 1 H, one proton of CH_2), 2.57–2.36 (m, 4 H, 2 CH_2), 1.72–1.37 (m, 6 H, 3 CH_2), 1.19 (d, J = 6.9 Hz, 3 H, CH_3), 1.11 (d, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.1, 166.0, 147.7, 103.2, 99.6, 79.7, 50.7, 42.2, 37.5, 32.5, 28.1, 27.3, 26.7, 26.4, 19.62, 19.60 ppm. IR (neat): $\tilde{\nu}$ = 2970, 2931, 2854, 1700, 1638, 1468, 1435, 1350, 1261, 1228, 1119, 1065, 1046 cm^{-1}. MS (70 eV, EI): m/z (%) = 390 (14.95) $[M]^+$, 181 (100). HRMS: calcd. for $C_{16}H_{23}O_3I$ $[M]^+$ 390.0692; found 390.0693.

5-(1′-Iodo-1′-undecenyl)-2-isopropyl-3-(methoxycarbonyl)-4,5-dihydrofuran (2k): The reaction of CaH_2 (5.3 mg, 0.12 mmol), I_2 (205.0 mg, 0.8 mmol), and **1k** (63.3 mg, 0.2 mmol) in THF (2 mL) afforded **2k** (75.6 mg, 86%, Z/E = 87:13) after chromatography (petroleum ether/diethyl ether, 20:1) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = [6.34 (t, J = 7.8 Hz, 0.13 H, C=CH, E-isomer), 5.94 (t, J = 6.8 Hz, 0.87 H, C=CH, Z-isomer)], [4.92 (t, J = 9.5 Hz, 0.13 H, OCH, E-isomer), 4.81 (dd, J = 10.4 Hz, 8.0 Hz, 0.86 H, OCH, Z-isomer)], 3.74–3.55 (m, 4 H, OCH_3 and C=CCH), 3.07–2.92 (m, 1 H, one proton of CH_2), 2.82–2.62 (m, 1 H, one proton of CH_2), 2.16 (q, J = 7.0 Hz, 2 H, CH_2), 1.47–1.05 (m, 20 H), 0.87 (t, J = 6.2 Hz, 3 H, CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2926, 2855, 1705, 1643, 1467, 1435, 1349, 1254, 1230, 1187, 1120, 1065, 1046 cm^{-1}. MS (70 eV, EI): m/z (%) = 448 (16.32) $[M]^+$, 321 (100). HRMS: calcd. for $C_{20}H_{33}O_3I$ $[M]^+$ 448.1474; found 448.1473. $C_{20}H_{33}IO_3$ (448.38): calcd. C 53.57, H 7.42; found C 54.01, H 7.51.

5-(2′-Cyclohexyl-1′-iodovinyl)-2-isopropyl-3-(methoxycarbonyl)-4,5-dihydrofuran (2l): The reaction of CaH_2 (5.2 mg, 0.12 mmol), I_2 (203.1 mg, 0.8 mmol), and **1l** (56.0 mg, 0.2 mmol) in THF (2 mL) afforded **2l** (70.3 mg, 86%, Z/E = 85:15) after chromatography (petroleum ether/diethyl ether, 20:1) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = [6.21 (d, J = 9.9 Hz, 0.15 H, C=CH, E-isomer), 5.74 (d, J = 8.7 Hz, 0.83 H, C=CH, Z-isomer)], [4.93 (t, J = 9.5 Hz, 0.15 H, OCH, E-isomer), 4.77 (dd, J = 10.4, 8.1 Hz, 0.83 H, OCH, Z-isomer)], 3.75–3.55 (m, 4 H, OCH_3 and C=CCH), 3.10–2.93 (m, 1 H, one proton of CH_2), 2.81–2.62 (m, 1 H, one proton of CH_2), 2.45–2.22 (m, 1 H, CH), 1.81–1.54 (m, 5 H), 1.42–1.02 (m, 11 H) ppm. IR (neat): $\tilde{\nu}$ = 2970, 2927, 2851, 1697, 1639, 1468, 1436, 1348, 1300, 1258, 1230, 1189, 1120, 1065, 1044, 1009 cm^{-1}. MS (70 eV, EI): m/z (%) = 404 (15.48) $[M]^+$, 43 (100). HRMS: calcd. for $C_{17}H_{25}O_3I$ $[M]^+$ 404.0848; found 404.0851. $C_{17}H_{25}IO_3$ (404.29): calcd. C 50.50, H 6.23; found C 50.87, H 6.44.

