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Synthesis of 2-Alkyl- and Aryl-3-ethoxycarbonyl-2,5-dihydrofurans through Gold-Catalyzed Intramolecular Hydroalkoxylation

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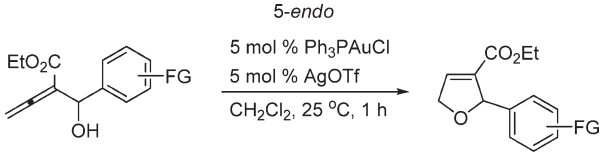

FG-C_6H_4 = H, *n*-Pr, $PhCH_2CH_2$, C_6H_{11}, Ph, 4-Cl-C_6H_4, 2-I-C_6H_4, 4-Ac-C_6H_4, 4-MeO_2C-C_6H_4, 4-NO_2-C_6H_4, 4-Me-C_6H_4, 2,4,6-$(Me)_3$-C_6H_2, 3-MeO-C_6H_4

Treatment of a wide range of functionalized hydroxyallenic esters with 5 mol % Ph_3PAuCl and 5 mol % AgOTf in CH_2Cl_2 at 25 °C for 1 h produced selectively 2-alkyl- and aryl-3-ethoxycarbonyl-2,5-dihydrofurans in good to excellent yield through intramolecular hydroalkoxylation by a 5-*endo* mode.

Because functionalized 2,5-dihydrofuran is an important structural motif frequently found in natural products and has been used as an essential skeleton in pharmaceutics, development of efficient and versatile synthetic methods for these compounds has been continuously required,[1] and many synthetic strategies for functionalized 2,5-dihydrofurans have been reported in the literature.[2] First, Krause and Hoffmann-Roder developed a novel gold-catalyzed cyclization reaction of highly functionalized α-hydroxyallenes to the corrersponding 2,5-dihydrofurans.[3] On the basis of these results, valuable cyclization reactions of a variety of hydroxyallenes[4] and mercaptoallenes[5] were demonstrated. We described a selective synthesis of 2,5-dihydrofuran having two substituents at the 2- and 3-positions via 5-*endo* intramolecular hydroalkoxylation of allenyne-1,6-diols catalyzed by gold.[6] Recently, the α-hydroxybenzyl allenic esters possessing hydroxy and methoxy group as electron-donating group were cyclized to ethyl 2-naphthoates through gold-catalyzed 6-*endo* intramolecular hydroarylation.[7] However, an efficient synthetic method for 2,5-dihydrofurans is needed to overcome the difficult introduction of specific substituents or the requirements of multistep synthesis. Furthermore, many synthetic methods required preorganized hydroxyallenes possessing functional groups on the 2- and 3-positions. Therefore, an alternate method having various functional group variations on the 2,5-dihydrofuran nucleus is highly desirable to study structural and biological activity. Especially, a direct preparation of 3-ethoxycarbonyl-2,5-dihydrofurans from hydroxyallenes through intramolecular hydroalkoxylation is more challenging because of their reactivity as a Michael acceptor. In the pursuit of an ongoing medicinal chemistry program, we have been recently interested in introducing a wide range of substituents on the 2- and 3-positions, especially an ethoxycarbonyl group on the 3-position, of 2,5-dihydrofuran. In this respect, we envisioned that functionalized α-hydroxy allenic esters might be cyclized to functionalized 2,5-dihydrofurans through cyclization. In this paper, we report an efficient synthesis of 2-alkyl- and aryl-3-ethoxycarbonyl-2,5-dihydrofurans through gold-catalyzed intramolecular hydroalkoxylation by the 5-*endo* mode (Scheme 1).

First, the functionalized α-hydroxyaryl allenic esters were selectively prepared from reaction of aldehydes with

