JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

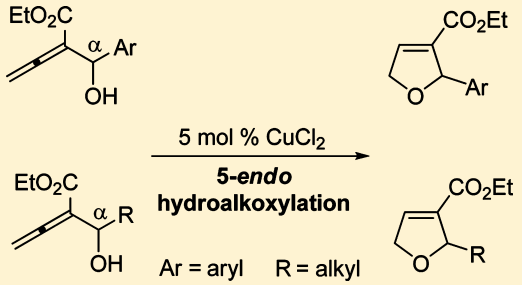
Copper-Catalyzed Intramolecular Hydroalkoxylation of α-(1-Hydroxy-1-alkyl- and -aryl)methylallenoates by a 5-*Endo* Mode for Preparation of 2-Alkyl- and 2-Aryl-2,5-dihydrofurans

Sanghyuck Kim and Phil Ho Lee*

Department of Chemistry, Kangwon National University, Chuncheon 200-701, Republic of Korea

Supporting Information

ABSTRACT: Ethyl α-(1-hydroxy-1-alkyl)methylallenoates and α-(1-hydroxy-1-aryl)methylallenoates containing not only electron-donating groups but also an electron-withdrawing group on the aryl group at the α-position have been shown to undergo an efficient and selective copper-catalyzed intramolecular hydroalkoxylation to give functionalized 3-ethoxycarbonyl-2-alkyl- and -aryl-2,5-dihydrofurans in good to excellent yields through a 5-*endo* mode.



INTRODUCTION

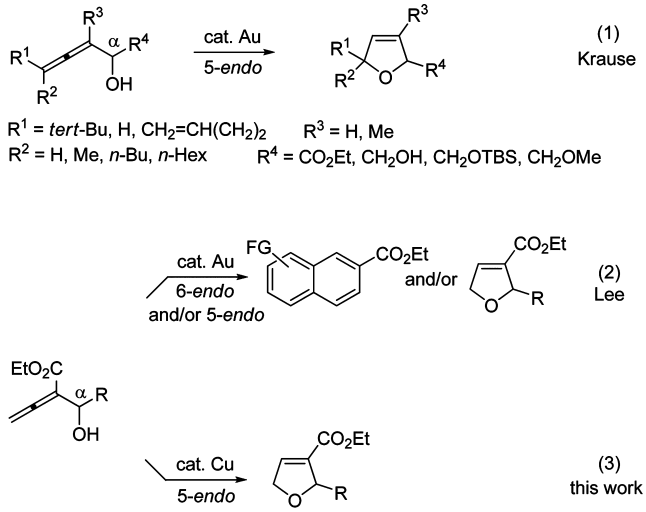
2,5-Dihydrofurans are important heterocycles that are widely used in pharmaceuticals and as flavor and fragrance compounds[1] and are found in naturally occurring and biologically important molecules.[2] Accordingly, substantial attention has been given to developing efficient methods for the synthesis of 2,5-dihydrofurans. Consequently, the development of synthetic approaches of functionalized 2,5-dihydrofurans is of major interest.[3] Krause et al. reported a highly efficient and stereoselective synthesis of 2,5-dihydrofurans by gold-catalyzed intramolecular hydroalkoxylation of α-hydroxyallenes by a 5-*endo* mode (Scheme 1, eq 1).[4]

In contrast with Krause's results,[4] we recently demonstrated that α-hydroxyallenes possessing electron-donating groups on the phenyl ring at the α-position were cyclized to produce ethyl 2-naphthoate derivatives through a gold-catalyzed selective intramolecular hydroarylation by a 6-*endo* mode followed by dehydration (eq 2).[5] Because the major consideration in transition metal-catalyzed reactions is selectivity, control of reaction pathway between 2,5-dihydrofurans and ethyl 2-naphthoates depending on metal catalyst is of synthetic importance and is a very challenging problem. Herein, we report the conversion of functionalized α-hydroxyallenes into the corresponding 2,5-dihydrofurans in good to excellent yields through a selective 5-*endo* mode by using 10 mol % of copper(II) chloride as the catalyst (eq 3).[6]

RESULTS AND DISCUSSION

First, the functionalized α-hydroxyallenes with an electron-donating group and an electron-withdrawing group on the aromatic ring at the α-position were selectively prepared by the treatment of a wide range of aldehydes with organoindium reagent generated in situ from indium and ethyl 4-bromobutynoate (Scheme 2).[5,7]

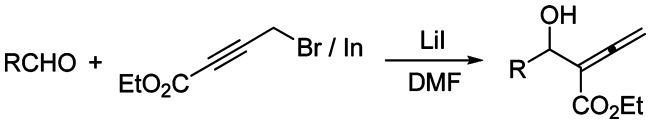
Scheme 1. Cu-Catalyzed Intramolecular Hydroalkoxylation by a Selective 5-*Endo* Mode



Although the gold-catalyzed intramolecular hydroalkoxylation is mild and efficient,[4,8] a method using a widely available transition-metal catalyst instead of an expensive catalyst would be advantageous. Accordingly, intramolecular hydroalkoxylation of α-hydroxyallenes that selectively produce 2,5-dihydrofurans with more available copper catalysts was examined. The results are summarized in Table 1. The treatment of **1a** with 10 mol %