Procedure for Kinetic Resolution of the *Z*/*E* Isomer of 2l

Synthesis of 5-[2′(*Z*)-Cyclohexyl-1′-iodovinyl]-2-isopropyl-3-(methoxycarbonyl)-4,5-dihydrofuran (*Z*-2l):[12] To a flame-dried Schlenk tube were added $Pd(PPh_3)Cl_2$ (3.7 mg, 5.25 μmol), CuI (1.0 mg, 5.25 μmol), Et_2NH (4.0 mg, 0.053 mmol), CH_3CN (0.5 mL), prop-2-yn-1-ol (3.0 mg, 0.053 mmol), CH_3CN (0.5 mL), **2l** (58.4 mg, 0.15 mmol, Z/E = 85:15), and CH_3CN (0.5 mL) sequentially at 3 °C. After being stirred at 3 °C for 1.5 h under an atmosphere of argon, the reaction mixture was concentrated and purified by chromatography on silica gel (petroleum ether/diethyl ether, 15:1) to afford *Z*-**2l** (45.6 mg, 78%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75 (d, J = 8.4 Hz, 1 H, C=CH), 4.78 (dd, J = 9.9, 8.4 Hz, 1 H, OCH), 3.73–3.55 (m, 4 H, OCH_3 and C=CCH), 3.01 (dd, J = 14.9, 11.0 Hz, 1 H, one proton of CH_2), 2.75 (dd, J = 14.9, 7.7 Hz, 1 H, one proton of CH_2), 2.37–2.22 (m, 1 H, CH), 1.82–1.59 (m, 5 H), 1.42–1.02 (m, 11 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.1, 166.0, 142.1, 106.9, 99.3, 85.8, 50.8, 44.2, 37.0, 31.4, 26.7, 25.8, 25.5, 25.4, 19.7, 19.5 ppm. IR (neat): $\tilde{\nu}$ = 2927, 2851, 1697, 1639, 1468, 1436, 1348, 1300, 1258, 1230, 1189, 1120, 1065, 1044, 1009 cm^{-1}. MS (70 eV, EI): m/z (%) = 404 (17.70) $[M]^+$, 43 (100). HRMS: calcd. for $C_{17}H_{25}O_3I$ $[M]^+$ 404.0848; found 404.0850.

Typical Procedure for Suzuki–Miyaura Coupling of 2a

3-(Ethoxycarbonyl)-2-methyl-5-(1′-phenylvinyl)-4,5-dihydrofuran (3): To a flame-dried Schlenk tube were added $Pd(PPh_3)_4$ (8.5 mg, 7.5 μmol), $K_3PO_4{\cdot}3H_2O$ (80.9 mg, 0.3 mmol), phenylboronic acid (27.1 mg, 0.225 mmol), toluene (1 mL), **2a** (45.3 mg, 0.15 mmol), and toluene (0.5 mL) sequentially under an atmosphere of argon. The mixture was stirred at 110 °C in a preheated oil bath. Upon completion of the reaction as monitored by TLC, the resulting mix-

ture was concentrated and purified by chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) to afford **3**[11a] (31.1 mg, 82%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 5 H, Ar-H), 5.53 (t, J = 9.6 Hz, 1 H, OCH), 5.43 (s, 1 H, one proton of H_2C=C), 5.35 (s, 1 H, one proton of H_2C=C), 4.14 (q, J = 7.1 Hz, 2 H, CO_2CH_2), 3.12 (dd, J = 13.2, 11.7 Hz, 1 H, one proton of C=CCH_2), 2.67 (dd, J = 14.3, 8.3 Hz, 1 H, one proton of C=CCH_2), 2.28 (s, 3 H, C=CCH_3), 1.24 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 167.5, 166.1, 147.3, 138.2, 128.5, 128.0, 126.6, 112.4, 101.8, 82.3, 59.5, 36.1, 14.4, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2980, 1697, 1651, 1496, 1444, 1384, 1324, 1259, 1224, 1143, 1081 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 258 (2.16) $[M]^+$, 141 (100).