(1) (a) *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1 and 2. (b) Yamamoto, Y.; Takuma, R.; Hotta, T.; Yamashita, K. *J. Org. Chem.* **2009**, *74*, 4324. (c) Bongers, N.; Krause, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 2178. (d) Deng, Y.; Yu, Y.; Ma, S. *J. Org. Chem.* **2008**, *73*, 585. (e) Yeom, H.-S.; Shin, S. *Tetrahedron Lett.* **2007**, *48*, 4817. (f) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387. (g) Alcaide, B.; Almendros, P.; Rodrıguez-Acebes, R. *Chem.—Eur. J.* **2005**, *11*, 5708. (h) Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104. (i) Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, *41*, 8933. (j) Carda, M.; Castillo, E.; Rodrıguez, S.; Uriel, S.; Marco, J. A. *Synlett* **1999**, 1639. (k) Saimoto, H.; Yasui, M.; Ohrai, S.; Oikawa, H.; Yokoyama, K.; Shigemasa, Y. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 279. (l) Darcel, C.; Bruneau, C.; Albert, M.; Dixneuf, P. H. *Chem. Commun.* **1996**, 919. (m) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966. (n) Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550. (o) Shigemasa, Y.; Yasui, M.; Ohrai, S.; Sasaki, M.; Sashiwa, H.; Saimoto, H. *J. Org. Chem.* **1991**, *56*, 910. (p) Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1987**, *28*, 1023. (q) Nikam, S. S.; Chu, K. H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 745. (r) Sato, F.; Kanbara, H.; Tanaka, Y. *Tetrahedron Lett.* **1984**, *25*, 5063. (s) Olsson, L. I.; Claesson, A. *Synthesis* **1979**, 743.

(2) (a) Deng, Y.; Shi, Y.; Ma, S. *Org. Lett.* **2009**, *11*, 1205. (b) Brasholz, M.; Ressig, H.-U. *Angew. Chem., Int. Ed.* **2007**, *46*, 1634. (c) Hyland, C. J. T.; Hegedus, L. S. *J. Org. Chem.* **2006**, *71*, 8658. (d) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957. (e) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957. (f) Kim, J. M.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 2805. (g) Yang, C.; Murray, W. V.; Wilson, L. J. *Tetrahedron Lett.* **2003**, *44*, 1783. (h) Chen, J.; Song, Q.; Li, P.; Guan, H.; Jin, X.; Xi, Z. *Org. Lett.* **2002**, *4*, 2269. (i) Xi, C.; Kotora, M.; Takahashi, T. *Tetrahedron Lett.* **1999**, *40*, 2375. (j) Tiecco, M.; Testaferri, L.; Santi, C. *Eur. J. Org. Chem.* **1999**, 797. (k) Kim, S.; Kim, K. H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1095. (l) Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, A. *Synthesis* **1997**, 1415. (m) Shieh, S.-J.; Fan, J.-S.; Chandrasekharam, M.; Liao, F.-L.; Wang, S.-L.; Liu, R.-S. *Organometallics* **1997**, *16*, 3987. (n) Hojo, M.; Ishbashi, N.; Hosomi, A. *Synlett* **1996**, 234. (o) Shieh, S.-J.; Tang, T.-C.; Lee, J.-S.; Lee, G.-H.; Peng, S.-M.; Liu, R.-S. *J. Org. Chem.* **1996**, *61*, 3245. (p) Yamada, O.; Ogasawara, K. *Synlett* **1995**, 427. (q) Marshall, J. A.; Yu, B. *J. Org. Chem.* **1994**, *59*, 324. (r) Hojo, M.; Ohkuma, M.; Ishibashi, N.; Hosomi, A. *Tetrahedron Lett.* **1993**, *34*, 5943. (s) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180.

(3) (a) Hoffmann-Roder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537. (b) Krause, N.; Hoffmann-Roder, A.; Cansius, J. *Synthesis* **2002**, 1759. (c) Aksin, O.; Krause, N. *Adv. Synth. Catal.* **2008**, *350*, 1106. (d) Poonoth, M.; Krause, N. *Adv. Synth. Catal.* **2009**, *351*, 117.

(4) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485.

(5) Morita, N.; Krause, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1897.

(6) (a) Kim, S.; Lee, P. H. *Adv. Synth. Catal.* **2008**, *350*, 547. (b) Kim, S.; Kang, D.; Shin, S.; Lee, P. H. *Tetrahedron Lett.* **2010**, *51*, 1899.

(7) Park, C.; Lee, P. H. *Org. Lett.* **2008**, *10*, 3359.

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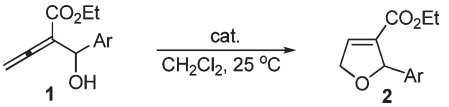
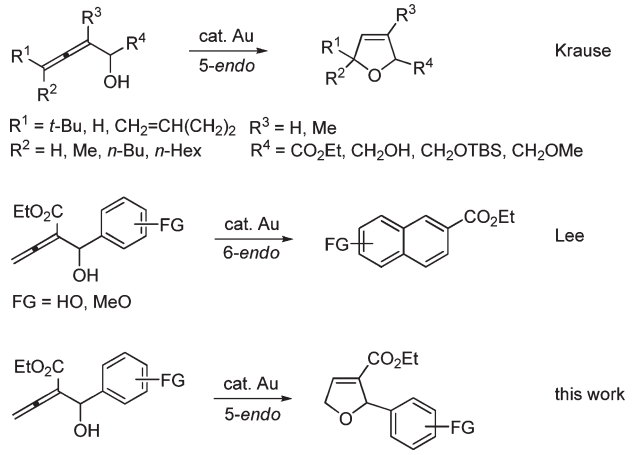
TABLE 1. Synthesis of 2-Aryl-3-ethoxycarbonyl-2,5-dihydrofuran via Gold-Catalyzed Cyclization