Received: September 1, 2011
Published: November 21, 2011

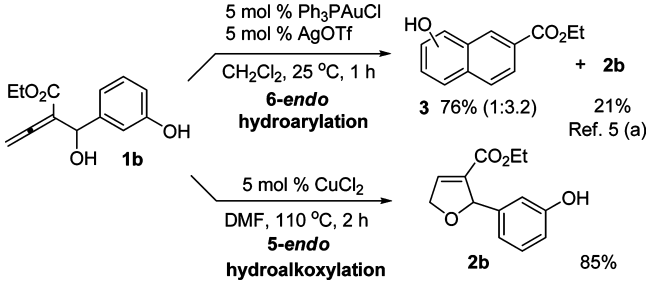
Scheme 2. Preparation of α-Hydroxyallenes



of CuCl and CuI in DMF (110 °C, 2 h) produced 3-ethoxycarbonyl-2-phenyl-2,5-dihydrofuran (**2a**) in 32% and 30% yields, respectively, through a selective intramolecular hydroalkoxylation by a 5-*endo* mode (entries 1 and 3). The use of CuBr in DMF increased the product yield to 59% (entry 2). Addition of triethylamine to reaction mixture as an additive did not affect the efficiency of the cyclization (entries 2 and 4 and entries 9 and 11). Although a variety of solvents (CH_2Cl_2, THF, and toluene) with triethylamine were examined, none of these solvents gave the desired cyclized product (entries 6–8). However, DMA gave similar result (58% yield) to DMF (entry 5). Next, different copper(II) halides were examined. The desired product **2a** was obtained in 74% yield with 10 mol % of copper(II) bromide and chloride (entries 9 and 10). Of the reactions screened, the best result was obtained with the treatment of **1a** with 5 mol % of copper(II) chloride in DMF at 110 °C for 2 h under a nitrogen atmosphere, producing selectively **2a** in 82% yield by a 5-*endo* mode (entry 13). Two mol % of copper(II) acetate produced **2a** in 40% yield (entry 15). When **1a** was treated with 5 mol % of $CuCl_2$ (purity 99.999%) in DMF at 110 °C for 2 h, the desired product was obtained in 71% yield.[9] Therefore, the present cyclization proceeded by the copper salt that is the real catalyst. In the case of vinyl group instead of ethoxycarbonyl group, 2-phenyl-4-vinyl-2,5-dihydrofuran was obtained in 44% yield in DMF at 110 °C for 2 h, indicating that ethoxycarbonyl group is important but it is not necessary in cyclization.

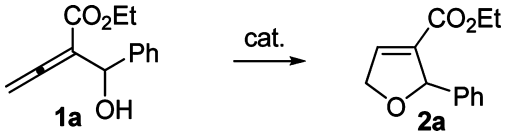
With these results in hand, the intramolecular hydroalkoxylation of an α-hydroxyallene tethering oxygen atom having nonbonding electron such as methoxy or hydroxy on the phenyl group at the α-position was investigated. The treatment of **1b** with 5 mol % of Ph_3PAuCl and 5 mol % of AgOTf provided ethyl 5-hydroxy- and 7-hydroxy-2-naphthoate (**3**) in 76% yield (isomeric ratio = 1:3.2) through an intramolecular hydroarylation by a 6-*endo* mode followed by dehydration and **2b** (21% yield) through an intramolecular hydroalkoxylation by a 5-*endo* mode (Scheme 3).

Scheme 3. Cu-Catalyzed Intramolecular Hydroalkoxylation by Selective 5-*Endo* Mode



However, surprisingly, reaction of **1b** with 5 mol % of copper(II) chloride selectively produced 2,5-dihydrofuran (**2b**) in 85%. Next, α-hydroxyallene **1c** and **1d** having a 2- and 3-methoxyphenyl group at the α-position was treated with 5 mol % of copper(II) chloride, affording selectively 2,5-dihydrofuran (**2c** and **2d**) in 65% and 80% yields, respectively (Table 2, entries 1 and 2). Although elimination followed by Michael reaction of hydroxy group due to instability of **1e** gave ethyl 2-acetyl-3-methoxyphenylpropenoate in 30% yield, intramolecularly hydroalkoxylated product **2e** was obtained in 44% yield without contamination of naphthoate (entry 3). A wide range of an α-hydroxyallene having phenyl group containing fluoro and methoxy substituent at the α-position was treated with 5 mol % of $CuCl_2$ in DMF for 110 °C produced selectively 2,5-dihydrofuran derivatives (**2f**, **2g**, **2h**, and **2i**) in ca. 60% yields through 5-*endo-dig* mode (entries 4–7). In contrast with using