3-(Ethoxycarbonyl)-2-methyl-5-[octa-1′,3′(*E*)-dien-2′-yl]-4,5-dihydrofuran (4): The reaction of $Pd(PPh_3)_4$ (9.0 mg, 7.5 μmol), $K_3PO_4{\cdot}3H_2O$ (79.1 mg, 0.3 mmol), (1*E*)-hexenylboronic acid (29.2 mg, 0.225 mmol), and **2a** (46.2 mg, 0.15 mmol) in toluene (1.5 mL) afforded **4** (32.1 mg, 81%) after chromatography (petroleum ether/diethyl ether, 25:1) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.03 [d, J = 16.2 Hz, 1 H, (C=C)CH=C], 5.62 [dt, J = 15.9, 6.9 Hz, 1 H, (C=C)C=CH], 5.23 (dd, J = 10.5, 8.7 Hz, 1 H, OCH), 5.07 (s, 1 H, one proton of H_2C=C), 5.01 (s, 1 H, one proton of H_2C=C), 4.16 (q, J = 7.1 Hz, 2 H, CO_2CH_2), 3.15 (t, J = 12.3 Hz, 1 H, one proton of C=CCH_2), 2.68 (dd, J_1 = 13.8, J_2 = 7.8 Hz, 1 H, one proton of C=CCH_2), 2.24 (s, 3 H, C=CCH_3), 2.10 (q, J = 6.7 Hz, 2 H, CH_2), 1.46–1.20 (m, 7 H, 2 CH_2 and CH_3), 0.90 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 167.6, 166.1, 145.3, 131.9, 128.3, 111.5, 101.8, 81.0, 59.4, 36.4, 32.8, 31.3, 22.2, 14.4, 14.0, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2957, 2929, 1703, 1655, 1647, 1461, 1383, 1331, 1257, 1227, 1142, 1084 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 264 (8.50) $[M]^+$, 43 (100). HRMS: calcd. for $C_{16}H_{24}O_3$ $[M]^+$ 264.1725; found 264.1727.

Procedure for Sonogashira Coupling of 2a.

3-(Ethoxycarbonyl)-2-methyl-5-(oct-1′-en-3′-yn-2′-yl)-4,5-dihydrofuran (5): To a flame-dried Schlenk tube was added $Pd(PPh_3)_2Cl_2$ (4.1 mg, 6.0 μmol), CuI (1.2 mg, 6.0 μmol), Et_3N (24.8 mg, 0.24 mmol), CH_3CN (1 mL), 1-hexyne (34.7 mg, 0.4 mmol), CH_3CN (0.5 mL), **2a** (60.5 mg, 0.2 mmol), and CH_3CN (0.5 mL) sequentially under an atmosphere of argon. The mixture was stirred at room temperature and monitored by TLC. Upon completion, the resulting mixture was concentrated and purified by chromatography on silica gel (petroleum ether/diethyl ether, 40:1) to afford **5** (43.7 mg, 84%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.38 (s, 1 H, one proton of H_2C=C), 5.35 (s, 1 H, one proton of H_2C=C), 4.98 (dd, J = 10.1, 8.0 Hz, 1 H, OCH), 4.15 (q, J = 7.1 Hz, 2 H, CO_2CH_2), 3.05 (dd, J = 14.4, 10.8 Hz,1 H, one proton of C=CCH_2), 2.89 (dd, J = 14.7, 7.5 Hz, 1 H, one proton of C=CCH_2), 2.29 (t, J = 6.8 Hz, 2 H, CH_2), 2.20 (s, 3 H, C=CCH_3), 1.53–1.31 (m, 4 H, 2 CH_2), 1.26 (t, J = 7.2 Hz, 3 H, CH_3), 0.88 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 167.3, 165.9, 131.5, 119.9, 101.9, 92.6, 82.9, 76.9, 59.4, 35.2, 30.5, 21.8, 18.9, 14.4, 13.9, 13.5 ppm. IR (neat): $\tilde{\nu}$ = 2959, 2933, 2871, 2224, 1702, 1654, 1462, 1383, 1321, 1255, 1224, 1142, 1085 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 262 (1.77) $[M]^+$, 43 (100). HRMS: calcd. for $C_{16}H_{22}O_3$ $[M]^+$ 262.1569; found 262.1569.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra of the products.

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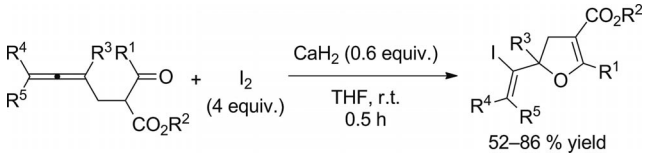
Cyclization



A facile and efficient protocol for the synthesis of 4,5-dihydrofuran derivatives via iodine-mediated cyclization of various 2-(2′,3′-allenyl)acetylacetates with CaH_2 as the base has been developed. The yields range from moderate to good. The resulting products can be used for further elaboration by palladium-catalyzed coupling reactions.

Keywords: Cyclization / Iodine / Allenes / Oxygen heterocycles