entry	catalyst	Ar	time (h)	yield (%)[a]
1	5 mol % $AuCl_3$	Ph (**a**)	15	15
2	5 mol % $AuCl_3$/15 mol %AgOTf	Ph	10	30[b]
3	5 mol % Ph_3PAuCl/5 mol % AgOTf	Ph	1	80
4	5 mol % Ph_3PAuCl/5 mol % AgOTf	3-MeO-C_6H_4 (**b**)	1	78 (3)[c] (9)[d]
5	5 mol % Ph_3PAuCl/5 mol % $AgBF_4$	3-MeO-C_6H_4	1	32 (10)[c] (40)[d]
6	5 mol % Ph_3PAuCl/5 mol % $AgAsF_6$	3-MeO-C_6H_4	1	50 (5)[c] (27)[d]
7	5 mol % Ph_3PAuCl/5 mol % $AgSbF_6$	3-MeO-C_6H_4	1	33 (9)[c] (35)[d]
8	5 mol % Ph_3PAuCl/5 mol % $AgPF_6$	3-MeO-C_6H_4	1	68 (3)[c] (14)[d]

[a]Isolated yield. [b]Ethyl 2-ethynyl-3-phenylpropenoate. [c]Ethyl 5-methoxy-2-naphthoate. [d]Ethyl 7-methoxy-2-naphthoate.

SCHEME 1. Selective Synthesis of 2-Alkyl- and Aryl-3-ethoxycarbonyl-2,5-dihydrofurans



organoindium reagent generated in situ from indium and ethyl 4-bromobutynoate.[8] Intramolecular hydroalkoxylation **1a** and **1b** with gold catalyst was initially examined (Table 1). Treatment of **1a** with 5 mol % $AuCl_3$ afforded **2a** in 15% yield (entry 1). Although treatment of **1a** with 5 mol % $AuCl_3$ and 15 mol % AgOTf gave ethyl 2-ethynyl-3-phenylpropenoate in 30% yield (entry 2), use of 5 mol % Ph_3PAuCl and 5 mol % AgOTf gave 5-*endo* intramolecular hydroalkoxylated product **2a** in 80% yield in CH_2Cl_2 at 25 °C for 1 h (entry 3). Allenic ester **1b** having 3-methoxyphenyl group was treated with 5 mol % of Ph_3PAuCl and 5 mol % of $AgBF_4$ to give ethyl 5-methoxy- and 7-methoxy-2-naphthoate in 10% and 40% yields, respectively, through intramolecular hydroarylation by the 6-*endo* mode and **2b** in 32% yield through intramolecular hydroalkoxylation by the 5-*endo* mode (entry 5). To suppress hydroarylation and increase hydroalkoxylation, a variety of silver salts such as AgOTf, $AgAsF_6$, $AgSbF_6$, and $AgPF_6$ were examined (entries 4, 6, 7, and 8). Of the reactions screened, the best results were obtained from treatment of **1b** with 5 mol % Ph_3PAuCl and 5 mol % AgOTf in CH_2Cl_2 at 25 °C for 1 h under nitrogen atmosphere, producing selectively **2b** in 78% yield by the 5-*endo* mode together with ethyl 2-naphthoate in 12% yield by the 6-*endo* mode (entry 4).