Table 1. Optimization of Cu-Catalyzed Intramolecular Hydroalkoxylation

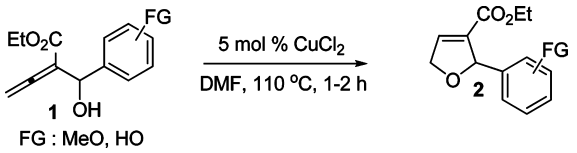


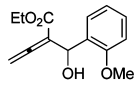
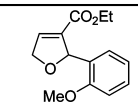
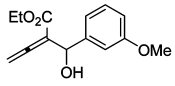
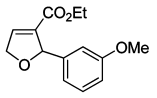
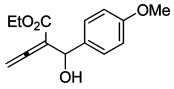
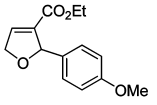
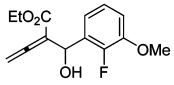
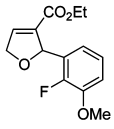
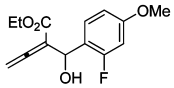
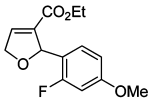
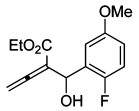
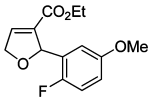
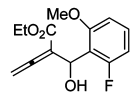
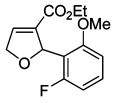
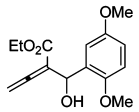
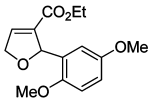
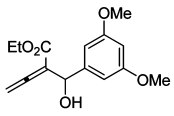
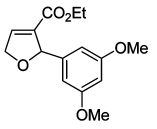
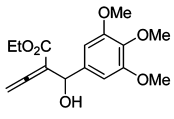
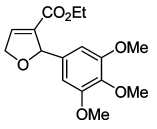
entry	cat.	solvent	temp (°C)	time (h)	yield (%)
1	10 mol % CuCl	DMF	110	2	32
2	10 mol % CuBr	DMF	110	2	59
3	10 mol % CuI	DMF	110	2	30
4	10 mol % CuBr	DMF	110	2	61[a]
5	10 mol % CuBr	DMA	130	2	58[a]
6	10 mol % CuBr	CH_2Cl_2	40	6	0[a]
7	10 mol % CuBr	THF	80	6	0[a]
8	10 mol % CuBr	toluene	110	6	0[a]
9	10 mol % $CuBr_2$	DMF	110	2	74
10	10 mol % $CuCl_2$	DMF	110	2	74
11	10 mol % $CuBr_2$	DMF	110	2	52[a]
12	5 mol % $CuBr_2$	DMF	110	2	63
13	5 mol % $CuCl_2$	DMF	110	2	82
14	2 mol % $CuCl_2$	DMF	110	2	76
15	2 mol % $Cu(OAc)_2$	DMF	110	2	40

[a] Et_3N (20 mol %) was added.

dx.doi.org/10.1021/jo2018125 | J. Org. Chem. 2012, 77, 215–220

Table 2. Cu-Catalyzed Intramolecular Hydroalkoxylation of α-Hydroxyallenes Having Methoxy on the Aryl Group by a 5-*Endo* Mode



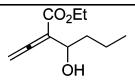
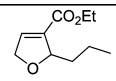
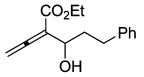
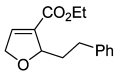
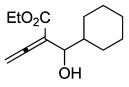
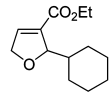
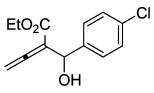
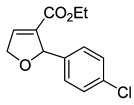
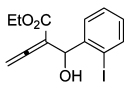
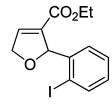
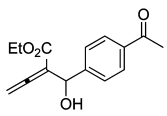
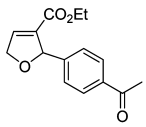
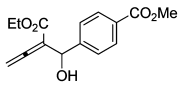
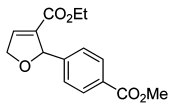
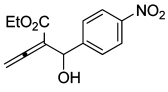
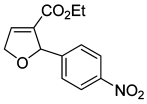
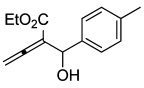
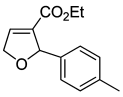
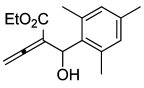
entry	hydroxyallene		dihydrofuran		yield (%)
1		**1c**		**2c**	65
2		**1d**		**2d**	80
3		**1e**		**2e**	44 (30)[a]
4		**1f**		**2f**	62
5		**1g**		**2g**	60
6		**1h**		**2h**	60
7		**1i**		**2i**	61
8		**1j**		**2j**	53 (3.8 : 1)[b]
9		**1k**		**2k**	95 (3.5 : 1)[b]
10		**1l**		**2l**	72

[a]Ethyl 2-acetyl-4-methoxyphenyl propenoate. [b]Ratio of 2,5-dihydrofuran and naphthaoate.

gold catalyst, exposure of **1k** to 5 mol % of copper(II) chloride provided 2,5-dihydrofuran **2k** as major product (entry 9). We were pleased to obtain **2l** selectively in 72% yield through a 5-*endo* mode from α-hydroxyallene **1l**, which contains 3,4,5-trimethoxyphenyl group (entry 10).

Next, the intramolecular hydroalkoxylation of an α-hydroxyallene having an alkyl group at the α-position and a wide range of electron-withdrawing or -donating group on the phenyl ring at the α-position was examined. Under the optimum reaction conditions, a wide range of α-hydroxyallenes underwent selective intramolecular hydroalkoxylation through a 5-*endo* mode without any intramolecular hydroarylation by a 6-*endo* mode (Table 3). The treatment of the *n*-propyl-

Table 3. Cu-Catalyzed Intramolecular Hydroalkoxylation by a 5-*Endo* Mode

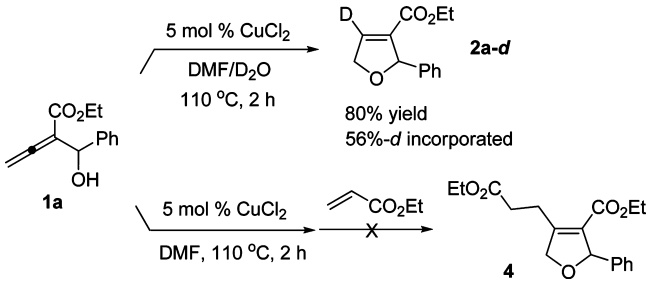
entry	hydroxyallene		dihydrofuran		yield (%)
1		**1m**		**2m**	78
2		**1n**		**2n**	77
3		**1o**		**2o**	86
4		**1p**		**2p**	86
5		**1q**		**2q**	82
6		**1r**		**2r**	77
7		**1s**		**2s**	84
8		**1t**		**2t**	80
9		**1u**		**2u**	70
10		**1v**		**2v**	76

substituted α-hydroxyallene **1m** with 5 mol % of copper(II) chloride gave 2,5-dihydrofuran **2m** in 78% yield (entry 1). Phenethyl-substituted α-hydroxyallene **1n** and cyclohexyl-substituted α-hydroxyallene **1o** were subjected to a selective intramolecular hydroalkoxylation under the above conditions, producing **2n** and **2o** in 77% and 86% yields, respectively (entries 2 and 3). We were pleased to obtain halophenyl-3-ethoxycarbonyl-2,5-dihydrofurans **2p** and **2q** selectively from the reaction of 4-chlorophenyl α-hydroxyallene **1p** and 2-iodophenyl α-hydroxyallene **1q** with copper catalyst (entries 4 and 5). α-Hydroxyallenes **1r**, **1s**, and **1t** having electron-withdrawing groups such as 4-acetyl, 4-ethoxycarbonyl, and 4-nitro on the aryl ring turned out to be compatible with the reaction conditions (entries 6–8). The present method worked equally well even with 4-methyl and 2,4,6-trimethyl substituents on the phenyl ring (entries 9 and 10).

dx.doi.org/10.1021/jo2018125 | J. Org. Chem. 2012, 77, 215–220

The intramolecular hydroalkoxylation of **1a** in DMF and D_2O gave rise to the corresponding deuterated product **2a** in 80% yield with 56% *d*-incorporation, indicating that a vinylcopper intermediate might be formed (Scheme 4). Based

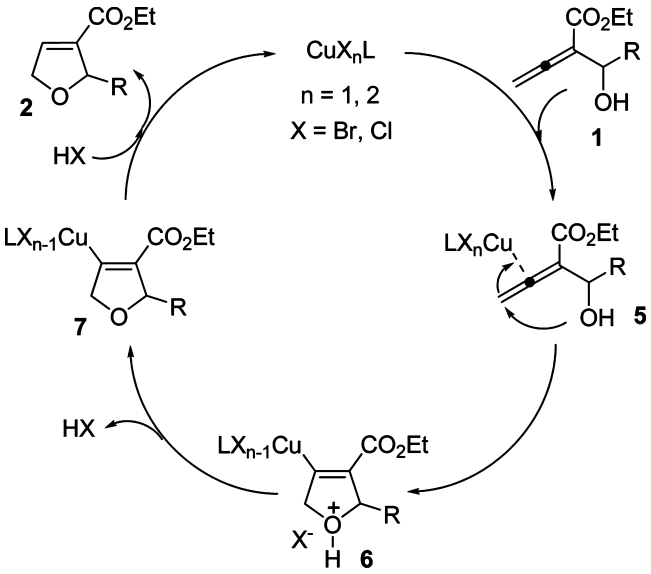
Scheme 4. Deuterium Incorporation in Hydroalkoxylation



on these results, we were also interested in the functionalization at C-4 and envisioned that this might be possible through an in situ trapping of the copper intermediate with an α,β-unsaturated enone. Unfortunately, when the intramolecular hydroalkoxylation was carried out in the presence of ethyl acrylate and 5 mol % copper(II) chloride, only protonolysis product (**2a**) was observed.

Although the mechanism of the present reaction has not been established, a possible reaction mechanism for intramolecular Cu-catalyzed hydroalkoxylation is shown in Scheme

Scheme 5. Plausible Mechanism



5. The reaction would be initiated by the activation of the allenyl group by the copper catalyst,[5] followed by a 5-*endo* cyclization to afford the vinylcopper intermediate **6**, which then gives intermediate **7**. Subsequent protonation of the transient vinylcopper intermediate **7** produces **2** and regenerates copper to continue the catalytic cycle. In addition, a direct protonation by HX formed by reduction of CuX_2 might explain the result that the reaction with ethyl acrylate did not proceed.

CONCLUSION

We developed an efficient and selective copper-catalyzed intramolecular hydroalkoxylation of α-hydroxyallenes for the synthesis of highly functionalized 2,5-dihdrofurans through a 5-*endo* mode that eliminates the need to use an expensive catalyst. In particular, the intramolecular hydroalkoxylation of α-hydroxyallenes having electron-donating groups such as methoxy and hydroxy on the aryl ring at the α-position proceeded smoothly to produce 2,5-dihydrofurans selectively without contamination of naphthoate through a 6-*endo* mode. This method provides a valuable new way to synthesize a wide range of functionalized 2,5-dihydrofuran derivatives.

EXPERIMENTAL SECTION

General Methods for the Synthesis of Dihydrofurans. To a solution of 5 mol % of copper chloride (2.02 mg, 0.015 mmol) in DMF (1 mL) was added ethyl α-hydroxyallenoate **1** (0.3 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 110 °C. After being stirred for 2 h, the reaction mixture was cooled to room temperature and then filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (ethyl acetate/hexane = 1:10) to give the desired products **2**.