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to a wide range of hydroxyallenes (Table 2). Reaction of ethyl 2-hydroxymethyl-2,3-butadienoate (**1c**) with 5 mol % Ph_3PAuCl and 5 mol % AgOTf provided 3-ethoxycarbonyl-2,5-dihydrofuran (**2c**) in 70% yield by the 5-*endo* mode (entry 1). Under the optimum reaction conditions, various hydroxyallenes **1d**, **1e**, and **1f** obtained from aliphatic aldehydes such as *n*-butanal, hydrocinnamaldehyde, and cyclohexancarbaldehyde were converted to 2-alkyl-3-ethoxycarbonyl-2,5-dihydrofuran catalyzed by gold in good to excellent yields (entries 2, 3, and 4). Next, intramolecular hydroalkoxylation of a wide range of hydroxyallenes obtained from aromatic aldehydes were examined (entries 5−11). The presence of 4-chloro and 2-iodo groups on the phenyl ring did not affect either the reaction rate or product yield (entries 5 and 6). Hydroxyallenes (**1i** and **1j**) having a carbonyl group such as 4-acetyl and 4-ethoxycarbonyl on the aromatic ring were smoothly converted to the corresponding dihydrofurans **2i** and **2j** in 89% and 97% yield, respectively (entries 7 and 8). Compound **1k** generated from 4-nitrobenzaldehyde was treated with gold catalyst to produce **2k** in 85% yield (entry 9). In the case of hydroxyallenes derived from aromatic aldehydes possessing a methyl group as an electron-donating group, yield of product was low (**2l**, 49% and **2m**, 28%). Therefore, 10 mol % Ph_3PAuCl and 10 mol % AgOTf was required to complete the intramolecular hydroalkoxylation with the same efficiency. It was gratifying to selectively obtain 2,5-dihydrofuran **2l** possessing a 4-methyl group in 83% yield (entry 10). When hydroxyallene **1m** bearing three methyl groups was subjected to gold catalyst, the corresponding 3-ethoxycarbonyl-2,5-dihydrofuran **2m** was selectively obtained in 77% yield (entry 11). However, when **1b** was treated with gold catalyst, ethyl 2-naphthoate was contaminated in 12% yield through intramolecular hydroarylation by the 6-*endo* mode, indicating that the reaction pathway (hydroalkoxylation by the 5-*endo* mode *vs* hydroarylation by the 6-*endo* mode) was divided between the methyl and methoxy groups.

Next, 2-fold intramolecular hydroalkoxylations were briefly examined (Scheme 2). 1,4-Diformylbenzene was treated with organoindium reagent generated in situ from ethyl 4-bromobutynoate (1.5 equiv) and indium (1 equiv) in the presence of lithium iodide (3 equiv) to produce selectively hydroxyallene **2n** in 77% yield, which was smoothly converted to 2-(4-formylphenyl)-3-ethoxycarbonyl-2,5-dihydrofuran (**2o**) in 85% yield by the 5-*endo* mode. Again, indium-mediated allenyl addition to **2o** to afford **2p** in 60%

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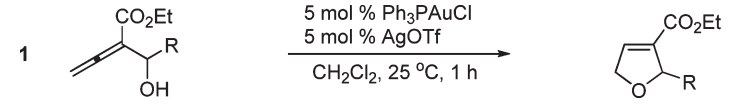
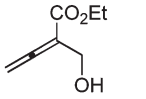
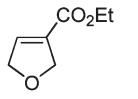
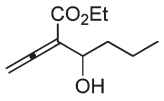
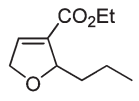
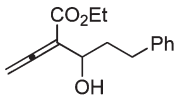
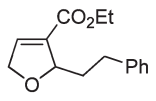
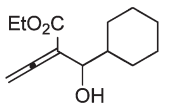
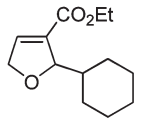
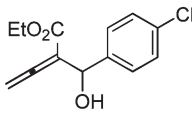
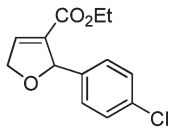
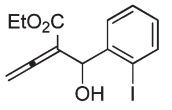
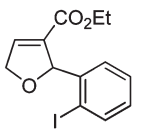
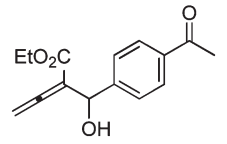
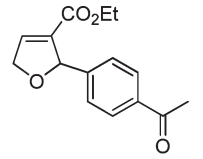
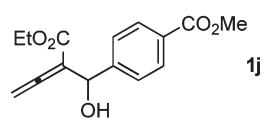
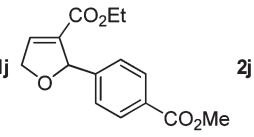
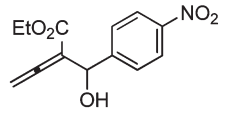
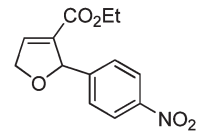
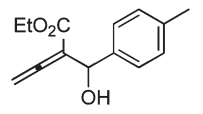
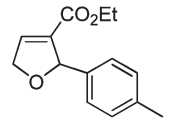
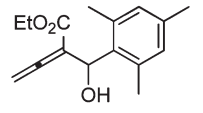
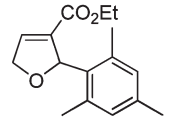
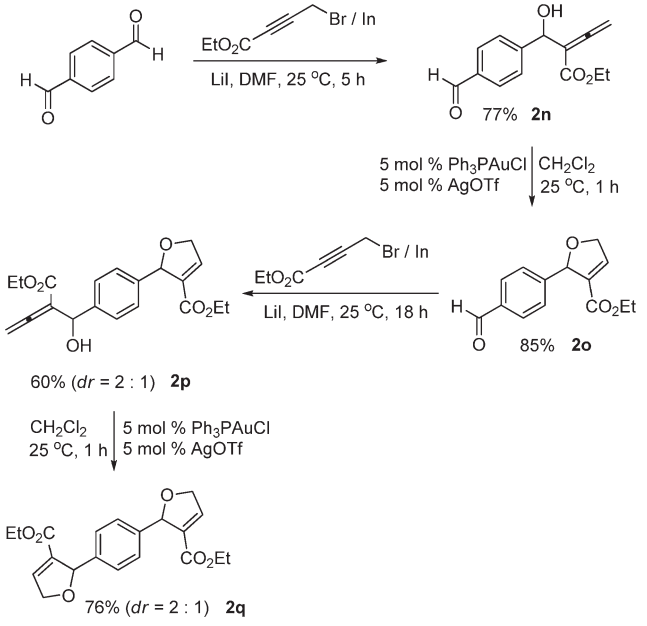
TABLE 2. Synthesis of 3-Ethoxycarbonyl-2,5-dihydrofurans Having 2-Alkyl and Aryl Group via Gold-Catalyzed Cyclization of Hydroxyallene