3-Ethoxycarbonyl-2-phenyl-2,5-dihydrofuran (2a). To a solution of 5 mol % of copper chloride (2.02 mg, 0.015 mmol) in DMF (1 mL) under nitrogen atmosphere was added ethyl 2-(1-hydroxybenzyl)buta-2,3-dienoate (63.0 mg, 0.3 mmol). The reaction mixture was stirred at 110 °C. After being stirred for 2 h, the reaction mixture was cooled to room temperature and then filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (ethyl acetate/hexane = 1:10) to give 3-ethoxycarbonyl-2-phenyl-2,5-dihydrofuran (51.0 mg, 82%): ^{1}H NMR (400 MHz, CDCl) δ 7.35−7.27 (m, 5H), 7.01 (s, 1H), 5.94−5.91 (m, 1H), 5.02 (dd, J = 6.20 Hz, J = 6.2 Hz, 1H), 4.88 (d, J = 15.80 Hz, 1H), 4.15−4.06 (m, 2H), 1.16 (t, J = 7.09 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 140.9, 138.3, 136.0, 128.3, 128.2, 127.2, 87.0, 75.3, 60.6, 14.0; IR (film) 3431, 3054, 2987, 2123, 1716, 1421, 1265, 1108, 1056, 896 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0947.

3-Ethoxycarbonyl-2-(3-hydroxyphenyl)-2,5-dihydrofuran (2b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, J = 7.86 Hz, 1H), 7.01 (s, 1H), 6.90 (d, J = 7.86 Hz, 1H), 6.79 (s, 1H), 6.74 (d, J = 7.86 Hz, 1H), 5.88−5.86 (m, 1H), 5.74 (s, 1H), 4.99 (dd, J = 6.05 Hz, J = 6.05 Hz, 1H), 4.86 (d, J = 15.88 Hz, 1H), 4.18−4.04 (m, 2H), 1.78 (s, 1H), 1.18 (t, J = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 156.3, 142.7, 138.9, 136.1, 130.0, 119.8, 115.8, 114.6, 87.1, 75.7, 61.2, 14.4; IR (film) 3433, 2253, 1643, 1265, 907, 728, 650, 494 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{14}O_4$ 234.0892, found 234.0894.

3-Ethoxycarbonyl-2-(2-methoxyphenyl)-2,5-dihydrofuran (2c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, J = 8.03 Hz, 1H), 7.13 (dd, J = 1.65 Hz, J = 6.25 Hz, 1H), 7.05 (m, 1H), 6.91 (t, J = 7.82 Hz, 2H), 6.37 (m, 1H), 4.87 (dd, J = 15.78 Hz, J = 20.93 Hz, 2H), 4.09 (m, 2H), 3.86 (s, 3H), 1.14 (t, J = 7.06 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 158.0, 139.5, 137.7, 135.4, 128.7, 120.9, 111.4, 81.5, 75.3, 60.9, 56.1, 14.4; IR (film) 2986, 2937, 2839, 1719, 1492, 1260, 1051, 754 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{16}O_4$ 248.1049, found 248.1051.

3-Ethoxycarbonyl-2-(3-methoxyphenyl)-2,5-dihydrofuran (2d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, J = 7.79 Hz, 1H), 7.00 (s, 1H), 6.94 (d, J = 7.79 Hz, 1H), 6.89 (s, 1H), 6.83 (d, J = 7.79 Hz, 1H), 5.91−5.88 (m, 1H), 5.01 (dd, J = 6.18 Hz, J = 6.18 Hz, 1H), 4.86 (d, J = 15.92 Hz, 1H), 4.18−4.08 (m, 2H), 3.80 (s, 3H), 1.17 (t, J = 7.09 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 160.0, 142.8, 138.8, 136.3, 129.8, 120.0, 114.0, 113.2, 87.2, 75.7, 61.0, 55.6, 14.4; IR (film) 3422, 2981, 1719, 1645, 1601, 1487, 1373, 1260, 1155, 1106, 1051, 774 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{16}O_4$ 248.1049, found 248.1053.

3-Ethoxycarbonyl-2-(4-methoxyphenyl)-2,5-dihydrofuran (2e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.69 Hz, 2H), 7.00 (s, 1H), 6.87 (d, J = 8.76 Hz, 1H), 5.90−5.87 (m, 1H), 4.99 (dd, J = 6.14 Hz, J = 6.14 Hz, 1H), 4.86 (d, J = 15.81 Hz, 1H), 4.18−4.01 (m, 2H), 3.79 (s, 3H), 1.17 (t, J = 7.14 Hz, 3H); ^{13}C NMR (100 MHz,

dx.doi.org/10.1021/jo2018125 | J. Org. Chem. 2012, 77, 215−220

$CDCl_3$) δ 162.4, 159.5, 138.2, 136.0, 133.1, 128.4, 113.7, 86.5,75.0, 60.6, 55.2, 14.0; IR (film) 3422, 2981, 1719, 1645, 1601, 1487, 1373, 1260, 1155, 1106, 1051, 774 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{16}O_4$ 248.1049, found 248.1050.

3-Ethoxycarbonyl-2-(2-fluoro-3-methoxyphenyl)-2,5-dihydrofuran (2f): ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 7.04 (t, J = 7.96, 1H), 6.9 (t, J = 8.08 Hz, 1H), 6.82 (t, J = 6.08 Hz, 1H), 6.21 (m, 1H), 4.93 (dd, J = 6.3 Hz, J = 15.8 Hz, 2H), 4.09 (m, 2H), 3.87 (s, 3H), 1.15 (t, J = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 152.4, 149.9, 139.5, 134.9, 129.1, 124.1, 120.6, 113.6, 81.4, 75.8, 61.0, 56.7, 14.3; IR (film) 2982, 2940, 2905, 2845, 1719, 1649, 1619, 1588, 1489, 1271, 1108, 1052, 779 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{15}FO_4$ 266.0954, found 266.0954.