entry	hydroxyallene		product		yield (%)
1		**1c**		**2c**	70
2		**1d**		**2d**	90
3		**1e**		**2e**	78
4		**1f**		**2f**	83
5		**1g**		**2g**	86
6		**1h**		**2h**	90
7		**1i**		**2i**	89
8		**1j**		**2j**	97
9		**1k**		**2k**	85
10		**1l**		**2l**	49 83[a]
11		**1m**		**2m**	28 77[a]

[a] 10 mol % Ph_3PAuCl and 10 mol % AgOTf was used.

SCHEME 2. Synthesis of 1,4-Bis(3-ethoxycarbonyl-2,5-dihydrofuran-2-yl)benzene Catalyzed by Gold



yield (*dr* = 2:1) and sequential gold-catalyzed intramolecular hydroalkoxylation by the 5-*endo* mode produced 1,4-bis(3-ethoxycarbonyl-2,5-dihydrofuran-2-yl)benzene (**2q**) in 76% yield (*dr* = 2:1). When 1,4-diformylbenzene was treated with In (2 equiv), lithium iodide (6 equiv), and ethyl 4-bromobutynoate (3 equiv) for 2-fold allenylation, the desired diallenyl compound was produced in 18% yield together with **2n** in 70% yield.

In summary, we developed an efficient synthetic method of 2-alkyl- and aryl-3-ethoxycarbonyl-2,5-dihydrofurans through gold-catalyzed intramolecular hydroalkoxylation of hydroxyallenes by a 5-*endo* mode. This method would pave a new way to synthetically valuable processes of a wide range of functionalized 2,5-dihydrofuran derivatives.

Experimental Section

3-Ethoxycarbonyl-2,5-dihydrofuran (2c). To a solution of 5 mol % triphenylphosphine gold chloride (12.4 mg, 0.025 mmol) and 5 mol % silver trifluoromethanesulfonate (6.4 mg, 0.025 mmol) in dry dichloromethane (2.5 mL) under nitrogen atmosphere was added ethyl 2-hydroxymethyl-2,3-butadienoate (71.1 mg, 0.5 mmol). The reaction mixture was stirred at room temperature for 1 h. Then, the reaction mixture was filtered and concentrated under reduced pressure. The residue

was purified by flash column chromatography on silica gel (ethyl acetate:hexane = 1:7) to give 3-ethoxycarbonyl-2,5-dihydrofuran (49.8 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1H), 4.81 (s, 4H), 4.23 (q, J = 7.11 Hz, 2H), 1.31 (t, J = 7.11 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 137.8, 133.1, 76.2, 74.1, 60.7, 14.2; IR (film) 3432, 2924, 1716, 1644, 1376, 1267, 1111, 1065, 895 cm^{-1}; HRMS (EI): m/z calcd for $C_7H_{10}O_3$ 142.0630, found 142.0635.

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Supporting Information Available: Experimental procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.