3-Ethoxycarbonyl-2-(2-fluoro-4-methoxyphenyl)-2,5-dihydrofuran (2g): ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, J = 8.53, 1H), 7.03 (s, 1H), 6.66 (dd, J = 2.46 Hz, J = 8.64 Hz, 1H), 6.59 (dd, J = 2.48 Hz, J = 12.12 Hz, 1H), 6.15 (m, 1H), 4.91 (dd, J = 15.73 Hz, J = 38.99 Hz, 2H), 4.09 (m, 2H), 3.78 (s, 3H), 1.17 (t, J = 7.11 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 162.6, 160.6, 139.3, 135.1, 130.0, 120.3, 110.3, 102.1, 81.3, 75.5, 60.9, 55.9, 14.3; IR (film) 2982, 2938, 2906, 2854, 1719, 1500, 1263, 1206, 919, 817, 740 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{15}FO_4$ 266.0954, found 266.0953.

3-Ethoxycarbonyl-2-(2-fluoro-5-methoxyphenyl)-2,5-dihydrofuran (2h): ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.96 (t, J = 9.11 Hz, 1H), 6.77 (m, 1H), 6.17 (m, 1H), 4.93 (dd, J = 15.79 Hz, J = 41.55 Hz, 2H), 4.11 (m, 2H), 3.76 (s, 3H), 1.16 (t, J = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 155.9, 154.4, 139.5, 135.1, 128.8, 116.6, 115.1, 114.4, 81.4, 75.8, 61.0, 56.1, 14.3; IR (film) 2981, 2938, 2906, 2848, 1720, 1625, 1465, 1445, 1262, 834 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{15}FO_4$ 266.0954, found 266.0956.

3-Ethoxycarbonyl-2-(2-fluoro-5-methoxyphenyl)-2,5-dihydrofuran (2i): ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (q, J = 8.41 Hz 1H), 6.97 (s, 1H), 6.65 (m, 2H), 6.49 (m, 1H), 4.92 (dd, J = 15.17 Hz, J = 40.85 Hz, 2H), 4.09 (m, 2H), 3.83 (s, 3H), 1.14 (t, J = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 162.8, 161.4, 159.6, 138.9, 133.9, 130.1, 116.6, 108.8, 107.1, 75.9, 60.8, 56.5, 14.3; IR (film) 2981, 2938, 2904, 2852, 1719, 1586, 1474, 1264, 1238, 1107, 1084, 782 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{15}FO_4$ 266.0954, found 266.0956.

3-Ethoxycarbonyl-2-(2,5-dimethoxyphenyl)-2,5-dihydrofuran (2j): ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.86–6.78 (m, 2H), 6.70 (d, J = 2.81, 1H), 6.34 (m, 1H), 4.91 (dd, J = 6.13 Hz, J = 6.13 Hz, 1H), 4.85 (d, J = 15.80 Hz, 1H), 4.15–4.05 (m, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 1.16 (t, J = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 153.6, 152.0, 139.2, 135.0, 129.6, 114.4, 113.8, 112.4, 80.9, 74.9, 60.5, 56.5, 55.7, 14.0; IR (film) 3627, 2939, 2839, 1717, 1662, 1593, 1506, 1463, 1422, 1329, 1261, 1126, 1008, 831, 772 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{18}O_5$ 278.1154, found 278.1153.

3-Ethoxycarbonyl-2-(3,5-dimthoxyphenyl)-2,5-dihydrofuran (2k): ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.51 (s, 2H), 6.40 (s, 1H), 5.86 (m, 1H), 5.01 (dd, J = 6.22 Hz, J = 6.22 Hz, 1H), 4.87 (d, J = 15.80 Hz, 1H), 4.12 (m, 2H), 3.78 (s, 3H), 1.20 (t, J = 7.11 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 160.7, 143.1, 138.4, 135.7, 105.2, 100.2, 75.3, 60.6, 55.3, 53.4, 14.1; IR (film) 3627, 2939, 2839, 1717, 1598, 1463, 1430, 1327, 1261, 1204, 1157, 1106, 1051, 839, 773 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{18}O_5$ 278.1154, found 278.1154.

3-Ethoxycarbonyl-2-(3,4,5-trimethoxyphenyl)-2,5-dihydrofuran (2l): ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.57 (s, 2H), 5.88 (m, 1H), 5.01 (dd, J = 6.17 Hz, J = 6.17 Hz, 1H), 4.88 (d, J = 15.85 Hz, 1H), 4.18–4.08 (m, 2H), 3.86 (s, 6H), 3.83 (s, 3H) 0.20 (t, J = 7.10 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 162.8, 153.7, 153.6, 141.6, 138.9, 138.3, 136.7, 136.1, 128.6, 107.4, 104.5, 87.5, 75.6, 61.2, 61.1, 56.5, 56.4; IR (film) 3627, 2939, 2839, 1717, 1662, 1593, 1506, 1463, 1422, 1329, 1235, 1126, 1008, 921, 831 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{20}O_6$ 308.1260, found 308.1257.

3-Ethoxycarbonyl-2-propyl-2,5-dihydrofuran (2m): ^1H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1H), 5.05–5.01 (m, 1H), 4.77 (dd, J = 5.98 Hz, J = 5.98 Hz, 1H), 4.70 (d, J = 15.69 Hz, 1H), 4.27–4.18 (m, 2H), 1.86–1.78 (m, 1H), 1.66–1.57 (m, 1H), 1.46–1.37 (m, 2H), 1.31 (t, J = 7.18 Hz, 3H), 0.94 (t, J = 7.35 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 138.8, 136.0, 85.2, 74.8, 60.9, 37.0, 18.6, 14.6, 14.5; IR (film) 2959, 1720, 1464, 1374, 1257, 1096, 1044 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1098.

3-Ethoxycarbonyl-2-phenethyl-2,5-dihydrofuran (2n): ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.15 (m, 5H), 6.86 (s, 1H), 5.07–5.04 (m, 1H), 4.81 (dd, J = 6.02 Hz, J = 6.02 Hz, 1H), 4.73 (d, J = 15.82 Hz, 1H), 4.25–4.16 (m, 2H), 2.78–2.66 (m, 2H), 2.25–2.17 (m, 2H), 1.99–1.90 (m, 1H), 1.29 (t, J = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 142.5, 139.2, 135.7, 128.9, 128.7, 126.1, 84.7, 74.9, 61.0, 36.5, 31.6, 14.6; IR (film) 3422, 2984, 2252, 1714, 1644, 1455, 1375, 1265, 1240, 1110, 908, 729 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1254 .

2-Cyclohexyl-3-ethoxycarbonyl-2,5-dihydrofuran (2o): ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 4.91 (s, 1H), 4.71 (d, J = 4.89 Hz, 2H), 4.29–4.16 (m, 2H), 1.86–1.66 (m, 5H), 1.48–1.03 (m, 6H), 1.31 (t, J = 7.17 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 138.8, 134.2, 89.2, 75.2, 60.5, 41.4, 30.2, 26.7, 26.4, 26.1, 25.4, 14.2; IR (film) 3423, 3054, 2986, 2929, 2854, 1715, 1265, 1108, 909, 742 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1412.

2-(4-Chlorophenyl)-3-ethoxycarbonyl-2,5-dihydrofuran (2p): ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 4H), 7.01 (s, 1H), 5.91–5.88 (m, 1H), 5.01 (dd, J = 6.22 Hz, J = 6.22 Hz, 1H), 4.87 (d, J = 15.93 Hz, 1H), 4.13–4.06 (m, 2H), 1.18 (t, J = 7.13 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 139.9, 138.9, 136.1, 134.3, 129.0, 128.9, 86.6, 75.8, 61.1, 14.4; IR (film) 2850, 1720, 1647, 1489, 1373, 1327, 1259, 1236, 1106, 1089, 1060, 1015, 922, 815 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{13}ClO_3$ 252.0553, found 252.0551.

3-Ethoxycarbonyl-2-(2-iodophenyl)-2,5-dihydrofuran (2q): ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.90 Hz, 1H), 7.31 (t, J = 7.51 Hz, 1H), 7.17–7.13 (m, 2H), 6.98 (t, J = 7.90 Hz, 1H), 6.27–6.24 (m, 1H), 4.95 (dd, J = 6.13 Hz, J = 6.13 Hz, 1H), 4.85 (d, J = 15.94 Hz, 1H), 4.14–4.05 (m, 2H), 1.14 (t, J = 7.19 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 142.6, 140.14, 140.12, 135.9, 130.4, 128.9, 128.5, 100.3, 90.6, 75.6, 61.1, 14.4; IR (film) 3433, 2253, 1643, 1265, 907, 728, 649 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{13}IO_3$ 343.9909, found 343.9910.

2-(4-Acetylphenyl)-3-ethoxycarbonyl-2,5-dihydrofuran (2r): ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.29 Hz, 2H), 7.46 (d, J = 8.29 Hz, 2H), 7.03 (s, 1H), 5.98–5.95 (m, 1H), 5.05 (dd, J = 6.19 Hz, J = 6.19 Hz, 1H), 4.91 (d, J = 15.92 Hz, 1H), 4.16–4.03 (m, 2H), 2.58 (s, 3H), 1.17 (t, J = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 162.4, 146.5, 139.1, 137.3, 136.0, 128.8, 127.8, 86.8, 76.1, 61.1, 27.0, 14.4; IR (film) 2852, 1719, 1683, 1608, 1415, 1359, 1327, 1266, 1106, 1061, 1016, 826 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{16}O_4$ 260.1049, found 260.1050.

3-Ethoxycarbonyl-2-(4-methoxycarbonylphenyl)-2,5-dihydrofuran (2s): ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.26 Hz, 2H), 7.43 (d, J = 8.26 Hz, 2H), 7.02 (s, 1H), 5.98–5.95 (m, 1H), 5.05 (dd, J = 6.24 Hz, J = 6.24 Hz, 1H), 4.90 (d, J = 15.95 Hz, 1H), 4.15–4.02 (m, 2H), 3.90 (s, 3H), 1.16 (t, J = 7.11 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 162.4, 146.4, 139.1, 136.0, 130.3, 130.0, 127.6, 86.8, 76.0, 61.1, 52.5, 14.4; IR (film) 3405, 1719, 1435, 1280, 1104, 1060, 1018, 760, 435 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{16}O_5$ 276.0998, found 276.0998.

3-Ethoxycarbonyl-2-(4-nitrophenyl)-2,5-dihydrofuran (2t): ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.63 Hz, 2H), 7.54 (d, J = 8.63 Hz, 2H), 7.04 (s, 1H), 6.00–5.98 (m, 1H), 5.07 (dd, J = 6.19 Hz, J = 6.19 Hz, 1H), 4.92 (d, J = 16.04 Hz, 1H), 4.16–4.03 (m, 2H), 1.18 (t, J = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 147.2, 146.7, 138.0, 134.2, 127.1, 122.5, 84.9, 74.9, 59.9, 13.0; IR (film) 3424, 1714, 1646, 1521, 1465, 1348, 1259, 1106, 1062, 749 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{13}NO_5$ 263.0794, found 263.0796.

3-Ethoxycarbonyl-2-(4-methylphenyl)-2,5-dihydrofuran (2u): ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 7.98 Hz, 2H), 7.14 (d, J = 7.98 Hz, 2H), 6.99 (s, 1H), 5.91–5.88 (m, 1H), 4.99 (dd, J = 6.18 Hz, J = 6.18 Hz, 1H), 4.85 (d, J = 15.75 Hz, 1H), 4.16–4.02 (m, 2H), 2.32 (s, 3H), 1.17 (t, J = 7.15 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 138.6, 138.33, 138.28, 136.4, 129.4, 127.5, 87.2, 75.6, 61.0, 21.6, 14.4; IR (film) 2981, 1720, 1372, 1259, 1105, 1058, 1020,

dx.doi.org/10.1021/jo2018125 | J. Org. Chem. 2012, 77, 215–220

811, 734 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{14}H_{16}O_3$ 232.1099, found 232.1097.

3-Ethoxycarbonyl-2-(2,4,6-trimethylphenyl)-2,5-dihydrofuran (2v): ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.79 (s, 1H), 6.42 (t, *J* = 6.25 Hz, 1H), 4.95 (dd, *J* = 6.65 Hz, *J* = 6.65 Hz, 1H), 4.87 (dd, *J* = 5.85 Hz, *J* = 5.85 Hz, 1H), 4.10−4.02 (m, 2H), 2.36 (s, 6H), 2.23 (s, 3H), 1.13 (t, *J* = 7.11 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 138.6, 138.0, 137.8, 135.3, 132.1, 83.3, 75.0, 60.9, 21.3, 14.3; IR (film) 3432, 2253, 1714, 1644, 1265, 1108, 1054, 906, 728, 649 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1415.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: phlee@kangwon.ac.kr.

■ ACKNOWLEDGMENTS

This work was supported by the CRI Program (2011-0009011) funded by the National Research Foundation of Korea (NRF), by an NRF grant funded by the Korea government (MEST) (2009-0087013), and by the second phase of the Brain Korea 21 Program in 2009. Dr. Sung Hong Kim at the KBSI (Daegu) is thanked for obtaining the HRMS data. The NMR data were obtained from the central instrumental facility in KNU.

■ REFERENCES

(1) (a) Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550. (b) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966. (c) Darcel, C.; Bruneau, C.; Albert, M.; Dixneuf, P. H. *Chem. Commun.* **1996**, 919. (d) Saimoto, H.; Yasui, M.; Ohrai, S.; Oikawa, H.; Yokoyama, K.; Shigemasa, Y. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 279. (e) Krause, N., Hashmi, A. S. K., Eds. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, 2004; Vols. *1 and 2*. (f) Yeom, H.-S.; Shin, S. *Tetrahedron Lett.* **2007**, *48*, 4817. (g) Bongers, N.; Krause, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 2178. (h) Deng, Y.; Yu, Y.; Ma, S. *J. Org. Chem.* **2008**, *73*, 585. (i) Yamamoto, Y.; Takuma, R.; Hotta, T.; Yamashita, K. *J. Org. Chem.* **2009**, *74*, 4324.

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

(3) (a) Carda, M.; Castillo, E.; Rodrıguez, S.; Uriel, S.; Marco, J. A. *Synlett* **1999**, 1639. (b) Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, *41*, 8933. (c) Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104. (d) Kim, J. M.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 2805. (e) Alcaide, B.; Almendros, P.; Rodrıguez-Acebes, R. *Chem.—Eur. J.* **2005**, *11*, 5708. (f) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387. (g) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957.

(4) (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. (e) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994.

(5) (a) Park, C.; Lee, P. H. *Org. Lett.* **2008**, *10*, 3359. (b) Kong, W.; Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2010**, 6545.

(6) (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **1995**, *34*, 1581. (b) Ma, S.; Yu, Z. *Synthesis* **2006**, 3711. (c) Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314. (d) Ma, S.; Wu, S. *Tetrahedron Lett.* **2001**, *42*, 4075. (e) Ma, S.; Wu, S. *Chem. Commun.* **2001**, 441. (f) Ma, S.; Xie, H. *Org. Lett.* **2000**, *2*, 3801. (g) Yu, F.; Lian, X.; Zhao, J.; Yu, Y.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1130.

(7) MacInnes, I.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1077.

(8) (a) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489. (b) Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669. (c) Kim, S.; Lee, P. H. *Adv. Synth. Catal.* **2008**, *350*, 547. (d) Tarselli, M. A.; Zuccarello, J. L.; Lee, S. J.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 3490. (e) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121. (f) Murai, M.; Uenishi, J.-i.; Uemura, M. *Org. Lett.* **2010**, *12*, 4788. (g) Eom, D.; Kang, D.; Lee, P. H. *J. Org. Chem.* **2010**, *75*, 7447.

(9) Larsson, P.; Correa, A.; Carril, M.; Norrby, P.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5691.